The fundamental plan of the retina

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The retina, like many other central nervous system structures, contains a huge diversity of neuronal types. Mammalian retinas contain approximately 55 distinct cell types, each with a different function. The census of cell types is nearing completion, as the development of quantitative methods makes it possible to be reasonably confident that few additional types exist. Although much remains to be learned, the fundamental structural principles are now becoming clear. They give a bottom-up view of the strategies used in the retina's processing of visual information and suggest new questions for physiological experiments and modeling.

A simple concept of the retina's function—lateral inhibition by horizontal and amacrine cells, a direct pathway mediated by bipolar cells—is part of the everyday canon of neurobiology. In reality, the retina is a more complex and more subtle structure than the textbooks imply. This is of course true also for other structures of the central nervous system—such as the hippocampus or cortex—where a similar mismatch exists between a simple iconic physiology and the facts of the biological structure. Here I make an initial attempt to come to grips with the real retina, to encompass the system's actual cellular complexity.

Neuroanatomical studies have reached a milestone. The identification and classification of retinal neurons (**Fig. 1**), begun more than 100 years ago by Santiago Ramon y Cajal, is nearing completion—the first time that this has been accomplished for any significantly complex structure of the mammalian CNS. This statement is possible because much of the recent work on retinal cell populations has been quantitative. Staining cells as whole populations permits comparison of their numerical frequency. More importantly, when the number of cells of a general class (such as amacrine cells) is known, one can then determine when the identified types add up to the class total[1–4]. Much detail remains to be learned, and a few additional cell types are sure to be discovered. However, we now know at least that no large cell populations remain unidentified, that there are no major pieces 'missing' within the retina's machinery[5].

Unexpectedly, for most mammals, the numbers of bipolar and amacrine cells are distributed fairly evenly among the different types. This differs from initial impressions, which were much influenced by early studies in primates. The primate fovea is anomalous in being dominated numerically by a single type of retinal ganglion cell, with an associated, specialized type of bipolar cell (see below). In other mammalian retinas, and away from the fovea in primates, individual bipolar, amacrine and ganglion cell types are numerically distributed in a more level way. Although variations certainly exist (generally, there are fewer wide-field than narrow-field neurons), there are no dominant types. In other words, the retina is not composed of a few major players surrounded by a diverse cast of minor ones. Instead, it consists of many parallel, anatomically equipotent microcircuits.

How can this awesome list of cell types be sorted? What unifying principles might allow us to conceive of the retina more simply? From the work of many laboratories[6–11], the fundamental backbone of the retina's structural organization has come into view. It reinforces certain principles learned from physiological experiments, and suggests new questions for further ones. Here I review the retina's structure and point out some unresolved functional issues that it suggests.

Parallel pathways from cones to ganglion cells

A typical mammalian retina contains 9–11 different types of cone-driven bipolar cells. These represent an assortment of pathways from cones to the inner retina, each carrying a different type of information. This diversity was initially shown in the cells' structures and the distinct proteins that each expresses. Electrophysiological experiments are now beginning to reveal its functional consequences.

In most mammalian species, rods outnumber cones by approximately 20-fold, and rods were once considered the primordial photoreceptors. However, molecular cloning of the visual pigments (opsins) that render these cells light-sensitive led to the conclusion that cone pigments evolved long before rhodopsin, the rod pigment[12–14]. The early photoreceptor thus seems to have been some type of cone (**Fig. 2a**). In retrospect, this makes sense; in building a cell to detect light, one would surely design it for times when copious light is available. (In starlight, a human rod photoreceptor has been calculated to receive only one photon every 10 minutes[8,15].) Cones are associated with a complex network of postsynaptic cells, whereas the circuitry strictly associated with rods is minimal; even though rods outnumber cones, most mammalian retinas have 8 to 10 cone-driven neurons for every cell associated primarily with the rod pathway.

The existence of multiple subclasses of cone-driven bipolar cells ('cone bipolars') was initially predicted on structural and molecular grounds[11,16,17]. First, bipolar cells branch at different levels of the inner plexiform layer[18], which contain processes of different types of amacrine and ganglion cells. Some ganglion cell types have dendrites confined mainly to level 1 of the inner plexiform layer, others to level 2, and so on. The inner plexiform layer, named as though it formed a single, tangled 'plexus,' is in fact an ordered stack of synaptic planes, more like a club sandwich than a plate of spaghetti. Specific bipolar cells make their synapses within specific planes,

and this confines their possible synaptic partners to cells with processes that occupy those same levels. Second, different types of bipolar cells have different numbers and distributions of synapses, without a gradation of intermediate forms between the types. The conclusion reflects more than neuroanatomical anecdote; a formal cluster analysis showed that cone bipolars segregate into discrete groups based on synapse number and distribution[16,19]. Third, individual bipolar cell types have characteristic sets of neurotransmitter receptors and calcium-binding proteins[20–22]. These molecular distinctions reflect different modes of intracellular signaling and different types of excitatory and inhibitory inputs from other retinal neurons, either at their inputs from cones or from amacrine cells that synapse on their axon terminals. At the cone synapses, different glutamate receptors are present. At their axon terminals, different bipolar cells can receive inhibitory glycinergic or GABAergic input via one of two different kinds of GABA receptors. The different receptors and their channels have differing affinities and rates of activation and inactivation, which give the cells different postsynaptic responsiveness[22–25].

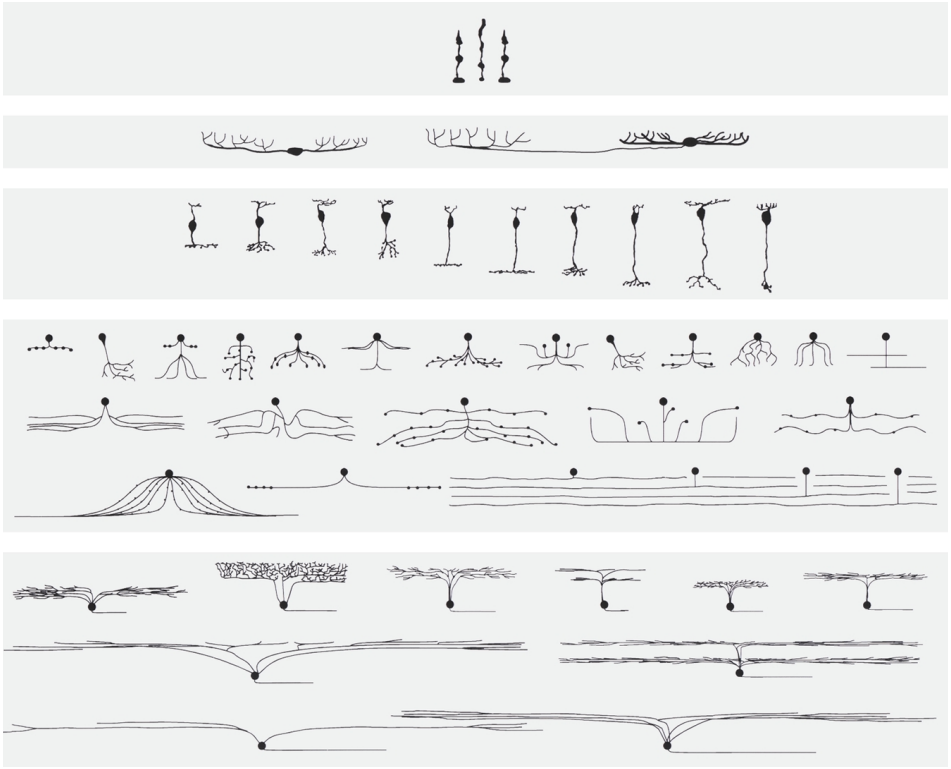

Fig. 1. The major cell types of a typical mammalian retina. From the top row to the bottom, photoreceptors, horizontal cells, bipolar cells, amacrine cells and ganglion cells. Amacrine cells, the most diverse class, have been studied most systematically in the rabbit[3,4], and the illustration is based primarily on work in the rabbit. Most of the cells are also seen in a variety of mammalian species. The bipolar cells are from work in the rat[39]; similar ones have been observed in the rabbit, cat[16] and monkey[17]. For steric reasons, only a subset of the wide-field amacrine cells is shown.

How are these differences manifested physiologically? First, the output of the cone photoreceptors is separated into ON and OFF signals (**Fig. 2b**). All cone synapses release glutamate, but bipolar cell types respond to glutamate differently. Some bipolar cells have ionotropic glutamate receptors: glutamate opens a cation channel, and the cell depolarizes. Other bipolar cells have a sign-inverting synapse mediated by metabotropic glutamate receptors, mainly mGluR6; these bipolar cells hyperpolarize in response to glutamate[26,27]. As it happens, photoreceptor cells work 'backward' (they hyperpolarize when excited by light, causing their synapses to release less glutamate), but the ensuing series of sign-reversals is not important for present purposes. When the retina is stimulated by light, one type of bipolar cell hyperpolarizes, and the other type depolarizes. OFF and ON bipolar cells occur in approximately equal numbers. The distinction, created at the first retinal synapse, is propagated throughout the visual system.

The classes of ON and OFF bipolars are each further subdivided; there are three to five distinct types of ON and three to five types of OFF bipolars (**Figs. 2c** and **3**). The purpose of the subdivision is, at least in part, to provide separate channels for high-frequency (transient) and low-frequency (sustained) information. Thus, there are separate ON-transient, ON-sustained, OFF-transient and OFF-sustained bipolar cells[28–30]. An elegant series of experiments shows that the distinction is caused by different glutamate receptors on the respective OFF bipolar cells; they recover from desensitization quickly in the transient cells and more slowly in the sustained cells[31].

An often-cited reason for splitting the output of the cones into separate temporal channels is to expand the overall bandwidth of the system. However, this would imply that the frequency bandwidth present at the output of a cone is too broad for transmission through the cone-to-bipolar synapse, which is uncertain given the many modes of synaptic transmission available. An alternative is that fractionating the temporal domain facilitates the creation of temporally distinct types of ganglion cells (**Fig. 4**).

An important point here is that there are no dedicated cones—cones that provide input, say, only to ON bipolars or only to OFF bipolars (as shown for simplicity in **Fig. 2**). Instead, the output of each cone is tapped by several bipolar cell types to provide many parallel channels, each communicating a different version of the cone's output to the inner retina (**Figs. 3**, **4** and **6**).

The foundations of color vision

The bipolar cells discussed so far are not chromatically selective, and this would prevent the retina from discriminating among wavelengths. A single type of cone, no matter how narrow its spectral tuning, cannot create color vision. A cone's synaptic output is a single signal, which can vary only in magnitude. For that reason, a cone's signal to the brain is inevitably ambiguous; there are many combinations of wavelength and intensity that will evoke the same output from the cone. To specify the wavelength of a stimulus, the outputs of at least two cones must be compared.

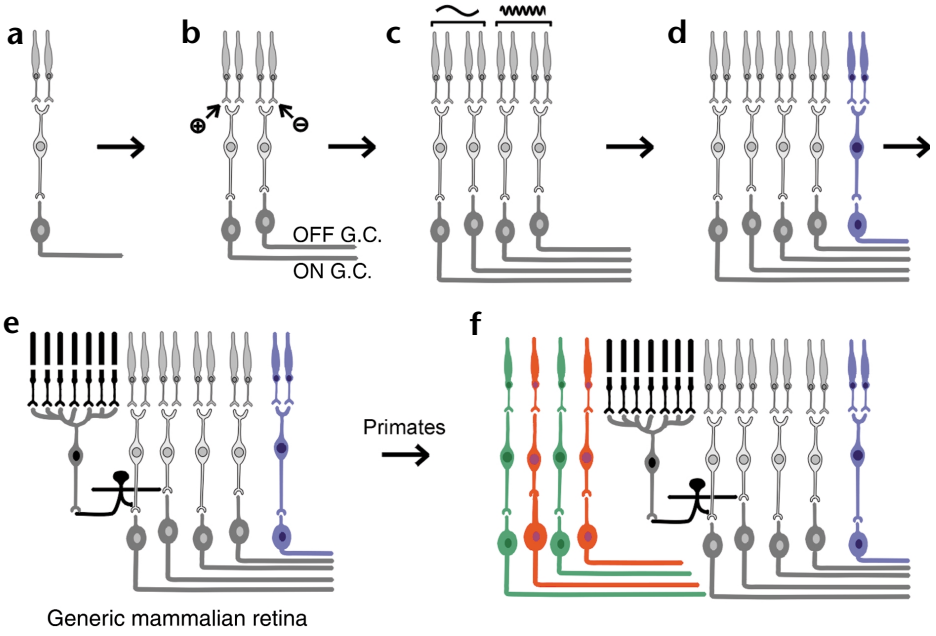

Fig. 2. The bipolar cell pathways of mammalian retinas, assembled from individual components. This diagram is intended to emphasize the overall organization of the parallel channels, and much detail is omitted. Many primate retinas have midget bipolar and ganglion cells, but only a few have a separate red and green channels. Rods are not as clumped as would be suggested here. For visual clarity, cones are shown contacting only a single bipolar cell each; in fact, all cones contact several bipolar cells, as shown in Figs. 3, 4 and 6. For the detailed synaptology of the rod pathway, see refs. 36, 37, 125.

Early in evolution, two cone opsins diverged, one with maximal absorption at long wavelengths and one with maximal absorption at short wavelengths[12–14]. Because an individual cone contains only a single spectral type of opsin, this creates two types of cones, one reporting on long wavelengths and one on short; by comparing their outputs, the retina can create a single signal that reflects the spectral composition of the stimulus.

The short-wavelength-sensitive cone, familiarly termed the 'blue cone,' occupies a distinct and simple position in the array of retinal circuitry: blue cones synapse on their own specialized type of bipolar cell, which in turn synapses on a dedicated class of retinal ganglion cells[32,33]. Blue cones generally make up less than 15% of all cones. The retina thus contains many long-wavelength cones, which communicate to ganglion cells via a variety of bipolar cells, a single type of blue cone, and a single type of blue cone-driven bipolar cell (**Figs. 2d** and **3**).

The synaptic connections of the inner retina are arranged so that the outputs of some ganglion cells compare the responses of the blue cones with those of the long-wavelength cones. For example, the ganglion cell may be excited by short-wavelength stimuli and inhibited by long wavelengths. This represents an economy; a single signal tells the brain where along the spectrum from blue to yellow the stimulus lies.

This combination of a short-wavelength cone and one or more long-wavelength cones is a virtually universal feature of mammalian retinas[14]. At one time, many mammals were thought to lack color vision, and indeed an animal with only these two visual pigments is a dichromat—in everyday language, red–green 'color blind.' But the phrase is misleading; the distance between the peak sensitivities of the short and long opsins spans the wavelengths reflected by important objects in the natural world, and an animal with only those opsins has a strong form of color vision. If any doubt exists on this point, one should remember that roughly 5% of humans inherit this form of dichromacy, but many learn of it only during adulthood, when first confronted by tests designed to reveal variations in color vision.

The pathway from rods to ganglion cells

Most amacrine cells and all ganglion cells receive their main bipolar cell synapses from cone bipolars, but retinas work in starlight as well as daylight, and this range is created by a division of labor between cones (for bright light) and rods (for dim light). Signals originating in rod photoreceptors reach the retinal ganglion cells via an indirect route using as its final path the axon terminals of the cone bipolar cells[34–37].

That a single set of ganglion cells is used for both starlight and sunlight represents an obvious efficiency, long known from electrophysiological findings. However, it was not obvious *a pri-*

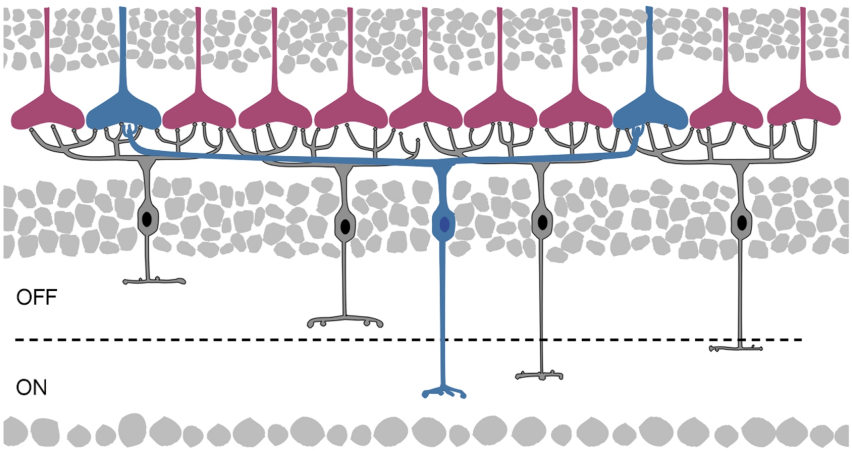

Fig. 3. The connections with cones and axonal stratification of different types of bipolar cells. Five different types of bipolar cells are illustrated. Two of them are diffuse (chromatically nonselective) ON bipolar cells terminating in the inner half of the inner plexiform layer. Two are diffuse OFF bipolar cells terminating in the outer half. Each samples indiscriminately from the spectral classes of cones. The blue cone bipolar, however, contacts only blue cones and thus is spectrally tuned to short wavelengths. Within the ON or OFF sublayer, axons of the bipolar cells terminate at different levels, indicating that they contact different sets of postsynaptic partners. After refs. 9 and 17.

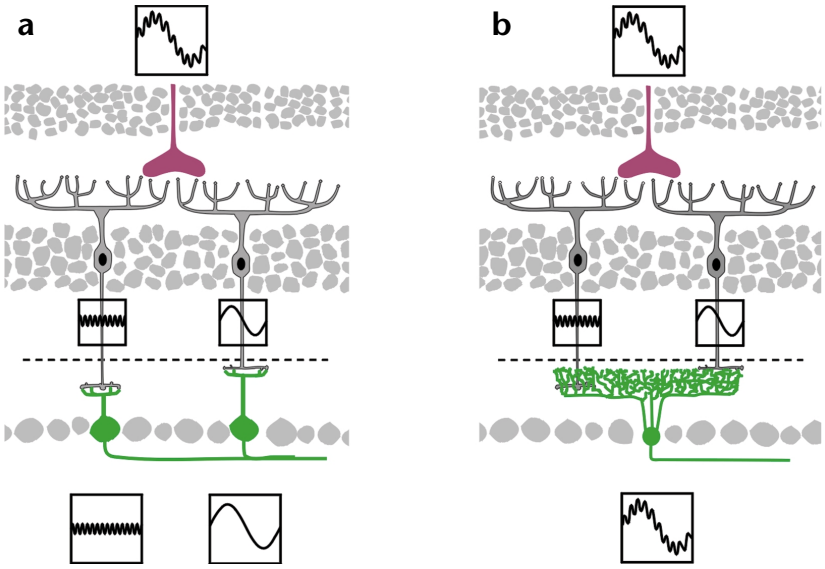

Fig. 4. How transient (high-pass) and sustained (low-pass) bipolar cells decompose the output of a cone. The resulting high- and low-frequency channels can contact narrowly stratified ganglion cells (**a**), in which case the two frequency bands are transmitted via separate, parallel channels to the brain. Bottom, a more broadly stratified ganglion cell (such as a beta cell) receives input from both types of bipolar cells[123]. Such a ganglion cell (**b**) has a broadband response. Many such combinations are possible, as are many permutations of input from amacrine cells.

ori that rod-driven information would reach the ganglion cells by an indirect path. Furthermore, rod photoreceptors far outnumber cones in most mammalian retinas; it was a surprise to learn, when quantitative methods became available, that cone bipolars outnumber rod bipolars in all but a few mammalian retinas[2,38]. The reason is that more rods converge onto a single rod bipolar than cones onto cone bipolars; the rod system trades acuity for sensitivity, and the circuitry associated with rods is simpler than that of cones (**Fig. 2e**).

Because rods evolved after cones, the likely scenario is that the rod circuitry was grafted onto the cone pathways. Only one kind of rod photoreceptor exists, and rods drive only a single type of bipolar cell. It synapses on a specialized amacrine cell, termed AII, which then transmits the output of rod bipolar cells to ganglion cells. This occurs largely via synapses (chemical or gap junctional) by AII onto axon terminals of cone bipolar cells, which then excite the ganglion cells.

It may seem strange that rod bipolar cells would not simply drive retinal ganglion cells directly, but seems less strange when one appreciates the complexity of the pre-existing inner retinal circuitry of the cone pathways. By synapsing on the axon of the cone bipolar cell, the rod pathway gains access to the elaborate circuitry of the cone pathway, including its associated amacrine circuitry. For example, the directionally selective type of ganglion cell retains its function in very dim light, even though it receives no direct synapses from the rod bipolar cells. The rod system piggybacks on the cone circuitry rather than re-inventing it.

Added complexities in the primate retina

At one time, primate retinas were thought to be somehow simpler than those of lower mammals, because recordings from the central retina of monkeys show mainly a simple type of center–surround ganglion cell physiology; complex properties like direction selectivity are statistically rare. However, the relative conservation of bipolar and amacrine cell types in monkeys and other mammals is now well documented[7,17,22,38–41]. Furthermore, such a conclusion would imply, remarkably, that retinal circuitry evolved over millennia was discarded. Instead, to the already existing retina were added three specializations: an additional chromatic class of cone, a rod-free fovea, and a huge number of small bipolar and ganglion cells, the so-called midget system (**Fig. 2f**).

The retina of a macaque monkey contains approximately 1,500,000 retinal ganglion cells; a cat, 160,000; a rabbit, 380,000 (refs. 1, 9, 42) . Around 70% of the ganglion cells of the monkey's retina are midget cells. They have a simple center–surround organization with linear spatial summation in the receptive field center. Associated with midget ganglion cells is a special midget bipolar cell. In the fovea, an individual ganglion cell receives direct input from only a single cone. The fundamental advantage offered by a midget system is a high sampling density, which enables great spatial resolution. In the central fovea, the spatial resolution of the entire system—photoreceptors, bipolars and ganglion cells—is limited only by the cone packing density[43].

In humans and some species of monkey, gene duplication followed by mutations affecting a few amino acids caused the long-wavelength opsin present in all mammals to evolve into two closely related opsins with slightly different absorption maxima[44,45]. Such retinas thus contain the widely conserved blue cone (with its specialized bipolar and ganglion cells), a long-wavelength 'green' cone and a slightly different long-wavelength 'red' cone. This does not change the fundamental organization of color vision; it simply creates better color discrimination between long wavelengths.

How the output of red and green cones is transmitted to the central visual system is a matter of controversy. The majority opinion is that it is transmitted via the midget system[10,11,46,47]. Midget bipolar and ganglion cells automatically have the spectral sensitivity of the single cone from which they receive input, so that the existence of the midget system perforce creates separate channels for the two longer wavelengths. A minority view holds that there is an as-yet-undiscovered ganglion cell, analogous in its circuitry to the blue/yellow ganglion cell, that compares red and green wavelengths[48].

Two types of horizontal cells

All rods and cones receive feedback from horizontal cells, but these cells are a numerically small proportion of the retina's interneurons, generally less than 5% of cells of the inner nuclear layer[2,38,40]. In most mammals, there are two morphologically distinct types of horizontal cells[49–52]. (Mice and rats have only one.) In monkeys, these have different numbers of synapses with different types of cones. The reason for this biasing is not yet certain; it may involve chromatic opponency in the red–green system. Traditionally, horizontal cells are said to enhance contrast between adjacent light and dark regions. Excitation of a central cone causes feedback inhibition of both the excited cone and a ring of neighboring ones. Because each cone—both the central one and its neighbors—transmits a sig-

nal to the inner retina, the upshot is that a small stimulus excites those ganglion cells that lie directly under the stimulus, but inhibits neighboring ganglion cells. This is the classical 'center–surround' organization, in which a ganglion cell is excited or inhibited by stimuli falling in its receptive field center, whereas stimulation of the surrounding region has an opposite effect.

An alternate formulation of the same facts is that horizontal cells adjust the system's response to the overall level of illumination—they measure illumination across a broad region and subtract it from the signal that is transmitted to the inner retina about a local image[8]. In effect, this reduces redundancy in the signal transmitted to the inner retina. The mean luminance across a large region of retina is shared by many cones and contains little information. When a local stimulus occurs, it exceeds or falls below the mean; the occurrence of that local event is the main signal transmitted to the inner retina.

Rods receive a separate type of horizontal cell feedback; this is accomplished by a specialization of one of the horizontal cells (the b/H2 type) that contacts cones. An axonal process of this horizontal cell contacts the rods, but does it far enough away from the horizontal cell's soma that the axonal arbor is electrotonically isolated[53]. The rod feedback system is thus isolated from the cone feedback system, sensibly because the ranges of brightness covered by rods and cones are so enormously different. This may be another consequence of the late evolution of rods. It allows the rods to have an independent horizontal cell feedback, driven by rods and feeding back to rods, without the creation of a third type of horizontal cell.

Twenty-nine types of amacrine cells

All retinal ganglion cells receive input from cone bipolar cells, but direct synapses from bipolar cells are a minority of all synapses on the ganglion cells; most are from amacrine cells[54–56]. The exact fraction varies among different functional types of ganglion cells, ranging from roughly 70% for alpha cells (large, movement-sensitive ganglion cells found in most mammals) to 50% for the midget ganglion cells located in the monkey central fovea. Amacrine cells also make inhibitory synapses on the axon terminals of bipolar cells, thus controlling their output to ganglion cells. In contrast to horizontal cells, which have a single broad role, amacrine cells have dedicated functions—they carry out narrow tasks concerned with shaping and control of ganglion cell responses.

Traditional presentations of the retina underweight the importance of amacrine cells, which are sometimes illustrated in a 1:1 ratio with horizontal cells[57,58]. They in fact outnumber horizontal cells by amounts that range from 4:1 to 10:1 (depending on the species) and can outnumber ganglion cells by 15 to 1 (refs. 2, 38, 40) . How can this complexity be understood? A first impulse is to deny that it exists—perhaps the taxonomy has been made artificially complex, or cells that look different actually have identical functions? It turns out that neither of these is tenable. The different amacrine cells have distinct pre- and postsynaptic partners, contain a variety of neurotransmitters, survey narrow areas of the visual scene or broad ones, branch within one level of the inner synaptic layer or communicate among many[3,4]. Both their molecules and their form point to diverse functions.

Amacrine cells seem to account for correlated firing among ganglion cells. Shared input from a common amacrine cell will tend to make ganglion cells fire together; the cross-correlation is broad if mediated by chemical synapses and narrower if mediated by gap junctions, known to couple amacrine and ganglion cells[59]. Correlated firing between ganglion cells has been proposed to represent a form of multiplexing, which could expand the information-carrying capacity of the optic nerve[60,61].

Those amacrine cells with functions that are more precisely understood do remarkably specific jobs. The dopaminergic amacrine cells globally adjust the retina's responsiveness under bright or dim light[62–64]. They are numerically sparse (9000 cells in a rabbit retina that has 4,500,000 amacrine and 380,000 ganglion cells)[65] and have wide-spreading arbors located in inner plexiform layer 1. Dopamine affects many elements of the retina's circuitry; it alters the gap-junctional conductance between horizontal cells and between amacrine cells[66,67], potentiates the responses of ionotropic glutamate receptors on bipolar cells, and ultimately affects the center–surround balance of ganglion cells[68,69]. Remarkably, retinal dopamine can even cause pigment migration in cells of the retinal pigment epithelium, a neighboring non-neural tissue[70]. In the latter case (and very likely some of the former as well), this is mediated non-synaptically, via a diffuse, paracrine release of the neurotransmitter. Elegant experiments using transgenically labeled amacrine cells in culture show that the extrasynaptic release is controlled by spontaneous action potentials in the absence of synaptic input and modulated by inputs, presumably also paracrine ones, from other retinal neurons[71,72].

In contrast, the starburst amacrine cells seem to be narrowly associated with a particular computational circuit. They arborize in thin (2–4 μm) strata within the inner plexiform layer, where they make excitatory cholinergic synapses on certain retinal ganglion cells, notably those particularly sensitive to moving stimuli. By feedforward excitation and/or inhibition (these neurons release both acetylcholine and GABA[73]), they are important for direction selectivity[74–76].

Ten to fifteen types of retinal ganglion cells

It became possible to record from retinal ganglion cells before modern anatomical techniques were invented, and early ideas of this population were much influenced by electrophysiological results, with their inherent sampling biases. These described two types of concentrically organized receptive fields, one with a small, linearly summing receptive field center (X cell) and another with a large, non-linear responsive area (Y cell). Systematic anatomical studies now make it apparent that many other types of ganglion cells exist. These are easily distinguished by their branching level, their dendritic arbor width (that is, the area of the visual field that they sample), and in many cases, their directly recorded physiology[77–80] (**Figs. 1** and **5**).

In all cases studied thus far, cells distinguished by structural criteria have turned out to have distinct physiologies. In the cat, the correspondence between X-cells and β, and Y-cells and α was established long ago, as was the analogous match between P and M, midget and parasol cells in the monkey[17]. Other cell types were studied early in the rabbit, using direct recording from the retina (where the problem of electrode selectivity is lessened)[81–85]. A bistratified neuron is the famous ON–OFF direction-selective cell. A similar but monostratified medium-field neuron is the ON-type direction-selective cell, which projects to the accessory optic system and provides an error signal for eye velocity in optokinetic nystagmus. An extremely small, monostratified neuron is the local edge detector described in classic electrophysiological studies.

In the monkey, a small bistratified neuron is the blue ON cell, and a larger, sparser neuron is a blue OFF cell. In both the

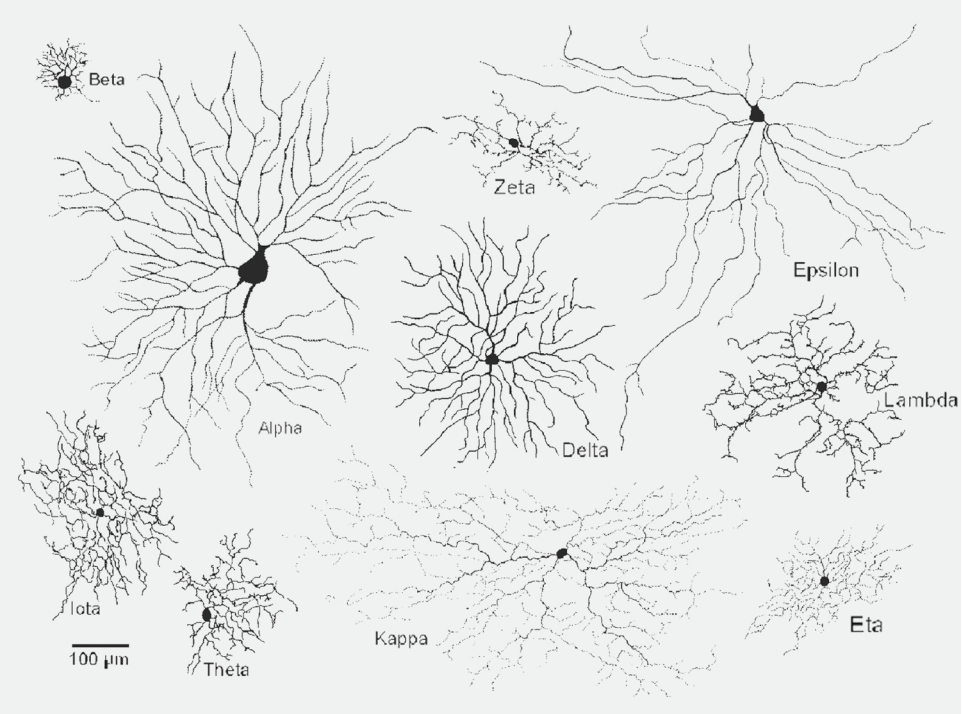

Fig. 5. The types of ganglion cells identified thus far in the retina of the cat. Ongoing work in the rabbit and monkey confirms this diversity, and many of the cells observed are probably homologs of those seen in the cat. Courtesy of D. Berson[77–80].

cat and monkey, a very large, very rare neuron has tonic responses to light and projects to a pretectal nucleus; it seems to control pupillary size. A similarly rare neuron projects to the cat suprachiasmatic nucleus, presumably to entrain circadian rhythms. Remarkably, this cell seems to be directly photosensitive (D.M. Berson, F.A. Dunn & M. Takao, *Invest. Ophthalmol. Vis. Sci.* **42**, S113, 2001)[86].

The primate fovea, with its huge number of midget cells, seems to have been superimposed upon existing ganglion cell populations that were little changed during the primate's evolution from earlier mammals. Some of these cells seem to correspond to neurons present in lower mammals and carry out 'vegetative' functions, such as the control of pupil size and optokinetic responses. Evidence for autonomous subcortical pathways that mediate these functions in the monkey is that both survive combined lesions of the visual cortex and superior colliculus[87]. It takes only a few neurons to measure the ambient level of illumination, which controls the pupillary aperture. There is no particular need for this number to increase as the total number of ganglion cells increases, and they end up as a small fraction of the total cells. A monkey retina that has 1,050,000 midget ganglion cells could comfortably 'contain' the ganglion cell population of an entire cat or rabbit retina within its remaining 450,000 cells[11].

For this purely statistical reason, non-midget, non-parasol cells in the monkey have largely been ignored. However, modern methods, notably, visually guided microinjection[88,89], are now providing an increasingly clear anatomical view of the other ganglion cells of the monkey[90–93]. There is some reason to suspect that the geniculostriate system receives non-midget, non-parasol types of information, and learning more about these cells' physiology seems important (see below).

Visual function: new certainties and new questions

A reward of structural studies is the level of certainty that their hard-won conclusions provide. The demonstration that X and Y cells are anatomically distinct entities helped still an acrimonious taxonomic controversy among electrophysiologists. Psychophysicists had long suspected that vision along the blue–yellow axis is different from vision along the red and green axis, which is given a concrete basis in the sparseness of blue cones and their bipolar cells. An exact synaptic wiring[33,47,91,94] now underpins the receptive field of the blue-ON ganglion cell, accurately predicted 35 years ago[95].

A different kind of contribution comes from the quantitative nature of such studies. Human visual acuity, for example, is now known to precisely match the packing density of the foveal cones[43,96]. This contribution is sometimes taken for granted, but should not be; our concept of central visual processing would be different if primate M cells were not 8% of all ganglion cells, as shown anatomically, but 30–50%, as would be concluded from their encounter frequency in electrophysiological experiments. As modeling of higher visual processes becomes more precise, knowledge of such physical parameters becomes increasingly useful.

Structural results also raise new questions; the cell populations of the retina hint at unsuspected subtleties in the retina's input–output relationships, some of which must have consequences for vision. For example, what are the remaining physiological types of retinal ganglion cells, and how do they contribute to behavior? The question here is the physiological response properties of the non-concentric (X and Y, M and P) types of cells and their function in the central structures to which they project. For subcortically projecting cells, those roles may be very sophisticated. The ON directionally selective cell of the rabbit, for example, projects to the accessory optic system and drives optokinetic responses[85,97]; the baroque morphologies of non-midget, non-parasol cells that project subcortically in the monkey suggest equally subtle physiologies. These questions should be answerable by *in vitro* recording followed by microinjection[89,92].

We need to complete our understanding of the synaptic basis of color vision. Here our colleagues who study higher visual centers are struggling; the cortical coding of color has been a tangled subject[98–100]. If the red–green axis is coded in the retina by a distinct, dedicated set of retinal ganglion cells, then one might expect a single cortical mechanism to code for color along both the red–green and blue–yellow axes. If red and green are transmitted separately, via the late-evolving midget system, higher centers may have anatomically and/or computationally independent ways of handling the two axes.

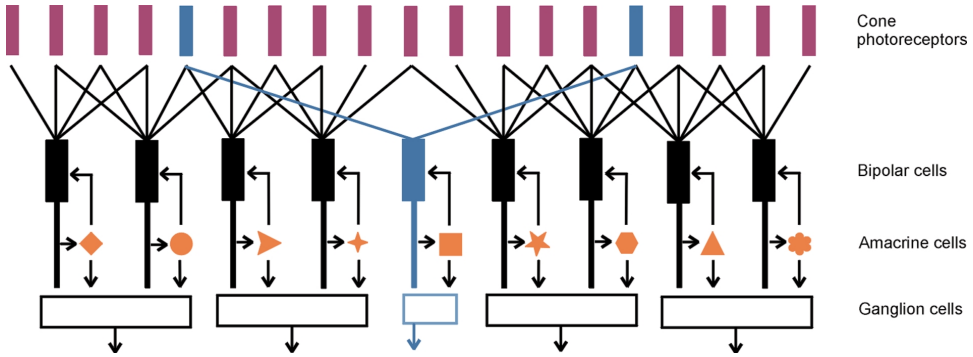

Fig. 6. The fundamental signal-carrying pathways of a generic mammalian retina, reduced to a conceptual minimum. Each type of bipolar cell (black) transmits a different type of information to the inner retina. The information that it transmits is determined by the bandwidth of the cones that it contacts, the number and type of those cones, the transfer function of the cone to bipolar synapse, and its interplay with amacrine cells. This is a minimal representation of the amacrine cells, which also include wide-field cells and which have synaptic contacts among each other. The different types of bipolar cells are contacted by distinct types of amacrine cells, in a variety of synaptic arrangements. These converge upon the retinal ganglion cells, in which specific combinations of bipolar and amacrine inputs create many functional types of ganglion cells.

In the lateral geniculate body of the monkey, several specialized types of cells project to the K (koniocellular) layers of the lateral geniculate body[101,102]. There are hints of other types of cells mixed among the cells of the magnocellular and parvocellular layers, and history teaches that it is possible to miss even a sizable class of cells when using metal microelectrodes[103]. Even though the remaining cells may be few in number, they are not necessarily unimportant for vision. The blue-ON ganglion cells make up less than 6% of all ganglion cells in the monkey but are a fundamental basis of primate color vision. Similarly, parasol cells make up 8% of all ganglion cells, yet are thought to be the source of a major stream of cortical information flow. Newly expanded techniques for recording from ganglion cells backfilled from specific central targets (D.M. Dacey *et al.*, *Invest. Ophthalmol. Vis. Sci.* **42**, 114, 2001) should soon provide a more complete description of the information that enters the geniculostriate system.

Microstructure within the receptive field center

A surprise when the complete array of amacrine cells was revealed was the plethora of narrow-field amacrines, which make up almost 50% of amacrine cells in the rabbit, rat and monkey and thus represent 20–30% of neurons in the inner nuclear layer[3,4,104,105]. How do they affect ganglion cell physiology?

In addition to amacrine AII (a link between the rod system and the ganglion cells), there are, in the mid-periphery of the rabbit retina, 11 types of amacrine cells with dendritic arbors less than 100 μm in diameter. In the same region, the diameters of retinal ganglion cell arbors range from 200 to 1000 μm. This means that many narrow-field amacrine cells exist within the dendritic field, and thus the receptive field center, of most ganglion cells.

If nothing else, the finding invalidates the textbook generalization that the function of amacrine cells is to carry information laterally across the retina; these cells are scarcely more laterally conducting than are the bipolar cells. It also suggests that more information processing occurs within the center of the ganglion cell's receptive field than is usually credited. Indeed, many narrow-field amacrine cells of each of several types tile the retina within each ganglion cell's receptive field. They must affect the transfer of information through the retina, with a spatial resolution similar to that of the bipolar cells, but the nature of the transformation remains to be learned.

A likely possibility is that some of the narrow-field amacrines are involved in contrast gain control[106], which may cause, among other things, a 'predictive' response of ganglion cells to moving stimuli[107]. However, it is not at all apparent why a conceptually simple function such as a negative, contrast-driven feedback would require 11 different kinds of amacrine cells. Other narrow-field amacrine cells carry out temporal sharpening; amacrine AII generates regenerative currents, which give the leading edge of its response to light a fast rise time[108,109]. Many narrow-field cells communicate among several layers of the inner plexiform layer and thus carry out 'vertical inhibition'[110], named by analogy to the familiar lateral inhibition mediated by horizontal cells.

Too many wide-field amacrines

Why there are so many wide-field amacrine cells? The rabbit has five kinds of medium-field amacrine cells (dendritic arbors ~175 μm) and at least ten wide-field types[3,4]. The latter can have dendrites that run for millimeters across the retinal surface[111,112], suggesting that long-range lateral integration, spreading far across the retina, may be more important than has been recognized[113]. Some of the cells have sparse, relatively simple arbors. Others have garden-variety dendritic arbors but also have axon-like processes that can span 5 to 10 mm across the retina's surface. Recording from two types in mammals reveals that they have receptive fields coterminous with their dendritic arbors and that they generate action potentials, which should conduct activity far from the main dendritic arbor[114,115].

Hints that activity spreads over long trans-retinal distances were evident long ago from the 'periphery effect,' a simple demonstration that stimulation outside the classical receptive field can change retinal sensitivity within the receptive field. There is also a recent report of oscillatory 40-Hz activity correlated for up to 10 mm across the cat's retina[116,117]. However, the exact function of these lateral effects is not known, nor is the need for multiple types of wide-field amacrine cells explained. Perhaps lateral conduction is required in viewing natural scenes, which contain wider ranges of contrast and more complex trans-retinal motion than the usual laboratory stimuli.

Contrast gain control is a critical 'normalization' function at the front end of the visual system, and there is direct evidence for both narrow and wide forms of it. Recently, two studies eval-

uated temporal contrast adaptation using reverse correlation and flickering checkerboards. They produced evidence for both a mechanism that works on a large spatial scale[118] and one that is extremely local—operating on a scale, in the rabbit, of approximately 100 μm, a fraction of the size of the receptive field center for many ganglion cells[119]. There is some evidence that the rate of adaptation is different for different-sized stimuli. This suggests the existence of multiple, independent forms of contrast adaptation. One form of temporal contrast adaptation seems to operate entirely within the bipolar cells themselves, because it persists in the presence of pharmacological agents that should block amacrine cell function. For larger stimuli, the array of amacrine cells may contain several mechanisms by which the responsiveness of the retina is tuned to the characteristics of the visual environment.

What are the fundamental channels of vision?

A final question concerns events at the heart of the retina's design. What are the separate filters represented by the different types of bipolar cells, and how are they reflected in the information transmitted centrally?

The diffuse bipolar cells represent as-yet-undeciphered parallel channels by which the retina parses the visual input (**Fig. 6**). In some cases, the operation performed by bipolar cells is obvious. The blue bipolar cell acts as a spectral filter tuned to wavelengths peaking at about 420 nm, and to moderate spatial frequencies. The red and green midget bipolars of primates are tuned to their particular wavelengths and to higher spatial frequencies. Roughly half the diffuse bipolar cells carry out a sign inversion creating the ON and OFF classes of response. Within each broad class (ON or OFF) of diffuse bipolars, though, there are at least four specific subtypes of bipolar cells of uncertain tuning. We learn their approximate spatial tuning from their dendritic spread, but we have only hints from their neurotransmitter receptors and channels about their dynamic properties.

From early studies in cold-blooded vertebrates[28,29,120], and more recent studies in mammals, bipolar cells were found to come in sustained (low-pass) and transient (high-pass) varieties. Results from salamander retina[30,121] point to even greater diversity, and this is also clear in the existing recordings from cone bipolar cells of mammals[25,31,122]. Although these experiments are technically difficult, a critically important challenge to physiologists is to precisely characterize the behavior of each channel.

Another challenge is to learn how the bipolar channels are recombined at the level of the ganglion cell (**Figs. 4** and **6**). Here, modeling techniques may be useful. The central problem is to understand, especially in the temporal domain, how the final response of a ganglion cells is created from one or several bipolar cell inputs[123]. It is unlikely that anyone will soon record simultaneously from one ganglion cell and two bipolar cells; models or simulations may clarify our thinking in this realm.

A higher-order question is how the parallel channels created by bipolar cells are reflected in the central visual system. The first limiting event for scotopic vision is the capture of photons by the cone mosaic. Even though cones' output is much transformed later—within the retina and higher in the visual system—vision's overall sensitivity, chromatic selectivity and resolution depend exactly on the number and spacing of the different types of cones[43,124]. The second limiting event in vision is the transmission of signals from the cones to the inner retina by the bipolar cells. Bipolar cells are the mandatory link between cones (or rods) and the rest of the visual system—all visual information must flow through them. Even though these signals, too, are later shaped and recombined, it is inescapable that the separate channels inherent in bipolar cell diversity represent fundamentals of vision, basic building blocks from which all further codings are constructed. In principle, we should eventually be able to deconvolve the outputs of individual bipolar channels from signals encountered even deep within the central visual system.

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