CHAPTER 1

Regions and Subregions of the Cingulate Cortex

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Chapter contents

The regional and subregional organization of the primate cingulate cortex is in dispute long after the seminal cytoarchitectural work of Brodmann (1909). He defined the anterior and posterior cingulate cortices and their component areas; however, no functions were known for these regions a century ago and this duality only referred to broad anatomical variations. Recent human neuroimaging studies seek to localize functional responses and refer to parts of the cingulate gyrus in terms of anterior or posterior locations and the Brodmann areas based on the co-registration of the Brodmann's map to a single case by Talairach and Tournoux (1988). Since most neuroimaging studies do not draw conclusions about the cytoarchitectural bases of functional observations and the Brodmann duality is generally taken at face value, a confusing overlay of adjectives has evolved for different parts of the cortex. Thus, functional references to places on the cingulate gyrus do not refer to a comprehensive model with predictive power or histologically bounded areas, but provide site coordinates with general functional inferences. It is striking that no functional study has ever activated the entire anterior cingulate cortex of Brodmann to demonstrate its functional uniformity as implied by current usage of Brodmann's hypotheses.

An alternative approach to cingulate cortex is embodied in the concept of a neurobiological model that is derived from more than one disciplinary research resource, it is based on structure/function correlations and connections, and it makes predictions about the role of a region in specific aspects of information processing. The goal of such a model is *not* to attribute broad psychological concepts such as "attention," "emotion," and "pain" to groups of neurons that cannot possibly code such complex information but rather to evaluate small aggregates of neurons (areas or subregions) that are capable of processing limited amounts of information; for example, different cognitive aspects of pain processing or components of emotion such as autonomic regulation, sensory information linked to happy contexts, and episodic memory. In this framework, a region is a theoretical construct with predictive power, it can be modified based on a coherent and evolving logic, and it is based on observed outcomes from diverse research activities. Indeed, the cross-checking among disciplinary outcomes provides a validating approach for any neurobiological model of cingulate cortex.

Classical functional studies often viewed cingulate cortex as a single region involved in emotion (Papez, 1937; MacLean, 1990) in spite of the early work of Brodmann and others in the early twentieth century. As our understanding of the mechanisms of cognitive processing in lateral neocortical areas has expanded, however, insight into processing in cingulate cortex has lagged because of the difficulty of reducing emotion to simple neuronal codes and circuit processing activities. One step toward defining the components of emotion processing is to re-conceptualize the cingulate cortex in terms of structure/function regions that address current histological and functional findings.

Generally speaking, a cortical region is comprised of a number of areas involved in similar aspects of information processing. For example, each primary sensory cortex and its association areas comprise functional regions and are usually linked via a series of hierarchical connections that process and extract sequentially more complex sensory features. In limbic cortex, however, input/output relationships are not obvious (i.e., where does processing "begin"?) and a serial processing stream in the cingulate gyrus is only now emerging as discussed in Chapter 13. In this context, defining separate regions has been difficult and needs to proceed according to a consistent and non-sensory system logic.

A region should be qualitatively different from adjacent regions rather than part of a quantitative progression in cytoarchitecture, connections, or functions. The concept of a "transition region" in neuroanatomy has been thought to apply to the boundary between Brodmann's anterior and posterior cortices and it suggests that structural differences between two regions are graded, quantitative, and occurring in a narrow zone of a few millimeters. A transition zone is not a region in the qualitative sense of the term. For example, a structural transition between agranular area 24 without a layer IV and area 23 with a granular layer IV occurs somewhere in the middle of the cingulate gyrus. If this change occurs over a few millimeters and has a progressively increasing density of layer IV neurons, it might comprise a transitional cortex and validate the century-old anterior/posterior dichotomy. If, however, this transition is characterized by many laminar changes that occur over one-third of the cingulate gyrus and the associated "transitional" areas have unique connections and qualitatively unique functions, this is not a transition zone and the anterior/posterior dichotomy fails. In this latter instance, referring to caudal or posterior ACC to localize an activation site overlooks the fact that it may be engaged in *qualitatively unique* contributions to brain function, it has a unique neurochemistry, and it is not simply a caudal part of ACC. Thus, the character of transition between areas 24 and 23 is crucial to evaluating any regional model.

The definition of a cingulate region begins with neuroanatomical research as it has for the entire history of neuroscience. The essential logic of neuroanatomy includes a central principle that structural differences in the form of cytoarchitectural (laminar), cytological (neuron size, shape, and phenotype) and connectional (monkey monosynaptic; human correlation connections)

differences are the prelude to understanding information processing. An excellent example of how the neuroanatomical process evolved into a full neurobiological undertaking was the identification of the primitive gigantopyramidal motor field in the human caudal cingulate sulcus by Braak (1976). Although numerous electrical stimulation studies in the middle of the cingulate gyrus reported complex and context-dependent skeletomotor responses that were often bilateral, these were thought to result from current spread to adjacent motor structures; even though electrical stimulation of adjacent structures with similar currents failed to produce such movements. Cingulospinal projections were soon identified (Biber *et al*., 1978) and it was later shown that "caudal/posterior ACC" has a unique structure, connections, and motor functions. In this framework, the midcingulate cortex (MCC) concept was proposed as a *qualitatively unique* cingulate region (Vogt, 1993). The last decade of human functional imaging and experimental monkey studies support the cingulate motor and midcingulate concepts, and information on subregional characteristics, connections, and functions are now available.

The implications and ultimate test of a regional model is the extent to which each region is selectively vulnerable to disease. This fact is often not appreciated in human neuroimaging studies that report changes in control and patient populations in "ACC." In many instances, the pivotal changes in patient populations are lost by the application of Brodmann's 1909 model of cingulate cortex as discussed from some examples later in this chapter and in many other chapters in this volume. Since each region has its own neurochemical and intrinsic organization, this leads to a differential impact of neuron disease and provides new and more specific avenues for therapeutic interventions. Indeed, the neurobiological model provides specific hypotheses to guide explorations for the etiology of particular neuron diseases. The last section of this chapter "Therapeutic Targeting of Cingulate Regions" reviews the current status of regional assessments of disease etiology and therapeutics as presented in this volume and the reader should consider Chapter 11 in this framework. Additionally, as functional imaging methodologies improve, more precise features of particular regions and areas will be uncovered and this will contribute further to the ultimate goal of identifying and treating neuron diseases. This volume provides a master plan to search for selective disease vulnerabilities in cingulate cortex.

Goals of this Chapter

This chapter provides an overview of the cingulate cortex and a context and framework for many of the following chapters. It summarizes findings the author used to develop in the four-region model including the midcingulate concept, while the richness of the primate structural and functional imaging literature will be thoroughly developed in subsequent chapters. Our understanding of the subregional organization of the cingulate gyrus has been progressing rapidly and is based on the same essential logic used for the four-region model itself. The latter process has become quite challenging as there are now thousands of human imaging studies that report activation of some part of cingulate cortex. This chapter has the following specific goals:

1 Consider the historical context, strengths, and weaknesses of one- and two-region models.

2 Evaluate regions as histological entities rather than places/coordinates in the cingulate gyrus.

3 Assess the differential cytology, neurochemistry, and circuits for each region.

4 Summarize key electrical stimulation, stroke, and functional imaging findings for each region.

5 Evaluate subregional organization and functions.

6 Discuss limbic cingulate cortex and the paralimbic misnomer.

7 Consider the importance of disease vulnerabilities by region, the ultimate hallmark of a region, and targets for therapeutic interventions.

8 Present the main challenge for cingulocentric research in the next century: *define the connections, functions, and disease vulnerabilities of 30 cingulate areas.*

One- and Two-Region Models of Cingulate Organization

For most of the past century, the cingulate cortex was viewed as a uniform functional entity. Gerdy (1838; see Broca, 1878; MacLean, 1990) identified the annular convolution that included the cingulate gyrus and later Broca (1878) observed the grand limbic lobe. These observations were anatomical and, according to their authors, did not imply theoretical considerations about function. The important work of Papez (1937) and MacLean (1954, 1990) also viewed cingulate cortex as a single functional entity and emphasized its role in emotion. Papez defined emotion as internal feelings and associated responses, however, his model failed to provide outputs to emotional motor systems. Indeed, many of the structures identified as part of his "system" are actually involved in memory and visuospatial orientation rather than emotion *per se* according to his own definition. The primary difficulty for Papez in this undertaking was the large size of strokes and tumors

from which he derived his conclusions. For Paul MacLean (1990), the limbic system was comprised of three divisions and his views of cingulate cortex functions were embodied in the thalamocingulate division of this triune brain. His very important view attributed the role of cingulate cortex in emotion to such complex functions as maternal care, vocalization, sexual arousal, and other conspecific engagements. To this day, the Papez-MacLean model of limbic organization is the focus of many didactic efforts to explain limbic system organization and function. The need for specific cellular mechanisms for these complex behaviors has not been achieved, however, there is little doubt that the single model of cingulate cortex organization cannot provide answers to the complex functions performed by limbic cortex.

Paradoxically, Brodmann (1909), C. and O. Vogt (1919), Rose (1927) and von Economo (1929) showed that as many as 40 cytologically unique areas comprised the cingulate gyrus, while functional studies proposed a single, overarching function throughout most of the past century. Since differentiation of unique structural entities is the prelude to uncovering important functional aggregates of neurons, unitary functional models of the cingulate gyrus such as the Papez-MacLean model could not succeed in the context of such heterogeneous anatomical organization.

It is generally agreed that Brodmann (1909) established the dual model of the cingulate gyrus with anterior and posterior divisions. He referred to area 32 as the dorsal part of anterior cingulate cortex around area 24 and area 31 as the dorsal part of posterior cingulate cortex around area 23. The transition to a dual model of cingulate function in the early 1970s was presaged by studies of circuit dualities (Baleydier and Mauguiere, 1980; Vogt *et al.*, 1979) and efforts to conceptualize cingulate functions in terms of its anterior and posterior divisions. One view proposed that anterior cingulate cortex (ACC) is involved in executive functions, while the posterior cingulate cortex (PCC) is involved in evaluative processes and the past two decades of research have shown that this view of cingulate cortex is seriously at odds with neurobiological observations and needs substantial revision.

The dual model provided the conceptual framework in which the book *Neurobiology of Cingulate Cortex and Limbic Thalamus* (Vogt and Gabriel, 1993) was organized. This was a watershed year because the 44 authors raised questions about whether or not all of cingulate cortex was involved in emotion and how emotion, reward, and cognition might interact. For example, Carl Olson and his colleagues questioned if PCC had a role in emotion, since visuospatial processing need not involve emotion and they observed that neuron discharges were tightly associated with visual field stimulation and the orbital position of the eye but not task reward. In another example, autonomic connections and electrically stimulated responses were reported for subgenual ACC by Neafsey and his colleagues and PCC did not have projections to autonomic brainstem nuclei. Surely, if PCC has a role in emotion, it must be an indirect one. Such views had radical implications because the massive anterior thalamic afferents of retrosplenial cortex (RSC) were a pivotal part of the Papez-MacLean model and RSC and many of the hypothetical interactions in this model might have little to do with emotion and more to do with general memory and visuospatial orientation. These observations and questions, of course, raised additional problems about what constituted a limbic cortex and the levels of functional differentiation achieved in such a system. There may be intermediate levels of processing that are not easily categorized by the limbic/cognitive dichotomy of cortical information processing; particularly in cingulate cortex where emotional and cognitive processing transforms decision making to apply the internal needs of the organism into successful problem solving behaviors (Devinsky *et al.*, 1995). These concepts are among the most important to emerge from the 1993 volume and set in motion the effort to regionalize the cingulate cortex in structure/function entities with a view to grades of emotional involvement rather than a single functional output.

Ironically, although no functional imaging data or logic supports the dual model, the ACC/PCC dichotomy is the dominant perspective used to discuss such findings today. For example, reviews of cingulate activation during simple emotions clearly show that cingulate cortex is not uniformly engaged because there is a large swath of relatively inactive cortex in the middle of the cingulate gyrus (Phan *et al.*, 2002) and PCC activation is not limited to emotion because non-emotional words and scripts also activate this region (Vogt *et al.*, 2003). Furthermore, functional imaging studies have never activated fully either ACC or PCC with any testing paradigm as would be predicted for a region with a unifying function. There is no way the two-region model can be supported because of the numerous functional attributions made for different parts of ACC. The problem is to understand the essence of information processing within each part of ACC and to determine which overlapping circuits might explain the functional heterogeneity. Simply applying umbrella terms such as "attention" and "emotion" fail to address the information processing functions among cingulate areas and complex interactions with parallel and distributed cortical networks.

Cytological Regions: Intrinsic Organization

The cytoarchitecture of a cortical region reflects its essential intrinsic circuits, efferent projections, functions, and neurochemical vulnerabilities to disease. Key differences in laminar and neuron architecture are the bases for significant differences in intracortical processing. Although most areas of the cingulate cortex have five or six layers, there are varying degrees of differentiation and unique neuron phenotypes in different layers and areas. For example, the largest neurons in the cingulate gyrus are in layer Vb of area 24d, they project a long distance to the spinal cord, and express high levels of cytoskeletal proteins including non-phosphorylated intermediate neurofilaments. Differences in the composition and density of layer Va and Vb neurons provide the basis for differentiating many cingulate areas and provide important clues about the information processing functions of an area. In another example, a dense layer IV is important for intrinsic processing in areas 23 and 31, however, areas 24 and 25 do not have this layer and associated intrinsic processing. Thus, it is possible that intracortical processing speed differs in areas without a layer IV such as ACC. The details of cytoarchitecture for the cingulate areas and regions are provided in the context of a comparative analysis in Chapter 3; however, a brief overview is presented here to consider the cellular basis for the regionalized cingulate gyrus.

Figure 1.1 shows some of the key differences between the ACC and PCC in human brain. An underlying tenet of all neuroanatomical research is that, once a structural differentiation has been identified, it will represent a functional distinction. Thus, cytological studies provide the substrate upon which subsequent neuroscience research is crafted. Traditionally, Nissl stains such as cresyl violet or thionin were used to assess neuron and laminar structure, however, they also stain glia and vascular elements and this detracts from the overall laminar architecture patterns expressed by neurons. Figure 1.1 provides two macrophotographs through sections reacted for an antibody to neuron-specific nuclear binding protein (NeuN) in area 24 and dorsal, posterior area 23/retrosplenial areas 29 and 30. NeuN immunohistochemistry has important advantages over traditional Nissl stains because there is no co-staining of glia and endothelial cells (Mullen *et al.*, 1992) that are diffuse and distract from the essential laminar architectures and neuron characteristics. The brown reaction product is also so intense and stark in relation to the background staining that neuron features are easily identified at higher magnifications as shown throughout Chapter 3. It should be noted that the NeuN-immunoreacted tissue is counterstained with thionin (blue) in human cases to assure that latent neuropathology is not missed. In Alzheimer's disease, for example, many thionin-stained neurons do not express NeuN. Even in "neurologically intact" human cases, there can be places with reduced NeuN staining suggesting dysfunctional tissue and these are not included in cytoarchitectural analyses.

Immunohistochemistry can stain for unique neuron phenotypes such as the antibody to non-phosphorylated, intermediate neurofilament proteins (NFP; SMI32 antibody). Consider Figure 1.1 in terms of the importance that SMI32 has in evaluating laminar architectures and differentiating cortical areas in combination with NeuN. Each NeuN section was co-registered to an adjacent SMI32 section and all four photographs were aligned at the top of layer Va along a thin black line. This comparison between ACC and dorsal PCC provides the essential arguments for concluding that these two regions have substantially different intrinsic organization and neurochemistries.

There are 7 asterisks among the four magnified images in Figure 1.1 that draw the eye to important features of ACC and dPCC:

1 Emphasizes the heavy dendritic and somatic expression of NFP in all of layer III of area d23b, while those in layer III of area 24b are almost non-existent. Since large neurons are well known to express high levels of NFP (e.g., Nimchinsky *et al.*, 1996, 1997), this suggests that layer III neurons are particularly small in area 24b. Indeed, the fifth asterisk in layer III of area 24b emphasizes that there are no large, layer IIIc neurons in this area only a slight clearing in the deep part of layer III where there are mostly NFP-negative, medium-sized pyramidal neurons.

2 Emphasizes the presence of layer IV which characterizes PCC as granular cortex. This layer is not present in ACC except as a "dysgranular" specialization in area 32 (see Chapter 3). To the extent that layer IV provides an important circuit for intrinsic regulation of pyramidal neurons in other layers, the presence or absence of an entire layer must be viewed as pivotal to understanding structure/function correlations. Nothing is known about the function of layer IV in cingulate cortex.

3 Although layer IV is the most prominent layer in isocortical areas, it is a surprising fact that the most prominent layer in PCC is layer Va. Also important is the fact that there are many more large and small neurons in PCC layer Va than the same layer in ACC. To the extent that layer Va and Vb provide outputs to motor systems, this difference may suggest a slower and less responsive output system in granular cortices.

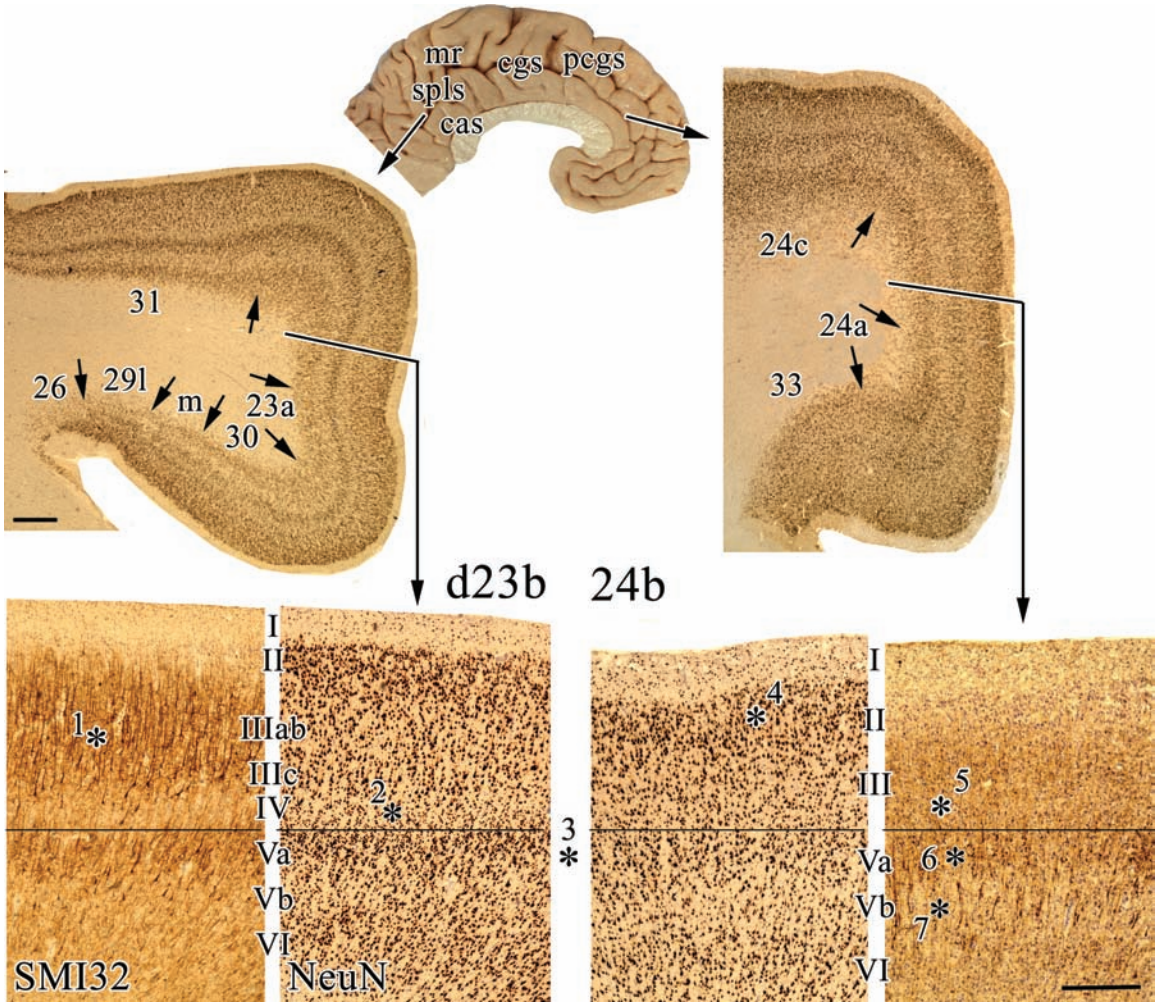

Fig. 1.1 Regional differentiation is a neuroanatomical problem based on laminar cytoarchitecture and neurocytology. The substantial differences between ACC (area 24b) and PCC (area d23b) are shown as are the rostrocaudal levels of each coronal section with the arrows on the medial surface photograph. A NeuN-immunoreacted area from the ACC and PCC was co-registered to adjacent SMI32 sections, and aligned along the top of layer Va (black lines). Seven asterisks emphasize important features that differentiate these two areas and regions as discussed in the text. Sulci labeled according to the abbreviation list. Scale bars; 1 mm (top left), 500 μm (bottom right).

4 Emphasizes the broad layer II in area 24b that is characteristic of poorly differentiated cortical regions. These are small pyramidal neurons that do not express NFP and the only staining in these layers is due to the thionin counterstain. Notice that layer II in area d23b is much thinner than in ACC.

5 See 1.

6 Emphasizes there is a dense dendritic plexus rich in NFP in layer Va of area 24b. Notice that neurons in this layer are substantially larger than those in layer IIIc, which is the converse of that for area d23b. Also notice that the large neurons in area d23b express relatively less NFP in layer Va and compare each to layer III as noted above.

7 Layer Vb in area 24b has a large population of vertically oriented, NFP-expressing neurons, many of which are referred to as spindle neurons. They have axons that project into the white matter (Nimchinsky *et al.*, 1995) and they are not present in MCC or PCC. The specific role of these neurons in cingulate information processing is not known, however, their presence signals a fundamentally different neuron population in ACC that must contribute to the unique functional output of ACC areas.

The concept of transition in relation to midcingulate cortex

A major concern for studies of regional identification is the composition of transition between regions and

their constituent areas. As discussed in Chapter 3, laminar organization is often framed in terms of transitional links between two or more areas. In the cingulate gyrus, there are two major dimensions of transition: in the rostrocaudal or y axis and lateromedial or x axis. Transition between areas 24 and 23 characterizes the first and that between areas 29 and 31 the second form of transition.

The transition between areas 24 and 23 appears to be gradual and is not a uniform change in which layer IV neurons (characteristic of posterior cingulate cortex) simply increases in density to produce two extremes of a single continuum. Rather, there are qualitatively unique patterns of cytology, connections, and functions that lead to further regional differentiations. The dramatic differences in basal dendritic elaboration by large layer V pyramidal neurons have been reported by Schlaug *et al.* (1993). Indeed, the progressive elaboration of the basal dendritic tree in layers III and V are responsible for the progressive decrease in neuron densities in both x and y planes in the cingulate gyrus. Differences in both layers can be seen in Figure 1.1, for example, when comparing examples of anterior and posterior areas.

The problem of transition has been recently reconsidered (Vogt *et al.*, 2003; 2006) and we pose this question from the perspective of key connections and functions below. From an anatomical point of view, there are four qualitatively different changes that support the view that MCC is not simply a transition cortex with a linear increase in the number of layer IV neurons. First, the anterior MCC has a layer Va that is similar to ACC but differing layer IIIc characteristics, while the posterior MCC has a layer Va with many small neurons that give it a granular and dense appearance. Second, binding to 8 of 15 neurotransmitter receptors has different laminar patterns in the anterior and posterior parts of area 24 as discussed below and in Chapter 2. Third, the dPCC has a transitional area 23d with a dysgranular layer IV (i.e., variable thickness as discussed in detail in Chapter 3) and a dense layer Va. Fourth, areas 23a-b have a granular layer IV. It is pivotal for the midcingulate concept that the features of the midcingulate region form a qualitatively unique architectural pattern and not simply a progressive change in a single laminar characteristic. These qualitative, neuroanatomical differences must be reflected in unique circuitries, functions, and disease vulnerabilities; otherwise, the null hypothesis that the midcingulate region does not exist must be accepted.

Transition in the x axis is characterized by rapid changes in the number of layers and their differentiation as discussed in detail in Chapter 3. In addition to progressive additions of layers to the ectosplenial area 26 in human and subicular rudiment in monkey, there are also progressive elaborations of basal dendritic tress of pyramidal neurons in all layers. This elaboration has long been known and underpins changes in neuron densities in layers III and V as noted above for the y axis changes (Vogt, 1976). Transitions associated with the addition and differentiation of layers mark important area boundaries and subserve fundamental differences in cortical information processing. It is for these reasons that RSC must be differentiated as a separate region from posterior cingulate areas 23 and 31.

Regional Circuits: Input/Output Organization

Monosynaptic connections provide a primary feature for differentiating regions and the critical circuit(s) for any one region will determine its primary role(s) in brain function. Cingulate cortex has extensive frontal, parietal, temporal, and occipital connections; however, some project throughout the entire cingulate gyrus and do not provide clues to regional differentiation like those from prefrontal cortex (Chapter 5) and the locus coeruleus (Chapter 22). In some instances, such as serotonergic inputs, there are important hints like the distribution of serotonin transporter proteins but not conclusive anatomical data in the human on connection specificity. Since particular monosynaptic connections played an important role in defining the four cingulate regions (Vogt, 1993), these are emphasized here and summarized in Figure 1.2 which is based on a flat map of monkey cingulate gyrus (Vogt *et al.*, 2005). Although the four regions are outlined below, the first four panels are information that was available in 1993 and served as the original substrates for proposing this model. Notice that, although the flat map was derived from cynomolgus monkeys, similar findings were made in a rhesus monkey. Also, the Dua and MacLean (1964) observations in panel B were in squirrel monkeys. The co-registrations to the flat map of cortical areas based on the genu of the corpus callosum and cingulate sulcus seems to reflect the distribution of reported activity and the consequences for the regionalized map are valid.

The amygdala has a well-established role in emotion and fear as discussed in Chapter 9 and reciprocal connections between the amygdala and cingulate cortex should help identify emotion-specific processing areas as discussed in Chapter 6. Amygdala connections are not evenly distributed throughout the cingulate gyrus and their specialization is associated with important regional borders (Vogt and Pandya, 1987). Figure 1.2A has a co-registration of projections of the basolateral and accessory basal nuclei following tritiated amino acid injections to the cingulate cortex. The greatest amount of labeling is in pregenual areas 25, 24, and 32. There is also a limited extension of labeled proteins into area a24′ and almost none posterior to this area. To the extent that the amygdala is involved in emotions such as fear (Chapters 8, 9, and 22), the latter areas are

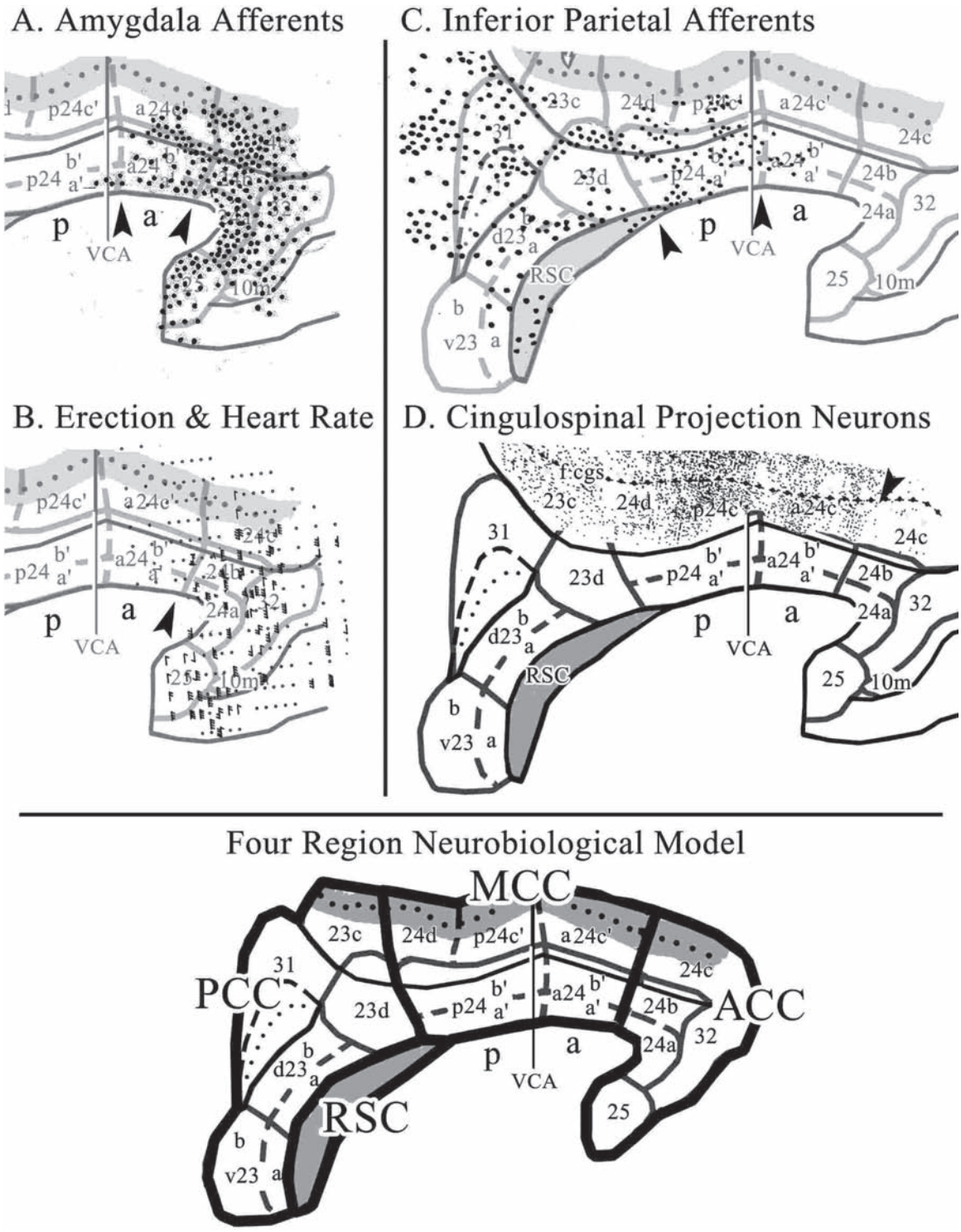

Fig. 1.2 Flat map of monkey cingulate areas and four regions outlined (bottom). This map was coregistered to the findings of 4 studies to evaluate regional circuitry and functions. The "a" and "p" refer to anterior and posterior MCC and the arrowheads emphasize these borders in relation to the reported findings: A. & C. Vogt and Pandya (1987), B. Dua and MacLean (1964), D. Dum and Strick (1991), flat map, Vogt *et al*. (2005).

specifically involved in emotion and may be involved in facial expressions associated with it (Morecraft *et al.*, 2007). In contrast, caudal areas including pMCC, PCC, and RSC may have little direct involvement in emotion and no connections with the amygdala. This prediction of the four-region model is currently assisting in parsing the individual processing functions of each cingulate subregion.

A test of the autonomic/emotion conclusion for ACC is possible with the electrical stimulation studies of Kaada (1951) and MacLean (1990) that report autonomic activity following anterior cingulate stimulation. Although these stimulation currents were high and of long duration relative to primary and supplementary motor studies, similar stimulation parameters in adjacent cortex do not evoke such responses (Pool, 1954) and disprove that the cingulate responses were merely the result of current spread to other motor areas. Equally important are the autonomic responses evoked from ACC that validate these responses in the context of direct projections of area 25 to autonomic nuclei including the lateral hypothalamus, periaqueductal gray, parabrachial nucleus and, to a much lesser extent in primates, the nucleus of the solitary tract and dorsal motor nucleus of the vagus (details and references in Chapter 10). Dua and MacLean (1964) reported sites generating penile tumescence overlapping with reduced heart rate and these sites are co-registered in Figure 1.2B. Sites generating no activity are also plotted and it is striking how localized the active sites are to perigenual areas 25, 24, and 32. It is surprising that a24′ had no active sites. Thus, autonomic activity is generated from pregenual ACC *not from ACC as classically defined by Brodmann*. The role of cingulate cortex in emotion is considered in detail in Chapters 8 and 9 and its role in autonomic functions in Chapter 10.

Reciprocal connections between cingulate and parietal cortices are well known and they are thoroughly reviewed in Chapter 13. The distribution of inferior parietal projections is co-registered to the flat map in Figure 1.2C and they were pivotal to differentiating between pregenual ACC and MCC (Vogt, 1993; Vogt *et al.*, 2004). Although the major projection is to PCC and RSC, it does extend with equal density into pMCC and minimally into aMCC. No parietal projections were observed to pregenual ACC and this is pivotal to differentiating the functions of PCC and ACC.

The value of the cingulospinal projection system cannot be over emphasized and is discussed in detail in Chapter 5. The observations of Dum and Strick (1991) are provided for co-registration to the flat map in Figure 1.2D because the investigators injected horseradish peroxidase into as many corticospinal projection axons as possible and the results provide an overview of the entire system on both lateral and medial surfaces. According to this co-registration, the most extensive cingulate labeling was in p24c′. Robust labeling was also in area a24c′ and almost none was in area 24c. The border between areas a24c′ and 24c represents the border between skeletomotor and autonomic regulation as well as the border between arm and facial nucleus innervation, respectively. These differences must be viewed as pivotal between ACC and MCC, and Morecraft and Tanji note in Chapter 5 that area 24c projects to the facial motor nucleus to regulate the muscles of facial expression (Morecraft *et al.*, 2007). This notion fits quite nicely with the role of area 24c in emotion because the muscles of facial expression are the only group that explicitly transmits information about emotional states as discussed in Chapter 15. It does not appear to be an accident that the head representation of the rostral cingulate motor subregion is located in area 24c.

Based on this information alone, Brodmann's view of anterior cingulate cortex does not reflect the circuitry and functions of this region. It is not possible for midcingulate cortex to be incorporated into ACC and the past decade of human functional imaging supports this model.

Midcingulate Cortex ≠ "Caudal" ACC

It has become a common practice in neuroimaging to refer to a rostral and caudal ACC because no functional studies activate the entire anterior cingulate cortex as defined by Brodmann. Moreover, many observations of the cytoarchitecture and connections fail to support the notion that caudal ACC is a division of Brodmann's anterior region (above) and no cytoarchitectural studies have ever evaluated this concept; that is, what are the cytological characteristics of "caudal" ACC and what are its anatomical borders with "rostral" ACC? A report by Palomero-Gallagher *et al.* (2008b) provides important new observations of why "caudal" ACC ≠ MCC and "caudal" ACC is *not* a division of ACC. Indeed, this study evaluated the homogeneity of Brodmann's area 24 with 15 neurotransmitter receptors in a ligand binding autoradiography study of postmortem cingulate cortices. The null hypothesis stated that rostral and caudal ACC were the same and midcingulate cortex does not exist as a qualitatively unique region.

The anterior cingulate region of Brodmann was divided into anterior/rostral and posterior/caudal parts as shown in Figure 1.3 (pointer divides this region and arrows show approximately where the sections were taken). Coronal sections are shown in Figure 1.3B of two of the 15 receptors evaluated. They were chosen for demonstration because an "asymmetry index" for anterior and posterior parts of this region showed them to be statistically different (see Palomero-Gallagher *et al.*, 2008b, for calculation of the index). Clearly, $GABA_A$

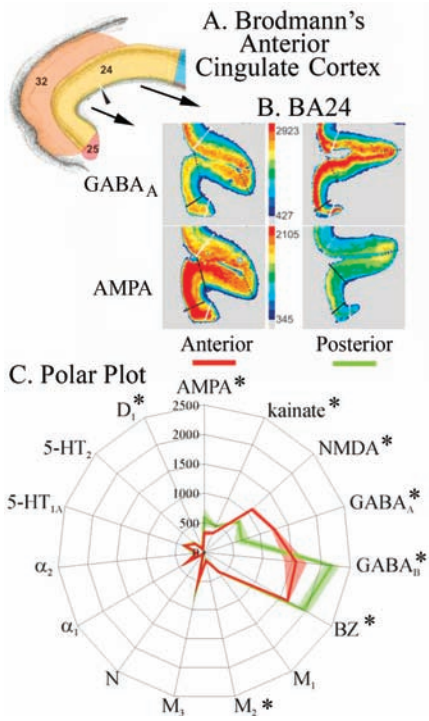

Fig. 1.3 Assessment of 15 neurotransmitter receptors in the anterior and posterior parts of Brodmann's area 24. A. Map of anterior cingulate region of Brodmann with a pointer separating its two parts used in the analysis. B. Coronal sections for two receptors through each part show a radical difference in the laminar patterns of binding. C. Polar plots for anterior (red line ± SD) and posterior (green line ± SD) with asterisks emphasizing the receptors that are statistically significant. The null hypothesis was rejected and these findings validate the midcingulate concept; that is, *caudal ACC is not a part of ACC.*

receptors are quite low throughout anterior area 24, while they are extremely high in layers I-III of posterior area 24. In contrast, AMPA receptors were very high in layers I-V in anterior area 24 but extremely low in posterior area 24. Details of receptor localization and abbreviations are provided in Chapter 2.

A polar plot of all 15 receptors is shown in Figure 1.3C. The plot is of binding throughout the entire area (i.e., not by layer) and receptors that are significantly different in each subregion are noted with asterisks. Eight of the 15 neurotransmitter receptors were significantly different in the two subregions. We conclude from these observations that the anterior/rostral and posterior/caudal anterior cingulate subregions are qualitatively different in their neurochemistry and the null hypothesis that MCC does not exist was rejected. Thus, caudal ACC as used in the neuroimaging literature does not exist. That is to say, caudal anterior cingulate cortex is not a division of ACC but, rather, it is a qualitatively unique structure/function entity. The purpose of the midcingulate concept is to emphasize this and many other differences and provide hypotheses about how its unique organization subserves functions that differ from ACC and how it might be differentially vulnerable to neuronal diseases.

Regional Functions

Essential differences in the cytology, circuits, and chemistries of each region have been reviewed (Vogt *et al.*, 1997, 2004; Pallomero-Gallagher *et al.*, 2008), however, this information needs to be placed in the context of specific functional observations. With the passing of each generation of neuroscience research, observations are re-considered as improved techniques provide new details and associated logic, however, sometimes the earlier observations are simply "lost" and later "re-discovered." Although the reassessment process is underway with the powerful observations of human functional imaging, there are certain classes of information from past research that cannot be simply replicated even with higher resolution imaging modalities. This includes morphological studies with resolution greater than 5 mm, monosynaptic circuit studies in monkey, and human electrical stimulation and subdural electrode recording studies. This section brings this information to bear and integrates it with that in each region with functions discussed in other chapters where the detailed information and arguments are provided.

Anterior cingulate cortex: ACC

One of the primary reasons for differentiating between ACC and MCC was the profound connections with the amygdala and projections to visceral motor nuclei including the central nucleus of the amygdala and nuclei in the brainstem (Chapter 10), including the lateral hypothalamus, periaqueductal gray, and parabrachial nucleus. Projections to the dorsal motor nucleus of the vagus and nucleus of the tractus solitarius are significant in rodents but modest in monkey. No other part of the cingulate gyrus has these particular connections and they mediate autonomic regulation evoked during electrical stimulation. Bancaud and Talairach (1992) reported that the most frequent response in a series of medial surface stimulations was intense or overwhelming fear including one individual who reported the feeling that death was imminent. Stimulation of ACC produced the report, "I was afraid and my heart started to beat," whereas stimulation of MCC evoked the report, "I felt something, as though I was going to leave." The former report is of pure fear, while the latter is one of an early premotor planning with motivational characteristics. In other studies, electrical stimulation of areas 25 and 24 evoked increases

and decreases in respiratory and cardiac rate and blood pressure, mydriasis, piloerection, and facial flushing (Pool, 1954; Escobedo *et al*., 1973; Talairach *et al*., 1973). Gastrointestinal responses included nausea, vomiting, epigastric sensation, salivation or bowel or bladder evacuation (Pool and Ransohoff, 1949; Lewin and Whitty, 1960; Meyer *et al*., 1973) and they are reviewed in Chapters 10 and 28.

The modern era of functional imaging with PET and MRI began with a number of important studies that showed a role for ACC in emotion. Cerebral blood flow was elevated in subgenual ACC (sACC) when healthy women recalled sad experiences (George *et al*., 1995; Mayberg *et al*., 1999) and when subjects were involved in a face-recognition task where the faces expressed emotional content (George *et al*., 1993). Whalen *et al*. (1998) used the emotional-counting Stroop paradigm to evaluate the distribution of emotional responses in ACC and provided the first independent functional imaging verification of the location of the border between ACC and MCC based on previous histological analyses (Vogt *et al*., 1995). The many subsequent studies of the role of ACC in emotion are considered in Chapters 8, 9, 10, 11, 12, 13, and 24 and will not be reviewed in detail here. Instead, we refer to a summary of findings that was performed in the context of the regionalized model to identify structure/function correlations.

Brain activity generated by viewing faces or listening to stories with emotional content has produced a number of interesting outcomes (Phan *et al*., 2002). In most such studies, ACC has a robust activation. Interestingly, however, so do other parts of the cingulate cortex. One might conclude from these studies that the entire cingulate gyrus is involved in emotion as early postulated by the Papez-MacLean model (Papez, 1937; MacLean, 1954). A consideration of simple emotion activation sites co-registered to histologically analyzed cases led us to a different conclusion (Vogt *et al*., 2003). Figure 1.4 shows a postmortem case and the borders for each region aligned to the VCA and AC-PC lines according to the atlas of Talairach and Tournoux (1988). The predictions of the regional model were and still are quite specific and provide the context for accepting the null hypothesis; that is, there are no regionalized functions in cingulate cortex and the differential circuitry previously noted has no relevance to emotion processing therein.

The sites coded with white dots in Figure 1.4 are for activity associated with non-emotional faces and scripts and are similar to the control conditions used in studies of emotion (references for each activation site provided in Vogt, 2005). Notice there are only 5 peak activations in MCC and four non-emotion peaks. This suggests that MCC is essentially free of activity during simple

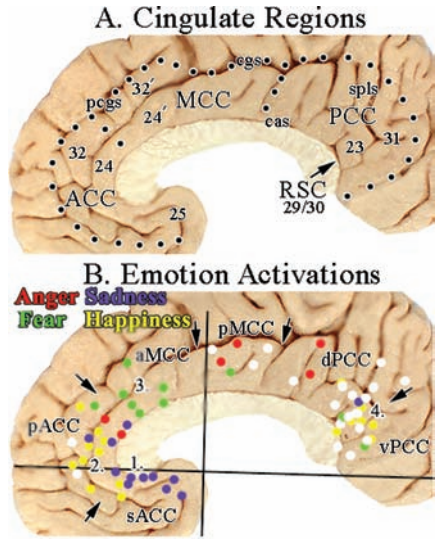

Fig. 1.4 Distribution of regions plotted onto postmortem case GPC that was co-registered to a stereotaxic atlas. The RSC is located in the caudal callosal sulcus (cas; arrow) and is not observed on the exposed medial surface. Onto this surface was plotted the peak voxels associated with activations during simple emotion-generating tasks, while the white dots are for control tasks that do not involve emotion but use similar stimuli. This provides a comparison of histological information with emotion activations where the sites are color coded and numbered to enhance some of the subregional localizations. The subregion designations (xXCC) are provided in "Cingulate Subregions."

emotion. Notice also, however, that the greatest number of "fear" activations occur in the anterior part of MCC and not in ACC. A number of important points emerge from this analysis of simple emotion activations in the context of cytoarchitecture. P*oint #1* is that fear processing is not uniform in the cingulate gyrus and mainly drives aMCC as discussed below. Indeed, this particular group of activations may be more closely linked with motor output associated with nocifensive behaviors than with affect *per se*. P*oint #2* is that happiness activity was most often encountered in pACC and that for sadness in sACC. These are weakly activated regions for both and suggest that cardiovascular hypotension and bradycardia may be generated in cortex associated with sadness and that for happiness is generated in cortex that electrical stimulation evokes pressor and tachycardia responses as reviewed in Chapter 10. It is also important that the subgenual subregion may have a pivotal role in negatively valenced emotional memories as first suggested by George *et al*. (1995). P*oint #3* is that there are sites of peak activity during emotion in PCC, however, they are intermingled with those associated with non-emotional activity as is not the case for ACC (Vogt *et al*., 2003). This suggests that PCC has a different role in emotion than does ACC.

Indeed, electrical stimulation of MCC and PCC does not evoke autonomic activity as in ACC and there is no evidence for storage of negative emotions in PCC. As discussed in detail below, PCC does not have a *primary* role in emotion. P*oint #4* is that each region of cingulate cortex has a different role in emotion and the null hypothesis was rejected following coregistration of peak activation sites with subregional borders. The final conceptualization of ACC function is best undertaken in a later section where the subregional organization is considered along with specific circuits that underpin autonomic and emotional activity.

Midcingulate cortex: MCC

The primary reason for separating MCC from ACC, instead of simply proposing a "caudal" ACC, is that *MCC is qualitatively different from ACC* as shown above with connections and receptor binding. The MCC has two corticospinal projection systems in the cingulate sulcus (Biber *et al*., 1978; Dum and Strick, 1991, 1993), these spinal projection neurons do not extend into ACC (Fig. 1.2D), and their presence adds a population of large, layer Vb pyramids that are not characteristic of other parts of cingulate cortex. The first demonstration of these large pyramidal neurons by Heiko Braak (1976) suggested the presence of a motor field in the human cingulate gyrus and this discovery had a profound and long-lasting impact on how the functions of cingulate cortex are viewed, that is, as a premotor region that may not always be engaged in emotion. It should also be noted that area 24c in the rostral cingulate sulcus projects to the facial motor nucleus and forms the head/face part of the rostral cingulate motor area. Since the face is a pivotal medium for expressing emotion and internal states such as pain it is part of the primary affective system in the pACC (see also Chapters 13, 14, and 15).

The original topography of the cingulate motor areas and their cytoarchitectural localization was described by Luppino *et al*. (1991) and Matelli *et al*. (1991). A summary of the organization and connections of the cingulate motor areas are provided in Chapter 5 and include those to motor, supplementary motor, and pre-supplementary motor cortices (Morecraft and Van Hoesen, 1992; Van Hoesen *et al*., 1993). Also important to formation of the MCC concept was the projection of parietal cortex to this region but not ACC as shown in Figure 1.2B (Vogt and Pandya, 1987). These connections and reciprocal, intrinsic connections between cingulate gyral areas and the cingulate motor areas suggested a primary function of MCC in premotor functions which was conceptualized in the four-region model as broadly involving response selection (Fig. 1.7). This term continues to be used in the most general sense because the specific contributions of each premotor area and adjacent cortex is still not resolved. It is also true, that many cognitive processes involve selections that do not require movement and they employ MCC to this end.

Electrical stimulation of MCC evokes complex and context-dependent gestures such as touching, kneading, rubbing or pressing the fingers or hands together, and lip puckering or sucking (Escobedo *et al*., 1973; Meyer *et al*., 1973; Talairach *et al*., 1973). These movements are often adapted to the environment; they can be modified by sensory stimuli, and at times, resisted. These areas contain neurons with premotor discharge properties (Shima *et al*., 1991) that are coded according to the changing reward properties of particular behaviors (Shima and Tanji, 1998; Chapter 5). Finally, functional imaging studies show altered blood flow in this region during sequences of complex finger apposition movements (Kwan *et al*., 2000).

The concept of "attention-for-action" proposed by Posner *et al*. (1988) provided the first premotor orientation for MCC function. This designation is useful because it does not preclude its potential role in mismatch detection/conflict resolution (Carter *et al*., 1998, 2000), selecting among cognitive options that do not require movement (Corbetta *et al*., 1992; Bench *et al*., 1992), selecting action verbs to noun lists that may or may not generate movement (Raichle, 2000), anticipation of cognitive processing (Murtha *et al*., 1996), or working memory (Petit *et al*., 1998). The question as to its primary role in behavior remains controversial and these issues are addressed in detail in Chapters 12 and 16.

A recent study of cases with aMCC lesions (Fellows and Farah, 2005) raised questions about a strict role for this region in cognitive control. Since Bush *et al*. (1998) show involvement in enhancing response reaction times and in mediating reward responses (Bush *et al*., 2002), it is necessary to consider this region in the broader context of response selection toward either reward or punishment and this is one of the values of the response selection designation; it can occur toward any outcome and may be determined by feedback parameters that guide behavior. Hadland *et al*. (2003) used monkeys to show that cingulate cortex is involved in selecting responses related to different reward outcomes, although their lesions involved substantial white matter and dorsal supplementary motor cortex and Chapter 8 considers the role of cingulate cortex in reward processes. Response selection does not refer to a single cognitive activity as sometimes implied because MCC has many areas and individual layers in each area might contribute to more than one function. Midcingulotomy lesions can disrupt reward-guided response selection (Williams *et al*., 2004). Finally, the role of MCC in punishment and avoidance is stressed by a substantial literature on acute nociceptive stimulation (Chapter 14; Vogt *et al*., 2003).

In conclusion, MCC provides a cognitive interface with skeletomotor systems via projections to the spinal cord, striatum, supplementary/pre-supplementary motor cortices, and other motor systems. The MCC is critical to decisions selecting between pain or reward outcomes. The response selection process may require movement and/or corollary discharges associated with it, mismatch and/or outcome assessment, assessment of internal requirements and reward consequences, and defining optimal output and reprogramming other motor areas for routine behaviors. The dorsal MCC may play a pivotal role in reorganizing activity in many motor structures to produce new behavioral outputs that adapt to changing rewards and punishments. Patterns of neuronal activity in cingulate cortex likely reflect the differential contributions of each region to different aspects of task acquisition and performance as well as cognitive processing in the absence of movement. The challenge will be to understand how each function is performed within MCC.

Posterior cingulate cortex: PCC

The PCC has one of the highest levels of metabolism in the brain (Maquet *et al*., 1997; Laureys *et al*., 2004) and its metabolism is significantly modulated during sleep (Maquet *et al*., 1996; review, Vogt and Laureys, 2005) and it is reduced during altered consciousness as under general anesthesia with propofol (Bonhomme *et al*., 2001). These facts in conjunction with its isocortical cytoarchitecture (Zilles, 2004) and RSC connections validates the place of PCC as a separate region in the cingulate gyrus as discussed in Chapter 13. From a functional perspective, the PCC is involved in topographic and topokinetic memory, that is, orientation of the body in space. Olson *et al*. (1993, 1996) suggested that PCC is involved in large visual scene assessment, part of which is subserved by activity generated by the orbital position of the eye and that information regarding the orbital position of the eye was used to generate a map of the head and body in space. Furthermore, mental navigation along memorized routes elevates blood flow in PCC (Berthoz, 1997; Ghaem *et al*., 1997; Maguire *et al*., 1998) and topographic disorientation is produced by large, right hemisphere lesions of perisplenial cortex without associated changes in consciousness (Takahashi *et al*., 1997). Finally, an elegant study by Sugiura *et al*. (2005) showed that ventral PCC (vPCC) has a particularly high level of activity during exposure to familiar places over objects and dorsal PCC (dPCC) is most active during presentation of familiar objects and places over unfamiliar objects and places. The co-activation of RSC in particular along with dPCC suggests that reciprocal circuitries among these regions have important functional consequences.

The PCC has many interconnections that subserve memory and visuospatial functions and their close relations to ACC suggest a coupling of the activity in these regions. It is possible, for example, that memories associated with emotional states are stored in sACC but their release for conscious consideration is mediated by the activity of RSC and vPCC; Chapter 13 provides a 6-stage model for this process. Area 23a and RSC are adjacent to each other and reciprocally connected (Vogt and Pandya, 1987) and relationships between pACC and perisplenial cortices are profound. Thus, the subgenual and perisplenial connection is reciprocal and involves only a small part of MCC as shown by tracer injections into different parts of the cingulate gyrus. The reciprocal, intracingulate connection between sACC and vPCC may involve a joint activation of both via a common auditory input (Grasby *et al*., 1993). The linkage between sACC and vPCC is even tighter when other cortical connections are considered. A limbic convergence zone in area 11m receives major inputs from both subgenual and perisplenial cortices with none from MCC (Carmichael and Price, 1995). Thus, primary sensory inputs, reciprocal intracingulate connections, and connections among limbic association areas preserve the functional integration of pregenual and perisplenial cortices.

Retrosplenial cortex: RSC

Since RSC and PCC are adjacent to each other and heavily interconnected, it has been difficult to disentangle their unique contributions to brain function. An additional problem in the human brain is the small size of RSC in relation to the spatial resolution of imaging modalities. Of course, there is no *a priori* reason to expect they are necessarily involved in different functions, although the cytoarchitecture of each component of RSC is easily identified as they proceed through significant histological transitions that can be easily demonstrated as shown in Chapter 3. In instances where a clear involvement of RSC can be shown in human studies, it has been implicated in working and long-term memory and visuospatial functions as discussed in more detail in Chapter 13.

Valenstein *et al*. (1987) reported a case with extensive anterograde and retrograde amnesia following removal of an arteriovenous malformation near the splenium and referred to the syndrome as *retrosplenial amnesia*. Since involvement of the fornix may have contributed to the presentation in this case, Parker and Gaffan (1997) placed massive cingulate cortical or anterior thalamic lesions in monkeys and tested object-in-place memory. Although cingulate lesions failed to show a significant deficit, there was substantial impairment in the anterior thalamic group. Since the anterior thalamic nuclei have as their primary projection the RSC

(Vogt *et al*., 1987), it is surprising that no deficit was observed following cortical lesions. Other evidence links these cingulate areas to memory and visuospatial functions. The RSC and PCC are activated during the "memory component" of tasks that require assigning valences to visual images (Paradiso *et al*., 1999). Working memory tasks elevate glucose metabolism in the anterior thalamic nuclei (Friedman *et al*., 1990), one of the highest levels of basal glucose metabolism in the monkey brain is in RSC, and glucose metabolism in RSC is elevated when performing a delayed-response task (Matsunami *et al*., 1989). There is a striking correlation between anterior thalamic inputs to RSC and basal glucose metabolism in the monkey (Vogt and Laureys, 2005). The tight link between anterior thalamic projections to RSC, high levels of basal glucose metabolism, and its modulation in both structures suggest that the anterior thalamic/RSC system is a pivotal player in memory.

The retrosplenial region is involved in visuospatial orientation and body movement in large visual spaces. Focal lesions that involve RSC impair memory of spatial-positional relationships and are associated with topokinetic (movement in space) disorientation (Rudge and Warrington, 1991; Takahashi *et al*., 1997). It should be realized that these strokes encompass both RSC and dPCC and are better termed *perisplenial strokes* so as to not implicate their damage to any one cytoarchitectural area. Tasks that require subjects to employ memory in relation to previously learned routes in an environment activate RSC (Ghaem *et al*., 1997; Mellet *et al*., 2000) and support a specific role of RSC in body in space orientation functions.

Recent neuroimaging observations by Sugiura *et al*. (2005) have made strides in resolving two important issues relating to the functions of RSC. First, it is activated along with dPCC by familiar places. Second, RSC is involved in the episodic retrieval of personally familiar places and objects. Thus, this region likely plays an important role in working memory in relation to the functions of PCC as discussed above. Storage of this information in a working memory system provides for guiding particular behaviors in a multisensory space as discussed in detail in Chapter 13.

ACC/MCC Border and Metabolic Unit

The most profound change in the map of cingulate gyral organization in the past century is the midcingulate concept which flowed from the work of Heiko Braak (1976) who identified the primitive gigantopyramidal field in the cingulate sulcus. The midcingulate concept was introduced (Vogt, 1993) to account for significant differences in the structure, connections, and functions of the anteroposterior parts of ACC and these include the cingulospinal projections of the cingulate motor areas and associated response selection functions. A review by Bush *et al*. (2000) was the first to validate the border between the affective and cognitive-motor divisions of ACC which we referred to as the border between ACC and MCC (Vogt *et al*., 1995) and the location of the ACC/MCC border is an important issue.

The ACC/MCC border can be assessed in many ways and a new strategy for studying functional "connections" among cortical areas in the human is useful in this regard. This approach evaluates correlations among clusters of voxels in basal glucose metabolism with PET. The essential premise of the method is that regions that rest at similar levels of basal glucose metabolism are more likely to discharge together and engage in information transfers rather than regions that have resting levels of metabolism that differ substantially. If direct connections have been demonstrated between a pair of areas in the monkey cortex, there is a high probability that such a sharing will occur, although this need not be the case. In a broader program of research using this method to study the functional organization of the posterior cingulate and precuneal cortices (Vogt, Vogt, Laureys, 2006; Chapter 13), we were surprised to observe the precision of the ACC/MCC border.

Figure 1.5 shows this rather striking finding in a statistical parametric mapping (SPM) for 153 normal control cases. The correlation was seeded with area s32 and correlated clusters of interest in the basal metabolic state (bCCOI) were identified with SPM (methodological details in Vogt *et al*., 2006). This figure demonstrates two important principles. First, it is a striking fact that the entire ACC had highly significant ($p<0.05$) bCCOI with area s32. This suggests that the region identified histologically as ACC operates as a metabolic unit rather than as part of a broader anterior cingulate construct according to Brodmann's hypothesis. Second, the ACC/MCC border identified histologically is almost exactly identified with this new method. The ACC and MCC have significantly different levels of basal metabolism and support further the distinction between these two regions and their independent functionality.

Reciprocal Suppression: A Key to Functional Segregation of ACC and MCC

More than a decade of human imaging has overwhelmingly shown that the structural border between ACC and MCC has functional relevance. One of the first such demonstrations was provided by Bush *et al*. (2000) who showed that emotional and cognitive tasks differentially activated ACC and aMCC and similar views were proposed in other studies (Mayberg *et al*., 1999).

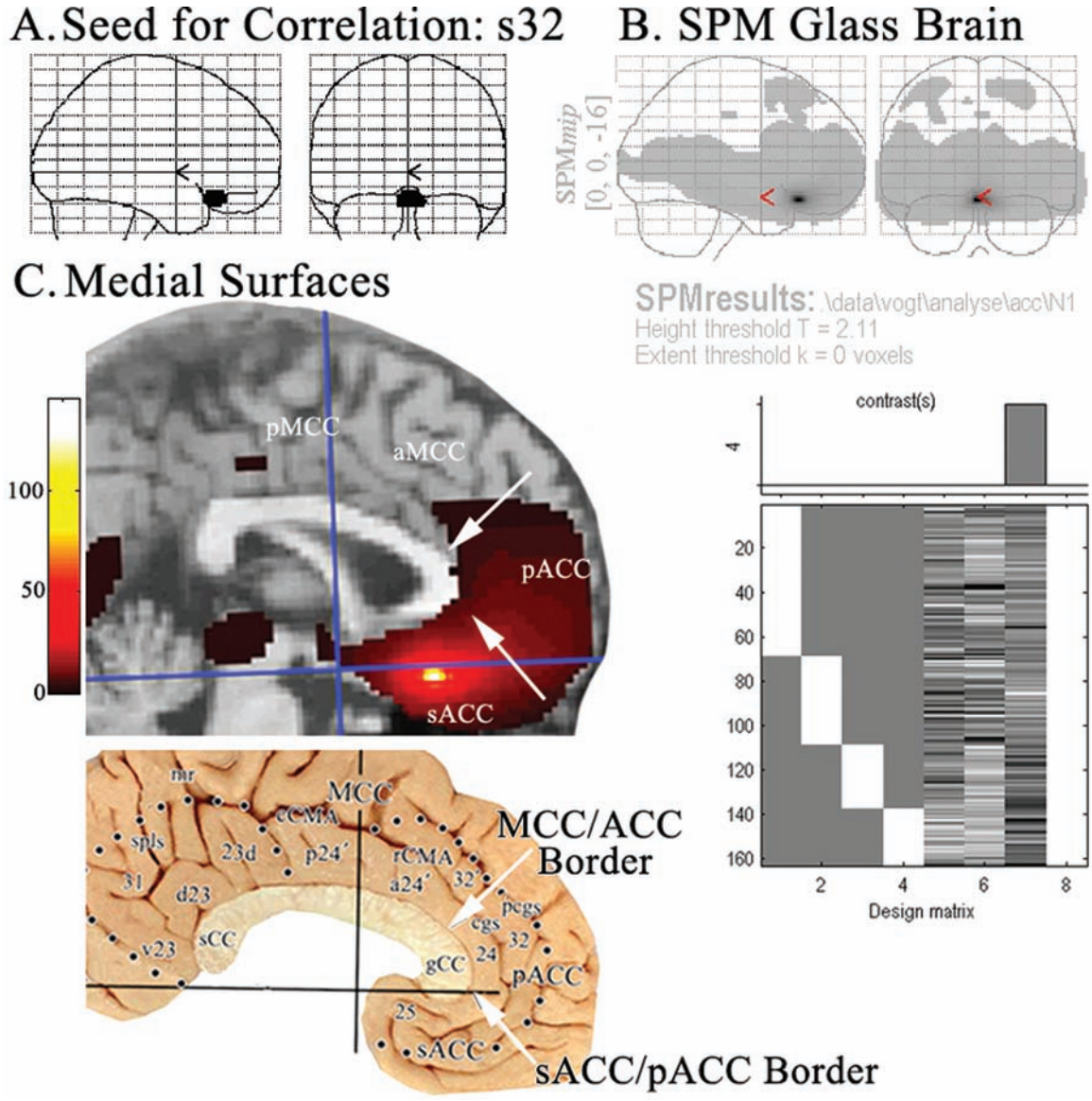

Fig. 1.5 Functional definition of the ACC/MCC border A. Basal metabolism for a correlation study was seeded with s32. B. SPM output and design matrix. C. Medial surfaces from the SPM analysis (top) and a histological case (bottom). Both medial surfaces were aligned using the dorsum of the corpus callosum (s, splenium; g, genu; CC), cingulate sulcus (cgs), anterior commissure, and apex of the superior frontal gyrus. The two borders are shown with white arrows (below), the area s32 seed is seen in yellow in the SPM (top), and the distribution of areas is provided from the histological map (below). The dorsal edge of the bCCOIs almost exactly overlaps with the ACC/MCC border in the histological case GPC and ACC is a separate metabolic unit.

Additionally, Bush *et al*. (2000) noted that activity in the aMCC was suppressed during intense emotional states and that patients with depression and subjects anticipating pain and film-induced emotion deactivated activity in "cognitive" aMCC. They proposed that "reciprocal suppression of the cognitive subdivision" of ACC occurred during intense emotion. This is a critical observation because it goes beyond simply segregating functions to subdivisions of cingulate cortex and may be pivotal to understanding interactions between ACC and aMCC.

Reciprocal suppression suggests that processing in one or the other of these regions can be mutually exclusive and requires a mechanism whereby each region can shut the other off during information processing. Moreover, it may suggest why sACC is more vulnerable to depression than other parts of cingulate cortex; not enhanced sadness *per se*, but may produce alterations in

cognitive processing in aMCC and skeletomotor activation through the rostral cingulate motor area. Gruber *et al*. (2004) showed that normal activation of aMCC during a Stroop-interference task was abolished in patients with bipolar disorder and Chapter 24 considers the impact of depression in all cingulate regions.

The mechanism of reciprocal suppression is still a matter of investigation. A direct and reciprocal interaction is the first hypothesis. The bCCOI study above showed almost no basal correlations between these regions. Review of specific connections in the monkey suggests few such interactions. Figure 5.13 shows no connections with the rostral cingulate motor area with amino acid injections and Figure 5.3 no connections when horseradish peroxidase is used as the tracer. Although a little labeling suggestive of an interaction between these regions can be shown in Figure 5.5, there is also involvement of pACC in the injection. Overall, we conclude at this time that based on monkey connection studies there is little evidence for strong and direct connections between ACC and aMCC.

An alternative mechanism of reciprocal suppression may arise from layer VI neurons driving thalamic afferents to the other region, some other subcortical structure such as the amygdala which has major projections to ACC and minor ones to aMCC. Das *et al*. (2005) evaluated physiological connections during fear generated by pictures and observed that the thalamus-aMCC interaction had a negative interaction with the amygdala, while the thalamus–sACC had a positive correlation with the left amygdala. These observations support the prediction of a differential involvement of the thalamus in functions of aMCC and sACC but whether or not this is a demonstration of the substrate of reciprocal suppression remains to be determined.

Recent Imaging Approaches to Cingulate Nomenclature

During the 1990s, human imaging studies routinely referred to Brodmann areas based on the Talairach and Tournoux (1988) extrapolation of his map to their case. Although investigators sought to link functional assessments with a structural substrate, it has been long known that cingulate cortex does not reflect two homogeneous regions as hypothesized by Brodmann and his areas were never evaluated in the context of brains that had undergone MRI. It was inevitable, therefore, that structure/function correlations would not emerge and many diverse sources of activations were identified and have yet to be integrated in a common structure/function framework.

To evaluate current usage of the ACC designation, "anterior cingulate" was entered as a primary search term in *NeuroImage* for 2005 and the first half of 2006. The search generated 64 studies; those that reconstructed electrophysiological findings, neurochemical studies with a single ROI, and schematic models were excluded as were studies that did not provide a medial surface reconstruction. The medial surface reconstructions in each of the remaining studies were digitized and co-registered to a flat map of the medial surface of Case GPC as shown in Figure 1.6. The top of Figure 1.6 shows the orientation of flattening and a few sulci. Onto the flattened map in A. is plotted the location of Brodmann's border between areas 24 and 23 at the vertical arrow, the depths of the sulci are a uniform gray, and the callosal sulcus (cas) was opened by rotating the corpus callosum ventrally to expose RSC. Three sites from one study were plotted onto the medial surface (discussed below) and reports that claimed activity in the "anterior cingulate" without subregional locations were plotted onto the flat map in A. with some distortion to accommodate the flattened surface; all sites retain the same relative orientation to each other on this map. The most ventral, dorsal, and caudal sites reported as in ACC are marked with three, two, and one asterisk, respectively, and the histological borders of the ACC/MCC and MCC/PCC regions are marked with dotted lines. This map of activations shows that ACC is used to designate the anterior cingulate gyrus as it surrounds the rostral and ventral parts of the genu of the corpus callosum and it reaches Brodmann's border with PCC.

Since ACC is not homogeneously activated, many investigators now subdivide Brodmann's anterior cingulate region. However, since these imaging studies are not guided by histological analysis and are based on activation sites of limited and variable sizes as determined by task designs, it is difficult to determine where the physical borders are located for designated ROIs within cingulate cortex. Arbitrary coordinate systems available for neuron-free, structural images of the human brain do not provide such information.

At the turn of this decade, it was increasingly clear that subgenual and dorsal cingulate cortex were functionally separable as well as differentially vulnerable to depression (Mayberg *et al*., 1999; Duncan and Owen, 2000). Figure 1.6B shows plots of activation sites claimed to be in parts of the ACC according to the same journal search protocol noted above. It appears that dorsal ACC (dACC) and supracallosal ACC (SACC) refers to any ACC that lies dorsal to the corpus callosum. According to this usage, the dACC includes all midcingulate cortex and part of pACC. Dorsal and supracallosal ACC have also been referred to as posterior, mid-caudal, and caudal ACC as well as the rostral cingulate zone anterior. Amodio and Frith (2006) took a unique, "frontal-lobe" view of the cingulate gyrus to designate the dACC as posterior rostral medial frontal cortex (prMFC). Thus, the

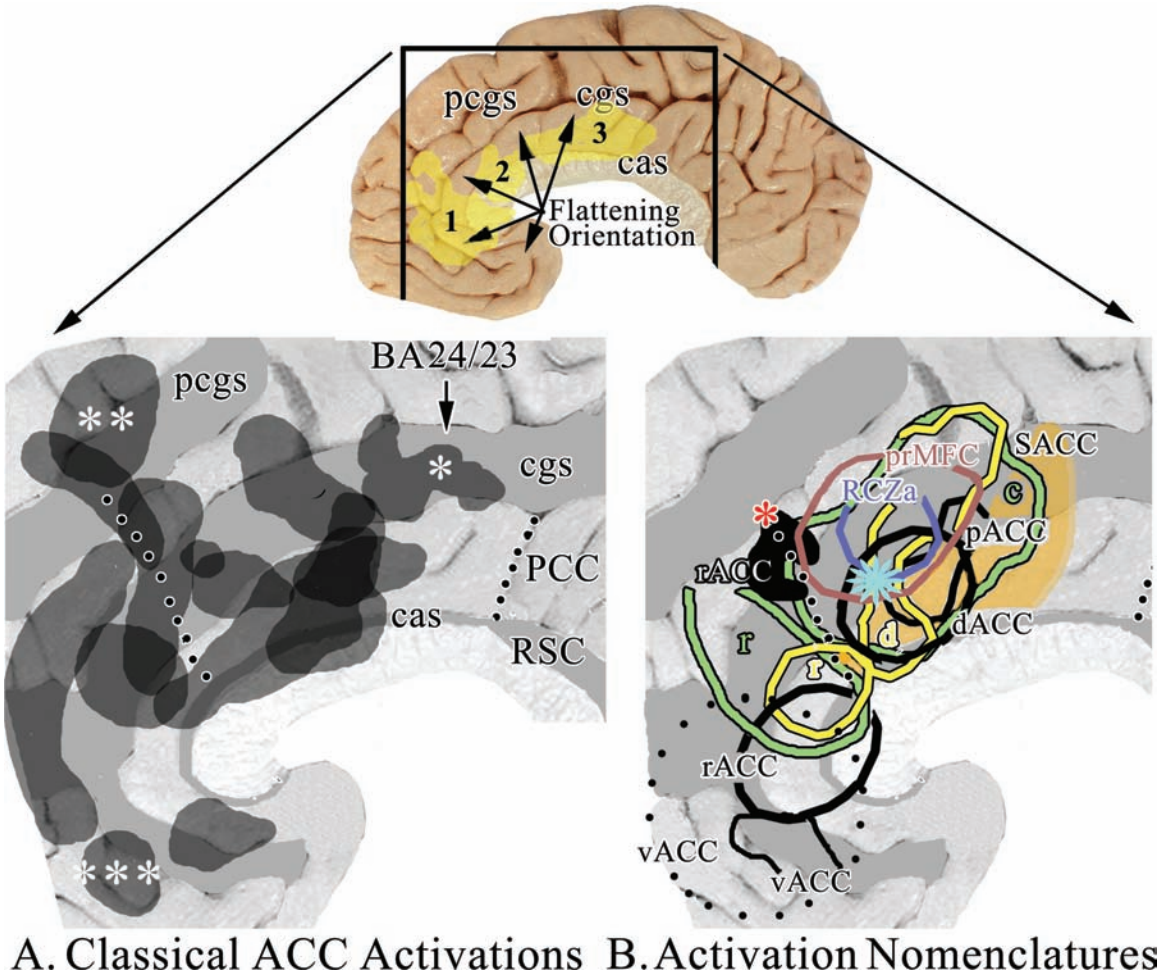

Fig. 1.6 Flat map of medial cortex in Case GPC with 5 arrows showing the orientation of flattening and three yellow regions locating remifentanil activations. A. The border of Brodmann's areas 24 and 23 is shown (vertical arrow at BA) and the depths of sulci are a uniform grey. Co-registrations of reported activity in "ACC" are shown and asterisks emphasize the most ventral/3, dorsal/2, and caudal/1 sites. B. Activity in parts of ACC designated in the same journal and time period with adjectives locating parts of ACC include: c, caudal; d, dorsal; p, posterior; prMFC, posterior rostral medial frontal cortex; r, rostral; RCZa, rostral cingulate zone anterior; S, supracallosal; v, ventral. The voxel cluster with the most numerous designations is marked with a turquoise star. The dotted lines are at the histological borders between ACC/MCC and MCC/PCC. Notice in B. that the ACC/MCC border (red asterisk) established in 1995 by Vogt *et al*. was corroborated a decade later in reports of differential functions in ACC.

dACC concept does not embody any specific histological entity and its variously named constituents in the same region have no specific boundaries. The turquoise star in Figure 1.6B represents a site that received 7 designations in 1.5 years: RCZa (Mars *et al*., 2005), prMFC (Amodio and Frith, 2006), dACC (Nitschke *et al*., 2006), cACC (Maltby *et al*., 2005), pACC (Jackson *et al*., 2005), mid-caudal ACC (Leppä *et al*., 2006), supracallosal ACC (Bermpohl *et al*., 2006). Providing new adjectives for each one, pair, or triad of activations in ACC to account for findings in each imaging study may eventually lead to some confusion, since the number of tasks that activate parts of ACC is almost limitless and their topographical distribution is not uniform or linked to a cellular substrate.

Most studies distinguish a subregion anterior to the border of pACC/aMCC and it is often termed rostral ACC. When a further division of the rACC is noted, it usually is termed ventral ACC (Das *et al*., 2005; Simmons *et al*., 2006), although this does not link in any apparent way to sACC or pACC based on cytological analyses. The nomenclature of Leppä *et al*. (2006) for activity generated by remifentanil raised the possibility of another area between rostral and caudal ACC and these three cingulate sites are co-registered to the medial surface in Figure 1.6 (yellow) and numbered: 1. rostral anterior

cingulate cortex, 2. mid-caudal anterior cingulate cortex, 3. caudal anterior cingulate cortex. The mid-caudal anterior cingulate cortex is a difficult concept because a consistent nomenclature requires that one must consider where the ant-caudal anterior cingulate cortex is located including an ant-caudal and caud-caudal divisions. Although one would expect the ant-caudal region to be located caudal to the rostral anterior cingulate cortex, there is no cortex located between these two sites to provide for such a designation. Thus, it is unlikely that non-systematic and non-cellular designations can resolve the confusion of ACC nomenclatures.

These many designations were reported during only 18 months in a limited journal sampling and the current proliferation rate of unique adjectives for places in ACC assures many more to come. A uniform cytological nomenclature is fundamental to progress in neuroscience because it provides a platform on which to integrate past and future findings relating to the functions and diseases of the cingulate cortex. The subregions identified for the four-region neurobiological model resolves these problems and provides the cytologically based framework needed for a broad-based, interdisciplinary, neurobiological assessment of the cingulate cortex including an approach for neuropathological studies as discussed in many of the subsequent chapters.

Cingulate Subregions

As imaging resolution and behavioral task-parameter control improves, our understanding of functional cingulate units will be reduced to individual areas rather than broad regions. An intermediate step in this process is to evaluate cingulate subregion functions. A subregion is a small aggregate of areas with subroutine processing functions within a particular region. The chances of interconnections among a small group of areas are quite high and enhance their common functionality. It still must be required that subregions have a neuroanatomical basis in cell structure and overall connectivity. Input and output information provided above for the human and the monkey (Fig. 1.2) are considered here in the context of subregion organization and Figure 1.7 is an overview of cingulate subregions.

Subgenual and pregenual ACC: sACC/pACC

There are a number of reasons for defining sACC separately from pACC. First, it is comprised mainly of areas 25, s24, and s32, while caudal pACC is mainly areas 24a-c and rostral pACC is mainly areas p32 and d32. Area 25 has a very rudimentary cytoarchitecture with external and internal pyramidal layers that have little differentiation, while that for areas 24 and 32 have layers III and Va differentiation. Second, negatively

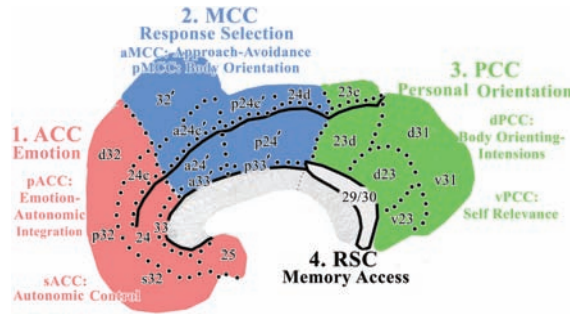

Fig. 1.7 Location of each subregion in a flat map from Figure 3.18 including some of the key areas and a summary of overall functions for each.

valenced and episodic memories appear to be most frequently stored in sACC than in pACC (Fig. 1.4B), while happiness and associated memories are most often stored in the rostral part of pACC mainly in area p32. The role of area 32 in pACC is in subjective emotional events as reported by Lane *et al.* (1997). Third, area 25 is heavily connected with the central nucleus of the amygdala, lateral hypothalamus, and parabrachial nucleus. These projections clearly differentiate sACC as an autonomic control center, while area 24 of pACC does not have these projections as discussed in Chapter 10. Fourth, electrical stimulation to ameliorate treatment-resistant depression is effective in the white matter beneath area 25 (Mayberg *et al.*, 2005; Chapter 24). Although we do not yet know that similar stimulation of area 24 is not effective nor that area 25 white matter stimulation does not activate area 24 directly, this may eventually prove to be a differentiating feature of sACC. Finally, both regions have a unique neurochemistry as shown with 15 neurotransmitter receptors in Chapter 2 and by Palomero-Gallagher *et al.* (2008a). This report indicated that sACC, in comparison to pACC, has a significantly higher density of $GABA_A$, $GABA_B$, benzodiazepine, alpha1, and serotonin1A receptors. This differential innervation by three neurotransmitter systems implies significantly different functional outputs for both subregions.

Thus, the two subregions of ACC can be identified according to anatomical, functional, and neurotransmitter receptor criteria. Their involvement in psychiatric disease may be differentially addressable with deep brain stimulation and other therapeutic interventions including drug modulation of the GABAergic, norepinephrinergic, and serotonergic systems.

Anterior and posterior midcingulate cortex: aMCC/pMCC

Although the midcingulate concept was derived from its predominant role in skeletomotor regulation, there

are two cingulate premotor areas in and along the human cingulate sulcus and each level of the cingulate gyrus has a different involvement in emotion. The aMCC is active during fear as shown in Figure 1.4B, while the pMCC appears to have no responsivity during simple emotions. Even the involvement of aMCC is limited to fear with a more profound role in emotion for ACC. Meyer *et al.* (1973) provide a valuable demonstration of this dissociation with cingulotomy lesions. They evaluated affective responses evoked by electrical stimulation in aMCC before placing cingulotomy lesions for obsessive-compulsive disorder, depression, schizophrenia, alcoholism, and chronic pain. Although the patient population was heterogeneous, 65 of 75 cases had categorical responses including 25 with affective responses. Of these patients, 11 reported fear with two being very intense, 6 moderate agitation, and 8 reported pleasure. In view of patient characteristics and lack of detailed localization of effective electrode sites, one cannot over interpret these findings, however, a preponderance of fear was evoked in these patients. It is interesting that the amygdala projection extends into aMCC and this may contribute to its involvement in fear and Figure 1.2A shows this projection.

The pMCC is associated with the caudal cingulate premotor area and neurons in this cortex have a shorter duration time period between discharge and muscle contraction than do neurons in the rostral cingulate motor area. The caudal area is also more easily driven by passive movements and appears to play a lesser role in the reward coding of behavior than the rostral region (Shima *et al.*, 1991; Shima and Tanji, 1998) as discussed in detail in Chapter 5. Finally, the cytoarchitecture of the two cingulate premotor areas in monkey and human brains is established by the differential expression of neurofilament proteins and neuron densities and sizes in layer Vb where the cingulospinal projection neurons reside (Nimchinsky *et al.*, 1995, 1996; Vogt *et al.*, 2004, 2005). Thus, the key to identifying the two subdivisions of MCC lie in the unique cytologies of these two subregions and differentiation of the functions of the rostral and caudal cingulate premotor areas.

Dorsal and ventral posterior cingulate cortex: dPCC/vPCC

The PCC can be differentiated into two divisions based on primate cytology (Vogt *et al.*, 2005), monkey connections (Shibata and Yukie, 2003), human functional imaging (Vogt *et al.*, 2006) and neurotransmitter receptor architecture (Pallomero-Gallagher *et al.*, 2008b). Since a consideration of these issues is part of Chapters 2, 4, 6, and 13, they are noted here only briefly. The vPCC region was first emphasized in monkey connection studies. Goldman-Rakic *et al.* (1984) recognized the unique structure of the caudomedial lobule and its frontal connections, while we emphasized its unique intracingulate connections with sACC (Vogt and Pandya, 1987). Shibata and Yukie (2003) showed differential thalamic afferents with dPCC receiving unique inputs from the mediodorsal, central lateral, ventral anterior, and lateral nuclei. The vPCC has a predominant role in sensory evaluation in terms of the self relevance of objects and places (Johnson *et al.*, 2002; Phan *et al.*, 2002), it is activated to a greater extent by familiar places than objects (Sugiura *et al.*, 2005), and it receives input from the ventral visual stream (Vogt *et al.*, 2006).

The dPCC, in contrast to vPCC, has a more profound role in visuospatial functions, receives input via the dorsal visual stream, has heavier interconnections with MCC (*op cit*), and is activated by familiar over unfamiliar objects and places (Sugiura *et al.*, 2005). The cytological differences between these regions is determined by the composition of layers III and V with the vPCC having much larger layer III, neurofilament expressing neurons than does dPCC and the same is true for layer V. Thus, vPCC evaluates emotional and non-emotional sensory inputs, it determines their self relevance via connections with sACC where long-term memories of valenced events are stored, and then such information is directed to MCC for motor system output. The dPCC, in contrast, has a closer link with the MCC and appears to be more closely associated with sensorimotor orientation in space and rapid adjustments to visuospatial needs in the context of dorsal visual stream input.

Limbic Cingulate Cortex

The term "limbic system" has been used in many ways through the history of neuroscience. As limbic functions such as olfaction (rhinencephalon) and sexual responses were associated with the limbic lobe of Broca, a general association evolved between cortical areas on the limbus of the medial surface and their "simple" laminar organization (review of the early literature by MacLean, 1990). Cingulate cortex, however, does not have a "simple" laminar organization and the cytoarchitecture of its areas span the entire range of cortical differentiation from the agranular area 33 and granular retrosplenial areas to the fully differentiated area 31 with its thick layer IV in PCC (Chapter 3). During the 1970s and 1980s, some investigators attempted to apply connections as a basis for defining limbic cortex and one such example was that of the projections of the mediodorsal thalamic nucleus to define prefrontal cortex. This method does not work in cingulate cortex because ACC, MCC, and PCC all receive mediodorsal thalamic afferents (Vogt *et al.*, 1987; Chapter 4). Thus, no single anatomical approach adequately defines the

nature of limbic cortex in the cingulate gyrus and we must default to a functional approach.

Papez (1937) correctly concluded that emotion involves internal feelings, memories, and associated movements and these constitute criteria for evaluating the extent of limbic cortex in the cingulate gyrus. Unfortunately, his large stroke and tumor cases proved to be of almost no use to functional localization and he identified medially located structures that are now known to be involved in general memory and visuospatial functions rather than specifically in emotion. Moreover, his "circuit" had few actual connections as it was based on early and rudimentary anatomical methods and it had no motor outputs to implement "associated movements." As stoke, epilepsy, and electrical stimulation findings were reported during the 1960-1980 period, an effort was made to identify structure/function entities and the boundary between structural criteria and functional outcomes blurred. This blurring was intensified with terms such as "prelimbic" and "paralimbic" for parts of cingulate cortex that are frankly limbic. It appears that the use of various brain atlases has engendered a thoughtless approach to the functional organization of cingulate cortex (Vogt *et al.*, 2004).

The pivotal linkage between autonomic activity and emotion in generating somatic markers (James, 1884; Damasio *et al.*, 1990) suggests that any definition of limbic cortex that depends on emotion requires both autonomic integration as well as long-term memory storage of emotional/valenced incidents. Only one region in the cingulate gyrus fulfills this definition: ACC. A functional designation for the limbic concept involves affect/autonomic activation, emotional responses and memories of valenced objects and events, and mood as it relates to motor activation for emotional motor output. As discussed above, the sACC regulates autonomic output, projects to autonomic brainstem nuclei, and stores long-term, episodic emotional memories and this certainly fulfills the criteria for limbic cortex.

The "paralimbic" concept was introduced for a broad swath of cortex that lies adjacent to the hippocampus and dorsal hippocampal rudiment (Mesulam, 1995). These cortical regions include orbitofrontal, cingulate and parahippocampal cortices, and the temporal pole. Although the designation is a convenient reference for large swaths of cortex without reference to particular regions and functions, the question remains, does one or more cingulate areas constitute a "para"limbic area, that is, is part of cingulate cortex and not limbic but rather adjacent thereto? To the extent that the induseum griseum and hippocampus are involved in general short-term memory functions that are not limited to emotion and they do no have specific roles in emotion or mood, it is appropriate to view the hippocampus as a paralimbic cortex. Characterizing cingulate cortex as "paralimbic" says nothing about the structure or functions of the paralimbic areas; only that, in the case of cingulate cortex, it is adjacent to the induseum griseum. Since the indusium griseum equates to only about 0.01% of the volume of the human cingulate gyrus, this seems an unreasonable criterion on which to characterize the entire cingulate gyrus. It makes more sense to term the induseum griseum a paracingulate area rather than *vice versa*.

The view that ACC is the primary site of emotional memories and that other cingulate regions play a lesser role in emotion raises the fact that limbic functions in cingulate cortex must be graded in terms of emotional storage and processing. For example, Chapter 13 shows that both emotional and non-emotional events and stimuli activate the PCC and this region is most likely involved in selecting the sensory events in any modality that have previously been associated with valence and are contained within a particular context. This region sorts for valenced and contextually relevant events and objects for further processing in cingulate cortex. In contrast, the pMCC has the fewest activations associated with any emotional stimuli, its responses are rapid and likely modulate body orientation before emotional information is processed. Thus, it has the least if any role in emotion as such and is the "least" limbic. From the observations reported throughout this volume, we realize that each cingulate region has a different level of emotional processing and access to autonomic output according to the following hierarchy: sACC/pACC > aMCC > vPCC > dPCC > pMCC. It appears that we can no longer simply apply the term "emotion" to any one part of cingulate cortex and the concept of a limbic cortex is determined by its relative role in a range of emotion and emotion supporting functions including autonomic regulation.

Resolving limbic cingulate functions by subregion

Although the vPCC and pMCC do not appear to have a specific role in emotion, they do play a supportive role in emotional orientation, sensory context evaluation, and premotor functions. These functions appear to be intermediate between the extremes of emotion and cognition; how might these functions be characterized? Even vPCC, which may not have a specific role in emotion and autonomic output, engages in the analysis of emotional content of many self-relevant objects and events via its connections with sACC (Vogt *et al.*, 2006; Chapter 13). The reason this subregion is not emotion specific is that it also responds during control conditions in neuroimaging studies; conditions not involving emotion. The vPCC is involved in selection among all sensory inputs for events and objects

with self-relevance based on context and long-term memories and, based on current information, it may be termed "limbic sensory assessment" cortex. Since vPCC has no autonomic projections and does not appear to store long-term emotional memories, it is not limbic cortex in the primary sense. In contrast, the aMCC region is limbic in terms of responses during fear (Vogt *et al*., 2003), has motor output systems, and is involved in reward/approach and punishment/avoidance behaviors (Chapters 7, 8, and 14). Thus, aMCC is a "limbic premotor" cortex. Finally, the pMCC has a rapid skeletomotor output system but does not seem to have emotional activity, storage, or outputs. As it can quickly orient the body to noxious stimulation (Chapter 14), the overall function of this region might best be termed "limbic premotor orientation" cortex. To summarize:

ACC, primary limbic cortex

aMCC, limbic premotor cortex

pMCC, limbic premotor orientation cortex

dPCC, limbic association cortex

vPCC, limbic sensory assessment cortex

These precise conclusions may come as a surprise to investigators with a global view of brain function and who consider emotion to be a highly distributed function of the entire cerebral cortex. Nevertheless, one must wonder why there is such an elegant cytological and connectional differentiation along the cingulate gyrus and such precise functional segregations. It appears that emotion is not processed in terms of broad perceptual, introspective viewpoints as often attributed to cingulate cortex. Rather, aggregates of neurons extract sensory context information and code events that have access to cingulate cortex through vPCC and these codes are the substrate for further cingulate processing, orientation, and premotor control.

The Question of Attention

A role in attention has been one of the most frequent attributions for cingulate function for both anterior and posterior cingulate cortices over the past 5 decades. Indeed, large stroke cases following hemorrhage of the anterior cerebral artery early demonstrated akinetic mutism with a paucity of movement and speech (Barris and Schuman, 1953). Lesions in MCC in monkeys produce a contralateral hemineglect (Watson *et al*., 1973) and large cortical networks including PCC have been thought to play a role in attention (Mesulam *et al*., 2001). In none of these instances are the mechanisms of attention fully explained in terms of small parts of cingulate cortex including subregions and areas. Although it is true that attention to and anticipation of a particular processing function, say a mathematical calculation (Murtha *et al*., 1996) or spatial orientation (Mesulam *et al*., 2001), is required to perform the function and preparation for the calculation that can activate MCC, the question remains as to the specific role of small parts of cingulate cortex in a broad substrate of cognitive processing.

An important step forward was made by Posner *et al*. (1988) when it was proposed that anterior cingulate cortex is involved in "attention-to-action." We have long viewed skeletomotor action mediated by cingulospinal and other motor projections to be pivotal in understanding the role of MCC in planning and coordinating premotor outputs as discussed above and in numerous publications reviewed in Chapter 5. However, the notion that "attention" itself is regulated by small parts of cingulate cortex finds no support in specific mechanisms of cingulate function. Once the issue of small aggregates of neurons that store and process units of information is adopted as must be when considering the cytoarchitecture or cingulate cortical units, the question of specific circuits that subserve information flow needs to be considered rather than broad cognitive constructs that can be applied to large forebrain structures such as all of PCC/RSC or networks therein. In another example, a study of "attention-to-unpleasantness" (Kulkarni *et al*., 2006) showed that attention to the unpleasantness associated with a noxious stimulus activates pACC rather than MCC.

Clearly, the unique functions of different parts of cingulate cortex are driven to attention-to-X with the focus on "X" as the cingulate function; action monitoring and output for MCC and unpleasantness for pACC, and spatial orientation for PCC. Communicating with a subject to select a sensory event to "attend to" is the means by which a function in one specific domain of cognition is generated in a cingulate subregion. Attentional activation is a necessary prerequisite for activating any part of cingulate cortex and, in this regard, all of cingulate cortex is involved in attention as claimed. The problem arises when subregions and areas of cingulate cortex are evaluated in terms of neuronal information processing. It is at this point that the attribution of "attention" becomes less useful.

Selective Disease Vulnerabilities of Cingulate Regions: A Key Test of the Four-Region Model

The concept of selective vulnerability of cortical units to different diseases based on variations in neurochemistry was first recognized by C. and O. Vogt (1922; see also Hopf, 1970). The original Vogts found that diseases

of the nervous system are often confined to structures they termed "topistic" units. They defined "pathoclisis" as the phenomenon that only part of the organism undergoes pathological changes when the entire organism was exposed to a noxious agent and concluded that, since topistic units respond differently, each must have its own unique physiochemical properties.

As important as cytoarchitecture, circuitry, chemoarchitecture, and functions are, these are just factors which together contribute to the selective vulnerabilities of each region or subregion of the cingulate cortex to particular diseases. Indeed, selective disease vulnerability provides an independent method of testing the veracity of the four-region neurobiological model. Moreover, unique circuit chemistries and activations during particular conditions can lead to these vulnerabilities, such as during chronic pain or intense emotional stress, and this theme permeates many chapters of the present volume.

Neuropsychiatric disease vulnerability

The differential involvement of cingulate cortex in neuropsychiatric diseases is considered in detail in Chapter 11. Since selective regional vulnerability is a key rationale for the ACC/MCC dissociation, the vulnerability of ACC to major depression, particularly sACC, is crucial to the four-region neurobiological model. Glucose metabolism is reduced in this region in major depression (Drevets *et al.*, 1997), electrical stimulation in the white matter underlying area 25 can alleviate depression in drug-resistant patients (Chapter 24), and glucose metabolism for drug responders and non-responders occurs in pACC (Mayberg *et al.*, 1997). At present the entire ACC must be viewed as vulnerable to depression, while MCC appears to have no such vulnerability. Although there is conflicting evidence for a structural basis for depression as discussed in Chapter 25, the organization, connections, and chemistry of this region in monkey and its potential to develop a model of major depression makes further assessment of ACC pivotal to understanding human neuron diseases.

Shin *et al.* (Chapter 21) observe another vulnerability of ACC that is not shared with MCC; that is associated with posttraumatic stress (PTSD) and panic disorders. Symptoms of PTSD include flashbacks to memories of triggering events and these memories might be stored in sACC, while disordered sleep and other symptoms could result from changes in noradrenergic systems including those in the amygdala. The heavy interactions between ACC and the amygdala served as one of the primary reasons for differentiating it from the MCC as discussed above. The selective vulnerability of ACC to depression and PTSD assures that the fundamental distinction between the ACC and MCC is valid and will provide new strategies for analyzing the structural, functional, and neurochemical bases of these disorders.

Chronic pain vulnerability

To the extent that the ACC/MCC distinction has value for assessing disease etiologies, it predicts a selective vulnerability of MCC to another class of disease, that is, those related to sensorimotor and cognitive processing rather than affect and valenced memory storage. The MCC has a prominent role in the anticipation of painful events as discussed by Porro and Lui in Chapter 16 and in acute pain processing as reviewed in Chapter 14. This excitatory engagement during pain and its anticipation appears to generate a selective vulnerability in MCC. Importantly, neuropathic pain and some chronic pain syndromes produce selective reductions in activity in MCC as discussed by Jones and Kulkarni in Chapter 18, Derbyshire and Bremner in Chapter 23, and Vogt *et al.* in Chapter 10.

Albuquerque *et al.* (2006) reported that noxious thermal stimulation on facial skin of patients with burning mouth disorder produces a qualitatively different pattern of activation than that in control subjects. Their use of Brodmann's anterior cingulate concept, however, distracts from the qualitative differences in activation patterns instead of quantitative (algebraic) changes at the same sites. These activations are plotted in Figure 1.8 onto our Case GPC with the same color code for patients (yellow) and control (green) cases as in the original article. Indeed, during acute noxious stimulation of the face, the control subjects activate ACC and it is likely associated with the affective component of pain (see also Chapter 14), while the patients activate only MCC. The responses may be driven more by previous/conditioned responses and enhanced anticipation of the pain than a simple pain affect as in control subjects. Activation of

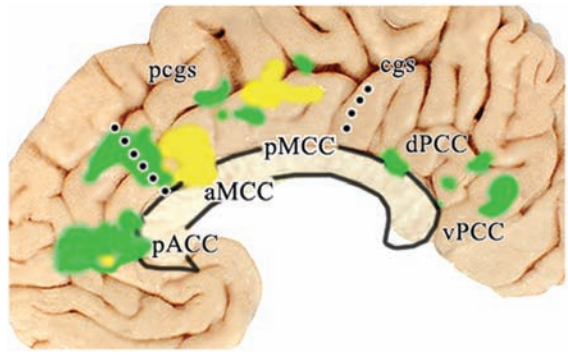

Fig. 1.8 Reconstruction of cingulate activation sites during acute thermal stimulation of the face in control (green) and patients with burning mouth disorder (yellow). The sites were collected from the four parasagittal midline slices of Albuquerque *et al.* (2006) and co-registered with the outlined corpus callosum to histological Case GPC; borders between ACC/MCC/PCC identified as in Figure 3.3. The patient group activates qualitatively different parts of the cingulate gyrus including MCC, while the control cases activate mainly the ACC and vPCC. All neuron diseases that have a proclivity for the cingulate cortex will likely have selective vulnerabilities therein and provide pivotal tests of the four-region neurobiological model.

different regions indicates a qualitatively different response pattern in the patient population.

Based on the reciprocal suppression model discussed above, the activity in MCC might be enhanced in association with premotor processing and a cognitive effort leads to reducing activity, and presumably emotion, that is normally generated in ACC. Since all responses were aggregated under a single "ACC region" in the original report, the pivotal dissociation between the control and pain groups was not fully appreciated. Furthermore, changes in PCC might also be better clarified in the regional model where it appears that burning mouth patients had no activation of PCC, while controls had activity mainly in vPCC and to a lesser extent in dPCC. It is quite likely that keys to the etiology of burning mouth disorder lie in the altered activation of qualitatively unique parts of the cingulate gyrus. The four-region neurobiological model requires a consideration of the connections and neurotransmitter systems that are modified by this chronic pain state to determine the physical substrate that is altered by chronic trigeminal activation.

Finally, the MCC is vulnerable to disorders of motivation and movement. Thus, the anterior part of MCC has a prominent role in cognitive processes and it is at risk for alteration in attention deficit/hyperactivity disorder as discussed by Bush in Chapter 12. The ACC/MCC are also differentially impacted by obsessive-compulsive disorder as discussed by Saxena *et al.* in Chapter 27, and a model of altered motor circuitries for these two regions is considered by Middleton in Chapter 28.

Neurodegenerative disease vulnerability

Neurodegenerative diseases may also have selective "targets" in the cingulate gyrus, however, many studies in the past have used cases at late stages of the disease, sampling in the cingulate gyrus is often limited to only one region, and these diseases tend to be more "promiscuous" throughout the cingulate gyrus as they progress. Neurodegenerative diseases can be evaluated according to two types of cingulate specificity; cellular and regional. In schizophrenia there are clear regional differences in function and treatment outcomes as discussed by Preda *et al.* in Chapter 30, while neuropathological and animal model studies emphasize neuronal alterations, particularly those associated with GABAergic interneurons as discussed by Benes in Chapter 31. The long-term goal for studies of schizophrenia and other neurodegenerative diseases is to merge cellular and cingulate region approaches to identify primary etiologies of neurodegeneration.

Alzheimer's disease severely impacts cingulate functions and has a particularly profound and early influence in PCC as discussed by Salmon and Laureys in Chapter 34. These authors note involvement of ACC in some cases and this theme is considered in detail in Chapter 35. Most intriguing is the fact that many cases of mild cognitive impairment (MCI) may evolve into Alzheimer's disease as discussed by Johnson *et al.* in Chapter 33. The first sites of impact of MCI are in dPCC and pMCC; regions involved in self-relevant visuospatial orientation and sensorimotor orientation, respectively. There may be other forms of MCI that have not yet been identified and will have a proclivity for damaging ACC or aMCC. The presence of cases with early PCC damage is a specific prediction from studies of the cingulate gyrus. Thus, neurodegenerative diseases also have specific "targets" in cingulate cortex and they will follow along the lines of regional vulnerabilities. The regional vulnerability theme will continue to provide ongoing impetus to refine models of cingulate organization and function and they will challenge us to assess mechanisms of disease and identify cingulate-mediated etiologies at the cellular level.

Therapeutic Targeting of Cingulate Subregions and Challenges for Cingulocentric Research

An exciting aspect of work presented in this volume is the extent to which logical strategies have already been devised to target particular cingulate regions and subregions for therapeutic interventions and objective assessment of the mechanisms of therapeutic outcomes. Although such activities were possible before the 1990s, the advent of routine human neuroimaging provides the most important tool for testing cingulate-mediated therapies and assessing their outcomes and the first examples of this strategy are provided in this volume. A multi-nodal network model is used by Holtzheimer and Mayberg in Chapter 24 to evaluate drug, electrical stimulation, and other therapies for depression including deep brain electrical stimulation in the white matter underlying sACC. In Chapter 17, Faymonville *et al.* present a new mechanism by which hypnosis can be used to engage cingulate projections to the periaqueductal gray and generate a surgical level of analgesia. Garcia-Larrea *et al.* in Chapter 20 provide documentation for a thalamocingulate mechanism of pain relief induced with transcranial electrical stimulation of motor cortex. None of these reports would have been possible without rigorous *in vivo* imaging before and after treatment and they demonstrate the pivotal nature of cingulate-mediated therapeutics.

The circuit models used to define cingulate mechanisms of therapeutic intervention in this volume are based on factual observations about brain responses under each condition and even consider changes in correlations among functional activations before and after intervention. These are not just speculations about what might change in the brain but rather strong and

objective observations about organic changes in brain function. Ironically, the specificity of cingulate-mediated therapeutics is much greater than with any drug therapeutic like the opiates which act at many, if not all, levels of the central nervous system. Nevertheless, the most important feature of the present volume is the objective demonstration of cingulate-mediated interventions for acute and chronic pain and depression.

Drug therapeutics have an important role in cingulate-mediated therapy, particularly as the binding localizations for particular ligands and transmitter systems are refined with high resolution autoradiographic methods like those of Palomero-Gallagher and Zilles in Chapter 2. Drug therapies with imaging verification strategies are described for depression (Holtzheimer and Mayberg, Chapter 24), obsessive-compulsive disorder (Saxena *et al.*, Chapter 27), and schizophrenia (Preda *et al.*, Chapter 30). It may soon be possible to match individual cingulate-mediated therapies to particular psychiatric conditions and provide objective imaging of outcomes as discussed by Bush in Chapter 12.

One of the paradoxes of the first century of cingulate research was that functional models treated the entire gyrus as a single entity, while cytoarchitectural studies observed dozens of discrete areas. Human imaging research has been tremendously productive and has opened our eyes to the important role of cingulate cortex in many brain functions and diseases. Nevertheless, the main challenge to the cingulate research enterprise, as posed more than 100 years ago by cytoarchitectural analyses, remains today that there are approximately 30 areas in the human cingulate gyrus and each represents a unique architecture, intrinsic circuitry, afferent/efferent connection pattern, neurotransmitter receptor innervation, and contribution to brain function. Although functions of some of the larger areas are being uncovered, the unique functions of most areas remain a mystery for a number of reasons. The use of standardized maps based on retrofitting the Brodmann areas rather than direct histological analyses of MRI cingulate cortices continues to limit precise links between structural and functional observations. Complex experimental designs and paradigms are needed to sort through observations in control subjects and provide the behavioral control needed for studies of emotion. Temporal and spatial resolution of imaging is still too crude to evaluate the specific functions of many areas such as the retrosplenial areas 29l, 29m, and 30.

As the spatial and temporal resolution of human neuroimaging increases and circuitry studies are refined for the cerebral cortex, the functions of each cingulate area will be clarified, functional circuits and disease vulnerabilities determined, and linkages with genetic and other disease trait markers and prodromal cingulate endophenotypes established. The future for cingulocentric research and therapeutics has never been brighter.

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