Chapter 9 - Limbic System

The limbic system is a convenient way of describing several functionally and anatomically interconnected nuclei and cortical structures that are located in the telencephalon and diencephalon. These nuclei serve several functions, however most have to do with control of functions necessary for self preservation and species preservation. They regulate autonomic and endocrine function, particularly in response to emotional stimuli. They set the level of arousal and are involved in motivation and reinforcing behaviors. Additionally, many of these areas are critical to particular types of memory. Some of these regions are closely connected to the olfactory system, since this system is critical to survival of many species.

Areas that are typically included in the limbic system fall into two categories. Some of these are subcortical structures, while many are portions of the cerebral cortex. Cortical regions that are involved in the limbic system include the hippocampus as well as areas of neocortex including the insular cortex, orbital frontal cortex, subcallosal gyrus, cingulate gyrus and parahippocampal gyrus. This cortex has been termed the "limbic lobe" because it makes a rim surrounding the corpus callosum, following the lateral ventricle. Subcortical portions of the limbic system include the olfactory bulb, hypothalamus, amygdala, septal nuclei and some thalamic nuclei, including the anterior nucleus and possibly the dorsomedial nucleus.

One way in which the limbic system has been conceptualized is as the "feeling and reacting brain" that is interposed between the "thinking brain" and the output mechanisms of the nervous system. In this construct, the limbic system is usually under control of the "thinking brain" but obviously can react on its own. Additionally, the limbic system has its input and processing side (the limbic cortex, amygdala and hippocampus) and an output side (the
septal nuclei and hypothalamus). Most of these regions are connected by pathways that are shown in figure 31.

**Hypothalamus**

The hypothalamus, the primary output node for the limbic system, has many important connections. It is connected with the frontal lobes, septal nuclei and the brain stem reticular formation via the medial forebrain bundle. It also receives inputs from the hippocampus via the fornix and the amygdala via two pathways (ventral amygdalofugal pathway and stria terminalis). The hypothalamus has centers involved in sexual function, endocrine function, behavioral function and autonomic control.

In order to perform its essential functions, the hypothalamus requires several types of inputs. There are inputs from most of the body as well as from olfaction, the viscera and the retina. It also has internal sensors for temperature, osmolarity, glucose and sodium concentration. In addition, there are receptors for various internal signals, particularly hormones. These include steroid hormones, and other hormones as well as internal signals (such as hormones involved in appetite control such as leptin and orexin).

The hypothalamus strongly influences many functions including autonemics, endocrine functions and behaviors. Autonomic functions are controlled via projections to the brain stem and spinal cord. There are localized areas in the hypothalamus that will activate the sympathetic nervous system and some that will increase parasympathetic activity. Endocrine functions are controlled either by direct axonal connections to the posterior pituitary gland (vasopressin and oxytocin control) or via release of releasing factors into the hypothalamic-hypophyseal portal system (to influence anterior pituitary function). There are also projections to the reticular formation that are involved in certain behaviors, particularly emotional reactions.
Some functions are intrinsic to the hypothalamus. These are functions that require a direct input to the hypothalamus and where the response is generated directly via hypothalamic outputs. Included are such things as temperature and osmolarity regulation. There are many functions where the hypothalamus monitors the internal milieu and produces a regulatory response. These include the regulation of endocrine functions and appetite. For example, the ventromedial nucleus of the hypothalamus is considered a satiety area, while the lateral hypothalamic area is a feeding center.

Additionally, there are many complex behaviors that are patterned by the hypothalamus, including sexual responses. The preoptic area is one of the areas of greatest sexual dimorphism (i.e., difference in structure between the sexes) and, along with the septal nuclei, is an area of gonadotropin releasing hormone projections to the median eminence region of the hypothalamus. These sexual responses involve autonomic, endocrine and behavioral responses.

Finally, the suprachiasmatic nucleus receives direct retinal input. This nucleus is responsible for entraining circadian rhythms to the day-night cycle.

**Amygdala**

The amygdala is an important structure located in the anterior temporal lobe within the uncus. The amygdala makes reciprocal connections with many brain regions (figure 32) including the thalamus, hypothalamus, septal nuclei, orbital frontal cortex, cingulate gyrus, hippocampus, parahippocampal gyrus, and brain stem. The olfactory bulb is the only area that makes input to the amygdala and does not receive reciprocal projections from the amygdala.

The amygdala is a critical center for coordinating behavioral, autonomic and endocrine responses to environmental stimuli, especially those with emotional content. It is important to the coordinated responses to stress and
integrates many behavioral reactions involved in the survival of the individual or of the species, particularly to stress and anxiety. Lesions of the amygdala reduce responses to stress, particularly conditioned emotional responses. Stimulation of the amygdala produces behavioral arousal and can produce directed rage reactions.

Various stimuli produce responses mediated by the amygdala. The convergence of inputs is important since it allows the generation of learned emotional responses to a variety of situations. The amygdala responds to a variety of emotional stimuli, but mostly those related to fear and anxiety.

**Hippocampus**

The hippocampus is an ancient area of cerebral cortex that has three layers. This is located in the medial aspect of the temporal lobe, forming the medial wall of the lateral ventricle in this area. The hippocampus has several parts. The dentate gyrus contains densely packed granule cells. There is a curved area of cortex called the Cornu Ammonis (CA) that is divided into four regions called the CA fields. These are designated as CA1 to CA4. These contain prominent pyramidal cells. The CA fields blend into the adjacent subiculum, which, in turn, is connected to the entorhinal cortex on the parahippocampal gyrus of the temporal lobe.

There are several sources of hippocampal afferents. These are primarily from the septum and hypothalamus via the fornix and from the adjacent entorhinal cortex. This cortical region receives input from diffuse areas of the neocortex, especially the limbic cortex, and from the amygdala. The entorhinal cortex projects to the dentate gyrus of the hippocampus via the perforant pathway, synapsing on granule cells. These granule cells connect to pyramidal neurons in the CA3 region, which, in turn, project by Sheaffer collaterals to CA1 pyramidal cells. It is these latter cells that give rise primarily to the fornix.
The physiology of these pathways has been studied extensively, particularly in terms of long-term physiological changes associated with memory. Hippocampal neurons have been studied extensively in terms of long-term potentiation. This requires activation of glutamate receptors and results in long-term changes in neuronal excitability by way of calcium mediated physiologic effects.

Outputs from the hippocampus pass primarily via two pathways. The first of these outputs is through the fornix. These fibers project to the mamillary bodies via the post-commissural fornix, to the septal nuclei, to the preoptic nucleus of the hypothalamus, to the ventral striatum and to portions of the frontal lobe through the precommissural fornix. There are large numbers of projections from the hippocampus back to the entorhinal cortex.

Figure 31 demonstrates many of the important pathways within the limbic system. Note the hippocampus has reciprocal connections with the cortex as well as outputs along the fornix. Historically, the loop starting with the hippocampus projecting to the mamillary bodies, with relay to the anterior thalamic nucleus, then the cingulate gyrus, entorhinal cortex and back to the hippocampus was thought to be an important circuit. This received the name "Papez circuit". The circular nature of this connection, however, does not appear to be of functional significance.

The hippocampus has several functions. It helps control corticosteroid production. It also has significant contribution to understanding spatial relations within the environment. Additionally the hippocampus is critically involved in many declarative memory functions.

There are several types of memory. Explicit, or declarative memory refers to the memory of facts and events. Any memory that can be completely explained in words is of this type. Implicit or non-declarative memory,
however, is also very important. The learning of skills as well as associative learning, such as conditioned and emotional responses are common examples of non-declarative or implicit memory. Explicit memory depends on the medial temporal lobe and the relationship between the hippocampus and entorhinal region of the parahippocampal gyrus.

There are several areas involved in explicit memory. The hippocampus plays a critical role in short-term memory, which is absolutely necessary if long-term memory patterns are to be established. Lesions of the hippocampus do not affect old, established memories. These lesions affect new declarative learning. Ultimately, memory storage is transferred to other areas of the cerebral cortex, and the location of encoding of these memories may be a function of the type of memory. Established memories involve association areas in the frontal lobe and parieto-temporo-occipital association cortex.

The hippocampus is not only active in encoding memories but also in retrieval of them. Activation of the hippocampus can be seen in this case of learning about new surroundings and of retrieving directions.

**Limbic cortex**

The prefrontal cortex is anterior to the premotor cortex. The orbital frontal cortex is the portion over the orbits. This part of the cortex is extremely well-developed in humans and is critical to judgment, insight, motivation and mood. It is also important for conditioned emotional reactions. The prefrontal cortex receives input from the other areas of limbic cortex, from the amygdala and from septal nuclei and has reciprocal connections with each of these areas and with the dorsomedial nucleus of the thalamus.

Damage to the prefrontal area produces difficulties with abstract reasoning, judgment moods and puzzle solving. The effect of frontal lobe damage on mood depends on the specific part of the prefrontal cortex damaged. The
patient's behavior is often described as tactless. Also, this part of the cortex can also be strongly affected by alcohol.

Prefrontal cortex function is abnormal in mood disorders. Depression is most often associated with increased activity in portions of the frontal lobe, especially the medial regions including the subgenual portion of the anterior cingulate cortex, and decreased activity in the posterior cingulate gyrus.

Olfaction makes strong connections with the anterior portions of the temporal lobe and the amygdala. The olfactory cortex is structurally simpler than other portions of the cerebral cortex and is termed allocortex (see section XI). It includes the prepiriform and periamygdaloid cortex that comprises the anterior part of the parahippocampal gyrus covering the uncus. In some species, of course, olfaction is more important than in others. Olfactory filaments cross the cribiform plate and synapse with mitral cells in the olfactory bulbs. Axons from these cells make up the olfactory tract which extends to anterior temporal structures bilaterally as well as the basal forebrain.

Olfactory signals are relayed to several other brain regions after their initial termination in the olfactory cortex. The olfactory cortex affects the frontal lobe through connections with the dorsomedial nucleus of the thalamus. Olfactory cortex projections to the amygdala can influence emotional and endocrine reactions particularly via connections with the hypothalamus.

There are several interesting syndromes that elucidate aspects of limbic functions. The Kluver-Bucy syndrome occurs with bilateral lesions of the temporal lobes. It blocks emotional responses in animals, which become quite docile. They are unafraid of things that their species should react to, for example, in the case of an ape, a length of rope. Animals become hypersexual and engage in compulsive exploration behavior, especially with the mouth.
As previously described, there are pathways through the forebrain that are involved in reinforcement of behaviors and in "reward". Electrical stimulation of these sites is highly reinforcing for behavior. Many of these pathways involve dopamine and are commonly affected by drugs of addiction. Habituation in these pathways with chronic administration of addicting drugs is one of the most important targets of addiction research. Figure 26 shows the ventral striatal projections to the ventral pallidum which, in turn, projects through the dorsomedial nucleus of the thalamus to limbic areas of cortex. The ventral striatum mostly consists of the nucleus accumbens, which is an important target of dopaminergic projections from the ventral tegmental area.

Various addictive compounds affect activity of the dopamine transmission in the nucleus accumbens (mesolimbic) and frontal cortical (mesocortical) systems. Additionally, these pathways appear to be functionally unbalanced in patients with schizophrenia. It appears that patients with schizophrenia have diminished dopamine effects through mesocortical systems to the prefrontal cortex. This could produce symptoms such as social withdrawal and diminished emotional responsiveness. Concurrently, there is a relative increase in dopamine effects via the mesolimbic system to the ventral striatal system, resulting in positive symptoms of delusions and hallucinations.