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Common circuit design in fly and mammalian motion vision

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Motion-sensitive neurons have long been studied in both the mammalian retina and the insect optic lobe, yet striking similarities have become obvious only recently. Detailed studies at the circuit level revealed that, in both systems, (i) motion information is extracted from primary visual information in parallel ON and OFF pathways; (ii) in each pathway, the process of elementary motion detection involves the correlation of signals with different temporal dynamics; and (iii) primary motion information from both pathways converges at the next synapse, resulting in four groups of ON-OFF neurons, selective for the four cardinal directions. Given that the last common ancestor of insects and mammals lived about 550 million years ago, this general strategy seems to be a robust solution for how to compute the direction of visual motion with neural hardware.

The visual scene as projected onto the retina contains a wealth of information about the environment, such as the color of individual objects, their depth in space and the direction in which they are moving. However, all these attributes are not explicitly represented at the level of the photoreceptors but rather must be computed by subsequent circuits. Here we focus on the computation of the direction of motion as one of the most basic and important processing steps of the early visual system and compare our current understanding of its implementation in flies and mice. Seeing the direction in which a predator, a prey or a potential mating partner is moving is of particular importance for the survival of an animal. Moreover, self-motion will also cause the images of the environment to move across the retina in a way that depends on the specific maneuver. Thus, motion vision is at the basis of visual course control, helping the animal to safely navigate through an environment. Given that, it is not surprising that neurons responding selectively to a particular direction of motion have been found in almost every species in the animal kingdom that has been studied so far. Research on motion vision has been focused with particular emphasis on the mammalian retina and the insect optic lobe, probably because of the orderly arrangement of these neuropils, with a clear, layered structure housing a comparatively small number of different cell types. More recently, two species, mice and fruit flies, have become particularly instrumental for studies on direction selectivity because both species offer genetic access to specific cell types and their manipulation, allowing the interrogation of its functional organization at the single-cell level.

Technically speaking, to distinguish moving visual stimuli from stationary ones, the luminance values L from at least two locations in visual space separated by a distance dx must be combined. This combination can involve the explicit calculation of the velocity dx/dt by taking the ratio of the temporal and the spatial gradient $(dL/dt)/(dL/dx)$ (refs. 1–4) or can be based on the correlation of the two spatially separated signals $L(x_0,t+\Delta t)$, $L(x_0+\Delta x,t)$ (refs. 5–7), one of which has been delayed in time. Gradient-based models have been refuted mainly on the basis of their prediction of contrast invariance in the fly visual system, leaving correlation-based models as the primary algorithmic solution to motion computation[8–13]. Here we will review the cellular implementation of two very similar models extensively discussed in the literature: the Hassenstein-Reichardt model[5] and the Barlow-Levick model[13] (**Fig. 1** and **Box 1**). Both models use a delay-and-compare mechanism to compute the direction of motion. Recent years have seen much progress in our understanding of the neural circuits underlying this computation in the vertebrate retina and in the insect optic lobe. Comparing the neural implementation of this computation in two such evolutionarily distant animal groups yields amazing similarities that point toward convergent solutions for how neurons may best perform these computations.

Motion processing in the mammalian retina

General anatomy. All mammalian retinas have a layered structure in common and contain five principal cell types[14]: photoreceptors, horizontal cells, bipolar cells, amacrine cells and ganglion cells (**Fig. 2a**). The mammalian retina contains two main types of photoreceptor, cones and rods. Rods outnumber cones by a factor of about 20 in human and about 30 in mouse[15] and are mainly responsible for the ability to see at night, but they have recently suggested to also contribute to bright-light vision[16]. In daylight, photons detected by cone photopigment are thought to be the main source of visual processing.

The most direct synaptic transmission cascade from photoreceptors to the rest of the brain involves two types of excitatory synapse in the retina: the photoreceptor-to-bipolar cell synapse, located in the outer plexiform layer, and the bipolar-to-ganglion-cell synapse, located in the inner plexiform layer (**Fig. 2a**). In darkness, photoreceptors are depolarized and release glutamate (producing the 'dark current'). In response to light, they become hyperpolarized and reduce their glutamate release. Thus, the photoreceptor's response to light represents an OFF signal. This signal is next split and processed separately in two parallel channels, an ON and an OFF channel. It is

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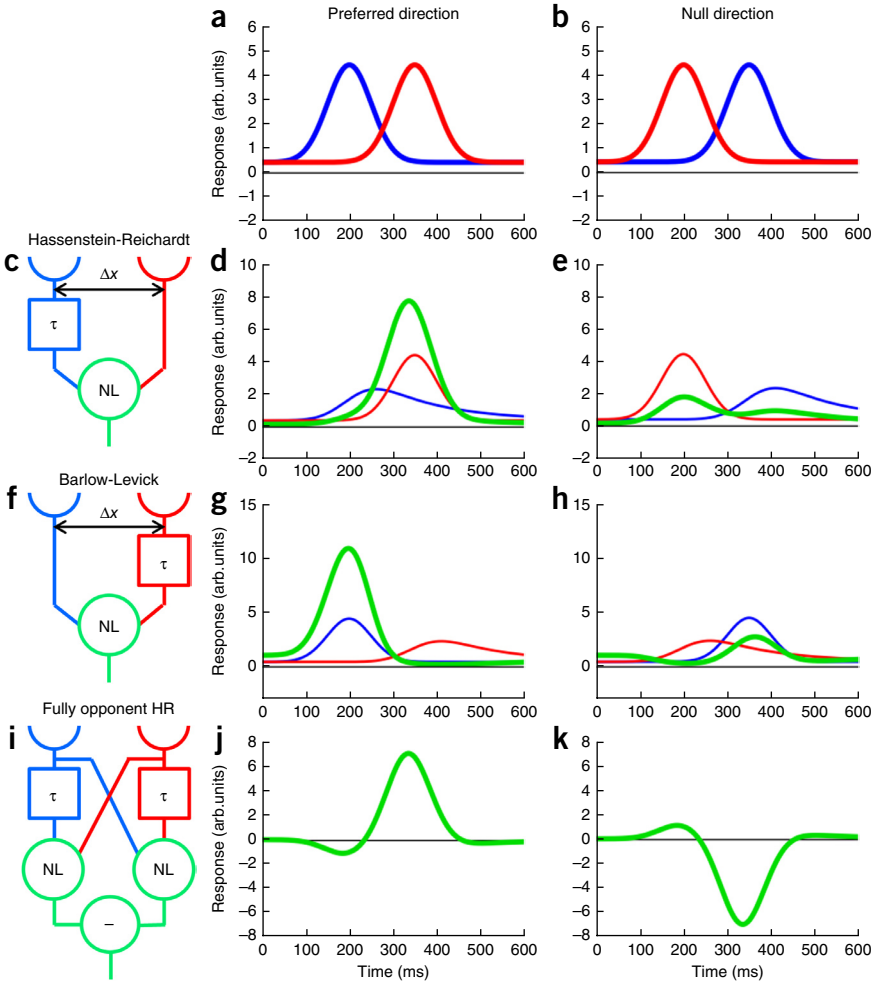

Figure 1 Models of motion detection. (**a**,**b**) Sequences of activation of two neighboring photoreceptors (left, blue; right, red) at a distance Δx for light stimuli moving in the preferred direction (left to right) (**a**) and null direction (right to left) (**b**). Arb., arbitrary. (**c**) Schematic of the half-detector in the Hassenstein-Reichardt model. The signal from the left photoreceptor (blue) is delayed by a temporal filter (τ) and fed, together with the instantaneous signal from the right photoreceptor (red), into an excitatory nonlinearity (NL, green). (**d**,**e**) Input (blue and red lines) and output (heavy green line) signals for motion in the preferred (**d**) and null (**e**) directions. A multiplication was used as the nonlinear operation. (**f**) Schematic of the Barlow-Levick motion detector. The signal from the right photoreceptor (red) is delayed by a temporal filter (τ) and fed, together with the instantaneous signal from the left photoreceptor (blue), into a suppressive nonlinearity (NL, green). (**g**,**h**) Input (blue and red lines) and output (heavy green line) signals for motion in the preferred (**g**) and null (**h**) directions. A division (left signal divided by right signal) was used as the nonlinear operation. (**i**–**k**) Fully opponent Hassenstein-Reichardt (HR) model (**i**) consisting of two mirror-symmetrical motion detection subunits to generate a positive signal for preferred-direction motion (**j**) and negative signal for null-direction motion (**k**).

directly transmitted, without sign inversion, by ionotropic glutamate receptors expressed by the dendrites of OFF bipolar cells[17]. In ON bipolar cells, the photoreceptor signal is sign-inverted by the hyperpolarizing effect[18] of metabotropic glutamate receptors expressed on the cells' dendrites[19]. ON and OFF bipolar cells terminate in separate, adjacent strata of the inner plexiform layer, accordingly called the ON and the OFF strata. The separated ON and OFF channels are recombined at the next synapse, such that the postsynaptic ganglion cells come in ON, OFF and ON-OFF response variants[20]. In most cases, the ganglion cell's response sign can already be predicted by the extent of their dendrites in the ON, the OFF or in both the ON and the OFF strata of

Box 1 Motion detector models

Analyzing the optomotor response of a beetle walking on a spherical Y-maze, Hassenstein and Reichardt developed a model of motion detection that faithfully replicated their behavioral observations[5]. At the core of this model is a motion-sensitive subunit (**Fig. 1c**), in which the luminance values obtained at adjacent image pixels become differentially filtered in time and subsequently interact in a nonlinear way: for example, by a multiplication. This leads to a direction-selective signal: motion in one direction elicits a signal (**Fig. 1d**) that is different in time course and amplitude from the signal generated upon motion in the opposite direction (**Fig. 1e**). The magnitude of this difference depends on the choice of temporal filters and the speed and structure of the moving object: if the time needed to travel from one input to the other is roughly equal to the time constant of the filter, the peaks of the two signals will overlap at the multiplication stage, resulting in a large output signal (**Fig. 1d**; 'preferred direction'). For motion in the opposite direction, the detector's 'null direction', the signals hardly overlap at the multiplier, resulting in only a small output signal (**Fig. 1e**).

To account for their recordings from rabbit retinal ganglion cells, Barlow and Levick[13] proposed a similar model (**Fig. 1f**) that is equivalent to the subunit of the Hassenstein-Reichardt model. Again, the luminance values obtained at adjacent image points are differentially filtered. For the nonlinear interaction, Barlow and Levick use an inhibition, such that one signal vetoes the other. In this way, when the two signals coincide at the nonlinear interaction stage, the output signal will be suppressed (**Fig. 1h**), whereas for motion along the opposite direction, the veto signal comes too late and the signal from the other input is allowed to pass (**Fig. 1g**). Thus, both models are based on a delay-and-compare mechanism—that is, asymmetric temporal filtering followed by a nonlinearity—and are very similar in their principal functional design.

However, the two models differ from each other in the way that a direction-selective signal is produced. When the two input signals coincide, the Hassenstein-Reichardt detector generates an enhancement of the preferred-direction signals due to the multiplicative interaction (**Fig. 1d**), whereas the Barlow-Levick detector generates a suppression of the non-preferred signals due to the veto gate (**Fig. 1h**). Thus, the essential nonlinearity is a multiplicative one in the Hassenstein-Reichardt detector and a divisive one in the Barlow-Levick detector. Furthermore, the Hassenstein-Reichardt detector contains an additional processing stage: it subtracts the output signals of two such subunits (also known as half-detectors), one being the mirror image of the other (**Fig. 1i**). As a result, a fully opponent signal is obtained; that is, motion in opposite directions result in output signals, which have identical time courses and amplitudes but differ in their signs. The sign is positive when motion is along the detector's preferred direction (**Fig. 1j**); the sign is negative when motion is along the opposite direction, the detector's null direction (**Fig. 1k**).

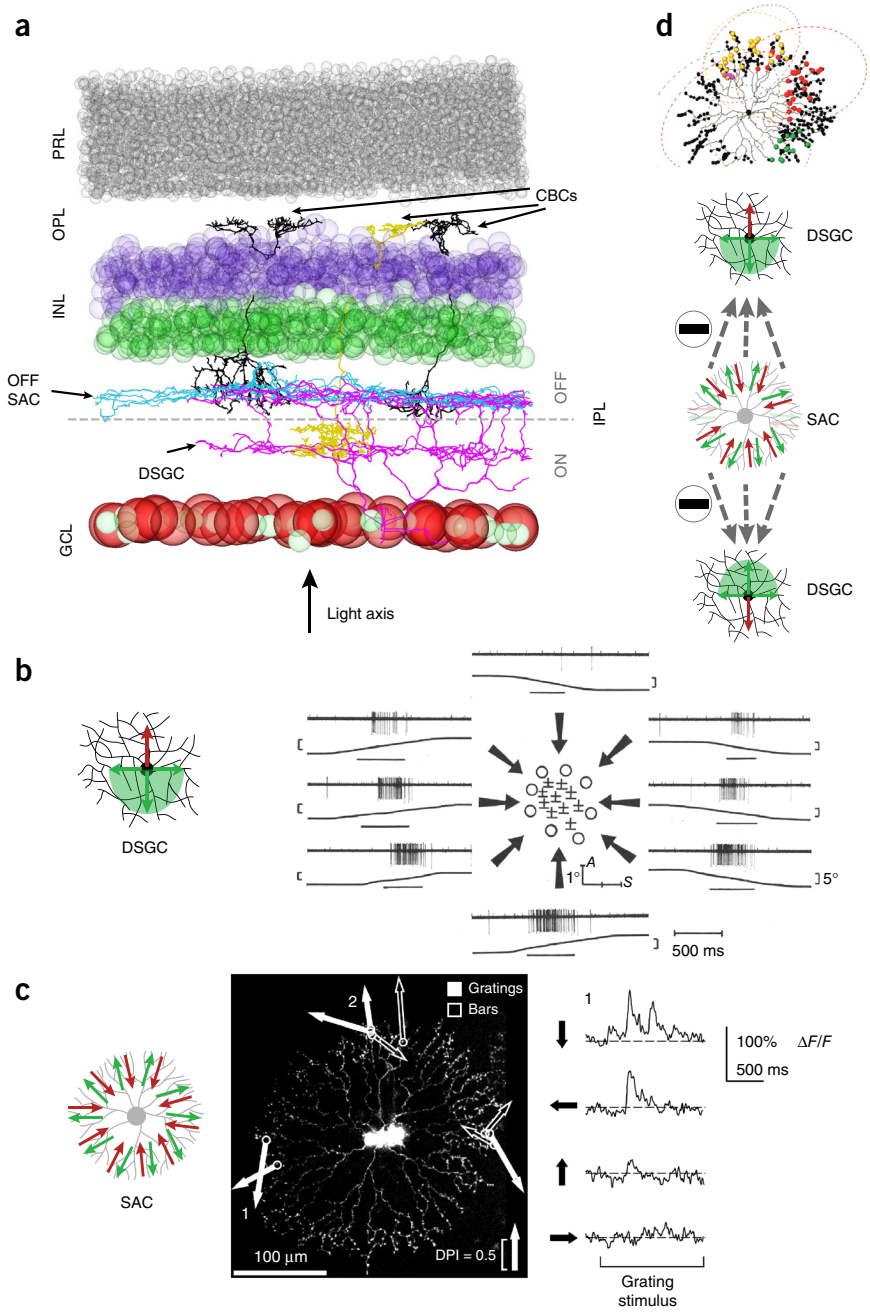

Figure 2 Motion detection in the mouse retina: direction-selective neurons and direction-specific circuits. (**a**) Layout of the retina from a densely reconstructed EM data set[22]. Cell body positions of photoreceptors (gray), bipolar cells (blue) and ganglion cells (red) as well as amacrine cells (green) are shown. PRL, photoreceptor layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer, GCL, ganglion cell layer. Reconstructions of a direction-selective ON-OFF ganglion cell (DSGC, magenta; note bistratification in ON and OFF sublayers), an OFF starburst amacrine cell (SAC, cyan) and type 2 (black), 3A (black) and 5B/C (yellow) cone bipolar cells (CBCs) are shown. All these cell types are involved in motion detection. (Adapted from ref. 22, Nature Publishing Group.) (**b**) Discovery of direction-selective responses in ganglion cells in rabbit retina (left, reproduced from ref. 96, John Wiley and Sons). Unit recordings (top traces) from a DSGC axon in response to moving light spots (trajectories in bottom traces) presented in eight movement directions (black arrows). ON-OFF receptive field (±) and non-responsive surround (circles) are shown (inner scale bars represent 1° for the respective in-plane directions). Horizontal lines indicate approximately when the light spot was crossing the receptive field. Left, DSGC schematic (black). One directional quadrant (the NULL direction, red) is suppressed, while the neuron stays responsive to the other directions of motion (green). (**c**) Discovery of direction-selective responses in starburst amacrine cell dendrites[31]. A fluorescent dye-filled SAC in the plane of the retina (center panel; DPI, directional preference index) and Ca^{2+} responses to moving gratings presented in four movement directions (right) are shown (center and right adapted from ref. 31, Nature Publishing Group). Left, SAC schematic (gray). Each of the radially directed dendrites has its own preferred direction of motion; this preferred direction (green) is oriented from the SAC soma to the dendrite tip. Directional preference is thus represented not just for the four cardinal directions but at a higher angular density. (**d**) Proof of directionally specific neuronal wiring from SAC dendrites to direction-selective ganglion cells[37] (top; adapted from ref. 37, Nature Publishing Group). The output synapses of one SAC (black) are color-coded by the directional preference of the respective postsynaptic ganglion cells (yellow, green, red and magenta for downward, upward, leftward and rightward motion, respectively). These data and the population average imply that these ganglion cells in fact inherit their direction selectivity from SACs. Bottom, schematic. A range of directions is suppressed by the inhibitory effect of SAC dendrites, which release GABA, generating the null direction in the postsynaptic direction-selective ganglion cells.

the inner plexiform layer. The axons of the ganglion cells collectively form the optical nerve and synapse onto targets in, among others, the tectal, pretectal and thalamic regions of the brain[21].

In addition to excitatory synapses, the mammalian retina also contains inhibitory connections. One type of neuron with inhibitory synaptic effects, the horizontal cell, participates in the synapse from photoreceptor to bipolar cell in the outer plexiform layer. The second type of inhibitory neuron, the amacrine cell, shapes the visual response properties of retinal ganglion cells in the inner plexiform layer. Amacrine cells release mainly glycine and GABA[14]. They are as frequent as bipolar cells[22], but have been subdivided into at least 5 times as many classes. Amacrine cells are about 50 times more numerous than horizontal cells. They come in two main categories: the local, mostly glycine-releasing cells of roughly bipolar-cell size, and the medium- to wide-field, mostly GABA-releasing ones.

The spatial resolution of the mammalian retina is defined by the density of cones and the spatial extent of the axonal and dendritic fields of bipolar cells. The visual signal is multiplexed into at least 13 channels in the mouse retina by transmission to at least 13 cone bipolar cell types (**Figs. 2** and **3a**). Ten of these cone bipolar cells have small dendritic and axonal arbors, whose field size in the plane of the retina effectively determines the spatial sampling of the visual response. To a first approximation, the mosaics created by bipolar cells of one type can be viewed as a pixelated representation of the

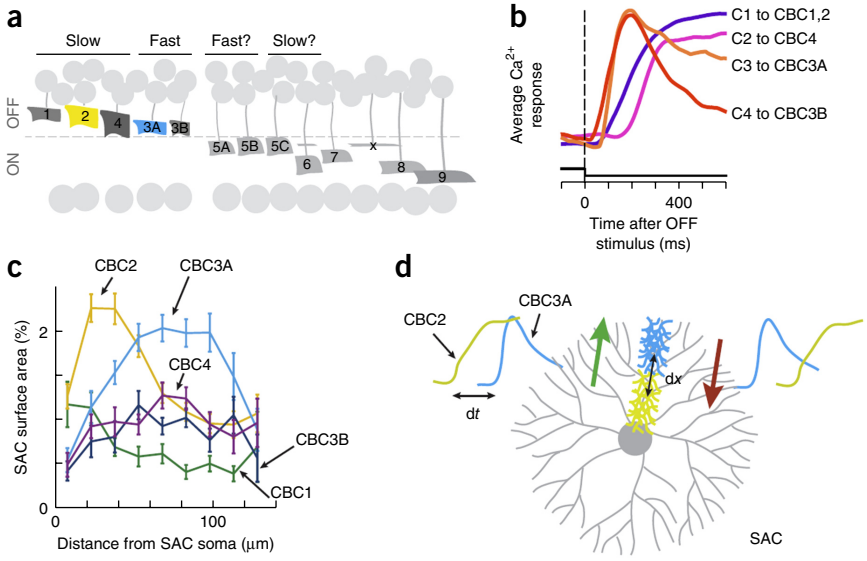

Figure 3 Motion detection in the mouse retina: generation of direction selectivity. (**a**) Schematic summary of the 13 cone bipolar cell (CBC) types known in mouse so far (10 small-field and 3 wide-field). CBCs 2 and 3A are likely involved in the generation of direction-selective OFF signals; the relevant CBCs for ON motion detection are not yet definitively identified. (**b**) The kinetics of OFF bipolar cell terminals (reported as average Ca^{2+} responses, peak-normalized for each transient) grouped into functional clusters (C1–C4). On the basis of the locations in the inner plexiform layer at which these kinetics were found, the likely corresponding CBC types were suggested for each functional cluster[40]. While the relationship between morphological CBC type and response kinetic is suggestive, at least for the OFF cone bipolar cells, direct proof of this correspondence is still missing (adapted from ref. 40, Elsevier). (**c**) Discovery of spatially inhomogeneous bipolar cell contacts along OFF starburst amacrine cell (SAC) dendrites[41] (reproduced from ref. 41, Nature Publishing Group), displayed as the fractional contact area that each CBC type establishes with the postsynaptic SAC as a function of distance along the SAC dendrites. Error bars are s.e.m. per pair and distance bin. (**d**) Spatially offset cone bipolar cell inputs (see **c**) together with the differences in synaptic kinetics for these cone bipolar cell types (see **b**) instantiates a Hassenstein-Reichardt-type motion detection unit at the input to the starburst amacrine cell dendrite: type 2 CBCs (yellow) with slower and longer-latency release innervate the SAC dendrite (gray) more proximally, while 3A CBCs (cyan) with faster and short-latency responses innervate the starburst amacrine cell dendrite more distally, establishing a spatial (Δx) and temporal (Δt) offset as required in the Hassenstein-Reichardt model (**Fig. 1**), yielding an outward preferred (green arrow) and inward suppressed (red arrow) directional response.

visual scene. However, at the level of the cone bipolar cells the retina provides not just 1 but at least 10 of such pixelated representations in parallel. These representations feed into more than 20 different types of ganglion cell, which thus provide an even more differentiated view of the world—at, however, mostly lower spatial resolution.

Motion pathways. Three groups of retinal ganglion cell are known to respond to visual motion in a directionally selective way: ON-OFF ganglion cells, with four subtypes according to their preferred direction along one of the four cardinal directions[23,24]; ON ganglion cells, with three subtypes and 120 degrees separation between their preferred directions[23,25]; and OFF JAM-B cells, all of which prefer upward motion[26]. In the following, we will concentrate on ON-OFF ganglion cells and their input circuit, which were the first neurons in the mammalian retina found to be direction selective[13,27]. Barlow and colleagues recorded from rabbit ganglion cells while presenting moving bars to the eye. They found that action potential responses were substantially stronger when the bar moved in the cell's 'preferred direction' than when it moved in the opposite, the cell's 'null direction' (**Fig. 2b**). This seminal finding first of all demonstrated that the retina, unlike a simple pixel-array camera, already preprocesses visual information. Furthermore, it opened the search for the neuronal implementation of motion detection in mammals.

One of the first questions along this route was whether motion detection is implemented solely via the bipolar-to-ganglion-cell pathway or whether inhibitory neurons are involved. First Wyatt and Daw[28] found that GABA blockers abolish direction selectivity in rabbit ganglion cells. Then the discovery of the starburst amacrine cells[29] and their necessity for directionally selective signals in the ON-OFF direction-selective ganglion cells[30] marked important steps in our understanding of how direction selectivity arises in the retina: when starburst amacrine cells are ablated by targeted application of immunotoxin, ganglion cells lose their direction selectivity[30]. In a crucial set of experiments, ON starburst amacrine cells themselves were shown to exhibit direction-selective responses when exposed to moving stimuli[31] (**Fig. 2c**): measuring calcium entry at the synaptic terminals located at the outer rim of their dendrites, the output of the starburst amacrine cells is increased for centrifugal—that is, soma-to-tip—and decreased for centripetal—tip-to-soma—stimuli[31].

The intrinsic centrifugal direction selectivity of starburst amacrine cells and their necessity for direction selectivity in the ganglion cells might, at first sight, be rather puzzling: how can the output signals of neurons responding to all directions of motion lead to selectivity for just one direction in the postsynaptic cell? Directionally specific inhibitory synaptic inputs to ganglion cells were first suggested on the basis of whole-cell voltage recordings in rabbit ganglion cells in an attempt to segregate inhibitory and excitatory synaptic conductances on the basis of somatic holding potentials[32,33]. Such recordings are, however, difficult to interpret for lack of space clamp in extended dendrites when recording from the cell body[34]. Paired whole-cell recordings between starburst amacrine cells and ON-OFF directionally selective ganglion cells indicated that the magnitude of the postsynaptic potential in the ganglion cells elicited by starburst cells has a spatial asymmetry: when the soma of the starburst cell is on the side from which a moving stimulus leads to no response in the ganglion cell (the 'null' side), postsynaptic responses are stronger than in cases in which the soma is on the 'preferred' side[35]. However, it remained unclear whether such an asymmetry is the result of synapse strength or specific wiring—and, in the latter case, at what level of specificity the direction-selective wiring is implemented. These questions were resolved by combining two-photon microscopy–based functional recordings of direction-selective ganglion cells with subsequent high-resolution circuit reconstruction via serial block face electron microscopy[36]. Using this approach, Briggman *et al.*[37] showed that individual dendrites of starburst amacrine cells connect specifically to those ganglion cells that have a directional preference opposite to the one of the starburst dendrites (**Fig. 2d**). These data showed that the starburst-to-ganglion-cell circuits are able to explain the direction selectivity in the postsynaptic ganglion cells by a direction-selective

inhibitory signal from the starburst amacrine cells. The wiring selectivity is substantial: about 8–10 times more synapses are made when starburst cell dendrites and ganglion cells have opposite preferred directions than when they are parallel[37]. The magnitude of this selectivity, together with the finding that GABA blockade invariably abolishes direction selectivity in the ganglion cell output as well as the optokinetic nystagmus[30], make the inhibitory source of direction selectivity in ganglion cells convincing. It should be noted, though, that postsynaptic mechanisms such as asymmetry of dendritic arbors or dendritic Ca^{2+} spikes could enhance direction selectivity[38,39].

Selective starburst-to-ganglion-cell connectivity has several interesting consequences. First, it requires a dendrite-specific wiring mechanism during development that ensures that the different branches of a radially symmetric starburst amacrine cell connect to four different subtypes of ganglion cells, according to whether the postsynaptic ganglion cell is tuned to rightward, leftward, upward or downward motion. As seen from an individual postsynaptic ON-OFF ganglion cell, this connectivity furthermore has to agree in both the ON and the OFF stratum. Second, together with the functional data, it explains the initial finding of null-direction inhibition, made by Barlow and Levick[13]—with, however, a different interpretation: the signals arriving in the ganglion cell are not, as originally presumed, nondirectional in nature, but are already direction-selective themselves. Third, the question of the origin of direction selectivity is pushed to one synapse upstream: how does the dendrite of the starburst amacrine cell become direction selective in the first place?

As explained above, the detection of directional motion requires a combination of signals separate in space and time. The topographic arrangement of the retinal neuropil implies that an elongated dendrite of a starburst cell extended in the plane of the inner plexiform layer can sample different points in visual space via bipolar cell inputs. Thus a starburst dendrite represents positional distance between its origin and its end. What about the separation in time? Here, two alternative hypotheses seem feasible: either the presynaptic bipolar cell terminals themselves have different temporal dynamics depending on the synapse location on the starburst dendrite, or bipolar signals have the same dynamics but timing differences are created on the postsynaptic side, either by transmitter receptors with different kinetics or by low-pass characteristics of the starburst dendrite. Important evidence comes from a study reporting, in fact, varying response kinetics in bipolar cell terminals[40] (**Fig. 3a**). Interestingly, these response kinetics vary systematically across the depth of the inner plexiform layer: both in the OFF and the ON sublaminae, slower kinetics (that is, more sustained responses) are found toward the edges and faster (that is, more transient ones) toward the center of the inner plexiform layer (**Fig. 3b**,**c**). By relating the distribution of the observed responses to the axonal width of known bipolar cell types, Baden *et al.*[40] found evidence suggesting that OFF cone bipolar cell types 1 and 2 (as well as ON cone bipolar cells type 6 or 7) are slow, exhibiting a sustained response, while cone bipolar cells of type 3a, 3b, 4 and 5 are fast, with low-latency, transient responses to visual stimuli.

Thus, assuming precise wiring, a motion detector could be implemented by selectively connecting slow bipolar cells to the proximal parts of a starburst dendrite and fast bipolar cells to the distal. With this, visual stimuli moving outward along the dendrite would be able to elicit strong depolarization in the starburst dendrite while those moving inward would activate fast responses first, which would have subsided before the slow, proximal ones kicked in. In fact, reanalyzing the data set used for unraveling the starburst-to-ganglion-cell circuit[37], a recent study found that cone bipolar cells in the OFF lamina of the inner plexiform layer contact the dendrites of starburst dendrites in a spatially selective fashion[41]: cone bipolar cells of type 2 preferentially contact the proximal parts of starburst dendrites, while cone bipolar cells of type 3A preferentially contact the distal (**Fig. 3d**). Together with the suggestion that type 2 bipolar cells exhibit slow responses while type 3A bipolar cells exhibit fast[40], these data could in fact explain the generation of motion selectivity in the dendrites of starburst amacrine cells. Mammalian retinas would implement a Hassenstein-Reichardt-type motion detector at the input synapse to the dendrites of starburst amacrine cells, with the delay generated in the presynaptic bipolar cell terminals.

Motion processing in the fly optic lobe

General anatomy. In contrast to vertebrates, flies have compound eyes that consist, depending on the species, of many hundreds to thousands of individual facets, or ommatidia. Each facet has its own little lens and houses a set of photoreceptors that are grouped into six outer photoreceptors, R1–6, and two inner, R7 and 8, stacked on top of each other. Visual information delivered by the photoreceptors is processed in several layers of neuropil, collectively forming the optic lobe. Repeating the columnar organization of the eye, these layers are called lamina, medulla, lobula and lobula plate (**Fig. 4a**). While the lamina and the medulla are arranged sequentially, the lobula and the lobula plate are linked to the medulla in parallel, together forming the lobula complex. Except for the lamina, these neuropils exhibit distinct numbers of strata. The optic lobe contains roughly 100 different cell types, most of which exist once per column[42,43]. The major columnar cell types are as follows: (i) the lamina monopolar cells L1–5, which connect the lamina to different strata of the medulla; (ii) the medulla intrinsic (Mi) neurons, connecting different strata of the medulla to each other; (iii) the transmedulla (Tm) neurons, connecting distinct medulla strata to the lobula; (iv) the TmY neurons, connecting distinct medulla strata to the lobula and the lobula plate; and (v) two groups of 'bushy' T-cells, each of which consist of four subtypes per columns, termed a–d: T4 cells in the most proximal medulla strata and T5 cells in the most posterior strata of the lobula both connect to one of the four directional layers of the lobula plate (**Fig. 4b**). Besides these columnar cells, the optic lobe also contains neurons that spread their input-output arborizations over many columns. The most important of these in the present context are the tangential cells of the lobula plate. These cells respond to visual motion in a directionally selective way and were first anatomically described and functionally characterized in blow flies[44–49]. Owing to their accessibility for electrophysiological recordings, they formed the starting point of the analysis presented further below[9–11,50–53].

Image formation in the vertebrate and the fly eye is strikingly different: whereas in vertebrates the lens focuses the photons reflected across a large angle by a single point in the object plane onto a single point in the image plane of the photoreceptors, the photoreceptors in each facet of the fly's eye receive photons from only a narrow angle, giving rise to a single image point. This results in a much reduced light sensitivity compared to that of the vertebrate eye. Furthermore, while the spatial resolution of the vertebrate eye is largely determined by the photoreceptor density, the spatial resolution of the fly eye is given by the angular separation between neighboring facets. In case of *Drosophila*, this value is in the range of 5 degrees of visual angle. However, the compound eye provides flies with a panoramic view of the world with no need to move their eyes. In addition, dipterans, such as *Drosophila*, use a special trick called 'neural superposition' to maximize their light sensitivity and visual acuity at the same time: since each of the outer photoreceptors, as a result of their different placements in the image plane of the facet lens, has a slightly different optical axis, those photoreceptors in neighboring ommatidia that have the same optical axis connect to same neurons in the lamina[54,55]. All photoreceptors

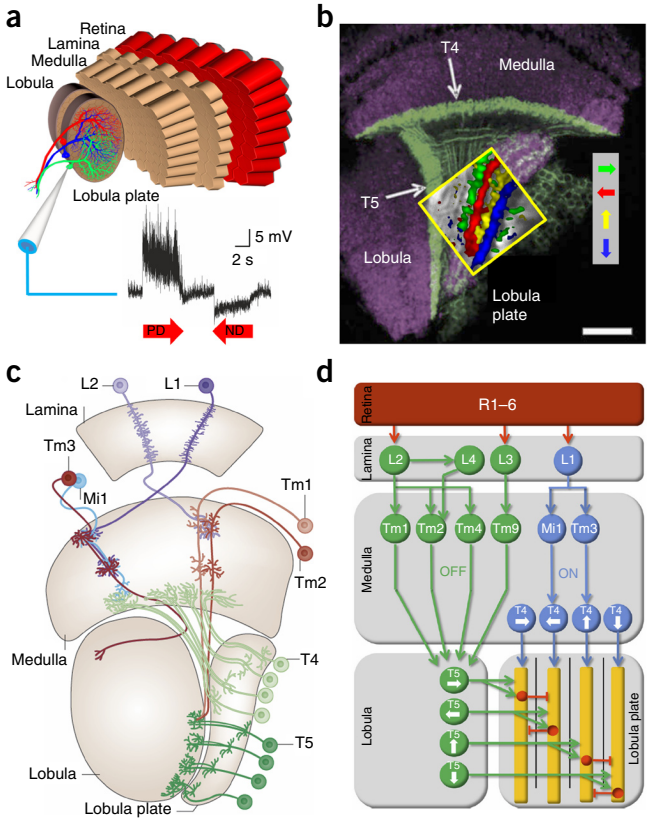

Figure 4 The fly motion vision system. (**a**) The fly optic lobe receives input from the photoreceptors located in the facets of the compound eye (in red) and consists of several retinotopically arranged neuropils, called lamina, medulla, lobula and lobula plate. In the lobula plate, large-field tangential cells pool the signals of hundreds of columnar, motion-sensitive T4 and T5 cells originating in the medulla and lobula, respectively. As an example, three cells of the horizontal system are shown, together with a typical motion response from one such cell. They depolarize in response to front-to-back motion, their preferred direction (PD), and hyperpolarize in response to back-to-front motion, their null direction (ND) (adapted from ref. 72, Nature Publishing Group). (**b**) Confocal image of T4 and T5 cells and their directional tuning. The light green bands indicate the dendrites of T4 and T5 cells. Their cell bodies (right) are located posterior to the lobula plate. The presynaptic terminals of both T4 and T5 cells form four distinct layers within the lobula plate. The inset shows the result of two-photon calcium imaging, revealing four subgroups of T4 and T5 cells tuned to the four cardinal directions that project to the four directional layers within the lobula plate; subpopulations and directions are color-coded. Scale bar, 20 µm (adapted from ref. 72, Nature Publishing Group). (**c**) Schematic morphology of main columnar cell types forming the elementary motion detector. Shown are the lamina cells L1 and L2, together with medulla interneurons Mi1, Tm3, Tm1 and Tm2, as well as the four subpopulations of T4 and T5 cells (reproduced from ref. 97, Nature Publishing Group). (**d**) Circuit diagram of the ON and the OFF pathway of fly motion vision. Visual input from photoreceptors R1–6 is split into parallel pathways at the level of the lamina. The ON pathway (blue, right) is shown to involve lamina neuron L1 and two postsynaptic cells, Mi1 and Tm3, in the medulla. These cells contact the dendrites of T4 cells. The OFF pathway (green, left) involves more neurons. Here lamina cells L2 and L4 synapse onto medulla neurons Tm1, Tm2 and Tm4. In addition, lamina cell L3 synapses onto Tm9. All four medulla neurons contact the dendrites of T5 cells. Directionally selective signals are carried via T4 and T5 cells to the four layers of the lobula plate, where T4 and T5 cells with the same preferred direction converge again on the dendrites of the tangential cells (yellow). Inhibition is conveyed via hypothetical local interneurons (red) from one layer to the adjacent one (reproduced from ref. 98, John Wiley and Sons).

depolarize upon illumination[56]. Inner and outer photoreceptors differ, however, with respect to their spectral sensitivity: while R1–6 possess an identical broad-band opsin with peak sensitivity in the green and support achromatic vision such as motion vision[57,58], inner photoreceptors (R7 and R8) express one of four opsins with different, more narrow spectral sensitivities, supporting color vision[59].

Motion pathways. The termination of the different lamina neurons in different strata of the medulla already suggests a split of the primary visual information into different parallel processing pathways. In the case of motion processing, this functional specialization is understood fairly well. At the very first synapse, the photoreceptor signal is inverted by the use of histamine as a neurotransmitter, which opens chloride channels in the lamina neurons[60]. Thus, lamina monopolar cells transiently hyperpolarize upon illumination and respond with a rebound excitation when light is turned off[61]. Recording from L1 and L2 reveals no difference between their responses. However, when synaptic output from L1 is blocked genetically, tangential cells of the lobula plate fail to respond specifically to moving brightness increments (ON edges) while their responses to moving brightness decrements (OFF edges) are unaffected. Conversely, if synaptic output from L2 cells is blocked, tangential cells no longer respond to moving OFF edges while their responses to moving ON edges are intact[62]. This demonstrates that L1 and L2, via their termination in different strata of the medulla, provide the entry to two parallel motion processing pathways, one for ON and the other for OFF signals[62–64].

As an important step for further circuit analysis, dense reconstruction of serial electron microscopy sections of the *Drosophila* optic lobe identified many of the neuron types postsynaptic to the different lamina neurons (**Fig. 4c,d**). Medulla neurons Mi1 and Tm3 are postsynaptic to L1 and synapse onto the dendrites of T4 cells[65]; medulla neurons Tm1, Tm2 and Tm4 are postsynaptic to L2 and synapse onto the dendrites of T5 cells[66,67]. T5 cells receive additional input from Tm9 cells, which are postsynaptic to L3 cells. The functional relevance of some of these cells for motion detection has been demonstrated by selectively blocking them, resulting in a deficit at the level of the tangential cells or in behavior[68,69]. This specificity for ON versus OFF signals in neurons postsynaptic to L1 and L2 has been directly observed, either through the use of genetically encoded calcium indicators or via whole-cell patch clamping: while Mi1 and Tm3 neurons depolarize upon illumination, Tm1 and Tm2 cells hyperpolarize during illumination and respond with a strong depolarization at the end of the stimulus[68,70,71]. Furthermore, none of the neurons postsynaptic to lamina cells reveals any sign of direction selectivity.

The first neurons responding to visual motion in a directionally selective way are found at the next synaptic stage, T4 and T5 cells: as predicted from the above-mentioned blocking experiments[62], T4 are found to be selective for ON motion while T5 cells respond exclusively to OFF motion[72]. Within both T4 and T5 cells, four distinct response types exist that respond maximally to one of the four cardinal directions and terminate in one of the four strata of the lobula plate (**Fig. 3c**): T4 and T5 cells most sensitive to front-to-back motion have their axon terminals in the most anterior layer 1 of the lobula plate, those sensitive to back-to-front motion terminate in layer 2, those responding preferentially to upward motion terminate in layer 3, and those sensitive to downward motion terminate in the most posterior stratum, layer 4 (ref. 72). This mapping of directional preference to distinct layers of the lobula plate, previously described using deoxyglucose activity labeling[73], matches the preferred directions of different tangential cells: those of the

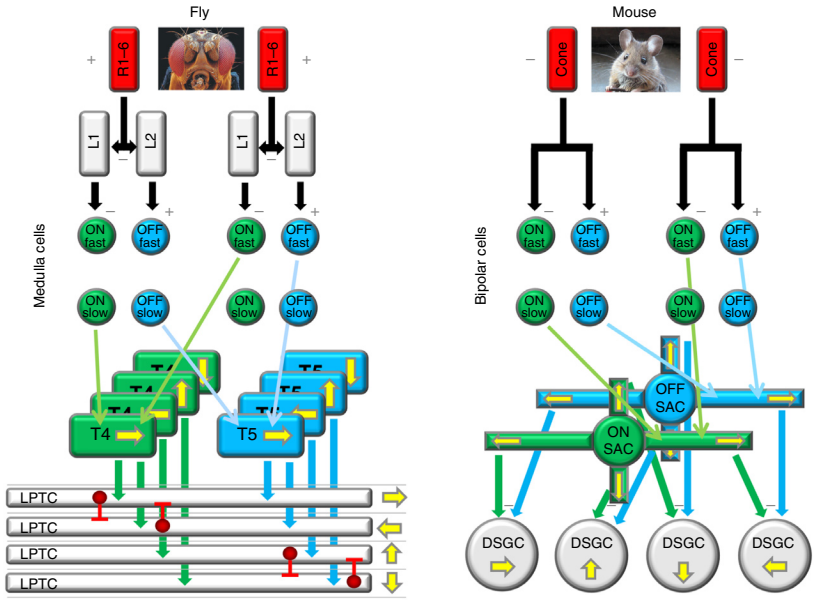

Figure 5 Fly and mouse motion detection circuits side by side. In the fly, photoreceptors R1–6 synapse onto, among others, lamina monopolar cells L1 and L2, with a sign-inverting synapse. L1 and L2 provide the entry to ON and OFF pathways within the medulla. In the mouse, cone photoreceptors themselves split the signal onto ON and OFF bipolar cells. The first cells displaying direction selectivity are the T4 and T5 cells in the fly optic lobe and the ON and OFF starburst amacrine cells (SAC) in the mouse retina. Motion information from the two pathways becomes fused at the next synapse: on the dendrites of the lobula plate tangential cells (LPTC) in the fly and ON-OFF direction-selective ganglion cells (DSGC) in the mouse retina. Whether, as shown, the input to T4 and T5 cells is provided by spatially displaced slow and fast medulla neurons and the input to starburst cells by spatially displaced slow and fast bipolar cells has not been demonstrated experimentally as yet[41,65].

horizontal system (HS cells) ramify in layer 1 and have front-to-back as their preferred direction, while tangential cells of the vertical system (VS cells) ramify in layer 4 and have downward as their preferred direction[74–76]. This strongly suggests that T4 and T5 cells provide excitatory input to the dendrites of the tangential cells. Indeed, when synaptic output of T4 cells is blocked, tangential cells fail to respond to moving ON edges; when synaptic output of T5 cells is blocked, tangential cells no longer respond to moving OFF edges[72]. When both T4 and T5 cells are blocked, tangential cells lose all their directional responses to visual motion[77] and flies become completely motion-blind[78].

All of the above demonstrates that the large tangential cells integrate the excitatory signals provided by T4 and T5 cells. However, tangential cells not only depolarize during motion along their preferred direction, they also hyperpolarize during motion stimuli along the opposite direction. Recent experiments have investigated the mechanism behind the null-direction suppression in more detail. Expressing the light-sensitive cation channel Channelrhodopsin 2 in T4 and T5 cells and illuminating the optic lobe with a brief light flash of 2 ms duration, Mauss *et al.*[79] observed a fast excitatory postsynaptic potential (EPSP) in tangential cells, followed by a delayed inhibitory postsynaptic potential (IPSP). Applying various pharmacological blockers revealed that the EPSP is cholinergic, while the IPSP is based on a chloride conductance, opened by either GABA or glutamate[79]. The delayed IPSP suggests that inhibition is mediated indirectly via local inhibitory interneurons, rather than via another set of local, motion-sensitive neurons in parallel to T4 and T5 cells. This conclusion is also in agreement with the observation that upon blocking both T4 and T5 cells, tangential cells no longer respond to motion along either their preferred or their null direction[77]. In summary, thus, the motion-opponent behavior of lobula plate tangential cells is based on direct excitation they receive from cholinergic T4 and T5 cells with the appropriate preferred direction and indirect inhibition they receive from T4 and T5 cells terminating in the adjacent layer with an opposite preferred direction, which contact local inhibitory interneurons[79]. The identity of these interneurons has not yet been revealed.

But how is direction selectivity computed in the fly visual system in the first place? Whole-cell patch recordings from both type of input neuron to T4 cells, Mi1 and Tm3 cells, have revealed a slightly different low-pass characteristic between Mi and Tm3, such that the time constant differs by about 18 ms (ref. 71). This, together with the finding of a small spatial offset between the receptive fields of Mi and Tm3 (ref. 65), led to the proposal that differences in the dynamics of the input signals are indeed sufficient to account for direction selectivity of T4 cells[71]. This would imply that, as in the mouse retina, motion detection is implemented by spatially offset synaptic input of different neuron types with different intrinsic dynamics.

Mouse and fly: commonalities and differences

The most striking commonality between the retina and fly optic lobe is the early splitting of the pathways into ON and OFF channels (**Fig. 5**). While this splitting happens right at the photoreceptor-bipolar synapse in the vertebrate retina, it is realized one synapse later in the fly optic lobe. The lamina seems to be an intermediate layer with no correspondence in vertebrates. Intriguingly, due to the ON characteristic of fly photoreceptor and the sign reversal at their output synapse, luminance is represented in the same way in both systems: that is, by a hyperpolarization of membrane potential of photoreceptors in the vertebrate retina as well as lamina monopolar cells in the fly optic lobe. Along with the ON-OFF splitting, the computation of motion direction is done separately in each pathway in both systems (see below). Once the direction of motion is detected, this information from both ON and OFF pathways is fused at the very next synapse: in the fly optic lobe, T4 and T5 cells jointly synapse onto lobula plate tangential cells, establishing a motion signal independent of its origin from either moving brightness increments or decrements. The same is observed in the vertebrate retina, where starburst amacrine cells from both ON and OFF layers contact ON-OFF retinal ganglion cells. The next parallel between vertebrate retina and insect optic lobe representation of motion information along four orthogonal directions. This is all the more amazing given that the primary receptor lattice has a hexagonal geometry in the insect eye, with a 60-degree angle between neighboring axes. While this arrangement is retained through all neuropil layers, T4 and T5 cells nevertheless come in four flavors with a 90-degree angle between their preferred axes, owing to a combination of the oblique h- and y-rows of the hexagonal lattice to establish horizontal motion directionality[80]. Finally, the optimal temporal frequency of both systems seems to be similar (around 1–2 Hz).

Beside all these similarities, there are also some remarkable differences between the two systems. The first difference relates to the

directional sampling: in the vertebrate retina, the range of directions along which primary motion information is extracted covers the continuum of all possible directions as represented by the radial dendrites of starburst amacrine cells in both ON and OFF layers. This information is compressed onto four axes only in the next stage, from starburst amacrine onto ganglion cells, together with the fusion of ON and OFF pathways[81]. In the insect optic lobe, motion information is extracted at the very first stage along these four cardinal directions. Accordingly, the directional tuning curves of fly motion vision appear narrower than those of mouse (compare Fig. 3 in ref. 72 with Fig. 5 in ref. 37). This difference may be a result of direction selectivity being synaptically imposed on the postsynaptic neuron by an excitatory drive from presynaptic neurons aligned with the four cardinal directions (fly) versus the suppression of a range of non-preferred directions sampled at much smaller radial intervals (mouse). But why is the direction-selectivity circuit in the mouse implemented at the level of an inhibitory neuron and not directly at the input synapse to the direction-selective ganglion cells? In contrast to fly, the mammalian retina contains many different types of direction selective output neurons with different preferred directions, such as ON-OFF JAM-B[23,24], ON JAM-B[23,25] and OFF JAM-B ganglion cells[26]. By equipping the mouse retina with a ubiquitous and versatile direction-selective inhibitory neuron, postsynaptic ganglion cells of various response types can be made selective for an almost arbitrary range of motion directions by simply connecting to the appropriate range of starburst amacrine cell dendrites, without the need to re-implement the direction-selectivity circuit in each of these ganglion cell types. Examples of more ganglion cell types with prominent starburst amacrine contact are reported in refs. 22,82.

The next difference relates to the place where motion information provided by ON and OFF pathways is fused: in the vertebrate retina, these are again local cells, namely the direction-selective ganglion cells covering a few degrees of the visual field each. In the insect optic lobe, this fusion happens on the large dendrites of wide-field, motion-sensing tangential cells with a receptive field diameter of up to 180 degrees. No local, motion-sensing cells have been reported so far in the fly that are sensitive to both ON and OFF motion. Furthermore, lobula plate tangential cells exhibit motion opponency while this response feature is not found in retinal ganglion cells. This hints at motion opponency being a particular feature of wide-field motion-sensitive neurons, but not local ones; compare, for example, cortical neurons in area V1 and MT[83]. Finally, in the fly, the ON-OFF tangential cells seem to be the only direction-selective neurons found downstream, leading to the impression that, as soon as primary motion information is extracted, the separation of ON and OFF is no longer needed. In contrast, the mouse retina, in addition to ON-OFF ganglion cells, also houses direction-selective ganglion cells that are fed preferentially by either the ON or the OFF pathway[26,84–86]. Some of these differences may relate to use of ON-OFF direction-selective signals for the perception of global motion in flies but, more likely, for object detection in mice. Conversely, large-field direction-selective neurons in mouse may serve the equivalent purpose of global motion detection, but seem to be separately selective for ON or OFF motion.

Direct comparison of the first stage where direction selectivity emerges

In both mouse and fly visual system, ON and OFF signals are separated. What might the advantage of such splitting be? Motion results in a temporal correlation of similar events at two spatial locations: if a bright object passes two neighboring points in space, luminance first increases sequentially when the object's leading edge passes, and then decreases again when the object's trailing edge passes. A motion-sensitive postsynaptic neuron receiving input from these two locations should signal motion in each case, for the leading and the trailing edge. However, in the first case, it should become excited if both inputs increase their membrane potential, and in the second, it should be excited if both inputs decrease their membrane potential. There is no biophysical mechanism known so far that allows such an implementation of the sign rule of multiplication. If, however, the inputs are split into an ON and OFF channel, brightness increments and decrements are handled separately with a positive sign within each pathway, and then motion-sensitive neurons only face the task of correlating two positive input signals by whatever cellular mechanism. This seems to greatly alleviate the problem of implementing such a correlation biophysically.

In this regard, two principally different mechanisms have been discussed[87]. The first possibility is a signal enhancement during the preferred direction. This could be realized, for example, by a so-called log-exponential transform—that is, taking the logarithm of both inputs, adding these and then calculating the exponential[88,89]: $xy = e^{(\log x + \log y)}$—with the supralinear response in the postsynaptic neuron mediated by either voltage-gated ion channels[90], NMDA receptors[87] or release from inhibition[67]. The second possibility is a specific signal suppression during null-direction motion, produced, for example, by shunting inhibition[67,91]. If both the spatial offset of the two inputs and their dynamics (that is, which signal is delayed and which is non-delayed) are known, the above alternatives can be told apart: in the case of preferred direction enhancement, the direction from delayed to non-delayed inputs should be the preferred direction of the postsynaptic neuron (**Fig. 1d**), whereas in the case of null direction suppression it should be the null direction (**Fig. 1h**). In case of the starburst amacrine cells, the preferred direction of its dendrites is centrifugal. Here the proposed placement of slow inputs on its proximal and fast inputs on its distal dendrites supports preferred direction enhancement as the mechanism underlying direction selectivity. In case of T4 cells in the fly optic lobe, the preferred direction goes along with motion from Tm3 to Mi1. Together with the slight delay of Mi1 signals with respect to Tm3, this would support a null direction inhibition. However, these conclusions are still far from being firmly established (see below).

Beside the nonlinear signal combination, the other key algorithmic step in motion detection is asymmetric temporal filtering, creating a signal delay between the two inputs. Here the first question is where the delay is generated. Three different scenarios seem plausible. First, the input signals could exhibit different release dynamics. Second, different dendritic receptors on the motion-computing neuron could give rise to intracellular signals with different dynamics. Third, input signal and postsynaptic receptor could result in signals of identical dynamics, with the delay generated intracellularly in the postsynaptic neuron by the specific geometry of the dendrite or inhomogeneous distribution of transmembrane conductances[90]. The lines of evidence described above suggest that the signal delay is implemented via spatially separated innervation by two different cell types with different dynamics: cone bipolar cells type 2 versus 3a in the case of OFF direction selectivity in the mouse[40,41] and Tm3 versus Mi1 in the case of T4 ON direction selectivity in the fly[65,71].

In the mouse, support for the first model is provided by combined evidence based on calcium recording from axon terminals of retinal bipolar cells[40] and EM-based connectivity analysis[41] (**Fig. 3**). Still, several remaining caveats should be mentioned. The relationship between morphological bipolar cell types and different response kinetics of bipolar cell terminals is based only on the depth within the inner plexiform layer where the various kinetics types were measured[40]. This makes a direct dynamic classification of bipolar cells difficult, especially on the ON side, where, for example, three

subtypes of type 5 bipolar cells largely co-stratify[22]. Furthermore, recent evidence indicates that strong visual stimulation can alter the direction selectivity of ganglion cells[92,93]. This phenomenon may be attributed to changes in the synaptic dynamics presynaptic to the starburst amacrine cells due to either an experience-dependent mechanism or an exhaustive synaptic depletion. In addition, the evidence for spatially segregated innervation of starburst dendrite by bipolar cells with different dynamics is so far based on neurite contacts[41], not yet on identified synapses. The ideal experiment would aim to directly observe the temporal kinetics of identified bipolar cell type terminals when presenting a directional stimulus, followed by structural proof of the implied circuit. Another interesting question concerns the ON channel, where the laminar distribution of response kinetics in bipolar cell types seems to be less distinct[40]: is there a differential bipolar-to-starburst circuit implemented as well? If so, which are the contributing bipolar cell types? These questions will need to be addressed by future studies. In this context, it should also be kept in mind that the specific geometry of starburst amacrine cell dendrites together with a transmembrane conductance gradient can support direction selectivity by itself, without any delay in the input signals[90], providing support for the third model of temporal filter implementation. It remains to be determined whether multiple mechanisms based on synaptic delays, postsynaptic effects and asymmetric dendritic geometries are implemented in parallel, and to what relative degrees they contribute to the functional direction-selective signals in the retina.

In the fly ON channel of motion computation, a half-detector of the Hassenstein-Reichardt type (**Fig. 1c**) was proposed to be implemented via Mi1 and Tm3 cells synapsing onto T4 cells[65,71]. However, the spatial offset between the anatomical receptive field centers of Mi1 and Tm3 amounts to only about 20% of the inter-ommatidial distance[65], thus significantly reducing the signal difference between the two potential inputs to the T4 cell. Furthermore, the average offset per T4 neuron was found to have a high degree of variability and is only properly aligned for three of the four cardinal directions. The same holds true for the difference in temporal dynamics in Mi1 and Tm3 cells[71]: again, this difference is small (about 18 ms), exhibits a wide range of fluctuations and reproduces a temporal tuning curve consistent with experimental data from T4 cells[72] only after subtraction of mirror-symmetrical subunits, a process generally thought to be implemented only on the postsynaptic tangential cells[52,79]. The situation is even less clear in case of T5 cells, which receive input from four types of interneuron, without any immediate correspondence to a simple motion-detection scheme[67]. In support of an alternative implementation of the delay via different receptor kinetics, mRNA sequencing reveals expression of slow, muscarinic and fast, nicotinic acetylcholine receptors in both T4 and T5 cells[67]. Furthermore, detailed anatomical analysis reveals distinct morphological features that could potentially support production of delays via tapered dendrites in T4 cells[65]. More experiments are needed to clarify the role of each of the input neurons for motion detection in T4 as well as T5 cells.

Conclusion

In the first account describing the cellular composition of the fly optic lobe, exactly 100 years ago, Cajal and Sanchez could not resist the temptation to draw analogies to the vertebrate retina[94]. Since then, others have extended such a comparison to developmental steps of the visual system, including molecular mechanisms[95]. Here we have compared the two systems with respect to a specific function, motion vision. In doing so, we have found several amazing parallels, not just at an abstract algorithmic level but at the very neural architecture and cellular design of the underlying circuits. These parallels, whether due to a common urbilaterian ancestor or to convergent evolution, point toward a robust solution of how to compute the direction of motion with neurons. Whether such parallels even extend to the biophysical mechanisms underlying the generation of signal delays and nonlinear interactions in the dendrite of motion-sensitive neurons remains to be seen. Despite much recent progress, these fundamental processes of motion vision are not yet understood, either in the mouse or in the fly. Given the seemingly trivial computation (to tell leftward from rightward), this should teach us a lesson in modesty when trying to explain higher brain functions. But conversely, once such basic operations as creation of signal delays and nonlinear signal interactions have been elucidated in the context of motion vision, it can be directly tested whether, for example, cortical circuits use the same or different means to perform similar computations. Even if it turns out that such a 'basic algebra of neural computation' does not exist, it will be extremely rewarding to see, at least in one specific case, how an interesting computation is performed by the nervous system at a detailed cellular and biophysical level. In our view, the tools are all there and the goal seems within reach.

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