Section D

THE LIMBIC SYSTEM

INTRODUCTION

The term limbic is almost synonymous with the term emotional brain — the parts of the brain involved with our emotional state. In 1937, Dr. James Papez initiated the limbic era by proposing that a number of limbic structures in our brain formed the anatomical substratum for emotion.

EVOLUTIONARY PERSPECTIVE

Dr. Paul MacLean has postulated that there are in fact three separable "brains" that have evolved. The pre-mammalian (reptilian) brain has the capacity to look after the basic life functions and has organized ritualistic stylized patterns of behavior. In higher species, including mammals, forebrain structures have evolved that relate to the external world (e.g., visual input). These are adaptive, allowing for a modification of behavior depending upon the situation.

MacLean has suggested that the limbic system arises in early mammals to link these two brain functions; according to this scheme, the limbic system relates the reptilian brain, which monitors the internal milieu, with the newer forebrain areas of mammals responsible for analyzing the external environment. Many now view the limbic system from this perspective.

DEFINITION

Most of us are quite aware or have a general sense of what we mean when we use the term "emotion" or feelings, yet it is somewhat difficult to explain or define precisely. Stedman's Medical Dictionary defines emotion as "a strong feeling, aroused mental state, or intense state of drive or unrest directed toward a definite object and evidenced in both behavior and in psychological changes." Thus, emotions involve:

- Physiological changes: This includes basic drives such as thirst, sexual behavior, and appetite. These changes are often manifested as alterations of the autonomic nervous system or the endocrine system.
- Behavior: The animal or human does something, that is, performs some type of motor activity, for example fighting, fleeing, displaying anger, mating; in humans, this may include facial expression.
- Alterations in the mental state: This can be understood as a subjective change in the way the organism "feels" or reacts to the state of being or to events occurring in the outside world. In humans, we use the term psychological reaction.

It is clear, at least in humans, that some of these psychological functions and behaviors must engage the cerebral cortex. In addition, many of these alterations are conscious and involve association areas. In fact, humans are sometimes able to describe and verbalize their reactions or the way they feel. Both cortical and subcortical areas (e.g., basal ganglia) may be involved in the behavioral reactions associated with emotional responses. The hypothalamus controls the autonomic changes, along with brainstem nuclei, and also the activity of the pituitary gland underlying the endocrine responses.

Therefore, we can finally arrive at a *definition* of the limbic system as an interrelated group of cortical and subcortical (noncortical) structures that are involved in the regulation of the internal or emotional state, with the accompanying physiological, behavioral, and psychological responses.

NEURAL STRUCTURES

In neuroanatomical terms, the limbic system is thought to include cortical and noncortical (subcortical, diencephalic, and brainstem) structures. The following is a listing of the structures:

- *Core* structures are those definitely associated with the limbic system.
- *Extended* structures are those closely connected with limbic functions.

a. Cortical:
   - **Core**: The hippocampal formation, which consists of three subparts (which are "buried" in the medial temporal lobe in humans), parahippocampal gyrus, cingulate gyrus
   - **Extended**: Parts of the prefrontal and orbitofrontal cortex (the limbic forebrain)

b. Noncortical:
   - Forebrain:
     - Core: Amygdala, septal region, ventral portions of the basal ganglia, including the nucleus accumbens

    - Extended: the basal forebrain
- Diencephalic and Brainstem:
    - Core: Certain nuclei of the thalamus, the hypothalamus
    - Extended: Parts of the midbrain (the limbic midbrain), and medulla

All of these structures are collectively called **the limbic system**. The particular role of the olfactory system and its connections will be discussed in the context of the limbic system.

OVERVIEW OF "KEY" LIMBIC STRUCTURES

There are key structures of the limbic system that integrate information and relate the external and internal worlds — the hippocampal formation, the parahippocampal gyrus, the amygdala, and the hypothalamus.

- The hippocampal formation is an older cortical region that is involved with integrating information; its role in the formation of memory for facts and events will be discussed below.
- The parahippocampal gyrus has widespread connections with many cortical (particularly sensory) areas and is probably the source of the most significant afferents to the hippocampal information.
- The amygdala is in part a subcortical nucleus involved with internal (visceral afferent) information, as well as receiving sensory input about olfaction (our sense of smell).
- The hypothalamus oversees autonomic physiological and hormonal regulation.

Both the amygdala and the hypothalamus are involved with the motor (i.e., behavioral) responses of the organism (the amygdala, in part, via the hypothalamus), and both are involved along with other structures in generating "emotional" reactions.

LIMBIC CONNECTIONS

The limbic system has internal circuits connecting the key structures; these link the hippocampal formation, the parahippocampal gyrus, the amygdala, and the hypothalamus, as well as other structures of the limbic system. There are multiple interconnections within and between these structures, and knowledge of the circuits of the limbic system (which are quite complex) allows one to trace pathways within the limbic system. Only some of these pathways will be presented. The best known of these functionally (and for historical reasons) is the Papez circuit (discussed with Figure 77A). Additional pathways that connect the limbic structures to the remainder of the nervous system and through which the limbic system influences the activity of the nervous system will be discussed.

MEMORY

Unfortunately, the definition and description of the limbic system does not include one aspect of brain function that seems to have evolved in conjunction with the limbic system — memory. Memory systems are usually grouped into two types:

- Memory for skills and procedures called **procedural** memory
- Memory for facts and events called **declarative** or **episodic** memory

A part of the hippocampal formation is specifically necessary for the initial formation of episodic memories. It is critical to understand that this initial step is an absolute prerequisite to the formation of any *new* memory trace. Once encoded by the hippocampal formation, the memory trace is then transferred to other parts of the brain for short- and long-term storage. The limbic system seems not to be involved in the storage and retrieval of long term memories.

It is interesting to speculate that forgetting may be theoretically more appropriate for this unique aspect of limbic function. This idea proposes that to undo or unlock the fixed behavioral patterns of the old reptilian brain, some part of the brain must be assigned the function of "recording" that something has happened. In order to change a response, the organism needs to "remember" what happened the last time when faced with a similar situation, hence the development of memory functions of the brain in association with the evolution of the limbic system. The availability of stored memories makes it possible for mammals to override or overrule the stereotypical behaviors of the reptile, allowing for more flexibility and adaptiveness when faced with a changing environment or altered circumstances. Therefore, we have suggested that the "F" mnemonic — forgetting — may be applicable for this "memory" function.

OTHER "LIMBIC" FUNCTIONS

In summary, the limbic system — both cortical and noncortical components — includes a set of "F" functions: feeding (and other basic drives), fornication (reproduction), fighting and fleeing (behavioral), feeling (psychological), and "forgetting" (memory).

It has also been suggested that some mammalian behavior associated with caring for its young is associated with the limbic structures, such as recognizing and responding to the vocalizations of the "pups" in rodents, cats, and other animals; a mother responds to the unique tone of her own baby's crying. The cingulate gyrus seems to be the area of the brain involved in this activity. This notion of rearing and "family" would add another "F" to our list of limbic functions.

It is also interesting to speculate that the elaboration of limbic functions is closely associated with the development of self-awareness, consciousness of the self (not an "F" word).

These functions will be reviewed and discussed at the end of this section of the atlas.

FIGURE 70A
THE LIMBIC LOBE 1

CORTICAL STRUCTURES

The limbic lobe refers to cortical areas of the limbic system. These cortical areas, which were given the name "limbic," form a border (limbus) around the inner structures of the diencephalon and midbrain (see Figure 17 and Figure 70B). The core cortical areas include the hippocampal formation, the parahippocampal gyrus, and the cingulate gyrus.

There are a number of cortical areas located in the most medial (also called mesial) aspects of the temporal lobe in humans that form part of this "limbus." These areas are collectively called the **hippocampal formation**; it is made up of three portions — the hippocampus proper, the dentate gyrus, and the subicular region (see Figure 72A and Figure 72B). The **hippocampus proper** is, in fact, no longer found at the surface of the brain as would be expected for any cortical area. The **dentate gyrus** is a very small band of cortex, part of which can be found at the surface, and the **subicular** region is located at the surface but far within the temporal area. These structures are the central structures of the limbic lobe.

The typical cortex of the various lobes of the brain consists of six layers (and sometimes sublayers), called the neocortex. One of the distinguishing features of the limbic cortical areas is the fact that, for the most part, these are older cortical areas consisting of three to five layers, termed the allocortex. The hippocampus proper and the dentate cortex are three-layered cortical areas, while the subicular region has four to five layers.

Note to the Learner: At this stage, it is very challenging to understand where these structures are located. The component parts of the hippocampal formation are "buried" in the temporal lobe and remain somewhat obscure. It is suggested that the learner preview some of the illustrations of the "hippocampus" (see Figure 73), as well as sections through the hippocampal formation (see Figure 38 and Figure 72B) in order to better understand the configuration of the three component parts and the relationship to the parahippocampal gyrus. The details of these various limbic structures, including their important connections and the functional aspects, will be discussed with the appropriate diagram.

The **parahippocampal gyrus,** which is situated on the inferior aspect of the brain (see Figure 15A and Figure 15B) is a foremost structure of the limbic lobe. It is also composed of a five- and six-layered cortex. It is heavily connected (reciprocally) with the hippocampal formation. This gyrus also has widespread connections with many areas of the cerebral cortex, including all the sensory cortical regions, as well as the cingulate gyrus. It is thought to play a key role in memory function.

The **cingulate gyrus**, which is situated above the corpus callosum (see Figure 17), consists of a five-layered cortex, as well as neocortex. The cingulate gyrus is connected reciprocally with the parahippocampal gyrus via a bundle of fibers in the white matter, known as the cingulum bundle (see next illustration). This connection unites the various portions of the limbic "lobe." It also has widespread connections with the frontal lobe.

Of the many tracts of the limbic system, two major tracts have been included in this diagram, the fornix and the anterior commissure.

- The **fornix** is one of the more visible tracts and is often encountered during dissections of the brain (e.g., see Figure 17). This fiber bundle connects the hippocampal formation with other areas (to be discussed with Figure 72A and Figure 72B).
- The **anterior commissure** is an older commissure than the corpus callosum and connects several structures of the limbic system on the two sides of the brain; these include the amygdala, the hippocampal formation, and parts of the parahippocampal gyrus, as well as the anterior portions of the temporal lobe. The anterior commissure will be seen on many of the limbic diagrams and can also be a useful reference point for orientation (e.g., see Figure 75B).

The other structures shown in this diagram include the diencephalon (the thalamus) and the brainstem. The corpus callosum "area" is indicated as a reference point in these illustrations (see next illustration).

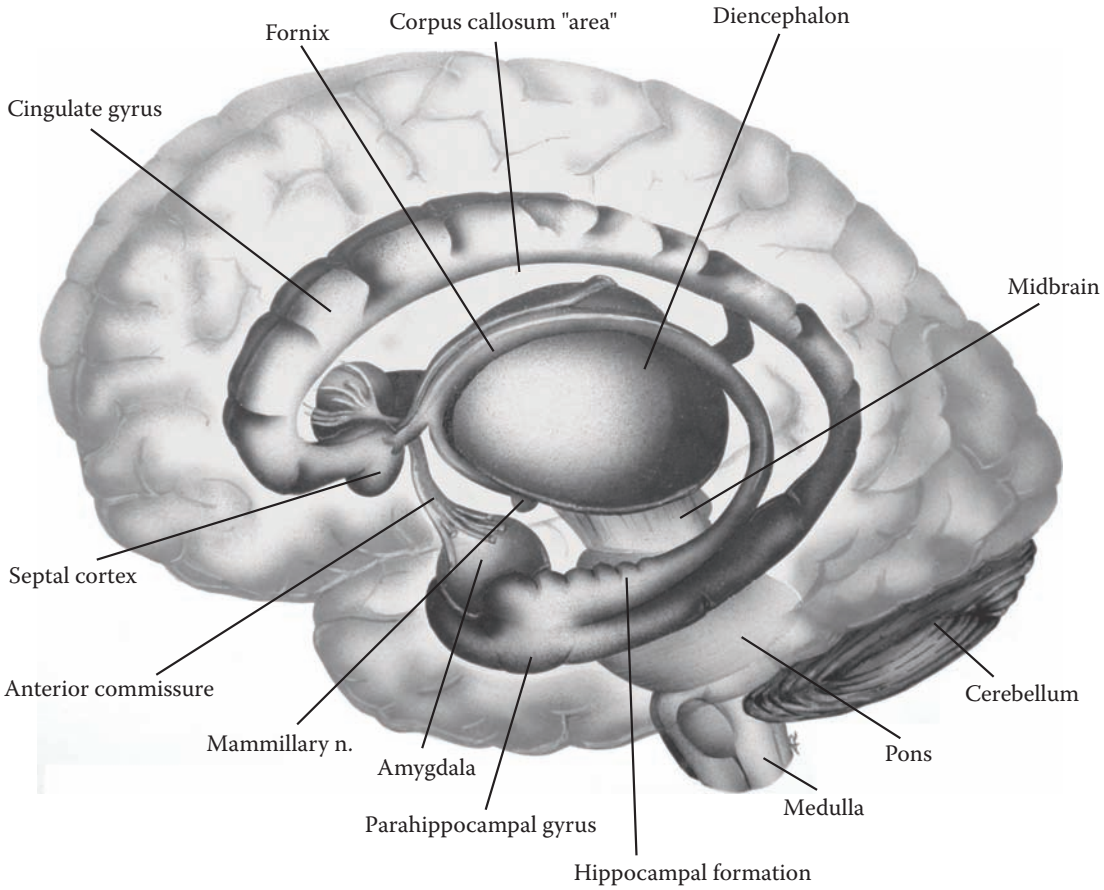


FIGURE 70A: Limbic Lobe 1 — Cortical

FIGURE 70B
LIMBIC LOBE 2

CINGULUM BUNDLE (PHOTOGRAPHIC VIEW)

This is a dissection of the brain, from the medial perspective, as depicted in the previous illustration (see also Figure 17). The brainstem and cerebellum have been removed from this specimen. The specimen has been tilted slightly to show more of the inferior aspect of the temporal lobe. The thalamus (diencephalon) has been excised, revealing the fibers of the internal capsule (see Figure 26).

The cortex of the cingulate gyrus has been scraped away (with a blunt instrument), revealing a bundle of fibers just below the surface. The dissection is continued to the parahippocampal gyrus, as demarcated by the collateral sulcus/fissure (see Figure 15A and Figure 15B). This fiber bundle, called the cingulum bundle, is seen to course between these two gyri of the limbic system. This association tract will be discussed as part of a limbic circuit known as the Papez circuit (discussed with Figure 77A).

The brain is dissected in such a way to reveal the fornix (of both sides) as this fiber tract courses from the hippocampal formation in the temporal lobe, passes over the diencephalon, and heads toward its connections (see Figure 72A and Figure 72B).

CINGULATE GYRUS

MacLean's studies have indicated that the development of this gyrus is correlated with the evolution of the mammalian species. He has postulated that this gyrus is important for nursing and play behavior, characteristics that are associated with the rearing of the young in mammals. It is this cluster of behavioral patterns that forms the basis for the other "F" in the list of functions of the limbic system — family (see Introduction to this section). The cingulate gyrus also seems to have an important role in attention, an important aspect of behavior, with connections to the prefrontal cortex.

A small cortical region under the anterior part (the rostrum) of the corpus callosum is also included with the limbic system. These small gyri (not labeled; located just in front of the anterior commissure in Figure 41B) are named the septal cortex (see previous illustration); this area along with the septal nuclei (to be shown in the next illustration) are collectively called the septal region (see Figure 78B).

EXTENDED LIMBIC LOBE

Other areas of the brain are now known to be involved in limbic functions and are included in the functional aspects of the limbic system. This includes large parts of the "prefrontal cortex," particularly cortical areas lying above the orbit, the orbitofrontal cortex (not labeled), as well as the cortex on the medial aspect of the frontal lobe (to be discussed with Figure 77B).

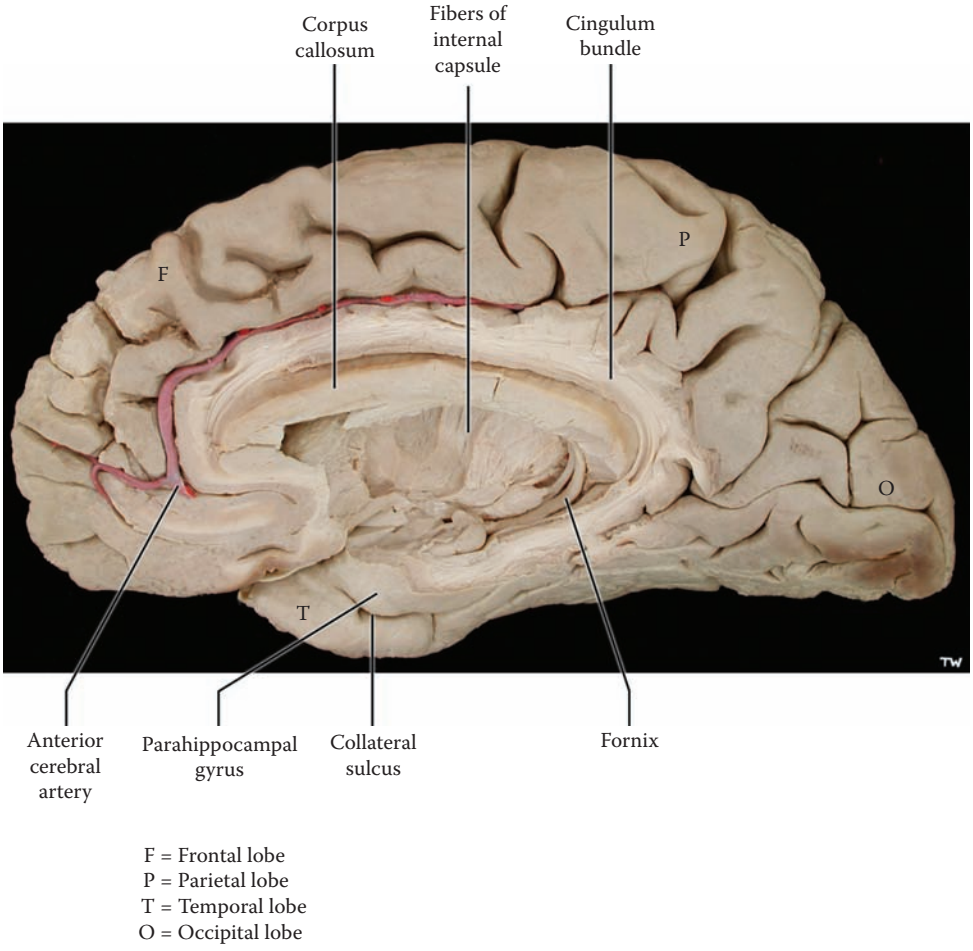


FIGURE 70B: **Limbic Lobe 2** — Cingulum Bundle (photograph)

FIGURE 71
LIMBIC SYSTEM

NONCORTICAL STRUCTURES

The term limbic system is the concept now used to include those parts of the brain that are associated with the functional definition of the limbic system.

This is an overall diagram focusing on the noncortical components of the limbic system, both core and extended. These structures are found in the forebrain, the diencephalon, and also in the midbrain. Each of the structures, including the connections, will be discussed in greater detail in subsequent illustrations when this diagram, indicated appropriately, will be used showing only the structures of the limbic system that are being described.

The noncortical areas include:

- Amygdala
- Septal nuclei (region)
- Basal forebrain
- Basal ganglia
- Thalamus
- Hypothalamas
- Limbic midbrain
- Olfactory system

Forebrain

The **amygdala**, also called the amygdaloid nucleus, a core limbic structure, is anatomically one of the basal ganglia (as discussed earlier with Figure 22; see Figure OL and Figure 25). Functionally, and through its connections, it is part of the limbic system. Therefore, it will be considered in this section of the atlas (see Figure 75A and Figure 75B).

The **septal region** includes two components, the cortical gyri below the rostrum of the corpus callosum, the septal cortex (see Figure 70A), and some nuclei deep to them, the septal nuclei; these nuclei are not located within the septum pellucidum in humans. The term septal region includes both the cortical gyri and the nuclei (see Figure 78B).

Not represented in this diagram is the area known as the **basal forebrain**. This subcortical region is composed of several cell groups located beside the hypothalamus and below the anterior commissure (see Figure 80A and Figure 80B). This somewhat obscure region has connections with several limbic areas and the prefrontal cortex.

Basal Ganglia

The ventral portions of the putamen and globus pallidus are now known to be connected with limbic functions and are part of the extended limbic system (see Figure 80B). These functional parts are being identified as the ventral striatum and ventral pallidum.

The **nucleus accumbens** is a specific nuclear area adjacent to the septal nuclei and the neostriatum (see Figure 24). It has recently been found to have a critically important function in activities where there is an aspect of reward and punishment; this is now thought to be the critical area of the brain involved in addiction.

Diencephalon

Two of the nuclei of the **thalamus**, the anterior group of nuclei and the dorsomedial nucleus (see Figure 12 and Figure 63), are part of the pathways of the limbic system, relaying information from subcortical nuclei to limbic parts of the cortex (the cingulate gyrus and areas of the prefrontal cortex).

The **hypothalamus** lies below and somewhat anterior to the thalamus (see Figure 17). Many nuclei of the hypothalamus function as part of the core limbic system. Only a few of these nuclei are shown, and among these is the prominent **mammillary nucleus**, which is visible on the inferior view of the brain (see Figure 15B). The connection of the hypothalamus to the pituitary gland is not shown.

Midbrain

The extended limbic system also includes nuclei of the midbrain, the "**limbic midbrain**." Some of the descending limbic pathways terminate in this region, and it is important to consider the role of this area in limbic functions. An important limbic pathway, the medial forebrain bundle interconnects the septal region, the hypothalamus, and the limbic midbrain (see Figure 78B).

Olfactory

The **olfactory system** is described with the limbic system, as many of its connections are directly with limbic areas. Years ago it was commonplace to think of various limbic structures as part of the "smell brain," the rhinencephalon. We now know that this is only partially correct. The olfactory input connects directly into the limbic system (and not via the thalamus, see Figure 79), but the limbic system is now known to have many other functional capabilities.

Tracts

The various tracts that interconnect the limbic structures — fornix, stria terminalis, ventral amygdalofugal pathway — will be discussed at the appropriate time with the relevant structure(s).

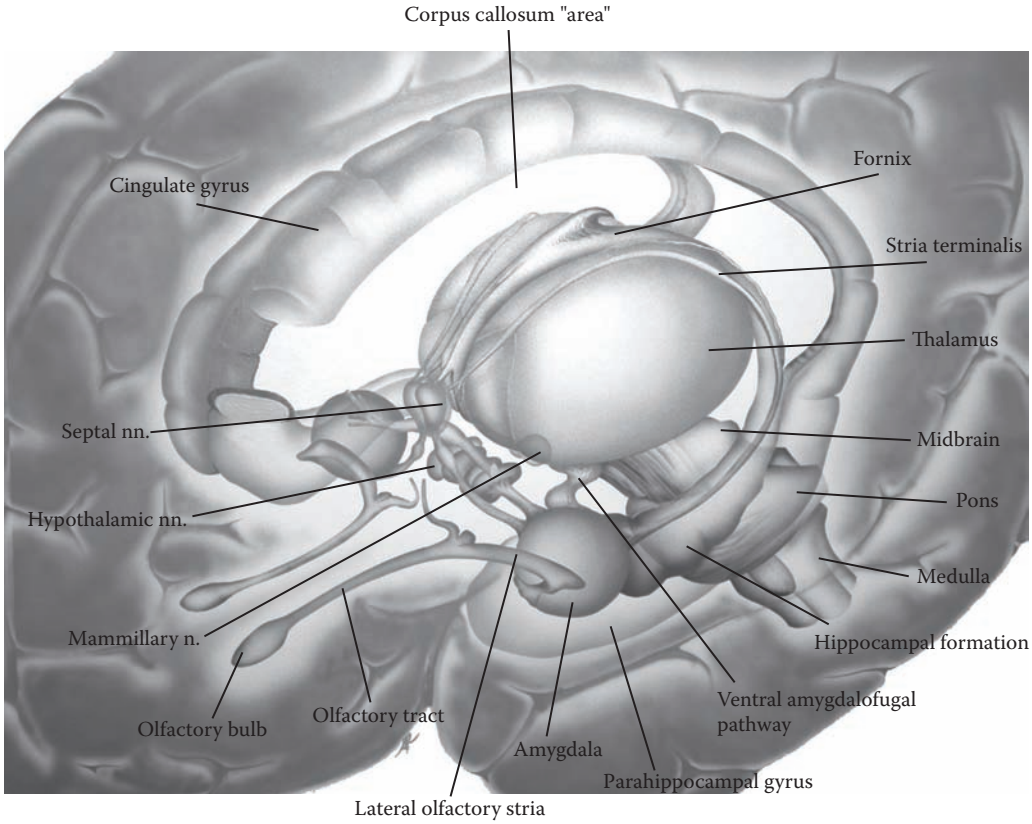


FIGURE 71: Limbic System — Noncortical

FIGURE 72A "HIPPOCAMPUS" 1

HIPPOCAMPAL FORMATION

This diagram, which is the same as Figure 71, highlights the functional portion of the limbic lobe to be discussed — the "hippocampus" (i.e., the hippocampal formation) and the pathway known as the fornix.

The hippocampal formation includes older cortical regions, all consisting of less than six layers, which are located deep within the most medial aspect of the temporal lobe in humans. The location and complex arrangement of the structures are illustrated and explained in this series of diagrams.

In the rat, the hippocampal formation is located dorsally, above the thalamus. During the evolution of the temporal lobe, these structures have migrated into the temporal lobe, leaving behind a fiber pathway, the fornix, which is located above the thalamus.

The term hippocampal formation includes (see Figure 72B):

- The **hippocampus proper**, a three-layered cortical area that, during development, becomes "rolled-up" and is no longer found at the surface of the hemispheres (as is the case for all other cortical regions)
- The **dentate gyrus**, a three-layered cortical area that is partly found on the surface of the brain, although its location is so deep that it presents a challenge to nonexperts to locate and visualize this thin ridge of cortex
- The **subicular region**, a transitional cortical area of three to five layers that becomes continuous with the parahippocampal gyrus located on the inferior aspect of the brain (see Figure 15B)

The fornix is a fiber bundle that is visible on medial views of the brain (see Figure 17 and Figure 41B). These fibers emerge from the hippocampal formation (shown in Figure 73; see also Figure 70B) and course over the thalamus, where they are found just below the corpus callosum (see coronal sections, Figure 29 and Figure 74). The fibers end in the septal region and in the mammillary nucleus of the hypothalamus (shown in the next illustration). Some fibers in the fornix are conveying information from these regions to the hippocampal formation. It is perhaps best to regard the fornix as an association bundle, part of the limbic pathways. It has attracted much attention because of its connections and because of its visibility and accessibility for research into the function of the hippocampal formation, particularly with regard to memory.

MEMORY

Recent studies in humans have indicated that the neurons located in one portion of the hippocampus proper, called the CA3 region, are critical for the formation of new memories — declarative or episodic types of memories (not procedural). This means that in order to "remember" some new fact or event, the new information must be registered within the hippocampal formation. This information is "processed" through some complex circuitry in these structures and is retained for a brief period of seconds. In order for it to be remembered for longer periods, some partially understood process occurs so that the transient memory trace is transferred to other parts of the brain, and this is now stored in working memory or as a long-term memory. The process of memory storage consolidation may require a period of hours, if not days.

In the study of the function of the hippocampus in animals, there is considerable evidence that the hippocampal formation is involved in constructing a "spatial map." According to this literature, this part of the brain is needed to orient in a complex environment (such as a maze). It is not quite clear whether this is a memory function or whether this spatial representation depends upon the connections of the hippocampal formation and parahippocampal gyrus with other parts of the brain.

Clinical Aspect

The clinical implications of the functional involvement of the hippocampal formation in memory will be further elaborated with Figure 73.

It is now possible to view the hippocampal area in detail on MRI and to assess the volume of tissue. Bilateral damage here apparently correlates with the loss of memory function in humans with Alzheimer's dementia, particularly for the formation of memories for new events or for new information (further discussed with Figure 73).

Additional Detail

A vestigial part of the hippocampal formation is still found above the corpus callosum, as shown in this illustration — not labeled.

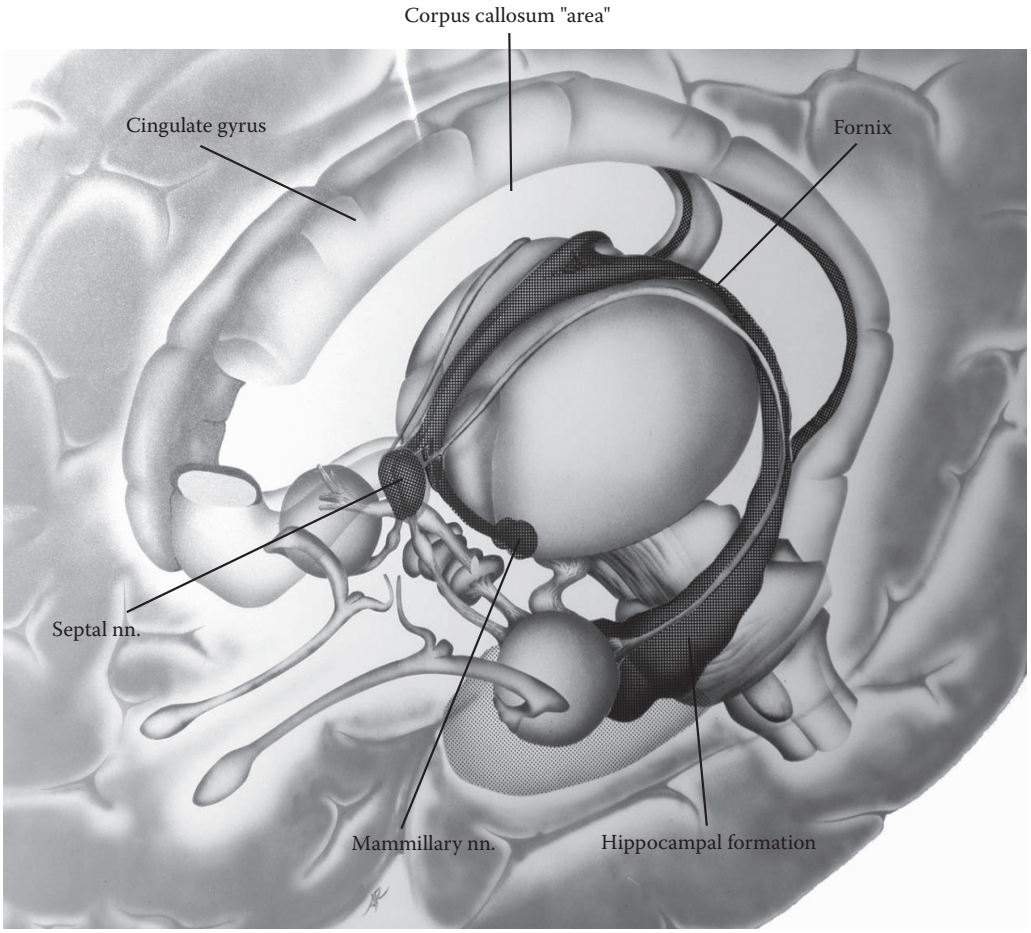


FIGURE 72A: **Hippocampus 1** — Hippocampal Formation

FIGURE 72B "HIPPOCAMPUS" 2

HIPPOCAMPAL FORMATION: THREE PARTS

The hippocampal formation is one of the most important structures of the limbic system in humans. It is certainly the most complex. This diagram isolates the component parts of the hippocampal formation, on both sides.

One expects a cortical area to be found at the surface of the brain, even if this surface is located deep within a fissure. During the evolution and development of the hippocampal formation, these areas became "rolled up" within the brain. The photographic view of the hippocampal formation is shown in Figure 74.

Note to the Learner: The learner is advised to consult Williams and Warwick, one of the reference books, for a detailed visualization and understanding of this developmental phenomenon.

THE HIPPOCAMPUS PROPER

The hippocampus proper consists of a three-layered cortical area. This forms a large mass, which actually intrudes into the ventricular space of the inferior horn of the lateral ventricle (see Figure 73 and Figure 74). In a coronal section through this region, there is a certain resemblance of the hippocampal structures to the shape of a seahorse (see Figure 38 and Figure 74). It is from this shape that the name "hippocampus" is derived, from the French word for seahorse. The other name for this area is **Ammon's horn** or *cornu ammonis* (**CA**), named after an Egyptian deity with ram's horns because of the curvature of the hippocampus in the brain. (This cortical region has been divided into a number of subportions, CA 1–4, usually studied in more advanced courses.)

THE DENTATE GYRUS

The dentate gyrus is also a phylogenetically older cortical area consisting of only three layers. During the formation discussed above, the leading edge of the cortex detaches itself and becomes the dentate gyrus. Parts of it remain visible at the surface of the brain. Since this small surface is buried on the most medial aspect of the temporal lobe and is located deep within a fissure, it is rarely located in studies of the gross brain. Its cortical surface has serrations, which led to its name, dentate (referring to teeth).

The appearance of the dentate gyrus is shown on the view of the medial aspect of the temporal lobe (on the far side of the illustration; see also Figure 76). A "cut" section through the temporal lobe (as seen in the lower portion of this illustration) indicates that the dentate gyrus is more extensive than its exposed surface portion.

THE SUBICULAR REGION

The next part of the cortically rolled-in structures that make up the hippocampal formation is the subicular region (see also Figure 29 and Figure 74). The cortical thickness is transitional, starting from the three-layered hippocampal formation to the six-layered parahippocampal gyrus. (Again, there are a number of subparts of this area, which are rarely studied in an introductory course.)

CONNECTIONS AND FUNCTION

In the temporal lobe, the six-layered parahippocampal gyrus provides extensive input to the adjacent hippocampal formation. The hippocampal formation also receives input from the amygdala. There are extensive interconnections within the component parts of the hippocampal formation itself.

Part of the output of the hippocampal formation is directed back to the parahippocampal gyrus, establishing a strong reciprocal connection. This is analogous to the cortical association pathways described earlier. The parahippocampal gyrus has widespread connections with other cortical areas of the brain, particularly sensory areas.

The other major output of the hippocampal formation is through the **fornix**. Only the hippocampus proper and the subicular region project fibers into the fornix. This tract can be regarded as a subcortical pathway that terminates in the septal region (via the precommissural fibers, discussed with Figure 78B) and in the mammillary nucleus of the hypothalamus (via the post-commissural fibers, discussed with Figure 78A). There are also connections in the fornix from the septal region back to the hippocampal formation. The dentate gyrus only connects with other parts of the hippocampal formation and does not project beyond.

Clinical Aspect

The term medial or mesial temporal sclerosis is a general term for damage to the hippocampal region and adjacent structures located in this part of the brain. Lesions in this area are known to be associated with epilepsy (particularly psychomotor seizures), classified as a partial complex seizure disorder.

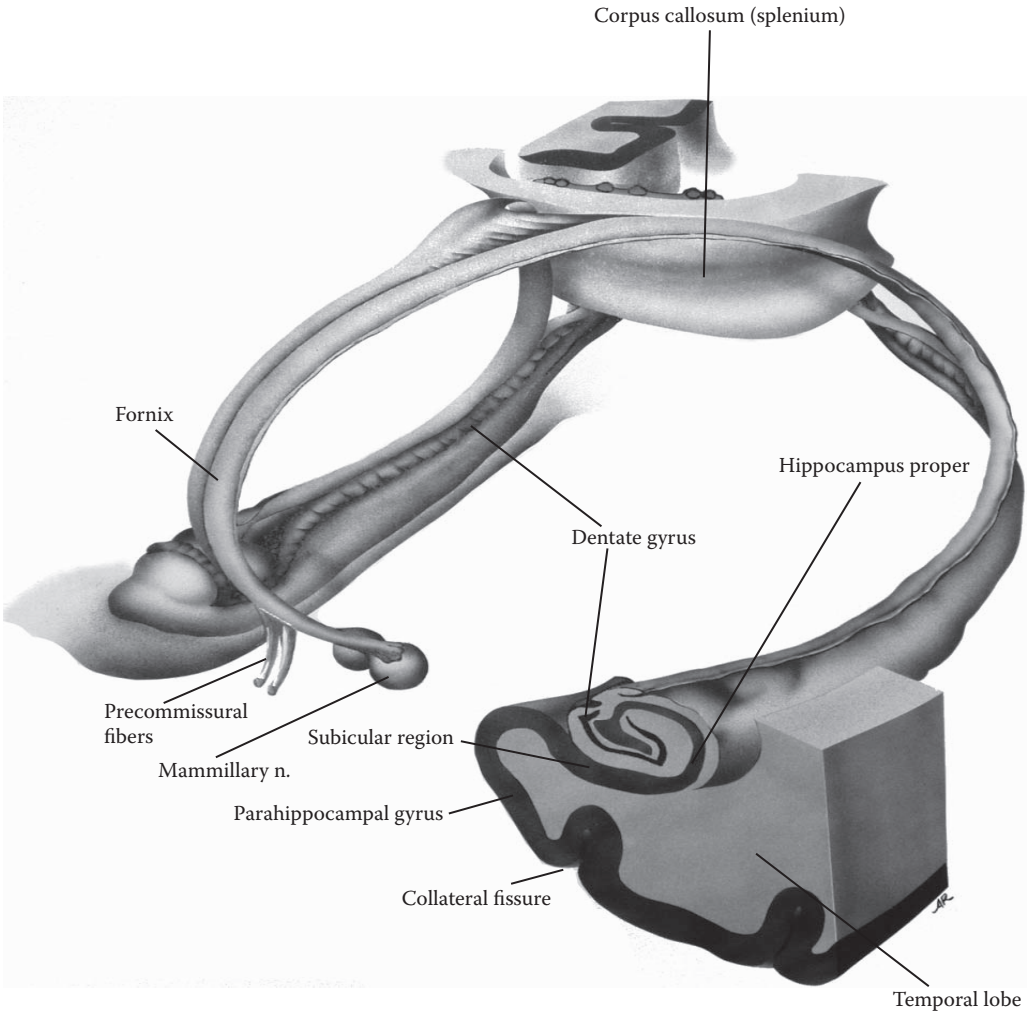


FIGURE 72B: **Hippocampus 2** — Hippocampal Formation (3 parts)

FIGURE 73
"HIPPOCAMPUS" 3

THE HIPPOCAMPAL FORMATION (PHOTOGRAPHIC VIEW)

The brain is being shown from the dorsolateral aspect (as in Figure 14A). The left hemisphere has been dissected by removing the cortex and white matter above the corpus callosum: the lateral ventricle has been exposed from this perspective. The choroid plexus tissue has been removed from the ventricle in order to improve visualization of the structures (see Figure 20A). This dissection also shows the lateral aspect of the lenticular nucleus, the putamen, and the fibers of the internal capsule emerging between it and the thalamus (see Figure OA, Figure OL, Figure 7, Figure 25, and Figure 27).

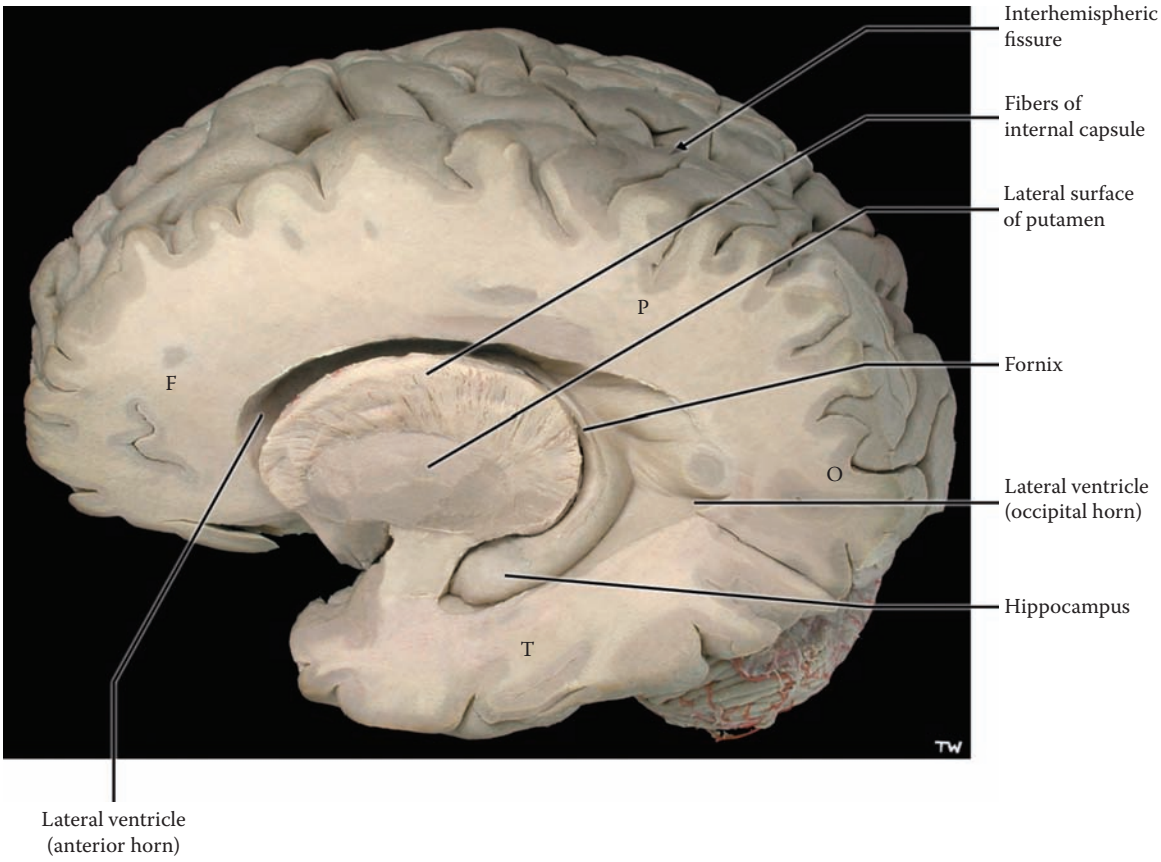
A similar dissection has been performed in the temporal lobe, thereby exposing the inferior horn of the lateral ventricle (see Figure 20A). A large mass of tissue is found protruding into the inferior horn of this ventricle — named the hippocampus, a visible gross brain structure. In fact, the correct term now used is the hippocampal formation. In a coronal section through this region the protrusion of the hippocampus into the inferior horn of the lateral ventricle also can be seen, almost obliterating the ventricular space (shown in the next illustration; see also Figure 29, Figure 30, Figure 38, and Figure 76).

The hippocampal formation is composed of three distinct regions — the hippocampus proper (Ammon's horn), the dentate gyrus, and the subicular region, as explained in the previous diagram. The fiber bundle that arises from the visible "hippocampus," the fornix, can be seen adjacent to the hippocampus in the temporal lobe (see Figure 70A and Figure 70B), and it continues over the top of the thalamus to the septal region and mammillary nucleus (discussed with the previous illustration).

Clinical Aspect — Memory

We now know that the hippocampal formation is one of the critical structures for memory. This function of the hippocampal formation became understood because of an individual known in the literature as H.M., who has been extensively studied by neuropsychologists. H.M. had surgery several decades ago for a valid therapeutic reason — the removal of an epileptic area in the temporal lobe of one side, which was the source of intractable seizures. Most importantly, the surgeons did not know, and could not know according to the methods available at that time, that the contralateral hippocampal area was also severely damaged. This surgery occurred, unfortunately, before the functional contribution of this area to memory formation was known. Since the surgery, H.M. has not been able to form any new memory for events or facts, although he has been taught new motor skills (called procedural memory). (The full story of H.M. and his deficits is found in Kolb and Whishaw — see the Annotated Bibliography.)

We now know that bilateral damage or removal of the anterior temporal lobe structures, including the amygdala and the hippocampal formation, leads to a unique condition in which the person can no longer form new declarative or episodic memories, although older memories are intact. The individual cannot remember what occurred moments before. Therefore, the individual is unable to learn (i.e., to acquire new information) and is not able to function independently. If surgery is to be performed in this region nowadays, special testing is done to ascertain that the side contralateral to the surgery is intact and functioning.



F = Frontal lobe
P = Parietal lobe
T = Temporal lobe
O = Occipital lobe

FIGURE 73: Hippocampus 3 — The Hippocampus (photograph)

FIGURE 74
"HIPPOCAMPUS" 4

CORONAL BRAIN SECTION (PHOTOGRAPHIC VIEW)

This section is taken posterior to the one shown in Figure 29 and includes the inferior horn of the lateral ventricle (see Figure 20A and Figure 73). The basal ganglia, putamen and globus pallidus, are no longer present (see Figure 22 and Figure 25). The corpus callosum is seen in the depth of the interhemispheric fissure, and at this plane of section the fornix is found just below the corpus calluosum. The lateral ventricles are present, as the body of the ventricle, and choroid plexus is seen on its medial corner (see Figure 20A). The section passes through the midbrain (with the red nucleus and the substantia nigra) and the pons, as shown in the upper right image.

The inferior horn of the lateral ventricles is found in the temporal lobes on both sides and is seen as only a small crescent-shaped cavity (shown also in Figure 38). The inferior horn of the lateral ventricle is reduced to a narrow slit because a mass of tissue protrudes into this part of the ventricle from its medial-inferior aspect. Closer inspection of this tissue reveals that it is gray matter; this gray matter is in fact the hippocampal formation.

LOWER INSERT

This higher magnification of the hippocampal area allows one to follow the gray matter from the hippocampus proper medially and through an intermediate zone, known as the subicular region (as in Figure 72B), until it becomes continuous with the gray matter of the parahippocampal gyrus. The hippocampus proper has only three cortical layers. The subicular region consists of four to five layers; the parahippocampal gyrus is mostly a six-layered cortex. The configuration of the dentate gyrus also can be seen. This view also allows us to understand that the parahippocampal gyrus is named because it lies beside the "hippocampus."

Clinical Aspect

The neurons of the hippocampal area are prone to damage for a variety of reasons, including vascular conditions. The key neurons for the memory function are located in area CA 3 of the hippocampus proper, and these neurons are extremely sensitive to anoxic states. An acute hypoxic event, such as occurs in a cardiac arrest, is thought to trigger a delayed death of these neurons, several days later, termed *apoptosis*, programmed cell death. Much research is now in progress to try to understand this cellular phenomenon and to devise methods to stop this reaction of these neurons.

Currently, studies indicate that in certain forms of dementia, particularly Alzheimer's, there is a loss of neurons in this same region of the hippocampus proper. This loss is due to involvement of these neurons in the disease process. Again, this correlates with the type of memory deficit seen in this condition — loss of short-term memory — although the disease clearly involves other neocortical areas, which goes along with the other cognitive deficits typical for this disease.

Additional Detail

The relationship of the caudate nucleus with the lateral ventricle is shown in two locations, the body with the body of the ventricle, and the tail in the "roof" of the inferior horn (see Figure 25).

The space between the thalamic areas in this section is not the third ventricle; it is a cistern of the subarachnoid space, outside the brain, because this coronal section has been taken at the posterior tip of the diencephalic region (see Figure 29 and Figure 30). It is located posterior to the pineal and the colliculi, named the quadrigeminal cistern (the four colliculi are also called the quadrigeminal plate, see Figure 10, Figure 21, and Figure 28A). It has extensions or wings laterally called the cisterna ambiens (see Figure 28A). The posterior commissure also is seen.

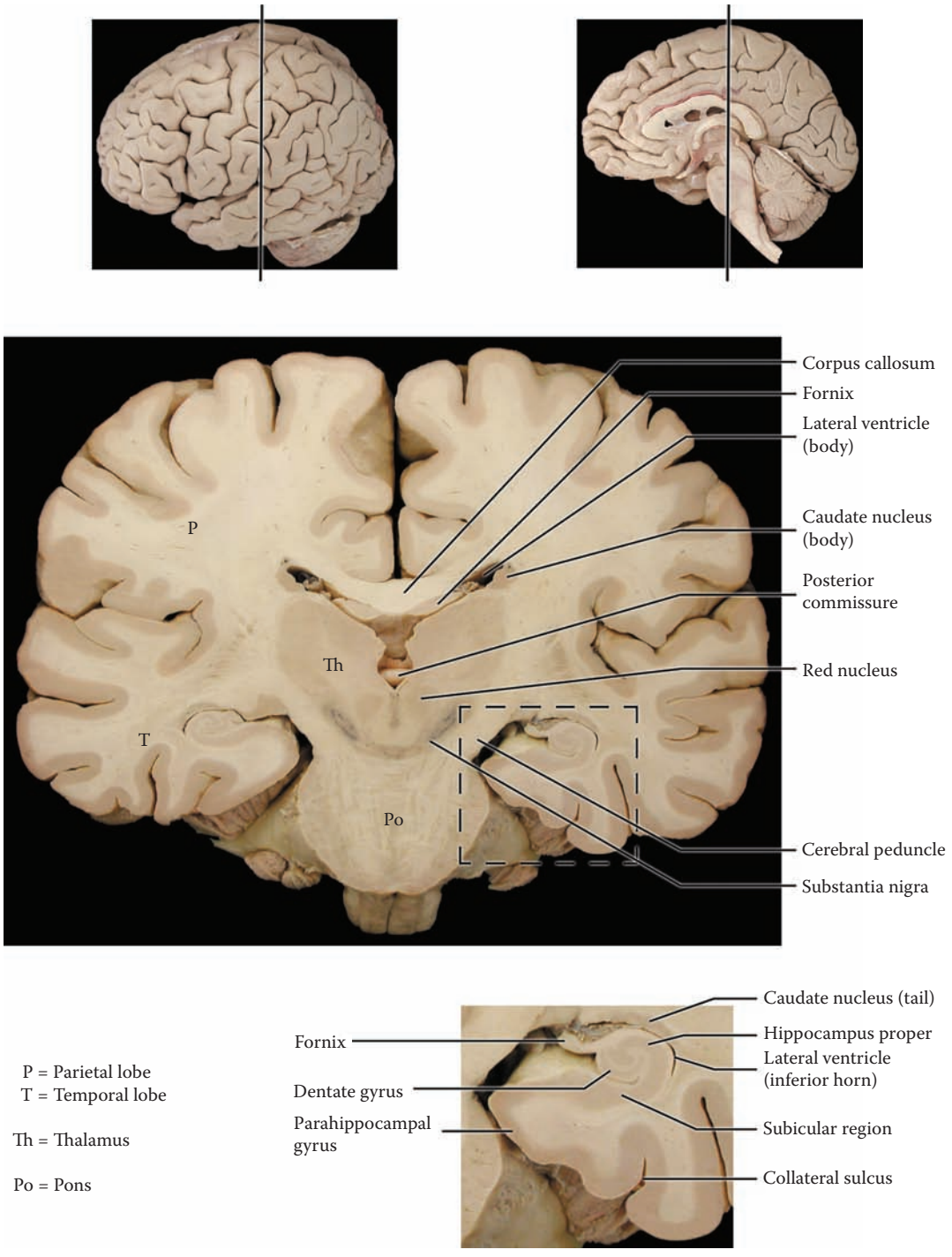


FIGURE 74: **Hippocampus 4** — Coronal View (photograph)

FIGURE 75A
AMYGDALA 1

AMYGDALA — LOCATION AND FUNCTION

This diagram, which is the same as Figure 71, highlights a functional portion of the limbic system — the amygdala and its pathways, the stria terminalis and the ventral amygdalofugal pathway. The septal region and functionally connected portions of the midbrain and medulla are also marked.

The amygdala (amygdaloid nucleus) is a subcortical nuclear structure located in the temporal lobe in humans (see Figure 25 and Figure 29). As a subcortical nucleus of the forebrain, it belongs by definition with the basal ganglia, but its connections are with limbic structures and it is now almost always described with the limbic system.

The amygdala is located between the temporal pole (the most anterior tip of the temporal lobe) and the end of the inferior horn of the lateral ventricle (in the temporal lobe, see Figure OL and Figure 25). The nucleus is located "inside" the uncus, which is seen on the inferior aspect of the brain as a large medial protrusion of the anterior aspect of the temporal lobe (see Figure 15A and Figure 15B).

The amygdala receives input from the olfactory system, as well as from visceral structures. Two fiber tracts are shown connecting the amygdala to other limbic structures, a dorsal one (the stria terminalis) and a ventral one (the ventral amygdalofugal pathway, consisting of two parts). These will be described in detail with the following diagram.

The amygdala in humans is now being shown, using functional MRI imaging, to be the area of the brain that is best correlated with emotional reactions. The emotional aspect of the response of the individual is passed on to the frontal cortex (discussed with the connections in the next illustration), where "decisions" are made regarding possible responses. In this way, the response of the individual incorporates the emotional aspect of the situation.

Stimulation of the amygdaloid nucleus produces a variety of vegetative responses, including licking and chewing movements. Functionally, in animal experimentation, stimulation of the amygdala may produce a rage response, whereas removal of the amygdala (bilaterally) results in docility. Similar responses are also seen with stimulation or lesions in the hypothalamus. Some of these responses may occur through nuclei in the midbrain and medulla.

In monkeys, bilateral removal of the anterior parts of the temporal lobe (including the amygdala) produces a number of behavioral effects which are collectively called the **Kluver-Bucy syndrome**. The monkeys evidently become tamer after the surgery, put everything into their mouths, and display inappropriate sexual behavior.

The amygdala is also known to contain a high amount of enkephalins. It is not clear why this is so and what may be the functional significance.

Clinical Aspect

The amygdala is known to have a low threshold for electrical discharges, which may make it prone to be the focus for the development of seizures. This seems to occur in *kindling*, an experimental model of epilepsy. In humans, epilepsy from this part of the brain (anterior and medial temporal regions) usually gives rise to complex partial seizures, sometimes called temporal lobe seizures, in which oral and licking movements are often seen, along with a loss of conscious activity (see also Figure 72B).

In very rare circumstances, bilateral destruction of the amygdala is recommended in humans for individuals whose violent behavior cannot be controlled by other means. This type of treatment is called psychosurgery.

The role of the amygdala in the formation of memory is not clear. Bilateral removal of the anterior portions of the temporal lobe in humans, for the treatment of severe cases of epilepsy, results in a memory disorder, which has been described with the hippocampal formation (discussed with Figure 73). It is possible that the role of the amygdala in the formation of memories is mediated either through the connections of this nuclear complex with the hippocampus, or with the dorsomedial nucleus of the thalamus.

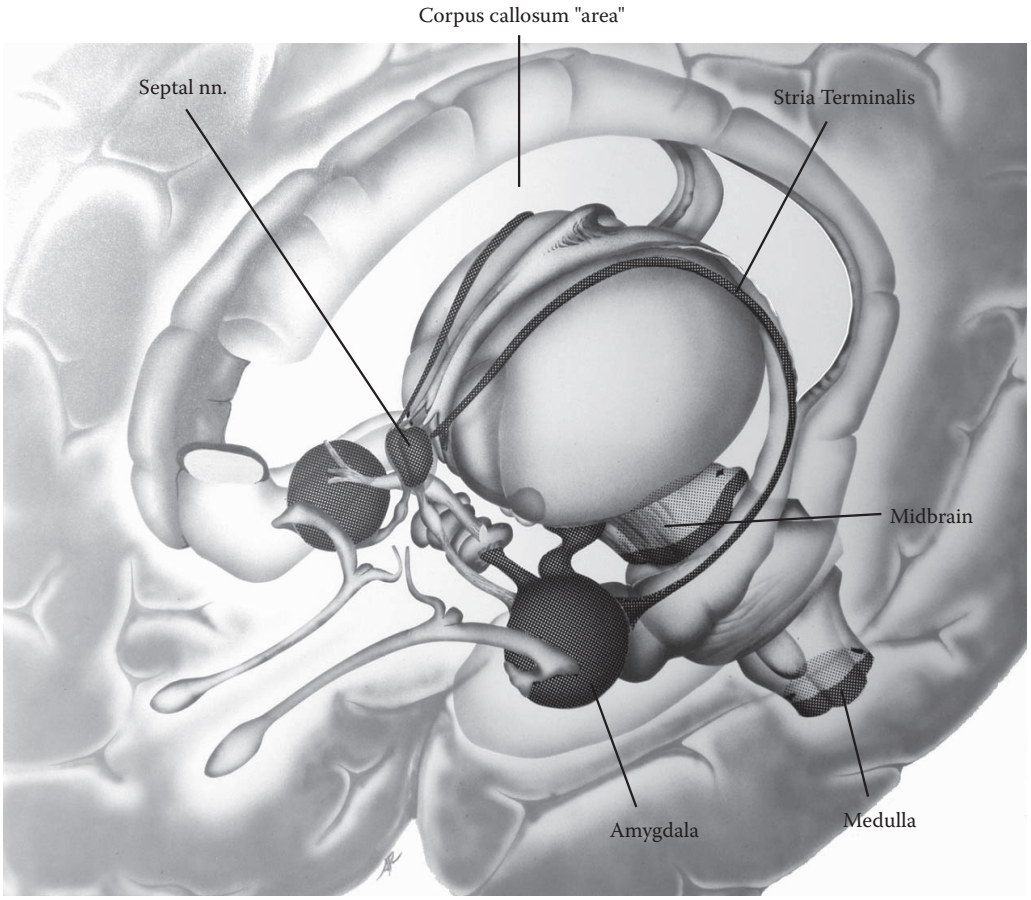


FIGURE 75A: Amygdala 1 — Location

FIGURE 75B
AMYGDALA 2

THE AMYGDALA — CONNECTIONS

One of the major differences between the amygdala and the other parts of the basal ganglia is that the amygdala is not a homogeneous nuclear structure but is composed of different component parts. These are not usually studied in an introductory course.

The amygdala receives a variety of inputs from other parts of the brain, including the adjacent parahippocampal gyrus (not illustrated). It receives olfactory input directly (via the lateral olfactory stria, see Figure 79) and indirectly from the cortex of the uncal region (as shown on the left side of the diagram).

The amygdaloid nuclei are connected to the hypothalamus, thalamus (mainly the dorsomedial nucleus), and the septal region. The connections, which are reciprocal, travel through two routes:

- A dorsal route, known as the **stria terminalis**, which follows the ventricular curve and is found on the upper aspect of the thalamus (see previous illustration). The stria terminalis lies adjacent to the body of the caudate nucleus in this location (see Figure 76). This connects the amygdala with the hypothalamus and the septal region.
- A ventral route, known as the ventral pathway or the **ventral amygdalofugal** pathway. This pathway, which goes through the basal forebrain region (see Figure 80B), connects the amygdala to the hypothalamus (as shown) and to the thalamus (the fibers are shown "en route"), particularly the dorsomedial nucleus (see Figure 63 and Figure 77B).

The connection with the hypothalamus is likely the basis for the similarity of responses seen in animals with stimulation of the amygdala and the hypothalamus (see previous illustration and Figure 78A). This pathway to the hypothalamus may result in hormonal responses, and the connections with the midbrain and medulla may lead to autonomic responses (see Figure 78A).

Further possible connections of the amygdala with other limbic structures and other parts of the brain can occur via the septal region (see Figure 78B), and via the dorsomedial nucleus of the thalamus to the prefrontal cortex (see Figure 77B).

The anterior commissure conveys connections between the nuclei of the two sides.

Clinical Aspect

Seizure activity in the anterior temporal region may spread to the orbitofrontal region, via a particular group of fibers called the uncinate bundle.

Additional Detail

The association pathway, called the uncinate fasciculus, is a "U-shaped" bundle of fibers between the anterior temporal region and the inferior portion of the frontal lobe. (It is suggested that the learner consult Carpenter — see the Annotated Bibliography — for an illustration of this structure).

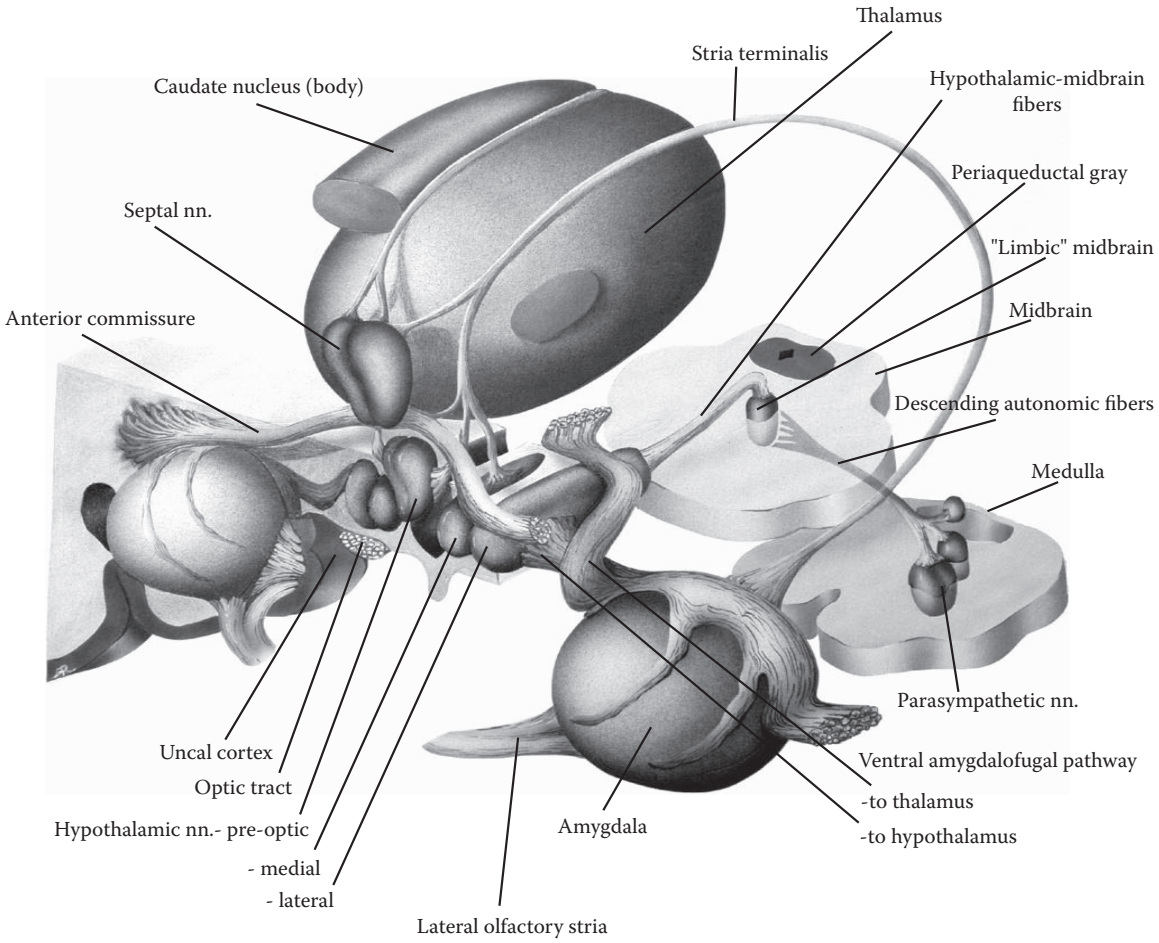


FIGURE 75B: Amygdala 2 — Connections

FIGURE 76
LIMBIC "CRESCENT"

LIMBIC STRUCTURES AND THE LATERAL VENTRICLE

The temporal lobe is a more recent addition in the evolution of the hemispheres and develops later in the formation of the brain. During the development of the temporal lobe, a number of structures migrate into it — the lateral ventricle, the hippocampal formation, the caudate nucleus, as well as various tracts, the fornix and stria terminalis.

The lateral ventricle and associated structures form a crescent in the shape of a reverse letter C (see Figure OL and Figure 20A). These relationships are shown in this diagram by showing detailed "cuts" at various points along the lateral ventricle:

- The first section is through the anterior horn of the ventricle, in front of the interventricular foramen (of Monro).
- The following section is through the body of the ventricle, over the dorsal aspect of the thalamus.
- The next section shows the ventricle at its curvature into the temporal lobe, the area called the atrium or the trigone.
- The last section is through the inferior horn of the ventricle, in the temporal lobe, including the hippocampal formation.

Note to the Learner: The initials used in these sections to identify structures are found in brackets after the labeled structure in the main part of the diagram.

- **Caudate Nucleus** (see Figure OL, Figure 23, Figure 24, and Figure 25):
  The various parts of the caudate nucleus, the head, the body, and the tail, follow the inner curvature of the lateral ventricle. The large head is found in relation to the anterior horn of the lateral ventricle, where it bulges into the space of the ventricle (see Figure 27 and Figure 28A). The body of the caudate nucleus is coincident with the body of the lateral ventricle, on its lateral aspect (see Figure 29, Figure 30, and Figure 74). As the caudate follows the ventricle into the temporal lobe, it becomes the tail of the caudate nucleus, where it is found on the upper aspect of the inferior horn, its roof (see Figure 38).
- **Hippocampal formation** (see Figure 72A, Figure 72B, Figure 73, and Figure 74):
  The hippocampal formation is found in the temporal lobe situated medial and inferior to the ventricle. It bulges into the ventricle, almost obliterating the space; it is often difficult to visualize the small crevice of the ventricle in specimens and radiograms. The dentate gyrus is again seen (on the far side) with its indented surface (see also Figure 72B). The configuration of the three parts of the hippocampal formation is shown in the lower inset (see Figure 74).
- **Fornix**:
  The fornix is easily found in studies of the gross brain (e.g., see Figure 17 and Figure 41B). Its fibers can be seen as a continuation of the hippocampal formation (see Figure 72B and Figure 73), and these fibers course on the inner aspect of the ventricle as they sweep forward above the thalamus. In the area above the thalamus and below the corpus callosum (see coronal section, Figure 29 and Figure 30), the fornix is found at the lower edge of the septum pellucidum. In this location, the fornix of one side is adjacent to that of the other side (see also Figure 71); there are some interconnections between the two sides in this area.
  The fibers of the fornix pass in front of the interventricular foramen (see medial view of brain in Figure 17). It then divides into precommissural fibers to the septal region (see Figure 78B), and post-commissural fibers, through the hypothalamus, to the mammillary nucleus (which is not portrayed in this diagram, see Figure 72B and Figure 78B).
- **Amygdala** (see Figure 25 and Figure 75A):
  The amygdala is clearly situated anterior to the inferior horn of the lateral ventricle and in front of the hippocampal formation.
- **Stria Terminalis**:
  The stria terminalis follows essentially the same course as the fornix (see Figure 71), connecting the amygdala with the septal region and hypothalamus (see Figure 78B).

Additional Detail

In the temporal lobe, the stria is found in the roof of the inferior horn of the lateral ventricle. The stria terminalis is found slightly more medially than the fornix on the dorsal aspect of the thalamus, in the floor of the body of the lateral ventricle.

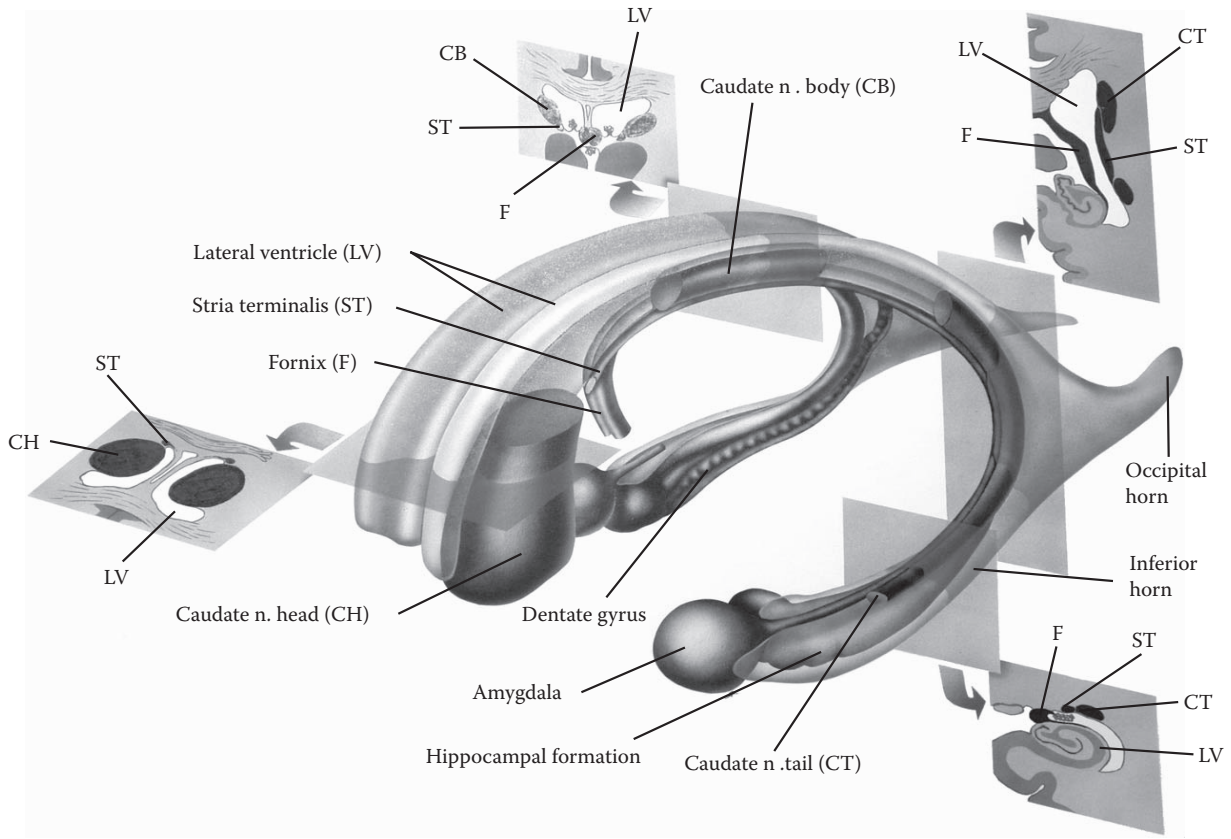


FIGURE 76: Limbic Structures and Lateral Ventricle

FIGURE 77A
LIMBIC DIENCEPHALON 1

ANTERIOR NUCLEUS

This detailed diagram shows one of the major connections of the limbic system via the thalamus. This diagram shows an enlarged view of the thalamus of one side (see Figure 11 and Figure 12), the head of the caudate nucleus, as well as a small portion of the cingulate gyrus (see Figure 17). Immediately below is the hypothalamus, with only the two mammillary nuclei being shown (see Figure 71).

ANTERIOR NUCLEUS — CINGULATE GYRUS

The fibers of the fornix (carrying information from the hippocampal formation) have been followed to the mammillary nuclei (as the post-commissural fibers, see Figure 72B). A major tract leaves the mammillary nuclei, the **mammillo-thalamic tract**, and its fibers are headed for a group of association nuclei of the thalamus called the **anterior nuclei** (see Figure 12 and Figure 63). (**Note to the Learner**: The learner is advised to refer to the classification of the thalamic nuclei, see Figure 12 and also Figure 63.)

Axons leave the anterior nuclei of the thalamus and course through the anterior limb of the internal capsule (see Figure 26). These fibers course between the caudate nucleus (head and body) and the lentiform nucleus (which is just visible in the background). The axons terminate in the cortex of the cingulate gyrus after passing through the corpus callosum (see Figure 17). The continuation of this circuit is discussed below.

PAPEZ CIRCUIT

About 60 years ago, James Papez described a pathway involving some limbic and cortical structures and associated pathways. These, he postulated, formed the anatomical substrate for emotional experiences. The pathway forms a series of connections, which has since been called the Papez circuit. We have continued to learn about many other pathways and structures involved in processing "emotion," but this marked the beginning of the unfolding of our understanding.

To review, fibers leave the hippocampal formation and proceed through the fornix, and some of these fibers have been shown to terminate in the mammillary nuclei of the hypothalamus. From here, a new pathway, the mammillothalamic tract, ascends to the anterior group of thalamic nuclei. This group of nuclei projects to the cingulate gyrus (see Figure 63).

From the cingulate gyrus, there is an association bundle, the cingulum, which connects the cingulate gyrus (reciprocally) with the parahippocampal gyrus as part of the limbic lobe (refer to Figure 70A and Figure 70B). The parahippocampal gyrus projects to the hippocampal formation, which processes the information and sends it via the fornix to the mammillary nuclei of the hypothalamus (and the septal region). Hence, the circuit is formed.

We now have a broader view of the limbic system, and the precise functional role of the Papez circuit is not completely understood. It should be realized that although there is a circuitry that forms a loop, the various structures have connections with other parts of the limbic system and other areas of the brain, and thus can influence other neuronal functions (to be discussed with the limbic system synthesis at the end of this section).

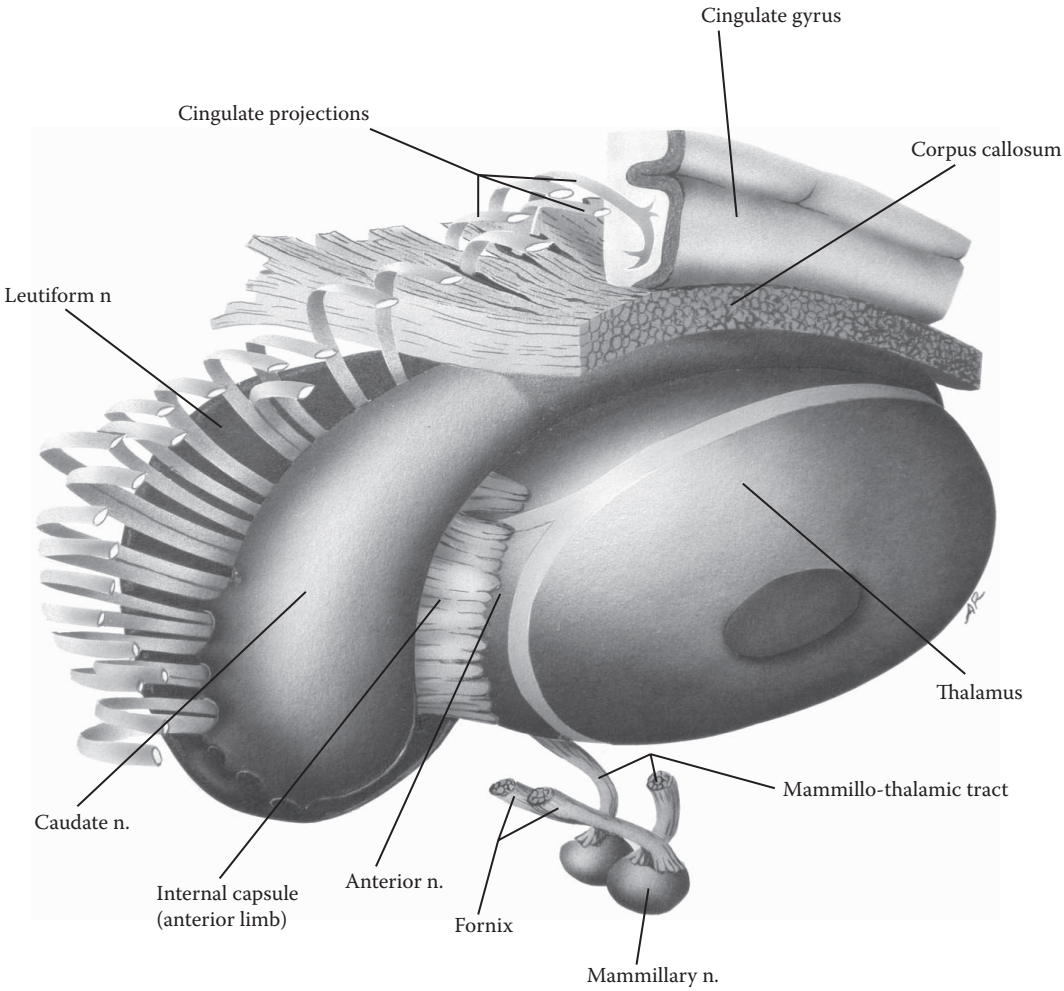


FIGURE 77A: **Limbic Diencephalon 1** — Anterior Nucleus

FIGURE 77B
LIMBIC DIENCEPHALON 2

DORSOMEDIAL NUCLEUS

The thalamus of both sides is shown in this diagram, focusing on the medial nuclear mass of the thalamus, the dorsomedial nucleus, one of the most important of the association nuclei of the thalamus (see Figure 11 and Figure 12).

Shown below is the amygdala with one if its pathways, the ventral amygdalofugal fibers, projecting to the dorsomedial nucleus (see Figure 75A and Figure 75B). This pathway brings "emotional" information to the thalamus. The dorsomedial nucleus collects information from a variety of sources, including other thalamic nuclei, as well as from various hypothalamic nuclei (see Figure 63).

The dorsomedial nucleus projects heavily to the frontal lobe, particularly to the cortical area that has been called the prefrontal cortex (see Figure 14A). The projection thus includes the emotional component of the experience. This pathway passes through the anterior limb of the internal capsule, between the head of the caudate nucleus and the lentiform nucleus (see Figure 26). The fibers course in the white matter of the frontal lobes.

Our expanded view of the limbic system now includes its extension to this prefrontal cortex, specifically the orbital and medial portions of the frontal lobe; this has been called the **limbic forebrain**. Widespread areas of the limbic system and association cortex of the frontal lobe, particularly the medial and orbital portions, are involved with human reactions to pain, particularly to chronic pain, as well as the human experiences of grief and reactions to the tragedies of life.

Clinical Aspect — Psychosurgery

The projection of the dorsomedial nucleus to the prefrontal cortex has been implicated as the key pathway that is interrupted in a now-banned surgical procedure. Before the era of medication for psychiatric disorders, when up to one-half of state institutions were filled with patients with mental illness, a psychosurgical procedure was attempted to help alleviate the distressing symptoms of these diseases.

The procedure involved the introduction of a blunt instrument into the frontal lobes, passing the instrument (bilaterally) through the orbital bone (which is a very thin plate of bone) above the eye. This interrupts the fibers projecting through the white matter, presumably including the projection from the dorsomedial nucleus. This operation became known as a *frontal lobotomy.*

Long-term studies of individuals who have had frontal lobotomies have shown profound personality changes in these individuals. These people become emotionally "flat" and lose some hard-to-define human quality in their interpersonal interactions. In addition, such an individual may perform socially inappropriate acts that are not in keeping with the personality of that individual prior to the surgery.

Once the long term effects of this surgery became clear, and since powerful and selective drugs became widely available for various psychiatric conditions, this surgery was abandoned in the 1960s and is not performed nowadays.

This same procedure had also been recommended for the treatment of pain in terminal cancer patients, as part of the palliative care of an individual. After the surgery, the individual is said to still have the pain but no longer "suffers" from it, that is, the psychic aspect of the pain has been removed. There may even be a reduced demand for pain medication such as morphine. Again, other approaches to pain management are now used.

PHINEAS GAGE

Phineas Gage has become a legendary figure in the annals of the history of the brain. In brief, Gage was working on the construction of a railway in the 1800s, when an untimely explosion drove a steel peg through his brain. The steel peg is said to have penetrated the orbit and the frontal lobes, much like the surgical procedure described above, emerging through the skull. He survived and lived on; his personality changes, which have been well documented, subsequent to this accident concur with those described following a frontal lobotomy. The story of Phineas showing a reconstruction of his injury and describing the changes in his personality can be found in Kolb and Whishaw (see the Annotateed Bibliography).

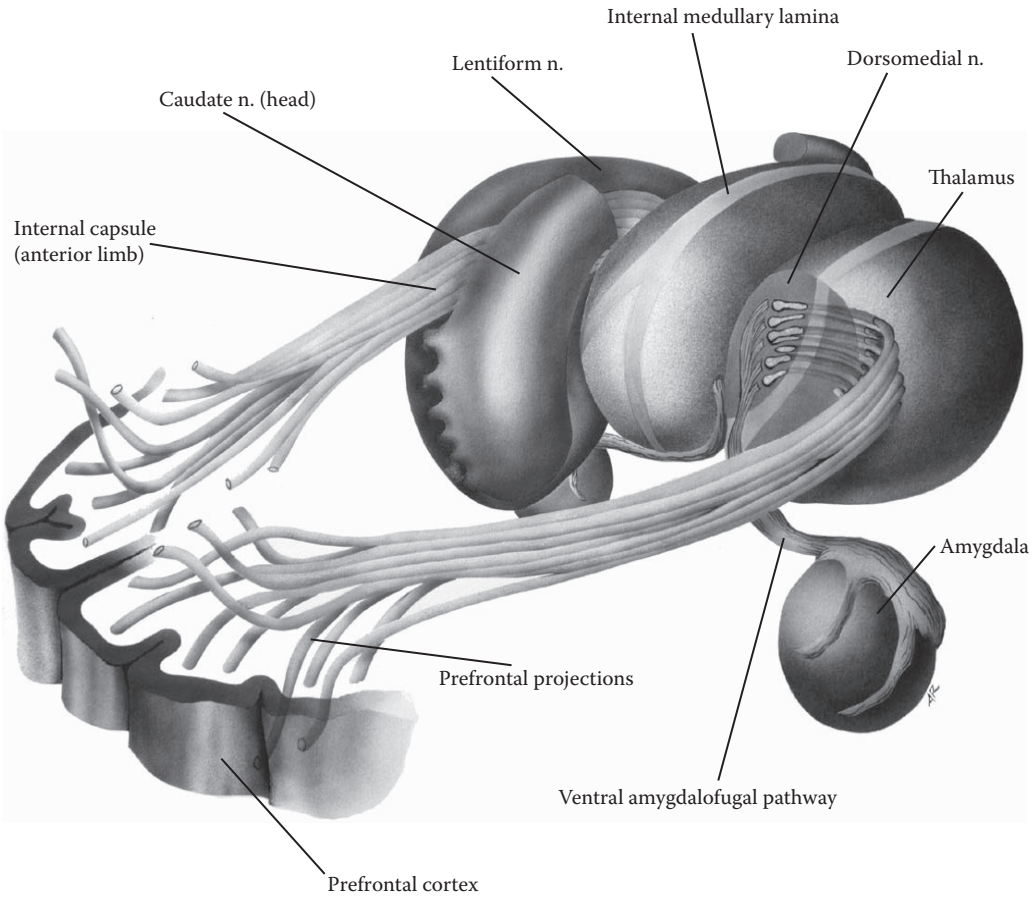


FIGURE 77B: **Limbic Diencephalon 2** — Dorsomedial Nucleus

FIGURE 78A HYPOTHALAMUS

THE NEURAL HYPOTHALAMUS

This diagram, which is the same as Figure 71, highlights the hypothalamus, one of the core structures of the limbic system, with the prominent mammillary nuclei as part of the hypothalamus. The third ventricle is situated between the two diencephalic parts of the brain, (e.g. see Figure 9A and Figure 27) and the hypothalamic tissue of both sides joins together at its inferior portion as the median eminence (see next illustration and Figure 15A and Figure 15B).

The hypothalamus is usually divided into a medial and lateral group of nuclei (see next illustration), and pre-optic nuclei (see Figure 75B). A number of nuclei that control the anterior pituitary gland are located in the medial group. This occurs via the median eminence and the portal system of veins along the pituitary stalk; other nuclei in the supraoptic region (above the optic chiasm) connect directly with the posterior pituitary via the pituitary stalk (see Figure 15A and Figure 15B).

Some of the major inputs to the hypothalamus come from limbic structures, including the amygdala (via the stria terminalis and the ventral pathway, see Figure 75A and Figure 75B) and the hippocampal formation (via the fornix, see Figure 72B). Stimulation of particular small areas of the hypothalamus can lead to a variety of behaviors (e.g., sham rage), similar to that which occurs following stimulation of the amygdala.

Certain basic drives (as these are known in the field of psychology), such as hunger (feeding), thirst (drinking), sex (fornication), and body temperature, are regulated through limbic structures. Many of the receptor mechanisms for these functions are now known to be located in highly specialized hypothalamic neurons. The hypothalamus responds in two ways — as a neuroendocrine structure controlling the activities of the pituitary gland and as a neural structure linked to the limbic system.

In its neural role there are small areas of the hypothalamus that act as the "head ganglion" of the autonomic nervous system, influencing both sympathetic and parasympathetic activities. The response to hunger or thirst or a cold environment usually leads to a complex series of motor activities that are almost automatic, as well as autonomic adjustments and hormonal changes. In addition, in humans, there is an internal state of discomfort to being cold, or hungry, or thirsty, which we call an emotional response. Additional connections are required for the behavioral (motor) activities, and the accompanying psychological reaction requires the forebrain, as well as the limbic cortical areas (to be discussed with the limbic system synthesis at the end of this section).

The mammillary nuclei are of special importance as part of the limbic system. They receive a direct input from the hippocampal formation via the fornix (see Figure 72B) and give rise to the mammillo-thalamic tract to the thalamic anterior group of nuclei as part of the Papez circuit (discussed with Figure 77A). In addition, there are fibers that connect directly to the limbic midbrain (shown in the next illustration).

Running through the lateral mass of the hypothalamus is a prominent fiber tract, the medial forebrain bundle, which interconnects the hypothalamus with two areas, the septal region of the forebrain and certain midbrain nuclei associated with the limbic system, the "limbic midbrain" (both to be discussed with the next illustration). Other fiber bundles connect the hypothalamus with the "limbic midbrain." There are also some indirect connections to nuclei of the medulla via descending autonomic fibers. Both parts of the brainstem are therefore "highlighted" in this illustration.

Additional Detail

The Habenula (not illustrated)

The habenular nuclei are a group of small nuclei situated at the posterior end of the thalamus on its upper surface (see Figure 11). The pineal gland is attached in this region (see Figure 9A).

There is another circuit whereby septal influences are conveyed to the midbrain. The first part of the pathway is the stria medullaris (note the possible confusion of terminology), which connects the septal nuclei (region) with the habenular nuclei. The stria medullaris is found on the medial surface of the thalamus. From the habenular nuclei, the habenulo-interpeduncular tract descends to the midbrain reticular formation, mainly to the interpeduncular nucleus located between the cerebral peduncles (see midbrain cross-section, Figure 65B). (This tract is also called the fasciculus retroflexus.)

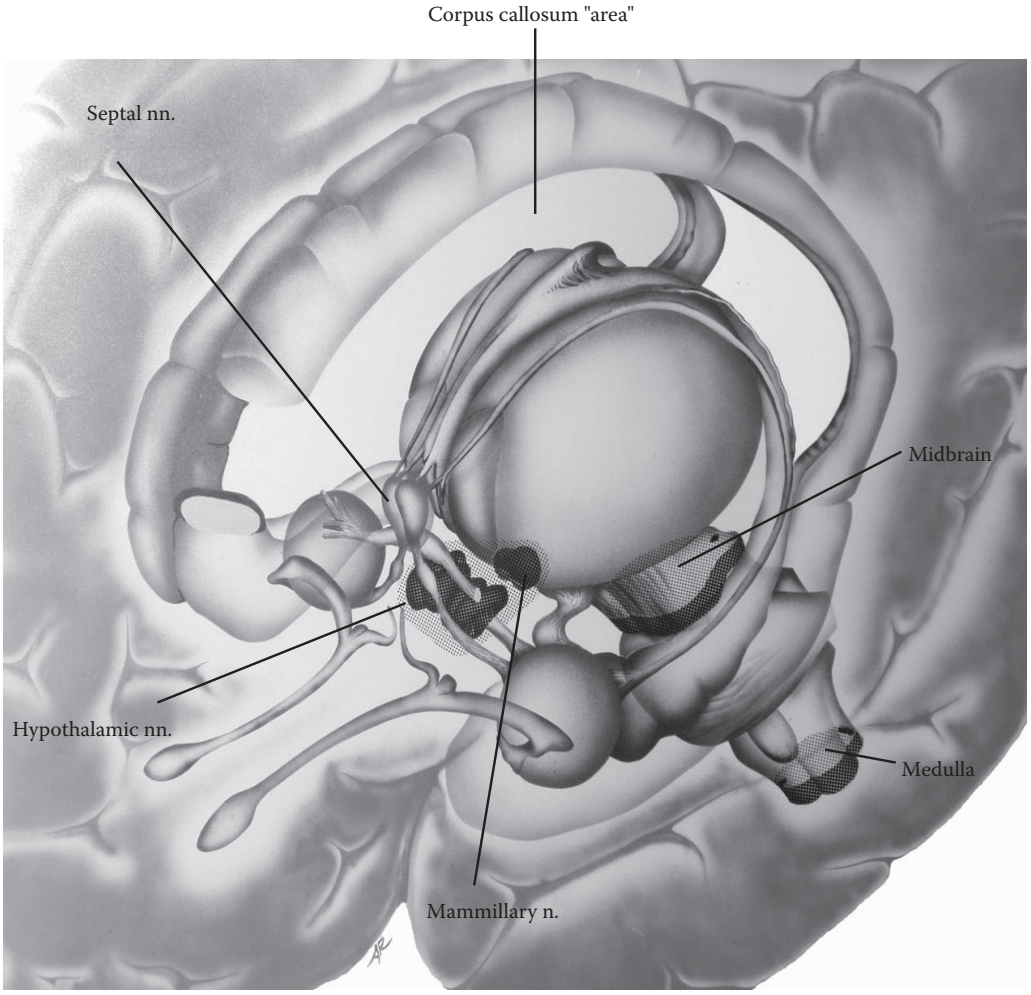


FIGURE 78A: Hypothalamus

FIGURE 78B
MEDIAL FOREBRAIN BUNDLE

SEPTAL REGION AND LIMBIC MIDBRAIN

This illustration provides detailed information about other important parts of the limbic system, the septal region and the limbic midbrain. The pathway that interconnects the hypothalamus and these areas is the **medial forebrain bundle**.

The Septal Region

The septal region includes both cortical and subcortical areas that belong to the forebrain. The cortical areas, named the septal cortex, are found under the rostrum of the corpus callosum (the thin "inferior" portion of the corpus callosum, see Figure 17 and Figure 70A). Nuclei lying deep to this region are called the septal nuclei and in some species (not humans) are located within the septum pellucidum (the septum that separates the anterior horns of the lateral ventricles, see Figure 17 and Figure 30). In this atlas, both areas are included in the term septal region.

The septal region receives input from the hippocampal formation (via the precommissural fibers of the fornix, see Figure 72B) and from the amygdala (via the stria terminalis, see Figure 75B). The major connection of the septal region with the hypothalamus and the limbic midbrain occurs via the medial forebrain bundle. (Refer also to the Additional Detail with the previous illustration.)

Several decades ago, experiments were done in rats with a small electrode implanted in the septal region; pressing of the bar completed an electrical circuit that resulted in a tiny (harmless) electric current going through this area of brain tissue. It was shown that rats will quickly learn to press a bar to deliver a small electric current to the septal region. In fact, the animals will continue pressing the bar virtually nonstop, even in preference to food. From this result it has been inferred that the animals derive some type of "pleasant sensation" from stimulation of this region, and it was named the "pleasure center"; it has since been shown that there are other areas where a similar behavior can be produced. However, this type of positive effect is not seen in all parts of the brain, and in some areas an opposite (negative) reaction may be seen.

The Limbic Midbrain

A number of limbic pathways terminate within the reticular formation of the midbrain, including the periaqueductal gray, leading to the notion that these areas are to be incorporated in the structures that comprise the extended limbic system (discussed in the Introduction to this section). This has led to the use of the term limbic midbrain.

The two major limbic pathways, the medial forebrain bundle and a descending tract from the mammillary nuclei (the mammillo-tegmental tract), terminate in the midbrain reticular formation. From here, there are apparently descending pathways that convey the "commands" to the parasympathetic and other nuclei of the pons and medulla (e.g., the dorsal motor nucleus of the vagus, the facial nucleus for emotional facial responses), and areas of the reticular formation of the medulla concerned with cardiovascular and respiratory control mechanisms (discussed with Figure 42A and Figure 42B). Other connections are certainly made with autonomic neurons in the spinal cord (i.e., for sympathetic-type responses).

MEDIAL FOREBRAIN BUNDLE

Knowledge of this bundle of fibers is necessary if one is to understand the circuitry of the limbic system and how the limbic system influences the activity of the nervous system.

The medial forebrain bundle (MFB) connects the septal region with the hypothalamus and extends into the limbic midbrain; it is a two-way pathway. Part of its course is through the lateral part of the hypothalamus where the fibers become somewhat dispersed (as illustrated). There are further connections to nuclei in the medulla. It is relatively easy to understand how the septal region and the hypothalamus can influence autonomic activity and the behavior of the animal.

Additional Detail

There are other pathways from the hypothalamus to the limbic midbrain, such as the dorsal longitudinal bundle.

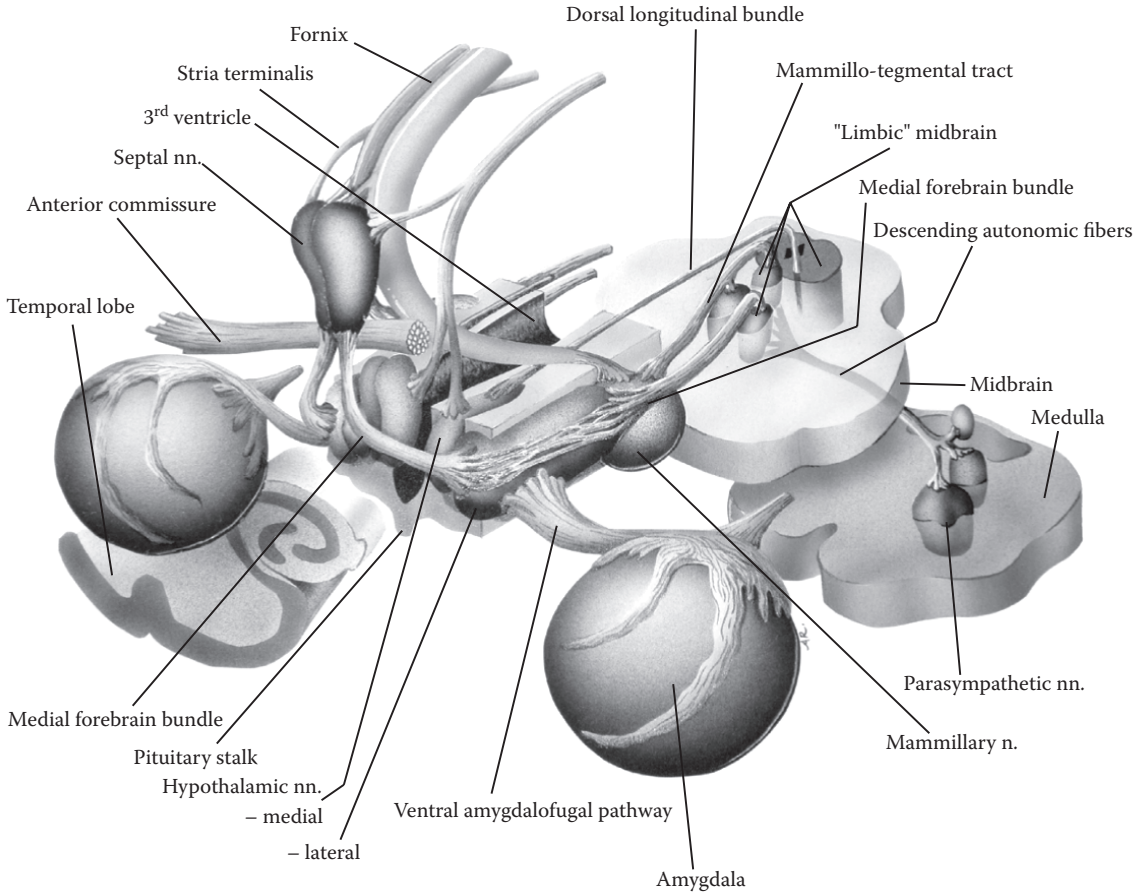


FIGURE 78B: Medial Forebrain Bundle — Septal Region and Limbic Midbrain

FIGURE 79
OLFACTORY SYSTEM

SENSE OF SMELL

The olfactory system, our sense of smell, is a sensory system that inputs directly into the limbic system and does not have a thalamic nucleus (see Figure 12 and Figure 63).

The olfactory system is a phylogenetically older sensory system. Its size depends somewhat on the species, being larger in animals that have a highly developed sense of smell; this is not the case in humans in whom the olfactory system is small. Its component parts are the olfactory nerve, bulb, and tract, and various areas where the primary olfactory fibers terminate, including the amygdala and the cortex over the uncal region.

OLFACTORY NERVE, BULB, AND TRACT

The sensory cells in the nasal mucosa project their axons into the CNS. These tiny fibers, which constitute the actual peripheral olfactory nerve (CN I), pierce the bony (cribriform) plate in the roof of the nose and terminate in the olfactory bulb, which is a part of the CNS. There is a complex series of interactions in the olfactory bulb, and one cell type then projects its axon into the olfactory tract, a CNS pathway.

The olfactory tract runs posteriorly along the inferior surface of the frontal lobe (see Figure 15A and Figure 15B) and divides into lateral and medial tracts, called stria. At this dividing point there are a number of small holes for the entry of several blood vessels to the interior of the brain, the striate arteries (see Figure 62 and Figure 80B); this triangular area is known as the anterior perforated space or area.

It is best to remember only the lateral tract as the principal tract of the olfactory system. It is said to have cortical tissue along its course for the termination of some olfactory fibers. The lateral tract ends in the cortex of the uncal area (see Figure 15A and Figure 15B), with some of the fibers terminating in an adjacent part of the amygdaloid nucleus (see Figure 75A and Figure 75B). It is important to note that the olfactory system terminates directly in primary olfactory areas of the cortex without a thalamic relay.

OLFACTORY CONNECTIONS

The connections of the olfactory system involve the limbic cortex, called the secondary olfactory areas. These include the cortex in the anterior portion of the parahippocampal gyrus, an area that has been referred to as the entorhinal cortex. (The term rhinencephalon refers to the olfactory parts of the CNS, the "smell brain.") This input of olfactory information into the limbic system makes sense if one remembers that one of the functions of the limbic system is procreation of the species. Smell is important in many species for mating behavior and for identification of the nest and territory.

Olfactory influences may spread to other parts of the limbic system, including the amygdala and the septal region. Through these various connections, information may reach the dorsomedial nucleus of the thalamus.

Smell is an interesting sensory system. We have all had the experience of a particular smell evoking a flood of memories, often associated with strong emotional overtones. This simply demonstrates the extensive connections that the olfactory system has with components of the limbic system and, therefore, with other parts of the brain.

Clinical Aspect

One form of epilepsy often has a significant olfactory aura (which precedes the seizure itself). In such cases, the "trigger" area is often orbitofrontal cortex. This particular form of epilepsy has unfortunately been called "uncinate fits." The name is derived from a significant association bundle, the uncinate bundle (an association bundle), which interconnects this part of the frontal lobe and the anterior parts of the temporal lobe where olfactory connections are located (see also Figure 75B).

Additional Detail

Diagonal Band

This obscure fiber bundle and nuclei associated with it are additional olfactory connections, some of which interconnect the amygdala with the septal region (see Figure 80B).

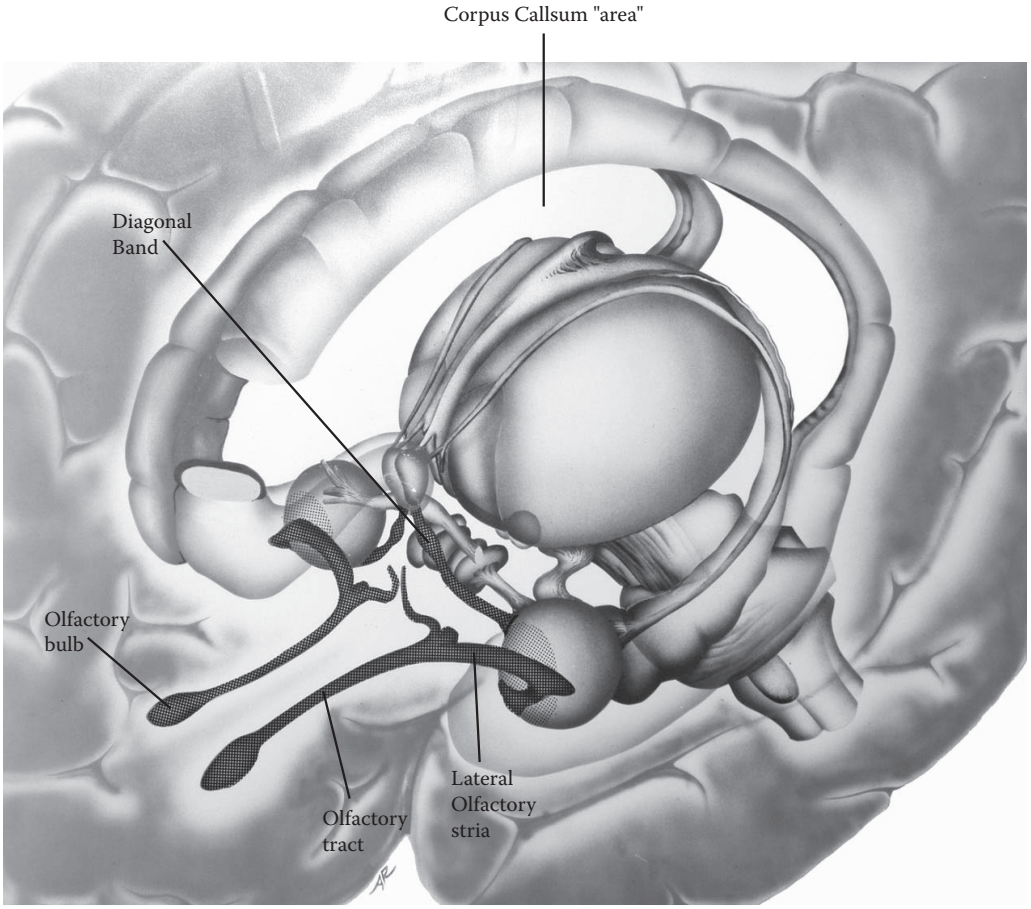


FIGURE 79: Olfactory System

FIGURE 80A
BASAL FOREBRAIN 1

BASAL FOREBRAIN REGION

The basal forebrain is shown using the same diagram of the limbic system (Figure 71). This area, previously called the substantia innominata, contains a variety of neurons.

This area is located below the anterior commissure and lateral to the hypothalamus. On the gross brain, this region can be found by viewing the inferior surface of the brain where the olfactory tract ends and divides into medial and lateral stria (see Figure 15A and Figure 15B). This particular spot is the location where a number of blood vessels, the striate arteries, penetrate the brain substance and is called the anterior perforated space (shown in the next illustration). The basal forebrain region is found "above" this area.

The basal forebrain contains a group of diverse structures:

- Clusters of large cells that are cholinergic, and which have been collectively called the basal nucleus (of Meynert)
- The ventral portions of the putamen and globus pallidus, namely, the ventral striatum and ventral pallidum
- The nucleus accumbens, which may include a number of diverse neurons within its boundaries
- Groups of cells that are continuous with the amygdala, now called the extended amygdala

CHOLINERGIC BASAL NUCLEUS

These rather large neurons are found in clusters throughout this region. These cells project to widespread areas of the prefrontal cortex, providing that cortical area with cholinergic innervation.

THE EXTENDED AMYGDALA

A group of cells extends medially from the amygdaloid nucleus and follows the ventral pathway (the ventral amygdalofugal pathway, Figure 75B and Figure 77B) through this basal forebrain region. These neurons receive a variety of inputs from the limbic cortical areas and from other parts of the amygdala. Its output projects to the hypothalamus and to autonomic-related areas of the brainstem, thereby influencing neuroendocrine, autonomic, and, perhaps, somatomotor activities.

Clinical Aspect

Dementia is a general term for an acquired progressive decline of cognitive function whose hallmark is a loss of short-term memory. It is an age-related disease where the clinical manifestations become evident in older individuals; with the increase in lifespan in the industrialized world, there is an increase in the number of individuals afflicted with this disease. These people eventually require more and more care, often necessitating institutional placement. **Alzheimer's** dementia is the most prevalent clinical syndrome, accompanied by certain neuropathological changes in the brain.

Several years ago, it was reported that there was a depletion of acetylcholine in the frontal lobe areas in Alzheimer patients. Subsequent reports indicated that this was accompanied by a loss of these cholinergic cells in the basal forebrain. Many thought that the "cause" of Alzheimer's disease had been uncovered, that is, a cellular degeneration of a unique group of cells and a neurotransmitter deficit. (The model for this way of thinking is Parkinson's disease.) This was followed immediately by several therapeutic trials using medication to boost the acetylcholine levels of the brain.

It is currently thought that cortical degeneration is the primary event in Alzheimer's dementia, starting often in the parietal areas of the brain. We now know that several other neurotransmitters are depleted in the cortex in Alzheimer's disease. This information would lead us to postulate that the loss of the target neurons in the prefrontal cortex, the site of termination for the cholinergic neurons, would be followed, or accompanied, by the degeneration of the cholinergic cells of the basal forebrain. In addition, there is the hippocampal degeneration that goes along with the memory loss (discussed with Figure 74).

Notwithstanding this current state of our knowledge, therapeutic intervention to boost the cholinergic levels of the brain is currently considered a valid therapeutic approach, particularly in the early stages of this tragic human disease. New drugs that maintain or boost the level of acetylcholine in the brain are currently undergoing evaluation. The reports have shown some improvement, or at least a stabilization of the decline, in both memory and cognitive functions for a period of weeks or months.

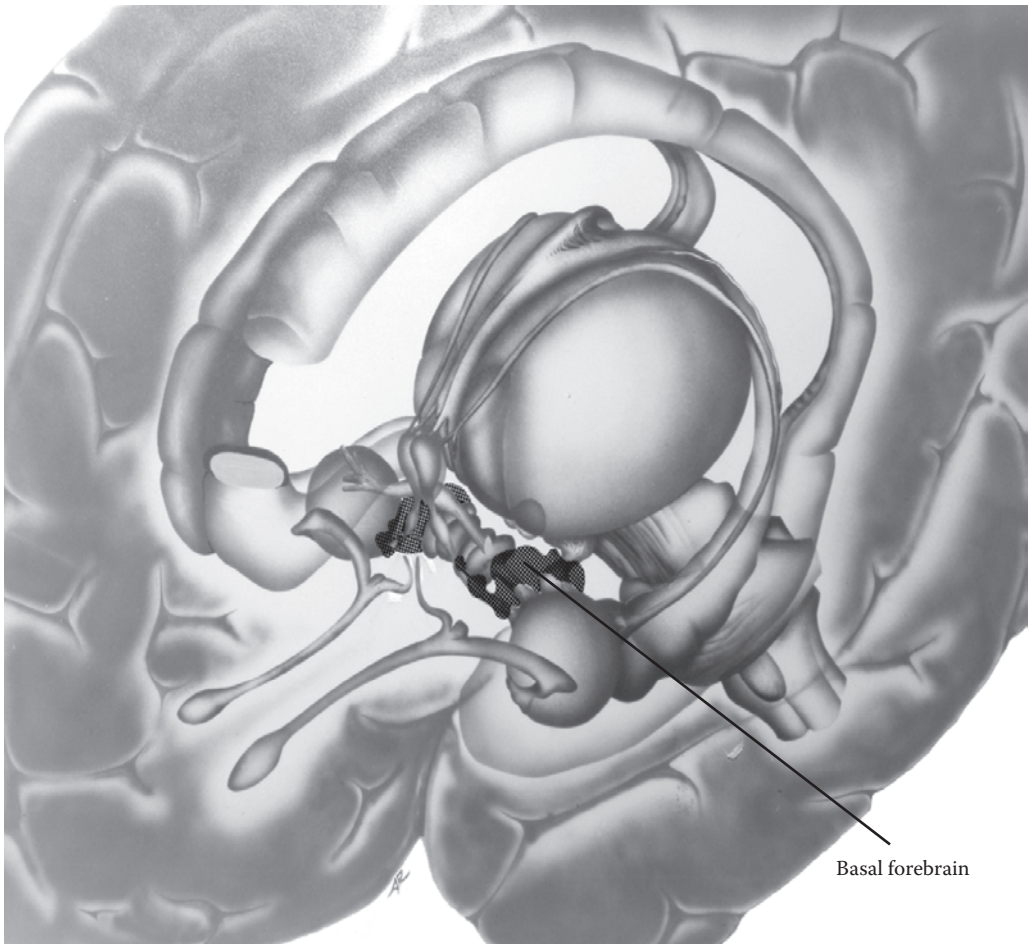


FIGURE 80A: **Basal Forebrain 1** — Basal Nucleus

FIGURE 80B
BASAL FOREBRAIN 2

BASAL GANGLIA

This is a somewhat schematic view of the various "nuclei" located in the basal forebrain area. The hypothalamus is shown in the midline, with the third ventricle. The penetrating striate arteries are seen in the anterior perforated area (see Figure 62). This view shows the ventral pathway emerging from the amygdala and some of the fibers going to the hypothalamus, and the others on their way to the dorsomedial nucleus of the thalamus (see Figure 75B and Figure 77B). The anterior commissure demarcates the upper boundary of this area (see Figure 70A). The cell clusters that form the basal (cholinergic) nucleus are contained within this area but are not portrayed.

THE VENTRAL STRIATUM AND PALLIDUM

The lowermost portions of the putamen and globus pallidus are found in the basal forebrain area; here they are referred to as the ventral striatum and ventral pallidum (see Figure 29).

The ventral part of the striatum (the putamen) receives input from limbic cortical areas, as well as a dopaminergic pathway from a group of dopamine-containing cells in the midbrain. The information is then relayed to the ventral pallidum (both parts of the globus pallidus are seen on the left side of the diagram). This area has a significant projection to the dorsomedial nucleus of the thalamus (and, hence, to the prefrontal cortex).

The overall organization is therefore quite similar to that of the dorsal parts of the basal ganglia, although the sites of relay and termination are different. Just as the amygdala is now considered a limbic nucleus, many now argue that the ventral striatum and pallidum should be included with the limbic system.

THE NUCLEUS ACCUMBENS

This nucleus (see also Figure 24) is composed of various groups of neurons, some that are part of the basal ganglia and others, possibly limbic neurons. It has many of the connections of the ventral striatum as well as those of the extended amygdala. Functionally, this neural area becomes activated in situations that involve reward and punishment, integrating certain cognitive aspects of the situation with the emotional component. There is strong evidence that this area is involved in addiction behavior in animals and likely in humans.

In summary, the region of the basal forebrain has important links with other parts of the limbic system. There is a major output to the prefrontal cortex, via the dorsomedial nucleus of the thalamus, which is considered by some to be the forebrain component of the limbic system. The basal forebrain is thus thought to have a strong influence on "drives" and emotions, as well as higher cognitive functions that have an emotional component. The cholinergic neurons in this area may have a critical role in memory.

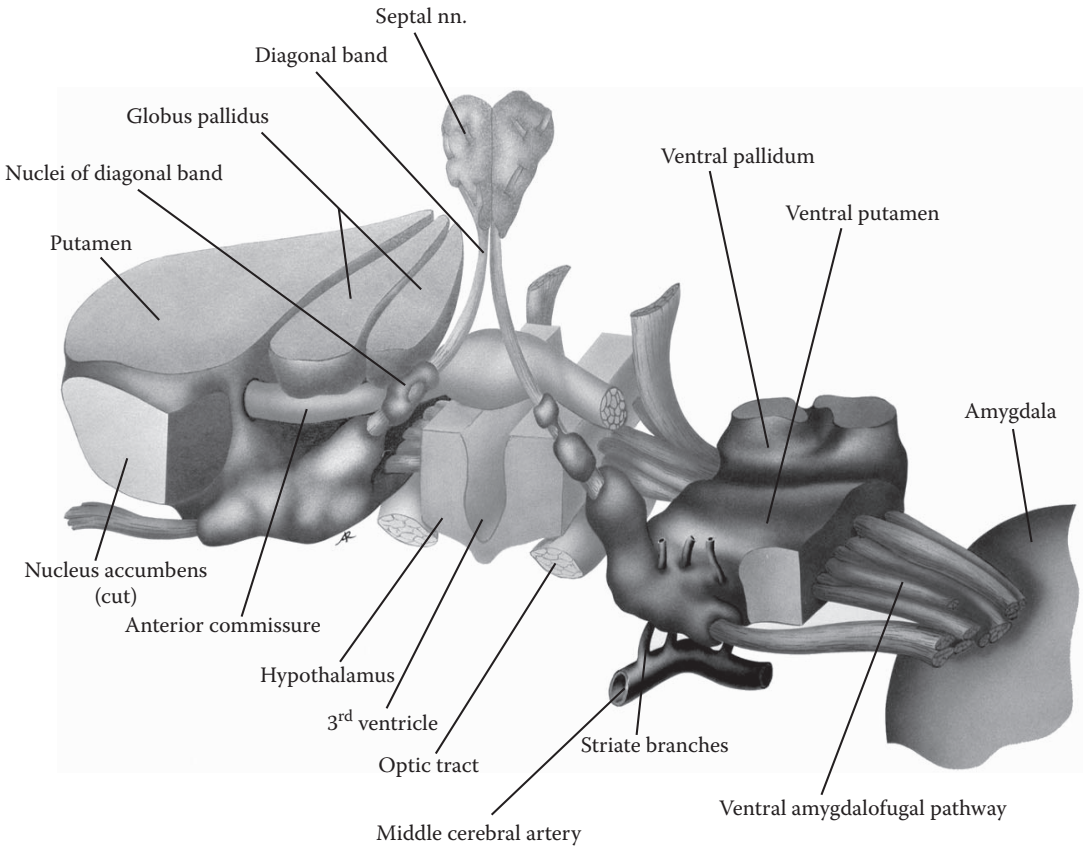


FIGURE 80B: **Basal Forebrain 2** — Basal Ganglia

LIMBIC SYSTEM: SYNTHESIS

After studying the structures and connections of the limbic system in some detail a synthesis of the anatomical information with the notion of an "emotional" part of the brain seems appropriate. It is not easy to understand how the limbic system is responsible for the reactions required by the definition of "emotion" proposed in the Introduction to this section.

The "key" structures of the limbic system are the limbic lobe (the cortical regions, including the hippocampal formation and the parahippocampal and cingulate gyri), the amygdala, the hypothalamus, and the septal region. The limbic pathways interconnect these limbic areas (e.g., the Papez circuit). In many ways it seems that the limbic structures communicate only with each other. What is not clear is how activity in these structures influences the rest of the brain. How does the limbic system influence changes in the physiological systems (endocrine and autonomic), motor activity (behavior), and the mental state (psychological reactions)?

The following discussion is presented as a way of understanding the outcome or output of limbic function — the categories of responses are the same as those discussed in the Introduction to this section.

Physiological Responses:

- Hormonal and "homeostatic" responses: Hormonal changes, as regulated by the hypothalamus, are part of the physiological responses to emotional states, both acute and chronic. The work of Dr. Hans Selye, for example, has shown how chronic stress influences our body and may lead to structural damage to select areas of the brain (e.g., the hippocampal formation).
- Autonomic responses: A wide number of parasympathetic and sympathetic responses accompany emotional states, including the diameter of the pupil (in states of fear), salivation, respiration, blood pressure, pulse, and various gastrointestinal functions. These are controlled in part by the hypothalamus and by the limbic connections in the midbrain and medulla.

Behavioral Responses:

The physiologic adjustments often involve complex motor actions. Consider, for example, the motor activities associated with thirst, temperature regulation, and satisfying other basic drives. The amygdala and hypothalamus are likely involved in the motor patterns associated with these basic drives.

Limbic activity involves areas of the midbrain reticular formation and other brainstem nuclei in specific ways. The best examples are perhaps the facial expressions associated with emotions, the responses to pain that are generated in part in the brainstem, and the basic "fight or flight" response to emergency situations. All of these activate a considerable number of motor circuits. The ventral parts of the basal ganglia and various cortical areas are likely the areas of the CNS involved with the motor activities associated with emotional reactions.

Psychological Reactions:

Neocortical areas that are involved in limbic function include portions of the prefrontal cortex, the cingulate gyrus, and the parahippocampal gyrus. Activities in these limbic cortices (and the associated thalamic nuclei) are clearly candidates for the psychological (mental) reactions of emotion. These enter consciousness and become part of the substrate that is used by humans in decision making.

In summary, the limbic system has many connections outside itself through which it influences the hormonal, autonomic, motor, and psychological functions of the brain.

The older cortical regions of the hippocampal formation seem to have an additional function related to the formation of new episodic memories, specifically related to events and factual information. Why this is so and how this evolved is a matter of speculation.

The limbic system is intricate and intriguing, providing a window into human behavior beyond our sensory and motor activities. It is not always clear what each part contributes to the overall functional system. In addition, the pathways are obscure and, perhaps, confusing. Nevertheless, they are part of the neuroanatomical framework for a discussion of the contribution of the limbic system to the function of the human organism.

On a final note, one can only wish that the basic activities of the limbic system that are involved in preservation of the self and species can be controlled and tamed by higher-order cortical influences, leading humankind to a more human and hopefully a more humane future.