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SPECIAL ISSUE

Short Wavelength-Sensitive Cones and the Processing of Their Signals

REVIEW ARTICLE

S-cone psychophysics

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Abstract

We review the features of the S-cone system that appeal to the psychophysicist and summarize the celebrated characteristics of S-cone mediated vision. Two factors are emphasized: First, the fine stimulus control that is required to isolate putative visual mechanisms and second, the relationship between physiological data and psychophysical approaches. We review convergent findings from physiology and psychophysics with respect to asymmetries in the retinal wiring of S-ON and S-OFF visual pathways, and the associated treatment of increments and decrements in the S-cone system. Beyond the retina, we consider the lack of S-cone projections to superior colliculus and the use of S-cone stimuli in experimental psychology, for example to address questions about the mechanisms of visually driven attention. Careful selection of stimulus parameters enables psychophysicists to produce entirely reversible, temporary, "lesions," and to assess behavior in the absence of specific neural subsystems.

Introduction

Within the human cone mosaic, it is clear that the S-cones are different (Curcio et al., 1991), and as such they have attracted considerable interest in psychophysical studies. Part of the attraction stems from practical considerations. The S-cones are the least numerous in the primate retina, comprising between 5% and 10% of all cones, evenly distributed across the retina, except for an S-cone free region in the central fovea that is surrounded by a ring of relatively high S-cone density (Ahnelt & Kolb, 2000; Hunt & Peichl, 2013). The relative sparsity of the S-cone mosaic provides a perfect opportunity to probe the relationship between the sampling arrangement of photoreceptors and perceptual performance. Twenty years before adaptive optics was applied to increase the resolution of *in vivo* retinal imaging and stimulation, Williams et al. (1981) were able to map discrete peaks in psychophysical sensitivity that were spaced roughly 10 min of arc apart and thought to correspond to individual S-cones. In addition, the spectral sensitivity of the S-cones is quite different from that of the L- and M-cones, so that the isolation of S-cone mediated vision *via* selective adaptation to suppress the sensitivity of the L- and M-cones is relatively easy (Wyszecki & Stiles, 1982).

The S-cones are also alluring for theoretical reasons. The S-opponent subsystem of color vision is thought to be phylogenetically ancient (Mollon, 1989), offering to the majority of mammals that are dichromatic the possibility of color vision through the comparison of two classes of photoreceptors: those that are sensitive in the short-wavelength range (S-cones) and those that are sensitive in the middle-to-long wavelength range (Jacobs, 1993). It has been thought that the S-cones subserve only chromatic vision (for counterarguments, see Conway, 2013 and Xiao, 2013), and so they provide a means by which to test specializations of visual function. The evolution of the S-cone pathways, arguably for functions that are separate both from high acuity spatial vision and from the phylogenetically recent L/M-opponent color processing in trichromatic primates (see Hunt & Peichl, 2013), has left anatomical and physiological signatures that can be exploited to probe general questions about the links between neural circuitry and human visual performance.

Measuring S-cone mediated vision

Performance that depends on signals originating in the S-cones

The psychophysical approach requires a measurement of visual behavior in response to stimuli that have been carefully constructed to isolate some putative visual mechanism or process. Anatomical and physiological evidence suggests that the S-cone signal feeds only selective parts of the visual system, and so it should be possible to design stimuli that depend only on the S-cones and their associated pathways, whilst restricting the involvement of other visual pathways. Since the spectral sensitivities of the cones are overlapping (see Figs. 1a and 1b), it is not possible to find a wavelength of light that stimulates only the S-cones. There are two primary methods, summarized below, that have been used to isolate the S-cone subsystem.

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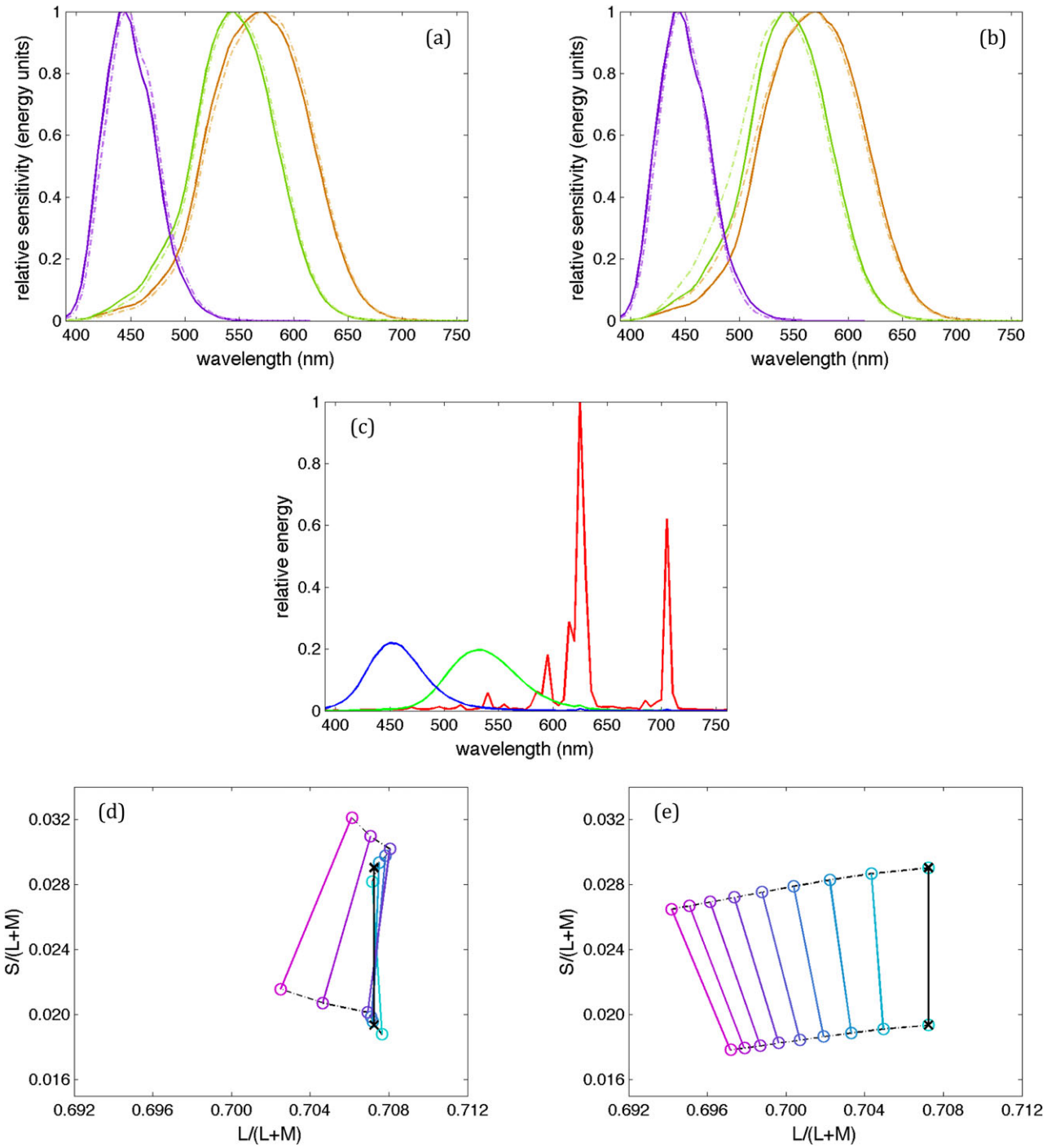


Fig. 1. (**a** and **b**) CIE 2006 "physiologically relevant" cone LMS cone fundamentals. Solid lines are sensitivities for the standard 2° observer (parameterized by age 32 years and field size 2°); (**a**) dashed lines are sensitivities for an older observer (age 60 years; field size 2°); (**b**) dashed lines are sensitivities for a standard 10° observer (age 32 years; field size 10°); (**c**) relative spectral energy distributions for the RGB primaries of an example CRT (Sony FD Trinitron); (**d** and **e**) MacLeod-Boynton chromaticity diagrams showing paired coordinates of stimuli produced from the CRT primaries and selected to be tritan increments from equal energy white ($\Delta L/L = 0.0$; $\Delta M/M = 0$; $\Delta S/S = 0.5$) for the standard 2° observer and re-plotted in terms of the cone signals they offer to alternative observers. When the alternative observer is the same as the standard observer (solid black lines and crosses) the paired coordinates align with the tritan axis. When the alternative observers differ from the standard (solid cyan to purple series) the paired coordinates are rotated and displaced from the desired locus in color space; (**d**) alternative observers of age 20, 40, 50, 60, 70, and 80 years; (**e**) alternative observers with field size 3, 4, 5, 6, 7, 8, 9, and 10°.

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The two-color increment threshold technique

Much of the early psychophysical work on the S-cone system rests on the "two-color increment threshold" technique of Stiles (see Stiles, 1959 for review). For a test light and a background light of the same wavelength composition, the smallest change in intensity that can be detected increases with increasing intensity of the background, typically rising slowly from absolute threshold and then following Weber's law before saturating. Multiple mechanisms might be revealed by multiple branches of this threshold-versus-radiance (t.v.r.) curve, and the wavelength composition of test and background lights can be systematically varied to map out the spectral response of the mechanisms. Stiles' π mechanisms are defined in this way. Fig. 2 shows the so-called field sensitivities of the π mechanisms – the reciprocals of the field radiances (in log quanta s^{-1} deg^{-2}) required to raise the threshold of each "isolated" π-mechanism by one log unit above its absolute threshold. Stiles typically used a 1-deg test flash of 200 ms duration, superimposed on a 10-deg background. By using an adapting background that preferentially stimulates the L- and M-cones and thereby reduces their sensitivity (e.g. a light of 610 nm), but which has little effect on the S-cones, it is possible to generate conditions in which detection of short-wave increments depends on signals that originate in the S-cones. There are three short-wavelength sensitive branches of the two-color threshold curves – $\pi1$, $\pi2$, and $\pi3$. The spectral sensitivity of $\pi3$ is close to the S-cone sensitivity measured in blue-cone monochromats (Stockman et al., 1999).

An important and recurrent concept in psychophysical models of S-cone mediated vision is that the S-cone signal can be attenuated by gain controls at two sites. Pugh and Mollon (1979), for example, argue that $\pi1$ and $\pi3$ correspond to a single pathway originating in the S-cones. They relate the two branches to adaptation at the "first site" (which may be the receptors themselves) and at the "second site" (proximal to the convergence of antagonistic signals from the L- and M-cones).

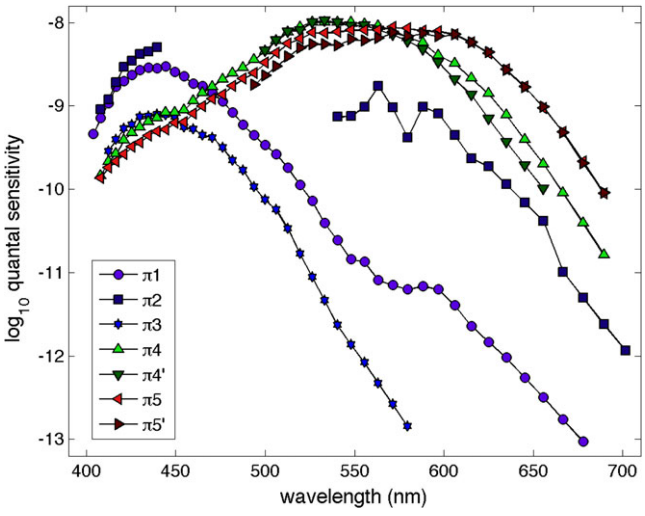


Fig. 2. Stiles' π mechanisms. Field sensitivities – the reciprocals of the field radiances (in log quanta s^{-1} deg^{-2}) required to raise the threshold of each "isolated" π-mechanism by one log unit above its absolute threshold – of the seven photopic π mechanisms. Three are predominantly S-cone mechanisms ($\pi1$, $\pi2$, and $\pi3$), two M-cone ($\pi4$ and $\pi4'$), and two L-cone ($\pi5$ and $\pi5'$). [*Data from Table 2(7.4.3) of Wyszecki and Stiles*].

Silent substitution

For a trichromatic observer, metameric color matching can be achieved by combining three spectrally independent primaries to match a test light of arbitrary wavelength composition. At the match-point, the test light and the mixture produce equivalent excitations in the three cone classes, and are indistinguishable. These lights can be exchanged without changing the cone excitations, making a so-called silent substitution for all three cones. Adjusting the relative intensities of the primaries allows the cone signals to be modified, and with three primaries it is possible to control independently the relative excitations of three cone classes. Indeed for a given set of primaries and cone spectral sensitivity functions, a 3-by-3 transformation matrix can be used to convert from values specifying the relative outputs of the three primaries to the resultant cone excitations, and *vice versa* (see Brainard & Stockman, 2009). Lights that are matched in the L- and M-cone excitations they offer but that differ in the S-cone signal are said to lie on a tritan confusion line, since they would be indiscriminable to a tritanopic observer lacking S-cones, and this approach has been widely used in psychophysical studies that seek to understand S-cone vision.

The physical lights that are required depend not only on the spectral sensitivity of the photoreceptors, but also on spectrally selective prereceptoral filtering. Spectral transmission properties of the lens vary with age (Pokorny et al., 1987) and there are large variations in the normal population in the amount and distribution of macular pigment (Moreland & Bhatt, 1984; Hammond et al., 1997). These factors modify the light that reaches the retina, so lights that isolate a tritan line for one observer (typically published estimates of the "standard" observer) may offer significant modulations to the L- and M-cones for a second observer.

The Stockman and Sharpe cone fundamentals (Stockman et al., 1999; Stockman & Sharpe, 2000*a*) represent the spectral sensitivity functions of the cones measured in the corneal plane of the standard observer. By considering the absorption of the ocular media and the macula, and taking into account the densities of the visual pigments, the CIE Technical Committee 1-36 (2006) additionally allows construction of "alternative observers" (defined by age and field size). This model permits calculation of representative errors that might be expected for particular individuals. These can be conveniently represented in a MacLeod-Boynton chromaticity diagram, with appropriately scaled axes L/(L + M) and S/(L + M) (Macleod & Boynton, 1979). First, we specify the relative L-, M-, and S-coordinates of the stimuli we wish to produce. Tritan pairs are plotted as black vertical lines in Figs. 1d and 1e. For a given 3-primary display (Fig. 1c), this determines a particular stimulus, specified by a red, green and blue (RGB) triplet. Now, we can calculate the relative L-, M-, and S-coordinates for an alternative observer viewing this stimulus. The resultant cone coordinates are represented as series of colored lines in Fig. 1d for alternative observers of ages 20, 40, 50, 60, 70, and 80 years and in Fig. 1e for alternative observers with field sizes 3, 4, 5, 6, 7, 8, 9, and 10°.

When the alternative observers differ from the standard, the paired coordinates are rotated and displaced from the desired locus in color space. The rotations specify the L- and M-cone contamination of the nominally tritan stimuli. In the worst cases, ~5% of the ΔS/S cone-contrast leaks into ΔL/L and ΔM/M cone-contrast. Whilst this is a relatively small contamination in absolute terms, it must be considered in relation to the relative thresholds of the chromatic detection mechanisms (see the section on Detection mechanisms and cardinal axes), which are approximately ten times more sensitive for the L/M-opponent mechanism than for the

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S-opponent mechanism (Eskew et al., 1999). Furthermore, such contamination is particularly significant for high-gain cells that amplify contrast (see Martin & Lee, 2013).

With broadband primaries (such as those from a cathode ray tube (CRT) display, see Fig. 1c), there is no straightforward way to determine the tritan line for an individual observer. Psychophysical procedures to determine an individual's tritan confusion line depend on some characteristic of S-cone vision that is reflected in visual performance. Many of the characteristics discussed in later sections are potential candidates, but three published methods are the Webster method (Webster et al., 1990; Webster & Mollon, 1994), the minimally distinct border method (Tansley & Boynton, 1976; Boynton & Kaiser, 1978), and the transient tritanopia method (Smithson et al., 2003).

If a silent substitution is performed with monochromatic (as opposed to broadband) lights, one advantage is that prereceptoral absorptions do not alter the ratios in which (a given set of) fundamentals are excited. So, for example, a pair of lights (such as 436 nm and c. 490 nm) that are luminance equated and that match under tritanopic conditions (induced by presenting near-threshold targets on an intense 420 nm background) can be used to achieve S-cone isolation (Stockman & Sharpe, 2000*b*). Similarly, a 4-primary system with narrowband primaries at c. 460, 516, 558, and 660 nm can be calibrated for an individual observer simply by determining the relative intensities of lights that produce a unique color match between a mixture of 460 and 558 nm and a mixture of 516 and 660 nm (Pokorny et al., 2004).

Chromatic adaptation

There is now ample evidence for sensitivity regulation in cone-specific pathways, prior to any opponent combination (see Eskew et al., 1999 for review), and psychophysically local adaptation has been shown to occur at the spatial resolution of single cones (Macleod & He, 1993). To first approximation, Weber's law holds independently for the three cone classes, but, two significant failures – transient tritanopia (Stiles, 1949; Mollon & Polden, 1975) and combinative euchromatopsia (Polden & Mollon, 1980), described below – have been influential in providing evidence for sensitivity adjustments at a post-receptoral opponent site.

We can infer that a 200 ms test flash of short-wavelength light (435 nm) superimposed on a bright long-wavelength auxiliary field (570 nm) is detected by the S-cones (Wyszecki & Stiles, 1982). An additional adapting light would increase the intensity of 435 nm test flash required for detection and, if two adapting lights of different wavelengths (430 nm and 590 nm) are separately adjusted in radiance so that they raise detection threshold by the same amount, we infer that they have the same effect on the S-cone mechanism. Extinguishing the adapting light should, if Weber's law holds, reduce the detection threshold, and it does for the short-wave adapting light. But, for the long-wave adapting light, thresholds for the S-cone test flash are transiently increased following extinction of the adapting light (Pugh & Mollon, 1979). The result – transient tritanopia – is strong evidence that the sensitivity of the S-cone mechanism is controlled not only by the quantal catch of the S-cones, but additionally by a mechanism with a different, long-wavelength dominated, sensitivity. A similar post-receptoral adjustment to sensitivity is suggested by the observation – dubbed combinative euchromatopsia – that detectability of a violet test flash on a steady blue field increases when yellow light is added to the blue field so as to yield a composite field that appears white (Polden & Mollon, 1980).

Intense long-wavelength adapting fields have often been used to isolate the short-wave π mechanisms, but such fields may do more than suppress the long- and middle-wave cones. It is possible that several seemingly conflicting results for S-cone mediated vision are dependent on differences in chromatic adaptation at a post-receptoral site.

S-cone mechanisms

Color vision mechanisms

The dominant model of human color processing suggests two chromatically opponent post-receptoral channels, one comparing the signals in the L- and M-cones and the other comparing the S-cone signal with some combination of signals from the L- and M-cones. Models of this type that consider two stages of color processing – a trichromatic receptoral stage followed by an opponent post-receptoral stage – are covered in detail by Stockman and Brainard (2009). Much of the psychophysical evidence for the second stage derives from threshold measurements of color detection and discrimination. To account for color appearance a third stage, with different spectral sensitivity from the second stage, is required. In the brief discussion below, we follow the convention of referring to the chromatic color-discrimination mechanisms according to their predominant cone inputs: L–M and S–(L + M).

Detection mechanisms and cardinal axes

The null planes of chromatic responses of neurons in the lateral geniculate nucleus (LGN) cluster along the constant-S and constant-[L and M] directions (Derrington et al., 1984). The relative independence of the effects of adaptation to modulations along the constant-S or constant-[L and M] axes on psychophysical detection thresholds has been used to define these axes as the cardinal axes of color space (Krauskopf et al., 1982).

One way to investigate the processing of cone signals is to measure detection contours in a cone-contrast space, specified as the change in the cone signals produced by the target stimulus (ΔL, ΔM, ΔS) relative to the cone signals of the background (L_0, M_0, S_0). Sankeralli and Mullen (1996) used sinusoidal gratings whose spatiotemporal parameters were chosen to favor each of three post-receptoral mechanisms. Their data were consistent with (i) an L–M mechanism with equal and opposite L- and M-cone inputs with a small 2% S-cone input added to either L or M for different observers; (ii) a luminance mechanism with a weighting of kL + M, where k varies between 3 and 5, with a 5% S-cone input in opposition to L- and M-cones; and (iii) an S-opponent mechanism with S inputs in closely balanced opposition to L and M inputs. These results are broadly in agreement with earlier measurements from Cole et al. (1993). They used a Gaussian-blurred 2°, 200 ms spot that favors chromatic detection, and found three independent mechanisms: an L–M mechanism with equal and opposite L- and M-cone inputs but no S-cone input; an L + M mechanism with unequal inputs and a small positive S-cone input; and an S–(L + M) mechanism. The discrepancies are in the signs and magnitudes of the small S-cone inputs to the L–M and L + M mechanisms (see the section on S-cones and luminance), which is perhaps inevitable given the difficulties in estimating the cone spectral sensitivities at short wavelengths (Stockman & Sharpe, 1999), and the individual differences in prereceptoral filtering.

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Stromeyer et al. (1998) show evidence for a weak S-cone signal in the L/M-opponent detection mechanism, which supports the L signal and equally opposes M. The S contrast weight is small relative to the L and M contrast weights, but importantly, the S-cone contrast contribution to the L/M-opponent detection mechanism is 25–33% the strength of the S contribution to the S-opponent detection mechanism.

Danilova and Mollon (2010, 2012*b*) have measured discrimination thresholds in parafoveal and foveal vision to reveal a line of enhanced discrimination that corresponds to the subjective transition between reddish and greenish hues. Importantly, this line is not parallel to either of the cardinal axes of color space. Further discrimination data, obtained at different levels of S-cone excitation, but with target stimuli that differed only in the ratio of L- to M-cone excitation, suggest the existence of a neural channel that draws synergistic inputs from L- and S-cones and an opposed input from M-cones (Danilova & Mollon, 2012*a*).

Higher order mechanisms

Krauskopf et al. (1986) re-analyzed the data from Krauskopf et al. (1982) and concluded that there must exist "higher-order" color mechanisms, in addition to the putative cardinal mechanisms. However, the nature of these higher-order mechanisms has been difficult to pin down, and their existence remains controversial (see Eskew, 2009 for critical review). When S-cone test stimuli have been included in detection experiments, particularly in combination with noise masking (e.g. Gegenfurtner & Kiper, 1992; Hansen & Gegenfurtner, 2013) or background color changes (Zaidi & Halevy, 1993), some groups find evidence for "nonclassical mechanisms," tuned to intermediate hues, such as orange. Measuring detection and discrimination of target stimuli that included S-cone modulation, and using noise masking to desensitize the highly sensitive red-green mechanisms, Eskew et al. (2001) hoped to reveal evidence for less-sensitive mechanisms tuned to other directions; but they did not.

One important methodological point here is that complex patterns of detection and discrimination results can be generated by classical mechanisms alone. Eskew et al. (2001) used a Bayesian classifier to analyze their data, based on the combination of binary chromatic mechanism decisions and the shape of the psychometric function for detection. Abrupt changes in detection and discrimination performance for particular chromatic directions can arise if the underlying mechanisms are not orthogonal, and if the psychometric functions are not linear. A similar conclusion is evident from the measurements of habituation of responses in striate cortex of macaque – narrowly tuned habituation responses can be consistent with response adaptation in neurons that receive input from two fundamental mechanisms (defined along L–M and S-cone axes), since these mechanisms contribute to both excitation and to regulatory gain controls (Tailby et al., 2008*a*).

S-cones and luminance

The perception of fast flicker is thought to be mediated by a "color-blind" pathway that simply sums the cone inputs it receives. As such, this flicker can be canceled or nulled simply by adjusting the relative intensity of two alternating lights, which can be of any chromaticity (Ives, 1912). Here, we ask whether signals in all cone classes are equal in their capacity to drive flicker perception, and the associated characteristic of luminance (and V(λ), the spectral-luminosity function) as defined by hetero-chromatic flicker photometry (HFP). In particular, is this the domain of only the L- and M-cones, or do the S-cones also contribute?

On dim backgrounds, the S-cones make little or no contribution to luminance (Eisner & Macleod, 1980; Verdon & Adams, 1987). The magnocellular pathway has been widely regarded as the physiological substrate of V(λ) (Lennie et al., 1993). The relevance of this association in the present context is that the magnocellular pathway is thought to receive negligible, if any, input from S-cones (e.g. Sun et al., 2006).

However, in the presence of intense long-wavelength adaptation, S-cone signals make a small but robust contribution to luminance defined by HFP (Stockman et al., 1991) or by motion (Lee & Stromeyer, 1989). Both studies find that the S-cone signal is inverted and delayed with respect to the L- and M-cone signals. Ripamonti et al. (2009) have investigated the dependence of the S-cone luminance input on changes in the wavelength and radiance of the background field. In the absence of a background, the S-cone input to luminance disappears completely. With background field of 491 nm and longer wavelengths, a clear S-cone contribution is found, but only if the background exceeds a critical radiance. The spectral sensitivity of the radiance requirement follows a kL + M sensitivity, with $k \sim 2$. The characteristics of the S-cone contribution to luminance are suggestive of a specific physiological substrate. Since the signal is inverted, contingent on L- and M-cone input, and delayed by around 25 ms, Ripamonti et al. (2009) postulate that it could be carried by an S-OFF inhibitory response from horizontal cells (for further discussion of relevant retinal circuitry see the section on Predictions based on the underlying physiology).

S-cone spatial and temporal vision

Spatial vision

The spatial contrast-sensitivity-function (CSF) of the isolated S-cone mechanism typically exhibits a peak close to 1 cycle-per-degree (cpd) and shows a maximum acuity of 10 cpd (Cavonius & Estevez, 1975). Even under the most favorable conditions, S-cone acuity does not exceed 12 cpd in normal trichromats (Stromeyer et al., 1978), and has been shown to be 15 cpd in two blue-cone monochromats (Hess et al., 1989), which is lower than that obtained for achromatic stimuli or for L/M-opponent stimuli (see Mollon, 1982*b* for review). Indeed, the relative inability of the S-cone system to contribute to the detection of sharp edges has been exploited in the so-called minimally distinct border method of determining an individual's tritan line (Tansley & Boynton, 1976, 1978).

The sampling properties of the photoreceptor mosaic, and of subsequent neural stages, should have inevitable consequences for spatial vision, and the S-cone system provides a means of testing specific theoretical predictions. Williams et al. (1983) investigated spatial sampling by the S-cone mosaic in the fovea. When thresholds were determined by S-cones, all observers reported seeing splotchy percepts in high spatial frequency gratings, which the authors attributed to aliasing by the sparse photoreceptor mosaic. Metha and Lennie (2001) compared detection and orientation-identification (horizontal or vertical) thresholds at a range of eccentricities for S-cone isolating interference fringes formed directly on the retina. Performance in the fovea exceeded the nominal Nyquist limit of a crystalline triangular mosaic having the mean cone spacing found by Curcio et al. (1991), whereas performance in the periphery fell short of this prediction. But the absence of Moiré

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patterns with S-cone isolating gratings suggests that the S-cone mosaic is too irregular to generate coherent aliases and that the assumption of a crystalline mosaic is implausible. A model incorporating the irregular sampling properties of the constituent mosaics of the S-cone system can predict performance, with just two additional assumptions – first, that noise is added to the cone signals and second, that those signals are increasingly pooled by post-receptoral mechanisms as eccentricity increases.

Vassilev et al. (2005) measured S-cone contrast threshold for stimuli of different sizes modulated along a tritan line, as a function of retinal eccentricity. Ricco's area increased toward the retinal periphery. Vassilev et al. were able to relate this increase to the dendritic field area of the small bistratified and parasol retinal ganglion cells, estimating that Ricco's area incorporated a constant number (three to four) of small bistratified cells.

The longitudinal chromatic aberration of the eye means that a spectrally broadband stimulus that is sharply focused on the retina for wavelengths near the peak of the L- and M-cone sensitivities will be blurred in the short-wavelength components, which might explain the relatively sparsity of the S-cone mosaic. However, the monochromatic wave aberrations that are also present in real eyes mean that in fact the potential image quality for S-cones is comparable to that for L- and M-cones (McLellan et al., 2002). Foveal resolution performance for S-cone isolating gratings exhibits only limited robustness to optical defocus, whereas in the periphery, resolution remains limited by the sampling density of the neural array for large changes in stimulus luminance and optical defocus (Anderson et al., 2003).

Temporal response

The chromatic pathways are thought to be more sluggish than the luminance pathways, and the S-cone pathways particularly so. However, psychophysical tests of the temporal response of the S-cone chromatic system are not straightforward to construct. First, the stimuli must isolate only the relevant pathways. This means eliminating any luminance contribution, and any contribution from the L/M-opponent subsystem, to detection. Adaptation state must be matched across the visual subsystems to be compared, since photoreceptor time constants shorten with increasing light adaptation (Stockman et al., 2006) and, if a direct behavioral response is to be measured, stimulus strength must be equated since it is known that stronger stimuli elicit faster responses, perhaps because the internal graded response to the stimulus must rise to a threshold level before triggering the motor response (e.g. Mollon & Krauskopf, 1973).

Temporal CSF

Using long-wavelength adaptation to isolate the S-cone mechanisms, Brindley et al. (1966) reported a maximum critical flicker fusion frequency of 18 Hz, which is about three times lower than that found for the long-wavelength sensitive mechanisms. Kelly (1974) and Wisowaty and Boynton (1980) measured the full S-cone mediated CSF, using long-wavelength adaptation and silent substitution, respectively, and both report a rapid decline in modulation sensitivity with increasing temporal frequency and a peak sensitivity around 2 Hz. Stockman et al. (1991) find that, although the S-cone flicker response is confined to low temporal frequencies when S-cone adaptation levels are low, a high-intensity adapting field of 617 nm (with an orange appearance) that produces higher S-cone adaptation reveals a fast S-cone flicker signal that Stockman et al. argue is carried in luminance pathways (see the section on S-cones and luminance).

Timing of motor responses

Smithson and Mollon (2004) measured reaction times to S/(L + M) and L/(L + M) increments from a gray field. Both the equiluminant plane and the tritan line were empirically determined and spatiotemporal luminance noise was used to mask luminance cues. An adaptive staircase progressed according to observers' performance on a "go, no-go" task and provided concomitant estimates of threshold and of reaction time. Smithson and Mollon estimated the latency difference in visually triggered reaction times for the two chromatic pathways to be no more than 20–30 ms. McKeefry et al. (2003) find a reliable dependence of reaction time on chromatic direction in a cone-contrast space, that persists even when stimuli are equated in threshold units.

Bompas and Sumner (2008) compared manual and saccadic reaction times to S-cone isolating and luminance stimuli presented on the left or right of fixation. Individual equiluminance and tritanopic settings were obtained for each observer, stimuli were presented in temporal luminance noise, and stimulus strength was set to measured 80% detection threshold. Averaged over 12 observers, luminance stimuli were reliably faster than S-cone stimuli in eliciting motor responses. The advantage was larger for saccadic responses (44 ms) than for manual responses (23 ms). Interestingly, this difference in motor responses was not reflected in a perceptual measure: The point of subjective simultaneity in a temporal order judgment between S-cone and luminance stimuli was not significantly different from zero.

Stimulus interactions

An alternative approach is to measure the interaction between two temporally separated but spatially superposed stimuli. Several experiments fall under this broad description, but the most fundamental are those that use the two-pulse method. For a linear system, the impulse-response function (IRF) is the inverse Fourier transform of the temporal contrast sensitivity function (tCSF). It represents a theoretical response of a system to an input of infinitely short duration. An estimate of the IRF can be derived by measuring the response to two brief pulses separated by varying inter-stimulus intervals (e.g. Ikeda, 1965, 1986). Shinomori and Werner (2008) tested for asymmetries in the temporal response to S-cone Gaussian blobs, defined along individually determined tritan lines. The IRFs obtained were characterized by a single excitatory phase (equivalent to a low-pass tCSF), with a much longer time course than for luminance pulses.

Smithson and Mollon (2001) measured forward and backward masking functions for stimuli defined along the S-opponent or L/M-opponent directions. The chromatic targets and masks were embedded in spatiotemporal luminance noise to render unreliable any response from transient, magnocellular pathways that might otherwise support detection. Within-channel masking functions were extended in time for both S-opponent stimuli and for L/M-opponent stimuli, with maximum masking when mask and target were simultaneous. Between-channel masking functions showed maximum masking when mask followed target, but importantly, the location of this peak was virtually unchanged whether the S-opponent stimulus was the mask or the target, implying very little latency difference between the two chromatic channels at the point of mask and target interaction.

Blake et al. (2008) used a moving Vernier task to estimate the temporal response to test stimuli as they were swept across an adapting field. When light adaptation and stimulus conditions were

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equated – by choosing adaptation fields that raised S-cone thresholds and L-cone thresholds equally above absolute threshold and that were close to neutral so they did not polarize post-receptoral channels, and by choosing stimuli that were equally above increment thresholds for the S- and L-cones – there was very little difference either in the perceived latency or in the perceived duration of the short-wave and long-wave stimuli.

A phase lag of the S-cone signal has been inferred from psychophysical thresholds for discriminating combinations of simultaneous sinusoidal modulations along ±[L–M] and ±[S–(L + M)] directions (Stromeyer et al., 1991). Lee et al. (2009) extended this work to show that a perceptual null was possible only when the phase advance (corresponding to c. 12 ms at 10 Hz) was added to an S-cone isolating modulation, and not to modulations that included L- and M-cone exchanges. Given that post-receptoral mechanisms show diverse tuning around the tritan axis (for further discussion see Miyagishima, 2013; Dacey et al., 2013; Marshak, 2013 and the section on Predictions based on the underlying physiology), this result suggests that the delay arises before the S-opponent channels are constructed, possibly in the S-cones themselves.

Asymmetries in S-ON and S-OFF responses

Predictions based on the underlying physiology

A basic question in vision science is whether increments and decrements receive equal treatment in the visual system. For stimuli detected by the S-opponent subsystem, this question has received particular attention because the S-OFF color opponent pathways in primate retina have been more difficult to characterize than the S-ON color opponent pathways.

Extracellular recordings encountered S-OFF ganglion or LGN cells so infrequently that Malpeli and Schiller (1978) and Zrenner and Gouras (1981) argued against the functional importance and even the existence of an excitatory S-OFF response. However, there was physiological evidence (for example Derrington et al., 1984; Valberg et al., 1986) for a distinctive cell class that receives inhibitory S-cone input, although the anatomy of the S-OFF ganglion cell type remained elusive.

Calkins (2001) reviewed anatomical evidence, from his own laboratory, and from Klug and colleagues (Klug et al., 1993) for an OFF-pathway that originates in the S-cone, contacts a midget OFF-bipolar, and in turn contacts a midget ganglion cell. However, there was no direct evidence linking this to the S-opponent color channel (as identified physiologically and psychophysically).

The current understanding of S-ON and S-OFF circuitry in primate retina is discussed in detail by Dacey et al. (2013) and by Martin and Lee (2013). For the S-ON pathway the signal from the S-cone selective blue-cone bipolar is opposed in the small bistratified ganglion cell by signals from OFF-center diffuse bipolar cells. For the S-OFF pathway, the picture is less clear. S-OFF responses have been observed in ganglion cells with large receptive fields and in intrinsically photosensitive melanopsin-containing ganglion cells. There is also some anatomical, but not physiological, evidence for OFF S-cone connections to midget bipolar cells, which have very small receptive fields.

Differences in the origin of the opponent signal in ON and OFF pathways should in principle leave signatures that are detectable in psychophysical experiments. Comparisons can be drawn between the responses of putative ON and OFF mechanisms, and the way in which these mechanisms change from central to peripheral retina. Candidate asymmetries are primarily differences in the L- to M-cone weighting in the signal opposing the S-cones, and differences in the spatial response to stimuli that tap these very different receptive fields. Differences in the underlying pathways might also have indirect consequences, such as different susceptibilities to aging or to toxins, and might confer different latencies.

Early psychophysical observations by Boynton (1978) are consistent with the signal opposing the S-cones having a spectral sensitivity similar to that of the photopic luminous efficiency function, as if it were derived indiscriminately from nearby L- and M-cones and in agreement with physiological data from S-ON ganglion cells (Smith et al., 1992). However, there have been a number of psychophysical studies suggesting that S-ON and S-OFF pathways may have different contributions from L and M cones (see the section on Asymmetries in spectral sensitivity).

Psychophysical separation of putative ON- and OFF-pathway responses

In a psychophysical study, it is not immediately clear how one should isolate ON and OFF pathways. One approach is to use incremental and decremental stimuli (e.g. Schwartz, 1996), but increment and decrement pulses may be detected by either the onset or offset and do not isolate responses to positive- and negative-going parts of the waveform. So, the psychophysical response to brief stimuli must be combined with some additional analysis or manipulation to allow inferences about the mediating mechanisms.

In an analog system, such as that seen at the level of the photoreceptors, the direction of polarization has no effect on the efficiency of the system, at least for small stimulus perturbations where the response function is effectively linear. However, once such signals are converted into action potentials, as observed at the ganglion cell level, information is best conveyed by increases in action potential rate. It is often argued that by providing excitatory signals for both increments and decrements – in separate ON and OFF channels – the visual system is able to optimize the transmission of information about both increases and decreases in light level (e.g. Valberg, 2001).

Kremers et al. (1993) demonstrated that sawtooth stimuli can isolate ON and OFF retinal ganglion cell populations. For square wave stimulation, both ON and OFF magnocellular units gave a vigorous response, which was synchronized with the positive going part of the waveform for ON cells, and with the negative going part of the waveform for OFF cells. Sawtooth stimulation, however, produced asymmetric responses in ON and OFF cells: OFF cells were practically silent for the rapid-on sawtooth and ON cells were practically silent for the rapid-off sawtooth. Similar results were obtained with parvocellular units, though, owing to the low-pass temporal response of these cells, the segregation was less pronounced.

For threshold perturbations, just a small advantage in one pathway will bias detection to that pathway, and Krauskopf and Zaidi (1986) presented psychophysical evidence that chromatic habituation to rapid-on or rapid-off sawtooth modulation can produce asymmetries in increment and decrement thresholds that are dependent on the polarity of the rapid phase of the sawtooth. It is likely that rapid-on and rapid-off ramps (single pulses rather than repetitive sawtooth modulation) will bias detection to ON and OFF pathways, respectively. With ramps (rather than the sawtooth modulation used by (Kremers et al., 1993)) maintained firing before presentation of the test should be low giving a pronounced

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increment and decrement asymmetry, even in chromatically opponent cells.

Racheva and Vassilev (2008) measured detection thresholds for 100 ms S-cone stimuli (*via* Stiles' two-color increment threshold technique). Increments and decrements were presented in three conditions: rectangular pulse, rapid-onset ramp, and rapid-offset ramp. For both increments and decrements, thresholds measured with rapid-onset probes were lower than those measured with rapid-offset probes, implying that the onset of the stimulus is critical in determining performance. Consistent results were obtained with reaction time measurements: For 500 ms pulses, reaction time distributions were unimodal and followed stimulus onset, whereas for 1000 ms or 2000 ms pulses, offset responses were additionally apparent, presumably due to slow post-receptoral adaptation.

Asymmetries in spectral sensitivity

Using S-isolating rapid-on or rapid-off probe stimuli, DeMarco et al. (1994) found similar thresholds for the two temporal waveforms, implying either that there are ON- and OFF-channels that are matched in sensitivity, or that the ON-pathway is equally good at processing both waveforms. Shinomori et al. (1999) combined the use of rapid-on and rapid-off sawtooth test probes with adaptation to sawtooth flicker. Test probes were S-isolating; adapting stimuli were rapid-on or rapid-off luminance modulations of monochromatic lights. They reported an asymmetry in the elevation of threshold for the two types of S-cone probe. For short-wave adapting lights that appeared blue with just a little red (420 nm or 450 nm depending on the observer), this asymmetry depended on the temporal waveform of the adapting light (adaptation to rapid-off flicker raised threshold for rapid-off sawtooth probes more than for rapid-on sawtooth probes, and *vice versa*); but for lights of shorter wavelengths that appeared reddish, although threshold elevation was asymmetric, it did not depend on the adapting waveform. An interaction between polarity of the probe and the adapting stimulus strongly implies a separation of ON- and OFF-pathways. The further interaction with the appearance of the adapting light suggests that the separation of ON- and OFF-pathways may not be equally well maintained through the two chromatic post-receptoral channels that are sensitive at short-wavelengths (see the section on S-cone mechanisms).

McLellan and Eskew (2000) found that the action spectrum for transient tritanopia differed when probed with (rectangular) increment or decrement pulses. They measured detection of 200-ms increment and decrement pulses on a neutral reference field, 400 ms after the offset of a long-wavelength adapting field, as a function of the retinal illuminance of this adapting field. By varying parametrically the wavelength of the adapting field, they showed that the relationship between increment and decrement t.v.r. curves was not constant across wavelengths. In fact, as the wavelength of the adapting field was increased, the decrement thresholds became relatively lower. McLellan and Eskew (2000) interpret this as evidence that S-cone decrements are opposed by a smaller L-cone signal than are S-cone increments, and they suggest that a likely reason for this would be that S-OFF units are M-cone dominated, while S-ON units have more balanced L:M weighting.

A possible asymmetry in the L:M cone weights to ON and OFF S-cone pathways would be interesting. The L and M pigment genes are highly homologous and as yet no one has identified an extracellular label that could be used to achieve L and M cone-specific connections with post-receptoral cells. This is not a problem for midget ganglion cell L–M cone opponency since with a center putatively derived from a single cone, mixed input to the surround is sufficient to provide separation in the net spectral response of center and surround (Lennie et al., 1991). There is little evidence for L–M selectivity in outer retina (Dacey et al., 1996) or inner retina (Calkins & Sterling, 1996; Jusuf et al., 2006), but direct physiological measurements from L–M opponent cells in retina and LGN are consistent with selectivity or partial selectivity (Lee et al., 1998; Reid & Shapley, 1992, 2002), and Tailby et al. (2008*a*,*b*) found in LGN signals from L-cones opposed to an S + M signal.

A consistent overweighting of the M-cone input to S-OFF units compared to S-ON units could be important in disentangling the pathways through which cones provide inputs to ganglion cell receptive fields. As summarized above, S-ON and S-OFF pathways certainly exhibit asymmetries in their retinal connectivity (Dacey et al., 2013), but it is not clear from the underlying biology what might be driving a difference in L- to M-cone weight.

Asymmetries in temporal response

The S-cone system has often been characterized as being "sluggish" (see the section on S-cone spatial and temporal vision). Shinomori and Werner (2008) tested for asymmetries in the temporal response to S-cone increments and decrements, defined along individually determined tritan lines. S-cone increment IRFs were faster than S-cone decrement IRFs, with a time-to-peak of 50–70 ms and 100–120 ms respectively. Field et al. (2007) have shown that the (L + M)-OFF response in small bistratified cells is slower than the S-ON response. The relative slowness of the S-cone decrement responses might therefore be consistent with the opponent yellow-ON response in this pathway. However, there was no L- or M-cone modulation in the pulses used by Shinomori and Werner, so it seems unlikely that the effect was driven by L- or M-cone input.

The latencies extracted from the two-pulse summation method should relate to latencies estimated from reaction time data. However, McKeefry et al. (2003) find slower reaction times to S-cone increments than decrements. Shinomori and Werner attribute the difference to minor individual deviations in the angle of the tritan line, that were not estimated by McKeefry et al. (2003) and that could introduce L- and M-cone modulation, which would reduce reaction times. This does not however directly predict the asymmetry for increments and decrements.

Reaction time experiments require stimuli that are at or above threshold, and as such are plagued with the problem of equating stimuli that share a common physical scale but that give rise to different threshold sensitivities. McKeefry et al. (2003) used root-mean-squared Weber cone contrast as their metric. For rod-isolating stimuli, neither Weber contrast nor its transform to detection-threshold units equates human reaction times to increments and decrements (Zele et al., 2007). Vassilev et al. (2009) have shown however that these rod-mediated reaction times, and reaction times to parafoveal S-cone selective increments and decrements, are better equated when described by the spatial luminance ratio (L_{max}/L_{min}) than by Weber contrast ($\Delta L/L$). Using this to infer that the relative latencies of ON- and OFF-pathways are matched is clearly circular, unless there is an independent justification for using the spatial metric. Vassilev et al. suggest that the appropriate metric depends on whether the detection mechanism operates by drawing temporal or spatial comparisons, and that this criterion might be used to resolve the circular argument.

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Asymmetries in spatial response

Vassilev et al. (2000) measured detection thresholds for 100 ms S-cone pulses (determined *via* Stiles' two-color increment threshold technique, verified through comparison of spectral sensitivity with the Stiles' $\pi 1$ template) as a function of stimulus area. At a retinal eccentricity of 12.5°, increases in stimulus area reduced the decrement threshold more than the increment threshold, and Ricco's area of complete spatial summation was larger for decrements (0.8–2°) than for increments (0.6–0.9°). Importantly, this asymmetry was not found for red-on-red stimuli that favored the L-cones.

Redmond et al. (2013) have shown that Ricco's area, measured under S-cone isolating conditions, decreases with increasing background luminance. An analogous effect for achromatic stimuli has been interpreted as evidence for increased center-surround antagonism within the retinal ganglion cell receptive fields as background luminance increases (Glezer, 1965). Clearly, this interpretation is of interest in relation to the receptive field structures within the S-cone retinal circuitry. Measured with increment pulses at 10° retinal eccentricity, the data from Redmond et al. do not directly probe the differences that might be expected for ON- or OFF-pathways, or for central or peripheral retina.

Asymmetries that depend on retinal eccentricity

Zlatkova et al. (2008) found that, at retinal locations within 10°, resolution acuity was similar for S-cone isolating gratings that differed in their S-cone contrast polarity; but, beyond 10°, resolution acuity for gratings with negative S-cone contrast was consistently lower than that for gratings with positive S-cone contrast. The finding is consistent with two independent and rectified S-cone mechanisms that differ in their spatial properties, at least for peripheral vision. The larger spatial extent of the putative S-OFF response, particularly in peripheral retina is broadly consistent with the retinal circuitry described by Dacey et al. (2013).

Terasaki et al. (1999) report data from blue-on-yellow perimetry performed in five patients with the complete form of congenital stationary night blindness (CSNB1) showing that S-cone function is preserved only in the fovea and becomes abnormal in the periphery. It is likely that there is a selective dysfunction of the ON-bipolar cells in both rod and cone visual pathways in these patients. So, it is possible that their residual S-cone function is supported by a central midget S-OFF pathway.

Exploiting the pattern of S-cone projections

Attention and the superior colliculus

The relative paucity of direct S-cone projections to superior colliculus (e.g. see Tailby et al., 2012 for recent data) has drawn the attention of human experimental psychologists. For, by using S-cone isolating stimuli, it should be possible to test human visual performance in the absence of collicular involvement.

Neural activity in the superior colliculus is important for the initiation of stimulus-driven saccadic eye-movements (Sparks, 1986; Dorris et al., 1997). The retinal projection to the superior colliculus has also been implicated in the involuntary capture of attention (Rafal et al., 1991). Indeed, the so-called premotor theory of attention proposes that eye-movement planning and attentional orienting share common neural mechanisms (Rizzolatti et al., 1987; Kustov & Robinson, 1996).

Sumner et al. (2002) compared the effects of S-cone isolating stimuli in two tasks: an oculomotor task, and exogenous orienting of attention. In both tasks, the target was a small black rectangle, briefly flashed to the left or right of fixation. In the oculomotor task, participants were required to make a saccade to the location of the target; in the attention task, participants were required to respond with a single button release whenever the target appeared.

In both cases, task-irrelevant S-cone or luminance stimuli were also presented. These stimuli were larger than the targets and could appear either on the contralateral or ipsilateral side of fixation. For the oculomotor task, the irrelevant stimulus appeared simultaneously with the target and, according to the "oculomotor distractor effect," irrelevant contralateral stimuli should increase saccade latencies. For the attention task, the irrelevant stimulus appeared 100 ms before the target. This is an example of the standard exogenous cueing paradigm introduced by Posner (1980) to study spatial attention: Reaction times to targets that can appear in more than one location are generally shorter if they are preceded by a peripheral cue that is spatially co-located with the target, and longer if the cue and target locations do not match (Jonides, 1981).

S-cone isolating stimuli did not produce the oculomotor distractor effect that is found with luminance stimuli, but they did produce normal attentional orienting effects. It is likely that the oculomotor distractor effect is mediated through superior colliculus, since cells activated by distractor stimuli inhibit cells activated in response to the saccade target (Olivier et al., 1999), and the finding that it does not occur for S-cone distractors is consistent with the electrophysiological studies that have reported that there are no projections to the superior colliculus from color-opponent cells in the retina and, specifically, no projections from S-cones at all (Marrocco & Li, 1977; Schiller & Malpeli, 1977; de Monasterio, 1978). The demonstration that S-cone stimuli give standard results in the Posner paradigm suggests however that exogenous orienting of attention does not require a signal in the direct retinotectal pathway.

Sumner et al. (2002) ran their experiments with continuous temporal luminance noise at the distractor and cue locations. If there is S-cone input to the collicular pathway, it is small and, because it is thought not to be chromatically opponent, it should be masked by the luminance noise. Similarly, a small S-cone contribution to the magnocellular pathway, as has been suggested by some researchers (see the section on S-cones and luminance), would not overcome the luminance noise. So, Sumner et al. are additionally able to use S-cone stimuli to infer that exogenous orienting does not require a signal in the magnocellular pathway.

A further signature of attentional mechanisms is the phenomenon of inhibition of return (IOR), which is the bias against making eye movements that return to recently fixated locations. Sumner et al. (2004) have found that S-cone stimuli produced IOR when assessed by traditional manual responses, but not when saccadic eye-movement responses were required. They argue that the S-cone stimuli dissociate separate cortical and collicular mechanisms of IOR for manual and saccadic responses. Again, this points to a dissociation of visual orienting of attention and gaze.

The S-cone signal that arrives in the cortex is not however equal in all respects to the signals originating in the L- and M-cones, and one difference that is likely to be important in the capacity to drive orienting responses is signal latency (see the section on S-cone spatial and temporal vision). By varying the delay between target and distractor, Bompas and Sumner (2009) found that S-cone stimuli do in fact produce an oculomotor distractor effect, but that the optimal delay differs from that for luminance distractors. Additionally, they show that S-cone stimuli are able to produce saccadic capture,

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eliciting directional errors. So, with the appropriate adjustments for sensory transmission time, S-cone stimuli can elicit signals that drive saccadic competition, presumably neither in the retinotectal pathway, nor in the magnocellular pathway, since these pathways are blind to the luminance-masked S-cone stimuli.

Naso-temporal asymmetry

Collicular mediation, *via* the evolutionarily ancient retinotectal pathway that directly connects the retina to the superficial layers of superior colliculus, has been suggested for a large number of visually guided processes, such as attention, "blindsight" (see the section on Subcortical mediation in blindsight) and face perception. A commonly employed psychophysical diagnostic has been the presence of a naso-temporal asymmetry (i.e. an asymmetry under monocular viewing conditions between stimuli presented in the temporal and nasal visual fields), since anatomically, superficial layers of superior colliculus in cats predominantly receive inputs from the nasal retina sampling the temporal visual field (Sterling, 1973), and in monkeys, the asymmetry is less pronounced but still clear (see Williams et al., 1995 for review). If the naso-temporal asymmetry is mediated by an underlying asymmetry in the retinotectal pathway, it should not be present for S-cone stimuli. Bompas et al. (2008) found that the observed naso-temporal asymmetry in choice saccades to bilateral stimuli was no less present for S-cone stimuli than for luminance stimuli, suggesting that the naso-temporal asymmetry is not a good diagnostic for retinotectal mediation.

Neonatal tritanopia

The S-cones differ from the L- and M-cones in many respects, and it is quite possible that they may also differ in their pattern of ontogenesis. Certainly, a number of behavioral studies have suggested that infants are tritanopic. Teller et al. (1978) used a forced-choice preferential looking technique to assess 2-month old infants' abilities to discriminate (brightness matched) colored stimuli from white. The discrimination failures lay on a tritanopic confusion axis. Pulos et al. (1980) used preferential looking to assess increment thresholds on long-wavelength adapting fields, and again found tritanopic impairments. However, the visual behavior of young infants in preferential looking may well be controlled by the superior colliculus, which because it receives little or no S-cone input might underlie the tritanopic pattern of results (Mollon, 1982*a*). By measuring visually evoked cortical potentials, Volbrecht and Werner (1987) find reliable responses to S-cone mediated flicker on long-wavelength backgrounds in 4- to 6-week-old human infants.

Subcortical mediation in blindsight

Patients who are cortically blind following destruction of the occipital cortex can nevertheless demonstrate some residual visual function, and the ability to respond to visual stimuli in the blind visual field without consciously experiencing them has been termed "blindsight" (Weiskrantz et al., 1974). The neural pathway mediating blindsight has been controversial, but the most likely candidate based on the nature of residual function has been the superior colliculus. Leh et al. (2006) showed, using a computer-based reaction time test in a group of hemispherectomized participants, that human 'attention-blindsight' can be measured for achromatic stimuli but disappears for stimuli that solely activate S-cones. A follow-up study with one hemispherectomized blindsight patient provides functional magnetic resonance imaging (fMRI) evidence that only the achromatic stimuli and not the S-cone stimuli activated the superior colliculus, and that, in the blind field, only the achromatic stimuli elicited activation patterns in V5 and frontal eye fields (FEF), but not in V1 and V2, consistent with the behavioral data (Leh et al., 2010). Following hemispherectomy it is not possible that spared islands of visual cortex or any direct geniculo-extrastriate projections could have mediated the results. The selective effects with S-cone stimuli mean that a direct retino-pulvinar-cortical connection is also unlikely as the pulvinar nucleus is known to receive input from S-cones (Felsten et al., 1983; Cowey et al., 1994).

S-cone damage

Vulnerability

There has been a long history of suggestion that the S-cone photoreceptors and their associated pathways are particularly vulnerable to damage and disease. Mollon (1982*c*) reports a panel discussion at the 6th meeting of the International Research Group on Colour Vision Deficiencies in which several plausible explanations were advanced. They are worth reiterating here as they highlight classes of explanation that ought to be kept in mind when interpreting test results.

First, it is possible that the seemingly disproportionate vulnerability of S-cone mediated vision is a result of bias in the measurement techniques. Acquired S-cone deficiencies are typically revealed *via* standard color vision tests (though note that the Ishihara plates do not assess tritan deficiencies). Two tests that are sensitive to S-cone deficiencies – the Farnsworth-Munsell 100-hue test and the D15 – are biased toward giving tritan results (Verriest et al., 1982). It is also clear that the S-cone photoreceptors are relatively rare, so even if their susceptibility to damage were the same as that of the L- and M-cone photoreceptors, the consequences of this damage might more readily be revealed in a perceptual test, particularly one with small targets.

It is also possible that there is a real physiological weakness in the S-cone system. The S-cone photoreceptors themselves may be particularly fragile – perhaps because their membranes are more permeable to toxins (de Monasterio et al., 1981), or because they are less well connected to the pigment epithelium owing to morphological differences between them and the L- and M-cones. However, with at least one visually active toxin, selective S-cone tritan deficits are not obvious: Visual field measurements in individuals that have suffered mercury poisoning suggest a generalized visual impairment (Barboni et al., 2008) associated with increases in tritan, deutan, and protan thresholds (Feitosa-Santana et al., 2008). Phototoxicity also seems not to differ substantially between cone classes (Organisciak & Vaughan, 2010).

The drug sildenafil citrate (Viagra®) has been associated with changes in vision, and it has been suggested that it has a disproportionate effect on tritan discriminations in the FM-100 hue test (Laties & Zrenner, 2002). Sensitive tests of the temporal response of L-, M-, and S-cone mediated responses in four participants after ingestion of a 100-mg dose of Viagra found S-cone impairments in all participants, with those who showed the largest S-cone sensitivity losses also showing comparable losses for L- and M-cone mediated responses, commensurate with the effect of the drug on PDE6, an essential enzyme in the activation and modulation of the phototransduction cascade (Stockman et al., 2007).

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Since we know that the S-cone signals contribute only selectively to post-receptoral pathways, an anatomical locus of damage that is beyond the receptors might also be revealed as a tritan deficit (Greenstein et al., 1989). Unlike the L- and M-cone signals, the S-cone signals are largely confined to chromatically opponent pathways. L- or M-cone increments, and even equiluminant L–M flicker (Lee et al., 1989), can stimulate non-opponent post-receptoral pathways. So, a selective impairment for S-cone stimuli might reflect the relative ease with which signals from the different classes of cone can be corralled in chromatic channels. Moreover, since chromatically opponent pathways are most sensitive in the middle of their operating range, when their chromatic inputs are balanced (e.g. Pugh & Mollon, 1979), tritan deficits might be particularly sensitive indicators of more general damage to the adaptation mechanisms that maintain sensitivity, and these effects may reveal themselves particularly strongly under adaptation to a yellow field used to isolate S-cone mediated responses. Identifying the locus of damage revealed in different tests of tritan function remains a significant challenge.

Aging

Age-related elevation in threshold occurs for all the three cone mechanisms under comparable states of light adaptation (i.e. on the plateau of each mechanism's t.v.i. function) (Werner et al., 2000), presumably reflecting the many physiological changes that occur in the aging retina (Marshall, 1987).

There are significant changes in color vision with age. For example, the mean normal score on the FM 100 hue test for the 60 to 65-year-age group falls outside the 99.9% confidence interval limit for the 30 to 35-year-age group (Verriest et al., 1982) and these changes are characterized by tritan-like defects in the older group (Knoblauch et al., 1987). It is tempting to relate these age-dependent changes to yellowing of the lens, and such changes in ocular media do reduce S-cone sensitivities by 30–40% (Haegerstrom-Portnoy et al., 1989), but simulation of lens yellowing in younger observers using filters has little effect on FM 100 hue error score (Beirne et al., 2008). The tritan-like distribution of errors on the FM 100 hue test for older participants is similar to those obtained with younger groups at low illuminance levels, suggesting that at least some of the aging effect is like the effect of attenuation by a neutral filter (Knoblauch et al., 1987). In aging eyes, pupils certainly become miotic, though the reduction in retinal illuminance with smaller pupil diameter is insufficient to fully explain the reduction in performance. Motivational and neural factors are also likely to contribute.

To maintain constancy of color appearance across the lifetime, in the face of spectrally selective filtering by the ocular media, the visual system must undergo some process of long-term adaptation, both at receptoral and at post-receptoral sites (Werner, 1996). The spectral tuning of filtering by the ocular media and macular pigment dictates that compensation would require substantially greater gain changes in S-cone mechanisms than in L- or M-cone mechanisms (Werner et al., 2000; Stringham et al., 2013).

Schefrin et al. (1992) compared increment threshold data (t.v.r. functions) for nine older participants (mean age 71.0 years) and six younger participants (mean age 24.4 years). Importantly, they used a modeling approach intended to distinguish the effects of age-related changes at the receptoral level from effects of pre-retinal filtering by the ocular media and other neural changes occurring in the S-cone pathway. They found that much of the loss of sensitivity in the S-cone mechanism (68%) could be attributed to changes in the ocular media or receptor sensitivities. However, for five of the older participants, a model in which gain depends on the rate of photon capture in the cones systematically underestimated thresholds, particularly at the higher adapting-field intensities, suggesting that other neural factors must be contributing.

To further dissect the age-related changes that occur in the S-cone pathways, Shinomori and Werner (2012) measured S-cone mediated temporal IRFs in younger and older observers. While response amplitudes for increment and decrement responses were well correlated across individuals, the response timing was not. The response to decrements was relatively delayed, and this difference increased for older individuals. Since many of the pathways that could carry the S-OFF signal additionally subserve other functions (see the section on Predictions based on the underlying physiology), this polarity-specific impairment might reveal more general senescent declines, for example in inhibitory circuitry or circadian regulation.

Clinical measures

A decline in visual performance may be an important indicator of retinal disease, or of other neurological disorders. Since visual performance testing is non-invasive it can be a particularly useful clinical tool, especially in cases where it can provide an early warning of disease. The interest here is that, if S-cone mediated visual performance shows a disproportionate vulnerability, it may provide particularly sensitive metrics. For a screening test, the underlying reasons for S-cone specificity are not as important as the power of the test to predict disease progression. However, if the aim is to understand the mechanisms of disease progression, or to optimize the test sensitivity, the interpretation of a seemingly S-cone specific impairment (see the section on Vulnerability) may become important.

Short-wavelength automated perimetry (SWAP), in which S-cone increment thresholds are measured across the central visual field, has become a primary clinical tool for measuring functional abnormalities, such as those produced in glaucoma, neuro-ophthalmic disorders, age-related maculopathy, and diabetes (Felius & Swanson, 2003). SWAP, however, has higher threshold variability than conventional achromatic perimetry. Felius and Swanson (2003) attribute this to an imbalance of the adaptational states of the S-cones and the L- and M-cones in the standard test conditions, and they show that the variability can be reduced either by using a higher level of S-cone adaptation (placing the system in the Weber region, rather than near absolute threshold) or by using a more balanced ratio between L + M and S-cone adaptation (and therefore not driving the S-opponent system to one extreme of its operating range). This is a nice example of how a deeper understanding of the underlying mechanisms governing test performance can enhance the statistical significance that is critical for early detection of disease or for monitoring its progression.

Greenstein et al. (1989) measured S-cone and M-cone increment thresholds in patients with retinitis pigmentosa (which differentially affects the receptors and retinal pigment epithelium), insulin-dependent diabetes mellitus (producing metabolic abnormalities and hypoxia), and open-angle glaucoma (associated with damage to the ganglion cell layer). All three diseases were associated with decreased S-cone pathway sensitivity, suggesting that S-cone sensitivity can be impaired at multiple sites.

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Future directions

The S-cones and their associated visual pathways continue to fascinate and frustrate the humble psychophysicist. Increased understanding of the complexities of retinal wiring, should disabuse us of any over-simplistic or superficial mapping from cone signals to mechanisms. But at the same time, it is reassuring that many of the psychophysical results that did not fit neatly within the standard models of color processing – for example, the S-cone contributions to luminance, and the nature of the asymmetries between responses to increment and decrement stimuli – now seem to sit in broad agreement with new physiological findings. Further explicit tests of the predictions from retinal physiology, including careful consideration of the spatial extent and retinal eccentricity of visual stimuli, should yield exciting results.

S-cone vision is now no longer only the domain of the visual psychophysicist, since the selectivity of subcortical projections permits the use of S-cone stimuli as a probe for superior collicular involvement, and opens-up questions of broad significance in experimental psychology. However, the appropriate determination of S-cone isolating stimuli for individual observers remains a challenge. Intense long-wavelength adapting fields could influence visual performance in unpredictable ways, but such effects may also be turned to our advantage in probing different stages of the visual pathway.

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