The machinery of colour vision

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Abstract | Some fundamental principles of colour vision, deduced from perceptual studies, have been understood for a long time. Physiological studies have confirmed the existence of three classes of cone photoreceptors, and of colour-opponent neurons that compare the signals from cones, but modern work has drawn attention to unexpected complexities of early organization: the proportions of cones of different types vary widely among individuals, without great effect on colour vision; the arrangement of different types of cones in the mosaic seems to be random, making it hard to optimize the connections to colour-opponent mechanisms; and new forms of colour-opponent mechanisms have recently been discovered. At a higher level, in the primary visual cortex, recent studies have revealed a simpler organization than had earlier been supposed, and in some respects have made it easier to reconcile physiological and perceptual findings.

Opsin
A G protein membrane-bound receptor usually found in rod and cone photoreceptors that initiates phototransduction. Its spectral sensitivity depends on the sequence of amino acids.

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Two hundred years ago, Young[1] suggested that colour vision depends on the excitation of three fundamental mechanisms with different but overlapping spectral sensitivities. More than a hundred years ago, Hering[2] suggested that the appearance of colours depends on mechanisms that bring together in opposition (for example, red versus green) the signals that are elicited by lights from different parts of the spectrum. These perceptual observations have guided physiological investigations, which over the past 40 years have confirmed the existence of three fundamental mechanisms whose signals are later brought together in opposition. This seemingly simple hierarchical organization indicates that specific visual tasks might be readily assigned to neural mechanisms at each stage of the pathway (BOX 1). However, recent work has revealed an unexpected richness of physiological organization that is invisible to the perceptual scientist.

We review here the machinery through which the brain might provide for colour vision, proceeding from the photoreceptors to the cerebral cortex (BOX 1). We focus on the mechanisms of primate colour vision, in humans and in our closest animal model, the macaque monkey. We describe, in the retina and in the lateral geniculate nucleus, many more pathways for colour signals than seemed possible only 15 years ago. We then show that signal transformations within the primary visual cortex (V1) accomplish much of what needs to be done to accommodate findings from perceptual studies. New work has also provided much clearer evidence than we have had until now about which cells in the cortex convey information about colour, and has sharpened our understanding of the relationship between colour vision and binocular vision.

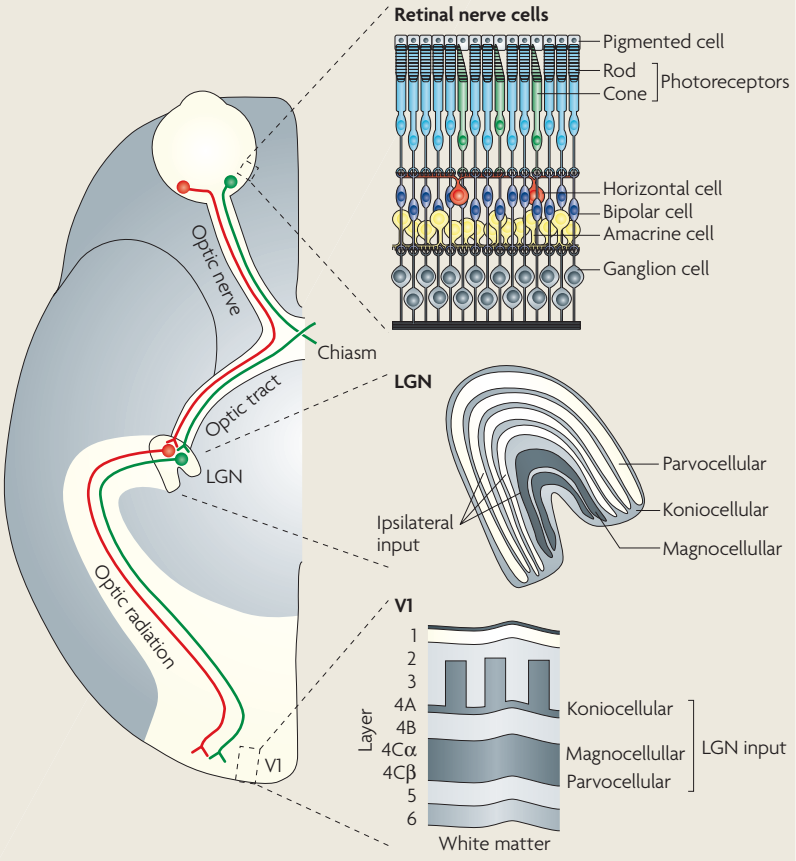
The building blocks of colour vision

Photoreception. The spectrum of light that is visible to humans and most other mammals spans wavelengths of ~400–700 nm. Humans with normal colour vision can distinguish many thousands of colours[3]. To accomplish this we use the signals from three types of cone photoreceptor, whose greatest sensitivities are to short (S, ~430 nm), medium (M, ~530 nm) and long (L, ~560 nm) wavelengths, but whose tuning is broad enough that each responds to light throughout much of the visible spectrum (FIG. 1). The spectral sensitivity of a photoreceptor is best understood as a measure of the probability that the receptor will absorb a photon of a particular wavelength. Once absorbed, the identity of the photon is lost, so no single photoreceptor can distinguish a change in the wavelength of light from a change in its intensity. This is the principle of univariance[4]. Colour vision, the ability to distinguish lights of different spectral composition, regardless of intensity, depends on the comparison of signals from photoreceptors with different spectral sensitivities. The presence of three types of cone photoreceptor makes human colour vision 'trichromatic'. It is dichromatic when there are two types, as is the case in some humans, most New World primates, and most other mammals. Some nocturnal mammals, including owl monkeys[5], have only one type of cone photoreceptor.

The spectral sensitivity of a mammalian photoreceptor is determined by the opsin it expresses,

Box 1 | **The dominant visual pathway in primates**

The left panel shows a schematic drawing of the pathway from the retina to the primary visual cortex (V1) through the dorsal lateral geniculate nucleus (LGN) of the thalamus. The right panels highlight the important anatomical structures. Light entering the eye passes through the ganglion cells and is imaged on the photoreceptor layer (rod photoreceptors, which are not active in colour vision, are found between the cones). Signals from photoreceptors pass through bipolar cells to ganglion cells, the axons of which form the optic nerve, which projects principally to the LGN. The horizontal and amacrine cell pathways within the retina allow spatial comparisons of cone signals. Ganglion cells from the temporal retina project to the ipsilateral LGN (red lines) and those from the nasal retina project to the contralateral LGN (green lines). Within the LGN, the projections from the two eyes are aligned, so the same topographic map (of the contralateral half of the visual field) is found in all layers. The axons of LGN neurons project almost exclusively to V1, where they terminate primarily in layer 4 and form ocular dominance columns (a small fraction of LGN cells project to extrastriate areas: see REF. 163 and the references therein). The termination site within layer 4 depends on the layer in which the LGN neuron is found: parvocellular (P) cells project mainly to layer 4Cβ, magnocellular (M) to layer 4Cα, and koniocellular (K) cells to layer 4A and lower layer 3. The shading depicts the distinct pattern that emerges when slices through V1 are stained for cytochrome oxidase activity. Reactivity is particularly high in layer 4 and in patches that dot the superficial layers 2 and 3.



which in the outer segment is covalently bound to a chromophore[6]. The spectral sensitivity of this compound is determined by the sequence of amino acids that make up the opsin protein. Small changes in the opsin sequence can shift the most effective wavelength: for example, differences in two of the ~350 amino acids in the L- and M-opsins of the human retina account for most of the 30 nm difference in their peak wavelengths[7,8], and differences at a further 5 sites can introduce more subtle variants. Although animals of other phyla can express four different opsins in the cone photoreceptors, mammals seem to have lost all but two (one sensitive to short wavelengths and another sensitive to long wavelengths). Subsequently in evolution, primates seem to have regained a third opsin (for a review, see REF. 9), providing two opsins (M- and L-) that cover the middle- and long-wavelength parts of the spectrum. The genes that code for the L- and M- opsins are found in an array on the X-chromosome, with the L-opsin gene being closest to the region that controls gene expression, with one or more M-opsin genes downstream of it, although only the first seems to be expressed[10,11]. The genes are vulnerable to alteration or loss, resulting (much more often in men than in women) in loss or impairment of the capacity to distinguish colours in the middle- and long-wavelength parts of the spectrum. The close similarity and concatenation of the L- and M-genes in Old World primates makes it likely that the ancestor of macaques and humans possessed a single L-opsin gene on the X-chromosome, and that this gene then duplicated and mutated into the gene for the M-opsin.

If one of the L- or M-opsin genes is deleted or fatally mutated and not expressed, dichromacy is inevitable (although see REF. 12). In Old World primates, there are two potential dichromatic phenotypes: all the non-S-cone photoreceptors might express the same opsin, or the photoreceptors that would otherwise have expressed the dysfunctional opsin express no opsin at all. These are not mutually exclusive — the phenotype should depend on the type of mutation — and there is evidence for both[13,14].

Other variations in the properties of photoreceptors should affect trichromatic vision. First, the peak sensitivity of the opsins can be changed by non-fatal mutations, through crossing over. Such shifts in spectral sensitivity give rise to characteristic anomalies of colour vision (almost exclusively in men), depending on the opsin that is affected: deuternomaly arises when the spectral sensitivity of the M-opsin shifts, and protanomaly when that of the L-opsin shifts. Genetic screening has shown that there are many anomalous opsins among the human population[15,16], but only large shifts seem to cause noticeable deficits in colour vision. Second, the ratio of L- to M-cones in the photoreceptor mosaic varies widely, from approximately 0.4 to more than 10 (REFS 17–19). This might be expected to influence colour vision, but does not; for example, the wavelength that individuals describe as uniquely yellow does not depend on the proportion of L-cones in the mosaic[19].

One to three percent of ganglion cells in most mammalian retinas are intrinsically photosensitive: they express the photo-pigment melanopsin, a G-protein-coupled receptor. The light response of this pigment is much slower than that of cones or rods, so it probably does not contribute to colour vision as it is normally studied (although it is important for the control of circadian rhythms[20], and probably for the pupillary light reflex[21]). Nevertheless, these ganglion cells project to the dorsal lateral geniculate nucleus (LGN) of the thalamus, the main

Chromophore
A molecule, or part of one, that changes conformation upon absorbing light, inducing a conformational change in the opsin bound to it and thereby triggering phototransduction.

Crossing over
During meiosis, two like-chromosomes can both break; each can reconnect with the fragment from the other, exchanging genes or parts of genes in the process.

Deuteranomaly
Small deviations of colour vision from the normal observer (often only revealed in tasks requiring fine discriminations) brought about by mutations that shift the spectral sensitivity of the M-cone opsin.

Protanomaly
Small deviations of colour vision from the normal observer (often only revealed in tasks requiring fine discriminations) brought about by mutations that shift the spectral sensitivity of the L-cone opsin.

Ganzfelds
Formless fields of light, and ineffective stimuli for ganglion cells driven by photoreceptors.

Receptive fields
The region of visual space (or, equivalently, an area on the retinal surface) where presentation of an appropriate pattern of light causes changes in the activity of a neuron.

pathway for vision, so they might contribute directly to perception[22]. Their intrinsic photosensitivity does not adapt to the ambient light, and so they could provide a signal for absolute brightness[22]. Were the signal from melanopsin important for the perception of brightness, its distinctive spectral sensitivity should allow this to be revealed (FIG. 1): the prediction being that ganzfelds illuminated by different monochromatic lights that equally excite melanopsin should be judged as equally bright.

The photoreceptor mosaic. Colour vision depends on the comparison of activity in different photoreceptors, but these photoreceptors lie in a two-dimensional sheet, with only a single photoreceptor at any one position. So, for colour vision we must make comparisons across space. For the best spatial resolution of colour variations, we might want photoreceptors to be arranged in a triangular lattice (much like a shadow-mask television tube). Indeed, we might expect the mechanisms that determine which opsin is expressed in each photoreceptor to also confer spatial order on the cone mosaic (such that, for example, neighbouring photoreceptors act mutually to suppress the expression of the same opsin). The S-cones in primates are histologically distinctive, and their proportion (5–10% of all cones) and quasi-regular distribution in the retina have been known for some time[18,23–25]. Until recently, it was assumed that L- and M-cones (which are not easy to distinguish) were arranged in a regular lattice. However, modern measurements[26,27], culminating in the extraordinary images of the living primate retina provided by recent studies[18,28,29], one of which is shown in FIG. 1, have now refuted this assumption.

Rather than lying in a triangular lattice, the L- and M-cones are distributed as if the type (L or M) of each cone is determined randomly[8]. Little is known about the developmental mechanisms of cone differentiation and migration, and the apparently random mosaic might arise from the interplay of non-stochastic processes[18]. The ratio of L-:M-cones seems to depend on the cones' location in the retina, generally increasing in the far periphery, and this does not easily fit the random hypothesis[18,30–33]. Across large areas and for purely chromatic L–M modulation[18], a random mosaic will produce the same spatial frequency resolution as a crystalline one. Nevertheless, the clusters of cones of one type that develop in these mosaics have significant implications for colour vision: they make the achievable spatial resolution of colour vision different in each local region of the retina, and will cause a physically identical stimulus to evoke different patterns of activity depending on its location on the mosaic. In perception this might have its corollary in the various colour sensations that can be elicited by the same small light[34,35]. The upshot is that, in a mosaic containing clusters of cones of a single type, the area of the retina that must be sampled to form a neural representation of hue that does not depend on retinal location is larger than it would be were the mosaic crystalline. This must limit the acuity of colour vision.

Organization of subcortical pathways

Because a single photoreceptor cannot distinguish between a change in the wavelength of light and a change in its intensity, the analysis of colour requires the comparison of signals from different types of cones. Early perceptual observations[2,36] indicated that the representation of hue is organized along two fundamental dimensions — red–green variation and blue–yellow variation (BOX 2).

Early neurophysiological investigations of post-receptor colour mechanisms looked at neurons in the primate LGN. Neurons in this relay station, which have receptive fields that are largely indistinguishable from those of the retinal ganglion cells that drive them (BOX 1), have chromatic properties that at first sight

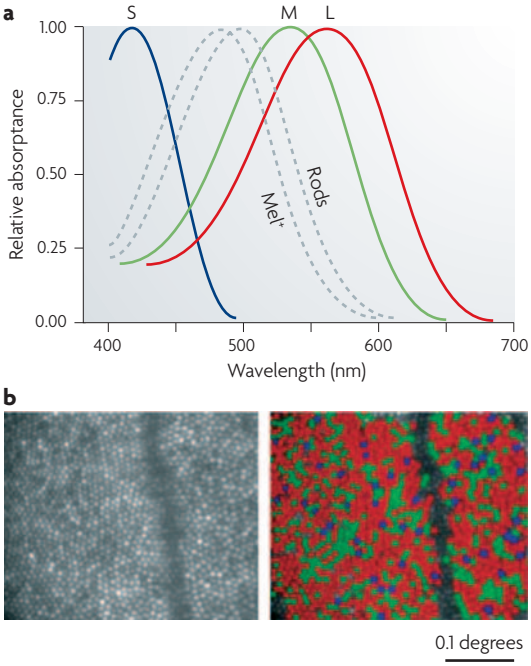


Figure 1 | **Spectral sensitivity and spatial distribution of photoreceptors in the primate retina. a** | Spectral sensitivities of L-cones, M-cones and S-cones. Shown for comparison are the spectral sensitivities of rods and intrinsically photosensitive ganglion cells (which express melanopsin, *Mel*$^+$; from REF. 22). **b** | Spatial arrangement of the different types of cones in the photoreceptor mosaic in the human retina[18]. The images are the mosaic of a single individual, JP, 0.8 degrees from the fovea in the temporal retina. The greyscale image shows the arrangement of photoreceptors. Three additional images are then obtained, each after exposure to intense lights of different wavelengths, and compared to this reference. Each intense light bleaches photopigment in some cone types more than others, so the type — S, M or L — of cone can be recovered by comparing changes in absorptance induced by each of the three conditions. On the right, false colouring shows the type of cone — red for L-cones, green for M and blue for S. In this mosaic, the L-cones outnumber the M-cones by a ratio of ~2.3:1. The S-cones are much less numerous, roughly 4% of all cones here. The L-and M-cones are distributed randomly, so there are frequent clumps of cones of one type.

seemed strikingly like those suggested by perceptual work[37,38]. Later work firmly established two distinct groups of neurons and characterized them quantitatively[39–41]. Neurons in one group oppose the signals of L- and M-cones: these are the midget ganglion cells and their targets are in the parvocellular (P) layers of the LGN. Neurons in the other group receive strong signals from S-cones, opposed to some combination of signals from L- and M-cones (FIG. 2): these are usually found in zones bordering the principal layers of the LGN. As we have learned more about these groups, it has become increasingly clear that they have no simple connections with the fundamental perceptual dimensions.

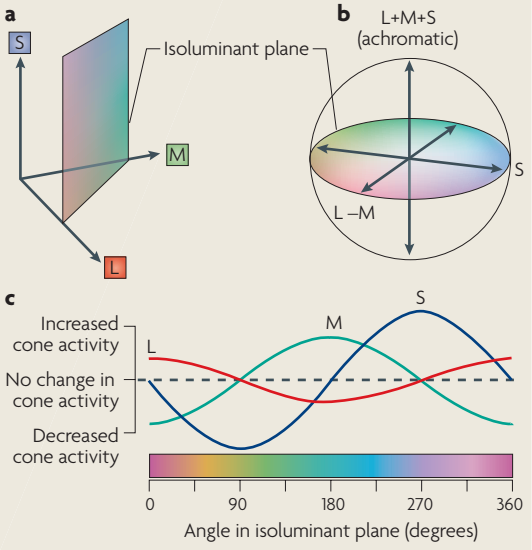
The receptive fields of P-cells. P-cells receive inputs from only L- and M-cones, and these inputs generally have opposite signs (FIG. 2), which indicates that P-cells are important for red–green colour vision (for an alternative view, see REFS 42,43). However, there seem to be many more P-cells than are necessary to support colour vision, and no other pathway provides the sampling density that is needed to support fine spatial resolution, indicating that the P-pathway is essential for spatial vision. It was recognized early on that cone-opponency in P-cell receptive fields might be provided by their centre-surround spatial structure (with, for example, L-cones providing the main input to the centre, and M-cones providing the main input to the surround), so the capacity to support red–green colour vision might have exploited mechanisms that were developed for spatial vision[44–48].

The complexity of supporting these two roles is highlighted by the recent discovery[28,29] that the apparently random distribution of L- and M-cones can lead to large clusters of one type, making it hard to construct receptive fields that have both precise spatial and precise chromatic properties. To understand how this is accomplished we need to know two things. First, does colour vision require receptive fields where the inputs from different types of cone are tightly specified? Second, do cone inputs to the receptive fields of P-cells differ from what we would expect from indiscriminate sampling of the cone mosaic? The answer to the first question is probably 'no': models without selective wiring of cone inputs in retinal receptive fields can account for many aspects of human colour vision[49,50]. Moreover, individuals with different L:M-cone ratios have similar colour vision[18,19]. It seems unlikely that, in these individuals, retinal receptive fields have managed to assign fixed weights to each cone type without loss of spatial acuity. The second question has proved much more difficult to answer.

Cone-specific inputs to the centre and surround will confer on a P-cell receptive field the highest possible sensitivity to chromatic signals. But chromatic opponency can also arise through the antagonistic interactions of two mechanisms that have substantial spectral overlap, as would be the case if the centre and surround drew inputs randomly from the photoreceptor mosaic. There is no known anatomical mechanism through which the centre and surround select inputs from specific types of cone[51–53], but we know almost nothing of the chromatic properties of amacrine and bipolar cells in the primate retina[54,55] (BOX 1), so it has been hard to discern the pathways through which cones provide input to ganglion cell receptive fields. In the central retina, P-cells probably derive their principal excitatory input from only one cone[56,57]; physiological investigations of the cone specificity of inputs to P-cell surrounds in the central retina have generally been inconclusive[41,58–62]. This is not surprising, because the functional difference between cone-selective and indiscriminate connections is small. Given this, and the absence of selective connections to M- or L-cones in the outer retina, there seems no reason to suppose that the opponent mechanisms in P-cell receptive fields are cone-selective.

Box 2 | **Colour space and isoluminance**

Panel **a** shows a three-dimensional colour space, the axes of which are the activation level of each cone type (L, M and S). Within this space is a series of parallel surfaces; in each of these the activity of L- and M-cones varies so that their sum remains constant (L ≈ –2M). These surfaces are called isoluminant, where lights differ in hue and saturation but not in luminance; one surface is shown in the figure. S-cones do not usually contribute to the sensation of luminance, so in the space formed by the cone activations the surface forms a plane parallel to the axis of S-cone activation. A physiologically relevant transformation of this space[39,164] is shown in panel **b**, where the same surface is redrawn. Two axes now define it as a plane. One axis represents the level of S-cone activation (S), the other is the difference between L- and M-cone activation (L –M). The plane formed by these two axes is isoluminant because throughout it the sum of L- and M-cone activity is constant. When stimuli are defined by excursions from the centre of this plane (the white point), the angle within the plane defines the level of cone activation and hue, as is shown in panel **c**. Here, 0 degrees is an excursion from the white point to +L –M (increased L-cone activity and decreased M-cone activity) and 270 degrees is increased S-cone activity. Normal to this plane is an achromatic axis along which the signals of all cones vary.



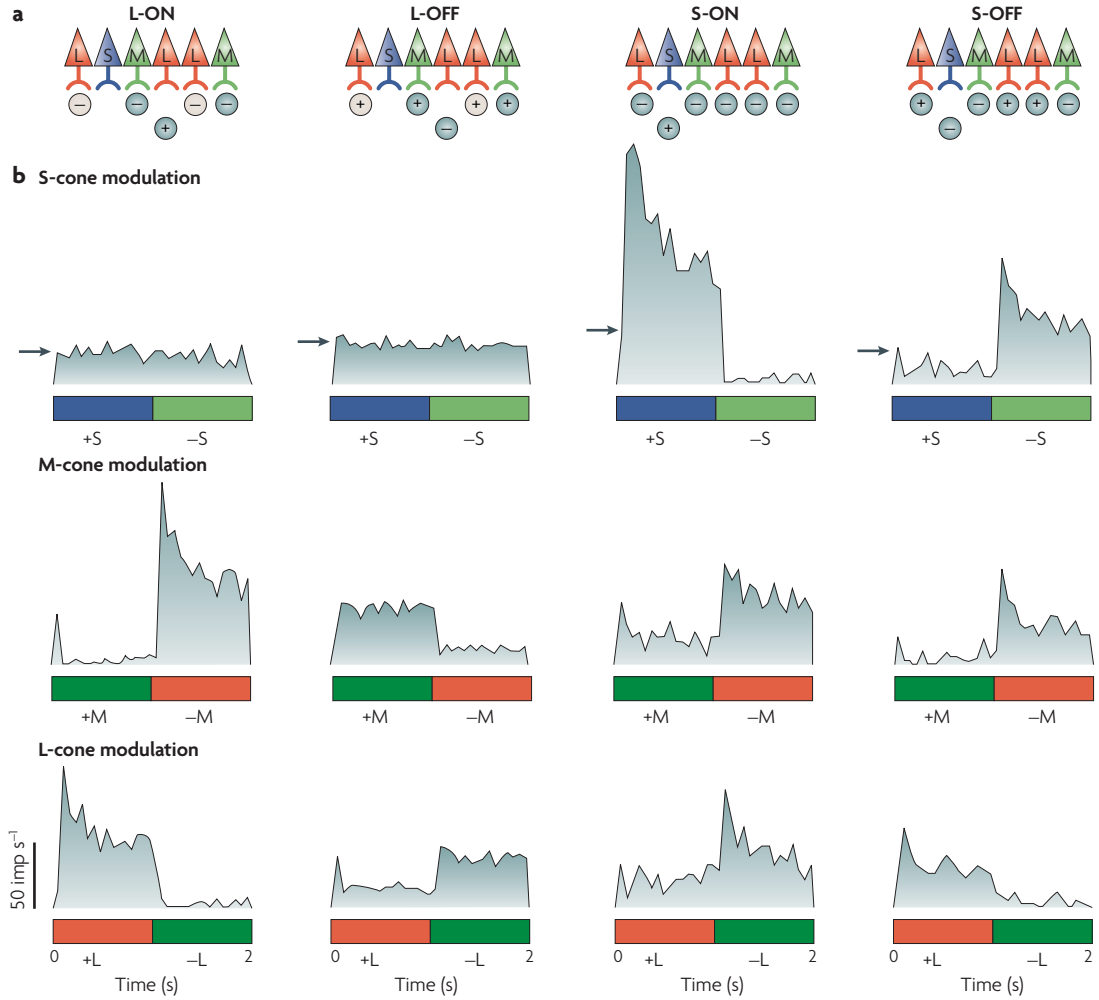


Figure 2 | **Cone inputs to four different types of neuron in the macaque lateral geniculate nucleus. a** | Which cones contribute inputs to the receptive field are shown — the plus sign indicates cones for which increases in activation lead to increased firing of the neuron, the minus indicates the cones where decreases in activation lead to increased firing. Cones that probably provide input to the surround are shown in the upper level, and to the centre in the lower level. Lighter shading of the circles indicates that the contribution of that class of cone to the opponent mechanism is uncertain. **b** | The average firing rates during selective modulation of cone activity (upper, modulation of the S-cones only; middle, M-cones; lower, L-cones). Two P-cells (L-cone ON, L-cone OFF) receive input only from L- and M-cones; two K-cells (S-ON, S-OFF) also receive input from S-cones. Two other neuron types important in colour vision — M-ON and M-OFF — are not shown, and their responses would be the mirror image of L-ON and L-OFF cells. Arrows in the top panels show the spontaneous discharge rate. imp s^{-1}, impulses per second.

Outside the central retina, the receptive field centres of P-cells draw on several cones, so indiscriminate sampling of the cone mosaic would cause the colour-opponent organization to become more variable. Nevertheless, although opponency is weaker on average in the peripheral retina than in the central retina, it is not absent[61,63]. The surrounds of P-cells are also larger in the peripheral retina and may draw on hundreds of cones, so without selective wiring most of them should have the same spectral sensitivity (that of the average of L- and M-cones in the photoreceptor mosaic), and there is some evidence for this[61]. Chromatic opponency in peripheral P-cells must arise through dominance of the centre mechanism by cones of a particular class, but to understand whether this arises through chance will require a quantitative model of the impact of clusters of cones of one type[64].

Pathways that carry signals from S-cones. Subcortical receptive fields are commonly described by the sign, 'ON' or 'OFF', of the centre mechanism. This sign is determined by the response of the neuron to uniform illumination by white light: ON when activity increases with increasing illumination, OFF when activity increases with decreasing illumination. In the same way, increased activity accompanying increasing S-cone activation means that the sign of the majority of S-cone input to the receptive field is ON. We usually think of ON and OFF pathways as providing complimentary representations of the retinal image, but recent work indicates that for S-cone signals this is not the case.

It has long been known that a specialized bipolar cell provides ON S-cone signals ('S-ON', often called 'blue-ON') to later visual processes[65,66]. It now seems clear

that this S-cone pathway, which is preserved in diurnal primates[67] and found in other mammals[68], is phylogenetically ancient. S-cones are sparsely distributed, so they cannot support high visual acuity. It is therefore likely that the S-cone pathway evolved to provide colour vision in a common (dichromatic) ancestor of these mammals[69].

We have learned much about some S-cone pathways through *in vitro* intracellular recordings of primate retinal ganglion cells, which are then stained to identify their morphology[22,70,71]. Early recordings showed that the ganglion cells that give S-ON responses have a distinctive bistratified morphology and form part of a pathway that is separate from the long-established midget–parvocellular system. S-ON neurons are generally found in the koniocellular (K) layers of the LGN[38,72,73] (BOX 1). In macaques in which the activity of cortical neurons has been silenced by application of muscimol (an agonist of $GABA_A$ (γ-aminobutyric acid A) receptors) to reveal the activity of LGN afferents to different cortical layers, S-ON responses are found only in the superficial layers 3 and 4A[74], to which the neurons in the LGN K-layers project[75,76]. The receptive fields of S-ON cells in the retina and LGN are larger than those of P-cells, consistent with the large dendritic tree of the small-bistratified retinal ganglion cell[54,61,77,78]. Their receptive fields are also distinctive in other ways: they are often sensitive to the direction of motion of an achromatic drifting grating[79,80], a property that is not usually thought to be present in the retinogeniculate pathway to the visual cortex.

Recent work, using injections of a retrograde dye into the LGN and microelectrode recording from the subsequently labelled ganglion cells[22,71,81], has identified three further morphologically distinct types of ganglion cell that carry signals from S-cones. One type receives excitatory input from S-cones and two receive inhibitory input from S-cones — one of these is the intrinsically photosensitive (melanopsin-expressing) ganglion cell described earlier. The source of OFF S-cone signals in ganglion cells remains unclear — a recent description of an OFF S-cone bipolar cell has proved controversial[82,83].

Some recent observations have helped to identify the possible roles of some of the different types of ganglion cell that carry S-cone signals. We have re-examined the cone inputs to the receptive fields of macaque LGN neurons[79,84]. As expected, most receptive fields in the P-layers are L–M opponent with little or no input from S-cones; some magnocellular cells might respond to S-cone modulation, but they are always much more sensitive to modulation of the L- or M-cones[58,85–87]. In addition to these cells, we found many neurons that responded strongly to modulation of the S-cones in and around the koniocellular zones separating the P-layers. S-cone input to these neurons was as likely to be 'OFF' as it was 'ON' (FIG. 2). The colour preferences of S-ON cells were reasonably homogenous, with excitatory S-cone input usually opposed to the summed activity of L- and M-cones; thus, they gave little response to isoluminant red–green (L–M) modulation[39,41,88] (BOX 2). The colour preference of S-OFF cells was more heterogeneous[89], but usually intermediate between that of S-ON cells and red–green opponent P-cells. This arises because in many S-OFF cells the input from M-cones has the same sign as that of the S-cones, and both are opposed to the input from L-cones (FIG. 2). S-OFF cells in the LGN also differ reliably from S-ON cells in preferring higher rates of drift and having lower contrast sensitivity. All this indicates that functionally distinct pathways signal increments and decrements in S-cone activity, consistent with the morphological differences in the retinal ganglion cells from which they originate.

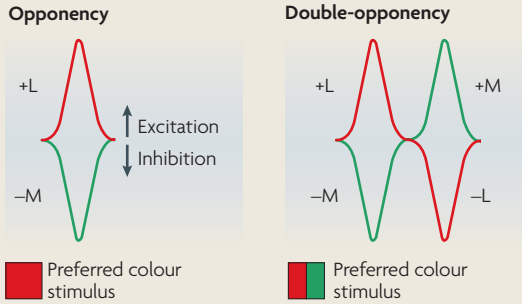
Early signal transformations in the cortex

Signals that are important for colour vision are provided by several groups of LGN neurons, the axons of which project to different layers of V1 (REF. 74). However, the receptive field properties of neurons in V1 are rarely like those of the LGN: few cortical neurons respond to spatially uniform stimulation and most are selective for the orientation of edges; most respond well to achromatic modulation and less well or not at all to chromatic modulation (a powerful stimulus to most LGN cells). There remains substantial disagreement about the role of these neurons in colour vision. About 5–10% of neurons in V1 respond robustly to purely chromatic modulation and little, if at all, to achromatic modulation: these are most obviously important for colour vision. Among them, colour preferences are widely distributed, with only a slight bias towards those that predominate in LGN, but how these preferences are formed is a matter of debate.

Colour preferences of receptive fields. One of the most remarkable properties of V1 is that, despite being at least four (and often more) synapses away from the photoreceptors, the receptive fields of many neurons can be well characterized by supposing a linear combination of cone signals[88,90–94]. Other neurons have more complex receptive field properties, but even in these the linear models can be very informative[84,90,95,96]. This has allowed us to interpret the chromatic responses of cortical receptive fields in terms of the cone signals that provide their input.

The L- and M-cone inputs to cortical receptive fields have been extensively studied. In many neurons these inputs are of the same sign, so the receptive field is generally insensitive to chromatic modulation. This organization resembles that found in LGN magnocellular cells[97], although it does not imply that those cells provide the input: the receptive fields of cortical cells are much larger than those in the LGN, so they must get input from many LGN cells[98]. As would be the case for a retinal receptive field drawing indiscriminately from many photoreceptors, a cortical receptive field that draws indiscriminately from many P-cells will also tend to be non-opponent[99]. Other V1 receptive fields show weakly opponent interactions between L- and M-cone signals, and respond well to both chromatic and achromatic modulation[84,90,96,100–102]. We cannot rule out the possibility that cone-opponency in many of these cells has arisen by chance (as has been argued for the receptive fields of P-cells), but some of their other properties are important and we discuss them in more detail below.

Box 3 | Two types of receptive field that might be important for colour vision



Each panel shows a schematic of the one-dimensional spatial profile of sensitivity, with L- and M-cone inputs of opposite sign; the preferred colour stimulus is shown below. The left panel shows a receptive field in which the opposed inputs from different cone types are largely overlapping in space, so the neuron gives strong responses to uniform coloured fields (but not to white ones). Such receptive fields are sometimes called single-opponent, because there is cone-opponency but not spatial opponency. The right panel shows a double-opponent receptive field, which can be conceived as two single-opponent receptive fields, of opposite sign, placed side-by-side. The resultant receptive field has balanced, spatially displaced, excitatory and inhibitory inputs from each cone type. It therefore does not respond to uniform fields of any colour, or to white light. It does respond well to purely chromatic edges.

Finally, roughly 10% of neurons show well-balanced, strongly opponent L- and M-cone inputs.

In most cortical receptive fields the S-cones provide much less input than the L- and M-cones[88,90,96]. Nevertheless, a substantial fraction of V1 neurons, larger than that in the LGN, receive at least some input from S-cones[84,88,96]. The prevalence of weak S-cone signals in V1 neurons indicates that these signals spread rapidly after entering the cortex, but it is not clear what function this might have[93,103,104]. As in the LGN, receptive fields with a strong S-cone input are encountered rarely, even among the subset of cells that respond best to isoluminant modulation, and are presumed to be important for colour vision[84,96]. Among these the arrangement of cone inputs to the receptive field varies and includes every possible type, but the most common chromatic signature is that found in the S-OFF cells of the LGN (with L-cone signals opposed to those of S- and M-cones [84,91]).

The variety of colour preferences shown by neurons in all layers of V1 indicates that signals from the LGN are recombined early in the cortex. Some direct evidence for this comes from recent work that has exploited contrast adaptation to reveal 'fundamental' chromatic mechanisms. Contrast adaptation has proved to be a powerful tool in the study of human colour vision[105,106], and we know that the contrast sensitivity of most cortical neurons is reduced by prolonged modulation of their preferred stimulus[107]. Those that respond well to isoluminant modulation are also desensitized by contrast adaptation[108], despite the fact that the P-cells which drive them are not[109]. Adaptation also deforms the chromatic tuning of these neurons, in complex ways: it usually reduces sensitivity, especially to the adapted colour direction, but responses to other colour directions can increase during adaptation; adaptation to either the L–M or S direction generally leaves responses to the other unaffected. This rich range of behaviours can be readily explained by supposing that cortical neurons and the inhibitory mechanisms that regulate their sensitivity are both[84] driven by a sum of inputs from two fatigable mechanisms in the input layers: one driven by opposed inputs from L- and M-cones, the other driven by inputs from S-cones[108]. The chromatic signature of the S-mechanism is like that of LGN cells that receive strong S-cone input, but the chromatic signature of the L–M mechanism is unlike that of P-cells — it is not sensitive to achromatic modulation.

Spatial properties of receptive fields. Perceptual studies have revealed much about the properties of mechanisms that might allow us to distinguish the spatial forms of patterns defined solely by variations in hue[110–114]. To encode both the spatial and chromatic contrast in a local spatial region, a neuron requires a receptive field in which the spatially antagonistic regions are chromatically opponent. The 'double-opponent' receptive field exemplifies one form of this (BOX 3). The arrangement of this field's subregions causes a neuron to respond well to a small chromatic stimulus, or one containing spatial colour contrast, but much less well to a larger uniform one and not at all to an achromatic stimulus of any spatial structure. Neurons with this kind of receptive field have been found in the goldfish retina[115] but not in the primate retina; they have been sought in the monkey visual cortex[116–121], but clear-cut examples have rarely been found[94]. Some reports of V1 neurons thought to possess this kind of receptive field[91,92,116,122] have been challenged on methodological grounds[123,124]. The relatively few V1 neurons that clearly prefer a chromatic stimulus to an achromatic one are usually insensitive to the precise spatial form (orientation, width) of that stimulus, so the receptive fields are spatially homogeneous[90,100,101] (BOX 4).

If V1 neurons that are strongly chromatically opponent show little evidence of spatial opponency, how is the spatial structure of chromatic patterns to be discerned? One possibility for which there is a little evidence is that neurons with double-opponent receptive fields emerge in V2 or beyond[101,118,120,121,125–129]. Another possibility is that the capacity to encode the spatial structure of chromatic patterns depends on V1 neurons that respond to both colour contrast and brightness contrast. The receptive fields of these neurons are often selective for the width and orientation of edges, defined either by colour or by brightness[90,96,100–102,130,131].

Most neurons in the visual cortex have receptive fields in both eyes, but early physiological studies indicated that those carrying chromatic signals were distinctively monocular[116,122,132]. Indirect support for this came from findings that colour-preferring cells were localized in the 'blobs' of dense cytochrome oxidase reactivity that characterize the upper layers of V1 (REFS 116,124), and lie in the centres of ocular dominance columns[133,134]. Later work found little relationship between blobs and the colour-preference of receptive fields[90,131], and recent optical imaging confirms that the relationship is weaker than first reported[135,136]. But why should we expect the machinery of colour vision to be monocular? Although stereopsis is poor when stimuli are isoluminant[137–139], there have been frequent findings of binocular

Contrast adaptation
The change in sensitivity (of human perception, or of individual neurons) to stimulus contrast that results from prolonged exposure to modulation of a visual stimulus.

Stereopsis
The capacity to determine the distance to a surface through the comparison of the disparate images formed in the two eyes.

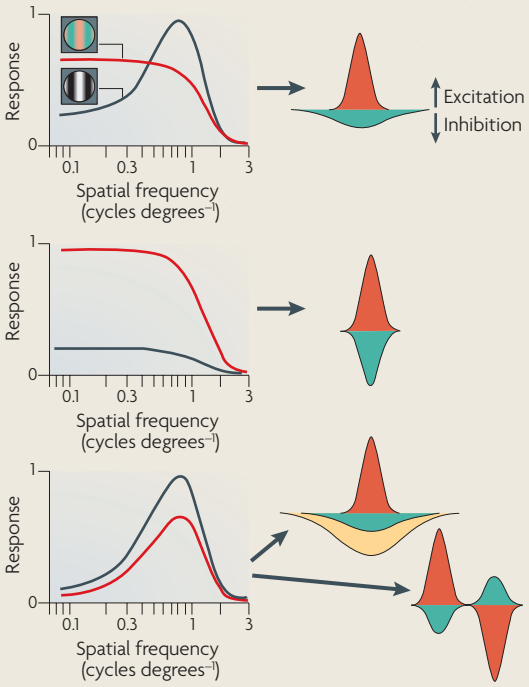
interactions in human colour vision even for the most basic of tasks[140,141]. Consistent with this, colour-preferring neurons in V1 are at least as likely to be binocular as any other type of neuron[136,142]. Moreover, as is the case for other early cortical neurons[143], the colour-preferring neurons combine fairly linearly the inputs from the two eyes (FIG. 3). The receptive fields of colour-preferring neurons seem well equipped to support binocular single vision and the perception of surface colour, but because they generally lack spatial structure they are not well suited to coding fine stereoscopic detail.

Specialized cortical pathways for colour vision? Distinct populations of neurons carry the signals for colour vision to V1; within V1 there are functionally distinct classes of chromatically selective neurons. The signals about colour that leave V1 provide the capacity to isolate changes in colour from changes in brightness, to specify hue, and to combine information from the two eyes; these representations are substantially invariant to changes in spatial structure and contrast. Assuming these signals reach perception (which might not always be the case[144–146]), what further analysis of colour remains to be done? We usually think of the cortical areas that ascend from V1 to the inferotemporal cortex as supporting 'mid-level' visual tasks, such as constructing contour and texture representations and segregating surfaces in depth, or as generating object-centred representations. For colour vision this presumably means the 'colouring-in' of surfaces, and the identification of regions that belong together.

In areas beyond V1, the functional properties of neurons depend increasingly on extraretinal signals, so it is harder to study them in anaesthetized animals; we know correspondingly less about the chromatic properties of receptive fields and about the distinctiveness of chromatic pathways. Nevertheless, we have some information about how colour signals are propagated and transformed.

In area V2 there are colour-preferring neurons, the colour sensitivity of which depends on the surrounding context[101]. This attribute has often been considered a distinctive property of neurons in the macaque V4 (REFS 118,120,121,129), a visual area that is the gateway to the temporal lobe and is broadly important for the representation of object structure[147,148]. V4 and its presumed homologue in humans have attracted attention as regions that might have a special significance for colour vision. Some humans with lesions to the ventromedial occipital cortex have impaired colour vision, although this is often accompanied by other deficits[149–152]. Functional imaging of this region provides more equivocal evidence on a special role in colour vision[153–155]: chromatic stimuli induce activity, but so do various kinds of achromatic visual stimuli. This is perhaps not unexpected, as colour experience embraces both the hue and the brightness of surfaces, but it points to the difficulty of establishing the

Box 4 | **Spatial and chromatic structure of receptive fields in V1**



The left panels show schematics of the most common types of spatial frequency tuning curves obtained from neurons in the macaque primary visual cortex (V1)[90,96,100–102]. Tuning curves for achromatic gratings are shown by the black lines, and for isoluminant L–M gratings by the red lines. The right panels show the spatial and chromatic structure of the receptive fields that might give rise to these tuning curves. In each case the L-cones (red) provide the principal excitatory input. The top panels show a type I cell[116], where L-cones provide input to an excitatory mechanism; an inhibitory mechanism, which accumulates signals over a different spatial region, draws mainly from M-cones. For achromatic gratings the signals of L- and M-cones are opposed to each other (reflecting the signs of their inputs), but for isoluminant gratings their signals sum (because as L-cone activity increases, M-cone activity decreases). Thus, the spatial frequency tuning curves are band-pass for achromatic gratings but not for isoluminant gratings. The middle panels show a type II receptive field. Here, the mechanisms that accumulate M-cone signals and L-cone signals are the same size, so there is no spatial tuning for either achromatic or isoluminant gratings. Because the M-cone input is slightly weaker than the L-cone input, the cell responds weakly to achromatic modulation. The bottom panels show band-pass spatial frequency tuning curves for both isoluminant and achromatic gratings. This might arise if the receptive field had two subregions, each of which resembled the receptive field of a type II cell[123], but with cone-inputs that were not well balanced. The spatial structure would attenuate responses to low spatial frequencies for both achromatic and isoluminant gratings. Band-pass spatial tuning could also arise if in some type I cells (top panels) there was an extra component (depicted by the yellow shading) to the receptive field: a suppressive region sensitive to all colours[101,124], and more sensitive to low spatial frequencies than to high frequencies[165].

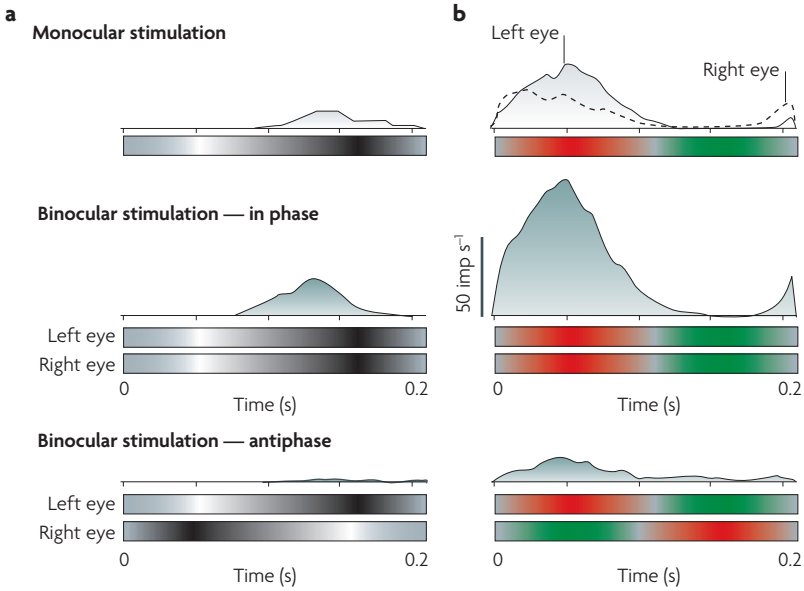


Figure 3 | **Binocular responses of a colour-preferring neuron in the visual cortex of a macaque. a** | Responses to achromatic drifting gratings presented to each eye alone (top panel), to both eyes, in the same phase (middle panel) and to both eyes, but in antiphase (lower panel). When the gratings in the two eyes have the same phase, both receptive fields are stimulated together and the response is greater than for stimulation of either eye alone. In antiphase, the left eye sees white at the same time as the right eye sees black, and vice versa. The signals from the two eyes' receptive fields therefore interfere, and there is little response from the neuron. **b** | Same, for isoluminant L–M gratings. In this case, antiphase stimulation means that the left eye receptive field sees red while the right sees green, and vice versa. The responses shown here and in FIG. 2 were obtained from extracellular recordings in anaesthetized macaques.

function of a cortical area on the basis of its responses to a limited number of rather simple and constrained stimuli.

Bearing in mind these cautions, the most promising functional imaging studies might be those that seek to define the visual areas involved in colour vision by determining how their chromatic sensitivities change with parametric variation of, for example, temporal frequency of the visual stimulus or adaptation state[156–158]. These manipulations have well-characterized effects on human vision, and understanding how they influence signals in different cortical regions could help us to identify likely and unlikely chromatic pathways.

Future directions

This brief review of recent work demonstrates that we have made major advances. Nevertheless, there remain substantial gaps in our knowledge of all stages of colour vision. In the retina we still know little about the pathways from cones to ganglion cells, or why human colour vision seems to be hardly affected by variation in the proportions of cones of different types. Introducing genes for novel pigments into animals with reduced colour vision[159,160] could help us to understand how these early networks are constructed and how plastic they can be. In primates, retinal ganglion cells of types that are not yet well characterized might also be important in colour vision: without knowledge of these, it is difficult to constrain models of receptive field properties at later stages. In the cortex, the problems are different, and stem principally from our not having a clear idea of the properties to be expected of neurons that are responsible for colour perception. We have suggested[84] that one requirement of neurons involved in the analysis of colour is that their chromatic properties be stable in the face of changes in other properties of a stimulus (such as orientation, size and contrast). Relatively few neurons in V1 meet this requirement, and those that do are ill-equipped to represent the spatial attributes of surfaces. Given the great differences between the attributes of neurons that are most obviously relevant to colour vision and those most obviously relevant to spatial vision, perhaps the most interesting challenge will be to understand how the chromatic properties of objects are perceptually bound to their spatial properties. Functional imaging might be helpful here, but to understand the roles of individual neurons will probably require the recording or stimulation of candidate neurons, or groups of neurons, during tasks that rely on the analysis of colour[161,162].

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