Neurobiological hypothesis of color appearance and hue perception

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De Valois and De Valois [Vis. Res. **33**, 1053 (1993)] showed that to explain hue appearance, S-cone signals have to be combined with M versus L opponent signals in two different ways to produce red–green and yellow–blue axes, respectively. Recently, it has been shown that color appearance is normal for individuals with genetic mutations that block S-cone input to blue-ON ganglion cells. This is inconsistent with the De Valois hypothesis in which S-opponent konio-geniculate signals are combined with L-M signals at a third processing stage in cortex. Instead, here we show that color appearance, including individual differences never explained before, are predicted by a model in which S-cone signals are combined with L versus M signals in the outer retina.

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1. INTRODUCTION

The theory of color opponency maintains that primate trichromacy arises through the comparison of two dichromatic systems, red versus green (RG) and blue versus yellow (BY) [1,2]. The existence of four unique hues, red, green, blue, and yellow, occurring at the spectral neutral points of these two systems is a corollary prediction of opponency; consequently, determining the spectral positions of unique hues has received considerable attention in color science.

Across populations of color normal individuals the spectral position of uncontaminated hues exhibit substantial intersubject variability (for review see [3]). The most notable variation occurs with unique green, which can deviate as much as 65 nm between individuals [4–8]. A complete neurobiological explanation of color appearance must, therefore, specify the neurons and pathways responsible for hue perception, accurately predict the wavelength of each unique hue, while simultaneously explaining the variability between observers. Such an account has never been developed [3,9].

Hering [10] originally proposed opposing pairs of BY and RG processes as an alternative to trichromatic theory. Later, von Kries [11] proposed the possible resolution that trichromacy could be valid at the receptor level, while opponent processing might apply to a higher level of neural processing. Zone theories with multiple processes at higher stages were developed and elaborated by several people including Schrödinger (1925), Müller [12], and Judd [13]. Hurvich and Jameson [1] successfully formulated theoretical equations to describe the relationship between the cone inputs and opponent processes that could reasonably fit measures of chromatic-opponent response functions from a hue cancellation task, thus providing quantitative empirical support for multiprocess theories. The questions that have remained concern the underlying physiological processes responsible for opponent hue perception. Addressed here are the neurobiological postreceptoral mechanisms underlying specifically hue perception, the aspect of color in which stimuli are classified as red, blue, green, or yellow.

The current ideas of the neurobiological basis for hue perception have focused on the small bistratified ganglion cells that receive S-(M + L) cone input as the retinal origin of the BY channel, while midget ganglion cells with opponent interaction between L-M cones are believed to be the retinal origin of the RG channel. If hue perception is based on retinal small bistratified S-(L + M) cells and L-M and M-L midget ganglion cells, then our perceptions should be predictable from the responses of those cells. However, in fact, there are conspicuous differences between human hue perception and what is predicted from the responses of S versus (L + M) and L versus M cells.

The standard model in which midget L versus M and small bistratified ganglion cells are assumed to form the physiological basis of hue perception grew out of a proposal by De Valois *et al.* [14] that spectrally opponent neurons in the LGN could account for human hue perception. Nonetheless, later, De Valois and De Valois [15] wrote that from early on they were aware of a large contradiction at shorter wavelengths between human hue appearance and LGN cell responses, which the group made note of in their 1966 paper. The problem is that M-L midget ganglion cells, which have been hypothesized to be the substrate for perception of green, fire vigorously to wavelengths below 475 nm. For example, for a 470 nm light, the putative "green-ON" ganglion cells typically have response amplitudes (in spikes/s) of about 80% of peak. Yet, normal human observers do not perceive any greenness in 470 nm lights. A similarly glaring problem exists for the sensation of red. "Red-ON" L-M cells, which are putatively responsible for the sensation of redness, increase firing for

wavelengths longer than about 580 nm. This predicts that long wavelengths should be the only spectral region where redness is perceived; however, this is not the case. Red sensations "reemerge" at short wavelengths below about 470–480 nm and wavelengths below about 440 nm evoke nearly equal red and blue sensations; however, the "red-ON" L-M midget ganglion cells of the standard model do not respond to short wavelengths.

De Valois and De Valois [15] point out how the standard model disagrees with experiment in terms of the appearance of hue in color space. The angular direction of the L versus M chromatic axis is not along either the red–green or the blue–yellow unique hue axis, but is roughly in-between them, along an orange–cyan chromatic axis. They had the profound insight that color experience can only be explained by opponent mechanisms in which S-cone signals modulate the L versus M opponent interactions in two different ways. First, adding S signals to the L-cone side of an L versus M opponent process produces (S + L) versus M opponency rotating the axis so it corresponds with the RG direction in color space. Second, adding S-cone signals to the M-cone side of an L versus M opponent process produces (S + M) versus L opponency rotating the axis so it corresponds with the BY direction in color space. Thus, M versus L opponency is not just the main contributor to the RG system, but to both the RG and the YB systems. So ultimately, for example, the M not the S, cones provide the primary contribution to the blue signal (especially for wavelengths above 460 nm). The discrepancy in the sign of the M contribution to blueness has become well recognized in the psychophysical literature [9,16–20]; however, the problem is often ignored in accounts of the neurobiological basis of hue perception that have emphasized the S-(M + L) small bistratified ganglion cells as the basis for hue perception.

The persistence of the standard model in spite of being inconsistent with the experimental facts of human hue perception is probably partially because the sensation of yellow based on the summed activity of M + L cones is more intuitive than yellow perceptions based on L-cones opposed to S + M. Moreover, the small bistratified ganglion cell with S-(L + M) cone inputs matches the configuration of cone inputs in models proposed by Müller [12], Judd [13], and Hurvich and Jameson [1]. Perhaps even more importantly, the classical study defining the cardinal directions of color space [21] found that psychophysical detection of thresholds using an adaptation paradigm matched ganglion cell physiology not only for the L versus M opponent mechanism but for detection involving an S-(L + M) opponent system. Vision scientists have had much more confidence in measurements of detection threshold as representing a physiological reality than measures of hue appearance, which are more subjective. Nonetheless, the analysis presented here is based on the premise that the question of whether or not hue perception, and specifically, the spectral locations of unique hues have neurobiological basis can be addressed scientifically by experiment. We argue that if a neurobiological hypothesis explains and accurately predicts what hues are seen, including biological correlates of individual differences, it can be taken as evidence that hue perception has a legitimate biological basis.

The standard model in which L versus M midget and small bistratified ganglion cells are the direct physiological substrates for the RG and BY hue channels neither explains nor predicts peoples hue experience. As Richard Feynman famously said in his lecture on the scientific method at Cornell University in 1964, if a model "disagrees with experiment, its wrong. In that simple statement is the key to science." Thus, the standard model is wrong with respect to explaining hue experience. However, rather than coming up with an entirely new model when a compelling theory has become widely accepted but proven wrong by experiment, it is natural to try to modify the model in an attempt to rescue it. The De Valois and De Valois [15] insight that the L versus M axis can be rotated appropriately to form the RG and BY axes by the addition of S-cone signals to L- or M-center opponent signals, respectively, offered a logical revision to the standard model. The revision required only additional stages localized in the cortex in which S-ON signals originating in the small bistratified ganglion cells of the retina are combined with M versus L signals of the midget ganglion cells. However, *ad hoc* revisions often add complexity and are susceptible to the addition of unknown and therefore untestable entities. The weakness in the serial model proposed by De Valois is that the transformations theorized to occur in the cortex are not based on any known circuitry. Cortical cells with input from all three cone types arranged as required to account for hue perception have been demonstrated [22,23], but the locus where they are combined is not known and the relative weights of the three cone inputs cannot be predicted from the theory.

The De Valois and De Valois [15] theory holds that S-cone signals from the small bistratified ganglion cells are required to rotate the L-M axis to the RG and BY axes. That prediction can be evaluated by examining hue appearance in individuals that have mutations in genes encoding the glutamate receptor, mGluR6, responsible for signaling between the S-cones and the blue cone bipolar cells [24]. Glutamate released by cones produces a hyperpolarizing synaptic potential in on-bipolar cells by binding to the metabotropic glutamate receptor mGluR6 [25]. In people who have inactivating mutations in the GRM6 gene there is no direct feed-forward communication between S-cones and S-cone bipolar cells. This, in turn, interrupts feed-forward of S-cone signals to the small bistratified cells. Thus, the De Valois and De Valois theory predicts that individuals who lack S-cone inputs to small bistratified cells should base their hue perceptions on a single, unrotated, L versus M axis. In individuals with gene mutations that render mGluR6 nonfunctional, the loss of direct feed-forward photoreceptor-to-on-bipolar signaling can be clearly demonstrated by the absence of the ERG b-wave [26,27]. Individuals with these mutations also manifest complete autosomal recessive congenital stationary night blindness (ARCSNB) resulting from the loss of synaptic transmission between rods and rod on-bipolar cells. However, despite the synaptic defect, the best visual acuities are nearly normal (20/15–20/40) and people with this form of complete CSNB have normal hue perception for central vision [26,28,29]. De Valois and De Valois postulated that S-cone signals via the small bistratified cells are required for both normal BY and RG hue perception, but neither are disturbed when S-cone transmission to the small bistratified cell is blocked. The hypothesis of a cortical locus of S-cone signals from small bistratified cells being combined with L versus M opponent signals to produce the RG and BY hue axes does not appear to be borne out by experiment.

In summary, predictions of both the standard model in which hue perception is based on L versus M midget and small bistratified ganglion cells or a revision of it where S-cone signals from small bistratified cells are combined with L versus M signals in the cortex are not consistent with experimental findings. Here, we examine an alternative to the standard hypothesis that is compatible with the finding of unaltered hue perception in individuals with mGluR6 mutations. S-, M-, and L-cone signals are known to be combined in the H2 horizontal cells of the outer retina. Earlier, it was proposed that H2 horizontal cells could be the basis for a subset of midget ganglion cells having (S + L) versus M and (S + M) versus L inputs required to explain hue perception. We have proposed that S-cone feedback to a subset of L- and M-cones would rotate the color axes of a small subset of L versus M midget ganglion cells as required by De Valois and De Valois [30,31]. According to this hypothesis, neurons with the combinations of cone inputs required for hue perception arise in the retina, not in the cortex. H2 horizontal cells may also employ a signaling pathway, originally described in rodents [32,33], using GABA (gamma-aminobutyric acid) to send feed-forward signals directly to bipolar cells [34–36]. In macaque retina, the molecular components of this putative feed-forward pathway are highly enriched beneath S-cones and they colocalize with a marker for H2 horizontal cells. The enrichment at S-cones was not observed in either mouse or ground squirrel indicating this specialization may have evolved in the primate lineage specifically for hue perception. This feed-forward pathway is an even more likely candidate than horizontal cell feedback because it provides a mechanism whereby S-ON and S-OFF signals could be injected directly into midget bipolar cells carrying L vesus M opponent signals. The midget system has been greatly expanded in primates and it predominately projects to the ventral visual stream. The elaboration of this feed-forward system may have been an important step in the evolution of color processing associated with the ventral occipitotemporal cortex, which is related to the conscious perception of hue and not well developed in other mammals. These GABA mediated signals bypass the cone-to-bipolar glutamatergic synapse so S-cone signals in this putative pathway would be unaffected in people with mGluR6 mutations, explaining their normal hue perception.

It is clear that the majority of M versus L ganglion cells do not receive any significant amount of S-cone input (e.g., Sun *et al.* [37]). However, the theory requires only a small subset of midget ganglion cells to carry S-cone signals to account for hue perception. Recordings from large samples of cells in LGN have identified a group of cells, about equal in number to S-(M + L) cells, that have input from M-cones with the same sign as S-cones, i.e., they are (S + M)-L cells as required by the proposed retinal locus for hue perception [38]. Because the only cells in the retina known to carry opponent signals from M versus L cones are midget ganglion cells, this second class of blue sensitive cells appears to reflect the existence of a small subclass of midget ganglion cells that could be the substrate for the blue side of the perceptual BY hue opponent system. Tailby *et al.* [38] found the chromatic properties of S-OFF cells in the LGN to be heterogeneous, and one population had L-(S + M) inputs as required for the yellow side of BY hue opponency and predicted by the hypothesis that S-OFF signals may be injected directly into midget bipolar cells by GABA mediated feed-forward. Cells with the required cone inputs were also reported in the retina in the classical studies of de Monasterio and co-workers [39,40]. Although, in their studies, beta-band absorption of L-cones was found to mimic S-cone input [41], chromatic adaptation could be used to distinguish responses mediated by S-cones from those mediated by beta-band absorption of L-cones, revealing a small subset of ganglion cell receiving (S + L) versus M and (S + M) versus L inputs.

The theory that the opponent interactions in the arrangement proposed by De Valois occur within the retina greatly simplifies the mechanisms of color appearance. The current work develops this theory and tests its predictions against established observations of hue experience. We focus, in particular, on unique green because it has proven particularly challenging to explain with previous neurobiological or perceptual models.

2. METHODS

A. Constructing a Color Space

Color spaces, such as the CIE *rgb* space, derived from color-matching functions are, by design, organized such that the percepts associated with monochromatic lights fall on the perimeter of the space. All points within the space are, therefore, associated with colors elicited by all spectra other than monochromatic stimuli. This mathematical formalism offers a precise and economical way of representing color in a three-dimensional coordinate system.

A trichromatic color space was derived from a set of known spectral sensitivity functions [42], with peak sensitivities of 559, 530, and 419 nm for L, M, and S pigments, respectively. Correction for photoreceptor optical density and lens and macular filtering were introduced according to [43], creating $l(\lambda)$, $m(\lambda)$, $s(\lambda)$ fundamentals. Color-matching functions, $R(\lambda)$, $G(\lambda)$, $B(\lambda)$, were then derived through Grassman's law,

$$\begin{bmatrix} l_r & l_g & l_b \\ m_r & m_g & m_b \\ s_r & s_g & s_b \end{bmatrix}^{-1} \begin{bmatrix} l(\lambda) \\ m(\lambda) \\ s(\lambda) \end{bmatrix} = \begin{bmatrix} R(\lambda) \\ G(\lambda) \\ B(\lambda) \end{bmatrix}, \tag{1}$$

where $l_r \ldots$ represent the sensitivity of the corrected photopigments to each of the lights that define the color space, here 650, 530, and 460 nm. To ensure that equal energy white falls at (1/3, 1/3, 1/3) in the space, the color-matching functions were normalized to integrate to 1 across the visible spectrum. Finally, $R(\lambda)$, $G(\lambda)$, $B(\lambda)$ were transformed into *rgb* space with the usual equations [44]:

$$r = \frac{R}{R+G+B}, \qquad g = \frac{G}{R+G+B}, \qquad b = \frac{B}{R+G+B}. \tag{2}$$

The Cartesian location of the copunctual point, **b**, of any dichromatic system within the *rgb* space can be found through matrix multiplication:

$$A\mathbf{x} = \mathbf{b}, \tag{3}$$

where A is the system matrix from Eq. (1) (left most matrix), and $\mathbf{x}$ is a 3×1 vector indicating the absent dimension. For

example, the tritan copunctual point can be found with Eq. (3) when $\mathbf{x} = (0 \quad 0 \quad 1)^T$. The location of a more complex dichromatic system, such as S-(L + M), can be obtained if the same principle is applied with the weights of the L and M inputs after they have been normalized to sum to 1, $\mathbf{x} = (0.75 \quad -0.25 \quad 0)^T$. Note, the weight of the M-cones must be made negative.

B. Model

1. Phototransduction

The sensors responsible for the absorption of photons are known to be the three classes of cone photoreceptors. Since the cone opsin sequences were first reported by Nathans *et al.* [45], a class of L and M opsins, differing each by as few as a single nucleotide, have been identified with distinct peak sensitivities [46] (see [31] for review). To incorporate these normal shifts in peak absorption, we used sensitivity functions that include a parameter for peak sensitivity [42], allowing us to assess the impact of this variability on hue perception. To complete the first step in hue processing (Fig. 1), the spectral sensitivity functions are corrected for optical filtering [43]. Intersubject variability in lens and macula filtering are not considered here, but are expected to play a role. In particular, the lens is known to increase in optical filtering as a function of age [47]. Photopigment optical densities were assumed to be 0.4, 0.38, and 0.33 for LMS cones. Variability in optical density has been observed to modulate color appearance [48], the impact of this variability on the model is considered in Discussion section.

2. Cone Opponency

After phototransduction, the second step in processing (Fig. 2), is hypothesized to take place in the midget system. Here, feed-forward input from cones is expected to be combined with input from horizontal cells, creating cone opponent signals aligned with the unique hue axes. This transformation of information differs most significantly from the De Valois model, in which the final combination of cone signals required to explain hue perception was assumed to occur at a higher level [15]. Instead, we propose that hue perception is mediated exclusively by a small subset of midget ganglion cells in which central L- or M-cones are adjacent to S-cones and there is sufficient interconnection via H2 horizontal cells to introduce significant S-cone input. In this scenario S signals feed through H2 horizontal cells, producing L versus (S + M) and M versus (S + L) interactions at the level of the bipolar cells. Support for opponency in the outer retina has been observed experimentally in recordings from S-cones [49] and H2 horizontal cells [50], which carry S, M, and L signals.

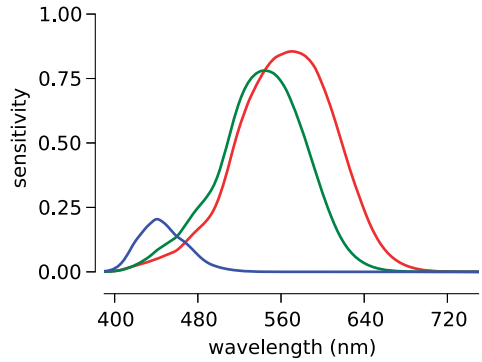

Fig. 1. Cone fundamentals. Spectral sensitivity functions with peaks of 559, 529, and 519 nm were corrected for lens and macular filtering to produce the curves shown here.

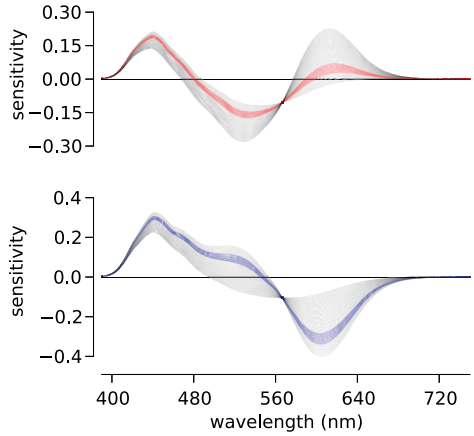

Fig. 2. Family of sensitivity curves produced by the RG and BY mechanisms. Each curve represents a different value for l in Eq. (4). Highlighted in red and blue are the most probable curves in a retina with an L:(L + M) cone ratio of 0.75. The upper plot are the predicted sensitivity curves for the RG mechanism and the lower for BY.

In the central retina there are four types of midget bipolar cell/cone combinations. The cones are either L or M and the bipolar cells are either ON or OFF cells. In each case, the S-cone inputs are sign reversed compared to the direct feed-forward from cone to bipolar cell. In other words, OFF bipolar cells receive S-ON input and ON bipolar cells receive S-OFF input via the H2 horizontal cells. Thus, we propose S-cone input transforms the analogous four types of midget ganglion cells into four lines transmitting the four hue sensations, yellow, blue, green, and red, respectively. A significant difference between this model and all other previous models is that hue mechanisms are specifically associated with ON versus OFF bipolar cells, with yellow and green associated with ON bipolar cells and red and blue hue sensations associated with OFF bipolar cells, as shown in Table 1.

For simplicity, here the pair of mechanisms, blue and yellow, are taken to be the inverse of each other, so mathematically the BY system is treated as a single entity. The same is true of the RG system. However, physiologically we propose discrete mechanisms for each of the four hues as given above. We presume that each of the four is rectified at some stage, as in the De Valois and De Valois model.

In our model, for each hue mechanism, one side of the opponency is derived from summed horizontal cell input that combines S-, L-, and M-cone responses. Because of this arrangement, the character of opponent interactions responsible for hue perception will vary based on the ratio of L- and M-cones in the mosaic surrounding a given cone. In the case of

Table 1. Proposed Mechanisms

L-(S + M)	Yellow	ON-bipolar
(S + M)-L	Blue	OFF-bipolar
M-(S + L)	Green	ON-bipolar
(S + L)-M	Red	OFF-bipolar

the central retina where midget ganglion cells receive excitatory input from only a single L- or M-cone [51], this produces a ganglion cell with the spectral sensitivity, $g(\lambda)$, described by

$$g(\lambda) = \delta(\lambda) - \omega(\rho S(\lambda) + (1-l)M(\lambda) + lL(\lambda)), \tag{4}$$

where $\delta(\lambda)$ is taken to represent the direct pathway of the cone-to-bipolar circuit that involves a single synapse from a cone onto an ON midget bipolar cell. An OFF midget is created by $-1 * g(\lambda)$. In the case of the BY system $\delta = L(\lambda)$, while $\delta = M(\lambda)$ in the RG system. l is the proportion of L to (L + M) in the indirect pathway, signaling through horizontal cells that contact L-, M-, and S-cones [50]. Lower thermal noise of the S-cones [52] was assumed to amplify the S signal, ρ, into the indirect pathway by 1.3, or the ratio between M + L and S thermal noise (544.5/417). Our only assumption is that at this ganglion cell level, responses of chromatically opponent cells null to equal energy white, requiring that ω in Eq. (4) is adjusted such that

$$0 = \int_{\lambda=390}^{750} g(\lambda)\mathrm{d}\lambda. \tag{5}$$

This assumption is supported by our earlier demonstration that changes in an observer's chromatic environment modulate the appearance of unique yellow [53]. It was observed that the wavelength of a subject's unique yellow shifted after exposure to long periods of chromatic alteration. Afterward, when subjects were exposed to the everyday environment, unique yellow shifted back to baseline. A simple normalization mechanism based on a resetting to an equal energy spectrum after exposure to altered chromatic experience is well described the data. That mechanism is formalized here. The model presented predicts precisely how differences in chromatic environment will change the unique hues. The earlier results suggest that the majority of individuals are exposed to environments that average overtime to a close match to equal energy white. For simplicity, we assume here that everyone is adapted to an equal energy spectrum though variability in white settings has been noted [54] (see below).

3. Frequency Summation

Equation (4) produces physiologically based spectral sensitivity functions for midget ganglion cells that closely match hue appearance data. However, the scaling constant associated with the L and M input, l, must be specified. The final component of this model (Fig. 3) assumes a random wiring hypothesis [55] and uses the L:M cone ratio to specify the input of L and M into the surround of an average ganglion cell in the observer's retina. We accomplish this mathematically by first iteratively computing all possible curves [Eq. (2)], which amounts to changing the proportion of L to (L + M) in Eq. (4). The generated units are then weighted based on the probability of occurrence and summed:

$$\alpha(\lambda) = \sum_{r=0}^{n} g_r(\lambda)P(S|r) \tag{6}$$

with l in Eq. (4) equal to r/n and $n = 100$. The weights for each unit are computed with a binomial distribution parameterized by P_L, or the L:(L + M) ratio across the entire retina:

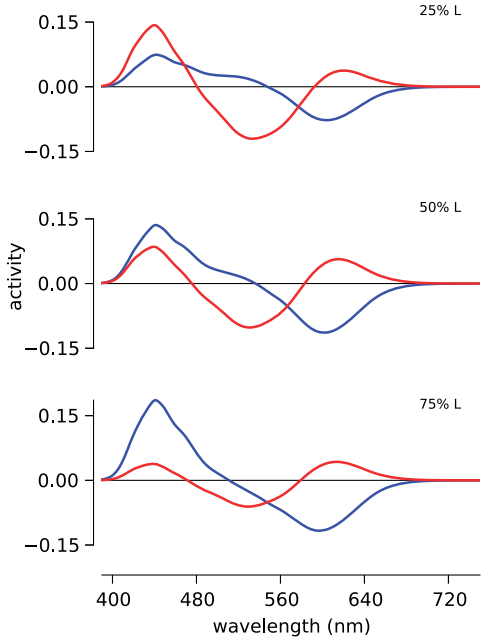

Fig. 3. Sensitivity of the chromatic mechanisms. By changing the %L (L/(L + M) × 100) cones in the observer's retina, a family of valence curves is produced for the RG (red lines) and BY (blue lines) mechanisms. Note the null point of the BY curves shifts considerably between the three conditions plotted.

$$P(S|r) = \binom{n}{r} P_L^r (1-P_L)^{n-r}. \tag{7}$$

The above model can be extended to cases where more than one cone contacts a single bipolar cell, as is the case in the periphery [56]. In this scenario, both L and M signals are assumed to contact midget bipolar cells through the direct pathway, $\delta = L(\lambda) + M(\lambda)$. These signals are then weighted by a binomial distribution parameterized by the L:M ratio, as in Eq. (7). This scenario produces exponentially more combinations of direct and indirect cone arrangements. However, as previously noted [15], increasing the number of cones contributing to the direct pathway decreases the number of strongly opponent cells. The implications of this change on color appearance are considered below.

All of the equations above were implemented in the open source programming language Python http://www.python.org/. Source code can be freely obtained from https://github.com/bps10/color/tree/JOSA.

3. RESULTS

A. Color Space and Unique Green

We used a custom physiologically based color space and the concept of confusion lines to determine the basis for published individual differences in unique green [57]. A dichromatic system represented in a trichromatic space necessarily contains directions along which the relative activation of its two receptors do not change. This is often shown as confusion lines emanating from a copunctual point. An example of this is drawn in Fig. 4(a) for a tritan observer in chromaticity space. Extending this logic, the confusion lines of any dichromatic system based on the same three cone photopigments, including those based on constant weighted sums of

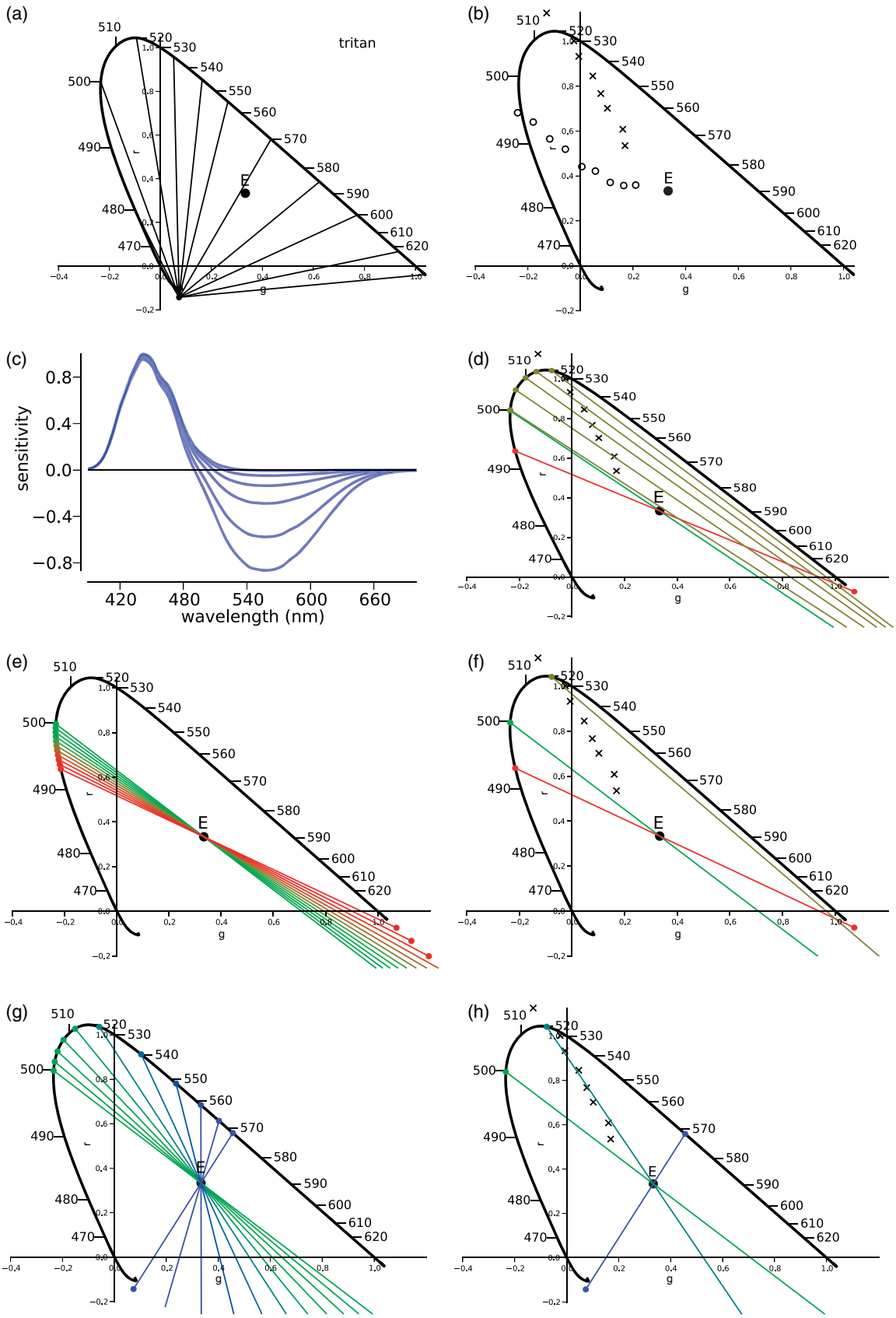

Fig. 4. Comparison of the standard model with the BY midget ganglion cell theory proposed here. A *rgb* color space (a) was constructed from the Neitz fundamentals [42] and data from [57] was best fit to the space in a least squares sense (b). (c) Demonstrates the effect of varying k in $S - k(L + M)$. This scenario is not capable of matching the 522 nm unique green of observer 2 and simultaneously passing through equal energy white (d). (e) Simulates changing k in $S - (kL + (1 - k)M)$, again failing to fit the data from observer 2 (f). Finally, varying k in $L - (kS + (1 - k)M)$ results in a good fit with the data (g) and (h).

two of the photopigments opposed to the third with a single null point, can also be represented in color space.

In the case of the BY system, there is a confusion line that nulls the system and corresponds to a line along which lights will be identified by a trichromatic viewer as uniquely green. This implies that for a linear model of hue perception to be accurate, a line from the systems copunctual point to the wavelength identified as uncontaminated green must be possible.

Unique green data, reprinted from [57], for two observers at 10 trolands illumination is plotted in Fig. 4(b) after transformation into *rgb* space derived from the Neitz spectral sensitivity functions [42] as described in *Creating a Color Space*. The points do not transform exactly into the current space due to the nonlinear differences between Judd–Vos fundamentals that the data are reported in and the fundamentals employed here. These differences result in two points falling outside of the color space. However, this irregularity does not impact the current analysis.

At 100% purity, the two observers identify 498 and 522 nm light as uniquely green, respectively. These observers both fall well within the range of normal observers [3,9], demonstrating the wide variability in the perception of unique green. For both observers, as the purity of the match light is decreased the identified light approaches equal energy white at the (x, y) coordinate of $(1/3, 1/3)$, as expected.

To account for the variability in unique green, a BY system based on comparing S versus (L + M) signals has two means of shifting the spectral location of green. The first, demonstrated in Fig. 4(c), involves modulating the contribution of S into the BY sensitivity function. This leads to a situation where the confusion line does not pass through equal energy white (Fig. 4(d)). The second possibility for modulating the null point of an S-(L + M) system is to vary the contribution of L and M (Fig. 4(e)). The range of values possible for unique green under this manipulation, however, only varies from roughly 490 to 500 nm, or the spectral neutral points for a protan and deutan observer. This again results in a situation where the confusion line of the system cannot be drawn through equal energy white (Fig. 4(f)). These results demonstrate that a BY system based on the output of S versus (L + M) neurons is not able to account for either the location or axis along which the BY system nulls for the vast majority of individuals or the known variability in unique green.

In contrast, for a BY system derived from the comparison between L and (M + S) signals, there is a considerable spectrum of values possible for unique green. As the ratio of S to M goes from a pure L versus S opponency [protan confusion line, red line in (Fig. 4(h))] to a pure L versus M opponency [deutan confusion line, green line in (Fig. 4(h))], the range of values exceeds 60 nm (Fig. 4(f)). Consequently, we were able to produce a good fit to the data for observer 2 that passes through equal energy white. This demonstrates conclusively that S-cones contribute to BY hue appearance by summing with M-cones. In the case of this observer, the expected contribution of S is about 0.48 and 0.52 for M.

One caveat to our analysis is that we assumed all observers see an equal energy stimulus as their white point. A large population study of achromatic points indicates that this simplification is a reasonable assumption [54]. The mean location of white was approximately equal energy $(x, y = 0.31, 0.31)$ with relatively little variability, particularly within an age group. Observer 2 falls close to the population mean for the percept of unique green and the extrapolation of a white point near equal energy is consistent with population measures.

B. Spectral Location of Unique Hues

On the basis of the findings above, we developed a color model that includes S-cone contribution to both BY and RG hue perception (see "Methods"). The spectral sensitivities of the BY and RG systems (Fig. 3) under the BY midget ganglion cell theory, are parameterized most significantly by the ratio of the L- to M-cones in the retina. To further appreciate the extent to which color appearance is expected to change as a function of L:M ratio, we iteratively changed the L:M ratio in our model. The expected null points of the BY and RG systems were found for each cone ratio producing the relationship between L:M cone ratio and unique hues plotted in Fig. 5.

Most notably the model produces a range of 495–555 nm for unique green, with the greatest action occurring between L:M cone ratios of 0.4–0.8. Importantly, this is the range of ratios in which most individuals are known to fall [58]. In comparison, yellow and blue are expected to produce considerably smaller spectral ranges. Figure 5 also demonstrates the effect of L-cone peak sensitivity on unique hue perception. The effect is largest in the case of unique green, though the general relationship between hue and L:M ratio is unchanged. Effects of a similar magnitude are found when varying the peak sensitivity of M- and S-cones.

C. Agreement with Observed Data

Wide variability in L:M cone ratios between normal observers has been established in the literature [42,53,58–60]. We used the L:M ratio and peak L-cone sensitivity of each observer reported in Table 1 of Carroll *et al.* [58] to find the expected wavelengths identified as uniquely blue, green, and yellow.

For this analysis we assumed peak sensitivities of 529 and 417 nm for the M- and S-cones. The results produced a distribution of unique green that closely matches that observed by Volbrecht *et al.* [61] (Fig. 6). Similarly, RG hue perception based on M versus (S + L) inputs accurately predicts the narrow distributions for unique blue and yellow as observed experimentally. Table 2 displays the mean and standard deviation (StDv) expected for these three hues.

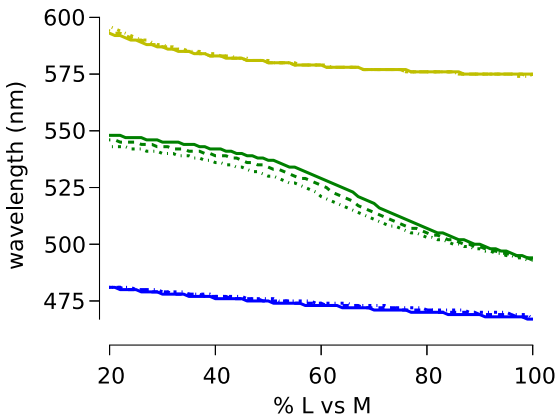

Fig. 5. Spectral locations of unique hues as a function of %L (L/(L + M) × 100). The color of the line represents the unique hue and style of the line indicates the peak sensitivity of the L photopigment: solid = 559 nm, dashed = 557 nm, dashed – dotted = 555 nm

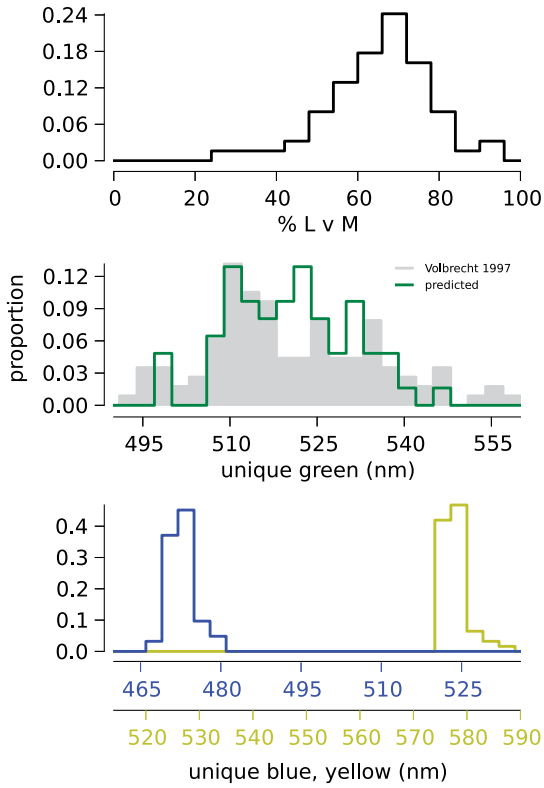

Fig. 6. BY ganglion cell theory predicts unique hue variability. A distribution of L:M cone ratios (represented as %L) is plotted in the top figure. Using this data, a predicted distribution of unique green was produced (green trace) and overlaid over an observed plot from [61] (gray area). The bottom plot displays predicted distributions for unique blue and yellow.

Table 2. Predicted Values of Unique Hues

Hue	Mean (nm)	StDv (nm)	N
Green	520.6	10.8	62
Yellow	577.2	2.3	62
Blue	471.9	2.3	62

D. Variation with Eccentricity

Finally, the number of cones directly synapsing on each midget ganglion cell is known to increase with eccentricity. To account for these changes, we introduce multiple cones to the direct pathway, δ in Eq. (4). This greatly increases the possible combinations of L- and M-cones in both the direct and indirect pathways. Accounting for all possible arrangements leads to a large shift in unique green toward shorter wavelengths similar in direction and magnitude to reports in the literature [62,63] (Fig. 7). This analysis also predicts a desaturating effect of increasing eccentricity [15], which has been observed psychophysically [8,62,63].

4. DISCUSSION

The BY midget ganglion cell model presented here has both explanatory and predictive power. First, it meets the criteria of a good scientific hypothesis that its predictions are falsifiable by experiment. Second, the model provides an explanation of why hue perception is not disturbed in individuals with GRM6 mutations that have no S-cone input to small

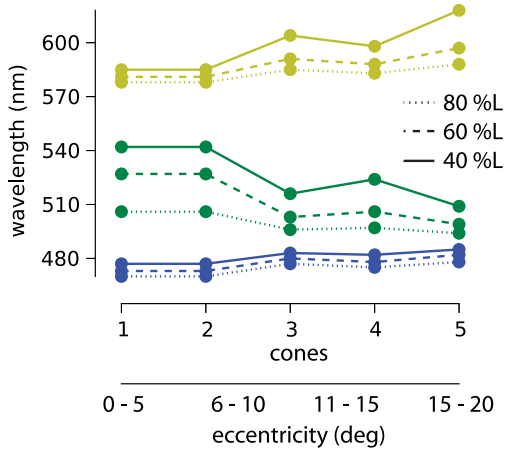

Fig. 7. Change in unique hues with eccentricity. Hue is expected to vary with eccentricity due to the increasing number of cones with direct input to midget ganglion cells at more eccentric locations. The eccentricity indicated here is approximate.

bistratified ganglion cells. In the model proposed here, S-cone contributions to hue perception arise from horizontal cell input that bypasses the defective synapses in mGluR6 patients. Third, the model explains why there is such large range of individual differences in unique green but little variability in unique yellow. S versus M cone weights to the percept of blueness that occur with variation in L:M cone ratio produce large shifts in unique green but similar variation in S versus L weights to the precept of redness produce little change in unique yellow. Fourth, it can explain the hue shifts in unique green that are observed for peripheral versus central vision. Fifth, the model explains why we have unique hues at all—they are the null points of opponent dichromatic subsystems that have their origins in a subset of retinal ganglion cells. This is in contrast to alternative accounts that have been offered over the years involving cultural or linguistic arguments, the nature of real-world stimuli [64], or interactions between the three cone types and exposure to natural illuminants and surfaces [65]. Finally, the model predicts the spectral locations of the unique hues without the addition of any *post hoc* assumptions. A model capable of accurately capturing both the mean and spectral location of these three hues, as well as the variation between observers, is unprecedented as far as we are aware. Moreover, it can predict how unique hues will vary as a function of spectral environment, lens and macular pigment density, cone photopigment spectral sensitivity, and cone ratio, each of which can be addressed by experiment.

A. Hue Appearance

A recent review by Kuehni [3] reported the mean and standard deviations of the unique hues across a series of studies using a variety of experimental paradigms. We have aggregated the reported values, weighted the mean and standard deviation based on the number of subjects, and produced a population estimate for green, yellow, and blue.

These results, shown in Table 3, demonstrate very similar characteristics to the ones we predict (Table 2) for a smaller population of observers. Both the mean and standard deviation of our simulations closely resemble the meta-analysis findings. The deviation between the predicted and

Table 3. Observed Values of Unique Hues

Hue	Mean (nm)	StDv (nm)	N
Green	527.2	14.8	648
Yellow	577.8	2.9	411
Blue	476.8	5.3	411

observed distribution (Table 3 versus Table 2 and Fig. 6) may be due at least in part to the fact that the population of L:M cone ratios included only men, while observed data plotted in Fig. 6 (gray histogram) and the aggregate data in Table 3 assessed color appearance in both men and women. Female subjects introduce the possibility of multiple opsin genes with both a 555.5 and 559 nm L peak expressed. Indeed, Volbrecht *et al.* found significant differences in the performance between males and females on unique green, with females tending toward shorter wavelengths and greater variability [61]. Both of these trends are predicted by the current model.

Shifts in optical filtering are also expected to introduce between-subject variability. For example, a change of L and M optical densities from 0.5 to 0.3 shifts the expected mean unique yellow for our population of observers from 579 to 575 nm, while blue and yellow shift only about 1 nm. Variation in optical density together with the introduction of females to the population of observers is expected to increase the standard deviation associated with each of the three hues. Together these factors may account for the systematic underestimation of variability in the model (Table 2) relative to the meta-analysis above (Table 3). The L:M ratio of an observer is predicted to have a substantial impact on color appearance under the current theory. In particular, the location of uncontaminated green is expected to vary widely, shortening as the proportion of L increases, as shown Fig. 6. The small spectral shifts in peak sensitivity resulting from single nucleotide polymorphisms in the opsin sequence give rise to a family of L and M pigment sensitivity curves. While most observers have an M peak of 530 nm and a peak L of either 555.5 or 559 nm (or both) [58], the model can be adjusted to predict color appearance for observers with more rarely observed sequences. The effects of these shifts on hue perception are expected to be smaller in magnitude than the impact of L:M ratio (Fig. 5). The change in uncontaminated blue and yellow are negligible for all observers. Interestingly, the common 3.5 nm variation in L peak is expected to shorten unique green by almost 10 nm for an observer with a 0.5 L:M ratio.

We have also explored the effect of increasing the number of cones with direct input to midget ganglion cells, as occurs in the periphery [66]. Increasing the number of direct contacts will produce many more combinations of opponent cells than appear in the fovea. The consequence of such an arrangement is that fewer cells will have a single cone type with direct input to the midget ganglion cell. This decrease in strongly opponent cells will serve to desaturate color appearance [15], consistent with observations reported in the literature [8]. Moreover, as demonstrated in Fig. 7, this model predicts a shortening of unique green with increasing eccentricity. This relationship has been noted by Nerger *et al.* [62]. It is also worth noting that we have not accounted for the change in expression of L- and M-cones at increasing eccentricities [31]. These changes will impact hue perception in the very far periphery and can be introduced by simply changing the assumed L:M cone ratio.

B. Physiology

The BY midget ganglion cell theory requires the existence of midget cells that carry L versus (M + S) opponency. The existence of these cells is consistent with recordings in LGN [38] and were previously reported in ganglion cell recordings [39,40]. A schematic representation of the proposed BY ganglion cell model is shown in Fig. 8. The BY circuit is built by summing the input from L-, M-, and S-cones and then differencing this signal from an L-cone directly contacting a bipolar cell. In the case of the ON pathway, this will produce a yellow signal, while the OFF pathway will result in blue. For the RG system an M-cone is differenced from neighboring cones to produce red (OFF pathway) or green (ON pathway).

These circuits could be built via inhibitory horizontal cell input from neighboring cones through a feedback pathway, but we think it is more likely based on a newly described feed-forward pathway. Either way, H2 horizontal cells receiving S, M, and L signals and H1 cells with input from L- and M-cones, are opposed to inputs from a central cone. Recent anatomical experiments from our laboratory provide evidence for the existence of the feed-forward pathway [34–36]. Such a mechanism would differ substantially from classical horizontal cell feedback. In this scenario, signals from nearby cones would be integrated in the horizontal cells and fed forward directly into the bipolar cells, creating a bipolar cell with input in which the single center cone opposes a sum of surrounding cones. In addition to this central opponency, there would be the color opponent horizontal feedback onto cones from a larger surround; thus, the proposed arrangement would produce a "double opponent" character. For example, S-cones contributing an ON signal to OFF bipolar cells via H2 horizontal cell feed-forward would receive inhibitory S-cone feedback from surrounding S-cones. This could contribute to color constancy of conscious hue perception. Also, it is possible that if the spatial aspects of the double-opponent-like behavior

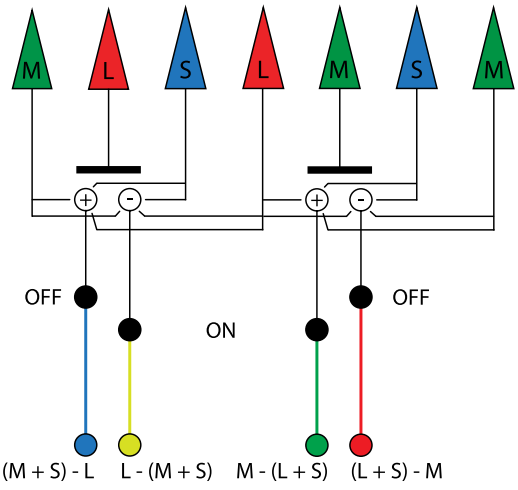

Fig. 8. Schematic representation of the BY midget ganglion cell theory. A BY system is built by summing the input from L-, M-, and S-cones and then differencing this signal from an L-cone directly contacting a bipolar cell. In the case of the ON pathway, this will produce a yellow signal, while the OFF pathway will result in blue. In the case of the RG system an M-cone is differenced from neighboring cones to produce red (OFF pathway) or green (ON pathway).

of the cells are configured appropriately, the subset of midgets carrying hue information would not respond to white-dark edges. This would make their response properties quite distinct from conventional L versus M midget ganglion cells that respond well to white-dark boundaries.

C. Parallel versus Serial Models

Classically, detection thresholds have been considered to be mediated by S versus L + M and L versus M neural channels that correspond to the cardinal directions in color space. Serial models are the favored explanation for why unique hues lie along lines that are rotated relative to the cardinal directions. In these models [2,15] an early stage of color processing is accomplished by L versus M midget and small bistratified ganglion cells and the outputs of the precortical neurons are recombined at a later stage to produce color opponent channels responsible for hue perception. However, parallel models have been considered. Danilova and Mollon [67] recently demonstrated a region of enhanced discrimination in color space that corresponds to the subjective category boundary between reddish and greenish hues and suggest that the discrimination is based on a "noncardinal" opponent neural channel in equilibrium. They offered a parallel model as one possible explanation of why the performance of certain tasks is based on cardinal opponent neural channels while the performance of other perceptual tasks is based on "noncardinal" channels. They point out that the absolute number of a given cell type may not be so important and that "central decisions in a particular task may well be based on the signals of a minority type of cell."

The possibility of a parallel model was also considered in the classical study defining the "cardinal directions of color space" [21]. It was noted that results of one observer suggested a residual selective habituation effect of stimuli at 45° relative to the cardinal axes. In addition to offering a serial model that has become the most conventional explanation, saying there may be "yet another set of adaptable mechanisms at a third level in the visual system," they also suggest the possibility of a parallel model in which there could be "two populations of mechanisms with their maximum sensitivities distributed about the cardinal axes".

Our results are consistent with these earlier proposals of a parallel model. Here, we demonstrate the explanatory and predictive power of a parallel model in which a small subset of midget ganglion cells mediate conscious hue perception. At the same time, the large majority of midget ganglion cells that have L versus M opponency may mediate performance on detection tasks. Similarly, the small bistratified ganglion cells could be important for certain kinds of detection tasks while the (S + M) versus L midget ganglion cells proposed here mediate conscious hue perception. This could explain the finding that color vision was normal in CSNB1 patients assessed with the FM 100-hue test [28]. However, B-Y perimetry demonstrated detection of S-cone isolating flashes was reduced significantly at 15°-to-30° compared to 0°-to-15° in CSNB1 compared control subjects.

D. Alternative Models

The model proposed here offers an explanation of why hue perception is undisturbed in people with mutations that interrupt S-cone signals to small bistratified cells. Earlier, it occurred to us that a parallel model might explain how gene therapy was capable of conferring trichromatic color vision in adult monkeys [30,68]; however, it was the observation of preserved hue perception in individuals with mGluR6 mutations that further inspired the work presented here. Thus, it is worth considering the possibility of other explanations for the preserved color vision in individuals with mGluR6 mutations.

S-OFF signals have been observed in primate LGN [38,69]. As introduced earlier, a subset of S-OFF LGN cells have L-(S + M) inputs as expected from the GABA mediated feed-forward hypothesis presented here. However, a population of S-OFF LGN cells with (L + M)-S inputs is also observed, suggesting the possibility of a different S-OFF pathway carrying S-cone signals out of the retina that could provide an alternative explanation for the preserved color vision in mGluR6 mutants. Though the retinal basis of the (L + M)-S cells is unknown, there are a few potential sources of their S-OFF signals. In primates, besides the small-bistratified ganglion cell, the only anatomically distinct and physiologically characterized ganglion cell type that has S-cone specific input is the "giant" melanopsin-containing ganglion cell. These cells are S-OFF/(L + M)-ON and project to LGN in addition to other targets [70]. Remarkably, application of the ON-pathway agonist, 2-amino-4-phosphonobutyric acid (L-AP4), completely blocks the S-OFF light response in the primate melanopsin ganglion cells [71], indicating S-OFF signals are transmitted to the inner retina via the ON S-cone bipolar cell, which does not communicate with S-cones in mGluR6 mutant individuals. The arrangement in melanopsin ganglion cells is similar to S-OFF ganglion cells recently discovered in ground squirrel [72,73] in which S-OFF responses arise from S-ON bipolar cells and are sign reversed by an S-cone selective amacrine cell. Like macaque melanopsin ganglion cells, the S-OFF responses are blocked by application of L-AP4. Whether an analogous cell type exists in the primate retina is unknown, but if they do exist and contribute to the population of (L + M)-S LGN cells, along with the melanopsin ganglion cells, S-cone inputs to them would be blocked in mGluR6 mutant individuals. The same would also be true of the large bistratified type of retinal ganglion cell, which draws excitatory inputs from S-cones via ON-bipolar cells [74].

Another potential source of S-cone signals is the occasional S-cone input to the centers of OFF midget bipolar cells observed in the far periphery by Field *et al.* [75]. These inputs would be intact in mGluR6 mutant individuals but they are sparse and are only known to occur in peripheral midget ganglion cells that draw from around a dozen cones. If these do provide a significant S-cone signal it might be expected to be most prominent in the periphery. Instead, the opposite is true for individuals with CSNB who show deficits in S-cone mediated detection specifically in the periphery [28]. Finally, one anatomical study by Klug *et al.* [76] has reported the existence of S-cone OFF midget ganglion cells in the central retina of macaques. However, the existence of an S-cone OFF midget bipolar cell is uncertain. The putative S-cones were not identified by any kind of functional marker in the Klug experiment, and it is possible that "S-cone" terminals they reconstructed belonged to L- or M-cones that happened to be missing an ON midget bipolar cell. Additionally, it is possible that the

S-cone ON bipolar cells connecting to the misidentified cones were not S-cone ON-bipolar cells but the recently described "giant bipolar cell" [77]. Regardless, they propose the existence of an S-cone OFF midget ganglion cell for every S-cone in the central retina, yet to date no S-cone midget ganglion cells have been identified physiologically in the central retina. If S-OFF midget ganglion cells do exist or if the peripheral S-cone inputs described by Field *et al.* are important for color vision, a model would have to be developed to explain how cells with a (L + M)-S configuration could be responsible for all the aspects of normal hue perception explained here.

E. Future Work

The model elaborated here is dependent upon H2 horizontal cells generating opponency at the level of the midget bipolar cells. H2 horizontal cells are known to carry sign reversed S + M + L potentials [50], and they have been shown to generate an L + M surround in S-cone terminals [49]. Anatomical evidence has demonstrated sites of synaptic contact between H2 horizontals and L- and M-cone pedicles [50]; however, there is no published evidence for feedback from H2 horizontal cells onto other types of cones. Our model predicts an S-cone component to the H2 mediated surround in a small subset of L- and M-cones neighboring S-cones. It has been possible to visualize S-cone terminals morphologically [49]. Thus, in future work it should be possible to test this prediction of the model by recording responses to S-cone isolating stimuli from L- and M-cone terminals adjacent to S-cones in an *in vitro*, whole-mount preparation of macaque retina. The model also predicts a GABA mediated feed-forward pathway from H2 horizontal cells onto bipolar cells, which will be manifest in S-cone responses detectable in a subset of midget ganglion cells that can be suppressed by application of GABA antagonists. In the future, this prediction could be tested by recording midget ganglion cell responses to S-cone isolating stimuli with and without application of GABA antagonists.

Another area of future work will be to directly explore the nonlinear behavior of hue perception that has been noted throughout the literature. One example is the nonlinear interaction between hue and saturation, known as the Abney effect [78,79]. As a spectral hue is desaturated, the location of the unique hues are known to deviate from an expected linear trajectory toward equal energy white. In the future, a further elaboration of our model could be tested by evaluating its ability to account for these nonlinearities. Desaturating a spectral light will change the weights on the RG and BY mechanisms, due to differential adaptation of the S versus L/M cones, introducing nonlinear behavior. The most extreme case will occur with the percept of unique red. A monochromatic long wavelength light will drive L- and M-cones in almost equal proportion, but produce virtually no excitation of S-cones. As more white is added to the red light, more S contribution will be added to the percept, causing a reweighting of the (S + L) and (S + M) side of the RG and BY mechanisms, thereby nonlinearly changing the position of red as a function of saturation. This could explain the noncomplementary nature of the red and green unique hues.

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