Early Olfactory Processing in *Drosophila*: Mechanisms and Principles

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Annu. Rev. Neurosci. 2013. 36:217–41

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

This article's doi: 10.1146/annurev-neuro-062111-150533

Keywords

olfactory receptor neurons, transduction, synapses, antennal lobe, concentration, lateral inhibition

Abstract

In the olfactory system of *Drosophila* melanogaster, it is relatively straightforward to target in vivo measurements of neural activity to specific processing channels. This, together with the numerical simplicity of the *Drosophila* olfactory system, has produced rapid gains in our understanding of *Drosophila* olfaction. This review summarizes the neurophysiology of the first two layers of this system: the peripheral olfactory receptor neurons and their postsynaptic targets in the antennal lobe. We now understand in some detail the cellular and synaptic mechanisms that shape odor representations in these neurons. Together, these mechanisms imply that interesting neural adaptations to environmental statistics have occurred. These mechanisms also place some fundamental constraints on early sensory processing that pose challenges for higher brain regions. These findings suggest some general principles with broad relevance to early sensory processing in other modalities.

Contents

INTRODUCTION

This review focuses on the physiology of the first stages of the adult olfactory system in *Drosophila melanogaster*. Recent reviews have surveyed the development of this system (Brochtrup & Hummel 2011) as well as that of homologous structures in the larvae (Stocker 2008). These topics are not covered here. The study of olfactory processing in *Drosophila* also owes an enormous debt to the study of olfactory processing in other insects—chiefly locusts, moths, and bees (Martin et al. 2011)—but that literature is not reviewed here for space reasons.

This review is divided into two major sections corresponding to the first two layers of the olfactory system. Each section begins with general observations of how odors are represented in one of these layers, followed by a discussion of the underlying mechanisms at play in that layer. Next, I have tried to extract some general principles and to relate them to higher olfactory processing and the challenges faced by the organism. Finally, each section closes with a summary of key open questions.

Why the fly? One can perform certain experiments in *Drosophila* that are not currently possible in any other species. In particular, one can easily monitor neural activity from individual neurons corresponding to a targeted olfactory processing channel. These neurons are "identified" in the strongest sense of the word: Not only do they have known (or knowable) connectivity to other neurons in the circuit, but their connectivity and odor responses are also relatively stereotyped across individuals.

A major reason for studying the *Drosophila* olfactory system is its strong similarity to the vertebrate olfactory system. Beyond this, there are also looser analogies between the anatomy of this structure and that of other structures that perform early sensory processing. In particular, there are appealing parallels between olfactory structures and visual processing circuits. Thus, studies of the *Drosophila* olfactory system should yield insight into fundamental principles of sensory processing that have general relevance across sensory modalities (Cleland 2010, Mu et al. 2012, Singer et al. 2009).

It is currently taken for granted that the *Drosophila* central nervous system (CNS) is a useful preparation for systems neurophysiology; however, this viewpoint is relatively recent. Until the past decade or so, the neurophysiology of the *Drosophila* CNS was a black box. This situation changed with the

CNS: central nervous system

widespread application of the visualized "blow and seal" technique for whole-cell patch-clamp recording (Stuart et al. 1993). Starting in the late 1990s, this technique was applied to the intact larval or embryonic *Drosophila* CNS (Baines & Bate 1998, Choi et al. 2004, Rohrbough & Broadie 2002). The development of genetically encoded fluorescent sensors of neural activity, together with the development of modular transgenic systems for expressing these sensors in the fly, was another revolution (Brand & Perrimon 1993, Miesenböck 2004). The first studies to exploit these fluorescent sensors studied the adult brain in semireduced preparations (Ng et al. 2002, Wang et al. 2003). These studies were soon followed by the first field potential recordings (Nitz et al. 2002) and whole-cell patch-clamp recordings (Wilson et al. 2004) from the adult brain in vivo.

OLFACTORY PROCESSING IN RECEPTOR NEURONS

Anatomical Organization

The fly is unusual in that its olfactory receptor neurons (ORNs) are relatively accessible to in vivo electrophysiological recording. ORNs are housed in the antennae and maxillary palps, which are covered by finger-like protrusions called sensilla. These sensilla contain the dendrites of ORNs, and each sensillum typically houses exactly two ORNs (although some types of sensilla house three or four ORNs). By inserting a tungsten or glass electrode into a sensillum, the spikes of both of its ORNs can be recorded simultaneously, and each spike can typically be attributed unequivocally to one of the two ORNs in that sensillum.

ORNs can be segregated into discrete types on the basis of their odor responses (de Bruyne et al. 1999, 2001; van der Goes van Naters & Carlson 2007; Yao et al. 2005). These types turn out to map rather neatly onto patterns of odorant receptor expression (Benton et al. 2009, Hallem et al. 2004). In total, there are ~50 ORN types, corresponding roughly to the 50–60 odorant receptors expressed in the adult antennae and maxillary palps (Benton et al. 2009; Couto et al. 2005; de Bruyne et al. 1999, 2001; Elmore et al. 2003; Fishilevich et al. 2005; van der Goes van Naters & Carlson 2007; Yao et al. 2005).

ORN: olfactory receptor neuron

Phenomenology of Odor Responses

Several studies have systematically surveyed ORN responses using large and chemically diverse sets of stimuli. These studies have characterized odorant receptors either in their native context (de Bruyne et al. 1999, 2001; Silbering et al. 2011; Yao et al. 2005) or in an expression system that captures most of their native properties (Dobritsa et al. 2003, Hallem & Carlson 2006, Hallem et al. 2004). As a result, the chemical selectivities of almost all ORN types have now been described, which is an enormous asset to the field. In addition, several other studies have surveyed ORN responses by systematically varying stimuli in the time domain (A.J. Kim et al. 2011; Nagel & Wilson 2011; Schuckel & French 2008; Schuckel et al. 2008, 2009). As a group, these studies have revealed some general observations about how stimuli are encoded in *Drosophila* ORNs.

- Most individual ORN types respond to multiple ligands, and most individual ligands activate multiple ORN types. The best ligands for a neuron often do not fall into a single chemical class (de Bruyne et al. 1999, 2001; Hallem & Carlson 2006; Silbering et al. 2011; Yao et al. 2005).
- Individual ORN types can be broadly tuned, narrowly tuned, or in between (Hallem & Carlson 2006).
- ORN firing rates rise with increasing ligand concentration; they have a typical dynamic range of approximately two orders of magnitude in odor concentration. Increasing concentration tends to recruit responses in a larger number of ORN types, and ORNs become more broadly tuned at higher concentrations (Hallem & Carlson 2006).
- ORNs spike even in the absence of ligands. Some ligands are actually inhibitory, meaning they suppress the cell's

spike rate below its spontaneous rate (de Bruyne et al. 1999, 2001; Hallem & Carlson 2006; Nagel & Wilson 2011; Schuckel et al. 2009; Silbering et al. 2011; Yao et al. 2005).

- ORN responses are dynamic. Spike rates peak rapidly and subsequently relax to a tonic level of activity. After odor offset, spike rates are often suppressed below spontaneous rates. The dynamics of these responses depend on ORN type, ligand, and concentration (A.J. Kim et al. 2011; Nagel & Wilson 2011; Schuckel & French 2008; Schuckel et al. 2008, 2009).

The mechanisms underlying these observations are now understood at the molecular and cellular levels, at least to a large degree. The next several sections summarize these mechanisms and some of their proposed functional consequences.

Diverse Receptors, Generic Cells

In general, each *Drosophila* ORN expresses a single odorant receptor gene that specifies the odor tuning of that neuron (Vosshall et al. 2000), although a few types of ORNs express multiple receptors (Abuin et al. 2011, Dobritsa et al. 2003, Goldman et al. 2005). Importantly, swapping receptors between ORNs swaps their odor responses (Hallem et al. 2004). Receptor swap also recapitulates the dynamics of odor responses. Thus, all of the diversity in ORN odor responses is likely due to diversity in ORN odorant receptor expression. In other words, the different ORN types are functionally generic, except that they express different receptors. The only exception to this rule is that some ORNs also have specialized accessory protein machinery needed to traffic the transduction complex to the correct subcellular location (Abuin et al. 2011, Larsson et al. 2004).

Given that the diversity among ORNs can be attributed to diversity in odorant receptor expression, we can understand many of the principles of ORN odor coding as arising from the properties of odorant receptor proteins themselves, namely, the molecular pharmacology of these receptors (Hallem et al. 2004, Nagel & Wilson 2011). In general, each receptor binds multiple ligands, and each ligand binds multiple receptors. Some receptors evidently have high affinity for many ligands, whereas others have high affinity for only a few ligands. At high ligand concentrations, a receptor can be activated by both low- and high-affinity ligands. A receptor is less selective at high concentrations versus low concentrations because high ligand concentrations tend to saturate the receptor.

Receptors for Social Odors

Some of the most selective ORNs respond to social odors. For example, two types of ORNs respond to *cis*-vaccenyl acetate, which is produced exclusively by males (Clyne et al. 1997, Ha & Smith 2006, van der Goes van Naters & Carlson 2007, Xu et al. 2005). Other ORN types respond to other male scents or to scents produced by female virgins (van der Goes van Naters & Carlson 2007). These ORNs have not yet been characterized in detail, in part because most of the chemical constituents of social odors have not yet been identified. Notably, ORN types that respond to social odors are generally inhibited by most other odors, which is unusual. Social odors are interesting to neurobiologists because these odors trigger robust behaviors. Some of the central neurons postsynaptic to these ORNs have unusual properties or patterns of connectivity, suggesting specialization for social odor processing (Chou et al. 2010, Datta et al. 2008, Jefferis et al. 2007, Ruta et al. 2010, Schlief & Wilson 2007). Identifying the chemical constituents of social odors will be an important step in understanding the specialization of central circuits and the roles of social odors and their cognate ORNs in various social behaviors.

Spontaneous Transduction and Odor-Evoked Inhibition

All ORNs fire spontaneously, and each ORN type has a characteristic spontaneous firing

rate (de Bruyne et al. 1999, 2001; van der Goes van Naters & Carlson 2007; Yao et al. 2005). Mutating the odorant receptor that an ORN normally expresses diminishes its spontaneous firing rate (Dobritsa et al. 2003, Olsen et al. 2007), implying that spontaneous firing reflects the receptor's tendency to reside in the active state even in the absence of ligand. Different odorant receptors likely have different equilibria between their active and inactive states, which would explain why swapping receptors between ORNs can swap their spontaneous firing rates (Hallem et al. 2004).

In some cases, an odor can inhibit spontaneous spiking. Most odors inhibit at least one ORN type while exciting other types (Hallem & Carlson 2006), meaning no odors are inhibitory per se. If an odorant receptor mediates inhibition in response to a particular ligand in its native ORN, it will also generate an inhibitory response to the same ligand in a different ORN whose native receptor has been removed (Hallem et al. 2004). This result argues that inhibitory responses simply reflect inverse agonism; that is, the ligand stabilizes the inactive state more than it stabilizes the active state and thereby suppresses activation below spontaneous levels (Hallem et al. 2004, Nagel & Wilson 2011). Inhibitory responses can also suppress responses to simultaneously applied excitatory odors (Turner & Ray 2009).

Spontaneous activity in ORNs is puzzling from a functional standpoint because it simply adds noise to the system. Why hasn't the fly evolved odorant receptors that are inactive when unbound? Spontaneous transduction might be useful because it depolarizes the cell's resting potential to near its spike threshold. Alternatively, it might just be difficult to evolve a receptor protein with the requisite specificity and kinetics that is never activated in the absence of a ligand.

Transduction Speed

Current evidence suggests that odorant receptors in *Drosophila* are ligand-gated ion channels, not metabotropic receptors (as they are in vertebrates). This is clear for the so-called IR family of odorant receptors, which bears structural homology to ionotropic glutamate receptors in vertebrates (Abuin et al. 2011, Benton et al. 2009), but the issue is less clear for the OR family of odorant receptors, for which most evidence favors an ionotropic mechanism (Benton et al. 2006, Sato et al. 2008, Smart et al. 2008; but see Wicher et al. 2008, Yao & Carlson 2010).

Although ionotropic transduction should be faster than metabotropic transduction, transduction in *Drosophila* is still slower than the dynamics of the odor stimuli themselves, in part because of the time required for odors to diffuse from the surface of the olfactory organ to the receptor sites. The concentration of an odor near its source can fluctuate steeply at high rates, with substantial power at frequencies >10 Hz (Dekker & Carde 2011, Nagel & Wilson 2011, Schuckel & French 2008). Transduction is slower than the fastest odor fluctuations, so responses to odor plume fluctuations are severely attenuated at frequencies greater than 1–10 Hz, and the cutoff frequency depends on the odor-receptor combination (Nagel & Wilson 2011). The onset and decay rates of transduction depend on both the odor and the receptor, implying that different ligand-receptor combinations produce different rise and decay times for receptor activation.

Adaptation in Transduction

In response to a prolonged and steady odor stimulus, ORN responses peak rapidly, then decay. A prolonged stimulus also reduces responses to subsequent stimuli (de Bruyne et al. 1999). What mechanisms produce adaptation? If an ORN is engineered to simultaneously express two different receptors that are activated independently by different ligands, these receptors can cross-adapt each other. Also, an inhibitory odor response can actually potentiate a subsequent excitatory response, suggesting that spontaneous transduction produces a basal level of adaptation and that the excitatory response has been de-adapted following

inhibition of spontaneous transduction (Nagel & Wilson 2011). Together, these results argue that adaptation is mediated by a diffusible factor that accumulates in the cell as a result of transduction. This diffusible factor might be calcium, as odorant receptor activation increases the cytoplasmic calcium concentration (Sato et al. 2008). Consistent with a role for cytoplasmic calcium, adaptation is reduced by mutations in either IP_3 receptors or the TRP channel (Deshpande et al. 2000, Stortkuhl et al. 1999). Adaptation slows transduction onset rates, suggesting that it involves a decrease in ligand binding affinity and/or a decrease in the efficacy of receptor activation (Nagel & Wilson 2011). In functional terms, adaptation in sensory systems is thought to be useful because it allows neurons to use their dynamic range efficiently: neurons decrease their sensitivity when stimuli are strong and increase it when stimuli are weak (Wark et al. 2007).

After odor offset, ORN firing rates are often inhibited below spontaneous rates (de Bruyne et al. 1999, 2001). Both offset inhibition and adaptation increase with odor pulse duration (Nagel & Wilson 2011), suggesting that both processes reflect a common mechanism. Adaptation and offset inhibition may be due to a decrease in the efficacy of receptor activation. Assuming that there is some basal level of receptor activation in the absence of odor, a process that inhibits receptor activation will suppress spontaneous activity. Both adaptation and offset inhibition depend on the identity of the receptor and the identity of the odor (Hallem et al. 2004, Nagel & Wilson 2011). This makes sense because changing the ligand-receptor combination would change the rate constants governing transitions between the active and inactive states of the receptor.

From Transduction to Spiking

In some circumstances, isolated receptor potentials and spikes can be recorded simultaneously from the same ORNs (Nagel & Wilson 2011). These experiments demonstrate that spike rate in ORNs is not simply related to the magnitude of transduction. Rather, it is related to both the magnitude and rate of change of transduction. Spike rates peak when transduction is increasing rapidly, and they can be suppressed below baseline when transduction begins to rapidly decay. As a result, ORN spike rates encode both odor concentration and its rate of change (A.J. Kim et al. 2011). Consistent with theoretical models of spiking behavior, ORN spiking behavior can be altered by manipulating sodium channel expression levels in these neurons (Nagel & Wilson 2011).

Because the spike rate of an ORN depends on the rate of change in transduction, the dynamics of spiking tend to be more complex than the dynamics of transduction (Nagel & Wilson 2011). Nevertheless, the relationship between transduction and spiking is similar across ORN types. This similarity helps explain why swapping odorant receptors is sufficient to swap all of the dynamics of an ORN's response to a ligand: Because the relationship between spiking and transduction is similar, receptor swap recapitulates not only the simpler dynamics of transduction but also the more complex dynamics of spiking.

Some Fundamental Principles

The previous sections have detailed the mechanisms underlying ORN odor responses. What do these mechanisms mean for downstream neurons? The following list of fundamental principles of odor coding in *Drosophila* ORNs places special emphasis on how peripheral mechanisms shape the format of information flowing to higher brain regions. These themes are revisited in the second half of this review, which follows olfactory information into the brain.

ORNs are noisy. On average, a *Drosophila* ORN fires 8 spikes/s in the absence of an odor (de Bruyne et al. 1999, 2001). Because each antenna contains 1,200 ORNs (Stocker et al. 1990), the brain is continuously barraged by ~20,000 ORN spikes/s, even when no odor is present. Moreover, ORN odor responses are

also noisy, so ORN noise likely places a fundamental limit on the ability of downstream neurons to detect dilute or transient odor stimuli.

ORNs fire most strongly at odor onset. At the onset of a rapid increase in odor concentration, transduction rises more slowly than odor concentration. As a result, ORN responses are delayed and responses to transient stimuli are attenuated. This should limit downstream neurons' abilities to detect odor rapidly and to detect transient odor filaments. However, because the spike rates of ORNs depend on the rate of change in transduction, not the absolute transduction level, spike rates peak before transduction does. This increases the speed with which rapid odor fluctuations are encoded. As discussed below, a similar process of speeding also occurs downstream.

Most odors are encoded by the combined activity of several ORN types with overlapping receptive fields. Multiple ORN types are generally coactivated by a single stimulus, which has important implications for downstream odor processing. As we shall see, the signals sent by different ORN types can influence each other at the very first stage of olfactory processing in the brain. The recruitment of multiple ORN types is also important because each type is sensitive to concentration over a restricted concentration range. Thus, the organism's ability to resolve concentration differences over a wide range likely depends on the recruitment of multiple receptors with different affinities for the same ligand (Kreher et al. 2008).

ORNs conjointly encode physical features of the stimulus that must be extracted independently. Every ORN odor response depends on (*a*) odor identity, (*b*) odor concentration, and (*c*) the rate of change in odor concentration. In the natural world, all three of these features are constantly changing. Nevertheless, behavioral experiments indicate that odor identity and concentration are encoded independently in the *Drosophila* brain. Flies can be conditioned to avoid an odor irrespective of its concentration and to discriminate between different concentrations of the same odor (Borst 1983, Dudai 1977, Masek & Heisenberg 2008, Yarali et al. 2009). The problem of encoding odor identity and concentration independently creates a challenge for downstream neurons.

ORNs have correlated odor selectivity. A stimulus that evokes a high firing rate in a given ORN type also tends to evoke a high firing rate in many other ORN types. Conversely, a stimulus that elicits unusually weak activity in a given ORN type also tends to evoke weak or little activity in most other ORNs. In other words, there is substantial redundancy in ORN odor representations (Haddad et al. 2010, Luo et al. 2010, Olsen et al. 2010). This too has important implications for downstream odor processing.

Comparisons with Vertebrates

There are many similarities between *Drosophila* and vertebrate ORNs. In vertebrates, most odors are encoded by the combined activity of several ORN types, and increasing the concentration of an odor recruits more ORNs (Reisert & Restrepo 2009). Vertebrate receptors can be narrowly tuned, broadly tuned, or anything in between (Saito et al. 2009). Vertebrate ORNs are noisy and spontaneously active, partly owing to spontaneous transduction in odorant receptors (Reisert 2010). Vertebrate ORNs also preferentially signal the onset of odor responses, owing to adaptation in transduction and spike generation (Reisert & Matthews 2000). As in *Drosophila*, adaptation in vertebrate transduction reflects, at least in part, an apparent reduction in receptor affinity, such that adapted responses resemble responses to a lower ligand concentration (Liu et al. 1994). Finally, vertebrate ORNs resemble *Drosophila* ORNs in that both have correlated odor selectivity (Haddad et al. 2010).

An important difference between vertebrate and *Drosophila* ORNs is the speed of transduction. In vertebrates, the response to a brief pulse of odor (25 ms) requires 400 ms to peak and

Glomerulus: a neuropil compartment where ORN axons form synapses with PN and LN dendrites

1,000 ms to terminate (Bhandawat et al. 2005). By comparison, *Drosophila* ORN responses can peak in 30 ms and terminate in 200 ms (Nagel & Wilson 2011, Schuckel et al. 2009). Speed may be more important for insects because they experience rapidly fluctuating, wind-borne odor filaments, and they can potentially use the information contained in these fluctuations to locate an odor source (Murlis et al. 1992, Silbering & Benton 2010). By contrast, speed is probably less important for vertebrates; terrestrial vertebrates draw air into their noses before it encounters ORNs, a process that likely disperses odor filaments and smoothes fluctuations in concentration (Schoenfeld & Cleland 2005).

Another difference is that vertebrate ORNs are reportedly sensitive to air speed (Mozell et al. 1991, Scott et al. 2006, Sobel & Tank 1993). Terrestrial vertebrates actively control air flow through their noses and thereby use air speed to modulate olfactory transduction (Johnson et al. 2003, Schoenfeld & Cleland 2005). *Drosophila* have comparatively little control over air flow across their olfactory organs, so it may be advantageous that *Drosophila* ORNs are insensitive to air speed (Zhou & Wilson 2012).

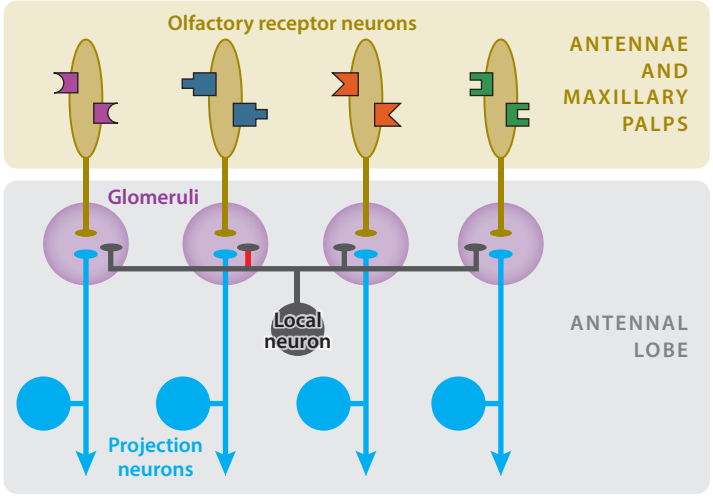


Figure 1

Anatomy of the *Drosophila* olfactory system. Olfactory receptor neuron (ORN) cell bodies and dendrites (*brown*) reside in peripheral olfactory organs. All of the ORNs that express a given odorant receptor converge onto the same glomerulus in the antennal lobe, schematized here as a single ORN per glomerulus. Each projection neuron (PN) (*blue*) sends a dendrite into a single glomerulus (*purple*), where it receives monosynaptic input from ORNs. Although each glomerulus contains the dendrites of several PNs, only one PN for each glomerulus is shown here. Glomeruli are laterally interconnected by a network of local neurons (LNs) (*gray*), which interact with PNs, ORNs, and other LNs. Many individual LNs innervate most or all glomeruli, but some are more selective.

Key Open Questions

Although olfactory processing in ORNs is arguably better understood in *Drosophila* than in any other species, several important questions remain unanswered:

- **Are odorant receptors in the OR family really ligand-gated ion channels?** If so, the structure of these receptors must be unusual, as they are predicted to have seven transmembrane domains (Vosshall et al. 1999). Neither the structure nor the function of these receptors has received much attention from structural biologists or biophysicists.
- **Might ORs also be metabotropic?** It has been suggested that ORs might be both ion channels and G protein–coupled receptors, although the latter pathway might be a minor one. This would reconcile some recent findings (Wicher et al. 2008, Yao & Carlson 2010).
- **What are the mechanisms of transduction adaptation?** Progress on this question depends on a better understanding of transduction mechanisms.
- **What molecules do *Drosophila* use for olfactory social communication?** Also, what receptors and ORN types mediate responses to each of these ligands?

OLFACTORY PROCESSING IN THE ANTENNAL LOBE

Anatomical Organization

The antennal lobe is the first brain region of the fly olfactory system. Thus, it is analogous to the vertebrate olfactory bulb, and like the bulb, it is organized into discrete neuropil compartments, called glomeruli (**Figure 1**). All of the ORNs that express a given odorant

receptor converge onto the same glomerulus (Vosshall et al. 2000). There they make excitatory synapses with second-order neurons called projection neurons (PNs). Like mitral cells in the vertebrate olfactory bulb, each antennal lobe PN is postsynaptic to a single glomerulus (Stocker et al. 1990). Each glomerulus contains the dendrites of several PNs, termed sister PNs; these sister PNs have highly correlated patterns of activity (Kazama & Wilson 2009).

Glomeruli are interconnected by a network of local neurons (LNs). LNs lack axons and release the inhibitory neurotransmitter γ-aminobutyric acid (GABA) from their dendrites instead. PNs also release neurotransmitters from their dendrites (Ng et al. 2002, Wilson et al. 2004). Thus, each glomerulus is potentially the site of reciprocal interactions between these three cell types.

Phenomenology of Odor Responses

Most odorant receptors and ORN types have now been matched with their cognate glomeruli in the brain (Couto et al. 2005, Fishilevich & Vosshall 2005, Silbering et al. 2011). Several studies have made systematic comparisons between odor coding in ORNs and their cognate PNs. These studies demonstrate a coarse resemblance between the odor responses of ORNs and their postsynaptic PNs (Bhandawat et al. 2007, Ng et al. 2002, Schlief & Wilson 2007, Silbering et al. 2008, Wang et al. 2003, Wilson et al. 2004). Specifically, ligands that are unusually effective in stimulating an ORN (particularly at low concentrations) also tend to be unusually effective in stimulating postsynaptic PNs. This result is consistent with the idea that ORNs provide the major source of excitation to PNs.

That said, PN odor representations are not identical to ORN odor representations. Specifically, PN and ORN odor responses differ as follows:

- PN responses show less variability in trial-to-trial spike count than do the responses of their presynaptic ORNs to the same stimulus (Bhandawat et al. 2007).
- PN responses generally peak earlier than ORN responses and decay more quickly (Bhandawat et al. 2007, Wilson et al. 2004). This means that PNs respond most vigorously to odor onset.
- In general, PNs are more broadly tuned to odors (i.e., less selective) than their presynaptic ORNs (**Figure 2**) (Bhandawat et al. 2007, Olsen & Wilson 2008, Wilson et al. 2004).
- When only one ORN type is active, and when those ORNs are firing at a low rate, their postsynaptic PNs are disproportionately sensitive to small changes in ORN input. However, when those same ORNs are firing at a high rate, their PNs are less sensitive to small changes in presynaptic input (**Figure 2**). That is, the relationship between ORN and PN activity exhibits a compressive nonlinearity (Olsen et al. 2010).
- The odor responses of a PN can be suppressed by recruiting additional activity in other glomeruli. For example, when mixed with a second odor, an odor that elicits no response in a given PN when presented alone can inhibit that PN's response to the second odor (Olsen et al. 2010, Silbering & Galizia 2007), implying the existence of inhibitory interactions between glomerular processing channels.

The following section summarizes the mechanisms underlying these transformations and the reasons they might be useful to the organism.

Convergence

Why are PN odor responses so sensitive to weak inputs, and why are they so reliable? Part of the answer lies in the convergence of ORNs onto PNs. Each odorant receptor is expressed in multiple ORNs, ranging from ~10 to ~100 ORNs per antenna or palp, depending on the receptor (de Bruyne et al. 2001, Shanbhag et al. 1999). Most individual ORNs project bilaterally (Stocker et al. 1990), and each PN receives input from all of the ORN axons that enter its

PN: antennal lobe projection neuron

LN: antennal lobe local neuron

GABA: γ-aminobutyric acid

Unitary synaptic event: a synaptic event produced by a spike in a single axon synapsing onto the postsynaptic cell; this axon may form multiple vesicular release sites onto the postsynaptic neuron

cognate glomerulus (Kazama & Wilson 2009). Thus, each PN receives convergent bilateral input from all of the ORNs that express a given odorant receptor.

The high convergence of ORNs onto PNs helps account for PN sensitivity to weak levels of presynaptic ORN input. It also helps account for why PN responses show less trial-to-trial variability than the responses of their presynaptic ORNs to the same stimulus. Recall that sister ORNs spike independently (Kazama & Wilson 2009), so pooling many ORN inputs should allow for reduced trial-to-trial variability in PN odor responses (Abbott 2008).

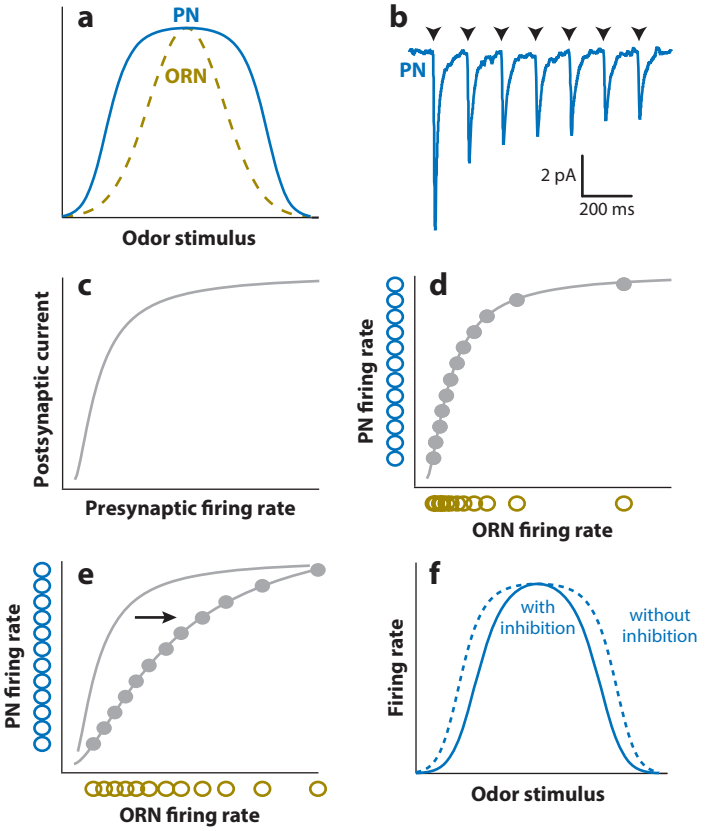
Olfactory Receptor Neuron Synapses

The properties of ORN-to-PN synapses also promote reliability. Each ORN spike produces a large, excitatory, unitary synaptic event in a PN (5–7 mV in amplitude; Kazama & Wilson 2008). Each ORN axon forms several dozen synaptic sites onto each postsynaptic PN, and each release site has a high vesicular release probability. Thus, each ORN spike releases several dozen vesicles onto the PN, thereby producing a highly reliable synapse. The strength of these synapses also helps explain why PNs are very sensitive to weak levels of ORN input. ORN-to-PN synapses are cholinergic and are blocked by a nicotinic acetylcholine receptor antagonist (Kazama & Wilson 2008).

Why are PN responses more transient than ORN responses? This is partly explained by the properties of ORN-to-PN synapses. A high vesicular release probability means that synaptic vesicles should be easily depleted from this synapse. Consistent with this, ORN-to-PN synapses exhibit strong short-term depression (Kazama & Wilson 2008). Short-term synaptic depression should make PN responses more transient, meaning that PNs should respond most strongly at the onset of an odor pulse.

Why does the relationship between PN and ORN exhibit a compressive nonlinearity? Thus, it must reflect either a process at ORN-to-PN synapses or a process intrinsic to PNs. Short-term depression at ORN-to-PN synapses likely explains most of this phenomenon. Short-term synaptic depression suppresses steady-state postsynaptic responses to high presynaptic firing rates. This flattens the peak of a neuron's tuning curve (Abbott et al. 1997), and so this phenomenon can also account for why PNs are more broadly tuned than their presynaptic ORNs. Short-term synaptic depression is not the only mechanism that broadens PN tuning; lateral excitation also contributes (see below). However, contrary to early conjectures (Borst 2007, Wilson et al. 2004), lateral excitation is not strictly necessary to explain the basic phenomenon of broad PN tuning.

Interestingly, most individual ORNs arborize bilaterally (Stocker et al. 1990), which should make it difficult for the fly to lateralize odor stimuli. Nevertheless, odor lateralization behavior can be robust and rapid (Borst & Heisenberg 1982, Duistermars et al. 2009,



Gaudry et al. 2013). This is explained by a small asymmetry in ORN neurotransmitter release properties: The ORN releases ~40% more neurotransmitter per spike from its ipsilateral axon branch than from its contralateral axon branch. As a result, when an odor stimulus is lateralized, the PNs that are ipsilateral to the stimulus spike at slightly higher rates and with a slightly shorter latency than do those that are contralateral to the stimulus (Gaudry et al. 2013).

Projection Neurons

Almost all PNs send a dendritic arbor into a single glomerulus (Jefferis et al. 2001, Stocker et al. 1990), meaning that they receive direct input from a single ORN type. Analysis of a passive compartmental model suggests that approximately three synchronous unitary ORN synaptic inputs should be required to drive a PN from its resting potential to its spike initiation threshold (Gouwens & Wilson 2009). PNs express a variety of voltage-dependent conductances (Gu et al. 2009), but the contribution(s) of these conductances to PN odor responses has not been investigated. PNs spike spontaneously in the absence of odors; this behavior is mainly due to spiking input from ORNs that produces large spontaneous fluctuations in the membrane potential of the postsynaptic PN (Gouwens & Wilson 2009, Kazama & Wilson 2009).

Almost all PNs are cholinergic (Yasuyama & Salvaterra 1999). They release acetylcholine from their axonal arbors in higher brain regions and also from their dendrites in the antennal lobe (Kazama & Wilson 2008, Ng et al. 2002, Wilson et al. 2004, Yaksi & Wilson 2010). Within the antennal lobe, PNs excite other PNs in the same glomerulus; they also excite LNs.

Most individual glomeruli contain several sister PNs (Stocker 1994, Tanaka et al. 2004). Sister PNs carry highly correlated signals—i.e., they have very similar trial-averaged odor responses, particularly when sister PNs are recorded in the same fly. This finding argues that brain-to-brain variability is much larger than stochastic variability in cellular or circuit properties. In addition, sister PNs display correlated noise; i.e., trial-to-trial odor response fluctuations are similar in sister PNs, and they show correlated spiking in the absence of odors. Both correlated signals and correlated noise are consequences of the fact that sister PNs receive input from precisely the same set of ORNs (Kazama & Wilson 2009).

Figure 2

The nonlinear relationship between olfactory receptor neuron (ORN) and projection neuron (PN) firing rates. (*a*) Schematic tuning curves (i.e., plots of firing rate versus stimulus number) for an ORN (*dashed brown curve*) and a PN (*solid blue curve*). Stimuli are arbitrarily ordered so that the strongest responses are in the center of the plot because this ordering makes it easier to visually assess tuning breadth. In this example, the ORN tuning curve is shown as Gaussian, although this may not be typical. The PN tuning curve was created by transforming the ORN tuning curve using a hyperbolic ratio function (like that in panel *d*). Tuning curves are normalized to the same peak. (*b*) A recording from a PN showing synaptic currents elicited by electrical stimulation of a train of spikes in ORN axons (*arrowheads*). The synaptic currents are depressed during the train. Modified from Kazama & Wilson (2008). (*c*) Schematic illustration of how total postsynaptic current increases sublinearly as presynaptic firing rates increase, owing to synaptic depression (as in panel *b*). Modified from Kazama & Wilson (2008). (*d*) Schematic showing the typical relationship between the odor-evoked firing rates of ORNs and PNs in the same glomerulus. Each black symbol represents a different odor stimulus; odor stimuli might be different concentrations of the same chemical or different chemicals. The relationship between ORN and PN firing rates is monotonic (as shown in this schematic) in a situation in which only one ORN type is activated by the odor. The relationship is strongly sublinear, probably due to the sublinear relationship between presynaptic spiking and postsynaptic current. Projecting these points into the x- and y-axes (*brown* and *blue symbols*, respectively) makes it clear that most of the ORN responses cluster near the bottom of the cell's dynamic range; this behavior is typical of ORNs. By contrast, PN responses are more uniformly distributed throughout the cell's dynamic range. Modified from Bhandawat et al. (2007), Olsen et al. (2010). (*e*) Lateral inhibition (*black arrow*) inhibits neurotransmitter release from ORNs and thereby increases the level of ORN input required to drive the PNs to saturation. The magnitude of lateral inhibition is correlated with total ORN activity, as is the activity of each ORN type; thus, a glomerulus tends to receive strong lateral inhibition when its ORN inputs are also strong. The distribution of ORN firing rates in this schematic has been shifted to the right to represent this idea, and this shift means that a shallower curve is needed to make the PN odor responses uniformly distributed within its dynamic range (compare *brown symbols* to those in panel *d*). In this schematic, the magnitude of lateral inhibition is the same for all the odor stimuli; however, in a situation where different stimuli elicit different levels of lateral inhibition, the relationship between ORN and PN activity would not be monotonic. (*f*) Lateral inhibition makes PNs more narrowly tuned than they otherwise would be, although it does not necessarily make PNs more narrowly tuned than ORNs.

Targets of Lateral Inhibition

Lateral inhibition: inhibitory interactions between principal neurons (ORNs or PNs) in different glomeruli; this term does not necessarily imply any particular spatial organization for interglomerular interactions

The net effect of lateral input to a PN is generally inhibitory. This is clear from the fact that a PN's odor responses are typically disinhibited by silencing input to other glomeruli (Asahina et al. 2009, Olsen & Wilson 2008). Conversely, adding new odors to an odor mixture typically produces either sublinear summation or frank suppression (Olsen et al. 2010, Silbering & Galizia 2007). A PN can even be inhibited by a stimulus that actually excites its ORNs (Olsen & Wilson 2008). These sorts of mixture effects can be blocked by a combination of $GABA_A$ and $GABA_B$ receptor antagonists (Olsen et al. 2010, Silbering & Galizia 2007). Together, these results demonstrate the existence of odor-evoked lateral inhibition.

The site of lateral inhibition is predominantly presynaptic, at the ORN axon terminal. This locus of inhibition is implied by the finding that robust lateral inhibition requires active neurotransmitter release from ORN axons. When ORNs are silent, most lateral inhibition disappears (Olsen & Wilson 2008). Moreover, ORN axon terminals show immunoreactivity for GABA receptors (Root et al. 2008), and iontophoretic GABA inhibits ORN-to-PN synaptic transmission at a presynaptic locus (Olsen & Wilson 2008, Root et al. 2008). Similarly, activating LNs with odor stimuli also inhibits ORN-to-PN synaptic currents at a presynaptic locus (Olsen & Wilson 2008).

Although ORNs are perhaps the most functionally important targets of inhibition, PNs also receive synaptic inhibition. Iontophoretic GABA hyperpolarizes PNs via $GABA_A$ and $GABA_B$ receptors (Wilson & Laurent 2005). In paired recordings from GABAergic LNs and PNs, injecting depolarizing current into the LN produces a train of spikes in the LN and weak hyperpolarization of the PN (Yaksi & Wilson 2010). Interestingly, clear unitary synaptic connections are never observed in these paired recordings. Rather, a train of spikes in the LN is always required to see any measurable PN response in single trials, and the PN response grows slowly throughout the train. This suggests these connections might represent volume transmission rather than true synapses.

LNs themselves are also likely targets of inhibition. LNs are hyperpolarized by iontophoretic GABA (Wilson & Laurent 2005), and paired recordings from LN-LN pairs reveal inhibitory connections (Huang et al. 2010, Yaksi & Wilson 2010). Like LN-to-PN connections, these connections seem to be weak and slow.

Selectivity of Lateral Inhibition

In general, the overall level of inhibition in the antennal lobe rises with increasing stimulus intensity (Olsen et al. 2010, Silbering & Galizia 2007, Silbering et al. 2008). But how does the spatial pattern of inhibition depend on the odor? One study addressed this question by measuring GABA release in different glomeruli using a fluorescent sensor of vesicular release that was expressed specifically in LNs (Ng et al. 2002). That study found that the stimulus dictated the identity of the glomerulus with the largest fractional fluorescence change. For example, banana odor produced a substantial increase in fluorescence in glomerulus VA3 but hardly any change in glomerulus D; conversely, apple odor produced a fluorescence increase in glomerulus D but very little change in fluorescence in VA3. These results imply that the spatial pattern of GABA release depends on the stimulus, thereby suggesting a model where specific subsets of glomeruli are linked by inhibitory subnetworks and ORN input to a glomerulus recruits LN input to a specific subset of other glomeruli (**Figure 3**).

An alternative approach is to compare ORN and PN responses to many stimuli and to ask what determines a PN's sensitivity to its ORN inputs. Using this approach, one study found that a PN's sensitivity to its ORN inputs could be predicted on the basis of total ORN activity alone; that is, the identity of the active ORNs did not matter. Indeed, PN odor responses could be predicted with high accuracy on the basis of only two factors: the firing rate of the PN's cognate ORNs and the total firing rate

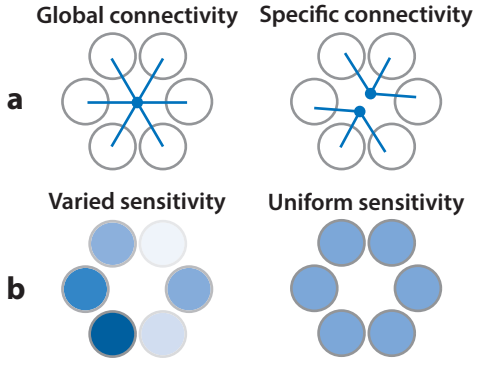


Figure 3

Possible components of specificity in lateral inhibition. (*a*) All glomeruli may be mutually interconnected, as implied by the finding that many lateral neurons (LNs) innervate most or all glomeruli. Alternatively, some glomeruli might be interconnected in specific subnetworks. These subnetworks might be created by LNs with sparse innervation patterns or by electrical compartmentalization within the arbors of broadly innervating LNs. (*b*) Glomeruli may have varied sensitivity to LN activity, possibly reflecting heterogeneous levels of GABA receptor expression or heterogeneous release properties of LN arbors. Alternatively, all glomeruli might have similar levels of sensitivity to LN activity. Note that spatial inhomogeneity would create glomerulus-specific levels of inhibition, but these spatial patterns may or may not be odor specific.

of the entire ORN population (Olsen et al. 2010). This finding suggests a model whereby inhibition is global, meaning all glomeruli inhibit each other (**Figure 3**). However, this approach is indirect, and it is impossible to exclude the idea of spatially specific inhibition using this method.

LN anatomy is consistent with either global or specific inhibition. Some LNs innervate a relatively small subset of glomeruli and could therefore permit specific interactions between glomeruli. However, most individual LNs innervate most or all glomeruli (Chou et al. 2010, Das et al. 2008, Lai et al. 2008, Okada et al. 2009, Seki et al. 2010, Shang et al. 2007, Stocker et al. 1990, Wilson & Laurent 2005). Overall, highly specific LNs represent a small fraction of all LNs. Based on the largest data set available, the individual LNs that innervate fewer than half of all glomeruli represent only 11% of all LNs (Chou et al. 2010). Most LNs are broadly tuned to odors; such tuning is consistent with broad connectivity (Chou et al. 2010, Wilson & Laurent 2005).

Notably, odor invariance in the spatial pattern of inhibition does not necessarily imply that all glomeruli receive the same level of inhibition. In principle, at least, the pattern of inhibition may be not only odor invariant but also spatially inhomogeneous (**Figure 3**). Indeed, there is evidence that the spatial pattern of inhibition may vary across glomeruli (whether or not this pattern is odor invariant). For example, a comparison of mixture suppression in two glomeruli showed that one glomerulus was systematically more sensitive to suppression than the other, although both were suppressed by the same component of the odor mix, and the suppressive component was known to act laterally (Olsen et al. 2010). The mechanistic basis for this observation is not clear. Some glomeruli are avoided by a subpopulation of LNs; this avoidance could produce unusually low levels of GABA release in those glomeruli (Chou et al. 2010, Okada et al. 2009, Seki et al. 2010). In addition, some glomeruli also have relatively low levels of GABA receptor expression (Root et al. 2008).

In summary, this important topic appears to remain an active area of debate. There are two distinct issues at hand: (*a*) whether inhibition is odor-selective and (*b*) whether sensitivity to inhibition is heterogeneous across glomeruli. Future progress on both issues will likely depend on using improved optical sensors, more selective odor stimuli, and more direct methods of measuring functional inhibition.

Functional Consequences of Lateral Inhibition

One functional consequence of inhibition is that it makes PNs less sensitive to their ORN inputs. When inhibition is absent, and when ORNs are firing at a low rate, PNs are very sensitive to small changes in ORN firing rates.

eLN: excitatory antennal lobe local neuron

In the absence of inhibition, PNs saturate only when their presynaptic ORNs fire at a high rate (**Figure 2**). In the presence of inhibition, however, PNs can be much less sensitive to small changes in ORN input, meaning that inhibition increases the ORN firing rate that is needed to drive PN firing rates to saturation (**Figure 2**). Thus, lateral inhibition allows PNs to encode changes in concentration over a broader range of concentrations.

Another functional consequence of lateral inhibition is that PN responses become more transient (Olsen et al. 2010). Because the major locus of inhibition is presynaptic rather than postsynaptic, the increased transience of PN responses is probably not dependent on any changes in the time constant of the postsynaptic membrane. Rather, it may reflect the fact that excitation is monosynaptic (ORN-to-PN), whereas the minimal pathway for inhibition is multisynaptic. As a result, inhibition is likely to be recruited later than excitation, and inhibition would have the largest effect on the later part of the PN response.

A final functional proposed consequence of inhibition is that it coordinates synchronous oscillations among PNs. Under certain conditions, odor stimuli can entrain PNs to fire oscillatory bursts of spikes. The power of these oscillations is reduced by reducing neurotransmitter release from a specific class of LNs (Tanaka et al. 2009). Oscillatory synchrony is less prominent in the *Drosophila* olfactory system than in the olfactory systems of other insects (Turner et al. 2007) and is thought to make a smaller contribution to olfactory processing in *Drosophila* than in other insects (Tanaka et al. 2009).

Lateral Excitation

Odor-induced depolarization of ORNs and PNs in a glomerulus tends to suppress activity in other glomeruli via GABAergic LNs. At the same time, however, this depolarization also tends to boost activity in other glomeruli via excitatory LNs. Thus, activity in one glomerulus elicits both excitation and inhibition in other glomeruli. This is one of the more intriguing and mysterious aspects of antennal lobe processing.

Several groups of investigators discovered lateral excitation in the *Drosophila* antennal lobe simultaneously. The basic experiment was simple: stimulate the fly with odors while recording signals from PNs directly postsynaptic to silent ORNs (ORNs silenced using either genetic tools or microdissections). As it turns out, little to no lateral inhibition was observed in these PNs, probably because the main target of lateral inhibition is the ORN axon terminal, and there is nothing to inhibit if the ORNs are essentially silent. Instead, under these conditions, an odor stimulus excites the PNs postsynaptic to the mutant ORNs, implying the existence of lateral excitation (Olsen et al. 2007, Root et al. 2007, Shang et al. 2007).

Which LNs might mediate lateral excitation? Odor-evoked lateral excitation is not blocked by GABA receptor antagonists, so it cannot be an excitatory effect of GABA. Because a minority of LNs are cholinergic, these neurons seemed like attractive candidates (Shang et al. 2007). Indeed, PNs are depolarized when cholinergic LNs are directly excited (using an optogenetic stimulus or current injection via a patch pipette). Thus, these LNs were dubbed excitatory LNs (eLNs). However, PN responses to eLNs are essentially unaffected by pharmacological blockade of nicotinic acetylcholine receptors or voltage-dependent calcium channels. Also, eLN-to-PN connections transmit both hyperpolarizing and depolarizing voltage steps (Huang et al. 2010, Yaksi & Wilson 2010). Moreover, these connections are abolished by a mutation in a gap junction subunit, and the same mutation abolishes odor-evoked lateral excitation (Yaksi & Wilson 2010), implying that lateral excitation is attributable to electrical connections formed by eLNs onto PNs. Thus, although eLNs are cholinergic, they evidently do not release acetylcholine onto PNs. eLNs themselves receive cholinergic excitation from both ORNs and PNs (Huang et al. 2010, Yaksi & Wilson 2010). Electrical connections should be

fast, which helps explain why lateral excitation to a PN lags direct excitation from ORNs by less than 2 ms (Kazama & Wilson 2008).

The major source of excitatory drive to a PN is the powerful cholinergic input it receives from its cognate ORNs. That said, the contribution of eLNs to PN odor responses is not negligible. Using a gap junction mutation to remove the contribution of the eLN-PN network modestly but significantly diminishes the strength of some PN odor responses (Yaksi & Wilson 2010). Less intuitively, the same mutation actually potentiates some PN odor responses, probably because eLNs can excite GABAergic LNs, thereby recruiting PN inhibition. Consistent with this idea, after application of GABA receptor antagonists, odor responses that are potentiated by the mutation are less disinhibited. The net effect of the eLN network on a PN—either excitation or inhibition—appears to depend on both the glomerulus and the odor stimulus. Overall, the functional consequences of the eLN network are poorly understood.

Some LNs are glutamatergic (Chou et al. 2010, Das et al. 2011), and some researchers have suggested that these LNs mediate lateral excitation. However, given that lateral excitation is blocked by a gap junction mutation, it seems unlikely that glutamate plays a key role in its mediation. The synaptic actions of glutamate in the *Drosophila* brain are unknown, although they are probably widespread (Daniels et al. 2008).

Long-Term Plasticity

A variety of sensory stimuli and experimental manipulations can produce persistent changes in the output of the antennal lobe. These modulations fall into two categories: (*a*) local forms of plasticity that tend to compensate for altered overall levels of neural activity and (*b*) top-down forms of plasticity that tend to adjust the salience of sensory cues on the basis of behavioral state.

Persistent local modulations can be viewed as forms of adaptation over long timescales. These modulations are generally compensatory, meaning that they at least partially counteract changes in the overall level of neural activity. For example, rearing flies in a high concentration of carbon dioxide produces a persistent suppression of PN responses to this odor. This suppression reflects a selective increase in the density of GABAergic LN innervation in the glomerulus where these PNs reside (Sachse et al. 2007). Conversely, chronic removal of some ORN types leads to the gradual recovery of odor responsiveness in deafferented PNs, reflecting an upregulation of lateral excitation mediated by an increase in the strength of the electrical connections between eLNs and PNs (Kazama et al. 2011). Finally, decreasing PN excitability by overexpressing a potassium channel produces a compensatory increase in the strength of ORN-to-PN synaptic currents in the affected PNs. This compensatory behavior may represent a natural homeostatic mechanism for coping with the systematic differences across glomeruli in PN input resistance (Kazama & Wilson 2008). All of these phenomena appear to be local to the antennal lobe.

Persistent top-down modulations can result from changes in behavioral state. For example, hunger potentiates PN odor responses: Falling levels of circulating insulin lead to upregulation of an autocrine neuropeptide signaling pathway in ORNs, which in turn produces increased ORN neurotransmitter release. Interfering with this signaling cascade reduces searching behavior in hungry flies (Root et al. 2011). Top-down plasticity can also result from classical conditioning. Pairing an odor with an aversive electric shock to the fly's abdomen causes an increase in the odor-evoked activity of some PNs (Yu et al. 2004), but the mechanism that underlies this phenomenon is still unknown.

Some Fundamental Principles

What follows is a short list of fundamental principles of olfactory processing in the *Drosophila* antennal lobe. Creating such a list is necessarily a selective and somewhat speculative exercise; the following focuses on the relevance of olfactory processing in this circuit for downstream neurons and for the organism as a whole.

Each glomerulus pools many inputs from neurons with essentially identical odor tuning. All of the ORNs that express the same odorant receptor wire precisely to the same PNs. Why would it be useful to segregate each ORN type into a different glomerulus? Recall that even when no odor is present, ORNs as a population continuously barrage the brain with ~20,000 ORN spikes/s. If ORNs wired randomly to PNs, then the task of detecting (for example) 10 odor-evoked spikes in this barrage would seem hopeless. But, if all 10 spikes were fired nearly synchronously by ORNs that were presynaptic to the same glomerulus, then they would likely summate effectively enough to drive a PN above its spike threshold. Thus, the orderly wiring of the olfactory system represents a computational machine par excellence: an extreme and illustrative example of what has been proposed to be a generally useful strategy for organizing neural connectivity (Abbott 2008).

PNs respond most strongly at the onset of ORN spiking. Two mechanisms cause this behavior: lateral inhibition and synaptic depression at ORN-to-PN synapses. This response profile is functionally important because it predicts that PNs should respond better to fluctuating inputs than to sustained inputs. Moreover, this behavior should also speed olfactory processing. Because natural odor plumes produce large fluctuations in odor concentration (Murlis et al. 1992), onset-oriented PN responses may be an adaptation to the natural distribution of odors in the environment as well as a selective pressure for speed in olfactory behaviors. Indeed, olfactory behaviors in *Drosophila* can be observed within 100 ms of the onset of ORN activity (Bhandawat et al. 2010, Gaudry et al. 2013). Recall that ORNs spike most strongly at the onset of transduction. Here, we see that PNs spike most strongly at the onset of ORN spiking; thus, there is an iterative process of response speeding. This phenomenon is analogous to what occurs in the vertebrate retina (Field et al. 2005), where there is a similar process of response speeding that promotes rapid visual perception despite the slow dynamics of visual transduction.

PNs are most sensitive to low ORN firing rates. When sister ORNs are firing at a low rate, small increases in their firing rate cause relatively large increases in the firing rates of their postsynaptic PNs (Olsen et al. 2010). When ORNs are firing at high rates, they tend to saturate their postsynaptic PNs. Consequently, odor stimuli that elicit low ORN firing rates occupy the lion's share of a PN's dynamic range (Bhandawat et al. 2007). Because most odor-evoked ORN firing rates are low (<50 spikes/s) compared with the maximum ORN firing rate (~300 spikes/s) (Hallem & Carlson 2006), most of a PN's dynamic range may be devoted to the most common odor stimuli (**Figure 2**). Thus, this property of PN tuning should maximize rates of information transmission (termed histogram equalization; Laughlin 1981). In simulations, the compressive nonlinearity in the relationship between ORN and PN firing rates substantially improves odor discrimination by a linear encoder (Luo et al. 2010, Olsen et al. 2010).

Lateral inhibition adjusts PN sensitivity to the level of total ORN activity. LNs collectively pool input from all glomeruli, and they inhibit ORN neurotransmitter release as ORN activity increases. This behavior makes PNs less sensitive to the firing rates of their cognate ORNs (Olsen et al. 2010, Olsen & Wilson 2008, Root et al. 2008). As a consequence of inhibition, PN firing rates do not saturate as easily as they would otherwise, and their dynamic range becomes more closely matched to that of their inputs (**Figure 2**). In simulations, this type of lateral inhibition substantially improves odor discrimination by a linear decoder. In particular, it improves a decoder's ability to identify an odor in a concentration-invariant manner (Luo et al. 2010, Olsen et al. 2010), implying that lateral inhibition may help flies identify odors in spite of natural variations in odor concentration. Lateral inhibition also decorrelates the activity of different PNs.

Indeed, the need for lateral inhibition can be seen as a consequence of the highly correlated activity of different ORN types; highly correlated ORN activity could easily lead to network saturation at high firing rates in the absence of gain control (Haddad et al. 2010, Luo et al. 2010, Olsen et al. 2010). The computation implemented by this type of lateral inhibition has been called divisive normalization, and it appears to play a role in a wide variety of sensory systems (Carandini & Heeger 2012).

Comparisons with Vertebrates

The most widely noted similarity between *Drosophila* and vertebrate olfaction is that in both cases, each glomerulus pools many inputs with essentially identical odor tuning (Bargmann 2006, Su et al. 2009). The similarity between the glomerular organization of the vertebrate and *Drosophila* olfactory systems is a spectacular case of evolution hitting upon the same solution to a general problem (Eisthen 2002).

However, there are other parallels as well. For example, the properties of neurotransmitter release from ORN axon terminals are similar in *Drosophila* and vertebrates. Specifically, the probability of vesicular release from ORN axon terminals is unusually high, and synapses are strongly depressed at high presynaptic firing rates (Kazama & Wilson 2008, Murphy et al. 2004).

Another parallel is the relationship between presynaptic and postsynaptic odor-evoked firing rates within a glomerulus. ORN and mitral cell responses have been compared systematically in only one study, which focused on a single, gene-targeted glomerulus in the mouse. That study found that the firing rates of mitral cells saturate at lower odor concentrations than do those of their cognate ORNs (Tan et al. 2010). Thus, when these mitral cell firing rates are plotted against the firing rates of their presynaptic ORNs, one should see a compressive nonlinearity (**Figure 2**). This finding is exactly analogous to the situation in *Drosophila* (Olsen et al. 2010) in that it implies that, like *Drosophila* PNs, mitral cells may be more broadly tuned than their presynaptic ORNs (**Figure 2**).

Similar to the synaptic coupling of *Drosophila* PNs (Kazama & Wilson 2009), sister mitral cells are reciprocally coupled by electrochemical synapses (Christie & Westbrook 2006). However, in *Drosophila*, sister PNs have similar trial-averaged odor responses, especially when recordings are conducted in the same brain. This similarity extends to spike timing at the millisecond timescale (Kazama & Wilson 2009). Sister mitral cells in the mouse olfactory bulb are not as similar in this way: Although odor-evoked changes in their firing rates are highly correlated, spike rate modulations in sister mitral cells occur at different times within the respiration cycle (Dhawale et al. 2010). These differences in modulation timing could be due in part to differences in intrinsic properties among sister neurons (Padmanabhan & Urban 2010). When odor stimuli are not fluctuating rapidly, spike timing can become an additional dimension for encoding odor identity (Laurent 2002). Thus, diversity among sister mitral cells could expand the available coding space.

The selectivity of lateral inhibition is a major open question in vertebrates, just as it is in *Drosophila*. Although two studies have proposed the existence of highly sparse and specific interactions among olfactory bulb glomeruli (Fantana et al. 2008, D.H. Kim et al. 2011), the evidence for this phenomenon was relatively indirect. Adjacent glomeruli in the olfactory bulb can have very different odor tuning (Soucy et al. 2009), so even a small region of local connectivity could produce relatively nonselective inhibition.

Key Open Questions

Although we understand some of the fundamental principles of olfactory processing in the *Drosophila* antennal lobe, some key questions remain unanswered:

How do PNs encode rapidly fluctuating stimuli? In a natural turbulent plume, odor

concentration can fluctuate rapidly (Murlis et al. 1992). No studies have examined how these sorts of stimuli are encoded at the PN level. Given that inhibition lags excitation, it is unclear whether inhibition is recruited by transient odor encounters.

Do glomeruli perform specialized computations? There are characteristic differences between identifiable glomeruli that are stereotyped across flies. For example, the number of ORNs in a given glomerulus varies across glomeruli by a factor of about four (de Bruyne et al. 2001, Shanbhag et al. 1999) and is correlated with glomerular size (Dekker et al. 2006, Kazama & Wilson 2008). Also, the number of LNs varies across glomeruli by factor of about five (Chou et al. 2010). Glomeruli differ in their levels of neuropeptide and neurotransmitter receptor expression; they may also differ in sensitivity to neurotransmitters (Nassel et al. 2008; Root et al. 2008, 2011). Finally, there are variations in the strength of lateral inhibition and lateral excitation (Olsen et al. 2007, 2010; Yaksi & Wilson 2010) as well as variations in the intrinsic properties of PNs (Kazama & Wilson 2008). These variations among glomeruli raise the following questions: Are these variables correlated or independent? Do they represent adaptations to the odors that are processed by each ORN type (Martin et al. 2011)? Are there specialized adaptations for processing social odors?

Why are LNs so diverse? Different LNs can target different portions of a glomerular compartment and can form either dense or sparse arbors within that compartment (Chou et al. 2010, Sachse et al. 2007, Seki et al. 2010). LNs also have diverse intrinsic electrophysiological (Chou et al. 2010, Seki et al. 2010) and neurochemical properties (Carlsson et al. 2010; Ignell et al. 2009; Winther et al. 2003, 2006). Do different types of LNs play different functional roles? Some evidence supports this idea (Sachse et al. 2007, Tanaka et al. 2009), but the number of characterized LN types seems to be outrunning the conceivable number of distinct functions of local interneurons. Before this idea can be tested, we need better tools for directing transgenic expression to specific LN types.

What is the function of excitatory LNs? Are these neurons actually important for boosting sensitivity near the absolute threshold for odor detection? Do they play an important role in recruiting GABAergic LNs, and if so, why (given that ORNs and PNs also provide excitatory input to GABAergic LNs)? Better genetic tools for mapping and manipulating electrical connections would help address these questions.

How is olfactory processing in the antennal lobe modulated by changes in the behavioral state of the organism? In particular, the effects of biogenic amines on antennal lobe physiology are largely uncharacterized. Serotonin reportedly inhibits ORN axon terminals while increasing PN odor responses (Dacks et al. 2009), but the mechanism of this effect is not known.

What dictates the innate hedonic valence of a particular pattern of PN activity? There is evidence that certain glomeruli are innately associated with a fixed hedonic weight. When activated individually, one glomerulus can be sufficient to elicit aversion (Suh et al. 2007), whereas the activation of a different individual glomerulus can be sufficient to elicit attraction (Semmelhack & Wang 2009). Odors that activate multiple glomeruli elicit a behavior that can be accounted for by summing the weights associated with each glomerulus (Semmelhack & Wang 2009). This summation would predict that coactivating two attractive glomeruli would always produce attraction, never aversion. Is this true? Notably, many odors are attractive at low concentrations but aversive at higher concentrations (Schlief & Wilson 2007, Wang et al. 2001). This observation can be reconciled with the sum-of-weights model, but only if the receptors for aversive glomeruli are systematically recruited only at high odor concentrations, implying low ligand-receptor affinities.

FUTURE DIRECTIONS

Ultimately, sensory systems neurophysiology has succeeded when it can account for the precision of the organism's behavioral responses (Parker & Newsome 1998). Thus, the field must develop better ways of measuring the precision of olfactory perception in *Drosophila*. What is the most dilute or transient odor stimulus that the fly can detect? What are the fastest fluctuations in odor concentration that the fly can resolve? What are the most chemically similar mixtures that the fly can discriminate? Some of the most exciting recent studies of olfaction have revealed surprising levels of behavioral performance in mammals (Smear et al. 2011, Uchida & Mainen 2003). Similar studies in the fly would be extremely useful in defining what *Drosophila* olfactory neurophysiology needs to account for.

A second important task for the field is to define the natural statistics of odors. A general principle of sensory neurophysiology is that neurons and circuits are adapted to maximize the rate of information transmission under stimulus conditions that are typical for a given organism (Simoncelli 2003, Wark et al. 2007). It is therefore important to define what constitutes a typical (or "natural") olfactory stimulus. More precisely, we would like to know the statistical distribution of olfactory stimulus parameters. What odors and what odor concentrations are typical of the natural environment? What odors naturally occur together? What are the natural temporal patterns of odor fluctuation in turbulent plumes? Answers to these questions will help us define the olfactory scenes that the nervous system might be adapted to encode.

DISCLOSURE STATEMENT

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

ACKNOWLEDGMENTS

Mehmet Fisek, Elizabeth J. Hong, Katherine I. Nagel, and Andreas Liu provided critical comments on the manuscript. Work in the author's laboratory is funded by the National Institutes of Health (R01DC008174) and a Howard Hughes Medical Institute Early Career Scientist Award.

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RELATED RESOURCES

An atlas of the *Drosophila* brain: **http://www.virtualflybrain.org**

A database of *Drosophila* neuronal morphologies and long-range connectivity patterns: **http://www.flycircuit.tw**

A tool for visualizing odors in the space defined by the major axes of their physicochemical properties: **http://odorspace.weizmann.ac.il/content/physicochemical-space**

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Annual Review of Neuroscience

Volume 36, 2013

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