# Representation of cone signals in the primate retina

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Vision begins with specialized retinal circuits that encode diverse types of information. For Old World primates, these circuits sample three submosaics formed by cone photoreceptors sensitive to short, middle, and long wavelengths. For spatial acuity, the photon catch between any two cones is compared for discrimination of patterns as fine as the cone mosaic. For color vision, the photon catch between different cone types is compared for discrimination of fine spectral differences on the basis of hue. The retinal circuits for these two tasks differ at the synaptic level to form distinct representations of signals from the cone mosaic. © 2000 Optical Society of America [S0740-3232(00)00603-7]

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## 1. INTRODUCTION

Visual perception in daylight involves a diverse range of spectral, spatial, and temporal information that is processed with high sensitivity to small differences, yet over a broad range of operation. How central mechanisms of the brain interpret these diverse types of information to produce a seamless visual representation of the world depends critically on how cone photoreceptors parcel information to neural pathways early on in the retina. In the central fovea, where cones are packed most densely, we are able to discriminate a spatial difference between the photon catches of adjacent cones.[1] This suggests that, within the tight packing of neurons postsynaptic to foveal cones (Fig. 1), the cone sampling rate is represented accurately by a mosaic of neurons whose sampling aperture matches that of a single cone.[3] However, we also discriminate spectral differences between photon catches because cones form three mosaics, each sensitive to short (S), middle (M), or long (L) wavelengths.[4] This suggests that, also within the set of postsynaptic neurons, the difference between the outputs of distinct cone types is represented as a basis for color discrimination.

How do retinal representations for spatial and spectral discrimination differ? In the traditional view, a single retinal circuit—the midget or P (parvocellular) cell circuit—underlies our discrimination of both spatial and spectral differences, and it is left to complex, but unknown, circuits in the visual cortices to decipher or demultiplex the two types of information. This view implies that cortical circuitry not only must integrate different types of information across the visual scene, but must first disintegrate confounded spatial and spectral information.[3] Though this strategy is likely to demand more-complex central wiring, one could nevertheless argue that it falls on the short side of Occam's razor. In the early visual cortex, more than 50% of the representation of the visual field is devoted to the mere 2% or so of the retinal surface comprising the fovea. This is due to the enormous burgeoning in ganglion cell number necessary to support spatial acuity limited only by the cone spacing. Thus the circuitry for spatial acuity in the fovea has its price: more central hardware to accommodate a higher sampling rate of information. One might argue that adding more retinal circuitry for color discrimination would require substantially more ganglion cells and would unduly burden the cortical wiring.

In this sense, it is tempting to attribute the dense packing of the fovea (approximately ten postsynaptic neurons for each cone) to the circuitry necessary to support the highest possible spatial acuity. However, this view glosses over the great diversity of different neuronal cell types represented in this dense packing, approximately 60 cell types across retinal layers. This diversity suggests an alternative evolutionary strategy to arrive at such complexity. Simply stated, this strategy supplies each visual channel—say, spatial acuity or color vision—with a unique retinal circuit whose design is to maximize a particular type of information with minimum redundancy between different types of circuit. The strong form of this hypothesis assigns to each circuit a corresponding ganglion cell type for carrying each specialized message. For example, circuits for high-contrast, spatial detail would differ structurally from those for lower-contrast, spectral detail.[3] The question is whether such circuits exist within the immense diversity of retinal neurons.

In our investigations of these and other hypotheses concerning retinal architecture, my colleagues and I have exploited the level of detail afforded by electron microscopy to examine the ultrastructure of neuronal circuits postsynaptic to S, M, and L cones. The details of our methods for tracing complete circuits and their synaptic connections through volumes of retinal tissue are described elsewhere.[2,5–8] Below I will focus on describing some of the connections of specific cone types; in particular, I will focus on how their retinal circuits differ and what these differences tell us about how the retina encodes spatial versus spectral signals.

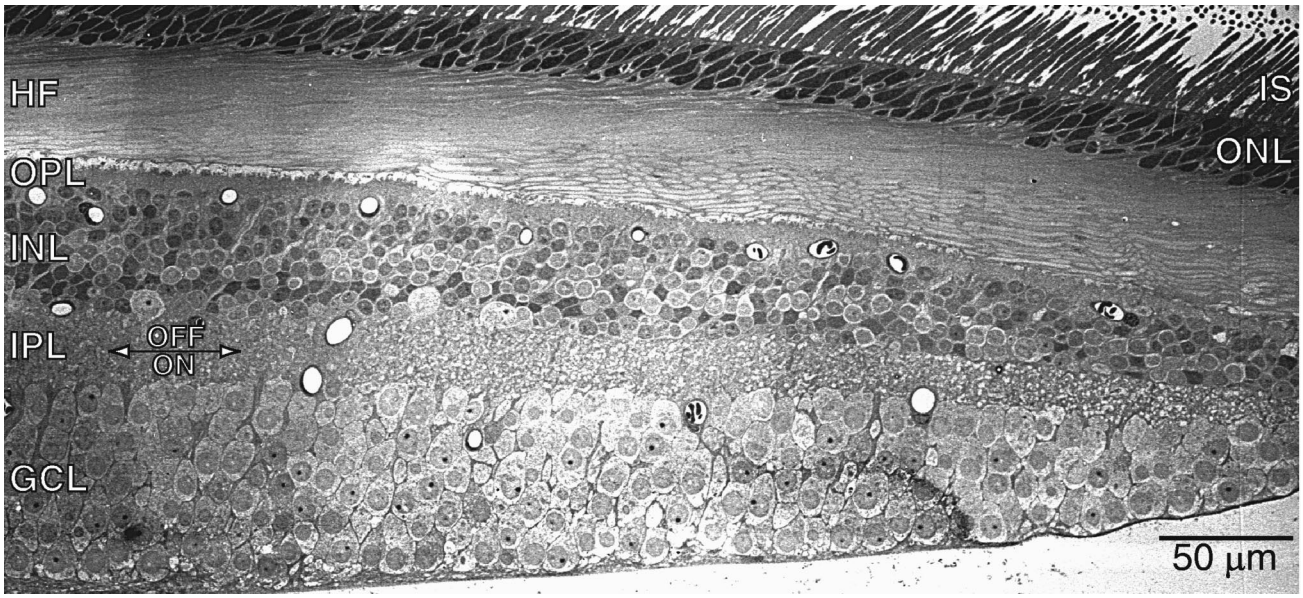


Fig. 1. Electron micrograph of a vertical thin section along the foveal slope of macaque retina.[2] The cone inner segments (IS) contacting the bipolar and ganglion cell circuits that we studied were centered at ~1° nasal of the center fovea. The tight packing of cones is accompanied by tight packing of their axons or Henle fibers (HF) and cell bodies in the outer nuclear layer (ONL). The high sampling rate of the cone mosaic correlates with multiple rows of neurons across the inner nuclear layer (INL) and the ganglion cell layer (GCL). The dendrites of bipolar cells penetrate the cone terminal space in the outer plexiform layer (OPL), while their axons form connections with ganglion cell dendrites in the inner plexiform layer (IPL).

## 2. RESULTS

### A. Diversity at the Cone Synapse

The great diversity of neuronal cell types in the retina is reflected in the estimated 250 processes that penetrate the postsynaptic space of the foveal cone; in the periphery this number probably rises to greater than 500.[9] Each site of glutamate release at the cone terminal is marked by an electron-dense ribbon that points between a pair of horizontal cell processes to an invagination of the terminal membrane that houses a central, bipolar cell dendrite (Fig. 2). This arrangement is usually called a triad,[10,11] although sometimes an invagination houses more than one bipolar cell dendrite in the central position.[6,9] This is clear from Table 1, which shows, for each cone, between one and three more central dendrites than actual ribbon synapses. In the primate retina these invaginating dendrites invariably arise from a bipolar cell with axon terminals stratifying in the **b** or ON sublamina of the IPL.[6] These bipolar cells provide the excitatory connections to ON-center ganglion cells[12]; thus "invaginating" is likely to be synonymous with a depolarizing response to light.

Of the 250 processes penetrating the foveal cone, the invaginating bipolar and horizontal cell members of each triad account for approximately 100.[6,9] Separate bipolar cell dendritic twigs that abut the membrane of the cone terminal at sites of basal contact contribute the remaining processes.[13] In the primate these are the only sites of contact between cones and those bipolar cells that have axon terminals that stratify in the **a** or OFF sublamina of the IPL; these cells provide excitatory connections to OFF-center ganglion cells.[12] Interestingly, in the fovea, the dendrites of large-field or diffuse ON bipolar cells occupy a few of the multiple basal sites adjacent to the invaginating dendrite of the ribbon synapse.[6] These basal contacts are termed semi-invaginating or triad associated because of their proximity to the triad. Thus "basal" is not necessarily synonymous with a hyperpolarizing response to light.[14]

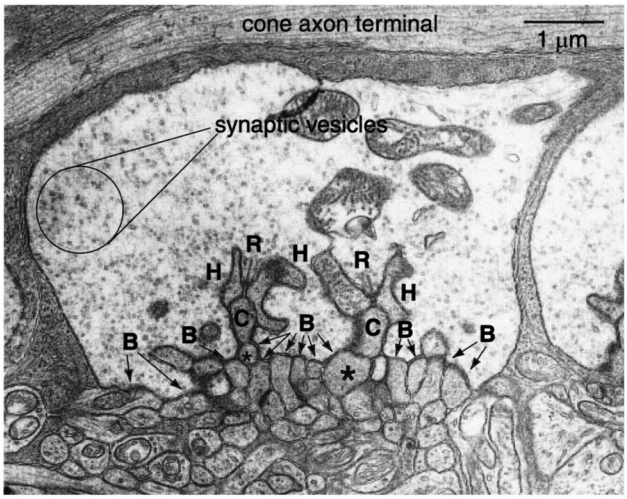


Fig. 2. Electron micrograph of a vertical section through the base of a cone terminal.[6] Two active zones are each marked by a synaptic ribbon (R) that serves as a docking site for glutamate-containing vesicles. Each ribbon points between a pair of horizontal cell processes (H) to an invagination of the terminal membrane that houses a central bipolar cell dendrite (C) in an arrangement called a triad. Sites of basal contact (B) with bipolar cell dendrites occur adjacent to the invaginating dendrites of triads (triad associated or semi-invaginating, indicated by an asterisk) or outside the invagination (nontriad associated), depending on the type of bipolar cell.

### B. Private Lines from M and L Cones

With such great numbers of postsynaptic processes, the potential for each cone to diverge to distinct circuits is immense. In the fovea, while most of the 250 or so pro-

cesses are parceled among 8–10 different bipolar and horizontal cell types, two cell types contribute 25% or more of these. The dendritic tree of a midget ON bipolar cell contributes nearly every invaginating dendrite to the axon terminal of an M or an L cone (Ref. 6; Table 1). Over most of the retina, each midget ON bipolar cell collects input from only a single cone, and each cone contacts only one midget ON bipolar cell.[15] Similarly, each cone also contacts a single midget OFF bipolar cell, primarily at semi-invaginating basal sites.[16] Like its ON counterpart, each midget OFF bipolar cell collects input from only one cone over most of the retina.[15] Thus both a midget ON and a midget OFF bipolar cell represent nearly every M and L cone.

In our published studies of midget bipolar cells in the fovea, we have never observed a cell that collects input from more than one cone; conversely, we have never observed a cone that diverges to more than one ON and one OFF midget bipolar cell.[5] Thus the midget bipolar cell is highly specialized for representing and preserving the neural image of a single cone. While this is advantageous for spatial acuity, it is deleterious for the contrast sensitivity of the bipolar cell, which would increase with a greater number of presynaptic cones.[17] The great density of dendrites that each midget cell contributes to the cone's postsynaptic space may partially compensate for the cell's minimal cone input. For example, the midget ON bipolar cell collects approximately 20 synapses from one cone (Table 1). Interestingly, this is close to the 25 or so synapses that a diffuse ON bipolar cell collects from approximately 10 cones.[6]

The private line from each foveal cone continues in the IPL, where each midget bipolar cell directs virtually all its synapses to the dendritic tree of a single midget ganglion cell [Refs. 5, 18, and 19; Fig. 3(a)]. Within the central 6–7 deg, each ON and OFF midget ganglion cell collects input from one cone via a single midget bipolar cell.[3,5,20] Therefore, in and around the fovea, two physiological distinct mosaics of midget ganglion cell (ON and OFF) represent each M and L cone. The precision of the synaptic junction between midget bipolar and ganglion cells is such that the ganglion cell never collects a synapse from a neighbor's bipolar cell.[5] This is an impressive developmental feat, given the proximity of neighboring midget circuits in the inner retina.

Our reconstructions divide the M and L cone mosaic into two populations on the basis of differences in the number of synapses between midget bipolar and ganglion cells [Fig. 3(b)]. Some cones have midget bipolar cells that each contact a sparsely branching midget ganglion cell at approximately 30 synapses; other cone terminals have midget bipolar cells that each contact a more densely branching ganglion cell at approximately 50 synapses.[5] The ON and OFF midget circuits from any particular cone are similar, forming two distinct clusters when plotted against each other [Figs. 3(b) and 3(c)]. Since there is neither convergence nor divergence be-

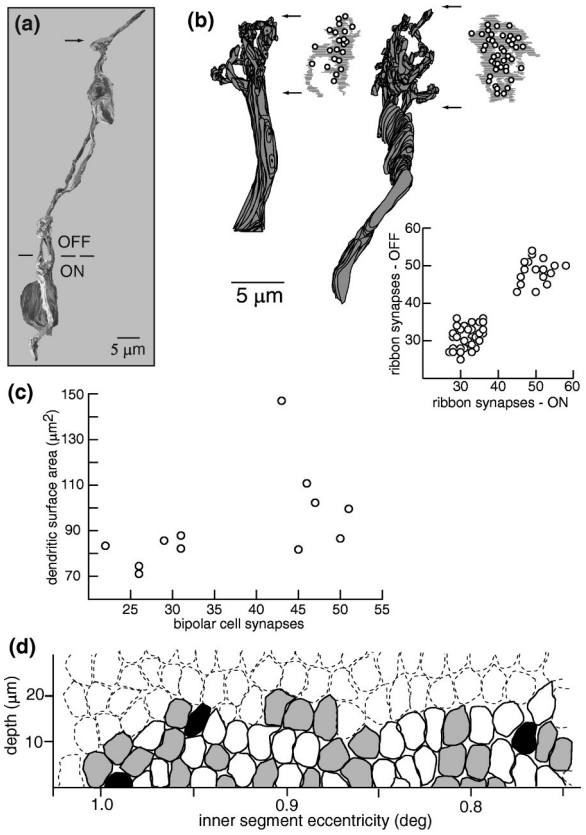


Fig. 3. (a) Reconstructions of the midget OFF and ON pathways from a single cone terminal.[5] Each M and L cone terminal (arrow) contacts one midget OFF ganglion cell (dark cell body) via a midget OFF bipolar cell and one midget ON ganglion cell (cell body truncated) via a midget ON bipolar cell. (b) Reconstructions of the dendritic trees of two neighboring midget OFF ganglion cells in vertical and horizontal view with their bipolar cell synapses (open circles). The cell on the left branched sparsely and received ~30 ribbon synapses from its midget bipolar cell, while the cell on the right branched more densely and received ~50 synapses. Inset (plot): Across a larger sample, the OFF and ON midget pathways from the same cone had highly correlated numbers of ribbon synapses.[5] Therefore this difference in number of synapses partitions the M and L cone mosaic into two groups. (c) The surface area of the dendritic tree of the midget ganglion cell increases as a function of the number of ribbon synapses that the bipolar cell provides (ON and OFF cells pooled). Area corresponds to the sum of the membrane over the region contained within the arrows shown in (b). ON and OFF cells from the same cone were highly correlated (see Ref. 5 for details). (d) Reconstruction of the mosaic of foveal cone terminals in our electron microscopy (EM) series rotated to horizontal view. The depth scale marks the progression of ~320 serial sections cut at 90-nm intervals. Some cones contacted midget pathways with ~30 synapses between bipolar and ganglion cell (white) or ~50 synapses between the bipolar and the ganglion cell (gray). S cone terminals (black) were identified by other means (see Subsection 2.C). Cones near the edge of the series could not be classified (dashed outlines).

**Table 1. Invaginating Dendrites at M and L Cones**

| M–L Cone Ribbon Synapses | | Postsynaptic Invaginating Dendrites | | |
|---|---|---|---|---|
| Cone | Ribbons | Total | Midget ON | Diffuse ON |
| 1 | 21 | 22 | 20 | 2 |
| 2 | 18 | 21 | 17 | 4 |
| 3 | 20 | 22 | 16 | 5 |
| 4 | 20 | 21 | 19 | 3 |

tween a cone and a midget bipolar cell or between midget bipolar and ganglion cells, this difference in number of synapses essentially partitions the cone mosaic into two types of cone [Fig. 3(d)].

Naturally, we have proposed that these two cone types, distinguished by their postsynaptic connections, are in fact M and L,[5] although we cannot yet say which is M and which is L. This hypothesis is supported by other observations. By correlating with cone terminals a much larger, contiguous patch of midget ON and midget OFF bipolar cells [Fig. 4(a)], we found that the two types of cone are present in equal numbers. The ratio of cones with small circuits (approximately 30 synapses) to those with large circuits (approximately 50 synapses) is 1.2, with 95% binomial confidence limits of 1.8–0.8. This is similar to the ratio of M and L cones found for another Old World species, *Cercopithecus talapoin*, and for *Macaca* through direct measurements of the spectral sensitivity of cones in intact patches of living retina.[21–23] Also, when we projected the cone terminals and their midget pathways onto a triangulation of the inner segment mosaic, the two types of cone distributed into small clusters of like type [Fig. 4(b)]. Such clustering of events is precisely what one expects from a binomial process: consecutive flips of an unbiased coin result in runs of heads or tails. We confirmed randomness by using the statistical runs test for a binomial process; this result, too, agrees with the direct M and L cone measurements.[21–23]

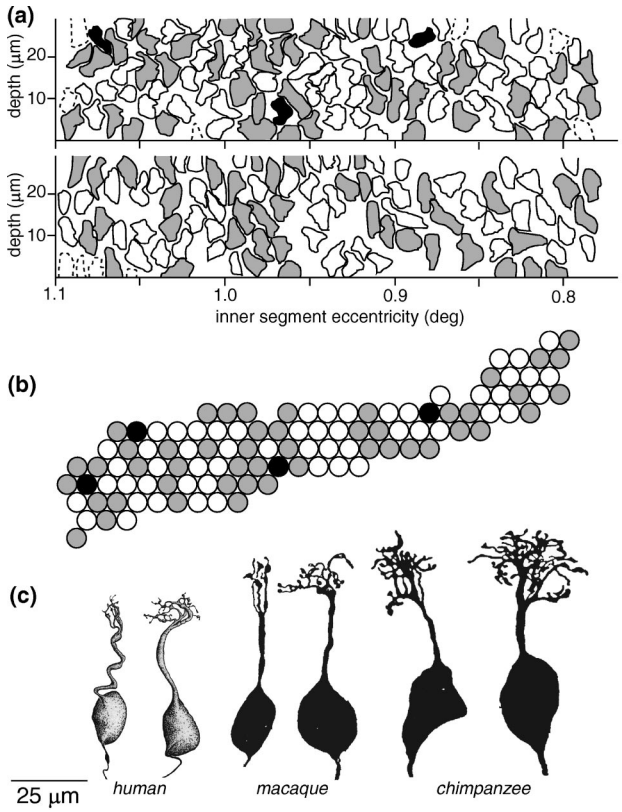


Fig. 4. (a) Outlines of the footprint of each midget OFF (top) and midget ON (bottom) bipolar cell axon terminal in our EM series. The depth scale is the same as in Fig. 3(d). Terminals contacted their corresponding midget ganglion cell either via ~30 ribbon synapses (white) or via ~50 ribbon synapses (gray); some terminals were not complete (dashed outlines). Each of three S cones contacted a midget OFF bipolar cell (black), but not a midget ON bipolar cell. (b) The bipolar cell terminals in (a) were traced to their corresponding cone terminals, and these were projected onto a triangulation of their inner segment mosaic. Cones with small (white) or large (gray) midget pathways were approximately equally numerous (56 versus 48) and distributed into small clusters of like type after performance of a binomial process (see Subsection 2.B). (c) Drawings of pairs of neighboring midget ganglion cells near the fovea of three Old World species indicate that sparsely versus densely branching cells may be representative of the trichromatic retina (sketch of human retina modified from Ref. 20; those of macaque and chimpanzee, from Ref. 18).

Finally, sparsely and densely branching midget ganglion cells are also apparent in drawings of pairs of neighboring midget cells from different Old World species [Fig. 4(c)]. While this is a qualitative inference, such a trend may be characteristic of differences in the numbers of synapses used by M and L cone midget pathways across trichromatic retina. We have not yet tested directly our hypothesis that this difference in circuitry does in fact partition the M and L cone mosaic, but we have adopted it for the moment to test whether other aspects of their postsynaptic circuitry differ.[7,24]

### C. Divergence from the S Cone

The postsynaptic space of an S cone, like that of the M or the L cone, contains myriad horizontal and bipolar cell processes [Fig. 5(a)]. The axon terminal of the S cone has a few more ribbon synapses than that of an M or an L cone. Also, most of these ribbons have two or three invaginating dendrites (Table 2); like an M or an L cone, an ON bipolar cell contributes each of these. In contrast to M and L cones, S cones completely lack a representation in the mosaic of midget ON bipolar cells.[25] This is demonstrated in the map of midget cells presented in Fig. 4.

The so-called blue cone or S bipolar cell contributes nearly all of the 35 or so invaginating dendrites at the S cone[8,25–27] [Fig. 5(b), Table 2]. These are the only bipolar cells in the mammalian retina whose dendrites skip underneath cone terminals to receive select contact from a few widely spaced cones, so they form a conspicuous morphological marker for S cones [Fig. 6(a)]. Certainly some S bipolar cells collect from only a single S cone[15] and in this sense arguably could be called midget. However, the S bipolar cell forms a single type and is completely distinct from the midget cell by other morphological parameters.[8] Like the midget and diffuse ON bipolar cells, the S bipolar cell collects approximately 20 synapses, but from two or three S cones. However, a single S cone provides some 70% of these synapses.[8] Conversely, for each S cone, a single S bipolar cell contributes most of the invaginating dendrites[8,15] (Table 3). In this sense each S cone in the fovea is represented as a peak in the mosaic of S bipolar cells.

An earlier impression, based on a limited sample, was that diffuse ON bipolar cells collect input from every M and L cone within reach of their dendrites but skip any sort of synaptic contact with S cones.[6] This was consistent with earlier tracings of invaginating dendrites from S cones.[25] However, a more complete taxonomy of bipolar cell dendrites penetrating an S cone indicates that diffuse ON bipolar cells do contribute a few invaginating den-

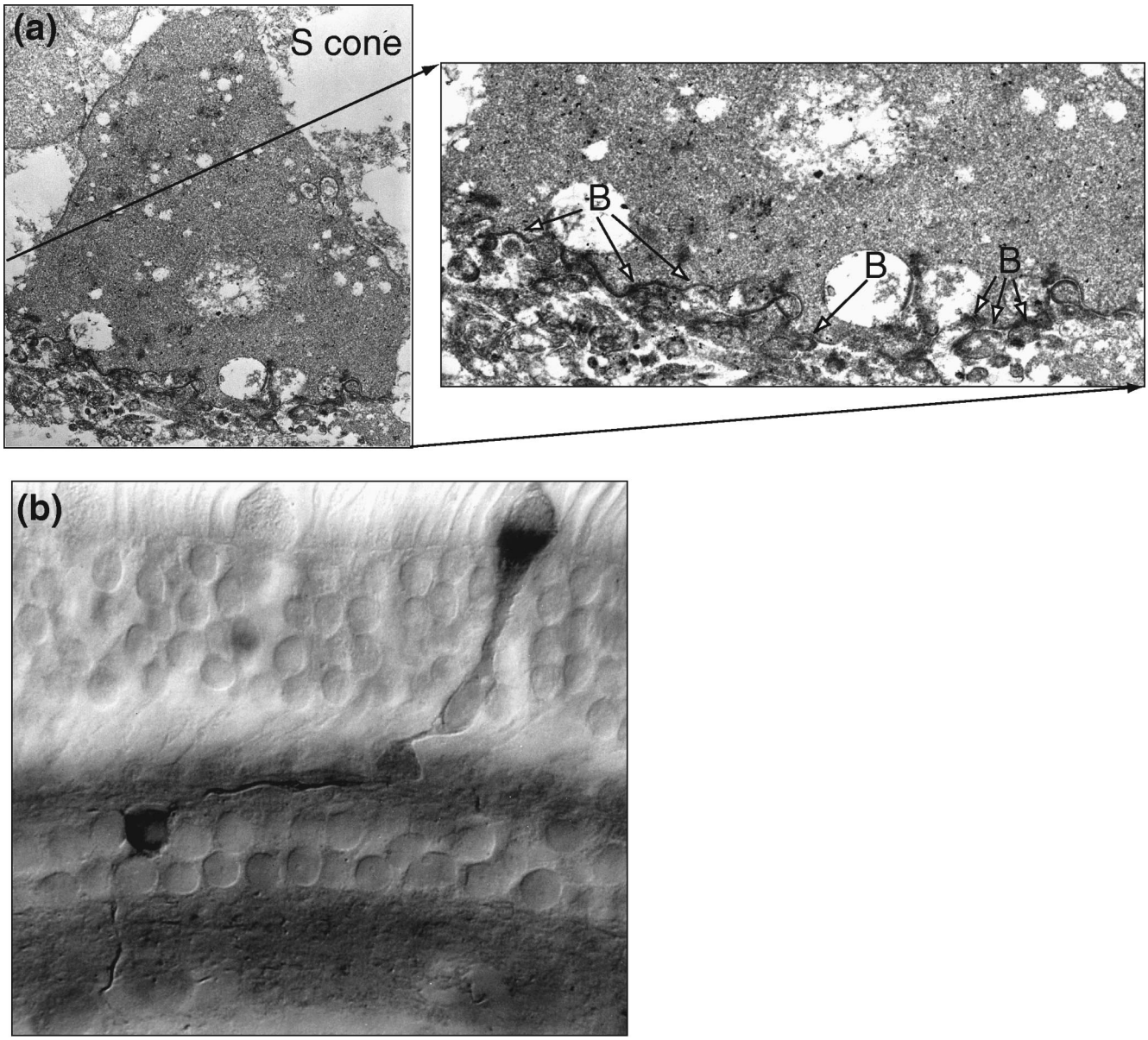


Fig. 5. (a) Electron micrograph of a vertical section of an extrafoveal S cone axon terminal from the human retina, stained with markers against the S opsin and a kainate glutamate receptor (antibodies provided courtesy of J. Nathans and Chemicon, Inc.). The base of the terminal is enlarged (right) to illustrate the locations of basal junctions with bipolar cell dendrites (arrows). These locations generally mark contact with diffuse OFF bipolar cells. Dark particles in the terminal represent gold-toned reaction product for the S cone marker, while those in the postsynaptic cleft represent the gold-toned product for the kainate receptor. (b) Light micrograph of a marked S cone stained as in (a), contacting the dendritic tree of an S bipolar cell marked with antibodies against cholecystokinin (courtesy of J. Del Valle). The bipolar cell axon penetrates deeply to ramify at the border between the IPL and the ganglion cell layer (see Fig. 1).

**Table 2. Invaginating Dendrites at an S Cone**

| S cone Ribbons | Postsynaptic Invaginating Dendrites | | |
|---|---|---|---|
| | Total | S ON | Diffuse ON |
| 26 | 35 | 33 | 2 |

drites and also form basal contact at semi-invaginating positions [Fig. 6(b) and Table 2]. It is not known whether this is so for each type of diffuse ON cell.

Across the body of physiological recordings from the primate retina, there are sparse examples of OFF ganglion cells with S input.[28] Moreover, since more-recent recordings from morphologically identified ganglion cells in the primate retina have failed to find such input,[29] it is increasingly popular to assume that these examples are errant. However, electron micrographs of labeled S cones indicate a large complement of bipolar cell dendrites running along basal positions of the axon terminal [Fig. 5(a)]. Our reconstructions indicate that S cones do contact a midget OFF bipolar cell[30,31] [Fig. 4(a)]. These contacts are similar to those between an M or L cone and its midget OFF bipolar cell and may explain the few ganglion cells identified physiologically as having narrow S-OFF receptive field centers.[28] Also, a reconstruction of the partial dendritic tree of a DB3 diffuse OFF bipolar cell demonstrates basal contact with an identified S cone (Fig. 7).

These contacts suggest that some parasol OFF ganglion cells should hyperpolarize in response to stimulation of S cones.[32]

### D. Preserving the Neural Image of the S Cone Mosaic

In our EM studies of S cone pathways in the fovea we cataloged the ganglion and amacrine cell processes postsynaptic to the axon terminal of the S bipolar cell.[8] While this bipolar cell directs approximately 40% of its output to amacrine cell processes,[8] it is likely to direct the remaining 60% to a single type of small bistratified ganglion cell that corresponds to the S-ON/(M + L)-OFF cell identified physiologically.[29,33–35] This cell collects synapses from two or three S bipolar cells [Fig. 6(c)], with one of these providing the major input.[8] Thus a single S cone provides most of the depolarizing input to the ganglion cell. Also, we found for each S cone in our material one S-ON/(M + L)-OFF ganglion cell. This implies that in the fovea the neural image of each S cone is represented as the dominant input to one S-ON/(M + L)-OFF ganglion cell.[8]

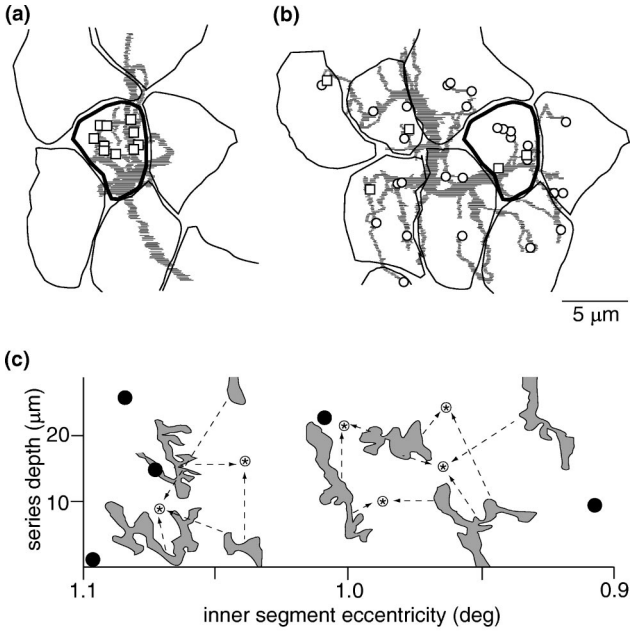


Fig. 6. (a) Horizontal view of a reconstruction of the dendritic tree of an S bipolar cell receiving select contact (squares) at the invaginations of an S cone (boldface outline). These cells usually receive contact from two or three S cones, with one of these providing most of the synaptic input.[8] (b) A diffuse ON bipolar cell beneath the same patch of cone terminals receives contact from all cones, including the same S cone (boldface outline), at a few invaginating positions (squares) and more numerously at semi-invaginating basal positions (circles). This finding is based on more-recent and exhaustive tracing of every postsynaptic process from the S cone and on contrasts with earlier suggestions that diffuse ON bipolar cells may skip S cones.[6,25] (c) Horizontal view of the footprints of S bipolar cell terminals (gray) and the locations of S-ON/(M + L)-OFF ganglion cells (circled asterisks) and S cone terminals (filled circles) in our EM series as a function of the corresponding eccentricity of cone inner segments feeding these circuits.[8] Two or three bipolar cells converge upon each ganglion cell, although one of these provides most of the synaptic input. There is one ganglion cell for every S cone.

**Table 3. Divergence at an S Cone**

| S Bipolar Cell Dendrites | |
|---|---|
| Bipolar Cell | Invaginations |
| 1 | 16 |
| 2 | 13 |
| 3 | 2 |
| 4 | 1 |
| 5 | 1 |

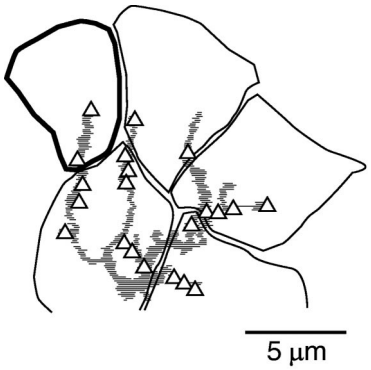


Fig. 7. Horizontal view of a reconstruction of the partial dendritic tree of a DB3 cell receiving contact from all cones within its reach, including the S cone shown in Fig. 6 (boldface outline), at basal positions[32] (triangles).

The S-ON/(M + L)-OFF ganglion cell is apparently the only ganglion cell postsynaptic to the axon terminal of the S bipolar cell.[8] Since S cones lack a midget ON bipolar cell[25] [Fig. 4(a)] and diffuse ON bipolar cells collect input from all cones [Ref. 6; Fig. 6(b)]; the representation of a purely S cone depolarizing signal seems to be restricted to a single ganglion cell type. This is consistent with physiological measurements.[29,33]

## 3. DISCUSSION

### A. Circuits for Spatial Acuity

Observers resolve spatial gratings down to the spacing of foveal cones,[1] or approximately 60 cycles/degree (c/deg). This suggests that, perceptually, the information from a single cone is preserved in subsequent representations throughout the psychophysical channel. The midget pathways are well suited to carrying spatial signals from the retina.[20,36] Each cone contacts an OFF and an ON midget pathway to divide the dynamic range between light decrements and light increments. That these pathways never share a synapse, either from cone to midget bipolar cell or from bipolar to midget ganglion cell, is testimony to the evolutionary pressures to construct a system of highest possible sampling rate. The price is not only a thicker fovea and a larger foveal representation in the cortex but also a decrease in sensitivity. With only a single cone input, the midget ganglion cell's constrast sensitivity is quite poor.[37] This is consistent with the psychophysical observation that discrimination of very high spatial frequencies requires the highest possible constrast.[38]

In the trichromatic retina the expression of different cone types confounds spatial discrimination. This is especially so for white light or middle wavelengths where the M and L cone absorption spectra overlap.[39] For a

surface with uniform spectral content, a perceived spatial edge could correspond to an actual difference in photon density across space or, spuriously, to a difference in photon catch between patches of different types of cone. The first possibility arises from the physics of light; the second, from a sampling artifact between submosaics of cone type.[39] Thus it is natural to ask whether midget circuits are adapted to counter this ambiguity.

We have partitioned the cone mosaic into two cone types based on structural differences in their midget pathways. Some cones have small midget circuits with approximately 30 synapses between bipolar and ganglion cell, while others have larger circuits with approximately 50 synapses.[5] These two non-S-cone types are approximately equally numerous and randomly distribute input into small patches of like type. These same two cone types may differ by other morphological criteria as well.[24,32] Thus it is natural to hypothesize that these are M and L cones.

We have argued elsewhere that the midget circuit, while optimized for spatial acuity, is ill suited for carrying chromatic signals to the brain.[2] It is generally agreed that the midget mosaics evolved from selective pressure to support the highest possible spatial acuity and that whatever role these cells may play in color discrimination was secondary to the expression of a second M–L pigment. Our data indicate that the midget pathways for M and L cones may differ by a factor of 1.6 or so in the number of synapses that they use. If so, this difference indicates that the expression of the second M–L pigment correlates with modifications of cone postsynaptic pathways. This is not so for the lateral inhibitory neurons forming the midget ganglion cell surround, which collect indiscriminately from M and L cones.[7,40–42] Thus apparently there was little evolutionary pressure to sharpen the highly variable spectral difference between an individual cell's center and surround.

In contrast, perhaps the factor of 1.6 between M and L midget circuits reflects pressure not to sharpen a difference within a cell's receptive field but to decrease a difference between neighboring midget cells. For any uniform surface producing unequal photon catches in M and L cones, the activity across the midget ganglion cell mosaic will demonstrate spurious spatial bumps.[39] For example, a scene for which the mean photon catch is higher for L than for M cones could be interpreted by the brain as containing edges at higher spatial frequencies than are actually present. Across a pool of natural scenes, the quantum catch for L cones is moderately greater than that for M cones.[43,44] Thus, assuming otherwise equivalent circuits, the factor-of-1.6 more synapses may represent a mechanism to comparably boost the output of midget ganglion cells from M cones to counter the spatial ambiguity inherent to a trichromatic cone mosaic.

### B. Distinct Circuits for Color Vision

Anatomical studies of color vision have evolved into a critical examination of the sites of convergence of signals from S, M, and L cones—in particular, those sites at which these signals converge with opposite sign. This avenue arose naturally from how we perceive color. While normal trichromatic observers experience a diverse range of hues, blue versus yellow and red versus green are pairs of mutually exclusive or opponent percepts.[45] Color cancellation experiments and measurements of increment thresholds for the color-opponent channels imply that the critical neural event is spatially coextensive antagonism between different cone types.[45–47] Thus, for blue–yellow opponency, signals from S cones are combined antagonistically with those from M and L cones. These combinations do not preclude other interactions between pathways but are minimal conditions consistent with the opponency of the color channels.

Physiological and anatomical evidence suggests that, at least for blue–yellow opponency, a distinct ganglion cell carries color signals to the brain.[8,29,33–35] The S-ON/(M + L)-OFF, small bistratified ganglion cell in the fovea collects input from three or four S cones via S bipolar cells and from approximately 20 M and L cones via diffuse bipolar cells (Fig. 8). Such circuitry predicts spatially co-

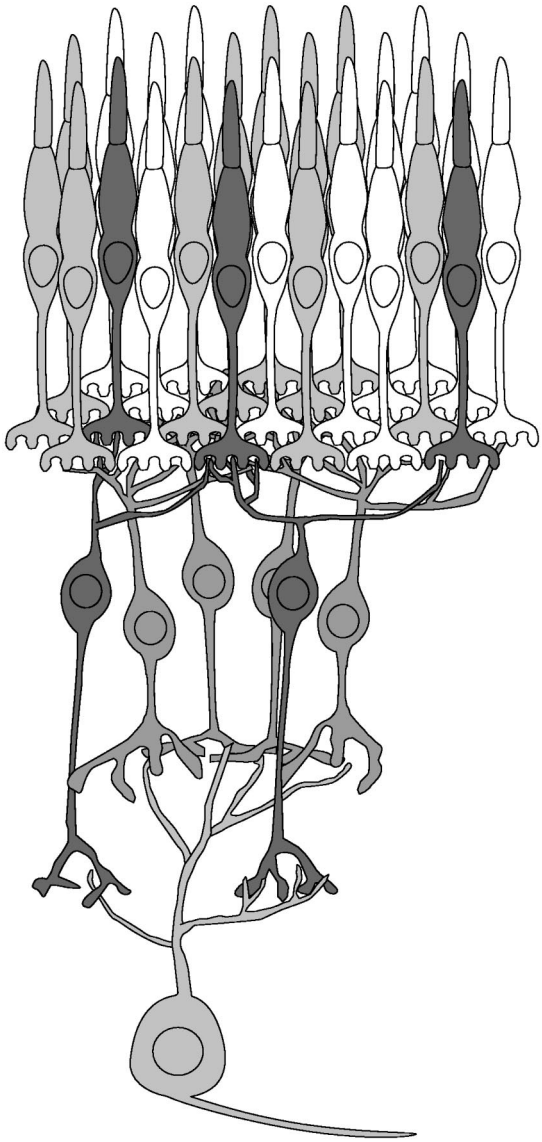

Fig. 8. The S-ON/(M + L)-OFF ganglion cell collects input from three or four S cones via two or three S bipolar cells (dark gray) and from approximately 20 M (light gray) and L (white) cones via approximately four diffuse OFF bipolar cells.[8]

extensive, excitatory receptive field regions responding to either S or M + L stimuli.[8] Thus, at least qualitatively, the spatial and spectral profiles of the S-ON/(M + L)-OFF ganglion cell are consistent with cells involved in blue–yellow opponency.[48] Inhibitory lateral elements (horizontal and amacrine cells) are also likely to contribute to the net S/(M + L) antagonism, but the pattern of bipolar cell convergence within the dendritic tree suggests that a critical step in establishing blue–yellow opponency begins at the parceling of cone signals into ON and OFF pathways.

For a given psychophysical channel, spatial resolution is limited by the sampling density of its dedicated ganglion cell.[12] Thus achromatic spatial acuity is set by the midget ganglion cell density–not only in the fovea, but over the retinal mosaic.[20,36] Similarly, one might expect spatial acuity for the blue–yellow channel to be set by the S-ON/(M + L)-OFF ganglion cell. In the fovea the cell's sampling density corresponds to one for every S cone. This would support detection of a blue–yellow grating down to approximately 10 c/deg, the actual psychophysical limit.[49] At approximately 20° eccentricity the dendritic field spans approximately 200 $\mu$m; assuming that the dendritic fields tile the retina, this corresponds to detection of a blue–yellow grating down to approximately 1.5 c/deg, again close to the actual psychophysical limit.[2,50,51] Thus, although the S-ON/(M + L)-OFF ganglion cell is much sparser than the midget ganglion cell, its sampling density is sufficient across the retina to support the spatial acuity of the blue–yellow channel.

Our reconstructions indicate that a single S cone provides the largest portion of input to an S-ON/(M + L)-OFF ganglion cell; this is so in the periphery as well.[52] Thus, with one S-ON/(M + L)-OFF ganglion cell per S cone in the fovea, the representation is similar to that of a midget ON ganglion cell for each M or L cone. However, unlike the midget system, each ganglion cell collects input from multiple S cones via multiple S bipolar cells. Thus the mosaic of S-ON/(M + L)-OFF cells is able to preserve the spatial resolution afforded the S cone mosaic, while each ganglion cell improves its signal-to-noise ratio by collecting input from multiple, neighboring S cones. Computations suggest that the advantage of this collective coding strategy is the same regardless of whether a cell collects input from a few closely spaced cones or from many widely spaced cones.[17] So the actual number of S cones from which the S-ON/(M + L)-OFF cell collects input—three or four in the fovea—is probably matched to the spacing of the S cones in much the same way that S cone spacing is matched to the blurring of short wavelengths by the optics of the eye.[53]

In the fovea the S-ON/(M + L)-OFF ganglion cell accounts for approximately 3% of all the optic nerve axons.[8] This fraction represents the anatomical price for a retinal circuit dedicated to spectral but not spatial differences. At least for blue–yellow color discrimination, the short side of Occam's razor apparently tends toward a unique retinal circuit whose design is to maximize a particular type of information—in this case, spectral differences between S cones and M or L cones. This raises the possibility that among the great diversity of other retinal cell types there exists a similar circuit, perhaps better suited than the midget circuit, for red–green color vision.[2,48]

### C. Other Pathways from S Cones

Complementary ON and OFF mosaics for a particular ganglion cell type effectively partition the dynamic range of the pathway about the mean light level. Thus each ganglion cell can utilize the full range of its spiking capacity to signal either graded increments or graded decrements from the mean. This strategy is apparent in the wiring of the midget system. If a similar strategy is used by the color channels, one would expect a complementary S-OFF/(M + L)-ON ganglion cell with receptive field structure and sampling density similar to those of the S-ON/(M + L)-OFF ganglion cell. The S midget OFF bipolar cell is likely to contact a single midget ganglion cell that does not qualitatively differ from other midget ganglion cells.[31] A better candidate might be a ganglion cell whose dendrites collect synapses from the S bipolar cell not at the axon terminal but at ribbons located in the descending axon itself within the OFF region of the IPL.[8] These contacts could supply the ganglion cell with pure S signals. However, the full extent of these dendrites is not known, so more than one type of bipolar cell could contact them.

It is not known whether each portion of the spectral, temporal, and spatial visual spectrum is encoded along its own dedicated retinal circuit. Certainly the great divergence demonstrated in the postsynaptic space of the first synapse from cone photoreceptors is evidence of the potential for a variety of parallel circuits. Our detailed examination of the synaptic connectivity of just a few of these circuits indicates that the psychophysical channels for high spatial acuity and for blue–yellow color discrimination likely have their origins in distinct types of ganglion cell. That these circuits appear uniquely suited for a particular visual function is congruous with the idea that retinal diversity evolved to provide each visual message with a particular line to the brain.

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