Behavioral Neuroanatomy
Large-Scale Networks, Association Cortex, Frontal Syndromes, the Limbic System, and Hemispheric Specializations

M. - MAR SEL MESULAM

Faced with an anatomical fact proven beyond doubt, any physiological result that stands in contradiction to it loses all its meaning. ... So, first anatomy and then physiology; but if first physiology, then not without anatomy.
—BERNHARD VON GUDDEN (1824-1886), QUOTED BY KORBINIAN BRODMANN, IN LAURENCE GAREY’S TRANSLATION

I. INTRODUCTION

The human brain displays marked regional variations in architecture, connectivity, neurochemistry, and physiology. This chapter explores the relevance of these regional variations to cognition and behavior. Some topics have been included mostly for the sake of completeness and continuity. Their coverage is brief, either because the available information is limited or because its relevance to behavior and cognition is tangential. Other subjects, such as the processing of visual information, are reviewed in extensive detail, both because a lot is known and also because the information helps to articulate general principles relevant to all other domains of behavior.

Experiments on laboratory primates will receive considerable emphasis, especially in those areas of cerebral connectivity and physiology where relevant information is not yet available in the human. Structural homologies across species are always incomplete, and many complex behaviors, particularly those that are of greatest interest to the clinician and cognitive neuroscientist, are either rudimentary or absent in other animals. Nonetheless, the reliance on animal data in this chapter is unlikely to be too misleading since the focus will be on principles rather than specifics and since principles of organization are likely to remain relatively stable across closely related species.

The nature of the relationship between brain structure and behavior is a central theme for all chapters in this book. Neuroscience texts tend to highlight the relatively invariant relationships between anatomy and function. Damage to the optic
tract or striate cortex, for example, always leads to a contralateral homonymous hemianopia and a thoracic cord transection always leads to paraplegia and incontinence. The approach to cognition and comportment was initially based on the expectation that analogous relationships would be uncovered and that it would be possible to identify centers for “hearing words,” “perceiving space,” or “storing memories.” These expectations need to be modified to accommodate modern observations which show that the structural foundations of cognitive and behavioral domains take the form of partially overlapping large-scale networks organized around reciprocally interconnected cortical epicenters.329,334,339 The components of these networks can be divided into critical versus participating areas. Lesions which irreversibly impair performance in a cognitive domain help to identify network components that are critical for its integrity, whereas activations obtained by functional imaging when subjects are performing tasks related to the same domain also reveal the areas that participate in its coordination. The traditional approach based on the investigation of patients with focal brain disease can thus be integrated with functional imaging experiments in order to obtain a more complete picture of the relationships between brain structure and behavior.

At least five large-scale networks can be identified in the human brain: (1) a right hemisphere-dominant spatial attention network with epicenters in dorsal posterior parietal cortex, the frontal eye fields, and the cingulate gyrus; (2) a left hemisphere-dominant language network with epicenters in Wernicke’s and Broca’s areas; (3) a memory-emotion network with epicenters in the hippocampus–entorhinal regions and the amygdaloid complex; (4) an executive function-comportment network with epicenters in lateral prefrontal cortex, orbitofrontal cortex, and posterior parietal cortex; and (5) a face-and-object identification network with epicenters in lateral temporal and temporopolar cortices. The neuroanatomical building blocks and overall organizational principles of these networks are reviewed in this chapter. The purpose is to provide a broad perspective which can serve as a background for the more detailed discussions in Chapter 3 (spatial attention), Chapters 4, 8, and 9 (memory and emotion), Chapters 5 and 6 (language), and Chapter 7 (face and object recognition).

II. PARTS OF THE CEREBRAL CORTEX

The human cerebral cortex contains approximately 20 billion neurons spread over nearly 2000 square centimeters of surface area.394,520 The study of the cerebral cortex can be quite challenging. There is no universal agreement on terminology, no distinct boundaries that demarcate one region from another, and, in most instances, no clear correspondence among lobar designations, traditional topographic landmarks, cytoarchitectonic boundaries, and behavioral specializations. Furthermore, one part of the brain can have more than one descriptive name, and cytoarchitectonic (striate cortex), functional (primary visual cortex), topographic (calcarine cortex), and eponymic (Brodmann’s area [BA] 17) terms can be used interchangeably to designate the same area.
Cytoarchitectonic maps, such as the one by Brodmann, show that the cerebral hemispheres can be subdivided into numerous regions based on microscopically identified variations in neuronal architecture. In contemporary usage, however, a statement such as "activation was seen in area 9" is based on a topographically identified match between the target region and the region labeled as area 9 on Brodmann's map. This usage can lead to potential inaccuracies since some brains have topographical landmarks which differ from those of the brain illustrated by Brodmann, and since there may be substantial interindividual differences in the distribution of cytoarchitectonic areas, even when sulcal and gyral landmarks are identical. For these reasons, a descriptive neuroanatomical designation such as the "middle temporal gyrus," based on an easily identifiable topographic landmark, may be potentially more accurate than a cytoarchitectonic designation such as "area 21," which requires microscopic examination for verification. Brodmann's map is also quite uninformative when it comes to the cytoarchitectonic parcellation of the cortex within the banks of the cortical sulci. This is a major problem since much of the cerebral cortex lies buried within sulcal banks. Although there are no immediate means for resolving these challenges, it is important to recognize their existence in order to avoid potentially misleading conclusions. Since the anatomical information in this chapter is highly condensed, the reader may want to consult more comprehensive texts by Brodmann (now available in English translation), Duvernoy, Mai, and Nieuwenhuys and associates.

The absence of clear anatomical boundaries has encouraged the development of numerous approaches to the subdivision of the cerebral cortex. The resultant maps can be divided into two groups: those based primarily on structural (architectonic) features and those based primarily on functional affiliations. Proponents of the first school have constructed a variety of cortical maps, ranging in complexity from the map of Exner, which boasted hundreds of sharply delineated subdivisions, to the more modest and also more widely accepted ones of Brodmann, the Vogts, von Economo, and Flechsig. The second school is more difficult to identify since few of its proponents have produced systematic surveys of the entire brain. Members of this second school include theoreticians of brain function such as Campbell, Broca, Filimonoff, Yakovlev, and Sanides. The thinking of this second school has led to the subdivision of the cerebral cortex into the five major functional subtypes which are reviewed below: limbic, paralimbic, heteromodal association, unimodal association, and primary sensory-motor. The principal factual base for this parcellation is derived from anatomical, physiological, and behavioral experiments in macaque monkeys. The homologies to the human brain have been inferred from comparative cytoarchitectonics, electrophysiological recordings, functional imaging, and the behavioral effects of focal lesions (Figs. 1-1 through 1-7).

The Limbic Zone (Corticoid and Allocortical Formations)

The basal forebrain is usually considered a subcortical structure. However, some of its constituents can be included within the boundaries of the cerebral cortex because they are situated directly on the ventral and medial surfaces of the cerebral hemi-
FIGURE 1-1. Coronal section through the basal forebrain of 25-year-old human brain stained for myelin. The substantia innominata (si) and the amygdaloid complex (a) are located on the surface of the brain. They represent "corticoid" components of the cerebral hemispheres. Other abbreviations: c = head of the caudate nucleus; cg = cingulate gyrus; g = globus pallidus; i = insula. Magnification X 1.6.

These basal forebrain structures include the septal region, the substantia innominata, the amygdaloid complex, and perhaps also the anterior olfactory nucleus (Fig. 1-1). Because of their simplified cytoarchitecture, these structures can be designated "corticoid," or cortex-like. In some corticoid areas such as the septal region and the substantia innominata, the organization of neurons is so rudimentary that no consistent lamination can be discerned and the orientation of dendrites is haphazard (Fig. 1–2a). All corticoid areas have architectonic features which are in part cortical and in part nuclear. This duality is particularly conspicuous in the amygdala (Fig. 1-3a).

The next stage of cortical organization carries the designation of "allocortex." This type of cortex contains one or two bands of neurons arranged into moderately well-differentiated layers (Figs. 1-2b, and 1-3b). The apical dendrites of the constituent neurons are well developed and display orderly patterns of orientation. There are two allocortical formations in the mammalian brain: (1) the hippocampal complex (that is, the dentate gyrus, the CA14 fields, and the subicular areas), which also carries the designation of "archicortex;" and (2) the piriform or primary olfactory cortex, which is also known as "paleocortex." The corticoid and allocortical formations collectively make up the limbic zone of the cerebral cortex.
FIGURE 1–2. Four types of cortex in the human brain as shown with cresyl violet staining. In order to facilitate comparison, the pial surface is toward the top in all four photomicrographs. a. An example of corticoid cytoarchitecture. This is a photomicrograph of the substantia innominata showing the nucleus basalis of Meynert (nbm) and the more superficial horizontal limb nucleus of the diagonal band (nhl). The lamination is incomplete and there is no uniformity in the orientation of neurons. b. An example of allocortex from the subicular portion of the hippocampal formation. Two layers can be identified: an external pyramidal layer (arrows) and an internal pyramidal layer. Dendrites within each layer have a relatively uniform orientation. c. An example of homotypical isocortex from prefrontal heteromodal cortex. There are six distinct layers including two granular bands in layers ii and iv. d. An example of idiotypic cortex from the striate visual area. There are at least seven layers, many strongly granular. From corticoid to idiotypic cortex there is a gradual increase of cell density and laminar differentiation. Magnification X10.
FIGURE 1-3. Amygdala in a 25-year-old human brain sectioned coronally. The cortical nucleus (co) extends to the surface of the brain (curved arrow). As in the case of other corticoid areas, the amygdala has a cytoarchitecture that is partly cortical partly nuclear. There is direct continuity with entorhinal cortex (EC). There is also direct continuity between EC and the hippocampus (fh). Other abbreviations: ab = accessory basal nucleus of the amygdala; bl = basolateral nucleus of the amygdala; cs = collateral sulcus; L = lateral nucleus of the amygdala. Magnification X6. b. Hippocampal complex in a 25-year-old human brain sectioned coronally. Through the CA1 and subiculum (S), the hippocampal complex merges into parahippocampal paralimbic areas such as the presubiculum (Pres), entorhinal cortex (EC), and transentorhinal (perirhinal) cortex (Te). The allocortical architecture of the CA1-4 and subicular sectors undergoes a gradual transition into the multilayered architecture of EC. In contrast to isocortical areas which contain a band of granular neurons in layer II, layer II of EC contains an agranular band of stellate cell islands. Other abbreviations: CS = collateral sulcus; dg = dentate gyrus; hs = hippocampal sulcus. The scale bar in the lower right represents 1 mm. Both a and b were stained with cresyl violet.
FIGURE 1–4. Insula of the rhesus monkey. The single arrowhead points to the direct continuity between piriform allocortex (P) and the insular paralimbic cortex. Adjacent to piriform allocortex, the insula has two or three agranular layers. More dorsally, a granular layer IV begins to appear (double arrowhead). There is further differentiation of insular cortex in the dorsal direction toward parietal isocortex. Abbreviations: Cl = claustrum; INS = insula; P = piriform cortex; SF = sylvian fissure. Magnification X 30.

The Paralimbic Zone (Mesocortex)

The next level of structural complexity is encountered in the paralimbic regions of the brain, also known as "mesocortex." These areas are intercalated between allocortex and isocortex so as to provide a gradual transition from one to the other. Allocortical cell layers often extend into paralimbic areas (Figs. 1-3b, and 1-4). The sectors of paralimbic areas which abut upon allocortex are also known as "periallocortical" or "juxtaallocortical" whereas the sectors which abut upon isocortex can be designated "proisocortical" or "periisocortical." The demarcations among these sectors are never sharp and always include zones of gradual transition. In most paralimbic areas, the transitional changes from periallocortex to periisocortex include:
FIGURE 1–5. The belt of olfactocentric (black) and hippocampocentric (gray) paralimbic areas in the brain of the rhesus monkey. Abbreviations: CG=cingulate cortex; CGS=cingulate sulcus; I = insula; MOS = medial orbitofrontal sulcus; OF= posterior orbitofrontal cortex; OTS= occipitotemporal sulcus; PH = parahippocampal region; PO = parolfactory area; RS= rhinal sulcus; RSp = retrosplenial area; TP= temporopolar cortex.

EXTRAPERSONAL SPACE

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HYPOTHALAMUS

INTERNAL MILIEU

Figure 1–6. Cortical zones of the human brain.
1. Progressively greater accumulation of small granular neurons (star pyramids) first in layer IV and then in layer II
2. Sublamination and columnarization of layer III
3. Differentiation of layer V from layer VI and of layer VI from the underlying white matter,
4. An increase of intracortical myelin, especially along the outer layer of Baillarger (layer IV).

In general, the emergence of relatively well-differentiated granular cell bands in layers IV and II, the sublamination of layer III, and the differentiation of layer V from layer VI mark the end of the paralimbic zone and the onset of six-layered homotypical isocortex.

There are five major paralimbic formations in the human brain: (1) the orbitofrontal cortex (posterior parts of Brodmann’s area [BA]11-12 and all of BA13); (2) the insula (BA14-16); (3) the temporal pole (BA38); (4) the parahippocampal cortices (including the presubiculum and parasubiculum, the entorhinal area, the prorhinal area, and the perirhinal (transentorhinal) area, corresponding to BA27–28 and 33); and (5) the cingulate complex (including the retrosplenial, ventral cingulate, and parolfactory areas, corresponding at least in part to BA23–26, 29–33).

These five paralimbic regions form an uninterrupted girdle surrounding the medial and basal aspects of the cerebral hemispheres. The paralimbic belt can be divided into two major groups: the olfactocentric and the hippocampocentric (Fig. 1-5). The olfactory piriform cortex provides the allocortical nidus for the orbitofrontal, insular, and temporopolar paralimbic areas (Fig. 1-4), whereas the hippocampus and its supracallosal rudiment (known as the induseum griseum) provide the allocortical nidus for the cingulate and parahippocampal components of the paralimbic brain (Fig. 1-3b). The olfactocentric and hippocampocentric sectors of the paralimbic belt merge into each other within the orbitofrontal and anterior parahippocampal cortices.

**Homotypical Association Isocortex (the Heteromodal and Unimodal Zones)**

By far the greatest area of the cerebral cortex in the human brain is devoted to six-layered homotypical isocortex (or neocortex), also known as “association isocortex” (Fig. 1–2c). Association isocortex can be subdivided into two major zones: modality-specific (unimodal) and high-order (heteromodal) (Fig. 1-6). Unimodal sensory association areas are further divided into "upstream” and “downstream” components: Upstream areas are only one synapse away from the relevant primary sensory area whereas downstream areas are at a distance of two or more synapses from the corresponding primary area. Unimodal sensory association isocortex is defined by three essential characteristics:

1. The constituent neurons respond predominantly, if not exclusively, to stimulation in only a single sensory modality.
2. The predominant sensory information comes from the primary sensory cortex and other unimodal regions of that same modality.
3. Lesions yield deficits only in tasks guided by that modality.

Unimodal visual association cortex can be divided into an upstream peristriate component which includes areas BA18–19, and a downstream temporal component which includes inferotemporal cortex (BA21–20) in the monkey and the fusiform, inferior temporal and probably parts of the middle temporal gyri in the human.339 Unimodal auditory association cortex covers the superior temporal gyrus (BA22) and perhaps also parts of the middle temporal gyrus (BA21) in the human.98 The connectivity of the monkey brain would suggest that the posterior part of the superior temporal cortex (BA22) displays the properties of upstream auditory association cortex whereas the more anterior part of this gyrus and the dorsal banks of the superior temporal culcus may fit the designation of downstream auditory association cortex.398

In the monkey brain, BA5 in the superior parietal lobule represents an upstream component of somatosensory unimodal association cortex whereas parts of BA7b in the inferior parietal lobule and the posterior insula may represent its downstream components.343,398 In the human, unimodal somatosensory association cortex may include parts of BA5 and BA7 in the superior parietal lobule and perhaps parts of BA40 in the anterior parts of the inferior parietal lobule (Fig. 1–7). The subdivision of unimodal auditory and somatosensory association cortices into upstream and downstream areas in the human remains to be elucidated. Unimodal association areas for olfaction, taste, and vestibular sensation have not been fully characterized. Premotor regions (anterior BA6 and posterior SAS) fulfill the role of motor “association” areas because they provide the principal cortical input into primary motor cortex.

The heteromodal component of association isocortex is identified by the following characteristics:

1. Neuronal responses are not confined to any single sensory modality.
2. The predominant sensory inputs come from unimodal areas in multiple modalities and from other heteromodal areas.
3. Deficits resulting from lesions in these areas are always multimodal, and never confined to tasks under the guidance of a single modality.

Some neurons in heteromodal association areas respond to stimulation in more than one modality, indicating the presence of direct multimodal convergence.34,46 More commonly, however, there is an admixture of neurons with different preferred modalities.232,237 Many neurons have sensory as well as motor contingencies.233,374 Others change firing in ways that are responsive to motivational relevance. Defined in this fashion, heteromodal cortex includes the 305 of regions which have been designated as high order association cortex, polymodal cortex, multimodal cortex, polysensory areas, and supramodal cortex.350 The monkey brain contains heteromodal areas in prefrontal cortex (BA9, 10, 45, 46, anterior BAS, an-
terior BA1 1-12), the inferior parietal lobule (parts of BA7), lateral temporal cortex within the banks of the superior temporal sulcus (junction of BA22 with BA21), and the parahippocampal region. In the human brain the analogous zones of heteromodal cortex are located in prefrontal cortex (BA9–10, 45-47, anterior 11–12, anterior s), posterior parietal cortex (posterior BA7, BA39-40), lateral temporal cortex (including parts of BA37 and BA21 in the middle temporal gyrus), and portions of the parahippocampal gyrus (parts of BA36–37).

Unimodal and heteromodal areas are characterized by a six-layered homotypical architecture. There are some relatively subtle architectonic differences between unimodal and heteromodal areas. In general, the unimodal areas have a more differentiated organization, especially with respect to sublamination in layers III and V, columnarization in layer III, and more extensive granularization in layer IV and layer II. On these architectonic grounds, it would appear that heteromodal cortex is closer in structure to paralimbic cortex and that it provides a stage of cytoarchitectonic differentiation intercalated between paralimbic and unimodal areas.

**Idiotypic Cortex (the Primary Sensory-Motor Zones)**

Primary visual, auditory, somatosensory, and motor cortices are easily delineated on cytoarchitectonic and functional grounds. Primary visual cortex (also known as V1, striate cortex, calcarine cortex or BA17) covers the banks of the calcarine fissure; primary auditory cortex (also known as AI, or BA41-42) covers Heschl's gyrus on the floor of the Sylvian cistern; primary somatosensory cortex (also known as S1, usually meant to include BA3a, 3b, 1, and 2) is located in the postcentral gyrus; and primary motor cortex (also known as M1) includes BA4 and probably also a posterior rim of BA6 in the precentral gyrus.

There are two divergent opinions about these primary areas. One is to consider them as the most elementary (even rudimentary) component of the cerebral cortex; the other is to consider them as its most advanced and highly differentiated component. The latter point of view can be supported from the vantage point of cytoarchitectonics. Thus, the primary visual, somatosensory, and auditory cortices display a "konio cortical" architecture representing the highest level of development with respect to granularization and lamination (Fig. 1–26), whereas primary motor cortex displays a unique "macropyramidal" architecture characterized by highly specialized giant pyramidal neurons known as Betz cells.

The visual, auditory, and somatosensory systems provide the major channels of communication with the extrapersonal world. The information transmitted by these channels plays a critical role in shaping all aspects of cognition and comportment. The primary and unimodal areas related to these modalities are cytoarchitectonically highly differentiated and quite large. The vestibular, gustatory, and olfactory sensations do not have the same type of prominence in the primate brain. The corresponding primary areas are cytoarchitectonically less differentiated, smaller, and closer to limbic structures. Primary gustatory cortex is located at the in BA43; the primary vestibular area lies within the posterior Sylvian fissure, where the temporal lobe joins the insula and parietal lobe; and the primary olfactory cortex is a
core limbic region located at the confluence of the insular, orbitofrontal, and temporopolar areas.195,341,407

III. CORTICAL ORGANIZATION, CONNECTIVITY, AND TRANSMODAL AREAS

As shown above, the cerebral hemispheres can be subdivided into five essential types of cortex which collectively display a spectrum of cytoarchitectonic differentiation ranging from the simplest to the most complex (Fig. 1-6). The corticoid and allocortical areas, collectively designated core "limbic" structures, are extensively interconnected with the hypothalamus. Through neural and also humoral mechanisms, the hypothalamus is in a position to control electrolyte balance, glucose levels, basal temperature, metabolic rate, autonomic tone, hormonal state, sexual phase, circadian oscillations, and immunoregulation, and to modulate the experience and expression of hunger, aggression, fear, flight, thirst, and libido.42,58,365,463,515,559 In keeping with these functions of the hypothalamus, the cortical areas of the limbic zone assume pivotal roles in the regulation of memory, emotion, motivation, hormonal balance, and autonomic function. These specializations of limbic structures are related to the upkeep of the internal milieu (homeostasis) and the associated operations necessary for the preservation of the self and the species.

The opposite pole of Figure 1-6 is occupied by the architectonically highly differentiated and functionally highly specialized priman; sensory and motor areas. These parts of the cerebral cortex are most closely related to the extrapersonal space: primary sensory cortex provides an obligatory portal for the entry of information from the environment into cortical circuitry, and primary motor cortex provides a final common pathway for coordinating the motor acts which allow us to manipulate the environment and alter our position within it. Unimodal, heteromodal, and paralimbic cortices are intercalated between the two poles of Figure 6. They provide neural bridges that mediate between the internal and the external worlds so that the needs of the internal milieu are discharged according to the opportunities and restrictions that prevail in the extrapersonal environment. These three intercalated zones enable the associative elaboration of sensory information, its linkage to motor strategies, and the integration of experience with drive, emotion, and autonomic states. Two of these zones, the unimodal and heteromodal, are most closely involved in perceptual elaboration and motor planning whereas the paralimbic zone plays a critical role in channeling emotion and motivation to behaviorally relevant motor acts, mental content, and extrapersonal events.

Connectivity of the Cerebral Cortex

Components of each zone in Figure 1–6 have extramural connections with components of other functional zones and intramural connections within the same zone. Experimental evidence, gathered mostly in the brain of the monkey, shows that the most intense extramural connectivity of an individual cortical area occurs with com-
ponents of the two immediately adjacent functional zones in Figure 1–6. For example, although all types of cortical areas, including association isocortex, receive direct hypothalamic projections,344 such connections reach their highest intensity within components of the limbic zone. The constituents of this zone, the septal area, the nucleus basalis of the substantia innominata, the amygdaloid complex, piriform cortex, and the hippocampus, are the parts of the cerebral cortex which have the most intense reciprocal connections with the hypothalamus.11,342,562 In keeping with the organization shown in Figure 1–6, the second major source of extramural connections for limbic structures originates in the paralimbic zone. Thus, the amygdala receives one of its most extensive extramural cortical inputs from the insula; the hippocampus from the entorhinal sector of the parahippocampal region; and the piriform cortex as well as the nucleus basalis from the group of olfactocentric paralimbic areas.342,343,533

An analogous analysis can be extended to the other zones in Figure 1-6. Paralimbic areas, for example, have the most extensive extramural connections with limbic and heterornodal areas. This has been demonstrated experimentally in the case of the anterior insula, the parahippocampal formation, the temporal pole, the cingulate complex, and posterior orbitofrontal cortex.343,367,369,397,533,534 Furthermore, the most extensive extramural interconnections of heteromodal areas are with components of the paralimbic zone, on one hand, and with those of the unimodal zone, on the other.23,24,249,350,395,398 Finally, the major extramural connections of unimodal areas occur with primary areas, on one hand, and heteromodal areas, on the other, while primary areas derive their major inputs from unimodal areas and the external world.249,395 Although some connections jump across the levels shown in Figure 1-6, they are not as prominent as those that link two immediately adjacent levels. Thus, the amygdala is known to have monosynaptic connections with unimodal association isocortex and even primary visual cortex, but these are not nearly as substantial as its connections with the hypothalamus and paralimbic regions.1 The position of a cortical area in Figure 1–6 thus helps to specify its most salient connections with other cortical areas.

Within the context of this general plan of organization, Figure 1-8 summarizes the sensory–fugal pathways which sequentially convey sensorv information from primary sensory to unimodal, heteromodal, paralimbic, limbic, and hypothalamic areas of the monkey brain.3,343,367,369,397,398,530 This pattern of connectivity displays a polarization which fits the basic plan shown in Figure 1-6. The pathways in Figure 1–8 are based on the organization of visual and auditory pathways, two modalities that play a crucial role in shaping cognition and comportment. Although somatosensory pathways follow many of the same principles of organization, they also display unique properties such as the existence of monosynaptic connections between primary sensory and primary motor areas. Olfactory and gustatory pathways have a different plan of organization, reflecting their closer relationship to the internal rather than the external milieu.

Many cortical areas also have intramural cortical connections with other components of the same functional zone. These are extremely well developed within the limbic, paralimbic, and heteromodal zones. Of all the nonfrontal cortical neu-
FIGURE 1–7. Distribution of functional zones in relationship to Brodmann's map of the human brain. The boundaries are not intended to be precise. Much of this information is based on experimental evidence obtained from laboratory animals and needs to be confirmed in the human brain. Abbreviations: AA = auditory association cortex; ag = angular gyrus; AI = primary auditory cortex; B = Broca's area; cg = cingulate cortex; f = fusiform gyrus; FEF = frontal eye fields; ins = insula; ipl = inferior parietal lobule; it = inferior temporal gyrus; MA = motor association cortex; mpo = medial parietooccipital area; mt = middle temporal gyrus; M1 = primary motor area; of = orbitofrontal region; pc = prefrontal cortex; ph = parahippocampal region; po = parolfactory area; ps = peristriate cortex; rs = retrosplenial area; SA = somatosensory association cortex; sg = supramarginal gyrus; spl = superior parietal lobule; st = superior temporal gyrus; S1 = primary somatosensory area; tp = temporopolar cortex; VA = visual association cortex; V1 = primary visual cortex; W = Wernicke's area.
FIGURE 1-8. The straight arrows illustrate monosynaptic sensory-fugal neural connections in the visual and auditory modalities. Thick arrows represent more massive connections than thin arrows. The broken arrows illustrate motor output pathways.

rons which projected to a subsector of prefrontal heteromodal cortex, for example, 37% were located with unimodal areas, 18% in paralimbic regions, and 44% in other heteromodal cortices. Paralimbic formations such as the insula, posterior orbitofrontal cortex, the temporal pole, entorhinal cortex and cingulate cortex also have very prominent interconnections with each other. In contrast, the intramural connections of primary sensory-motor and upstream unimodal sensory association areas have a particularly restricted distribution. Upstream unimodal association areas in different modalities, for example, have no interconnections with each other. Except for the connection from primary somatosensory to primary motor cortex, there are also no neural projections interconnecting primary areas in different modalities. It appears, therefore, that there is a premium on channel width with the limbic, paralimbic, and heteromodal regions of the cerebral cortex whereas the emphasis is on fidelity within the upstream unimodal and primary sensory-motor areas.

**Intermediary Processing and Transmodal Areas**

A fundamental characteristic of the primate brain is the insertion of obligatory synaptic relays between stimulus and response, and also between the representation of the internal milieu (at the level of the hypothalamus) and that of the external world (at the level of primary sensory-motor cortex). These intercalated synaptic relays collectively provide the substrates for "intermediary" or "integrative" processing (Fig. 1–8). The psychological outcomes of intermediary processing are known as "cognition," "consciousness," and "comportment" and include the diverse man-
manifestations of memory, emotion, attention, language, planning, judgment, insight, and thought. Intermediary processing has a dual purpose. First, it protects channels of sensory input and motor output from the motivationally-driven influence of the internal milieu. Secondly, it enables identical stimuli to trigger different responses depending on situational context, past experience, present needs, and contemplated consequences. The neurons that support intermediary processing are located with the unimodal, heteromodal, paralimbic, and limbic zones of the cerebral cortex.

The synaptic architecture of intermediary processing shapes the nature of cognition and comportment. In species with simpler brains, intermediary processing is shallow and does not allow much of a distinction to be made between appearance and significance. The automatic linkage between stimulus and response in such species leads to the many manifestations of instinctual behaviors. A turkey hen with a newly hatched brood, for example, will treat every moving object with the nest as an enemy unless it utters the specific peep of its chicks. If a hen is experimentally made deaf, it will invariably lull all its own newly hatched progeny. Furthermore, male sticklebacks (which are red on the ventral side) will automatically attack any stimulus with a "red below" pattern as if it were a rival. In these behaviors, the physical dimensions of a stimulus trigger preprogrammed behavioral sequences which are relatively impervious to contextual peculiarities. A major role of intermediary processing is to transcend such rigid stimulus–response linkages and to enable behavior to be guided by contextual significance rather than appearance.

Unimodal areas contain the initial synaptic relays for intermediary processing. These areas are extremely well developed in the human brain. The absence of interconnections linking a unimodal area in one sensory modality with another in a different modality protects the sensory fidelity of experience and delays cross-modal contamination until further encoding has been accomplished. Unimodal areas are thus in a position to register the most accurate representation of sensory experience. These areas can encode the perceptual characteristics of specific sensory events, determine if the sensory features of complex entities such as words or faces are identical or not, and even store all the necessary information in stable memory traces. However, in the absence of access to information in other modalities, unimodal areas do not have the ability to lead from word to meaning, from physiognomy to facial recognition, or from isolated sensory events to coherent experiences. Such integration of sensation into cognition necessitates the participation of "transmodal" areas.

The defining feature of a transmodal area is the ability to support cross-modal integration and, thus, the lack of specificity for any single modality of sensory-processing. All components of heteromodal, paralimbic, and limbic zones are therefore also transmodal. A precise localization of transmodal areas became possible through the tracing of corticocortical connections in the monkey brain. The basic organization of these connections was first described in two classic papers, one by Pandya and Kuypers and the other by Jones and Powell. These papers revealed the existence of a hierarchically organized set of pathways for linking sensory cortices to primary, secondary, and sometimes even tertiary modality-
specific association areas which, in turn, sent convergent projections to heteromodal sensory association zones.

The field of neuroscience had been primed to anticipate such a sequential organization through the work of Hubel and Wiesel, who had demonstrated: hierarchy of simple, complex, and hypercomplex neurons in primary visual cortex, each successive level encoding a more composite aspect of visual information. The discoveries of Pandya and Kuypers and Jones and Powell seemed to be extending this serial and convergent organization from the realms of sensation to those of cognition. A great deal of emphasis was placed on the pivotal role of multimodal convergence in all aspects of mental function, including the storage of memories, the formation of concepts, and the acquisition of language. 169,249,331,395,396,533

While the importance of serial processing and multimodal convergent function was widely accepted, some potentially serious computational limitations of such an arrangement were also acknowledged. 178,334,456 Two of these objections are particularly relevant: (1) If knowledge of \( \alpha \) is to be encoded in convergent form by a small number of neurons, the brain would have to resolve the cumbersome problem of conveying \( \alpha \)-related information in all relevant modalities to the one highly specific address where this convergent synthesis is located. (2) The modality-specific attributes of \( \alpha \) would succumb to cross-modal contamination during the process of convergence and the sensory fidelity of the experience would be lost. This second circumstance can be likened to the mixing of yellow and blue to obtain green, a process which precludes the subsequent extraction of the original hues from the resultant mixture.

The surfacing of these concerns coincided with the development of newer and more powerful neuroanatomical methods based on the intra-axonal transport of horseradish peroxidase and tritiated amino acids. Experiments based on these methods started to show that the sensory-fugal flow of information was more complicated than previously surmised: there was a central thread of serial processing from one synaptic level to another but there were also multiple parallel pathways, feed-forward and feedback connections, and multiple sites for divergence and convergence. The synaptic templates based on this type of connectivity appeared to have much greater computational power. The objections to the convergent encoding of knowledge, for example, could be addressed by assuming that the principal role of transmodal areas is to create directories (addresses, maps, look-up tables) for binding (rather than mixing) modality-specific fragments of information into coherent experiences, memories, and thoughts. This alternative process can be likened to obtaining green by superimposing a blue and a yellow lens which can then be separated from each other to yield back the original uncontaminated colors. Transmodal areas appeared to fulfill two functions: (1) the establishment of limited cross-modal associations related to the target event and (2) the formation of a directory pointing to the distributed components of the related information. 339 Transmodal areas could thus enable the binding of modality-specific information into multimodal representations that protect the fidelity of the initial encoding.

Transmodal areas are not centers for storing convergent knowledge but rather critical gateways for integrating and accessing the relevant distributed informa-
They also provide "neural bottlenecks" in the sense that they constitute regions of maximum vulnerability for lesion-induced deficits in the pertinent cognitive domain. All transmodal areas receive similar sets of sensory information and mediate analogous neural computations. However, each transmodal area displays a distinctive profile of behavioral specializations which is determined by its overall pattern of neural connections and physiological characteristics. This chapter will review several illustrative examples of this organization, including the pivotal role of midtemporal cortex for face and object recognition, Wernicke’s area for lexical labeling, the hippocampo-entorhinal complex for explicit memory, prefrontal cortex for working memory, the amygdala for emotion, and dorsal parietal cortex for spatial attention.

IV. FUNCTIONS OF INDIVIDUAL CORTICAL ZONES: PRIMARY SENSORY AND MOTOR AREAS

Primary Visual Cortex

Primary visual cortex (V1, BA17 in Fig. 1–7) covers the occipital pole and the banks of the calcarine fissure. This region is also known as striate cortex because of the conspicuous myelinated stripe of Gennari (or of Vicq d'Azyr) which is easily detected in layer IV even by the naked eye inspection of unstained specimens. Retinal input is relayed to striate cortex through the lateral geniculate nucleus. The importance of visual input to striate cortex is shown by the fact that fully 70% of all its neural input comes from the lateral geniculate nucleus. The entire visual field is mapped onto striate cortex with great spatial precision. The striate cortex in each hemisphere receives input from the contralateral visual field. Dorsal parts of striate cortex contain a representation of the lower visual field while the ventral parts represent the upper visual field. The central (macular, foveal) part of the visual field is mapped onto the most posterior part of striate cortex and has the greatest magnification factor. More anterior parts of V1 along the calcarine fissure contain representations of progressively more peripheral parts of the visual field. Except for the representation of the vertical meridian, striate cortex in the monkey does not have callosal interhemispheric connections.

The physiological exploration of neurons in primary visual cortex (V1) has led to one of the most exciting chapters in neuroscience. These neurons have an exquisite organization of connectivity which leads to the orderly encoding of information about the orientation, movement, binocular disparity, color, length, spatial frequency, and luminance of objects. Individual neurons preferentially sensitive to different aspects of visual information display a relative segregation into a multi-dimensional mosaic of columns, layers, and cytochemically differentiated patches.

In the rhesus monkey, extensive (but almost certainly incomplete) bilateral removals of striate cortex lead to a loss of fine visual discrimination of stationary objects. However, visuospatial orientation and the ability to reach toward moving peripheral targets may remain relatively intact.
In humans, partial destruction of geniculostriate pathways leads to characteristic visual field deficits within which conscious form perception of still objects is lost. Some ability for reaching towards visual stimuli in the blind field may be retained even though the patient may deny awareness of the stimulus. This residual capacity, known as "blindsight," may be subserved by retinocollicular projections which are subsequently relayed to the pulvinar nucleus of the thalamus and ultimately to visual association and parietal areas. It appears that the retinogeniculocalcarine pathway is necessary for conscious visual experience whereas the parallel retinocolliculothalamic pathway may be sufficient to support visual reaching, even when the targets are not consciously perceived (also see Chapter 7).

Primary Auditory Cortex

The primary auditory koniocortex (BA41 and 42), also known as A1, is located on Heschl’s gyrus within the posterior aspect of the superior temporal plane (Fig. 1–7). This area receives inputs from the part of the medial geniculate body which functions as the thalamic relay nucleus in the auditory modality. There is a tonotopic organization in A1 so that the low frequencies are represented more anteriorly than the higher frequencies. In addition to A1, the superior temporal plane of the monkey also contains a second tonotopically organized area, R, which also receives input from the medial geniculate nucleus. Both of these areas can be activated by pure tones.

Single unit recordings in monkeys show that A1 units are sensitive to the location of sound sources. For example, some A1 units are much more active when the animal is required to identify the location of a sound source than when the task is merely the detection of the sound. Neurons in the A1 region of each hemisphere are likely to give a brisker response to sounds originating in the contralateral extraperconal space. Furthermore, bilateral ablations of A1 (usually extending into adjacent association cortex) lead to deficits in a task that requires the monkey to walk toward the source of a sound. However, the spatial map in A1 is not nearly as specific as the map in V1.

Primary auditory cortex does not display the type of strictly contralateral representation characteristic of primary visual and somatosensory cortices. Through multisynaptic pathways which have extensive decussations in the brainstem, the A1 of each hemisphere has access to information from both ears even though the influence of the contralateral ear appears to be stronger. Therefore, unilateral A1 lesions do not lead to contralateral deafness. In fact, such lesions would probably remain undetectable without the assistance of auditory evoked potentials or dichotic listening tasks. In the latter test, the simultaneous delivery of stimuli to both ears yields excessive suppression of the input into the ear contralateral to the A1 lesion. In contrast to the primary visual and somatosensory thalamic relay nuclei, which have no substantial connections with the pertinent unimodal association areas, the medial geniculate body has major projections not only to A1 but also to the unimodal auditory association areas in the adjacent superior temporal gyrus.
Therefore, complete cortical deafness is unlikely to arise unless there is bilateral damage both to Al and also to the adjacent auditory association areas.

**Primary Somatosensory Cortex**

The postcentral gyrus contains the primary somatosensory cortex, S1 (Fig. 1–7). This area is the major recipient of projections from the lateral, medial, and superior sectors of the ventroposterior lateral thalamic nucleus, which is the principal thalamic relay for the ascending somatosensory pathways. Some investigators have convincingly argued that only BA3b should be included in S1 since BA1 and especially BA2 have characteristics more consistent with those of upstream unimodal somatosensory association cortex. The designation "S1" in the literature, however, usually refers collectively to BA3a, 3b, 1 and 2, a usage that will be followed here. The contralateral half of the body surface is somatotopically mapped onto S1 in each hemisphere. The mouth and face areas are represented most ventrally; the hand, arm, trunk, and thigh more dorsally, and the leg and foot medially.

In the monkey brain, single unit recordings show that BA3a is preferentially activated by muscle spindle afferents; BA3b and 1 by cutaneous input, and BA2 by joint receptors. In the monkey, BA2 lesions impair size and curvature discrimination, BA1 lesions impair texture discrimination, and both types of deficits arise after BA3b lesions. Neurons in S1 are particularly responsive to active tactile exploration. Thus, in one study, tactile stimulation of the finger led to the activation of 13 of 76 S1 neurons only when the monkey’s finger was moving but not when it was at rest. In humans, SI damage (usually encroaching on BA3, 1 and 2) tends to be associated with a selective impairment of the so-called "cortical" sensations such as two-point discrimination, touch localization, graphesthesia, position sense, and stereognosis, whereas touch, pain, and temperature detection may remain relatively preserved.

**Primary Motor Cortex**

The primary motor cortex (M1) is located in front of the central sulcus (Fig. 1–7). The M1 contains a body representation which closely parallels that of S1. The M1 region can be identified on the basis of three characteristics:

1. The cytoarchitecture is dominated by the presence of large pyramidal neurons which reach their greatest size in BA4 (Betz cells).
2. The threshold for eliciting movement upon stimulation is lower in M1 than in any other cortical area.
3. The M1 region contains the greatest density of neurons giving rise to corticospinal and corticobulbar fibers.

The literature is not always clear about the distinction between M1 and premotor cortex. Some have argued that only BA4 (the Betz cell zone) deserves to be included
FIGURE 1–9. The MRI scans from four patients. Left side of the head is on the right side of each scan. a. A 91-year-old woman with an anaplastic neoplasm confined to the postcentral gyrus of the right hemisphere (double arrows), probably involving mostly BA2. Touch and temperature sensations were preserved but two-point discrimination and graphesthesia were impaired in the upper left extremity. In keeping with the sparing of more posterior parts of parietal cortex, reaching, grasping, and manual exploration were intact. b. A 63-year-old woman after the removal of an olfactory groove meningioma. There is almost no brain tissue left in the region that should have contained orbitofrontal cortex (of). The remaining orbitofrontal cortex is reduced to a sclerotic ribbon (curved arrow). The dorsolateral prefrontal cortex was completely spared. The patient displayed severe disinhibition and other comportmental abnormalities despite relatively intact cognitive functions. c. A 47-year-old man after the removal of a left prefrontal glioma. The area of encephalomalacia in the left dorsolateral prefrontal cortex is shown by the single arrows. A shunt was introduced through the right dorsolateral prefrontal cortex and caused tissue injury (double arrow). The additional signal void on that side is probably an artifact due to the shunt. Úrbitofrontal cortex (of) was spared. The patient displayed the abulic type of frontal lobe syndrome as well as attentional deficits. d. A 41-year-old man suffered an acute stroke which involved the mediodorsal nucleus (m) of the thalamus on the left (arrow). He displayed a clinical picture which contained elements of amnesia and a frontal lobe syndrome.
in M1, others that M1 should include not only BA4 but also the posterior half of BA6. Many neurons in M1 fire in conjunction with reaching movements. Single cells display a coarse directional tuning but populations of neurons can encode vectors pointing in the direction of the upcoming reaching movement. Experiments in monkeys show that the M1 output is especially important in controlling the early recruited portion of the motoneuron pool involved in precise fine movements. In keeping with these physiological characteristics, extensive M1 removals in monkeys lead to relatively subtle deficits, mostly confined to individual finger movements, while other movements and especially posture and gait remain relatively intact.

The clinical consequences of lesions confined to M1 in humans are poorly understood. Some would argue that such lesions may only impair fractionated distal limb movements while leaving muscle tone and strength of proximal muscles intact. Others argue that M1 lesions lead to increased tendon reflexes and to widespread paralysis of entire limbs. Experiments based on transcranial magnetic stimulation suggest that the human M1 plays a greater role in the performance of complex than simple finger movements. "Idiomotor apraxia" refers to an inability to convert verbal commands into skilled movements which require the fractionated control of distal limb musculature (Chapter 2). This type of apraxia may result from lesions which interrupt the multisynaptic pathways leading from posterior association areas to M1 via intermediary relays in premotor and supplementary motor areas. The execution of commands aimed at the axial musculature may remain preserved in these patients since such movements may not depend on the integrity of pyramidal pathways. As in S1, the hand and foot representations of M1 have no callosal connectivity. Since this arrangement is likely to promote hemispheric independence of hand control, it may provide at least one essential anatomical substrate for the development of handedness.

V. FUNCTIONS OF MODALITY-SPECIFIC (UNIMODAL) SENSORY ASSOCIATION AREAS

The sensorv-fugal streams of information processing enter their first "associative" stage within modality-specific (unimodal) association areas. Each group of modal areas conveys modality-specific information to the limbic system (for memory and emotion), prefrontal cortex (for working memory and other executive functions), perisylvian cortex (for language functions), temporal cortex (for object recognition), dorsal parietal cortex (for spatial attention) and premotor cortex (for the sensory guidance of movement and praxis). Lesions that damage unimodal sensory association cortex or its connections may give rise to two major types of behavioral deficits.

1. Selective perceptual deficits (such as "achromatopsia" and "akinetopsia") even when other functions in that sensory modality remain intact.
2. Modality-specific “agnosias” and “disconnection syndromes” (such as “prosopagnosia” and “pure word deafness.”)

Visual Unimodal Association Areas — Color, Motion, Shape, Objects, Faces, Words and Spatial Targets

The unimodal visual association areas in the human brain occupy peristriate cortex (BA18–19), and parts of the fusiform, inferior temporal, and middle temporal gyri (BA37, 20, 21). In the monkey, primary visual cortex (V1) projects to V2 (BA18) in a topographically well-ordered fashion. Areas V1 and V2 then give rise to multiple parallel pathways that project to numerous specialized peristriate visual association areas, located mostly within BA19 and designated V3, VA, V5 (MT), VP, V6 (PO), V7, and V8. The further occipitofugal flow of visual information takes the form of two divergent multisynaptic pathways, a dorsal one (also known as the "where" pathway) directed toward parietal and frontal cortex, and a ventral one (also known as the "what" pathway) directed toward downstream temporal visual association areas and the limbic system. A similar organization is likely to exist in the human brain (Figs. 1-10 and 1-11a, b).

Figure 1-11a summarizes the cortical connectivity of the visual system of the monkey brain based on the review by Felleman and Van Essen. Virtually all of these connections are reciprocal. They are represented on a template of: concentric circles where each circle is separated from the next by at least one unit of synaptic distance. V1 occupies the first synaptic level. The subsequent synaptic levels follow.
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a "downstream," "feedforward," "sensory–fugal," or "bottom-up" direction with respect to the visual modality, whereas descending levels can be described as following a "feedback," "sensory–petal," or "top-down" direction.

In the monkey, areas V2, V3, V4, and V5 (MT) are monosynaptically connected with V1 and therefore constitute “upstream” visual association areas whereas MST (medial superior temporal area), LIP (lateral intraparietal sulcus), posterior and anterior inferotemporal cortex (PIT and AIT in BA20–21), temporal area TF (SA 20), and the posterior inferior parietal lobule (BA7a) constitute some of the "downstream" visual association areas at the third and fourth synaptic levels. Although areas LIP, TF, and 7a also display features of heterornodal cortex, they appear to have subregions (such as Opt in the inferior parietal lobule and the posterior part of area TF) that may be engaged predominantly in the processing of visual information.13,350,398 The LIP, TF, 7a nodes in Figure 1-11a represent these relatively modality-specific subregions.

The primary dimension of visual mapping is retinotopic and is achieved by finely tuned neurons which provide an exquisitely ordered spatial representation of the visual fields in V1. Other dimensions of visual experience such as color and motion are mapped in V1 and V2 by coarsely tuned neurons and become more fully characterized at further synaptic stages, including V4 and perhaps V8 (corresponding in part to area PIT or TEO) for color and V5 (MT) and MST for motion. The gradual increase of response latency, visual field size, and response complexity in the progression from V1 to V2, V4, PIS, and AIT confirms the existence of a synaptic hierarchy in the organization of visuofugal pathways. Although a visual event activates nodes at higher levels of this hierarchy with increasing latencies (11 ms between V1 and V2 and 9 ms between V1 and V3, but 40 ms from V1 to PIT-AIT), all areas eventually become concurrently active in the course of visual processing.123,424 It seems as if each node is continuously passing on information to the others rather than fulfilling its part of the processing and then transmitting a completed product to the next station.518

COLOR AND MOVEMENT

The specialization of V4 (and perhaps V8) for color and of V5 (MT) and MST for movement have been documented in the monkey and human.198,221,530 Studies based on functional imaging—for example, have shown that the posterior parts of the lingual and, to a lesser extent, fusiform gyri in the human brain are sensitive to color stimulation.80,303 The unilateral destruction of these areas in patients is usually associated with a contralateral loss of color perception (“hemian-chromatopsia”) without equivalent impairments of visual acuity-, movement perception, or object identification.103,335 Lesions which interrupt the output of these areas to language cortex can lead to "color amnesia," an inability to name colors despite intact color perception.

Other functional activation studies have shown that a laterally situated area in the middle temporal gyrus, at the confluence of BA19 and 37, displays selective activation in response to visual motion.545 This region appears to represent the human homologue of area V5 (MT) and perhaps also MST in the monkey. Its bilateral destruction causes a state known as akinetopsia” where the patient cannot per-
ceive visual motion although acuity and color perception may be relatively preserved 335,577,578 The clinical dissociation of achromatopsia from akinetopsia proves that the V1 projections to color-sensitive and motion-sensitive areas are organized in parallel rather than in series. The presence of such parallel pathways would be expected to increase processing efficiency by allowing the simultaneous analysis of multiple attributes associated with a visual event.

**FORM AND COMPLEX PATTERNS**

The elementary sensory features encoded at the first two synaptic levels are used by more downstream areas along the ventral visuofugal pathway for the discrimination of form and complex patterns. In the monkey, a posterolateral inferotemporal region (area TEO or PIT, at the junction of lateral BA19 with BA20-21) plays a critical role in form and pattern discrimination.564 A homologous area in the human brain includes parts of the fusiform gyrus, just anterior to V4, and probably extends into the adjacent lingual and inferior occipital gyri.199,259 This region appears to be involved in the construction of shape from simpler visual features since it becomes activated by tasks that require attention to both simple and complex shapes and does not give differential responses to upright versus inverted faces.

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**Figure 1-11.** a, b. Each concentric ring represents a different synaptic level. Any two consecutive levels are separated by at least one unit of synaptic distance. Level 1 is occupied by the primary sensory cortex. Small empty circles represent macroscopic cortical areas or "nodes," one to several centimeters in diameter. Nodes at the same synaptic level are reciprocally interconnected by the black arcs of the concentric rings. Colored lines represent reciprocal monosynaptic connections from one synaptic level to another. a. Visual pathways as demonstrated by experimental neuroanatomical methods in the macaque brain. b. Visual (green), auditory (blue), and transmodal (red) pathways in the human brain. Individual pathways are inferred from the experimental work in the monkey. The anatomical identity of many of the nodes is not specified because their exact anatomical location is not critical. The assumption is that these types of anatomical interconnections and functionally specialized nodes exist in the human brain even though their exact location has not yet been determined. The terms "dorsal" and "ventral" refer to the separation of visuofugal pathways, especially at the fourth synaptic level, into dorsal and ventral streams of processing. The gaps in the circles at the first four levels indicate the absence of monosynaptic connections between modality-specific components of auditory and visual pathways. Abbreviations: A1=primary auditory cortex; AIT=anterior inferotemporal cortex; f=area specialized for face encoding; L=the hippocampal-entorhinal or amygdaloid components of the limbic system; LIP=lateral intraparietal cortex; MST=medial superior temporal cortex; P=hemispheric posterior parietal cortex; Pf=lateral prefrontal cortex; s=area specialized for encoding spatial location; PIT=posterior inferotemporal cortex; T=hemispheric lateral temporal cortex; TF=part of medial inferotemporal cortex; v=area specialized for identifying individual voice patterns, V1=primary visual cortex, V2, V3, V4, V5=additional visual areas; W=Wernicke’s area; wr=area specialized for encoding word forms; 7a(Opt)=part of dorsal parieto-occipital cortex. c. Disconnection syndromes that arise when unimodal sensory-fugal pathways in the visual (green), auditory (blue), and somatosensory (purple) modalities become disconnected from motor-premotor cortex, the language network, the limbic system, and the heteromodal cortices involved in face and object recognition. Question marks indicate that the proposed syndromes have not yet been identified.
real versus nonsense objects, or novel versus familiar stimuli. In comparison to the brain of the macaque monkey, the components of the ventral visuofugal pathway in the human appear to have been tucked ventromedially, probably in response to the expansion of the lateral temporal and posterior parietal cortices.

Ventral Pathway: Faces, Objects, and Words

If the identification of complex visual events and objects had to be based on a sequential compilation of the orientation, contour, color, form, and motion data encoded at the first three synaptic levels, perception would probably take an inordinately long time and might not allow the rapid recognition of frequently encountered and behaviorally significant patterns. This potential limitation is overcome at the fourth synaptic level of the ventral visuofugal pathways where neuronal groups selectively tuned to specific visual categories promote the rapid identification of entities such as faces, objects, and words. In the monkey, the anterior inferotemporal area (AIT or anterior BA20–21) contains neuronal ensembles specialized for face and object identification. In the human brain, functional imaging studies, electrophysiological evoked responses, and the location of lesions in patients with the syndrome of prosopagnosia indicate that the homologous areas specialized for face and object identification are located predominantly within the midportion of the fusiform gyrus (BA37 and BA20).

The "face" area in the human brain ("f" in Fig. 1-11b) is more strongly activated by faces than by other objects. It is also more strongly activated by upright and intact faces than by inverted or scrambled ones but does not show a differential response to familiar versus novel faces. This area therefore appears to encode faces at a categorical or generic level prior to the stage of individual recognition. The fourth synaptic level of the human brain contains additional regions specialized for the identification of other common objects such as chairs and houses. An area specialized for the encoding of word forms and word-like letter strings ("wr" in Fig. 1-11b) has also been identified in this region, at a location perhaps slightly more lateral to that of the fusiform face areas. A second potential visual word-form identification area may be located in a more lateral occipitotemporal region, at the confluence of BA19 with BA37. Considering the extremely recent emergence of written language in human phylogeny, the word-form area is almost certainly not genetically programmed. A more likely possibility is that it represents an experiential modification of neuronal subgroups within populations specialized for the encoding of faces and objects. The visual word-form areas could thus mediate a sort of processing where written words are handled as objects rather than as symbols.

Neurological lesions which damage these face, object, and word areas (or their outputs to transmodal object recognition and language areas) lead to the syndromes of "prosopagnosia" (face recognition deficit), "associative visual object agnosia" (object recognition deficit), and "pure alexia" (visual word recognition deficit) (Fig. 1-11c). These conditions are described in greater detail in Chapters 5 and 7. In other patients, lesions which interrupt the connections from the visual association cortices...
to the limbic system give rise to states of “visual hypoemotionality” (where visual experiences no longer elicit the appropriate emotional response) and “visual amnesia” (where new memories cannot be formed when the input is in the visual modality) (Fig. 11c). In one patient, damage to visuoamygdaloid pathways prompted a cancellation of a Playboy subscription, apparently because the visual evocation of erotic feelings had become blunted.

DORSAL PATHWAY AND SPATIAL ORIENTATION

The fourth synaptic level in Figure 1-11b also contains components of the dorsal visuofugal pathways (“s” in Fig. 1-11b). This part of visual association cortex encodes visual information in the form of spatial vectors which can be used to guide attentional behaviors (Chapter 3). Neurons in parts of area 7a of the macaque, for example, can compute the spatial coordinates of extrapersonal visual events by combining retinotopic location with information about eye position. Some of these neurons display a tuning for visual events in head-centered or even world-centered coordinates so that relevant events can become targets of visual or manual grasp (Chapter 3). Functional imaging experiments based on tasks of spatial localization indicate that the analogous region in the human brain may be located in the dorsal occipitoparietal region, at the junction of BA19 with BA7, probably including the banks of the posterior intraparietal sulcus. Damage to these dorsal visual areas or to their connections contributes to the emergence of visuospatial disorientation syndromes such as “hemispatial visual neglect,” “dressing apraxia” (inability to align body axis with garment), “simultanagnosia” (inability to integrate visual detail into a coherent whole), “optic ataxia” (deficits of reaching toward visual targets), and “optic apraxia” (oculomotor exploration deficits). The latter three manifestations are collectively known as “Bálint’s syndrome.” These visuospatial syndromes are described in greater detail in Chapters 3 and 7.

GROUP ENCODING AND DISTRIBUTED PROCESSING

Neuronal ensembles within downstream visual association areas provide representations of objects and faces through a process of group encoding. The tuning is broad and coarse: One neuron may be activated by several faces and the same face may excite several neurons. The face neurons in inferotemporal cortex are selectively responsive to category-specific canonical features such as intereye distance, style of hair, expression, and direction of gaze. Neurons sensitive to similar types of canonical features form vertical columns measuring approximately 0.4 mm in diameter. Several adjacent columns responsive to similar features may be linked to form larger “patches” or modules measuring several millimeters. Groups of such patches may form interconnected but distributed ensembles collectively tuned to the entire set of canonical features that define an object class. The tangential interpatch connections that are necessary for establishing such an organization could be stabilized during the period of cortical development and subsequently strengthened by experience through the mediation of temporally correlated multifocal activity.

Although neurons in a given column respond preferentially to similar canonical features of an object or face, optimal tuning properties vary among constituent cells.
so that columnar activation may encode generic properties whereas the activities of individual cells within the column may help to encode distinguishing (subordinate) features of unique exemplars. In response to an object, a small subset of neurons in a given column can fire maximally and set constraints to guide the interpretation of less active neurons within the same ensemble. Identification can thus start by matching the coarse (or generic) features and then focusing on finer (subordinate) detail. A visual entity may be represented by a small number of modules, each broadly selective for some reference object or face, which collectively measure the similarity of the target stimulus to the reference entities. This type of encoding, also known as "second-order isomorphism," is thought to be computationally more parsimonious than representations based on a more direct isomorphic mapping of the target shape.

The processing parsimony offered by this organization is substantial. A very large number of faces can be encoded by a small number of neurons, recognition can be graded (rather than all or none) and based on partial information, the same information can be probed through multiple associations, generalizations based on few common features (or analysis based on differences) can be achieved rapidly, the progression from categorical to subordinate identification can proceed smoothly, and damage or refractory states in a subset of neurons within the ensemble can lead to a graceful, partial degradation of function. These neurons can achieve a rapid detection of behaviorally relevant, recurrent, and composite visual events, obviating the need for a cumbersome sequential compilation of the more elementary sensory features. The face-responsive ensembles also display considerable plasticity, so some neurons alter their firing rate to a given face when it becomes more familiar or when a new one is added to the set, suggesting that the identity of an individual face is not encoded by fixed rates or firing but by the relative firing frequencies (and perhaps interneuronal correlation patterns) across the entire ensemble. The general principles that guide the visual identification of faces probably also apply to the encoding of other classes of objects, words, and spatial targets.

The downstream unimodal association areas of the cerebral cortex display prominent learning effects. Following the pairing of pattern \( x \) to pattern \( y \) in a paired-associates task, for example, an anterior inferotemporal (AIT) neuron responsive to \( y \) but not to \( x \) increases its firing in anticipation of \( y \) toward the end of the delay period following stimulation by \( x \), showing that it has learned the arbitrary association between the two stimuli. Neurons in AIT also display a familiarity response to faces encountered as long as 24 hours ago, indicating that the initial exposure had been stored in long-term memory. These observations have led to the suggestion that the downstream visual association cortices in the temporal lobe act as a "memory storehouse" for object vision. Modifications of synaptic efficacy, such as those necessary for long-term potentiation and depression, have been obtained in the human middle and inferior temporal gyri and could mediate similar long-term encoding. The downstream components of unimodal visual association areas can thus not only identify but also record visual events.

The anatomical areas that play crucial roles in the identification of color, movement, faces, words, objects and spatial targets display relative rather that absolute
specializations. For example, V4 participates not only in color perception but also in selective attention, the identification of salience, and the encoding of form.92,366,470 In turn, the identification of color information may involve not only V4 and V8 but also a part of lateral peristriate cortex.84 Furthermore, neuronal ensembles selectively tuned to canonical features of faces participate, although to a lesser extent, in encoding other visual entities.447 Any visual input can probably activate all of the nodes along the visual pathways shown in Figure 11b. However, stimuli with canonical features of faces are likely to cause optimal activation in the face area, those with the canonical features of words in the word area, and so on. Thus, the neural representation of a face could be conceptualized as a plane that has its highest peak over the face area but which also has lesser peaks over numerous other nodes of visual association cortex. This organization has been designated “selectively distributed processing”336,480 to set it apart from other models based on equipotentiality285 and modularity.78

Auditory Unimodal Association Areas

Primary auditory areas Al and R receive their thalamic input from the medial geniculate nucleus and are responsive to pure tones. Another auditory area, CM, depends on inputs from Al and R for its pure-tone responses. Area CM is more responsive to complex broad-band stimuli and to the high frequencies used for sound localization.433 It appears, therefore, that the primate brain may contain multiple auditory areas just as it contains multiple visual areas (Fig. 1-11b).

In the monkey, pitch and pure tone discrimination are accomplished at the level of Al and closely related upstream auditory association areas of the posterior superior temporal gyrus. The identification of complex auditory sequences, the discrimination of species-specific calls, and the localization of sounds, however, engage more downstream auditory association areas of the superior temporal gyrus.91,214 The role of the superior temporal gyrus in the identification of species-specific calls appears analogous to the role of downstream visual association cortex in face identification, both processes serving crucial functions in social communication.

In keeping with the organization of visuofugal pathways, the auditory pathways of the monkey brain may also be divided into dorsal and ventral components. Area Tpt of the posterior superior temporal gyrus, for example, may belong to the dorsal audiofugal stream of processing and may be specialized for detecting the spatial localization of sound sources, whereas the more anterior and ventral parts of the superior temporal gyrus may be specialized for identifying complex auditory sequences and species-specific vocalizations.91,214,289 As in the case of visual pathways, unimodal auditory cortex can also store modality-specific memories. Thus, lesions that destroy auditory unimodal association areas impair the retention of auditory sequences.

A similar organization may exist in the human brain. Neurons in Al of the human brain are sensitive to pure tones and pitch whereas those of the mid-to anterior parts of the superior temporal gyrus are relatively unresponsive to pure tones and nonlinguistic noises but respond to specific phonetic parameters of spo-
ken language. The superior temporal gyrus neurons are broadly tuned to the segmentation and sequencing of phonemes as well as to their coherence within polysyllabic and compound words. They encode speech at a presemantic level since they respond to spoken real words as readily as to distorted backward speech. These neurons may be analogous to the visual word-form neurons of the fusiform and adjacent inferotemporal areas where words and letter strings are processed as perceptual patterns rather than symbols. Approximately half of the neurons in parts of the middle temporal gyrus (BA21) give highly selective responses, mostly in the form of suppression, to understandable speech but not to distorted speech.

Although the evidence is not as easily interpreted as in the case of visual pathways, it appears that upstream auditory areas in the human brain tend to encode more elementary features of sound such as frequency and pitch, whereas downstream areas may contain neuronal groups that encode more composite features related to the identification of words ("wr" in Fig. 1-11B), the localization of sound sources for attentional targeting ("s" in Fig. 1-11B), the categorization of object-specific sounds, and perhaps also the characterization of individual voice patterns (area "v" in Fig. 1-11B). Lesions of unimodal auditory-association cortex or of its connections give rise to complex "auditory perceptual impairments" (such as the inability to identify variations in timber or sound sequences), "cortical deafness" (inability to recognize meaningful verbal and nonverbal auditory patterns despite normal brainstem auditory potentials), "pure word deafness" (inability to understand or repeat spoken language despite good recognition of environmental sounds and no other language deficit), "auditory agnosia for environmental sounds" (inability to identify sounds characteristic of objects despite good speech comprehension), and "phonagnosia" (inability to recognize the identity of familiar voices despite preserved recognition of spoken words and environmental sounds). The first two deficits are caused by damage to upstream unimodal auditory association cortex (usually in the presence of variable AI involvement) whereas the latter three may reflect damage to downstream auditory association cortex or functional disconnections of auditory association areas from transmodal cortices related to language comprehension and object recognition (Fig. 1-11c).

Pure word deafness and auditory agnosia can have "apperceptive" as well as "associative" subtypes (or components). In the apperceptive form, the clinical deficit can be attributed to a degradation of the auditory-percept, whereas in the associative form it is caused by the inability of an otherwise intact auditory percept to activate transmodal areas related to language comprehension and object recognition. The exact anatomical correlates underlying these clinical subtypes have not yet been identified. Conceivably, the apperceptive component becomes prominent when the lesion encroaches on AI and upstream unimodal association cortex whereas the apperceptive component dominates when the lesion is confined to the downstream auditory association cortex and its outputs.

The traditional literature gives the impression that Wernicke’s area is confined to auditory association cortex in the posterior third of the superior temporal gyrus. This is quite unlikely since the deficit in Wernicke’s aphasia is multimodal and
impairs language comprehension in all modalities of input. A more likely possibility is that Wernicke’s area extends into heteromodal cortical areas and that the posterior third of the superior temporal gyrus constitutes only one of its components. Damage to this component is likely to be responsible for the auditory aspects (such as word deafness) of Wernicke’s aphasia.

_Somatosensory Association Areas and Secondary Somatosensory Cortex_

As mentioned in the section on primary somatosensory cortex, FA1 and 2 have characteristics of upstream unimodal association cortex although they are traditionally included within S1. In the monkey, the superior parietal lobule (BA5) is the major recipient of S1 projections (mostly from BA2) and displays the properties of an upstream unimodal somatosensory association area. The sensory responses of approximately 98% of the neurons in BA5 are confined to the somatosensory modality. However, the firing patterns show an intramodal convergence among deep and superficial sensations, thus indicating a higher order neuronal processing than in S1. The superior parietal lobule is a major source of projections to dorsal premotor cortex and therefore plays an important role in the coordination of complex movements. For example, neurons in BA3 have somatosensory receptive fields with directionally tuned responses coded in arm- or body-centered coordinates. Neurons in BA5 give responses that are more closely related to the significance of the stimulus and the motor planning that it elicits than the actual execution of the movement.” Anterior parts of the inferior parietal lobule (BA7b) and parts of the insula may contain the downstream somatosensory association areas of the monkey brain. Some BA7b neurons are activated when the monkey attempts to grasp an object of interest, even in the absence of visual input, but not when the arm is moved passively.

A Secondary Somatosensory area (S2) has been identified within the sylvian fissure of the monkey brain at the junction of the insula with the parietal operculum. It contains a somatotopic representation which is somewhat coarser than the one in S1. The S2 area receives inputs from the inferior ventroposterior nucleus (VPI) of the thalamus, from all components of S1, and from the anterior part of the inferior parietal lobule (BA7b). It is a major source of somatosensory projections to the posterior insula which relays this information to the limbic system via the amygdala? Damage to S2 can impair tactile learning in the monkey, probably because it induces a somatosensory–limbic disconnection. These observations suggest that S2 has mixed characteristics of primary somatosensory cortex as well as of unimodal somatosensory association cortex.

In the rhesus monkey, the entire superior parietal lobule has been designated as area 5 by Brodmann. In the human, BA5 is confined to an anterior rim of the superior parietal lobule. The rest of the human superior parietal lobule is designated BA7 (Fig. 1–7). In the monkey, however, BA7 was used by Brodmann to designate the cortex of the inferior parietal lobule. For the purposes of this chapter, BA5, the anterior part of BA7 in the superior parietal lobule, parts of the posterior insula, and an anterior segment of the supramarginal gyrus (BA40) will be included within
the group of unimodal somatosensory association areas in the human brain (Fig. 1-7). Based on topographic similarities, BA5 and anterior BA7 of the human brain may be homologous to BA5 in the monkey whereas anterior BA40 and the anterior intraparietal sulcus may be homologous to BA7b.

In the human, an S2 area has been located in a region of the parietal operculum adjacent to the dorsal insula. Functional imaging suggests that S2 may participate in pain perception. In some patients, lesions in the region of S2 give rise to a loss of pain perception without impaireing other discriminative somatosensory modalities. This is the only lesion site which gives rise to such a dissociation: Thalamic lesions impair all modalities and S1 lesions cause the reverse dissociation (Fig 1-9a). In other patients, lesions in the region of S2 (but also involving the insula and parietal operculum) can give rise to painful contralesional disesthesias of the type seen in the thalamic Dejerine-Roussy syndrome. Similar lesions can also lead to "pain asymbolia," a condition where the patient fails to display the expected aversive and emotional response to pain anywhere in the body although the ability to discriminate sharp from dull may be intact? The syndrome of pain asymbolia (and the tactile amnesia which has been described in monkeys with S2 lesions) would appear to represent somatosensory–limbic disconnection syndromes (Fig. 1-11C). Pain asymbolia can be conceptualized as a somatosensory analogue of visual hypoemotionality.

The somatosensory association areas (BA5, 7, and perhaps also anterior BA40 and the posterior insula) in the human brain are likely to play essential roles in the her aspects of touch localization, active manual exploration, the somatosensory coordination of reaching and grasping, and the encoding of complex somatosensory memories. The anterior bank of the intraparietal sulcus (corresponding mostly to BA40) has, in fact, been shown to play a critical role in coordinating the prehensile movements required for object grasping. In Braille readers, unimodal somatosensory areas may encode word forms in a manner that is similar to the modality-specific encoding of word forms in visual and auditory association cortices.

Neural outputs of somatosensory association cortex in the human brain are likely to have the same types of targets as those of visual and auditory association cortices. They would therefore be expected to follow a posterior pathway directed to heteromodal association areas of the parietal lobe, an anterior pathway directed toward premotor and prefrontal cortices, and ventral pathways directed toward the language areas, the limbic system, and temporoparietal heteromodal cortex. The projections directed to the limbic system are likely to originate predominantly from S2 and the insula whereas the others are likely to arise also from BA5, anterior BA7, and perhaps anterior BA40.

Interrupting the projections from somatosensory cortex to parietal heteromodal areas may disrupt spatial orientation, tactile search, and the ability to align the body-axis with other solid objects during the process of dressing, sitting in a chair, or getting into bed. These types of lesions may therefore give rise to the somatosensory integration deficits associated with dressing apraxia, hemispatial neglect, and other aspects of spatial disorientation. Other types of posterior parietal or insular lesions may interrupt somatosensory projections to temporoparietal transmodal areas and may be responsible for the emergence of a somatosensory object recognition
deficit known as "tactile agnosia" (inability to recognize an object by palpation alone in a patient who can draw the palpated object and has no other somatosensory deficit).75 Lesions which disconnect somatosensory areas from the language network could conceivably give rise to "pure agraphesthesia" (or pure somesthetic alexia), a syndrome which could be considered the somatosensory analogue of pure word deafness and pure alexia (Fig. 1-11c).158 The interruption of the pathway from somatosensory cortex to premotor and supplementary motor areas may be responsible for the emergence of a modality-specific "tactile apraxia" wherein objects cannot be handled without visual guidance.110 Functional imaging experiments suggest that this pathway is likely to originate from the anterior intraparietal sulcus.47

VI. MOTOR ASSOCIATION AREAS (PREMOTOR CORTEX, SUPPLEMENTARY MOTOR AREA, FRONTAL EYE FIELDS)

The motor association areas anterior to M1 constitute the principal, if not exclusive, source of cortical projections into M1. Premotor cortex contributes a substantial number of descending corticospinal and corticobulbar fibers but at a lower density than M1.519 Microstimulation of this region elicits movement but the threshold for this is higher than in M1.547 Furthermore, the movement patterns that are elicited upon stimulation of motor association cortex are much more intricate than those elicited by M1 stimulation and often involve both sides of the body. Lesions in motor association areas yield complex deficits of movement in the absence of weakness, dystonia, dysmetria, or hyperreflexia. In the human brain, motor association cortex includes the premotor cortex (anterolateral BA6), the frontal eye fields in BA6, the supplementary motor area in the medial wall of the cerebral hemisphere (mostly BA6), the supplementary eye fields, the posterior parts of Broca’s area (BAU), and perhaps parts of BAS.

Investigations of motor association areas in the monkey are revealing an organization with a level of complexity that rivals that of visual pathways. Several premotor areas have been identified within the traditional boundaries of BA6, each with a potentially different specialization.314,440,556 According to one nomenclature, these areas have been designated F2-F7.440 Premotor areas receive input from numerous unimodal and heteromodal areas of the brain so that they have access to complex information in all major sensory modalities.547 Although premotor neurons respond to sensory stimuli, the responses usually vary according to the movement that will follow. For example, visually responsive neurons in premotor cortex show one response to a visual cue that triggers a movement and a different response when the same cue requires the animal to withhold movement.557

In the monkey, the interconnections between posterior parietal cortex and the premotor areas of BA6 are organized with exquisite anatomical and functional specificity. The projection from anterior intraparietal cortex (AIP) to frontal premotor area F5, for example, is part of a visuomotor circuit for preshaping the hand as it prepares to grasp a three dimensional tool (see Fig. 3–14). Neurons in F5 fire not only during grasping but also while viewing a graspable object even when no motor response is required, perhaps reflecting the stage at which a visually elicited motor
program is unfolding. A similar organization may exist in the human brain, where the lateral bank of the anterior intraparietal sulcus may provide the source of projections that allow premotor and supplementary motor cortices to coordinate object grasping and other aspects of prehension. As in the monkey, the visual observation of tools leads to the activation of the human dorsal premotor cortex even when no movement is emitted, suggesting that this area may play an important role in the visually triggered programming of movements related to tool usage.

In monkeys which were taught to elevate a lever to obtain reward, a surface-negative slow potential appears over premotor cortex about 1 second prior to the movement and gradually increases until about 100 ms before the movement. This slow potential may reflect the neural mechanisms which subserve motor intention and initiation. The proportion of neurons showing activity only during such preparatory phases of a movement is much higher in the supplementary motor area than in M1. Furthermore, neurons that can store information related to an entire sequence of goal-directed movements are frequently found in the supplementary motor area but not in M1, suggesting that the supplementary motor area plays an important role in coordinating multistep movement strategies and perhaps also in the encoding of procedural learning.

In keeping with these observations, finger movements lead to the activation of M1 as well as the supplementary motor area whereas imagined movements activate predominantly the latter. Furthermore, experiments based on transcranial magnetic stimulation show that premotor cortex plays a critical role in the early stages of movement selection when choices among competing alternatives need to be made. The supplementary motor cortex and premotor cortices therefore play important roles in motor planning and response selection. These areas may play a critical role in the initiation of motor responses and the ability to sustain motor output. The paucity of speech output in "transcortical motor aphasia" (a nonfluent aphasia with intact repetition and Comprehension) and "aphemia" (a nonaphasic, nondysarthric impairment of fluency) may thus result from a disconnection of the premotor and supplementary motor cortices from Broca's area.

Components of motor association cortex modulate the sensory, guidance, initiation, inhibition, planning, and perhaps also learning of complex movements. Damage to these areas results in category-specific (or conditional) disturbances of movement. Monkeys with lesions in area 6, for example, have no primary weakness but are no longer able to change the nature of a motor act in response to differential sensory cues. In the human, lesions in the frontal eye fields lead to impaired exploratory eye movements even when spontaneous eye movements remain intact; lesions in the premotor part of Broca's area lead to dysarthria for speech but do not interfere with singing; and damage to the supplementary motor cortex may interfere with motor initiation but not with the other phases of the movement.

The frontal epicenter of the language network is known as Broca's area. It includes premotor cortex in BA44 and also adjacent heterornodal cortex (Fig. 1–7). The examination of patients with focal lesions indicates that Broca's area is likely to play a critical role in translating neural word forms into their articulatory se-
quences and also in sequencing words and their endings into utterances that have a meaning-appropriate syntactic structure. This sequencing role attributed to Broca’s area is consistent with the other specializations of premotor and prefrontal cortex. In keeping with these functional characteristics, inferred on the basis of clinical observations, Broca’s area shows preferential metabolic activation in tasks that require neurologically intact subjects to decipher the meaning of a syntactically complex sentence and also in tasks that entail grapheme-to-phoneme transformations, even when the articulatory output is imaginary.70,173

Lesions that disconnect BA6 from the posterior components of the language network may cause multimodal “ideomotor apraxia” (inability to pantomime the use of an object upon verbal command) although the patient may have no difficulty making the same movement upon being handed or shown the actual object.169 Two types of “modality-specific apraxias” have also been reported: Some patients cannot pantomime the use of an object presented visually although they can perform the movement correctly when asked to do so verbally; others cannot perform the correct movements if asked to handle an object in the absence of visual guidance.110,566 These deficits, respectively designated “visual apraxia” and “tactile (or palpatory) apraxia,” appear to be caused by lesions which interrupt visual or somatosensory projections to premotor and supplementary motor areas (Fig. 1-11c). The movement deficits caused by damage to motor association areas reflect a disconnection between cognition and action rather than an impairment of strength or mobility.

VII. TEMPORAL HETEROMODAL CORTEX AND AGNOSIAS—
TRANSMODAL GATEWAYS FOR THE RECOGNITION OF FACES, OBJECTS, AND VOICES

As discussed above, downstream visual association cortices (such as “f” in Fig. 1-11b) are essential for the perceptual encoding of faces and objects. By itself, this information would provide an isolated percept devoid of meaning or context. The ability of this modality-specific information to activate the relevant multimodal associations that lead to recognition requires the mediation of transmodal cortical areas. In the monkey, for example, unimodal anterior inferotemporal cortex (AIT) neurons are sensitive to the visual properties of faces whereas more downstream transmodal neurons of the superior temporal sulcus also encode their familiarity.573 In humans, exposure to unfamiliar faces activates unimodal visual association areas in the fusiform face region, whereas familiar faces also activate transmodal nodes, including those in lateral midtemporal cortex.183 Heteromodal cortices in the middle temporal gyrus (represented by area T in Fig. 1-11b) may therefore act as transmodal gateways for linking the visual representation of faces with the additional associations (such as the name, voice, and personal recollections) that collectively lead to recognition.

Some neurological lesions lead to a specific face recognition deficit known as “associative prosopagnosia.” This syndrome is most commonly caused by bilateral lesions in the mid-to-anterior parts of the lingual and fusiform gyri (Chapter 7). As
noted earlier, these are the parts of the brain that contain the unimodal visual association areas specialized for the encoding of faces and other complex objects. According to Fig. 1-11b prosopagnosia can potentially arise as a consequence of at least three types of lesions: (1) those that damage area "f," (2) those that interrupt the connections between upstream visual association areas and area "f," and (3) those that interrupt the connections between area "f" and transmodal node T. Relatively simpler aspects of perception (for example, the ability to tell if two faces have an identical shape or not) can be preserved in these patients, presumably because more upstream visual association areas remain intact. Face recognition and identification can also be impaired in patients who have the simultanagnosia of Bálint's syndrome. This is known as an "apperceptive prosopagnosia" because it reflects a deficit in the spatial integration of the visual percept itself. In contrast to associative prosopagnosia, the patient with apperceptive prosopaposis is usually unable to determine if two faces are perceptually identical or not.

Although patients with associative prosopagnosia cannot recognize familiar faces by visual inspection, recognition becomes possible when information in a nonvisual modality, for example, the voice pattern characteristic of that person, becomes available. This auditory dorma tion can presumably access transmodal area T through area “v” of unimodal auditory cortex in Fig. 1-11b, leading to the activation of the other distributed associations that lead to recognition. Furthermore, a face that is not consciously recognized can occasionally still elicit a physiological emotional response, presumably because the damage is located downstream to “f” and interrupts its connections to area T but not to limbic areas such as those represented by area L in Fig. 1-11b.

As described in Chapter 7, patients with prosopagnosia may have no difficulty in the generic recognition and naming of object classes (for example, they may recognize and name a car as a car or a face as a face) but may not be able to determine the make of a particular car, recognize a favorite pet, or identify a personal object from among other examples of the same category. This additional feature of prosopagnosia, a generalized impairment in recognizing unique members of a larger object group, raises the possibility that area “f” may also participate in the identification of objects other than faces or, alternatively, that the lesion sites may involve adjacent regions that encode additional object categories.

If prosopagnosia represents an inability to recognize unique exemplars of visually encoded object categories, "associative visual object agnosia" represents an impairment that extends to the level of categorical recognition. The patient with this syndrome can neither name a familiar object nor describe its nature and use. While a prosopagnosic patient can tell that a face is a face and a pencil is a pencil, a patient with object agnosia is unable to perform this task but retains the ability to determine if two objects are perceptually identical or not. Since the encoding of proprietary features may require more information than the encoding of generic features, prosopagnosia may represent the outcome of a smaller or more downstream lesion than that associated with object agnosia. Although clinical reports show that the lesions in object agnosia appear very similar to those in prosopagnosia, minor differences in lesion size or location could easily escape detection in case studies.
A second potential distinction between prosopagnosia and object agnosia may be based on the memory systems that support the recognition of generic versus proprietary information. The generic recognition of familiar objects is part of semantic knowledge, whereas the recognition of familiar faces and objects is more closely related to personal experience. Although prosopagnosia and object agnosia are usually seen after bilateral lesions, these syndromes do occasionally arise after unilateral lesions, in which case prosopagnosia tends to result from lesions in the right hemisphere and object agnosia from lesions in the left. This dissociation is interesting since the right hemisphere appears to have a greater role in the activation of autobiographical memories.

Associative agnosias have also been identified in the auditory and tactile modalities. Patients with a condition known as "auditory (object) agnosia" fail to associate the ringing of a telephone or the siren of an ambulance with the corresponding object although more elementary auditory perceptual abilities remain relatively preserved. This syndrome may reflect a disconnection of unimodal auditory areas specialized for encoding the auditory properties of familiar objects from transmodal nodes (such as T in Fig. 11b) that coordinate their multimodal recognition. The lesions that give rise to auditory agnosia typically involve auditory association cortex, usually in the right hemisphere, but the more detailed anatomical correlates of this relatively rare syndrome remain to be elucidated. The auditory analog of prosopagnosia is known as "phonagnosia." It reflects an inability to recognize the identity of familiar voices, potentially in the absence of other major auditory deficits. This rare syndrome may reflect a disconnection of area "v" in unimodal auditory association cortex from transmodal node T.

"Tactile agnosia," the inability to recognize objects by palpation, in the absence of any other somatosensory or aphasic deficits, is a much less frequently encountered condition. It can theoretically be differentiated from astereognosis by showing that patients with tactile agnosia (as opposed to those with astereognosis) can draw the objects they palpate, even when the palpation fails to elicit recognition. Stereognosis is an apperceptive deficit whereas tactile agnosia is an associative deficit of somatosensory object recognition. The responsible lesion, usually located in the insula or posterior parietal cortex, would be expected to interrupt the projections from downstream somatosensory association cortex to a transmodal node equivalent to T in Figure 11b.

The modality-specific agnosias highlight the importance of sensory–fugal pathways to the process of recognition and offer a neuroanatomical basis for distinguishing perception from recognition. Associative agnosias arise when unimodal areas specialized for the perceptual encoding of objects are damaged or when they fail to access pivotal transmodal gateways that enable multimodal integration. More elementary perceptual processes, subserved by more upstream unimodal areas, remain relatively intact in patients with associative agnosias. The relevant transmodal areas, such as the heteromodal cortices of the middle temporal gyrus, are not centers for the convergent storage of knowledge related to faces and objects, but optimal conduits for accessing the relevant distributed associations that collectively lead to accurate recognition. Other cognitive domains, such as language, spatial
awareness, explicit memory, and emotion, display analogous principles of organization but revolve around transmodal gateways located in different parts of the brain.

VIII. WERNICKE’S AREA AS A TEMPOROPARIETAL TRANSMODAL GATEWAY FOR LANGUAGE

Language allows the elaboration and communication of experiences and thoughts through the mediation of arbitrary symbols known as words. Broca’s and Wernicke’s areas constitute the two epicenters of a distributed language network. Broca’s area, located in BAU and adjacent heteromodal prefrontal cortices, occupies the syntactic/articulatory pole of the language network whereas Wernicke’s area occupies its lexical/semantic pole. Wernicke’s area has no universally accepted boundary. It is usually defined as “the region which causes Wernicke’s aphasia when damaged.” Some investigators would confine Wernicke’s area to auditory association cortex in the posterior third of the superior temporal gyrus (BA22). As noted above, the multimodal nature of Wernicke’s aphasia argues against this possibility. There are numerous reasons for concluding that Wernicke’s area includes not only the posterior third of BA22 but also the immediately adjacent parts of heteromodal cortex in BA39-40 and perhaps also parts of the middle temporal gyrus.

As described in Chapter 5, damage to almost any component of the language network can give rise to naming and word-finding deficits. However, Wernicke’s area is one of the very few lesion sites that elicits two-way naming deficits where the patient can neither retrieve the name for an object nor point to the appropriate object when the name is supplied by the examiner. Such observations may give the impression that Wernicke’s area is a storage site for word representations. However, clinical research shows that Wernicke’s area is as unlikely to be the repository of a mental lexicon as the middle temporal cortex is to be the repository of the knowledge of faces and objects. Instead, the role of Wernicke’s area might be conceptualized as that of a transmodal gateway which coordinates reciprocal interactions between the sensory representations of word forms and the arbitrary (second-order or symbolic) associations that give them meaning. According to this formulation, damage to Wernicke’s area does not necessarily obliterate word representations but makes it impossible to understand (decode) words in any modality of input or to link (encode) percepts and concepts into corresponding word forms. This is why Wernicke’s aphasia entails not only a deficit in comprehending language in all modalities of input but also a deficit in expressing thoughts in meaning-appropriate words.

Experiments based on functional imaging show that naming (lexical access) is a highly distributed function mediated by “prelexical” areas adjacent to those that support the perceptual encoding of the object or feature to be named. Lexical labeling is thus anchored to the perceptual mapping of the corresponding experience. These category-specific prelexical areas are located outside of Werni-
Wernicke's area. They are necessary but not sufficient for naming since damage to Wernicke's area causes severe naming deficits even when these prelexical areas are intact. The prelexical areas provide implicit lexical representations that need to be made explicit through the mediation of Wernicke's area and other components of the language network.

Although its spontaneous development only in humans endows language with a sense of uniqueness, its neurological foundations are quite analogous to those of other cognitive domains. Word forms, for example, are likely to be encoded within unimodal auditory and visual areas according to the principles that also guide the encoding of faces and objects. Lexical labeling, furthermore, can be conceptualized as a component of object recognition in the sense that a name is as much an attribute of an object as its color, location, or past associations. Word comprehension is also an object recognition task where the perceptual features first lead to the categorical identification of a word as a word, then to a subordinate-level identification of the individual word, and finally to the establishment of the multiple arbitrary associations that define its meaning through the mediation of transmodal nodes in Wernicke's area and adjacent perisylvian language areas. Word recognition and retrieval thus proceed according to principles that also pide object recognition, except that the critical transmodal gateways are located in perisylvian cortex rather than in midtemporal cortex.

The analogy between the neural organization of language and object recognition is further emphasized by the existence of two types of verbal associativeagnosias known as pure alexia and pure word deafness. In contrast to prosopagnosia and object agnosia, which emerge when visual information cannot access area T in Fig. 1-11b, pure alexia (word blindness) emerges when areas that encode visual word forms ("wr" in Fig. 1-11b) are disconnected from visual input or when they cannot communicate with Wernicke's area and related components of the left hemisphere language network (W in Fig. 1-11b). This usually happens when a lesion of area V1 in the left hemisphere (which, by itself, yields a right homonymous hemianopia) occurs in conjunction with a lesion of the splenium, a region of the corpus callosum which conveys visual information from one hemisphere to the other. The splenial lesion interferes with the transcallosal transfer of visual information from the intact visual areas of the right hemisphere to the visual word-form areas ("wr" in Fig. 1-11b) and transmodal language areas (area W) of the left hemisphere. These areas thus become completely disconnected from ipsilateral as well as contralateral visual input. The patient with pure alexia is not blind since objects and faces presented to the left hemifield can be recognized with no difficulty as they activate area T. There is no aphasia either since Wernicke's area and other core language areas are intact and can receive word-form information in the auditory modality. However, upon being asked to read, the patient appears illiterate since language-related transmodal nodes such as area W in Fig. 1-11b can no longer receive word-form information in the visual modality.

A similar analysis applies to pure word deafness which arises when area "wr" in unimodal auditory cortex is cut off from auditory input or when it cannot communicate with relevant transmodal nodes in area W (Fig. 1-11b). Pure word deafness can be seen after bilateral lesions or after unilateral temporal lobe lesions in the language-
dominant hemisphere (usually left) which disconnect ipsilateral as well as transcallosal auditory inputs from components of the language network. The patient with pure word deafness is not deaf and can readily interpret most environmental sounds since parts of primary auditory cortex and auditory association areas are usually intact. Such patients are not aphasic and show no impairment of reading, writing, or speaking since the language areas are mostly intact. When exposed to speech, however, the patient reacts to it as an alien tongue that cannot be deciphered since the auditory information cannot reach language-related transmodal nodes such as those in Wernicke’s area. The term ”pure” word deafness can be used in a strong sense, meaning that the only auditory deficit is for understanding spoken language, or in a weak sense, meaning that the only language deficit is for auditory comprehension.417 This second definition encompasses a larger number of patients.

The somatosensory equivalent of pure alexia and pure word deafness can be designated “pure agraphesthesia” (or somesthetic alexia) (Fig. 1-11c). One patient with this syndrome could not identify letters presented in the tactile modality to either hand despite a preservation of other somatosensory functions including stereognosis (naming the object by palpation) and the ability to determine if two letters presented in the somatosensory modality were same or different? The responsible lesion was located in the posterior parietal cortex of the left hemisphere and appears to have disconnected somatosensory association cortex from Wernicke’s area and other components of the language network.

Domains as different as object recognition and language can thus share common principles of organization. In each case, specialized transmodal nodes act as critical gateways for looking up and binding distributed multimodal information upon being queried by relevant unimodal inputs. Each of these processes entails multimodal integration, but much of this integration is based on knowing where to look up the information rather than on the presence of a privileged site where an ultimate convergent synthesis becomes stored.

IX. FUNCTIONS AND SYNDROMES OF POSTERIOR PARIETAL HETEROMODAL CORTEX

The posterior parietal heteromodal cortices (BA7, 39, 40) of the human brain provide sites for multimodal interactions related to praxis, language, visuomotor integration, generation of motor plans, and spatial attention.9,29,90,390,505 Clinical observations have led to the suggestion that the inferior parietal lobule of the language-dominant (usually left) hemisphere may contain spatiotemporal representations of learned skilled movements ("praxicons") which are then translated into the appropriate motor output through the mediation of premotor cortex.215 Damage to this part of the brain gives rise to a type of ideomotor apraxia where the patient is unable either to pantomime the use of an object specified by the examiner or to infer the nature of the object when the examiner pantomimes its use.215

Lesions which spare Wernicke’s area but which involve the adjacent heteromodal fields of the angular gyrus in the language-dominant hemisphere give rise to complex combinations of anomia, alexia, acalculia, dysgraphia, finger identifi-
cation disturbances, and left-right naming difficulties in the absence of additional language deficits. This collection of impairments is collectively known as the "left angular gyrus (or left parietal) syndrome." When only the last four of these deficits emerge in isolation, the term "Gerstmann syndrome" is used to identify the clinical picture. Both syndromes indicate a breakdown in complex multimodal interactions related to verbal processing. In contrast to "pure alexia," which is a modality-specific disconnection syndrome, the alexia which arises in conjunction with angular gyrus damage is caused by a breakdown of multimodal associations related to language and is known as a "central alexia."

Damage to the heteromodal cortices of the inferior parietal lobule in the right hemisphere leads to deficits in tasks of spatial attention, visuospatial integration, and drawing (construction). This is known as the "right parietal lobe syndrome." Patients fail tasks of mental rotation and cannot identify objects viewed from uncommon perspectives. The posterior parietal cortex also plays a pivotal role in spatial attention and causes contralesional neglect when damaged (Chapter 3). Functional imaging experiments show that the part of posterior parietal cortex that is critical for spatial attention (area P in Fig. 1-11b) is centered around the intraparietal cortex. Its proposed role in the attentional network is to integrate distributed spatial information (originating from "s" in multiple modalities as shown in Fig. 1-11b) in all relevant sensory modalities. When this area is damaged, the modality-specific channels of information related to the extrapersonal space may remain intact but cannot be bound into the type of coherent and interactive representation that is necessary for the adaptive deployment of spatial attention. As in the relationship of transmodal nodes to other cognitive domains, posterior parietal cortex is not a dedicated center which contains a spatial map but a critical gateway for accessing and integrating information related to the attention-related representation and exploration of the extrapersonal space. This aspect of posterior parietal function is reviewed in greater detail in Chapter 3.

Other components of the right parietal syndrome include "anosognosia" (minimization or denial of illness), "dressing apraxia" (inability to align the body axis with the axis of the garment), "construction apraxia" (drawing difficulty), confusional states, route finding deficits, and disturbances in navigating the body with respect to solid objects such as beds and chairs. As noted above, Bálint’s syndrome represents a breakdown of all visuospatial integration and usually arises after bilateral dorsal lesions in posterior parietal cortex. Stich lesions interrupt the dorsal visuofugal pathway shown in Fig. 1-10, giving rise to optic apraxia, optic ataxia and simultanagnosia as described in Chapter 7.

In addition to these deficits, lesions in parietotemporal heteromodal cortices also yield perturbations of mood and motivation. The neglect which results from parietal lesions, for example, includes an aspect of motivational indifference for the contralateral hemispace, and anosognosia reflects a global impairment in the emotional response to disability. In other patients, lesions in the posterior parietotemporal regions of the right hemisphere lead to psychotic and affective disturbances. Furthermore, patients with Wernicke’s aphasia can show severe mood alterations ranging from anger to paranoia and indifference. These clinical manifestations
might reflect a disruption of the complex sensory–limbic interactions which take place within heterornodal cortices.

In the brain of the monkey, anatomical and physiological evidence suggests the presence of an additional heterornodal field in the ventromedial parts of the temporal lobe, corresponding to the medial part of BA20. An analogous area may also be present in the human brain, perhaps including parts of BA36, 20 and 37, along the banks of the collateral sulcus (Fig. 1–7). Cerebrovascular accidents that involve this heterornodal association area and adjacent paralimbic regions give rise to agitated confusional states (Chapter 3).

X. PREFRONTAL HETEROMODAL CORTEX AND FRONTAL LOBE SYNDROMES: ATTENTION, EXECUTIVE FUNCTIONS, AND COMPORTMENT

The frontal lobes undergo a striking expansion in the course of phylogenetic evolution. In the human brain, they occupy approximately one-third of the cerebral hemispheres. The frontal lobes can be divided into three functional sectors (Fig. 1–7).

1. A "motor–premotor" sector includes BA4 and 6, the supplementary motor area (medial aspect of BA6), the frontal eye fields (BA6 in the human, BAS in the monkey), the supplementary-eye fields (BA6), and parts of Broca's area (BA44). Depending on the exact location of the lesion, damage to this component of the frontal lobe results in weakness, alteration of muscle tone, release of grasp reflexes, incontinence, akinesia, mutism, aprosody, apraxia, and some motor components of unilateral neglect and Broca's aphasia.

2. A "paralimbic" sector is located in the ventral and medial part of the frontal lobe and contains the cortices of the anterior cingulate complex (BA23, 32), the parolfactorv gyrus (gyrus rectus, BA25), and the posterior orbitofrontal regions (BA11–B).

3. An extensive "heterornodal" sector contains BA9-10, anterior BA11–12, and BA45-47. In the monkey, this region receives neural inputs from unimodal areas in all the major sensory modalities, from all the other heterornodal regions of the brain, and from many paralimbic areas23,24,78,343,369,398. As in the case of parietotemporal heterornodal cortices, some neurons respond to a single preferred modality but are intermixed with those which respond to another; others are truly multimodal and respond to several kinds of sensory input.34,46,237

The terms "prefrontal cortex" and "frontal lobe syndrome" generally refer only to the paralimbic and heterornodal sectors of the frontal lobe. Prefrontal cortex can be conceptualized as a site for the confluence of two functional axes: one for working memory–executive function–attention (with transmodal epicenters in prefrontal and posterior parietal cortex), and another for comportment (with transmodal epicenters in prefrontal cortex and orbitofrontal paralimbic cortex). The head of the
caudate nucleus and the mediodorsal nucleus of the thalamus are critical subcortical components for both of these functional axes.

The Clinical Picture of Frontal Lobe Syndromes

Few subjects have engendered as much enigma, paradox and fascination as the behavioral affiliations of prefrontal cortex. While some authors have attributed the highest integrative faculties of the human mind to this part of the brain, others have emphasized the surprising paucity of cognitive deficits in patients with substantial frontal lobe damage. The case of Phineas Gage (also known as the Boston Crowbar Case), reported more than a century ago by Harlow, remains paradigmatic for research on the frontal lobes. Gage was a reliable and upright foreman who became profane, irascible, and irresponsible following an accident during which a tamping rod was blown through his frontal lobes. The many reports that have been published since Harlow’s paper have provided additional support for the conclusions derived from the case of Phineas Gage—namely that frontal lobe damage can lead to dramatic alterations of strategic thinking, personality, emotional integration, and comportment (conduct) while leaving language, memory, and sensorimotor functions relatively intact. In an almost equally remarkable account, for example, Penfield recorded the effects of a right sided prefrontal lobectomy he had performed on his own sister. Following the acute postoperative period, Penfield noted that his sister’s judgment, insight, social graces, and cognitive abilities were quite preserved. When he visited her home as a dinner guest, however, he noticed a diminished capacity for the planned preparation and administration of the meal and a slowing of thinking.

The spectrum of behavioral changes observed in patients with prefrontal lesions is very broad. Some of these patients become puerile, profane, slovenly, facetious, grandiose, and irascible; others lose spontaneity, curiosity, and initiative and develop an apathetic blunting of feeling, drive, mentation, and behavior; others show an erosion of foresight, judgment, and insight, and lose the ability to delay gratification and often the capacity for remorse; still others show an impairment of abstract reasoning, creativity, problem solving, and mental flexibility, and become excessively concrete or stimulus-bound. The orderly planning and sequencing of complex behaviors, strategic decision making based on the assessment of differential risks, the ability to heed several events simultaneously and flexibly shift the focus of concentration from one to the other, the capacity for grasping the context and gist of a complex situation, the resistance to distraction and interference, the ability to follow multistep instructions, the inhibition of immediate but inappropriate response tendencies, and the ability to sustain behavioral output without Perseveration may each become markedly disrupted.

Although the designation "frontal syndrome" is used as an umbrella term for the entire panoply of the behavioral changes noted above, each patient may have a different distribution of salient deficits. The specific pattern of the behavioral deficits in an individual patient is probably determined by the site, size, laterality, nature, and temporal course of the lesion and perhaps even by the past personality...
and age of the patient. In general, two types of frontal syndromes are seen. In one type, the loss of creativity, initiative and curiosity predominates and the patient shows apathy and emotional blunting. This can be designated as the "syndrome of frontal abulia." In a second type, the patient displays a dramatic impulsivity, together with a loss of judgment, insight, and foresight. This can be designated as the "syndrome of frontal disinhibition." In this second type of frontal syndrome, the dissociation between relatively intact "cognitive" functions and dramatically impaired comportment and emotional reactions can be quite striking?

Following the surgical removal of an olfactory groove meningioma, for example, a 63-year-old administrator started to initiate intimate relations with total strangers, one of whom had just been released from jail. She agreed that her behavior was unwise and admitted that she "lacked brakes." However, neither the theft of personal belongings nor a bout of sexually transmitted disease could curb her poor judgment. In the office, her performance in so-called "frontal" tasks such as the Luria motor sequence, the Stroop Interference Task, the Wisconsin Card Sorting Test, and the Tower of London were all in the normal range. Her postsurgical scans indicated that the major area of damage involved the orbitofrontal cortex and that the dorsolateral prefrontal areas were relatively intact (Fig. 1–9b). A somewhat different clinical picture emerged in a 47-year-old attorney following the removal of a left prefrontal meningioma. Neuropsychological tests revealed some impairments of memory retrieval and reasoning abilities. The most dramatic changes, however, took the form of an amotivational state, emotional blunting, and a slowing of thinking. These impairments interfered with his professional activities and led to early retirement. The postsurgical scans showed a large left prefrontal lesion involving mostly the dorsolateral prefrontal cortex and sparing much of the orbitofrontal region (Fig. 1–9c). The lesion was predominantly unilateral but a shunt tube had been inserted through the dorsolateral prefrontal cortex of the contralateral hemisphere into the lateral ventricle and caused additional damage in the right hemisphere.

In keeping with these two examples, clinical experience suggests that lesions in orbitofrontal and medial frontal areas (that is, parts of the frontal lobe that contain paralimbic cortex) are more likely to trigger the disinhibition syndrome whereas lesions in the dorsolateral frontal lobe (the parts containing heterornodal cortex) are more likely to cause the abulic syndrome.171,355 In chimpanzees and monkeys, dorsolateral prefrontal lesions elicit a predominantly abulic state whereas orbitofrontal lesions lead to emotional impulsivity.64,241 The more dramatic manifestations of frontal lobe damage are seen after bilateral involvement. The deficits associated with unilateral lesions can be quite subtle and often elusive. The abulia of frontal lobe disease may be misinterpreted as a sign of depression whereas the disinhibition may occasionally lead to the mistaken diagnosis of mania.

Neuropsychology of Frontal Lobe Disease

As also noted in Chapter 3, prefrontal cortex plays a particularly critical role in attentional behaviors. The P300 response evoked by novel or deviant stimuli, for
example, is critically dependent on the integrity of prefrontal cortex; an N2–P3 response over prefrontal cortex appears to determine the attentional resources that will be allocated to novel events; and the region of the frontal eye fields belongs to a distributed network for exploring the extrapersonal space and seeking motivationally relevant targets. The abulic state resulting from frontal lobe lesions could thus represent the loss of neural mechanisms involved in novelty-seeking behaviors.

Frontal lobe lesions often impair "working memory," an attentional faculty which enables the mental manipulation and on-line holding of information for durations that fall between those of iconic memory and long-term "off-line" storage (Chapter 3). Such lesions also interfere with performance in tasks that require the inhibition of impulsive responses. In keeping with these clinical correlations, single unit recordings in monkeys show that many prefrontal neurons after their activity during the response inhibition phase of behavioral paradigms and that they emit responses related to the on-line holding of information during working memory tasks. Furthermore, prefrontal neurons can also support the on-line convergence of information. In one experiment, for example, monkeys were given a task that required them to retain first the identity of an object and then its location. After participating in the on-line retention of object information in the initial working memory interval, many prefrontal neurons switched modes and maintained the on-line representation of spatial information during the second interval.

As shown in Chapter 3, each part of unimodal association cortex seems to participate in the maintenance of working memory in its own area of specialization. Lateral prefrontal cortex, however, plays a critical supramodal role in orchestrating working memory in all domains of processing. As a transmodal zone at the fifth and sixth synaptic levels in Figure 1-11b, prefrontal cortex (area Pf in Figure 1-11b) is interconnected with numerous transmodal and downstream unimodal areas and can exert a top-down influence upon the working memory activity of neurons in all of these areas. Prefrontal cortex may thus play the role of a critical transmodal gateway for coordinating working memory in a manner analogous to the role of temporal transmodal cortex in object recognition, and of Wernicke’s area in language.

Working memory is usually divided into two groups of processes: the attentional on-line maintenance of information and its volitional manipulation. The latter aspect is attributed to the function of a "central executive" agency. In human subjects, tasks emphasizing the executive aspects of working memory elicit the activation of prefrontal dorsolateral cortex, whereas tasks emphasizing the on-line maintenance of information elicit the activation of both prefrontal cortex and posterior parietal cortex. These two interconnected heteromodal areas may thus function as the epicenters of a distributed network for the on-line holding aspect of working memory. In fact, working memory tasks enhance the electrophysiological coherence between the prefrontal and posterior parietal regions of the human brain. Furthermore, clinical experience indicates that working memory deficits can arise after lesions in prefrontal as well as in posterior parietal cortex. In the
latter instance, however, the clinical picture tends to be overshadowed by the other components of the parietal lobe syndrome. In contrast, working memory deficits may dominate the clinical presentation of many patients with prefrontal lesions.

Neuropsychological test results in patients with frontal lobe disease are consistent with the critical role of this area in working memory, executive function, and the inhibition of inappropriate impulses. Thus, concentration (as assessed by digit span), the ability to resist interference, hypothesis testing (as assessed by the Wisconsin Card Sorting Test), the ability to maintain a coherent stream of thought, the ability to scan mental content (as assessed by verbal fluency and memory retrieval tasks), the ability to resist immediate but inappropriate response tendencies (as assessed by the go–no-go task), and the ability to internally program, select and sequence responses are usually impaired after prefrontal lesions. Cognitive flexibility, especially when behavior needs to be modified to fit novel contexts, is also vulnerable to frontal lobe damage? During reasoning tasks, patients with frontal lobe disease tend to reach closure prematurely, jump to conclusions on the basis of incomplete information, perseverate, and find it difficult to explore alternative solutions to the same problem. Many of these cognitive deficits are attributed to a loss of “executive” functions because they reflect a failure to manipulate existing information rather than a failure to perceive, recognize, name, or remember. In keeping with these correlations, prefrontal activation is seen during the performance of verbal fluency and go–no-go tasks and during the initial exposure to a reasoning test but not during its second presentation.76,144,304,412,438,439

Frontal lobe disease leads to the emergence of stimulus-bound and concrete behaviors. Some patients display a remarkable tendency to imitate the examiner's gestures and behaviors even when no instruction has been given to do so; others feel compelled to use objects that they encounter even when the context is inappropriate.293,294 These tendencies, descriptively labeled “imitation” and “utilization” behaviors, reflect slavish and reflex responses to the environment. Many cognitive functions coordinated by prefrontal cortex, including working memory, require rapid and reversible shifts of the attentional focus between external sensory events and internal mental representations. In a very general sense, prefrontal cortex can be said to orient the attentional focus toward internal mental processes whereas posterior parietal cortex orients it toward extrapersonal events.;”’When the brain is intact, these two tendencies balance each other and provide a setting where flexible transitions from one realm to the other can unfold without fixed bias. Prefrontal lesions disrupt this balance by tilting the emphasis away from internal mental processes toward stimulus-bound utilization behaviors, whereas posterior parietal lesions may tilt the emphasis away from external sensory events and promote sensory neglect.

The connectivity pattern in Figure 1–12 indicates that the frontal lobe provides a site where association cortices and the limbic system interact. The limbic connections may allow the frontal lobes, especially their paralimbic components, to link the sensorial aspects of external events with the visceral and emotional states they elicit. The establishment of such linkages would allow the original visceral state to
be reactivated upon the recurrence or even anticipation of a similar event. The anticipatory induction of such a visceral state could then generate a positive or negative valence that biases the choice of subsequent behaviors. In neurologically intact individuals, such visceral states can play important roles in the covert guidance of decision making, especially when the decisions require an instantaneous assessment of relative risk.

Damage to the orbitofrontal or medial components of the frontal lobes can interfere with the interactions between behavior and visceral state and may provide a physiological substrate for poor judgment and foresight. As opposed to normal subjects who emitted anticipatory changes of skin conductance when pondering risky choices, for example, patients with ventral and medial prefrontal lesions failed to generate such responses, appeared unresponsive to the consequences of their actions, and failed to acquire a successful strategy for making advantageous decisions. This disengagement of behavior from emotional guidance may underlie the failure of these patients to learn from experience and their inability to inhibit behaviors which consistently have disastrous consequences. Prefrontal disease acquired early in life may thus interfere with the development of social restraint, leading to a syndrome of "compartmental" learning disabilities.

Frontal lobe damage may also lead to a "task difficulty effect," whereby performance in virtually all areas begins to decline rapidly when the effort required of the patient exceeds a certain level. This indicates a motivational deficit rather than impairment of additional cognitive skills. Explicit memory is usually preserved except when there is major damage to the paralimbic components of the frontal lobes or when the lesions extend into the basal forebrain and hypothalamus. Secondary memory disturbances emerge quite frequently as a consequence of the inattention, poor motivation, perseveration, and especially inefficient retrieval
(Chapter 4). Performance in most tests of perception, construction, language, and directed spatial attention can be quite intact even after massive damage to the anterior and ventromedial parts of prefrontal cortex.

Some patients with sizable frontal lobe lesions may have routine neurological and neuropsychological examinations that are quite unremarkable. This paucity of "objectis-e"findings is sometimes responsible for overlooking the possibility of brain damage in some of these patients. Patients with known frontal lobe lesions and a history of major behavioral difficulties may behave impeccably in the office. This is in keeping with the notion that these patients are most impaired under circumstances with minimal external control, when self-guidance becomes critical. The office setting may introduce sufficient external structure to suppress some of these behavioral tendencies. The same patient who gives perfect answers to questions about hypothetical social or moral dilemmas in the office may also act with a total lack of judgment when faced with the real situation. The clinical adage that judgment and complex comportment cannot be tested in the office is particularly pertinent to the evaluation of patients with frontal lobe damage. It is also important to realize that the great majority of patients with frontal lobe disease do not have "frontal release signs" such as grasping, rooting, or sticking. These primitive reflexes emerge only if the lesion extends into the motor–premotor sectors of the frontal lobe.

Metaphysiology of Prefrontal Cortex

Frontal cortex is so heterogeneous with respect to structure, connectivity, and physiology that no single descriptive formulation can account for its multiple behavioral affiliations. There are, however, at least six key themes that help to provide a metaphysiological basis for the behavioral specializations of prefrontal cortex:

1. Even massive damage to prefrontal cortex leaves all sensation, perception, movement, and homeostatic functions intact. The heteromodal sector of the frontal lobe is probably the only nonlimbic part of the cerebral cortex entirely devoted to complex mental integration.

2. Prefrontal cortex has a high density of interconnections with almost all other heteromodal, unimodal, paralimbic, and limbic sectors of the cerebral cortex. Through these widespread connections, prefrontal cortex would be in a position to activate a given network, suppress another, and orchestrate network interactions.

3. As noted above, some prefrontal neurons display preferential activity during the response inhibition phase of go–no-go and delayed alteration tasks. Prefrontal cortex may thus play an important role in inhibiting impulses that are not appropriate for the context and in disengaging stimuli from their customary responses so that alternative scenarios can be played out internally in a way that promotes flexibility, foresight, and planning.

4. Many of the visually responsive neurons in prefrontal cortex have far less specificity for color, size, orientation, or movement than for the behavioral relevance of the stimulus. A neuron which responds briskly to a stimulus when it is associated with reward, for example, may drastically alter its response when the same stimulus becomes associated with an aversive or neutral outcome. These
response contingencies suggest that the neurons of prefrontal cortex can help to establish a subjective reality which is sensitive to significance rather than surface properties.

5. Its relationship to working memory suggests that prefrontal cortex can transform information access from a sequential process, where only one item can be heeded at any given time, to a conjunctive pattern where multiple items become concurrently accessible. Through the mediation of working memory, representations of multiple external events and internal phenomena can unfold concurrently and interactively so that the focus of attention can move from one to the other. The resultant increase in the number of factors and variables that can be apprehended simultaneously would seem essential for dissociating appearance from significance, grasping changes of context, shifting from one mental set to another, assuming multiple perspectives, and comparing potential outcomes of contemplated actions. Disruptions in these aspects of mental function could lead to impairments of foresight, strategic thinking, and risk management.

6. The orbitofrontal cortex and other paralimbic components of the frontal lobe provide transmodal nodes for binding thoughts, memories, and experiences with corresponding visceral and emotional states. Damage to this component interferes with the ability of emotion and visceral state to guide behavior, especially in complex and ambiguous situations.

Despite considerable advances in this area of research, it is difficult to dismiss the sense of uniqueness associated with frontal lobe function. It is quite remarkable, for example, that sizable frontal lobe lesions can remain clinically silent for many years. Even after massive bifrontal lesions in monkeys, chimpanzees, and humans, change can often be detected only in comparison with the previous personality of that individual rather than in reference to any set of absolute behavioral standards. In fact, many of the alterations associated with prefrontal lesions appear to overlap with the range of normal human behavior: There is a vast number of improvident, imprudent, irresponsible, inappropriate, and facetious individuals who have no evidence of demonstrable brain damage. In contrast, the lack of visible damage to the pertinent cerebral area is a rare occurrence in individuals with aphasia, amnesia, apraxia, or unilateral neglect. Perhaps this means that the prefrontal cortex underlies functions that are much less “hard wired” and that it acts predominantly as an orchestrator for integrating other cortical areas and for calling up behavior programs that are appropriate for context. Damage to this part of the brain would thus result in behavioral deficits that are context-dependent rather than absolute.

Frontal Lobe Versus Frontal Network Syndromes

The major cortical connections of the head of the caudate nucleus and the mediodorsal nucleus of the thalamus come from prefrontal cortex. These two structures can therefore be considered as subcortical components of the prefrontal network. In fact, clinical deficits identical to the frontal lobe syndromes can also be seen in patients with lesions in the head of the caudate nucleus or in the mediodorsal nucleus of the thalamus. This may explain why so many extrapyramidal
diseases tend to be associated with behavioral and cognitive changes that display at least some characteristic of the frontal syndrome.

Frontal syndromes can also emerge as common manifestations of multifocal white matter diseases or even metabolic encephalopathy. Assuming that at least one physiological function of the frontal lobe is to integrate networks for combined action, multifocal partial lesions (none of which is individually severe enough to disrupt specific cognitive domains such as language or memory) could collectively undermine internetwork coordination and therefore lead to the manifestations of a frontal lobe syndrome. In fact, clinical experience suggests that subcortical lesions (as in cerebrovascular or demyelinating diseases) and toxic–metabolic encephalopathies are more frequent causes of the frontal syndrome than lesions which involve prefrontal cortex directly. In order to avoid the embarrassment of diagnosing frontal lobe disease in patients with no frontal pathology, it is preferable to use the term "frontal network syndrome" and to emphasize that the responsible lesion can be anywhere within the cortical or subcortical components of a distributed prefrontal network.

XI. PARALIMBIC (MESOCORTICAL) AREAS

A belt of paralimbic areas encircles the basal and medial aspects of the cerebral hemispheres (Figs. 1–5 and 1–7). The olfactocentric paralimbic formations include the temporal pole, the insula, and posterior orbitofrontal cortex. The hippocampo-centric paralimbic formations include the parahippocampal "rhinal" cortices, the retrosplenial area, the cingulate gyrus, and the subcallosal (parolfactory) regions. Paralimbic areas provide zones of architectonic transitions from allocortical limbic areas to isocortical association cortex (Figs. 1–3Band 1-4). The peri-allocortical sectors of individual paralimbic areas are most heavily interconnected with the peri-allocortical sectors of other paralimbic areas and with core limbic areas, whereas the peri-isocortical sectors are more heavily interconnected with the peri-isocortical sectors of the other paralimbic areas and with sensory association cortices. Reciprocal hypothalamic projections of medium density are found in all paralimbic areas and tend to be directed mostly to their peri-allucortical sectors. In keeping with this pattern of connectit-ity, the peri-allocortical sectors of paralimbic areas have more "limbic" behavioral specializations whereas the peri-isocortical sectors have specializations more similar to those of adjacent unimodal and heterornodal association cortices.

Paralimbic areas play an important role in linking cognition with visceral states and emotion. Even to a greater extent than heteromodal areas, paralimbic cortices are in a position to emphasize the behavioral relevance of a stimulus over its physical aspects. Paralimbic cortices make critical contributions to at least four types of behavior: (1) memory and learning, (2) the channeling of emotion and affiliative behaviors, (3) the linkage of visceral state, immune responses, and endocrine balance to mental state, (4) and the perception of pain, smell, and taste. The relationship of paralimbic areas to memory and emotion is discussed in subsequent sections on the hippocampus and amygdala (section XIII and XIV). The relationship to au-
tonomic function, immune system, endocrine control, pain, smell and taste is reviewed in this section.

The Insula

The human insula contains up to seven sulci and could be considered as a separate lobe of the brain. The region where the insula becomes joined to the anterior part of the temporal lobe contains the piriform cortex and the agrandar peri-docortical sector of the insula (Fig. 1-4). Cytoarchitectonic differentiation emanates radially from this agranular peri-allo-cortical sector and establishes a gradual transition into the peri-isocortical sectors. The insula abuts upon the frontal and parietal opercula dorsally and the supratemporal plane ventrally. The peri-insular part of the frontoparietal operculum contains the gustatory cortex anteriorly and area SII posteriorly. The peri-insular parts of the temporal lobe contain piriform olfactory cortex anteriorly and the auditory and vestibular areas posteriorly. In the monkey, the more peri-allo-cortical anterior and ventral parts of the insula tend to be associated with autonomic, olfactory, gustatory, and other "limbic" functions whereas the peri-isocortical posterior insula displays many characteristics of somatosensory association cortex dorsally, auditory cortex ventrally, and vestibular cortex posteriorly.

The limbic inputs into the insula come from primary olfactory cortex, the amygdala, and the nucleus basalis. The amygdaloid connections are reciprocal and directed predominantly to the peri-allo-cortical sectors of the insula. Through these pathways, the insula can relay somatosensory and other types of sensory information into the amygdala and can play an important role in mediating tactile learning and the reaction to pain. Insular lesions may thus contribute to the emergence of pain asymbolia and tactile learning impairments. Connectivity patterns suggest that the insula may provide a synaptic relay between Wernicke’s and Broca’s areas. These heterogeneous anatomical relationships and behavioral affiliations help to explain why so many functional imaging studies, based on so many different paradigms, include the insula in the list of cortical areas activated by the experimental task.

Orbitofrontal Cortex

The term “orbitofrontal cortex” is used to designate the entire ventral surface of the frontal lobes. The posterior part of orbitofrontal cortex abuts upon the parolfactory component of the cingulate complex, piriform olfactory cortex, the anterior olfactory nucleus, and the insula. This part of orbitofrontal cortex is architectonically more primitive and behaviorally more “limbic” in character. It has reciprocal hypothalamic projections of intermediate intensity. The limbic inputs into orbitofrontal cortex, directed predominantly to its posterior part, come from primary olfactory cortex, the nucleus basalis, the hippocampus, and the amygdala. The hippocampal projections are directed predominantly to the medial part of posterior
Anterior orbitofrontal cortex has the appearance of granular isocortex and blends into the dorsolateral heteromodal components of prefrontal cortex. Its behavioral affiliations are likely to have many similarities with those of dorsolateral heteromodal prefrontal cortex. Orbitofrontal cortex is likely to play a critical role in the integration of visceral and emotional states with cognition and comportment. The most florid comportmental deficits associated with frontal lobe lesions can probably be attributed to the involvement of the orbitofrontal and adjacent medial frontal areas.

The Temporal Pole

The temporopolar cortex caps the anterior tip of the temporal lobe. Its junction with the insula occurs through piriform cortex. This junctional area also contains the peri-alloccortical part of temporopolar cortex. Gradual cytoarchitectonic differentiation emanates radially from this sector and leads to the emergence of the peri-isocortical sectors dorsally and ventrally. In addition to inputs from primary olfactory cortex, limbic connections are also established with the nucleus basalis, hippocampus, and especially the amygdala. The principal behavioral affiliations of temporopolar cortex include olfactory-gustatory-visceral function medially, auditory function dorsally, visual function ventrally, and multimodal integration laterally. The medial, dorsal and ventral parts of temporopolar cortex mediate sensory-limbic interactions whereas its lateral part may fulfill the role of a transmodal epicenter for face recognition.

The Cingulate Complex and the Medial Frontal Area

The cingulate complex belongs to the hippocampocentric group of paralimbic areas. It includes the retrosplenial region, the cingulate gyrus, and the parolfactory area (Fig. 1-7). The peri-alloccortical parts of the parolfactory and cingulate cortices abut upon the hippocampal rudiment (induseum griseum), display a distinctively non-isocortical architecture, and have the most prominent "limbic" affiliations. The more dorsal peri-isocortical part of the cingulate gyrus has characteristics of sensory association cortex posteriorly where it borders medial parietal cortex and of premotor cortex anteriorly where it borders the supplementary motor area.

The cingulate complex can be conceptualized as a supracallosal extension of the hippocampal–parahippocampal region: The induseum griseum is a dorsal extension of the hippocampus, the retrosplenial cortex of the presubiculum, and the cingulate gyrus of the parahippocampal gyrus. The parolfactory component (BA25) of the cingulate complex is in direct continuity with the gyrus rectus of orbitofrontal cortex and has reciprocal hypothalamic connections similar in intensity to those of orbitofrontal cortex. The major limbic connections of the cingulate complex come from the hippocampus and the amygdala. The hippocampal projections reach mostly the posterior parts of the cingulate complex whereas the amygdaloid projections are directed mostly to its anterior parts. In keeping with the character-
istic pattern of paralimbic areas, the behavioral affiliations are heterogeneous and include attention, memory, learning, motivation, emotion, pain perception, and visceral function.76,118,234 The role of the cingulate cortex in attention is discussed in Chapter 3.

There is often a tendency to refer to "medial frontal cortex" as if it represented a distinct and uniform entity. This region represents a confluence of the cingulate complex (BA32 and BA25), orbitofrontal cortex (posterior parts of BA11-13), and dorsolateral heteromodal prefrontal cortex (BA9-10). Neurological lesions in this part of the brain can thus give rise to complex combinations of comportmental, cognitive, attentional, and emotional disturbances.288

The “Rhinal” Cortices and the Parahippocampal Region

The parahippocampal component of the paralimbic belt contains the "rhinal" cortices (entorhinal, prorhinal, and perirhinal (transentorhinal) areas), the presubiculum, and the parasubiculum. Each of these components has a distinctly nonisocortical architecture. The entorhinal area is in direct anatomical continuity with the hippocampal complex and can be conceptualized as the peri-allocortical sector of the parahippocampal paralimbic region. (Fig. 1–3b). In the monkey, the prorhinal and perirhinal components are separated from each other by a prominent rhinal sulcus. The prorhinal cortex and the rhinal sulcus are both quite inconspicuous in the human brain. Instead, the collateral sulcus emerges as the dominant sulcal landmark and contains the perirhinal cortex in its medial bank. The banks of the collateral sulcus contain the transitional and peri-isocortical sectors of the parahippocampal paralimbic region (Fig. 3a, b).

The entorhinal and perirhinal (transentorhinal) areas are very prominent in the human brain. The entorhinal cortex reaches the crest of the collateral sulcus and blends into the transentorhinal (perirhinal) cortex on the medial bank of the sulcus. The rhinal cortices receive limbic connections from olfactory cortex, the nucleus basalis, the amygdala, and especially the hippocampus. Additional inputs come from multiple unimodal and heteromodal areas. The entorhinal and transentorhinal cortices collectively provide the single most critical relay for transmitting information from heteromodal and unimodal association areas into the hippocampal formation.531 These projections travel within the perforant pathway. Reciprocal hippocampo-entorhinal projections originate from the subiculum and CA1 sector of the hippocampus. The two-way interconnections between the entorhinal–transentorhinal cortex and the hippocampus are so massive that the two structures could be conceptualized as forming a unified hippocampo-entorhinal complex. Although the rhinal cortices also have olfactory, emotional, and visceral functions, their major behavioral affiliations are in the areas of memory and learning (Section XIV).

Visceral, Immune, and Endocrine Regulation in Paralimbic and Limbic Areas

The intimate association of limbic and paralimbic areas with autonomic function has led to their collective characterization as the "visceral brain."306 This character-
ization is supported by numerous experiments which show that electrical stimulations in the amygdala, hippocampus, anterior insula, anterior cingulate gyrus, posterior orbitofrontal cortex, and the temporal pole yield marked and consistent autonomic responses. This is why autonomic discharges and visceral sensations are so common in patients with temporolimbic epilepsy (Chapter 8). The efferent limb of these autonomic responses is based on projections from limbic and paralimbic areas to the hypothalamus and brainstem whereas the afferent limb is based on multisynaptic visceral inputs from the brainstem and thalamus.

Insular stimulation is most likely to yield gastrointestinal responses whereas stimulation in the each of the other areas (including the insula) yields cardiovascular and respiratory changes. Some autonomic effects of paralimbic stimulation can be quite dramatic and include inhibition of gastric peristalsis, respiratory arrest, and blood pressure changes of as much as 100 mm of mercury. Even multifocal cardiac necrosis can be obtained when monkeys with no intrinsic cardiovascular disease receive electrical stimulation to orbitofrontal cortex. Furthermore, cingulate lesions and amygdaloid stimulation can lead to the development of gastric ulcers in rats.

Normal human emotions are associated with distinctive changes of heart rate, blood pressure, gastrointestinal motility, salivation, and sweating. These visceral correlates influence the way in which the emotion is expressed and experienced. On the maladaptive side, psychological stress increases blood pressure, promotes the formation of ulcers, leads to abnormalities of esophageal motility and can even induce potentially lethal cardiac arrhythmias in the absence of cardiovascular predisposing factors. Cognitive processes ranging from mental arithmetic to decision making can also elicit specific patterns of autonomic activity. Such autonomic responses vary according to the difficulty of the task, the type of ongoing information processing, the anticipated consequences of the contemplated response, and the significance of the task to the individual. Paralimbic cortices are likely to play important roles in these linkages of visceral patterns to mood and cognition. Dysfunction of limbic or paralimbic areas may thus perturb the adaptive interactions between mental activity and visceral state, distort the experience of emotion, undermine the visceral guidance of comportment (as described in section X, on the frontal lobes), and perhaps even lead to the maladaptive (psychosomatic) autonomic manifestations of stress and anxiety.

Limbic and paralimbic areas also influence the function of the immune and endocrine systems. Associating a taste with an immunosuppressive drug causes rats to show an inhibition of immune responses when subsequently exposed to the same taste. This conditioned immunosuppression is severely impaired after insular (but not parietal) lesions. Furthermore, lesions of the amygdala (as well as of the hippocampus and hypothalamus) lead to marked alterations in lymphoid cell number and lymphocyte activation. Limbic and paralimbic areas may thus provide potential anatomical substrates for the putative influence of mental state upon immune responses and autoimmune disorders. Through hypothalamic connections,
limbic and paralimbic areas can influence the secretion of releasing factors which regulate the adrenal, thyroid, and gonadal endocrine systems. The reciprocal influence between limbic dysfunction and gonadal steroids is reviewed in Chapter 8.

**Taste, Smell, and Pain in Paralimbic Areas**

In contrast to the auditory, visual, and somatosensory sensations which are processed predominantly within association isocortex, olfaction, gustation, and pain are closely related to paralimbic and limbic zones of the brain. The primary olfactory cortex is itself an allocortical limbic structure, whereas the primary gustatory cortex is situated in the frontal operculum, immediately adjacent to the anterior insula.465 In monkeys, cortical responses to olfactory and gustatory stimulation are readily obtained in the orbitofrontal and insular paralimbic areas.511,512,516 Damage to temporopolar, anterior insular, or posterior orbitofrontal cortex in monkeys impairs behaviors that depend on olfactory and gustatory discrimination.20,511,512

In humans, anterior temporal lobectomy disrupts olfactory learning and discrimination whereas olfactory Stimulation activates orbitofrontal, anterior insular, and amygdaloid regions.131,264,432,575 In one experiment, exposure to a salty taste led to the activation of the insula, anterior cingulate, and parahippocampal gyrus, emphasizing the sensitivity of the entire paralimbic zone to gustatory stimulation.268 In one of our patients, the appreciation of flavor was impaired by a stroke which involved the insula of the right hemisphere. A former gourmet with a penchant for French food and fine wine, the patient reported that he was no longer able to appreciate subtle flavors and that he had started to crave highly spiced foods he would have shunned in the past. This change occurred despite a preservation of the patient’s ability to discriminate basic gustatory stimuli.

The close anatomical linkage between paralimbic regions and olfactory-gustatory sensation explains why olfactory and gustatory hallucinations are so common in temporolimbic epilepsy. Olfactory and gustatory sensations may have a close affiliation with the limbic and paralimbic zones of the brain because they have evolved from chemical senses closely related to the monitoring of the internal milieu. The limbic affiliations of these two modalities are consistent with the critical roles they play in the guidance of apetitive behaviors, the identification of territorial markers, and the regulation of sexual behaviors.

Another sensation closely linked to emotion and visceral state is pain. Paralimbic areas contain a particularly high density of endogenous opiates.291 Functional imaging experiments have detected anterior insular and cingulate activation in response to noxious stimuli applied either to the viscera or to the periphery.19,77 The relay of pain-related somatosensory information into limbic areas may be mediated by SII and the posterior insula. As described earlier, damage to these areas can cause an emotional indifference to noxious stimuli known as “pain asymbolia” (section V).
XII. LIMBIC STRUCTURES OF THE SEPTAL AREA, NUCLEUS BASALIS, AND PIRIFORM CORTEX

The constituents of the limbic zone include the septal area, the substantia innominata, the amygdala, the piriform cortex, and the hippocampal formation. These are the parts of the cerebral cortex which have the most intense reciprocal interconnections with the hypothalamus. The behavioral specializations of these limbic structures are similar to those of paralimbic regions but are even more closely related to memory, drive, and emotion.

Septal Nuclei and the Nucleus Basalis of the Substantia Innominata

The basal forebrain contains several interdigitated cell groups. Four of these cell groups (the medial septal nucleus, the vertical and horizontal nuclei of Broca's diagonal band, and the nucleus basalis of Meynert) contain neurons which provide the major cholinergic innervation for the cortical surface (Figs. 1-1 and 1-2a). In addition to cholinergic neurons, many of these cell groups also contain GABAergic neurons which project to the cerebral cortex. The cholinergic cell bodies within the medial septal nucleus (also designated as Ch1) and those within the vertical limb nucleus of the diagonal band (Ch2) provide the major cholinergic input of the hippocampus, those of the horizontal limb nucleus (Ch3) provide the major cholinergic input into olfactory structures, and the cholinergic neurons of the nucleus basalis (Ch4) give rise to the major cholinergic innervation for all the other cortical zones and for the amygdala. These cholinergic nuclei receive substantial neural inputs from the hypothalamus and from components of the limbic and paralimbic zones of the cerebral cortex. In keeping with the organization illustrated in Figure 1-6, the Ch1-Ch4 cell groups send more massive projections to limbic and paralimbic areas than to other parts of the cerebral cortex.

The septohippocampal pathway plays a critical role in the generation of the arousal-related rhythm in the hippocampus. Septal lesions in rats result in pathologically exaggerated emotional reactivity, hyperdipsia, transient hyperphagia, and alterations in taste preferences. Electrical spike activity has been reported in the septal area of patients with schizophrenia and electrical stimulation of this area has apparently lead to pleasurable sensations of an erotic nature. From the vantage point of neuroanatomy, the nucleus basalis belongs to the limbic zone of the cerebral cortex and is also a telencephalic extension of the brainstem reticular core. In keeping with this dual nature, the cholinergic pathways from the nucleus basalis to the cerebral cortex play critical roles in both memory and attentional functions. In rats, lesions of Ch4 neurons interfere with spatial memory. In humans, the amnestic state in patients with anterior communicating artery aneurysms and septal tumors may be caused, at least in part, by the destruction of the Ch1-Ch4 cholinergic nuclei. In Alzheimer's disease, where memory loss is the single most salient aspect of the clinical picture, there is profound neurofibrillary degeneration of Ch4 neurons and loss of cortical cholinergic innervation (Chapter 10). However, in the presence of so many additional neuropathological lesions, the exact relationship between the
cortical cholinergic depletion and the amnesia of Alzheimer's disease is difficult to determine. In the monkey, single unit recordings show that neurons of the nucleus basalis are sensitive to the motivational valence and novelty of sensory stimuli. These neurons alter their activity when the animal detects an edible object, especially if it is hungry and if the object happens to be a favorite food item. This pattern of activity indicates that neurons of the nucleus basalis establish complex associations between sensory events and their motivational valence. The relevance of these cholinergic pathways to attentional tone, memory, and Alzheimer's disease is discussed further in section XVIII of this chapter and also in Chapters 3 and 10.

The Piriform Cortex

Piriform cortex (primary olfactory cortex) receives inputs from the olfactory bulb and is interconnected with the hypothalamus. In contrast to the other sensory modalities, olfactory information does not have to be relayed through the thalamus to reach the cerebral cortex since piriform cortex is directly interconnected with nearly all paralimbic and limbic areas of the brain. The unique importance of olfactory sensation to sexual, territorial, and feeding behaviors is consistent with the location of piriform cortex within the limbic zone of cortical areas. Anosmic cetaceans such as whales and dolphins have a well-developed piriform cortex, raising the possibility that this region might have nonolfactory functions. In the cat, for example, piriform cortex lesions induce hypersexuality whereas stimulation of this region alters the trigeminal receptive fields which elicit attack behavior upon stimulation.

XIII. THE AMYGDALA, EMOTION, AND AFFILIATIVE BEHAVIORS: GATEWAY INTO THE NEUROLOGY OF VALUE

The primate amygdala contains more than a dozen nuclei, each with a different set of connections and physiological properties (Fig. 1–3a). Many of these nuclei have extensive reciprocal connections with the hypothalamus, the hippocampus and with the other components of the limbic and paralimbic zones. The amygdala receives olfactory information from piriform cortex, gustatory and somatosensory information through a relay in the insula, and auditory and visual information through relays in unimodal areas of the temporal lobe. Piriform and hypothalamic connections are more prominent in the medially situated nuclei whereas connections with unimodal and heteromodal association areas are more prominent in the lateral nucleus.

The critical role of the amygdala in the channeling of drive and emotion was highlighted by Downer's experiments in monkeys. In these experiments, the forebrain commissures, including the optic chiasm, were sectioned and the amygdala on one side was ablated. As a consequence of these surgical manipulations, each eye could convey visual information only to the ipsilateral hemisphere and only one eye could convey visual information to an intact amygdala. In the preoperative
period, monkeys reacted to human onlookers with characteristic aggressive displays. Following surgery, the animals remained quite placid when they viewed the onlookers through the eye ipsilateral to the amygdalectomy. When the eye ipsilateral to the intact amygdala was uncovered, however, the customary aggressive response was triggered. These experiments suggest that naturalistic visual experiences trigger the appropriate emotional response only if they have access to an intact amygdala.

The Downer experiments can be said to have created a state of monocular visual hypoemotionality by disconnecting one eye from the amygdala. A more extensive visuolimbic disconnection leads to the "Klüver-Bucy syndrome," which is seen in monkeys after bilateral lesions of the anterior temporal lobe, including the amygdala.169,227 These animals show three salient behavioral changes: (1) They indiscriminately initiate sexual activity without regard to the appropriateness of the object. (2) They no longer show the customary aggressive–aversive reaction to their human keepers. (3) They seem to have lost the ability for visually distinguishing edible from inedible objects and keep mouthing all kinds of objects, discarding inedible ones only after buccal inspection. The one common denominator for these behaviors is a breakdown in the channeling of drive to the appropriate visual target in the extrapersonal space. It is not the drive that is necessarily altered, but its association with the proper object. Despite excessive mouthing, for example, monkeys with the Klüver-Bucy syndrome do not become obese.

The emotional valence of a sensory stimulus is based on its intrinsic hedonic properties, its acquired associations with other primary reinforcers and the current motivational state of the individual. The human amygdala plays a crucial role in modulating the neural impact of sensory stimuli according to each of these three factors. Thus, the amygdala is selectively activated by aversive (but not neutral) olfactory stimuli and fearful (but not neutral) facial expressions.370,575 The amygdala also plays an important role in emotional conditioning, so neutral auditory stimuli which do not initially elicit amygdaloid activation start to do so after they are associated with conditioned fear.280,287 Furthermore, the amygdala can give differential responses to identical sensory events when the state of the relevant motivation changes. Thus, the amygdala was activated by pictures of food when the subject was hungry but not when satiated; no such differential effect was elicited by pictures of tools.278 Amygdaloid lesions can cause states of hypoemotionality in humans and can interfere with the acquisition of conditioned emotional responses to previously neutral stimuli.3,33 In analogy to the organization of the other transmodal nodes in the cerebral cortex, the amygdala (represented by node L in Fig. 1-11b) may thus act as a transmodal gateway for linking the sensory representations of primary and secondary reinforcers with each other and with the mental and autonomic correlates of emotional and motivational valence. Through these processes, the amygdala can modulate the impact of a sensory event in a manner that reflects its intrinsic value and acquired significance.

Spontaneous discharges and electrical stimulations in the amygdala frequently trigger emotional experiences and other emotionally charged experiential phenomena in patients with temporolimbic epilepsy.174 This relationship suggests that the
amygdala may play an important role in linking drive and emotion not only to extrapersonal events but also to mental contents. A balanced mental life is built on congruous and relatively predictable interactions among experience and emotion so that pleasurable experiences and thoughts lead to positive emotions whereas painful ones trigger negative emotions. Severe disruptions in these fundamental relationships may arise as a consequence of disease in limbic and paralimbic regions of the brain, especially the amygdala. This may lead to an unpredictable and incongruous mapping of emotion onto experience in a way that may distort the entire texture of psychological reality. Such disruptions may account for the wide spectrum of acute and chronic psychiatric syndromes ranging from panic attacks to dissociative states, depression, and schizophreniform conditions which have been described in patients with temporolimbic epilepsy (Chapters 8 and 9).

The participation of the amygdala in memory and learning is somewhat controversial (Chapter 4). In humans, bilateral amygdalectomy does not cause a major amnesia. However, the amnesia resulting from hippocampal damage in monkeys becomes more severe if there is additional involvement of the amygdala. In humans, amygdaloid lesions attenuate the facilitatory effects of emotional valence on memory processes, and functional imaging shows that amygdaloid activation mediates the influence of emotional valence upon learning. The amygdala thus appears to have a dual role related to both attention and memory. Its role in attention is to selectively enhance the processing resources allocated to events with high emotional value, whereas its role in memory is to mediate the impact of emotional valence on memorability and also to encode the emotional valence of experience. The roles of the hippocampus and of the amygdala in memory can be dissociated from each other. Hippocampal lesions interfere with the explicit recall of specific events but not with the autonomic responses they elicit on the basis of their emotional significance, whereas amygdaloid lesions leave explicit recall intact but abolish the associated autonomic responses.

The amygdala also participates in a wide range of behaviors related to conspecific affiliative behaviors, social emotions, and their communication. In monkeys, for example, amygdalectomy interferes with emotional vocalizations. Radiotelemetered activity in freely moving monkeys shows intense amygdaloid activity during sexual and aggressive encounters. In fact, amygdalectomy in monkeys alters conspecific aggressive behaviors and reverses the individual's position within dominance hierarchies. Free-ranging rhesus monkeys with bilateral ablations in the amygdala and adjacent cortex fail to display appropriate aggressive and submissive gestures to the point where they become expelled from their social group. In general, amygdaloid hyperactivity appears to enhance aggressive behaviors whereas hypoactivity appears to promote docility. Aggressive outbursts in temporolimbic epilepsy and in patients with episodic dyscontrol are occasionally time-locked to amygdaloid seizure activity and stereotaxic amygdalectomy has been performed to control intractable aggressive behaviors in some of these patients.

In addition to the amygdala, paralimbic areas, especially those that receive their major limbic input from the amygdala, also play similar roles in modulating emo-
tional responses, particularly those related to complex social situations and affiliative behaviors. In monkeys, for example, lesions which involve paralimbic parts of orbitofrontal cortex dramatically alter the emotional response to novel or threatening stimuli. These animals show enhanced aversive responses to relatively novel objects but a lowered aggressive reaction to humans and to a model snake. Furthermore, bilateral ablations in the anterior cingulate region are associated with enhanced startle responses and a greater resilience to handling. The olfactocentric component of the paralimbic belt plays an important role in the coordination of conspecific affiliative behaviors. Thus, orbitofrontal and temporopolar damage in monkeys decreases the effectiveness of aggressive encounters and results in a reduction of positive affiliative behaviors (such as grooming), eventually leading to the ostracism of the lesioned animal. In keeping with these behavioral specializations, neurons in the amygdala and surrounding paralimbic areas are selectively responsive to eye contact with conspecifics.

As in the monkey, the paralimbic areas of the human brain have also been implicated in behaviors related to emotion and motivation. Electrical stimulations of the anterior cingulate, insula and parahippocampal regions, for example, elicit mood alterations, dreamlike states, feelings of familiarity, and memory flashbacks. Selective and persistent impairments in the ability to express emotion through modulations in the intonation of speech have been attributed to lesions in the cingulate area. This area also plays an essential role in the motivational guidance of attentional functions. Bilateral anterior cingulate lesions can lead to severe apathy and personality changes, occasionally reaching the severity of akinetic mutism. Cingulotomy has helped some patients with intractable depression and obsessive compulsive disorders, perhaps because it relieves states of rigid hyperattention to pathological thoughts and emotions.

XIV. THE HIPPOCAMPUS AND THE BINDING OF DISTRIBUTED INFORMATION INTO EXPLICIT MEMORY: GATEWAY INTO THE NEUROLOGY OF RECOLLECTION

The encoding of distance, color, movement, and form displays considerable species-specific invariance and is relatively unaffected by peculiarities of individual experience. Much of mental content, however, is based on idiosyncratic associations which endow percepts and events with contextual anchors and personal significance. Components of the limbic and paralimbic zones of the cerebral cortex, especially the hippocampus and entorhinal cortex, play critical roles in the long-term storage and explicit recall of such arbitrary associations.

In monkeys, lesions of orbitofrontal and parolfactory cortex impair visual recognition and the ability to form associations between objects and reward; insular damage yields modality-specific learning deficits in tasks of tactile discrimination; temporopolar damage impairs visual memory; and bilateral damage to the cingulate gyrus impairs performance in tasks that require the retention of spatial
information.\textsuperscript{377,420} In humans, orbitofrontal lesions have been associated with amnesias; and memory impairments of variable severity have been reported after damage to the cingulate region and retrosplenial cortex.\textsuperscript{68,529,551} Despite the involvement of these paralimbic areas in memory and learning, however, the most severe amnestic states in monkeys and humans occur only when the hippocampo-entorhinal complex and its diencephalic connections are damaged (Chapter 4).

Through relays in entorhinal and transentorhinal (perirhinal) cortex, the hippocampus receives inputs from numerous paralimbic, heteromodal, and downstream unimodal association areas.\textsuperscript{510,531} These multisynaptic pathways allow the hippocampus to receive information in all sensory modalities. As mentioned above, the reciprocal interconnections between the entorhinal-transentorhinal cortex and the hippocampus are so strong that the two may be conceptualized as forming a unified hippocampo-entorhinal complex. The hippocampal formation is also interconnected with the mammillary body of the hypothalamus, the limbic nuclei of the thalamus, and with other components of the limbic zone such as the amygdala and the septal area.\textsuperscript{344,453} Although the hippocampo-entorhinal complex also participates in the neural regulation of emotion, autonomic activity, endocrine control, and immunoregulation, its principal behavioral affiliation is in the realms of memory and learning. In monkeys, selective hippocampal lesions yield only modest deficits in the retrieval phase of learning but the memory disturbance becomes much more severe when the entorhinal cortex is also damaged.\textsuperscript{308,358} On occasion, apparently-isolated hippocampal damage in humans can lead severe memory deficits.\textsuperscript{581} However, the most severe human amnesias result when bilateral lesions involve both the hippocampus and the rhinal cortices.

In accessing established knowledge, such as the name of a color, the meaning of a word, or the identity of a familiar face, recall is based on stable associations that have been consolidated for many years. The recall of such consolidated semantic knowledge is coordinated by transmodal nodes (such as those in Wernicke's area and other parts of the temporal lobe) located outside of the limbic and paralimbic zones of the cerebral cortex. In order to encode and access new facts and experiences, however, fragile and initially sparse linkages have to be established, nurtured, and inserted into the matrix of existing knowledge.\textsuperscript{339} This kind of learning, which is necessary for sustaining explicit, declarative, and episodic memory, is critically dependent on transmodal gateways within the limbic system, especially those of the hippocampo-entorhinal complex (represented by L in Fig. 1-11B).

As described in Chapter 4, the amnestic state caused by lesions of the hippocampo-entorhinal complex is characterized by a dissociation between the explicit learning of new experience, which is severely impaired, and the implicit-procedural learning of motor tasks and perceptual associations, which is relatively preserved. An amnestic patient, for example, may develop new motor skills, improve performance in priming and stem completion tasks, and learn to avoid situations that have recently been associated with aversive consequences, even when he or she has no conscious memories of the experiences that have led to this learning.\textsuperscript{357,468} In addition to the impairment of new learning ("anterograde amnesia"), these patients also display a "retrograde amnesia" for events that occurred before the onset of the limbic lesion. The retrograde amnesia tends to be more
severe for recent than for remote events, a temporal gradient known as "Ribot's law."

During the recovery stage of the retrograde amnesia, some patients display a gradual shrinkage of the time period encompassed by the retrograde memory loss, indicating that at least some of the retrograde amnesia had been due to a retrieval block rather than an obliteration of memory traces. This set of circumstances raises the possibility that the limbic system may play its critical role in memory and learning by acting as a neural gateway for encoding and retrieval, without necessarily constituting the site where the memories (or engrams) are stored. According to this model, facts and events are initially recorded at multiple sites with an anatomical distribution that reflects the modality and category specificity of their constituent components. This information is relayed, through reciprocal multisynaptic pathways, to limbic transmodal nodes including the hippocampo-entorhinal complex (L in Fig. 1–11B). These limbic transmodal nodes are not storage sites of individual experiences. Instead, they enable the construction of directories (or address books) which can be used to look up and bind the distributed fragments of the relevant experience.

The major role of limbic-paralimbic areas, especially the hippocampo-entorhinal complex, may thus be to orchestrate the coherent storage and reactivation of this distributed information. As a consequence of this organization, the fidelity of the original information is not corrupted by convergence, and the same memory can be probed through numerous associative approaches. In addition to mediating multifocal binding, the hippocampo-entorhinal complex also enhances the robustness with which other association areas encode the relevant components of information. The role of the hippocampo-entorhinal complex in explicit memory is thus analogous to the role of Wernicke's area in language, prefrontal cortex in working memory, temporal cortex in face and object recognition, and posterior parietal cortex in spatial attention. Although some convergence may occur in limbic and paralimbic areas, the most detailed information related to recent experiences remains distributed in neocortical areas.

When a critical volume of the hippocampo-entorhinal complex is destroyed, the encoding of new information becomes less reliable, the binding of components becomes jeopardized, and retrieval loses its effectiveness. Consequently, fragments of new events cannot be integrated with the type of coherence that is necessary for supporting explicit-declarative-episodic memory, leading to the emergence of an amnestic state. However, at least some of the information related to new events continues to be encoded in nonlimbic association cortex in a manner that supports implicit learning. The unlinked form of this information helps to explain why implicit learning tasks such as priming are so sensitive to the surface (rather than associative) properties of the stimuli and why they are resistant to transmodal generalization. There is probably no fundamental difference in the type of encoding that is involved in implicit versus explicit memory. In implicit memory, the information remains sequestered, within unimodal and heteromodal association areas; in explicit memory, it becomes incorporated into a coherent context through the binding function of limbic nodes, especially those within the hippocampo-entorhinal complex. In keeping with this formulation, tasks of explicit memory
lead to the activation of medial temporolimbic as well as neocortical areas whereas
tasks of implicit memory lead to the activation predominantly of neocortical
areas.\textsuperscript{207,479,503}

The hippocampo-entorhinal complex and association neocortex are involved in
continuing processes of reconstruction, updating, and associative elaboration which
collectively lead to the consolidation of new memories. At the initial stage of
encoding, a new fact or event has few associations and depends on the limbic system
for maintenance and coherent retrieval. In time, as additional linkages become estab-
lished through reciprocal connections with other transmodal and unimodal areas,
the relevant information becomes less dependent on the limbic system and can be
accessed through numerous associative approaches, some of which may entirely
by-pass the hippocampo-entorhinal complex. The role of the hippocampo-entor-
hinal complex is likely to be most critical for the most recently acquired memories,
for those that have limited resonance with other mental contents, for those that
have been registered casually rather than intentionally, for those with relatively
weak emotional valence, for those that require extensive cross-modal integration,
for those that have been recalled rarely and have therefore failed to establish as-
sociative elaboration, and for those that require the reactivation of idiosyncratic
contextual anchors related to temporal and spatial circumstances. The existence of
such multiple factors helps to explain why the vulnerability of a memory to retro-
grade amnesia is not always a simple function of its time of acquisition and why
clear temporal gradients are not universally found in amnestic patients.\textsuperscript{339}

Why is new learning so dependent on the limbic structures of the medial tem-
poral lobe? A tentative answer may be based on the constraints that the CNS faces:
The number of neurons is fixed with little hope of obtaining many new ones, every
existing neuron is already occupied by previously stored information, new infor-
mation needs to be written on top of existing items, and the amount of new infor-
mation is boundless. The CNS may therefore need to be protected from learning
too rapidly and indiscriminately since this could jeopardize the stability of existing
knowledge.\textsuperscript{319} An initial filtering is provided by attentional systems which select
subsets of behaviorally relevant events for further consideration. The limbic system
appears to erect a second line of defense. It provides a mechanism that allows the
rapid learning of behaviorally relevant relationships but, in an initially transient
(limbic-dependent) form that may induce a relatively small amount of permanent
change in association cortex. This transitional period may allow new memories to
enter associative readjustments before being assimilated in a more permanent form
and also to compete with each other, allowing only the fittest to solidify their hold
on precious synaptic space. Through these processes, the limbic system simulta-
neously satisfies the need to limit the indiscriminate influx of new learning and the
need to adapt to a rapidly changing environment.\textsuperscript{318}

The question may also be asked, why a function as vital as explicit memory
displays a critical dependency on a phylogenetically primitive part of the brain such
as the limbic system. One explanation is that explicit and declarative memory could
have developed to recall contingencies associated with food and danger. In the
course of phylogenetic development, the scope of explicit memory could have ex-
panded beyond the confines of apetitive and defensive behaviors while maintaining its anatomical dependency on the limbic system. The obligatory involvement of the limbic system in memory and learning also insures that sensory events with high emotional and motivational valence will enjoy a competitive advantage. Furthermore, the limbic system is particularly prone to long-term potentiation effects and is also one of the few areas that continue to display axonal sprouting during adulthood. These properties make the limbic system highly suitable for serving a critical role in the organization of new learning.

The way in which the hippocampo-entorhinal complex constructs a directory (or look-up table) for binding and looking up distributed information remains poorly understood. At least one mechanism may be based on the Hebbian rule of covariance according to which the temporal coherence of neural activity with a set of simultaneously active and reciprocally interconnected neurons produces a record that can be used for the subsequent reactivation of the entire set in response to the activation of one of its components. The orderly connections which lead from the entorhinal cortex to the dentate gyrus of the hippocampus (via the perforant path), from the dentate gyrus to CA4 and CA3 (via the mossy fibers), from CA3 to CA1 (via the Shaffer collaterals), from CA1 to the subiculum, from the subiculum back to the entorhinal cortex, and the pathways which interconnect the hippocampo-entorhinal complex with nearly all components of heteromodal and unimodal areas contain the synaptic architecture that could use Hebbian processes for binding and reactivating the distributed components of explicit memory.

The registration, storage, and recall of recent experience involves a great deal of sorting, associative search, recombination, selection, and on-line reintegration, processes that are generally attributed to working memory and the related executive functions of prefrontal heteromodal cortex as reviewed in section X of this chapter. In fact, prefrontal cortex does participate in numerous memory-related functions, including the reconstruction of context and temporal order, the on-line manipulation of encoding and retrieval, and the associative search of internal data stores. It also provides contextual constraints to keep the reconstructed memories within the bounds of plausibility. Damage to prefrontal cortex undermines the effectiveness of encoding and retrieval, causes an impoverishment of associative linkages that are necessary for reconstructing context and temporal order, decreases the speed with which internal data stores are searched, and also increases the tendency to confabulate. In keeping with these clinical observations, almost all tasks of explicit memory yield consistent activation in heteromodal association cortices, especially in prefrontal areas. Although they share a common nomenclature, it is important to emphasize that working memory and explicit memory are behaviorally and neurologically distinct phenomena. Lateral prefrontal cortex lesions interfere with working memory and occasionally impair the efficiency of encoding and retrieval but never give rise to severe amnesias. Conversely, limbic lesions which give rise to severe amnesias usually leave working memory abilities quite intact.

The process of explicit memory allows each person to construct a unique record of experience and knowledge based on events of personal significance. The encoding and retrieval of a memory can involve almost all parts of the cerebral cortex,
but with an orderly anatomical distribution of component processes: relevant unimodal and transmodal areas encode the sensory aspects; the limbic system, especially the hippocampo-entorhinal complex, binds this information into a coherent whole; and prefrontal areas guide the orderliness of storage and retrieval.

XV. THE LIMBIC SYSTEM

The boundaries of the “limbic system” have ebbed and welled to fit the whims of individual investigators. Some have even denied the existence of a limbic system, mostly because of uncertainties in defining its boundaries. There are, however, many sound anatomical and functional reasons for postulating the existence of such a neural system. The following components are usually included within the limbic system. Collectively, they define what is probably its most extensive boundaries:

1. The hypothalamus
2. The limbic (allocortical and corticoid) components of cortex
3. The paralimbic cortical belt
4. The limbic striatum (olfactory tubercle and the nucleus accumbens), the limbic pallidum, the ventral tegmental area of Tsai, and the habenula
5. The limbic and paralimbic thalamic nuclei (anterior dorsal [AD], anterior ventral [AV], anterior medial [AM], laterodorsal [LD], mediodorsal [MD], medial pulvinar [PM] and other midline nuclei)

One justification for lumping these five groups of structures into a unified system is based on the fact that they are tightly interconnected (Fig. 1–12). These connections form many distinct circuits. One of these, based on synaptic relays that lead from the hippocampus sequentially to the mammillary body (via the fornix), to the anterior thalamic nuclei (via the mammillothalamic tract), to the cingulate gyrus, to the presubiculum, to the entorhinal cortex, and back to the hippocampus (via the perforant pathway), is known as the Papez circuit. Components of this circuit play crucial roles in memory and learning. Some of the connections shown in Figure 1–13 are so strong that damage to their sites of origin or termination tends to trigger retrograde or transsynaptic degeneration in the areas with which they are interconnected.

Components of the limbic system also have common neurochemical, physiological, and perhaps even immunological properties. Dopaminergic, cholinergic, and endogenous opiate markers, for example, are more concentrated within the cortical components of the limbic system than in other parts of the cerebral cortex. Furthermore, as discussed in Chapter 9, topical anesthetics such as lidocaine, procaine, and cocaine are powerful activators of limbic and paralimbic areas whereas they tend to depress the activity of other cortical regions. Components of the limbic system also have a greater capacity for synaptic plasticity than other parts of the cerebral cortex. They are therefore highly suited to the encoding of new associations but also highly vulnerable to pathological processes such as kindling and epilepsy (Chapter 8). The preferential affinity of the herpes simplex virus for
almost all cortical components of the limbic system suggests that these cortical areas may even share antigenically common sites recognized by the virus.

The single most important feature which unifies the constituents of the limbic system is the presence of shared behavioral specializations. These can be summarized under five categories:

1. The binding of distributed information related to recent events and experiences in a manner that supports declarative/episodic/explicit memory
2. The channeling of emotion and drives (such as hunger, thirst, libido) to extrapersonal events and mental content
3. The linking of mental activity with autonomic, hormonal, and immunological states
4. The coordination of affiliative behaviors related to social cohesion
5. Perception of smell, taste, and pain

Each of these behavioral realms has been discussed earlier in the course of reviewing the behavioral neuroanatomy of individual limbic and paralimbic structures. Damage to any of the structures shown in Figure 1–13 can cause impairments in one or more of these behavioral categories. However, the limbic system can also be divided into amygdaloid and hippocampal spheres of influence. The olfactocen-
tric paralimbic areas tend to fall within the amygdaloid sphere of influence whereas the components of the Papez circuit fall within the hippocampal sphere of influence. The former are more closely associated with emotion, motivation, affiliative behaviors, and autonomic–hormonal–immunological function, whereas the latter are more involved in learning and memory.

The clinical diagnosis of a persistent global amnestic state always indicates the presence of bilateral limbic lesions, usually within the hippocampal sphere of influence. The most common damage sites associated with severe amnesia are the hippocampo-entorhinal complex, the limbic thalamus, the hypothalamus (especially the mammillary bodies), the fornix, and the basal forebrain (Chapter 4). The concept of a unified network gains further support from the observation that the amnesias resulting from hippocampo-entorhinal lesions and those resulting from thalamic or hypothalamic lesions display clinical features that are nearly indistinguishable. Limbic lesions almost always give rise to multimodal impairments. In contrast, lesions that interrupt connections between unimodal areas and the limbic system give rise to modality-specific disconnection syndromes such as asymbolia for pain, visual hypoemotionality, visual amnesia, and tactile learning deficits (Fig. 1-11c).

Considering its behavioral affiliations, the limbic system would also appear to constitute the most likely site of dysfunction for those psychiatric diseases that might turn out to have identifiable biological causes. Schizophrenia, major depression, post-traumatic stress syndromes, and panic states have each been associated with variable sorts of structural and metabolic dysfunction within components of the limbic system (Chapter 9). Conversely, known lesions within the limbic system can commonly induce a great variety of "psychiatric" symptomatology. Examples include the experiential phenomena, panic attacks, dissociative states, fugues, and schizophreniform states of temporolimbic epilepsy; the agitated confusional states of parahippocampal infarctions; the sexual and apetitive dysfunctions of septal-hypothalamic lesions; and the comportmental abnormalities of the medial and basal frontal lobe syndromes.

XVI. BASAL GANGLIA AND CEREBELLUM

The importance of the basal ganglia (striatum and globus pallidus) and cerebellum to motor function is well known. The basal ganglia play a critical role in the automatic execution of learned motor plans, and the cerebellum regulates the rate, range, and force of movement. Several lines of investigation indicate that these areas may also influence the neural control of cognition and comportment.

The Striatum (Caudate, Putamen, Nucleus Accumbens, Olfactory Tuber
cle)

The striatum receives neural inputs from the substantia nigra and cerebral cortex but does not send reciprocal projections back to the cerebral cortex. The inputs from the cerebral cortex are glutamatergic and those from the substantia nigra are do-
The output of the striatum is directed predominantly to the globus pallidus and uses GABA, enkephalin, and substance P as the transmitter substances. The globus pallidus projects to the ventrolateral and ventral anterior nuclei of the thalamus which, in turn, project to the frontal lobe, giving rise to a multisynaptic striatopallidothalamocorticostral loop. Some of these connections are organized to form relatively distinct skeletomotor, oculomotor, prefrontal, and limbic circuits.8

The striatum contains four components: the caudate, the putamen, the olfactory tubercle, and the nucleus accumbens. The caudate and putamen receive cortical inputs predominantly from association cortex and primary sensory-motor areas. The dopaminergic input to these striatal components originates in the pars compacta of the substantia nigra. The olfactory tubercle and nucleus accumbens receive cortical inputs from limbic and paralimbic parts of the brain, including the insula, amygdala, and hippocampus.54,189,385,532 The dopaminergic innervation of these two striatal components originates in the ventral tegmental area of Tsai, which is just medial to the substantia nigra.196 On the basis of this connectivity pattern, the nucleus accumbens and olfactory tubercle can be designated the “limbic striatum” whereas the caudate and putamen are usually designated the “dorsal striatum” or “neostriatum.”

Dopamine turnover is higher in the limbic striatum than in the neostriatum.542 The limbic striatum also has behavioral specializations which are different from those of the dorsal striatum. For example, disrupting the dopaminergic pathways from the ventral tegmental area to the limbic striatum of the rat results in locomotor hyperactivity and deficits in passive avoidance learning whereas interrupting the nigrostriatal pathway to the dorsal striatum yields hypoactivity and bradykinesia.286 In the cat, activation of the nucleus accumbens reduces the receptive field for the hypothalamic biting reflex and therefore modulates the channeling of aggression to extrapersonal targets.7 The human limbic striatum is involved in the neuropathology of Parkinson’s disease, Alzheimer’s disease, and perhaps also Huntington’s disease.30,244,481 However, its behavioral specializations remain poorly understood. Although the nucleus accumbens has been implicated in the pathogenesis of schizophrenia, the evidence remains circumstantial at best.507

The projections from the cerebral cortex to the dorsal striatum display a complex topographic arrangement. Projections from each cortical area form multiple patches of terminals within the striatum. Patches of projections from separate areas of association cortex are more likely to show partial overlap or interdigitation if the relevant cortical areas are interconnected with each other.483,570 This organization implies that there may be some mirroring of corticocortical interaction patterns within the striatum. Although this arrangement may largely subserve motor control, it may also reflect the role of the striatum in nonmotor integrative functions. In the monkey, for example, a subgroup of caudate and putamen neurons responds during the visual presentation of primary reward but not necessarily during the motor act of pressing the bar which leads to the reward.14,387 Damage to the basal ganglia causes selective learning deficits in tasks which require the switching between response strategies, suggesting that the caudate and putamen may play a critical role in the acquisition and retention of procedural knowledge.414 This func-
tional affiliation may help to explain why procedural learning can remain relatively preserved in patients who develop severe amnestic states as a consequence of cortical lesions.

The head of the caudate nucleus receives most of its input from dorsolateral prefrontal cortex. In monkeys, lesions in this sector of the caudate yield deficits which are essentially identical to those that emerge upon ablating prefrontal cortex, supporting the view that striatal regions have behavioral specializations which are similar to those of the cortical areas from which they receive their major cortical input. In keeping with this formulation, patients with caudate lesions can develop the abulic form of the frontal network syndrome and display a severe loss of self-motivation.

Mental-state impairments with features of the frontal lobe syndrome emerge in almost all basal ganglia diseases. In Parkinson’s disease, for example, prominent cognitive changes, especially related to “executive” functions, arise quite frequently. In Huntington’s disease, cognitive and comportmental changes reminiscent of the frontal lobe syndrome may precede the motor symptoms and may emerge at a time when the pathological changes appear confined to the caudate nucleus.

In some patients, lesions in the caudate and putamen have also been associated with the emergence of agitation, aphasia, and unilateral neglect. In almost all such cases, the adjacent white matter is also involved, making it difficult to determine whether these deficits reflect damage to the striatum or to the adjacent fibers. Experiments based on functional imaging show that the human neostriatum is frequently activated by tasks which require the shifting of spatial attention (Chapter 3).

Lesions and metabolic hyperactivity in the striatum have both been described in obsessive-compulsive disorders as well as in patients with Tourette’s syndrome, a condition characterized by tics and obsessive-compulsive symptoms. Although the relationship to motor function is considered a general property of the entire neostriatum, motor cortex sends projections only to the putamen, not to the caudate. The motor deficits in extrapyramidal diseases may thus have a closer correlation with pathological changes in the putamen whereas the cognitive deficits may have a closer correlation with pathology in the caudate and limbic striatum.

The Globus Pallidus

The globus pallidus receives striatal outflow and projects to the ventrolateral and anterior ventral thalamic nuclei, the habenula, and the subthalamic nucleus. The primate globus pallidus has four easily identifiable components: (1) the outer (lateral) segment, (2) the inner (medial) segment, (3) the ventral pallidum located under the anterior commissure, and (4) the pars reticulata of the substantia nigra.

There is essentially no disagreement about the crucial role of the globus pallidus in motor control. In the monkey, approximately 50% of the neurons of the lateral and internal globus pallidus fire in relationship to the direction of movement. The reversible inactivation of the globus pallidus in monkeys yields a severe and reversible breakdown of a learned flexion–extension movement but only when the
animal is blindfolded. In humans, lesions of the globus pallidus (caused by anoxia, carbon monoxide or cyanide poisoning, cerebrovascular accidents, wasp stings, Wilson’s disease, or Hallervorden-Spatz disease) are frequently associated with severe rigidity and bradykinesia.

The lateral pallidum and the dorsal parts of the medial pallidum receive their striatal input predominantly from the caudate and putamen. The ventral pallidum, however, receives a major striatal projections from the nucleus accumbens. Many neurons of the ventral pallidum respond to amygdaloid stimulation, and this response is probably mediated through the nucleus accumbens. In the monkey, the core of the internal pallidal segment projects to the motor thalamus. However, a medial crescent of this pallidal segment projects predominantly to the lateral habenula, which is generally considered a structure closely related to the limbic system. Damage to the medial globus pallidus of monkeys severely disrupts species-specific sexual display patterns. Furthermore, only very few neurons of the ventral pallidum fire in relationship to movements.

These observations have led to the inclusion of the ventral and medial parts of the pallidum within the limbic system and to the suggestion that these pallidal components may have predominantly nonmotor behavioral affiliations. In the human, pallidal lesions can be associated with severe deficits of motivation, judgment, and insight. Some of these patients may display a profound abulia and occasionally obsessive-compulsive symptomatology. As in the case of striatal lesions, pallidal lesions also lead to a clinical picture that has many features of the frontal lobe syndrome. The pars reticulata of the substantia nigra is a posterior extension of the globus pallidus and may participate in the programming of saccadic eye movements toward actual or remembered targets. Its behavioral correlates in the human brain are not understood.

The Cerebellum

The cerebellum receives inputs through the inferior cerebellar peduncle (carrying fibers from the ipsilateral spinal cord, inferior olive, vestibular nuclei) and the middle cerebellar peduncle (carrying information from the contralateral pontine nuclei). It sends its major projection, through the superior cerebellar peduncle, to the ventrolateral nucleus of the contralateral thalamus. The ventrolateral nucleus then projects predominantly to the motor–premotor areas of the frontal lobe which, in turn, project to the pontine nuclei, completing the multisynaptic cerebellothalamocorticopontocerebellar loop. Each cerebellar hemisphere receives input from the ipsilateral side of the body and is interconnected with the contralateral cerebral hemisphere. Cerebellar lesions thus give rise to ipsilesional motor symptoms. As in the case of limbic pathways, cerebellar connections are remarkably robust and create linkages that exert transsynaptic trophic influences. Thus, through a mechanism known as "diaschisis," frontal infarctions cause acute contralateral cerebellar hypometabolism, and cerebellar lesions can cause widespread contralateral cortical inactivation. Eventually, frontal lobe lesions can even lead to a severe transsynaptic atrophy of the contralateral cerebellum.
Neuroanatomical experiments in monkeys have shown that the inputs to the pontine nuclei come not only from motor–premotor cortex but also from multiple association cortices in the occipital, parietal, temporal, and frontal lobes and also from components of the limbic system. Through these connections, cortical areas related to nearly every cognitive and comportmental domain have potential access to the cerebellar hemispheres via a synaptic relay in the pontine nuclei. The reciprocal cerebellofugal projections appear to have a more restricted distribution since cerebellar projections (relayed via the dentate nucleus and other deep cerebellar nuclei) are directed predominantly to the ventrolateral nucleus of the thalamus, which projects mostly to premotor cortex. Although the ventrolateral nucleus may also project to cortical areas beyond motor–premotor cortex, such projections are likely to be relatively minor or multisynaptic.

Traditional neurological textbooks tend to confine the discussion of the cerebellum to its motor functions. However, the clinical examination of patients with Cerebellar damage and the functional imaging of neurologically intact subjects have raised the possibility that the cerebellum may have nonmotor behavioral affiliations. Even unilateral cerebellar lesions, for example, can impair performance in tasks of attention (as assessed by digit span), verbal fluency, and reasoning and can lead to a flattening of affect and to the emergence of disinhibited behaviors. These cognitive and behavioral deficits can be quite prominent in some patients.

Reports of visuospatial deficits after cerebellar lesions are difficult to interpret because they have usually been based on poor performance in construction tasks which require motor coordination. Difficulties of articulation have been recorded but true aphasic disorders are rare. Deficits of explicit–declarative memory have also been detected but can probably be attributed to the underlying attentional impairments. It is interesting to note that the cerebellar activation seen during word generation tasks in neurologically intact subjects tends to disappear with practice and there is no evidence that cerebellar lesions interfere with spatial attention. It is therefore unlikely that the cerebellum plays a major role in the control of explicit memory, spatial attention, or language. The nonmotor symptomatology (of attention, reasoning and comportment) in patients with cerebellar damage seems to display many features of the frontal lobe syndrome, a relationship which is consistent with the preferential funneling of the cerebellothalamic outflow pathways into the frontal lobes.

Although the cerebellum is unlikely to play a major role in explicit memory, cerebellar lesions impair the acquisition of eyeblink conditioning. Furthermore, the major output nucleus of the cerebellum (the dentate) shows much greater activation during attempts at solving a pegboard puzzle than during the execution of comparable movements not related to problem solving. These observations suggest that the cerebellum, together with the basal ganglia, may play an important role in motor (procedural) learning. Cerebellar neuronal loss has been reported in infantile autism but does not appear to be a consistent feature of this mysterious condition.

In contrast to basal ganglia lesions which frequently lead to severe and easily observable cognitive and comportmental deficits, cerebellar lesions do so less frequently and less prominently. Considering its neural connectivity, however, it is
quite likely that the cerebellum influences the function of many, if not all, cognitive
domains. This relationship could take the form of a global influence upon the state
of information processing (perhaps similar to the role of ascending cholinergic and
noradrenergic pathways) or it could display regional variations that link specific
parts of the cerebellum to specific behavioral domains (as in the relationship of the
basal ganglia and thalamus to behavior). The striatopallidothalamocorticostriatal as
well as the cerebellothalamocorticotopontocerebellar loops are both organized so as
to receive afferents from nearly all cortical areas (through the mediation of the
striatum and pontine nuclei) but confine the outputs (through the mediation of the
thalamus) preferentially into the frontal lobes. This funneling of projections into the
frontal lobes may help to explain why patients with either basal ganglia or cere-
bellar lesions display clinical pictures reminiscent of the frontal lobe syndrome.

XVII. THE THALAMUS

Almost all thalamic nuclei have extensive reciprocal connections with the cerebral
cortex. The one exception is the reticular nucleus, which receives cortical input but
does not project back to cortex. 246 Except for the reticular and perhaps intralaminar
nuclei, thalamic nuclei have very few, if any, interconnections with each other. Each
thalamic nucleus, with the possible exception of the primary sensory-relay nuclei,
projects to multiple cortical areas and each cortical area is interconnected with many
thalamic nuclei. However, most thalamic nuclei have preferred cortical targets and
each cortical area has a principal source of thalamic input. Single thalamic neurons
projecting to multiple cortical areas through axonal collaterals are rare. 40,368 In gen-
eral, primary sensory and motor areas have the most restricted thalamic connectiv-
ity whereas heteromodal and paralimbic areas have the most heterogeneous con-
nections. The principal thalamic nucleus of a cortical area tends to project
predominantly to layer IV whereas the less specific thalamic inputs also reach the
more superficial cortical layers. Thalamic nuclei can be subdivided on the basis of
the specializations of their preferred cortical targets (Fig. 1–14). Boundaries of thal-
amic nuclei are rarely sharp and the nomenclature is subject to variation. In the
following account, the nomenclature will follow that of the Carpenter and Sutin 74
and will be supplemented, wherever necessary, by the nomenclature of Olszewski 392
and Jones 247.

Thalamic Nuclei of Primary Sensory and Motor Areas

The sensory relay nuclei are the easiest to identify. The posterior part of the vent-
troposterior lateral nucleus (VPLp), the principal division of the ventroposterior
medial nucleus (VPM), the posterior part of the ventromedial nucleus (VMp), and
the ventroposterior inferior nucleus (VPI) are the major sensory relay nuclei of the
somatosensory modality: They receive fibers from the medial lemniscus, trigemi-
nothalamic tract, and the spinothalamic tract and project to primary somatosensory
cortex (S1) and S2. The VMp nucleus receives input predominantly from the spi-
nothalamic tract and may relay pain sensation to the insula and perhaps S2. 96 The
VPM nucleus also receives input from the nucleus of the tractus solitarius and relays taste information to the primary gustatory area and the anterior insula. The lateral geniculate nucleus (LGN) is the sensory relay nucleus for the visual modality: it receives input from the eye and projects to primary visual cortex (V1). The medial geniculate nucleus (MGN) is the sensory relay nucleus for the auditory modality: it receives input from the inferior colliculus and projects to primary auditory cortex (A1).

Damage to the VPLp or to the LGN gives rise to contralateral hemihypesthesia and hemianopia, respectively. In contrast to S1 lesions, which do not abolish pain sensation (probably because the thalamic projections to S2 are spared), VPLp lesions generally lead to a loss of pain sensation as well. Since inputs from both ears reach the MGN in each hemisphere, unilateral damage to this thalamic nucleus does not lead to contralateral ear deafness. In fact, unilateral MGN lesions may be extremely difficult to detect clinically and may only cause contralateral suppression during dichotic auditory stimulation. The major thalamic input into primary motor cortex

**Figure 1-14.** A schematic diagram of the four major groups of thalamic nuclei. Abbreviations: AD=anterior dorsal; AM=anterior medial; AV=anterior ventral; LD=laterodorsal; LGN=lateral geniculate; LP=latereoposterior; MD=mediodorsal; MGN=medial geniculate; Pi=inferior pulvinar; Pl=lateral pulvinar; Pm=medial pulvinar; Pa=anterior pulvinar; VA=ventral anterior; VL=ventral lateral; VPL=ventroposterior lateral; VPM=ventroposterior medial.
(M1) comes from the ventrolateral nucleus (VL) and the anterior ventroposterior lateral nucleus (VPLa).\textsuperscript{250,469} Lesions involving these motor nuclei of the thalamus may give rise to contralateral clumsiness and dysmetria.

**Thalamic Nuclei of Modality-Specific (Unimodal) Association Cortex**

In the rhesus monkey, the major thalamic projections to the somatosensory association cortex of the superior parietal lobule (BA5) come from the lateroposterior nucleus (LP) and perhaps also from the anterior subdivision of the pulvinar nucleus (Pa).\textsuperscript{250} The nuclei which provide the major projection to visual unimodal association areas include the inferior (Pi) and lateral (Pl) subdivisions of the pulvinar nucleus.\textsuperscript{35,63,527} The Pi receives inputs from the superior colliculus and may mediate "blindsight" in patients with V1 lesions. In the monkey, Pi and Pl neurons give retinotopically mapped responses to visual stimuli and lesions of the inferior pulvinar disrupt visual discrimination behaviors.\textsuperscript{79,410} The unimodal auditory association cortex receives its major thalamic input from the MGN and probably also from an adjacent rim of the pulvinar.\textsuperscript{63,347} Thus, the MGN is the source of thalamic projections not only to Al but also to the auditory association cortex. The motor association cortex receives its major thalamic input from the ventrolateral nucleus (VL) and perhaps from parts of the ventral anterior nucleus (VA).\textsuperscript{469,489} The VL nucleus receives pallidal and cerebellar output and is the principal nucleus through which the basal ganglia and cerebellum influence the cerebral cortex.

**Transmodal Nuclei of the Thalamus: Nuclei of Heteromodal, Par-alindic, and Limbic Cortex**

The lateral part of the medial dorsal nucleus (MD) is the major thalamic nucleus for prefrontal heteromodal cortex. In keeping with this connectivity pattern, bilateral MD lesions in the monkey reproduce deficits in spatial delayed alternation similar to those associated with prefrontal ablations.\textsuperscript{236} The medial pulvinar nucleus (Pm) and parts of the adjacent lateral posterior nucleus (LP) are the major nuclei for the heteromodal cortices of the inferior parietal lobule, the banks of the superior temporal sulcus and the parahippocampal region.\textsuperscript{350,522,569} In contrast to Pi and Pl, which give retinotopically organized responses to simple visual stimuli, Pm neurons respond to the attentional salience of stimuli and may play a role in the focusing of selective attention.\textsuperscript{441}

The close interconnectivity between the heteromodal and paralimbic zones of the cerebral cortex is also reflected in the arrangement of thalamic connections. Thus, the MD and Pm are major thalamic nuclei not only for prefrontal and posterior parietal heteromodal cortices but also for the entire paralimbic belt. The medial parts of MD (including the magnocellular component), for example, give rise to the major thalamic projections of the orbitofrontal and anterior cingulate regions whereas the Pm has prominent reciprocal projections with the insula, temporal pole, orbitofrontal cortex, parolfactory gyrus, posterior cingulate, parahippocampal gyrus, and temporopolar cortex.\textsuperscript{184,185,367,375,451,569} The MD and Pm also have direct limbic connections. Thus, the medial and magnocellular parts of MD have connections
with the amygdala, piriform cortex, and the septal region whereas Pm has connections with the amygdala and the hippocampal complex. In addition to sharing many common connections, the MD and Pm nuclei blend into each other without distinct boundaries.

Another group of nuclei are collectively known as the nuclei of the "anterior tubercle." These nuclei include the anterior thalamic nucleus (its dorsal [AD], ventral [AV], and medial [AM] components) and the laterodorsal nucleus (LD). They provide the major thalamic connections for the posterior cingulate cortex, the retrosplenial area, entorhinal cortex, and the hippocampal complex. The anterior thalamic nucleus receives direct hypothalamic input through the mammillothalamic tract and is therefore an important component of the Papez circuit. Nuclei situated close to the thalamic midline are collectively designated midline or parmedian nuclei. These include the paratenial, paraventricular, subfascicular, central, and reuniens nuclei. They have extensive projections with paralimbic areas such as the temporal pole and anterior cingulate gyrus and also with the hippocampal formation.

On the basis of these connectivity patterns, the midline, anterior, MD, and Pm nuclei have been included within the limbic system. The paraventricular and MD nuclei in the monkey contain neurons that are sensitive to the previous occurrence of stimuli, suggesting that they could play important roles in recognition memory. In monkeys, lesions which involve the medial parts of the MD nucleus and adjacent midline nuclei lead to visual object recognition deficits similar to those obtained after the ablation of limbic and paralimbic cortex in the medial temporal lobe.

In patients, the clinical consequences of lesions in the MD nucleus reflect its frontal and limbic connections. Cerebrovascular lesions that involve the medial part of MD bilaterally can give rise to amnestic states that are almost indistinguishable from those associated with hippocampo-entorhinal lesions, the one difference being that confabulations appear to be more likely after the thalamic lesions. However, the lesions in many of these cases also extend into the anterior and midline nuclei and into the mamillothalamic tract, so the exact role of the MD lesion in the genesis of human "thalamic amnesia" is not entirely clear. In the Wernicke-Korsakoff encephalopathy, severe amnestic states are associated with MD and Pm lesions, but almost always in conjunction with additional lesions of the mammillary bodies.

A rather frequent clinical consequence of a unilateral left MD lesion is characterized by the triad of a frontal lobe syndrome, verbal memory loss, and anomia. In such patients, the MD lesion may induce a remote EEG slowing and hypoperfusion within dorsolateral prefrontal cortex, and, less frequently, within the temporal lobe. Loss of judgment and insight is the predominant finding in some patients with unilateral MD lesions, and amnesia in others. The anomia is rarely severe. Lesions of the right pulvinar nucleus, including its medial component, have been associated with contralateral neglect for the left extrapersonal space, and electrical stimulation of the left medial pulvinar has been reported to induce transient anomia. Bilateral MD thalamotomies are also said to reduce schizophrenic agitation and intractable anxiety.
These observations show that the transmodal thalamic nuclei display behavioral affiliations that are similar to those of their principal cortical targets. While it is easy to understand how thalamic sensory relay nuclei influence the function of their cortical projection sites, it is much more difficult to surmise the role of the transmodal nuclei. Corticothalamocortical loops involving heteromodal, paralimbic, and limbic areas could conceivably help to imprint local associative linkages, reactivate them under specific behavioral conditions, and, as will be described below, maintain coactivation boundaries for large-scale neurocognitive networks.

The Reticular and Intralaminar Nuclei of the Thalamus

The reticular nucleus of the thalamus as well as the intralaminar nuclei (e.g., the limitans, paracentralis, centralis lateralis, centromedian, and parafascicularis) have strong associations with the ascending reticular activating pathways. The putative role of these thalamic nuclei in the control of arousal and attention is discussed in Chapter 3.
Many axonal pathways that interconnect one cortical area with another (or with specific sectors of the basal ganglia and thalamus) are organized in the form of reciprocal point-to-point channels where the principal sites of origin and the major fields of termination are of approximately equivalent size. This point-to-point connectivity provides the basic anatomical substrate of specific channel functions. Damage to channels such as the splenium of the corpus callosum, the frontotemporal uncinate fasciculus, or the insulo-amygdaloid pathway leads to specific impairments such as pure alexia, memory retrieval deficits, and asymbolia for pain. In addition to these point-to-point channels, each cortical area also receives widespread modulatory connections which arise from small groups of neurons and which innervate the entire cerebral cortex either directly- or through thalamic relays. These pathways employ small amines and GABA as transmitters and determine the overall state of information processing rather than the contents of the information that is being transmitted along the point-to-point channels. These modulatory pathways play important roles in coordinating behavioral states related to arousal, attention, mood, and motivation. At least six such pathways can be identified in the primate brain (Fig. 1–16). Five of these reach the cerebral cortex directly without a thalamic relay whereas the sixth is relayed through the thalamus.

1. Cholinergic and GABAergic projections from the basal forebrain to the cerebral cortex
2. Histaminergic projections from the lateral and medial hypothalamus to the cerebral cortex
3. Serotonergic projections from the brainstem raphe nuclei to the cerebral cortex
4. Noradrenergic projections from the nucleus locus coeruleus to the cerebral cortex
5. Dopaminergic projections from the substantia nigra and the ventral tegmental area of Tsai to the cerebral cortex
6. Cholinergic projections from the brainstem reticular formation to the thalamus

Each of these modulatory pathways is organized in such a way that a relatively small group of neurons can induce rapid modulations in the information processing state of the entire cerebral cortex. The cholinergic projection from the brainstem to the thalamus, for example, promotes arousal by facilitating the transthalamic passage of sensory information toward the cerebral cortex. The other five modulatory pathways have direct access to the cerebral cortex without any thalamic relay. Each of these pathways displays a slightly different pattern of cortical distribution and physiological specialization. Thus, cortical cholinergic innervation is most intense within limbic areas whereas the noradrenergic projections tend to favor primary sensory areas. Furthermore, cholinergic projections tend to synapse onto cortical
pyramidal neurons whereas the serotonergic projections synapse onto inhibitory interneurons. The cholinergic innervation of the cerebral cortex arises predominantly from the nucleus basalis of the substantia innominata. The neurons of this nucleus are particularly responsive to novel and motivationally relevant sensory events. The major effect of acetylcholine upon neurons of the cerebral cortex is mediated through the m1 subtype of muscarinic receptors and causes a prolonged reduction of potassium conductance so as to make cortical neurons more receptive to other excitatory inputs. Cortical cholinergic pathways also promote EEG desynchronization, long term potentiation (LTP), and experience-induced synaptic remodeling. The ascending cholinergic pathway from the basal forebrain is therefore in a position to enhance the immediate neural impact and long-term memorability of motivationally relevant events. The nucleus basalis also gives rise to a GABAergic projection directed to the cerebral cortex. At least in the rat, this pathway innervates inhibitory cortical interneurons but its functional specializations remain poorly understood.

The noradrenergic innervation of the cerebral cortex arises from the nucleus locus coeruleus. The neurons of this nucleus are more responsive to the motivational relevance (or meaning) of a stimulus than to its sensorial properties. Neocortical norepinephrine increases the signal-to-noise ratio and timing precision of cortical neurons in a way that enhances the specificity of neural responses to
sensory events. The cortical response to the stimulation of a single vibrissa in rats, for example, loses some of its discrete localization when the norepinephrine innervation to cortex is interrupted. At the behavioral level, noradrenergic transmission modulates novelty-seeking behaviors, the focusing of attention and also resistance to distraction.

The dopaminergic projections of the cerebral cortex arise from the substantia nigra and ventral tegmental area of Tsai. These dopaminergic cells are selectively responsive to motivationally relevant stimuli and to cues that signal their existence. They appear to encode discrepancies between the prediction and occurrence of reward and may therefore convey teaching signals for learning appetitive behaviors. In keeping with these characteristics, the dopaminergic projections from the ventral tegmental area to the cerebral cortex and nucleus accumbens appear to play an important role in mediating the neural processes related to substance addiction. Furthermore, both dopamine and acetylcholine promote cortical responses related to working memory.

The serotonergic projection to the cerebral cortex arises from the brainstem raphe nuclei. The electrical stimulation of these neurons can induce an arousal-related pattern of low voltage fast activity in the cerebral cortex. Serotonergic agonists reduce distractibility in a two-choice runway task, suggesting that serotonin may modulate the sensory gating of behaviorally relevant cues in the environment. Ascending serotonergic pathways can also influence the state of hunger and aggressivity and may mediate the subjective effects of alcohol. The hypothalamus is the source of a relatively light histaminergic projections to the cerebral cortex. Histamine receptors are widely distributed throughout the cerebral cortex and have been implicated in the regulation of cortical arousal, energy metabolism, autonomic function, and sensitivity to pain.

One anatomical feature common to all of these modulatory corticopetal projections is the absence of equally well-developed reciprocal projections from the cerebral cortex. The nucleus basalis, for example, projects to all parts of the cerebral cortex but receives cortical projections from only a handful of limbic and paralimbic areas. The other cortically projecting cell groups shown in Figure 1–16 also receive sparse cortical projections, most of which come from limbic and paralimbic areas. This asymmetry of corticofugal versus corticopetal connections allows the neurons of the basal forebrain, substantia nigra-ventral tegmental area, brainstem raphe, and nucleus locus coerules to rapidly shift information processing states throughout the cerebral cortex in a way that is responsive primarily to the demands of the limbic system and internal milieu with relatively little intervention from feedback loops emanating from heterornodal, unimodal, and primary cortices.

Many psychiatric diseases, including mania, depression, paranoia, obsessive-compulsive disorders, and chronic anxiety, are characterized by pathological biases in the interpretation of events and experiences. When compared to control subjects, for example, patients with generalized anxiety disorder show greater metabolic activation of temporal and frontal cortex during the passive viewing of neutral
stimuli. Such altered responses, even to neutral stimuli, may indicate the existence of a fundamental processing state abnormality which biases the impact of all experience. Indirect evidence based on the pharmacological treatment of depression and anxiety with noradrenergic and serotonergic agents and of paranoia with dopamine blockers suggests that the modulatory pathways of the cerebral cortex may play important roles in setting such fixed attitudinal biases in the processing of sensory experience.

It is unlikely that there will be a one-to-one relationship between any of these modulatory pathways and specific cognitive or comportmental domains. In general, however, the activation of these modulatory pathways provides a mechanism for augmenting the neural responses to motivationally relevant events, facilitating their storage in memory, enhancing their access to on-line processing resources, sharpening the attentional focusing they elicit, and increasing their impact on consciousness. These projections are in a position to alter the tone, coloring, and interpretation of experience rather than its content. In addition to cholinergic and monoaminergic receptors, many areas of the cerebral cortex, but especially components of the limbic system, also contain receptors for estrogen, testosterone, and other steroids. Alterations in the circulating level of these hormones, as in puberty or menopause, could influence behavioral states in a manner analogous to the effect of the modulatory projection systems.

The modulatory projections reviewed in this section are part of the ascending reticular activating system, which is discussed in greater detail in Chapter 3. These pathways highlight the multiple factors that contribute to the neural control of cognition and comportment. Language, spatial orientation, attention, memory, and emotion are each subserved by large-scale networks which contain multiple point-to-point channels. These pathways encode the perceptual, motor, visceral, and affective components of the relevant behavior and the way in which these components are interlinked. The modulatory pathways influence the processing states within which these domain-specific channels function. In the course of remembering, for example, the content of what is recalled is determined primarily by the information that flows along the point-to-point sensory–limbic interconnections. The speed and efficiency of the recall, and perhaps the perspective from which the information is interpreted, however, may be regulated by the activity of the modulatory pathways that innervate the relevant regions of limbic and association cortex. In the realm of emotion, the point-to-point projections of the amygdala and related limbic structures may determine the linkage of a specific thought or event with a specific feeling and visceral state whereas the modulatory pathways may introduce an intrinsic bias favoring one mood over another and may determine the intensity of the emotion and its influence on other aspects of mental activity. Among all the complex factors involved in the neural control of comportment and cognition, those that represent the contributions of these modulatory pathways are the most accessible to therapeutic manipulation by existing pharmacological agents. This is why the pathways shown in Figure 1–16 represent the major targets of modern psychopharmacology.
XIX. HEMISPHERIC SPECIALIZATION AND ASYMMETRY

The functional organization of the human brain is characterized by multiple hemispheric asymmetries. Asymmetry of structure and function is not unique to the human brain. The frog's habenula has two subnuclei on the left but only one in the right, the chimpanzee's temporal plane is larger on the left, and the hypoglossal nerve displays an asymmetrical influence on bird song. The purpose of asymmetry is unknown but may reflect the biological advantage of concentrating the controlling components of a network within a single hemisphere in order to minimize transcallosal conduction delays.

Left Hemisphere Specializations: Praxis and Language

One aspect of hemispheric asymmetry that is accessible to everyday experience is handedness. Ninety percent of the population is said to be right handed. In this vast majority of the population, the right hand can easily master complex movements, especially those associated with the usage of tools, whereas the left hand tends to be remarkably clumsy when asked to perform the same task. The words dexterity (from Latin, dexter, right) and adroitness (from French, droit, right) are used as synonyms for skillfulness, and the word gauche (from French, gauche, left) as a synonym for all that is awkward. Since the two hands are mirror images of each other and have an identical musculature and innervation, handedness is clearly based on an asymmetrical CNS control of movement rather than on a physical peculiarity of the left hand.

The prevalence of right-handedness has led to the assumption that the contralateral left hemisphere of the human brain is more highly specialized for skilled movements (praxis). Support for this hypothesis has come from several directions. First, apraxias are more commonly seen after damage to the left hemisphere. Secondly, functional imaging experiments in right handers show that the right motor cortex displays substantial activation only when complex finger movements are performed by the contralateral left hand whereas the left hemisphere displays substantial activation during the performance of these movements by either hand. The execution of simple movements is not associated with such asymmetry. Furthermore, transcranial magnetic stimulation of left premotor cortex impairs response selection in both hands whereas stimulation in the right premotor cortex cause a disruption only in the contralateral hand. The left hemisphere, thus controls complex movements in both sides of the body whereas the influence of the right hemisphere is confined to the contralateral side.

The absence of direct callosal connections in the hand representation of M1 may promote the independent control of each hand and may make handedness possible. The influence of the left motor cortex upon the ipsilateral limbs may be exerted through the uncrossed contingent of the pyramidal tract or through callosal connections. There is apparently no anatomical asymmetry in either M1 or S1 of the human brain, but the putamen and globus pallidus may be approximately 10%
larger on the left than on the right, and the left pyramidal tract may be the first to cross in the medulla. The conclusion that the left hemisphere is also specialized for language function has been based on clinical observations showing that approximately 90% or right handers and 60% of left handers develop aphasia only after damage to the left hemisphere. The fact that more than half of left handers develop aphasia after left hemisphere lesions also shows that the specialization for language and handedness can have dissociable anatomical substrates. Only a few right handers become aphasic after right hemisphere lesions (a condition which is usually designated “crossed aphasia”). Non-right-handers have a better chance of recovery from aphasia caused by left hemisphere damage, presumably because the intact right hemisphere has a greater potential for mediating language functions.

Experiments on split-brain patients have shown that the left hemisphere in most right handers contains all the machinery for language function, whereas the right hemisphere cannot produce spoken or written language but has a rudimentary capacity for understanding the meaning of some words. In keeping with these observations, experiments based on dichotic listening and on the tachistoscopic presentation of visual stimuli show a right ear and visual field (and therefore left hemisphere) advantage for all language-mediated tasks in neurologically intact subjects. In functional imaging experiments, language tasks elicit prominent left hemisphere activation whereas the contralateral right hemisphere activation can be quite negligible.” Clinical observations have shown that acalculia is more common after damage to the left hemisphere, suggesting that the left hemisphere is also specialized for the verbal manipulation of numbers.

The supratemporal plane, a region which is generally included in Wernicke’s area, is frequently larger on the left side of the human brain. This anatomical asymmetry is noticeable even during embryonic development. In one study, nearly 90% of chimpanzee brains that were investigated also displayed a larger supratemporal plane on the left. Since this asymmetry seems to be almost as frequent in the chimpanzee as in humans, since the absence of supratemporal plane asymmetry does not prevent humans from acquiring language, and since chimpanzees have shown little enthusiasm for developing language during the past several million years, it appears that the anatomical asymmetry of the supratemporal plane is neither necessary nor sufficient for the emergence of language function.

Right Hemisphere Specialization for Complex Non-Linguistic Perceptual Skills, including Face Identification

The specialized functions of the left hemisphere have been appreciated for more than a hundred years. In contrast, the specializations of the right hemisphere did not gain widespread acceptance until much later, leading to its initial characterization as the ”minor” or ”silent” hemisphere. A great deal of clinical and experimental evidence gathered since then has now led to the conclusion that the right hemisphere has numerous behavioral specializations and that these can be divided
into at least four realms of function: (1) Complex and nonlinguistic perceptual tasks, including face identification, (2) Spatial distribution of attention, (3) emotion and affect, (4) and paralinguistic aspects of communication.

Experiments based on dichotic listening show a left ear (and therefore right hemisphere) advantage for pitch and melody identification; and tachistoscopic experiments show a left visual-field (and therefore right hemisphere) superiority for depth perception, spatial localization, and the identification of complex geometric shapes. Furthermore, the left hand is usually more accurate in judging the orientation of a rod by palpation. In keeping with these observations, experiments based on functional imaging and event-related potentials have reported a greater activation of the right hemisphere during the performance of nonverbal complex perceptual tasks, including those that require mental rotation.

A left visual-field superiority can also be demonstrated in the processing of perceptual information related to unfamiliar faces. If subjects who are briefly exposed to a new face are subsequently presented with two photographic composites, one consisting of the two left sides and the other of the two right sides of the face, they tend to conclude that the composite made of the right side (which had been viewed through the left visual field) more closely resembles the original face. Thus, the information in the left visual field (coming from the right side of the other person’s face) plays the more important role in determining the way in which the face is remembered. This phenomenon can acquire potential behavioral relevance during everyday life since most faces are distinctly asymmetrical. Despite this apparent superiority of the right hemisphere in the processing of information related to faces, severe prosopagnosia is usually seen in the context of bilateral lesions, suggesting that both hemispheres take part in the recognition of faces (Chapter 7).

In keeping with these functional asymmetries shown in neurologically intact subjects, a voluminous and continuously expanding literature shows that right hemisphere lesions, especially those located in the posterior aspects of the hemisphere, lead to a much greater impairment of complex visuospatial tasks. Thus, the judgment of line orientation, visually guided stylus maze performance, the Block Design Test of the Wechsler Adult Intelligence Scale, the tactile judgment of rod orientation, the ability to identify objects presented from an unusual visual perspective, and the ability to detect variations in a familiar melody are more impaired after right hemisphere lesions when compared to left hemisphere lesions. Constructional tasks, especially those that require the reproduction of three-dimensional perspective, are also more severely impaired after by in the right hemisphere. Even memory processes show hemispheric asymmetry (Fig. 1–15). Thus, patients with left temporal lobectomy are more impaired in learning verbal material whereas patients with right temporal lobectomies are more impaired in the memorization of nonlinguistic complex perceptual material, especially those that involve spatial relationships.

The right hemisphere specialization for complex perceptual function becomes more pronounced if the task is made especially difficult and also if some memorization is required for successful performance. Prior experience with the task, individual skills, and peculiarities in the mode of information processing may
also influence the extent of hemispheric asymmetry. While naïve listeners show a right hemisphere superiority in recognizing melodies and tone sequences, for example, musically experienced individuals as well as those who use a more analytical style of information processing may show a greater activation of the left hemisphere. However, during the processing of particularly complex musical material, such as the recognition of fugue themes, even professional musicians showed greater right hemisphere activation. There are also gender differences: For example, the left hemisphere superiority for language and the right hemisphere superiority for complex perceptual tasks may both be more pronounced in males than in females. In women, hemispheric asymmetry in cognitive tasks may vary according to the stage of the menstrual cycle. It seems, therefore, that the most consistent right hemisphere specializations for complex perceptual tasks are likely to be obtained in right-handed male subjects who are performing unfamiliar and difficult perceptual tasks. It also appears advisable to specify the menstrual state of female subjects participating in such experiments.

**Right Hemisphere Specialization for Spatial Attention**

Numerous observations lead to the conclusion that the right hemisphere is specialized for distributing attention within the extrapersonal space. According to a model that is described in Chapter 3, the right hemisphere contains the neural machinery for shifting attention symmetrically to both sides of space whereas the left hemisphere contains the machinery for shifting attention almost exclusively in the contralateral hemispace and in a contraversive direction. This leads to the emergence of marked contralateral neglect after right hemisphere injury but not after equivalent left hemisphere injury. This pattern of right hemisphere specialization is seen even in left handers and even in those with documented right hemisphere dominance for language. It appears, therefore, that the right hemisphere specialization for spatial attention may be more tightly conserved than the left hemisphere specialization for language. Preliminary morphometric investigations show that parts of the posterior parietal cortex may be larger in the right hemisphere, especially in right-handed males. The relevance of this anatomical asymmetry to the hemispheric specialization for spatial attention remains poorly understood.

**Right Hemisphere, Emotion, and Affect**

Inappropriate jocularity in response to hemiplegia (also known as "anosognosia") is seen almost exclusively in patients right hemisphere infarcts. In contrast, deep dejection and dysphoria (sometimes leading to what is known as the "catastrophic reaction") are more common in patients with left hemisphere infarcts. This clinical observation has led to the inference that the right hemisphere may normally introduce a negative (dysphoric) emotional bias to experience whereas the left hemisphere may introduce a more positive (euphoric) bias. According to this hypothesis, normal mood reflects a balance between these two tendencies. Right hemisphere lesions would tilt the balance toward inappropriate jocularity whereas
left hemisphere lesions would tilt it toward despondency and depression.229,442 Such hemispheric asymmetries may originate quite early in life. For example, there is greater EEG activation over the left hemisphere when 10-month-old infants are shown happy faces.108

The inferences derived from the nature of the emotional reactions to hemiplegia are based on the assumption that the despondency in response to right hemiplegia is comparable to the jocularity which emerges after right hemiplegia, except that it is of the opposite valence. However, one could also argue that the despondency of right hemiplegics is an entirely appropriate reaction to a devastating event whereas the jocularity of left hemiplegics is always inappropriate. The phenomenon of anosognosia may thus show that the right hemisphere plays a more essential role in promoting appropriate emotional reactions to life experiences.

In keeping with this last inference, numerous observations suggest that the right hemisphere is more highly specialized for coordinating nearly all aspects of emotional expression (affect) and experience (mood). For example, the ability to express emotional tone through speech prosody, facial expression, or gesture and also the ability to identify the nature of the emotion expressed through prosody and facial expression are both more impaired after lesions in the right side of the brain.2,6,36,273,523 Furthermore, experiments in neurologically intact subjects show that the right hemisphere is better equipped for encoding (expressing) and decoding (identifying) affect. Thus, emotional expressions are more accentuated on the left side of the face and there is a left visual field advantage in the identification of emotional expressions.218,373-460

Additional evidence favors a right hemisphere specialization also for the experience of emotions. For example, experiments which used the electrodermal response as an index of emotional experience found that patients with right hemisphere lesions were markedly impaired in their visceral responses to emotional stimuli whereas those with left hemisphere injury were not.580 Furthermore, emotionally loaded questions elicited a larger number of leftward eye movements, a finding which some would interpret as an indication of greater right hemispheric activation in response to the induced emotional state.478 In a rather remarkable study, neurologically intact subjects were asked to stimulate themselves into sexual climax while their EEGs were being monitored. The results showed that the EEG amplitude during orgasm was greater over the right hemisphere.89

There are also indications that affective disease may be more closely associated with right hemisphere dysfunction. It has been suggested, for example, that left-sided temporolimbic seizure foci are more likely to be associated with ideational disorders whereas right-sided foci are more likely to be associated with mood disturbances.31 blood disorders are also more common in conjunction with right- than-left sided brain damage.297 Even in patients with otherwise typical manic-depressive disturbances, the EEG power spectra tend to show greater disturbances over the right hemisphere.149 In fact, when patients with manic-depressive disease were given a dichotic listening task, their performance was similar to the performance of individuals with right temporal lobectomy.574 Furthermore, neurological signs indicative of right hemisphere dysfunction may be seen during depression and may
disappear when the depression is treated? The relationship between unconscious mental content and the motor system also shows a more intimate linkage in the right hemisphere. Thus, the left side of the body appears more responsive to hypnotic suggestion. Furthermore, unilateral hysterical paralysis is more frequently encountered in the left side of the body, even in left-handers. In view of the close interrelation between emotion and autonomic tone, it is also interesting to note that the right hemisphere may have a greater influence on determining heart rate.

In summary, while each hemisphere may impart an emotional perspective of opposite polarity to the interpretation of experience, this asymmetry seems to be embedded within a greater right hemisphere specialization for all processes related to mood and affect. The modulation of mood and affect is coordinated by limbic and nonlimbic components of the cerebral hemispheres: the nonlimbic neocortical components may play important roles in integrating, interpreting, and communicating emotions, whereas the limbic components may play a more fundamental role in generating emotions, linking them to visceral responses, and channeling them to appropriate targets. Functional asymmetry related to mood and affect is probably much more pronounced in the non-limbic than limbic areas which participate in these realms of behavior.

Paralinguistic Aspects of Communication, Communicative Competence, and the Right Hemisphere

Phoneme production, word choice, syntax, and grammar constitute the linguistic aspects of speech. They are under the dominant control of the left hemisphere in the vast majority of the population. As shown in Chapter 6, however, there is much more to communication, and even to speech, than these formal linguistic features. For want of better terminology, such additional components can be designated the "paralinguistic" aspects of communication. They collectively contribute to the emergence of communicative competence. The encoding and decoding of mood through variations of emotional prosody, facial expression and gestures are some of the paralinguistic aspects of communication. As noted above and in Chapter 6, these channels of communication are under the influence of the right hemisphere.

In addition to mood, speech prosody is also used to denote emphasis and attitude. The same word choice and word order, for example, could convey completely different messages depending on the distribution of stress and inflection in the utterance. These attitudinal aspects of prosody are also controlled by the right hemisphere. Another aspect of paralinguistic communication is the ability to comprehend situational context through nonlinguistic cues. Patients with right hemisphere injury are impaired in this very important area of communicative competence. Furthermore, neurologically intact individuals show a left ear (right hemisphere) advantage in the ability to infer context and intent during the dichotic presentation of sentences which have been altered to render the verbal material indecipherable while keeping the melodic structure intact.

The modulation of verbal output (how much to say and when to yield the floor),
digitating projections to the striatum. Since the striatum receives cortical inputs but does not project back to the cerebral cortex, it could serve the role of an efference synchronizer (or filter) for coordinating the outputs of cortical areas in a given network. The human brain contains at least five large-scale neurocognitive networks that are organized in this fashion.

**Dorsal Parietofrontal Network for Spatial Orientation**

The cortex around the intraparietal sulcus, the frontal eye fields, and the cingulate gyrus constitute the three interconnected epicenters. The parietal component displays a relative specialization for the perceptual representation of behaviorally relevant locations and their transformation into targets for attentional actions; the frontal component displays a relative specialization for choosing and sequencing exploratory and orienting movements; and the cingulate gyrus displays a relative specialization for the distribution of effort and motivation. Additional critical components are located in the striatum and thalamus. Damage to this network yields deficits of spatial attention and exploration such as contralesional hemispatial neglect, simultanagnosia, and the other components of Bálint’s syndrome. For reasons that have been reviewed, contralesional neglect occurs almost exclusively after right-sided damage to this network whereas Bálint’s syndrome tends to arise after bilateral lesions. (See Chapters 3 and 7 for further detail.)

**Limbic Network for Memory and Emotion**

The hippocampo-entorhinal complex and the amygdala constitute the two interconnected epicenters. The former displays a relative specialization for memory and learning, and the latter for drive, emotion, and visceral tone. Additional critical components are located in the paralimbic cortices, the hypothalamus, the limbic thalamus, and the limbic striatum. Damage to this network yields deficits of memory, emotion, affiliative behaviors, and autonomic regulation. Severe deficits usually occur only after bilateral lesions. On occasion, unilateral left sided lesions give rise to a multimodal amnesia but this is transient. More frequently, unilateral lesions in the left give rise to prominent deficits of verbal memory whereas unilateral lesions on the right give rise to nonverbal memory deficits which are usually quite mild. (See Chapter 4 for further detail.)

**Perisylvian Network for Language**

The two epicenters of this network are known as Broca’s area and Wernicke’s area. According to the opinions expressed in this chapter, Broca’s area includes the premotor region BA44 and the adjacent heterornodal fields of BA45-47; Wernicke’s area includes the posterior part of auditory association cortex in BA22 and also adjacent heterornodal fields in BA39-40 and perhaps BA21. Broca’s area displays a relative specialization for the articulatory, syntactic, and grammatical aspects of language whereas Wernicke’s area displays a specialization for the lexical and
the emotion-memory network, Wernicke's area and Broca's area in the language network, and prefrontal cortex and posterior parietal cortex in the working memory-executive function network. The axonal transport experiments mentioned above indicate that if one member of such a pair, say A, is interconnected with additional cortical areas such as 1, 2, and 3, then B is also interconnected with the same three cortical areas. Consequently, if A transmits a message, B will receive it directly, but also through the alternative vantage points provided by areas 1, 2, and 3. This arrangement enables parallel processing and contains multiple nodes where seamless transitions between parallel and serial processing can occur. In resolving a complex cognitive problem such as reconstructing a past memory, selecting words to express a thought, or figuring out the identity of a face, a set of cortical areas interconnected in this fashion can execute an extremely rapid survey of a vast informational landscape while considering numerous goals, constraints, scenarios, and hypotheses until the entire system settles into a state of least conflict which becomes identified as the solution to the cognitive problem.

Because cortical areas tend to have very extensive corticocortical projections, individual sectors of association cortex are likely to belong to multiple intersecting networks. With rare exceptions, however, thalamic subnuclei have almost no connections among each other. As shown in the anatomical experiments mentioned earlier, some thalamic subnuclei can project to both epicenters of an individual large scale neural network. Thalamic subnuclei can thus fulfill the very important role of setting coactivation boundaries for separating the activity of one network from the activity of others. A similar view was expressed by Penfield, who suggested that thalamic nuclei could act as integrators of the cortical areas involved in speech and language. As noted earlier, interconnected cortical areas are likely to send inter-
determine whether all network components are activated simultaneously or if the temporal sequence of activation varies according to the nature of the task. Such questions can be addressed by combining functional imaging with event-related potentials. 402

**Selectively Distributed Processing and Shifts of Network Affiliations**

As noted in section V, unimodal association areas display regional specializations which follow the principles of selectively distributed processing. A similar organization can be discerned in large-scale neural networks. For example, Wernicke’s area occupies the lexical–semantic pole of the language network but also participates in articulation and syntax whereas Broca’s area occupies the articulatory–syntactic pole of the network but also participates in phonological discrimination and lexical access. 71,334 In the case of spatial attention, the frontal eye fields occupy the motor–exploratory pole of the relevant network but also participate in the compilation of perceptual representations whereas posterior parietal cortex occupies the sensory–representational pole but also participates in the programming of exploratory movements. 329 In the limbic network, the hippocampal complex is most closely related to explicit memory but also plays a role in emotional modulation whereas the amygdaloid complex is most closely related to emotional modulation but also participates in the encoding of emotionally salient memories. 65,363

The nature of selectively distributed processing was probed experimentally in subjects undergoing depth electrode recordings as they were being investigated for the surgical treatment of epilepsy. The subjects were shown a large number of faces and common objects and were asked to engage in one of four tasks: detection of familiarity, perceptual matching, perceptual categorization, and working memory. Recording sites were located in the hippocampus, amygdala, inferotemporal cortex, and lateral prefrontal cortex. A recording site was noted to be engaged by a given task if the averaged evoked potentials to two contrasting stimuli (e.g., familiar versus unfamiliar faces) differed significantly. 480

The results showed that all four recording sites were engaged by multiple tasks, but each with a distinct profile of selectivity. The hippocampus was the one area that did not seem to show a definite preference for one task over another, probably because none of the tasks required long-term explicit memory. The probability of activation was highest in the amygdala when the goal of the task was the detection of familiarity and emotional relevance; in the inferotemporal cortex when the goal was perceptual categorization or perceptual matching; and in prefrontal cortex when the goal was to hold informational in working memory. These results show that there are no object or face “centers” in the brain but that activation is selectively distributed according to a probabilistic function determined by the goal of the task. 480

According to the plan of organization shown in Figure 1–17, cortical nodes are likely to participate in the function of more than one network. How (or whether) a cortical area can be recruited differentially into one network versus another remains poorly understood. Top-down connections could conceivably play a role in this process. For example, Friston showed that a region of inferotemporal cortex
semantic aspects. Additional components of this network are located in the striatum, thalamus and the association areas of the frontal, temporal, and parietal lobes. Damage to this network yields aphasia, alexia, and agraphia. Such deficits are seen only after damage to the left hemisphere in the majority of the population. (See Chapters 3 and 6 for further detail.)

**Ventral Occipitotemporal Network for Face and Object Recognition**

The middle temporal gyrus and the temporal pole appear to contain the transmodal epicenters for this network. Additional critical components are located in the fusiform gyrus and inferior temporal gyrus. Damage to this network yields recognition deficits such as object agnosia and prosopagnosia. The lesions that cause such deficits are almost always bilateral. The fusiform gyrus is the most common site of lesions, probably because it is the only part of this network with a vascular supply that makes bilateral damage likely. On occasion, unilateral left-sided lesions can lead to object agnosia, and unilateral right-sided lesions to prosopagnosia. (See Chapter 7 for further detail.)

**Prefrontal Network for Executive Function and Comportment**

Prefrontal heteromodal cortex and orbitofrontal cortex are the major cortical epicenters involved in the coordination of “comportment,” whereas prefrontal heteromodal cortex and posterior parietal cortex provide epicenters for a network involved in working memory and related executive functions. The head of the caudate nucleus and the mediodorsal nucleus of the thalamus are additional critical components. Deficits of comportment are more frequently associated with lesions of orbitofrontal and adjacent medial frontal cortex whereas deficits of executive function and working memory are more frequently associated with damage to dorso-lateral prefrontal cortex. Clinically significant deficits are usually seen only after bilateral lesions. On occasion, unilateral left-sided lesions give rise to a syndrome of abulia whereas unilateral right-sided lesions give rise to behavioral disinhibition. The network for working memory displays a partial overlap with the network for spatial attention (Chapter 3).

Neuroanatomical experiments in the homologous regions of the monkey brain have shown that the components of these five networks are interconnected according to the pattern shown in Figure 1-17. All of these networks receive their sensory information from the common set of unimodal cortical areas shown in Figure 1-11b. The differences in the resultant cognitive functions are determined by the anatomical location and specializations of the relevant transmodal epicenters. The large-scale network approach predicts that many, if not all, network components will be activated in concert during the performance of any task in a given cognitive domain. In keeping with this prediction, tasks related to spatial awareness, language, working memory, explicit memory, and object identification in human subjects have each led to the collective activation of the relevant epicenters noted earlier. Functional imaging experiments cannot yet
mation into cognition and consciousness. At the first synaptic level, sensation is mapped by finely tuned neurons into a primary dimension—retinotopic for vision and tonotopic for audition. The second synaptic level mediates the more differentiated extraction of specific attributes such as color and motion. The third and fourth synaptic levels play critical roles in the perceptual encoding of faces, objects, words, and extrapersonal targets by ensembles of coarsely-tuned neurons. Motivational, emotional, and attentional modulations are relatively weak at the first two synaptic levels but become increasingly more influential at higher synaptic levels where they help to depict a version of the world based on significance rather than appearance.

The fifth and sixth synaptic levels contain the heteromodal, paralimbic and limbic regions of the cerebral cortex, collectively known as transmodal areas. Transmodal areas enable the coherent binding of distributed multimodal information. They are critical for transforming perception into recognition, words into meaning, scenes and events into experiences, and spatial locations into targets for exploration. They also constitute epicenters for large-scale distributed networks. Cortical components of networks are interconnected with an architecture that enables rapid transitions from parallel to serial processing. Their functional organization follows the principles of selectively distributed processing. Each cortical node of a network can potentially belong to several intersecting networks and can dynamically shift allegiance from one to the other depending on the goal of the task.

One of the most important functions of the CNS is to convert the product of neural activity into stable memories. Facts and events that are destined to be registered in memory are composed of modality-specific sensory components. The initial encoding of these components occurs with unimodal areas and provides the perceptual information that can mediate implicit memory. The construction of consciously accessible memories necessitates a transformation of these isolated fragments into coherent multimodal representations. The multimodal binding that subserves this process is coordinated by the hippocampo-entorhinal complex and related limbic structures. Since behaviorally relevant events are more likely to elicit limbic activation, this arrangement promotes the preferential learning of behaviorally relevant experiences. Newly encoded memories remain more heavily dependent on the integrity of limbic connections for months to years as they gradually become consolidated through extensive associative linkages. Once memories are consolidated, the binding of their constituents becomes more dependent on transmodal areas outside of the limbic system and they become less vulnerable to limbic lesions. Thus, recently acquired facts, experiences, and associations are vulnerable to limbic lesions whereas memories of early childhood, the names of objects, and general facts about the world are not.

Since the nature, purpose, and consequences of environmental incidents are relatively unpredictable, any new event is likely to activate many, if not all, networks, at least initially. The steps of perceptual identification, deployment of spatial attention, lexical labeling, association with past experiences, linkage to emotional and visceral patterns, assessment of present context, planning of options, and prediction of consequences are likely to proceed simultaneously and iteratively as a rapid succession of scripts, scenarios, and hypotheses. The most relevant ensembles and
was able to yield differential activation to faces versus other objects only when there was a high level of activation in a region of posterior parietal cortex. In another experiment, the same set of subjects were given two tasks, one of face identification, the other of spatial attention. A region that corresponds to the parietal component of the attentional network (BA7), a region of prefrontal cortex (BA46) related to the frontal component of the same network, and a part of inferotemporal cortex (BA21) involved in face and object identification were activated by both tasks. However, the activation of BA7 in the task of object identification was much more strongly correlated with the activation of BA21 than with that of BA46, whereas the converse relationship was observed during the task of spatial attention. These results suggest that individual cortical areas can dynamically shift affiliation from one network to another depending on the overall goal of the task.

The mechanisms underlying these shifts of network affiliation have not been elucidated. Changes in behavioral context can alter the way in which the activity of a neuron is temporally correlated with the activity of another in the same area of the cerebral cortex. Such effects could allow a rapid association and dissociation of local clusters into distinct functional subgroups, each favoring a different network linkage. These types of dynamic network reconfigurations occur in the stomatogastric ganglion of decapod crustacea, where they appear to be controlled by monoaminergic inputs. Furthermore, in the lamprey, the same group of neurons mediates swimming, burrowing, and crawling and can be reoriented from one task-specific network to the other by serotonin through the modulation of a calcium-activated potassium current. Conceivably, network realignments in the primate brain could also be influenced by the modulatory monoaminergic and cholinergic synapses of the cerebral cortex.

XXI. OVERVIEW AND CONCLUSIONS

The evidence reviewed in this chapter shows that the cerebral cortex of the human brain can be divided into five functional zones which collectively provide a spectrum of architectonic differentiation and functional specialization. The zone with the least differentiated architecture and the strongest hypothalamic connectivity is designated "limbic." Its behavioral affiliations are polarized toward the coordination of visceral state, endocrine balance, immunoregulation, drive, emotion and memory. These neural functions emphasize homeostasis, the internal milieu, self preservation, and the propagation of the species. At the other end of the spectrum, the zone of primary sensory–motor cortex displays the most differentiated architecture and has the most immediate contact with the extrapersonal world. Its constituents coordinate skilled movements and encode accurate representations of sensory events. The intervening zones of unimodal, heteromodal, and paralimbic cortex enable the associative elaboration of incoming information and its linkage to action, drive, visceral state and emotion. These intervening zones support the type of integrative processes that are necessary for consciousness and cognition.

Multisynaptic streams of processing mediate the incorporation of sensory infor-
the choice of appropriate address (tu versus vous), and the choice of proper pitch (using a higher frequency and simpler language when speaking to a child) constitute additional paralinguistic functions which could conceivably also fall under the preferential control of the right hemisphere. In fact, right hemisphere lesions, especially those that involve the superior temporal gyrus, promote excessive language output and the use of unnecessarily complicated technical vocabulary. One of our patients with a right temporal lesion, for example, became uncharacteristically brazen and abrasive following a right temporal infarction. From his hospital room he would keep calling the physician's office and use forms of address and a conversational style which reflected inappropriate familiarity. The same patient also talked excessively would not take the cue to "yield the floor" during conversation. The inappropriate conduct of patients with right hemisphere injury may reflect, at least in part, an inability to decipher nonlinguistic channels of communication and to adjust behavior to fit the demands of the prevailing context.

XX. DISTRIBUTED LARGE-SCALE NETWORKS AND THEIR CORtical EPICENTERS

Transmodal nodes in midtemporal cortex, Wernicke's area, posterior parietal cortex, prefrontal cortex, amygdala, and the hippocampo-entorhinal complex link distribute information into coherent multimodal assemblies necessary for face and object recognition, naming, working memory, spatial attention, emotional channeling, and explicit memory. These transmodal areas provide the cortical epicenters of large-scale distributed networks.

The domain of spatial attention was used to explore the internal organization of such networks. As shown in Chapter 3, the distribution of attention within the extrapersonal space is coordinated by a large-scale network built around three epicenters: one in the region of the frontal eye fields, another in the region of the intraparietal sulcus, and a third in the cingulate gyrus. The architecture of connectivity among the components of this network was investigated in an experiment where the regions of the frontal eye fields and posterior parietal cortex were each injected with a different retrogradely transported tracer. The resultant pattern of retrograde labeling showed that these two epicenters of the attentional network were interconnected not only with each other and the cingulate gyrus but also with an identical set of 12 additional cortical areas. Furthermore, both injection sites received common projections from the mediodorsal and medial pulvinar nuclei of the thalamus and sent interdigitating and partially overlapping projections to the striatum.

This pattern of connectivity, summarized in Figure 1–17, may reflect an organization that is common to all large-scale networks. In this figure, A and B represent two interconnected epicenters of any large-scale neural network. They could represent the frontal eye fields and posterior parietal cortex in the network for spatial attention, midtemporal and temporopolar cortices in the network for face and object recognition, the amygdala and the hippocampo-entorhinal complex in
networks are gradually expected to dominate the landscape of neural activity as they become more and more resonant with current goals and constraints. The solution to a cognitive problem or task could be defined as the settling of the entire system into a state of best fit. This would not constitute the final product of a hierarchical assembly line but rather a complex surface with many peaks and valleys spread over much of the cerebral cortex. There would be both localization (phrenology) and equipotentiality in the course of this process but the localization would be distributed and the equipotentiality would display regional selectivity.

From a strictly behavioral point of view, the existence of consciousness might be inferred when a living organism responds to environmental events in an adaptive way that is not entirely automatic. According to such a definition, consciousness is a property shared by numerous species. There are, however, differences of detail. The path from sensation to cognition in simpler brains with less intermediary processing is straight and narrow, leading to an equally modest texture of consciousness. In the human brain, the multiple paths inserted between the first and sixth synaptic levels of Figure 1-11b introduce a vast spatial expansion of the neural landscape that links sensation to cognition. Each node in Figure 1-11b provides a nexus for the convergence of afferents and the divergence of efferents. The resulting template allows the emergence of a large number of alternative trajectories as sensation becomes transformed into cognition. In the course of this process, obligatory one-to-one linkages between stimulus and response become transcended in a manner that greatly increases cognitive and behavioral flexibility. Working memory further expands the horizon of consciousness by stretching the temporal influence of internally or externally generated events and by increasing the number of processing channels that can be accommodated simultaneously.

Not all sensory events that activate the nodes in Figure 1-11b are necessarily accessible to consciousness. Some facts and events can be encoded in ways that covertly influence subsequent behavior even when the subject appears to have no conscious awareness of the relevant information. The phenomena of blindsight in hemianopic patients, implicit memory in amnesic patients, and autonomic responsivity to familiar faces in prosopagnosic patients have been reviewed earlier and provide examples of dissociations between neural encoding and conscious awareness. Furthermore, the conscious awareness of some sensory experiences may be delayed by up to 500 ms beyond the time of the initial cortical response, during which the incoming impulses appear to acquire "neuronal adequacy." 295,296 It appears, therefore, that the accessibility of an event to explicit consciousness and introspective commentary is the byproduct of a special type of cortical activity and not an automatic consequence of sensory encoding. Access to the level of explicit consciousness would appear to be most likely for components of experience that can elicit coherent binding and multimodal associative elaboration through the intercession of transmodal nodes.

Considering this remarkably complex organization, it is hardly surprising that the diseases of the human brain cause equally complex symptom clusters, some of which may appear to defy plausibility. One purpose of this chapter has been to show that basic facts related to the anatomy and physiology of the human brain
can help to elucidate the relationship between the site of disease and the nature of the behavioral impairment. An equally important purpose has been to show that these facts may also guide the exploration of neurobiological principles which link brain structure to cognition and comportment.

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REFERENCES