Early Events in Olfactory Processing

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Annu. Rev. Neurosci. 2006. 29:163–201

The Annual Review of Neuroscience is online at neuro.annualreviews.org

doi: 10.1146/ annurev.neuro.29.051605.112950

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0147-006X/06/0721-0163\$20.00

Key Words

olfactory bulb, antennal lobe, chemotopy, temporal coding, synchrony, concentration, segmentation

Abstract

Olfactory space has a higher dimensionality than does any other class of sensory stimuli, and the olfactory system receives input from an unusually large number of unique information channels. This suggests that aspects of olfactory processing may differ fundamentally from processing in other sensory modalities. This review summarizes current understanding of early events in olfactory processing. We focus on how odors are encoded by the activity of primary olfactory receptor neurons, how odor codes may be transformed in the olfactory bulb, and what relevance these codes may have for downstream neurons in higher brain centers. Recent findings in synaptic physiology, neural coding, and psychophysics are discussed, with reference to both vertebrate and insect model systems.

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CHALLENGES TO UNDERSTANDING OLFACTORY PROCESSING

Two questions ground most approaches to understanding sensory processing. First, how are sensory stimuli encoded in the activity

of an ensemble of neurons? Second, how is activity progressively transformed as information moves through a sensory processing stream? These are both essential questions in olfaction, but both have proved difficult to answer.

A physiologist would like to describe objectively and manipulate the physical variables relevant to the sensory system. Yet chemical stimuli are notoriously difficult to parameterize or manipulate. The dimensionality of odor space is very high, if it can be defined at all. From a physical chemist's point of view, odor molecules differ in many physical respects-shape, size, polarity, polarizability, and flexibility, to name a few. From a biochemical perspective, different classes of odor molecules are associated with different metabolic pathways that may convey information about relevant biological processes, e.g., the availability of nutrients. The differences between volatile compounds cannot be adequately captured by just a few variables. Furthermore, the differences between chemicals are discrete. One may define a series of alcohols with increasing carbon chain lengths, for example, but not a continuous progression of alcohols. Thus, it has not been possible to define objectively the degree of similarity between any two molecules or to produce a set of test stimuli to cover the entire range of odor space. Olfactory physiologists do not have the luxury of exploring chemical stimulus space as systematically (or as quickly) as a visual physiologist with a computer monitor.

The inferred vastness of odor stimuli is matched by the complexity of the olfactory sensory receptors. The number of unique olfactory receptor (OR) types is very large in most species-from 60 to 1000-making olfaction fundamentally different from sensory modalities with a small number of receptors (Hopfield 1999). ORs are typically treated as if they constitute a unified cohort that together forms a distributed code for an odor so that knowledge from a few receptors can be generalized to all. However, investigators have long known that there are specialized olfactory processing channels (e.g., the macroglomerular complex in moths) and that these may constitute distinct processing streams. Immunohistochemistry and activity mapping techniques indicate striking differences in the molecular and functional properties of different parts of the bulb. It is convenient to ignore these complexities, but progress may depend on using genetic markers to focus on identified glomeruli/receptors (Meister & Bonhoeffer 2001, Wachowiak & Cohen 2001, Bozza et al. 2002). Invertebrate models with fewer glomerular channels can also provide important insights (Galizia & Menzel 2001, Hallem & Carlson 2004).

OR: olfactory

ORN: olfactory

receptor neuron

OB: olfactory bulb

receptor

These features make olfaction particularly difficult to study, but they also make it particularly interesting. This review aims to summarize current findings and models in the field of early olfactory processing. Our focus is on the neural code for odors in olfactory receptor neurons (ORNs) and the ways in which this code is transformed as it moves through the olfactory bulb (OB) toward higher brain centers. Mammalian olfaction is our main emphasis, but we also discuss insect models. We do not attempt to summarize the cellular, developmental, and molecular genetic aspects of ORNs, and we have neglected the accessory olfactory system. Where appropriate, we suggest how future experiments may potentially resolve outstanding puzzles. We also attempt to clarify some nebulous jargon in hopes of putting some tired controversies to rest.

CIRCUITRY UNDERLYING EARLY OLFACTORY PROCESSING

The olfactory system is an extremely flat processing stream. From the peripheral receptors, olfactory information must cross only one synapse in the OB before it reaches highlevel emotional or cognitive areas such as the amygdala and entorhinal cortex (**Figure 1**). Unlike other vertebrate sensory modalities, the olfactory system does not relay most information through the thalamus, but instead passes signals directly from receptor neurons, via the OB, to the olfactory cortex. From there, projections target regions including the orbitofrontal cortex, amygdala, entorhinal cortex, and ventral striatum. Only the orbitofrontal cortex receives information via a

Vertebrate olfactory system



Figure 1

Gross anatomy of the olfactory system. Olfactory receptor neurons in primary sensory organs project to a single region of the brain: (a) the olfactory bulb (in vertebrates) or (b) the antennal lobe (in insects). From there, second-order olfactory neurons send direct projections to higher brain regions involved in multimodal sensory integration, learning, and higher cognitive function. This implies that much olfactory processing occurs in the olfactory bulb or antennal lobe. Panel a after Haberly (2001).

AL: antennal lobe M/T: mitral and/or tufted (cell) second, indirect thalamic pathway. Therefore, the OB alone must perform all the sensory processing necessary to translate peripheral olfactory information into a language intelligible to the rest of the brain. The few steps of processing suggest that olfactory information requires less preprocessing than other sensory modalities. Nevertheless, the diversity and complexity of synaptic interactions in the OB attest to a critical and active role of the bulb in olfactory processing.

Receptor Neuron Projections

Odors bind OR proteins on the dendritic surface of ORNs. ORs constitute a large and diverse gene family in mammals (\sim 1000 genes in rodents, \sim 350 genes in humans), united by a common homology to other G protein– coupled receptors (Buck & Axel 1991, Young et al. 2002). It is likely that most ORNs express a single OR out of the entire repertoire. This idea has become something of a shibboleth and, although plausible, has been difficult to prove in mammals (Ressler et al. 1993, Vassar et al. 1993, Mombaerts 2004). In *Drosophila*, where the OR repertoire is smaller (~60), there is good evidence that most ORNs express one OR. Some *Drosophila* ORNs express two or three ORs, but the same OR is never expressed by more than one ORN type (Vosshall et al. 1999, Hallem et al. 2004a, Couto et al. 2005, Fishilevich & Vosshall 2005, Goldman et al. 2005).

The olfactory epithelium (and insect antenna) is divided into a few large zones. All the ORNs expressing a particular receptor are confined to the same zone, but different ORN types intermingle widely within each zone (Ressler et al. 1993, de Bruyne et al. 2001). In the brain, this peripheral chaos resolves into wonderful precision. In the OB [and its insect equivalent, the antennal lobe (AL)] ORN axon terminals segregate into discrete glomeruli (Figure 2). All ORNs expressing a particular OR converge onto the same target. In fruit flies, each ORN type projects to a single glomerulus (Vosshall et al. 2000, Couto et al. 2005). In mice, most ORN types target a pair of glomeruli, forming a mirror-symmetric pair of glomerular maps on two sides of the OB (Ressler et al. 1994, Vassar et al. 1994, Mombaerts et al. 1996), although some ventral glomeruli are unpaired (Strotmann et al. 2000, Johnson et al. 2002). Each mirror pair of glomeruli is reciprocally linked by precise intrabulbar connections (Ressler et al. 1994, Vassar et al. 1994, Mombaerts et al. 1996, Lodovichi et al. 2003). The functional significance of this intrabulbar symmetry is an open question. It will be important to determine whether these pairs represent redundant or independent processing streams.

ORN axons course through the olfactory nerve layer to reach their target glomeruli. Just below the nerve layer is the glomerular layer, divided into spherical neuropil compartments (**Figure 2**). In each glomerulus, ORN axons make excitatory synapses onto mitral and tufted (M/T) cells, the principal neurons of the OB. M/T cells are glutamatergic and are the only output neurons of the OB.



Centrifugal inputs (glutamate, noradrenaline, acetylcholine, serotonin)

Figure 2

Olfactory bulb circuitry. Excitatory neurons are shown in red, inhibitory neurons in blue, and neuromodulatory or mixed populations in purple. Question marks indicate unknown or speculative synaptic connections. For clarity, some intraglomerular interactions are not shown (see text).

Each M/T cell sends a primary apical dendrite into a single glomerulus, where it forms a tuft containing both postsynaptic sites and presynaptic sites. In an exception to this pattern, M/T cells in some amphibians and fish are multiglomerular (Nezlin & Schild 2000). The ORN-to-M/T synapse is unusually reliable, with a basal probability of synaptic vesicle release approaching 1 (Murphy et al. 2004).

A striking feature of the epithelium-tobulb projection is its high convergence ratio in rodents the ratio of ORNs to glomeruli is estimated at >5000:1 (Shepherd & Greer 1998). This convergence could represent a powerful amplification step. Convergence could also increase the signal-to-noise ratio for olfactory information, allowing postsynaptic neurons to pool many inputs from different spatial points on the peripheral organ. Another interesting notion is that convergence could extend the dynamic range of each glomerulus if the ORNs targeting that glomerulus have diverse thresholds (Cleland & Linster 1999). Concentration detection thresholds tend to covary across species according to the magnitude of ORNto-glomerulus convergence (Passe & Walker 1985). Defining the functional significance of this convergence calls for psychophysical testing, ideally in conjunction with manipulation of effective convergence.

PG: periglomerular (cell)

GABA: γ-aminobutyric acid

Lateral interactions in the OB transform the precise array of ORN inputs. These interactions occur in two distinct layers, the glomerular layer and the external plexiform layer, which may represent two different stages of processing (Figure 2). To resolve these stages it will be necessary to develop methods for mapping M/T cell activity both at the level of the apical tuft (transformed by intra- and interglomerular processing in the OB glomerular layer) and at the soma/axon initial segment (transformed by interactions through lateral dendrites in the OB external plexiform layer). We discuss briefly the synaptic and neuronal organization of these layers before returning to a discussion of coding.

Synaptic Interactions in the Olfactory Bulb Glomerular Layer

A shell of cell bodies belonging to intrinsic interneurons and astrocytes surrounds each glomerulus. The interneurons are collectively termed juxtaglomerular cells (**Figure 2**), the largest class of which is the periglomerular (PG) cells. A PG cell usually extends its dendrites into a single glomerulus. This dendritic tuft contains both pre- and postsynaptic sites. PG cells are inhibitory, releasing GABA (γ -aminobutyric acid), dopamine, or both (Shipley & Ennis 1996, Shepherd & Greer 1998).

ORNs form direct excitatory synapses onto PG dendrites, and neurotransmitters released from PG cells act in a retrograde fashion to inhibit release from ORN axons (Nickell et al. 1994, Wachowiak & Cohen 1999, Aroniadou-Anderjaska et al. 2000, Ennis et al. 2001, Wachowiak et al. 2005). Because the basal probability of release at ORN axon terminals is very high (Murphy et al. 2004), thousands or even tens of thousands of ORNs might release glutamate into a single glomerulus at the onset of a strong odor stimulus. This implies that PG cells may provide the presynaptic inhibition necessary to prevent swamping the glomerulus with glutamate and to extend its dynamic range. Within

a glomerulus, PG cells also form reciprocal dendrodendritic synapses with M/T cells. PG cells within a glomerulus can also inhibit each other (Murphy et al. 2005), and M/T cells can inhibit each other via an intervening PG cell (Urban & Sakmann 2002).

Interactions within a glomerulus are excitatory as well as inhibitory. Some classes of juxtaglomerular cells are glutamatergic, including the external tufted cells (tufted cells displaced into the glomerular layer). Also, a *M*/T cell can excite all the other *M*/T cells in the same glomerulus via glutamate release from its apical tuft. Finally, *M*/T cells in the same glomerulus can also be electrically coupled (Carlson et al. 2000; Schoppa & Westbrook 2001, 2002; Urban & Sakmann 2002).

Some juxtaglomerular neurons project axons to other glomeruli. Historically, interglomerular connections in the glomerular layer have been thought to be mainly GABAergic. However, a recent study reported that focal stimulation of the isolated glomerular layer elicited glutamatergic synaptic currents in juxtaglomerular neurons at distances of hundreds of microns (Aungst et al. 2003). Whereas PG cells are inhibitory and project to glomeruli a short distance away (<5 glomerular diameters) (Shepherd & Greer 1998), many of these glutamatergic projections were long range (>15 glomerular diameters). These glutamatergic projections are thought to originate from the so-called short axon cells of the OB. The postsynaptic targets of these connections included both PG cells and external tufted cells (Aungst et al. 2003). It will be important to clarify in future experiments whether, from a mitral cell's point of view, the net effect of this long-range interglomerular connection is inhibitory or excitatory.

Synaptic Interactions in the Olfactory Bulb External Plexiform Layer

Just below the glomerular layer lies the external plexiform layer (Figure 2). Each

M/T cell extends several secondary dendrites through this layer, contacting the dendrites of GABAergic granule cells. Granule cells lack an axon, and their dendrites are confined to the external plexiform layer (Shepherd & Greer 1998). M/T cells and granule cells form dendrodendritic reciprocal synapses, where both cellular partners contribute both preand postsynaptic elements (**Figure 2**).

The physiology of these dendrodendritic reciprocal synapses is understood in some detail. Action potentials in M/T cells propagate actively from the soma into secondary dendrites. This opens voltage-dependent Ca²⁺ channels, triggering vesicular release of glutamate from dendrites. Glutamate depolarizes granule cells via ionotropic glutamate receptors [both NMDA (N-methyl-D-aspartate) and AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors]. This leads to voltage-dependent Ca²⁺ channel activation, triggering GABA release. Ca2+ entering through NMDA receptors can also contribute to GABA release under certain conditions. Finally, M/T cells are inhibited via GABAA receptors. This circuit can mediate inhibition between pairs of M/T cells and also mediates self-inhibition of single M/T cells (Isaacson & Strowbridge 1998, Schoppa et al. 1998, Chen et al. 2000, Halabisky et al. 2000, Isaacson 2001, Margrie et al. 2001). Ca²⁺ transients in granule cells can be either local or global, supporting either mode of inhibition (Egger et al. 2005). The spatial extent of lateral interactions is subject to active control, whereby action potential propagation within the M/T secondary dendrites depends on the amount of GABAergic feedback from granule cells (Xiong & Chen 2002).

Dendrodendritic interactions between M/T cells and granule cells have three main proposed functions. First, they may control the gain of OB output. In the extreme case, global gain control could simply perform divisive scaling of all M/T cell responses without changing the specificity of any M/T cell tuning curve. However, because the inhibitory region recruited by an M/T cell

spans only a fraction of the bulb, any gain control is likely to be spatially heterogenous, not global. A second proposed function for dendrodendritic inhibition is to selectively decrease the response of particular M/T cells to some odors. If all interactions in the OB were inhibitory, this would tend to narrow the molecular receptive range (MRR) of M/T cells (see below, The Mori Model). If the timing of inhibition were odor and cell specific, this could produce a temporal code for odors among M/T cells (see below, Odor-Evoked Temporal Patterns). Third, inhibition may orchestrate temporal synchrony among M/T cells (see below, Odor-Evoked Synchronous Oscillations). Inhibition may perform all three of these functions in the bulb at once.

The functional effects of these inhibitory interactions may be quite long range. Although the dendrites of a granule cell span just 1–2 glomerular diameters, M/T secondary dendrites extend across 10–12 glomerular diameters in mammals (Orona et al. 1984, Shepherd & Greer 1998). It will be critical to determine whether, within this radius, inhibitory interactions are glomerulus specific or not.

Interactions between M/T cells in the external plexiform layer are not exclusively inhibitory. M/T secondary dendrites do not synapse directly on one another (Price & Powell 1970b), but glutamate can diffuse (spill over) between neighboring mitral cells to activate (high-affinity) NMDA receptors (Nicoll & Jahr 1982, Aroniadou-Anderjaska et al. 1999, Isaacson 1999, Salin et al. 2001). It remains an important open question whether M/T cells innervating different glomeruli can excite each other via spillover. Paired recordings from M/T cells suggest that more than half of all nearby pairs are connected via spillover, and given this high probability of connectivity, this process must reflect interglomerular excitation (Urban & Sakmann 2002), but this has not been directly demonstrated. Also, spillover interactions between M/T secondary dendrites are substantially weaker than that observed between the apical NMDA: N-methyl-D-aspartate MRR: molecular receptive range **PN:** antennal lobe projection neuron

LN: antennal lobe local neuron

dendrites of M/T cells in the same glomerulus (Carlson et al. 2000; Schoppa & Westbrook 2001, 2002; Urban & Sakmann 2002).

The Insect Antennal Lobe Circuit

As noted, both vertebrates and insects segregate ORN axons into discrete glomeruli in the brain. OR expression patterns have not been established for most insects, but *Drosophila* ORNs resemble vertebrate ORNs in that they express just one or a few ORs. This appears to be a striking example of convergent evolution. This resemblance argues that vertebrate and invertebrate olfactory systems evolved in response to the same set of fundamental sensory problems, or similar developmental/evolutionary constraints (Eisthen 2002).

Insect antennal lobe projection neurons (PNs) are the analogs of vertebrate M/T cells (Figure 3). Most PNs send a dendrite into a single glomerulus, analogous to the apical dendrite of M/T cells. This is true of fruit flies, moths, honeybees, and most other insects. These uniglomerular PNs have been the focus of almost all physiological studies in these species. In these insects, there are also some PNs that innervate multiple glomeruli. These multiglomerular PNs might be functionally equivalent to multiglomerular tufted cells, but almost nothing is known of their physiology. In locusts, the situation is unusual: All locust PNs appear to innervate multiple glomeruli, and glomerular boundaries are ill defined (Anton & Homberg 1999).

Both PNs and ORNs release acetylcholine, the major fast excitatory neurotransmitter in the insect brain. Another class of cells, termed local neurons (LNs), connect different glomeruli. Like granule cells in the bulb, LNs lack an axon. Most antennal lobe LNs are GABAergic, but some may also release neuropeptides, amines, or nitric oxide (Anton & Homberg 1999).

Both PNs and LNs receive direct excitatory synapses from ORNs. PNs also form direct excitatory synapses onto LNs. LNs, in turn, can synaptically inhibit PNs (Christensen et al. 1993, MacLeod & Laurent 1996, Wilson et al. 2004b, Wilson & Laurent 2005). These are reciprocal dendrodendritic interactions, such as those between M/T cells and granule cells in the OB. Because the AL is a compact structure, a single LN can span its entire volume, in some cases innervating every glomerulus. Nevertheless, anatomical studies show that many individual LNs make specific synaptic connections within particular glomeruli, and physiological results also imply a degree of specific functional connectivity between glomeruli (Anton & Homberg 1999, Ng et al. 2002, Sachse & Galizia 2002, Wilson & Laurent 2005).

Finally, the insect AL receives abundant centrifugal inputs from other brain regions (**Figure 3**). These include connections from octopaminergic and serotonergic neurons, and in some species dopaminergic inputs as well (Anton & Homberg 1999). There is no cholinergic centrifugal input to the AL. Thus, olfactory processing in the insect olfactory system is largely bottom up. This stands in contrast to the mammalian olfactory system, where abundant glutamatergic inputs descending from the piriform cortex feed back onto the OB, potentially adding a substantial top-down component to olfactory processing (**Figure 1**).

RECEPTIVE FIELDS AND RESPONSE SPECIFICITY

Understanding Feature Detection by Olfactory Receptors

Feature detection is considered a basic task of sensory processing. Therefore, a major goal of olfaction research has been to characterize the molecular features detected by ORs. ORs are seven-transmembrane G protein–coupled receptors (Buck & Axel 1991). As a group, ORs can detect and discriminate among almost any volatile hydrophobic molecules of less than approximately 300 Daltons molecular weight. ORs are essentially just G protein–coupled receptors for extracellular small molecules



Antennal lobe circuitry. The synaptic organization of the antennal lobe shows some important similarities to the olfactory bulb. However, the antennal lobe lacks the distinctive two-stage organization of synaptic inhibition that characterizes the olfactory bulb. Excitatory neurons are shown in red, inhibitory neurons in blue, and neuromodulatory or mixed populations in purple. Question marks indicate unknown or speculative synaptic connections.

and, in this sense, are conceptually similar to metabotropic neurotransmitter receptors. ORs bind ligands at a site formed by residues from three transmembrane domains, analogous to the ligand binding site of metabotropic neurotransmitter receptors (Floriano et al. 2004, Man et al. 2004, Katada et al. 2005).

Historically, the analogy between ORs and other G protein–coupled receptors has suggested that ORs might recognize one or a few ligands with high specificity. In this case, these ligands would define the molecular feature represented by this OR. Such ligands could be discovered by a pharmacological approach, i.e., screening an OR against candidate odors. However, this approach has so far not defined the kind of clear molecular feature suggested by the analogy with neurotransmitter receptors. First, most odors activate many ORs, and most ORs can be activated by multiple ligands. In some cases, these ligands share a clear molecular feature: For example, the rat I7 receptor is activated preferentially by certain aliphatic aldehydes. For these ORs, it could make sense to define the feature recognized by these ORs in terms of a particular functional group (here, the aldehyde moiety). In many other cases, however, the set of ligands activating a single OR cannot be defined by a single obvious molecular property, and we would be hard pressed to define what feature these ORs represent (Revial et al. 1982, Malnic et al. 1999, Araneda et al. 2000, Wetzel et al. 2001, Bozza et al. 2002, Araneda et al. 2004, Hallem et al. 2004a, Yao et al. 2005). Second, there is some evidence that EC_{50} values for ligand-OR interactions are higher than those of other G-protein-coupled receptors (Masu et al. 1991, Firestein et al. 1993, Jones et al. 1998, Kajiya et al. 2001, Bozza et al. 2002, Katada et al. 2005). This suggests that ligand-OR interactions may be relatively nonspecific. If so, this would imply that the traditional analogy between the immune and olfactory systems is inappropriate for the main olfactory system. Whereas antibodies have high affinity and specificity for antigens, ORs may have relatively low affinity and broad sensitivity, responding to many chemicals. Evaluating this statement will require measuring the apparent affinity constants of several receptors for multiple ligands.

Ultimately, we may not be able to define the molecular feature recognized by most individual ORs in terms of a single ligand, or even a single functional group or moiety. How, then, can we make progress in understanding what kind of information is encoded by ORs (and thus ORNs)? Three issues seem most urgent.

First, it would be helpful to have a general explanation in molecular terms for the nature of ligand-OR binding. If ORs do have relatively broad specificity compared with other G-protein-coupled receptors, what kinds of intermolecular interactions at the ligand binding site underlie this difference? Here, detailed structure-function studies should be the most informative approach, especially those combining molecular simulations with point mutagenesis and functional assays. For example, a recent study (Katada et al. 2005) found that the ligand binding pocket of a mouse OR recognizes odor molecules mainly through hydrophobic interactions dominated by van der Waals forces. By contrast, most G-protein-coupled receptors recognize their ligands mainly through hydrogen and ionic bonds. If this generalizes to other ORs, it could account for the apparently somewhat nonspecific quality of ligand-OR interactions.

It could also account for why the ligand-OR complex is extremely transient, with an odorant dwell time of <1 ms (Bhandawat et al. 2005). One barrier to this type of structurefunction study has been the difficulty of expressing ORs in heterologous cells. Carlson and colleagues have recently laid the foundation for a different strategy in *Drosophila* by developing techniques to replace the native OR of an ORN with a different OR (Dobritsa et al. 2003, Hallem et al. 2004a, Goldman et al. 2005, Kreher et al. 2005, Yao et al. 2005). This could speed the progress of structure-function analyses.

Second, insight into this problem should also come from thinking more carefully about the odor stimuli used in experiments. In trying to understand the molecular features recognized by ORs, a fundamental goal has been to discover the major variables (or axes) that the nervous system uses to represent odors. Rather than reasoning from OR structurefunction studies alone, a more efficient avenue to this goal might be to find odors that define these axes on a purely empirical basis. It is useful to envision this as a kind of olfactory "basis set." This would be the smallest odor set that (*a*) spans the range of sensitivity of all ORNs, (b) covers this range in some detail, and (c) collectively generates a maximally diverse set of ORN responses. In the ideal case, it would be possible to use such a basis set to synthesize any possible smell using a linear combination of basis odors. Because odors cannot assume negative values, odor perceptions would have to be constructed under non-negativity constraints. A more serious difficulty is that in real olfactory systems, odors do not sum linearly even at the receptor level (Duchamp-Viret et al. 2003, Oka et al. 2004b). Although it will probably prove impossible to develop a true basis set, an odor panel approximating this would be extremely useful. So far, no experiments in mammals have used anything approaching this kind of odor test set. Given the large number of mammalian ORN types, screening for such a set may require highthroughput stimulus delivery combined with

functional imaging. In *Drosophila*, which have only ~40 distinct ORN types, the task should be easier. Using an odor test set comprising ~40 stimuli, it is already possible to elicit robust responses in each *Drosophila* ORN type and to discriminate unequivocally between genetically defined ORN types on the basis of odor responses alone (Clyne et al. 1997, de Bruyne et al. 1999, de Bruyne et al. 2001, Hallem et al. 2004a, Yao et al. 2005).

Third, we would argue that it is not possible to understand the function (in terms of feature coding) of single ORs. Natural selection has not shaped the structure and function of each OR in isolation, but rather in the context of the entire organism and its ecology. Compare cosmopolitan generalists (rats, fruit flies) with local specialists (koalas): Different selective pressures should produce ORs whose receptive fields are distributed very differently in odor space. And within the OR gene family of a single species, the selection for or against mutations in a particular OR should also depend on the degree to which this OR's receptive field overlaps with those of other ORs (Figure 4). Thus, each species may have a somewhat different set of major olfactory axes, meaning its own way of categorizing odors; comparative studies should help us understand if selective pressures have produced any particular arrangement. For example, many Drosophila ORs are particularly sensitive to fruity odors (de Bruyne et al. 2001), but we would predict a different olfactory focus for flies who feed on carrion or dung.

Receptive Ranges and Selectivity

The set of all odors eliciting a response in an olfactory neuron has been termed its molecular receptive range (MRR), analogous to the concept of a visual receptive field (Mori & Shepherd 1994). In general, studies that have challenged multiple ORNs with large odor sets consistently report a striking diversity in MRR size (**Figure 4**). Some ORNs respond to many odors in a test set, whereas other ORNs respond to just one or



Figure 4

A model of olfactory receptor neuron (ORN) receptive fields. High-dimensional olfactory space is represented here as a two-dimensional plot. Circles represent the molecular receptive ranges (MRRs) of ORN1, ORN2, ORN3, etc. The MRRs of different ORNs overlap in chemical space. MRR sizes are also diverse. In some regions of olfactory space, overlap between MRRs may be atypically high, and/or MRR sizes may be small (*blue circles*). Olfactory acuity should be high in these regions, which could correspond to odors that are especially important to the organism's ecology. Some MRRs are especially small (*red circles*), corresponding to specialist olfactory receptor neurons.

two test odors. This is observed even within a specific experimental preparation using a single odor test set, usually at an arbitrary fixed concentration (Pfaff & Gregory 1971, Revial et al. 1982, de Bruyne et al. 1999, Malnic et al. 1999, Uchida et al. 2000, de Bruyne et al. 2001, Wachowiak & Cohen 2001, Wang et al. 2003, Araneda et al. 2004).

Like ORNs, M/T cells in the OB also show a broad and graded distribution of MRR sizes (Duchamp 1982, Imamura et al. 1992, Mori et al. 1992, Katoh et al. 1993). Similarly, antennal lobe PNs display diverse MRRs, ranging from promiscuous to selective in the same preparation (Anton & Hansson 1994, Perez-Orive et al. 2002, Wang et al. 2003, Wilson et al. 2004b).

SV: saturated vapor

In considering the results of these studies, it is important to keep in mind that a cell's MRR will depend on the choice of odors in the test set. A limited or unimaginative odor set may produce a distorted estimate of MRR size. Estimates of MRR size are also highly dependent on the concentration of the test odors. High odor concentrations will produce larger apparent MRR sizes. Given this, and the diversity of MRR sizes within the same cell population, it seems pointless to argue about whether olfactory neurons are narrowly or broadly tuned.

Olfactory tuning has been discussed mainly in terms of MRR size. However, it is important to keep in mind that a cell with a large MRR can nevertheless display very selective responses. This is because even a cell with a large MRR can respond to different odors with different spike rates. Selective but broad and overlapping receptive fields are the hallmark of distributed population coding strategies in the cortex (Pouget et al. 2000). Adequate characterization of response properties in the olfactory system should include an analog measure of response strength for each test odor. The kurtosis of the distribution of firing rates across a set of test odors can provide a useful measure of tuning sharpness. Finally, if firing rates are measured in large bins, even this measure will not capture information contained in the temporal features of a neuron's response (see below, Odor-Evoked Temporal Patterns).

The selectivity of an ORN will primarily reflect the affinity of its OR for each of the odors within its receptive range. Conversely, for each odor, we can identify both high- and low-affinity ORs. High-affinity receptors are sometimes assumed to be most salient for the organism (Wang et al. 2003). However, we would argue that low-affinity receptors should also be very important for stimulus discrimination. For example, consider the task of discriminating between two rather high concentrations of the same odor. In general, the relationship between ORN activation and log(concentration) approximates a sigmoid curve (O'Connell & Mozell 1969, Firestein et al. 1993, Trotier 1994, de Bruyne et al. 2001, Meister & Bonhoeffer 2001, Reisert & Matthews 2001, Wachowiak & Cohen 2001). High-affinity sites will saturate at relatively low concentrations. This means than when concentration is high, the most useful information will come from lowaffinity ORs that are near the middle of their dynamic range. Because the highest-affinity sites can saturate at <0.1% of saturated vapor (SV) pressure (Bozza et al. 2004), lowaffinity sites should provide useful information over several orders of magnitude in odor concentration.

Specialist Channels

A number of electrophysiological studies have reported that a substantial minority of firstand second-order olfactory neurons cannot be excited by any odors in a relatively large and diverse test set (Duchamp 1982, Clyne et al. 1997, Duchamp-Viret et al. 2000, Wilson et al. 2004b, Yao et al. 2005). These cells may belong to information processing channels with specialized functions and correspondingly specific chemical selectivity. For example, anatomical studies have identified sets of glomeruli at the posterior margin of the bulb that possess unique molecular markers and that appear to respond to unconventional odorants-e.g., the glomerular complex activated by suckling, and the socalled necklace glomeruli (Teicher et al. 1980, Shinoda et al. 1989, Ring et al. 1997). In insects, such specialized channels have been documented in detail. For example, particular ORN and PN types in the moth are dedicated to pheromones or to the odors of specific plant hosts (Boeckh et al. 1965, Christensen & Hildebrand 1987, Kaissling et al. 1989, Anton & Hansson 1994). In the mosquito, one ORN type is highly tuned to a molecule found in human sweat (Hallem et al. 2004b). In many insect species, one ORN type is selective for CO_2 , which is released by insects and their hosts (Stange & Stowe 1999, Suh et al. 2004). Collectively, these ORN types have been termed specialist channels, in contrast to the generalist properties attributed to most ORNs (Hildebrand & Shepherd 1997) (**Figure 4**).

It will be interesting to see whether, with insects, behaviorally by analogy relevant ligands can be identified mammalian glomeruli that are generally unresponsive. Recently, a group of M/T cells in the ventrolateral mouse OB was found to respond specifically to one compound among many in mouse urine. This compound, (methylthio)methanethiol, is specific to male mouse urine, and it increased behavioral investigation in females, suggesting that these cells play a role in social behavior (Lin et al. 2005). Although other general odors were not tested on these cells, this study suggests that some OB channels may be dedicated to odors with special behavioral relevance. If these glomerular channels are more segregated from the OB network than the typical generalist channel, and if their specialist status persists up into the olfactory processing hierarchy, then this may constitute a labeled line, a neural circuit where at each level in the processing stream all the information about a stimulus is contained in the responses of a single neuron (or homogenous population of neurons), rather than a diverse neural ensemble.

HIERARCHICAL TRANSFORMATION OF ODOR RESPONSES

Neurons in the olfactory system respond to multiple stimuli, but can nevertheless be informative in their responses. Some firstand second-order cells are probably specialists, but many are evidently generalists. Individual olfactory neurons seem not to detect obvious molecular features. How, then, can we think systematically about what computations the olfactory system is performing? Concretely, how are olfactory representations transformed as information moves from ORNs through the OB?

The Mori Model: Transformation Through Molecular Receptive Range Narrowing

Mori and colleagues (Yokoi et al. 1995) have proposed one model of ORN-to-M/T cell transformation. They have suggested that M/T cells receive polysynaptic inhibitory input specifically from nearby glomeruli with overlapping but nonidentical MRRs. For example, the ORNs targeting a particular M/T cell may be strongly excited by an n-carbon aldehyde and weakly excited by n - 1 and n + 1 aldehydes. Neighboring glomeruli, which are optimally excited by n - 1 or n + 1aldehydes, would trigger lateral inhibition onto this M/T cell, inhibiting its responses to nonoptimal ligands. According to this model, the net effect of the OB circuit would be to narrow the MRR of each M/T cell. This could be implemented by interglomerular inhibition in the external plexiform layer, or the glomerular layer, or both. This model is supported by recordings from rabbit M/T cells in the dorsomedial bulb using a series of naliphatic aldehydes as stimuli (Yokoi et al. 1995). Approximately half of M/T cells were excited by some odor(s) in this set, typically responding to 2-4 odors with consecutive carbon chain lengths. Among these cells, roughly half were also inhibited by other odors in this set. These investigators reported that a given cell would often be selectively inhibited by a ligand with n + 1 carbons (or n - 1 carbons), as compared with the ligands that excited the cell. Blocking GABAA receptors broadened the MRR of these cells. Although this study has been influential in shaping opinions in the field, it remains the only major piece of evidence in favor of this hypothesis. These experiments need to be replicated in other regions of the bulb, using a much larger odor set.

Predictions Based on the Model of Molecular Receptive Range Narrowing

The Mori hypothesis makes several strong predictions. The strongest prediction is that the MRR of a given M/T cell should be narrower than the MRR of its corresponding ORNs. This question has catalyzed much debate, but not a corresponding amount of experimentation. Only two studies in vertebrates have compared the MRR size of ORNs and M/T cells, and neither was performed in mammals. Both studies used relatively large and diverse odor sets and kept odor stimulus parameters constant across all recordings. In the tortoise, Mathews (1972) found that M/T cells actually had larger MRRs than primary receptor neurons. Less than half of all ORNs responded to at least one of the test odors, whereas all M/T cells responded to at least one. In contrast, Duchamp (1982) found that frog OB neurons had smaller MRRs than primary receptor neurons. As noted, a cell's selectivity is best captured not by its MRR size, but by analog measures of response strength and response timing. Unfortunately, neither of these studies reported selectivity in these terms, and neither study compared ORNs and M/T cells corresponding to the same glomerulus.

Several recent studies have addressed this question in the Drosophila AL. Two functional imaging studies used promoters specific to ORNs or PNs to drive expression of a genetically encoded fluorescent activity reporter. These studies found that, for each glomerulus, the odor responses of ORNs and their corresponding PNs were essentially identical (Ng et al. 2002, Wang et al. 2003). A caveat of these studies is the low sensitivity of the fluorescent reporters (Sankaranarayanan & Ryan 2000, Pologruto et al. 2004). In contrast, an electrophysiological study in Drosophila found that the PNs postsynaptic to a particular glomerulus had a larger MRR than their corresponding ORNs and that the PN tuning curve had less kurtosis (sharpness) than the ORN tuning curve (Wilson et al. 2004b). A weakness of this study was that only one glomerulus was analyzed in detail.

A second strong prediction of the Mori model is that the probability of inhibitory connectivity between any two glomeruli should correlate with the degree of overlap between the MRRs of their ORNs. This idea has not been tested in any system. A third prediction is that, insofar as connectivity between neurons generally falls off with increasing distance, there should be a correlation between MRR overlap and interglomerular distance. This last issue has been addressed by many functional imaging studies, which in sum tend to affirm this prediction, although this organization appears to break down at fine spatial scales (see below, Chemotopy). Testing all of these predictions in detail is necessary to a critical evaluation of this model. Importantly, the spatial scale of the relationship between MRR overlap and interglomerular distance should match the spatial scale of synaptic inhibition surrounding foci of glomerular excitation (Luo & Katz 2001).

Alternative Models of Hierarchical Transformation

It is worth noting some theoretical criticisms of the concept of MRR narrowing. Importantly, narrow tuning curves are not always better than broad ones. In other words, narrowing the MRR of a M/T cell will not automatically improve the ability of downstream neurons to make olfactory discriminations (Laurent 1999). For example, in primary sensory neurons, optimal tuning width depends on the dimensionality of the stimulus (Zhang & Sejnowski 1999). For second- and higher-order neurons, the optimality of narrow tuning depends on exactly how narrowing is achieved (Seriès et al. 2004). Another sobering consideration is the difficulty of collapsing high-order olfactory space onto the two-dimensional surface of the OB

in a way that maintains a systematic relationship between the degree of MRR overlap and interglomerular distance (see below, Systematic Progression in Molecular Feature Representation).

If the OB (or AL) is not sharpening tuning curves, what computations is it performing? In particular, what could be the function of inhibitory synaptic interactions so prominent in the OB circuit? There are several possibilities, none of them mutually exclusive. First, inhibitory synapses in the OB/AL may serve an important gain control function. Second, these synapses may be important in orchestrating synchrony among the spikes of second-order olfactory neurons. Third, inhibitory interactions may work together with excitatory interactions to decorrelate odor representations according to a scheme different from the Mori model-for example, by progressively redistributing odor activity across a population of neurons. We discuss these ideas (synchrony, and decorrelation by redistribution) in greater detail below.

SPATIAL DISTRIBUTION OF ODOR RESPONSES

Sensory Maps

It is often said that the OB (or AL) represents a map of odor space. In its most general sense, this statement simply implies that different odors activate distinct spatial patterns of neurons in the bulb. Because we have known for decades that different olfactory neurons show distinct tuning, and because all neurons must be located somewhere, this statement is hardly falsifiable. A more interesting question is whether the OB is truly a map in the sense that other sensory modalities are mapped (Figure 5). Some central sensory maps simply reproduce the spatial organization of peripheral receptor organs-for example, retinotopic maps in visual cortex or somatotopic maps in somatosensory cortex. Isofrequency bands in auditory cortex reproduce the arrangement of hair cells in the cochlea. One might call this a feedforward map. In other cases, the tuning variable that is systematically related to position arises synthetically in central circuitry. This has been termed a computational map. Examples of computational maps include orientation pinwheels in the cat visual cortex, or maps of interaural time difference (corresponding to horizontal spatial location) in the owl optic tectum (Knudsen et al. 1987).

Following Knudsen et al. (1987), a map can be defined as a sensory representation where (*a*) responses to particular stimuli are spatially clustered, rather than scattered uniformly, and (*b*) where there is a systematic relationship between a neuron's tuning and its spatial position. Not all features for which neurons are specifically tuned are necessarily mapped in brain space. Is odor space mapped in the OB according to this definition? If so, what sort of map is this?

Chemotopy

Certainly the OB fulfills the first of these two criteria defining a sensory map. M/T cells responding to a given odor are not distributed uniformly across the OB. This has been apparent since the earliest days of OB recordings and has been confirmed by subsequent electrophysiological studies. More recently, optical techniques (imaging intrinsic signals, Ca²⁺ concentration, voltage, 2deoxyglucose uptake, immediate-early gene expression, blood flow, or synaptic vesicle release) have permitted a more efficient and comprehensive mapping of the spatial distribution of odor responses. These studies have shown that in general the glomeruli activated by a monomolecular odorant are loosely clustered rather than uniformly scattered across the OB surface (Figure 5). On the dorsal surface of the mammalian OB, responses to aliphatic aldehydes and carboxylic acids tend to cluster disproportionately in the anteromedial portion of the bulb. Responses to ketones, aliphatic alcohols, and phenols cluster in the lateral portion. Responses to



Spatial representations of sensory stimuli. (*a*) A feedforward map. The surface of the hand is represented in somatosensory cortex in a way that systematically preserves the spatial relations of mechanoreceptors in the skin. (*b*) A computational map. Preferred stimulus orientation is represented systematically and continuously as pinwheels in visual cortex. Orientation is not represented explicitly by upstream neurons in the visual stream, but rather is computed locally in the cortex. (*c*) Olfactory representations. Odors are represented on the surface of the olfactory bulb according to a gross chemotopy. It is not yet clear whether the bulb contains an olfactory map, i.e., a systematic relationship between particular chemical variables and glomerular position.

hydrocarbons cluster in the ventral portion of the bulb (Rubin & Katz 1999, Johnson & Leon 2000, Uchida et al. 2000, Meister & Bonhoeffer 2001, Wachowiak & Cohen 2001, Inaki et al. 2002, Spors & Grinvald 2002, Xu et al. 2003, Bozza et al. 2004, Takahashi et al. 2004a, Igarashi & Mori 2005). Similarly, amino acids, bile acids, and nucleotides activate distinct but partly overlapping regions of the zebrafish OB (Friedrich & Korsching 1998).

Together, these studies support the notion that nearby glomeruli tend to have more overlapping MRRs than do distant glomeruli. In other words, the OB appears to display a rough chemotopy, meaning that glomerular position is related to glomerular MRR. This is an important and nontrivial conclusion. A conceptual distinction should be made between this idea and the idea that chemically similar odors activate similar spatial patterns of activity. The latter conclusion is relatively trivial. Insofar as chemically similar odors tend to interact with ORs in a similar way, they will activate similar populations of ORNs and similar glomeruli. This in itself demonstrates neither chemotopy nor mapping.

Exactly how tightly clustered are the glomeruli that respond to a single odor? Most of these studies have not been able to examine this issue at the level of single glomeruli, instead focusing on broad regional divisions in the bulb. There is recent evidence that, at the spatial scales of single glomeruli, OB chemotopy breaks down. When single glomeruli are resolved by applying a high-pass spatial filter to intrinsic signals, it appears that nearby glomeruli can differ dramatically in their odor tuning (Fantana et al. 2002). This Annu. Rev. Neurosci. 2006.29:163-201. Downloaded from arjournals.annualreviews.org by HARVARD UNIVERSITY on 07/17/06. For personal use only.

is consistent with older electrophysiological data, which shows that M/T cells separated by a few glomerular diameters can have very different MRRs (Buonviso & Chaput 1990, Buonviso et al. 1992, Motokizawa 1996). Of course, the latter could also reflect postsynaptic processes that might work to decorrelate M/T responses in neighboring glomeruli. However, there is also evidence that ORN inputs do not obey a rigid fine-scale chemotopy, as the relative positions of near-neighbor glomeruli vary across individual animals (Strotmann et al. 2000). Also, a recent functional imaging study using a genetically encoded sensor localized to ORNs, and capable of singleglomerulus resolution, reported less finely organized chemotopy than had been previously imagined (Bozza et al. 2004).

Systematic Progression in Molecular Feature Representation

The second criterion defining a neural map is a systematic relationship between a neuron's tuning and its spatial position. Several studies of intrinsic signals or 2-deoxyglucose uptake have reported a systematic relationship between glomerular position and the carbon chain length of the optimal odor stimulus. These studies have used homologous series of aliphatic aldehydes, carboxylic acids, alcohols, and esters (Johnson & Leon 2000, Uchida et al. 2000, Belluscio & Katz 2001, Meister & Bonhoeffer 2001). However, some investigators have recently challenged this finding (Bozza et al. 2004). One proposed alternative explanation for the shift seen with carbon chain length is that molecules with shorter carbon chains have higher vapor pressures, meaning that if all test odors are used at the same dilution, molar concentration varies systematically across each homologous series.

Systematic directional representations of other chemical features (size, polarity, etc.) have not been described in the OB. Indeed, given the high dimensionality of odor space, it is not obvious how a truly systematic representation of all salient odor properties could be accomplished in two dimensions. Although sensory maps may contain a few fractures such as the centers of visual cortex orientation pinwheels (**Figure 5**)—any two-dimensional projection of chemical space would be far more discontinuous. It will be difficult to determine whether chemical space is truly mapped onto the OB in this sense. If so, this would not be a feedforward map, as no such organization exists in the sensory epithelium.

ODOR-EVOKED TEMPORAL PATTERNS

Temporal Coding: A Definition

Many investigators, beginning with the pioneering work of E.D. Adrian (1950), have suggested that the temporal spike pattern of a second-order olfactory neuron encodes information about odor quality. This has been proposed to constitute a temporal code for odors. The term temporal code is sometimes applied to any neural response where spike timing carries information to a potential decoder. However, this usage tends to muddle the debate. Dayan & Abbott (2001) have suggested a useful definition: A temporal code is a neural response where information about the stimulus is contained in spike fluctuations on timescales faster than the fastest timescales of stimulus fluctuation. According to this definition, a neuron firing bursts of spike trains at 5 Hz in response to a 5 Hz visual flicker would not constitute a temporal code. However, the same bursts could plausibly represent a temporal code if they carried specific information about odor identity in response to a one-second square wave odor pulse. By this criterion, OB temporal patterns fluctuate rapidly enough to qualify as potential temporal codes, relative to the timescales of the odor test stimuli that elicited these responses. In principle, we could also extend Dayan & Abbott's definition to include spike trains that are modulated on timescales substantially slower than the timescales of stimulus fluctuation. Brief (100 ms) odor stimuli produce odor-specific temporal spike patterns that evolve over seconds (Brown et al. 2005). If these patterns were informative to downstream neurons, they would constitute a temporal code as well.

Temporal Patterns on the Theta Scale

In terrestrial mammals, respiration produces a rhythmic pattern of airflow over the olfactory mucosa. In some M/T cells, this produces a rhythmic pattern of spontaneous activity with a period equal to the respiratory theta cycle, approximately 4–8 Hz (Onoda & Mori 1980). Recent results in brain slices show that the OB network also has an intrinsic tendency to burst rhythmically at these frequencies (Isaacson 1999, Schoppa & Westbrook 2001, Balu et al. 2004, Hayar et al. 2004).

Odor stimulation substantially increases the respiration locking of M/T spikes (Sobel & Tank 1993). In a given M/T cell, the distribution of spikes evoked by a sustained pulse of a given odor tends to peak reproducibly at a particular point in the respiration cycle (Figure 6). This peak can be anywhere in the cycle, corresponding to either inhalation, exhalation, or somewhere in between (Buonviso et al. 1992). Many odor responses in the bulb contain a period of inhibition within the respiration cycle, when a M/T cell is hyperpolarized and its spike rate falls below baseline. An inhibitory epoch can either precede or follow an excitatory burst, and some M/T odor responses are purely inhibitory. The result is a substantial qualitative and quantitative diversity in the temporal distribution of spikes within the respiration cycle (Figure 6). We term this theta-scale patterning. Importantly, theta-scale patterns are odor and cell specific (Macrides & Chorover 1972, Chaput & Holley 1980, Wellis et al. 1989, Buonviso et al. 1992, Motokizawa 1996, Margrie et al. 2001, Cang & Isaacson 2003).

Olfactory stimuli also elicit odor-specific temporal patterns in antennal lobe PNs.

These patterns can occur on timescales similar to theta-scale patterns in vertebrates (Kanzaki et al. 1989, Perez-Orive et al. 2002, Stopfer et al. 2003, Lei et al. 2004). And although respiration does not produce periodic theta-scale odor sampling in insects, flying insects are likely to repeatedly encounter fragments of the same odor plume (Vickers 2000). Such brief, repetitive odor stimuli reliably elicit characteristic temporal patterns in PNs (Brown et al. 2005). Importantly, PNs innervating the same glomerulus, but recorded in different individuals, generate similar odor-specific temporal patterns (Wilson et al. 2004b). This suggests that the mechanisms underlying these stereotyped glomerulus-specific patterns may be developmentally specified.

What mechanisms underlie these patterns? Because ORNs are recruited serially, in descending order of their OR's affinity for the ligand, inhalation or odor onset will produce a temporally patterned input to secondorder neurons. Similarly, a single odor can elicit kinetically distinct off-responses in different ORNs (de Bruyne et al. 2001), and this will produce patterned input during exhalation or odor termination. These temporally patterned ORN inputs should recruit an odor-specific sequence of polysynaptic interglomerular inputs onto M/T cells and PNs. However, there is also evidence that some temporal patterning is intrinsic to central olfactory circuits and does not merely reflect staggered ORN recruitment. In locusts, for example, a single electrical shock to the antennal nerve elicits complex temporal patterns in PN spike trains (Wehr & Laurent 1996).

Temporal Patterns on Slower Timescales

Odors can also elicit slower temporal patterns (on the order of several seconds) in second-order olfactory neurons. These are prominent in insects and in nonmammalian vertebrates (fish and amphibians) lacking a



A model of odor encoding by theta-scale temporal patterning. The respiratory cycle draws air periodically over olfactory receptors. Below, rasters show the timing of spikes in four hypothetical second-order olfactory neurons in the bulb. When odor is present, each of these cells spikes at characteristic time points in the respiratory cycle. Because different odor stimuli produce somewhat different characteristic spike times in each cell, this information could potentially be used by downstream neurons to help identify the odor. Downstream neurons survey inputs from multiple second-order neurons and respond only if coactivated by a sufficient fraction of their inputs. In this example, the hypothetical neuron integrating inputs from cells 1, 2, and 4 is activated by the odor, whereas neurons integrating inputs from other input combinations are not. This converts the temporal code into a neuron-identity code. In insects, there is evidence that third-order neurons detect co-activation of specific PN combinations, have high thresholds, integrate over ~50-ms timescales, and fire just one or a few spikes per stimulus event (Perez-Orive et al. 2002).

respiration cycle (Meredith & Moulton 1978, Duchamp 1982, Hamilton & Kauer 1989. Friedrich & Laurent 2001, Perez-Orive et al. 2002). Whether mammalian M/T spike trains also encode information in very slow temporal patterning across respiration cycles is less clear. There is some evidence for crosscycle temporal profiles outlasting the nominal stimulation period, but in none of these cases was a detailed analysis of patterns attempted (Chaput & Holley 1980, Luo & Katz 2001, Spors & Grinvald 2002). An important limitation of all the mammalian studies is that they were carried out in anesthetized animals. In awake animals, behavioral variables can strongly modulate responses on these slow timescales (see below, Olfactory Processing in Awake, Behaving Animals).

Odor Encoding with Temporal Patterns

What specific computations might temporal patterns implement? Laurent and colleagues (Friedrich & Laurent 2001) have suggested that these patterns represent a progressive decorrelation of the spatial patterns elicited by similar odors. This idea arises, in part, from recordings of zebrafish M/T cells. Odor stimuli for this study were amino acids important to fish ecology. The degree of similarity between any pair of these odors could be defined in terms of zebrafish ORN responses on the basis of a previous functional imaging study (Friedrich & Korsching 1997). These recordings showed that similar amino acids initially elicited similar responses from a given M/T cell, but that over time these responses diverged. From the point of view of the entire M/T ensemble, similar amino acids initially elicited similar spatial patterns of excitation and inhibition, but after several hundred milliseconds, these spatial patterns were no more similar than the spatial patterns elicited by dissimilar stimuli. Also, the MRRs of single M/T cells did not narrow over time; rather, at the time point when an excitatory response to one odor ended, a response to another odor began. ORN responses did not change substantially over time, implying that these temporal patterns arise in the bulb. Like Mori and colleagues (Yokoi et al. 1995), these investigators hypothesized that the function of OB circuitry is to decorrelate responses to similar stimuli. However, their model proposes that this is accomplished by redistributing activity across the M/T cell ensemble, rather than by narrowing the MRRs of M/T cells.

One caveat of this study is that the temporal patterns of zebrafish M/T cells are notably slow and were not analyzed on timescales finer than 200 ms. In other species, a similar process may occur on faster timescales. In the locust AL, the discriminability of ensemble odor responses increases progressively over the first 200–300 ms after stimulus onset, when spatiotemporal patterns among PNs are evolving rapidly (Stopfer et al. 2003).

Decoding Temporal Patterns

A critical issue in evaluating putative temporal codes is whether and how they are decoded. We have specified two criteria defining a temporal code: (*a*) the spike fluctuations of a neuron must be faster than stimulus fluctuations and (*b*) spike fluctuations must contain information about the stimulus from the point of view of a decoder. How can we assess what information is available to a decoder?

A useful approach is to analyze spike trains using a particular algorithm that tries to decode the odor stimulus that generated that spike train. By applying this algorithm to different time points in a neural response, investigators can estimate the timescales on which spikes could be informative to downstream neurons. In recent studies of PNs, algorithms based on Euclidean distance and principal component analysis (PCA) show a progressive increase in decoding success over the first several hundred milliseconds of the ensemble response; another informative epoch in the ensemble odor response occurs in the 300 ms after odor offset. Downstream mushroom body neurons-the natural decoders of PN signals-fire odor-specific spikes during these informative epochs, but are nearly silent at other times (Stopfer et al. 2003, Mazor & Laurent 2005). This is consistent with the conclusion that these time windows define informative epochs from the organism's point of view. Note that recordings cannot be collected simultaneously from all the cells in the same preparation. Thus, these studies decoded virtual ensembles of cells recorded at different times and in different animals and could not therefore consider the effects of interneuronal correlations, which may affect the representation of information in a population (Zohary et al. 1994, Abbott & Dayan 1999).

In these analyses, the goal was to track decoding success over time, given the fixed assumptions of a particular algorithm. To provide an optimal readout of the information available in a spike train, it would be necessary to use ideal-observer decoding methods that have been developed in other sensory systems (Geisler 2003). An ideal observer is an optimal algorithm for classifying a neuronal signal into one of several discrete alternatives (e.g., odor identities). Ideal observers come in many forms, each expressing different assumptions about coding. As much as possible, these assumptions should be constrained by empirical observations. For example, in the locust olfactory system, neurons postsynaptic to the AL integrate incoming spikes over very brief, 50ms time windows that are periodically reset by network oscillations (Perez-Orive et al. 2002). Decoding using such a coincidence detector means that sequential patterns are lost to these neurons. Instead, as the population of odorresponsive neurons evolves, downstream

neurons may simply read out one ensemble code after another (Figure 6). In this scheme, odors are encoded as an ensemble of ensembles.

By comparing classifiers built on different assumptions (i.e., different ways of reading the spike trains), one can assess their relative information content. Important constraints can come from comparing the performance of different classifiers to the behavior of an animal in an analogous task (see below, Odor Discrimination). In particular, it is important to understand which timescales actually carry information relevant to behavioral tasks. Recent studies have shown that trained rats and mice can make accurate olfactory discriminations within 200-300 ms. This is strong evidence that, under these conditions, any temporal patterns must be decoded within this time (Uchida & Mainen 2003, Abraham et al. 2004). This window could encompass within-sniff temporal patterns in mammals and some of the faster patterns described in insects. There is also evidence that previous exposure to the test odor increases spike precision (Stopfer & Laurent 1999) and the speed of odor-evoked temporal patterns (Harrison & Scott 1986), suggesting that temporal coding may be faster in trained animals than naïve ones. These issues should be resolved by a combination of psychophysical and physiological measurements. We also need to better understand the behavioral task parameters that govern odor discrimination latencies in psychophysical assays.

ODOR-EVOKED SYNCHRONOUS OSCILLATIONS

Local Field Potential Oscillations

In many sensory brain regions, sensory stimuli trigger oscillations in the local field potential (LFP), which is an average measure of current density in the region of the recording electrode. LFP oscillations imply that currents are flowing roughly synchronously in an oscillatory pattern through neurons in the

recorded region. Stimulus-evoked LFP oscillations have been studied in the visual cortex, but are also found widely throughout cortical and subcortical areas (reviewed in Gray 1999). The original report of LFP oscillations dates to the first electrophysiological recordings from the hedgehog OB (Adrian 1942). Since then, LFP oscillations have been described by many investigators in the awake and anesthetized OB (Freeman 1978, Mori et al. 1992, Friedrich & Laurent 2001). Odor-evoked LFP oscillations are also prominent in the AL of locusts, bees, and moths (Laurent & Davidowitz 1994, Stopfer et al. 1997, Heinbockel et al. 1998). The amplitude of LFP oscillations increases with increased odor concentration or prior odor exposure and in some behavioral states (Kay & Freeman 1998, Stopfer & Laurent 1999, Stopfer et al. 2003).

Such oscillatory synchrony is sometimes termed emergent synchrony because it is an emergent property of large neural ensembles. This is conceptually distinct from synchrony that simply reflects the coactivation of two neurons by the same stimulus or by the same presynaptic neurons. In the OB, gammaband oscillations (35-80 Hz) are thought to emerge from dendrodendritic interactions between M/T cells and GABAergic granule cells (Rall & Shepherd 1968, Gray & Skinner 1988, Neville & Haberly 2003). However, the slow kinetics of dendrodendritic interactions does not fit neatly with the faster timescales of OB synchrony. In the AL, there is evidence that gamma oscillations arise from dendrodendritic interactions between principal neurons and GABAergic LNs (MacLeod & Laurent 1996). Chemical and electrical coupling between principal cells may also enforce fine-scale synchrony (Schoppa & Westbrook 2002, Urban & Sakmann 2002).

In general terms, not all neural synchrony is necessarily oscillatory, and not all oscillations in membrane potential or spike rate are necessarily synchronous across neurons. Also, although roughly coincident activity of two olfactory neurons has been termed synchrony (Lei et al. 2002), this use of the term is confusing. Conventionally, single spikes in two different neurons are termed synchronous if the difference in their timing is substantially smaller than the current typical interspike interval in either neuron (Usrey & Reid 1999). Spike-timing coincidences on timescales longer than the interspike interval simply reflect the fact that two neurons are firing at high rates.

Synchrony in Neural Codes

What is the impact of oscillatory synchrony on odor coding? Synchronous oscillations in the olfactory system redistribute spikes into a particular phase of the oscillatory cycle (Eeckman & Freeman 1990, Laurent & Davidowitz 1994, Heinbockel et al. 1998, Kashiwadani et al. 1999, Perez-Orive et al. 2002). Because gamma oscillations are approximately coherent across the OB, they can increase spike coincidence among even spatially distant neurons (Freeman 1978, Kashiwadani et al. 1999). If these neurons synapse onto a common postsynaptic cell, their synchrony should increase their ability to drive postsynaptic spikes. There is evidence that single neurons are not equally synchronized to population oscillations at all time points in an odor response. Individual neurons in the OB or AL appear to be phase-locked in some cycles, but not all cycles (Laurent & Davidowitz 1994, Wehr & Laurent 1996, Kashiwadani et al. 1999, Lam et al. 2000). During the cycles when a neuron is phaselocked to the LFP oscillation, it should have a disproportionate impact on postsynaptic targets.

Although synchronous oscillations should increase the impact of phase-locked odorevoked spikes for downstream decoders, these considerations do not necessarily imply that olfaction requires such oscillations. Consistent with this, there is evidence that disrupting synchronous oscillations affects fine olfactory behavioral discriminations, but does not prevent coarse discriminations (Stopfer et al. 1997, Teyke & Gelperin 1999). Furthermore, gamma-band synchronous oscillations are evidently absent from the immature rat OB and the *Drosophila* AL (Fletcher et al. 2005, Wilson & Laurent 2005), and the olfactory prowess of these animals is not especially poor.

Hopfield (1995) has pointed out that oscillations could also serve other functions in olfactory processing. Synchronous oscillations in a population of neurons will convert information about input intensity into spiketiming information. This could be used by a neural network to detect when a specific ensemble of neurons is being driven to approximately equal levels and, thereby, to compare odor-evoked activity to a stimulus template (Brody & Hopfield 2003).

Because odor-evoked oscillations have been studied in detail only in insects, more work is required to clarify the role of oscillations in vertebrate olfactory processing. First, there is still no strong evidence that odors are encoded by differential synchrony in any vertebrate system; this needs to be tested experimentally. Second, the vertebrate olfactory system exhibits multiple oscillation frequencies; future experiments should aim to clarify which frequency bands dominate in each olfactory region during olfactory behavior and how fast or slow oscillations may serve different functions in olfactory processing.

OLFACTORY PROCESSING IN AWAKE, BEHAVING ANIMALS

Top-Down Influences on Bulb Processing

The bulb receives nonolfactory information from multiple sources. These can be separated broadly into three classes. First, olfaction is an active sense, particularly in mammals, for whom sniffing is required to bring odorant molecules into the nasal cavity. The rate and depth of sniffing are controlled via central pattern generators in the brainstem, which in turn are subject to forebrain control (Ramirez & Richter 1996). Thus, the sniffing

Second, the bulb receives reciprocal projections from most of its output regions, including the olfactory cortex, amygdala, and hippocampal formation (de Olmos et al. 1978, Shipley & Adamek 1984). Some of these connections, particularly with the olfactory cortex, are short range and form tight feedback loops. The majority of these connections target granule cells, via a class of dendritic spines distinct from those involved in the reciprocal M/T cell dendrodendritic interactions (Price & Powell 1970a). This implies that cortical feedback to the bulb should have a net inhibitory effect. However, in awake animals, inactivating the olfactory cortex reportedly reduces M/T cell firing rates, while increasing the coherence of rhythmic bursting (Gray & Skinner 1988). Furthermore, the function of cortical feedback is still a wide-open question. One intriguing possibility is that cortical feedback supplies top-down expectations in the form of an odor search image that is used to facilitate detection of that odor. Such top-down processing is prominent in the visual system (Tsodyks & Gilbert 2004).

The third class of centrifugal influences comes from diffuse ascending neuromodulators (norepinephrine, acetylcholine, and serotonin). Norepinephrine and acetylcholine target primarily the external plexiform layer. where M/T cell-granule cell synapses are formed. By contrast, serotonin targets primarily the glomerular layer (McLean & Shipley 1987). Serotonin excites juxtaglomerular cells via 5HT2c receptors and excites M/T cells via 5HT2a receptors (Hardy et al. 2005). All three of these modulators have been implicated in olfactory learning using the paradigm of neonatal olfactory conditioning (Sullivan & Wilson 1994, McLean et al. 1996, Price et al. 1998, Wilson et al. 2004a). Less is known about learning in adult animals, although norepinephrine release has been reported during olfactory reinforcement learning (Bouret & Sara 2004).

How do modulators affect OB function? Generally speaking, norepinephrine and acetylcholine are thought to have a role in controlling attention, setting the gain of neural circuits in a task-appropriate manner, allocating memory, and detecting uncertainty about stimuli (Hasselmo 1999, Bouret & Sara 2004, Aston-Jones & Cohen 2005, Yu & Davan 2005). The function of the serotonin system remains more mysterious. In the brain stem, serotonin modulates respiratory drive (Richerson 2004). In the olfactory bulb, serotonin input could provide an efference copy of such respiration-related signals. Serotonin is also widely implicated in the control of oscillations (Jacobs & Fornal 1993).

In sum, these considerations suggest strongly that it is necessary to approach vertebrate olfactory processing in a broader behavioral context, rather than as a simple feedforward behavioral pathway. Experiments in awake, behaving animals are needed to determine how these descending projections influence OB odor responses.

Recordings in Awake, Behaving Animals

Most OB physiology has been performed in vitro or in anesthetized animals. Adrian (1950) documented the profound affect of anesthesia on the electrical activity of the OB using LFP recordings. Later, Freeman & Skarda's (1987) studies on awake animals using multi-electrode LFP arrays documented complex spatiotemporal dynamics in the bulb and built a dense body of theoretical work that has remained largely unpenetrated by subsequent researchers. Nevertheless, some of the most striking and important conclusions of this early work have so far held true. In the awake animal, the responses of OB neurons are determined not solely by the stimulus itself, but also by the behavioral state. Responses are highly dynamic, changing with exposure to the stimulus, with learning, and with the expectations of the animal.

In awake animals, OB LFP oscillations span the theta (4-12 Hz), beta (12-35 Hz), and gamma (35-80 Hz) frequencies. The thetafrequency oscillations occur at a frequency similar to the sniffing cycle, but the two may not always be synchronized in behaving animals (Chaput & Holley 1980, Bhalla & Bower 1997, Kay & Laurent 1999), perhaps owing to centrifugal influences (Gray & Skinner 1988). Gamma oscillations are typically coupled to the theta waves (Kay & Freeman 1998). In behaving animals these different modes of oscillations appear to be state and context dependent, and their relationship to olfactory processing needs clarification. Whereas gamma oscillations are more prominent in anesthetized animals, beta oscillations are more common in awake animals. Beta and gamma oscillations tend to appear during different behavioral states (Martin et al. 2004) and are linked to different parts of the respiration cycle (Buonviso et al. 2003). Bursts of beta oscillations are observed during odor sampling, are increased by learning (Kay & Freeman 1998, Martin et al. 2004), and depend on intact feedback pathways from olfactory cortex (Neville & Haberly 2003). Interestingly, certain noxious odors such as toluene can elicit similar beta oscillations in anaesthetized animals (Vanderwolf 1992, Neville & Haberly 2003), which may be related to their ethological meaning as antifeedants (Vanderwolf & Zibrowski 2001).

Single-unit OB recordings in awake, behaving animals have been relatively rare (Pager 1983, Chaput & Holley 1985, Pager 1985, Bhalla & Bower 1997, Kay & Laurent 1999, Rinberg et al. 2004a, 2004b). Compared with an anesthetized preparation, in which odor-selective neurons are encountered relatively frequently, surprisingly few OB neurons appear to be odor selective in behaving animals. Kay & Laurent (1999) recorded singleunit responses in the OB of rats performing an odor discrimination task. Strikingly, although only approximately 10% of M/T units were significantly modulated by the identity of the odor presented, >90% of M/T units showed some modulation by the task contingencies, namely whether the odor was associated with reward or not. Comparison of the same neurons in different states (anesthetized versus awake) may shed light on this issue (Rinberg et al. 2004b).

THE PROBLEM OF STIMULUS DISCRIMINATION

The final part of this review considers, from behavioral, physiological, and theoretical perspectives, three important olfactory tasks: odor discrimination, concentration-invariant recognition, and odor segmentation.

Odor Discrimination

A variety of behavioral paradigms have been used to probe a subject's ability to discriminate between odors. Studies in rodents have typically used operant conditioning paradigms (Slotnick 1994, Schoenbaum & Eichenbaum 1995, Bodyak & Slotnick 1999, Kay & Laurent 1999, Uchida & Mainen 2003, Abraham et al. 2004, Bouret & Sara 2004, Martin et al. 2004). In these paradigms (also known as reinforcement learning) differential reward or punishment produces odor-specific behavioral responses (e.g., pushing different levers or making different nose pokes). This form of learning relies on feedback about the outcome of an animal's actions. This stands in contrast to classical conditioning tasks, in which a neutral odor stimulus (the conditioned stimulus) is paired with an intrinsically significant stimulus (the unconditioned stimulus) that produces a specific response (e.g., freezing). Classical conditioning has been the dominant paradigm in insect olfactory psychophysics (Quinn et al. 1974, Smith & Menzel 1989, Daly & Smith 2000).

Extensive reinforcement training is very powerful. Rodents can learn to discriminate between virtually any pair of pure odors,

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including highly related stereoisomers or even binary mixtures of stereoisomers (Lu & Slotnick 1998, Rubin & Katz 1999, Linster et al. 2002, Uchida & Mainen 2003), and these discriminations can be made within 200-300 ms (Uchida & Mainen 2003, Abraham et al. 2004). Rats can even perform difficult odor discrimination problems after extensive lesions of the OB (Lu & Slotnick 1998). Do such feats imply the need for special processing mechanisms? Computationally, the answer is likely "no." For a two-alternative decision (e.g., go/no-go or left/right), just a single bit of information must be extracted from the entire sensory ensemble. Thus, odor discrimination is a fundamental task of olfactory processing, but is not necessarily a computationally difficult problem in the context of a constrained behavioral scenario.

An important avenue for future experiments will be to combine discrimination paradigms with simultaneous measurement of activity in the OB. However, a challenge in interpreting this data is to disambiguate olfactory and nonolfactory information (the influences of reward and other task contingencies carried by centrifugal inputs). This is particularly true of the widely-used go/no-go paradigm in which one odor is reinforced with reward and the other odor is unreinforced or reinforced with punishment. In this way, comparisons between odor responses cannot readily distinguish the identity of the odor and the value of the reward. There are solutions to this problem, including the use of a twoalternative choice paradigm in which odors are rewarded at different locations (Uchida & Mainen 2003) and the use of contingency reversals in which the value of the odors is reversed (Schoenbaum et al. 2000).

Concentration-Invariant Recognition

A fundamental problem of sensory neuroscience is how the brain disambiguates stimulus quality from intensity. In the visual system, for example, one puzzle is how cortical

neurons preserve strict orientation selectivity with increasing stimulus contrast (Ferster & Miller 2000). In olfaction, the analogous problem is the concentration invariance of odor quality. In our everyday experience, odor quality is generally similar across wide variations in odor concentration. For example, baking bread tends to smell the same, whether vou're a block from the bakery or burying your nose in a freshly cut slice. Although this phenomenon is remarkably poorly documented in the literature (Uchida & Mainen 2004), and there are some notable exceptions to this rule (e.g., Bhagavan & Smith 1997), concentration invariance is probably a general property of olfactory processing. How is this accomplished? To understand the magnitude of the problem, consider two features of OB odor coding: the identity (spatial pattern) of responsive M/T cells, and the temporal patterning of M/T responses. Both change dramatically with odor concentration.

The effect of concentration on spatial response patterns follows from the concentration dependence of ORN responses. It is useful to recall that the response of a given ORN reflects the affinity constant of its OR for the test odor. As concentration increases. ORNs will be serially recruited, starting with the ORNs corresponding to the lowest affinity constants. Some ORNs will never be recruited because their affinity constants are higher than the saturated vapor (SV) concentration for that odor. Nevertheless, many odors recruit large fractions of ORNs even at submaximal concentrations (Duchamp-Viret et al. 2000, Rospars et al. 2003). This recruitment is directly illustrated by functional imaging in the OB and AL: As concentration increases, signals appear in more and more glomeruli (Rubin & Katz 1999, Meister & Bonhoeffer 2001, Wachowiak & Cohen 2001, Wang et al. 2003). Therefore, insofar as the odor code is a spatial (identity) code, it will be confounded by stimulus concentration.

Similarly, temporal codes are also confounded by concentration. Odor-evoked temporal patterns in the OB and AL show SV: saturated vapor

increasing complexity with increasing odor concentration. Similar concentrations of the same odor elicit similar temporal patterns, but across a wide concentration range, the change in patterns can be dramatic. Some aspects of a pattern are compressed, others are expanded. Inhibitory epochs can convert to excitatory ones, or vice versa (Kauer & Moulton 1974, Harrison & Scott 1986, Meredith 1986, Wellis et al. 1989, Stopfer et al. 2003). This presumably reflects an increasing recruitment of polysynaptic inhibitory and excitatory interactions in the bulb at higher concentrations.

Neural Algorithms for Concentration Invariance

Several strategies have been proposed to solve this conundrum. First, we may expect that the ORNs recruited by low concentrations would also be the ORNs with the strongest responses at high concentrations. If so, the relation between ligand-OR affinity and rank-order response magnitude should remain roughly constant across concentrations. Downstream neurons may then be able to identify odors on the basis of the comparative magnitudes of ORN responses, rather than the mere identity of all responsive ORNs (O'Connell & Mozell 1969, Wachowiak et al. 2001). Insects use the ratios of chemical components of pheromones to produce signals that are invariant to concentration changes, facilitating mate recognition (Baker et al. 1976). Rats also adopt a discrimination strategy that exploits the ratios of odor components, suggesting that decoding could involve a mechanism based on comparing the ratios of pairs of receptor activation (Uchida & Mainen 2004). However, a potential complication for this strategy is that although ORN receptor currents increase monotonically with concentration, ORN spike rates can in fact decrease at the highest odor concentrations, presumably reflecting sodium channel inactivation (Reisert & Matthews 2001).

A second, related strategy is for decoder neurons to exploit the relationship between spike timing and concentration. Increasing odor concentration decreases the response latency of ORNs (Reisert & Matthews 1999, Rospars et al. 2003). This transforms spikerate coding into the spike-timing domain, producing a code on the basis of the rank order of recruitment latency (sometimes termed a rank-order code) (VanRullen et al. 2005). Because increasing concentration decreases ORN latencies across the board, this latency code would be concentration invariant (Spors & Grinvald 2002). A latency code is limited to stimulus onset, but during a prolonged odor stimulus, synchronous oscillations in the brain could reset and recapitulate the recruitment order computation with every cycle (Hopfield 1995). In the OB, either the theta respiration rhythm, or faster beta/gamma oscillations, could serve this purpose. However, there is little evidence as yet in support of such a systematic relationship between latency and concentration among second-order olfactory neurons. In the brain, feedforward and feedback inhibitory and excitatory intrabulbar circuits may produce a complex relationship between stimuli and patterns.

A third potential strategy also exploits spike-timing information in an ensemble, but on timescales that extend beyond onset latency to encompass synaptic dynamics in the brain. This idea derives in part from recordings in the locust, where temporal patterns in individual PNs change unpredictably with concentration. However, when these spike trains are decoded across large ensembles, relatively odor-specific and concentrationinvariant sequences of activity emerge in this high-dimensional encoding space. This means that ensemble responses to different concentrations of the same odor share more elements (namely, the identity of activated PNs and times of coactivation) than do responses to different odors. Furthermore, the responses of neurons downstream from PNs are highly odor-specific, and some of these

responses are concentration-invariant (Stopfer et al. 2003). This implies that some downstream neurons witness roughly the same odor-specific PN ensembles regardless of odor concentration.

What Concentrations Are Relevant for Olfactory Processing?

Some investigators have suggested that only low odor concentrations are physiological or biologically relevant (Wang et al. 2003, Lin et al. 2005). However, at present, there is virtually no data on the natural statistics of chemical experience, especially in comparison to the large literature on natural visual statistics. Thus, an important distinction needs to be made between naturalistic concentrations and physiological concentrations. Two criteria can reasonably define physiological concentrations: These concentrations must (a) lie within the dynamic range of the ORN ensemble and (b) support olfactory discrimination behavior. The evidence suggests that, according to these critera, a wide range of concentrations should be considered physiological.

First, the dynamic range of the ORN ensemble spans several orders of magnitude. Electrophysiological recordings of ORNs in vivo document odor thresholds in the range of 0.00001-0.001% SV. As concentration increases, ORNs with the lowest threshold can saturate before 0.1-1% SV, but highthreshold ORNs are still within their dynamic range near 100% SV (de Bruyne et al. 1999, Duchamp-Viret et al. 2000, de Bruyne et al. 2001, Meister & Bonhoeffer 2001, Bozza et al. 2004). Second, behavioral experiments show that subjects can perform olfactory discriminations over a similarly wide range of concentrations. Consistently, increasing odor concentration produces more accurate odor quality discrimination (Pelz et al. 1997, Cleland & Narla 2003, Wright & Smith 2004). This is the opposite of what one would expect if only low concentrations (activating sparse ensembles) were decipherable to downstream decoders. In the future, it will be important not just to characterize the natural statistics of odor experience, but also to understand how the olfactory system can perform so well under such a wide range of stimulus conditions.

The Problem of Odor Segmentation

A final important problem for olfaction is that of odor segmentation, the ability to identify individual odor objects in a sea of background odors. This may be likened to the "cocktail party problem" in audition—how does one pluck a unique voice out of a cacophony of conversation? Because olfactory information is mixed thoroughly at the receptor level, how is it possible to segment the data to recover the original sources?

The simplest form of odor segmentation is the ability to identify a single odor despite the presence of background odors, termed background suppression. Adaptation can provide background invariance by suppressing the responses to continuously present odors. Background invariance may also benefit from imperfect mixing. Hendin et al. (1994) used temporal fluctuations in concentration to segment multiple odor sources. This algorithm makes use of the idea that separate odor sources will be conveyed to the subject by different air currents producing unique temporal patterns. The algorithm can parse out different odor sources by latching onto the temporal correlations between groups of receptors.

A more difficult computation is the ability to separate several different blended chemicals from one another (mixture segmentation)—for example, in distinguishing the different fruits making up the bouquet of a wine or the different spices in a stew. But mixture segmentation is not simply a problem for wine connoisseurs and chefs. Humans can identify as many as 8–12 familiar odors in a blend (Jinks & Laing 1999) and rodents can likely do better. For example, the

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components of urine convey a number of distinct pieces of information—genomic information such as species, sex, and individual identity, as well as variable metabolic information such as one's current social, reproductive, and health status, and food resources (Hurst & Beynon 2004).

In general, blind source separation is an important problem in signal processing, and the olfactory system may adopt algorithms similar to those at work in other systems. The olfactory system may also exploit its unique advantages. Hopfield (1999) described algorithms for background suppression and segmentation that exploit the large number of ORs. These algorithms have been implemented in a neural model using spike-timing computations (Brody & Hopfield 2003). An important requirement of many algorithms is that before odor segmentation is achieved, different sources should interact in a linear or quasi-linear fashion. Imaging at the glomerular level has so far suggested roughly linear additivity (Belluscio & Katz 2001), but there is evidence for more complex, and even antagonistic, actions between ligands at ORs (de Bruyne et al. 2001; Duchamp-Viret et al. 2003; Oka et al. 2004a,b). Furthermore, strongly nonlinear synaptic interactions appear to occur within the OB and cortex. Together, all these nonlinearities likely contribute to incomplete odor segmentation. This can be useful; the phenomenon of odor masking, for example, can hide malodors in food (Laing et al. 1989, Takahashi et al. 2004b).

CONCLUSIONS

The study of olfactory processing may no longer be in its infancy, but it has not yet matured beyond a stormy adolescence. There is no consensus in the field on many fundamental issues. This review notes some of the pressing questions we find most interesting. Future progress depends in part on technical innovations-expression systems for ORs, high-resolution functional imaging of the OB/AL, genetic markers for specific glomeruli, and simultaneous large-ensemble recording in awake, behaving animals. But other obstacles are conceptual rather than technological. How can we envision odor space and explore it systematically in our experiments? If the olfactory system does not detect molecular features that are easy to conceptualize, how can we design experiments that illuminate the basic principles of olfactory processing? How can we follow transformations in a hierarchical processing stream if there are so many unique glomerular information channels? Fifteen years ago, molecular genetics revolutionized olfaction. These studies not only revealed a precise molecular patterning of receptor neuron projections, but also provided a conceptual handle on a system that had been described as "utter chaos" (Gesteland et al. 1965). Now, the challenge is to push our understanding of olfactory coding beyond the receptor level and to fathom how the brain decodes information in this uniquely high-dimensional and mysteriously evocative sensory modality.

ACKNOWLEDGMENTS

The authors thank Vikas Bhandawat, Vivek Jayaraman, and Adam Kepecs for critical comments on earlier versions of the manuscript. Work in our laboratories is funded by the Pew Charitable Trusts (R.I.W.), a Smith Family New Investigator Award (R.I.W.), a Loreen Arbus Scholarship in Neuroscience (R.I.W.), the Swartz Foundation (Z.F.M.), and the National Institutes of Health (Z.F.M., R.I.W.).

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ERRATA

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