CHAPTER 5

Cingulofrontal Interactions and the Cingulate Motor Areas

Robert J. Morecraft and Jun Tanji

Chapter contents

The cingulate gyrus forms a prominent part of the medial wall of the cerebral cortex. In traditional terms, it is a major component of the limbic lobe and is uniquely characterized by its vast network of interconnections with other limbic cortices, as well as with a number of multimodal association regions throughout the neocortex. Originally viewed as functioning solely within the domain of olfaction (Broca 1878), our understanding of cingulate function has steadily grown from observations following isolated brain injury and neurosurgical treatments as well as from many neuroimaging, electrophysiological, and neuroanatomical advancements. Without question, interest in the functional role of the cingulate cortex has reached epic proportions in the field of neurobiology as the list of behavioral correlates is extensive, and includes critical roles in emotional expression, pain processing, cognitive control, and spatial memory to highlight a few (Vogt *et al.*, 1992; Devinsky *et al.*, 1995).

In recent years, many neurocognitive studies employing a combination of neuropsychological and neuroimaging methodologies have convincingly and frequently activated the cingulate and prefrontal regions in a broad range of complex and challenging behavioral paradigms. In consideration of these findings, it is not surprising that even a casual review of the neuroanatomical literature dating back to studies employing degeneration tract tracing methods, which from the present perspective would have predicted this close functional relationship based upon the powerful interconnections that link these important higher order, association areas. Contemporary neuroanatomical studies using refined and highly sensitive tract tracing techniques have not only verified these classic observations with great confidence, but significantly extended our understanding of the organization of prefrontal-cingulate interconnections while simultaneously adding a new chapter of knowledge on the organization of cingulate interconnections with the agranular frontal cortices; that is, motor and premotor areas of the frontal lobe.

A recent and active area of cingulate investigation has focused on understanding the role of the cingulate cortex in the context of motor systems and motor control. Although our recognition of structures involved in motor control has expanded over the years, the frontal lobes have historically been acknowledged as the central cortical region involved in regulating higher order motor behaviors. Indeed, the importance of the frontal lobes in motor behavior is underscored by the relatively low current intensity required to evoke movements from the primary and premotor cortices, its rich interconnections with subcortical motor system structures, and its expansive prefrontal domain which is widely known for its critical role in higher order cognitive processes such as planning of action, decision making, and working memory.

Pivotal to the role of cingulate cortex in motor functions are the two cingulate motor areas (CMA). The first identification of the caudal CMA was made by Braak (1976) who used pigment architecture preparations to define the human primitive gigantopyramidal field. It is noteworthy that the cingulate motor fields, which form the ventral bank of cingulate sulcus in the monkey are firmly established for their role in motor control (Shima *et al.*, 1991; Vogt *et al.*, 1992; Devinsky *et al.* 1995; Picard and Strick, 1996; Shima and Tanji, 1998; Bacus *et al.*, 2001; Tanji, 2001; Akkal *et al.*, 2002; Russo *et al.*, 2002; Tanji *et al.*, 2002; Morecraft and Van Hoesen, 2003). It is also well documented that this part of the cingulate gyrus has neurons that project directly to classic motor control targets including the primary motor cortex, premotor cortices, facial nucleus, and spinal cord (Picard and Strick, 1996; Morecraft and Van Hoesen, 2003).

The extensive literature on the circuitry and functions of these two areas is one of the main subjects of this review. It seems reasonable to expect that the anatomical interrelationships between the frontal lobe and cingulate cortex forms an important underlying template that shapes the functional correlates of cingulate contributions to choices of action and motor-related activity, but also serve to bring together on structural terms, parts of the cerebral cortex that were once viewed as isolated and unrelated functional entities. Many chapters in the present volume invoke the CMAs in terms of cognition (Chapter 12), engagements with the dorsal posterior cingulate cortex (Chapter 13), nociceptive processing (Chapter 14), closed loop circuits with the basal ganglia (Chapter 28), and regulation by dopaminergic afferents (Chapter 7).

Goals and Organization of this Chapter

Cingulate cortex has long been known to have dense and reciprocal connections with the frontal lobe. Although reports of mechanisms relating to working memory suggest that the frontal lobe mediates working memory, the detailed functions of dorsolateral, orbitofrontal, and mediofrontal connections with cingulate cortex are poorly understood. Additionally, a pivotal finding in cingulate organization has been the presence, organization, and neuronal functions of the CMAs. These are the two essential issues of the present chapter. It presents a contemporary overview of cingulate interconnections with the frontal cortices in non-human primates and it summarizes emerging concepts on the functions of the CMAs in the regulation of motor behaviors.

For each section we have selected two types of illustrations. One is a representative from the literature of single experimental cases that depict the overall pattern and regional distributions of corticocortical connections. These overview figures can be used as a general reference for many other connections in addition to those with the frontal lobe. Another is a summary figure of cingulofrontal connections which represent a compilation of projections reported throughout the literature. The specific goals of this chapter include the following:

1. Review the full range of frontal projections to anterior cingulate areas 25, 24, and 32 with specific cases and in summary overview as well as midcingulate area 24´.
2. Evaluate the frontal lobe connections of posterior cingulate areas 23 and 31 with an emphasis on dorsal area 23.
3. Summarize retrosplenial areas 29 and 30 reciprocal connections with the dorsal prefrontal and orbitofrontal cortices.
4. Detail the frontal lobe connections of the rostral and caudal cingulate motor areas; critical differences in their connections subserve their differential participation in movement and behavior.
5. Summarize neuronal coding of the motor parameters and somatotopic organization of cingulate motor areas in the monkey and characterize the behavioral relevance of these discharge properties in the context of rewarded actions.
6. Evaluate cingulate motor functions with human functional imaging and relate these findings to single neuron recording studies in the monkey.
7. Present a summary and table of the structure, connections, and physiological properties of the two cingulate motor areas for easy access to the key differences of these areas in addition to references of chapters throughout this volume that consider other aspects of the structure, function, and diseases that impact each of them.

Overview of Monkey Cingulate Cortex

Contemporary neuroanatomical studies with refined and highly sensitive tract tracing techniques have significantly extended our understanding of the organization of prefrontal-cingulate interconnections, while simultaneously adding new information on the organization of cingulate interconnections with the agranular frontal cortices (i.e., motor and premotor areas of the frontal lobe). The experimental injection sites often involve several major areas of the cingulate cortex that can be identified by their spatial relation to the various cytoarchitectural subdivisions and these can be related to parts of the corpus callosum including the genu, body, and splenium as shown in Figure 5.1. In general, from anterior to posterior, they include subgenual and pregenual parts of anterior cingulate cortex (sACC and pACC), midcingulate area 24´, the retrosplenial areas 29 and 30, and the dorsal and ventral parts of posterior cingulate cortex/gyrus (d, vPCC/PCG) including areas 23 and 31. This anatomical perspective allows investigators to interpret the location of injection sites with the variety of cingulate cytoarchitectonic templates which have emerged in recent years. In addition, for the purposes of this chapter, we adopted a traditional cytoarchitectonic viewpoint of cingulate and frontal organization because most, if not all published reports on the connectional organization of cingulofrontal interactions have utilized this format for reporting their findings. Architecturally, the pACC and sACC are formed by an inferior extension of area 24 as well as adjacent areas 32 and 25 (Fig. 5.1; Vogt *et al.*, 1987; Barbas and Pandya 1989; Petrides and Pandya 1994; Carmichael and Price 1994; Dombrowski *et al.*, 2001; Vogt *et al.*, 2005).

Pregenual Areas 24 and 32 and Subgenual Area 25 Connections

Injections of tract tracers in the pACC often involve areas 24 and 32 and demonstrate that this subregion of cortex is interconnected with the insula as well as temporal (auditory, superior temporal, temporal polar), frontal (prefrontal), and limbic (anterior and posterior cingulate, entorhinal, subiculular, hippocampal, and posterior parahippocampal) association cortices (see below; Rosene and Van Hoesen, 1977; Pandya *et al.*, 1981; Moran *et al.*, 1987; Vogt and Pandya, 1987; Barbas, 1992; Morecraft *et al.*, 1992, 1993; Arikuni *et al.*, 1994; Barbas and Blatt, 1995; Carmichael and Price, 1996; Barbas *et al.*, 1999, Romanski *et al.*, 1999). In reference to cingulofrontal connections, the pACC and sACC are both significantly interconnected with the rostral half of the frontal lobe including medial, lateral, and orbital portions as shown in Figures 5.2, 5.3, and 5.4 (Vogt and Pandya 1987; Morecraft *et al.*, 1992; Barbas *et al.*, 1999). Medial prefrontal connections of the pACC and sACC are particularly robust (Pandya *et al.*, 1981; Vogt and Pandya, 1987; Barbas *et al.*, 1999). For example, areas 24 and 32 receive extensive projections from adjacent area 25 and 14 below the rostral sulcus, medial areas 10m and 9m above the cingulate sulcus, as well as area 24 above the genu and body of the corpus callosum including the cortex lining the cingulate sulcus as shown in Figure 5.3 (Vogt and Pandya, 1987; Carmichael and Price, 1996; Barbas *et al.*, 1999). Pregenual area 24,

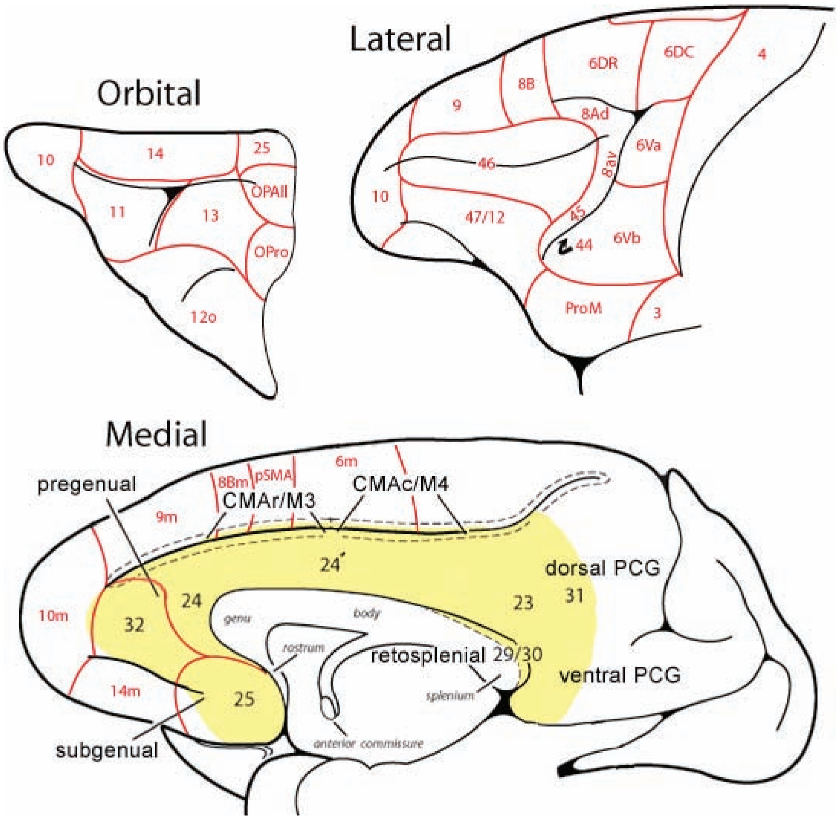

Fig. 5.1 Medial: Schematic diagram of the monkey cingulate gyrus and corpus callosum. The general location of major areas and regions utilized in the original reports surveyed in this analysis of cingulofrontal connections are identified. The cingulate sulcus has been opened (dashed line) to demonstrate the general location of the rostral (CMAr/M3) and caudal (CMAc/M4) CMAs. Lateral and Orbital: Schematic diagrams of the major cytoarchitectonic subdivisions of the anterior cerebral cortex. (Adapted from Barbas and Pandya 1989; Petrides and Pandya 1994, Barbas 2000, and Dombrowski *et al*., 2001; Vogt *et al*., 2005).

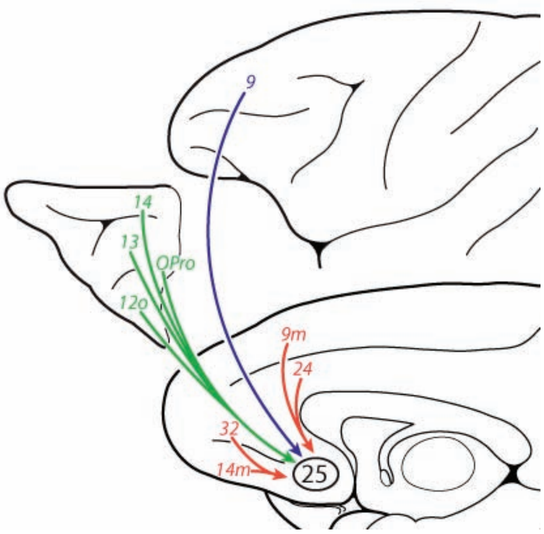

Fig. 5.2 Summary of the frontal lobe and ACC inputs to subgenual area 25.

as well as the caudal part of area 32, are also interconnected with area 23 (Barbas *et al*., 1999). Area 25, which is located anterior to the rostrum of the corpus callosum, receives projections from area 24, the cortex lining the cingulate sulcus (area 24c) as well as medial frontal areas 9m and 14m (Fig. 5.2; Barbas *et al*., 1999). A weak projection from dorsal area 23 has also been noted (Kobayashi and Amaral, 2003). Finally, a survey of cases with isolated injections of retrograde and anterograde tracers located in areas 32, 24, and 25 demonstrate that these adjacent areas are heavily interconnected via reciprocal corticocortical axonal projections (Pandya *et al*., 1981; Vogt and Pandya, 1987; Barbas and Pandya, 1989; Barbas *et al*., 1999).

The orbitofrontal cortex is powerfully and reciprocally interconnected with both pACC and sACC (Figs 5.2 and 5.4). In terms of areas 24 and 32, these connections include orbital areas 11 and 14 (Pandya and Kuypers, 1969; Vogt and Pandya, 1987, Morecraft *et al*., 1992; Carmichael and Price, 1995a; Barbas *et al*., 1999) as well as posterior orbitofrontal areas 12o and 13, including the proisocortical (OPro) and periallocortical (OPAll) regions of the ventral frontal lobe (Barbas and Pandya 1989; Morecraft *et al*., 1992; Barbas, 1993; Carmichael and Price, 1996a, 1996b; Barbas *et al*., 1999). Areas OPro and OPall are located in the posterior most part of the orbitofrontal surface and are unique from a cytoarchitectonic perspective (Fig. 5.1). For example, in contrast to the 5 or 6 layered cortex that forms most of the prefrontal cortex, area OPAll is characterized by the only three definable layers (i.e., a plexiform layer and

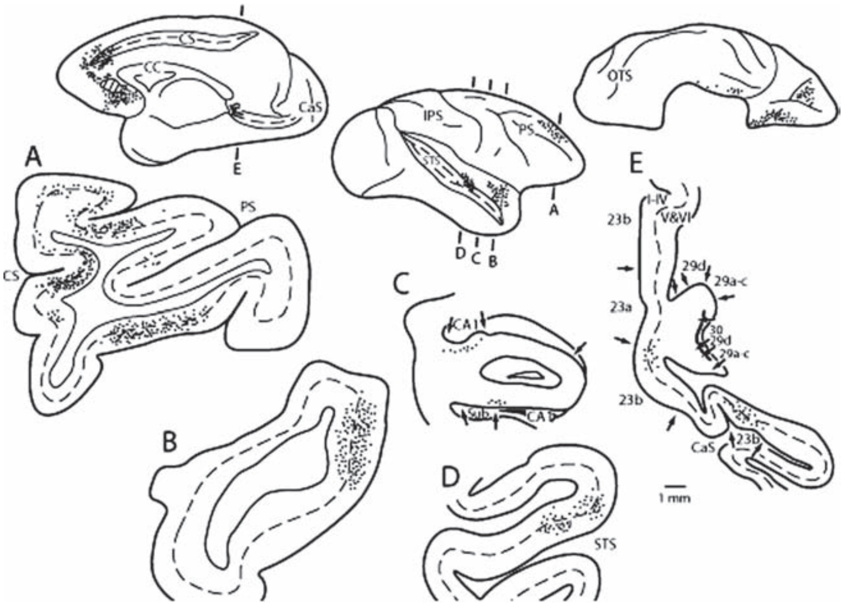

Fig. 5.3 Distribution of horseradish peroxidase (HRP)-positive neurons (dots) following an HRP injection (hatched) into the sACC. Panels A-D illustrate representative coronal views of retrogradely labeled neurons (From Vogt and Pandya, 1987).

an outer and inner striatum), while area OPro is comparatively more developed and stratified than OPAll with the emergence of a poorly defined granular layer II and comparatively higher cell density, particularly in the deeper cellular layers (Barbas and Pandya, 1989; Morecraft *et al.*, 1992). Finally, areas 24 and 32 receive a weak projection from the gustatory area of orbitofrontal cortex which provides a source of taste-related input to the anterior cingulate cortex (Barbas *et al.*, 1999). Area 25 has been found to receive orbitofrontal projections from area 14 (Barbas *et al.*, 1999) and injections of anterograde tract tracers placed into the orbitofrontal cortex demonstrate that area 25 receives additional orbitofrontal input from areas OPro, 13, and 12o (Fig. 5.2; Barbas and Pandya, 1989). The area 12 projection is reciprocated by cortical efferents from area 25 (Chiba *et al.*, 2001).

The lateral prefrontal cortex, and in particular the cortex located dorsal to the principle sulcus, including areas 46d, 9, and 10, as well as area 46v, which lies ventral to the principle sulcus have been found to be reciprocally interconnected with the perigenual areas 24 and 32 of the anterior cingulate cortex (Fig. 5.4; Vogt and Pandya, 1987; Barbas and Pandya, 1989; Barbas *et al*, 1999). The area 46 projection with area 24 appears to be more robust than the area 46 projection with area 32 (Barbas *et al.*, 1999; Cavada *et al.*, 2000). Injections of retrograde tracer involving both areas 24 and 32 (Barbas *et al.*, 1999) and injections in cortex rostral to the inferior limb of the arcuate sulcus (Pandya and Yeterian, 1996; Petrides and Pandya, 2002) indicate a reciprocal interconnection between the pACC and lateral prefrontal area 47/12. Finally, connections with lateral prefrontal cortex to subgenual area 25 appear relatively weak as it involves a small number of cells in area 9 (Fig. 5.2; Barbas *et al.*, 1999).

Anterior Cingulofrontal Connections: Midcingulate Area 24´

Injections of neural tract tracers into the cingulate gyral surface that involve areas 24a´ and 24b´ demonstrate

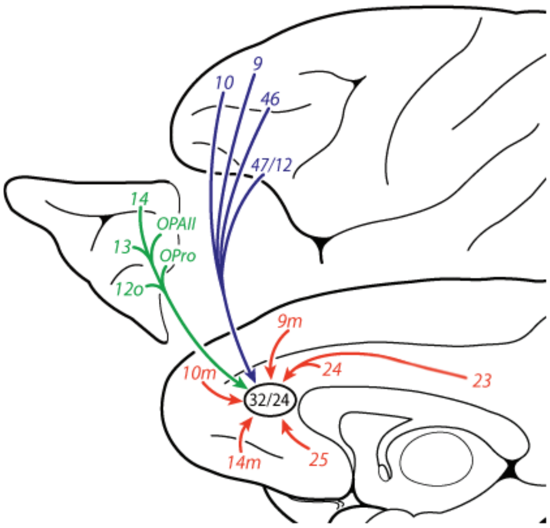

Fig. 5.4 Summary diagram of the frontal lobe and anterior cingulate inputs to pregenual ACC areas 32/24.

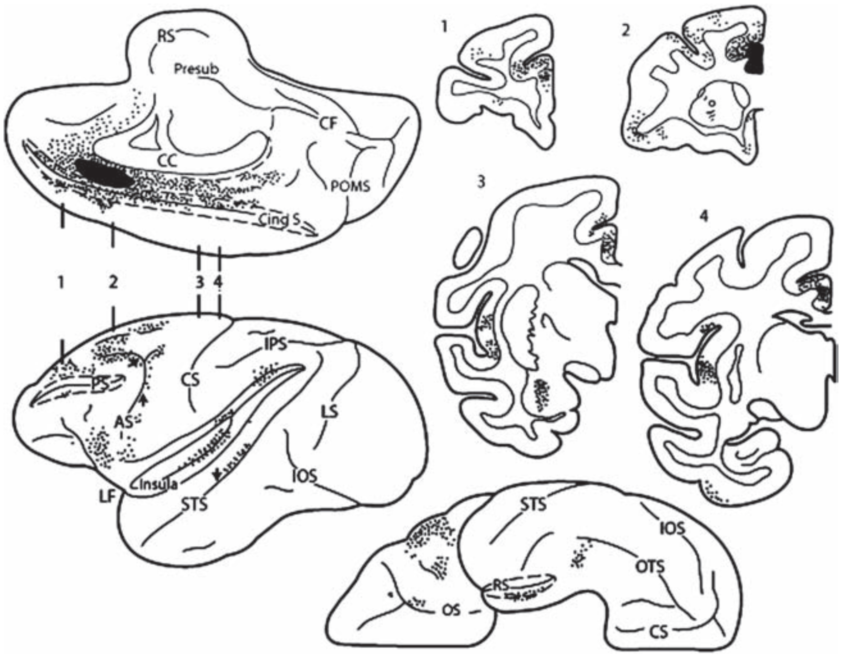

Fig. 5.5 Distribution of cortical terminal labeling (black dots) following an injection of tritiated amino acids mainly into the midcingulate area 24´. Panels 1-4 illustrate representative coronal views of terminal labeling interpreted by the presence of resulting silver grains under dark-field illumination. (From Pandya *et al.,* 1981).

widespread corticocortical connections with the agranular and dysgranular parts of the insula, as well as temporal (auditory, superior temporal, temporal polar), parietal, frontal (prefrontal cortex), and limbic (pACC, sACC, PCC, RSC, entorhinal, subiculular, hippocampal, and posterior parahippocampal) association cortices as shown in Figure 5.5 (Mesulam *et al.*, 1977; Vogt *et al.*, 1979; Rosene and Van Hoesen, 1977; Baleydier and Mauguiere, 1980; Pandya *et al.*, 1981; Mufson and Mesulam, 1982, Mesulam and Mufson, 1982; Moran *et al.*, 1987; Vogt and Pandya, 1987; Selemon and Goldman-Rakic, 1988; Morecraft *et al.*, 1993; Arikuni *et al.*, 1994; Cipolloni and Pandya, 1999).

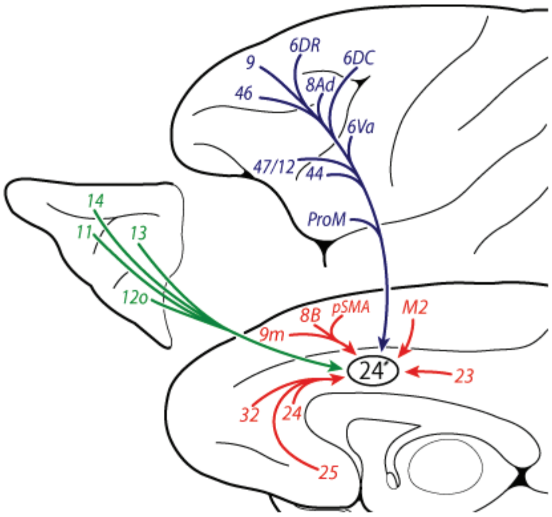

Fig. 5.6 Summary of the frontal lobe and ACC inputs to the anterior MCC area 24´.

Like the pACC and sACC, prefrontal interconnections are strong with midcingulate area 24´ (Figs. 5.5 and 5.6). Globally, these involve medial, orbitofrontal as well as lateral sectors of the prefrontal cortex. Medial connections are firmly established with neighboring areas 25, 32, and 9m, cortex lining the anterior cingulate sulcus (i.e., areas 24c and 32), as well as with the caudal PCC area 23 (Vogt *et al.*, 1979; Pandya *et al.*, 1981; Vogt and Pandya, 1987; Van Hoesen *et al.*, 1993; Carmichael and Price, 1996; Cavada *et al.*, 2000). In terms of orbitofrontal connections, the literature indicates areas 24a and 24b are heavily interconnected with the caudal and caudolateral sectors of the orbitofrontal surface (i.e., areas 13 and 12o) and less so with area 14 medially and area 11 rostrally (Pandya and Kuypers, 1969; Vogt *et al.*, 1979; Pandya *et al.*, 1981; Vogt and Pandya, 1987; Barbas, 1992; Morecraft *et al.*, 1992; Barbas, 1993; Carmichael and Price, 1995a). Lateral prefrontal interconnections with the midcingulate area 24´ are established with areas 46d and 9 above the principal sulcus which include cortex lining the fundus and upper bank of the principal sulcus as well as opercular area 47/12, anterior to the inferior region of the arcuate sulcus (Pandya and Kuypers, 1969; Pandya *et al.*, 1971; Goldman and Nauta, 1977; Jacobson and Trojanowski, 1977; Kunzle, 1978; Barbas and Mesulam, 1985; Vogt and Pandya, 1987; Baleydier and Mauguiere, 1980; Pandya *et al.*, 1981;

Selemon and Goldman-Rakic, 1988). A moderate projection has been reported from area 46v, close to and within the depths of the lower bank of the principle sulcus (Pandya *et al.*, 1981; Vogt and Pandya, 1987). Functionally, the lateral prefrontal areas in and around the principle sulcus have been implicated in a number of behaviors. These include self monitoring, information integration, planning and sequencing of action (Goldman-Rakic *et al.*, 1992; Damasio, 1994; Petrides, 1994, 2000; Bechara *et al.*, 1998; Mesulam, 1998; Hoshi *et al.*, 2000; Tanji and Hoshi, 2001; Ninokura *et al.*, 2003a, 2003b), visuospatial processing (Goldman-Rakic, 1987; Wilson *et al.*, 1993), as well as working memory (Goldman-Rakic, 1987, 1996).

As alluded to earlier, the strong interconnections established between the peri-principalis region and the ACC forms an important linkage that mediates the functional relations between these two cortical regions. These may include mediating the control of attention and cognitive activities as indicated in the recent neuroimaging literature (Gehring and Knight, 2000; MacDonald *et al.*, 2000; Kerns *et al.*, 2004; Holroyd *et al.*, 2004; Williams *et al.*, 2004; Weissman *et al.*, 2005). It is also noteworthy that the projection to area 24 from opercular area 47/12 provides an indirect but potentially rich source of auditory association input to the ACC (Romanski *et al.*, 1999; Petrides and Pandya, 2002). Specifically, this indirect cingulate input, which may pass through the area 47/12 nodal point, originates from the caudal and rostral parts of the auditory association belt as well as from the parabelt auditory association cortices. Finally, dorsal periarcuate area 8Ad, a critical component of the frontal eye fields, is reciprocally interconnected with areas 24a as well as 24b (Pandya and Kuypers, 1969; Jacobson and Trojanowski, 1977; Barbas and Mesulam, 1981; Pandya *et al.*, 1981; Huerta *et al.*, 1987; Morecraft *et al.*, 1993; Wang *et al.*, 2004). This interesting connection establishes a unique linkage between the ACC and an important cortical oculomotor/visuospatial processing center that is densely interconnected with the dorsal visual stream of the posterior parietal cortices (Cavada and Goldman-Rakic, 1989; Morecraft *et al.*, 1993).

In addition to these classically described prefrontal-cingulate connections, areas 24a´ and 24b´ have been shown to be connected to some of the motor-related cortices of the medial portion of the frontal lobe (Figs. 5.5 and 5.6). Reciprocal projections have been found to the rostral part of area 6DR with areas 24a´ and 24b´ (Pandya and Vignolo, 1971; Kunzel, 1978; Vogt and Pandya, 1987; Pandya *et al.*, 1981; Barbas and Pandya, 1987; Arikuni *et al.*, 1994; Pandya and Yeterian, 1996; Kobayashi and Amaral, 2003; Luppino *et al.*, 2003; Takada *et al.*, 2004). Weak interconnections between the posterior area 24b´ and area 6DC near the superior precentral dimple have also been reported (Pandya and Vignolo, 1971; Kurata, 1991; Luppino *et al.*, 2003). Injections of retrograde tracers in the pre-SMA (Luppino *et al.*, 1993; Wang *et al.*, 2001) and supplementary motor cortex (area 6m, M2, or SMA) (Jurgens 1984; Luppino *et al.*, 1993; Morecraft *et al.*, 1996, 1997; Wang *et al.*, 2001) also demonstrate projection neurons in the anterior and posterior parts of MCC areas 24a´ and 24b´ with the pre-SMA projection being quite robust. Injections of anterograde tracers into the general region of M2 and the pre-SMA indicate a reciprocal projection with area 24b´ (Kunzle, 1978; Jurgens, 1984).

These premotor projections place area 24b´ in an influential position on motor-control structures involved in generating motor plans and strategies in response to an instruction signal (i.e., the pre-SMA) and the initiation of movement (i.e., M2) (Tanji and Shima, 1994; Shima and Tanji, 2000; Tanji, 2001). Areas 24a´ and 24b´ are also interconnected with postarcuate area 6V (Baleydier and Mauguiere, 1980; Pandya *et al.*, 1981; Barbas and Pandya, 1987), area ProM (Pandya *et al.*, 1981; Matelli *et al.*, 1986; Cipolloni and Pandya, 1999; Simonyan and Jurgens, 2002), and area 44 along the caudal bank of the inferior limb of the arcuate sulcus (Pandya *et al.*, 1981; Barbas and Pandya, 1987; Arikuni *et al.*, 1994; Pandya and Yeterian, 1996).

It is noteworthy that the cingulate motor fields, which form the ventral bank of cingulate gyrus in the monkey are firmly established for their role in motor control which will be discussed in detail below (Shima *et al.*, 1991; Picard and Strick 1996; Shima and Tanji 1998; Bacus *et al.*, 2001; Tanji 2001; Akkal *et al.*, 2002; Russo *et al.*, 2002; Tanji *et al.*, 2002; Morecraft and Van Hoesen 2003). It is also well documented that this subregion of the cingulate gyrus has projection neurons that establish direct interconnections with classic motor control targets including the primary motor cortex, premotor cortices, facial nucleus, and spinal cord (Picard and Strick, 1996; Paus, 2001; Morecraft and Van Hoesen, 2003). However, the connectional observations which demonstrate direct linkages between frontal motor areas and cingulate areas 24b´ and 24a´ would serve to broaden the contemporary viewpoint of cingulate motor interactions. In other words, cortex lining the surface of the cingulate gyrus may not contain neurons whose descending axons end directly in subcortical motor structures innervating the peripheral musculature, but may directly exchange information with parts of the premotor cortices that do contain such neurons.

Injections in midcingulate cortex involving posterior area 24´ and rostral area 23 demonstrate medial prefrontal connections with the dorsal region of area 32 around the anterior tip of the cingulate sulcus and area 24 above the genu of the corpus callosum (Vogt and

Pandya, 1987; Fig. 2). Lateral prefrontal area 46 located above and in the principal sulcus, and the ventral opercular part of area 47/12 and orbitofrontal area 11 have been found to project to this region of cingulate cortex. Finally, a small projection from area 6DR targets this midcingulate cortex.

Posterior Cingulofrontal Connections: Areas 23 and 31

Research on the PCC points to the importance of area 23 in numerous functions including visuospatial orientation, memory, and attention (Mesulam, 1981, 1998; Vogt *et al.*, 1992; Devinsky *et al.*, 1995; Kobayashi and Amaral, 2003; Chapter 13). Underscoring these functional attributes is the constellation of direct corticocortical connections that area 23 forms with the insula as well as temporal, parietal, occipital, frontal, and limbic association cortices (Fig. 5.7; Mesulam *et al.*, 1977; Rosene and Van Hoesen, 1977; Vogt *et al.*, 1979; Baleydier and Mauguiere, 1980; Pandya *et al.*, 1981; Mufson and Mesulam, 1982, Mesulam and Mufson, 1982; Moran *et al.*, 1987; Vogt and Pandya, 1987; Selemon and Goldman-Rakic, 1988; Morecraft *et al.*, 1993; Kobayashi and Amaral, 2003; Morecraft *et al.*, 2004a). Cytoarchitecturally, PCC has been parcellated into ventral and dorsal subdivisions that include extensions of both areas 23a and 23b as well as a sulcal area 23c in dorsal PCC. Since most injection sites reported in the literature involve areas 23a and b, the frontal projections reported here are associated with area 23 in general.

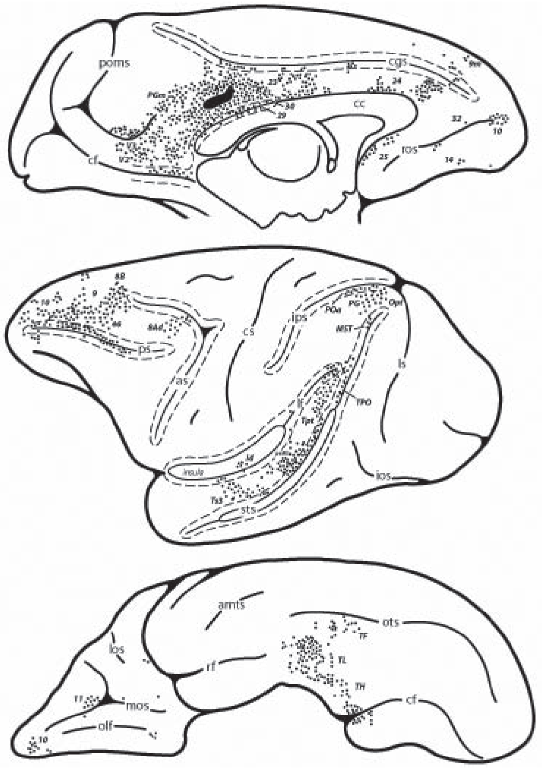

Fig. 5.7 Retrogradely labeled neurons (black dots) following an injection of fast blue (irregular black oval) into dorsal area 23. (From Morecraft *et al.*, 2004a).

The frontal lobe connections of dorsal area 23 are largely associated with the prefrontal domain as shown in Figures 5.7 and 5.8. In terms of density and topography, medial prefrontal connections with dorsal area 23 appear to be relatively weak and patchy (Fig. 5.7). On the medial surface, injections in dorsal area 23 give rise to small groups of labeled cells in area 9m and the caudal part of area 10m (Vogt *et al.*, 1979; Pandya *et al.*, 1981; Vogt and Pandya, 1987; Morris *et al.*, 1999; Morecraft *et al.*, 2004a). Interestingly, the linkage between areas 9m and 23 may be critical for establishing an interface between attention and motivation (Small *et al.*, 2003). Similarly, isolated patches of cells occur inferior to the cingulate sulcus in areas 24, 32, 25, and 14 (Baleydier and Mauguiere, 1980; Pandya *et al.*, 1981; Vogt and Pandya, 1987; Morris *et al.*, 1999; Morecraft *et al.*, 2004a).

Several localized sites within the lateral prefrontal region are interconnected with dorsal area 23 (Fig. 5.8). The most prominent connections appear to involve the lateral part of area 9 and area 46d, including the cortex lining the upper and lower banks of the principal sulcus (Kunzle, 1978; Vogt *et al.*, 1979; Baleydier and Mauguiere, 1980; Pandya *et al.*, 1981; Barbas and Mesulam, 1985; Vogt and Pandya, 1987; Morris *et al.*, 1999; Kobayashi and Amaral, 2003; Morecraft *et al.*, 2004a). Projections from area 10 to area 23 have also been described as well as projections from area 8B (Morris *et al.*, 2002, Morecraft *et al.*, 2004a), and periarcuate

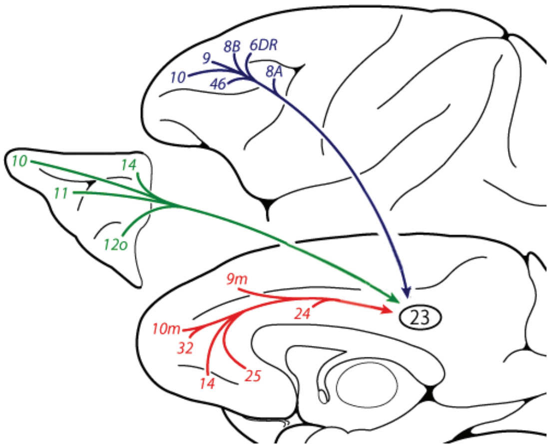

Fig. 5.8 Frontal lobe and ACC inputs to dorsal area 23.

areas 8Ad (Pandya *et al.*, 1981; Kobayashi and Amaral 2003; Morecraft, *et al.*, 2004a) and 8Av (Kobayashi and Amaral 2003). Finally projections from premotor area 6m (SMA or M2), area 6DR and area 6 DC as well as area 4 of the primary motor cortex to area 23 have been reported (Kunzle, 1978; Pandya *et al.*, 1981; Morris *et al.*, 1999; Morecraft *et al.*, 2004a). The posterior cingulate projection from area 6DR as in Kobayashi and Amaral (2004; case FB-M13-98L) and areas 6DC and 4 may represent some injectate involvement of cingulate area 31, which receives strong afferent input from area 6DR and a weaker projection from areas 6DC and 4 (Morecraft *et al.*, 2004a). Collectively, these cases suggest that the posterior cingulate projection from frontal areas 6 and 4 gradually increases in the caudodorsal direction to involve more architectonically differentiated cortical regions of the posterior medial wall.

The most consistent orbitofrontal connection reported with dorsal area 23 appears to be with the rostral part of orbitofrontal cortex, mainly involving area 11 (Figs 5.7 and 5.8; Vogt *et al.*, 1979; Baleydier and Mauguiere, 1980; Pandya *et al.*, 1981; Vogt and Pandya, 1987; Bates and Goldman-Rakic, 1993; Carmichael and Price, 1994; Morecraft *et al.*, 2004a). Other small patches of projection neurons to dorsal area 23 have been reported to occur in the frontopolar region of area 10, area 12o near the ventrolateral convexity, and the caudal region of area 14 of the gyrus rectus (Vogt *et al.*, 1979; Vogt and Pandya, 1987; Morecraft *et al.*, 2004a).

Ventral area 23 displays a relatively similar set of frontal interconnections as the dorsal area 23 in that prominent prefrontal input arises from lateral areas 46 and 9 (cases M14-98L and M12-98L of Kobayashi and Amaral, 2003). The ventral posterior cingulate subregions also receive a projection from area 10. Medial prefrontal input to the perisplenial cortex (i.e., case M14-98L) also involves the rostral part of area 24 and isolated parts of areas 32 and 25. In terms of orbitofrontal afferents, the ventral subregion receives weak input from area 11, as well as the caudal region of 14. Thus, the orbitofrontal projection appears to gradually diminish and eventually subside in the ventral subregion of the PCC. However, it should be emphasized that the extensive range of this projection system effectively bridges the rostral region of the frontal lobe with cingulate cortex abutting the visually-oriented occipital lobe.

Dorsal and caudal to area 23 lies area 31. Although this cortex is adjacent to the parietal lobe, the overall pattern of cortical connections as reviewed below, and the strong thalamic inputs from the anterior thalamic nuclei (Buckwalter *et al.*, 2004) reinforce its categorization as cingulate cortex on structural grounds. Although the functions of this area are presently unknown, the corticocortical afferents to area 31 have recently been described (Morecraft *et al.*, 2004a). Much like adjacent area 23, the corticocortical connections of area 31 are widespread and diverse as they involve the insula as well as temporal, parietal, occipital, limbic, and frontal association cortices including portions of the medial and dorsolateral agranular motor cortices as shown in Figure 5.9. With regard to similarities in the frontocingulate connection with adjacent dorsal area 23, projections to area 31 arise from dorsolateral prefrontal areas 10, 46, and 9 as well as the oculomotor related areas 8Ad and 8B (Figs 5.9 and 5.10). The projection from the lateral surface continues caudally to involve extensive afferents from areas 6DR, moderate projections from area 6DC and a few projection neurons from M1. From rostral to caudal, the medial frontal projection involves areas 9m, 8Bm, the pre-SMA, area 6m, and M1.

A major difference between the frontal projections to areas 23 and 31 centers around those established with the orbitofrontal surface. It appears there is a significant reduction in the projection from orbitofrontal cortex to area 31 which may constitute only a few cells

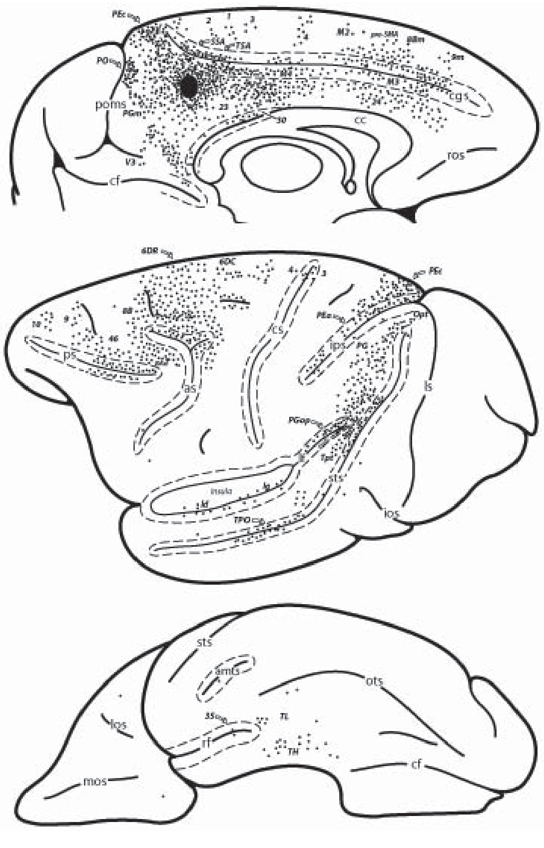

Fig. 5.9 Distribution of retrogradely labeled cortical neurons (black dots) following an injection of fast blue (irregular black sphere) into area 31. (From Morecraft *et al.*, 2004a).

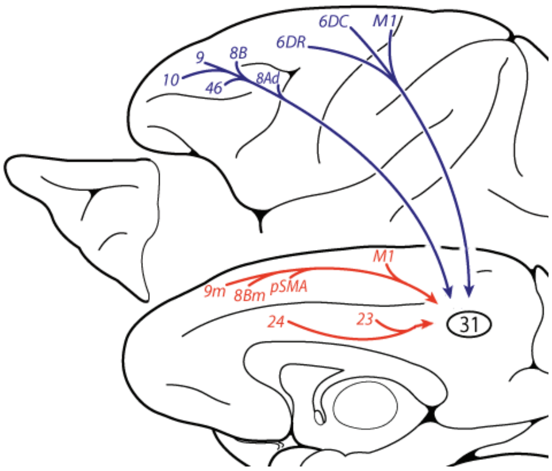

Fig. 5.10 Summary of frontal lobe and anterior cingulate inputs to cingulate area 31.

in the caudal orbitofrontal region. Although the fundamental functions of area 31 remain an active area of speculation and interest, the projection patterns indicate that significant influence from the medial and lateral prefrontal association areas will play an influential role in shaping the outcome of these functions as well as the contingent of premotor and motor projections that target area 31.

Retrosplenial-frontal Connections: Areas 29 and 30

The RSC occupies the ventral bank of the PCG dorsal and caudal to the splenium of the corpus callosum and lateral to the caudomedial lobule (Fig. 5.1; Vogt 1976; Goldman-Rakic *et al.*, 1984; Vogt, 1985; Morris *et al.*, 1999; Ding *et al.*, 2003; Vogt *et al.*, 2005). Cytoarchitecturally, this cortex corresponds to areas 29 and 30. Although very difficult to expose surgically because of its location buried in the callosal sulcus, several successful cases have been reported with injections of neuroanatomical tract tracers involving to some extent, both areas 29 and 30; one of which is shown in Figure 5.11 (Morris *et al.*, 1999; Kobayashi and Amaral, 2003). These cases show that RSC is linked to many regions of the cortex that are commonly interconnected with other parts of the cingulate gyrus such as dorsal area 23 and midcingulate area 24′ and area 31. For example, RSC is interconnected with adjacent cingulate area 23, area 19 of the occipital lobe, area PGm of the posterior parietal

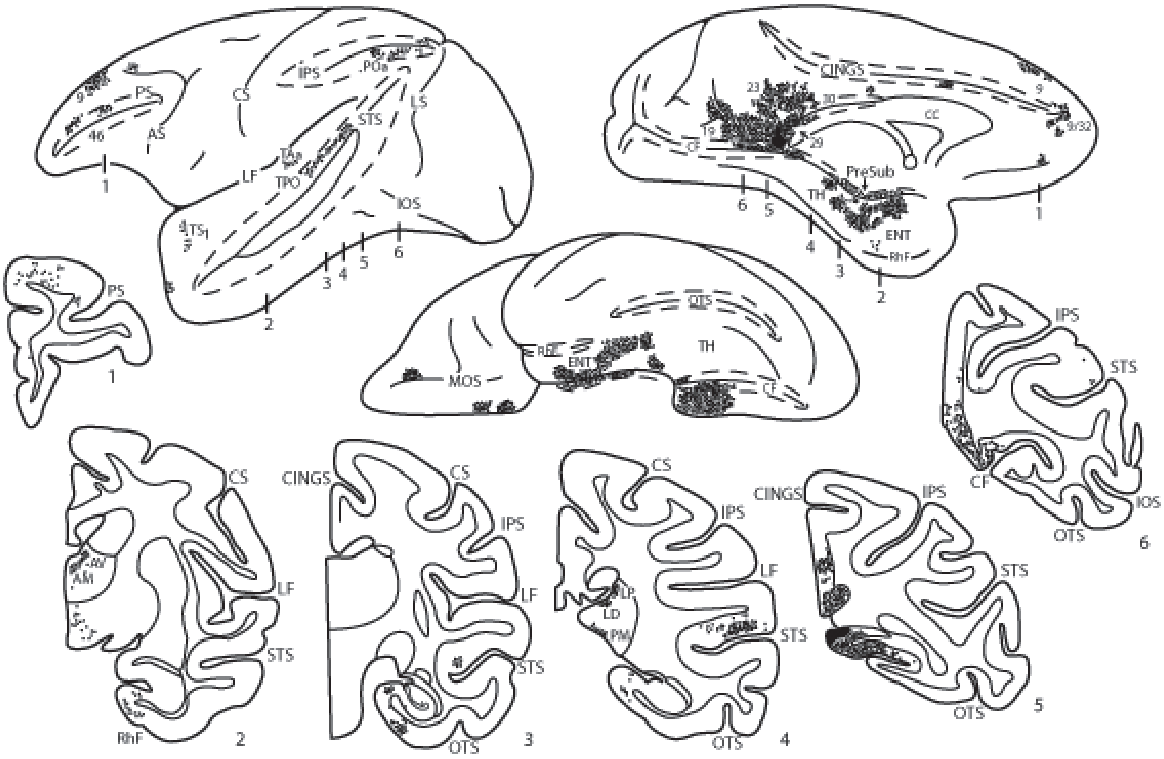

Fig. 5.11 Topography of retrogradely labeled neurons (black dots) following an injection of fast blue (black sphere) into area 30 of the RSC. Panels 1-5 are representative coronal views of labeled neurons. (From Morris *et al.*, 1999).

region, prefrontal cortex, multimodal area TPO of the superior temporal sulcus and key regions of the medial temporal lobe including the posterior parahippocampal cortex, presubiculum, and the entorhinal cortex (Fig. 5.11; Vogt and Pandya *et al.*, 1987; Morris *et al.*, 1999). This overall pattern of connectivity, when highlighting the frontal and temporal lobe connections, provides strong support for the suggestion that the RSC serves as a critical interface between the working memory functions of the prefrontal cortex and the long-term memory and visuospatial functions mediated by the medial temporal lobe structures (Morris *et al.*, 1999; Kobayashi and Amaral, 2003).

Frontal-retrosplenial interconnections involve medial, lateral, and orbitofrontal prefrontal regions (Morris *et al.*, 1999) with the lateral surface interconnections being the most prominent (Kobayashi and Amaral, 2003) (Fig. 5.12). Specifically, medial projections arise from cingulate areas 23, 24, and 32 as well as prefrontal area 9m. Lateral frontal projections have been reported to arise from dorsal principalis region including both areas 46 and 9. Kobayashi and Amaral (2003) identified a retrosplenial projection from area 8Ad and Morris and colleagues (1999) a projection from frontopolar area 10. Finally, a small projection to the RSC arises from part of premotor area 6DR that is adjacent to the anterior tip of the superior limb of the arcuate sulcus, including the dorsal bank of the sulcus. Orbitofrontal afferents have been found in area 11 and the middle and caudal parts of area 14. Sparse labeling following injections of retrograde tracer into areas 29 and 30 has also been noted in the rostral region of area 13 indicating a weak connection, but one that may be influenced by amygdala circuitry.

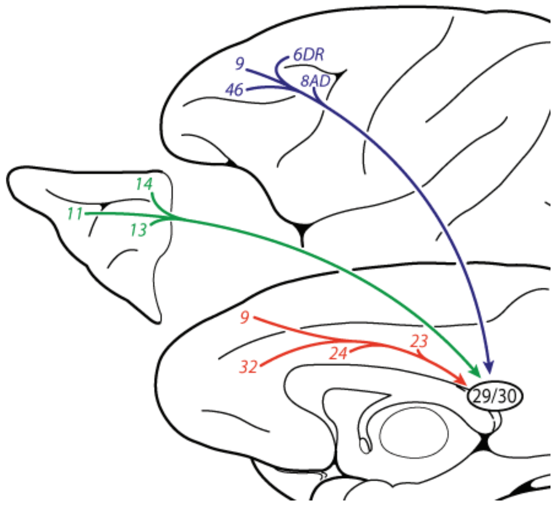

Fig. 5.12 Summary diagram of the frontal lobe and cingulate inputs to retrosplenial areas 29 and 30.

Frontal Interconnections of the Rostral and Caudal Cingulate Motor Areas

Studies of the network of interconnections that characterize the cortex lining the banks and fundus of the cingulate sulcus have been a priority over the past decade for many important reasons that stem largely from increasing evidence of the unique motor-related neuronal properties of this region as discussed in detail below. The findings of corticofugal projection neurons in this cortex which target many subcortical motor centers including the putamen (Van Hoesen, 1993; Takada *et al.*, 2001), motor thalamus (Van Hoesen *et al*, 1993; McFarland and Haber, 2000; Hatanaka *et al.*, 2003), red nucleus (Van Hoesen *et al.*, 1993; Burman *et al.*, 2000), facial nucleus (Morecraft *et al.*, 1996, 2001), and spinal cord (Biber *et al.*, 1978; Murray and Coulter, 1981; Hutchins *et al.*, 1988; Dum and Strick, 1991; Galea and Darian-Smith, 1994; Luppino *et al.*, 1994; He *et al.*, 1995; Morecraft *et al.*, 1997; 2002) support the view of the essential motor functions of this region. In fact, along with the many important motor-related behavioral correlates, this corticofugal circuitry has been highly instrumental in molding our present conceptualization of the cingulate motor cortex as well as underscoring the potential that this brain region has on directly affecting motor structures in the brainstem and spinal cord.

Although debate continues over the precise nature of the organization and functions of the cingulate motor areas, most authorities recognize a rostral cingulate motor area (CMAr) and caudal cingulate motor area (CMAc) with some authors further subdividing the caudal cingulate motor cortex into dorsal and ventral portions. Therefore, the question arises where is the approximate boundary between the rostral and caudal cingulate motor fields? Unlike the sharp cytoarchitectonic boundary that differentiates area 4 of the primary motor cortex from adjacent area 3 of the primary somatosensory cortex in the peri-Rolandic region, one finds numerous viewpoints on the cytoarchitectural boundaries of the cortex lining the depths of the midcingulate sulcus (Bonin and Bailey, 1947; Lupino *et al.*, 1991; Dum and Strick, 1991; Morecraft and Van Hoesen, 1992, 1998; Bates and Goldman-Rakic, 1993; Carmichael and Price, 1994; Galea and Darian Smith, 1994; Lu *et al.*, 1995; Nimchinsky *et al.*, 1996; Morecraft *et al.*, 2004). This is due in part to the gradual nature of architectonic differentiation that characterizes this region from a rostral to caudal perspective as well as a medial to lateral perspective. In fact, it has been noted that this "transition zone" may span several millimeters in a given experimental case (Luppino *et al.*, 1991; Morecraft and

Van Hoesen, 1992; Bates and Goldman-Rakic, 1993). There is also the problem of cortical stretching in the depths of the cingulate sulcus that impairs resolution of a continuous architecture with Nissl stains of frozen sections, a problem that is resolved with immunohistochemistry. Connections in conjunction with cytoarchitecture add an additional informational element to assist in interpreting the location of the general boundary between the rostral cingulate motor area (CMAr or M3) and the caudal cingulate motor area (CMAc or M4; Fig. 5.1).

In the monkey, the location of the border between the rostral and caudal cingulate motor areas corresponds to the region of cortex which lies within coronal levels including the genu and spur of the arcuate sulcus (Dum and Strick, 1991; Morecraft and Van Hoesen 1992, 1998; Nimchinsky *et al.*, 1996). Subcortically, this level often contains the anterior commissure. For example, following injections of neuronal tracer in the arm representation of the primary motor cortex (M1), a label-free zone of cortex occurs at this location that is flanked anteriorly by a group of positively labeled cells in the CMAr, and posteriorly by a group of labeled cells in the CMAc (Dum and Strick, 1991; Morecraft and Van Hoesen, 1992; Stepniewska *et al.*, 1993; Lu *et al.*, 1994; Morecraft al., 1996; Wang *et al.*, 2001, 2004). In another study, two spatially separate groups of cells have been found in the rostral cingulate motor region and two within the CMAc (Tokuno *et al.*, 1997) which could reflect the spatial distribution of cingulate cells projecting to two spatially separate injection sites within the forelimb area of M1. The general organization of spinal cord projections correlate with this boundary by the nature of neuronal labeling patterns, and label-free zones that occur following injections of retrograde tracer placed into brachial and lumbosacral spinal levels (Biber *et al.*, 1978; Hutchins *et al.*, 1988; Dum and Strick, 1991; Galea and Darian Smith, 1994; He *et al.*, 1995). These findings, along with unit recording and intracortical microstimulation observations as highlighted below, suggest a forelimb representation in both CMAs.

Likewise, cingulate motor cortex projections to the face/head area of M1, M2, and the primary sensory cortex (S1) represent an additional structural characteristic for assisting in the localization of this general border, and specifically aids in locating the rostral part of the CMAc. For example, injections of tracer located in either the face/head representation of M1, M2, and S1 consistently give rise to a small patch of labeled neurons that falls within coronal sections that include the genu or spur of the arcuate sulcus thus corresponding the rostral sector of the caudal cingulate motor cortex (i.e. face/head region) (Morecraft *et al.*, 1996, 2004; Tokuno *et al.*, 1997). This same region of cortex innervates the facial motor nucleus (Morecraft *et al.*, 1996, 2001) and this general area of the CMAc also projects to the frontal eye fields (Wang *et al.*, 2004). In general, neurons in the cingulate sulcus projecting to head/face regions of M1, M2, and S1 are anterior to neurons projecting to arm representations of M1 and S1 suggesting a cingulate somatotopic organization which will be discussed in the following section on CMA functions.

Another question that arises is what general location demarcates the rostral region, or boundary, of the CMAr? In the past, the rostral extent of the spinal cord projection field, which significantly diminishes in intensity at the level of the corpus callosum genu, has commonly been used to define this limit. However, based upon the discrete patterns of connections with eye, head and face related parts of the frontal lobe, the rostral part of the CMAr (i.e., face/head representation) corresponds to coronal levels positioned over, and slightly anterior to the genu of the corpus callosum. Specifically, this region of cingulate cortex selectively projects to the face/head area of M1 (Muakkassa and Strick, 1979; Morecraft and Van Hoesen, 1992; Morecraft *et al.*, 1996, 2004; Tokuno *et al.*, 1997), the face/head area of the supplementary motor cortex (Morecraft *et al.*, 1996), the face/head area of the primary sensory cortex (S1) (Morecraft *et al.*, 2004a), as well as the frontal eye fields (Wang *et al.*, 2004). This portion of the cingulate cortex also gives rise to corticofugal projections targeting the facial motor nucleus (Morecraft *et al.*, 1996, 2001). This selective network of corticocortical interconnections amongst the frontal, parietal, and cingulate face representations as well as the finding that all frontal and cingulate face areas project directly to the facial nucleus suggests a potential large-scale neural network involved in mediating facial expression (Morecraft *et al.*, 2004b). It has been further suggested that the cingulate face regions may form an important anatomical conduit for emotional facial expressions (Morecraft *et al.*, 2001, 2004b) which has received support in the clinical literature (Jox *et al.*, 2004; Rao and Hogan in press).

The caudal part of the CMAr is marked by neurons within the fundus and upper bank of the cingulate sulcus which project to the hind limb representation of M1 (Morecraft and Van Hoesen, 1992; unpublished observations) and S1 (Morecraft *et al.*, 2004a). This region corresponds to coronal levels approximating the closure of the arcuate sulcus and the projection neurons primarily occupy the cingulate fundus and medial sector of the upper bank. Neurons with proprioceptive and cutaneous receptive fields associated with the leg have been identified in this location (Cadoret and Smith, 1995). Thus, face, arm, and leg regions occupy rostral to caudal levels of the CMAr as will be summarized in the following section on cingulate motor functions.

The corticocortical connections of the CMAr and CMAc are extensive and link them with numerous local and distant cortices. In a sense, the widespread nature of corticocortical interconnections appear to reflect a hybrid of the long range connections with multimodal association areas that characterize the neighboring cingulate cortices on the one hand (i.e., areas 24a´ and 24b´), and the motor and sensory-related interconnections that characterize the adjacent medial frontal cortices on the other. Specifically, both the rostral (Figs. 5.13 and 5.14) and caudal (Figs. 5.15 and 5.16) cingulate motor cortices are interconnected with frontal association, premotor and motor cortices, parietal association and sensory cortices, lateral and medial temporal association cortices, limbic cortices as well as the insula (Muakkassa and Strick, 1979; Morecraft *et al.*, 1988; Dum and Strick, 1991; Morecraft and Van Hoesen, 1992, 1993, 1998; Bates and Goldman-Rakic, 1993; Tokuno and Tanji, 1993; Van Hoesen *et al.*, 1993; Lu *et al.*, 1994; Morecraft *et al.*, 1996, 1997, 2004a; Nimchinsky *et al.*, 1996; Tokuno *et al.*, 1997; Wu *et al.*, 2000; Wang *et al.*, 2001, 2004; Hatanaka *et al.*, 2003).

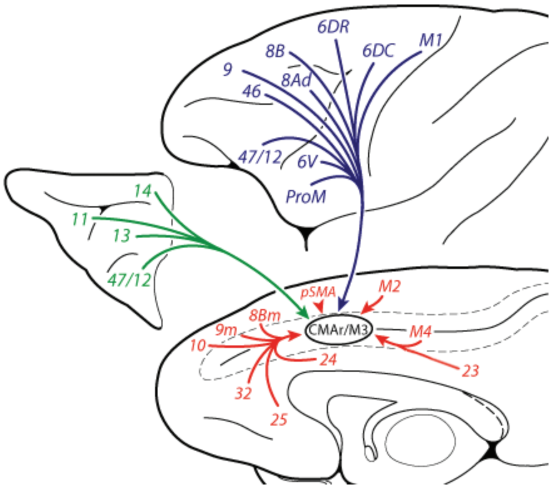

Fig. 5.14 Summary diagram of the frontal lobe and cingulate inputs to the CMAr (M3).

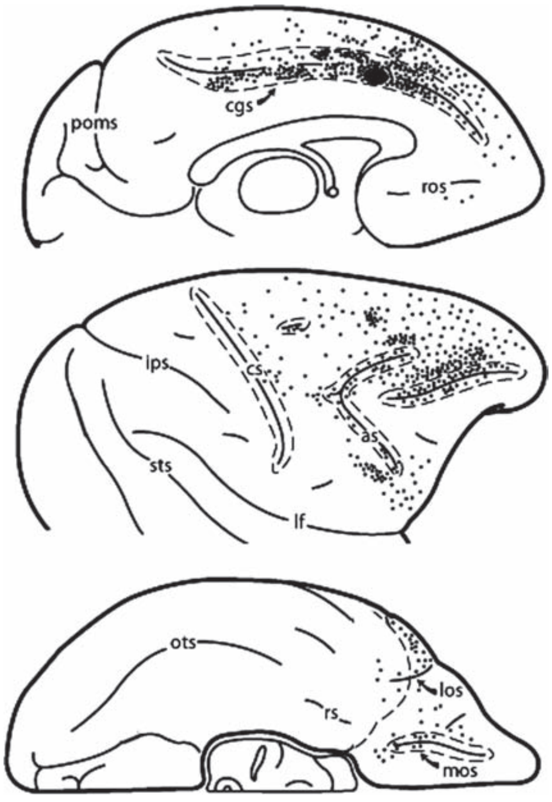

Fig. 5.13 Labeled neurons in the frontal lobe following an injection of fast blue into area 24c (CMAr). Black dots represent locations of retrogradely labeled cells. Only labeled cells in the frontal lobe and cingulate sulcus are illustrated. (From Morecraft and Van Hoesen, 1993).

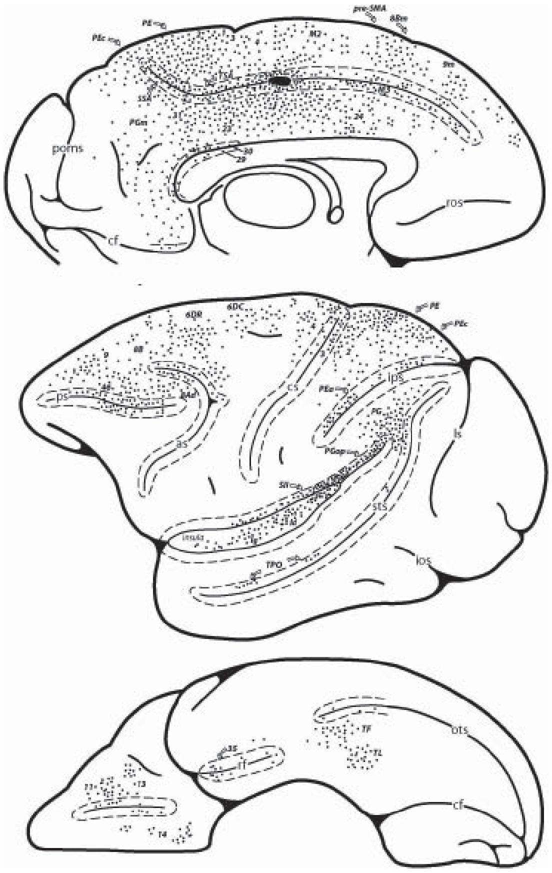

Fig. 5.15 Distribution of retrogradely labeled cells (black dots) on the lateral, medial, and ventral surfaces following an injection of fast blue into area 23c of the lower bank of the cingulate sulcus. (From Morecraft *et al.*, 2004a).

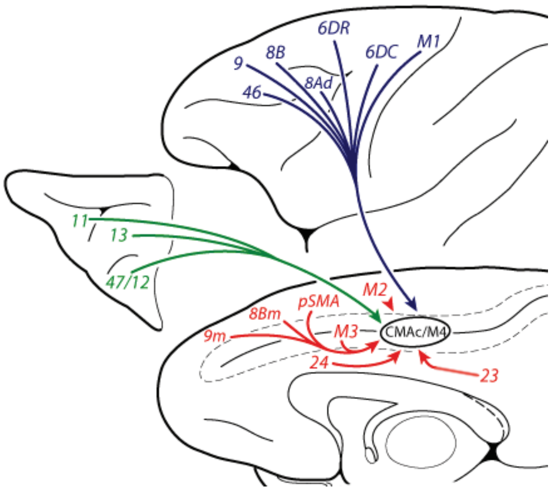

Fig. 5.16 Summary of frontal lobe and cingulate inputs to the CMAc (M4).

In terms of specific frontocingulate interconnections, the CMAr and CMAc are linked to multiple regions of the frontal lobe. Like areas 24a´/24b´ and 23a/23b of the surface of the cingulate gyrus, lateral prefrontal projections innervate the CMAr and CMAc (Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1993; Lu *et al*., 1994; Morecraft *et al*., 2004a; Takada *et al*., 2004). These projections arise from area 10 of the frontal pole, area 46 within and around the principal sulcus, and area 9 located dorsal to area 46 (Figs 5.13 and 5.15). Some controversy exists over the extent and intensity of dorsolateral prefrontal projection to the CMAr. For example, studies have shown a significant projection from areas 9 and 46 following injections of tracer placed into area 24c of the lower bank of the cingulate sulcus (Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen 1993) or into area 46 (McGuire *et al*., 1991; Bates and Goldman-Rakic, 1993; Lu *et al*., 1994). However a recent study has shown a very weak projection from area 46 to part of area 24 in the fundus of the cingulate sulcus (Takada *et al*., 2004). These differences may be attributable in part, to the relative strength of the projection to the various parts of the cortex lining the lower bank versus the fundus of the cingulate sulcus (see Fig. 3 of Morecraft and Van Hoesen, 1992). For instance, the area 46 projection may diminish in intensity when progressing from the medial region of the lower bank toward the fundus of the sulcus. Injections involving the medial region of the lower bank may therefore, demonstrate a much stronger prefrontal projection than injections seated more laterally or within the fundus. In line with this potential trend, it has been reported that cortex lining the upper bank of the sulcus in the region of the caudal cingulate motor cortex is devoid of prefrontal projections from area 46 (Bates and Goldman-Rakic, 1993; Lu *et al*., 1994). These discrepancies may also be a consequence of the rostral to caudal locations of injection sites. It is also possible that more rostral levels of area 24c may be more strongly interconnected with area 46 than caudal levels of area 24c (i.e., area 24c´ of Vogt, 1993).

Other lateral prefrontal connections with the CMAr and CMAc include areas 8Ad and 8B (Barbas and Mesulam, 1981; Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1993; Van Hoesen *et al*., 1993; Morecraft *et al*., 2004; Wang *et al*., 2004). The cingulate projection to the frontal eye field (area 8A) arises from two distinct foci, one within the rostral region of the CMAr and a second in the rostroventral region of the CMAc which includes cortex on the interhemispheric surface of the gyrus (Wang *et al*., 2004). This projection may provide an important source of cingulate influence in the realm of attention and emotion on cortically mediated eye movements. The lateral opercular portion of area 47/12 has also been found to be reciprocally interconnected with the CMAr (Morecraft and Van Hoesen, 1993; Pandya and Yeterian, 1996; Petrides and Pandya, 2002).

In terms of medial prefrontal connections, a dense projection from areas 9m and 8Bm targets CMAr (Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1993; Barbas *et al*., 1999; Hatanaka *et al*., 2003). Other medial wall connections with the rostral cingulate motor cortex include a dense projection from areas 24a and 24b as shown in Figure 5.13 (Morecraft and Van Hoesen, 1998; Hatanaka *et al*., 2003), a moderate to weak projection from pregenual area 32/24 (Morecraft and Van Hoesen, 1998; Barbas *et al*., 1999), and weak projection from subgenual area 25 which may target relatively rostral levels (Morecraft and Van Hoesen, 1993). The CMAc receives weak medial prefrontal inputs from areas 9m and 8Bm (Morecraft *et al*., 2004).

Orbitofrontal projections to the CMAr arise from areas 11, 12, 13, and the opercular region of area 12 (Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1993, 1998; Morecraft *et al*., 2004a). The projection from areas 11, 12 and 13 to the CMAr heavily innervate levels over the genu of the corpus callosum which corresponds to the face/head area (Bates and Goldman, 1993; Morecraft and Van Hoesen, 1998; Carmichael and Price, 1995). Furthermore, this projection progressively diminishes in strength from the medial region of the lower bank toward the fundus of the sulcus (Morecraft and Van Hoesen, 1998). A small projection to area 14 from the rostral part of area 24c located over the genu of the corpus callosum has also been noted (Barbas *et al*., 1999). Orbitofrontal projections to the CMAc arise primarily form area 11 (Bates and

Goldman-Rakic, 1993; Morecraft *et al.*, 2004a). A few projection neurons have also been found in area 13, the caudal region of area 14 of the gyrus rectus and area 12 of the lateral orbital cortex (Morecraft and Van Hoesen, 1998; Morecraft *et al.*, 2004a).

Both the CMAr and CMAc are interconnected with the agranular premotor cortices as well as the agranular motor cortices as mentioned in the discussion on the relative boundaries of the CMAr and CMAc. In general, this establishes a significant and pivotal interface between the frontal motor cortices on the one hand and the traditional limbic cingulate cortices on the other (Morecraft and Van Hoesen, 1998). On the medial wall of the hemisphere, the pre-SMA receives projections from both the CMAr and CMAc (Morecraft and Van Hoesen, 1993; Luppino *et al.*, 1993; Wang *et al.*, 2001; Hatanaka *et al.*, 2003; Morecraft *et al.*, 2004a) with the strongest pre-SMA connection formed by the CMAr (Wang *et al.*, 2001). Caudal to the pre-SMA is the supplementary motor area (SMA or M2) which corresponds to cytoarchitectural area 6m. This cortex is also interconnected with both the CMAr and CMAc (Jürgens, 1984; Morecraft and Van Hoesen, 1992; Luppino *et al.*, 1993; Tokuno and Tanji, 1994; Morecraft *et al.*, 1996; Wang *et al.*, 2001). As mentioned earlier, in terms of topography the rostral region of area 6m (i.e., the face/head region) is connected with the rostral region of both cingulate motor cortices (Morecraft *et al.*, 1996). The mid-portion of area 6m (i.e., the arm region) is also heavily connected with both CMAr and CMAc (Luppino *et al.*, 1993; Morecraft and Van Hoesen, 1992; Morecraft *et al.*, 1996; Wang *et al.*, 2001). Following small injections in the arm region, one group of labeled neurons occur in the CMAr and another spatially separate group in the CMAc (Morecraft *et al.*, 1996; Wang *et al.*, 2001). These groups of neurons reside caudal to neurons projecting to the rostral (i.e., face/head region) of the supplementary motor cortex (Morecraft *et al.*, 1996). The caudal-most region of area 6m (i.e., the leg region) is also connected with the CMAr and CMAc (Luppino *et al.*, 1993; Tokuno and Tanji, 1994). This projection arises from the caudal most regions of both the CMAr and CMAc (i.e., the leg regions of CMAr and CMAc).

Lateral motor and premotor connections with the CMAs are also extensive as shown in Figures 5.14 and 5.16. Both areas 6DR and 6DC are reciprocally interconnected with the CMAr and CMAc (Pandya and Vignolo, 1971; Barbas and Pandya, 1987; Kurata, 1991; Van Hoesen *et al.*, 1993; Luppino *et al.*, 2003; Morecraft *et al.*, 2004a). Injections or ablations involving the ventrolateral premotor region also demonstrate strong interconnections with the cortex lining the banks of cingulate sulcus (Pandya and Vignolo, 1971; Matelli *et al.*, 1986; Barbas and Pandya, 1987; Kurata, 1991). Of interest is that some experiments demonstrate that two spatially separate groups of cells project to the rostral part of area 6V (see Fig. 7 of Barbas and Pandya, 1987 and Fig. 7 of Kurata, 1991). The general locations of these cell groups correspond to the rostral region of the CMAr, in coronal sections over the genu of the corpus callosum and the rostral region of the CMAc, in coronal sections at the level of the spur of the arcuate sulcus. Finally, the lateral region of area 4 (M1) also projects to both motor areas (Pandya and Vignolo, 1971; Matsumura and Kubota, 1979; Muakkassa and Strick, 1979; Godschalk *et al.*, 1984; Leichnetz, 1986; Ghosh *et al.*, 1987; Dum and Strick, 1991; Morecraft and Van Hoesen, 1992; Darian-Smith *et al.*, 1993; Tokuno and Tanji, 1993; Stepniewska *et al.*, 1993; Wu *et al.*, 2000) where small injections located in the face/head and arm regions do so in topographic fashion as discussed. The connection with the M1 face area appears more prevalent with the CMAr (Muakkassa and Strick, 1979, Morecraft and Van Hoesen, 1992; Morecraft *et al.*, 1996), while the M1 arm projection has been reported to be more prominent with the CMAc (Nimchinsky *et al.*, 1996; Wang *et al.*, 2001). The dorsal portion of area 4 of the primary motor cortex (i.e., leg region) has been shown to be interconnected with both cingulate motor cortices (Pandya and Vignolo, 1971; Muakkassa and Strick, 1979; Godschalk *et al.*, 1984; Morecraft and Van Hoesen, 1992; Luppino *et al.*, 1993; Hatanaka *et al.*, 2001). Studies with experimental cases having one tracer injected into the M1 leg region (Morecraft *et al.*, 1992; Hatanaka *et al.*, 2001) and another tracer into either the M1 face region (Morecraft *et al.*, 1992) or M1 arm region (Hatanaka *et al.*, 2001) indicate that there is little overlap of cingulate projection neurons to these discrete regions of M1 supporting the concept of cingulate somatotopy. A similar organization appears to reflect cingulate projections to the face and hind limb regions of S1 (Morecraft *et al.*, 2004a; Fig. 14).

Intrinsic Cingulate Connections

In addition to the important contingent of prefrontal connections with the cingulate cortex, an analysis of experimental cases with injection sites seated with the various cingulate subregions suggest some distinct patterns of intrinsic connections (Vogt and Pandya, 1987; Van Hoesen *et al.*, 1993). For instance, rostral cingulate injections heavily label regions in and around the injection site and in distant ventral PCC. Between the two heavily labeled zones is a light and patchy, and sometimes label-free region (Vogt and Pandya, 1987). Likewise ventral PCC injections heavily label regions in and around the injection site as well as in distant ACC around and above the genu of the corpus callosum. In between, over midcingulate cortex, neuronal labeling is often inconsistent producing a mosaic pattern of label-free zones amongst groups of labeled cells (Vogt *et al*., 1987; Van Hoesen *et al*., 1993; Morecraft *et al*., 2004a) and this pattern includes the intrinsic cingulate projections to area 31 (Morecraft *et al*., 2004a). The sACC is not interconnected with the caudal medial lobule. Thus, anatomical linkage of these two polarized regions of the cingulate cortex is likely to occur through a series of intrinsic corticocortical connections.

Finally, the CMAr and CMAc are extensively interconnected. The CMAr also receives massive input from areas 24b and 24a. Injections made directly into CMAr indicate that this projection arises from cingulate cortex directly around or inferior to the injection site (Van Hoesen *et al*., 1993; 1998). Likewise, the CMAc receives extensive projections from adjacent areas 23b and 23a as shown in Figure 5.15. Thus, from a structural perspective, these local projections from the cingulate gyral surface to the cortex in the depths of the cingulate sulcus form a short but massive, and highly influential terminal projection. As reviewed, although CMAr and CMAc receive inputs from key frontal regions of the lateral prefrontal and orbitofrontal cortices, the available data clearly indicate that the "a" and "b" subdivisions of the midcingulate cortices receive significantly more extensive direct inputs from the same lateral prefrontal and orbitofrontal regions. Thus, the short but powerful projection from the cingulate gyral surface to the cortex in the lower bank and fundus of the cingulate sulcus shown in Figure 5.17 may provide the most substantial indirect prefrontal influence on the CMAs; in effect, heavily influencing the output of this region in a manner that would have devastating effects on indirect prefrontal influences to the CMAs, if areas 24a or 24b, for example, were selectively damaged.

Summary of Cingulofrontal Interconnections

Dorsolateral prefrontal-cingulate connections

Cingulofrontal projections are very widespread. Perhaps the most striking and reoccurring pattern of corticocortical frontal linkages with the cingulate cortex is that established with dorsolateral prefrontal areas 46 and 9 as summarized in Figure 5.18. In fact this observation can even be traced back to classic degeneration studies which detected peri-principalis connections with the anterior, midcingulate, and posterior cingulate cortices (Pandya *et al*., 1971). Indeed, all cingulate regions are reciprocally connected with these multimodal, frontal association areas. It is noteworthy to mention that this linkage also involves the cingulate motor areas buried

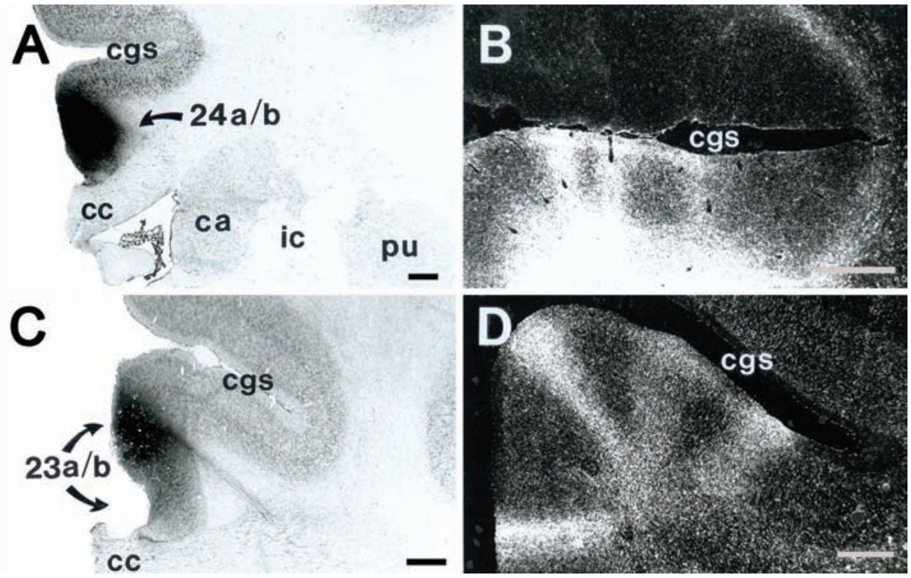

Fig. 5.17 A. Photographic demonstration of cingulate gyrus inputs to the CMA: A. Brightfield photomacrograph of a Nissl-stained coronal section where tritiated amino acids (blackened cortex) were injected into areas 24a and 24b. B. Darkfield photograph demonstrating adjacent columns of terminal label over cortex in the lower bank of the cingulate sulcus (area 24c). C. Brightfield photomacrograph of a Nissl-stained section where tritiated amino acids (blackened cortex) were injected into areas 23a and 23b. D. Darkfield photograph showing multiple columns of terminal label over cortex in the lower bank of the cingulate sulcus (area 23c). These powerful projections are a rich source of indirect prefrontal cortex inputs to the CMAs. (From Morecraft and Van Hoesen 1998) ca, caudate nucleus; pu, putamen ec, coephscallosum; cgs, cingulate sulcus; ic, internal capsule; cc, corpus callosum.

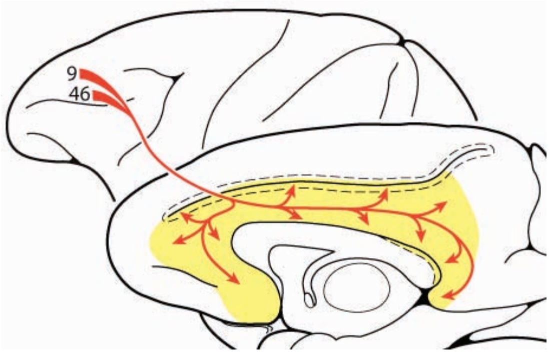

Fig. 5.18 Summary of the widespread projections of peri-principalis cortex throughout the entire cingulate gyrus.

within the depth of the cingulate sulcus. This unique relationship places an extensive expanse of cingulate cortex in a pivotal position to be in direct communication with mid region of the dorsolateral prefrontal cortex. Area 46 is itself, interconnected with cortices representing relatively early stages of auditory and visual processing (Selemon and Goldman-Rakic, 1988; Barbas and Pandya, 1989; Cavada and Goldman-Rakic, 1989). There is also evidence to indicate that this region of the prefrontal cortex selects sensory and environmental information to guide decision-making behavior and access to this input is critical for the appropriate execution of this process.

This neuroanatomical substrate therefore, places all cingulate subregions in direct communication with part of the frontal cortex that has classically been associated with attention, self-monitoring, personality, planning, working memory, and decision making. Working memory refers to the ordering of behavior, or the manner in which time is bridged neurally to complete a sequence of acts on a short-term basis. Spatial abilities, appropriate choices, and motor acts are essential to place one in favorable positions to carry out an appropriately intended behavior. Decision-making behavior complements working memory in critical ways and involves the assessment of somatic markers (Damasio 1994; Bechara *et al.*, 2000) that impart personal reality to choices of behavior and their ultimate consequences. Thus, in consideration of the connections bridging widespread parts of the cingulate with the dorsolateral prefrontal cortex, it is not surprising that contemporary neuroimaging studies investigating cognitive, emotional, and attentional control mechanisms find cingulate activation often associated with dorsolateral prefrontal cortex activation (Gehring and Knight, 2000; MacDonald *et al.*, 2000; Bunge *et al.*, 2001; Rowe and Passingham, 2001; Kerns *et al.*, 2004, Holroyd *et al.*, 2004; Weissman *et al.*, 2005).

From a clinical perspective, this special neuroanatomical relationship makes it reasonable to suggest that diseases or traumatic insults affecting the cingulate cortex will have a major impact on the function of prefrontal cortex by removing this important limbic influence. The efferent projections from the anterior cingulate cortex to the prefrontal cortex arise primarily from the infragranular layers and terminate in the supragranular layers of prefrontal cortex suggesting a role in feed back communication (Barbas 1986, 2000b). Neurodegenerative diseases affecting the ACC may therefore disconnect this potential feed back system and severely alter the decision-making process. On the other hand, the efferent projection from the dorsolateral prefrontal cortex arises from supragranular layers and these axons terminate heavily in the deeper layers of the ACC suggesting a potential feed forward system of communication. Thus, diseases or injury selectively damaging the lateral prefrontal cortices are likely to attenuate or abolish significant prefrontal influence on cingulate neural activity.

Orbitofrontal-cingulate connections

Functionally, the orbitofrontal cortices have been associated with a variety of autonomic, mnemonic, and emotional processes and are involved in the control of goal directed behavior (Barbas 2000a, 2000b; Rolls 2000). Neurons in this region respond to rewards in a manner that correlates with expectation or detection of a reward for reinforcing behavioral reactions (Tremblay and Schultz, 2000) and the functional interaction between the amygdala and orbitofrontal cortex appears to be essential for adaptive response selection based upon reinforced values (Chapter 8; Baxter *et al.*, 2000). With the exception of area 31, orbitofrontal cortex is interconnected with all of the major cingulate subdivisions (i.e., areas 25, 32, 24, 23, 29, and 30). The orbitofrontal cortex itself receives extensive sensory inputs from visual, auditory, somatosensory, gustatory, and primary olfactory cortices (Barbas, 1993; Morecraft *et al.*, 1993; Carmichael and Price, 1995a) as well as the amygdala as indicated above (Barbas and DeOlmos 1990; Morecraft *et al.*, 1993; Carmichael and Price, 1994; Ghashghaei and Barbas, 2002). This enables orbitofrontal cortex to sample the external and internal environment within the context of emotional significance and through its projection to the ACC, possibly influencing cingulate-mediated action with highly integrated sensory stimuli.

In terms of the topography of orbitofrontal-cingulate projection, several trends appear to occur. The caudal orbitofrontal region including areas OPall, OPro, 12o, and 13 project heavily to the subgenual and pregenual areas 25 and 32/24, respectively. These cingulate areas, as well as the caudal orbitofrontal cortex collectively receive strong efferent projections from the amygdala that are associated with memory and emotion (Barbas 2000a, 2000b; Chapter 6). These same cortical areas also receive projections from medial temporal structures affiliated with long-term memory (Barbas *et al.*, 1999). Dorsally and caudally in the midcingulate area 24′, there is the addition of a projection from the caudal region of orbitofrontal areas 11 and 14. Area 11 does not receive amygdala inputs. Further posteriorly in the cingulate areas 23 and 29/30, the projection from area 11 increases in intensity and area 23 cases indicate involvement of a projection from rostral orbitofrontal area 10. Thus, caudal cingulate cortex appears to be preferentially interconnected with rostral orbitofrontal targets and conversely, rostral cingulate cortex appears to be interconnected preferentially, but not exclusively with caudal orbitofrontal subdivisions. As indicated above, complementing this pattern are amygdala projections which target the caudal orbitofrontal cortex and ACC, but not the rostral orbitofrontal and caudal cingulate cortices. This may serve in dual manner to minimize direct amygdala influence on both the rostral orbital and caudal cingulate cortices which in turn are reciprocally interconnected.

Cingulate Motor Functions

Many lines of evidence have established the existence of areas in the cingulate gyrus that are involved in the regulation and control of motor behavior. Recent developments reveal how each cingulate motor area regulates specific aspects of behavioral control. While the CMAc regulates motor functions, the CMAr is also involved in cognitive control of broad aspects of behavior, including generation of motor intention, behavioral selection, behavioral monitoring, and monitoring of behavioral outcomes. The CMAs in the monkey reside in the lower bank of the cingulate sulcus but do not extend onto the cingulate gyrus surface. The cingulate gyral surface has few anatomical projections to cortical motor areas (above) and no projections to the spinal cord supplying axons to the peripheral muscles. Physiological studies demonstrated that this part of the cortex is not excitable with microstimulation, and cellular activity related to movement execution has not been found. Thus, the surface of the cingulate gyrus and ACC, rather than being directly involved in motor functions, appears to be involved in other behaviors such as the control of autonomic functions, the expression of emotions or inner drives, and avoidance responses generated by noxious stimulation.

The two CMAs in the lower bank of the cingulate sulcus have been defined above on the basis of anatomical criteria. Physiological criteria, however, are also important in distinguishing the contribution of these areas to motor control and set the framework for interpreting their involvement in complex behavioral processing. Physiological studies have confirmed the existence of CMAr and CMAc by demonstrating that cells within these areas are active during performance of limb movements (Shima *et al.*, 1991), and by revealing that intracortical microstimulation evokes limb movements (Luppino *et al.*, 1991).

Somatotopic organization

The existence of forelimb representation in the CMAs has been established on anatomical evidence and on physiological grounds. Regions projecting to the forelimb area in the primary motor cortex or cervical segments of the spinal cord have been found in the CMAr and in CMAc (Dum and Strick, 1991; Morecraft and Van Hoesen, 1992; Wang *et al.*, 2001). The rostral region is located ventral to the pre-SMA, and the caudal region is situated ventral to the hindlimb part of the SMA. Physiological studies employing intracortical microstimulation or single-cell recording support the existence of forelimb representation areas as will be discussed (Shima *et al.*, 1991). Regions projecting to the lumbar segments of the spinal cord (Hutchins *et al.*, 1988) or hindlimb area of the primary motor cortex are also in both the CMAr and CMAc (Morecraft and Van Hoesen, 1992). The rostral region is located ventral to the forelimb area of the SMA, and the caudal region is located ventral to the hindlimb area of M1. Compared to the forelimb regions, physiological studies concerning the hindlimb part of cingulate motor areas are meager and have yet to be systematically studied. Cellular activity related to hindlimb movements in awake animals has not been studied, and intracortical microstimulation has not provided detailed or reproducible results related to hindlimb representation. However, the hindlimb area of the CMAc can be regarded as lying caudal to the forelimb region of the CMAc, and the hindlimb area of the CMAr seems to be located caudal to its forelimb part. The face areas have been identified in the rostral part of the CMAr and in the rostral part of the CMAc with neuroanatomical methods as reviewed earlier (Morecraft *et al.*, 1996; Tokuno *et al.*, 1997). Thus in both CMAr and CMAc, face, forelimb, and hindlimb regions appear to be arranged rostrocaudally. This somatotopic arrangement is supplemented with a finding that regions projecting to the frontal eye field are located in the rostral-most part of each of the CMAr and CMAc (Wang *et al.*, 2004). Physiologically, the rostral field in CMAr elicits eye movements following microstimulation (Mitz and Godshalk, 1989).

Motor control functions

The CMAs have anatomical connectivity with other cortical motor areas, the brain stem, and the spinal cord with somatotopical arrangements. Electrical stimulation studies have confirmed somatotopical organization in the CMAs (Godschalk *et al.*, 1995; Luppino *et al.*, 1991; Mitz and Wise, 1987). Based on this, the contribution to specific aspects of motor control were investigated. However, physiological studies examining cellular activity during the execution of motor behavior have been few because of the location of the CMAs in the cingulate sulcus. An early report by Niki and Watanabe (1979) showed that cells in the vicinity of CMAr were active during a delayed-response task followed by 15 years to the time when CMA cells were systematically studied for their involvement in motor tasks. Shima *et al.* (1991) demonstrated that neurons in both CMAr and CMAc change their activity before and during a key-press movement with a hand. The activity was observed when movements were initiated either in response to visual, auditory, or somatosensory signals, or initiated internally. CMAc cells tended to change their activity more intensely than CMAr cells, while CMAr neurons tended to be more active when the hand movement was self initiated than signal triggered. Some CMAr cells exhibited activity long before the initiation of self-paced movement. Subsequently, Cadoret and Smith (1995) reported activity modulations of CMAc cells during grasping, lifting, and holding an object with the contralateral thumb and index fingers. Force pulse perturbations applied to the object elicited excitatory responses at latencies of 45 ms.

The next step was to explore what aspect of motor behavior the neuronal activity signifies. One of the issues of prime importance was to understand how the sensorimotor variables are represented in the CMAs. In this respect, recent studies have revealed striking differences in the properties of cellular activity in the CMAr and CMAc. Russo *et al.* (2002) studied activity in the CMAc during visually guided arm-shoulder movements destined to eight directions. They assessed cellular activity associated with the onset of a visual cue, delay (motor-set), and motor responses for directional tuning. It was found that 24% of cue responses, 46% of motor-set activity, and 66% of movement-related activity were directionally tuned. They also found that the directional tuning appeared similar in the CMAc. Furthermore, properties of these neurons were similar to properties of SMA cells with respect to onset latencies, response magnitudes, and directionality.

In contrast to the CMAc, studies of the CMAr showed very different results. Akkal *et al.* (2002) studied activity during performance of a sequential reaching task with delay. No CMAr cells were influenced by the spatial location of targets during the visual cue and delay periods. As for the activity during movement, only 5% of cells showed selectivity to the spatial location of four targets to reach. Subsequently, Isomura *et al.* (2003) studied activity in the CMAs during performance of a GO/NO-GO task instructed with spatial or color cues. Despite the abundance of CMA activity selectively coding during either a GO or NO-GO response of the animal, only a small number of CMAr cells showed selectivity for visual signals; 1.7 % of task-related cells were selective for the location of spatial cues. Recently, Hoshi *et al.* (2005) examined neuronal activity in the CMAr with respect to multiple behavioral factors including the retrieval and processing of associative visual signals to the planning and execution of instructed actions. Neuronal activity was analyzed while monkeys performed a behavioral task in which two visual instruction cues were given, each followed by a delay: one cue for the location of the target to be reached and the other for the arm to be used as shown in Figure 5.19. Neuronal activity in the CMAr changed profoundly in each epoch of the behavioral task; however, it was only modestly selective for the spatial location of the visual cues or for the instructional information delivered with the signals (target location or arm use). Activity during motor planning or movement execution, though robust and intense, also exhibited modest selectivity for motor parameters.

These reports indicate that the CMAr and CMAc take part in controlling different aspects of motor behavior. The CMAc, which has strong connections with M1 and the spinal cord, seems to be intimately involved in preparing and controlling movements, specifying parameters of movements. This view is in line with findings reported with a 2-deoxy-D-glucose imaging technique (Picard and Strick, 1997). In contrast, CMAr does not seem to take a major part in selecting or regulating specific details of movements. Rather, the CMAr is more useful in delineating individual phases of behavior that has complex temporal structures, by monitoring individual behavioral events to keep track of the progress of required behavioral tasks. On the other hand, CMAr activity during delay or motor set period is likely to reflect the emergence of a general intention for action, or decisions of whether or not to initiate action.

Cognitive Aspects of Behavioral Control

The CMAs are at a pivotal position in the cortex between input sources from limbic and association areas and motor areas to which the cingulate outputs are targeted. This unique connectivity invites physiological studies examining participation of the CMAs in motivational or emotional aspects of behavioral control on one hand, and in integrative regulation of perceptual or memorized information for behavioral regulation on the other. Animal studies in search of such aspects of cingulate function are still at an early stage, leaving many issues to be investigated. Reported findings,

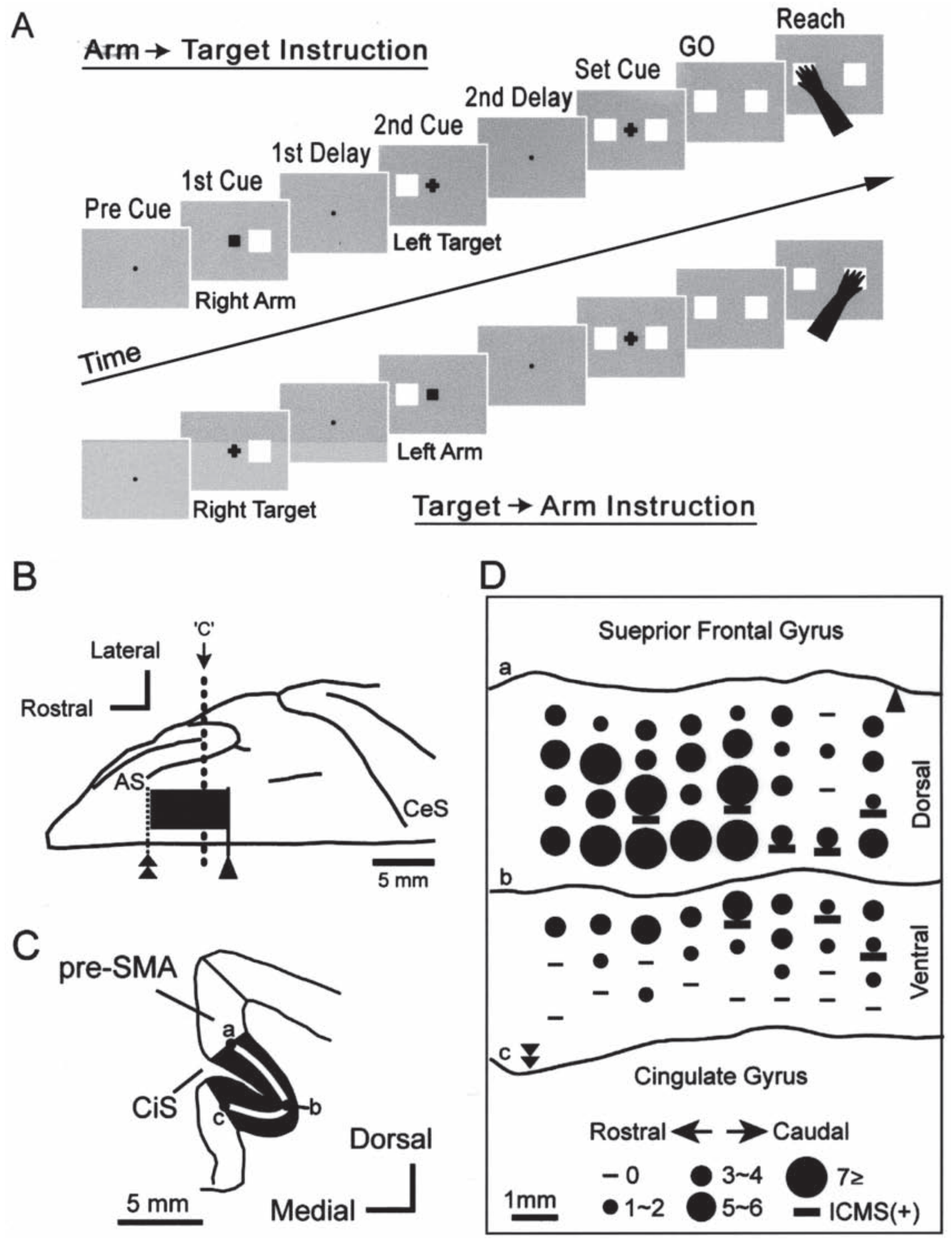

Fig. 5.19 Behavioral task and recording sites. A: Sequence of behavioral events. The top row shows a trial in which two instructions were given, that is, which arm to use ('arm') and which target to be reached ('target'), in that order. The bottom row shows a trial in which the two instructions were reversed. B: Dorsal view of the surface of the right frontal cortex. The gray box indicates an area within which the CMAr was projected. The double arrowhead with a dotted line indicates the most rostral extent of the corpus callosum. The single arrowhead with a solid line represents the border between the SMA and pre-SMA motor areas. C: Coronal section through the CMAr along the dotted line labeled 'C' in panel B. Gray area represents the extent of the CMAr. AS, arcuate sulcus; CeS, central sulcus; CiS, cingulate sulcus. Scale bars in B and C = 5 mm. D: Distribution of task-related neurons and intracortical microstimulation (ICMS) effects in the CMAr of Monkey 2. Electrode tracks were reconstructed from the coronal sections. Sites where task-related neurons were found or where ICMS evoked forelimb movement were projected to a cortical map unfolded along the line passing through the middle of the gray matter (the white line in panel C). The letters, a, b, and c, on the unfolded map correspond to those in the section in panel C. The size of the filled circle indicates the number of task-related neurons at each site and the black horizontal bars indicate the recording point where no task-related neurons were found. The gray horizontal bar indicates the site where ICMS evoked forelimb movements. The double arrowhead indicates the rostral extent of the corpus callosum. The arrowhead represents the border between the SMA and Pre-SMA. Scale bar = 1 mm.

however, support the hypothesis that the CMAs are a part of a medial frontal network involved in supervisory control of action.

Reward-based control of behaviour

The relation of the CMAr and its adjacent areas to the occurrence of reward was initially reported by Niki and Watanabe (1979). In common with other medial motor areas, it is now generally accepted that cells in the CMAs respond to the occurrence of reward (Shima and Tanji, 1998; Akkal *et al.*, 2002; Ito *et al.*, 2003). It is important to note, however, that cellular responses to the occurrence of reward vary greatly depending on the nature of behavioral conditions. Hoshi and colleagues (2005) examined reward-related activity in the CMAr of monkeys that were highly trained for more than two years and found that cells responding to reward delivery were small in number. Thus, CMAr responses to reward are greatly attenuated if motor behavior is automatic and depends little on reward properties (Koechlin *et al.*, 2002).

More interesting is the question of how the reward information captured with CMAr cells is used for behavioral planning or modification. Shima and Tanji (1998) trained monkeys to select and perform two different arm movements triggered with a visual signal. The selection of the motor task was made by the monkeys themselves, based on the amount of reward. During a series of constant-reward trials, monkeys had to keep selecting a particular movement. If they detected reduction of the reward, they chose to perform the alternate movement, because, if they did, the reward returned to its full amount. Muscimol injection revealed that CMAr inactivation led to the impairment of proper selection based on the reward-amount. Furthermore, CMAr cells were found to exhibit changes in activity during the interval between the detection of the reduced reward and the initiation of a newly selected movement as shown in Figure 5.20. A group of neurons responded shortly after the occurrence of the reduced reward, and others were active progressively before selecting the alternate movement. These findings support a view that CMAr cells take part in selection of action based on the reward obtained as a result of an action. In a subsequent study, the effect of ablation of the CMAr and its adjacent region was examined in monkeys performing a reward-conditional response selection task (Hadland *et al.*, 2003). These authors concluded that the CMAr is concerned with action-reward associations, not limited to just detecting when actions lead to errors, and the role of CMAr is limited to action-reinforcer associations and it is not concerned with stimulus-reward association.

A different aspect of CMAr involvement in reward-based behavioral control was proposed by Shidara and Richmond (2002) who trained monkeys to perform a color-discrimination response. To obtain a reward, monkeys had to complete a set of trials that was scheduled to vary from one to four. A set of visual signals told the animal the progress of the trial schedule, that is, the proximity to reward. They found that midcingulate neurons had responses that progressively changed strength with reward expectancy. Interestingly, cells of this type were recorded from the ventral bank of the CMAr, a region that receives strong inputs from limbic structures (above). This signal encoding the degree of reward expectancy may be related to the feelings of increasing anticipation that are experienced over stages toward predicted outcome. The involvement of the cingulate cortex in reward-related behavioral decision was also studied in rats. Walton *et al.* (2002) studied the effects of lesions in a large swath of anterior and midcingulate cortex of rats on motivational cost-benefit decisions. They found that these large lesions led to the impairment in selecting actions to obtain greater rewards that require greater efforts (Walton *et al.*, 2003).

Error detection, behavioral monitoring, and conflict monitoring

Since the early report of cellular activity related to the occurrence of errors in the vicinity of CMAr (Niki and Watanabe, 1979), animal studies on the role of CMAs in error detection have not been reported until recently. Interpretation of error related activity is problematic because the occurrence of error causes the animals to get excited or frustrated, resulting in a number of confounding behavioral responses. Ito *et al.* (2003) avoided this problem by designing an oculomotor behavioral task. Monkeys were trained to perform an eye-movement countermanding task. On trials with no stop signal, the monkeys were rewarded following a saccade to a target. On trials with a stop signal, the monkeys earned reinforcement when the partially prepared saccade to the target was cancelled and fixation was maintained. They found error-related cells that were active with the mean latency of 180 ms after the initiation of incorrect saccades; however, they were not active during correct saccades or reward delivery.

Interestingly, Ito and coworkers were unable to locate cells monitoring conflict during performance of that behavioral task, despite the fact that they found such cells in the supplementary eye field (Stuphorn *et al.*, 2003). In a report by Nakamura *et al.* (2005), conflict-monitoring cells were not found in the CMAr, although the authors designed an oculomotor task in which conflict was evident in behavioral measures. How do these reports reconcile with a number of human studies reporting apparent conflict-related activity in the anterior cingulate (Botvinick *et al.*, 1999, 2001)? One explanation may be that these studies employed

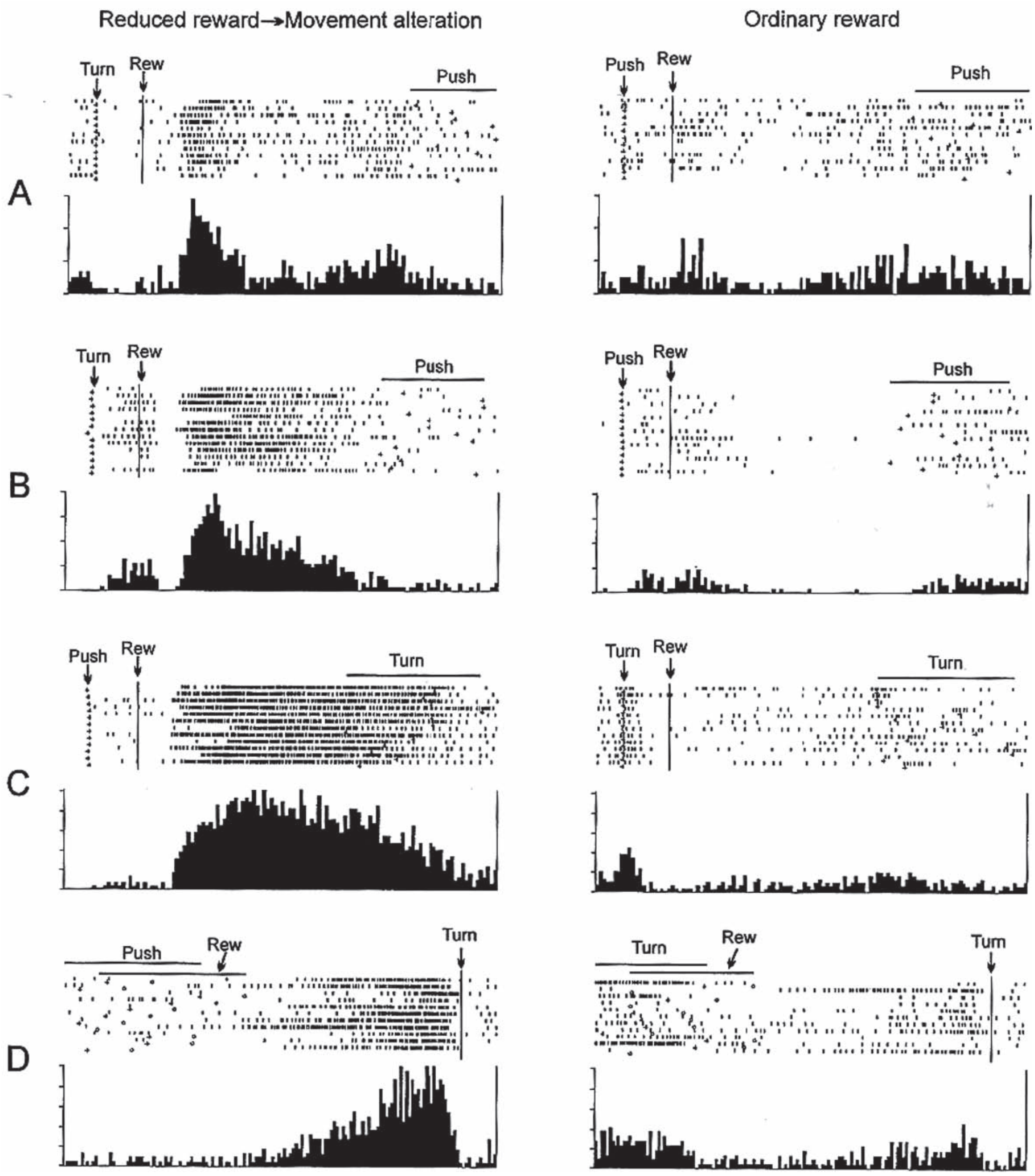

Fig. 5.20 Left: activity of four types of CMAr cells (A-D) showing increased discharges after the reward was reduced and before initiation of a new movement. Each raster is a single trial when the animal switched from Turn to Push (A and B) or Push to Turn (C and D) with 5-12 trials in between. (A) Short-lasting activity after the reward. (B) Long-lasting but decaying activity. (C) Continuous activity. (D) Activity that increases progressively before the next movement. Right: the same four neurons were not as active under the constant reward condition when subjects could not select an alternative movement. In the raster displays, dots represent individual discharges of a single cell, and small crosses denote the onset of movement. Histograms show discharges over 11 trials aligned at the onset of the reward and summed, except for (D), which is aligned at onset of next movement. A step in the ordinate denotes 10 spikes/sec; horizontal bar in the top right of a raster is the time of the next movement (From Shima *et al*., 1998).

oculomotor tasks. As mentioned in a previous section of this chapter, an oculomotor part of the CMA of monkeys is located in small regions rostral to the forelimb regions within CMAr and CMAc. It is possible that oculomotor CMA was not penetrated with electrodes in both studies. Another possibility may be that conflict monitoring may be achieved in the midcingulate cortex located outside of the CMAr. This possibility should be tested in future studies using subhuman primates where exact localization of relevant activity is possible. In the prefrontal cortex rostral to the CMAr, Matsumoto *et al.* (2003) found that cellular responses to color cues or delay activity appeared strongly with specific action-reward combinations. It remains possible that cells monitoring behavioral conflict may reside in the anterior cingulate region in the medial prefrontal cortex.

The role of CMAr in behavioral monitoring was already discussed above. A different aspect of behavioral monitoring was studied by Procyk *et al.* (2000). They examined activity of CMAr cells while monkeys performed a sequence-searching task reaching to three spatial targets in a correct order. They found that cells encoded the serial order of the sequence, that is, they were preferentially active during any one of first, second, or third reach to the target. This CMAr activity appears to be similar to that found in the pre-SMA (Shima and Tanji, 2000). Procyk and colleagues also found that activity of CMAr neurons differed depending on whether monkeys were searching for a correct sequence or the sequence of serial-reaching was already learned. This may indicate that the CMAr activity discriminates routine and non-routine sequential behavior.

Human Studies

There are an enormous number of studies concerning the functions of ACC and MCC in human subjects as discussed throughout this volume. In this section, we consider studies relevant to the regulation of motor behavior. For extensive considerations on the functions of ACC and MCC, see reviews with broad perspectives (Vogt *et al.*, 1992; Posner and Dehaene, 1994; Devinsky *et al.*, 1995; Picard and Strick, 1996, 2001; Posner and Rothbart, 1998; Carter *et al.*, 1999; Chapter 12).

Motor control functions

Although it is well known that electrical stimulation of human cingulate cortex elicits motor effects (Penfield and Welch, 1951), notably mimicking highly integrated types of motor behavior (Talairach *et al.*, 1973), the nature of its involvement in specific aspects of motor behavior is not well understood. Owing to the morphological complexity of the cingulate cortex and technical difficulties in approaching its subregions, even a simple question of the spatial localization of the CMAs has not been satisfactorily answered and not enough is known about their somatotopy. Paus *et al.* (1993) measured changes in regional cerebral blood flow during performance of manual, oculomotor, and verbal motor tasks. With motor tasks performed with a hand, two foci of activity increase were found close to the cingulate sulcus anterior to and posterior to the vertical plane that passes through the anterior commissure (Paus, 2001). Their oculomotor task yielded two activation foci: rostrally within the ACC just above the genu of the corpus callosum, and caudally in an area rostral to the forelimb focus. Further, their verbal task requiring the utterance of a pronoun yielded activations in the paracingulate gyrus and the pregenual aspect of the cingulate sulcus, with an additional focus just anterior to the caudal oculomotor focus. These findings suggest the existence of somatotopic organization for cingulate motor areas basically similar to that found in subhuman primates.

Contemporary studies focusing on deficits occurring after localized lesions in the cingulate cortex (Gaymard *et al.*, 1998; Paus *et al.*, 1991; Stephan *et al.*, 1999; Turken and Swick, 1999) lend support to this view of somatotopic organization. One possibility is that the caudal focus for the forelimb task corresponds to the caudal cingulate zone (CCZ) (Picard and Strick, 1996), and the rostral focus may reside in the rostral cingulate zone (RCZ). However, before the concept of somatotopy is firmly established in the human cingulate cortex, more studies are necessary. Hindlimb regions of the human CMAs remain to be found and the oculomotor representation area needs further clarification. Although the CCZ has been viewed as being involved in execution of simple motor tasks (Fink *et al.*, 1997; Petit *et al.*, 1998; Kwan *et al.*, 2000), no studies have attempted to investigate the contribution of human cingulate cortex to the control of parameters for motor outputs, such as direction or force. This seems to be related to the fact that deficits caused by cingulate lesions do not include apparent paralysis or motor ataxia.

Published reports point to the role of the midcingulate cortex in response initiation and maintaining a state of motor readiness (Turken and Swick, 1999; Hoshi *et al*, 2005). For the rostral activation foci, on the other hand, the magnitudes of activation varies greatly depending on the nature of the behavioral task, being greater during unlearned motor tasks, and more importantly, in the presence of stimulus-response conflict (Paus *et al.*, 1993). Human studies on the RCZ, therefore, are directed to explore the role of cingulate cortex in cognitive aspects of motor behavior.

Executive control, conflict/error detection, action-outcome monitoring

Accumulation of findings obtained with human brain imaging has led to a view that the MCC has a role in executive control of behavior, together with the lateral prefrontal cortex (Cohen *et al.*, 1997; Courtney *et al.*, 1998; Duncan and Owen, 2000). Behavioral conditions requiring working memory (Petit *et al.*, 1998) or requiring task interference or task switching (Botvinick *et al.*, 2001;Kerns *et al.*, 2004), activate both areas. A subsequent study, however, revealed that the lateral prefrontal cortex is more involved in maintaining the attentional demands of the behavioral task, while the MCC is primarily involved in evaluative processes (Macdonald *et al.*, 2000). It was also found that the MCC is more active when there is a change in response set or when there is conflict between possible responses, and less active when stimulus selection is at issue (Van Veen *et al.*, 2001; Rushworth *et al.*, 2002). Lesion studies have supported the notion that the MCC and the lateral prefrontal cortex mediate different aspects of behavioral tasks. MCC lesions appear to have little effect on working memory tasks (Murray *et al.*, 1989; Rushworth *et al.*, 2003) which is in contrast to prefrontal lesions which cause devastating impairment. Such lesions led to impairment of response preparation task with response conflict, but not of selective-attention or divided-attention task (Turken and Swick, 1999). Taken together, the MCC appears to be more involved in behavioral adjustments based on assessment of the individual's own actions or its outcome, rather than exerting top-down regulation of behavior in accordance with memorized information.

From a different perspective, the issue of error detection and conflict monitoring by the MCC has been a subject of great interest. An event related potential, termed the error-related negativity (ERN) was recorded when subjects committed error responses, with peaks between 80 and 130 ms thereafter (Falkenstein *et al.*, 1991). Subsequent study of combined ERP and fMRI measurements revealed an error associated activity centered on the anterior cingulate region (Ullsperger and Cramon, 2001). Although the ERN may reflect the detection of an error, an alternative interpretation suggests that the activity may reflect response conflict (Botvinik *et al.*, 2001). The response conflict account argues that errors tend to occur on trials when representations of more than one response are coactivated. Although the conflict hypothesis has been strengthened by the demonstration that the MCC is activated on high conflict trials even when the performance was correct (Carter *et al.*, 1998) and a report that the conflict-related activity predicts both greater prefrontal cortex activity and adjustments in behavior (Kerns *et al.*, 2004), the debate remains to be solved. A possibility is that the source of error- and conflict- detecting activity may reside in different portions in the MCC. Despite this remaining dispute, it seems reasonable to sum up relevant literatures as indicating that the MCC has a role in encoding the relationship between an action and the reinforcement value of its outcome. Two recent reports support this view. A recent fMRI study (Bush *et al.*, 2002; Chapter 12) found that dorsal anterior MCC (daMCC) is active when subjects performed reward-based decision making. The second study, which performed an analysis of single cells in the daMCC, pointed to its role in linking reward information with alternative actions (Williams *et al.*, 2004). In future studies, it seems essential to clarify regional differences of MCC activity participating in specific aspects of functions that cover broad ranges of cognitive action control (Rushworth *et al.*, 2004).

Summary of the Properties of the Cingulate Motor Areas

One of the most important contributions to understanding the functions of cingulate cortex over the past three decades has been demonstration of the location, connections, and functions of the CMAs. Interestingly, they are involved in more than skeletomotor functions and include cognitive processes involved in action reinforcement, anticipation, and relating expectations to outcomes as discussed by Bush in Chapter 12. Other chapters in this volume consider the CMAs in different structural, functional, and disease contexts. Each area is comprised of different cytoarchitectural areas as demonstrated in Chapter 3 and summarized in the table below and they are differentially regulated by dopaminergic afferents as discussed in Chapter 7 by Miller and colleagues. The prominent role that the CMAr has in reinforced behaviors discussed by Rolls in Chapter 8 and the high level of dopaminergic innervation to the CMAr but not the CMAc (Chapter 7) suggests a neurochemical basis for this important distinction between these areas that is reflected in reward coding mechanisms. Finally, the CMAc is a pivotal interface between dorsal area 23 and the posterior parietal cortex as discussed in Chapter 13 and it is involved early in mild cognitive impairment as detailed by Johnson and colleagues in Chapter 33.

The two CMAs do not perform the same functions and one of the main outcomes of this systematic review of their circuitry and functions is a clear understanding of the differences between them. Since these differences are pivotal to many of the functions and diseases evaluated throughout the present volume, Table 1 provides a summary of the key differences between the CMAr and CMAc. Many models of altered brain activity in

TABLE 5.1 Properties of Rostral and Caudal Cingulate Motor Areas

	CMAr (M3)	CMAc (M4)
Cytoarchitecture	Head, area 24c; body, area a24c´	Head, area p24c´; body, areas 24d, 23c
Frontal connections unique to CMAr	Areas 10, 14, 6V, ProM	Subset of those with CMAr
	Cingulate areas 25, 32	
Motor parameters	Action-reinforce associations	Visual and spatial location
	Modest selectivity	Tuning for force and direction
Onset latency to movement	Long and variable	Short
Optimal activation	Self-initiated movements	Passive (signal-triggered) movement
	Temporal monitoring of events	Direction tuning
	Non-routine movements	Target acquisition
	Reward monitoring and expectancy	Orienting movements in sensory space
	Reinforcing reward associations	
Dopamine innervation	High	Low-moderate

diseases such as obsessive-compulsive disorder and attention deficit/hyperactivity disorder will need to consider the differential contributions of the two cingulate motor areas to primate brain function.

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