The brain is organized into three tiers; a lower tier made up by the brainstem and cerebellum, a middle tier containing the thalamus, basal ganglia and many components of the limbic system and an upper tier comprised by the cortex (Figure 2). The brainstem regulates arousal, autonomic function and internal states. The cell bodies for the key neurotransmitters that regulate behavior are found in the upper brainstem. The central core modulates emotion and memory and helps control speed of movement and rate of thinking. The upper tier carries out higher level sensory processing and motor control, complex thought, and memory storage. This lecture will focus on the middle tier with special emphasis on the limbic system and the prefrontal-subcortical circuits that regulate behavior.

The term limbic, meaning belt or border, was introduced by Paul Broca in 1878 because the cingulate and paraippocampal gyri appeared to form a border or edge around the diencephalon (Figure 3). Papez later proposed that the hypothalamus, anterior nucleus of the thalamus, cingulate gyrus, hippocampus and their connections formed a system that mediated emotional expression. Today the limbic system has expanded to include the amygdala and entorhinal cortex in the medial temporal lobe, the septal nucleus at the base of the frontal lobe, the anterior cingulate gyrus and orbitofrontal cortex. The limbic system plays a key role in memory, cognition, mood and anxiety, social behavior, and regulation of drives and impulses.

Figure 1
Figure 2A: Le grand lobe limbique common to all mammals as identified by Broca in 1878. Figure 2B: The medial circuit of Papez, as depicted by MacLean, was proposed in 1937 to support emotional processing.
The Cognitive Belt

Hippocampus, Fornix, Mammillary Bodies, Anterior Nucleus of the Thalamus, Anterior Cingulate Gyrus, Cingulum Bundle, Hippocampus

The **hippocampus** (hc), meaning seahorse because of its shape, is located underneath the parahippocampal gyrus. The blood supply to the posterior two thirds is provided by the posterior...
cerebral artery and the anterior third by the middle cerebral artery. It is composed of a three layer archicortex. The main gateway to the hippocampus is via the entorhinal cortex and subiculum. The hippocampus is made up of regions called CA1-4 which surround the dentate gyrus (Figure 6). The main outflow is via a thick white matter bundle called the fornix (Figure 7) which connects the hc to the septal nuclei and mammillary bodies. The hippocampus is involved in short-term memory formation, spatial memory and orientation, attention and regulation of mood. The right hippocampus is specialized for spatial memory and the left hippocampus is dominant for verbal memory. Experienced London cabbies were recently found to have a thicker right hippocampus than their more pedestrian peers. The hc is richly innervated by forebrain cholinergic, brainstem dopamine, noradrenaline and serotonin, plus local glutamatergic and gabaergic neurons. Activity in the hippocampus is modulated by adrenal steroids and estrogen. The hc is frequently involved in partial complex seizures and is a focal area of infection in herpes encephalitis and is sensitive to anoxic injury. The entorhinal cortex degenerates early in Alzheimer’s disease (AD) and the hippocampus is a site of heavy plaque and tangle formation in AD. The septal nuclei are rich in cholinergic neurons and degeneration of the hippocampal-septal pathway underlies the memory disturbance seen in AD. Histologic abnormalities have also been reported in the hc and
entorhinal cortex in schizophrenia and autism.

The mammillary bodies are the most posterior nuclei of the hypothalamus. Necrosis of the mammillary bodies may occur due to thiamine deficiency in alcoholics. This is associated with amnesia, confusion and confabulation called the Wernicke-Korsakoff syndrome. The mammillothalamic track connects the mammillary bodies to the anterior nucleus of the thalamus. A lesion in the anterior nucleus of the thalamus caused by infarction in one of the small perforating arteries from the posterior cerebral artery can produce significant amnesia. Thalamocortical projections connect the anterior nucleus of the thalamus with the anterior cingulate gyrus (Figure 8). The anterior cingulate is involved in attention, drive motivation, and initiation of speech. Lesions to the anterior cingulate most commonly cause apathy. Bilateral injury to the anterior cingulate can produce a condition of akinetic mutism in which the person is alert but has tremendous inertia with little spontaneous movement or speech. This profound inertia is called abulia. The anterior cingulate sits at the crossroads between cognitive and emotional components of the limbic system and activity in this area may predict response to antidepressant treatment.

The anterior cingulate gyrus communicates back to the hippocampus via the cingulum bundle (Figure 8). Cingulotomies (small cuts in the cingulum bundle) are still occasionally used for the treatment of refractory depression, pain and obsessive compulsive disorder.

**Processing of Emotional Stimuli**

**Amygdala/Olfactory/Orbitofrontal Division**

The amygdala, or almond, lies anterior and medial to the hippocampus. It is comprised of a cluster of nuclei divided into basolateral and corticomedial divisions. The basolateral region of the amygdala receives major input from the visual system and
other sensory modalities. The amygdala has been referred to as the valence center because it attaches affective color and social meaning to sensory information. The amygdala also receives primary olfactory afferents from the olfactory stria which probably accounts for the major role that olfaction plays in emotion and behavior, especially in lower animals. The amygdala has rich reciprocal connections with the orbitofrontal cortex. The amygdala connects to the basal forebrain cholinergic neurons in the septal nucleus via the stria terminalis and to hypothalamic and brainstem autonomic areas via the ventral amygdalofugal pathway. The amygdala also connects to the nucleus accumbens in the ventral striatum via the extended amygdala.

The amygdala (Figure 9) plays a key role in the startle reflex and can generate flight or fight responses. The amygdala also helps regulate appetite, mood, aggressive and sexual behavior, social behavior, and comprehension of social cues. Auras from partial seizures arising in the amygdala can cause olfactory sensations (funny smells like burning rubber), autonomic sensations (a gnawing in the stomach or heart racing), automatic behaviors such as picking at clothing, or psychic experiences such as déjà vu, dreamy states, depersonalization, hallucinations and a wave of fear. Many of these symptoms may be present during panic attacks. The amygdala and overlying parahippocampal gyrus receive rich noradrenergic innervation from the locus ceruleus in the pons. These structures have been implicated in panic disorder. Rare cases of individuals with degeneration of the bilateral amygdala can not recognize fear in others, though they are capable of feeling fear themselves. Surgical bilateral amygdalecтомies for refractory epilepsy or aggression have produced the Kluver Bucy syndrome. This syndrome causes individuals to be placid. Hyperorality is prominent and they may attempt to eat non-food items and animals with this syndrome may fail to recognize dominant animals and may initiate sex with animals from other species.
The amygdala also plays an important role in forming **emotional memories**. Emotionally arousing experiences tend to be well and long-remembered. Extensive evidence indicates that stress-released adrenal hormones, norepinephrine and cortisol regulate the strength of emotional memory. These hormones act on the amygdala to enhance the storage of recent experiences. Lesions of the amygdala and beta blockers block the memory enhancing effects of emotional arousal and infusion of norepinephrine in the amygdala enhances emotional memory. Post-traumatic stress disorder may represent a hyperactivation of this system.