CHAPTER 19

The Role of Cingulate Cortex in Central Neuropathic Pain: Functional Imaging and Cortical Model of Allodynia

Anthony K. P. Jones and Bhavna Kulkarni

Chapter contents

Central neuropathic pain (CNP) may result from damage anywhere in the central nervous system. The focus of this discussion is on CNP rather than peripheral neuropathic pain because at present, although there are likely to be important central mechanisms that contribute to peripheral neuropathic pain, the explanatory mechanisms emphasize peripheral and/or spinal cord mechanisms rather than cortical mechanisms. However, in terms of symptoms and clinical signs there are many similarities between the two types of pain and therefore, where relevant, information about peripheral neuropathic pain will be used. It is not the intention to provide an exhaustive review of the clinical presentation and epidemiology of CNP which has been done elsewhere (Hansson, 2004, 2005). However, there are certain key clinical features that distinguish CNP from other types of pain, although these are quite variable.

Neuropathic pain in general is characterized by its unpleasantness and is often described as being unlike any pain previously experienced (Jones *et al*., 2004). Because of the unfamiliar nature of the sensation, patients will often have difficulty describing it. When given time, a sensation that is initially described as a pain may be further described as just a very unpleasant burning, numbness or cold sensation that is not really painful. It is likely that a number of published findings will include such very aversive or dysaesthetic but non-painful sensations, as patients will often call them pain for lack of a better word. CNP may occur after any kind of damage to the central nervous system such as stroke, demyelinating disease such as multiple sclerosis and syringomyelia (Hansson, 2005). Most commonly CNP is described as a burning pain or deep ache or occasionally unpleasant cold. However, it may quite often be described in quite bizarre terms such as 'like someone clawing the flesh from inside' or 'like a red-hot poker being inserted into the muscles'. These kinds of descriptions are very uncommon with other types of pain. Such descriptions of pain by patients in the first half of the last century were considered to be a sign of hysteria or psychosis.

In contrast to peripheral neuropathic pain, which is usually quite well localized to an area of neurological deficit, CNP is often imprecisely localized to a whole limb or the whole of one side of the body. A further feature is that it is frequently associated with unpleasant autonomic symptoms such a flushing and sweating. Changes in body temperature may also worsen the CNP.

CNP is usually present most of the time with varying severity. It is also frequently provoked by sensory stimulation such as light brush, touch, pressure, or cool that would not normally be painful. Motor activity may occasionally be the main provocation of further pain. The phenomenon of allodynia was previously considered as diagnostic of neuropathic pain of any sort. However, chronic widespread pain (CWP or fibromyalgia) and chronic regional pain syndromes (CRP) are defined by allodynia to light pressure. CWP and CRP are not usually associated with allodynia to light touch or brush, but can be rarely in their more severe form. CWP/CRP also do not usually present with any neurological deficit or central lesion associated with this. However, the persistence, the level of unpleasantness and some of the descriptors of the pain and disability associated with CWP/CRP and CNP bear some striking similarities. The incidence of classical CNP as defined by pain and allodynia in the territory of the neurological deficit after stroke is between 5% and 8% (Andersen *et al*., 1995) and can occur at any time after a stroke. However, other types of pain such as post-stroke shoulder pain may be as high as 50% and usually occurs within 6 months of the stroke. The latter probably contains a spectrum of pain from nociceptive pain resulting from mechanical damage to more centrally driven pain, that is related to the extent of neurological damage and depression (Gamble *et al*., 1999, 2000, 2002). Its presence can seriously impair rehabilitation. The incidence of CNP in syringomyelia is over 70% (Boivie, 1999) and 35% in multiple sclerosis.

So far it has not been possible to attribute CNP to a lesion or set of lesions in the brain or spinal cord. However, lesions that involve the spinothalamic tract, its projections and the constituents of the human pain matrix are more common (Jones *et al*., 2004). Within the context of post-stroke pain, the loss of inhibition of reverberating circuits involving the medial, lateral, and reticular thalamic nuclei is one possible mechanism (Jeanmonod *et al*., 1996; Llinas *et al*., 1999). However, many patients with lesions in similar places never develop CNP. Some clues about potential common pharmacological mechanisms come from evidence from pharmacological interventions. Whereas CNP was originally thought to be resistant to the analgesic effects of opiates (Arner & Meyerson, 1988; Rowbotham *et al*., 2003) we now know that it is opiate responsive but generally at higher doses (Jones *et al*., 2004). The clinical impression is that a similar response may apply to CWP as applies to CNP with poor response in those that are severely psychologically distressed, but large systematic trials in this conditions have not so far been conducted. Interestingly, both neuropathic pain (including CNP) and CWP are responsive to tri-cyclic antidepressants (Nicholson, 2004).

Goals of This Chapter

With this background, we examine functional imaging and electrophysiological studies that have been performed in patients with neuropathic pain, including

CNP, and formulate a plausible common mechanism for allodynia. We hypothesize that such a mechanism is damage to the circuitry regulating the endogenous opioid system within the perigenual anterior cingulate cortex (pACC) and anterior midcingulate cortex (aMCC). We then extend this hypothesis to patients with chronic widespread and regional pains and suggest a similar failure due to stress- and depression-related malfunction rather than damage (Chapter 23). However, we will emphasize that the pACC and aMCC are part of the limbic circuitry that regulates mood, autonomic function and that are also concerned with the affective processing of pain. We will suggest that the failure of or damage to the opioid circuitry within pACC/aMCC may be responsible for both altered nociception and an inability to maintain or attend to other cognitive tasks. The conclusions of this chapter will converge very substantially with those of Garcia-Larrea *et al.* (Chapter 20) and Vogt *et al.* (Chapter 14). This chapter seeks to accomplish the following specific goals:

1 Discuss the main issues surrounding the interpretation of functional imaging studies of pain.
2 Summarize the contribution of functional imaging to the understanding of the role of the cingulate cortex in pain perception, with particular reference to normal pain-free subjects, experimental allodynia and patients with different types of neuropathic pain.
3 Describe the potential contribution of the endogenous opioid system to the modulation of the affective components of pain perception.
4 Provide a unifying theory that may explain the presence of allodynia in both neuropathic pain and chronic regional and widespread pain syndromes.

Functional Imaging of the Medial and Lateral Nociceptive Systems in Humans

A very detailed account of the role of the cingulate cortex and its nociceptive connections is to be found in Chapter 14. This section will briefly review components of the medial and lateral systems and how the pACC may contribute to the experience of pain within this system. Until recently, it has been unclear to what extent cortical areas subserve the experience of pain. This uncertainty has been partly due to the sparse direct termination of anterolateral spinothalamic tract fibers to the thalamus found in human postmortem studies (Bowsher, 1957) and the even more sparse nociceptive projections to the primary somatosensory (S1) cortex (Apkarian & Hodge, 1989).

Uncertainty about the role of the cortex in pain experience also dates back to early systematic cerebral stimulation studies in 16 patients (Head & Holmes, 1911) which reported the difficulties in eliciting pain when stimulating S1. This finding had further support from careful studies of patients with cortical and subcortical lesions by the same authors. By contrast, more recently, other authors have documented reduced pain sensation following cortical lesions (Marshall, 1951; Ploner *et al.*, 1999), but these reports are relatively sparse, and analgesia is often not a major feature (for a review see Kenshalo & Willis, 1991).

Many years ago, single-unit recordings in the monkey established that nociceptive pathways in the somatosensory system project to areas 3b and 1 of the primary somatosensory cortex (Kenshalo & Willis, 1991), as well as to the secondary somatosensory cortex (S2) and the neighboring posterior parietal cortex (Dong *et al.*, 1989). However, nociceptive units are relatively sparse, particularly in S1, which may explain some of the variability of functional imaging studies in this area. This finding may also explain why it has taken so long for the role of the cerebral cortex in pain experience to be accepted.

It has been widely accepted that pain is a multidimensional experience that has sensory-discriminative, affective, motivational, and evaluative components (Melzack & Casey, 1968). It has been suggested that these different components are likely to be processed within a 'neuromatrix,' rather than in one center (Melzack, 1990). Functional imaging experiments have identified such a matrix. A number of cortical structures such as S1 and S2, the anterior insula, and cingulate and dorsolateral prefrontal cortices (DLPFC) are reproducibly involved in nociceptive processing (Derbyshire, 2000; Peyron *et al.*, 2000), as are subcortical structures including the amygdala (Derbyshire *et al.*, 1997) and the thalamus and hypothalamus (Hsieh *et al.*, 1996; Kulkarni *et al.*, 2005; Derbyshire, 1999). The anatomical connections, with their nociceptive inputs to these areas, have been extensively reviewed elsewhere, as has the collective evidence for their involvement in human pain perception (Jones *et al.*, 2003; Jones, 1999; Vogt *et al.*, 1993; Apkarian, 1995; Kakigi *et al.*, 2005; Rainville, 2002; Petrovic & Ingvar, 2002; Peyron *et al.*, 2000; Jones & Derbyshire, 1996; Treede *et al.*, 1999; Chapter 14). However, the concept of a matrix with parallel processing within its components is perhaps fundamental to understanding some of the human observations that have been discussed so far. If pain results from integrating processing within such a matrix, then it should not be surprising that ablation of one component of that matrix may not have immediately obvious effects, if other components of the matrix are able to compensate in some way. A clue to this possibility comes from the predominantly bilateral nociceptive inputs to most cortical components of the matrix on both anatomical and functional grounds

(Schlereth *et al*., 2003; Youell *et al*., 2004). This parallel processing probably provides for considerable redundancy within this system, which is so essential for species survival. For instance, so far there is no evidence that magnetic stimulation of S1 significantly reduces pain intensity or the ability to localize pain (Kakigi *et al*., 2005).

A division of function between the lateral and medial components of the human pain system was originally proposed several decades ago by Bowsher (1957) and was iterated more formally by Albe-Fessard *et al*. (1985) based on quite small numbers of human postmortem and neurosurgical observations. The lateral pain system comprises the lateral thalamic nuclei and the somatosensory cortices. It is fast and somatotopic and may subserve the sensory-discriminative aspects of pain, which include localization, intensity, and duration. The insular cortex also has some somatotopic nociceptive inputs and may be involved in integrating them with inputs from other sensory modalities (Ostrowsky *et al*., 2002). The insular cortex may subserve both medial and lateral pain systems in that, in addition to its somatotopic nociceptive inputs from the ventromedial posterior (VmPO) nucleus of the thalamus (Craig, 2003), it also has input from medial thalamic nuclei and reciprocal connections with the amygdala. This may also explain why activation responses to noxious stimuli of the insula are bilateral in many functional imaging experiments (Youell *et al*., 2004). There is also evidence that the insula is involved in affective responses to pain (Kulkarni *et al*., 2005). The medial pain system is slow (polysynaptic) and non-somatotopic, and is thought to process the affective components of pain (Treede *et al*., 1999). It includes the midline and intralaminar thalamic nuclei, anterior cingulate and midcingulate cortices, and DLPFC and possibly structures concerned with the processing of fear, such as the amygdala.

Further evidence for this functional division in the human brain was based on clinical observations of the effects of selective midcingulate lesions in alleviating the affective components of pain (Foltz & White, 1962) and effects of lesions in the region of S1 on the sensory-discriminative components of pain (Ploner *et al*., 1999, 2000). Deafferentation of the midcingulate cortex (MCC) in patients with chronic intractable pain produces a state where patients still experience pain but it no longer bothers them (Foltz & White, 1962; Chapter 18). These effects are quite similar to the clinical observations of the effects of synthetic opiates, which are rarely pain-ablative but substantially reduce the unpleasantness of acute and chronic pain.

Functional imaging techniques have enabled researchers to investigate this division of function further. Several studies have attempted to address this issue by attentional manipulations, hypnosis, and use of the variable stimulus-response functions (Rainville *et al*., 1997; Bushnell *et al*., 1999; Peyron *et al*., 1999; Tolle *et al*., 1999; Bantick *et al*., 2002). These studies have used intensity of pain to access the sensory-discriminative components of pain and unpleasantness to access the affective components of pain. They have mainly identified the MCC as subserving the affective processing of painful stimuli. However, it has been demonstrated that intensity is probably encoded throughout the pain matrix (Derbyshire *et al*., 1997; Coghill *et al*., 1999), although in some studies discrete intensity-coding areas have been identified within, for instance, the MCC (Büchel *et al*., 2002; Hofbauer *et al*., 2001).

Substantial psychophysical data suggest a positive correlation between unpleasantness and intensity of pain (Rainville *et al*., 1999; Chapter 17). It is difficult to dissociate unpleasantness and intensity without resorting to techniques such as hypnosis. Intensity may not therefore be the best component to disclose a division of function between the sensory-discriminative and affective components of pain. Hypnosis itself introduces issues related to monitoring of conflict between the instruction under hypnosis and what the subject may be really feeling, which is an activity also localized within the MCC. An alternative approach is to use the localization of a pain stimulus as a measure of discriminatory function instead of pain intensity.

We used this approach using a CO_2 laser to stimulate four quadrants on the back of the arm at painful and non-painful levels with a simple difference in instruction to attend either to the unpleasantness of the stimulus or to its localization. Factorial analysis to investigate the interaction between pain and different attentional contexts was performed on 17 healthy right-handed men and statistical maps were created using SPM99b. Subjects were asked to selectively attend to unpleasantness and location of experimental radiant heat pain stimuli delivered to the left forearm, using a CO_2 laser, during separate scans. Attention to unpleasantness was associated with an increased cerebral blood flow in bilateral orbitofrontal (OFC) and pACC, contralateral (right) amygdala, ipsilateral (left) hypothalamus, posterior insula, and frontal pole. Attention to localization was associated with an increased cerebral blood flow in contralateral (right) S1 and inferior parietal cortex (IPC). Using this technique, we very clearly identified the pACC extending into the aMCC described by Vogt *et al*. (2003), OFC, insula, and amygdala, in addition to the hypothalamus, that respond to the affective components of pain more than its localization; attending to the localization of the painful stimulus produced greater activations of S1 and IPC (Kulkarni *et al*., 2005; Figs 19.1 and 19.2). Collectively, these data suggest that the main division of function between the medial and

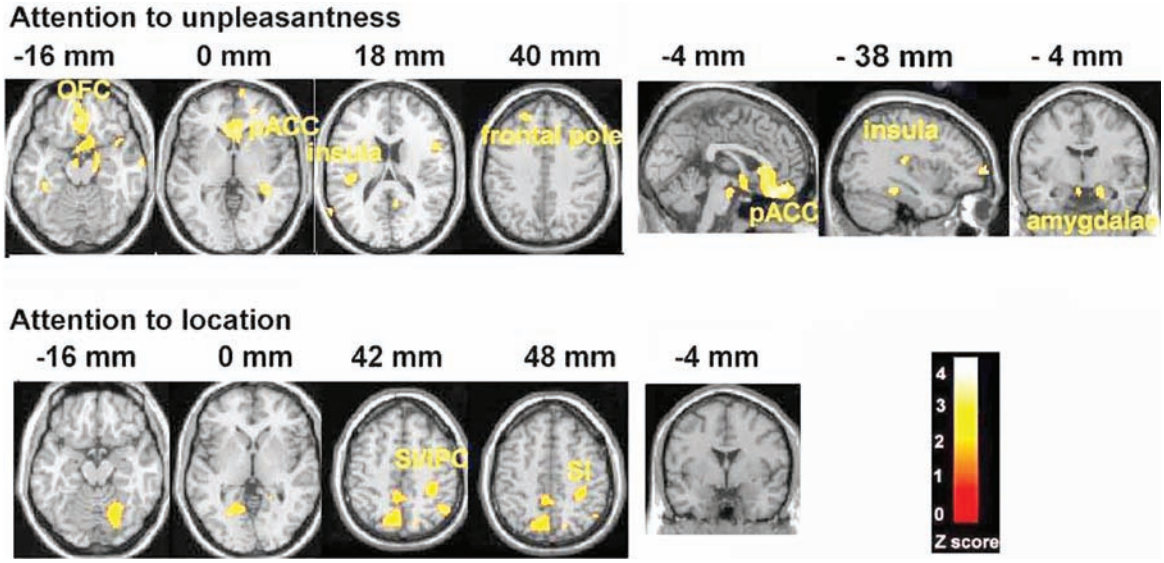

Fig. 19.1 PET images of correlates of altered blood flow when attending to unpleasantness or localization of an experimental heat stimulus. Attention to unpleasantness was associated with an increased blood flow in bilateral orbitofrontal cortex (OFC) and pACC, contralateral (right) amygdala, ipsilateral (left) hypothalamus, posterior insula, and frontal pole. Attention to localization was associated with an increased blood flow in contralateral (right) SI and inferior parietal cortex (IPC). Talairach coordinates for the axial sections are in mm on z-axis and the sagittal sections are at x = -4 mm. The correlates are statistical maps thresholded at corrected $p < 0.05$ following small volume correction.

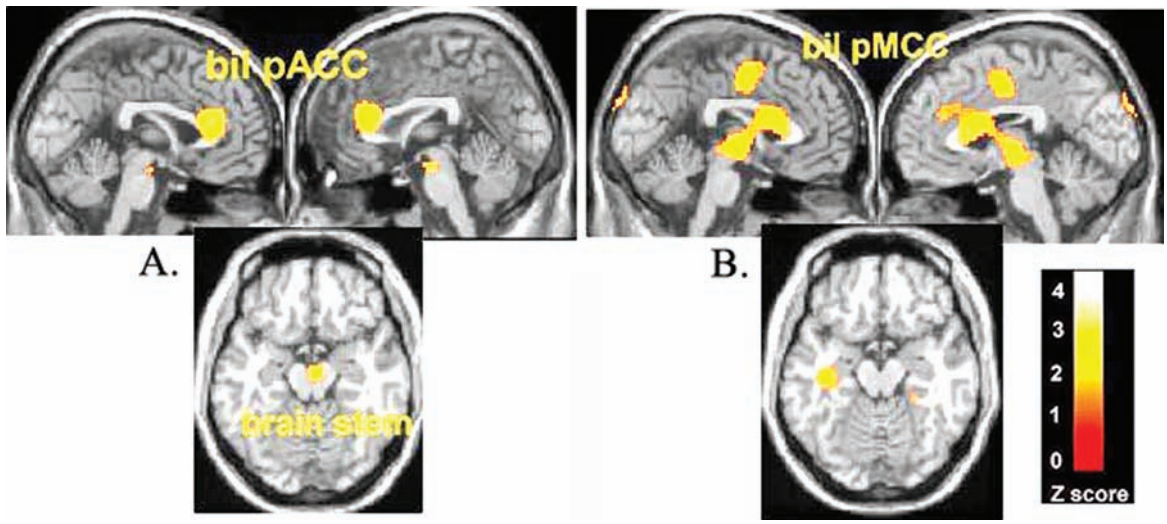

Fig. 19.2 Correlation analysis between perceived unpleasantness ratings and cerebral blood flow during painful and non-painful stimuli. A: Positive correlation between blood flow during painful stimulation and subjective ratings of unpleasantness. The correlation was maximal in pACC and right PAG (contralateral to the side of stimulation). B: Positive correlation between blood flow during non-painful stimulation and subjective ratings of unpleasantness was maximal in bilateral MCC. Each PET scan had either painful or non-painful stimuli and subjects rated each stimulus during the scan. Talairach coordinates of slices are z = -16 mm for axial sections and x = ± 4 mm for sagittal sections. The correlates are represented as in Figure 19.1.

lateral pain systems is likely to be that of affective and sensory-discriminatory processing, respectively, with intensity probably being processed throughout the matrix.

Role of pACC, Orbitofrontal and Insular Cortices, Amygdala, and Hypothalamus in Pain Affect

To explain the symptoms of CNP, we need to explain the persistence of severely distressing pain, autonomic dysfunction and mood disturbance that is not amenable to normal distraction. This may be done with a matrix of structures involved in focused attention.

Pregenual anterior cingulate cortex

Indirect evidence for the involvement of the ACC in processing the affective components of pain comes from both clinical observations (Foltz & White, 1962) and PET studies (Derbyshire *et al.*, 1994; Tolle *et al.*, 1999). The pACC in particular appears to be concerned with affective responses (George *et al.*, 1996) including vocalization, autonomic control, and fear (Bancaud & Talairach, 1992; Bush *et al.*, 2000). The pACC is activated in studies where pain is strongly aversive, such as those using tonic cold pain (Kwan *et al.*, 2000) or capsaicin-treated skin (Andersson *et al.*, 1997; Lorenz *et al.*, 2002). This may explain why the pACC is less commonly activated in studies using experimental pain, except when the pain stimulus is very unpleasant (allodynia, clinical pain) or attention is directed to the unpleasantness of pain (Kulkarni *et al.*, 2005). The activation of the anterior MCC in this study is consistent with this area being more concerned with fear as discussed in Chapter 14 (Vogt *et al.*, 2003) and the greater activation of the amygdala (Vogt *et al.*, 2003).

The observation that the cingulate cortex is the most commonly activated structure in functional imaging studies of pain (Derbyshire, 1999) suggests that it has a pivotal role in nociceptive processing. There is substantial variability of the location of anterior and mid-cingulate responses to nociceptive stimuli (Vogt *et al.*, 1996; Derbyshire, 2000). These locations extend from the pACC (Lorenz *et al.*, 2002; Vogt *et al.*, 1996), also observed in the our study, to the more posterior areas of the MCC (Bentley *et al.*, 2003; Vogt *et al.*, 1996). This finding raises the issue of both pain-specific and more generalized divisions of cognitive function within cingulate cortex.

The MCC is also an important component of the anterior attentional system (Bush *et al.*, 2000; Posner & Petersen, 1990) although nociceptive responses appear to locate to discrete areas that are distinct from those concerned with these more general attentional functions (Davis *et al.*, 1997; Derbyshire *et al.*, 1998). Understanding the dynamic interactions between these areas of ACC will provide a better understanding of their relative contribution to the human pain experience. In this context, it is interesting that source localization of anticipation of pain-related potentials identifies MCC as one of the main locations for the time-locked processing of the anticipation of pain prior to an experimental pain stimulus (Brown *et al.*, 2005). This fits well with the division of MCC function as proposed in Chapter 14.

Our results (Kulkarni *et al.*, 2005) also demonstrated that cingulate responses are exquisitely sensitive to attentional instruction, as has been previously suggested (Peyron *et al.*, 1999) and illustrate the importance of such cortically driven 'top–down' effects (Frith, 2001). This is consistent with observations of other 'top–down' effects on the pain matrix during anticipation (Porro *et al.*, 2002) and distraction (Bantick *et al.*, 2002). It also fits in with the large-scale neurocognitive network model (Mesulam, 1990; Morecraft *et al.*, 1993), which proposed that cingulate cortex is the main contributor to a motivational map that interacts with a perceptual map provided by posterior parietal cortex. These results also support the potential use of psychological approaches in pain therapy.

Orbitofrontal cortex, amygdala, insula, MI, and hypothalamus

During 'attention to unpleasantness', the activation of the OFC, amygdala, and hypothalamus in our study (Kulkarni *et al.*, 2005) is interesting in the context of the role of these structures in emotional processing, reward, aversive conditioning, autonomic regulation, and fear (Rolls, 1999). Medial thalamic nuclei, basolateral amygdala and the ACC participate in a circuit involved in avoidance learning (Maren *et al.*, 1991; Rolls, 1999). The OFC is known to have anatomical connections with areas of the limbic system and hence may have a role in modulating affective processes and autonomic regulation. These areas have reciprocal anatomical connections with each other (Aggleton *et al.*, 1980; Carmichael & Price, 1995). Activation of the OFC has been consistently observed in functional imaging studies of clinical (Hsieh *et al.*, 1996, 1995; Rosen *et al.*, 1994) and experimental pain (Bantick *et al.*, 2002; Lorenz *et al.*, 2002; Petrovic *et al.*, 2002; Tolle *et al.*, 1999). A recent functional magnetic resonance imaging (fMRI) study compared activations produced by pleasant touch, painful touch, and neutral touch (Rolls *et al.*, 2003). The regions of the OFC were activated more by pleasant touch and pin prick compared with neutral touch. Interestingly, the same area is known to be involved in depression (Drevets, 2000a,b), which is one of the main risk factors for developing certain types of chronic pain such as Fibromyalgia or Chronic

TABLE 19.1 Perigenual Cingulate Responses in Functional Imaging Studies

Study	Methods	G Gender	Stimulation	Responses in pACC
Tonic heat pain				
Svensson *et al.* (71)	PET	4F + 6M	45°C to 49°C	C↑ (with tonic heat)
Craig *et al.* (72)	PET	3F + 8M	47°C (thermal grill)	C ↑ with thermal grill (illusion of pain)
Ploghaus *et al.* (73)	fMRI	8M	Thermal resistor	B↑(pa in modulated by anxiety)
Casey *et al.* (74)	PET	4F + 10M	40°C to 50°C	C↑ (early phase)
Ploghaus *et al.* (75)	fMRI	5F +7 M	Thermode	C↑ (with anticipation)
Petrovic *et al.* (76)	PET		48°C	B↑ (R > L)
Bantick *et al.* (48)	FMRI	2F + 6M	Thermal resistor 50–53°C	B↑ (+ interaction when pain & stroop occurred together)
Simpson *et al.* (77)	PET	4F + 12M	Electric stimulator (1–10 volts)	↓ with anxiety
Rèmy *et al.* (78)	fMRI	6F + 6M	Thermode	I↓ (Negative modulation of pain on cognition)
Wager *et al.* (79)	fMRI2 studies	Unknown	Electric shock + Thermode	I↓ with placebo during electric shock
Valet *et al.* (80)	fMRI	1F +6M	Thermode	C↑ during distraction from pain
Mohr *et al.* (81)	fMRI	16 M	Thermode	I↑ with self adm. of pain I↓ with ext adm of pain
Phasic heat pain				
Bornhovd *et al.* (82)	fMRI	3F + 6M	Tm:YAG laser 300–600 mJ	I↑
Derbyshire *et al.* (83)	PET	10F+11M	CO_2 laser	I↑ (in females > males)
Raij *et al.* (84)	fMRI	11F +3 M	Tm:YAG laser	B↑ during suggestion-induced pain
Kulkarni *et al.* (27)	PET	17 M	C CO_2 laser	B↑ during selective attention to pain affect
Tonic cold pain				
Petrovic *et al.* (85)	PET	7 M	C Cold pressor 0–0.5 °C	B↑
Kwan *et al.* (58)	fMRI	6F+ 7M	4 7.5°C	B ↑ (area 32)
Frankenstein *et al.* (86)	FMRI	6F + 6M	Cold compress 2–6°C/verbal attention as distractor	B↑ (pain modulated by distraction)
Miscellaneous				
Andersson *et al.* (59)	PET	6M	C Capsaicin (i.c)	C↑
Lorenz *et al.* (60)	PET	14M	Capsaicin (top)	B↑
L Garcia-Larrea *et al.* (87)	PET	5F + M	Motor cortex stimulation	C↑ (contralateral to MCS)
Hsieh *et al.* (88)	PET	2F + 5M	N Nitoglycerin-induced cluster headache	B↑ (R > L)
Jones *et al.* (89)	PET	6M	T trigeminal neuralgia	R↑ (↑ binding of ^{11}C diprenorphine)
Davis *et al.* (90)	PET	-	Deep brain stimulation of sensory thalamus	B ↑
Porro *et al.* (91)	fMRI	-	sc ascorbic acid	Negative correlation with pain intensity
Porro *et al.* (68)	fMRI	-	sc ascorbic acid	Negative correlation with anticipation and + correlation with pain
Firestone *et al.* (92)	PET	4F + 2M	i.v fentanyl versus placebo	B↑
Visceral pain				
Ladabaum *et al.* (93)	PET	9F + 6M	Gastric distension	B↑
Naliboff *et al.* (94)	PET	2F+10M	Rectal distension	R↑
Casey *et al.* (95)	PET	20M	i.v fentanyl versus (cold pressor and vibration)	B↑
Dunckley *et al.* (96)	fMRI	5F + 5M	Rectaldistension &Thermal resistor to skin	B ↓

PET, positron-emission tomography; **fMRI**, functional magnetic resonance imaging; **C,** contralateral;I, ipsilateral; **B**, bilateral; **R**, right; **L**, left**.**
MCS, motor cortex stimulation.

Widespread Pain (McBeth *et al.*, 2001). These observations suggest that neural circuits involving the OFC may be implicated in the processing of emotional aspects of pain. Activity in these circuits may be greater in certain clinical pain states or when attentional resources are diverted to the affective aspect of pain.

Our demonstration of greater amygdala responses during attention to unpleasantness is supported by recent functional imaging studies in humans demonstrating amygdala activation during nociceptive processing (Bornhovd *et al.*, 2002). Electrophysiological, neuropharmacological, and lesion studies in animals also support the role of the amygdala in nociceptive processing (Bernard *et al.*, 1992, 1996; Büchel *et al.*, 1999; Schneider *et al.*, 2001). Nociceptive neurons have been demonstrated in the lateral and central nuclei of the amygdala (Romanski *et al.*, 1993). In a rat study by Shi *et al.* (1999), two parallel somatic pain pathways, (1) insula-amygdala and (2) posterior intralaminar nulei of the thalamus-amygdala, have been shown to be involved in fear conditioning. Also the affective areas of the cingulate cortex (area 25, 24, and 32) in primates are a projection site of the amygdala (Barbas & De Olmos, 1990; Vogt & Pandya, 1987; Chapter 6). This supports our results of co-activation of the perigenual cingulate and amygdala in the 'attention to unpleasantness' condition. Its precise role in nociceptive processing is unclear but it may influence the experience of fear and anxiety associated with the pain experience.

It has been suggested that the hypothalamus may act as a common autonomic and neuroendocrine output system for OFC and amygdala responses to emotions, including fear (Bohus *et al.*, 1996). Our demonstration of increased hypothalamic activity during attention to unpleasantness is consistent with this hypothesis. Hsieh *et al.* (1996) demonstrated hypothalamic responses during severe pain and suggested that the hypothalamus may be involved in generating the autonomic output responses to the affective components of pain. This region has also been implicated in acupuncture-mediated analgesia (Hsieh *et al.*, 2001). Bester *et al.* (1999) have demonstrated projections from the parabrachial nucleus to the ventromedial nucleus of the hypothalamus, which projects densely to the dorsal periaqueductal gray (PAG). This parabrachial–hypothalamus–PAG loop is thought to have a major role in aversive behaviors. Hence it is proposed that this tract may play an important role in motivational behavior such as defense and aggression in response to noxious stimulation (Bester *et al.*, 1999). This idea may explain why few functional imaging studies in humans show hypothalamic activations, as moderate experimental pain may not evoke an aversive or aggressive response.

We have demonstrated posterior insular activation in the 'attention to unpleasantness' condition. Anterior insula is reported to be most consistently activated in the previous pain studies. However, activations reported in insula in some of the previous functional imaging studies extend over a broad region including both anterior and posterior insula (see review by Peyron *et al.*, 2000). Posterior insular activations have been reported in many pain studies (Valet *et al.*, 2004; Casey *et al.*, 1996; also see review by Derbyshire, 1999).

We found primary motor cortex (M1) activation in the 'attention to unpleasantness' condition but not during 'attention to localization', despite the fact that subjects did not withdraw from the stimuli at any time and button-press responses were matched across conditions. In addition, rCBF in M1 positively correlated with affective ratings during the 'attention to unpleasantness' condition, suggesting a relationship between M1 activity and affective processing. M1 is classically thought to be involved in the execution of motor responses. However, although not frequently reported, some functional imaging studies of pain have shown M1 activation even in the absence of actual movement (Lu *et al.*, 2004; Peyron *et al.*, 2004; Lotze *et al.*, 2001; Casey *et al.*, 1996). Interestingly, all of these studies involved particularly unpleasant pain sensations such as visceral distension and stimulation, cold pain, neuropathic pain, and capsaicin-induced pain. This is consistent with the M1 activation seen only in the 'attention to unpleasantness' condition in our study. This indicates a possible role of M1 in an affective-motivational system that may be involved in avoidance and/or escape responses. If M1 were involved is such an affective circuit this might explain why motor activation in patients with CNP may provoke unpleasant pain if such a circuit where functioning abnormally. It is not implausible that stimulation of MI and related areas of cortex may modulate the pain matrix therapeutically as discussed in Chapter 20.

Problems with Group Comparisons and their Interpretation

There is a problem with the comparison of cerebral responses in patients with different types of pain and pain-free volunteers that is intrinsic to the subjective nature of pain. Simply stated, it is not possible to directly compare one person's pain with that of another because there are no objective measures to validate their similarities or differences. Therefore, the best that can be done is to either compare cerebral responses with an evoked noxious stimulus that is either rated at the same level of intensity or unpleasantness or to compare responses with similar energies of peripheral stimulation. Neither of these is any more objective than

the other. Comparisons of similar intensities of stimulation may reveal differences that are merely due to differences in processing anywhere from the peripheral nociceptor to the brain stem or may even be due to differences in physical properties of the skin. Whereas comparisons of similar intensities of experience may be due to the differences in the way these are rated between the two groups. For example, if all areas of the pain matrix are more active in one group than another when experiencing pain that was rated the same intensity, this may be merely due to differences in magnitude estimations of pain that may not necessarily tell us very much about differences in nociceptive processing between the two groups. However, differences in the pattern of responses such that one cortical area may show increased responses with another demonstrating decreased responses compared with controls, are much less likely to be due to differences in magnitude estimation.

These inherent problems have resulted in relatively few studies comparing responses with noxious stimulation between patients and pain-free controls. They have also lead some reviewers to dismiss differences that have been found as 'uninterpretable' (Apkarian *et al.*, 2005). The assumption here is that there is a perfect solution and that completely objective methods can be found to compare one person's pain with another's. Unfortunately, philosophically this is impossible. As with all subjective sensations, there is no way to perfectly match one person's pain with another's. Any claims for this can only be as flawed as the criticisms of studies on the basis that the pain experiences between two groups were not perfectly matched (Apkarian *et al.*, 2005). Pain scores can be perfectly matched, but pain experience cannot, by definition. However, this does not mean that no clinical studies should be performed comparing groups of individuals. There can only be any point to functional brain imaging of pain perception if it allows us to generate hypotheses about abnormal mechanisms of pain perception in patients with different types of clinical pain. Any overarching hypothesis will need to stand the test of recurrent studies and ultimately by the effects of therapeutic interventions.

There are also ways of decreasing the uncertainties of group comparisons where these do not depend, to the same extent, on compatibility of pain experience. Recent studies in our laboratory have achieved this by asking the subject to switch their attention between localization and unpleasantness rating at the same level of pain intensity. The comparison between groups is therefore a reflection of their ability to switch attention between two different components of pain providing a greater internal consistency that is more independent of pain magnitude estimations. This approach has been used not only to define the main division of function of the pain matrix (see previous sections), but also to compare responses in a group of patients with fibromyalgia with normal pain-free controls (Brown *et al.*, 1905). Clinical studies in our own laboratory and those of Peyron and Garcia-Laria (Chapter 20) have generated data in patients to suggest that the pACC performs a pivotal role in the processing of the affective aspects of pain experience both in normal volunteers and in patients. Early evidence suggests that abnormalities of processing in this area of cortex are associated with the perseveration of pain in patients with neuropathic and psychogenic pain. Work by Peyron and Garcia-Larria also implicates the perigenual-cingulate cortex in determining therapeutic response to motor cortical stimulation as discussed in Chapter 20. These findings in patients and normal volunteers provide converging evidence for the pivotal role of pACC in normal and abnormal pain perception that would not otherwise have been possible from animal or other types of human studies. Such clinical studies are very difficult to perform and can of coarse be criticized on the grounds of imperfect matching of pain experience. However, they have also led to a new and unexpected hypothesis about the cortical basis of pain perception that will be explored in the next section.

Patterns of Neural Activity in Clinical Pain Syndromes and Experimental Allodynia

Psychogenically maintained and nociceptive pain

These types of pain syndrome have been extensively reviewed in Chapters 23. The purpose of this section is to provide a context and focus for observations of brain responses in CNP. Some of the more recent studies on modulation of nociceptive processing may aid the interpretation of earlier clinical studies that reported substantial differences in responses to thermal pain stimuli in patients with different types of clinical pain. In general, the same areas of the pain matrix are activated during thermal- and pressure-induced pain (Gracely *et al.*, 2002) in patients with chronic pain syndromes as in normal volunteers. The differences are in the subtle patterns of response within the matrix rather than in the presence or absence of response in any one component of the matrix.

Responses to standardized acute thermal pain stimuli were reduced in patients with acute (post-dental extraction) inflammatory pain and in those with ongoing chronic arthritic pain compared with controls (Jones & Derbyshire, 1997; Derbyshire *et al.*, 1999). Patients with chronic psychogenically maintained pain (atypical

facial pain) demonstrated enhanced responses to acute thermal stimulation compared to controls in the ACC, with reduced responses in the right DLPFC (Derbyshire *et al.*, 1994). The enhanced responses in the ACC were thought to represent abnormal attention to the affective processing of nociceptive inputs that might contribute to the perseveration of chronic pain in these individuals, perhaps resulting from a failure of supervision of attention by the DLPF. The observation that attention can profoundly affect the pattern of nociceptive responses within the pain matrix gives some credence to this concept (Jones *et al.*, 2002, 2003; Kulkarni *et al.*, 2005; Bentley *et al.*, 2004). Recent studies have shown increased correlation of catastrophizing with ACC activity in patients with fibromyalgia or chronic widespread pain (Gracely *et al.*, 2004), which is also consistent with earlier reports (Gibson *et al.*, 1994). The reduced activity in the DLPFC in the atypical facial pain group is interesting in the context of a recent PET study of experimental allodynia that indicated that activity in this area of the right DLPFC may be negatively correlated with connectivity between the midbrain and thalamus. The suggestion emerging from this study was that DLPFC may exert an active higher 'control on pain perception by modulating cortico-subcortical and cortico-cortical pathways' (Lorenz *et al.*, 2003). However, studies in patients with low back pain and depression did not demonstrate significant differences in nociceptive processing between this group and pain-free controls (Derbyshire *et al.*, 2002).

Neuropathic pain and allodynia

Pharmacological mechanisms have been demonstrated in the dorsal horn in association with neuropathic and inflammatory pain models (Woolf, 1994) that may contribute to some forms of allodynia; pain induced by sensory modalities such as touch that would not normally induce pain. However, in terms of what signals get to the brain, these spinal mechanisms convert what would normally be signaled in non-nociceptive ascending pathways to signals within the ascending nociceptive channels (ascending spinothalamic tracts). So far, there is little evidence in humans that such pains are processed within different brain structures when acutely induced experimentally (capsaicin-induced allodynia; Iadarola *et al.*, 1998) or when studied in patients with chronic neuropathic pain (Hsieh *et al.*, 1995; Peyron *et al.*, 1998, 2004). Studies by Hsieh *et al.* (1995) observed the effects of the presence and absence of peripheral neuropathic pain before and after peripheral nerve block. MCC was activated during pain in addition to other components of the pain matrix. In PET studies of CNP secondary to brain stem lesions (Wallenberg's Syndrome) the cerebral effects of provoked allodynia in response to cold on the affected side when compared with the same intensity experimental stimulation of the unaffected side (Peyron *et al.*, 1998). Significant decreases in the pACC, but not the MCC, were observed when allodynic pain was compared with experimental pain in the same individuals. This is a particularly interesting study in that the two pains were matched for intensity.

These observations are interesting in relation to the pACC activation observed during experimental allodynia in normal volunteers discussed in previous sections of this chapter (Lorenz *et al.*, 2002). However, allodynic pain is much more unpleasant than experimental pain and it seems likely that both in this study and the study by Lorenz *et al.* (2002) that the pACC activation is most likely due to the high emotional salience of the pain. Subsequent fMRI studies of a range of peripheral and central neuropathic pains were studied by the same research group comparing provoked allodynia with non-painful stimulation of the non-affected side (Peyron *et al.*, 2004). Interestingly in this study, MCC activations were seen when the allodynia was compared with non-painful stimulation, which did not survive the most rigorous statistical analysis. This suggests that this was probably not common to all patients studied, and as discussed by the authors, may be more related to motivational and attentional responses and not specific to pain. There is no particular explanation for the absence of pACC activation in this group of patients. However, it may be due to the heterogeneity of the group or the less aversive nature of the allodynia in this group compared with their ongoing neuropathic pain. The other possibility is that there were susceptibility issues reducing the signal from perigenual and orbitofrontal structures which can be a problem with fMRI. Currently, there are no studies comparing provoked CNP in patients with experimental allodynia in normal controls or patients with other types of pain. As Peyron *et al.* (2004) have commented, it seems unlikely that there are any particular components of the pain matrix which are uniquely activated in CNP. However, it is interesting that in a recent study, where experimental pain and arthritic pain were compared at the same intensities in patients with osteoarthritis, one of the main areas that was activated more in arthritic pain was an area including the pACC/aMCC (Kulkarni *et al.*, 2005), consistent with the arthritic pain having greater emotional salience than the experimental pain. It therefore seems very unlikely that the perigenual cingulate cortical activation observed in the study by Lorenz *et al.* (2002) was in any way unique to neuropathic pain as suggested.

There is a trend toward reduced activity within the thalamus during ongoing neuropathic pain (Di Piero *et al.*, 1991; Hsieh *et al.*, 1995; Iadarola *et al.*, 1995). Formal comparisons with other types of pain have not

been made, but it is possible that this trend may represent reduced activity of inhibitory interneurons within the thalamus. However, there have also been some studies which have shown increased thalamic responses during provoked pain, so it is too early to draw any conclusion from these observations (Cesaro *et al*., 1991; Cesaro, 1987).

In summary, in the few studies of experimental and clinical peripheral neuropathic pain and CNP there is no evidence of any components of the pain matrix that are uniquely activated. There is an impression that pACC may feature more frequently in response to allodynia than with other types of provoked pain. However, the only formal comparison was a within-patient comparison (Peyron *et al*., 1998). In the context of recent imaging studies it is likely that differences in activation of pACC observed in these studies represents altered affective processing.

Cingulate Cortex, CNP, and Endogenous Opioids: Pharmacological Explanation for Allodynia

The role of the cingulate cortex in processing a variety of cognitive, motor, and nociceptive information has been well described (Vogt *et al*., 1993; Devinsky *et al*., 1995; Paus *et al*., 1998; Bush *et al*., 2000). The nociceptive inputs to the cingulate cortex have been described in Chapter 14. Single-unit recordings in rabbits (Sikes & Vogt, 1992) and humans (Hutchison *et al*., 1999) have identified nociceptive responses in area 24 of the ACC and MCC, respectively, and evidence for the involvement of MCC and pACC in processing the affective components of pain has been discussed in previous sections of this chapter.

The activity within the pACC during attention to unpleasantness is consistent with its relatively high concentration of opioid receptors (Jones *et al*., 1991b; Vogt *et al*., 1995a) as compared with the more executive areas of the cingulate cortex, and also with the perigenual changes in occupation by endogenous opioid peptides during chronic inflammatory and neuropathic (trigeminal neuralgia) pain (Jones *et al*., 1994, 1999; Spetea *et al*., 2002).

There are relatively high concentrations of opioid receptors in associated cortices and components of the limbic system, including the amygdala, and low concentrations in the S1, motor, and visual cortices. Therefore, these regions may have some function related to the modulation of selective attention in addition to their more direct role in modulation of nociception (Lewis *et al*., 1981). This is consistent with the effects of fentanyl on both cortical processing of vibration and nociceptive stimulation in pACC (Casey *et al*., 2000). Changes in occupation of opioid receptors consistent with increased occupation by endogenous opioid peptides during pain have been demonstrated within the cortical components of the medial pain system in acute experimental pain (Zubieta *et al*., 2001), chronic neuropathic pain (Jones *et al*., 1999), and chronic arthritic pain (Jones *et al*., 1994).

These findings may be relevant to recent observations of shared responses within aMCC/pACC to placebo and opioid analgesia (Petrovic *et al*., 2002). Recent observations suggest that placebo analgesia is at least partially mediated by endogenous opioid peptides (Benedetti *et al*., 1999). Clinical observations suggest that synthetic opioids do not ablate pain but substantially reduce its unpleasantness. This is strikingly similar to the effects of deafferentation of the pACC/MCC (Foltz & White, 1962). Opioid-mediated analgesia results in significant changes in activity in the pACC in addition to other components of the medial pain system (Jones *et al*., 1991a; Casey *et al*., 2000). The cerebral mechanisms of opioid actions are still uncertain, but anatomical studies suggest μ-opioid modulation of thalamocortical loops projecting through the ACC (Vogt *et al*., 1995b). The pACC therefore provides candidate mechanisms for some of the analgesic effects of synthetic and endogenous opioids on the affective components of pain experience. From the studies outlined in Chapter 20 by Garcia-Larrea and colleagues, there is also evidence that the pACC may also determine the therapeutic outcome of motor cortical stimulation, although the precise pathways involved remain uncertain.

We have measured specific decreases in opioid receptor binding within most of the main components of the medial pain system including the pACC/aMCC and thalamus in a group of patients with CNP (Jones *et al*., 2004; Fig. 19.3). These measurements were made using [^{11}C]diprenorphine, which has equal affinity for the mu, delta and kappa receptor subtypes, and PET to derive parametric images of specific binding potential. The CNP in these patients was mainly due to stroke with either no lesions on MRI or small lesions outside the pain matrix. Similar findings have been reported by other groups (Willoch *et al*., 1999). We interpreted these findings as being most likely due to selective damage to opioid receptor-bearing neurons within the medial pain system. The lack of any change in ongoing pain in response to high-dose naloxone infusions in our study suggests the reduced opioid receptor binding was not due to increased occupation by endogenous opioid peptides. This may explain the reduced sensitivity to synthetic opiates in CNP.

It is interesting that in patients we studied with peripheral neuropathic pain (trigeminal neuralgia) before and after surgical intervention we showed substantial changes in [^{11}C]diprenorphine binding. These

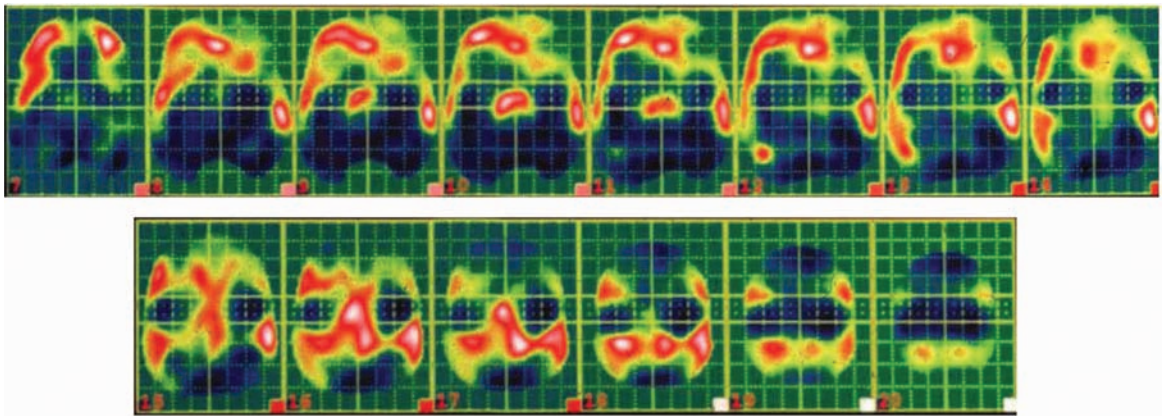

Fig. 19.3 Statistical parametric map of significant decreases in opioid receptor binding between the patient with CNP and a normal control group. Parametric images of volume of distribution (VD) of opioid receptor ([^{11}C]diprenorphine) binding were quantified using serial PET images and a continuous metabolite-corrected plasma input function. Statistical comparisons between the patients and normal controls were made using statistical parametric mapping (Jones et al., 2004). Significant increases in binding were in DLPFC areas 44 and 8, ACC area 32, insular and pACC and aMCC, inferior parietal area 40, putamen, and thalamus. These results are consistent with reduced availability of opioid binding sites due to occupation by endogenous opioid peptides during trigeminal pain.

were consistent with increased occupation of opioid receptors by endogenous opioid peptides during pain, again, mainly within the medial pain system (Jones *et al.*, 1999). The main changes within the cingulate cortex were in the pACC. These were interpreted as adaptive responses to the severely unpleasant nature of the pain.

pACC is Central to the Maintenance of Strongly Aversive Pain

It is proposed that the pACC/aMCC and associated structures are most likely to be concerned with processing the affective components of pain, whereas the pMCC is more likely to be concerned with executive processing (response selection and monitoring) and control of attention. We suggest that pACC/aMCC is central to circuitry within the medial pain system that includes the amygdala (concerned with fear), OFC (concerned with reward), and hypothalamus (concerned with stress and maintenance of homeostasis) that regulate affective responses to severely aversive pain.

This circuitry is unreliably activated during many experimental studies unless attention is directed to the unpleasantness of the stimulus or the stimulus is strongly aversive. Evidence of release of endogenous opioid peptides within the pACC/aMCC during chronic peripheral neuropathic and inflammatory pain suggest that natural opioids have the potential for modifying affective responses to pain (Jones *et al.*, 1999, 1994).

Loss of critical opioid inhibitory circuits particularly within the pACC/aMCC and medial thalamic nuclei are more likely to result from the perseveration of reverberating circuits within the medial pain system (Jeanmonod *et al.*, 1996; Llinas *et al.*, 1999). These are likely to result in a loss of descending control of nociceptive processing within particularly the PAG as discussed in Chapter 15.

Likewise, we propose that functional deficits of the endogenous opioid system result in similar abnormalities in patients with CWP/CRP. The failure to change nociceptive processing within pACC/aMCC in response to attentional instruction in patients with CWP could be due to a failure of the endogenous opioid system within this area of the limbic system. In addition to the resulting attentional deficits, the failure of modulation of nociceptive processing in pACC/aMCC could result in the poorly localized allodynia that occurs in this condition. Obviously, this is highly speculative but may provide a unifying pharmacological explanation for chronic allodynic pain that metabolic studies have so far not achieved. The more precise definition of neuropharmacological deficits that contribute to allodynia, chronic CNP, and CWP may eventually allow us to develop more effective therapies for patients with these very distressing types of pain. On the basis of the physiological observations outlined in this chapter and the shared therapeutic responses to tricyclic antidepressants, we would predict there are likely to be some common pharmacological mechanisms for allodynia associated with CNP and CWP.

References

Aggleton, J. P., Burton, M. J., & Passingham, R. E. (1980) Cortical and subcortical afferents to the amygdala of the rhesus monkey (*Macaca mulatta*). *Brain Res*: *190*: 347–368.

Albe-Fessard, D., Berkley, K. J., Kruger, L., Ralston, H. J., & Willis, W. D. (1985) Diencephalic mechanisms of pain sensation. *Brain Res Rev 356*: 217–296.

Andersen, G., Vestergaard, K., Ingeman-Nielsen, M., & Jensen, T. S. (1995) Incidence of central post-stroke pain. *Pain 61*: 187–193.

Andersson, J. L., Lilja, A., Hartvig, P., Langstrom, B., Gordh, T., Handwerker, H., & Torebjork, E. (1997) Somatotopic organization along the central sulcus, for pain localization in humans, as revealed by positron emission tomography. *Exp Brain Res 117*: 192–199.

Apkarian, A. V. (1995) Functional imaging of pain: new insights regarding the role of the cerebral cortex in human pain perception. *Sem Neurosci' 7*: 279–293.

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

Apkarian, A. V., & Hodge, C. J. (1989) Primate spinothalamic pathways: III. Thalamic terminations of the dorsolateral and ventral spinothalamic pathways. *J Comp Neurol 288*: 493–511.

Arner, S., & Meyerson, B. A. (1988) Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain. *Pain 33*: 11–23.

Bancaud, J., & Talairach, J. (1992) Clinical semiology of frontal lobe seizures. *Adv Neurol 57*: 3–58.

Bantick, S. J., Wise, R. G., Ploghaus, A., Clare, S., Smith, S. M., & Tracey, I. (2002) Imaging how attention modulates pain in humans using functional MRI. *Brai 125*: 310–319.

Barbas, H., & De Olmos, J. (1990) Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the rhesus monkey. *J Comp Neurol 300*: 549–571.

Benedetti, F., Arduino, C., & Amanzio, M. (1999) Somatotopic activation of opioid systems by target-directed expectations of analgesia. *J Neurosci 19*: 3639–3648.

Bentley, D. E., Derbyshire, S. W., Youell, P. D., & Jones, A. K. (2003) Caudal cingulate cortex involvement in pain processing: an inter-individual laser evoked potential source localisation study using realistic head models. *Pain 102*: 265–271.

Bentley, D. E., Watson, A., Treede, R. D., Barrett, G., Youell, P. D., Kulkarni, B., & Jones, A. K. (2004) Differential effects on the laser evoked potential of selectively attending to pain localisation versus pain unpleasantness. *Clin Neurophysiol 115*: 1846–1856.

Bernard, J. F., Bester, H., & Besson, J. M. (1996) Involvement of the spino-parabrachio -amygdaloid and -hypothalamic pathways in the autonomic and affective emotional aspects of pain. *Prog Brain Res 107*: 243–255.

Bernard, J. F., Huang, G. F., & Besson, J. M. (1992) Nucleus centralis of the amygdala and the globus pallidus ventralis: electrophysiological evidence for an involvement in pain processes. *J Neurophysiol 68*: 551–569.

Bester, H., Bourgeais, L., Villanueva, L., Besson, J. M., & Bernard, J. F. (1999) Differential projections to the intralaminar and gustatory thalamus from the parabrachial area: a PHA-L study in the rat. *J Comp Neurol 405*: 421–449.

Bohus, B., Koolhaas, J. M., Luiten, P. G., Korte, S. M., Roozendaal, B., Wiersma, A. (1996) The neurobiology of the central nucleus of the amygdala in relation to neuroendocrine and autonomic outflow. *Prog Brain Res 107*: 447–460.

Boivie, J. (1999) Central pain. *Textbook of pain*. Churchill Livingstone, 879–914.

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

Bowsher, D. (1957) Termination of the central pain pathway in man:the concious appreciation of pain. *Brain 80*: 607–622.

Brown, C. A., Boyle, Y., Watson, A, Bentley, D. E., Boger, E. J, Townley, B., & Jones, A. K. P. (2005) The expectancy of pain in fibromyalgia, osteoarthritis and healthy volunteers. *IASP Proceedings 11th World Congress on Pain*, Sydney. 178.

Büchel, C., Bornhovd, K., Quante, M., Glauche, V., Bromm, B., & Weiller, C. (2002) Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study. *J Neurosci 22*: 970–976.

Büchel, C., Dolan, R. J., Armony, J. L., & Friston, K. J. (1999) Amygdala-hippocampal involvement in human aversive trace conditioning revealed through event-related functional magnetic resonance imaging. *J Neurosci 19*: 10869–10876.

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

Bushnell, M. C., Duncan, G. H., & Hofbauer R. K. (1999) Human functional brain imaging. *Pain Forum 8*: 133–135.

Carmichael, S. T., & Price, J. L. (1995) Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *J Comp Neurol 363*: 615–641.

Casey, K. L., Minoshima, S., Morrow, T. J., & Koeppe, R. A. (1996) Comparison of human

cerebral activation pattern during cutaneous warmth, heat pain, and deep cold pain. *J Neurophysiol 76*: 571–581.

Casey, K. L., Svensson, P., Morrow, T. J., Raz, J., Jone, C., & Minoshima, S. (2000) Selective opiate modulation of nociceptive processing in the human brain. *J Neurophysiol 84*: 525–533.

Cesaro, P. (1987) Thalamic pain. In J. Besson, G. Guilbaud, M. Peschanski (eds), *Thalamus and Pain*, (pp. 259–270). Elsevier Science.

Cesaro, P., Mann, M. W., Moretti, J. L., Defer, G., Roualdes, B., Nguyen, J. P., & Degos, J. D. (1991) Central pain and thalamic hyperactivity: a single photon emission computerized tomographic study. *Pain 47*: 329–336.

Coghill, R. C., Sang, C. N., Maisog, J. M., & Iadarola, M. J. (1999) Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J Neurophysiol 82*: 1934–1943.

Craig, A. D. (2003) A new view of pain as a homeostatic emotion. *Trends Neurosci 26*: 303–307.

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. *J Neurophysiol 77*: 3370 –3380.

Derbyshire, S. W., Jones, A. K., Creed, F., Starz, T., Meltzer, C. C., Townsend, D. W., Peterson, A. M., & Firestone, L. (2002) Cerebral responses to noxious thermal stimulation in chronic low back pain patients and normal controls. *Neuroimage 16*: 158–168.

Derbyshire, S. W. G. (1999) Meta-analysis of thirty-four independent samples studied using PET reveals a significantly attenuated centrral response to noxious stimulation in clinical pain patients. *Curr Rev Pain 3*: 265–280.

Derbyshire, S. W. G. (2000) Exploring the pain "Neuromatrix". *Curr Rev Pain 4*: 467–477.

Derbyshire, S. W. G., Jones, A. K. P., Collins, M., Feinmann, C., & Harris, M. (1999) Cerebral responses to pain in patients suffering acute post-dental extraction pain measured by positron emission tomography (PET). *Eur J Pain 3*: 103–113.

Derbyshire, S. W. G., Jones, A. K. P., Devani, P., Friston, K. J., Feinmann, C., Harris, M., Pearce, S., Watson, J. D. G., & Frackowiak, R. S. J. (1994) Cerebral responses to pain in patients with atypical facial pain measured by positron emission tomography. *J Neurol Neurosurg Psychiatry 57*: 1166–1172.

Derbyshire, S. W. G., Jones, A. K. P., Gyulai, F., Clark, S., Townsend, D., & Firestone, L. L. (1997) Pain processing during three levels of noxious stimulation produces differential patterns of central activity. *Pain 73*: 431–445.

Derbyshire, S. W. G., Vogt, B. A., & Jones, A. K. P. (1998) Pain and Stroop interference tasks activate separate processing modules in anterior cingulate cortex. *Exp Brain Res 118*: 52–60.

Devinsky, O., Morrell, M. J., Vogt, B. A. (1995) Contributions of anterior cingulate cortex to behaviour. *Brain 118*: 279–306.

Di Piero, V., Jones, A. K. P., Iannotti, F., Powell, M., Perani, D., Lenzi, G. L., & Frackowiak, R. S. J. (1991) Chronic pain: A PET study of the central effects of percutaneous high cervical cordotomy. *Pain 46*: 9–12.

Dong, W. K., Salonen, L. D., Kawakami, Y., Shiwaku, T., Kaukoranta, E. M., & Martin, R. F. (1989) Nociceptive responses of trigeminal neurons in SII-7b cortex of awake monkeys. *Brain Res 484*: 314–324.

Drevets, W. C. (2000a) Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. *Prog Brain Res 126*: 413–431.

Drevets, W. C. (2000b) Neuroimaging studies of mood disorders. *Biol Psychiatry 48*: 813–829.

Foltz, E. L., & White, L. E. J. (1962) Pain relief by frontal cingulotomy. *Neurosurgery 19*: 89–100.

Frith, C. (2001) A framework for studying the neural basis of attention. *Neuropsychologia 39*: 1367–1371.

Gamble, G. E., Barberan, E., Bowsher, D., Tyrrell, P. J., & Jones, A. K. P. (2000) Post stroke shoulder pain: more common than previously realised. *Eur J Pain 4*: 313–315.

Gamble, G. E., Barberan, E., Laasch, H-U., Bowsher, D., Tyrrell, P. J., & Jones, A. K. P. (2002) Postroke shoulder pain: a prospective study of the association and risk factors in 152 patients from a consecutive cohort of 205 patients presenting with stroke. *Eur J Pain 6*: 467–474.

Gamble, G. E., Jones, A. K. P., & Tyrrell, P. J. (1999) Shoulder pain after stroke: case report and review. *Ann Rheum Dis 58*:7.

George, M. S., Ketter, T. A., Parekh, P. I., Herscovitch, P., & Post, R. M. (1996) Gender differences in regional cerebral blood flow during transient self-induced sadness or happiness. *Biol Psychiatry 40*: 859–871.

Gibson, S. J., Littlejohn, G. O., Gorman, M. M., Helme, R. D., & Granges, G. (1994) Altered heat pain thresholds and cerebral event-related potentials following painful CO2 laser stimulation in subjects with fibromyalgia syndrome. *Pain 58*: 185–193.

Gracely, R. H., Geisser, M. E., Giesecke, T., Grant, M. A., Petzke, F., Williams, D. A., & Clauw, D. J. (2004) Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain 127*: 835–843.

Gracely, R. H., Petzke, F., Wolf, J. M., & Clauw, D. J. (2002) Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum 46*: 1333–1343.

Hansson, P. (2004) Post-stroke pain case study: clinical characteristics, therapeutic options and long-term follow-up. *Eur J Neurol 11* (Suppl 1): 22–30.

Hansson, P. (2005) Neuropathic pain: definition, epidemiology, classification and diagnostic work-up. In D. M. Justins (Ed.), *Pain 2005 – an Updated Review* (pp. 91–95).

Head, H., & Holmes, G. (1911) Sensory disturbances from cerebral lesions. *Brain 34*: 102–254.

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

Hsieh, J. C., Belfrage, M., Stone-Elander, S., Hansson, P., & Ingvar, M. (1995) Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. *Pain 63*: 225–236.

Hsieh, J. C., Stahle-Backdahl, M., Hagermark, O., Stone-Elander, S., Rosenquist, G., & Ingvar, M. (1996) Traumatic nociceptive pain activates the hypothalamus and the periaqueductal gray: a positron emission tomography study. *Pain 64*: 303–314.

Hsieh, J. C., Tu, C. H., Chen, F. P., Chen, M. C., Yeh, T. C., Cheng, H. C., Wu, Y-T., Liu, R. S., & Ho, L. T. (2001) Activation of the hypothalamus characterizes the acupuncture stimulation at the analgesic point in human: a positron emission tomography study. *Neurosci Lett 307*: 105–108.

Hutchison, W. D., Davis, K. D., Lozano, A. M., Tasker, R. R., & Dostrovsky, J. O. (1999) Pain-related neurons in the human cingulate cortex. *Nat Neurosci* 2: 403–405.

Iadarola, M. J., Berman, K. F., Zeffiro, T. A., Byas-Smith, M. G., Gracely, R. H., Max, M. B., & Bennett, G. J. (1998) Neural activation during acute capsaicin-evoked pain and allodynia assessed with PET. *Brain 121*: 931–947.

Iadarola, M. J., Max, M. B., Berman, K. F., Byas-Smith, M. G., Coghill, R. C., Gracely, R. H., & Bennett, G. J. (1995) Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain. *Pain 63*: 55–64.

Jeanmonod, D., Magnin, M., & Morel, A. (1996) Low-threshold calcium spike bursts in the human thalamus. Common physiopathology for sensory, motor and limbic positive symptoms. *Brain 119*: 363–375.

Jones, A. K., Kitchen, N. D., Watabe, H., Cunningham, V. J., Jones, T., Luthra, S. K., & Thomas, D. G. (1999) Measurement of changes in opioid receptor binding in vivo during trigeminal neuralgic pain using [^{11}C] diprenorphine and positron emission tomography. *J Cereb Blood Flow Metab 19*: 803–808.

Jones, A. K., Kulkarni, B., & Derbyshire, S. W. (2002) Functional imaging of pain perception. *Curr Rheumatol Reports 4*: 329–333.

Jones, A. K. P. (1999) The contribution of functional imaging techniques to our understanding of rheumatic pain. *Rheum Dis Clin North Am 25*: 123–152.

Jones, A. K. P., Cunningham, V. J., Ha-Kawa, S., Fujiwara, T., Luthra, S. K., Silva, S., Derbyshire, S., & Jones, T. (1994) Changes in central opioid receptor binding in relation to inflammation and pain in patients with rheumatoid arthritis. *Br J Rheumatol 33*: 909–916.

Jones, A. K. P., & Derbyshire, S. W. G. (1996) Cerebral mechanisms operating in the presence and absence of inflammatory pain. *Ann Rheum Dis 55*: 411–420.

Jones, A. K. P., & Derbyshire, S. W. G. (1997) Reduced cortical responses to noxious heat in patients with rheumatoid arthritis. *Ann Rheum Dis 56*: 601–607.

Jones, A. K. P., Friston, K. J., Qi, L. Y., Harris, M., Cunningham, V. J., Jones, T., Feinman, C., & Frackowiak, R. S. J. (1991a) Sites of action of morphine in the brain. *Lancet 338*: 825.

Jones, A. K. P., Kulkarni, B., & Derbyshire, S. W. G. (2003) Pain mechanisms and their disorders. In R. S. J. Frackowiak, T. Jones,(Eds) *British Medical Bulletin* (pp. 83–93) Oxford University Press:.

Jones, A. K. P, Pike, V. W., Luthra, S. K., *et al.* (1985) ^{11}C-diprenorphine and 11C-meptazinol: new specific and non-specific probes for studying opioid binding sites using positron tomography. *J Cereb Blood Flow Metab 5*: 603–604.

Jones, A. K. P., Qi, L. Y., Fujirawa, T., Luthra, S. K., Ashburner, J., Bloomfield, P., Cunningham, V. J., Itoh, M., Fukuda, H., & Jones, T. (1991b) In vivo distribution of opioid receptors in man in relation to the cortical projections of the medial and lateral pain systems measured with positron emission tomography. *Neurosci Lett 126*: 25–28.

Jones, A. K. P., Watabe, H., Cunningham, V. J., & Jones, T. (2004) Cerebral decreases in opioid receptor binding in patients with central neuropathic pain measured by [^{11}C]diprenorphine binding and PET. *Eur J Pain 8*: 479–485.

Kakigi, R., Inui, K., & Tamura, Y. (2005) Electrophysiological studies on human pain perception. *Clin Neurophysical 116*: 743–763.

Kenshalo, D. R., & Willis, W. D. (1991) The role of the cerebral cortex in pain sensation. In A. Peters, (Ed.), *Cerebral cortex* (pp. 153–212), New York: Plenum Press.

Kulkarni, B., Bentley, D. E., Elliott, R., Youell, P. D., Watson, A., Derbyshire, S. W. G., Frackowiak, R. S. J., Friston, K. J., & Jones, A. K. P. (2005) Attention to pain localisation and unpleasantness discriminates the functions of the medial and lateral pain systems. *Eur J Neurosci 21*: 3133–3142.

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 cutaneous heat and cold stimuli. *Pain 85*: 359–374.

Lewis, M. E., Mishkin, M., Bragin, E., Brown, R. M., Pert, C. B., & Pert, A. (1981) Opiate receptor gradients in monkey cerebral cortex: correspondence with sensory processing hierarchies. *Science 211*: 1166–1169.

Llinas, R. R., Ribary, U., Jeanmonod, D., Kronberg, E., & Mitra, P. P. (1999) Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci* USA *96*: 15222–15227.

Lorenz, J., Cross, D. J., Minoshima, S., Morrow, T. J., Paulson, P. E., & Casey, K. L. (2002) A unique representation of heat allodynia in the human brain. *Neuron 35*: 383–393.

Lorenz, J., Minoshima, S., & Casey, K. L. (2003) Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. *Brain 126*: 1079–1091.

Lotze, M., Wietek, B., Birbaumer, N., Ehrhardt, J., Grodd, W., & Enck, P. (2001) Cerebral activation during anal and rectal stimulation. *Neuroimage 14*: 1027–1034.

Lu, C. L., Wu, Y. T., Yeh, T. C., Chen, L. F., Chang, F. Y., Lee, S. D., Ho, L. T., & Hsieh, J. C. (2004) Neuronal correlates of gastric pain induced by fundus distension: a 3T-fMRI study. *Neurogastroenterol Motil 16*: 575–587.

Maren, S., Poremba, A., & Gabriel, M. (1991) Basolateral amygdaloid multi-unit neuronal correlates of discriminative avoidance learning in rabbits. *Brain Res 549*: 311–316.

Marshall, J. (1951) Sensory disturbances in cortical wounds with special reference to pain. *J Neurol Neurosurg Psychiatry 14*: 187–204.

McBeth, J., Macfarlane, G. J., Benjamin, S., & Silman, A. J. (2001) Features of somatization predict the onset of chronic widespread pain: results of a large population-based study. *Arthritis Rheum 44*: 940–946.

Melzack, R. (1990) Phantom limbs and the concept of a neuromatrix. *Trends Neurosci 13*: 88–92.

Melzack, R., & Casey, K. L. (1968) Sensory, motivational, and central control determinants of pain. In D. R. Kenshalo, (Ed.): *The Skin Senses* (pp. 423–439), Springfield: CC Thomas.

Mesulam, M. M. (1990) Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Ann Neurol 28*: 597–613.

Morecraft, R. J., Geula, C., & Mesulam, M. M. (1993) Architecture of connectivity within a cingulo-fronto-parietal neurocognitive network for directed attention. *Arch Neurol 50*: 279–284.

Nicholson, B. D. (2004) Evaluation and treatment of central pain syndromes. *Neurology 62*: S30–S36.

Ostrowsky, K., Magnin, M., Ryvlin, P., Isnard, J., Guenot, M., & Mauguiere, F. (2002) Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cerebral Cortex 12*: 376–385.

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

Petrovic, P., & Ingvar, M. (2002) Imaging cognitive modulation of pain processing. *Pain 95*: 1–5.

Petrovic, P., Kalso, E., Petersson, K. M., & Ingvar, M. (2002) Placebo and opioid analgesia – Imaging a shared neuronal network. *Science 295*: 1737–1740.

Peyron, R., Garcia-Larrea, L., Gregoire, M. C., Convers, P., Lavenne, F., Veyre, L., Froment, J. C., Mauguiere, F., Michel, D., & Laurent, B. (1998) Allodynia after lateral-medullary (Wallenberg) infarct. A PET study. *Brain 121*: 345–356.

Peyron, R., Garcia-Larrea, L., Gregoire, M. C., Costes, N., Convers, P., Lavenne, F., Mauguiere, F., Michel, D., & Laurent, B. (1999) Haemodynamic brain responses to acute pain in humans: sensory and attentional networks. *Brain 122*: 1765–1779.

Peyron, R., Laurent, B., & Garcia-Larrea, L. (2000) Functional imaging of brain responses to pain. A review and meta-analysis. *Neurophysiol Clin 30*: 263–288.

Peyron, R., Schneider, F., Faillenot, I., Convers, P., Barral, F. G., Garcia-Larrea, L., & Laurent, B. (2004) An fMRI study of cortical representation of mechanical allodynia in patients with neuropathic pain. *Neurology 63*: 1838–1846.

Ploner, M., Freund, H. J., & Schnitzler, A. (1999) Pain affect without pain sensation in a patient with a postecentral lesion. *Pain 81*: 211–214.

Ploner, M., Schmitz, F., Freund, H. J., & Schnitzler, A. (2000) Differential organization of touch and pain in human primary somatosensory cortex. *J Neurophysiol 83*: 1770–1776.

Porro, C. A., Baraldi, P., Pagnoni, G., Serafini, M., Facchin, P., Maieron, M., & Nichelli, P. (2002) Does anticipation of pain affect cortical nociceptive systems? *J Neurosci 22*: 3206–3214.

Posner, M. I., & Petersen, S. E. (1990) The attention system of the human brain. *Ann Rev Neurosci 13*: 25–42.

Rainville, P. (2002) Brain mechanisms of pain affect and pain modulation. *Curr Opin Neurobiol 12*: 195–204.

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., Hofbauer, R. K., Paus, T., Duncan, G. H., Bushnell, M. C., & Price, D. D. (1999) Cerebral mechanisms of hypnotic induction and suggestion. *J Cogn Neurosci 11*: 110–125.

Rolls, E. T. (1999) The neural bases of emotion. In Rolls E, (Ed.), *The Brain and Emotion* (pp. 75–147) Oxford University Press.

Rolls, E. T., O'Doherty, J., Kringelbach, M. L., Francis, S., Bowtell, R., & McGlone, F. (2003) Representations of pleasant and painful touch in the human orbitofrontal and cingulate cortices. *Cerebral Cortex 13*: 308–317.

Romanski, L. M., Clugnet, M. C., Bordi, F., & LeDoux, J. E. (1993) Somatosensory and auditory convergence in the lateral nucleus of the amygdala. *Behav Neurosci 107*: 444–450.

Rosen, S. D., Paulesu, E., Frith, C. D., Frackowiak, R. S. J., Davies, G. J., Jones, T., & Camici, P. G. (1994) Central nervous pathways mediating angina pectoris. *Lancet 344*: 147–150.

Rowbotham, M. C., Twilling, L., Davies, P. S., Reisner, L., Taylor, K., & Mohr, D. (2003) Oral opioid therapy for chronic peripheral and central neuropathic pain. *New Engl J Med 348*: 1223–1232.

Schlereth, T., Baumgartner, U., Magerl, W., Stoeter, P., & Treede, R. D. (2003) Left-hemisphere dominance in early nociceptive processing in the human parasylvian cortex. *Neuroimage 20*: 441–454.

Schneider, F., Habel, U., Holthusen, H., Kessler, C., Posse, S., Muller-Gartner, H. W., & Arndt, J. O. (2001) Subjective ratings of pain correlate with subcortical-limbic blood flow: an fMRI study. *Neuropsychobiology 43*: 175–185.

Shi, C., & Davis, M. (1999) Pain pathways involved in fear conditioning measured with fear-potentiated startle: lesion studies. *J Neurosci 19*: 420–430.

Sikes, R. W., & Vogt, B. A. (1992) Nociceptive neurons in area 24 of rabbit cingulate cortex. *J Neurophysiol 68*: 1720–1732.

Spetea, M., Rydelius, G., Nylander, I., Ahmed, M., Bileviciute-Ljungar, I., Lundeberg, T., Svensson, S., & Kreicbergs, A. (2002) Alteration in endogenous opioid systems due to chronic inflammatory pain conditions. *Eur J Pharmacol 435*: 245–252.

Tolle, T. R., Kaufmann, T., Siessmeier, T., Lautenbacher, S., Berthele, A., Munz, F., Zieglgansberger, W., Willoch, F., Schwaiger, M., Conrad, B., & Bartenstein, P. (1999) Region-specific encoding of sensory and affective components of pain in the human brain: a positron emission tomography correlation analysis. *Ann Neurol 45*: 40–47.

Treede, R. D., Kenshalo, D. R., Gracely, R. H., & Jones A. K. P. (1999) The cortical representation of pain. *Pain 79*: 105–111.

Valet, M., Sprenger, T., Boecker, H., Willoch, F., Rummeny, E., Conrad, B., Erhard, P., & Tolle, T. R. (2004) Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain – an fMRI analysis. *Pain 109*: 399–408.

Vogt, B. A., Berger, G. R., & Derbyshire, S. W. (2003) Structural and functional dichotomy of human midcingulate cortex. *Eur J Neurosci 18*: 3134–3144.

Vogt, B. A., Derbyshire, S., & Jones, A. K. P. (1996) Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging. *Eur J Neurosci 8*: 1461–1473.

Vogt, B. A., & Pandya, D. N. (1987) Cingulate cortex of the rhesus monkey: II. Cortical afferents. *J Comp Neurol 262*: 271–289.

Vogt, B. A., Sikes, R. W., & Vogt, L. J. (1993) Anterior cingulate cortex and the medial pain system. In B. A. Vogt, & G. Birkhauser (Eds), *Neurobiology of Cingulate Cortex and Limbic Thalamus* (pp. 313–344) Boston: Basel, Berlin.

Vogt, B. A., Watabe, H., Grootoonk, S., & Jones, A. K. P. (1995a) Topography of diprenorphine binding in human cingulate gyrus and adjacent cortex derived from coregistered PET and MR images. *Human Brain Mapping 3*: 1–12.

Vogt, B. A., Wiley, R. G., & Jensen, E. L. (1995b) Localization of mu and delta opioid receptors to anterior cingulate afferents and projection neurons and input/output model of mu regulation. *Exp Neurol 135*: 83–92.

Willoch, F., Tolle, T. R., Wester, H. J., Munz, F., Petzold, A., Schwaiger, M., Conrad, B., & Bartenstein, P. (1999) Central pain after pontine infarction is associated with changes in opioid receptor binding: a PET study with ^{11}C-diprenorphine. *Am J Neuroradiol 20*: 686–690.

Woolf, C. J. (1994) A new strategy for the treatment of inflammatory pain. Prevention or elimination of central sensitization. *Drugs* 47 (Suppl 5): 1–9.

Youell, P. D., Wise, R. G., Bentley, D. E., Dickinson, M. R., King, T. A., Tracey, I., & Jones, A. K. (2004) Lateralisation of nociceptive processing in the human brain: a functional magnetic resonance imaging study. *Neuroimage 23*: 1068–1077.

Zubieta, J. K., Smith, Y. R., Bueller, J. A., Xu, Y., Kilbourn, M. R., Jewett, D- M., Meyer, C. R., Koeppe, R. A., & Stohler, C. S. (2001) Regional mu opioid receptor regulation of sensory and affective dimensions of pain. *Science 293*: 311–315.