CHAPTER 22
Limbic System

INTRODUCTION

Rhinencephalon

The neurologist Paul Broca in the later half of the 19th century initially designated all of the structures on the medial surface of the cerebral hemisphere the "great limbic lobe." This region, due to its strong olfactory input, was also designated the rhinencephalon.

The olfactory portion of the brain (rhinencephalon, or archipallium) comprises much of the telencephalon in fish, amphibians, and most mammals. In mammals the presence of a large olfactory lobe adjacent to the hippocampus was once considered to be evidence of the important olfactory functions of these regions. However, when a comparative neuroanatomist examined the brains of sea mammals that had rudimentary olfactory apparatus, e.g., dolphins and whales, the presence of a large hippocampus suggested other than olfactory functions for this region.

In 1937, Papez proposed that olfactory input was not the prime input for this region, and the experiments of Kluver and Bucy (1937, 1939) and Kluver (1952 and 1958) demonstrated the behavioral deficits seen after lesions in this zone. More recently, it has been shown that in primates only a small portion of the limbic lobe is purely olfactory: the olfactory bulb, olfactory tract, olfactory tubercle, pyriform cortex of the uncus, and corticoamygdaloid nuclei *(Fig. 22-1)*. The other portions--hippocampal formation, fornix, parahippocampal gyrus, and cingulate gyrus--are now known to be the cortical regions of the limbic system (Fulton, 1953; Green, 1958; Papez, 1958; Scheer, 1963; Isaaccson, 1982).

Emotional Brain

Since the initial observations of Kluver and Bucy (1937) and Papez (1937), which localized emotions in the telencephalon, many other investigators have added information concerning the localization of behavior. We now know that many cortical and subcortical regions are incorporated in the "emotional brain."

Different investigators have coined different terms to succinctly describe the limbic system, particularly the visceral, vital, or emotional brain. The term "visceral brain" would seem appropriate since much of our emotional response is characterized by specific responses in the viscera (Fulton, 1953). On the other hand, the importance of the emotional response for the self-preservation of the individual and the perpetuation of the species has

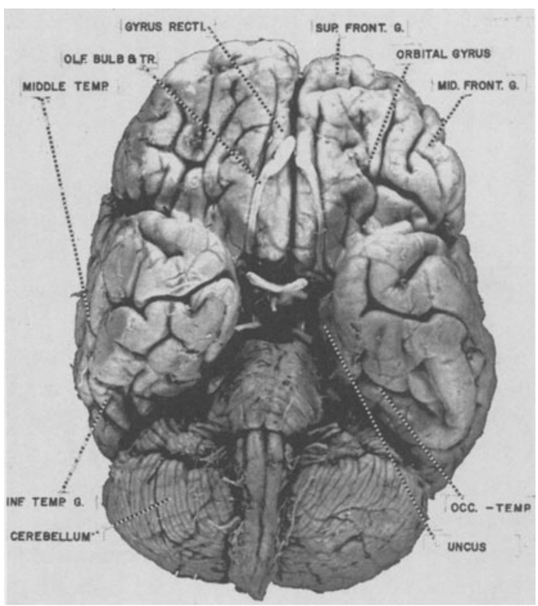

Figure 22-1 Gross view of ventral surface of brain demonstrating olfactory bulb and olfactory tract.

E. M. Marcus et al., *Integrated Neuroscience*

led other investigators to call this region the "vital brain" (MacLean, 1955). The term used most commonly by investigators and the one used in this chapter is limbic lobe (limbus = margin) because the involved region is located on the medial margin of the cerebrum and surrounds the brain stem as it enters the diencephalon.

We can separate the entire central nervous system into a "somatic brain," which controls the external environment through the skeletal muscles, and a " visceral brain," which controls the internal environment through the control of smooth muscles and glands. Our discussion of this region begins with the olfactory system and continues into the Limbic System

I. OLFACTORY SYSTEM

The olfactory system must be included in any discussion of the emotional brain as it sends fibers directly into the medial temporal lobe, and this olfactory information is especially important to the emotional brain.

Olfactory Nerve. The olfactory nerve (cranial nerve I) originates from the uppermost portions of both nasal fossae, which occupy the mucous membrane covering the superior nasal conchae and adjacent septum. The mucous membrane is attached to the walls of the nasal septum that in this region is formed by the ethmoid bone.

Olfactory Receptors. The 100 million or more bipolar receptor cells are embedded in sustentacular cells. The dendrites of the receptor cells are short and ciliated. The cilia are embedded in the odor-absorbing secretion secreted by the Bowman glands that forms the mucosa. New cells from the basal layer are constantly replacing the olfactory receptor cells. All of the axons from the olfactory neuroreceptor cells are unmyelinated. They gather together into about 20 bundles (fila olfactoria), which then pass through openings in the cribriform plate of the ethmoid bone to synapse in the olfactory bulb.

Olfactory Discrimination. Vertebrates with a well-developed sense of smell are called macrosmatic, while those with a poorly developed sense of smell are called microsmatic. Dogs and cats are macrosmatic animals, while humans and all of the great apes are microsmatic *(Fig 22-2)*. In the dog, 15% of the brain

Relates to olfaction while in the human brain, the portion devoted to olfaction is minute. Most dogs and cats have an olfactory system that is infinitely superior to ours both in sensitivity and the ability to discriminate among odors. Nevertheless, we can still distinguish thousands of different odors, and a multimillion-dollar industry has developed to stimulate our olfactory system. In fact, many people have built careers on their olfactory acuity (wine and coffee sniffers and perfumers). Many blind or deaf people have such a refined sense of smell that they can detect subtle changes in their environment.

The olfactory information is distributed from the olfactory bulb through three olfactory stria:

1. Intermediate stria -- olfactory tubercle.
2. Medial olfactory stria -- septal region and via the anterior commissure into the opposite olfactory bulb and,
3. Lateral olfactory stria -- olfactory cortex of the uncus and corticomedial amygdaloid. The terminations in the amygdala produce a strong response in the emotional brain to substances that stimulate the olfactory systems especially smoke, food and pheromones.

Details on the structure of the olfactory bulb, the olfactory connections and the transduction of odors into neuronal signals are included in the CD-ROM section on special senses.

II. LIMBIC REGIONS IN THE BRAIN

The limbic/emotional brain is divided into cortical and subcortical regions.

Cortical Areas are located in: Frontal Lobe, Temporal Lobe and Cingulate Gyrus while Subcortical areas are found in the brain stem, diencephalon and septum.

Table 22-1 identifies the cortical and subcortical limbic structures

SUBCORTICAL STRUCTURES REFER TO CHAPTER 11)

Reticular Formation of the Brain Stem and Spinal Cord. The spinal and cranial nerve roots are the first-order neurons for sensory information to reach the somatic and visceral brain. These peripheral nerves send much sensory information via axon collaterals into the reticular formation of the spinal cord, medulla, pons, and midbrain. The reticular formation is organized longitudinally, with the lateral area being the receptor zone and the medial area being the effector. In the medial zone are the ascending and descending multisynaptic fiber tracts of the reticular formation: the central tegmental tract.

Throughout the levels of the brain stem there are also certain important limbic nuclear groupings in the reticular formation:

1. The mesencephalic portion of the reticular formation seems to be especially important, since this zone provides a direct reciprocal pathway to the hypothalamus, thalamus, and septum.
2. From the locus caeruleus of the upper pons and the raphe of the midbrain the ascending

TABLE 22-1. THE SUBCORTICAL AND CORTICAL NUCLEI OF THE LIMBIC SYSTEM

SUBCORTICAL NUCLEI OF THE LIMBIC SYSTEM:	CORTICAL STRUCTURES OF THE LIMBIC SYSTEM:
1. Reticular formation of the brain stem and spinal cord --Midbrain limbic nuclei (Interpeduncular nucleus, Paramedian nucleus, ventral tegmental area, Ventral half of the periaqueductal gray.	1.Temporal Lobe: --Amygdala --Hippocampal formation- --Parahippocampal cortex --Rostral portion of temporal lobes
2. Hypothalamus (preoptic, lateral, Lateral mammillary nuclei)	2. Frontal Lobe --Frontal association areas --Supracallosal gyrus and longitudinal stria --Subcallosal gyrus -Orbital frontal cortex
3. Thalamus (midline, intralaminar, anterior,and dorsal medial nuclei)	3. Cingulate gyrus and cingulate isthmus
4. Epithalamus	
5. Septum	
6. Nucleus accumbens	

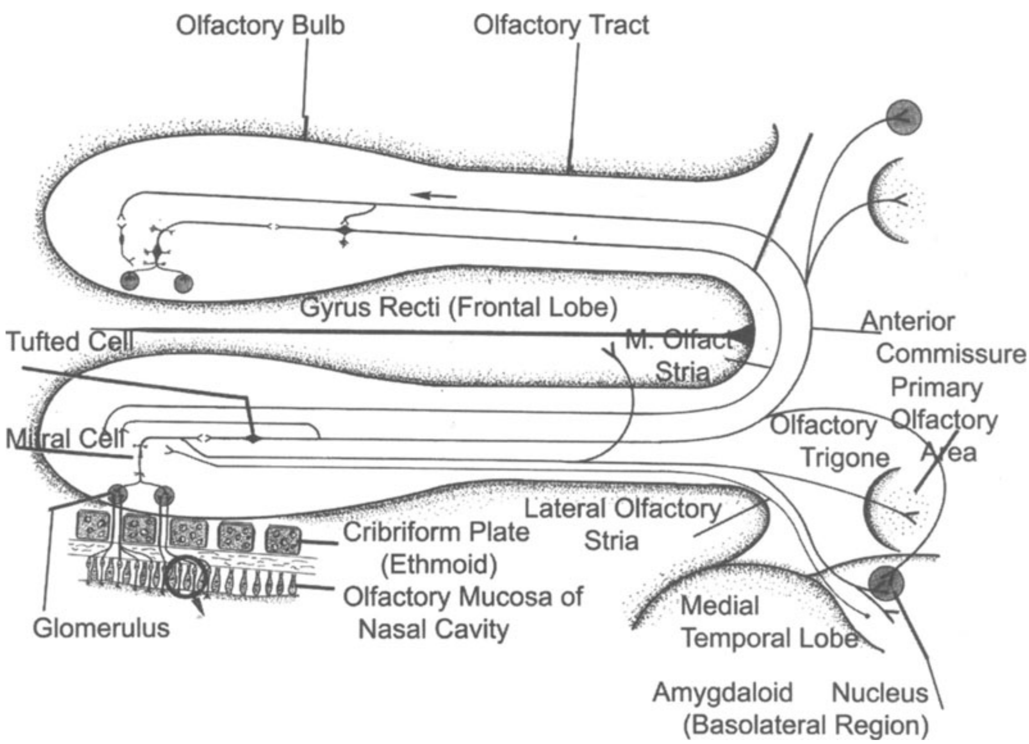

Figure 22-2 Diagrammatic representation of the olfactory system and its connections

serotoninergic and adrenergic systems run into the diencephalon and telencephalon and provide direct input into these regions.

Interpeduncular Nucleus. The interpeduncular nucleus (posterior perforated substance) is found on the anterior surface of the midbrain in the interpeduncular fossa extending from the posterior end of the mammillary body to the anterior end of the pons. It receives fibers from the habenular nuclei (habenulopeduncular tract) and has reciprocal connections with the hypothalamus and the midbrain limbic region. Amygdaloid information reaches this region through connections via the stria terminalis to the septum and then from the septum to the interpeduncular nucleus. Hypothalamic input and septal input are also important parts of the autonomic information to the brain stem passing through this nucleus.

Hypothalamus *(Figs. 22-3, 22-4,* and chapter 16). The hypothalamus is the highest subcortical center of the visceral brain. The basic function of this region is to maintain internal homeostasis (body temperature, appetite, water balance, and pituitary functions) and to establish emotional content. It is a most potent subcortical center due to its control of the autonomic nervous system.

The hypothalamus receives input from all portions of the limbic system, as well as from the reticular formation, basal ganglia, and frontal association cortex. The hypothalamus connects to the thalamus, midbrain, pons, and medulla via the medial forebrain bundle and the dorsal longitudinal fasciculus (Nauta, 1963). Autonomic fibers from the hypothalamus run in the lateral portion of the reticular formation and descend to the cranial nerves and the thoracolumbar (sympathetic) and sacral levels (parasympathetic). The most potent effects result from hypothalamic control of the pituitary gland and the adrenal medulla. The adrenal medulla releases epinephrine and norepinephrine, which produce a decrease in peripheral blood flow, an increase in central blood flow, and an increase in heart rate and force. These agents also stimulate release of glycogen stores from the liver, providing energy for muscular contractions that

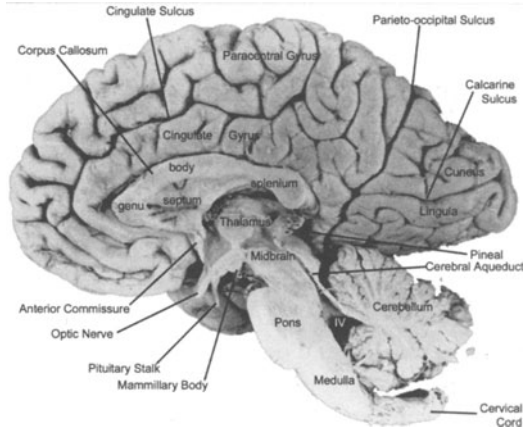

Figure 22-3. Medial surface of a cerebral hemisphere including entire brain stem and cerebellum.

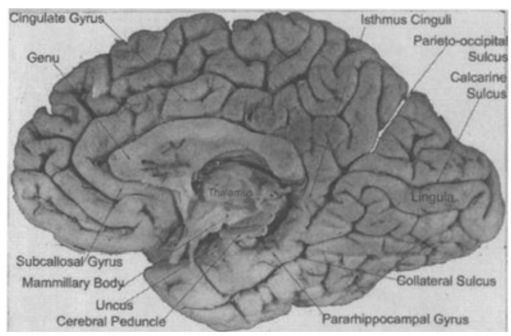

Figure 22-4. Medial surface of a cerebral hemisphere with medulla, pons, and cerebellum removed.

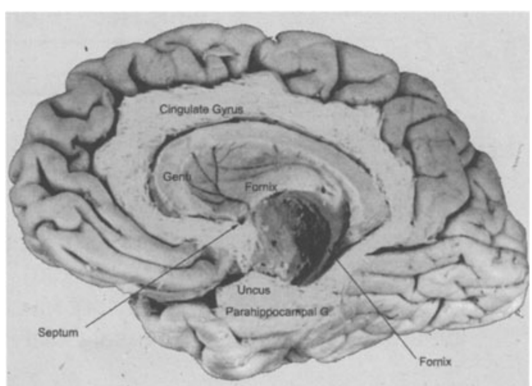

Figure 22-5. Medial surface of a cerebral hemisphere with thalamus removed, demonstrating relationship between fornix and hippocampus.

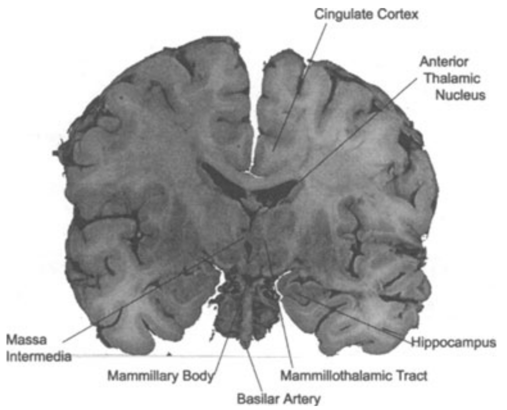

Figure 22-6. Coronal section through diencephalon at level of Massa intermedia showing mammillothalamic tract leaving mamillary body. Weil myelin stain.

accompany the response.

The mammillary nuclei *(Figs. 22-3, 22-4, 22-6)* of the hypothalamus connect to the anterior thalamic nuclei and habenula, via the mammillothalamic tract, and to nuclei in the brain-stem tegmentum via the mammillotegmental tract. The lateral mammillary nucleus receives axons via the fornix from the hippocampus, axons from other portions of the hypothalamus and septum through the medial forebrain bundle, and input from the midbrain tegmentum and substantia nigra via the mammillary peduncle. Effects of hypothalamic stimulation on the autonomic system are listed in Table 22-2.

TABLE 22-2 EFFECTS OF HYPOTHALAMIC STIMULATION ON THE AUTONOMIC NERVOUS SYSTEM

STIMULATION OF ANTERIOR HYPOTHALAMUS= PARASYMPATHETIC RESPONSE	STIMULATION OF POSTERIOR HYPOTHALAMUS = SYMPATHETIC RESPONSE OR ANXIETY RESPONSE
Decrease in - heart rate, respiration, and blood pressure; Increase in peristalsis and in gastric and duodenal secretions; Increased salivation; and depending on the internal milieu, even evacuation of the bowels and bladder. Constriction of the pupils; Concomitant with the parasympathetic excitation is sympathetic inhibition.	Increase in- heart rate, respiration, blood pressure, Decrease in peristalsis and in gastric and duodenal secretions, Decreased salivation with sweating, and piloerection. Dilation of Pupils Concomitant with sympathetic excitation there is parasympathetic inhibition.

Stimulation of the hypothalamus can produce the flight-or-fight response (fear or rage), as well as several visceral responses--sweating, salivation, defecation, and retching. These can be produced in adjacent regions or by moving the electrode site or changing the stimulation parameters (e.g., by varying the current). Another interesting result has been noted in cats made docile with amygdaloid lesions; these animals become savage when a lesion is placed in the ventromedial hypothalamic nuclei. The effects of hypothalamic stimulation and ablation on sleep will be considered in chapter 29.

Thalamus *(Fig. 22-3, 22-4)*. The anterior, medial, midline, and intralaminar dorsal thalamic nuclei receive input from the ascending nociceptive pathways, hypothalamus, reticular system (especially the midbrain reticular formation), cingulate, and frontal association cortex. The intralaminar and midline nuclei connect to the medial and other specific dorsal thalamic nuclei, which then project to the cerebral cortex.

Epithalamus (see chapter 16). The habenular nuclei (epithalamus) give origin to the habenulopeduncular tract, which projects to the midbrain tegmentum and interpeduncular nucleus. The habenular nuclei receive afferents from the septum and preoptic region via the stria medullaris and connect to the intralaminar nuclei.

Septum *(Fig. 22-5)*. The septum forms the medial wall of the frontal horn of the lateral ventricle. The septum consists of two parts: the septum pellucidum containing the septal nuclei (dorsal, lateral and medial) and the caudal velum interpositum. The septum pellucidum is rostral to the interventricular foramen. The septum pellucidum consists of glial membrane and some pia arachnoid (velum interpositum), with the bulk consisting of the column of the fornix. This paired glial membrane, along with the fornix, separates the bodies of the lateral ventricles.

The lower part of the septum pellucidum (septal area) consists of many neurons and glia.

This zone receives strong input from the amygdala via the stria terminalis and hypothalamus. The septum connects with the:

1. Hypothalamus, interpeduncular nucleus, and the midbrain tegmentum via the medial forebrain bundle,
2. Habenula via the stria medullaris, and
3. Basolateral amygdaloid nuclei through the diagonal band.

Destruction of the septum in cats causes docile animals to become fearful or aggressive, but only for a short time. Complete destruction of the septum may produce coma, probably because it destroys the strong connections between the septum and hypothalamus.

Nucleus Acumbens (see chapter 19. This nucleus lies below the caudate, and receives fibers from the amygdala via the ventral amygdalofugal pathway and from the basal ganglia and thus provides a major link between the limbic and basal nuclei. This nucleus has a high content of acetylcholine. In Alzheimer's disease, there is a significant loss of cholinergic neurons in this nucleus.

ROLE OF CORTICAL STRUCTURES IN EMOTIONS

TEMPORAL LOBE

Parahippcampal Gyrus. The uncus (a hook in Latin) forms the anteriormost region in the parahippocampal gyrus on the medial surface of the temporal lobe. Its surface is the olfactory cortex and the principal nucleus of the amygdala lies internally *(Fig 22-4, 22-5)*.

Amygdaloid Nuclei *(Figs. 22-6, 22-7, 22-8)*. The amygdala is uniquely located to provide the intersection between the primary motivational drives of the hypothalamus and septum and the associative learning that occurs at the hippocampal and neocortical levels.

The amygdala *(Fig. 22-9)* consists of three main groupings of nuclei: corticomedial, basolateral, and central. In addition to these principal nuclei there are extratemporal neurons including the nucleus of the stria terminalis

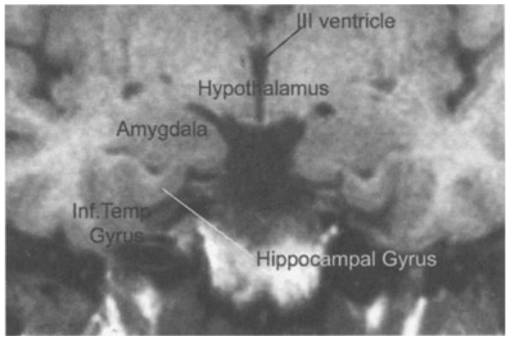

Figure 22-7. Coronal Section through amygdala and hypothalamus. MRI-T1. Hippocampal gyrus = parahippocampal gyrus

and the sublenticular substantia innominata. The amygdala receives extensive projections from many cortical areas and in turn sends projections to these areas. In primates as one expects in comparison to rodents, there has been a significant increase in the projections from and to isocortex (neocortex) as opposed to allocortex and mesocortex. These projections originate from: 1) the multimodality sensory areas, 2) tertiary unimodal sensory association areas, 3) visual association areas which are particularly prominent in the primates, 4) first and second order central sensory neurons of the olfactory system.

From the standpoint of the role of the amygdala in emotion and instinctive behavior, there are important connections with the basal forebrain, medial thalamus (medial dorsal nucleus), hypothalamus (preoptic, anterior and ventromedial and lateral areas), and the tegmentum of the midbrain, pons and medulla (to various nuclei concerned with visceral function such as chewing, licking and the motor components of emotional expression). The more specific connections of the amygdaloid nuclei are listed below

(1) *Olfactory Nuclei.* The corticomedial group receives olfactory information from the lateral olfactory stria and interconnects with the contralateral corticomedial nuclei (via anterior commissure) and ipsilateral basolateral nuclei. The primary efferent pathway of the corticomedial nucleus is the stria terminalis, which projects to the septum, medial hypo-

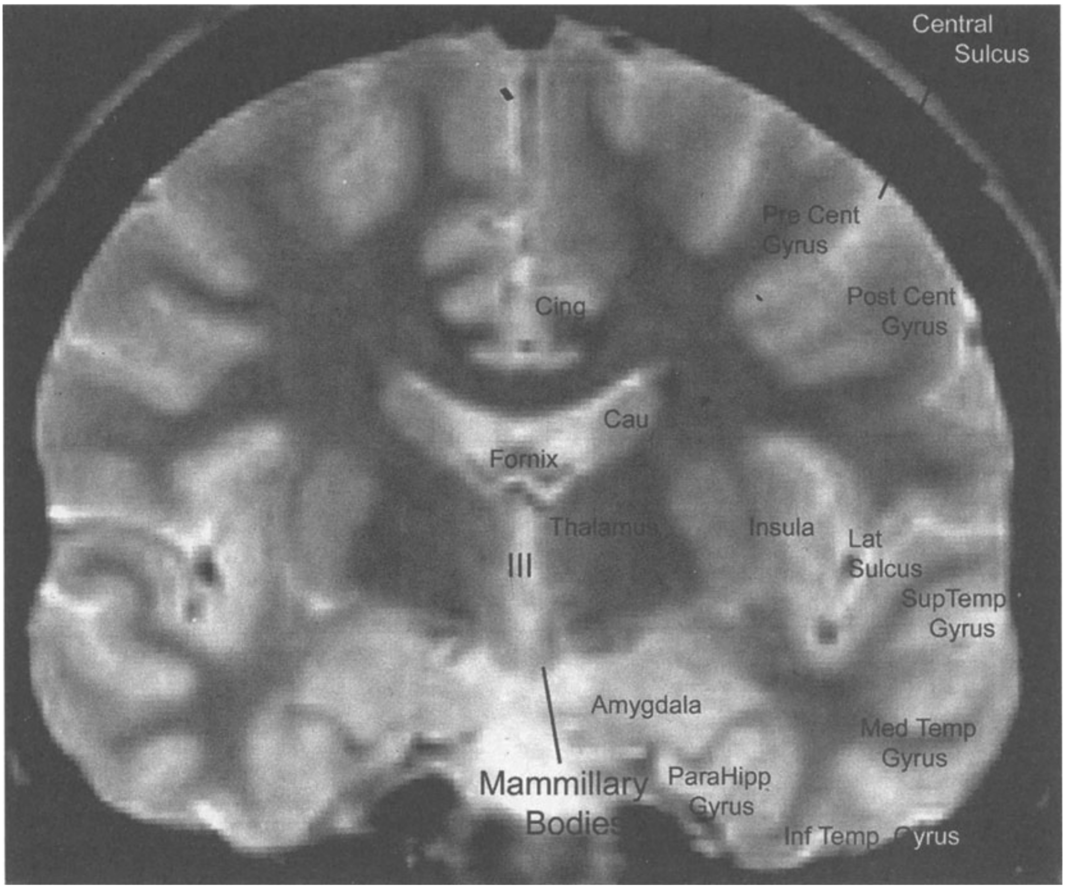

Figure 22-8. Coronal Section through mammillary bodies and amygdala. MRI-T2.

thalamus including preoptic nucleus of the hypothalamus, and to the corticomedial nucleus in the opposite hemisphere.

(2). *Limbic Nuclei.* The central and basolateral nuclear grouping is associated with the limbic brain, and has connections with the parahippocampal cortex, temporal pole, frontal lobe, orbital frontal gyri, cingulate lobe, thalamus (especially dorsomedial nucleus), catecholamine containing nuclei of the reticular formation, and substantia nigra.

(3). The *ventral amygdalofugal pathway* projects from the central nucleus to the brain stem and to the septum, the preoptic, lateral,

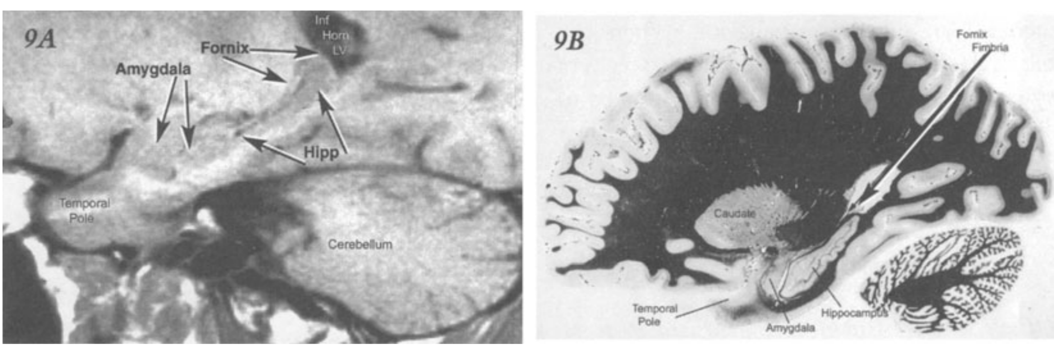

Figure 22-9 A) Sagittal Section. Temporal lobe with amygdala and hippocampus. MRI-T1. B) Sagittal section Weil myelin stain. Inferior horn LV is the junction of posterior and inferior horns of lateral ventricle.

and ventral hypothalamus, and--in the dorsal thalamus--to the dorsomedial, intralaminar, and midline thalamus.

Stimulation of the amygdaloid region. In monkeys, cats, and rats stimulation produces aggressive behavior. The stimulated cats have a sympathetic response of dilated pupils, increased heartbeat, extension of claws, piloerection, and attack behavior. When the stimulus stops, they become friendly. Animals will even fight when the amygdala is stimulated and stop fighting if the stimulus is off. Eating, sniffing, licking, biting, chewing, and gagging may also be stimulated here. In contrast studies in the cat indicate that stimulation of the prefrontal areas will prevent aggressive behavior. In humans, stimulation of the amygdala produces feelings of fear or anger (Cendes et al–1994). A role in sexual behavior has also been postulated, although this may be more prominent in the female.

Ablation of Amygdala. In the studies of Amaral selective bilateral lesions of the amygdala[1] in the adult monkey significantly decreased the fear response to inanimate objects such as an artificial toy snake. This object was now picked up whereas previously, such an object had triggered intense fear responses. The social interactions of the lesioned monkey with other members of a colony were significantly altered. The lesioned animals were more sociable with more sexual and nonsexual friendly contacts with other members of the colony. They were described as socially uninhibited. In the male, aggression was decreased, but occasional females had an increase in aggressive behavior. When the bilateral lesions were produced at two weeks of age, there was a decrease in fear responses to inanimate objects but an increase in fear responses to other monkeys. This latter effect interfered with their social integration into the colony.

In the human, bilateral lesions of the amygdala have been produced for control of aggression. In patients with bilateral lesions of the amygdala there is an impairment of the ability to interpret the emotional aspects of facial expression. (Young et al 1995, Adolph, et al 1998, Anderson et al, 2000). Patients with high functioning autism have a similar disorder (Adolphs et al 2001). On functional MRI studies, these patients failed to activate the left amygdala, as well as the cortical face area or the left cerebellum when implicitly processing facial expressions (Baron-Cohen et al, 2000 Critchley et al 2000). When quantitative MRI is performed in such autistic patients, there is significant enlargement of the volume of the amygdala. Howard et al (2000) suggest that these results may indicate that a developmental malformation of the amygdala (possibly an incomplete neuronal pruning) may underlie the social-cognitive impairments of the autistic patient.

HIPPOCAMPAL FORMATION (22-9, 22-10, 22-13)

This region of the limbic system has been of critical importance in our understanding of both the clinical aspects and underlying biological substrate of memory and of complex partial epilepsy.

Anatomical Correlates:

From an anatomical standpoint, compared to other lobes of the brain, the temporal lobe

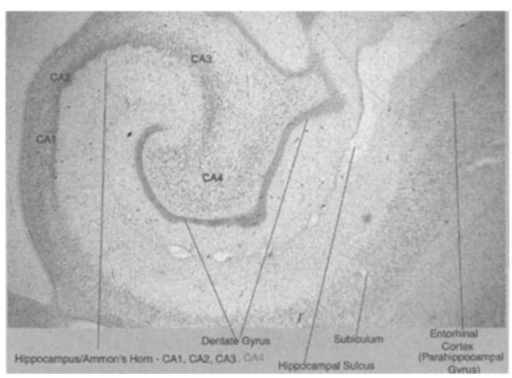

Figure 22-10. The sectors or fields of the hippocampus. The dentate gyrus ,subiculum and related structures are demonstrated. Nissl stain.

---

[1] These selective lesions were produced by injection of ibotenic acid which damages neurons but does not affect fibers of passage

is a complex structure. It contains four diverse components:

Neocortex- 6 layers: superior, middle and inferior temporal gyri (see chapter 17)

Allocortex – 3-layers: the olfactory cortex, hippocampal formation and subiculum.

Mesocortex- a transitional type of 6-layer cortex (transitional between neocortex & allocortex): entorhinal/parahippocampal gyrus (the large posterior segment of the pyriform region), presubiculum and para subiculum.

Cortical Nucleus - the amygdala (discussed above).

The *hippocampus* is phylogenetically the older part of the cerebral cortex termed allocortex and consists of three layers: polymorphic, pyramidal, and molecular. The dentate gyrus[2] fits inside the hippocampus and, like the hippocampus, has three layers: molecular, granular, and polymorphic. The most primitive cortex is the paleocortex of the olfactory bulb.

The fibers of the dentate gyrus are confined to the hippocampal formation while the hippocampal fibers leave the hippocampal formation through the fornix and project to either septum or to the mammillary bodies and mesencephalic tegmentum. The cortex adjacent to the hippocampus changes from three layers to six layers and is classified as transitional mesocortex and includes the parahippocampal gyrus (medial to the collateral sulcus), including entorhinal cortex. The pyriform lobe consists of the lateral olfactory stria, uncus and the anterior part of the parahippocampal gyrus.

Entorhinal Region: The entorhinal/parahippocampal gyrus forms the large posterior segment of the piriform region. This is Brodmann's area 28 and constitutes the bulk of the parahippocampal gyrus. This area has extensive interconnection with the higher association cortex throughout the neocortex and also receives olfactory information from the olfactory stria. This is the major pathway for relating neocortex to the limbic cortex of the hippocampus.[3]

Older classifications have used the terms archicortex for the hippocampus, paleocortex for the piriform area and neocortex for lateral temporal areas based on presumed phylogenetic considerations. Here we will follow in general the terminology as above, employed in the recent monumental work of Gloor (1997). The hippocampus is divided into sectors (referred to as fields) based on cytoarchitectural differences *(Fig.22-10)* CA1-CA4, (or fields of Rose h1-h5). (Note that an older term for the hippocampus is Ammon's {the ram} horn, thus–Cornu Ammonis = CA). CA4, the end folium or end blade merges with the hilus of the dentate gyrus. CA1, the sector closest to the subiculum is referred to as the Sommer's sector. This sector is most severely affected by cell loss following hypoglycemia, anoxia, and status epilepticus *(Fig.22-11)*. However this selective vulnerability may also involve CA3 and CA4 with relative sparing of CA2 and the dentate granule cells. The subsequent gliosis (mesial sclerosis) of the hippocampus is the pathology found at surgery or autopsy in 75% of cases of complex partial seizures arising in the hippocampus.

The hippocampal regions are interconnected by a commissure, the hippocampal commissure. In the primate, the dorsal commissure originates in the entorhinal cortex and presubiculum. The ventral commissure originates

[2]*In the dentate gyrus in common with the olfactory epithelium and cerebellum, new neurons are formed throughout life. In the vast remainder of the brain there is no differentiation of nerve cells after birth, and when these nerve cells die they are not replaced (Altman 1962, Gage 1994). One must expect considerable research in the future to focus on just which genes permit the continued replacement of nerve cells in these regions.*

[3]*Note that the "entorhinal gyrus" of lower mammals corresponds in humans to a much larger region that includes the middle, inferior, and parahippocampal gyri and the temporal portion of the fusiform gyrus.*

in the CA3 sector and the dentate hilus primarily in their more rostral areas e.g. in relation to the uncus

Cytoarchitecture of the Hippocampus: In the hippocampus, the three layers are as follows:

1. *Molecular* in which the apical dendrites of the pyramidal cells arborize. This layer is usually divided into a more external stratum lacunosum-moleculare and a more internal stratum radiatum. It is continuous with molecular layer of dentate gyrus and adjacent temporal neocortex.
2. *Pyramidal cell layer* (stratum pyramidalis) contains pyramidal cells that are the principal cells of the hippocampus. Dendrites extend into molecular layer and Schaffer axon collaterals arise from pyramidal neurons and synapse in the molecular layer on dendrites of other pyramidal cells.
3. *Polymorphic layer* (stratum oriens)-in, which the basilar dendrites of the pyramidal cells are found. Contains axons, dendrites and interneurons. This layer in CA3 is continuous with hilus of the dentates gyrus. Only the hippocampus sends axons outside the hippocampal formation.

Cytoarchitecture of the Dentate Gyrus: In the dentate gyrus, the following three layers are found:

1. *Molecular layer* contains dendrites of granule cells
2. *Granule cell layer.* These small neurons replace the pyramidal cell layer of hippocampus. The granule cells are unipolar; all of the dendrites emerge from the apical end of the cell into the molecular layer. Efferent neurons from the granule cells are mossy fibers that synapse only with cells of hippocampal areas CA2 and CA 3.
3. *Polymorphic cell.* Also referred to as the hilus, this layer is continuous with CA3 of hippocampus.

The pyramidal and granule cell neurons are excitatory utilizing glutamine as the transmitter. In addition there are inhibitory interneurons (GABA-ergic), basket cells, in the polymorphic layer of both the hippocampus and dentate gyrus. There are also mossy cells in the polymorph layer probably excitatory interneurons. There are also scattered interneurons in the molecular layers. The connections of the hippocampal formation are summarized in Table 22-3.

The **Selective Vulnerability of Hippocampus** *(Fig.2-11)* occurs in diseases such as anoxia and hypoglycemia. In addition the hippocampus appears to be significantly involved in most seizures of temporal lobe origin.

1. *Why does this selective vulnerability occur?* The CA 1 region is rich in NMDA receptors. The dentate hilus and the CA3 sector are rich in kainate receptors. Activation of these receptors by glutamate would allow a considerable entry of calcium ions into the pyramidal neurons beginning a cascade that

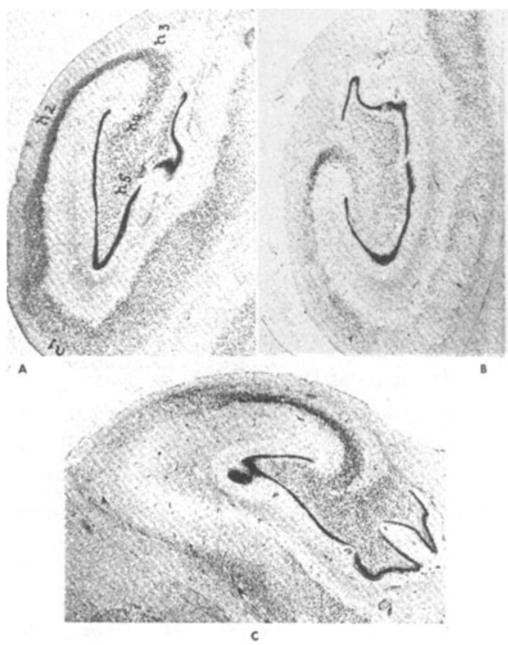

Figure 22-11. Selective vulnerability of the hippocampus demonstrated in Nissl stains. A, Normal Ammon's horn with labels for fields hl-h5 of Rose inserted. B, Anesthetic death: recent necrosis in Sommer sector (hl) and partial loss of neurons in h3 and the end plate (h4, h5). C, Hypoglycemic coma: there has been significant loss of pyramidal cells in section hl. (From Meyer, A. (in) Greenfield, J., et al., Neuropathology 2nd Edition. Baltimore, Williams & Wilkins, 196 p.256).

TABLE 22-3 - CONNECTIONS OF HIPPOCAMPAL FORMATION

AFFERENT INPUT:
1. Perforant pathway from adjacent lateral entorhinal cortex onto granule cells of dentate gyrus and the alvear pathway from the medial entorhinal cortex. The entorhinal areas, in turn, receive their input from many of the highest level of associational cortex in the frontal, orbital, temporal (amygdala), parietal, and cingulate cortex through the cingulum bundle.
2. Septum through the stria terminalis.
3. Contralateral hippocampus, via the hippocampal commissure.
EFFERENT PROJECTIONS:
These fibers, the axons of hippocampal and subiculum pyramidal neurons form the fornix and have connections with the following structures.
1. Lateral mammillary nuclei, habenulae nuclei, anterior midline and intralaminar thalamic nuclei, lateral hypothalamic nuclei, midbrain tegmentum, and periaqueductal grey via a column of the fornix
2. Septum, preoptic region, parolfactory and cingulate cortex via the precommissural fornix and supracallosal fornix

could result in cell death. Moreover the pyramidal neurons of these sectors as compared to CA 2 and the granular cells of the dentate gyrus contain very little calcium buffering protein calbinden.

2. *Seizure Activity.* Most seizures beginning after age 15 are classified as partial, and the majority of these are classified as complex partial. Approximately 75% of the complex partial seizures arise in the temporal lobe, the remainder in the frontal lobe. While these seizures may arise in temporal neocortex, the majority arise in the mesial temporal structures particularly the hippocampus. The hippocampus has a low threshold for seizure discharge; consequently, stimulation of any region that supplies hippocampal afferents or stimulation of the hippocampus itself may produce seizures. Hippocampal stimulation produces respiratory and cardiovascular changes, as well as automatisms (stereotyped movements) involving face, limb, and trunk.
3. *Why do not all of the various pathological processes in the hippocampus produce seizures?* There appears to be a critical age during infancy and early childhood for the acquisition of the pathology that is associated with seizures originating in mesial temporal lobe. There may be an age related remodeling of intrinsic hippocampal connections. Whether a single episode of epileptic status during infancy is sufficient to produce these changes or whether, multiple episodes may be required is still under discussion.
4. *Is the hippocampal pathology alone sufficient to explain the complex partial seizures of temporal lobe origin?* As reviewed by Gloor (1997), many of the specimens examined after surgery or at autopsy also demonstrate extensive changes in the amygdala as well as mesial and lateral isocortex. (Overall however, in the autopsy studies of Margerison and Corsellis (1966) the most frequent site of damage and cell loss was in the hippocampus.) Rather than using the more restrictive term of hippocampal sclerosis, it is more appropriate to use the term mesial temporal sclerosis. Even this term fails to include the involvement of more laterally placed neocortex in some of the symptoms in seizures originating in temporal lobe. (see below)

HIPPOCAMPAL SYSTEM & MEMORY (see also Chapter 30 on Learning and Memory).

The studies of Milner (1972) have shown that bilateral removal or damage of the hippocampus produces great difficulty in learning new information, a condition called anterograde amnesia. The excitatory amino acids, l-glutamate and l-aspartate are important in learning and memory through the mechanism of long-term potentiation. Long-term potentiation is a long lasting facilitation after repeated activation of excitatory amino acid pathways and is most pronounced in the hippocampus and may be related to the initiation of the memory trace

The amygdala and its connections are associated with the conditioning of the emotional response of fear (Refer to review of LeDoux, 2000) and above.

OTHER CORTICAL REGIONS OF THE LIMBIC SYSTEM

Cingulate Cortex. This region *(Fig. 22-5)* receives reciprocal innervation from the anterior thalamic nuclei, contralateral and ipsilateral cingulate cortex, and temporal lobe via the cingulum bundle, as well as projecting to the corpus striatum and most of the subcortical limbic nuclei. The cingulate cortex is continuous with the parahippocampal gyrus at the isthmus behind the splenium of the corpus callosum.

Stimulation of cingulate cortex also produces respiratory, vascular, and visceral changes, but these changes are less than those produced by hypothalamic stimulation. Interruption of the cingulum bundle, which lies deep to the cingulate cortex and the parahippocampal gyrus, has been proposed as a less devastating way to produce the effects of prefrontal lobotomy without a major reduction in intellectual capacity. (For additional discussion of the effects of stimulation and of lesions of the anterior cingulate area on autonomic function and behavior refer to Devinsky et al, 1995)

PRINCIPAL PATHWAYS OF THE LIMBIC SYSTEM

1. *Entorhinal Reverberating Circuit (Fig. 22-12A).* This fiber system is an adjunct to the circuit described by Papez (see below). The entorhinal reverberating circuit functions as follows:

a. Entorhinal cortex receives input from polysensory (multi-model sensory association cortex) cerebral cortex and amygdala

b. Entorhinal fibers project via the perforant pathway to the granule cells of the dentate gyrus via the perforant pathway. There are

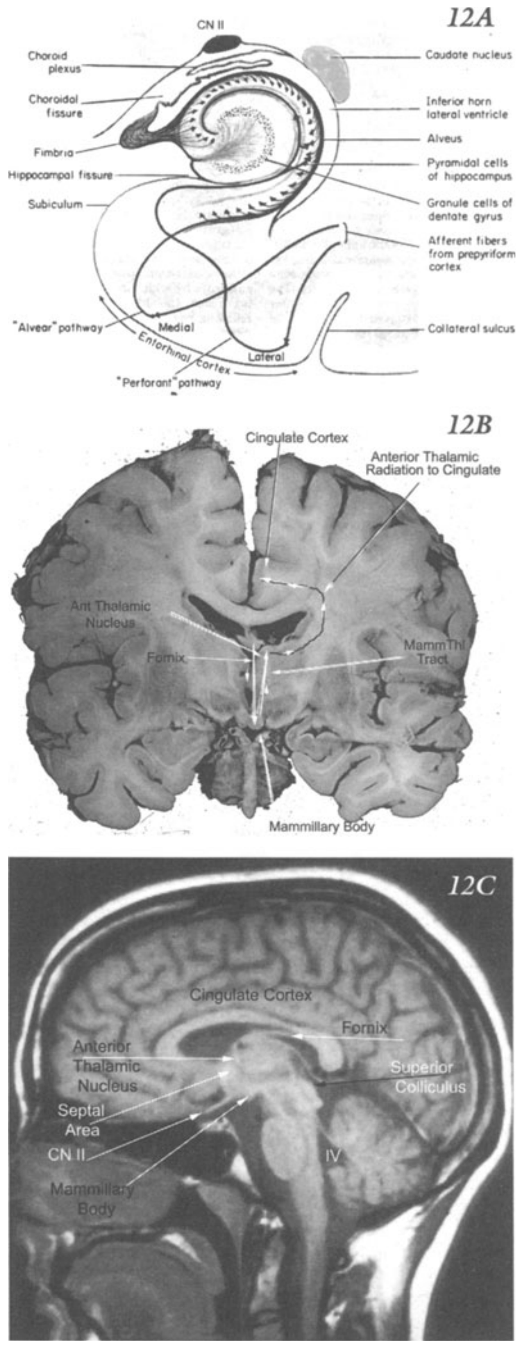

Figure 22-12. A) The perforant pathway modified. From Carpenter MB Core Text of Neuroanatomy, Baltimore William and Wilkins B) The Papez circuit C) Sagittal section showing medial surface of cerebrum demonstrating the limbic structures which surround the brain stem and are on the medial surface of the cerebrum. Portions of Papez Circuit are shown including- fornix, anterior nuclei, mammillary bodies, cingulate cortex and cingulum. MRI-T2.

also direct projections to CA1, CA3 and to subiculum

c. The major projection of the dentate gyrus is to the proximal dendrites of the CA3 hippocampal pyramidal cells. There are also synapses on the neurons of the polymorphic layer.

d. The CA3 pyramidal cells project via Schaffer collaterals to CA1 pyramidal cells.

e. CA1 pyramidal cells collaterals project to the subiculum and entorhinal cortex.

f. The entorhinal cortex projects back to each of the neocortical polysensory projection areas completing a reverberating system.

2. *Papez Circuit*

a. Many hippocampal pyramidal cells synapse on the pyramidal cells of the adjacent subiculum. The pyramidal cells of the subiculum constitute the origin of most of the fibers in the fornix,

b. Fornix projects primarily to the mammillary bodies of the hypothalamus and septum,

c. Mammillary bodies then project via the mammillothalamic tract to the anterior nuclei of the thalamus,

d. Anterior thalamic nuclei project to cingulate gyrus,

e. Cingulate gyrus then projects via the cingulum bundle of fibers to the parahippocampal/entorhinal cortex, which subsequently projects to the hippocampus as outlined above completing the circuit.

3.*Fornix* (*Figs. 22-5, 22-6, 22-7* and chapter 16). Note that the fornix is the efferent pathway from the hippocampus and subiculum and is connected to the hypothalamus, septum, and midbrain. This tract takes a rather circuitous pathway to reach the hypothalamus. The fornix originates from the medial surface of the temporal lobe and runs in the medial wall of the inferior horn of the lateral ventricle, passing onto the undersurface of the corpus callosum at the junction of the inferior horn and body of the ventricles, and running in the medial wall of the body of the lateral ventricle suspended from the corpus callosum. The fornix finally enters the substance of the hypothalamus at the level of the interventricular foramen. Different portions of the fornix have specific names:

- Portio fimbria (fringe) of the fornix found on the medial surface of the hippocampus and consists of fibers from the fornix and hippocampal commissure.
- Portio alveus, band of fornix fibers covering ventricular surface of the hippocampus.
- Portio tenia, connecting the hippocampus to the corpus callosum.
- Portio corpus, located underneath the corpus callosum and entering the hypothalamus
- Portio columnaris, found in the substance of the hypothalamus.

The fornix is also divided into a precommissural portion (in front of the anterior commissure), that enters the septum (from the hippocampus), and the postcommissural portion (behind the anterior commissure), that distributes in the mammillary bodies and midbrain (from subiculum). These relationships should be traced out in the atlas section.

4. *Stria Terminalis.* The pathway of the stria terminalis (the efferent fiber tract of the amygdala) parallels the fornix but it is found adjacent to the body and tail of the caudate nucleus on its medial surface (refer to atlas and chapter 16) The stria terminalis interconnects the medial corticoamygdaloid nuclei, as well as connecting the amygdala to the hypothalamus and septum. There is also a strong termination in the red nucleus of the stria terminalis, which is found above the anterior commissure and lateral to the column of the fornix.
5. *Ventral Amygdalofugal Pathway.* This fiber pathway originates primarily from the basolateral amygdaloid nuclei and to a lesser degree from the olfactory cortex, spreads beneath the lentiform nuclei and enters the lateral hypothalamus and peoptic region, the septum and the diagonal band nucleus, Some of these fibers bypass the hypothalamus and terminate on the magnocellular portions of the dorsomedial thalamic nuclei.

6. *Cingulum.* This fiber bundle is found on the medial surface of the hemisphere and interconnects primarily the medial cortical limbic areas, especially the parahippocampal formation, with one another.
7. *The Intracortical Association Fiber System.* The superior and inferior longitudinal fasciculus, and uncinate fasciculus. The limbic regions on the lateral surface of the hemisphere have strong interconnections with polysensory and third order sensory cortical regions throughout the cerebral cortex through this system
8. *Limbic System and the Corticospinal and Corticobulbar Pathway.* The bulk of the pyramidal pathway originates in the motor/sensory strip. However, most movements begin with a "thought" in the frontal association areas. A possible example of release of the bulbar areas for emotional expression from frontal-lobe control is seen in pseudobulbar palsy. Such patients exhibit inappropriate response to situations because the interrupted corticonuclear/corticobulbar pathway no longer dampens the strong descending autonomic/limbic input to the brain-stem cranial nuclei. The resultant inappropriate behavior is termed emotional lability. A sad story may trigger excessive crying, a funny story excessive laughter.

III. THE NEOCORTEX OF THE TEMPORAL LOBE

Lateral Neocortical Areas. As regards the neocortical areas, (area 41) the primary auditory projection area, is located on the more anterior of the transverse gyri of Heschl *(Fig. 22-13).* This area is a primary special sensory region and has a pronounced layer IV (granular or koniocortex) similar to but considerably thicker than areas 17 and 3. Area 41 receives

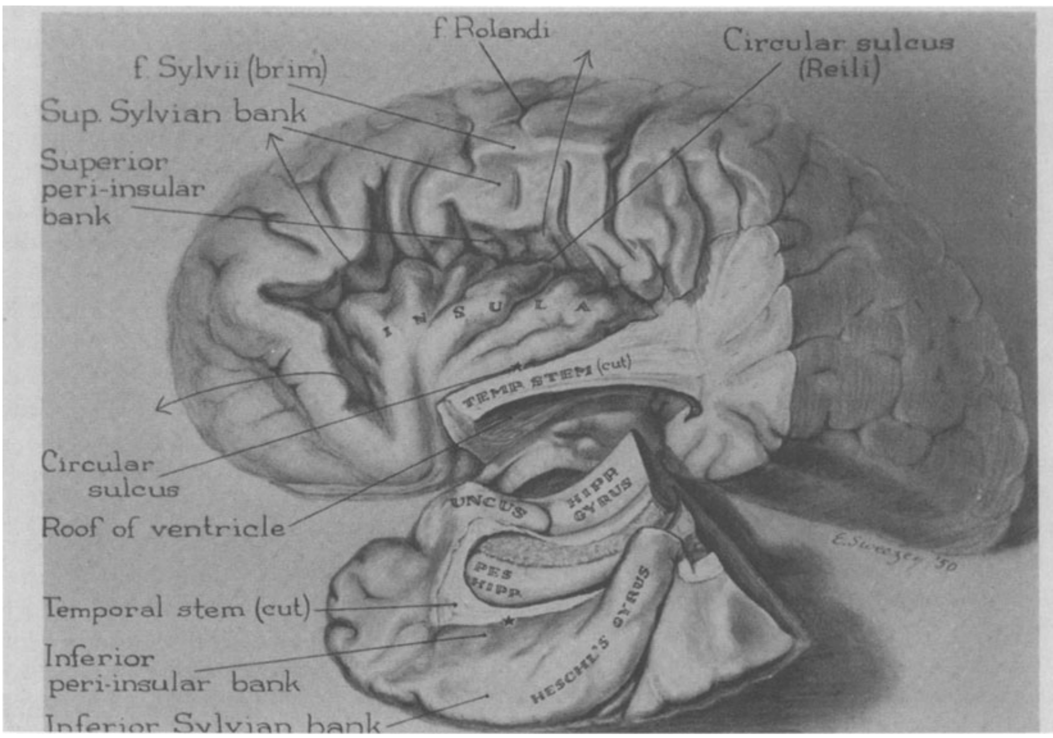

Fig. 22-13 The superior and medial surfaces of the temporal lobe. The transverse gyrus of Heschl and the relationships of the temporal lobe to the gyri of other structures surrounding the sylvian fissure are demonstrated. The temporal stem refers to the core of white matter relating the temporal lobe to the remainder of the cerebral hemisphere. The hippocampal gyrus of the figure is now termed the parahippocampal gyrus. (From Penfield, W., and Jasper, H.: Epilepsy and the Functional Anatomy of the Human Brain. Boston, Little, Brown and Company, 1954, p.52).

the main projection from the medial geniculate nucleus of the thalamus. Our understanding of the tonal organization in this region comes from studies in the monkey and chimpanzee where the lowest frequencies project to the more rostral areas. Some investigators limit the term "Heschl's gyrus" to the more anterior of the transverse gyri and localize the primary auditory cortex to the posterior aspects of that gyrus (Liegeois-Chauvel et al., 1991).

The remaining neocortical areas of the temporal lobe have a well-defined six cortical layers and are classified as homotypical.

Auditory and Auditory Association. Area 42 surrounds area 41 and receives association fibers from this area. Area 22, in turn, surrounds area 42 and communicates with areas 41 and 42. Both areas 42 and 22 are often designated as auditory association areas, and in the dominant hemisphere they are important in understanding speech as Wernicke's area.

Visual Perceptions. The inferior temporal areas have significant connections with area 18, providing a pathway by which visual perceptions, processed at the cortical level, may then be related to the limbic areas.

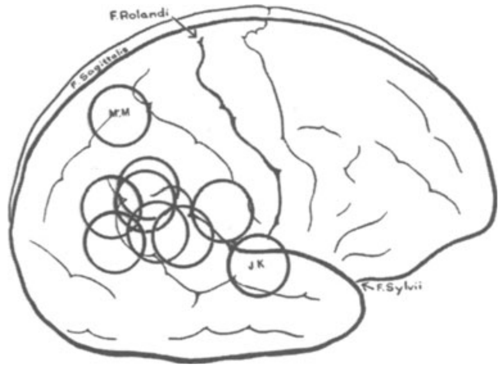

Fig. 22-14 Effects of focal discharge in superior temporal gyrus. The location of the discharging lesion at surgery in nine patients with focal seizures beginning with a sensation of vertigo is demonstrated to be primarily superior temporal gyrus (From Penfield, W., and Kristiansen, K.: Epileptic Seizure Patterns. Springfield, Ill., Charles C. Thomas, 1951, p.49.)

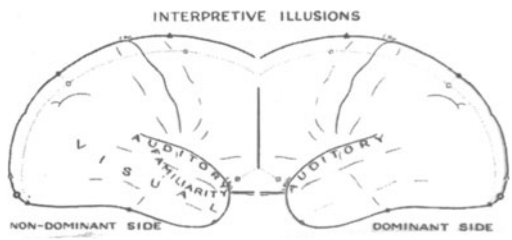

Fig. 22-15. Interpretive illusions (disturbances of perception) produced by stimulation at surgery of temporal lobe cortex in patients with temporal lobe seizures. Visual illusions were produced predominantly in the minor (that is, non-dominant) hemisphere. Auditory illusions were produced from both sides chiefly in the superior temporal gyrus. Illusions of familiarity (déjà-vu) were produced predominantly from the non-dominant hemisphere. Sensations of fear, unreality, loneliness, or of detachment were produced from stimulation in either temporal region. From Penfield, W., and Perot, P.: Brain, 86:599, 1963 (Oxford Univ. Press). After Mullan and Penfield: Archives of Neurology & Psychiatry, 81:269, 1959.)

SYMPTOMS OF DISEASE INVOLVING THE TEMPORAL LOBE

In considering the functions of the temporal lobe and the effects of temporal lobe lesions, one must bear in mind as discussed above that the temporal lobe has several structural, phylogenetic, and functional subdivisions. Thus, one may distinguish as discussed above:

1 - the allocortex of the hippocampal formation,

2 - the transitional mesocortex bordering this area,

3 - the neocortex that occupies all of the lateral surface and the inferior temporal areas.

4 - the amygdala already considered above

When one considers disease processes affecting the temporal lobe, signs and symptoms obviously do not follow the precise subdivisions outlined above. There are several reasons for this:

1. The basic lesion (such as a glioma) often involves both neocortical and non-neocortical areas of the temporal lobe.

2. The threshold of the hippocampus for seizure discharge is relatively low, whereas that of the neocortical areas on the lateral surface is relatively high. Since connections from the

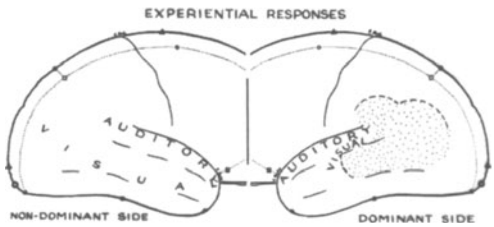

Fig. 22-16 Experiental responses (hallucinations) to stimulation at surgery of temporal lobe and adjacent inferior parietal area in patients with temporal lobe seizures. Auditory responses occur from stimulation in either dominant or nondominant hemisphere, (primarily superior temporal gyri). Visual responses occur primarily from stimulation of the nondominant hemisphere. The stippled area within the interrupted lines indicates the posterior speech area of the dominant hemisphere. No experiential responses occur on stimulation of this speech area in the dominant hemisphere. From Penfield, W., and Perot, P., Brain, 86:676, 1963 (Oxford Univ. Press).

lateral temporal and inferior temporal area to the hippocampus exist, seizure discharges beginning in the lateral temporal neocortex often activate discharge in the hippocampus.

3. Lesions in the more posterior temporal areas often involve the adjacent posterior parietal areas, that is, the inferior parietal lobule. In contrast anteriorly placed lesions of the temporal lobe often involve the adjacent inferior frontal gyrus. Lesions spreading into the deeper white matter of the temporal lobe (particularly in its middle and posterior thirds) often involve part or all of the optic radiation.

Symptoms following Stimulation of the Temporal Lobe.:

Seizures involving the temporal lobe are frequent and produce a variety of symptoms. These may be classified as simple partial if awareness is retained or complex partial if awareness is not retained and the patient is amnestic for the symptoms. A simple partial seizure may progress to a complex partial seizure and may subsequently generalize. These symptoms are outlined in Table 22-4 with the most likely anatomical correlate.

A detailed discussion of the correlation between symptoms in simple and complex

TABLE 22-4 CORRELATION OF TEMPORAL LOBE SEIZURE /LIMITED STIMULATION SYMPTOMS WITH ANATOMY

SYMPTOMS	ANATOMICAL CORRELATION
Autonomic phenomena	Amygdala. Less often cingulate gyrus or orbital frontal
Fear, less often anger or other emotion	Amygdala
Crude auditory sensation: tinnitus	Heschl's transverse gyrus (primary auditory projection)
Visual and auditory illusions: perceptual distortions (22-15)	Higher order visual and auditory association cortex. Superior temporal gyrus in studies of Penfield. For visual predominantly non dominant hemisphere in studies of Penfield
Vestibular sensations: dizziness/vertigo (22-14)	Superior temporal gyrus posterior to auditory cortex
Arrest of speech	Wernicke's area and posterior speech area (posterior temporal/ parietal (angular-supramarginal)-dominant hemisphere
Olfactory hallucinations	Olfactory cortex of the uncus (termination of lateral olfactory stria)."Uncinate epilepsy of Jackson"
Experiential phenomena/dreamy states: More complex illusions such as déjà vu*, déjà vécu*, jamais vu*, other illusions of recognitions, visual and auditory hallucinations (often of past experience) (22-15, 22-16)	Lateral temporal cortex: primarily superior temporal gyrus. Controversial. However ictal phenomena is abolished by ablation limited to lateral temporal neocortex (Blume et al 1993, Mullan &Penfield, 1959) Refer to CD ROM
Automatisms= repetitive simple or complex often stereotyped motor acts, most commonly involving mouth, lips etc. Speech or limbs may be involved.	Primary or secondary bilateral involvement of amygdala / hippocampus. Invariably accompanied by confusion and amnesia for the acts
Defects in memory recording followed by amnesia for the event	Hippocampus

*Déjà vu=sensation of familiarity, déjà vécu =sensation of strangeness, jamais vu =perception is dream like partial epilepsy with temporal structures is included on the CD for this chapter.

In general, as we have indicated, there is mixed symptomatology during partial seizures of temporal lobe origin. The following case history illustrates many of the points just discussed regarding seizures of temporal lobe origin.

Case 22-1: Three months before admission, this 56-year-old right-handed male baker had the onset of 4-minute episodes of vertigo and tinnitus, unrelated to position, followed by increasing forgetfulness. Later that month he had a generalized convulsive seizure that occurred without any warning. The patient then developed episodes of confusion and unresponsiveness, followed by a left frontal headache. Several studies; EEG, pneumoencephalogram, and carotid arteriogram were all negative. One month before admission, the patient began to have minor episodes, characterized by lip smacking and a vertiginous sensation, during which he reported seeing several well-formed, colorful scenes. At times, he had hallucinations of "loaves of bread being laid out on the wall." In addition, he would have a perceptual disturbance (e.g., objects would appear larger than normal). He also had colorful visions and terrifying nightmares "terrifying dreams, crazy things".

Neurological examination: *Seizures observed:* The patient had frequent transient episodes of distress characterized by saying, "Oh, oh, oh, my" and at times accompanied by automatisms: fluttering of the eyelids, smacking of the lips, and repetitive picking at bedclothes with his right hand. Consciousness was not completely impaired during these episodes, which lasted from 30 seconds to 3 minutes. The patient reported afterward that at the onset of the seizure he had seen loaves of bread on the wall and smelled a poorly described unpleasant odor. At other times, the olfactory hallucination was described as pleasant, resembling the aroma of freshly baked bread. *Mental status:* The patient was disoriented to time, could not recall his street address and could not pronounce the name of the hospital. *Cranial nerves:* A possible deficit in the periphery of the right visual field and a minor right central facial weakness were present. *Reflexes:* A right Babinski sign was present

Clinical diagnosis: Simple and complex partial seizures originating left temporal lobe probably involving at various times left lateral superior temporal gyrus, uncus, amygdala and hippocampus, with tumor the most likely etiology in view of age and the focal neurological findings.

Laboratory data: *EEG:* Frequent focal spike discharge was present throughout the left temporal and parietal areas consistent with a focal seizure disorder (Fig. 29-1 and CD atlas). A recording 6 days later indicated almost continuous 3 to 5 (Hz) focal slow-wave activity (focal damage) in the left temporal area (fig. 29-1 and CD Atlas). *Imaging studies:* Left carotid arteriogram indicated a possible avascular mass lesion left posterior lateral frontal.

Subsequent course: These episodes were eventually controlled with anticonvulsant medication. Seizures recurred 7 months after onset of symptoms. An aura of unpleasant odor was followed by a generalized convulsion followed by four or five subsequent seizures of a somewhat different character (deviation of the head and eyes to the right, then tonic and clonic movements of the right hand spreading to the arm, foot, and leg lasting approximately 1 to 2 minutes, followed by a post-ictal right hemiparesis). He also experienced minor seizures characterized by sensory phenomena on the right side of the body. Neurologic examination now indicated progression with a marked expressive aphasia, with little spontaneous speech and difficulty in naming objects. There was a dense right homonymous hemianopia, a flattening of the right nasolabial fold, and a right hemiparesis, with a right Babinski sign. The symptoms and findings suggested that the basic disease process might well have spread to involve the adjacent areas across the sylvian fissure--the speech areas of the inferior frontal convolution, premotor areas, and sen-

Figure. 22-17. Complex and simple partial seizures: cystic-mixed glial tumor and cortical dysplasia right temporal lobe. Case 22-2.CT scan demonstrated an area of atrophy or cyst right anterior temporal lobe with possible minimum enhancement at the border. This 17-year-old right-handed male, at age 4 years began to have "staring spells and bizarre behavior" with some proceeded by the "sound a musical rhythm". An EEG spike discharge was present in the right anterior-middle temporal area. (Refer to text).

sory motor cortex. An arteriogram indicated a large space-occupying tumor of the left temporal lobe, and with additional progression, craniotomy was performed by Dr. Robert Yuan 16 months after the onset of symptoms. A necrotic glioblastoma was found involving the superior temporal gyrus, the deeper temporal and extending superficially under the Sylvian fissure to involve the adjacent posterior portion of the inferior frontal gyrus. A temporal lobectomy was performed (from the anterior temporal pole posteriorly for a distance of 6 cm).

Today, CT scan and MRI would be employed for early diagnosis in patients with this type of seizure disorder as in the following cases and surgery might be limited to a stereotaxic biopsy.

Case 22-2. This 17-year-old right-handed male, at age 4 years began to have "staring spells and bizarre behavior." Some episodes had been preceded by the "sound of a musical rhythm". EEG at that time indicated a right temporal spike discharge Seizures were controlled for ten years with anticonvulsants but then recurred and were poorly controlled

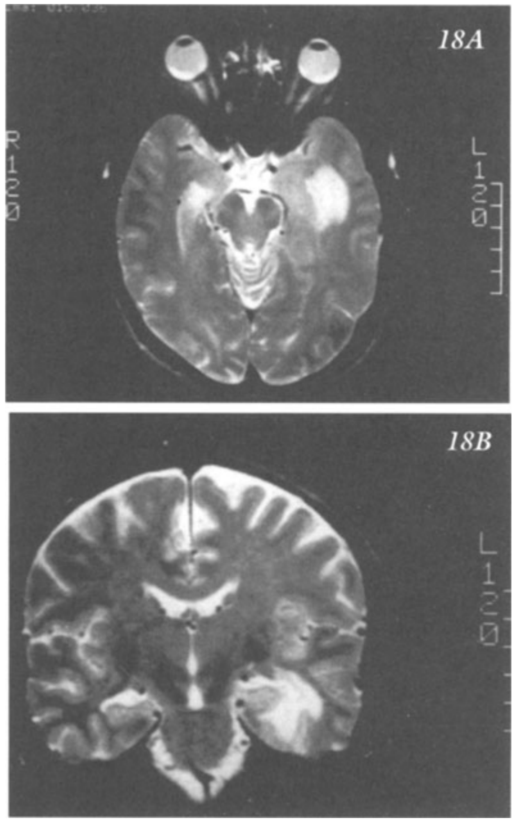

Figure. 22-18.Glioblastoma left temporal lobe. Complex partial seizures with secondary generalization in a 47 year old. Case 22-3. MRI T2 non-enhanced. A) Horizontal section; B) coronal section. (Refer to text.)

occurring several times per day.

Neurological examination: *Observed 3-minute seizure:* The seizure began with loss of contact and a stare and then automatisms of the hands. He stood up, walked around the room, went to the physician's desk and attempted to pull open a nonexistent middle drawer. He answered questions vaguely with one or two word answers. Confusion was present for 1-2 minutes after the end of the episode. *Cranial nerves:* a left central facial weakness was present.

Clinical diagnosis: **Focal seizures originating** right temporal lobe. Observed seizure was complex partial. The seizures beginning with the musical sound might be classified as simple partial with secondary complex partial.

Laboratory data: *EEG:* Intermittent focal spike discharge anterior-middle temporal area. *CT scan (Fig.22-17): An area of focal atrophy* was present in the right anterior temporal lobe with possible enhancement at the border. MRI: AT the Yale Epilepsy Center was more consistent with a tumor in the right anterior temporal lobe.

Subsequent course: Dr. Dennis Spencer at the Yale Epilepsy Center performed a temporal lobectomy. This demonstrated a cystic glial tumor with components of astrocytes and oligodendrocytes. Cerebral cortex also demonstrated abnormal lamination and dysplastic features. Seizures were fully controlled over the next three years.

Case 22-3. This 47-year-old ambidextrous male experienced his first seizure one month prior to admission. He felt light-headed and warm. Then he was observed to walk 100 feet down a hallway, appearing "dazed" and not recognizing people. He fell to the floor, with a loss of consciousness, bit his tongue and was confused afterwards for several minutes.

Neurological examination at 2, 16 and 48 hours after the episode a persistent right Babinski sign, and slight right hyperreflexia were present.

Clinical diagnosis: Complex partial seizures. In view of age of onset and persistent focal signs a brain tumor should be suspected as the etiology.

Laboratory diagnosis: *Sleep deprived EEG:* normal. *CT and MRI scans (Fig. 22-18)* demonstrated an extensive infiltrating tumor of the left temporal lobe most likely a glioblastoma.

Subsequent course: Despite Anticonvulsant therapy (phenytoin) additional episodes occurred over the next month: loss of train of thought while talking and several minutes of loss of memory. A subtotal resection by Dr. Bernard Stone (St. Vincent Hospital) demonstrated a Grade III-IV astrocytoma (glioblastoma). Despite radiotherapy and chemotherapy, the disease pursued a relentless course producing early and severe disability prior to death, approximately one year after onset of symptoms.

Symptoms from Ablation of or damage to the Temporal Lobe.

1. *Effects on Hearing.* Unilateral lesion of auditory projection areaway result in an inability to localize a sound. Bilateral lesions may produce cortical deafness.
2. *Aphasia.* Destruction of area 22 in the dominant hemisphere produces a Wernicke's receptive aphasia. Such a patient not only has difficulty in interpreting speech but also, in a sense, has lost the ability to use previous auditory associations. Lesions that deprive the receptive aphasia area of Wernicke in the dominant temporal lobe (area 22) of information from the auditory projection areas of the right and left hemispheres result in pure word deafness. Such a patient can hear sounds and words but is unable to interpret them.
3. *Visual Defects.* Unilateral lesions of the temporal lobe that involve the subcortical white matter often produce damage to the geniculocalcarine radiations. Since the most inferior fibers of the radiation that swing forward around the temporal horn (representing the inferior parts of the retina and referred to as "Meyer's loop") are often the first to be involved, the initial field defect may be a contralateral superior field quadrantanopia.
4. *Klüver-Bucy Syndrome.* This syndrome results from bilateral ablation of the temporal pole, amygdaloid nuclei, and hippocampus in the monkey (Klüver and Bucy 1937). The animals could see and find objects, but they could not identify objects (visual agnosia). The animal showed marked deficits in visual discrimination, particularly in regard to visual stimuli related to various motivations. They also had a release of very strong oral automatisms and compulsively placed objects in their mouths, which, if not edible, were dropped. They had a tendency to mouth and touch all visible objects and manifested indiscriminate sexual practice. They willingly ate food not normally a part of their diet (such as corn-beef sandwiches). They showed a lack of response to aversive

stimuli and had no recollection or judgment. The animals also lost their fear (release phenomenon) and, in the case of wild monkeys, became tame and docile creatures. They had a marked absence of the fight-or-flight response and also lost fears of unknown objects or objects that previously had frightened them. (See amygdala above). The problems in visual discrimination may reflect a disconnection of the visual association areas from the amygdala/ hippocampal areas.

5. *Memory:* Bilateral damage to the hippocampus produces a marked impairment of the ability to form new associations, an inability to establish new memories at a time when remote memory is well preserved.
6. *Unilateral effects on memory:* Patients with resection of the left temporal lobe may lose the ability to retain verbally related material but gain the ability to retain visually related material relevant to the right hemisphere. The reverse is true for right temporal lobectomy patients.
7. *Psychiatric disturbances:* Waxman and Geschwind (1975) have described an interictal personality disorder characterized by hyposexuality, hyper religiosity, hypergraphia, and a so-called stickiness or viscosity in interpersonal relationships. In some patients a psychosis may be apparent in periods between seizures (the interictal period) that is often most severe during periods when the seizure disorder is well under control. In other patients a transient psychosis may be related to the actual seizure discharge or the postictal period. There is controversy regarding this issue.
8. *Aggressive behavior:* aggressive behavior and episodic dyscontrol may be related to dysfunction of the amygdala or to damage to prefrontal areas, which inhibit the amygdala. This remains an area of considerable controversy (Mark and Ervin, 1970; Geschwind, 1983 Ferguson et al, 1986).
9. Complex partial seizures as discussed above may follow mesial temporal sclerosis.

IV. FRONTAL LOBE: PREFRONTAL CORTEX AND EMOTIONS (Areas 9, 10, 11, 12, 46, 13, 14)

The term prefrontal refers to those portions of the frontal lobe anterior to the agranular motor and premotor areas. The prefrontal region is in a unique position in the brain as it receives a vast stream of information from polysensory, third order sensory and from cortical and subcortical limbic areas including especially dorsomedial nucleus, hypothalamus and indirectly the amygdala.

In the prefrontal cortex three regions are usually delineated:

1) Lateral - dorsal convexity,

2) Medial, and

3) Orbital.

All three are concerned with executive function and relate to the dorsomedial thalamic nuclei. In general the lateral-dorsal relates to motor association executive function, the orbital –ventral and the medial to the limbic –emotional control executive system. Recent studies have questioned this simplistic approach. Thus certain functions previously considered to be associated with dorsolateral location have been now localized to a medial location (Stuss et al 2000). In addition, there is evidence that dorsal lateral lesions also alter affect and motivation. Moreover as the clinical examples will demonstrate, most pathological processes involve the functions associated with more than one division either directly or through pressure effects.

Although the term prefrontal traditionally included areas 9, 10, 11 and 12,most studies of stimulation or of ablative lesions involving the prefrontal areas have included, within the general meaning of the term prefrontal, areas beyond these Brodmann designations. Thus the posterior orbital cortex (area 13) and the posteromedial orbital cortex (area 14) have been added to the orbital frontal group (Fig. 18-28). These areas all share a common relationship to the medial dorsal nucleus of the thalamus. Areas 46 and 47, located in man on the lateral surface of the hemisphere, are also often grouped with areas 9, 10, 11, and 12.

Another area, the anterior cingulate gyrus (area 24) is also included in the prefrontal area, although it relates to the anterior thalamic nuclei. Some authors (particularly in discussing frontal epilepsy) also include area 8 and the supplementary motor cortex already discussed above in relationship to premotor cortex.

The multiple connections of the prefrontal areas are discussed by Damasio 1985, Goldman-Rakic 1987, Jacobson and Trojanowski 1977, Nauta 1964, Pandya et al 1971 and Stuss and Benson 1986. Essentially, all sensory association and polysensory (multimodal) areas and the olfactory cortex project to the prefrontal areas. The prefrontal areas in turn have reciprocal connections to the premotor, temporal, inferior parietal and limbic cortex. The connections to the limbic system include (a) cingulate gyrus and then via cingulum to hippocampus and (b) uncinate fasciculus. Subcortical bidirectional connections are prominent in relationship to the medial dorsal nucleus of the thalamus, amygdala, and hippocampus. Significant projections to the caudate nucleus - putamen and the premotor areas provide the anatomical substrate for influencing motor function. Projections to the superior colliculus provide the substrate for modifying eye movements - e.g., "look to the direction opposite to the target."

Here we will briefly outline the major connections of the major subdivisions

(1) *Orbitofrontal Cortex.* The orbitofrontal cortex (areas 11 and 12) receives input from the cingulate regions, other sections of the prefrontal cortex, the magnocellular division of the dorsomedial nucleus, the amygdala and temporal areas. The orbitofrontal cortex in turn has strong projections to the autonomic regions of the hypothalamus and magnocellular dorsomedial nucleus of the thalamus in addition to the amygdala and temporal structures. Stimulation of the posterior orbital surface, like stimulation of the cingulate, parahippocampal gyrus, and amygdala changes the respiration, cardiac rhythm, and visceral contractions. These responses are believed to be the somatic basis of the emotional changes that originate in the limbic cortex.

(2) *Frontal Association Areas/Lateral Prefrontal Granular Frontal Cortex.* This region that is important in controlling behavior lays rostral to the premotor cortex, area 6 & 8 and has already been discussed in chapter 18. The frontal association areas (areas 9, 10, 11, and 12) receive their input from the cingulate regions and cortical association areas in the temporal, parietal and occipital lobes. They also have a strong reciprocal connection with the parvicellular portions of the dorsal medial thalamic nucleus via the anterior thalamic radiation. The dorsal medial thalamic nucleus, in turn, receives most of its input from the hypothalamus and the midbrain limbic nuclei. The frontal association region has strong projections to the hypothalamus and thalamus.

Overview of the role of the prefrontal area in motor and cognitive function: this topic has already been discussed in chapter 18.

Stimulation complex partial seizures. These seizures, partial seizures with impairment of consciousness, were formerly considered to be entirely temporal lobe in origin. It is now recognized that 20-30% of such seizures are extratemporal in origin - predominantly frontal lobe (Schwartz et al 1989, Williamson et al 1988). Compared to complex partial seizures of temporal lobe origin, complex partial seizures of frontal lobe origin are usually briefer, occur more frequently and tend to have a much shorter post ictal period of confusion. Recent studies of St.Hilaire at al; Wada and Weiser (see Chauvel et al 1992) suggest that these automatisms of orbital or medial parasagittal origin are often complex involving both arms or both legs or trunk or pelvis, at times in organized kicking, struggling, running or screaming. In contrast, automatisms of temporal lobe origin are more often oral or alimentary (licking, chewing, swallowing, etc). Such frontal lobe seizures must also be differ-

TABLE 22-5: SUMMARY OF THE LOCALIZATION TYPES OF FRONTAL EPILEPSY

LOCATION OF SEIZURE	BEHAVIORAL EFFECTS
Supplementary motor	Tonic, postural and speech arrest;
Cingulate	Complex partial
Anterior frontal polar	Forced thinking or initial loss of consciousness plus adversive components
Orbital frontal	Complex partial plus olfactory hallucinations plus illusions;
Dorsolateral	Tonic plus or minus aversion
Opercular	Mastication, salivation, swallowing plus speech arrest plus or minus epigastric and gustatory symptoms (see under parietal) plus or minus secondary spread to other simple partial.

entiated from seizures of psychogenic origin and from the "petit" absence seizures of generalized epilepsy (see Chapter 29). Thus, orbital frontal seizures present many features previously associated with pseudo or psychogenic seizures. Frontal polar seizures or dorsolateral convexity may present as forced thinking or apparent absence seizures. Quesney et al, 1990 make a distinction between discharges originating in the dorsolateral convexity, which are more likely to present with automatisms and affective components compared to parasagittal discharges that are more likely to present with motor or somatosensory components.

The present International Classification (see Commission - 1989) provides a summary of the localization types of frontal epilepsy that includes more than the prefrontal areas and is presented in Table 22-5:

Additional information concerning frontal lobe seizures/epilepsy will be found on the CD ROM.

Prefrontal cortex damage in humans: In general, most studies of prefrontal function have dealt with bilateral damage or with a unilateral lesion which, because of its parasagittal location in relation to the medial aspect of the prefrontal area, has produced essentially bilateral effects.

The first well-authenticated case of the frontal lobe syndrome is the crowbar case of Mr. Phineas P. Gage reported by Harlow in 1868. In an explosion in 1848, a pointed tamping iron shot through the skull of the patient, an efficient, well-balanced, shrewd, and energetic railroad foreman. The bar, 3.5 feet in length and 1.25 inches in greatest diameter, entered below the left orbit and merged in the midline vertex, anterior to the coronal suture, lacerating the superior sagittal sinus in the process. Following the injury, a marked personality change was noted. The balance "between his intellectual faculties and animal propensities" had been destroyed. He was "impatient of restraint or advice which conflicts with his desires; at times - obstinate yet capricious and vacillating, devising many plans of future operations which are no sooner arranged than they are abandoned in turn for others appearing more feasible."

Additional studies of such patients with bilateral damage to prefrontal areas have been reviewed by Damasio (1985), Damasio et al, 1994 and by Stuss and Benson, (1986). In humans, gross correlation of location of pathology (trauma and mass lesions) with major behavioral syndromes has been suggested.

(1) A *syndrome of "frontal retardation" or "pseudo depression" (abulia)* manifested by apathy, non-concern, lack of motivational drive and a lack of motivational drive and a lack of emotional reactivity has been associated with lesions involving the *frontal poles and/or the medial aspects of both hemispheres.* In its most severe form a syndrome of akinetic mutism occurs. Some have also noted aspects of this syndrome with dorsolateral frontal lesions.

(2) In contrast, the *"pseudopsychopathic" syndrome* is distinguished by a lack of inhibi-

tion including: facetiousness ("Witzelsucht"), sexual and personal hedonism, and lack of concern for others has been associated with *orbital frontal* pathology. Some of these patients with ventromedial orbital lesions have been described as manifesting confabulation, a particular disorder of memory found in patients with the Korsakoff syndrome; (a syndrome in which lesions of the dorsal medial nucleus of the thalamus have been implicated (chapter 30)). Patients with lesions of lateral orbital and lateral convexity have been described as restless, hyperkinetic, explosive and impulsive. As indicated above, damage in the dorsolateral sector appears to result in impairment of that high level cognitive ability which allows for abstraction, and creative activities. A rigidity or concreteness of response often is present. Additional discussion of the effects of frontal lobe lesions on emotional regulation will be found in Grafman et al 1986.Most patients do not fall into these discrete groups as regards the effects on emotion and personality and the correlation with tumor location is often not precise. Large prefrontal tumors often involve several prefrontal regions.

Prefrontal Lobotomy. Based on the initial reports of Jacobsen regarding the effects of prefrontal lobotomy on the emotional responses of the Chimpanzee, Moniz, a neuropsychiatrist and Lima a neurosurgeon introduced in 1936 the surgical procedures of prefrontal lobotomy to modify the behavior and affect of psychotic patients. Subsequently, Moniz introduced the procedure of prefrontal leukotomy: bilateral disconnection of prefrontal areas from subcortical (thalamic and basal ganglia) and other cortical areas *(Fig. 22-19)*. A more specific approach to problems of severe anxiety, manic behavior, and chronic pain was the procedure of stereotaxic anterior cingulotomy introduced by Ballantine et al, 1967. A number of lobotomies were performed in the 1940s and early 1950s for psychiatric reasons or to modify the emotional

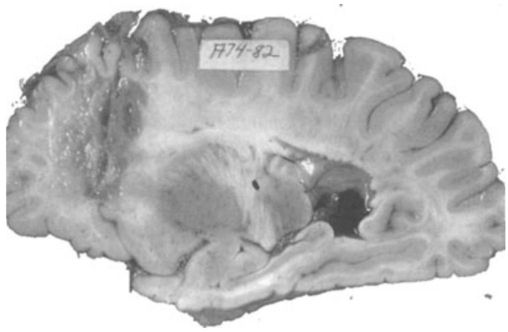

Figure 22-19. Prefrontal leukotomy. A surgical section has separated the prefrontal connections with the thalamus. Courtesy of Dr. Thomas Sabin and Dr. Thomas Kemper.

response of patient with chronic pain previously requiring large doses of narcotics. Such studies must be interpreted with a certain degree of caution. In the psychiatric patients, the lesions are produced in individuals with preoperative abnormalities of personality function. The effects are not necessarily those that the same lesion would produce in otherwise normal individuals. There is, however, a considerable resemblance in these cases to the effects produced by trauma (to the prefrontal areas) in relatively normal individuals.

The early results did suggest that these procedures did produce an alteration in the emotional response with a reduction of anxiety generated in conflict and painful situations. Emotional response was often detached from the pain and conflicts.

However, these effects on emotion can now be produced by the use of the tranquilizing drugs that were developed beginning in the middle 1950s. The development of these drugs, in addition to the frequent postoperative complications including seizures and personality alterations, led to the discontinuation of the procedure. (Valenstein, 1986). The personality changes are those that have been elaborated above. The personality change results from the isolation of the limbic subcortical structures from input provided by the prefrontal areas. Following prefrontal lobotomy or leukotomy, these patients were often impulsive and distractible. Their emotional responses were often uninhibited with an apparent lack of concern over the consequences of their actions. A related finding was an inability to plan ahead for future goals; at times, the patients were unable to postpone gratification, responding to their motivations of the moment. (In a sense, a loss of the reality principle had occurred). Although distractible, a certain perseveration of response was noted with an inability to shift responses to meet a change in environmental stimuli or cues. A rigidity and concreteness of response was apparent with deficits in abstract reasoning. A somewhat similar but less drastic personality change can be produced by bilateral severance of the anterior thalamic radiation from the medial nucleus or by direct destruction of the medial nuclei or orbital cortex. This less massive resection of cortex lessens anxiety with fewer personality changes. Destruction of the anterior cingulate regions also produces this less drastic change. Current psychosurgical or functional neurosurgical procedures have been reviewed by Diering and Bell(1991).

The results of partial or complete prefrontal lobotomy have shown that this region is important in motivation, intellect, judgment, abstract reasoning, and emotional control.

Parasagittal Lesions. It must be noted that lesions (e.g., meningiomas) which were initially parasagittal or subfrontal in relation to the prefrontal areas may, as they progress, compromise the function of adjacent premotor areas (8 and 6 and the supplementary motor cortex). The resultant clinical picture may then include not only the changes in personality but also the release of an instinctive tactile grasp and of a suck reflex. An incontinence of urine and feces may be present in addition to an apraxia of gait - an unsteadiness of gait, which is apparent as the patient attempts to stand and begins to walk but clears up once the act has been initiated. The following case histories illustrate many of the features of focal disease involving the prefrontal areas.

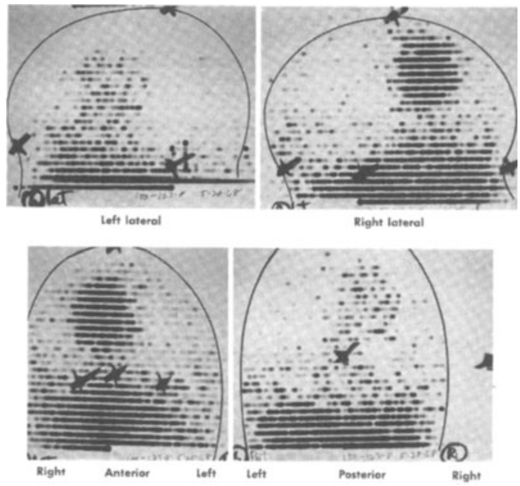

Figure 22-21. Frontal parasagittal meningioma. Case 22-4 refer to text. Radioactive brain scan (Hg^{197}) demonstrates dense uptake in right frontal parasagittal area.

Case 22-4: Two years before admission, this 69-year-old right handed white housewife; visited a relative (a physician) in Israel whom she had not seen in a number of years. He noted a change in the patient's personality. The patient was described as apathetic with silly immature reactions. In retrospect, the patient's husband felt that these alternations had begun insidiously a number of years previously. Her letters became incoherent .Ten months prior to evaluation, a left central facial weakness was first noted followed two months later by a decreased left arm swing. Six months prior to evaluation, her husband noted, she was purchasing items for which she had no need: 24 pairs of shoes, 15 brassieres. Subsequently she became careless in her housework. On occasions she lost her purse. Her ability to play bridge had decreased over the last year, although her golf game was unchanged.

Neurological examination: *Mental status:* There was a marked impersistence in motor activities. She was often inattentive. There was inappropriate joking. Her answers were often irrelevant. (According to her husband this had been present for many years). Digit span was decreased to 5 forward and 3 in reverses. There were marked deficits in serial 7 substractions. At times she began to subtract other numbers, at times she added rather than subtracted. There was a significant spatial disorientation. There was a marked impairment in the ability to copy a cube and deficits in drawing a house. There was disorientation in locating cities on a map. *Cranial nerves:* There was a significant neglect of single stimulus objects in the left visual field and a greater neglect when bilateral simultaneous stimuli were utilized. At times there was a limitation of voluntary gaze to the left. A left central facial weakness was present. *Motor system*: There was minimal weakness of the left arm and leg. Variable resistance was present on passive motion at left wrist and elbow suggesting the "gegenhalten"of frontal lobe disease. There was a decreased swing of the left arm in walking. The gait was initially apraxic but improved as the patient picked up speed. *Reflexes* Deep tendon stretch reflexes were increased on the left, with a left Babinski sign and a bilateral release of the grasp reflex.

Clinical diagnosis: Right frontal lobe tumor: probably a meningioma based on the long history.

Laboratory data: EEG (Fig 22-20 on CD Atlas), and *imaging studies (Fig. 22-21)* all indicated a right frontal parasagittal lesion. A meningioma was considered most likely since vascular supply was derived from the left and right middle meningeal and left anterior meningeal arteries.

Hospital course: At craniotomy, Dr. Samuel Brendler found a large right posterior parasagittal frontal fibrous, meningothelial meningioma measuring 8x8cm attached to the right side of the superior sagittal sinus.

Case history 22-5 presented on CD ROM provides an example of a patient with a slowly progressive subfrontal meningioma manifested by symptoms of apathy, loss of ambition, "depression" of mood, emotional lability, with a tendency to introspection and a slowness of mental processes. All of these symptoms were initially attributed to depression and a hypothyroid state. As gait and memory problems developed, these symptoms were attributed to Alzheimer's type senile dementia. When increased intracranial pressure and coma suddenly developed, neurological and neurosurgical intervention occurred.

Limbic Brain as a Functional System.

The emotional brain is organized into a hierarchy of function proceeding from the reticular formation, including mesencephalic midbrain nuclei to the hypothalamus and thalamus to the limbic and neocortical regions.

Reticular Formation. The reticular formation is the site where information is received from the peripheral nerves. This system is so organized that only certain stimuli trigger it to alert the brain. If it were possible for any response to trigger this system, then the individual's survival would be threatened. The response, however, is selective because throughout our lives we have evolved a set of emotional responses that determine whether we will respond to situations calmly or with rage or fear. What happens is that the reticular system, based on the sensory information with probably some subconscious cortical assistance, focuses the attention by sorting out the relevant information, thus enabling the central nervous system to continue functioning efficiently throughout a crisis.

Hypothalamus. By the time the data reaches the hypothalamus there are already distinct, well-organized emotional responses. The hypothalamus, with some assistance from the thalamus, sets the level of arousal needed for the emotional state and organizes and mobilizes the cortical and subcortical centers (especially the autonomic nervous system).

Pleasure/Punishment Areas. Throughout the limbic brain are found pleasure or punishment centers. These were located by implanting electrodes at various subcortical sites in an animal and training it to press a bar that connects the electrode to an electrical current (Olds, 1958). If the electrode is in certain pleasure centers, the animal will self-stimulate until it is exhausted. In fact, the animal would rather press the lever than eat. The pleasure centers are located throughout the limbic system, but especially in the septum and preoptic

TABLE 22-6:THE NEUROLOGICAL SUBSTRATES OF PSYCHIATRIC DISORDERS

DISORDER	DEFINING FEATURES	NEUROLOGIC CORRELATE
Schizophrenia	Progressive psychotic* disturbance with deterioration -Positive symptoms: thought disorder: delusions and hallucinations -Negative symptoms: poverty of speech, decreased movements poverty of affect, withdrawal from interpersonal relations Rx Respond to neuroleptics**	Based on neuropathology, MRI, PET -Decreased gray matter in temporal areas- left posterior superior temporal and mesial temporal -Prefrontal, left parietal and bilateral temporal
Affective disorders	Majority is not psychotic. Disorder is not progressive and no deterioration occurs. -Bipolar –Unipolar-manic -Unipolar depression ***	In post stroke depression, variable location of infarct: left lateral frontal &basal ganglia, or right frontal or right temporal/parietal - Metabolites norepinephrine (+) in csf - Norepinephrine &serotonin (-), Also Hypothalamic with (+) ACTH
Anxiety/panic	Autonomic activation is similar to pattern with fear responses	Brain stem adrenergic and serotonergic centers are implicated in anxiety. In panic attack patients blood flow to right limbic system increased between attacks
Obsessive/compulsive	Recurring thoughts trigger repetitive motor acts.	Increased metabolic activity in dorsolateral prefrontal, anterior cingulate and caudate nucleus
Personality disorders	Various types: hysterical, passive aggressive, antisocial (overlaps with criminal), passive dependent, schizoid, obsessive/compulsive, paranoid	Pseudopsychopathic syndrome may follow prefrontal damage. Studies of violent antisocial individuals indicate smaller prefrontal areas
Autism	Retarded development of social/emotional interactions with development of stereotyped motor automatisms	Cerebellar hypoplasia plus alterations in many limbic structures including amygdala, hippocampus, entorhinal cortex, septal nuclei, mammillary
Asperger's	Milder form of autism	Neocortical migration disorders

* Psychosis=gross impairment in reality testing affecting perception, thought and insight.

** Neuroleptics=dopamine antagonists

*** Anti depressants such as tricyclic agents and monoamine oxidase inhibitors increase norepinephrine and serotonin at selective receptor sites in hypothalamus and the limbic system by inhibition of reuptake of biogenic amines. Selective serotonin reuptake inhibitors (SSRI's) are effective for less severe cases of depression. For mania and bipolar disorder, lithium carbonate is effective. Neuroleptics may decrease manic behavior. For severe affective disorders electroshock therapy may be utilized.

region of the hypothalamus.

Other brain centers when stimulated produce fear responses: pupil dilation, piloerection, and sweating. In these "punishment regions," located in the amygdala, hypothalamus, thalamus, and midbrain tegmentum, the animal quickly stops pressing the bar. If the situation is non-threatening, the normal operations of the viscera continue. In a mildly stressful situation, such as one involving anger or heavy work, some of the digestive processes slow down, and the heart rate and blood flow increase. If the situation is threatening--triggering the reactions of fear, pain, intense hunger or thirst, or sexual arousal--most of the digestive processes slow down and heart rate, blood flow, and respiration increase. Once the threatening situation passes, conditions quickly return to a normal balance between the sympathetic and parasympathetic nervous systems.

Limbic Cortical Regions. The limbic cortical regions are strongly influenced by the emotional patterns set by the hypothalamus and amygdala which are then transmitted with only a very few synaptic interruptions into the limbic cortex where the emotional pattern is elaborated and efficiently organized. The neocortex (prefrontal cortex and, to a lesser degree, the temporal lobe), based on past experience, examines the situation, sorts out the emotional responses from the intellectual, and inhibits or controls the situation based on what past experience has proven to be expedient for individual survival.

Consider the following examples: a mother responds to her baby's crying, while the father sleeps on; in the middle of the night a jet airplane thundering overhead causes no response, while a whiff of smoke or breaking glass quickly arouses the central nervous system and keeps it focused.

Various types of dysfunction in this system will produce those significant alterations in behavior that represent the spectrum of psychiatric disease, briefly summarized in the next section

The Role Of The Limbic System In Psychiatric Disorders

The involvement of the limbic system either from a structural or functional standpoint is central to the psychiatric disorders which affect large numbers of patients. These disorders may affect perception, cognition and affect.

The neurological substrate is presented in Table 22-6. The epidemiology and genetics of the major disorders are presented in Table 22-7. Additional information will be found on the CD ROM.

TABLE 22-7: EPIDEMIOLOGY AND GENETIC ASPECTS OF THE MAJOR PSYCHIATRIC DISORDERS*

Disorder	Population Frequency %	Concordance in Monozygotic Twins %	Concordance in Dizygotic twins, Siblings, Parents %
Schizophrenia	0.5-1	68**	11
Affective disorders	10-20		14-25**
-Unipolar	18-19	40	11
-Bipolar	1-2	72	14

* Anxiety disorders and personality disorders affect large numbers of the population

** Risk is unchanged when adopted at birth and removed from biologic family