NOTE: This year, for the first time, Dr Binder will give a lecture on the olfactory system in NBIO 401. We do not have the notes for this lecture as this course pack goes to press. We will distribute the images that Dr Binder will use in his lecture before the lecture. The notes below are from the olfactory system lecture in the fall of 2010 and will provide useful background for this year’s lecture.

Objectives
1) Know the location and morphology of olfactory epithelial neurons.
2) Know the signal transduction cascade that starts with odorant binding to an olfactory receptor neuron and ends with depolarization of the cell.
3) Know how an individual odorant is detected, how the olfactory system is capable of discriminating between thousands of odors.
4) Know the phenomenon of olfactory desensitization.
5) Know the basic connections from the olfactory epithelium to the olfactory bulb, and the projections from the olfactory bulb to other regions of the brain.
6) Know that the olfactory system differs from other sensory systems in that its central projections do not necessarily involve the thalamus.
7) Know the main causes of anosmia.

I. Overview
The chemical sense of smell, which detects airborne molecules called odorants, is mediated by one of the oldest neuronal systems in the mammalian nervous system. Smell provides animals with information that is used constantly in daily life – to recognize food, dangerous substances, potential mates. Olfactory information can influence feeding behavior, social interactions, and in many animals, reproduction. Humans, who rely on smell less than many other mammals, can distinguish between 5,000 and 10,000 different odorants.

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**Figure 1**

Olfactory sensory neurons are embedded in a small area of specialized epithelium in the dorsal posterior recess of the nasal cavity. These neurons project axons to the olfactory bulb of the brain, a small ovoid structure that rests on the cribriform plate of the ethmoid bone.

**Figure 2**

The vertebrate olfactory epithelium contains receptor, supporting, and basal cells (adapted from Andres, 1966.)
II. Olfactory Epithelium and Olfactory Receptor Neurons

A. The sense of smell begins with an odorant molecule binding to a receptor on the cilia of olfactory receptor neurons in the olfactory epithelium.
1 - The olfactory epithelium resides in the back of the nasal cavity below the olfactory bulbs (Figure 1).
2 - The olfactory epithelium contains roughly 5-10 million olfactory receptor neurons (ORNs). These receptors are true bipolar neurons, extending a dendrite toward the epithelial surface and an axon that projects into the olfactory bulb. The ends of the ORN dendrites are knobs that contain fine cilia projecting into a layer of mucus (Figure 2). The odorant receptors are located on these cilia. Odorants are dissolved in the mucus layer and bind to the receptors, initiating the transduction process that leads to an action potential in the ORN.
3 - The olfactory epithelium contains two other cell types, in addition to ORNs - supporting cells and basal cells (Figure 2).
4 - The small, unmyelinated axons of olfactory receptor neurons extend through the cribriform plate, a region of porous bone, to synapse with neurons in the olfactory bulb. The paired olfactory bulbs sit underneath the frontal lobes of the cerebral hemispheres. ORN axons make up the olfactory nerve (1st cranial nerve). Sensory endings of the trigeminal nerve (cranial nerve V) also extend into the nasal cavity and respond to noxious chemicals, like ammonia.

B. Olfactory receptor proteins mediate signal transduction in olfactory receptor neurons.
1 - Odorants bind to olfactory receptor proteins (ORPs) on the cilia of ORNs. There are approximately 1000 different ORPs, each of which binds to a unique group of odorants (Figure 3). The 1000 or so genes coding for these ORPs comprise upwards of 1% of our genome (a much smaller percentage of these genes are active in humans compared to rodents). The ORPs are found in lampreys, chickens, mice and humans, suggesting that olfaction is one of our most conserved sensory modalities.
2 - Each ORN probably expresses just one olfactory receptor protein. Evidence comes from studies of mRNA expression in single cells and patch clamp studies in ORNs exposed to odorants.
3 - Each ORP binds chemicals with specific molecular features. Consequently, each ORP binds an array of odorants, an array that overlaps but is different from that bound by other ORPs (Figure 3). Discrimination of different smells is achieved by activation of different ORNs or combinations of ORNs.
4 - ORPs are members of a highly conserved G-protein coupled receptor family and contain seven transmembrane domains. ORPs work via the regulation of associated G proteins that bind tightly to the intracellular region of the ORP when the ligand is not bound (Figure 4). When an odorant binds to the ORP, G protein is released and stimulates adenylyl cyclase to produce cAMP (cyclic adenosine monophosphate). Elevated cAMP opens cyclic-nucleotide gated cation channels in the cilia membrane, causing a depolarization and the generation of an action potential in the ORN.
5. Additional molecular pathways, involving cGMP (cyclic guanosine monophosphate), phosphodiesterases (PDEs), and carbon dioxide, are also activated by odorant binding and regulate the sensitivity and firing of ORNs. For example, PDEs reduce the level of cGMP in receptor neurons.

C. Olfactory receptor neurons desensitize to continuous exposure to odorants.
1 - With continued binding of odorant to an ORP, the current flowing through the cyclic nucleotide gated channels decreases (Figure 5A), and consequently the firing rate of the
ORNs is reduced (Figure 5B). The desensitization time varies, but is usually in the range of 7-10 seconds. The phenomena of desensitization in ORNs is probably due to a combination of factors: the rate of cAMP removal, the rate of Ca\(^2+\) increase and the rate of cGMP formation.

2 - Receptor desensitization underlies the adaptation to odorants that we experience at the perceptual level.

**Figure 3**

![Figure 3](image.png)

*Fig. 3* Individual olfactory sensory neurons respond to different odorants. The records are from patch clamp recordings of the responses of three neurons (A, B, C) to three odorants. Each at a concentration of 5x10\(^{-4}\) M. One cell responded only to one of the odorants while another responded to two odorants; the third cell was stimulated by all three odorants (adapted from Firestein et al. 1993)

**Figure 4**

![Figure 4](image.png)

*Fig. 4* Olfactory signal transduction. In this model binding of an odorant to an odorant receptor causes the receptor to interact with a G protein whose GTP-coupled \(\alpha\)-subunit (\(G_{\alpha_{olf}}\)) then stimulates adenylyl cyclase type III. The resultant increase in cAMP opens cyclic nucleotide-gated cation channels, leading to cation influx and a change in membrane potential in the cilium membrane.
III. Olfactory bulb

A. The axons of the ORNs synapse in the olfactory bulb in anatomically discrete units called glomeruli (Figure 6; another illustration of the structure of the olfactory bulb is shown at the end of the notes).

1 - Each glomerulus consists of the dendritic arborizations of 3 types of olfactory bulb neurons and the axonal branches of many ORNs. The ORNs make synapses with mitral cells, tufted cells, and periglomerular cells. There are about 1000 glomeruli in humans.

2 - The axons of several thousand ORNs converge on between 20-50 olfactory bulb neurons in each glomerulus. Each ORN projects to just one glomerulus, and the primary dendrite of each mitral and tufted cell is restricted to one glomerulus.

3 - The glomeruli serve as functional units. All ORNs that express a given ORP project to just one or two glomeruli. These ORNs are located throughout the olfactory epithelium. Consequently, mitral cells connected to the same glomerulus generally respond to the same sets of odorants. Glomeruli that receive input from a given type of ORP have the same locations in the olfactory bulbs of different animals. Thus, there is a stereotyped spatial map of odorants in the olfactory bulb.

4 - The identity of an odorant is encoded by activation of a combination of ORPs that recognize different molecular features of that odorant. This stimulates a pattern of glomeruli in the olfactory bulb that is different for each odorant, although individual glomeruli may be activated by a variety of odorants.

B. ORNs in the olfactory epithelium live for only ~60 days before dying. They are constantly being replaced by new olfactory neurons that are born in the basal cell layer. Consequently, ORNs are constantly making new connections to the olfactory bulbs. Since an ORN must contact the same glomerulus as all the other ORNs with the same odorant receptor, the olfactory bulb is a place where targeted axonal connections are being made throughout the life of an organism. Olfactory neurons are being studied as a model of how CNS neurons can regenerate, and how neurons make connections after reaching their destination.

C. Mitral cells and tufted cells are projection neurons - their axons leave the olfactory bulb and project to the olfactory cortex. Periglomerular neurons, and granule cells deep in the olfactory bulb, are local inhibitory interneurons. These interneurons mediate extensive information processing within the bulb.
IV. The Olfactory Circuit

A. The axons of mitral and tufted neurons of the olfactory bulb travel centrally through the olfactory tract. They make connections in 5 main regions (Figures 8,9), which collectively are called primary olfactory cortex. Projections of the olfactory bulb are to the ipsilateral hemisphere of the cerebral cortex.

1 - The first connections that mitral and tufted axons make are in the anterior olfactory nucleus (AON). The AON connects the two bulbs to each other, via the anterior commissure (Figure 7). The AON projects to contralateral granule cells, completing an inhibitory circuit between the bulbs. It is thought that this system of inhibitory neurons in the olfactory bulbs allows for spatial resolution of smell, which allows animals to follow a gradient of odor. This nucleus is also thought to mediate habituation to odors.

2 - The next major site is the olfactory tubercule. This is the last projection reached by the tufted cells. Cholinergic neurons from the olfactory tubercule send projections into regions of the thalamus that project to the orbitofrontal cortex. This pathway may regulate cortical excitability and influence processing of odor information. Lesions of the orbitofrontal cortex result in an inability to perceive and discriminate odors.

3 - The piriform cortex is the next region where mitral neurons synapse. The piriform cortex transmits information to the frontal cortex and the thalamus (and in turn to the orbitofrontal cortex). Lesion studies of the piriform cortex demonstrate that it is also important in initial signal processing leading to conscious odor perception.

4 - Mitral cells, and another group of neurons from the accessory olfactory bulb, also synapse in the amygdala. The amygdala projects to the hypothalamus. Accessory olfactory bulb neurons are thought to mediate pheromone signaling for mating behavior, while these mitral neurons convey information for behaviors such as food intake regulation. Neither connection appears to be involved in the conscious perception of
odors, but is likely involved in mediating emotional and motivational aspects of smell.

5. The final connection from mitral cells in the olfactory bulb is to the entorhinal cortex, the gateway to the hippocampus. The hippocampus is associated with memory formation and this pathway evokes memories from odors. This is one of the strongest ways to evoke old (and sometimes, lost) memories in humans.

B. Note that most olfactory bulb projections reach the olfactory cortex without synapsing in the thalamus. This is the one exception to the rule that sensory information reaches the cerebral cortex via the thalamus. However, as described above, the thalamus is involved in the pathway from olfactory bulb to olfactory association cortex in the orbital regions of the frontal lobe.

C. Remember that the piriform and entorhinal cortices, located in the parahippocampal gyrus, are three layered paleocortex.

**Figure 8**

Fig. 8 Olfactory information reaches several central structures: the piriform cortex (3), amygdala (4), and via the amygdala, the hypothalamus, entorhinal cortex (5), and via it the hippocampus and frontal cortex. The thalamus also receives olfactory information from several sources (2,3,4,5) and projects to orbitofrontal cortex.

**Figure 9.**

Fig. 9 An anatomical display of the olfactory circuit. No connections to the cortex are shown. The olfactory nucleus is shown circled.
V. Olfactory Deficits
A. In humans, deprivation of the sense of smell is called anosmia. Anosmia can be caused in two major ways.
1. Conductive olfactory deficits occur when odorants can’t reach the olfactory epithelium. Nasal polyps, septal deviations and inflammation of the nasal passage can cause this type of deficit.
2. Sensorineural olfactory deficits occur when the olfactory epithelium or parts of the olfactory CNS are damaged. Head trauma that damages the nasal epithelium or the cribriform plate can inhibit signaling by damaging the olfactory receptor neurons. Pathological conditions, like Parkinson’s disease or Alzheimer’s disease, can damage cells in the olfactory cortex. In some situations, an excess of smell sensation can be induced by tumors that press against the piriform cortex.

B. Unpleasant odors can be sensed prior to the initiation of some seizures, specifically if seizure activity initiates in the uncus, close to the piriform cortex.

Below Figure 10 shows the locations of the olfactory tracts on the ventromedial surface of the frontal lobes.

**Figure 10.**

*Fig 10* Ventral view of the cerebral hemispheres. Anterior (rostral) is at the top. Frontal and temporal lobes are well-displayed in this view. The floor of the hypothalamus is located between the mamillary bodies and the optic chiasm. The bilateral olfactory tracts lie adjacent to the gyrus rectus on the ventral surface of the frontal lobes.
Figure 11 shows another schematic view of the neurons and connection in the olfactory bulb.

**Figure 11.**

*Fig 11* Schematic drawing of the olfactory bulb, showing the laminar organization, the major cell types, and the basic neuronal circuitry. Receptor neurons are shown in blue, interneurons in red, the efferent neurons of the bulb in green, and centrifugal fibers in black.