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Functional Neuroanatomy of the Limbic System and Prefrontal Cortex

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The limbic system concept was coined by MacLean (1) near the midpoint of this century to reintroduce and reemphasize the seminal thinking of Papez (2) on the neuroanatomical correlates of emotion and to integrate his deductions with advances from both the clinic and the laboratory. This led to a larger "circuit for emotion" in neuroanatomical terms and a somewhat more multifaceted one in functional terms. A scant 5 years later, memory function was added to the functional correlates (3) because acquiring new information and learning rely critically on an intact Papez's circuit. MacLean's efforts, along with Brodal's influential review (4) a few years earlier, laid to rest the "small brain" or rhinencephalon concept of limbic lobe function, relegating olfactory sensation to its appropriate place as only one of several sensory inputs to the limbic system.

Although slightly obscured by anatomical detail, the backbone of Papez's circuit deals with the rather simple anatomical notion of how the cerebral cortex (and, by definition all sensory systems) influences the hypothalamus (the building up of the "emotive process") and how the latter influences the cerebral cortex ("psychic coloring"). He was successful in elaborating one facet of these relationships, but the full panorama was not appreciated until the past four decades with the advent of newer experimental neuroanatomical methodology and a major effort by neuroanatomists. These have led to an expanded conception of the limbic system both in neuroanatomical and functional terms. Although confusing because the term "system" implies unity of function, the core of the concept is the limbic system as the mediator of two-way communication between the cerebral cortex and the external world, and the hypothalamus and the internal world of the organism. Behavior in general, whether it be the consequence of autonomic, endocrine, or somatic effects, is governed by this interplay of the external and internal worlds. Thus, a multifunctional limbic system should be expected (5).

The term prefrontal cortex is attributed to Sir Richard Owen (6). It refers to that cortex anterior to the electrically excitable motor cortex. This is a large area of cortex in the human and nonhuman primate brain and includes a large dorsolateral sector, orbital sector, and medial sector. The latter typically includes the anterior cortices of the cingulate gyrus, which wrap around the genu of the corpus callosum and follow its rostrum ventrally and posteriorly.

There have been many conceptualizations of prefrontal cortical function, ranging from the most lofty domains of behavior to those dealing with more fundamental matters such as emotion, motivation, social behavior, and inhibition. Recent studies have linked it to working memory (7) and decision making (8). The former refers to the ordering of behavior, or the manner in which time is bridged neurally to enable completion of a sequence of intended acts or tasks. The latter function, decision-making behavior, complements working memory in critical ways and involves an assessment of somatic markers (9) that impart reason and reality to choices of behavior. Some patients with frontal lobe damage have preserved intellect, analytical abilities, social consciousness, and sensory awareness, but lack the ability to make accurate predictions about the outcome of decisions on their own well-being. The apparent overlap between functional correlates of the prefrontal cortices and limbic system is of great interest and a matter of active inquiry in neuropsychiatric research (10).

Our goal in this chapter is to examine recent neuroanatomical findings regarding the major parts of the limbic system and the prefrontal cortices and new concepts that emerge from them. We close with a consideration of degenerative diseases that affect these parts of the brain, evolutionary issues, and the implications that these and functional neuroanatomy have for neuropsychiatric disorders.

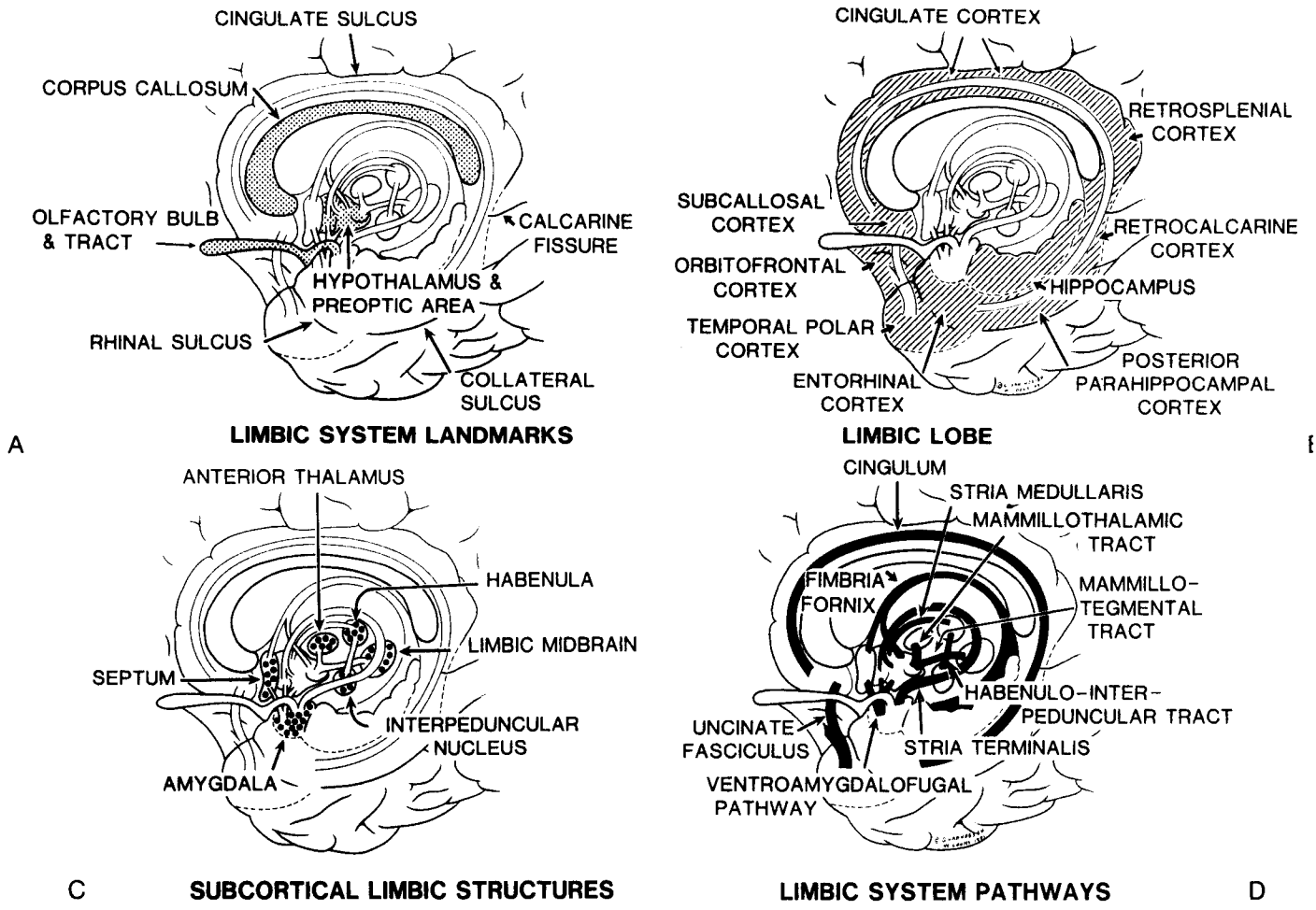

Figure 7.1. Four schematic representations of the medial surface of the cerebral hemisphere depicting the anatomical components of the limbic system. **A,** The relevant landmarks. **B,** The limbic lobe or cortical components. **C,** Subcortical limbic structures (the nucleus basalis of Meynert and the diagonal bands of Broca, both of which contain cholinergic neurons, are not shown). **D,** Interconnecting limbic system pathways. From Damasio and Van Hoesen, 1983, Guilford Press, with permission.

LIMBIC SYSTEM

Anatomical structures included under the term limbic system have diverse locations in the cerebral hemisphere and occupy parts of the telencephalon, diencephalon, and mesencephalon. In general, they are the so-called "conservative" parts of the brain—those found in a wide range of mammals and to some extent vertebrates in general. The cortical parts comprise what are frequently termed the "older" parts of the cerebral cortex, those parts of the cerebral cortex common to many species that form the edge or "limbus" of the cerebral cortex (11). Care has to be taken in the use of terms such as "older" and "conservative". They are best reserved for discussions relating to phylogeny, since, limbic system structures have evolved like all other parts of the cerebral hemisphere, and have assumed functional roles specific to the adaptations of a given species. Although a general core of behaviors may unite diverse species, species-specific functions may be more impressive. However, these may be mediated neurally by structures that resemble each other across species.

A useful way of dealing with the complex anatomy of the limbic system is shown in Figures 7.1, which divides the term into four conceptual units: landmarks, cortical components, subcortical structures, and interconnecting pathways. The cortical structures of the limbic system are well demarcated on the medial surface of the hemisphere by the cingulate sulcus dorsally and the collateral sulcus ventrally (Fig. 7.1*A*). Bridging areas such as the subcallosal gyrus, the posterior orbital, anterior insular, temporal polar, and perirhinal cortices connect the cingulate and parahippocampal gyri rostrally, while the retrosplenial and retrocalcarine cortices provide a bridge caudally. Altogether, they form the classic "limbus" in the sense of Broca's original intent (Fig. 7.1*B*). The areas differ widely in cytoarchitecture and include Brodmann's areas 23–29, 35, 36, and 38. None is a true isocortical area. Rather, they fall under the categories of periallocortex and proisocortex of Sanides's terminology, or when combined, the mesocortices of Filimonoff, which are intermediate in structure between the allocortices and the isocortices (5).

The subcortical structures included in the limbic system

(Fig. 7.1C) vary widely among authors and are scattered throughout many parts of the hemisphere. However, it seems appropriate to include the amygdala, septum, nucleus basalis of Meynert, anterior thalamus, habenula complex, interpeduncular nucleus, and some additional limbic midbrain areas. A structural criterion common to this list relates to the fact that all are connected among themselves as well as with the hypothalamus. Additionally, as noted later, many of these nuclei receive direct cortical projections from one or more parts of the limbic lobe.

The final units of the limbic system are the interconnecting pathways (Fig. 7.1D), those within the limbic lobe, those that connect limbic lobe areas with subcortical limbic structures, those that connect subcortical limbic structures to each other, and lastly, those that connect elements of the limbic system to the hypothalamus. These include such pathways as the cingulum, uncinate fasciculus, fimbria-fornix, stria terminalis, ventroamygdalofugal pathway, mammillothalamic tract, mammillotegmental tract, stria medullaris, and habenulointerpeduncular pathway.

All aspects of this extensive topic of neuroanatomy are not reviewed here. Instead, we deal with it selectively, with an emphasis on new concepts and on the relationship of the limbic system to the frontal lobe.

Cingulate Gyrus

The cingulate gyrus is the major dorsal part of the limbic lobe on the medial wall of the cerebral hemisphere, and forms the upper half of the cortical ring of gray matter (Fig. 7.2). Its main portion is located dorsal to the corpus callosum and callosal sulcus and ventral to the cingulate sulcus, although it extends into the depths of the latter. Its anterior part coincides with Brodmann's area 24 and its posterior part with area 23 (12–14). The cingulate gyrus continues anteriorly and arches ventrally, around the genu of

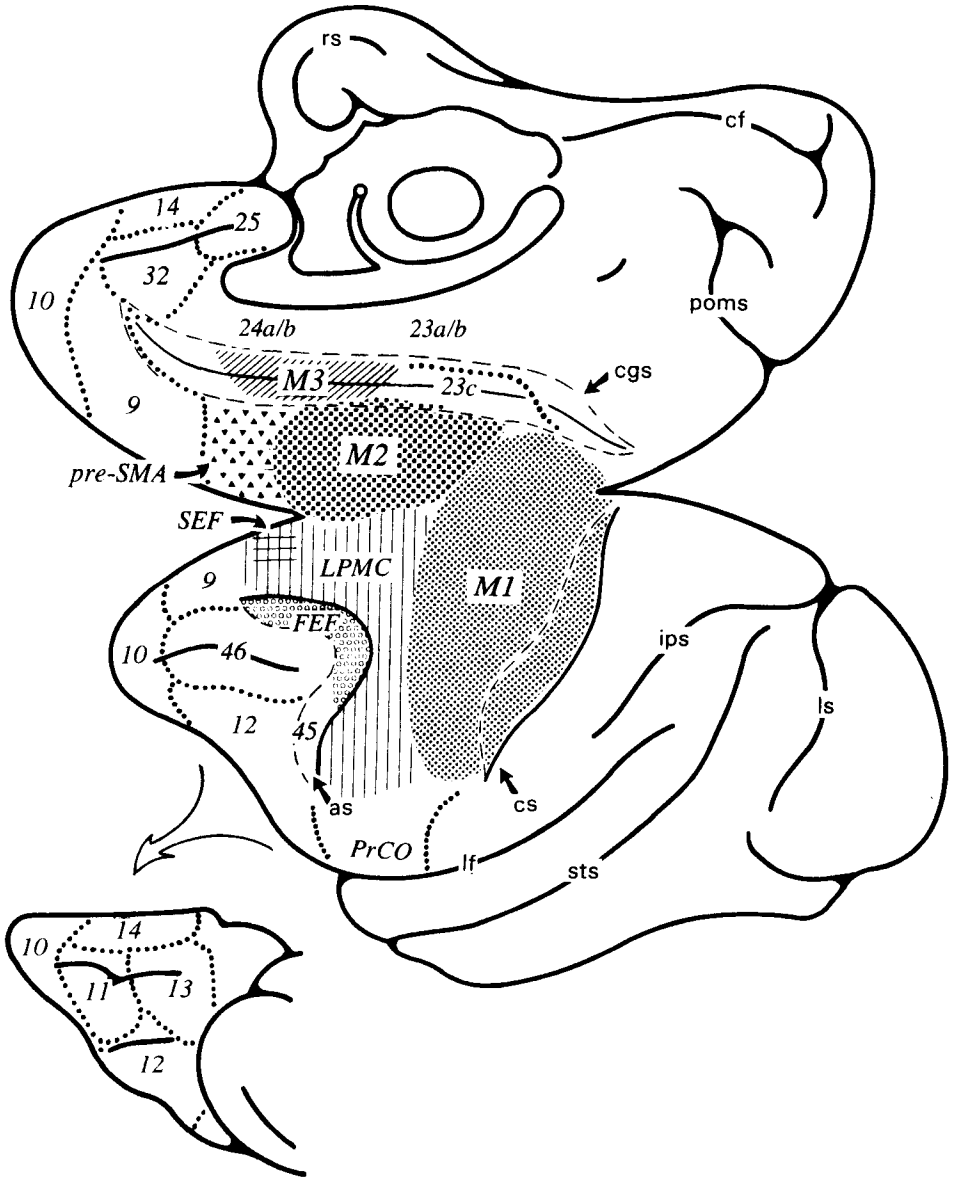

Figure 7.2. Medial, lateral, and orbital views of the rhesus monkey cerebral hemisphere depicting the functional parts of the frontal lobe, Brodmann and Walker's cytoarchitectural fields, and the cingulate gyrus. Note the three motor representations, M1, M2, and M3, the lateral premotor cortex (LPMC) and the frontal and supplementary eye fields (FEF and SEF). M1 is synonymous with the term primary motor cortex and Brodmann's area 4. M2 is synonymous with the supplementary motor cortex and medial area 6. It, along with the LPMC, corresponds to Brodmann's lateral area 6. The supplementary motor cortex is separated from prefrontal area 9 by a presupplementary motor cortex (pre-SMA). M3 is synonymous with the cingulate motor area and lies in the fundus and lower bank of cingulate sulcus. It corresponds to Brodmann's area 24 and particularly area 24c. Area 23c is also thought to be a component of the cingulate motor area. All other (unhatched) fields correspond to prefrontal association areas or to anterior and medial parts of the limbic lobe adjacent to or within the frontal lobe. (Abbreviations: *as* = arcuate sulcus; *cf* = calcarine fissure; *cgs* = cingulate sulcus; *cs* = central sulcus; *ips* = intraparietal sulcus; *lf* = lateral fissure; *ls* = lunate sulcus; *poms* = parieto-occipital medial sulcus; *rs* = rhinal sulcus.

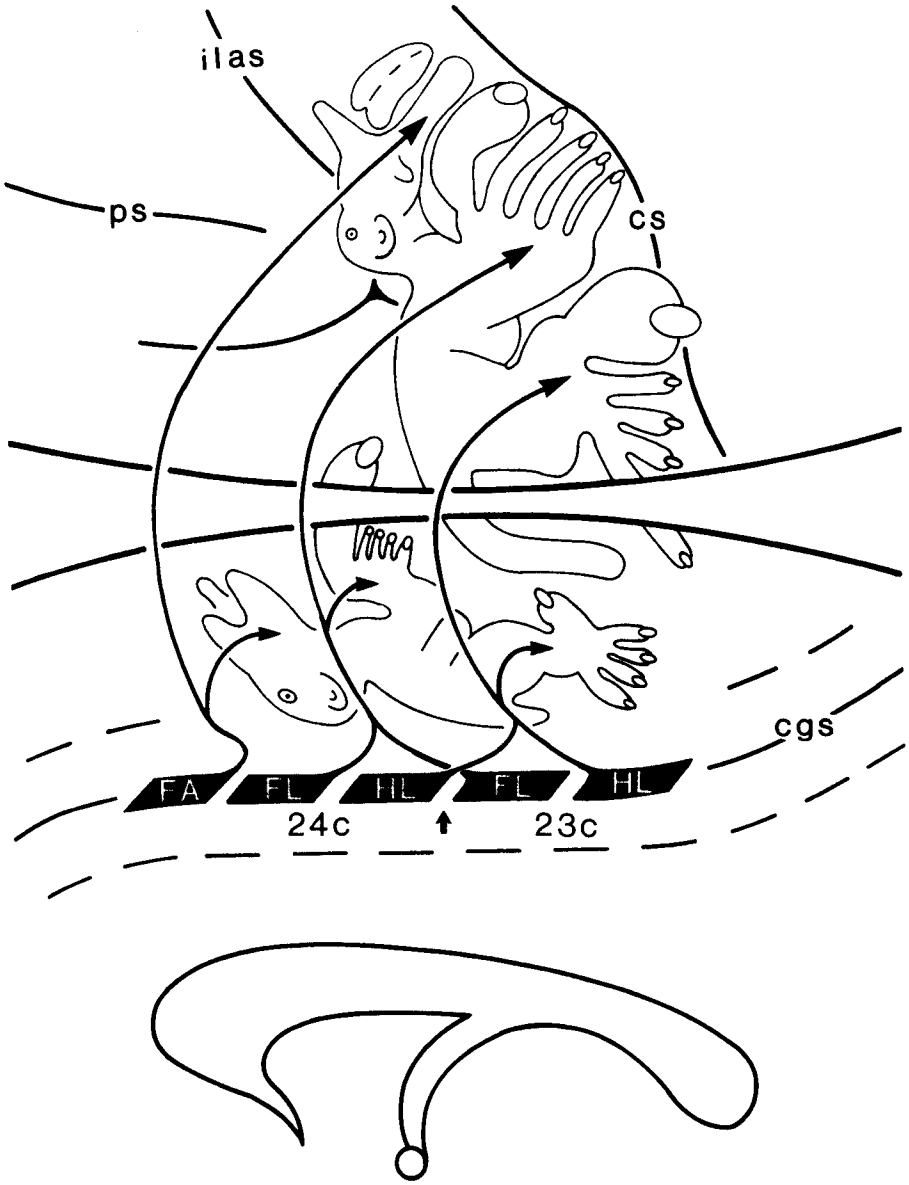

Figure 7.3. The somatic topography of the primary and supplementary motor cortices is shown on a partial flattened view of the monkey hemisphere. The opposing convex lines in the center of the illustration represent the true dorsal convexity of the superior frontal lobule such that the lateral surface extends inverted toward the top of the page, and the medial surface of the hemisphere extends upright toward the bottom of the page. The projections of cingulate motor areas 24c or M3 and 23c with the somatic topography of the supplementary and primary motor cortices are shown. Note that the face area (FA) forelimb (FL) and hindlimb (HL) of 24c or M3 projects the appropriate representations of the other motor maps. Area 23c seems to lack a face representation, but forelimb (FL) and hindlimb (HL) parts are in register. Both areas 24c and 23c contribute to the corticospinal projection (Abbreviations: *cgs* = cingulate sulcus, *ilas* = inferior limb of arcuate sulcus, *ps* = principal sulcus).

the corpus callosum. This ventral extension forms area 25. Posteriorly, the cingulate gyrus arches ventrally, around the splenium of the corpus callosum. Most of this ventral extension is designated as area 23 except for cortex buried in the callosal sulcus, which is referred to as retrosplenial cortex (areas 29 and 30). The most ventral part of this posterior continuation is called the isthmus of the cingulate gyrus and ends at the level of the calcarine sulcus. Buried within the gyrus is a prominent interconnecting white matter pathway known as the cingulum bundle. The cingulum bundle follows the curvature of the cingulate gyrus, and some of its axons form the longest corticocortical association connections in the cerebral hemisphere. Along its length, axons enter and exit to interconnect the cingulate cortex with a multiple cortical and subcortical targets, including the basal ganglia and thalamus.

The various subsectors of the cingulate cortex, and in particular, areas 24 and 23, are coupled anatomically by a vast and organized set of intracingulate connections (15–17). The cingulate gyrus also is connected to the frontal lobe, parietal lobe, occipital lobe, temporal lobe, other parts of the limbic lobe, as well as to the insula (15, 18, 19–30). In general, both the anterior and posterior divisions of the cingulate gyrus are connected with the prefrontal, orbitofrontal, posterior parietal, posterior parahippocampal, perirhinal, entorhinal and lateral temporal cortices as well as the presubicular and subicular/CA1 parts of the hippocampal formation. Topographic differences in these connections occur. For instance, more anterior levels of the orbitofrontal cortex are linked primarily to area 23, while more posterior levels are linked to area 24. The superior and inferior parietal lobules are both connected with area 23, while the parietal connection with area 24 is less strong and involves primarily the inferior parietal lobule. With respect to the parahippocampal region, medial levels are linked primarily to area 24, whereas lateral levels are linked to area 23.

Other connections are known to target only the anterior cingulate region, which underscores the cytoarchitectural distinction of this more anterior "agranular" part of the cingulate gyrus (areas 24, 25, and 32) from the more posterior "granular" part of the cingulate gyrus (area 23). For example, frontal area 32, temporal polar area 38, and the amygdala are connected with only the anterior cingulate gyrus. This unique set of projections would suggest that neural events taking place in the anterior cingulate gyrus are different in part, from those occurring posteriorly. However, because area 24 and 23 are strongly interconnected, it is likely that projections to the anterior cingulate gyrus influence the posterior cingulate gyrus.

Like the different patterns of connectivity that distinguish the anterior from posterior parts of the cingulate gyrus, the dorsal part of the cingulate gyrus (subdivision c) differs on a connectional basis from the more ventral parts of the cingulate gyrus (subdivisions a and b). For example, input from the prefrontal and limbic cortices more heavily target cingulate cortex located on the surface of the gyrus (areas 24a, 24b, 23a, and 23b) than cingulate cortex lining the lower bank of the cingulate sulcus (areas 24c and 23c). The subicular/CA1 sector of the hippocampal formation projects only to the more ventrally located cingulate areas (areas 24a, 23a, and 25). Areas 24c and 23c, which form the dorsal part of the cingulate gyrus, are located in the depths of the cingulate sulcus and are the only parts of the cingulate gyrus connected with the primary motor cortex (M1) (Fig. 7.3). Similarly, areas 24c and 23c are strongly interconnected with the supplementary motor cortex (M2), while fewer cells in area 24b project to M2. Area 24C is the only part of the cingulate gyrus connected with the ventral part of the lateral premotor cortex and area prostriata of the retrocalcarine region. Likewise, area 23c appears to be the only part of the cingulate gyrus connected with the adjacent primary somatosensory cortex (areas 1 and 2).

Based on the anatomical observations just summarized, several conclusions can be drawn. First, the vast network of intracingulate connections, and in particular, those linking area 24 with area 23, provide multifaceted avenues for information exchange between anterior and posterior parts of the cingulate gyrus. Second, widespread parts of the cingulate gyrus are linked to multimodal and limbic cortices. Multimodal sources would include prefrontal, rostral orbitofrontal, posterior parietal, and lateral temporal cortices. Limbic sources include posterior orbitofrontal, temporopolar, posterior parahippocampal, perirhinal, and entorhinal cortices (Fig. 7.4). Thus, highly processed and abstract

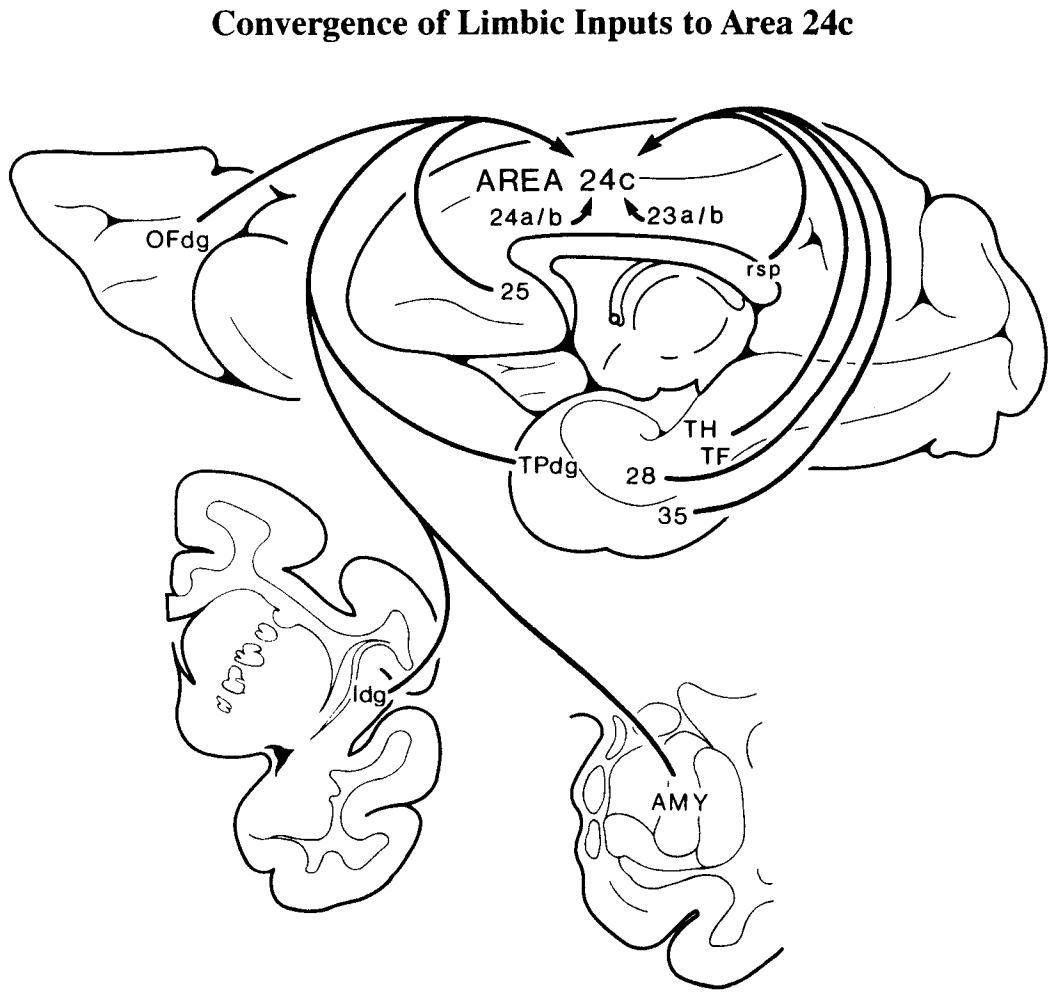

Figure 7.4. Schematic representation of the convergence of limbic system inputs to area 24c or M3. Note the extensive input from other parts of the limbic lobe as well as the amygdala (AMY) (Other abbreviations: *ldg* = insular dysgranular cortex; *Ofdg* = orbitofrontal dysgranular cortex; *rsp* = retrosplenial cortex; and *Tpdg* = temporopolar dysgranular cortex).

information from neocortical association areas, and perhaps, emotionally and motivationally relevant information from limbic sources, can influence a wide variety of cingulate subsectors. Third, cingulocortical connections appear to be made throughout much of the cingulate gyrus. Direct motor cortex interactions appear to occur through cingulate cortex lining the depths of the cingulate sulcus (areas 24c and 23c), and direct somatosensory cortex interactions occur through area 23c.

SUMMARY AND FUNCTIONAL CONSIDERATIONS

Although the cingulate gyrus does not contain areas that specifically subserve a primary modality, selected parts of it may be involved in regulating the fundamental outcome of specific complex behaviors. For example, lesions of the posterior cingulate gyrus alter an animal's ability to navigate appropriately in its environment despite receiving extended training to accomplish a learned task (31). Therefore, posterior cingulate cortex may be an essential component of spatially-guided orientation.

Available data suggest that the anterior cingulate gyrus may be implicated in the expression of affectively-triggered movements related to painful stimuli (32). For example, units here respond selectively to a variety of noxious stimuli. In line with this observation, it has been demonstrated that the anterior cingulate cortex may mediate vocal expressions that reflect the internal state of the animal. For example, stimulation of the anterior cingulate gyrus evokes simple vocalizations, whereas lesions placed rostral to the periaqueductal gray matter, which apparently disrupt the cinguloperiaqueductal projection, abolish the response. It is well known that the periaqueductal gray matter has a role in brainstem pain mechanisms and vocalization.

The anterior cingulate cortex has been implicated in the production of other forms of vocal expression that are linked to emotional expression. The separation cry, produced by primates for maintaining contact with a distant group of individuals, and induced by separating a mother from her offspring, is adversely affected following ablation of the anterior subcallosal region of the cingulate gyrus (33). A different form of emotion-related vocalization, namely that of laughter, may also be mediated by the anterior cingulate gyrus (34). Based upon observations of patients with epileptic seizures, Arroyo and colleagues suggested that the anterior cingulate gyrus is involved in generating the motor act of laughter and basal temporal cortex with the development of laughter's emotional content. It seems that regardless of the emotional phenomena expressed, the anterior cingulate gyrus plays an important role in developing the associated motor response. It would also appear from the common engagement of the head and neck region in these responses, that brainstem centers mediating the operation of structures such as the larynx, tongue, and muscles of facial expression, are heavily influenced by ongoing activity in the anterior cingulate gyrus.

The anterior cingulate gyrus may also regulate autonomic responses because its stimulation evokes pupillary dilation, piloerection, altered heart rate, and changes in blood pressure (35–38). Specifically, these are elicited from the cortex located below the genu of the corpus callosum, or Brodmann's area 25. These physiological findings, coupled with the underlying neuroanatomical circuitry described for this part of the cingulate gyrus, has led to the suggestion that this part of the cingulate gyrus serves as a "visceral motor cortex" (39).

In addition to autonomic responses, electrical stimulation of the anterior cingulate gyrus in humans (40) and nonhuman primates (35, 36) also gives rise to complex forms of somatic movement. Although surface stimulation studies conducted over 50 years ago had noted the potential influence of the primate cingulate gyrus on somatomotor mechanisms, more recent physiological (41–43) and anatomical (13, 18, 27, 28, 44–46) studies have been able to pinpoint a cingulate motor region and identify within this region an organized somatotopy (Fig. 7.3). The cingulate motor cortex lies in the depths of the cingulate sulcus and corresponds cytoarchitectonically to areas 24c and 23c. In area 24c of the monkey, the face representation is anterior to the forelimb representation, which in turn, is anterior to the hindlimb representation. Utilizing neuroimaging techniques, Paus and colleagues have demonstrated that the somatotopic organization in the human anterior cingulate cortex is consistent with the reported somatotopy in the monkey anterior cingulate cortex (47). Their observations also indicated that the anterior cingulate gyrus mediates the execution of appropriate motor responses and suppresses inappropriate ones. Based upon the suggestive physiological and anatomical data collected in nonhuman primates, as well as the suggestion that area 24 may be the developmental progenitor of the isocortical motor fields M1 and M2 (48), area 24c may be conceptualized as an M3 in the scheme of cortical motor representation (28) (Fig. 7.5). Like the more traditional isocortical motor areas (M1 and M2), modern tract tracing techniques employed in monkeys show that M3 and area 23c give rise to a host of projections that target various motor centers positioned at all parts of the neuraxis. For example, M3 and area 23c give rise to somatotopically organized projections that target the primary and supplementary motor cortices (Fig. 7.3). Therefore, M1, M2, M3, and area 23c are highly interconnected at the cortical level. From a subcortical standpoint, the same motor centers targeted by M1 and M2 are targeted by M3. For example, area M3 projects heavily to the ventrolateral part of the putamen, medial and dorsal parts of the parvocellular red nucleus, ventromedial part of the pontine nuclei, and the intermediate zone of the cervical enlargement of the spinal cord (17, 27, 44, 49–51). Judging from detailed comparisons of the descending projections arising from M1 and M2, those from M3 target different and similar parts of the basal ganglia, red nucleus, and pontine gray matter, as well as spinal cord (50, 51). Therefore, the highly interconnected motor cortices seem to also be characterized by an overlap in their corticofugal projection zones. As noted before, the

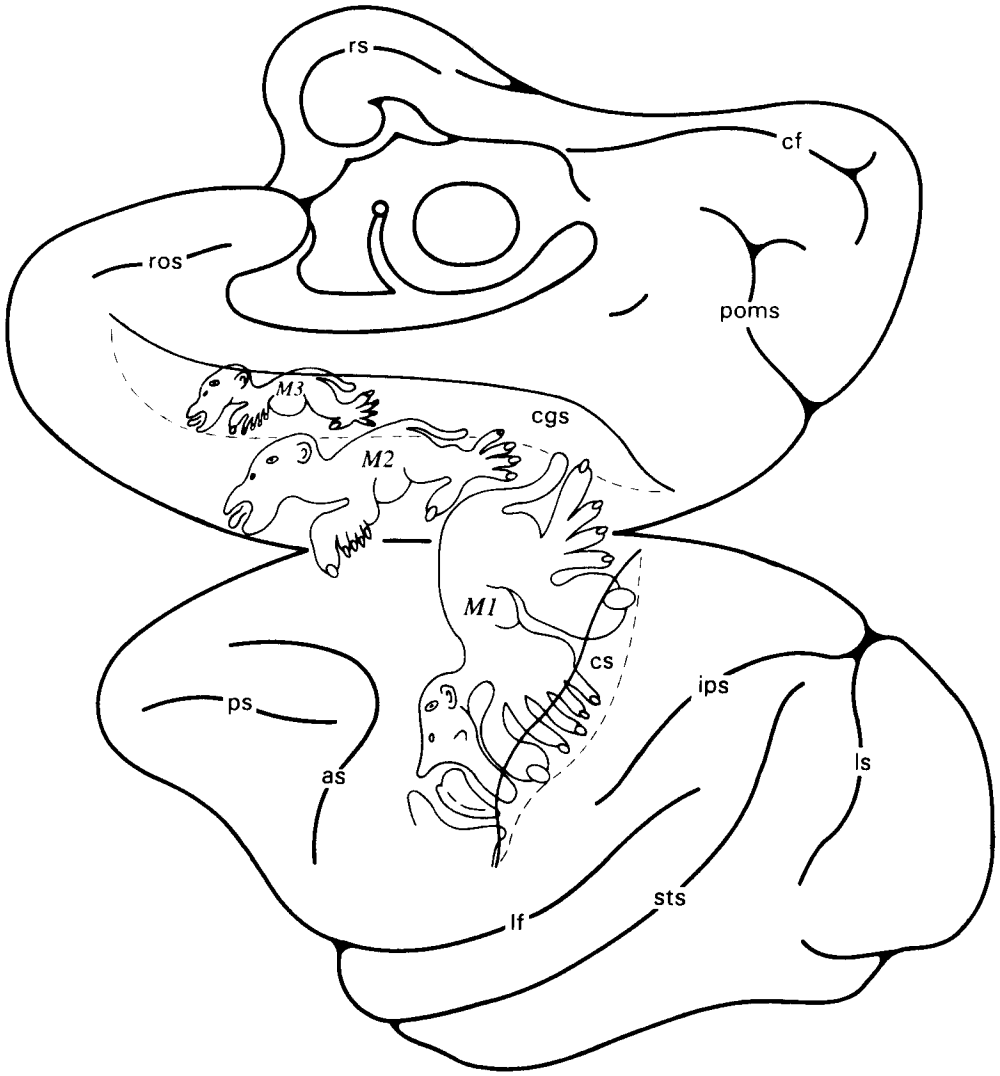

Figure 7.5. Schematic representation of the three motor representations (M1, M2, and M3) found in the agranular cortex of the frontal lobe. As discussed in the text, M3 is the major entry point for both limbic and prefrontal input to motor cortex that gives rise to corticospinal projections (Abbreviations: *as* = arcuate sulcus; *cf* = calcarine fissure; *cgs* = cingulate sulcus; *ips* = intraparietal sulcus; *lf* = lateral fissure; *ls* = lunate sulcus; *poms* = parieto-occipital medial sulcus; *ps* = principal sulcus; *ros* = rostral sulcus; *rs* = rhinal sulcus, *sts* = superior temporal sulcus).

cortical inputs to the cingulate motor cortex are unique when compared with those targeting M2 and M1 in that the cingulate motor cortex receives strong and widespread inputs from the prefrontal cortex and limbic lobes (29, 52–54). From the perspective of motor cortex organization, the powerful and direct input from prefrontal cortex, limbic lobe, and amygdala serve in part, as a distinguishing element of M3.

Hippocampal Formation and Parahippocampal Gyrus

The hippocampal formation is comprised of three allocortical areas: *(a)* the pyramids that form the CA zones of the hippocampus (CA1, CA2, CA3); *(b)* the dentate gyrus, including the CA4 polymorph neurons that are found in its hilum; and *(c)* the various subicular cortices (55–59). The latter includes the subiculum proper, a true allocortical zone, and two periallocortical zones, the presubiculum and parasubiculum. The latter are multilayered and are associated closely with the hippocampal formation. They have continuity with the subiculum in their deep layers. Because they are multilayered periallocortical areas related to the entorhinal cortex of the parahippocampal gyrus, it is appropriate to include them with this part of the ventromedial temporal lobe. In short, they form the medial boundary of the parahippocampal gyrus, intervening between the entorhinal cortex and the subiculum proper of the hippocampal formation.

Cajal (60, 61) published many seminal observations on the cytoarchitecture, fiberarchitecture, and connections of the hippocampal formation using descriptive methods such as the Golgi technique. His work led to a conceptualization of the hippocampal formation that persisted for many decades. It is only in recent years (56) that these findings have been embellished using newer experimental methods

(Fig. 7.6). The major input to the hippocampal formation was thought to arrive via two conspicuous white-matter pathways, the fimbria-fornix system and what Cajal termed the temporoammonic or perforant pathway. Axons from these were observed to end on the pyramidal cells of the hippocampus and the granule cells of the dentate gyrus. A two-part sequential series of intrinsic connections was also demonstrated. The first part is a large projection from the dentate gyrus granule cells to the proximal part of the apical dendrites of the CA3 pyramidal cells. This system sends no axons outside of the hippocampal formation and is known as the mossy fiber system. The second part is known as the Schaffer collateral system. It arises from the axons of CA3 pyramids and terminates on the basal and apical dendrites of the adjacent CA1 pyramids.

The view that emerged from these studies of hippocampal connectivity held that input would arrive via the fimbria-fornix and perforant pathway and activate the pyramidal neurons directly, or indirectly, via the dentate gyrus and intrinsic pathways. Pyramidal axons entered the alveus and the fimbria-fornix system and conveyed hippocampal output to subcortical structures. There are no errors in this anatomy, and indeed, nearly all aspects of Cajal's careful research observations have been verified. However, both he and his student, Lorente de Nó, failed to fully document an important extension of the intrinsic circuitry of the hippo-

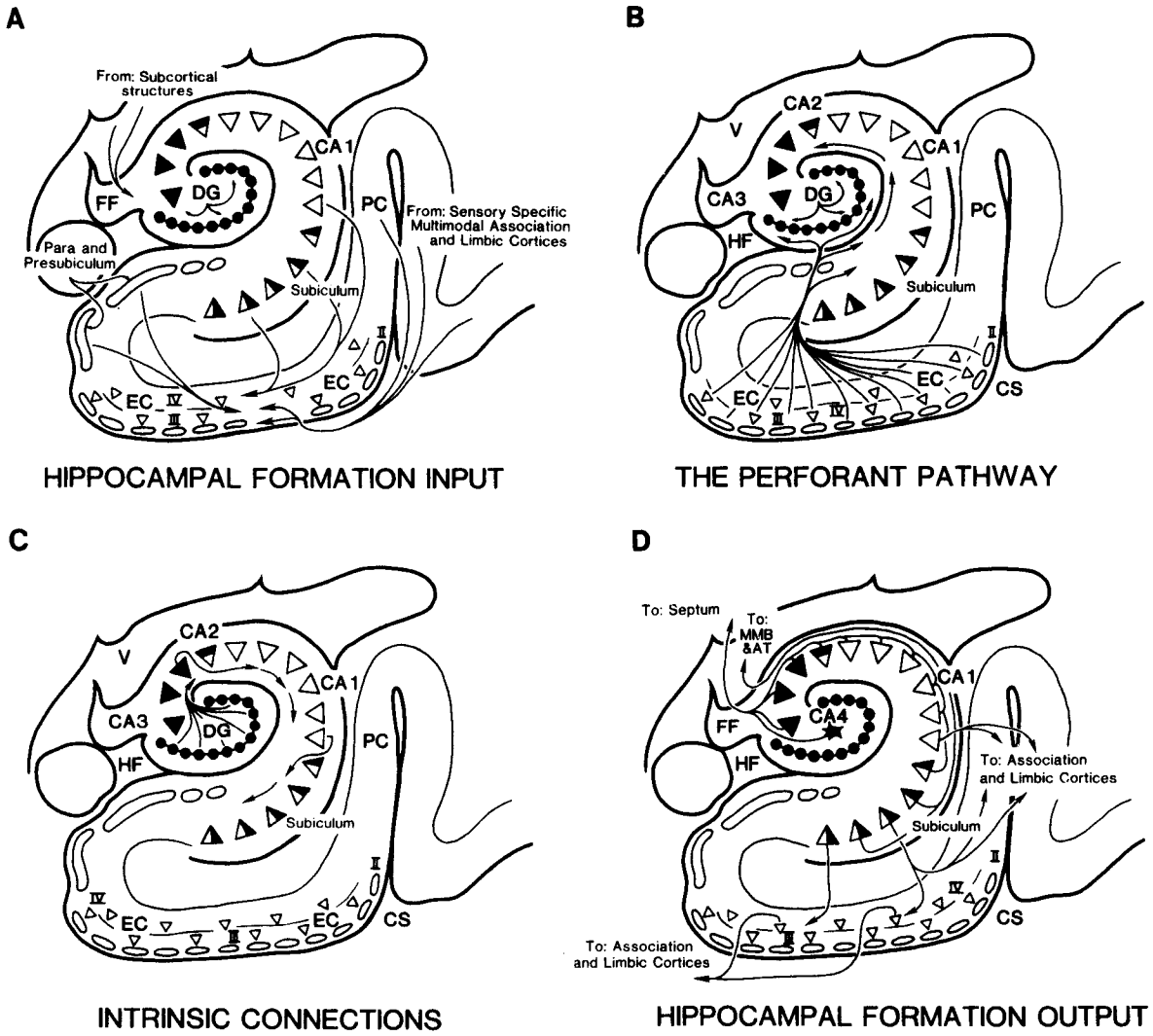

Figure 7.6. Cross-sections of the ventromedial temporal lobe showing the major connection of the entorhinal *(EC)* and perirhinal cortices *(PC)* and the hippocampal formation. **A,** Entorhinal input from neighboring cortical areas, the subiculum, and from the sensory-specific and multimodal association areas and the limbic lobe. Subcortical input directly to the hippocampal formation arrives via the fimbria-fornix *(FF)*. **B,** The origin and course of the major output pathway of the EC, the perforant pathway. Note its strong distribution to the pyramidal neurons of the subiculum, hippocampus *(CA1–CA3)* and dentate gyrus *(DG)*. **C,** The major intrinsic connections of the hippocampal formation. Note in particular the *DG* projections to the CA3 pyramids, CA3 pyramid projections to CA1 pyramids, and CA2 pyramid projections to the subiculum. **D,** The major output projections of the hippocampal formation and the EC. Note that all hippocampal formation pyramidal neurons project to the anterior thalamus (AT) and mamillary bodies (MMB). However, these neurons give rise to output projections to the association and limbic cortices. Direct projection to the deep layers of the EC and their projections to the same areas provide the anatomical basis for a powerful hippocampal influence on other cortical areas. (Other abbreviations: *cs* = collateral sulcus, *hf* = hippocampal fissure, *v* = inferior horn of the lateral ventricle.)

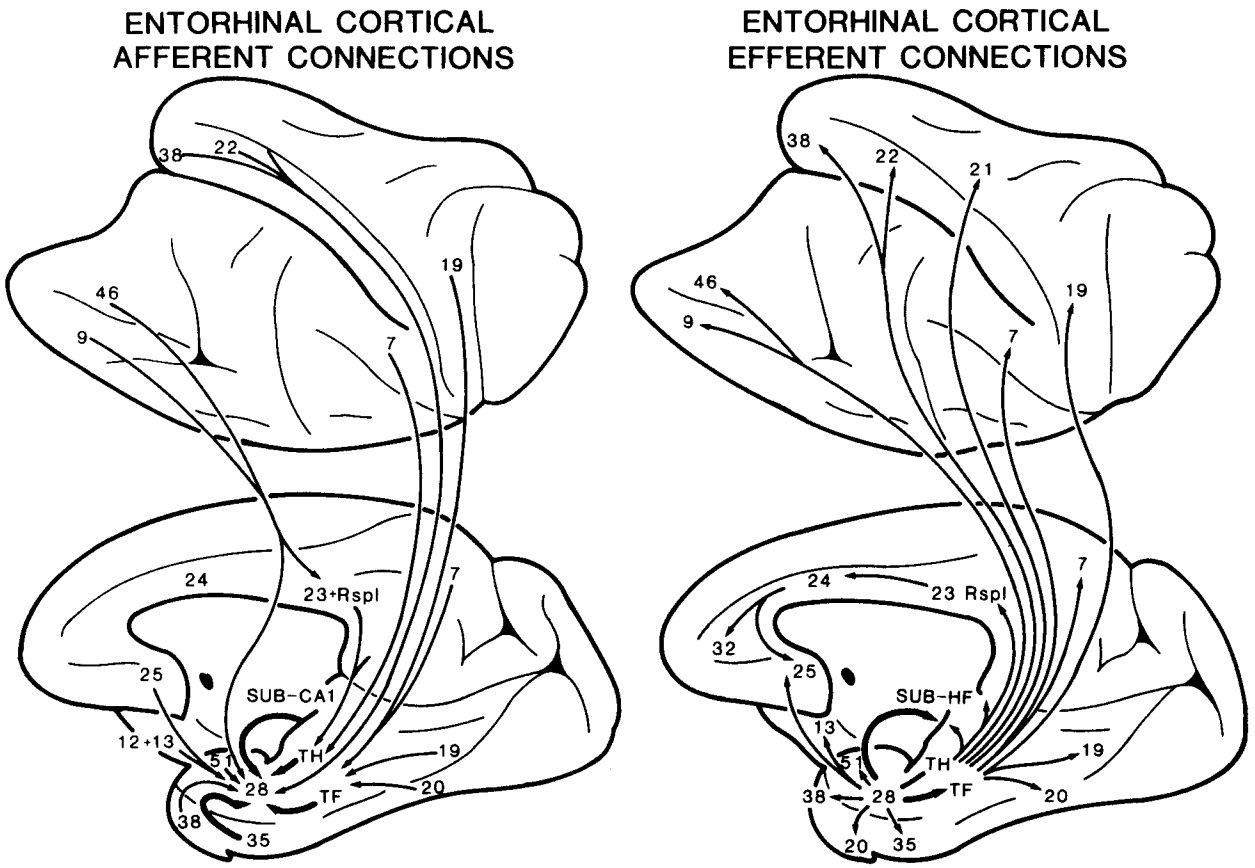

Figure 7.7. The major afferent or input and efferent or output connections of the entorhinal (Brodmann's area 28) and posterior parahippocampal (area TF and FH) cortices are summarized on lateral (inverted) and medial (upright) views of the rhesus monkey hemisphere. Note the convergence of afferents to this part of ventromedial temporal lobe and the divergence of efferents from it back to the association and limbic cortices. These link the hippocampal formation to the association and limbic cortices in a bi-directional manner.

campal formation, namely, CA1 projections to the adjacent subicular cortices (62, 63). It is now known that the neurons that form the subiculum, and not the hippocampal pyramids per se, are responsible for a large amount of hippocampal formation output and nearly all of its diversity with regard to influencing other brain areas (64–66). For example, the axons of CA3 pyramids project mainly to the septum, although they also give rise to major intrinsic and commissural inter- and intrahippocampal projections. With the exception of commissural projections, this is somewhat true for CA1 pyramidal neurons as well. However, the neurons that form the subicular cortices, and to a lesser extent those of the CA1 zone, have extensive extrinsic projections that divide hippocampal output into major components; one to a variety of cortical areas and another to a variety of subcortical structures such as the basal forebrain, amygdala, thalamus, and hypothalamus (64, 66–68). Thus, hippocampal output is disseminated much more widely than previously thought, and importantly, projects not to only subcortical areas, but to cortical ones as well. The latter are thought to be the neural basis of whether information is stored or remembered (56).

Another feature of hippocampal anatomy not described by early anatomists concerns the issue of afferent input, and, in particular, the input to the entorhinal cortex. Early investigators saw axons entering the entorhinal cortex, but use of the Golgi method precluded ascertaining their origin. This meant that the input to the major source of afferents to the hippocampal formation was left uncharacterized. It has been shown in recent studies that the entorhinal cortex receives powerful projections from many cortical areas (Figs. 7.7 and 7.8) in the temporal lobe (69–76) and from subcortical structures, such as the amygdala and midline thalamus (77–79). It is important to note that amygdaloid input to the entorhinal cortex is derived from amygdaloid nuclei that receive both limbic cortical input as well as input from association cortices located in both the frontal and temporal lobes (80–84). Additionally, these same nuclei receive direct or indirect hypothalamic (84) and basal forebrain input (85, 86). Thus, input to the entorhinal cortex is extensive. It arises largely from the cortices that form the limbic lobe, the amygdala, and the midline thalamus. In terms of cortex, proisocortical areas such as the perirhinal, posterior parahippocampal, cingulate, temporal polar, and posterior orbitofrontal cortices, and periallocortical areas such as the retrosplenial, presubicular, and parasubicular cortices are the major contributors. These transitional cortical areas, interposed between the allocortex and neocortex, receive major

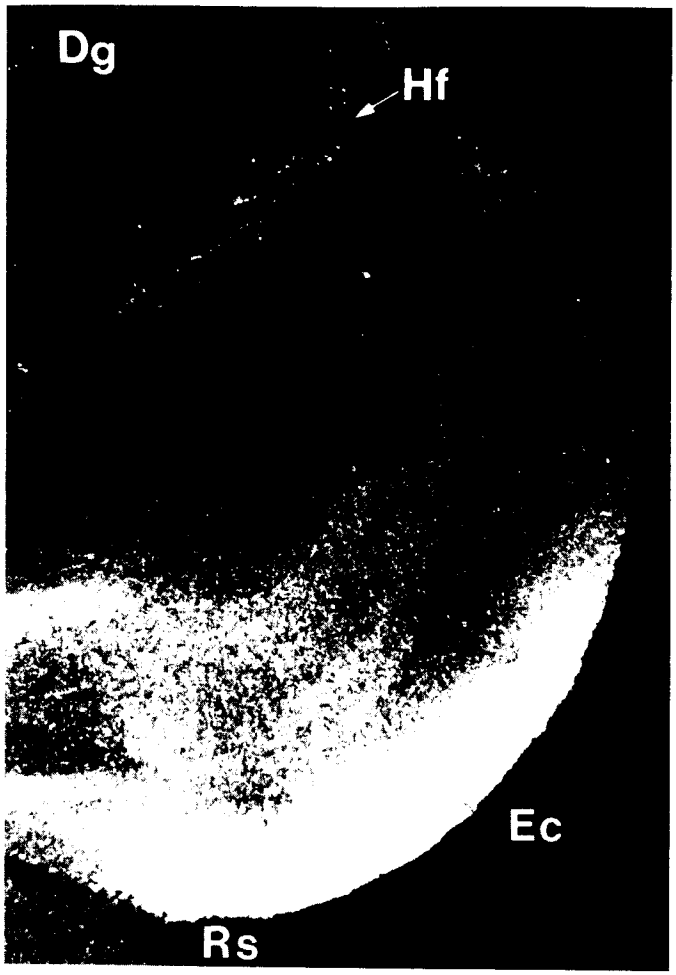

Figure 7.8. A dark-field photomicrograph of the entorhinal cortex *(EC)* in a rhesus monkey experiment where tritiated amino acids were injected into the posterior parahippocampal cortex to label axons and their terminals. White areas indicate the location of terminal labeling. Note the dense band of labeling in the superficial layer of the EC, indicating that the posterior parahippocampal area projects powerfully to the EC. (Other abbreviations: *Dg* = dentate gyrus, *HF* = hippocampal fissure, *Rs* = rhinhal sulcus.)

projections from both sensory-specific and multimodal association cortices. Thus, the entorhinal cortices receive a digest or abstract of the sensory output generated by subcortical and cortical areas, that includes both interoceptive and exteroceptive information. Like a censor and archivist, it seems to determine whether this is good for the organism or not, worthy of storage, or to be left to decay.

SUMMARY AND FUNCTIONAL CONSIDERATIONS

The hippocampal formation is the focal point for major forebrain neural systems that are interconnected with the sensory-specific association cortices and the multimodal association cortices. These are widespread systems that involve much of the cortical mantle. As mentioned, the cortices that form the limbic lobe in general, and the amygdala and posterior parahippocampal area in particular, receive input from the various association cortices and either project directly to the hippocampal formation or first to the entorhinal cortex, which then project to the hippocampal formation. The most compact part of this latter system, the perforant pathway, is the major output system of the entorhinal cortex (Fig. 7.9). It mediates a powerful excitatory input to the hippocampal formation that culminates in extrinsic output to the septum via the fimbria-fornix or intrinsic output to the subicular cortices. These latter areas then project to several basal forebrain areas, including the amygdala, various diencephalic nuclei, and many parts of the limbic lobe and association cortex. Thus, hippocampal output is disseminated widely by the subicular and CA1 pyramids of the hippocampal formation (Figs. 7.7, 7.10, and 7.11).

Amygdaloid Complex

As mentioned previously, several amygdaloid nuclei receive inputs from the cerebral cortex (Fig. 7.12) and from

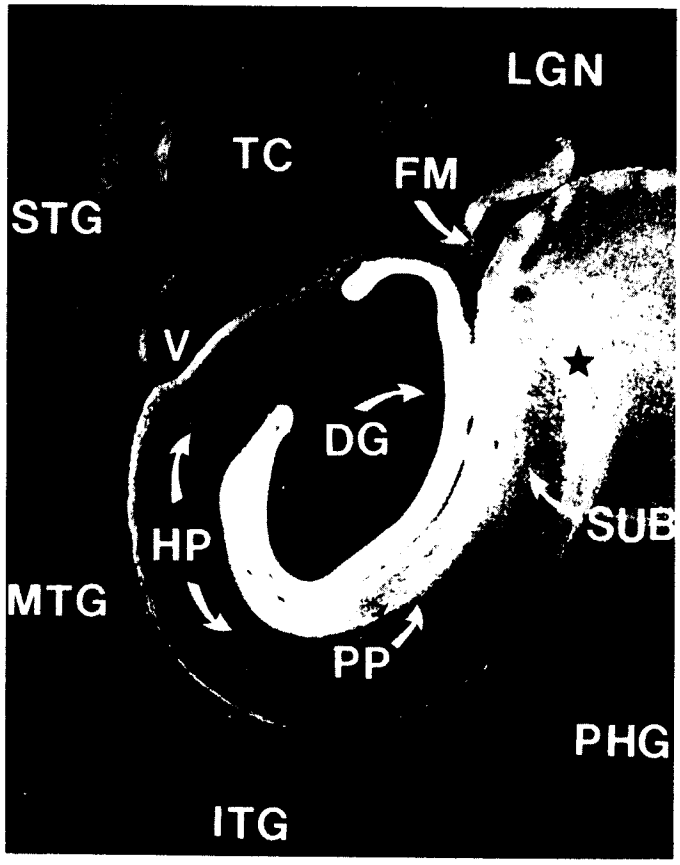

Figure 7.9. A dark-field photomicrograph of the hippocampal formation in a rhesus monkey experiment where tritiated amino acids were injected into the entorhinal cortex to label perforant pathway axons and their terminals. White areas indicate the location of terminal labeling. Note the dense terminal labeling in the subiculum (Sub) CA1, CA3, and dentate gyrus (Dg) molecular layers, indicating a powerful linkage between the entorhinal cortex and hippocampal formation. The perforant pathway is one of the largest projections of the cerebral cortex and the major avenue by which the limbic and association cortices influence the hippocampal formation. (Other abbreviations: *Tc* = tail If caudate nucleus, *V* = ventricle, *ITG* = inferior temporal gyrus, *MTG* = middle temporal gyrus, *STG* = Superior temporal gyrus, *HP* = Hippocampus, *PHG* = parahippocampal gyrus, *LGN* = Lateral geniculate nucleus, *PP* = perforant pathway.)

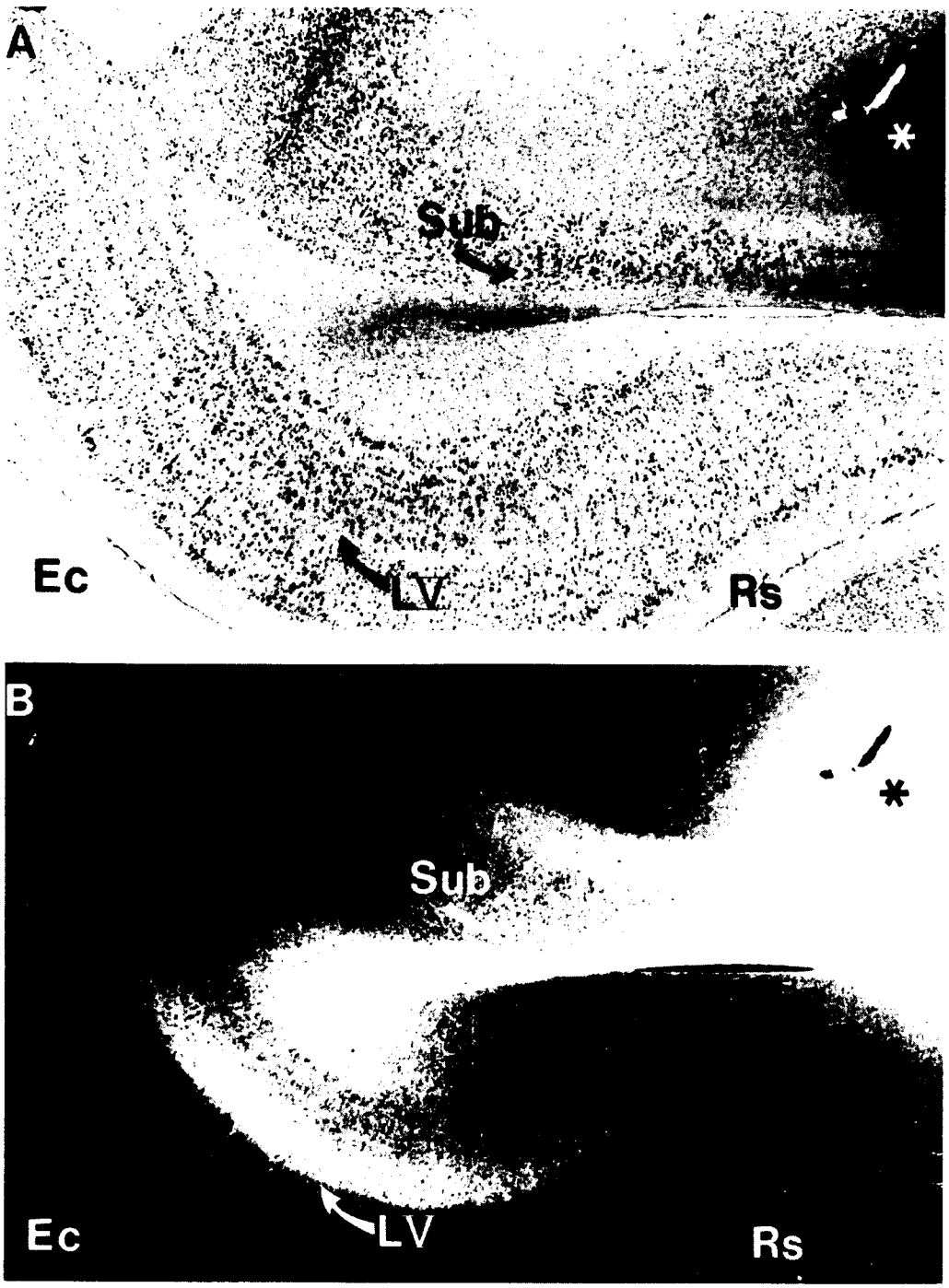

Figure 7.10. **A,** Nissl-stained bright-field photograph of the anterior subiculum *(Sub)* and the entorhinal cortex *(EC)* in a rhesus monkey. The dark area (marked with an *asterisk*) shows where tritiated amino acids are injected into the subiculum *(Sub)*. **B,** The same microscopic field shown in *A,* but with dark-field viewing conditions. Note the dense subicular projection to layer V of the EC. This direct projection from the hippocampal formation to the cortex is one of many cortical projections that arise from the subiculum and CA1 parts of the hippocampal formation. (Other abbreviations: *Lv* = lateral ventricle, *Rs* = rhinal sulcus.)

a host of subcortical structures of both diencephalic and mesencephalic origin. The latter includes such structures as the hypothalamus, periaqueductal gray matter, peripeduncular nucleus, ventral tegmental area, supramammillary nucleus, and midline thalamic nuclei (84, 85, 87).

Unlike the hippocampal formation, whose input is derived largely from limbic lobe areas that receive input from the association cortices, many association areas project directly to the amygdala without relays in the limbic lobe. For example, the visual association cortices of the lateral temporal neocortex send direct projections to the lateral amygdaloid nucleus and to the dorsal part of the laterobasal amygdaloid nucleus (80–82, 88, 89). Some investigators have shown also that the auditory association cortex of the superior temporal gyrus also projects directly to the lateral amygdaloid nucleus. Input related to somatic sensation also converges on this nucleus from the insular cortex (90).

Although neocortical input from association cortices constitutes a major source of input to the lateral amygdaloid nucleus, it is erroneous to characterize all corticoamygdaloid input as derived from the neocortex. Indeed, the proisocortices, periallocortices, and allocortices make a large contribution (83). For example, the medial half of the lateral nucleus receives input from the insular, temporal polar, and

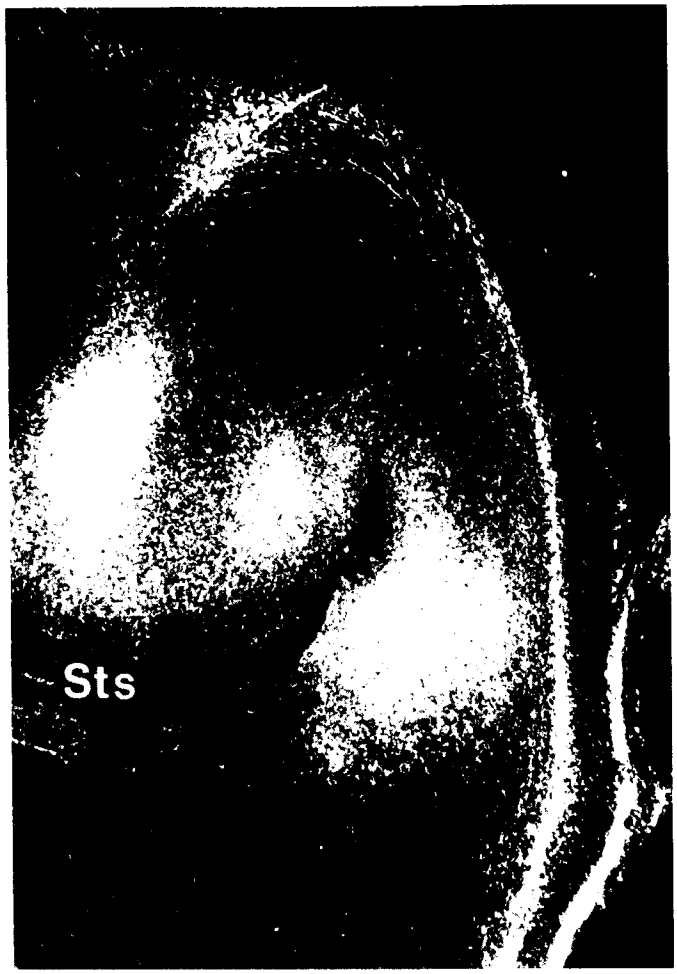

Figure 7.11. A dark-field photomicrograph showing terminal labeling in the depths of the superior temporal sulcus (Sts) in a rhesus monkey experiment where labeled amino acids were injected into the cortex of the posterior parahippocampal gyrus. The latter receives a strong hippocampal output and projects in turn to association areas in all other lobes.

orbitofrontal cortices, and all parts of the limbic lobe (Fig. 7.12). The basal complex of the amygdala, consisting of the laterobasal, accessory basal, and mediobasal nuclei, receives cortical projections derived almost exclusively from the proisocortices and the periallocortices. The accessory basal nucleus, for example, receives strong projections from the temporal polar cortex, the insular cortex, the medial frontal cortex, and to some extent, the orbitofrontal cortex. The mediobasal nucleus is not well characterized in terms of input, but receives projections from the perirhinal and subicular cortices (66). The laterobasal nucleus receives input from many of the cortical areas just listed, but additionally, is characterized by having input from the anterior cingulate cortex. The subiculum and entorhinal cortices also project to part of the basal amygdaloid complex. These nuclei collectively form the basal complex, the largest mass of the amygdala, and thus, limbic lobe input must be regarded as the major source of cortical input.

The central amygdaloid nucleus is unusual in the sense that it receives input derived from all types of cortex. For example, it receives input from the lateral temporal isocortex, the temporal polar, orbitofrontal, and insular proisocortex, the entorhinal periallocortex, and the periamygdaloid and primary olfactory allocortex (83). The superficial nuclei of the amygdala, such as the medial nucleus and the various cortical nuclei, receive input largely from allocortical regions, such as the subicular and periamygdaloid cortices and olfactory piriform cortex.

Until quite recently, it was believed that the major input and output relationships of the amygdala were with the hypothalamus. Such connections are strong (84) but the diversity of amygdaloid output is far more extensive than appreciated previously. For example, the lateral nucleus and some components of the basal complex project strongly to the entorhinal cortex (91), to several association areas, and even to the primary visual cortex (92). Additionally, the basal amygdaloid complex has strong reciprocal interconnections with the subiculum, the major source of hippocampal output

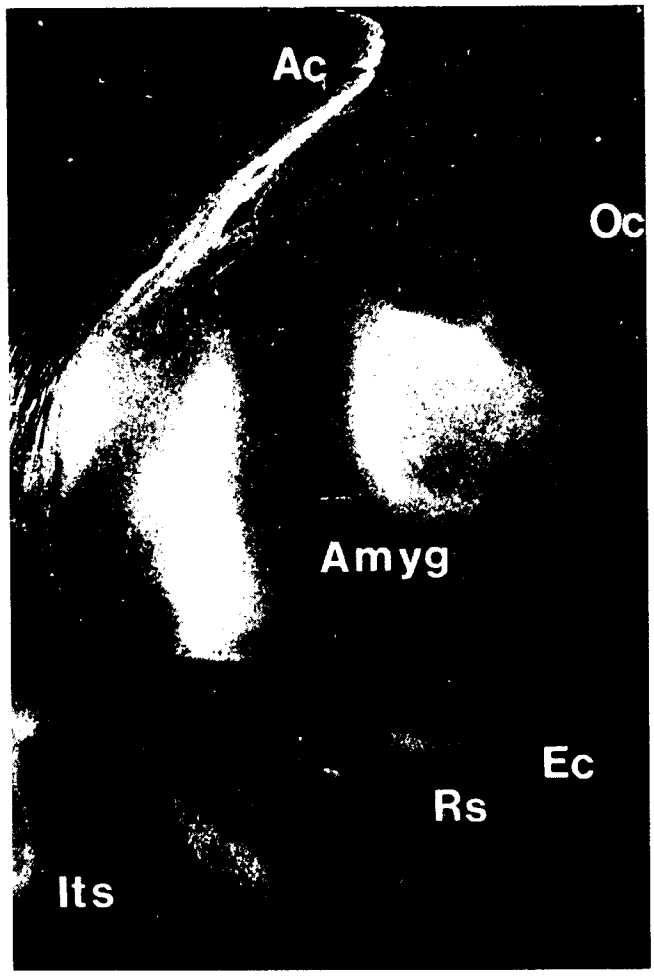

Figure 7.12. A dark-field photomicrograph of the amygdala (*Amyg*) and entorhinal cortex (Ec) showing terminal labeling in a rhesus monkey experiment where labeled amino acids were injected into the cortex of the temporal pole. The amygdaloid terminal labeling is primary over the medial part of the lateral nucleus and over the accessory basal nucleus (other abbreviations: *Ac* = anterior commissure, *Its* = inferior temporal sulcus, *Oc* = optic chiasm, *Rs* = rhinal sulcus).

(66, 91, 93, 94). From these studies, it is clear that the amygdala is very much interrelated with the hippocampal formation in anatomical terms and that these two temporal neighbors undoubtedly influence each other to a great degree.

Nonhypothalamic subcortical projections arise from several amygdaloid nuclei and link the structure with many parts of the neuraxis. Of special interest are powerful projections to parts of the basal forebrain, including the nucleus basalis of Meynert (95). Additional nonhypothalamic subcortical projections course to the dorsomedial thalamic nucleus (96–98) and to several autonomic centers in the brainstem (95, 99).

Among the more surprising aspects of amygdaloid anatomy described recently is that this structure has strong projections to many parts of the temporal association, insular, and frontal cortices (90, 94, 96, 97, 100–102). In the frontal lobe, these projections end on parts of the isocortices that form the frontal granular cortex, the frontal agranular cortex, and the cingulate, medial frontal, and posterior orbitofrontal proisocortices. Powerful projections from the basal complex of the amygdala to the neostriatum and ventral striatum also have been described (103).

SUMMARY AND FUNCTIONAL CONSIDERATIONS

From a neural systems viewpoint, the amygdala must be considered from a broader perspective than its classically-described interrelationships with the hypothalamus and olfactory system. For example, the amygdala has powerful direct interconnections with much of the anterior cortex of the limbic lobe and with neocortical areas of the frontal, temporal, and even occipital lobes. Additional smaller projections have been reported to terminate in the premotor cortices and limbic lobe area 24, both of which project directly to the supplementary motor cortex. Moreover, projections to the cingulate motor area, and especially M3, provide a means for it to influence corticospinal axons. Additional projections connect the amygdala with the neostriatum and ventral striatum, involving it in basal ganglia circuitry. Certain amygdaloid nuclei also project strongly to the nucleus basalis of Meynert, whose axons provide a powerful cholinergic input to the cortex. Descending amygdaloid projections from the central amygdaloid nucleus also provide input to autonomic centers in the brainstem. Although much of the input to the amygdala, particularly from subcortical areas, cannot be characterized well in functional terms, this is not the case for amygdaloid output. Overall, it can be concluded that amygdaloid output is directed toward the origin of what may be termed effector systems that influence motor, endocrine, and autonomic areas along the full extent of the neuraxis. Thus, it is very much unlike the hippocampal formation, whose output to such areas is either less strong or more indirect, and instead shifted more toward the association cortices. A persuasive argument could be made that the amygdala more greatly influences overt behavior, while the hippocampus more greatly influences more covert aspects of behavior such as cognition and memory.

Nucleus Basalis of Meynert

The neurons that form the nucleus basalis of Meynert have attracted substantial attention because they project to the cerebral cortex (104–108) and they are affected frequently in Alzheimer's disease (AD) (109). Such projections had been suggested in earlier ablation experiments, but the magnitude of this projection was not appreciated. It is now clear that probably all of the nucleus basalis of Meynert projects to the cortex and all parts of it. These findings are intriguing, but they assume added significance with the demonstration that the majority of these neurons contain cholinergic enzymes, and, in fact, provide the major source of cholinergic input to the cortex (107, 110). Thus, they mirror the cholinergic projections of their counterparts in the diagonal band nuclei and medial septum that project to the allocortices of the hippocampal formation.

The neurons forming the nucleus basalis are large, hyperchromatic, multipolar, and fusiform-shaped cells that lie among the ascending and descending limbic, hypothalamic, and brainstem pathways that course through the basal forebrain. Part of the nucleus is found within the substantia innominata, but cholinergic neurons span the anterior-posterior expanse of the ventral surface of the hemisphere all the way from the septum anteriorly to the midbrain posteriorly. They also have a lateral extension that follows the course of the anterior commissure into the temporal lobe (106, 110). Scattered acetylcholinesterase and choline acetyltransferase-positive neurons are also found within the internal and external medullary lamina of the globus pallidus, in the lateral hypothalamus, and in the dorsal parts of various amygdaloid nuclei. Calling this a "nucleus" somewhat stretches the imagination, although the common cholinergic nature of its neurons somewhat salvages the term.

The output of the nucleus basalis to the cortex has been well characterized in the rat and monkey. These studies reveal that a rigid topography exists with regard to where in the cortical mantle they end (108, 110–112). Additionally, it has been demonstrated recently that the nucleus basalis projects to the basal complex of the amygdala (85, 86). Importantly, it is also known that this nucleus projects to the reticular nucleus of the thalamus (113–116). This places the nucleus basalis in a position to influence the cortex directly as well as indirectly, because the reticular nucleus governs thalamic transmission via intrinsic thalamic connections (117). However, beyond these observations, little else is known about the efferent connections of the nucleus basalis of Meynert, and there remains a fundamental need for further study of this in experimental neuroanatomy. Suggestive evidence was provided in early studies that nucleus basalis axons project at least as far caudally as the midbrain (105).

The input to the nucleus basalis of Meynert is better understood. In terms of cortex, it has been shown that it receives projections from only a small percentage of the

cortical areas to which it sends axons (118). These include such areas as the olfactory, orbitofrontal, anterior insular, temporal polar, entorhinal, and medial temporal cortices—all components of the limbic lobe. Subcortical projections to the nucleus basalis arise from the septum, nucleus accumbens, hypothalamus, amygdala, preoptic nucleus, and from the peripeduncular nucleus of the midbrain (106, 119–121).

SUMMARY AND FUNCTIONAL CONSIDERATIONS

With regard to neural systems, it is reasonable to believe that the nucleus basalis of Meynert is a key structure. For example, the widespread projections to the cortex and the fact that acetylcholine serves as the transmitter for these projections are of fundamental importance. These neurons are much like serotonergic neurons in the raphe complex, noradrenergic neurons in the locus ceruleus, and dopaminergic neurons in the ventral tegmental area with similar cortical projections. Like these neurons, many of their projections are not reciprocated by projections from the cortex their axons innervate. The input to nucleus basalis neurons seems topographically organized and rather specific. At least two investigations have reported afferent input that seemingly "picks out" the clusters of nucleus basalis neurons. Some of these originate in the amygdala and may provide a highly specific, albeit indirect, manner for this structure to exert its influence on widespread parts of the cortical mantle. These projections arise from amygdaloid nuclei that receive intrinsic amygdaloid projections, suggesting that, at least in so far as the amygdala is concerned, its output to the nucleus basalis reflects output deriving from much of the structure. In this context, it should not be overlooked that the subiculum of the hippocampal formation projects both to the basal complex of the amygdala and to other basal forebrain areas that project to the nucleus basalis. Thus, a highly synthesized output from the hippocampal formation would seem plausible. On these grounds, and on the basis of its direct limbic cortical input, it can be concluded that the major input to the nucleus basalis originates with the entire limbic system as a whole. Interestingly, the nucleus basalis of Meynert is not influenced directly by the major part of the cortex to which it projects. It is only influenced indirectly, after the whole sequence of corticocortical connections is retraced.

Finally, the nucleus basalis of Meynert receives projections from the hypothalamus. These need further study, but provide a structural basis by which the internal state of the organism can indirectly influence both the motor and the sensory cortices and influence the manner by which the organism interacts with its environment. Many well-documented behavioral observations suggesting such influences have not had strong anatomical backing in the past. In this regard, however, it should be noted that several limbic structures, notably the amygdala and hippocampal formation, receive hypothalamic projections and project back to the cortex. Thus, the nucleus basalis of Meynert is not unique in this sense.

Dorsomedial and Midline Thalamic Nuclei

The dorsomedial thalamic nucleus is known to play a role in many behaviors in humans, including visuospatial processing, attention, and memory. Contributing roles have also been argued for aphasia, dementia, and temporal disorientation when the nucleus is diseased or damaged. Some authors attribute damage to this nucleus as the pathological basis for the debilitating cognitive changes that occur in the alcoholic Korsakoff syndrome (122). Evidence from penetrating wounds (123) and thalamic infarcts (124) support this contention. The literature regarding prefrontal lobotomy also applies here, because one would think that this surgery would cause extensive retrograde cell changes in the dorsomedial thalamic nucleus. However, only a subset of the behavioral changes listed earlier was reported in individuals having this surgical procedure, and proportedly, these were confined largely to the realm of personality changes.

The dorsomedial thalamic nucleus is a large midline association nucleus having powerful interconnections with the prefrontal granular association cortex (125–127). From a cytoarchitectural viewpoint, it is a complex composed of several subdivisions. These form partially concentric areas around the third ventricle. In general terms, they have topographically organized reciprocal connections with the prefrontal cortex in the monkey (125–129). For example, the most medial subdivision of the dorsomedial nucleus projects to and receives projections from the posterior orbital, anterior cingulate, and medial frontal cortex. A more lateral subdivision projects to and receives projections from the prefrontal association cortex dorsal and ventral to the principal sulcus and the anteriormost parts of the orbitofrontal cortex. The most lateral subdivision of the dorsomedial nucleus sends projections to and receives projections from the periarcuate cortex in the anterior bank of the arcuate sulcus.

With the exception of its prefrontal cortex connections, the neural systems of the dorsomedial nucleus are understood poorly. In fact, known input and output relationships with other structures are decidedly sparse in comparison with other nuclei of the thalamus and even other association nuclei, such as the pulvinar nuclei.

Some evidence, however, is accumulating that enables at least a partial characterization of this structure. For example, early ablation-degeneration experiments identified another cortical projection to this large nucleus from the lateral temporal cortex (80). Additional evidence suggests that certain cortical areas of the limbic lobe, such as the anterior cingulate cortex, have connections with the dorsomedial nucleus (130). This is of some interest because this part of the cingulate cortex (Brodmann's area 24) contributes axons to the corticospinal pathway directly to the supplementary and primary motor cortices.

A direct input from the amygdala to the dorsomedial nucleus has been known for several years. Recent tracing experiments buttress and extend these findings (77, 97, 98). These axons arise from the basal complex of the amygdala

and terminate in the more medial parts of the dorsomedial nucleus. The mediobasal nucleus seems to be the primary focus for this projection, although other basal nuclei (laterobasal and accessory basal) appear to contribute as well. These axons course largely via the ventroamygdalofugal pathway and the inferior thalamic peduncle. Curiously, the temporal cortical projections to the dorsomedial nucleus and those that arise from the amygdala are not reciprocated by thalamocortical or thalamoamygdaloid projections. Additional input from the ventral pallidum, substantia nigra, septum, superior colliculus, and hypothalamus have been reported.

SUMMARY AND FUNCTIONAL CONSIDERATIONS

Overall, the neural systems involving the dorsomedial thalamic nucleus are not well known. The position of this nucleus ventral to two large fiber systems, the fimbria-fornix and corpus callosum, its encasement within the internal medullary lamina of the thalamus, and the fact that the mammillothalamic tract traverses its ventral parts, have discouraged experimental study. Investigators' attention has focused primarily on the amygdalothalamic and temporothalamic projections. These link the dorsomedial nucleus with temporal structures known to play a role in memory. For example, the lateral temporal cortex has been characterized as playing a mnemonic role in certain perceptual learning tasks. Also, the mediobasal amygdaloid nucleus, which contributes strongly to the amygdalothalamic projection, is a direct recipient of subicular output from the hippocampal formation. Finally, recent anatomical findings reveal that the frontal association cortices that receive powerful input from the dorsomedial nucleus themselves receive projections from the hippocampal formation and project to the cortex around the rhinal sulcus, which, in turn, projects directly to the subiculum.

The findings themselves may be sufficient to implicate the dorsomedial thalamic nucleus in at least some aspects of memory and many other behaviors. However, caution must be exercised when making clinicopathologic inferences involving this nucleus. Several midline nuclei of the thalamus project directly to the hippocampal formation, entorhinal cortices, and amygdala. These include the nucleus reuniens, the paracentral nucleus, and the thalamic paraventricular nucleus. These are likely to be involved in hemorrhagic and nonhemorrhagic infarcts to the midline thalamus, and to be damaged penetrating wounds that involve the thalamus. They also are likely to be damaged in patients with alcoholic Korsakoffs syndrome. At present, an association of midline thalamic damage with memory impairments and behavioral changes is known, but the role of specific thalamic nuclei remains to be evaluated by further study.

PREFRONTAL CORTEX

The frontal lobe lies anterior to the central sulcus and can be divided into two major parts, a caudal part containing the electrophysiologically "excitable" motor cortices and a rostral part containing the prefrontal association cortex (Fig. 7.2). The motor cortices include the primary (M1 or area 4), supplementary (M2 or area 6m), and lateral premotor cortices (LPMC or areas 6D and 6V) (131–135). All are characterized as agranular cortex, attesting to the fact that their internal granular layer, or layer IV, is not conspicuous. It is well known that M1 plays a critical role in activating and facilitating independent body movements. On the other hand, M2 seems more involved with whole body movements and internally generated movements that are integrated in orderly fashion. Significant modulation of neuronal activity in the lateral premotor cortex, and, in particular, the ventral part of lateral area 6, has been shown to be coupled with stimulus-triggered (visual and somatosensory cued) motor responses and during the execution of purposeful movements such as grasping and/or bringing the hand to the mouth.

Also included as part of the motor cortices are the frontal eye field (FEF or area 8), supplementary eye field (SEF or area F6) and presupplementary motor area (pre-SMA) (Fig. 7.2) The FEF and SEF are located on the lateral surface of the hemisphere (136–138). The FEF is located anterior to the midportion of lateral premotor cortex and has a dysgranular cytoarchitecture. This refers to the fact that FEF is characterized by a poorly defined or incipient, internal granular layer IV. The SEF appears to be a subfield within area 6D. The rostral part of area 6D of the lateral premotor cortex has also been shown to be dysgranular (139). Both the FEF and SEF regulate contralateral saccadic eye movements. The pre-SMA is located on the medial wall of the hemisphere (140), rostral to M2, and corresponds to Walker's area 8B (141). Neurons in this field modulate their activity prior to and during movement.

The prefrontal cortex lies rostral to the motor-related cortices and extends to the frontal pole (Fig. 7.2). On the medial surface, the prefrontal cortex lies anterior to the medial component of motor cortex as well as the anterior part of cingulate gyrus. The primate prefrontal cortex is subdivided commonly on broad, anatomical grounds. Its major partitions include ventrolateral, dorsolateral, medial, and orbitofrontal regions. In the monkey, the principal sulcus is located on the lateral surface of the hemisphere, and its depths form the boundary between the ventrolateral and dorsolateral regions of prefrontal cortex. As named, the medial region of the prefrontal cortex is located on the medial surface of the hemisphere. Finally, the orbitofrontal region of the prefrontal cortex lies in the anterior cranial fossa above the bony orbit and forms the basal, or ventral, surface of the frontal lobe.

A large portion of the prefrontal cortex is classified cytoarchitecturally as granular cortex and has six well-differentiated layers, including a prominent external granular layer II and internal granular layer IV (142, 143). However, differences in layers II and IV as well as the other cortical laminae serve as a basis for partitioning the frontal granular cortex into several subfields. They are designated numeri-

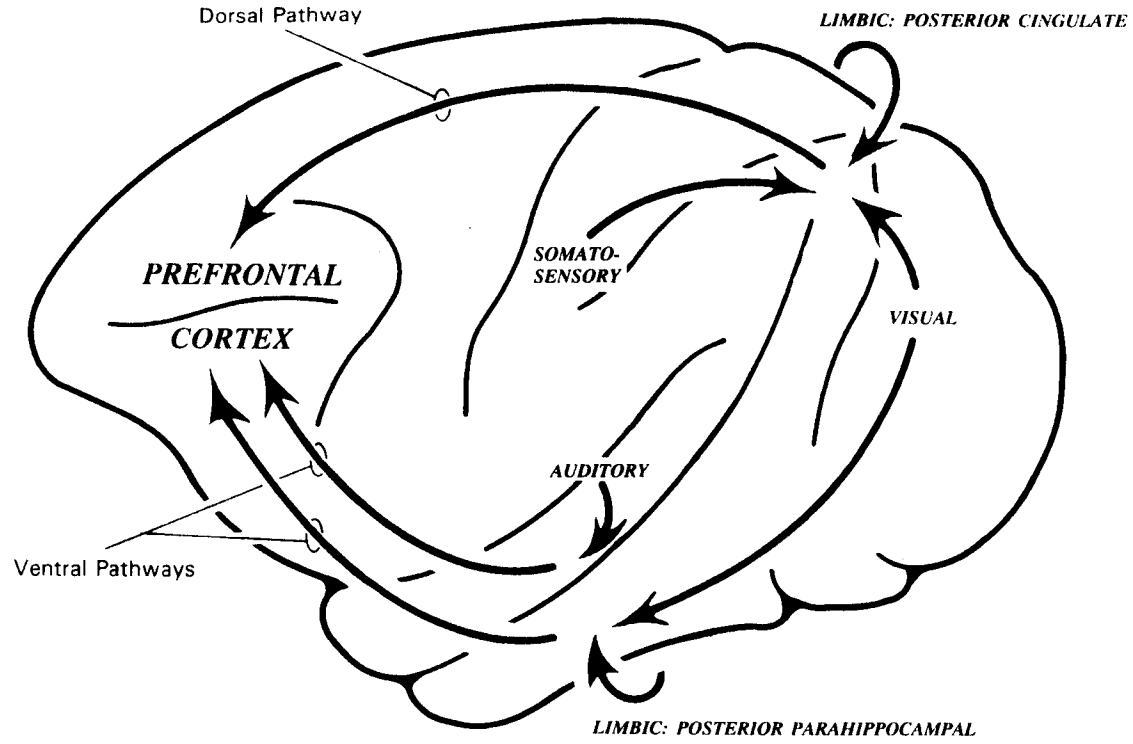

Figure 7.13. Some of the major cortical association input to the prefrontal cortex is depicted on a lateral view of the monkey cerebral hemisphere. Not the dorsal pathway from the inferior parietal gyrus and dorsal peristriate area carrying cingulate information and the ventral pathways carrying auditory, visua and posterior parahippocampal information. These provide cortical information from all of the other lobes, including the limbic lobe.

cally, according to Brodmann and others. The prefrontal cortex includes areas: 45, 12, 46, 10 and 9 laterally, 9, 10 and 32 medially; and 12, 13, 11, 10 and 14 ventrally (Fig. 7.2). Many of these areas have recently been redefined and further subdivided.

Cortex on the orbitofrontal surface lobe can also be subdivided on cytoarchitectural criteria into a caudal agranular sector, an anterior granular sector, and a transitional dysgranular sector between them (142, 144, 145). From this perspective, general trends and distinguishing features of major orbitofrontal organization are clearly recognizable. For example, agranular and dysgranular components are located caudally on the orbitofrontal surface and are strongly connected with the limbic cortices, amygdala, and midline nuclei of the thalamus. In contrast, the granular component is situated rostrally on the orbitofrontal surface. This cortex is linked strongly to isocortical association areas and association nuclei of the thalamus. As expected, these unique patterns of neural interconnections would differentially influence activity and events processed in rostral versus caudal parts of the orbitofrontal cortex. Lesions rarely affect small parts of the orbitofrontal surface, and thus are correlated with more global behavioral changes and not specific impairments. For example, posterior lesions disrupt limbic and medial temporal connections and lead to changes in emotional and social behavior, as well as in autonomic regulation. More anterior lesions disrupt association inputs and affect more complex behaviors.

Cortical Association Connections of Prefrontal Cortex

In addition to its obvious role in motor behavior, fronta lobe function has long been associated with a variety o higher-order behaviors and cognitive processes. Some of the more notable ones include working memory, motor planning, developing and implementing long-term strategies, decision making, and problem solving (146–153). Wher considering the higher-order functions mediated by the prefrontal cortex, the finding that prefrontal cortex is linkec directly to a constellation of cortical association areas shoulc not be surprising. Indeed, the prefrontal cortex is wel known for its widespread corticocortical connections with distal parts of the cerebral cortex, specifically including primary association and multimodal association cortices (Fig. 7.13).

Primary association cortex is committed functionally to the early processing of sensory data, conveyed by the neurons of an adjacent primary sensory area. Primary association cortex operates in a more integrative fashion than primary sensory area. In contrast, multimodal association cortex is not committed to processing information related to one modality, but rather integrates highly transformed information, whose source can be traced back to multiple sensory modalities. Although the traditional dogma suggests that multimodal association cortex represents the end stages of cortical processing, it is becoming more clear that information flowing in the reverse direction, i.e. directed

from multimodal association back to the primary association areas, may initiate and synchronize neural elements that are responsible for forming selective preceptions (154).

The prefrontal cortex is linked to sensory association and multimodal association cortices of the parietal lobe (areas 7a, 7b, and 7m) and temporal lobe (areas V4t, MT, and MST) as well as sensory association cortices of the anterior part of the occipital lobe (area V3) (22, 24, 26, 88, 144, 155, 156). It has been shown in the monkey that the posterior part of the inferior parietal lobule (area 7a), anterior part of the occipital lobe, and the medial parietal lobule (area 7m) are reciprocally connected with the dorsolateral and sulcal principalis regions of the prefrontal cortex. Anatomical and behavioral investigations conducted over the past three decades have led to the conclusion that long association pathways, reciprocally linking posterior parietal cortex and prefrontal cortex, are particularly important for the appropriate execution of visually guided movements. Presumably, somatosensory and visual inputs converge on posterior part of the inferior parietal lobule, and information related to spatial orientation and motion analysis is conveyed to the dorsolateral prefrontal cortex (Fig. 7.13) (157, 158). Therefore, the dorsolateral part of the prefrontal cortex is thought to process information concerned with understanding *where* an object is in space. It is also known that the more rostral part of the inferior parietal lobule (area 7b) and ventrolateral part of the temporal lobe project to the ventrolateral part of the prefrontal cortex. Specifically, the projection from the ventrolateral part of temporal lobe is thought to carry information dealing with form and object recognition. Therefore, it has been suggested that the ventral pathway may constitute a processing stream that addresses *what* an object represents in the extrapersonal environment. The prefrontal cortex is also influenced by other parts of the temporal lobe through a subcomponent of the ventral pathway, whose origin arises from the rostral part of the superior temporal gyrus as well from the temporal pole. This projection probably represents an important source of auditory input to the ventrolateral part of the prefrontal cortex.

In addition to the long association pathways linking the prefrontal cortex with the parietal, occipital, and temporal lobes, short association pathways interlock the various parts of the prefrontal cortex with one another in an organized fashion (142). The less-differentiated (in terms of cytoarchitectonic lamination) agranular and dysgranular cortices, located posteriorly on the basal and medial surface of the prefrontal cortex, give rise to widespread *intrinsic* prefrontal connections. In contrast, the more differentiated isocortical granular areas, which are situated anteriorly and laterally, are characterized by more limited *intrinsic* connections; they account instead for a large component of the frontal lobe's widespread *extrinsic* prefrontal connections.

Cortical Limbic Connections of the Prefrontal Cortex

The strong structural relation between prefrontal cortex and association cortex has played a dominant role in shaping our views on prefrontal organization and function. However, it is important not to neglect the structural interaction between the prefrontal cortex and limbic lobe, which is also very strong. There are many direct connections between the limbic lobe and the prefrontal cortex. Limbic projections to the prefrontal cortex arise from diverse and widespread parts of the limbic lobe, including the cingulate, orbitofrontal, temporopolar, perirhinal, entorhinal, posterior parahippocampal and the insular cortices (20, 21, 26, 30, 70, 74, 76, 159, 160). Although the lateral prefrontal cortex is a target for some of these connections, the bulk of this anatomical interrelationship is established with the posterior orbitofrontal and medial prefrontal regions.

As outlined previously, the prefrontal cortex maintains a highly organized anatomical affiliation with the cingulate gyrus. The more anterior dorsolateral prefrontal cortex is connected with the posterior cingulate cortex (area 23), while the posterior dorsolateral prefrontal cortex is more strongly linked to the anterior cingulate gyrus. Similarly, the anterior orbitofrontal cortex is connected to area 23 and the posterior part is connected to area 24.

Early studies that relied on the Marchi technique to trace neural connections failed to recognize a strong connection between the frontal and temporal lobes. However, use of more sensitive tracing techniques enabled investigators to demonstrate that fibers forming a subcomponent of the uncinate fasciculus, as well as the extreme capsule, interconnect the frontal and temporal lobes in a strong and highly specific fashion. The strongest links with the limbic portion of temporal lobe involve the posterior orbitofrontal cortex and medial prefrontal cortex, followed by the lateral prefrontal cortex.

Although a precise topography has yet to be determined, a number of other areas in the temporal portion of the limbic lobe are connected to the prefrontal cortex. They include the temporal pole (area 38), perirhinal (area 35), entorhinal (area 28), posterior parahippocampal (areas TH and TF), presubicular, and subicular cortices. All but the subicular connection have been shown to be reciprocal. The subiculum of the hippocampal formation projects to the posterior part of the orbitofrontal cortex and send some afferents to the dorsolateral part of the prefrontal cortex. A particularly heavy component of this projection terminates in the posterior part of the gyrus rectus, on the orbitofrontal surface. Hippocampal output is known to be mediated heavily by the subiculum and to some extent the CA1 sector of the hippocampal formation. Thus, subicular/CA1 output represents a direct hippocampal influence on the prefrontal cortex.

All parts of the prefrontal cortex are reciprocally connected with the insula, and a distinct anatomical relationship between cortex forming the orbitofrontal surface and the insula has been demonstrated. The agranular part of the orbitofrontal cortex is preferentially linked to the agranular part of the insula. In terms of topography, this translates into distinct connections between the posterior orbitofrontal cortex and the anterior insula. Likewise, granular orbitofrontal cortex is preferentially linked to granular insula.

Anterior parts of the insula receive direct input from the gustatory and olfactory cortex, and the posterior parts receive input from primary somatosensory and auditory areas. This suggests that the insula may be a common site of *direct* convergence of all nonvisual sensory afferents. This is remarkable because integration of multimodal sensory information occurs elsewhere in the brain *after* a polysynaptic relay through sensory association cortex to multimodal cortex. All parts of the insula appear to receive input from sensory association and multimodal association cortices. The diversity of projections to the insula implies that prefrontal input from the insula may either be as little as one synapse away from a primary sensory area, or may be highly processed.

Amygdala projections to prefrontal cortex arise primarily from the basolateral and accessory basal nuclei, and to a lesser extent from cortical and lateral nuclei (92, 144, 161). The strongest amygdalofrontal projection ends in the posterior part (agranular and dysgranular sectors) of the orbitofrontal cortex. Another strong projection terminates in the medial prefrontal cortices (areas 14, 25, and 32). Projections to isocortical areas on the lateral convexity (areas 9, 10, 45, and 46) are less strong. As mentioned previously, the amygdala is the recipient of a wide variety of cortical inputs from allocortical, periallocortical, proisocortical, and isocortical association areas. The latter includes converging input from both auditory and visual association areas as well as multimodal association cortices. Therefore, there is reason to believe that amygdala output directed toward the prefrontal cortices is influenced by a variety of neural systems related to the interplay of both the internal and external environments of the organism.

Motor Cortex Connections with Prefrontal Cortex

It is well known that the prefrontal corticofugal axons are not directed to cranial nerve nuclei or the spinal cord. However, since the latter part of the 19th century, it has been appreciated that prefrontal cortex plays a special and important role in guiding the outcome of voluntary motor behavior. How this is accomplished anatomically has been an enigma for many years. The view that emerged from classic studies suggested that corticospinal neurons in M1 were influenced by prefrontal input through an indirect series of connections passing through lateral area 6, or premotor cortex (88, 155). However, the discovery that cortex located outside the primary motor cortex, including the lateral premotor cortex, supplementary motor cortex, and cingulate motor cortex, contained corticospinal neurons, suggested otherwise (46, 162–164).

As summarized in Figure 7.14, more recent efforts have shown clearly that the prefrontal cortex projects directly to parts of the motor cortices, giving rise to the corticospinal axons (29, 52, 53). In the lateral premotor cortex, only the very rostral parts of areas 6D and 6V that contain corticospinal neurons receive prefrontal input, with area 6V being the primary link. Prefrontal input to M2 converges on the rostral part of M2 that contains the face area and less so on corticospinal output zones that subserve the arm. Thus, the more rostral parts of the lateral premotor cortex and supplementary motor cortex receive prefrontal input. However, the cingulate motor cortex (M3 or area 24c) and area 23c has also been shown to receive strong prefrontal input that converges on parts of these cortices that rise to corticospinal axons. Thus, recent work implies that several anatomically distinct sources of corticospinal axons are directly influenced by prefrontal output. Moreover the ventral part of M1 receives input from the caudal part of the ventrolateral operculum of the prefrontal cortex. The target of this projection resides outside the M1-corticospinal projection zone, and may correspond to the face representation. In many nonhuman primate models, the frontal eye field has been shown to give rise to projections that innervate midbrain centers regulating ocular motor behavior. Although no corticospinal projections arise from the frontal eye field, it does receive strong prefrontal input.

Subcortical Connections of Prefrontal Cortex

The corticostriate projection from the prefrontal cortex is substantial. It is directed toward targets in the caudate nucleus and, to a much lesser extent, the putamen (24, 165–167). Because a portion of the outflow of the basal ganglia is directed to the thalamus and eventually back to all parts of the frontal lobe, the corticostriate projection represents initial stages of a sequential pathway by which prefrontal cortex can influence a wide variety of neural systems.

The corticothalamic projection is one of the most studied corticofugal pathways leaving from the prefrontal cortex (126, 127, 168–171). The work of Akert (125) and Nauta (168) demonstrated that the mediodorsal thalamic nucleus is connected to all parts of the prefrontal cortex in the primate, including the granular sectors located anteriorly and laterally, as well as dysgranular and agranular sectors located medially and ventrally (the posterior orbitofrontal cortex). The medial part of the magnocellular division of the mediodorsal nucleus was found to be connected primarily with the orbital surface of the prefrontal cortex and the lateral part (parvocellular division) with the lateral surface of the prefrontal cortex. Anatomical findings and functional observations have since combined to suggest that the prefrontal cortex can be viewed as having at least four major subdivisions. They include dorsolateral, ventrolateral, medial, and orbitofrontal divisions, with each having its own unique thalamic projection pattern. Although the strong reciprocal anatomical relationship between the mediodorsal nucleus and prefrontal cortex is often emphasized, like all other cortical areas, numerous thalamic nuclei are linked to this brain region. They include the midline, ventral anterior, intralaminar, anterior medial and pulvinar nuclei.

Several important brainstem projections from prefrontal cortex have been identified that may play a role in motor control (24, 172, 173). Corticotectal projections have been

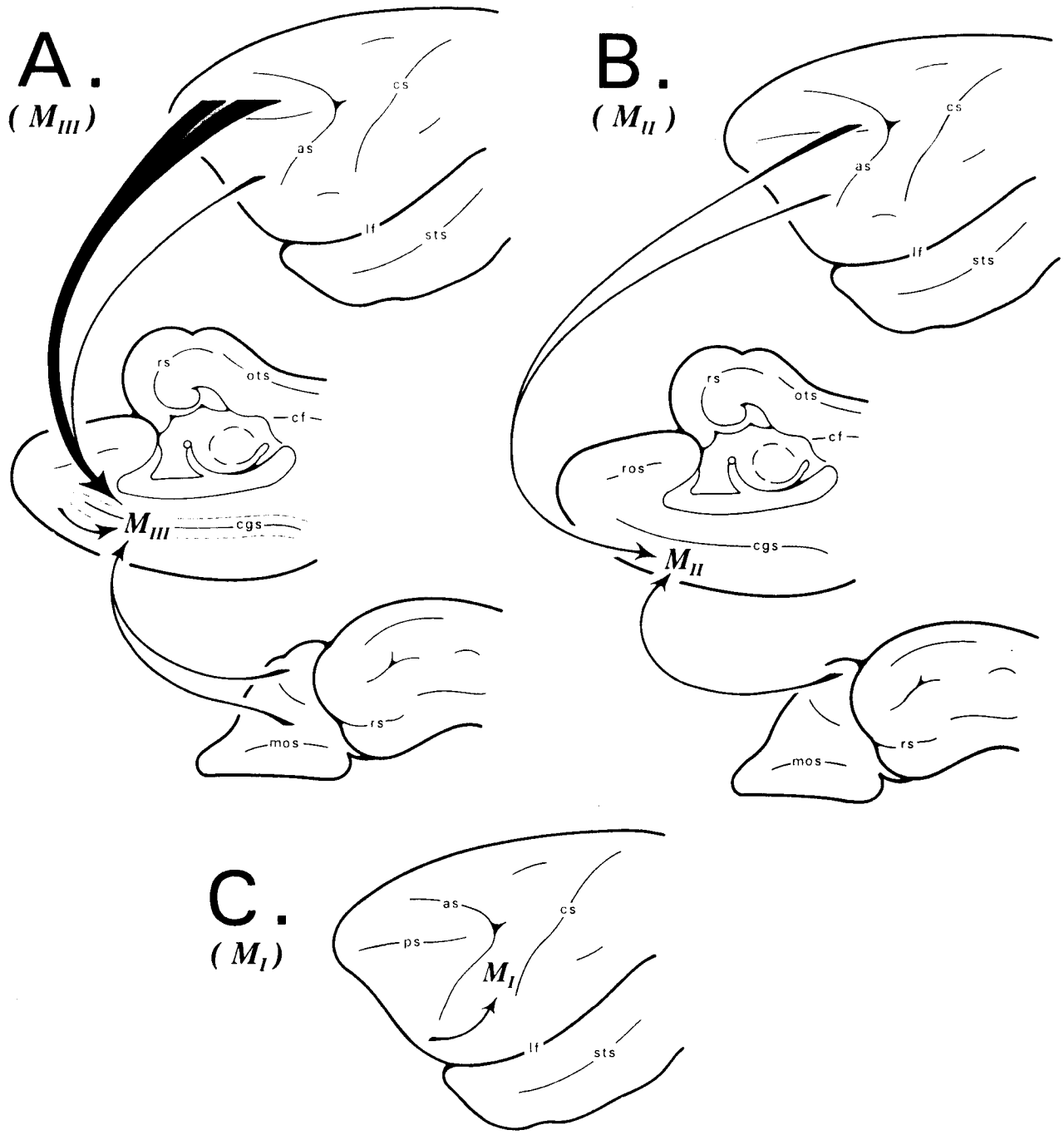

Figure 7.14. The diversity and strength of prefrontal input to M3 **(A)**, M2 **(B)**, and M1 **(C)**. Note, that M3 receives dorsolateral, medial, and orbitofrontal projections. M2 or supplementary motor cortex receives some direct prefrontal input, but M1 or primary motor cortex receives virtually no direct prefrontal cortex input. (Abbreviations: sulcus labeling is the same as for Fig. 7.5, except for the additions of *cs* = central sulcus, *mos* = medial orbital sulcus, and *ots* = occipitotemporal sulcus.)

demonstrated to arise from the dorsolateral-principalis region in the monkey and terminate in the intermediate and deep layers of the superior colliculus. Such projections are likely candidates for influencing behaviors linked to eye movement, particularly those ocular motor tasks requiring on-line, or working memory, to order and issue an appropriate set of behavioral commands. Projections from prefrontal cortex to the pontine reticular formation have also been reported. This projection appears to be distributed over the paramedian portion reticular formation, an area corresponding in location to the central superior nucleus.

The prefrontal cortex also gives rise to a strong corticopontine projection that ends in the medial part of the basilar pontine gray matter (173, 174). This projection is a major component of the corticopontocerebellar system. Transneuronal labeling techniques have shown that cerebellar as well as pallidal neurons are labeled following injections of herpes simplex virus type 1 into the dorsolateral prefrontal cortex

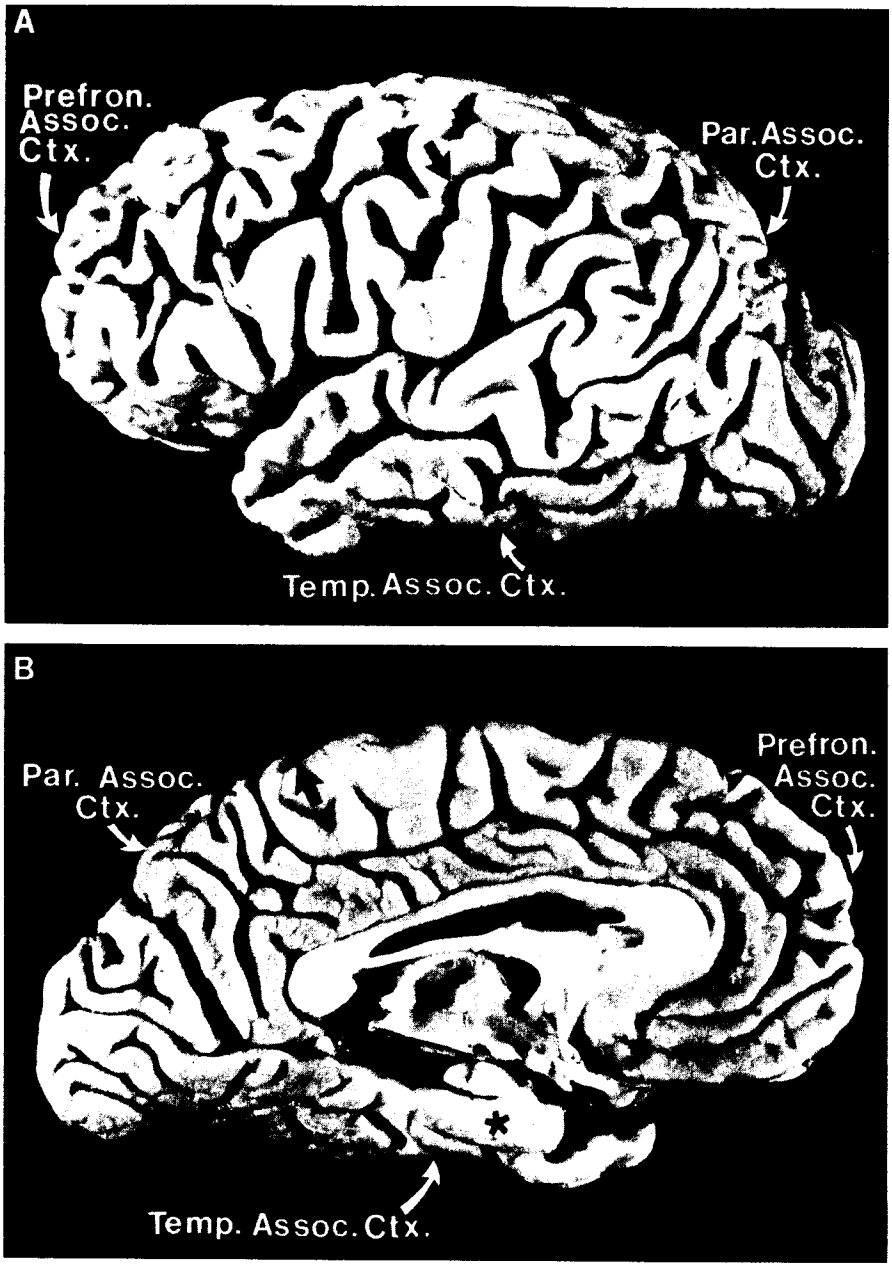

Figure 7.15. Lateral **(A)** and medial **(B)** views of the cerebral hemisphere at end-stage Alzheimer's disease after a long duration of illness (13 years) in an 83-year-old female. Note, the pronounced atrophic changes in the prefrontal, parietal, and temporal association cortices, but the relative preservation of the pre- and postcentral gyri on either side of the central sulcus (the latter is marked by the *arrow* in both photographs). The *asterisk* in **B** marks the location of the entorhinal cortex.

(175). This indicates that thalamocortical input to the prefrontal cortex is influenced by both basal ganglia as well as cerebellar circuits. If the basal ganglia and cerebellar loops are organized in parallel, it is likely that corticopontine projection from the prefrontal cortex is involved with the cerebellothalamocortical pathway that converges back onto the prefrontal cortex.

The prefrontal cortex is connected to several small but important brainstem nuclei that synthesize and transmit selective neurotransmitters to widespread parts of the prefrontal cortex. It has been suggested that these projections may play an important role in regulating global as well as discrete behavioral states (176, 177). For example, as discussed previously, the nucleus basalis of Meynert gives rise to cholinergic projections that innervate all parts of the prefrontal cortex. The ventral tegmental area, dorsal raphe nucleus, and locus ceruleus also belong to pharmacologically distinct classes of subcortical nuclei, and like the nucleus basalis, also project to all parts of the prefrontal cortex. The ventral tegmental area (VTA) is a dopaminergic mesencephalic nucleus located ventral and caudal to the red nucleus. The dorsal raphe nucleus (DR) is situated in the midbrain and pons, immediately ventral to the periaqueductal gray matter and consists of serotonergic neurons. Finally, neurons of the locus ceruleus (LC) give rise to norepinephrine projections. There are several notable and interesting exceptions regarding the issue of reciprocity when considering the pharmacologically specific subcortical nuclei. For example, the nucleus basalis appears to project to all the cerebral cortex, including the prefrontal cortex, but receives

input from only the limbic lobe. From the standpoint of the frontal lobe, this would include the posterior parts of the orbitofrontal cortex and medial prefrontal cortex. Also, unlike the rest of the cerebral cortex, which probably does not send projections back to the VTA, DR, and LC, the dorsolateral and medial parts of the prefrontal cortex have been found to send a reciprocal subcortical efferent projection to these brainstem centers (178). Therefore, the selective reciprocity of these connections gives distinct parts of the prefrontal cortex feedback control over their own monoaminergic and cholinergic innervation as well as influencing innervation that distributes to widespread parts of the cerebral cortex.

SUMMARY AND CONCLUSIONS

The widespread extent of prefrontal cortex connections underlies the complex functions subserved by it. The diverse set of associative connections converging on prefrontal cortex indicate that transformed and integrated information, associated with multiple sensory modalities, shape the outcome of prefrontal-guided behaviors. The anatomical interaction between prefrontal and limbic cortices may affect the motivational state and emotional tone or temperament of prefrontal behaviors in addition to involving memory features, such as the storage and retrieval of information.

Moreover, the prefrontal cortex gives rise to a host of descending projections that contribute to the corticostriate, corticothalamic, corticotectal, corticoreticular, and corticopontine pathways. Information directed away from the prefrontal cortex through nonreciprocating projections, such as the corticostriate and corticopontine projections, eventually converges back on the prefrontal cortex only after coursing through a sequential and parallel set of subcortical circuits or "loops." Others, such as the corticothalamic projections, being heavily reciprocated, allow for direct interaction between prefrontal and discrete subcortical diencephalic nuclei. Finally, chemically-specific subcortical projections from cholinergic and monoaminergic sources to all parts of the prefrontal cortex may globally and perhaps homogeneously affect the operation of cortical states associated with arousal, attention, motivation, and learning. Likewise, projections from selected parts of the prefrontal cortex to the monoaminergic and cholinergic centers suggest that prefrontal cortex may modulate its own afferent neurochemical innervation.

Degenerative Diseases Affecting the Prefrontal Cortex and Limbic System

It has been recognized for many years (179) that the limbic system and, to some degree, the frontal lobes are the preferred targets for particular disease mechanisms. For example, this is the case for degenerative diseases such as AD and Pick's disease (180, 181) as well as schizophrenia (182–184). Several of the viral encephalitides also somewhat selectively attack these brain areas (185–187). Why this is the case, and why the parietal and occipital lobes as well as numerous subcortical brain areas are not targeted as greatly is an open question of fundamental importance. AD has been well-characterized in terms of topographical neuropathology and neuroanatomy (Fig. 7.15): the limbic system and temporal lobe (Fig. 7.16) are damaged disproportionately in this disorder (188, 189). The frontal lobe always contains pathology, but its involvement is moderate and may not be heavily damaged until closer to the end stage of the disease (190). Neurofibrillary tangles occur first in the cortex of the limbic lobe and only later in the illness do they involve the association areas. The perirhinal and entorhinal cortices (Figs. 7.16 and 7.17) are first affected (190–192), followed closely by the temporal polar cortex (193). Curiously, the entorhinal and cingulate cortices are altered in

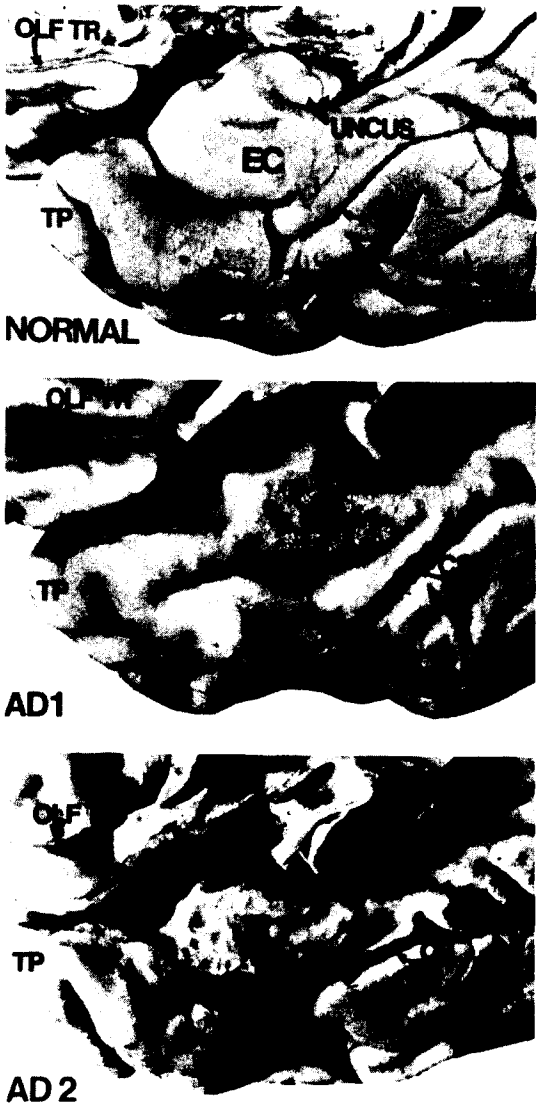

Figure 7.16. Three views of the ventromedial temporal area focusing on the entorhinal cortex *(EC)*. The top photo is from a normal nondemented elderly donor (age 76 years). The bottom two photos (AD1 and AD2) are from pathologically confirmed Alzheimer's disease donors (ages 71 and 79). Note the atrophic pitted appearance of the EC (other abbreviations: *cs* = collateral sulcus, *OLF TR* = olfactory tracts, *TP* = temporal pole).

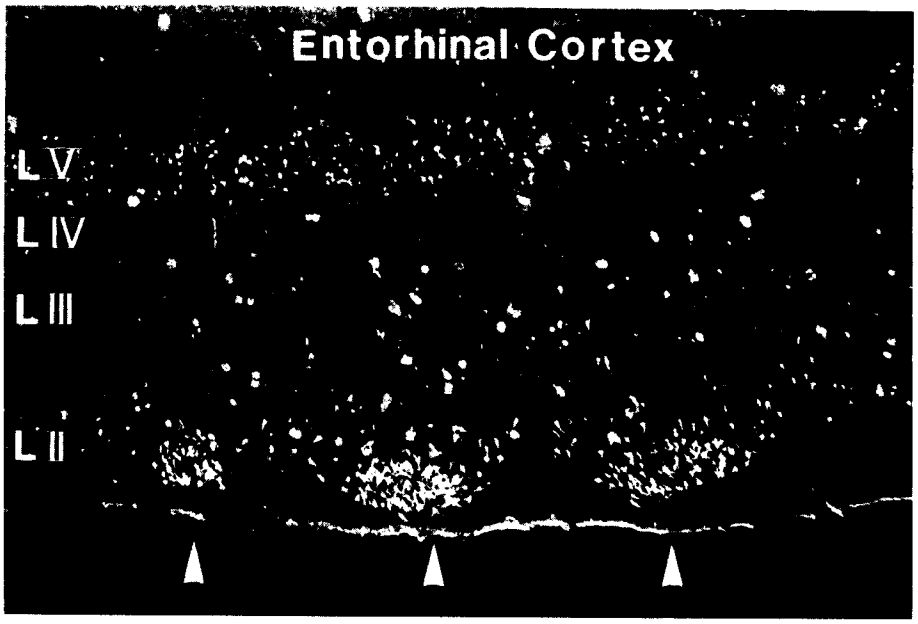

Figure 7.17. A cross-section through the EC in Alzheimer's disease stained with the fluorochrome thioflavin S to reveal neurofibrillary tangles. Note that the neurons of layers II and V are heavily invested with this form of pathology. The former link the hippocampal formation to the cortex, whereas the latter receive hippocampal output and project to the cerebral cortex. The disease-related pathology of Alzheimer's disease thereby disconnects the hippocampal formation from the cerebral cortex.

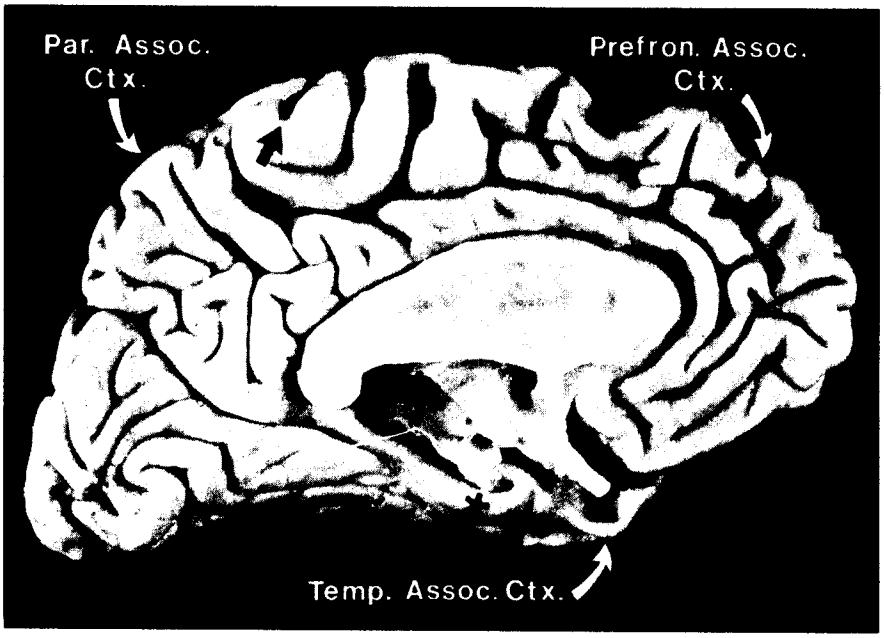

Figure 7.18. A medial view of the cerebral hemisphere from a donor with pathologically confirmed Pick's disease. The arrow marks the medial tip of the central sulcus, and the asterisk marks the location of the entorhinal cortex. Note the marked atrophy of the prefrontal association and the temporal association cortices compared with the preservation of the parietal association cortices. Neuron loss, gliosis, and occasional Pick's bodies were observed in the former areas.

some schizophrenics (189, 194, 195), and the prefrontal and the temporal polar cortices are frequently atrophic in Pick's disease (Fig. 7.18) (193). Although there are neuroanatomical and some behavioral similarities between these three disorders, their overall profile is not isomorphic, and the pathological picture is quite disimilar. In AD, for example, changes in memory and cognition are correlated with neurofibrillary tangles, while in Pick's disease, they are associated with cell loss and cytoplasmic inclusion bodies. In schizophrenia, more subtle cell or gray matter loss occurs in the temporal lobe (196) and anterior cingulate gyrus (195), but laminar alterations in cytoarchitecture hint also of a preexisting developmental disorder in the genesis or sculpting of the cortex (194).

For many of the neural systems and connections of the limbic system and frontal lobe described previously, the projection neurons that give rise to association axons reside in layer III of the cerebral cortex and to some extent in layer V. A subset of layer III also mediates callosal connections, and various subsets of layer V give rise to corticofugal axons that course to subcortical targets. In both AD and Pick's disease, these larger projection neurons of layers III and V are targeted for pathology, whether it be neurofibrillary tangles in the former case (198) or cell loss and cytoplasmic inclusion bodies in the latter case. Thus, although the etiology of cortical neuronal death is different in both diseases, the outcome can be somewhat similar because corticocortical connections are destroyed.

Less information is available on this issue with regard to schizophrenia, but a strong possibility exists that some of the clinical signs of this disorder reflect a disconnection (183). The "frontal-like" signs of certain psychiatric diseases may be due to subtle cortical neuroanatomical changes elsewhere yielding behavior that is more a manifestation of frontal lobe deafferentation than the direct result of diffuse and subtle lesions in the areas that provide afferent input to the frontal lobes. AD, Pick's disease, schizophrenia, and other disorders characterized by changes in behavior, all affect cortical association systems that supply input to the frontal lobes. They share some clinical features with lobar atrophy of the frontal cortex (197–199), where the pathological change involves not an afferent or input to the frontal cortex coming from elsewhere, but the efferent or projection neurons of the frontal lobe itself. If the major degenerative disorders serve in any way as a model for the seemingly more subtle developmental disorders of schizophrenia, (200, 201), the entire cerebral cortex will have to be screened carefully because of the extensive limbic and association connections of the frontal lobe (202).

CONTEMPORARY ISSUES REGARDING THE EVOLUTION OF THE FRONTAL LOBE

Historical Observations and Biases

The frontal lobes were in all likelihood first associated with higher mental functions by the Greeks, who represented some gods, demigods, poets, and artists with large foreheads in their sculptures and paintings (6). Anatomical records and illustrations that originated in classical antiquity have been traced by way of Byzantium to both the Medieval West and East (203), and the association between large frontal lobes and special cognitive abilities accompanied them.

During the Renaissance, clinical observations began to emerge, suggesting a special role of the frontal lobes for the human intellect. Studies included frontal lobe injuries in soldiers and cases of patients with brain tumors (6). Also, comparative studies between human and animal brains attracted the attention of many anatomists like Willis and, later, Tiedemann and Owen (203).

In the late 18th century, physiognomists devised the first anthropometric measures associating mental characteristics with physical features. Larger facial angles caught their fancy, and more fully developed foreheads were attributed more to whites than blacks and an increase in the facial angle was found when apes and humans were compared in the "natural chain of being" (6).

Phrenology and craniometry were both introduced in the 19th century. Supporters of the former believed in the notion that distinct functional units in the cerebrum correlated with cranial surface features, while supporters of craniometry saw a strong association between brain size and intellectual capacities (204). Higher functions especially were associated with a presumably larger frontal lobe in humans, while smaller frontal lobes present in monkeys and dogs represented rudimentary forms of intellect (6). Gall's phrenological system included eight organs in the frontal lobe that set humans apart from animals. These included poetic talent, kindness and moral sense, faculty to imitate, and religion (205).

Burdach in the 1820s (6) supported the idea that the frontal region is more developed in humans than in other mammals and therefore it logically had to be involved in intellectual functions. In keeping with the racist ideology of the mid 19th century, Huschke declared the Caucasian race the "frontal race." Gratiolet stated that it is the frontal lobes that distinguish humans from other animals (6).

Reports of actual measurements that compare the size of the frontal lobes in humans and other mammals were absent from the 19th century literature, but the support of the idea linking unique human intellectual capacities with large frontal lobes was abundant and persisted throughout the next century. Bianchi (206) stated that intellect appeared to be correlated with the growth of the prefrontal cortex and that the progression is clear from cats to dogs to monkeys and to humans. A notable exception was Monakow (6), who disputed the link on the basis of the large frontal lobes that he identified in the horse brain (which he estimated to be 30% of the cortical volume).

With the turn of this century, actual measurements started being performed on comparative material. For example, Brodmann performed measurements on parts of the human and nonhuman primate cortex (207). The surface area of the neocortex, the prefrontal cortex (regio frontalis), and the frontal lobe (lobus frontalis) were estimated for the human, chimpanzee, gibbon, and macaque, along with a few other monkeys and prosimians. The size of the surface area for the entire *frontal lobe* was reported to be 36.3% for the human, 30.5% for the chimpanzee, and 21.4% for the gibbon. The size of the *prefrontal cortex* relative to total neocortical size was reported to be 29% for the human, 16.9% for the chimpanzee, 11.3% for the gibbon, and 11.3% for the macaque (the other primates ranging from 11.3–7.2%).

Leboucq (208) found that the volume of the frontal lobe in the human is 38.3% (surface, 36.5%), 39% in the chimpanzee (surface, 37%), and 30% in the macaque (surface, 30.4%).

Tilney (209) estimated the surface area of the frontal lobe in relationship to the "neopallium" to be: 47% for the human, 33% for the chimpanzee, and 32% for the gorilla. Combining these results and his studies of hominid endocasts, he also concluded: "A distinguishing metrical feature in the development of the human brain is the consistent gain in length and height from *Pithecanthropus erectus* to *Homo sapiens*. The gain in length is to be ascribed largely to frontal increments."

Weil (210) measured the surface of endocranial casts and favored the idea of an enlarged human frontal lobe. He concluded that "the frontal part of the cap of the casts, which

was limited by a line perpendicular to the horizontal base line at the intersecting point of frontal and temporal lobes, is best developed in the specimen of living races which were investigated. Measured in percentages of the total surface of the cap, this part, in the specimen of living races, is from 28 to 31; in the casts of the other prehistoric men, from 21 to 25; and in the casts of the four anthropoids that were investigated, from 17 to 20 per cent" (210). It should be noted that his measurements included only the external cortical surface and not that buried within the sulci. Additionally, as he himself admitted, "naturally, the subdivisions which were introduced for comparative purposes of the cast do not indicate which parts of the brain were compared" (210). Furthermore, Holloway reported that Weil's measurements were criticized by Weidenreich (211), who was an expert in endocasts and who instead suggested a relative increase in the size of the parietal and temporal lobes.

In summary, the historical record reveals that sources of information regarding the size of the frontal lobe are available. One consists of the promotions of the phrenologists of the last century, who suggested that the human frontal lobe is associated with high mental functions, and is larger in humans than in other primates.

The second source of information consists of a few studies from the first half of the 20th century that involved measurements of the size of the frontal lobes on hominid and hominoid endocasts (209, 210). These supported the idea of an enlarged human frontal lobe, but their accuracy has been criticized by other researchers.

The last source of information comes from surface and volume measurements on human and nonhuman primate brain specimens, also performed in the beginning of this century. These studies were few in number and their methods varied considerably (207–209). Some suggested that the human frontal lobe is relatively larger, and some supported a similar relative size in humans and apes. Figure 7.19 illustrates the relative size of the prefrontal regions in four primate species.

FUNCTIONAL OBSERVATIONS

The idea that frontal lobe function and personality characteristics might be related had already emerged during the last century, when Harlow reported on his famous patient Phineas Gage, the so-called "crowbar case" (5). Gage underwent major personality changes after partial damage in his frontal lobes (153) and, in Harlow's words, "was no longer Gage" after the accident.

Early in this century it became clear that an association indeed exists between frontal lobe function and aspects of emotional behavior. At the International Neurological Congress in London in the summer of 1935, great interest was generated in the presentation of the results of frontal lobe extirpation in two chimpanzees, Becky and Lucy (212, 213).

After bilateral prefrontal cortex removal, Becky and Lucy's behavior changed strikingly. They did not show their usual excitement, but rather knelt quietly before the cage or ambled around. Whenever they would make a mistake when choosing between an empty or reforced cup, they showed no emotional disturbance, but quietly awaited the next trial. "They merely continued to play quietly and did not pick over their fur . . . It was as if the animals had joined the happiness cult of the Elder Micheaux, and had placed their burdens in the hands of Lord" (214).

Egaz Moniz, a Portuguese neurosurgeon participating in the congress, commented to Dr. Fulton and Dr. Jacobsen that, "if after frontal lobe removal, an animal no longer tends to develop an experimental neurosis and no longer has temper tantrums when frustrated, why would this not be an ideal operation for human beings suffering from persistent anxiety states?" (213). Within a year of that meeting, his now famous monograph on frontal leucotomy was published (215, 216), describing the neurosurgical procedure he used on psychotic patients and its outcome, which involved an improvement in the anxiety symptoms in many of his patients.

Brickner (5) described patient *A* who was disciplined, organized, and motivated prior to developing a tumor in the frontal lobes and undergoing its removal, but became socially uninhibited, not concerned with his profession, or the planning of his daily routine and future responsibilities.

Ackerly and Benton (217) reported on another patient who also suffered a bilateral frontal lobe defect of major proportions, but maintained most aspects of his average intelligence level. Because aspects of his personality were damaged, the authors suggested that the concept of "primary social defect" might best characterize his symptoms.

Thus, a mutual reinforcement pervaded the literature combining myth, mismeasurement, and emerging clinical observations to preserve the primacy of the frontal lobes in humans for both intellect and emotional stability.

Modern Forms of Frontal Lobe Measurement

In the second half of this century more serious studies emerged on the issue of the size of the frontal lobes. Blinkov and Glezer (218) estimated the surface area of the "frontal region" (prefrontal cortex) and of the precentral region (areas 4 and 6) in relation to total surface of the hemisphere to be: 32.8% in the human, 22.1% in the chimpanzee, 21.3% in the orangutan, and 21.2% in the gibbon.

Von Bonin (219) plotted Brodmann's figures on the surface of the frontal lobes and concluded that "they illustrate a very simple case of relative growth, and that man has precisely the frontal lobe which he deserves by virtue of the overall size of his brain." Holloway (211) emphasized that "the measurements which are most direct, that directly measure cortical area or volume rather than endocasts, give little basis for accepting relative increase." Also, Clarke and Dewhurst (203) concluded that "this association between the frontal lobe and highest intellectual capacity must finally be abandoned."

Despite the aforementioned criticisms, the long-

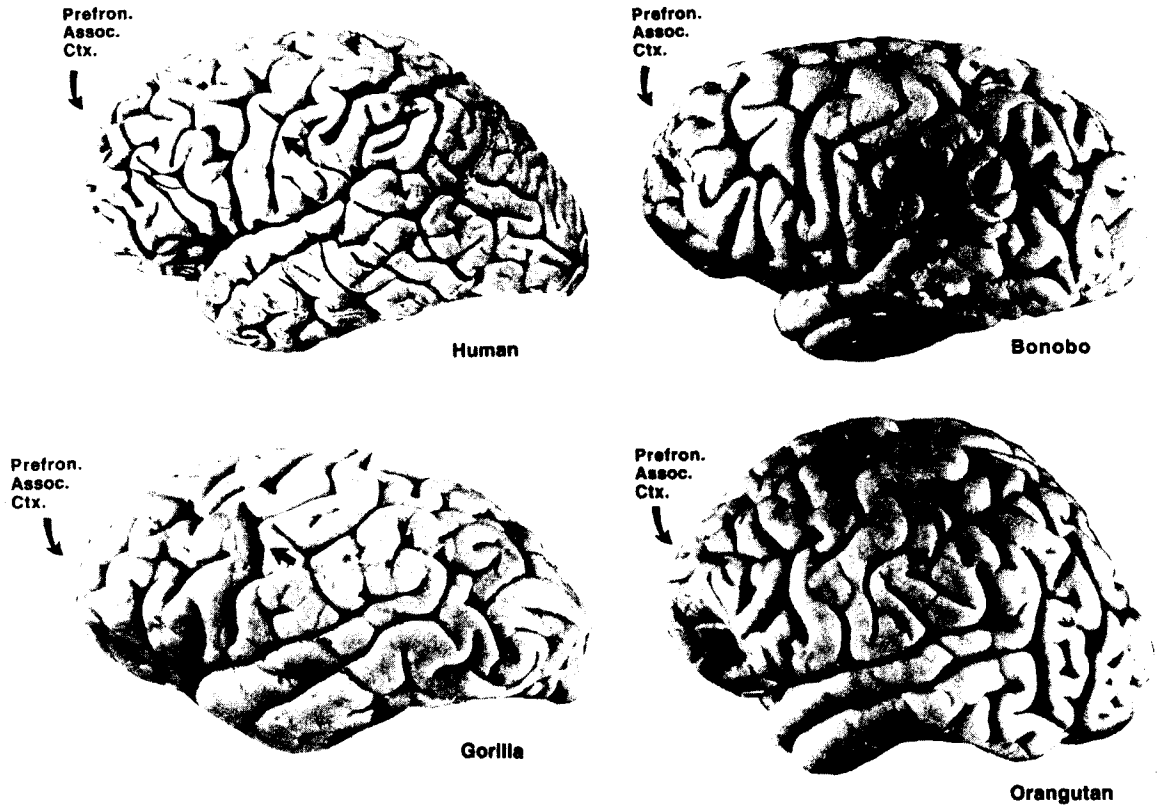

Figure 7.19. Lateral views of cerebral hemisphere for the human, bonobo (pygmy chimpanzee), gorilla, and orangutan. The arrow indicates the central sulcus in each species. Recent volumetric comparisons indicate that the human brain contains the largest frontal lobe among hominids in terms of absolute size, but with regard to relative size, it is no larger than that of the great apes.

cherished notion of an association between a large frontal lobe and high mental capacities persisted and is still the "common wisdom" promoted in textbooks and teaching as well as research rationale. Notable caution by Passingham (220) and Armstrong (221) pointed out that conflicting data existed and more studies are necessary.

Recent comparative studies of the human and ape frontal lobes have addressed the issue of size of specific cortical areas and their internal organization (222), as well as the issue of the volume and cortical surface of the hominoid frontal lobe and its subdivisions (223, 224) using modern imaging and quantitative techniques.

In a cytoarchitectonic study of the hominoid prefrontal cortex, the frontal pole region (area 10) and the posterior parts of the orbitofrontal cortex (area 13) were analyzed in the human, chimpanzee, bonobo, gorilla, orangutan, and gibbon, as well as in the well-studied rhesus monkey. The presence, qualitative appearance (based on Gallyas cell stains), aspects of the internal organization (relative size of cortical layers, neuropil space, and neuronal numbers), as well as total volumes were investigated for the two areas across species.

It was found that area 13 is present in all hominoids in the posterior parts of the orbitofrontal cortex. It is a small cortical area, particularly in the human and the bonobo brains. Its internal organization is similar among humans and apes. The infragranular layers are larger than the supragranular layers in all species, and the neuropil space (reflecting possibly dendritic and postsynaptic space) is larger in the supragranular layers and smaller in the infragranular layers across species.

Area 13 is part of the limbic lobe and cortical parts of the limbic system. It is involved in emotional reactions, inhibitory mechanisms, decision making, and social behavior. Area 13 is thus viewed as a conservative feature of brain evolution that provides a function common in all hominoids. The results suggest that it was part of the ancestral hominoid and hominid brain.

Area 10 forms the hominoid frontal pole and is larger than area 13 in all species. Its structural features present slight variations among hominoids, with the gorilla frontal pole having the most distinct ones. In contrast to area 13, the internal organization of area 10 is more species-specific. Area 10 is part of the prefrontal association cortex involved in cognition, planning of future actions, and the undertaking of initiatives. It is here suggested that its relative size increased considerably during hominid evolution after the hominids' divergence from the line leading to modern African apes.

In additional studies, the volume and cortical surface of the frontal lobe and its subdivisions were investigated, using three-dimensional reconstructed images from MR scans of human and ape brains. It has been observed that although

the whole volume of the brain is largest in the human, the relative size of the frontal lobes in relation to the brain is similar across hominids. Human frontal lobes are not larger than expected on the basis of the ape data, and the human and chimpanzee frontal lobe have similar relative values. Also, the proportions accorded to the volume of the dorsolateral, mesial, and orbital frontal lobe sectors are similar across species. However, a remarkable difference exists in the proportion of white matter in the sector of the frontal lobes anterior to the basal ganglia, which indeed is largest in the human.

Thus, the anatomical correlates for the remarkable cognitive and behavioral differences among primates should probably not be sought at the level of large cortical sectors. It is possible that differentiation of cortical areas within each sector of the frontal lobe, along with interconnectivity among them and between them, as well as cortical areas in other lobes, are the key to the neural correlates of complex human capacities. Moreover, structural differences should also be sought in other cortical areas that coevolved with the frontal lobe, such as the temporal and parietal cortices.

SUMMARY AND FUNCTIONAL CONSIDERATIONS

More modern cytoarchitectural and volumetric analyses of frontal lobe evolution are inconsistent with the assumptions and dogma that have accrued historically. Humans undoubtedly have the largest frontal lobe in absolute terms, outstripping our extant ape kin. But we have larger brains in general, and the part devoted to frontal lobe is not significantly different between apes and humans in relative terms. To paraphrase von Bonin and Bailey, we have about what we deserve. However, the picture is much more complicated than this. For example, there is the suggestion that among hominids the pie is sliced differentially to meet species-specific adaptations. Although the general cytoarchitectural plan is similar, some cell fields may be more elaborate than others, and, in fact, may be so at the expense of others. Humans, for example, have a highly differentiated frontal pole (area 10), whereas a comparable area in the gorilla is difficult to find. The largely solitary orangutan appears to have a less elaborate orbitofrontal area, which is thought to be the neural substrate for social behavior.

In short, the human frontal lobe may be unique, not so much for quantity of frontal lobe, but instead, for other reasons relating to its internal structure and convectivity. We share with our ape relatives many basic behaviors, a tendency to be social, to band together in units, to be intelligent, and to manipulate our environment. But, we may be set apart by a greater balance to deal frontally with other parts of our neuraxis and the events provoked in these areas by our environment. In this regard, it is of great interest to find that white-matter volume of the prefrontal cortices is, in fact, the one anatomical variable that distinguishes humans from apes. Indeed, this is the neural substrate that governs the balance and precision of neural systems' communication. In essence, we are better wired.

CONCLUSIONS

The neural systems of the limbic system and frontal lobes have been studied extensively for over a century. The results attest to a continually evolving experimental neuroanatomy, where progressively better methods have supplanted earlier and less informative ones, or ones that had very restrictive application such as the Golgi method. Despite the neuroanatomical complexity of these brain areas, the skeleton, or the common wisdom that has survived is largely accurate. For example, Papez's original circuit has been found to have few flaws; Cajal's early descriptions of hippocampal and limbic lobe circuitry remain intact and the descriptions of extensive interconnections of the frontal lobe with other association areas and the limbic system are truer than ever. It seems that what has changed the most has been an appreciation for the degree of interaction between structures. These findings have provided fresh insights. In the case of more recent research, the strength and topography of connections between the limbic system and the association cortices has been one of the major payoffs of better methodology. Structures such as the amygdala, cingulate cortex, and hippocampal formation are now known to have extensive and widespread connections with the association cortices. These occur directly rather than via the pathways of Papez's circuit. For example, both the amygdala and hippocampal formation project strongly to parts of the prefrontal cortex, and the amygdala has output to the occipital lobe and to cingulate cortex neurons that give rise to corticospinal projections. The entorhinal cortex conveys cortical association input to the hippocampal formation and, after receiving hippocampal output, projects back strongly to association areas. Among the truly new findings, the nucleus basalis of Meynert projections to all of the cerebral cortex link the hypothalamus to the cortex and provide a manner for the basal forebrain to have widespread cholinergic influence on the cortical mantle. Its projections to the reticular nucleus of the thalamus also establish a morphological basis for it to influence thalamic output before it relays to the cortex. Direct amygdaloid projections to the dorsomedial thalamic nucleus provide a manner for this temporal limbic structure to influence not only the orbital and medial prefrontal cortices, but the extensive dorsolateral prefrontal cortices as well. Lastly, and of critical importance, direct projections from cingulate area M3 to the spinal cord provides an unambiguous manner for the limbic system to influence somatic effectors and behavior, and the extensive prefrontal cortex output to this area gives this cortex more direct influence on lower motor neurons than previously appreciated.

Thus, refined and augmented older findings, and truly new neuroanatomical findings, insure the generation of fruitful hypotheses regarding neural networks that might explain behavior. Furthermore, they provide a richer description of normality against which neurological and psychiatric diseases affecting the limbic system and frontal cortex can be assessed.

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