CHAPTER 10

Visceral Circuits and Cingulate-Mediated Autonomic Functions

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Chapter contents

Involvement of cingulate cortex in visceral function has been long known. The classical electrical stimulation studies of Smith (1945), Pool and Ransohoff (1949), and Kaada (1951) provided a rich substrate of information showing that anterior cingulate cortex (ACC) was part of a broad swath of orbitofrontal, insular, and temporal pole cortex that regulates visceral functions. In spite of technical issues relating to the intensity and duration of stimulation, these investigators showed that autonomic responses were not the result of current spread from the cingulate gyrus because electrical stimulation in adjacent cortex did not produce such changes and ablation outcomes were as predicted. Most importantly, subsequent studies such as those of MacLean (1990) and Talairach *et al*. (1973) confirmed autonomic and skeletomotor responses and circuitry studies showing cingulate projections to visceral autonomic nuclei, the lateral hypothalamus (LH), periaqueductal gray (PAG), and intermediolateral nucleus of the spinal cord (IML) provided mechanisms to support the conclusion that evoked responses originated in cingulate cortex and were not due to current spread. A new generation of mechanistic studies in rodents emerged in the 1980s and 1990s in conjunction with very precise connection studies and validated the concept that autonomic activity could be generated by electrical stimulation of the subgenual ACC (sACC) and some of the subcortical intermediates to autonomic motor centers.

In the last decade human functional imaging studies have provided important new insights into the role of cingulate cortex in visceral function and raise questions about its role in conscious perception of visceral events, stress-mediated activity, and cognitive processing. Surprisingly, however, this literature is often uninformed by the earlier work which provided information that cannot be acquired in any other way than direct electrical stimulation of the cortical surface. Interestingly, the human imaging studies during visceral stimulation do not resolve the extent to which cingulate activations are the result of sensory, motor, stress, and/or anticipatory responses and the extent to which cingulate-mediated autonomic and skeletomotor drive are coordinated. Correlation studies that consider brain activity in relation to measures of autonomic output, such as heart rate and systolic blood pressure, provide new information about the contributions of subregions of cingulate cortex; particularly when subtraction methods are used to analyze the data.

Goals of This Chapter

One of the primary goals of this chapter is to merge two bodies of research findings including stimulation/circuitry and functional imaging in the context of the four-region model of cingulate cortex. Indeed, one of the main reasons for differentiating MCC from ACC is that they both engage in qualitatively different activities (skeletomotor versus autonomic, respectively) that are mediated by different subcortical projections and have different roles in emotion, response selection, and cognitive functions (Vogt *et al*., 2004). Ideally, the model makes specific predictions and provides a logical framework to interpr*et all* cingulate activations regardless of the paradigm and statistical methods used to localize cingulate activity. In reality, the model is not complete and some of the interpretive leaps require clarification in the coming decades. Before the functional imaging literature can be interpreted, however, it must be resolved to what extent there are sources of visceral sensory input and motor outputs from each subregion and their underlying circuitries. The specific goals include the following:

1 Summarize electrical stimulation findings emphasizing ACC-associated changes with cardiovascular hypotensive responses and pilomotor activity.

2 Identify primary and secondary sources of viscerosensory inputs to cingulate cortex including baroreceptor and colon nociceptor afferents through the thalamus, as well as innocuous, mechanical, chemical, and taste afferents. A seamless integration of animal and human studies attempts to remove barriers between these categories of research.

3 Define visceromotor output functions of cingulate cortex and their underlying circuits including those to the amygdala, hypothalamus, and periaqueductal gray.

4 Micturition provides a well-controlled experimental paradigm for regulating visceral sensory afferents, parasympathetic motor control of sphincters, and cognitive control in terms of anticipation, intent, and successful release.

5 Clinical intervention in stress urinary incontinence is reviewed as an exciting new strategy for treating cingulate-mediated disruptions in visceral control functions.

6 Based on the four-region model, two fundamental paradoxes are considered in terms of the role of ACC in visceral integration. The first assesses the role of MCC in visceral functions and the second considers the possible roles of PCC and RSC in them to resolve these paradoxes on the basis of model predictions.

7 Evaluate human functional imaging findings in the context of circuitry and cognitive issues including innocuous and noxious gastrointestinal activity, anticipation, thirst, and premotor orientation of the body is spatial contexts.

Electrically Evoked Autonomic Activity

The most prominent and consistent finding of electrical stimulation studies, regardless of species including rat, cat, monkey, and human, is that electrical stimulation of ACC evokes changes in autonomic activity. The primary changes included reduced blood pressure, inhibition of respiration, penile erection, and a reduction in heart rate (Ward, 1948; Kaada, 1951; Dua and MacLean, 1964). Increases in gastric motility (Hurley-Gius and Neafsey, 1986) and gastric acid secretion (Henke, 1983) also have been reported in rodents.

In many instances, human studies supported these observations; although some responses were likely due to patient characteristics. Pool and Ransohoff (1949), for example, reduced respiration by stimulating pregenual ACC (pACC), but in all cases elevated blood pressure. Their subjects were schizophrenics that had received extensive electroconvulsive shock treatments. A study by Smith (1945) made the interesting observation that cardioinhibitory effects following electrical stimulation were accentuated with the acetylcholinesterase inhibitor physostigmine. The effect was an enhanced inhibition and prolonged beyond the period of cingulate cortex electrical stimulation. He suggested this was a result of activating vagal inhibitory innervation of the heart. Finally, a case of pilomotor seizures originating in ACC (Seo *et al.*, 2003) is discussed in detail by Nadkarni and Devinsky in Chapter 29. This patient's seizures validate the role of ACC in autonomic responses shown with electrical stimulation.

Complete reviews of the extensive electrical stimulation literature are provided by MacLean (1990), Neafsey (1990), Neafsey *et al.* (1993), and Buchanan and Powell (1993). Consideration of the distribution of negative and positive sites that drive autonomic output suggests that the entire cingulate gyrus is not equally engaged; rather, the ACC is the most active region. Moreover, although there are limited reports of anterior midcingulate cortex (aMCC) driving of autonomic activity, there appears to be no such activation during stimulation of posterior MCC (pMCC), PCC, or RSC. This selective autonomic driving by ACC raises one of the essential paradoxes in the human functional imaging literature as discussed below.

Visceral Sensory Afferents

Baroreceptor afferents

Direct linkage between single cingulate neuron discharges and cardiac and respiratory outputs suggests a direct corollary discharge from viscerosensory brainstem nuclei. Frysinger and Harper (1986) reported ACC and aMCC neuron discharges that correlated with maximal arterial pressure and breath-breath cycle respiration in freely moving cats. Moreover, Gibbs and Powell (1991) reported different classes of ACC neuron responses in rabbits during classical conditioning and heart rate monitoring (see also Buchanan and Powell, 1993). More than half of the neurons that demonstrated a conditioning-related change "exhibited tone-evoked activity changes that were reliably correlated with concomitant heart rate changes on a trial-by-trial basis." They concluded that neuronal activity in ACC is related to Pavlovian conditioning changes in heart rate activity, whereas that in the insula is not; drawing an important distinction between insular and ACC autonomic-related activity. These findings together support the hypothesis that ACC receives a heart rate signal that plays a role in conditioning and this signal arises from baroreceptor afferents. The CNS circuitry mediating baroreceptor afferents supports this hypothesis.

A key source of cardiosensory inputs to ACC likely arises from corollary discharges of the noradrenergic A5 cell group in relation to baroreceptor reflexes. A photograph of this nucleus immunoreacted for Microtubule-Associated Protein 2 (MAP2) in the monkey is shown in Figure 15.7. The A5 nucleus is noradrenergic, expresses the synthetic enzyme dopamine-β hydroxylase (DBH), lies just dorsal to the lateral superior olive, and mediates the baroreflex response. Thus, electrical stimulation therein changes blood pressure and heart rate as reviewed by Byrum and Guyenet (1987). Most importantly in the present context is the fact that the A5 nucleus projects to many autonomic regulatory sites (Byrum and Guynet, 1987). Nuclei receiving A5 afferents include the central nucleus of the amygdala (CeA), lateral hypothalamus (LH), PAG, parabrachial nucleus (PB), nucleus of the tractus solitarius (NTS), and the paraventricular nucleus of thalamus (Pv). Thus, A5 provides a heart rate signal for key limbic structures including the Pv of thalamus.

The Pv projects directly and most prominently to ACC in the monkey (Vogt *et al.*, 1987). Since the Pv is one of the primary projection sites of the A5 nucleus, the Pv provides direct access of baroreceptor output from A5 to ACC. A similar projection of Pv does not appear to terminate in PCC. Moreover, ablation of area 25 in the rat sACC blunts baroreceptor reflexes (Verberne *et al.*, 1987) and classically conditioned changes in heart rate and blood pressure (Frysztak and Neafsey, 1994). This suggests a pivotal role for area 25 in cardiovascular function, particularly for behavioral performance.

Figure 10.1 is an overview of circuitry that may provide corollary baroreceptor inputs to limbic structures and is based in part on the work of Byrum and Guyenet (1987) in the rat and Vogt *et al.* (1987) and Chapter 22 in the monkey. A heart rate signal arises from baroreceptor projections via the IX and X cranial nerves projecting to

NTS and projections from there to A5 as shown by the blue pathway in Figure 10.1. The A5 nucleus has massive and reciprocal connections with PB and NTS and significant projections to PBl, PAGvl, and Pv. Innervation of PBl and PAG are shown because these are important targets of descending outflow from ACC and CeA. The noradrengeric, DBH+ axons in Pv are shown in Chapter 22 suggesting that the Pv nucleus in monkey is also heavily innervated by A5. Finally, the heaviest retrograde labeling of Pv neurons following horseradish peroxidase injections into monkey cingulate cortex followed those in area 24 (Vogt *et al.*, 1987). No such labeling was observed following injections into MCC, PCC, or RSC. In the cat, Pv projects heavily to ACC including area 25 (Royce *et al.*, 1989). Thus, ACC has a source of baroreceptor input through the Pv nucleus of thalamus and this fact provides a hypothesis for baroreceptor responses in human functional imaging studies.

Mechanical and chemical afferents

Although most studies employing noxious gastrointestinal stimulation evoke activity in cingulate cortex, innocuous stimulation produces small and more variable responses and some none at all. Ladabaum *et al.* (2001) evoked a substantial pair of cingulate activations during innocuous distension of the esophagus (coded black, second plate, Fig. 10.2). Hobday *et al.* (2001) applied innocuous pressure to the rectum and anus on two separate testing days and a MCC response was generated during stimulation. Although there may not be a pathway specific for innocuous mechanical input to cingulate cortex, these responses may be part of a wide-dynamic range pathway that includes a more prominent nociceptive component. This organization has been reported for the thalamus and ACC in studies of cutaneous stimulation. Thalamic (Dong *et al.*, 1978) and cingulate cortical (Sikes and Vogt, 1992) neurons

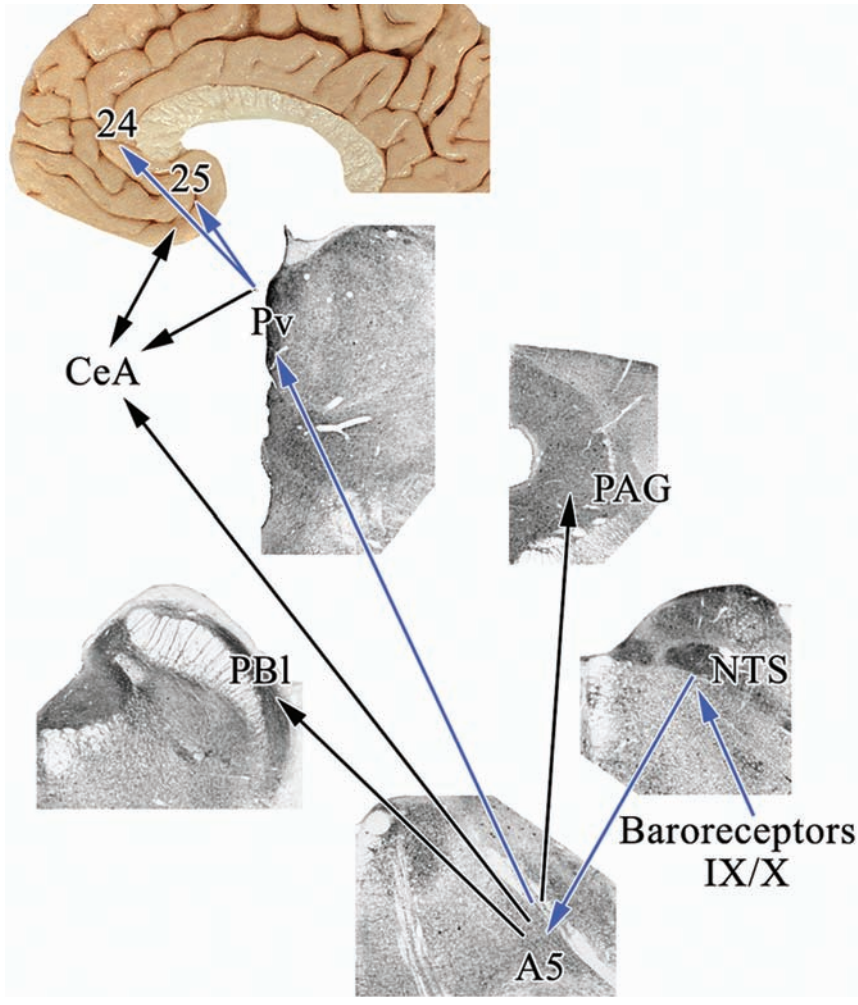

Fig. 10.1 Coronal sections from a monkey in Figure 15.7 were used to construct a circuit diagram of baroreceptor afferents to A5 and corollary discharge throughout visceral and limbic structures. The medial surface is from a human case. Importantly, the CeA receives direct input from A5 and Pv, while areas 25 and 24 of ACC receive input from Pv and this projection does not appear to extend beyond ACC.

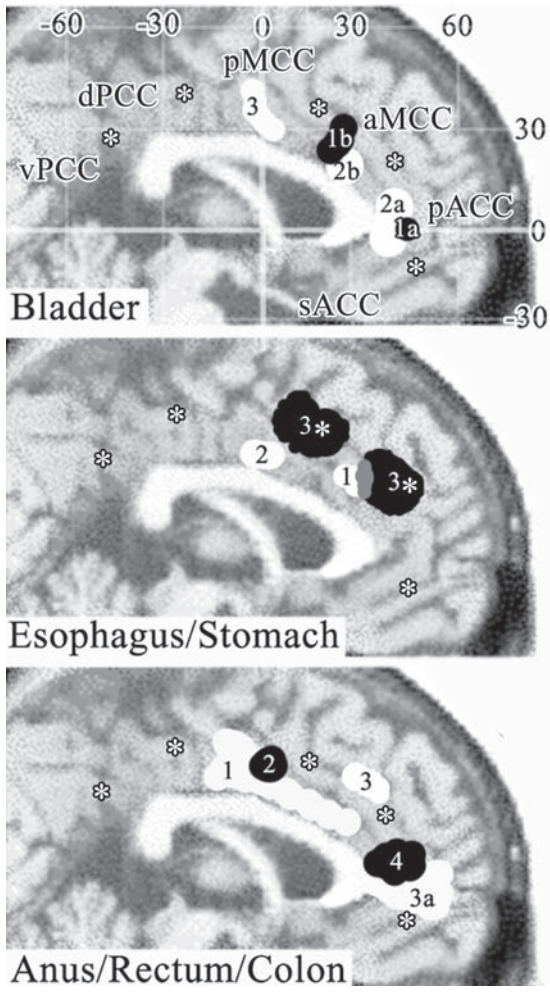

Fig. 10.2 Distribution of activity during stimulation of three visceral organ systems. Bladder: Matsuura *et al.* (2002) 1a, distension/maximum desire to void, 1b, ice-cold water; Blok *et al.* (1997) 2a, micturition successful, 2b, unsuccessful; Nour *et al.* (2000) 3, urge to micturate. Esophagus/Stomach: Strigo *et al.* (2002) 1; Binkofski *et al.* (1998) 2; Ladabaum *et al.* (2001) 3. Anus/Recutm/Colon: Lotze *et al.* (2001) 1, non-painful rectum and anus; Hobday *et al.* (2001) 2 innocuous rectum; Naliboff *et al.* (2001) noxious colon and anticipation of stimulation 3a; Mertz *et al.* (2000) 4 noxious rectal distension. Black, stroked asterisks mark borders between each subregion.

respond primarily to noxious cutaneous stimulation but also have a tap response that could result from innervation of pressure receptors by nociceptive afferents. In a similar manner, a primarily noxious visceral pathway may also provide a limited amount of innocuous information and this may not be distinguished in some imaging paradigms. Finally, it is possible that cognitive reports of discomfort during bowel distension cannot make a clear distinction of innocuous and painful perceptions because of the organization of this afferent system.

Visceral afferents arising from innocuous mechanical and chemoreceptors appear to have limited access to cingulate cortex. The only nucleus in the thalamus to receive direct NTS input is the ventroposterior medial nucleus (Beckstead *et al.*, 1980) which does not project to cingulate cortex. A major projection, however, does terminate in both divisions of the PB nucleus (Beckstead *et al.*, 1980) which in turn projects to the parafascicular thalamic (Pf) nucleus (Pritchard *et al.*, 2000). Since the Pf itself projects to cingulate cortex (Vogt *et al.*, 1987; Royce *et al.*, 1989; Hatanaka *et al.*, 2003), this is a likely source of cingulate afferents. The blue-labeled pathway with thin arrows in Figure 10.3 shows this visceral afferent circuit. This is more than speculation on how such a system is organized because many human imaging studies have shown activity in cingulate cortex associated with innocuous distension of the gastrointestinal tract as discussed above.

It should also be noted in Figure 10.3 that the PB source likely intermingles innocuous with nociceptive inputs from the spinal cord. The PB nucleus, therefore, is a visceral nociceptive integration center (Ma *et al.*, 1989; Bester *et al.*, 1995; Saper, 2000). At this time it appears unlikely that the innocuous and nociceptive pathways are segregated into separate channels through PB and Pf, however, such a segregation may not be necessary when interpreting human imaging responses in cingulate cortex.

Taste

One of the striking findings of an electrical stimulation study in awake monkeys was that ACC stimulation was associated with water intake (Robinson and Mishkin, 1968). Decades later, a number of important human imaging studies have shown activity in cingulate cortex associated with taste, food texture, and odors. Here we emphasize taste and Chapter 8 considers these stimuli in terms of their reward properties including thirst quenching.

Figure 10.4 is a reconstruction of activation sites generated by oral stimulation in human functional imaging studies and numbered as follows: 1. Intravenous infusion of hypertonic saline induced thirst and elevated rCBF in ACC and aMCC bilaterally (Denton *et al.*, 1999a). 2. Zald *et al.* (1998) stimulated the mouths of healthy women with an aversive hypertonic saline solution and elevated rCBF in ACC and aMCC. A subset of subjects with a moderately unpleasant experience rather than an extremely unpleasant one had a much smaller change in rCBF suggesting that the aversive perception was generated in the cingulate gyrus. 3. A sucrose solution contrasted to a tasteless solution was shown by de Araujo *et al.* (2003) to elevate activity in pACC. It is interesting to note that all three studies activated an overlapping site in pACC, although the Zald site

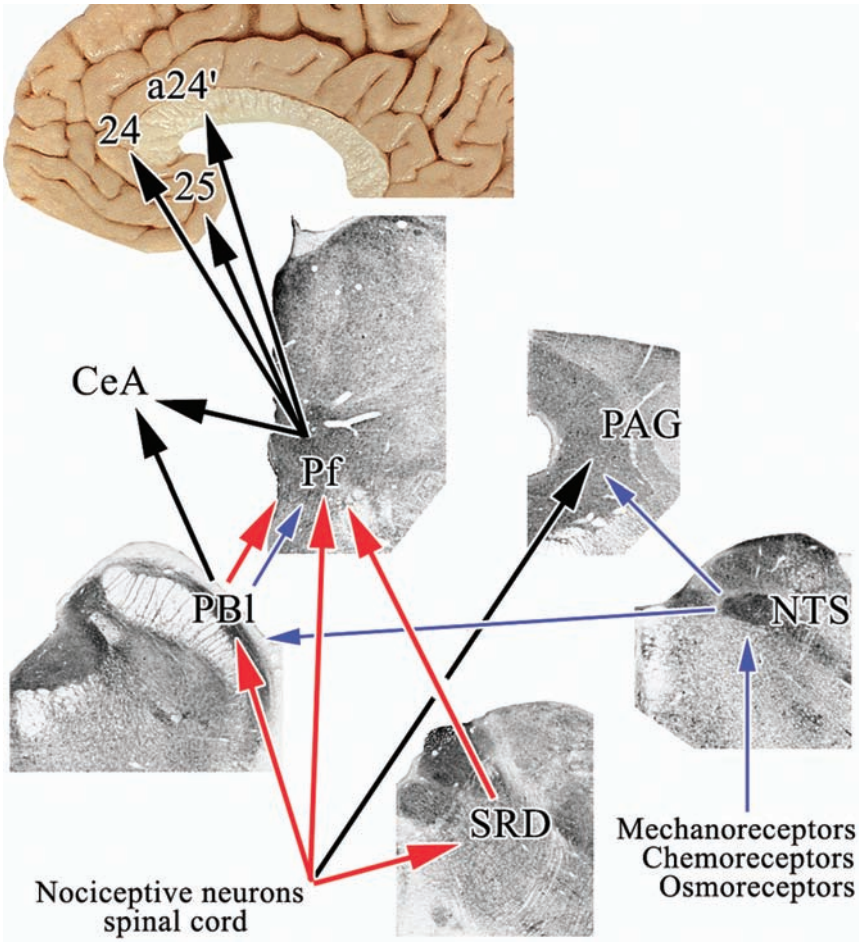

Fig. 10.3 There is likely limited access of innocuous visceral inputs to cingulate cortex from NTS (thin, blue arrows). In contrast, there are many routes by which nociceptive visceral inputs access this system (thick, red arrows) including the SRD and PB and directly from the spinal cord via the spinothalamic tract.

extended into sACC, and Zald and Denton also engaged individual sites in aMCC and pMCC. Oral stimulation generated by hypertonic saline did not evoke activity in PCC or RSC; however, while these three studies confirm a role in thirst and seeking water, the correlation of thirst rating, regardless of how it was generated (hypertonic solution i.v. or on tongue) or resolved (washing tongue with water), Denton *et al.* (1999b) uncovered a large site in vPCC/RSC that was correlated with thirst (1a, Fig. 10.4) and this will be considered below in terms of the behavioral relevance of these activations.

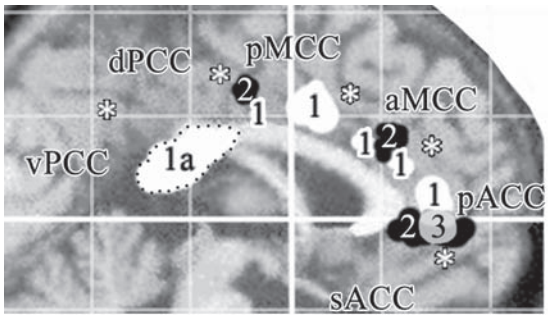

Fig. 10.4 Reconstruction of activity generated by oral stimulation in three studies; A. Denton *et al.* (1999a), B. Zald *et al.* (1998), and C. de Araujo *et al.* (2003). All three studies activated an overlapping site in pACC.

Nociceptive visceral afferents

The effectiveness of visceral throughput to cingulate cortex is demonstrated by numerous visceral stimulation studies. Since these responses are mainly nociceptive, Chapter 14 considers in detail the nociceptive processing of visceral and somatic stimulation. A pair of units in an anesthetized rabbit is shown in Figure 10.5 from our preliminary studies (Sikes and Vogt) to emphasize the latter point. These units were recorded simultaneously from the superficial and deep layers of pACC during balloon distension of the distal colon. Since the units were recorded simultaneously, differences in the responses can be attributed to differences in circuitry and not to variations in the response to anesthesia (Halothane and pancuronium). The anesthetic protocol

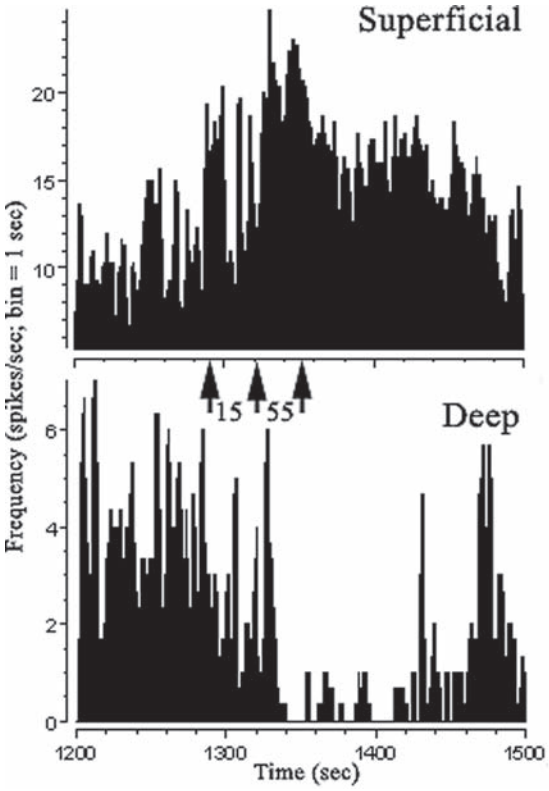

Fig. 10.5 Simultaneous extracellular recordings from a neuron in the superficial and one in the deep layers of rabbit pACC during balloon distension of the distal colon. The onset of innocuous (15 mmHg) and noxious (55 mmHg) stimuli are shown with arrows in these rate histograms as is the offset of stimulation with the third arrow.

also assures that motor reflex pathways are not engaged and the cingulate responses are sensory and not corollary discharges from motor nuclei involved in reflex responses.

The onset of innocuous (15 mmHg) and noxious (55 mmHg) distension are shown with arrows in these rate histograms as is the offset of stimulation with the third arrow in Figure 10.5. Although there is a small change in activity in the superficial unit to 15 mmHg stimulation; the primary excitatory response was evoked by noxious stimulation and it was maintained for about 2 minutes. In contrast, the deep-layer unit was slightly inhibited with the innocuous stimulus, while the noxious stimulation generated a prolonged period of inhibition and it was slow to recover to baseline firing. Thus, as predicted from circuitry studies, a major visceral afferent signal to cingulate cortex is nociceptive and intrinsic circuitry in pACC generates different patterns of activity. This finding along with human imaging observations establishes that the role of ACC in visceral function is not simply visceromotor regulation as early conceived in rodent studies by Neafsey *et al*. (1993) but must be generalized to a visceral, sensorimotor integration site.

The most consistent finding during visceral stimulation anywhere in the human gastrointestinal tract is that noxious stimuli are the most effective in driving excitatory cingulate activity. Activation sites for some of these studies are outlined in Figure 10.2. Binkofski *et al*. (1998) stimulated the distal esophagus and could only activate MCC with noxious distension, while Strigo *et al*. (2003) activated a part of aMCC following similar stimulations. This was also true for the rectum (Mertz *et al*., 2000) and urinary bladder (Matsuura *et al*., 2002). Some studies that showed innocuous responses also showed noxious activations (Ladabaum *et al*., 2001), although a number of studies did not evaluate nociceptive responses (Hobday *et al*., 2001; Lotze *et al*., 2001). Thus, noxious distensions of the viscera activate ACC and MCC. The question raised in the human studies is to what extent the activity is associated with primary sensory afferent drive from the viscera and to what extent it is associated with cognitive variables such as anticipation, orienting the body to the noxious stimuli, or nocifensive responses.

Visceral nociceptive circuitry

Visceral input to the cingulate gyrus is associated mainly with nociception and the likely sources of such inputs are shown in Figure 10.3 and contrasted with a likely source of innocuous inputs. Although these issues are considered in detail in Chapter 14, they are summarized here because of the prominant role of nociception in cingulate-mediated visceral responses. There are two major sources, and possibly a third of nociceptive visceral inputs to cingulate cortex and they all appear to pass through Pf (Vogt, 2005). First, visceral nociceptive responses are a prominent part of PB activity (Bester *et al*., 1995; Saper, 2000) and the PB nucleus projects to Pf (Bester *et al*., 1999). Second, the subnucleus reticularis dorsalis (SRD) is comprised of neurons that are primarily nociceptive and respond to stimulation of the entire body including the viscera (Roy *et al*., 1992; Le Bars, 2002; Lima and Almeida, 2002). The SRD has a massive projection to Pf (Villanueva *et al*., 1998). Third, there is some evidence that inputs to Pf are viscerosomatic (Ammons *et al*., 1985) and the spinothalamic tract terminates in CM/Pf (Apkarian and Hodge, 1989). Figure 10.3 summarizes the termination of spinal projections in PBl, SRD, and Pf and subsequent projections of the two former nuclei to Pf.

The projection of Pf to cingulate cortex is mainly to area 24 and some to area 25 (Vogt *et al*., 1987) although it does project to the aMCC and much less to the pMCC. This latter point is supported by centre medianum/Pf projections reported for the rostral and caudal cingulate motor areas by Hatanaka *et al*. (2003). They showed

that about 26% of retrogradely labeled thalamic neurons were in this nucleus after rostral injections, while only about 12% were in centre medianum/Pf following posterior injections. No neurons labeled in Pf after large horseradish peroxidase injections in PCC/RSC (Vogt *et al*., 1987).

One difficulty interpreting human imaging studies of visceral functions relate to distinguishing anticipatory responses generated without the actual sensory stimulus from the stimulation response itself. Anticipation of noxious stimulation engages ACC and this is consistent with the fact that this region is involved in sadness and negative affect (Mayberg *et al*., 1999; Vogt *et al*., 2003). Naliboff *et al*. (2001) reported increases in rCBF in ACC associated with the anticipation of noxious distension of the sigmoid colon in control subjects. It is an interesting fact that the anticipatory and colon stimulation-evoked activity in pACC co-localize to the same cortex.

Simpson *et al*. (2001) reported anticipatory anxiety associated with noxious electrical finger shock that had an inverse relation with anxiety with least anxious subjects evoking the largest anticipatory reductions in ACC. Thus, the Naliboff *et al*. site is not only associated with anticipation of visceral pain and responses may be negative, not only positive. Finally, Porro *et al*. (2003) reported that anticipation of ascorbic acid injections into the foot was associated with negatively correlated sites in pACC (Chapter 16; Porro *et al*., 2002). Thus, studies involving noxious stimulation, visceral or cutaneous, will generate anticipatory activity in ACC whether or not innocuous control stimulation is interleaved in the paradigm. It is very difficult to "control" for anticipation, since it is part of the informed consent and the first few noxious stimuli generate enhanced-subject sensitivity even during innocuous control trials.

One corollary of these observations is that there is a high chance of reducing neuronal activity/rCBF during anticipation and this may bias pain studies to report increased activity in MCC and under reporting involvement of ACC. Finally, in terms of the consideration of visceral response paradoxes below, anticipation of visceral noxious stimuli does not explain visceral induced activity in MCC as anticipatory changes occur in ACC.

Efferent Cingulate Projections Regulate Autonomic Output

Electrical stimulation studies generally support the conclusion that sACC is involved in depressor responses including heart rate reduction, while pressor responses are more frequently observed during stimulation of area p32 sites and occasionally from aMCC; however, this latter structure is not a consistent player and is not considered further in this context. Gastric motility has also been observed during electrical stimulation of area 25 (Hurley-Gius and Neafsey, 1986; Neafsey *et al*., 1993) and ACC lesions block gastric ulcers caused by restraint stress in rats (Henke, 1983). The descending projections of ACC to autonomic regulatory structures mediate these responses. The major projections of areas 25 and 32 are to the CeA, lateral hypothalamus (LH), PAG, and PB, while much smaller projections to NTS and dorsal motor nucleus of the vagus (X) occur in monkey (Chiba *et al*., 2001) than in rat (Neafsey *et al*., 1993) and rabbit (Buchanan and Powell, 1993).

Figure 10.6 is an overview of essential outputs of ACC. Although the thalamus is reciprocally connected with all cortical areas including interactions of areas 24 and 25 with the parafascicular nucleus, the midline and intralaminar thalamic nuclei have no known role in descending visceral influences and are not included in the figure. Area 25 is the main part of ACC to mediate depressor cardiovascular responses through the LH and PAG, while the role of area 32 in pressor responses is less well understood. The four major subcortical projections of area 25 that mediate visceromotor control are shown with red arrows and numbered in the figure. The projections to the PAG, PBl, and NTS are essential intermediates in these responses and are discussed in detail in Chapters 14, 15 and 17 and experimental findings in rodents reviewed below. Since autonomic activity may be modulated by area 25 projections to the dorsal motor nucleus of the vagus (X) and NTS are weak in the monkey (Chiba *et al*., 2001), the projection is shown in the figure with small black arrows. Finally, Figure 10.6 shows a few of the essential efferent projections of PAG, PBl, and NTS that subserve autonomic regulation to emphasize their direct role in regulating autonomic output and the position of ACC in these circuits.

Rodent research has played an important role in uncovering the mechanisms of autonomic regulation and these culminated in a model of cingulate-mediated visceromotor control by EJ Neafsey and colleagues (1993). They conceived of the insula as the primary site of viscerosensory function, while ACC would receive its primary sensory afferents from the insula that would then drive subcortical visceral responses. It appears a reasonable conclusion from the entire electrical stimulation literature that sACC/area 25 reduces heart rate, while area 32 and possibly a24′, increase heart rate. Burns and Wyss (1985) showed that the largest hypotensive responses were evoked from area 25 in anesthetized rats. In a subsequent study, Fisk and Wyss (2000) injected lidocaine into either the lateral hypothalamus or PAG during electrical stimulation of area 25 and reported that greatest reductions occurred during block of PAG activity, although that in the LH was also significant. The projections of area 25 to the LH and PAG are well known and shown in Figure 10.6. They have been

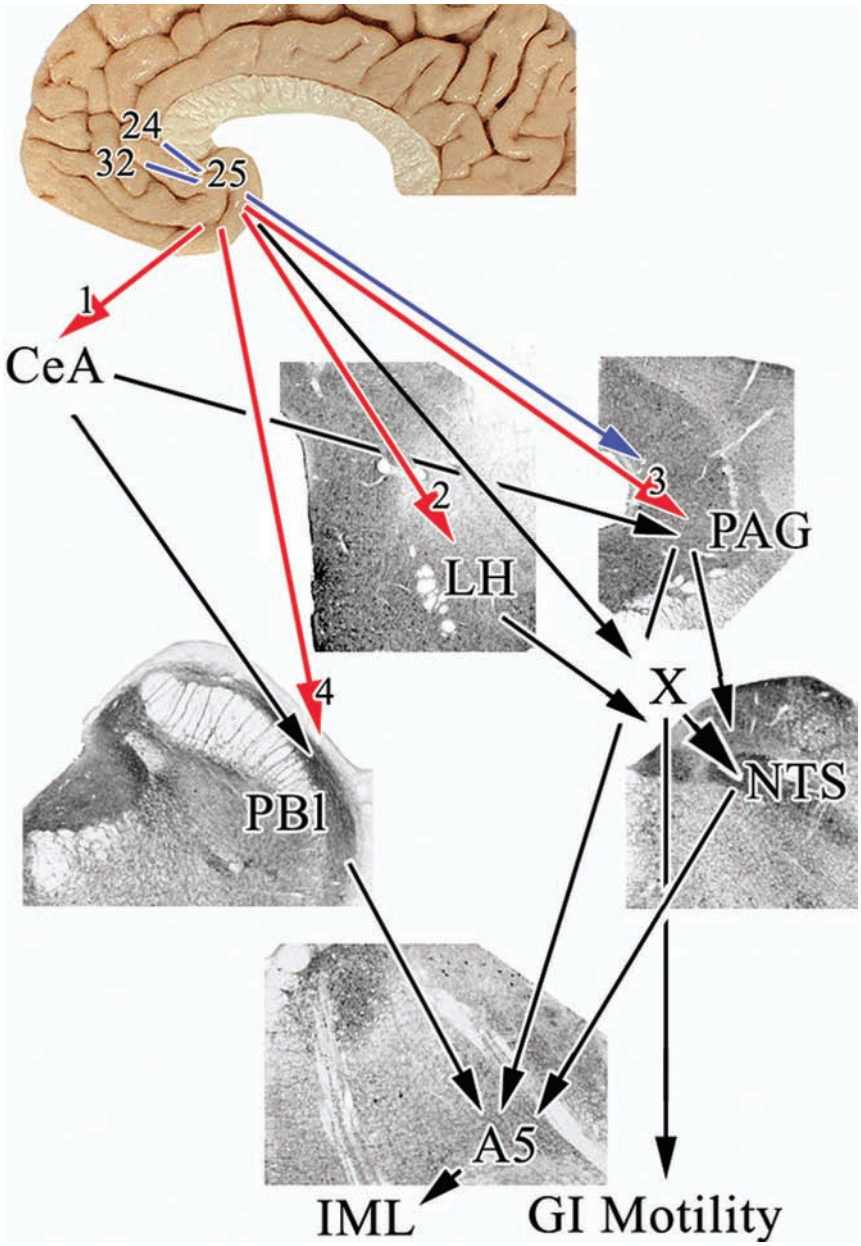

Fig. 10.6 The efferent control of cardiovascular, GI motility, and other visceral functions are mediated primarily by reciprocally connected CeA and area 25. The four main area 25 subcortical projections are emphasized with large red and numbered arrows. Areas 24 and 32 project to the PAG (blue arrow), while a small projection in primates is shown to the dorsal motor nucleus of X (small black arrows). A few of the prominent projections of each of these four structures are shown to emphasize their direct role in visceromotor control (large black arrows).

shown in monkey (An *et al*., 1998; Chiba *et al*., 2001), and cat (Room *et al*., 1985), and Fisk and Wyss (2000) initiated their studies in rat by showing both connections.

Fernandes *et al*. (2003) demonstrated that a pressor response evoked from area 32 was modulated by norepinephrine when injected into this region in unanesthetized rats. They also demonstrated that these responses were mediated by excitatory α1 receptors. The differential role of areas 32 and 25 in blood pressure may be important because both project massively to the PAG and could help to select the appropriate autonomic and skeletomotor reflexes during emotional motor activity. Indeed, norepinephrine exposure in the PAG selects between behavioral states in the PAG itself and enhances fight-or-flight responses (Bandler and Keay, 1996).

Finally, a moderate level of exercise that increases heart rate by 60-70% is associated with a post-exercise hypotension and this is associated with a significant reduction in rCBF in ACC (Williamson *et al*., 2004). Thus, the circuitry, functional activation/inactivation, and electrical stimulation and particular epilepsy cases support the role of ACC in a wide range of autonomic functions including specific cardiovascular changes.

Micturition

Although there are only a few studies available, together they provide a relatively complete perspective on the regulation of a complex parasympathetic function; one that requires sensory input and feedback and, in the male, successful acquisition of a target devise. This is one of the rare instances where experimental control is so tight that all observations produce a complimentary and compelling account of cingulate responses. Distension of the urinary bladder with room temperature water is associated with activation of pACC (area p32) and, injection of ice water, in aMCC (areas a24a′-c′; Matsuura *et al*., 2002; Fig. 10.2, Bladder 1a/b). During micturition, pMCC (areas p24a′-c′) activation has been reported (Nour *et al*., 2000; Fig. 10.2, Bladder 3), while during successful urination, pACC (area p24) is activated (Blok *et al*., 1997; Fig. 10.2, Bladder 2a) and unsuccessful voiding (full bladder but no release) aMCC (area 24b′; Fig. 10.2, Bladder 2b) is active.

These observations together demonstrate four different activation states associated with cingulate cortex: 1) innocuous sensory activation of pACC with room temperature water, 2) noxious sensory activation with ice water of aMCC, 3) micturition is associated with activity in pMCC or pACC, and 4) attempts to urinate without success, that is, a mismatch between anticipated and actual performance, occur in aMCC. These conclusions are consistent with predictions of the four-region model and numerous previous studies in other tasks including innocuous and noxious processing of visceral stimulation as discussed above, mismatch detection as discussed in Chapter 12, anticipation in Chapter 16, and visceromotor control. The only apparent conflict in these data is between micturition activation of pMCC and pACC in two studies and this is due to the subtraction methodology. Blok *et al*. (1997) compared successful micturition with voluntary withholding to generate the pACC site, while Nour *et al*. (2000) compared it to rest to generate the pMCC site. The four-region model requires that we consider the pACC activity the result of a subtraction demonstrating visceromotor control functions, while the subtraction generating the pMCC is likely associated with orienting the body to the urination target; a challenging task particularly for males depending on target size.

Circuit model

The visceromotor control of urination by pACC should be considered in terms of the subcortical model of urination provided by Blok *et al*. (1997). The model provides the CNS circuitry that leads to activation of parasympathetic outflow from Onuf's nucleus in the sacral spinal cord. Pivotal to this consideration are the points in this system that interface with pACC and there are two such sites: the medial preoptic area of the hypothalamus and the PAG. Although it is possible that the dense innervation of the PAG by pACC could be sufficient to mediate micturition (Fig. 10.6; Chapter 15), the medial preoptic area projects directly to the pontine micturition center (Barrington's nucleus) and plays a pivotal role in initiating micturition. The subgenual and pregenual parts of ACC have moderate projections to the medial preoptic area in monkey (Freedman *et al*., 2000; Chiba *et al*., 2001) and cat (Room *et al*., 1985).

Thus, visceromotor control of micturition by ACC is likely regulated by interfacing with two levels of the subcortical reflex pathway: 1) as a trigger to initiate and orient the behavior from the pACC to the medial preoptic area/PAG projections and another from the pMCC to the PAG, respectively, and 2) to assess mismatches between release and target acquisition in aMCC that might be mediated by input to the PAG to alter the course of outflow.

Clinical intervention with biofeedback

Biofeedback has been employed to treat stress urinary incontinence (Freeman, 2004) and this approach should have direct relevance to cingulate-mediated, visceral functions. An fMRI study of 10 female patients with stress urinary incontinence before and after a 12 week pelvic-floor-muscle-training period evaluated the CNS mechanisms of this biofeedback method (Di Gangi Herms *et al*., 2006). This study demonstrated reductions in activity in aMCC. One interpretation of these findings is that stress urinary incontinence is associated with a hyperactive mismatch detection system (see below, Paradox #1) that can be altered with biofeedback. This important study invites the use of this strategy for other aMCC-mediated conditions such as irritable bowel syndrome. These patients can have a high level of aMCC activation as discussed by Drossman *et al*. (2003; Chapter 22). The value of biofeedback methods in treating cingulate-mediated visceral pathology is an exciting new approach to solving medical problems by direct interventions in cingulate cortex.

Visceral Response Paradox #1: ACC "versus" MCC

Derbyshire (2003) reviewed reports of functional imaging during visceral stimulation and observed that gastrointestinal stimulation evokes clusters of activation sites that suggest a differentiation of gastrointestinal sensation. While this is true for activations in primary and secondary somatosensory cortices where the role in visceral sensation is established, the functional activation of MCC during viscus distension or chemical challenge is far from obvious. Moreover, Critchley *et al*. (2003) correlated indices of heart rate variability during

the performance of various cognitive tasks including the "n-back" paradigm and showed activity in MCC that is "related" to sympathetic modulation of heart rate. Although there is no direct brainstem circuitry for autonomic driving during cognitive processing, the correlations were evaluated by Critchley *et al.* (2003) with large stroke cases that involved ACC as well as MCC and had extensive damage to the cingulum bundle. Of course, large strokes are not effective tools in cortical localization of function and this is particularly true of the cingulate gyrus where damage to the transverse course of the cingulum bundle generates symptoms distant to the site of damage.

The four-region neurobiological model predicts that ACC directly regulates autonomic activity via brainstem projections (i.e., it is not merely associated with it) and MCC is involved in cognitive processing and regulates response selection and skeletomotor control via direct projections to the spinal cord (i.e., is not simply related to such activity). It is important to reiterate the properties that MCC does *not* have: 1) electrical stimulation in MCC does not evoke consistent visceromotor responses, 2) there does not appear to be a source of visceral afferents for innocuous mechanical responses to the viscera such as NTS inputs, and 3) any nociceptive visceral responsivity is likely associated with whole body receptive fields; hardly a specific visceral sensory response system. As argued above and in Chapters 15, 17, and 22, both visceral and skeletomotor control functions can be coordinated via projections to the PAG.

The independent regulation of both functions by separate cortical regions, however, does not conflict with the correlation findings when the role of ACC in cardiovascular control and the principle of reciprocal suppression are considered. First, as discussed earlier, the main action of electrical stimulation of ACC on cardiovascular and respiratory output is one of depression. Second, Bush *et al.* (2000) proposed that activity in ACC and MCC tend to be inversely related during emotional and cognitive tasks. That is to say, when an emotional task activates ACC it tends to decrease activity in MCC and the reverse is true for cognitive tasks that activate MCC. Demonstration of this principle in the same group of subjects has been shown when acute increases in breathing are generated with carbon dioxide (Liotti *et al.*, 2001). During breathlessness, these subjects had a substantial increase in activity throughout MCC and a simultaneous decrease in ACC activity. Third, driving of MCC during cognitively challenging tasks (Stroop, n-back, and the Multi-Source Interference Task) is associated with reduced activity in ACC which would release the ACC baseline depressor control and might allow the sympathetic system at brainstem and spinal cord sites to drive cardiovascular output; one possible intermediate integration site could be through the PAG. Hence, the correlation between MCC activity during cognitively demanding tasks and peripheral measures of autonomic function is a natural consequence of the circuitry and functions of both regions.

Of course, there is another reason why aMCC might be active in a range of behavioral settings including cognitively challenging tasks; fear of failure. The aMCC is the only cingulate region primarily activated during fear (Vogt *et al.*, 2003) and it has been proposed to play a role in generating nocifensive behaviors such as avoidance responses organized by the rostral cingulate motor area as discussed in Chapter 14 (Vogt, 2005). The four-region model predicts these responses generate pre-motor outputs rather than emotion *per se*. In other words, the aMCC is driven by fearful events and memories to produce avoidance responses including those generated during challenging cognitive processing.

Interestingly, Paradox #1 does not end in aMCC but continues to pMCC. Cameron and Minoshima (2002) designed an experiment in which isoproterenol was injected i.v. for 30 min to drive heart rate to more than twice normal levels (120 beats/min) before initiating PET scanning for glucose metabolism. This method effectively drives baroreceptor output without stimulating β-receptors centrally because of the low, first-pass transport of isoproterenol into the CNS. Although they were unable to decide where the activation was located based on Brodmann's two-region model of cingulate cortex, the peak activation coordinates were in MCC and the site appears to have heavily involved pMCC. As noted above, although there is a direct route for baroreceptor afferents mediated by the Pv thalamic nucleus to ACC and possibly aMCC, there is no such projection to pMCC or dPCC. Thus, Paradox #1 continues; why is pMCC activated during tachycardia?

We propose that pMCC is active during tachycardia for the same reason that it is active during noxious stimulation at a very brief latency measured by evoked potentials (Bentley *et al.*, 2003; Chapter 14 and reconstruction of their sources in Fig. 14.11). The four-region model predicts that the pMCC response to noxious somatic and visceral stimulation, when it occurs, is a pre-motor response related to orienting the body to the somatic site of noxious stimulation and anticipatory activity. A similar body-orienting response would be expected when the heart is beating at more than two times its normal rate.

Thus, the aMCC and pMCC do not play a direct role in viscerosensory or visceromotor control like ACC and they do not require a similar circuitry. The four-region model helps to resolve Paradox #1 by describing the essential role of each MCC subregion in pre-motor functions linked to fear/nocifensive behaviors (aMCC) and body-orienting to somatic-visceral stimulation with or without overt movement (pMCC).

Visceral Response Paradox #2: ACC "versus" PCC

The four-region model has no explicit role for PCC in direct autonomic regulation because it has no projections to brainstem autonomic motor nuclei, no visceral responses to electrical stimulation, and no autonomic symptoms during seizure activity in this region. Since it is one of the least likely regions to have a role in autonomic functions along with retrosplenial cortex (RSC), it is surprising that a study assessing systolic blood pressure during a Stroop-interference task (Gianaros *et al.*, 2005a) and one correlating a thirst rating score to CNS activity (Denton *et al.*, 1999b) identified dPCC and RSC as involved in these processes. Paradox #2 states that, at first blush, "stress-induced" elevations in systolic blood pressure and thirst assessment should be performed in ACC rather than PCC or RSC because the former is involved in direct cardiovascular control and taste as discussed above.

Gianaros *et al.* (2005a) were able to correlate systolic blood pressure with activity in dPCC during the Stroop-interference task. They generated cognitive "stress" with the task and evaluated two groups of subjects of high- and low-systolic blood pressure responders. Both groups showed an elevation in activity in aMCC and this might be explained by the logic applied in the previous section. Amazingly, the difference in cingulate responses between high- and low-systolic blood pressure responders was an elevation in activity in dPCC area 23 in the high responders and a reduction in activity in the same subregion in low responders. Equally paradoxical are the findings of Denton *et al.* (1999a) who reported extensive activation along ACC and MCC when subjects were infused with hypertonic saline to generate thirst (Fig. 10.4; #1). A correlation analysis of brain activity with thirst ratings, however, showed a robust activation mainly in dPCC and dorsal RSC (Denton *et al.*, 1999b; Fig. 10.4, #1a).

While the ACC contributes to the aversive valence associated with cardiovascular activation (Gianaros *et al.*, 2005b) and hypertonic saline, co-activation of parts of MCC, PCC, and RSC are involved in other aspects of interoceptive processing. A brief consideration of each region in these two conditions leads us to the following conclusions: 1) aMCC; a high level of baroreceptor input via Pv may enhance fear associated with stress to increase avoidance behaviors, while increasing thirst may enhance fear associated with attempts to resolve thirst by generating water seeking. 2) pMCC; activity in this subregion may be associated with prediction of where water is located, evaluating outcomes, orienting the body to stress avoidance targets and water availability, and assessing incorrect attempts to avoid stress and to find water. 3) dPCC; orientation of the body in space in relation to stress reduction targets in the larger visuospatial context and large spatial maps for water availability. 4) vPCC and RSC; activity associated with the level of stress or thirst may be involved in the importance of finding water in reference to self, sensory context, and negative outcomes, to provide memory of previous water locations, relevance of resolving thirst to personal survival and internal valence. The role of vPCC in ongoing assessment of sensory inputs for self relevance is evaluated in Chapter 13 (Vogt *et al.*, 2006). Thus, each cingulate subregion may have a role in different aspects of stress responses and thirst and each will be differentially activated depending on the paradigm used and the subtraction protocol used to analyze the functional data.

Body orientation to visceral activity and pain

Since noxious stimulation is the primary source of visceral-evoked activation in the cingulate gyrus, many investigators conclude it has a role in the affective dimension of pain processing as discussed in a number of chapters in the section on pain in this volume. The circuitry of what has been traditionally known as ACC does not support a single-function viewpoint. Certainly the projections of area 25 and some of area 24 are pivotal regulators of visceral function and projections of area 24′ are not to these structures but rather skeletomotor systems. The four-region model makes specific predictions about the role of visceral activations and raises new questions. Figure 10.2 plots 14 sites associated with visceral stimulation. Four of these are in ACC and 10 are in MCC with the largest of all sites in the latter group (#1 in the third reconstruction). Even those responses that are in ACC are in pregenual rather than subgenual ACC that includes area 25.

Keeping the proviso in mind that anticipatory induced reductions may limit area 25 activity in many of these studies, it appears that most visceral activity is not in the visceromotor control areas 25 and 32 as defined by electrical stimulation studies in rodents (Neafsey *et al.*, 1993). In some instances (4 of 14) there are activations in ACC, but in most cases they are in MCC. Paradoxically, MCC has no known projections to autonomic brainstem nuclei and no interactions with the CeA which would validate its participation in visceromotor, particularly, cardiovascular circuits. On the input side, the only known source of visceral inputs would be a system that is shared with cutaneous nociceptive inputs via the Pf nucleus of the thalamus and this predicts that visceral and somatic noxious activations should essentially overlap. One imaging center (Svensson *et al.*, 1997) shows that cutaneous activations in pMCC overlap with those evoked by innocuous and

noxious distension of the stomach (Fig. 10.6; Ladabaum *et al*., 2001), while gastric stimulation evokes additional activity in aMCC (#3 in second plate of Fig. 10.6). Strigo *et al*. (2003) directly compared subject responses to noxious cutaneous and visceral stimulation and pMCC was again activated mainly during cutaneous and aMCC mainly during esophageal stimulation. Thus, the afferent system conducting nociceptive information through Pf must diverge or there is a cortical mechanism whereby aMCC preferentially interprets the incoming signal as visceral, while pMCC interprets a similar signal as mainly cutaneous; the mechanism of this differentiation could be a cognitive one.

A thalamic mechanism

The only known direct source of visceral nociceptive information are the reuniens and Pf nuclei which receive significant inputs from the spinal cord, SRD, and PB nuclei as discussed earlier. The signal itself may not be a simple sensory signal, since visceral responses in MCC may provide information for premotor response selection as predicted by the four-region neurobiological model. In other words, although the organ stimulation is noxious, the contribution of MCC may not be affect or emotion *per se*. The question remains as to what extent noxious distension of an organ triggers behaviors organized in the cingulate gyrus. For example, distension of the urinary bladder evokes the urge to urinate and evokes a substantial signal in pMCC. To the extent that micturition is mediated by PAG projections to the pontine micturition center (Holstege *et al*., 2004) and inputs to PAG arise from MCC as discussed earlier, the MCC is in a position to evaluate the level of distension and associated urgency to urinate. The final decision that the context is appropriate to urinate is made in MCC and this triggers the PAG to initiate urination. One consequence of micturition is possibly pain relief and this may form an indirect form of reward for successful release.

Multiple Roles of Cingulate Cortex in Visceral Integration

Rodent research has played an important role in understanding the mechanisms of autonomic regulation and these culminated in a model of cingulate-mediated visceromotor control by EJ Neafsey and colleagues (1993). They conceived of the insula as the primary site of viscerosensory function, while ACC would receive its primary sensory afferents from the insula that would then drive subcortical visceral responses. Although the mechanisms of visceromotor control are partially understood, ACC also has visceral sensory afferents shown in rabbits and responses of noxious visceral stimulation of the distal colon shown in humans. Thus, the visceromotor model limited to the subgenual ACC requires modification.

In light of the differential activation of cingulate subregions, it has been concluded that the pMCC activation links behavioral responses that are often paired with cutaneous stimulation and orienting to noxious stimuli. In contrast, aMCC is more heavily visceral than cutaneous and generates fear and related skeletomotor activity from the rCMA. Finally, there is no doubt that ACC is pivotally involved in visceromotor regulation; the circuitry is indisputable in this regard. This is a less frequently activated region during noxious visceral stimulation. Although anticipatory responses may reduce activations in this area, another possibility is suggested by the four-region neurobiological model; the cardiovascular responses are critically linked to subject-specific emotional memories and experiences. This linkage assures that part of deeply negative memories is generation of a peripheral-autonomic response along the line of somatic markers as links with emotional memories proposed by William James (1884), Damasio *et al*. (1990), and Neafsey *et al*. (1993). It is also impressive that electrical stimulation in this region can have a profound influence on depression (Mayberg *et al*., 2005).

Cingulate cortex appears to have six roles in visceral function and they are not limited to visceromotor control: 1) ACC: linkage between emotional memories and autonomic output, 2) aMCC: linkage of nociceptive inputs with fear with skeletomotor avoidance of threatening visceral activity like uncontrolled micturition or defecation in public places, 3) pMCC: linkage of discomfort and skeletomotor seeking for conditions to micturate/defecate with less fear and under less threatening conditions, 4) dPCC: rapid orientation of the body to noxious or innocuous somatovisceral stimulation and orients the body in a large spatial context, 5) vPCC: assessment of the context and self relevance of innocuous stimulation (noxious stimulation bypasses this structure as discussed in Chapter 13), 6) RSC: engages in working memory functions linked to emotional stimuli.

The links between gastrointestinal sensation and cingulate activations are still poorly understood as are the conditions under which the normal and abused cingulate gyrus responds to visceral stimulation, regulates autonomic functions, and is associated with depressive symptoms. Hypothesis-driven imaging research over the coming decades will resolve bidirectional viscerocingulate interactions. Most importantly, specific targeting of behavioral, intracranial electrical stimulation, extracranial magnetic stimulation, and drug therapeutics to the primary source of long-term impairment in the cingulate cortex will drive innovative and less invasive strategies for resolving numerous diseases of limbic systems.

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