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Smelling on the fly: sensory cues and strategies for olfactory navigation in *Drosophila*

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Navigating toward (or away from) a remote odor source is a challenging problem that requires integrating olfactory information with visual and mechanosensory cues. *Drosophila melanogaster* is a useful organism for studying the neural mechanisms of these navigation behaviors. There are a wealth of genetic tools in this organism, as well as a history of inventive behavioral experiments. There is also a large and growing literature in *Drosophila* on the neural coding of olfactory, visual, and mechanosensory stimuli. Here we review recent progress in understanding how these stimulus modalities are encoded in the *Drosophila* nervous system. We also discuss what strategies a fly might use to navigate in a natural olfactory landscape while making use of all these sources of sensory information. We emphasize that *Drosophila* are likely to switch between multiple strategies for olfactory navigation, depending on the availability of various sensory cues. Finally, we highlight future research directions that will be important in understanding the neural circuits that underlie these behaviors.

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Introduction

Chemical cues can signal the presence of food, a mate, a competitor, a predator, or a hazard. Thus, chemotaxis — defined as movement toward (or away from) a source of chemical cues — is central to the ecology of most animals. However, chemotaxis is not a purely olfactory behavior. Because an odor may be encountered far downwind from its source, navigation may also depend on information about wind direction and the visual environment. Thus, chemotaxis involves integrating information across sensory modalities. This makes chemotaxis an interesting

case study for understanding how the nervous system combines information from multiple sources.

Importantly, the optimal strategy for finding a chemical source may change as the environment changes. To take an obvious example, visual cues may be useful in the daytime but less useful at night. This makes chemotaxis an interesting behavior from the perspective of understanding how the nervous system selects a particular program of action among different alternatives.

In this review, we will focus on chemotaxis in *Drosophila melanogaster* (here called ‘the fly’, with apologies to other flies). *D. melanogaster* is an attractive model system for linking neural coding to behavior. Most notably, it is possible to make *in vivo* physiological recordings in this organism from single neurons within genetically identified populations [1,2].

We will begin by describing the strategies that flies and other insects use for chemotaxis. Next, we will discuss how the fly nervous system encodes olfactory information important for chemotaxis. Then, we will briefly discuss the roles of visual and mechanosensory cues in chemotaxis. Finally, we will discuss situations in which flies are likely to switch between chemotaxis strategies. We will neglect the topic of chemotaxis in *Drosophila* larvae, which is reviewed elsewhere in this issue [3]. Some of the topics we discuss have been previously reviewed with a different focus [4,5].

Chemotaxis strategies and the olfactory landscape

Insects have been shown to use multiple strategies to navigate toward odors. One strategy depends on measuring instantaneous concentration differences between two spatially separated odor sensors, and turning toward the side of the higher concentration (‘osmotropotaxis’). This behavior can be observed in tethered *Drosophila* walking on a spherical treadmill. The fly is exposed to two air streams having different odor concentrations, each directed at one antenna. Under these conditions, flies turn toward the antenna that is exposed to the higher concentration [6]. In other experiments, flies are tethered in the air so that they can rotate freely in the horizontal plane, and a narrow odor plume is created within a wedge of the rotational plane. In this apparatus, flies turn into the plume, but not when the antenna ipsilateral to the plume is shielded from odors. This suggests that the fly can measure concentration differences across the antennae during flight [7].

Osmotropotaxis is clearly important for chemotaxis in some insects, because spatially reversing the antennae of a locust (by crossing and fixing the antennae) hinders their ability to navigate toward the odor source in an airborne plume [8]. However, eliminating osmotropotaxis generally disrupts but does not abolish odor tracking in freely behaving animals [8–10]. This implies that animals rely on multiple strategies for tracking odors.

A second strategy involves flying upwind when an odor is sensed. This behavior is known as ‘optomotor anemotaxis’, and has been studied most extensively in moths, although similar behaviors have also been observed in *Drosophila*. On encountering an odor plume, both moths and flies in flight will turn and surge upwind [11–17]. When the plume is lost, moths switch to crosswind flight, which may help them track the unpredictable meandering of a plume [14,15,17,18]. It is not clear whether *Drosophila* engage in crosswind flight under the same circumstances. Anecdotal evidence suggests that flying and walking *Drosophila* produce zigzag movements when approaching an odor, suggestive of crosswind movement [19]. However, *Drosophila* can fly upwind in both continuous and pulsed odor streams [20*,21], unlike moths which do not fly upwind in a continuous stream. It has also been reported that tethered flying *Drosophila* will orient into continuous plumes, or plumes pulsed at high frequencies, but not plumes pulsed at low frequencies [22]. In the future, it will be important to clarify how *Drosophila* respond to temporal fluctuations in odor concentration, and how this promotes navigation.

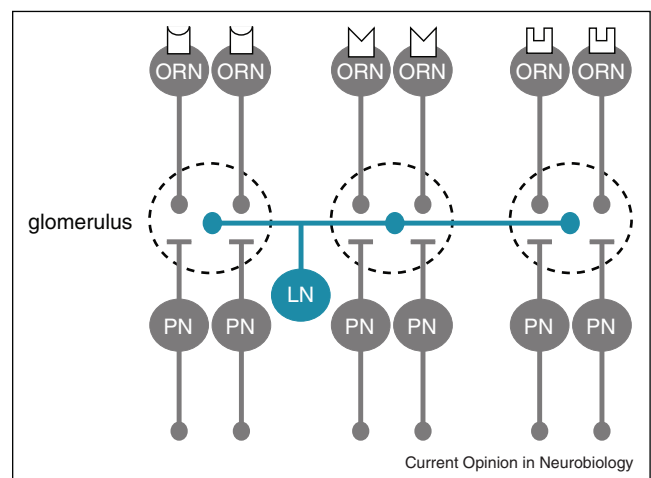
The current natural statistics of the olfactory landscape influence what navigation strategies will be most successful at a given moment. For a flying insect, the olfactory landscape is often dominated by temporal fluctuations in odor concentration. These temporal fluctuations are governed by the physics of turbulent airflow [18,23,24]. Importantly, the statistics of temporal fluctuations change as one approaches the odor source. For example, fluctuations tend to be largest close to the odor source, where wandering motions of the air break up the odor into concentrated filaments. Concentration fluctuations decrease as one moves downwind, both because odor filaments are broken into smaller pieces, and because diffusion moves odor into nearby patches of air [23,25]. It would be useful for a flying insect to take account of these systematic changes in temporal fluctuations, but it is unclear how much insects actually do this. It is also worth noting that the olfactory landscape can be quite different close to the ground. Specifically, rapid temporal fluctuations in odor concentration are reduced when the odor source is near ground level [23,25]. For this reason, different statistical features of the olfactory landscape (such as slow temporal modulations, or spatial gradients) may become relatively more important for walking insects, as compared to flying insects.

Neural encoding of odor cues

Thanks to recent advances in genetics and physiology, much is now known about how odor stimuli are encoded in the *Drosophila* brain. A key problem in odor encoding is maintaining sensitivity over a wide range of concentrations. Near an odor source, the instantaneous concentration of an odor can approach saturated vapor, especially at low air speeds. At the same time, the fly olfactory system can also detect very low odor concentrations: peripheral and central neurons have been identified that can respond to trillion-fold dilutions of saturated vapor [26]. How does the olfactory system achieve sensitivity to low concentrations while avoiding saturation at high concentrations?

Several properties of the fly olfactory system promote sensitivity to low odor concentrations. Flies have evolved a cohort of odorant receptors with a relatively high affinity for ligands with behavioral relevance. Specifically, receptors with high affinity for fruit odors and social odors appear to be over-represented [27*,28]. Additional mechanisms that promote sensitivity are found in the antennal lobe, where olfactory receptor neuron (ORN) axons terminate (Figure 1). Here, all the ORNs that express the same odorant receptor converge on the same postsynaptic projection neurons (PNs). Convergence should increase sensitivity, and indeed the number of ORNs that converges on a glomerulus seems to grow with the importance of their cognate ligands. For example,

Figure 1



Organization of the early olfactory system in *Drosophila*. Each olfactory receptor neuron (ORN) typically expresses a single odorant receptor, and all the ORNs that express the same receptor project their axons to the same compartment (glomerulus) in the antennal lobe. There, ORNs make excitatory synapses onto second-order projection neurons (PNs). Each PN dendrite innervates a single glomerulus, and receives direct input from all the ORNs that target that glomerulus. Glomeruli are also interconnected by local neurons (LNs), most of which are GABAergic. The major target of GABAergic inhibition in each glomerulus is the ORN axon terminal.

pheromone-sensitive glomeruli are innervated by unusually large numbers of converging ORNs [28,29]. Also, in a related *Drosophila* species, which lays eggs exclusively on morinda fruit, the glomerulus most sensitive to morinda volatiles is innervated by a particularly large number of ORNs [30]. The synapses from ORNs onto PNs are unusually strong and reliable, further promoting sensitivity [31].

Sensitivity can easily lead to saturation, but mechanisms that prevent saturation are also found at several levels of the olfactory system. Prolonged exposure to high concentrations of odor produces adaptation in ORN firing rates [32,33]. After adaptation, ORN transduction currents are both smaller and slower, as if the concentration of ligand were lower than it actually is [34]. Mechanisms that prevent saturation are also present in the antennal lobe. First, ORN-to-PN synapses become weaker when ORNs are stimulated to fire at high rates [31]. Some of this depression may reflect depletion of synaptic vesicles from ORN axon terminals. Vesicular release probability at these synapses is unusually high, and thus vesicles should be easily depleted [31]. In addition, high odor concentrations tend to drive more activity in GABAergic interneurons [35], which further decreases the gain of ORN-to-PN synapses [36,37]. GABAergic inhibition tends to prevent saturation of PN firing rates, and helps ensure that even intense stimuli remain discriminable [26,38].

As noted above, the olfactory system would benefit from encoding rapid temporal fluctuations in odor concentration. The *Drosophila* olfactory system is well suited for this: fly ORNs can encode concentration fluctuations up to ~ 10 Hz [34,39]. At the next level of encoding, in the antennal lobe, PN spike trains emphasize the high-frequency temporal information found in ORN responses, because PNs preferentially respond to rapid onsets in ORN activity [40]. This in turn depends both on the properties of the synapse from ORNs to PNs [31] and on inhibition from GABAergic interneurons [26,41]. Blockade of GABAergic inhibition in the antennal lobe has been shown to reduce the ability of moth PNs to encode rapid fluctuations in pheromone stimuli, and to inhibit moths from correctly tracking pheromone plumes [42].

The circuit mechanisms that allow *Drosophila* to detect concentration differences across the antennae are mysterious. This is because the vast majority of ORNs project bilaterally to both the ipsilateral and contralateral antennal lobes [43]. Furthermore, these bilateral ORNs synapse onto ipsilateral and contralateral PNs with equal connection probability [44] and similar synaptic strength [31]. One possibility is that asymmetric ORN stimulation could recruit asymmetric GABAergic inhibition. This is supported by a recent study of a glomerulus specialized for detecting pheromones in *Drosophila* [45]. Using

calcium imaging, this study found that responses in this glomerulus are asymmetric, and that GABAergic inhibition is important for this asymmetry. However, this study found no asymmetry for other glomeruli, which is puzzling, because flies can lateralize a variety of non-pheromonal odors [6,7].

Most of the studies on olfactory encoding in the *Drosophila* brain have used relatively static odor presentations. However, in the natural environment, odor concentration often fluctuates rapidly. In the future, it will be important to understand how neurons in the brain respond to rapidly fluctuating stimuli, especially because many of the mechanisms that shape PN odor responses — including synaptic depression and GABAergic inhibition — are time-dependent processes.

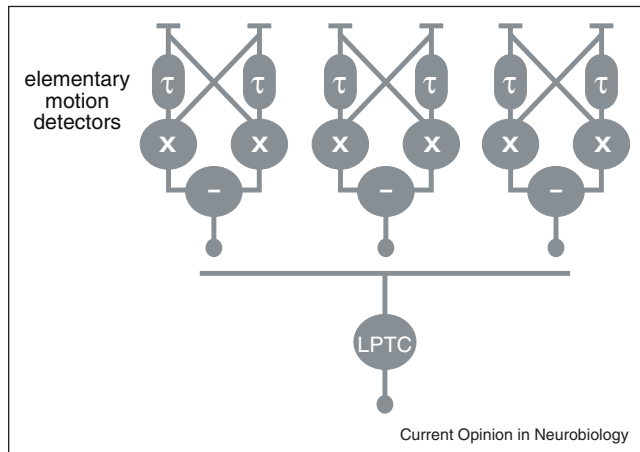
Visual contributions to chemotaxis

Insects often rely heavily on visual cues for chemotaxis, particularly in flight. An important visual cue is large-scale optic flow, produced when the fly moves relative to the ground — either under its own power, or when displaced by wind. Optic flow provides the most reliable information about groundspeed [4,46,47]. Optic flow can also provide information about wind direction. If an insect is flying straight upwind, it perceives optic flow purely along its longitudinal axis, but if the fly deviates from its upwind course, it will perceive a translational component to the optic flow and can turn accordingly to correct its trajectory [4].

Optic flow processing in the early visual system of the fly has been well characterized in the blowfly *Calliphora* [48] (Figure 2). Optic flow-sensitive neurons appear to be tuned for the axes of rotation that a fly is most likely to experience during flight [49]. Neurons responsive to optic flow have recently been discovered in *Drosophila* [50–55]. These studies not only confirm the generality of the findings in *Calliphora*, but are also beginning to go beyond the *Calliphora* literature in unraveling the circuit mechanisms of optic flow processing.

In addition to allowing flies to maintain constant ground speed, visual objects also serve as landmarks to orient flies during odor tracking. Indeed, in some contexts, visual landmarks can be critical. In a uniformly illuminated arena without visual texture, freely flying flies do not move toward an odor source [56] and tethered flying flies do not actively rotate into an odorized segment of space [57]. However, when a wide-field visual pattern is added to the same arena, flies now move toward the odor source [56,57]. In these experiments, ambient air speeds were low, and thus there may have been no reliable air flow cues to indicate the direction of the odor source. By contrast, in other experiments where air speeds were higher but the arena was nearly dark, tethered flying flies reliably turned upwind to face the odor source, implying

Figure 2



Organization of the wide-field visual motion processing system in *Drosophila*. The optic lobe is thought to contain an array of elementary motion detectors, each of which receives input from two adjacent photoreceptor sites. In algorithmic terms, each elementary motion detector consists of two arms, each of which low-pass filters the luminance at one site, and then multiplies it by the unfiltered luminance at the adjacent site (schematized by τ and \times). The output of the detector is the difference between the two arms, which will be sensitive to the direction of motion. The cellular components of the elementary motion detectors have not yet been identified. Individual lobula plate tangential cells (LPTCs) are thought to integrate excitatory input from an array of elementary motion detectors which have the same preferred direction, and which are arranged along one axis of the retina (horizontal or vertical). This creates selectivity for horizontal or vertical global translational motion. Interconnections among LPTCs broaden their receptive fields, and also confer selectivity for rotational motion. Such wide-field motion patterns tend to arise in the context of self-movement, rather than the movement of an object in the environment. See [48] for a comprehensive review. Note that this wide-field motion processing system is distinct from the small motion detection system reviewed elsewhere in this issue [70].

that vision is not absolutely required for flies to orient toward an odor [58].

Mechanosensory contributions to chemotaxis

Although flying flies are thought to rely mainly on vision for determining wind direction, wind can also be sensed using the antennae. Each antenna contains a mechanosensitive structure known as Johnston’s organ (JO) [59]. A feather-like structure on the antenna (called the arista) acts as a sail which makes the antenna sensitive to small air velocities. The arista also confers direction-selectivity on JO, because air velocity vectors that are perpendicular to the arista are most effective at displacing it [60]. The two arista on either side of the head are angled in different directions, and so a fly should be able to compute both the direction and the magnitude of the wind by combining information from the two JOs (Figure 3).

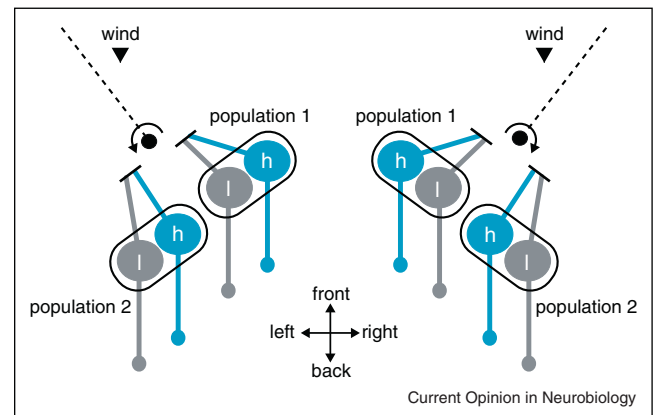
Behavioral experiments demonstrate that flies use JO to obtain information about wind direction. First, there is indirect evidence that flies make an initial estimate of

wind direction before taking flight. This estimate would have to rely on mechanosensory rather than visual information [4,61]. Second, tethered flies flying in the dark orient upwind (a behavior known as ‘anemotaxis’), and this behavior is impaired when the antennae are stabilized, implicating JO [62].

Odors promote anemotaxis: freely flying *Drosophila* tend to turn upwind in response to an odor [20], as do freely rotating tethered flies, and this is abolished by clipping the arista [58]. This implies that JO is necessary for directing the turn. (Another study using a similar tethered paradigm found that manipulating JO had a more modest effect [7], but this study used much lower air speeds and a smaller odor plume, thereby likely minimizing air speed cues but also providing spatial olfactory cues.)

Johnston’s organ neurons (JONs), like ORNs, are capable of both high sensitivity and wide dynamic range. This is due in part to a diversity of JON types: calcium imaging experiments suggest that different JONs have different sensitivities. Namely, some JONs are only recruited by ‘sound’ (high-frequency, low-amplitude air movements) whereas other JONs are only recruited by ‘wind’ (low-frequency, high-amplitude air movements) [60] (Figure 3). In order to better understand how mechanosensory cues

Figure 3



Organization of the wind sensing system in *Drosophila*. Wind-sensitive neurons are located in Johnston’s organ, which senses the movement of the most distal antennal segment relative to the rest of the antenna. This figure schematizes one pair of Johnston’s organs as viewed from above the dorsal side of the fly’s head. The dashed line represents the plane of the arista, a feather-like structure which protrudes from the distal antennal segment. Wind pushing on the arista rotates the distal antennal segment, and this stretches the dendrites of one population of neurons within Johnston’s organ while compressing the dendrites of the opponent population in the same organ. In this diagram, wind pointing toward the rear of the fly (arrowhead) is rotating the arista as indicated by the arrows, thereby stretching (exciting) population 1 and compressing (inhibiting) population 2. The magnitude of arisal movement should depend on both the velocity and direction of air movement. Each population of Johnston’s organ neurons is thought to contain cells tuned to high-frequency (h) and low-frequency (l) movement.

are encoded in *Drosophila*, it will be important to clarify these differences among JON types, and also to characterize how mechanosensory cues are encoded by the central neurons that receive input from JONs.

Although JO is likely to contribute most to sensing wind when flies are standing on the ground, it may also play a role in flight. In flight, the arista moves in response to the fly's own wing beats [63]. If the fly is turning, then the wing contralateral to the turn should be beating with a larger amplitude, and so the JO contralateral to the turn will be more strongly activated. If each JO tends to suppress the amplitude of wing beats on the side of the body which is opposite to that JO, this would tend to stabilize and amplify turning maneuvers [63]. Because each JO responds preferentially to contralateral wind [60], JO suppression of wing beat amplitudes on the opposite side of the body could also promote upwind turning in flight [63].

Switching between navigation strategies

Because natural olfactory environments are complex and constantly changing, flies are likely to use multiple sensory cues to navigate toward attractive odors. Which strategy is most useful depends on which cues are available. For instance, if spatial concentration gradients of an odor are not sufficiently steep to support osmotropotaxis, flies may rely more on the statistics of temporal fluctuations or on wind direction. Conversely, if temporal fluctuations are minimal (near the ground, for example), flies may rely more heavily on osmotropotaxis.

To take another example, flies may also switch strategies when the wind switches from a constant direction to a shifting pattern. If the wind direction is relatively constant, then the best way to find the plume may be to fly crosswind. However, if the wind direction is shifting, then it may be more useful to fly upwind or downwind, because the crosswind extent of the plume will be larger than its downwind extent [4,64]. Indeed, a fly flying in a wind tunnel tends to fly crosswind when the wind direction is constant, but upwind when the wind is shifting [65].

Much of the conceptual interest of chemotaxis lies in understanding how multimodal sensory cues are integrated, and how the organism can switch between different behavioral programs in response to changing cues. To tackle this problem, one would need to know which neurons combine multimodal cues and control the switch in behavioral programs. While such neurons currently remain elusive, the future for such endeavors in *Drosophila* is promising. For vision [50–55] and olfaction [66–68], sensory neurons up to or beyond the third layer of sensory processing have been characterized, and genetic markers for these neurons have been identified. Wind-sensitive neurons and their targets in the brain are also beginning to be characterized in detail [60,69]. New

optical and genetic techniques are allowing researchers to map connected circuits reaching from the sensory periphery to the thoracic ganglion [68]. While the study of olfactory navigation in *Drosophila* currently lags behind the study of chemotaxis in other well-characterized insects, the unique advantages of the *Drosophila* preparation should lead to many exciting new discoveries in the years to come.

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