Olfaction

Our understanding of the initial stages of smell perception has advanced very rapidly, primarily due to the work of Axel and Buck, who won this year's (2004) Nobel prize for their discoveries (see http://nobelprize.org/medicine/laureates/2004/press.html; http://www.hhmi.org/research/investigators/axel.html;

Smell starts with the olfactory sensory neurons in the nose. These cells have threadlike cilia surrounded by a thin (50 um) layer of mucus which is exposed to the air entering the nose.

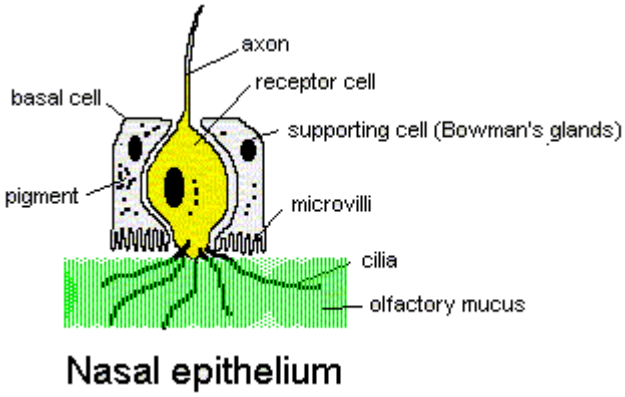
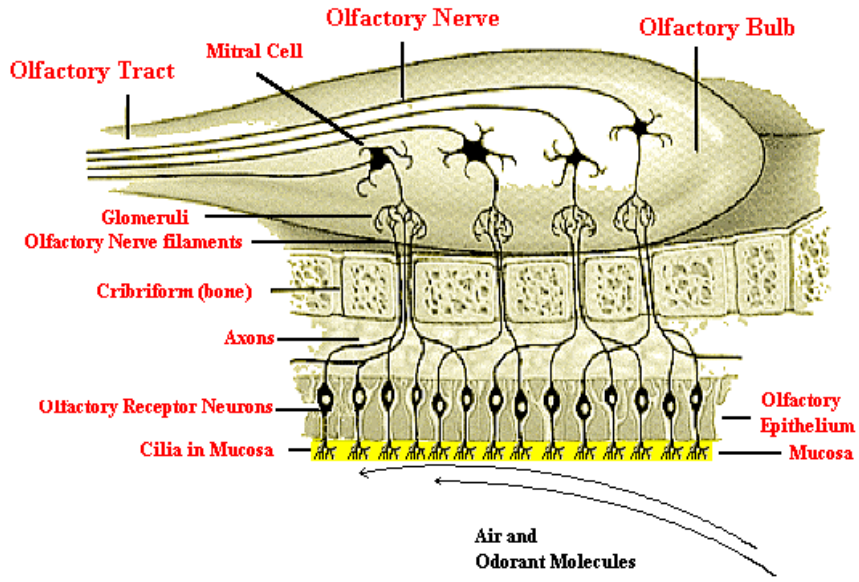


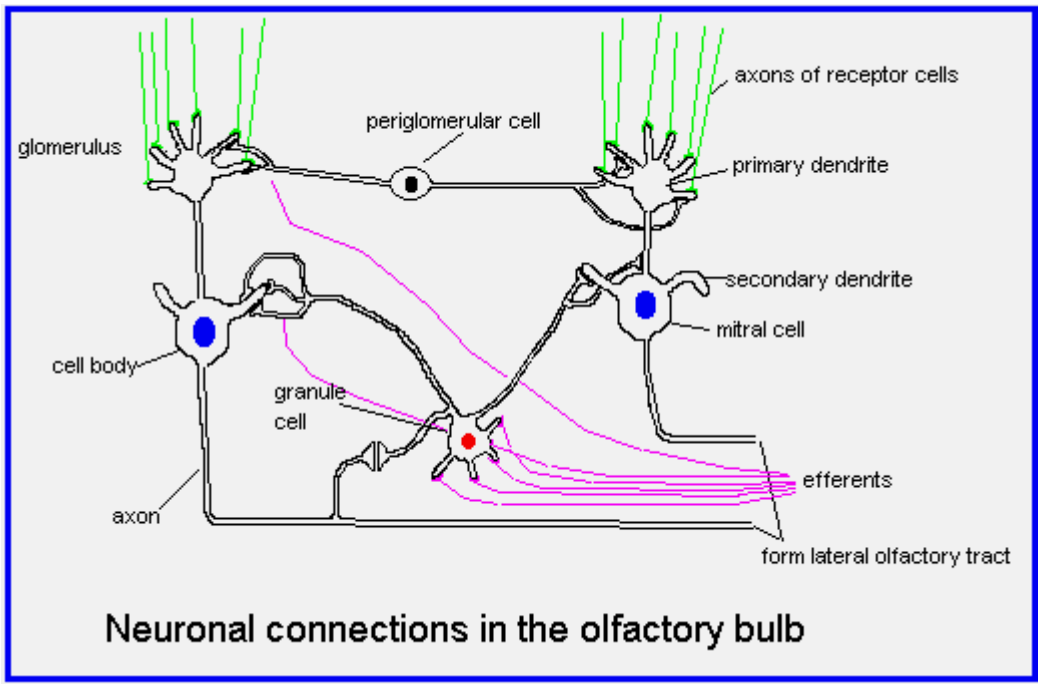
Fig 1. Olfactory sensory neuron.

At their other end they have axons which penetrate through a thin bone into the brain, where they end in paired structures called the olfactory bulbs. These axons make excitatory synapses onto the primary dendrites of excitatory second-order neurons called mitral and tufted cells, which send their axons to the olfactory cortex. The secondary dendrites of these cells form synapses on the dendrites of inhibitory granule cells, which in turn make synapses back onto the secondary dendrites of the mitral and tufted cells (this is an exception to the general rule that synapses are made by axon terminals).

Fig 2 (see below) Axons of olfactory sensory neurons synapse in the glomeruli in the bulb.

Fig 3 (see below). Axons of sensory cells (green) synapse on the primary dendrite of mitral (and tufted) cells in the bulb, in special structures called glomeruli. Glomeruli also get input from periglomerular cells. Inhibitory interneurons (granule cells) make dendrodendritic synapses on the secondary dendrites of mitral cells. Mitral cells send axons to the olfactory cortex, with a collateral branch to granule cells. The bulb also received feedback axons from olfactory cortex, (efferents, in pink).





The numerous synapses between sensory axon terminals and the primary dendrites of mitral (and tufted) cells are all made within ball-shaped structures called glomeruli. Each glomerulus received about 1000 sensory axons and the dendrites from about 40 second order neurons: there is thus enormous convergence, allowing a mitral cell to combine weak signals from many inputs.

Each sensory cell expresses one particular olfactory receptor protein (ORP) from a very large (1000 in rodents) of possible ORPs. Each different ORP is encoded by a different gene, so ORPs alone represent a significant fraction of the entire genome. There are

millions of sensory cells, so several thousand sensory neurons express 1, and only 1, type of ORP.

The ORPs are G-protein coupled 7-membrane spanning receptors located in the cilia. The G protein here is G_{olf}, which when activated by a liganded ORP (the ligand being an odorant) dissociates into alpha and beta-gamma subunits. The alpha subunits undergo GDP-GTP exchange, and the GTP-alpha subunit stimulates adenyl cyclase, which increases the cytoplasmic cAMP level. cAMP then binds to a cyclic-nucleotide gated ion channel (CNGC), causing it to open. Sodium (and calcium) flow into the sensory neuron through the open CNGC, causing depolarization, which triggers spikes in the sensory axons.

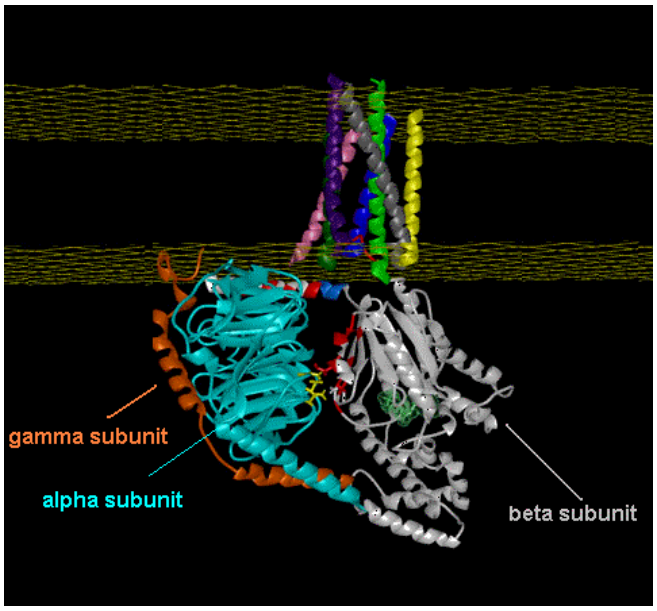


Fig 4. Interaction between a 7-membrane spanning receptor and the G-protein.

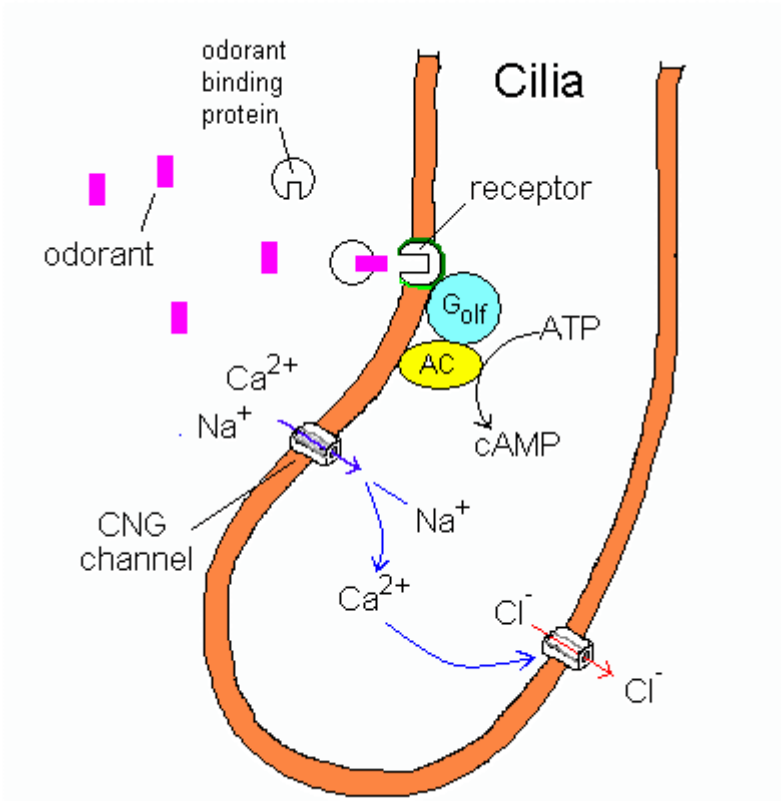


Fig 5. Signal transduction cascade in the cilia. Odorants bind to receptors which activate Golf which in turn activated adenyl cyclase, which increases the cAMP concentration. CAMP then binds to a cyclic nucleotide gated (CNG) channel, which opens, letting in sodium, which depolarizes the cell, triggering spikes which are sent to the bulb.

A typical smell, like a rose, fresh bread or coffee, is composed of a complex set of volatile odorant molecules, each of which has a unique molecular signature – such as a combination of various chemical bonds. The ORPs bind odorant molecules in a highly specific, matching way. Thus a given odorant (especially at low concentrations) will bind only to the thousand sensory cells that express the particular ORP that best matches its unique molecular signature. The signals from all the sensory neurons expressing a particular ORP all converge on the same glomerulus, so that the rather noisy signals from individual sensory neurons can be combined to give a less noisy estimate of the concentration of a given odorant. (Noisiness is at least partly due to the fact that odorants can be detected at extremely low concentrations, so that individual sensory neurons may be responding to individual molecules, whose arrival is necessarily random). These estimates of the overall molecular composition of an odor are then sent to the olfactory cortex for further analysis.

The thousand or so sensory neurons that express a particular ORP are scattered randomly all over a given zone of olfactory epithelium, yet their axons all converge into the same glomerulus. This is a remarkable feat of specific wiring. How is such specific wiring achieved?

There are 2 general mechanisms thought to underlie the formation of specific connections in the brain. (1) Chemoaffinity: there are specific matching molecular tags on particular axons and their targets. (2) Activity-dependent sorting: correct connections are reinforced by the correlated firing of axon and target, incorrect connections are eliminated by uncorrelated firing. Both mechanisms probably contribute to some extent to the establishment of all specific connections, but their relative importance may vary. Also, to some extent the 2 processes can be interdependent: excitatory connections created by chemoaffinity tend to promote correlated firing, and the firing of neurons can influence their expression of surface markers and other tags. Notice that because chemoaffinity ultimately involves the differential expression of specific proteins, it is ultimately under the control of the genome. The effect of the environment on the genome is mediated by the very slow process of Darwinian evolution, and affects all members of a species in a similar way (which is why species exist). Thus wiring via chemoaffinity is not easily tailored to the quirks of individual experience. Activity-dependent wiring can, in principle, benefit from the experiences of the individual; however, to the extent that all members of a species have similar experiences, activity-dependent wiring can have similar results to genetically-controlled chemoaffinity mechanisms. At bottom this all boils down to the eternal debate between “nature” and “nurture”, which has philosophical and religious implications.

In the case of nose-bulb wiring, there is good evidence that chemoaffinity mechanisms play the major role. In particular, the ORPs themselves seem to function as specific tags: all the sensory axons that converge on a particular glomerulus do so because they all express the same ORP, and if sensory neurons are genetically engineered to express the wrong ORP, they end in the wrong glomerulus.

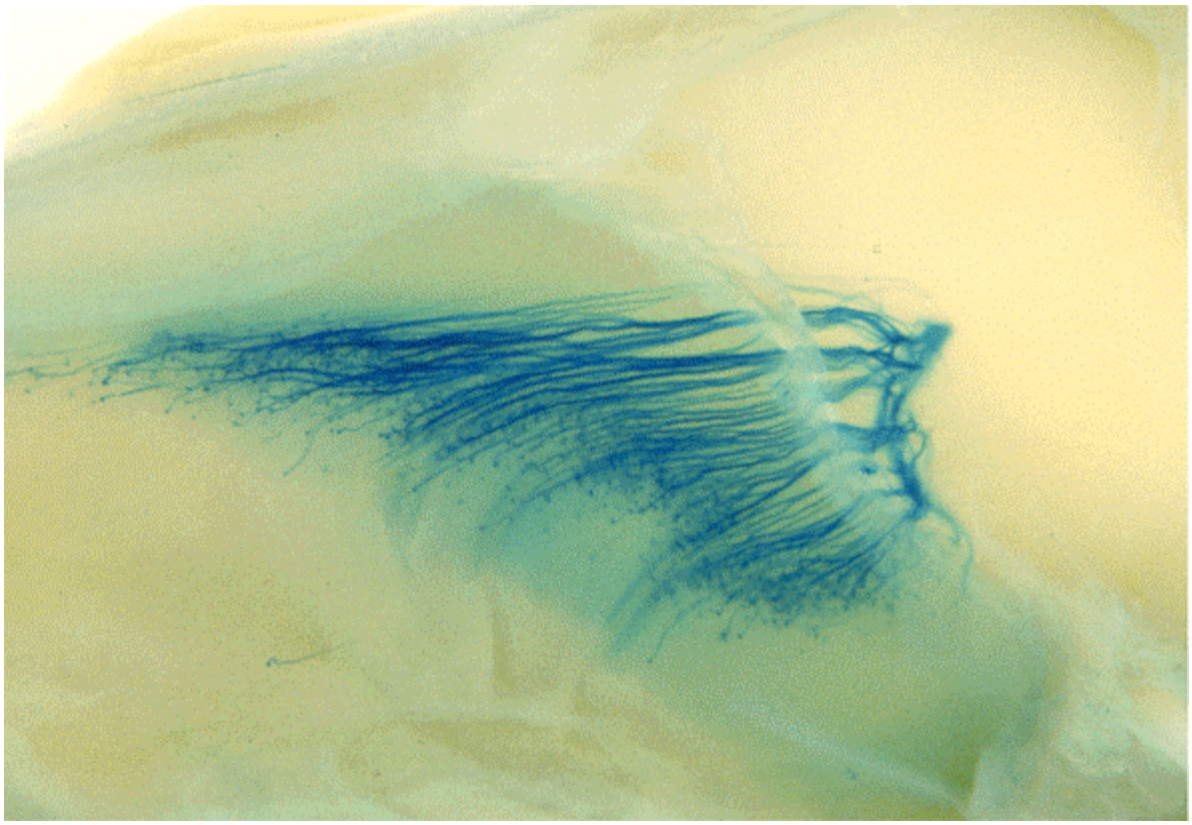
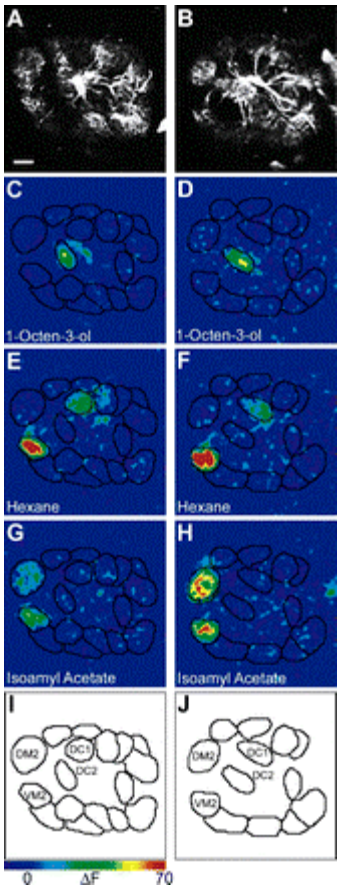


Fig 6. All the sensory cells that express a particular odorant receptor were genetically engineered to express a blue marker. These cells are the small blue dots in the bottom left sector of the image. Their axons then travel to the bulb, where thet converge onto a few glomeruli.

It is not known what the target matching tags are: presumably the resemble the odorant molecules that best bind to a specific ORP. Also, it is not thought likely that the target cells (mitral and tufted cells) each express one of a thousand different target tags matching the thousand different ORPs. Instead it is more likely that there are relatively few target tags, whose concentrations gradually change over the surface of the bulb, forming a guiding chemical gradient. If the specific activity patterns of sensory neurons are disrupted by “knocking-out” the CNG-channels, there is little disruption of nose-bulb wiring. The formation of stereotypical chemically-induced wiring is also supported by the observation that the locations of glomeruli responding to particular odorants are similar in different animals of the same species.

Fig 7. The same glomeruli respond to different odors in different flies. Olfaction in flies and mammals has independently converged, over hundreds of millions of years, to use similar circuits. The 2 columns show results in 2 different animals. The top images show the structure of a group of glomeruli, identified in the bottom images. The other images show glomeruli activity (assayed using 2 photon microscopy) in response to various odorants. Each odorant activates a small subset of glomeruli, which therefore represents a molecular signature of that odorant. From Wang et al, Cell.



However, the fact that chemoaffinity is so important in wiring the nose to the bulb may be a special case, because this system is in its very nature ideally suited to chemoaffinity wiring: the tags, which are the ORPs themselves, are available "gratis" because they are in any case necessary for olfactory functioning, and so it is not necessary to use up additional genomic resources. However, clearly if 1000 genes are already required to specifically wire up only a few thousand glomeruli, the remaining 22,000 genes would not be enough to specifically wire the remaining 100 billion neurons of the brain. It is inevitable that most of the detailed wiring of the brain is done by activity-dependent mechanisms.

Does Electrical Matching Work?

The alternative to specifying connections by molecular matching of chemical labels is electrical matching – formation of synapses as a result of a match between pre- and postsynaptic activity. Let us briefly consider a simple example of how this could work in wiring up the nose-bulb pathways. Consider a bulb neuron that gets input from just 2 nose cells, an orange-detecting cell and a coffee-detecting cell. The o-cell provides 60 synapses and the c-cell provided 40 synapses. We want to know how an "electrical matching rule" could lead to complete segregation, so that we end up with a bulb neuron that has 100 synapses from the o-cell and none from the c-cell. We will assume that the

number of functional (and ultimately anatomical) synapse is set by a “Hebb rule” : neurons that fire together, wire together. Specifically we will assume that the change in the number of synapses comprising a connection is 10% of the product of the pre- and post-synaptic firing rates. We will further assume that the postsynaptic firing rate is set by the product of the presynaptic firing rate and the number of synapses. If the animal is equally likely to smell oranges as coffee, and the presynaptic firing rate in both situations is 1/sec, then while smelling oranges the postsynaptic firing rate will be 60/sec, and when smelling oranges it will be 40/sec. Therefore after smelling oranges and coffee the number of o-synapses added will be 6, and the number of c-synapses will be 4, resulting in 110 synapses altogether. We will now assume that some mechanism (which we will call “normalization”) brings the total number of synapses back down to 100, and this mechanism cannot discriminate between o-synapses and c-synapses, subtracting 5 from each. So we end up with 61 o-synapses and 39 c-synapses. So next time the animal smell oranges and coffee, the postsynaptic firing rate produced by smelling oranges will be greater than before, and the postsynaptic firing rate produced by smelling coffee will be less than before, so that the number of synapses added to the o-connection will be even greater than the number added to the c-connection, and the connection asymmetry will increase. We can see that repeated rounds of this asymmetric pattern will eventually lead to 100 o-synapses and 0 c-synapses. In fact, even if the initial asymmetry was very small (say, 51 synapses versus 49), we will end up with complete asymmetry as a result of our Hebbian learning rule. If the initial asymmetry had been the other way, we would have ended up with a 100% c-connection. So the Hebb rule converts the sort of tiny initial asymmetries that could arise from a purely random initial growth process, to an exclusively 1-to one connection. (You will notice that the argument is rather similar to the reason why all the spins in a ferromagnet end up pointing the same way).
Furthermore, even if the 60 o-synapses are all contributed by *different* nose o-cells, the mechanism still works (because all those o-cells will be firing together when the animal smells oranges). It even works if we have 1000 different types of nose cells, each of which innervates the bulb randomly, provided that the animal gets to smell sufficient different odors.
But although this mechanism works in principle, it is clearly wrong in the case of the nose-bulb pathway, because completely specific wiring develops in mice genetically engineered to lack CNG-channels, and therefore lacking in odor-evoked electrical activity.

It is useful to compare olfaction to color vision. The cones photoreceptors also express unique sensory proteins, the red, green and blue photopigments. Just as different odors stimulate different combinations of 1000 basic ORPs, different colored lights stimulate different combinations of 3 basic visual RPs. We can consider a color as a point in a 3D wavelength space, and an odor as a point in a 1000 D molecular-feature space. In both cases, the degree of stimulation of a particular RP will depend on 2 factors: the quality (wavelength or molecular configuration) and the quantity (light intensity or odor concentration). However the ultimate goal of both vision and olfaction is to identify objects and events in the world, and the apparent smell and color of objects may be influenced by irrelevent accidents (green light from nearby bushes reflected of a red fruit; high background concentrations of distracting odors). The color identification task may

be much easier than the smell identification task, since wavelength is a single variable, while molecular features can be very complex; however, the visual system must also contend with additional complexities introduced by the varying directions of different lights; the nose cannot resolve direction.

There is a good account of smell in the textbook Squire, Bloom etc (see Syllabus).

Further reference:
http://www.sciencedirect.com.proxy.hsclib.sunysb.edu/science?_ob=ArticleURL&_udi=B6WSS-4HG6BDW-4&_user=334567&_handle=V-WA-A-W-AA-MsSAYZW-UUA-U-AABVCBZEBU-AABWAADDBU-VDBWZUCYZ-AA-U&_fmt=full&_coverDate=11%2F03%2F2005&_rdoc=4&_orig=browse&_srch=%23toc%237054%232005%23999519996%23609637!&_cdi=7054&view=c&_acct=C000017318&_version=1&_urlVersion=0&_userid=334567&md5=eaed04556fd8818b9a9b0e9c174ac785