

The spectral identity of foveal cones is preserved in hue perception

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Abstract

Organisms are faced with the challenge of making inferences about the physical world from incomplete incoming sensory information. One strategy to combat ambiguity in this process is to combine new information with prior experiences. We investigated the strategy of combining these information sources in color vision. Single cones in human subjects were stimulated and the associated percepts were recorded. Subjects rated each flash for brightness, hue and saturation. Brightness ratings were proportional to stimulus intensity. Saturation was independent of intensity, but varied between cones. Hue, in contrast, was assigned in a stereotyped manner that was predicted by cone type. These experiments revealed that, near the fovea, long (L) and middle (M) wavelength sensitive cones produce sensations that can be reliably distinguished on the basis of hue, but not saturation or brightness. Taken together, these observations implicate the high-resolution, color-opponent parvocellular pathway in this low-level visual task.

Introduction

Incoming sensory information is inherently noisy and ambiguous. The retinal image and the subsequent signals encoded by the photoreceptors can be interpreted infinitely many ways. Helmholtz (1924) posited that perception represents the brain's best guess about the state of the world after taking into account both the ambiguous incoming signals and prior experience. Investigating the rules through which incoming sensory signals are combined with prior evidence is an important area of brain research (Knill and Pouget, 2004). Here, we studied the color appearance of light targeted to a single receptor in order to elucidate the rules the visual system follows when presented with impoverished information from its primary sensory neurons. Understanding these rules will provide insight into how the visual system handles uncertainty in more naturalistic tasks as well.

A light of fixed wavelength that is sufficiently small in diameter and weak in intensity will fluctuate in appearance across presentations (Krauskopf, 1964; Krauskopf and Srebro, 1965; Otake and Cicerone, 2000). To understand why, consider a spot small enough to stimulate only a single cone. An individual cone is colorblind; information about wavelength is not retained after a photoreceptor captures a photon (Rushton, 1972). The visual system computes color information by comparing relative activity across the three cone types. If light falls on only a single cone, the visual system will be missing samples from the other two cone types and the color of the spot will be ambiguous. One possible solution to this problem is that the visual system could use prior experience to infer the activity of the two missing classes when judging the color of the spot (Brainard et al., 2008). The reason why the spot fluctuates in appearance from trial to trial is that the eye makes tiny movements from moment to moment. As a result of this incessant movement, the light will strike a different cone each time it is flashed on the retina and, thus, a small spot of light with a fixed

38 wavelength will fluctuate in appearance across presentations (Krauskopf, 1964; Krauskopf and Srebro, 1965;
39 Krauskopf, 1978).

40 In a pioneering examination into this phenomenon, Krauskopf and Srebro (1965) asked subjects to match
41 small, dim flashes on a dark background to monochromatic light. Under these conditions, they discovered
42 that matches fell into one of two distinct clusters: one centered around orangish-red wavelengths and the
43 other blueish-green. They hypothesized that (1) the two perceptual distributions corresponded to two distinct
44 detectors – L- and M-cones, respectively – and that (2) white sensations arose when an L- and an M-cone
45 were activated together. Due to technological limitations, they were unable to isolate single cones, identify
46 the cone type targeted or repeatedly target the same cone. Thus, a conclusive test their hypotheses was
47 not possible. More recently, Hofer et al. (2005b) improved single cone isolation with adaptive optics, which
48 corrects for each subject's optical imperfections. Contradicting the second hypothesis of Krauskopf and
49 Srebro (1965), they concluded that the frequency of white reports was too high to be caused exclusively
50 by trials where L- and M-cones were stimulated together: at least some single cone flashes produced white
51 sensations. The authors also argued that the variability they observed was too great for the response of a
52 single cone to depend only on its spectral class. However, Hofer et al. (2005b) were not able to target light
53 to receptors of known spectral type and, therefore, could not directly relate cone activity to color reports.

54 Recently, we combined high-resolution eye-tracking with adaptive optics to additionally compensate for
55 natural eye movements (Arathorn et al., 2007; Harmening et al., 2014). With this technology, we stimulated
56 individual cones and identified their spectral type (Sabesan et al., 2015). Our results confirmed the prediction
57 that most of the variability in chromatic percepts could be attributed to the type of cone that was targeted
58 (Sabesan et al., 2016; Schmidt et al., 2018). On average, L-cones mediated red sensations, while M-cone trials
59 gave rise to green or blue, depending on the background context. At a supra-threshold intensity and against
60 a white background (Sabesan et al., 2016), a majority of trials were judged white. This was consistent with
61 the observations of Hofer et al. (2005b) and contradicted the second hypothesis of Krauskopf and Srebro
62 (1965) that light absorbed by a single cone always produces saturated color percepts. However, unlike the
63 older studies, our experiments were conducted on a white background which may reduce variability in color
64 ratings (Schmidt et al., 2018; Hofer et al., 2012).

65 The discrepancy between these studies raises new questions about how the visual system parses hue and
66 achromatic sensations from a mosaic of detectors that are individually colorblind. Firstly, do sensations from
67 individually targeted L and M cones truly vary in saturation (amount of whiteness)? More specifically, do
68 single-cone color percepts exist on a continuum, with each cone producing a mixture of hue and achromatic
69 sensation (Wool et al., 2018) or is there a discrete subclass of cones wired specifically into chromatic or
70 achromatic pathways (Neitz and Neitz, 2017)? In our prior work, subjects reported on their perception with
71 only a single color name (Sabesan et al., 2016; Schmidt et al., 2018). The limited range of response options
72 may have obscured more subtle variation in hue and saturation. Secondly, color and brightness perception
73 of small spots are known to change with intensity (Kaiser, 1968; Weitzman and Kinney, 1969). However, the
74 mechanism underlying this phenomenon is unclear. A higher luminance spot will both activate more cones
75 and do so more strongly. We sought to understand whether individually targeted cones would systematically
76 change in appearance – perhaps from white to colored – as the number of photons per flash was increased.

77 The relationship between stimulus intensity and color appearance at a cellular-scale was quantified using
78 precise measurements of the sensation elicited by each spot. The results revealed that subjects used color
79 terms in a stereotypical manner predicted by cone type, but largely independent of stimulus intensity.

80 Methods

81 Subjects

82 Three highly experienced subjects (two male, one female [S20092]) between the ages of 27 and 34 participated
83 in the study. All subjects had normal color vision and two (S20076 and S20092) were authors of the study.
84 All procedures were approved by the Institutional Review Board at the University of California Berkeley and
85 adhere to the tenets of the Declaration of Helsinki. Informed consent was obtained from each subject before
86 the experiments. At the start of each session, cycloplegia and mydriasis were induced with drops of 1.0%
87 tropicamide and 2.5% phenylephrine hydrochloride ophthalmic solution.

88 Cone-resolved imaging and stimulation

89 A multi-wavelength adaptive optics scanning laser ophthalmoscope (AOSLO) was used to image and present
90 stimuli to the retina. The objective of this study was to confine a small stimulus probe (543 nm) to targeted
91 locations on the retina, *i.e.* individual cones. Monochromatic imperfections were measured with a wavefront
92 sensor (940 nm) and corrected with a deformable mirror (Roorda et al., 2002). Imaging was performed with
93 840 nm light, which was collected into a photo-multiplier tube through a confocal pinhole and rendered into
94 a video stream. The video stream was registered to a reference image in real-time with a strip based cross-
95 correlation procedure (Arathorn et al., 2007). The output of this procedure produced retinal coordinates
96 that were used to drive an acousto-optic modulator, a high-speed optical switch, which delivered 543 nm
97 visual stimuli to the retina whenever the raster scan passed over the targeted cell. Chromatic aberration was
98 measured and corrected with established procedures (Harmening et al., 2012). In these experiments, a 512 x
99 512 pixel imaging raster subtended a 0.95° field, with a sampling resolution of ~ 0.11 arcmin pixel⁻¹.

100 The challenges involved in targeting single cones and the technology for overcoming these challenges
101 has been described elsewhere (Roorda et al., 2002; Arathorn et al., 2007; Harmening et al., 2012, 2014;
102 Sincich et al., 2015) and a full consideration of the issues involved in stimulating individual receptors is
103 beyond the scope of this paper. However, before analyzing the psychophysical results, the ability of our
104 system to confine stimulus light to the targeted cone is worth considering. Briefly, there are three main
105 sources of noise that causes a point source to be blurred at the retinal plane: eye-motion, residual optical
106 imperfections and forward light-scatter. All three potentially limit image quality and the isolation of single
107 cones. Forward-scatter manifests as a large, dim halo surrounding the peak of the point-spread-function.
108 The magnitude of scatter relative to the core of the PSF has been estimated to be 1:10,000 (Hofer et al.,
109 2005b; Harmening et al., 2014; van den Berg et al., 2010). In the dark, these scattered photons may have
110 visual consequences. However, in the present work, a photopic background (see below) raised thresholds for
111 each cone and minimized the influence of uncontrolled scatter.

112 To assess the impact of any residual blur or eye-motion, the light profile of the stimulus was modeled
113 at the retinal plane and the fraction of light absorbed by the cone mosaic was computed (Harmening et al.,
114 2014). The location of each stimulus was first determined. During each trial of the experiment, a video
115 of the retina was recorded and the location of the stimulus in each frame was indicated with a digital
116 mark. The digital mark was recovered from each frame after the experiment to assess how closely the
117 actual stimulus was delivered to the desired location. The contours in the left plot of Figure 1A represent
118 the distribution of stimulus delivery locations over all frames from all trials during an example session.
119 The highest density of those distributions is concentrated at the center of the five targeted cones. Next,
120 the image of each stimulus on the retina was modeled by convolving a near diffraction-limited (0.05 D
121 residual defocus) point spread function with the 3 x 3 pixel (~ 0.35 arcmin) stimulus; 0.05 D was chosen as
122 a conservative magnitude of uncorrected optical aberration (Harmening et al., 2014). The contours in right
123 panel of Figure 1A demonstrate that most of the stimulus light was confined to the targeted cone, even

124 after accounting for uncorrected eye-movement and optical defocus. At the eccentricity (1.5°) tested in this
125 subject (S20076), cones were separated by approximately 9-12 pixels or slightly more than one arcmin. Had
126 cones been more tightly packed, for instance closer to the fovea, a greater fraction of the light would have
127 been inadvertently delivered to neighboring cones.

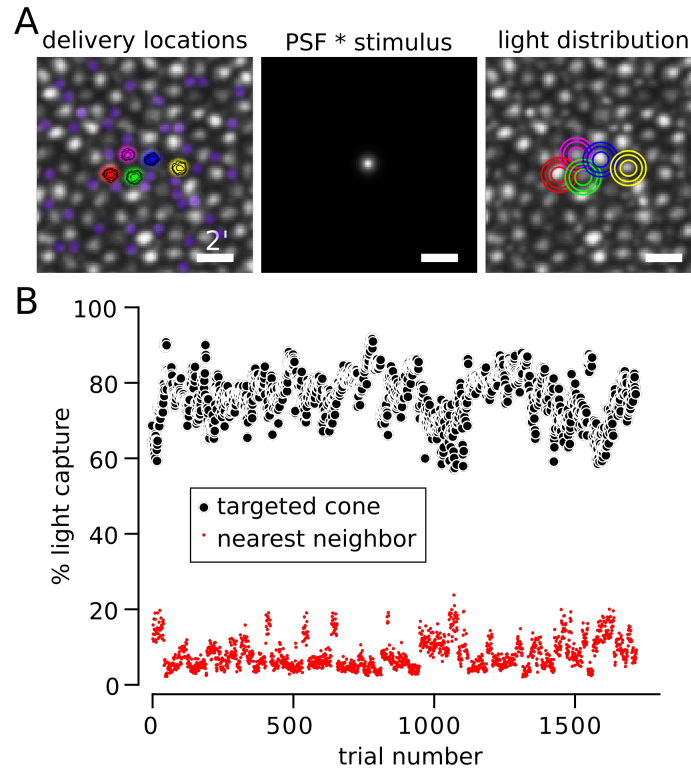


Figure 1: Targeting light to individual cones. **A.** *Left:* Delivery locations of 5 cones from S20076. The location of the stimulus was recovered on each frame of each trial (15 frames, 500 ms) and recorded. Contours indicate that delivery locations were concentrated at cone centers. Rods were pseudo-colored purple to distinguish them from cones (the larger, gray-scale, cells). *Middle:* 3 x 3 pixel stimulus convolved with a near diffraction-limited PSF (6.5 mm pupil with 0.05 diopters of defocus (Harmening et al., 2014)). *Right:* density profile of light capture in each cone computed by summing the PSF * stimulus at each delivery location. For both *Left* and *Right* plots contours encompass 50, 80 and 90% of delivered light from smallest to largest. Scale bar = 2 arcmin. **B.** Estimated percentage of light captured by the targeted cone (black circles) and its nearest neighbor (red circles) during each trial. Light spread was modeled as described in **A** and each cone aperture was assumed to be Gaussian with a width at half height of 0.48 relative to the diameter of cone inner segments (MacLeod et al., 1992; Chen et al., 1993). Trials with delivery errors greater than 0.35 arcmin were excluded from analysis.

128 In Figure 1B, we modeled how much light was absorbed by the targeted cone versus its nearest neighbor
129 after taking into account the aperture of cones at this eccentricity (Harmening et al., 2014), which was
130 assumed to be a Gaussian profile with a full-width half-max of 0.48 of the cone inner segment diameter
131 (MacLeod et al., 1992; Chen et al., 1993). This analysis was repeated for each trial. Of the light absorbed
132 by the mosaic, the targeted cone captured, on average, 76.4% ($\sigma = 6.2\%$) in this subject. The next nearest
133 neighbor captured 8.1% ($\sigma = 4.0\%$), while most of the remaining 15.5% of absorbed light fell on the five other
134 adjacent cones. Therefore, in theory (Harmening et al., 2014), the targeted cone in this subject absorbed 9-10
135 times more light than any of its neighbors. Allowing the cone aperture to vary over physiologically plausible
136 values (0.4-0.56) (MacLeod et al., 1992; Chen et al., 1993) caused only modest impact on the estimated

percentage of light captured by the targeted cone (80.2 - 72.1). This analysis produced similar estimates for the other two subjects (aperture=0.48; S20053: targeted cone $\mu = 67.3\%$, $\sigma = 6.6\%$, nearest neighbor $\mu = 9.9\%$, $\sigma = 3.6\%$; S20092: targeted cone $\mu = 82.1\%$, $\sigma = 4.2\%$, nearest neighbor $\mu = 6.7\%$, $\sigma = 2.9\%$. $\mu = \text{mean}$, $\sigma = \text{standard deviation}$). The lower light capture in S20053 was predominantly driven by a higher packing density of cones at the location tested ($\sim 1^\circ$). The potential influence of greater light capture by neighboring cones is considered in the Results section.

Stimulus and background parameters

Cones were targeted with spots (543 nm; 500 ms; 0.35 arcmin) that varied in intensity. Flash intensity was defined in linearized arbitrary units (a.u.) of the maximum intensity presented. A flash strength with a.u. = 1 delivered approximately 3.69×10^6 photons to the cornea or 5.19 \log_{10} Trolands (Nygaard and Schuchard, 2001). The background in these experiments was composed of four sources: (1) an invisible 940 nm wavefront sensing beam, (2) a dimly visible 840 nm imaging raster (2.02 \log_{10} Trolands), (3) leak from 543 nm stimulation channel (1.99 \log_{10} Trolands) and (4) an external projector. The external projector was imaged onto the subject's retina in Maxwellian view. Before each session, the subject adjusted the chromaticity and luminance of the projector until the entire mixture appeared white. The luminance was approximately 2.52 \log_{10} Trolands. Together, the four background sources produced $\sim 2.73 \log_{10}$ Trolands. Thus, at one a.u. the stimulus was approximately 290 times more luminous than the background. Each cone location was tested at three intensities. Flash strength was chosen to sample the entire range of the frequency of seeing curve. S20053 and S20076 were tested at identical stimulus intensities. S20092 was first tested at the intensities used for the other two subjects. However, due to overall lower sensitivity to the stimulus, S20092 was subsequently tested at slightly higher intensities.

Psychophysical procedure

At the start of each psychophysics session, a high SNR image was collected from an average of 90 frames. From that image, the locations of four to six cones were marked. Each cone was targeted ten times at each of three intensities and an additional 10% of blank trials were added. Trials were randomly interleaved between cone locations and stimulus intensities. A dataset of roughly 40-100 cones from each subject was collected over a minimum of ten sessions, which were spread over multiple days. Where possible, cones were targeted contiguous to previously tested locations. The analyses presented here consider all of the cones tested in each subject.

The subject initiated each trial with a button press, which was accompanied by an audible beep. After each flash, the subject rated the brightness of each stimulus on a scale from 0 to 5 (brightest). The subjects were given at least three practice sessions (~ 500 trials) to develop an internal criterion for assigning ratings. No reference stimulus or feedback was given. Trials that received brightness ratings above zero were also rated for hue and saturation (Gordon et al., 1994). The subject indicated the percent of red, green, blue, yellow and white contained in each stimulus using five button presses such that each press represented 20% ($5 \times 20\% = 100\%$). At least three full practice sessions were completed to develop familiarity with the task and the range of percepts experienced.

Cone classification

A small mosaic of cones $1-2^\circ$ from the fovea in each subject was selected for study. The spectral class of targeted cones were identified using densitometry (Hofer et al., 2005a; Roorda and Williams, 1999; Sabesan et al., 2015). Densitometry measurements were collected in imaging sessions separate from the psychophysical experiments. In one subject (S20092), we were unable to collect densitometry data due to time limitations.

Analysis

Data were aggregated across all experimental sessions. Responses from each trial were organized by cone location and stimulus intensity. Before inclusion into the data set, each trial was analyzed for delivery error. The location of the stimulus on each frame of the recorded video was recovered. Delivery error was defined as the standard deviation of those recovered locations. Trials with delivery errors greater than 0.35 arcmin were discarded.

Frequency of seeing (FoS) curves were computed by binarizing brightness ratings: ratings above one were seen. FoS data was analyzed on both a cone-by-cone basis as well as in aggregate over all cones within a single class. In both cases, the data were fit with a Weibull function, Φ , defined as:

$$\Phi = 1 - (1 - g)e^{-\left(\frac{kx}{t}\right)^b} \quad (1)$$

where

$$k = -\log\left(\frac{1 - a}{1 - g}\right)^{\frac{1}{b}} \quad (2)$$

In this parameterization of the Weibull function, g represented the performance measured during blank trials, t was the threshold and a was the proportion correct that defined the threshold (here $a = 0.5$). The slope of the function was defined by b . Model parameters were fit to the data using a maximum likelihood routine. Only t and b were treated as free parameters.

Hue and saturation were analyzed for all seen trials. Responses from each trial were converted into a uniform appearance diagram (UAD) (Gordon et al., 1994; Abramov et al., 2009). The axes in this space were defined as $y = \frac{\bar{g}-\bar{r}}{T}$ and $x = \frac{\bar{y}-\bar{b}}{T}$, where \bar{g} , \bar{r} , \bar{y} , \bar{b} correspond to the number of green, red, yellow, blue responses, respectively, and T was the total number of button presses, which was five. Saturation was computed as distance from the origin in city block metric (Gordon et al., 1994), *i.e.* $|x| + |y|$. A purely white response falls at the origin of this space, while a purely saturated response falls along boundary where $|x| + |y| = 1$. Hue angles relative to the origin were also computed from the x and y position of each data point. $x > 0$ and $y = 0$ represented an angle of 0° . Trials with pure white responses (5 white button presses) were excluded from this analysis because the angle is undefined.

The percent variance in hue angle, θ , or saturation, \mathbf{S} , explained by cone type was computed following a procedure adapted from Carandini et al. (1997). The mean square difference between two sets of responses $\mathbf{x} = x_c$ and $\mathbf{y} = y_c$ was computed:

$$d(\mathbf{x}, \mathbf{y}) = 1/N \sum |x_c - y_c|^2 \quad (3)$$

where the sum was taken over tested cones, c , and N was the number of tested cones. The percent variance explained, **% variance**, by cone type was then expressed as:

$$\% \text{ variance} = 100 * \left(1 - \frac{d(X_c, X_{LM})}{d(X_c, X_{\bar{c}})}\right) \quad (4)$$

where X_c was the mean hue angle or saturation for each cone, X_{LM} was the mean hue angle or saturation across L- and M-cones separately and $X_{\bar{c}}$ was the mean hue angle or saturation across all cones, regardless of cone type.

All analyses were carried out in MATLAB. Analysis code and raw data may be freely downloaded from GitHub (https://github.com/bps10/SchmidtBoehmFooteRoorda_2018).

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Results

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Cone photoreceptors in three human volunteers were imaged and stimulated with an adaptive optics scanning laser ophthalmoscope (AOSLO). Figure 2 illustrates the results from an example session. Five cones were selected: one M-cone and four L-cones. Each cone was tested ten times at three different stimulus intensities and an additional 10% of trials were blanks. Stimulus intensity was randomized across trials. After each flash, the subject first judged the brightness on a scale from 0 (not seen) to 5. Each subject developed his or her own criterion for brightness during practice sessions. Secondly, on trials that were seen the subject additionally judged the hue and saturation of each flash with a rating scale (Abramov et al., 2009; Gordon et al., 1994). The subject indicated the proportion of red, green, blue, yellow and white in increments of 20% (for a total of 100%). For instance, a desaturated teal might be 20% blue, 20% green and 60% white. Hue scaling data were then transformed into a uniform appearance diagram (UAD) (Figure 2D). In a UAD the x-axis indicates to the strength of yellow-blue sensations ($\frac{yellow-blue}{N_{trials}}$) and the y-axis indicates green-red bias ($\frac{green-red}{N_{trials}}$). White falls at the origin of this diagram and completely saturated responses (0% white) fall on the outer edge, as defined by the dotted lines. Saturation was computed as the distance from the origin (in city-block metric).

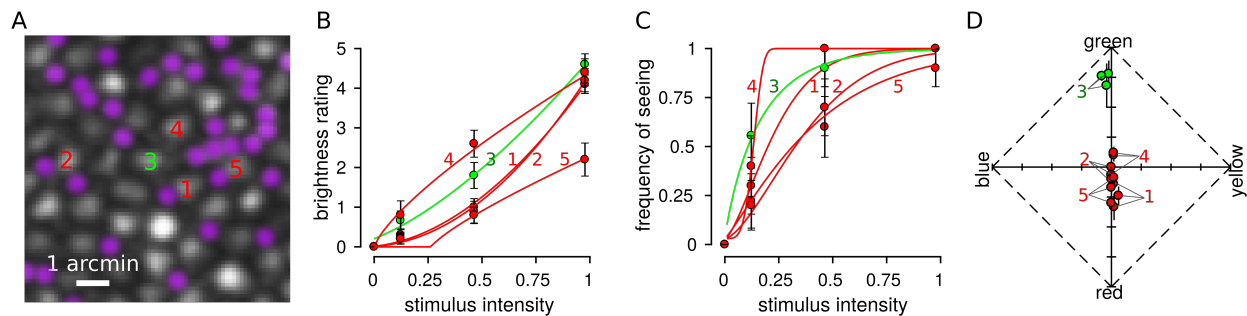


Figure 2: Hue, saturation and brightness scaling from spots targeted to single cones. **A.** AOSLO image from S20076 at 1.5° eccentricity. Numbers indicate the five cone centers that were selected for targeting during the experimental session. A roughly equal proportion of rods and cones are visible at this eccentricity (rods have been pseudo-colored purple). Scale bar indicates 1 arcmin. **B.** On each trial, a flash was targeted at one of the selected location and trials were randomly interleaved between the five locations. After each flash, the subject rated brightness on a scale from 0 to 5 and data were fit according to Steven’s Law (Eq. 5). A brightness rating greater than zero indicated the trial was seen. **C.** FoS data were fit with Weibull functions (Eq. 1). **D.** Subjects additionally reported the hue and saturation of the flash with a scaling procedure. The results from hue and saturation scaling from the five tested cones are plotted in a uniform appearance diagram (Abramov et al., 2009; Gordon et al., 1994). Each cone was tested at three intensities and the average response across all seen trials is plotted for each intensity. Error bars represent SEM; some error bars are smaller than the size of the symbol. Colors denote cone type (green = M-cones, red = L-cones.)

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The cone mosaics and position of targeted cones from three subjects are plotted in Figure 3. These datasets were amassed over numerous experimental sessions. Targeted cone locations are indicated by the presence of a pie chart. The pie chart represents a histogram of all button presses (red, green, blue, yellow, white) from all seen trials. The tested locations were between 1 and 2 degrees of eccentricity. The region targeted in S20053 was closest to the foveal center ($\sim 1^\circ$) and had the highest cone density. Subjects S20053 and S20076 used “white” more frequently than any other color category. Subject S20092 used hue categories more often than “white.” These plots illustrate that hue and saturation judgments were variable from cone to cone and possibly even between those with the same photopigment. Below, we examine these observations

235 in more detail.

236 Influence of stimulus intensity on detection and brightness

237 The influence of stimulus intensity on detection and brightness judgments were first analyzed across cone
238 classes. Trials were grouped according to cone type and stimulus intensity. FoS was then computed from
239 binarized brightness ratings (ratings above 0 were seen). Figure 4 reports the FoS across our three subjects.
240 In S20053 and S20076, L- and M-cone thresholds (defined here as 50% FoS) were similar (Table 1). This
241 finding is expected based on the sensitivity of L- and M-cones to our 543 nm stimulus (Stockman and Sharpe,
242 2000). Single cone thresholds were higher on average in S20092, but within the normal range expected for
243 healthy volunteers (Harmening et al., 2014; Bruce et al., 2015).

244 Threshold for seeing was higher on trials targeted at S-cones. 543 nm light is about 300 times less
245 effective at activating S-cones relative to either L- or M-cones (Stockman and Sharpe, 2000). Therefore,
246 trials targeted at S-cones should be undetectable. In cases where a spot was detected, we assume that either
247 neighboring L/M-cones absorbed some fraction of the light or the cone was mis-classified and was in reality
248 an L- or M-cone. Threshold measurements have been previously used to elucidate S-cone topography near
249 the fovea (Williams et al., 1981). The FoS curves measured in S20076 and S20092 approximately adhere to
250 these expectations. In S20076, S-cone thresholds were significantly elevated relative to L- and M-cones. In
251 S20092, two (out of 62) cones had elevated thresholds and were purported to be S-cones (Table 1). Only at
252 the highest intensities tested did S-cone FoS increase above 50% in either subject (Figure 4B,C). In contrast,
253 S20053 did not exhibit this behavior. S-cones thresholds were indistinguishable from L- and M-cones. This
254 finding may indicate that single cones were less well isolated in this subject. However, were this the case,
255 FoS should nonetheless be systematically lower than L/M-cones due to at least a fraction of the light falling
256 on the targeted S-cone. A more likely explanation is the tested S-cones were mis-classified and were actually
257 L- or M-cones. We consider these two possibilities below.

Table 1: FoS psychometric function fits

	S20053				S20076				S20092			
	N	t	b	log-likelihood	N	t	b	log-likelihood	N	t	b	log-likelihood
L-cones	22	0.237	2.206	15.74	77	0.263	1.656	76.84	60	0.468	2.25	70.52
M-cones	18	0.278	2.161	15.84	33	0.25	1.531	39.37				
S-cones	2	0.244	1.729	2.08	9	0.851	3.305	11.89	2	0.877	6.701	1.94

Data were fit according to the Weibull function defined in Eq 1. t represents the threshold for 50% frequency of seeing in arbitrary stimulus units. b controls the slope of the function.

258 Brightness ratings from L-, M- and S-cones are displayed in Figure 4D-F. The three subjects in our study
259 exhibited similar gross reports of brightness ratings, which increased predictably with stimulus intensity. The
260 dependence of intensity I on perceived brightness, ψ , was modeled according to Steven’s Law (Stevens, 1966,
261 1961):

$$\psi = \kappa(I - I_{\theta})^n \quad (5)$$

262 where κ represents a scaling constant and I_{θ} has been interpreted as a threshold (Stevens, 1961). When
263 $n < 1$ the relationship follows a compressive non-linearity and when $n > 1$ the non-linearity becomes
264 expansive. In S20053 and S20092, n was less than one. This finding was consistent with a compressive
265 non-linearity that has been previously reported for brightness scaling of small spots (Stevens, 1966, 1960).
266 S20076 was best fit by a nearly linear relationship (Figure 4E; L-cones: $n = 1.26$; M-cones: $n = 1.11$).

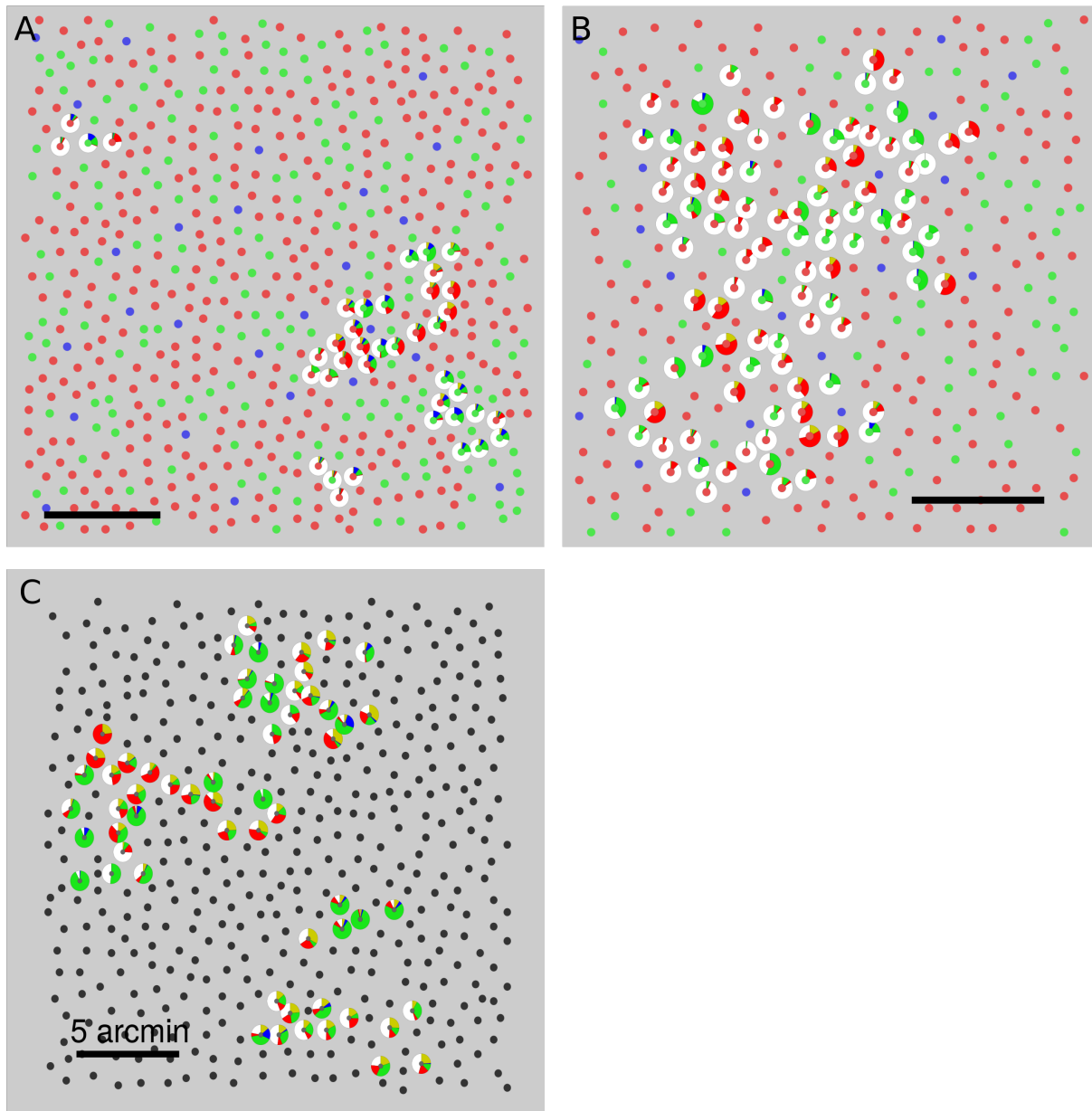


Figure 3: Spatial variation of hue and saturation scaling. Targeted cones are surrounded by a pie chart that represents the fraction of times a given color was reported. Each seen flash was scaled with five button presses. Pie charts illustrate all button presses from every seen trial across all three stimulus intensities. Cone locations are denoted by smaller circles. The spectral class of each cone is indicated by the color. L-cones = red, M-cones = green, S-cones = blue, Unclassified = black. **A.** S20053, **B** S20076, **C.** S20092. Scale bars indicate 5 arcmin or $\sim 24\mu\text{m}$.

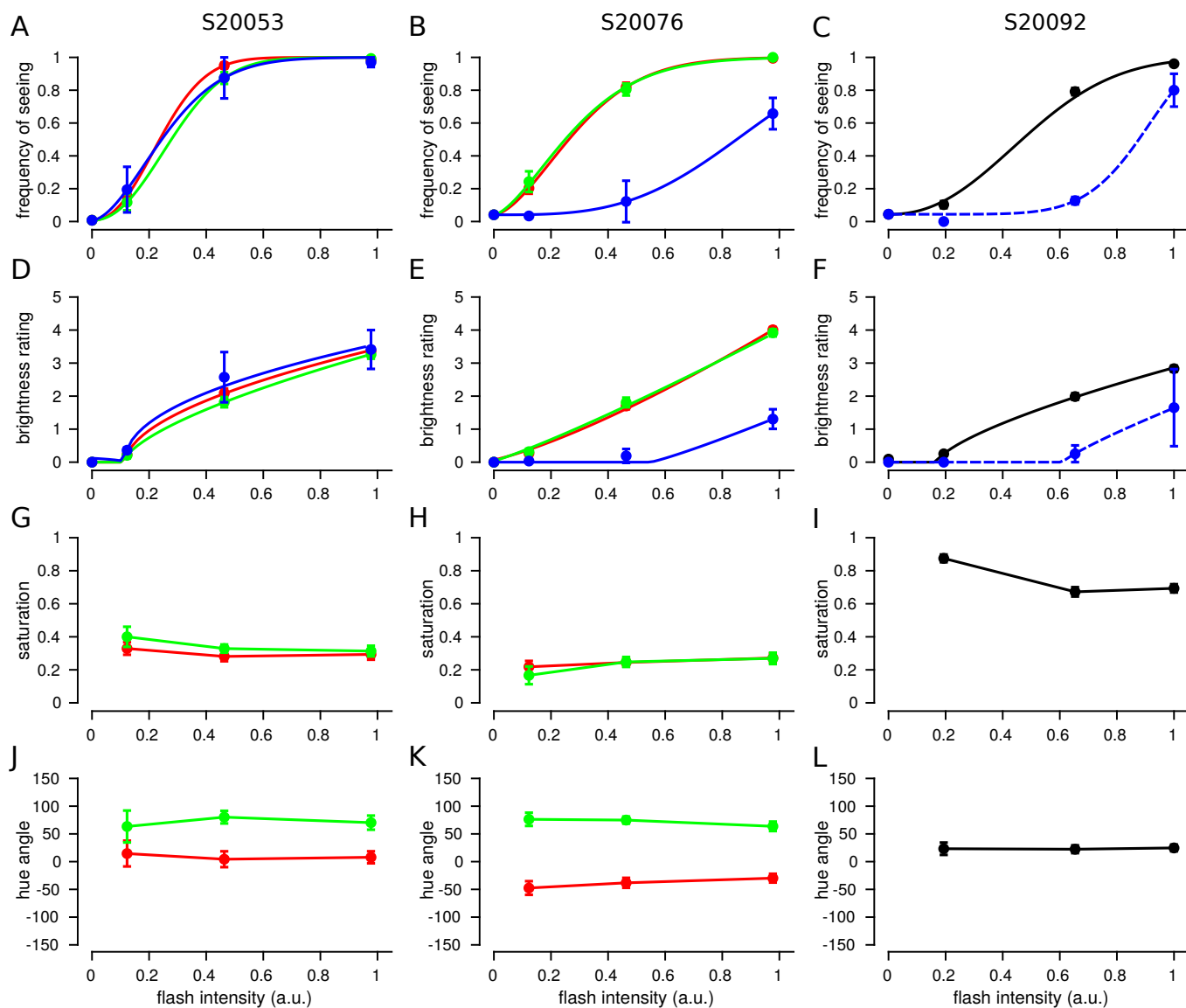


Figure 4: Brightness is dependent upon stimulus intensity, but hue and saturation are not. Trials from each cone were grouped according to flash intensity and the mean response was computed. The data plotted represent the mean and SEM across tested cones. Each column represents data from one subject. *Left*: S20053, *middle*: S20076, *right*: S20092. **A-C**: Frequency of seeing. Data were best fit with Weibull functions (Eq 1). **D-F**: Mean brightness ratings for each subject. Data were fit with exponential Steven's Law functions (Eq 5). **G-I**: Mean saturation ratings. **J-L**: Mean hue angles. Color denotes spectral identity of cone targeted: red = L, green = M, blue = S, black = unclassified L or M cone, blue dotted = purported S-cones. *Left column*: S20053. Error bars represent SEM.

267 S-cone targeted brightness ratings were expected to be lower than L/M-cone trials due to lower sensitivity
268 to the stimulus wavelength. Judgments from S20076 and S20092 followed this expectation (Figure 4E&F).
269 For the two S-cones targeted in S20053, brightness ratings were no different from L/M-cone trials. This
270 observation is more consistent with the interpretation that the two S-cones tested in this subject were mis-
271 classified by the densitometry procedure and were actually L- or M-cones. Of the three cone types, S-cone
272 classification is the least reliable (Roorda and Williams, 1999; Hofer et al., 2005a; Sabesan et al., 2015).
273 Weakly reflective L- and M-cones can, in some cases, be classified as S-cones.

274 Hue and saturation do not depend on intensity

275 The results above demonstrated that FoS and brightness ratings depended on stimulus intensity. We next
276 asked to what degree hue and saturation ratings correlated with stimulus intensity. In comparison to bright-
277 ness, stimulus intensity did not substantially influence hue or saturation ratings over the range studied
278 (Figure 4G-L). The largest shifts were observed between the lowest and highest energy stimuli. However, the
279 standard error of the mean was high in low intensity conditions due to low FoS (< 0.25 in all subjects).

280 The influence of stimulus intensity was also analyzed on a cone-by-cone basis. In all three subjects, hue
281 and saturation judgments were correlated across the two highest intensities (all comparisons, all subjects:
282 $p < 0.001$) and had slopes close to unity. Figure 5 shows the results from S20076 (*hue*: $R^2 = 0.881$, slope
283 $= 0.85$; *saturation*: $R^2 = 0.514$, slope $= 0.81$). The results from S20053 (*hue*: $R^2 = 0.735$, slope $= 0.76$;
284 *saturation*: $R^2 = 0.572$, slope $= 0.88$) and S20092 (*hue*: $R^2 = 0.687$, slope $= 0.74$; *saturation*: $R^2 = 0.503$,
285 slope $= 0.63$) were similar. Hue angles from cones with low saturation ratings (< 0.1) were excluded from
286 the analysis (29 of 187 cones). Hue angle values below 0.1 were inherently noisy due to the small number
287 of button presses that indicated the presence of a hue. Inclusion of low saturation cones did not materially
288 change the results. Overall, these findings lend further support to the conclusion that hue and saturation
289 judgments were largely independent of intensity.

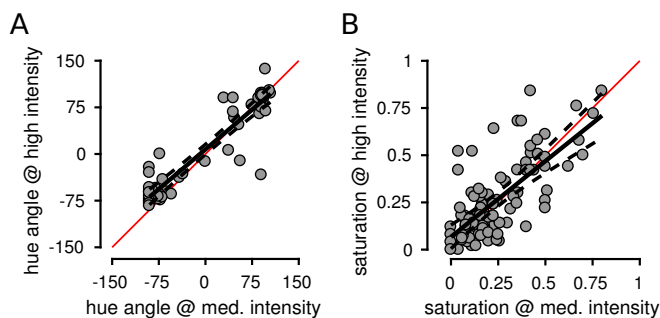


Figure 5: Hue and saturation judgments were correlated across stimulus intensities. Medium and high stimulus intensities were compared. Each point represents the mean response from an individual L- or M-cone across all seen trials at the indicated stimulus intensity. Data are shown from S20076. Hue angles (A) and saturation values (B) were highly correlated across stimulus intensity levels. Solid black line indicates best fit regression and dotted lines are 95% confidence intervals. Red line = unity.

290 Variability in color sensations from cones with the same photopigment

291 Unlike stimulus intensity, cone type imparted a substantial bias on hue reports. Figure 4J-L reveals clear
292 differences in the mean hue angle, μ_θ , recorded from spots targeted at L- (S20076: $\mu_\theta = -35.6 \pm 2.6^\circ$,
293 $N_{trials} = 793$; S20053: $\mu_\theta = 1.9 \pm 5.3^\circ$, $N_{trials} = 326$) versus M-cones (S20076: $\mu_\theta = 74.5 \pm 2.7^\circ$, $N_{trials} = 421$;

294 S20053: $\mu_\theta = 80.5 \pm 4.7^\circ$, $N_{trials} = 263$). On the other hand, saturation was not dependent on spectral class
 295 (Figure 4G&H).

296 To understand this observation in more detail, color reports were analyzed on a cone-by-cone basis.
 297 Responses from each trial were grouped by the cone targeted, regardless of stimulus intensity. Figure 6
 298 represents the data collected from each L- and M-cone in a UAD. The appearance of spots directed to L-cones
 299 clearly display a tendency towards reddish-yellow, while M-cone targeted spots were identified as green or
 300 greenish-blue in appearance. To quantitatively measure this tendency, the percentage of hue scaling variance
 301 explained by cone type was computed according to Eq. 4. Cone type accounted for 29.9% ($N=40$) and 41.4%
 302 ($N=97$) of the between cone variance in hue angle judgments in S20053 and S20076, respectively. Those
 303 numbers increased when cones with saturation values < 0.1 were excluded from analysis (S20053: 32.7%,
 304 $N=38$; S20076: 50.1%, $N=83$). In comparison, between cone variability in saturation was not predicted by
 305 cone type (S20053: 2.0%, $N=40$; S20076: 0.01%, $N=97$).

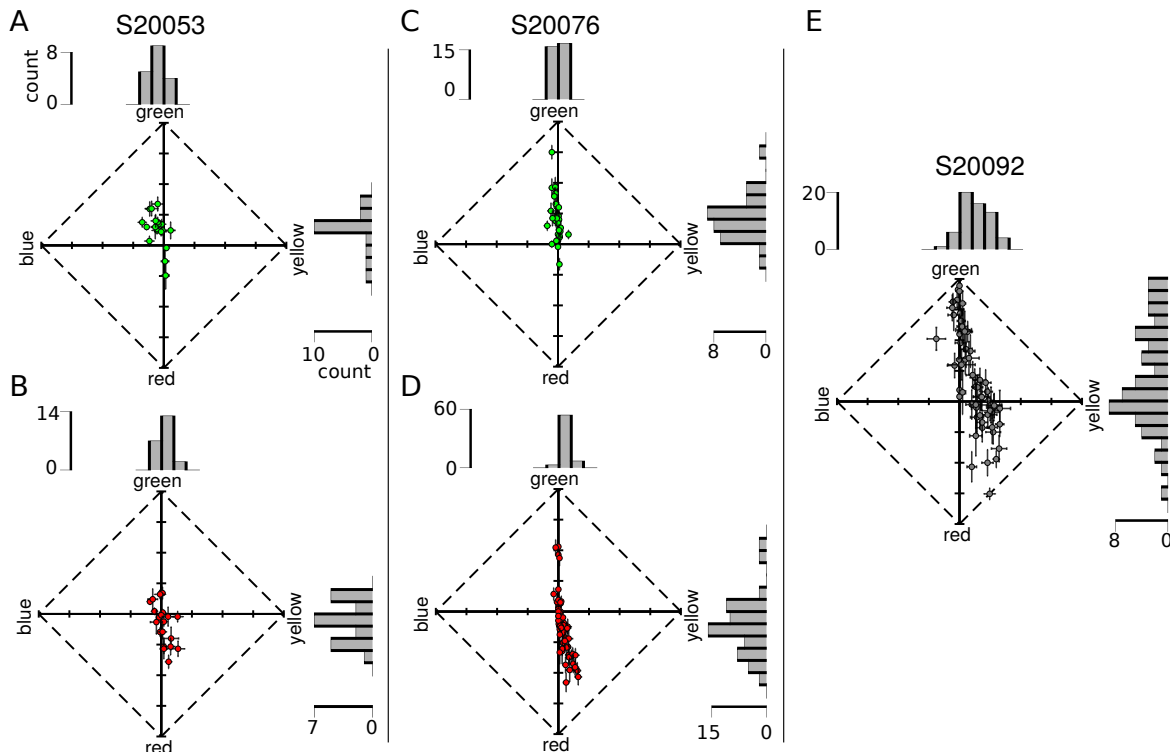


Figure 6: Hue and saturation reports from targeted cones. Each dot represents the mean response (of all seen trials, across all stimulus intensities) from an individual cone. Data are represented in a uniform appearance diagram, where the y-axis denotes a bias of responses towards greenness versus redness and the x-axis denotes a bias towards blueness versus yellowness. (A) M-cones and (B) L-cones tested in S20053. (C) M-cones and (D) L-cones tested in S20076. (E) Data from unclassified L- and M-cones in S20092. Error bars indicate SEM. Histograms above and to the right of each plot illustrate the distribution of responses along each dimension. Scale bars denote the number of cones in each bin.

306 Next, we asked whether cones sharing the same photopigment produced statistically distinguishable re-
 307 sponses. As reviewed in the Introduction, Krauskopf and Srebro (1965) proposed that L-cones stimulated
 308 in isolation would produce red/yellow sensations, while M-cones would elicit green/blue reports. To address
 309 this hypothesis, we first ran a one-way analysis of variance (ANOVA) to establish whether hue/saturation
 310 responses differed significantly between cones (Figure 6). The $y-b$ and $g-r$ dimensions of UAD space were
 311 assessed separately. In all three subjects, there was a main effect for cone targeted in both response dimen-

sions ($p < 0.01$ for all comparisons; S20053 *y-b*: $F_{39,766}=4.0$, *g-r*: $F_{39,766}=10.6$; S20076 *y-b*: $F_{96,2286}=8.3$, *g-r*: $F_{96,2286}=23.8$; S20092 *y-b*: $F_{59,1054}=6.5$, *g-r*: $F_{59,1054}=13.0$). Subsequently, post-hoc analyses (Tukey-Kramer) were run to determine which cones differed from one another.

The heatmaps in Figure 7 displays the statistical significance (\log_{10} transformed) of each comparison. Each square represents a single post-hoc comparison between two cones. Results were organized according to cone class. Yellow squares indicate that mean responses did not differ; blue squares indicate that the two cones elicited significantly different responses. If cones with the same photopigment produce a single color sensation, we should find a clump of yellow squares when cones of the same photopigment were compared and blue clumps corresponding to L- and M-cone comparisons. The results did not support the strongest form of this hypothesis. The heatmaps in Figure 7 reveal that while cones of the same type were often very similar, they were not universally so – many produced statistically different mean color ratings. These effects were most clear in the green-red dimension of S20076 and to a lesser degree S20053 (Figure 7B,D). Overall, the yellow-blue dimension was more uniformly distributed across cone types (more yellow, less blue), owing to less frequent usage of these terms. The results from S20092, whose cone types were not known, are shown in Figure 7E,F. In general, a similar pattern emerged from this subject. Responses from cones were statistically distinguishable from about a third of the other cones. Together, this analysis confirms that many L- and M-cones elicited distinct hue sensations as hypothesized by Krauskopf and Srebro (1965). However, these results also indicate that variability between cones with the same photopigment also exists, which confirms the observations of Hofer et al. (2005b).

Hue percepts predict cone type

The tendency for cones to produce responses consistent with cone type encouraged us to ask how well cone type could be predicted from hue scaling. The results from S20053 and S20076 were collected into a single dataset and a support vector machine (SVM) was fit to the data. SVMs are a supervised approach to learning categorical labels. The SVM was given the position of each cone in UAD coordinates and its objectively classified (via densitometry) cone type and the algorithm learned a decision criterion. The learned boundary between L- and M-cones is shown by a solid diagonal line in Figure 8A. The trained SVM was then used to predict cone types based on the measured UAD position; a procedure we termed subjective classification. Following this procedure, it was found that subjective and objective classification agreed $79.0 \pm 3.5\%$ (108/137) of the time, which was statistically higher than expected by chance (Cohen's Kappa = 0.534, $p < 0.001$). Similar results were obtained when the SVM was trained on each subject's data separately. Based on the robustness and accuracy of this procedure, the trained SVM was used to predict the data from S20092. The UAD data and SVM boundary are shown in Figure 8B and the spatial location of each subjectively classified cone is represented in Figure 8C. This procedure identified 33/60 L-cones. However, it is worth noting that S20053 and S20076 had very similar L:M cone ratios (near 2:1) and it is not known whether the SVM boundary would be influenced by this ratio.

Possible influence of neighboring cones

Lastly, we explored the factors that potentially caused some cones to produce sensations that were inconsistent with their photopigment. One factor that could influence color sensations are other cones spatially proximal to the targeted cone. The local neighborhood of a targeted cone could influence perception in at least three ways: (1) differential baseline activity might either adapt or sensitize post-receptoral pathways (Schmidt et al., 2018; Tuten et al., 2017), (2) light from the flash might leak into neighboring cones and (3) neighboring cones may influence the hard-wired or learned hue sensation associated with each cone (Benson et al., 2014). In these experiments, the baseline activity of L- and M-cones was approximately equal and unlikely to have been a major factor. The latter two possibilities are worth considering in more detail.

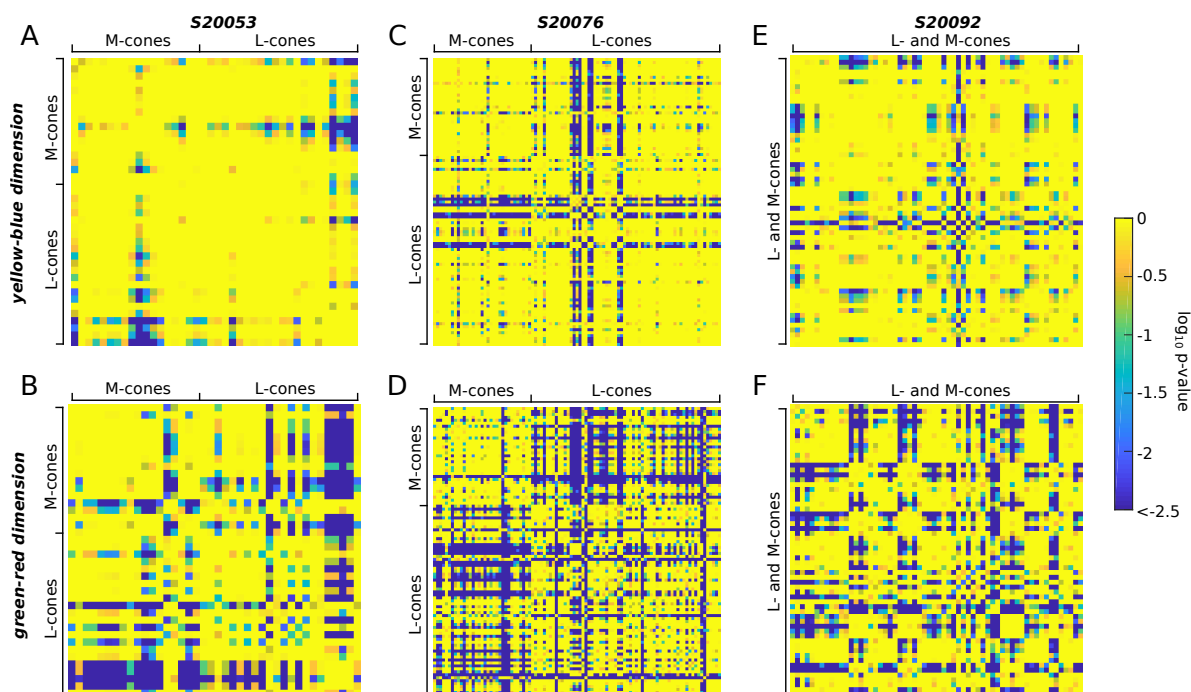


Figure 7: Cones with the same photopigment yield different sensations. An ANOVA revealed a main effect for cone targeted on hue/saturation scaling. The results of post-hoc tests (Tukey-Kramer) are shown. The mean response (UAD) measured for each cone was compared to all other cones. Comparisons were organized according to cone class. Heat maps represent the statistical significance of each comparison. Bluer colors indicate that the mean responses were statistically different (deep blue denotes $p \leq 10^{-2.5}$). Yellow-blue (**A**, **C**, **E**) and green-red (**B**, **D**, **F**) dimensions of UAD space were assessed separately. **A**, **B** S20053, **C**, **D** S20076, **E**, **F** S20092. The diagonal yellow line in each plot corresponds to the location where each cone was compared with itself. Each matrix is symmetric along the diagonal axis, *i.e.* the top and bottom triangles are mirror images.

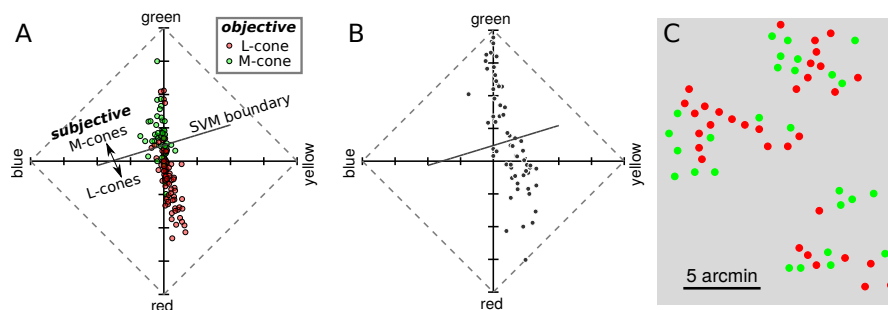


Figure 8: Hue and saturation reports predict cone type. **A** Data from S20053 and S20076 were collected into a UAD coordinates and fit with a SVM classifier. The classifier identified each cone as either L- or M-cone based on its mean UAD position. The learned decision boundary is shown by the solid diagonal line. This procedure is referred to as subjectively derived classification. For comparison, the objectively derived, densitometry based, classifications are represented by the color of each dot. **B** The results from S20092, whose cones have not been objectively classified, are re-plotted in an UAD and the SVM decision boundary learned in **A** is shown. Cones above the line were classified as M-cones and those below as L-cones. **C** Spatial location of each cone in the mosaic. The color of each dot indicates the subjectively inferred cone type (red=L, green=M).

356 The possibility that uncontrolled light leaking into neighboring cones had a significant influence on per-
357 ception was tested first. The mean saturation of each cone was computed as a function of the number of
358 non-like neighbors in its immediate surround. If the small proportion of light reaching neighboring cones
359 were influencing hue and saturation judgments for single cone-targeted stimuli, one expectation is that satu-
360 ration judgments should decrease as the number of non-like neighbors increases. The intuition being that if,
361 for example, an L-cone with six surrounding M-cones was targeted, then light leaking into the neighboring
362 M-cones would generate a less saturated (whiter) sensation (Krauskopf and Srebro, 1965). Alternatively, the
363 local neighborhood may influence color judgment through prior expectation. Some models of small spot color
364 appearance, *e.g.* Brainard et al. (2008), predict that an L-cone surrounded by six M-cones should produce
365 a more saturated red sensation than a mixed surround, since post-receptoral pathways would carry a strong
366 chromatically opponent signal in the former case. Figure 9 demonstrates that neither expectation was borne
367 out: saturation ratings were not dependent upon the number of non-like neighbors. Similarly, the mean hue
368 angle from each cone was not significantly influenced by the number of non-like neighbors ($p > 0.05$).

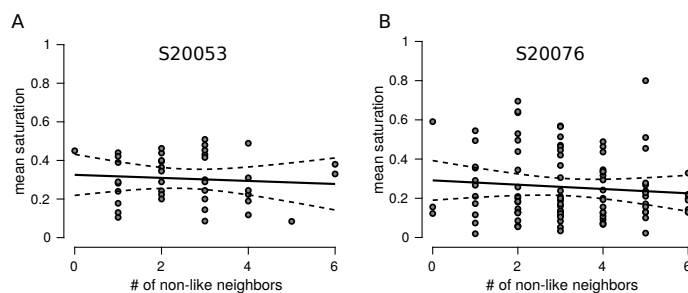


Figure 9: Influence of neighboring cones on saturation judgments. Each data points represents the mean saturation judgment as a function of number of non-like neighbors from a tested L- or M-cone in S20053 (A) and S20076 (B). Data includes all seen trials across all intensities. Solid black line indicates best fit regression and dotted lines are 95% confidence intervals. $p > 0.05$ for both correlation analyses.

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Discussion

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The neural computation of color depends on both relative activity across the three cone types and previous experience (Brainard, 2015; Gegenfurtner, 2003). In the case of very small spots, like the ones used here, the visual system is unable to compare stimulus-driven activity across the cone classes and must rely on prior experience, or hard-wired connections, alone. Despite the unnatural nature of such a stimulus, subjects often see colored spots and we report here that hue sensations were predicted based on the photopigment of the cone probed (Figure 8). These results support the idea that, near the fovea, the visual system maintains information about the spectral class of each cone in its own receptor mosaic.

We found that the spectral identity of $79.0 \pm 3.5\%$ of targeted cones could be correctly identified based on the color they generated (Figure 8) and as much as 50% of the variability in hue judgments could be attributed to the cone type targeted. These observations are remarkable for a few reasons. First, a light capture model indicated that the targeted cone did not absorb 100% of the stimulus light (Figure 1). Between 18 and 33% of absorbed light was captured by the nearest six cones. Theoretically, light leak into these nearby cones could have had a profound influence on the perceived color or saturation of stimuli. However, we did not find evidence in support of such an influence (Figure 9). This observation was consistent with the targeted cone acting as the dominant driver of hue reports. Second, the present subjective cone classification was at least as good as a recent study that was designed to classify cones psychophysically. Tuten et al. (2018), using adaptive optics, measured sensitivity to cone targeted flashes and compared those results to objectively

387 identified cone classes. The authors used two chromatic backgrounds and stimulus wavelengths to selectively
388 bias detection towards either L- or M-cones. With this procedure they found $77\pm 2.9\%$ of cones classes were
389 correctly predicted. In the current paradigm, both baseline activity and sensitivity to the stimulus probe were
390 equalized between L- and M-cones. Thus, at the level of the receptor mosaic, each stimulus flash produced
391 an identical pattern of activity. Thirdly, the objective classification method itself has an error rate estimated
392 to be between 3-5% (Sabesan et al., 2015), which sets the upper bound on how well any comparison can
393 do. Despite all of these challenges and limitations, subjectively derived cone classification, based solely on
394 hue and saturation scaling, agreed well with objective measurements. This evidence indicates that the visual
395 system has prior information, either hard-wired during development or learned through experience, about
396 each cone in its mosaic – a “lookup table” of sorts – that it leverages during the process of assigning a hue
397 sensation.

398 The presence of a “lookup table”, which associates each receptor in the human cone mosaic with a type
399 specific hue, may be surprising given the arrangement of the cone mosaic. There are no known molecular
400 markers that differentiate L- from M-cones and the spatial topography of L- and M-cones near the fovea follows
401 an approximately random distribution (Hofer et al., 2005a; Roorda and Williams, 1999; Roorda et al., 2001).
402 During development, the expression of a single opsin gene in each cone is thought to arise through a stochastic
403 process (Knoblauch et al., 2006; Neitz and Neitz, 2011). Furthermore, cones migrate during development
404 towards the fovea (Hendrickson, 1994), which introduces additional spatial randomization. Thus, acquiring
405 a spatially detailed representation of the cone mosaic is a challenge for the visual system. One possibility
406 is that the brain learns a map of the location (Ahumada and Mulligan, 1990) and spectral identity of the
407 cone mosaic through visual experience (Brainard, 2015; Benson et al., 2014). The intuition behind this
408 idea is that during natural viewing the activity across a cone mosaic will be correlated in space, time and
409 across spectral classes due to the statistics of natural scenes, eye movements and the action spectra of the
410 photopigments. Benson et al. (2014) demonstrated that spatial and spectral correlations are theoretically
411 sufficient to distinguish the spectral identity of cones in a mosaic. The parvocellular pathway is an obvious
412 candidate for representing information at such fine spatial scales. Near the fovea, parvocellular (midget)
413 ganglion cells receive input from a single cone (Kolb and Marshak, 2003; Dacey, 2000) and this private line
414 is thought to be approximately preserved through at least the lateral geniculate nucleus (McMahon et al.,
415 2000; Schein, 1988). In cortex, receptive fields of visual neurons increase in size (Dumoulin and Wandell,
416 2008; Felleman and Van Essen, 1991) and pool signals from more and more neurons. Therefore, information
417 about cone type is unlikely to arise *de novo* at later centers.

418 Further insight into the neural pathways most likely involved in this task comes from the variability in
419 color judgments when cones with the same photopigment were targeted (Figure 6&7). Classically, small spot
420 experiments were interpreted in the tradition of Muller’s Law (Krauskopf, 1978; Krauskopf and Srebro, 1965;
421 Krauskopf, 1964; Ingling et al., 1970; Otake and Cicerone, 2000; Hartridge, 1946). Within this framework a
422 single neuron was thought to represent the presence or absence of a single variable, such as a red surface or
423 an oriented bar – *i.e.* a labeled line (Muller, 1930). Accordingly, a higher firing rate was thought to indicate
424 a redder stimulus, for example. Krauskopf and Srebro (1965) argued that the appearance of spots detected
425 by a single cone would carry a single chromatic sensation: light absorbed by an L-cone would appear red,
426 while an M-cone greenish-blue. Our results were only partially consistent with that prediction. Red/yellow
427 was most frequently reported when an L-cone was targeted, while green/blue was used most often on M-cone
428 trials (Figure 4&6). However, the present work, along with previous reports (Sabesan et al., 2016; Schmidt
429 et al., 2018; Hofer et al., 2005b), demonstrated that cones within a spectral class often elicited different
430 percepts (Figure 7) and the most common response was white. Together these observations contradict the
431 strongest form of Krauskopf and Srebro’s hypothesis.

432 A single cone contributes to the receptive field of at least 20 classes of ganglion cells that each tile the
433 retina (Masland, 2011; Dacey, 2004). For this study the two numerically dominant classes of ganglion cells

434 – the parasol and midget classes – are most relevant for consideration. Both classes are known to be excited
435 by single cone stimuli (Li et al., 2014; Freeman et al., 2015; Sincich et al., 2009) and project to the lateral
436 geniculate nucleus (Dacey, 2004). Midget ganglion cells have been proposed as the retinal substrate for
437 red-green chromatic sensations and high acuity vision (Lee, 2011; Dacey, 2000), while parasol ganglion cells
438 constitute a channel carrying achromatic and motion information (Manookin et al., 2018; Schiller et al., 1990).
439 Presumably each cone targeted in our study contributes to both midget and parasol channels. However, the
440 relative strength of those connections may differ between cones (Li et al., 2014). Differences in connection
441 strength could underly the within class variability in saturation ratings we observed. Were this the case,
442 then altering the contrast (intensity) of the stimulus should favor one pathway over the other. At lower
443 contrasts, parasol cells would be favored owing to their higher contrast response gain (Kaplan and Shapley,
444 1986; Shapley, 1990). At higher contrasts, the lower sensitivity midget (parvocellular) pathway will be more
445 strongly recruited. Thus according to this idea, saturation should increase proportionally with intensity.
446 However, we did not observe this phenomenon. Saturation judgments were relatively independent of stimulus
447 intensity (Figure 4) and in two of the three subjects the relationship went in the opposite direction. These
448 conclusions are further supported by previous work using small spots (Finkelstein and Hood, 1982, 1984;
449 Finkelstein, 1988).

450 Alternatively, a population of neurons together may represent a property, such as color, as a probability
451 distribution (Pouget et al., 2013). This could be accomplished if sensory input is encoded across a population
452 of neurons with variable tuning (Ma et al., 2006; Finkelstein and Hood, 1984). Numerous authors have
453 proposed that a representation of color space could be built in such a manner by cortical circuits that
454 combine input from lower visual areas (Bohon et al., 2016; Kellner and Wachtler, 2013; Brainard et al., 2008;
455 Emery et al., 2017; Finkelstein and Hood, 1984). For instance, midget ganglion cells multiplex chromatic
456 and achromatic signals, an idea known as “double duty” (Rodieck, 1991; Dacey, 2000; Shapley, 1990). The
457 relative strength of chromatic versus achromatic information varies between cells due to random wiring (Wool
458 et al., 2018; Crook et al., 2011). Near the fovea, each midget cell would have an L- or M-cone in its center and
459 variable cone weights in the surround, based on the cone types of its closest neighbors. Models explaining
460 how randomly wired midget ganglion cells may sub-serve both chromatic and achromatic sensation have been
461 described previously (Sabesan et al., 2016; Schmidt et al., 2014, 2016; De Valois and De Valois, 1993; Ingling
462 Jr. and Martinez, 1983; Finkelstein, 1988; Finkelstein and Hood, 1984; Wool et al., 2018). Since each midget
463 cell carries a unique chromatic/achromatic signature, the visual system could learn to associate different
464 prior information with the output of each midget ganglion cell through experience (Benson et al., 2014). The
465 color reported when a single cone is targeted with light may be a reflection of that prior experience. Finally,
466 this theory makes the testable prediction that color reports in the peripheral retina, where the centers of
467 midget-cell receptive fields pool signals from multiple cones (Dacey, 2000), will be less tightly predicted by
468 the cone type stimulated.

469 In summary, using a middle wavelength small spot probe we found (1) brightness ratings and frequency
470 of seeing depended upon stimulus intensity, but were not influenced by cone class. (2) Cones with the same
471 photopigment often produced statistically different responses. (3) Despite this within cone class variability,
472 hue responses varied so predictably between L- and M-cones that spectral identity was predicted from color
473 reports with high accuracy. (4) Local neighborhoods had little, to no, influence on cone targeted sensations.
474 These observations demonstrate that the visual system possesses a model of the world with enough precision
475 to assign a meaningful hue label to spots of light that modulates the activity of only a single cone.

476 Acknowledgments

477 We thank Professor Ramkumar Sabesan for providing helpful feedback on an earlier draft of this manuscript.
478 We are grateful for technical assistance from Dr. Nicolas Bensaid, Dr. Francesco LaRocca and Pavan

479 Tiruveedhula. This work was supported by grants from National Eye Institute National Institute of Health
480 (R01EY023591, F32EY027637 and T32EY7043-38), the Minnie Flora Turner Memorial Fund for Impaired
481 Vision Research and the Michael G. Harris Ezell Fellowship.

482 **Competing interests** A.R. has a patent (USPTO#7118216) assigned to the University of Houston and
483 the University of Rochester which is currently licensed to Boston Micromachines Corp (Watertown, MA,
484 USA). Both he and the company stand to gain financially from the publication of these results.

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