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Chapter 3

Retinal ganglion cells and the magnocellular, parvocellular, and koniocellular subcortical visual pathways from the eye to the brain

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Abstract

In primates including humans, most retinal ganglion cells send signals to the lateral geniculate nucleus (LGN) of the thalamus. The anatomical and functional properties of the two major pathways through the LGN, the parvocellular (P) and magnocellular (M) pathways, are now well understood. Neurones in these pathways appear to convey a filtered version of the retinal image to primary visual cortex for further analysis. The properties of the P-pathway suggest it is important for high spatial acuity and red–green color vision, while those of the M-pathway suggest it is important for achromatic visual sensitivity and motion vision. Recent work has sharpened our understanding of how these properties are built in the retina, and described subtle but important nonlinearities that shape the signals that cortex receives. In addition to the P- and M-pathways, other retinal ganglion cells also project to the LGN. These ganglion cells are larger than those in the P- and M-pathways, have different retinal connectivity, and project to distinct regions of the LGN, together forming heterogenous koniocellular (K) pathways. Recent work has started to reveal the properties of these K-pathways, in the retina and in the LGN. The functional properties of K-pathways are more complex than those in the P- and M-pathways, and the K-pathways are likely to have a distinct contribution to vision. They provide a complementary pathway to the primary visual cortex, but can also send signals directly to extrastriate visual cortex. At the level of the LGN, many neurones in the K-pathways seem to integrate retinal with non-retinal inputs, and some may provide an early site of binocular convergence.

In the standard model the input to visual cortex is the retinal image, filtered by center-surround receptive fields but otherwise largely unaltered. Two parallel pathways from retina to visual cortex—the parvocellular (P) and magnocellular (M) pathways—carry complementary signals about the retinal image, which together extend the range of vision, and their task is primarily to convey that retinal image to cortex for further processing. This simple view of early visual processing has been given unexpected richness by more recent work that has revealed diverse pathways from photoreceptor to visual cortex—the so-called koniocellular (K) pathways.

THE STANDARD MODEL OF EARLY VISUAL FUNCTION

We start by describing a standard model of early vision (Fig. 3.1), much of which was set down in the 1970s and 1980s by a burst of physiological and anatomical work, first in cat and then in macaque monkey, which was informed by and in turn informed precise measurements of human visual performance. Both the perceptual and physiological work were strongly influenced by concepts of signal processing brought from engineering. The standard model remains useful and is also an

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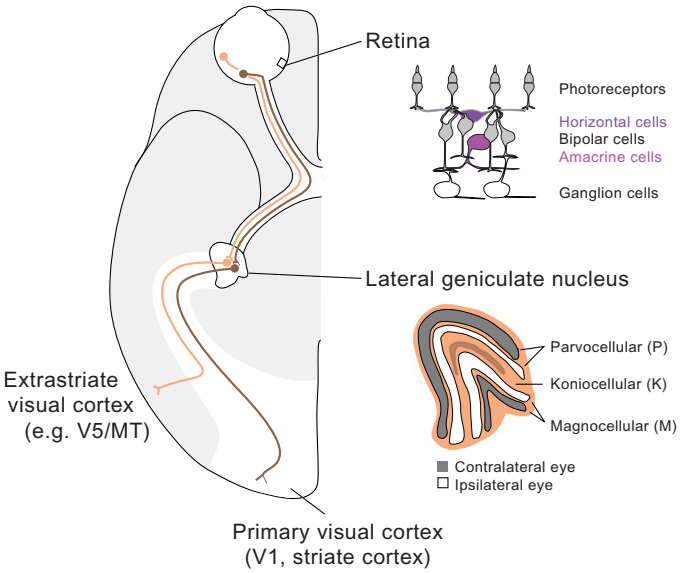

Fig. 3.1. Major visual pathway in primates. In the retina, the signals of photoreceptors are passed to ganglion cells via bipolar cells, and these signals are subject to modulation by horizontal and amacrine cell inputs. The axons of retinal ganglion cells project to many central brain areas, but the majority are sent to the dorsal lateral geniculate nucleus of the thalamus (LGN). The LGN can be partitioned into three subdivisions—the parvocellular (P) layers, the magnocellular (M) layers, and the koniocellular (K) layers. Each layer in the P- and M-subdivisions receives input from ganglion cells in one eye (contralateral or ipsilateral). The eye-of-origin of ganglion cell axons projecting to each of the K-layers is less distinct. Thalamocortical neurons in the P- and M-layers project to primary visual cortex; some thalamocortical neurons in the K-layers project to primary visual cortex, but others project to extrastriate visual cortical areas.

important starting point for understanding of subsequent processing in the visual brain.

Structural basis of parvocellular and magnocellular pathways

Retina

Fig. 3.1 shows a grossly simplified view of retinal organization. Many aspects have been covered in depth elsewhere, but it is useful to reiterate some basic principles. Photons are converted into electrochemical signals in the photoreceptors, and these signals are passed via bipolar cells to ganglion cells, whose axons form the optic nerve. The signals from photoreceptor to bipolar cell and then from bipolar to ganglion cell are considered excitatory. This pathway from photoreceptor to bipolar cells and then ganglion cells is often called the "vertical" pathway—but each photoreceptor sends signals to each of several bipolar cells, providing several parallel pathways from photoreceptor to the central brain.

Photoreceptors make synaptic connections with bipolar cells in the synaptic layer that lies between the photoreceptor cell bodies and bipolar cell bodies (outer plexiform layer). The bipolar cells can be subdivided into cells that are excited by increases in light (ON) and cells that are excited by decreases in light (OFF). The bipolar cells then pass their signals to ganglion cells via connections in the synaptic layer that lies between the bipolar cell bodies and ganglion cell bodies (inner plexiform layer). Strikingly, the axon terminals of the ON and OFF bipolar cells are stratified into sublaminae in the inner plexiform layer. The dendrites of ganglion cells also stratify into these sublaminae. Consequently, the different types of bipolar cells can make connections with different types of ganglion cell, and the majority of ganglion cells therefore become "ON" or "OFF" ganglion cells. This segregation into ON and OFF pathways is the major subdivision of early vision.

Lateral connections in the retina modulate the signals provided by the vertical pathway from photoreceptor to bipolar to ganglion cell. In the outer plexiform layer, the lateral connections are provided by the processes of "horizontal" cells, which interact with the photoreceptor–bipolar synapse. The horizontal cells allow signals from nearby photoreceptors to suppress the flow of signals from photoreceptors to bipolar cells and therefore help provide an inhibitory "surround" to the receptive field of bipolar cells. In the inner plexiform layer, the lateral connections are instead provided by the "amacrine" cells, which receive inputs from bipolar cells and in turn provide outputs to ganglion cells, bipolar cells, and other amacrine cells. These amacrine cells are also inhibitory, but the more complex circuitry of the inner retina means that amacrine cells can have more

complex effects on retinal signals. For example, some amacrine cells directly inhibit ganglion cells; but because these amacrine cells can also be inhibited by other amacrine cells, an appropriate visual stimulus might increase or reduce (disinhibition) the total inhibition onto ganglion cells. Also note that the retina has many distinct classes of amacrine cells, each of which may have distinct connections, and we still know little of them (Grunert and Martin, 2020).

There is more than one type of photoreceptor. The cone photoreceptors, which are less sensitive to photons and therefore more useful in day vision, provide the major signal for the vertical pathways outlined above. The signals of rod photoreceptors, which are more sensitive to photons and are therefore more useful in night vision, take a different route to ganglion cells. A specialized "rod-bipolar" cell conveys the rod photoreceptor signal to amacrine cells—including a very particular amacrine cell, the "A2" amacrine cell. The A2 amacrine cell in turn provides outputs onto cone-bipolar cells that then convey rod signals through the pathways described above. This arrangement allows the same ganglion cells to carry cone photoreceptor signals in the day and rod photoreceptor signals in the night.

Primate specializations

Variants of the blueprint outlined above are found in all mammals. Primates, however, show particular specializations that are important in understanding the signals that are sent to their visual cortex. Anatomical work suggests strong homology between the retinae of humans and other primates (see Grunert and Martin, 2020, for a recent review).

In most Old World primates—including humans—the cone photoreceptors come in three types, being sensitive to long-, medium- or short wavelengths of light (thus, L, M, and S-cone photoreceptors, often called "red," "green," or "blue" photoreceptors). The particular wavelength that a cone photoreceptor is sensitive to depends on the molecular composition of the light sensor (opsin) that it expresses in its outer segment. In S-cone photoreceptors, this opsin is encoded on an autosomal chromosome, and these photoreceptors are histologically and biochemically distinct (Curcio et al., 1991; Baudin et al., 2019). By contrast, the opsins in L- and M-cone photoreceptors are encoded in a single sequence on the X-chromosome, and these photoreceptors appear identical except for the opsin that is expressed. Accordingly, while there are specialized bipolar and ganglion cells that form an "S-cone" pathway, no cell types appear to discriminate the identity of L- and M-cone photoreceptors.

In all primates so far studied, including humans, the ON and OFF bipolar cells can be subdivided into "diffuse" bipolar cells, which connect to multiple photoreceptors, and "midget" bipolar cells, which connect only to one or few photoreceptors (Fig. 3.2A). The axons of these bipolar cells break the basic ON–OFF subdivision of the inner plexiform layer into even finer sublaminae. Their axons in turn form contacts with the dendrites of distinct ganglion cell classes that we will call "magnocellular" (M) and "parvocellular" (P) ganglion cells, after the target of their axons in the thalamus. The M-ganglion cells have large dendritic fields and contact tens or hundreds of diffuse bipolar cells. The P-ganglion cells have much smaller dendritic fields and can contact as few as one bipolar cell. The convergence of photoreceptor signals onto diffuse bipolar cells, and convergence of diffuse bipolar cells onto M-ganglion cells, has the result that each M-ganglion cell effectively samples excitatory input from 10s or 100s of photoreceptors. By contrast each P-ganglion cell effectively samples excitatory input from one, or very few, photoreceptors. The segregation of P- and M-pathways is a major subdivision of early vision in primates, including humans (Dacey and Petersen, 1992; Dacey, 1993; Grunert and Martin, 2020). The one-to-one connectivity and therefore very high sampling of the photoreceptor mosaic that is provided by the P-pathway may be unique to primates, and the presence of homologous or even analogous pathways in other animals remains controversial. While M-ganglion cells are known to accumulate rod signals, how much of the rod signal reaches P-ganglion cells remains unclear.

In many animals, the organization of retinal circuits depends on position in the retina. A particularly defining feature of the primate retina is the presence of a fovea—a region where the cone photoreceptors are smaller than in the rest of the retina and are packed more tightly. Rod photoreceptors and "blue" or S-cone photoreceptors are generally absent and other retinal cells and blood vessels are pushed to the side, providing a clear optical path from the lens to a dense array of cone photoreceptors sensitive to longer wavelengths (the L- and M-cones). The combination of high cone photoreceptor density and optical clarity, along with the narrower range of wavelengths that need to be focused increases the spatial resolution of the retinal image, and the fovea is therefore the region of the retina that we use to analyze small objects or fine textures such as the words you are reading. There are additional quantitative changes in the structure of the retina away from the fovea. In particular, the dendritic fields of bipolar and ganglion cells, in both the P- and M-pathways, increase in size (Goodchild et al., 1996). The consequence is that the number of photoreceptors providing input to each bipolar cell increases, and the number of bipolar cells providing input to each ganglion cell also increases. Thus, a P-ganglion cell in peripheral retina may effectively sample from 10 or more cone photoreceptors and an M-ganglion cell may sample from 1000s of cone photoreceptors. It is

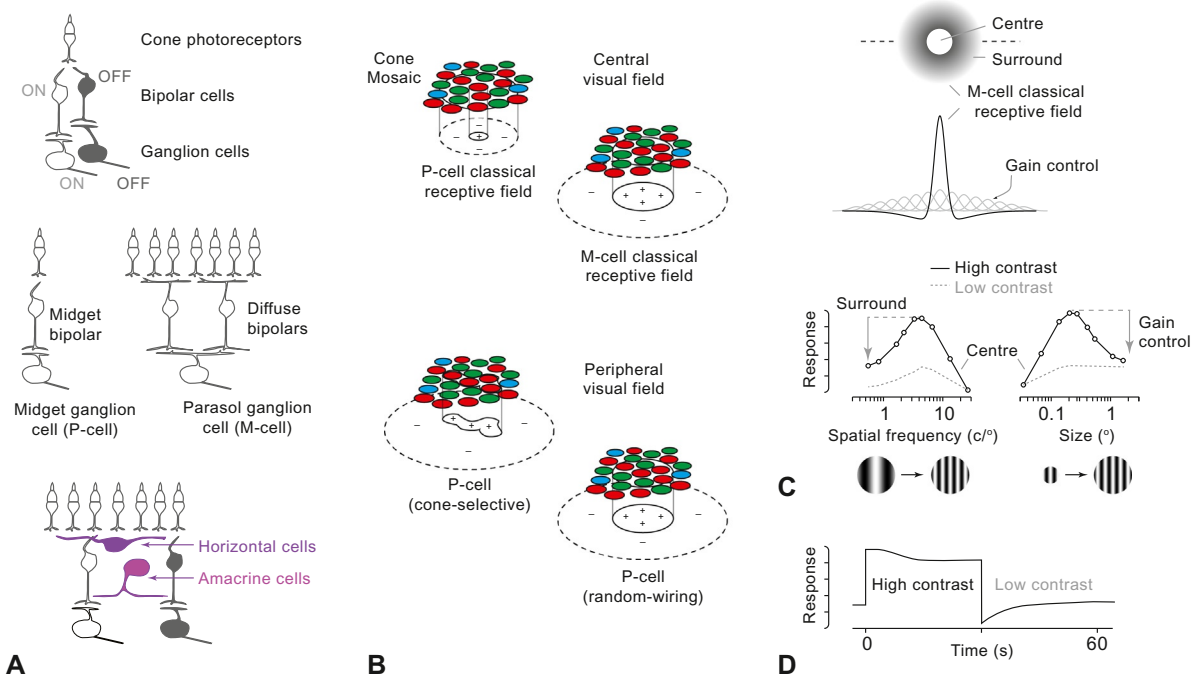

Fig. 3.2. Parvocellular and magnocellular pathways. (A) Retinal organization for photopic (daylight) vision. The output of each cone photoreceptor is provided to several classes of bipolar cells, which in turn make contact with distinct classes of ganglion cells. *Upper panel*: most mammalian bipolar cells can be classed as ON- or OFF (responding to increments or decrements in light). *Middle panel*: in primate retina, the numerically dominant bipolar cells are the "midget" bipolar, which provide output to midget ganglion cells, which in turn project to the P-layers of the LGN. There are also several classes of diffuse bipolar cells; some of these provide output to parasol ganglion cells, which in turn project to the M-layers of the LGN. There are on- and OFF (not shown) subclasses of midget and diffuse bipolar cells, and ganglion cells. *Lower panel*: lateral inhibition in the retina is provided by horizontal cells and amacrine cells. Some amacrine cells provide "cross-over" inhibition from OFF- to ON-pathways, or vice versa. (B) Cone input to receptive fields of P- and M-ganglion cells. In central visual field (foveal retina), a P-cell receptive field center can be as small as a single-cone photoreceptor, making them color selective; M-cells draw excitatory input from several cone photoreceptors and are therefore not color selective. In peripheral visual field, P-cell receptive fields are large enough to draw input from several cone photoreceptors; whether the receptive field is biased toward one photoreceptor type (cone-selective) or not (random-wiring) remains a matter of debate. (C). Gain controls in M-cell receptive fields. Together the receptive field center and surround form the classical receptive field: the classical surround suppresses response to coarse spatial patterns (*middle-left panel*). Gain controls regulate the activity of the classical receptive field. Because they extend beyond the classical receptive field center, some gain controls suppress response to large patterns (*middle-right panel*). Other gain controls reduce response to prolonged presentation of a visual stimulus, and induce aftereffects ("adaptation"; *lower panel*).

less clear if there are changes in the balance of P and M pathways with distance from the fovea. It seems likely that the P-pathway is relatively more important in conveying foveal signals, and the M-pathway is more important for conveying peripheral signals, but it has proved difficult to obtain convincing evidence for this.

Thalamus

In primates, the major target of retinal ganglion cell axons is the dorsal lateral geniculate nucleus of the thalamus (hereafter the "LGN"). Staining histological sections to reveal the cell bodies of neurons the LGN reveals layers of densely packed cell bodies (Fig. 3.1). In coronal sections, midway along the anterior–posterior axis of the nucleus, these layers show clear organization, with more dorsal layers enveloping more ventral layers. These sections also show that there are two histologically distinct types of layers: the two most ventral layers have larger cell bodies and are therefore named the "magnocellular" (M) layers; the more dorsal layers have smaller cell bodies and are therefore named the "parvocellular" (P) layers. In some primates, there are only two parvocellular layers, but in humans and some other primates, there are often four. The neurons in these layers are primarily "relay cells." That is, they receive synaptic input from retinal ganglion cells and send axons to the visual cortex. It is likely that all of the relay cells in the P- and M-layers of the LGN send their axons to primary visual cortex ("V1"; also called striate cortex or area 17 in Brodmann's nomenclature), where

they terminate primarily in layer 4C. A small proportion of neurons in the LGN (~10%) are inhibitory interneurons that also receive retinal input. The dendrites and axons of these interneurons appear to be largely restricted to a single layer, suggesting that they help organize activity within but not between layers.

Early work showed a striking segregation of retinal input to the different layers of the LGN: each layer receives the great majority of its input from retinal ganglion cells in one of the two eyes. The most ventral M-layer, and the most dorsal P-layer, receives input from the nasal part of the contralateral eye via ganglion cell axons that cross the optic chiasm; the adjacent layers receive input from the temporal part of the ipsilateral eye via axons that do not cross at the optic chiasm. When there are four P-layers the pattern repeats, such that from dorsal to ventral the P-layers form a contra-ipsi-contra-ipsi rhythm. The four (or six) LGN layers are astonishingly aligned—a toothpick placed through these layers would connect neurons concerned with the same part of the visual world. For example, nearby neurons in the ventral M-layer (contralateral eye input) and dorsal M-layer (ipsilateral eye input) receive input from retinal ganglion cells that "see" the same small part of the contralateral visual field. Their nearby colleagues in the ipsilateral and contralateral P-layers also "see" that same small part of the visual field. Why there is such exquisite alignment of the topographic maps in each layer remains largely unclear. It may be important for organizing the projections of the LGN onto the visual cortex or it may be important in enabling feedback signals from cortex and other structures to modulate all the thalamic neurons that are providing signals about the same part of visual field.

In primates, unlike some other mammals, there appears to be limited convergence of retinal ganglion cells onto LGN relay cells. There is approximately the same number of relay cells as there are retinal ganglion cells and the axon terminals of the retinal ganglion cells are of similar size to the dendritic fields of the LGN cells. While each retinal ganglion cell probably makes synaptic contacts with more than one LGN cell, it has been difficult to ascertain the functional strength of these connections. No intracellular measurements from primate LGN have been reported (it is located many millimeters below the surface of the brain), but the retinogeniculate synapse is one of the larger synapses in the central nervous system and in rare favorable extracellular recordings a "slow" (S)-potential can be observed. This S-potential is known to reflect the presynaptic activity generated by the action potential of a single retinal ganglion cell and can be recorded alongside the action potentials of the postsynaptic LGN cell. In these recordings, all or nearly all of the LGN action potentials are preceded by an S-potential, while some S-potentials are not followed by an LGN action potential (Kaplan and Shapley, 1984; Carandini et al., 2007). This suggests that primate LGN cells receive most and perhaps almost all of their functional input from a single retinal ganglion cell. Processing within the LGN dictates which of the retinal action potentials is then sent to cortex.

Functional organization of parvocellular and magnocellular pathways

The standard description of early visual function is that the P-pathway is important for high spatial acuity and color vision, while the M-pathway is important for high visual sensitivity and motion vision. This description was developed from careful analysis of extracellular measurements of visual responses, with additional support from measurements of visual function in primates with lesions to one of the pathways (see for example, Schiller et al., 1990; Merigan et al., 1991; Merigan and Maunsell, 1993). Most of this knowledge arises from work that has been conducted on nonhuman primates, but very recent recordings from human retina (Kling et al., 2020) suggest basic conservation of P- and M-cell functional properties. To provide a basis for understanding these claims, we will first review the basic functional organization of retinal ganglion cells and their thalamic targets and then the features that distinguish the P- and M-pathways, focusing on more recent work that has provided greater detail on the mechanisms involved.

Center-surround receptive fields

The receptive field of a retinal ganglion cell is classically defined as the region of the retina or, equivalently, the region of the visual field, where presentation of a stimulus changes the membrane potential of the neuron or (if measured from outside the neuron) the rate of action potentials produced (Kuffler, 1953). Early work measured receptive fields by imaging small spots of light onto the retina and establishing how the presentation or withdrawal of that light changed the rate of action potentials. These measurements yielded maps of the receptive field that had characteristic shape (Fig. 3.2B). First, each neuron showed a central excitatory component to the receptive field, usually located near the cell body. The firing rate of some ganglion cells increased when the small spot of light was in this small, approximately circular region of visual space. These are the "ON" cells. In other cells, the firing rate instead increased when the light was withdrawn. These are the "OFF" cells. The functional segregation of ON and OFF signals is thought to be important in extending the range of light levels that the retina can encode. Second, each neuron showed a surrounding inhibitory component to the receptive field, which extended some distance from the cell body. Here, the effective stimulus

(presentation of light for an ON cell or withdrawal of light for an OFF cell) suppressed firing rate. The smaller excitatory and larger inhibitory components make what we call a center-surround receptive field, and this is the major functional property of neurons in the P- and M-pathways.

The receptive field center of a retinal ganglion cell largely reflects the organization of the excitatory vertical pathway through the retina—the direct route from photoreceptors to bipolar cells to ganglion cells. The receptive field surround instead reflects the organization of the inhibitory lateral pathways through the retina, which arises in horizontal cells and amacrine cells. The relative contribution of horizontal and amacrine cell pathways to the receptive field surrounds of ganglion cells remains controversial. The receptive fields of midget and diffuse bipolar cells, measured at the soma of those cells, show center-surround organization (Dacey et al., 2000) and measurements of the excitatory synaptic input to ganglion cells, which arise in those bipolar cells, also show center-surround organization (Crook et al., 2014; Protti et al., 2014). The receptive field surround of bipolar cells likely arises in the action of horizontal cells, and indeed the synaptic output of a cone photoreceptor onto a bipolar cell may already show center-surround receptive field organization (Packer et al., 2010). In addition, however, there are clear inhibitory inputs to ganglion cells, which arise in amacrine cells. Though the contribution of these inhibitory inputs are difficult to determine (most chemical manipulations of amacrine cell outputs also affect the outputs of horizontal cells), these inhibitory inputs do modulate responses (Cafaro and Rieke, 2013; Crook et al., 2014; Protti et al., 2014), and there is some evidence that amacrine cells may enhance center-surround organization in ganglion cells (Protti et al., 2014; Huang and Protti, 2016). In addition, some M-pathway ganglion cells appear to be electrically coupled to amacrine cells by gap junctions, which may act to suppress responses (Greschner et al., 2016).

The presence of a center-surround receptive field makes neurons more sensitive to edges and spots than to large and uniform surfaces. This is commonly shown by constructing an "area tuning curve," but it can also be shown by measuring responses to sinusoidal grating patterns of varying spatial frequency (Fig. 3.2C). The center mechanism, being small, responds to both coarse (low spatial frequency) and fine (high spatial frequency) patterns. The spatial resolution—the finest grating the neuron responds to—increases as the center size decreases. The surround, being larger, responds only to coarse patterns and therefore only suppresses responses to coarse patterns. The result of center-surround receptive fields is therefore the characteristic "inverted U" shape of retinal ganglion cell tuning curves for spatial frequency. The center-surround organization of retinal receptive fields is thought to be why humans are less sensitive to coarse patterns than finer patterns.

Sensitivity and temporal response

Ganglion cells with larger dendritic fields sample from a larger area of the retina (or equivalently, the visual field) and therefore a greater number of photoreceptors. The dendritic fields of ganglion cells are larger in the peripheral retina, so we expect that receptive field size should increase with distance from the fovea. This is the case—the receptive field center size of P-cells increases with distance from the fovea and so does the receptive field center size of M-cells. This increase in receptive field size is thought to be why human spatial acuity for patterns (including letters) is poorer in the peripheral visual field than at the center of gaze.

While receptive field size increases with distance from the fovea, at any given place in the retina, the M-cells have larger receptive fields than the P-cells. The larger receptive fields of M-cells mean that they effectively draw on the input of more photoreceptors than P-cells, and M-cells should therefore be more sensitive to visual stimuli. This is partly because noise in individual photoreceptors can be "averaged out," making it possible to detect coherent changes in their activity. Indeed, the contrast sensitivity of M-cells is much higher than that of P-cells (Kaplan and Shapley, 1986). It is useful to note here that because M-cells have higher sensitivity than P-cells, the spatial resolution of individual M-cells is often similar to or even better than that of individual P-cells, which have smaller receptive fields but lower sensitivity.

The sensitivity advantage of M-cells is most pronounced when the light stimulus is rapidly modulated: the "flicker fusion rate" (the highest modulation frequency a neuron can respond to) is substantially greater in M-cells than P-cells (e.g., Solomon et al., 2002a). Notably, though, the flicker fusion rate of neurons in both pathways is higher than is found in human perception. A related and major distinguishing feature of P- and M-cells is the time course of their response to a change in luminance (Dreher et al., 1976). While in both cases the initial response is stronger than later responses, the response of a P-cell is relatively "sustained" and that of a M-cell is much more "transient."

Peripheral photoreceptors are larger than foveal photoreceptors. The theoretical consequence is that they should be more capable of signaling photon flux (Tyler, 1985), and there is evidence that the temporal response of peripheral cone photoreceptors and bipolar cells is faster than that of their foveal counterparts (Sinha et al., 2017). Combined with the larger receptive fields of neurons in the peripheral retina, the prediction, therefore, is that neurons

in the peripheral retina should be more sensitive than neurons in the fovea. There is evidence for an increase in sensitivity at high temporal frequencies in peripheral P- and M-cells (Solomon et al., 2002a, 2005; Sinha et al., 2017). There is less evidence for an overall increase in the sensitivity of these cells (Croner and Kaplan, 1995), which may reflect increased amacrine-cell-mediated inhibition onto peripheral ganglion cells (Sinha et al., 2017). A related prediction is that peripheral P-cells and foveal M-cells, which have similar receptive field size, should show similar sensitivity. This does not seem to be the case (Croner and Kaplan, 1995), though it is not clear if this is because peripheral P-cells are less sensitive than expected or central M-cells are more sensitive.

Color selectivity

It was recognized early on that P-cells preferred colored lights to white lights of the same intensity. White light, which contains photons from throughout the visible spectrum, activates all receptors equally, but colored lights contain photons from only a limited part of the spectrum, and therefore activate one photoreceptor more than another. Color vision—the capacity to distinguish lights of different wavelength—relies on the ability of cells to compare the signals of photoreceptors. This is what the receptive fields of many P-cells do: they effectively compare the signals of the long wavelength sensitive ("L," "red") cone photoreceptors with those of medium-wavelength sensitive ("M," "green") photoreceptors, producing color-selective responses (Derrington et al., 1984). The receptive fields of M-cells, by contrast, do not show color selectivity—they respond best to lights that modulate both the L- and the M-cones (which would normally appear as yellow) (Lennie et al., 1993). The contribution of short-wavelength sensitive ("S," "blue") photoreceptors to P- and M-cell receptive fields remains controversial, but there is some anatomical evidence that cells in the P-pathway draw input from presumptive S-cones (particularly OFF-cells; Klug et al., 2003; Wool et al., 2019, but see Lee et al., 2005), and recordings from P-pathway retinal ganglion cells are also consistent with a contribution of S-cones to some P-pathway receptive fields (Field et al., 2010; Wool et al., 2019); similarly, some M-cells may draw small contributions from S-cones. For a recent comprehensive review, the reader is directed to Thoreson and Dacey (2019).

Why are P-cells able to compare the signals of red (L) and green (M) photoreceptors but M-cells cannot? At least near the fovea, a simple answer is that the receptive field center of a P-cell samples from a single cone photoreceptor (Fig. 3.2B). That single photoreceptor can be an L-cone or M-cone, but not both. The receptive field surround is larger and should therefore sample from many photoreceptors. Some of these will be L-cones and some will be M-cones; so the color sensitivity of the surround will be different to the color sensitivity of the center. The combination of center-surround receptive field organization and very small receptive field centers therefore forces foveal P-cells to be color sensitive. This "random-wiring" hypothesis (Lennie et al., 1991) supposes that there is no mechanism in the retina that distinguishes L- from M-cone photoreceptors: the color selectivity of P-cells simply arises from the fact that the surround is large and samples randomly from cone photoreceptors, while the center is small and therefore does not: it has been difficult to disprove the random-wiring hypothesis for receptive fields near the fovea (e.g., Solomon et al., 2005; Buzas et al., 2006; but see Lee et al., 2012).

Presuming no qualitative differences between foveal and peripheral retinal ganglion cells, measurements from peripheral retinal ganglion cells—where multiple cones can contribute to the receptive field center of P-cells—offer the opportunity for a stricter test of the random-wiring hypothesis. Indeed, there is some evidence for nonrandom sampling of cone photoreceptors in individual receptive fields (Field et al., 2010) and peripheral P-cells (and their bipolar cell input) can often be color selective (Martin et al., 2001; Solomon et al., 2005; Crook et al., 2011). Nevertheless, some color-selective receptive fields are expected by random wiring, so the question is whether the fraction of color-selective receptive fields is greater than chance—this is a probabilistic question, and it has been hard to generate data sets that can settle it (Martin et al., 2001; Crook et al., 2011; Wool et al., 2018).

Nonlinearity and gain controls

The description of receptive fields provided previously contains an implicit assumption that they perform relatively linear operations. That is, responses increase in proportion to stimulus strength, and the different parts of the receptive field interact in an additive way. So for example, if the response of the receptive field center to a light was +0.8 (arbitrary) units, and the response of the surround was −0.2 units, then the response of a receptive field to simultaneous activation of the center and surround should be 0.6; and if the intensity of the stimulus doubled, then the response would be 1.2. If the receptive field were linear, this would be important for experimenters because it would then be possible to predict the response of a neuron to an arbitrary pattern after characterizing its response properties with a limited set of measurements. It may also be important for subsequent brain areas because the output of these linear filters can be used to reconstruct the retinal image (Stanley et al., 1999). That is, the early visual pathways are able

to defer decisions about the content of the retinal image to a stage (in cortex), where the signals from different neurons can be interrogated and recombined, to support ever more subtle and parallel computations on the same small part of the visual field.

The receptive fields of foveal P-cells often appear approximately linear. Their response increases almost proportionally with stimulus contrast (Kaplan and Shapley, 1986; Solomon and Lennie, 2005), and the response to one stimulus can generally be well predicted from responses to other stimuli (Lee et al., 1994). There are some deviations from linearity—particularly in peripheral P-cells—including descriptions of nonlinear temporal–chromatic interactions (Solomon et al., 2005) and nonlinear spatial interactions between the subunits of the receptive field (Freeman et al., 2015). The responses of M-cells are substantially less linear. The receptive fields of foveal and peripheral M-cells often show a subunit structure that endows nonlinear responses to fine patterns (Kaplan and Shapley, 1982; White et al., 2002; Crook et al., 2008b; Dhruv et al., 2009; Turner and Rieke, 2016; Shah et al., 2020). This nonlinearity may reflect a rectification in the bipolar cell output onto ganglion cells and is most prominent in OFF cells (Crook et al., 2008b; Turner and Rieke, 2016). Additional nonlinearities in the bipolar cells may enhance M-cell sensitivity to moving stimuli (Manookin et al., 2018).

Other deviations from linearity in M-cells can be explained by the presence of fast and slow mechanisms that act to regulate their sensitivity. These mechanisms are often called gain controls. The fast gain control allows M-cells to adapt their responses to the prevailing image contrast. This gain control can be thought of as an additional, latent component of the receptive field that extends throughout the receptive field and into surrounding regions (Benardete and Kaplan, 1999; Solomon et al., 2002b; Solomon et al., 2006; Alitto and Usrey, 2008). Activation of the gain control by itself does not cause a response from the receptive field but does modulate it. The result of this gain control is that cell responses saturate at high contrast and become more transient. Because the gain control extends some distance across the retina, it also makes neurons sensitive to the distribution of image contrast surrounding the receptive field (Fig. 3.2C). The slower gain control has different impact. It appears to allow M-cells to adjust their sensitivity to the persistent image contrast provided by different environments (for example, overall image contrast is reduced in foggy viewing conditions) (Chander and Chichilnisky, 2001; Solomon et al., 2004; Camp et al., 2009; Appleby and Manookin, 2019). This gain control may take several seconds to activate (Fig. 3.2D) and seems to reduce responsivity but has less impact on the temporal profile of responses.

Extending the standard model

Diversity of retinal ganglion cell types

Substances that are taken up by synapses and transported back along the axon to the cell body have allowed researchers to identify which ganglion cells project from retina to central brain regions. Injection of these substances into the LGN, followed by processing of retinal tissue, can reveal the cell bodies and (in favorable circumstances) the dendritic processes of the retinal ganglion cells that project to the LGN. Early work in macaque monkey was important in showing the major types of ganglion cells that project to the P and M layers of the LGN (Leventhal et al., 1981; Perry et al., 1984). Subsequent work, with higher sensitivity, has revealed additional ganglion cell classes that are substantially different in morphology to the P- and M-pathways (Rodieck and Watanabe, 1993; Dacey et al., 2003; Szmajda et al., 2008). Indeed, molecular analyses suggest the presence of 16–18 ganglion cell types in the primate retina (Peng et al., 2019). This work, and retinal anatomical measurements without target-tracing, in both humans and nonhuman primates (e.g., Ghosh et al., 1996; Peterson and Dacey, 2000), shows that the "not-P-not-M" ganglion cells generally have large dendritic fields, usually substantially larger than those of P- and M-cells at the same retinal location (Fig. 3.3A). Some have dendrites with thorny or bushy appearance, while others have much smoother dendritic fields. In some ganglion cells, the dendrites even form two distinct tiers in the inner plexiform layer (and are therefore called "bistratified cells").

The newly recognized ganglion cells have dendritic processes that localize in different sublaminae of the inner plexiform layer than those of P- and M-pathway ganglion cells. This suggests that these not-P-not-M ganglion cells may receive input from distinct classes of bipolar and amacrine cells, and this appears to be the case. For example, one of the tiers of dendrites of the "small bistratified ganglion cell" sweeps across the bottom of the inner plexiform layer where it forms contacts with a very distinct ON bipolar cell—the S-cone bipolar cell—which, as the name suggests, derives input from short wavelength sensitive (S, "blue") cone photoreceptors. The other tier extends deeper into the inner plexiform layer, where the axon terminals of OFF bipolar cells are found. This tier forms connections with diffuse bipolar cells, like those that provide input to M-ganglion cells, and which derive input from both the L- and M-cones (Ghosh and Grunert, 1999; Percival et al., 2009). This suggests that the small-bistratified cell receives ON input from the S-cones and OFF input from a combination of L- and M-cones. Beautiful physiological work showed that this is precisely the case (Dacey and Lee, 1994)—the small bistratified cell is depolarized by the onset of a blue light or the offset

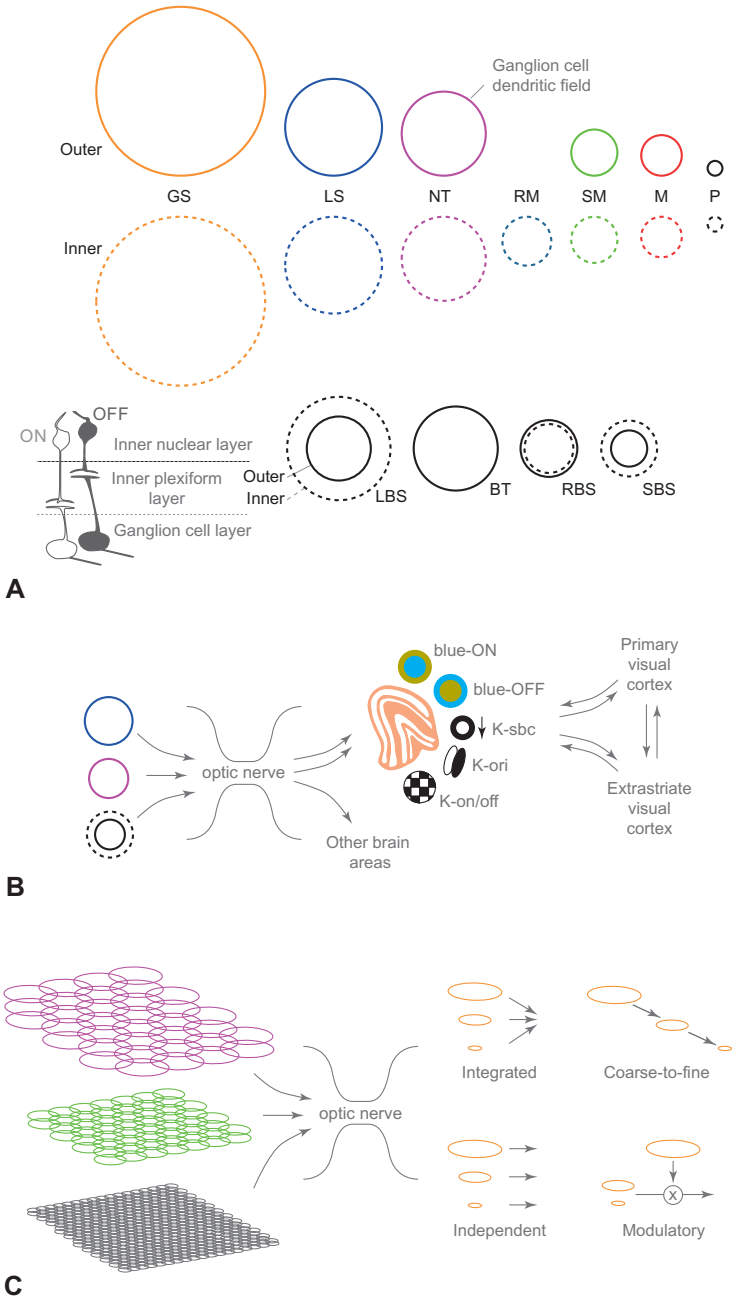

Fig. 3.3. Koniocellular pathways. (A) Survey of ganglion cell classes in primate retina. The *upper two rows* show the ganglion cell classes whose dendrites are restricted to a single sublamina of the inner plexiform layer. Ganglion cells with dendrites in the outer sublaminae are presumptive OFF, and those with dendrites in the inner sublaminae are presumptive ON. Pairs of ganglion cell classes with similar appearance in outer and inner sublaminae are grouped together: GS—giant sparse (intrinsically photosensitive); LS—large sparse; NT—narrow thorny; SM—smooth monostratified; M; P. Other ganglion cells do not have a pair (RM—recursive monostratified) or have dendrites in both outer and inner sublaminae (LBS—large bistratified; RBS—recursive bistratified; SBS—small bistratified) or span multiple sublaminae (BT—broad thorny). (B) K-cells carry diverse functional signals from retina to LGN and potentially other brain areas. K-pathways through LGN can provide signals to extrastriate cortical areas as well as primary visual cortex. Additional reciprocal connections between thalamus and cortex, and within cortex, provide capacity for K-pathways to influence widespread cortical activity. (C) Hypothetical functional impact of K-cells. K-pathway signals may remain independent or be integrated with those of P- and M-pathways. K-pathways provide coarser sampling of retinal image than do P- and M-pathways and may therefore provide useful "coarse sketch" to guide subsequent, fine-grained processing. Alternatively, K-pathways may modulate the efficacy of signaling in P- and M-pathways, highlighting regions of the image that may be important for further analysis.

of a yellow light. As we return to below, it is now thought that this ganglion cell is the major substrate for blue–yellow color vision. What other pathways convey blue-cone signals to central brain areas remains controversial.

The dendrites of the other ganglion cell types also appear to draw input from distinct bipolar cell classes. Much of what we know about these classes has come from studies of a New World primate, the marmoset monkey (e.g., Grunert and Martin, 2020; Percival et al., 2013). The dendrites of these diverse ganglion cells generally show distinct lamination patterns in the inner plexiform layer. For example, the dendrites of broad thorny and narrow thorny ganglion cells have much broader stratification than either P- or M-cell dendrites (and overlap both), while the dendrites of large sparse ganglion cells are much closer to the ganglion cell layer than are either P- or M-cells. The dendrites of other cell types (such as the smooth monostratified and the recursive monostratified ganglion cells) form more sharply defined sublaminae that lie close to the dendrites of P- and M-cells, but can be distinguished (as their names suggest) by the appearance of their dendrites.

Parallel pathways to the lateral geniculate nucleus

Where do these not-P-not-M ganglion cells project to? Experiments in Old World macaque monkeys (the most common nonhuman primate model in vision research) placed fairly large injections of labeling agents in the LGN and often encroached on other nearby nuclei, making it difficult to determine where exactly the labeled ganglion cells projected to. In addition, the P- and M-layers are not the only defining feature of the LGN. Lying between the P- and M-layers are zones of neurons with very small cell bodies: these layers are called koniocellular (K) layers, or zones, "konio" from the Greek for dust, and the neurons in these zones form approximately 10% of all the neurons in the LGN (Solomon, 2002). While K-cells are present in all primates, in macaque monkeys, they form thin and often indistinct layers between the P- and M-layers, or small isolated zones within the P- and M-layers. They are possible to detect because K-cells express calcium-related proteins ("calbindin," "CamKII") that are not expressed by P- and M-cells (Hendry and Yoshioka, 1994), but they are hard to target (or avoid) during injection of tracing substances (Roy et al., 2009).

More recent work in the New World marmoset monkey has allowed better identification of the central targets of some of the not-P-not-M retinal ganglion cells. The marmoset has a simpler LGN than macaques or humans, with two rather than four P-layers, and the K-layers are easier to target (Goodchild and Martin, 1998), making it possible to make small injections primarily confined to K-layers (Szmajda et al., 2008; Percival et al., 2014). Morphological analysis of retinal ganglion cells labeled by these small injections suggests that (1) not-P-not-M ganglion cells are more likely to be labeled by injections into K-layers than into P- and M-layers and (2) different K-layers of the LGN may receive input from different classes of not-P-not-M ganglion cells. For example, broad thorny cells are likely to be a major input to the most ventral K-layer (K1; below the ventral M-layer), while large sparse and small-bistratified cells are likely to be major inputs to the K-layer that lies between the P- and M-layers (K3).

Parallel pathways from the lateral geniculate nucleus

Where do the koniocellular LGN neurons that likely receive these retinal inputs project to? While P- and M-cells in the LGN form a large projection to layer IVC of primary visual cortex (V1), it has long been known that some neurons in the LGN send axons to the more superficial layers I, II, and III of primary visual cortex (V1), avoiding the usual target of layer IVC. Antidromic activation of LGN cells from visual cortex in marmoset monkey confirms that at least some K-cells provide a direct projection to V1 (Cheong and Johannes Pietersen, 2014). Two lines of evidence suggest that the projections to the superficial layers are primarily from K-cells. First, injections of labeling substances into the superficial layers primarily label cell bodies in the koniocellular zones of the LGN, and these cells express the cellular markers of K-cells (Hendry and Yoshioka, 1994; Solomon, 2002). Second, recordings of thalamocortical synaptic activity in the superficial layers of macaque monkey shows characteristic blue–yellow color selectivity that characterizes some K-pathway neurons, but not the red–green color selectivity that characterizes P-pathway neurons (Chatterjee and Callaway, 2003).

While it seems likely that all P- and all M-cells in the LGN project to V1, some K-cells project to extrastriate areas of the visual cortex (Benevento and Yoshida, 1981; Dick et al., 1991). Most interest has centered on a projection to area V5/MT, a cortical area known to be important in motion vision. In both macaque and marmoset monkeys, there is now good evidence that a fraction of K-cells project to area MT (Sincich et al., 2004; Warner et al., 2010). The K-cells in the LGN that project to V1 and MT appear to be distinct populations—no neurons projecting to both V1 and MT have been encountered, though it is difficult to rule out the possibility that a perfect experiment would yield positive results.

The projection from some K-cells to extrastriate cortex suggests that K-cells may form a circuit that "bypasses" V1 (Sincich et al., 2004), allowing rapid communication of sensory signals to cortical areas that are downstream of V1. The broad projections of K-cells also suggest that they may modulate the flow of information within and between cortical areas (Jones, 2001). The potential projections of K-cells to layer I of cortex, which is known to be important in modulation of cortical networks, are particularly suggestive of a role in modulation of cortical activity. Indeed, recent work suggests that (at least some) K-cells may be anatomically related to neurons in the nearby pulvinar (Huo et al., 2019), which also has postulated role in coordination of cortical activity, and like K-cells may receive direct retinal inputs (Warner et al., 2010; Huo et al., 2019).

The projection from K-layers to extrastriate visual cortex may be important in any preservation of visual function after loss of primary visual cortex (sometimes called "blindsight"). In marmoset monkey, the projection from K-layers to area MT is at least partially preserved, alongside an enhanced pulvinar projection, after early-life lesions to V1 (Warner et al., 2015). In macaque monkeys that have suffered lesions to V1, blockade of the LGN abolishes residual visual behavioral capacity and fMRI response from extrastriate visual areas (Schmid et al., 2010), suggesting that a pathway from LGN to extrastriate cortex is important in these responses and behaviors. Consistently, human MRI work shows the presence of a white matter tract from LGN to the human analogue of monkey area MT, which may support these residual visual responses and behaviors (Ajina et al., 2015a,b; Ajina and Bridge, 2019). It should be noted that it is difficult to dissect the contribution of thalamocortical pathways that emerge in the LGN, from the thalamocortical pathways that emerge in the nearby pulvinar, and there remains substantial debate about their relative contribution to blindsight (the reader is directed to references above).

Functional signals provided by nonstandard pathways

The functional properties of P- and M-cells are well understood. Their center-surround receptive fields may be important because they filter the retinal image and allow these cells to convey signals only about particular aspects of it (such as the color or presence of an edge). Alternatively, the center-surround organization can be thought of as allowing predictive encoding (Srinivasan et al., 1982). That is, the surround provides a prediction of the luminance over the receptive field center, which can be compared with the actual luminance over the center. Predictive coding may allow neurons to reduce the redundancy of the signals that they send.

The functional properties of K-pathway neurons are less well understood. In the retina, with the notable exception of the small-bistratified (blue ON) cell described previously, it has proved difficult to target these ganglion cells for intracellular recording, partly because these ganglion cells are quite rare. There has, however, been some progress. One additional class of ganglion cell that has been labeled after large injections into the thalamus (Rodieck and Watanabe, 1993), and been targeted for retinal recordings (Dacey et al., 2005), is the giant sparse cell, an intrinsically photosensitive retinal ganglion cell (ipRGC) (Hattar et al., 2002). These ganglion cells receive photoreceptor input via bipolar cells but also express a membrane bound opsin-protein that makes these cells intrinsically sensitive to light. The intrinsic light response is much slower than the photoreceptor-mediated light response, and unlike photoreceptors, the intrinsic response does not adapt to light level, thus providing these ganglion cells with the capacity to signal overall light levels. At least two subpopulations of these ipRGCs are present in primate retina (Liao et al., 2016; Hannibal et al., 2017; Nasir-Ahmad et al., 2019) and some are known to project to the suprachiasmatic nucleus and pretectal olivary nucleus among others (Hannibal et al., 2014), suggesting a role in control of diurnal rhythms and pupil light response. Indeed, the visual properties of these cells are consistent with these proposed roles (Dacey et al., 2005; Gamlin et al., 2007). Whether and how these neurons contribute to image-forming vision is unclear, but they do appear to project to the LGN as well as the other areas above (Hannibal et al., 2014). In addition, the "smooth monostratified" cells (with, like P- and M-cells, both ON- and OFF-subtypes) project to both thalamus and colliculus. These cells show pronounced nonlinearities and high visual sensitivity but little evidence of a receptive field "surround" (Crook et al., 2008a; Rhoades et al., 2019; see also Petrusca et al., 2007). Finally, the "broad thorny" cells, also known to project to LGN, show ON–OFF responses, with both ON- and OFF-components of the receptive field showing center-surround organization (Puller et al., 2015).

Additional information about the functional properties of these pathways has come from extracellular measurements in and around the K-layers of the LGN (Fig. 3.3B). In what follows the reader should note that it has not yet been possible to verify where these K-cells project to—they may project to V1 or to extrastriate cortex, and some may even be interneurons. Nevertheless, a striking aspect of watching the activity on an electrode as it is passed through the LGN is the sheer number of action potentials emerging from densely packed, spontaneously active neurons. At intervals as the electrode is lowered, this activity fades away. This is probably

because the electrode is recording from the koniocellular zones between the main layers, where neurons are smaller and less densely packed. In the macaque monkey, neurons in these (tentatively and functionally) identified K-layers can have distinct functional properties including the blue-ON signature discussed above (Roy et al., 2009), but in addition "blue-OFF" and "suppressed-by-contrast" receptive fields (Tailby et al., 2007, 2008b). The receptive fields of the blue-OFF cells respond best to the removal of short wavelength light, opposite to the preferred stimulus of blue-ON cells. Yet while the functional properties of ON- and OFF-cells in the P- or M-pathways are quite similar (there are relatively small differences—e.g., Komban et al., 2014), the receptive fields of blue-ON cells and blue-OFF cells are quite different (Tailby et al., 2008a,b). First, the spatial receptive fields of blue-OFF cells are much more variable than that of blue-ON cells. Some blue-OFF receptive fields are smaller than those of blue-ON cells—and may be as small as P-pathway receptive fields—while others are substantially larger (Tailby et al., 2008b). Second, almost all blue-ON cells oppose the signals of blue cones to the sum of red- and green cones ("blue-ON/yellow-OFF"). By contrast, while some blue-OFF cells show "blue-OFF/yellow-ON" property others have more complex color selectivity (Tailby et al., 2008b; see also Wool et al., 2019). Whether there is more than one population of cells carrying these blue-OFF signals through the LGN, and whether they should all be classified as "K-cells" remains to be determined. The receptive fields of suppressed-by-contrast cells are very different to those of other neurons in the LGN—they are inhibited by the presence of a spatial pattern and are most active when presented with large homogeneous fields of light (Tailby et al., 2007). These properties are very similar to those of a subclass of ganglion cells in rabbit retina (Rodieck, 1967; Sivyer et al., 2010).

Experiments in marmoset monkeys, where the zones of K-cells can be targeted for electrophysiological recordings, provide better evidence that the nonstandard receptive fields are part of the K-pathway. The blue-ON, blue-OFF, and suppressed-by-contrast cells are primarily found in the koniocellular layers in marmoset monkeys (Martin et al., 1997; White et al., 1998; Tailby et al., 2008c; Solomon et al., 2010; Eiber et al., 2018a), and their receptive field properties are very similar to those described for macaque monkeys previously. The recordings in marmoset monkeys also show the presence of small populations of orientation selective in the koniocellular layers of the marmoset LGN (Cheong et al., 2013). The receptive fields of these neurons resemble those of visual cortical neurons—they are tightly tuned for the orientation and spatial frequency of a grating pattern, and direct measurement of receptive field shape reveals spatially offset ON- and OFF subunits like those found in visual cortical neurons. The reader should note that the receptive fields of neurons in the P- and M-pathways (in the retina and the LGN), while generally characterized as circular and untuned for orientation, can show weak orientation biases. This is because their receptive fields are not quite circular and can therefore prefer some orientations of some patterns over others. The tuning of orientation-selective K-cells cannot be explained by weak biases like this. In addition to these orientation selective neurons, other K-cells show distinct ON–OFF response (Eiber et al., 2018b). These neurons show very transient visual responses, high sensitivity to stimulus contrast, and strong suppression from surrounding regions. These response properties sound like extreme versions of M-cells, and these units are generally found in the K-layers surrounding the M-layers; their receptive fields can nevertheless be distinguished along several quantitative dimensions. The source(s) of retinal ganglion cell input to either orientation-selective or ON–OFF cells is unclear, but the "broad thorny" ganglion cell, which is known to project to LGN in marmoset (Szmajda et al., 2008), is a good candidate input to the ON–OFF cells.

Binocular processing in the lateral geniculate nucleus

Bringing the signals of the two eyes together may both improve visual sensitivity and allow analysis of stereoscopic depth. A defining characteristic of the primate LGN is that each P- or M-layer derives input from only a single eye, and the signals from the two eyes are therefore generally thought to first converge in the primary visual cortex (V1). Early investigations found that P- and M-cells in the LGN were indeed monocular; finer measurements from macaque monkey revealed some interocular interactions in a small fraction of P- and M-cells (Marrocco and McClurkin, 1979) or interocular suppression in some M-cells (Rodieck and Dreher, 1979). The binocular interactions may be more apparent in multiunit recordings (Schroeder et al., 1990), but regardless these effects in P- or M-cells must be weak if present at all (Lehky and Maunsell, 1996). For a recent review, see Dougherty et al. (2019).

Recent work in marmoset monkey shows clearly that the K-layers can receive input from both eyes, appearing as sublaminae within the main K-layers (Kwan et al., 2019) (Fig. 3.1). Consistently, a substantial fraction of K-cells show vigorous responses to visual stimuli presented to either eye (Zeater et al., 2015). The functional properties of those binocular K-cells are diverse (including blue-ON and suppressed-by-contrast cells) but well matched between the two eyes. This functional alignment suggests that the binocular responsivity is not simply a result of random developmental aberrations.

The input from the weaker eye is slightly slower, and binocular stimulation is generally less effective than would be expected from summation of the monocular inputs (Belluccini et al., 2019). The source of binocular input to these K-cells is not clear. If the dendrites of K-cells spanned these sublaminae, that may be sufficient. Alternatively, the binocular signal may be provided through nonretinal inputs.

Nonretinal inputs to thalamic neurons

Strikingly, most of the synaptic inputs to neurons in the LGN are not derived from retinal ganglion cells. The relative paucity of retinothalamic synapses does not imply that they are unimportant—as described above, retinothalamic synaptic events precede nearly all of the action potentials that an LGN neuron produces—but it does imply that the visual signals that are conveyed by LGN neurons can be modulated by processing within the thalamus, via inhibitory interneurons, and by inputs from other parts of the brain. In other animals, the sensitivity of thalamic neurons, including those in the LGN, is known to depend on brain state (Steriade and Llinas, 1988). For example, during slow wave thalamocortical oscillations, thalamic neurons in many sensory modalities are hyperpolarized, and relatively few sensory inputs are capable of producing thalamic action potentials. However, the hyperpolarization also activates a form of calcium channel, such that some sensory inputs trigger a brief burst of action potentials from the thalamic neuron. This "burst" mode of signal transmission contrasts with the usually more reliable transmission of sensory signals ("tonic" mode) seen outside these slow wave states. While clear in several thalamic sensory pathways in several species, it has been frustratingly difficult to find clear differentiation of burst and tonic modes in primate lateral geniculate nucleus (e.g., Ramcharan et al., 2000; Pietersen et al., 2017). Whether this reflects a particular specialization of the primate LGN, or unknown dependence on, for example, a particular choice of anesthetic, is unclear.

The major source of nonretinal input is the synapses of corticothalamic neurons whose cell bodies lie in layer 6 of the primary visual cortex. These corticothalamic neurons are not all alike—different layers (P-, M-, and K) of the LGN seem to receive input from distinct groups of layer 6 neurons (Fitzpatrick et al., 1994; Usrey and Fitzpatrick, 1996). Beautiful recordings from corticothalamic neurons in layer 6 of macaque monkey show functional segregation resembling that seen in the thalamic neurons themselves (Briggs and Usrey, 2009)—for example, some corticothalamic neurons show slower visual responses and sensitivity to blue–yellow color stimuli, like thalamocortical neurons in the K-layers of the LGN, while other corticothalamic neurons show faster visual responses and high achromatic contrast sensitivity, like those in the M-layers. It is likely that these functional subclasses correspond to the parallel anatomical pathways from layer 6 to the different LGN layers. Recent work with high sensitivity tracers also confirms a substantial corticothalamic projection to the LGN from layer 6 neurons in the secondary visual cortex (V2; Briggs et al., 2016). The corticothalamic neurons in area V2 can be divided into anatomical subclasses that resemble the classes of layer 6 neurons seen in area V1—whether they convey different functional signals to the different layers of the LGN remains to be discovered.

There is some evidence that nonretinal inputs have different functional impact on the pathways through LGN. At least under anesthesia, the spiking activity of K-cells in marmoset LGN, but not P- and M-cells, fluctuates over the course of many seconds (Cheong et al., 2011; Munn et al., 2020). These fluctuations in spiking activity appear to be independent of—and additive to—the visually driven response (Pietersen et al., 2017). The fluctuations are not simply due to intrinsic cellular mechanisms, as they are correlated across many K-cells, even when those neurons are some distance apart in the LGN. Increases in K-cell spike rate cooccur with epochs of desynchronization in the primary visual cortex (Cheong et al., 2011; Pietersen et al., 2017), but the basis of this relationship is not known. One possibility is that thalamocortical loops are pathway specific and have different impact on activity in the different pathways. Alternatively, the activity of K-cells and cortex may be both under the influence of a third actor. For example, the K-layers of the LGN are preferentially targeted by the superior colliculus (Harting et al., 1991; Stepniewska et al., 1999; Kwan et al., 2019).

PERCEPTUAL CORRELATES OF SUBCORTICAL PATHWAYS

The brief review above makes clear that the parallel pathways that are first forged by different bipolar cell classes, reinforced by multiple ganglion cell classes, and carried largely in parallel through subcortical brain areas, carry different signals. There is therefore considerable hope that the presence and progression of retinal or central visual disorders, or normal aging, may be tracked by appropriate visual tasks that "tap into" these different signals. In addition, these pathways may be affected as part of more general disorders. For example, changes within a "magnocellular pathway" have been hypothesized in dyslexia (Stein, 2019) and schizophrenia (see Almonte et al., 2020 for a recent review). Finally, the visual system is plastic, and targeting therapies toward particular

pathways may improve rehabilitation of function after damage to the retina or central visual brain areas.

The question here is how what is known about the signals carried by the parallel pathways to visual cortex might inform the design and interpretation of tests for detecting and diagnosing dysfunction. In what follows the reader should bear in mind that not all the activity of early visual pathways seems to be available to perception. For example, a brief flash of light drives strong changes in retinal activity and is easily perceived. However, rapidly flickering light (modulated above about 40 Hz) also drives strong changes in retinal ganglion cell activity but is usually imperceptible, at least in foveal vision (Solomon et al., 2002a). Similarly, we find it very difficult to see the flicker of an alternating-color stimulus when the modulation rate is above about 15 Hz, but these stimuli are capable of driving strong modulation in retinal ganglion cell activity (Solomon et al., 2005).

Color

The most robust functional differentiation of the pathways through the LGN is their sensitivity to chromatic modulation. The receptive fields of M-cells are dominated by the summed activity of L- and M-cones, therefore responding best to luminance modulation, while those of P-cells are L-M cone-opponent (at least in central visual field) and therefore respond best to red–green chromatic modulation. A substantial fraction of K-cell receptive fields, by contrast, derive input from S-cones and are sensitive to blue–yellow chromatic modulation. Because the signals of S-cones appear to be primarily conveyed by K-cells, stimuli that only modulate S-cone activity may be useful for establishing the progression of some K-cell signals through central brain regions (e.g., Kaestner et al., 2019) and perception. The lower density and different genetic basis of the S-cone photoreceptor, and the distinct asymmetries between ON- and OFF-pathways for S-cone signals, means that tasks that depend on S-cone signals might also be good tests of retinal function (e.g., Bosten et al., 2014), though there is only limited evidence for an improvement over other measures (see, e.g., Chen and Gardner, 2020). Similarly, the wavelength sensitivity and time-course of the melanopsin that confers intrinsic photosensitivity on "large sparse" ganglion cells is different to that of the cone photoreceptors. The contribution of these cells to basic visual function such as pupil light reflex is clear (Gamlin et al., 2007; Zele et al., 2019a), and they may also have distinct contribution to perception (Cao et al., 2018; Zele et al., 2019b).

The reader should note, however, that the receptive fields of cortical neurons show greater diversity of chromatic signatures than do their thalamic inputs (e.g., Tailby et al., 2008a,b). The cortical diversity is easily achieved by combining over the different thalamic inputs, but this recombination also makes it more difficult to use different types of chromatic modulation to target particular pathways. For example, a cortical neuron may combine inputs from P-cells excited by L-cones, with those excited by M-cones, with the result that its receptive field will be more sensitive to luminance modulation than chromatic modulation (Lennie and D'Zmura, 1988). Thus, while we often talk about the P-pathway being more sensitive to red–green chromatic modulation, and the M-pathway being more sensitive to luminance modulation, the signals of the P-pathway may be used to support luminance vision as well as color vision, particularly when the stimulus is of high contrast.

Nonlinearities

The receptive fields of P-cells are quasilinear, but those of M-cells and other pathways are often less linear. Tasks that exploit those nonlinearities may therefore be useful targets for distinguishing the contribution of P-cells from those of other pathways. Three lines of work have exploited different aspects of these nonlinearities.

The contrast-response of P-cells is linear, such that response increases slowly and in proportion to contrast. The contrast-response of M-cells is nonlinear: these cells show high-contrast sensitivity and saturation of response at high contrast, because of the action of a fast gain control. Elegant work from Pokorny and Smith and their collaborators developed paradigms that use *steady or pulsed pedestals* to create regimes in which visual performance is biased toward the activity of M-cell contrast response or P-cell contrast response (for a review, see Pokorny, 2011). These experiments are relatively easy to conduct and have been used extensively (e.g., McKendrick and Badcock, 2003; McKendrick et al., 2007; Cao et al., 2011). However, some K-cells show similar contrast-response to M-cells, and others show similar contrast response to P-cells. Whether K-cells contribute to these tasks is unknown.

The response of P-cells to a flickering grating is linear, such that cells respond to either the increment (white) or decrement (black) phase of the grating, but not both, and there is a spatial phase (position) of the flickering grating that elicits no response (the "null" phase). The response of M-cells is less linear: some cells can respond to both the increment and decrement phases, likely because of the rectification of bipolar cell inputs to ganglion cells. *Frequency-doubled perimetry* is a method that is thought to reveal the impact of this nonlinearity on perception. An achromatic, low spatial frequency pattern that is rapidly flickered appears to have a spatial frequency double that of what is actually presented (Richards and Felton, 1973; Kelly, 1981; Anderson and Johnson, 2003). These

experiments are relatively easy to conduct and have been used extensively. However, their interpretation remains a matter of debate (White et al., 2002) and some K-cells show even stronger response nonlinearities for this stimulus than do M-cells. How and whether M-cells or K-cells contribute to these tasks remains unclear.

Most P-cells show little change in contrast sensitivity during the repeated presentation of a visual stimulus. Most M-cells instead show a reduction in contrast sensitivity over a time course of several seconds (contrast adaptation) because of the action of a slow gain control. Whether K-cells are also susceptible to adaptation's effects is not generally clear. Measurements of contrast sensitivity for grating patterns, before and during adaptation, have been used extensively in perceptual work. Early studies showed that contrast adaptation resulted in a specific loss of sensitivity to stimuli that had the same orientation and spatial frequency (Movshon and Blakemore, 1973), implying a cortical locus, where neurons are tightly tuned for orientation and spatial frequency. The orientation selectivity of perceptual contrast adaptation is, however, reduced when the grating is rapidly flickered (Kelly and Burbeck, 1987), and the untuned component of contrast adaptation seems primarily monocular, while the tuned component is more binocular (Cass et al., 2012). Physiological measurements in macaque visual cortex also suggest the presence of untuned and tuned contributions to contrast adaptation (Dhruv et al., 2011), and the untuned component of perceptual contrast adaptation may reflect a contribution of M-cells. Contrast adaptation is straightforward to measure (though time-demanding) and has been used (e.g., Zhuang et al., 2015), though not always in conditions that may favor subcortical processing (e.g., McKendrick et al., 2010).

Opportunities

There are two clear avenues for development of new tasks to establish the role of the different pathways and potential changes in their integrity. First, most studies have used only one approach and whether these methods would all provide the same inference is not clear (Goodbourn et al., 2012). Combinations or elaborations of the tasks above may provide better inference and improved specificity. For example, there is growing evidence for asymmetries in the processing of ON- and OFF photoreceptor signals and distinguishing them is likely to be useful (e.g., Pons et al., 2019). Second, increased knowledge of the functional properties of the K-pathways should provide better tasks for tracing their contribution to central brain function and perception. Some of the tentative properties already appear to be good targets: the suppressed-by-contrast cells have a distinct functional signature that should be possible to isolate; the partial binocular convergence among K-cells in the LGN should also.

CONCLUSION

Our understanding of the P- and M-pathways in early vision is mature, but that of the diverse components of the K-pathways is not. We lack basic knowledge of important aspects of these pathways, including the functional properties of many of the retinal ganglion cell classes, their central projections, and the subsequent route(s) they then take. We do not know how the signals of these pathways interact with those of the P- and M-pathways. Their signals may be integrated, or fused, as appears to be the case for the blue–yellow color signals that reach primary visual cortex, or they may be carried largely independently through subsequent processing (Fig. 3.3C). The lower sampling density of the K-pathways encourages the idea that they could provide a "coarse sketch" of the retinal image, which guides finer analysis. Or the K-pathways may regulate the signals of the P- and M-pathways, perhaps helping highlight regions of the retinal image that may be of particular importance. Note that these speculations are not mutually exclusive—the K-pathways are heterogeneous.

In primate we have particularly limited knowledge of the ganglion cells that project to regions other than the lateral geniculate nucleus, including those that project to the superior colliculus, the major visual center in many other animals including rodents. A good deal of recent effort has explored the visual pathways of rodents, particularly mice, but what this will tell us about the human visual system remains a matter of debate. What is clear is that the intense work on rodents has provided new tools, including viral-based methods to measure and manipulate specific pathways. These new tools offer exciting opportunities to trace, measure, and manipulate the different visual pathways in primates, from specific ganglion cell classes to specific cortical targets, which should allow better understanding of how these pathways contribute to visual behavior, in health and in disease.

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