Behavioral algorithms and neural mechanisms underlying odor-modulated locomotion in insects.

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Abstract
Odors released from resources such as a mate, host, and food are often the first signals to reach an animal. Changes in locomotion produced by odors is an important mechanism by which animals discover resources important to their survival. Odor-modulated changes in locomotion in insect is a whole-suite of flexible behaviors that allow insects to close-in on these resources from long distances, perform local searches to locate these resources, and to assess them. Here we review, the changes in locomotion across many insect species. We emphasize that changes in locomotion induced by odors are diverse. In particular, the olfactory stimulus is sporadic at long distances and becomes more continuous at short distances. This change in temporal profile produces a corresponding change in an insect's locomotory strategy. We also discuss the neural circuits underlying odor-modulation of locomotion. The review seeks to bring together insights gleaned by researchers working across multiple insect species.

A question that we often get from layperson and expert scientists alike is how sharks find their victim a mile away. The ability of sharks to home in on their prey from large distances remains persistent despite efforts both in popular science and in peer-reviewed work to dispel this myth. Sharks do possess a nervous system that is exquisitely sensitive to chemicals in blood and can likely detect a prey from a mile away; despite this sensitivity they cannot track the prey over such long distances. Tracking resources based on their smell – odor-tracking – is challenging because odor gradients are not preserved beyond the immediate vicinity of the animal. Instead, animals typically experience concentrated patches of odor followed by clean air; these patches of odors are detectable far from the odor source but contain no directional information. This difference between detection and tracking is best quantified in the context of the champion smellers in the insect world – male moths; males of many moth species can detect a single molecule of the female pheromone (Kaissling, 1986). However, this exquisite sensitivity does not allow it to track down females from a kilometer away as suggested by earlier studies (Bossert and Wilson, 1963; Collins and Potts, 1932). Later work has demonstrated that it is hard for moths to locate females even 80 meters away (Elkinton et al., 1987).

Nevertheless, odor-tracking is ubiquitous and keen across the animal kingdom, albeit not over kilometers, and underpin many behaviors essential to an animal's survival. To truly appreciate the complexity of odor tracking, a short description of odor dispersal, a topic covered in detail in other reviews (Capelli et al., 2013; Celani et al., 2014; Elkinton et al., 1984; Murlis et al., 1992; Riffell et al., 2008), is essential. Consider a small source of odor such as a female moth. Pheromones released by a gypsy moth can spread by diffusion, a process in which the odor molecule move down a concentration gradient. However, the diffusion rates are so low that it can be discounted as an important mechanism for odor dispersal beyond a few centimeters from the

odor source (Riffell et al., 2008). Instead, much of the dispersal of odor occurs through advection and convection, processes by which a whole mass of air moves due to spatial differences in air density, pressure, and temperature, carrying odor molecules with it. In regard to odor-tracking, there are two noteworthy features of this mass transport: First, odors move in packets such that local odor concentration is above the detection threshold for long distances from the odor source; this makes odors the first source of information about a resource. Second, the distribution of odor packets in space is not a strong predictor of the location of the odor source. Therefore, odors provide crucial information about objects from afar without providing a roadmap to the object that other senses such as vision might.

How does an animal go about finding the source of an odor in the absence of direct directional cues? The best potential source of directional information during odor-tracking is the wind direction. When the wind direction is constant, and the landscape flat, flying upwind upon odor contact is an excellent strategy because the odor source is likely to be upwind. However, in the real world, odor sources are not point sources, wind direction changes frequently (David et al., 1982), and our world is not flat but irregular. Each of these three features make the relationship between odor encounter and the source of odor unpredictable (Cardé and Willis, 2008) as upwind direction is no longer a good predictor of the source of the odor (Brady et al., 1989). As an example, pheromones from a gypsy moth perched on a tree will be affected by eddies generated by the tree and can acquire the size of the tree itself. Similarly, wind speed and direction changes regularly; change in wind direction means that the relationship between upwind direction and the direction of odor source no longer holds. Finally, odor dispersal depends on topography and vegetation. Obviously, an animal that encounters an odor does not know all the factors that influence its dispersion in a given condition, or the optimal strategy (or

any strategy for that matter) to reach the odor source in a given condition (Vergassola et al., 2007). Thus, the problem confronting any animal performing odor-tracking is how the sporadic detection of odor can be efficiently used to get closer to the source of the odor.

Even under the best of circumstances, odor tracking itself only leads the animal to the vicinity of the source, and not directly to the source itself. There are various reasons. In the case of the moth, due to the eddies under the tree, odor-tracking cannot place it on the source, just the right tree. Similarly, odor plumes emanating from a mammal can be as large as the entire animal, but a mosquito will still feed preferentially from different body parts (De Jong and Knols, 1996). Long-range odor tracking is replaced by a different strategy near the source of the odor. Using a male moth as an example: once odor-tracking leads the moth to the right tree, the moth makes vertical flight in the immediate vicinity of the tree, lands on the tree trunk, and walks the last few centimeters to the female (Charlton and Cardé, 1990). Over short distances near the female, visual cues might play a role (Charlton and Cardé, 1990; De Jong and Knols, 1996; Doane, 1968). In some cases, such as flower feeding by moths, a conjunction between olfaction and vision is necessary for successful feeding (Raguso and Willis, 2002).

A problem orthogonal to locating the source of the odor is to determine the identity of the odor and its implication to an animal's behavior. The identity of the odor affects the behavioral response. The behavior towards a given odor is also highly dependent on the state of the animal such as feeding or mating status.

In summary, odor modulation of locomotion is not a single behavior optimized to find the source of odor. Rather it is a suite of behaviors that together ensure that animals can find and exploit resources critical to their survival (Figure 1). Odor-guided locomotion require exquisite sensitivity to multiple sensory systems, neural circuits to process and integrate sensory

information, spatial memory, behavioral flexibility, and the ability to act with incomplete information. Insects possess all these capabilities. In this review, we will consider behavioral algorithms underlying odor modulation of locomotion in insects, and the neural circuits underpinning this behavior. This review is divided into three sections. We start by reviewing behavioral algorithms that underpin different aspects of an insect's odor-tracking behavior followed by a review of how the behavioral algorithm is implemented in the insect's brain. We end by reviewing the neural circuits underlying odor identification.

Behavioral algorithms underlying odor-modulation of locomotion

Experiments aimed at understanding behavioral algorithms in odor-modulated locomotion face three challenges that are important to keep in mind when discussing the behavioral algorithm that animals employ. First, the complexity and diversity of the odor landscape experienced by insects in nature is difficult to replicate in the lab. Second, even in simplified laboratory experiments, it is difficult to quantify when the animal encountered an odor making it difficult to evaluate the animal's underlying strategy. Finally, inferring strategy from an animal's circuitous walking or flight paths is itself a daunting problem.

Despite these challenges, much progress has been made in understanding the behavioral algorithms at play during odor-modulated locomotion by doing experiments in simpler behavioral arenas that do not replicate the full complexity of natural behaviors. With a few important exceptions, most of the experiments in odor tracking can be divided into three major types, with the first type being experiments involving insects navigating towards an odor-source in a laminar plume. These experiments are performed in a wind tunnel at low wind speeds such that there is a small cylinder of odorized region within the tunnel. The second type of experiments use similar methods but with turbulent rather than laminar plumes. These turbulent

plumes still do not capture the complexity of real-world plumes because the wind direction is still constant, and much of the spatial scales of turbulence observed in nature are too large to be observed within a wind tunnel. Finally, there are experiments conducted in still air without any wind. These three types of experiments reveal both the conserved nature of an insect's behavioral strategy and its flexibility. We describe behavioral algorithms in two parts: In the first part we describe medium-range navigation to the source of odor; these processes affect navigation over about 100 meters from the odor source. In this regime, the animal has detected an odor but does not know the source location and seeks to find this source. In the second part, we review near-range navigation during which the insect has either narrowed down the source considerably or has already found it and it is taking the last few steps to engage with the source.

Navigation towards an odor source. In both walking and flying insects, there are two conserved motor programs that aid in medium-range navigation to an odor source. First is odor-gated anemotaxis or locomotion upwind: Many insects either show little directional preference or walk downwind in the absence of odor, but will locomote upwind in the presence of odor (Alvarez-Salvado et al., 2018; Budick and Dickinson, 2006; Willis and Arbas, 1998; Willis and Avondet, 2005; Wolf and Wehner, 2000). This upwind locomotion is part of a two-component motor program called odor-gated anemotaxis (Kennedy and Marsh, 1974), both components are sensorimotor reflexes to an encounter with an odor patch (Figure 1). The first component is a surge during which contact with an odor result in a short, rapid upwind movement (surge). In most cases, surge is phasic as the rapid upwind progression decays soon after odor contact. Second, a loss of odor causes an insect to cease upwind progress and execute gradually widening series of turns; between each turn is straight flight perpendicular to the wind direction (cast). In the context of moth flight, casts are often supposed to halt upwind progress with locomotion

perpendicular to the upwind direction. Unlike a surge, the cast can be tonic and can continue until the insect encounters another odor patch.

This strategy – cast and surge and its origin as a sensorimotor reflex was first proposed by Baker and colleagues (Baker, 1990) after observing that moths appear to respond to pheromones with sub-second latency (Baker and Haynes, 1987) and deducing from electroantennogram measurements that encounter rate, too, varies between 2-3 Hz (Baker and Haynes, 1989). Putting these two facts together, it appeared that flight behavior could be explained as a sensorimotor response to each contact. This view started to gain prominence when free flight behavior could be measured at the same time as odor contact in two moth species, *Heliothis virescens*, and *Cadra Cautella* (Mafra-Neto and Cardé, 1994; Vickers and Baker, 1994a). Both studies found that contact with a pulse of female pheromone led to an upwind surge with a ~200 millisecond delay that lasted about 500 millisecond and terminated in a cast. Since these pioneering studies, the cast and surge strategy has been demonstrated in other flying insects (Dekker and Cardé, 2011; Thiery and Visser, 1986; van Breugel and Dickinson, 2014) which also perform cast and surge with response latencies strikingly similar to those of moths. A strategy akin to cast and surge is also observed in walking cockroaches where turns were made at the border between odor and no-odor regions (Bell and Tobin, 1981), and *Drosophila* which were shown to surge in response to a pulse of odor, and increases their turning-rate at the end of the odor pulse (Alvarez-Salvado et al., 2018).

The basic idea behind cast and surge is that when the direction of air is constant, an iterative cast and surge strategy will bring the insect closer to the source of odor. Work in moths has demonstrated both this iterative strategy as well as how it explains the difference in behavior under different stimulus conditions. In laminar plumes, the moth turns frequently and flies

crosswind because each surge takes the insect out of the odor, and a contact is only made after the moth turns around (Mafra-Neto and Cardé, 1994). In turbulent plumes, where the contact with odors is intermittent, the moth's trajectory is straighter owing to the fact that each contact with the odor results in a surge that is barely extinguished before the next contact with an odor is made resulting in another upwind surge (Mafra-Neto and Cardé, 1994; Mafra-Neto and Cardé, 1995). Strikingly, when pheromones are pulsed at high enough frequency even the tracks in a ribbon plume becomes straight because each surge ends in another odor stimulation leading to another surge and completely extinguishing turns (Mafra-Neto and Cardé, 1996; Mafra-Neto and Cardé, 1994; Mafra-Neto and Cardé, 1995).

A second conserved motor program requires the presence of odor for its expression but is not a direct response to individual odor encounters; odors play a permissive rather than an instructive role. This motor program is a long-lasting internally generated motor program (Baker et al., 1984; Kennedy and Marsh, 1974; Willis and Arbas, 1991; Wright, 1958) and has two components that are roughly analogous to cast and surge but have different mechanisms (Figure 1). First, equivalent to surge but not resulting from a direct contact with odor, the insect has straight flight segments during which it maintains constant ground speed and orientation in relation to wind direction. This constancy has been observed in many studies (David and Kennedy, 1987a; Haynes and Baker, 1989; Marsh et al., 1978; Von Keyserlingk, 1984; Willis and Baker, 1994; WILLIS et al., 1991) and reflects visually guided anemotaxis. Second, these straight segments are interrupted by crosswind turns that occur at remarkably regular intervals (David and Kennedy, 1987a; Haynes and Baker, 1989; Von Keyserlingk, 1984). The regularity of the turns suggest that the turns result from internally-generated turning (Willis and Arbas, 1991) rather than from discrete odor encounters which are unlikely to be regular. Apart from

gating this motor program, odors also modulate this program. One modulatory effect of odor is to decrease the overall locomotion speed as the number of encounters increase (Baker and Haynes, 1987; Kennedy, 1983; Marsh et al., 1978; Willis and Baker, 1994). Because the speed decreases as the insect approaches the source of odor, the crosswind excursions become smaller giving the impression that the insect is homing in on the odor source (Marsh et al., 1978). In some moths the frequency of counter-turning also increased as the moth approached the odor source, once again giving an impression that moths are homing in on the odor source (Willis and Arbas, 1991). Similar results have been reported elsewhere (Kennedy, 1983; Kuenen and Baker, 1982). In contrast, decreasing encounters lead to wider casts (David and Kennedy, 1987b).

The cast and surge motor program, and the internally generated program are similar and might appear to be just a single motor program. Some authors have made a distinction between them based on the characteristics of the cross-wind movement, which they classified as either zigzagging and casting: casting being movement perpendicular to wind direction without any upwind progress, and, zigzagging being movement with upwind progress (Kennedy et al., 1981; Preiss and Kramer, 1986). These differences could be real and significant; however, it is difficult to convincingly distinguish between the different mechanisms without quantifying the relation between sensory stimulus and each turn. Recent work has emphasized the reflexive aspects of the tracking behavior over the internally generated program (Baker and Haynes, 1987; Baker and Vickers, 1997; Budick and Dickinson, 2006; van Breugel and Dickinson, 2014). However, the most parsimonious interpretation of the data is that the reflexive cast and surge strategy is superposed on top of the internally generated motor program, and both are necessary to explain an insect's overall behavior: It is clear that encounters with odor filaments have a dramatic effect on insect behavior. It is equally clear that many aspects of odor-tracking behavior do not rely on

sensorimotor reflex; only a prior encounter with odor appears sufficient. In many scenarios there is a cast-like behavior well within the odor boundary; i.e., loss of odor is not necessary (Jung et al., 2015; Kennedy et al., 1981; Kuenen and Baker, 1982; Tao et al., 2020). Similarly, many features of the behavior, including turn rates and alternation in turning, are preserved in still air (Baker and Kuenen, 1982; David and Kennedy, 1987b; Saxena et al., 2018), and in extended bouts in odorless air, and characterize a moth's behavior even while tethered and in the absence of wind, visual or odor information (Willis and Arbas, 1991).

There are many reasons why both a reflexive and internally driven motor programs are necessary. First, tracking an odor plume, particularly in flight, is difficult even in laminar flow. Recent studies found that flies can only stay within a predictable, cylindrical plume for just 500 millisecond (van Breugel and Dickinson, 2014). Similarly, sensory delays of 200 millisecond typically associated with cast-and-surge strategies imply that an animal is always reacting to its past rather than its present. These small errors and sensorimotor delays are not too debilitating when the wind direction is constant because sequential casts would eventually lead the insect back into the plume, and a purely reflexive strategy would succeed. However, realistic plumes with variable wind direction and speed likely result in long intervals during which there is no odor contact. An internally generated turn strategy is likely to be necessary under these conditions. These conclusions are supported by modeling studies that employ agent-based models. One example is work performed by Belanger and Willis (Belanger and Willis, 1996) to evaluate the usefulness of a sensory-driven strategy versus an internally-generated strategy. They found that a reflexive strategy works well in a laminar plume but not in a turbulent plume.

Another important conclusion from the Belanger and Willis study (Belanger and Willis, 1996) is that the known mechanisms of odor-tracking did not come close to the performance of the

actual moth demonstrating that there are mechanisms at play that are left to be discovered. One limitation of most studies – even those that heroically try to control odor stimulus - is that the control over stimulus is unlikely to be precise. Another is the lack of detailed analysis of an insect's tracks and generative models that establish that most features of the behavioral response have been captured. Recent studies in walking Drosophila have begun to remedy these limitations. A recent study which took advantage of optogenetic stimulation to create a precise pattern of olfactory stimulation showed that activating a fly's olfactory system did not change the fly's propensity to turn while exiting an odorized area (Tao et al., 2020). Rather, flies slowed down as they exited the odor plume giving the impression that there is increased turning at the border. Even more remarkably, the turns made at the border of the odorized area were much larger. This study also found that there are kinematic changes associated with olfactory stimulation which cause the flies to slow down in the stimulus and increase its speed outside the stimulus region. Another recent study that replicated turbulent plumes with more precise stimulus control than in previous experiments demonstrated that the fly's behavior is much better modeled as stochastic than as a pure sensorimotor reflex (Demir et al., 2020). Another important result from this study is that odor encounters modulated the stop-to-walk transition, an important movement characteristic. An additional recent study in flies found that odors affect multiple aspects of locomotion (Jung et al., 2015).

Although wind direction and odor encounter play an overt role in odor-tracking, visual feedback is critical. Anemotaxis in flight is optomotor anemotaxis (Kennedy, 1940) because without visual feedback, it is difficult for flying insects to disambiguate wind flow due to their own movement from the direction of the wind. Wind causes a discrepancy between the direction of insect's movement and stationary objects; resolution of this discrepancy allows upwind

progress (Vickers and Baker, 1994b). Crosswind drift is detected by transverse image flow. Flying insects also use visual feedback to maintain a constant groundspeed (Zanen and Cardé, 1999).

Local search near the odor source and harvesting the resource Behavior near the odor source is markedly different from the behavior during odor-tracking as the insect's objective changes from getting near the odor source to locating the resource, assessing, and utilizing it. One change is that the insect's locomotion strategy is altered into a local search strategy (Figure 1). Local search in insects was first characterized in the context of blowflies that change their locomotion to a local search after feeding on sugar and was thought to be initiated by resource utilization (Dethier, 1957; Murdie and Hassell, 1973; Vinson, 1977). However, it is now clear that resource-specific cues such as food odors or sex pheromones, will also evoke local search (Jung et al., 2015; Sabelis et al., 1984).

Just as navigation to the odor source, local search is not a single motor program but a constellation of mechanisms that ultimately result in the animal being restricted to a given area. One mechanism is looping or spiraling in which the animal increases its turn rate and maintains a turn bias in a single direction resulting in looping trajectories; this was the behavior originally observed in blowflies; but has also been observed in response to odors (Beevers et al., 1981; Sabelis et al., 1984). Another mechanism is a decrease in run-length or the distance between each subsequent stop. Such a mechanism of local search was observed in bumblebees (Heinrich, 1979) and honeybees in a patch of flower (Schmid-Hempel and Schmid-Hempel, 1986); and has been observed in flies in response to odor alone (Jung et al., 2015).

A mechanism that has received particular attention is turning back into the resource patch when the patch border is encountered. Unlike spiraling or change in run-length, turning back requires a

sense of directionality. A decreasing odor concentration can serve as a directional cue eliciting a turn. Indeed, many insects can compare odor concentrations across the two antennae to turn towards the side that experiences the higher concentration (Borst and Heisenberg, 1982; Duistermars et al., 2009; Martin, 1965). However, bilateral input is not necessary for turning back into the odor. Temporal comparisons between odor concentration at two locations can also be made (Bell and Tobin, 1982; Lockey and Willis, 2015). However, insects successfully turn at the border even when the patch abruptly ends, and there is little scope to evaluate concentration. An important component of the mechanism appears to be a large increase in turn amplitude. Both mites and wasps make large turns back into a resource patch (Sabelis et al., 1984; Waage, 1978). These large turns were also observed in *Drosophila* (Tao et al., 2020). In the *Drosophila* study, both a large decrease in speed coupled with an increase in turn amplitude was shown to be important. Importantly, all the local search mechanisms can be elicited by modalities other than olfaction. Patch-edge recognition can occur through gustation (Mayor et al., 1987; Nelson, 1977) or vision (Bell et al., 1983; Lawrence, 1982) alone, which suggests that local search mechanism can utilize the sensory modality that provides the most salient stimulus.

Unlike the change in locomotor strategy which can be driven by many different stimuli, acceptance of the resource as food, oviposition site or mate often requires conjunction of multiple modalities such as touch, vision and gustation (Figure 1). The synergism between vision and olfaction in the landing of insects on objects is well-documented. An interesting recent study in *Drosophila* has explored the interaction between odors and visual object, and found that as the fly tracks an odor plume, its normal cast-surge behavioral pattern is altered when the fly encounters an odor plume in the presence of an object: the fly slows down and lands on the closest object (Saxena et al., 2018). Indeed, many visual behaviors such as landing on an object

only occur in the presence of odors in both flies and mosquito (Van Breugel et al., 2015; Vinauger et al., 2019). In other studies, it has been demonstrated that flying flies cannot locate the source of odors without high contrast visual stimuli (Frye et al., 2003; Stewart et al., 2010).

Similarly, there are many instances in which acceptance of a resource depends on non-olfactory cues. Diamondback moths' acceptance of a site for oviposition depend both on texture and odor (Spencer et al., 1999). Onion maggot flies assess plants for oviposition based on olfaction, vision and contact (Harris and Miller, 1982). Moths will approach a hidden odor source, hover around it but not initiate feeding in the absence of odors (Raguso and Willis, 2002). Similarly, courtship behavior in flies and other insects require multisensory integration (Krstic et al., 2009; Pan et al., 2012).

As summarized in Figure 1, odor-modulation of locomotion involves distance dependent locomotor strategies. At each distance, a whole suite of changes in locomotion characterizes changes in behavior.

Neural mechanisms underlying odor-modulation of locomotion

The behaviors described above require many computational abilities: The first ability is sensory processing and multimodal integration. Navigation to an odor source begins with detection of an odor. Odor information is combined with wind direction and full field visual signals such as optic flow to navigate towards the odor from large distances. Near the odor source, visual recognition of small objects is combined with other sensory cues to land on the object if the animal navigates to the odor in flight. Gustatory and mechanosensory information is combined with olfactory information to decide whether to accept or reject the resource. A second ability is memory – both spatial and episodic. Spatial memory is required to keep track of one's position

in space to direct the next movement. Episodic memory is also required to recall past odor encounters and make decisions based on odor history. Finally, behavior depends on other circumstances such as an animal's risk assessment and its own state. We will discuss these capabilities in insects, and how they aid or limit an insect's ability to locate and utilize resources. It is important to note that the circuits are conserved enough across insects that, despite some differences, the basic computation and logic are likely similar; therefore, in discussing the role of different circuits, we draw on research across insects.

Unimodal sensory processing of odors, wind, and photons. Odor detection occurs in the olfactory receptor neurons (ORNs) in the antennae and palps (Figure 2A). Each ORN expresses one or few odorant receptors (ORs); the number of receptors range from just ten in some lice (Hansson and Stensmyr, 2011; Kirkness et al., 2010) to a few hundred in bees (Robertson et al., 2003). The ORs expressed in each ORN determines its odor response profile. In many (Schachtner et al., 2005), but not all insects, ORNs expressing a given receptor project to a single glomerulus where they interact with second-order neurons called projection neurons (PNs). About half of the PNs in *Drosophila* are themselves uniglomerular, and the other half are multiglomerular. A large majority of the uniglomerular PNs use acetylcholine, the major excitatory neurotransmitter in invertebrates; a minority use GABA as their neurotransmitter. The division of multiglomerular PNs into excitatory versus inhibitory is more equal. The output of the antennal lobe are four different channels of information: excitatory and inhibitory uniglomerular PNs (uPNs); excitatory and inhibitory multiglomerular PNs (Bates et al., 2020). The presence of these parallel pathways from the antennal lobe to higher brain centers is conserved across insect orders, but there are also important differences (Galizia and Rössler, 2010).

ORs can be specific and highly sensitive to ecologically relevant molecules such as pheromones; estimates suggest that a single moth pheromone molecule can produce a change in firing rate in an ORN (Kaissling, 1986). Even when ORNs are not specific to a single odor, they can still be highly sensitive to odors (Hallem and Carlson, 2006; Olsen et al., 2010a). An insect's ability to detect odors is further enhanced through convergence from the ORNs to the PNs (Kazama and Wilson, 2009). In *Drosophila*, 40-100 ORNs project to the same glomerulus; each ORN synapses on each uPN (Kazama and Wilson, 2009). This large convergence provides a mechanism for amplification. Indeed, weak odor responses are highly amplified in the PNs (Bhandawat et al., 2007; Olsen et al., 2010b). Convergence can also shorten the time required to detect an odor encounter, clearly an important consideration when tracking odors in an everchanging environment (Jeanne and Wilson, 2015).

There is circumstantial evidence that convergence is an important mechanism for increasing odor sensitivity (Hansson and Stensmyr, 2011): In male moths, the antennae are highly branched to provide a large surface area to accommodate a massive number of ~42,000 pheromone sensitive sensilla (Keil, 1989). Similarly, cockroaches have ~36,000 pheromone sensitive sensilla (Nishino et al., 2018). An overrepresentation of ORNs that respond to critical pheromones supports the idea that convergence is important for sensitivity. Moths also have a sexually dimorphic macroglomerular complex (Koontz and Schneider, 1987) – a set of glomeruli that process sex pheromones – that is enlarged in males (Boeckh and Boeckh, 1979; Hansson et al., 1992). A large expansion of glomeruli related to processing of sex pheromones is also observed in *Drosophilid* flies (Kondoh et al., 2003). The increased glomerular size is likely related to an increase in the number of ORNs that respond to pheromones. This increase is observed not just in the case of pheromones, but also for ORNs that support other ecologically important processes

that are under environmental selection such as expansion in ORNs related to detection of odors related to its specific food source, observed in the specialist *D.sechellia* compared to the generalist *D. melanogaster* (Dekker et al., 2006). A similar expansion is also reported in mosquitoes (Syed and Leal, 2009). The sensitivity of individual ORNs and the convergence from ORNs to PNs allows insect to detect odors at low concentration with short latency.

Olfactory circuits play a role not only in detection of odor but also comparison of instantaneous odor concentration near different parts of the body. As discussed in the previous section, it is unlikely that an instantaneous concentration comparison between ORNs in different parts of the body such as the two antennae plays a large role in odor tracking over long distances. However, they appear to play a crucial role in trail tracking across the animal kingdom (Hangartner, 1967; Rajan et al., 2006; Takasaki et al., 2012), and also play a role in determining the borders of a resource patch (Bell, 1985). It is also likely that they can play a crucial role under conditions in which there are sharp odor gradients despite the fact that in many conditions, it does not appear to be the only factor (Tao et al., 2020). Regardless of whether bilateral comparisons are mission critical, there are neural mechanisms that can extract and accentuate local concentration differences at the two antennae. Even in *Drosophila*, where most ORNs project bilaterally, the PNs can differentiate between ipsilateral and contralateral ORNs, likely based on the different axon lengths of the ipsilateral and contralateral axons (Gaudry et al., 2013). In both moths and cockroaches, a more elaborate architecture exists to take advantage of different spatial patterns of odors (Nishino et al., 2018). A recent study in cockroaches showed that different pheromone-related ORNs in different parts of the antennae project to small sub-regions of the glomerulus (Nishino et al., 2018). PN responses, too, were responsive to the location of the odor stimulus on the antennae. This topographical arrangement appears to be maintained in higher-order olfactory

circuits, thus providing neural substrate for comparing concentration at different spatial locations. The topographical arrangement can, in principle, create a map of instantaneous pheromone concentrations. Whether an instantaneous map of the local distribution of pheromone (or other odors) concentration is created and how these instantaneous comparisons are employed in driving behavior is an important avenue for future investigation.

Apart from olfactory information, mechanosensation and vision are crucial for odor-guided behavior, and we will discuss them briefly. Both mechanosensation and vision have been covered in greater detail in other reviews (Borst et al., 2020; Borst et al., 2010; Krishnan and Sane, 2015; Silies et al., 2014). There are many mechanoreceptors in insects that can detect airflow. Additionally, airflow causes activation of neurons in the antennal lobe (Anton and Hansson, 1994; Galizia et al., 2000; Han et al., 2005) through projections of mechanosensory hairs or the responses of ORNs to mechanosensory stimuli. However, the specialized mechanoreceptor for detecting airflow is found in the Johnston's organ in insect antennae (Ai et al., 2007; Kamikouchi et al., 2009; Kamikouchi et al., 2006; Schneider, 1964; Yorozu et al., 2009). These receptors are highly sensitive to airflow; Drosophila can behaviorally respond to air speeds as low as 0.5 cm/s – a flow rate that is well within speeds described as "calm" by humans. Both the first-order Johnston's organ neurons and their second-order counterparts are sensitive to the direction of airflow (Figure 2B). The information from the two antennae can be combined to decode the direction of wind. One class of third-order neurons in *Drosophila* do appear to compare inputs from the two antennae to directly encode the wind direction (Suver et al., 2019). Work in flies have also shown that flies pick a heading with respect to the direction of airflow and can respond to changes in direction with changes in heading (Currier et al., 2020; Okubo et al., 2020). Nevertheless, work is needed to assess how well insects can disambiguate exogenous

airflow from motion generated airflow. It is also unknown how well insects can assess the mean wind direction in a natural environment during which wind speed and direction vary constantly.

The result of visual processing is two kinds of visual information (Figure 2B): The first kind is wide-field motion created by self-motion; as the animal moves, the world moves past it. This pattern of movement is critical for controlling speed and assessing whether one is going straight or turning, and for stabilizing flight paths. Wide-field information is carried by lobula plate tangential cells or LPTCs (Figure 1B). These LPTCs connect to various higher brain centers such as the neuropils of the central complex, a region of the brain important for computing an insect's spatial orientation. The LPTCs also project to a region of the brain called the superior slope where visual and olfactory information is integrated to generate motor commands. The activity of the LPTCs themselves are modulated by odors (Wasserman et al., 2015). Odors result in increased activity in the LPTCs which is likely important for a correct orientation into the wind during the surge. A second type of behaviorally critical visual information is the detection of visual features in the environment such as the long vertical shapes resembling a tree or detecting a small object as a conspecific. Information about visual features is carried by another set of neurons called the lobula columnar neurons or LCs (Figure 2B). A comprehensive analysis using genetic tools in Drosophila has revealed that there are 22 LCs that encode different visual features, and likely play an important role in olfactory behavior (Wu et al., 2016) that is directed at an object. LCs directly contact descending neurons and mediate visuo-motor behaviors (Bidaye et al., 2020; Cheong et al., 2020); LC inputs are also integrated with other inputs in the posterior part of the brain. Through mechanisms that are not well-understood, neurons downstream of the LCs likely play an important role in integrating visual information about objects with its smell to drive behavior.

Higher-order olfactory processing and multi-modal integration: PNs from the antennal lobe project to two higher-order processing centers – mushroom body and lateral horn (Galizia and Rössler, 2010; Kirschner et al., 2006; Martin et al., 2011; Masse et al., 2009); although minor connections to other protocerebral regions also exist (Aso et al., 2014b; Tanaka et al., 2012). Both the mushroom body and lateral horn are centers for multi-modal integration and participate in a wide array of computations through their multimodal input and through connections to other higher brain centers (Figure 1B). Although there are differences, the mushroom body and lateral horn of insects share many design features. As discussed below, these two brain centers are highly divergent in their organization.

The mushroom body has a highly organized anatomy (Aso et al., 2014a; Frank et al., 2015; Li et al., 2020) that reveals its basic function (Aso et al., 2014b). The major sensory input into the mushroom body in many insects is from PNs; in flies, only excitatory PNs provide input into the mushroom body, whereas the situation for other insects is unclear. The mushroom body also receives inputs from other sensory modalities, encoding information about temperature (Frank et al., 2015; Liu et al., 2015), humidity (Marin et al., 2020), taste (Kirkhart and Scott, 2015; Masek et al., 2015), visual stimuli (Ehmer and Gronenberg, 2002{Li, 2020 #48; Vogt et al., 2016)} and mechanical stimuli (Li and Strausfeld, 1999). The relative importance of these inputs might depend on the species: cockroaches appear to receive more mechanosensory input, whereas bees more visual input (Menzel, 2012) implying that mushroom body is a site for multimodal integration with different sensory input weighed differently. These sensory inputs interact with the main local neurons of the mushroom body called the Kenyon cells in a region of the mushroom body called the calyx. In *Drosophila*, each Kenyon cell contacts approximately seven PNs (Caron et al., 2013; Eichler et al., 2017). Importantly, the connectivity between PNs and

Kenyon cells is not stereotyped from animal to animal, and despite contacting seven PNs, most Kenyon cells respond to far fewer odors (sparse representation) compared to PNs, a conserved property of Kenyon cells across all insects studied thus far (Honegger et al., 2011; Perez-Orive et al., 2002). The axons of the Kenyon cells project to the lobes of the mushroom body. Although the lobes are a contiguous neuropil, they are segmented in terms of processing: Each segment receives input from a small subset of dopaminergic neurons, and outputs to a small subset of mushroom body output neurons (Strausfeld et al., 2009). The input-output relationship between Kenyon cells that carry input sensory information and mushroom body output neurons that carry output behavioral messages are modified by signals from the dopaminergic neurons to affect learning.

Recent work has elucidated the detailed anatomy of *Drosophila* mushroom body so that we understand almost the entire circuit (Aso et al., 2014a; Li et al., 2020). There are 22 types of output neurons whose dendrites tile the length of the lobes; 20 types of dopaminergic neurons also arborize in corresponding zones to form processing modules. A large body of work, reviewed elsewhere (Modi et al., 2020), shows that these zones are computational units that perform associative processing with the dopaminergic neurons and provide the reinforcement signals that modulate the transfer of information from the Kenyon cells to the mushroom body output neurons. The dopaminergic neurons appear to play a role in determining the type and time-scale of the association being performed within each compartment (Aso and Rubin, 2016; Aso et al., 2010; Burke et al., 2012; Cohn et al., 2015; Hattori et al., 2017; Liu et al., 2012; Tsao et al., 2018). The inputs into dopaminergic neurons, the diversity of plasticity rules, and diverse dynamics of dopaminergic synapses, including a variety of co-neurotransmitter all make it

possible to employ the same circuit architecture to make associations of different complexity and timescales.

The architecture of mushroom body is perfect for learning associations between odors and other sensory stimuli. This idea is well-supported by multiple lines of evidence including physiological experiments, the massive expansion of mushroom body in insects that perform more complex olfactory association tasks (O'Donnell et al., 2004) and in social insects(Heisenberg, 2003), and its requirement in many olfactory memory acquisition behaviors. However, associating odors with events in the world is not its only role in odor-guided behavior. A block in the mushroom body leads to elevated locomotor activity in bees (Martin et al., 1998), crickets and grasshoppers (Huber, 1974). Activating individual mushroom body output neurons can produce attraction or repulsion to odors (Aso et al., 2014b). It has been hypothesized that in a complex environment where there are multiple sources of odors, mushroom body can tie together inputs from PNs that are activated at the same time allowing disambiguation of different olfactory stimuli (Baker and Hansson, 2016). Both the dopaminergic neurons and the output neurons interact with premotor circuits, and with the output neurons from lateral horn. It is likely that these neurons together play a major role in odor-guided locomotion. Little is known about the nature of these computations.

The circuit architecture of the lateral horn is strikingly different from that of mushroom body. The lateral horn in all insects studied receives input from all PNs (Galizia and Rössler, 2010); in flies this includes the excitatory PNs that also project to the mushroom body as well as the inhibitory PNs. The lateral horn also receives input from other sensory modalities including gustation, mechanosensation, thermosensation and vision (Chakraborty and Sachse, 2021) as well as from the mushroom body. Two salient differences in the organization of mushroom body

and lateral horn are: First, unlike mushroom body which is segmented into clear and well-defined processing units, lateral horn is not, and the underlying computational logic appears unclear. Second, unlike mushroom body, connectivity pattern between projection neurons, the intrinsic and output neurons of the lateral horn is stereotyped enough that the same neurons – similar anatomy, connections, and responses - can be identified across animals. Based on this connectivity pattern, lateral horn consists of ~500 cell-types in Drosophila compared to only 15 types of Kenyon cells (Schlegel et al., 2021). There are also >37 types of output neurons from the lateral horn. Although there is some disagreement among different studies, neurons in the same morphological class have similar odor response profiles (Frechter et al., 2019; Jeanne et al., 2018), once again highlighting the stereotyped circuit of the lateral horn.

Most physiological studies of the lateral horn have tried to assess its function as a site of olfactory sensory integration, and as a result there is some evidence that the lateral horn can function as a site for computing odor valence, i.e., whether an odor is attractive or repulsive (Strutz et al., 2014), or as a site for encoding odors based on chemical structure (Frechter et al., 2019). However, there is hardly any consensus regarding the fundamental computations performed in the lateral horn. The lateral horn output neurons project to different regions of the protocerebrum where they interact with outputs from the mushroom body, and with premotor circuits. Given that the lateral horn receives multisensory input, receives inputs from mushroom body, and receives input from downstream motor areas, it is unlikely that the fundamental logic underlying the function of lateral horn can be uncovered from an assessment based purely as a center for integration of olfactory input. This conclusion is supported by a recent comprehensive analysis of the anatomy of the lateral horn in *Drosophila* which found that many neurons in the

lateral horn are strongly influenced by feedback from motor areas rather than feedforward projections from olfactory neurons (Schlegel et al., 2021).

Lateral horn appears to play an important role in many innate behaviors driven by ecologically important stimuli that does not require great deal of sensory integration. One example is the behavioral responses of Drosophila to CO_2, which is sensed by a single ORN class, appears to be completely mediated by lateral horn (Varela et al., 2019); behavioral response to geosmin is another example (Huoviala et al., 2020). In the context of a moth's behavioral response to pheromones, a region adjacent to lateral horn – often referred to as inferior lateral protocerebrum - is a site where inputs from mono-glomerular PNs, multiglomerular PNs, and inhibitory PNs are integrated (Anton et al., 1997; Kanzaki et al., 2003; Kárpáti et al., 2008; Kárpáti et al., 2010; Lee et al., 2019). One hypothesis is that this integration is important for a differentiation between individual pheromone components versus a blend. Another hypothesis is that the different kinetics of response and different axonal lengths might provide important information about the stimulus (Lee et al., 2019). In most insects – flies are an exception because their antennal lobe receives bilateral inputs – the lateral horn is also a site for integration of information from the two antennae. Finally, some of the integration of pheromonal inputs with wind and visual input also occurs in the lateral horn.

In sum, both the mushroom body and the lateral horn should be treated as highly recurrent circuits for sensorimotor transformation and not as feedforward processing centers along the pathway from sensation to behavior.

Circuits that integrate spatial information with sensory input to produce motor commands. The spatial context for orientation and navigation is computed in the central complex, which is a collection of central brain neuropils. Many recent reviews describe the computation performed in

the central complex (Pfeiffer and Homberg, 2014; Turner-Evans and Jayaraman, 2016; Webb and Wystrach, 2016). In brief, three of the central complex neuropils, the ellipsoid body, the fan-shaped body, and the protocerebral bridge form a ring attractor that records the current heading of the insect. Central complex also receives direct information related to wind direction (Okubo et al., 2020) which allows it to reference internal representations to external directional stimuli such as wind direction and is used by insects to orient relative to airflow (Figure 1B). Silencing fan-shaped body neurons affects the ability of flies to make corrective turns with respect to the wind (Currier et al., 2020).

Orientation-related information is communicated from the central complex to the lateral accessory lobe. In moths, medial protocerebral neurons that respond to pheromones also project to lateral accessory lobe (Seki et al., 2005). These medial protocerebral neurons in turn receive their information from lateral horn (Namiki et al., 2014). Many descending neurons receive input from the lateral accessory lobe (Figure 1C). These descending neurons, therefore, have much of the information needed to send navigation-related motor commands; many are responsive to pheromones. These neurons have an interesting property that they are bistable and are referred to as flip-flop neurons (Kanzaki et al., 1994); each state lasts upto 30 seconds with state-transitions being mediated by stimuli. Thus, these flip-flop neurons have the correct properties necessary to mediate an insect's behavior which include the internally generated counterturns that are non-reflexive.

As described above, one pathway that controls odor-gated behavior arises from the descending neurons (DNs) that receive input from the lateral accessory lobe (Figure 1C). There is another pathway: the neurons from the medial protocerebrum also project to the posterior surface of the brain to a region called the posterior slope, from which many DNs originate (Figure 1C). At least

in the case of moth pheromones, these DNs have a more phasic response to pheromones (Namiki et al., 2018) and are likely responsible for mediating stimulus triggered responses such as the phasic surge response or the turn response to odor.

It is likely that much remains to be discovered in terms of which DNs respond to odor stimuli as well as the relationship between DNs and behavior. Nevertheless, modelling studies seeking to model plume tracking show that turns driven by the flip-flopping neurons can serve (Adden et al., 2020; Ando et al., 2013) as a mechanism for odor tracking. In these two studies that are similar to each other, outputs of flip-flopping neurons were used to guide turns; two mutually inhibiting flip-flop neurons drive turns on each side of the body. Such a simple system appears to replicate the moth's odor-tracking behavior.

Identification of odor and how the behavior depends on odor identity

Thus far the review has largely focused on the neural mechanisms involved in locating the odor source. Another important problem is identifying the odor, a task for which the olfactory system is optimized. The large family of ORs with different odor tuning, and connections between ORNs and higher-order neurons provide an ideal substrate for odor identification. Because most odors activate multiple ORN classes, olfactory systems can, in principle, encode innumerable odors. Many studies across a range of insects have focused on the problem of circuit mechanisms of odor discrimination, and this topic has been extensively reviewed elsewhere (Laurent, 2002; Masse et al., 2009; Su et al., 2009; Wilson, 2013). This ability to discriminate between odors can be used to associate different odors with other stimuli that indicate resources. Associative conditioning with olfactory stimulus is an important model for learning and has yielded many seminal insights on the cellular, molecular and circuit mechanisms underlying learning (Davis, 2011; Margulies et al., 2005; Menzel et al., 2006; Modi et al., 2020).

Another theme that has emerged is that many ORNs are specialists and respond specifically to a single ecologically relevant odor. These odors are important for a range of odor-gated behavior such as courtship (Dickson, 2008), aggregation, food avoidance and approach, aggression, choice of substrate for egg-laying among others (Anderson, 2016; Aranha and Vasconcelos, 2018). Much work has been done to elucidate the roles of such specialist odors and the circuits by which their detection modulates behavior. One surprise from recent EM reconstruction of the *Drosophila* olfactory circuit is that, particularly at the level of lateral horn and beyond, the signals from these ORN classes diverge to many downstream neurons. Thus, it is unlikely that many olfactory behaviors function as labeled line (Huoviala et al., 2020). This divergence makes sense because most of the ecologically important behaviors are multimodal as well as plastic – properties that require extensive integration.

Moth sex pheromones are also specialist odors. A major component of most moth pheromone, bombykal, activates a single ORN-type with high specificity. In many moth species, odor-tracking behavior is elicited by a specific blend of odors rather than a single compound (Berg et al., 2014; Mustaparta, 1997; Vickers et al., 1991), a characteristic that is important in ensuring that a male is tracking only its conspecific. In many moths, the odor-tracking response is highly sensitive not only to the components of the blend but the exact ratio between them (Baker, 2008; Vickers, 2002). One interesting question is whether a moth waits for the exact blend or if aspects of the behavior can be triggered by a non-optimal blend. This question has not been studied as intensely as the odor-tracking algorithm itself, but existing data suggests that even in moth species in which the full tracking program relies on the exact blend, the requirement is less stringent for aspects of the behavior such as initiation of upwind flight (Vickers, 2002). Moreover, addition of exogenous pheromone component from a closely related species affected

some aspects of the tracking motor program (Mustaparta, 1997; Vickers, 2002; Wu et al., 2015) while leaving others intact. These data suggest that odor-tracking is not organized as a unitary behavior; rather, it is a result of parallel sensorimotor loops that connect activity in known ORNs to aspects of the overall behavior.

This question – whether odor modulation of locomotion is composed of independent sensorimotor loops – was addressed in targeted experiments designed to ask how different combinations of active ORNs affect a fly's locomotion (Jung et al., 2015). The authors created an arena in which a known combination of ORNs could be activated and found that each ORN-class only affected a subset of locomotor behaviors. These results are best interpreted as a sensory-motor transformation between ORN classes active and the eventual behavior. As an example, they found that activating just one ORN class – one containing the *Or42b* receptor - affects the run duration. However, a combination of multiple active ORNs is essential to change the propensity to turn sharply. Thus, each combination of active ORN class can be thought of as a sensory-motor feature that affects a particular aspect of locomotion. The olfactory circuits – particularly those in LH – are tailor-made to make these sensory motor transformations.

Conclusion and future work

As described above, over the last few decades much progress has been made in discovering the behavioral algorithms that underlie insects' behavioral response and their neural implementation. This progress provides a strong framework with which gaps in our knowledge can be approached.

One deficit is the absence of the complete dataset required to understand olfactory behavior in nature: Simultaneous position of the animal along with odor stimulus, wind direction and other sensory signals. With modern positioning techniques to locate an insect's position(Knight et al.,

2019), wireless electronics to sense the environment and measure electrical signals in real-time(Harrison et al., 2011; Pawson et al., 2020; Thomas et al., 2012), it seems possible to study odor-guided locomotion in a natural environment, particularly in the context of large insects. These datasets when combined with modern statistical methods (Datta et al., 2019) for analyzing behavior and the relationship between neural responses and behavior have the potential to not only illuminate odor-guided locomotion in detail but also contribute immensely to the inner workings on the brain.

Another rich area for future work is understanding the neural implementation of odor-guided behaviors in the brain. Here recent progress in *Drosophila* in generating genetic tools to probe specific neurons(Luan et al., 2020), and to activate and inactive(Simpson and Looger, 2018) these neurons as well as large scale datasets(Dorkenwald et al., 2020) that describe connectivity between neurons in the brain make it possible that we will be able to make progress on understanding the sensorimotor transformation at the level of single neurons. Finally, great strides have been made in introducing genetic tools in other insects(Mansourian et al., 2019).

In summary, we predict a productive future for a comparative approach to understanding odor-guided locomotion through use of large insects in field studies, through leveraging the power of genetic tools and neuroanatomy in Drosophila, and finally through the introduction of powerful genetic tools widely across the insect class.

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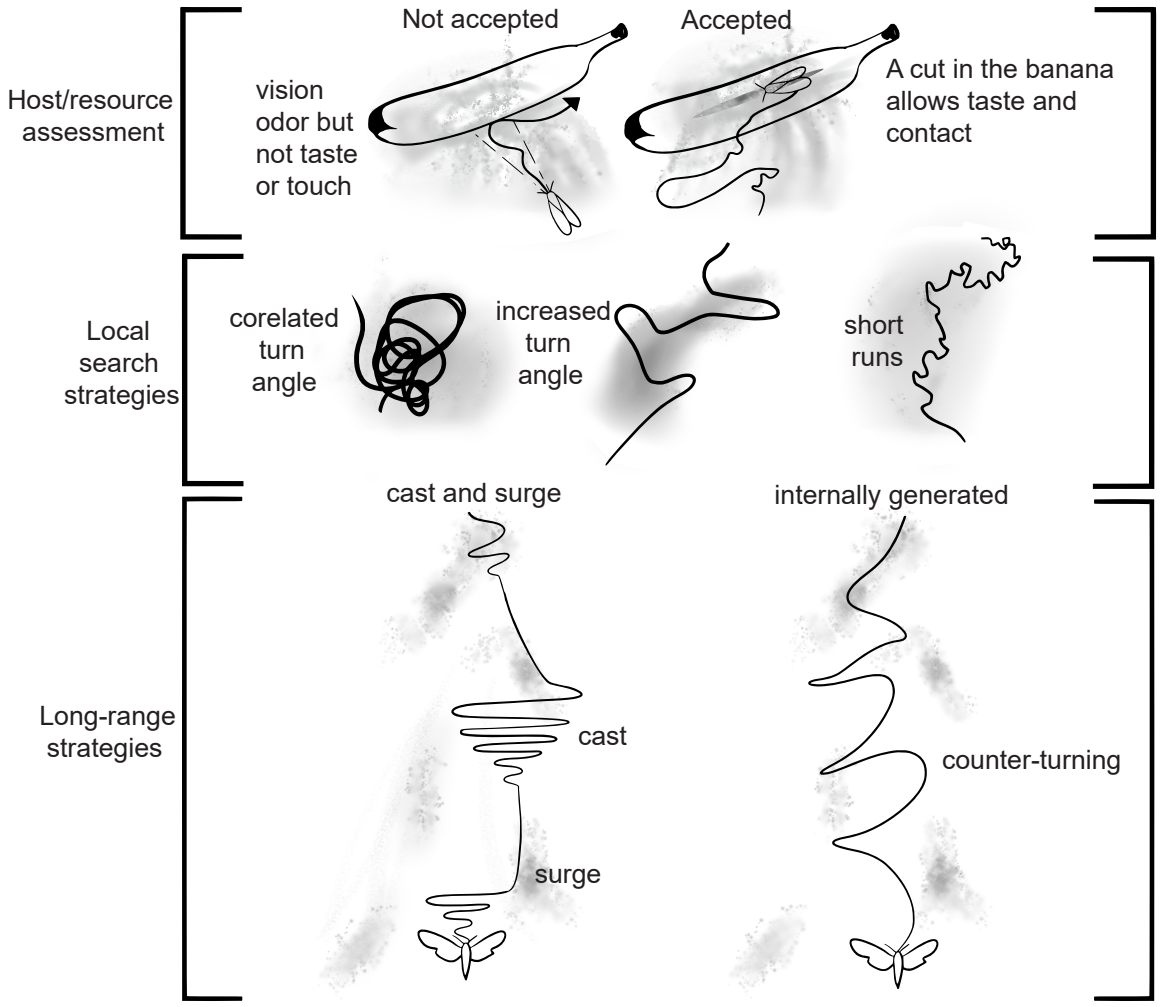

Figure 1. Insects employ distance-dependent locomotor strategies. Odor profile is very different at long distances from the odor-source where they are patchy (gray shading) and near the odor source (where they are continous). In response, the behavioral strategies are different as well. The behavioral strategies are detailed in the text but the important point is that there are a whole-range of strategies that change with distance from the odor. Only a small number of strategies are depicted above.

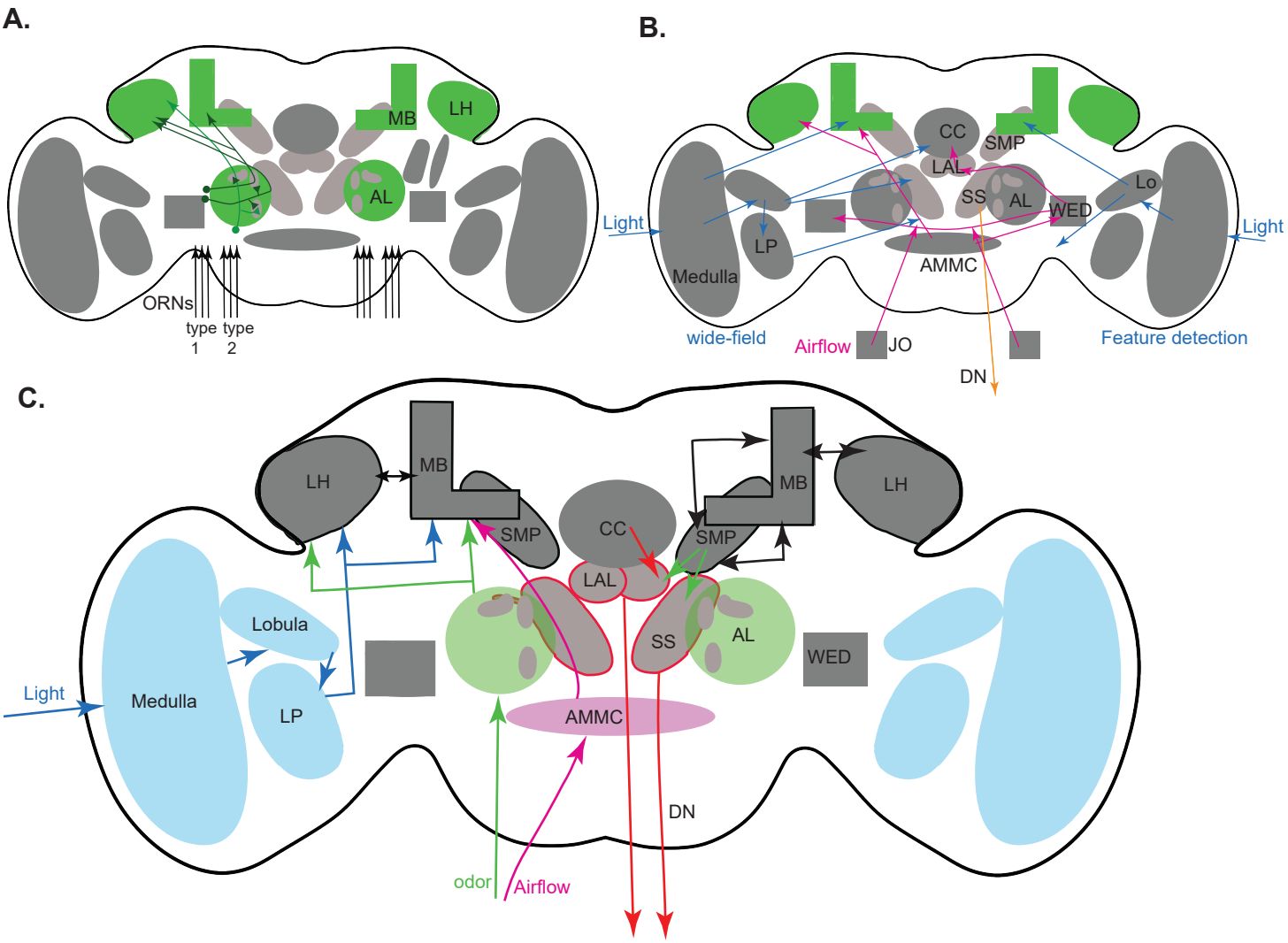

Figure 2: Circuits underlying Odor-guided locomotion. A. Regions of the brain important for olfactory processing. There are many types of ORNs depending on the olfactory receptors that they express. Multiple ORNs of the same type converge on to a glomerulus (shown in grey) within the antennal lobe (AL). There are many classes of PNs - uniglomerular, multiglomerular, excitatory (dark green) and inhibitory (light green). The third-order processing center for olfactory information is mushroom body (MB) and lateral horn (LH). MB only receives excitatory PN inputs. Almost all PNs project to LH. **B.** Visual (in blue) and airflow (in magenta) information are also important for odor-guided behavior. Two parallel streams of visual information - widefield information such as that arises from motion, and feature detectors are important for odor-guided behavior. Airflow is detected by the Johnston organ (JO) neurons in the antenna, and through various intermediate centers connect to central complex (CC) neuropils to allow insects to orient themselves with respect to airflow. One important point to note is that third-order olfactory centers such as MB and LH are centers for multimodal integration and receive visual or air flow information. **C.** Flow of information underlying odor-guided locomotion. Neuropils in green, blue, and magenta are largely unimodal sensory processing centers that process olfactory, visual and mechanosensory information. Many central brain regions such as MB, LH, superior medial protocerebrum (SMP) play an important role in multi-modal integration through connections from multiple sensory systems and recurrent connections between each other (marked with black border). Motor commands originate from lateral accessory lobe (LAL) and from superior slope (SS). Motor regions are marked with a red border.