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The Neuronal Organization of the Retina

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Abstract

The mammalian retina consists of neurons of >60 distinct types, each playing a specific role in processing visual images. They are arranged in three main stages. The first decomposes the outputs of the rod and cone photoreceptors into ~12 parallel information streams. The second connects these streams to specific types of retinal ganglion cells. The third combines bipolar and amacrine cell activity to create the diverse encodings of the visual world—roughly 20 of them—that the retina transmits to the brain. New transformations of the visual input continue to be found: at least half of the encodings sent to the brain (ganglion cell response selectivities) remain to be discovered. This diversity of the retina's outputs has yet to be incorporated into our understanding of higher visual function.

Charles Darwin famously wrote that the eye caused him to doubt that random selection could create the intricacies of nature. Fortunately, Darwin did not know the structure of the retina: if he had, his slowly gestating treatise on evolution might never have been published at all. Among other wonders, the neurons of the retina are tiny (Figure 1). The ~100 million rod photoreceptors appear to be the second most numerous neurons of the human body, after only the cerebellar granule cells. The retina's projection neuron, the retinal ganglion cell, has less than 1% the soma-dendritic volume of a cortical or hippocampal pyramidal cell. Although the retina forms a sheet of tissue only ~200 μm thick, its neural networks carry out feats of image processing that were unimagined even a few years ago (Gollisch and Meister, 2010). They require a rethinking not only of the retina's function, but of the brain mechanisms that shape these signals into behaviorally useful visual perception.

The retinal neurome—the census of its component cells—continues to be refined. An initial estimate of 55 cell types in the retina (Masland, 2001) appears to have been something of an underestimate. Our understanding of the fundamental plan of the retina remains the same, but new image processing mechanisms are coming into view. My aims here are to see how close we have come to a complete census, to review the principles by which the diverse cell types are organized, to illustrate some of the ways in which they create the retina's abilities, and to forecast the path by which we may progress. I will begin by outlining three large rules that govern relations among the retina's neurons.

Principle #1: The Signal Generated by Any Individual Cone Is Decomposed into ~12 Different Components, Each of Which Is Transmitted Separately to

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the Inner Retina by a Structurally and Molecularly Distinct Type of Bipolar Cell

The retina's processing of information begins with the sampling of the mosaic of rod and cone photoreceptors by the bipolar and horizontal cells. The photoreceptors form a single sheet of regularly spaced cells. Rod photoreceptors, specialized for vision in dim light, outnumber cone photoreceptors by about 20-fold in all but a few mammalian retinas. All rods contain the same light-sensitive pigment, rhodopsin. With one known exception (so far), each cone contains one—and only one—of several cone opsins, each with a different spectral absorption; as will be discussed later, these are the basis of color vision. Both rods and cones respond to light by hyperpolarizing. Rods and the chromatic classes of cones can be easily identified in intact retinas by morphology and by their expression of the different opsins.

This review will pass lightly over the rod system, which molecular dating shows to have been a late evolutionary addition to the retina's tool kit. This is not to say that rods are unimportant, nor that they are uninteresting. Yet the retinal circuitry truly dedicated to rod function includes only four cell types: the rod itself, a bipolar cell that receives input only from rods ("rod bipolar cell"), an amacrine cell that modulates the bipolar cell's output, and an amacrine cell that feeds the output of the rod system into the circuitry that processes information derived from cones. A second pathway from rods to ganglion cells exists in some animals (it involves gap junctions with cones), but in either case the strategy is the same: the late-evolving rods inject their signals into circuitry that had already developed to service the cones (Famiglietti and Kolb, 1975; Nelson, 1982; Nelson and Kolb, 1985; Sandell et al., 1989; Strettoi et al., 1990, 1994; Strettoi et al., 1992).

The types of cones are structurally and, as far as is known, functionally similar. (This review pertains primarily to mammalian retinas.) Their functional types are defined by the opsin that each type expresses. A generic mammal expresses one short wavelength-sensitive cone and one long wavelength. Comparison of the two outputs forms the basis of most color vision. The numbers of rods and cones are known with great precision. They have been counted and their topography mapped for dozens of mammalian and nonmammalian species. These have been collected at http://www.retinalmaps.com.au (Collin, 2008). For humans and the common laboratory animals, the accounting of photoreceptor cells is complete.

Horizontal Cells

As neural populations, horizontal cells are equally simple. The large majority of mammals have two types of horizontal cells. Both of them feed back onto the rod or cone photoreceptors. Some rodents have only one type, and there have occasionally been proposals of a third type in some animals. Despite some variation in morphological detail, though, horizontal cells appear to follow a fairly simple plan (Müller and Peichl, 1993; Peichl et al., 1998). Horizontal cells provide inhibitory feedback to rods and cones and possibly to the dendrites of bipolar cells, though this remains controversial (Herrmann et al., 2011). The leading interpretation of this function is that it provides a mechanism of local gain control to the retina. The horizontal cell, which has a moderately wide lateral spread and is coupled to its neighbors by gap junctions, measures the average level of illumination falling upon a region of the retinal surface. It then subtracts a proportionate value from the output of the photoreceptors. This serves to hold the signal input to the inner retinal circuitry within its operating range, an extremely useful function in a natural world where any scene may contain individual objects with brightness that varies across several orders of magnitude. The signal representing the brightest objects would otherwise dazzle the retina at

those locations, just as a bright object in a dim room saturates a camera's film or chip, making it impossible to photograph the bright object at the same time as the dimmer ones.

Because the horizontal cells are widely spreading cells, their feedback signal spatially overshoots the edges of a bright object. This means that objects neighboring a bright object have their signal reduced as well; in the extreme, the area just outside a white object on a black field is made to be blacker than black. This creates edge enhancement and is part of the famous "center-surround" organization described in classic visual physiology (Hartline, 1938; Kuffler, 1953). But the inner retina contains many more lateral pathways than the outer, and creates both simple and sophisticated contextual effects. Indeed, Peichl and González-Soriano (1994) pointed out that the ganglion cells of mice and rats have a quite ordinary center-surround organization, but these retinas lack one type of horizontal cell altogether. Perhaps the horizontal cells are best imagined as carrying out a step of signal conditioning, which globally adjusts the signal for reception by the inner retina, rather than being tasked primarily with the detection of edges.

The synapses by which horizontal cells provide their feedback signals appear to use both conventional and unconventional mechanisms; they remain a matter of active investigation (Hirano et al., 2005; Jackman et al., 2011; Klaassen et al., 2011). Taken as morphological populations, however, the horizontal cells are relatively simple. They can be stained for a variety of marker proteins in different animals. They, too, have been quantitatively mapped across the retinal surface in many species (Collin, 2008).

Bipolar Cells

Early physiological recordings suggested that there were four types of bipolar cells: ON, OFF, sustained, and transient (Kaneko, 1970; Werblin and Dowling, 1969). Modern anatomical work and subsequent physiological evidence indicate that the true number of bipolar cell types is about 12. This has been a gradual realization. Initial studies used synapse densities (Cohen and Sterling, 1990) to distinguish the types. As marker proteins of increasing specificity were discovered, the number of putative bipolar cell types gradually increased. Recent studies seem to have brought this to its conclusion.

A set of intersecting methods was used to classify the bipolar cells of the rabbit (MacNeil et al., 2004). The strategy was to seek a complete survey of bipolar cell types by using several methods with different sampling biases. For purposes of classification, the purely anatomical samples were complemented by a set of cells injected with Lucifer yellow after physiological recording, so that their responses to light could be used as part of the classification. The bipolar cells of the rabbit were divided into a rod bipolar cell and 12 types of cone bipolar cells. In near-perfect agreement, Wässle et al. (2009) classified the bipolar cells of the mouse using immunostaining for recently discovered type-specific markers and transgenic strains in which one or a few types of bipolar cells express a fluorescent marker. These were supplemented by microinjection, to reveal the cells' finest processes and their contacts. They found one type of rod driven bipolar cell and 11 types that receive inputs primarily from cones (Figure 2). Because they are population stains, these methods allowed an estimate of the total number of bipolar cells of each type, which could then be added up for comparison with the total number of bipolar cells known by independent methods to exist in the mouse (Jeon et al., 1998). The identified individual cell types correctly added up to the known total number of bipolar cells. Thus, "…the catalog of 11 cone bipolar cells and one rod bipolar cell is complete, and all major bipolar cell types of the mouse retina appear to have been discovered" (Wässle et al., 2009).

The Synapses of Cones with Bipolar Cells Create Parallel Informational Channels

This concept is simple, but it is topologically fairly subtle (Figure 3). From partial evidence, it was suspected a decade ago that each cone makes output to each of the types of bipolar cells—a critical principle for the signal processing of the retina. Wässle et al. (2009) could confirm that this occurs for each of the 11 types of bipolar cells that they identified in the mouse. The exception is a specialized “blue cone bipolar,” which selectively contacts the short wavelength sensitive cones, as is necessary if the chromatic information is not to be degraded. Symmetrically, some bipolar cells avoid the terminals—they are numerically infrequent—of blue cones. And there is some crosstalk with the rods. But the central principle, which dominates the structural and functional organization of the retina, is that each bipolar cell contacts all of the cone terminals within the spread of its dendritic arbor. This is a geographically simple rule.

Functionally, however, this arrangement allows something more sophisticated. By tuning the characteristics of the cone-to-bipolar synapses, each type of bipolar cell can transmit a different parsing of the cone’s output. Bipolar cells express distinctive sets of receptors, ion channels, and intracellular signaling systems. This right away suggests that each of the cells has a unique physiology, and so far that has consistently turned out to be the case. As a consequence, it is believed that each of the ~12 anatomical types of bipolar cell that contacts a given cone transmits to the inner retina a different component extracted from the output of that cone.

What types of information are segregated into the dozen parallel channels? A simple case is the blue cone bipolar. In the inner retina, this type of bipolar cell contacts a ganglion cell that compares short and long wavelengths; the ganglion cell then becomes a blue-ON, green-OFF ganglion cell. In the ground squirrel (a favorite because it contains a large number of cones), the bipolar cells that contact both classes of cones have been shown to have the expected broad spectral sensitivity, and presumably transmit the simple brightness of a stimulus, independent of its color (Breuninger et al., 2011; Li and DeVries, 2006).

Among the non-chromatic bipolar cells, a classic example is the segregation of responses into ON and OFF channels, the ON channels having their axon terminals in the inner half of the inner plexiform layer (IPL) and the OFF bipolars having their terminals in the outer half (Famiglietti et al., 1977; Nelson et al., 1978). The difference between ON and OFF responses is due to the expression of two classes of glutamate receptor. OFF bipolar cells express AMPA and kainate type receptors, which are cation channels opened by glutamate; since photoreceptor cells hyperpolarize in response to light, these bipolar cells hyperpolarize in response to light as well, because less glutamate arrives from the cone synapse. ON bipolar cells express mGluR6, a metabotropic receptor, which, when glutamate binds to the receptor, leads to closing of the cation channel TRPM1. The receptor is thus sign inverting. When light causes less glutamate to be received from the photoreceptor terminal, cation channels open and the cell depolarizes (Morgans et al., 2009; Shen et al., 2009).

Similarly, the distinction between sustained and transient bipolar cells is caused by the expression of rapidly or slowly inactivating glutamate receptors (Awatramani and Slaughter, 2000; DeVries, 2000). This creates four classes of bipolar cells: ON-sustained, ON-transient, OFF-sustained, and OFF-transient. In detail, the different structural/molecular types of bipolar cells show a wide diversity of response waveforms in response to light; aside from the simple tonic versus phasic dimension, these responses display complex mixtures of the two (Wu et al., 2001). The functional meanings of these are only beginning to be understood (Freed, 2000). A case in point is the expression of differing sets of regulation of G protein signaling (RGS) proteins, which control the kinetics of the response to synaptic input in ON bipolar cells (Cao et al., 2012). Another is a type of bipolar cell that generates Na^+ action

potentials. Na^+ currents have been known to occur from studies of many retinas, but their functions are unclear (Ichinose and Lukasiewicz, 2007; Ichinose et al., 2005; Ma et al., 2005; Zenisek et al., 2001). In the ground squirrel, the structurally defined bipolar cell termed cb5b has a large tetrodotoxin (TTX)-sensitive Na^+ current. These cells signal the onset of a light step with a few all-or-nothing action potentials (Figure 4). In response to a continually graded noise stimulus (more closely representing a natural scene), they generate both graded and spiking responses, the spikes occurring with millisecond precision. The cells select for stimulus sequences in which transitions to light are preceded by a period of darkness. Their axon terminals costratify with the dendrites of a specific group of ganglion cells, and these ganglion cells encode light onset with a short latency burst of spikes. It thus appears that this bipolar cell trades the band-width inherent in graded signaling for spikes that can elicit a rapid and reliable response in transient-type ganglion cells (Saszik and DeVries, 2012).

Principle #2: The Outputs of These Bipolar Cell Channels Are Sampled by Different Sets of Retinal Ganglion Cells

The central structural characteristic that defines the ~12 types of bipolar cells is the level of the inner plexiform layer at which their axons terminate. In other words, the bipolar cells receive input from all of the cones within their reach, as just described, but they terminate on very restricted sets of postsynaptic partners. Distinction of functional types on this basis is confirmed by molecular differences that correlate with types that have been defined in this way. The specificity is again confirmed by the fact that different sets of ganglion cells (as well as amacrine cells) costratify with them. These, too, represent distinct types: they have different central projections, different physiologies, and different molecular signatures. Although there is amacrine cell crosstalk between the layers (see below) the bulk of the inner retina's connectivity occurs within the layers. The stalks of bipolar cell axons, and the proximal dendrites of ganglion cells, often pass through several laminae to reach their final level of stratification, but few synapses are made with these connecting processes en passant: the main work of synaptic connectivity is done within the layers. Indeed, the lamination of the inner plexiform layer is a fundamental guide to the retina's wiring diagram.

All bipolar cells and all ganglion cells are stratified—some in narrow layers, some in broader ones, some in multiple ones, but always stratified. One may imagine the array of bipolar cell axon terminals as transmitting a cafeteria of stimulus properties, among which the ganglion cell chooses depending on the type of information that particular ganglion cell will finally transmit to central visual structures. This connectivity builds the initial foundation of the response selectivity that distinguishes functional types of ganglion cell: if the different retinal ganglion cells get selective inputs from differently responding bipolar cells, they are right away imbued with differing types of response to light themselves. Note that these connections are not limited to the one-to-one case—ganglion cells that stratify in several layers can take some of their properties from one type of bipolar cell, and other properties from a different one.

A slightly tricky conceptual issue should be clarified here. There are two main influences upon the responses to light of bipolar cells. As just described, the first is their synaptic drive from the rod or cone photoreceptors, as expressed through the bipolar cells' differing glutamate receptors and modified by their signaling proteins and ion channels. These features are intrinsic to the bipolar cells, controlled by the set of proteins that each type of bipolar cell expresses. But the bipolar cells are also influenced by inputs from amacrine cells (Figure 5), and those effects are included in the bipolar cell's "response to light" as well. Bipolar cells are short, fat neurons (Figure 1) and are electrotonically compact. Thus, a

recording from the soma of the bipolar cell does not simply monitor a signal transmitted from dendrite to soma to axon of the bipolar cell, like watching a railway train pass a vantage point alongside its tracks. Instead, a soma recording monitors the effects of all of the bipolar cell's inputs, including the signals that impinge on its axon terminals from amacrine cells (Bieda and Copenhagen, 2000; DeVries and Schwartz, 1999; Euler and Masland, 2000; Matsui et al., 1998; Saszik and DeVries, 2012). Thus, the output of the bipolar cell onto the ganglion cell includes both the intrinsic response properties of the bipolar cell and the actions of amacrine cells upon the bipolar cell. The bipolar cell is as much an integrating center as it is a conduit from outer retina to inner.

Principle #3: The Partially Selective Responses Mediated by Bipolar Cells Are Refined by Amacrine Cells—A Few per Ganglion Cell Type—To Create Arrays of Precisely Specific Ganglion Cell Subtypes

The second controller of the ganglion cell response is direct input from amacrine cells. Amacrine cells occupy a central but inaccessible place in the retinal circuitry. Most are axonless neurons and their lack of a clear polarity makes it hard to recognize the sites of their inputs and outputs. Because of their multiple connectivity, they are hard to conceptualize: they feed back to the bipolar cells that drive them, they synapse upon retinal ganglion cells, and they synapse on each other (Figure 5; Dowling and Boycott, 1966; Eggers and Lukasiewicz, 2011; Jusuf et al., 2005; Lin et al., 2000). Their great structural diversity makes them a daunting target for experimentation. In the absence of some feature —natural or man-made—that allows a single type to be systematically targeted, obtaining an adequate experimental sample is virtually impossible. But progress is being made, especially in cases where an amacrine cell type is structurally distinctive or can be genetically marked.

An early survey of amacrine cell types counted 29 types of amacrine cell in the rabbit retina (MacNeil et al., 1999; MacNeil and Masland, 1998). How well has this estimate stood up, and what have we subsequently learned about the functions of amacrine cells? The answer to the first question is that there has been no subsequent survey of this type, but there have been no big surprises and nothing to suggest that the populations of amacrine cells in other species are less complex. Those types of amacrine cells for which we have specific stains are generally the same in other species. But there were two weaknesses to the original survey. First, some of the cells were classified on the basis of very few examples. So far, better methods have confirmed the original descriptions (Wright and Vaney, 2000), but it is to be expected that they will need, at the very least, a fine-tuning. Second, there was uncertainty about the number of wide-field amacrine cell types, which can cover the retina with a very small, absolute number of cells, and thus are rarely encountered. Recent studies show that there are more wide-field cells than originally described. If the traditional definition of a retinal cell type is followed, there would be at least 16 types of wide-field amacrine cell (Lin and Masland, 2006). However, the difference between them is primarily that they stratify at different levels. By far the most striking feature of these cells is their huge spread (Figure 6), and it is economical (though somewhat inconsistent) to classify them as a single cell type that performs the same function for different sets of partners. Using this definition, the total number of known amacrine cell types would remain around 30.

Three Generalizations about Amacrine Cell Functions

First, amacrine cells create contextual effects for the responses of retinal ganglion cells. This includes the classic "center surround" antagonism, but also a variety of other, more subtle, effects (review, Gollisch and Meister, 2010). A nice example is object motion detection, a phenomenon in which a retinal ganglion cell responds to stimulus motion, but only to

motion relative to the overall background of the scene. This provides a signal that distinguishes true motion of an object in the world from self-induced motions of the observer, especially eye movements, which cause everything to shift across the retina at the same time (Figure 6). Interestingly, this computation was observed for only a subset of retinal ganglion cells. The plethora of wide-field amacrine cells suggests that other context dependencies, as yet unimagined, remain to be discovered.

Second, many amacrine cells—perhaps a majority of the total number—perform some variety of vertical integration (the term is meant to contrast with lateral integration, as carried out by horizontal and wide-field amacrine cells). Only a small fraction of the 13 narrow field amacrine cell types found by MacNeil et al. (1999) were restricted to branching in narrow strata; the rest communicate among several, sometimes all, of the layers of the IPL, like the cell shown in Figure 5. This means that they carry ON information into the OFF strata, and vice versa. This is termed crossover (for the crossing between ON and OFF layers) inhibition (because amacrine cells release GABA or glycine). It is the subject of very active investigation, which reveals a variety of interesting controls on the flow of information through the retina. The details are beyond the scope of this review, but an example is the finding that some “excitatory” responses of ganglion cells to light are actually a release of amacrine mediated inhibition (Buldyrev et al., 2012; Demb and Singer, 2012; Farajian et al., 2011; Grimes et al., 2011; Molnar et al., 2009; Nobles et al., 2012; Sivyer et al., 2010; Werblin, 2010).

Third, most of the functions of amacrine cells are narrowly task-specific. An example is amacrine cell A17, a widely spreading neuron that places hundreds of electrotonically isolated synaptic boutons in contact with the output sites of the rod bipolar cell. At those points, the amacrine cell feeds back an inhibitory signal that improves the fidelity of information transmission by the rod bipolar cell (Grimes et al., 2010; Sandell et al., 1989). This is the A17 cell’s primary, perhaps sole, task: and the A17 amacrine is in any case irrelevant to events that happen under daylight conditions. Another highly specialized amacrine cell, recently discovered in the ground squirrel retina, creates a specific receptive field property in a single type of ganglion cell (Chen and Li, 2012; Sher and DeVries, 2012). A blue-ON ganglion cell is well-known: it is excited by the blue-ON bipolar cell that selectively contacts blue cones. But electrophysiological recordings have encountered a blue-OFF ganglion cell, inhibited when the stimulus lies at the short wavelength end of the spectrum. How can this happen if the only path through the retina is the blue-ON bipolar, carrying an excitatory signal? It turns out that a specific amacrine is driven directly by the blue-ON bipolar cell. The amacrine cell, like virtually all amacrine cells, is inhibitory to its postsynaptic partners. When excited by the blue-ON bipolar cell, this amacrine cell performs a sign inversion: it inhibits the ganglion cell upon which it synapses, thus creating a ganglion cell that is selective for blue stimuli and responds to a blue stimulus by slowing its firing—a blue-OFF ganglion cell.

A final task-specific case is the role of the starburst amacrine cell. In 1965, Horace Barlow and William Levick reported that certain ganglion cells of the rabbit retina respond selectively to the direction of stimulus motion, and, in a report classic for its intelligence and detail, described the key features of the cells (Barlow and Levick, 1965). The directional preference is the same for all small regions within the receptive field of the cell; a ganglion cell with a receptive field 500 μm in diameter can discriminate 40 μm movements anywhere within its receptive field (Figure 7). This “local subunit,” is a critical property because it distinguishes this discrimination from a trivial form of direction selectivity that can be predicted simply from the presence of adjacent ON and OFF regions. It is direction per se that the cell detects, not any simple spatial pattern of excitatory and inhibitory zones.

The search for a mechanism settled eventually on the starburst amacrine cell. Critically, the starburst cells have enormously overlapping dendritic arbors (Tauchi and Masland, 1984). The starburst cells do not tile the retina; they shingle the retina, like roofing shingles, and it was suggested that the reason for their apparent redundancy of coverage was to create the local subunit of the DS receptive field (Masland et al., 1984). In 1988, Vaney and Young proposed what turned out to be the correct mechanism of direction selectivity (Figure 7). They suggested that (1) individual sectors of the starburst dendritic arbor act as independent units, (2) dendritic sectors of the starburst cell pointing in a single direction selectively synapse upon any individual DS ganglion cell, and (3) these sectors are individually direction selective, creating a directional input to the ganglion (Vaney, 1991; Vaney and Young, 1988).

A direct test of this idea came from paired recordings between a DS cell and an overlapping starburst cell (Fried et al., 2002). As predicted, stimulation of a null-side starburst cell produced a GABAergic inhibition of the cell, while stimulation of starburst cells at other locations produced only a mild excitation (Lee and Zhou, 2006). At about the same time, two photon Ca^{2+} imaging showed that the sectors of a starburst cell are indeed functionally isolated units, and that they are directionally polarized in their responses, with greater Ca^{2+} influx resulting from stimulus movement outward (away from the soma) than inward (Euler et al., 2002). The coup de grace was provided by Briggman et al. (2011), who used high-throughput electron microscopic reconstruction (see below) to confirm that starburst cells pointing in the null direction selectively contact the DS ganglion cell. This work is discussed in a definitive recent review (Vaney et al., 2012).

Very Diverse Encodings of the Visual Scene Are Sent to the Brain

Because inputs from bipolar and amacrine cells combine, the number of functional types of ganglion cell exceeds the number of types of bipolar cell (Taylor and Smith, 2011). Their classification has been a difficult problem—most or all of the ganglion cell types have almost certainly been stained in one study or another, but it has not yet been possible to achieve a definitive classification in any mammalian species. How many types of ganglion cells exist? The number of putative ganglion cell types estimated in a series of five recent studies in the mouse was 11, 12, 14, 19, and 22 (review, Masland, 2012). New cell types have emerged since those studies were conducted. The apparent number of ganglion cell types depends a lot on how they are counted: should ON and OFF variants of the same response pattern be considered as one cell type or two? Do the four cardinal direction preferences of DS cells represent four cell types or one? No matter how one counts, the number of types is surely not less than a dozen in any mammal yet studied, and many workers feel that the minimal number of structurally distinct types in the mouse, rabbit, cat, or monkey is in the neighborhood of 20.

What can be the uses of 20 types of ganglion cells? There is more extensive information for the rabbit retina than any other. The ganglion cell types for which a morphological/physiological identification is secure are as follows: a local edge detector, much like the “bug detector” described long ago in the frog by Maturana et al. (1960); ON-tonic and OFF-tonic cells; blue-ON and blue-OFF ganglion cells; an ON direction selective cell, which projects to the accessory optic system and subserves optokinetic nystagmus; an ON-OFF directionally selective cell, function unknown; two large, ON-transient or OFF-transient cells; a recently identified “transient ON-OFF ganglion cell,” which responds much like an ON-OFF DS cell but is not directionally selective and has a different stratification; a uniformity detector, which responds to changes in the visual input by decreasing its firing rate; cells selective to each of two preferred orientations; and the sparse intrinsically photosensitive (melanopsin) cells, whose long-lasting responses to light synchronize the

circadian oscillator, drive pupillary responses, and carry out other functions still being explored. In the mouse, a curiously shaped cell with a weak form of direction selectivity has been discovered, as has an apparent homolog of the local edge detector (Amthor et al., 1989; Ecker et al., 2010; Kim et al., 2008; Levick, 1967; Rockhill et al., 2002; Roska and Werblin, 2001; Schmidt et al., 2011; Sivyer et al., 2010, 2011; Taylor and Smith, 2011; van Wyk et al., 2006,2009; Vaney et al., 2012; Venkataramani and Taylor, 2010; Zhang et al., 2012).

This may seem like a long list. Note, however, that there are nine modality-specific channels for touch, five for taste, and >300 for smell. Truly remarkable would have been for vision, said to occupy ~50% of the cortex in primates (Van Essen, 2004), to have only the two types of retinal ganglion cell stressed in the standard canon. If we assume 20 morphologically distinguishable cell types, at least half of the structurally identified ganglion cells of the rabbit still have functions that have not yet been characterized. An even smaller fraction of the morphological cell types have been characterized in the rat, mouse, cat, or monkey.

Mosaics, Tiling, and How Retinal Cells Survey the Visual Scene

How does the multitude of retinal cells array itself across the retinal surface? The answer reveals an elegant feat of developmental engineering (review, Reese et al., 2011). Each of the retina's >60 cell types is regularly spaced, so that the cells cover the retinal surface evenly. This assures that the cell types survey the visual scene efficiently (Cook, 1996; Wässle et al., 1981; Wässle and Riemann, 1978). But retinal cells of a particular type are evenly spaced only with respect to other cells of the same type. With respect to cells of other types—even those to which they are synaptically connected—their positions are random (Rockhill et al., 2000). Not only do the cell bodies space themselves, the dendritic arbors of most cell types arrange not to overlap very much, as though dendrites of neighboring cells of the same type repel each other. This efficient coverage is observed physiologically as well as morphologically (Devries and Baylor, 1997; Gauthier et al., 2009).

The phenomenon is called "tiling," but the term—invoking bathroom tiles—conflates two different concepts: regular spacing of the cell bodies (mosaic spacing), and fitting together of the dendritic arbors at their edges. A measure of the latter is the coverage factor, given by the spatial density of the cells (cells/mm^2) times the dendritic field area of each cell (mm^2/cell). A coverage factor of 1.0 represents perfect tiling: no empty spaces between the arbors, and no overlap between the arbors. Bathroom tiles have both a regularly spaced mosaic and a coverage factor of one. All genuine cell types thus far discovered have regular mosaics. Many ganglion cells and the axon terminals of bipolar cells have coverage factors near 1.0. Other types of ganglion cells, especially in lower mammals, have coverage factors of three to five, and thus partial overlap in their arbors. And wide-field amacrine cells have enormous coverage factors, representing the specialized functions of these cells. The starburst amacrine cell of a rabbit has a coverage factor that ranges from 25 centrally to 70 peripherally, an overlap that serves their unique function for direction selectivity.

Because of their regular spacing, the arbors of each of the ~20 types of retinal ganglion cells cover the retina completely and evenly. This means that every point in the retinal surface is reported upon at least once—in the limiting case, exactly once—by each of the diverse types of retinal ganglion cell. This is represented pictorially in Figure 8, where the mosaics of four different types of ganglion cell are superimposed on an image. The first represents the X-type cell, responding in a linear way to the total brightness captured within its aperture. The second represents the Y cell, with a larger aperture and sensitivity to movement. The third represents a DS cell, responding to movement in a particular direction. The last represents the blue-ON (or blue-OFF) ganglion cell, transmitting the mean spectral luminance along the spectrum from blue to green. These tilings are independent, so that the mosaics are simultaneously superimposed upon each other. The same principle holds for the remaining

functional types of ganglion cell, so that every point in the visual scene is simultaneously reported to the brain by ~20 independent filters, each transmitting a different aspect of the stimulus.

Implications for Central Visual Processing

The signals sent by the retinal ganglion cells to the brain are the fundamental stuff of vision. Surprisingly, textbook accounts of higher visual function take little notice of their diversity. Indeed, the textbook view of spatial integration in the visual cortex is built upon a retina that conveys only two types of signal—the X and Y cells, M and P cells in the primate—to the brain. Trivial explanations, such as the idea that the more complex retinal cells project only to subcortical centers, are no longer tenable (Dacey, 2004; Gollisch and Meister, 2010; Masland and Martin, 2007). Some emerging points are as follows:

The Brain Must "Bind" More Representations Than Previously Thought

A large field cell (alpha cell) can tell the brain that something is moving, but cannot specify where, within a large area, the moving thing is located. How the brain incorporates this information into useful perception is part of the classic "binding problem," important for both experimentalists and theorists. The problem is more than binding a signal about form and a signal about motion; there are several types of signal about form, there is the directionality of motion, etc. The local edge detector (not the X cell) is the most numerous type of retinal ganglion cell in the mouse and rabbit retinas (van Wyk et al., 2006; Zeck et al., 2005; Zhang et al., 2012). Why does the mouse retina use this instead of (or in addition to) an X cell? All of the retinal encodings must converge to a unified representation of the visual world. Where does this convergence occur? Do they converge in primary visual cortex, or could the diverse retinal encodings create multiple, as-yet-unrecognized, parallel streams in higher visual centers? If they converge in primary visual cortex, what is the consequence for receptive fields encountered there?

Ganglion Cells Have Context-Dependent Dynamic Properties

The classic descriptions of ganglion cell receptive fields were essentially static—the term "receptive field" has its roots as a spatial "field." But a host of dynamic properties have now been discovered. These include a wide variety of contextual influences, such as the object motion segmentation, shown in Figure 6; a response to "looming" stimuli, saccadic suppression of ganglion cell responses, and most recently, new forms of direction selectivity and anticipatory responses to moving stimuli (Hosoya et al., 2005; Münch et al., 2009; Ölveczky et al., 2003; Roska and Werblin, 2003). In the latter case, it can be shown that retinal movement-sensitive neurons begin responding before they should, based on static mapping of their receptive field; their responses anticipate the incursion of a moving stimulus. This is an instructive example, because it is yet another case in which the retina's responses are tuned to the probabilistic structure of the natural world. A moving stimulus is more likely than not to continue along a straight path; the retina gains an advantage in speed by predicting that this probable stimulus will continue (Schwartz et al., 2007). A related example is the retina's numerical bias toward OFF cells, which mirrors a bias toward darkening events in the natural world (Ratliff et al., 2010). Perhaps this matching to the statistics of natural scenes will provide clues to the response tuning of the many as-yet-unclassified types of retinal ganglion cells.

Plasticity and Overlapping Functions Allow the Brain to See Well using Varied Retinal Inputs

It is a commonplace among clinicians that a very small number of surviving retinal ganglion cells allows substantial vision. A subtler point is made by the clinical condition of stationary

night blindness, which results from an inactivating mutation in mGluR6, the glutamate receptor expressed by ON bipolar cells or its signaling partners. This eliminates roughly half of the light-evoked signals that the retina sends to the brain. To be sure, patients with this mutation (or monkeys in which ON responses are blocked by excess of an mGluR6 agonist) lose their night vision, because the rod bipolar cell is an ON bipolar and signals from rods then reach the inner retina only under limited circumstances. In ordinary daylight, however, they are remarkably little handicapped, manifesting a deficit that is only revealed by specialized testing. Whether this represents plasticity—a literal rewiring of central visual circuits—or just the wealth of information present in even a partial retinal output, remains to be learned (Dryja et al., 2005; Maddox et al., 2008; Schiller et al., 1986; van Genderen et al., 2009).

There is also evidence that the brain can correctly interpret new information transmitted down the same old wires. This comes from experiments in which gene transfer was used to create trichromatic vision in normally dichromatic animals—to cure their color blindness. The experiment is to speed up evolution—to artificially create new cone types and see how vision is changed. Would changing the color selectivity of the cones produce different visual capabilities in the animal, or would the animal simply be confused? This has been done in two different experiments. In the first, Jacobs and colleagues created a mouse strain that expresses in some of its cones a red opsin, sensitive to wavelengths longer than those of the normal green opsin (normal mice have the usual pattern of one short and one long wavelength opsin). These mice see further into the red than any mouse has ever seen before. More importantly, careful behavioral experiments show that they can use their new three-cone array to have true trichromatic color vision (Jacobs et al., 2007).

The second experiment had two differences: first, it was carried out in the monkey; second, the transgene for the new opsin was introduced into adult animals instead of being present throughout the animal’s life. Most New World monkeys are natural dichromats; they have the generic mammalian array of two cone types. The experiment was to virally introduce a third opsin, on top of the already existing green opsin, into the green cones. Each cone thus contained the blue opsin, the green opsin, or the green opsin plus a red opsin. Even though their spectral sensitivity is mixed, the transgenic cones have a spectral tuning distinct from that of the green cone; functionally, they constitute a third type of cone. Behavioral testing showed that these monkeys have trichromatic color vision. Since no special neural circuitry for dealing with the red-green axis was introduced, the result means that the brain had learned to use the new chromatic information without any neural circuits purpose-built for red-green color vision.

The exact circuits that mediate the restored red-green vision are still being worked out—both for the retina and for higher visual centers—and alternative, though somewhat forced, explanations exist. (For a thoughtful review, see Neitz and Neitz, 2011). No matter what circuits one assumes to be in play, however, these animals must necessarily make the discrimination by using inputs that are different from the ones with which the animal was born.

Quite aside from its implications for the evolution of color vision, the finding is encouraging for certain proposed treatments of human blindness. In retinitis pigmentosa and age-related macular degeneration, blindness often results from degeneration of the retina’s rods and cones. In patients who suffer from these conditions, many neurons of the inner retina survive. Thus, simple vision might be restored by an optogenetic strategy, in which a new light-sensitive protein is inserted, by gene therapy methods, into the surviving bipolar or ganglion cells. Proof of this principle has been accomplished in mice that were blind because of inherited photoreceptor degenerations analogous to those that occur in humans

(Lagali et al., 2008; Lin et al., 2008). Several different ways of reaching the goal are being tried, but whichever optogenetic manipulation proves to be best, it will almost certainly send to the brain an encoding of the visual stimulus different from the native one (Busskamp et al., 2010; Caporale et al., 2011; Greenberg et al., 2011; Polosukhina et al., 2012). That the brain can use new chromatic signals suggests that it will also be able to use new kinds of spatial signals, encouraging the hope that some level of useful spatial vision might be restored in previously blind human patients.

We Do Not Understand Why the Brain Needs All of the Encodings that the Retina Transmits

The poster child is a type of retinal ganglion cell in the macaque monkey, named the "smooth cell," for a distinguishing feature of its dendrites, and meticulously studied by Crook and her colleagues (Crook et al., 2008, 2009). It has a physiology indistinguishable—to standard testing—from the classic Y/parasol cell, nonlinearly summing its inputs so that it is particularly sensitive to stimuli that flash or move. And yet it is clearly a different cell: (1) the smooth cell is instantly distinguishable from parasol cells in dendritic morphology, (2) it has twice the dendritic field diameter of a parasol cell, and (3) it tiles the retina with a uniform mosaic independent of the mosaic of parasol cells. Thus, the smooth cells send to the brain a coding of the visual input similar to that of the parasol cells, but each smooth cell reports upon a region of visual space about four times as big as that sampled by a parasol cell. The smooth cells project to the lateral geniculate body, way station to the cortex. Why does the cortex need to view the same feature of the world through two different-sized apertures? Is there some other difference in the encoding transmitted by the smooth cell, something not revealed by testing with standard grating stimuli? And how do these separate representations combine to create visual perception? Perhaps the nonstandard visual signals are somehow incorporated into the canonical pattern of visual cortical responses (Hubel and Wiesel, 1965). The alternative is that a fundamentally new concept of higher visual processing will be necessary.

The Road to Completion

The broad view of the retina's organization is now complete, but it remains studded with approximations— "around thirty" types of amacrine cell, "twelve to twenty" types of ganglion cell—and little has been said about synaptic connectivity. How do we get to the next level of precision? It is important here to recognize that the aim is a possibly utopian one: we seek an *exact* enumeration of the retina's component cell types. This is different from the traditional view, which is that the brain is so hopelessly complex (and plastic into the bargain) that the best hope is only a description of selected neural subcircuits, containing just a few types of neurons. Instead, the goal here is to be able to say: "These are the cells of the retina, and the list includes all the cell types that exist." For rods, cones, horizontal, and bipolar cells, our present census is pretty definitive: we can identify the cell types and we can describe them quantitatively. But amacrine cells have been enumerated only in the rabbit retina, and retinal ganglion cells remain a struggle. All workers agree on their broad diversity, and different imaging methods repeatedly show the same cells; but a consensus on a classification of the ganglion cell types has not emerged. How do we get to a definitive description?

The Joys and the Frustrations of Genetically Labeled Cells

In the past few years, strategies for introducing fluorescent labels into subgroups of retinal neurons have appeared (Feng et al., 2000; Huang et al., 2003; Huberman et al., 2009; Kim et al., 2008; Siegert et al., 2009; Yonehara et al., 2008, 2009). The importance of this advance is hard to overstate. These mouse strains breach the barrier that neuronal diversity raises for

electrophysiological studies: the rarity of encountering any particular cell type in repeated experiments. They allow the same ganglion or amacrine cell to be visually targeted for recording. Even if several cell types express the fluorescent marker, one can use the anatomy of the cells to separate them, so that a single type can repeatedly be patched or imaged. An example where the expression is almost “pure” is the Jam-B cell, a ganglion cell type with a curious, wedge-of-pie shape and its own version of direction selectivity (Kim et al., 2008). This cell had been reported in anatomical surveys, but no particular attention had been paid (indeed, one study—by the author of this review—mistakenly classified them as developmental accidents) until a mouse in which they were selectively labeled was available.

These mice will also be useful for validating the retina neurome, because they provide an additional criterion for what constitutes a cell type, but they have a limitation when it comes to accounting for the retinal cell populations. The creation of these mouse strains is still a highly inexact science. This compromises the endgame—the attempt to learn when the census of cell types is complete. Most of the strains that exist so far show mixed expression of the marker in several cell types, or expression in only parts of a true cell population. And there is no way to know anything about the cells that are NOT labeled—no way to know where the labeled cell stands in the whole population of ganglion cells and how many unlabeled cell types remain. How many cells remain for which no one has yet hit upon an effective promoter strategy? What is the true mosaic of genetically marked cells, when one cannot count on reporter expression to mark all of the cell type’s members? Sooner or later, when the molecular fundamentals of gene expression are under better experimental control, a precise algorithm for the creation of cell type-specific lines will be devised and these obstacles will be overcome. In the meantime, other methods will also be required.

High-Throughput Electron Microscopy

An approach that avoids the sampling problem is provided by high throughput electron microscopy, also known as connectomics (Anderson et al., 2009; Briggman and Denk, 2006; Denk et al., 2012; Denk and Horstmann, 2004; Kleinfeld et al., 2011; Lichtman and Sanes, 2008; Seung, 2009). The method, a descendent of early, hand-implemented, serial sectioning (Cohen and Sterling, 1991), requires still-developing computational methods, but even now it is extremely powerful. A small area of retina is serially sectioned and high-resolution images of every cell are reconstructed. In these images, the synapses between the cells can be identified and connections traced. Furthermore, the reconstruction can be made to include a cell of known physiological function, so that synaptic contributions to that particular cell’s response are identified (Briggman et al., 2011). The small size of the retina’s cells—the bane of electrophysiologists—suddenly becomes an asset, because the size of the necessary field and the number of sections are relatively small. This method proved itself in confirming the central postulate of direction selectivity, where special attention was paid to a particular set of amacrine-to-ganglion cell synapses. But it can also be used in less focused ways. For example, a patch of mouse retina 200 μm^2, which is well within the capability of reconstruction technology, contains ~1,500 bipolar cells (Jeon et al., 1998). On average, this would amount to 125 bipolar cells of each of 12 types, more than enough for an independent verification of the types defined using light microscopy and an analysis of their synaptic connectivity. The same could be done for narrow field amacrine and ganglion cells.

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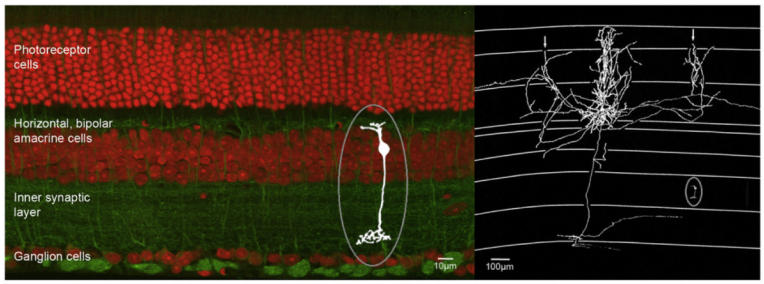

Figure 1. By the Standards of Other CNS Regions, Retinal Neurons Are Miniscule

(A) The layers of the mouse retina. A single bipolar cell is shown in white (adapted with permission from Wässle et al. (2009)). (B) The bipolar cell shown in A is reproduced at its correct scale on an image showing a cortical pyramidal cell. Cortical cell republished from (Gilbert, 1992).

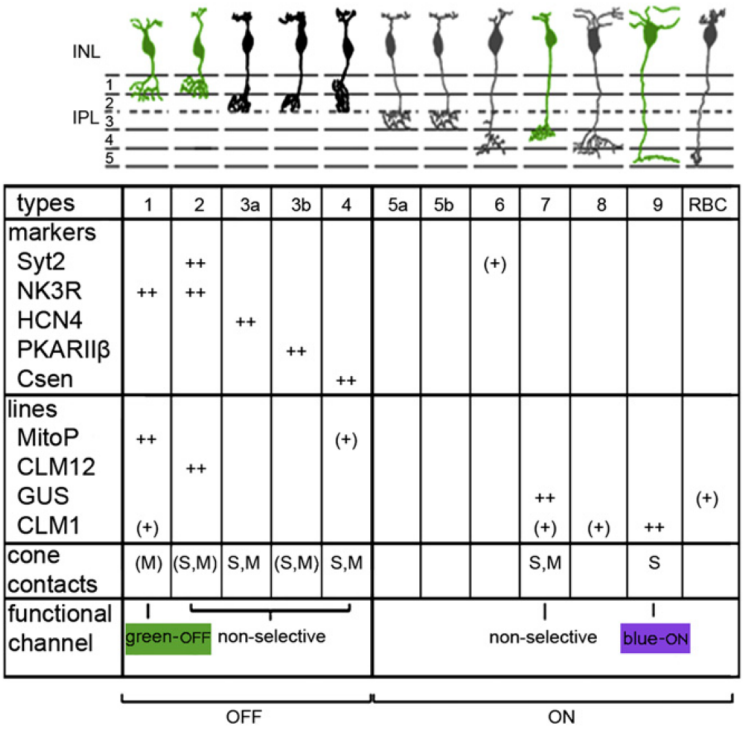

Figure 2. The Types of Bipolar Cells Observed in the Mouse Retina

Note the different stratification within the inner plexiform layer and the molecular diversity of the cells. Reproduced with permission from Breuninger et al. (2011).

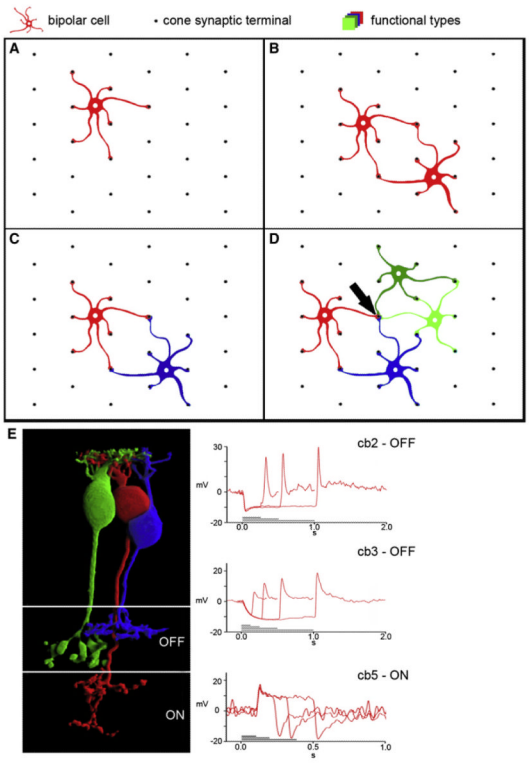

Figure 3. Divergence of the Cone Output into Separate Bipolar-Cell-Mediated Channels

(A) A single bipolar cell contacts all of the cones within its reach.

(B) The dendritic arbors of the bipolar cells can overlap, and this means that each cone can be contacted by more than one bipolar cell. In this panel are shown two bipolar cells, each contacting all of the cones within their reach. Where the two bipolar cells partially overlap, they share a set of cones. For illustration, consider that these two cones transmit the same type of information away from the cones (both are shown in red).

(C) The same two bipolar cells, contacting the same sets of cones, but this time transmitting different types of information away from the cones.

(D) In fact, the dendritic arbors of ~12 types of bipolar cells overlap at any point on the retina. This means that the output of any particular cone is sampled by ~12 different bipolar cells. In principle, each of these types of bipolar cell carries a different reporting of the output of that cone. Four of the bipolar cells that contact one of the cone terminals (arrow) are shown here. Each of these can carry a different signal about the cone's activity, as shown by the different colors in which they are drawn.

(E) Left, structural diversity in three types of bipolar cell from the ground squirrel retina. The overlap of their dendrites shows that these three bipolar cells contact a nearly identical, overlapping, set of cones. Bipolar cells with axons that terminate in the upper half of the IPL are OFF type, whereas those that terminate in the bottom half are ON type. To the right are shown the responses of three morphological types of bipolar cells, two OFF and one ON, during light flashes of different durations. OFF bipolar cells hyperpolarize in the light and produce a transient depolarization at light OFF; ON bipolar cells display the opposite behavior. The shapes of the cb2 and cb3 cell light responses differ in subtle but characteristic ways. Previously unpublished bipolar cell images and responses are courtesy of Drs. Steven DeVries and Adam Light (see DeVries, 2000).

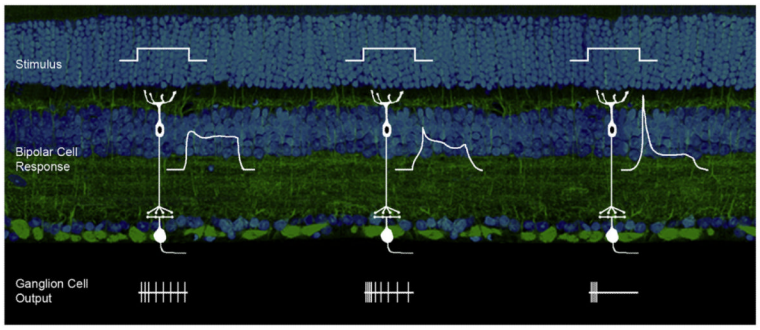

Figure 4. Bipolar Cells with Different Temporal Properties Give Rise to Ganglion Cells with Different Properties

For purposes of illustration, the spiking response of the ganglion cells is shown as though it were driven primarily by the bipolar cell, an approximation that ignores the contribution of amacrine cells. It is important to note that amacrine cells exert substantial control over the responses to light of the bipolar cells themselves. Amacrine cells have feedback synapses upon the axon terminals of the bipolar cells. The bipolar cells are small and electrotonically compact; as a consequence, the response recorded at the soma of a bipolar cell includes the effects of feedback by amacrine cells to that bipolar cell (see text). The stimulus to the bipolar cells was direct injection of current into a connected cone. The responses of bipolar cells are adapted from Saszik and DeVries (2012). Responses of the ganglion cells and bipolar cells are schematic; they do not derive from paired recordings.

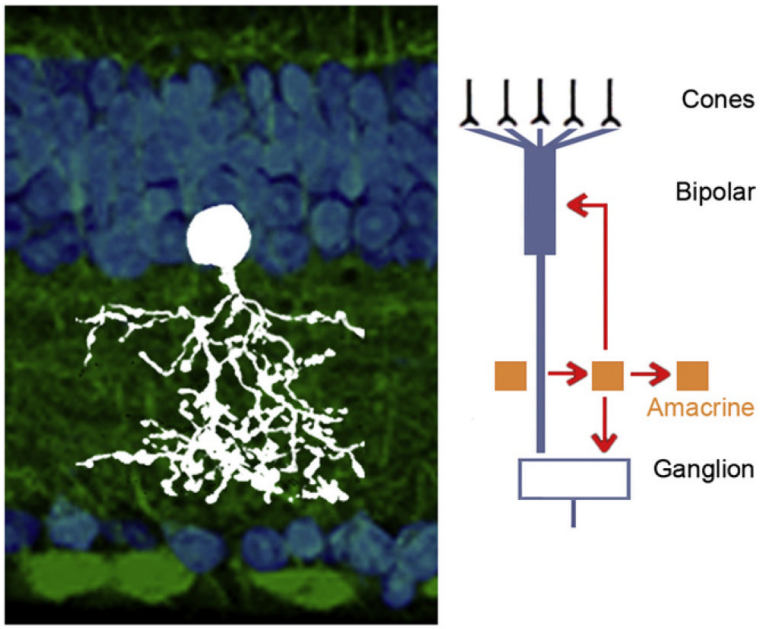

Figure 5. The Structure and Generalized Connectivity of Narrow Field Amacrine Cells

(A) Type 7 glycinergic amacrine cell of the mouse retina. Note that this cell communicates "vertically," interconnecting the ON and the OFF layers of the IPL. Cell image is adapted from Menger et al. (1998).

(B) Block diagram of amacrine cell pathways. Amacrine cells receive input from bipolar cells and other amacrine cells. They make outputs back upon bipolar cells, to ganglion cells, or to other amacrine cells. Thus amacrine cells participate in feedback inhibition, feed-forward inhibition, and lateral inhibition. A single amacrine cell can have all of these arrangements or a subset of them.

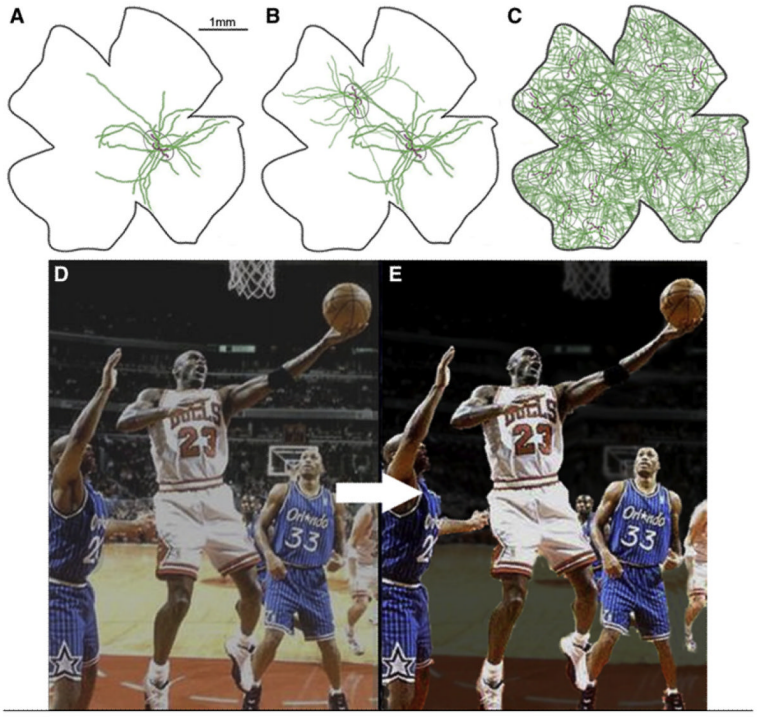

Figure 6. Wide-Field Amacrine Cells Can Span Most of the Surface of the Retina

(A) Whole-mount view of a wide-field amacrine cell termed WA5-1 in the survey of Lin and Masland (2006). This cell's axonal arbor (green) would affect visual stimuli falling in approximately half of the animal's field of view. But the cell receives input from only a limited region of their dendritic fields (red), and presumably the population of cells of this type seamlessly affect images throughout the field, without the gaps that appear when a single cell or only a few of them are taken in isolation, as shown in (B). It does not take a large number of these cells to achieve the nearly complete axonal (green) coverage of the retina shown in (C). If we assume that the dendritic fields (ellipses) nearly tile the retina, the network of axonal processes is dense enough to affect the visual input with an adequate spatial resolution. In fact, the illustration shown here does not achieve tiling of the dendritic fields. If we assume a dendritic coverage of at least unity—higher than is shown here—the axonal coverage would blanket the retina at a very high density indeed. This is the arrangement to be predicted from other known types of retinal cells; whether or not it pertains to this cell will await a population stain.

(D and E) These cells appear to mediate a variety of contextual effects, in which visual events surrounding a particular stimulus condition the response of a ganglion cell to that stimulus. An example is "object motion detection," in which objects that move relative to the general visual field are preferentially reported to the brain (Ölveczky et al., 2003). The effect of this computation is artificially simulated in the lower panels. A native image is shown in (D). The image transmitted to the brain after object motion enhancement is shown in (E): the retinal ganglion cells respond most strongly to objects that are moving relative to the stationary surroundings. (D) and (E) reprinted from (Masland, 2003).

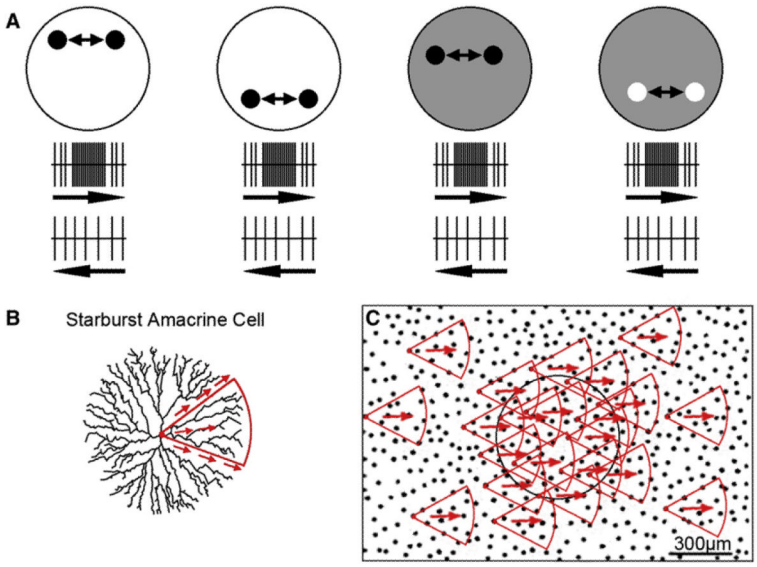

Figure 7. The Cardinal Features of the ON-OFF Direction-Selective Cell, and the Mechanism by Which Direction Selectivity Is Created

(A) The cell can discriminate the direction of motion of small stimuli falling within its receptive field (large circle), and it does not matter where within the field the small stimulus falls—there is a local subunit that is direction selective.

(B and C) The fundamental mechanism of direction selectivity. (B) Shows the dendritic arbor of a starburst amacrine cell. A sector of the arbor (outlined in red) is (1) an independent functional unit, electrically separate from the rest of the cell, and (2) directionally polarized, such that it releases GABA when the stimulus moves in one direction—left to right in this example—and not in others. (C) Starburst sectors pointing in a single direction (red) selectively synapse upon dendrites of an ON-OFF DS ganglion cell (outlined by the black circle). In this example, they would provide inhibition when the stimulus moves from left to right. This cell would thus have a preferred direction for movement right-to-left and a null direction for movement left-to-right. The sectors are smaller than the dendritic field, thus accounting for the ganglion cell's ability to discriminate small movements within the field. Other sectors of the starburst cell, pointing in other directions, would contact other direction selective ganglion cells; those cells would prefer different directions of stimulus movement.

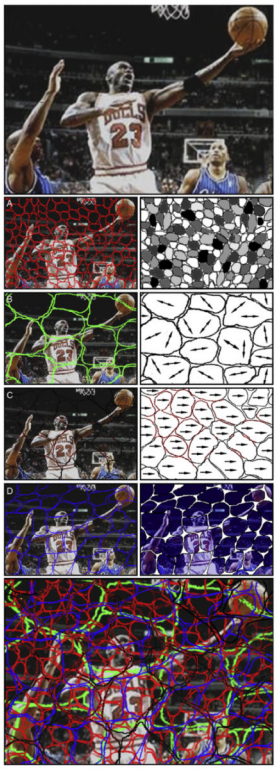

Figure 8. How the Retina Surveys the World

Each type of retinal ganglion cell tiles the retinal surface, and thus covers every visual image completely. The tiles represented by different ganglion cell types are independent of each other. The different types of retinal ganglion cell sample the world through apertures of a different size (determined by the size of their dendritic field). Not only are their apertures different, the sensitivity to features of the stimulus within that aperture is different. This series of panels represents a visual image as sampled by four different types of ganglion cell of a generic subprimate mammalian retina, a subset from a total of about 20 ganglion cell types. (A) The traditional X/midget/brisk-sustained cell. This cell has a small receptive field center with an antagonistic surround, usually modeled as a difference of positive and negative Gaussians. This cell linearly sums inputs falling within its aperture. It therefore can effectively represent gradations of intensity.

(B) The classic alpha/Y/brisk-sustained cell, which nonlinearly sums its inputs and is most sensitive to stimuli that change or move. Note that the sampling aperture (receptive field size) of this cell is large. It can report that something is moving, but cannot tell the brain where, within coarse bounds, the moving object is located.

(C) Direction selective cells also have relatively large receptive fields. They transmit the information that something is moving within the receptive field, but, again, an individual cell cannot accurately tell the brain where inside the receptive field the stimulus lies.

(D) Color coded cells. These report where on the axis from blue to green the spectrum of light within the cell's receptive field is located. In a generic mammalian retina, which has only one short wavelength and one long wavelength cone, this information is transmitted by the blue-ON and blue-OFF ganglion cells.