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Colour coding in the primate retina: diverse cell types and cone-specific circuitry
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How is the trichromatic cone mosaic of Old World primates sampled by retinal circuits to create wavelength opponency? Red-green (L versus M cone) opponency appears to be mediated largely by the segregation of L versus M cone signals to the centre versus the surround of the midget ganglion cell receptive field, implying a complex cone type-specific wiring, the basis of which remains mysterious. Blue-yellow (S versus L + M cone) opponency is mediated by a growing family of low-density ganglion types that receive either excitatory or inhibitory input from S cones. Thus, the retinal circuits that underlie colour signalling in primates may be both more complex and more diverse then previously appreciated.

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Abbreviations
LGN lateral geniculate nucleus

Introduction
Human trichromatic colour vision begins when the retinal image is sampled by a mosaic of three cone photoreceptor types, maximally sensitive to long (L-cone), middle (M-cone) and short (S-cone) wavelengths [1]. Both the density of photons on the cone outer segment and the spectral composition of the light determine the probability that an individual cone will capture a photon [2]. The response of a cone is therefore truly 'colour-blind', as photon flux and wavelength are confounded in its output. To begin the neural creation of a colour code, the output of the three cone types is compared at a second, opponent stage of neural processing. Spectral opponency begins in the primate retina, when cone signalling pathways converge antagonistically in the receptive fields of a subset of anatomically distinct ganglion cell populations [3]. Spectrally opponent ganglion cells project to the lateral geniculate nucleus (LGN). These chromatic signals reach primary visual cortex [4–6] and higher cortical visual

areas, in which more complex interactions occur among chromatic and achromatic pathways [7,8].

At the level of the retina and the LGN two cone opponent pathways are classically recognised: a 'red-green' pathway in which L and M-cone signals are antagonistic and a 'blue-yellow' pathway in which S-cones are opposed by a combined L + M-cone signal [9]. These two physiologically defined parallel pathways are the first stage in the creation of the separable red-green and blue-yellow perceptual opponent axes of human colour vision [10]. The underlying retinal circuitry that establishes the opponent transformation and creates these parallel pathways has been more difficult to characterise. The midget ganglion cell has long been implicated in transmitting the L-versus M- cone signal to the LGN [11]. However, the cellular mechanisms by which this pathway can achieve such an apparently simple opponent transformation have been surprisingly difficult to identify. Here, we first review new evidence that suggests a surprising degree of connectional specificity in the wiring of the midget pathway, together with recent attempts to discover the possible substrate for such L versus M cone selective wiring. The results suggest that the specificity needed for L versus M cone opponency is unlikely to have a straightforward anatomical basis. In contrast, at least one S-cone opponent pathway has been more recently associated with a separate and distinct 'small-bistratified' ganglion cell type whose excitatory input derives from an S-cone selective pathway. We also review new evidence that S-cone opponent signals may actually be associated with some number of distinct ganglion cell pathways, whose specific properties and contribution to colour vision remain to be determined.

Red-green opponency and the midget pathway: hard-wired for colour or hard up for a solution?
The L and M cones together make up the great majority of cones, roughly 90%, randomly arranged with respect to one another in the cone mosaic [12,13••]. In about the central 10 degrees, a single midget bipolar cell gets all of its photoreceptor input from a single L or M cone and connects in turn exclusively to a single midget ganglion cell, establishing a 'private-line' from a single cone to the brain [14,15]. It has long been recognised that this private line pathway may be all that is required to create L versus M cone opponency [16]. Given random cone connectivity to an antagonistic receptive field surround, strong opponency would still ensue because the high gain, single cone centre could cancel the same cone input

Figure 1
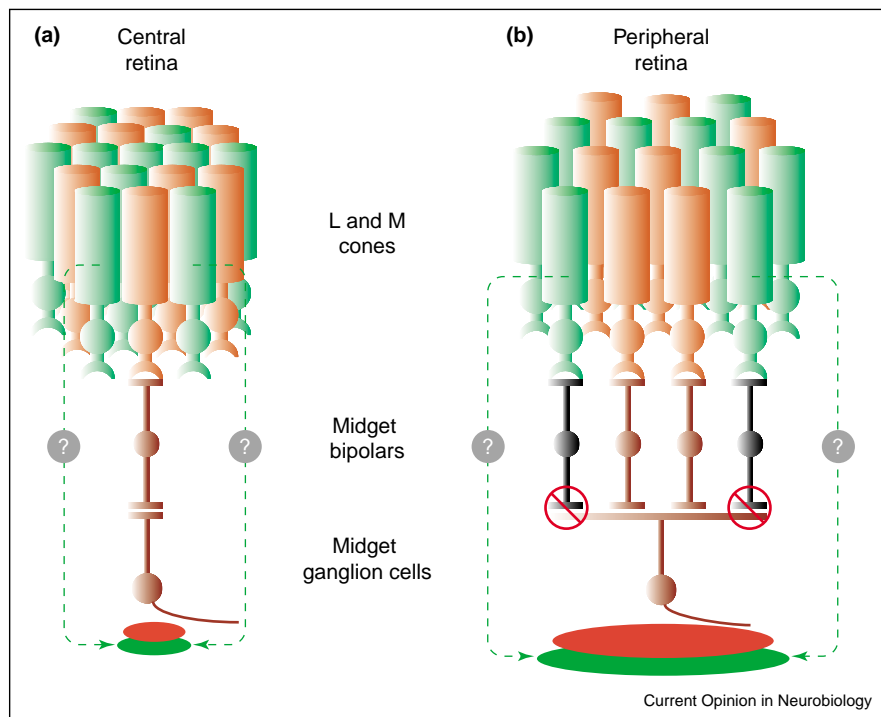
How does the midget circuit create L- versus M-cone opponency? Recent physiological evidence, discussed in the text [28••,33], argues strongly that L versus M cone opponency occurs by the selective segregation of L versus M cone inputs to the excitatory versus inhibitory components of the receptive field. **(a)** In the central 10 degrees a 'private line' synaptic pathway — cone → midget bipolar → ganglion cell — is the likely basis for a cone type-selective excitatory receptive field component. However, the basis for the creation of the critical cone type-selective inhibitory pathway is currently unknown. **(b)** In the peripheral retina the anatomical organisation presents a greater problem for L versus M cone wiring. The midget pathway changes such that single-cone connecting midget bipolar cells converge onto enlarged dendritic trees of midget ganglion cells. Strong red-green opponency in midget ganglion cells in the retinal periphery necessitates that the receptive field centre is also driven largely by a single cone-type: in this example L-cones make functional connections and M-cones are rejected. It has been speculated that this could be achieved in the periphery if dendritic branches of a given midget ganglion cell selectively connected to either L or M-cone connecting midget bipolar cells [31••]. Currently there is no direct evidence for this or any other mechanism for selectivity.

to the surround, leaving a pure L versus M cone signal ([17]; Figure 1a).

Several lines of recent evidence support the random-wiring hypothesis (reviewed by Lennie [18]). First, the direct demonstration of the random distribution of L and M cones in both human and macaque retina, together with the large variability in their relative numbers, shows unequivocally that these cells do not form distinct spatial arrangements [19••]. Second, horizontal cells of the outer retina, implicated in surround formation, connect to L and M cones without selectivity, and the strength of L and M cone input reflects the variability of L and M cone numbers in the horizontal cell receptive field [20,21]. Recent macaque recordings direct from L and M cones also demonstrate a surround in the cones themselves that is spectrally mixed [22•] and likely to originate from a horizontal cell negative feedback signal [23•]. Finally, at the level of the inner retina, amacrine cell connectivity also does not appear to support cone-selective inhibition [24].

Two recent studies, however, argue strongly for the polar opposite picture — that the midget pathway is indeed precisely hard-wired for L versus M cone opponency. The first study by Reid and Shapley, consistent with earlier reports [25,26], used cone-isolating stimuli to measure the identity and strength of L and M cone inputs to the centre and the surround of parvocellular-cell receptive fields, while recording from LGN relay cells in the parvocellular layers [27••]. The results indicate almost universal cone purity in the surround as well as the centre, and thus argue strongly for some sort of circuitry, either anatomically or physiologically based, that sets up cone type-selective inhibition to the surround. Can horizontal cells somehow support such cone-specific surround wiring? Recent measurements of the spatial receptive field of L and M cone-connecting H1 horizontal cells show that the receptive field can become very small, encompassing only several cones with a greatly reduced dendritic tree size in the parafoveal retina [28••]. The situation in primate retina appears to be an exception to the rule that horizontal cells form an electrically coupled syncytium

and show extremely large receptive fields. However, even with weak or absent coupling, neural simulations strongly suggest that these horizontal cells must still make selective connections with either L or M cones to subserve a cone type-specific surround [29]. Thus far, the chromatic properties of foveal H1 cells have not been measured to directly test this hypothesis.

A second study puts an even more rigorous constraint on L versus M cone-selective wiring. In the retinal periphery from 20–50 degrees eccentricity, the private line pathway breaks down as numerous midget bipolar cells converge on single midget ganglion cells with enlarged dendritic tree diameters ([29]; Figure 1b). In a random wiring model, L versus M cone opponency should therefore drastically decline in the retinal periphery, and recent recordings from midget ganglion cells in the far retinal periphery in the *in vitro* retina suggested that this was indeed the case [30]. However, Martin *et al.* [31••] used recordings from the intact eye of the macaque to show that the strength of L versus M opponency across the retinal periphery is basically identical to that in the fovea. Because of this result, they suggest that the large dendritic trees of midget ganglion cells may seek out and selectively connect to either L or M cone connecting midget bipolar cells that are randomly arranged with respect to one another [29]. As yet there is no direct evidence that such connectivity occurs. A second major question raised by the results of Martin *et al.* [31••] is that the chromatic sensitivity estimated for the retinal periphery far exceeded that measured for human vision with the same stimulus. Indeed, the sharp decline in human chromatic sensitivity in the visual periphery [32–34] was one argument in favour of the random wiring hypothesis! Why would the retina go to the trouble to precisely sort out the L and M cone signal pathways, and then discard this information at a later processing stage? Despite these striking results, views about the anatomy and physiology of the midget pathway and its role in colour vision will remain unsettled [35] until underlying neural mechanisms are clarified.

## Blue-yellow opponency: a growing diversity of S-cone pathways

The S cones make up only 5–10% of the cones and, not surprisingly, the retinal circuitry associated with this sparsely distributed mosaic has been difficult to access experimentally. A breakthrough in understanding S-cone pathways came with the identification of several key elements in S-cone selective opponent circuitry. First, a distinctive ganglion cell population — the small bistratified ganglion cells — was recognised as the morphological basis for the well-established 'blue-ON-yellow-OFF' opponent pathway [36]. These ganglion cells receive a direct ON input from a distinctive 'blue-cone' bipolar cell that makes selective connections with S cones [37,38]. Second, a distinct horizontal cell type, the H2

cell, receives a strong S-cone input and weaker L and M cone inputs [20]. These H2 cells could provide a basis for L- and M-cone signal feedback to the S cone, creating an L + M cone surround in the receptive field of the blue-cone bipolar cell [3]. Finally, the small bistratified ganglion cell also receives a weak OFF input from diffuse cone bipolar cells connected to L and M cones, which could contribute to the overall S versus L + M opponent response [39]. Until recently, these small bistratified ganglion cells seemed to be all that was available to support the psychophysically based blue-yellow perceptual axis of human colour vision, either alone [40•] or in combination with L versus M chromatic pathways [39,41]. Evidence from a recent study by Dacey *et al.* [42••] however, which employed a new tracing technique to determine the morphology and physiology of LGN-projecting ganglion cells (Figure 2), showed that S-cone opponent signals in fact arise from several distinct ganglion cell populations. These experiments raise new questions about the retinal origins and mechanisms of colour opponency.

In this study the retrograde tracer rhodamine-dextran was injected into the LGN, then transported to the retina and sequestered in the cell bodies of ganglion cells as expected. However, when these ganglion cells were observed under microscopic illumination in an *in vitro* preparation of the retina, the result was unexpected: the sequestered rhodamine granules appeared to literally burst, creating a firework-like display in the cytoplasm. The liberated tracer diffused throughout the cytoplasm of the ganglion cell and completely revealed its detailed dendritic morphology. The upshot of this 'photostaining' phenomenon was that diverse LGN-projecting ganglion cell types could now be characterised anatomically and selectively targeted for intracellular recording and physiological study. This provided a significant experimental advantage, as the great majority of ganglion cell types exist at very low densities (around 1–2% of the total population) and are nearly impossible to systematically study without some method for reliably identifying them. Preliminary results using retrograde photostaining revealed at least eight new low-density LGN-projecting ganglion cell populations, in addition to the five previously recognised types (the ON- and OFF-midget, ON- and OFF-parasol cells and the S-ON, small bistratified cell). Physiological analysis of these cell types is only just beginning, but thus far at least two of these types receive an S-cone input and are cone opponent (Figure 3).

One of these identified cell types receives an inhibitory input from S cones, and may therefore provide an OFF cell counterpart to the S-ON chromatic pathway ([43••]; Figure 3a). This would be a welcome addition to our picture of primate retinal organisation, as there have been consistent, although infrequent, recordings of S-OFF signals at the retinal and LGN levels throughout the
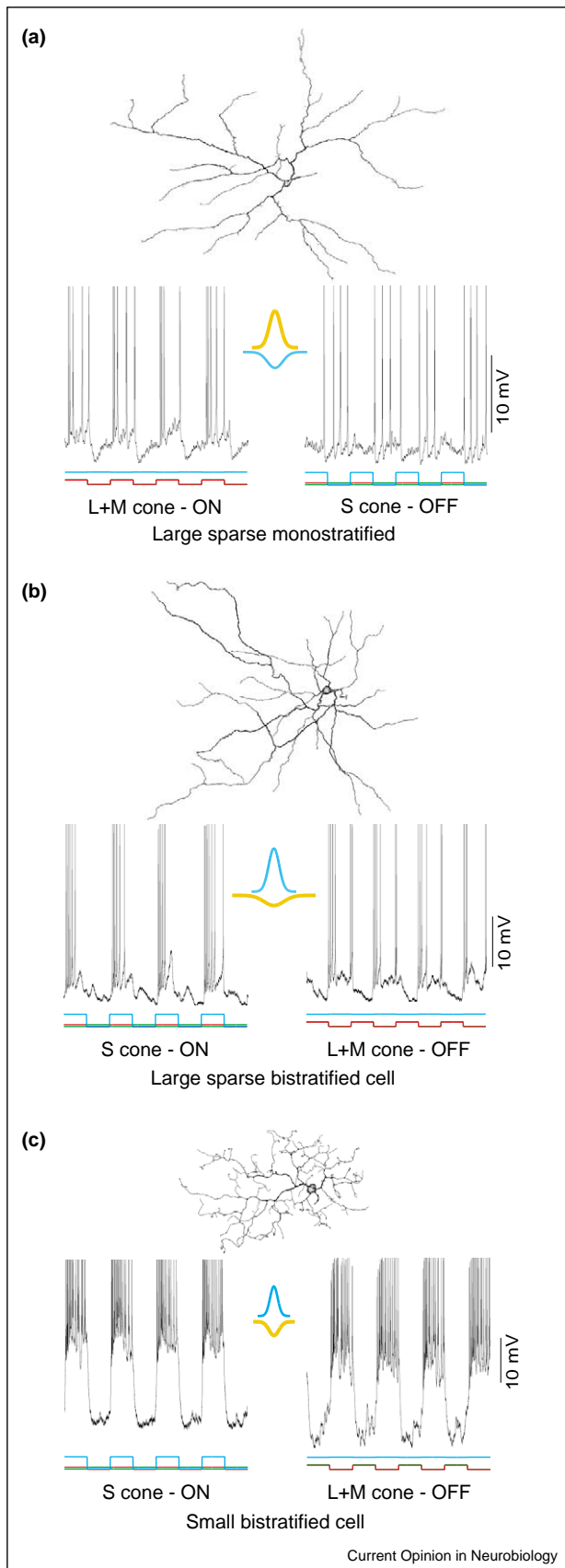
Figure 2
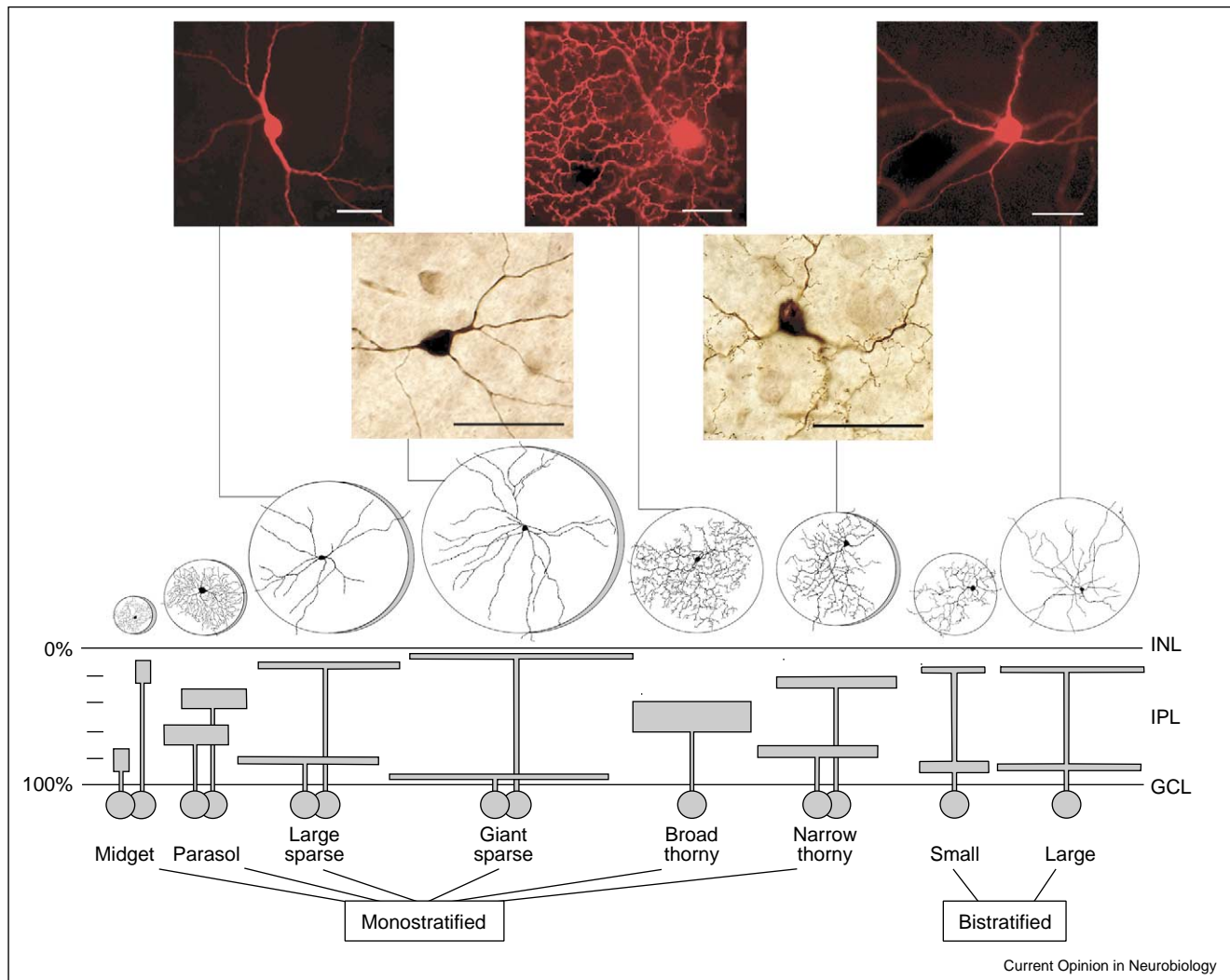
Schematic summary of the morphology of 13 LGN-projecting cell populations recognised by retrograde photostaining [45]. Retrograde photodynamics reveals diverse low-density ganglion cell populations that project to the LGN. Photomicrographs are shown above camera lucida tracings of each newly identified cell type. Ganglion cells were tracer labelled following retrograde transport of biotinylated rhodamine dextran injections from the LGN, and observed in the *in vitro* retina following photodynamic staining (top 3 micrographs — see text for discussion of how this method works). Subsequent horseradish peroxidase (HRP) histochemistry provided a permanent morphological record of labelled cells (e.g. lower two micrographs). Scale bars = 50 μm. GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer. Depth of dendritic stratification in the IPL is estimated as a percentage depth with respect to the total measured thickness of the IPL, with the GCL at 100% depth.

history of primate visual physiology [44]. In addition, an inhibitory S-cone signal appears to be an important component in colour processing at the level of primary visual cortex [45,46]. However, our understanding of this retinal pathway is still limited, and the source of the S-OFF signal is unclear. No S-cone selective OFF-bipolar cells have been identified as a counterpart of the S-ON bipolar, and the large sparsely branching dendritic trees of the S-OFF ganglion cells are stratified in the inner portion of the inner plexiform layer, where S-ON-pathway signals are transmitted. Either the inhibitory S-signal reaches this cell by a sign inversion of the S-ON bipolar signal or the

S-cone signal is in some way introduced to the inhibitory surround of this cell. Measurements of receptive field structure and pharmacological manipulations of ON and OFF signals can address this question in the future.

The second S-cone opponent type receives an excitatory input from S cones and, at least superficially, shows a light response much like that of the previously identified S-ON small bistratified cells (Figure 3b, c). These newly identified S-ON cells are also bistratified with the inner tier of dendrites a likely location for direct input from the S-cone bipolar cell, and the outer tier of dendrites a possible

Figure 3

(a)

10 mV

L+M cone - ON   S cone - OFF

Large sparse monostratified

(b)

10 mV

S cone - ON   L+M cone - OFF

Large sparse bistratified cell

(c)

10 mV

S cone - ON   L+M cone - OFF

Small bistratified cell

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Multiple S-cone opponent pathways. S-cone opponency occurs when S-cone signals are antagonistic to some combination of L and M cone signals. Recent evidence suggests that multiple anatomically distinct ganglion cell populations transmit S-cone signals to the LGN [45,47••]. This figure shows the dendritic morphology, intracellularly recorded light response and receptive field structure for three S-cone opponent ganglion cell types. **(a)** Large, sparse monostratified ganglion cells show L + M ON, S-OFF opponent receptive fields; these cells are stratified in the inner, ON portion of the IPL but the source of the inhibitory S-cone signal has not been determined. **(b)** Large bistratified ganglion cells show S-ON responses much like that of the S-ON small-bistratified ganglion cell illustrated in **(c)** and are likely to also receive direct excitatory input from the S-cone bipolar cell. However, the nature of the L + M cone input to this cell type and how it compares to the L and M cone input to the small bistratified ganglion cell remains to be studied in detail. The stimulus was a 2Hz square wave modulation; the relative amplitudes of red, green and blue lights to create cone-isolating conditions are indicated. Receptive field structure was measured by the spatial frequency response to drifting gratings that modulated either the S-cones or the L + M cones in isolation for each of these cells. The data was fit with a difference of Gaussian receptive field model, shown in between the intracellular voltage traces; blue Gaussian indicates S-cone field, yellow Gaussian indicates L + M cone field.

source of an OFF-pathway input for some combination of L and M cone signals. In contrast with the small bistratified cells, these newly identified S-ON cells show sparse dendritic branching and, at least in the retinal periphery, slightly larger dendritic fields. The unique role that these 'large' bistratified cells might play in chromatic processing is not yet clear. However, it will be important to characterise more carefully the nature of the overall cone opponency of these cells in reference to the small bistratified S-ON cells to begin to answer this question.

Conclusions

First, regarding L versus M cone spectral opponency in the midget pathway, the focus of attention is now squarely on discovering the mechanisms that can produce highly cone specific signals to both centre and surround in the face of apparently non-selective cone wiring. With no evidence from the traditional pathway for the surround through horizontal cell feedback in outer retina or amacrine cell inhibition in inner retina, one is left with the speculation that there must be considerable physiological plasticity in the weighting of L and M cone signals at the ganglion cell level. There is new evidence that such plasticity occurs at the cortical level, where the relative weights of L and M cone inputs to the red-green chromatic channel can be altered by long-term changes in the chromatic environment in both normal and colour-deficient human adults [47••].

Second, the addition of diverse new ganglion cell populations to the retinogeniculate pathway, which includes at least two new S-cone opponent types, indicates that our fundamental understanding of the identity and properties of retinal colour-coding circuits and their relationship to human colour perception remains incomplete. Previously

inaccessible low-density ganglion cells appear to play important roles, and should provide future surprises.

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This study demonstrates a visual-experience-dependent neural plasticity in normal adult colour vision. When daily chromatic experience was altered by placing coloured filters over the eyes a shift in colour perception occurred (as measured by a shift in the wavelength perceived as unique yellow) that persisted for many days after they were removed. The authors argued that a neural normalisation mechanism must operate at the level of visual cortex to compensate for changes in the chromatic environment, and that this mechanism may underlie the uniformity of normal human colour vision despite a large variation in the ratios of L to M cones across individuals (see Roorda and Williams [12]).