11

The Role of Cat Cingulate Cortex in Sensorimotor Integration

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The cingulate gyrus, encompassing Brodmann's areas 23, 24, 29, 30, and 31, is a major division of the cerebral cortical mantle found in all mammals including humans. As a large cortical district conserved across mammalian evolution, the cingulate gyrus might be expected to serve a clearly identifiable function, but the behavioral significance of cingulate cortex remains unclear. Theories of cingulate function that have been put forward rest, in large part, on indirect evidence, which includes the "paralimbic" connectional pattern whereby cingulate cortex is linked both to structures of the limbic system and to neocortical areas (Papez, 1937; MacLean, 1949; Mesulam, 1981; Pandya and Seltzer, 1982; Pandya and Yeterian, 1985). It is thought that this connectional pattern indicates that cingulate cortex must subserve some process combining sensorimotor features that are dependent on neocortical connections, with mnemonic or visceral features that are dependent on limbic connections. Functions proposed on this basis have included emotion and motivation (MacLean, 1949; Papez, 1937), spatial memory (Goldberg, 1984; Mishkin and Bachevalier, 1986; Pandya and Yeterian, 1984), attention (Mesulam, 1981; Pandya and Yeterian, 1984), registration of errors (Brooks, 1986), and modulation of behavior in accord with environmental context (Gabriel et al., 1988).

This chapter summarizes connectional and physiological studies in the cat that have afforded insight into the functional nature of cingulate cortex. Neuroanatomical tracer studies have demonstrated that sensory, motor, and limbic connections undergo marked and systematic regional variation across the cingulate gyrus. Single-neuron recording studies, carried out in alert cats trained to perform sensorimotor tasks for reward, have shown that cingulate neurons carry signals clearly related to certain sensory and motor events. These results, in conjunction with other findings, suggest that the two major divisions of cingulate cortex carry out specialized functions, with posterior cingulate cortex dedicated to processes underlying spatial memory and anterior cingulate cortex dedicated to the initiation of behavior. They also indicate that within each area there is a previously unsuspected pattern of regional specialization whereby information concerning somatosensory, visual, and suprasensory events is processed in discrete zones.

Anatomical Organization of Posterior Cingulate Cortex

Location, Extent, and Traditional Divisions

Cingulate cortex of cats is a distinct region identifiable, as in other species, by cytoar-

Neurobiology of Cingulate Cortex and Limbic Thalamus: A Comprehensive Handbook
Brent A. Vogt and Michael Gabriel, Editors

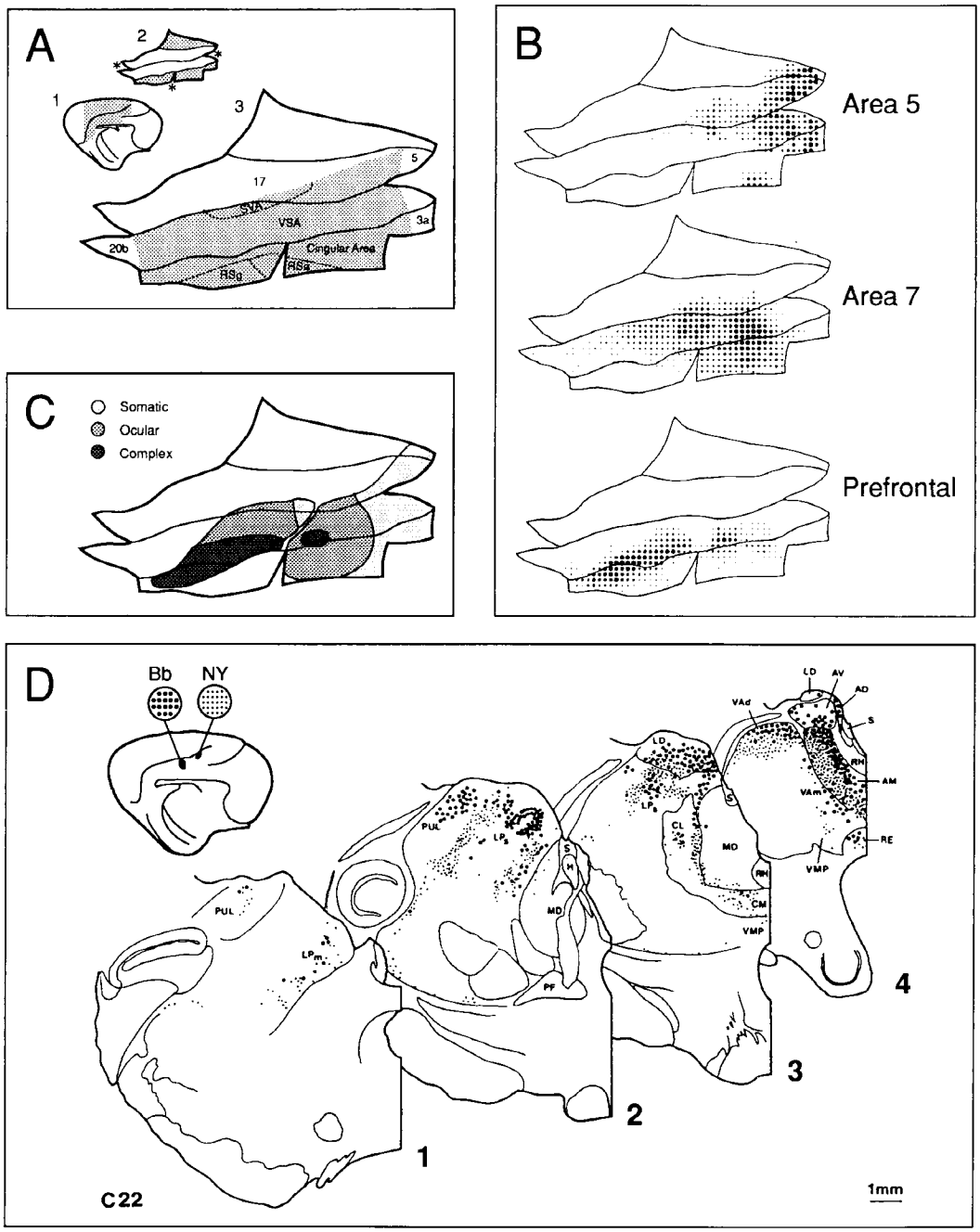

FIGURE 11.1. Anatomical organization of posterior cingulate cortex (CGp) in the cat. *A*. Location, extent, and subdivisions of CGp are indicated on a flattened map of medial-face cortex. In the medial view of the left hemisphere (1) shading indicates cortex included in the flattened map. In the small flattened map (2) shading indicates cortex initially exposed on gyral faces and nonshading indicates cortex initially hidden in the splenial sulcus; asterisks indicate cuts made in the cortical sheet to permit flattening. In the large flattened map (3) CGp is indicated by shading and traditional subdivisions are labeled. These include the cingular area, agranular retrosplenial (RSa) cortex, granular retrosplenial (RSg) cortex, ventral splenial area (VSA), and splenial visual area (SVA). Bounding areas include visual cortex (areas 17 and 20b) and somatosensory cortex (areas 3a and 5).

chitecture and by its input from the anterior complex of thalamic nuclei (Robertson and Kaitz, 1981; Rose and Woolsey, 1948). Within the cingulate region, there are two major divisions, the posterior and anterior cingulate areas, referred to hereafter as CGp and CGa, respectively. These regions are easily distinguished by cytoarchitecture—CGp possesses a granular layer IV, whereas CGa does not—and by thalamic connectivity—all three anterior nuclei project to CGp, whereas only the anteromedial nucleus projects to CGa (Robertson and Kaitz, 1981; Rose and Woolsey, 1948).

The posterior cingulate area extends across the ventral bank of the splenial sulcus and the adjacent parasplenial gyrus. The location of CGp is indicated on an a flattened map of medial-face cortex in Figure 11.1*A*. In Figure 11.1*A*.1, there is a medial view of the left hemisphere in which the extent of cortex included in the flattened map is indicated by shading. Figure 11.1*A*.2 shows a flattened map of cortex. In this map, cortex visible on gyral surfaces prior to flattening is indicated by shading, and cortex formerly hidden within the splenial sulcus is unshaded. The flattened map encompasses (from top to bottom) the medial face of the marginal gyrus, the dorsal and ventral banks of the splenial sulcus, and the parasplenial gyrus. In Figure 11.1*A*.3, CGp is indicated by shading and adjoins visual cortical areas 17 and 20b as well as somatosensory areas 3a and 5. Other adjoining structures including the parahippocampal cortex, anterior cingulate cortex, and the corpus callosum are not shown because the edges of the map were chosen to coincide with the lines where these areas abut on CGp.

Five subdivisions have been distinguished within CGp: the granular retrosplenial area, (RSg), the dysgranular retrosplenial area, (RSa), the cingular area, the ventral splenial area (VSA), and the splenial visual area (SVA) (Fig. 11.1*A*.3). The history of this system of parcellation is complex. Rose and Woolsey (1948) defined two divisions of retrosplenial cortex: granular area RSg, comparatively primitive in cytoarchitecture, and agranular area RSa, exhibiting a more differentiated laminar pattern. They delimited a third cortical division, the cingular area, which is located dorsal and anterior to the retrosplenial areas on the exposed face of the cingulate gyrus. They did not describe or parcellate cortex within the splenial sulcus, although they identified it as belonging to the posterior cingulate region. Subsequently, a small area close to the sulcal fundus, the splenial visual area, (SVA), was defined by Kalia and Whitteridge (1973) on the basis of its visual responsiveness in anesthetized cats. Graybiel and Berson (1981) initiated the practice of referring to the remainder of

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B. Distribution of neurons labeled by retrograde transport from somatosensory cortex (area 5), visual cortex (area 7), and cortex lacking simple sensory or motor functions (medial prefrontal area). In each map, the size of each dot corresponds to the percentage of cases in which neurons were present at the corresponding location.

C. The arrangement of somatic, ocular, and complex subregions within CGp as inferred from results including data in part *B* of this figure.

D. Distribution of thalamic neurons labeled by retrograde transport from two tracer injections in CGp. In general, neurons labeled by transport from the more caudal cortical tracer deposit (large dots) are located at more dorsal levels in the anteromedial (AM) nucleus, the dorsal division of the ventral anterior (VAd) nucleus, the laterodorsal (LD) nucleus, and the shell zone of the lateroposterior (LPs) nucleus. Sections 1–4 are arranged in caudal-to-rostral order. Other abbreviations: Anterodorsal nucleus, AD; anteroventral nucleus, AV; bisbenzimide, Bb; centrolateral nucleus, CL; centromedial nucleus, CM; lateral habenula, H; lateroposterior nucleus, medial division, LPm; mediodorsal nucleus, MD; Nuclear Yellow, NY; parafascicular nucleus, PF; pulvinar, PUL; reuniens nucleus, RE; rhomboid nucleus, RH; stria medullaris thalami, S; ventroanterior nucleus, medial division, VAm; principal ventromedial nucleus, VMP.

cingulate cortex in the splenial sulcus as the ventral splenial area (VSA).

The internal divisions of feline cingulate cortex, although designated with an unusual and confusing nomenclature, are fundamentally similar to those seen in other species where subdivisions are designated by Brodmann's numbering system (Vogt, 1985; Vogt et al., 1987; Chapter 1 of this volume). On cytoarchitectural and connectional grounds, Rose and Woolsey (1948) speculated that the two retrosplenial areas and the cingular area, considered collectively, are equivalent to areas 29 and 30 in other species, whereas cortex in the ventral bank of the splenial sulcus is equivalent to areas 23 and 31. Regardless of the precise nature of area-to-area correspondences, it is clear that the feline areas form a sequence, running from retrosplenial to cingular to splenial cortex, in which cytoarchitectural differentiation becomes progressively greater just as in the sequence formed by areas 29, 30, 23 and 31 of other species.

Subregional Differences in Cortical Input

Transcortical afferents of CGp derive from a diverse set of late-stage sensory areas, association areas, and premotor areas (Olson and Musil, 1992a). Dorsal prefrontal cortex is the source of an extremely strong projection pathway, containing approximately one-third of all cortical neurons that innervate CGp. Anterior cingulate cortex also is a source of robust input, harboring, despite its comparatively restricted volume, another one-fifth of afferent cortical neurons. Areas with known oculomotor functions including parietal area 7 and the frontal eye fields are a significant source of afferents. So, too, are high-order visual areas 19, 20, and 21 and the visual belt of the posterior ectosylvian gyrus. Finally, parahippocampal cortices including the entorhinal and perirhinal divisions give rise to an input pathway of moderate strength. Quantitative results supporting these conclusions are summarized in Table 11.1.

This table presents data collected by counting retrogradely labeled neurons in six cases. Counts were carried out by scanning 50 μm sections at intervals of 600 μm. For each deposit, the number of labeled neurons in a given area is expressed as a percentage of the total number of cortical neurons labeled by transport from that injection. Labeled neurons within CGp were not counted following tracer injections in CGp, and labeled neurons within CGa were not counted following tracer deposits in CGa.

Many features of transcortical connectivity in the cat mirror connectivity patterns in other experimental species, as discussed in

TABLE 11.1. Percentage of labeled cortical neurons in each area following six retrograde tracer deposits in cingulate cortex

	Posterior Cingulate Cortex			Anterior Cingulate Cortex		
Cortical area	Rostral	Middle	Caudal	Dorsal	Middle	Ventral
Somatosensory	12	0	0	10	0	0
Motor/premotor	3	0	0	8	0	1
Frontal eye fields	14	13	0	15	9	10
Area 7	11	30	0	1	0	0
Visual belt	11	4	5	0	1	0
19/20/21	3	4	2	0	2	0
Cingulate	14	10	30	34	56	42
Prefrontal	19	31	49	18	16	43
Parahippocampal	9	5	12	6	12	3
Insular	2	2	1	9	3	2
Auditory	1	0	0	0	0	0

Chapters 7 and 8 of this volume. Patterns notable for their consistency across species include the dominance of prefrontal and anterior cingulate afferents. However, some noteworthy differences exist. With respect to afferents from visual cortex, the cat appears to be intermediate between the rat, in which even primary visual cortex projects to the posterior cingulate cortex, and the monkey, in which no direct projection arises from any retinotopically organized visual area. With respect to input from the subicular sector of the hippocampal formation, the cat and monkey, in which afferents are very weak, differ markedly from the rat, in which there is a strong subicular projection. Other aspects of cross-species differentiation have been considered elsewhere (Olson and Musil, 1992a).

The nature of transcortical inputs varies markedly with respect to location in CGp (Olson and Musil, 1992a). At the level of first approximation, cortical afferent connections can be said to change with respect to the rostrocaudal axis in CGp, but not with respect to the mediolateral axis. On the basis of rostrocaudal transitions in connectivity, at least three subregions of CGp can be defined: a rostral zone with input from somesthetic or somatomotor areas, an intermediate zone with input from visual and oculomotor areas, and a caudal zone lacking input from cortical areas with well-defined sensory or motor functions. At very rostral sites with CGp, afferents originate from somatomotor area 6c of the frontal lobe and somatosensory area 5 of the parietal region. This suggests that rostral CGp is specialized for processing cutaneous or proprioceptive information or controlling somatomotor output. At intermediate levels in CGp, afferents from visual and oculomotor areas are most apparent. Projections to this zone arise from area 7, the frontal eye fields, the granular insula, and the posterior ectosylvian gyrus. Neurons in area 7p (Olson, 1988; Straschill and Schick, 1974) and the frontal eye fields (Guitton and Mandl, 1978) are activated in conjunction with eye movements. Neurons in area 7p (Olson, 1988), the frontal eye fields (Weyand et al., 1990), the granular insula (Benedek et al., 1986), and the posterior ectosylvian gyrus (Updyke, 1986; Bowman et al., 1988) respond strongly to visual stimuli and are probably vision-dominated but, in some instances, respond also to stimuli in nonvisual sensory modalities. Afferents also arise from well-characterized unimodal retinotopic extrastriate visual areas including area 20 and several divisions of lateral suprasylvian cortex (Tusa et al., 1981). At very caudal sites in CGp, projections from sensory and motor areas are minor or absent and inputs arise instead from ventral prefrontal cortex and a temporal pole area at the base of the posterior ectosylvian gyrus.

Subregional Differences in Thalamic Input

Thalamic projections to CGp arise from a large and diverse set of thalamic nuclei. As shown in Figure 11.1*D*, these include the anterior complex (anterodorsal, AD; anteroventral, AV; anteromedial, AM), the nucleus reuniens (Re), restricted portions of the ventral complex (dorsal and medial divisions of ventral anterior, VAd and VAm; posterior division of ventral medial, VMp), discrete sectors of the lateral complex (laterodorsal, LD; shell and medial divisions of lateroposterior, LPs and LPm), and the rostral intralaminar nuclei (central medial; paracentral; centrolateral, CL). These structures correspond with minor exceptions to nuclei innervating posterior cingulate cortex in other species (Olson and Musil, 1992a; Chapters 2 and 3 of this volume).

It has long been known that thalamic connections vary with respect to the rostrocaudal extent of CGp (Niimi, 1978; Niimi et al., 1978, 1983; Fujii, 1983; Robertson and Kaitz, 1981; Yasui et al., 1988), but the overall pattern of thalamocortical topography has not been clear. Experiments in which deposits of distinguishable fluorescent retrograde tracers were placed at discrete loci in CGp have facilitated the analysis of to-

pography by making it possible to compare in the same case the locations of thalamic neurons projecting to different zones in CGp (Olson and Musil, 1992a). The general finding is that projections from many thalamic nuclei are organized topographically and that connectional topography obeys a simple rule whereby a particular axis in each thalamic nucleus is mapped onto the rostrocaudal axis in CGp. This point is supported with illustrative data in Figure 11.1*D*. This represents a case in which two tracers were injected into the parasplenial gyrus—Nuclear Yellow (NY) at a comparatively rostral site, and bisbenzimide (Bb) at a comparatively caudal site. Neurons labeled by retrograde transport are indicated by stippling in sections through the thalamus numbered in order from posterior to anterior levels. Neurons labeled by transport from the more caudal cortical site (coarse stippling) occupy a comparatively dorsal level in the AM, VAd, LD, and LPs nuclei. It was a general rule that as injections were placed at progressively more caudal levels in CGp, the zone of labeling in each of these nuclei shifted to a more dorsal level. Other thalamic nuclei including the Re, AD, AV, CL, and LPm project to CGp without obvious topography.

The results obtained in these experiments are of interest because they suggest that several thalamic nuclei projecting to CGp may contain functional maps equivalent to that found in CGp itself. For example, it can be argued with reasonable assurance that ventral, intermediate, and dorsal populations of neurons in LD carry signals related to somatosensory and somatomotor processes, visual and oculomotor processes, and complex processes, respectively. In light of the paucity of current information concerning the functions of these nuclei, such a strong prediction is welcome.

Delineation of Somatic, Ocular, and Complex Subregions

The approach of placing tracer deposits at different loci in CGp, as described earlier, established that subregions with somatic, ocular, and complex connections are situated at rostral, intermediate, and caudal levels of CGp, respectively. To demonstrate the precise extent and location of each subregion required a different approach in which tracer deposits were placed in distant cortical areas with known functions and the distribution of labeled neurons in CGp was analyzed. This analysis was based on data obtained in a lengthy series of experiments in which retrograde tracers were placed in distant cortical areas to which CGp projects (Olson and Lawler, 1987; Olson and Jeffers, 1987; Bowman and Olson, 1988; Musil and Olson, 1988a,b, 1991). In every case of that series, neurons labeled by retrograde transport from the injected area were charted onto frontal sections through CGp. Then, by an objective procedure, the labeled neurons were projected onto a standard flattened map of CGp. All the flattened maps were entered into a computerized database, and, for each distant area, a composite map was generated representing the distribution within CGp of neurons projecting to that area.

Three of the resulting maps are shown in Figure 11.1*B*. The top map is based on 9 cases in which the tracer was deposited in parietal somatosensory area 5; the central map is based on 12 cases in which the tracer was deposited in parietal visual area 7; the bottom map is based on 10 cases in which the tracer was deposited in medial prefrontal cortex at levels ventral to the medial frontal eye field. In each map, the size of each dot corresponds to the percentage of cases in which labeled neurons were present at the corresponding location. The results confirm strikingly the overall trend noted in studies of afferent connectivity. They add to previous results by permitting precise delineation of connectionally distinct subregions within CGp. We have indicated the arrangement of somatic, ocular, and complex subregions, as inferred from this study, in Figure 11.1*C*. Following DeLong et al. (1984), we apply the term *complex* to dorsal prefrontal

and related areas lacking clearly defined sensory, motor, or limbic functions.

Comment on Limbic Connectivity

Cingulate cortex has been regarded for many years as a close affiliate of the limbic system (Papez, 1937; MacLean, 1949). This view captures an obvious truth insofar as the cingulate gyrus is the target of an ascending mamillothalamocortical pathway presumed to carry signals originating in the hippocampus. However, the general notion of an affiliation between the cingulate gyrus and the limbic system has also been conceived in a broader sense as applying to transcortical pathways (Pandya and Yeterian, 1985). The notion that CGp receives dominant or unusually strong transcortical inputs from limbic areas can be tested by quantitative analysis of afferent pathway strength (Table 11.1).

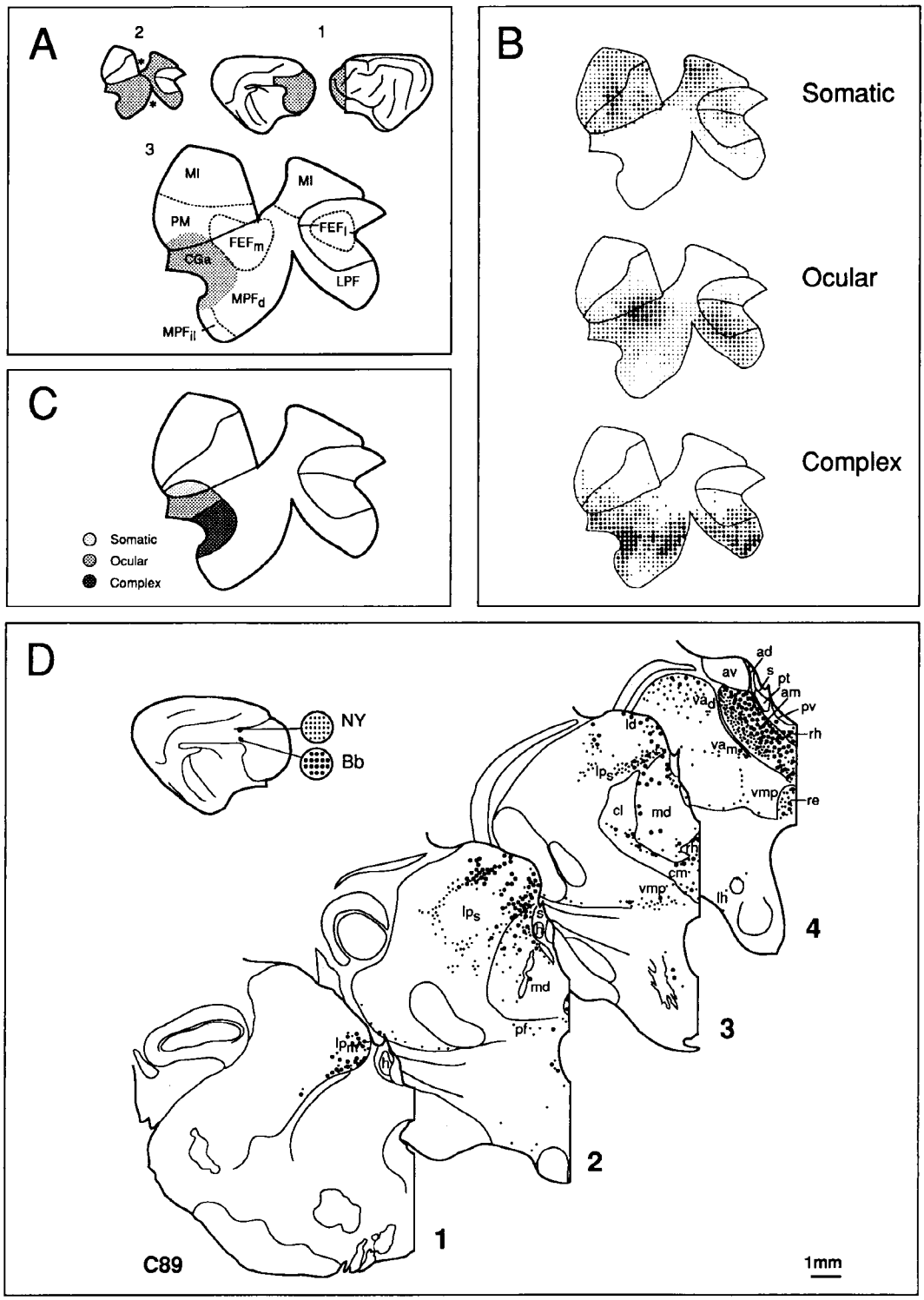
The general conclusion arising from this analysis is that neocortical association areas, not limbic areas, are the dominant source of input to CGp in the cat. Only around 9% of cortical neurons projecting to CGp are in cortical areas considered to be part of the limbic system, notably subicular, entorhinal, perirhinal, agranular insula, and prepiriform cortices. Cortical limbic connections of CGp are comparable in strength to those of dorsal prefrontal cortex and are much weaker than those of the infralimbic area, a ventral prefrontal area genuinely dominated by limbic afferents (Musil and Olson, 1988b). Thus the posterior cingulate gyrus, while placed under limbic influence via transcortical pathways, is neither dominated by limbic input nor distinguished by strength of limbic input from other cortical association areas.

Limbic projections impinging on CGp are restricted not only in strength but also in origin. They derive predominantly from structures selectively related to the hippocampal formation and thought to be involved in memory (i.e., the anterior nuclei and parahippocampal gyrus). Projections from divisions of the limbic system thought to contribute to motivation and emotion including the hypothalamus, amygdala, insular cortex, and orbitofrontal cortex are very weak or absent. This fact carries import with respect to possible functions of CGp and will be discussed in a later section.

Anatomical Organization of Anterior Cingulate Cortex

Location and Extent

The CGa of the cat consists of cortex overlying the anterior fourth of the corpus callosum. The feline CGa is thought to be a homologue of anterior cingulate area 24 in primates and rodents on the basis of its hemispheric location, agranular cytoarchitecture (Rose and Woolsey, 1948), and strong afferents from the thalamic anteromedial nucleus (Rose and Woolsey, 1948; Niimi, 1978; Niimi et al., 1978; Robertson and Kaitz, 1981; Musil and Olson, 1988a). Figure 11.2*A* depicts CGa with respect to a flattened map of frontal cortex of the cat. The shaded area of Figure 11.2*A*.1 shows the extent of cortex included in the flattened map on medial and lateral views of the left hemisphere. In Figure 11.2*A*.2, there is a flattened map in which cortex visible on gyral surfaces prior to flattening is indicated by shading and cortex formerly hidden within the cruciate and presylvian sulci is unshaded. The flattened map encompasses medial (left) and lateral (right) aspects of the frontal lobe. In Figure 11.2*A*.3 the CGa is shown with shading in relation to other frontal areas including primary motor cortex, premotor cortex, the medial and lateral frontal eye fields, and medial, lateral, and infralimbic divisions of prefrontal cortex. Criteria for delineating these areas have been described previously (Olson and Jeffers, 1987; Musil and Olson, 1988a,b, 1991). The CGa, infralimbic area, and "prelimbic" area adjoining CGa rostrally have sometimes been grouped together under the heading of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"anterior limbic" cortex (Rose and Woolsey, 1948), but we include the prelimbic and infralimbic areas in prefrontal cortex rather than cingulate cortex (Musil and Olson, 1988a,b, 1991).

Subregional Differences in Cortical Input

Cortical projections to CGa derive in descending order of strength from the following: CGp, prefrontal cortex, motor areas 4 and 6, parahippocampal cortex (entorhinal, perirhinal, postsubicular, parasubicular, and subicular areas), insular cortex, somesthetic cortex (areas 5 and SIV) and visual cortex (areas 7 and 20 and the posterior ectosylvian visual belt) (Musil and Olson, 1988a). The overall pattern of afferent cortical connectivity is remarkably similar to that of CGp with one major exception. Visual areas of the posterior cerebral hemisphere, which contain approximately 30% of cortical neurons projecting to CGp, contain only a small percentage of cortical neurons innervating CGa (Musil and Olson, 1988a; Olson and Musil, 1992a).

The transcortical afferent connections of CGa in the cat correspond rather closely to connections observed in other species (Musil and Olson, 1988a; Chapters 7 and 8 of this volume). However a few clear differences may be noted. In the monkey, as opposed to the cat, CGa receives a significant projection from area 7 and does not receive a projection from the frontal eye fields. In the rat, as opposed to the cat, few projections derive from areas outside the frontal lobe and the posterior cingulate gyrus with the notable exception of direct pathways from visual areas 17 and 18b.

The transcortical afferent connections of CGa, like thalamic afferent connections, undergo crude but unmistakable gradation with respect to the dorsoventral axis (Musil and Olson, 1988a). There is a tendency for connections to shift from a somatic pattern through an ocular pattern to a complex pattern along an axis running from the dorsal to the ventral border of CGa. This trend is parallel to the one seen in CGp but is

FIGURE 11.2. Anatomical organization of anterior cingulate cortex (CGa) in the cat. *A.* Location, extent, and subdivisions of CGa are indicated on a flattened map of frontal cortex. In the medial and lateral views of the left hemisphere (1) shading indicates cortex included in the flattened map. In the small flattened map (2) shading indicates cortex initially exposed on gyral faces and nonshading indicates cortex initially hidden in the cruciate and presylvian sulci; asterisks indicate cuts made in the cortical sheet to permit flattening. In the large flattened map (3) CGa is indicated by shading and adjoining areas are labeled. These include the infralimbic division of medial prefrontal (MPF_{il}) cortex, the dorsal division of medial prefrontal (MPF_d) cortex, the medial frontal eye field (FEF_m), and premotor (PM) cortex. Nonbordering frontal areas include lateral prefrontal (LPF) cortex, the lateral frontal eye field (FEF_l), and primary motor (MI) cortex.

B. Distribution of neurons labeled by retrograde transport from somatic, ocular, and complex divisions of CGp (as depicted in Figure 11.1.*C*). In each map, the size of each dot corresponds to the percentage of cases in which labeled neurons were present at the corresponding location.

C. The arrangement of somatic, ocular, and complex subregions within CGp as inferred from results including data in part *B* of this figure.

D. Distribution of thalamic neurons labeled by retrograde transport from two tracer injections in CGa. In general, neurons labeled by transport from the more ventral cortical tracer deposit (large dots) are located at more dorsal levels in the anteromedial (AM) nucleus, the dorsal division of the ventral anterior (VAd) nucleus, the laterodorsal (LD) nucleus, and the shell zone of the lateroposterior (LP_s) nucleus. Other abbreviations are defined in the legend to Figure 11.1D with the following exceptions: parataenial nucleus, pt; paraventricular nucleus, pv. Sections 1–4 are arranged in caudal-to-rostral order.

less clear because connections to visual and somatosensory areas in the posterior hemisphere are vanishingly weak in CGa. At successively more ventral levels in CGa, frontal lobe afferents derive from premotor cortex, frontal eye fields, and prefrontal cortex, respectively. Likewise, at successively more ventral sites, posterior cingulate afferents derive from somatic, ocular, and complex subregions of CGp. There is a topographic pattern in projections from the granular insula as well. Projections to the most dorsal part of CGa derive from a very anterior and dorsal sector of the granular insula including somatosensory area SIV (Clemo and Stein, 1983).

Subregional Differences in Thalamic Input

Ascending projections to CGa originate in the same broad swath of thalamic tissue that gives rise to innervation of CGp (Niimi, 1978; Niimi et al., 1978, 1983; Fujii, 1983; Robertson and Kaitz, 1981; Yasui et al., 1988; Musil and Olson, 1988a). Afferent projections originate in AM, LP, VA, Re, MD, and LD nuclei and rostral intralaminar complex, as shown in Figure 11.2*D*. Only two nuclei projecting to CGp do not send comparable projections to CGa; these are the AV and AD. Minor ascending projections to CGa arise in the paraventricular (Pv), parataenial (Pt), parafascicular (Pf), and subparafascicular thalamic nuclei. These nuclei correspond very closely to nuclei innervating CGa in the rat and monkey, as discussed previously (Musil and Olson, 1988a).

The thalamic afferents of CGa have been analyzed by use of multiple distinguishable fluorescent retrograde tracers in order to resolve details of pathway topography and thereby throw light on the pattern of internal organization of CGa (Musil and Olson, 1988a). The results indicate that thalamic inputs to CGa are organized topographically with respect to the dorsoventral axis in CGa. This point is supported by data in Figure 11.2*D*. In the illustrated case, distinguishable tracers were deposited at two sites in CGa, NY at a comparatively dorsal site and Bb at a comparatively ventral site. Neurons labeled by retrograde transport are indicated by stippling in sections through the thalamus numbered in order from posterior to anterior levels. Neurons labeled by transport from the more ventral cortical site (coarse stippling) occupy a relatively dorsal level in AM, VAd, LD, and LPs. In general, tracer deposited at progressively more ventral levels in CGp was transported to progressively more dorsal levels in these nuclei.

This result has particular significance in that it suggests a system of correspondence between CGa and CGp. Each thalamic nucleus that projects topographically to one area also projects topographically to the other, and, in each nucleus, the pattern is such that neurons innervating ventral (vs. dorsal) CGa are intermingled with neurons innervating caudal (vs. rostral) CGp. This fact should be apparent on comparison of the results illustrated in Figures 11.1*D* and 11.2*D*.

Delineation of Somatic, Ocular, and Complex Subregions

It should be apparent from the preceding description of afferent connections that CGa probably contains somatic, ocular, and complex subregions. The presence of such subregions has been supported by extensive analysis of labeling in CGa produced by retrograde transport of tracer from injection sites in areas with known functions. Neurons projecting to somatosensory and skeletomotor areas, to visual and oculomotor areas, and to complex areas are located at progressively more ventral levels in CGa as predicted from the analysis of cortical afferents. This point is supported by maps representing the distribution within the frontal lobe of neurons projecting to the somatic, ocular, and complex subregions of CGp, as shown in Figure 11.2*B*. The maps are based on four injections in the somatic subregion

of CGp, six injections in the ocular subregion of CGp, and five injections in the complex subregion of CGp (Olson and Musil, 1992a). The maps were prepared in the manner described earlier. Thus, the pattern of subregional specialization in CGa is directly comparable to that observed in CGp with the sole difference that a trend occurring along the dorsoventral axis in CGa occurs instead along the rostrocaudal axis in CGp.

Comment on Limbic Connectivity

Projections originating in limbic cortical areas are no stronger in CGa than in CGp, as established by counts of neurons labeled throughout the cerebral hemisphere by transport from deposits of retrograde tracer in CGa (Musil and Olson, 1988a). Representative results are summarized in Table 11.1. Cortical areas with obvious limbic affiliations, including the subiculum, entorhinal cortex, perirhinal cortex, agranular insula, and prepiriform cortex, contain only around 8% of the cortical neurons projecting to CGa.

Single-Neuron Responses in Posterior Cingulate Cortex of the Alert Cat

Visual and Oculomotor Paradigm

To record from neurons in CGp while cats make visually guided eye movements is logical in light of the connectional patterns of CGp. Nearly half of the cortical neurons projecting to area 7 are located in the ocular subregion of CGp, and around a quarter of cortical neurons projecting to the ocular subregion of CGp are in area 7 (Olson and Lawler, 1987; Olson and Musil, 1992a). Neurons in area 7 fire vigorously in response to visual stimulation and before and during saccadic eye movements (Straschill and Schick, 1974; Komatsu et al., 1983; Olson, 1988, 1991). Accordingly, it is to be expected that neurons in the ocular division of CGp carry visual and oculomotor signals. The presence and nature of these signals have now been analyzed in studies of alert cats (Olson and Musil, 1992b).

Cats were equipped with implanted head-restraint devices and habituated to light body restraint by a nylon mesh vest. They were rewarded with beef puree for facing a perimeter and making eye movements to visual stimuli presented under computer control. The eye-movement targets were arrays of light-emitting diodes arranged at 10° intervals along the horizontal perimeter. Eye movements were monitored by the scleral search-coil method (Judge et al., 1980; Remmel, 1984). Neuronal activity was monitored through varnish-coated tungsten microelectrodes inserted into the brain at the start of each day's session through a sterile chamber. Neuronal and eye position data, together with time-markers for stimulus events, were stored on a disk with 10 msec resolution, and task-related firing was assessed off-line by appropriate statistical measures.

By use of this approach, task-related activity was assessed in 198 single neurons of CGp of three cats (Olson and Musil, 1992b). Determining when the microelectrode was in CGp was comparatively straightforward, because a regular sequence of events occurred during the vertical downward traverse through overlying cortex. First, visually responsive neurons in primary visual area 17 were encountered. Then there was electrical silence as the tip of the electrode crossed the fissure of the splenial sulcus. Next, neural activity was again encountered as the tip of the electrode entered cingulate cortex. To mark each recording site was not possible because traces of marking microlesions disappear over the course of weeks and months. The tracks left by the shaft of the microelectrode, however, often remained visible until the brain was processed. Furthermore, at selected sites encountered toward the close of the experimental period, marking microlesions were placed. Figure 11.3*A* is a composite diagram based on all three brains with histologically reconstructed microelectrode

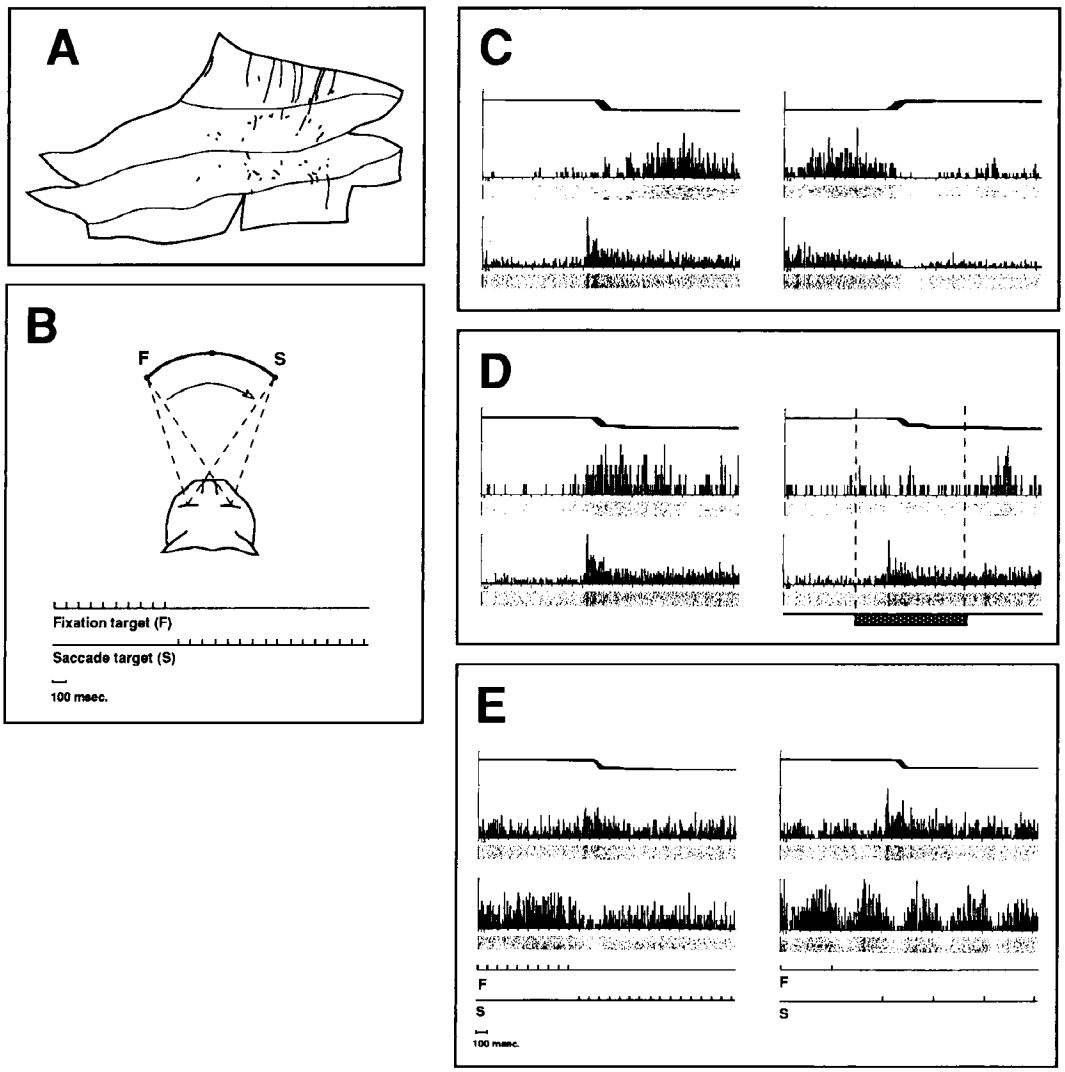

FIGURE 11.3. Functional properties of single neurons in posterior cingulate cortex of alert cats trained to perform visually guided eye movements. *A*. Electrode tracks recovered on histological analysis from three brains used in this study are projected onto a flattened map of CGp (cf. Fig. 11.1*A–C*).

B. In the standard saccade task, cats faced a perimeter containing light-emitting diode arrays 10° to the right and 10° to the left of the sagittal midline. At the outset of each trial, one array began flashing and the cats were required to fixate it for one second. Then the opposite array began flashing, and the cats were required to execute a saccadic eye movement to the second array and maintain fixation on it until reward delivery. The flashes were of 10 msec duration and were presented at a rate of 10 per second (tick marks on traces at bottom).

C. It is common for neurons in CGp to fire differentially according to the angle of the eye in the orbit. The histograms in the top and bottom rows represent the mean rate of firing of two neurons in CGp studied in the context of the standard saccade task. In both neurons, firing was greatest when the cat's gaze was directed to the right. This was true both in trials when rightward gaze followed the operant saccade (left column) and in trials when rightward gaze preceded the operant saccade (right column). The display at the top of each column represents the horizontal angle of gaze as a function of time (rightward down; traces from successive trials are superimposed). In the dot raster display underlying each histogram, each line of dots represents a trial and each dot represents an action potential.

tracks projected onto a standard flattened map of midline posterior cortex (cf. Fig. 11.1*A*). The traces mark the trajectory of the electrode as it penetrated area 17 on the marginal gyrus and in the dorsal bank of the splenial sulcus and traveled into cingulate cortex in the ventral bank of the sulcus. At anterior levels, cingulate neurons were also encountered in the dorsal bank of the sulcus.

To accomplish the initial characterization of each neuron, its activity was monitored while the cats performed a routine task involving rightward and leftward eye movements. This "standard" test, as presented in Figure 11.3*B*, utilized two targets placed at locations 10° left of the center and 10° right of the center on the perimeter. Each target, when activated, was illuminated in 10 msec flashes at regular 100 msec intervals. At the outset of each trial, one target—F: the fixation target—was presented, and the cats were required to attain fixation of it within 500 msec, whereupon it was extinguished for 200 msec and then turned back on. At the instant of reonset of F, the trial proper began, together with data collection. Target F remained on for 1 sec and then was extinguished and replaced by the second target—S: The saccade target—which remained on for an additional 1.5 sec. Cats were required to maintain fixation of target F until its offset. Cats then were to transfer their gaze to target S and maintain fixation of the latter until its offset, at which point the reward was delivered if the task had been correctly performed. Cats were allowed 700 msec in which to shift their gaze from F to S, although the saccade nearly always occurred at less than 200 msec latency. Trials involving leftward and rightward saccades were interleaved in pseudorandom sequence until data had been collected during 15 trials of each type.

Neuronal Activity Related to Orbital Position

The pattern of task-related modulation observed most commonly in these experiments was a prolonged shift in the level of activation that occurred at or shortly after the time of each saccadic eye movement. The sign and magnitude of this shift usually were related to the direction of the eye movement. Data from two neurons exhibiting this pattern are shown in Figure 11.3*C*. Both neurons were in the left hemisphere and conformed to the rule that firing increased after rightward eye movements (left column) and decreased after leftward eye movements (right column). In the bar histograms, the height of each bar indicates mean firing rate and the horizontal axis represents time during the trial. The onset of the saccade target occurred 1 sec into the 2.5 sec trial period. A superimposed set of traces representing horizontal eye position is presented above each histogram. In the raster display under each histogram, each line represents one trial and each dot represents a single action potential. In 157 of 195 neurons

D. Eye-movement-related firing occurs even in total darkness in some neurons, but, in others, is attenuated or abolished when visual feedback resulting from the eye movement is removed by extinguishing ambient illumination. The histograms represent the mean rate of firing of two neurons, one exhibiting dependence on room illumination (top row) and one exhibiting task-related firing even in total darkness (bottom row). Data in the left column were collected when the cat performed eye movements under normal ambient illumination. Data in the right column were collected during trials when room lighting was extinguished 200 msec prior to the onset of the saccade target and reilluminated 1 sec later (period of darkness indicated by dark bar on time scale). Trials of the two types were interleaved in pseudorandom sequence.

E. Phasic responses to flashes of the fixated visual target depend dramatically on the rate of presentation. These responses are of two neurons (top and bottom rows) on interleaved trials when the target was flashed at a rate of 10 Hz (left column) and 2 Hz (right column). Phasic modulation of activity time-locked to the stimulus appears only under the low-frequency condition.

tested by this procedure, a significant prolonged deviation above or below the baseline firing rate occurred during at least one of the four fixation epochs.

Apparent dependence on the orbital position of the eye could result from neuronal sensitivity to the angle of the eye in the orbit, from neuronal sensitivity to the direction of the preceding saccade, or from neuronal responsiveness to visual stimulation by patterns in the environment toward which the eye is directed during rightward and leftward fixation. To distinguish among these factors required several control experiments. We made use of two major controls and found, in each case, that firing was dependent in part on the angle of the eye in the orbit and in part on other factors.

The first control was to extinguish all ambient illumination during a brief period centered on the eye movement. Results obtained by this procedure are illustrated in Figure 11.3*D*. Histograms in the left column represent activity recorded during rightward eye movements in a lighted room; each neuron was excited during and following the eye movement. Histograms in the right column represent activity collected under conditions that were identical in all respects except that the room lights were extinguished for a period of 1 sec spanning the eye movement. In the neuron whose activity is represented by histograms in the top row, task-related activity was abolished in the dark. In the neuron whose activity is represented by histograms in the bottom row, task-related firing was unaffected by darkness. It should be stressed that in all experiments, the trials involving the two conditions were pseudorandomly interleaved. These neurons represent extremes on a continuum. The most common pattern was for task-related activity to be diminished but not abolished in darkness.

The second control involved reorienting the restraint apparatus by rotating it to the right or left between trials on which the cats executed an identical saccade between the same two targets. In this way, the size and direction of the saccade and the nature of the visual background were held constant while the angle of the eye in the orbit changed. The typical result was a reduction but not an abolition of neuronal activity dependent on the angle of the eye in the orbit. We conclude that dependence on orbital position was mediated in part but not in whole by visual feedback.

Timing of Bursts Relative to Onset of Saccadic Movements

In one-half of all neurons tested by the standard procedure, there was a discernible shift in the level of activity roughly at the time of saccade execution. To assess the timing of the shift relative to the saccade necessitated analysis of action potential histograms in which events from successive trials were aligned with respect to the time of onset of the saccade. This approach was required because the saccadic reaction time varied from trial to trial. We found that in the majority of neurons the first sign of modulation occurred in a period extending from the beginning of the saccade to 70 msec after its onset. This was true both for contraversive and for ipsiversive saccades.

Sensory Responsiveness

Only a small percentage of neurons in CGp gave significant responses to visual stimuli employed in the standard task. A rare instance of visual responsiveness is presented in the bottom row of Figure 11.1*D*, where the tall narrow peak in each histogram represents a phasic excitatory response to the first flash of the peripheral target. Since nearly all cingulate neurons do not respond to an event that the cat both detects and responds to motorically, it may be concluded that cingulate circuitry probably is not crucially involved in dynamic processes underlying detection of sensory events and sensorimotor gating.

Neurons unresponsive to targets presented in the context of the standard task did,

however, respond to the same targets in other contexts. In the standard task, the visual stimulus was presented in brief flashes at a steady rate of 10 Hz. The displacement of the target from its initial position to its subsequent position was accomplished without any break in the regular series of flashes. On systematic variation of the flash rate in a control paradigm, it was found that phasic responses to individual flashes of the target began to emerge as the rate of presentation was reduced below 5 Hz. At a rate of 2 Hz, approximately one-half of neurons in CGp gave statistically significant phasic responses to a flashing fixated target. This effect is illustrated in Figure 11.3*E*. The histograms in the left column represent activity elicited when fixation and saccade targets were presented at a high rate of 10 Hz and the histograms in the right column represent activity elicited at a low flash rate of 2 Hz. The tick marks on the event trace at the base of each column represent individual flashes. Neither neuron gave significant phasic responses to individual flashes in the 10 Hz condition. When the targets were flashed at 2 Hz, the neuron represented in the top row gave muted but statistically significant phasic responses, while the neuron in the bottom row gave obvious and highly significant responses. The pattern visible in the bottom histogram (i.e., a prolonged reduction of activity followed by gradual recovery) is typical. Responses to repeated presentations of the fixation target, even at low rates, never took the form of crisp excitatory bursts. Given the sluggish nature of these responses, we are uncertain whether to regard them as genuine sensory responses or as the correlates of state changes (e.g., changes of attentiveness) dependent on the intermittent presentations of the target.

In 51 neurons, systematic testing was carried out with salient but behaviorally irrelevant visual, auditory, and somatosensory stimuli. The visual stimulus was a sudden whole-field flash, the auditory stimulus was an 85 dB broad-spectrum pulse, and the somatosensory stimulus was a light tap delivered to the cat's back. Approximately 39% of tested neurons responded to stimulation in at least one modality. Cases of unimodal, bimodal, and trimodal responsiveness were noted. There was a tendency for neurons responsive in one modality to be responsive in others as well. It may be concluded that even in the ocular division of CGp, as defined by connectivity, neurons are not sensitive exclusively to visual stimulation.

General Issues and Conclusions

Parallel Processing by Somatic, Ocular, and Complex Subregions

An entirely new aspect of the connectional findings described here is the pattern of topography whereby distinct subdivisions of CGa and CGp are linked to different functional classes of cortical areas (Musil and Olson, 1988a; Olson and Musil, 1992a).

Somatic subdivisions receive input from somatosensory and somatomotor areas.
Ocular subdivisions receive input from visual and oculomotor areas.
Complex subdivisions receive input from prefrontal cortex and other areas without clearly defined sensory or motor functions.

One might interpret this pattern as indicating that each area is a mosaic of distinct and unrelated components, however, that would place too little weight on the presence, throughout each area, of numerous unvarying traits that establish its fundamental unity. A less extreme and more palatable interpretation is that the component modules carry out a single input-output operation characteristic of the area as a whole and that they differ only with respect to the type of information on which the operation is carried out. From this scheme, it follows that, for any given contribution to somatosensory function arising in the somatic module of CGp, parallel contributions to vision and to high-order interpretative processes should arise in

the ocular and complex modules, respectively. Because neurons in the ocular module of CGp carry tonic signals related to the angle of the eye in the orbit, one might infer, e.g., that neurons in the somatic module should carry tonic signals related to the posture of the limbs and that neurons in the complex module should carry tonic signals related to central states lacking an external correlate.

A tripartite pattern of modular organization may well be present in species other than the cat, as indicated by previously described patterns of connectional topography. In CGp of the monkey, projections from cortical areas with known visual functions including area 7 and the superior temporal sulcus tend to terminate dorsally, while projections from areas lacking clearly defined sensory and motor functions including ventral medial prefrontal cortex and the subiculum tend to terminate ventrally (Vogt and Pandya, 1987). In CGp of the rat, afferents from visual cortex are strongest dorsally (Vogt and Miller, 1983) and subicular inputs predominate ventrally (Meibach and Siegel, 1977). Both sets of results imply that CGp contains a comparatively ventral complex zone and a more dorsal ocular zone. One would predict, then, that a still more dorsal sector of CGp should possess links to somatosensory and somatomotor areas. In the monkey, this notion is plausible, because CGp, at its dorsal border, adjoins the supplementary sensory area—a medial division of area 5 with somatosensory functions and connections (Bowker and Coulter, 1981; Murray and Coulter, 1981). Somatosensory afferents may impinge on a somatic subregion of cingulate cortex in the region of this border. However, in the rat there appears to be no somatosensory area at the dorsal border of CGp, as indicated by the absence of labeling following large tracer deposits in somatosensory areas (Paperna and Malach, 1991).

Cingulate Cortex and Midline Visceromotor Cortex

Findings described here tend to undercut the widespread view that all of cingulate cortex serves visceromotor functions. Cingulate cortical areas in the cat receive little input from brain areas of a frankly visceral nature (Musil and Olson, 1988a; Olson and Musil, 1992a), and neuronal activity in CGp of the feline is not obviously related to situational variables associated with visceral changes, such as delivery or withholding of reward (Olson and Musil, 1992b). These conclusions can be reconciled with decades of research demonstrating that lesions and electrical stimulation of cingulate cortex exercise a clear effect on visceral processes as long as one bears in mind the distinction between cingulate cortex "proper" (areas 29, 30, 23, 31 and 24) and ventral cortex on the medial face of the frontal lobe (areas 32 and 25). It is the ventral medial frontal areas from which nearly all robust effects on autonomic functioning have been achieved (Neafsey, 1990; Chapters 6 and 13 of this volume). In the cat, the line of division between cingulate and prefrontal cortical districts, defined by dominant input from the anterior and mediodorsal thalamic nuclei, respectively, is comparatively sharp. Area 24 (CGa) falls on the cingulate side of the line, whereas areas 25 (MPFil) and 32 (ventral MPFd) fall on the prefrontal side (Musil and Olson, 1988b, 1991). These visceral prefrontal areas are not strongly linked either to CGa or to CGp (Musil and Olson, 1988a,b; Olson and Musil, 1992a). Thus there is little reason to suppose that processes carried out in CGa and CGp relate intimately to autonomic function.

Anterior vs. Posterior Cingulate Cortex: Behavioral Control vs. Spatial Memory

On the basis of connectional patterns alone, one would be forced to conclude that the anterior and posterior cingulate areas serve very closely related functions and exhibit only a minor degree of specialization. This is because the two divisions are very strongly joined to each other and are linked by pathways of commensurate strength to nearly

identical sets of distant cortical areas (Musil and Olson, 1988a; Olson and Musil, 1992a). They are differentiated from each other most consistently by four traits of connectivity:

1. Not only in the cat but in all species that have been examined, CGp alone receives input from the anterodorsal and anteroventral thalamic nuclei. These nuclei may well carry signals from the hippocampomamillary system different from those that are relayed both to CGp and to CGa through the anteromedial nucleus (Rose and Woolsey, 1948; Baleydier and Mauguière, 1980; Robertson and Kaitz, 1981; Finch et al., 1984; Vogt et al., 1987; Musil and Olson, 1988a; Olson and Musil, 1992a).

2. In the cat and monkey, CGp receives much stronger input from parietotemporal sensory association areas (Baleydier and Mauguière, 1980; Vogt and Pandya, 1987; Musil and Olson, 1988a; Olson and Musil, 1992a). A comparable difference may exist in the rat but the homologues of parietotemporal cortex of the cat and monkey have not been clearly identified in the rat.

3. In the rat, cat, and monkey, CGa receives stronger projections from the amygdala and thalamic mediodorsal nucleus (Baleydier and Mauguière, 1980; Amaral and Price, 1984; Sripanidkulchai et al., 1984; Musil and Olson, 1988a, 1991; Olson and Musil, 1992a; Chapter 8 of this volume).

4. In the cat and monkey, CGa receives stronger input from insular cortex (Vogt and Pandya, 1987; Musil and Olson, 1988a; Olson and Musil, 1992a).

On the basis of these distinctive connectional traits, it would be reasonable to suppose that CGp is preferentially involved in processes that depend on the hippocampus and parietotemporal cortex—notably memory and spatial orientation—whereas CGa is preferentially involved in processes that depend on the mediodorsal nucleus, amygdala, and insular cortex—notably motivation and the initiation of behavior.

That CGa is specialized connectionally for processes related to spontaneous motivation and the voluntary initiation of behavior is a commonly held view (Vogt et al., 1979; Baleydier and Mauguière, 1980). This notion receives support from the nature of symptoms that follow from anterior cingulate injury, as discussed in Chapter 18 of this volume, including indifference to pain (Barris and Schuman, 1953), distractibility (Laplane et al., 1981), and akinetic mutism (Barris and Schuman, 1953; Damasio and Van Hoesen, 1983). It is also supported by the observation in a positron emission tomography study that painful cutaneous stimuli induce a heightening of blood flow in CGa (Talbot et al., 1991). Other positron emission tomography studies have demonstrated that anterior cingulate activity is enhanced during performance of tasks involving cognitively demanding discriminations or divided attention (Pardo et al., 1991; Posner and Petersen, 1990; Corbetta et al., 1991). This set of findings has been reconciled with the motivation-emotion hypothesis by supposing that the central function of CGa is to initiate motor output in response to cognitive processes, including complex discriminations, dependent on dorsolateral prefrontal cortex (Corbetta et al., 1991).

The view that CGp is specialized connectionally for mnemonic or spatial processes (Goldberg, 1984; Mishkin and Bachevalier, 1986; Pandya and Yeterian, 1984) has only begun to receive support from functional studies. In humans, there is still no clear syndrome attached to posterior cingulate damage, and positron emission tomography studies have failed as yet to identify conditions under which metabolic activity in CGp is selectively enhanced. However, in rats (Sutherland et al., 1988; Markowska et al., 1989; Chapter 16 of this volume) and in monkeys (Murray et al., 1989), large lesions of the cingulate gyrus are now known to induce a marked impairment of spatial reference and working memory. Of particular interest is the fact that navigational impairment is greater after injury of posterior as compared to anterior cingulate cortex (Sutherland et al., 1988; Chapter 16 of this volume).

Behavioral Significance of Sensory and Motor Activity

The findings described here establish that neurons in CGp of the cat are active in conjunction with eye movements and respond to multimodal sensory stimulation both inside and outside the context of oculomotor task performance. The finding that cingulate neurons carry oculomotor signals is compatible with a previous report that neurons in CGp of the rabbit discharge during the quick-phase eye movements of nystagmus (Sikes et al., 1988). The finding of sensory responsiveness is compatible with previous descriptions of visual responsiveness in cingulate cortex of the cat (Kalia and Whitteridge, 1973; Stwertka, 1985) and of auditory and somatosensory responsiveness in the rabbit (Chapters 10 and 17 of this volume). The behavioral significance of sensory and motor signals carried by posterior cingulate neurons remains to be established, but it is clear that they do not serve a simple or direct role either in sensory information processing or in motor control.

Posterior cingulate neurons respond phasically to intermittent low-frequency stimulation by a fixated visual target and thus may be said to give visual responses. However, above a frequency of a few flashes per second, nearly all neurons become unresponsive despite the fact that flicker is detectable as such at frequencies an order of magnitude higher. Failure to follow even at comparatively low frequencies might be taken to indicate that posterior cingulate neurons do not register the occurrence of a perceptible visual event as such, but rather are the substrate for a slow and refractory central process (e.g., the capture of attention), set in motion by the visual event.

Posterior cingulate neurons tend to fire at a level related to the angle of the eye in the orbit during periods of fixation and thus may be said to carry a motor signal. However, they appear to monitor rather than control ocular movements as indicated by the late timing of shifts in level of activity relative to displacements of gaze. The same is true of posterior cingulate neurons in the monkey, as discussed in Chapter 12 of this volume. Why should any high-order cortical area monitor eye movements? An organism must take into account the angle of the eye in the orbit in order to perceive correctly the spatial relation between the body and visible objects in the environment. Thus, the presence of neurons sensitive to orbital position is compatible with the view, developed in the preceding section, that CGp performs functions related to the maintenance of spatial orientation.

Acknowledgments

This work was supported by grants to C.R.O from National Institutes of Health (RO1 NS27287) and from the McDonnell-Pew Program in Cognitive Neuroscience. We thank the editors for their conscientious and thoughtful oversight of all stages in the production of this volume.

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