CHAPTER 22

Shared Norepinephrinergic and Cingulate Circuits, Nociceptive and Allostatic Interactions, and Models of Functional Pain and Stress Disorders

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Chapter contents

The cingulate cortex and locus coeruleus (LC) are reciprocally connected and they share many common functions including mediating aspects of fight-or-flight responses. Indeed, one of the primary functions of the LC is to coordinate these responses via projections throughout the limbic/emotional motor systems including those to cingulate cortex. Although the fight-or-flight responses are often referred to as acute 'stress' responses, 'stress' is generally associated with negative physiological outcomes and McEwen and Lasley (2002) suggest the term 'allostasis' for normal autonomic responses during fight-or-flight behaviors, while pathological changes are associated with chronic stress or 'allostatic load.'

A number of observations support the role of anterior cingulate cortex (ACC) in allostasis and chronic stress. The Stroop interference task has been used to generate allostasis by Gianaros *et al.* (2005) and they showed a correlation between mean arterial blood pressure and functional activity mainly in pregenual ACC. Lesions of ACC block gastric ulcers caused by restraint stress in rats (Henke, 1983). Intermittent footshock and restraint stress enhance cFos expression in pACC area 32 (Sawchenko *et al.*, 2000; Rosene *et al.*, 2004). Finally, maternal withdrawal in monkeys generates changes in metabolism in cingulate cortex and metabolism in part of area 32 is negatively correlated with cortisol levels (Rilling *et al.*, 2001).

Evidence for the involvement of norepinepheinergic (NEergic) systems in allostasis and chronic stress is overwhelming. (1) The LC projects massively to the paraventricular hypothalamic nucleus (PVN) which regulates the pituitary response to allostasis including release of adrenocorticotrophin hormone (ACTH) and the LC is active during chronic stress (Sawchenko *et al.*, 2000). Corticotropin releasing hormone (CRH) is pivotal in hypothalamic responses during allostasis and is released from the central nucleus of the amygdala (CeM) in the LC (Valentino *et al.*, 1993; Van Brockstaele *et al.*, 2001) and from the PVN in the anterior pituitary gland. (2) Restraint and white-noise evoke LC discharges associated with generalized behavioral arousal (Abercrombie & Jacobs, 1987) and part of this response is due to excitatory CRH inputs to the LC (Jedema & Grace, 2004). (3) Disturbances in chronic stress disorders are linked to altered visceral and LC functions and impairments in LC activity implicate it in sleep disturbances, hypervigilance, and altered startle reflexes (Aston-Jones *et al.*, 1999). (4) The LC responds during low amplitude colon distension via a CRH mechanism (Lechner *et al.*, 1997), NEergic systems are involved in visceral disorders, and Barrington's nucleus mediates micturition and other pelvic floor functions and projects to visceral brainstem nuclei (Valentino *et al.*, 1998). (5) Chronic administration of monoamine uptake inhibitors and the atypical antidepressant mianserin greatly reduce sensory-evoked, bursting activity in the LC (Grant & Weiss, 2001) and drugs that reduce LC discharges (clonidine, phenelzine, imipramine) improve posttraumatic stress disorder (PTSD) symptoms and reduce nightmare, flashback and intensive recollection frequency (review, Aston-Jones *et al.*, 1994).

Key links between chronic pain and stress

In addition to a common role in allostasis, cingulate cortex and the LC are driven by similar cognitive processing modes and noxious stimuli as discussed in detail below. The co-activation of these structures by acute noxious stimulation is important because this could serve to link pain and stress and eventually should lead to an understanding of the forebrain network that is vulnerable to chronic pain and stress syndromes. The midline, mediodorsal, and intralaminar thalamic nuclei (MITN) are a primary source of nociceptive information to ACC and midcingulate cortex (MCC; Chapter 14; Vogt *et al.*, 1987; Vogt, 2005), while for the LC it is the paragigantocellular nucleus of the reticular formation (PGi; Ennis & Aston-Jones, 1988; Ennis *et al.*, 1992) and to a lesser extent the spinal cord (Westlund & Craig, 1996).

When considering the role of cingulate cortex in chronic pain and stress, it is paramount that the output of the MITN be considered. Rinaldi *et al.* (1991) showed that patients with deafferentation pain including post-herpetic neuralgia, radiculopathy, and spinal cord injury have hyperactive neurons in the MITN. These hyperactive responses may be a marker for forebrain changes associated with chronic pain and they likely enhance excitatory drive in the ACC and MCC to which these nuclei project. The projections of ACC and MCC to the LC may be pivotal in further driving allostatic circuits.

The parafascicular nucleus (Pf) of the MITN and the periaqueductal gray (PAG) are both nociceptive and both receive dense cingulate and LC inputs. The Pf and PAG both contribute to descending pain control and receive cingulate afferents (Marchand & Hagino, 1983); a pathway that is reciprocal (Mantyh, 1983). Electrical stimulation of the Pf generates mainly excitatory responses in the PAG as does noxious heat or pressure stimulation of the skin (Sakata *et al.*, 1988). In addition, electrical stimulation in the periventricular gray matter, which likely includes this descending system, is associated with pain reduction in chronic pain patients (Richardson & Akil, 1977). To the extent that the Pf and PAG are both nociceptive and both receive cingulate and LC inputs, they represent a major site of vulnerability for chronic pain and stress syndromes.

The wide NE innervation of the forebrain arises from the LC and selectively to the paraventricular thalmic (Pv) nucleus from the A1 and A5 nuclei (Byrum & Guyenet, 1987; Woulfe *et al.*, 1990). As discussed below, the LC, Pv, and A1/A5 nuclei receive spinal, nociceptive and nucleus of the tractus solitatrius (NTS) cardiovascular afferents. They respond to acute noxious stimulation and either interact with cingulate cortex directly (LC) or indirectly via the thalamus (LC, Pv, A1/A5). NEergic projections also interact indirectly via key cingulate autonomic output sites including the CeM, lateral hypothalamus (LH), PAG, and parabrachial (PB) nuclei. Thus, *the role of cingulate cortex in chronic pain and stress may be determined by direct impairment of cingulate function, disruption of its NEergic afferents, and/or alterations in NEergic subcortical circuits where it interfaces with NEergic projections from the LC.*

Reciprocal locus coeruleus–cingulate interactions

There are direct and reciprocal connections between NEergic systems and the cingulate gyrus that could be associated both with mutual information processing modes as well as pain/stress-induced alterations. The descending cingulate projections to the LC have been shown in monkey and cat (Chiba *et al.*, 2001; Room *et al.*, 1985). Nociceptive MCC is in a position to drive the LC and this descending influence could be pivotal to determining vulnerabilities to chronic pain and stress. As NEergic inputs to the cingulate gyrus are moderate and diffuse, another route by which the LC might modulate cingulate function is via inputs and outputs of subcortical systems such as the MITN, hypothalamus, amygdala, PAG, and PB. Indeed, cingulate cortex may engage in conjunction with the LC in other regions to produce alerting, conditioning, memory, and autonomic and somatic motor responses. These direct reciprocal and subcortical interactions provide a logical context in which to study network organization and dysfunction in chronic states of activation.

Diffuse/non-selective 'versus' dense/selective LC innervations

It appears that every structure in the brain receives at least some LC input (Foote, 1997). Indeed, this wide innervation pattern lead the latter investigator to conclude, 'There is no readily evident organizational scheme for this vast efferent arbor which encompasses every major level of the neuraxis, with the basal ganglia being the only major brain region that is not substantially innervated.' Thus, this wide innervation pattern has lead to the conclusion of general functions rather than roles in particular brain functions. Without detracting from the fact that the LC/NEergic system is widely distributed, here we raise an alternative hypothesis and emphasize those targets of the LC that have the heaviest innervation and consider the consequences of these innervations as associated with cingulate-specific and selected coordination of functional systems. Indeed, we calculated the densities of different

NEergic innervations to emphasize that within the wide distribution pattern, there are structures that receive prominent innervations and these provide for a primary role of the LC in particular functions including coordination of fight-or-flight responses and are the likely substrate for selective vulnerabilities to chronic pain and stress syndromes. For example, the LC projects throughout the PAG, yet activation of this input selects for fight-or-flight behaviors involving both skeletomotor and sympathetic activation (Bandler & Keay, 1996; Vaughan *et al*., 1996). One can view LC projections throughout the central nervous system in the same way as those to the PAG. Although all parts of the CNS receive some level of NEergic input, there are a limited number of targets that receive particularly dense inputs and define its primary role in integrating fight-or-flight behaviors throughout the limbic/emotional motor systems.

It is a telling fact that most of the heavily innervated telencephalic structures by the LC have important links with cingulate cortex and functions. Thus, the immunohistochemical analysis below identifies those structures with heavy innervations from the LC and then evaluates their joint cingulate innervation and the role that both LC and cingulate systems have in mediating different aspects of fight-or-flight responses. This approach leaves us with a detailed understanding of what allostasis means and which circuits are likely the most vulnerable to chronic pain and stress syndromes.

Rationale and Goals of this Chapter

The cingulate cortex is involved in emotion, response selection, and aspects of fight-or-flight rather than homeostasis and the LC has been implicated in similar functions, it receives direct cingulate inputs, and it mediates acute nociceptive and chronic stress responses. Many human neuroimaging studies demonstrate these functions in cingulate cortex and shows impairment in cingulate activity in patient populations with chronic stress disorders (Chapters 21 and 23). As the LC is a small structure, it is not possible with current imaging modalities to evaluate the specific functions and impairments of the LC and other thalamic, hypothalamic, and mesencephalic nuclei with the same resolution. The primary goals of this chapter are to evaluate the shared circuits of NEergic and cingulate cortex along with their mutual functions, evaluate their alterations in chronic pain and stress syndromes and provide the first systematic circuit models by which to interpret this disparate literature in the context of nocigenic- and psychogenic-driven stress disorders. The critical links between cingulate cortex and subcortical stress circuits are not well understood and these models provide the first effort to interweave how cingulate cortex and the LC interact with specific subcortical targets. The specific goals of this chapter are the following:

1 Review the basic neuroanatomy of the hypothalamic-pituitary-adrenal gland axis (HPA axis) in relation to LC and cingulate cortex connections.

2 Assess the 'hot spots' of LC projection targets and evaluate them with qualitative and quantitative immunohistochemistry for the NE synthetic enzyme dopamine-β hydroxylase (DBH). In addition to the DBH distribution in cingulate cortex, the subcortical nuclei of particular interest are those with dense DBH innervation and inputs from cingulate cortex including the thalamic Pv, limitans and Pf nuclei, CeM, lateral PB nucleus, and ventrolateral PAG.

3 The basic neurophysiology of the LC is reviewed in terms of its two primary modes of discharge (tonic and phasic) and their associated behavioral states. Functional interactions with cingulate cortex are then considered as the LC is heavily dependent on cingulate afferents to establish these modes of neuronal activation.

4 Nociceptive driving of the LC and cingulate cortex is reviewed as are the sources of such afferent drive and a model is provided summarizing these circuits. These circuits serve a pivotal role in nocigenic mechanisms of chronic stress conditions and the vulnerability of particular structures to such syndromes is determined to a large extent by the overlap of pain and stress circuits.

5 Review the role of pACC in allostasis and the blunting of its function in chronic stress disorders such as posttraumatic stress disorder (PTSD).

6 Review the hyperactivation of aMCC by fear, anxiety, and anticipation of pain in functional pain disorders such as irritable bowel syndrome.

7 Present nocigenic (sensory bottom up) and psychogenic (cognitive top down) models of chronic stress circuits in the context of altered cingulate activations and inactivations. The contribution of the LC and subcortical regulation of autonomic functions is considered in the context of stress sensitization. Although the neurochemical mechanisms in each node of the model are not yet known, these models provide a first overview of the work that must be undertaken to understand the role of cingulate cortex in chronic pain and stress syndromes.

Interactions of the sACC and LC with the HPA Axis

The human research literature approaches acute and chronic stress in two parallel pathways; one associated

with cerebral cortical responses as supported with functional imaging and a second approach mediated by the HPA axis and hormone and receptor binding studies. As these stress substrates do not operate in isolation and chronic pain may drive some allostatic systems and vulnerabilities to allostatic loads (chronic stress), explicit links of cingulate cortex and the HPA axis need to be established. The most direct connection between these two systems would be the projection from ACC to the hypothalamus. However, the PVN, which mediates the HPA response, does not receive direct cortical inputs (Armstrong, 2004). Rather, the lateral hypothalamus (LH) receives glutamatergic (Glu) inputs from cingulate cortex. Kita and Oomura (1981) showed that medial prefrontal cortex, including areas 25 and 24, project to the LH and electrical stimulation in this region evokes excitatory/inhibitory and pure inhibitory responses; 44% of the latter were consistent with monosynaptic inhibition. Since projections of the LH to the PVN have been reported (Berk & Finkelstein, 1982) and they appear to be Gluergic (Csaki *et al*., 2002), the likely intermediate projection in this system linking the ACC and PVN responses is via an excitatory projection of LH to the PVN. A more complex disinhibitory interaction is also possible in view of the large proportion of cortical monosynaptic inhibitory inputs to the LH, although the specific contribution of cingulate cortex in this circuit is not known. A similar projection of ACC, mainly from areas 25 and 32, to the LH has been shown in the cat (Room *et al*., 1985) and monkey (Chiba *et al*., 2001). Finally, restraint stress increases cFos activity in the PVN (Figueirdo *et al*., 2003). These findings are summarized in Figure 22.1 and suggest a two neuron excitatory chain between the ACC and PVN. Sawchenko *et al*. (2000) activated this system during restraint and footshock-induced stress but not by cytokine exposure.

Electrical stimulation studies support mediation of the hypothalamic functions by ACC. Thus, stimulation of sACC area 25 reduces heart rate, while area 32 and possibly area a24' increase heart rate. Burns and Wyss (1985) showed that the largest hypotensive responses were evoked from area 25 in anesthetized rats and Fisk and Wyss (2000) injected lidocaine into the lateral hypothalamus during this stimulation and reported reductions during block of the LH.

Chronic pain and stress responses appear to be more frequent in MCC and are displaced somewhat from sACC. The mechanism of reciprocal suppression discussed by Bush *et al*. (2000), however, suggests these two regions interact in a reciprocal manner. The sACC has the greatest direct interaction with the HPA axis as well as direct visceromotor control. Rilling *et al*. (2001) showed that maternal separation was associated with elevated plasma cortisol and this was negatively correlated with blood flow in aMCC (mainly area a24c') measured with [F^{18}]-fluorodeoxyglucose positron-emission tomography. A positive correlation with plasma cortisol was observed in dorsal posterior cingulate cortex (dPCC; possibly area 23c). Human studies show that the PTSD vulnerable region (Fig. 22.1a; Chapter 21) is in area 32 mainly. Furthermore, chronic visceral pain/stress (Fig. 22.1-b) and somatic pain vulnerable regions (Fig. 22.1c; Chapter 25) are in pACC and MCC, respectively. The dissociation of HPA axis driving by sACC and areas vulnerable to stress raises important questions about the mechanisms by which the subregions of ACC and MCC interact with allostatic systems.

Thus, the sACC and LC may normally operate together to drive the HPA axis. To the extent that both are engaged in similar functions and are excited by nociceptive inputs including unpredictable footshock (an animal model of stress), we evaluate the common functions of these regions and their role in pain processing.

Functional Interactions of Cingulate Cortex and the LC

It is a striking fact that some of the functions attributed to cingulate cortex have also been demonstrated in the LC. As these structures are reciprocally connected, this may not be surprising. Of course, some of the functions of cingulate cortex including long-term and working memories, decision making, and conflict resolution cannot be performed by LC because it does not have the information or processing capabilities for such manipulations. Simple functions, however, such as attending to targets, responding to noxious stimuli, and synchronizing conscious limbic functions are shared by both of these structures. Indeed, the hypothesis of this chapter stresses that it is the joint activation of these structures by nociceptive stimulation and during chronic pain that may mediate the symptoms that characterize chronic stress syndromes. Nociceptive inputs generate a different processing mode in both the cingulate gyrus and LC.

Phasic and tonic modes of LC neuron discharges

The first step to understand LC-cingulate cortex interactions is to assess the response properties of LC neurons during waking behaviors. While LC neurons have decreased discharges during sleep and automatic behaviors such as grooming and eating, there are two waking, behavioral states with unique LC neuron discharge properties (Aston-Jones *et al*., 1999). In the *phasic mode* of firing, there is a moderate level of tonic discharge and phasic LC activation facilitates behavioral responses to target stimuli with short-LC responses as shown in Figure 22.2. Phasic activation appears to code the meaning or salience of the reward properties of a

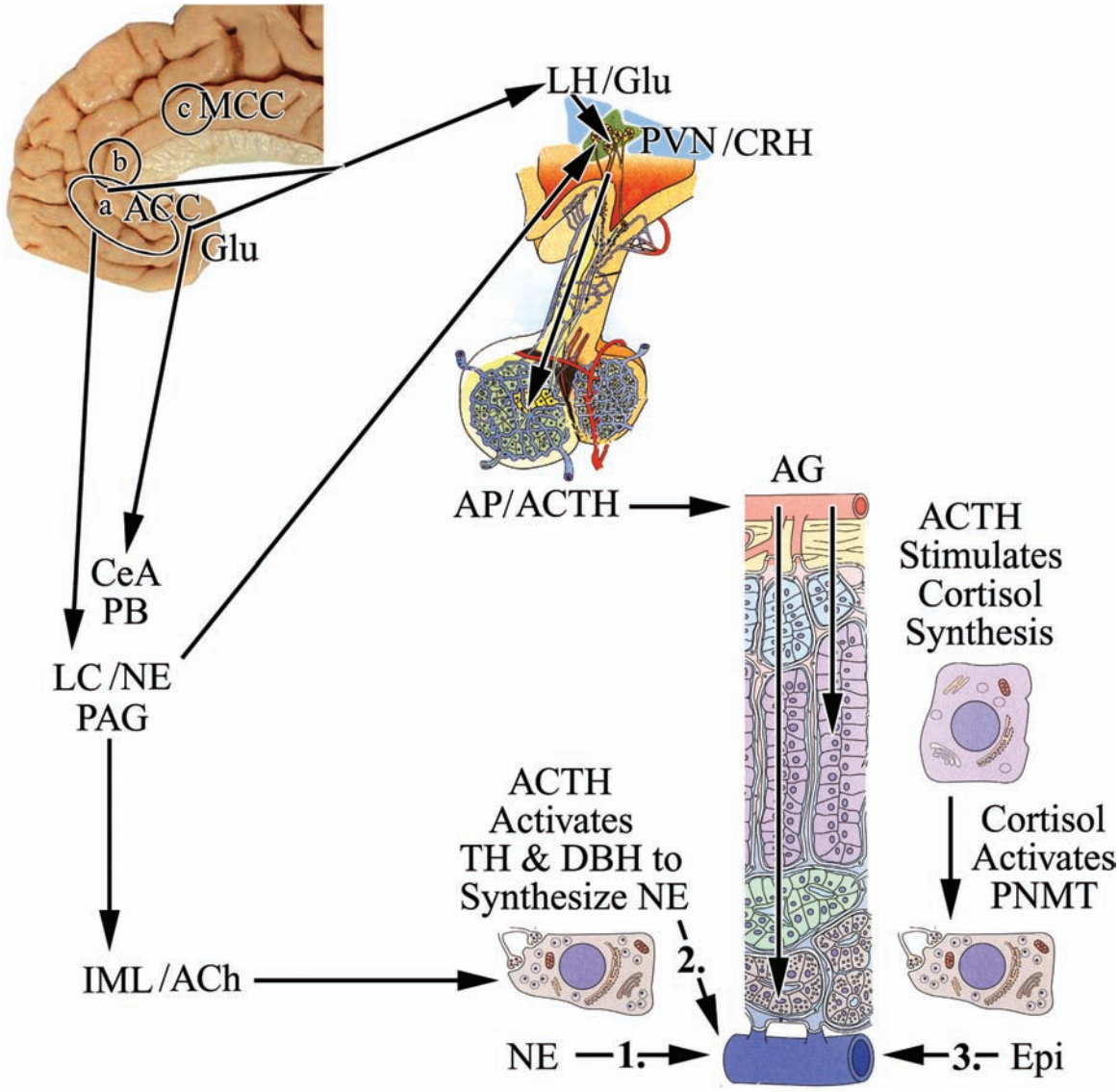

Fig. 22.1 Cingulate cortex drives the HPA axis and sympathetic systems. The former via the PVN/CRH, anterior pituitary (AP) corticotrophs (ACTH), and the adrenal gland (AG) that generates NE, cortisol, and epinephrine (Epi). The LC innervates the PVN to directly drive the HPA axis, while ACC projects to the LH (Glu) and the latter makes an excitatory projection to the PVN. ACC also projects to other autonomic centers including the central nucleus of the amygdala (CeA), LC, PAG, and PB nuclei which innervate the cholinergic intermediolateral nucleus of the spinal cord (IML/ACh). Catecholamine activation occurs via three neuron/hormonal pathways: 1. Driving of the cholinergic IML by the CeA/LC/PAG/PB to release stored NE; 2. ACTH activation of NE synthesis; 3. ACTH/cortisol-mediated synthesis of Epi. The PTSD-vulnerable region is marked 'a' (Chapter 21), 'b' indicates chronic visceral pain/stress, and 'c' somatic pain vulnerable regions (Chapter 23).

stimulus and not other aspects of the task including sensory attributes, target frequency, lever release, fixation spot, or non-target (context) stimuli (Aston-Jones *et al*., 1997).

During the *tonic mode* of firing, LC neurons have high ongoing activity during poor task performance and weak and poorly discriminative, phasic responses to sensory stimuli during visual-discrimination testing. This is a state of high arousal and sensory scanning rather than high resolution behavioral performance. A number of pivotal issues derive from these observations. First, shifting between modes provides two different types of behavioral output that are linked to cingulate cortex function in two ways. During phasic discharges, processing of specific sensory cues is efficient as the animal's attention to behavioral output is

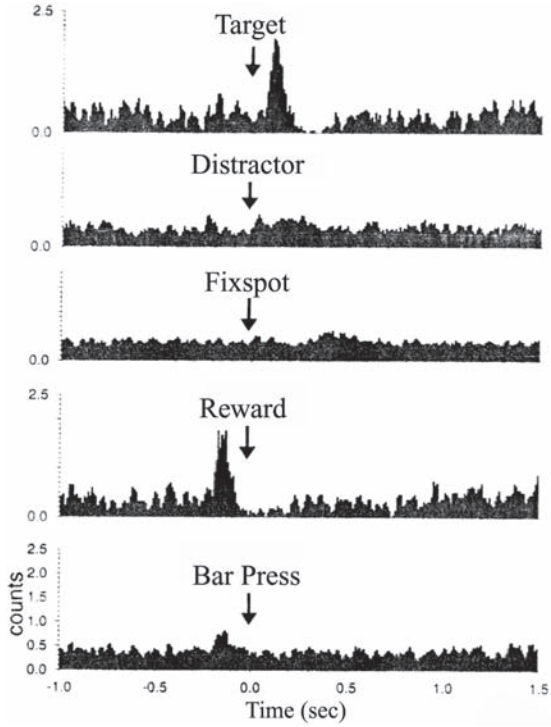

Fig. 22.2 Peri-stimulus time histograms for 100 epochs of activity of a single LC neuron in a monkey during a visual discrimination task. The target cue generated the greatest response, while that before the juice reward was evoked by the target stimulus as well.

coupled, possibly directly, to MCC outputs because this region regulates detailed skeletomotor functions as discussed in Chapter 5. During the tonic mode of LC firing, sensory processing and links to particular sensory stimuli are weak and the high tonic discharge rate may be adaptive to changing or unpredictable outcomes and more responsive to unexpected events. In this instance, the LC may be disengaged from MCC and more profoundly engaged with sACC that mediates more general autonomic activation and reflexive orienting. The specific contribution of each cingulate subregion to LC output, of course, awaits selective lesion studies.

These two states, scanning, labile-attention with sensory driving versus focused, task-oriented phasic behavior are summarized in Table 22.1. Responses during noxious footshock stimulation are of particular importance because unpredictable footshock is an animal model of chronic stress and it is particularly effective in driving LC output during the tonic mode of firing. The table also notes that MCC driving or coordination of LC activity is likely high during phasic and low during tonic modes of firing and the former involves detailed sensory inputs, cingulate driving, and accurate behavioral output. In contrast, the tonic mode

TABLE 22.1 Characteristics of LC Neuron Discharges

Features	Phasic mode	Tonic mode
Target detection accuracy	High	Low
Activity during predictable outcomes	High	Low
Level of MCC driving	High	Low
Level of ACC driving	Low	High
External awareness	Low	High
Noxious stimulus driving	Low	High

is a state of high arousal and lacks sensory details as shown with target detection and a higher correlation of discharges is possible with ACC. Thus, a functional circuit for cingulate-mediated, sensorimotor processing occurs during phasic-mode LC firing and is disengaged during tonic-mode firing. To evaluate the projections of LC including interactions with cingulate and nociceptive systems, we use immunohistochemistry for dopamine-β hydroxylase (DBH), the rate-limiting enzyme involved in synthesis of NE.

Methodological note. DBH-immunoreacted tissues for this chapter are from three adult cynomolgus monkeys cut in coronal section, perpendicular to the longitudinal brainstem axis. Alternate sections were reacted for neuron-specific nuclear binding protein (NeuN), microtubule-associated protein-2 (MAP2), and the SMI32 antibody to non-phosphorylated intermediate neurofilaments to assess the cytoarchitecture of each structure analyzed. The details of antibody concentrations and other methods have been published (Vogt *et al*., 2008). Some semi-quantitative assessments of the densities of DBH+ pixels are provided in constant areas (0.563 mm²) to enhance understanding the relative magnitude of differences within a region when viewing the photographs. Only one structure appeared to have essentially no DBH-labeled axons and that was the caudate nucleus (Foote, 1997), while all other nuclei have measurable DBH activity. In this framework, we emphasize those nuclei that have the heaviest DBH activity which is 2–5 times that in nuclei with low levels and assume that high-density regions have a higher drive by the LC and will tend to be most vulnerable to chronic stress.

Norepinephrinergic cingulate afferents

The distribution of NEergic inputs throughout the cingulate gyrus has been reported with DBH immunohistochemistry and compared with those with tyrosine hydroxylase (primarily dopaminergic axons). Gaspar *et al*. (1989) reported a light and homogeneous distribution throughout limbic cortex with least overall activity in layer I. Anterior and posterior cingulate

cortices were part of their analysis and fit this pattern. Figure 22.3 shows DBH activity in gyral area a24ab′ and in the sulcus in rostral cingulate premotor area a24c′. These two areas were selected because they are most profoundly impacted in irritable bowel and other functional visceral and somatic pain disorders discussed in Chapter 23. The distribution looks essentially the same for both areas. The number of pixels with supra-threshold levels of DBH activity in six random samples without reference to layer showed 5,238±356 in a24c′ and 6,233±443 in area a24ab′ confirming visual inspection that there is little or no difference between these areas. More important is the fact that DBH-immunoreactive axons in dorsal area 23a were also homogeneous and quite similar to that in area a24 with 7,320±474 pixels in the same area. Comparison with gyral area a24a′b′ suggests little difference.

In view of the dual nature of cingulate efferents to subcortical structures which includes area 25 projecting to different parts of most nuclei associated with autonomic outputs and area 24 and MCC projecting to those prominently involved in skeletomotor functions, area 25 was also considered in these preparations. There was the same level of DBH activity in area 25 as that shown for other cingulate areas. Thus, LC innervation does not appear to have any preference in the cingulate gyrus, it is diffuse, and it is in a position to generally influence all functions of cingulate cortex and does not appear to selectively drive any one part of the cingulate gyrus. This is one of the major reasons for considering subcortical sites of interactions between cingulate and NAergic systems as providing a better explanation of specific NEergic influence on cingulate functions.

In view of the homogeneous LC innervation of the cingulate gyrus, there are three means by which LC/NE activation could become associated with selective vulnerability in subregions of the cingulate gyrus in various chronic pain and stress syndromes: (1) Subcortical interactions between cingulate cortex and the LC in the PB, PAG, amygdala, and/or MITN. (2) Receptor

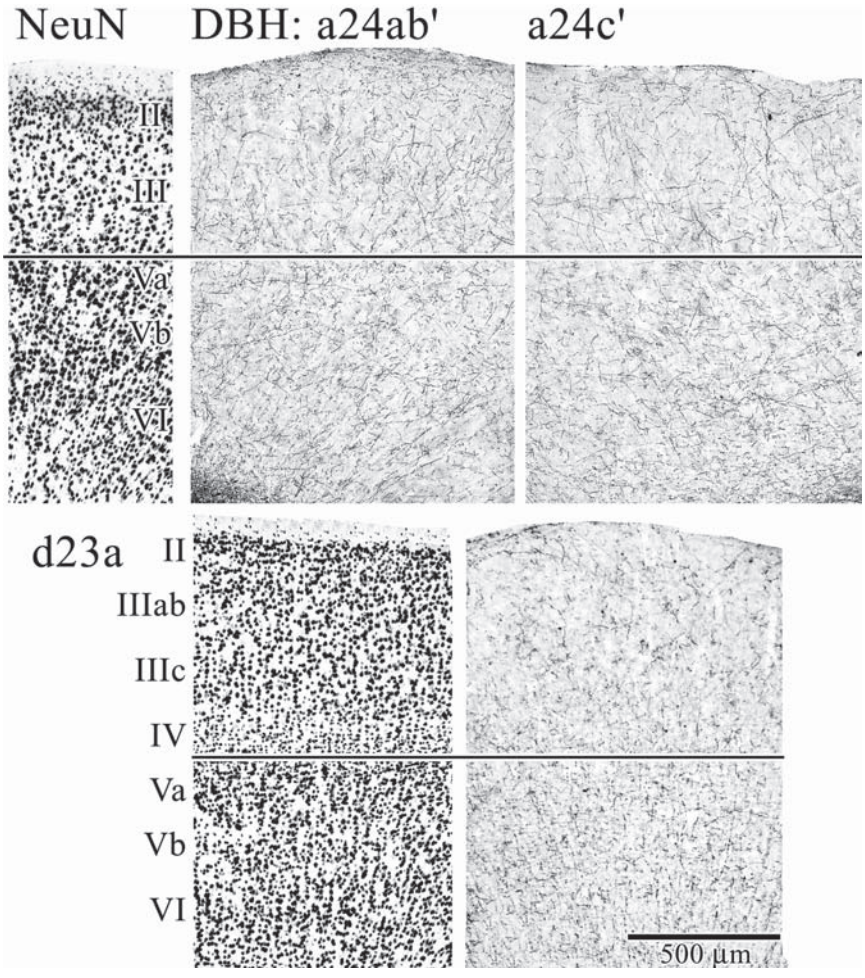

Fig. 22.3 DBH immunoreactivity is homogenous throughout the cingulate gyrus. The horizontal line is at the border between layers IIIc/Va in area a24′ and layers IV/Va in area d23a. Although there appears to be slightly fewer axons in layer III of area a24c′ and slightly more in layer V of area d23a, these differences are not significant.

distribution heterogeneities such as heavy α2 receptor localization in particular subregions such as area 32 in ACC (Chapter 2). (3) Co-activation by nociceptive inputs biasing toward autonomic system activity and area 25 in ACC and the skeletomotor system and area 24′ in aMCC (Chapter 14).

Cortical projections to LC: Top–down interactions

The role of the LC in modulating behavioral states has been reviewed above and by Berridge and Waterhouse (2003). As LC neuron discharges tend to occur in large groups and may be linked by gap junctions that synchronize output, it is unlikely that the details of responsivity, particularly during sensory-discriminative tasks with various cues and rewards, anticipatory responses, and rapid-training reversal, are derived by information processing within the LC; that is, they are not generated *de novo* in the LC. More likely, these responses are the result of driving from prefrontal cortical sources including cingulate cortex. Indeed, many of the anticipatory, reward coding, and response selection functions attributed to the LC have also been demonstrated in the cingulate gyrus as discussed in Chapters 12, 16, and 28. Even the role of the LC in the autonomic aspects of emotion (Aston-Jones *et al.*, 1996) could be partially explained by efferent projections from sACC area 25 to the LC.

The descending projection from prefrontal cortex to the LC has been demonstrated in three studies in cat and monkey. Arnsten and Goldman-Rakic (1984) showed that dorsolateral and dorsomedial prefrontal cortex project directly into and around the LC. Studies of sACC and pACC projections confirm the prefrontal findings in the monkey (Chiba *et al.*, 2001) and cat (Room *et al.*, 1985). Thus, the functional similarities among these structures are a consequence of reciprocal connectivity as well as common inputs. Specifically, the phasic mode of LC neuron firing associated with high resolution target detection and reward coding are likely due to driving from MCC, while tonic mode firing is more likely associated with ACC projections to LC. This view is part of Table 22.1.

Nociceptive Viscerosomatic Driving: LC, PB, MITN, Amygdala, and Cingulate Cortex

The ability of the LC to generate valence-independent responses to a wide range of sensory stimuli and environments has been noted above. It is known that LC neurons discharge during slowly conducting, C-fiber activation associated with the burning aspect of pain; an effect that can be blocked by injection of capsaisin directly into the sciatic nerve (Hirata & Aston-Jones, 1994). An example of a neuron discharge during C-fiber activation is shown in Figure 22.4B at two amplitudes of sciatic nerve stimulation (Fig. 22.4A). The peristimulus time histograms show robust discharges over baseline following footshock that resolve into two components; an excitatory output between #1 and #2 in Figure 22.4B and a secondary inhibitory component after #3 at low levels of stimulation (top plate at 0.5 msec duration pulse).

The key source of nociceptive excitation of LC neurons is the paragigantocellular nucleus in the reticular formation (PGi; Ennis & Aston-Jones, 1988; Ennis *et al.*, 1992). Electrical stimulation of PGi or injection of kainate receptor agonists into PGi drive activity of LC as does footshock stimulation, while blockade of kainate receptors in PGi prevented the activation of LC neurons by noxious footshock. Chang and Aston-Jones (1993) showed that a general block of PGi activity with Lidocaine also prevents nociceptive activation of LC and this finding is replicated in Figure 22.4C because it is so important in the present context.

The source of nociceptive input to PGi arises in the spinal cord (Kerr, 1975; Abols & Basbaum, 1981; Menetrey *et al.*, 1983). Thus, acute noxious stimulation drives spinal inputs to the PGi and these are transmitted to the LC in an excitatory pathway; one of two major inputs to the LC (Aston-Jones *et al.*, 1993). Although noxious inputs arise from the MITN to ACC and MCC (Chapter 14), both the LC and cingulate cortex are jointly and powerfully driven by noxious stimulation and such activity converts LC neuronal discharges to the tonic, search mode.

Figure 22.5 summarizes the dual function inputs throughout the CNS that are mediated by NEergic nuclei in the brainstem, cardiovascular (CV), and nociceptive (Noci). The CV inputs arrive in the A1/A5 nuclei and LC from the caudal NTS. The A1 and A5 NEergic nuclei are primarily involved in baroreceptor responses and buffering sudden blood pressure changes. These nuclei provide a heart rate signal for monitoring CV function and a means for descending systems to modify output according to current behavioral needs. The A1 and A5 nuclei project to PBl, vlPAG, CeA, and the MITN (Byrum & Guyenet, 1987; Woulfe *et al.*, 1990). Visceral input to these nuclei also arrives from the caudal part of the NTS (Beckstead *et al.*, 1980). As the rostral projections of A1 and A5 are NEergic and intermingle with LC projections, projections to the Pv, PB, PAG, and CeA in the DBH preparations must be viewed as a common input from A1, A5, and the LC. Finally, the common activation of this system by nociceptive and visceral afferents assures synchronization of NEergic and cingulate system functions including behavioral states associated with LC neuron discharges.

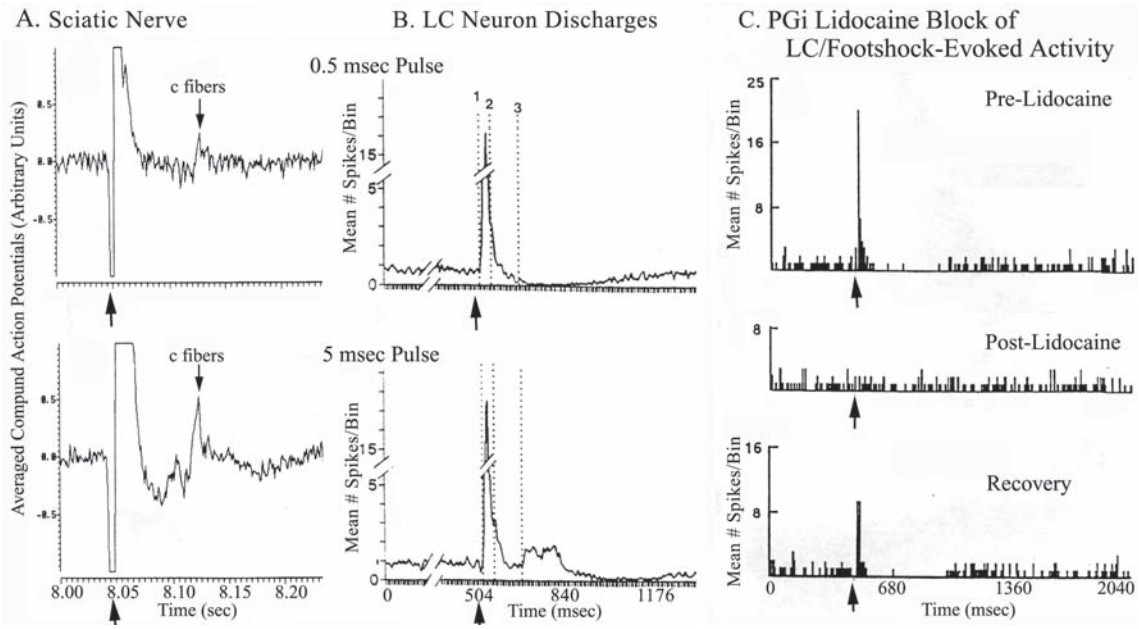

Fig. 22.4 The LC responds to noxious footshock via an excitatory pathway originating in PGi. A. Compound action potentials in arbitrary units showing two levels of sciatic nerve stimulation and C-fiber activation. B. Peri-stimulus time histograms at two levels of sciatic nerve stimulation showing excitatory discharges between #1 and #2 and inhibitory (after #3) phases for a single neuron in LC. C. Block of PGi with Lidocaine blocks excitatory transmission of noxious footshock through this circuit.

Nociceptive afferents arrive in PGi from the spinal cord as discussed above. The CV and nociceptive inputs together provide CV/nociceptive drive through four ascending projections from both the A1/A5 and LC nuclei as shown in Figure 22.5: (1) lateral PB; (2) ventrolateral PAG (vlPAG); (3) CeA; and (4) MITN; particularly the Pv, Pf, and limitans (Li) nuclei. The LC projects to all of the cingulate gyrus. The spinal cord nociceptive neurons project to the NEergic brainstem nuclei including the LC, Subcoeruleus (SubC), A1, and A5 nuclei. To the extent that A5 and LC are driven by noxious inputs, it is important that these nuclei project to structures that also receive cingulate inputs: PBl, vlPAG, CeA, and MITN. These common inputs assure that activity in the NEergic system is synchronized during noxious stimulation and this common driving assures that allostasis involves both somatic and visceral pain components and that the evolution of chronic stress syndromes may involve visceral impairments.

Norepinephrinergic Enhancement of Multiple System Processing: A Network Perspective

Consideration of NE-mediated functions in cingulate cortex cannot be limited to its NE innervation and cingulocoeruleal projections because NE regulation is not restricted to single sites but operates on broader functional networks. In this context, the essential reports of NE in enhancing the signal-to-noise ratio are important. NEergic projections enhance sensory-evoked activity over baseline discharges in the visual (Morrison & Foote, 1986; Ego-Stengel *et al.*, 2002) and somatosensory (Devilbiss & Waterhouse, 2004) systems. Coordinated driving of this function in the thalamus and cortex provides a mechanism whereby the LC enhances system function along an entire circuit rather than in single and discrete nuclei/areas. This network function enables the integration of system outputs that is not possible when the LC is not active and this is the context in which we consider LC function in relation to the cingulate cortex.

We are looking here for regions that receive both LC and cingulate inputs, share common functions, and where NE enhances a system's function rather than focusing on a single cingulate activity. The rationale involves identifying subcortical nuclei that receive moderate-to-high densities of LC (DBH) inputs and a projection directly from cingulate cortex. These subcortical points of LC/cingulate cortex engagement provide important insight into the role of NEergic activity in cingulate functions including activities that both structures drive together. Let us begin with the amygdala

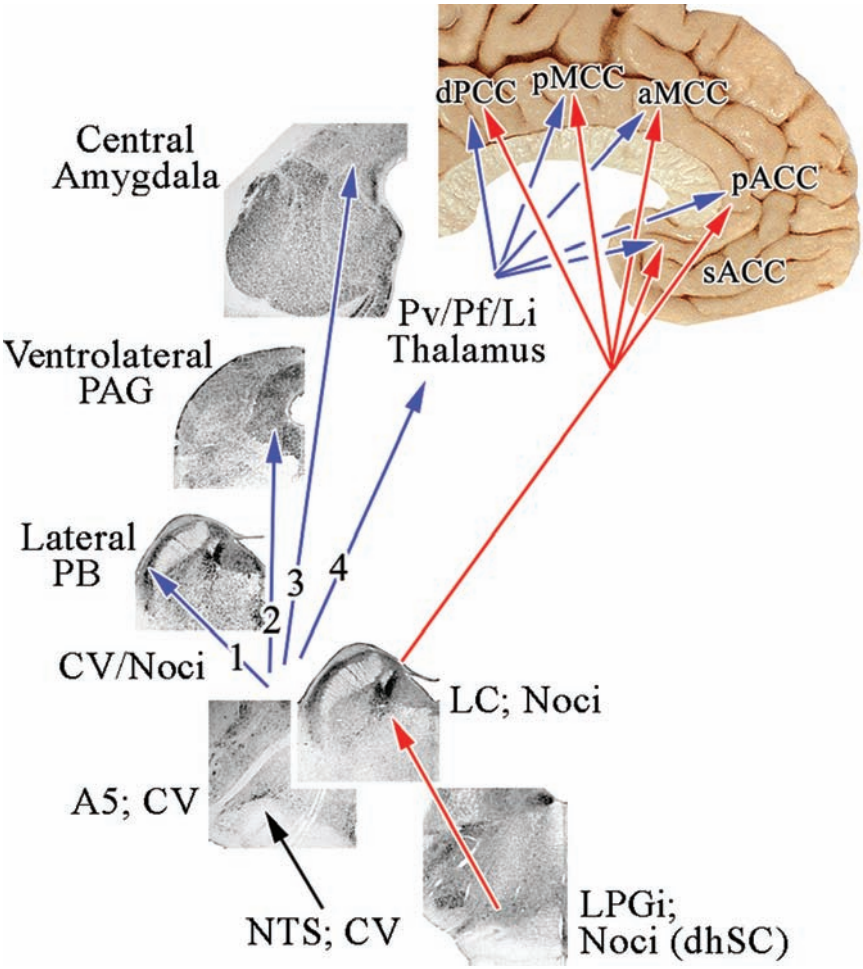

Fig. 22.5 NEergic afferents from the NTS, laminae I/V–VII of the spinal cord (dhSC), and nucleus caudalis in the trigeminal system (not shown) provide two types of information to this system; the CV signal generated by baroreceptor discharges and nociceptive driving. The CV/Nociceptive signals are transmitted dorsally via four pathways (blue arrows) from both sets of NEergic nuclei and the LC projects throughout cingulate cortex (red arrows). The A5 and LC sections are DBH-immunoreacted, while other sections are reacted for NeuN from the monkey, and the medial surface is from a human postmortem case.

because it is involved in functions also associated with the cingulate gyrus and specific amygdala nuclei receive both LC and cingulate cortex input. On these grounds, pain responses, fear conditioning, and autonomic and skeletomotor drive during orienting and conditioning are all enhanced and coordinated by LC/NE driving of this system.

Amygdala: Behavioral Orienting and Conditioning

The amygdala has neurons that respond maximally to novel stimuli (conversely, they habituate quickly), code for the reward properties of stimuli, respond to noxious stimulation, have a role in emotion including fear, engage in emotion/valence-specific conditioning, and regulate autonomic output (Chapter 9; Davis, 2001; LeDoux, 2001; Rolls, 2001). Each of these claims can be made for the LC and ACC/MCC. Both area 25 of sACC and the LC project to CeA (Room *et al.*, 1985; Yasui *et al.*, 1985) and they likely regulate cardiovascular responses to unconditioned stimuli such as noxious and electrical footshock. The LC also projects to the basolateral nucleus and NE plays a pivotal role in memory in the amygdala; particularly the basolateral nucleus (McGaugh *et al.*, 2001). For these reasons, it is proposed that LC input to the amygdala enhances common functions between the ACC/CeA on one hand and the anterior MCC/BLA on the other; rather than driving amygdala-specific functions. Although the aMCC also receives LC inputs and has a reciprocal projection to LC, it does not directly regulate autonomic functions (Chapter 10) and it plays a more prominent role in response selection and cognitive functions relating to skeletomotor systems (Chapters 1 and 5). As the LC may enhance the reward value of particular stimuli, its interactions with cingulate cortex may enhance the movement value of reward/positive or punishment/negative outcomes. Thus, both divisions of cingulate cortex interact differently with the amygdala,

and the LC may enhance the flow of information through both pathways.

The dorsal basolateral (BLD) and accessory basal (also termed magnocellular basomedial, BMMC) nuclei project extensively to ACC (areas 24, 25, and 32) and somewhat less to aMCC area a24′ (Amaral & Price, 1984; Vogt & Pandya, 1987). The pMCC, PCC, and retrosplenial cortex do not receive amygdala afferents and do not participate directly in interactions between the LC, amygdala, and cingulate gyrus. Figure 22.6 shows a coronal section through the amygdala to emphasize the two main connections between the amygdala and cingulate cortex via these nuclei. Both nuclei, however, are differentially innervated by the LC. The DBH section shows that BMMC has very few DBH-labeled axons (little LC input), while BLD has a moderate density of

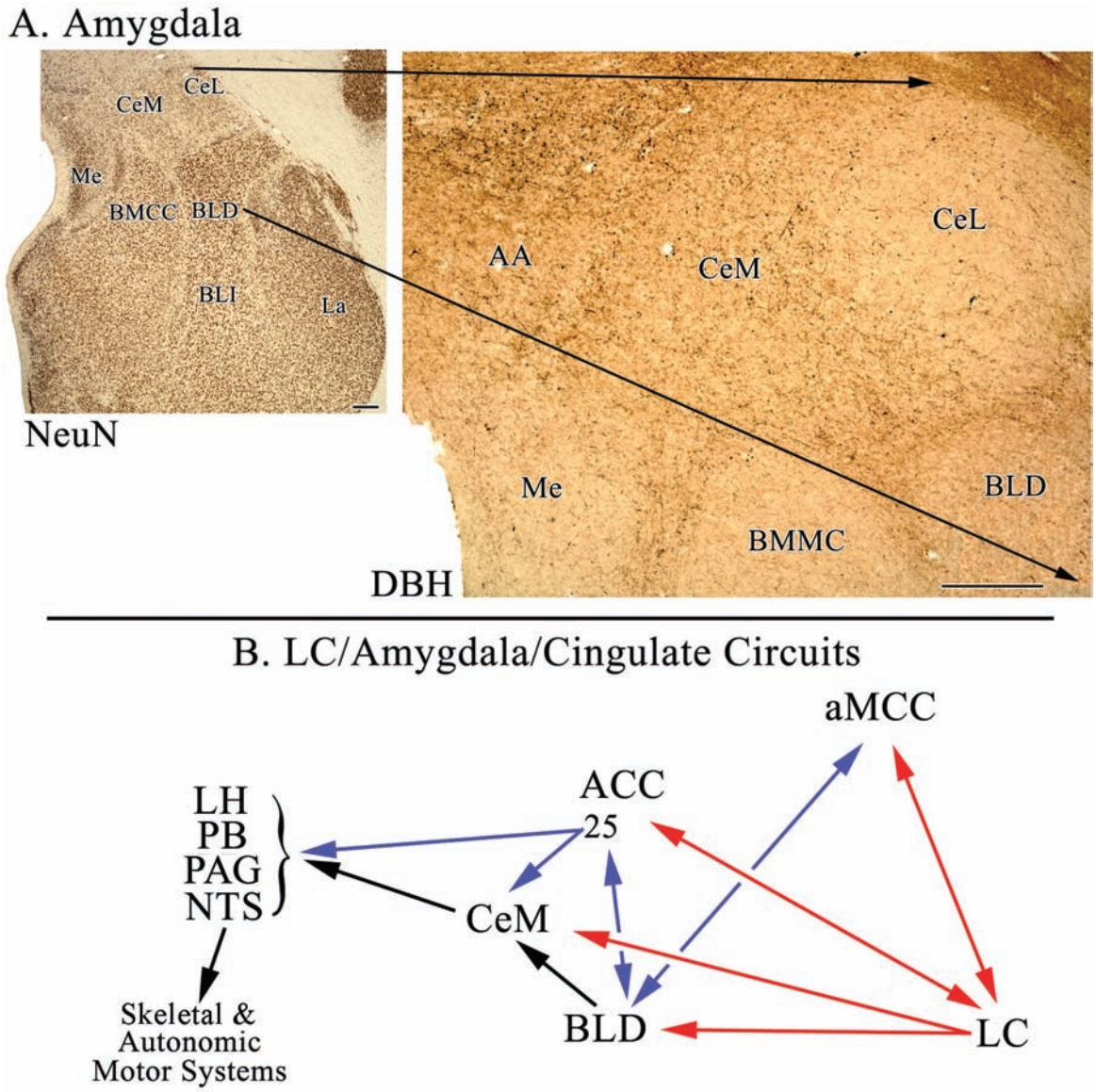

Fig. 22.6 A. NeuN and DBH (X1.5) sections of the monkey amygdala that emphasize the dorsal nuclei including the dorsal basolateral (BLD), medial (Me), medial central (CeM), lateral central (CeL), basomedial magnocellular (BMMC), and lateral (La) nuclei. The black arrow shows equivalent points in both sections for orientation. Heaviest DBH activity is in the BLD and CeM nuclei and these are emphasized in the circuits in B. (red arrows). Cingulate cortex interacts (blue arrows) mainly with BLD, however, area 25 (sACC) also projects to the CeA. In addition to direct connections, BLD projects to CeM and this entire circuit is bathed with NE from the LC. Thus, the cingulate output pathways to the amygdala and amygdala output to brainstem motor systems are simultaneously modulated by NE. AA, anterior amygdaloid nucleus; and Me, medial amygdaloid nucleus.

DBH immunoreactive axons. Sadikot and Parent (1990) saw light DBH activity in this latter nucleus, while Freedman and Shi (2001) reported a moderate level of immunoreactivity. Thus, the cingulate projection originating from the BMMC is not regulated by LC input, while that from BLD is so influenced.

Figure 22.6 also shows that the medial division of the central nucleus (CeM) has substantial DBH-labeled axons, while the lateral division of CeA has very few. In the rat, the NEergic A5 group also projects to the CeM and all DBH-labeled axons in these monkey preparations may not be from the LC (Byrum & Guyenet, 1987). Finally, there is a substantial projection from the BLD to the central and medial amygdalar nuclei (Price & Amaral, 1981; Aggleton, 1985) and this is shown in Figure 22.6B. Summarizing the LC-driven amygdala circuit in Figure 22.6B, there is a significant LC innervation of BLD and CeM, a supporting projection of BLD to CeM and outputs from CeM to the LH, PAG, and NTS (Price & Amaral, 1981). Thus, a main conclusion is that the LC/NE input to the amygdala enhances processing through the BLD/CeM pathway which in turn regulates skeletomotor and autonomic motor systems.

It has already been noted that the ACC and aMCC project to BLD and that the ACC, particularly sACC area 25, projects to the LH, PB, PAG, and NTS. Electrical stimulation of ACC evokes many of the same autonomic and skeletomotor responses reported for CeM including cessation of ongoing behavior, pupillary dilation, and bradycardia (reviewed by Davis, 2001) and similar responses have been reported for stimulation of ACC including inhibition of ongoing behavior, bradycardia, pupillay dilation, and piloerection (Kaada, 1951). As ACC and aMCC both project to BLD (Fig. 22.6B), their influences together on skeletal and autonomic motor systems are direct and indirect by supporting the BLD/CeM amygdala circuit. Finally, a double dissociation with BLA and CeA lesions has demonstrated that lesions of the BLA selectively abolish sensitivity to changes in the reward value of an instrumental outcome, while sparing the general motivational effects of the Pavlovian cues, while CeA lesions abolished the general motivational but spared the specific effects of the cues (Corbit & Balleine, 2005). From a circuit perspective, the LC coordinates and enhances flow of information from cingulate cortex through two pathways; the direct autonomic regulatory CeA center and the one engaged primarily in fear conditioning and memory via the BLA (Maren & Fanselow, 1996; McGaugh *et al*., 1988, 2001).

As both system functions are mediated by NEergic inputs, the model of NE enhancement of dual cingulate functions via the amygdala is supported and may be critical in the evolution of chronic pain and stress syndromes. Of course, the LC and sACC join forces to mediate common functions in structures other than the amygdala and these include the PB, PAG, and MITN.

Lateral Parabrachial Nucleus: VisceroSomatic Nociceptive Integration Center

Although the lateral and medial divisions of the PB nucleus receive input from sACC area 25 (Room *et al*., 1985; Yasui *et al*., 1985), NEergic inputs are not uniform to these nuclei. Figure 22.7 shows very heavy DBH activity in the lateral division when compared with the medial division. The density of DBH-positive pixels was 7,483±735 in the PBl and 3,412±217 in PBm or a factor of more than two times in PBl. Although the CeA has an essentially even distribution of inputs to these two nuclei (Price & Amaral, 1981), projections to the CeA arise mainly from the PBl and not PBm (Pritchard *et al*., 2000). Thus, sACC and NEergic innervation of the PBl may enhance activity in sites that project to the CeA and we emphasize them here.

The importance of the PBl nucleus to visceral nociception has been made on the basis of both spinal inputs and its outputs (Saper, 2000). The PBl has nociceptive-specific neurons with relatively large receptive fields; some with modality specificity and others without such specificity (Bester *et al*., 1995; Menendez *et al*., 1996). Efferents from the PB/SubC participate in the descending noxious inhibitory system and electrical stimulation of this region inhibits wide-dynamic range, spinothalamic projection neuron activity (Girardot *et al*., 1987). Moreover, ascending visceral nociceptive signals likely pass through the PBl and provide nociceptive inputs to the Pf and other MITN that project directly to cingulate cortex (Chapter 14).

The PBl is a visceral nociceptive integration region and NEergic inputs are in a position to mediate cingulate-initiated, descending spinal inhibitory systems as well as the flow of afferent nociceptive information *into* the cingulate gyrus. The recurring theme is that NEergic innervations enhance the flow of information within a network that contributes to a common behavioral output; in this instance, the network is the pain neuromatrix.

Ventrolateral Periaqueductal Gray: Coordination of Skeletomotor-Autonomic Reflexes

The PAG coordinates complex and behaviorally relevant skeletal and autonomic motor reflexes including those associated with fight-or-flight responses and this system has been thoroughly reviewed (Dapaulis & Bandler,

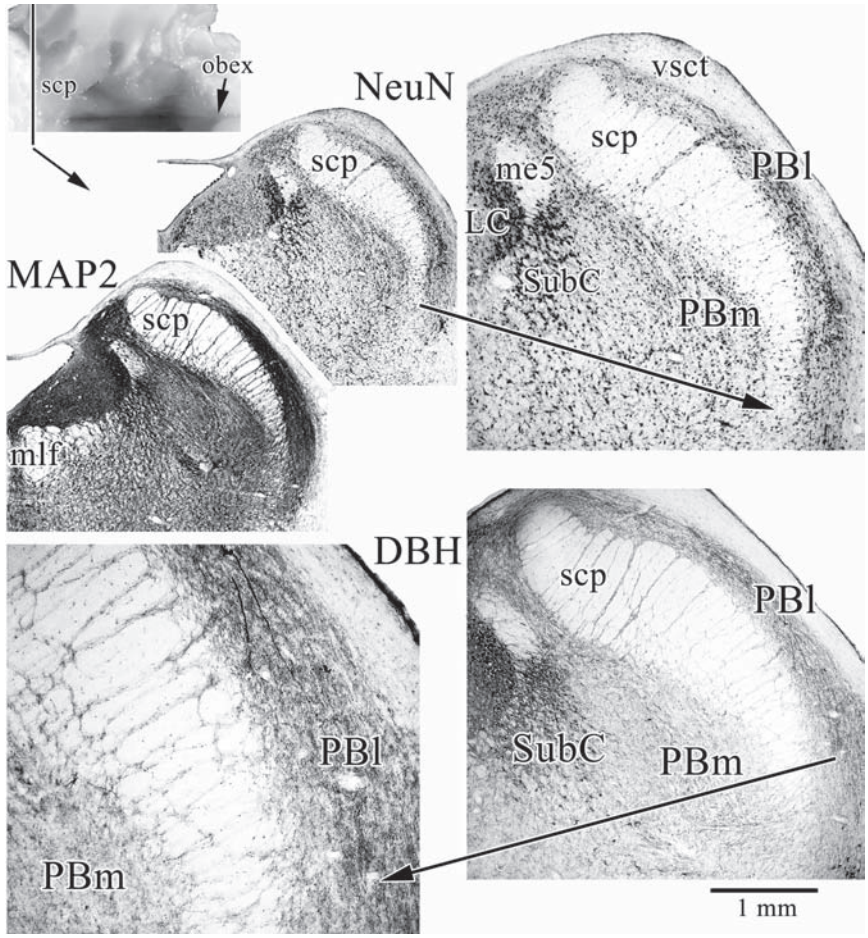

Fig. 22.7 PB architecture and DBH immunohistochemistry. The sections are oriented from the superior cerebellar peduncle (scp) and the obex at the caudal end of the floor of the fourth ventricle as shown in a dorsal view of the floor of the fourth ventricle (top left). The microtubule-associated protein-2 (MAP2) and NeuN-immunoreacted sections show mainly large dendrites and neuronal somata, respectively. In both, the LC, subcoeruleus (SubC) and PBl/m are distinguished. The arrows in the NeuN and DBH sections orient photographs taken at higher magnification (two black arrows between sections identify equivalent points in the two magnifications). The profoundly higher levels of DBH-positive axons in PBl versus PBm are shown. mlf, medial longitudinal fasciculus; me5, descending tract of the mesencephalic nucleus of V.

1991; Carrive & Morgan, 2004). Linkages between cingulate cortex projections and NEergic axons occur in the PAG. The A1, A5, and LC nuclei all project to the PAG. The heaviest NEergic innervation in the PAG of the rat is in the ventrolateral division (vlPAG) and this is the same region that receives substantial input from the NTS (Woulfe *et al.*, 1990; Herbert & Saper, 1992). The A1 nucleus projects mainly to dPAG and lPAG (Woulfe *et al.*, 1990), A5 to d, l, and vl (Byrum & Guyenet, 1987), and the LC to all subnuclei (Mantyh, 1983).

Figure 22.8 shows that heaviest DBH activity in monkey PAG is in vlPAG with much less in dorsal and lateral divisions. There were 11,900±903 thresholded pixels for DBH-immunoreactivity in vlPAG, while there were only 6,124±535 in the dmPAG; confirming the visual impression of at least two times greater activity in the vlPAG. Thus, the primary site of NEergic regulation in the PAG is in the vlPAG, though the dorsal and lateral nuclei are not free of such input.

Cingulate cortex has two PAG targets and may play a major role in selecting among PAG output functions. Areas 25 and 32 terminate in the dl and vlPAG, while area 24 terminates mainly in the lPAG and vlPAG (An *et al.*, 1998; Room *et al.*, 1985; Yasui *et al.*, 1985). Nociceptive inputs from spinal cord arise from laminae I and V/VII and terminate mainly in lPAG (Zhang *et al.*, 1990) and nucleus caudalis mainly in rostral lateral and cervical very heavy to dl and vl at caudal levels of the PAG (Wiberg *et al.*, 1987). Thus, spinal inputs can also participate in this differentiation during nociceptive driving. Interestingly, the projection of the CeA is massive in the vlPAG (Price & Amaral, 1981; An *et al.*, 1998) and would support the actions of both areas 25 and 24 in the vlPAG and some of the nociceptive spinal activations that are likely involved in the descending noxious inhibitory system.

Outputs from the vlPAG might be disturbed in chronic pain and stress states. These include projections of dPAG and vlPAG to the thalamic Pv, Pf, reuniens, and mediodorsal nuclei and the dorsal and anterior LH nuclei (Comans & Snow, 1981; Mantyh, 1983). These are critically innervated by the NEergic nuclei and provide the pivotal source of nociceptive inputs to the cingulate gyrus as discussed below.

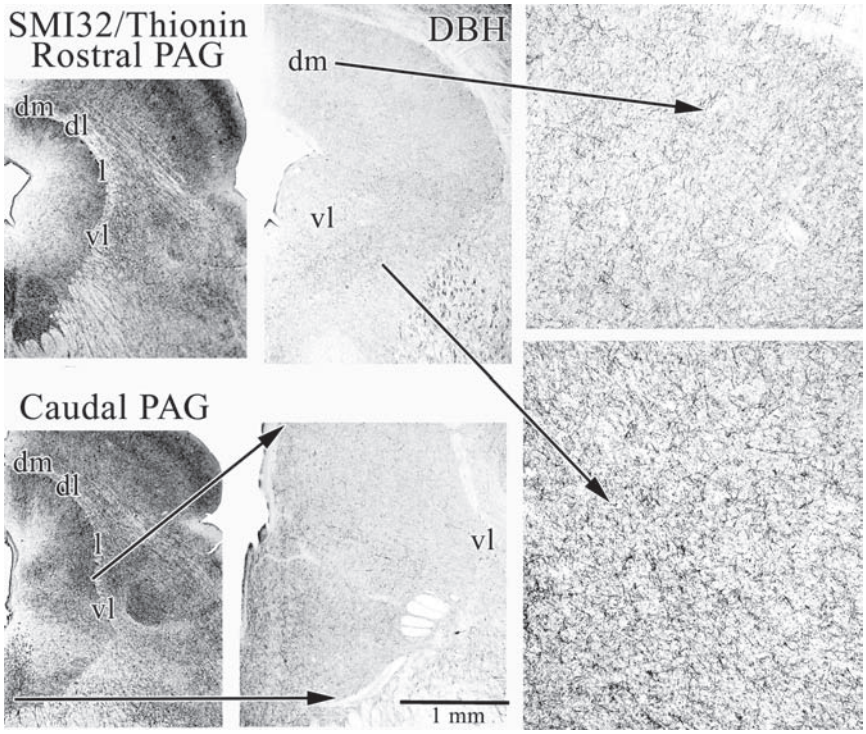

Fig. 22.8 Architecture and NEergic innervation of PAG. Two levels of the PAG are shown with the SMI32 antibody counterstained with thionin. The DBH activity is provided at two magnifications in the dm and vl nuclei at the rostral level with arrows showing points of magnification. Semi-quantitative analyses confirm there is two times more activity in vl than dm. One structural basis for the differential action of NE in the PAG is the different densities of NEergic input.

Midline, Mediodorsal, and Intralaminar Thalamic Nuclei: Nociceptive Gateway to Limbic, Allostatic Systems

The MITN are the pivotal source of nociceptive input to cingulate cortex and the Pf component is active during chronic, deafferentation pain (Rinaldi *et al.*, 1991). Although all thalamic nuclei receive some NEergic input, there are a few particularly heavily innervated MITN and this provides for important circuit interactions between cingulate and NEergic systems (Vogt *et al.*, 2008). Particular thalamic nuclei might be viewed as pain portals that can be modified by activity in the A5 and LC and they may be preferentially vulnerable to nociceptive driving in chronic stress syndromes.

Nociceptive MITN that project to cingulate cortex include the Pf, centrolateral (Cl), paracentral (PCN), reuniens (Re), Pv, central (Ce), ventromedial (VM), parvicellular mediodorsal (MDpc), and limitans (Li) as reviewed in Chapter 14. Although all of these nuclei have some DBH activity, a few have moderate to high levels. As shown in Figure 22.9, one of the highest densities of DBH is in Pv nucleus which receives both

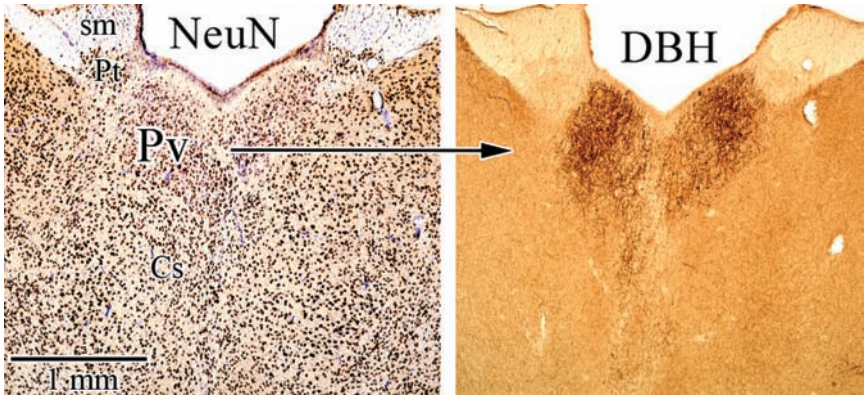

Fig. 22.9 A level of the monkey medial thalamus (NeuN) and adjacent DBH preparation with an arrow pointing from the Pv nucleus to the high DBH activity. This nucleus also receives substantial spinothalamic, PB, and CeA afferents and projects to cingulate cortex. sm, stria medullaris.

A5 (Byrum & Guyenet, 1987) and LC inputs (Comans & Snow, 1981; Jones & Yang, 1985).

There is a high density of DBH immunoreactivity in caudal parts of the Pf nucleus and throughout Li. Figure 22.10 shows this caudal level of thalamus and the significant cytoarchitectural heterogeneity of the Pf and its differential innervation by DBH+ axons. We have identified a lateral Pf with limited DBH innervation, a medial Pf (Pfm) that receives high but not uniform innervation and a multiformis Pf (Pfmf) that has many different-sized neurons and almost no DBH+ input (Vogt *et al.*, 2008). Nuclei that have high DBH-immunoreactivity also express high densities of calbindin-immunoreactive neurons and to a lesser extent calretinin-expressing neurons. A similar pattern of reactivity is shown at a more rostral level of the medial thalamus that includes high DBH activity in the MDmc, Pv, and Cl nuclei as shown in Figure 22.11.

This survey suggests that the following nociceptive nuclei that project to cingulate cortex receive NEergic inputs in descending order for density of DBH-immunoreactive axons: Pfm, Pv, Li, Cl, Ce, and Re. Thus, NEergic afferents are at a pivotal point in six MITN to modulate nociceptive activity *before* it arrives in the cingulate gyrus and in states of chronic pain activation could disrupt nociceptive processing in this system.

Acute Noxious Driving of LC and Cingulate Cortex: Summary

Cardiovascular and nociceptive inputs drive neurons in both the LC and ACC/MCC. Figure 22.12 summarizes some of these connections with an emphasis on activations generated during acute noxious stimulation and these are the circuits that are at first risk during chronic pain and stress. Although the diagram is best viewed in terms of CV and nociceptive limbs, even the CV can be driven by nociceptive inputs. The CV limb is mediated by baroreceptor driving of A5 and its projections to LC

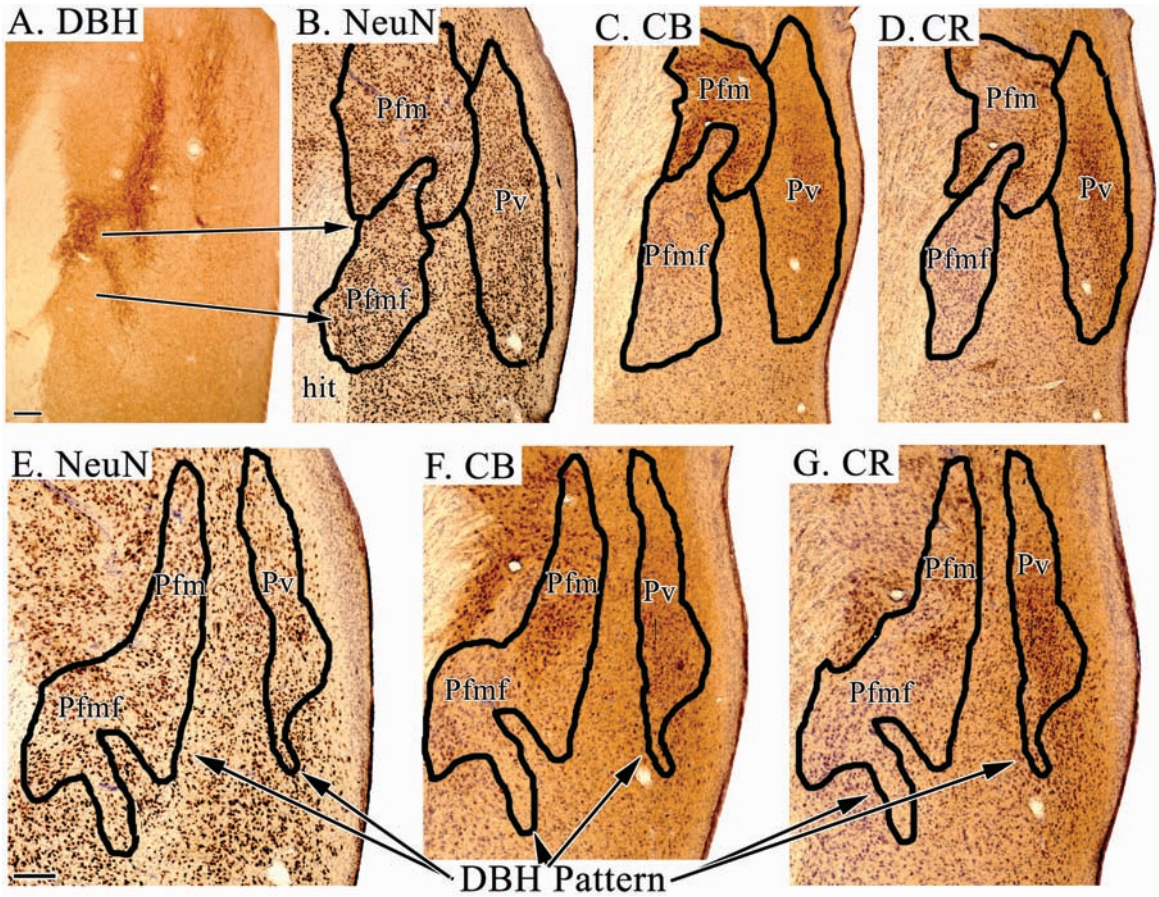

Fig. 22.10 Adjacent sections show the distribution of DBH, NeuN, and the calcium-binding proteins (CB, CR) in the medial Pf (Pfm), and multi-formis (Pfmf) divisions of Pf. Sections in B–D were magnified by 50% in E–G and the DBH pattern outlined with black lines co-registered to show the extent of overlap of this projection with divisions of Pf and Pv. Magnification bars are 200 μm.

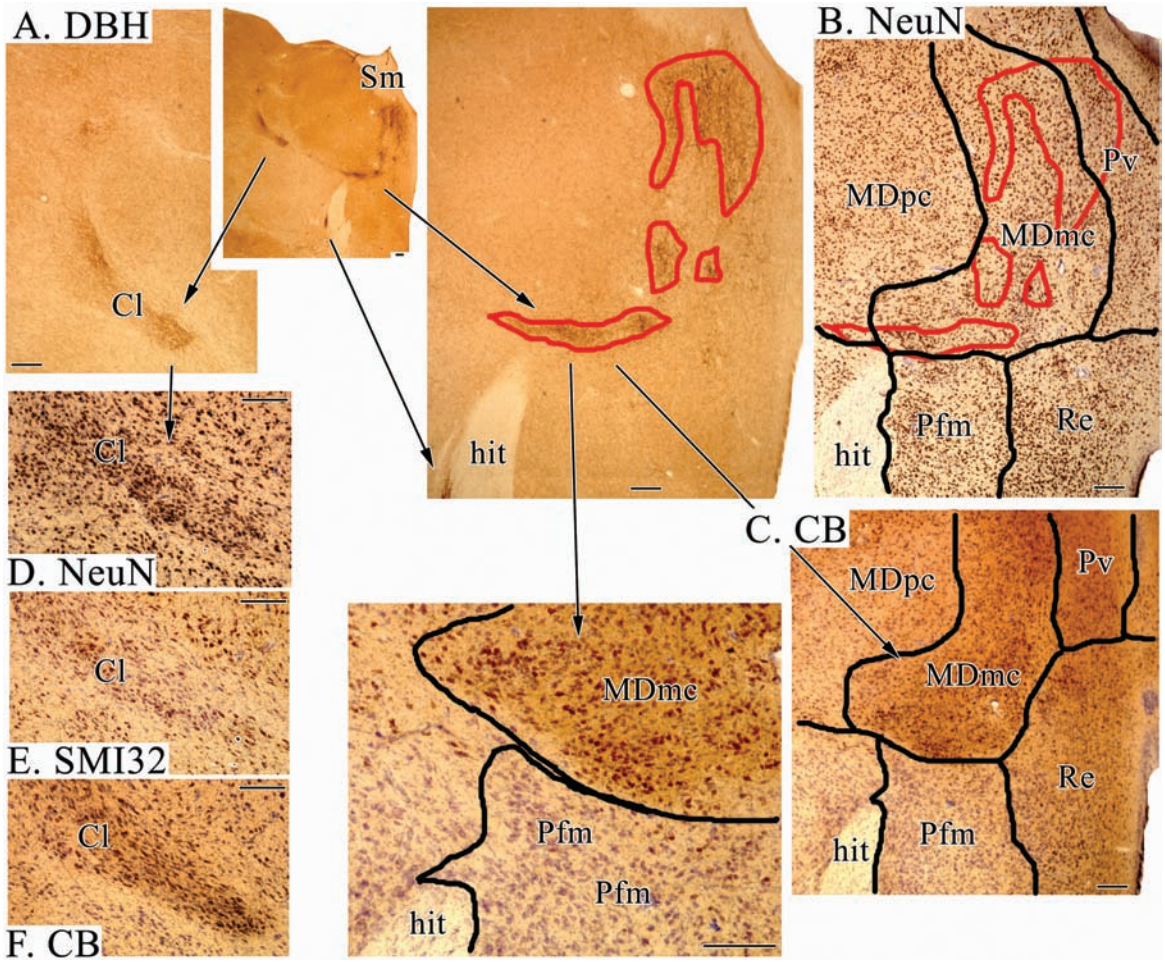

Fig. 22.11 DBH immunoreactivity at a mid-rostrocaudal level of monkey thalamus. Four aggregates of DBH-immunoreactive axons are outlined in red and were transferred to the NeuN section with an extension into the Pv. The greatest DBH innervation at this level is in MDmc where there is also a high density of CB-immunoreactive neurons. hit, habenulointerpreduncular tract. Calibration bars are 200 μm.

and the Pv thalamic nucleus which in turn projects to sACC as discussed above. This signal is employed in ACC and the CeA for visceromotor control via descending systems (Chapter 15). Nociceptive inputs derive from a wide range of nuclei with large somatic and visceral receptive fields and, to a much lesser extent, driving by innocuous afferents by LPGi, SRD, and PBl. Indeed, the receptive field properties of neurons in Pf are predicted from the wide variety of somatic and visceral nociceptive afferents into this nucleus (Vogt, 2005).

The NEergic projections to the CeA, MITN, PAG, and PB may explain why they are so consistently involved in stress syndromes and involvement of cingulate pain processing and stress vulnerability. The PBl is a major target of NAergic and amygdala afferents and efferents, and projects to Pf and paracentral nuclei (Bester *et al.*, 1999). Visceral and spinothalamic projections to these nuclei assure that visceral and somatic activity drives the Pf and paracentral nucleus and the LC/A5 modulates sensory activity throughout these nuclei. The fact that LC is driven by lamina I spinal nociceptive afferents as well as those derived from the PGi as discussed above and visceral brainstem inputs assures that NEergic projections regulate nociceptive processing at all levels of cingulate interaction; that is, in the medulla, midbrain, hypothalamus, and thalamus.

The right side of Figure 22.12 summarizes the structures that receive both nociceptive inputs and have dense NEergic inputs. The NEergic projections from the LC transmit both nociceptive and allostatic signals and may coordinate key parts of limbic motor systems; also termed emotional motor systems. The sites of prominent overlap are shown with red–blue circles to emphasize that these are the sites that are vulnerable

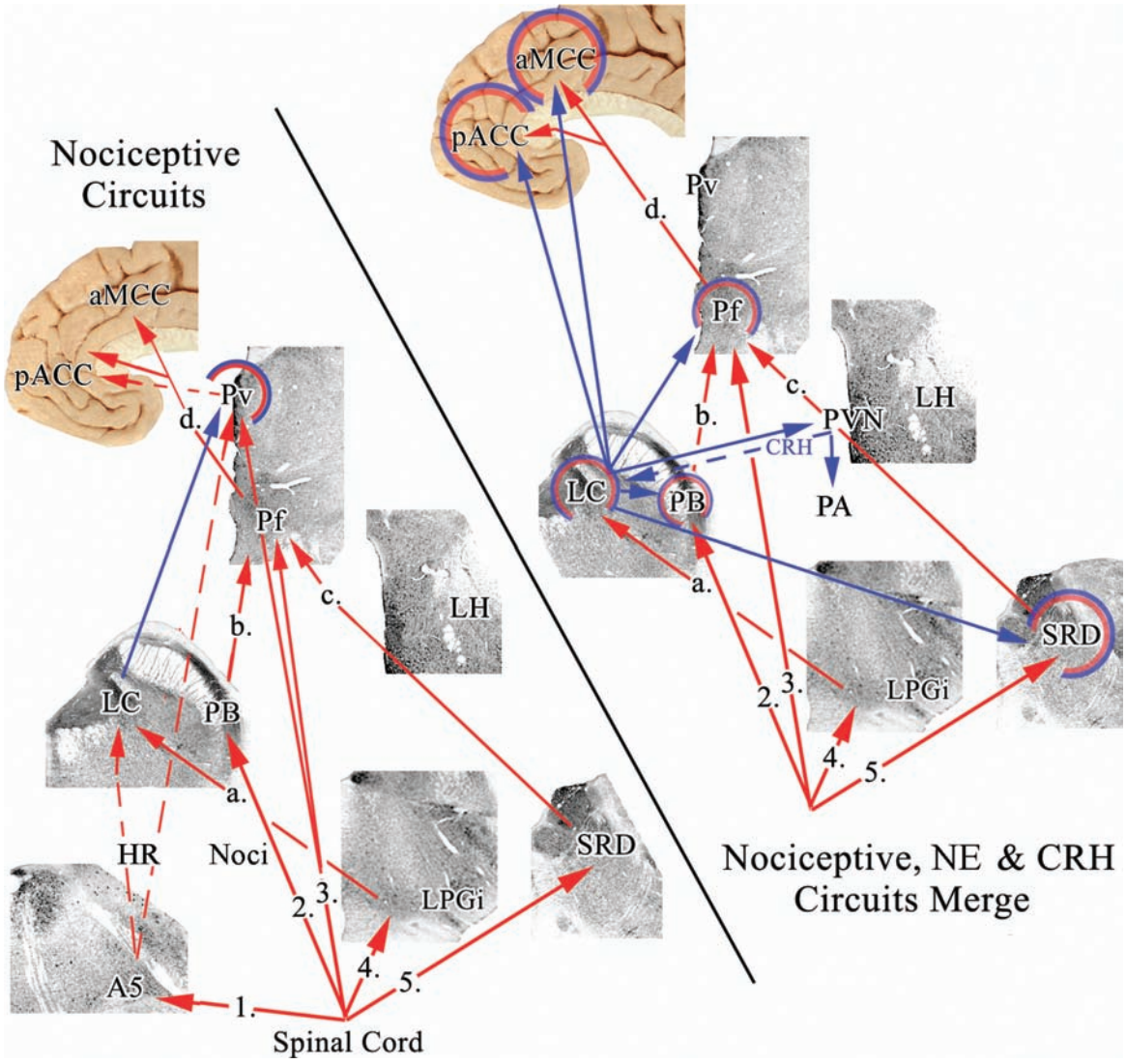

Fig. 22.12 *Left: Nociceptive circuitry*. Driving of heart rate (HR; A5; dashed red lines) and nociceptive processing (Noci; LPGi, SRD, PBl; solid red lines). The primary afferent nociceptive drive for five pathways is shown with numbers and secondary pathways transmitting these signals is labeled a.-d. The wide range of HR and nociceptive inputs to Pf (also Re and Li) emphasizes the pivotal nature of the MITN as a gateway for this input to the cingulate gyrus. The red and blue circles around Pv emphasize this is a nucleus that joins CV, nociceptive and allostatic responses. *Right: Overlap circuitry*. Nuclei and areas are identified with red/blue circles that receive nociceptive (red arrows) and allostatic (blue arrows) signals. This circuit is an extension of the one on the left and emphasizes acute processing of both signals and structures that are at risk for changes during chronic pain and stress.

to chronic stress and are active during acute and chronic nociceptive processing: pACC, aMCC, Pv, Pf, LC, PB, and SRD.

Some Actions of NE and Descending Projections

Ebert (1996) showed that neurons in the cochlear nucleus had an enhanced NE, α1-mediated responses to tone stimulations. He suggested that NE-increased sensory sensitivity might lower thresholds during short-latency, acoustic-startle reflexes. These mechanisms could be active in other areas with NEergic innervation and the behavioral outcomes could be relevant in other modalities as well. Thus, the massive NEergic inputs to PBl may enhance nocifensive responses evoked by noxious stimulation by lowering the threshold of activation and this may enhance activity in descending

noxious inhibitory system from the PB, the vlPAG, and cingulate cortex itself. To the extent that the d, l, and vl PAG nuclei have different functions and NEergic innervations, the cingulate areas and A1/A5/LC may select among PAG functions and mediate spinal cord nociceptive responses. Importantly, activity of the vlPAG engages quiescence, hyporeactivity, hypotension, and bradycardia, while the lPAG is involved in defensive behavior, hypertension, and tachycardia (Bandler & Keay, 1996). The net effect of NE administration into the lPAG and vlPAG is to bias activity towards the former vlPAG-mediated response pattern (Vaughan *et al.*, 1996).

Although information on NE actions in thalamus is limited, the parataenial nucleus projects to ACC/MCC (Vogt *et al.*, 1987) and observations of McCormick and Prince (1988) are noteworthy. In their study, NE evoked slow depolarization, reduced slow, after-hyperpolarizations, and inhibited rhythmic activity. They proposed that NE facilitates transfer of information through the thalamus to the cerebral cortex and this is also likely in terms of nociceptive flow to the cingulate gyrus (Chapter 14).

The importance of many descending systems in the NEergic circuits is in reducing nociceptive processing. (1) During the initial noxious stimulation period, ACC projections to PAG and PB trigger inhibitory responses; however, over time and with anticipatory shutdown of the ACC this system may become inactivated. (2) The amygdala has NE, β-adrenoceptor-mediated enhancement of gluatamate transmission in the BLA (Ferry *et al.*, 1997) and this may enhance conditioning and memory associated with fear as reviewed above. Importantly, CRH-releasing neurons in the CeM project to the LC and CRH inhibits nociceptive activity in the LC (Valentino *et al.*, 1993; Van Brockstaele *et al.*, 2001); in spite of the fact that CRH activates LC neurons by reducing a potassium conductance (Jedema & Grace, 2004). Thus, even during active fear conditioning, it is possible the stress response dampens activation through NEergic systems. (3) The descending noxious inhibitory system has one limb that is NEergic. NEergic neurons innervate spinothalamic neurons (Westlund *et al.*, 1990) and NE inhibits the action of these neurons (Willcockson *et al.*, 1984). Thus, descending systems together seem to inhibit processing of nociceptive information through a number of NEergic pathways.

Multi-system Sensitization

The central nervous system undergoes plastic changes as it evolves from passively responding to noxious sensory stimulation to a chronic stressor in which there is a general lack of attention to detailed information processing in the cerebral cortex and possibly longer durations of tonic mode firing in the LC. Bremner *et al.* (1996) introduced the term 'stress sensitization' to refer to the increase in responsiveness that occurs with re-exposure to a stressor in organisms with previous exposure to that specific stimulus. They provide many examples of this in the preclinical literature including an increase in LC neuron discharge with chronic stress possibly mediated by changes in the density of α2 adrenoreceptors. In another example of stress sensitization, Bremner *et al.* (1993) showed that combat veterans with combat-related PTSD occurred at an increased rate when childhood physical abuse occurred. In contrast, veterans with no physical abuse history had a lower rate of PTSD. Thus, early life stress may sensitize an individual to develop stress-related disorders upon exposure to subsequent traumatic stressors; not necessarily the same ones. We propose that the structures and key circuits summarized in Figure 22.12 are at risk for stress sensitization.

The concept of stress sensitization suggests that the HPA axis has a chronic enhancement of negative feedback regulated by glucocorticoid receptors in the pituitary (Yehuda *et al.*, 2004) and a higher level of activity during acute challenges when previous events of a similar traumatic nature had occurred. The amplified hormone responses during allostasis can be maintained for decades after the traumatic trigger(s) (Heim *et al.*, 2000) and multiple serious traumas may enhance subsequent events not only in the HPA axis but also in the cortex and its descending projection sites.

Central sensitization has long been known in processing nociceptive information, particularly in the spinal cord and brainstem. Central sensitization occurs after tissue or nerve injury and is activity-dependent much like other calcium-mediated events such as long-term potentiation. It is associated with lowered thresholds for evoking sensory responses and prolonged after-discharges that can last for hours or days. Like long-term potentiation, central sensitization is mediated by glutamate receptors and has been thoroughly studied in the spinal cord (Rowbotham *et al.*, 2006). Surprisingly, little is known of the mechanisms of central sensitization in the telencephalon, although this is the site of conscious reporting of the phenomenon. It is possible that hyperactive neurons in the MITN (Rinaldi *et al.*, 1991) in deafferentation pain patients are one reflection of central sensitization; however, much more work in this area is needed.

Allostasis and pACC Activation

It is crucial to chronic stress vulnerability and information processing models below that pACC is directly activated during allostasis in addition to its role in cardiovascular regulation discussed in Chapter 10. Using the Stroop interference task to generate allostasis,

Gianaros *et al.* (2005) showed a correlation between mean arterial blood pressure and Blood Oxygen-dependent (BOLD) activity mainly in pACC. Inputs from the Pv assure that a CV signal is available to pACC. This link provides a site of potential vulnerability to chronic stress.

Cortisol modulates fear conditioning and Stark *et al.* (2006) provided another pivotal link between pACC activity and allostasis. They showed that a single dose of cortisol (30 mg) reduced activity in pACC during discriminative fear conditioning in males, while it increased the signal in females. Interestingly, cortisol enhanced the response to noxious electrical shock (the unconditioned stimulus) in both pACC and PCC in a gender independent fashion. In support of the hypothesis of the present review, allostasis and stress hormones regulate activity in the pACC. Whether this is strictly related to cardiovascular events or is associated with enhancing memory of allostatic experiences or both has not yet been evaluated in this part of the human brain. These studies together support the expectation that chronic stress directly targets the pACC and generates a site of stress vulnerability.

Pain Processing and Links to Chronic Stress: pACC

Acute pain drives allostatic circuits as mediated by the LC and there are nodes of interaction with cingulate cortex for these structures in the thalamus, hypothalamus, PAG, PGi, and PB nuclei. Furthermore, there is evidence that frequent nociceptive stimulation in human (Taddio *et al.*, 1997) and animal (Anand *et al.*, 1999) neonates and premature, human infants (Grunau *et al.*, 1994) can lead to chronic stress including increased tonic inhibition of the HPA axis. As these latter infants achieve adolescence, they experience an abnormally high rate of attention-deficit/hyperactivity disorder and depressive symptoms (Botting *et al.*, 1997; review, Anand, 2000). In rats, intermittent footshock enhances cFos expression in this same circuit including the LC, BLA, PAG, and pACC area 32 (Sawchenko *et al.*, 2000). These observations support the role of nociceptive mechanisms in chronic stress disorders.

Some animal models of 'psychogenic' stress employ restraint or maternal withdrawal. These models show both enhanced negative feedback through the HPA axis with elevated ACTH and enhanced negative feedback via glucocorticoids (Ladd *et al.*, 2000). Restraint stress and white-noise-induced stress evokes discharges in the LC that are not due to generalized behavioral arousal (Abercrombie & Jacobs, 1987). Restraint-stressed animals have inhibitory activity in area 32 as would be predicted from human studies (Figueiredo *et al.*, 2003) and this latter effect leads to enhancement of cFos expression in the PVN and enhanced stress responsivity. Prenatally malnourished rats express a higher level of cFos activity in pACC during restraint stress than do normally nourished animals (Rosene *et al.*, 2004). Finally, maternal withdrawal in monkeys also generates changes in metabolism that are positively and negatively correlated with cortisol levels, however, the changes in the cingulate gyrus are not consistent within individual regions; although part of area 32 does seem to be negatively correlated with cortisol levels (Rilling *et al.*, 2001). Thus, both human imaging in chronic stress populations and animal models point to a predilection of pACC for selective vulnerability to allostatic loads.

Role of Cingulate Cortex in a Nocigenic Model of Functional Pain Syndromes: aMCC

Animal models suggest there are two fundamentally different sources of system drive in chronic stress syndromes. One arises from a primarily viscerosomatic nociceptive impairment such as chronic and unavoidable footshock and another arises from psychogenic sources such as restraint stress and maternal withdrawal associated with anxiety and fear. Examples of different central nervous system mechanisms for both have been shown by Sawchenko *et al.* (2000). For example, cFos expression is not increased in area 25 of rat during interlukin-1 injections, while footshock-induced activation of cFos is greatly increased in this same region including area 32. The rodent, however, cannot be used to model all features of pain processing as it lacks one of the essential output regions in the cingulate sulcus (cingulate premotor areas). Nevertheless, the dissociation of two mechanisms for different types of allostatic load are pivotal to interpreting human responses to them. To explore the cingulate-mediated mechanisms of chronic pain and stress syndromes, we will use an example of each; irritable bowel syndrome (IBS) for nocigenic stress and PTSD for psychogenic stress. Interestingly, each of these has been reported to have different cingulate-predominant subregions of activation or inactivation.

The fact that IBS engages primarily MCC and PTSD impairs mainly ACC is one of the most important successes of the four-region neurobiological model as discussed in many of the previous and subsequent chapters. The fundamental differences between ACC and MCC in terms of their circuitry and phenotypic expression of particular proteins provide the final test as to the distinct nature of these two regions.

Irritable bowel syndrome

The functional pain disorders lack peripheral, structural, and biochemical markers yet are associated with

profound and diffuse pain and include IBS, fibromyalgia, lower back pain, and atypical facial pain as discussed in Chapter 23. IBS is associated with severe visceral pain in the middle to lower gastrointestinal tract and stress increases with the intensity of gas and pain sensations and relaxation decreases the intensity of both (Ford *et al.*, 1995). Application of lidocaine to the rectum reduces both visceral and cutaneous secondary hyperalgesia in IBS patients (Verne *et al.*, 2003) and this demonstrates a role of peripheral maintenance of a tonic output from the rectum. Peripheral mechanisms, however, are not independent of central mechanisms of secondary hyperalgesia.

The psychological contribution to IBS symptoms is emphasized in a study that showed distraction influences the intensity of the pain sensation (Accarino *et al.*, 1997). Indeed, the role of psychological influences is a well-known correlate of IBS (Whitehead & Palsson, 1998) and depression and catastrophizing is significantly greater in patients with severe functional bowel disorders than those with moderate symptoms (Drossman *et al.*, 2000). Finally, a history of sexual and physical abuse increases the probability of expressing IBS (Leserman *et al.*, 1997). Interestingly, this factor does not change rectal pain thresholds when responses are compared to patients with IBS but no abuse history (Ringel *et al.*, 2004). This suggests that much of the cingulate response during noxious distension of the lower GI tract may be due to non-sensory functions of cingulate cortex itself. Thus, IBS fulfills the expectation that pain and stress symptoms overlap, provides an example of stress sensitization and insight into the cingulate-mediated experiences associated with psychological factors including the anticipation of chronic stress and pain.

Mertz *et al.* (2000) and Naliboff *et al.* (2001) showed that MCC has an elevated activation during noxious distension of the rectum in IBS. Moreover, anticipation of the noxious stimulus also generated an aMCC activation that was not observed in control subjects (Naliboff *et al.*, 2001; see their Fig. 3). Drossman *et al.* (2003) reported a case of severe IBS in a woman with a history of childhood rape and abuse. During the period of adult illness, the patient had major psychosocial impairment, high life stress, and a low visceral pain threshold. Figure 22.13 shows a medial surface reconstruction of this patient while experiencing severe pain induced by a 50 mmHg distension of the rectum compared with that of a 15 mmHg distension. The activations were co-registered to a postmortem histological case to localize the sites of greatest activity. The massive activation mainly of aMCC is apparent and it extends into premotor area 6aβ and into pMCC. Following 8 months of psychotherapy and a divorce from an abusive husband, the IBS symptoms resolved including

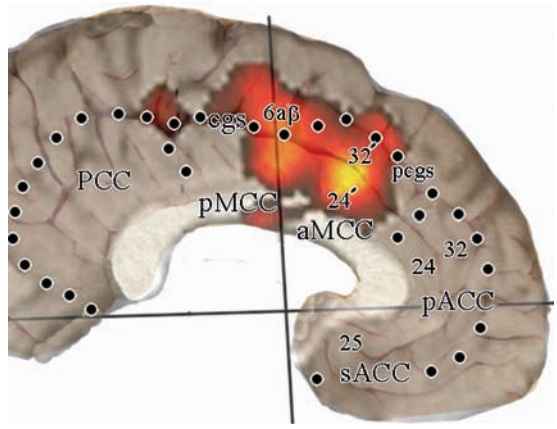

Fig. 22.13 Medial surface reconstruction from a patient with severe IBS during a 50 mmHg distension of the rectum contrasted with that of 15 mmHg distensions. The color calibrations represent z scores of 5–6 (red) and 7–8 (yellow–orange). The reconstruction was co-registered to our postmortem control brain for evaluation of the histologically verified cingulate subregions engaged in the activation. For case details, information on other areas and resolution of the aMCC activity see Drossman et al. (2003).

a normalizing of visceral pain and aMCC activation was greatly reduced along with changes in a number of other cortical regions as reported by Drossman *et al.* (2003). The high level of aMCC activation in IBS plays a pivotal role in our nocigenic model of cingulate-mediated changes in chronic pain and stress syndromes.

Role of Anticipation in IBS

As Naliboff *et al.* (2001) show an important elevation of activity in aMCC during anticipation of noxious rectal stimuli, it is important to repeat that the aMCC has a prominent role in anticipation of pain and general cognitive processing; particularly because it contributes prominently in the nocigenic model below. Anticipation and premotor planning of the consequences of noxious stimulation are discussed in detail in Chapter 16 and Figure 16.11 shows that anticipatory responses are most frequently observed in aMCC. Anticipation of pain also reduces processing in pACC (Porro *et al.*, 2003) and this response may also contribute to impaired visceral processing in the functional bowel disorders. Another feature of the functional pain disorders is a high prevalence of visceral pain symptoms. As noted in Chapter 14 and previously (Naliboff *et al.*, 2001; Vogt, 2005), visceral activity is generally higher in ACC than in MCC. Thus, nocigenic mechanisms of chronic stress may be associated with both chronic and unpredictable noxious stimulation and by a top–down, anticipatory hyperactivation of aMCC.

Overview of models in Figures 22.14 and 22.15

There are a number of alternatives for laying out a complex circuitry such as those for the two models of chronic pain and stress in the next two figures. One is in the form of a flow diagram with connections between geometric shapes for each area and nucleus. Although this can show interconnections clearly, it does not represent the anatomical information in any meaningful way. As the functional imaging studies that support many of these findings do not have neuron resolution, it is instructive to work with histological sections to reinforce anatomical concepts. Thus, we have chosen sample coronal sections first shown in color in Figure 15.7 to discuss possible circuitries in the two different states of central nervous system function. At first glance, they look quite complicated. Upon recognizing the anatomy of each section; look at each class of arrow separately according to color, site of origin in the cingulate gyrus, multi-arrowed, or solid/hatched. These designations guide the statements made in the text. Disruption of connections is shown with short, double lines. Even when there is overlap of the arrows, the differential coding for them makes it easier to follow the claims being made for each system.

Unpredictable, viscerosomatic nociceptive drive

The nocigenic model is driven and maintained by chronic but unpredictable activation of nociceptive pathways as encountered in IBS and other functional pain disorders. As an overview, it is proposed that these perceptions may be driven either by misfunctioning peripheral receptors or by centrally active sites including the MITN and possibly cingulate cortex. Sensory activity likely generates anticipatory responses associated with impaired bowel habits, motor hypervigilance, fear and anxiety. These actions together in the pain neuromatrix including cingulate cortex may alter pain processing through the descending noxious inhibitory system. Figure 22.14 provides a detailed consideration of the essential features of such a reorganized circuitry that uses key changes in activation in IBS when compared to control group responses.

Figure 22.14 shows the initiation of nocigenic processes at the red asterisk by unpredictable, viscerosomatic nociceptive activity and its transmission via five numbered pathways with red arrows as in Figure 22.12: A5, PBl, Pf, lareral PGi, and SRD. Multi-synaptic, nociceptive projections throughout the emotion/limbic motor systems are continued with red arrows. Secondary transmission of nociceptive information is extensive, however, and two key outputs are emphasized in the diagram; those from LPGi to drive the LC and sympathetic outflow in the IML, the extensive projections of Pf and many other MITN as shown here to cingulate cortex and the amygdala (CeM) and projections of a heart rate signal through Pv to sACC.

Activity in the HPA axis is shown with blue arrows as relatively uninterrupted, although the up-regulation of glucocorticoid receptors and many other changes are known to mediate negative feedback mechanisms in the pituitary gland and elsewhere in PTSD (Yehuda *et al*., 2004). The blue asterisk under IML links the final common outputs of these systems in the adrenal gland (AG). The HPA axis is shown without alterations for simplicity and does not imply unchanged responses, but rather to emphasize the position of cingulate cortex in the circuit.

Reduced activity in pACC is highlighted in Figure 22.14 with no efferent projections. Although this reduction is not well documented in imaging studies, it is predicted here based on the mechanism of reciprocal suppression discussed in Chapter 1 and by Bush *et al*. (2000). The latter authors showed that emotional and cognitive tasks differentially activated ACC and aMCC and observed that activity in the aMCC was suppressed during intense emotional states and patients with depression and subjects anticipating pain and film-induced emotion deactivated activity in aMCC. They proposed that reciprocal suppression of ACC occurred during intense emotion; a condition that is clearly present in IBS and other functional pain disorders.

In a situation where the activity in pACC is not robust and sACC activity may be normal, the sACC projections (dashed black lines) to the CeM, LC, and LH are viewed as intact. This fact may account in part for the autonomic drive of allostatic responses in chronic stress syndromes mediated by cingulate cortex, but it is not the only one.

Hyperactivated aMCC

A combination of enhanced viscerosomatic nociceptive activity and anticipatory activity associated with impaired bowel habits generates a massive output from aMCC in IBS. Fear also generates activity in aMCC (Vogt *et al*., 2003) and this endogenous activity along with a generalized anxiety could further drive activity in this cingulate subregion. These many factors enhance output from aMCC as shown in Figure 22.14 with multiple arrowhead arrows to emphasize the heavy driving of autonomic activity via the PAG, LC, and LH. The model predicts that high levels of nociceptive and anticipatory activity drive specific subcortical structures engaged in autonomic activation. The role of cingulate cortex in supporting some of the symptoms of IBS include

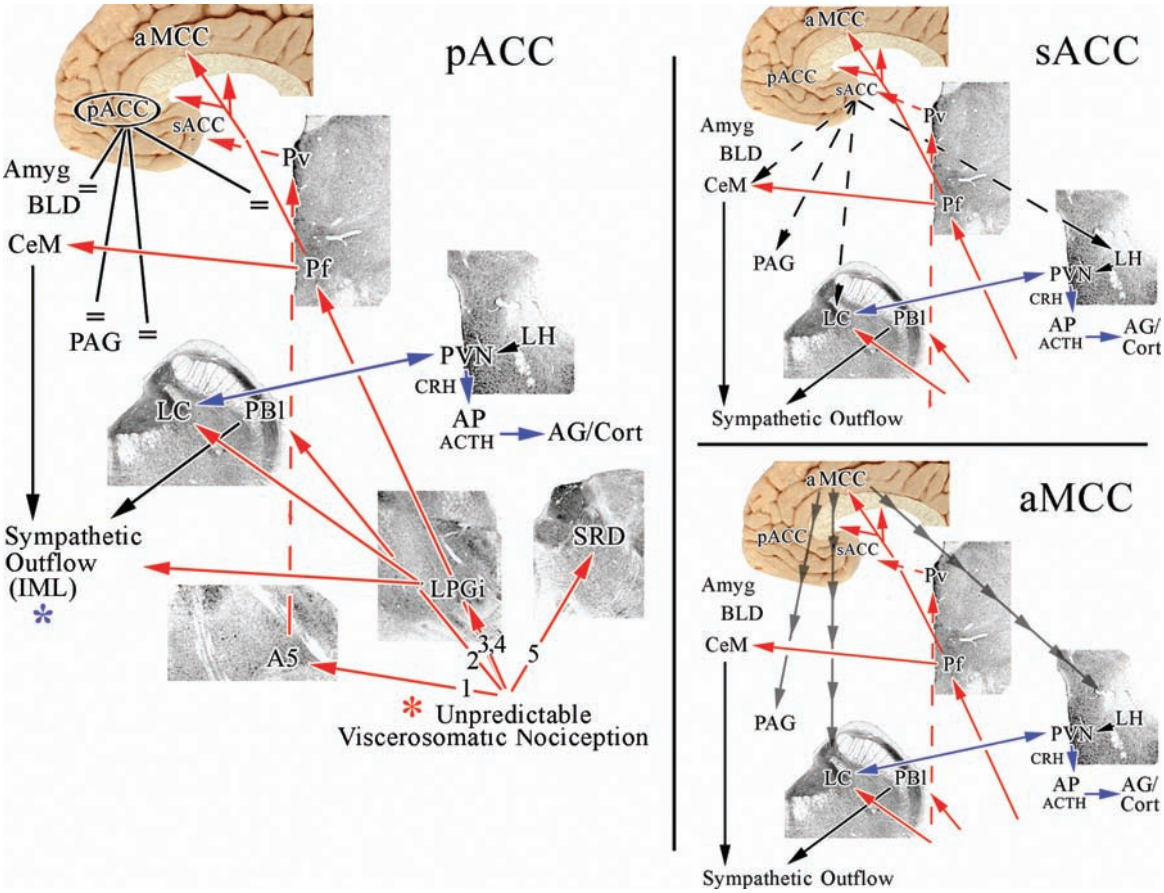

Fig. 22.14 Nocigenic model of cingulate-mediated changes in chronic pain and stress circuits (e.g., IBS). pACC: The underlying drive in the model is chronic and unpredictable viscerosomatic nociceptive stimuli as shown with the red asterisk (left panel) and via projections with numbered arrows to five subcortical sites. Subsequent projections of CV (red, dashed) and nociceptive (solid red) are the same as in Fig. 22.12. Reduced output from pACC is considered with blocking of its output (black double lines). sACC: This subregion may be disregulated but functional and this influence on subcortical autonomic systems is highlighted with dashed arrows. Finally, the LC driving of the HPA axis (blue) is shown to link driving of the stress and autonomic output circuits including the IML (blue asterisk). aMCC: A pivotal feature of this model is hyperactivation of aMCC and driving of particular subcortical structures including the PAG, LC, and LH (multiple, shaded arrowheads). Pain may be enhanced by a disinhibitory action of aMCC on the PAG and by SRD projections to the DNFS.

(1) elevated outputs of aMCC, (2) 'normal' output of sACC and likely (3) reduced output from pACC into allostatic circuits.

Altered pain processing need not be only linked to afferent nociceptive systems as shown initiating the nocigenic model in Figure 22.14, but they may also include facilitation of afferent nociceptive signals via descending systems as reviewed in Chapter 15. There are two potential mechanisms for pain facilitation that have been shown in rodents: inhibition of PAG presumably by removing activity in the DNIS and facilitation of pain via the descending noxious facilitatory system (DNFS) through the SRD. Activity via either of these mechanisms may enhance pain perception and the aMCC hyperactivation could facilitate pain via the SRD. As neither of these mechanisms have been demonstrated in primates, there is a need for both their demonstration in primates as well as their potential role in chronic pain and stress syndromes.

Role of Cingulate Cortex in a Psychogenic Model of Stress Disorders: pACC

No chronic pain/stress model can be devoid of psychogenic forces and the role of anticipatory activation of aMCC noted above is certainly critical to the 'nocigenic'

model. The implication in a 'psychogenic' model, however, is that cognitive, top–down processing is the predominant feature of the symptom etiology rather than sensory afferents. Certainly, anticipatory responses are also relevant here but there is not a nociceptive trigger in the periphery. Rather, in the psychogenic model, there is a critical blocking of self-relevant and context-dependent information flow into the cingulate gyrus. In Chapter 13 a six-stage model is developed according to how such information accesses the cingulate gyrus through the ventral posterior cingulate cortex (vPCC). One of the cardinal symptoms of PTSD is avoidance of triggers associated with the traumatic event and we model this in Figure 12.15 as a block (double red lines) of processing of multi-sensory inputs to vPCC and a subsequent inactivation of pACC processing (oval around pACC). As discussed in Chapter 21, the cardinal cingulate-mediated response in PTSD is an inactivation of pACC.

Posttraumatic stress disorder

PTSD is an example of a psychogenic form of chronic stress in that it can be generated without activation of nociceptive afferents but by traumatic visual or auditory events and alters the functions of ACC (Shin *et al.*, 1997, 2001; Chapter 21). Symptom severity in PTSD assessed with fearful versus happy faces is negatively correlated with activity in pACC (Shin *et al.*, 2005). As the pACC has a prominent role in cardiovascular regulation (Chapter 10), it is not surprising that traumatic imagery generated in PTSD-combat veterans is associated with a three-to-six fold increase in heart rate, skin conductance, and electromyographic responses (Shin *et al.*, 2004). In these same patients, there was a reduction in blood flow in pACC, while there were increases in activity in the amygdala (see also Chapter 9). Finally, there is a reduction in pACC activity in veterans with PTSD during exposure to combat sounds when compared to veterans without PTSD. Thus, it is well established that pACC has impaired function in PTSD and this correlates with an increase in amygdala activity.

PTSD-dominant blunting of pACC output

One of the pivotal features of the rewired circuitry shown in Figure 22.15 is the blunting of pACC output. This is a prominent feature of the model because most changes in the functional assessment of PTSD discussed above and in Chapter 21 are associated with reduced activity such as those to combat sounds in veterans with PTSD versus those without PTSD. There is some involvement of sACC but area 25 is not a prominent part of most reports reviewed in this chapter. The blunted response has been demonstrated with many different stimulation paradigms and changes in ACC are generally an inverse function to those observed in the amygdala. In this context, the amygdala increase in activity has been proposed to be critical to uncontrolled fear and anxiety in PTSD (Chapters 9 and 21).

Beyond the amygdala BLD, as well as other nuclei with neocortical inputs, blunting is shown in other major sites of pACC inputs including PAG, LC, Pf, Pv, and LH. We cannot yet predict the multi-synaptic outcomes through these systems but we can suggest a number of possibilities without going into great detail. First, deafferenting the PAG could be associated with uncovering rage and heightened fight-or-flight responses as shown with electrical stimulation into the PAG that generate sham rage. Second, deafferentation of the LC could reduce its discharges in relation to emotional stimuli and remove context-dependent firing. Such an outcome could enhance the general attentive and sensory scanning mode of activity (tonic mode of firing) at the expense of detailed sensory information processing. Third, deafferentation of the Pf and Pv thalamic nuclei could lead to impaired transmission of nociceptive information to cingulate cortex and might leave the MITN more active as shown in deafferentation pain syndromes (Rinaldi *et al.*, 1991). This could also disrupt processing through the descending noxious inhibitory system via the PAG. Fourth, the LH is left deafferented by the pACC, however, elevated sACC and aMCC activity could actually lead to an excess driving of the LH and changes in the HPA axis during allostasis.

Unrestrained sympathetic-outflow: sACC/amygdala

The model in Figure 22.15 leaves many of the allostatic systems intact during acute stimulation. In the framework of reduced regulation by pACC and enhanced activity in the CeM nucleus of the amygdala, the overall sympathetic flow through this system is enhanced during allostasis. Although enhanced sACC is not recognized in most imaging studies, it is part of the same autonomic outflow system reviewed in Chapter 10. The enhanced outflow to the IML, of course, interfaces with the HPA axis in the adrenal gland as shown in Figure 22.1 and this leads to acute enhancement of cortisol release.

As anticipatory responding does not appear to alter activity in sACC, we include the descending projections from area 25 as a critical link that continues to drive the LH and LC. This may be one of the most important cingulate dissociations to resolve from the present analysis; anticipatory disruption of descending area 32 projections to the PAG with intact area 25 projections that drive cardiovascular and hormonal responses. A block of area 32 may remove inhibitory control of the LH and also lead to increased activity in the HPA axis

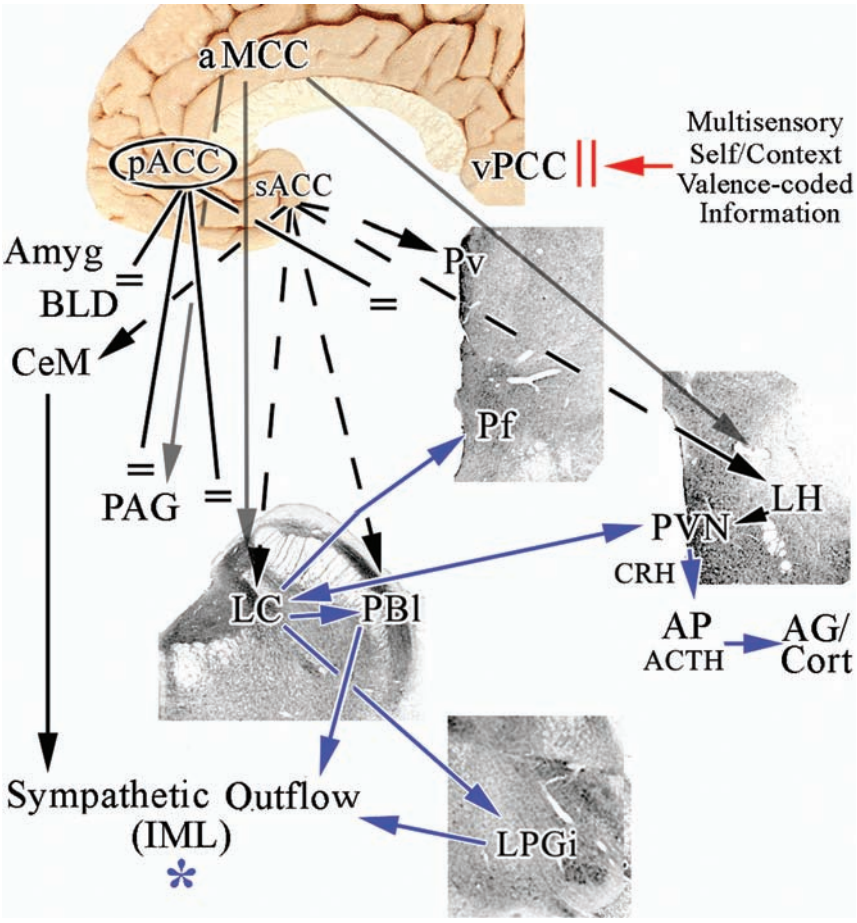

Fig. 22.15 Psychogenic model of cingulate-mediated changes in PTSD. The PTSD-dominant cingulate response involves blunting of pACC projections (double black lines). The model assumes an impairment of multi-sensory processing that normally delivers self- and context-dependent, valence-coded information to the cingulate gyrus (shown in red as a block of vPCC inputs). The sACC may not have an enhanced output in the chronic pain and stress syndromes, although it has been implicated in a few studies. Its output nonetheless, in the absence of pACC, may enhance autonomic functions as might projections from aMCC (shaded, non-stroked arrows). A pivotal aspect of the model is the LC-mediated driving of the HPA axis and other autonomic motor structures including the PBl and LPGi (blue arrows).

in addition to continued driving by sACC as discussed for intact systems above.

Completing the Model Circuits: The Locus Coeruleus Revisited

A complex argument and many facts have been presented as we moved from NEergic and cingulate circuit overlap, through issues relating to acute and chronic pain and stress to two key-circuit models of detailed mechanisms by which cingulate-mediated alterations interact with subcortical structures to generate symptoms associated with chronic diseases. Both circuits must now be completed with a few comments from the previous text on the impact these changes may have on the LC as an extrapolation from the two behavioral states of neuron firing.

Two modes of LC discharges and disruption of cingulate inputs

During the tonic mode of firing, LC neurons have high ongoing activity during poor task performance and weak and poorly discriminative, phasic responses to sensory stimuli during visual-discrimination testing. This is a state of high arousal and sensory scanning rather than high-resolution behavioral performance. During the tonic mode of LC firing, sensory processing and links to particular sensory stimuli are weak and the high tonic discharge rate may be adaptive to changing or unpredictable outcomes and more responsive to unexpected events. In this instance, the LC is involved in reflexive orienting and peripheral-sensitive driving. We propose that this state of high autonomic-mediated arousal is driven by sACC and reinforced by massive activation of aMCC which originates from anticipatory, fear, and anxiety and the blue circuits maximally drive this state in the models.

One consequence of the hyperdrive of the LC by the 'autonomic' input from sACC and support from the aMCC may be an over activation of the LC. This might prevent processing of specific sensory cues and associated orientation of the animal's attention to behavioral output and generally disrupt behavior associated with allostatic loads. Thus, the two states of scanning,

labile-attention with sensory driving is unbalanced with focused, task-oriented phasic behavior under allostatic loads. Responses during noxious footshock are of particular importance because unpredictable footshock is an animal model of chronic stress and it is particularly effective in driving LC output during the tonic mode of firing. Cingulate driving of LC activity is likely high during phasic and low during tonic modes of firing. The tonic mode is a state of high arousal and lacks sensory details as shown with target detection. In contrast, the phasic state of firing involves detailed sensory inputs, cingulate driving and accurate behavioral output. Thus, a functional circuit for cingulate-mediated, sensorimotor processing occurs during phasic-mode LC firing.

This model predicts that cingulate cortex driving of the LC changes in chronic stress. During early nociceptive activation such as physical abuse or rape, the tonic mode of firing is initiated and cognitively demanding processing dependent on cingulate cortex is not possible with pain-driven processing distracting MCC from cognitive processing tasks (divided attention of Corbetta *et al*., 1991). Intermittent and unpredictable noxious stimulation may turn this into a persistent, cingulate state of impaired processing and may have permanent consequences for cingulate cortical processing; even when noxious stimulation is discontinued. The long-term consequences of physical abuse and rape have been documented in terms of functional gastrointestinal syndromes, altered stress-hormone responses, and in the execution of cognitively demanding behaviors (Leserman *et al*., 1997; Devroede, 2000; Heim *et al*., 2000).

LC output and stress sensitization drive autonomic circuits in both models

Although the blue arrows reflecting allostatic circuits are similar in both circuits presented in Figures 22.14 and 22.15, we noted already that the LC may be differentially engaged by cingulate disruptions. Stress sensitization assures that the LC has an abnormally elevated activation during aMCC driving in the former and sACC/aMCC drive in the absence of pACC control. The hyperdrive of LC during stress sensitization has been thoroughly considered by Bremner *et al*. (1996). Support for this notion is extensive and depends on the key observation that chronic stress (stress sensitization) drives an increase in LC neuron output (Pavcovich *et al*., 1990). Thus, in both circuits balancing the LC to a tonic mode of discharge by altered cingulate inputs and enhanced LC discharges into subcortical circuits that mediate autonomic activation result in uncontrolled autonomic output and enhances fear, anxiety, and arousal via direct connections in the CNS and by autonomic feedback to the NTS, PB, and PAG.

Beyond Multi-system Circuitry

One of the hypotheses explored here is that central nociceptive sensitization and stress sensitization share common sites of action defined by the major targets of nociceptive and DBH inputs. These sites include ACC, MCC, LC, and particular parts of the MITN, amygdala, hypothalamus, PAG, and PB. We conclude with the possibility that pain processing and allostasis might enhance sensitization in both systems where convergence of circuits is greatest and these are the network nodes at greatest risk in chronic pain and stress syndromes.

Although this view provides an outline of vulnerable structures and hypotheses as to which aspects of information flow are impaired, much is left to be done. The actions of transmitters in most systems beyond the HPA axis are not known before and after chronic stress, mechanisms of transduction including alterations in receptors and G-protein coupling will need analysis as will the specific changes in neuron discharge properties in each structure. The circuits outlined above are just the bare bones of system organization and the relevant players in this drama.

The new age of human neuroimaging will continue to provide key information about the involvement of particular cortical areas in chronic pain and stress syndromes, but there will also be continuing shortcomings in these efforts unless resolution improves greatly. Involvement of particular nuclei and small areas are still out of the range of functional imaging modalities. Simple increases and decreases in blood flow are far removed from neurochemical and electrophysiological mechanisms of action.

The potential for further insights from human neuroimaging in this area of research are still great. Although animal models have emphasized the HPA axis, functional imaging is filling in a new dimension of pain and stress alterations associated with cortical regions that may not be present in some species. As a consensus in observations evolves over the coming years, we can expect to understand the detailed relationships between subregions of cingulate cortex in acute pain and the evolution of complex chronic stress syndromes that may have etiologies in childhood. Of equal importance is work on the cortical mechanisms of pain and stress sensitization in limbic structures that eventually will emerge from this line of investigation.

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