26

Low-Level Visual Processing: The Retina

The retina is the brain's window on the world. All visual experience is based on information processed by this neural circuit in the eye. The retina's output is conveyed to the brain by just one million optic nerve fibers, and yet almost half of the cerebral cortex is used to process these signals. Visual information lost in the retina—by design or deficiency—can never be recovered. Because retinal processing sets fundamental limits on what can be seen, there is great interest in understanding how the retina functions.

On the surface the vertebrate eye appears to act much like a camera. The pupil forms a variable diaphragm, and the cornea and lens provide the refractive optics that project a small image of the outside world onto the light-sensitive retina lining the back of the eyeball (Figure 26–1). But this is where the analogy ends. The retina is a thin sheet of neurons, a few hundred micrometers thick, composed of five major cell types that are arranged in three cellular layers separated by two synaptic layers (Figure 26–2).

The photoreceptor cells, in the outermost layer, absorb light and convert it into a neural signal, an essential process known as phototransduction.

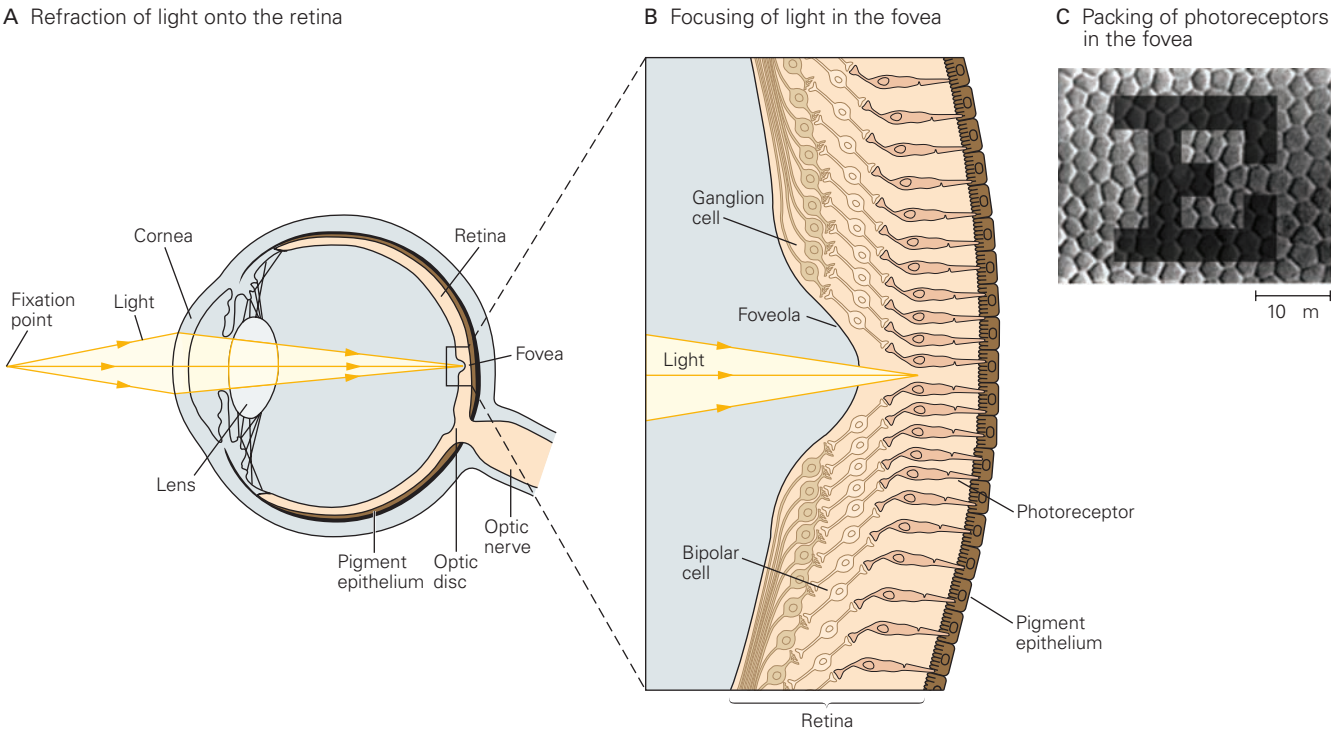


Figure 26–1 The eye projects the visual scene onto the retina's photoreceptors.

A. Light from an object in the visual field is refracted by the cornea and lens and focused onto the retina.

B. In the foveola, corresponding to the very center of gaze, the proximal neurons of the retina are shifted aside so light has direct access to the photoreceptors.

C. A letter from the eye chart for normal visual acuity is projected onto the densely packed photoreceptors in the fovea. Although less sharply focused than shown here as a result of diffraction by the eye's optics, the smallest discernible strokes of the letter are approximately one cone diameter in width. (Adapted, with permission, from Curcio and Hendrickson 1982.)

These signals are passed synaptically to bipolar cells, which in turn connect to retinal ganglion cells in the innermost layer. Retinal ganglion cells are the output neurons of the retina and their axons form the optic nerve. In addition to this vertical pathway from sensory to output neurons, the retinal circuit includes many lateral connections provided by horizontal cells in the outer synaptic layer and amacrine cells in the inner synaptic layer (Figure 26–3).

The retinal circuit performs low-level visual processing, the initial stage in the analysis of visual images. It extracts from the raw images in the left and right eyes certain spatial and temporal features and conveys them to higher visual centers. The rules of this processing are very plastic. In particular, the retina must adjust its sensitivity to ever-changing conditions of illumination. This adaptation allows our vision to remain more or less stable despite the vast range of light intensities encountered during the course of each day.

In this chapter we discuss in turn the three important aspects of retinal function: phototransduction, preprocessing, and adaptation. We will illustrate both the neural mechanisms by which they are achieved and their consequences for visual perception.

The Photoreceptor Layer Samples the Visual Image

Ocular Optics Limit the Quality of the Retinal Image

The sharpness of the retinal image is determined by several factors: diffraction at the pupil's aperture, refractive errors in the cornea and lens, and scattering due to material in the light path. A point in the outside world is generally focused into a small blurred circle on the retina. As in other optical devices this blur is smallest near the optical axis, where the image

quality approaches the limit imposed by diffraction at the pupil. Away from the axis the image is degraded significantly owing to aberrations in the cornea and lens. The image may be degraded further by abnormal conditions such as light-scattering cataracts or refractive errors such as myopia.

The area of retina near the optical axis, the *fovea,* is where vision is sharpest and corresponds to the center of gaze that we direct toward the objects of our attention. The density of photoreceptors, bipolar cells, and ganglion cells is highest at the fovea. The spacing between photoreceptors there is well matched to the size of the optical blur circle, and thus samples the image in an ideal fashion. Light must generally traverse several layers of cells before reaching the photoreceptors, but in the center of the fovea, called the *foveola*, the other cellular layers are pushed aside to reduce additional blur from light scattering (Figure 26–1B). Finally, the back of the eye is lined by a black pigment epithelium that absorbs light and keeps it from scattering back into the eye.

The retina contains another special site, the optic disc, where the axons of retinal ganglion cells converge

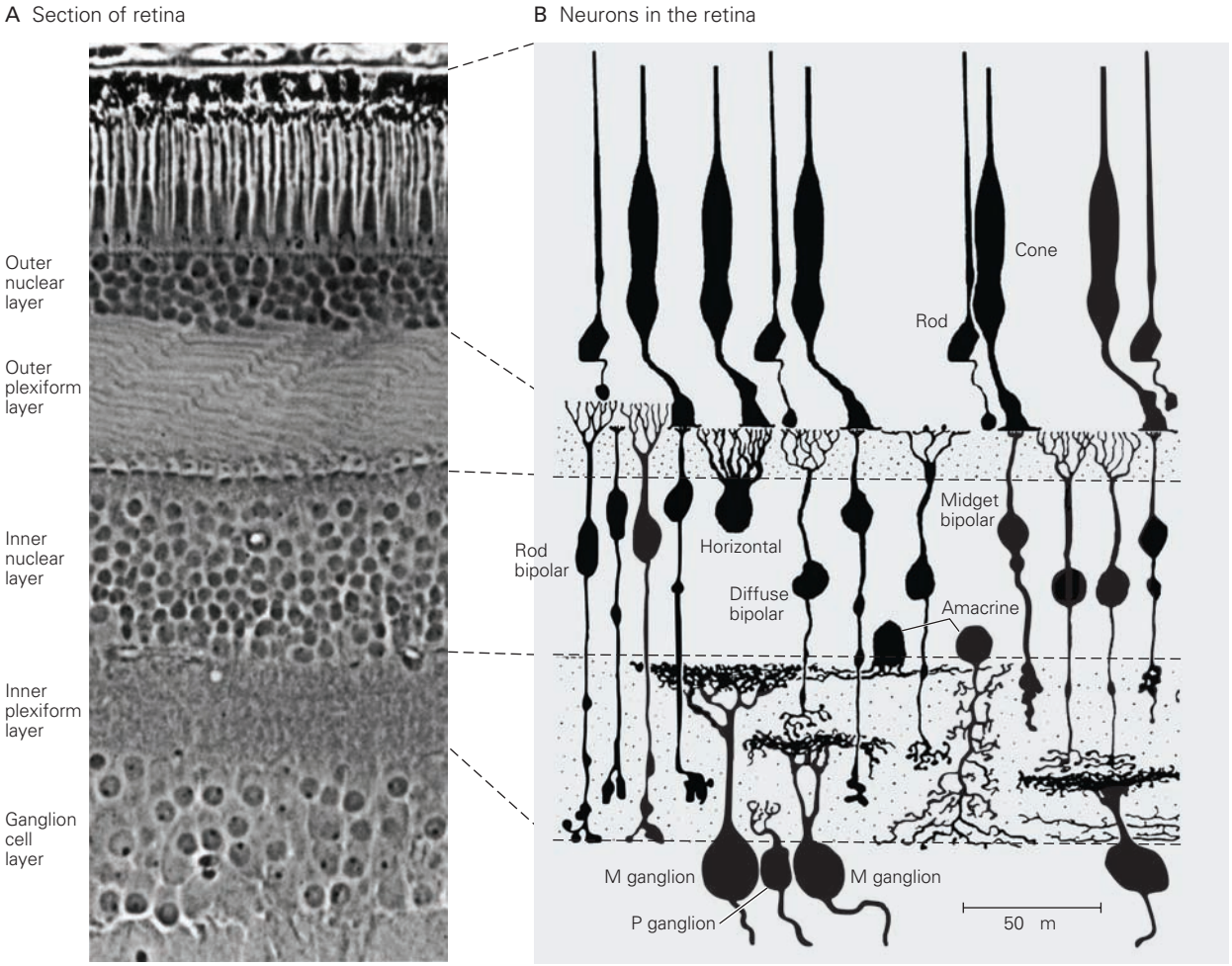


Figure 26–2 The retina comprises five distinct layers of neurons and synapses.

A. A perpendicular section of the human retina seen through the light microscope. Three layers of cell bodies are evident. The outer nuclear layer contains cell bodies of photoreceptors; the inner nuclear layer includes horizontal, bipolar, and amacrine cells; and the ganglion cell layer contains ganglion cells and some displaced amacrine cells. Two layers of fibers and synapses separate these: the outer plexiform layer and the inner plexiform layer. (Reproduced, with permission, from Boycott and Dowling 1969.)

B. Neurons in the retina of the macaque monkey based on Golgi staining. The cellular and synaptic layers are aligned with the image in part A. (**M ganglion**, magnocellular ganglion cell; **P ganglion**, parvocellular ganglion cell.) (Reproduced, with permission, from Polyak 1941.)

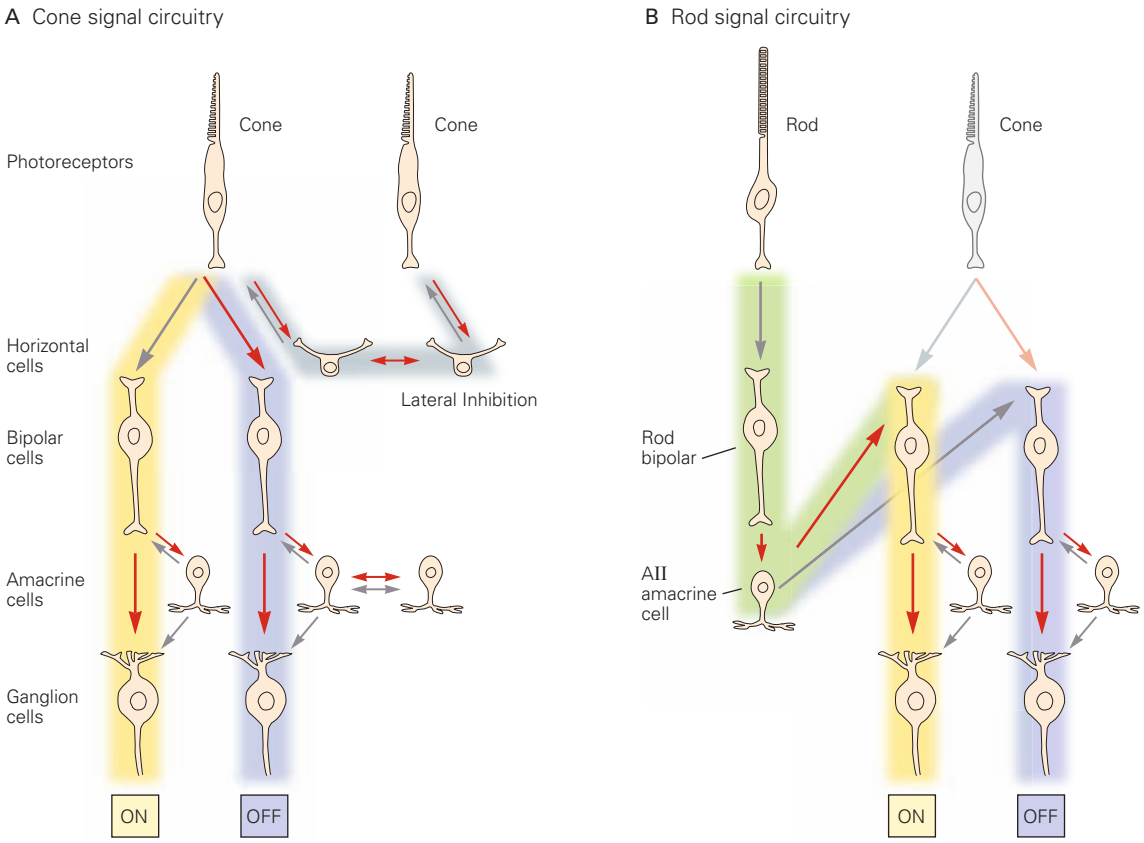


Figure 26–3 The retinal circuitry.

A. The circuitry for cone signals, highlighting the split into ON and OFF pathways as well as the pathway for lateral inhibition in the outer layer. **Red arrows** indicate sign-preserving connections through electrical or glutamatergic synapses. **Gray arrows** represent sign-inverting connections through GABAergic, glycinergic, or glutamatergic synapses.

B. Rod signals feed into the cone circuitry through the AII amacrine cell, which serves to split the ON and OFF pathways.

and extend through the retina to emerge from the back of the eye as the optic nerve. By necessity this area is devoid of photoreceptors and thus corresponds to a *blind spot* in the visual field of each eye. Because the disc lies nasal to the fovea of each eye, light coming from a single point never falls on both blind spots simultaneously, and thus normally we are unaware of them. We can experience the blind spot only by using one eye (Figure 26–4). The blind spot demonstrates what blind people experience—not blackness, but simply nothing. This explains why damage to the peripheral retina often goes unnoticed. It is usually through accidents, such as bumping into an unnoticed object, or through clinical testing that a deficit of sight is revealed.

The blind spot is a necessary consequence of the inside-out design of the retina, which has puzzled and amused biologists for generations. The purpose of this organization may be to enable the tight apposition of photoreceptors with the retinal pigment epithelium, which plays an essential role in the turnover of retinal pigment and recycles photoreceptor membranes by phagocytosis.

There Are Two Types of Photoreceptors: Rods and Cones

All photoreceptor cells have a common structure with four functional regions: the outer segment, located at the distal surface of the neural retina; the inner segment, located more proximally; the cell body; and the synaptic terminal (Figure 26–5A).

Most vertebrates have two types of photoreceptors, rods and cones, distinguished by their morphology.

Figure 26–4 The blind spot of the human retina. Locate the blind spot in your left eye by shutting the right eye and fixating the cross with the left eye. Hold the book about 12 inches from your eye and move it slightly nearer or farther until the circle on the left disappears. Now place a pencil vertically on the page and sweep it sideways over the circle. Note the pencil appears unbroken, even though no light can reach your retina from the region of the circle. Next move the pencil lengthwise and observe what happens when its tip enters the circle. (Adapted, with permission, from Hurvich 1981.)

A rod has a long, cylindrical outer segment within which the stacks of discs are separated from the plasma membrane, whereas a cone often has a shorter, tapered outer segment, and the discs are continuous with the outer membrane (Figure 26–5B).

Rods and cones also differ in function, most importantly in their sensitivity to light. Rods can signal the absorption of a single photon and are responsible for vision under dim illumination such as moonlight. But as the light level increases toward dawn, the electrical

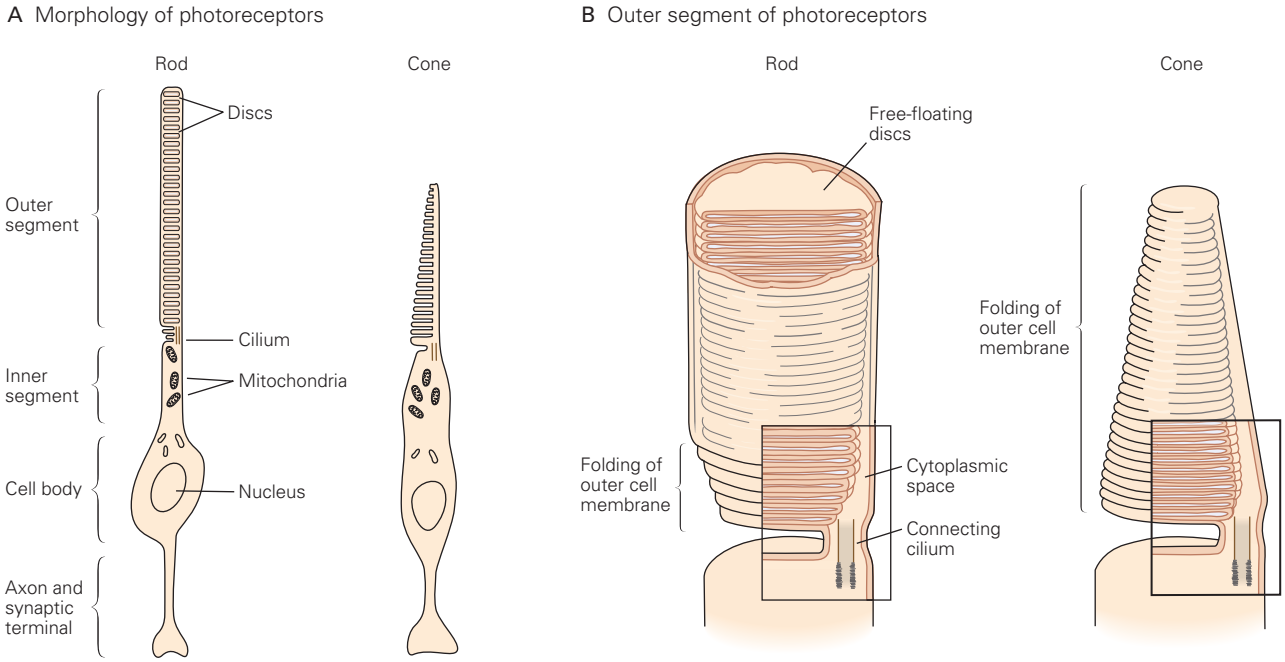


Figure 26–5 Rod and cone photoreceptors have similar structures.

A. Both rod and cone cells have specialized regions called the outer and inner segments. The outer segment, which is attached to the inner segment by a cilium, contains the light-transducing apparatus. The inner segment holds mitochondria and much of the machinery for protein synthesis.

B. The outer segment consists of a stack of membranous discs that contain the light-absorbing photopigments. In both types of cells these discs are formed by infolding of the plasma membrane. In rods, however, the folds pinch off from the membrane so that the discs are free-floating within the outer segment, whereas in cones the discs remain part of the plasma membrane. (Adapted, with permission, from O'Brien 1982; and Young 1970.)

response of rods becomes saturated and the cells cease to respond to variations in intensity. Cones are much less sensitive to light; they make no contribution to night vision, but are solely responsible for vision in daylight. Their response is considerably faster than that of rods. Primates have only one type of rod but three kinds of cone photoreceptors, distinguished by the range of wavelengths to which they respond: the L (long-wave), M (medium-wave), and S (short-wave) cones (Figure 26–6).

The human retina contains approximately 100 million rods and 6 million cones, but the two cell types are differently distributed. The central fovea contains no rods but is densely packed with small cones. A few millimeters outside the fovea rods greatly outnumber cones. All photoreceptors become larger and more widely spaced toward the periphery of the retina. The S cones make up only 10% of all cones and are absent from the central fovea.

The retinal center of gaze is clearly specialized for daytime vision. The dense packing of cone photoreceptors in the fovea sets the limits of our visual acuity. In fact, the smallest letters we can read on a doctor's eye chart have strokes whose images are just 1–2 cone diameters wide on the retina, a visual angle of about 1 minute of arc (Figure 26–1C). At night the central fovea is blind owing to the absence of rods. Astronomers know that one must look just to the side of a dim star to see it at all. During nighttime walks in the forest we nonastronomers tend to follow our daytime reflex of looking straight at the source of a suspicious sound. Mysteriously, the object disappears, only to jump back into our peripheral field of view as we avert our gaze.

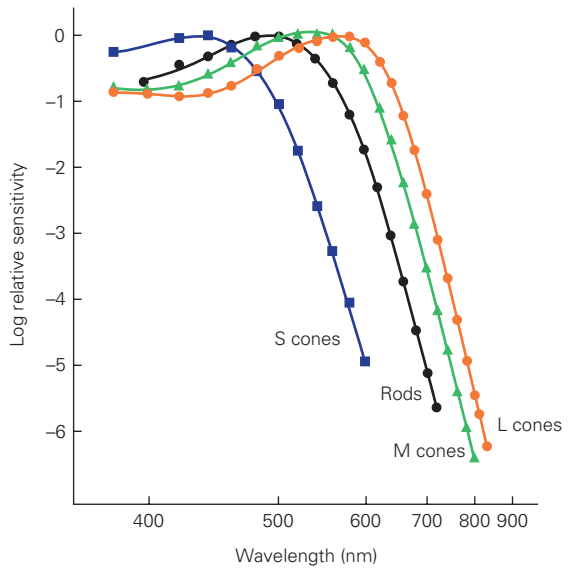


Figure 26–6 Sensitivity spectra for the three cones and the rod. At each wavelength the sensitivity is inversely proportional to the intensity of light required to elicit a criterion neural response. Sensitivity varies over a large range and thus is shown on a logarithmic scale. The different classes of photoreceptors are sensitive to broad and overlapping ranges of wavelengths. (Reproduced, with permission, from Schnapf et al. 1988.)

Phototransduction Links the Absorption of a Photon to a Change in Membrane Conductance

As in many other neurons the membrane potential of a photoreceptor is regulated by the balance of membrane conductances to Na^+ and K^+ ions, whose transmembrane gradients are maintained by metabolically active pumps (see Chapter 6). In the dark, Na^+ ions flow into the photoreceptor through nonselective cation channels that are activated by the second messenger cyclic guanosine 3′-5′ monophosphate (cGMP).

Absorption of a photon by the pigment protein sets in motion a biochemical cascade that ultimately lowers the concentration of cGMP, thus closing the cGMP-gated channels and moving the cell closer to the K^+ equilibrium potential. In this way light hyperpolarizes the photoreceptor (Figure 26–7). Here we describe this sequence of events in detail. Most of this knowledge derives from studies of rods, but the mechanism in cones is very similar.

Light Activates Pigment Molecules in the Photoreceptors

Rhodopsin, the visual pigment in rod cells, has two components. The protein portion, *opsin,* is embedded in the disc membrane and does not by itself absorb visible light. The light-absorbing moiety, *retinal,* is a small molecule whose 11-*cis* isomer is covalently linked to a lysine residue of opsin (Figure 26–8A). Absorption of a photon by retinal causes it to flip from the 11-*cis* to the all-*trans* configuration. This reaction is the only light-dependent step in vision.

The change in shape of the retinal molecule causes a conformational change in the opsin to an activated state called *metarhodopsin II*, which triggers the second step of phototransduction. Metarhodopsin II is unstable and splits within minutes, yielding opsin and free all-*trans* retinal. The all-*trans* retinal is then transported from rods to pigment epithelial cells, where it is reduced to all-*trans* retinol (vitamin A), the precursor of 11-*cis* retinal, which is subsequently transported back to rods.

All-*trans* retinal is thus a crucial compound in the visual system. Its precursors, such as vitamin A, cannot be synthesized by humans and so must be a regular part of the diet. Deficiencies of vitamin A can lead to night blindness and, if untreated, to deterioration of receptor outer segments and eventually to blindness.

Each type of cone in the human retina produces a variant of the opsin protein. These three cone pigments are distinguished by their *absorption spectrum,* the dependence on wavelength of the efficiency of light absorption (see Figure 26–6). The spectrum is determined by the protein sequence through the interaction between retinal and certain amino-acid side chains near the binding pocket. Red light excites L cones more than the M cones, whereas green light excites the M cones more. Therefore the relative degree of excitation in these cone types contains information about the spectrum of the light, independent of its intensity. The brain's comparison of signals from different cone types is the basis for color vision.

In night vision only the rods are active, so all functional photoreceptors have the same absorption spectrum. A green light consequently has exactly the same effect on the visual system as a red light of a greater intensity. Because a single-photoreceptor system cannot distinguish the spectrum of a light from its intensity, "at night all cats are gray." By comparing the sensitivity of a rod to different wavelengths of light, one obtains the absorption spectrum of rhodopsin. It is a remarkable fact that one can measure this molecular property accurately just by asking human subjects about the appearance of various colored lights (Figure 26–9). The quantitative study of perception, or psychophysics, provides similar insights into other mechanisms of brain processing.

Excited Rhodopsin Activates a Phosphodiesterase Through the G Protein Transducin

Activated rhodopsin, in the form of metarhodopsin II, diffuses within the disc membrane where it encounters transducin, a member of the G protein family (Chapter 11). As is the case for other G proteins, the inactive form of transducin binds a molecule of guanosine diphosphate (GDP). Interaction with metarhodopsin II promotes the exchange of GDP for guanosine triphosphate (GTP). This leads to dissociation of transducin's subunits into an active α subunit carrying the GTP (Tα-GTP) and the β and γ subunits (T$\beta\gamma$). Metarhodopsin II can activate hundreds of additional transducin molecules, thus significantly amplifying the cell's response.

The active transducin subunit Tα-GTP forms a complex with a cyclic nucleotide phosphodiesterase, another protein associated with the disc membrane. This interaction greatly increases the rate at which the enzyme hydrolyzes cGMP to 5′-GMP. Each phosphodiesterase molecule can hydrolyze more than 1,000 molecules of cGMP per second, thus increasing the degree of amplification.

The concentration of cGMP controls the activity of the cGMP-gated channels in the plasma membrane of the outer segment. In darkness, when the cGMP concentration is high, a sizeable Na^+ influx through the open channels maintains the cell at a depolarized level of approximately –40 mV. As a consequence, the cell's synaptic terminal continuously releases the transmitter glutamate. The light-evoked decrease in cGMP results in the closure of the cGMP-gated channels, thus reducing the inward flux of Na^+ ions and hyperpolarizing the cell (Figure 26–7B1). Hyperpolarization slows the release of neurotransmitter from the photoreceptor terminal, thereby initiating a neural signal.

Multiple Mechanisms Shut Off the Cascade

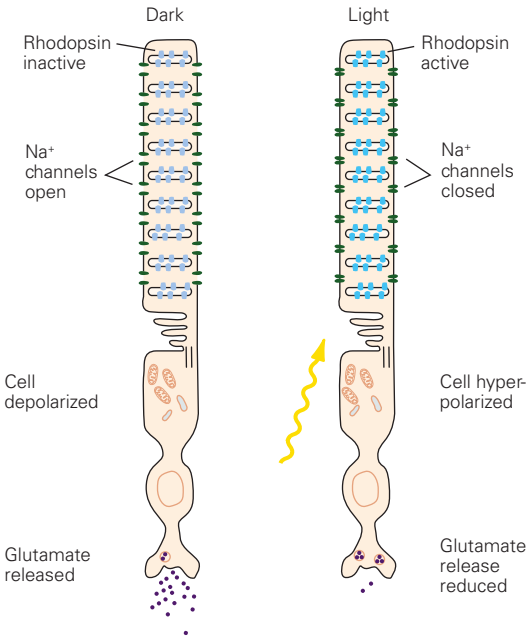
The photoreceptor's response to a single photon must be terminated so that the cell can respond to another photon. Metarhodopsin II is inactivated through phosphorylation by a specific rhodopsin kinase followed by binding of the soluble protein arrestin, which blocks the interaction with transducin.

Active transducin (Tα-GTP) has an intrinsic GTPase activity, which eventually converts bound GTP to GDP. Tα-GDP then releases phosphodiesterase and recombines with T$\beta\gamma$, ready again for excitation by rhodopsin. Once the phosphodiesterase has been inactivated, the cGMP concentration is restored by a guanylate cyclase that produces cGMP from GTP. At this point the membrane channels open, the Na^+ current resumes, and the photoreceptor depolarizes back to its dark potential.

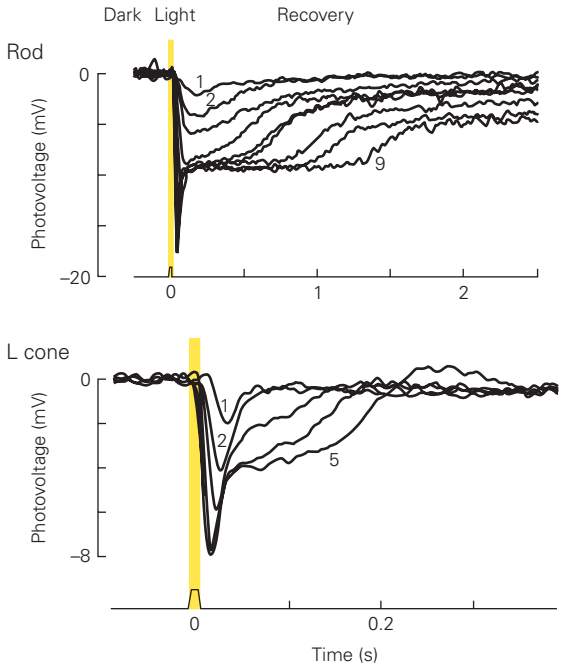
In addition to these independent mechanisms that shut off individual elements of the cascade, an important feedback mechanism ensures that large responses are terminated more quickly. This is mediated by a change in the Ca^{2+} concentration in the cell. Calcium ions enter the cell through the cGMP-gated channels and are extruded by rapid cation exchangers. In the dark the intracellular Ca^{2+} concentration is high; but during the cell's light response when the cGMP-gated channels close, the Ca^{2+} level drops quickly to a few percent of the dark level.

This reduction in Ca^{2+} concentration modulates the biochemical reactions in many ways (Figure 26–7B2).

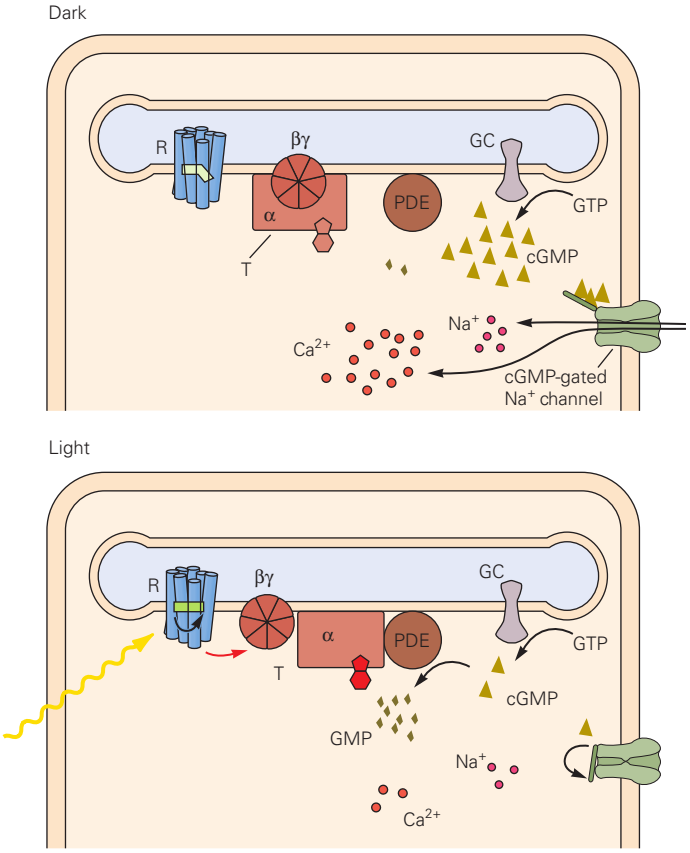
A Phototransduction and neural signaling



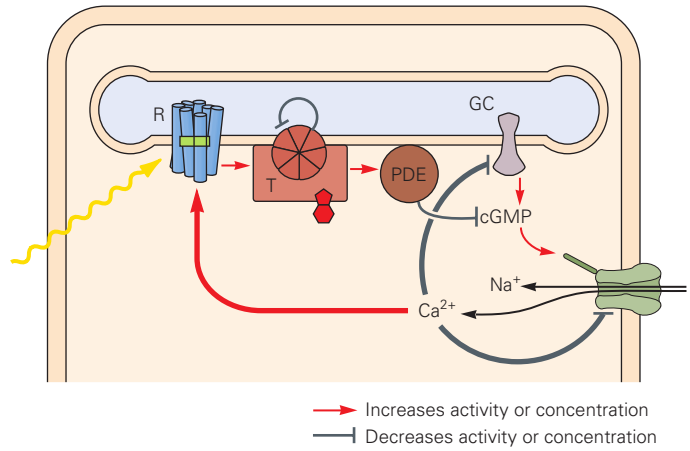
C Voltage response to light



B_1 Molecular processes in phototransduction



B_2 Reaction network in phototransduction



Rhodopsin phosphorylation is accelerated through the action of the Ca^{2+}-binding protein recoverin on rhodopsin kinase, thus reducing activation of transducin. The activity of guanylyl cyclase is accelerated by Ca^{2+}-dependent guanylyl cyclase-activating proteins. Finally, the affinity of the cGMP-gated channel is increased through the action of Ca^{2+}-calmodulin. All these effects promote the return of the photoreceptor to the dark state.

Defects in Phototransduction Cause Disease

Not surprisingly, defects in the phototransduction machinery have serious consequences. One prominent defect is color blindness, which results from loss or abnormality in the genes for cone pigments, as discussed below.

Stationary night blindness results when rod function has been lost but cone function remains intact. This disease is heritable, and mutations have been identified in many components of the phototransduction cascade: rhodopsin, rod transducin, rod phosphodiesterase, rhodopsin kinase, and arrestin. In some cases it appears that the rods are permanently activated, as if exposed to a constant blinding light.

Unfortunately, many defects in phototransduction lead to *retinitis pigmentosa*, a progressive degeneration of the retina that ultimately results in blindness. The disease has multiple forms, many of which have been associated with mutations that affect signal transduction in rods. Why these changes in function lead to death of the rods and subsequent degeneration of the cones is not understood.

Ganglion Cells Transmit Neural Images to the Brain

The photoreceptor layer produces a relatively simple neural representation of the visual scene: Neurons in bright regions are hyperpolarized, whereas those in dark regions are depolarized. Because the optic nerve has only about 1% as many axons as there are receptor cells, the retinal circuit must edit the information in the photoreceptors before it is conveyed to the brain.

This step constitutes *low-level visual processing*, the first stage in deriving visual percepts from the pattern of light falling on the retina. To understand this selective process we must first understand the neural image at the retina's output and how retinal ganglion cells respond to various patterns of light.

The Two Major Types of Ganglion Cells Are ON Cells and OFF Cells

Many retinal ganglion cells fire action potentials spontaneously even in darkness or constant illumination. If the light intensity is suddenly increased, so-called ON cells fire more rapidly. Other ganglion cells, the OFF cells, fire more slowly or cease firing altogether. When the intensity diminishes again, the ON cells fire less and OFF cells fire more. The retinal output thus includes two complementary representations that differ in the polarity of their response to light.

This arrangement serves to communicate rapidly both brightening and dimming in the visual scene. If the retina had only ON cells, a dark object would be

Figure 26–7 (Opposite) Phototransduction.

A. The rod cell responds to light. Rhodopsin molecules in the outer-segment discs absorb photons, which leads to the closure of cGMP-gated channels in the plasma membrane. This channel closure hyperpolarizes the membrane and reduces the rate of release of the neurotransmitter glutamate. (Adapted, with permission, from Alberts 2008.)

B. 1. Cyclic GMP (cyclic guanosine 3′-5′ monophosphate) is produced by a guanylate cyclase (**GC**) and hydrolyzed by a phosphodiesterase (**PDE**). In the dark the phosphodiesterase activity is low, the cGMP concentration is high, and the cGMP-gated channels are open, allowing the influx of Na^+ and Ca^{2+}. In the light rhodopsin (**R**) is excited by absorption of a photon, then activates transducin (**T**), which in turn activates the phosphodiesterase; the cGMP level drops, the membrane channels close, and less Na^+ and Ca^{2+} enter the cell. The transduction enzymes are all located in the internal membrane discs, and the soluble ligand cGMP serves as a messenger to the plasma membrane.

2. Calcium ions have a negative feedback role in the reaction cascade in phototransduction. Stimulation of the network by light leads to the closure of the cGMP-gated channels. This causes a drop in the intracellular concentration of Ca^{2+}. Because Ca^{2+} modulates the function of at least three components of the cascade—rhodopsin, guanylyl cyclase, and the cGMP-gated channel—the drop in Ca^{2+} counteracts the excitation caused by light.

C. Voltage response of a primate rod and cone to brief flashes of light of increasing intensity. Higher numbers on the traces indicate greater intensities of illumination (not all traces are labeled). For dim flashes the response amplitude increases linearly with intensity. At high intensities the receptor saturates and remains hyperpolarized steadily for some time after the flash; this leads to the afterimages that we perceive after a bright flash. Note that the response peaks earlier for brighter flashes and that cones respond faster than rods. (Reproduced, with permission, from Schneeweis and Schnapf 1995.)

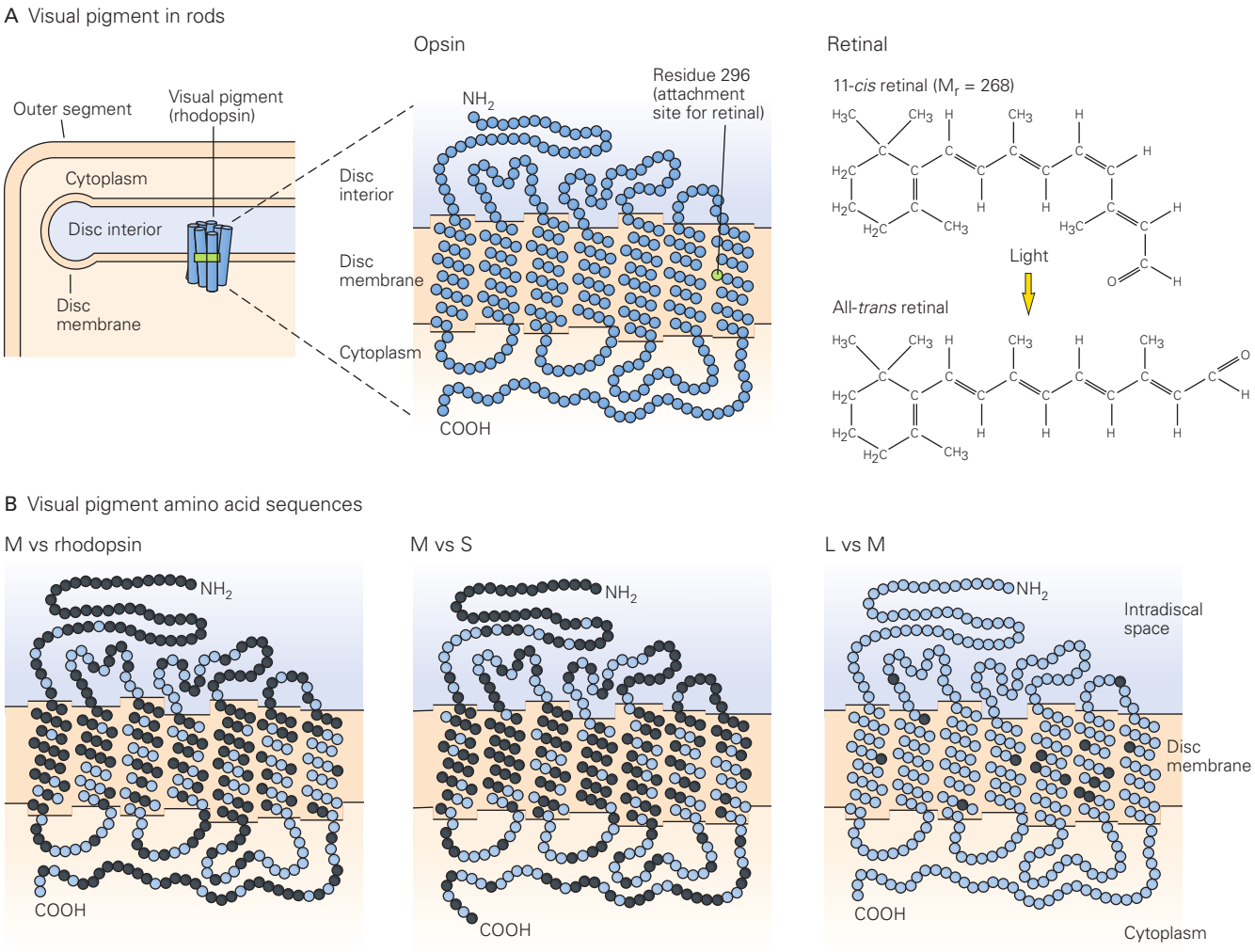


Figure 26–8 Structure of the visual pigments.

A. Rhodopsin, the visual pigment in rod cells, is the covalent complex of a large protein, opsin, and a small light-absorbing compound, retinal. Opsin has 348 amino acids and a molecular mass of approximately 40,000 daltons. It loops back and forth seven times across the membrane of the rod disc. Retinal is covalently attached to a side chain of lysine 296 in the protein's seventh membrane-spanning region. Absorption of light by 11-*cis* retinal causes a rotation around the double bond. As retinal adopts the more stable all-*trans* configuration, it causes a conformational change in the protein that triggers the subsequent events of visual transduction. (Adapted, with permission, from Nathans and Hogness 1984.)

B. Amino acid sequences of cone and rod pigments. **Blue circles** denote identical amino acids; **black circles** denote differences. The three types of cone opsins resemble each other and rhodopsin, suggesting that all four evolved from a common precursor by duplication and divergence. The L and M opsins are most closely related, with 96% identity in their amino acid sequences. They are thought to derive from a gene-duplication event approximately 30 million years ago, after Old World monkeys, which have three pigments, separated from New World monkeys, which generally have only two.

encoded by a decrease in firing rate. If the ganglion cell fired at a maintained rate of 10 spikes per second and then decreased its rate, it would take about 100 ms for the postsynaptic neuron to notice the change in frequency of action potentials. In contrast, an increase in firing rate to 200 spikes per second is noticeable within only 5 ms.

Many Ganglion Cells Respond Strongly to Edges in the Image

To probe the responses of a ganglion cell in more detail, one can focus a small spot of light on different portions of the retina to test how the cell's firing varies with the location and time course of the spot.

A typical ganglion cell is sensitive to light in a compact region of the retina near the cell body, called the cell's *receptive field.* Within that area one can often distinguish a *center* region and *surround* region in which light produces opposite responses. An ON cell, for example, fires faster when a bright spot shines on its receptive field's center but decreases its firing when the spot shines on the surround. If light covers both the center and the surround, the response is much weaker than for center-only illumination. A bright spot on the center combined with a dark annulus on the surround elicits very strong firing. For an OFF cell these relationships are reversed; the cell is strongly excited by a dark spot in a bright annulus (Figure 26–10).

The output produced by a population of retinal ganglion cells thus enhances regions of spatial contrast in the input, such as an edge between two areas of different intensity, and gives less emphasis to regions of homogeneous illumination.

The Output of Ganglion Cells Emphasizes Temporal Changes in Stimuli

When an effective light stimulus appears, a ganglion cell's firing typically increases sharply from the resting level to a peak and then relaxes to an intermediate rate. When the stimulus turns off, the firing rate drops sharply then gradually recovers to the resting level.

The rapidity of decline from the peak to the resting level varies among ganglion cell types. *Transient neurons* produce a burst of spikes only at the onset of the stimulus whereas *sustained neurons* maintain an almost steady firing rate for several seconds during stimulation (Figure 26–10).

In general, however, the output of ganglion cells emphasizes temporal changes in the visual input over periods of constant light intensity. In fact, when the image is stabilized on the retina with an eye-tracking device, it fades from view within seconds. Fortunately this never happens in normal vision; even when we attempt to fix our gaze, small automatic eye movements (saccades) continually scan the image across the retina and prevent the world from disappearing.

Retinal Output Emphasizes Moving Objects

Based on these observations we can understand more generally the response of ganglion cells to visual inputs. For example, a moving object elicits strong firing in the ganglion cell population near the edges of the object's image because these are the only regions of spatial contrast and the only regions where the light intensity changes over time (Figure 26–11).

We can imagine why the retina highlights these features. The outline of an object is particularly useful for inferring its shape and identity. Similarly, objects that move or change suddenly are more worthy of immediate attention than those that do not. Retinal processing thus extracts low-level features of the scene that are useful for guiding behavior and transmits those selectively to the brain. In fact, the rejection of features that are constant either in space or in time accounts for the spatiotemporal sensitivity of human perception (Box 26–1).

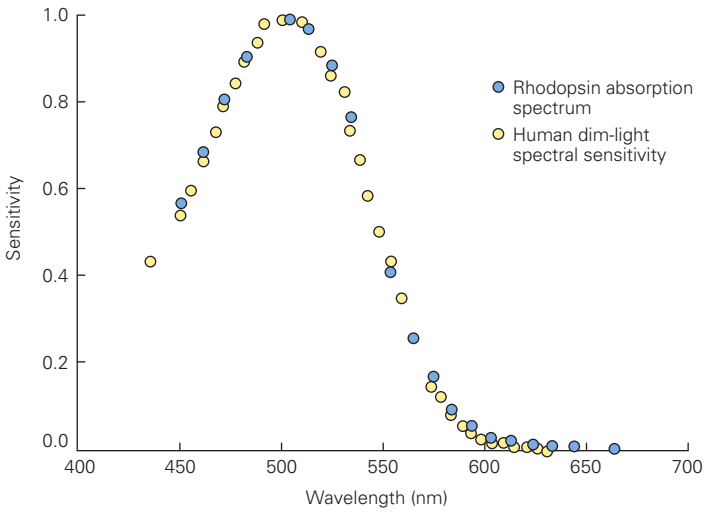


Figure 26–9 Absorption spectrum of rhodopsin. This plot compares the absorption spectrum of human rhodopsin measured in a cuvette and the spectral sensitivity of human observers to very dim light flashes. The psychophysical data have been corrected for absorption by the ocular media. (Reproduced, with permission, from Wald and Brown 1956.)

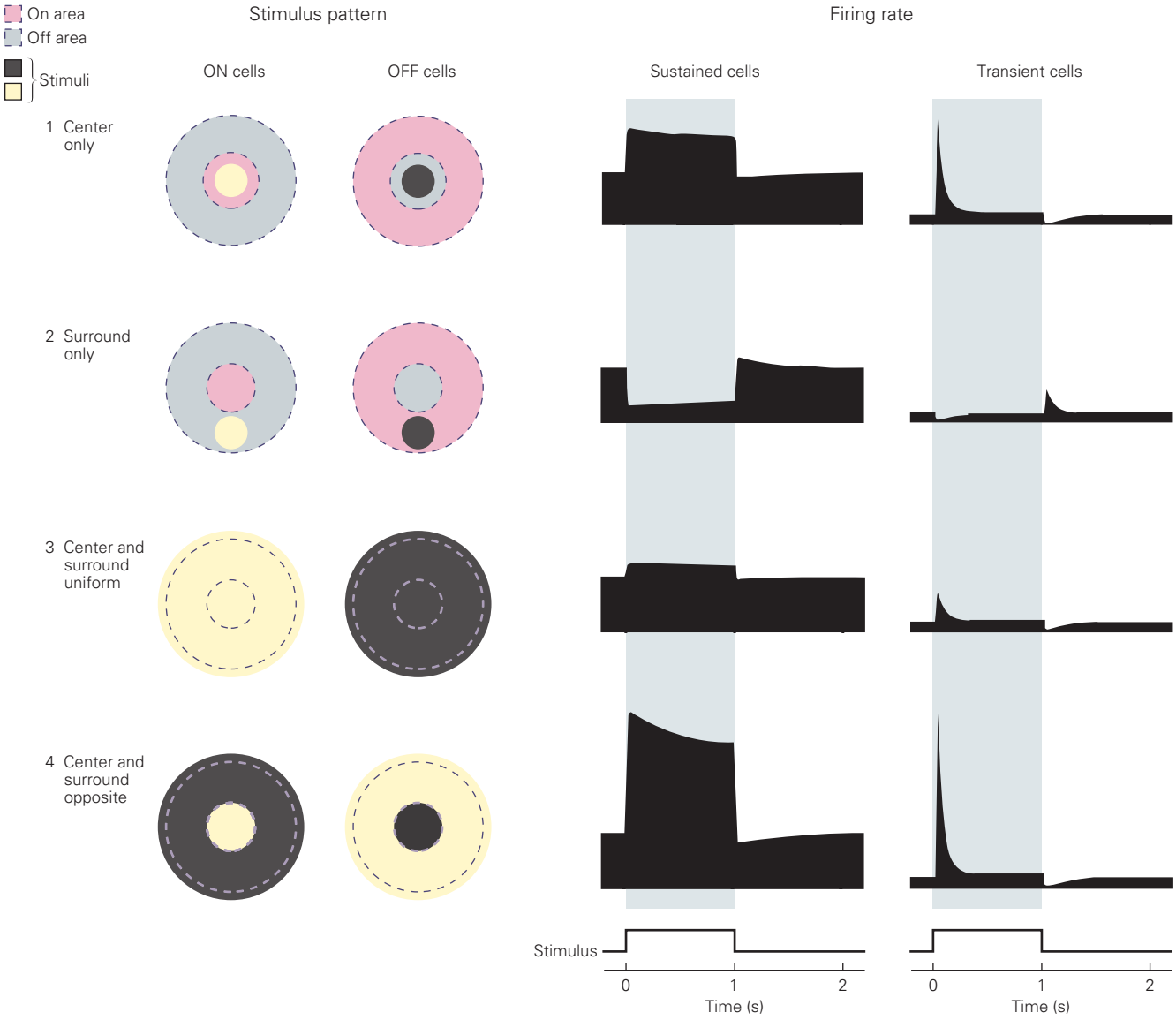


Figure 26–10 Responses of retinal ganglion cells with center-surround receptive fields. In these idealized experiments the stimulus changes from a uniform gray field to the pattern of bright (yellow) and dark (black) regions indicated on the left. **1.** ON cells are excited by a bright spot in the receptive field center, OFF cells by a dark spot. In *sustained cells* the excitation persists throughout stimulation, whereas in *transient cells* a brief burst of spikes occurs just after the onset of stimulation. **2.** If the same stimulus that excites the center is applied to the surround, firing is suppressed. **3.** Uniform stimulation of both center and surround elicits a response like that of the center, but much smaller in amplitude. **4.** Stimulation of the center combined with the opposite stimulus in the surround produces the strongest response.

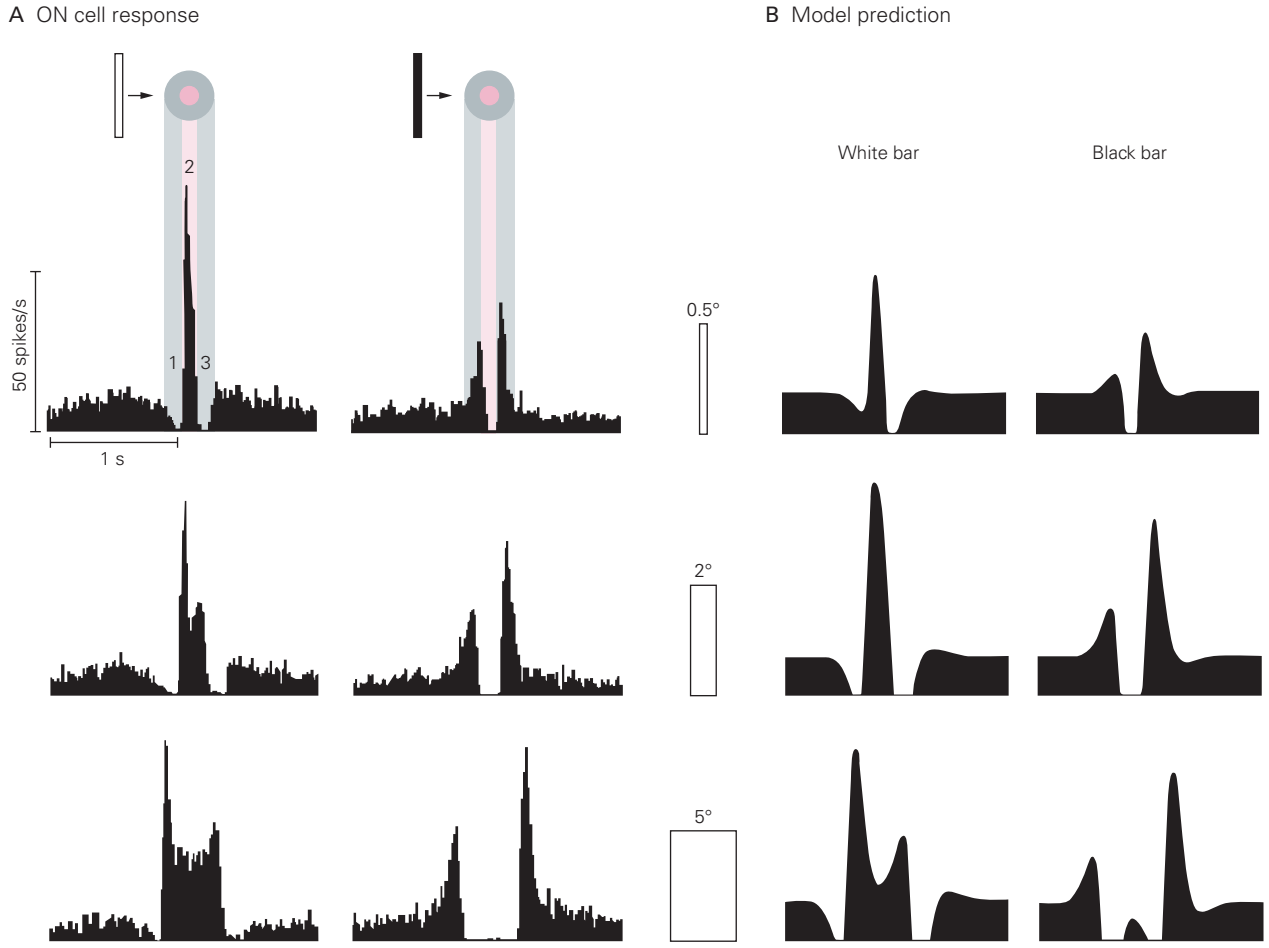


Figure 26–11 The representation of moving objects by retinal ganglion cells.

A. The firing rate of an ON ganglion cell in the cat's retina in response to a variety of bars (white or black, various widths) moving across the retina. Each bar moves at 10° per second; 1 degree corresponds to 180 μm on the retina. In response to the white bar the firing rate first decreases as the bar passes over the receptive-field surround (**1**), increases as the bar enters the center (**2**), and decreases again as the bar passes through the surround on the opposite side (**3**). The dark bar elicits responses of the opposite sign. Because retinal ganglion cells similar to this one are distributed throughout the retina, one can also interpret this curve as an instantaneous snapshot of activity in many different ganglion cells, plotting firing rate as a function of location on the retina. In effect this is the neural representation of the moving bar transmitted to the brain. A complementary population of OFF ganglion cells (not shown here) conveys another neural image in parallel. In this way both bright edges and dark edges can be signaled by a sharp increase in firing.

B. A simple model of retinal processing that incorporates center-surround antagonism and a transient temporal filter is used to predict ganglion-cell firing rates. The predictions match the essential features of the responses in part A. (Reproduced, with permission, from Rodieck 1965.)

Box 26–1 Spatiotemporal Sensitivity of Human Perception

Whereas small spots of light are useful for probing the receptive fields of single neurons, different stimuli are needed to learn about human visual perception. One method to probe how our visual system deals with spatial and temporal patterns uses *grating stimuli.*

The subject views a display in which the intensity varies about the mean as a sinusoidal function of space (Figure 26–12). Then the contrast of the display—defined as the peak-to-peak amplitude of the sinusoid divided by the mean—is reduced to a threshold at which the grating is barely visible. One then repeats this measurement for gratings of different spatial frequencies, measuring the threshold contrast in each case.

Plotting the inverse of this threshold against the spatial frequency, one obtains the *contrast sensitivity curve,* a measure of sensitivity of visual perception to patterns of different scales (Figure 26–13A). When measured at high light intensity, sensitivity declines sharply at high spatial frequencies, with an absolute threshold at approximately 50 cycles per degree. This sensitivity is limited fundamentally by the quality of the optical image and the spacing of cone cells in the fovea (see Figure 26–1C).

Interestingly, sensitivity also declines at low spatial frequencies. Patterns with a frequency of approximately 5 cycles per degree are most visible. The visual system is said to have *band-pass* behavior because it rejects all but a band of spatial frequencies.

One can measure the sensitivity of individual ganglion cells to spatial contrast by stimulating the primate retina with the same displays. The results resemble those for human visual perception (Figure 26–13A), suggesting that the perceptual effects originate in the retina.

The band-pass behavior can be understood on the basis of spatial antagonism in center-surround receptive fields (Figure 26–13B). A very fine grating presents many dark and bright stripes within the receptive-field center; their effects cancel one another and thus provide no net excitation. With a very coarse grating, a single stripe can cover both the center and surround of the receptive field, and their antagonism again provides the ganglion cell little net excitation. The strongest response is produced by a grating of intermediate spatial frequency that just covers the center with one stripe and most of the surround with stripes of the opposite polarity.

In dim light the visual system's contrast sensitivity declines, but more so at high than at low spatial frequencies (Figure 26–13A). Thus the peak sensitivity shifts to lower spatial frequencies, and eventually the curve loses its peak altogether. In this state the visual system has so-called *low-pass* behavior, for it selectively passes stimuli of low spatial frequency. It has been shown that the receptive fields of ganglion cell lose their antagonistic surrounds in dim light, which can explain this transition from band-pass to low-pass spatial filtering (Figure 26–13B).

Similar experiments can be done to test visual sensitivity to temporal patterns. Here the intensity of a test stimulus flickers sinusoidally in time, while the contrast is gradually brought to the threshold level of detection. For humans, contrast sensitivity declines sharply at very high flicker frequencies, but it also declines at very low frequencies (Figure 26–14A). Flicker at approximately 10 Hz is the most effective stimulus. One finds similar band-pass behavior in the flicker sensitivity of macaque retinal ganglion cells (Figure 26–14B).

Sensitivity to temporal contrast also depends on the mean light level. For human subjects the optimum flicker frequency shifts downward, and the peak in the curve becomes less and less prominent at lower stimulus intensities (Figure 26–14). The fact that primate retinal ganglion cells duplicate this behavior suggests that retinal processing limits visual perception in these simple tasks.

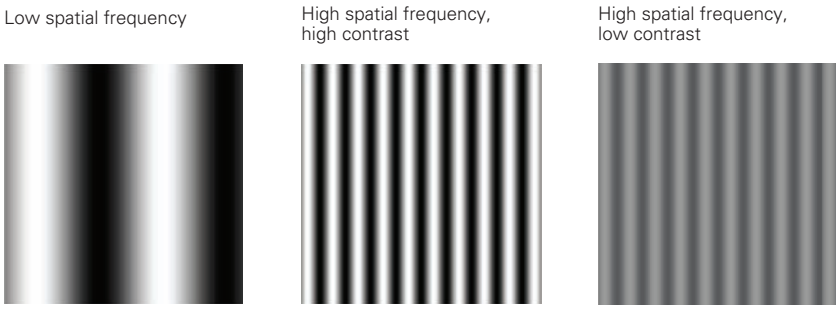


Figure 26–12 Sinusoid grating displays used in psychophysical experiments with human subjects. These stimuli are employed in the experiments discussed in Figure 26–13.

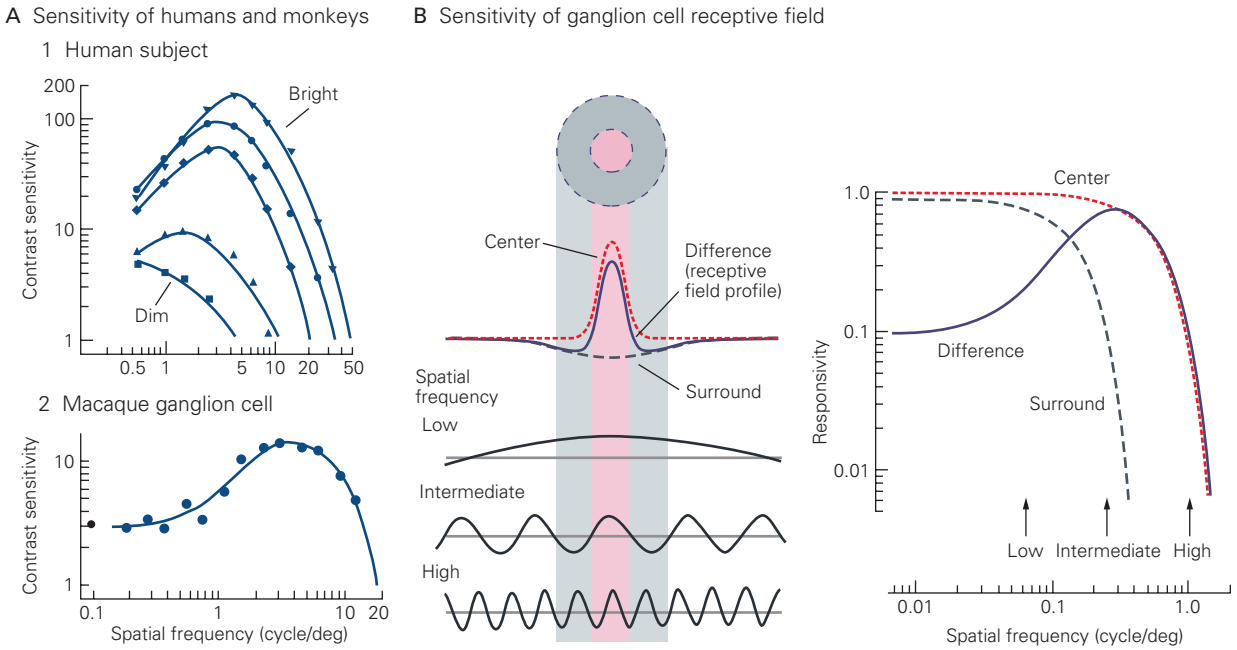


Figure 26–13 Spatial contrast sensitivity.

A. 1. Contrast sensitivity of human subjects. Using gratings at different spatial frequencies, the threshold contrast required for detection was measured and the inverse of that contrast value was plotted against spatial frequency. The curves were obtained at different mean intensities, decreasing by factors of 10 from the top to the bottom curve. (Reproduced, with permission, from DeValois, Morgan, and Snodderly 1974.) 2. Contrast sensitivity of a P-type ganglion cell in the macaque retina measured at high intensity. At each spatial frequency the contrast was gradually increased until it produced detectable modulation of the neuron's firing rate. The inverse of that threshold contrast was plotted as in part A. The isolated dot at left marks the sensitivity at zero spatial frequency, a spatially uniform field. (Reproduced, with permission, from Derrington and Lennie 1984.)

B. Stimulation of a center-surround receptive field with sinusoid gratings. The neuron's sensitivity to light at different points on the retina is modeled as a "difference-of-Gaussians" receptive field, with a narrow positive Gaussian for the excitatory center and a broad negative Gaussian for the inhibitory surround. Multiplying the spatial frequency with the receptive-field profile and integrating over all space calculates the stimulus strength delivered by a particular grating. The resulting sensitivity of the receptive field to gratings of different frequency is shown in the plot on the right. At low spatial frequencies the negative contribution from the surround cancels the contribution from the center, leading to a drop in the difference curve. (Reproduced, with permission, from Enroth-Cugell and Robson 1984.)

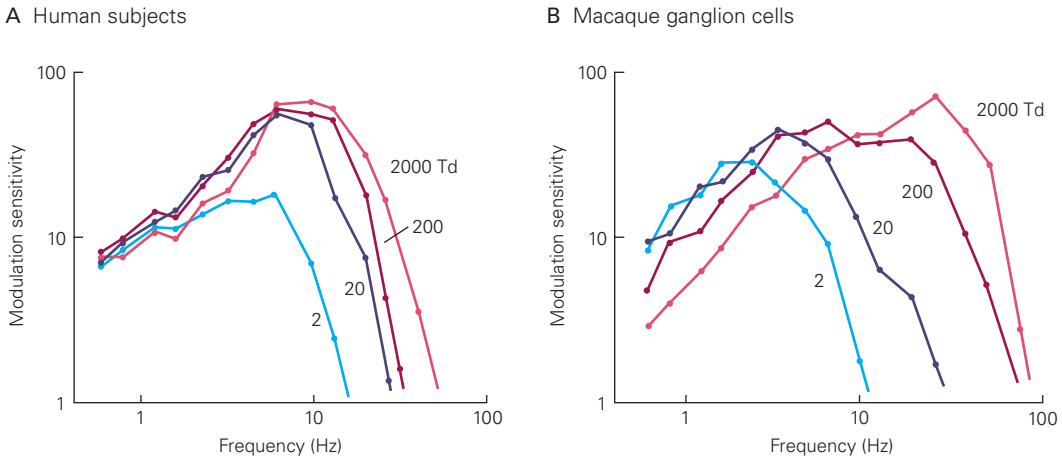


Figure 26–14 Temporal contrast sensitivity. (Reproduced, with permission, from Lee et al. 1990.)

A. Perceptual sensitivity of human observers. These measurements are similar to those in Figure 26–13, but the stimulus was a large spot, 4.6° in diameter, with an intensity that varied sinusoidally in time rather than space. The inverse of the minimal contrast required for detection is plotted against the flicker frequency. Sensitivity declines at both high and low frequencies. The mean light level varied, decreasing by factors of 10 from the top to the bottom trace.

B. Sensitivity of M-type ganglion cells in the macaque retina. These experiments were identical to those on human subjects in part A. The detection threshold for the neural response was defined as a variation of 20 spikes per second in the cell's firing rate in phase with the flicker.

Several Ganglion Cell Types Project to the Brain Through Parallel Pathways

Several different types of ganglion cells have been identified on the basis of their shapes and light responses. The ON and OFF cells occur in every vertebrate retina, and in the primate retina two major classes of cells, the P-cells and M-cells, each include ON and OFF types (see Figure 26–2B). At any given distance from the fovea the receptive fields of M-cells (Latin *magno,* large) are much larger than those of P-cells (Latin *parvo,* small). The M-cells also have faster and more transient responses than P-cells. A type of ganglion cell discovered recently is intrinsically light-sensitive owing to expression of the visual pigment melanopsin.

In total about 20 ganglion-cell types have been described. Each type covers the retina in a tiled fashion, such that any point on the retina lies within the receptive field center of at least one ganglion cell. One can envision each separate population as sending a distinct neural representation of the visual field to the brain, where the firing of an individual ganglion cell represents one pixel in the representation. In this view the optic nerve conveys about 20 neural representations of the world that differ in polarity (ON or OFF), spatial resolution (fine or coarse), temporal responsiveness (sustained or transient), spectral filtering (broadband or dominated by red, green, or blue), and selectivity for other image features such as motion.

These neural representations are directed to various visual centers in the brain, including the lateral geniculate nucleus of the thalamus, a relay to the visual cortex; the superior colliculus, a midbrain region involved in spatial attention and orienting movements; the pretectum, involved in control of the pupil; the accessory optic system, which analyzes self-motion to stabilize gaze; and the suprachiasmatic nucleus, a central clock that directs circadian rhythm and whose phase can be set by light cues (Chapter 51). In many cases the same ganglion-cell type sends axon collaterals to multiple target areas; M-cells, for example, project to the thalamus and the superior colliculus.

A Network of Interneurons Shapes the Retinal Output

We now consider in more detail the basic retinal circuit and how it accounts for the intricate response properties of retinal ganglion cells.

Parallel Pathways Originate in Bipolar Cells

The photoreceptor forms synapses with bipolar cells and horizontal cells (see Figure 26–3A). In the dark the cell's synaptic terminal releases glutamate continuously. On illumination the photoreceptor hyperpolarizes, less Ca^{2+} enters the terminal, and the terminal releases less glutamate. Photoreceptors do not fire action potentials; like bipolar cells they release neurotransmitter in a graded fashion using a specialized structure, the *ribbon synapse.* In fact, most retinal processing is accomplished with graded membrane potentials: Action potentials occur only in certain amacrine cells and in ganglion cells.

The two principal varieties of bipolar cells, ON and OFF cells, respond to glutamate at the synapse through distinct mechanisms. The OFF cells use ionotropic receptors, namely glutamate-gated cation channels of the AMPA-kainate variety (AMPA = α-amino-3-hydroxy-5-methylisoxazole-4-propionate). The glutamate released in darkness depolarizes these cells. The ON cells use metabotropic receptors that are linked to a G protein whose action ultimately closes cation channels. Glutamate activation of these receptors thus hyperpolarizes the cells in the dark.

Bipolar ON and OFF cells differ in shape and especially in the levels within the inner plexiform layer where their axons terminate. The axons of ON cells end in the proximal (lower) half, those of OFF cells in the distal (upper) half (Figure 26–15). There they form specific synaptic connections with amacrine and ganglion cells whose dendritic trees ramify in specific levels of the inner plexiform layer. The ON bipolar cells excite ON ganglion cells, while OFF bipolar cells excite OFF ganglion cells (see Figure 26–3A). Thus the two principal subdivisions of the retinal output signal, the ON and OFF pathways, are already established at the level of bipolar cells.

Bipolar cells can also be distinguished by the morphology of their dendrites (Figure 26–15). In the central region of the primate retina the *midget bipolar cell* receives input from a single cone and excites a P-type ganglion cell. This explains why the centers of P-cell receptive fields are so small. The *diffuse bipolar cell* receives input from many cones and excites an M-type ganglion cell. The receptive-field centers of M-cells are accordingly much larger. Thus stimulus representations in the ganglion cell population originate in dedicated bipolar cell pathways that are differentiated by their selective connections to photoreceptors and postsynaptic targets.

Spatial Filtering Is Accomplished by Lateral Inhibition

Signals in the parallel vertical pathways are modified by lateral interactions with horizontal and amacrine cells (see Figure 26–3A). Horizontal cells have broadly

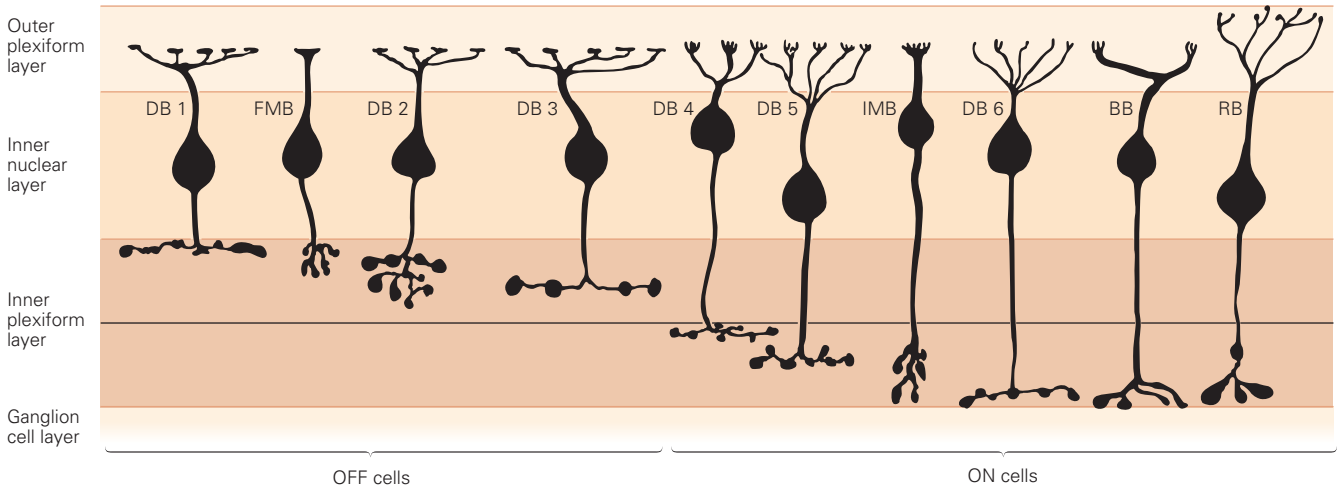


Figure 26–15 Bipolar cells in the macaque retina. The cells are arranged according to the depth of their terminal arbors in the inner plexiform layer. The horizontal line dividing the distal and proximal levels of this layer represents the border between the axonal terminals of OFF and ON types. Bipolar cells with axonal terminals in the upper (distal) half are presumed to be OFF cells, those in the lower (proximal) half ON cells. Cell types are diffuse bipolar cells (**DB**), ON and OFF midget bipolars (**IMB, FMB**), S-cone ON bipolar (**BB**), and rod bipolar (**RB**). (Reproduced, with permission, from Boycott and Wässle 1999.)

arborizing dendrites that spread laterally in the outer plexiform layer. The tips of these arbors contact photoreceptors at terminals shared with bipolar cells. Glutamate released by the photoreceptors excites the horizontal cell. In addition, horizontal cells are electrically coupled with each other through gap junctions.

A horizontal cell effectively measures the average level of excitation of the photoreceptor population over a broad region. This signal is fed back to the photoreceptor terminal through an inhibitory synapse. Thus the photoreceptor terminal is under two opposing influences: light falling on the receptor hyperpolarizes it, but light falling on the surrounding region depolarizes it through the sign-inverting synapses from horizontal cells. As a result, the bipolar cell, which shares the photoreceptor's glutamatergic terminals with the horizontal cells, has an antagonistic receptive field structure.

This spatial antagonism in the receptive field is enhanced by lateral inhibition from amacrine cells in the inner retina. Amacrine cells are axonless neurons with dendrites that ramify in the inner plexiform layer. Approximately 30 types of amacrine cells are known, some with small arbors only tens of micrometers across, and others with processes that extend all across the retina. Amacrine cells generally receive excitatory signals from bipolar cells at glutamatergic synapses. Some amacrine cells feed back directly to the presynaptic bipolar cell at a *reciprocal inhibitory synapse*. Some amacrine cells are electrically coupled to others of the same type, forming an electrical network much like that of the horizontal cells.

Through this inhibitory network a bipolar cell terminal can receive inhibition driven by other, distant bipolar cells, in a manner closely analogous to the lateral inhibition of photoreceptor terminals (see Figure 26–3A). Amacrine cells also inhibit retinal ganglion cells directly. These lateral inhibitory connections contribute substantially to the antagonistic receptive field component of retinal ganglion cells.

Temporal Filtering Occurs in Synapses and Feedback Circuits

For many ganglion cells a step change in light intensity produces a transient response, an initial peak in firing that declines to a smaller steady rate (see Figure 26–10). Part of this sensitivity originates in the negative-feedback circuits involving horizontal and amacrine cells.

For example, a sudden decrease in light intensity depolarizes the cone terminal, which excites the horizontal cell, which in turn repolarizes the cone terminal (see Figure 26–3A). Because this feedback loop involves a brief delay, the voltage response of the cone peaks abruptly and then settles to a smaller steady level. Similar processing occurs at the reciprocal synapses between bipolar and amacrine cells in the inner retina.

In both cases the delayed-inhibition circuit favors rapidly changing inputs over slowly changing inputs. The effects of this filtering, which can be observed in

visual perception, are most pronounced for large stimuli that drive the horizontal cell and amacrine cell networks most effectively. For example, a large spot can be seen easily when it flickers at a rate of 10 Hz but not at a low rate (see Figure 26–14).

In addition to these circuit properties, certain cellular processes contribute to shaping the temporal response. For example, the AMPA-kainate type of glutamate receptor undergoes strong desensitization. A step increase in the concentration of glutamate at the dendrite of a bipolar or ganglion cell leads to an immediate opening of additional glutamate receptors. As these receptors desensitize, the postsynaptic conductance decreases again. The effect is to render a step response more transient.

Retinal circuits seem to go to great lengths to speed up their responses and emphasize temporal changes. One likely reason is that the very first neuron in the retinal circuit, the photoreceptor, is exceptionally slow (see Figure 26–7C). Following a flash of light a cone takes about 40 ms to reach the peak response, an intolerable delay for proper visual function. Through the various filtering mechanisms in retinal circuitry, subsequent neurons respond sensitively during the rising phase of the cone's response. Indeed, some ganglion cells have a response peak only 20 ms after the flash. Temporal processing in the retina clearly helps to reduce visual reaction times, a life-extending trait in highway traffic as on the savannas of our ancestors.

Color Vision Begins in Cone-Selective Circuits

Throughout recorded history philosophers and scientists have been fascinated by the perception of color. This interest was fueled by the relevance of color to art, later by its relation to the physical properties of light, and finally by commercial interests in television and photography. The 19th century witnessed a profusion of theories to explain color perception, of which two have survived modern scrutiny. They are based on careful psychophysics that placed strong constraints on the underlying neural mechanisms.

Early experiments on color matching showed that the percept of any given light could be matched by mixing together appropriate amounts of three primary lights. Thomas Young and Hermann von Helmholtz accordingly postulated the trichromatic theory of color perception based on absorption of light by three mechanisms, each with a different sensitivity spectrum. We now know that these correspond to the three cone types (see Figure 26–6), whose measured absorption spectra fully explain the color-matching results both in normal individuals and those with genetic anomalies in the pigment genes.

In an effort to explain our perception of different hues, Ewald Hering proposed the opponent-process theory, later formalized by Leo Hurvich and Dorothea Jameson. According to this theory, color vision involves three processes that respond in opposite ways to light of different colors: (y–b) would be stimulated by yellow and inhibited by blue light; (r–g) stimulated by red and inhibited by green; and (w–bk) stimulated by white and inhibited by black. We can now recognize some of these processes in the post-receptor circuitry of the retina.

In the central 10° of the human retina a single midget bipolar cell that receives input from a single cone excites each P-type ganglion cell. An L-ON ganglion cell, for example, has a receptive field center consisting of a single L cone and an antagonistic surround involving a mixture of L and M cones. When stimulated with a large spot that extends over both the center and the surround, this neuron is depolarized by red light and hyperpolarized by green light. Similar antagonism holds for the three other P-cells: L-OFF, M-ON, and M-OFF. These P-cells send their signals to the parvocellular layers of the lateral geniculate nucleus.

Although S cones are relatively rare, a dedicated type of S-ON bipolar cell collects their signals selectively and transmits them to ganglion cells of the small bistratified type. Because this ganglion cell also receives excitation from L-OFF and M-OFF bipolar cells, it is depolarized by blue light and hyperpolarized by yellow light. Another ganglion cell type shows the opposite signature: S-OFF and (L + M)-ON. These signals are transmitted to the koniocellular layers of the lateral geniculate nucleus.

The M cells are excited by diffuse bipolar cells, which in turn collect inputs from many cones regardless of pigment type. These ganglion cells therefore have large receptive fields with broad spectral sensitivity. Their axons project to the magnocellular layers of the lateral geniculate nucleus.

In this way chromatic signals are combined and formatted by the retina for transmission to the thalamus and cortex. In the primary visual cortex these signals are recombined in different ways, leading to a great variety of receptive field layouts. Note that only about 10% of cortical neurons are preferentially driven by color contrast rather than luminance contrast. This likely reflects the fact that color vision—despite its great esthetic appeal—makes only a small contribution to our overall fitness. As an illustration of this, recall that colorblind individuals, who in a sense have lost half of their color space, can grow up without noticing that defect.

Congenital Color Blindness Takes Several Forms

Few people are truly colorblind in the sense of being wholly unable to distinguish a change in color from a change in the intensity of light, but many individuals have impaired color vision and experience difficulties in making distinctions that for most of us are trivial, for example between red and green. Most such abnormalities of color vision are congenital and have been characterized in detail; some other abnormalities result from injury or disease of the visual pathway.

The study of inherited variation in color vision has contributed in important ways to our understanding of the mechanisms of normal color vision. The first major insight, well understood in the 19th century, is that some people have only two classes of receptors instead of the three in normal trichromatic vision. These dichromats find it difficult or impossible to distinguish some surfaces whose colors appear distinct to trichromats. The dichromat's problem is that every surface reflectance function is represented by a two-value description rather than a three-value one, and this reduced description causes dichromats to confuse many more surfaces than do trichromats. Simple tests for color-blindness exploit this fact. Figure 26–16 shows an example from the Ishihara test, in which the numerals defined by colored dots are seen by normal trichromats but not by most dichromats.

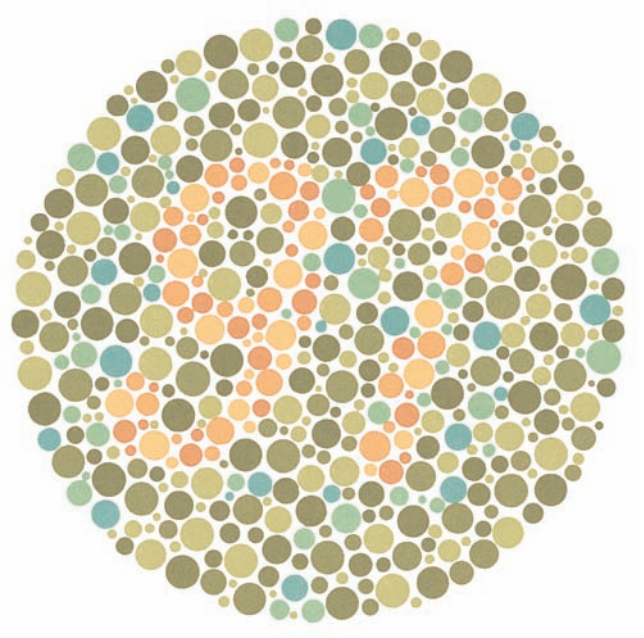


Figure 26–16 A test for some forms of color blindness. The numerals embedded in this color pattern can be distinguished by people with trichromatic vision but not by certain dichromats, including the Editor of this section of the book, who are weak in red–green discrimination. (Reproduced, with permission, from Ishihara 1993.)

When a person with normal color vision fails to distinguish two physically different surface reflectance functions, a dichromat will also fail to distinguish them. This failure means that each class of cone gives rise to the same signal when absorbing light reflected by either surface, so the fact that the dichromat is confused by the same surfaces that confuse a trichromat shows that the cones in the dichromat have normal pigments.

Although there are three forms of dichromacy, corresponding to the loss of each of the three types of cones, two kinds of dichromacy are much more common than the third. The common forms correspond to the loss of the L cones or M cones and are called *protanopia* and *deuteranopia*, respectively. Protanopia and deuteranopia almost always occur in males, each with a frequency of about 1%. The conditions are transmitted by women who are not themselves affected, and so implicate genes on the X chromosome. A third form of dichromacy, *tritanopia*, corresponds to the loss or dysfunction of the S cone. It affects only about 1 in 10,000 people, afflicts women and men with equal frequency and has a gene on chromosome 7.

Because the L and M cones exist in large numbers, one might think that the loss of one or the other type would impair vision more broadly than just weakening color vision. In fact, this does not happen because the total number of L and M cones in the dichromat retina is not altered. All cells destined to become L or M cones are probably converted to L cones in deuteranopes and to M cones in protanopes.

In addition to the relatively severe forms of color-blindness represented by dichromacy, there are milder forms, again affecting mostly males, that result in an impaired capacity to distinguish different reflectance functions that are readily distinguished by normal trichromats. People with these milder impairments are referred to as anomalous trichromats, for their cones provide three-value descriptions of the light reflected by surfaces. In contrast to dichromats, however, they do not see as identical the physically different spectral functions distinguished by a normal trichromat.

These anomalous trichromats have cones whose spectral sensitivities differ from those of cones in normal trichromats. Anomalous trichromacy occurs in different forms, corresponding to the replacement of one of the normal cone pigments by an altered protein with a different spectral sensitivity. Two common forms, protanomaly and deuteranomaly, together affect about

7% of males and represent respectively the replacement of the L or M cones by a pigment with some intermediate spectral sensitivity.

The occurrence of sex-linked inherited defects of color vision points to the X chromosome as the locus of genes that encode the visual pigments of L and M cones. These genes, and the amino acid sequences of the pigments they encode, have now been identified, largely through the work of Jeremy Nathans and his colleagues. Their discovery reveals some interesting complexities in the molecular organization underlying color vision. Molecular cloning of the genes for the L and M pigments shows the genes to be very similar and arranged head-to-tail on the X chromosome (Figure 26–17A). The pigments also have very similar structures, differing in only 4% of their amino acids.

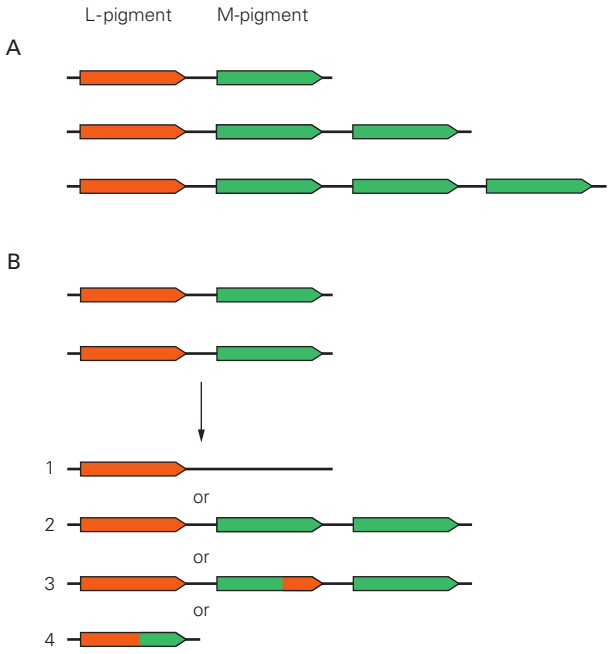


Figure 26–17 L- and M-pigment genes on the X chromosome.

A. Arrangement of L- and M-pigment genes in color-normal males. The base of each arrow corresponds to the 5′ end of the gene, and the tip corresponds to the 3′ end. Males with normal color vision can have one, two, or three copies of the gene for the M pigment on each X chromosome. (Adapted, with permission, from Nathans, Thomas, and Hogness 1986.)

B. Because they lie next to each other on the chromosome, the L- and M-pigment genes can undergo recombinations that lead to the generation of a hybrid gene (3 and 4) or the loss of a gene (1), the patterns observed in colorblind men. Spurious recombination can also cause gene duplication (2), a pattern observed in some people with normal color vision. (Adapted, with permission, from Stryer 1988.)

People with normal color vision possess a single copy of the gene for the L pigment and from one to three—occasionally as many as five—nearly identical copies of the gene for the M pigment.

The proximity and similarity of these genes is thought to predispose them to varied forms of recombination, leading either to the loss of a gene or to the formation of hybrid genes that account for the common forms of red-green defect (Figure 26–17B). Examination of these genes in dichromats reveals a loss of the L-pigment gene in protanopes and a loss of one or more M-pigment genes in deuteranopes. Anomalous trichromats have L-M or M-L hybrid genes that code for visual pigments with shifted spectral sensitivity, the extent of the shift depending on the point of recombination. In tritanopes, the loss of S-cone function arises from mutations in the S-pigment gene.

Rod and Cone Circuits Merge in the Inner Retina

For vision under low-light conditions the mammalian retina has an ON bipolar cell that is exclusively connected to rods (see Figure 26–3B). By collecting inputs from up to 50 rods, this rod bipolar cell can pool the effects of dispersed single-photon absorptions in a small patch of retina. This neuron is excited by light and there is no corresponding OFF bipolar cell dedicated to rods.

Unlike all other bipolar cells, the rod bipolar cell does not contact ganglion cells directly but instead excites a dedicated neuron called the AII amacrine cell. This amacrine cell receives inputs from several rod bipolar cells and conveys its output to cone bipolar cells. It sends excitatory signals to ON bipolar cells through gap junctions as well as glycinergic inhibitory signals to OFF bipolar cells. These cone bipolar cells in turn excite ON and OFF ganglion cells as described above. Thus the rod signal is fed into the cone system after a detour, involving the rod bipolar and AII amacrine cells, that produces the appropriate signal polarities for the ON and OFF pathways. The purpose of these added interneurons may be to allow greater pooling of rod signals than of cone signals.

Rod signals also enter the cone system through two other pathways. Rods can drive neighboring cones directly through electrical junctions, and they make connections with an OFF bipolar cell that services primarily cones. Once the rod signal has reached the cone bipolars through these pathways, it can take advantage of the same intricate circuitry of the inner retina. One gets the impression that the rod system of the mammalian retina is an evolutionary afterthought added to the cone circuits.

The Retina's Sensitivity Adapts to Changes in Illumination

Vision operates under many different lighting conditions. The intensity of the light coming from an object depends on the intensity of the illuminating light and the fraction of this light reflected by the object's surface, called the *reflectance*. The range of intensities encountered in a day is enormous, with variation spanning 10 orders of magnitude, but most of this variation is useless for the purpose of guiding behavior.

The illuminant intensity varies by about nine logarithmic units, mostly because our planet turns about its axis once a day, while the object reflectance varies much less, by about one order of magnitude in a typical scene. But this reflectance is the interesting quantity for vision, for it characterizes objects and distinguishes them from the background. In fact, our visual system is remarkably good at calculating surface reflectances independently of the illuminant intensity (Figure 26–18).

When illumination becomes stronger, all points in the retinal image increase in intensity by the same factor. If the retina could simply reduce its sensitivity by the same factor, the neural representation of the retinal image would remain unchanged at the level of the ganglion cells and could be processed by the rest of the brain in the same way as before the change in illumination. Moreover, the retinal ganglion cells would only need to encode the tenfold range of image intensities owing to the different object reflectances, instead of the 10-billionfold range that includes variations in illumination. In fact, the retina does perform such an automatic gain control, called *light adaptation*, that approaches the ideal normalization we have imagined here.

Light Adaptation Is Apparent in Retinal Processing and Visual Perception

The responses of a retinal ganglion cell to varying flashes of light with a steady background illumination fit a sigmoidal curve (Figure 26–19A). The weakest flashes elicit

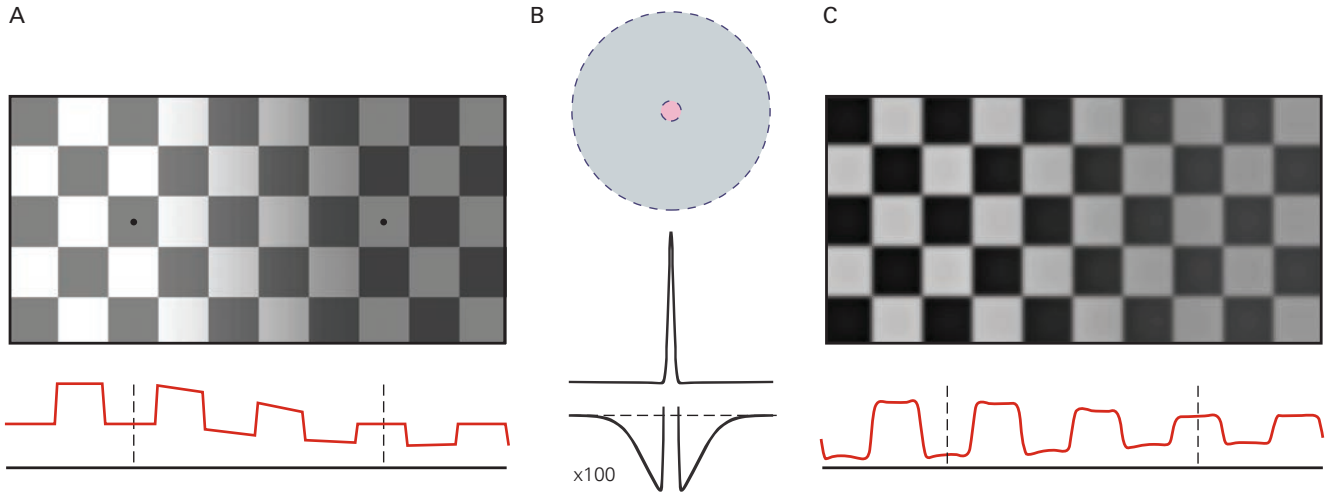


Figure 26–18 A brightness illusion.

A. The two tiles marked with small dots appear to have different brightness but actually reflect the same light intensity. (To see this, fold the page so they touch.) The trace underneath plots a profile of light intensity at the level of the arrowheads. Your visual system interprets this retinal image as a regular tile pattern under graded illumination with a diffuse shadow in the right half. Perceptual processing tries to discount this shadow to extract the underlying surface reflectance, and thus assigns a greater lightness to the right tile than the left. As you can see, this process is automatic and requires no conscious analysis.

B. Retinal processing contributes to the perception of "lightness" by discounting the shadow's smooth gradients of illumination and accentuating the sharp edges between checkerboard fields. The profile of the receptive field for a visual neuron with an excitatory center and an inhibitory surround is shown at the top. As shown in a hundredfold magnification at the bottom, the surround is weak but extends over a much larger area than the center.

C. The result when a population of visual neurons with receptive fields as in B processes the image in A. This operation—the convolution of the image in A with the profile in B—subtracts from each point in the input image the average intensity in a large surrounding region. The output image has largely lost the effects of shading, and the two tiles in question do indeed have different lightness values in this representation.

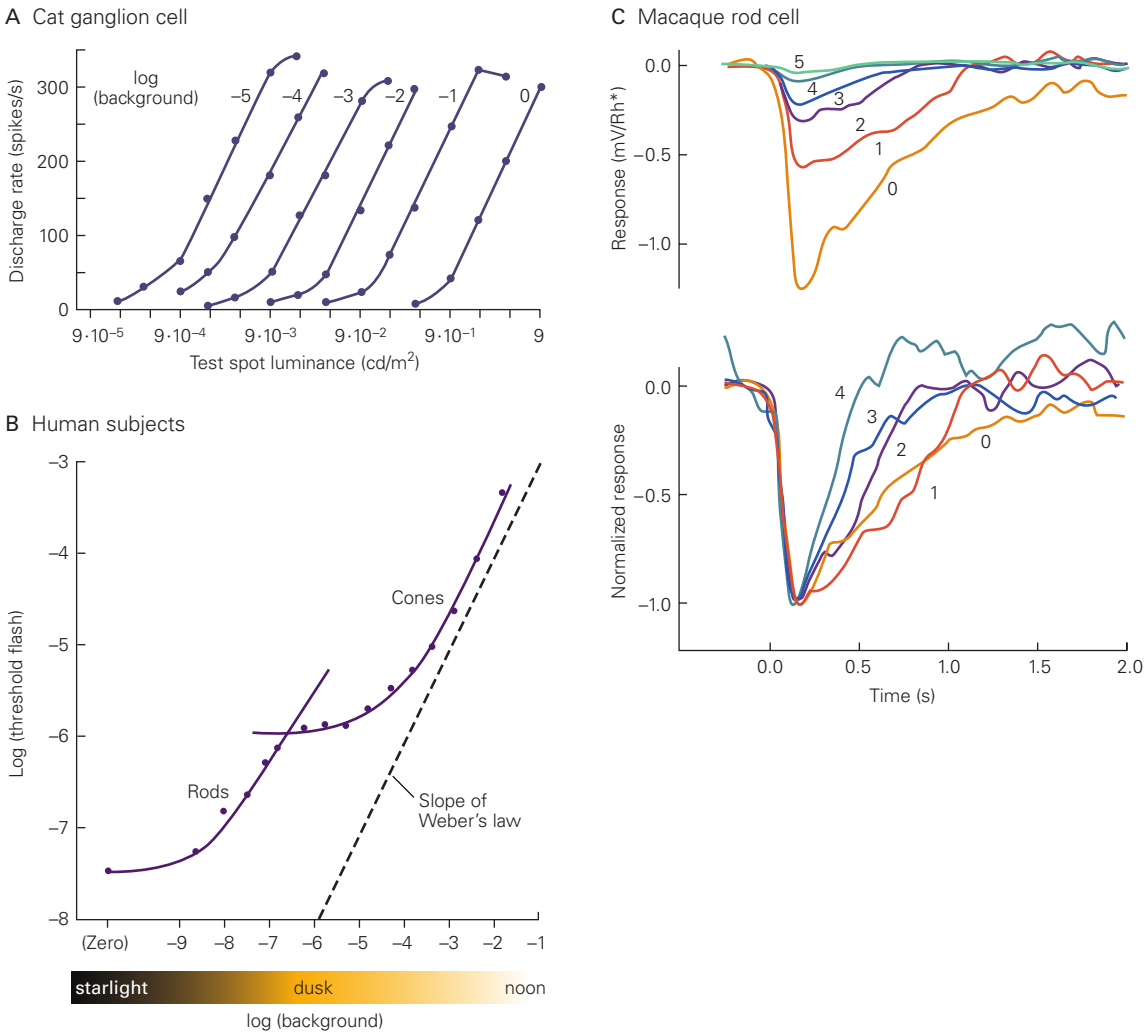


Figure 26–19 Light adaptation.

A. Light adaptation in a cat's retinal ganglion cell. The receptive field was illuminated uniformly at a steady background intensity, and a test spot was flashed briefly on the receptive field center. The peak firing rate following the flash was measured and plotted against the logarithm of the flash intensity. Each curve corresponds to a different background intensity, increasing by factors of 10 from left to right. (Reproduced, with permission, from Sakmann and Creutzfeldt 1969.)

B. Light adaptation in human vision. A small test spot was flashed briefly on a steadily illuminated background, and the intensity at which human subjects just detected the flash is plotted against the background intensity. The curve has two branches connected by a distinct kink: These correspond to the regimes of rod-and-cone vision. The slope of Weber's law represents the idealization in which the threshold intensity is proportional to the background intensity. (Reproduced, with permission, from Wyszecki and Stiles 1967.)

C. Light adaptation in the macaque monkey. The top plot shows the responses of a macaque monkey's rod cell to flashes delivered at varying background intensities. The cell's single-photon response was calculated from the recorded membrane potential divided by the number of rhodopsins (Rh) activated by the flash. The gain of the single-photon response decreases substantially with increasing background intensity. The background intensity, in photon/μm^2/s, is 0 for trace 0, 3.1 for trace 1, 12 for trace 2, 41 for trace 3, 84 for trace 4, and 162 for trace 5. In the bottom plot the same data (except for the smallest response) are normalized to the same amplitude, showing that the time course of the single-photon response accelerates at high intensity. (Reproduced, with permission, from Schneeweis and Schnapf 2000.)

no response, a graded increase in flash intensity elicits graded responses, and the brightest flashes elicit saturation. When the background illumination is increased, the response curve maintains the same shape but is shifted to higher flash intensities. Compensating for the increase in background illumination, the ganglion cell is now less sensitive to light variations: In the presence of a higher background, a larger change is needed to cause the same response. This lateral shifting of the stimulus-response relationship is a hallmark of light adaptation in the retina.

The consequences of this gain change for human visual perception are readily apparent in psychophysical experiments. When a human subject is asked to detect a flash on a background field of constant illumination, a brighter background necessitates brighter flashes for detection (Figure 26–19B). Under the ideal gain-control mechanism discussed above, two stimuli would produce the same response if they caused the same fractional change from the background intensity. In that case the threshold flash intensity should be proportional to the background intensity, a relationship known as *Weber's law of adaptation,* which we encountered in considering somatic sensitivity (Chapter 21). The visual system follows Weber's law approximately: Over the entire range of vision, sensitivity decreases somewhat less steeply with increasing background intensity (Figure 26–19B).

Multiple Gain Controls Occur Within the Retina

Light adaptation occurs at multiple sites within the retina that together produce the enormous changes in gain that are required. In starlight a single rod cell is stimulated by a photon only every few seconds, a rate insufficient to alter the cell's adaptation status. However, a retinal ganglion cell combines signals from many rods, thus receiving a steady stream of photon signals that can elicit a light-dependent gain change in the cell.

At somewhat higher light intensities a rod bipolar cell begins to adapt, changing its responsiveness depending on the average light level. Next we reach a light intensity at which the gain of individual rod cells gradually decreases. Beyond that the rods saturate: All their cGMP-dependent channels are closed, and the membrane potential no longer responds to the light stimulus. By this time, around dawn, the much less sensitive cone cells are being stimulated effectively and gradually take over from the rods. As the illumination increases further toward noon, light adaptation results principally from gain changes within the cones.

The cellular mechanisms of light adaptation are best understood in the photoreceptors. The Ca^{2+}-dependent feedback pathways discussed above have a prominent role. Recall that when a light flash closes the cGMP-gated channels, the resulting decrease in intracellular Ca^{2+} accelerates several biochemical reactions that terminate the response to the flash (see Figure 26–7B). When illumination is continuous the Ca^{2+} concentration remains low, and all these reactions are therefore in a steady state that both lowers the gain and accelerates the time course of the receptor's response to light (Figure 26–19C). As a result, the light-adapted photoreceptor can respond to rapid changes in intensity much more quickly. This has important consequences for human visual perception; the contrast sensitivity to high-frequency flicker increases with intensity, an effect observed in primate retinal ganglion cells as well (see Figure 26–14).

Light Adaptation Alters Spatial Processing

In addition to the sensitivity and speed of the retinal response, light adaptation also changes the rules of spatial processing. In bright light many ganglion cells have a sharp center-surround structure in their receptive fields (see Figure 26–10). As the light dims, the antagonistic surround becomes broad and weak and eventually disappears. Under these conditions the ganglion cell is concerned with accumulating the rare photons over its receptive field rather than computing local intensity gradients. These changes in receptive-field properties occur because of changes in the lateral inhibition produced by the networks of horizontal and amacrine cells (see Figure 26–3). An important regulator of these processes is dopamine, released in a light-dependent manner by specialized amacrine cells.

These retinal effects leave their signature on human perception. In bright light our visual system prefers fine gratings to coarse gratings. But in dim light we are most sensitive to coarse gratings: With the loss of center-surround antagonism, the low spatial frequencies are no longer attenuated (see Box 26–1 and Figure 26–13).

In conclusion, light adaptation has two important roles. One is to discard information about the intensity of ambient light while retaining information about object reflectances. The other is to match the small dynamic range of firing in a retinal ganglion cell to the large range of light intensities in the environment. The retina must accomplish these large gain changes with graded neuronal signals before action potentials are produced in optic nerve fibers, for their firing rates can vary effectively over only two orders of magnitude.

In fact, the crucial need for light adaptation may be why the neural circuitry resides in the eye and not in the brain at the other end of the optic nerve.

An Overall View

The retina transforms light patterns projected onto photoreceptors into neural signals that are conveyed through the optic nerve to specialized visual centers in the brain. Different populations of ganglion cells transmit multiple neural representations of the retinal image along parallel pathways.

In producing its output the retina discards much of the stimulus information available at the receptor level and extracts certain low-level features of the visual field useful to the central visual system. Fine spatial resolution is maintained only in a narrow region at the center of gaze. Intensity gradients in the image, such as object edges, are emphasized over spatially uniform portions; temporal changes are enhanced over unchanging parts of the scene.

The retina adapts flexibly to the changing conditions for vision, especially the large diurnal changes in illumination. With increases in average light level the retina becomes progressively less sensitive, so that the response to a fractional change in intensity is almost independent of the overall illumination. Information about the absolute light level is largely discarded, favoring the subsequent analysis of object reflectances within the scene.

The transduction of light stimuli begins in the outer segment of the photoreceptor cell when a pigment molecule absorbs a photon. This sets in motion an amplifying G protein cascade that ultimately reduces the membrane conductance, hyperpolarizes the photoreceptor, and decreases glutamate release at the synapse. Multiple feedback mechanisms, in which intracellular Ca^{2+} has an important role, serve to turn off the enzymes in the cascade and terminate the light response.

Rod photoreceptors are efficient collectors of light and serve nocturnal vision. Cones are much less sensitive and function throughout the day. Cones synapse onto bipolar cells that in turn excite ganglion cells. Rods connect to specialized rod bipolar cells whose signals are conveyed through amacrine cells to the cone bipolar cells. These vertical excitatory pathways are modulated by horizontal connections that are primarily inhibitory. Through these lateral networks light in the receptive-field surround of a ganglion cell counteracts the effect of light in the center. The same negative-feedback circuits also sharpen the transient response of ganglion cells.

As we shall see in subsequent chapters, the segregation of information into parallel pathways and the shaping of response properties by inhibitory lateral connections are pervasive organizational principles in the visual system.

Markus Meister
Marc Tessier-Lavigne

Selected Readings

Dacey DM. 2004. Origins of perception: retinal ganglion cell diversity and the creation of parallel visual pathways. In: MS Gazzaniga (ed). *The Cognitive Neurosciences,* pp. 281–301. Cambridge, MA: MIT Press.

Dowling JE. 1987. *The Retina: An Approachable Part of the Brain.* Cambridge, MA: Harvard Univ. Press.

Fain GL, Matthews HR, Cornwall MC, Koutalos Y. 2001. Adaptation in vertebrate photoreceptors. Physiol Rev 81:117–151.

Gollisch T, Meister M. 2010. Eye smarter than scientists believed: neural computations in circuits of the retina. Neuron 65:150–164.

Lee BB. 1996. Receptive field structure in the primate retina. Vision Res 36:631–644.

MacNeil MA, Brown SP, Rockhill RL, Masland RH. 2000. Retinal cell mosaics and neurotransmitters. In: DM Albert, FA Jakobiec (eds). *Principles and Practice of Ophthalmology,* pp. 1729–1745. Philadelphia: Saunders.

Meister M, Berry MJ. 1999. The neural code of the retina. Neuron 22:435–450.

Oyster CW. 1999. *The Human Eye: Structure and Function.* Sunderland, MA: Sinauer.

Roof DJ, Makino CL. 2000. The structure and function of retinal photoreceptors. In: DM Albert, FA Jakobiec (eds). *Principles and Practice of Ophthalmology,* pp. 1624–1673. Philadelphia: Saunders.

Shapley R, Enroth-Cugell C. 1984. Visual adaptation and retinal gain controls. Prog Retin Eye Res 3:263–346.

Wandell BA. 1995. *Foundations of Vision.* Sunderland, MA: Sinauer.

Wässle, H. 2004. Parallel processing in the mammalian retina. Nat Rev Neurosci 5:747–757.

References

Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. 2008. *Molecular Biology of the Cell,* 5th ed. New York: Garland Science.

Boycott B, Wässle H. 1999. Parallel processing in the mammalian retina: the Proctor Lecture. Invest Ophthalmol Vis Sci 40:1313–1327.

Boycott BB, Dowling JE. 1969. Organization of the primate retina: light microscopy. Philos Trans R Soc Lond B Biol Sci 255:109–184.

Curcio CA, Hendrickson A. 1982. Organization and development of the primate photoreceptor mosaic. Prog Retinal Res 10:89–120.

De Valois RL, Morgan H, Snodderly DM. 1974. Psychophysical studies of monkey vision. 3. Spatial luminance contrast sensitivity tests of macaque and human observers. Vision Res 14:75–81.

Derrington AM, Lennie P. 1984. Spatial and temporal contrast sensitivities of neurones in lateral geniculate nucleus of macaque. J Physiol 357:219–240.

Enroth-Cugell C, Robson JG. 1984. Functional characteristics and diversity of cat retinal ganglion cells. Basic characteristics and quantitative description. Invest Ophthalmol Vis Sci 25:250–267.

Hurvich LM. 1981. *Color Vision.* Sunderland, MA: Sinauer.

Ishihara S. 1993. Ishihara's Tests for Colour-blindness. Tokyo: Kanehara & Co.

Lee BB, Pokorny J, Smith VC, Martin PR, Valberg A. 1990. Luminance and chromatic modulation sensitivity of macaque ganglion cells and human observers. J Opt Soc Am A 7:2223–2236.

Nathans J, Hogness DS. 1984. Isolation and nucleotide sequence of the gene encoding human rhodopsin. Proc Natl Acad Sci U S A 81:4851–4855.

Nathans J, Thomas D, Hogness DS. 1986. Molecular genetics of human color vision: the genes encoding blue, green, and red pigments. Science 232:193–202.

O'Brien DF. 1982. The chemistry of vision. Science 218: 961–966.

Polyak SL. 1941. *The Retina.* Chicago: Univ of Chicago Press.

Rodieck RW. 1965. Quantitative analysis of cat retinal ganglion cell response to visual stimuli. Vision Res 5:583–601.

Sakmann B, Creutzfeldt OD. 1969. Scotopic and mesopic light adaptation in the cat's retina. Pflügers Arch 313:168–185.

Schnapf JL, Kraft TW, Nunn BJ, Baylor DA. 1988. Spectral sensitivity of primate photoreceptors. Vis Neurosci 1:255–261.

Schneeweis DM, Schnapf JL. 1995. Photovoltage of rods and cones in the macaque retina. Science 268:1053–1056.

Schneeweis DM, Schnapf JL. 2000. Noise and light adaptation in rods of the macaque monkey. Vis Neurosci 17:659–666.

Solomon GS, Lennie P. 2007. The machinery of color vision. Nat Rev Neurosci 8:276–286.

Stryer L. 1988. *Biochemistry,* 3rd ed. New York: Freeman.

Wade NJ. 1998. *A Natural History of Vision.* Cambridge: MIT Press.

Wald G, Brown PK. 1956. Synthesis and bleaching of rhodopsin. Nature 177:174–176.

Wyszecki G, Stiles WS. 1982. *Color Science: Concepts and Methods, Quantitative Data and Formulas,* Chapter 7 "Visual Thresholds." New York: Wiley.

Young RW. 1970. Visual cells. Sci Am 223:80–91.