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Mechanisms of vision in the fruit fly

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Vision is essential to maximize the efficiency of daily tasks such as feeding, avoiding predators or finding mating partners. An advantageous model is *Drosophila melanogaster*, since it offers tools that allow genetic and neuronal manipulation with high spatial and temporal resolution, which can be combined with behavioral, anatomical and physiological assays. Recent advances have expanded our knowledge on the neural circuitry underlying such important behaviors as color vision (role of reciprocal inhibition to enhance color signal at the level of the ommatidia); motion vision (motion-detection neurones receive both excitatory and inhibitory input), and sensory processing (role of the central complex in spatial navigation, and in orchestrating the information from other senses and the inner state). Research on synergies between pathways is shaping the field.

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Introduction

The importance of vision for survival cannot be overstated for a vast majority of animals. Therefore, many species have developed extremely complex and precise visual systems, and they allocate a fair amount of energy building them and maintaining them. Light detection implies collecting data about its physical attributes such as intensity, wavelength or polarization. Moreover, this information must be later decoded in the brain before motor decisions are made. Such processing of the physical input is necessary to discriminate patterns, shades, changes of illumination, and motion, either related to moving objects or to the animal's own displacement.

Visual perception starts in the eye, and there are many different kinds of eyes with a wide range of purposes and sensitivities; such as eyecups, eyespots or in the case of insects, the compound eye. *Drosophila* compound eyes are typically composed of around 750 smaller units called ommatidia (Figure 1a,b). Each of these ommatidia has both a simple lens and several photoreceptors, with specialized membrane structures (rhabdomeres) in which light-sensing Rhodopsins are located. The Rhodopsin proteins are organized within a rhabdomeric structure and are predominantly oriented along one axis, thereby making insect photoreceptor cells inherently polarization-sensitive [1]. Light comes in and stimulates the retinal molecule that is embedded within Rhodopsin, triggering the isomerization of retinal. This conformational switch changes the affinity of Rhodopsin from guanosine diphosphate (GDP) to Guanosine-5'-triphosphate (GTP), which subsequently triggers the downstream phototransduction cascade [2,3] (Figure 1b,c).

The visual information is then further processed, in particular in a specialized region of the insect brain: the optic lobes. One optic lobe can be functionally divided into three neuropiles: the lamina, the medulla and the lobula complex (Figure 1d), which depending on the species are either anatomically combined or subdivided. The anatomical reference map done by [4] enables a comparison between different insect species.

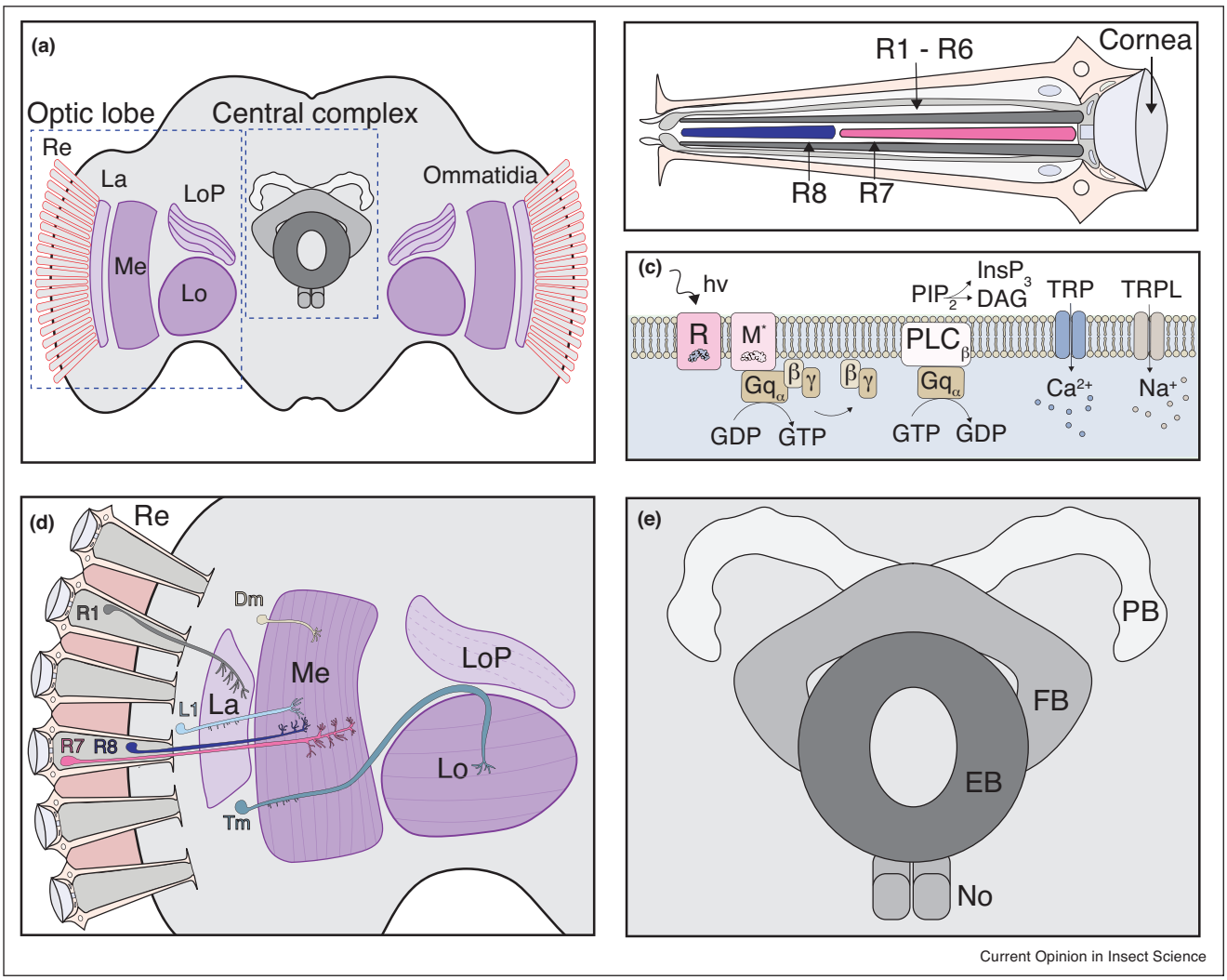
In this review, we will focus on the latest research done in three key topics of *Drosophila* vision: color vision, motion vision and multisensory integration. These three fields have benefited from the genetic tools available for *Drosophila* and from recent connectomics and functional studies to elucidate the function at a neuronal and at a circuit level. We will briefly compare the state of these fields in insects, mainly focusing on *Drosophila melanogaster*.

Decoding chromatic information: from the eye to the brain

Color-vision is important for survival as it confers rich information about the external world, such as the time of the day or the type of food and mating partners. What is commonly known as color-vision can make reference both to 'true color vision', where chromatic information is sensed independently of the intensity; and to 'wavelength-specific behavior', which is a behavior that is dependent on the intensity within each wavelength. The processing of this chromatic information relies both on physical structures in the eyes and in underlying neuronal circuits to decode this information in the brain.

At the level of the retina, color vision depends on several photoreceptor properties, such as their spectral sensitivity [5–7] or their spatial distribution [8]. In *Drosophila*, there

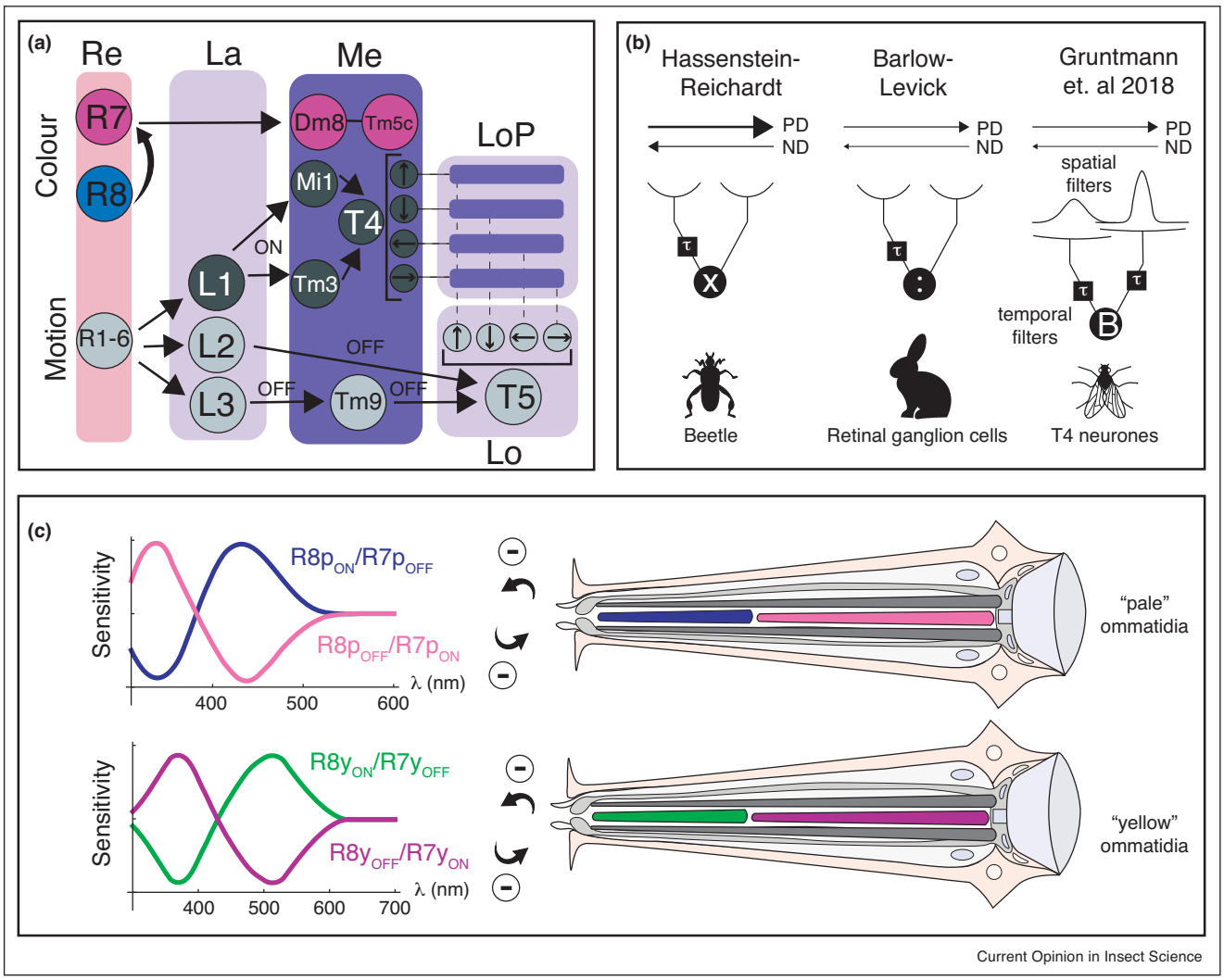
Figure 1



Anatomical structures involved in visual sensory processing in the *Drosophila melanogaster* brain.
(a) General vision of a fly brain. Light goes in through the retina (Re), where it excites the photoreceptor cells. These photoreceptor cells target different structures in the optic lobe: the lamina (La), medulla (Me) and lobula complex, which is in turn composed of the lobula (Lo) and the lobula plate (LoP). The central complex is a structure specialized in sensory integration that is located in the middle of the brain. **(b)** Enlarged view of an ommatidium containing the cornea and photoreceptors R1–R8. The R1–R6 photoreceptors are located in the outer part of the ommatidia, while R7 and R8 are located in the middle, R7 being on top of R8. Light goes in through the lens (right) and enters the rhabdomeres of the different photoreceptors to stimulate rhodopsin. **(c)** *Drosophila* rhabdomere, where the key players involved in the phototransduction cascade within the rhabdomere membrane are shown. After light enters the retina, a photon triggers the isomerization of retinal within the rhodopsin molecule, which leads to the conformational change of rhodopsin (R) to metarhodopsin (M*). This triggers the activation of a heterotrimeric G-protein (Gα q) that activates the phospholipase C β (PLCβ) and hydrolyses PIP_2 into $InsP_3$ and the membrane-bound DAG. This ultimately leads to the opening of TRP and TRPL channels, which leads to the entrance of Ca^{2+} ions and Na^{+} ions. **(d)** Enlarged view of the *Drosophila* visual system including the retina (Re) and four neuropiles within the optic lobe. The outer photoreceptors (R1–R6) project to the lamina, while the inner photoreceptors (R7 and R8) project to the medulla. Different types of neurones are shown: the Lamina neurons (Lm) are directly downstream of R1–R6 photoreceptors. The transmedulla (Tm) neurons span the medulla and project to the lobula, while the distal medulla (Dm) neurons project to distal layers of the medulla. **(e)** Enlarged view of the central complex. It is composed of the protocerebral bridge (PB), the fan-shaped body (FB), the ellipsoid body (EB), and the noduli (NO).

are several types of photoreceptor cells: six outer ones (R1–R6), which project their axons to the first visual neuropile – the lamina, and two inner ones (R7 and R8), which extend their axons to the second visual neuropile – the medulla (Figures 1d, 2 a). The outer R1–R6 photoreceptors have a broadband spectral tuning, while the inner R7 and R8 photoreceptors have a narrower one [7]. Even though R1–R6 have traditionally been

Figure 2



Color vision and motion vision are two nearly independent pathways in *Drosophila* vision.
(a) Diagram of the two parallel pathways in *Drosophila* vision from the retina (Re) to the optic lobe. The inner R7 and R8 photoreceptors project to the medulla (Me) and are mostly involved in color vision. Both the distal medula neuron Dm8 and the transmedulla neuron Tm5 are downstream of the R7 pathway. R1–R6 photoreceptors project to the lamina (La) and are mostly involved in motion detection. The lamina neurones L1–L3 receive information from R1-R6 and then synapse to the transmedulla neurones like Tm9, which in turn synapse to the motion-sensitive T4 and T5 neurones in the lobula (Lo) and lobula plate (LoP). **(b)** Classical motion-detection models include detectors that are spatially separated and that make use of temporal filters (τ) which ultimately lead either to the signal being amplified in the preferred direction (PD, Hassenstein–Reichardt model) or suppressed in the null direction (ND, Barlow–Levick). The Hassenstein–Reichardt model was formulated based on data from the *Chlorophanus* beetle, while the Barlow–Levick model was based on experimental data from rabbit retinal ganglion cells. More recent models, like the one proposed by Gruntman *et al.* [21••] for *Drosophila* T4 neurones, incorporate experimental evidence that they have both excitatory and inhibitory input that are spatially separated and also takes into account some biophysical nonlinearity (b). The model proposes both spatial and temporal filters, which ultimately lead to a suppression of the null direction. **(c)** 'pale' and 'yellow' ommatidia differ in the *rhodopsin* expression in R7 and R8 photoreceptors and therefore in their spectral preference. Recent evidence from Ref. [13••] has shown that within 'pale' or 'yellow' ommatidia, R7 and R8 inhibit each other, which can be seen in their spectral tuning when shown a composite light stimulus.

associated with motion-detection, recent work has shown that they also play a role in color-detection [9]. In contrast, the inner R7 and R8 photoreceptors are sufficient for color vision, although they have recently been shown to have some role in the motion-detection pathway as well [10]. This shows increasing evidence that there is crosstalk between both circuits.

There are different types of R7 and R8 photoreceptors: in the dorsal rim area we can find a few ommatidia that are

responsible for polarization vision, although the most common ones are distributed throughout the eye and are called 'yellow' or 'pale' depending on which pair of *rhodopsins* are expressed in R7 and R8.

True color vision cannot be executed by a single photoreceptor on its own and requires complex further comparisons as can be simple subtractions. These comparisons have been shown to take place in the synaptic terminals of R7 and R8 in the fly medulla through mutual inhibition [11,12]. Recent work using two-photon calcium imaging with genetically encoded calcium indicators, has shown that the signal from R7 and R8 undergoes a comparison within one ommatidium. The mechanism used for this comparison is through reciprocal inhibition at the presynaptic terminal [13••] (Figure 2c).

However, color vision is not only related to the detection of photons of a given wavelength: the chromatic visual input must be further decoded in the brain. The direct synaptic targets of R7 and R8 are neurones present in the medulla: either transmedulla (Tm), or distal medulla (Dm) amacrine neurones [11]. The determination of the downstream synaptic partners of R7 along with functional studies have shown that there is a single pathway mediating the innate UV preference, which involves both Dm8 and Tm5c [11,14] (Figure 2a). This contrasts with the great redundancy found in the color-discrimination pathway for longer wavelengths, such as green and blue. Four transmedulla neurones (Tm5a-c and Tm20) have been shown to be involved in this behavior but the inactivation of any single one of these neurones is not enough to prevent color-learning [15].

More recent studies have focused in the reconstruction of visual projection neurones connecting the lobula with the central brain. The use of a modified GFP reconstruction across synaptic partners (GRASP) [16] has allowed the characterization of the downstream targets of the chromatic Tm neurones in the lobula [17•]. Furthermore, some of these visual projection neurones (VPNs), also called lobula columnar cells, can already link visual input to specific behavioral actions, such as taking off before flying or walking backwards [18•].

Motion-vision: the update of a paradigm

A classic aspect of insect vision with great historic significance is motion-detection. To avoid predators and to capture prey, insects need to determine both their flying direction w.r.t fixed references and their relative position to other moving individuals. However, motion detection is not trivial: it cannot only rely on signal detection at the photoreceptor level, but it requires complex computations in the brain itself. Therefore, the interest in models mimicking neural computations has never stopped growing. Classical examples would be the Hassenstein-Reichardt correlator [19], which was developed from behavioral studies on the beetle *Chlorophanus*, or the Barlow-Lewick extension [20], where an inhibitory or excitatory signal is generated according to the direction of motion and these signals are subsequently compared to detect motion (Figure 2b, for reviews check [24–27]). More recently, Gruntman *et al.* have documented the role of T4 on the detection of the offsets between excitatory and inhibitory inputs [21••], and Borst *et al.* have mapped the neural circuit into the ON and OFF pathways [22]. Further research is needed to clarify a few elements, like the role of non-linearity, which is present in the Hassenstein–Reichardt correlator, and has been challenged by Gruntman *et al.*, who claim that non-linearity is not needed. Another example would be groups only observing null-direction suppression, but no preferred direction enhancement, while Borst *et al.* argue that both exist. Clearly, possessing such models has value in itself, and the interest to develop them is not reduced to adult *Drosophila*. An example of this is the recent successful application of a generalized Markov chain to model the taxis of *Drosophila* larvae [23]. Approaches based on a cost function and a Markovian-like process weighting the involved decision-making landscape open up a quantitative way of measuring the balance between stochastic and driven processes operating in the brain (chance and necessity), which are ingrained after a robust evolutionary process.

To be able to compute motion-vision, it is essential to have detectors with receptive fields that are separated in space, whose input can be temporally compared. As a consequence, downstream of the detectors, flies have direction-selective neurones: cells that respond differently to visual cues moving in opposite directions.

In *Drosophila*, the first real direction-selective cells along the pathway were found a long time ago: The T4 and T5 neurones differentially respond either to light increments (T4, ON pathway) or light decrements (T5, OFF pathway) in a direction-selective manner [28,29] and are crucial components for motion detection [28]. Furthermore, both T4 and T5 have four different subtypes of neurones (T4a-d and T5a-d), which are all columnar neurones and extend their dendrites over a few columns. Each one of these subtypes of neurones is tuned for detecting movement in one the four cardinal directions and consequently projects to one of the four layers of the lobula plate [28,30]. T4 and T5 are postsynaptic to the medulla neurons, which have been extensively studied both at the anatomical level and at the physiological level [26–30]. These medulla neurons are postsynaptic to L1 and L2 neurons in the lamina, which in turn receive the visual input from R1-R6 photoreceptors [31] (Figure 2a). However, T4 and T5 are the first neurones in this network that show direction-selectivity [28].

Recent work focused on the synaptic inputs to T4 and T5 has shown that they receive both excitatory and inhibitory

inputs [32,33,34••]. Furthermore, anatomical efforts to map these neurones using novel high-precision EM and calcium imaging assays, have shown that there is a spatial separation between the two components, which can be produced by spatial or temporal delays of inputs along spatially oriented T4 dendritic branches [34••,35••]. Most recently, Gruntman *et al.* [21••] have used *in vivo* whole-cell recordings of T4 to find that directional selectivity derives from the combination of spatially offset fast excitatory and slow inhibitory inputs. Such a conclusion has been reinforced by simulations that prove how a significant part of the directional information drawn from the T4 dendrites is related to different input signals acquired over spatially separated regions of the flies' eye. Apart from the spatial separation, both types of input differ in their temporal profile: excitation is a fast event while inhibition is slower one [21••]. These recent findings have challenged the classical motion-detection models, and lead to the formulation of newer and integrative ones, which are based on passive conductance biophysical properties. This has prompted models that describe the physiological properties of the T4 neurones more accurately than before by exploiting the idea of combining excitation and inhibition both temporally and spatially [21••,22] (Figure 2b).

Sensory integration

Once the visual input is perceived and processed in the early processing centres, such as the retina and the optic lobe, the signal is transmitted to higher brain regions through the visual projection neurones (VPNs). The visual input must be integrated with other sensory information as well as with the individual's inner state before the appropriate response is coordinated. In arthropods, the structure that has been linked to this process is called the central complex.

The central complex is a highly conserved structure in insects, which is organized in modular neuropiles (For review, see Ref. [36]). These neuropiles are called the ellipsoid body (EB), the fan-shaped body (FB), the noduli (NO) and the protocerebral bridge (PB) [4]. The function of these neuropiles seems to be largely conserved among different insect species and it has recently been shown that some of these neuropiles come from homologous developmental lineages in flies and grasshoppers [37].

The central complex has long been known to be involved in diverse functions such as memory and motor control. Recently, there have been a lot of studies analyzing its role in processing visual information. Most of the studies hint towards the importance of the central complex in spatial orientation through different mechanisms: by the use of landmark detection [38,39], or using the so-called 'compass cells' to calculate the position of the sun [40], or the animal's heading, as encoded by head-direction cells [39,41,42].

Moreover, work by Omoto *et al.* has started elucidating the way in which the central complex receives visual input, and the lineages from which these neurones come [43]. It had also been previously hypothesized that the visual system must input into the ellipsoid body neurones as these neurones are sensitive to visual input [38]. The input of visual neurones into the central complex has also been analysed in other insects, also suggesting that the central complex might have a role in efficient navigation aided by the detection of polarized light in the UV-rich sky [44,45].

The central complex is a structure where we can see how the use of genetic techniques available for *Drosophila* [46] combined with the effort to have a morphological map of the structure with a single-cell level resolution [47–49] have paved the way for functional predictions. For example, Turner-Evans *et al.* have made use of the anatomical data available for two of the Central Complex neuropiles (EB and PB) to propose a conceptual model of how the brain would be able to keep track of compass-like information. For such a model, they had to make several hypotheses: Firstly, that a group of neurones called P-EN would encode the animal's angular velocity. Secondly, that the activity of the subpopulations of P-EN neurones on both sides of the PB would co-localize in a 'bump', which corresponds to a group of neurones that are active at the same time, and that it would encode for the fly's rotational velocity and heading. Lastly, that the P-EN group of neurones would update a second group of neurones, the so-called 'compass neurones', which encode the fly's heading both when the fly turns in the darkness and when there are visual cues. Using the genetic tools available for *D. melanogaster*, they were able to record the synaptic activity of these neurones using calcium imaging and electrophysiology and confirm these assumptions. Furthermore, they recorded the synaptic activity of both populations of neurones simultaneously and were able to complete the model and add the requirement of a third additional component: recurrent inhibition [42]. Despite other species not having such a vast number of genetic tools, a body of work on the central complex is also being generated due to physiological recordings and anatomical mappings [50].

Apart from the central complex, there are other more direct circuits that are in charge of visual sensory integration. This is the case of some descending neurones that are downstream of large-field visual interneurons and that synapse directly into motor centres, consequently controlling flight behavior [51] or the looming-sensitive neurones that directly synapse onto the giant fibre driving an escape response [52,53].

Another form of sensory integration is to relate the sensory input to the animal's inner state. The central complex has been shown to be involved in this type of

sensory integration for a long time but newer work shows that other structures, such as the optic lobes, are involved in the behavioral modulation of visual processing [54–57]. More recent work has also shown that the behavioral state (either walking or tethered flying flies) plays a role in the activity of neurones in the fan-shaped body: These neurones are only responsive to visual stimuli in tethered flying flies [58,59]. Interestingly, Zacharias *et al.* have also shown that different behavioral states (such as the speed of walking) also influence quick responses such as the ones processed by the looming-sensitive neurones [60].

Discussion

Visual processing in *Drosophila* is divided into two parallel pathways within the first neuropiles of the optic lobe: motion vision and color vision. In turn, motion vision is computed in two parallel pathways as well: one that is specialized in detection of light increments (ON pathway) and another one that is specialized in detecting light decrements (OFF path-way). This parallelization of vision tasks presumably confers a high efficiency. After this first decoding of visual information, it is subsequently pooled in the central complex with inputs from other senses and with the flies' inner state in the central brain.

The availability of a sophisticated toolbox and the fact that insects present robust and stereotypic behaviors that can be easily quantified renders the topic of vision in insects an informative research venue. It is possible to combine behavioral data with anatomical data from Electron Microscopy (EM) and with physiological data from calcium imaging or electrophysiology experiments, yielding understanding of the process of vision at different levels. Each of these techniques has its own advantages and drawbacks: EM does not give information about the functionality of synapses, but it can provide a general understanding of the circuit, calcium imaging is technically easier to perform than electrophysiology, but it lacks temporal resolution and the possibility of measuring inhibition. Finally, genome-editing techniques, such as CRISPR–Cas9 [61], have widened the possibility to perform genetical manipulations in species that were not originally established as genetic models.

In conclusion, a combination of sophisticated behavioral assays [62] and functional recording techniques such as electrophysiology or calcium imaging even in walking or tethered flying flies [63], has helped to establish causal links between visual input and behavioral output and a clear correlation between anatomical structures and functional units. Bridging all that information together, mechanistic insight from the processing of visual information at different levels has been obtained: from genes, to molecules, to individual neurones and even to neuronal circuits.

Conflict of interest statement

Nothing declared.

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