Keywords

odor map, chemotopy, neural computation

Abstract

The responses of neural elements in many sensory areas of the brain vary systematically with their physical position, leading to a topographic representation of the outside world. Sensory representation in the olfactory system has been harder to decipher, in part because it is difficult to find appropriate metrics to characterize odor space and to sample this space densely. Recent experiments have shown that the arrangement of glomeruli, the elementary units of processing, is relatively invariant across individuals in a species, yet it is flexible enough to accommodate new sensors that might be added. Evidence supports the existence of coarse spatial domains carved out on a genetic or functional basis, but a systematic organization of odor responses or neural circuits on a local scale is not evident. Experiments and theory that relate the properties of odorant receptors to the detailed wiring diagram of the downstream olfactory circuits and to behaviors they trigger may reveal the design principles that have emerged during evolution.
INTRODUCTION: NEURAL MAPS
A topographic map (neuroanatomy) is the ordered projection of a sensory surface, like the retina or the skin, or an effector system, like the musculature, to one or more structures of the central nervous system.

-Wikipedia

A map in the brain refers to an orderly representation of some physical feature of the outside world or a computed value derived from these features (Chklovskii & Koulakov 2004, Kaas 1997, Knudsen et al. 1987, Kohonen & Hari 1999). Such maps are typically found in sensory or motor systems. A common type of sensory map is a topographic map, which is an ordered projection of the sensory surface to higher brain regions; for example, neighboring points in visual space activate neighboring points on the retina, and this relation is preserved through several subsequent stages of processing (Knierim & Van Essen 1992, Talbot & Marshall 1941, Wandell et al. 2007). Another type of neural map is the computational map, in which the value of a computed parameter is mapped systematically across a neural structure—for example, a map of sound source location in the auditory brain stem (Knudsen et al. 1987).

One plausible theory for the existence of such ordered maps is based on the cost of wiring in the brain (Chklovskii & Koulakov 2004, Mitchison 1991). The idea is that it is better to construct a network in which most computation is local, relying on short connections between nearby neurons (Chklovskii & Koulakov...
Shorter axons cost less in terms of volume occupied and energy expended, as well as in terms of guidance defects during development (Chklovskii & Koulakov 2004). In many sensory systems, computations are local because important interactions usually occur between neighboring points in the stimulus space. Indeed, the very arrangement of sensory information in a given brain region—the sensory map—can reveal something about which neuronal signals are combined in subsequent circuits.

We have some intuition about which sensory stimuli should be mapped close to each other in the cases of vision, touch, and hearing. The nature of maps is much less obvious for olfaction. Odorant molecules are diverse and vary in size, charge distribution, bond saturation, and three-dimensional structure; indeed, a small molecule can be characterized by hundreds of parameters (Haddad et al. 2008b, Rossiter 1996). Therefore, on the face of it, even a fraction of these parameters cannot be systematically mapped onto a two-dimensional surface (Cleland 2010). Some investigators have argued that some privileged parameters are selected for during evolution and can be mapped systematically over the bulb. However, in the absence of a sensory ethology of olfaction in the commonly studied species, it is difficult to know which odors have special meaning to the animal (other than pheromones, which are not discussed here). This issue is less straightforward than it may appear; the use of natural images to dissect neural circuits is in its infancy even in the visual system, where the stimulus is more readily parameterized (Rieke & Rudd 2009).

It is important to note at the outset that a region of the brain may respond to sensory stimuli in a repeatable, but arbitrary pattern with no smooth or gradual representation of some stimulus attribute. Such a fragmented pattern is not really a map in the conventional neurobiological sense, but is instead a sort of look-up table for neural circuits that read it (Figure 1). In Knudsen’s words (Knudsen et al. 1987), “neurons selective for a particular parameter value or set of parameter values often are clustered to form functional modules in the brain, but there is no systematic variation in their tuning, i.e., there is no map” (pp. 41–42).

In this review, I discuss the organization of olfactory sensory regions in relation to odorant receptors (ORs) and odorant molecules. The focus is decidedly on mammals, but I occasionally invoke insect and fish studies to draw parallels. In addition, the discussion for mammals is restricted to the main olfactory system, with only occasional reference to the pheromone system. There is also a slant toward recent studies, and older work is frequently referenced indirectly through key review articles.

THE SPACE OF ODORS

Which metrics should be used to characterize odor space? Historically, this question has been tackled by asking humans to assign a set of perceptual descriptors to odorants, which can then be compared with chemical descriptors of these odorants (Amoore 1974, Schiffman 1974, Wise et al. 2000). Attempts to obtain a small set of olfactory primaries, a set of basic odors, upon which all odor percepts are built were not satisfactory, and investigators focused on defining some basic axes along which odor perception may lawfully vary (Wise et al. 2000).

This approach has been revived recently, and investigators have found interesting relations between odor quality and physicochemical structure of odors. Sobel and colleagues have found that variation in physicochemical properties along a single principal component can reasonably predict the pleasantness of an odor (Haddad et al. 2008a, Khan et al. 2007). Koulakov and colleagues (unpublished material; http://arxiv.org/ftp/arxiv/papers/0907/0907.3964.pdf) have analyzed previously cataloged data and found that psychophysical descriptors vary along a small number of dimensions that could be related to physicochemical parameters. The basic axes (or eigenvectors) that describe the relevant physicochemical descriptors seem to be related to the size of odorants, but not to measures such as carbon chain length or presence of aromatic
Figure 1
Map versus look-up table. A neural map is present when a variable, intensity of light in space in this example, is smoothly represented by a population of neurons (bottom left). By contrast, if a neural layer represents this variable in a fragmented pattern, it is not a map, even if the pattern is predictable.

THE SENSORY SURFACE: Olfactory Epithelium in Mammals
Odorants are sensed by a family of ORs expressed in olfactory sensory neurons (OSNs) (Buck & Axel 1991). This family has ~1,000 members in mice and rats (Zhang & Firestein 2002), ~50 in adult *Drosophila* (Brochtrup & Hummel 2011), and ~140 in zebrafish (Yoshihara 2009). Other chemosensory epithelia such as the vomeronasal organ and receptors in mammals (Kaupp 2010) are not discussed here. ORs transduce odor binding to groups. An important question that remains unanswered is whether odors that lie close together in the perceptual space are mapped systematically in the olfactory epithelium (OE) or the olfactory bulb (OB). A recent survey of the responses of a large number of mouse and human ORs to a large panel of odorants is a valuable starting point (Saito et al. 2009). If the spatial location of the sensory neurons expressing these tested mouse ORs or their glomerular targets can be determined, one can ask whether a specific physicochemical parameter is systematically mapped in physical space.
electrical activity in OSNs through signaling mechanisms that remain to be fully clarified (Kaupp 2010). In the main olfactory system of the mouse, each sensory neuron expresses only one type of receptor, and neurons expressing a particular receptor type are scattered in a large zone within the OE (Mombaerts 2004, Serizawa et al. 2004). Different receptors are expressed in distinct zones that are continuous and highly overlapping (Miyamichi et al. 2005). In effect, there is a coarse map of receptors in the OE (Figure 2), but even in a small region of the epithelium there will be a mosaic of neurons expressing dozens of OR types. What restricts the expression of a given receptor to a subregion of the epithelium is not fully clear (Imai et al. 2010, Sakano 2010).

OSN: olfactory sensory neuron

Figure 2
Mapping from the olfactory epithelium (OE) to the olfactory bulb (OB). (a) OR expression varies gradually in a rough dorsoventral direction in the OE, schematized by shading that goes from blue to red. A given OR is expressed by olfactory sensory neurons (OSNs) located within a subregion of the OE, which spans the entire OE in the rostrocaudal direction. A coronal section of the turbinates is illustrated; the shading represents the progression of OR expression. Homotypic OSNs (shown by small circles in the OE) are shown to converge on glomeruli. The dorsal-most region delineated by the yellow line is the DI domain, where OSNs expressing class I ORs converge. (b) Dorsal view of the OB shows the DI and DII domains, as well as the axis of reflection of the mirror-image maps (dotted black line). Lateral view is shown at right. (c) Illustration of how linear variation of a parameter can be mapped onto a closed contour. If the mapping occurs over all 360°, there will be a singularity (where 1 and 5 meet). If the map takes up 180° and is reflected, then there is no seam. Circles represent coronal sections of the OB.
The expression of several molecular markers carves out two zones—dorsal (D) and ventral (V)—within the OE (Sakano 2010). An additional segregation arises in the expression of the so-called class I and II ORs, whose genes are also segregated in chromosome loci (Zhang et al. 2004). These two classes of OR genes are phylogenetically distinct (Niimura & Nei 2005b), and class II ORs are expressed everywhere in the OE. Class I ORs, however, have restricted expression in the dorsal part of the OE (Miyamichi et al. 2005, Tsuboi et al. 2006, Zhang et al. 2004) and may code for special odorants (Freitag et al. 1995). Class I and II ORs are spatially mixed in the dorsal OE.

Even though each OSN expresses only one type of OR, it can still respond to a range of chemicals with different affinities, and a given odor can activate many different ORs with different efficacies (Araneda et al. 2000, Hallem et al. 2004, Malnic et al. 1999, Saito et al. 2009). Odor recognition, at least in generalist olfactory systems, likely occurs by combinatorial activation of many different types of OSNs.

Is there any functional significance to the preorganized (coarse) spatial map in the epithelium, or is it simply a developmental convenience to help enforce the one neuron/one OR rule (Sakano 2010, Zou et al. 2009)? To shed light on this question, one must know the relation between an OR and its ligand specificity. Unlike in other sensory systems, there is no clear a priori functional meaning for the position of the sensory neuron within the epithelium. Positional information in the OE could become important if the differential solubility of odorants or size segregate them within the olfactory sensory organ (Schoenfeld & Cleland 2005). Intriguingly, class I ORs, which are expressed in the dorsal parts of the OE, may preferentially bind to hydrophilic molecules (Saito et al. 2009). The dorsal OE, however, is also populated by class II ORs. In sum, no clear relation has been determined between the spatial position of an OSN and its odor tuning, and direct measurements from the OE may be necessary.

Olfactory receptors in adult *Drosophila* are found in the antennae and in the maxillary palp (Clyne et al. 1999, Vosshall et al. 1999). The sensilla, structures that house the sensory neurons, fall into distinct morphological classes—basiconic, trichoid, and coeloconic sensilla—that may selectively signal pheromone or general-purpose chemicals (Brochtrup & Hummel 2011, Imai et al. 2010, Luo & Flanagan 2007, Su et al. 2009). The morphological classes of sensilla also have preferential distribution on the sense organs, but a given OR is expressed in a wide region of the antenna or maxillary palp, with an apparently stochastic nearest-neighbor relationship (Couto et al. 2005, Luo & Flanagan 2007).

Zebrafish have two major types of OSNs (ciliated and microvillous) that express different classes of receptors that resemble the main olfactory and the vomeronasal systems of mice (Sato et al. 2005). The morphology, the OR class, the signal transduction machinery, and the projection patterns all point to differences in the function of these two types (Yoshihara 2009). Within each class, no systematic differences in receptor location have been described. OSNs projecting to a single glomerulus (and therefore likely to express the same receptor) are scattered throughout the OE (Baier et al. 1994).

In sum, other than broad expression domains, no obvious topography akin to those in other sensory systems has been identified in the olfactory sensory surface.

**WIRING FROM OLFACTORY EPITHELIUM TO OLFACTORY BULB**

In vertebrates, OSNs in the nose project their axons to the brain and form anatomical units known as glomeruli, arrayed in a layer on the surface of the OB (Mombaerts 1996, Mombaerts et al. 1996). Each glomerulus receives input from OSNs that express a single OR type. Conversely, OSNs expressing a particular OR project to (usually) two glomeruli...
in the ipsilateral OB (Mombaerts et al. 1996); not surprisingly, the number of glomeruli is approximately twice the number of receptor genes. Because each glomerulus receives input from only one OR type, its spectrum of odor responses is defined by the ligand-binding properties of the OR. The layout of glomeruli on the bulb forms a two-dimensional map of ORs, and by extension odorants (Figure 2).

Three types of topographic projections have been discussed in the literature pertaining to projection from the sensory epithelium to the first brain region: rhinotopy, odotopy, and chemotopy (Johnson & Leon 2007, Xu et al. 2000). Rhinotopy refers to a pattern of projection in which the position in the nose (the OE, to be precise) is mapped on the target area. This mapping can also be translated into a form of “receptoro-topy” if the position in the nasal epithelium dictates which type of receptor is expressed. Odotopy refers to the general idea that individual odors activate distinct parts of the OB. Such an activation pattern can now be rationalized given the one glomerulus/one OR organization. Chemotopy refers to a systematic representation in spatial coordinates of some feature of odorants, for example, the number of carbon chains in an aliphatic molecule. As discussed below, there is evidence for rhinotopy and odotopy in mammalian brains, but chemotopy has been more difficult to understand.

The sorting of like axons (i.e., axons of OSNs expressing the same OR) and their glomerular coalescence is guided by a hierarchical set of guidance mechanisms (Luo & Flanagan 2007, Mombaerts 2006, Sakano 2010). In addition to the identity of the OR itself, the glomerular position is influenced by many contextual factors (Feinstein & Mombaerts 2004). The postsynaptic targets in the OB are largely dispensable for the formation of the glomerular layout, and OSN axons may even be presorted before they arrive in the bulb (Bozza et al. 2009, Kobayakawa et al. 2007, Sakano 2010). The position of the OSN in the OE is mapped in the dorsoventral (D-V) direction in the OB, as appreciated even before the discovery of ORs (Aestic & Saucier 1986). We now know that the zone of expression of a particular OR is correlated with the dorsoventral position of the target glomerulus in the OB (Miyamichi et al. 2005, Sakano 2010) (Figure 2). Because of the overlapping expression of the class I and II ORs in the dorsal OE, OSNs expressing either class can go to the dorsal surface of the OB. However, these two classes are cleanly separated in the dorsal OB, with an anteriormedial DI domain and a caudalventral DII domain (Sakano 2010) (Figure 2). The rest of the class II ORs are represented on the ventral side of the OB. The mapping in the D-V axis of the OB is thought to involve at least two sets of repulsive ligand/receptor pairs: Slits/Robo2 and Sema3F/Nrp2 (Takeuchi et al. 2010). In the proposed mechanism (Sakano 2010), the OR–glomerulus relation is indirect because the OSN position independently controls both.

Unlike for the D-V axis, there is no relation between glomerular position in the anterior-posterior (A-P) axis and the OSN position in the epithelium. Instead, OR-mediated intracellular signaling may provide a rough glomerular address in the A-P direction (Imai et al. 2006). Clear evidence exists for the role of cAMP in glomerular targeting (Col et al. 2007, Imai et al. 2006, Zou et al. 2007). A gradient of cAMP levels is thought somehow to cause transcriptional regulation of classic axon guidance molecules such as Nrp1 and Sema3A (in opposite directions), leading to pretarget axon sorting that then establishes the A-P position (Sakano 2010).

In addition to these global positioning mechanisms, local sorting of axons and the final glomerular coalescence are thought to occur through hemophilic and heterophilic axon-axon interactions mediated by molecules such as the ORs themselves, Kirrel2/3, and ephrin-A/EphA (Mombaerts 2006, Sakano 2010). The final stages of axon segregation and coalescence into glomeruli may also involve neural
activity, perhaps through its effect on expression of the different cell surface molecules (Mombaerts 2006, Sakano 2010).

A peculiar feature of the mammalian OB is that each OR has two cognate glomeruli on the OB, leading to two glomerular layouts in each hemisphere (Johnson & Leon 2007, Mori et al. 2006). The two layouts are placed such that they are “reflections” of one another on the bulbar surface (Figure 2). Their function remains obscure, but it may be that mirror layouts arose as a developmental convenience that avoids a severe discontinuity or fracture. An open two-dimensional sheet (the OE) needs to be mapped to a closed two-dimensional sheet (the OB), and a simple linear map in both dimensions will lead to a discontinuity (Figure 2). Having duplicated mirror-symmetric maps may help avoid this. The axis of symmetry of the mirror-image layouts is along the A-P axis, approximately perpendicular to the D-V progression of the glomerular position signal.

The basic wiring from the sensory organ to the first stage of processing is preserved across a wide variety of species. In *Drosophila*, OSNs expressing a particular receptor converge on an anatomically identifiable glomerulus in the antennal lobe (Gao et al. 2000, Vosshall et al. 2000). The three types of sensilla that house OSNs have differential distribution on the sense organs, and they are also loosely mapped on the antennal lobe (Couto et al. 2005, Imai et al. 2010, Luo & Flanagan 2007). OSNs belonging to the same sensillum (therefore, located physically close to each other) can project to glomeruli that are close together or far apart (Couto et al. 2005, Endo et al. 2007). A detailed analysis of responses of ORs to a large set of odorants concluded that the cognate glomeruli had no neighborhood relation in functional space—that is, adjacent glomeruli are functionally no more similar than distant ones (Hallem & Carlson 2006). In the zebrafish, OSNs that converge to a single glomerulus are randomly scattered over the OE, and no known connectional topography exists (Baier et al. 1994). The one glomerulus/one receptor rule may be largely preserved, but there is no obvious order in the projection from OE to OB (Sato et al. 2007).

**REPRODUCIBLE ARRANGEMENT OF ODORANT RECEPTORS IN THE GLOMERULAR LAYER**

The elaborate sequence of events that lead to the convergence of axons to glomeruli and their proper segregation may suggest that the final spatial layout of glomeruli is variable across hemispheres or individuals because of accumulating errors. However, genetic studies using tagged olfactory receptors and visual observation in relation to anatomical landmarks have made it clear that the position of a glomerulus is not random and lies within a region of ~30 glomeruli (Mombaerts 2006, Mombaerts et al. 1996).

Functional studies have also noted that roughly similar glomerular activation patterns are recorded across animals when specific odorants are used (Johnson & Leon 2007, Rubin & Katz 1999, Uchida et al. 2000, Wachowiak & Cohen 2001), again suggesting some degree of repeatability of glomerular position. A global layout of activated regions in the glomerular layer using 2-deoxyglucose uptake has been painstakingly constructed by Leon and colleagues for a large number of odorants (Johnson & Leon 2007), which points to relative stereotypy of activation at least on a coarse level. A recent study used a large set of odorants to image ~200 glomeruli at higher resolution in mice and rats and determined that the average error in the relative position of dorsal glomeruli was on the order of 1 glomerular diameter (Soucy et al. 2009), both across two hemispheres of an individual and across different individuals.

The precision in relative glomerular position, with only some local jitter, supports a model of glomerular targeting that involves some degree of stochasticity in the final step. Glomeruli are placed more precisely in the mediolateral axis than in the A-P axis (Oka et al. 2006, Soucy et al. 2009). Because the mediolateral axis is essentially collinear with the
D-V direction, the data suggest that the placement guided by cues related to the position of the OSNs (Slits/Robo2 and Sema3F/Nrp2) may have better accuracy than those driving the A-P position (Nrp1/Sema3A). Glomerular positions are invariant across individuals in flies, and each glomerulus can be assigned a specific label (Imai et al. 2010). Glomerular layout is thought to be precise in fish, although the exact positional precision has not been quantified.

The available data indicate that for a given repertoire of ORs, the corresponding glomeruli are arranged in a predictable and precise pattern on the surface of the OB.

**RELATION BETWEEN ODORS AND GLOMERULAR POSITION**

Does the fact that glomeruli have specific spatial addresses lead to something more than a look-up table for downstream neural circuits, for example, a meaningful map in the space of odorants?

The idea that some metric of odorant structure will be smoothly mapped on the OB surface has inspired many studies. Early work in zebrafish noted that different classes of odorants activate distinct regions of the OB (Friedrich & Korsching 1998). This idea has been pursued in rats and mice using different odorants from several chemical classes such as aldehydes, ketones, alcohols, and acids, and a vast catalog of glomerular activity patterns has been obtained (Johnson & Leon 2007, Mori et al. 2006, Xu et al. 2000). As noted by Johnson & Leon (2007), three general features of odor responses in the rodent OB require explanation, and they are discussed in sequence.

**Clustered Responses**

Responses to a particular class of odorants appear in localized clusters, and each cluster may represent a particular odor quality (Mori et al. 2006). The fact that glomeruli responding to a particular odorant often cluster together is likely to be the consequence of the similarity of the corresponding ORs (see below).

Because glomerular responses are a function of the ORs expressed by the corresponding OSNs, an important consideration is how the coarse organization of odor responses is related to the domains carved out by ORs themselves, for example, class I and II ORs (Zhang et al. 2004). Two recent studies reported that at least some odorants activate the DI and DII domains, specifically (Bozza et al. 2009, Matsumoto et al. 2010). More extensive sampling of the odor space is necessary before firm conclusions can be drawn. The positional mapping of OSNs along the D-V axis in the bulb is not accompanied by any obvious progression of odor responses, other than a tendency for heavier molecules to activate the ventral OB in rats.

Activation domains have also been identified in the fish OB (Friedrich & Korsching 1998, Nikonov & Caprio 2001). Amino acids activate glomeruli in the anterior-lateral subregion of the bulb, and bile acids activate a medial subregion (Friedrich & Korsching 1998). Odorants were chosen on the basis of behavioral responses and educated guesses about natural stimuli that fish might encounter (Hara 1994), and it is interesting to consider whether adding other chemically diverse odorants will redistrict or preserve these domains.

**Fine-Scale Organization of Responding Glomeruli**

In addition to clustering of responses in spatial domains, several studies have emphasized within-domain ordering of responses (Johnson & Leon 2007, Mori et al. 2006). A frequently studied “chemotopic” progression involves straight-chain aldehydes or alcohols, with varying carbon chain lengths (Johnson & Leon 2000, Uchida et al. 2000). Each class of these odorants activates a cluster of glomeruli, and within a cluster response foci seem to shift gradually as chain length is altered. Such a progression is not observed for all odor domains, and when present it heads in a D-V direction (Johnson & Leon 2007). Because a rough D-V positional map exists between the OE and the
OB, it will be of interest to determine whether there is a systematic progression of response tuning in the OE position.

The gradual spatial procession of glomerular responses to odorants is not readily seen in higher-resolution imaging studies. In particular, active glomeruli that are activated by the domain-specific class of odorants (aliphatic aldehydes, for example) are interrupted by many inactive glomeruli (Bozza et al. 2004, Soucy et al. 2009), leading to a rather discontinuous progression of responses (Figure 3). These inactive glomeruli, however, can respond readily to other odorants not obviously related to aldehydes (Soucy et al. 2009). Indeed, the use of a large set of chemically diverse odorants to activate dorsal glomeruli in the same animal allowed investigators to compare response tuning of different glomeruli. Several interesting observations were made (Soucy et al. 2009). First, even though different odorants of a given chemical class activate clusters of glomeruli within a domain, they are not always the same glomeruli. Coarse-scale analysis will be unable to differentiate distinct responses of adjacent glomeruli. Second, odors of a particular class activate only a subset of the glomeruli present within a domain or module. Third, neighboring glomeruli were no more similar to each other than were glomeruli separated by greater distances, when all odors were considered (and not just a few classes of odorants).
Neighboring glomeruli in flies can have diverse odor responses, and odors of a given class can activate distinct glomeruli (Hallem & Carlson 2006). Although a direct analysis of glomerular response similarity and spatial separation has not been reported in fish, inspection of published response patterns indicates a strong neighborhood relation (Friedrich & Korsching 1998).

The existence of local diversity of glomerular responses is not necessarily at odds with a domain organization for a set of odorants. The coarse-scale order in odor responses may arise from some overall similarity of ORs that innervate a given region of the OB (Feinstein & Mombaerts 2004, Miyamichi et al. 2005). The fine-scale diversity may arise because it is possible for ORs with similar sequences to bind to different ligands (Araneda et al. 2000, Saito et al. 2009). Therefore, although a degree of similarity at a coarse, domain level is possible owing to overall similarity of ORs, fine-scale organization may be difficult, given the disconnect between mechanisms that select for ligand binding and those that determine glomerular location (see below).

Similar Glomerular Activity Patterns for Chemically Similar Odorants

A final aspect of the spatial organization of functional odor responses is that the patterns of glomerular activity for chemically related odorants can be very similar. This similarity, however, is inevitable because (a) a given OR often responds to chemically similar odorants (Araneda et al. 2000, Saito et al. 2009), (b) a given glomerulus receives inputs from OSNs expressing the same OR (Mombaerts 1996), and (c) the position of a glomerulus is relatively precise (Soucy et al. 2009). If a given odorant activates a set of ORs, then a related odorant (how one defines that may be tricky) would likely activate similar ORs. But this similarity does not automatically imply the existence of a map.

Quantitative and unbiased clustering of odorants based on their OSN response patterns in *Drosophila* indicated that odors of a particular chemical class fall into groups, but there are many outliers (Hallem & Carlson 2006). A global analysis in the rat and mouse OB using lower-resolution methods revealed that the overall activation pattern is indeed similar for odorants within a particular class (Johnson & Leon 2007). Metrics derived from an exhaustive set of physicochemical properties of odorants can be used to predict the pattern of neural responses in several species, including mice (Haddad et al. 2008a, Saito et al. 2009), but these metrics are not simple measures such as carbon chain length.

Data from different species have failed to identify general principles of functional organization of glomeruli in OB analogs. Within a given species, there may be some large domains of functionally similar glomeruli, but fine-scale diversity seems to be the norm.

**POTENTIAL INDEPENDENCE OF LIGAND SPECIFICITY AND GLOMERULAR POSITION**

Although there may not (yet) be a way of predicting the location of a glomerulus just by its sequence, the overall glomerular layout is predictable for a given repertoire of ORs and genomic loci. For example, although the layouts for mice and rats are different from each other, they are individually predictable (Soucy et al. 2009). Why is it that the glomerular layout is repeatable, but the neighborhood relation among glomeruli in functional terms is difficult to predict? The major reason is likely the complex relation among OR sequence, its ligand specificity, and the location on the glomerular surface.

There is a coarse relation between the sequence of an OR and the location of its corresponding glomerulus; similar sequences may have a tendency to go to neighboring bulb locations, but the displacement can sometimes be substantial for even small differences in sequence (Feinstein & Mombaerts 2004, Miyamichi et al. 2005, Wang et al. 1998). It became clear from these heroic gene-targeting experiments that the receptor sequence does
not provide a unique address on the bulb, and other factors strongly influence the position. One clear determinant of glomerular position is the chromosome locus from which the OR gene is expressed; the same OR gene expressed from different loci can target very different glomerular positions (Bozza et al. 2009, Feinstein & Mombaerts 2004, Miyamichi et al. 2005). The large OR gene repertoire in mice seems to have arisen mainly from tandem gene duplication (Niimura & Nei 2005a), so novel receptors appearing during evolution may be somewhat constrained in their target choice within the glomerular layout. Another, potentially related, factor that determines the glomerular target is the identity of the OSN itself, independent of its OR choice (Bozza et al. 2009).

Glomerular position, therefore, arises from developmental constraints, with neighborhood relation established by similarity of sequence, proximity on chromosome, transcriptional time, enhancer elements, etc. A newly evolved receptor may, by virtue of sequence similarity, go to a bulbar position that is close to another receptor. However, even small mutations can alter odor selectivity unpredictably. In particular, because odor binding depends on many residues, such small changes may leave intact binding affinity for many odorants but may introduce new odor-binding ability. Displacement in the space of sequence may not correspond to commensurate displacements in functional space (Figure 3).

In summary, it seems most useful to consider the glomerular layout on the OB surface as an arbitrary, but relatively stable look-up table for any particular species and examine how the higher brain areas interpret these.

### POSTSYNAPTIC TRANSFORMATION IN THE GLOMERULAR LAYER

OSN axons make synaptic connections with several targets in the OB, including juxtaglomerular (JG), mitral (M), and tufted (T) cells (Figure 4). I discuss how odor representation is transformed by bulbar circuits, mainly in relation to the spatial layout, ignoring temporal modulations (Laurent et al. 2001).

A vast majority of neurons that send their dendrites to the glomerular layer elaborate their dendritic arbors within a single glomerulus (Shepherd et al. 2004), which makes a compelling argument for the independence of glomeruli and no special relation between neighboring glomeruli. In addition to the principal cells (M/T cells), several JG neurons ramify their dendrites within the glomerulus. These cells are diverse and variously release GABA, glutamate, or dopamine (Shepherd et al. 2004, Wachowiak & Shipley 2006). One class of JG neuron has its processes in many glomeruli; these are the short axon (SA) cells, which are dopaminergic as well as GABAergic (Kiyokage et al. 2010).

Intraglomerular interactions can alter signal strength in postsynaptic neurons and alter the spatial pattern of odor-induced activity. Excitatory connections within the glomerulus, in the form of both gap junctions and synaptic connections (Wachowiak & Shipley 2006), can lead to signal amplification. Recurrent and feedforward inhibition arises from periglomerular (PG) cells excited by OSN inputs directly or through recurrent excitation from M/T cells (De Saint Jan et al. 2009, Hayar et al. 2005). Intraglomerular inhibition may serve as a gain-control mechanism acting presynaptically on OSN synapses or through postsynaptic inhibition of principal cells (Gire & Schoppa 2009, Shao et al. 2009, Wachowiak et al. 2005). Weak sensory inputs may be shunted out by PG cells (Gire & Schoppa 2009), helping sharpen odor-tuning curves in principal cells (Cleland 2010).

More elaborate changes in the spatial pattern of active regions can be achieved through interglomerular interactions. Interglomerular interactions in the glomerular layer are likely mediated by SA cells, which are expected to be inhibitory because of their GABAergic/dopaminergic identity. There is also some evidence for excitatory interactions (Aungst et al. 2003), which remains to be further explored. SA cells project to dozens of glomeruli (Kiyokage et al. 2010), but it is not clear whether

---

**Abbreviations**

- **JG**: juxtaglomerular
- **M**: mitral
- **T**: tufted
- **SA**: short axon
- **PG**: periglomerular
the long projections are axons or dendrites and whether their connection strength is distance dependent.

If lateral interactions are not specific, interglomerular inhibition could mediate a form of normalization that averages activity across many glomeruli and leads to a general suppression of responses, similar to that seen in insects (Olsen et al. 2010). If, however, lateral inhibition is specific (genetically pre-defined?), the spatial pattern of odor responses could be altered in more complex ways (Figure 4b). A recent study found that PG cells had very broad responses compared with their genetically tagged parent glomerulus (Tan et al. 2010), presenting direct functional evidence

---

**Figure 4**

Circuits in the OB. (a) Schematic of the major neuronal types in the olfactory bulb (OB) and their connections. Filled circles on the intersection of overlapping processes denote bidirectional synaptic connections, and filled circles that abut neurons indicate polarized axo-dendritic synapses. (b) Overhead view of the OB showing glomeruli as a two-dimensional array (dashed circles). Mitral cell activity can be influenced by a number of scattered glomeruli, as illustrated by arrows. Domain boundary is shown by a thick dashed line, and whether there are interactions across domain boundaries is not known (question mark). (c) Mitral cells affiliated with neighboring glomeruli (separated by green and gray colors) are likely to be intermingled. Lateral dendrites are sketched as radiating lines from the cell bodies. (d) Granule cells within reach of lateral dendrites of mitral cells affiliated with one glomerulus are shown by blue dots. The geometry of mitral cell dendrites dictates that their density falls off with distance and that the density of connected granule cells will also drop off with distance. Abbreviations: G, granule; ET, external tufted; M, mitral; OSN, olfactory sensory neuron; PG, periglomerular; SA, short axon; T, tufted.
that PG cells integrate information from multiple glomeruli.

Glutamatergic external tufted (ET) cells, the principal cells in the glomerular region, receive direct inputs from OSNs (Hayar et al. 2005) and are involved in integrating information between homologous, mirror-image glomeruli with the bulb (Belluscio et al. 2002). A recent study noted that all T cells (presumably including some ET cells) had much sparser responses than did their inputs (Tan et al. 2010), suggesting intra- or interglomerular GABAergic inhibition. It is important for future experiments to obtain cellular-resolution spatial layout of identified JG cell responses in relation to the glomerular responses. Multiphoton imaging may offer a way forward.

No clear distinctions exist between glomerular and deeper-layer circuits in flies and fish, and they are discussed below in the section, Spatial Organization of Functionally Related Granule Cells.

**SPATIAL PATTERNS IN OUTPUT NEURON LAYER**

The major relay cells in the OB, the M/T cells, are thought to receive direct inputs from OSNs and lateral excitation through dendrodendritic contacts within glomeruli. Inhibitory inputs arise from PG cells in the glomerular layer and granule cells in the external plexiform layer (EPL). Each M/T cell has its primary dendrite in a single glomerulus, and the 20 or so M/T cells associated with a single glomerulus are located below the glomerulus within a radius of 2–5 glomeruli (Buonviso et al. 1991). On the basis of geometric considerations, a small region in the M cell layer should contain M cells from multiple glomeruli (Figure 4c). Indeed, pairs of M cells adjacent to each other have a probability of 0.3 or less of innervating the single glomerulus (Dhawale et al. 2010). Whether there is a preferential arrangement of M cells of a particular kind (functionally or glomerular-identity based) in a local neighborhood remains to be determined. Given the local diversity of glomerular odor tuning, it would not be entirely surprising if M cells within a local region have diverse odor tuning; this author’s unpublished data support this supposition (Albeanu et al. 2009).

The circuitry and the synaptic properties of connections between M/T cells and granule cells have been extensively investigated in vitro (Egger & Urban 2006, Schoppa & Urban 2003). Similarly, odor responses of M/T cells have been studied for several decades, and much is known about the odor selectivity and dynamics of odor responses (recent examples include Cury & Uchida 2010, Fantana et al. 2008, Tan et al. 2010). However, much less is known about the spatial organization and to what extent it reflects the inputs. Intrabulbar interactions are likely to help sharpen the tuning curves of M/T cells, perhaps without changing the overall spatial pattern of responses (Mori et al. 1999, Tan et al. 2010).

A direct comparison of the responses of the input and output neurons associated with a genetically identified glomerulus recently revealed that M cells responded more sparsely to a large set of odorants than did the cognate input neurons (Tan et al. 2010). If these findings are generalized to other glomeruli, one would predict that the spatial pattern of M cell responses would be a sparser version of the glomerular patterns. More complex transformation of information in the OB is certainly possible because of the extensive connectivity and the feedback projections from higher brain areas (Restrepo et al. 2009). In addition, the temporal evolution of responses in M/T cells (Cury & Uchida 2010) could lead to systematic changes in spatial patterns of activity, as seen in zebrafish.

An important question raised by the presence of coarse-scale domain organization is how M/T cells across the domain boundaries interact anatomically and functionally. If indeed the class of receptors and their domains are important for segregating functional responses in the input layer, one might expect that M/T cells situated close to the boundaries have asymmetric or at least specialized interactions. More generally, it seems imperative to understand
how many of the lateral interactions among M/T cells are hard-wired and invariant, and how many of them vary across hemispheres or individuals (Figure 4b). Exciting developments in the field of optogenetics promise to help uncover the connection logic in the OB. In particular, the ability to activate individual glomeruli using light will allow a detailed mapping of the effective connections between a large number of glomeruli and an individual M/T cell (Arenkiel et al. 2007, Dhawale et al. 2010). These techniques will inform us about any asymmetry or anisotropy in M/T cell connections, for example, across domain boundaries.

The spatial organization of M cell responses has been studied in zebrafish using multiphoton imaging (Yaksi et al. 2007, 2009). Most M cells in fish have their apical tufts in single glomeruli just as they do in mammals and insects (Fuller et al. 2006, Miyasaka et al. 2009). Odor responses of M/T cells appear to follow the spatial pattern of inputs soon after odor presentation (Yaksi et al. 2007). Neighboring M cells are more similar to each other in odor tuning than are those with greater separation (Yaksi et al. 2007). The spatial patterns of responses become sparse and the chemotopic organization largely disappears with increasing time after odor exposure (Yaksi et al. 2007). Odor responses in principal neurons in the antennal lobe of flies have also been characterized using calcium imaging as well as electrophysiology, and the emerging view is that principal cells are more broadly tuned than are their OSN inputs (Masse et al. 2009). No specific organization by spatial location is evident, perhaps not surprising given the lack of positional information noted above.

**SPATIAL ORGANIZATION OF FUNCTIONALLY RELATED GRANULE CELLS**

Granule cells in the mammalian OB, which outnumber principal cells by a large margin, receive input via lateral dendrites and axon collaterals of M cells, as well as axons from cortical areas (Shepherd et al. 2004). The connectivity patterns of granule cells are not fully understood. A given M cell extends lateral dendrites to distances exceeding 800 microns in rodents, but whether they are capable of exciting granule cells uniformly over this distance is unknown. Similarly, whether a given granule cell receives inputs from M/T cells spread over a radius of 800 microns is also unknown. Granule cells are heterogeneous in their soma location, the principal cells they target, and their age, raising the distinct possibility that they are part of distinct microcircuits in the OB (Kelsch et al. 2010, Lledo et al. 2006).

Granule cell responses to odorants can be subthreshold or can involve action potentials (Cang & Isaacson 2003, Wells & Scott 1990). Recordings from granule cells have been sparse, in part because they are technically challenging. Although earlier studies hinted that granule cell responses may be sparse, a recent study reported denser responses to a large panel of odorants (Tan et al. 2010). The density of responses increased with odor concentration, indicating that lateral inhibition may be more prominent at higher concentrations. However, none of these studies sheds light on any spatial pattern of responses. Lower-resolution, “one-shot” experiments using immediate-early genes or 2-deoxyglucose to report activity indicate that there might be a columnar organization in granule cell responses (Guthrie et al. 1993), perhaps owing to geometric reasons (Figure 4d). Real-time imaging studies in the future may shed light on whether granule cells can mediate long-distance interactions between M/T cells and whether there are functional correlates to the patchy organization hinted at by viral tracing studies (Willhite et al. 2006).

Imaging studies in zebrafish indicate that interneurons equivalent to granule cells responded more densely to odorants (Yaksi et al. 2007). The coarse spatial segregation observed at the level of M cells was much less obvious, and interneurons could respond to multiple classes of odorants that normally do not activate the same M cells. All these indicate that interneurons integrate input from a
disparate set of M cells. Lateral interactions mediated by interneurons in *Drosophila* are complicated and include excitation and inhibition (Masse et al. 2009), with no noteworthy spatial aspect.

**STEREOTYPY OF CIRCUITRY WITHIN THE OLFACTORY BULB**

How much of the computation in the OB is predicated on precise or prespecified circuitry? For example, if specific glomeruli are placed close together by design to allow neighbors to interact, then there would be preferential connections between neurons getting inputs from these glomeruli. If such interactions are mediated by lateral inhibition, which has been suggested to have a center-surround organization (Yokoi et al. 1995), connections could be somewhat nonspecific, but distance dependent. However, recent data suggest that only a few scattered glomeruli are likely to influence the firing of a given M/T cell (Fantana et al. 2008). We do not know if these surround interactions are specific and repeatable across animals.

A specific type of intrabulbar connection—the one linking homologous glomeruli within a bulb—is indeed rather precise and plastic (Lodovichi et al. 2003, Marks et al. 2006). ET cells from one glomerulus send their axons to a small region of the internal plexiform layer below the homologous glomerulus and make synapses on granule cells. Whether these granule cells affect only M/T cells that are associated with the homologous glomerulus is unknown, but seems likely. The cellular and functional specificity of this circuit will help formulate its precise role.

**MAPS IN HIGHER BRAIN REGIONS**

M/T cells of the OB project through the lateral olfactory tract to many different brain regions, including the anterior olfactory nucleus (AON), the anterior and posterior piriform cortices (aPC and pPC), the olfactory tubercle (OT), the cortical amygdala (coA), and the entorhinal cortex (EC) (Shipley & Ennis 1996). Classic anatomical studies using anterograde and retrograde tracers have found very little evidence for any sort of positional topography in projections, with the exception of a subregion of the AON (Shipley & Ennis 1996).

The AON, which is considered a cortical area, has strong reciprocal connections with the OB and piriform cortex (PC) (Brunjes et al. 2005). Broadly, the AON can be divided into pars principalis (the core of the AON) and the pars externa, a thin ring of cells surrounding the core region. The anterior olfactory nucleus, pars externa (AONpE), has strong back projections to the OB but does not seem to project to downstream cortical areas such as the PC (Brunjes et al. 2005).

The lateral olfactory tract (LOT) maintains a broad organization in the D-V axis to match the source M/T cells in the OB (Walz et al. 2006). The projections of M/T cells to the AONpE maintain a rough topography, with M/T cells from the medial side of the OB projecting to medial AONpE and similarly for the lateral side (Brunjes et al. 2005). There is also recent evidence for topographic projections in the A-P axis, as well (Yan et al. 2008). Projections from the OB to other parts of the AON show no topography (Brunjes et al. 2005).

A very interesting feature of the AON is its backprojections to the OB (Brunjes et al. 2005). The AONpE again exhibits topography in the backprojection; for example, dorsal and ventral AONpE project to dorsal and ventral OB, respectively (Brunjes et al. 2005). A recent study extended these findings to the A-P axis of the OB and found exquisite topography in the backprojections, even to the contralateral bulb (Yan et al. 2008). Similar to the intrabulbar projections between homologous glomeruli, the excitatory projections from AONpE terminate in the granule cell layer and presumably activate those granule cells that are closest to the somata of M/T cells with apical dendrites in the appropriate glomerulus. These precise bilateral connections must have a role in coordinating information from the two nostrils (Yan et al. 2008).
The PC is the largest target area of the OB in mammals and has been divided into subregions—the aPC and the pPC—with the aPC divided further into dorsal and ventral parts (Haberly 2001). The three-layered PC is phylogenetically older than the more widespread six-layer cortex. Inputs from the OB arrive through the lateral olfactory tract, with synapses made in layer 1a of the PC (Haberly 2001, Isaacson 2010). Cortico-cortical association synapses are made in layer 1b (Haberly 2001, Isaacson 2010). Layers 2 and 3 contain cell bodies of pyramidal cells as well as some interneurons (Isaacson 2010).

M/T cell axons innervating the PC have widespread but patchy arbors, with no specific topography (Ojima et al. 1984). M cells project throughout the PC, but T cells do not reach much of the pPC (Haberly 2001, Nagayama et al. 2010). Single M cell axons make collaterals throughout the PC (Ojima et al. 1984). Indirect functional studies using immediate-early gene expression to assay neuronal activity (Illig & Haberly 2003), as well as extracellular spike recordings, have found that cells activated by a particular odor are distributed widely in the PC (Litaudon et al. 2003, Rennaker et al. 2007). Whole cell patch clamp recordings of PC cells indicated that they responded to only a few of the odorants tested, and the fraction of cells responding to a given odor was estimated to be ∼10% (Poo & Isaacson 2009). More heterogeneous responses were reported in awake, head-fixed mice using cell-attached recordings and post hoc cell identification (Zhan & Luo 2010). In addition to finding sparse responders, investigators also saw cells with broad receptive fields and cells exhibiting inhibitory responses (Zhan & Luo 2010). Using multiphoton microscopy, Stettler & Axel (2009) directly demonstrated spatially distributed PC cell responses to odors. This method allows researchers to examine responses from a large population of neurons to many odors at the same time. Any given odor activated ∼10% of the imaged neurons, widely distributed across the cortex. Neighboring cells had diverse odor receptive fields, with no evidence of clustering or patchiness.

The anatomical and physiological evidence converges on a model of connectivity from the bulb to the cortex that is spatially nonspecific and integrating inputs from multiple glomeruli (Haberly 2001). Exactly how many glomeruli project to a single pyramidal cell and whether there are specific connections preferentially from the different broad domains in the OB remain unknown. The cellular mechanisms of sparse odor responses are beginning to be elucidated and may involve widespread inhibition as well as recurrent corticocortical connections (Isaacson 2010). Lest one become too enamored with sparse responses, it is worth recalling theoretical arguments indicating that an optimal tuning curve width (narrow versus wide) depends on noise covariance, the number of variables being coded, and their impact on downstream circuits (Salinas 2006). A better understanding of these properties in the olfactory system may shed light on the coding strategy and the type of feature extraction.

In addition to direct input from the OB, the PC also receives profuse corticocortical connections arising locally from the ipsilateral PC, arriving from both ipsi- and contralateral anterior olfactory nucleus as well as from the contralateral PC (Haberly 2001). These connections have been invoked in models of the PC as an associative memory network (Haberly 2001). None of the regions giving rise to these corticocortical projections is known to have topographic projections from the OB; AONpE, the one region that has a map of the bulb, does not send projections to other cortical areas (Brunjes et al. 2005). A given PC cell is likely to receive inputs from both hemispheres and respond to odors from both nostrils, but the details of binasal interactions are not fully clear (Wilson 1997). An intriguing question is how association inputs modify the response tuning of PC cells. At first blush, it might seem that recurrent excitation should serve to broaden responses unless they are made very selectively. Distinct subregions within the PC are anatomically and functionally different, but whether they differ in the spatial arrangement of odor responses is not known (Haberly 2001).
The OT is considered part of the ventral striatum, a high-level cognitive region, but it receives direct monosynaptic inputs from the OB, perhaps preferentially from T cells (Nagayama et al. 2010, Shipley & Ennis 1996). Odor responses have been recorded in the OT (Wesson & Wilson 2010). To date, there is no evidence for organized projections from the OB or PC to the OT. There is also no known systematic organization of response properties in either odor space or brain space in OB targets such as the olfactory amygdala, the entorhinal cortex, and the tenia tecta (Shipley & Ennis 1996).

In the zebrafish, as in mammals, M cells send their projections to many higher areas (Miyasaka et al. 2009). Individual M cell axons innervate large regions of the telencephalon, but MCs from different domains of the bulb may have distinct patterns of innervations (Miyasaka et al. 2009). Functionally, there are reports of odotopic maps in higher brain areas in the catfish (Nikonov et al. 2005). Recent imaging studies in the zebrafish shed light on odor responses in two telencephalic target regions, Vv and Dp (Yaksi et al. 2009). Neurons in the Vv, a subpallial region, pool information from M cells and respond to more odors than do individual M cells. Neurons in Dp, a region homologous to the PC, have sparser responses with widespread inhibitory synaptic inputs (Yaksi et al. 2009). There is, however, no topographic map of responses, and cells responding to specific chemical classes (amino acids, for example) are distributed across the entire region.

Projections from the antennal lobe to higher regions in insects exhibit varying degrees of stereotypy. Of the two major projection regions, the lateral horn is thought to be sufficient for basic olfactory behaviors, and accordingly, the spatial pattern of axonal input from antennal lobe is highly stereotyped across animals (Jefferis et al. 2007, Marin et al. 2002, Tanaka et al. 2004, Wong et al. 2002). Furthermore, principal neurons associated with glomeruli that sense fruity odors appear to have projection areas distinct from those associated with pheromone-sensing glomeruli (Jefferis et al. 2007). Whether these correspond to functional segregation remains to be seen. The other target of the antennal lobe is the mushroom body, which is important for associative learning (Keene & Waddell 2007). Projection neurons from the antennal lobe have variable axonal arbors in the mushroom body, and Kenyon cells are thought to integrate information from multiple glomeruli (Masse et al. 2009). At the present level of understanding, synaptic integration and response properties in the mushroom body are quite similar to those in the mammalian PC.

**HOW CAN MAPS AID COMPUTATION IN THE OLFAC TORY SYSTEM?**

In the end, we must return to the question of what maps might actually do for the olfactory system. I consider some of the potential reasons for the existence of and the potential function of olfactory maps.

**Wiring Length**

As noted in the introduction, sensory maps could reduce wiring cost. In the OB, very few of the identified connections involve preferential nearest-neighbor interactions. In the glomerular layer, most dendrites are localized to a single glomerulus. Therefore, considerations of wiring optimization do not, at present, shed light on why there should be odor maps. More information on whether there are preferential connections that are invariant across individuals may catalyze further thinking about wiring optimization—for example, do granule cells link preferred pairs of M/T cells?

**Decorrelation**

Local circuits with lateral inhibition are thought to sharpen response tuning to stimuli, to decorrelate stimuli, and to reduce redundancy. In the OB, because neighboring glomeruli are not particularly similar to each other functionally (Soucy et al. 2009), lateral...
interactions cannot be confined to nearest neighbors. In fact, placing a diverse set of glomeruli within a small region may facilitate greater sampling of the odor space with local interactions. Such spatially unstructured lateral inhibition can be used to decorrelate M cell activity (Arevian et al. 2008, Cleland 2010). Even M/T cells targeting the same glomerulus can become decorrelated in their responses to odors, presumably through lateral inhibition (Dhawale et al. 2010).

Clustering of responses to a particular class of odorants may facilitate local processing, for example to discriminate among similar odorants, sometimes referred to as contrast enhancement (Mori et al. 1999). Although the nature of contrast enhancement in olfaction is not clear, discussions have typically focused on discriminating among molecules within a chemical class (Johnson & Leon 2007, Yokoi et al. 1995). The main evidence for contrast enhancement is the increase in the strength of M cell responses to nonoptimal stimuli when GABAergic inhibition is blocked (Tan et al. 2010, Yokoi et al. 1995). Lateral inhibitory interactions are usually assumed to occur in the deeper layers but may also occur in the glomerular layer (Aungst et al. 2003, McGann et al. 2005, Vucinic et al. 2006). However, because local representations are rather fragmented, lateral interactions may need to be specific (Fantana et al. 2008). An alternate hypothesis to explain contrast enhancement discounts lateral interactions altogether and invokes intraglomerular processing (Cleland 2010). Additional experiments blocking inhibition caused by a specific population of cells (using optogenetics, for example) are necessary to test these hypotheses.

Beyond decorrelating the responses of different neurons, Friedrich and colleagues have proposed that the OB performs pattern decorrelation (Niesing & Friedrich 2010, Wiechert et al. 2010). In this process, the overall population response is orthogonalized to allow easier discrimination of the activity patterns by downstream circuits. Whether pattern decorrelation is necessary in mammalian OB, with its fragmented map and greater local diversity in glomerular responses (Soucy et al. 2009), is not clear.

**Domain Organization**

What could be the function of broad domains within the OB, identified either by chemical classes of odors activating various glomeruli or by classes of odorant receptors innervating the glomeruli? These coarse maps may be helpful for genetically defining connectivity to different downstream areas. For example, the dorsal and ventral parts of the OB may project to different brain regions. Indeed, recent studies note that although both dorsal and ventral regions may contain glomeruli responding to specific odorants, abolishing dorsal glomeruli genetically affects innate fear responses but not learned fear responses to predator odors (Kobayakawa et al. 2007). This intriguing study suggests that odor maps cannot be interpreted without additional knowledge of projection patterns. Studies in fish have also offered tantalizing hints of this sort of domain-specific connectivity (Koide et al. 2009).

Another important question to be addressed is whether there are privileged lateral interactions between M/T cells within a domain or those located between domains (Figure 4b). Fantana et al. (2008) could predict M/T cell odor tuning by taking into consideration only ~200 visualized glomeruli (only about one-tenth of all glomeruli). Whether this is simply a consequence of the total length of the lateral dendrites of M/T cells or whether this hints at some domain organization remains to be seen.

**Gain Control**

Another computation thought to happen in the OB is gain control, which is essential for sensory systems to deal with a large range of stimulus intensities. In the olfactory system, one major form of gain control is localized to the presynaptic terminals of OSNs (Kazama & Wilson 2008, Murphy et al. 2004, Wachowiak et al. 2006).
2005, Wachowiak & Shipley 2006), which together reduce the activation of principal cells. A precise and organized layout of glomeruli is presumably not necessary to carry out gain control independently in each glomerulus. A different sort of gain control can also be achieved by interglomerular inhibition, in which the overall activity levels of glomeruli may be used to reduce the activity of all responding glomeruli proportionately (Cleland et al. 2007, Olsen et al. 2010). Such an interglomerular normalization, which can be divisive or subtractive, will preserve the relative activity levels of glomeruli and may be important for any coding strategy that does not involve simple labeled lines. Even interglomerular inhibition may not require maps in the traditional sense because there is not much evidence for preferential nearest-neighbor interactions. If lateral interactions in the OB are, in fact, sparse and distance independent (Fantana et al. 2008), an important question is whether the interactions are selective and precise. Gain control operations, as proposed to date, do not seem to need ordered topographic maps.

**Multiple Maps for Different Scenes**

In the retina, it has been apparent for some time that multiple views of the visual scene are broadcast to the brain by different classes of ganglion cells (Wassle 2004). Is there a similar strategy in the olfactory system, by which multiple odor images are relayed from the OB? For example, M and T cells may be relaying different aspects of the odor scene—M cells carrying more processed, fine features and T cells carrying more broad categories—to different target areas. Because there are two dozen or so M cells associated with an individual glomerulus, it is also interesting to speculate whether there are systematic distinctions among them; anatomical evidence indicates such differences (Orona et al. 1984). Combining molecular genetics and targeted recordings from identified cells has led to dramatic advances in retinal neurobiology in recent years, and this approach is likely to bear fruit in the olfactory system, as well.

Mirror-image representation in the mammalian OB is also an interesting issue. Are the two layouts essentially redundant and serve to increase signal to noise? Or do they have distinct functions and targets? Mirror-image layouts may have arisen as a developmental convenience and were subsequently harnessed for some yet-unknown function (Figure 2c).

**SUMMARY**

Solid evidence now supports the existence of a coarse topographic map from the receptor sheet to the first stage of processing at least in some animals. If and how such a map translates to a functional olfactory map continues to be difficult to resolve. Any functional organization in terms of local neighborhood similarity has to arise, in part, in the receptor sheet itself. An alternate hypothesis for positional mapping in the periphery is that it is essential for a predictable arrangement of glomeruli. A broad mapping from OE to OB is achieved with chemical gradients and positional cues, but local diversity may be inevitable. The OB circuit will have to be built to cope with this fractured layout, relying less on neighborhood relation and more on spatially distributed lateral interactions.

Future studies aimed at neural circuit analysis will likely bear the most fruit. These might include (a) analysis of the projection patterns of M/T cells from different bulbar domains, (b) examination of M/T cell lateral dendrites to determine any rules they may obey at domain boundaries, (c) analysis of any reproducibility and precision in the lateral interaction circuits within the OB, (d) analysis of the glomerular receptive fields of various cell types in the OB and its targets, (e) a detailed comparison of OR sequence and spatial position of the cognate glomerulus, and (f) analysis of potential scaling or morphological rules governing M/T and granule cell dendritic arbors.
DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

I thank the members of my laboratory for stimulating discussions. Work in my laboratory related to this review was supported by an anonymous foundation and funds from Harvard University.

LITERATURE CITED


258 Murthy

258 Murthy