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THE LIMBIC SYSTEM: An Anatomical and Functional Orientation

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Introduction

More than three centuries ago, Thomas Willis referred to a ring of cortical regions resembling a boundary zone or border (limbus) around the brainstem as "cerebri limbus." One illustration, ascribed to Sir Christopher Wren, the architect of St. Paul's Cathedral in London, corresponds in part to Figure 6-1 (b). It is not clear whether Broca was aware of this term in 1878 when he described the occurrence of a phylogenetically ancient portion of the cerebral cortex in several vertebrate species as "le grand lobe limbique"; in man, this designation included the subcallosal, cingulate, and parahippocampal gyri, as well as some portions of the hippocampal formation.

Extensive comparative anatomical studies on the development and evolution of the forebrain followed Broca's investigation. Most of the descriptions were based on normal, that is nonexperimental material: the superficial relationships of the limbic lobe with the olfactory bulb, peduncle, and tracts on the basal aspect of the brain were readily apparent. No wonder that by the middle of this century the term "rhinencephalon" (olfactory brain or smell brain) was generally used to indicate the aggregate of these cortical regions with their fiber tracts, traditionally depicted as seen on the medial wall of the hemisphere (Figure 6-1 [a]). In a proposed reorientation of this anatomical bias of the limbic system concept, the horizontal view from below is favored, hereby demonstrating anew that the limbic apparatus seen this way likewise forms a “limbus” encircling the brainstem (Figure 6-1 [b]).

It is of interest to note that early in mammalian phylogeny a more medially complete belt of cortex binds the hemispheres to the diencephalic portion of the brainstem. During ontogeny in man the structures surrounding the site of the laterally evaginated telencephalic vesicles, later becoming the cerebral hemispheres, become less readily recognizable as cortex. In the developing human brain these circumhilar structures are displaced downward and backward as they are stretched out and become overgrown with the massive neocortical regions on either side and their correspondingly conspicuous commissure, the corpus callosum (see Figures 6-2, 6-3, and 6-1 [a]).

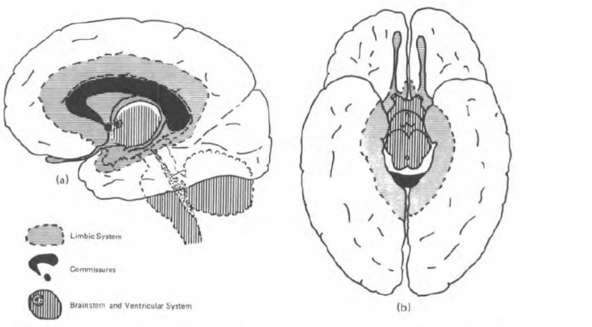

Figure 6-1.
Diagrams of adult human brain surrounding the upper portions of the brainstem; (a) the right telencephalic hemisphere seen from its medial aspect to show the limbic system structures; (b) the whole forebrain seen from below.

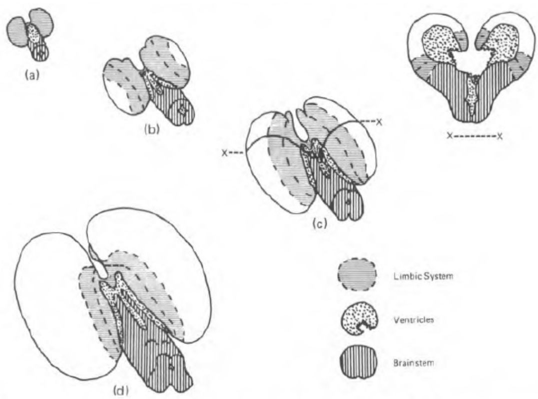

Figure 6-2.
a-d: Schematic representation of the developing forebrain as seen obliquely from above, modified after Elliot. The limbic cortex is seen restricted to the region where the hemispheres merge into the di3ecephalic portion of the brainstem. A coronal section x-x shows the relations to the ventricles in a plane behind the interventricular foramina (compare Figure 6-4).

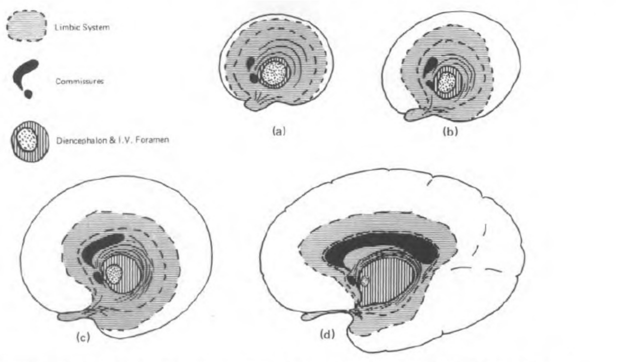

Figure 6-3.
a-d: Schematic representation of the medial aspect of the developing telencephalon in man: the limbic system cortex surrounding the hilus of the hemisphere; the gradual displacement of the bulk of the inner cortical ring towards the temporal lobe; the semicircular fiber bundles in the limbic cortex; the development of the cnetral olfactory structures; the overgrowth of the neowcortex; the growth of the corpus callosum resulting in a partially "split" cortex.

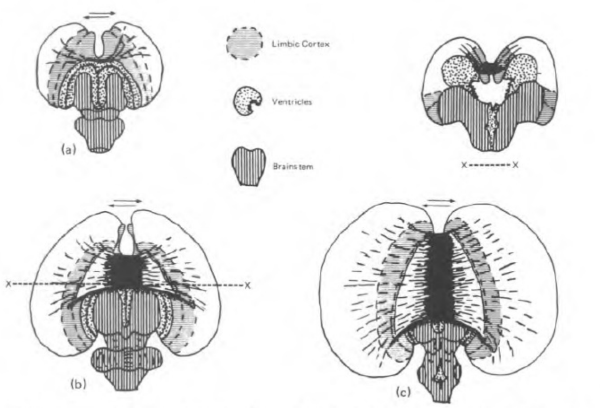

Figure 6-4.
a-c: Diagram of the developing human forebrain as seen from above; the hemispheres have been pulled apart to show the formation of the neocortical commissure or corpus callosum (black) (modified after C. G. Smith). The limbic system cortex is "split" into a supracallosal portion that is largely transitional cortex, and an infracallosal, older portion. A coronal section x-x shows the effect of the "split" in a plane behind the interventricular foramina, and with a corpus callosum (compare Figure 6-2).

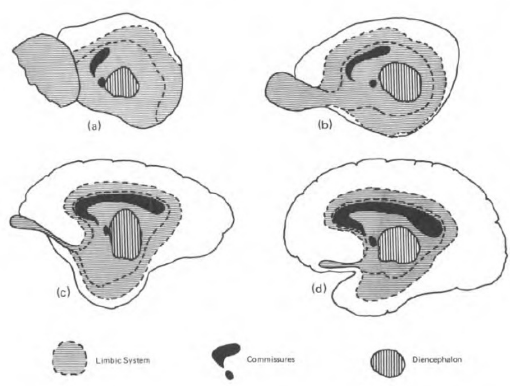

Figure 6-5.
Diagrams to illustrate the medial aspect of the telencephalon in (a) hedgehog; (b) rabbit; (c) monkey; (d) man. Note the development of the corpus callosum, the decrease in size of olfactory structures, and concentric arrangement of old cortex around the hilus of the hemisphere (compare Figure 6-4).

The growing corpus callosum appears to split the “limbic” cortex into a supracallosal portion that is largely transitional cortex, and an infracallosal, older portion (Figures 6-3 and 6-4).

Vertebrate macrosmatic species with a keen sense of smell display a well-developed, primary olfactory brain apparatus. The degree of development of the sense of smell is not necessarily related to phyletic position, however, in contrast to the more constant pattern of evolution of the cortex as a whole. The more or less concentric arrangements in a medial view (compared by Broca to a tennis racket with an olfactory “handle”) are more obvious than in man: in lower forms, the limbic cortex represents a relatively bulky segment of the entire telencephalon, while with ascending phylogeny the neocortex expands unequally in every direction to all but obscure the ancient girdle of allocortex and other limbic system structures that lie as a junctional zone around the hilum of the hemisphere (Figure 6-5).

In the last few decades an increasing number of anatomical investigations" have shown that in higher forms the functions of much of the "olfactory brain" are not olfactory in nature, at least not directly or primarily. Aspects of autonomic nervous system physiology, certain features of neuroendocrinological regulation, expression of emotion, facets of learning and memory, patterns of behavior, "drives," as well as olfaction in the strict sense, all of these functions seem to have their neuroanatomical substrate in the "rhinencephalon." In view of such recent attempts to elucidate its physiology, several names have been proposed for this ancient portion of the mammalian brain, e.g., "visceral brain," "emotion brain," "vital brain," "limbic brain," or "limbic system."

The last name is now widely accepted, although no unanimity exists concerning the exact definition and precise list of limbic-system components.

In 1969, Brodal, who in 1947 showed the error of including many nonolfactory structures under the designation "rhinencephalon," emphasized that "it is even less justifiable to speak of a limbic system.' " He stated that "it becomes increasingly difficult to separate functionally different regions of the brain as research progresses, and that ‘the limbic system’ appears to be on its way to including all brain functions. As this process continues the value of the term as a useful concept is correspondingly reduced.” It could be argued that in the strict sense the term rhinencephalon should now be limited to cerebral structures that are primarily involved in the reception, projection, and recognition of olfactory signals. However, since olfaction has been shown to influence affective and instinctual behavior as well as hypothalamic activity and since the limbic system indeed includes connections between true olfactory structures and other brain components, even the restricted use of the term rhinencephalon is, besides being confusing, not helpful. Perhaps for such reasons and in order to emphasize that in microsmatic man many limbic system structures do not subserve olfactory functions, the term rhinencephalon should be abandoned altogether, as was recommended in the reorganization of nomenclature pertaining to human anatomy (Paris, 1955).

The general term, limbic system, as used in this chapter is mainly based on its morphological merits; it includes phylogenetically ancient portions of the cerebral cortex and related subcortical derivatives, as well as intrinsic or intracortical fiber connections and extrinsic pathways linking these cortical components with the diencephalon and other areas in the brainstem (Figure 6-6). The aggregate of these structures constitutes the limbic system in the strict sense of the word. Efferent fiber tracts are to be included if the cells of origin are situated within gray components of the system. Afferent pathways can less readily be considered parts of the limbic system. However, through less than careful usage of the term or through emphasis on common functional manifestations, certain structures in the diencephalon (habenular complex, medial forebrain bundle) in the midbrain (ventral tegmental area) and in the frontal lobes are often included in the enumeration of limbic-system components. Transitional or junctional categories of cerebral cortex add to the difficulty of an explicit listing.

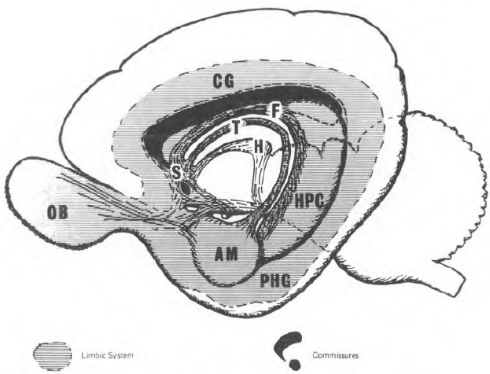

Figure 6-6.
The major components of the limbic system in the cat as seen in a "phantom" diagram projected on a sagittal plane.

AM = amygdaloid nuclear complex	OB = olfactory bulb
CG = cingulate gyrus	PHG = parahippocampal gyrus
F = fornix	S = septum complex

H = Habenula T = stria terminalis

HPC = hippocampus

Medial forebrain bundle, olfactory tracts, stria medullaris, mammillary peduncle, habenulo-interpeduncular tract are sketched bun not labeled.

Anatomical Considerations

In the subsequent pages, a brief description is given of the major morphological aspects of limbic system: cortex, subcortical gray derivatives, and pathways intrinsic to the system. In addition, the medial forebrain bundle, habenular complex, and some relationships with the neocortex are discussed in a few paragraphs, since in the strict sense these structures appear closely related in function to the telencephalic limbic system.

Hippocampal Formation

The hippocampal formation in man includes the hippocampus proper, the dentate gyrus with its attenuated continuation over the corpus callosum, called supracallosal gyrus or indusium griseum, intrinsic fiber systems, and a cortical transitional area, the subiculum: this area is located at the uncus, a surface landmark term referring to the most medial, somewhat hook-shaped portion of the temporal lobe. The hippocampal formation is derived from the anteromedial wall of the primitive cerebral hemisphere; its gray matter is allocortical or archicortical in nature. As the neocortical or isocortical portion of the hemisphere increases enormously in size during development, the major portion of hippocampal formation becomes displaced caudally, somewhat laterally, then ventrally, to lie as part of the temporal lobe along the juxtallocortical or mescocortical parahippocampal gyrus. In addition, the formation is rolled inward, with the result that the hippocampus proper forms a bulge in the floor of the inferior or temporal horn of the lateral ventricle.

The hippocampus, in certain planes of section, faintly resembles a sea horse or perhaps its tail; in earlier times, descriptive morphologists likened this structure to a dolphin, a silkworm, a triton, even an equestrian statue. A name often used in England is Ammon’s horn or cornu Ammonis, referring to its curved shape as it follows the semicircular sweep of the lateral ventricle. The deepest layer of the hippocampal cortex is covered by heavily myelinated fibers forming a thin layer of white matter toward the ventricular lumen. These efferent fibers collect as fimbria (fringe) and it increases in bulk as more fibers are added along the medial rim of the hippocampus, rising from the inferior horn to about the atrium of the lateral ventricle. Here the fiber bundle, now called fornix (vault or dome) curves around and over the thalamus and joins its fellow from the other hemisphere to run alongside each other forward under the corpus callosum. A variable system of commissural fibers crosses the midsagittal plane as the fomices meet to link one hippocampal formation with similar, contralateral structures. The fornix bundles do not decussate; they curve rather sharply around the interventricular foramina (of Monro) to terminate in various regions of the diencephalon and in gray matter around the anterior commissure (cf. Figure 6). Many of the 1,200,000 fornix fibers reach the mammillary body nuclei; some have been traced to the rostral part of the periaqueductal gray matter, some to the septal nuclei, and others to the anterior thalamus directly.

Most efferent fibers are contained in the fimbria-fornix systems, although some afferent fibers reach the hippocampal by this route or by the somewhat longer trajectory from septum around the corpus callosum along the indusium griseum into the dentate gyrus.' Most afferent impulses reach the hippocampus by way of the fiber systems of the cingulum, a bundle coursing within the cingulate and parahippocampal gyri and reflecting the extent and shape of Broca's limbic lobe.' The cingulum receives inputs from adjacent cortical areas, as well as from the anterior thalamus, which in turn is linked to the mammillary bodies by way of the mammillo-thalamic tracts. A special region of the parahippocampal gyrus, the entorhinal area, projects in rather specific ways to the various areas within the hippocampus. In recent years it has become evident that notwithstanding the relatively simple organization of the primitive hippocampal formation, differences exist between various areas—in terms of cytoarchitectonic composition—of efferent and afferent connections, of histochemistry, and probably also with respect to function.

It must be clear from this brief description of the hippocampal formation and its associated fiber systems that it relates closely to many other regions of the brain, cortical as well as in the diencephalon. Moreover, it appears as if a circuitous trajectory of fiber connections is traversing a large part of the limbic system, without clear beginning or end. It is this circuit—hippocampus-fornix-mammillary body-anterior thalamus-cingulum-hippocampus—that Papez described in 1937 as subserving a proposed mechanism of emotion. However, the subsequent detailed anatomical analyses as well as functional studies of the hippocampal formation have demonstrated that even the hippocampus proper cannot be considered a physiological unit.'

Olfactory Structures and Pathways

An elongated evagination of the primitive cortex on the basal surface of each hemisphere, known as the olfactory bulb, is connected to other limbic-system structures by way of flattened fiber bundles, which separate from the olfactory tract or peduncle, f In man, the medial bundle or stria reaches the region of the subcallosal gyrus, the septum, and perhaps the habenular complex, as well as the olfactory structures on the opposite side, by way of the anterior commissure (see Figures 6-1 and 6-6). The lateral bundle or olfactory stria appears to be the main projection pathway for the sense of smell. It courses along with a thin layer of gray via the limen insulae (the anterior threshold of the lateral fissure) to terminate in a limited area at the uncus, both in the rostral extent of the parahippocampal gyrus as well as in medial and cortical nuclei of the amygdala. Some fibers from the olfactory peduncle end in a triangular area of gray, cortical matter between the divergent lateral and medial olfactory striae, the olfactory trigone, approximately the anterior perforated space in the human brain. From this area, and from other structures where olfactory stria fibers terminate, a diffuse system of short neurons connects to the lateral region of the hypothalamus and hence further down the brainstem tegmentum. This system of interconnected neurons, the medial forebrain bundle, receives additional afferents from other limbic-system areas and serves as a collection and distribution mechanism for reflexes triggered by olfactory sensations and other sensory signals.

Efferent projections from the primary olfactory cortex have not had a detailed analysis in all forms; connections with the amygdaloid nuclear complex and the entorhinal area of the parahippocampal gyrus have been described, as forming other, more circuitous links with nuclei in the diencephalon. The contiguity of lateral olfactory stria terminations and efferent connections from the uncus to the hippocampus had led to the early concept that the latter structure represented the cortical projection area for the sense of smell. In the last few decades this concept, mainly extrapolated from comparative studies, has been shown to be erroneous on the basis of careful anatomical studies, clinical case histories, and experiments in animals. It should be noted, however, that the primitive sense of smell is somewhat unique when compared to the other special senses: there are but two neurons involved in the pathway between olfactory receptor and primary projection cortex; there is no decussation, partial or complete; and there is no thalamic relay nucleus. On the other hand, subcortical reflex paths are abundantly present even in man and impinge on visceral regulatory centers in the brainstem, including the diencephalon. It is especially in this context that the terms rhinencephalon, visceral brain, and limbic system, sometimes used interchangeably, have unfortunately led to confusion, to controversial concepts, and occasionally even to contentious contradiction.

Amygdaloid Nuclear Complex (Amygdala)

In man, a surprisingly large subcortical gray mass, the amygdala, is found at the tip of the inferior horn of the lateral ventricle, just rostral to the hippocampus and under the uncus (see Figure 6-6). Mainly on the basis of comparative anatomical studies, this mass can be subdivided into (1) the corticomedial group of nuclei; (2) the basolateral group of nuclei (well-developed in man); (3) the anterior amygdaloid area; and (4) other aggregates of nerve cells. The various nuclei of the amygdaloid (almond-shaped) complex appear to have somewhat different fiber connections and correspondingly diverse functions, although the analysis is far from complete.

Efferent projections from the amygdala include fiber systems of the stria terminalis, coursing alongside the caudate nucleus and paralleling the sweep of the lateral ventricle and the anterior commissure as well as diffuse amygdalofugal projections. These efferents terminate in the anterior hypothalamus, the septum complex, probably the habenular complex, possibly other nuclear groups, and they contribute to the medial forebrain bundle.

The amygdaloid nuclear complex receives afferents from the olfactory bulb by way of the lateral stria, terminating in the corticomedial group of nuclei, from adjacent regions of the parahippocampal gyrus (in some species named piriform cortex since the basal aspect of the temporal lobe resembles a pear) and possibly indirectly from various other cortical areas. The amygdaloid complex, the olfactory gray structures, and an interconnecting band of cortex (diagonal gyrus, or band, of Broca) are often described as paleocortical in nature, referring to a type of allocortex at the base of the forebrain.

Septum Complex

A mass of gray matter, mostly subcortical and derived from the medial wall of the primitive cerebral hemispheres, is found between and below the anterior horns of the lateral ventricles. It is well developed in most mammalian forms (cf. Figure 6-6). However, in primates and especially in man, it has been partially stretched out by the increase in bulk of the neocortical region and the corpus callosum. This thin portion is known as the septum lucidum. Other components include aggregates of gray matter around the anterior commissure, close to midplane and the transition to the mediobasal walls of the hemispheres and merging into subcallosal or paraterminal gyri.

The septum complex is connected or adjacent to hypothalamus, preoptic area and medial forebrain bundle, amygdaloid nuclear complex and hippocampal formation, as well as to the habenular complex. No wonder that this component of the limbic system has invited investigation in recent years, not only by neuroanatomists and neuroendocrinologists but also by students of behavior and emotional reactions. An integrative function has been suggested by its very position, at the crossroads as it were, between limbic system, diencephalon, and neocortex. However, the complexity and limitations in size require strictly controlled experiments as well as a cautious interpretation of the results.

Limbic Lobe

As mentioned in the introduction to this chapter, the comparative neuroanatomical concept of a limbic lobe, viz., a convolution of cortical gray encircling the attachment of hemisphere to upper brainstem, can be traced back several centuries. The growth of the corpus callosum, concomitant with the development of the large lateral mass of neocortex and underlying white matter, seems to split through part of the border of primitive cortical gray (Figure 6-4). The result is a circular mass of allocortex and white fiber tracts (septum, fornix, and hippocampus) curving below the corpus callosum, and a histologically less primitive convolution above or outside it, with merged ends on either side; namely, in the subcallosal-gyrus area and in the hippocampus-parahippocampal-uncus region (Figures 6-1 and 6-3).

It is not immediately clear from the earlier descriptions whether or not the hippocampal formation in all cases was to be included in this lobe, also referred to as gyrus limbicus or gyrus fornicatus, since it showed a vault-like extent; nor are its boundaries sharply defined. Two concepts are therefore encountered in the current literature concerning this.' There is (1) Broca's "grand lobe limbique," mostly juxtallocortical in nature, comprising subcallosal, cingulate, retrosplenial, and para-hippocampal gyri or synonyms thereof; and (2) these structures as well as the allocortical structures described above as hippocampal formation.

In this chapter the first concept is preferred, although the transitional type of cortex found in much of this limbic lobe would indicate its more intermediary position between the innermost, truly limbic, more primitive or older, allocortical structures and more recent neocortex. The olfactory gray and gyrus diagonalis, linking septum complex and subcallosal area with amygdala and adjacent hippocampal formation, complete the innermost encirclement of the diencephalon (Figures 6-2, 6-3 and 6-5).

Mainly based on functional findings, some regions of the frontal lobe adjacent to the subcallosal area and connected by a well-developed association bundle (uncinate fasciculus) to the temporal lobe are sometimes mentioned as portions of the limbic system. However, these orbitofrontal gyri display cytoarchitectonic characteristics that suggest their neocortical nature.

Pathways Linking Limbic-System Cortex with Diencephalon

It should be clear by now that extensive reciprocal connections exist between the limbic -system structures in the temporal lobe and the diencephalon, especially the hypothalamus. The conspicuous fimbria-fornix system, the less pronounced stria terminalis bundle from and to the amygdala through the anterior commissure, and more diffuse direct connections dipping under the limen insulae have been mentioned above. These links constitute well-developed, rather circuitous routes between the basofrontal and mediotemporal telencephalic components of the limbic system on the one hand, and the brainstem on the other hand, especially the basal diencephalon extending into preoptic area rostrally and ventral mesencephalic tegmentum caudally (see Figure 6-6).

It should be emphasized that these links are often both afferent and efferent with respect to the brainstem, albeit not to air equal degree. Also, the termination sites on the brainstem are not restricted to a few loci, but they are rather diverse and have been analyzed in several anatomical studies. Equally interesting is the growing awareness that the major gray masses in the temporal lobe (hippocampus, amygdala, parahippocampal gyrus) are not homogenous in nature but appear to have different and often specific connections with other structures as well as typical histological and histochemical characteristics.

Medial Forebrain Bundle

A multi-neuron, multi-synaptic, often diffuse system of fibers can be found in the lateral hypothalamus. This system extends from and connects with olfactory trigone gray, septum complex, uncus areas, and amygdaloid nuclei to the ventral gray of the tegmentum in the midbrain (see Figure 6-6). This medial forebrain bundle, as opposed to the lateral forebrain bundle or more modern internal capsule system, is essentially a limbic-system, projection pathway to the brainstem directions. Signals from several subcortical and cortical structures pertaining to the limbic system can thus be relayed to basal diencephalic and mesencephalic nuclei. Additional ascending fibers have been described, among these the mammillary peduncle, which is a discrete connection between ventral tegmentum and mammillary nuclei. It has been postulated that the medial forebrain bundle constitutes the rostral portion of the reticular formation of the brainstem. Its diffuse nature, consisting as it does of multiple short neurons and ascending and descending fibers, suggests that nonspecific stimuli as well as special sensory signals may influence the limbic-system function as a whole. Conversely, discharges from the limbic system, triggered by olfactory cues or set off by primitive, basic cortical activity, may also reach the visceral and endocrine regulatory centers in the brainstem by way of the medial forebrain bundle.

Habenular Complex and Connections

The habenular complex, inconspicuous in man, consists of a long-stretched mass of nuclei and afferent fibers (stria medullaris) along either side of the roof attachment of the third ventricle (taenia thalami), the habenular commissure (coursing through the upper portion of the pineal stalk), and efferent fiber bundles. The latter connect the epithalamic habenular complex with several ventral and possibly also dorsal tegmental regions in the midbrain. Among these the habenulo-interpeduncular tract (fasciculus retroflexus) can be readily identified in man. It is noteworthy that the habenular complex essentially parallels the medial forebrain bundle by spanning between preoptic, septal, and subcallosal limbic regions rostrally and ventral tegmental areas in the mesencephalon. The direction of conduction is mainly toward the midbrain, in contrast to the medial forebrain bundle. Another difference is that the latter, by traversing the hypothalamus, impinges on its many functions whereas the habenula does not nor does it appear to relate to thalamic activity. Neither the significance of the habenular commissure nor its relation to the pineal gland is clear.

Just as the medial forebrain bundle per se cannot be included in the limbic system, if one adheres to a strict morphological and anatomical definition derived from allocortex in the medial wall of the telencephalon, similarly the habenular complex cannot be considered a component of that system as it is treated in this chapter. Nevertheless, the intimate relationships, neuronally as well as functionally, of these two structures to limbic-system components make it possible to include them readily in the functional concepts of an extended limbic system. Insight into the functional importance of the habenular complex is far from complete; curiously, this is in contrast to its constant occurrence and conspicuous contours in many animal species. Recent investigations have suggested that the habenula has a modulatory role in the regulation of pituitary hormone secretion and with respect to aspects of sexual behavior in rodents. So far, however, the habenular complex in man has not been related to any physiological activity.

Relationships with the Neocortex

In earlier discussions'' of the concept of the limbic system, it is suggested that the neocortex functions almost independently from activity of the older limbic cortex. While that idea does not appear too difficult to accept, the reverse statement is. For, direct connections between the cortical portions of the limbic system and the rest of the telencephalic hemisphere have been reported'' along large extents of the limbic lobe where juxtallocortex borders on neocortex. More specifically, the parahippocampal gyms is related to the fusiform and lingual gyri through short association bundles, the posterior and retrosplenial gyri to the precuneus, the anterior cingulate gyrus to the superior frontal convolution, and the subcallosal region to the ventromedial region of the frontal lobe. In addition, the thin gray band of primitive cortex extending along lateral olfactory tract, limen insulae, and uncus appears to relate to the posterior orbital gyri, the insula, and its opercula.

In short, the limbic system cortex is more or less connected with all secondary-sensory and many association areas but not with the primary projection areas for vision, audition, or general body sensation. These connections between the limbic system and neocortex are all mediated by short, mostly diffuse fiber systems that link the limbic lobe with the neocortex. Within the limbic lobe the distinct, long association bundles of the cingulum and the uncinate fasciculus impinge on many allocortical structures. Therefore, although the relations between neocortex and the oldest portions of the limbic system and hence the hypothalamus appear to be indirect ones by way of the limbic lobe or the thalamus, nevertheless, the neuronal substrate appears able to subserve and transduce neocortical influence on basic patterns of behavior and concomitant alterations in autonomic, endocrine, or motor activity.

Functional Considerations

For most of the structures discussed above the functional connotation of rhinencephalon was deemed too all-inclusive a few decades ago. This was when experimental neuroanatomical investigations confirmed a nonolfactory function for much of the limbic system. Some have been tempted to substitute a term that either avoids the implication of a singular function by erring on the side of vagueness or that emphasizes anatomical characteristics.

No substitute has been entirely satisfactory. “Visceral brain,” “vital brain,” “emotional brain,” all seemed to deemphasize olfaction without including enough in their associative functional terminology. As used here, limbic system appears to stress a neutral morphological concept, provided it does not conjure up some implicit, unified, systemic function. At a time when many seemingly diverse activities are shown to relate to one or more neuroanatomical substrates that comprise components of the limbic system, the dangers of spurious generalization may be replaced by the pitfalls of a too detailed analysis into unrelated facets of function, bodily or otherwise. Nevertheless, as information accumulates, attempts to synthesize our understanding of function should periodically accompany analysis.

Much of what is known today about the functions of limbic-system components is based on observation and experimentation in animal species, especially mammalian forms. Man may have analogous functions, but direct extrapolation is full of risks, even though phylogenetic development is well defined in this portion of the brain. For example, olfactory acuity may vary considerably, independent of the phyletic position. Animal investigations are cumbersome and they can be misleading when alterations in feelings or drives or aspects of memory are tested. On the other hand, controlled human experiments are rare and the clinical results often unreliable either because of a lack of circumscribed pathology or because of a protracted time element that allows for adaptation. In addition, since lower echelons often attempt to compensate for or stabilize dysfunction following experimental manipulation, the hierarchical organizations of basic, almost autonomous visceral functions and instinctual patterns of behavior, generally tend to resist clear-cut effects. Finally, confusion and redundancy in terminology versus incomplete insight in hodology and complexity of neuroanatomical substrate may result.

Nevertheless, even in microsmatic man, some progress in understanding the functional activities of the limbic system has been made in recent years. But there still is both a lack of clear comprehension and of comprehensive knowledge.

Olfaction

The sense of smell, one of the chemical senses, is a basic function for most lower vertebrate forms. It draws attention to potential danger from enemies or to possible prey; it can attract partners of the opposite sex or differentiate between certain life-sustaining foodstuffs and nonedible material.- At the top of the phylogenetic scale, in *Homo sapiens,* the other senses are much more important in vegetative behavior.

Nevertheless, the ability of man to tell one smell from another is at least a useful adjunct in eating and drinking, pleasures that a bad nose cold can spoil. The continuation of the human race may not be so dependent on the sense of smell as many vertebrate species are, yet olfaction does not play a negligible role in our society as any perfume manufacturer or husband knows. Moreover, in primitive ethnic situations man's sense of smell may play an even bigger role with respect to social and reproductive behavior. Olfaction may not be a vital asset, but pleasant smells can make life more agreeable just as disagreeable smells can be very unpleasant and emotionally upsetting. While the human hippocampus and its connections are no longer considered olfactory substrates, the regions at the rostromedial tip of the parahippocampal gyrus (uncus) and efferents to the brainstem have been shown to be important in this context. Irritation or stimulation of the temporal lobe may lead to so-called uncinate fits; olfactory cues may trigger patterns of behavior, emotions, even memories.

Aspects of Behavior

An extensive analysis of the role of limbic-system structures in human behavior is not within the competence of the author nor the organizational purview of this chapter. A few remarks should suffice.

First studied in animals, later at least partially confirmed in man, the effects of bilateral lesions in the temporal lobe lead to characteristic changes in behavior as well as to alterations in the mechanism of memory (see below); the "Klüver and Bucy syndrome" consists of visual agnosia, absence of emotional responses, a tendency to examine objects by mouth, indiscriminate eating habits, increased reproductive behavior, etc.

Temporal lobe epilepsy is not uncommon,- but so far it has been difficult to match precise pathology with the symptoms. Olfactory or acoustic auras, some disturbance of consciousness, episodes of amnesia without loss of motor control, epileptiform seizures with a "march" of motor disturbances, all tend to make clinico-pathological analysis a formidable and arduous task.- Brodal states that "in view of the ample interconnections and functional interrelations between the different structures contained in the temporal lobe, it is not astonishing that approximately identical disturbances may result from an abnormal activity starting in almost any of these structures. The initial symptoms may in some instances point to the site of origin (for example, olfactory sensations to the uncus).”

The simple, stratified nature of the allocortex has attracted fundamental neurocyto-physiological investigations. Electro-physiological studies concerned with hippocampal potentials have shown that this structure has a very low seizure threshold, and that it is quite likely to show hypoxia- or hypoglycemia-induced changes in electrical activity. Hippocampal seizures, taking off from the intrinsic four-to-seven-second theta wave activity, may easily spread to other regions of the cortex. Thus, when hippocampal activity is desynchronized, the neocortex shows synchronization. Stimulation of the hippocampus in unanesthetized cats may result’ in reduced reaction to external stimuli and increased attention, with bizarre motor manifestations, to “something” in the environment; this type of behavior has been compared to hallucinations, or “arrest,” and sometimes may be interpreted as a prodrome for a temporal lobe seizure.

Other changes in behavior, notably altered drinking and feeding activities, have been described following destruction or irritation of limbic-system components, especially the lateral portions of the amygdala.® The oral behavior aspects of the Klüver -Bucy syndrome may be associated with this particular pathology. A review of the relation of limbic-system structures to hypothalamic regulation of food and water intake suggests that the role of extra-hypothalamic structures in altered patterns of food intake is probably different from the regulatory function of relevant diencephalic structures.

These past few years it has become evident that a workable concept of a hierarchical organization of *autonomic nervous system functions* must include the "visceral brain," here referred to as the limbic system. This does not exclude a further cortical influence on autonomic function; indeed, there are easy examples of neocortically induced *emotional feelings*—shame, anger, fright, perhaps lust— "gut" reactions that may trigger visceral reflexes. Whether such manifestations of emotion are routed through the limbic system' or directly to the hypothalamic regulatory centers is not clear. However, experimental work of various nature suggests that stimulation of limbic structures may result in altered autonomic functions.'' The increase in oral activity seen in the Klüver-Bucy syndrome—biting, licking, chewing, gagging— may be relevant in this context.

Aggressive behavior, with concomitant autonomic (sympathetic) reactions, and its counterpart *fear,* apprehension, or avoidance have found a neurological substrate in temporal lobe structures, especially the amygdala, as well as in other parts of the limbic system f Stimulation of the amygdaloid complex, which often occurs at the start of an epileptic seizure emanating from the temporal lobe, has produced feelings of anger or fear in conscious patients. It appears, therefore, that the amygdala is a nodal point, functionally related to emotional reactions and experiences. However, the same can be said about other components of the limbic system such as the septum complex. Keepers and investigators attacked by laboratory animals with septum lesions have suffered similar scars. Conversely, ferocious animals may exhibit a remarkable docility after temporal lobe ablation. In this and other behavioral changes such as lack of discrimination, loss of memory, visual agnosia, absence of inhibition, the common threads may begin to weave themselves into an emerging pattern of a general limbic system function.

In an attempt to separate the various components of the Klüver-Bucy syndrome in male cats, Green and coworkers have suggested that the uninhibited and undiscriminating sexual activities displayed by their animals were due to lesions in parts of the amygdala and associated limbic cortex; a loss of the sense of “territory” was evident as well. Similar profound changes in *reproductive behavior* have been reported in other species, including man, following the ablation of temporal lobe structures The results of many of these studies, whether experimentally induced or clinical cases, are difficult to interpret, possibly because the pathology of the structures and the pathways involved are often surprisingly complex.

Whereas in lower forms, olfaction or pheromones appear to play an essential role in the control of reproductive behavior as well as pituitary gonadotrophin secretion, little is known concerning such a mechanism in man. The exceptional and perhaps unexpected importance of smell has been reported even in so-called microsmatic animals. In the comparative analysis of the interrelationships between pituitary function, behavior, and the olfactory component of the limbic system, it makes sense not only to pay attention to species differences in patterns of sexual behavior but also to consider factors such as emotional, experiential, visceral, hormonal, and perceptual correlates in any given setting within a species.

Endocrine System

In the past two decades, the role of nervous afferents to hypothalamic centers that control mammalian pituitary function, which influence reproductive and other patterns of behavior as well as stress reactions, has received attention from an increasing number of investigators in various fields. Important examples of these extra-hypothalamic pathways impinging on the highly complex basal brainstem are the limbic-system efferents—especially the amygdalo-hypothalamic tracts—the olfactory afferents to the medial forebrain bundle, and the fornix system. In the broader sense, other portions of the limbic system such as the habenula, the cingulate gyrus, and possibly Nauta's limbic midbrain area appear to contribute little to human pituitary function, although in experimental animals some suggestive evidence has been reported.

In suitably primed animals, stimulation of the amygdala, its efferent fibers or pertinent hypothalamic nuclei may result in ovulation; the opposite phenomenon, i.e., the impairment of a nervous mechanism that normally enhances luteinizing hormone output by the pituitary gland, has been described, with lesions occurring in these regions.' The secretion of other hormones may likewise be influenced by limbic-system activation.

The effects of lesions in the hippocampal formation, or of stimulation there, impinge on a diversity of manifestations: endocrine, visceral-autonomic, behavioral, related to aspects of memory, etc. Of interest for neuroendocrinologists is the course of some efferent fornix fibers toward posterior portions of the hypothalamus, a small bundle of fibers, described by Cajal in normal rodent material in 1901, ending in the tuber cinereum close to the pituitary infundibulum. Changes in diurnal variation of adrenocortical activity, of recent interest because of the so-called jet-lag phenomenon, have been reported in some species after fornix transection or hippocampal pathology, but these changes are not generally confirmed.

The notion of feedback arcs in neuroendocrinology now appears to be complemented by the concept of bias-setting mechanisms. Such unquestionably complex mechanisms, investigated profitably only if one regulatory factor can be isolated to the stable exclusion of all others, must contain morphological substrates and circuits with certain properties: they must be phylogenetically old; they must be linked (in a functional sense) to "higher" cerebral centers mediating e.g., stresses or emotions; and they require prolonged stimulation in order to produce their effects. The suggestion has been made that the effects of stimulation, ablation, or manipulation of limbic-system components point to the possibility that the morphological substrate and the circuits for the bias-setting mechanisms as well as the switch for the hypothalamo-pituitary "homeostat" might be among the phylogenetically old parts of the brain. This could explain both the lack of a conspicuous role, under "normal" conditions, and the pronounced effects, in certain situations, of lesion or stimulation of the limbic system.

Memory

In recent years, the role of the hippocampus in certain aspects of remembering has attracted considerable attention. Surgical ablation of temporal lobe structures, including large portions of the hippocampus, may result not only in an inability to retain current experiences or to learn but, in addition, a significant forgetting of things past. Ischemia of medial-temporal areas has been associated with episodes of transient global amnesia. It is quite likely that the hippocampus is involved although the actual vascular etiology has not been clearly proven. The well-known vulnerability of this structure to anoxia may underlie this phenomenon. Persistent memory defects have been described, with infarction in the hippocampal formation and fornix as well as in the mammillary bodies. As seen in cases of Wernicke-Korsakoff encephalopathy, the amnestic confabulatory syndrome is usually associated with lesions in the mammillary bodies and medial-anterior thalamic areas. A severe loss of memory of things in the recent past is often present while events from the distant past can be easily recalled. There need be no concomitant deterioration in personality or general intelligence.

The current view, therefore, is that the integrity of the hippocampus is essential to memorizing recent events. Brodal cautions that this statement may be too explicit. Isolated damage to the hippocampus is rare and, in cases of Korsakoff’s syndrome, there are often other changes in addition to those seen in the mammillary bodies. Bilateral transection of the fornix in man may be without demonstrable defects in recent memory, a term itself not easy to define. Besides, there is no evidence that the function of recent memory belongs to the hippocampus alone. Memory as well as learning disturbances have been described following bilateral ablation of the anterior cingulate gyrus or other limbic-system structures.

Associated in some way with memory mechanisms and the limbic system is probably the instinctive behavior shown in animal species as well as the concepts of drives or motivational appetitive behavior such as hunger, thirst, sexual appetites, anger, fear, and so on. This is less clear in contemporary man, although it could lead to intriguing speculation. That is, a more or less fixed pattern of behavior, triggered by a certain cue, sometimes olfactory in nature, often involving extensive participation of autonomic nervous and musculoskeletal systems.

Conclusion

The relatively recent introduction of modern neuroanatomical techniques has resulted in a clarification of the reciprocal neural pathways linking phylogenetically ancient parts of the telencephalon with diencephalic nuclei as well as certain other brainstem areas, thus necessitating a reappraisal of the neural control of pituitary function, of visceral activity, of appetitive or motivational mechanisms, of patterns of behavior and of expressions of emotion. The anatomical substrates for the function of olfaction have been (re)defined; the influence of olfactory reflexes awaits further elucidation.

From the foregoing pages two things should begin to emerge: on the one hand, a continuing clarification of the morphology, hodology, phylogeny, and ontogeny of the limbic system; on the other hand, an almost overwhelming wealth of semi-related functional facets of this system. Activities pertaining to neuroendocrinology of reproduction, stress and associated behavior; autonomic nervous function and olfactory reflexes; certain patterns of visceral behavior, all these can be aggregated as basic contributions to two somewhat conflicting major vital processes: preservation of the individual versus continuation of the species. Certain memory and learning mechanisms, or electroneurophysiological manifestations characteristic of temporal lobe structures (e.g., forms of psychomotor epilepsy) do not readily fit into a unified concept of limbic-system function.

It is fashionable to contemplate how much has been studied and learned since Papez’s speculation on the “mechanism of emotion” in 1937 released a wave of investigations, interest and insight about the form and function of the olfactory brain in man. It is fascinating to speculate whether or not the next decade or two will demonstrate that a simplified, general approach to the significance of these temporal lobe structures and their outflow *is* feasible. It seems likely that some retrenchment and further analysis, anatomical as well as functional, will have to occur before a refined concept of the human limbic system is either accepted or put to rest alongside the rhinencephalon.

> False facts are highly injurious to the progress of science, for they often long endure; but false views, if supported by some evidence, do little harm, as everyone takes a salutary pleasure in proving their falseness.

Charles Darwin
The Descent of Man

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