13 The Retina Dissects the Visual Scene into Distinct Features

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TWENTY RETINAL PATHWAYS CONVEY VISUAL INFORMATION FROM THE EYE TO THE BRAIN

Classical studies of the functional architecture of the retina have found that the image projected onto the retina and captured by the photoreceptors is processed locally by multiple parallel circuits (Masland, 2001; Wässle, 2004). This parallel processing results in several different dynamic activity patterns at the retinal output (Roska & Werblin, 2001) that are simultaneously transmitted to the brain by ganglion cells, the output neurons of the retina (figure 13.1).

There is a growing consensus that the ganglion cell population comprises ~20 different types. Each type forms a subpopulation that covers the entire retina, usually in a regularly spaced arrangement called a "mosaic." Thus, the unit of cellular infrastructure that underlies parallel processing in the retina is a mosaic of ganglion cells with similar morphology and response properties, together with an associated mosaic of local circuits (figure 13.2). The retina embodies 20 such mosaics that independently extract different features from the visual world, although the underlying circuits share many of the interneurons. It is as if our eye comprised multiple different TV crews pointing their cameras at the same event but each broadcasting to their audience (the relevant brain region) a subjectively cut and processed version of the captured image flow (figure 13.3). Some workers are shared among all of the different crews, others specialize for jobs with few crews, and some are only participating in one crew.

Each ganglion cell in a given mosaic has a local circuit with different circuit elements. These elements can be ranked according to how many synapses separate them from the sensory receptors. Rods and cones are first-order neurons; bipolar and horizontal cells are second-order; amacrine and ganglion cells are third-order. The ganglion cells, as the sole output element of the retina, are positioned clearly at the top of the hierarchy in these circuits. Bipolar, amacrine, and horizontal cells each come in a variety of different morphological and physiological variants. Again, neurons with the same shapes and response properties are arranged in a mosaic (Wässle, 2004). Thus, the retina is built from multiple mosaics of cells, which we will call "cell types" for short.

Because each retinal patch contains 20 different ganglion cell circuits with more than 60 different circuit elements, it is not surprising that there are strict organizational rules for the spatial arrangement of the various circuit components. The first rule is that the cell bodies of different circuits are packed in three different cell body layers. Connections between circuit elements occur between these three layers in two "plexiform" layers of synapses. The second rule is that the dendrites of the various ganglion cell types and the axon terminals of the different bipolar cell types are stacked vertically above each other in the inner plexiform layer, forming ~10 narrow strata (Siegert et al., 2009) (figure 13.4). If the axon terminals of a bipolar cell type and the dendrites of a given ganglion cell type are in different strata, there can be no direct communication between the two. Some bipolar cells have axon terminals in more than one stratum and therefore give input to these strata. There are more ganglion cell types than bipolar cell types, and, therefore, the axon terminals of a bipolar type typically excite more than one ganglion cell type. Consistent with this, each stratum of the IPL tends to contain dendrites of more than one ganglion cell type.

Comparing the stratification of the three main cell classes of the inner retina, the bipolar, ganglion, and amacrine cells, we find striking differences. The processes of ganglion and bipolar cells are generally confined to one or two IPL strata. By contrast certain amacrine cells, such as the AII amacrines, are arranged vertically. With only a narrow horizontal extent, they receive input or provide output in several strata. Other amacrines, such as the starburst cells and polyaxonal cells, are thinly stratified with a wide horizontal extent within the stratum (Masland, 2012). It appears that the "tall and narrow" amacrines and their "flat and broad" classmates have entirely different computational roles.

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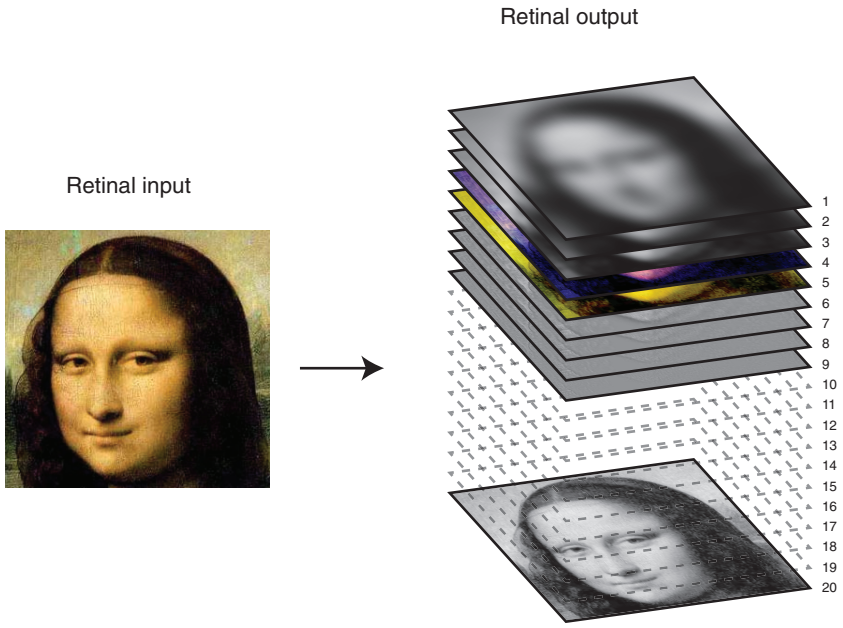


FIGURE 13.1 The retina creates 20 neural representations of the "movie" that enters the eye.

In evolution, the 20 retinal circuits could have been organized into 20 separate pairs of eyes with overlapping fields of view. Although this would have been simpler with regard to the wiring and positioning of the circuit elements, some cell types, such as photoreceptors, are needed for all circuits. Photoreceptors are indeed numerous—they account for >80% of all retinal neurons (Jeon, Strettoi, & Masland, 1998)—and it is economical to share bulk common resources across circuits. The layered structure presented above, which allows an efficient use of common resources, gives rise to a hierarchical organization of cell types. Cells at the bottom of the hierarchy, such as photoreceptors, provide input to many ganglion cell types, whereas a specialized amacrine cell higher in the hierarchy influences few ganglion cell types. Shared resources and cell type hierarchy have important consequences for understanding both retinal processing and visual disorders. Common operations needed for all circuits, such as the gain control required for light adaptation (Fain, 2011), are more likely to be carried out at the front by common elements. Similarly, one expects that cells whose dysfunction gives rise to noticeable visual defects are low in the hierarchy. On the other hand circuit elements responsible for specialized ganglion cell computations are higher in the hierarchy.

The structure of the retina appears to be tailor-made to extract many different features from the visual scene. Under daylight conditions the image is captured by cone photoreceptors. The first processing stage, an interaction with the inhibitory horizontal cells, contributes a step of lateral inhibition that affects all downstream circuits (Kamermans & Fahrenfort, 2004; Wu, 1992). In dim light visual transduction is accomplished by the rods, and their signals are subsequently fed into the cone system by several elaborate pathways (Bloomfield & Dacheux, 2001). From then on the rod-derived signals are largely processed as though they came from cones. For the purposes of this chapter, we therefore focus on circuits downstream of the cone bipolar cells.

Each cone is connected to ~10 types of bipolar cell (Wässle et al., 2009). Some of these bipolar types are distinguished by their neurotransmitter receptors with different kinetics (DeVries, 2000), and in turn they terminate at different levels of the inner plexiform layer. Therefore, the signals in different strata of the inner retina already parse the visual input according to different temporal features. Because there are more ganglion cell types than strata, the activity carried from the outer to the inner retina by each bipolar cell type is further diversified. Different features can emerge within a stratum because ganglion cell types have different spatial extents and different receptors, and their circuits may include different amacrine cell types (Taylor & Smith, 2011). Notably, features carried by bipolar cells can also be recombined locally by the action of vertical amacrine cells.

The elaboration of visual features as discussed above is a columnar operation: restricted in space and organized across or within strata. Retinal processing also occurs laterally across space as a result of the lateral

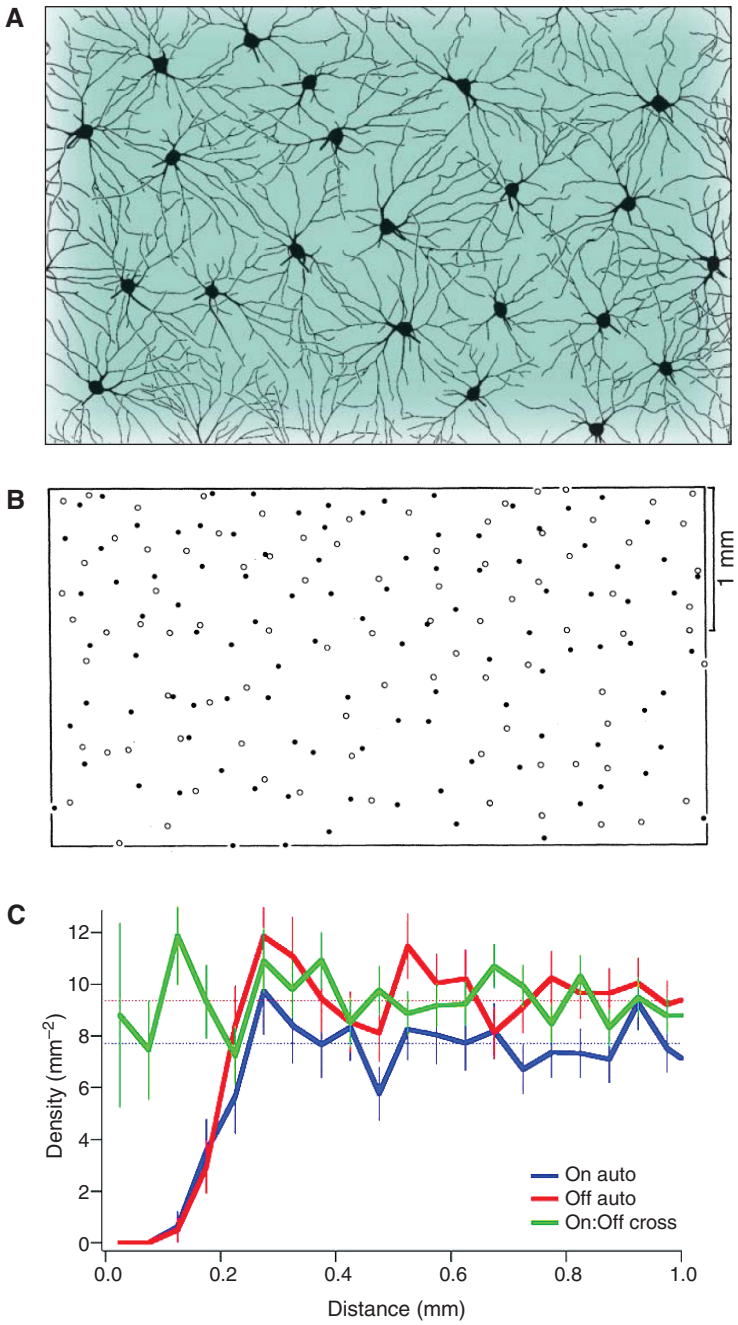


FIGURE 13.2 Ganglion cells of one type cover the retina with a regular mosaic. (A) Cell bodies and dendrites of ON alpha ganglion cells in a wholemount view of the cat retina. Note that the dendrites cover space uniformly, and the cell bodies are placed at regular distances (Wässle, 2004). (B) Cell body locations of ON alpha (open circles) and OFF alpha (closed circles) ganglion cells in a patch of cat retina (Wässle, Peichl, & Boycott, 1981). (C) Each of the two cell types forms a regular mosaic independent of the other. Spatial autocorrelation of the ON (solid blue line) and OFF (red) cell locations, showing the probability per unit area of finding a cell at a given distance from another cell of the same type. Note the prominent hole for distances <0.2 mm. Cross-correlation (green) shows the probability of finding an OFF cell at a given distance from an ON cell. Dotted lines are the average densities of ON (blue) and OFF (red) cells in this patch.

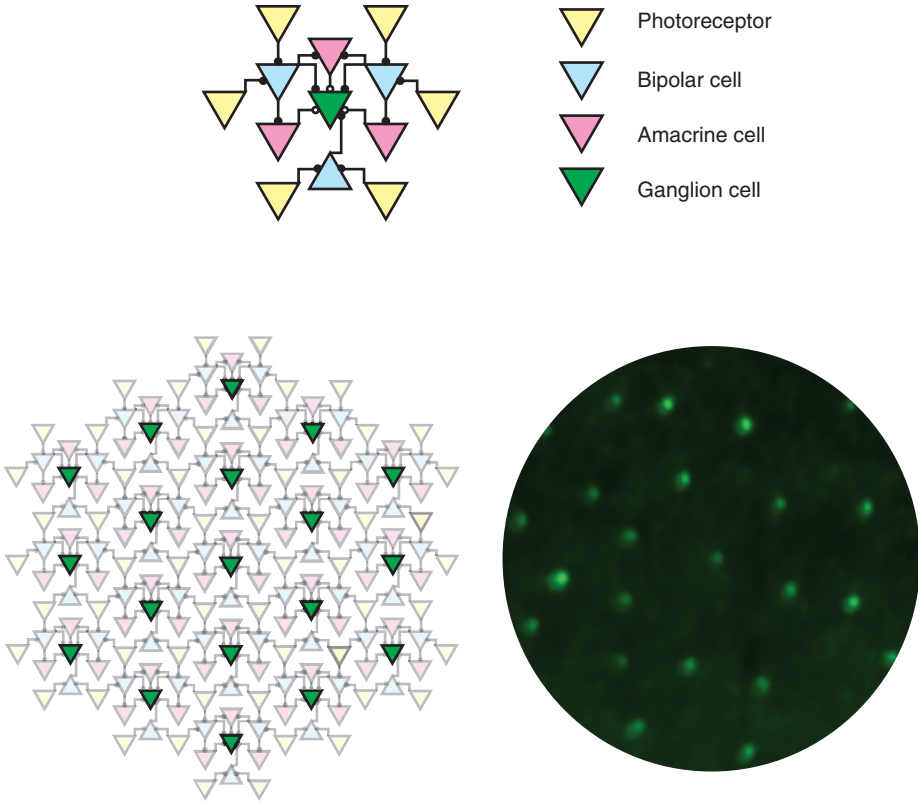


FIGURE 13.3 The unit of retinal infrastructure is a ganglion cell circuit mosaic. (Top) A single ganglion cell surrounded by first- and second-order circuit elements. (Bottom, left) The same circuit is repeated across the retina forming a mosaic. (Bottom, right) Actual mosaic locations of retinal ganglion cells of a specific type.

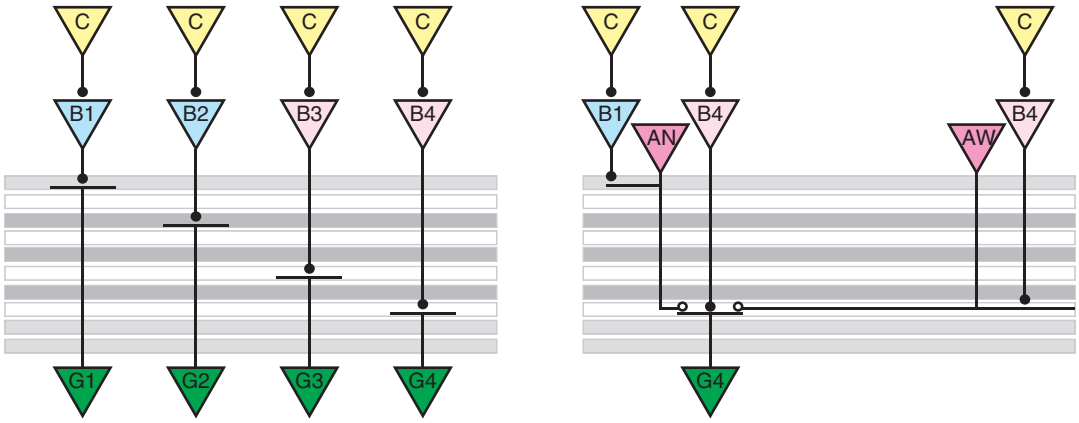


FIGURE 13.4 Retinal features are stacked in the inner retina. (Left) Bipolar cell terminals and ganglion cell dendrites are laid down in different strata of the IPL. (Right) Some amacrine cells (AN) are narrow and tall; their inputs and outputs are in different strata. Other amacrine cells (AW) are wide and flat, with long processes in one stratum; these cells carry information across the local circuits of the same mosaic.

connections by horizontal cells, large amacrine cells, and electric coupling between cells of the same and different types.

Several aspects of the functional organization of the retina are evolutionarily conserved. The layered arrangement of cell bodies and cellular processes, the major cell classes, and their general connectivity are common to all vertebrates. In comparing across mammals from mouse to human, one finds even greater similarities that extend to the level of cell types and

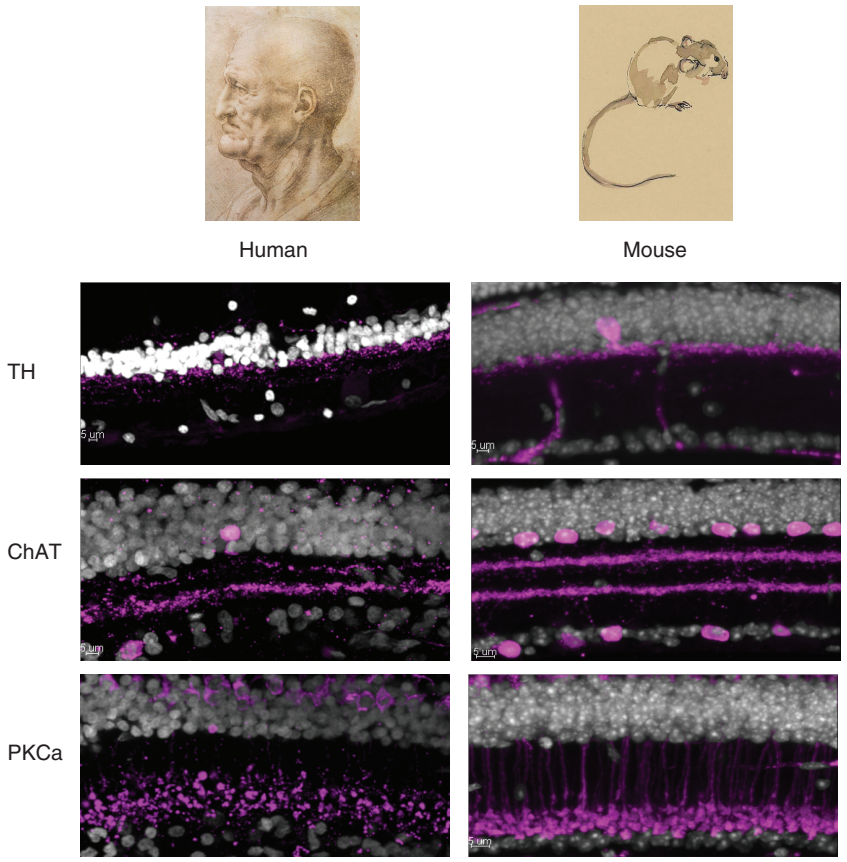


FIGURE 13.5 Comparing the retinas of humans and mice. Vertical sections of human (left) and mouse (right) retinas. Staining with three antibodies against tyrosine hydroxylase (TH), choline acetyl transferase (ChAT), and protein kinase C alpha (PKCa) identifies strata with similar positions in the two species.

their lamination (figure 13.5). Several antibody markers label the same strata across these species, and a number of cell types are conserved. For example, both the mouse (Puller & Haverkamp, 2011) and the macaque (Dacey & Packer, 2003) have a bipolar cell specialized for signals from blue cones. In table 13.1 we compile a catalog of retinal ganglion cell types across the major species in which the topic has been studied. This illustrates a number of "canonical" cell types found in many species (Berson, 2008). For other cell types the correspondence is more difficult to identify, although this may improve as we learn more about their visual responses.

There are also distinct differences among mammals. For example, in the mouse retina the spacing of cells in a given mosaic is almost uniform across the retina; at the other extreme, in the primate retina the cell density rises sharply toward a small patch of retina in the center called the fovea. The fovea has, therefore, high spatial resolution and is used for encoding details in the visual scene. Different mammals have different degrees of nonuniformity in the spatial density of ganglion cell mosaics, resulting in specialized retinal regions such as the area centralis in cats or the visual streak in rabbits.

A second difference is in the circuits processing color. Most mammals have two cone types, one expressing a short-wavelength pigment and the other medium wavelength. Some primates also have cones with a long-wavelength pigment. The circuitry connected to short-wavelength cones has common circuit motifs across mammals, such as the specialized blue cone cell, but the differential handling of color information for medium and long wavelengths is unique to a group of primates. Some mammals such as mice and rats express more than one pigment in many of their cones, and the ratio of these pigments varies in a dorsoventral gradient. Because of this gradient the part of the eye that looks at the blue sky is more sensitive at short wavelengths, and the part that looks at the ground is more sensitive at longer wavelengths.

The anatomical evidence that the retina contains 20 ganglion cell mosaics along with their associated circuits has emerged gradually over the last 50 years.

TABLE 13.1

A catalog of retinal ganglion cell types in the mammalian retina[a]

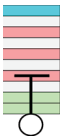
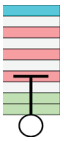
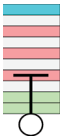
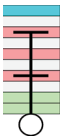
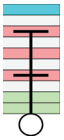
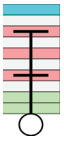
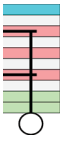
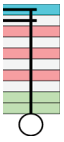
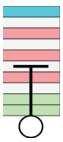
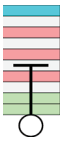
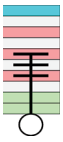
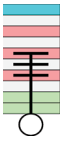
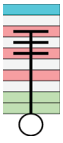
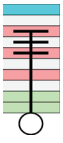
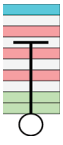
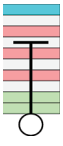
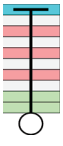
Icon	Mouse	Rabbit	Cat	Macaque	Properties
	M1[1,2]			Outer melanopsin[3]	Large sparse dendrites. ON sluggish synaptic response.
	M2[1,2]			Inner melanopsin[3]	Large complex dendrites. ON sluggish synaptic response.
	ON DS temporal[4]	ON DS temporal[5]			ON DS. Preferred direction temporal.
	ON DS ventral,[4] Spig-1 EGFP[6,7]	ON DS ventral[5]			ON DS. Preferred direction ventral.
	ON, DS dorsal[4,6,7]	ON DS dorsal[5]			ON DS. Preferred direction dorsal.
	ON–OFF DS temporal[8]	ON–OFF DS temporal[9]	Theta?[10]	Recursive bistratified?[11]	ON-OFF DS. Preferred direction temporal.
	ON-OFF DS dorsal[8]	ON-OFF DS dorsal[9]	Theta?[10]	Recursive bistratified?[11]	ON-OFF DS. Preferred direction dorsal.
	Drd4-EGFP,[12] W9[8]	ON–OFF, DS nasal[9]	Theta?[10]	Recursive bistratified?[11]	ON-OFF DS. Preferred direction nasal.
	BD-CreER,[8] Hb9-EGFP[13]	ON–OFF, DS ventral[9]	Theta?[10]	Recursive bistratified?[11]	ON-OFF DS. Preferred direction ventral. Asymmetric dendrites in mouse.
	JAM-B[14]	OFF coupled[15], G3[16]			OFF DS. Preferred direction ventral. Highly asymmetric dendrites point ventral.

TABLE 13.1

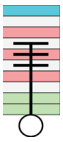
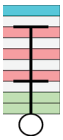
A catalog of retinal ganglion cell types in the mammalian retina[a] (Continued)

Icon	Mouse	Rabbit	Cat	Macaque	Properties
	ON alpha,[17] PV-Cre-1[18]	ON alpha[19]	ON alpha[20,21]		Large dendritic field. ON response.
	PV-Cre-3[18]	ON parasol[15]		ON parasol[22]	Medium dendritic field. ON response.
				ON smooth[23]	
		ON beta[15]	ON beta[24]		Small dendritic field. ON response.
				ON midget[22]	Small dendritic field. ON response.
		OFF beta[15]	OFF beta[24]		Small dendritic field. OFF response.
				OFF midget[22]	Small dendritic field. OFF response.
	PV-Cre-4[18]	OFF parasol[15]	Eta?[25]	OFF parasol[22]	Medium dendritic field. OFF response.
	OFF alpha transient[17], PV-Cre-5[18]	OFF alpha[19]	OFF alpha[24]	OFF smooth[23]	Large dendritic field. OFF response.
	OFF alpha Sustained,[17] PV-Cre-6[18]	OFF delta[15]	OFF delta[10]		Large dendritic field. OFF sustained response.

continued

Table 13.1

A catalog of retinal ganglion cell types in the mammalian retina[a] (Continued)

Icon	Mouse	Rabbit	Cat	Macaque	Properties
		ON-bistratified?[15]		Small-bistratified[11]	ON excitation, OFF inhibition, blue-yellow opponent in macaque.
				Large-bistratified[11]	Blue-yellow opponent.
	W3[26]	Local edge Detector[5,27]	Zeta[28]	Broad thorny[11]	ON–OFF, strong surround, fast ON–OFF inhibition.
			Epsilon?[29]	Recursive monostratified[11]	
				ON narrow thorny[11]	
				OFF narrow thorny[11]	
		Uniformity Detector[30]	Uniformity Detector[31]		Transiently suppressed by visual stimuli. ON-OFF response. Dendrites just outside the ChAT bands.

[a]Each graphic icon illustrates stratification of the dendritic tree in the IPL, divided into 10 laminae (Siegert et al., 2009). For each type we list the defining morphological and physiological features and identify its plausible correspondences in four species, as supported by the cited literature. For further detail on cross-species comparisons, see Berson (2008). Note that many of these ganglion cell types have only sparse and partial entries, emphasizing the need for future work to round out the catalog of retinal output signals.

References: [1]Hattar et al. (2006). [2]Schmidt et al. (2011b). [3]Dacey et al. (2005). [4]Sun et al. (2006). [5]Barlow, Hill, & Levick (1964), but see Kanjhan & Sivyer (2010) and Hoshi et al. (2011) for finer divisions. [6]Yonehara et al. (2009). [7]Yonehara et al. (2008). [8]Kay et al. (2011). [9]Oyster & Barlow (1967). [10]Isayama, Berson, & Pu (2000). [11]Dacey (2004). [12]Huberman et al. (2009). [13]Trenholm et al. (2011) erroneously identified the preferred direction as temporal. [14]Kim et al. (2008). [15]Roska, Molnar, & Werblin (2006). [16]Hoshi et al. (2011). [17]Pang, Gao, & Wu (2003). [18]Münch et al. (2009). [19]Zhang et al. (2005). [20]Cleland, Levick, & Wässle (1975). [21]Wässle, Peichl, & Boycott (1981). [22]Dacey & Packer (2003). [23]Crook et al. (2008). [24]Wässle, Boycott, & Illing (1981). [25]Berson, Isayama, & Pu (1999). [26]Kim et al. (2010). [27]van Wyk, Taylor, & Vaney (2006). [28]Berson, Pu, & Famiglietti (1998). [29]Pu, Berson, & Pan (1994). [30]Sivyer & Vaney (2010). [31]Cleland & Levick (1974).

However, with exception of a few ganglion cell types, the functional distinctions among all these visual pathways have been more difficult to understand. Recent technical advances have greatly accelerated this research program, in particular the ability to genetically mark and manipulate cell types (Azeredo da Silveira & Roska, 2011; Huberman et al., 2009; Kay et al., 2011; Kim et al., 2008; Yonehara et al., 2008). The fundamental new insight is that the gene expression patterns of distinct cell types are quite different. With advanced molecular,

genetic, and viral tools one can hijack the cellular machinery that controls these expression patterns to manipulate neurons selectively. Now it is possible to target specific cell types for physiological recording, to modify them, to observe the effects on network function, and—importantly—to communicate the scientific results without ambiguity about the identity of retinal neurons under study.

In the following two sections we discuss what these various ganglion mosaics extract from the visual scene and how the associated circuitry performs the necessary computations.

PIXEL SENSORS VERSUS FEATURE DETECTORS

What is the role of the retina for the overall function of the visual system? In the conventional view—still dominant in textbooks and held by many vision researchers today—the retina's primary task is to get the visual image transmitted to the brain, where the cortex and other heavy-duty circuits can get on with the challenges of processing the information. For that purpose, the retina must first format the image signals a bit to deal with the vicissitudes of the physical environment. Because the illumination conditions can change so dramatically, the retina applies a gain control through the cellular processes of light adaptation. And because natural images tend to be highly redundant in their pixel patterns, the retina performs some image compression through the circuits that implement lateral inhibition. In this view the defining characteristics of retinal ganglion cell function are the center-surround receptive field and gain control.

In an alternate view the retina shapes the visual representation much more dramatically. Rather than simply recoding the image for more efficient transmission through the optic nerve, the retina extracts from the scene only a few specific features and transmits those very selectively to the brain through several specific image channels. In this picture much of the raw information in the visual scene is discarded. The ganglion cells transmit signals that result from very nonlinear computations, for example, the speed of image motion in a specific direction, that relate only distantly to the raw data of image intensity.

Both of these rival conceptions of retinal processing date back to the earliest days of retinal neurophysiology (Barlow, 1953; Kuffler, 1953; Lettvin et al., 1959). Today, with a complete catalog of ganglion cell types within reach, one can envision an end to this debate. As usual, the resolution will likely be a compromise. It appears that a few ganglion cell types match the notion of "pixel sensors," whereas many others are better described as "feature detectors." Here we give these two concepts explicit meaning and assess how they apply to the different retinal pathways.

Pixel Sensor

In its idealized form a pixel sensor ganglion cell would simply measure the light intensity at a particular point on the retina and convey that value directly to the brain. A technological example of this is a single pixel sensor of a digital camera. In practice, of course, ganglion cells do not observe light at a single point but over a receptive field. Furthermore, they cannot signal instantaneously but integrate the light over the retina's response time. Finally, they cannot put out a continuous signal but only spikes. With these realistic constraints we can define a pixel sensor retinal ganglion cell as one that performs these image operations: compute a weighted average of the light intensity over the receptive field and the integration time and then use the result to modulate the firing rate accordingly (Meister & Berry, 1999). Such neural responses are generally characterized as "linear" because they derive from a linear summation of light intensity across time and space in the receptive field (see appendix 13.1).

Remarkably, there are in fact retinal ganglion cells that approach this ideal. For example, the midget P cells in the primate fovea (including our own) receive excitation mostly from a single bipolar cell, which in turn gets input from a single cone (Kolb & Marshak, 2003). Their response is truly dominated by a single pixel in the photoreceptor array, and thus, there is no opportunity for sophisticated nonlinear image computations. Actual response measurements from ganglion cells in the fovea are rare (McMahon et al., 2000), but midget cells at greater eccentricity seem to integrate light in a mostly linear manner (Benardete & Kaplan, 1997a, 1997b).

Similarly, the X cells of the cat retina respond quite linearly to light (Enroth-Cugell et al., 1983). They have a substantial maintained firing rate when the stimulus remains constant. When the light increases they fire more; when it decreases they fire less (or vice versa, depending on polarity of the ganglion cell). A brightening in one part of the receptive field can be counterbalanced by a dimming in another part to completely cancel the response, which illustrates that the circuit sums light over space (Enroth-Cugell & Robson, 1966). If the visual stimulus varies in time like a sine-wave function, the firing rate is modulated like a sine wave of the same frequency; this is a common indicator of linear processing.

Both macaque P cells and cat X cells are the smallest ganglion cells in the respective retinas. A tempting

suggestion is that in any given species the ganglion cells with the finest receptive fields are pixel sensors that convey a high-resolution version of the scene to the brain. However, the mouse violates this simple notion: The smallest ganglion cells in the mouse retina (called local edge detectors or "W3" cells) do not participate at all in the signaling of routine visual scenes and respond only very sparsely to specific events (Zhang et al., 2012).

Feature Detector

A prototype of feature detection, again using a man-made example, would be the face-detection circuit used in current point-and-shoot cameras. Recognizing a face in the visual scene requires an interesting combination of selectivity and invariance: selectivity so the detector remains silent in the many image regions that do not contain a face; invariance so it responds to many different faces under different views and illuminations. Obviously, this kind of performance requires computations that are very different from mere linear filtering of the image.

Again, there exist retinal ganglion cell types whose performance approaches this ideal. One example would be the "bug perceivers" described early on in the frog retina (Lettvin et al., 1959): These cells fire if a small fly moves against a patterned background but not if the same fly and the background move together. Among the new ganglion cell types that were identified or better explored in recent years, most have the characteristics of feature detectors: highly nonlinear behavior, selectivity for a certain visual feature, and invariance to many other aspects of the scene. Often one can understand the feature selectivity from ecological and ethological considerations: the particular images produced by the natural environment, the needs of the visual system, and the observer's own behavior during active vision. In the following section we illustrate some of these cases.

MANY RETINAL GANGLION CELLS ARE FEATURE DETECTORS

For each of the sample ganglion cell types we begin by discussing what it computes, namely what aspects of the visual scene define its selectivity and its invariance. In many cases we also understand how this stimulus selectivity emerges from the interaction of retinal neurons, and we present these explanations in the form of a circuit diagram that summarizes the relevant connectivity and signal flow. These circuits are not intended to be complete and exhaustive, so some cautionary comments are in order.

First, for simplicity all the circuits begin with bipolar cells. The outer retina circuits of photoreceptors and horizontal cells perform some low-level formatting of the visual signal, including light adaptation and lateral inhibition. As a result of this processing, bipolar cells have simple center-surround receptive fields. They produce essentially linear light responses under the same conditions where ganglion cells act as nonlinear feature detectors (Baccus et al., 2008). Therefore, not much computation has occurred by the bipolar cell level. Interesting selectivity emerges largely in the inner retina through the interaction of bipolars, amacrines, and ganglion cells. Second, the circuit diagram is intended as schematic, not accurate in detail. For example, the diagram does not spell out the correct number of elements: a single component marked "A" may stand for an entire population of amacrine cells of that type. Third, the diagram is not exhaustive: It spells out the minimal circuit that has been confirmed and is essential to producing the function in question, but the full circuit likely includes other components.

Y Cells

These ganglion cells drew attention in early studies of cat retina because they clearly violate the notion of linear summation (Enroth-Cugell & Robson, 1966). If the receptive field center is divided into a dark half and a light half, and then the two regions are switched, the X cells described above will remain silent because the total light on the receptive field remains unchanged. By contrast, the Y cells fire a strong burst on each of these transitions. Y cells come in both polarities: An ON Y cell is excited transiently by an ON transition in any small region of the receptive field, even if it coincides with a dimming elsewhere. These neurons are exquisitely sensitive to a moving pattern because any such motion will produce a brightening somewhere in the receptive field (figure 13.6A). The same applies to OFF Y cells, which are excited by local OFF transitions. Thus, the Y cell shows a form of invariance: It responds well to a fine stimulus independent of where it occurs within the receptive field or of the direction of motion. However, the Y cells are not usually described as selective. They do have an antagonistic surround that also includes some nonlinear pooling over space similar to that in the center (Crook et al., 2008; Enroth-Cugell & Freeman, 1987), but it has not been associated with isolating any specific visual feature.

The unique response properties of the Y cell suggest that its circuit pools excitatory inputs from small subregions in the receptive field whose signals are individually rectified (Enroth-Cugell & Freeman, 1987) (figure

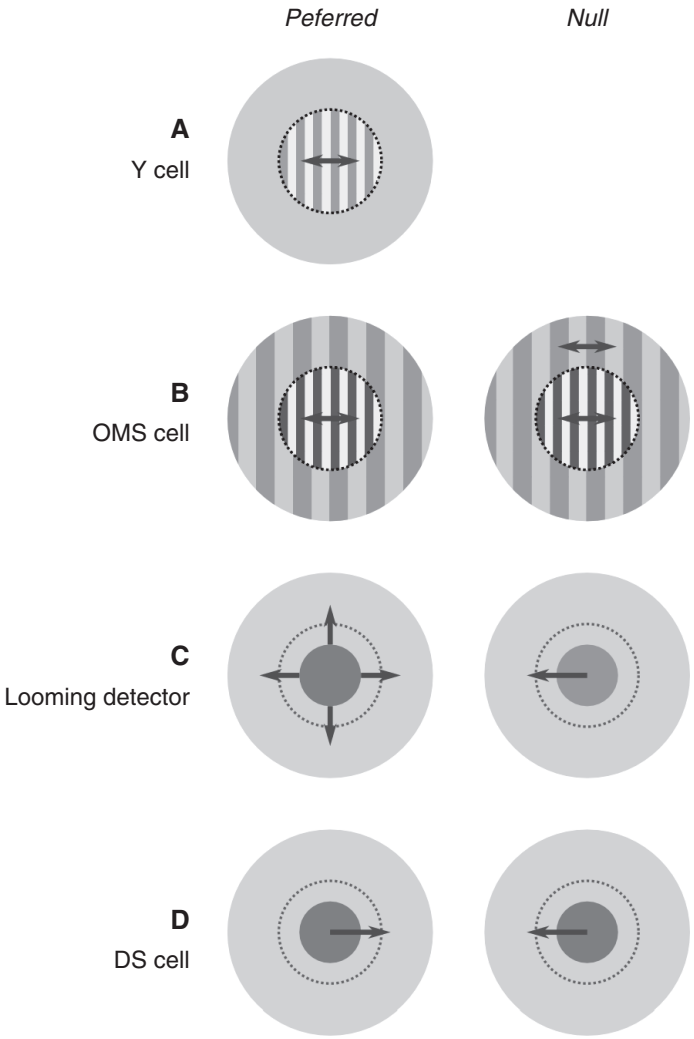


FIGURE 13.6 Visual features extracted by retinal ganglion cells. For each of the four types of ganglion cells highlighted in the text, this illustrates visual stimuli that excite the neuron (preferred) or suppress it (null). Arrows indicate movement. Dotted line marks the receptive field center. The examples are taken from conditions that occur during natural vision: (A) excitation by pattern motion on the receptive field center (Y cell and OMS cell); (B) suppression by a simultaneous pattern motion in the surround (OMS cell); (C) excitation by expanding motion but not translating motion (looming detector); and (D) movement in one direction but not in the opposite direction (DS cell).

13.7A).There is good evidence now that the subfields correspond to individual bipolar cells: These interneurons match the size of the subfields (Crook et al., 2008; Demb et al., 2001), and their synaptic output can indeed show strong rectification (Baccus et al., 2008; Demb et al., 2001). At a rectifying bipolar cell synapse, only the depolarizations of the bipolar cell are transmitted to the ganglion cell as excitation, whereas hyperpolarizations have no postsynaptic effect. This rectification arises when the basal transmitter release rate at the bipolar cell synapse is low because the resting potential lies below the activation voltage of synaptic calcium channels (Matsui, Hosoi, & Tachibana, 1998; Palmer, 2010). The Y-cell circuit (figure 13.7A) explains qualitatively how the neuron responds to moving textures regardless of the direction or the spatial pattern. Small features of the texture activate different bipolar cells as they move around. Bipolar cells often have biphasic impulse responses (Awatramani & Slaughter, 2000; Baccus et al., 2008; DeVries, 2000), which make them sensitive to rapid changes but not to static patterns. The rectification at the bipolar cell synapse then allows accumulation of these transient signals from the activated bipolars while it prevents cancellation from other bipolars that experience opposite stimulus changes. A time-varying velocity of the image pattern leads to a time-varying firing rate, and the simple Y-cell circuit model (figure 13.7A) can indeed predict this

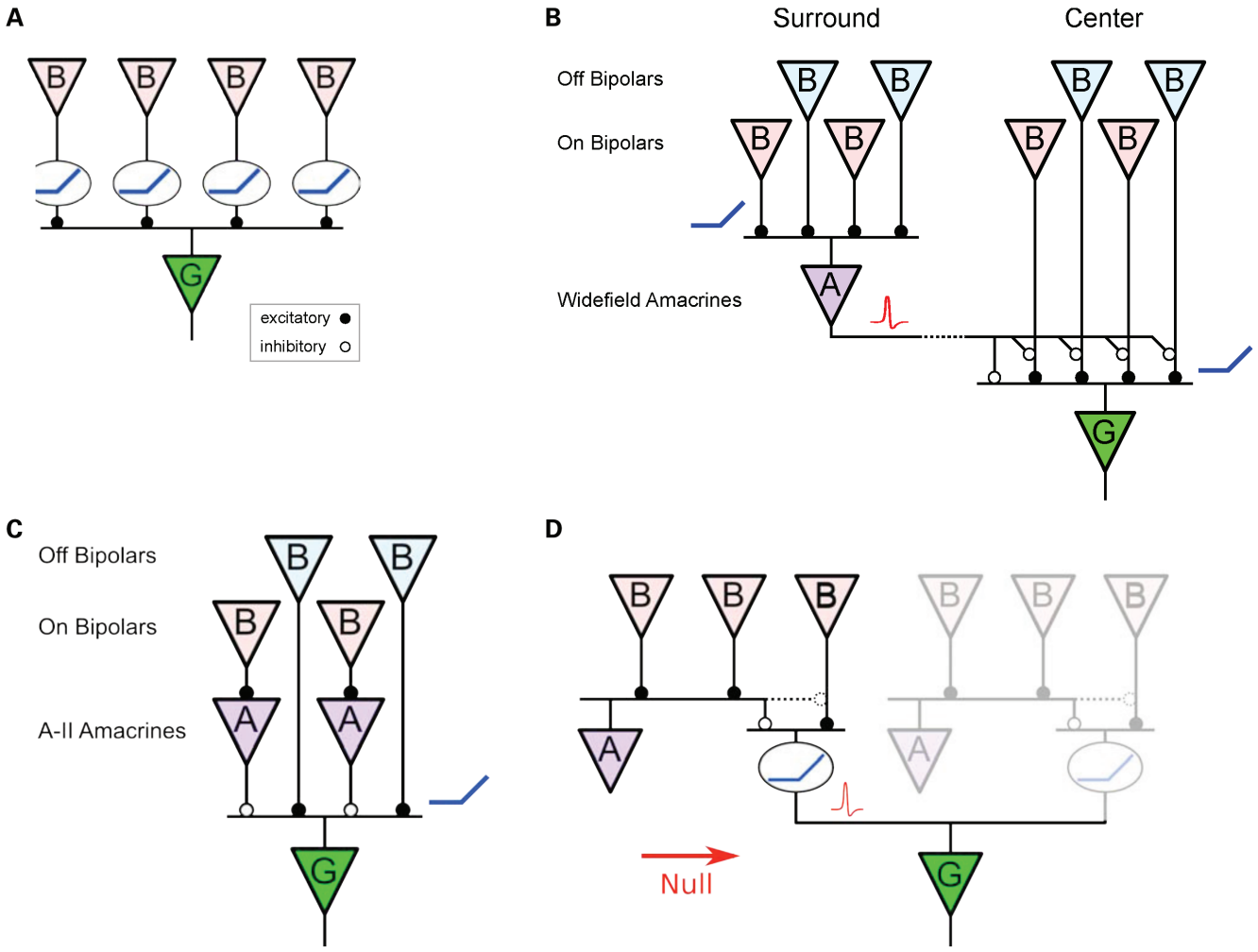


FIGURE 13.7 Retinal circuits leading to different feature detector ganglion cells. (A) The Y-type ganglion cell. This ganglion cell collects excitation from many bipolar cells. The bipolar cell synapses are rectifying: At baseline the release rate of transmitter is low, so depolarization increases transmitter release, but hyperpolarization has little or no effect. In subsequent panels, this rectifying quality is assumed for all bipolar cell synapses. (B) The object-motion-sensitive cell. Note that the ganglion cell pools over both ON and OFF bipolars, but this process is gated by the action of a wide-field amacrine cell. (C) The looming detector. Again there is pooling over ON and OFF channels, but with opposite sign because of an interposed narrow amacrine cell. (D) The direction-selective ganglion cell. The asymmetric interaction that defines the null direction occurs between the dendrite of a starburst amacrine cell and local bipolar cells. An additional threshold nonlinearity arises from spike generation within the dendritic tree of the ganglion cell.

output quantitatively (Baccus et al., 2008; Enroth-Cugell & Freeman, 1987; Victor & Shapley, 1979).

The defining Y-cell characteristic of nonlinear summation over space has now been encountered in many types of ganglion cell, but these differ strongly in other response features that confer certain selectivities, as seen in the following examples.

Object-Motion-Sensitive Cells

Ganglion cells of the "bug perceiver" type (Lettvin et al., 1959) have now been identified in several species, and they likely represent one of the canonical types. They have been called "OMS" cells in the salamander (Ölveczky, Baccus, & Meister, 2003), "W3" cells in the mouse retina (Zhang et al., 2012), and "local edge detector" cells in the rabbit retina (Levick, 1967). They produce transient responses to both ON and OFF events in the receptive field center; thus, they process the stimulus in a very nonlinear fashion, beyond that of the Y cells. They are highly sensitive to moving patterns within the receptive field center, for the most part independent of the precise content of the pattern. But if the receptive field surround experiences pattern

motion, and the motion is synchronized with that of the center, the ganglion cell remains silent (figure 13.6B).

One can speculate that such ganglion cells would be very useful for detecting a moving object within a visual scene. The ethological challenge here is that the eye of the observer is almost always in motion, be it from small fixational jitter or from the observer's own locomotion through the environment (Kowler, 1990; Martinez-Conde, Macknik, & Hubel, 2004). Thus, the default condition on the retina is one of incessant image flow, and identifying a moving object requires more than simply flagging locations where the image moves. Instead, the computation performed by the OMS cells identifies image regions that move with a trajectory different from the surroundings. These are likely small objects that move relative to the larger background, such as bugs among leaves.

We now understand how this computation is performed. The OMS ganglion cell pools excitation from many bipolar cells with rectifying synapses (figure 13.7B). Moreover, unlike the typical Y cell, it receives excitation from both ON- and OFF-type bipolars (Levick, 1967; Zhang et al., 2012). Thus, movement of a small object anywhere within the receptive field will depolarize some bipolars and hyperpolarize others, and in each case the ganglion cell receives a short pulse of excitation. This will happen regardless of the exact shape or pattern of the object or its direction of motion. We see that the nonlinear summation over space and over bipolars of opposite polarity already introduces a great deal of invariance.

What about selectivity? The same ganglion cell receives strong inhibition from amacrine cells in the receptive field surround, up to large distances from the center. The amacrine cell synapses act both directly on the ganglion cell and at the bipolar cell terminal, where they suppress transmission presynaptically (Baccus et al., 2008; Zhang et al., 2012). The amacrine cells are themselves driven by the same kind of nonlinear pooling mechanism that excites the ganglion cell (Baccus et al., 2008; Russell & Werblin, 2010; van Wyk, Taylor, & Vaney, 2006; Zhang et al., 2012). So if the visual pattern in the surround moves at the same time as the pattern in the center, excitation and inhibition cancel each other in the ganglion cell, and it remains silent. But if a spurt of motion in the center occurs independently of that in the surround, the ganglion cell fires (Ölveczky, Baccus, & Meister, 2003). This selectivity can be exquisite; for example, the mouse W3 ganglion cell remains completely silent during natural stimuli that result from the animal's own locomotion because they contain a great deal of global optic flow. These neurons are induced to fire only in special conditions where a small target moves against a static background (Zhang et al., 2012).

Looming Detectors

These ganglion cells, called PV5 in the mouse retina, fire strongly when a dark spot expands within the receptive field, as would occur when an object approaches the observer (figure 13.6C). Again, the receptive field center is sensitive to both ON and OFF events in the stimulus but now with opposite sign (Münch et al., 2009). A local dimming produces a transient excitation, whereas a local brightening produces transient inhibition. When a dark spot moves through the receptive field laterally, the leading edge produces excitation, and the trailing edge inhibition; the two effects cancel, and the ganglion cell remains silent. However, if a dark spot expands within the receptive field, there is no ON edge to contribute inhibition, and the ganglion cell fires strongly. A symmetric looming detector for bright objects has not been found.

The circuit that achieves the approach-specific responses is based on the pooling of excitation from the OFF pathway and inhibition from the ON pathway (figure 13.7C). The PV5 ganglion cell is excited by OFF bipolar cells and inhibited by AII amacrine cells (Münch et al., 2009). The AII cell is a local interneuron that in turn is excited by ON bipolar cells. Again, these synaptic inputs to the ganglion cell are rectified. As an edge travels across the receptive field, it stimulates in turn each of the small bipolar-size subunits, triggering a transient pulse of excitation or inhibition. When a dark object expands over the receptive field, the excitatory pulses are unopposed by any inhibition, and the ganglion cell fires throughout the period of expansion. If the object moves laterally, on the other hand, excitation from its leading edge is balanced by inhibition from the trailing edge, and the ganglion cell remains silent.

Inhibition thus serves to suppress responses to the nonpreferred motion signal, similar to the strategy of the OMS cell circuit. In contrast to the OMS cells, however, it is essential that the inhibition act postsynaptically rather than presynaptically at bipolar terminals because signals from different parts of the object must be combined. Again, rectification at the bipolar synapse constitutes an essential element in the circuit, but here we encounter an additional twist. This ganglion cell combines rectified excitation and inhibition from pathways of opposite polarities. It has been suggested that such "crossover inhibition" serves to make the overall response of ganglion cells more linear (Werblin, 2011), with the ON pathway implementing responses to brightening and the OFF pathway those to dimming. This is

not the case for PV5 cells. A neuron that pools the light stimulus linearly over its receptive field can at best make a dimming sensor but will not be selective for looming objects. By contrast, the looming detector is excited by an expanding dark edge, even if other parts of the receptive field experience a gradual brightening. This can be understood if the inhibitory pathway has a high threshold such that a gradual brightening is ignored but the sudden brightening at a traveling ON edge gets transmitted (Münch et al., 2009).

Note that the AII amacrine cell in this circuit also serves an entirely different function during scotopic vision, namely to feed rod signals into the cone bipolar cells (Bloomfield & Dacheux, 2001; Demb & Singer, 2012). This is an interesting example of a single cell type that serves quite different roles, even signaling in opposite directions (Manookin et al., 2008).

Direction-Selective Cells

Again these ganglion cells are very sensitive to movement within the receptive field. However, they respond preferentially to motion in one direction and remain silent to motion in the opposite direction (Vaney, Sivyer, & Taylor, 2012) (figure 13.6D). In some cases this direction selectivity applies even for tiny spots moving as little as 1/10 of the RF diameter; thus, the computation is performed on a very local scale, and the overall result is pooled over the receptive field (Barlow & Levick, 1965). Such a direction-selective (DS) cell is invariant to the precise pattern or shape that moves within its receptive field but selective for the direction in which it moves.

Three classes of DS ganglion cells have been identified, distinguished by the polarity of the response in the receptive field center. ON–OFF DS cells are excited transiently by both ON and OFF steps of light (Barlow & Levick, 1965; Weng, Sun, & He, 2005), ON DS cells by ON steps only (Oyster, 1968; Sun et al., 2006), and OFF DS cells by OFF steps (Kim et al., 2008). These three classes encompass multiple distinct cell types. The four types of ON–OFF DS cells in the mammalian retina have different preferred directions of motion in the receptive field center, aligned with the cardinal directions on the eye: dorsal, ventral, nasal, and temporal (Elstrott et al., 2008; Kay et al., 2011; Oyster, 1968). Motion in the surround exerts a powerful suppression (Barlow & Levick, 1965; Wyatt & Daw, 1975). As for OMS cells, this suppression is particularly strong when surround motion matches the center motion in speed and direction (Chiao & Masland, 2003; Ölveczky, Baccus, & Meister, 2003). Thus, the ON–OFF DS ganglion cells appear tuned to the local motion of objects within the scene. Their axons project to both the thalamus and the superior colliculus (Huberman et al., 2009; Kay et al., 2011; Stewart, Chow, & Masland, 1971; Vaney, Sivyer, & Taylor, 2012) and thus make this information available to the two major streams for higher visual processing. By contrast, the ON DS cells include three types, with preferred directions on the retina roughly dorsal, ventral, and temporal (Oyster, 1968; Yonehara et al., 2009). They are not suppressed by surround motion and respond very well to moving patterns that extend over the whole retina. Thus, they can serve to encode the overall optic flow in the scene, as produced by slip of the image on the retina when the animal or the eye moves relative to the scene. Interestingly these neurons do not project to the major visual pathways but exclusively into the accessory optic system (Buhl & Peichl, 1986; Oyster et al., 1980; Yonehara et al., 2008, 2009) whose role is to sense self-motion for the regulation of eye movements (Simpson, 1984; Giolli, Blanks, & Lui, 2006). Finally, a single type of OFF DS cell has been described that prefers motion in the ventral direction (Kim et al., 2008). Again, these neurons project to both superior colliculus and thalamus, but their role in downstream processing remains unclear. This list represents the consensus types of DS ganglion cells (DSGC), but there are recent indications that the population may yet split into finer types whose distinctions and downstream projections remain to be established (Hoshi et al., 2011; Kanjhan & Sivyer, 2010; Rivlin-Etzion et al., 2011).

The retinal circuitry underlying the ON–OFF DSGC has been studied intensely, and we now have a great wealth of physiological, anatomical, and computational results available. As may be expected, there is some discordance in this large set of reports. As a result it has become difficult to integrate all the observations into a coherent model of neuronal circuitry. We present here one subcircuit that almost certainly contributes to the observed direction selectivity, although it leaves some aspects unexplained (figure 13.7D). In this we largely follow a recent review (Vaney, Sivyer, & Taylor, 2012), which is recommended for an overview of this retinal subcircuit.

The discoverers of retinal direction selectivity proposed a simple model of how it might be achieved through the interaction of excitatory and inhibitory synaptic inputs to the ganglion cell (Barlow & Levick, 1965). This model has four required ingredients: spatial asymmetry—inhibition should be laterally offset from excitation; temporal asymmetry—inhibition should be delayed relative to excitation; nonlinear pooling—the ganglion cell responds only if its pooled synaptic input exceeds a threshold; and small subunits—this pooling

should occur independently within many small subunits of the receptive field, to explain the selectivity for even small motions. There now exists compelling evidence that assigns these various functions to specific cellular elements in the inner retina (Vaney, Sivyer, & Taylor, 2012).

In this circuit (figure 13.7D), the independent subunits correspond to individual electrotonically distinct dendritic compartments of the DSGC. Each such compartment pools excitation and inhibition and generates a spike if the net depolarization exceeds a threshold. These dendritic spikes travel to the soma reliably and cause a spike in the axon. Each compartment receives excitation from bipolar cells and inhibition from starburst amacrine cells (SACs). Whereas the receptive field of a bipolar cell directly overlies its terminal, the receptive field of the starburst cell is displaced laterally toward the null side (the side from which null stimuli arrive). This spatial asymmetry results from a peculiar rule of connectivity between the two cell types. First, although the SAC receives bipolar cell inputs all along the dendrite, its inhibitory terminals are at the dendritic tips. Second, the DSGC connects preferentially to those SAC dendrites that course in the null direction, by a factor of 10 to 1 (Briggman, Holmstaedter, & Denk, 2011). As a result the receptive field of the contributing starburst dendrite is displaced toward the null side of the DSGC (figure 13.7D). Another cellular mechanism contributes to asymmetry: The depolarization at the SAC dendritic tip is itself direction-selective, favoring outward motion over inward motion (Euler, Detwiler, & Denk, 2002). Thus, the DSGC receives stronger inhibition for null than for preferred motion. Finally, the temporal delay and extended duration of inhibition result from the additional synapse in the SAC pathway as well as the prolonged time course of GABA release.

Given this circuit, one can understand the direction-selective processing of moving stimuli (figure 13.7D). A small spot moving in the null direction first excites the SAC and then the bipolar cell. Because the SAC input is delayed and more sustained, inhibition and excitation arrive at the GC dendrite at the same time, the resulting signal remains below threshold, and no spikes are produced. The same sequence recurs in each of the other compartments. With motion in the preferred direction, excitation from the bipolar cell is triggered before the inhibition can quench it, and this launches a dendritic spike followed by somatic firing. The same circuit is found in both the inner and the outer starburst stratum of the IPL, allowing the DSGC to process ON and OFF edges independently.

As mentioned above, this should be considered a minimal circuit. It leaves a number of observations unexplained, for example, that excitatory inputs to the DSGC are already direction selective (Borg-Graham, 2001; Taylor & Vaney, 2002). This might occur if SACs also inhibit the bipolar cell terminals (figure 13.7D). Starburst amacrines also release acetylcholine, which excites the DSGC; the function of these synapses is unclear. The minimal circuit also does not account for the suppressive effects of motion in the surround, which may involve input from another type of amacrine cell.

The circuits for the other DS ganglion cells are less well understood. Some ON DS cells seem to interact with starburst amacrines (Yonehara et al., 2011) much as the ON–OFF DS cells do. However, the newly described ON DS types that ramify outside the starburst stratum suggest there must be other mechanisms to achieve the same effects (Hoshi et al., 2011). The same holds for the OFF DS cells. This cell type has a strongly asymmetic dendritic tree that points in the preferred direction of motion (Kim et al., 2008). In that case the key asymmetry may well be provided by the morphology of the ganglion cell itself, although the details of its function remain to be explored.

Diverse Circuits Using Common Components

Although the various feature detectors discussed above seem to select very different visual features, their underlying circuits share much in common. In fact, all these circuits make use of the same kinds of simple elements: small-field bipolar cells of two polarities, rectification at a bipolar cell synapse, spatial pooling, narrow-field amacrines for sign inversion, wide-field amacrines for lateral inhibition. The only differences lie in the sequence and combination of the elements. As in the man-made field of electronics, varying the arrangement and combination of simple elements results in dramatically different functions. Still the above account falls short of filling out the catalog of all 20 morphological ganglion cells, which suggests that other retinal feature detectors and their associated circuit computations remain to be identified (table 13.1).

OPEN QUESTIONS

Visual Features and Ecology

The above examples motivate a deeper consideration of feature selectivity. Are these neurons truly selective for just one type of stimulus, and if not, can one justify associating them with a specific feature? The answer to the first question is clearly negative: For example, every known ganglion cell will respond to a small spot flashing in the receptive field center. This includes the

object-motion cells and the looming detectors. However, under conditions of natural vision, flashing spots simply do not happen very often. Except right after an eye blink, objects rarely appear on the retina out of thin air; instead, they move into a neuron's receptive field from a neighboring region, or they move within the receptive field. Within the rather constrained set of stimuli that occur commonly in natural vision, the looming detector is selective primarily for objects that expand, and the OMS cell for those that move differently from their background.

An interesting theme is that most of the feature detectors identified to date seem to process some form of image motion: wide-field, local, or differential. This has a simple ethological interpretation: Moving objects in the visual scene tend to be interesting points, either as threats or opportunities. Similarly the global image flow on the retina is a useful indicator of self-motion through the environment. It is perhaps not surprising that specific circuits have evolved to extract and separate these important cues from the image rapidly and efficiently. However, these qualitative arguments will need to be tested more seriously. One approach is to study retinal signaling under conditions that truly reflect vision in the natural environment, including the ever-present observer and eye motion. Such stimuli can be gathered now thanks to ultralight video cameras that can travel on the head of a rodent moving freely in the natural environment (Zhang et al., 2012). It will be important to test for each ganglion cell type how selective it is under these conditions and whether the trigger features are indeed those identified using the more conventional synthetic stimuli.

Downstream Processing

Where in the brain are all these different parallel representations sent? A simple suggestion, consistent with the concept of a retina with many independent image processors, would be that each ganglion cell type provides input to a different retinorecipient region. But that is not the case. There are three patterns of ganglion cell projections (figure 13.8). A few ganglion cell types project to a single target region, such as the three types of ON DS cells (Vaney, Sivyer, & Taylor, 2012). A few others project to multiple regions such as some of the melanopsin-expressing ganglion cells (Schmidt et al., 2011a). However, most ganglion cell types project to two main visual centers, the lateral geniculate nucleus (LGN) and the superior colliculus (SC). In fact, the axons of most individual ganglion cells branch and innervate both target areas.

There are two important points to note. First, many visual features are copied to both the LGN and the SC, and it is, therefore, intriguing to ask whether these copies will ever be compared or, alternatively, will live independent lives to drive behavior or perception. Second, in most species studied, including primates, many of the specialized visual features are sent to the LGN. On the other hand, most cortical researchers are convinced that only a few pathways—perhaps three—arrive at the primary cortex from the LGN. One

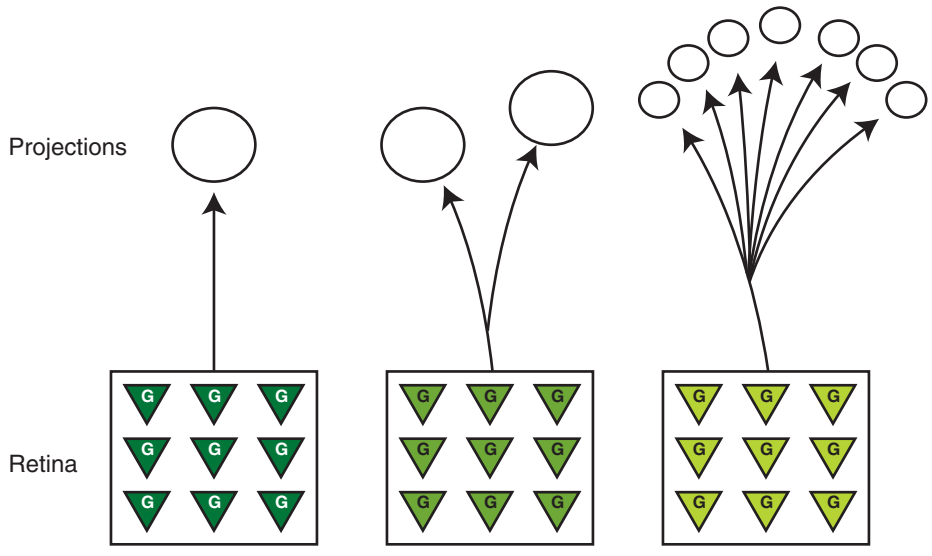


Figure 13.8 Three types of retinal projections. (Left) Ganglion cell mosaic projecting to a single nucleus. (Center) Ganglion cell mosaic projecting to two nuclei. (Right) Ganglion cell mosaic projecting to multiple nuclei.

possibility is that multiple retinal features combine immediately within the LGN into few visual channels. Alternatively we may still have an incomplete understanding of the pathways that drive the visual cortex. Fortunately a new set of tools is coming available that includes the means to trace the downstream pathways from genetically identified cells, to activate or silence specific types of ganglion cells, and to record activity from hundreds of neurons in the cortex. Therefore, it is likely that this controversy will be resolved soon. More broadly, it seems possible now to map out the relation between the distinct ganglion cell pathways and specific aspects of the animal's visual behavior.

So far the silencing of types of ganglion cells has led to controversial conclusions. Targeted elimination of a few or single types of melanopsin-containing ganglion cells caused well-defined behavioral deficits in mice (Chen, Badea, & Hattar, 2011; Guler et al., 2008; Hatori et al., 2008). Similar marked deficits in mouse behavior were found when the starburst amacrine cells were eliminated (Yoshida et al., 2001), and likely the directional selectivity of at least seven types of directional selective ganglion cells was abolished. In contrast, the acute silencing of all types of ON ganglion cells led to minor changes in primate visual behavior (Schiller, Sandell, & Maunsell, 1986). A mutation that is predicted to result in a similar silencing of all ON cells in humans does not lead to any major visual defects at light intensities where cones are active (Dryja et al., 2005; Zeitz et al., 2005). Many ganglion cell types come in pairs, including an ON and an OFF version. It appears that for a significant part of our visual perception and function one version of a type is enough.

Clinical Tests of Feature Processing

The conservation across species of retinal structure and function also provides new opportunities to diagnose retinal diseases. When we visit the ophthalmologist, our vision is tested on a chart from which we read small and large letters. This test mostly diagnoses the optics of the eye, based on the performance of 2 of the 20 types of ganglion cells, the ON and OFF midget cells. Although the retina incudes a massive infrastructure to analyze and dissect different categories of motion, there is, remarkably, not a single quantitative or even qualitative test used regularly by ophthalmologists that would evaluate how well we can perceive motion. If, for example, a mutation had produced a defect in the development of amacrine cell networks, the patient may be unable to see motion or, conversely, might see motion all the time. Such a patient would likely end up in the office of a psychiatrist, even though the defect originates in the sensory periphery. By understanding one by one the computations that different ganglion cells perform and by understanding the behavioral phenotypes that result from silencing identified ganglion cell mosaics, it may be possible to discover abnormalities in human visual perception that arise within the retina.

APPENDIX 13.1

Linear Visual Responses

Mathematically, a linear light response is derived by convolving the stimulus with a filter function:

$$r(t) = r_0 + \int\int s(x,t')F(x,t-t')dt'dx$$

In this expression, $s(x,t)$ is the stimulus intensity as a function of space and time, and r_0 is the firing rate in absence of any stimulus. The weighting function $F(x,t)$ specifies the weight applied to the intensity at location x and time t in the past and is commonly called the spatiotemporal receptive field of the neuron.

Clearly the range of a neuron's firing rate is restricted, namely to zero firing at the bottom, and some maximal rate determined by cellular biophysics at the top. Therefore, this linear relationship cannot persist when the light intensity varies over too large a range. In fact one generally finds distortions in the response to strong stimuli. A more general version of a pixel sensor allows for such distortions in the relation between stimulus and response:

$$r(t) = \mathcal{N}\left(\int\int s(x,t')F(x,t-t')dt'dx\right)$$

where the function $\mathcal{N}(\ )$ is the distortion function that relates the linear-weighted stimulus to the firing rate, generally with a sigmoid shape. A response function of this kind is often called an LN model: a linear filter followed by a nonlinearity (Chichilnisky, 2001). Note that the nonlinearity $\mathcal{N}(\ )$ does not fundamentally alter *what* the ganglion cell reports about the visual scene, only *how* it is reported. The visual meaning of the message is fully defined by the spatiotemporal receptive field $F(x,t)$. In summary then, we can consider a retinal ganglion cell a pixel sensor if its stimulus–response function follows the LN model under most visual stimuli. The spatial and temporal extent of the image pixel that this ganglion cell reports is embodied by the spatiotemporal receptive field $F(x,t)$.

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