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Review

Melanopsin and the Intrinsically Photosensitive Retinal Ganglion Cells: Biophysics to Behavior

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The mammalian visual system encodes information over a remarkable breadth of spatiotemporal scales and light intensities. This performance originates with its complement of photoreceptors: the classic rods and cones, as well as the intrinsically photosensitive retinal ganglion cells (ipRGCs). IpRGCs capture light with a G-protein-coupled receptor called melanopsin, depolarize like photoreceptors of invertebrates such as *Drosophila*, discharge electrical spikes, and innervate dozens of brain areas to influence physiology, behavior, perception, and mood. Several visual responses rely on melanopsin to be sustained and maximal. Some require ipRGCs to occur at all. IpRGCs fulfill their roles using mechanisms that include an unusual conformation of the melanopsin protein, an extraordinarily slow phototransduction cascade, divisions of labor even among cells of a morphological type, and unorthodox configurations of circuitry. The study of ipRGCs has yielded insight into general topics that include photoreceptor evolution, cellular diversity, and the steps from biophysical mechanisms to behavior.

Mammals sense light for diverse purposes. Resolving spatial and temporal detail supports object recognition and action guidance, such as during a chase through the woods. On the other hand, integrating over space and time blurs details together to provide a representation of ambient light intensity. This representation is used to synchronize the circadian clock with the solar day and to drive seasonal rhythms in physiology. Thus, the visual system encodes information over a variety of spatiotemporal scales and does so across the billion-fold change in light intensity that accompanies the earth's rotation. Mechanisms that serve these needs are found in the first steps in vision, where photoreceptors convert light into a biological response.

Until about twenty years ago, it was believed that the mammalian retina was duplex, possessing two types of photoreceptors: rods and cones (Figure 1A). An early fissure in this belief stemmed from observations of individuals who had profound degeneration of these neurons and lacked visual awareness. Light suppressed their melatonin level, much as it did in the normally sighted (Czeisler et al., 1995). Some "blind" individuals also woke and slept as if their circadian clocks maintained synchrony with the environmental cycle of illumination and darkness. A potential explanation was that enough rods and cones survived to support basic functions but not conscious perception. However, light also suppressed melatonin and set the circadian clocks of mice that were engineered to entirely lack these photoreceptors—provided that the eyes were intact (Freedman et al., 1999; Lucas et al., 1999). Moreover, even in normal animals, certain responses exhibited dependencies on the wavelength, intensity, and duration of illumination that were poorly explained by the properties of rods and cones (e.g., Brainard et al., 2001; Lucas et al., 2001; Takahashi et al., 1984). It appeared that an ocular source of photoreception awaited discovery (see Do and Yau, 2010 for additional historical perspective).

This source was found in an unlikely place within the eye. Rods and cones are part of the outer retina, which lies farthest from the incoming light. On the other side, in the inner retina, are retinal ganglion cells (RGCs). These neurons convey information from the eye to the brain. A small fraction of RGCs is distinguished by expression of a visual pigment called melanopsin (Opn4; see Box 1 as well as Figures 1B and 2; Hattar et al., 2002; Provencio et al., 1998; Provencio et al., 2002). These are the intrinsically photosensitive RGCs (ipRGCs; Berson et al., 2002). Light activates melanopsin to trigger a G protein cascade that causes membrane depolarization. This response is opposite to that of rods and cones, which hyperpolarize, but resembles that of photoreceptors found in invertebrates like fruit flies and horseshoe crabs. IpRGCs fire spikes. They are understood to use glutamate as their primary neurotransmitter; uniquely among RGCs, they also express a peptide neurotransmitter called PACAP (pituitary adenylate cyclase activating peptide; Hannibal et al., 2002a). IpRGCs have a widespread influence, innervating dozens of regions throughout the brain (Figures 1C and 3). Among them are the suprachiasmatic nucleus (SCN, master circadian clock), olivary pretectal nucleus (OPN, pupillary constriction), and dorsal lateral geniculate nucleus (dLGN, visual perception; Brown et al., 2010; Delwig et al., 2016; Ecker et al., 2010; Gooley et al., 2003; Hattar et al., 2006; Morin and Studholme, 2014; Quattrochi et al., 2019). Known influences of ipRGCs extend well beyond their direct targets. Examples are regulation of melatonin synthesis in the pineal gland and of synaptic plasticity in the hippocampus (LeGates et al., 2012). IpRGCs themselves are diverse, with six types identified in the mouse (called M1–M6; see below and Figure 2). The mammalian retina is not duplex but multiplex.

Box 1. A Primer on Animal Visual Pigments

An animal visual pigment has two parts, opsin (a G-protein-coupled receptor) and chromophore (the photosensitive ligand, a covalently linked derivative of vitamin A called retinaldehyde or, simply, retinal). Upon photon absorption, the chromophore has an opportunity to isomerize and drive a conformational change of the opsin. For activation, this isomerization is typically from 11-*cis* retinal to all-*trans* retinal.

Activated pigments take one of two principal paths. In the first, opsin and isomerized chromophore dissociate. This process is called bleaching because visible light is absorbed well by pigment but poorly by its separate parts (Fein and Szuts, 1982). Opsin must combine with new chromophore to regenerate functional pigment. In the second path, absorption of a subsequent photon drives pigment from the active state. Pigments whose active states are long lived tend to deactivate in this manner. Such pigments have an intrinsic capacity to be activated repeatedly during illumination. They are classified as bistable or, more generally, multistable. Bleaching and multistability are not mutually exclusive. Illumination of sufficient intensity may cause bleachable pigments to absorb photons in quick succession, switching them between active and inactive states (Ritter et al., 2008). Moreover, pigments with stable active states may bleach on occasion.

Two types of visual pigment are recognized in the animal kingdom, ciliary and rhabdomeric, which are typically found in the primary photoreceptors of vertebrates and invertebrates, respectively (Fain et al., 2010; Shichida and Matsuyama, 2009). They are recognized by their protein sequence and genomic structure. Ciliary pigments tend to be bleachable and rhabdomeric pigments bistable.

The spectra of all vitamin A-based pigments have shapes that are virtually identical (when plotted on a frequency or reciprocal-wavelength axis; Lamb, 1995). Given only the peak wavelength sensitivity (λ_{max}) of a pigment, its entire spectrum can be reconstructed using an empirical function that is referred to as the nomogram (Govardovskii et al., 2000). The uncommon exceptions are pigments that use accessory chromophores and therefore exhibit more complex spectral sensitivities (Kirschfeld et al., 1977).

Often, the conformational states of a pigment have distinct spectra, each defined by its λ_{max} and the nomogram (Hillman et al., 1983). Delivering wavelengths that are preferentially absorbed by one state will drive it to an adjoining state. If two states are close in spectral sensitivity, light will always produce a mixture of both states. On the other hand, if two states are well separated, light can drive practically all pigment molecules into one state or the other depending on wavelength. Pigment states and their interconversions underlie the spectral sensitivity of the cell's response (the "action spectrum").

An important note is that wavelength and intensity are interchangeable in determining the probability that a pigment absorbs a photon. For example, even if a pigment has a λ_{max} in the visible range, infrared or ultraviolet light can cause activation if sufficiently intense.

Rods, cones, and ipRGCs are presently the only mammalian cells known to convert light into electrical signals (Hattar et al., 2003; Panda et al., 2003). Rods are sensitive enough to support sight even in starlight, while cones are equipped for color vision in daylight (Ingram et al., 2016; Naarendorp et al., 2010); downstream of these outer photoreceptors are numerous RGC types that convey distinct features of the visual image to the brain (Gollisch and Meister, 2010; Sanes and Masland, 2015). This review is concerned with the roles that ipRGCs play, both as photoreceptors and retinal output neurons, and the mechanisms that support those roles. IpRGCs of the M1 type are examined most deeply because they are the best understood, allowing connections to be drawn from biophysics to behavior. A broad sweep will be made through additional topics, including the other ipRGC types, influences of melanopsin on development, potential roles of melanopsin in health, and challenges for future research. Nevertheless, aspects of this large and rapidly expanding field will be missed or only glimpsed. Expert reviews are cited along the way to help fill these gaps. Finally, the information given will concern common laboratory rodents unless noted; other species are discussed toward the end.

Inferring Properties of the IpRGC Pathway from Non-image Visual Functions

The part played by ipRGCs is most obvious for non-image vision, a set of functions that respond more to irradiance (the overall intensity of illumination) than to contrast (local, spatiotemporal differences in illumination; reviewed by Warthen and Provencio, 2012). Irradiance governs important parameters such as visibility, temperature, and the types of species that are active. Unsurprisingly, many functions that use irradiance information are essential. For example, irradiance is the principal regulator of the circadian clock, which establishes normal patterns of gene expression throughout the body. The clock encodes irradiance by pooling light over large portions of the visual scene and broad intervals of time (Dobb et al., 2017; Mouland et al., 2017; Nelson and Takahashi, 1991), raising the possibility that ipRGCs exhibit specializations for spatial and temporal integration.

Several properties of ipRGCs may be inferred from another non-image visual function, the pupillary light reflex (PLR), where contraction of the iris muscle limits the amount of light entering the eye. Photoreceptor contributions to the PLR have been studied extensively because it is relatively quick and readily quantified (Keenan et al., 2016; Lall et al., 2010; Lucas et al., 2001). The PLR sets the balance between visual sensitivity, which is supported by a large pupil, and spatial resolution, which benefits from a small pupil. This balance appears to maximize information transmission over environmental irradiances spanning many orders of magnitude (at least in humans, where this topic has been studied; Laughlin, 1992). Thus, examination of the PLR also provides insight into mechanisms of effective motor control.

Pupillary constriction increases with irradiance, up to saturation, and is sustained for as long as the stimulus lasts (Figure 4). Deleting the melanopsin gene removes the intrinsic

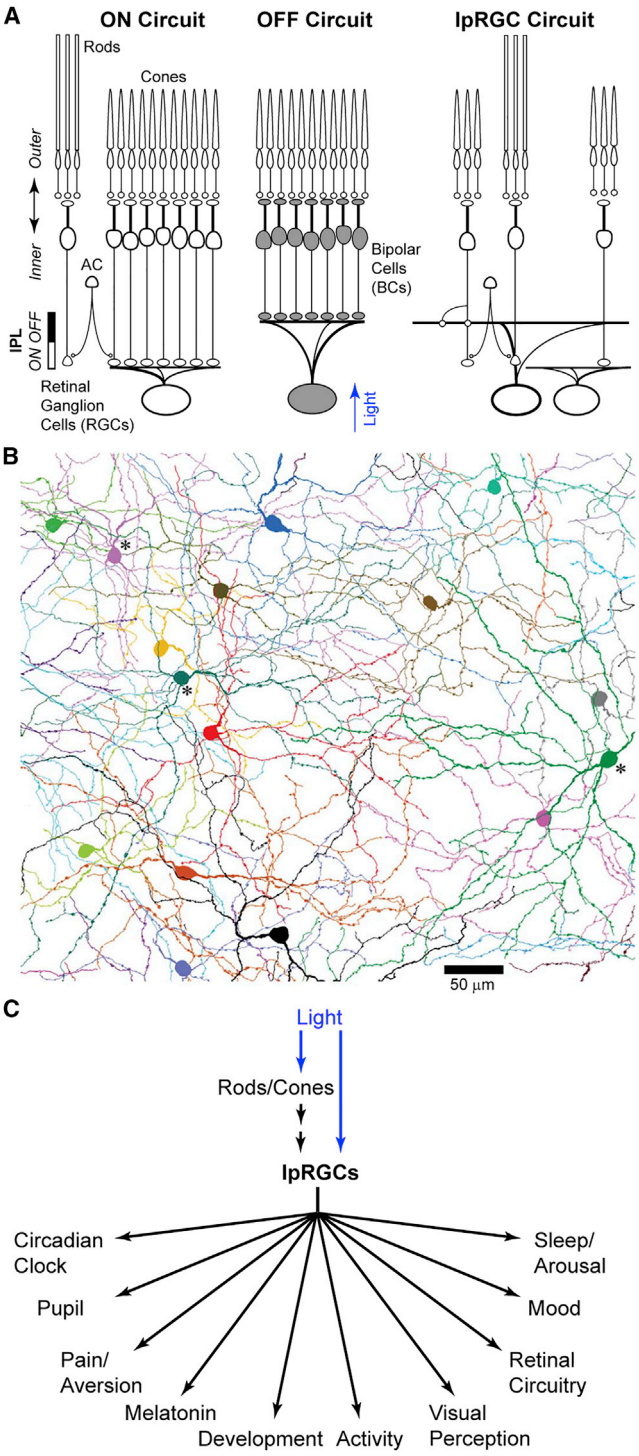

Figure 1. Overview of the Retina and IpRGCs

(A) A highly simplified schematic of the retina in cross-section, oriented with the inner aspect (nearer the center of the eye) down. The outer photoreceptors (i.e., rods/cones) drive bipolar cells (BCs). In the inner plexiform layer (IPL), BCs synapse with retinal ganglion cells (RGCs). Left: ON circuitry. Rods (top) drive rod BCs, whose signals pass through amacrine cells (ACs) to cone BCs. In the inner IPL, ON cone BCs convey signals to ON RGCs. ON RGCs show greater depolarization when light intensity increases. Center, OFF circuitry. In the outer IPL, OFF cone BCs provide synaptic input to OFF RGCs. OFF RGCs show greater depolarization when light intensity decreases. Right: a sample of circuits for outer- and inner-stratifying ipRGCs, which are both ON. ON cone BCs make ectopic synapses with the former and conventional synapses with the latter. Rod pathways also drive ipRGCs. IpRGCs make chemical and electrical synapses with ACs (not shown).

(B) *En face* view of mouse M1 ipRGCs that were revealed by melanopsin immunolabeling and traced (Berson et al., 2010). Asterisks mark cells with somata displaced from the RGC layer to above the IPL.

(C) A sample of ipRGC influences.

photosensitivity of ipRGCs and makes constriction abnormally transient. That is, it decays over minutes despite the continued presence of light (Keenan et al., 2016; Zhu et al., 2007). As a consequence, steady-state constriction never exceeds about a fifth of its normal maximum (transient constriction is less affected; Keenan et al., 2016; Lucas et al., 2003). Disabling the outer photoreceptors but sparing melanopsin reduces the speed and sensitivity of constriction. Nevertheless, it is sustained and reaches its normal maximum at high irradiances (Figure 4; Keenan et al., 2016; Lall et al., 2010; Lucas et al., 2003). These studies indicate that the PLR receives complementary drives: outer photoreceptors, which are especially important over seconds and low irradiances, and the intrinsic responses of ipRGCs, which become critical over minutes and irradiances that exceed moonlight. Ablating ipRGCs eliminates constriction even though rods, cones, and other RGC types remain functional (Güler et al., 2008; Hatori et al., 2008). It appears that retinal information must traverse ipRGCs to drive the PLR. To summarize, outer photoreceptors send signals through ipRGCs to mediate a sensitive and relatively quick PLR, while the intrinsic photosensitivity of ipRGCs holds the PLR steady over most irradiances and takes it to completion in bright light (note that the iris itself responds to bright light in some mammals; Wang et al., 2017; Xue et al., 2011).

Other aspects of non-image vision share much with the PLR in terms of their retinal origins, including the importance of ipRGCs. Photoregulation of the circadian clock depends in part on the outer photoreceptors, is attenuated in bright light if the melanopsin gene is deleted, exhibits lower sensitivity if only melanopsin phototransduction is active, and is undetectable if ipRGCs are ablated (Altimus et al., 2010; Dkhissi-Benyahya et al., 2007; Freedman et al., 1999; Güler et al., 2008; Hatori et al., 2008; Hattar et al., 2003; Panda et al., 2002; Ruby et al., 2002; van Oosterhout et al., 2012). The acute induction and maintenance of sleep by broadband (white) light in nocturnal species is abnormally transient without melanopsin and undetectable without ipRGCs (Altimus et al., 2008; Lupi et al., 2008; Muindi et al., 2013; Tsai et al., 2009). Light also causes a suppression of locomotor activity in nocturnal species, termed "negative masking," which is abnormally transient without melanopsin and absent without ipRGCs (Göz et al., 2008; Mrosovsky and Hattar, 2003). Consensus is lacking on some points, such as the relative roles of rods, cone types, and ipRGCs in these various functions. Nevertheless, the common thread is that ipRGCs are a key link between outer photoreceptors and downstream processes, while melanopsin phototransduction is important for sustained and maximal responses to light (Figure 4).

Variations among non-image functions point toward complexity in ipRGC signaling. In animals lacking melanopsin,

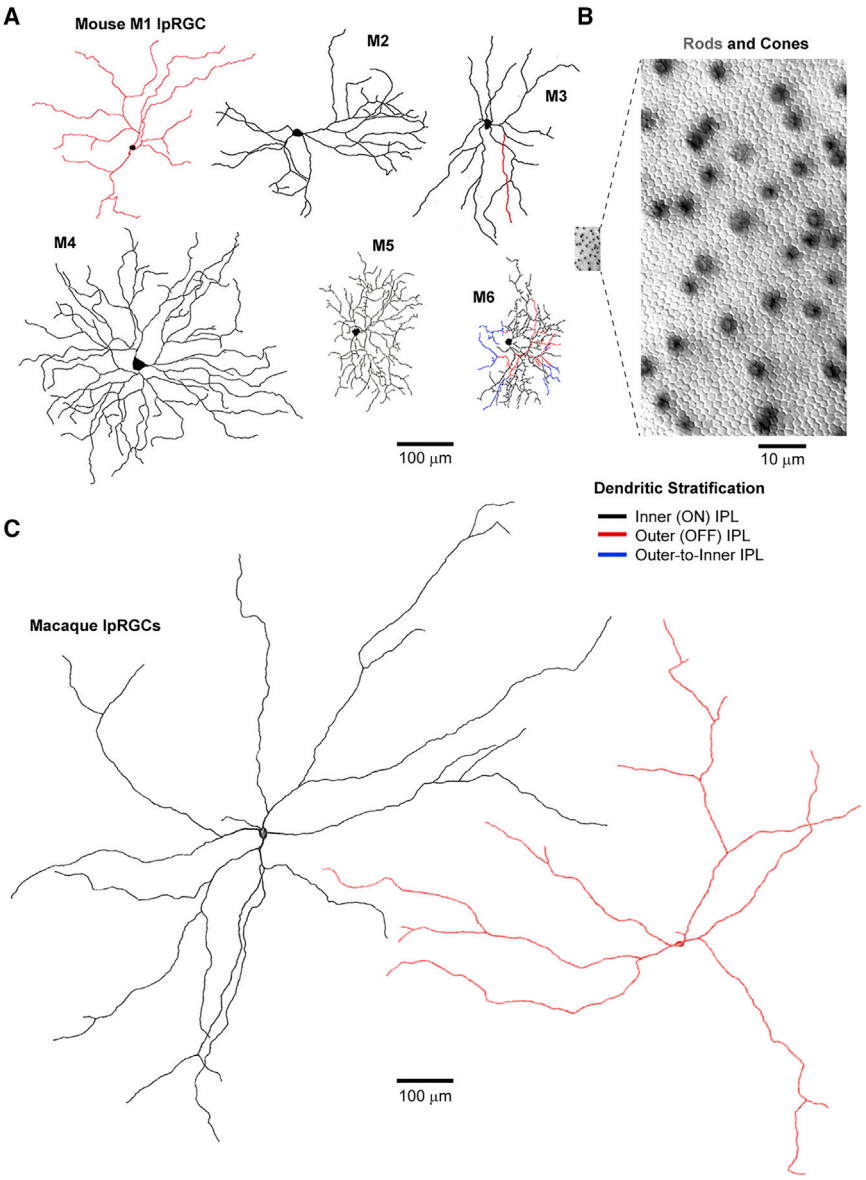

Figure 2. A Comparison of Mouse and Macaque ipRGCs

(A) The six types of ipRGC recognized in the mouse retina. Black and red dendrites are those that stratify in the inner (ON) and outer (OFF) IPL, respectively, while blue dendrites are those that visit the outer IPL before returning the inner IPL (Quattrochi et al., 2019).

(B) The outer photoreceptor mosaic of the mouse, to scale with the ipRGCs in (A) on the left and expanded on the right. Rods are small and numerous. Cones are stained (Jeon et al., 1998).

(C) Inner- and outer-stratifying ipRGCs of the macaque peripheral retina (Liao et al., 2016). The outer-stratifying ipRGCs tend to have their somata displaced from the ganglion cell layer to the opposite side of the IPL. Same scale as (A).

pupillary constriction decays over minutes (Keenan et al., 2016), while sleep and negative masking decay over hours (Mrosovsky and Hattar, 2003; Muindi et al., 2013). Hence, the requirement for melanopsin phototransduction manifests over timescales that span at least an order of magnitude across different functions. The irradiance required to evoke melanopsin-driven responses also varies. In animals lacking the outer photoreceptors, ipRGCs first drive pupillary constriction at an irradiance that is 1–2 log units greater than that needed to entrain the circadian clock (Hattar et al., 2003; Xue et al., 2011). The non-image visual functions of normal animals also show varied thresholds (e.g., circadian photoentrainment, pupillary constriction, and negative masking; Butler and Silver, 2011). IpRGC pathways appear to be diversified according to downstream needs.

To conclude, examination of non-image vision raises predictions about the melanopsin system of ocular photoreception. Mechanisms are likely to exist for integration over space and time, for the outer photoreceptors to drive ipRGCs, for ipRGC phototransduction to be relatively insensitive but sustained, and for the generation of functional diversity.

M1 IpRGCs: Molecular, Cellular, and Circuit Mechanisms that Support Non-image Vision

The M1 ipRGCs are central to non-image vision. These cells densely innervate brain areas that mediate it (e.g., SCN, OPN, and intergeniculate leaflet) while sparsely innervating those that support image vision (i.e., dLGN and SC; Figure 3); the innervation patterns of non-M1 cells follow a largely complementary pattern (Baver et al., 2008; Brown et al., 2010; Ecker et al., 2010; Hattar et al., 2006; Quattrochi et al., 2019). Moreover, circadian photoregulation is absent when all ipRGCs are ablated but persists even if only a subset of M1s survives (Chen et al., 2011; Güler et al., 2008). These points do not exclude other ipRGC types from non-image vision, nor do they exclude M1s from image vision (see below). Nevertheless, the molecular, cellular, and circuit properties of M1s appear the best suited of the ipRGC types for encoding irradiance.

This section begins with the phototransduction cascade used by M1s, where key molecules have been identified. The discussion then turns to mechanisms that allow M1s to integrate over space, time, and wavelength; to generate sustained responses; and to diversify for the establishment of dynamic range.

The M1 Phototransduction Cascade

Melanopsin is required for the intrinsic photosensitivity of ipRGCs, and no other visual pigment has been detected in these cells (reviewed by Do and Yau, 2010). Melanopsin is a pigment of

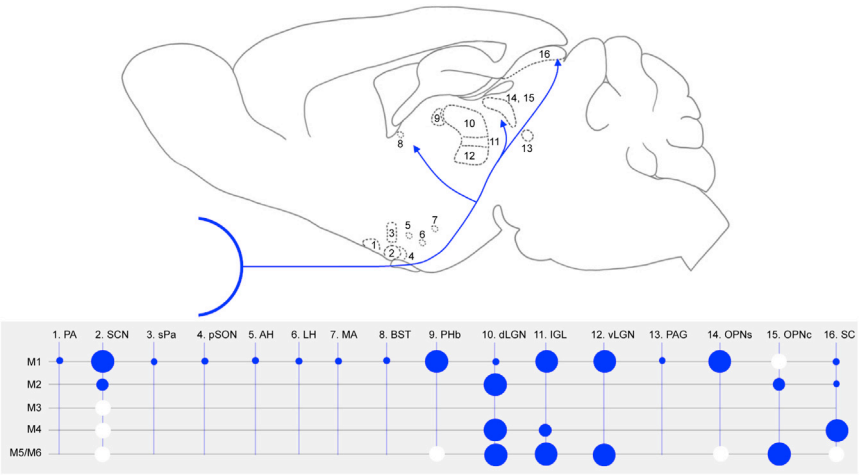

Figure 3. Major Brain Targets of Mouse ipRGCs

A sample of ipRGC brain targets is depicted in a quasi-sagittal schematic of the mouse brain. Below is a plot of innervation densities across ipRGC types, drawn after Berson and colleagues (Quattrochi et al., 2019) and incorporating additional information (Ecker et al., 2010; Hattar et al., 2006; Huang et al., 2019; Morin and Studholme, 2014; Zhao et al., 2014). Each blue dot indicates the approximate density of innervation by its size, a white dot indicates undetectable innervation, and lack of a dot indicates an absence of information. M5s and M6s are pooled because their projections were examined together for technical reasons. AH, anterior hypothalamus; BST, bed nucleus of the stria terminalis; dLGN, dorsal lateral geniculate nucleus; IGL, intergeniculate leaflet; LH, lateral hypothalamus; MA, medial amygdala; OPN, olivary pretectal nucleus (with shell, s, and core, c, regions); PA, preoptic area, which includes the VLPO (ventrolateral preoptic area); PAG, periaqueductal gray; PHb, perihabenular zone; pSON, peri-supraoptic nucleus; SC, superior colliculus; SCN, suprachiasmatic nucleus; sPa, subparaventricular zone; and vLGN, ventral lateral geniculate nucleus.

the rhabdomeric type (see Box 1), with human melanopsin bearing a closer resemblance to a scallop opsin in its protein sequence than to any vertebrate opsin known (Provencio et al., 2000). In mouse, two splice isoforms of melanopsin have been found, short (Opn4S) and long (Opn4L; Pires et al., 2009). Opn4S differs from Opn4L in its abbreviated C-terminal tail, which lacks four potential phosphorylation sites. The isoforms diverge in their expression patterns. Opn4S is enriched in M1s and Opn4L in non-M1s. Loss-of-function experiments suggest that Opn4S is important for the PLR, Opn4L for negative masking, and both for circadian photoentrainment and sleep regulation (Jagannath et al., 2015). It is not known whether these divergent effects reflect differences in the protein function of these splice isoforms, differences in their expression across ipRGC types, or both.

Downstream of melanopsin are G proteins of the q/11 family ($G\alpha_q$, $G\alpha_{11}$, and $G\alpha_{14}$), which drive PLCβ4 to open TrpC6/TrpC7 nonselective cation channels (Graham et al., 2008; Jiang et al., 2018; Sonoda et al., 2018; Warren et al., 2006; Xue et al., 2011). Eliminating these G proteins or PLCβ4 leaves only a tiny photocurrent, suggesting that they are the dominant players. By analogy to other PLC pathways, the second messenger may be a metabolite of PIP2, though not necessarily the usual candidates, IP3 and DAG. Indeed, PLCβ4 and TrpC6/7 are closely related to norpA and Trp in *Drosophila* photoreceptors, respectively, where PIP2 cleavage is thought to generate protons and mechanical force for channel activation (Hardie and Franze, 2012; Huang et al., 2010). With regard to response termination, melanopsin is subject to phosphorylation and arrestin binding, though these processes have yet to be explicitly examined in M1s (Blasic et al., 2012a, 2012b, 2014; Cameron and Robinson, 2014; Fahrenkrug et al., 2014; Mure et al., 2016, 2018; Somasundaram et al., 2017).

In pursuing additional components of M1 phototransduction, a challenge is that the photocurrent has a low density (less than ~0.2 pA μm^{-2}; Do et al., 2009). Consequently, applying agents to isolated patches of membrane might not produce enough of a response to identify the second messenger. Furthermore, if this low density corresponds to sparse expression of transduction molecules, some may be difficult to identify at the RNA and protein levels (Berg et al., 2019; Rheaume et al., 2018; Siegert et al., 2012). Overall, little is known about the properties, expression levels, and distributions of phototransduction components in M1s. These parameters are exquisitely tuned in rods, cones, and *Drosophila* photoreceptors (Hardie and Postma, 2008; Ingram et al., 2016; Luo et al., 2008), raising the possibility of a similar optimization in M1s for the specific requirements of non-image vision.

Mechanisms of Spatial Integration

Mouse M1s have a dendritic arbor that is ~300 μm in diameter, encompassing ~10° of visual angle (Berson et al., 2010). This is an ~150-fold wider view than that of a rod or cone (Figure 2B; Carter-Dawson and LaVail, 1979). M1s integrate over this patch of the visual scene, with excitation growing alongside the amount of the receptive field illuminated (Figure 5A; Zhao et al., 2014). By comparison, RGCs with the classic center-surround receptive field respond vigorously with stimulation of the center but not both center and surround, an arrangement that favors the encoding of spatial contrast (Barlow, 1953; Kuffler, 1953).

Spatial integration by M1s arises from both synaptic and intrinsic mechanisms. Synaptic input carries signals originating with the outer photoreceptors, is net excitatory, and appears uniform across the receptive field (Dumitrescu et al., 2009; Zhao et al., 2014). It is also of the ON variety, being activated when light intensifies. This last finding was initially puzzling because M1s spread their dendrites in a layer that was long understood to contain presynaptic terminals of OFF bipolar cells (BCs), which are activated when light dims, but only traveling axons of ON BCs. It turns out that ON BC axons make synapses with M1 dendrites *en passant* or via small branches (Figure 1A; Dumitrescu et al., 2009). This exception to retinal wiring rules contributes to the extensive spatial integration displayed by M1s.

With regard to intrinsic photosensitivity, each M1 expresses melanopsin over the entirety of its soma and dendrites (Berson et al., 2002; Hattar et al., 2002; Provencio et al., 2002). Light

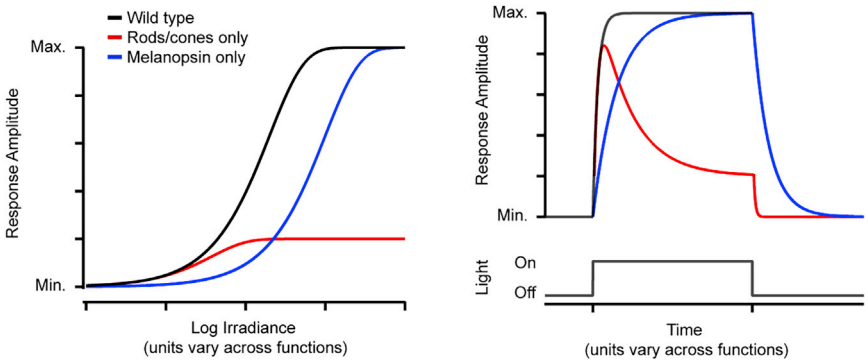

Figure 4. Contributions of ipRGCs and Outer Photoreceptors to Non-image Vision
Depicted are cases for animals that are wild-type (black), have only outer photoreceptors (i.e., rods/cones) for photoreceptors (melanopsin knockout; red), or have only ipRGCs for photoreceptors (outer photoreceptor loss or inactivation; blue). Left, without melanopsin, responses cannot reach their normal maxima in bright light. Without the outer photoreceptors, responses are insensitive but can reach their normal maxima. Right, without melanopsin, responses are abnormally transient. Without outer photoreceptors, responses are slow but sustained. These cartoons are not meant to be interpreted quantitatively, and the abscissae are undefined because the general understanding holds across functions that operate over different irradiances and timescales.

responses evoked from these two locations appear similar (Do et al., 2009). Thus, photons absorbed from different parts of the visual scene have uniform impacts, supporting spatial integration.

Photon Capture by Melanopsin

The probability of photon capture by M1s depends on their density of melanopsin molecules. A rough estimate is that each square micrometer of plasma membrane contains a handful, giving each cell ~10^4 molecules total (Do et al., 2009). By contrast, the outer photoreceptors express their pigment at ~30,000 μm^{-2} within hundreds of membrane specializations that are stacked in the light path, for a total of 10^8 per cell (Luo et al., 2008). The sparseness of melanopsin reduces the sensitivity of M1s, helping these cells operate over higher irradiances. Given the dense network of M1 dendrites (Figure 1B), melanopsin sparseness also prevents shadows from being cast on the underlying rods and cones.

This estimate of M1 pigment density is a snapshot. Melanopsin protein rises at the onset of illumination to peak at the end of the day and then falls in darkness (Hannibal et al., 2005; Mathes et al., 2007). Constant light or darkness causes a decrease or increase of melanopsin immunoreactivity over days, respectively (Hannibal et al., 2005). There is also evidence that the circadian clock controls melanopsin expression (Hannibal et al., 2005; Sakamoto et al., 2004). The functional consequences of these expression changes are not entirely clear. A clue is that a circadian variation in the highest firing rates of ipRGCs has been reported, though M1s have not been specifically examined (Weng et al., 2009).

A Large and Prolonged Single-Photon Response Increases Sensitivity and Mediates Temporal Integration over Tens of Seconds

The building block of the light response is the activation of one pigment molecule following the absorption of one photon, producing the single-photon response (SPR; its properties are often deduced from the "dim-flash" response, which is the linear superposition of several SPRs). The dark-adapted SPR of M1s is somewhat larger than that of rods (~1 pA versus ~0.5 pA) and far larger than that of cones (~0.04 pA; Cao et al., 2014; Do et al., 2009; Mendez et al., 2000). Because M1s have a high input resistance and tend to cross spike threshold occasionally even in darkness, a single-photon absorption may substantially influence the firing rate (Do et al., 2009; Emanuel et al., 2017).

This influence on M1 output is long-lasting. The duration of an SPR is often quantified as the integration time (t_i, the area under the normalized response), which gives the window in which responses will sum effectively (Baylor and Hodgkin, 1973). In mice, the dark-adapted t_i is ~200 ms for rods and ~80 ms for cones, respectively (Figure 5B; Cao et al., 2014; Mendez et al., 2000). That of M1s is measured on a different scale, being ~8 s (Do et al., 2009; Emanuel et al., 2017). The response has an overall lifetime of ~30 s, producing a representation of illumination that is extensively smoothed over time (Figure 5B).

Persistent Responses Support Temporal Integration over Minutes

If light is sufficiently bright, extinguishing it does not cause an immediate return of the M1 photocurrent to baseline. The photocurrent can continue for many minutes and, being graded with stimulus strength, supports temporal integration within this interval (Figure 5C). This persistent response reflects the stability of melanopsin's active state (Emanuel and Do, 2015). During decrements of irradiance, this stability is evident in a gradual relaxation of the photocurrent to a lower level (Milner and Do, 2017). Hence, the persistent response acts as a strong low-pass filter on fluctuating light.

How does the persistent response last minutes if the SPR only lasts tens of seconds? Likely, the persistent response arises from pigment molecules that have escaped the usual shut-off mechanisms. This is the case for a similar response observed in invertebrate photoreceptors, the "prolonged depolarizing afterpotential," which arises when more pigments have been activated than there are arrestin molecules to quench them (Hillman et al., 1983). Indeed, the SPR appears to be terminated actively in M1s. Removal of extracellular Ca^{2+} allows the response to continue far longer than usual, indicating the existence of strong negative feedback mechanisms that might be exceeded to produce the persistent response (discussed further below; Do and Yau, 2013). An open question is whether the persistent response is subject to negative feedbacks of its own, which would therefore be poised to increase the precision of temporal integration by M1s.

Conformational Changes of Melanopsin Support Spectral Integration and the Acute Suppression of Persistent Responses

While spectral changes at dawn and dusk can help set the circadian clock (Roenneberg and Foster, 1997; Solessio and

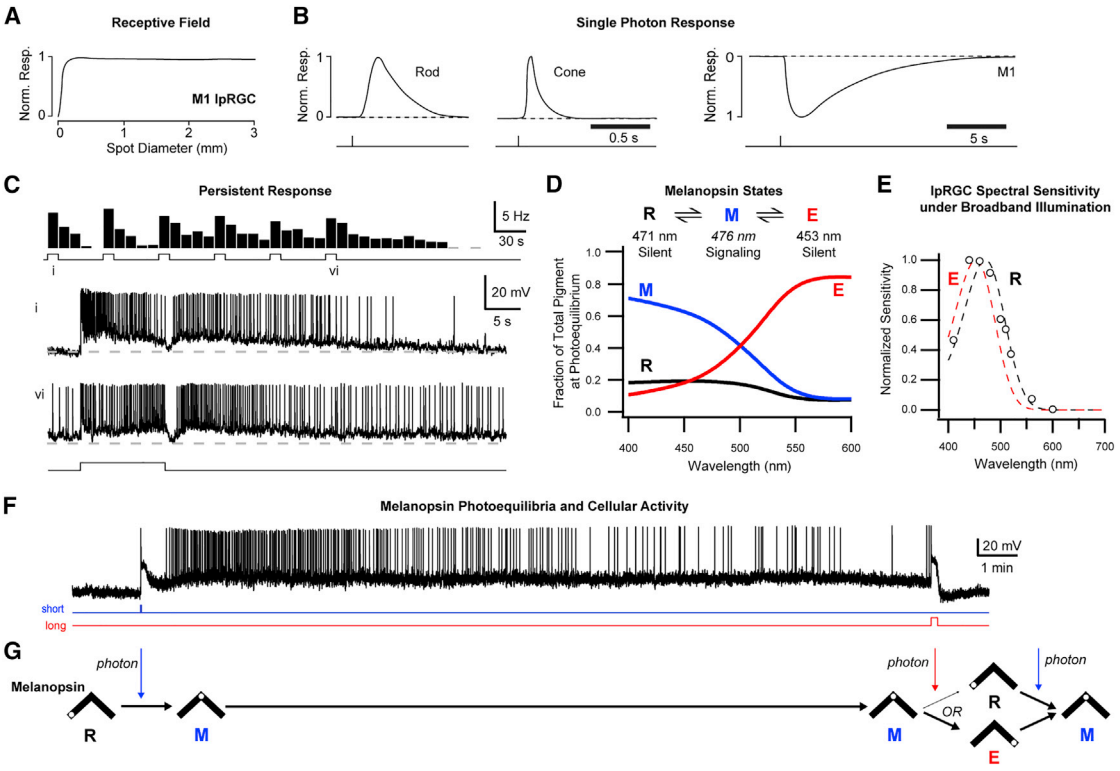

Figure 5. Spatial, Temporal, and Spectral Integration by Mouse M1 ipRGCs

(A) Increasing the size of a spot within the receptive field of an M1 causes the response (normalized photovoltage) to increase, up to saturation (Zhao et al., 2014).

(B) Dim-flash responses of outer photoreceptors and M1s (normalized photocurrent, having the same waveform as the single-photon response). Note the 10-fold longer time base for the M1. The dashed line indicates the baseline current and the timing of the flash is shown below the curves, which are traced from electrophysiological recordings (Emanuel et al., 2017; Field and Rieke, 2002; Nikonov et al., 2006).

(C) Top, repeated presentation of the same pulse of light causes a progressive increase in firing rate due to cumulative activation of melanopsin phototransduction. Bottom, traces taken from the first (i) and sixth (vi) presentations, highlighting persistent firing in darkness. At 35°C, as shown here, the subthreshold membrane voltage decays in subsequent darkness with an average time constant of ~2 min. No blockers of synaptic transmission.

(D) Top, mouse melanopsin is understood to have three states (R, M, and E). The peak spectral sensitivities of R and E are determined from the electrophysiological responses of M1s. Spectrophotometric measurements of purified melanopsin yielded similar values (467 and 446 nm, respectively) and gave information for M (476 nm; Matsuyama et al., 2012). Bottom, the distribution of melanopsin states as a function of wavelength, estimated from a model based on values from purified melanopsin.

(E) The action spectrum of an M1 measured atop a background of broadband (white) light. The spectrum is accounted for by roughly equal fractions of melanopsin molecules activating from R and E (the action spectra of which are shown in black and red, respectively).

(F) Voltage response of an M1 at room temperature (where persistent responses are extremely stable). A 50-ms flash of 440-nm light drives an initial burst of firing that is truncated by depolarization block. Adaptation returns the voltage to a range that produces firing, and firing persists in darkness until it is suppressed by a 10-s pulse of 560-nm light. Blockers of synaptic transmission included. Plots in (C)–(F) are reproduced from Emanuel and Do, 2015.

(G) An explanation of the cellular response in terms of melanopsin tristability. The only state found after prolonged darkness is R. Light drives R to M, which activates the cell. M has a high degree of thermal stability. Longer wavelengths of light drive M to E (and, to a lesser extent, R), which suppresses cellular activity. A subsequent short-wavelength or broadband stimulus can initiate another cycle.

Engbretson, 1993; Walmsley et al., 2015), integrating over the spectrum allows the total light intensity to be encoded. Properties of the melanopsin molecule mediate spectral integration (see Box 1 for background material). As illustrated in Figure 5D, purified mouse melanopsin exhibits three states: R ("melanopsin," bound to 11-*cis* retinal and displaying a peak wavelength sensitivity, λ_{max}, of 467 nm), M ("metamelanopsin," all-*trans* retinal, red shifted from R to 476 nm), and E ("extramelanopsin," 7-*cis* retinal, blue-shifted from R to 446 nm; Matsuyama et al., 2012). R and M are the expected ground and signaling states, respectively (Walker et al., 2008). Electrophysiological examination of M1s revealed the presence of a third state that matches the spectral sensitivity of E and is electrically silent (Emanuel and Do, 2015). Under common lighting conditions, melanopsin molecules activate from R or E with roughly even probability to trigger responses that are indistinguishable. The spectral sensitivity of the cell, reflecting both states, is unusually broad (Figure 5E). Therefore, conformational changes of melanopsin endow M1s with an intrinsic capacity for integration over wavelength (Emanuel and Do, 2015). The broad spectral sensitivity of M1s peaks at 460 nm, similar to the wavelength distribution at twilight and matching the λ_{max} of melatonin suppression in humans (Brainard et al., 2001; Emanuel and Do, 2015; Walmsley et al., 2015).

The interconversion of melanopsin states allows the persistent response to be acutely suppressed by light (Figure 5F). As mentioned above, the persistent response reflects the stability of melanopsin's signaling state, M. Long wavelengths are

absorbed more effectively by M than the other states (Figure 5D). Thus, long-wavelength illumination drives melanopsin molecules away from the M state. These molecules accumulate in the E state, which is the least effective at absorbing long wavelengths. Because E is electrically silent, the persistent response is suppressed. Practically, the effectiveness of suppression does not increase monotonically as wavelength is increased. Past about 560 nm, all states absorb photons so poorly that light has little effect unless it is extremely intense (Emanuel and Do, 2015). Whether any kind of natural illumination suppresses persistent responses is unknown.

Mouse melanopsin is currently the only pigment that is thought to be tristable or use 7-*cis* retinal. The extent to which these characteristics generalize to other pigments and what their structural determinants are remain to be understood.

Extrinsic Mechanisms of Spectral Integration

M1s are downstream of both rods and cones. Consequently, in mouse, the light responses of M1s can originate with four pigments: melanopsin (λ_{max} = 460 nm under broadband illumination), rhodopsin (500 nm), ultraviolet-wavelength-sensitive (UVS) opsin (360 nm), and medium-wavelength-sensitive (MWS) opsin (510 nm). These pigments have overlapping influences over a wide range of intensities and may therefore broaden the wavelength sensitivity of M1s to encompass a large region of the spectrum (Joesch and Meister, 2016; Naarendorp et al., 2010; Tikidji-Hamburyan et al., 2017). The degree of broadening may vary with topography because UVS and MWS opsins are expressed in reciprocal gradients across the mouse retina (Hughes et al., 2013).

Adaptation and the Production of Steady Responses

When given a step of light that is just intense enough to activate melanopsin phototransduction in M1s, the cascade produces a photocurrent that rises gradually to steady state. Brighter light causes the current to rise more rapidly, peak, and then relax to a plateau (Do and Yau, 2013). This relaxation reflects adaptation (Wong et al., 2005). As light intensifies further, both peak and plateau increase in magnitude until saturating. Their difference also widens; for the largest responses, the plateau is just a few percent of the peak (typically below ~80 pA), reflecting the high potency of adaptation (Milner and Do, 2017). Furthermore, over much of the cell's operating range, a change in irradiance drives an opposite and near-equal change in sensitivity (Do and Yau, 2013). That is, adaptation of phototransduction in M1s follows the classic Weber-Fechner law, as it does in rods and cones (Luo et al., 2008).

To appreciate the role of adaptation, consider that the steady photocurrent comprises a succession of SPRs that overlap according to their duration and frequency of occurrence. In dim light where SPRs are infrequent, they are large and prolonged to maximize sensitivity. In brighter light, they become smaller and briefer to blunt the approach to saturation, thereby extending dynamic range. This process is evident in the analog responses of rods, cones, and M1s. For M1s, adaptation also keeps the photocurrent from driving the spike generator into a refractory state, at least over a few log units of irradiance (see below; Do and Yau, 2013).

Recovery from adaptation occurs slowly for M1s. Examined at room temperature, this process requires hours (Wong et al., 2005). Recovery is likely to be faster at body temperature but remain far slower than the minutes and tens of minutes seen in cones and rods, respectively (Lamb and Pugh, 2004). An intriguing speculation is that this slowness allows adaptation to recover more completely over the long nights of winter to strengthen phototransduction during dim and short days, and less completely over the short nights of summer to weaken phototransduction during bright and long days (Wong et al., 2005). Therefore, in conferring flexibility to melanopsin phototransduction, adaptation may promote constancy in the output of M1s across environmental variations. This idea has yet to be tested. Also unknown is how the PLC-based phototransduction cascade used by M1s produces adaptation that is quantitatively similar to that of the cyclic nucleotide-based cascade used by rods and cones.

Maintaining Photosensitivity over Long Timescales

IpRGCs have been observed to fire continuously over hours of illumination (Wong, 2012) and M1s are likely to be no exception (Milner and Do, 2017). For phototransduction to be sustained, pigment molecules must remain available for activation. The output of an isolated rod or cone gradually diminishes because its pigments bleach in light (Box 1). M1s have a larger, intrinsic capacity for sustained signaling because the active state of melanopsin (M) is stable. As such, it has the opportunity to absorb a photon, convert to a silent state (R or E), and be reactivated (Figure 5G). An automatic mechanism of pigment regeneration is another commonality between M1s and the rhabdomeric photoreceptors of species like *Drosophila*.

Melanopsin is likely to regenerate through more than one pathway. When ipRGCs are deeply dark adapted, all melanopsin appears to be in the R state (Emanuel and Do, 2015; Walker et al., 2008). Light cannot produce this condition, as it always forms R in a mixture with the other states (Emanuel and Do, 2015). A possible mechanism is that melanopsin bleaches on occasion and then binds new 11-*cis* retinal, which defines the R state. Melanopsin is relatively resistant to bleaching (Emanuel and Do, 2015; Sexton et al., 2012). That said, experimental provision of chromophore to light-exposed M1s can increase their sensitivity by several-fold (Do et al., 2009; Fu et al., 2005). An endogenous supply route for 11-*cis* retinal has been traced from the retinal pigment epithelium (the principal source of chromophore in the retina) through the Müller glia to ipRGCs (Zhao et al., 2016). IpRGCs appear to be more intimately associated with Müller glia than conventional RGCs (Viney et al., 2007), perhaps in support of this pathway. Much is unknown about the processes that regenerate melanopsin (reviewed by Lucas, 2006). Notably, their rates are undefined, even though they set the magnitude of the steady response that sustains downstream processes over extended timescales.

Functional evidence for a sustained synaptic input to M1s is lacking (Milner and Do, 2017; Zhao et al., 2014), though an anatomical observation raises the possibility that such an input exists. Conventional RGCs tend to fire transiently at the onset and/or offset of light (Wong et al., 2007). This transience partially reflects the "dyad" circuit motif of the retina: a BC terminal drives both an RGC and an amacrine cell (AC), and the AC can curtail responses by providing both feedback inhibition to the BC and feedforward inhibition to the RGC. The ectopic synapses that ON BCs make with M1s appear to lack the AC component

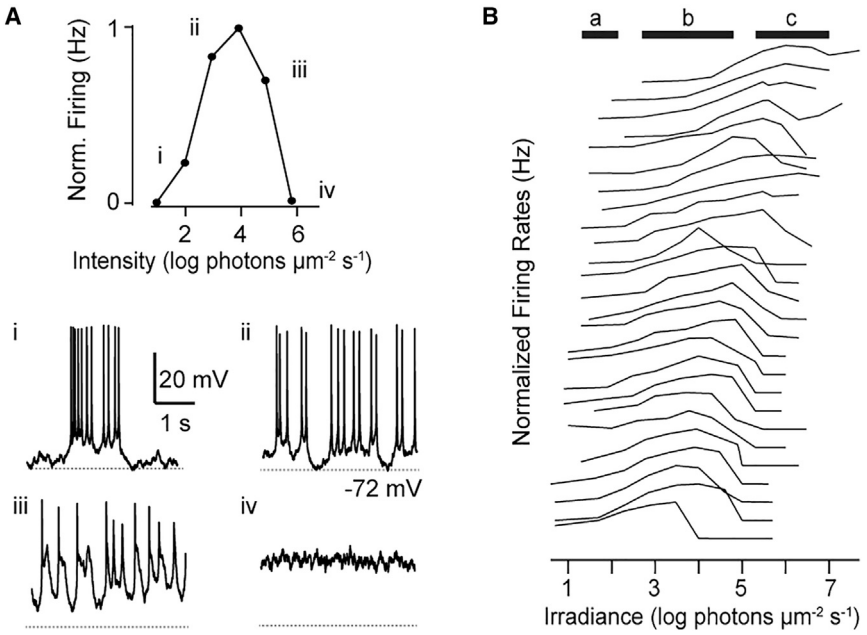

Figure 6. Irradiance Encoding by Mouse M1 ipRGCs

(A) Top, the irradiance-firing (IF) relation of a "unimodal" M1. Bottom, excerpts of voltage at the indicated points showing intrinsic depolarization block at high irradiance (iv).

(B) The IF relations of different M1s, offset vertically for visualization. These relations are naturally arrayed across the irradiance axis. Scattered in the top end of the range are a few IF relations that are monotonic rather than unimodal. Intensities correspond to moonlight (a), twilight (b), and daylight (c). The shapes and positions of these relations are similar whether synaptic transmission is blocked (as is the case here) or not (Milner and Do, 2017).

(Kim et al., 2012). If these monadic synapses operated in a distinct fashion, they would be another exception to retinal wiring rules that supports irradiance encoding by M1s. M1s are known to receive inhibition, but the sources and functional consequences have not been identified (Zhao et al., 2014). In principle, inhibition could promote signaling over long timescales; for example, intermittent hyperpolarization would allow voltage-gated channels to recover from inactivation, supporting the firing of spikes.

Dividing Labor for Dynamic Range

A hallmark of M1s is their functional heterogeneity (Emanuel et al., 2017). Most physiological parameters vary across the population, with many spanning a log unit or more. Furthermore, lack of covariation among parameters gives each cell a biophysical profile that is highly individualistic, with no actual profile resembling the average. Consequently, a fixed stimulus evokes varied spike patterns across the M1s that it activates.

These seemingly chaotic collections of parameters give rise to orderly behaviors. The most commonly encountered M1 has an irradiance-firing (IF) relation that is unimodal (Figure 6A; Milner and Do, 2017). That is, firing increases as irradiance exceeds threshold, reaches a peak rate at a higher irradiance, and then falls silent as irradiance rises further. Silencing results from the melanopsin-driven photocurrent growing large enough (even with adaptation) that the membrane voltage becomes too depolarized to support spike generation. In other words, intrinsic depolarization block confines spiking to a limited range of irradiances. Unimodal IF relations have a shape that is highly conserved among M1s. However, the intrinsic properties of these cells cause their IF relations to occupy different positions on the irradiance axis. This dispersion of sensitivities allows the population to operate from moonlight to full daylight (Figure 6B).

Image vision requires that a similar set of features is sampled across the scene. Accordingly, rods, cones, and conventional RGCs of a type are largely uniform in their responses. M1s, being relatively unconcerned with spatial information, have diversified for the collective encoding of irradiance. This strategy appears to have several advantages. First, the population covers a broader range than any given cell; sensitivity varies more across M1s, even with synaptic inputs blocked, than between rods and cones. Second, because some cells fire less as others fire more, metabolic costs are reduced. Third, downstream cells have the potential to sample from M1s of relevant tunings, perhaps helping to explain the varied thresholds of non-image visual functions. Additional advantages may be found in the effect of light history. One example concerns falling irradiance, when unimodal M1s exit depolarization block, resume firing, and then deactivate. Many of these cells resume firing at irradiances far below those that first activated them, likely because the persistence of melanopsin activity prolongs the period of depolarization block (Milner and Do, 2017). This extension of firing is expected to dampen the effect of falling irradiance, further reducing the impact of temporal contrast. These observations underscore open questions regarding how the M1 population responds to natural modulations of irradiance and how this population drives downstream circuits.

In summary, M1s are specialized at several stages for non-image vision. At the molecular level, intrinsic properties of melanopsin itself produce integration over time and wavelength. At the tissue level, interactions between the retina and pigment epithelium support continuous signaling over hours of illumination. In between are numerous biophysical and circuit mechanisms that meet the challenges of encoding environmental irradiance over a vast range, and despite spatiotemporal contrast in the scene.

Non-M1 ipRGCs and Their Involvement in Image Vision

Subconscious influences of light on physiology provided an early hint that ipRGCs exist. Additional study has indicated that ipRGCs contribute to visual perception, particularly non-M1 ipRGCs (reviewed by Sonoda and Schmidt, 2016). This expanded role and the mechanisms that support it are examined here.

Melanopsin and Human Perception

An individual with profound degeneration of the outer photoreceptors could report the presence of light if its wavelength was near the λ_{max} of melanopsin, suggesting that activation of this pigment impinges upon awareness (Zaidi et al., 2007). This possibility has been examined in sighted individuals using the technique of silent substitution. Here, the spectrum of light is changed to selectively modulate one pigment type. The degree of selectivity depends on several variables, such as how precisely the spectral sensitivities of the relevant pigments are defined, how different these sensitivities are from one another, and what the spectrum of illumination is after filtering by ocular elements (Snodderly et al., 1984; Spitschan et al., 2015). Targeting melanopsin in this manner produces a sense of brightness that is accompanied by activation of visual cortex (Spitschan et al., 2017). Coarse spatiotemporal patterns also can be discriminated (Allen et al., 2019). Moreover, increasing the activation of melanopsin enhances the brightness and sharpness of vision mediated by cones (Allen et al., 2019; Brown et al., 2012; Horiguchi et al., 2013; Saito et al., 2018; Yamakawa et al., 2019; Zele et al., 2018a, 2018b). These studies suggest that melanopsin phototransduction within ipRGCs influences image vision.

Two questions stand out for consideration. One is whether human melanopsin has multiple states with distinct spectral sensitivities, like mouse melanopsin (Emanuel and Do, 2015; Mure et al., 2009). If so, its spectral sensitivity depends on the balance of states, and this balance evolves over time according to the particular parameters of the stimulus. In other words, human melanopsin may be a moving target. Another question is whether melanopsin expression outside of ipRGCs is relevant to perception (see below). Immunohistochemistry suggests that melanopsin is even present in some human cones, a topic that has not been explored further (Dkhissi-Benyahya et al., 2006). The answers to these questions are pertinent to the design and interpretation of silent substitution experiments.

Influences of IpRGCs on Pathways for Image Vision

In mice that lack outer photoreceptors, the dLGN exhibits large receptive fields that are arranged in a retinotopic map (Procyk et al., 2015); downstream, the visual cortex shows light-evoked activity (Brown et al., 2010). These animals cannot navigate to a visual target (Lin et al., 2008), suggesting that signals originating with ipRGCs provide insufficient spatial information for this task (also see Allen et al., 2010; Ecker et al., 2010; Hattar et al., 2003). However, these signals do appear to influence image vision. Driving melanopsin phototransduction in normal mice produces several effects in the dLGN, including elevations of both baseline and evoked firing rates, a tuning of response selectivities, and a modulation of oscillations at the population level (Allen et al., 2017, 2014; Davis et al., 2015; Storchi et al., 2017, 2015). The result is a representation of irradiance and an improvement in response fidelity. Nearby, in the intergeniculate leaflet and ventral LGN, are neurons that encode differences in irradiance between the two eyes, presumably using signals from upstream ipRGCs (Pienaar et al., 2018). The superior colliculus (SC), a classic center for image vision, also shows modulation by ipRGCs (though subtle; Dasilva et al., 2016). Curiously, even brain regions traditionally considered to be exemplars of non-image vision show properties that appear suitable for image vision. Many neurons in the SCN respond preferentially to contrast, even color contrast, and display relatively small, monocular receptive fields with center-surround organization (Mouland et al., 2017; Walmsley and Brown, 2015; Walmsley et al., 2015). Taken together, these findings indicate that melanopsin phototransduction influences image vision in mice, in part by activating ipRGCs that innervate the dLGN.

IpRGCs may influence image vision by signaling within the retina itself. Chemical neurotransmission from ipRGCs can drive a subset of dopaminergic ACs to fire even when signals from the outer photoreceptors are blocked (Zhang et al., 2008; also see Perez-Fernandez et al., 2019; Viney et al., 2007). This drive is speculated to originate from axon collaterals that emerge occasionally from ipRGCs and ramify within the synaptic layer (Joo et al., 2013; Prigge et al., 2016). IpRGCs also form gap junctions with a striking variety of ACs (Müller et al., 2010; Reifler et al., 2015). In addition, stimulation of ipRGCs leads to the activation of other RGC types (Milosavljevic et al., 2018). IpRGCs even appear to influence the flow of information from cones to their postsynaptic BCs (Barnard et al., 2006; Hankins and Lucas, 2002). Additional complexity arises from the modulation of ipRGCs by retinal circuitry, with responses to adenosine, dopamine, melatonin, opioids, and somatostatin observed in these cells (Cleymaet et al., 2019; Pack et al., 2015; Sodhi and Hartwick, 2014; Van Hook et al., 2012; Vuong et al., 2015). Whether certain aspects of vision are best served by ipRGC influences within the retina, as compared to those within the brain, awaits investigation.

The Suitability of Non-M1 IpRGC Types for Image Vision

As mentioned above, ipRGCs are diverse (reviewed by Schmidt et al., 2011). In the mouse retina, six RGC types are understood to express melanopsin and respond directly to light, including the M1s (Figure 2A; Ecker et al., 2010; Quattrochi et al., 2019; Stabio et al., 2018; Zhao et al., 2014). With the exception of M3s, all ipRGCs meet criteria for being true cell types in the retina: they form independent mosaics, have distinguishable morphologies, and exhibit distinct responses to light. The M3s are consistently found across animals but are few in number and variable in morphology; physiologically, they are like M2s (Berson et al., 2010; Schmidt and Kofuji, 2011). M3s resemble developmental accidents in these respects (Masland et al., 1993). Little more is known about them, and they are omitted from subsequent discussion of "non-M1s." Unlike M1s, non-M1s densely innervate centers of the brain for image vision and exhibit center-surround receptive fields (Figure 3 and 7A), suggesting that they have parts to play in resolving spatial, temporal, and spectral contrast.

Melanopsin immunoreactivity is high in M1s, moderate in M2s, and typically undetectable in M4s–M6s without prodigious amplification (Ecker et al., 2010; Quattrochi et al., 2019; Stabio et al., 2018). Indeed, a pulse of saturating light triggers a photocurrent in M1s that is hundreds of picoamperes in size and easily maximizes or overdrives spike generation (see above). The same pulse produces tens of picoamperes in M2s and brings them to just a quarter of their maximum firing rate (Schmidt and Kofuji, 2009). Melanopsin phototransduction is also more sensitive in M1s than M2s, requiring a roughly 10-fold brighter pulse to be

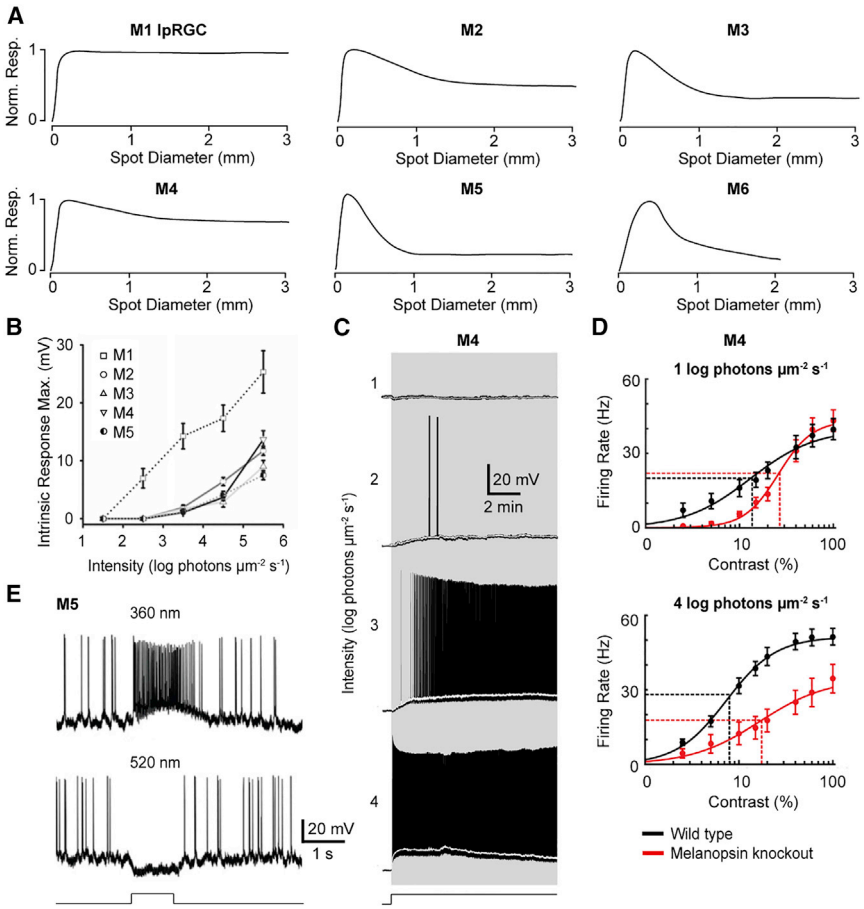

Figure 7. Functional Diversity of Mouse ipRGCs

(A) The receptive field of an M1 from Figure 5, replotted for comparison with the receptive fields of M2s–M6s. The responses of non-M1s decrease as larger stimuli activate increasing amounts of the inhibitory surround (drawn from Quattrochi et al., 2019; Zhao et al., 2014).

(B) The melanopsin-driven, intensity-voltage relations of ipRGC types. The stimulus was a relatively brief (10 s) pulse of light (Zhao et al., 2014). Intensity-current relations can show greater differences (Schmidt and Kofuji, 2009). Blockers of synaptic transmission included.

(C) Long-lasting steps of light (10 min) evoke relatively sensitive responses in M4s (Sonoda et al., 2018). Blockers of synaptic transmission included.

(D) Melanopsin phototransduction increases the contrast sensitivity of M4s (black, wild type and red, melanopsin knockout) even at light intensities that evoke no detectable depolarization (top, compare with C). The effect of melanopsin phototransduction is even more pronounced at higher irradiance (bottom). No blockers of synaptic transmission.

(E) Opposite responses to different wavelengths by M5s. Top, depolarization in ultraviolet light. Bottom, hyperpolarization in green light (Stabio et al., 2018). No blockers of synaptic transmission.

triggered in the latter. When M4s, M5s, and M6s are stimulated with a pulse of light, these cells produce intrinsic responses that are similar in size and sensitivity to those of M2s, if not even smaller and less sensitive (Figure 7B; Ecker et al., 2010; Estevez et al., 2012; Jiang et al., 2018; Quattrochi et al., 2019; Stabio et al., 2018; Zhao et al., 2014). From these experiments, it would seem that the intrinsic responses of non-M1s are diminutive and that these cells are driven primarily by their synaptic inputs.

The picture shifts when delivering steady light rather than brief pulses. In this condition, the intrinsic response of M4s increases over minutes to a plateau that is substantial in the rough equivalent of moonlight (Figure 7C; Sonoda et al., 2018). Therefore, the sensitivity of melanopsin phototransduction is comparable between M4s and M1s, at least under prolonged illumination (Milner and Do, 2017; Zhao et al., 2014). One possible explanation for the heightened sensitivity of M4s to steady light is temporal summation of extremely long-lived SPRs. The SPRs of non-M1s await characterization. Nevertheless, it would appear that cells expressing tiny amounts of melanopsin can generate intrinsic responses to light that are quite sensitive in certain circumstances.

The intrinsic responses of M4s have functional relevance. In proceeding, it is helpful to note that "M4" is a new alias for a classic RGC type, the "sustained ON α" RGC, which is considered to participate in image vision. Melanopsin phototransduction depolarizes M4s toward threshold and raises their input resistance, increasing the impact of their synaptic inputs. As a result, M4s are more sensitive to contrast (Figure 7D; Sonoda et al., 2018). In mice lacking the melanopsin gene, sensitivity to visual contrast is reduced in M4s and at the behavioral level (Schmidt et al., 2014).

Properties of the other non-M1 types appear suitable for image vision. M5s exhibit opposite responses to blue and yellow light, allowing them to encode color contrast. M6s have small receptive fields, likely supporting the discrimination of spatial detail (Figures 7A and 7E; Quattrochi et al., 2019; Stabio et al., 2018). How these ipRGC types use melanopsin is unclear. It is not required for the differential wavelength sensitivity or sustained responses of M5s, at least over the 10-s period examined. Melanopsin does have an intriguing expression pattern in these cells, being localized to the soma and most proximal dendrites. This pattern may help explain why M5s have a low intrinsic photosensitivity (there is less surface area for photon capture) and especially strong center-surround antagonism (melanopsin does not oppose inhibition in the dendrites; Stabio et al., 2018; Zhao et al., 2014). In exploring how melanopsin phototransduction may be tailored to non-M1 ipRGCs, it is worth minding the likely influences of these cells outside of image vision. For example, M2s provide a fifth of the retinal input to the SCN (M1s provide the rest; Baver et al., 2008). Meanwhile, M4s trigger a multisynaptic pathway that has been implicated in the regulation of mood (Huang et al.,

2019) and use melanopsin to encode irradiance (Schmidt et al., 2014; but see Schroeder et al., 2018).

Varieties of Melanopsin Phototransduction

The melanopsin phototransduction cascade varies across ipRGC types. While M1s primarily use PLCβ4 to open TrpC6/TrpC7 channels, M4s do not. One study finds that PLCβ4 closes a K^+ channel instead (producing the aforementioned increase in input resistance; Sonoda et al., 2018). Another finds that PLCβ4 is not involved. Rather, a rise in cyclic nucleotides causes nonselective cation channels to open (Jiang et al., 2018). The origin of this disagreement is a mystery (Do, 2018). Solving it would be of interest for the understanding of photoreceptor evolution because PLC and cyclic nucleotides represent the two principal lineages of phototransduction, which have appeared unmingled in cells across phylogeny (Fain et al., 2010; Yau and Hardie, 2009). The possibility now exists that they lie side by side in M1s and M4s—and even coexist within M2s (Jiang et al., 2018). Uncovering the molecular components of phototransduction in the remaining ipRGC types may provide additional insight into how cells have evolved specializations for their roles.

To summarize, ipRGCs of the M2, M4, M5, and M6 types are positioned to influence image vision. Their roles, and the mechanisms used to fulfill them, are new areas of exploration. Specializations can range from the configuration of melanopsin phototransduction to the map of functional connectivity within the brain. A lesson from these studies is that image and non-image vision are not always separable. For example, irradiance influences the encoding of patterns, in part through melanopsin-driven responses that are too sluggish to carry much information about temporal contrast. Representations of irradiance and the visual image can blend within ipRGC pathways.

Toward a Further Dissection of IpRGC Heterogeneity

Although ipRGCs are diverse, most knowledge concerns these cells as one population, having resulted from deletion of the melanopsin gene or hijacking of melanopsin expression for cellular manipulation. Lumping cells obscures their individual contributions and perhaps some of their collective contributions as well (e.g., if the various types mediated opposing effects, manipulating all could have little net outcome). Interpretation of such experiments is also complicated by the developmental roles of melanopsin (see below) and the expression of melanopsin in tissues that include cornea, iris, and vasculature (Delwig et al., 2018; Ondrusova et al., 2017; Sikka et al., 2014; Wang et al., 2017; Xue et al., 2011). The use of viruses for manipulation also carries the risk of transducing some ipRGC types more effectively than others and of inducing changes that are unrelated to the viral cargo (Jackman et al., 2014). As a consequence, much remains unclear about how the ipRGC types divide or pool labor for the various aspects of non-image and image vision. More specific methods of manipulation are needed.

The promise of such methods is illustrated by studies in which any cell that expresses both melanopsin and Brn3b (a transcription factor, often named POU4F2) is poisoned. All ipRGCs that survive into adulthood appear to be M1s and represent a quarter of the normal M1 population. These cells preferentially innervate the SCN and send few axons to other brain areas (Chen et al., 2011; Li and Schmidt, 2018). The animals appear normal in some regards (e.g., circadian photoentrainment) but not others (e.g., the PLR). Hence, subsets of M1s appear to mediate different downstream functions (Chen et al., 2011). Additional use of the Brn3b/melanopsin ablation model has uncovered a brain area that is implicated in regulating mood, the perihabenular region (Fernandez et al., 2018), and revealed mechanisms by which light regulates body temperature (Rupp et al., 2019) as well as development (see below; Chew et al., 2017). Thus, several insights have arisen from splitting the M1 population. It is possible that further subdivisions exist, given that these cells oversample visual space by ~4-fold and show heterogeneity of form as well as function (Berson et al., 2010; Emanuel et al., 2017; Hughes et al., 2013).

Several challenges lie ahead for the dissection of ipRGC types. One concern is that manipulating some cells may make others play parts that they ordinarily do not, causing the normal division of labor to be misjudged. Also troublesome is the potential for off-target effects. For example, the melanopsin gene locus is not immune to transient or stochastic activity; using it to drive a constitutive Cre recombinase results in Cre-dependent reporter expression even in cortical pyramidal neurons, which presumably lack melanopsin phototransduction (Ecker et al., 2010). Intersectional strategies should provide greater control. Even so, the Brn3b/melanopsin ablation model kills 3-fold more M1s than are immunoreactive for these proteins in the normal adult, suggesting that the pattern of melanopsin expression changes substantially during development (Chen et al., 2011; Jain et al., 2012). Additional challenges arise from the physiological diversity of ipRGCs. For example, illumination differentially activates M1s to evoke spike patterns that are highly uncorrelated (Emanuel et al., 2017; Hughes et al., 2013; Milner and Do, 2017). These patterns would be poorly mimicked by current methods of artificial activation, such as electrical shock or optogenetic stimulation, hindering the analysis of ipRGC circuits. These considerations invite the creation of new approaches.

A Survey of Melanopsins and IpRGCs across Species

Cells that express melanopsin are found throughout the animal kingdom. This section looks beyond rodents to other mammals, with an emphasis on primates. Sketches are also provided of melanopsin cells in non-mammalian vertebrates and beyond.

Melanopsin-Expressing RGCs of Various Mammalian Species

Melanopsin-expressing RGCs (mRGCs), which are likely to be intrinsically photosensitive, vary in proportion and form within the mammalian class. A striking example is the subterranean mole rat, *Spalax ehrenberghi*, which has mRGCs in abundance—they account for nearly 90% of all RGCs, compared to a few percent in mice and a fraction of a percent in primates (Hannibal et al., 2002b, 2017; Liao et al., 2016; Masri et al., 2019; Nasir-Ahmad et al., 2019). *Spalax* mRGCs give rise to brain pathways for non-image vision that are greatly hypertrophied (while pathways for image vision are atrophied; Cooper et al., 1993). The animal exhibits circadian photoentrainment even though its eyes reside permanently beneath fur and skin, suggesting that its mRGCs are specialized for heightened sensitivity. A milder expansion of mRGCs is found in the nocturnal microbat, where these cells compose >15% of all

RGCs (Jeong et al., 2018). In the tree shrew, mRGCs may release dopamine, which is typically the province of amacrine cells (Johnson et al., 2019). The Mongolian gerbil appears to lack M2s (Jeong and Jeon, 2015), the type that is reminiscent of the ancestral photoreceptor (see above). There are also similarities across species. For example, five types of mRGC, which are intrinsically photosensitive, have been found in the rat (Zhao et al., 2014). In addition, the outer-stratifying mRGCs of rabbits receive ectopic synapses from ON BCs, like their mouse orthologs (Hoshi et al., 2009). Unfortunately, a comprehensive comparison across species is not possible at this time. One reason is that most melanopsin immunostaining was performed without additional amplification, which is required to reliably observe the M4–M6 types in mouse. Another reason is that many analyses were performed when the catalog of mouse mRGCs contained fewer types for reference. Nonetheless, mRGCs are conserved across mammals and exhibit variations that are likely suited to the particular niche of each species.

A Comparison of Mouse and Primate ipRGCs

Closer to home are the ipRGCs of primates. Macaque ipRGCs have been studied most and exhibit many similarities with mouse ipRGCs; for example, in the existence of outer- and inner-stratifying types, pattern of brain innervation, reception of synaptic input carrying signals from the outer photoreceptors, expression of melanopsin throughout the somatodendritic arbor, PACAP immunoreactivity, and intrinsic responses to light that are prolonged and relatively insensitive (Dacey et al., 2005; Gamlin et al., 2007; Hannibal et al., 2014; Liao et al., 2016). Some of these characteristics have been examined in humans and marmosets, where they are conserved (Grünert et al., 2011; Hannibal et al., 2017; Liao et al., 2016; Nasir-Ahmad et al., 2019). Macaque and human ipRGCs drive pupillary constriction in a similar way to their mouse counterparts: melanopsin phototransduction provides a slow but sustained activation, and ipRGCs themselves are important for carrying signals from the outer photoreceptors (Gooley et al., 2012; McDougal and Gamlin, 2010; Ostrin et al., 2018). Hence, many features are shared between the ipRGC pathways of mice and primates (with "primates" referring to humans and macaques from this point onward).

IpRGC pathways also exhibit substantial differences between these species. For instance, the dendritic fields of primate ipRGCs can exceed a millimeter in diameter, while those of mouse ipRGCs tend to be no more than ~350 μm (Figure 2C; Berson et al., 2010; Quattrochi et al., 2019; Liao et al., 2016; Schmidt and Kofuji, 2011; Stabio et al., 2018). These retinal sizes translate into viewing angles of ~5° and ~12°, respectively, meaning that primate ipRGCs integrate light over a smaller region of the scene despite being gargantuan. Upstream of ipRGCs in humans and macaques are three cone pigments that are entirely or almost entirely unmixed within single cones, with λ_{max} values near 430, 531, and 561 nm (Peng et al., 2019; Schnapf et al., 1988). In the mouse, most cones co-express two pigments. In addition, primates and mice favor different rod pathways (Grimes et al., 2018; Tikidji-Hamburyan et al., 2017). Thus, the extrinsic drives to primate and mouse ipRGCs are likely to diverge under most environmental conditions. This divergence may underlie overt differences in visual responses. For example, short-wavelength-sensitive (SWS) cones and melanopsin appear antagonistic in controlling the primate but not murine pupil (Hayter and Brown, 2018; Spitschan et al., 2014). This antagonism is likely to reflect an OFF response in macaque ipRGCs driven by SWS cones (Dacey et al., 2005). To summarize, primate and mouse ipRGCs differ markedly in the kinds of spatial and spectral information they receive.

Primate and mouse ipRGCs may also have distinct intrinsic photosensitivities. Mouse melanopsin is tristable, conferring a degree of spectral integration (see above). Although parallel studies are lacking for primates, their melanopsin is argued to be bistable, which would not support spectral integration (Mure et al., 2007). Furthermore, there is cause to believe that the intrinsic responses of primate ipRGCs are shorter lived (Spoida et al., 2016; Tsukamoto et al., 2015), which would reduce their capacity for temporal integration. Finally, most M1s in the mouse fire spikes over a limited range of irradiances (see above; Milner and Do, 2017). The one electrophysiological study of primate ipRGCs observed that these cells change their firing rate monotonically with irradiance over a broad range (Dacey et al., 2005). This comparison raises the possibility that mouse and primate ipRGCs encode irradiance in qualitatively different ways. Due to the paucity of studies on the light responses of primate ipRGCs, it is too early to know whether these differences are real or only apparent. Nevertheless, caution is warranted in extrapolating from rodent to primate.

Melanopsin Cells beyond Mammals

Outside of *Mammalia* is a profusion of melanopsins and melanopsin-expressing cell types. Melanopsin genes fall into two families, *Opn4m* and *Opn4x* (Bellingham et al., 2006). While mammals appear to possess only one melanopsin gene, a member of *Opn4m*, other animals can have several. In the zebrafish retina are three melanopsins of the *Opn4m* family and two melanopsins of the *Opn4x* family, which have largely non-overlapping expression across the major neuron types (Davies et al., 2011). Melanopsin expression in the brain may allow larval zebrafish to seek light (Fernandes et al., 2012). Melanopsins are also varied and broadly expressed in chicken retina and brain, suggesting that this is a common theme among non-mammalian vertebrates (Bailey and Cassone, 2005; Chaurasia et al., 2005). The various melanopsins differ with regard to spectral sensitivity, propensity for bleaching, and downstream signaling (Davies et al., 2011; Torii et al., 2015, 2007). The functional consequences of this diversity are largely unexplored.

Outside of vertebrates, melanopsin-like genes have been found in species as distant as coral (reviewed by Do and Yau, 2010). Photoreceptors of the lancelet, *Branchiostoma*, deserve special mention. These cells express a melanopsin molecule that appears to be bistable, rather than tristable as in the mouse (Koyanagi et al., 2005). The downstream G protein cascade is extraordinarily fast—it produces an SPR lasting 2 ms, which is four orders of magnitude briefer than that of mouse M1s (Angueyra et al., 2012; Ferrer et al., 2012; Gomez et al., 2009). Additional work in this vein would provide insight into how photoreceptive cells and molecules are tailored to ethological needs.

The Influence of IpRGCs in Development

Mice express melanopsin as embryos, long before rod and cone pigments are detectable (Tarttelin et al., 2003). A mammal may seem too opaque for this to matter, but the body wall of a pigmented mouse only attenuates light by ~50-fold (Rao et al., 2013). In daylight, its womb is lit like an office, and embryos are quite translucent. Indeed, depriving the embryo of light or melanopsin causes an increase in the number of retinal neurons and interferes with development of the retinal blood vessels: the embryonic vasculature persists longer than it should, and the mature vasculature is overgrown (Rao et al., 2013). The vascular phenotype is reminiscent of retinopathy of prematurity, an abnormal proliferation of retinal vessels in pre-term infants that can cause blindness (Hellström et al., 2013; Rao et al., 2013).

IpRGCs are functional in the unopened eyes of neonatal mice, and some cells are more sensitive at this stage than in the adult, consistent with the need to sense light through overlying tissue (Sekaran et al., 2005; Sexton et al., 2015; Tu et al., 2005). Melanopsin phototransduction is sufficiently strong that light causes these young animals to vocalize and move away (rods and cones are too immature to signal light at this age; Delwig et al., 2012; Johnson et al., 2010). Another role for ipRGCs is found in the spontaneous waves of retinal activity that refine connectivity between the retina and dLGN. Light activates melanopsin to extend the duration of these waves (Kirkby and Feller, 2013; Renna et al., 2011). This extension appears dispensable for refinement under normal lighting conditions. However, ipRGCs themselves are not. Ablating them impairs refinement and reduces visual acuity (Chew et al., 2017). IpRGC ablation also prevents light from setting the endogenous period of the circadian clock during development (Chew et al., 2017). Collectively, these observations indicate that melanopsin and ipRGCs play several roles in early life, raising the possibility of a connection with developmental disorders.

IpRGCs and Human Health

The impacts of light on adult health have been reviewed from several perspectives in recent years, with reference to melanopsin and ipRGCs (Fisk et al., 2018; Jagannath et al., 2013; Ksendzovsky et al., 2017; Lazzerini Ospri et al., 2017; Lucas et al., 2014; Ramsey et al., 2013). Here, the aim is to provide an impression of these impacts and how they might be actively shaped using knowledge of ipRGCs.

Generally speaking, light affects humans as it does nocturnal mice, though with polarity reversals appropriate to the difference in temporal niche. For example, while broadband light induces sleep in mice, it improves alertness, attention, and reaction time in humans (Lucas et al., 2014). The connection of light to health is often made in the context of the circadian clock, whose effects on physiology are quite ubiquitous. Common sources of circadian disruption are jet lag and shift work. In the short term, they impair sleep, cognition, and mood. Chronic disruption may increase susceptibility to cancer, metabolic disorder, cardiovascular disease, and psychological illness (reviewed by Menet and Rosbash, 2011; Sahar and Sassone-Corsi, 2009; Takahashi et al., 2008). Circadian disruption is also reported to precipitate mania in individuals with bipolar disorder (Plante and Winkelman, 2008). The principal regulator of the circadian clock is light, and manipulating light has therapeutic potential. For example, controlling the timing and wavelength of illumination may help in the management of bipolar disorder (Phelps, 2016). For seasonal affective disorder (SAD), a depressive state that manifests when there is little light in the environment, illumination is an established treatment. The spectral sensitivities of these effects are consistent with a contribution from melanopsin. More directly, polymorphisms of melanopsin have been associated with cases of SAD as well as variations in the timing of sleep (reviewed by Roecklein et al., 2013). These research efforts are generally at a pioneering stage. Nonetheless, given the central role of ipRGCs in regulating the clock, sleep, and a diversity of other functions, these cells are in a position to broadly influence health.

Can knowledge of melanopsin and ipRGCs be used to redesign lighting for health? Studies in mouse models suggest strong effects of even simple manipulations. For example, while medium-wavelength light induces sleep, like broadband light, short-wavelength light produces signs of arousal instead (Pilorz et al., 2016). Additionally, while dim light increases locomotor activity, bright light suppresses it (Thompson et al., 2008). Translating such effects to humans is not straightforward. An illustrative case is the persistent response generated by mouse ipRGCs, which prolongs their activity for minutes unless acutely suppressed by light of particular wavelengths (Emanuel and Do, 2015). Exposure of individuals to these wavelengths could suppress ipRGCs at opportune times, such as before sleep. However, there are several unknowns. Whether human ipRGCs produce light-suppressible persistent responses is one. Another is whether suppression would have a net benefit, given that the outer photoreceptors will be activated while light is given for melanopsin suppression. Suppression may also potentiate ipRGC responses to subsequent illumination by reducing any ongoing adaptation (Mure et al., 2007). Similar unknowns surround the design of lighting that is meant to activate human ipRGCs. Filling these gaps in knowledge requires study of humans and species with similar visual systems (see above)—their ipRGCs receive extrinsic and intrinsic drives whose spectral and temporal characteristics require further definition, and whose dependencies on the intensity and history of illumination are incompletely known.

Optogenetic Uses of Melanopsin

Melanopsin activates G proteins of various families (Jiang et al., 2018; Newman et al., 2003), a promiscuity that allows it to confer photosensitivity to practically any cell type (Melyan et al., 2005; Panda et al., 2005; Qiu et al., 2005). Artificial expression of melanopsin has been used to control hormone secretion, the contraction of cardiomyocytes, and the activation of astrocytes (Beiert et al., 2014; Mederos et al., 2019; Tsunematsu et al., 2013; Ye et al., 2011). For mice that are blind from a lack of outer photoreceptors, ocular overexpression of melanopsin permits a degree of visual navigation (Lin et al., 2008). Melanopsin overexpression also has been observed to promote regeneration of the optic nerve (Li et al., 2016).

Melanopsin has several advantages as an optogenetic tool. Being a G-protein-coupled receptor, it can trigger intracellular signaling of many kinds; for example, to mobilize intracellular Ca^{2+} stores or regulate gene expression. Furthermore, because

most organisms already express a variant of their own, artificially expressed melanopsin is likely to be processed normally and evade immune surveillance. If melanopsin couples to a cascade that exhibits amplification and negative feedback, the light response gains sensitivity and dynamic range, features that are lacking in responses driven by channelrhodopsins. In addition, melanopsin tends to produce responses that rise and decay slowly (Bailes and Lucas, 2013; Lin et al., 2008; Spoida et al., 2016; but see Yasin et al., 2017), making the level of cellular activation more robust to fluctuations in illumination. At the same time, light of a particular composition can be used to suppress melanopsin activity, providing a measure of temporal control (Emanuel and Do, 2015; Spoida et al., 2016). The time course of activation also can be tuned by using different variants of melanopsin (Spoida et al., 2016; Tennigkeit et al., 2019; Tsukamoto et al., 2015). Given the large number of uncharacterized variants and advances in protein engineering, the artificial uses of melanopsin may expand in coming years.

Closing Remarks

The study of ipRGCs has emphasized that rare, small, and variable components can have major impacts on the organism. There may be fewer melanopsin molecules in all ipRGCs of a mouse retina than there are rhodopsins in a single rod, but deleting the melanopsin gene causes overt changes in physiology and behavior. Whether light increases the firing of an M1 or silences it depends on the particular cell in question and differences measured on a picoampere scale, the same used for current through a typical ion channel. Effects of this kind are difficult to detect using high-throughput techniques like multielectrode recording and Ca^{2+} imaging and are easily missed even with common methods of single-cell electrophysiology. In addition, ipRGCs comprise a few percent of the total output cells of the mouse retina yet are required for basic functions like the PLR and circadian photoregulation.

Another message is that molecules and signaling motifs that are conserved across cell types may nevertheless diverge in their functional outputs. M1s use effectors and channels that are close orthologs of those in *Drosophila* photoreceptors (Hardie and Postma, 2008). Even so, the single-photon response is measured on a timescale of seconds for the former and milliseconds for the latter (Do et al., 2009; Henderson et al., 2000). Conversely, M1s and M4s have different phototransduction cascades yet generate responses that share the same polarity and an extended time course (Emanuel and Do, 2015; Jiang et al., 2018; Sonoda et al., 2018).

Further study of ipRGCs has the potential to provide practical knowledge. For example, these cells are unusually regenerative, and examination of this capacity has identified a protein whose overexpression promotes axon regrowth (Bray et al., 2019). IpRGCs might also contain clues for neuroprotective mechanisms because of their high resistance to injury and to diseases like optic neuropathy (Ksendzovsky et al., 2017). Moreover, they drive the "post-illumination pupillary response," which has gained interest as a diagnostic tool for both neurodegenerative and affective disorders in humans (Gamlin et al., 2007; La Morgia et al., 2018; Tsunematsu et al., 2013). These emerging research directions were quite unanticipated when ipRGCs were discovered.

On a final note, irradiance encoding may appear to be a simple problem, but mammals use a mechanism in which pigments assume exotic conformations and labor is divided both across and within cell types, accruing benefits in dynamic range, temporal integration, spectral integration, and signaling flexibility. Additional complexity is likely to arise in the downstream processing of these signals, which is largely unexplored. Moreover, while mammals sense light primarily through the retina, there are also local reactions. For example, photon absorption by skin initiates pigmentation, vitamin D synthesis, and opioid release (Nguyen and Fisher, 2019). Some local effects are melanopsin-dependent, such as contraction of the iris and vasodilation, while others are not, like photoentrainment of the retinal clock (Sikka et al., 2014; Van Gelder and Buhr, 2016; Xue et al., 2011). Whether a logic exists for mediating photoresponses locally or centrally, using melanopsin or other pigments, is an open question.

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