Relating early olfactory processing with behavior: a perspective

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A fundamental goal in sensory neuroscience is to understand the rules that govern how neural activity evoked by a stimulus drives the final behavioral outcome. Here, focusing primarily on the insect olfactory system and its first two anatomical stages: olfactory sensory neurons in the insect antenna and their postsynaptic targets in the antennal lobe, we review the current understanding of the relationships between odor-evoked neural activity and behavior. The compiled evidences suggest that these olfactory circuits closer to the sensory periphery may already represent sensory information in a format that is easily translatable to behavior.

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Introduction

Olfactory systems of phylogenetically diverse animals have striking similarities indicating that a common set of organizational and information processing principles may be employed for translating chemosensory inputs into appropriate behavioral outputs [1,2]. In this review, we discuss some of the rules that have been identified to link physiology with behavior in this sensory modality. For the sake of conciseness, our focus here is primarily limited to the first two anatomical centers of the insect olfactory pathway, the antenna and the antennal lobe (analogous to the olfactory epithelium and the olfactory bulb in vertebrates [2]).

The architecture of the insect olfactory sensor

In insects, volatile chemicals are typically detected by olfactory receptor neurons (ORNs) in the antenna and maxillary palps. The current dogma is that most ORNs selectively express a specific receptor gene from a large family of olfactory receptors, along with a universally expressed co-receptor [3–5]. In addition, ORNs expressing gustatory and ionotropic receptors that detect certain classes of volatile chemical cues have also been found in the antenna [6–10]. Thus far, neurophysiological investigations suggest that the tuning of specific ORNs to specific sets of chemicals is determined by the molecular identity of the olfactory receptor gene they express [11,12]. Further, the seven transmembrane domain protein members of the olfactory receptors family were shown to function primarily as ligand-gated ion channels [13] ensuring rapid response initiation [14], which is in contrast with the vertebrate odorant transducers that act as a G-protein coupled receptors [15].

The olfactory receptor neurons, analogous to their gustatory counterparts also transduce chemical signals into trains of action potentials. These action potentials are generated through a signaling cascade that involves the upstream olfactory receptors that provide graded potentials and the downstream spike generation component [16]. Therefore, it is possible to block the olfactory sensory neurons from spiking without interfering with the olfactory receptor function [16], or to activate the spiking component independent of olfactory receptor stimulation [17]. Whether this cascaded two-stage arrangement offers additional advantages for odor processing right at the level of the olfactory receptors in the cilium is not known.

Organization of olfactory receptor neurons in the insect antenna

The ORNs are housed in sensory hairs called 'sensillum' distributed along the length of the antenna. The sensory hairs vary in their morphology, number of neurons they house, type of olfactory receptors expressed, and their sensing function (e.g., chemosensor [11,18,19], mechanosensor [20], humidity sensor [21], among others). These different sensilla types have a stereotyped placement in the antenna [22], and axons from sensory neurons that are housed in these sensillum types are spatially separated in the downstream antennal lobe [23,24]. Whether this organization facilitates competitive or cooperative lateral interactions between inputs driven by different sensillum types is yet to be determined.

Within a single sensillum, competitive interactions have been reported between the co-housed ORNs [25••] (Figure 1a). Within an individual sensillum, a common potential difference is maintained between the dendritic and the axonal compartments of the ORN due to the

electrical insulation of the sensillar lymph (a salty solution that bathes the dendrites) from the hemolymph (a fluid that bathes the somatic and axonal compartments). This arrangement can be considered analogous to an electrical circuit where two resistors are connected in parallel to a battery (note that the potential difference between the dendritic and somatic compartments is equivalent to the battery, and the individual ORNs can be regarded as variable resistors). Consequently, when one ORN is strongly activated, its input resistance is lowered, allowing most of the transduction current to flow through it while simultaneously reducing the input drive for the other co-housed neuron. This 'ephaptic' coupling mechanism allows transient firing in one ORN to inhibit generation of action potentials in the other co-housed ORN. Intriguingly, such lateral intra-sensillar interactions between groups of sensory neurons can modulate the innate behavioral preference of fruit flies to certain odor combinations [25**]. Therefore, these results suggest that even the organization of sensory neurons in the insect antenna may have been optimized to generate an appropriate behavioral response in environments where multiple cues can be encountered simultaneously.

Behaviorally important single sensory neuron activity

The presence of dedicated ORNs ('specialists') that drive a specific behavioral outcome forms another line of evidence to suggest neural activities closer to the sensory periphery can be good indicators of the final behavioral response. For example, one scheme for translating sensory input to behavior is the 'labeled-line' approach. In such a scheme, a 'private' odorant activates the 'specialist' ORN, which then drives subsequent neural activities in a dedicated information-processing channel or a 'labeled-line'. Furthermore, neural activity in this channel can be shown to be necessary, and sometimes sufficient, to generate or modulate the odor-evoked behavior. Note that either the sensory neuron activated or the odorant identity uniquely tags this channel. Therefore, this hypothesis can also be interpreted as a processing scheme that uniquely caters to odorant-driven innate behaviors. Several such labeled-line input–output mappings must co-exist to produce the repertoire of behavioral response exhibited by an organism. Some examples of such labeled-line approaches have come from studies of innate behaviors such as the response to alarm signals and stress avoidance [26,27], host-seeking [8,28], food attraction [9,29], food avoidance [10,30], and pheromone communications [31,32].

If such 'odor-specific' coding does exist, then it would be reasonable to expect that the neural activity in such dedicated olfactory channels are kept segregated from other sensory channels, and also treated differently than the 'generalist' inputs that might activate multiple ORNs. Indeed, previous studies have revealed that the second-

order neurons (projection neurons in the antennal lobe) that are driven by specialist ORNs are more likely to retain the odor specificity of their inputs [33•]. However, this one-to-one response mapping appears to be relinquished beyond the first two processing stages, and multiple labeled-lines tend to co-localize in the lateral horn (a third-order olfactory circuit associated with innate preferences) [34]. Nevertheless, different classes of sensory input, such as food versus pheromone, are segregated in the lateral horn [34] (Figure 1b). Similarly, it has been demonstrated that odorants that attract and those that repel insects are more likely to activate sensory neurons that drive activity in distinct loci within the lateral horn [34,35]. Hence, it is possible that distinct 'labeled-lines' may converge quickly onto overlapping higher-order neurons in order to drive similar odor-driven behaviors (i.e., response to generally attractive vs. repulsive odorants) [36].

A second line of evidence for labeled-line coding comes from the comparison of the strength of presynaptic inhibition at the ORN axonal terminals (Figure 1c). For example, it was found that a sensory neuron that detects a stress-related aversive odorant receives comparatively less pre-synaptic inhibition than a pheromone sensing ORN [37•]. Hence, processing in these sensory channels may activate distinct gain control mechanisms and thereby allow odor-specific processing to suit behavioral needs.

The case against this 'labeled-line' approach arises primarily with regards to processing stimulus intensity. As the stimulus intensity is increased, invariably most odorants recruit additional ORNs that are not dedicated to this 'private' odorant. Therefore, an odorant that is 'private' at a lower intensity may no longer be 'private' at higher stimulus intensities [11,38]. This observation taken together with the findings that have revealed a strong synapse between ORNs and second-order neurons [39], and existence of non-linear transformations that amplify weak ORN responses but quickly saturate stronger inputs [40], will complicate processing at higher intensities for most labeled-line schemes.

Global features of olfactory sensory neuron activity and behavior

By contrast to the labeled line scheme, it is possible to envision a mechanism where spiking activity from a large subset of sensory neurons is integrated to drive a behavioral response. We will refer to such an approach as a 'global' encoding scheme, since the same strategy for translating sensory input into behavior can be applied for all odorants. Such an approach has been particularly effective when behavioral preferences for larger odor panels are considered [41**,42]. For instance, the total spiking activity across all olfactory sensory neurons recorded in fruit fly larvae was found to be a good indicator of the degree of attraction or repulsion that

Figure 1
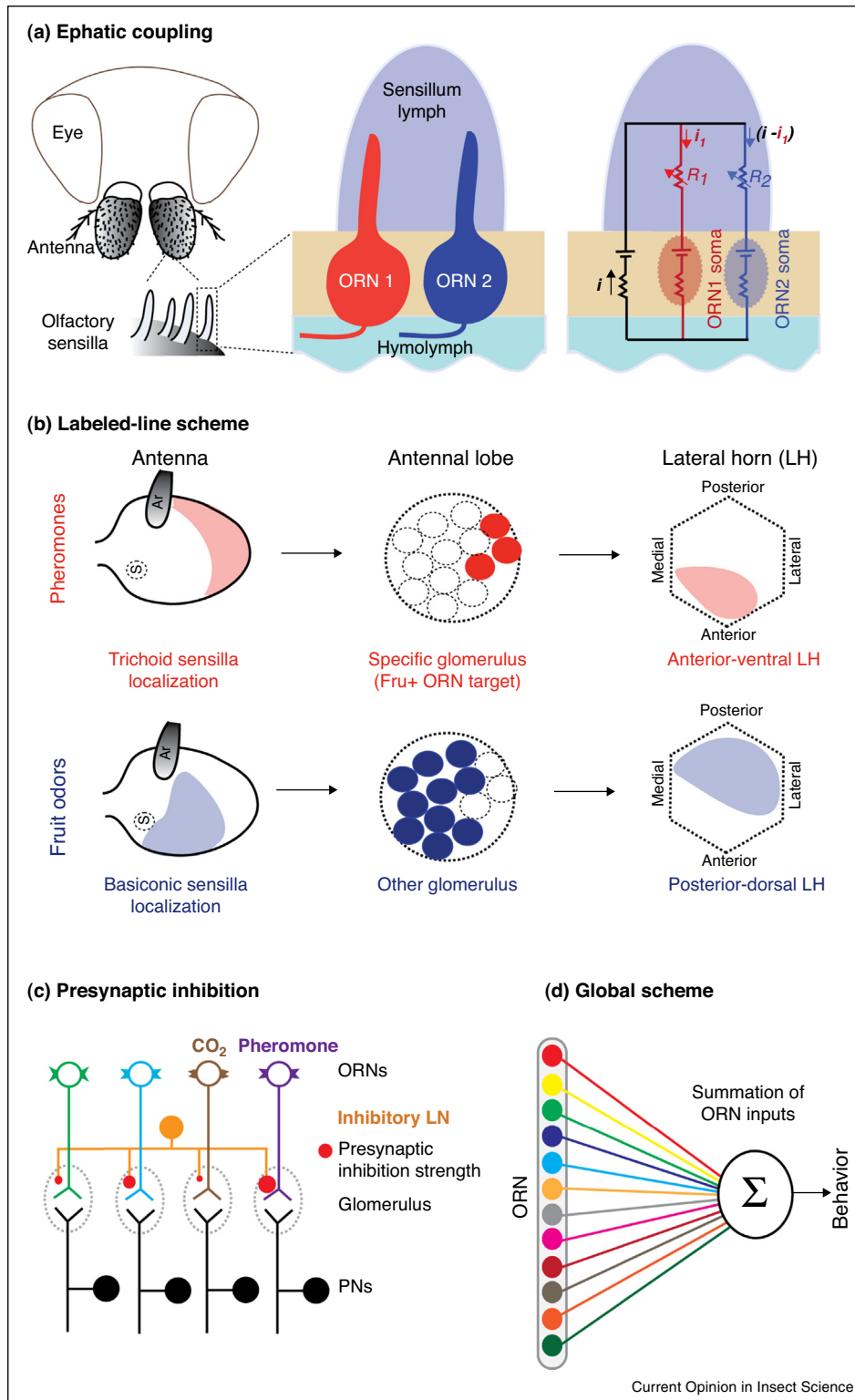
Linking sensory neuron activity with behavior. **(a)** Two ORNs housed in the same sensory hair indirectly communicate with each other. Due to their special arrangement, a potential difference between the dendritic and somatic/axonal compartments is achieved, and the dendritic compartments of the co-housed ORNs act as two resistors in parallel. Therefore, activating one ORN strongly reduces its input resistance and indirectly inactivates the other ORN. Intriguingly, this interaction is behaviorally relevant. Figure adapted from [25••]. **(b)** Pheromone and fruit odors activate spatially distinct neurons in the early olfactory pathway. Pheromones are detected by ORNs located in the *sensilla trichordia*, whereas fruity

an odorant would elicit [41••] (Figure 1d). In general, repellent odorants were found to evoke more inhibition and therefore less total spiking activity. By contrast, attractive odorants evoked relatively more spiking activity in most of the sensory neurons they activated. Such a global decision rule that is based on total spiking activity was shown to explain data obtained with both invertebrate and vertebrate models [42].

How could a coarse readout of sensory neuron activity have any relation with behavior at all? This surprising result can be clarified when we consider that the behavioral responses explored in these studies are primarily, attraction versus repulsion. Hence, these results indicate that the main source of variance in the neural data correlates with the biggest source of variance in the innate behavioral responses [42]. One way to think about these results is through the following analogy: The total sound levels in a football stadium can be expected to correlate with winning or losing of the home team. Quietness/less-activity indicates losing/repulsion, and loudness/high-activity corresponds to winning/attraction, respectively. Nevertheless, a careful examination of whether global features can also predict finer behavioral response features is still required.

Combinatorial features of olfactory sensory neuron activity and behavior

A compromise between the two extreme approaches considered so far, single neuron and global activity, is the combinatorial scheme, where a select few sensory neurons are combined to drive behavior. This strategy arguably has an advantage in terms of increasing the encoding capacity of the system [43–45]. Theoretically, even a simple system with fifty neurons, where ten randomly selected neurons represent each odorant (i.e., a 'combinatorial code'), can encode for ~ 10.2 billion distinct odorants (if the number of encoding neurons can also vary between stimuli then the number of combinations becomes 2^{50}!). Whether such an enormous coding space is actually necessary is worth further consideration. The paradox here will become apparent when we consider the discrimination power of these high-dimensional neural coding schemes together with the relatively few distinct behavioral responses that are finally generated (e.g., attraction vs. repulsion) [46].

Current evidences suggest that a linear combination of spiking activity in a pair of sensory channels or a few

sensory neurons is a sufficiently good indicator of the overall behavioral response elicited by the odorant [41••]. In some other cases, modulating activity in select channels without altering the activity in other co-activated channels has been sufficient to induce behavioral variations [47]. For the purposes of this review, we regard both results as a combinatorial scheme because more than one sensory channel is necessary to explain behavior. Overall, it appears that although an encoding scheme based on ensembles of sensory neurons may explain behavior, the size of the encoding ensembles for each odorant may be relatively small.

Temporal features of olfactory sensory neuron activity and behavior

So far, we have considered coding schemes that have ignored the contribution of information encoded in the temporal response dimension. How important are the specific patterns of spike trains elicited by each odorant? Answering this question has proved challenging for several reasons. First, most behavioral assays do not track responses with the same resolution as the neural activity. Second, it is difficult to manipulate temporal features without altering other response attributes, such as response amplitude or the total number of spikes generated. Hence, alternate interpretations of the same result cannot be ruled out.

Behavioral studies using transgenic flies with only one functional type of sensory neuron have been illuminating in this regard. Such flies are capable of discriminating different odorants, and distinguishing between different intensities of the same odorant as well [48]. This result clearly reveals that the olfactory circuits downstream from the sensory neurons can take advantage of whatever distinguishing set of features that is available. Furthermore, temporal features of sensory neuron activity have been shown to play an important role for encoding mixtures [49], and for eliciting a rich repertoire of temporal patterns in the second-order neurons [45]. Further work is still needed to examine the behavioral relevance of other temporal attributes of olfactory sensory neuron responses.

The organizational logic of the insect antennal lobe

The second anatomical stage in the insect olfactory pathway is the antennal lobe. Here, sensory neurons that express the same olfactory receptor gene converge onto a

(Figure 1 Legend Continued) odorants are detected by sensory neurons housed in the sensilla basiconica. These ORN inputs are kept segregated because they activate distinct second-order projection neurons in the antennal lobe and third-order intrinsic neurons in the lateral horn [34]. Illustration based on results reported in [22,24,34]. (c) ORN inputs are not treated equally. Presynaptic inhibition strength is varied to allow certain stress-related sensory inputs to be transmitted without reduction, whereas pheromone inputs do not enjoy the same benefit. Figure adapted from [37•]. (d) A global scheme for generating behavioral response combining various sensory inputs. In Drosophila larvae, most odorants evoke responses in multiple sensory neurons. Surprisingly, a simple summation of all or a selected subset of ORN spike counts is a good indicator of whether or not the odorant will attract or repel [41••].

single or a pair of spherical structures called glomeruli. This convergence of inputs from sensory neurons of the same type facilitates elimination of uncorrelated noise and improves the signal-to-noise ratio. As a direct consequence of this result, even when individual ORNs are only weakly activated by an odorant, their down-stream second-order projection neuron can become more sensitive to those inputs [40]. Further, such sensitivity enhancements can broaden the response tuning of individual projection neurons when compared to the first order ORNs [39,40]. Note that other circuit mechanisms within the antennal lobe, such as lateral excitation through cholinergic local neurons, could further contribute toward this response broadening as well [50,51].

In fruit flies, ORNs send axons to both ipsilateral and contralateral antennal lobe. These bilateral projections, however, activate the second-order neurons on the two sides with different efficacies [52]. The ipsilateral projection neurons are more intensely driven and therefore respond faster and stronger when compared to the contralateral neurons. These asymmetries are likely to assist a behaving animal in interpreting spatial information associated with an odor source.

Two additional topological features of the antennal lobe are also worth pointing out here. It appears that sensory inputs from different types of sensory hairs are spatially segregated in the insect antenna lobe [24]. Whether this input segregation is exploited while processing competing inputs from these sensory channels is not known. In addition, it has also been shown that attractants and repellants activate neurons located in distinct antennal lobe loci [53•]. Whether these spatial organizational features have any specific role in shaping behaviorally relevant neural interactions is yet to be understood.

A behaviorally important single projection neuron activity

Although a number of studies have focused on correlating single sensory neuron activity and the final behavioral output, such investigations are rare at the level of second-order projection neurons. Nonetheless, a study in the moth *Manduca sexta* pheromone sensing system showed that injection of a GABA antagonist (bicuculline methiodide) altered the firing patterns of projection neurons that innervate the macroglomerular complex (MGC) in these insects (a glomerulus specifically associated with processing pheromones in this species). This pharmacological manipulation disrupted the ability of the male moths to track and navigate toward a pheromone source in wind tunnel experiments [54] (Figure 2a). Hence, this work indicates that the temporal structure of MGC projection neuron spike trains is important for odor localization tasks.

Figure 2
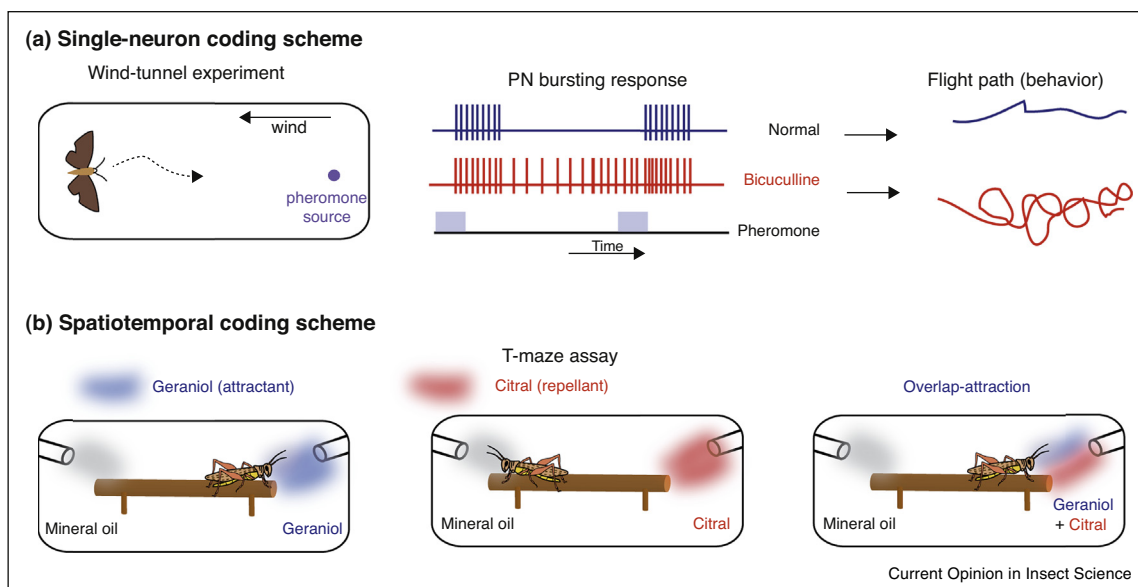
Correlating projection neuron activity in the antennal lobe with innate behavioral responses. **(a)** Altering the firing properties of a specific subset of projection neurons interferes with odor localization behavior in flying male moths. Illustration summarizing actual results reported in [54]. **(b)** Geraniol smells like a rose to humans and attracts locusts. Whereas Citral smells like lemon to humans and repels these insects. An odorant mixture of geraniol and citral evoked ensemble projection neuron responses that exclusively pattern-matched with geraniol. As can be expected, the rose–lemon mixture attracted locusts in the behavioral assay [62••].

Combinatorial features of projection neuron activity and behavior

Processing within the antennal lobe is thought to reshape the sensory inputs received from ORNs for achieving various important sensory computations [44,55]. These include,

- *Input reformatting*: creating a spatiotemporal basis for encoding stimulus-specific information [44,45,56,57]
- *Decorrelation:* refining information over time [58]
- *Normalization or gain control*: maintaining invariance with respect to changes in stimulus intensity [59,60], and
- *Non-linear amplification*: boosting weak signals and saturating strong signals [40].

The primary justification for most of these processing schemes has come from the computational viewpoint of discriminating odorants based on antennal lobe activity. The behavioral relevance of most of the signal processing mechanisms, although straightforward to envision, is yet to be demonstrated.

Recently, qualitative comparisons [61] and quantitative predictions [62**,63**,64] have revealed that the ensemble activities in the antennal lobe correlates with behavior. In moths, for example, combinatorial projection neuron response features were used to predict whether two odor mixtures with varying compositions could elicit similar behavioral responses [64]. Two ensemble response features were particularly found useful for this generalization task: (i) mean spiking activity across projection neurons, and (ii) features based on pairwise spiking synchrony (defined here as the fraction of coincident spikes relative to the total number of spikes observed in pairs of neurons). These results suggest that similarity in projection neuron combinatorial activities may correspond to similarity in the behavioral space.

Could manipulation of the neural responses in the antennal lobe lead to predictable changes in behavior? Studies again in moths suggest that this might be the case [61]. Here, the authors found that the time to take flight toward a flowery odor mixture in a wind tunnel could be expedited by adding a select additional component. Whether or not the added odor component reduced the latency of the behavioral responses was correlated with the type of transformation (linear vs. nonlinear) between the sensory neuron and antennal lobe activities. Note that nonlinearity in this study is defined as disproportionate changes in projection neuron activity that cannot be predicted directly from sensory neuron inputs. Therefore, non-linear signal processing is considered here as an indicator of significant involvement of antennal lobe circuits in reshaping stimulus-evoked responses.

Similarly, ensemble projection neuron firing patterns have been shown to be useful for predicting the recognition performances of locusts in an appetitive-conditioning assay. A recent study, found that locusts trained in an appetitive-conditioning assay, responded to the trained odorant (i.e., the conditioned stimulus) with varying probabilities depending on whether the odorant was presented solitarily or in overlapping sequences following a distracting cue. Nevertheless, the observed behavioral response variations were found to correlate with how well the ensemble neural activities following the introduction of the conditioned stimulus tracked the stimulus and pattern matched across conditions [62**] (Figure 3a) Interestingly, the authors found that even the innate behavioral preference of an odor mixture could be predicted from the spatiotemporal antennal lobe neural activities [62**] (Figure 2b). Taken together, these results suggest that ensemble projection neuron firing patterns can correlate with both acquired as well as innate preferences in the insect olfactory system.

Global features of projection neuron activity and behavior

In addition to altering the spiking activity in individual projection neurons, odor presentations tend to entrain oscillatory field potentials during stimulus exposures [65–68]. This stimulus-evoked oscillatory neural activity is thought to arise as a result of summation of electrical currents contributed by many projection neurons, and can be perturbed by blocking the feedback inhibition provided by the GABAergic local neurons in the antennal lobe [65,67–69]. Furthermore, spiking activities in individual projection neurons are phase locked with respect to these global field potential signals during certain epochs of stimulus exposure. However, neither the frequency of these oscillations nor the phase at which the projection neuron fire action potentials change in stimulus-specific manner. These observations raise questions regarding the relevance of oscillatory field potential activity in olfactory signal processing and therefore to behavior. A study in honeybees [68] addressed this issue by pharmacologically disrupting the field potential oscillatory activity. Intriguingly, such disruption did not affect coarse discrimination between dissimilar odorants, but selectively impaired finer discrimination between similar odorants (Figure 3b). Whether there are additional computational roles for these stimulus-evoked neural oscillations need further studies.

Temporal features of projection neuron activity and behavior

Most odorants evoke behavioral responses that are rapid and typically initiate within a few hundred milliseconds of stimulus onset [63**,64]. This raises a fundamental question regarding the role of neural activity patterned over time, especially those that happen on a slower timescale. Examination of how flying insects localize odor sources provided the first piece of evidence that maintaining the

Figure 3
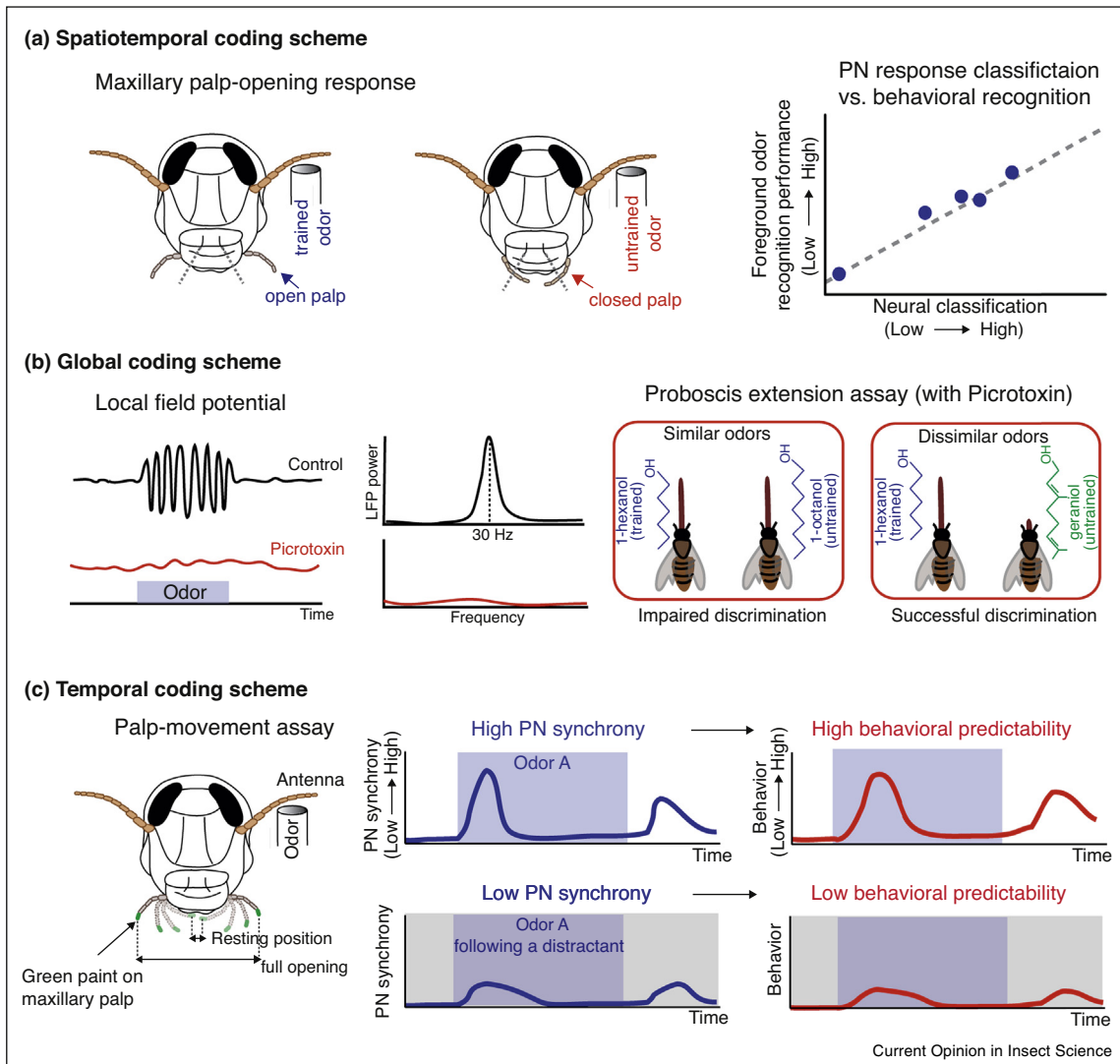
Correlating projection neuron activity in the antennal lobe with learned behavioral responses. **(a)** In an appetitive-conditioning assay, locusts open the sensory appendages close their mouths, called 'maxillary palps' to indicate odor recognition. How well the locusts could recognize the conditioned odorant when the same stimulus was presented atop different background cues could be predicted from the antennal lobe spatiotemporal neural activities. Illustration depicting actual results reported in [62••]. **(b)** Local field potential activity, a measure of global antennal lobe activities, reveals a distinct 20–30 Hz oscillation upon odorant exposure. In honeybees, disrupting this oscillatory neural activity using pharmacological manipulation leads to impairment only when discriminating two similar odorants. Illustration summarizing actual results reported in [68]. **(c)** A simple rule governing how ensemble neural activities are translated to behavior in locusts is that: synchronous neural activity leads to predictable behavior. Although variable, asynchronous neural activity can also evoke the same behavioral response. The only caveat is that the combination of neurons activated by the conditioned stimulus must be preserved across training and testing conditions. Illustration depicting actual results reported in [63••].

integrity of the temporal structure of projection neuron responses may be important for source localization tasks [54].

In addition, our recent work showed that although odor identity was insensitive to variations in the temporal structure of projection neuron ensemble responses, the level of spike synchrony is a good indicator of predictability of

behavioral responses [63••]. Hence, these results suggest a non-redundant role for temporal patterning that complements combinatorial coding in this olfactory system.

Conclusions
The synthesized view emerging from recent advances in the field of insect olfaction indicate that neural representations in the insect antenna and antennal lobe can be

readily mapped onto the final behavioral responses. Such a perspective raises several fundamental questions regarding the nature and relevance of processing performed by higher centers in the insect brain, such as the mushroom body and the lateral horn. For example,

- Do antennal lobe circuits facilitate stimulus discrimination, whereas the higher centers help consolidate sensory inputs so that different stimuli can elicit the same behavioral outcome?
- Under what conditions is a local (single or a few neurons), global (entire circuit) or combinatorial coding scheme used to encode the overall behavioral preference for an odorant?
- What behaviorally relevant information is encoded in the temporal coding dimension?

Investigating these issues would be necessary to identify the set of rules that govern how sensory inputs are translated into behavior in this sensory modality. More generally, a better understanding of the insect olfactory system's processing principles may lead to approaches for controlling insects in desirable ways, for example, attracting a pollinator or repelling a pest [70,71].

Acknowledgements

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