PARALLEL PROCESSING IN THE MAMMALIAN RETINA

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Abstract | Our eyes send different 'images' of the outside world to the brain — an image of contours (line drawing), a colour image (watercolour painting) or an image of moving objects (movie). This is commonly referred to as parallel processing, and starts as early as the first synapse of the retina, the cone pedicle. Here, the molecular composition of the transmitter receptors of the postsynaptic neurons defines which images are transferred to the inner retina. Within the second synaptic layer — the inner plexiform layer — circuits that involve complex inhibitory and excitatory interactions represent filters that select 'what the eye tells the brain'.

It is well known that visual signals in the brain are processed in parallel, with movement, colour, stereopsis and even specific features such as faces being processed in different parts of the cortex[1]. The projection from the eye to the brain is also organized into parallel routes, and the fibres of the optic tract terminate in different subcortical areas such as the suprachiasmatic nucleus, lateral geniculate complex, pretectum, superior colliculus and accessory optic nuclei. These areas have different roles in visual processing and receive inputs from different types of retinal ganglion cell (RGC). For example, the suprachiasmatic nucleus, which regulates circadian rhythms, and the pretectum, which adjusts the pupil size, receive inputs from a recently discovered type of RGC that transmits a sustained light signal and has a melanopsin-based intrinsic light response in its dendrites[2]. Parallel routes can also be distinguished in the visual pathway that subserves conscious vision — the projection from the eye through the lateral geniculate nucleus (LGN) to the visual cortex. Here, in primates, the parvocellular and magnocellular pathways are well established, and a third parallel tract has recently been found in the interlaminar regions (K-layers) of the geniculate[3]. This might carry a blue-cone signal[4].

Considerable processing and filtering of visual information occurs at the earliest stage in the mammalian visual system — the retina[5–8]. In this article, we review the circuitries that underly this processing, and discuss their synaptic mechanisms and molecular signatures[9,10].

The retina is about 200 μm thick and contains six main classes of cell (FIG. 1). The photoreceptors — rods and cones — transduce light into an electrical signal. At low light levels only rods have sufficient sensitivity to capture the few photons that are available. Colour vision is not possible at such low light levels, because signals from a single detector, the rod, cannot differentiate between spectral modulations. At higher light levels, in humans and old world primates, three types of cone respond selectively to photons in different regions of the visible spectrum — long-wavelength (red or L-), middle-wavelength (green or M-) and short wavelength (blue or S-) sensitive cones[11]. Comparison of L- and M-cone signals forms a chromatic channel that mediates red–green (R–G) discrimination. A second, blue–yellow (B–Y) channel is made by comparing S-cone signals against some combination of L- and M-cone signals. A third, luminosity channel (black/white) sums L- and M- and possibly also S-cone signals. Mammals other than primates have only two types of cone (L- and S-cones)[12].

At the synaptic terminals of rods and cones, the light-evoked signals are transferred onto bipolar and horizontal cells (FIG. 1). Horizontal cells, of which there are between one and three types in mammalian retinae, provide lateral interactions in the outer plexiform layer. One type of rod bipolar cell and at least nine types of cone bipolar cell transfer the light signals into the inner plexiform layer (IPL), onto the dendrites of amacrine and ganglion cells (FIG. 1d,e). Cone bipolar cells fall into two main groups: ON and OFF bipolar cells. Amacrine

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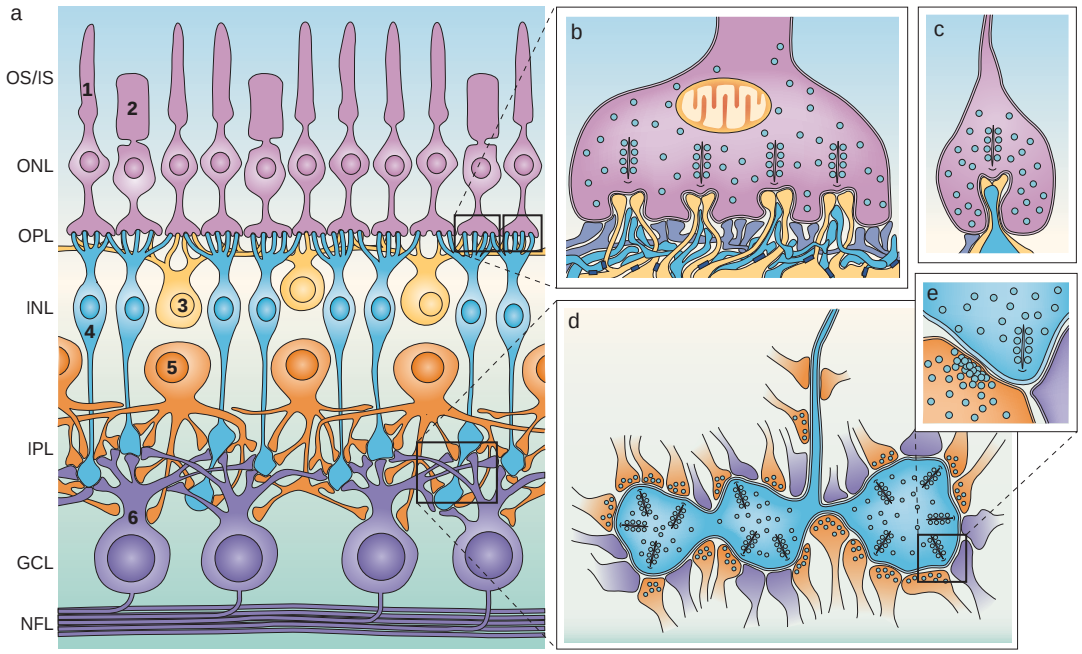

Figure 1 | **Schematic of the mammalian retina. a** | There are six classes of neuron in the mammalian retina: rods (1), cones (2), horizontal cells (3), bipolar cells (4), amacrine cells (5) and retinal ganglion cells (RGCs) (6). They have a laminar distribution (OS/IS, outer and inner segments of rods and cones; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer; NFL, optic nerve fibre layer). **b** | A cone pedicle, the synaptic terminal of cones. Four presynaptic ribbons are apposed to the invaginating dendrites of horizontal cells (yellow) and ON cone bipolar cells (blue). This synaptic arrangement is called a 'triad'. OFF cone bipolar cell dendrites form contacts at the cone pedicle base (purple). **c** | A rod spherule, the synaptic terminal of rods. The presynaptic ribbon is apposed to the invaginating axons of horizontal cells (yellow) and the dendrites of rod bipolar cells (blue). OFF cone bipolar cell dendrites form contacts at the base (purple). **d** | The axon terminal of a cone bipolar cell (blue) contains up to 50 presynaptic ribbons, and connects to postsynaptic amacrine cell processes (orange) and RGC dendrites (purple). **e** | A magnified view of a bipolar cell ribbon synapse (blue) with an amacrine cell process (orange) and an RGC dendrite (purple). The amacrine cell provides a feedback synapse onto the bipolar cell. This synaptic arrangement is called a 'dyad'. Amacrine cells also form numerous conventional synapses throughout the IPL with RGCs and other amacrine cells (not shown). Some amacrine cell processes reach out to the OPL and there they provide synaptic contacts (interplexiform processes). Panels **a**, **b** modified, with permission, from REF. 127 © (2002) Deutsche Akademie der Naturforscher Leopoldina.

cells are inhibitory interneurons, and there are as many as 50 morphological types[13]. Ganglion cell dendrites collect the signals of bipolar and amacrine cells and their axons transmit these signals to the visual centres of the brain. At least 10–15 morphological types of ganglion cell are found in any mammalian retina[14].

Transmission of the cone signal

Cones respond to a light stimulus with a graded hyperpolarization, and release glutamate at their specialized synaptic terminal, the cone pedicle (FIG. 1b). Transmitter release is high in darkness and is reduced by light. The cone pedicle is probably the most complex synapse in the CNS[15]. It contains between 20 and 50 presynaptic ribbons, each of which is flanked by synaptic vesicles. Invaginations at the ribbons allow horizontal and ON cone bipolar cell dendrites to be inserted. OFF cone bipolar cell contacts are found at the cone pedicle base. Each cone pedicle makes up to 500 contacts, although the number of postsynaptic cells is smaller because each one receives multiple contacts. Two types of horizontal cell and eight types of cone bipolar cell are engaged with every cone pedicle. So, at the first synapse of the retina the light signal is distributed into multiple pathways.

L- and M-cone pedicles are coupled to their immediate neighbours and to rod spherules (the synaptic terminals of rod photoreceptors) through electrical synapses (gap junctions) where connexin-36 is expressed. S-cone pedicles are only sparsely coupled[16–19]. This coupling allows the network to average out the uncorrelated noise in individual cones, and thereby to improve the response to a light stimulus[20].

The postsynaptic neurons express different sets of glutamate receptors (GluRs) at their contacts with the cone pedicles[21,22]. The main dichotomy is that horizontal and OFF cone bipolar cells express IONOTROPIC (AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and kainate) glutamate receptors, whereas ON cone bipolar cells express the METABOTROPIC glutamate receptor mGluR6 (REFS 23,24). Horizontal and OFF cone bipolar cells are hyperpolarized by light, and ON cone bipolar cells are depolarized. OFF cone bipolar cells transfer their signals in the IPL through excitatory synapses onto OFF ganglion cells, whereas ON cone bipolar cells form synapses onto ON ganglion cells. Therefore OFF ganglion cells are excited by stimuli that are darker than the background, and ON ganglion cells by stimuli that are brighter than the background.

IONOTROPIC RECEPTOR
A receptor that exerts its effects through modulation of ion channel activity.

METABOTROPIC RECEPTOR
A receptor that is associated with G proteins and exerts its effects through enzyme activation.

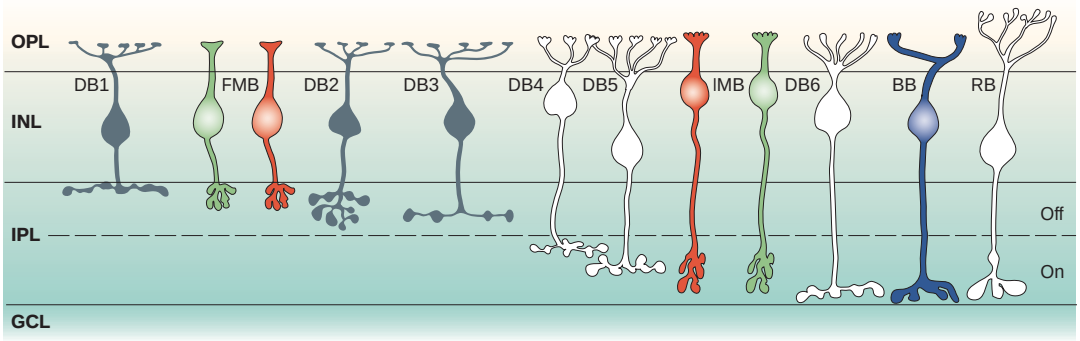

Figure 2 | **Bipolar cell types of the primate retina.** The cells were analysed in Golgi-stained whole-mounts and are shown here schematically in a vertical view. Their axons terminate at different levels in the IPL; those terminating in the outer half are putative OFF cone bipolar cells, those terminating in the inner half are ON bipolar cells. Diffuse bipolar cells (DB1–DB6) contact — non-selectively — between 5 and 10 L- and M-cone pedicles. Some DB cells also contact S-cone pedicles. Flat midget bipolar (FMB) cells contact a single L- or M-cone and carry a chromatic OFF signal. Recently, an FMB cell connected to S-cone pedicles has been described, but it is not known whether it contributes to the chromatic pathways. Invaginating midget bipolar (IMB) cells contact a single L- or M-cone and carry a chromatic ON signal. Blue cone bipolar (BB) cells selectively contact 1–5 S-cone pedicles and carry an S-cone ON signal. Rod bipolar (RB) cells contact between 6 rod spherules (at the fovea) and 40 (in the periphery) and carry a scotopic ON signal.

More than 100 years ago the physiologist Ewald Hering postulated the separate sensations of black and white[25]. It is only now that we know that these are caused by two molecularly different GluRs expressed by bipolar cells.

Bipolar cells. The axons of OFF and ON cone bipolar cells terminate at different levels (strata) within the IPL: OFF in the outer half, ON in the inner half. However, superimposed on this ON/OFF dichotomy, further bipolar cell types have been described (FIG. 2) and every mammalian retina that has been studied contains at least four types of OFF and four types of ON cone bipolar cell[26,27]. We are just beginning to understand their functional roles[28]. Double recordings from cone pedicles and identified OFF cone bipolar cells in slices of the ground squirrel retina have shown that one type of OFF cone bipolar cell (b2) expresses ionotropic AMPA receptors, resulting in more phasic synaptic transfer and, therefore, in transient responses to light. Meanwhile, two other types of OFF cone bipolar cell (b3 and b7) express kainate receptors, resulting in more tonic synaptic transfer and a sustained light response[29]. The axons of these bipolar cells terminate at different levels in the OFF stratum. Axons that carry more transient OFF light signals terminate in the middle of the IPL; those that carry sustained OFF light signals are found in a more peripheral position[30,31]. Although it has not been shown for the mammalian retina, there seems to be a comparable stratification of bipolar axons in the ON sublamina. Transient ON responses are transferred to the middle of the IPL; sustained ON-responses are found in the inner IPL. The preponderance of transient light responses in the middle of the IPL is further supported by the recent finding of voltage-dependent sodium channels at the axon terminals of these bipolar cells[32]. Such channels would speed up the light responses of the bipolar cells.

Most cone bipolar cells contact between five and ten cones (FIG. 2, diffuse bipolar cells). In the primate retina, in addition to these diffuse types, bipolar cells have been described that contact a single cone pedicle (FIG. 2, midget bipolar cells) and that selectively contact S-cone pedicles (FIG. 2, blue cone bipolar cells)[33,34]. Blue cone bipolar cells have also been described in the rat and mouse retina but their circuitry has only been worked out in primates. Here they contact between one and five S-cones at invaginating contacts, so they are ON bipolar cells and transfer an S-cone signal to the innermost part of the IPL.

Midget bipolar cells. Before discussing the function of midget bipolar cells, the distribution of cells across the retina (topography) has to be considered[35]. In the peripheral retina, the density of cones, bipolar cells and ganglion cells is low, whereas towards the centre of the retina (the central area of cats, or the fovea of primates) the density of these cells increases steeply. This results in greatly improved spatial resolution (visual acuity) at the fovea or central area. Concomitant with the increase in density, the cells' dendritic fields become smaller. During evolution, the spatial resolution of the primate eye and retina has been optimized. To achieve this, a high cone density and a low cone-to-RGC ratio have converged in the 'acuity pathway'. The anatomic limits for this optimization are reached when each cone is connected through a midget bipolar cell to a midget ganglion cell, establishing a private line to the brain. It has been suggested that only after this one-to-one connection in the central retina had evolved, 35 million years ago, did a subsequent mutation in the L-cone pigment create L- and M-cones of varying proportions at random spatial locations[6,11,36]. The midget system of the central retina could transmit this chromatic information to the brain where it could be used, for example, to detect red fruit among green leaves.

This 'midget theory' of the evolution of trichromacy in primates has its basis in the general pattern of mammalian wiring. It is not necessary to postulate, in addition, specific mutations to change the cone selectivity of bipolar cells, the cone selectivity of GluRs or the selectivity of

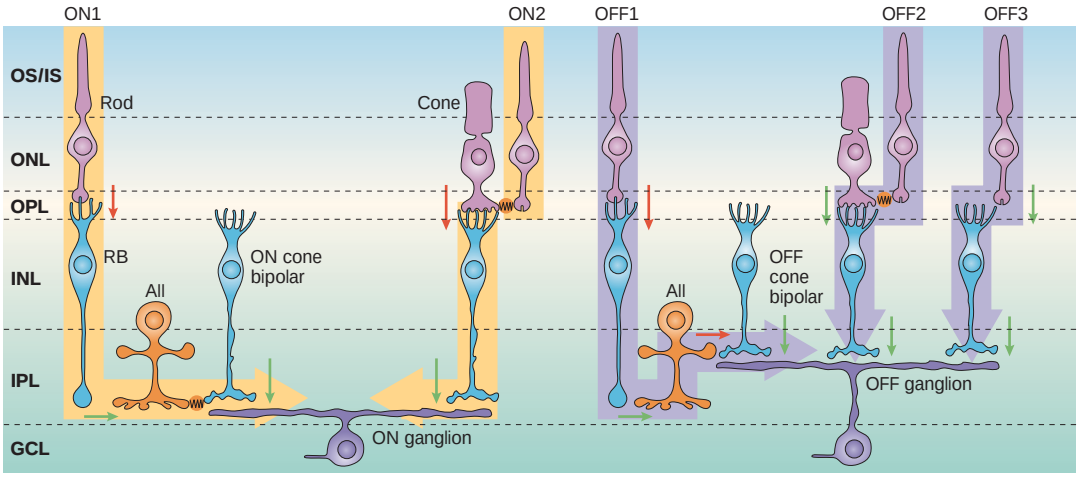

Figure 3 | **The rod pathways of the mammalian retina.** The neurons in the mammalian retina have a laminar distribution: OS/IS, outer and inner segments of rods and cones; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer. The 'classical' pathways are ON1 and OFF1. In the ON1 pathway, rods are hyperpolarized by light and transfer their signals onto the invaginating dendrites of rod bipolar (RB) cells. RB cells express the glutamate receptor mGluR6, causing a sign inversion at the synapse (red arrow). RB cells are therefore depolarized by light[47]. They transfer their signal through a glutamatergic (AMPA; α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) synapse (green arrow) onto All amacrine cells. All amacrine cells make gap junctions (electrical synapses expressing connexin-36) with the axons of ON cone bipolar cells, which in turn synapse (green arrow) with ON ganglion cells. In the OFF1 pathway, the pathway from rods to All cells is identical to ON1, but the output of All cells differs. They make inverting, glycinergic synapses (red arrow) with the axons of OFF cone bipolar cells, which in turn synapse (green arrow) with OFF ganglion cells. In the ON2 pathway, the rod signal is transmitted to the cone pedicle through gap junctions (expressing connexin-36) and then follows the cone pathway to the ON ganglion cells. The OFF2 pathway is comparable with that of ON2 to the OFF ganglion cells. In the OFF3 pathway, OFF cone bipolar cells make direct synaptic contacts with the base of rod spherules and transfer this signal directly onto OFF ganglion cells. These pathways can be pharmacologically dissected and the recent availability of a connexin-36-knockout mouse has shown that different pathways operate under different lighting conditions[52]. Modified, with permission, from REF. 123 © (2002) Elsevier Science.

ganglion cells. It also explains why mammals other than primates have not evolved trichromacy: their cone bipolar cells sum the signals of several cones and their RGCs sum the signals of many bipolar cells. A mutation that created M- and L-cones would be lost in this convergent network, which pools signals from many cones[37]. A transgenic mouse that expressed human L- and M-opsins in its cones could not perform trichromatic colour discrimination[38,39]. The idea that trichromacy 'piggy-backs' on the high-acuity system of primates also postulates that the midget bipolar cells perform a 'double duty' in visual signalling — acuity and trichromacy — an idea that has been promoted for some years[40].

However, other models for the L- and M-cone selective pathway of the primate retina have also been proposed[41,42]. In these models, chromatic bipolar cells contact several L- and M-cones: it is postulated that they express ionotropic GluRs (OFF-type) at their contacts with L-cones and metabotropic GluRs (ON-type) at their M-cone contacts. Such cells would be red OFF/green ON bipolar cells and similar types have been described in fish and turtle retinae[43]. So far no evidence has been presented in mammalian retinae, including primates, for such a cone-specific expression of GluRs at bipolar cell dendrites. So, it seems that diffuse bipolar cells transmit a luminosity signal to the IPL, midget bipolar cells an L- and M-cone signal and blue cone bipolar cells a S-cone selective signal.

Transmission of the rod signal

The synaptic terminal of rod photoreceptors, the rod spherule, contains a presynaptic ribbon, which is flanked by synaptic vesicles and is apposed to the invaginating processes of horizontal and bipolar cells (FIG. 1c). The horizontal cell processes, of which there are usually two, occupy a lateral position within the invagination, and between one and three rod bipolar cell dendrites occupy a central position. Like cones, rods release glutamate in darkness and this transmitter release is reduced when they are hyperpolarized by light. Horizontal cells express ionotropic GluRs at their dendritic tips, in the rod spherule, and rod bipolar cells express the metabotropic receptor mGluR6. Rod bipolar cells — of which there is only one type in any mammalian retina — are depolarized by a light stimulus and are ON-bipolar cells[44,45]. Each contacts 20–80 rod spherules, and their axons terminate in the inner IPL, close to the ganglion cell layer. However, rod bipolar cells do not send light signals directly into the ganglion cells but instead synapse with an AII amacrine cell[46,47] (FIG. 3). AII cells, which are also depolarized in response to a light stimulus, sum the input from many rod bipolar cells. They form electrical synapses (gap junctions) onto the axon terminals of ON cone bipolar cells (FIG. 3, ON1) and inhibitory chemical synapses onto those of OFF cone bipolar cells (FIG. 3, OFF1). In turn, these cone bipolar cells synapse onto the ganglion cells. This wiring diagram represents the 'classical rod pathway' through

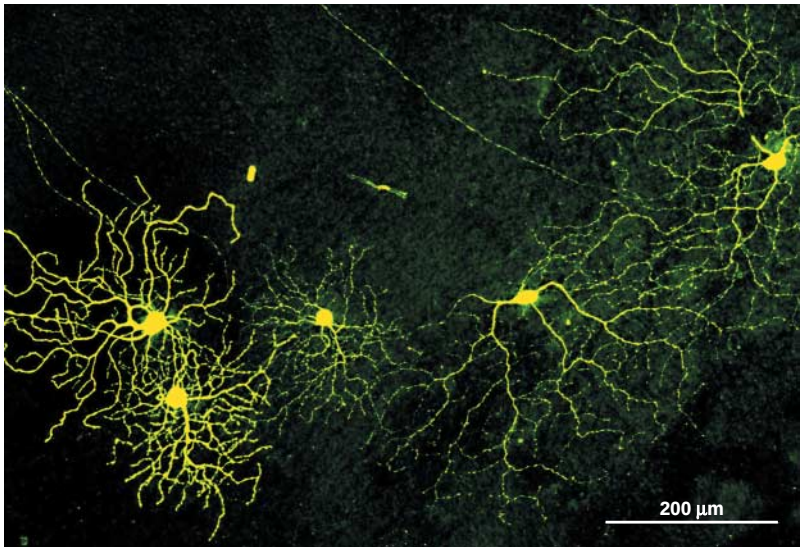

Figure 4 | **Ganglion cells of the mouse retina.** Fluorescence micrograph of five ganglion cells in a whole-mount of a transgenic mouse (courtesy of L. Heinze, Max-Planck-Insititut, Frankfurt). The cells express green fluorescent protein (GFP) under the control of the Thy-1 promoter[124]. Only a small portion of ganglion cells express GFP in this mouse line, but the cells are very nicely labelled. The morphological difference between the two wide-field cells to the right and the three small-field cells to the left is obvious. However, it is difficult to subdivide the three small-field cells without further information, such as the stratification of their dendrites within the inner plexiform layer. Altogether, 14 morphological types of ganglion cell have been defined in the mouse retina[125].

the mammalian retina[48]. It is the most sensitive pathway and can detect the absorption of a single photon. The detour through the AII–cone bipolar cell loop probably allows the rod pathway to take advantage of the cone bipolar circuitry in the IPL, such as direction-selective wiring or other complex operations.

Recent studies have shown that the rod signal can also be transmitted by alternative routes. One such route is through gap junctions between rod spherules and cone pedicles[48] (FIG. 3, ON2, OFF2). In addition, some OFF-cone bipolar cells contact rod spherules directly[49–51] (FIG. 3, OFF3). So, there are at least three circuits for the rod signal, and recent evidence indicates that the different ganglion cells of the mouse retina tap preferentially into one of these circuits[52].

Feedback from horizontal cells

Horizontal cell dendrites are inserted as lateral elements into the invaginating contacts of cone pedicles (FIG. 1b), and horizontal cell axon terminals form the lateral elements within rod spherules (FIG. 1c). Traditionally, it is assumed that horizontal cells release the inhibitory transmitter GABA (γ-aminobutyric acid) and provide feedback inhibition at the photoreceptor synaptic terminal. As horizontal cells summate light signals from several cones, such feedback would cause lateral inhibition, through which a cone's light response is reduced by the illumination of neighbouring cones. This mechanism is thought to enhance the response to the edges of visual stimuli and to reduce the response to areas of uniform brightness. However, the GABA-feedback model has recently been challenged because of the lack of classical synapses from horizontal cells onto cones, the lack of GABA receptors on mammalian cones and the lack of GABA uptake into horizontal cells from the medium. Two alternative hypotheses of horizontal cell function have been proposed. One assumes that horizontal cells express connexins at their processes, which are inserted into cone pedicles and rod spherules (hemigap junctions). Current that flows through the channels formed by the connexins changes the extracellular potential in the invaginations and thus shifts the activation curves of the cone pedicle Ca^{2+} channels. By this mechanism of electrical feedback, horizontal cells could modulate the glutamate release from cones and rods[53]. The second hypothesis also postulates modulation of the Ca^{2+} channels that regulate the release of glutamate from cones; however, the mechanism responsible is a change in pH within the invagination, caused by voltage-dependent ion transport through the horizontal cell membrane[54]. There is also evidence that light-dependent release of GABA from horizontal cells provides feed-forward inhibition of bipolar cell dendrites. Irrespective of their precise mode of action, horizontal cells sum light responses across a broad region, and subtract it from the local signal. Because horizontal cells are coupled through gap junctions, their receptive fields can be much wider than their dendritic fields[55]. Horizontal cell feedback in fish and turtle retinae seems to be cone-specific. However, no such chromatic organization of horizontal cell feedback has been observed in the primate retina[56].

Morphological types of ganglion cell

There are at least 10–15 different morphological types of ganglion cell in any mammalian retina[14,57]. Their main distinguishing features are the size and branching pattern of their dendritic trees, which can be seen in retinal flat mounts (FIG. 4). However, it is often difficult to classify ganglion cells by their shapes alone because this can vary across the retina. In the primate retina it has been helpful to label ganglion cells retrogradely through their axonal projections[58]. The best way to define and study different ganglion cell types is by applying selective markers that label the whole population of a given type[35]. This is illustrated for cat alpha cells in FIG. 5. Alpha cells have large cell bodies and wide, sparsely branched dendritic trees. They comprise about 3% of cat ganglion cells and can be more or less selectively immunolabelled with antibodies against neurofilaments. The cell bodies of alpha cells form a regular mosaic and their dendritic trees cover the retinal area in FIG. 5a without leaving gaps. The dendritic tree size and density of alpha cells show an inverse relation across the retina: in the peripheral retina the density is low, but the dendritic trees are large, whereas in the central retina the density is high and the dendritic trees are small. Alpha cells have been found in all mammalian retinae studied (cat, ferret, rabbit, guinea pig, mouse, rat and ox)[59]. They have the thickest axons of all RGCs and project to several subcortical visual centres. In the primate retina, parasol RGCs (or M-cells) are probably the homologues of alpha cells[58].

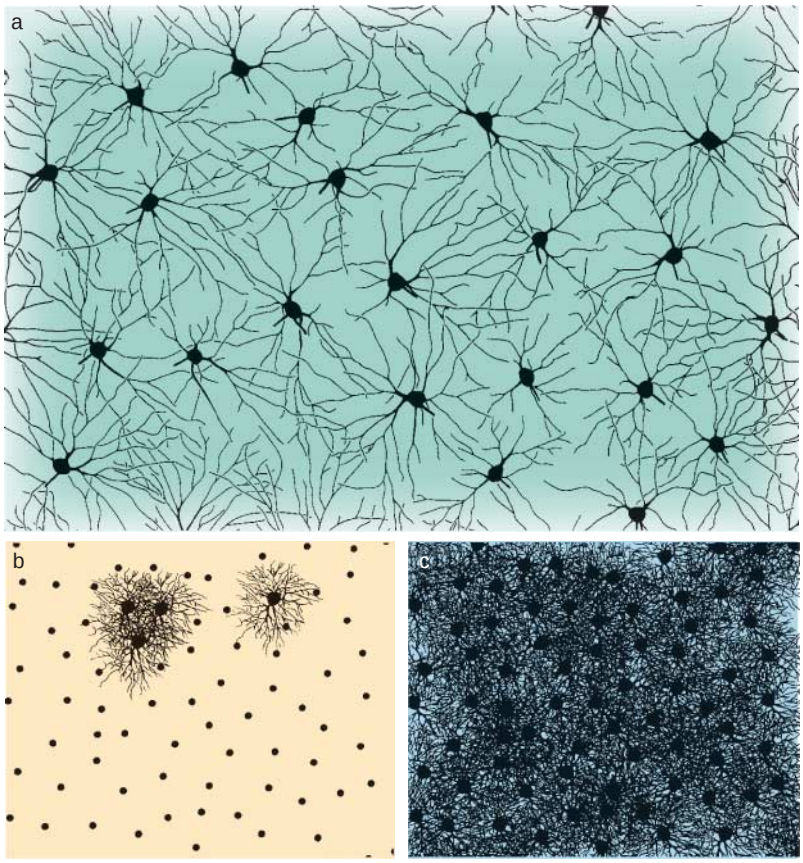

Figure 5 | **Tiling of the cat retina with ganglion cell dendritic fields. a** | This view of a flat-mounted retina (1.8 x 1.2 mm) shows the dendritic trees of ON alpha ganglion cells. Their cell bodies are regularly arrayed and their dendrites cover the area homogeneously without leaving gaps. **b** | The dots represent the positions of ON-beta ganglion cell perikarya. They were labelled by retrograde transport of a tracer injected at their axon terminals in the lateral geniculate nucleus. By computer graphics, a representative dendritic field was inserted for four beta cells. This shows the architecture of the network: the dendritic field is surrounded by the cell bodies of the next neighbours (see the single dendritic field) and three dendritic fields overlap at each point (see the triple dendritic field). **c** | When dendritic fields are inserted for all beta cell perikarya, a dense layer of dendrites overlaps the retina (courtesy of T. Euler, Max-Planck-Institut, Heidelberg). Modified, with permission, from REF. 126 © (2002) Deutsche Akademie der Naturforscher Leopoldina.

Another ganglion cell type of the cat retina, the beta cell, is illustrated in FIG. 5b,c. It is not possible to immunostain beta cells selectively, but they can be retrogradely labelled by the injection of tracers into the LGN, producing the cell body mosaic seen in FIG. 5b (REF. 60). The dense network of beta cell graphics shown in FIG. 5c was produced by repeating the dendritic tree of a single Golgi-stained beta cell. This is realistic because the sizes of the dendritic fields of Beta cells at a given eccentricity are similar. Beta cells are the most frequently occurring cat ganglion cell type, comprising about 50% of all RGCs in the cat retina, and represent, because of their high density and small dendritic field, the 'acuity' system of cat ganglion cells. They have also been described in other mammalian retinae (dog, ferret, rabbit and mouse), and the midget ganglion cells (P-cells) of the primate retina are probably homologous to beta cells. Midget ganglion cells are the most frequently occurring primate ganglion cell type (70–80%; REF. 61) and in the central retina their dendritic fields are extremely small, so they contact only a single midget bipolar cell which is connected to a single cone[62]. They therefore represent the 'acuity' system of the primate retina and, as previously mentioned, are the L–M-cone-selective ganglion cells[63].

Different staining techniques have been used to show the retinal mosaics of other classes of RGC. Bistratified ganglion cells were revealed by intracellular injections and dye-coupling[64], delta ganglion cells by serotonin uptake and intracellular injection[65], ganglion cells projecting to the accessory optic nucleus by retrograde labelling[66] and the recently discovered melanopsin-containing cells by immunostaining for melanopsin[2]. Each of these cell types provide complete coverage of the retina with their dendritic trees, and it is safe to predict that all 10–15 ganglion cell types do so. This has important consequences for visual processing in the retina. A light spot projected onto the retina — after transduction in the photoreceptors and transfer to the IPL by bipolar cells — can stimulate at least one ganglion cell of any given type. As the 10–15 ganglion cell types are dedicated to processing different aspects of this light spot (contrast, size, movement, wavelength and so on), information contained in the light spot is funnelled into 10–15 parallel channels.

How can the dendritic trees of so many different ganglion cells overlap? The dendrites of the different ganglion cell types branch (stratify) at different levels within the IPL and, therefore, avoid one another[58,67]. Within their respective strata they meet the axon terminals of the bipolar cells and the processes of the amacrine cells that they need to contact.

It is sometimes assumed that in the primate retina only parasol (M) and midget ganglion cells are present, and that the more 'exotic' ganglion cell types are found only in the retinae of other mammals. One reason for this is the high proportion (70–80%) of midget ganglion cells in the primate retina. However, the primate retina contains more than 1 million ganglion cells. If parasol and midget cells together comprise 80% of primate ganglion cells, that still leaves 200,000 ganglion cells of other types. This is more than the total number of ganglion cells in the cat retina, which has 14 types in an eye comparable in size to the primate eye. Previous results from Golgi staining and the recent application of retrograde labeling together with 'photofilling' indicate that the primate retina follows the general mammalian scheme and has 10–15 types of RGC[58].

Physiological types of ganglion cell

In 1953, Kuffler[68] described the concentric receptive field organization of cat RGCs. The receptive field centre is encompassed by a larger, antagonistic surround. He found two cell types: ON centre/OFF surround and OFF centre/ON surround cells. Ganglion cells with more complex receptive fields were later described, first in the frog retina and then in the rabbit retina. It was thought that they represented feature detectors that react to specific light stimuli. Among them were direction-selective ganglion cells, which respond to light spots that move in a certain direction across their receptive field. The concentrically organized receptive fields of the cat

retina were later subdivided into those with linear summation (X-cells) and nonlinear summation (Y-cells) of grating stimuli[69], and these were found to correspond to the morphologically defined beta and alpha cells, respectively[70]. Ganglion cells with more complex receptive fields were observed in the cat retina in about 1970 (REF. 71), and have been analysed physiologically and morphologically by Berson and co-workers[67]. They have described a minimum of 14 morphological types, and analysed the light responses of these types and the central projection of their axons. In the primate retina, two types of concentrically organized receptive field have been found. One type showed no chromatic receptive field organization, whereas in the other type the centre and surround were chromatically selective[72].

Recent progress in analysing the characteristics and underlying circuits of ganglion cell light responses has been made through the application of *in vitro* techniques and intracellular recordings to mammalian retinae. These techniques were originally applied with great success to non-mammalian retinae, such as those of the tiger salamander and the goldfish, and it is now possible to perform intracellular, patch-clamp and multielectrode recordings from slices and whole-mounts of mouse, rabbit and primate retinae. Here I will concentrate on four ganglion cell types: brisk transient (Y) cells, direction-selective ganglion cells, colour-coded ganglion cells of the primate retina, and melanopsin-containing ganglion cells.

Brisk transient (Y) cells. Brisk transient (Y) cells are the physiological correlate of alpha cells, and there are both ON and OFF varieties. They have the largest cell bodies, the shortest latency and the fastest axons of all RGCs. Their axons project through collateral branches into the main visual nuclei (LGN, superior colliculus and pretectum). The light-evoked signals of brisk transient (Y) cells are the first to arrive in the brain and probably act as a 'visual switch' that turns on visual attention. Because of their nonlinear summation, they are extremely sensitive to small, jerky stimulus movements, not only in their receptive fields but also in remote areas[71]. This 'periphery effect' can be blocked by the application of tetrodotoxin. So, to relay the response from distant regions of the receptive field requires a spiking interneuron, probably an amacrine cell[73]. It has been argued that the periphery effect represents anticipation of moving stimuli by the retina[74].

We perceive motion when a coarse grating drifts across the retina, causing spatiotemporal changes in luminance (first-order cue). We also perceive motion when luminance is constant and only contrast changes over space and time (second-order cue). This requires linear signals to be rectified and then summed in temporal order to compute direction. These operations have been attributed to the cortex, but it has been shown that brisk transient (Y) cells respond to spatiotemporal contrast modulations of these second-order motion stimuli. The rectification of the signals originates in the bipolar and amacrine cells presynaptic to the brisk transient (Y) cell[75,76].

Similarly, it was assumed that the segregation of object and background motion occurs in the cortex. However, Ölveczky and colleagues[77] showed that ganglion cells in the retina are selective for local object motion over global motion. They also identified the inhibitory network that mediates this selectivity and described polyaxonal amacrine cells as the main players.

Another function that has traditionally been attributed to cortical processing is contrast adaptation. However, recent studies have shown that the contrast sensitivity of RGCs can be adapted, and this mechanism has been attributed to bipolar cells[78,79].

Brisk transient (Y) cells also show the highest flicker fusion frequency (up to 100 Hz in the cat) of all RGCs. This requires input from bipolar cells that respond to high temporal frequencies. The dendrites of brisk transient (Y) cells ramify in the middle of the IPL, where they meet the axon terminals of specific classes of bipolar cell. Although we do not know their physiological properties in the cat retina, we can predict that such bipolar cells must respond to high-frequency light stimuli[80,81].

These examples show how structure and function can be correlated in the retina, probably more successfully than in any other neuronal tissue. They also show that the multiple roles of RGCs in visual processing are only revealed if adequate stimuli, close to the natural scene, are applied[82].

Direction-selective ganglion cells. Despite many efforts during the last 40 years, we still do not understand the synaptic connectivity and signalling that result in the direction selectivity of RGCs. According to the model proposed by Barlow and Levick[83], each direction-selective ganglion cell receives signals derived from two neighbouring image locations, one excitatory and one inhibitory (FIG. 6a). The inhibitory input is displaced towards the preferred direction of the ganglion cell and is delayed. So, a stimulus moving in the null direction would drive inhibition of the postsynaptic cell and shunt the subsequent excitatory input, whereas movement in the preferred direction would result in a delayed and therefore ineffective inhibitory input leading to net excitation of the postsynaptic cell. A recent study of whole-cell recordings from rabbit direction-selective ganglion cells supports this 'postsynaptic' model[84]. However, other studies indicate that cells presynaptic to ganglion cells exhibit direction-sensitive light responses[85,86]. One set of presynaptic cells that might be involved are the cholinergic amacrine cells (FIG. 6b). When these cells were deleted in a transgenic mouse retina, no direction-sensitive responses were found in ganglion cells[87]. TWO-PHOTON MICROSCOPY was used to record Ca^{2+} signals in the dendritic trees of cholinergic amacrine cells, and these signals showed direction-selective responses[88]. Double recordings from neighbouring pairs of cholinergic amacrine cells and direction-selective ganglion cells[89] showed that cholinergic amacrine cells at the preferred side provide more excitatory input, whereas cholinergic cells at the null side provide more inhibitory input, to the direction-selective ganglion cells (FIG. 6c). So, cholinergic amacrine

TWO-PHOTON MICROSCOPY
A form of microscopy in which a fluorochrome that would normally be excited by a single photon is stimulated quasi-simultaneously by two photons of lower energy. Under these conditions, only fluorochrome molecules near the plane of focus are excited, greatly reducing light scattering and photodamage of the sample.

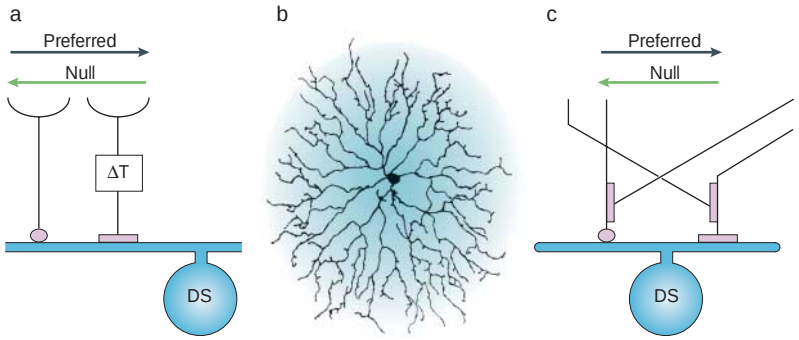

Figure 6 | **Scheme of circuits proposed to generate directionally-selective responses in retinal ganglion cells. a** | Model of a direction selective (DS) ganglion cell as proposed by Barlow and Levick[83]. A small part (a subunit) of the dendritic field of the DS cell is shown. It receives input from two neighbouring image locations (left, excitatory; right, inhibitory). The inhibitory input is delayed (ΔT). The cell responds to movement of a stimulus in the preferred direction but not in the null direction. **b** | Cholinergic amacrine cells are an important part of the DS circuitry. Cholinergic amacrine cells are dual transmitter cells, releasing both the excitatory transmitter acetylcholine and the inhibitory transmitter GABA (g-aminobutyric acid); however, the synaptic details of their connections with DS ganglion cells are unknown. **c** | Recent model of a DS ganglion cell showing the excitatory and inhibitory interactions that differ between the preferred and the null direction. The DS ganglion cell receives a direct excitatory input from the preferred side (left) and a direct inhibitory input from the null side (right). The excitatory input receives presynaptic inhibition from the null side and the inhibitory input receives presynaptic inhibition from the preferred side[127].

cells seem to be a key element of the direction-selective circuitry, and it is likely that both presynaptic and post-synaptic mechanisms are involved in the generation of direction-selective light responses[90,91].

Colour-coded ganglion cells. At the level of the retina, two cone-opponent pathways are classically recognized: a 'red–green' pathway, in which L- and M-cones are antagonistic, and a 'blue–yellow' pathway, in which S-cones are opposed to a combined L + M-cone signal[92]. Midget ganglion cells have long been thought to represent the red–green pathway. Like cells in non-mammalian (goldfish, turtle) retinae, it was thought that the receptive fields of primate midget ganglion cells had a colour-opponent organization: red centres opposed to green surrounds, and green centres opposed to red surrounds. However, more recent anatomical and physiological results indicate that the surrounds are not cone-selective, but show a random cone selectivity/connectivity[56]. Nonetheless, strong opponency could still ensue; because of its high gain, the single cone centre could cancel the low-gain input from the same type of cone to the surround[72].

Midget ganglion cells in the more peripheral area(s) of the retina receive input and sum signals from several midget bipolar cells. Two scenarios can be assumed. In the first, midget ganglion cells select midget bipolar cells connected to L-cones or to M-cones and therefore gain pure cone centres[93]. However, it is also possible that midget ganglion cells connect non-selectively to all midget bipolars within their dendritic fields, which would mean that cone selectivity would greatly decline in the retinal periphery[94]. There is a sharp decline in human chromatic sensitivity in the visual periphery[95]. However, Martin *et al.*[93] recorded ganglion cells from the intact eye of the macaque and showed that the strength of L- versus M- opponency across the retinal periphery is identical to that in the fovea. This result would predict selective wiring of midget bipolars and midget ganglion cells in the peripheral retina.

The retinal circuitry associated with the S-cone signals is quite different. A distinctive RGC — the small bistratified ganglion cell — forms the morphological basis for the 'blue-ON/yellow-OFF' opponent pathway[96]. These ganglion cells receive a direct input from the blue cone bipolar cell at their inner dendritic stratum, providing the S-cone-selective 'blue' ON input. At their outer dendritic stratum they also receive a direct input from diffuse bipolar cells connected to L- and M- cones, which provides the 'yellow' OFF input. Recently, based on retrogradely labelling their axons from the LGN, two further S-cone-specific RGCs were identified in the primate retina. One of them receives an S-cone-selective inhibitory input and represents a blue OFF ganglion cell; the other receives an S-cone-selective excitatory input and represents a blue ON ganglion cell[97]. S-cone-selective RGCs are also found in other mammals, and they represent the primordial dichromatic colour system of the mammalian retina.

Melanopsin-containing ganglion cells. Recently, the photopigment melanopsin was discovered in the mammalian retina (reviewed by Berson[2]). It was localized to a sparse population of morphologically distinct RGCs comprising about 1–3% of the RGC population. The dendritic fields of the cells provide complete coverage of the retina. Their axons project to the suprachiasmatic nucleus and to subcortical visual centres such as the pretectum. Electrophysiological recordings from melanopsin-containing cells revealed that they are intrinsically light-sensitive, as they respond to light even when synaptic transmission in the retina is blocked. The intrinsic light response shows a very long latency and little adaptation. However, these cells also receive inputs from rods and cones through bipolar cells. In the light-adapted retina, the luminance response of the melanopsin-containing cells is made up of a fast component, derived from the cone input, and a slower component, based on the intrinsic light response. In the primate retina, there are about 3,000 melanopsin-containing cells. Approximately 40% of them are displaced to the inner nuclear layer and their density peaks at the fovea. Their dendrites stratify close to the inner nuclear layer or close to the ganglion cell layer, but they seem to be ON-centre cells[98]. Melanopsin-containing ganglion cells are involved in the light entrainment of the circadian rhythm and with the pupillary light reflex.

More than 30 years ago, Barlow and Levick[99] discovered 'luminance units' by recording extracellularly from the cat retina. These units were extremely rare (only three out of several hundred ganglion cells) and ON-centre, and their maintained discharge rate monotonically increased with the luminance for at least 5 log units. There is little doubt that these luminance units are the melanopsin-containing cells. However, it is still unknown whether melanopsin-containing cells also project to the geniculocortical pathway. They would be

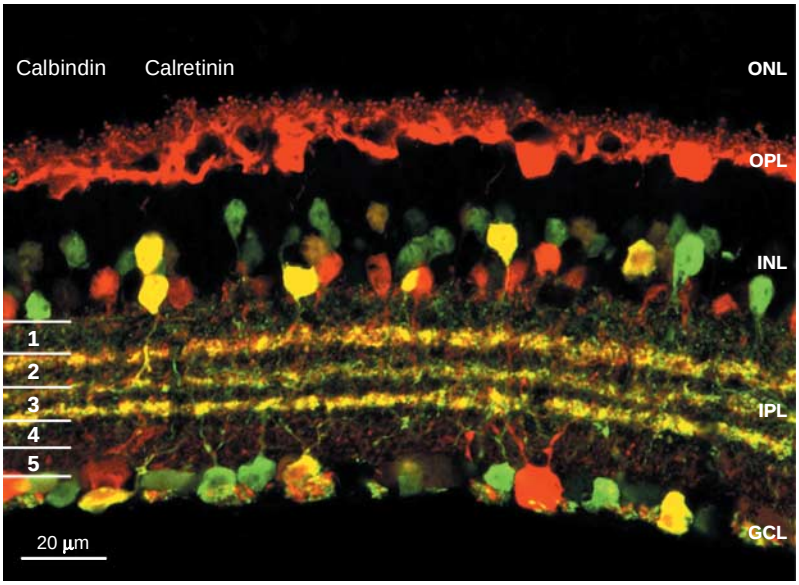

Figure 7 | **Stratification of the inner plexiform layer (IPL).** Vertical section through a mouse retina that was double immunostained for calbindin (red) and calretinin (green)[102]. Horizontal cells and their processes in the outer plexiform layer (OPL) express calbindin only. Amongst the amacrine cells in the inner nuclear layer (INL) and the ganglion cells, different levels of co-localization of calbindin and calretinin can be observed. The labelled dendrites of amacrine and ganglion cells are confined to three narrow bands, segregating four bands of reduced label. This shows that the IPL is precisely stratified and within these strata different aspects of the light signal are processed. GCL, ganglion cell layer; ONL, outer nuclear layer. Reproduced, with permission, from REF. 102 © (2000) Wiley-Liss.

an ideal system to provide the brain with information about the ambient light intensity, which cannot be derived from other ganglion cell classes that quickly adapt to the ambient light levels.

Stratification of the IPL

Axons of different bipolar cell types terminate at different strata within the IPL, where they meet the dendrites of specific ganglion cells[100,101] (FIG. 2). The IPL is subdivided into five strata of equal thickness. In the mouse retina, these strata can be easily defined by immunolabelling the retina for the calcium-binding proteins calbindin and calretinin (FIG. 7), which reveals three densely labelled horizontal bands of processes[26,102]. The outer band (stratum 1–2) contains the processes of the OFF-cholinergic amacrine cells, the dendrites of OFF-alpha cells and the outer dendritic branches of direction-selective cells. This band is densely packed with synapses and $GABA_A$ receptors[103], and transient light responses and OFF direction-selective responses are 'calculated' there[100]. The band in the centre of the IPL (stratum 2–3) seperates the OFF sublamina (outer) from the ON sublamina (inner). The polyaxonal amacrine cells mentioned above ramify in this band, as do two GABA-containing amacrine cells. As well as GABA, these cells contain a neuromodulator (nitric oxide and a catecholamine, respectively). Their functions are unknown. The band in the inner IPL (stratum 3–4) contains the axon terminals of an ON bipolar cell[104], the processes of the ON-cholinergic amacrine cells, the dendrites of ON-alpha cells and the inner dendritic branches of direction-selective cells. This band is also densely packed with synapses and $GABA_A$ receptors, providing the circuitry for ON-transient light responses and ON direction-selective responses.

There are about 30 types of GABA-containing amacrine cell in any mammalian retina and their functions are far from understood[13,105]. They are generally widefield, narrowly stratified amacrine cells and, in addition to GABA, they also contain neuromodulatory substances. They are involved with centre–surround interactions, periphery effects and direction-selective light responses.

At least 15 different glycinergic amacrine cells have also been identified in mammalian retinae[106]. Their common features are small, vertically oriented dendritic fields. Therefore, they are likely to provide inhibitory interactions between the different strata, and more mutual inhibitons between the OFF- and ON-pathways.

Conclusions

The main cell types of the mammalian retina have probably been discovered; there are more than 50 and less than 100 (REFS 7,14). It is surprising how similar the types are, when different mammals are compared. Mouse and rat retinae, which are both dominated by rod photoreceptors, have the same set of cone bipolar cells as primate or ground squirrel retinae, which are cone-dominated[26]. Individual neurons, such as the cholinergic amacrine cell, have strikingly similar shapes and possibly functions across the retinae of different mammals[35]. Because of the increasing availability of mutant mice, the mouse retina will become the most important tool for studying the synaptic and molecular details of mammalian retinal organization[102]. The mouse retina is also a good model in which to study retinal diseases. What happens to the inner retina when photoreceptors degenerate[107–109]? Do ganglion cells survive and are they accessible by retinal implants[110]? What retinal functions can be rescued by adeno-associated viral vectors for gene transfer[111]?

However, the retina will also continue to be one of the preferred sites at which to study structure–function relations in the CNS. The two-dimensional layout of the retina is advantageous for the application of multi-electrode arrays to study the light responses of different types of ganglion cell simultaneously[112,113]. Using this approach, it might be possible to determine whether the synchronized activity of neighbouring ganglion cells contains more information than the spike trains of individual cells, or how different ganglion cell types react to identical stimuli[114–117]. The flat-mounted retina is also an ideal preparation for imaging experiments. The retina is only 200 μm thick, transparent and precisely laminated, making it ideal for two-photon microscopy[88]. The precise lamination of the retina is also an advantage for patch-clamp recordings from vertical slices of the retina, because it is easy to select specific cell types in the individual layers and to measure their light responses[118]. Much remains to be clarified in retinal circuitry — not only complex operations such as the computation of motion, but also more 'simple'

mechanisms, such as centre–surround antagonism, are not yet understood[119,120].

The retina covers the astonishing range of at least 10 log units of light intensity, and this is achieved by multiple stages of adaptation and modulation[121]. The phototransduction cascade, the synaptic mechanisms and even the shape of neurons (horizontal cell spinules) are all modulated by light-dependent mechanisms. Revealing the actions of the modulators, such as dopamine[122], will help us to understand light adaptation in the retina, but, more importantly, will help us to understand their roles in other parts of the brain.

1. Casagrande, V. A. & Xu, X. in *The Visual Neurosciences* (eds Chalupa, L. & Werner, J. S.) 494–506 (MIT, Cambridge, 2004).
2. Berson, D. M. Strange vision: ganglion cells as circadian photoreceptors. *Trends Neurosci.* **26**, 314–320 (2003).
The author reviews the recent experiments on melanopsin-containing ganglion cells, and describes their retinal distribution, their light responses, their central projections and their role in entraining the circadian clock and regulating pupil size.
3. Hendry, S. H. & Reid, C. The koniocellular pathway in primate vision. *Annu. Rev. Neurosci.* **23**, 127–153 (2000).
4. Martin, P. R., White, A. J. R., Goodchild, A. K., Wilder, H. D. & Sefton, A. J. Evidence that blue-on cells are part of the third geniculocortical pathway in primates. *Eur. J. Neurosci.* **9**, 1536–1541 (1997).
5. Sterling, P. in *The Synaptic Organization of the Brain* Vol. 4 (ed. Shepherd, G. M.) 205–253 (Oxford Univ. Press, New York, 1998).
6. Boycott, B. B. & Wässle, H. Parallel processing in the mammalian retina: the Proctor Lecture. *Invest. Ophthalmol. Vis. Sci.* **40**, 1313–1327 (1999).
7. Masland, R. H. The fundamental plan of the retina. *Nature Neurosci.* **4**, 877–886 (2001).
8. He, S., Dong, W., Deng, Q., Wenig, S. & Sun W. Seeing more clearly: recent advances in understanding retinal circuitry. *Science* **302**, 408–411 (2003).
9. Masland, R. H. & Raviola, E. Confronting complexity: strategies for understanding the microcircuitry of the retina. *Annu. Rev. Neurosci.* **23**, 249–284 (2000).
10. Marc, R. E. & Jones, B. W. Molecular phenotyping of retinal ganglion cells. *J. Neurosci.* **22**, 413–427 (2002).
11. Nathans, J. The evolution and physiology of human color vision: insights from molecular genetic studies of visual pigments. *Neuron* **24**, 299–312 (1999).
The author describes the genes that encode the L-, M- and S-cone pigments and explains the evolution of colour vision in primates.
12. Jacobs, G. H. in *Handbook of Psychology.* Vol. 3 *Biological Psychology* (eds Gallagher, M. & Nelson, R. J.) 47–70 (Wiley, New York, 2002).
13. MacNeil, M. A. & Masland, R. H. Extreme diversity among amacrine cells: implications for function. *Neuron* **20**, 971–982 (1998).
14. Masland, R. H. Neuronal diversity in the retina. *Curr. Opin. Neurobiol.* **11**, 431–436 (2001).
The two reviews on the functional architecture of the retina by Masland (references 7 and 14) must be read by anybody interested in retinal function and vision.
15. Haverkamp, S., Grünert, U. & Wässle, H. The cone pedicle, a complex synapse in the retina. *Neuron* **27**, 85–95 (2000).
In a series of three papers (references 15, 21 and 22), Haverkamp *et al.* describe the molecular details and structure of the cone pedicle of the primate retina.
16. Feigenspan, A. *et al.* Expression of connexin36 in cone pedicles and OFF-cone bipolar cells of the mouse retina. *J. Neurosci.* **24**, 3325–3334 (2004).
17. Hornstein, E. P., Verweij, J. & Schnapf, J. L. Electrical coupling between red and green cones in primate retina. *Nature Neurosci.* **7**, 745–750 (2004).
18. Li, W. & DeVries, H. Separate blue and green cone networks in the mammalian retina. *Nature Neurosci.* **7**, 751–756 (2004).
19. O'Brien, J. J., Chen, X., MacLeish, P. R. & Massey S. S. Connexin 36 forms gap junctions between telodendria of primate cones. *Invest. Ophthalmol. Vis. Sci.* **45**, Assoc. Res. Vis. Ophthalmol. Meeting E Abstr. 1146 (2004).
20. Lamb, T. D. & Simon, E. J. The relation between intercellular coupling and electrical noise in turtle photoreceptors. *J. Physiol. (Lond.)* **263**, 257–286 (1976).
21. Haverkamp, S., Grünert, U. & Wässle, H. The synaptic architecture of AMPA receptors at the cone pedicle of the primate retina. *J. Neurosci.* **21**, 2488–2500 (2001).
22. Haverkamp, S., Grünert, U. & Wässle, H. Localization of kainate receptors at the cone pedicles of the primate retina. *J. Comp. Neurol.* **436**, 471–486 (2001).
23. Nomura, A. *et al.* Developmentally regulated postsynaptic localization of a metabotropic glutamate receptor in rat rod bipolar cells. *Cell* **77**, 361–369 (1994).
24. Vardi, N., Duvoisin, R., Wu, G. & Sterling, P. Localization of mGluR6 to dendrites of ON bipolar cells in primate retina. *J. Comp. Neurol.* **423**, 402–412 (2000).
25. Hering, E. Zur Lehre vom Lichtsinne IV. Über die sogenannte Intensität der Lichtempfindung und über die Empfindung des Schwarzen. *Sitzungsberichte Kaiserlichen Akademie Wissenschaften Wien. Mathematisch-naturwissenschaftlicheClasse Abth. III. Bd.* **69**, 85–104 (1874).
26. Ghosh, K. K., Bujan, S., Haverkamp, S., Feigenspan, A. & Wässle, H. Types of bipolar cells in the mouse retina. *J. Comp. Neurol.* **469**, 70–82 (2004).
27. MacNeil, M. A., Heussy, J. K., Dacheux, R. F., Raviola, E. & Masland, R. H. The population of bipolar cells in the rabbit retina. *J. Comp. Neurol.* **472**, 73–86 (2004).
The authors have studied the amacrine and bipolar cells of the rabbit retina and have identified most of the cell types present in that retina.
28. Freed, M. A. Parallel cone bipolar pathways to a ganglion cell use different rates and amplitudes of quantal excitation. *J. Neurosci.* **20**, 3956–3963 (2000).
29. DeVries, S. H. Bipolar cells use kainate and AMPA receptors to filter visual information into separate channels. *Neuron* **28**, 847–856 (2000).
The author has studied signal transfer from cones to bipolar cells by double recordings from cone pedicles and bipolar cells, and has revealed important details of this first synapse of the retina.
30. Awatramani, G. B. & Slaughter, M. M. Origin of transient and sustained responses in ganglion cells of the retina. *J. Neurosci.* **20**, 7087–7095 (2000).
31. Wu, S. M., Gao, F. & Maple, B. R. Functional architecture of synapses in the inner retina: segregation of visual signals by stratification of bipolar cell axon terminals. *J. Neurosci.* **20**, 4462–4470 (2000).
32. Pan, Z.-H. & Hu, H.-J. Voltage-dependent Na^+ currents in mammalian retinal cone bipolar cells. *J. Neurophysiol.* **84**, 2564–2571 (2000).
33. Kouyama, N. & Marshak, D. W. Bipolar cells specific for blue cones in the macaque retina. *J. Neurosci.* **12**, 1233–1252 (1992).
34. Calkins, D. J. Seeing with S cones. *Prog. Retin. Eye Res.* **20**, 255–287 (2001).
35. Wässle, H. & Boycott, B. B. Functional architecture of the mammalian retina. *Physiol. Rev.* **71**, 447–480 (1991).
36. Mollon, J. D. & Jordan, G. Eine evolutionäre Interpretation des menschlichen Farbensehens. *Die Farbe* **35/36**, 139–170 (1988).
37. Wässle, H. A patchwork of cones. *Nature* **397**, 473–475 (1999).
38. Jacobs, G. H., Fenwick, J. C., Calderone, J. B. & Deeb, S. S. Human cone pigment expressed in transgenic mice yields altered vision. *J. Neurosci.* **19**, 3258–3265 (1999).
39. Smallwood, P. M. *et al.* Genetically engineered mice with an additional class of cone photoreceptors: implications for the evolution of color vision. *Proc. Natl Acad. Sci. USA* **100**, 11706–11711 (2003).
40. Ingling, C. R. Jr & Martinez-Uriegas, E. The relationship between spectral sensitivity and spatial sensitivity for the primate r-g X-channel. *Vision Res.* **23**, 1495–1500 (1983).
41. Rodieck, R. W. in *From Pigments to Perception* (eds Valberg, A. & Lee, B.) 83–93 (Plenum, New York, 1991).
42. Calkins, D. J. & Sterling, P. Evidence that circuits for spatial and color vision segregate at the first retinal synapse. *Neuron* **24**, 313–321 (1999).
43. Haverkamp, S., Möckel, W. & Ammermüller, J. Different types of synapses with different spectral types of cones underlie color opponency in a bipolar cell of the turtle retina. *Vis. Neurosci.* **16**, 801–809 (1999).
44. Berntson, A. & Taylor, W. R. Response chracteristics and receptive field widths of on-bipolar cells in the mouse retina. *J. Physiol. (Lond.)* **524**, 879–889 (2000).
45. Euler, T. & Masland, R. H. Light-evoked responses of bipolar cells in a mammalian retina. *J. Neurophysiol.* **83**, 1817–1829 (2000).
46. Famiglietti, E. V. & Kolb, H. A bistratified amacrine cell and synaptic circuitry in the inner plexiform layer of the retina. *Brain Res.* **84**, 293–300 (1975).
47. Raviola, E. & Dacheux, R. F. Excitatory dyad synapse in rabbit retina. *Proc. Natl Acad. Sci. USA* **84**, 7324–7328 (1987).
48. DeVries, S. H. & Baylor, D. A. An alternative pathway for signal flow from rod photoreceptors to ganglion cells in mammalian retina. *Proc. Natl Acad. Sci. USA* **92**, 10658–10662 (1995).
49. Soucy, E., Wang, Y., Nirenberg, S., Nathans, J. & Meister, M. A novel signaling pathway from rod photoreceptors to ganglion cells in mammalian retina. *Neuron* **21**, 481–493 (1998).
50. Hack, I., Peichl, L. & Brandstätter, J. H. An alternative pathway for rod signals in the rodent retina: rod photoreceptors, cone bipolar cells, and the localization of glutamate receptors. *Proc. Natl Acad. Sci. USA* **96**, 14130–14135 (1999).
51. Tsukamoto, Y., Morigiwa, K., Ueda, M. & Sterling, P. Microcircuits for night vision in mouse retina. *J. Neurosci.* **21**, 8616–8623 (2001).
52. Deans, M. R., Volgyi, B., Goodenough, D. A., Bloomfield, S. A. & Paul, D. L. Connexin36 is essential for transmission of rod-mediated visual signals in the mammalian retina. *Neuron* **36**, 703–712 (2002).
The authors have studied the rod pathway in both wild-type and connexin-36-knockout mice. They showed that different RGC classes are specifically affected by the loss of gap junctions expressing connexin-36.
53. Kamermans, M. *et al.* Hemichannel-mediated inhibition in the outer retina. *Science* **292**, 1178–1180 (2001).
In recent years, Kamermans *et al.* have elaborated a model of horizontal cell feedback at the cone pedicle that is not based on the release of a transmitter but instead involves changes in electric potentials: shifts in the activation of Ca^{2+} channels modulate glutamate release from cone pedicles.
54. Hirasawa, H. & Kaneko, A. pH changes in the invaginating synaptic cleft mediate feedback from horizontal cells to cone photoreceptors by modulating Ca^{2+} channels. *J. Gen. Physiol.* **122**, 657–671 (2003).
55. Hombach, S. *et al.* Functional expression of connexin 57 in horizontal cells of the mouse retina. *Eur. J. Neurosci.* **19**, 2633–2640 (2004).
56. Dacey, D. M., Lee, B. B., Stafford, D. K., Pokorny, J. & Smith, V. C. Horizontal cells of the primate retina: cone specificity without spectral opponency. *Science* **271**, 656–659 (1996).
57. Rockhill, R. L., Daly, F. J., MacNeil, M. A., Brown, S. P. & Masland, R. H. The diversity of ganglion cells in a mammalian retina. *J. Neurosci.* **22**, 3831–3843 (2002).
58. Dacey, D. M., Peterson, B. B., Robinson, F. R., & Gamlin, P. D. Fireworks in the primate retina: neurotechnique *in vitro* photodynamics reveals diverse LGN-projecting ganglion cell types. *Neuron* **37**, 15–27 (2003).
The authors describe an exciting new technique for labelling neurons. Biotinylated rhodamine dextran is injected into the LGN, retrogradely transported and visualized by photodynamic staining.
59. Peichl, L. Alpha ganglion cells in mammalian retinae: common properties, species differences, and some comments on other ganglion cells. *Vis. Neurosci.* **7**, 155–169 (1991).
60. Wässle, H., Boycott, B. B. & Illing, R.-B. Morphology and mosaic of on- and off-beta cells in the cat retina and some functional considerations. *Proc. R. Soc. Lond. B* **212**, 177–195 (1981).
61. Perry, V. H., Oehler, R. & Cowey, A. Retinal ganglion cells that project to the dorsal lateral geniculate nucleus in the macaque monkey. *Neuroscience* **12**, 1101–1123 (1984).
62. Kolb, H. & Marshak, D. The midget pathways of the primate retina. *Doc. Ophthalmol.* **106**, 67–81 (2003).
63. Dacey, D. M. The mosaic of midget ganglion-cells in the human retina. *J. Neurosci.* **13**, 5334–5355 (1993).
64. Vaney, D. I. Territorial organization of direction-selective ganglion-cells in rabbit retina. *J. Neurosci.* **14**, 6301–6316 (1994).
65. Dacey, D. M. Monoamine-accumulating ganglion-cell type of the cat's retina. *J. Comp. Neurol.* **288**, 59–80 (1989).

66. Buhl, E. H. & Peichl, L. Morphology of rabbit retinal ganglion-cells projecting to the medial terminal nucleus of the accessory optic-system. *J. Comp. Neurol.* **253**, 163–174 (1986).
67. Isayama, T., Berson, D. M. & Pu, M. Theta ganglion cell type of cat retina. *J. Comp. Neurol*. **417**, 32–48 (2000).
Berson and colleagues have investigated the morphological and physiological classes and the central projections of cat RGCs in a series of careful papers. Their classification scheme of RGCs in the cat is the most advanced description of RGCs in any retina.
68. Kuffler, S. W. Discharge patterns and functional organization of mammalian retina. *J. Neurophysiol.* **16**, 37–68 (1953).
69. Enroth-Cugell, C. & Robson, J. C. The contrast sensitivity of retinal ganglion cells of the cat. *J. Physiol. (Lond.)* **187**, 517–552 (1966).
This classic paper has established parallel processing in the mammalian retina by showing that cat RGCs can be subdivided into those with linear summation of light stimuli (X-cells) and those with nonlinear summation (Y-cells).
70. Boycott, B. B. & Wässle, H. The morphological types of ganglion cells of the domestic cat's retina. *J. Physiol. (Lond.)* **240**, 397–419 (1974).
71. Levick, W. R. Receptive fields of cat retinal ganglion cells with special reference to the alpha cells. *Prog. Retin. Eye Res*. **15**, 457–500 (1996).
72. Dacey, D. M. & Packer, O. S. Colour coding in the primate retina: diverse cell types and cone-specific circuitry. *Curr. Opin. Neurobiol*. **13**, 421–427 (2003).
A review of the retinal circuits that are involved in the segregation of L- versus M-signals and with blue–yellow oppenency.
73. Demb, J. B., Haarsma, L., Freed, M. A. & Sterling, P. Functional circuitry of the retinal ganglion cell's nonlinear receptive field. *J. Neurosci.* **19**, 9756–9767 (1999).
74. Berry, M. J. II, Brivanlou, I. H., Jordan, T. A. & Meister, M. Anticipation of moving stimuli by the retina. *Nature* **398**, 334–338 (1999).
75. Demb, J. B., Zaghloul, K. & Sterling, P. Cellular basis for the response to second-order motion cues in Y retinal ganglion cells. *Neuron* **32**, 711–721 (2001).
76. Demb, J. B., Zaghloul, K., Haarsma, L. & Sterling, P. Bipolar cells contribute to nonlinear spatial summation in the brisk-transient (Y) ganglion cell in mammalian retina. *J. Neurosci*. **21**, 7447–7454 (2001).
In a series of excellent papers, Demb and colleagues have investigated the functional circuitry of brisk transient (Y) cells of the mammalian retina.
77. Ölveczky, B. P., Baccus, S. A. & Meister, M. Segregation of object and background motion in the retina. *Nature* **423**, 401–408 (2003).
78. Brown, S. P. & Masland, R. H. Spatial scale and cellular substrate of contrast adaptation by retinal ganglion cells. *Nature Neurosci*. **4**, 44–51 (2001).
79. Baccus, S. A. & Meister, M. Retina versus cortex: contrast adaptation in parallel visual pathways. *Neuron* **42**, 5–7 (2004).
80. Freed, M. A. Rate of quantal excitation to a retinal ganglion cell evoked by sensory input. *J. Neurophysiol*. **83**, 2956–2966 (2000).
81. Freed, M. A., Smith, R. G. & Sterling, P. Timing of quantal release from the retinal bipolar terminal is regulated by a feedback circuit. *Neuron* **38**, 89–101 (2003).
In a series of careful experiments the authors studied the signal transfer from cone bipolar cells onto RGCs.
82. Chiao, C.-C. & Masland, R. H. Contextual tuning of direction-selective retinal ganglion cells. *Nature Neurosci*. **6**, 1251–1252 (2003).
83. Barlow, H. B. & Levick, W. R. The mechanism of directionally selective units in rabbit's retina. *J. Physiol. (Lond.)* **178**, 477–504 (1965).
84. Taylor, W. R., He, S., Levick, W. R. & Vaney, D. I. Dendritic computation of direction selectivity by retinal ganglion cells. *Science* **289**, 2347–2350 (2000).
85. Borg-Graham, L. J. The computation of directional selectivity in the retina occurs presynaptic to the ganglion cell. *Nature Neurosci*. **4**, 176–183 (2001).
86. Fried, S. I., Münch, T. A. & Werblin, F. S. Mechanisms and circuitry underlying directional selectivity in the retina. *Nature* **420**, 411–414 (2002).
The authors recorded direction-selective ganglion cells and studied their synaptic inputs. They describe different connectivities for the preferred and the null direction.
87. Yoshida, K. *et al.* A key role of starburst amacrine cells in originating retinal directional selectivity and optokinetic eye movement. *Neuron* **30**, 771–780 (2001).
In an elegant experiment, using transgenic mouse technology, the authors were able to knock out cholinergic (starburst) amacrine cells and to show that directional selectivity was abolished. This strongly indicates that cholinergic amacrine cells are a vital participant in directional selectivity.
88. Euler, T., Detwiler, P. B. & Denk, W. Directionally selective calcium signals in dendrites of starburst amacrine cells. *Nature* **418**, 845–852 (2002).
By the application of two-photon microscopy and calcium-imaging, the authors showed that cholinergic amacrine cells (starburst cells) have directionally selective light responses.
89. Münch, T. A., Fried, S. I. & Werblin, F. S. Starburst cells initiate directional selective responses in rabbit retina. *Invest. Ophthalmol. Vis. Sci.* **43** (Suppl. 2), 2981 (2002).
90. Taylor, W. R. & Vaney, D. I. Diverse synaptic mechanisms generate direction selectivity in the rabbit retina. *J. Neurosci*. **22**, 7712–7720 (2002).
91. Taylor, W. R. & Vaney, D. I. New directions in retinal research. *Trends Neurosci*. **26**, 379–385 (2003).
The most recent and comprehensive review of the mechanisms underlying direction selectivity. Both the presynaptic and the postsynaptic mechanisms, as well as evidence for and against them, are discussed.
92. Martin, P. R. Colour processing in the primate retina: recent progress. *J. Physiol. (Lond.)* **513**, 631–638 (1998).
93. Martin, P. R., Lee, B. B., White, A. J. R., Solomon, S. G. & Rüttiger, L. Chromatic sensitivity of ganglion cells in the peripheral primate retina. *Nature* **410**, 933–935 (2001).
94. Diller, L. *et al.* L and M cone contributions to the midget and parasol ganglion cell receptive fields of macaque monkey retina. *J. Neurosci*. **24**, 1079–1088 (2004).
95. Mullen, K. T. & Kingdom, F. A. A. Differential distributions of red-green and blue-yellow cone opponency across the visual field. *Vis. Neurosci*. **19**, 109–118 (2002).
96. Dacey, D. M. & Lee, B. B. The blue-on opponent pathway in primate retina originates from a distinct bistratified ganglion-cell type. *Nature* **367**, 731–735 (1994).
97. Dacey, D. M., Peterson, B. B. & Robinson, F. R. Identification of an S-cone opponent OFF pathway in the macaque monkey retina: morphology, physiology and possible circuitry. *Invest. Ophthalmol. Vis. Sci.* **43** (Suppl. 2), 2983 (2002).
98. Peterson, B. B. *et al.* Functional architecture of the photoreceptive ganglion cells in the primate retina: morphology, mosaic organization and central targets of melanopsin immunostained cells. *Invest. Ophthalmol. Vis. Sci.* **44**, Assoc. Res. Vis. Ophthalmol. Meeting E-Abstr. 5182 (2003).
99. Barlow, H. B. & Levick, W. R. Changes in the maintained discharge with adaptation level in the cat retina. *J. Physiol. (Lond.)* **202**, 699–718 (1969).
100. Roska, B. & Werblin, F. Vertical interactions across ten parallel, stacked representations in the mammalian retina. *Nature* **410**, 583–587 (2001).
The authors studied light responses of the different RGC classes in the rabbit retina and correlated them with the stratification level of RGC dendrites within the IPL.
101. Werblin, F. S. & Roska, B. M. Parallel visual processing: a tutorial of retinal function. *Int. J. Bifurc. Chaos* **14**, 843–852 (2004).
102. Haverkamp, S. & Wässle, H. Immunocytochemical analysis of the mouse retina. *J. Comp. Neurol.* **424**, 1–23 (2000).
103. Brandstätter, J. H., Greferath, U., Euler, T. & Wässle, H. Co-stratification of $GABA_A$ receptors with the directionally selective circuitry of the rat retina. *Vis. Neurosci*. **12**, 345–358 (1995).
104. Brown, S. P. & Masland, R. H. Costratification of a population of bipolar cells with the direction-selective circuitry of the rabbit retina. *J. Comp. Neurol*. **408**, 97–106 (1999).
105. Vaney, D. I. Retinal neurons: cell types and coupled networks. *Perspect. Analyt. Philos*. **136**, 239–254 (2002).
106. Menger, N., Pow, D. V. & Wässle, H. Glycinergic amacrine cells of the rat retina. *J. Comp. Neurol*. **401**, 34–46 (1998).
107. Strettoi, E., Porciatti, V., Falsini, B., Pignatelli, V. & Rossi, C. Morphological and functional abnormalities in the inner retina of the *rd/rd* mouse. *J. Neurosci.* **22**, 5492–5504 (2002).
108. Marc, R. E., Jones, B. W., Watt, C. B. & Strettoi, E. Neural remodeling in retinal degeneration. *Prog. Retin. Eye Res*. **22**, 607–655 (2003).
This is an excellent review of the changes in the mammalian retina that are triggered by degeneration of the photoreceptors.
109. Marc, R. E. & Jones, B. W. Retinal remodeling in inherited photoreceptor degenerations. *Mol. Neurobiol*. **28**, 139–147 (2003).
110. Loewenstein, J. I., Montezuma, S. R. & Rizzo, J. F. 3rd. Outer retinal degeneration. *Arch. Ophthalmol*. **122**, 587–596 (2004).
111. Surace, E. M. & Auricchio, A. Adeno-associated viral vectors for retinal gene transfer. *Prog. Retin. Eye Res*. **22**, 705–719 (2003).
112. Meister, M. Multineuronal codes in retinal signaling. *Proc. Natl Acad. Sci. USA* **93**, 609–614 (1996).
113. Berry, M. J., Warland, D. K. & Meister M. The structure and precision of retinal spike trains. *Proc. Natl Acad. Sci. USA* **94**, 5411–5416 (1997).
114. Meister, M. & Berry, M. J. The neural code of the retina. *Neuron* **22**, 435–450 (1999).
One of several recently published papers describing how RGCs react to specific aspects of complex light stimuli and how they adapt to natural stimuli. Their studies are excellent examples of the application of multielectrode recordings for the study of neuronal assemblies.
115. Nirenberg, S. & Latham, P. E. Population coding in the retina. *Curr. Opin. Neurobiol.* **8**, 488–493 (1998).
116. Nirenberg, S. & Latham, P. E. Decoding neuronal spike trains: how important are correlations? *Proc. Natl Acad. Sci. USA* **100**, 7348–7353 (2003).
The authors address the question of whether the correlated firing of neighbouring RGCs transfers more information to the brain than uncorrelated signals.
117. Chichilnisky, E. J. & Kalmar, R. S. Temporal resolution of ensemble visual motion signals in primate retina. *J. Neurosci.* **23**, 6681–6689 (2003).
118. Boos, R., Schneider, H. & Wässle, H. Voltage-gated and transmitter-gated currents of All-amacrine cells in a slice preparation of the rat retina. *J. Neurosci*. **13**, 2874–2888 (1993).
119. Flores-Herr, N., Protti, D. A. & Wässle, H. Synaptic currents generating the inhibitory surround of ganglion cells in the mammalian retina. *J. Neurosci*. **21**, 4852–4863 (2001).
120. McMahon, M. J., Packer, O. S. & Dacey, D. M. The classical receptive field surround of primate parasol ganglion cells is mediated primarely by a non-GABAergic pathway. *J. Neurosci.* **24**, 3736–3745 (2004).
121. Rodieck, R. W. *The First Steps in Seeing* (Sinauer Ass. Inc., Sunderland, Massachusetts, 1998).
122. Witkovsky, P. Dopamine and retinal function. *Doc. Ophthalmol*. **108**, 17–40 (2004).
123. Demb, J. B. & Pugh, E. N. Jr. Connexin36 forms synapses essential for night vision. *Neuron* **36**, 551–553 (2002).
124. Feng, G. *et al.* Imaging neuronal subsets in transgenic mice expressing multiple spectral variants of GFP. *Neuron* **28**, 41–51 (2000).
125. Sun, W., Li, N. & He, S. Large-scale morphological survey of mouse retinal ganglion cells. *J. Comp. Neurol*. **451**, 115–126 (2002).
126. Wässle, H. Die Netzhaut ein Gehirn im Auge. *Jahrbuch 2001 Deutschen Akademie Naturforscher Leopoldina* **47**, 493–506 (2002).
127. Fried, S. I., Münch, T. A. & Werblin, F. S. The circuitry underlying directional excitation and inhibition to DS cells. Invest. Ophthalmol. Vis. Sci. **45**, Assoc. Res. Vis. Ophthalmol. Meeting E-Abstr. 2266 (2004).

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