Neuronal Compartmentalization: A Means to Integrate Sensory Input at the Earliest Stage of Information Processing?

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In numerous peripheral sense organs, external stimuli are detected by primary sensory neurons compartmentalized within specialized structures composed of cuticular or epithelial tissue. Beyond reflecting developmental constraints, such compartmentalization also provides opportunities for grouped neurons to functionally interact. Here, the authors review and illustrate the prevalence of these structural units, describe characteristics of compartmentalized neurons, and consider possible interactions between these cells. This article discusses instances of neuronal crosstalk, examples of which are observed in the vertebrate tastebuds and multiple types of arthropod chemosensory hairs. Partial attention is paid to insect olfaction, which presents especially well-characterized mechanisms of functional, cross-neuronal interactions. These examples highlight the potential impact of peripheral processing, which likely contributes more to signal integration than previously considered. In surveying a wide variety of structural units, it is hoped that this article will stimulate future research that determines whether grouped neurons in other sensory systems can also communicate to impact information processing.

1. Introduction

Encountered in nature as combinations of chemical and physical cues, environmental stimuli require sophisticated mechanisms for detection and integration. To that end, animals rely on dedicated sensory systems employing processing at multiple layers of nodes. While such processes in the central nervous system often form the focus of studies on signal integration, a more complete understanding of sensory neurobiology requires revealing how inputs are transformed at every node of the circuit, including neurons in the peripheral nervous system. In numerous sense organs, external cues are detected by receptor cells compartmentalized within specialized structures consisting of cuticular or epithelial tissues. Within each compartment, multiple neurons share a private microenvironment in which regulation of ionic composition, peri-receptor secretions, or paracrine signaling molecules occurs separately from other sensory units. Furthermore in certain compartments, adjacent neurons are directly connected via gap junctions or chemical synapses. As discussed below, each of these aforementioned features has been shown to enable functional interaction between compartmentalized sensory neurons. Anatomical organization thus provides opportunities for private neuronal crosstalk, which in principle can allow structural compartments to serve as the first processing units in sensory integration.

1.1. Sensory Neuron Compartmentalization is Broadly Observed across Animal Species

Sensory neuron compartmentalization is prevalent across species (Figure 1). In the nematode *C. elegans*, sensory hairs, also known as sensilla, of the phasmid variety each houses two chemosensory neurons, while inner labial sensilla contain one chemosensory and one mechanosensory cell[1] (Figure 1a). Compartmentalization is particularly prominent in arthropods, and has been broadly observed in studies on sensory organ ultrastructure. In arachnids, the pectine sensilla of the scorpion *E. italicus* groups 11 chemosensory neurons together with one mechanosensory cell[2] (Figure 1b). On average, the spiny lobster *P. argus* houses $\approx$300 olfactory receptor neurons (ORNs) per sensillum[3] (Figure 1c); similarly large numbers of grouped ORNs are also observed in other crustaceans.[4] Most prominently in insects, primary sensory neurons are compartmentalized across nearly all modalities (see sections below). A well-known example is the trichoid sensillum of the silk moth *B. mori*, which encases the dendrites of two ORNs that detect female pheromones[5,6] (Figure 1d).

Compartmentalization is not unique to invertebrate receptor neurons. Found in all fish, the lateralline detects water motions and pressure gradients.[7] This mechanosensory system's functional unit is the neuromast, which houses upwards of 30 hair
Sensory neuron compartmentalization is broadly observed across animal species. a) Inner labial sensillum of the nematode *C. elegans* with one mechano- and one chemosensory neuron in a uniporous cuticular hair. b) Pectine sensillum of the scorpion *E. italicus* with a mechanosensory neuron and typically 11 chemosensory neurons in a uniporous cuticular hair. c) Olfactory sensillum of the spiny lobster *P. argus* with ≈300 chemosensory neurons in a hair with thin, permeable cuticle. d) Olfactory sensillum of the silk moth *B. mori* with typically two chemosensory neurons in a multiporous cuticular hair. e) Neuromast of the fish lateral line with upwards of 30 mechanosensory hair cells whose tips are encased in a jellylike cupula. f) Vertebrate taste bud with 50–100 chemoreceptor cells in an ovoid structure embedded within gustatory epithelia. Compartmentalized cells are color coded based on their sensory modality: chemosensory (red) and mechanosensory (blue). Neurons with different shades of one color indicate detection of different stimulus types from the same sensory modality.

1.2. Examples of Communication between Neurons Sharing a Sensory Compartment

Many types of grouped receptor neurons share a common progenitor cell,[13,14] and their compartmentalization has been generally taken to reflect developmental constraints. However, such organization likely also contributes to information processing enabled by private communication between grouped neurons, through a shared microenvironment enveloping their dendrites and somata, and/or through the proximity of their axons projecting from the same peripheral unit. Consistent with this idea, synaptic or gap junction connections are observed between subsets of grouped receptor neurons in scorpions, ants, fruitflies, and bumblebees.[15–18] On the other hand a direct electric field effect, known as ephaptic coupling, occurs between ORNs in the same olfactory sensillum of *D. melanogaster*.[19,20]

Notably upon taste reception, extensive cell-to-cell signaling occurs within the taste bud via neurotransmitter-mediated crosstalk, a topic which has been thoroughly reviewed.[12,21] Briefly, activation of Type II cells—which express the metabotropic sweet, bitter, or umami receptors—triggers the secretion of ATP from these cells; meanwhile, sour tastants stimulate the ionotropic receptors[22] in Type III cells, which in turn release serotonin. In addition to acting on their respective gustatory afferent fibers, these two neurotransmitters also target neighboring cells through paracrine signaling. ATP excites Type III cells through activation of P2X receptors; in contrast, serotonin inhibits Type II cells via 5-HT receptors.[12,21] Consequently, lateral purinergic excitation broadens the receptive range of sour-sensing Type III cells to sweet, bitter, and umami,[12,21] while lateral serotonergic inhibition provides opportunities for sour tastants to suppress taste modalities sensed by Type II cells.[12,21,23] Taken together, it appears that neuronal interaction within a compartment can occur regardless of whether the sensory neurons express metabotropic or ionotropic receptors. These interactions may enhance the perceptual contrast of tastants in a mixture, or influence the temporal dynamics of afferent signaling. While the exact functional significance of such extensive crosstalk awaits further clarification, short-range paracrine signaling is evidently permitted by the proximity of cells within the taste bud.[21] Taken together, these observations highlight notable examples of intra-compartment communication, mediated by the close apposition of grouped neurons, which can in turn shape afferent outputs.
1.3. Sensory Neuron Compartmentalization: An Underexplored Means for Sensory Processing

Despite these characterized interactions between grouped receptor cells, neuronal compartmentalization’s contribution to signal processing remains largely underexplored and continue to pose open questions. How can such organization affect sensory coding? Does it alter characteristics of stimuli, such as their intensity and identity? What functional benefits might compartmentalization confer? These questions can be better informed through close examination of insects, whose sensory periphery offers several advantages for the purpose. Anatomically, their primary receptor neurons are typically compartmentalized. Many of their sense organs are accessible for in vivo electrophysiological recordings. In addition, the morphology and ultrastructure of insect sense organs have been extensively characterized through electron microscopy (EM), and are described in excellent reviews.\(^{[24,25]}\) Furthermore, the genetic tractability of select species has aided studies in causally linking molecules to morphology, function, and behavior. As such, insects afford unique opportunities for understanding how external stimuli are integrated at the earliest stage of sensory processing.

In the remainder of this article, we focus on compartmentalized receptor cells observed across the major sense organs of insects. We note that studies demonstrating unequivocal neuronal crosstalk remain relatively scant when compared to the anatomical and functional characterizations, compiled over decades, of compartmentalized receptor cells. Therefore by calling attention to the anatomy, response profiles, and interactivity of grouped neurons, we hope to stimulate deeper consideration and exploration of these prevalent organizational schemes. We focus on the following themes: that primary receptor neurons may be compartmentalized; that these cells may demonstrate distinct tuning properties or even confer multimodality within a functional unit; and that functional interactions may occur between grouped cells. Particular attention is paid to olfaction, as this sense has been extensively characterized. Finally, we discuss the functional significance of compartmentalized ORNs by considering how their organization enables olfactory sensilla to serve as processing units at the sensory periphery.

2. Receptor Neurons are Compartmentalized across the Major Sense Organs of Insects

2.1. Ommatidium: A Visual Receptive Unit

Insect compound eyes are made up of hundreds to thousands of receptive units named ommatidia, each typically containing eight elongated photoreceptor neurons (R1–R8)\(^{[26]}\) (Table 1). Some insects, such as bees and butterflies, have an additional photoreceptor (R9) at the compartment base.\(^{[27]}\) In *D. melanogaster*, R1–R6 cells occupy the outer regions of the ommatidium and are immediately surrounded by pigment cells, while R7 and R8 are positioned centrally, with R7 atop R8 (Figure 2a).\(^{[28]}\) R1–R6 photoreceptors express the same Rh1 rhodopsin and thus have identical spectral sensitivity. In contrast, R7 cells express a UV-sensitive rhodopsin, Rh3 or Rh4, and R8 cells express either the blue-sensitive Rh5 or the green-sensitive Rh6.\(^{[29,30]}\)

There is evidence to suggest that functional interactions occur between photoreceptors in the same ommatidial column. Within the first optic neuropil of locusts and butterflies, strong activation of one chromatic photoreceptor inhibits surrounding neighbors with differing spectral sensitivity.\(^{[66,67]}\) This lateral inhibition is likely mediated by a direct electric field effect, known as ephaptic coupling, which takes place between closely apposed neuronal structures in local environments exhibiting high extracellular resistance.\(^{[68]}\) Such as within an ommatidial column.\(^{[66]}\)

Briefly, current outflow from the axon terminal of the strongly activated cell enters the counterparts of neighboring photoreceptors, and thereby hyperpolarizes their presynaptic terminals.\(^{[66,67]}\)

Besides electric field effects, grouped photoreceptors can also communicate via chemical synapses. In the medulla of *D. melanogaster*, chemical synapses are found between the axons of the two chromatic photoreceptors from the same ommatidium. Specifically, both R7 and R8 express histamine-gated chloride channels, allowing these two histamine-releasing photoreceptors to inhibit each other through direct synaptic connections.\(^{[17]}\)

Although it is unclear whether this direct lateral inhibition can take place across different ommatidia, R7, and R8 synaptic connections appear to occur only between axons that project from the same ommatidium.\(^{[69]}\) Importantly, lateral inhibition between chromatically distinct photoreceptors is a hallmark of color opponency. Therefore, an interesting direction for future research will be to determine how such lateral inhibition influences color perception to regulate vision-guided behavior.

2.2. A Peripheral Taste-Processing Unit

Insect gustation plays a critical role for evaluating the quality of food and suitability of mates. Two main gustatory organs, the legs, and the labella (Table 1), are covered with taste sensilla that mediate gustation through contact chemosensation.\(^{[10]}\) Regardless of organ, these sensory hairs are uniporous cuticular structures that ensheath multiple bipolar receptor cells\(^{[31]}\) (Figure 2b,c). Each structural unit is typically innervated by four gustatory receptor neurons (GRNs), the dendrites of which extend into the sensillar lumen, together with one mechanosensory cell, whose dendritic tip terminates at the sensillum base (Figure 2c). Well-conserved among insects, this organization is prevalent in mosquitoes,\(^{[70,71]}\) honeybees,\(^{[72]}\), and Dipteran flies.\(^{[73,74,75]}\)

Grouped GRNs typically detect different stimuli from primary tastant classes including sugars, low- or high-salt levels, bitter compounds and water.\(^{[10]}\) Such organization potentially allows each gustatory sensillum to integrate information from foods containing all major tastant types. Although some organizational schemes diverge in the numbers and types of GRNs, it appears that each sensillum type processes specific kinds of taste mixtures. The ability to detect antagonistic taste modalities, such as sweet and bitter, is well-demonstrated in a dedicated subset of *Drosophila* labellar taste hairs (i-type) that only houses two GRNs that sense sugars or bitter compounds.\(^{[13,14]}\) Conversely in another sensillum type (l-type), its fourth GRN does not respond to bitter compounds.\(^{[35]}\) These examples illustrate how certain subtypes of taste hairs may diverge from the prevalent organizational scheme.
Table 1. Functional units and compartmentalized neurons in the external sensory organs of *D. melanogaster*. The numbers of sensory neurons housed in individual functional units are indicated in parentheses.

| Main sensory organs | Functional units | Compartmentalized sensory neurons | Sensory stimuli | References |
|---------------------|------------------|-----------------------------------|----------------|------------|
| **Vision**          |                  |                                   |                |            |
| Eye                 | Ommatidium       | Achromatic photoreceptors (6)     | Light, \(\lambda_{\text{max}}^*: \) 478 nm, Rh1 |            |
|                     |                  | Chromatic photoreceptors (2)      | Light, \(\lambda_{\text{max}}^*: \) 345 nm, Rh3 | [30]       |
|                     |                  | Rh3/Rh5 or Rh4/Rh6               | 375 nm, Rh4    |            |
|                     |                  |                                   | 437 nm, Rh5    |            |
|                     |                  |                                   | 508 nm, Rh6    |            |
|                     |                  | \^\(\lambda_{\text{max}}\) indicates the peak spectral sensitivity of the visual pigment, which can absorb photons with varying probabilities from a wide band of wavelengths. |            |            |
| **Gustation**       |                  |                                   |                |            |
| Labellum            | Gustatory sensillum | Gustatory receptor neurons, GRNs (2–4) | Tastants | [31–40]   |
|                     |                  | Mechanosensory neuron, MN (1)     | Food texture   |            |
| Leg                 | Gustatory sensillum | GRNs (4)                          | Tastants       | [32,33,41] |
|                     |                  | MN (1)                            | ?              |            |
|                     |                  | Pheromone sensillum               | Contact pheromones | [42–46] |
|                     |                  | Pheromone-sensitive GRNs (2)      | ?              |            |
|                     |                  | Other GRNs (2)                    | ?              |            |
|                     |                  | MN (1)                            | ?              |            |
| **Audition**        |                  |                                   |                |            |
| Johnston’s organ    | Scolopidium      | MNs (2–3)                         | Sound, vibrations, deflection, and gravity | [47–50]   |
| (2nd antennal segment connecting to the 3rd segment) | | | | |
| **Hygro- and Thermosensation** | | | | |
| Arista (3rd antennal segment) | Thermosensitive sensillum | Cold or cooling cell (1) | Cold/decreasing temperature | [51–54] |
| Saccus (3rd antennal segment) | Triads | Warm cell (1) | Warm temperature | [55–58] |
|                     |                   | Cold cell (1)                     | Cold temperature | [35–38] |
|                     |                   | Dry cell (1)                      | Aridity        |            |
|                     |                   | Moist cell (1)                    | Humidity       |            |
| **Olfaction**       |                  |                                   |                |            |
| Funiculus (3rd antennal segment) | Olfactory sensillum | Olfactory receptor neurons, ORNs (1–4) | Odorants | [60–65] |
|                     |                  | Pheromone sensillum               | Airborne pheromones | [42–46,78] |
|                     |                  | Pheromone-sensitive ORNs (1–3)    |                |            |
| Maxillary palp      | Olfactory sensillum | ORNs (2)                          | Odorants       | [40–45]   |

Why is an individual mechanosensory neuron (MN) compartmentalized with multiple chemosensory cells? During feeding, this multimodality may permit integration of texture and taste. For instance, strong activation of these MNs can inhibit sweet-sensing GRNs through GABAergic inhibition of their axon terminals, which mediates *D. melanogaster*’s preference for softer foods over sweeter, but harder foods. It remains an open question whether inhibitory synapses are formed exclusively between individual MN and sweet-sensing GRN from the same taste hair or broadly between the two neuronal populations across different sensilla. Interestingly, a non-compartmentalized MN is also found in each labellar lobe, where a single multi-dendritic md-L neuron extends its dendritic arbors to the bases of taste hairs and, in contrast with grouped MNs, appears to report absolute hardness of food substrates. Intriguingly, the ideal food texture—soft but not too soft—is encoded by the intermediate levels of md-L neuronal activity. These studies raise the possibility of functional distinctions between compartmentalized MNs and standalone md-L neurons, and furthermore suggest a unique role for the former, likely in the multimodal integration of texture and taste at the first synapses of the taste circuit.

In addition to evaluating food quality, taste sensilla mediate pheromonal responses: GRNs in fruitflies’ tarsal hairs detect pheromones to regulate sexual behavior. Notably within a specific sensillum subset, two co-housed chemosensory neurons detect pheromones specific to opposite sexes, which either promote or inhibit courtship behavior. This pair of cells—expressing different combinations of the DEG/ENaC subunits PPK23, 29, and/or 25—inhibits male-male courtship through the detection of male pheromones, while its neighbor promotes male-female courtship via responses to female pheromones. That is,
Compartmentalized neurons in major sensory organs of *D. melanogaster*. a) Ommatidium of the compound eye with eight photoreceptor neurons. b) Taste sensillum of the labellum with four GRNs and one mechanosensory neuron in a uniporous cuticular hair. c) Taste sensillum of the foreleg tarsi with four GRNs and one mechanosensory neuron in a uniporous cuticular hair. d) Scolopidium of the femoral chordotonal organ (FeCO) with two mechanosensory neurons. e) Scolopidium of the Johnston’s organ (JO), located in the second and connected to the third antennal segment, with two mechanosensory neurons. f) One cold-sensing and two hygrosensory neurons (triad) in a poreless sensillum within the sacculus. g) Temperature-sensitive sensillum of the arista with one warm- and one cold-sensing cells in a non-porous structure. h) Antennal olfactory sensillum with two ORNs in a multiporous cuticular hair. Compartmentalized cells are color coded based on their sensory modality: chemosensory (red), mechanosensory (blue), photoreceptor (green), thermosensory (yellow), and hygrosensory (purple). Neurons with different shades of one color indicate detection of different stimulus types from the same sensory modality.

Compartmentalized “male” and “female” cells exert opposing influences on courtship behavior.

The grouping of GRNs responsive to stimuli of different hedonic values suggests that taste sensilla may serve as functional processing units to integrate valence information at the sensory periphery. If so, these cells are expected to demonstrate cross-modality interaction and indeed, there is evidence for crosstalk between compartmentalized GRNs. Tarsal sensilla of the grasshopper *S. americana* house two neurons that respectively detect salt or bitter alkaloids: spiking of the first cell inhibits the tastant-evoked firing of its neighbor, resulting in disruption of uniform spike trains.[79] A similar example is observed in the galeal sensilla of bumblebees, wherein the spiking of a GRN interrupts the high-frequency spike trains of its compartmentalized neighbor, whose sustained sucrose-induced responses are transformed into bursts of spikes.[16]

Besides neuronal interactions, crosstalk between taste modalities can occur through other means. In *D. melanogaster*, bitter compounds suppress the response of sugar-sensing GRNs to prevent flies from ingesting food contaminated with bitter, probably toxic substances. This suppression is achieved through direct inhibition of sugar receptors by the bitter compounds themselves,[80] or through the action of an odorant binding protein (OBP)—OBP49a—enriched in the sensillum lumen.[81] Notably, the proboscis extension reflex (PER) is reduced when co-compartmentalized sugar- and bitter-sensing GRNs are simultaneously activated by a mixture, which in principle allows for integration of inputs at both peripheral
and higher brain centers. However as elegantly demonstrated by Marion-Poll and colleagues, PER is unaffected when non-neighboring sugar- and bitter-sensing GRNs are concurrently stimulated in a manipulation that precludes peripheral processing but retains central computation.[80] Thus, the gustatory periphery is critical for integrating opposing attractive and aversive inputs, and cannot be substituted by central mechanisms for informing feeding decisions. In summary, whether through neuronal or non-neuronal interactions, compartmentalized GRNs can engage in inter-modal crosstalk to provide the sensillium with the means to function as a peripheral taste processing unit.

2.3. Proprioceptive Neurons and their Structural Compartments

Insects detect the position and motion of their body parts through proprioceptive organs, consisting of mechanosensory neurons that provide feedback for coordinating movement.[47,82] Found in all insects, the femoral chordotonal organ (FeCO) is a well-characterized proprioceptive structure that monitors movement of the tibia in relation to femur[82] (Figure 2d). The organs' functional units—named scolopidia—typically compartmentalize two proprioceptive neurons,[47,83,84] unlike other sensory organs in which proprioceptive cells are singly-housed.[82,85] In Drosophila, FeCO scolopidia and their neurons are known to respond to different stimuli, including vibration, position, or directional movement of the leg.[86] However, it awaits future experimentation to determine whether paired FeCO neurons within each individual scolopidium exhibit identical tuning properties, or if not, what the organizing principle underlying neuronal pairing might be.

Do compartmentalized FeCO neurons functionally interact? While this remains an open question, desmosome-like junctions have been shown to connect their proximal dendrites, thus physically coupling both neurons.[86] It is plausible that desmosome structures are required for the structural integrity of the scolopodial unit. However, it is also possible that they serve to increase the displacement threshold of these coupled neurons, such that only sufficiently strong mechanical input can elicit neuronal outputs. Therefore, it remains to be determined whether the desmosome-like junctions are integral to the function of individual FeCO neurons, or if they also facilitate sensory processing by filtering out weaker mechanical stimuli.

2.4. Auditory Neurons of Johnston’s Organ

Finding mates, locating prey, and avoiding predators all require audition. Across Insecta, detection of near-field sound is mediated by the Johnston’s organ (JO), a specialized exteroceptive chordotonal organ consisting of a scolopidial array located in the second antennal segment[47,48] (Figure 2 and Table 1). Two to three bipolar mechanosensory cells, known as Johnston’s organ neurons (JONs), are compartmentalized within each auditory scolopidium, in contrast with tympanic and subgenual organs— which detect far-field sound and vibrations borne through solid substrates, respectively—but whose scolopidia each contain only one sensory neuron.[47,48,87,88] The JO connects the second and third antennal segments; when the distal segment(s) vibrates in response to acoustic stimuli, these movements are detected and transduced into electrical signals by the JONs.[89]

In D. melanogaster, each JO scolopidium typically compartmentalizes two morphologically similar neurons[49] (Figure 2e). In addition to vibration-sensitive JONs, which detect sound, JO neurons may also act as gravity and wind sensors by detecting static deflections.[88] Notably, JONs with distinct tuning properties appear to be grouped together in stereotypical combinations: a recent histological study suggests that a vibration-sensitive JON is paired with a deflection-sensitive neuron within the same scolopodial compartment.[90] In principle, this pairing allows an individual scolopidium to mediate hearing in addition to sensing wind and gravity, and to potentially integrate these stimuli at the sensory periphery.

Functional distinction between JONs within a scolopidium is also likely present in mosquitoes. A recent study in male C. pipiens provides evidence of acoustic opponency in the response profiles between compartmentalized JONs, which are shown to respond to either the phase or anti-phase component of the same sound stimulus.[91] Detection of opponent auditory stimuli by pairwise-organized JONs housed in the same structural unit could potentially permit weaker vibratory signals, such as low-frequency deflection by wind currents, to be filtered out at the level of the sensory periphery.[91,92] If so, a potential benefit conferred by this organization may be improved signal-to-noise ratios of auditory inputs at the initial stage of auditory processing.

2.5. Sensilla for Hygro- and Thermosensation

Given their small size and relatively large surface area, insects are especially vulnerable to desiccation, making their ability to detect temperature and humidity essential for survival. These sensory modalities are largely mediated by two types of poreless hairs: bimodal sensilla responsive to both temperature and humidity, and unimodal sensilla that sense temperature alone. The former of these, known as “triads”, houses three neurons activated by either temperature, moisture, or dryness (Table 1). Although the compartmentalization scheme is highly conserved for triads, their sensillar morphology varies greatly, including campaniform sensilla of ground beetles; mound-shaped sensilla of stick insects; coeloapticulur sensilla of honeybees; capitellum sensilla of cockroaches; styliform complex sensilla of moths; and coeloconic sensilla of mosquitoes.[91–100] While these hairs are all located on the antennal surface, the triads of fruitflies are instead housed in coeloconic sensilla contained within a specialized, pit-like structure known as the sacculus[53] (Figure 2f). The diversity of triad morphology raises questions about whether their form influences function, and whether their anatomical structure is in turn informed by the ecological requirements of individual insect species.

Why might a temperature-sensing cell be paired with two hygrosensory neurons? At the molecular level in D. melanogaster, three ionotropic receptors—IR25a, IR40a, and IR93a—are expressed in the hygrosensing cell and are necessary for sensing reductions in humidity.[56,57] On the other hand, IR68a is required for responses in the neighboring moist cell.[58,59] Surprisingly, genetic silencing of IR40a neurons, which include
the temperature- and dry-sensing cells, affects humidity but not temperature preference behavior.[56] This phenotype suggests an unanticipated role for the temperature-sensing neuron in modulating humidity preference; as such, it appears that all three cells within the triad inform the hygroregulatory behavior of fruitflies. It will be informative to determine whether this characteristic likewise applies to triads in other insect species.

Interestingly, dedicated thermosensitive sensilla sensing warmth and cold are found in Diptera, for whom thermosensory inputs are central in informing behavior. For mosquitoes, which rely on temperature cues to detect hosts,[101] thermosensitive sensilla contain warm- and cold-sensing neurons and are located at the distal ends of their antennae.[102,103] In D. melanogaster, similar sensilla are found in the arista, a specialized bristle located on the third antennal segment (Figure 2g and Table 1). The two grouped cells detect antagonistic temperature cues and are morphologically distinct—having either lamellated or unbranched outer dendrites.[100] In contrast with the thermosensory cells in saccus triads, the aristal neurons influence temperature-guided behavior.[52–54]

Close apposition between neurons is characteristic of thermo- and hygrosensory sensilla, whose receptor dendrites completely fill the luminal volume;[95–97,99,100,104] their proximity might also allow for intercellular interactions. Although gap junctions and other physical connections have not been reported, their absence does not preclude other forms of intra-sensillum signaling, such as ephaptic coupling. Rather unexpectedly, an OBP—Obp59a—is expressed in hygrosensitive sensilla in the saccus and is required for normal humidity preference in D. melanogaster.[105] Thus raising the possibility of OBP-mediated crosstalk similar to that observed between bitter- and sweet-sensing labellar GRNs.[81] An intriguing direction for future research will be to establish whether functional interactions indeed occur.

2.6. A Peripheral Olfactory Processing Unit

The olfactory system detects and discriminates a wide variety of environmental volatiles to guide most aspects of insect behavior including foraging, feeding, mating, egg-laying, and aggression. There are two major olfactory organs: the maxillary palp and the antenna, which contains the majority of olfactory sensilla[105] (Table 1). In Coleoptera, Lepidoptera, and Diptera, each multiporous sensillum typically encapsulates the dendrites of two to four ORNs (Figure 2h) that exhibit distinct extracellular spike amplitudes, and are correspondingly named “A”, “B”, “C”, or “D” by descending spike size. Serial block-face scanning electron microscopy (SBEM) of genetically identified ORNs[107] demonstrates that neuronal size differences reflect the disparity in spike amplitude, in that the large-spike “A” ORN is generally larger than its small-spike neighbor(s).[20] Thus, grouped ORNs are almost always morphologically inequivalent. At the molecular level, compartmentalized ORNs express distinct receptors, which define the unique odorant specificities for each cell. In nearly all characterized insect species, ORNs are grouped in stereotyped combinations, such that an ORN with a particular response profile is paired with ORNs of different tuning properties.[50,108–112] In all, the conserved pairing of anatomically and functionally distinct ORNs is highly prevalent, and suggests a critical role for such neuronal arrangement.

Given the stereotypy of ORN grouping, can neurons interact within a sensillum? Beetles offer examples whereby an olfactory stimulus activates one ORN and inhibits its neighbor.[113,114] Additionally in D. melanogaster, Su et al. showed that compartmentalized ORNs can inhibit each other in multiple sensillum types.[19] Despite the lack of direct synaptic connections,[61,62] strong activation of one ORN suppresses the activity of its neighbor.[19] Based on Vermeulen and Rospars’ electric circuit modeling,[115] it was predicted that ephaptic interaction underlies the crosstalk between grouped ORNs.[19] Indeed, by recording from pairs of olfactory sensilla impaled by the same tungsten electrode, Zhang et al. provide direct experimental evidence to demonstrate that ephaptic interaction alone is sufficient to drive lateral inhibition between ORNs that share the same electric field.[20] Remarkably, unequal cell sizes confer disparate circuit functions for compartmentalized neurons: most large-spike “A” ORNs exert greater ephaptic influence and are also less susceptible to electric field changes induced by neighbors,[20] allowing for asymmetric lateral inhibition. Unequal ephaptic interactions provide a potential peripheral mechanism to evaluate parallel inputs and selectively favor the propagation of signals carried by the dominant ORNs.[20] One possible advantage of ephaptic coupling is its low energy cost, in that physical, metabolically expensive synaptic connections are not required for circuit interaction. Furthermore, before entering higher brain centers, inputs are already filtered and constrained at the olfactory periphery, which in principle allows salient information to be more efficiently processed at subsequent nodes. Critically, this lateral inhibition also modulates behavior in response to odor mixtures,[19] highlighting the capability of peripheral processing in biasing olfactory-driven choices.

The olfactory sensilla of ants, bees, and wasps house over a dozen receptor cells,[18,116–118] and these exceptionally numerous neurons raise the possibility that grouped Hymenopteran ORNs can potentially employ another type of functional interaction. Indeed in Japanese carpenter ants, Ozaki and colleagues identified gap junction-like adhesions between the dendrites of the 100 or more compartmentalized ORNs. These cells presumably form an electrically coupled neural network, in which weak olfactory inputs have a low probability of generating spike responses.[18] This network computation may underlie the sensillum’s remarkable selectivity to cuticular hydrocarbons (CHCs) produced by nestmates.[119] Input currents in response to nestmate CHCs are expected to be small due to desensitization from chronic exposure, and such inputs should dissipate within a gap junction-coupled neural network. Conversely, input currents elicited by novel CHCs are likely larger and thus have a higher probability to induce strong spike responses.[18] It will be interesting to determine if such computation applies strictly to pheromone-sensing sensilla and, more generally, whether it is applicable for other Hymenopteran sensilla that house remarkably large numbers of ORNs.

Taken together, functional communication between compartmentalized ORNs may enable individual sensilla to serve as processing units in olfactory computation—either by enhancing stimulus contrast via ephaptic inhibition, or by filtering out weak stimuli through gap junction-coupled neural networks.
3. Information Processing Can Take Place at the Sensory Periphery

3.1. Means of Neuronal Interaction between Compartmentalized Sensory Cells

From the examples described, it emerges that three major types of neuronal interaction may occur between compartmentalized primary sensory cells. First, gap junction-coupled networking allows sensilla to function as intensity filters.\(^\text{[18]}\) Second, gap junction-mediated inhibitory coupling can affect the temporal response dynamics of compartmentalized neurons, as exemplified by the bumblebee galeal sensilla.\(^\text{[16]}\) Such inhibition underlies the burst spiking responses, which prevents adaptation from prolonged stimulation; the sugar-sensing GRN therefore maintains sustained responses for longer periods of time, a feature likely critical for feeding regulation.\(^\text{[16]}\) Third, lateral inhibition through ephaptic or synaptic interaction can influence the coding of stimulus identity. For instance, crosstalk between R7 and R8 photoreceptors likely permits color-opponent processing of light to support chromatic vision.\(^\text{[17]}\) As discussed below, ephaptic inhibition between grouped ORNs also potentially provide a peripheral mechanism for evaluating concurrent, countervailing olfactory cues.

3.2. Lateral Inhibition in Olfactory Sensilla Likely Functions to Process Valence Information

If lateral inhibition is expected to enhance contrast between parallel inputs, what then is accentuated by ephaptic coupling between grouped ORNs? Valence information is a probable answer. Across insects, a striking pairing pattern emerges: ORNs housed in the same sensillum appear to respond to odors from ecologically-related sources, but which elicit opposing behaviors (Table 2). In cotton bollworm moths, a large-spike “A” ORN senses a behavioral antagonist released by immature females, while the small-spike “B” ORN responds to a pheromone that is attractive at low levels.\(^\text{[120]}\) Antagonism also occurs in other insects but overwhelmingly, attractive odorants are detected by large-spike ORNs, whereas their small-spike neighbors detect aversive volatiles (Table 2). When presented with a blend of sex pheromones, silk moths detect attractive bombykol with a large-spike ORN, while its small-spike neighbor responds to aversive bombykal.\(^\text{[121]}\) In spruce bark beetles, the attractive aggregation pheromone excites an “A” ORN while an aversive cue released by damaged host plants is detected by the paired “B” neuron.\(^\text{[122]}\)

Moreover in Japanese beetles, an attractive conspecific sex pheromone is detected by the “A” ORN whereas a behavioral antagonist released by the sympatric Osaka beetle excites the “B” ORN housed in the same sensillum.\(^\text{[114]}\) This pairing principle—in which an ORN, sensing conspecific odors, is grouped with another neuron responsive to sympatric antagonistic volatiles—is observed in multiple insect species\(^\text{[123,125,126]}\) (Table 2). The prevalence of this antagonistic organization, together with its ability to discriminate sympatric from conspecific pheromones, both suggest an important role for peripheral processing in establishing reproductive isolation.\(^\text{[114]}\)

Such isolation is also achieved through the antagonistic detection of host odors; namely, by pairing one ORN that responds to attractive host volatiles with a neighbor that detects aversive, non-host odors. Two subgroups of \(R. \) pomonella prefer either hawthorns or apples. As shown by Olsson and colleagues, the hawthorn flies sense an attractive host odour (3-methyl-1-butanol) with an “A” ORN, which is paired with a small-spike neuron responding to butyl hexanoate, a behavioral antagonist emitted by apples. Conversely for the apple flies, butyl hexanoate is attractive and detected by an “A” ORN whereas 3-methyl-1-butanol is aversive and detected by a small-spike “B” cell in the same sensillum.\(^\text{[127]}\) (Table 2). This switch between these neurons’ response profiles, such that the dominant large-spike “A” cell responds to different attractive cues, likely contribute to the different host preferences between the two closely related \(R. \) pomonella subgroups.

Beyond the contexts mentioned above, antagonism is also observed in sensilla that inform other behaviors critical for survival, such as foraging and egg-laying behaviors in \(D. \) melanogaster (Table 2). Specifically in the \(ab1\) sensillum, the large-spike and small-spike ORNs detect attractive vinegary odors\(^\text{[128]}\) and aversive CO\(_2\),\(^\text{[129]}\) respectively, both of which are component odors of fermented fruit. Moreover in the \(ab4\) sensillum, the “A” neuron detects an aggregation pheromone to promote egg-laying.\(^\text{[132]}\) While the neighboring “B” neuron responds to an aversive mold volatile to inhibit oviposition.\(^\text{[113]}\) Given the ephaptic interactions known to occur in \(Drosophila\) ORNs,\(^\text{[19,20]}\) parallel countervailing inputs may be selectively propagated. This enhanced valence contrast of sensillar outputs is expected to facilitate behavioral decisions, a hypothesis that future research should test experimentally. To understand the meaning of asymmetric inhibition, it will also be important to address why dominant large-spike neurons typically convey inputs of positive valence.

Although the above examples support a valence-opponent organization in \(Drosophila\) olfaction, caution is warranted regarding whether this organizing principle is generalizable across sensillum types. Might there be grouped ORNs that all mediate the same behavioral outcome? Conversely, what is the functional significance of singly-housed ORNs, such as the pheromone-sensing Or67d neurons?\(^\text{[61,135]}\) Through future research, it will be important to determine the generality of valence opponency, perhaps through a comprehensive survey of olfaction that leverages the genetic tools and the wealth of information applicable to the fruitfly’s odorant receptors, their ligands and ecological significance.\(^\text{[106]}\)

4. Conclusion and Outlook

While far from exhaustive, the examples examined shed light on the prevalence and sophistication of compartmentalization, an underexplored aspect of sensory signaling. Here, we describe several characteristics of primary receptor neurons that, in numerous peripheral sense organs, are grouped within structural units. An advantage of such organization lies in the close apposition imposed between neurons, an arrangement which is conducive for neural communication via ephaptic coupling, gap junctions, or synaptic connections. Furthermore, receptor cells are grouped in stereotypical combinations that frequently allows
for the detection of multiple modalities—shown by gustatory and mechanical inputs detected by taste hairs—or multiple stimulus types from the same modality, such as aversive and attractive olfactory cues. Thus, the compartmentalization of multimodal or distinctly-tuned neurons is remarkable in its ability to confer a broad range of responses to individual structural units. In addition, the functional interactions between these neurons can enable cross-modal interactivity. Such intra-compartmental processes distinguish the sensory periphery by its ability to shape input signals—including their intensity and kinetics—when grouped receptor neurons functionally interact.

Taken together, these examples of interactions suggest that compartmentalized neurons can constitute more than the sum of their parts. They also highlight the diversity of signal computation mediated by the peripheral nervous system. However, much remains unknown about whether and how neuronal interactions occur between compartmentalized neurons in other sensory systems, such as in the insect auditory scolopidia, hygrosensory triads, or thermosensory sensilla. Also unclear is how such peripheral integration influences perception which, in all likelihood, would be very different without processing by compartmentalized primary sensory neurons. For instance, how might the flavors of food change if our taste receptor cells are not compartmentalized in taste buds? In surveying a wide variety of sensory units, we hope this article will stimulate future research that addresses these fascinating questions.

Table 2. Ligands and their behavioral significance for neighboring olfactory receptor neurons (ORNs) in select insect species. Compartmentalized ORNs are named “A,” “B,” or “C” based on their relative spike amplitudes in descending order. Odorant receptors, if known, are indicated in parentheses.

| Insect orders and species | Sensilla | ORNs | Ligands | Behavioral significance | References |
|---------------------------|----------|------|---------|-------------------------|------------|
| **Coleoptera**            |          |      |         |                         |            |
| Japanese beetle (Papillia japonica) |          | Type B | A | (R)-japonilure | Attractive sex pheromone released by conspecific females | [114] |
| Spruce bark beetle (Lasius typographus) |          | Trichoid | A | cis-verbenol | Attractive aggregation pheromone released by pioneering males | [122] |
| **Lepidoptera**           |          |      |         |                         |            |
| European corn borer (Ostrinia nubilalis) |          | Trichoid | A | E11:14:OAc | Attractive, major sex pheromone component | [123] |
| European corn borer (Ostrinia nubilalis) |          | Trichoid | A | Z11:14:OAc | Antagonistic, minor sex pheromone component & major pheromone component released by Z strain | [123] |
| Silk moth (Bombyx mori) |          | Trichoid | A | (BmOR-1) | Attractive, major sex pheromone component | [112,121,124] |
| Cotton bollworm moth (Helicoverpa armigera) |          | Trichoid | A | Bombykol | Attractive, major sex pheromone component | [110,120] |
| Gypsy moth (Lymantria dispar) |          | Trichoid | A | (+)-disparlure | Attractive, major sex pheromone component | [126] |
| **Diptera**               |          |      |         |                         |            |
| Hawthorn fly (Rhagoletis pomonella) | Basiconic | B | 3-methyl-1-butanal | Attractive volatile from downy hawthorns | [127] |
| Apple fly (Rhagoletis pomonella) | Basiconic | A | Butyl hexanoate | Behavioral antagonist, a volatile from apples | [127] |
| Fruit fly (Drosophila melanogaster) | Basiconic | A | 3-methyl-1-butanal | Behavioral antagonist, a volatile from hawthorns | [127] |

ORNs exhibiting similar spike amplitudes [20]

| **References** |          |      |         |                         |            |
|----------------|----------|------|---------|-------------------------|------------|
| [114]          |          |      |         |                         |            |
| [122]          |          |      |         |                         |            |
| [123]          |          |      |         |                         |            |
| [112,121,124]  |          |      |         |                         |            |
| [110,120]      |          |      |         |                         |            |
| [126]          |          |      |         |                         |            |
| [127]          |          |      |         |                         |            |
| [128]          |          |      |         |                         |            |
| [129–131]      |          |      |         |                         |            |
| [132]          |          |      |         |                         |            |
| [133]          |          |      |         |                         |            |
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Conflict of Interest

The authors declare no conflict of interest.

Keywords

ephaptic interaction, lateral inhibition, neuronal compartmentalization, ommatidium, sensillum, sensory processing, taste buds

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