Insect Nervous System

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The study of sensory systems in insects has a long-spanning history of almost an entire century. Olfaction, vision, and gustation are thoroughly researched in several robust insect models and new discoveries are made every day on the more elusive thermo- and mechano-sensory systems. Few specialized senses such as hygro- and magneto-reception are also identified in some insects. In light of recent advancements in the scientific investigation of insect behavior, it is not only important to study sensory modalities individually, but also as a combination of multimodal inputs. This is of particular significance, as a combinatorial approach to study sensory behaviors mimics the real-time environment of an insect with a wide spectrum of information available to it. As a fascinating field that is recently gaining new insight, multimodal integration in insects serves as a fundamental basis to understand complex insect behaviors including, but not limited to navigation, foraging, learning, and memory.

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1. Introduction

Insects perform precisely controlled tasks in extremely small time scales to navigate ecological niches and therefore serve as an excellent system to study complex behaviors and their origins. Reliable cues from an external environment are critical for decision-making and most insect behaviors occur as a consequence of simultaneous input-consolidation through multimodal sensory channels. For example, a predatory robber fly processes olfactory, visual, and directional cues simultaneously before executing a calculated aerial attack on a potential prey [1]. Similarly, a pollinating bumblebee in flight receives an overload of sensory information from a colorful flower emitting attractive volatiles [2]. In both these examples, diverse cues from the surroundings translate to information and elicit meaningful responses from the insects. Such multimodal integration has also been investigated in the context of courtship, mating, fleeing, and feeding behaviors of insects. Owing to the ease of approach and experimental design in laboratory conditions, unimodal sensory processing has been studied in different insect models and their isolated functioning has been extensively investigated [3][4][5][6][7]. However, multimodal integration, behaviors that utilize multimodal cues and their neuronal workings are still open fields for exploration. New discoveries made in this field emphasize the role of multimodal integration in improving the decision-making ability of insects, by altering the speed and accuracy of directed responses to stimuli. Therefore, it warrants the importance of investigating sensory signals in combination than individually. To that end, several studies have adapted virtual reality arenas to provide insects with the control of their own flight environments. This technique allows for the design of ecologically relevant experiments to study visual behaviors in navigation [8] and the mechanism of color learning in honeybees [9]. Aside from bridging gaps in our understanding of complex brain functions in tiny insects, research in this field also provides a wealthy foreground to inspire modern engineering feats such as bio-inspired development of micro-robotic control architectures [10].

2. The Insect Olfactory System—A High-End Chemosensor

Chemical cues present in the environment provide crucial information to the survival and thriving of all organisms. From food foraging to identifying potential mates, insects depend on the detection of chemosensory signals for all their behaviors. Chemosensory organs of insects spanning across different ecological niches have evolved with varying orders of sensitivity and remarkable structural modifications to adapt and serve different functions [11][12]. In a vast majority of insects, the antennae and the maxillary palps are the major organs associated with olfaction, while the sense of gustation heavily relies on the proboscis and the labial palps [13]. The olfactory system of the vinegar fly D. *melanogaster* has been studied extensively to understand the path of chemoreception of odor molecules, i.e., from the antennal apparatus on the periphery to the higher centers deep within the central brain where complex behaviors originate. Most of the following anatomical description of the olfactory system can be considered as a representative of other insects, except when specified otherwise. Fine, hair-like structures called sensilla housing olfactory sensory neurons (OSNs) are distributed on the antenna, acting as the primary sites of odor reception [6]. Odor molecules enter the sensilla through pores on the walls and after interacting with odorant binding proteins (OBPs) in the aqueous medium, they reach the dendrites of the OSNs. Each OSN possesses specialized olfactory receptors (ORs) and/or ionotropic receptors (IRs) that bind to specific odor ligands. This binding initiates a depolarization of the corresponding OSNs, leading to the generation of action potentials [14][15][16]. Single sensillum recordings monitor these generated action potentials and identify receptor-ligand interactions of hundreds of chemical compounds [17]. Once detected by the OSNs, odor information is then taken to the primary brain center of the olfactory pathway, the antennal lobes. Densely packed neuropil units called glomeruli in the antennal lobes act as the first synaptic site for the OSNs. These discrete glomeruli vary in number in different species, but follow a fundamental organization. Most glomeruli receive input from only a single type of OSNs and the evoked activity patterns in the antennal lobe confer valence and identity to the odors [5][18][19]. Local interneurons (LNs) and projection neurons (PNs) further innervate the glomeruli and are the next major players in the odor computation process. They either convey information between the glomeruli or wire them to higher centers such as the MB and the LH, which are parallel higher processing centers. The MBs have been investigated extensively and are seen as the center for learning- and memory-associated behaviors [20][21][22]. They receive input from many uniglomerular projection neurons (uPNs) and a few multiglomerular projection neurons (mPNs) from the antennal lobes, which is then redistributed across a large number of intrinsic neurons called the Kenyon cells (KCs) [23]. The parallel axons of the KCs form the different lobes of the MB (γ, α′/β′, and α/β), each lobe retaining odor associative functions of its own. Mushroom body output neurons (MBONs) connect with KC synapses to largely mediate behavioral output and communicate via axons to neuropils outside the MBs such as the LH.

3. The Insect Visual System—A Thousand Tiny Eyes Working as One

Visual cues are perceived in many different forms—shapes, patterns, colors, and contrasts—by the compound eye and are utilized by insects for guiding various behaviors. Differently adapted insects possess varying visual acuity that is more suited to their ecological niches and behavioral preferences (predatory, social/solitary, nocturnal/diurnal/crepuscular). The compound eyes are called so because of the arrangement of numerous small eye units termed as ommatidia “compounded” together. The number of ommatidia can vary anywhere between 10 and 30,000 and their structural organization can differ, catering specifically to the needs of the insect [24]. A fair bit of research has been done to decode the physiological underpinnings of this sensory modality by studying color perception, motion recognition, and polarized light detection as a function of the eye apparatus of insects. In D. *melanogaster*, the retina on the periphery contains over 800 ommatidia, each of which has eight photoreceptors (R1-R8). The roles of these eight photoreceptors have been studied extensively using electrophysiology and functional imaging experiments. While R1-R6 aid in the formation of images and vision during reduced light conditions, R7 and R8 are involved in color perception and detection of polarized light [25][26][27]. Although not directly required for color vision, recent studies have shown the contribution of photoreceptors R1-R6 in it [28]. Spectral information is derived at the very first synapse, closely resembling the vertebrate retina [29]. Specific rhodopsins provide spectral sensitivity to different wavelengths, with rh3 showing a peak to short ultraviolet (short UV), *rh4* to long UV, *rh5* to blue, and *rh6* to green [30].

The D. *melanogaster* visual apparatus is home to over 60% of the total neurons in the entire brain. Therefore, it represents the largest sensory neuropil in the fly nervous system [31]. It shares striking similarities in organization and information flow with the olfactory apparatus [32]. The topographical arrangement consists of a retina on the periphery and four optic neuropils—the lamina, medulla, lobula, and lobula plate. Axons arising from R1-R6 project to the lamina while those of R7 and R8 project to the medulla [33]. The medulla is the most complex optic neuropil and consists of approximately 100 different cell types, distributed between ten layers. The distal medullary region receives external input and wires it to the proximal region, which furthers the computation of visual information. Transmedullary neurons (Tm, TmY) connect the medulla to the lobula [27], which has 800 columns organized into six layers. Columnar neurons and the tangential (i.e., tree like) neurons of the lobula receive input from large visual fields similar to the medulla. Visual motion, direction-selective light inputs, and figure-ground discriminations are processed by the projection neurons of the lobula plate [34]. This consolidated information from the lobula and the lobula plate is then transmitted to the ventrolateral protocerebrum (vlPr) that is located directly beneath the optic lobes. Most of the visual information from the optic lobes reaches the ellipsoid body (EB) of the CX via the anterior optic tubercle (AOTU) and the bulb (BU) neurons. Representation of the medulla and the lobula is spatially separated in the AOTU to filter out specific information from both these regions before conveying them to the CX. The role of the AOTU as a relay site between the visual periphery and the central brain is known to be conserved across many insect taxa, especially in the detection of polarized light and celestial navigation [35]. Thus, the preliminary visual information conveyed from the retina through each of the optic neuropils finally reaches distinct sites in the central brain, especially the CX, where contexts are derived to generate specific motor behaviors.

4. Gustation and Mechanosensation

As briefly mentioned before, through the bristles on the proboscis apparatus, the labial palps on the head and the receptors on the tarsi, the fly receives gustatory cues from tastants and other non-volatile chemicals [36]. The suboesophageal ganglion serves as the primary site in the brain where gustatory input is received [37]. The fly head, along with specific structures distributed across the length of the body, also contains mechanosensory and thermosensory receptors that convey information such as heat, pain, pressure, and vibrations. Thermo- and hygrosensors are identified on the aristae of the antenna while tactile hairs on the legs and the thorax also serve as efficient mechanosensors. A specialized structure inside the antenna called the Johnston's organ conveys distinct acoustic information, proprioceptive feedback, and other mechanosensory cues to the brain via the antennal nerve. The Johnston's organ neurons (JONs) arborize throughout the brain region called the antennal mechanosensory motor center (AMMC), where specific cell types are known to respond to very selective mechanical stimuli [38][39]. Further downstream partners of the AMMC neurons include the wedge (WED) neurons, which receive diverse inputs from the AMMC that help in sensing the wind direction. This output then reaches the fan-shaped body (FB) of the CX via the lateral accessory lobe (LAL) [40]. However, the functional role of these neurons in regulating specific mechanosensory behaviors is only just beginning to be explored in detail.

5. The Mushroom Bodies

The French biologist Felix Dujardin made the discovery of the MBs in the hexapod brain in 1850. He named them so owing to the distinct shape of the bilaterally symmetrical calyx which is connected to the rest of the brain by a peduncle [41].

The relationship between the antennal lobes and the MB is one that has been widely investigated in the processing of olfactory input. As mentioned previously, thousands of KCs are packed densely in the calyces of the MBs. The KC dendrites synapse with the incoming second-order PN axons from the antennal lobes, while the KC axons form the peduncle of the MB. Three different kinds of KCs extend in a parallel fashion to form the distinct MB lobes (α/β, α'/β' and γ) where they proceed to form synaptic connections with a small number of (MBONs). The MBONs take inputs from the three lobes and project to other neuropils outside the MB such as the LH. Modulatory dopaminergic (DAN) neurons and octopaminergic neurons also innervate the MB lobes at specific subdomains and provide the substrates for aversive and associative learning behaviors. The detailed anatomy of the three MB lobes and their role in learning and memory can be found in these publications [21][23][42][43][44][45].

The main calyx receives most of its input only from the antennal lobes while the ventral accessory calyx receives input from the medulla of the optic lobe, the region that is known to process color and contrast information [46][47]. Using dextran dye injections at the primary sensory sites and genetic labelling techniques, multimodal sensory pathways from olfactory, visual and gustatory centers that project to the dorsal accessory calyx in D. *melanogaster* were identified [48], as was also previously observed in hymenopteran models [49][50]. The same dorsal accessory calyx was also recently shown to mostly integrate information received through two kinds of visual PNs, one set from the lobula of the optic lobe and the other from the posterior lateral protocerebrum [51]. The segregation of input occurring at the different calyces suggests a largely parallel functioning of the MB at the level of the KCs, similar to the concentric pattern of input segregation reported in honeybees and cockroaches [52][53].

The information from the KCs strongly converges onto very few (MBONs) which represent the next level of multisensory processing. Even in less commonly investigated models like the cricket, a single MBON was reported to respond to auditory, visual, and wind stimuli [54]. Studying the response properties of the honeybee MBONs revealed that about 42% of the total hits indicated visual sensitivity, while 32% indicated bimodal sensitivity to both light and odors. Only 9% of the MBONs showed unimodal odor sensitivity [55]. A more recent computation method done to map the connectivity between PNs and MBONs showed a similar distribution, with some MBONs predominantly assigned to non-olfactory modalities [23]. These findings are further supported by the role of MBONs in driving learned visual, olfactory, and bimodal behaviors, especially since they show distinct connectivity patterns with the DANs. An earlier study that employed the tethered flight set-up used MB mutants to elucidate the importance of this structure in the context generalization of visual learning [56]. However, studies that are more recent have directly implicated the role of the MBs in acquisition and retrieval of visual memories. Genetically blocking the output from the KCs to the MBONs abolished the ability of flies to acquire and retrieve aversive visual memories, showing that the MBs are also involved in the visual learning process. Another study also revealed a more interesting observation, where olfactory and visual inputs were coded by different sets of gamma KCs [46] while their respective associative memories (appetitive and aversive) are coded by overlapping, yet slightly distinct sets of KCs [57][58]. Additionally, KC dendrites of the main and the accessory calyx show sparse activation to gustatory cues and deficits in gustatory learning are seen when the function of the gamma lobes is impaired in mutant flies [59]. These findings conclusively illustrate the crucial role of the MBs in olfactory, visual, and gustatory associative learning and therefore not specific to a single sensory modality.

Putative relationships have been identified between the MBs and the CX as early as the 1990s, with one study illustrating the common effect light had in the sizes of the calyces of the MB and the CX [60]. While several MBONs send their projections to the CX, the connections from the CX to the MB are more limited. The information from the MB to the CX is primarily utilized by the navigation control system to derive experience-based instructions upon which motor behaviors are executed and controlled. However, an interesting study using the tethered flight arena identified the role of the MBs in a memory-independent olfactory modulation of visual response that is essential for flight control. The same study also notes that the reverse scenario (visual modulation of an olfactory response) is not regulated by the MBs [61].

With the advent of high-resolution microscopy and EM-derived mapping of the MB neural substrates, detailed connectomics of the insect brain has become known [23][42][62][63]. The anatomy and the physiology of the MB neuropils along with its conserved architecture (now elucidated), provide great insight into preliminary multimodal integration that was previously not substantiated. Moreover, the generation of specific and sparse transgenic neuronal lines in the MB can now be used as a tool to manipulate and knockout different candidate neurons, thereby elucidating the specific roles of the MB neurons in regulating multimodal integration and their corresponding behaviors. Such explorative and descriptive studies can lead to the design of further behavioral paradigms, to fully exploit the system and reveal the workings of more complex behaviors.

6. The Central Complex

Along the midline of the insect brain lies a modular structure called the central complex (CX). While its discovery dates back as early as the mid-1800s, definitive descriptions of its organization across the entire insect order only came later. The actual term was coined in 1943 by Maxwelle Power while describing the nervous system of the vinegar fly [64]. In the same article, Power wrote that the CX is an important association center as it receives input from different parts of the brain. A detailed review on the evolution of the CX can be found here [65]. The CX consists of four neuropils—the protocerebral bridge (PB), the fan shaped body (FB), the ellipsoid body (EB), and the noduli (NO). Each of these structures show stereotypical inter-connectivity and are also well-connected with structures external to the CX that control motor output.

As a structure that processes information from both the environment as well as internal states such as hunger and mating status, the functions of the CX are diverse, ranging from guided locomotion to long-term learning and memory behaviors [66][67][68][69]. Compartments of the EB are involved in resolving spatio-temporal cues required for landing maneuvers, flight control, and orientation. The FB plays an important role in executing walking behaviors and negotiating barriers in a path. Neurons of the ventral FB are also known to encode airflow direction, required for orienting toward a stimulus [70]. In a study that investigates nociceptive perception in the fly model, it was shown that harmful stimuli including electric shock are coded as innate and conditioned responses in the FB [71]. Given the extensive usage of electric shock punishments in aversive learning experiments, this finding suggests putative communication between the MB and the FB. Both the EB and the FB have tremendous contribution from the visual centers, especially in using polarization cues and the sky compass, which are essential for navigation [72]. Most motor behaviors require feedback processing from the signals of the environment and the detection of the insect’s internal axis. A specific type of recurrent networks called the ring attractors were long thought to regulate directionality and heading behaviors, by sustaining a bump-like activity pattern, which is modulated after every turn or shift in direction. This model was also physiologically proven [73][74].

The reception and processing of varying sensory inputs to generate an appropriate motor output is the most prominent function of the CX and has been characterized in several insect models such as moths, honeybees, ants, flies, and cockroaches [65][67][75][76]. Predictably, studies that utilized CX mutants show a wide range of motor deficits, including inability to localize targets and initiate walking. A recent study proposed a model of the steering circuit in the CX that utilizes a large array of olfactory, visual, and mechanosensory cues to relay context-dependent motor guidance, further strengthening the function of CX as the navigational switch of the insect nervous system [77].

Although the MBs have been long implied as the center for learning behaviors, the role of the CX in spatial learning has also been of interest. Goal-directed responses controlled by distinct layers of the FB are shown to aid the MBs in maintaining classical memories while also allowing for flexibility, as the fly’s situation changes [78]. Specific neurons in the EB are required for visual place learning (using distinct visual cues to direct navigation) and silencing the input to the EB hugely impairs this behavior [79]. A connection between the MBs and the CX was identified in honeybees with regard to spatial learning behaviors, where the CX was involved in goal-directed responses and the MBs performed associative behaviors. Targeted manipulation of specific neurons in either structure resulted in clear impairment of the behavior [80]. Such connections have also been reported in D.

melanogaster with a single MBON receiving input directly from the CX and several MBONs exhibiting direct connections to the fan-shaped body [23]. Mutant animals that had a defective CX also showed reduced olfactory learning performance [81]. Impaired ipsi- and contralateral gustatory habituation was observed in no-bridge^{KS49} (nob) mutants that have a disturbed protocerebral bridge, implying that some of the communication between the two brain hemispheres is mediated by the CX [82]. These observations support an information transfer between the MBs and the CX, so that learned information, internal state, and previous sensory experiences can be used to generate a sophisticated and rapid motor function [83][84].

With a myriad of functions that encompass olfactory, visual, gustatory, and mechanosensory modalities, the mechanistic framework of the CX remained elusive for several years, with new discoveries on its neuronal architecture and connectivity being continuously brought to light. Moreover, the ability of the CX structures to process highly variable (egocentric and geocentric) information from the environment and to generate a coherent motor output for navigational purposes signifies its complex computational potential, making it an excellent structure to study it as the neural substrate of sensory integration. Exploiting the genetic tools available in D. *melanogaster* to label and manipulate single neurons can allow future work to elucidate the role of each CX substructure and their neuronal connections to other brain centers, in the generation of behaviors influenced by multisensory inputs.

7. The Lateral Horn

The LH is another part of the protocerebrum in the insect brain, which has garnered major research interest in the last two decades, especially in the D. *melanogaster* model. It is one of the two major higher olfactory processing centers and is often linked to the control of innate olfactory behaviors by providing a biological context to the odor cues, as it receives stereotypical axonal projections from the antennal lobes [85]. Detailed reviews on the role of the LH in olfactory processing can be found[86][87][88]. Different regions of the LH are also known to respond to odors that have positive and negative hedonic valences [89]. It was also shown that LH neurons (LHNs) are more broadly tuned when compared to their input neurons and show different responses to odors belonging to different chemical classes [90]. A potential role for the LH in learned olfactory behaviors was first proposed in context-dependent long-term memory formation, indicating more diverse functions for the structure than previously described [91].

The first study to generate an array of neurogenetic reagents that labelled LHNs utilized the split-Gal4 technique that splits the components of the binary expression system, which reconstitute when expressed in the same cell and drive the expression of the downstream fluorescent reporter in only a sparse subset of neurons [92]. An astounding 2444 lines were generated and screened using this technique, which were further filtered for maximum efficiency to over a 100 lines. The lines in this repertoire further lead to the identification of LH input neurons (LHINs), LH output neurons (LHONs), and LH local neurons (LHLNs).

Studying the LHINs revealed that the LH receives input also from regions other than the antennal lobes, such as the auditory and mechanosensory system, the gustatory system and the lobula of the visual system [92]. Some neurons showed a strong presynaptic signal in the VNC, suggesting the transfer of putative pheromone-based or mechanosensory inputs from the VNC to the LH [93][94][95][96]. Another multimodal connection was also proposed in a specific LHON (AV2b1/b2), which potentially receives both visual and temperature input [92]. The position of this neuron is close to a site of several olfactory inputs, suggesting that it could be conferring visual context to an odorant. This observation is further supported by the tethered flight experiment done in the same study, where the optogenetic activation of the LHNs drove the flies to move towards a visual stimulus [92]. In a different study, it was shown that activation of higher-order LHONs (so-called VLPn) induced contralateral inhibition in the LH, influencing navigational responses of a fly to a gradient of odors across the two antennae [97]. Interestingly, these LH neurons have also been shown to receive inputs from other modalities, therefore providing further evidence for the LH being a site of multimodal convergence. It can also be hypothesized that the LH could be an intermediate site between multimodal input and motor output [98][99][100]. Specific connections were revealed between the LHONs and the MBONs implying a potential cross-modulation of associative behaviors between the MB and the LH and can be used to understand their combined role in eliciting complex behaviors [42][58]. A recent study done on the turning behavior of D. *melanogaster* larvae confirms functional connectivity between the LH and MB pathways and illustrates a mechanism by which innate and learned valences interact. A distinct sub-type of neurons called convergence neurons (CNs) is described, which is not only activated by the attractive LH pathway, but also receives excitatory and inhibitory input from MBONs that encode aversive valence [101].

In summary, in spite of receiving the majority of input from the olfactory PNs, the LH also collects inputs from centers processing other sensory modalities, such as vision, sound, temperature, mechanosensation, and gustation. It also receives input from the learning center via the MBONs. This postulates two potential roles for the LH: the multimodal repertoire of information reaching the LH can provide a context upon which the biological valence for an odor is built, and that the LH serves as a center for processing non-olfactory input that promotes downstream control of motor behaviors. Both roles emphasize the capacity of the LH in eliciting complex and context-dependent behaviors in insects and therefore provide a rich foundation for future work that can identify the underlying multimodal neuronal networks.

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