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The neural network behind the eyes of a fly

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With its regular, almost crystal-like structure, the fly optic lobe represents a particularly beautiful piece of nervous system, which consequently has attracted the attention of many researchers over the years. While the anatomy of the various cell types had been known from Golgi studies for long, their visual response properties could only recently be revealed thanks to the advent of cell-specific driver lines and genetically encoded indicators of neural activity. Furthermore, dense EM reconstruction of several columns of the fly optic lobe now provides information about the synaptic connections between the different cell types, and RNA sequencing sheds light on the transmitter systems and ionic conductances used for communication between them. Together with the molecular tools allowing for blocking and activating individual, genetically targeted cell types, the fly optic lobe can soon be one of the best-understood visual neuropils in neuroscience. In this review, we summarize what we have learned so far, and discuss the major difficulties that keep us from a complete understanding of visual processing in the fly optic lobe.

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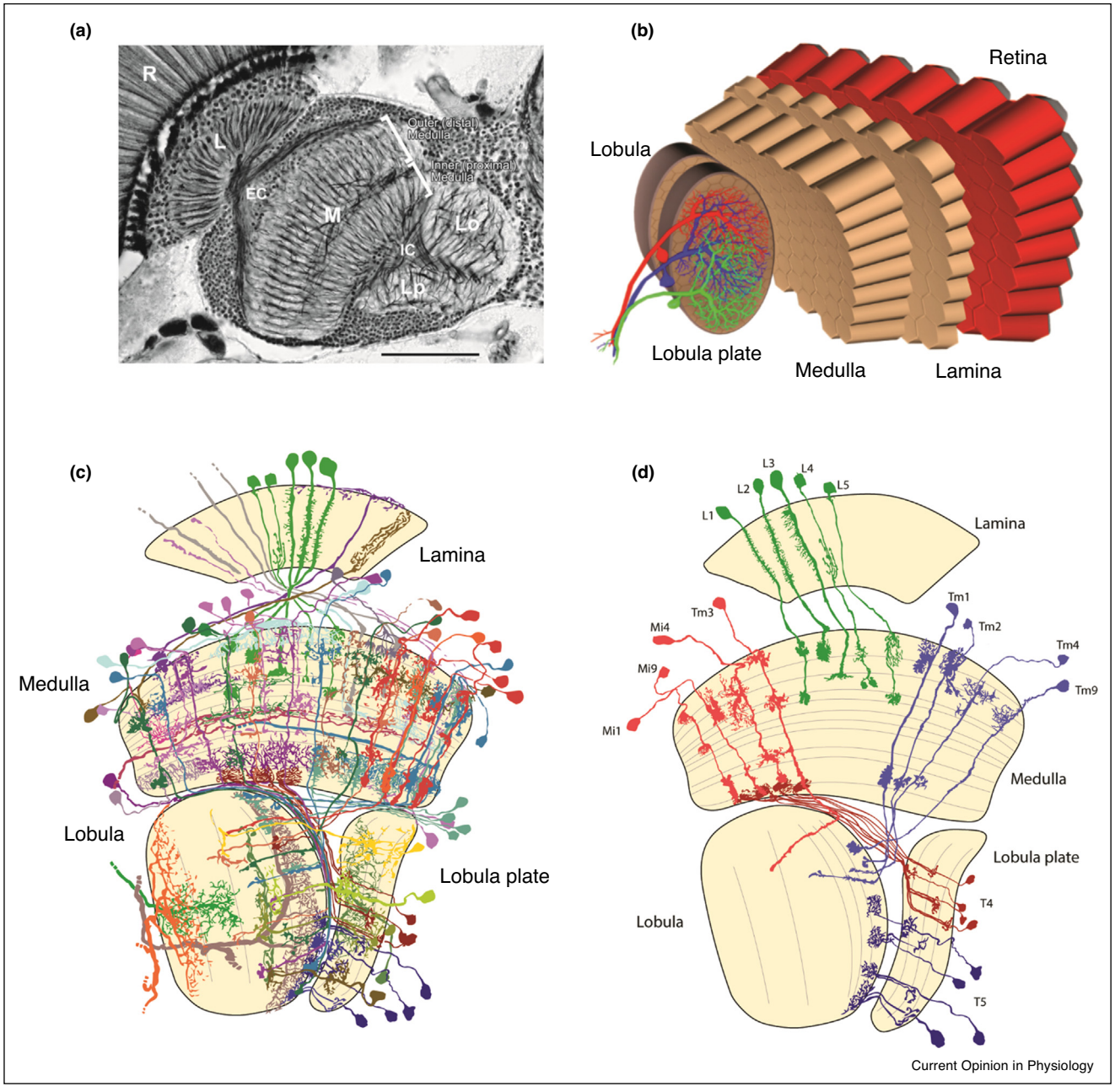
Introduction

Flies are known for their big facet eyes and use vision as their most prominent sensory system. Looking inside their head capsule, two large neuropils are found, one on each side, flanking the central brain. These are called the 'optic lobes' (Figure 1a, b) which, in the fruit fly *Drosophila melanogaster*, contain about 70 000 neurons each. The optic lobe consists of four parts: the lamina, located most distally, receiving input from the outer photoreceptors R1-6; the medulla, where the axons of the two inner photoreceptors R7/R8 as well as those of the lamina neurons terminate; and the lobula and the lobula plate, which are both rotated against the medulla by 90° around the vertical body axis and receive input from the medulla in parallel (for review, see Ref. [1]). All neuropil layers of the fly optic lobe are built from repetitive columns, with each column corresponding to one facet. The columns are arranged in a retinotopic way, representing a spatial map of the fly's field of view. In contrast to humans, this view is panoramic, but at a comparatively low spatial resolution of only about 5° of visual angle. The acceptance angle of an individual photoreceptor is in about the same range, filtering out higher spatial frequencies that, otherwise, would cause spatial aliasing (for review, see Ref. [2]).

The study of the neural circuitry in the fly goes back to Ramon y Cajal. In his monograph, the first drawings of individual neurons of the horse fly (*Tabanus bovinus*) optic lobe can be found, stained with the Golgi method [3]. Continued in the second half of the last century, Strausfeld [4] and Fischbach [5] provided a rather complete Golgi catalogue of all the different cell types in the fly optic lobe (Figure 1c). This catalogue comprises about 100 different cell types, each of which is found once per column. Interestingly, this roughly corresponds in complexity with an estimate of anatomically defined cell types found in the mouse retina [6]. Looking at the Golgi gestalt of visual interneurons in different groups of flies, Buschbeck and Strausfeld [7] found an astonishing degree of similarity between them: despite being separated for 200–300 million years in evolution [8], horse flies, hover flies, robber flies, long-legged flies, tsetse flies, blow flies and their likes all contain a set of neurons which, despite some species-specific variations, reveal a similar arborization pattern and stratification specificity in their dendritic and axonal branching depth within the neuropil layers of the optic lobe. This points to an important functional relevance of this highly conserved cell type diversity.

One particular group of evolutionarily conserved neurons, the bushy T cells (T4 and T5), have been in the focus of researchers for decades [9–14]. T4 and T5 cells have their dendritic branches in the proximal medulla (T4) and lobula (T5), respectively, both sending axonal processes to the lobula plate (Figure 1d). T4 and T5 cells represent the primary motion-sensitive neurons along the visual processing cascade [15,16]. Both T4 and T5 exist in four subtypes, each tuned to one of the four cardinal directions, sending their axons into one of the four layers of the lobula plate (front-to-back: layer 1; back-to-front: layer 2; upwards: layer 3; downwards: layer 4) [15]. The direction of motion is computed independently within each pathway [17–19]. While T4 cells respond selectively to the motion of bright edges, T5 cells respond only to dark moving edges [15]. This parallels the circuit design in the vertebrate retina [20], where visual signals are split into an

Figure 1



Anatomy of the fly optic lobe. **(a)** Horizontal cross section of a reduced silver stain, showing the columnar organization of the retina (R), lamina (L), external chiasm (EC), medulla (M), internal chiasm (IC), lobula (Lo) and lobula plate (Lp). Scale bar = 50 μm. Reproduced, with permission, from Ref. [22]. **(b)** Schematic illustration of the optic lobe, together with reconstruction of the three representatives of lobula plate tangential cells (Horizontal System or HS cells) (modified from Ref. [66]). **(c)** Collection of all the different columnar cell types found in the *Drosophila* optic lobe (after [5]). **(d)** Individual cell types involved in the extraction of local motion information (after [5]).

ON and an OFF pathway too (for a comparative review, see Ref. [21]). Together, T4 and T5 constitute a complete functional map encoding for all four cardinal directions of motion at each position of the visual field [15]. Thanks to dense electron microscopic reconstruction of the fruit fly optic lobe, all their presynaptic neurons are now identified, including their input from lamina neurons [22–26,27••], and most of these neurons have meanwhile also been characterized physiologically (e.g. [28•,29••]). Focusing mostly on this subset of neurons (Figure 1d), we will describe the neuronal computations performed by the network.

Linear and non-linear processing in columnar units

A first step toward understanding feature extraction in a neural network is to investigate the response characteristics of single units inside the circuit. In each column of the fly visual system, the stream of information coming from the same point in visual space is multiplexed into several parallel channels given by the different columnar cell types. What is the functional significance of this parallel processing?

Classical work in large flies has characterized signal processing in photoreceptors and lamina monopolar cells in great detail by means of sharp electrode recordings [30–33]. Together, the retina and the lamina serve as a pre-processing stage which converts the naturally occurring light intensities in the visual scene into a representation of local contrast. Under natural conditions, visual input signals vary over several orders of magnitude in light intensity. Photoreceptors in the retina scale these incoming signals approximately logarithmically to fit them onto the limited dynamic range of neurons. Lamina monopolar cells then subtract the background signal through a combination of spatial and temporal inhibition. Together, these mechanism compute in effect the relative luminance difference, that is, the local contrast, across the scene. This first signal transformation has been shown to be advantageous for further visual processing, and the resulting response properties of lamina monopolar cells can be well explained within theoretical frameworks such as predictive coding and information maximization [34,35].

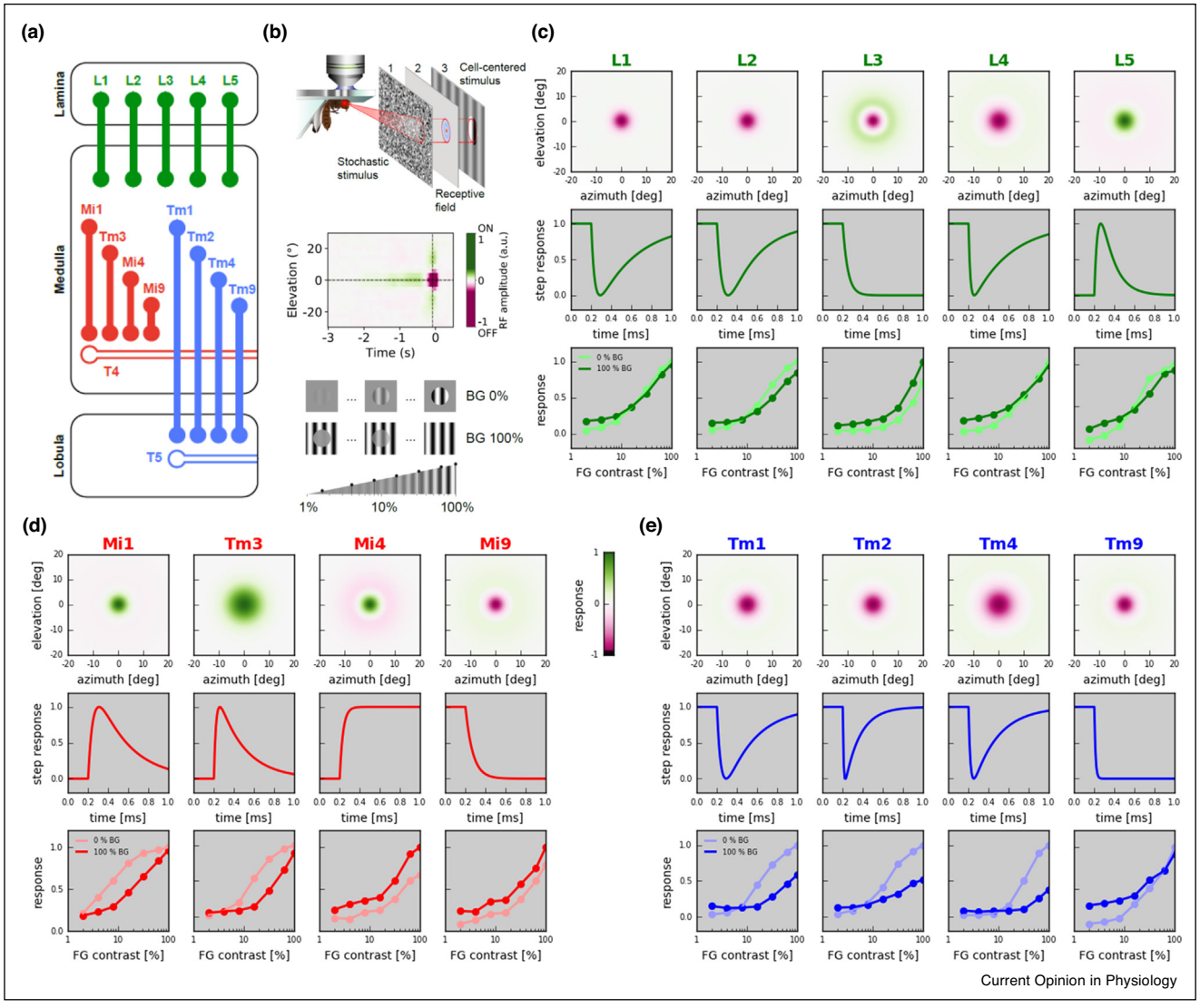
In the medulla, the circuit then splits into an ON-pathway, which is served by L1 cells and converges onto the dendrites of T4 cells, and an OFF-pathway, fed by L2 cells and converges onto the dendrites of T5 cells (Figure 2a) [17,27••]. L3 gives input to both pathways [24]. Over the recent years, new and powerful tools for functional imaging in *Drosophila* have complemented electrophysiology and this combination has brought unprecedented insight into signal processing in the medulla [36–48]. One way to characterize the function of a neuron is using linear filter theory by extracting its linear spatiotemporal receptive field. Receptive fields can be obtained by calculating the 'reverse correlation function' or the 'spike-triggered average' of a neuron's response to a stochastic stimulus, such as random pixels or bar noise (Figure 2b) [49,50]. Spatiotemporal receptive fields can be interpreted as the filter operation implemented by a neuron, or alternatively as a representation of their preferred stimulus, in both space and time.

In *Drosophila*, spatiotemporal receptive fields have been determined for most columnar cell types in the motion vision circuitry (Figure 2c–e; [28•,29••]) using calcium indicators [51] expressed by cell-type specific Gal4-driver lines [52,53] (for review see Refs. [1,54]). As anticipated from anatomy, all neurons possess local receptive fields (Figure 2c–e, first row). In the lamina, all neurons prefer OFF-stimuli except for L5. In the medulla, the receptive field polarity matches the classification into ON-pathway or OFF-pathway elements, except for Mi9 which has OFF-polarity but belongs to the ON-pathway. Furthermore, most receptive fields have antagonistic surrounds of varying strength. Interestingly, L3, Mi4, Mi9, and Tm9 show stronger surround inhibition than the other cell types.

The time axis of the spatiotemporal receptive field reveals the impulse response of a neuron, which can be used to reconstruct corresponding step responses (Figure 2c–e, second row). While most neurons respond transiently to an ON-step, with the sign of the response matching the polarity, L3, Mi4, Mi9, and Tm9 cells are tonic and keep a sustained response level upon stimulus presentation. Interestingly, these are exactly the cell types with a strong antagonistic surround in their spatial receptive fields. Hence, strong spatial antagonism implies weak temporal inhibition in this circuitry. It will be interesting to investigate whether there is a deeper rationale behind this observation, for example by applying theoretical frameworks based on the efficient coding hypothesis as was done for lamina monopolar cells [34,35].

In general, functional descriptions of these cell types using other methods or stimuli agre e qualitatively with the linear receptive fields presented here (e.g. [37,38,42,44]; but see Ref. [55]). A caveat, however, is that they provide nothing but a linear approximation to the complex function implemented by real biological neurons. Non-linear properties, such as response adaptation or saturation, are not captured by linear receptive field mapping. A recent study now reported evidence for a non-linear mechanism called 'contrast normalization' which emerges at the level of the medulla [29••]. The stimulus was divided into a foreground window, covering the linear spatial receptive field, and a background area surrounding it (Figure 2b, top). Modulating the contrast in both areas independently from each other, the authors measured the contrast sensitivity in the foreground as a function of background contrast. In lamina neurons, responses depend solely on the contrast of the foreground window (Figure 2c, third row). Non-linearities here were well explained by a static output saturation. In contrast, transient medulla cells (Mi1, Tm1, Tm2, Tm3, Tm4, as well as postsynaptic T4 and T5 cells) dynamically adapt their responses to the background contrast: increasing background contrast reduces the contrast sensitivity of the cell within its receptive field, which is reflected in a shift of the input–output function towards higher input contrasts (Figure 2d, e, third row). This phenomenon shows striking parallels to 'divisive normalization', a widespread circuit mechanism in the vertebrate visual system that appears to be of general computational

Figure 2



Linear and non-linear processing in columnar neurons. **(a)** Schematic of the motion circuit including all columnar neurons presynaptic of T4 and T5, which have been characterized physiologically in Refs. [28•,29••]. ON-pathway neurons are shown in red, OFF-pathway neurons in blue, lamina neurons in green. **(b)** *Top*: Illustration of the experimental method used in this figure [29••]. Linear receptive fields were obtained by reverse correlation from calcium responses to stochastic stimuli in tethered fruit flies. Contrast tunings were measured by placing custom stimuli on the receptive field centers of individual cells. *Middle:* 1D-projection of the Tm2 receptive field, obtained by reverse correlation from a 1D-stochastic stimulus (replotted from Ref. [28•]). *Bottom:* Illustration of the stimulus protocol for mapping of non-linear contrast processing properties. A drifting grating was shown in a local foreground window around the receptive field center with foreground contrast set independently from background contrast, which was either 0% or 100%. **(c)** Results for lamina columnar neurons L1-5. *Top*: False-color plot of the linear spatial receptive fields from a Difference-of-Gaussian model which was fit to the original data. Middle: Step responses of the cells from a model fit after deconvolution of a putative calcium indicator kernel. *Bottom:* Foreground contrast tuning of the cells for 0% or 100% background contrast (data from Ref. [29••]). **(d)** Same as in C for the columnar elements of the ON-pathway, Mi1, Tm3, Mi4 and Mi9 (data replotted from Refs. [28•,29••]). **(e)** Same as in C for the columnar elements of the OFF-pathway, Tm1, Tm2, Tm4 and Tm9 (data replotted from Refs. [28•,29••]).

advantage for sensory processing across species and even modalities ([56,57]; for review, see Ref. [58]).

In summary, transient medulla neurons serve as a second stage of pre-processing which transforms absolute local contrast, as given by the lamina, into a representation of relative contrast in the current scene. This could reduce the inherent contrast variability of natural images and render downstream feature-extracting neurons, such as motion detectors T4 and T5, more resilient against natural contrast fluctuations. Closer investigation reveals that this mechanism is fast and partially implemented

Figure 3

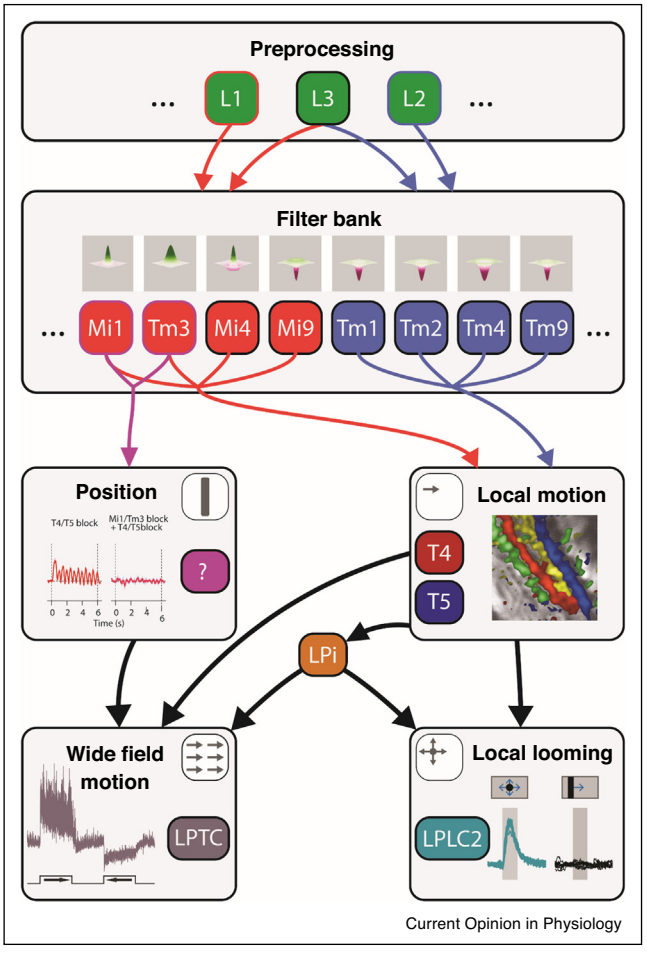


Diagram of feature extraction pathways in the fly visual system. Photoreceptor signals become preprocessed in lamina monopolar cells. L1 and L2 cells feed into the ON-pathway (red) and OFF-pathway (blue) respectively, while L3 provide input to both channels. The spatio-temporal filter bank in the medulla provides a variety of signals to downstream circuits. Output from presumably all depicted Mi and Tm cells converges on the dendrites of local motion detecting T4 and T5 cells. Lobula plate tangential cells integrate T4 and T5 signals spatially for each cardinal direction of visual motion and in each layer of the lobula plate. Additionally, they are inhibited in the respective opposite direction by local inhibitory neurons (LPi) that receive excitatory inputs from T4 and T5 cells in the neighboring layer. Both T4/T5 as well as LPis provide signals for local looming detectors (LPLC2) that respond exclusively to expanding stimuli. Finally, the position of visual objects is encoded in LPTCs, however independently of local motion detectors but through an unknown circuit element that receives input from Mi1 and Tm3. The example data depict the following: Filter bank: color coded 3D representation of linear spatial receptive fields in medulla neurons with responses to positive (green) and negative (purple) changes in luminance (replotted from Ref. [28•]); Position: voltage fluctuation of horizontal system (HS) LPTCs upon stimulation with counterphase flicker with only T4/T5 cells silenced (left) and T4/T5 and Mi1/Tm3 cells silenced (adapted from Ref. [84]); Local motion: color coded T4/T5 calcium responses in the four layers of the lobula plate when presented with sine-gratings moving in four directions (front-to-back (green), back-to-front (red), up (yellow), down (blue), from Ref. [15]); Wide field motion: example voltage trace of an HS cell recording upon wide field stimulation in its preferred and null-direction (adapted from Ref. [73]); Local looming: example calcium responses of a LPLC2 neuron upon stimulation with a local looming object (left) and a horizontally moving bar (right, adapted from Ref. [81••]).

via recurrent inhibitory interactions spanning several medulla columns [29••]. This indicates that the original picture of parallel processing by neighboring columns in the medulla has to be revised in favor of a more intricate circuit model involving non-linear interactions between remote neurons in visual space.

Extracting visual features

The motion vision pathway is one of the best studied examples of visual feature extraction in the fly. As outlined above, T4 and T5 cells represent a feature map for local motion cues across visual space. Since none of the medulla cells turned out to be directionally selective, the dendrites of T4 and T5 cells are the place where direction selectivity arises [15,16]. Algorithmic models had postulated for long that the computation of directional motion information requires a non-linear interaction between asymmetrically filtered signals in time derived from spatially offset small-field inputs (Figure 2f, g, [59,60]). Indeed, dense EM reconstruction [24,27••] demonstrated that T4 and T5 cells receive input from tonic neurons (such as Mi4, Mi9 and Tm9) that carry a slow, temporally low-pass filtered signal within one column, and from transient neurons (such as Mi1, Tm1, Tm2, Tm3 and Tm4) that carry a fast, temporally band-pass filtered signal within adjacent columns. These signals are then non-linearly combined within T4 and T5 cells so that stimuli travelling along one direction (the so-called 'preferred direction') are amplified, and stimuli in the opposite direction (the so-called' null direction') become suppressed [61–63]. This combination of preferred-direction enhancement and null-direction suppression results in a high degree of direction selectivity right at the first stage where the direction of motion is computed [61]. The ionic currents underlying amplification and suppression are currently being investigated ([64,65••]; for review see Ref. [66]).

This particular pattern of connectivity, which requires the wiring of temporally asymmetric input channels from adjacent columns onto a given T4 or T5 cell has been confirmed for each of the subtypes of T4 and T5 [27••]. As a result, the activity of the four subtypes of T4 and T5 cells across all four lobula plate layers represents the Cartesian values of the local motion vector at each position in visual space (Figure 3). From this map, information about behaviorally relevant optic flow-fields is extracted by a set of wide-field neurons called 'lobula plate tangential cells'. From work in blow flies, these cells have been known for long to respond to large-field motion that inform the fly about its ego motion, like rotation

around various body axes [67–71]. Studies on their counterparts in *Drosophila* [72,73] demonstrate that lobula plate tangential cells derive their flow-field sensitivity from integrating excitatory, cholinergic signals of T4 and T5 cells on their large dendrites within selected layers of the lobula plate (Figure 3) [74,75]. One characteristic feature of tangential cells is their motion opponency: they respond to motion along their preferred direction with depolarization while they hyperpolarize when stimulated by motion in the opposite direction. The origin and functional relevance of this motion-opponency is due to a group of lobula plate intrinsic neurons (LPi) that receive excitatory input from T4 and T5 cells in one layer of the lobula plate and send inhibitory output to tangential cells in the neighboring layer suppressing responses to null-direction motion [76]. As a result, lobula plate tangential cells are more specifically tuned to particular flow-fields and do not respond to other flow-fields even when they partially match their preferred flow-field within certain patches of the visual field (e.g. translation versus expansion).

A looming stimulus is a specific type of optic flow that informs the fly about an impending threat. Consequently, looming stimuli elicit strong behavioral responses in flies like escape jumps, avoidance steering or landing, in dependence on the location of the expansion pole within the visual surround [77,78]. While the neural circuitry underlying escape behaviors is well understood in other insects like the locust [79,80], important pieces of information have been missing in the fly, especially in the periphery of the sensory-motor transformation pathway. In principle, a neuron that selectively responds to expanding flow-fields would have to sample inputs from all four lobula plate layers simultaneously [78]. Indeed, Klapoetke *et al.* recently described a novel type of neurons that exactly matches this anatomical prediction [81••]. Physiological characterization of 'lobula plate/lobula columnar neuron type II' (LPLC2) revealed selective responses to looming stimuli that depend on the input from T4/T5 and LPi neurons (Figure 3). This discovery provides insight into the connection between the well-described visual response properties of columnar neurons in the optic lobe and pre-motor circuits in the central brain that initiate appropriate behavioral actions.

All circuits described thus far depend on the output of direction-selective T4 and T5 cells and the visual features extracted by them emphasize the ecological importance of motion vision for the fly. There are, however, other interesting visual feature motifs like local flicker that do not contain directional motion information. Turning responses elicited by flickering objects have first been described in larger fly species [82,83]. Obviously, information about the position of a visual object can be extracted, even if the object does not move. More recent studies in *Drosophila* provided evidence that such turning responses are mediated by Mi1 and Tm3 cells, independent of elementary motion detectors [84]. Flies with T4 and T5 cells silenced still orient towards flickering bars or static features changing in contrast in an open loop condition and stabilize dark objects in their frontal visual field during closed loop conditions [84,85]. Interestingly, these features are represented in the signals of lobula plate tangential cells, indicating an indirect connection between Mi1 and Tm3 and the lobula plate (Figure 3). More recently, a whole new class of visual projection neurons have been described, so-called 'lobula columnar' (LC) neurons [86], which provide output signals from the optic lobe to the 'optic glomeruli' in the central brain. Amongst them, only a few have been characterized so far: LC6 and LC16 neurons respond to looming stimuli [86], and LC11 mainly to small moving objects [86,87]. LC10 neurons also preferentially respond to small moving objects, but using an antagonistic motion-based center-surround mechanism [88•]. The latter study also showed that LC10 cells are indispensable for male courtship: Males with LC10 neurons silenced are unable to orient toward or maintain proximity to the female and fail to predominantly use the ipsilateral wing when singing [88•]. The exact functional and anatomical wiring of their inputs in the optic lobe, however, is not known to date and subject to ongoing investigations.

Current challenges, problems and promises

The above examples illustrate how different visual cues that are only implicitly represented in the spatio-temporal excitation pattern of the photoreceptors become extracted and, thus, explicitly represented in higher order neurons of the Drosophila optic lobe. This feature extraction is done in several, consecutive steps following the different layers of the optic lobe (Figure 3). As a first step, photoreceptor signals are multiplexed in the lamina onto a set of channels with different dynamics — transient (L1, L2) versus sustained (L3) — that provide input to the ON (L1) and the OFF (L2) pathway. In addition, signals adapt to and, thus, become largely independent of the mean luminance. In the next step, lamina signals are combined in several ways by a large number of different columnar neurons in the medulla. These neurons differ from each other i) with respect to their response polarity (ON and OFF neurons), ii) with respect to the extent and structure of their spatial receptive field (narrow or broad, with or without antagonistic surround, i.e. spatial band-pass or low-pass), and iii) with respect to their temporal response characteristics (transient versus sustained), covering a variety of time-constants. In addition, the responses of transient medulla neurons are normalized by the surround contrast. From this set of medulla neurons, higher-order visual cues become extracted through a motion-related processing pathway via T4/T5-cells (local motion, wide-field motion, looming signals) or by combining particular subsets of medulla neurons (local flickers). These are just examples, representing our

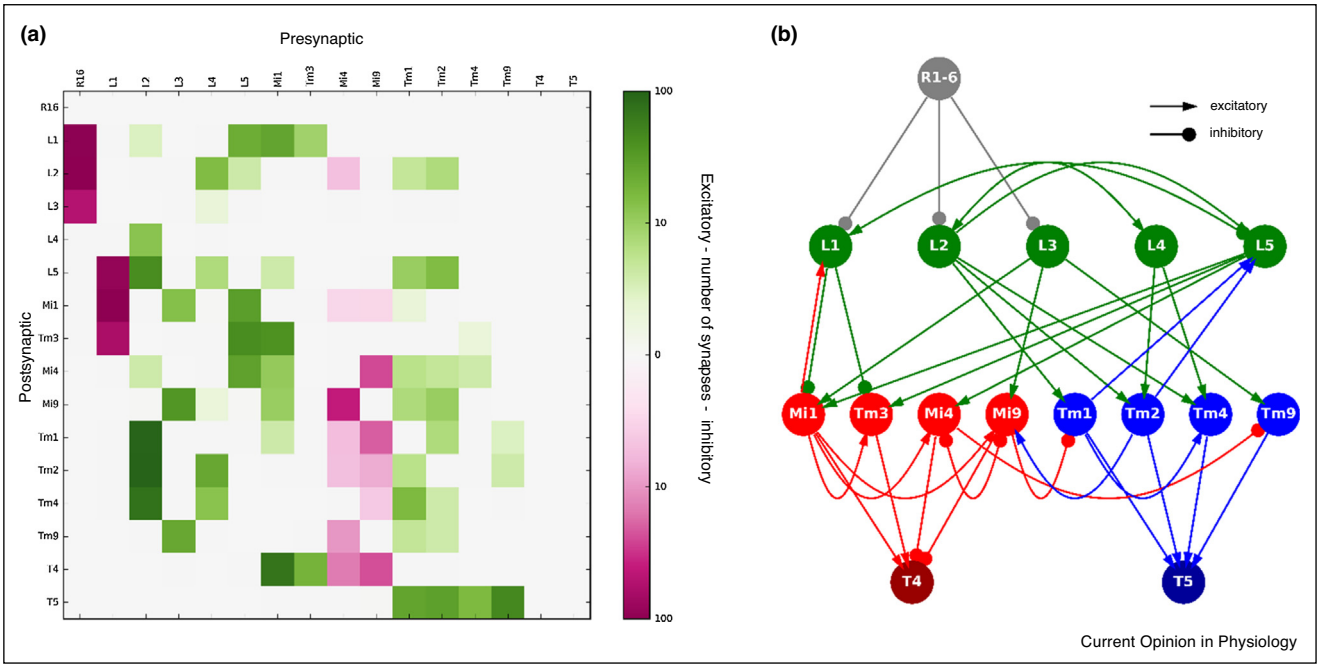
knowledge as of now. Future studies will reveal the processing and extraction of more visual cues, involving other sets of medulla and lobula neurons into the different optic glomeruli, additional pathways and levels of representation, thus completing the picture about visual information processing in the fly optic lobe.

Along this way, what are the challenges and problems lying ahead? Ideally, one would like to a) know the visual response properties, both in space and time, of each of the neurons, b) understand the mechanisms underlying these properties, and c) know the function a given neuron plays in a particular behavior. Studying the visual response properties of all neurons is a question of imagination (with respect to the choice of stimuli) and diligence (with respect to creating specific driver lines for all the different cell types and recording from them).

Understanding the mechanisms, however, is much harder. Why that? These mechanisms can be grouped into connectivity, intrinsic membrane properties and synaptic transmission characteristics, both at the presynaptic and the postsynaptic site. Data on connectivity are available at an almost complete level, at least for columnar neurons, thanks to the Janelia 7-column EM project [27••] (Figure 4a). Data on intrinsic membrane properties will come from more and more exhaustive bulk or single cell mRNA sequencing data, revealing what type of transmitter receptors and ligand or second messenger-gated ion channels are being expressed in each cell type [89–92]. However, the overall effect of such active membrane properties depends on the spatial distribution of the different membrane channels, where no general method exists to visualize them at a single cell level. Furthermore, whether transmitter release follows a constant presynaptic membrane depolarization or rapidly decays to zero depends on the size of the readily available vesicle pool and on the speed by which this pool is replenished. In a similar way, postsynaptic receptors can faithfully transmit a constant transmitter concentration or adapt to various degrees. All these factors can only be teased apart by painstaking experiments involving whole cell patch recordings and calcium imaging experiments, optical measurements of transmitter release as well as blocking and activation of presynaptic neurons.

Additional problems arise with the latter type of experiments, since a particular neuron is usually not only presynaptic to just the one whose response properties one wants to study, but also to many other neurons in the circuit. Therefore, blocking or activating one type of neuron may alter the function of many other cells and, thus, influence the postsynaptic neuron in many indirect ways (see also Ref. [93]). The amount of such 'lateral' or recurrent connectivity becomes obvious when looking at the subcircuit of neurons involved in motion vision

Figure 4



Connectivity matrix **(a)** and c ircuit diagram **(b)** of a subset of neurons involved in the extraction of local motion information (data from Ref. [27••]). Note that in B, only connections consisting of at least 10 synapses are shown. Arrows indicate excitatory, filled circles inhibitory connections, both presumed on the transmitter involved.

(Figure 4b). As one example, medulla neuron Mi1, providing the major excitatory input to T4 cells, not only feeds back onto its major input neuron L1, but also synapses onto three other neurons presynaptic to T4 cells, that is, Tm3, Mi4 and Mi9. Blocking Mi1 has been found to abolish the T4 response to ON-edges almost completely over a wide range of stimulus velocities [94]. However, the contribution of the direct synaptic input of Mi1 onto T4 cannot be deduced from such experiments.

A similar situation is found for the GABAergic Mi4 [27••] and the glutamatergic Mi9 cells [47] which are mutually connected to each other, both presumably being inhibitory [95,75]. Blocking either one of them will certainly influence the other cell as well, which makes the effect on T4 cells hard to interpret. Similar problems will arise when studying the function of a given type of neuron for certain behaviors by activation or blocking experiments, due to the connectivity between the different neurons representing different visual cues. Despite these obstacles, given all the tools and knowledge available in *Drosophila*, the fly optic lobe represents a unique opportunity where a complete picture of visual processing seems achievable in the not too distant future.

Conflict of interest statement

Nothing declared.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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