CHAPTER 14

Cingulate Nociceptive Circuitry and Roles in Pain Processing: The Cingulate Premotor Pain Model

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Chapter contents

The Medial Pain and Limbic Systems Converge in the Cingulate Gyrus

A long tradition conceptualizes pain processing according to sensory-discriminative and affective-motivational domains (Melzack & Casey, 1968; Melzack, 1975; Kenshalo & Willis, 1991). The sensory-discriminative domain engages stimulus localization and can be assessed with visual analogue scales for intensity, while the affective-motivational domain involves the affective component of pain and is measured with ratings of unpleasantness. This duality was framed in terms of *medial* and *lateral thalamic* processing by Albe-Fessard *et al*. (1985), who proposed that the lateral thalamic nuclei play a role in localization, whereas the medial thalamic nuclei are involved in affective responses to such stimuli. There is little doubt that the medial and lateral systems are engaged in these functions; however, it was unclear how thalamic nuclei engage in specific aspects of conscious pain processing, how they predict the consequences of behavioral outcomes, and how pain-linked memories are stored by thalamic nuclei. More importantly, the two-thalamic systems model failed to accommodate either joint or independent roles for the cerebral cortex in such processing modes because there were no links between the medial thalamic and limbic systems in the model.

The concept of lateral and medial pain systems was extended for cortical structures including somatosensory and anterior cingulate cortices (ACC), respectively, based on thalamic afferents and neurosurgical ablation outcomes (Vogt *et al*., 1993). This was the first model of the entire medial pain system from nociceptor to limbic termination sites. Subsequent observations of stroke cases verified the functions of the medial and lateral pain systems (e.g., Ploner *et al*., 1999), functional imaging studies show that enhancing a subject's attention to noxious stimulus localization or unpleasantness leads to enhanced activity in lateral and medial systems, respectively (Kulkarni *et al*., 2005), and cortisol has a profound influence on medial system processing during fear conditioning with an electric shock as the unconditional stimulus (Stark *et al*., 2006). Although the dual model of pain processing has been useful for theoretical reasons and for designing experiments to identify contributions of different forebrain structures to pain processing, the pain system is more complex both in terms of the number of functions performed by nociceptive regions and in terms of the number of structures involved in such processing.

With the introduction of human functional imaging, it has become clear that many telencephalic regions are engaged during acute noxious stimulation. There are a number of motor and premotor areas including supplementary and premotor cortices, cerebellar cortex, and the striatum that are active during acute noxious stimulation and they do not easily fit the two domains of pain processing based on sensation including sensory-generated affect. Indeed, to the extent that one considers the pain experience sensory, this produces inherent biases away from understanding important parts of the cingulate contributions to motor functions, not just general motivational issues, and the premotor relevance of nociceptive activation must be a part of understanding cingulate-mediated pain processing.

A number of limbic structures, in addition to ACC, are activated during noxious body stimulation and these medially located structures together comprise the medial pain system. This medial and limbic pain system includes the midline, mediodorsal, and intralaminar thalamic nuclei (MITN; Vogt *et al*., 1979, 1987) which project nociceptive information to limbic forebrain structures including the ACC, anterior insula, and the amygdala. Although it has a lateral location in the forebrain, it appears that the anterior insula lies between the lateral and medial systems and is involved in processing associated with each system including sensory coding, body state assessment, and autonomic regulation as well as emotional valence coding of sensory events. Thus, although the two-domain model may have general utility, activation of 6–10 areas during nociception suggests that there are many domains of pain processing. Indeed, consideration of cingulate cortex suggests that this region itself is involved in three aspects of pain processing that may use affect but is explicitly involved in avoidance/nocifensive behaviors.

Human functional imaging suggests that ACC mediates affective responses to noxious stimuli and the extensive studies of Paul MacLean (1990) and others support the general notion that cingulate cortex is a pivotal region for emotion-relevant processing. MacLean considered the role of cingulate cortex in emotional expression via vocalization and interactions among conspecifics such as in infant–mother interactions and male dominance. Vocalization and facial expression are important aspects of pain expression and are incorporated into our current model of cingulate cortex in the pain neurometrix. Interestingly, most of the electrical stimulation studies in which MacLean evaluated emotion-associated activity were focused in the ACC and he had no means of differentiating sensory cues and contexts from the valencing and expression of emotion. This led him to consider that posterior cingulate cortex (PCC) was equally involved in affect; however, as discussed below, this does not seem to be the case. Indeed, each region of the cingulate cortex appears to play a separate role in pain processing.

Not all pain-associated activity is affective, even in the cingulate gyrus. Although activations during emotion-generating tasks suggest some overlap of emotion (Phan *et al*., 2002) and pain processes (Vogt *et al*., 2003), there are a number of caveats to the proposition that pain and emotion are linked in the cingulate gyrus and these differences are pivotal to the cingulate premotor pain model. Most of the studies of noxious cerebral activation do not consider the fact that ACC and midcingulate cortices (MCC) are involved in decidedly non-painful functions including coding for the reward properties of particular behaviors (Rolls *et al*., 2003; Chapters 8 and 12), activation during romantic love (Bartels & Zeki, 2000) and while viewing erotic pictures (Redouté *et al*., 2000). Also, much of MCC is not involved in emotion though it is activated by noxious stimulation; most notably the posterior part of MCC (Vogt *et al*., 2003; Vogt, 2005). Finally, the dorsal PCC (dPCC) is occasionally activated with a short latency in evoked-potential studies (e.g., Bentley *et al*., 2003), but the linkage between this region and affect is weak and no models of pain processing have yet explained or accommodated the role of this region in pain processing. This region is more closely engaged in relating orientation of the body to the stimuli and multisensory orientation of the body in space to behavioral context rather than affect and autonomic regulation (Chapter 13).

Another general issue of concern to the roles of cingulate cortex in pain processing is the fact that "pain-centered" views such as the labeled-line theories seek to identify pain-specific processing functions and raise many paradoxes about the organization and functions of cingulate cortex. First, the effort to identify pain-specific, cingulate processing derives from nociceptive-specific lamina I neurons in the spinal cord, where labeled-line theories trace pain-specific processing through a small and ventral part of the mediodorsal thalamic nucleus (Craig, 2003). These connections have never been shown to be specific to any part of ACC, since many thalamic nuclei project to any one cingulate subregion rather than a single, nociceptive subregion. Moreover, many thalamic nuclei provide nociceptive input to cingulate cortex and they are not limited to one nucleus. Secondly, only part of ACC and MCC are involved in emotion. The subgenual ACC (sACC) is involved in autonomic and classical conditioning functions according to electrical stimulation and neuron recording (Phan *et al*., 2002; Vogt *et al*., 2003; Chapter 10), while emotion-associated activity is part of the most frequently pain-activated anterior but not pMCC. Thirdly, no part of cingulate cortex is activated only by noxious stimulation. Although there are nociceptive-specific neurons, this does not mean that such units do not also respond under other conditions; although there might be a nociceptive-specific circuitry that has not yet been identified. It certainly is not true that any region or area in the cingulate gyrus is engaged only by noxious responses and is strictly a "pain center." Thus, the relation between pain and affect *vis-à-vis* autonomic regulation and pain in relation to premotor planning and output remains a matter of debate. Answers to these questions derive from the four-region neurobiological model of the cingulate cortex and frames the essential goals of this chapter.

Goals of This Chapter

Assessing the role of cingulate cortex in pain begins with consideration of its functions in the regional/subregional neurobiological model of cingulate cortex. Rather than asking what role cingulate cortex has in pain processing, the first question is, *What are the functions of cingulate cortex and how does noxious stimulation deploy cingulate resources to resolve the evoked conflicts?* This approach requires analyzing pain in the context of broader circuit functions that generally resolve many cognitive problems and are redirected during noxious stimulation. While the organization of the full medial pain system from nociceptor to ACC was presented in *Neurobiology of Cingulate Cortex and Limbic Thalamus* (Vogt *et al*., 1993), the present chapter seeks to understand the multiple roles of cingulate cortex in premotor pain processing. This model is not a sensory model, although small regions of sensory-specific activation have been observed and certainly thalamic afferents provide a sensory signal, but rather a wide-ranging system for multiple sites of cingulate motor interventions to accommodate numerous aspects of movement associated with the anticipation and avoidance of noxious stimulation. The specific goals of this chapter are the following:

1 Characterize the properties of nociceptive cingulate subregions with human imaging.

2 Identify subregions of emotion-relevant processing and link them to pain processing.

3 Evaluate the midline, mediodorsasl, and intralaminar thalamic circuitry that are sources of nociceptive inputs to cingulate cortex and the origin of nociceptive inputs to these thalamic nuclei from the spinothalamic tract, parabrachial nucleus, and subnucleus reticularis dorsalis.

4 Characterize the *three roles of cingulate cortex in nociception* in terms of three tiers of organization:

- **a** suffering and facial expressions of anguish in pregenual ACC;
- **b** fear and avoidance behaviors in aMCC via the rostral cingulate motor area;

c orientation of the body to noxious somatic stimulation via pMCC and multisensory context via dorsal PCC and projections to the caudal cingulate motor area

5 Formally present the Cingulate Premotor Pain Model based on the full range of animal research and human functional imaging. It involves three tiers of information processing; thalamic afferents, gyral surface integrative events, and autonomic and skeletomotor outputs.

This chapter does not consider the important role of cingulate cortex in modulating pain inputs via the descending noxious inhibitory system as this subject is considered in four chapters of this volume: (a) Chapter 15 reviews descending systems including projections to the periaqueductal gray and opioid regulation of cingulate cortex, (b) Chapter 16 considers the anticipatory and placebo responses that cingulate cortex mediates by descending systems, (c) Chapter 17 evaluates hypnosedation for surgical analgesia that is likely mediated via cingulate projections to the periaqueductal gray and from there to the descending noxious inhibitory system, and (d) Chapter 20 evaluates this descending system as a means of reducing chronic pain following motor cortex stimulation.

Human Cingulate Nociceptive Responses

Noxious somatic stimuli evoke pain and avoidance behaviors and these are impaired with lesions of the cingulate gyrus in humans (Ballantine *et al*., 1967) and experimental animals (Gabriel, 1993). Moreover, destruction of somatosensory cortex greatly impairs stimulus localization without altering pain affect; presumably because the medial pain system, including cingulate cortex, is intact (Ploner *et al*., 1999). Acute nociceptive responses in human include cingulate cortex as one of the most frequently activated regions in the pain neuromatrix (Derbyshire, 2000; Peyron *et al*., 2000), and a summary of acute nociceptive responses in cingulate cortex is shown in Figure 14.1. We considered nociceptive responses in the context of the four-region neurobiological model using PET and showed that both pACC and MCC have elevated cerebral blood flow during noxious heat to the back of the hand when controlled for innocuous heating to the same skin (Vogt *et al*., 1996). Figure 14.1A was derived from a literature review that localized peak voxel activity co-registered to one of our cases (Vogt *et al*., 2003) and it shows that the most cutaneous activity is evoked in MCC with almost no preference for the anterior or posterior divisions, while there are fewer activations in pACC and dPCC and almost none in sACC or vPCC.

Although there are relatively few studies of nociceptive visceral responses, they show a preference for pACC and to a lesser extent aMCC. These responses were evoked with hypertonic saline on the tongue or administered intravenously or noxious distension of the esophagus, colon, or rectum (references for Figure 14.1A in Vogt, 2005). Finally, this region may be important in terms of the suffering component of pain because enhancement of unpleasantness during noxious cutaneous stimulation enhances activity in pACC (Kulkarni *et al*., 2005) and second pain induced by C fibers which is associated with burning activates this same subregion (Ploner *et al*., 2002). Thus, both visceral and cutaneous noxious stimulation enhances activity in pACC.

Two studies provide important documentation that cutaneous and deep tissue/visceral noxious stimulation activates a greater amount and different part of cingulate cortex because both modalities of stimulation were employed in the same subjects. Strigo *et al*. (2003) tried to balance noxious stimulation intensity in visceral and cutaneous sites and observed cutaneous activation of pMCC, while esophageal distention evoked activity more dorsal and anterior in aMCC (Fig. 14.1B). Svensson *et al*. (1997) showed a similar-sized laser-evoked, noxious cutaneous activation of pMCC compared to that of Strigo *et al*. (2003), while intramuscular electrical stimulation evoked a larger and more anterior site in aMCC.

Based on this extensive human imaging research, we come to a number of interesting conclusions. First, cutaneous nociceptive stimuli activate small areas of cortex mainly in pMCC and this may be associated primarily with the caudal cingulate motor area. This region has little to do with emotion *per se* as discussed later and is more likely involved in orienting the body to the noxious stimulation. Secondly, deep tissue stimulation tends to activate aMCC and this could be related to generation of emotion including fear, as discussed later, and avoidance behaviors. Thirdly, activity in aMCC suggests that deep tissue/visceral activation enhances activity of the rostral cingulate motor area in the rostral cingulate sulcus. This motor area appears to be pivotal in selecting among potential outputs to resolve internal conflicts and to achieve particular goals such as relieving and avoiding pain.

Thus, activation of large areas of the cingulate cortex does not reflect a simple algebraic summation of tissue responses. The progressive incorporation of larger areas of tissue involves activation of cortex with qualitatively unique roles in brain function. Activation of pMCC by cutaneous nociceptors generates a qualitatively

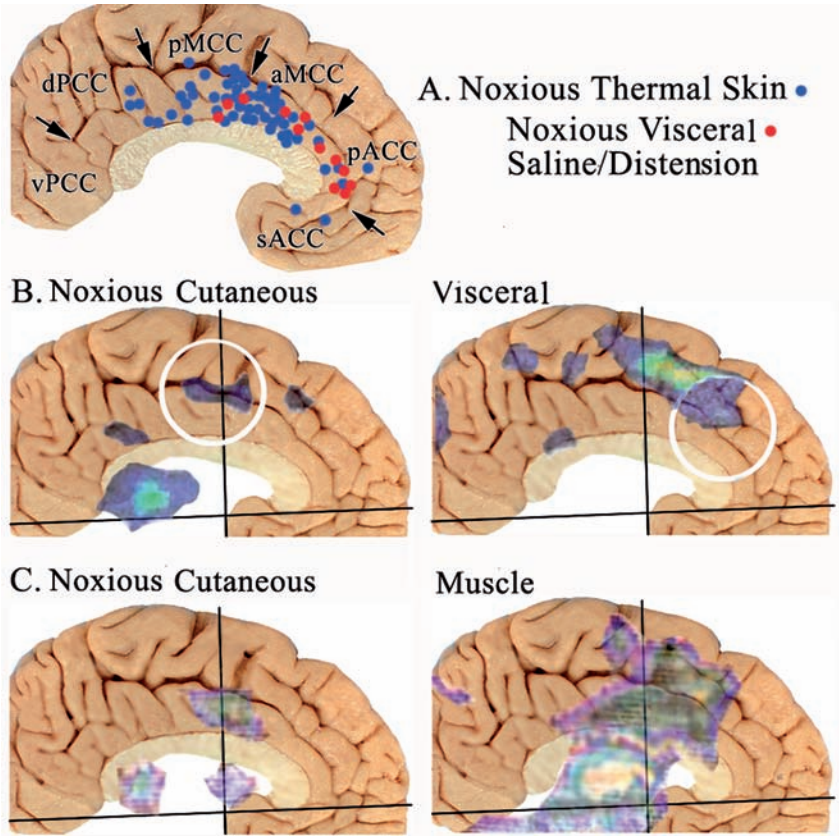

Fig. 14.1 Human imaging during acute noxious stimulation. (A) Summary of peak activation sites during noxious thermal stimulation of the skin and noxious hypertonic saline or visceral distension (modified from Vogt *et al.*, 2003; references in Vogt, 2005). Cutaneous activations were throughout MCC, while visceral activity was greatest in pACC and some in aMCC. Activations in two studies in which two noxious stimulation paradigms were applied to the same subjects and here the responses are co-registered to the same postmortem case. Noxious cutaneous stimulation evoked small and caudal activity in pMCC, while noxious esophageal distention (B. Strigo *et al.*, 2003) or electrical stimulation of muscle (C. Svensson *et al.*, 1997) evoked larger, aMCC activity.

different response than does deep tissue stimulation associated with aMCC and pACC activity.

Nociceptive Intensity Coding and Innocuous Stimulus Driving

Although most of the structures in the pain neuromatrix appear to code for the intensity of nociceptive stimuli, this does not mean that all structures are responsible for the perception of pain intensity or that all areas contribute equally to that perception. One of the present arguments is that intensity coding is present in cingulate cortex thalamic afferents but not necessary for its premotor processing functions. There is also a question as to whether or not cingulate cortex is active during innocuous sensory stimulation because many studies fail to activate this region during innocuous stimulation of the body surface and deep tissues. To the extent that this latter finding is a consequence of study design, there may be no reason to exclude cingulate cortex in the matrix of structures that respond to innocuous stimulation.

Intensity coding for noxious stimuli is localized for pACC and MCC in Figure 14.2B from regression analyses of positron emission tomography (PET) findings with thermal stimulation (Derbyshire *et al.*, 1997; Coghill *et al.*, 1999). The reasons for the pACC correlation in the former study and MCC correlation in the latter study are unclear except that Coghill *et al.* (Fig. 14.2B, 2a) used a range of stimuli including non-noxious stimulations and this may have enhanced the activity in pMCC. As noted below, innocuous stimulation is also known to drive this region in evoked potential studies. Additionally, Porro *et al.* (1998) used functional magnetic resonance imaging (fMRI) and subcutaneous ascorbic acid to generate an unpredictable noxious stimulus and reduced activity in pACC (Chapter 16). This supports the notion that pACC/aMCC activity is associated with the unpleasantness of a noxious stimulus during prolonged burning stimulation.

Many studies have failed to activate cingulate cortex with innocuous stimulation including the two that used transcutaneous electrical nerve stimulation that evoked a tingling sensation, while noxious levels of stimulation were effective (Davis *et al.*, 1997; Ibinson *et al.*, 2004). There are many human imaging studies, however, that report innocuous activity in MCC (Becerra *et al.*, 1999; Coghill *et al.*, 1999; Kwan *et al.*,

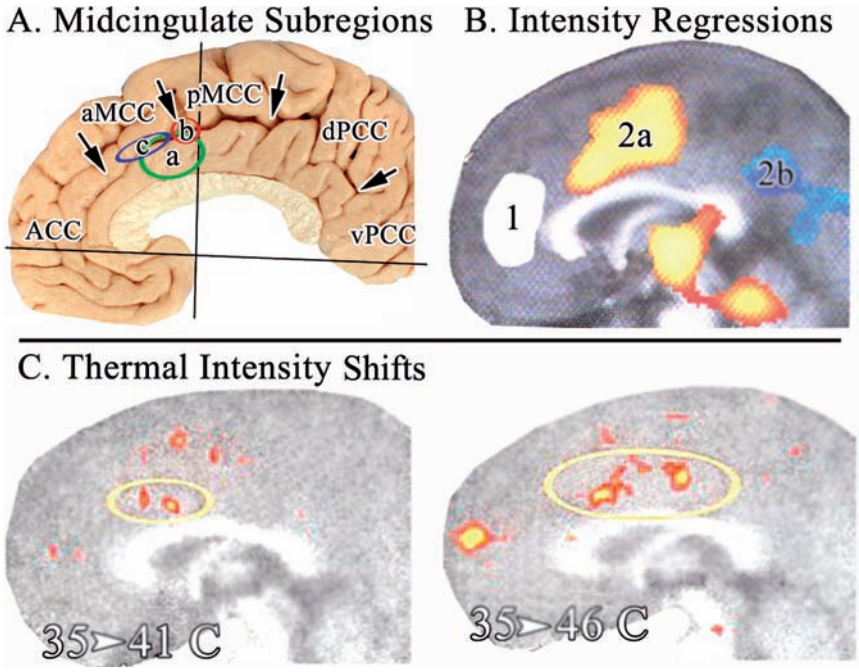

Fig. 14.2 Noxious stimulus intensity coding and innocuous responses: (A) Büchel *et al.* (2002); a/green, noxious thermal intensity; b/red, thermal coding; c/blue, cognitive differentiation of innocuous and noxious stimulations co-registered to postmortem case. (B) 1. Derbyshire *et al.* (1997); 2. Coghill *et al.* (1999) regression analyses (2a. Increases, 2b. Decreases). (C) Becerra *et al.* (1999).

2000 – Fig. 2C, 35–41°C; Büchel *et al.*, 2002 – Fig. 2Ab). The latter two studies are particularly important because Becerra *et al.* (1999) showed responses habituating over multiple presentations with stimuli they report subjects perceived as painful, while multiple innocuous stimuli did not habituate the cingulate responses. The study by Büchel *et al.* (2002) differentiated a region with intensity coding across all temperatures (Fig. 2Ab, coded red) and one that was more ventral and rostral that coded only noxious stimulation (Fig. 2Aa; coded green). Both sites were in aMCC and the border with pMCC. Moulton *et al.* (2005) reported that a small dorsal portion of MCC coded innocuous thermal stimulation. This active region appears to be in the cingulate sulcus in aMCC and suggests that, as was true for the study of Büchel *et al.* (2002) for innocuous stimulation, this is in the rostral cingulate motor area and likely has significance for the response selection processes mediated by this region.

The latter two higher-resolution studies emphasize that the parametrics of stimulation are pivotal to defining intensity-coding sites, innocuous- and noxious-coding regions may be spatially separated, and habituation may play a role in activating particular regions. The many studies that failed to identify innocuous responses may not have had adequate spatial and/or temporal resolution; the number of trials used in "control" conditions may not have provided adequate statistical power, and fluctuating responses associated with habituation in either the pain or the non-pain conditions may have obliterated the signals.

Pathways for innocuous cutaneous and visceral information

While the following text considers the pathways for nociceptive stimulus driving of cingulate cortex, the pathways for innocuous driving are poorly understood and could actually arise in the parietal lobe rather than the thalamus. Additionally, it has long been known that tap stimulation is the one innocuous stimulus that drives both MITN (Casey, 1966; Dong *et al.*, 1978) and ACC (Sikes & Vogt, 1992) neurons. The major source of innocuous driving of MITN is by spinothalamic projections of the wide dynamic range neurons (Kenshalo & Willis, 1991). Since Meissner corpuscles are innervated by substance P containing axons (Paré *et al.*, 2001), this may be one mechanism whereby noxious and innocuous driving of peripheral afferents and possible wide dynamic-range neurons in the spinal cord activate innocuous responses in the MITN and ACC/MCC.

There is also the question of how innocuous visceral stimulation might activate cingulate cortex. Although nociceptive stimulation most often activates ACC and aMCC (above), innocuous stimulation of the rectum also evokes activity in MCC (Hobday *et al.*, 2001; Lotze *et al.*, 2001). Visceral afferents arising from innocuous mechanical and chemoreceptors have limited access to the cingulate gyrus. The nucleus of the solitary tract (NTS) projects to the parabrachial nucleus (Beckstead *et al.*, 1980) which in turn projects to the parafascicular (Pf) thalamic nucleus (Pritchard *et al.*, 2000). Since the Pf projects to cingulate cortex (Vogt *et al.*, 1979,

1987; Royce *et al.*, 1989), the parabrachial nucleus may be a source of innocuous visceral afferents to cingulate cortex. It should be noted, however, that these afferents intermingle with nociceptive inputs from the spinal cord and the parabrachial nucleus is itself a visceral nociceptive integration center for both noxious and innocuous visceral afferents (Bester *et al.*, 1995; Saper, 2000).

Having stated there are sources of innocuous information from the skin and viscera to cingulate cortex, this does not simply resolve the information processing problem, i.e., toward what end is this input processed? To the extent that a single pathway conducts information from two sources, one of the following situations must be satisfied for cognitive differentiation between noxious and innocuous inputs. If there is a separate population of neurons for transmitting both inputs, a means of differentiating and cortical processing is possible. However, if the same neurons respond to both noxious and innocuous stimuli, there must be a cognitive cortical circuitry that provides for differentiation of the responses under separate stimulation conditions possibly through a network organization with other cortical areas. There could be an innocuous detection system/matrix and a noxious detection system/matrix. The information processing functions in this system present the same difficulty as that for the wide dynamic range neurons in the spinal cord. To the extent that a single neuron receives both inputs, what role might it play in brain function? If the high-resolution studies of Büchel *et al.* (2002) are supported and there is a spatial separation of such inputs, it is possible that the answer to these questions lies in intracingulate circuitry as well as interactions with parietal and other somatosensory detection and coding systems.

Emotion and Pain Linkages

Pivotal to the dual model of pain processing is the notion of an affective-motivational domain and the general view that cingulate cortex is partly responsible for this function. As a rule, this domain is evaluated in terms of the "unpleasantness" of a noxious stimulus. Since the anterior cingulate gyrus is not a uniform structural or functional entity and there are methodological hurdles to assessing this domain, cingulate cortex has not submitted in any simple way to the expectation that it subserves affect and motivation. As with nociception, we view emotion as being processed in different parts of the cingulate gyrus according to the memory valence, autonomic associations, and sensory driving necessary for the internal content and behavioral output relevant for each class of emotion. Accordingly, emotion may be processed on the basis of *submodalities* with each one preferentially engaged by different parts of the brain. We predicted that simple, negatively valenced emotions including sadness and fear would be colocalized to sites where pain affect is generated, since it is also negatively valenced. An analysis of simple emotions by Phan *et al.* (2002) plotted functional response peaks in the brain during happiness, sadness, anger, and fear generated with word pairs, scripts, or faces with emotional valence. At first glance, it appears that the cingulate gyrus is more or less completely engaged during emotion. It was not noticed, however, that all parts of cingulate cortex were not equally involved in emotion and this has profound consequences for understanding pain processing in particular and the processing of valenced emotional information in general.

pACC

Unpleasantness

Unpleasantness refers to an affective aspect of pain and, if cingulate cortex is involved in perceptions associated with pain, it may be via unpleasantness. Of course, many other aspects of pain such as conditioned responses with particular object and event associations are not part of "unpleasantness" testing. A response to noxious thermal stimulation has been evoked in pACC by Ploner *et al.* (2002; Fig. 14.3B) using magnetoencephalography. The latency of this response was 0.5–1.5 s and it suggests that it is associated with the perception of second pain which is characterized by greater unpleasantness and the sensation of burning. Kulkarni *et al.* (2005) had subjects assess the unpleasantness or location of noxious, laser-evoked heat stimuli independently and they observed that pACC was heavily activated during attention to unpleasantness (Fig. 14.3A), while MCC was active during attention to location of stimulation. Noxious distention of the sigmoid colon or anticipation of such distention increased activity in pACC (Naliboff *et al.*, 2001; Fig. 14.3E). Thus, the unpleasant nature of acute noxious stimuli may generate unpleasantness associated with activity in the pACC. In contrast, notice that happiness is associated with activation of area p32 rostral to area 24 suggesting that the pACC is divided into two functionally distinct sectors; a rostral one associated with happiness and a caudal one with unpleasantness.

The five dots in Figure 14.3D are a reminder that electrical stimulation of ACC evokes cardiovascular changes as discussed in detail in Chapter 10. This region has direct projections into autonomic motor brainstem nuclei (Neafsey *et al.*, 1993) and it is involved in classical conditioning (Buchanan & Powell, 1993). No other part of the cingulate gyrus directly regulates autonomic outflow and association with pain affect sites make it ideally suited for pain affect. Since visceral stimulation

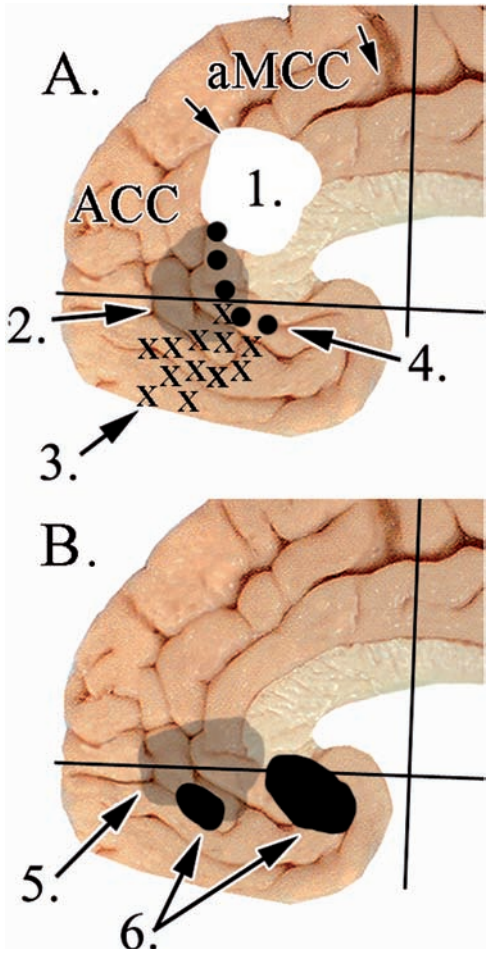

Fig. 14.3 Activity in ACC associated with nociceptive and electrical stimulation. (1) Activation due to enhancement of unpleasantness (Kulkarni *et al.*, 2005); (2) Site of second pain (Ploner *et al.*, 2002); (3) Negatively correlated voxels during anticipation of ascorbic acid injection (Porro *et al.*, 2002); (4) Electrical stimulation reduces cardiovascular activity (Kaada, 1951); (5) Activity evoked with actual and anticipated noxious colon distension (Naliboff *et al.*, 2001); (6) Anticipation of noxious electrical stimulation reduces activity in this region (Simpson *et al.*, 2001).

most often generates activity in this region (Fig. 14.1), it appears that the suffering component of pain might be associated with this site.

There are a number of problems associated with studying the nociceptive functions of ACC. One of them is the inhibitory activity that can be generated by anticipating noxious stimulation and the other is the linkage between the signal and motor output that could have little or nothing to do with sensation *per se*. Anticipatory inactivation of ACC has been shown by imaging the pre-stimulus state for ascorbic acid injection (Fig. 14.3.3), colon distention (Fig. 14.3.5), or noxious transcutaneous electrical stimulation (Fig. 14.3.6). In all instances, there is reduced activity in ACC and it could mean that studies of pain affect understate activity in this region as it is impossible to remove the negative anticipatory response completely.

Another problem assessing unpleasantness is the close link to the noxious stimulus which is a signal to trigger cingulate cortex premotor activity rather than as a sensory signal, i.e., the importance of a noxious sensory stimulus may not be coded in cingulate cortex in terms of the sensory stimulus itself as postulated in most pain studies but rather in terms of previous associations, emotional memory, and in the appropriate actions to escape and avoid future presentations of similar stimuli. It would appear that a measure of immediate personal relevance of the stimulus would be a better measure of the affective qualities of a noxious stimulus than is embodied in "unpleasantness" testing. Areas not activated during acute noxious stimulation may play a role in aspects of pain processing, but current task design and technical limitations may hinder understanding their contributions. For example, the ventral part of PCC often has reduced activity during noxious stimulation (Vogt *et al.*, 1996; Coghill *et al.*, 1999; Fig. 14.2, 2b) and may be involved in assessing the personal relevance of external sensory stimulation and/or early responses for orienting motor activity associated with noxious stimuli. There are reasons to expect that ventral PCC plays a role in pain processing, although current methods have not identified it as a player in this arena and this issue will be considered further later. Self-relevance of noxious stimulation is low for most acute pain studies. Amazingly, the area that codes for negatively valenced memories is sACC and it is generally not activated during noxious stimulation; although it is also vulnerable to susceptibility artifacts with high field strength magnets in fMRI studies.

aMCC and Fear

An assessment of responses during simple emotions considered the proposition that cingulate emotion processing is not equally distributed in the gyrus. The four-region neurobiological model based on cytoarchitecture, circuits, and functions predicts specialized contributions from each region and subregion (Vogt *et al.*, 2003) and the goal of this study was to link activations during emotion to particular cytoarchitectural entities. As shown in Figure 14.4, most of the MCC was not active during simple emotions, while those in perisplenial and perigenual regions were highly active. In terms of MCC, only the aMCC was active during fear, and this focal distribution supports the expectation that cingulate cortex is not uniformly involved in emotion and raises the problem that pain affect is typically thought to be mediated by cingulate cortex.

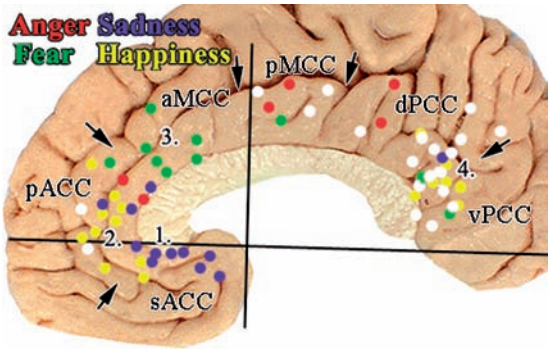

Fig. 14.4 Peak activation sites during simple emotions in the context of the cingulate subregions (Vogt *et al.*, 2003; references in Vogt, 2005). Four groups of active sites are numbered and control conditions with non-emotional scripts and faces are coded with white dots. Each numbered aggregate of sites is located in a different subregion and this suggests a different role in processing of emotional information in autonomic integration, skeletomotor output, and personal orientation as predicted by the four-region neurobiological model.

Information in Figure 14.4 can be taken further in terms of the submodal processing of emotion in the regionalized cingulate gyrus. Emotion submodalities refer to the various aspects of emotion that are coded in different parts of cingulate cortex. These include direct autonomic regulation, storage of valenced memories both positive or negative, and affective behavioral responses such as facial expressions, crying and laughing. Indeed, there are four aggregates of emotion-generated activity numbered in Figure 14.4 and we conclude the following from each one: (1) Activity during sadness is greatest in sACC and this location was first reported by George *et al.* (1995) and Mayberg *et al*. (1999). Importantly, this site of memory storage for negatively valenced events is comprised mainly of area 25 which has many direct projections to subcortical autonomic centers and we generally refer to its function as autonomic integration (Chapters 1 and 10). No other region has these specific connections (Neafsey *et al*., 1993; Vogt *et al*., 1997). (2) Activity during happiness occurs more rostrally and dorsally in pACC. Differentiation of these emotions into subregions of ACC emphasizes their specific role in mediating internal responses to different emotional states. (3) Fear is associated with activity mainly in aMCC. This part of MCC receives amygdala input (Vogt and Pandya, 1987) and the amygdala has been implicated in fear (Whalen *et al*., 1998; Chapter 9) and nociception (Bernard *et al*., 1992). No other cingulate region has high and direct amygdala input as well as a significant role in fear. Furthermore, hypnosis modifies the unpleasantness of a noxious stimulus and alters activation of aMCC in a predictable manner, i.e., as a positive and linear relationship with blood flow (Rainville *et al*., 1999; Faymonville *et al*., 2000; Chapter 17). (4) The vPCC has a high level of activity during happiness and this might be construed as equivalent to pACC, however, the four-region neurobiological model prevents this conclusion. Indeed, vPCC is active during both emotion and non-emotion conditions and this is not true for pACC. The vPCC does not have autonomic projections to subcortical autonomic motor nuclei nor does electrical stimulation evoke autonomic changes. The role of vPCC is better characterized in terms of assessing the self-relevance of emotional events and stimuli; more as an emotional pre-processor (submodality), so that emotional information can gain access to the cingulate emotion regions. Indeed, the vPCC has reciprocal connections with sACC that may assist in establishing the personal relevance of incoming information as discussed in Chapter 13.

Thus, there are regions that specialize for "submodalities" of emotion-relevant activity in cingulate cortex and they sort according to subregions: *sACC*, negative-valenced memories, and direct regulation of autonomic outflow; *rostral pACC*, coding for happiness and possibly generating cardiovascular activation (see Chapter 10); *caudal pACC*, coding for unpleasantness and possibly suffering; *aMCC*, fear coding and regulation of skeletomotor output for avoidance behaviors; *vPCC*, evaluation of the self relevance of happy events from a stream of afferent visual information flow from visual cortices (Vogt *et al*., 2006; Chapter 13). It appears that pMCC and dPCC have little or no role in emotion *per se*. Having plotted pain- and emotion-evoked activations into the same coordinate system as the postmortem histological analyses, we are in a position to consider direct relationships between pain and emotion in the cingulate gyrus.

Pain and emotion linkages

A new perspective on the literature about pain and emotion processing in cingulate cortex is provided by the regional/subregional view of the cingulate gyrus (Vogt, 2005). Indeed, linkages can be made directly on the basis of numerous studies rather than attempting a single group analysis and this provides added confidence of the conclusions. Furthermore, both matches and mismatches with expected parallels between processing in these two distributed networks become more apparent in this context which is now hypothesis driven rather than simply descriptive. By this, it is meant that functional designations for each subregion provide predictable expectations in subsequent studies. Amazingly, the most common pain and simple emotion plots suggest complex relationships between these two modes of cortical processing rather than a simple overlap of negative emotions and pain affect as predicted

from the dual-cognitive model of pain processing (Melzack, 1975). Of course, it needs to be reiterated that these plots are of peak voxel activity from many studies, they do not represent the full extent of activation as shown in Figure 14.1B,C, and the sample literature was based on studies with cingulate activations. In spite of these caveats, the following four observations appear to be justified and raise an intriguing conundrum relating to suffering and happiness. These observations form the basis for the cingulate premotor pain model that will be elaborated throughout the remainder of this chapter.

First, fear and pain sites overlap in aMCC and validate the conclusion that this region is involved in nocifensive behaviors. This systems match occurs in the context of heavy MITN inputs to this region.

Secondly, it is surprising that pMCC does not have consistent emotion activations yet robust nociceptive responses; a mismatch from *a prioiri* expectations. Assuming that nociceptive responses are generally short-latency, it seems reasonable to conclude that these evoke skeletomotor, body orientation to the noxious stimulus without affective (i.e., autonomic) or emotional (i.e., valenced) content. This would likely be mediated via the caudal cingulate premotor area which appears to operate more as a skeletomotor integrator rather than in the assessment of behavioral outcomes using valence-coded information.

Thirdly, visceral nociceptive activity is associated mainly with the pACC, yet this is not the autonomic integrative center like sACC. The four-region model predicts preferential sACC activation during noxious stimulation of skin and viscera and this is one of the most striking incongruities (mismatches) in these observations. Since pain anticipation can reduce blood flow in sACC (Simpson *et al.*, 2001; Porro *et al.*, 2002), this could contribute to a general lack of signal in this region during acute pain. Finally, sad events that evoked sACC activity tended to be associated with personally relevant events and not a simple and external, noxious stimulus. It appears that pain may engage sACC in a person-specific manner and is not limited to somatic stimulation but can also include events associated with remembered painful events.

Fourthly, acute nociceptive stimulation does not activate vPCC as part of a generalized self-relevance assessment. It appears that the MITN-mediated nociceptive signal can bypass processing in vPCC and this latter system is primarily involved in visual stimulus assessment. Thus, emotion activations of vPCC have little to do with pain affect. It should be noted, however, that the limitans nucleus has a strong projection to vPCC as discussed in Chapter 4 and shown in Figure 4.1, and some role in nociception is possible for this subregion.

Nociceptive Properties of Anterior Cingulate Neurons

It is difficult to infer the nociceptive properties of cingulate neurons from the large aggregate responses of functional human imaging and more precise information is available from experimental animals with single neuron discharges. Iwata *et al.* (2005) recorded from neurons in what appears to be the rostral cingulate premotor area on the ventral bank of the cingulate sulcus. Almost 90% of neurons with heat responses to facial stimulation had increased firing during behavioral escape responses. These neurons likely code complex conditions for escape because about 75% had depressed activity during a task that involved detection of the magnitude of illumination, and the authors concluded that cingulate neurons have mainly anticipatory and escape functions in the monkey ACC.

In another monkey study, Koyama *et al.* (2001) evaluated discharges during each phase of a task that involved discriminative responses to visual stimuli that predicted either noxious electrical stimulation or water reward. Of 196 neurons with a task-relevant response, 36 were engaged during the prediction period and can be viewed as having an anticipatory response, although not pain-specific. Seventy-one units were active during the red cue that predicted electrical stimulation and 37 were active during the pain response/avoidance. The positions of many of the responsive neurons were marked with lesions. Although most units appeared to be in MCC, some may have been in caudal parts of ACC. Most of the units in both regions appeared to be in the dorsal cingulate gyrus and in the cingulate sulcus, although it is not clear whether this reflects a sampling bias. Intermingled among these nocifensive units were a separate group of neurons coding for the water reward (visual cue, reward response, pre-reward ingestion periods; 95 of the 196 units with a task-relevant response).

The intermixing of neurons coding for both positive and negative rewards and association with different behavioral consequences indicates a complex intermingling of a least two distinct networks. Although it is well known that cingulotomy lesions in MCC produce analgesia (Ballantine *et al.*, 1967), the work of Williams *et al.* (2004) shows they also disrupt rewarded behaviors. Pre- and post-cingulotomy patients showed that aMCC cingulotomy lesions were associated with the subjects making more errors when there was a requirement to change a movement to garner a reward. In other words, the lesion disrupted the correct pairing of motor output to acquire a reward. This suggests there is *not* a segregated cortical region for nociception/nocifensive processing as often assumed in pain studies but rather a generalized system for selecting among different

behavioral alternatives. This is a surprising observation because the mechanisms of reward and avoidance output are quite different for the two behaviors, i.e., withdrawing from a noxious stimulus versus approaching and ingesting a water reward. Intermixing neurons with different reward properties and motor outputs emphasizes the role of ACC and MCC in selecting among motor outputs rather than simply driving a single output/reflex system.

Based on neurosurgical outcomes and connections with the MITN, we undertook a study in the late 1980's of neuron discharge properties in relation to noxious stimulation in the halothane-anesthetized rabbit preparation (Sikes & Vogt, 1992). The following essential facts became apparent: (1) Neurons in ACC do not recognize where the noxious stimulus is on the body surface because stimulation anywhere on their body can usually evoke a discharge. (2) Neurons respond mainly to noxious stimuli including intense pressure and temperatures over 46°C. Taping of the skin is the only innocuous stimulus to drive these neurons. (3) There is a major aggregate of nociceptive neurons just dorsal and rostral to the genu of the corpus callosum in the rabbit. (4) In a recent study, noxious balloon distension of the distal colon revealed activations that extended beyond ACC into both MCC and retrosplenial cortex and almost 40% of neurons in ACC responded to both cutaneous and visceral distension (Sikes *et al*., 2008).

Figure 14.5 shows three units that were simultaneously recorded from three electrodes in ACC during noxious cutaneous and colon distension. An array of four tungsten electrodes with a 250-µm spacing was positioned simultaneously at different cortical depths for sampling. Extracellularly recorded action potentials from multiple units at each electrode were separated with cluster cutting using principal components analysis and template matching techniques. The point at which responses were significant was determined with a cumulative summation analysis (Cusum) statistic that is associated with a *t* distribution. The Cusum statistic provides a precise determination of the onset of significant responses for each unit and is marked with an asterisk in Figure 14.5. Although all three units responded to noxious cutaneous stimulation, only two (#1 and #3) responded to noxious colon distension and no units responded to innocuous stimulation of either tissue. Since viscerocutaneous responses were 39% and 36% of ACC and MCC nociceptive responses, respectively, they represent an important part of ACC nociceptive responses and they degrade further the ability of single neurons to differentiate the occurrence of a noxious stimulus on a part of the body.

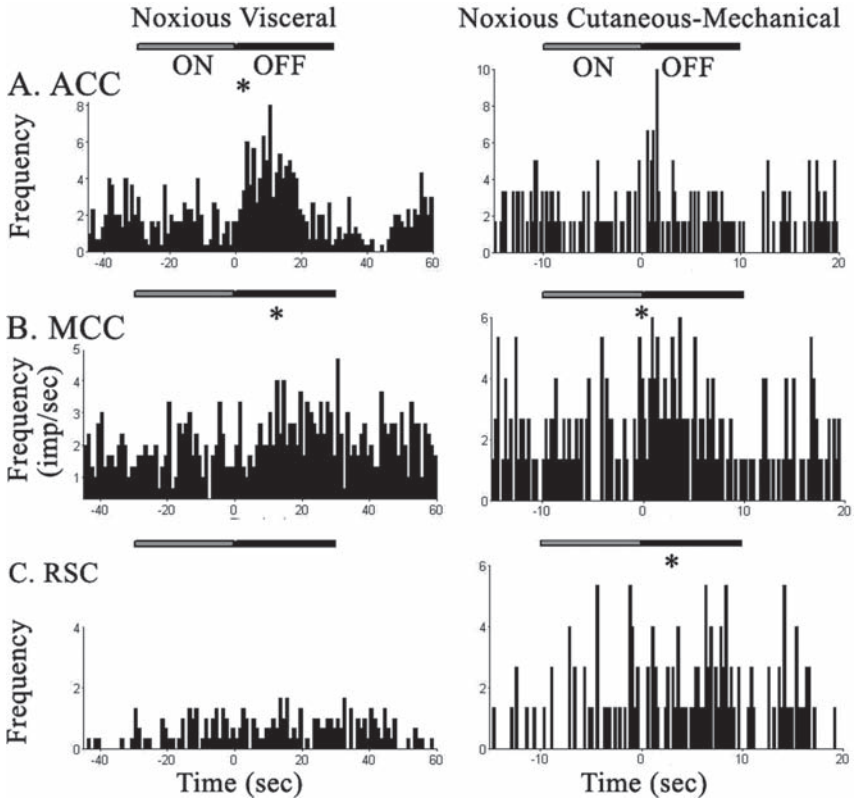

Fig. 14.5 Simultaneous recordings from neurons in each cingulate region. Each column of peristimulus time histograms (PSTHs) was simultaneously recorded with three different electrodes in each region during visceral and cutaneous stimulation (asterisk, significant response; Cusum $p < 0.01$). The onset and offset of innocuous (gray) and noxious (shaded) stimuli are marked with a bar above each response. The shift from prominent visceral drive in ACC to prominent cutaneous drive in retrosplenial cortex is apparent and, therefore, cannot be attributed to variations in the level of anesthetic (from Sikes *et al*., 2008).

The significance of viscerocutaneous neurons is likely found in irritable bowel syndrome as discussed in detail in Chapter 23. The presence of diffuse pain in functional pain disorders including irritable bowel syndrome could be associated with hypersensitivity of viscerosomatic neurons in ACC and possibly MCC. It is also possible that driving of somatic pain systems via the locus coeruleus in fibromyalgia as suggested in Chapter 22 could account for conversion of acute to chronic pain syndromes. Regardless of the final clinical consequences, the viscerosomatic neurons of cingulate cortex provide important linkages for pain affect and coupling of somatic and visceral responsivities.

Three Sources of Nociceptive Driving of Thalamo Cingulate Projection Nuclei

The midline, mediodorsal, and intralaminar thalamic nuclei (MITN) form a complex of about 25 cytoarchitecturally and chemically unique nuclei interspersed among other nuclei and forming the most medial part of the thalamus. Although the cholinergic system may drive the MITN to evoke a state of arousal (Kinomura *et al*., 1996; Steriade, 1996), this does not mean that all activity in the MITN is non-specific as is often assumed. Their functional specificity is emphasized by studies of neuronal discharges associated with eye movements. About 50% of neurons in the dorsocaudal part of the central lateral (Cl) and laterodorsal (LD) nuclei respond to orbital position of the eye and others respond to aspects of saccadic eye movements (Schlag-Rey & Schlag, 1984). These latter investigators concluded, *"Although widespread, the internal medullary lamina connections are not general, and, although complex, the activity of IML cells appears much more specific then originally suspected. If anything, the units described in this report were characterized by the individuality of the firing patterns among neighboring cells. This is exactly the reverse of what one would expect in a mass activation."*

The well-documented responses of cingulate cortex during nociceptive stimulation require a source by which such information can access this cortex. Our hypothesis that the MITN provides the primary source of nociceptive information is based on a number of observations. First, nociceptive responses are short latency within 200 ms of stimulus onset and this may not favor prior processing through other cortical sites, although latency alone does not discount such an alternative. Secondly, as also noted below, some MITN share nociceptive response properties with cingulate neurons suggesting a functional linkage. Thirdly, ablation of most cortical input to the rabbit nociceptive region does not block nociceptive responses, while lidocaine block of the MITN abolishes it (Sikes & Vogt, 1992). Finally, since a wide range of regions are activated during different pain paradigms including pACC, MCC, and dPCC, a source of input is needed that is not highly localized to a single subregion.

Figure 14.6 summarizes the primary sources of nociceptive inputs to cingulate cortex. The Pf refers to the Pf as representative of as many as 10 MITN that receive nociceptive input and project to cingulate cortex (e.g., reuniens and limitans). The three main nociceptive inputs to the MITN arise from the spinothalamic tract (STT; Bovie, 1979; Mantyh, 1983), the pronociceptive subnucleus reticularis dorsalis (SRD; Villanueva *et al*., 1990, 1998), and the parabrachial nucleus (PB; Bester *et al*., 1999; Saper, 2000). Each of these inputs to Pf, reuniens, and limitans likely transmits cutaneous, muscle, and visceral nociceptive signals, and the net consequence of these inputs is that neurons in cingulate cortex have almost full-body receptive fields for cutaneous, muscle, and visceral noxious stimuli.

The large arrow to aMCC in Figure 14.6 indicates that a more dense projection arises from the MITN to aMCC than to ACC and pMCC. One reason for this view is provided by restricted tracer injections made by Hatanaka *et al*. (2003; Figs 4.3 and 4.4) into the rostral cingulate premotor area in aMCC and the caudal cingulate premotor area in pMCC. They showed that the percentage of labeled thalamic neurons in the centrolateral, CM, and Pf nuclei after aMCC injections was 39%, whereas the percentage in these same nuclei following pMCC injections was only 14.6%. The distribution of labeled neurons in motor and nociceptive thalamic nuclei is summarized below in Figure 14.12. This substantial difference suggests a higher level of nociceptive activation in aMCC than in pMCC and differential involvement of the cingulate premotor areas in pain processing.

MITN nociceptive properties

Neurons in the Pf, Cl, Li, VM, and MD nuclei respond to noxious stimulation (Casey, 1966; Dong *et al*., 1978; Peschanski *et al*., 1981). These stimuli include intense pressures such as pinches to the skin with serrated forceps and temperatures over 43°C. Between 75% and 91% of these responses are excitatory and they can be brief (20–100 ms) or involve prolonged after discharges (2–30 s). The receptive fields are very large including one side of the body or the entire body surface and sometimes neurons received both visceral and somatic inputs (Ammons *et al*., 1985). Most studies report limited responses of medial thalamic neurons to innocuous stimuli. The only effective stimuli are brief taps to the skin, and many nociceptive neurons respond to tap (Dong *et al*., 1978). Intensity coding for noxious stimuli has been reported for neurons in monkey thalamus.

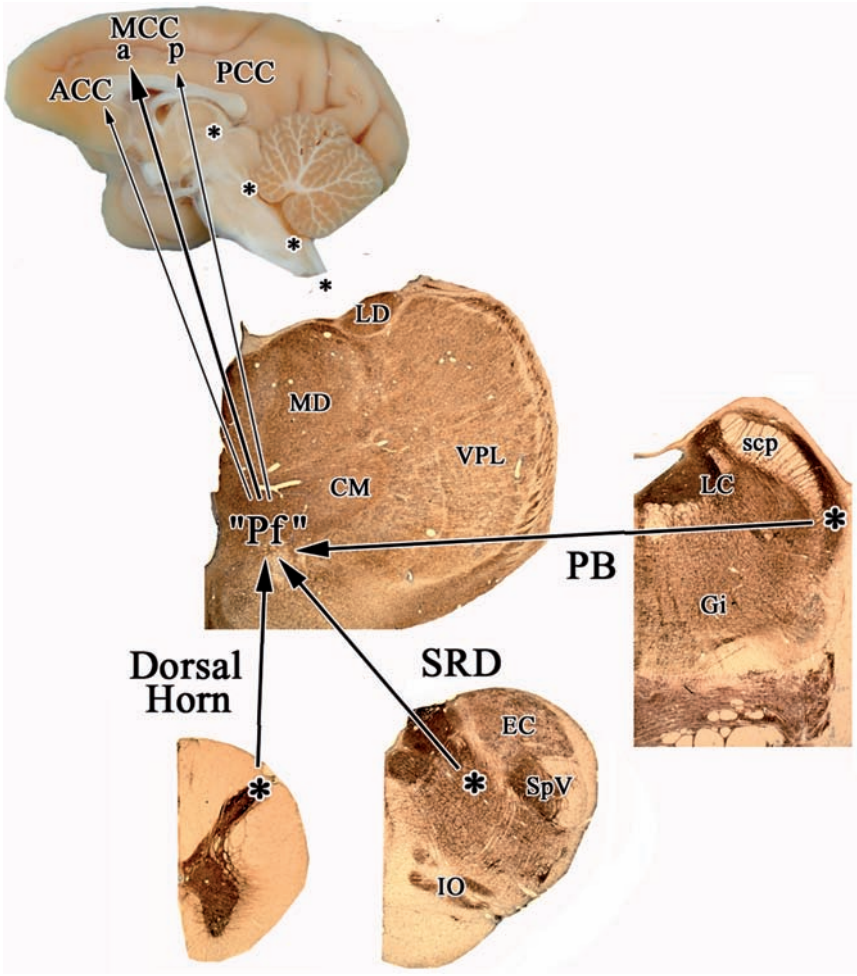

Fig. 14.6 Three major sources of nociceptive inputs to the MITN ("Pf") including the PB, SRD, and dorsal horn. "Pf" represents all MITN, although it is the pivotal one to receive all three inputs. No one thalamic afferent can account for the extensive nociceptive activation of cingulate cortex. Asterisks on the medial surface locate four coronal sections below. LD, laterodorsal; CM, centromedial; MD, mediodorsal; VPL, ventroposterolateral; SCP, superior cerebellar peduncle; LC, locus coeruleus; Gi, gigantocellular nucleus; EC, external cuneate; SpV, spinal nucleus of V; IO, inferior oeine.

One reported that neurons in the medial nuclei of anesthetized monkeys code for the intensity of noxious stimuli (Dong *et al*., 1978) and another showed that intensity coding can occur in the medial thalamus of alert monkeys (Bushnell & Duncan, 1989). Finally, neurons in human Pf respond to noxious stimulation with primarily excitatory and large, usually bilateral receptive fields (Ishijima *et al*., 1975).

The Pf, Cl, Li, and MD nuclei contain nociceptive neurons with large receptive fields and only a subset responded to brief taps. Generally speaking, responses in the halothane-anesthetized rabbit thalamus are similar and examples of our preliminary multiunit, cluster cutting studies with principal components analysis are shown in Figure 14.7. Neuron #1 responded only to noxious distension of the distal colon (55 mmHg pressure) and not to cutaneous stimulation with either noxious pinch or heat. Neuron #2 responded to both noxious cutaneous and visceral stimulation. The onset of the cutaneous response was significantly sooner than that following colon distension. The presence of viscerosomatic response properties is predicted from the work in cingulate cortex itself, they support previous findings, and raise questions about specific relationships between MITN and cingulate cortex discharge properties.

There is not a simple linkage between thalamic neuron discharge onset and properties and those of nociceptive neurons in ACC. Figure 14.8 shows neurons in both regions that were recorded simultaneously. In this paradigm, differences in responses cannot be attributed to variability in anesthetic but must be considered in terms of differential processing such as circuit organization. The cutaneous response in the thalamus leads that in ACC and it shut down more quickly than that in ACC. The noxious colon pressure response in thalamus also led that in ACC, although the cortical response was significantly more robust. This joint activation confirms the linkage between thalamic and cingulate cortical nociceptive responses, however, aspects of the cortical response onset, amplitude, and duration do not reflect a simple coupling of neuron responses.

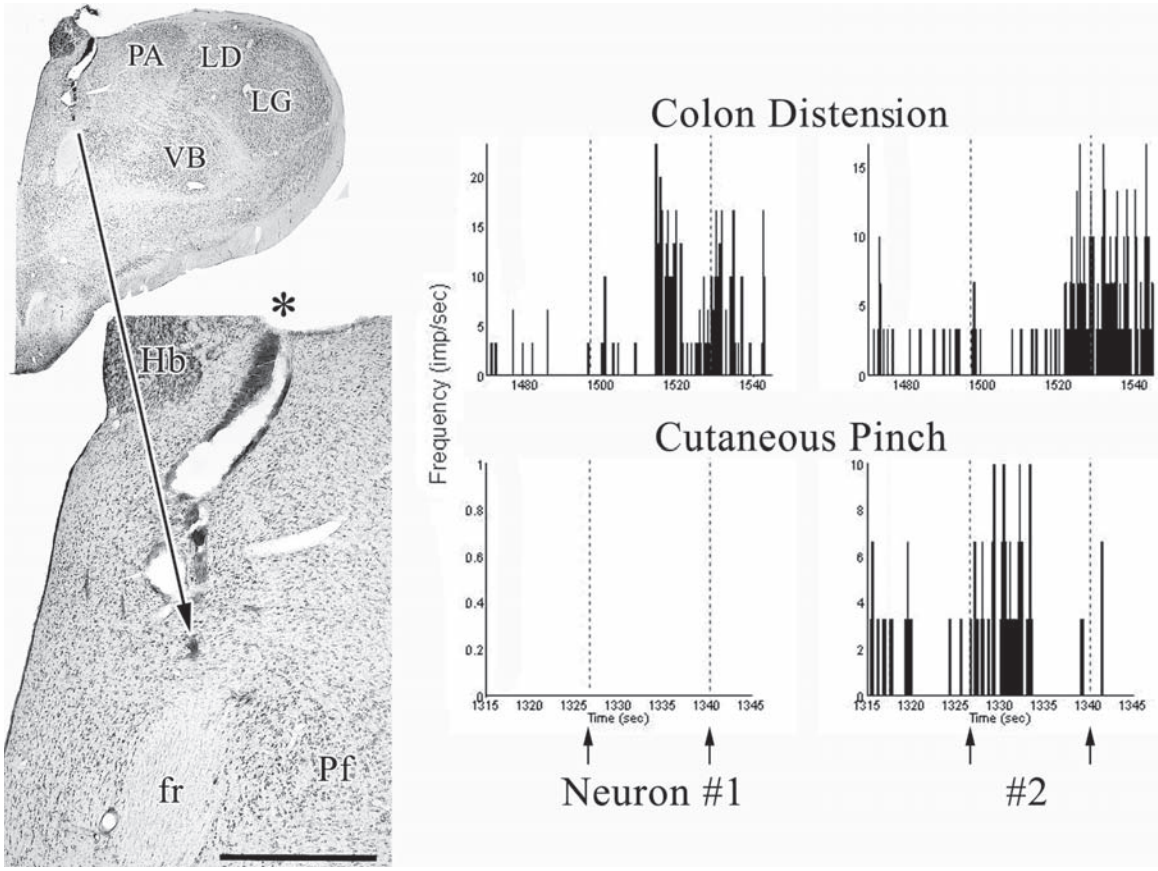

Fig. 14.7 Recordings from two Pf neurons in the rabbit thalamus. The electrode tip is marked with an arrow between the low and high magnification photographs of a thionin-stained section (calibration bar, 500 μm). Neuron #1 responded only to noxious distension of the distal colon (between arrows), while #2 responded to noxious cutaneous and visceral stimulation, with cutaneous onset occurring sooner than that for noxious colon distension. LD, laterodorsal; LG, lateral geniculate; PA, anterior pretectum; fr, fasciculus retroflexus; Hb, habenula; VB, ventrobasal nucleus.

The predominantly excitatory nature of thalmocingulate activation during noxious stimulation may reflect a glutamatergic system. Mullins *et al.* (2005) used proton magnetic resonance spectroscopy to evaluate metabolites including glutamate *in vivo* during baseline and noxious, cold pressor stimulation. They observed a significant elevation of glutamate in ACC during noxious stimulation. Although the sampling time precluded assessing samples for all cingulate regions, this is an important observation in the human for two reasons. First, it directly links cingulate nociceptive activity with excitatory inputs. Secondly, it suggests that glutamate mediates nociceptive responses and this could contribute to chronic pain conditions and lead to cortical neurodegenerative changes.

Spinothalamic tract MITN terminations

Thalamic terminations of spinal cord lamina I in monkey occur in nuclei that were previously shown to project to pACC/MCC including the Pf, Li, and VM (Minciacchi *et al.*, 1986; Vogt *et al.*, 1987). Large injections of horseradish peroxidase that included spinal lamina V labeled additional nuclei that also project to cingulate cortex including Ce, Re, Pv, and Pc (Bovie, 1979; Mantyh, 1983). There is little or no segmental organization of spinal cord inputs to the medial nuclei and some STT-projection neurons have broad receptive field properties. Giesler *et al.* (1981) identified a population of neurons in laminae VI and VII that have receptive fields that are not limited to individual dermatomes, and axons of these neurons have slow conduction rates when compared to those projecting to the lateral thalamus. Thus, the broad receptive fields of deep STT-projection neurons may account for the large receptive field properties of neurons in the MITN. Finally, cFos expression in the rat following noxious peripheral nerve electrical stimulation labels neurons in Pf, Pt, Pv, Re, and rhomboid nuclei (Bullitt, 1990). The Pf is adjacent to the habenulointerpeduncular tract (also

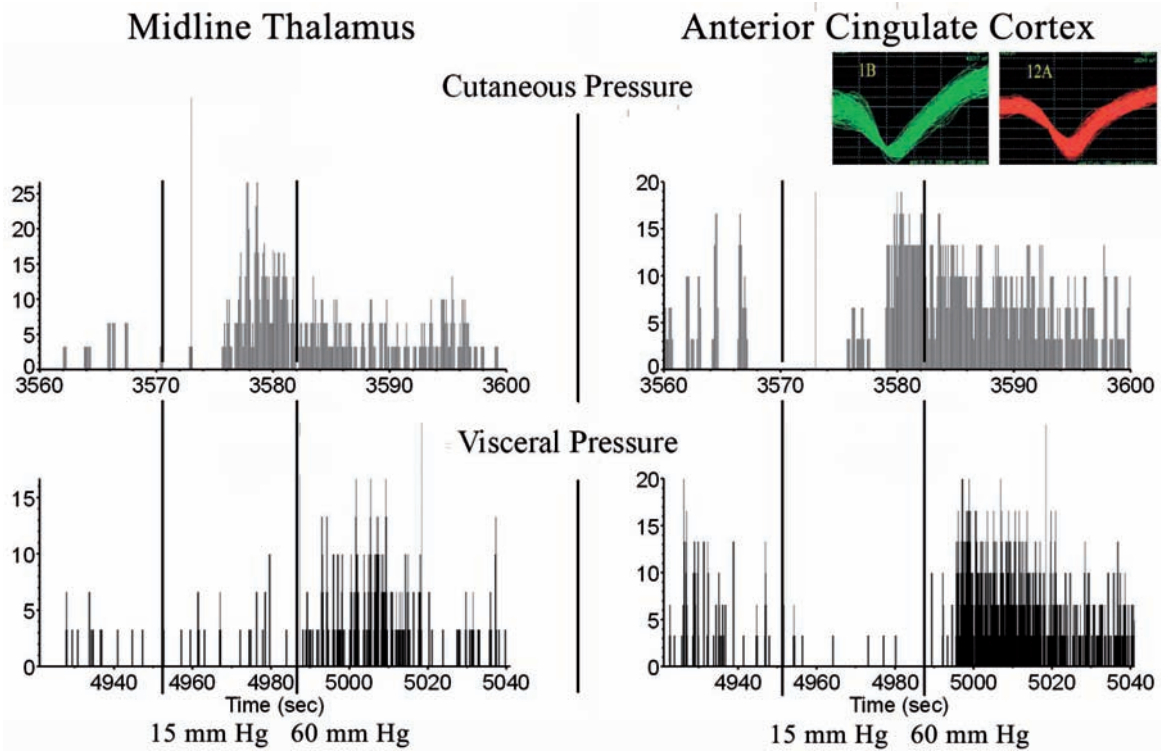

Fig. 14.8 Simultaneous neuron recordings in medial thalamus and ACC during noxious cutaneous (between vertical lines) and visceral (vertical lines are onset of 15 or 60 mmHg pressure) stimuli. Multiunit responses were cluster cut in both regions as shown by waveforms for two units in ACC. Although both neurons in each area were responsive to both stimulations, differences in the onset, shape, and duration of the responses suggest circuitry differences in both regions.

fasciculus retroflexus-fr; see Figs. 14.5 and 14.6) and is comprised of densely packed neurons that express high levels of intermediate neurofilament proteins. This nucleus receives inputs from the STT originating in Rexed's laminae I and V–VIII that project to the medial thalamus (Carstens & Trevino, 1978; Willis *et al*., 1979). About 60% of the lamina I, VII, and VIII projection neurons terminate in the medial thalamus and STT inputs, shown with horseradish peroxidase, terminate in MDpc and MDdc, Cl, supragenicular, subfascicular, Pf, and Pc nuclei have been observed in the above studies. Thus, STT projections appear to aggregate in the MITN and may provide for broad receptive field topography of nociceptive responses. The STT, however, is not the only source of large and nociceptive receptive field inputs to the medial thalamus.

Subnucleus reticularis dorsalis projections to MITN

The SRD may be critical to nociception in cingulate cortex because one means whereby MITN receptive fields attain a large size with a contralateral and rostral somatic bias in these nuclei and cingulate cortex could be due to inputs from SRD to the Pf. Figure 14.9 shows the location of this nucleus and some of its chemoarchitectonic features in the monkey because there are few such studies available and its links to the medial pain system are not generally appreciated. Villanueva *et al*. (1988) reported somatotopic convergence of nociceptive information in rodent and monkey SRD (Villanueva *et al*., 1990). The SRD is a nociceptive-specific region because it is not affected by processing in other sensory domains. Greatest input arises from cervical laminae I, V, VI, VII, VIII, and X, and all spinal cord levels provide input to this nucleus (Villanueva *et al*., 1991), although least comes from lamina I (Raboisson *et al*., 1996). The nucleus caudalis of the trigeminal complex also projects to this reticular nucleus as shown by co-activation of both with noxious facial stimulation (Strassman & Vos, 1993) and connection studies (Zerari-Mailly *et al*., 2001). The SRD plays two key roles in nociception. It contributes to the descending noxious inhibitory system (Bouhassira *et al*., 1992) and it projects to the MITN (Bernard *et al*., 1990). Thus, the SRD appears to be a pronociceptive and non-somatotopically organized system for the transmission

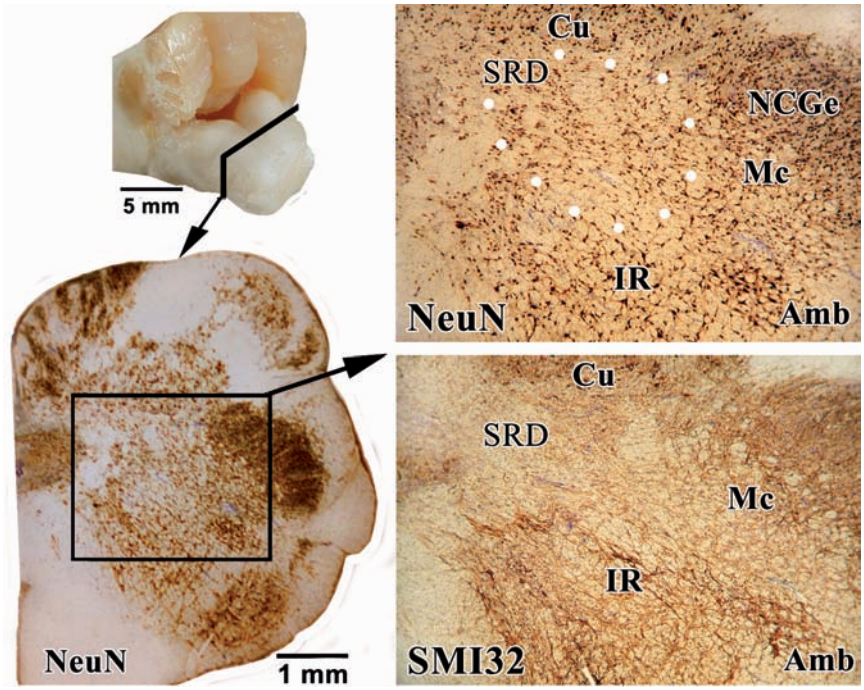

Fig. 14.9 Dorsal view of the floor of the fourth ventricle and level of coronal section caudal to the obex to show the monkey SRD. Higher magnification of NeuN with arrows showing magnified rectangle shows the SRD (white dots) dorsomedial to the intermediate reticular nucleus (IR) and ventral to the cuneate nucleus (Cu). Projections fro SRD to the Pf may account for some of the nociceptive properties of cingulate neurons. NeuN, neuron-specific nuclear binding protein; SMI32, antibody to intermediate neurofilament proteins.

of somatic and visceral nociceptive inputs to the MITN. Although the SRD itself regulates the descending noxious inhibitory system, this may be independent of cingulate activation.

Parabrachial projections to MITN

In view of the dominant role MITN have in generating nociceptive responses in cingulate cortex, the source of broad receptive field properties of these neurons is important and one explanation is inputs that are derived from the parabrachial nucleus (PB). This nucleus is a critical relay site for innocuous visceral afferents from the nucleus of the solitary tract which projects topographically to the PB (Herbert *et al*., 1990). Since there is extensive evidence for nociceptive driving of PB neurons (Bester *et al*., 1995; Menendez *et al*., 1996) and spinal and trigeminal pathways to mediate these responses (Cechetto *et al*., 1985; Blomqvist *et al*., 1989), Saper (2000) proposed that PB is a nociceptive integration center and he considered such a view in terms of insular cortex. Similar views, however, may be considered for the medial thalamus because the PB projects to the central lateral, Pf, and reuniens nuclei in primate thalamus (Pritchard *et al*., 2000) and, as noted earlier, each of these nuclei project to the cingulate cortex. In addition, the cingulate cortex has direct projections to PB that could provide for control of the descending noxious inhibitory system as discussed in detail in Chapter 15. Finally, the synaptic properties of this pathway cannot be easily predicted; however, excitatory, inhibitory, and signal-to-noise changes during vagal nerve stimulation have been generated in the thalamus following injections of peptides into the PB (Saleh & Cechetto, 1993). Thus, a third source of nociceptive information to MITN is viscerosensory from the PB, but it may not be a solely excitatory input and the features of transmission into the MITN and their impact on cingulate activation have yet to be explored.

Cortical MITN Projections

The MITN are the gateway for pain processing in the limbic system in general and cingulate cortex in particular and this has profound implications for which regions are activated and how they contribute to pain-processing events. Such an input may have topographical specificity but, based on human imaging studies, they must provide a source of nociceptive driving for pACC, aMCC, pMCC, and dPCC. No single nociceptive thalamic nucleus provides such a source of input to cingulate cortex. There are, however, a number of MITN that provide for different classes of such input including visceral and cutaneous driving. The monkey MCC appears to receive proportionately more inputs from the MITN than from the AM and VA nuclei. The fact that the MITN projections are widespread does not detract from them as a source of nociceptive inputs. Each termination site in the pain neuromatrix can

employ this information, as well as that from the "specific" thalamic nuclei, in different ways to achieve the individual information processing goals of each region separately.

Of the hundreds of cases we have used to assess cingulate thalamic connections in monkey, rat, and rabbit, the horseradish peroxidase injection into MCC shown in Figure 14.10 is the most important one. A comparison of retrograde labeling following these injections in this case with that in PCC shows the following nuclei project to MCC: Cdc, Clc, Cl, Re, Cif, Cs, VM, Pv, Pt, Pf, Li (Minciacchi *et al.*, 1986; Vogt *et al.*, 1987; see also Chapter 4). The MITN cortical projections are not evenly distributed throughout the cerebral cortex as shown in the cingulate gyrus. Only the mediodorsal, central superior lateral (Csl) and limitans (Li) nuclei project to both ACC and PCC (Vogt *et al.*, 1987). A comparison of retrograde labeling following horseradish peroxidase injections into ACC or PCC shows the following nuclei (nomenclature of Olszewski, 1952) project to ACC: central densocellular (Cdc), central latocellular (Clc), central lateral (Cl), reuniens (Re), central inferior (Cif), central superior (Csl), paraventricular (Pv), parataenial (Pt), Pf, limitans (Li).

Figure 14.10 presents an ACC/MCC horseradish peroxidase injection case and critical thalamic labeling. As this injection was large and encompassed a number of areas, it is necessary to re-evaluate the projections of each nucleus. Also, since the Pf and submedial nuclei in rabbit (Sikes & Vogt, 1992) and Pf, Cl, Re, and Li in monkey (Vogt *et al.*, 1979) may be involved in nociceptive transmission to ACC, it is crucial to evaluate differential inputs to the MITN and through-put to pACC and MCC.

pMCC and dPCC: Nociceptive Sensorimotor Orientation of the Body

One of the most striking outcomes of efforts to link simple emotion activity with that of pain is that one of the most frequently activated subregions during acute pain is pMCC and there is almost no evidence for a role in simple emotions for this subregion; certainly not in fear or sadness (Vogt *et al.*, 2003; Vogt, 2005). From these studies, we conclude that, although pMCC and dPCC are driven by nociceptive stimulation, these subregions may have little to do with emotion and autonomic function and their role in nocifensive behaviors is very early and in pre-emotional responses. If anything, emotional processing of nociceptive stimuli bypasses these two subregions.

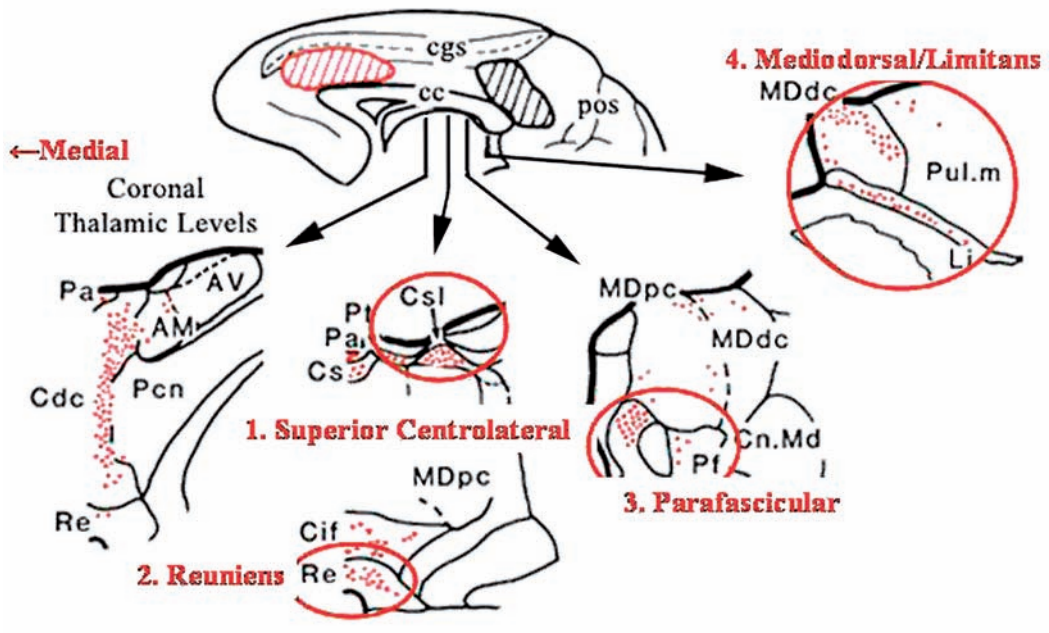

Fig. 14.10 Horseradish peroxidase labeling following ACC/MCC injection (red hatched on medial surface). Ellipses emphasize nuclei with highest density of labeling with each dot equal to three to five projection neurons. This pattern is close to the full extent of MITN projections, of which nociceptive cells are a subset in the four ellipses. The PCC injection (black hatched) is reported separately by Vogt *et al.* (1987).

Nociceptive activation of pMCC and dPCC

Lenz *et al.* (1996; Chapter 18) used noxious, laser stimulation to evoke short-latency (211–242 ms) negative and positive (325–352 ms) potentials from pMCC and smaller ones in dPCC. It is striking that evoked potential observations consistently evoke activity in caudal rather than rostral levels of cingulate cortex and Figure 14.11 summarizes some of these findings. Evoked-potential studies show frequent activation of dPCC and this activity can be associated with movement outside the context of any nociceptive stimulation. In each of five subjects with a head model derived from each individual's MRI, Bentley *et al.* (2003) showed that noxious thermal stimulation to the hand activated posterior levels of cingulate cortex and Fig. 14.11A shows these results co-registered to our postmortem brain; one site was in area p24′, one in area d23, and the other three were in area 23d. Are these sites nociceptive-specific and what is their role in brain function?

Niddam *et al.* (2005) applied noxious and innocuous electrical stimulation to the abductor pollicis brevis muscle and activated two cingulate sites. Both are plotted in Figure 14.11B; one appears to be in area 24d, where the cCMA is located and the other appears in area 23d. Therefore, although nociceptive stimulation activates these sites, they are not nociceptive-specific activations and the activation by muscle stimulation enhances the view these are motor-relevant activations. The motor relevance of these areas is made explicit in a study by Huang *et al.* (2004) who evaluated movement-associated activity during self-paced, finger lifting movements. They showed a site in area 23d of dPCC with MEG as co-registered to our postmortem case in Figure 14.11C. As there was no nociceptive stimulation in their study design, Huang *et al.* (2004) have shown that movement-associated activity occurs in dPCC and this is pivotal to understanding its role in nociception. What then is the source of nociceptive inputs to dPCC and what is the role of these subregions in pain processing?

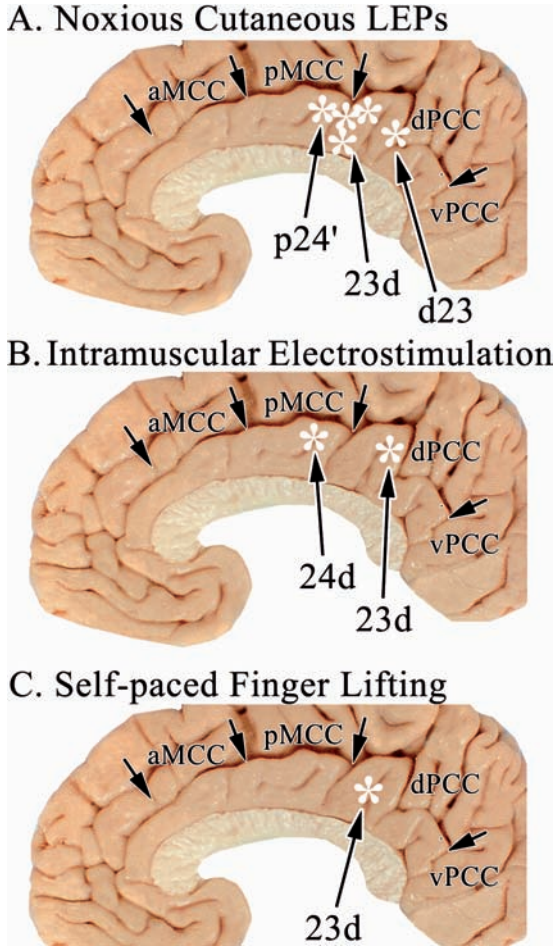

Fig. 14.11 Co-registration of evoked activity from three evoked-potential studies to a postmortem case with cingulate borders identified. (A) Bentley *et al.* (2003), (B) Niddam *et al.* (2005), (C) Huang *et al.* (2004). These studies together suggest a role of internal orientation of the body to sensorimotor events including noxious stimulation in pMCC and dPCC.

MITN input to PCC

Small injections into PCC do not label the full range of MITN noted above. There appear to be only three nociceptive nuclei that project to PCC: MD, Li and Csl (Vogt *et al.*, 1987; Shibata & Yukie, 2003; Chapter 4). The inputs from MD are from parts of MD that may not be positioned to receive STT inputs and it is not certain to what extent nociceptive information is transmitted through MD to PCC. Although a few functional imaging studies have shown nociceptive activation of PCC (Fig. 14.1A), most of them have not observed such activity. It is possible that signals generated by small afferent inputs like those derived from a few thalamic nuclei requires a more sensitive method of observation and better time resolution in relation to noxious stimuli.

Another comment is needed on the source of nociceptive input to PCC. Labelled-line theories emphasize that input from neurons in the ventral MD project to sulcal aMCC and account for specific nociceptive processing (Craig, 2003). This part of MD, however, does not project to PCC (Shibata & Yukie, 2003). It is known that the Li and Csl nuclei project to PCC (Vogt *et al.*, 1987) and Li projects to its dorsal and ventral divisions (Shibata & Yukie, 2003). Thus, these two nuclei may provide nociceptive input to dPCC and it could be of a short latency to mediate orientation responses. Whether or not it is specific to nociceptive activation and this is transmitted to PCC remains to be determined.

Cingulate Premotor Areas in Nociception

Since pMCC and dPCC are not involved in simple emotions and nociceptive-specific affect but do mediate short-latency, motor-orienting responses, the relationships of these subregions to nociceptive and motor circuits needs further consideration; particularly their connections with the caudal cingulate premotor area (cCPMA) that is partly in areas 24d and 23c. The rostral CPMA (rCPMA) and cCPMA lie on both banks of the human cingulate gyrus (Vogt *et al.*, 2004) and on the ventral bank and fundus in the monkey (Vogt *et al.*, 2005). Although these areas are generally referred to as the cingulate motor areas as discussed in Chapter 5, their activity before skeletomotor output and role in many other anticipatory and mismatch detection functions suggests that they are better characterized as premotor areas and we use these terms synonymously. Both CPMAs have topographically organized projections to the spinal cord and they receive different amounts of "motor afferents" from the thalamic ventral lateral and ventral anterior nuclei (Chapter 28). The rCPMA is of interest because it is involved in the general intensions to move in relation to punishment and the anticipation of pain plays an important role in the general intension to move and pain anticipatory functions have been recorded in the monkey (Koyama *et al.*, 1998). Since one of the most frequently activated regions in human cingulate cortex by noxious stimulation is the aMCC (Vogt *et al.*, 2003), it would not be remarkable to find that the rCPMA has a particularly robust nociceptive input. What are the nociceptive circuits of both CPMAs? There are direct and indirect mechanisms of information transfer: direct via the MITN and indirect via nociceptive cingulate gyral projections into the sulcus. These circuits together sculpt different aspects of nociceptive processing in the anterior and posterior MCC and dPCC.

Nociceptive activation of the cingulate premotor areas

There are now three direct lines of evidence for CPMA activation during noxious stimulation. First, Niddam *et al.* (2005) used evoked potentials to show activity that is likely in area 24d which is part of the cCPMA. Secondly, although not recognized as likely part of the rCPMA, it appears that most activity generated by noxious and innocuous stimulation by Moulton *et al.* (2005) was in the rCPMA. The fMRI study of Büchel *et al.* (2002) generated nociceptive activity in part of the rCPMA with stimulus intensity ramps and stimulus perception as well as a wider-spread activation with pain-related activity. Finally, Henderson *et al.* (2006) made an extremely interesting finding when comparing cingulate responses to noxious cutaneous and muscle stimulation in the context of the four-region model. They observed an increase in BOLD signal in the cCPMA during noxious muscle but not noxious cutaneous stimulation. This is the first demonstration of a nociceptive response in the cCPMA with fMRI and it suggests a pivotal link to muscle stimulation and confirms the evoked potential work of Niddam *et al.* (2005). Since we have been unable to identify emotional activations in this same region, it may be that deep tissue nociceptive driving of the cCPMA is linked to orienting the body toward the noxious stimulation rather than generating the affective response *per se*. Since noxious cutaneous stimulation did not produce a similar activation in the cCPMA, it may be that such activity is segregated to the rCPMA.

These observations together suggest that pMCC and dPCC orient the body to sensory stimuli including nociceptive ones and pMCC nociceptive activations may not be specific for noxious stimuli. These observations also suggest a role in internal orienting of the body in relation to noxious stimulation, i.e., an orienting response rather than a sensory or targeted motor response.

Role of the parafascicular nucleus in nocifensive behaviors

The Pf nucleus appears to be at a nodal point for processing premotor nociceptive information; both in terms of its sensory afferents as well as its projections to the CPMAs and striatum (below). A demonstration of its specific role in these functions was made in a study of the delayed vocalizations in rats 2 s after tailshock (Harte *et al.*, 2005). These investigators found that injection of the 5HT1A/7 agonist 8-hydroxy-2-(di-n-propylamino)-tetralin dose-dependently increased the stimulation threshold for evoking vocalizations during and after tail-shock, while not affecting spinal motor reflexes. Although the cannula tract produced significant damage to the cingulum bundle, which itself could influence such behaviors, the vehicle injections were inactive. Thus, blocking activity in the Pf nucleus and its striatal and cingulate projections abolishes nocifensive behaviors and this is pivotal to the cingulate premotor pain model.

MITN projections to cingulate premotor areas

A thorough investigation with multiple labeling shows significant inputs from nociceptive thalamic nuclei to the CPMAs (Hatanaka *et al.*, 2003; Figs. 4.3 and 4.4). Moreover, differences in the MITN to the rCPMA and cCPMA underlie unique profiles of nociceptive inputs. Hatanaka *et al.* (2003) used two retrograde tracers to label inputs to the rCPMA and cCPMA simultaneously. Figure 14.12 shows the percent labeling in different nuclei in this study according to motor nuclei (VA, VL),

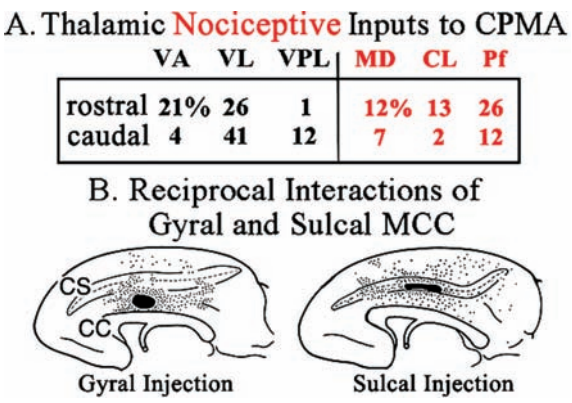

Fig. 14.12 Thalamic and cingulate gyrus connections of the cingulate premotor areas. (A) Summary of Hatanaka *et al.* (2003) in terms of percentages of labeled neurons for three classes of thalamic projections to the CPMAs; motor (VA, VL), somatosensory (VPL), and nociceptive (red; MD, Cl, Pf). The rCPMA has the most profound inputs from nociceptive MITN, while nociceptive projections to cCPMA are less pronounced. (B) Reciprocal innervation between sulcal and gyral cortex emphasizes that gyral nociceptive responses are not independent of the sulcal CPMAs. Here retrogradely labelled neurons following dye injections (solid black areas) were plotted on the medial surface of two monkeys (Van Hoesen *et al.*, 1993).

nociceptive nuclei as discussed above (MD, Cl, Pf), and somatosensory nuclei (VPL). The cCPMA had the highest percentage of "motor" input from VL and limited inputs from "nociceptive" thalamic nuclei. In contrast, the rCPMA had proportionately less input from VL and two to seven times more input from the MD, Cl, and Pf nuclei. These important observations underpin our contention that the rCPMA receives massive nociceptive inputs from the MITN and is involved in avoidance behaviors that are generated by fear and depend on corticospinal projections. In contrast, the cCPMA receives limited nociceptive input from the MITN, it is significantly responsive during noxious muscle stimulation (Henderson *et al.*, 2006), and it is likely engaged with orienting the body to sensory stimulation including nociceptive ones and employing multisensory cues about the body in space to provide this internal orientation. Chapter 13 considers in detail the postulated role of dPCC in such multisensory events.

Gyral and sulcal cortex interactions

Since both sulcal and gyral cortex likely receive nociceptive inputs and respond during noxious stimulation, the notion of interactions between these cingulate divisions may be subtle. It is likely that they mutually enhance nociceptive processing and link it directly to specific predictions and response outcomes. These interactions are quite strong as shown in Fig. 14.12. The retrograde tracers into the sulcal or gyral cortices massively label reciprocally connected regions and this is true for both rCPMA and cCPMA.

In the functional context of MCC, a noxious stimulus alerts the organism to a conflict or mismatch between what was expected and what actually occurred; as would be the case for a change in the reward properties for any movement. Since behavior is organized to avoid noxious stimuli, the occurrence of a noxious stimulus signals a major and unpredicted conflict that must be resolved by future behaviors. Evaluation of the sensory environment, previous experience, alternate motor options, and prediction of outcomes in MCC establishes the motivational properties of a particular movement. Even stress can be viewed as a disruption of conflict monitoring and motor functions. *Noxious stimuli signal a motor outcome mismatch. The circuit mechanisms of conflict monitoring and motor function in the cingulate premotor cortex and adjacent areas help resolve the apparent paradox that one of the most consistent pain activation sites is associated with premotor function rather than a "pain center."*

MITN Connections Synchronize Medial-Limbic Pain System Participants

The medial-limbic pain system is composed of dispersed and independent units at the terminal zone in nociceptive pain pathways and it is advantageous to synchronize such activity by the dominant source of nociceptive inputs to the forebrain. Indeed, the MITN project throughout the medial-limbic pain system and serve a role in providing a nociceptive signal that is used by each region separately for sensory and nocifensive responses. This joint activation of the anterior insula and ACC by the common MITN input has been considered (Vogt & Sikes, 2000). The Li, Pf, MDpc, Re, and Cif nuclei each project to the dysgranular anterior insula (Mufson & Mesulam, 1984; Friedman & Murray, 1986) and ACC/MCC. The topographic differences of MITN projections to the insula were elegantly demonstrated by Friedman and Murray (1986) and the insula and adjacent parasylvian cortex are nociceptive (Greenspan *et al.*, 1999). The amygdala also receives inputs from the MITN (Su & Bentivoglio, 1990; Moga *et al.*, 1995) and is known to be nociceptive as discussed below. Thus, pain as an integrated and conscious perception is likely coordinated by common inputs throughout the medial-limbic pain system.

MITN and CPMA Projections to the Striatum: Another Perspective on Nocifensive Behaviors

The pMCC and dPCC have a compelling role in orientation of the body in multiple sensory spaces toward noxious stimuli. The responses are early, not specific to noxious stimulation because they occur to innocuous stimulation and during finger lifting, and they are free

of emotional processing as discussed above. This very proximal role in internal orientation before movement is supported by projections of both the MITN and the SRD to subcortical motor structures including the striatum. Giménez-Amanaya *et al.* (1995) showed that the ventral and medial part of the striatum receives input from many nuclei that receive nociceptive inputs and neurons that project to cingulate cortex. These include Pv, Pt, Re, Rh, CeM, Csl, and Pf. Much less input arrives from VAmc and MDdc and MDpc. Many of these same projections were reported by Royce *et al.*, (1991) and Sadikot *et al.* (1992). Although with less intensity, many of these nuclei also project to the nucleus accumbens (Giménez-Amanaya *et al.*, 1995), where they could engage in terminating reward relevant responses.

Since the SRD receives somatosensory and motor cortex inputs (Desbois *et al.*, 1999), it has a role in sensorimotor functions that may include its projections to the Pf (Villanueva *et al.*, 1998). Thus, there is a strong link among the nociceptive MITN and the striatum and cingulate cortex that enhances their mutual engagement in motor functions at both cortical and subcortical levels of output.

Projections of the CPMAs are to different parts of the basal ganglia; particularly the striatum (Takada *et al.*, 2001). This projection provides a site of overlap with different parts of the skeletomotor system and likely helps to differentiate the functions of two different and parallel motor systems. The rCPMA projections overlap with those of pre-SMA, while the cCPMA has projections that overlap with primary motor cortex. Thus, the CPMAs operate in parallel with different cortical motor areas. To the extent that each are involved in different aspects of pain processing, their output likely defines different nocifensive behaviors.

The Cingulate Premotor Pain Model

The primary rationale for summarizing the extensive nociceptive activation and circuitry of cingulate cortex in this chapter is to provide a backdrop for integrating this wide range of facts into a single functional model. The model must account for how cingulate cortex sorts nociceptive information, integrates it with past experience to anticipate and avoid such stimulation when possible and generate a response when necessary within less than 15 s. Although cingulate cortex is part of the pain neuromatrix and may contribute to coding of pain intensity and unpleasantness, its primary and unique contribution to pain processing, i.e., its final

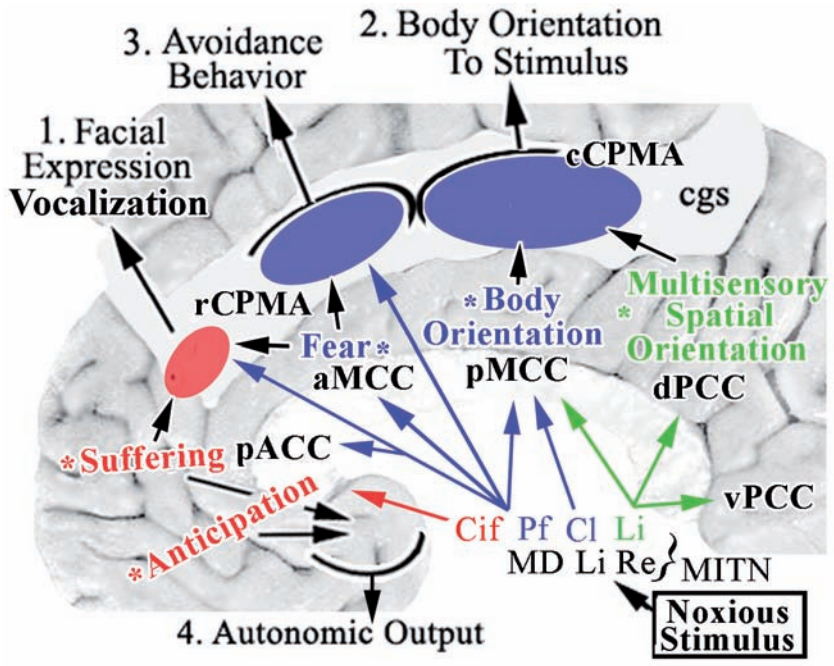

Fig. 14.13 The Cingulate Premotor Pain Model in three tiers of information processing. Tier 1: Cingulate processing is initiated with a noxious stimulus driving the MITN. Some nuclei are common to all cingulate areas (black; MD, Li, Re) and some have preferential driving of ACC (red, Cif), MCC (blue, Pf and Cl), and PCC (green, Li). Tier 2: each contribution of cingulate gyral areas is shown and highlighted with asterisks. Tier 3: Medial surface cortex dorsal to the cgs was cut and moved dorsally to expose the rCPMA and cCPMA in the cgs. The rCPMA was divided into a rostral part with the face/head representation (red ellipsoid) and trunk/limbs (blue ellipsoid), while the entire cCPMA is shown with a single, blue ellipsoid. The four motor outputs are numbered in an approximate sequence beginning with the earliest and ending with the longest duration responses.

and pain-relevant output that distinguishes it from other parts of the pain neuromatrix, is in its preprocessing of submodalities of emotional and sensory information, convergence with long-term memories of valenced objects and events and its net output via autonomic and skeletomotor projections. To accommodate both its pain "perception" and nocifensive functions, we present a formal model with three tiers of processing and these are summarized in Figure 14.13. The goal is to identify the unique contributions of cingulate cortex to pain processing, rather than its shared functions with other structures in the pain neuromatrix. This approach is now possible because human imaging studies are resolving functions at a level of temporal and spatial resolution capable of detecting changes likely associated with single premotor areas as reviewed earlier.

Tier 1: Noxious stimuli trigger and synchronize a series of events throughout cingulate cortex that are mediated by activation of the MITN. This input is shown in Figure 14.13 as a group of three projections that differentiate to some extent nociceptive inputs to different parts of the primate cingulate cortex. This summary is based on a number of works including the review of thalamocingulate projections in Chapter 4 (Vogt *et al*., 1987; Shibata & Yukie, 2003). According to this summary, the Li, Re, and MD nuclei project to all parts of cingulate cortex; it is not assumed that all MD projections are nociceptive. Some particularly dense projections arise from the central inferior nucleus to ACC, the Pf to aMCC, the centrolateral (Cl) to pMCC, and the Li to pMCC and PCC. Notice the particularly profound Li input to vPCC shown by Shibata and Yukie (2003; Chapter 4). These differential nociceptive inputs initiate a sequence of events on the cingulate gyrus that associate noxious stimuli with contextual information and internal states driven from Tier 2.

Tier 2: The cingulate gyrus has certain intrinsic information processing functions that are triggered by nociceptive afferents including emotion and sensorimotor orientation of the body. The specific functions and their localizations are identified with asterisks in Figure 14.13 and include the following: anticipation, suffering, fear, body orientation to the stimulus, and multisensory orientation in space. This information is then used by the CPMAs in Tier 3 to generate responses that are relevant to predictions about the stimulus or an impending noxious stimulus.

Tier 3: Motor output systems are the essence of the cingulate cortical contribution to pain processing in the pain neuromatrix. Each output function is driven by inputs from Tier 2, i.e., gyral-sulcal interactions discussed above and shown in Figure 14.12. The four output systems are shown by number in the figure according to the assumed temporal engagement of each:

1 Facial expression mediated by the head area of the rCPMA.

2 Orientation of the body to the noxious stimulus via output of the cCPMA.

3 Avoidance/nocifensive behaviors mediated mainly by the torso and limb parts of the rCPMA.

4 Autonomic output from ACC associated with anticipation and/or suffering associated with the actual stimulation.

Although not numbered in the figure, there may be an ongoing association of the noxious stimulus with the overall multisensory context via activity in PCC. This process is organized and driven by many sensory inputs including those through the posterior parietal lobe and these links are discussed in detail in Chapter 13. Such information processing provides a multisensory context within which possible responses are evaluated in terms of predicted outcomes.

According to the cingulate premotor pain model, the earliest outputs are likely generated in the rCPMA and cCPMA for facial expressions and internal and skeletomotor orientation of the body to the noxious stimulus. It is likely that the earliest output of the rCPMA is the facial expression of pain that signals to conspecifics the internal state of suffering. The increase in suffering could be associated with a reduction in "happiness" in pACC and this, along with fear, evokes facial expressions of anguish that are associated with pain sensation and nocifensive behaviors. The head part of the premotor homunculus in rCPMA is in the rostral pole of the cgs (Morecraft *et al*., 1996) and is particularly well localized for generation of facial expressions relevant to pain and other emotions.

The assessment of faces associated with pain expressions with increasing pain intensities has been reported (Prkachin, 2005) and has been utilized for an imaging study during the viewing of facial expressions of pain (Botvinick *et al*., 2005). The activation in the latter study was mainly in aMCC and did not occur in the rostral cingulate sulcus in pACC as predicted from the four-region neurobiological model. It appears that the activity recorded in aMCC is associated with the subject themselves selecting a premotor response for a similar event. In this context, the conspecific interprets the face and vocalizations and prepares to share in similar behaviors and it is known that "pain empathy" is associated with activity in MCC (Jackson *et al*., 2006). A similar empathy is observed in monkey troops when a predator is attacking the pack. Pain expressions with the face and fearful vocalizations are a means of both communicating and protecting the group (MacLean, 1990). It appears these mechanisms of communal protection are present in all primates and pain signals are potent mediators of such responses.

Premotor activity in the PCC is interpreted in a different context than that in ACC and aMCC. Relevant information is derived from dPCC for orientation of

the body including in visual space and pMCC as well provide two inputs that likely drive the cCPMA (Vogt *et al*., 2006; Chapter 13). Support for this view comes from Richer *et al*. (1993) who electrically stimulated the posterior cingulate region around the splenial sulci in epileptic patients and evoked complex proprioceptive sensations in the form of bilateral feelings of levitation unaccompanied by movement.

The noxious stimulus may evoke fear in aMCC as an assessment of context and predictions of the assortment of possible avoidance behaviors and outcomes before triggering a particular body movement through the rCPMA. Finally, the autonomic output is shown in the model with suffering emotion and anticipatory modulation of ACC. Although the specific role of this region in autonomic function is discussed in Chapter 10, it should be noted that pain anticipatory responses may actually reduce pACC activity in a region that when stimulated produces a reduction in heart rate and hypotension. Thus, anticipation of pain that generates inhibition in ACC could increase cardiovascular function temporarily. The role of cingulate cortex in anticipation of expected and unexpected noxious stimulation is discussed in detail in Chapter 16.

The Cingulate Premotor Pain Model proposes that three cingulate subregions play a unique role in pain processing: pACC in affect/unpleasantness, aMCC in fear/avoidance behaviors, pMCC and dPCC in orienting the body to the noxious stimulus and the body in space that precedes emotional information processing. Interestingly, a study by Mohr *et al*. (2005) shows three parts of cingulate cortex are differentially activated by either externally or self-administered noxious stimuli. Although their conclusions refer to single activation sites rather than three structure/function units, they show the following: (1) pACC is increasingly activated during self-administered noxious stimulation, (2) aMCC is activated independent of the mode of stimulation, (3) pMCC is active during the application of externally generated noxious stimuli. Indeed, this outcome is exactly as predicted for the subregional functions of the cingulate cortex. Particularly heartening is the driving of pMCC by external stimulation and the unavoidable unpleasantness generated by self-stimulation and activity in pACC. The high-resolution fMRI studies of Mohr *et al*. (2005) and Büchel *et al*. (2002) provide support for the above model as well as the spatial precision needed to study subregional functions of the cingulate gyrus.

The Limbic Medial Pain Neuromatrix: The Next Generation

The tsunami of human functional imaging research over the past decade has brought a huge body of information relating to the functions of different parts of cingulate cortex in nociception and pain processing, emotion, executive functions, and autonomic and skeletomotor outputs. In view of this extensive literature on the infrastructure and essential functions of cingulate cortex, where are we headed in terms of pain research focused on the medial-limbic pain system? The relationships between cognitive and pain processing are still poorly understood as are relations between punishment and reward and how cingulate cortex resolves conflicts among multiple approach and avoidance behavioral options in the context of overlapping intracingulate networks. The intracingulate circuits and their regulation by opioids and opioid drugs are not known. The mechanisms of processing in subcortical and cingulate gyral structures are still poorly understood because imaging provides a "surface" view of brain changes rather than their cellular source and neurochemical content. Specific interactions such as the inhibitory actions of anticipation on ACC are not understood nor are interactions with cardiovascular output.

We do not understand the role of most corticocortical circuits in pain processing; not even those in the parietal lobe. Evoked potential research has not yet considered the involvement of particular parietal lobe projections to the cingulate gyrus in pain processing. Interestingly, one of the key rationales for distinguishing the MCC from ACC was differential parietal lobe connections as reviewed in Chapter 1. In addition, one of the most frequently shown cingulate connections in generic models of pain processing is with the insula; yet the anterior insula has never been shown to transfer nociceptive information to cingulate cortex or *vice versa*. Reporting the presence of a connection in anatomical studies does not assure that a particular connection is involved in nociceptive processing and fails to consider the broad range of non-nociceptive processing by cingulate cortex and the anterior insula. Experimental demonstration of the content and direction of information transfer between the cingulate and insular cortices remains a significant challenge.

The pain neuromatrix is only one network to which the cingulate cortex contributes. It is a member of premotor, visuospatial, reward, emotion, mental, Theory of Mind, and consciousness networks. A critical challenge for the future is to determine the unique contributions of cingulate cortex to all of these networks and identify the mechanisms by which cingulate cortex shifts processing among them to generate responses that are consistent with historical experience, context, internal states, and predicted outcomes. Mismatches in the selection process among functional networks may lead to anxiety, depression and obsessive–compulsive symptoms. The emotional consequences of impaired cingulate functions raise the challenge for therapeutic interventions in pain/stress syndromes that are mediated by cingulate cortex.

The greatest challenge, of course, is to understand the specific neuronal mechanisms that subserve chronic pain and stress states. We do not fully appreciate how cingulate cortex functions are disrupted by chronic pain and stress, the underlying neurochemical changes or the extent to which drugs and cognitive-behavioral therapy may ameliorate such conditions. Needless to say, the psychiatric consequences of altered cingulate functions are relevant to chronic pain and include depression and anxiety, yet the relationships between pain and these syndromes in subregions of the cingulate gyrus remain a mystery.

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