8 THE LIMBIC SYSTEM/HYPOTHALAMUS

CHAPTER OVERVIEW

If the phrase "an enigma shrouded in a mystery" ever could be used to describe a portion of the central nervous system, then it might most aptly apply to the notion of the limbic system. As will be discussed, even considering the collection of phylogenetically older cortical type tissues that largely comprise Broca's "limbic lobe" as a meaningful functional system

repeatedly has been challenged. Part of the difficulty lies in the number of structures, their myriad connections, and the diversity of ascribed functions that would be represented by such a system. The problem appears twofold. First, is there sufficient functional cohesiveness to classify these limbic structures as a "system," as, for example, we might speak of a *motor* or a *visual system*? Second, there is the matter of boundaries; once we start including structures, where does one stop? Different authors have taken different stands on whether or not these structures should be construed as constituting an integrated system. Regardless, most authors will concede that this collection of allocortical tissues (along with the hypothalamus with which they are strongly connected) is critically important for a host of behaviors essential for the preservation of both the individual and the species. Listed among such behaviors typically are internally and externally stimulated drive states, emotional responsiveness, and the ability to encode into memory those life experiences relevant to those drive or emotional states.

Much of this chapter will focus on delineating those structures that are thought to play a central role in emotion, motivation (including basic biological drives), and memory. While the reader should attend to their basic anatomical features, even more critically the reader is encouraged to develop a working knowledge of their interconnections and a general understanding of their relationship to neocortical areas. Such knowledge and understanding in turn will be critical to appreciating their suspected behavioral and clinical correlates. A major goal of the authors, and presumably the readers, throughout this text.

As suggested by the opening sentence, the overall contribution of the "limbic system" or limbic structures to human behavior is still largely conjectural. Nevertheless, as clinicians and scientists it is incumbent upon us to develop and continually refine theories to help elucidate our understanding of brain–behavior relationships. Such knowledge not only is sought for its own sake, but also as a means of better understanding and appreciating pathological disease states. In trying to approach this goal, the apparent functional significance of each of these structures will be explored on an individual basis, based both on their cortical and subcortical connections, and behavioral correlates as derived from clinical and experimental studies. Having reviewed the structural and functional aspects of each of these individual structures, the chapter will conclude by summarizing a broader theoretical model of the potential role of limbic structures ("system," if you will) in the evolution of the brain and behavior.

INTRODUCTION

The first five chapters of this book focused almost exclusively on sensory and motor processes in relatively well-defined anatomical systems. Chapters 6 and 7 on the basal ganglia and the thalamus introduced systems concerned not only with sensorimotor functions, but also with what might be considered "higher-order" phenomena such as emotions and cognition. As we approach this chapter and the next on the cerebral cortex, there will be a continuing shift from more elementary sensory input and motor effector systems to an increasing focus on superordinate concepts involving emotion, motivation (drive), goals, intentions, perception, learning, memory, and cognition. From a historical perspective, it has not been that long ago that these latter processes often were ascribed to an entity (i.e., the soul) that was thought to operate independently of the central nervous system. Because of the controversies that have surrounded these more recently evolved brain structures and the speculative nature of their functional organization, it might be informative to depart from the format used in the preceding chapters. Here we will begin by looking at how the "limbic system" and its behavioral correlates have been viewed historically, even within the last century.[1]

HISTORY OF THE "LIMBIC SYSTEM"

In 1878, *Broca* defined the band of neuronal tissue that lies under the cortical mantle and more or less surrounds the upper part of the brainstem (the thalamus) as *le grande lobe limbique*. This area, which comprises a much larger percentage of the total brain in lower animals, was thought to be associated largely with the sense of smell, and hence, became known as the rhinencephalon (*smell-brain*). It included parts of the parahippocampal and cingulate gyri and the subcallosal area of frontal lobes (Figure 8–1).

In 1937, *James Papez* published a paper entitled, "A proposed mechanism of emotion." In it he describes a circuit (later referred to as **Papez's circuit**) that he felt served as the probable neurological substrate of emotional expression and, along with the contribution of the cerebral cortex, the neuronal basis for the subjective experience of emotion. This circuit was proposed based on what Papez observed to be a relatively direct series of interconnections between areas of the brain that had been implicated in emotional behaviors. Papez had noted, for example, the emotional disturbances that were commonly associated with rabies, a disease that selectively affects the hippocampal region (and cerebellum). Similarly, he noted behavioral or affective changes following lesions in the area of the cingulate gyrus, the mammillary bodies,[2] and the anterior nuclei of the thalamus. He also had noted that the precuneus (part of the medial parietal lobe that was thought to be an extension of the cingulate gyrus) was the one area of the brain that showed the greatest sex difference (being larger in males). As this also was an area that bordered on the sacral representation in the paracentral lobule, he figured this must be the area of the cortex where the sex organs were localized.[3]

Papez proposed that emotions could arise either from psychic origins (i.e., from one's cognitive or intellectual awareness of a situation) or from sensory input. With regard to the former, he suggested the following neural substrate. Cortical or psychic information first might be communicated to the hippocampal formation (e.g., via the cingulum, a pathway that connects the cingulate gyrus and other deep cortical structures with the hippocampal regions). From observations of animals and patients affected with rabies, it appeared that the hippocampal formation clearly was involved in the formation of emotions. Impulses then were thought to have been sent from the hippocampal formation to the mammillary bodies via the fornix. The earlier works of Bard (1928) and the study of "sham rage" in animals deprived of their cortex and basal ganglia had suggested that the hypothalamus was the likely source of "emotional expression." From the mammillary bodies, it was proposed

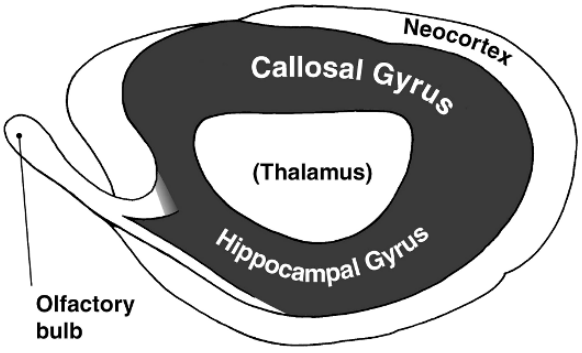


Figure 8–1. "Le Grande Lobe Limbique" as adapted from Broca's original 1878 drawing of an otter's brain. Broca's "callosal gyrus" is now termed the cingulate gyrus.

that impulses were sent to the anterior nucleus of the thalamus via the mammillothalamic tract and then from there to the cingulate gyrus. According to Papez, the cingulate gyrus was considered to be the primary receptive site for the subjective experience of emotion. From the cingulate gyrus this "emotional coloring" of the psychic experience could then be relayed to the cortex (Figure 8–2).

External sensory inputs (e.g., the sight of a snake, the roar of a lion) were thought to take on emotional tones through similar pathways. Papez recognized that most sensory input, except for olfaction, was transmitted to the cortex via the thalamus. However, he indicated that while the thalamus was relaying sensory impressions to the cortex, simultaneously the hypothalamus (again, the main source of emotional expression) also received sensory input from "primitive" sensory centers in the subthalamus. The hypothalamus, having imbued these sensory stimuli with an affective tone, conveyed this now emotionally charged information to the cingulate gyrus via the anterior nucleus of the thalamus as outlined above. Finally, these data were relayed on to the cortex, which concurrently was receiving a perceptual impression of the stimuli. These converging inputs thus attached "subjective emotional experience" (which only could be accomplished in the cortex) to the specific sensory stimulus.

This pathway (hippocampal formation → fornix → mammillary body → mammillothalamic tract → anterior thalamus → cingulate gyrus → and back to the hippocampus via the parahippocampal gyrus) was the groundwork for what later came to be known as Papez's circuit and served as the major starting point for descriptions of the "limbic system." The importance of Papez's paper was that:

1. For the first time, it attempted to lay down a systematic neurological substrate for emotional behavior.
2. It emphasized the close connection between the structures of the *limbic lobe* of Broca and the hypothalamus.
3. It served as an added impetus for research into the role of these structures or "systems" beyond olfaction.

While Papez's circuit probably is the more familiar, Yakovlev (1948) proposed a second limbic circuit that involved additional basolateral connections. This latter limbic circuit

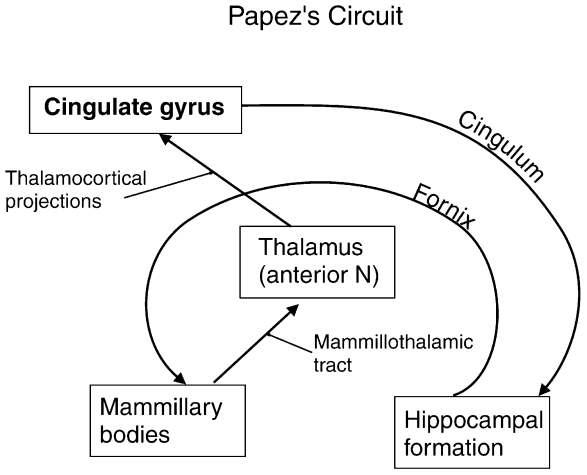


Figure 8–2. Papez's circuit.

incorporates the dorsomedial nucleus of the thalamus, orbitofrontal cortex, temporal pole, and amygdala. Figure 8–3 illustrates the differences between the two proposed circuits. Functionally, Yakovlev's circuit would appear to be more related to the visceral aspects of emotional–affective processing. However, components of both circuits have been implicated in the neural substrates underlying learning and memory (Goldberg, 1984; Victor, Adams, & Collins, 1989; Zola-Morgan & Squire, 1993). It is important to note that both Yakovlev's and Papez's papers describe circuits consisting of closed loops; hence, lesions that disrupt any portion of these circuits, including the white matter connections, would be expected to disrupt the behavior mediated by these circuits.

In 1949, 12 years after Papez published his paper, Paul MacLean (1964) published a very interestingly written article in the journal, *Psychosomatic Medicine* in which he further developed the role of Papez's circuit in mediating the basic visceral responses of the organism, including such activities as the four "F's" (*f*eeding, *f*ighting, *f*leeing, and "*f*ooling around"). He referred to this interconnected series of structures described by Papez as the *visceral brain*.[4] The main thrust of his paper was to establish this "visceral brain" as the source of the "unconscious" motivation or dynamics that underlie psychosomatic disorders. As he explained it, the cortex of this system (e.g., the hippocampal formation) is less well developed than that of the cerebral hemispheres. As a result, the hippocampal formation is forced to process all this visceral information (e.g., the need for food, fear, and sexual gratification, most of which began in infancy) at a very primitive, highly symbolic, nonverbal level. He also speculates that:

"[I]f the visceral brain were the kind of brain that could tie up symbolically a number of unrelated phenomena, and at the same time lack the analyzing ability of the word brain to make a nice discrimination of their differences, it is possible to conceive how it might become foolishly involved in a variety of ridiculous correlations leading to phobias, obsessive-compulsive behaviour, etc . . . Considered in light of Freudian psychology, the visceral brain would have many of the attributes of the unconscious id . . . the visceral brain [may not be] unconscious, but rather eludes the grasp of the intellect because its animalistic and primitive structure makes it impossible to communicate in verbal terms."[5]

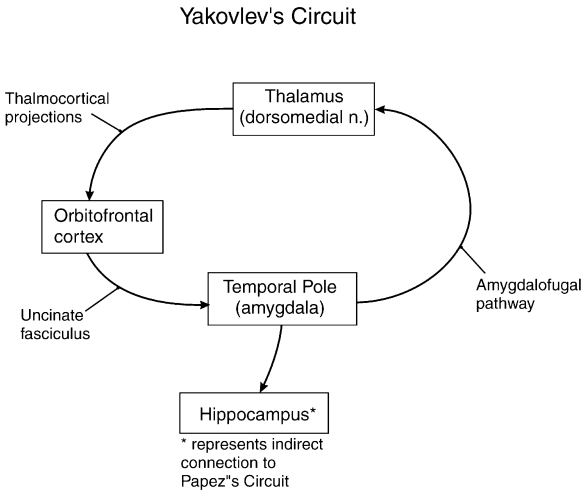


Figure 8–3. Yakovlev's circuit.

THE CONCEPT OF A "LIMBIC SYSTEM"

Since the time of Papez (1937), Yakovlev (1948), and MacLean (1949/1964), additional clinical data have served to strengthen the concept of these limbic structures as a *system* that likely plays a major role in such basic behaviors as motivation (drive), affective arousal, emotional responsiveness, and learning and memory. For example, in some of the early studies in intracranial self-stimulation, a number of sites within this "system" have been demonstrated to have extremely positive reinforcing valences for the organism when self-stimulation procedures were made available, with some sites apparently being negatively reinforcing (Olds, 1958; Olds & Forbes, 1981). Destructive lesions and electrical stimulation involving various structures within this system were found to be capable of producing marked changes in the organism's pattern of emotional and social behaviors, including (1) aggressiveness or passivity; (2) increased or reduced sexuality; (3) fear and panic, emotional indifference (e.g., loss of previously established fear responses); or, on more rare occasions (4) positive emotional responses. (Bard, 1928; Kluver & Bucy, 1939; Terzian & Ore, 1955; Downer, 1961; Trimble, 1984, Doane, 1986, Rolls, 1986, 1990; LeDoux, 1991; Joseph, 1992). Seizure foci or tumors located in the anterior temporal and basal frontal regions frequently are associated with psychiatric symptomatology (Gloor, 1990, 1991; Gloor et al., 1982; Hermann & Chambria, 1980; Strauss et al., 1982; Sweet et al., 1969) In addition, psychosurgical procedures employed to reduce pathological anxiety (e.g., severe, intractable obsessive–compulsive disorders) or uncontrollable aggressiveness typically targeted limbic structures or their frontal connections (Diering & Bell, 1991; Valenstein, 1977).

On the other hand, other authors, most notably Brodal (1981), argued that there is no firm logical or scientific basis for maintaining the notion that these structures should be considered to represent a specific functional–anatomical "system." His argument is based, in part, on the fact that despite being composed of phylogenetically older cortical tissue, there are considerable anatomical differences among the various structures. He and more recently Kotter and Meyer (1992) and Kotter and Stephan (1997) note the anatomical and functional disparities often present in the description of the "limbic system" by various authors. Kotter and his colleagues suggest, however, that while the "limbic system" should be viewed as a hypothetical concept rather than a clear, empirically defined anatomical (or neurobehavioral) construct, the concept of a "limbic system" may have constructive "heuristic and didactic aspects," as long as its current limitations are recognized. This position is shared by Nieuwenhuys (1996), who points out that most, if not all, functional systems within the brain are characterized by some degree of anatomical uncertainty.

This chapter will not presume to resolve this debate. Rather it will focus on exploring (1) the basic anatomy and major afferent and efferent connections of certain key "limbic" structures, (2) the functional correlates most commonly associated with these structures, and (3) how their collective organization and complementary functions may contribute to the overall teleological goals of the organism. Before proceeding with an exploration of individual structures and their interrelationships, a few general principles that may facilitate our understanding of these relationships will be reviewed.

GENERAL ORGANIZATIONAL PRINCIPLES

As noted above, even among those who subscribe to the meaningfulness of the construct, there is no universal agreement as to what structures constitute the "limbic system." However, practically all anatomical definitions of the limbic system begin with the **hypothalamus** and include several other more primitive structures that have substantial direct

connections with the hypothalamus. Most commonly mentioned in this regard are the **amygdala**, the **hippocampal formation**, and the **septal** nuclei. Other primitive areas that have been less frequently included are the **anterior** and **habenular** nuclei of the thalamus, the **preoptic** region, the **substantia innominata**, and the **pyriform cortex**.[6]

A second level of structural organization involves those areas defined as **paralimbic** structures (Mesulam, 1985). These areas, which are designated as *mesocortex*, include cortex within the **temporal poles**, the more caudal portions of the **orbitofrontal cortex**, the remaining portions of the **parahippocampal gyrus**, and the **cingulate gyrus**. While not having direct connections with the hypothalamus, these paralimbic regions have extensive connections with other limbic areas listed above and are thought to serve as an important link between them and the isocortex.

For the purposes of this chapter, only the following structures will be reviewed in detail: the hypothalamus, amygdala, septal nuclei, hippocampal formation, and cingulate gyrus. Although less consistently listed as part of the limbic system than the other four, the cingulate gyrus was included for both historical and practical reasons. Not only was the cingulate gyrus part of Broca's "grand limbic lobe," but it was an integral part of Papez's circuit and MacLean's original definition of the "limbic system." From a practical standpoint, as we shall see, many of the functions associated with this very prominent cortical structure appear to be directly related to the general functional constructs typically associated with the limbic system. Finally, again out of both historical and practical considerations, we also briefly will review the olfactory system and its relationship to limbic functions.

GENERAL FUNCTIONAL PRINCIPLES

As is the case with the anatomy, historically there has been less than a clear consensus regarding the primary function(s) served by the "limbic system." The "smell brain," the "visceral brain," the source of emotion and psychic energy, as well as the substrate of learning and memory are among the various designations that have been emphasized over the past century with regard to these collections of cortical and subcortical structures. Like the blind men and the elephant, each probably reflects an important element, but even collectively it is unlikely that they capture the true essence of the beast. While unraveling the mysteries of the "limbic system" is obviously still a work still in progress, there is much to be learned from what has been discovered thus far. Throughout this chapter, the probable functions of individual structures will be reviewed. But first, by way of introduction, the following represents a preliminary look at what are thought to be the major function(s) collectively subserved by these structures.

If there is one feature that is central to the notion of a "limbic system" it would have to be the *control and regulation of drive* states. As with all organisms, the most common and fundamental example of this is maintaining internal homeostasis. Without this, the organism simply does not survive. For the most part being reflexive or instinctual in nature, the drive states controlling these autonomic and visceral functions appear to reflect the most primitive core of the "limbic system." Beginning with the hypothalamus, the need for reciprocal control mechanisms readily becomes apparent. If the pupils dilate or the heart accelerates in response to a threatening stimulus, there needs to be an opposing action that results in pupillary constriction or cardiac deceleration when the threat is removed. Similarly, if eating and drinking are stimulated by low blood sugar or decreased osmotic pressure in arterial blood, there then needs to be some mechanism to inhibit these responses once these values are normalized.

However, as organisms evolved, behaviors and social structures became more complex.[7] The repertoire of animal behavior no longer was simply relegated to eating, sleeping, reproduction, and internal homeostasis. Beginning with birds, and even more evident in mammals, there was a tendency to care for the young over longer periods of time, social bonds and hierarchies became more intricate, social signaling or communication became more flexible and elaborate, and as noted by MacLean (1986) "*play behavior*" developed along with increased cortical development, particularly the cingulate gyrus. In addition, these more highly developed organisms appeared to have considerably more freedom or latitude in terms of behavioral responses to their environment. Behaviors became less ritualized and increasingly subject to modification as a result of "personal" experience (learning), a development that may be related to hippocampal expansion.

As part of this overall development, behavior not only became less "mechanical" and more individualistic (i.e., shaped by experience), but also more "emotional" (i.e., characterized by subjective arousal and drive states as positive and negative valences became experientially associated with specific stimuli). As we shall see, the amygdala apparently plays a major role in establishing these associations. This evolution of emotional responsiveness provided organisms with the means for richer and more adaptable responses to the natural environment, as well as the development of true social groups.[8] Table 8–1 provides a brief listing of several important functions served by emotions.

As the development of emotion allowed for more variable and complex drive states, the more primitive biological needs and impulses were still there and needed to be addressed. Thus, in addition to regulating internal drives, the organism needed to develop a means of regulating affective responses to external stimuli and the interactions or conflicts between the two. This was accomplished through an elaborate system of behavioral checks and balances involving diencephalic, endocrinological, limbic, and eventually cortical mechanisms. Such controls would have teleological significance not only for the individual, but also for maintaining order as social group interactions within the species became more complex. For example, while aggression and predatory behavior may be essential to meeting certain basic biological needs necessary for the survival of the individual (e.g., obtaining food) or even to maintaining the genetic viability of the species, unless controlled and directed, unrestricted aggressive or predatory behaviors might prove detrimental both for the individual and for the species.[9]

Finally, concurrent and conflicting emotions or drive states eventually would be supplemented by competition between more immediate versus long-range or even "abstract" plans or goals. As the cerebral cortex continued to develop, especially the frontal executive

Table 8–1. Role of Emotions[a]

1. Preparation of the body for action through the initiation of an appropriate autonomic response.
2. Provides a flexible and efficient means of responding to a given stimulus that is largely based on the individual's experience.
3. Provides drive or motivation to respond.
4. Facilitates the communication of one's mood state and response propensity (e.g., anger, aggression).
5. Facilitates social bonding, as well as communication.
6. Influences the cognitive evaluation of stimuli and resulting judgments.
7. Facilitates and enhances memory storage for specific events.
8. With the assistance of memory, provides persistent motivation and direction, even in the absence of a specific stimulus.
9. Triggers the recall of specific memories.

[a] Adapted from Rolls (1995).

Table 8–2. Proposed Functions of the "Limbic System"

Maintenance of homeostasis: Primarily reflects MacLean's (1949) emphasis on the limbic system as the "visceral brain," but may be expanded to include regulatory control over a broad range of behaviors that insure that one's basic biological needs are met.
Motivated and goal-oriented behaviors: Besides basic homeostatic mechanisms, reflects any affective valences (emotions) attached to real, imagined, recalled, or anticipated situations that result in a propensity to respond in a particular manner (drive state).
Survival of the individual: Requires responding not only to homeostatic demands, but also to external (e.g., "threatening") stimuli. Depending on the organism and situation this may elicit "fight or flight" responses with accompanying sympathetic arousal.
Survival of the species: Includes sexual activities, maternal and paternal behaviors, social bonding (including affective expressions and/or vocalizations),[11] and modulation of aggressive impulses (especially between members of the same social group).
Learning and memory: Although not included in Nieuwenhuys' definition, memory and emotions are intimately linked, establishing learned emotional associations that are critical for future drive states and survival.

system, certain advantages were provided if the organism could modify, control, or inhibit immediate emotional tendencies or basic urges in lieu of future or alternate, higher-order goals. Conversely, the drive (motivation) to achieve more abstract or distant goals required tapping into or recruiting more primitive brain mechanisms. All these latter changes coincided with the development of what Mesulam (1985) refers to as the "paralimbic" system, which could modify the expression of these behaviors depending on external circumstances.[10]

A definition of the limbic system offered by Nieuwenhuys reflects the probable functional role(s) of the "limbic system. He states, [the limbic system] "*is concerned with specific motivated or goal-oriented behaviors, directly aimed at the maintenance of homeostasis and at the survival of the individual (organism) and of the species*" (Nieuwenhuys, 1996, p. 574). The major functional implications of this definition are presented in Table 8–2.

The preceding paragraphs provide a brief overview of the possible roles of the limbic system in behavior. At the conclusion of this chapter, some of these functions will be discussed in greater detail, along with the possible interrelationships of various limbic structures and other neural systems. First, however, we will review the major anatomical and functional aspects of the individual structures within this system, including their interconnecting pathways. Figure 8–4 provides a highly schematic perspective of some of the major structures and pathways that will be discussed below. The reader should keep in mind that this limbic network is exceedingly complex and the functional role(s) of individual structures is still incompletely understood. Also, as noted above, there still is the more basic debate as to whether "the limbic system" is a viable construct, and if it is what structures constitute it. The reader is invited to draw his or her own conclusions.

NEUROANATOMY OF THE LIMBIC SYSTEM

Hypothalamus

Location and General Anatomy

The hypothalamus represents that portion of the diencephalon that lies below and slightly anterior to the main body of the thalamus proper. It essentially surrounds the lower aspect of the third ventricle (see Figures 6–1b,c,d; 6–2c,d). The anterior boundary of the hypothalamus

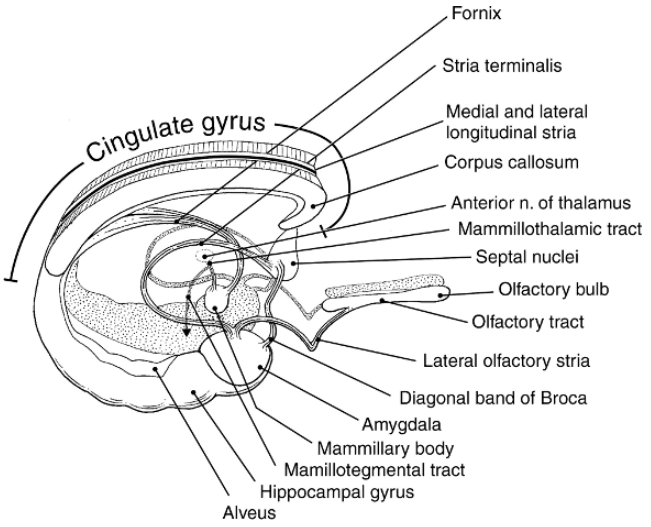


Figure 8–4. Schematic showing some of the major limbic structures and pathways.

is marked by the rostral edge of the optic chiasm ventrally and by the anterior commissure dorsally. The posterior extent of the hypothalamus generally is identified with the caudal or posterior extent of the mammillary bodies, which are part of the hypothalamus. Dorsally, the hypothalamus extends to the hypothalamic sulcus, a shallow indentation in the walls of the third ventricle. Despite its relatively small size (representing less than 0.5% of the total brain mass), the impact of the hypothalamus on behavior and normal bodily function is incalculable.

The hypothalamus is not a homogeneous structure, but rather a collection of numerous, discrete, bilateral nuclei. The hypothalamus commonly is divided into three anterior–posterior zones, a medial zone, and a lateral zone (Figure 8–5). The most **anterior zone** is represented by the nuclei above and immediately around the optic chiasm, among which are the medial and lateral preoptic nuclei and the supraoptic and suprachiasmatic nuclei. The **middle zone** is the area above the tuber cinereum and the infundibulum, which is the connection between the hypothalamus and the pituitary. Among the nuclei of note in this region are the dorsal and ventral medial nuclei and a good portion of the lateral nuclei, which will be discussed in greater detail below. The posterior **section** of the hypothalamus is the area that includes the mammillary bodies and the posterior hypothalamic nuclei. Finally, as mentioned, the hypothalamus also can be divided into **medial** and **lateral** zones. This latter division roughly is accomplished by a vertical line passing through the descending columns of the fornix. This separation will become meaningful as the effects of lesions in the ventromedial versus the lateral nuclei are discussed.

Afferent and Efferent Connections

Consistent with its role in governing multiple and diverse aspects of behavior, the hypothalamus has direct connections with the brainstem, the remaining diencephalic nuclei, many of the limbic structures, as well as the orbital frontal cortex. Structures that may not be directly connected to the hypothalamus have ample opportunity to influence, or be influenced by this center for emotional, autonomic, and endocrinological activity via indirect and neurochemical connections. For our present purposes, it will be sufficient to review only a few of the more well known pathways, but keep in mind there are additional hypothalamic

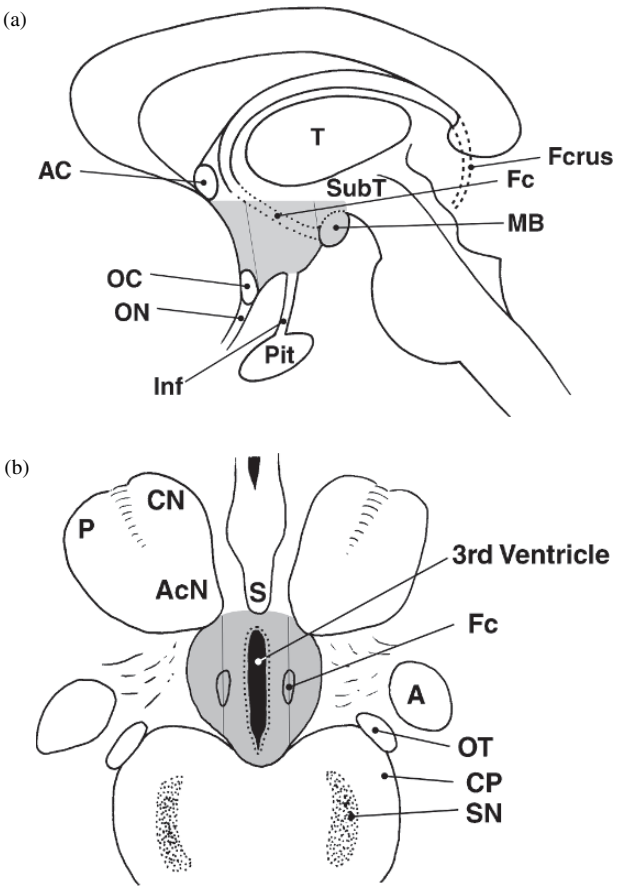


Figure 8–5. (a) The approximate boundaries of the anterior, middle, and posterior divisions, and (b) the medial and lateral zones of the hypothalamus (shaded). Hypothalamic cells immediately adjacent to the third ventricle represent a paraventricular zone. Abbreviations: A, amygdala; AC, anterior commissure; can, accumbens nucleus; CN, caudate nucleus; CP, cerebral peduncles; Fc, columns of the fornix; Fcrus, crus of fornix; Inf, infundibulum; MB, mammillary body; OC, optic chiasm; ON, optic nerve; OT, optic tract; P, putamen; Pit, pituitary gland; S, septal nuclei; SN, substantia nigra; SubT, subthalamus; T, thalamus.

connections beyond those discussed here. It is also important to remember that while some fiber tracts may be designated as primarily afferent or efferent, most probably contain reciprocal connections. This rule applies not only to hypothalamic connections, but also to most connections among the limbic structures.

As we have seen, one of the major pathways in Papez's circuit was the **fornix**. This very large and prominent subcortical fiber tract provides a major link from the hippocampal formation in the medial aspect of the temporal lobe to the mammillary bodies of the hypothalamus. As this tract loops around and over the dorsal thalamus and then recurves forward and ventrally to enter the mammillary bodies, it also gives off fibers to the anterior nucleus of the thalamus and to the septal regions. Two other major pathways into the hypothalamus from the temporal region are the **stria terminalis** and the **ventral amygdalofugal pathway**. These tracts appear to consist primarily of afferent fibers entering the hypothalamus (and preoptic areas) from the amygdala. Similar to the fornix, the stria terminalis loops around and

over the dorsolateral surface of the thalamus, whereas the ventral amygdalofugal pathway is more direct. This latter pathway merges with another very large fiber system that provides input into the hypothalamus, the **medial forebrain bundle** (MFB). However, the MFB is akin to a major freeway system, carrying two-way traffic connecting the orbital frontal cortex, including olfactory and septal areas, the lateral hypothalamus, and the brainstem. Through this system the hypothalamus not only receives input from these areas, but also contributes fibers that provide efferent feedback as well.

In addition to the efferent fibers the hypothalamus contributes to the medial forebrain bundle, there are two other hypothalamic pathways that are well known for their efferent connections from this nuclear complex. One is the **mammillothalamic tract,** which figures prominently in Papez's circuit. This tract originates from the medial portion of the mammillary bodies and terminates in the anterior nuclei of the thalamus (which, in turn, projects to the cingulate gyrus). Another is the **mammillotegmental tract,** which connects the hypothalamus with the brainstem, particularly with the mesencephalic (midbrain) reticular formation (see Figure 8–4). This latter tract starts out with the mammillothalamic tract as the **fasciculus mammillaris princeps,** or the *mammillary fasciculus*, but then branches caudally to the brainstem.

Another, more indirect route from the hypothalamus to the brainstem is represented by the **stria medullaris thalami**. As noted, the hypothalamus has reciprocal connections with the septal nuclei. The septal nuclei, in turn, give rise to the stria medullaris, which adheres to the dorsomedial surface of the thalamus on its way to the habenular nuclei on the posterior dorsal aspect of the thalamus. From the habenular nuclei, a tract (the **habenulointerpeduncular tract** or the *fasciculus retroflexus*) proceeds to the interpeduncular nuclei of the midbrain. Finally, although it likely also contains reciprocal ascending fibers, the **dorsal longitudinal fasciculus** provides efferent feedback to the periventricular and periaqueductal gray of the brainstem. Other direct and/or indirect connections are established between the hypothalamus and other brainstem nuclei (e.g., dorsal motor nuclei of the vagus nerve, the nucleus ambiguus, and the nucleus solitarius), as well as with the preganglionic neurons that lie in the lateral horn of the thoracic cord. Table 8–3 outlines some of these hypothalamic connections.

Table 8–3. Major Hypothalamic Tracts[a]

Tract	*Connections*
Medial forebrain bundle (MFB)	Orbital and midline frontal cortex, septal nuclei, midbrain tegmentum (A&E)
Fornix	Hippocampal complex (A)
Stria terminalis	Amygdala (A)
Ventral amygdalofugal pathway	Amygdala (via MFB) (A&E)
Mammillary peduncle	Midbrain reticular formation (A)
Mammillary fasciculus	
Mammillothalamic tract	Anterior nucleus of the thalamus (E)
Mammillotegmental tract	Midbrain reticular formation (E)
Dorsal longitudinal fasciculus	Periventricular and periaqueductal gray of brainstem (A&E)
Stria medullaris thalami	Habenular nucleus of the thalamus, via septal nuclei (E)
Hypothalamospinal tracts	Sympathetic nuclei in lateral horns of the spinal cord (E)

[a] While most pathways likely contain both afferent (A) and efferent (E) connections, the designations above refer to those tracts that are typically thought to be either primarily afferent (A), primarily efferent (E), or appear to have a balance of afferent and efferent fibers (A&E).

Among other possible functions, these various pathways provide a means for interconnecting the hypothalamus with the parasympathetic and sympathetic autonomic nervous systems, orbital and medial frontal cortices, limbic structures, as well as the brainstem reticular formation. The latter includes nuclei that are responsible for the production of neurotransmitters important in homeostatic activities (e.g., the raphe nuclei, a source of serotonin, which among its other roles is involved in sleep) and sympathetic arousal (e.g., locus coeruleus, a source of norepinephrine).[12] Thus, the hypothalamus not only plays a role in regulating autonomic arousal to internal emotional states and/or external, affectively provocative stimuli, but also allows for internal changes in homeostasis to influence arousal and affective drive states via its cortical–limbic and reticular connections.

The Hypothalamic–Pituitary Connection

While the various neuronal pathways discussed above enable the hypothalamus to be informed of the internal and external environment and to effect bodily changes to meet the demands imposed by these environmental changes, these connections do not represent the only means by which the hypothalamus can effect change. In addition to neural input, the hypothalamus is bathed in a very rich supply of capillary vessels. Many of the neurons in the hypothalamus have very sensitive chemoreceptive capacities that allow them to monitor and respond to changes in the blood. For example, by monitoring an increase in the osmotic pressure in the blood, the supraoptic nuclei can signal a release of antidiuretic hormones, which increase the reabsorption of water by the kidneys. The release of this agent (vasopressin) actually is accomplished by hypothalamic neurons that axonally transport this hormone to the posterior lobe (*neurohypophysis*) of the pituitary gland where it is absorbed in the blood. Disruption of this process (e.g., by a lesion to the anterior hypothalamus) could lead to diabetes insipidus. The relationship between the hypothalamus and the pituitary gland is exceedingly complex; however, for our present purposes, a relatively simplified account should suffice.

The pituitary gland lies in a recess at the base of the skull called the **sella turcica**. The pituitary gland is connected to the hypothalamus by the infundibulum or pituitary stalk (Figure 8–6). The pituitary gland can be divided into a smaller posterior portion, the **neurohypophysis**, and a larger anterior section, the **adenohypophysis** or the pituitary gland proper. The neurohypophysis is really a continuation of the diencephalon. The axons of the supraoptic and paraventricular hypothalamic nuclei continue into this posterior region of the pituitary via the **infundibulum** or the hypothalmohypophyseal tract and directly release hormones produced by the hypothalamic neurons into the bloodstream (see Table 8–4 for hypothalamic–pituitary hormones).. The two hormones thus released are **vasopressin** (discussed above) and **oxytocin**. The latter is important for uterine contractions and the production of milk. By contrast, the hypothalamus does not have direct, neural connections with the anterior lobe of the pituitary. It releases hormones that are transported by the vascular system to the adenohypophysis (anterior lobe) and where they stimulate the glandular cells in the anterior pituitary. The adenohypophysis in turn releases its own hormones. Among the hormones released by the anterior pituitary are:

- **ACTH** (adrenocorticotrophic hormone) which stimulates the adrenal gland)
- **TSH** (thyrotrophic hormone) which stimulates the thyroid gland
- **FSH** (follicle-stimulating hormone) which is important in the production of sex hormones
- **LH** (luetinizing hormone) which is important in reproduction
- **STH** (somatotrophic hormone) which stimulates growth
- **Prolactin** which stimulates lactation

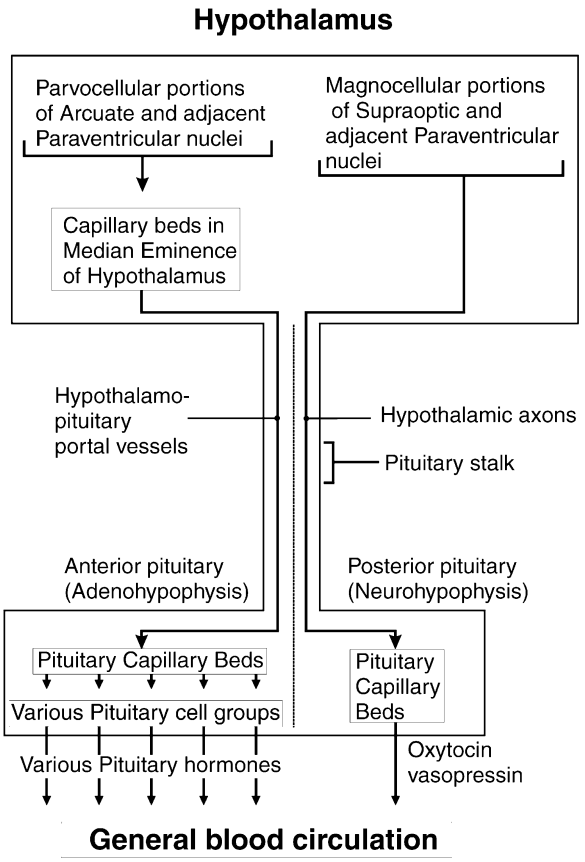


Figure 8–6. Hypothalamic–pituitary connections. The **posterior** portion of the pituitary (neurohypophysis) is innervated by hypothalamic neurons that transport the hypothalamic hormones (oxytocin and vasopressin) down their axons to be released into capillary beds of the posterior pituitary from where they enter the general circulation. By contrast, the capillary beds of the **anterior** pituitary (adenohypophysis) are supplied with hypothalamic hormones (either "releasing" or "inhibitory factors") via a blood portal system from capillary beds in the hypothalamus itself. Once released into the adenohypophysis, these hypothalamic hormones then stimulate pituitary cells to synthesize and secrete their own (pituitary) hormones, which then are released into the bloodstream. **Note**: Some hypothalamic hormones inhibit the production/secretion of pituitary hormones.

Thus, lesions to the hypothalamus can have profound effects on widespread organ systems via disruption of hormonal systems.

Functional Correlates

Trying to delineate the precise function(s) of any limbic or any other brain structure is difficult at best. This is especially true of the hypothalamus. Located deep within the brain, it is not readily accessible to study. More importantly perhaps, as has been pointed out, it is not a homogeneous structure but rather a collection of many individual nuclei with extensive, often overlapping direct and indirect connections to most brain systems and with indirect effects on distant organ systems via neurochemical influences. Most of our information about the hypothalamus has come from experimentation with animals (lesion or stimulation studies) or from analyzing the behavioral effects of naturally occurring lesions

Table 8–4. Hypothalamic–Pituitary Hormones

Anterior Pituitary: Adenohypophysis

Pituitary Hormone	*Hypothalamic Regulating Hormone*[a]	*Main Functions*
Growth hormone (GH)	Growth hormone-releasing hormone Somatostatin (inhibits release of GH)	Causes liver and other cells to secrete IGF-I (a growth promoting hormone); Stimulates protein synthesis
Thyroid stimulating H. (TSH)	Thyrotropin releasing H.	Prompts thyroid to secrete thyroxine and triidothyronine, resulting in increasing the metabolic rate
Adenocorticotropic H. (ACTH)	Corticotropin-releasing H.	Causes adrenal cortex to release cortisol, which mobilizes glucose, promotes protein catabolism, prepares body to cope with stress
Prolactin	Prolactin releasing H. Dopamine (inhibits release of prolactin)	Stimulates development of mammary glands, milk production
Follicle stimulating H. (FSH)	Gonadotropin releasing H.	Promotes secretion of estrogen, progesterone in females and testosterone in males; ovulation and spermatogenesis
Luteinizing H. (LH)	Same as for FSH	Similar to FSH; ovarian, sperm maturation

Posterior Pituitary: Neurohypophysis

Hypothalamic Hormone	*Hypothalamic Source*[b]	*Main Functions*
Oxytocin	Magnocellular hypothalamic nuclei (primarily supraoptic and anterior paraventricular nuclei)	Uterine contractions during childbirth; stimulates milk production
Vasopressin (ADH)	Same as for oxytocin	In response to increased salt concentrations in blood, increased vasopressin production causes kidneys to increase H_2O retention; in response to low blood volume/pressure, causes arterioles to constrict, increasing blood pressure.

[a] Most hypothalamic releasing hormones come from the arcuate nuclei and adjacent paraventricular nuclei.
[b] Unlike the hormones released to the adenohypophysis, these travel in vesicles down hypothalamic axons where they are released directly into the capillary beds of the neurohypophysis and from there directly into general circulation.

in humans. Among the problems with the former method are that data derived from animal subjects not always may be directly translatable to humans, and even under experimental paradigms one is never certain that the effects of the surgical lesion is confined to the particular nucleus and/or connecting fibers. Adjacent fiber systems and/or neighboring neurons also may be affected.[13] Similarly, stimulation of an area may not represent its normal physiologic operation and/or may involve other structures that are either physically adjacent or connected by neural networks. Additionally, the behaviors that we generally observe are highly complex, and therefore the same brain region may contribute to various behavioral patterns in different ways. In humans, naturally occurring lesions seldom respect anatomical boundaries, and even when they appear to be localized to a discrete region we are still faced with the same limitations described above. Actually, these problems are not peculiar to the study of the hypothalamus and generally apply to lesion studies throughout the CNS. With these caveats in mind, it may be useful to list a few of the syndromes associated with hypothalamic lesions in humans and to review a few of the experimental findings that offer some tentative hypotheses regarding the functional significance of the hypothalamus.

Lesions in the anterior portion of the hypothalamus are likely to result in hyperthermia (failure of the body's cooling mechanisms), while more posterior lesions generally are responsible for hypothermia (a failure of heat conservation). As has been mentioned, lesions involving the supraoptic and/or paraventricular nuclei can result in diabetes insipidus or other electrolyte disturbances. Anterolateral lesions are more likely to result in disturbances of the parasympathetic ANS, while the sympathetic division more commonly is affected by posteromedial lesions. Chronic overeating and obesity, along with inadequate sexual development, has been associated with lesions in the ventromedial aspect of the hypothalamus (see below). Other disturbances in sexual or reproductive functions, as well as sleep disorders, have been associated with various hypothalamic lesions. Acromegaly (*gigantism*), Cushing's syndrome (obesity of abdomen, shoulders, neck and face, along with other metabolic and endocrine disturbances), and hypopituitarism (dwarfism) all have been associated with tumors of the hypothalamus and pituitary gland. Among the more common tumors in this area are acidophil cell adenomas, chromophobe adenomas, and craniopharyngiomas.

Because these and other tumors that affect the hypothalamus and/or the pituitary gland grow in the area of the optic chiasm and optic tracts, visual disturbances, with or without accompanying headaches, are not uncommon. Emotional changes, from rage to increased sexual activity to apathy, also have been attributed to hypothalamic lesions. Less commonly, amnestic disturbances have been linked with discrete lesions that appeared to be centered in the hypothalamic regions (e.g., mammillary bodies, columns of the fornix, or the mammillothalamic tract); however, these regions frequently have been implicated in amnestic disorders with more diffuse lesions, such as in Korsakoff's syndrome.

Numerous, classic experiments in animals have revealed that lesions restricted to lateral hypothalamic nuclei will result in an anorexic syndrome [loss of eating (*aphagia*) and drinking (*adipsia*) responses] which may be so severe that the animal may die if not force-fed and hydrated. Conversely, lesions placed in the ventromedial nuclei of the hypothalamus typically will result in an animal that tends to overeat and becomes obese. The results of stimulation studies show the opposite effects of ablation studies. In these studies, stimulation of the ventromedial nuclei typically produces cessation of eating, while stimulation of the lateral nuclei leads to eating behavior even when the animal appears satiated.

Disturbances of eating and drinking are not the only behaviors associated with these sites. In addition to becoming obese and hypoactive, animals with lesions in the ventromedial nuclei typically will demonstrate aggressive and attack behaviors with minimal provocation

(e.g., simply the presence of the experimenter).[14] On the other hand, stimulation in the region of the ventromedial nuclei can have a quieting or calming effect. By contrast, lesions of the lateral hypothalamic (as well as the posterior nuclei) nuclei often have a quieting influence, whereas stimulation is more likely to elicit attack behavior. Perhaps contrary to what might be anticipated, stimulation in the region of the lateral hypothalamic nuclei (actually in many parts of the limbic system, including the medial forebrain bundle) seems to be "pleasurable" to the animal, since it will work tirelessly to deliver stimulation to this area. In contrast, stimulation of the ventromedial nuclei appears to have aversive properties, as the animal will actively attempt to avoid such stimulation. For reviews of these phenomena, see Olds and Forbes (1981), Isaacson (1982), and Joseph (1990, pp. 92–98).

Behavioral disturbances following hypothalamic lesions are not necessarily confined to those described above or to the sites listed. Neither are the behavioral manifestations as simple and straightforward as might be suggested by the above descriptions. The expression of such behaviors often changes over time and may vary depending on environmental or other physiological circumstances (Isaacson, 1982, Chapter 2). Comparable behavioral disturbances following hypothalamic lesions also occasionally can be found in human subjects as a result of injury or disease. The point of the above descriptions is to demonstrate the role of the hypothalamus in the expression of very primitive and basic responses of the organism to its environment. In fact, rage-like behavior can be exhibited by some animals (most commonly demonstrated in cats) deprived of all brain tissue except for the hypothalamus and brainstem; this phenomenon is referred to as "sham rage," since it is thought that the animal could not experience a normal rage reaction in the absence of these higher brain centers.

In summary, the hypothalamus would appear to be directly involved in a wide range of behaviors that are critical for both the survival of the individual and for the survival of the species. Although they are not mutually exclusive, for the sake of simplicity, some of the activities in which the hypothalamic nuclei appear to play a significant role include:

1. Maintaining a homeostatic, internal environment (e.g., oxygen, temperature, and water regulation; circadian rhythms; food intake and utilization).
2. The monitoring and control of the endocrine system (e.g., growth, protein synthesis, sexual responsiveness, and reproduction).
3. Control of the autonomic nervous system, balancing the actions of the sympathetic and parasympathetic branches to meet the demands of both the internal and external environment (e.g., stress or threat).
4. Emotional expression: While the subjective experience of emotions and the selection of an emotional response that is appropriate to external stimuli requires the cooperation of "higher neural networks" (e.g., cortex and other limbic structures), the hypothalamus appears capable of generating basic affective or drive states.
5. Arousal: It appears likely that arousal involves both ascending (external sensory stimulation → reticular system → hypothalamus) and descending (cortical activity → hypothalamus → reticular formation) capabilities. In addition, cortical input is crucial for the mediation of conscious arousal and attention.
6. Memory: This is probably the least well-documented aspect of possible hypothalamic function. While lesions of certain nuclei (particularly the mammillary bodies) and their nuclear connections (e.g., mammillothalamic tracts) have been associated with disturbances of learning and memory (e.g., Korsakoff's syndrome), the critical lesion(s) producing disturbances of memory are still a subject of some debate (Verfaellie & Cermak, 1997; Victor, Adams, & Collins, 1989).

Amygdala

Location and General Anatomy

When viewing the ventral surface of the brain, a small eminence approximately 12 to 15 mm in length is noted on the anteriomedial surface of the parahippocampal gyrus. This protrusion is known as the uncus and marks the general location of the underlying amygdala (see Figures 5–4b; 6–1b–e; 6–2a–c). The amygdala, like the hypothalamus, is not a homogeneous structure but rather consists of a number of smaller nuclear groups. For most practical purposes, it can be divided into three major components: the *corticomedial, central,* and the *basolateral* groups. As we saw in Chapter 5, the corticomedial group has strong connections with the olfactory system. The smaller central group has been closely linked to the hypothalamus and brainstem and is thought to be important for generating autonomic responses. As we shall see, the large basolateral group's extensive connections with the cerebral cortex and the hippocampus appears to reflect its role in attaching emotional significance to external stimuli and learning.

Afferent and Efferent Connections

The amygdaloid complex is subject to extensive cortical and subcortical influences. These include afferent and/or efferent connections with:

1. Olfactory system, including basal–orbital frontal and anterior–medial temporal allocortical areas
2. Other basal–medial nuclei
3. Ventral striatum
4. Hypothalamus
5. Brainstem
6. Thalamus
7. Allocortex and juxta-allocortex
8. Neocortex

In contrast to the corticomedial group's large input from the lateral olfactory stria, the basolateral group does not receive direct input from the olfactory system (it may receive indirect olfactory information from the surrounding primary olfactory cortices).

The amygdala has fairly extensive interconnections (afferent and efferent) with a number of basomedial frontal areas. These include the region in the vicinity of the anterior commissure known as the **substantia innominata** (which, in turn, includes the **nucleus basalis of Meynert**), the **septal nuclei**, the **bed nuclei of the stria terminalis**, and the **nuclei of the diagonal band of Broca**. The fiber pathways that connect the amygdala to these areas include a shorter, more direct route: the **ventral amygdalofugal pathway** and the **stria terminalis**, a long, looping fiber tract that follows the curvature of the lateral ventricles, dorsally over the thalamus (see Figures 6–1a,b; 8–4).

Connections between the amygdala and the basal ganglia are thought to be primarily efferent. These projections generally are to the ventral or "limbic" portions of the striatum, including the nucleus accumbens (see Figure 6–1a). These latter connections constitute a major part of the "limbic feedback loop" discussed in Chapter 6, and would appear to have significant implications for a variety of psychiatric syndromes (Heimer, 2003).

There also are extensive reciprocal connections between the nuclei of the amygdala (particularly the central and corticomedial groups) and the hypothalamus and brainstem. The majority of these connections are via the ventral amygdalofugal pathway. The amygdalofugal inputs extend from the hypothalamus to nuclei of the midbrain, pons,

and medulla, with some fibers continuing on to the spinal cord. These efferent pathways are thought to be important in generating appropriate autonomic or visceral responses to emotionally charged situations.

Thalamic input to the amygdala (primarily to the central group) comes largely from the midline nuclei, whereas amygdalothalamic connections are largely from the basolateral group and are projected mainly to the dorsomedial nucleus. It should be recalled that the dorsomedial nucleus, in turn, projects back to the prefrontal cortices.

As previously noted, the corticomedial amygdala receives input from the more "primitive" primary olfactory cortices along the more rostral, medial portions of the temporal lobe. In addition, the juxta-allocortex (from the parahippocampal and cingulate gyrus) appear to project primarily to the more medial or basal portions of the basolateral group. On the output side, there are substantial connections from the amygdaloid complex to the entorhinal cortex and from there to most parts of the hippocampal formation (except perhaps for the dentate gyrus). While the amygdala receives some afferent input from the hippocampal formation, it would appear to be considerably less than the efferent fibers it sends back to this region.

Finally, the more lateral portions of this group appear to receive input from frontal and posterior association areas of the neocortex, as well as the insula. These connections provide the amygdala access to both frontal control and executive functions, as well as to "processed" sensory information. There also are reciprocal connections from the amygdala back to the cortex, although perhaps not always to exactly the same areas from which they came. Most, if not all, areas of the frontal lobes appear to receive extensive efferent input from the amygdala. These connections would seem to ensure that the amygdala plays a significant role in both frontal and limbic feedback loops. As discussed in Chapter 6, these cortical loops have been implicated in mediating basic drives and goal-oriented behaviors, both of which often depend on emotional arousal.

In addition to these various connections with other outside structures, the various nuclear groups within the amygdala also have their own internal connections or communication networks. Thus, while the basolateral group does not have direct access to the olfactory system, it receives input from the corticomedial group. There also are reciprocal connections between the two amygdaloid nuclear complexes by way of the anterior commissure.[15]

Functional Correlates

The short answer to the question of the functional significance of the amygdala is that it appears to play an important role in the **attachment and/or recognition of emotional valences** associated with our sensory experiences. At least this is believed to be one of its major roles (Everitt & Robbins, 1992; Gaffan, 1992; LeDoux, 1989; Rolls, 1995). Before proceeding, however, the reader's attention is directed to a book, *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction* (Aggleton, 1992). This book is nearly 600 pages in length. Works of comparable size are available on the hypothalamus, cingulate gyrus, and the hippocampus (Cohen, 1995; Haymaker, Anderson, & Nauta, 1969; Isaacson & Pribram, 1986; Kato, 1995; O'Keefe & Nadel, 1978; Reichlin, Baldessarini, & Martin, 1978; Vogt & Gabriel, 1993). These references are pointed out merely to emphasize the complexity involved in trying to comprehend the behavioral correlates of any of these structures, much less the interactions of all the discrete behavioral systems from the cortex to the brainstem. It also is offered as a forewarning to the reader that the brief summary presented here in no way portends to offer anything near a complete explanation of the role of the amygdala in behavior. The same caveat obviously applies to the other limbic structures to be discussed.

Before attempting to review a few of the more common findings or theories regarding the possible functional significance of the amygdala, it also is helpful to remind ourselves of the inherent limitations in such a task. As was the case with the hypothalamus, the amygdala is not a homologous structure, but rather has multiple nuclei, each of which has its own unique connections and most likely its own behavioral correlates. While there is some commonality of findings in the literature, significant differences may be found depending on various factors. Such factors include the size and exact location of the lesion (or parameters of stimulation), the environmental context and/or time period in which the behavior is observed, and even the species that are the subject of study.

At about the same time that Papez was describing a subcortical circuit to help explain the neuroanatomical substrates of emotion, Kluver and Bucy (1939) were investigating the effects of bitemporal lesions in monkeys. They described the following behavioral syndrome that still bears their names. One of the more striking things they noted was that although these animals appeared to have no significant problems with visual acuity or visual discrimination per se, they nonetheless appeared to have a type of visual agnosia for objects, which they characterized as a *psychic blindness*. This behavior was manifested in two ways. First, whereas normal, intact primates tend to rely heavily on visual feedback to explore and identify things in their environment (including small objects), these lesioned animals tended to repeatedly explore objects by smelling or by placing them in their mouths (termed, hyperorality). Second, previously "feared" objects, when introduced into view, no longer elicited avoidant or aversive responses in these animals. This seemed to be true whether the "object" in question was one that appeared to be genetically programmed to elicit such a response (e.g., a snake) or one that may have been "learned" through experience (e.g., the net or glove used to catch or handle the animal). In these bitemporal-lesioned animals, the normal "fear response" was absent. These animals tended to "explore" (touch, handle, orally incorporate) any and all objects within their environment. This behavior (termed *hypermetamorphosis*) occurred regardless of the stimulus's previous capacity to elicit a withdrawal or fear response.

In addition to the loss of a normal fear response to visual stimuli (e.g., the sight of an unfamiliar human), Kluver and Bucy found that their bilaterally lesioned monkeys not only would tolerate physical contact with humans, but also actively facilitate such contacts (an extremely atypical response for rhesus monkeys). In addition to a loss of fear, these animals evidenced a marked reduction in normal aggressiveness, even when another animal attacked them. Finally, another behavioral abnormality demonstrated by these animals was an increase in sexual interest or sexual responsiveness, which was inferred by their increase in autosexual, homosexual, as well as heterosexual activities (*hypersexuality*).

While the original lesions produced by Kluver and Bucy (1939) were extensive, incorporating much of the lateral and medial temporal cortex as well as the hippocampus, subsequent studies have demonstrated that many of the observed changes in emotional and social behavior could be produced by lesions limited to the amygdala. For example, years later, Downer (1961) sectioned both the interhemispheric commissures and the optic chiasm in monkeys (see also Chapter 9 under "Disconnection Syndromes"), thus ensuring that the input to each eye remained isolated to the same hemisphere. Subsequent lesions then were confined to the amygdala in these animals, but only on one side. The amygdala on the other side was left intact. Such animals would show a normal fear response to appropriate visual stimuli when viewed through the eye on the side of the intact amygdala, but no such response when only using the eye ipsilateral to the amygdalectomy. In addition to amygdalectomies resulting in an abolished or an attenuated fear response to a previously conditioned stimulus, such lesions also have been shown to interfere with the subsequent postsurgical development of such conditioned fear responses (Blanchard & Blanchard, 1972;

Davis, 1992; LeDoux, Cicchetti, Xagoraris, & Romanski, 1990). Thus, the amygdala appears to be important not only for establishing associations between stimuli and associated reinforcements (i.e., affective contingencies), but also for prompting behavioral responses to those stimuli based on previously established affective associations (Gray, 1995: Rolls, 1995). In a related finding, it was demonstrated that following lesions of the amygdala in humans, the ability to recognize emotional expressions in faces was compromised, while facial recognition per se remained intact (Adolphs, Tranel, Damasio, & Damasio, 1994, 1995).

In addition to reducing the potential for conditioned fear responses, many of the other behavioral disturbances observed in the Kluver–Bucy syndrome are not limited to monkeys (Kling & Brothers, 1992). For example, reduced aggressiveness or an increase in docility also can be found following lesions confined to the amygdaloid nuclear complex in rats, cats, monkeys, and humans. In fact, based on the findings of Kluver and Bucy and others, surgical lesions of the amygdala have been used as a means of reducing aggressive or assaultive behavior in humans (Terzian & Ore, 1955; Narabayashi et al., 1963; Aggleton, 1992). Although infrequently employed now, such procedures, known as *psychosurgery* (surgery whose primary purpose is to effect changes in behavior or affect), typically involve(d) lesioning of limbic structures, pathways that interconnect limbic structures, or disconnection of the frontal lobes from the limbic system (frontal leucotomies) (Diering & Bell, 1991; Valenstein, 1977).

While lesions of the amygdala tend to have a "calming" effect for most animals, possibly by raising the threshold for affective responding ("emotional blunting"), stimulation generally has the opposite effect. Depending on a number of variables, including the specific site of the stimulation, the species involved, and the environmental circumstances, stimulation may lead to (1) a cessation of ongoing activities and increased alertness or watchfulness, (2) fearlessness or escape behaviors, and/or (3) aggressiveness or attack behaviors (Ursin & Kaada, 1960; Egger & Flynn, 1963; Zbrozyna, 1972). Often such stimulation is accompanied by increased sympathetic activity. It is interesting to note that violent behaviors associated with seizures are extremely rare,[16] although occasionally reported (Ferguson, Rayport, & Corrie, 1986; Mark & Ervin, 1970). On the other hand, subjective feelings of fear, anxiety, or impending doom are not uncommon auras in patients with seizures, particularly those associated with temporal lobe foci (Gloor, 1972; Spiers, Schomer, Blume, & Mesulam, 1985).[17]

Finally, there has been an ongoing debate within psychiatry for at least the past 30 years as to the possible relationship between seizure disorders, specifically those whose foci are in the temporal lobe (thus whose impact likely would include the amygdala), and certain behavioral or psychiatric disturbances. Most commonly, it has been argued that when compared with baseline populations or to patients with seizure disorders where the seizure focus is *non-temporal,* patients with right "temporal lobe epilepsy" tend to have a higher incidence of manic–depressive-type disorders, whereas left temporal focal lesions increase the probability of schizophreniform-type psychoses. It also has been argued that the presence of chronic seizure disorders with temporal lobe foci increase the likelihood of various behavioral or "personality" features such as hyperreligiosity or increased preoccupation with moral issues, decreased sexual interest, increased irritability, excessive rumination, obsessiveness, and/or cognitive–emotional rigidity. While on the whole there does appear to be some relationship between certain types of seizure disorders, increased incidence of psychopathology, and interictal behavior,[18] this entire area of research remains controversial (Bear & Fedio, 1977; Reynolds & Trimble, 1981; Sherwin, 1981; Bear et al., 1982; Hermann and Whitman, 1984; Spiers et al., 1985; Post, 1986; Adamec & Stark-Adamec, 1986; Stark-Adamec & Adamec, 1986).

Septal Area

Location and General Anatomy

The septal region is located in the posterior, inferior, and medial portion of the frontal lobes, immediately rostral to the anterior commissure and just below the rostrum of the corpus callosum (see Figure 6–1a; 6–2c–e). This area represents a somewhat poorly defined set of nuclei. Hence, in humans and other higher-order primates, the terms septal *area* or septal *region* often is substituted and refers to this general anatomical location without further subdivision into specific individual nuclei [although a more medial and a lateral division are often identified (Andy & Stephen, 1968)]. **Note:** Care should be taken to avoid confusing the septal area or nuclei with the septum pellucidum. The septum pellucidum consists of two thin sheaths of tissue that provide the medial separation of the anterior horns of the lateral ventricles and do not contain any nerve cells.

Afferent and Efferent Connections

At an earlier point in the evolution of the central nervous system, the septal nuclei probably were contiguous, or nearly so, with the posterior portion of the hippocampal gyrus. As the telencephalon (cerebral cortex) gradually expanded, these two structures anatomically were separated and came to occupy their present relative positions in the primate brain. However, several long C-shaped pathways carrying fibers to and from the septal area still reflect the evolutionary and functional relationships of these two structures. As previously noted, one of these C-shaped pathways is the **stria terminalis**, a fiber tract curving around and over the dorsolateral aspect of the thalamus carrying both afferent and efferent fibers between the amygdala and septal areas. The other, the **ventral amygdalofugal pathway,** establishes a more direct route between the amygdala and the septal area. Another major C-shaped pathway that also already has been discussed is the **fornix**. While it is primarily considered an efferent pathway from the hippocampal formation to the mammillary bodies, it also gives off collaterals (known as *precommissural fibers*) to the septal nuclei as it begins its descent to the hypothalamus. The fornix also carries afferent fibers from the septal area back to the thalamus and hippocampus.

The hippocampal gyrus also appears to have another dorsal connection with the septal region. There is a small gray band of tissue, the **indusium griseum**, which runs from the hippocampal region anteriorly along the dorsal surface of the corpus callosum (between the corpus callosum and the cingulate gyrus). Embedded within this band of neural tissue are two fiber tracts, the **medial** and lateral **longitudinal striae** (of Lancisi), which also make connections with the septal region. There is one final C-shaped or curved dorsal pathway that also was mentioned in conjunction with the hypothalamus, the **stria medullaris thalami**. This pathway, which is found on the dorsomedial surface of the thalamus, appears to be primarily an efferent fiber tract from the septal nuclei to the habenular (epithalamus) and other midline thalamic nuclei. From the habenular nuclei (which, in turn, also receive input from the hypothalamus and the basal ganglia) projections are carried to the interpeduncular nuclei of the brainstem (via the fasciculus retroflexus) and on to other brainstem nuclei that are important for mediating autonomic arousal.

In addition to the long, curved dorsal pathways discussed above, other, more ventral pathways interconnect the septal nuclei with the basal frontal cortex, amygdala, hypothalamus, and brainstem. In addition to the amygdalofugal pathway, two other previously noted fiber tracts provide ventral connections between the septal nuclei and the surrounding basilar frontal cortex, hypothalamus, and brainstem. These are the **diagonal band of Broca** and the **medial forebrain bundle** (MFB). As a result of connections to these cortical, subcortical, and brainstem sites, the septal area, like the amygdala, would appear to have access to

executive, emotional, sensory, and visceral information. Thus, as was true of the hypothalamus and the amygdala, the septal nuclei have substantial connections not only with "limbic" structures but also with the frontal lobes, the thalamus, and the brainstem.

Functional Correlates

If one reviews the literature on lesion and stimulation studies of the septal nuclei in mammals, it would appear that in many respects the results are directly opposite those found in the amygdala (DeFrance, 1976). One of the more dramatic phenomena to be witnessed in a physiological psychology laboratory is the sight of a 180-pound graduate student being chased up a chair by a white rat that may barely go over one pound. For anyone who may not be familiar with them, white laboratory rats, as opposed to their free-roaming ancestors, are typically rather docile creatures (scientists who routinely work with them generally prefer it that way). However, if the septal nuclei of one of these animals are destroyed by stereotaxic lesions, a major behavioral change may be seen. Left undisturbed, the rat may just sit there, appearing perfectly normal. However, given the proper provocation, sometimes as minimal as blowing on its fur or gently tapping on its back with a pencil, it may launch a full-fledged attack on the source of this "assault."

While this response to septal lesions is not limited to rats, neither is it invariably seen in all species. Even when initially present, the full effect is typically temporary and generally accommodates over time or with increased handling (Brady & Nauta, 1953; Ahmad & Harvey, 1968; Paxinos, 1975). In fact, most animals eventually will show a decreased tendency to respond aggressively, but this may be in part dependent on the specific nature of the stimulation or provocation. However, even this initial increased aggressiveness may be blocked by lesions of the amygdala, which as we have seen tend to reduce aggressiveness. Conversely, stimulation of the septal area has been shown to inhibit or abort aggressive behavior (Rubenstein & Delgado, 1963; Siegel & Skog, 1970).

In contrast to the social withdrawal that often can be seen with amygdala lesions, septal lesions can lead to what appears to be an increased need for social contact. At times, this will take the form of seeking physical contact or closeness with either inanimate objects or with representatives of other species that are normally actively avoided (Meyer, Ruth, & Lavond, 1978). In humans, such behavior occasionally has been described as *social stickiness* where, following lesions that encroach on the septal area, an individual may have difficulty responding to normal cues to maintain appropriate boundaries in social interactions (Joseph, 1990). Such behavior also might appear to be inconsistent with the aggressive tendency noted above, except if both are viewed as a failure to inhibit or modulate emotional/social behavioral responses. Such an interpretation also might be consistent with the observation that while passive–avoidance learning is typically impaired, active–avoidance learning is either unaffected or may be slightly enhanced. However, given the range and variability of behavioral responses both within and between species that can be found following lesions in the septal area, caution is advised against attributing any unimodal function, including response inhibition, to the septal nuclei.

In addition to inhibiting aggression, stimulation of the septal region in humans has been reported as "pleasurable" (Olds, 1958; Heath, 1959). Given a choice, the septal region is one area where animals may work to provide continuing stimulation, although again this effect may vary depending on the exact placement of the stimulating electrode. It is possible that such stimulation results in the release of endogenous opioid peptides from amygdaloid–hypothalamic areas. Stimulation of the septal region at times also will produce certain autonomic changes, a finding consistent with its anatomical connections to the hypothalamus and brainstem.

Hippocampal Formation

Location and General Anatomy

When viewing the ventral surface of the brain, one can identify the gyrus that lies on the most medial aspect of the temporal lobe. This area, separated from the more lateral occipitotemporal or fusiform gyrus by the collateral sulcus, is the **parahippocampal gyrus** (see Figure 5–4b). It even appears visually distinct from the adjacent cortical gyri in the fixed brain, having a somewhat broader and flatter appearance. The hippocampal formation is located within the parahippocampal gyrus. While not visible on the ventral surface, the hippocampal formation is very distinct on both coronal and horizontal sections (see Figures 6–1e–g; 6–2b–g). It can be seen as an enfolding of tissue on the medial surface of the parahippocampal gyrus along the hippocampal sulcus lying on the floor of the temporal horns of the lateral ventricles. Viewed in cross section, it has a spiral-type appearance, not unlike what is seen in a cinnamon roll. The *hippocampal formation* is divided into several anatomical subdivisions: the **subiculum**, the **dentate** gyrus, and the **hippocampus proper** (Figure 8–7).[19] The hippocampus proper derives its name from its resemblance to the shape of a seahorse [it is also referred to as *Ammon's* horn(from the Egyptian god with ram's horns) for the same reason], although as can be seen the dentate gyrus and the subiculum also take on a similar curved appearance. The hippocampus proper traditionally is divided into four contiguous sections based on slight differences in cellular structures. These sections, as seen in Figure 8–7, are referred to as CA1 through CA4 (with "CA" being an abbreviation for "cornu ammonis" or Ammon's horn). In what appears to be a remnant of the expansion

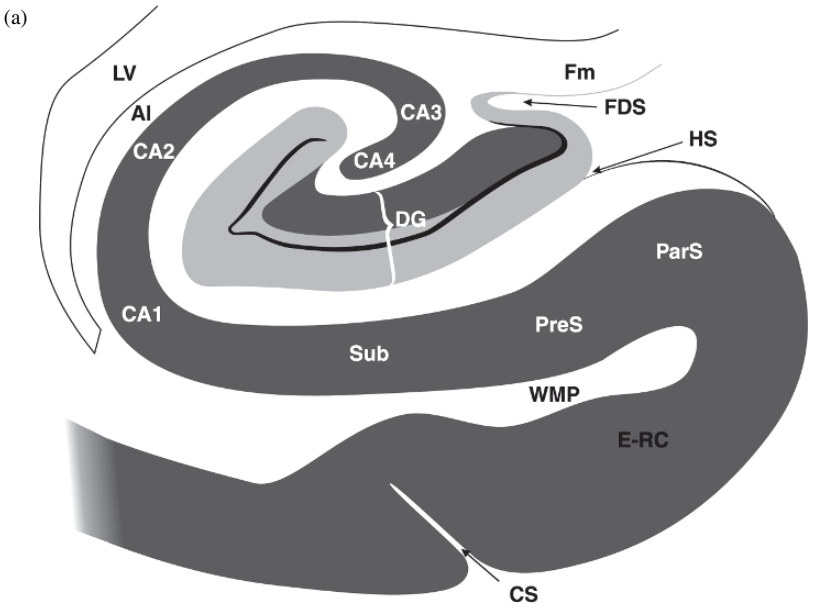


Figure 8–7. (a) Cross section of the hippocampal formation and parahippocampal gyrus. (b) The phylogenetic and ontogenetic development of the hippocampal formation as a result of the enfolding of the medial temporal cortex (adapted from P. Gloor, 1997). (c) through (e) The hippocampal formation in progressively deeper sagittal MRI images, and (f) on an axial cut at the level of the midbrain. Abbreviations: Al, alveus; CA1 → CA4, contiguous sections of the hippocampus proper; CS, collateral sulcus; DG, dentate gyrus; E-RC, entorhinal cortex; FDS, fimbriodentate sulcus; Fm, fimbria; HS, hippocampal sulcus; LV_{IH}, lateral ventricle, inferior horn PreS, presubiculum; ParS, parasubiculum; Sub, subiculum; WMP, white matter pathway.

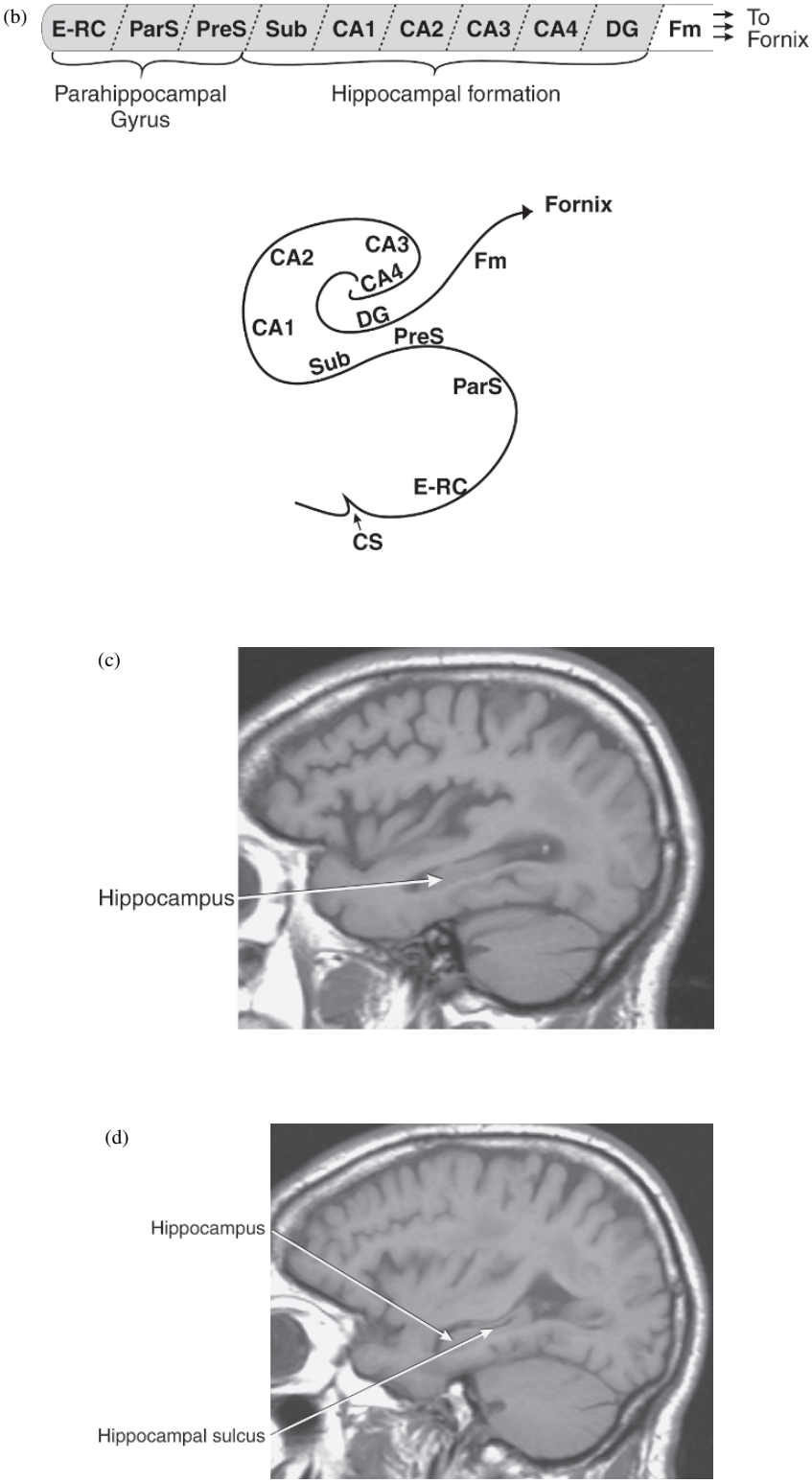


Figure 8–7. *(Continued)*

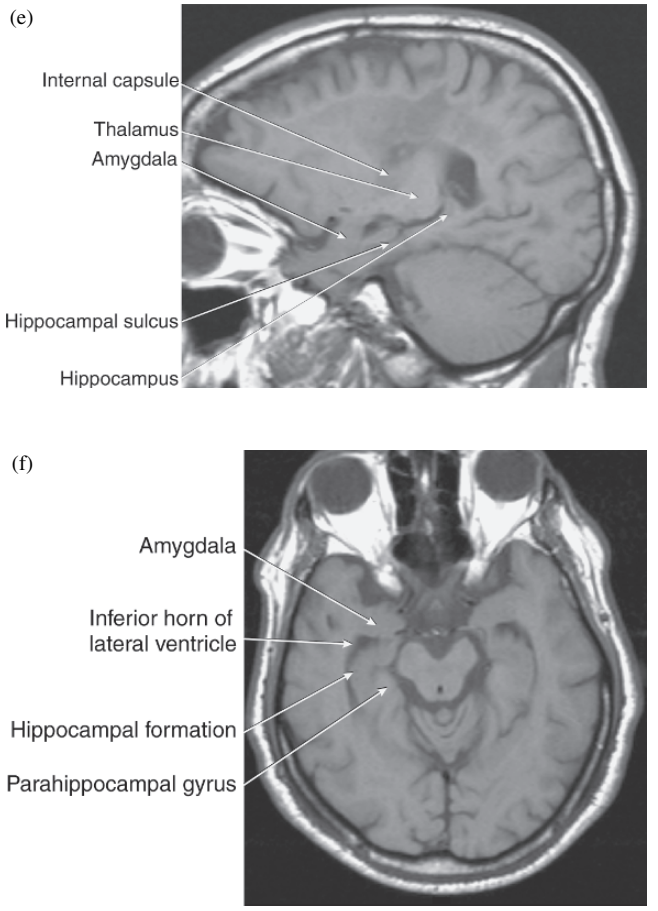


Figure 8–7. *(Continued)*

of the cortex around the diencephalic core, the most caudal portion of the hippocampal formation is continuous with the indusium griseum, which is a thin band of gray matter that lies over the medial surface of the corpus callosum. It extends from the hippocampus to the region of the septal nuclei. Finally, unlike the neocortex, which consists of six layers (see Chapter 9), the hippocampal formation is classified as **allocortex**, which consists of only three layers. The presubiculum and parasubiculum constitute a transitional zone between the hippocampal formation (allocortex) and the entorhinal (neocortical) tissue.

Afferent and Efferent Connections

Although some of the following will be a repetition of pathways and connections discussed elsewhere in this chapter, the major afferent and efferent fiber tracts interconnecting the hippocampal formation with other brain centers will be reviewed from the focal point of the hippocampus. Generally speaking, the connections of the hippocampal formation can be divided into three broad categories: cortical, subcortical (including the brainstem), and the contralateral hippocampus. While the internal connections of the hippocampal formation tend to be unidirectional, most of its external connections are reciprocal, conveying both efferent and afferent information from cortical and subcortical structures.

Cortical Connections

Most cortical projections eventually reach the hippocampal formation, primarily via the perforant pathway (see Figure 8–8) after having first synapsed in the entorhinal cortex (Brodmann's area 28). However, some cortical inputs may first synapse in the perirhinal areas prior to entering the entorhinal cortex, while others may proceed directly to the subiculum or presubiculum (Nieuwenhuys, Voogd, & van Huijzen, 1988). The hippocampal formation is believed to receive input from all secondary and tertiary cortices. This includes the juxta-allocortices of the cingulate, insular, and orbitofrontal areas, as well as the unimodal and multimodal association area of the frontal, parietal, temporal, and occipital lobes (see Figure 8–9). One prominent corticohippocampal connection is the cingulum, a long fiber pathway that travels with the cingulate gyrus (e.g., Figures 6–1f, 6–2f). Synapsing in the entorhinal cortex, the cingulum carries information not only from the cingulate gyrus, but probably ultimately from many other parts of the cortex that project to the cingulate gyrus (see below). Whereas the hippocampus receives information visual, auditory, somatosensory, and visceral information largely through unimodal association areas, it might be recalled that the olfactory system also has relatively direct connections with both the amygdala and the entorhinal cortex. In turn, both the amygdala (see below) and entorhinal cortex have direct connections with the hippocampal formation. These apparently relatively direct connections (i.e., bypassing the neocortex) between the hippocampus and the olfactory system might help account for what often seems to be the relative strength of olfactory memory. Additional discussion of the olfactory system and behavior can be found below.

The subiculum (what might be considered the outermost layer of the hippocampal formation) serves as the primary output channel for the hippocampus. It sends projections back out to the entorhinal cortex. As illustrated in Figure 8–9b, from the entorhinal cortex, efferent connections are established with more or less those same cortical areas that provide input into the entorhinal cortex/hippocampal formation. Thus, the hippocampal formation either directly or indirectly through the entorhinal cortex has access and provides feedback

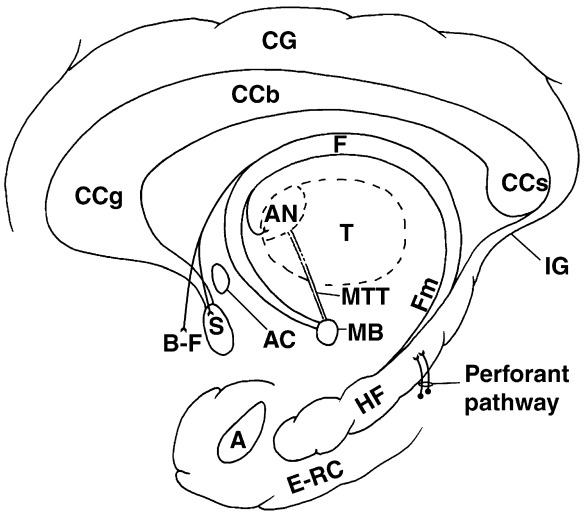


Figure 8–8. Hippocampal formation in relation to other limbic structures. Abbreviations: A, amygdala; AC, anterior commissure; AN, anterior nucleus of the thalamus; B-F, basofrontal region; CC, corpus callosum (b, body; g, genu; s, splenium); CG, cingulate gyrus; E-RC, entorhinal cortex; F, fornix; Fm, fimbria; HF, hippocampal formation; IG, indusium griseum; MB, mammillary bodies; MTT, mammillothalamic tract; S, septal area; T, thalamus.

to secondary sensorimotor, multimodal sensory, frontal executive, and limbic systems. These reciprocal cortical connections, primarily via the entorhinal cortex, likely serve as the basis for cortical long-term storage of information (i.e., memory).

Subcortical Connections

In addition to the extensive cortical inputs just described, the hippocampus receives afferent fibers from a number of subcortical structures. As was the case with the cortical inputs, these subcortical afferents appear to enter the hippocampus by way of the entorhinal cortex or the subiculum. Among the more prominent connections are those from the amygdaloid complex, septal region, hypothalamus, and thalamus. While the connections between the amygdala and the nearby hippocampus are apparently rather direct, the others are more circuitous. The septal region (septal nuclei, nuclei of the diagonal band) appears to primarily utilize the fornix (described below) to send fibers back to the hippocampus. With regard to the hypothalamus and thalamus (primarily the anterior and midline nuclei), recall the earlier description of Papez's circuit. The mammillary bodies (having received input from the hippocampus via the fornix) send projections to the anterior nucleus of the thalamus via the mammillothalamic tract. The anterior nucleus, in turn, sends projections to the cingulate gyrus and cingulum, which project back to the hippocampus. Other hypothalamic input may also return via the fornix.

The main source of subcortical efferents emerging from the hippocampus is the **fornix.** Containing over a million fibers, the fornix represents one of the more prominent pathways within the CNS (Figures 6–1b–f; 6–2c–h). The efferent fibers that make up the fornix appear to be derived from all three components of the hippocampal formation: the subiculum, hippocampus proper, and the dentate gyrus. Along the medial surface of the hippocampal formation there is a thin layer of white matter or nerve fibers (known as the **alveus**) that eventually coalesce to form the fimbria. The fimbria is a broad band of fibrous tissue lying along the dorsal surface of the hippocampal formation that resembles a foot and eventually evolves to become the *crus* of the fornix (Figures 6–1g; 6–2h; 8–8). As each of these fiber tracts proceeds rostrally, they come together just above the dorsomedial surface of the thalamus (and just below the corpus callosum) to form the body of the fornix (Figure 6–1f). At its anterior end, the fornix again splits, forming the *columns* of the fornix (Figures 6–1b; 6–2c–e). The fibers making up the columns themselves can be split into the pre- and postcommissural fibers (those passing in front of and behind the anterior commissure). The postcommissural fibers, which derive primarily from the subiculum, form the main projections to the mammillary bodies and the anterior nuclear groups and the lateral dorsal nuclei of the thalamus. The precommissural fibers, by contrast, which primarily have their origin in the hippocampus proper, tend to project mostly to the septal nuclei, the area of the diagonal band of Broca, nucleus accumbens, and other basal frontal areas. Some of the postcommissural fibers continue on to various midbrain nuclei. In addition to the fornix, the **longitudinal stria of Lancisi** represents another smaller pathway between the septal area and the hippocampal formation that travels along with the indusium griseum. Figure 8–9 offers a highly schematic view of the relationship of the hippocampal formation to some of the structures discussed above.

As was noted earlier, many of the fibers within the fornix also contain afferents to the hippocampal formation from the same nuclei to which it projects. Finally, the fornix also carries commissural fibers that transfer information from the hippocampal formation to the contralateral hemisphere (hippocampal formation and entorhinal cortex) via the hippocampal commissure, which is located just below the body of the fornix. For a more detailed review of the anatomical structure and connections of the hippocampus, the reader again is referred to Gloor's excellent volume on limbic structures (Gloor, 1997, Chapter 6).

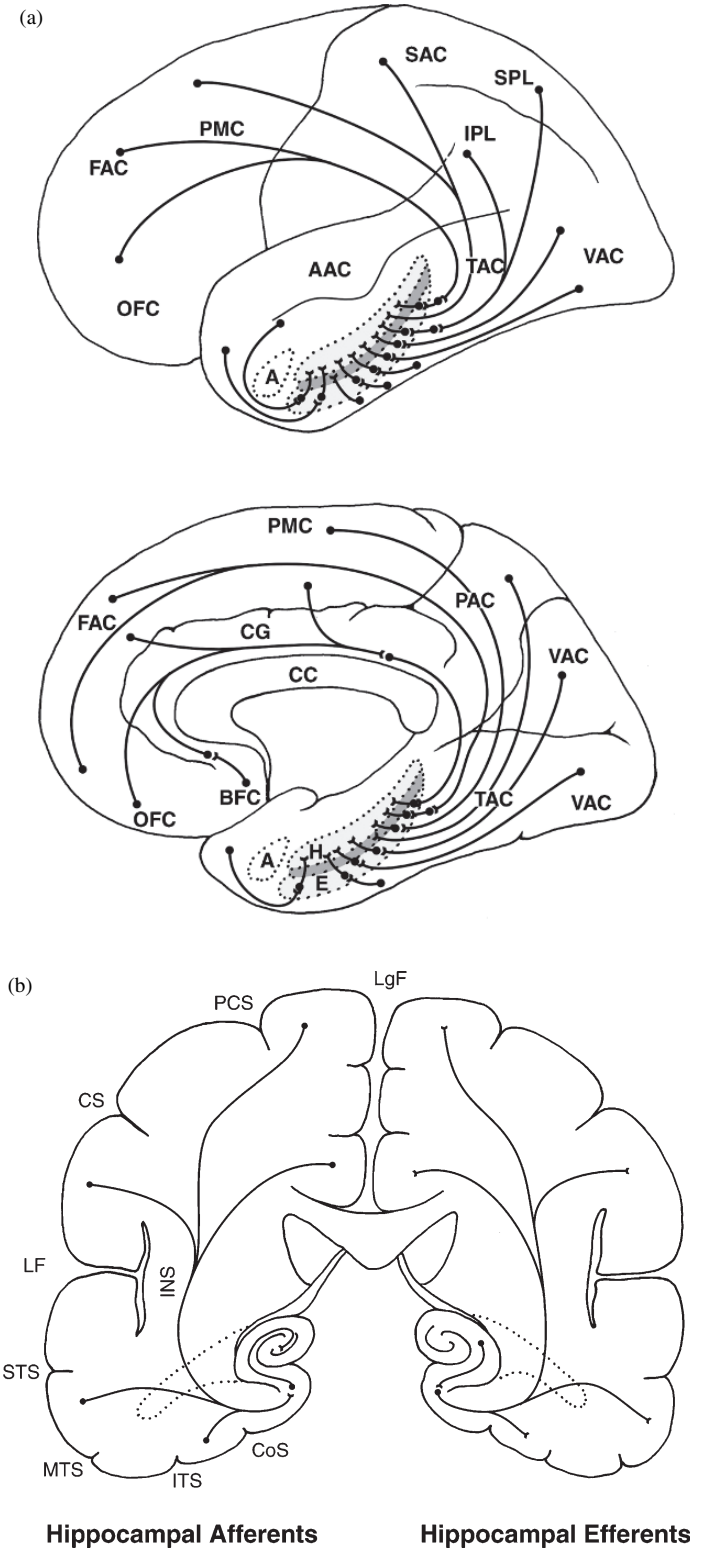


Figure 8–9. *(Continued)*

Functional Correlates

Similar to the other limbic structures considered thus far, the functions of the hippocampal formation are very complex. Given its extensive connections and the fact that it is made up of several distinct structures, it is unlikely that the hippocampal formation mediates a single or circumscribed "function." It likely contributes to various "functional systems." Lesion studies in animals have suggested a number of behavioral effects following lesions of the hippocampal formation depending in part on such variables as the species involved, the animal's previous experience, and environmental or testing conditions. Among the behavioral changes found in animals following lesions of the hippocampal formation have been increases in general activity, problems modulating attentions and arousal, decreased distractibility, increased reactivity to external cues, decreased behavioral flexibility, decreased ability to use spatial or cognitive maps, and impairments in learning and conditioning (Isaacson, 1982; O'Keefe & Nadel, 1978; Routtenberg, 1968). However, the most common and consistent behavioral deficit associated with hippocampal lesions in humans has been problems with memory, particularly the encoding of new memories (Signoret, 1985; Gloor, 1997; Zola, 1997).

Perhaps the most famous patient who has contributed to our modern understanding of the memory function of the hippocampal formation in humans is "HM." This individual was subjected to bilateral surgical ablation of the medial temporal cortices in an attempt to alleviate intractable seizures (Scoville, 1954; Scoville & Milner, 1957). Following the surgery, HM was noted to have a profound anterograde memory deficit or an inability to learn new information (declarative memory), despite being able to benefit from practice on certain sensorimotor tasks (procedural memory). This inability to retain new information was profound and included both verbal and visual–spatial type materials. This syndrome became synonymous with bilateral hippocampal lesions, although the lesions apparently extended well beyond the boundaries of the hippocampal formation and likely included the

Figure 8–9. Afferent and efferent cortical connections of the hippocampus. (a) Inputs to hippocampal formation from widespread cortical areas. As shown, while most inputs synapse in the entorhinal cortex prior to entry into the hippocampal formation via the perforant pathways, some proceed directly into the subicular area. Although not illustrated, it is thought that hippocampal–cortical efferents project back to the same general cortical areas from where inputs were derived (as shown in Figure 8–9b). (b) Coronal section illustrating both efferent and afferent hippocampal–cortical connections. As shown, most of these afferent connections likely originate in the subiculum and synapse in the entorhinal areas before going back out to the cortex (hippocampal formation is relatively enlarged). The darker area between the hippocampus proper and the entorhinal cortex represents the subiculum.

A, amygdala
AAC, auditory association cortex
BFC, basal frontal cortex
CC, corpus callosum
CG, cingulate gyrus
CoS, collateral sulcus
CS, central sulcus
E, entorhinal cortex
FAC, frontal association cortex
H, hippocampus proper
INS, insular cortex
IPL, inferior parietal lobule
ITS, inferior temporal sulcus
LF, lateral fissure
LgF, longitudinal fissure
MTS, middle temporal sulcus
OFC, orbitofrontal cortex
PAC, parietal association cortex
PCS, precentral sulcus
PMC, premotor cortex
S, subiculum
SAC, somatosensory cortex
SPL, superior parietal lobule
STS, superior temporal sulcus
TAC, temporal association cortex
VAC, visual association

amygdala. Horel (1978) came to the conclusion that the "temporal stem" (the white matter that connects the amygdala with the temporal neocortex) was the critical lesion producing such symptoms in humans, rather than damage to the hippocampus itself. However, in 1986, the case of another patient ("RB") was reported in which there was significant and permanent anterograde amnesia. In this instance the lesion, which was the result of an ischemic episode, appeared to be confined to CA1 of the hippocampus (Zola-Morgan, Squire & Amaral, 1986). Since that time (Squire, 1986; Squire & Zola-Morgan, 1993; Zola-Morgan & Squire, 1993), using primate models, reached the following conclusions:

1. Lesions confined to the fields of the hippocampus proper probably are sufficient to produce lasting memory loss.
2. As the lesions become more extensive, for example, beginning with the dentate gyrus and subiculum (hippocampal formation) and then extending to the entorhinal and perirhinal tissue, the more dense or severe the memory impairment.
3. Lesions confined to the perirhinal and parahippocampal cortices produced amnestic deficits that were more severe than lesions limited to the hippocampal formation (presumably because much of the cortical input to the hippocampus is funneled through these areas).
4. The inclusion of the amygdala in these lesions added little, if any, to the memory impairment in the experimental situations.

A variety of neuropathological conditions have been associated with bilateral lesions of the medial temporal areas, although the exact locus and extent of the lesion, and hence the nature and severity of the memory disturbances, will vary in individual cases. Included among these conditions are viral, particularly herpes, encephalitis (Drachman & Adams, 1962; Rose & Symonds, 1960), generalized ischemia, or anoxia (Zola-Morgan, Squire, & Amaral, 1986; Volpe & Hirst, 1983), occlusion of the posterior cerebral artery system (Victor, Angevine, Mancall, & Fisher, 1961; DeJong, Itabashi, & Olson, 1969; Benson, Marsden, & Meadows, 1974), primary degenerative disease processes (Hyman, Van Hoesen, & Damasio, 1990; Ball, 1979), and epilepsy (Gilbert, 1994; Adamec & Stark-Adamec, 1986; Babb et al., 1984). While definitive evidence appears to be lacking, transient global amnesia is suspected to result from temporary hypoperfusion of the medial temporal regions bilaterally.

The feature that is common to all these syndromes is difficulty encoding new memories (*new learning* or *anterograde amnesia*). It primarily is a disturbance *of episodic or declarative memory*, that is, the ability to recollect an experience in real-time and real-space parameters. Thus, for example, individuals might have difficulty recalling something they saw, heard, or experienced at a particular time, in a particular place, or under particular circumstances.[20] If reminded of the stimulus, event, or content of the to-be-remembered experience, patients may express some partial recollection or sense of familiarity but not be able to put it into his or her personal space–time continuum. That is, they may not recall where or when,or even if they saw, heard, or experienced the event in question. Nor will they be able to associate any personal meaning to it. With bilateral medial temporal lesions, all modalities and types of sensory input are likely to be affected.

Other types of memory are less likely to be affected. Thus immediate *memory*, or what might be termed "sensory" memory, generally is undisturbed. Thus individuals with medial bitemporal lesions may do perfectly well on digit span or even recite back most of the elements of a story or word list to which they were just exposed. *Procedural* memory, that is, the memory for how to do things, usually is preserved so that a patient with bilateral

hippocampal lesions may "learn" from practice how to perform a new sensorimotor task, although he or she may never remember having seen or done it before.[21] *Remote memory* or retrograde *amnesia*, that is, memory for events prior to the onset of the memory disorder, is more variable. Some individuals, even those with profound anterograde amnesia, may have essentially normal retrograde memory (or only a very restricted retrograde deficit which is isolated to a brief period just before the onset of the amnestic episode). Conversely, other patients with bilateral medial temporal lesions may have much more significant retrograde losses, sometimes extending back over decades. Zola (1997) reports several cases that suggest the difference may be in the degree to which the lesion extends beyond the hippocampal boundaries. Finally, semantic memory, that is, the memory for words and certain other types of overlearned information, also generally is fairly well preserved in the medial temporal amnesias.[22]

At this point it is important to note that amnestic disorders (i.e., more or less global impairment of new and possibly remote memory) also can result from lesions that lie outside the medial temporal region. As noted in the previous chapter, memory disorders have been associated with lesions affecting the dorsomedial and other midline thalamic nuclei, which can be global, if bilateral (see also Markowitsch, 1988). Basal forebrain lesions, especially those resulting from rupture of anterior communicating artery (ACA) aneurysms, typically present with severe, global memory deficits (Alexander & Freeman, 1984; DeLuca & Cicerone, 1989; Vilkki, 1985; Volpe & Hirst, 1983). However, perhaps the classic amnestic disorder is **Korsakoff's syndrome** (Butters & Cermak, 1980; Victor, Adams, & Collins, 1989). Frequently, but not invariably, associated with chronic alcohol abuse and thiamine deficiency, this syndrome, which may follow a more acute Wernicke's encephalopathy,[23] is characterized by varying degrees of anterograde memory impairment, a temporal gradient of retrograde memory loss (the more recent the time period, the denser the memory loss), and confabulations ("filling in the blanks"). While deficits in other cognitive areas (e.g., problem solving, executive abilities, visual–spatial skills) may be demonstrated, they generally pale by comparison with the memory deficits (Verfaellie & Cermak, 1997).

The critical lesion(s) producing the amnestic deficit in Korsakoff's syndrome is a matter of continuing debate (Bauer, Tobias, & Valenstein, 1993; Zola-Morgan & Squire, 1993). Pathological changes in Korsakoff's commonly are seen in the thalamus (usually in the dorsomedial nuclei, the mammillary bodies, and in the periventricular gray in the diencephalon and midbrain). While there is some evidence that the thalamic lesions may be more critical, the role of the mammillary bodies, mammillothalamic tracts, the anterior nucleus of the thalamus, or other related lesions cannot be ruled out at this time. As noted earlier, all of these structures have primary and/or secondary connections with the hippocampal/medial temporal area. Thus one might readily hypothesize that lesions that intrude upon this system adversely might affect memory processes. Finally, since confabulations are more likely to be encountered particularly in the more acute stages of Korsakoff's and ACA lesions and are relatively rare in pure medial temporal syndromes, it is likely that involvement of the basal forebrain or other frontal systems are responsible for this behavior (Damasio et al., 1985; Phillips, Sangalang, & Sterns, 1987).

Unilateral lesions affecting the hippocampal formation or related medial temporal structures (or unilateral thalamic lesions) do not produce the type of global amnesia seen with bilateral lesions but rather are likely to result in either verbal memory deficits (with left-sided lesions) or "nonverbal" (e.g., visual spatial) memory deficits following right-hemisphere involvement (e.g., Speedie & Heilman, 1982, 1983; Milner, 1968, 1972; Andrews, Puce, & Bladin, 1990; Christianson, Saisa, & Silfvenius, 1990; Frisk & Milner, 1990; Loring et al., 1991; Cohen, 1992; Saling et al., 1993; Gainotti, Cappa, Perri, & Silveri, 1994; Kaplan et al., 1994).[24] While the (sensory) modality of input generally is immaterial in such cases, lesions that

disconnect the hippocampus from modality-specific cortical areas may result in material-specific, as well as modality-specific, memory problems. For example, a patient may have difficulty remembering verbal information presented orally but not in written form.

Finally, for the sake of completeness, it also should be noted that patients might experience difficulties on specific memory tests as a result of a variety of focal cortical lesions. Posterior cortical lesions (i.e., lesions of the parietal, temporal, or occipital lobes) can compromise the processing or integration and analysis (perception and understanding) of the to-be-remembered material, hence making learning more difficult. Here the patient is more likely to experience difficulty in initial acquisition of the material, but unlike hippocampal or diencephalic lesions, show little additional decline following delayed recall. More frontally based lesions, on the other hand, are more likely to impede complex learning where guided attention and the planning or organizational strategies are required (e.g., long word lists as opposed to memory for a paragraph). Recall may be adversely affected by problems with selective retrieval and/or perseveration.

Cingulate Gyrus

Location and General Anatomy

The **cingulate gyrus** is most prominent on a midsagittal section of the brain (Fig. 8–10), but also is seen on both coronal and axial sections (see Figures 6–1 and 6–2). While the majority of the gyrus lies directly above the corpus callosum, anteriorly portions of it continue around the genu of the corpus callosum where it blends into the subcallosal gyrus of the medial orbitofrontal cortex. Posteriorly, the gyrus wraps around the splenium of the corpus callosum where it connects with the parahippocampal gyrus (via the isthmus of the cingulate gyrus). It is bounded dorsally by the cingulate sulcus and ventrally by the callosal sulcus. Within the fold of the gyrus itself, as seen in Figures 8–10e, lies a band of white matter that is known as the **cingulum**. This pathway contains both afferent and efferent, as well as association and projection fibers, representing both corticocortical and corticosubcortical connections (see below). The cingulate gyrus is classified as mesocortex and represents a transition between the allocortex of the hippocampal formation and the neocortex. While a number of different types of cytoarchitecture structure have been identified within the cingulate gyrus, for most clinical and experimental purposes frequently it is simply divided into an anterior (Brodmann's areas 24, 25, 33, and 32)[25] and a posterior region (areas 23, 29, 30, and 31). Given its inclusion in "Papez's circuit" and its extensive connections with the hippocampal gyrus, the cingulate gyrus generally is considered to be a part of "the limbic system."

Afferent and Efferent Connections

Perhaps the best known of the cingulate connections are those included in Papez's circuit. To review, this circuit went from the hippocampal formation → fornix → mammillary body → mammillothalamic tract → anterior nucleus (of the thalamus) → cingulate gyrus and back to the hippocampal formation.[26] We now know that the cingulate gyrus has connections with virtually all regions of the cerebral cortex (most of which are likely reciprocal), as well as extensive subcortical, brainstem, and even spinal connections. The anterior cingulate, as will be seen,primarily appears to be involved in modulating affect, motivation, and the selection and/or modulation of behavioral (voluntary) and autonomic responses and has extensive connection with the amygdala, orbitofrontal area, prefrontal ("executive"), and primary and secondary motor cortices. The posterior cingulate, which is thought to play a more substantial role in learning or memory, has extensive connections with parietal and posterior temporal cortices, the insula, and indirectly with the hippocampus via the parahippocampal

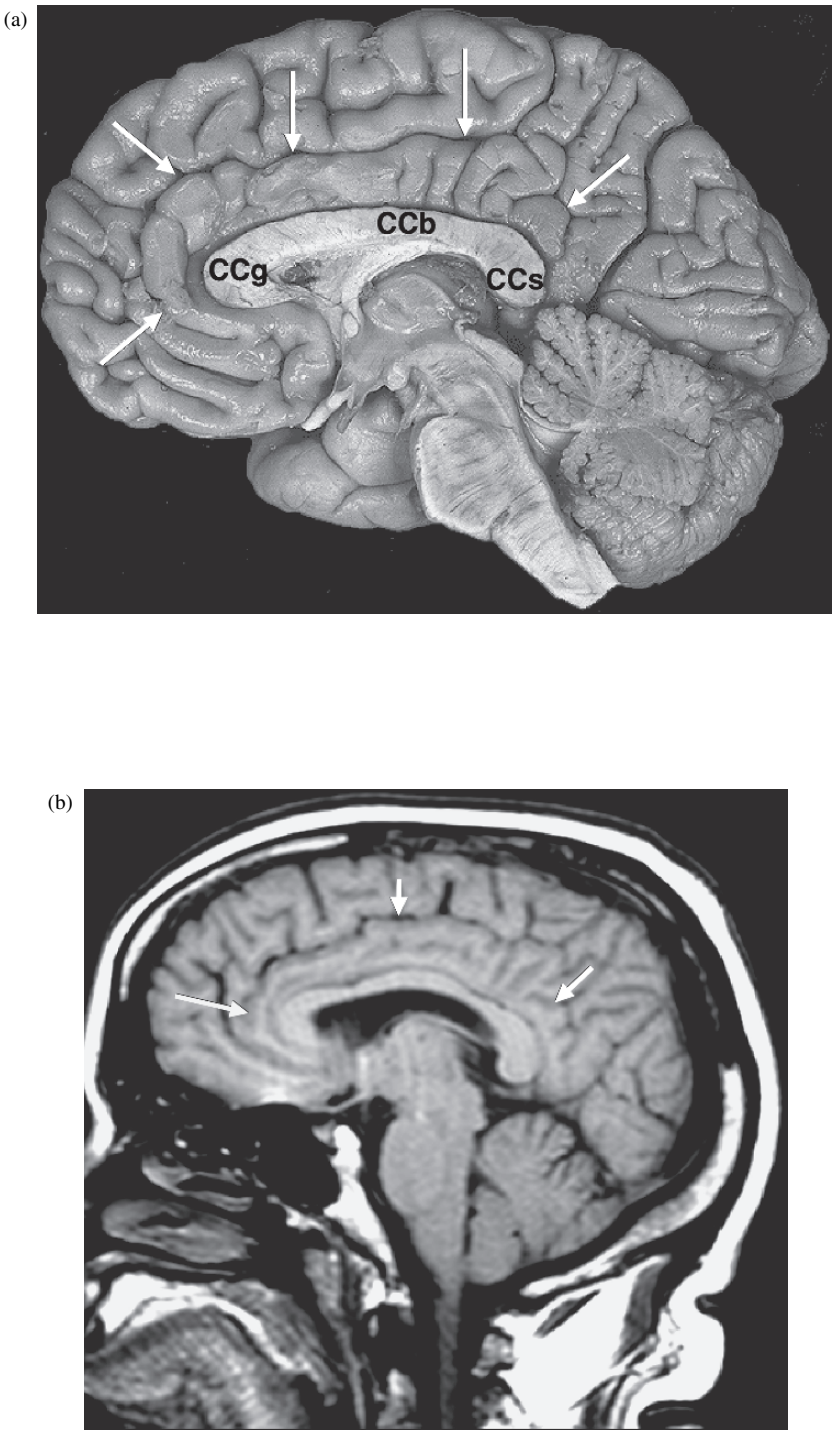
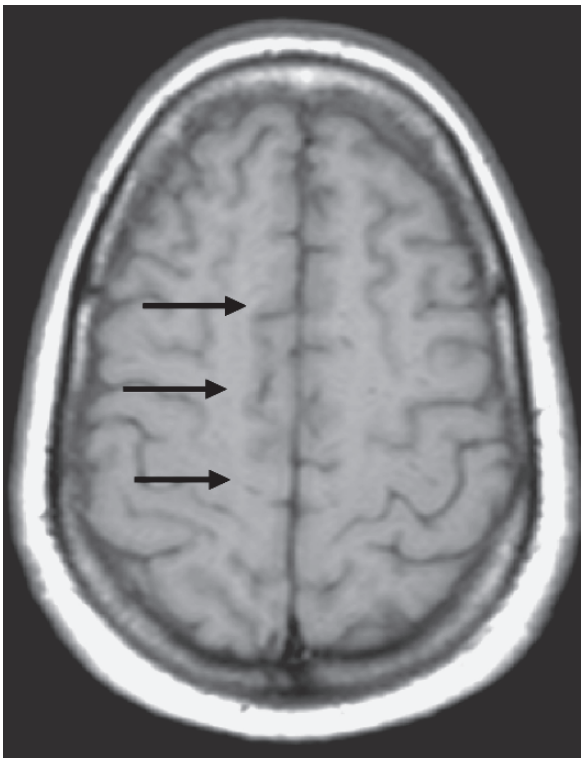


Figure 8–10. Cingulate gyrus as seen on (a) midsagittal brain section, on (b) midsagittal and (c) supracallosal axial MRI images. Cingulum can be seen on slightly more (d) parasagittal and (e) axial MRI images. Abbreviations: CCb, CCg, & CCs, the body, genu, and splenium of corpus callosum: CG cingulate g., Cg cingulum. Brain images were adapted from the *Interactive Brain Atlas* (1994), courtesy of the University of Washington.

(c)



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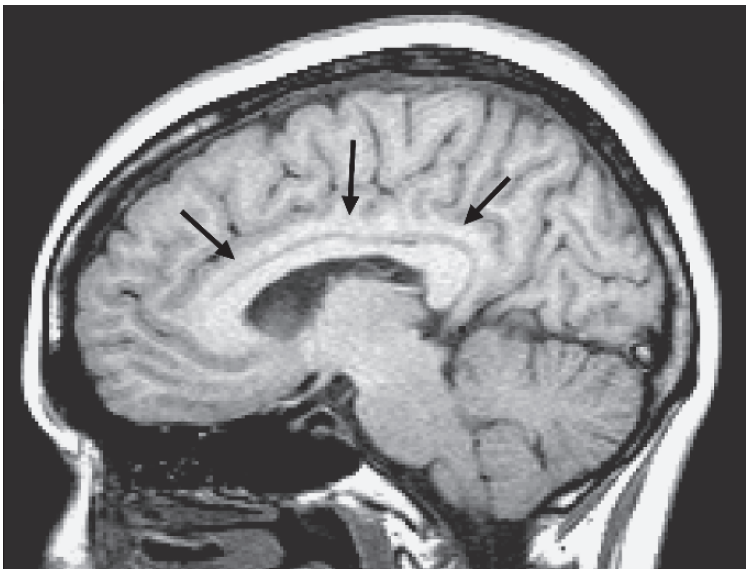

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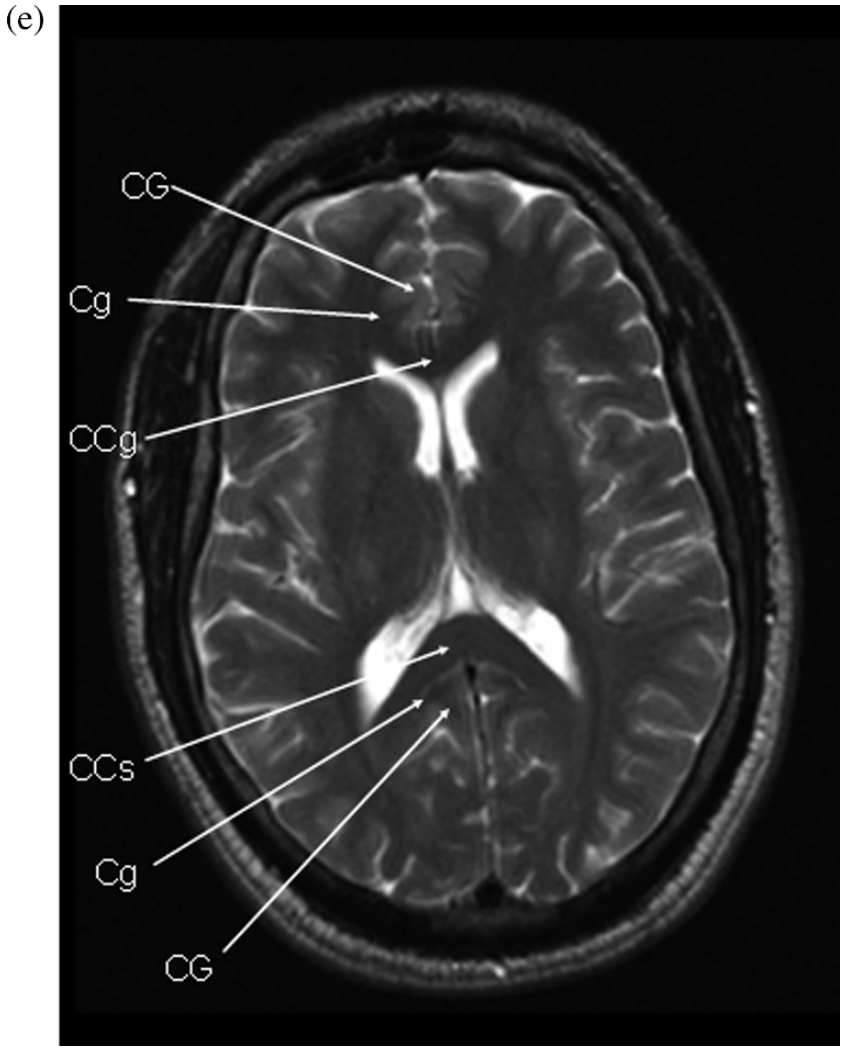

Figure 8–10. *(Continued)*

gyrus and entorhinal cortex of the hippocampal formation. Additional sensory input is suspected to reach the cingulate via the claustrum. As noted in Chapter 6, the cingulate gyrus, particularly the anterior cingulate, also has connections with the ventral striatum as part of the limbic circuit involving cortical–basal ganglia–thalamic feedback loops. It also since has been discovered that in addition to the anterior nucleus, various other thalamic nuclei, including the lateral, ventral, and dorsomedial groups, and the intralaminar and midline nuclei all appear to have some cingulate projections. In addition to these thalamic connections, the cingulate gyrus also has efferent projections to the midbrain (red nucleus), pons, and spinal cord. Finally, there appears to be two-way connections between the anterior and posterior portions of the cingulate gyrus itself which allows for reciprocal feedback between its effector and sensory/memory mechanisms. (Buchanan & Powel, 1993; Dum & Strick, 1991; Mega, Cummings, Salloway & Malloy, 1997; Mufson & Pandya, 1984; Musil and Olson, 1988; Olson and Musil, 1992; Van Hoesen, Morecraft & Vogt, 1993).

As noted above, many of these connections travel through the cingulum, the large fiber pathway that runs the length of the cingulate gyrus. It contains not only internal cingulate connections but serves as a connection between the frontal cortices and cingulate gyrus with the parahippocampal gyrus (and ultimately with the hippocampal formation). Thalamocingulate and other cingulofugal fibers also make use of this pathway. Thus, the cingulum represents a two-way communication system made up of both long and short association and projection fibers, containing both afferent and efferent fibers thattransmit information to and from the cingulate to most of the sites mentioned above. Finally, the cingulate gyri are interconnected via callosal fibers (Table 8–5 provides a brief review of some of the major limbic pathways).

Functional Correlates

Despite its substantial size, the role of the cingulate cortex in behavior remains relatively elusive. While this statement easily could be made with regard to any number of CNS structures, it seems particularly apropos of the cingulate gyrus. As will be discussed shortly, there certainly is no shortage of behavioral correlates that have been associated with either

Table 8–5. Summary of Major Pathways Affecting Limbic Structures

Cingulum: Interconnects subcallosal frontal areas with anterior and posterior cingulate gyrus with hippocampal formation.
Diagonal band of Broca: Connects subcallosal frontal and septal areas with the amygdala.
Dorsal longitudinal fasciculus: Interconnects the hypothalamus with the brainstem.
Fasciculus mammillary princeps: Pathway exiting from the mammillary bodies that bifurcates into the mammillothalamic and mammillotegmental tracts.
Fasciculus retroflexus (habenulointerpeduncular tract): Provides a connection between the habenular nuclei of the thalamus and the interpeduncular and other brainstem nuclei, especially those concerned with autonomic activity.
Fornix: A very prominent pathway between the hippocampal formation and the septal region, thalamus, basal forebrain, and mammillary bodies.
Hypothalamohypophyseal tract: Neuronal pathway connecting the hypothalamus with the neurohypophysis or posterior lobe of the pituitary gland.
Indusium griseum: This pathway includes the medial and lateral longitudinal stria of Lancisi and connects the hippocampal formation with the septal area.
Lateral olfactory stria: Connects the olfactory bulbs with the corticomedial aspect of the amygdaloid complex.
Mamillotegmental tract: Provides a connection between the mammillary bodies and the brainstem reticular formation.
Mamillothalamic tract: Connects the mammillary bodies to anterior nucleus of the thalamus
Medial forebrain bundle: Interconnects the orbital frontal and septal area with hypothalamus and with brainstem nuclei.
Perforant pathway: Interconnects the entorhinal cortex with the adjacent hippocampal formation.
Stria medullaris thalami: Discrete, midline pathway between the septal and habenular nuclei.
Stria terminalis: A very long, curved pathway connecting the amygdala to the septal nuclei, preoptic areas, and hypothalamus.
Ventral amygdalofugal pathways: Rather than a discrete pathway, this designation represents a diffuse fiber system that connects the amygdala (probably primarily the basolateral portion) and the surrounding pyriform cortex to the basal forebrain and subcallosal regions (including septal nuclei), the hypothalamus and dorsal thalamus, and the anterior hippocampal regions.

(**Note**: Most of these pathways probably reflect reciprocal connections. The use of the word "to" suggests the probable major direction of the pathway, otherwise strong reciprocal connections are likely.)

lesions or suspected dysfunction of this structure. Devinsky, Morrell, and Vogt (1995) have suggested that it is precisely this association with such a multiplicity of functions that has helped cloud the question of its behavioral significance. They suggest that the cingulate gyrus may serve as a link and/or modulator among different functional networks. At a more basic level, although a single appellation, *cingulate gyrus,* is applied to this entire expanse of tissue, it should be noted that this gyrus is composed of both agranular (anterior region) and more granular (posterior portion) type cortex. As we have just seen, these different regions have different patterns of connections, further suggesting a probable lack of uniformity of function. Finally, at least in humans, establishing structural–behavioral correlates is complicated further by the fact that, as in other cortical areas, naturally occurring lesions generally do not respect its anatomical boundaries. With these caveats in mind, we can at least explore some of the suspected behavioral phenomena associated with this intriguing region of the brain.

Paul MacLean (1986), it might be recalled, was the originator of the concept of the "limbic system" and took an interesting approach to trying to discover the role of the cingulate gyrus in behavior. He noted that the cingulate gyrus is a mammalian development, not present in reptiles. Thus, he asked, "What major classes of behavior seem to differentiate reptiles from even primitive mammals?" He concluded that there were three: (1) *play*, (2) *maternal care of the young*, and (3) v*ocal communication* (in particular, of the young in response to maternal separation).[27] However, most current theories about cingulate function in humans appear to derive largely from either on pathological data or imaging studies.

Anterior Cingulate–Behavioral Associations

One of the more well-documented behavioral syndromes associated with naturally occurring midline frontal lesions generally involving the anterior cingulate gyrus is apathy or diminished motivation. This phenomenon sometimes also is referred to as **abulia**, or lack of will, drive, or initiative. Such individuals often manifest varying degrees of psychomotor retardation and might appear depressed (anhedonic), except that they do not manifest dysphoric affect or acknowledge depressive-type cognitions (Faris, 1969; Freemon, 1971; Laplane, Degos, Baulac, & Gray, 1981; Degos, Fonseca, Gray, & Cesaro, 1993). While they may formulate plans or intentions, these are often never carried out, especially if sustained effort is required. The ultimate extreme of this state is akinetic mutism. Here the patient, while conscious and apparently alert, essentially is mute with little if any spontaneous goal-directed movement, except perhaps for visual tracking behavior. While this latter condition has been reported in brainstem/diencephalic lesions, it tends to more commonly be associated with bilateral, medial frontal lesions. (Stuss & Benson, 1986; Devinsky & Luciano, 1993; Devinsky, Morrell, & Vogt, 1995).

While the above pathological conditions are related to lesions thought to affect the cingulate gyri, surgical lesions that actually improve other conditions also provide some clues as to their potential behavioral contributions. Most notable in this regard are obsessive–compulsive disorders (OCD), anxiety, and chronic pain syndromes. Since at least the middle of the last century, anterior cingulate lesions have been shown to be effective in treating what otherwise had proved to be intractable and highly disruptive obsessive–compulsive symptoms. In addition to OCD, other chronic anxiety disorders also have been shown to have a positive response to these procedures (Whitty, Duffield, Tow, & Cairns, 1952; Tow & Whitty, 1953; Ballantine et al., 1975, 1987; Valenstein, 1977, 1980; Jenike et al., 1991; Insel, 1992; Devinsky & Luciano, 1993; Hay et al., 1993; McGuire et al., 1994). Similarly, anterior cingulotomies and cingulumotomies have proved to benefit patients suffering from chronic pain syndromes (Foltz & White, 1962; Devinsky & Luciano, 1993). Such patients typically report that while they still perceive or experience pain, it no longer is as disturbing

to them. In other words, it is as if the somatosensory perceptions are unchanged, but the affective response to those sensations has diminished.

As noted above, apathy without other common manifestations of depression can be associated with lesions involving the anterior cingulate. However, classic depressive syndromes also have been linked, at least in part, with the cingulate gyrus. Numerous functional imaging studies consistently have shown metabolic changes in the frontal and paralimbic regions associated both with the onset and recovery from depression (Ebert & Ebmeier, 1996; Ketter et al., 1996). While multiple, interconnected neural networks have been identified as participating in these behavioral changes, including cortical and limbic feedback loops involving striatal and diencephalic structures, the anterior cingulate cortex appears to play a prominent role. Specifically, it has been demonstrated that depression tends to be associated with *hypometabolism* of the more dorsal regions of the cingulate gyrus and portions of the frontal and parietal cortices, while subgenual portions of the cingulate gyrus (BA 25) and ventral frontal and hypothalamic areas tended to be *hypermetabolic*. Successful treatment of depression, on the other hand, was found to be characterized by just the opposite, namely increased metabolism in these dorsal regions and decreased metabolism in the ventral or subgenual cingulate and adjacent regions (Mayberg, 1997; Mayberg et al., 2000). Following up on these earlier studies, Mayberg and her colleagues have shown in preliminary studies that deep brain stimulation of the subgenual area of the cingulate gyrus (BA 25) in patients with otherwise intractable depression may prove beneficial where drugs and other treatments have failed (Mayberg et al., 2005). While the exact mechanisms behind this antidepressant effect are still unclear, such stimulation has the effect of reducing cerebral blood flow to the region, an effect comparable to that seen in standard treatments for depression when they are effective.

Although not as consistent or well documented as the above (especially inhumans), a number of other behavioral changes have been associated with lesions, stimulation, or other pathological changes in the anterior cingulate and/or adjacent frontal cortices. Among these have been schizophrenia, increased emotionality, neglect or attentional deficits, complex partial seizures, visceral (autonomic reactions), and Gilles de la Tourette syndrome (Benes, 1993; Devinsky & D'Esposito, 2004; Devinsky & Luciano, 1993; Devinsky, Morrell, & Vogt, 1995; Diering & Bell, 1991; Haznedar et al., 2004; Kunishio & Haber, 1994; Levin & Duchowny, 1991; Mazars, 1970; MacLean, 1993; Malamud, 1967; Spence, Silverman, & Corbett, 1985; Vogt, Finch, & Olson, 1992).

In summary, the anterior cingulate gyrus (BA 24, 25, 33, and 32) appears to be involved in the wedding of affect, cognition, and behavioral expression. Devinsky and his colleagues (1993, 1995, 2004) emphasize the need to integrate emotion and cognition as a means of providing motivation or drive. The nature and strength of those emotions might help dictate the direction, intensity, and tenacity of the behavioral response. Affectively driven behavior generally entails not only cognitive choices, but also behavioral (motor) displays or responses. Such responses might include skeletal–motor responses such as smiling, frowning, laughing, crying, or cursing. Equally important are visceral–motor responses. This perhaps most clearly is seen in situations where fear or anger predominate. In these situations, autonomic (sympathetic) activation is essential in preparing the organism for a "flight or fight" response. Vogt, Finch, and Olson (1992) characterize this as the "executive" role of the anterior cingulate cortex and point out that its interconnections with amygdala, frontal cortices, and skeletal and visceral–motor systems place it in an ideal position to mediate (modulate) such functions.

In this context, one also can offer potential explanations for some of the behavioral correlates of hypo- and hypermetabolic states of the anterior cingulate regions. For example, if the anterior cingulate is important in the interface between emotion and cognition, then it is

easy to see how disruption of certain components of this network might result in depression, loss of drive or motivation, neglect or inattention to potentially important environmental stimuli, hypokinesia, and in more extreme cases akinetic mutism. Failure to perceive pain as "distressful" (e.g., following cingulectomies) similarly can be viewed as a failure to properly wed the "emotional" aspect of pain to its cognitive representation. On the other hand, increased or disinhibited anterior cingulate activity might account for excess or overflow emotional and/or visceral arousal. This has been hypothesized to possibly play a role in the development of such disorders as OCD, other anxiety disorders, and tics and conversely their amelioration following surgery to these regions.

Posterior Cingulate

As noted earlier, the posterior cingulate is connected primarily with the parahippocampal gyrus and the parietal and temporal cortices. Unlike the anterior cingulate, it has no direct connections with the amygdala. Thus, as might be expected, it is thought to have little if any direct role in emotionally guided behavior. Vogt, Finch, and Olson (1992) suggest that the posterior cingulate is more involved in visual–spatial and somatosensory attention or awareness and memory. While these authors review evidence suggesting that the posterior cingulate likely is involved in memory for visual–spatial information, given the interconnections between the anterior and posterior cingulate cortices, it might be suspected that it also might play a role in the encoding of emotionally driven behaviors and/or the environmental context in which they occur. However, it should be noted that no studies addressing this issue could be found in a review of the literature.

OLFACTORY SYSTEM

As noted at the beginning of this chapter, many structures generally included when discussing the "limbic system" at one point collectively were referred to as the *rhinencephalon* or *smell brain* because of their close relationship with the olfactory system. Although less emphasis is placed on the olfactory connections when discussing these structures today (at least in primates), the olfactory connections are still present and play an important role in many aspects of emotionally charged behaviors or drive states. Evolutionarily speaking, olfaction, perhaps more so than hearing, vision, or somesthesia, has a history of being closely associated with approach–avoidance situations (i.e., with strong affective valences). Olfaction was critical in alerting the organism to the presence of food as well as threats (e.g., fire, predators). Whether prey or predators, olfaction also was important in mating, territoriality, and social identification and communication. While perhaps less critical to basic survival when compared with the animals that roam the plains and savannas, olfaction and affective drive states still retain their strong links in humans. The smell of a freshly baked apple pie or bacon sizzling in the pan usually has the capacity to elicit a strong (if not always prudent) approach response, while putrefaction normally elicits revulsion. Olfaction still plays an important role in sexual/social functions as witnessed in part by the multibillion-dollar perfume and cologne industry. While the teleological significance of other odors may be less clear, they nonetheless can be associated with positive responses (e.g., the fragrance honeysuckles or a pine forest). Finally, as with other types of stimuli, more neutral olfactory sensations (e.g., the smell of the salt sea air or the scent of a burning candle) may take on strong positive or negative associations, depending on the previous experiences of the individual. As was noted in Chapter 5, the reexperiencing of certain odors readily can be imbued with strong emotionally laden recollections.[28] The reverse also may be true, a strong emotional memory of an event may evoke associated

olfactory images. Rather than repeating the behavioral and anatomical bases that may underlie these phenomena, the reader is referred back to Chapter 5 where this topic was first introduced.

SUMMARY: CONTRIBUTIONS OF THE LIMBIC STRUCTURES TO BEHAVIOR

Having reviewed the basic anatomy, afferent and efferent connections, and suspected functional correlates of individual components of the "limbic system," it might be useful to speculate as to how these structures interact with other parts of the brain to regulate day-to-day behavior. While this is an important clinical and heuristic consideration, attempting to address such issues again is tantamount to trying to decipher the mystery of the brain. At best, one hopes to develop a few broad theoretical models or generate a few tentative hypotheses that might prove useful in forwarding our conceptualization of these functional relationships. Certainly, whatever models are generated, whether they attempt to define the possible interactions between two discrete areas of the brain or attempt a broader overview of brain systems as a whole, most assuredly they inevitably will represent a gross oversimplification of the actual reality. While two or more areas of the brain may work in concert to help effect a particular behavior, most behaviors including those that at first glance might appear to be rather "simple" typically are highly complex and likely involve an activation of all parts of the brain. When discussing behaviors as complex as drives, emotions, and memory, the more convoluted the problems become and the more they defy description or categorization. Thus, the following is intended as only a very elementary starting point, but one that might assist in providing a conceptual framework that may facilitate our attempt to understand some of the mysteries of brain–behavior relationships.

As a starting point, it might be suggested that one of the teleological goals behind the evolving brain was to permit organisms to gain increased understanding and mastery of the environment. As will be explored in Chapter 9, the expansion of the posterior association cortices in humans has resulted in an enhanced ability to integrate multimodal sensory input. This, in turn, has facilitated the development of abstract thought and ideas, the ability to manipulate spatial and temporal concepts, and to develop language by which these thoughts, concepts, and ideas can be communicated. At the same time, the evolution of the frontal association area has enabled us to plan, to anticipate future consequences, and to choose or prioritize among competing goals or ideas. Once a goal or plan of action has been selected, these association cortices enable us to determine how best to accomplish or execute that goal, monitor the progress of our actions, and where necessary alter the goal or the plan of action.

However, despite these advances, certain fundamental processes of the central nervous system remain relatively unaltered. We still must satisfy our basic biological and social needs. The capacities to attach emotional significance to and learn from our experiences still are essential adaptive mechanisms. Finally, *there needs to be some emotion or drive that initiates (motivates) us to pursue those goals (i.e., the will to act) in the first place and then sustains (energizes) those actions (i.e., keeps us on task). It would appear that it is the limbic structures that are primarily responsible for these latter tasks.*

As we have seen, the hypothalamus, one of the earliest parts of the brain to develop, appears to be responsible for monitoring and initiating basic, biological drive states. One example is the maintenance of internal homeostasis, such as ensuring proper oxygen, glucose, and water levels in the blood and cells. These functions are accomplished by creating internal drive states that "arouse" and "energize" the organism to engage in behaviors

designed to meet these needs or reduce the drive state. Simple examples would include the urge to surface after swimming underwater for an extended period or to search for food or drink when one is hungry or thirsty. Other drive states that are less directly related to maintaining internal homeostasis would appear "more complex" (i.e., likely involve other limbic structures to a greater extent). One example of the latter is the organism's need to defend itself against external threats or predators, which frequently results in the need to develop flight or fight responses. Another such drive is the need to ensure the survival of the species, hence the need to respond to sexual cues and stimuli that lead to the reproductive process. These drives not only are primitive, but can be very strong [all are near the top of Maslow's (1954) hierarchy of needs]. Witness, for example, states of panic and the strength of the drive to escape if trapped in an imminent, life-threatening situation. Under such circumstances, people often are reported to act "irrationally," that is, their actions would appear to be driven more by instinct under the influence of primitive brain mechanisms than by logical judgment as mediated by the tertiary cortical zones (Gorman, Liebowitz, Fyer, & Stein, 1989).

While under most normal (i.e., non-panic) circumstances, most drive states likely are heavily influenced by previous learning and experience, but can be modulated or even temporarily suppressed as a result of goals or drive deriving from higher, more recently developed brain centers. However, it is likely that the hypothalamus (and pituitary gland) still plays a crucial role in responding to drive states. For example, in order to prepare the organism to meet the physical demands involved in securing needs or drives, it often is necessary to increase the organism's heart rate and flow of oxygen to make more blood accessible to the peripheral musculature. These latter reactions help prepare the organism for fight or flight or, in the case of the predator, the chase. These functions are accomplished through the activation of the sympathetic nervous system, with parasympathetic arousal being necessary after the emergency (i.e., to conserve energy and/or digest the meal). Thus, hypothalamic arousal is closely linked, both behaviorally and neuroanatomically, with brainstem systems, including general arousal (ARAS) and activation of the autonomic nervous system. This hypothalamic–pituitary system might be conceived of as reflecting an "id" type of response, with the organism responding in a reflexive manner to both internal and external stimulus cues.

As organisms evolved, they developed increasingly sophisticated telereceptors to warn them of danger or signal the presence of stimuli that would satisfy their appetitive drives, such as thirst, hunger or sex. One of the earliest of these senses likely was the sense of smell. However, in order to benefit from these external cues, it was essential that the organism learn and remember from one instance to the next the meaning of these olfactory cues and the appropriate response to them. This, in turn, required close and fairly direct connections between these stimulus cues and those neural centers that were responsible for initiating and driving such behavior, that is, the hypothalamus. Second, it obviously was beneficial to ensure that a more or less permanent memory of this association would be established for future reference. The early (phylogenetically speaking) connections between the olfactory system and the hypothalamus would appear to reflect this intimate link between the sense of smell and these basic drive states. Likewise, the eventual development of the hippocampal formation and its close connections with both the hypothalamus (currently represented by the fornix) and the olfactory system (by way of the more primitive corticomedial portion of the amygdala and the surrounding pyriform cortex) would ensure that the organism could benefit from its prior experiences with similar stimuli. Such interactions might have laid the foundation for true "emotional" development.

Along with the evolution of the other senses, particularly vision and hearing, came the development of the supporting neocortex, which would allow for increasingly finer and more complex perceptual discriminations. Given the capacity to make such discriminations, the organism not only could make more effective use of its environment, but also was less at its mercy. The organism could begin to choose between stimuli or make individual judgments as to the more preferable response. Along with the ability to make finer and finer discriminations likely came the ability to make decisions as to whether the organism needed or wanted to respond at all. The organism could learn to differentially associate specific stimuli with different drive states under different circumstances based on its prior experience. For example, did this stimulus represent a threat the last time it appeared under these circumstances? Along with this increase in encephalization came an increase in social organization and complexity that also required choices or decisions based not only on internal or environmental stimuli but also on social context.[29]

For this system to work effectively, however, several things were important. First, it would have helped if these stimuli were imbued with some type of affective valence to signify their relative importance. If specific stimuli were associated with the reduction or temporary satisfaction of a primary drive state, such as hunger, these stimuli might acquire a "positive" (emotional) valence. Other stimuli may have become associated with self-preservation (e.g., an attack from a predator) and henceforth evoke fear, apprehension, or defensiveness or other "negative" affective valences. It equally was important for other stimuli to remain affectively neutral, as the organism cannot always be running either toward or away from every stimulus that reaches consciousness. It has been suggested that parts of the limbic system, particularly the amygdala, with its corticosensory connections on the one hand and its hypothalamic connections on the other, largely may be responsible for adding these emotional valences to specific stimuli.

However, it would do the organism little good to associate an experience with a particular drive reduction or emotional state if it could not retain that information from one time to the next. Hence, the organism needed to be able to learn, remember, and retrieve the information gained from such encounters and to be able to modify previous associations as circumstances changed. This latter purpose appears to be served by the extensive connections between the hippocampal regions and the posterior or sensory cortices. Of course, the organism did not "need to remember" all sensory experiences, just as it did not need to attach emotional significance to all sensory experiences. The connections between the amygdala and the hippocampus assisted in identifying those stimuli that were "important to remember," that is, the stronger the emotional impact of the stimulus, the greater the need (or likelihood) of its being remembered and the greater the strength of its connection. McGaugh (1992) has shown, for example, that the presence of adrenaline (i.e., emotional arousal) is important in laying down new memories.[30] The cingulate gyrus also is connected to the hippocampal formation and, as mentioned above, may be responsible for higher-order, social behaviors or interactions that need to be integrated into memory.

Once these connections between affective valences and particular stimuli were established (probably through classic conditioning) and stored, the stage was set for external (and/or "remembered") stimuli to initiate drive states. Certainly some fairly rigid and "preprogrammed" (instinctual) response patterns were "built into" many organisms (e.g., light-dimming detectors in the frog), but it was unlikely that these necessarily represented true emotional responses.[31] However, such associations that have been derived from personal experiences may have clearly manifested motivational (emotional) properties. Thus, such stimuli would have had the capacity to trigger emotional responses that then in

turn evoked or "drove" an approach, avoidance, or other idiosyncratic response from the organism. This arrangement would have allowed an "integrated" or "meaningful" multisensory images to elicit learned emotional, autonomic responses or "externally" triggered drive states in addition to "internally" driven (homeostatic) mechanisms. The potential benefit to the organism should be obvious. Having previously encountered (and survived) a potentially dangerous situation, an immediate "alarm" should have been activated, alerting the entire nervous system to adopt either an avoidance or defense response posture should the same situation again present itself. We now know that the same stimuli often can elicit highly individualized (learned) responses, differing not only in intensity from one person to another, but also in direction or valence. For example, the lyrics of a particular song or a visit to a particular place may elicit either a "pleasant" or "painful memory" depending on one's past experiences.[32]

The neuroanatomical substrates for such associations include connections between the heteromodal or tertiary cortices of the second functional unit (see Chapter 9) and the amygdala, cingulate gyrus, and parahippocampal gyrus, including the hippocampus proper. In turn, these paralimbic areas are connected to the hypothalamus with its own autonomic connections. It also is possible that certain stimuli may elicit an acquired emotional response, such as fear, without any conscious "memory" of its connection to previous life experiences. In this case, while the connections between the second functional unit and the paralimbic structures would appear to remain intact, the connections between these areas and episodic memory stores or the memory stores themselves may be dysfunctional. While one theory would suggest that functional "repressive" mechanisms block these memories from reaching conscious levels (Joseph, 1990), this also could reflect classic conditioning without the benefit of episodic memory for the event(s).

Commonly, the organism is faced not by one but by numerous converging external and internal stimuli. Many of these stimuli may have opposing valences or convey conflicting information. The organism must weigh and balance all this information to determine whether to respond or not. If the organism "decides" to respond, the precise nature and intensity of the response must be determined.[33] Thus, there is a need for a system of counterbalancing these various stimuli or conditions, that is, the capacity to override or inhibit responses. We have seen such a system not only within the hypothalamus itself (e.g., the ventromedial and lateral hypothalamic nuclei), but also with various other structures such as the interplay between the amygdala and the septal nuclei and the effects of anterior cingulate lesions on drive states. It has been suggested that perhaps one of the main roles of many of the limbic structures is to inhibit or modulate the influence of hypothalamic drives. Thus, in keeping with the earlier analogy, if the hypothalamic system can be seen as representing the "id," then this second (limbic–sensory) system might be seen as reflecting "ego" functioning, that is, integrating present reality to best serve the immediate needs of the organism.

At times, conflicting impulses (valences) need to be resolved by weighing the sum total of internal and external stimuli (i.e., the immediate circumstances) and "making an informed judgment." At times, this also may require considering not only immediate but future consequences, "higher-order," or longer-term goals. This subject will be discussed in greater detail in The Third Functional Unitin Chapter 9, Part III.. For now the following provides a simplified example. Suppose a monkey is glucose deficient (hungry) and engages in food-seeking behavior. It spots some fruit in a tree. The fruit triggers a positive emotional response, leading to increased salivation (a descending visceral response). However, as the monkey approaches, it sees not only the fruit, but also a snake. The visual image (percept) of the snake also is conveyed to the paralimbic structures which elicits a quite

different emotional response (fear), along with a competing set of visceral responses (increased heart rate, pupillary dilation). One could speculate as to what might happen next. If the monkey is only slightly hungry, the fruit is not ripe, and the snake is not only very large but also is curled up next to the fruit, chances are that the "negative" drive state (fear) will overwhelm the positive (sight of food). In such cases there might be no contest as to which behavioral response takes precedence. However, the hungrier the monkey, the riper the fruit, and the smaller and more distant from the fruit is the snake, neither emotional state (drive) may clearly dominate. At that point, the third (executive) functional unit is left with a decision to make or a plan of action to contemplate. Such a decision likely would take into account not only the sensory information available, but also the respective behavioral or affective relevance of those stimuli, memories of previous encounters, and/or "predicted outcome" and the general state of the organism (e.g., degree of hunger).

Finally, if the organism is motivated to act, then there needs to be a mechanism to translate that impulse into action. It may be here that the association between the limbic structures (particularly the anterior cingulate) and the prefrontal, frontal, and basal ganglia become increasingly important. For example, whereas it may be postulated that the function of the posterior cortices and paralimbic structures is to integrate sensory input and "evaluate" their relative valences in terms of previous associations (information that may incline the organism to respond in a particular manner), the function of the prefrontal association cortices may be geared to subordinate these instinctual or learned behavioral patterns in response to specific stimulus conditions to supraordinate, goals, plans, strategies, or anticipated long-range consequences.[34] In this manner, the input of the prefrontal association cortex to the limbic system may be conceptualized as that of a general overseer (or "superego") for drive states. In humans, this may mean submitting more primitive drive states or contemplated actions to tests of social judgment and/or inhibiting them long enough to consider potentially competing, long-range goals or consequences.

However, these hypothesized prefrontal–limbic interactions are probably only part of a larger, two-way neuronal highway. While the prefrontal–limbic systems may serve to inhibit or facilitate certain drive states depending on selected goals, the goals themselves (or more properly the actions necessary to effect these goals) must be initiated and maintained often in the face of distractions, obstacles, competing drives, or simple inertia. Certain stimuli, whether internal or external, may be imbued with strong affective drive states (either by "nature" or by previous associations); yet unless these drive states can affect motor and executive systems, they will not be converted into action. The same can be said for the "higher-order" goals, plans, or ambitions we normally associate with prefrontal, executive cortex. Without "affect" to drive them to fruition, they remain as just that: unfulfilled "plans," "goals," or "ambitions." It is suspected that this "drive" may be initiated at the limbic and reticular levels and interact (e.g., via the cingulate loop[35]) with the frontal and basal ganglia systems. Consistent with this hypothesis, lesions affecting this loop might be expected to result in apathy and/or akinesis (Devinsky & Esposito, 2004; Devinsky, Morrell, & Vogt, 1995; Mega & Cummings, 1994; Cummings, 1993).

In addition, the frontal lobes may impose specific strategies on learning and memory via connections with the hippocampus (e.g., "chunking" or associative strategies during the learning process and selective "search" strategies during retrieval). These and other possible interactions between the neocortex and the "limbic system" and the impact of lesions affecting these connections and hemispheric differences in emotional responses will be explored in greater detail in Chapter 9. In that chapter we will explore the role of arousal

Table 8–6. Summary of Major Functional Correlates of the Limbic System

Olfaction: Once known as the *rhinencephalon*, olfaction represents only a small part of the overall functional significance of the limbic system, particularly in primates. In humans, anteromedial temporal lobe seizure foci may produce olfactory auras (likely from stimulation of the corticomedial portions of the amygdaloid complex). In humans, smells often trigger affect-laden memories and are still often linked to primary approach/avoidant response patterns or drive states.

Homeostasis: The hypothalamus, in conjunction with the pituitary gland, plays a central role in maintaining internal homeostasis and modulating autonomic and endocrine activity. Lesions involving these structures can result in diabetes, eating disturbances, problems with temperature regulation, and growth, metabolic, and sexual (reproductive) abnormalities.

Preservation of the individual and of the species: In addition to maintaining internal homeostasis, interactions among the various limbic structures are critical in protecting the individual from external threats and in establishing social bonds and relationships that are conducive to the survival of the species. This entails recognizing and responding to affectively meaningful external stimuli, including social cues and communications. Emotions and drive states are integral aspects of these processes.

Emotions and drive: Central to most modern notions of a "limbic system," drive and emotion are closely related. **Emotion** is the affective–physiological response to a stimulus (external or internal). **Drive** reflects impetus to initiate an operant response (approach or avoidant). Although commonly linked, the two appear dissociable.

While multiply determined, the amygdala is the limbic structure most closely associated with emotions. It appears the amygdala is necessary in establishing affective–stimulus bonds, whereas both the amygdala and hypothalamus are crucial to the affective–physiological response. Stimulation of the amygdala often leads to exaggerated affective responses, while lesions frequently result in attenuated emotional responses. The septal region, although its functions are even less clear, apparently has a modulating influence on the amygdala, and stimulation of this region may result in the release of endorphins ("pleasure center"). The hypothalamus also may play an important role in the expression of emotion as lesions of the medial nucleus or stimulation of the lateral or posterior nuclei can result in aggressive behaviors.

The anatomical substrates for drive are less well understood. The hypothalamus probably is critical in ensuring proper "drive" to maintain internal equilibrium, as well as in certain aspects of sexual behavior. While emotions can be powerful motivators, sustained drive can be seen in the absence of any clear state of emotional "arousal." In humans, cognitive elements, including abstract ideas and long-range plans, often are at work, although likely not independently of limbic structures. Clinically, pathological inertia is most commonly seen in cases of bilateral mesial frontal lesions, especially where the anterior cingulate gyri are involved.

Memory: Although not exclusively related to "limbic functions," memory is closely associated to the limbic system, both anatomically and functionally. The presence of emotions often strengthens memory traces. Conversely, such memories often can rekindle emotions. The survival value of being able to store and recall emotionally salient events is readily apparent. Anatomically, the hippocampal formation is central to this process (bilateral destruction of this structure leads to severe amnestic deficits), although other structures have also been implicated.

Kluver–Bucy syndrome: Bilateral lesions of the medial temporal lobe were found to produce a characteristic pattern of behavior among lesioned monkeys. Among the behaviors noted were:

1. Decreased aggressiveness, along with increased "tameness"
2. Decreased "fear" or aversion responses to stimuli that would normally evoke such behavior, for example, snakes
3. Increased "sexual" behavior, indiscriminate mounting behaviors
4. Increased submissiveness, decreased social dominance
5. Increased activity
6. Increased oral tendencies, all objects explored by the mouth

At least part of this syndrome can be seen in humans with bilateral lesions to this area, as is the case in Pick's disease.

and motivation in the context of integrating the actions of the three functional units of the brain: arousal, gnostic, and executive. (Table 8–6 summarizes major limbic functions).

Endnotes

1. A more detailed review of the history of thought regarding the central nervous system is presented in Chapter 9.
2. The spelling of this nucleus varies among different authors, some choosing "*mammillary*," others opting for "*mamillary*."
3. In 1937, it may have been more fashionable (or, perhaps, more "politically correct") to view females as being less encumbered with the same degree of sexual passion or drive as males?
4. Owing to the confluence of all these various basic visceral mechanisms in this area, MacLean thought this could help explain the

   > "overlapping of oral and sexual behavior [as] more than a fortuitous circumstance. In this part of the brain . . . it is possible to conceive how sexual incitations could stimulate a crude, diffuse feeling of visceral yearning that would make the individual seek to mouth and incorporate the object of its desire. According to intensity, the sex–hunger pattern might lead anywhere from gentle kissing to the deviate forms of oral–sexual behavior. . .. Likewise, the hunger–rage pattern susceptible to sexual firing might express itself in all gradations from aggressive, sadistic behaviour to sex-murder and mutilation."

   He subsequently described this area as representing the "id, the beast or sin in man and noted that it was probably the role of the frontal lobes [the superego?] to "stand guard over this region"; a concept that still seems, at least partially, viable: witness the case of Phineas Gage, the 19th-century gentleman who had a metal tamping bar driven up through his face and skull wiping out a sizeable chuck of his frontal lobes, was described as being a very hard working, sober, and generally pleasant fellow before the accident; he reportedly became slovenly, indolent, capricious, impulsive, and given to fits of profanity afterward (see: Blumer & Benson, 1975).
5. This theme of the role of the limbic system and the unconscious most recently was revisited by Rhawn Joseph in his book, *Neuropsychology, Neuropsychiatry and Behavioral Neurology* (see Suggested Readings)
6. These structures represent what might be characterized as the "short list" of limbic structures. Because many of these structures also have strong associations with yet other structures (e.g., both the habenular hypothalamic nuclei have direct connections with brainstem nuclei), it is easy to expand the definition of "limbic structures" to include many other nuclei (Nieuwenhuys, Voogd, & van Huijzen, 1988; Nieuwenhuys, 1996).
7. Clearly, certain types of fairly complex social structure and social behavior, including communication, is still possible with extremely primitive nervous systems, as witnessed by bees and ants.
8. One hardly needs to rely on man, or even lower-order primates, to provide an example of "emotional" development. Dogs have served as close companions to man for thousands of years. While a certain symbiosis can help account for this long-term cohabitation—the dog provided an early warning system and protection against intruders in return for scraps from the human's kill—this alone probably cannot account for the closeness of this bond over the millennium. A more likely explanation lies in the emotional similarities shared by these two creatures. Anyone who has owned a house-dwelling dog has seen the richness of his or her emotional repertoire. Under the

proper circumstances, they can show what, in humans, might be characterized as joy, playfulness, excitement, affection, jealousy, irritability, aggression, fear, anxiety, guilt, and depression.

9. It would not be in the interest of the organism to become generally energized, or to engage in the strenuous activity of food-capturing behavior every time it saw an antelope on the hoof. If there were sufficient antelope around, it would soon die of exhaustion. Thus the behavioral relevance (drive state) associated with the stimulus will depend on other limbic mechanisms (e.g., state of hunger). On the other hand, there may be certain stimuli (e.g., the silhouette of a hawk or the outline of a snake) that are "programmed" to trigger an emotional (fear) response in the chicken or monkey, regardless of the state of the organism or immediate environmental circumstances.
10. Mesulam differentiates a zone of transitional cortical tissue that includes the caudal orbitofrontal cortex, the insula, the temporal pole, the parahippocampal gyrus, and the cingulate gyrus, from more cytoarchitecturally primitive tissue which includes the septal nuclei, the substantia innominata, the pyriform cortex, the amygdala, and the hippocampus proper (hippocampal formation). He designates the former as the *paralimbic areas*, while the latter is termed the *limbic zone*.
11. Holstege (1992) describes an emotional–motor system, related to the classically described limbic system, which is thought to mediate certain affective responses, such as emotionally driven vocalizations.
12. See Chapter 11 for a more detailed review of the neurotransmitters, including their source, major pathways, and probable functional significance.
13. An example is the lateral hypothalamic nuclei, which is traversed by the medial forebrain bundle and is likely affected by lesions of this area.
14. Lesions in the septal area also may result in increased rage reactions in some species. However, whereas lesions to the amygdala will counteract the effect of septal (lesion) aggressiveness, such lesions will have no impact on the aggression resulting from ventromedial hypothalamic lesions.
15. For additional reviews of the various subdivisions of the amygdala and its connections, see Pierre Gloor (1997) and Nieuwenhuys, Voogd, & van Huijzen (1988).
16. A notable exception may be the **episodic dyscontrol syndrome** or "pathological intoxication." While this syndrome would appear to resemble a type of ictal phenomenon, its specific etiology and/or neuroanatomical substrate remain unclear (Monroe, 1986).
17. The most common effects of either lesions or stimulation of the amygdala reported in the literature tend to be changes in aggression or fear type responses. This might lead to the speculation that the amygdala primarily may be responsible for processing "negative" emotions and that other structures process "positive" reinforcements. Actually, the amygdala appears to be involved in the formation of both positive and negative reinforcements (Gaffan, 1992; Rolls, 1995). As pointed out by LeDoux (1995), one possible explanation for the plethora of "negative" emotions reported is that such responses generally are easier to measure and are more amenable to experimental manipulation.
18. **Interictal behavior** refers to those behavioral patterns or traits that are manifested by the seizure-prone patient in between the actual seizure (ictal) episodes. One explanation that has been advanced for these longer-term changes has involved the concept of **kindling** (Goddard, McIntyre, & Leech, 1969). Broadly defined, kindling refers to the fact that repeated, low level (i.e., subclinical) electrical stimulation of the brain eventually will result in permanent changes to neural tissue. Hence, one assumption is that the repeated, subclinical, interictal abnormal electrical discharges that routinely occur in seizure patients with temporal lobe foci eventually produce changes in limbic struc-

tures which result in behavioral changes (Spiers, Schomer, Blume, & Mesulam, 1985; Post, 1986).

19. The hippocampus proper has been divided into subfields, commonly referred to as CA1 through CA4. CA1 represents the outermost segment of the hippocampus, merging with the subiculum. CA3 and CA4 (sometimes simply referred to as CA3) is the innermost portion of the hippocampus proper, lying adjacent to the dentate gyrus. The subiculum itself also can be subdivided into the subiculum proper (contiguous with CA1 of the hippocampus), the presubiculum, and the parasubiculum which lies adjacent to the entorhinal cortex. Some authors (e.g., Amaral & Insausti, 1990) include the entorhinal cortex as part of the hippocampal formation, although unlike the rest of the hippocampal formation, it has a six-layered cytoarchitectural structure that is associated with the neocortex, rather than the three layers characteristic of allocortex.
20. Depending on the nature and extent of the lesion, the observed deficit may be quite profound, so that the patient essentially is unable to lay down any new memories for persons or events, regardless of the length or frequency of exposure to the stimuli. In other instances, the deficit may be demonstrable, not absolute, and/or may show some gradual improvement over time.
21. There was a classic scene from a TV comedy series years ago in which one of the characters (Jim), whose brain was ostensibly fried from years of drug abuse, found himself at a small, but elite party of art patrons. The scheduled piano soloist for the evening having failed to arrive, Jim "volunteers" to provide entertainment. After going through a series of apparently randomly chosen notes (to the horror of his friend and escort who was utterly embarrassed), Jim proceeds to play, unerringly, a complex concerto. Surprised, his friend remarks, "*I didn't know you knew how to play the piano*." To which Jim responds, "*neither did I!*"
22. Again, depending on the particular etiology and the individual case, this pattern may vary. Anoxic lesions, for example, could affect other cortical or subcortical systems. Alzheimer's disease has extensive cortical involvement. In such cases, not only remote memories, but also procedural, semantic, or even immediate memories may be affected depending on the sites involved and the severity of the disease process.
23. Wernicke's encephalopathy typically has an acute or subacute onset manifested by ataxia, ophthalmoplegia, and mental confusion.
24. In the author's experience, while right temporal lesions likely will produce deficits in learning many visual spatial tasks while leaving verbal memory fairly intact, left temporal lesions are more likely to have an adverse effect on both verbal and visual spatial memory. This may result, at least in part, from the fact that humans typically tend to use verbal encoding strategies to remember, regardless of the nature of the material.
25. While most authors seem to identify only Brodmann's areas 24 and 25 as comprising the anterior cingulate region, others (e.g., Devinsky, Morrell, & Vogt, 1995; Vogt, Nimchinsky, Vogt, & Hof, 1995) include areas 33 and 32, with the latter being considered a transitional region between cingulate and frontal cortices.
26. Subsequent studies have demonstrated that the cingulate cortex likely does not project directly to the hippocampus, but rather to other areas of the parahippocampal gyrus (e.g., to the presubiculum and perirhinal cortices), which in turn project to the hippocampus via the entorhinal cortex and perforant pathway (Shipley & Sørensen, 1975). However, the cingulate cortex does receive afferent input directly from the hippocampus.
27. Newly hatched crocodiles make vocalizations to which female crocodiles respond by digging them out of the nest and carrying them to the water. Hungry baby birds, which

are believed to have evolved from a reptilian tree, are highly vocal when left alone in their nests, but,at least in part this may be their way of stimulating feeding behaviors from their parents. But in either case, it is not clear that these sounds are in response to maternal separation per se.

28. Perhaps reflecting the importance of this connection, at least phylogenetically, it is noted that olfaction alone, among the major external sensory receptors, has direct input into the hippocampus. Information derived from visual, auditory, or somatosensory input reach the hippocampus only after being processed by multimodal association cortex (Gloor, 1997).
29. **Note:** Complex social organization or behavioral patterns do not necessarily require complex cortical systems as witnessed by such "social" insects such as ants or bees. What the brain does allow is for more flexibility or "freedom of choice," that is, the capacity to learn from personal experience.
30. Such may be the explanation as to why those who were adults at the time vividly may emember what they were doing when they heard of the bombing of Pearl Harbor or the assassination of President Kennedy, or other events that were associated with strong personal feelings, even though some of the remembered details had little to do with the event itself.
31. This does not mean that all instinctual stimulus–response associations are devoid of emotional content. For example, there is something about the perceptual gestalt of the newborn or the sight of a decapitated body that tends to elicit a common behavioral response among most primates that would appear to have strong affective component and appears to be relatively independent of prior experiences.
32. The affective valence ("emotional coloring") associated with a particular set of stimulus parameters may not be absolute but dependent on circumstances. For example, the sight of a stack of 100-dollar bills being placed in one's palm might elicit very different reactions depending on (1) whether it is construed to be a gift or a bribe, and (2) the moral character of the recipient.
33. For example, if a "tasty morsel" appears sauntering lazily along on the horizon but the predator's belly is full, the arousal value of that stimulus will be affected by visceral and then hypothalamic feedback. Conversely, the sight or smell of a lion normally might trigger panic in the gazelle, but if certain conditions are met (e.g., the lion makes no moves in its direction) flight is unwarranted and wasteful.
34. It has been suggested that the orbitofrontal cortex is involved in the correction of previously learned reinforcement contingencies in situations where such responses are no longer reinforcing. This might help explain the failure to withhold responses to nonrewarded stimuli following certain frontal lesions in animals (Rolls, 1995).
35. See Chapter 6.

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