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Are ipRGCs involved in human color vision? Hints from physiology, psychophysics, and natural image statistics

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ABSTRACT

Human photoreceptors consist of cones, rods, and melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs). First studied in circadian regulation and pupillary control, ipRGCs project to a variety of brain centers suggesting a broader involvement beyond non-visual functions. IpRGC responses are stable, long-lasting, and with a particular codification of photoreceptor signals. In comparison with the transient and adaptive nature of cone and rod signals, ipRGCs' signaling might provide an ecological advantage to different attributes of color vision. Previous studies have indicated melanopsin's influence on visual responses yet its contribution to color perception in humans remains debated. We summarized evidence and hypotheses (from physiology, psychophysics, and natural image statistics) about direct and indirect involvement of ipRGCs in human color vision, by first briefly assessing the current knowledge about the role of melanopsin and ipRGCs in vision and codification of spectral signals. We then approached the question about melanopsin activation eliciting a color percept, discussing studies using the silent substitution method. Finally, we explore various avenues through which ipRGCs might impact color perception indirectly, such as through involvement in peripheral color matching, post-receptoral pathways, color constancy, long-term chromatic adaptation, and chromatic induction. While there is consensus about the role of ipRGCs in brightness perception, confirming its direct contribution to human color perception requires further investigation. We proposed potential approaches for future research, emphasizing the need for empirical validation and methodological thoroughness to elucidate the exact role of ipRGCs in human color vision.

1. Introduction

Color vision initiates in the retina, with spectral selectivity of photoreceptors and opponent mechanisms. In humans, photoreceptor cells consist of cones, rods, and melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs). Human cones are classified into three subtypes (L, M, and S), whose photopigments, expressed in their outer segment, have distinct wavelength sensitivity peaks: ~565 nm (L cones), ~535 nm (M cones), and ~ 419 nm (S cones) (Thoreson & Dacey, 2019). Cone opponency mechanisms consist of L-cone and M−cone signals with opposite signs, and S-cone signals in opposition to L- and M−cone signals. Signals from the retina are conveyed by post-receptoral pathways to several primary visual areas (Hannibal et al., 2014), such as the superior colliculus (SC) in the midbrain and the lateral geniculate nucleus (LGN) in the thalamus. The initial color mechanisms are located in the retina and LGN, however, color perception is built also from processing in different cortical areas (Gegenfurtner, 2003). Although color vision is a well-documented research field, the discovery of melanopsin-expressing ganglion cells has raised the question of whether this photopigment is somehow affecting the perception of color.

In humans, ipRGCs constitute a small group of ganglion cells (<1.5 %) with large somas and dendritic fields (Liao et al., 2016; Nasir-Ahmad et al., 2019). They cover the entire visual field except for the foveal pit (central ~ 1.2 deg), and they are mostly concentrated in the parafoveal region (Dacey et al., 2005). IpRGCs were discovered in mice at the beginning of this century (Berson et al., 2002; Hattar et al., 2002), and in primates, including humans, a few years later (Dacey et al., 2005;

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Hannibal et al., 2004). These cells express the photopigment melanopsin (Provencio et al., 2000). Melanopsin has a peak in the cyan region of the chromatic spectrum (~480 nm). The melanopsin-driven ipRGC response is excitatory and lasts several seconds after light stimulation (Dacey et al., 2005). Afferent signals from rods and cones are conveyed from bipolar and amacrines cells to the ipRGCs (Grünert et al., 2011; Jusuf et al., 2007; Liao et al., 2016). Interestingly, ipRGC responses show cone opponency, suggesting chromatic codification, i.e., wavelength-dependent response changes independent of intensity. IpRGCs have a main role in the photoentrainment of the circadian rhythm (R. G. Foster et al., 2020; Lucas, 2013) and the pupil light reflex (PLR) (Barrionuevo et al., 2023; Kelbsch et al., 2019; Spitschan, 2019b). These cells also affect other physiological functions, including visual perception. IpRGCs projections to brain centers involved in vision (Fig. 1A), the LGN and the SC, were reported in primates (Dacey et al., 2005; Hannibal et al., 2014). Evidence of the influence of ipRGCs in conscious visual perception has accumulated over the years (reviewed by Joyce et al., 2022; Lucas et al., 2020; Spitschan, 2019a). However, their role in human color vision is still up for debate.

To detect optical radiation, our visual system has been shaped by the statistics of the natural environment (Geisler, 2008; Simoncelli & Olshausen, 2001). Melanopsin is a photopigment conserved throughout evolution (Guido et al., 2022) and is strongly linked to development and health (Do, 2019). Therefore, natural image statistics studies could provide clues about how melanopsin can affect visual and non-visual functions.

Since the discovery of ipRGCs in humans, multiple studies have dealt with the intrusion of melanopsin and ipRGCs in color perception, although with uneven findings. In this work, we provide evidence and arguments from physiology, psychophysics, and natural image statistics to discuss the different manners in which ipRGCs can (and could) affect different dimensions of human color vision (Fig. 1B).

2. The role of melanopsin and ipRGCs in vision

There is a growing body of evidence, generated mostly from rodent studies, about the involvement of melanopsin and ipRGCs in visual responses (Lucas et al., 2020; Spitschan, 2019a). Schmidt and colleagues (2014) showed that mice with melanopsin deficits have reduced contrast sensitivity. Also studying mice, Dr. Lucas' group showed that melanopsin activation improves the LGN capacity to codify natural visual information and can serve as an independent irradiance measurement controlling visual adaptation at the retinal level (Allen et al., 2014); also, that a subset of LGN units can detect modest changes in irradiance employing melanopsin signals (Davis et al., 2015); that melanopsin generates information about light intensity change and produce an increment of signal noise ratio for fast visual responses in the dorsal LGN at dawn conditions (Storchi et al., 2015); and that melanopsin is involved in mouse form vision (Allen et al., 2017). These are just a selection of the antecedents suggesting that melanopsin activation can modulate important attributes of visual processing.

In humans, Spitschan and colleagues (2017) demonstrated that a high-contrast melanopsin-directed stimulus produced responses in the visual cortex that couldn't be explained by cone stimulation. Melanopsin intrusion in vision becomes firstly evident from studies of brightness perception as it is explained below. Interestingly, melanopsin in humans

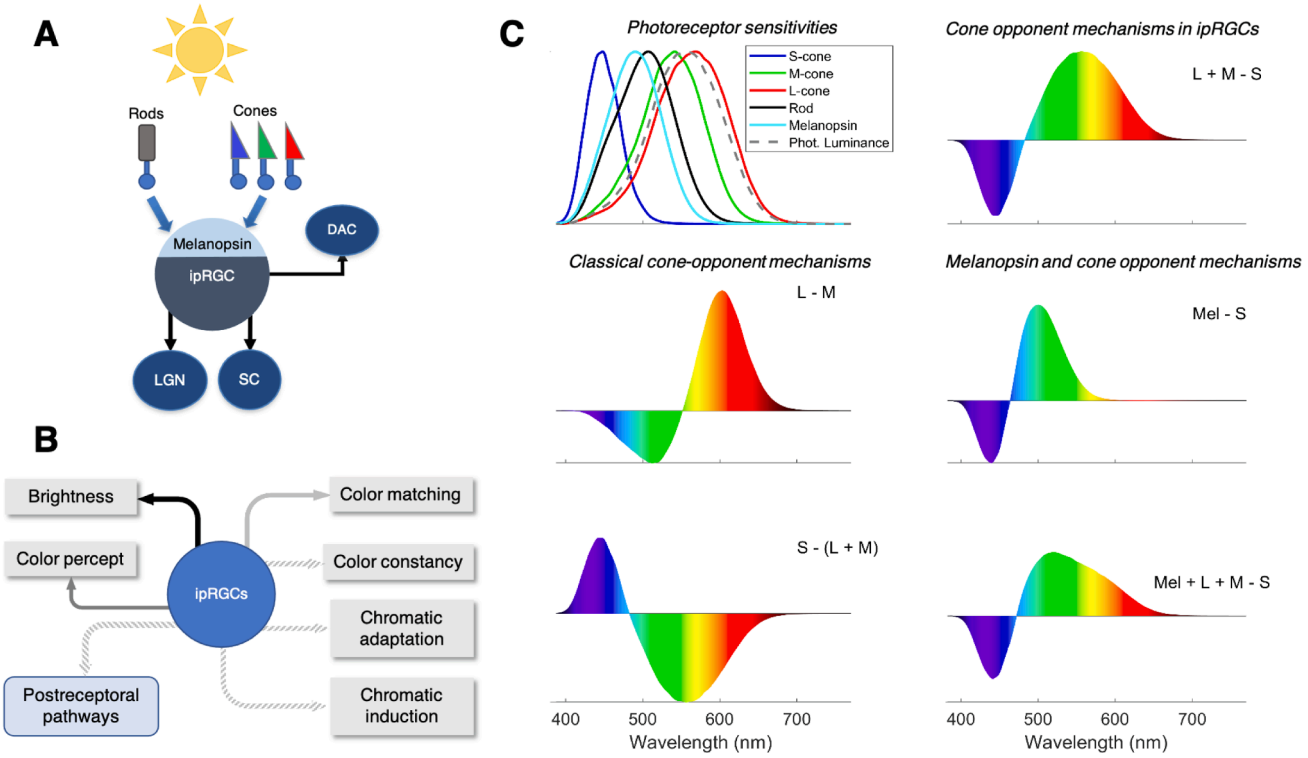

Fig. 1. A) Besides melanopsin photoreception, ipRGCs also receive light information from rods and cones. Efference signals of ipRGCs project to areas affecting vision (LGN and SC) and provide feedback signaling to dopaminergic amacrine cells (DAC). B) Influence of ipRGCs in dimensions of color vision, solid lines show dimensions with scientific evidence, and dashed lines show hypothetical influence (studies about postreceptoral pathways are also included here). C) Photoreceptor sensitivities are shown in the top of the left column, together with photopic luminance, which is based on the addition of L and M cone signals. Classical cone opponency mechanisms consist of L-M (and M−L) to codify "red" vs "green" (actually, "orange" vs "teal") signals, and S-(L+M) to codify "blue" vs "yellow" (actually, "lavender" vs "lime") channel (middle and bottom panels in the left column). The cone-opponent mechanism discovered in M1 ipRGCs is depicted in the top panel of the right column. The inclusion of melanopsin in the M1 ipRGC mechanism will involve sensitivity to signals from shorter wavelengths, hypothetically related to a "green" percept" (middle and bottom panel in the right column). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

was also found to contribute to visual detection and temporal vision (Zele, Feigl, et al., 2018), spatial vision (Allen et al., 2019), and active covert attention (Gnyawali et al., 2022). The effect of melanopsin on these visual functions is not addressed here, the reader can consult other reviews for further information (Joyce et al., 2022; Lucas et al., 2020; Spitschan, 2019a).

3. Codification of spectral signals

Human outer stratifying or M1 ipRGCs show cone opponency via excitatory responses to L- and M−cone inputs and inhibitory responses to S-cone inputs (Dacey et al., 2005). This S-cone OFF input is mediated by an S-cone amacrine cell that receives excitatory inputs from bipolar cells and provides inhibitory signals to ipRGCs (Patterson et al., 2020). This opponency found by Dacey and colleagues has been confirmed in human pupillary measurements (Barrionuevo & Cao, 2016; Cao et al., 2015; Spitschan et al., 2014). A slightly different codification (inhibitory contribution of M−cones) of human pupillary cone opponency was also reported (Murray et al., 2018; Woelders et al., 2018). Since L- and M-cone signals are not differentiated by inner retinal mechanisms (Thoreson & Dacey, 2019), this last codification might not arise from ipRGCs responses. Cone opponency is not particular to human M1 ipRGCs, primate inner stratifying or M2 ipRGCs showed S-cone ON/L+M OFF codification (Patterson et al., 2020), and a subgroup of mice ipRGCs (M5) showed opponent codification of cones (Stabio et al., 2018): these cells project to the LGN and this codification is thought to contribute to mice color vision (Aranda & Schmidt, 2020). In evolutive terms, it was suggested that the need for image-forming retinas has relegated melanopsin-expressing cells to be mostly involved in non-visual functions (Koyanagi et al., 2005). Therefore, the characteristic cone opponency in ipRGCs may have evolved as one of the oldest sensory systems to signal chromatic environmental changes at dawn and dusk (Neitz & Neitz, 2017). However, it has been shown that melatonin suppression was not affected by S-cone activation (Spitschan et al., 2019), and yellow light (instead of blue light) seems to have the most important effect on the mouse circadian system (Mouland et al., 2019). Whether human color vision takes advantage of ipRGC opponency is still unknown. Furthermore, it is important to note that the different kinetics and sensitivity ranges might play an important role regarding the interaction between melanopsin and cone responses. Situations such as extra-foveal, photopic gradual, slow, and sustained stimuli changes favor the interaction between cones and melanopsin as it was evident in the pupil light reflex (Barrionuevo & Cao, 2016; Spitschan et al., 2014).

4. Silent substitution

Most of the studies in humans about how melanopsin is involved in visual perception were carried out using the silent substitution method (Estévez & Spekreijse, 1982). With this technique it is possible to effectively obtain selective photoreceptor-driven differential responses while maintaining the same adaptation for all photoreceptor types. This method relies on the principle of univariance of photopigments (Mitchell & Rushton, 1971). In brief, a spectral change and an intensity change can't be distinguished in the photoreceptor electrical response. This property, together with the partial overlapping nature of photoreceptor sensitivities in the spectral domain, has made it possible to use silent substitution to study photopigments' contribution to vision and PLR (Barrionuevo et al., 2023; Nugent et al., 2023; Spitschan & Woelders, 2018). The number of photoreceptors that can be independently controlled depends on the number of primaries used to generate the stimuli. With four primaries, only four photoreceptors can be controlled. Meanwhile, with five primaries, full silent substitution can be achieved if we consider the three types of cones, rods, and melanopsin. Moreover, while it is feasible to achieve higher maximum contrasts by manipulating four primaries, it's important to note that stimuli generating maximum contrast for rhodopsin or melanopsin will also result in maximum contrast for the remaining uncontrolled photoreceptors (Nugent and Zele, 2022). In this trade-off, several studies have prioritized higher melanopsin contrast using four primaries with stimuli in light levels where rods should be saturated (Adelson, 1982), therefore, not responding to additional stimulation changes (Table 1). However, it was recently shown that flicker detection is affected by rods in higher light levels (Uprety et al., 2022). Additionally, in the context of employing silent substitution to regulate five photoreceptors, the highest achievable contrast directed towards melanopsin (with rods and cones silenced) is contingent on chromaticity (Nugent and Zele, 2022). Therefore, to design melanopsin-directed stimuli effectively avoiding intrusion of the other photoreceptors is technically demanding and susceptible to artifacts. First of all, the silent substitution technique is a computational process that relies on certain conditions, such as linearity, independence, additivity, and alignment of the primaries, which are not always fulfilled in optical systems (Barrionuevo, Preciado, et al., 2022; Preciado et al., 2023). Second, individual variations in prereceptoral filtering, photoreceptor polymorphisms, and retinal blood vessel filtering are not contemplated in the tabulated photoreceptor sensitivities at the corneal level. Therefore, it is usual to find residual stimulation variation in non-directed photoreceptors, also termed "splatter" (Spitschan et al., 2014, 2015, 2017). Here we comment on studies that have conducted controls or have taken measures to avoid potential artifacts, such as choosing spatio-temporal conditions that favor melanopsin stimulation.

5. Is melanopsin activation eliciting a color percept?

This question has been addressed using different approaches. Conscious observations of light appreciation ("brightness") by a patient with total loss of conventional photoreceptors were reported only for stimulation at 481 nm (around the melanopsin sensitivity peak), suggesting a contribution of melanopsin to visual perception (Zaidi et al., 2007). Furthermore, the physiological response in the visual cortex found by Spitschan and colleagues (2017) was accompanied by a visual percept distinct to both cone-directed and radiance changes. They reported a transient percept that rapidly vanishes similar to Troxler fading, and described it as "unpleasant, blurry, minimal brightening of the field". Participants associated the melanopsin-directed stimuli with yellow-orange (17 cases out of 20) or greenish (three cases out of 20) colored appearance (Spitschan et al., 2017). Interestingly, Danilova and Mollon (2022) pointed out that the verbal reports, registered by Spitschan and colleagues, are similar to the "momentary apparent brightening" documented more than half a century ago in photopic extra-foveal color-matching tasks (Brindley, 1960). A recent study found that a melanopsin-rich stimulus reduces the fading in the Troxler effect, suggesting that melanopsin is involved in image persistence (Woelders et al., 2023). Zele and colleagues (2018) quantified the melanopsin experience in terms of equivalent cone signals. Using a five-primary photostimulator (Cao et al., 2015), they found that an increment in combined L- and M-cone signals (cone luminance) together with a decrement in S-cone signals matched the percept of a melanopsin-directed stimulus (Zele, Feigl, et al., 2018). Therefore, suggesting a yellowish percept, which was explicitly reported by two of three subjects in another study with a similar device (Cao et al., 2018). Cao and colleagues (2018) also reported a greenish percept to melanopsin increment for the three participants tested. Allen and colleagues (2019) using complex spatiotemporal stimulation showed that an increment of melanopsin participation in a visual scene has been mostly judged as an increment in brightness with no change in apparent color, consistent with brightness discrimination results (Brown et al., 2012). There is a wide consensus about the direct relationship between brightness perception and melanopsin activation (Allen et al., 2019; Brown et al., 2012; DeLawyer et al., 2020; Spitschan et al., 2017; Yamakawa et al., 2019; Zele, Adhikari, et al., 2018). Instead, discrepancies regarding the chromatic contribution of the melanopsin-driven percept have made

Table 1
Studies that use the silent substitution method and report apparition or absence of a color percept to melanopsin increments.

Study	Melanopsin contrast (%)	Background chromaticity (CIE coordinates)	Background light level	Fundamentals*	Primaries used	Color percept? (participants)	Individual calibration	Rods control
Brown et al., 2012	11	x = 0.351, y = 0.311	356 cd/m^2 (>3556 scot. td)	CIE	4	No change	No	No
Spitschan et al., 2017	400	x = 0.54, y = 0.41	100–200 cd/m^2 (>3.3 log scot. td)	CIE	4	Yellow-orange (17/20), greenish (3/20)	Yes	No
Zele, Feigl et al., 2018	7	x = 0.33, y = 0.33	2000 phot. td (637 cd/m^2)	S&P	5	L+M−S, *inferred subtle yellow*	Yes	Yes
	22	x = 0.4772, y = 0.3234				L+M−S, *inferred yellow*		
	24	x = 0.5553, y = 0.4005				L+M−S, *inferred evident yellow*		
Cao et al., 2018	10.5	x = 0.33, y = 0.33	≥ 2000 phot. td (≥637 cd/m^2)	S&P	5	green (3/3), yellow (2/3)	Yes	Yes
Allen et al., 2019	17–20	x = 0.31, y = 0.33	214 cd/m^2	CIE	4	No change	No	Yes**
Woelders et al., 2023	30	x = 0.58, y = 0.38	210 cd/m^2 (1910 scot. td)	CIE	4	No change	Yes	No

*CIE fundamentals (CIE, 2006) are based on Stockman and Sharpe's work (Stockman & Sharpe, 2000), while Smith and Pokorny's fundamentals (S&P) are widely used in the vision research community (Smith & Pokorny, 1975). **Allen and colleagues discarded rod intrusion based on a grating detection experiment.

these phenomena more controversial (Lucas et al., 2020).

The apparition (or not) of a melanopsin chromatic contribution might be linked to differences in fundamentals, number of primaries, and contrast level (Table 1). Those studies using four primaries, CIE fundamentals (2006), and relatively low contrast, didn't report a color percept (Allen et al., 2019; Brown et al., 2012; Woelders et al., 2018); when contrast was much higher, a "yellow-orange" or "green" percept was elicited (Spitschan et al., 2017). Studies using five primaries and Smith and Pokorny's fundamentals (1975), showed a chromatic component in melanopsin increments, eliciting a green or yellow percept (Cao et al., 2018; Zele, Feigl, et al., 2018). This component is higher with increasing melanopsin contrast (Zele, Feigl, et al., 2018). Considering the visible spectrum, an excitatory contribution of melanopsin to the cone opponent mechanism L+M−ON/S—OFF will incorporate sensitivity to signals that might favor a greener (with a slight yellow) percept than the percept elicited purely by the cone opponent mechanism (Fig. 1C, right column), in agreement with the psychophysical findings listed in Table 1. Although this rationale might seem intuitive, to translate photoreceptor opponency to color appearance must be considered with caution (Conway et al., 2023).

Further studies should assess if a yellow or green percept is elicited exclusively by melanopsin or if the percept is due to residual but significant cone intrusion, since it was advised that penumbral cones might also add a green perceptual component to melanopsin increments (Zele, Feigl, et al., 2018). Studies using four primaries are conducted in light levels where rods are potentially saturated. However, it was shown that rods might be active at photopic light levels (up to 8000 Td) and a high melanopsin contrast stimulus is usually accompanied with a high rod contrast stimulus due to large overlapping for rhodopsin and melanopsin spectral sensitivities (Uprety et al., 2022). Five-primaries devices control for rod intrusion even at high light levels (Barrionuevo, Preciado, et al., 2022; Nugent & Zele, 2022). Therefore, it is possible that unmeant rod activation in four-primary displays could hide melanopsin-mediated color percept. The use of control experiments in conditions where rods are active and melanopsin is not (see for example, Allen et al., 2019), is advisable when using four-primary devices. New studies should address the extent of confounding effects caused by rod-driven responses. Confirmation about cone fundamentals playing a role in potential melanopsin color perception will contribute to the discussions about the validity of different cone fundamentals (Danilova & Mollon, 2022; Smith & Pokorny, 2003; Stockman, 2019). However, it is important to take into account that differences in fundamentals between real observers and the ideal observer are higher than differences between CIE and S&P fundamentals (Uprety et al., 2021). This fact emphasizes the importance of individual calibration and careful instrumentation control to minimize individual differences.

Last but not least, if the melanopsin-driven color percept is confirmed, then, is this perceptual contribution significant in real-world conditions? Does ipRGC chromatic codification provide any advantage? Insensitivity to low light levels, delayed and sustained responses, and large receptive fields of ipRGCs provide a clue about the conditions where melanopsin might contribute to the perception of color. An educated speculation is that color appearance might be slightly affected by melanopsin activation, in visual situations with sustained, photopic, and large extrafoveal stimuli; however, this change in color appearance doesn't seem evident in real-world conditions. It was suggested that classical cone vision might be complemented by the ipRGC opponency to bring an ecological advantage to color vision due to stable and long-lasting signaling in opposition to transient cone signals (Zele, Feigl, et al., 2018). Furthermore, these cells might help to build a coherent and fluid perception of the visual scene, since they contribute to image persistence (Woelders et al., 2023). In a world in constant movement with central/detailed vision dominance, the crucial role of a sensory system that codifies intense, steady, and broad signals might be overlooked. The role of ipRGC chromatic codification in natural-driven vision has not been explored so far and constitutes an open question.

6. Other sources for possible melanopsin effect on color perception

Melanopsin could also influence color perception in an indirect manner via modulation, adaptation, or induction. Besides the ipRGCs projection to the LGN, a unique characteristic of these cells is to provide feedback to the dopaminergic-amacrine cells in the retina (Fig. 1A), which, in turn, are involved in light adaptation (Zhang et al., 2008). Considering that ipRGCs cover the entire extra-foveal visual field in a mosaic arrangement (Jusuf et al., 2007), and have spectral opponent characteristics (Dacey et al., 2005), ipRGCs might provide chromatic global environmental information. Furthermore, the evidence of melanopsin's influence on photopic sustained brightness perception might affect the comparison of stimulus appearances. Below, we summarized studies and hypotheses that arise when considering the physiological and psychophysical substrate.

6.1. *Involvement in peripheral color matching*

The trichromacy of human color vision is based on the activation of the three types of cones. It states that at photopic light levels, any light

can be color-matched by mixing three spectrally different lights, called primaries. Any of these primaries can't be metameric to the combination of the other two. Color-matching functions (CMFs) represent the relative contributions of the primaries to match monochromatic test lights in the visible spectrum (Brainard & Stockman, 2010; Smith & Pokorny, 2003). However, trichromacy theory seems to fail in the periphery suggesting that a fourth photopigment could be involved in peripheral color vision (Horiguchi et al., 2013). Suggestions of melanopsin intrusion in classical color-matching experiments came from two different sources. Danilova and Mollon (2022) have rescued, translated, and commented on a study from 1956 by Mikhail Bongard and Mikhail Smirnov written originally in Russian (Smirnov & Bongard, 1956). Smirnov and Bongard reported that for extra-foveal vision four primaries were needed to exactly match two successive targets in appearance, which in turn suggest that, besides the three types of cones, a fourth photoreceptor type was involved in the matching. Danilova and Mollon, after analyzing the experimental conditions and associated reports, open the possibility of considering melanopsin photoreception instead of rods as this fourth photoreceptor type (Danilova & Mollon, 2022). Simultaneously, Barrionuevo and colleagues (2022) have reported that differences between extrafoveal and foveal photopic successive color matches cannot be explained completely by intraocular filtering as suggested previously (Stockman, 2019) or by rod intrusion (Trezona, 1970). Also, through statistical analysis performed on existing cone fundamentals, they found that the inclusion of melanopsin can better explain the differences between 2° and 10° S-cone fundamentals (Barrionuevo, Filgueira, et al., 2022). However, a recent study has found no effect on color matching regarding melanopsin intrusion (Woelders et al., 2023). Since color matching functions reflect the dimensions of color vision, further confirmation or refutation of melanopsin intrusion in these functions will be valuable for studying aspects of color in nature. In natural environments there is an important contribution of extra-foveal signals; therefore, colorimetry might need to be updated to consider tetra-chromaticity in extra-foveal full and large field stimuli.

6.2. Intrusion in post-receptoral pathways

Three main post-receptoral pathways convey cone visual information from the parasol, midget, and bistratified retinal ganglion cells to the magno-, parvo- and konio-cellular layers of the LGN, respectively (Barrionuevo et al., 2023). The first pathway consists of diffuse bipolar cells and parasol ganglion cells combining additive cone signals to mediate most of the luminance information and motion perception (Dacey, 2000; Lee, 2011). The second pathway includes midget bipolar cells and midget ganglion cells, combining L-cone and M-cone signals with opposite signs, therefore mediating chromatic perception, but also responding to achromatic stimuli (Dacey, 2000; Lee, 2011); this pathway is related to detail vision. Finally, the third pathway involves S-cone bipolar cells and small bistratified ganglion cells, combining excitatory S-cone signals with inhibitory L- and M-cone signals (Lee, 2011).

The evolution of these major post-receptoral pathways is believed to be influenced by the statistical properties of the natural visual environment (Geisler, 2008; Simoncelli & Olshausen, 2001). Principal component analysis (PCA) conducted on cone pigment excitations from natural images revealed three principal components that align well with cone combinations in the three post-receptoral pathways, i.e., L+M+S, S-(L+M), and ±L∓M (Barrionuevo & Cao, 2014; Ruderman et al., 1998).

Barrionuevo and Cao (2014) studied the contributions of rhodopsin (R), cone opsins, and melanopsin (Mel) to different post-receptoral pathways, investigating their optimal combinations based on PCA of natural images. The findings suggested that melanopsin may play a role in post-receptoral pathways (Barrionuevo & Cao, 2014). The first component represented the sum of all photoresponses (i.e., L+M+S+R+Mel), accounting for over 97 % of the variance. This is reasonable since changes in achromatic reflectance constitute the majority of information in the visual environment. The other minority principal components showed melanopsin contributions to opponent mechanisms (S+Mel-L-M, L+S-R-Mel, M+S+R–L–Mel, and L+R-M-Mel), suggesting contributions to chromatic codification (Barrionuevo & Cao, 2014).

6.3. Contribution to color constancy

Due to its characteristics, ipRGCs represent an ideal candidate to contribute to color constancy in natural environments (Barrionuevo & Cao, 2019; Garside, 2019). Color constancy refers to our ability to perceive relatively stable colors of objects despite changes in illumination (D. H. Foster, 2011; Witzel & Gegenfurtner, 2018), and it plays a crucial role in providing information about object properties (Brainard & Radonjić, 2014). Explanations of color constancy involve cognitive, sensory, and computational components (Smithson, 2005), suggesting that it is a multistage visual process. From an evolutive perspective, discounting illuminant changes in natural environments becomes important, as constancy is more effectively achieved under natural rather than artificial illumination (Lucassen & Walraven, 1996). This is particularly important considering the rapid development of solid-state technologies (Hurlbert, 2019). Calibration of cone signals to achieve color constancy is usually computationally implemented from the same photoreceptor-type signaling (Luo & Pointer, 2018). This implementation possesses a "circularity in self-calibration" problem (Garside, 2019). Therefore, an independent radiant information source, such as ipRGCs, might be helpful in color constancy. IpRGCs appear as a good candidate, since these cells have photon counting properties and low temporal and spatial resolution properties (Allen et al., 2019; Dacey et al., 2005; Zele, Feigl, et al., 2018). For high CCT illuminants, better color constancy would require a positive contribution of melanopsin to the small-bistratified pathway [S-(L+M)] and a negative contribution to the midget pathway (L-M), while the opposite holds true for low CCT illuminants, either considering a D65 Illuminant or an Equal Energy Spectrum illuminant as the reference (Fig. 2). Furthermore, when compared with commonly used color constancy algorithms, the inclusion of melanopsin has provided a better approximation in natural scenarios (Garside, 2019). These natural image studies suggest that melanopsin aids in achieving color constancy, however to our knowledge these hints were not confirmed or refuted by testing in humans.

6.4. Participation in long-term chromatic adaptation

Climate and seasons alter vegetation, from plant blossoms in spring to leaf drying in autumn or phenomena like snow in winter and bright sunlight in summer, all of which greatly impact the visual environment. Has the visual system developed strategies to react to these chromatic nature-induced changes? Some aspects of color vision are influenced by the colors of the habitat and the environment in which humans have evolved (Webster et al., 2007). The colors we perceive are relative to various factors, one of them being chromatic adaptation, a mechanism through which the sensitivity of the visual system is constantly adjusted according to the average luminosity or chromaticity of the environment (Webster, 1996). Receptor and post-receptoral signals can be optimized to better represent color contrast in natural scenes to the identification of various elements of the environment, such as identifying a reddish apple on green grass (Dominy & Lucas, 2001; Mollon, 1989; Osorio & Vorobyev, 2008; Regan et al., 2001). Long-term chromatic adaptation (occurring over several days) has been demonstrated in humans. Neitz and colleagues showed that adaptation for only four hours per day to goggles with colored filters, affects color vision, as measured by Unique Yellow setting, for several weeks after filter removal (Neitz et al., 2002). Also, a significant effect was found by long-term exposure to a CRT screen with a chromatic pattern (Belmore & Shevell, 2008). Similarly, removal of cataracts increases bluish percept and this effect can last up

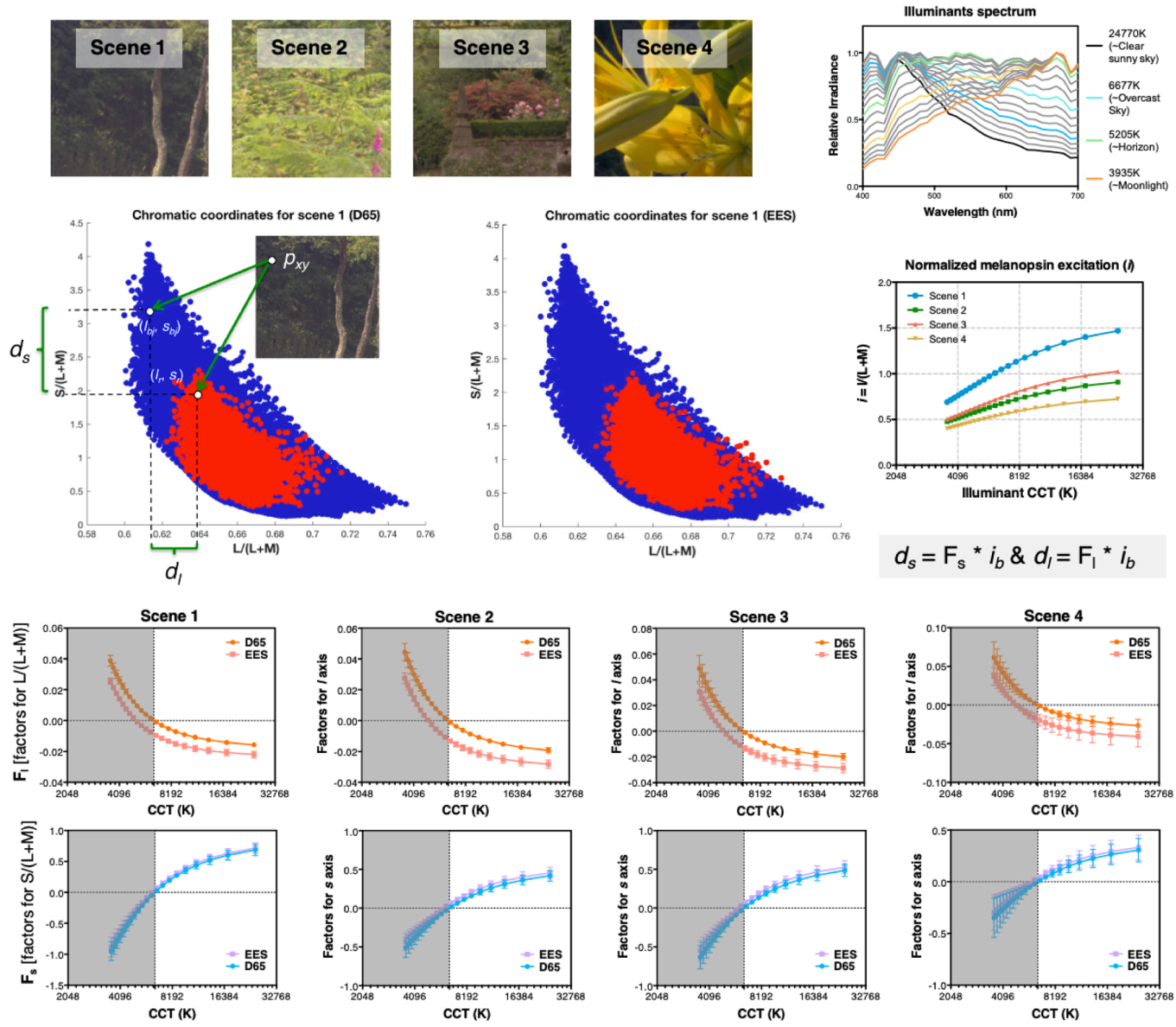

Fig. 2. Hypothetical melanopsin contribution to achieve color constancy in natural environments. Using hyperspectral natural scenes (D. H. Foster et al., 2006), and illuminants representing different day phases (Linhares & Nascimento, 2012; Wyszecki & Stiles, 2000) (top of the figure), excitations of each cone type (L, M, S) and melanopsin (I) were computed (panels in the second row). Blue dots represent chromaticities for all illuminants computed by the reflectance of each pixel. Red dots represent chromaticities computed considering only one illuminant, D65 or EES. The intrusion of melanopsin in inferred PC and KC pathways [l = L/(L+M) and s = S/(L+M), respectively] was computed based on the distances (d) in the chromatic cone space (Macleod & Boynton, 1979), between each daylight illuminant and a reference illuminant (EES or D65). Factors for l and s were obtained relating d to melanopsin excitation: $d_s = F_s * i_b$ and $d_l = F_l * i_b$. Factors for D65 and EES illuminants as references are shown in the bottom two row panels. Panels contain factor values for L/(L+M) and S/(L+M). Error bars are standard deviations. Data originally shown in Barrionuevo & Cao (2019) and reproduced with permission. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

to three months (Delahunt et al., 2004). Furthermore, color perception varies across ecosystems and with seasonal changes (Webster, 2015; Welbourne et al., 2015). The perceptual shift caused by the long-term chromatic adaptation was attributed to different weightings in the mechanisms of cone opponency in postreceptoral pathways, particularly in the L vs. M system (Neitz et al., 2002). It has been suggested that the melanopsin excitation level changes the equilibrium point of the L vs. M chromatic system (Cao et al., 2018), a phenomenon that is similar to the color vision shift observed across seasons (Welbourne et al., 2015) or through manipulation of pre-ocular light filtering (colored goggles). Studies about retinal circuitry modulation (adaptation) suggest the involvement of melanopsin expression driven by changes in light exposure, and melanopsin activation improves the LGN capacity to encode natural visual information and to work as an independent irradiance measurement to control visual adaptation in retinal level (Allen et al., 2014). Also, emergent studies in humans found a relationship between melanopsin excitation and both temporal (Zele et al., 2019) and spatial (Chien et al., 2023) contrast sensitivity, which is evidence of the role of ipRGCs to modify intra-retinal cone-driven adaptation. Therefore, ipRGCs could work as a link between environmental optical radiation and chromatic adaptation. A possible hypothesis is that alteration of chromaticities in the visual environment modulates the weightings of cone opponency mechanisms via variations in melanopsin excitation. However, this speculation has not been tested yet.

6.5. Engagement in chromatic induction

Since ipRGCs cover the extra-foveal visual field, have feedback to amacrine cells, and project to the LGN, it makes sense to think that foveal stimuli might be affected by lateral interaction with melanopsin signals. DeLawyer and Shinomori (2023) tested this hypothesis based on the effect of melanopsin in the equilibrium point of L vs M signals (Cao et al., 2018). An increment in surrounding melanopsin activation produced a green tinge of a yellow central patch (DeLawyer & Shinomori, 2023). However, this color induction to foveal targets from surrounding melanopsin signaling increments was not higher than individual variations and individual pre-receptoral differences were not corrected. Corroboration of these results in nature-driven melanopsin contrasts might have a great impact on the field, since previous studies only deal with effects in peripheral vision.

7. Conclusions

The discovery of ipRGCs is reshaping our understanding of how optical radiation is processed by visual centers. In this mini-review, we summarized evidence and hypotheses about the direct and indirect effects of melanopsin-expressing ipRGCs on color perception, a new field of research due to the recent development of multi-primary devices that allows this study in humans (Barrionuevo, Preciado, et al., 2022; Nugent & Zele, 2022).

Color perception may be affected by the physiological and anatomical characteristics of ipRGCs. These cells in humans include a spectral opponency mechanism (Dacey et al., 2005), conveying excitatory signals of melanopsin, L- and M-cones in opposition to S-cones signals. Therefore, their responses provide a chromatic codification that might contribute directly or indirectly to the perception of color. Furthermore, it is thought that these cells can provide steady and prolonged information about the scene that might complement the transient rod and cone responses. How and where this interaction occurs is currently unknown (Aguirre, 2024).

Natural image statistics revealed a positive contribution to rods and cones (Barrionuevo & Cao, 2014). This codification explains most of the variance in natural scenes, suggesting a contribution to brightness estimation. This result is in agreement with the consensus about brightness enhancement elicited by melanopsin increments. A chromatic visual experience is more controversial (Lucas et al., 2020). The predicted melanopsin percept of the ipRGC mechanism (green-yellowish) has been found psychophysically for some studies but not for all. Contrast level, fundamentals election, and unmeant rods contribution might play a role in the elicitation of a color percept, but the role of these factors constitute an open question.

Due to the sluggishness, receptive field properties, and photon counting characteristics of ipRGC responses, these cells might affect visual perception through the modulation of cone signals. Natural image studies have dealt with this possibility evaluating color constancy and generating hypotheses of this involvement. Here, we also propose that long-term chromatic adaptation to visual environments and seasons might be mediated by ipRGCs. Furthermore, these stable and long-lasting characteristics might place ipRGCs chromatic codification as a complement to the transient cone-driven color perception (Zele, Feigl, et al., 2018). However, a direct contribution of melanopsin to global color perception might be small due to constant eye movements in real-world conditions. Still, testing in humans is missing to confirm or refute these hypotheses.

Particular characteristics of ipRGC behavior pose challenges to the previously mentioned potential roles in color vision. For example, it has been recently mentioned in primates that all ipRGCs are not responding to the whole range of light intensities. Instead, different subsets of M1 ipRGCs respond to different intensity ranges, limited by depolarization block (Liu et al., 2023; Milner & Do, 2017). This might affect a constant representation of ambient light across the visual field. However, if the cells in these subsets are not clustered but randomly distributed, the responses of the cells might complement each other to give information across the visual field.

Another feature of mice and primates M1 ipRGCs is the tristable nature of melanopsin photopigment, with two active states and one silent state that have different spectral profiles (Emanuel & Do, 2015; Liu et al., 2023). First of all, this tristability could affect silent substitution; however, no effect on this technique has been identified so far (Lucas et al., 2014). Second, it was found in *ex vivo* studies that a red light shuts off the sustained melanopsin activation elicited by blue-rich light (Emanuel & Do, 2015; Liu et al., 2023); however, this finding was not investigated so far in living humans with normal ipRGC function.

Since the discovery of ipRGCs, comprehension of their role in non-image-forming functions has advanced promptly. In the vision field, agreement was achieved about their contribution to brightness perception; however, whether they play a role in other dimensions of color perception waits to be discovered.

CRediT authorship contribution statement

Pablo A. Barrionuevo: Writing – original draft, Investigation, Funding acquisition, Formal analysis, Data curation. **María L. Sandoval Salinas:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **José M. Fanchini:** Writing – original draft, Investigation, Data curation.

Data availability

No data was used for the research described in the article.

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