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Can We See with Melanopsin?

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Abstract

A small fraction of mammalian retinal ganglion cells are directly photoreceptive thanks to their expression of the photopigment melanopsin. These intrinsically photosensitive retinal ganglion cells (ipRGCs) have well-established roles in a variety of reflex responses to changes in ambient light intensity, including circadian photoentrainment. In this article, we review the growing evidence, obtained primarily from laboratory mice and humans, that the ability to sense light via melanopsin is also an important component of perceptual and form vision. Melanopsin photoreception has low temporal resolution, making it fundamentally biased toward detecting changes in ambient light and coarse patterns rather than fine details. Nevertheless, melanopsin can indirectly impact high-acuity vision by driving aspects of light adaptation ranging from pupil constriction to changes in visual circuit performance. Melanopsin also contributes directly to perceptions of brightness, and recent data suggest that this influences the appearance not only of overall scene brightness, but also of low-frequency patterns.

1. INTRODUCTION

It has been 20 years since it became clear that the mammalian retina contains photoreceptors other than rods and cones (Lucas et al. 1999), and nearly as long since that property was assigned to a subset of retinal ganglion cells (RGCs) expressing the photopigment melanopsin (Berson et al. 2002, Hattar et al. 2002). In that time, perhaps the most surprising realization regarding this inner retinal photoreceptor has been the extraordinary reach of its influence. The retina contains few melanopsin-expressing RGCs, and they absorb a tiny fraction of the photons captured by rods and cones. Nevertheless, visual signals originating with melanopsin appear in all of the major retinorecipient nuclei in the brain, and a melanopsin contribution has been identified in a growing list of visual responses. Melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs) were first discovered in the search to understand the mechanisms by which light:dark cycles entrain endogenous circadian clocks to local time. There was a consequent tendency to categorize ipRGCs as nonvisual photoreceptors (in contrast to the rods and cones that we use to see). That nomenclature was always imperfect and has appeared increasingly inaccurate as the numerous ways in which melanopsin contributes to vision have been elucidated. In this review, we concentrate on melanopsin's involvement in perceptual vision.

1.1. Melanopsin and Intrinsically Photosensitive Retinal Ganglion Cells

Melanopsin is an opsin photopigment that was first discovered in amphibian photosensitive dermal melanophores (Provencio et al. 1998). Across diverse species, melanopsin has maximal sensitivity in the short-wavelength part of the visible spectrum (λ_{max} approximately 480 nm) (Lucas et al. 2014). Expression in the mammalian retina is restricted to the small population of ipRGCs, in which melanopsin drives light-dependent excitation via a G-protein signaling cascade (Do 2019, Hughes et al. 2012, Schmidt et al. 2011). Melanopsin can excite ipRGCs and drive downstream responses such as circadian photoentrainment even in the absence of rods and cones (Czeisler et al. 1995, Freedman et al. 1999), but, critically, the ganglion cells in which it is expressed also act as conduits for signals originating in these outer retinal photoreceptors (Berson et al. 2002, Dacey et al. 2005) (**Figure 1**).

Cardinal sensory properties of what came to be identified as melanopsin photoreception were defined by studying mice lacking rods and cones, even before the discovery of ipRGCs. The residual photosensitivity of these animals was thus described as peaking in the short-wavelength part of the spectrum (λ_{max} approximately 480 nm) and requiring rather high light levels (several orders of magnitude above the cone threshold) (Lucas et al. 2001, Yoshimura & Ebihara 1996). These properties have since been confirmed in numerous studies (including direct recordings of ipRGCs) across a range of mammalian species (Berson et al. 2002, Dacey et al. 2005). The other fundamental feature of melanopsin photoreception is a bias toward detecting low-temporal-frequency modulations. Melanopsin-driven responses are typically sluggish and sustained and, to the extent that this has been studied, have poor ability to resolve rapid modulations in light intensity (Berson et al. 2002, Dacey et al. 2005, Walch et al. 2015). The fundamental features of low absolute sensitivity and poor temporal resolution are likely imposed to at least some degree by the very low quantity of melanopsin in the retina compared to those of rod or cone opsins. ipRGCs lack structures analogous to the outer segments of rods and cones containing large quantities of opsin. The low sensitivity of melanopsin is thus explained by the limited amount of melanopsin available to catch photons. Moreover, ipRGCs compensate for their fundamentally low rate of photon capture by employing a phototransduction cascade with high gain and long temporal integration, thus limiting temporal resolution (Do et al. 2009). The low concentration of melanopsin in ipRGCs might also be expected to limit their contrast sensitivity (their ability to detect small variations in light

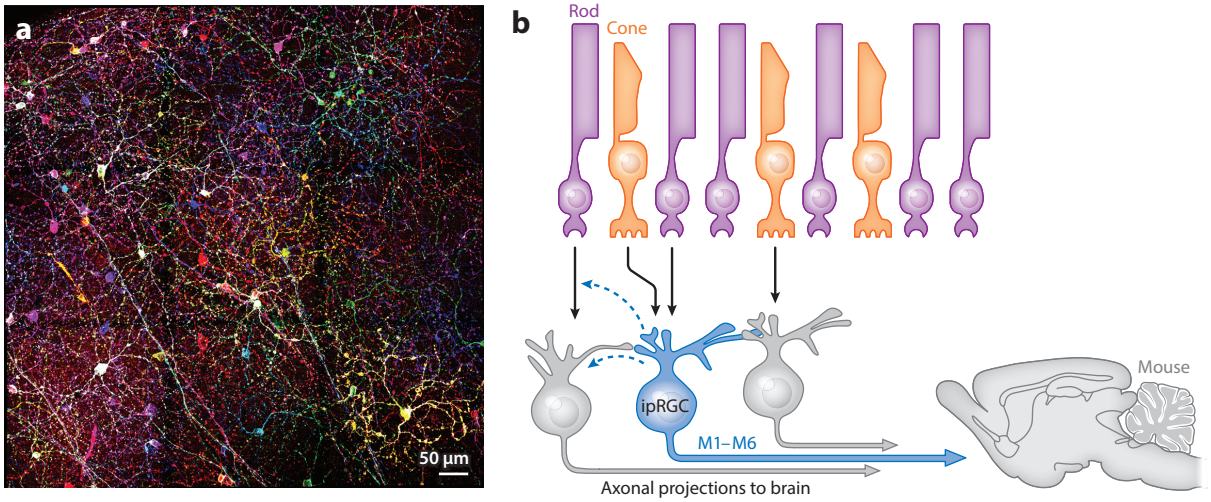


Figure 1

Melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs). (*a*) En face view of a portion of retina from an *Opn4*$^{Cre/+}$ mouse transduced with Brainbow viruses to provide multicolored labeling of the ipRGC population. The relatively sparse distribution of colored cells is indicative of the small fraction of the total ganglion cell population expressing melanopsin. Note also their morphological diversity (differences in soma size and dendritic tree complexity). (*b*) ipRGCs (*blue cell*) of all six subtypes (M1–6) lie in the inner retina and receive information from rods (*purple*) and cones (*orange*) via the conventional retinal circuitry (not shown). ipRGCs in turn convey information to the brain via their axonal projection and also to the other neurones in the retina (*dotted blue arrows*) via gap-junction and synaptic connections.

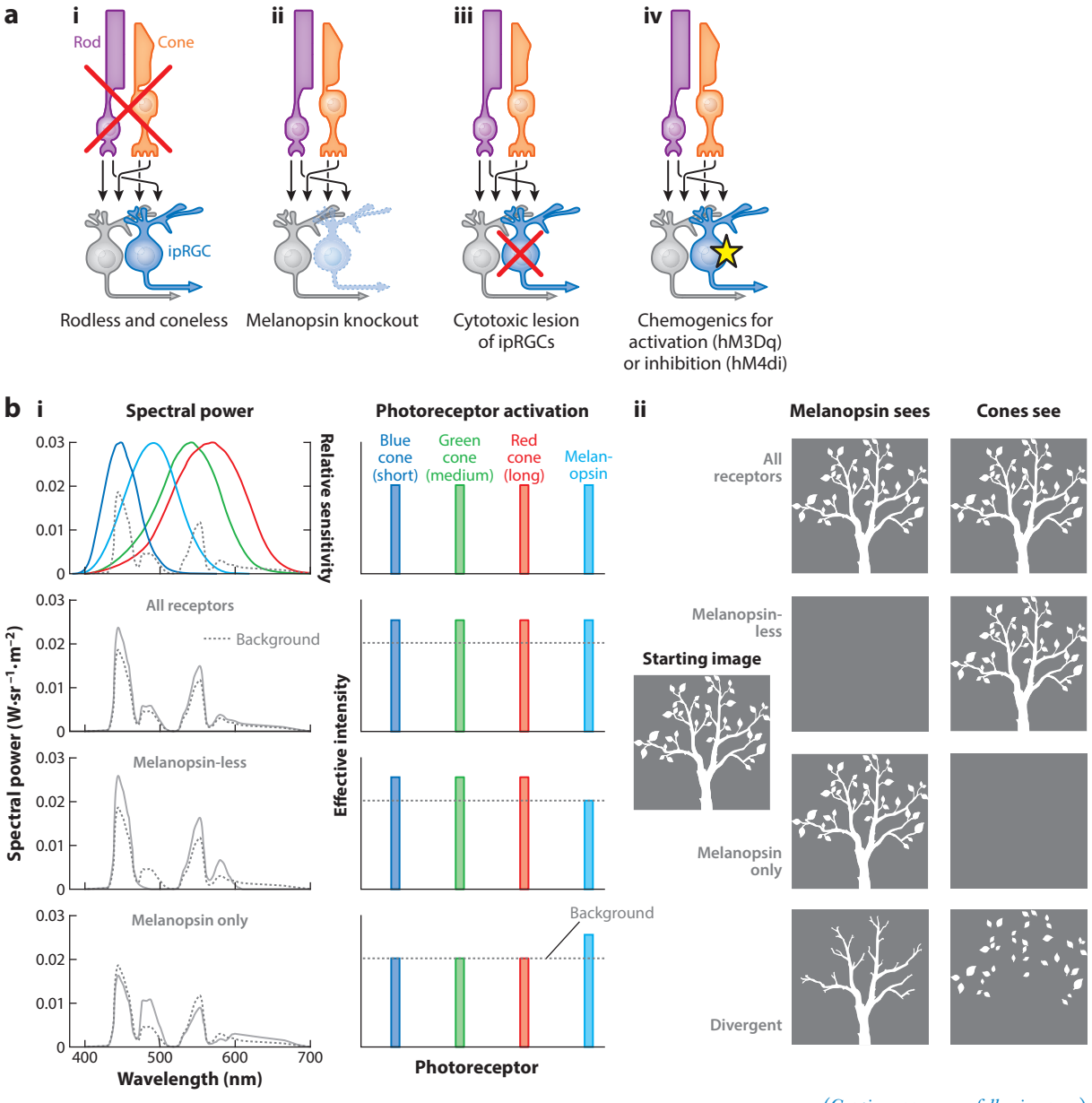
intensity). Uncertainty in light measurement is defined by the Poisson distribution and is thus inversely proportional to the total number of photons counted. The small amount of melanopsin and associated low photon capture rate therefore imply poor signal:noise for light measurement and poor ability to detect small differences. Indeed, to the extent that this has been examined, contrast sensitivity of melanopsin does appear to be substantially lower than that of rods or cones (Allen et al. 2017).

The first description of melanopsin photoreception was from RGCs projecting to the mouse suprachiasmatic nucleus, site of the master circadian clock (Berson et al. 2002). In the intervening years, it has become clear that RGCs expressing melanopsin in fact innervate all major retinorecipient nuclei (at least in mice) (Do 2019, Schmidt et al. 2011). This diversity in central projections is mirrored in anatomical diversity within the retina. Six subtypes of ipRGC (termed M1–6) have been described in the mouse based on differences in soma size and in dendritic arborization (Do 2019, Hughes et al. 2012, Quattrochi et al. 2019, Schmidt et al. 2011). Central projection patterns also vary substantially across this population, with, e.g., the M1 type of ipRGC dominating retinal innervation of the suprachiasmatic nucleus (SCN; site of the master circadian clock) but being largely absent from the dorsal lateral geniculate nucleus (dLGN) (thalamic relay for cortical vision). Several other subtypes disproportionately target the dLGN. The reader is directed elsewhere for a detailed description of the various subtypes (Do 2019, Schmidt et al. 2011), but for our purposes, the description of melanopsin in RGCs innervating the primary visual thalamus provides sufficient motivation to ask the question of how melanopsin may contribute to vision, while the anatomical diversity among melanopsin-expressing ganglion cells intimates that there may be more than one answer to this question.

1.2. Methods of Study

In the remainder of this review, we summarize the evidence for melanopsin involvement in various aspects of vision and discuss how these functions may relate to anatomical and physiological properties of ipRGCs. Before doing so, it is worth digressing briefly to consider the types of approaches that have been used to detect melanopsin's influence (**Figure 2**) and the strengths and weaknesses of the data that they provide.

The principal challenge in identifying melanopsin-driven responses at the systems or whole-animal level is disentangling the component of any given visual response originating from



(*Caption appears on following page*)

Figure 2 (*Figure appears on preceding page*)

Methods of studying melanopsin at the systems or whole-animal level. (*a*) The appearance of visual responses originating with rods and cones in intrinsically photosensitive retinal ganglion cells (ipRGCs) (and all downstream responses) presents a fundamental challenge to selectively modulating melanopsin or detecting melanopsin contributions to vision. Genetic solutions to this problem include (*i*) elimination of rods and cones, (*ii*) melanopsin knockout, (*iii*) chemogenetic activation or inhibition of ipRGCs, and (*iv*) cytotoxic lesion of ipRGCs. (*b*) An alternative approach is to use changes in spectral composition to generate visual stimuli that are differentially apparent to rods or cones versus melanopsin. (*i*) In this worked example, the output of five spectrally distinct lights is independently controlled. (*Top*) A starting combination (*dotted line*; termed background) superimposed upon the normalized spectral sensitivity of the three human cones (*blue*, *green*, and *red lines*) and melanopsin (*cyan line*) for reference. (*Bottom*) Graphs show the spectral composition of three different paired second lights (*solid line*), which, when replacing the background (*dotted line*), represent either a spectrally neutral increase in output to generate a light step visible to all receptors (graph second from top) or balancing adjustments across the five lights to present steps apparent to either cones but not melanopsin (melanopsin-less) or melanopsin but not cones (melanopsin only). Bar charts to the right depict effective intensity for each of the three cones (blue, green, red) and melanopsin of the corresponding spectrum relative to that of the background light (*dotted line*). (*ii*) In addition to switching between these spectra over time, the output of the five lights can be varied across space within an image to present patterns that are visible to all photoreceptors, visible to cones but not melanopsin, or visible to melanopsin but not cones, or even to present an image in which different patterns are visible to cones than to melanopsin.

melanopsin from that provided by rods and cones. To reject the null hypothesis that vision originates solely from rods and cones, one requires a method of presenting stimuli that are selective for melanopsin. The most obvious solution to this problem, and that most widely applied, has been to eliminate rod and cone photoreception (**Figure 2*a*, *i***). This leaves melanopsin as the only remaining photoreceptor and allows one to ask whether melanopsin alone is able to support any given visual response. Genetic, pharmacological, and physical isolation of ipRGCs from outer retinal influences have been used to reveal melanopsin signals in ex vivo recordings of the retina (Berson et al. 2002, Dacey et al. 2005, Hatori et al. 2008, Schmidt & Kofuji 2009, Tu et al. 2005). For in vivo studies, inherited degeneration and/or dysfunction of rods and cones have been applied to provide the same effect (Altimus et al. 2010, Freedman et al. 1999, Lucas et al. 1999). This powerful approach formed one of the foundations of the field by revealing the requirement for a non-rod, non-cone photoreceptor in circadian light responses, and it can be applied to both animal models and humans with retinal degeneration. It has three fundamental drawbacks. The first is that some rod or cone function may persist. This is a particular problem with humans, in which survival of some rod or cone activity in subjects with retinal degeneration is hard to exclude, but is even a concern in widely used animal models (Allen et al. 2010, Soucy et al. 1998, Thyagarajan et al. 2010). The second, more substantial, consideration is that such dystrophic preparations may provide an inaccurate picture of melanopsin's influence. On the one hand, remodeling may conceivably lead melanopsin to support functions that, in the intact retina, are the sole responsibility of rods and cones (although to date there is no direct evidence of this). On the other hand, melanopsin function may itself be impaired as a secondary consequence of rod+cone loss. Melanopsin photoreception certainly survives outer retinal degeneration to support light-driven behaviors but, as ipRGCs receive extensive outer retinal input, the cellular environment of melanopsin photoreception is likely highly unusual in these rod+cone-deficient preparations. The final limitation of this approach is that it cannot reveal emergent properties of the intact system (e.g., melanopsin influences on rod or cone vision).

A valuable complement to rodless+coneless preparations is the melanopsin-knockout mouse (Hattar et al. 2002, Lucas et al. 2003, Panda et al. 2003, Ruby et al. 2002). This animal has been used to answer the question of whether aspects of vision require melanopsin (**Figure 2*a*, *ii***). Melanopsin-knockout mice do indeed have deficits in responses to the sort of bright and sustained stimuli to which melanopsin is considered most responsive (Lucas et al. 2003, Schmidt et al. 2014). However, in interpreting the outcome of melanopsin-knockout experiments, the

potential for functional reorganization should be kept in mind, as should the possibility that recorded deficits could be distantly related to the primary lesion via, e.g., impacts on visual development or pupil size. A conditional knockout model in which melanopsin could be deleted after development and in particular subsets of ipRGCs would be a valuable extension of this approach.

A related strategy is to target the ipRGCs in which melanopsin is expressed for manipulation. In this way, the function of not only melanopsin but also rod+cone signals sent via these cells can be addressed. One variant of this approach—selective ablation of ipRGCs (**Figure 2*a*, *iii***)—has revealed that circadian entrainment is fully dependent on ipRGCs and has been applied to distinguish the physiological roles of different ipRGC subtypes (Chen et al. 2011, Guler et al. 2008, Hatori et al. 2008). More physiological and reversible manipulations are also possible, with, e.g., chemogenetic manipulations (**Figure 2*a*, *iv***) being applied to acutely excite or inhibit ipRGCs (Milosavljevic et al. 2016a,b, 2018; Sonoda et al. 2018; Storchi et al. 2015).

The final approach to manipulating melanopsin's activity is to use changes in the spectral composition of light to selectively modulate effective intensity for melanopsin versus rods and/or cones (**Figure 2*b***). Melanopsin spectral sensitivity peaks at approximately 480 nm, and early applications of this approach compared responses to stimuli in this part of the spectrum with longer- or shorter-wavelength lights calculated to provide equivalent activation of cones (Dkhissi-Benyahya et al. 2007, Lall et al. 2010). More recent studies have employed an extension of the psychophysical paradigm of receptor silent substitution, in which balancing alterations in the intensity of multiple wavelength bands can be employed to modulate effective photon flux for melanopsin while keeping that of rods and cones invariant (or vice versa) (Spitschan & Woelders 2018). This strategy (sometimes termed receptor silent substitution because energy at one wavelength is substituted by energy at another while rendering the transition silent to one or more classes of receptor) has several advantages over the alternatives outlined above: (*a*) It can reveal melanopsin function in an intact system with all photoreceptor types fully functional; (*b*) it can be applied to both animal models and human subjects; and (*c*) it can be used to produce not only stimuli visible only to melanopsin, but also stimuli visible to rods and cones but not melanopsin, allowing simultaneous exploration of whether melanopsin is sufficient and necessary for a given response, and revealing interactions between the two systems.

The silent substitution approach has important limitations. The most fundamental is that it relies on a difference in spectral sensitivity between the target receptor (melanopsin) and those to be kept silent (rods and cones). In the case of mice, the use of silent substitution may be facilitated by application of transgenic models in which the spectral sensitivity of cone vision has been shifted (Brown et al. 2012). In both mice and humans, separating melanopsin from rod activity is especially challenging given similarities in their spectral sensitivity (approximately 20 nm of difference in λ_{max}). Separate control over rods and melanopsin is possible, although many studies instead minimize rod signals by working at high light intensities [although note that rods may be active under surprisingly bright backgrounds (Tikidji-Hamburyan et al. 2017)]. A more fundamental constraint is that the degree of melanopsin modulation achievable while holding other receptors silent is modest (<10-fold for mice and <4-fold for humans) for a photoreceptor system thought to work across several decades of light intensity. A final point is that the silent substitution method is technically demanding and prone to artifact. It relies on accurate and simultaneous control over the intensity of multiple spectrally distinct light sources. Meanwhile, the high contrast sensitivity of outer retinal photoreceptors, along with differences in the spectral sensitivity of cones and rods between individuals and across the retina, makes it challenging to eliminate outer retinal intrusion in evoked responses (see, e.g., Spitschan et al. 2015). These challenges make it imperative to include appropriate controls in any experiment.

2. MELANOPSIN CONTRIBUTIONS TO VISION

2.1. Light Adaptation and the Pupil Light Reflex

Visual systems meet the challenge of maintaining perceptual constancy and optimal performance across huge variations in irradiance, with numerous adjustments in the response properties and connectivity of visual neurons. Such light adaptation can constitute a direct response of a single neurone to irradiance-dependent alterations in the characteristics of incoming signals. Alternatively, an assessment of long-term and global light intensity may also be used to drive coordinated systems-level adaptation. A concrete example of such a systems-level response is the pupil light reflex (in which changes in the size of the pupil aperture buffer retina light exposure against changes in corneal irradiance). Melanopsin's ability to present a time-averaged signal of light intensity makes it well placed to provide a measure of ambient light, and there is strong evidence for its contribution to light adaptation.

By far the most extensive description of melanopsin's contribution to vision relates to its ability to control pupil size (**Figure 3**). A pupil light reflex is retained in mice lacking rods+cones (Lucas et al. 2001) and is impaired in mice lacking melanopsin or ipRGCs (Guler et al. 2008, Lucas et al. 2003). Moreover, the spectral sensitivity of sustained pupil responses matches that of melanopsin in primates and humans (Gamlin et al. 2007), and pupil size is responsive to targeted modulation of melanopsin in humans using silent substitution (Barrionuevo et al. 2014, Spitschan et al. 2014, Tsujimura et al. 2010). In accordance with melanopsin's known sensory characteristics, its inclusion in this pathway is especially important for defining steady state pupil size.

Evidence for a more widespread contribution of melanopsin to aspects of light adaptation is more sporadic but nonetheless compelling. Selective increases in melanopic irradiance or chemogenetic activation of ipRGCs drive robust decreases in the amplitude of the flash electroretinogram (ERG) in mice (Allen et al. 2014, Milosavljevic et al. 2016a). In humans, the spectral sensitivity of light adaptation in the implicit time of the cone flash ERG matches that of melanopsin (Hankins & Lucas 2002). These findings indicate a widespread alteration in some aspect of retinal physiology, perhaps extending to the light response of photoreceptors themselves (Milosavljevic et al. 2016a). In the case of mice, one explanation for the reduction in global flash response amplitude is that melanopsin seems to drive an irradiance-dependent diversification in the feature selectivity of visual neurones. Thus, application of silent substitution to generate selective increases in melanopic irradiance elicits a change in spatial frequency tuning in a subset of dLGN neurones from long-pass to band-pass (**Figure 3**), increased temporal resolution in others, and an overall reduction in the similarity of responses to complex stimuli across the whole population (Allen et al. 2014). Taken together, these data suggest that one function of melanopsin-driven light adaptation is to allow a richer representation of the scene at higher irradiances by shifting circuits away from pooling responses across neurones and over time (Warrant 1999).

Another function of melanopsin in light adaptation in mice is to support irradiance-dependent increases in trial-to-trial reproducibility of visual responses (Storchi et al. 2015). This ability can be revealed using silent substitution to produce selective increases in irradiance for melanopsin and by chemogenetic activation of ipRGCs (Milosavljevic et al. 2016b, 2018) (**Figure 3**). At least one potential origin for this effect is an increase in the information rate of the optic nerve produced by a melanopsin-derived increase in excitability of RGCs at higher irradiance. Simply put, as irradiance increases, ipRGCs drive enhanced ganglion cell excitability and consequent increase in visual response amplitude. Such an effect has been recorded at the level of individual ipRGCs (at least in the ON alpha or M4 class), in which melanopsin drives a direct depolarization to enhance excitability (Sonoda et al. 2018). However, ipRGC-driven increases in spontaneous activity appear across the ganglion cell population to some extent (Milosavljevic et al. 2016b, 2018;

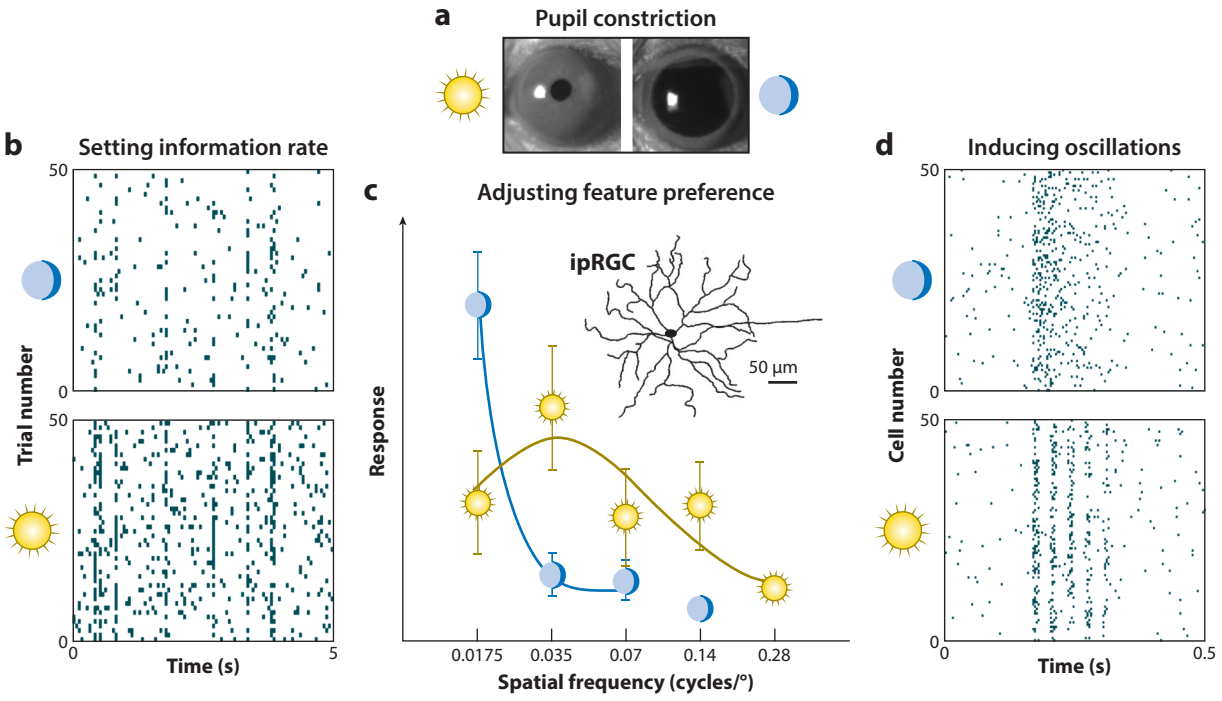


Figure 3

Melanopsin contributions to aspects of light adaptation. The ability of at least some intrinsically photosensitive retinal ganglion cells (ipRGCs) to encode ambient light intensity is applied to modulate visual system function at multiple levels. (*a*) ipRGCs drive light-dependent pupil constriction (depicted here as images of a mouse eye under dim versus bright light). (*b*) ipRGCs also drive increases in excitability and maintained activity of retinal ganglion cells (RGCs) at brighter light to produce improvements in the reliability of the visual code and contrast sensitivity. Shown are simulated raster plots for a single ganglion cell over multiple repeats of temporal white noise visual stimulus before (*upper*) versus during (*lower*) chemogenetic excitation of ipRGCs (after Milosavljevic et al. 2016b). Note the higher firing rate (more spikes) and more obvious similarity between trials (higher reliability) in the lower plot. (*c*) Recordings from the mouse dorsal lateral geniculate nucleus (dLGN) reveal that melanopsin also drives changes in visual feature selectivity. The graph at the bottom shows the outcome of an experiment in which a subset of neurons switched from showing maximum response (modulation in firing induced by inverting gratings) at lower spatial frequencies under dim light to preferring finer patterns when silent substitution was used to present a selective increase in ambient light for melanopsin. Panel adapted from Allen et al. (2014) (CC BY 3.0). (*d*) Melanopsin has also been implicated in driving the appearance of gamma oscillations in the mouse retina and dLGN at higher irradiance. Graphs depict simulated raster plots for a population of RGCs responding to a simple flash stimulus either in the absence (*top*) or in the presence (*bottom*) of coherent gamma oscillations (after Storchi et al. 2017).

Storchi et al. 2015), implying involvement of intraretinal outputs from ipRGCs. Such mechanisms could explain why melanopsin-knockout mice show reduced contrast sensitivity in behavioral tests (Schmidt et al. 2014). This aspect of melanopsin's influence has been proposed to represent an example of efficient coding, in which information capacity of the optic nerve rises to match increases in the amount of visual information available at high irradiances (Milosavljevic et al. 2016b, 2018).

A final impact of melanopsin on visual system activity is to support high-frequency gamma oscillations. The ability of neurones in the early visual system (visual thalamus and cortex) to show coordinated oscillations in spiking in the 30–90-Hz range has long been appreciated (for a review, see, e.g., Buzsaki & Wang 2012). These periodic narrowband oscillations synchronize spike activity either within neighboring neurons or in functionally related neurons in distant brain regions. While their ultimate function is not well established, such oscillations could ensure a temporally

unified response across neurones encoding different features of the same object (Gray 1999, Gray et al. 1989) (**Figure 3**) and/or favor transmission of information between connected brain areas oscillating in phase (Fries 2005, 2015). Such oscillations in the retina, dLGN, and cortex are a feature of brighter ambient light (Saleem et al. 2017, Storchi et al. 2017), and experiments using both silent substitution and melanopsin-knockout mice show that melanopsin contributes to this aspect of their physiology (Storchi et al. 2017).

Such generalized changes in visual network function imply the existence of mechanisms by which ipRGCs can influence the behavior of other neurones in the retinal network. ipRGCs make both synaptic and gap junction connections with neurons in the inner retina (Joo et al. 2013, Reifler et al. 2015, Zhang et al. 2008). An important unanswered question is how (if at all) such connections produce the alterations in systems-level performance described above. Targets for ipRGC connections include several amacrine cell types, including dopaminergic amacrine cells (Zhang et al. 2008). An obvious possibility, therefore, is that melanopsin signals influence retinal physiology by modulating neuromodulator release by these cells. Nevertheless, this route remains untested and, interestingly, dopamine release itself may not be influenced by melanopsin (Perez-Fernandez et al. 2019).

2.2. Action Selection and Perception

The appearance of electrophysiological responses to light originating with melanopsin in the primary visual thalamus and cortex (Brown et al. 2010, Spitschan et al. 2017, Storchi et al. 2015) raises the possibility that the functions of melanopsin could extend beyond its modulation of rod and cone signals: Melanopsin itself might represent a source of visual information. In mice lacking rods and cones, a substantial fraction of neurones in the dLGN respond to bright light steps with sluggish increases in firing that persist for many tens of seconds after termination of the light stimulus (Brown et al. 2010, Davis et al. 2015). These response characteristics are qualitatively consistent with those expected from studies of the melanopsin light response in deafferented RGCs (Wong 2012) but would appear to put a substantial limit on the types of visual features encoded by melanopsin. In particular, their very low temporal resolution implies a degree of motion blur under natural conditions that would restrict these melanopsin light responses to providing a representation of ambient light at best.

An important caveat to conclusions drawn from studies of rodless+coneless mice (or indeed deafferented ipRGCs) is the fundamentally unphysiological nature of these preparations. In the intact retina, melanopsin phototransduction in ipRGCs never occurs in the absence of incoming signals originating with rods and cones. Thus, even leaving aside the general possibility of disruptive consequences of degeneration, there is the realistic possibility that removal of this extrinsic influence could materially impact melanopsin's ability to influence ipRGC activity. Application of silent substitution to isolated melanopsin-derived responses in the dLGN of visually intact mice indicates that this may indeed be the case. Melanopsin-evoked responses identified in this way fit the qualitative description of melanopsin photoreception, being present at higher light intensities (Brown et al. 2012) and having poor temporal resolution (Allen et al. 2017). However, in visually intact mice, it has been shown that melanopsin can track light steps with much higher temporal acuity than do responses in rodless+coneless mice. Indeed, direct analysis of temporal frequency tuning in intact mice revealed a melanopsin component to responses driven by modulations at frequencies under approximately 1 Hz (Allen et al. 2017), while the rodless+coneless dLGN does not reliably track sinusoidal modulations even when presented at frequencies as low as 0.01 Hz (Procyk et al. 2015). The improved temporal resolution for melanopsin in intact mice begs the question of whether the melanopsin signal could also convey spatial information. This indeed

appears to be the case. Spatial receptive fields for melanopsin-isolating stimuli can be mapped in the mouse dLGN and, at the level of individual cells, have the same size and location as receptive fields recorded when using stimuli targeting rods and cones (Allen et al. 2017, Procyk et al. 2015). This implies not only that melanopsin signals can convey spatial information, but also that they retain the visuotopic order that is considered critical for this to occur.

Taken together, the electrophysiological recordings from the mouse thalamus reveal that melanopsin enhances the ability of a subset of dLGN neurones to encode local light intensity. Consistent with melanopsin's known characteristics, it does so at higher light intensities (within the photopic range), and with poor temporal resolution compared to rods and cones. Another characteristic of the melanopsin response is poor contrast sensitivity [threshold between 30% and 40% Michelson contrast for a detectable change in firing in dLGN neurons (Allen et al. 2017)]. These features are likely imposed by the poor photon capture of melanopsin (see above) and are thus inescapable. In the intact retina, however, they are not necessarily detrimental, as vision at scotopic and mesopic levels is supported by rods and cones, and under photopic conditions, cones provide high temporal fidelity and contrast sensitivity. Instead, they could allow melanopsin to augment the representation of low-frequency patterns and slowly changing light, allowing cones to be optimized for detecting high spatiotemporal frequency. This possibility has been tested in mice, in which silent substitution was used to generate images in which low-frequency patterns were visible to rods and cones but not melanopsin. Electrophysiological responses to presentation of such melanopsin-deficient images were deficient compared to matched images in which patterns were visible to all photoreceptors (Allen et al. 2017). This work suggests that melanopsin is necessary for the adequate representation of patterns over lower spatiotemporal scales in the mouse dLGN.

A great deal of work remains to determine the relevance for visually guided actions and perception of this electrophysiological evidence that melanopsin contributes to vision. Rodless+coneless mice show a preference for dim over bright environments (Carr et al. 2011), and retain some limited ability to use differences in brightness as a cue for maze navigation (Brown et al. 2012), but, to a first approximation, lack form vision. This phenotype matches the progressive loss of vision in humans with rod+cone degeneration [including those in which melanopsin photoreception is demonstrably retained (Czeisler et al. 1995)]. Thus, while it remains possible that melanopsin makes a material contribution to vision at intermediate stages of degeneration, at end stages, melanopsin alone probably has limited ability to support vision. These findings are consistent with the low quality of melanopsin-derived electrophysiological responses in rodless+coneless mice (see above).

Behavioral studies indicate that melanopsin makes a more substantial contribution to vision in sighted individuals. An early indication of this was the demonstration that mice with disrupted rod+cone phototransduction (but intact retinas) retain some spatial discrimination (Ecker et al. 2010). In fully sighted animals, the silent substitution approach has been used to show that mice use melanopsin alongside conventional photoreceptors to judge the brightness of targets in maze navigation tasks (Brown et al. 2012).

The idea that melanopsin contributes to assessments of brightness has been extensively supported by experiments with sighted human subjects. Several groups have applied silent substitution in conjunction with psychophysical paradigms to show that modulations in melanopic radiance appear as differences in brightness (Brown et al. 2012, Spitschan et al. 2017, Yamakawa et al. 2019, Zele et al. 2018a). The sensory characteristics of this melanopic percept are more or less consistent with those predicted for melanopsin. Thus, melanopic modulations are detectable at higher background light intensities (within the photopic range) and at lower temporal frequencies (variously

<1 Hz and <5 Hz). Allen et al. (2019) showed that this aspect of melanopsin vision extends to the ability to distinguish coarse spatial patterns, as predicted based on electrophysiological recordings in mice (Allen et al. 2017).

The question of whether melanopsin also contributes to color is more controversial. In mice, the M5 subset of ipRGCs receives opponent cone input (S-ON M-OFF) (Stabio et al. 2018). In primates, at least some ipRGCs innervating the dLGN receive color opponent (S-OFF L+M-ON) cone inputs (Dacey et al. 2005). As melanopsin excites these ipRGCs, this finding implies that melanopsin could provide a yellow percept. The psychophysical data reporting a color percept based on the silent substitution approach do not consistently match this prediction. On the one hand, Spitschan et al. (2017) reported that among the percepts elicited by melanopsin-directed steps produced by silent substitution was a yellow–orange appearance partially consistent with that predicted from the physiology. On the other hand, some subjects in that study reported a greenish percept, and a separate study by Cao et al. (2018) also reported a green hue for melanopsin steps. A different color percept was reported by Zele et al. (2018b), who found that reductions in S-cone activation were required to compensate for increases in the melanopsin dimension in a color-matching study. Finally, other studies have reported that melanopsin-directed steps do not themselves induce a change in apparent color (Allen et al. 2019, Brown et al. 2012). It remains to be determined whether these inconsistencies reflect an inherent complexity to melanopsin's contribution to color, or whether they are due to residual cone stimulation in some studies.

3. CONCLUSIONS AND PERSPECTIVES

Melanopsin photoreception differs from that provided by rods and cones in its high threshold light intensity and poor temporal resolution and contrast sensitivity. The poor temporal resolution and contrast sensitivity of melanopsin are superficially unhelpful characteristics for form vision, in which the ability to track motion and discern fine spatial patterns relies on resolution of often small differences in local light intensity with high spatiotemporal fidelity. However, there are ways in which they are beneficial.

The best-established application of melanopsin's low temporal fidelity is providing a time-averaged signal of ambient light intensity, and there is growing evidence that this capacity is employed by vision to provide aspects of light adaptation (the most obvious of which is the pupil light reflex). A melanopic representation of ambient light could also support perceptions of scene brightness, and indeed, there is good evidence that melanopsin contributes to estimates of brightness in humans and mice. More recent data indicate that, although the spatiotemporal resolution of melanopsin is poor compared to that of cone photoreception, it is sufficient to encode not only ambient light but also spatial patterns in brightness. In natural scenes, patterns exist over multiple spatial scales, and both electrophysiological (in mice) and psychophysical (humans) data reveal a melanopsin contribution to detecting lower-spatial-frequency (coarser) patterns (**Figure 4**). The performance of a visual system reliant on melanopsin alone would be poor indeed. However, these data show how melanopsin's distinct characteristics can be useful in a system that already has a photoreceptor system supporting high-acuity vision (cones). Thus, one way of describing melanopsin's contribution to vision is that, by providing a separate mechanism for augmenting the retina's ability to encode low spatiotemporal features (from ambient light to coarse patterns), melanopsin allows cone vision to be optimized for tracking motion and discerning fine spatial patterns.

The study of melanopic vision is in its infancy, and a great many questions remain unanswered. An important area for future work will be to link the fundamental cell biology of ipRGCs to

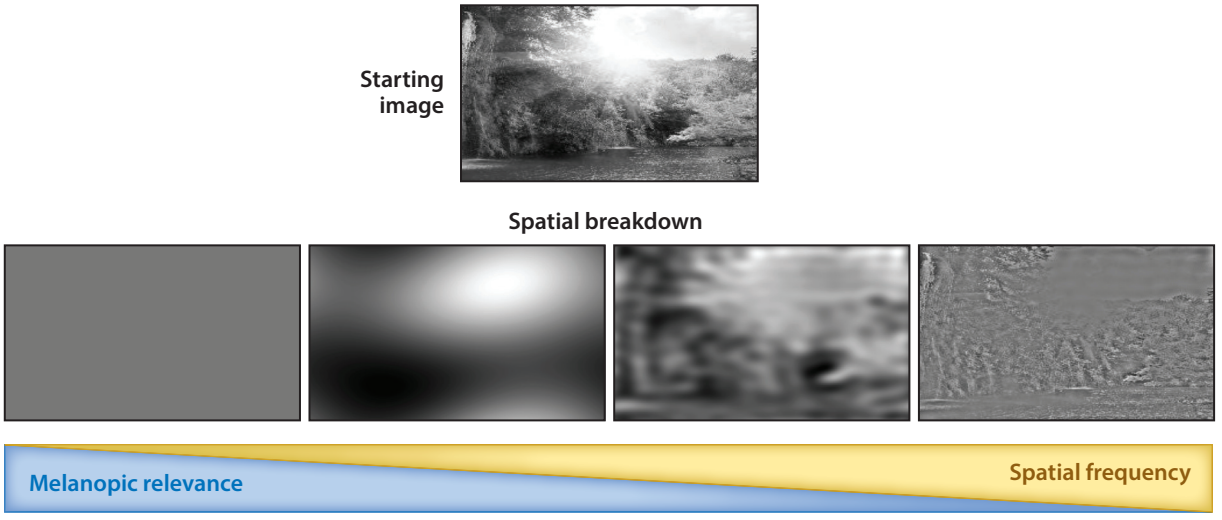


Figure 4

The world as seen by melanopsin. Patterns exist over multiple spatiotemporal scales, from gradual changes in ambient light across the day to the fine detail of an image. This feature is depicted in a series of versions of a representative image, each filtered to reveal a subset of spatial frequencies from lowest (*left*) to highest (*right*). Melanopsin's sensory characteristics preclude it from detecting fine details but allow it to detect the lowest frequency changes (modulations in ambient light). Recent data indicate that melanopsin may also be sensitive to moderate spatiotemporal frequencies, allowing it to encode coarse patterns.

the various ways in which melanopsin contributes to vision. Do the multiple ipRGC types make distinct contributions to vision (as seems to be the case for non-image-forming functions)? Via what mechanism(s) do ipRGCs drive light adaptation in visual circuits?

There is an equally urgent requirement to incorporate melanopsin into models of perceptual vision. It has been suggested that the melanopic brightness percept is equivalent to that provided by luminance (Yamakawa et al. 2019, Zele et al. 2018a). It will be important to confirm that these qualities really are perceptually interchangeable and, if so, how melanopsin contributes to our ability to distinguish variations in brightness over multiple spatiotemporal scales. Similarly, it will be important to determine how melanopsin's ability to modulate cone-based vision impacts performance. Finally, the questions of whether and how melanopsin contributes to color vision (an area in which data are currently contradictory) will need to be resolved. The technique of silent substitution will be critical in addressing these problems, as it is the only realistic option available for selectively modulating melanopsin activity in normally sighted humans. However, achieving selective control over melanopsin (without inadvertently also targeting rods and cones) using this approach is technically demanding. This highlights the need not only for carefully controlled experiments, but also for parallel experiments in model organisms in which other options for experimental modulation of melanopsin activity are available.

The prize for understanding melanopsin's contribution to vision is not just a deeper understanding of this valued sense. The artificial light sources and visual displays that play such an important role in our everyday life are designed according to the assumption that the appearance of any light can be predicted by its coordinate in a three-dimensional color map, which describes saturation, hue, and luminance and is anchored to the three types of human cone photoreceptors. Several studies have shown that modulations in a fourth (melanopic) dimension can alter appearance for stimuli that should be indistinguishable based on their three-dimensional color coordinates (Allen et al. 2019; Brown et al. 2012; Cao et al. 2018; Spitschan et al. 2017; Yamakawa

et al. 2019; Zele et al. 2018a,b). Appropriate application of this observation to improve the performance of light sources and displays will rely on a full understanding of how and under what circumstances melanopsin contributes to vision.

DISCLOSURE STATEMENT

A.E.A. and R.J.L. are named as inventors on patent application PCT/GB2017/050338 "Improvements in image formation." The other authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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