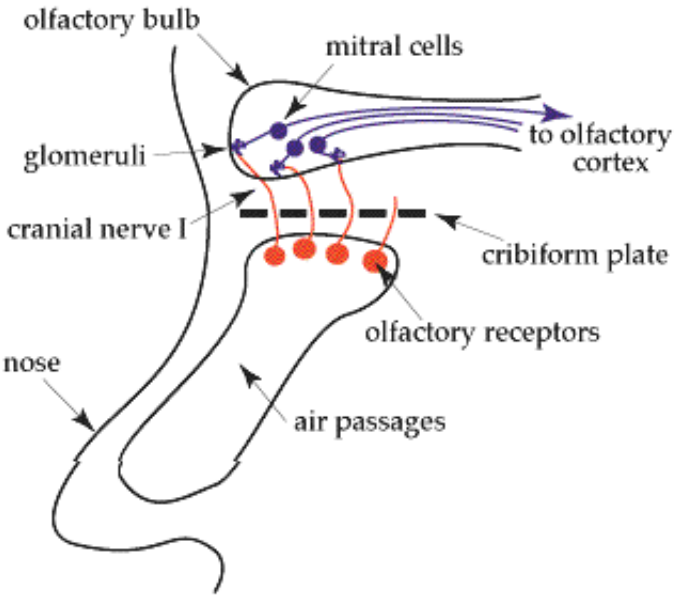
MEDIAL TEMPORAL LOBE (THE LIMBIC SYSTEM)

On the medial surface of the temporal lobe are three structures critical for normal human functioning. From rostral to caudal, they are the **olfactory cortex**, the **amygdala**, and the **hippocampus**. We will look at the anatomy and function of each separately, although they are often grouped together as "the limbic system".

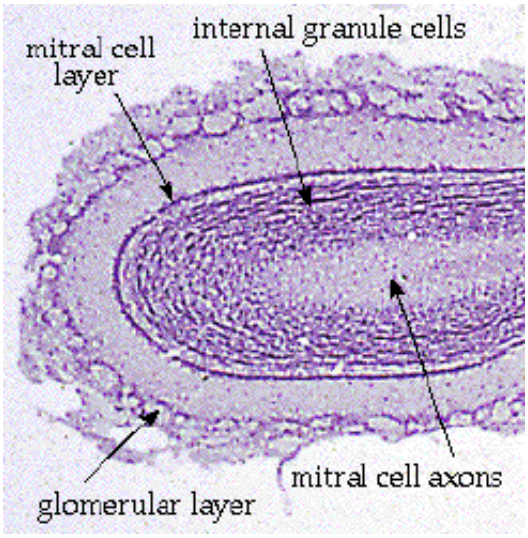
A. The olfactory system:

The olfactory system actually begins in the roof of the nasal cavity. The **olfactory receptors** are ciliated epithelial cells with an array of receptors capable of detecting thousands of different odors.



However, just as with any sensory system, the receptor neurons themselves do not project to the cerebral hemispheres. Their axons project up through the cribiform plate of the skull to synapse on the dendrites of the **mitral cells** of the **olfactory bulb**. The axons of the olfactory receptors make up the elusive cranial nerve I. This fragile tract is susceptible to shearing forces in head trauma, and loss of smell is a surprisingly debilitating injury.

Here is an example of a section through olfactory bulb. The olfactory bulb is not a simple relay (something which passively transmits the signal), but is a sophisticated structure in itself. The mitral cell-olfactory neuron synapse is actually within a tangle of axons and dendrites that is called a **glomerulus**. There is a second cell type tucked around these glomeruli which probably affects how the signal is transmitted. These cells are small and densely packed, which gives them the name "**granule cells**". However, they bear no relation to the granule cells of the cerebellum or cerebral cortex. In fact, they are GABA-ergic, unlike other cells of the same name.



There are two populations of granule cells in the olfactory bulb - the external, or periglomerular cells, and the internal granule cells. The latter lie deep to the mitral cell layer.

The mitral cell axons travel back to the brain via the olfactory tract. The main target of the olfactory tract is the **primary olfactory cortex** in the medial temporal lobe. However, the sense of smell is heavily interconnected with all parts of the limbic system.

Does anything about this system strike you as odd? The olfactory system disobeys a general rule of sensory systems - it does not have to pass through thalamus before reaching cortex. However, there is a very good reason why not; olfactory cortex is an old and primitive structure, and in fact has only four cellular layers, unlike the 6-layered cortex we are accustomed to. The rule that sensory information must pass through thalamus to get to cerebral cortex is still true, but only for 6-layered cortex, or **neocortex**. This description applies to almost every area in the frontal, parietal, occipital, and temporal lobes.

B. The amygdala:

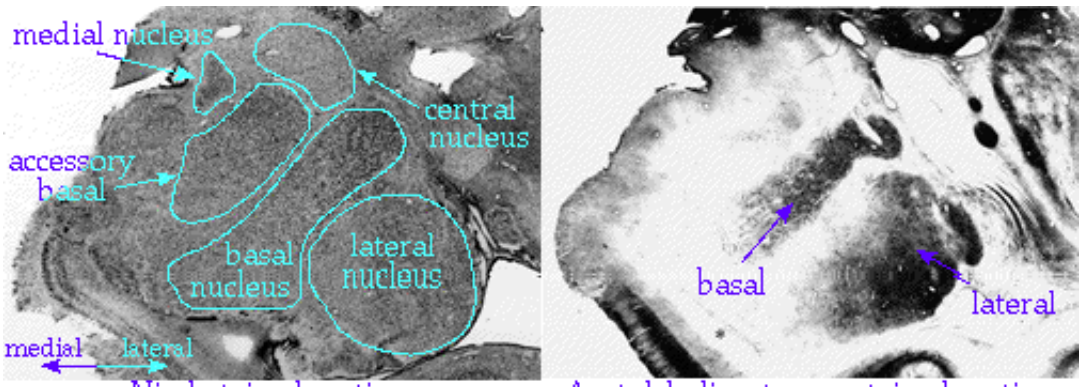
If you remember only one word about the amygdala, the word is FEAR. The

amygdala is the nucleus responsible for the lurch you feel in your stomach when you turn around in a dark alley and notice someone following you. It couples a learned sensory stimulus (man in ski mask in alley = danger) to an adaptive response (fight or flight). On the basis of this information, you should be able to guess the primary inputs to and outputs from the amygdala.

Inputs: the amygdala must get sensory input, and it must be fairly highly processed input to recognize the elements of a scene that signal danger. The association areas of visual, auditory, and somatosensory cortices are the main inputs to the amygdala.

Outputs: the amygdala must be able to control the autonomic system, to provoke such an instant sympathetic response. The main outputs of the amygdala are to the hypothalamus and brainstem autonomic centers, including the vagal nuclei and the sympathetic neurons.

The amygdala is also involved with mood and the conscious emotional response to an event, whether positive or negative. To this end, the amygdala is also extensively interconnected with **frontal cortex**, mediodorsal thalamus, and the medial striatum.



Nissl-stained section Acetylcholinesterase-stained section

These two images of the amygdala demonstrate that there are discrete groups of cells within the large nucleus. The deep group, which includes the **lateral, basal,** and **accessory basal nuclei**, is responsible for collecting the input from sensory cortex. The more dorsal group, which includes the **central** and **medial nuclei**, receives projections from the deep group and sends the signal out to autonomic centers.

It is very difficult to study the amygdala in humans, because selective bilateral damage of the amygdala is so rare. One of the few existing case studies reported a woman with a bilateral degenerative disease who was unable to recognize the expression of fear in human faces. Monkeys with lesioned amygdalas are unable to recognize the emotional significance of objects, and for example, show no fear when presented with a snake or another aggressive monkey. This has disastrous social consequences for the monkey.

Epilepsy surgery provides an opportunity to stimulate areas of the brain to determine the extent of the epileptic focus. In some such patients, the amygdala was electrically

stimulated, which caused intense hallucinations, often accompanied by fear.

C. The hippocampus and memory:

If the amygdala is FEAR, then the hippocampus is MEMORY. To understand exactly how the hippocampus is involved in memory, however, you must first know a little about memory.

There are at least three different types of memory. The most short term is **working memory**. Working memory is like the RAM of a computer. It is the type of memory that enables you to spit back the last sentence of a coversation when someone accuses you of not listening. Like the RAM of a computer, it is crucial for performing some common operations in your head: adding numbers, composing a sentence, following directions, etc. Also like a computer, the space devoted to that operation is recycled as soon as you turn to something else. It does not become a permanent memory. Working memory does not require the hippocampus; it is probably a cortical phenomenon.

The second type is what we most commonly associate with "memory". This is long-term or **declarative memory**, and is composed of all the facts, figures, and names you have ever learned. All of your experiences and conscious memory fall into this category. It is analogous to the hard drive of a computer. Although no one knows exactly where this enormous database is stored, it is clear that the hippocampus is necessary to file away new memories as they occur.

The third type is **procedural memory**, and is probably the most durable form of memory. These are actions, habits, or skills that are learned simply by repetition. Examples include playing tennis, playing an instrument, solving a puzzle, etc. The hippocampus is not involved in procedural memory, but it is likely that the cerebellum plays a role in some instances.

The significance of the hippocampus is driven home by a famous patient named H.M. As part of an epilepsy surgery, doctors removed most of his medial temporal lobes. Since that surgery, in 1953, he has formed no new memories. He can remember his childhood and everything before the surgery, and he still has working memory and the ability to form procedural memories. You can have a normal, lucid conversation with him, but if you leave the room for a moment, when you return he will not remember you or the conversation. He has completely lost the ability to lay down declarative memory.

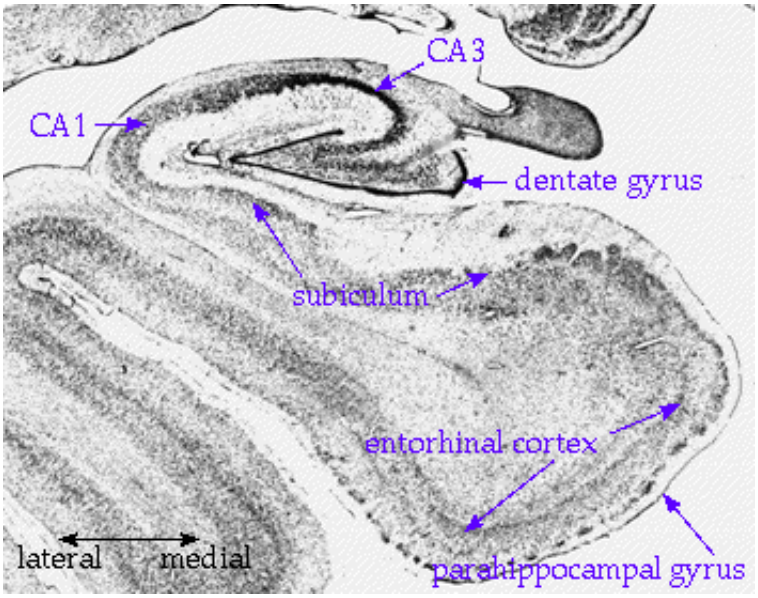
Therefore, the hippocampus is critical in laying down declarative memory, but is not necessary for working memory, procedural memory, or memory storage. Damage to the hippocampus will only affect the formation of new declarative memories.

The mechanisms of the hippocampus are not entirely understood. The formation of memories probably involves **long term potentiation**, or LTP. This is a molecular

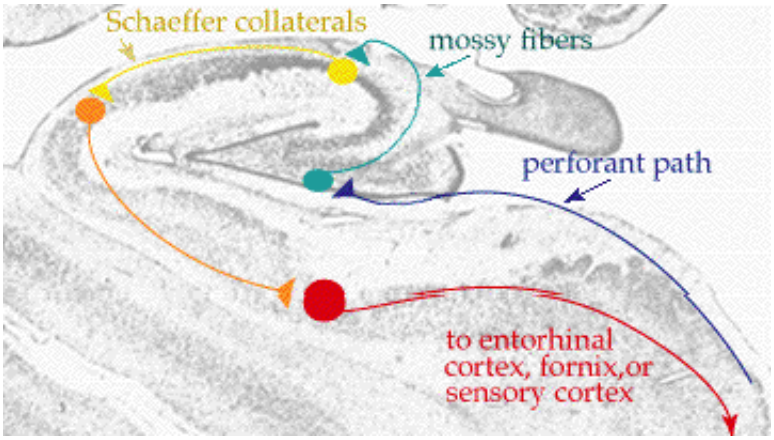
process which strengthens groups of synapses that are repeatedly used. LTP is not sufficient to explain the storage of memory, though.

D. The anatomy of the hippocampus:

The hippocampus is a scrolled structure located in the medial temporal lobe. In a coronal section, it looks like this:



The hippocampus can be divided into at least five different areas, as labeled above. The **dentate gyrus** is the dense dark layer of cells at the "tip" of the hippocampus. Areas **CA3** and **CA1** are more diffuse; the small CA2 is hard to distinguish between them. (CA stands for *cornu ammonis*, from its ram's horn shape.) The **subiculum** sits at the base of the hippocampus, and is continuous with **entorhinal cortex**, which is part of the parahippocampal gyrus. There is essentially a one-way flow of information through the hippocampus, as diagrammed below.

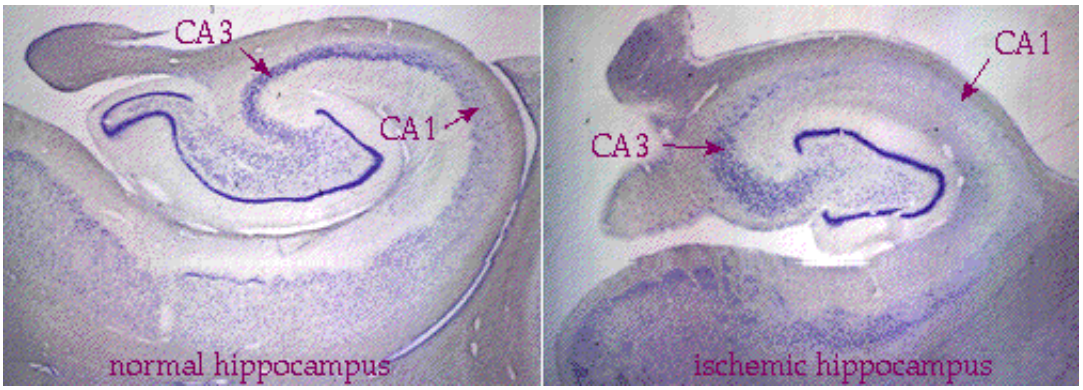


Information enters the hippocampus by jumping across what appears to be a gap between the subiculum and dentate gyrus. This tract is called the **perforant path**, as it perforates the space between the two. The entorhinal axons then synapse on cells in the dentate gyrus. The dentate neurons, in turn, send axons to CA3; these are

called **mossy fibers**. ("Mossy fibers" is a morphological description for axons with large bulbous terminals, and these are unrelated to those in the cerebellum.) CA3 sends axons called **Schaeffer collaterals** to CA1, which sends yet another set of fibers to the subiculum. The subiculum is responsible for the output of the hippocampus: it can either send axons directly to the hypothalamus and mammillary bodies via the **fornix** (remember the fornix?), or it can pass along the information back to entorhinal cortex, which will relay it all back to sensory cortex. It is essentially one continuous pathway that begins in sensory cortex, traverses the hippocampus (loop-the-loop), and returns to sensory cortex. Somewhere in there, memory is born.

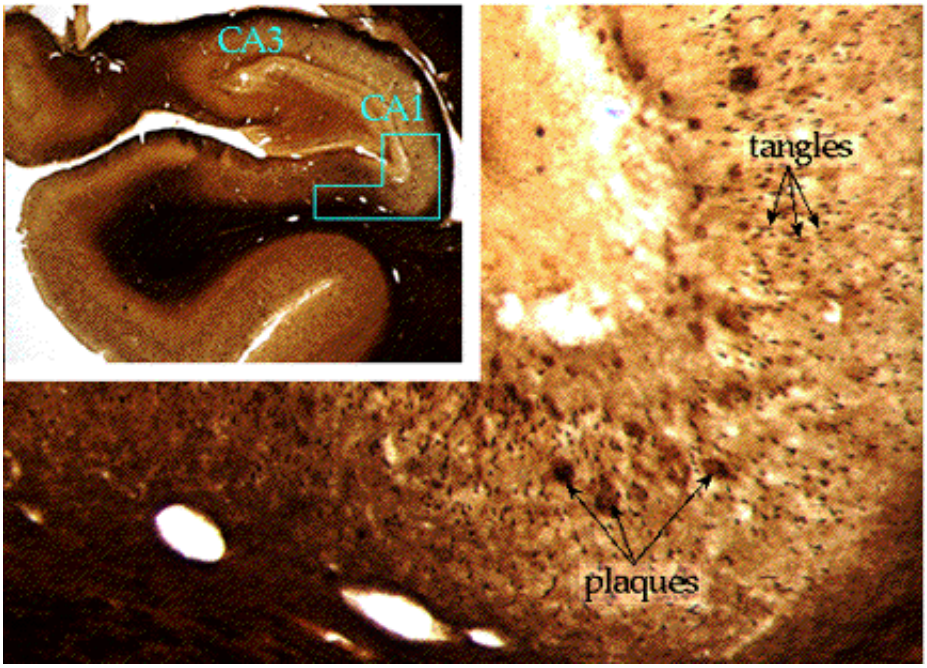
E. Diseases of the hippocampus:

The hippocampus is particularly vulnerable to several disease processes, including **ischemia**, which is any obstruction of blood flow or oxygen deprivation, **Alzheimer's disease**, and **epilepsy**. These diseases selectively attack CA1, which effectively cuts through the hippocampal circuit. Below is a photograph of a normal hippocampus and one which has been deprived of oxygen.



You should be able to see the degeneration of CA1 (labeled) and the absence of cell bodies (stained purple). A stroke can have this effect, but there must be bilateral damage of the hippocampi to affect memory. Therefore only situations that deplete blood or oxygen flow to the entire brain will produce a memory deficit. The pathology of severe temporal lobe epilepsy looks very similar to ischemic damage.

Alzheimer's disease, although it affects the entire brain, is particularly hard on the CA1 region. Below is a photograph of the hippocampus of an Alzheimer's patient, with the CA1 region magnified. Both extracellular plaques and intracellular tangles are visible - these are the pathological hallmarks of the disease.



RETURN TO HOME PAGE