To appear in the SAGE Encyclopedia of Perception (2009)
Thomas A. Cleland

Olfactory bulb: functional architecture

The neural architecture of a sensory system reflects two general principles: the physics of stimuli in the relevant sensory modality and the mechanisms and compromises implemented by the system to extract useful information for the organism at minimal metabolic cost. At a high level of abstraction, many of these problems are common to all sensory systems. For example, all sensory systems must be able to respond to wide ranges of stimulus qualities and intensities, separate out meaningful stimuli from a background of relatively unimportant stimuli, identify similarities among stimuli so as to be able to classify them accordingly, and learn from experience. The structure of the olfactory system reflects unique functional solutions to each of these common problems.

Organizational principles of odor representation

Odor representation by distributed coding

Primary olfactory sensory neurons (OSNs) are ciliated cells located in an epithelial cell layer lining the nasal cavity (see *Olfaction*, figure 2). Inhaled odorant molecules diffuse through a mucus layer and associate with olfactory receptor proteins (ORs) expressed on these OSN cilia. The OR type that an OSN expresses largely determines its olfactory *receptive field* (also known as its molecular receptive range) – i.e., the range of different odorant molecules that will bind to that OR and activate the OSN. While the OR gene family is extensive – approximately 350 functional genes in humans, over 1000 in mice and rats – each OSN expresses a very restricted subset of these OR genes; indeed, it is believed that each OSN usually expresses only one of these OR genes. Hence, each OSN is activated by only a subset of all possible inhaled odorants, although any single odorant will generally activate multiple different OSN types to different degrees. This is the fundamental mechanism for *odor representation* in the olfactory system: any odorant molecule, or combination of molecules, will evoke a unique and characteristic pattern of neuronal activation – a *distributed code* – across the population of OSNs (Figure 1A,B).

This coding scheme has several advantages over a hypothetical alternative in which one OR is specific for each odorant. Whereas the latter scheme could represent 1000 different odorants in a species expressing 1000 different OR types, the distributed coding exhibited by the olfactory system can represent far greater numbers of possible odors. Even if OSNs were only counted as "on" or "off", ignoring their capacity to represent intermediate levels of activation, a field of 1000 ORs could uniquely represent about 10^{300} different odors (compared to an estimated 10^{22} stars in the known universe). Perhaps more importantly, however, distributed coding enables the representation of *similarities* among odors: the more similar two odors are, the more highly overlapping are their neural representations in the nose, as they activate a greater number of ORs in common. This feature enables an animal to either categorize similar odors together – e.g., to identify the smell of "apples" by ignoring the differences in the odors of different apple cultivars or degrees of ripeness – or to discriminate among them depending on motivation and context.

OSN convergence

Perhaps the single most spectacular architectural feature of the olfactory system is the OR-selective convergence of OSN axons. The thousands of OSNs that express any one particular OR type are scattered across an animal's nasal epithelium, yet their axons converge together as they project from the nose into the brain – specifically, to the surface layer of the olfactory bulb (OB; Figure 1C; see also *Olfaction*, figure 2). In the OB, these converging OSN axons intertwine to form *glomeruli* – clusters of tangled neurites segregated from other glomeruli by a sheath of glial cells. Because of this strict segregation, each glomerulus is generally associated with exactly one OR. This enables odor-specific OR activation patterns to be directly measured via the optical imaging of glomeruli – that is, the activation of a given glomerulus means that the corresponding population of OSNs, expressing a single type of OR, has been stimulated by an odor.

The number of OSNs converging upon a single glomerulus is known as the *convergence ratio*, and it is not uniform among glomeruli. Rather, the ratios reflect functional trade-offs: higher convergence ratios improve the signal-to-noise ratio in OSN populations, increasing sensitivity to low-intensity odors; however, the additional OSNs required for higher convergence ratios consume metabolic energy and space within the

olfactory epithelium that otherwise could be utilized by an additional OR type, which would extend the range of detectable odors and/or improve the system's capacity to discriminate among odorants. Indeed, the OSN types that are expressed in a part of the rodent nose that tends to adsorb the most efficiently detectable classes of odor molecules exhibit lower convergence ratios than do OSN types expressed in other parts of the nose, suggesting that the olfactory system is tuned to compensate for the limitations imposed on it by the physics of odor adsorption and the anatomy of the nasal pathways. This also means that behavioral control over sniffing can alter odor representations to a limited extent.

Glomeruli: a consequence of OR diversity

Retinotopic mapping is common in several visual areas of the brain, in which adjacent points in space are represented by adjacent visual neurons; similarly, many auditory brain regions exhibit tonotopic mapping in which neighboring neurons in the brain are responsive to correspondingly similar sound frequencies. Chemotopic mapping within the OB is somewhat more complex. Because of distributed coding, uniquely identifying an odor requires information about its relative activation of hundreds of different ORs/OSN types. That is, instead of identifying a pure tone with a single frequency value or a point of light with its two-dimensional X-Y coordinates in space, quantifying a simple odorant stimulus requires a vector with as many dimensions as there are different ORs (Figure 1A-B). Humans express about 350 different ORs, whereas mice and rats express over 1000; therefore, quantifying odor quality in these coordinate systems requires a high-dimensional map. Interestingly, it has been shown mathematically that when high-dimensional maps (such as these chemotopic maps of olfactory receptive fields) are projected onto a two-dimensional surface (such as the glomerular layer of the OB), the maps must become fragmented into a clustered, non-topographical organization in which identically-tuned neurons can segregate together, but the physical proximity of differently-tuned neurons cannot systematically reflect the similarity or overlap of their receptive fields. This precisely describes the organization of the OB glomerular layer. The sheer diversity of ORs thereby can explain both the existence of discrete glomeruli and why the location of glomeruli within the olfactory bulb does not predict their receptive fields. Furthermore, this non-topographical

chemotopic organization fundamentally changes the underlying mechanisms needed to perform certain neural computations in the OB when compared with other sensory systems. Specifically, decorrelation and other computations that rely on neural representations of stimulus similarity cannot utilize spatially localized or center-surround neural mechanisms such as nearest-neighbor lateral inhibition, instead requiring non-topographical and learning-dependent mechanisms.

Neural circuits of the olfactory bulb

Within OB glomeruli, OSN axons contact the dendrites of two classes of OB principal neurons, mitral and tufted cells. These principal neurons in turn project axons out of the OB to multiple targets in the brain (Figure 1C). Despite this straightforward synaptic connection, the sensory information carried by OSNs is substantially modified within the OB by descending cortical and neuromodulatory inputs and several classes of intrinsic interneurons that shape the activation of mitral and tufted cells. The resulting transformations of odor representations can be grouped into two stages: (1) glomerular-layer processing that regulates the synaptic transfer of information from OSNs to mitral and tufted cells, and (2) subsequent computations in the external plexiform layer (EPL) that further modify the firing patterns of these cells.

Glomerular layer circuitry

Besides the axonal arbors of OSNs and the dendritic arbors of mitral (Mi) cells, glomeruli contain dendrites from inhibitory periglomerular (PG) cells and excitatory external tufted cells (ET cells, not to be confused with the projecting type of tufted cell discussed above). PG neurons inhibit mitral cells; in particular, a subclass of PG cells receives monosynaptic input from OSNs and directly inhibits mitral cell dendrites and OSN presynaptic terminals in a mixed feedforward/feedback loop. ET cells are interconnected by a network of superficial short axon (sSA) cells in a lateral excitatory network that also activates PG cells, thereby inhibiting mitral cells (Figure 1C). Interestingly, aside from this broad sSA cell network, and a relatively small number of PG cell axons that project to other glomeruli, the different glomeruli within the same OB are not substantially interconnected.

This glomerular circuitry contributes to *normalization* of the intensity of sensory input (Figure 2A). Whereas collective OSN activity levels can vary over orders of magnitude, average spike frequencies in mitral cells are considerably more constrained, generally being only modestly inhibited or excited by increasing odor concentrations. This probably improves the olfactory system's capacity to recognize the same odor at different intensities, and avoiding high rates of spiking also conserves metabolic energy. Normalization is sometimes confused with *adaptation*; the two processes do interact but are essentially distinct. Glomerular and EPL circuitry are both also credited with mediating *decorrelation* (contrast enhancement) among odors, which regulates the degree to which odors are represented as similar or dissimilar (Figure 2B).

External plexiform layer circuitry

In contrast to the glomerular layer, there is massive interconnection across the OB within the external plexiform layer (EPL). In addition to their dendrites that innervate glomeruli, mitral cells have a second type of dendrite that projects laterally within the EPL and excites the dendrites of granule cell interneurons (Gr; Figure 1C). The granule cell dendrites in turn reciprocally inhibit the lateral dendrites of the same mitral cell (*recurrent inhibition*) as well as those of other mitral cells (*lateral inhibition*). Lateral inhibitory interactions among mitral cells via intermediating granule cells are thought to mediate the EPL contribution to olfactory decorrelation (Figure 2B). Unlike the retina, however, the strength of this lateral inhibition between two mitral cells is probably unrelated to their proximity. The underlying synapses are plastic, being regulated by inputs received from other regions of the brain and probably by olfactory perceptual learning as well, suggesting that this OB layer contributes heavily to the learning of meaningful odors and mediates some of the effects that such odor memories may have on olfactory processing.

Descending regulation and neuromodulation of olfactory bulb circuitry

In addition to afferent olfactory input from OSNs, the OB receives incoming projections from higher olfactory brain areas as well as neuromodulatory projections from the locus coeruleus (norepinephrine), the horizontal limb of the diagonal band of Broca (acetylcholine), and the raphe nucleus (serotonin). Peptide neuromodulators also

are released into the OB both via similar projections and the general circulation. These extrinsic inputs regulate OB physiology and stimulus processing via multiple mechanisms, often with functionally related receptors expressed in different locations within the OB. For example, nicotinic acetylcholine receptors in the glomerular layer and muscarinic acetylcholine receptors in the EPL both respond to cholinergic inputs and together affect OB odor processing, in part by regulating the decorrelation of similar odorant representations (Figure 2B). Indeed, there are more descending projections into the OB than there are afferent projections out of the OB, indicating that the OB is considerably more integrated with higher centers than has often been appreciated.

Thomas A. Cleland

Cross-references

Context effects in perception, Experience-dependent plasticity, Neural representation/coding, Olfaction, Olfaction: Physiology, Olfactory adaptation, Olfactory quality, Sniffing.

Further readings

Cleland, T. A. & Linster, C. (2005). Computation in the olfactory system. *Chemical Senses, 30(9),* 801-813.

Cleland, T. A. & Sethupathy, P. (2006). Non-topographical contrast enhancement in the olfactory bulb. *BMC Neuroscience*, *7*, 7.

Farbman, A. I. (1992). *Cell biology of olfaction*. Cambridge (UK): Cambridge University Press.

Doty, R. L. (Ed.). (2003). *Handbook of olfaction and gustation*, 2nd ed. New York: Marcel Dekker.

Holscher, C. & Munk, M. (Ed.). (2008). *Mechanisms of information processing in the brain: encoding of information in neural populations*. Cambridge (UK): Cambridge University Press.

Kohonen, T. (1982). Self-organized formation of topology correct feature maps. *Biological Cybernetics, 43,* 59-69.

Schoenfeld, T. A. & Cleland, T. A. (2005). The anatomical logic of smell. *Trends in Neurosciences 28(11),* 620-627

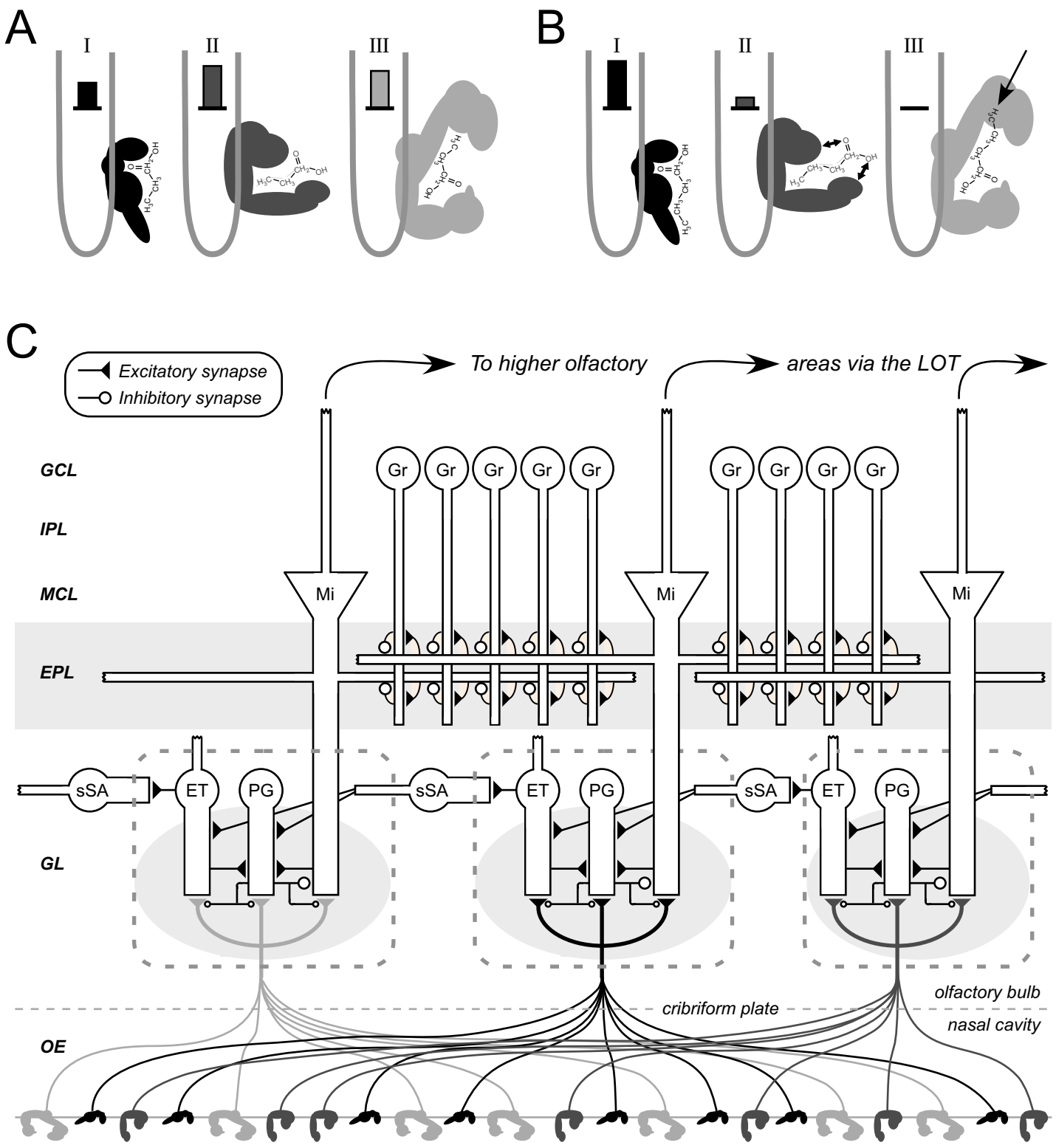
Wilson, D.A. & Stevenson, R. J. (2006). *Learning to Smell: olfactory perception from neurobiology to behavior*. Baltimore: Johns Hopkins University Press.

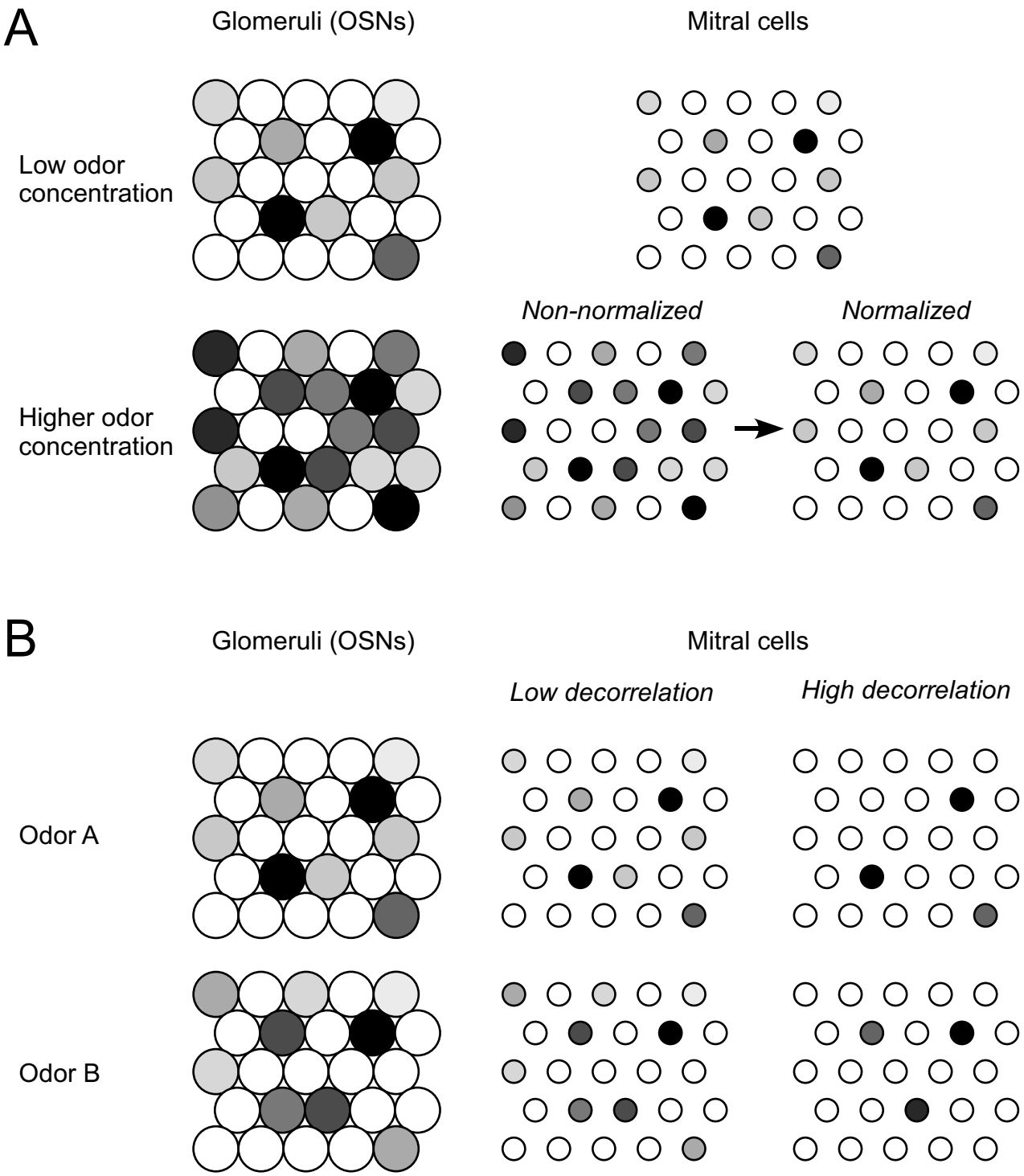
Figure Legends

***Figure 1*. A.** Illustration of distributed coding in olfactory sensory neurons. Three cilia arising from different OSNs each express a different odorant receptor protein. The three different receptors depicted are each activated to different degrees (vertical bars) by the three-carbon aliphatic odorant propanoic acid. **B.** Responses of the same three ORs to the structurally similar four-carbon aliphatic odorant butanoic acid. Receptor I interacts more favorably with this ligand than with propanoic acid, so that the corresponding OSN responds more strongly to butanoic acid at the same concentration. Receptor II, in contrast, does not bind butanoic acid as well as it did propanoic acid, as the polar end of the larger molecule is too far away from its cognate receptor moieties to interact optimally (*arrows*). Nevertheless, butanoic acid weakly activates the receptor. Finally, butanoic acid cannot fit in the binding pocket of Receptor III (*arrow* illustrates impossible fit), and hence does not activate it at all. Reading the relational pattern of activation levels across all three receptors (a three-dimensional vector) enables identification of the odor ligand. **C.** Illustration of major olfactory bulb circuit elements. OSNs (represented by their respective OR shapes) are distributed across the nasal olfactory epithelium (OE). The axons of OSNs that express the same OR cross the cribriform plate into the cranial cavity and converge together to form glomeruli (*shaded ovals*) on the surface of the OB. The OSN axon terminals form excitatory synapses (*filled triangles*) onto mitral (Mi), periglomerular (PG), and external tufted (ET) cells. External tufted cells in turn excite PG cells, superficial short axon (sSA) cells, and each other. Periglomerular cells inhibit mitral cell apical dendrites and OSN axon terminals (*open circles*). Mitral cell secondary dendrites extend laterally within the external

plexiform layer (EPL; *shaded box*) and form reciprocal synapses with the dendritic spines of inhibitory granule cells (Gr), hence delivering recurrent inhibition onto themselves and lateral inhibition onto other mitral cells. sSA cells are not affiliated with any given glomerulus, but extend between them, forming a lateral excitatory network consisting of themselves and the ET cells that proliferates in the deep glomerular layer. Shaded ovals connote the approximate physical boundaries of the glomerulus proper, whereas dotted boxes illustrate the group of neurons associated with a particular glomerulus. For visual clarity, only one cell of each type per glomerulus is depicted, and middle/deep (projecting) tufted cells, deep short axon (dSA) cells, and axons arriving from the rest of the brain have been omitted. LOT, lateral olfactory tract. Olfactory bulb layers, surface to deep: GL, glomerular layer; EPL, external plexiform layer; MCL, mitral cell layer; IPL, internal plexiform layer; GCL, granule cell layer.

***Figure 2*.** Illustrations of normalization and decorrelation in the olfactory bulb. Large circles depict glomerular activation levels that reflect OSN activity patterns; small circles depict the activation levels of the corresponding mitral cells, after the effects of OB neural computations have been applied. Darker shades indicate greater activation. **A.** Normalization. Higher odor concentrations increase the activity levels of sensitive OSNs and also recruit new, lower-affinity OSNs into the active ensemble. Normalization globally inhibits mitral cells so as to preserve a relational pattern of activation that is less strongly influenced by absolute odor concentration, which may help one recognize the same odor at different intensities. **B.** Decorrelation. Odor A and Odor B are relatively similar odors, as evidenced by the substantial overlap in the patterns of glomeruli that they activate. With decorrelation at a minimum, the mitral cell patterns of activation directly reflect these glomerular patterns. At higher decorrelation levels, however, the more weakly activated glomeruli are prevented from activating their corresponding mitral cells, such that the two odor representations become more dissimilar (activating only one mitral cell unit in common).


A
I
II
III
B
I
II
III
C
Excitatory synapse
Inhibitory synapse
To higher olfactory
areas via the LOT
GCL
IPL
MCL
EPL
GL
OE
Gr
Mi
sSA
ET
PG
cribriform plate
olfactory bulb
nasal cavity


A
Glomeruli (OSNs)
Mitral cells
Low odor concentration
Higher odor concentration
Non-normalized
Normalized
B
Glomeruli (OSNs)
Mitral cells
Low decorrelation
High decorrelation
Odor A
Odor B