

# The retinal basis of vertebrate color vision

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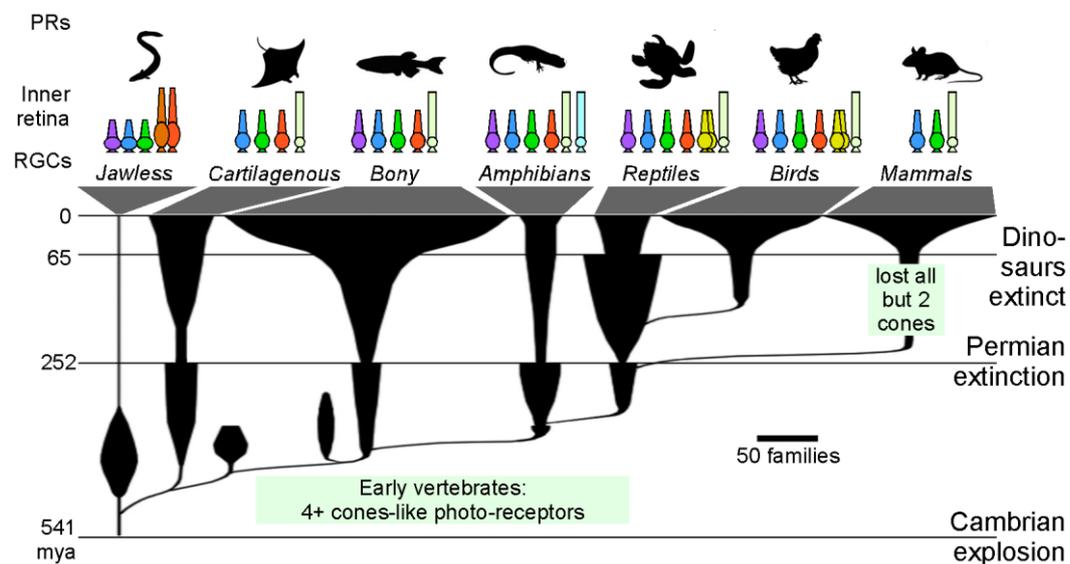
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## Graphical Abstract



## 17 SUMMARY

18 Vertebrate color vision is evolutionarily ancient. Jawless fish evolved four main  
19 spectral types of cone photoreceptor, almost certainly complemented by retinal  
20 circuits to process chromatic opponent signals. Subsequent evolution of  
21 photoreceptors and visual pigments are now documented for many vertebrate  
22 lineages and species, giving insight into evolutionary variation and ecological  
23 adaptation of color vision. We look at organization of the photoreceptor mosaic and  
24 the functions different types of cone in teleost fish, primates, and birds and reptiles.  
25 By comparison less is known about the underlying neural processing. Here we  
26 outline the diversity of vertebrate color vision and summarize our understanding of  
27 how spectral information picked up by animal photoreceptor arrays is adapted to  
28 natural signals. We then turn to the question of how spectral information is  
29 processed in the retina. Here, the quite well known and comparatively 'simple'  
30 system of mammals such as mice and primates reveals some evolutionarily  
31 conserved features such as the mammalian Blue<sup>ON</sup> system which compares short  
32 and long wavelength receptors signals.

33 We then survey our current understanding of the more complex circuits of fish,  
34 amphibians, birds and reptiles. Together, these clades make up more than 90% of  
35 vertebrate species, yet we know disturbingly little about their neural circuits for colour  
36 vision beyond the photoreceptors. Here, long-standing work on goldfish, freshwater  
37 turtles and other species is being complemented by new insights gained from the  
38 experimentally amendable retina of zebrafish. From this body of work, one thing is  
39 clear: The retinal basis of colour vision in non-mammalian vertebrates is substantially  
40 richer compared to mammals: Diverse and complex spectral tunings are established  
41 at the level of the cone output via horizontal cell feedforward circuits. From here,  
42 zebrafish use cone-selective wiring in bipolar cells to set-up color opponent synaptic  
43 layers in the inner retina, which in turn lead a large diversity of color-opponent  
44 channels for transmission to the brain. However, while we are starting to build an  
45 understanding of the richness of spectral properties in some of these species' retinal  
46 neurons, little is known about inner retinal connectivity and cell-type identify. To gain  
47 an understanding of their actual circuits, and thus to build a more generalised  
48 understanding of the vertebrate retinal basis of color vision, it will be paramount to  
49 expand ongoing efforts in deciphering the retinal circuits of non-mammalian models.

50

## 51 Introduction

52

53 '*...the belief that organic beings have been created beautiful for the delight of man,*  
54 *.... has been pronounced as subversive of my whole theory, ... C Darwin. Origin of*  
55 *Species. Ch. 6.'*

56

57 Study of the evolution and function of animal color vision originates from two  
58 nineteenth century insights into the imperfections of nature. In 1803 Thomas Young  
59 saw that measurement of the spatial location and the spectral composition of a light  
60 are fundamentally incompatible, and proposed trichromacy as the best compromise  
61 (Mollon 2003). Young also recognised that the spectrum extends to wavelengths  
62 beyond the range that humans can see. We do not know if Young directly influenced  
63 Darwin, but the idea that living organisms are imperfect was a mainspring of his  
64 theory of evolution (Darwin 1859), because natural selection could not change a  
65 perfect mechanism.

66 As an easily recognised character, 19<sup>th</sup> century evolutionary biologists took a keen  
67 interest in animal and plant coloration (Cronin 1991, Prum 2012). Why, for example,  
68 are some animals camouflaged when others have conspicuous coloration, and why  
69 do the sexes sometimes differ in their appearance? If coloration evolved by natural  
70 selection the same would apply to color vision. Wallace (Wallace 1879), noting the  
71 colors of foods eaten by different animals, observed that primates alone amongst  
72 mammals have 'tolerably perfect' color vision, and that this was 'probably inferior to  
73 that of birds'. We now know that most mammals have two spectral types of cone  
74 photoreceptor, many primates have three, and birds have four or five (Fig. 1).

75 The stimulating influence of Darwinism on research into animal color vision is  
76 exemplified by Darwin's friend and neighbour John Lubbock, a politician and  
77 gentleman naturalist, whose finding that ants moved their pupae away from UV light  
78 was the first demonstration that an animal could see beyond the human visible  
79 spectrum (Lubbock 1882). Later Lubbock found that water fleas (*Daphnia*) prefer  
80 yellow light to white independently of intensity, and argued that this behaviour can be  
81 regarded as color vision (Kelber & Osorio 2010, Lubbock 1889).

82 Color vision remains a powerful system for investigating how animal senses evolve  
83 under natural selection. Photoreceptor spectral tuning is known for many species,  
84 and there is a direct relationship between the genotype (the opsin DNA sequence)

85 and the photopigment spectral sensitivity. In addition, we can record the reflectance  
86 spectra of objects encountered by an animal in its daily life, and estimate receptor  
87 responses to them, thereby specifying the signals available to the brain. A wealth of  
88 studies on opsin evolution, and the ecological influences on photoreceptor spectral  
89 sensitivities (Bowmaker 2008, Osorio & Vorobyev 2008), is complemented by  
90 behavioral tests which show how photoreceptor signals are used for color and  
91 luminance vision (Kelber et al. 2003). In parallel, physiological studies of the retina  
92 have addressed questions about selective wiring, chromatic opponency and other  
93 aspects of color processing beyond the receptors, especially in mice and primates.  
94 In the future it will be important to extend retinal physiology across vertebrate  
95 phylogeny, especially to branches such as teleost fish and birds, which feature rich  
96 spectral receptor complements, and make much use of color vision (Fig. 1).

97

#### 98 *Behavioural study of animal color vision*

99 Until about 1980 psychophysical studies of human and animal color vision often had  
100 differing objectives, exemplified in key texts by Wyszecki and Stiles (1982) *Color*  
101 *Science*, and Jacobs' (1981) *Comparative Color Vision*. For humans the existence of  
102 color vision is not in doubt, and researchers were interested in mechanisms, starting  
103 with trichromacy and chromatic opponency, and extending to color constancy, color  
104 categorization and color appearance (Brainard & Stockman 2010, Gegenfurtner &  
105 Kiper 2003, Wyszecki & Stiles 1982). In animal research early work such a  
106 Lubbock's (Lubbock 1889) findings on *Daphnia* posed the question of whether a  
107 simple response to the spectral composition of a light can be described as color  
108 vision. We have no access to *Daphnia's* (or any other species') experience of color,  
109 so studies focussed on whether a given species had color vision (Jacobs 1981).  
110 Usually these entailed training an animal to associate a reward with a particular  
111 spectrum, and then testing it against a range of greys. According to this criterion a  
112 wide range of animals tested see color (Kelber et al. 2003). Studies have also  
113 measured color discrimination thresholds, either for the wavelength difference  
114 between two monochromatic lights ( $\delta\lambda$ ), or of monochromatic light added to an  
115 achromatic background (spectral sensitivity) (Kelber et al. 2003). More recently  
116 interest has moved to questions about color constancy (Chittka et al. 2014, Dörr &  
117 Neumeyer 2000, Olsson et al. 2016), color generalization (Baddeley et al. 2007,

118 Caves et al. 2018, Jones et al. 2001), and the ways in which specific sets of  
119 receptors serve particular behaviours (Orger & Baier 2005, Zimmermann et al.  
120 2018).

121

122 For non-human species it has however not been possible to use psychophysical  
123 methods to determine the spectral sensitivities of the color mechanisms (i.e.  
124 photoreceptors), which underpins work on human color vision (Wyszecki & Stiles  
125 1982). Research therefore benefits greatly from direct measurement of  
126 photoreceptor spectral sensitivities (Part 1), because spectral stimuli can then be  
127 defined in terms of receptor excitations. An important empirical finding is that color  
128 discrimination thresholds can often be predicted from receptor responses by  
129 assuming that they are set by noise arising from photoreceptors in (unspecified) in  
130 chromatic opponent channels, disregarding the achromatic/luminance signal (Olsson  
131 et al. 2018, Vorobyev & Osorio 1998). If this ‘receptor noise’ model describes  
132 experimental data this implies that the use of receptor signals is ideal, so it is not  
133 possible to make inferences about post receptor mechanisms from experimental  
134 data. Conversely, deviations from the predictions of the model can give insight into  
135 higher level mechanisms, such as color categorization and generalization (Baddeley  
136 et al. 2007).

137

## 138 **Part 1: Photoreceptors**

### 139 *Evolution of photoreceptor spectral sensitivities*

140 Ecological study of photoreceptor spectral sensitivities began in the 1930’s with the  
141 ‘sensitivity hypothesis’, which proposed that fish sensitivities match the ambient  
142 illumination (Clarke 1936, Collin et al. 2009, Loew & Lythgoe 1985, Luk et al. 2016).  
143 This subject is now grounded in evolutionary genetics, and has gone on to examine  
144 the relation of receptor sensitivities to reflectance spectra of objects relevant to a  
145 given species as well as to illumination (Davies et al. 2012, Lind et al. 2017, Nathans  
146 et al. 1986, Ödeen & Håstad 2003, Osorio & Vorobyev 2008). Here we give a brief  
147 background.

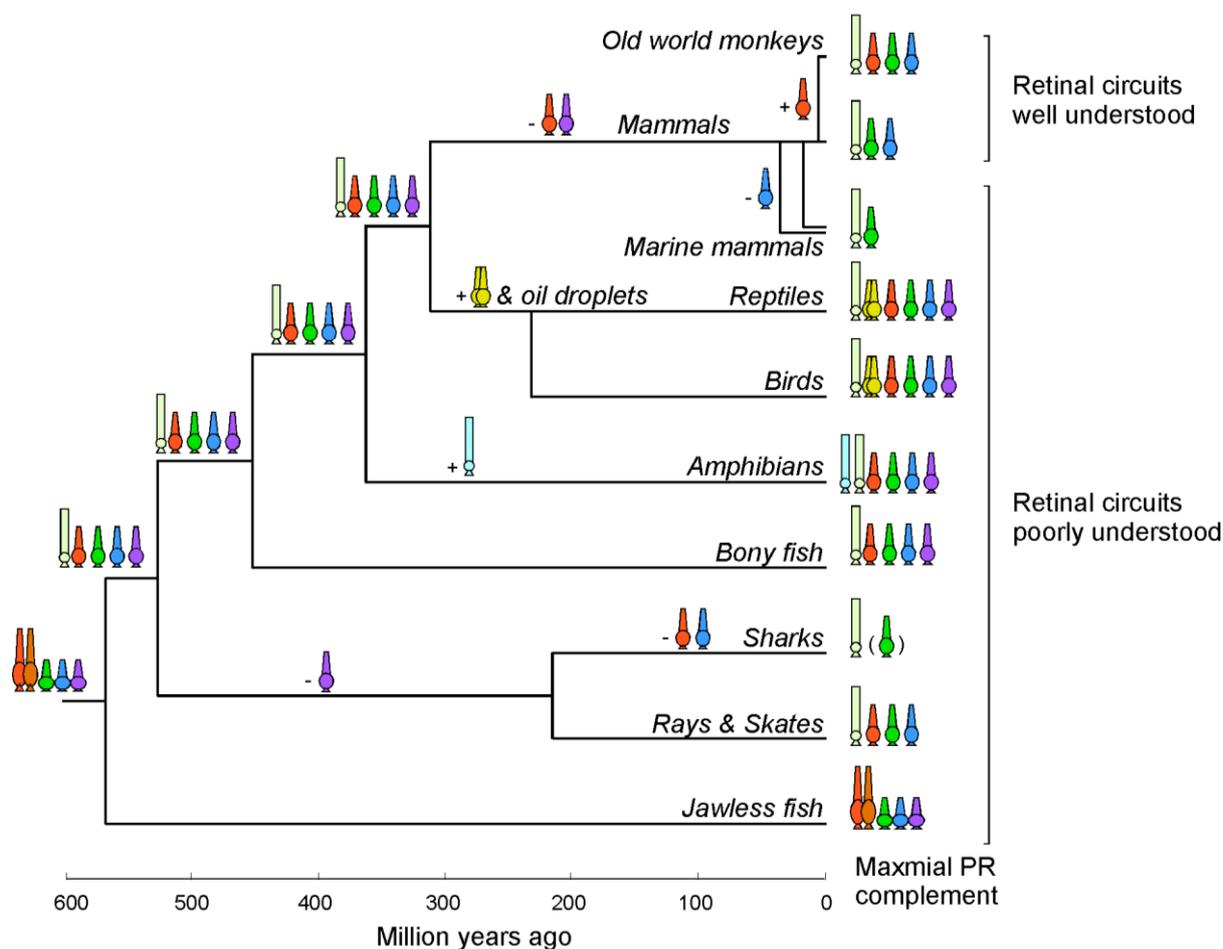
148 Visual pigments are G-protein coupled receptors, known as opsins, which bind a  
149 chromophore, namely retinal or a related carotenoid molecule (Arshavsky et al.

150 2002). Spectral tuning of the pigment is defined as the probability that a photon of a  
151 given wavelength incident on the molecule is absorbed by the chromophore to  
152 initiate the light response. This tuning is affected by the amino acid residues at key  
153 sites on the opsin protein (Patel et al. 2018, Porter et al. 2007, Wilkie et al. 2000,  
154 Yokoyama 2000). Opsin spectral tuning has only one degree of freedom, and is  
155 normally specified by the value to peak absorbance,  $\lambda_{max}$  (Govardovskii et al. 2000,  
156 Patel et al. 2018).

157 Photoreceptor spectral sensitivities should ideally be measured from intact eyes, and  
158 *in vivo* electrophysiological recordings are common in arthropods (Autrum & Zwehl  
159 1964), but the anatomy of the vertebrate eye makes such recordings difficult, so  
160 most studies measure visual pigment spectral absorbance by spectrophotometry of  
161 an isolated cone's outer segment (Bowmaker 1984), or infer it from the DNA  
162 sequence (see above).

163 Comparative studies of vertebrate opsin and photoreceptor spectral sensitivities find  
164 a striking combination of evolutionary conservatism and adaptive change (Lind et al.  
165 2017, Osorio & Vorobyev 2008). Some 500 million years ago the jawless fish which  
166 were ancestral to modern vertebrates evolved four classes of cone opsin, designated  
167 SWS1 ('UV/Violet'), SWS2 ('Blue'), MWS/RH2 ('Green') and LWS ('Red') (Bowmaker  
168 2008, Davies et al. 2012, Lamb 2013, Okano et al. 1994, Yokoyama 2000). Rod  
169 (RH1) opsins probably evolved from the RH2 opsins after the lineages of  
170 contemporary jawed vertebrates (gnathostomes) and lampreys (agnathans)  
171 diverged, so early gnathostomes saw the world through four sets of cone  
172 photoreceptors, and one rod. Contemporary vertebrates retain different subsets of  
173 the four cone pigment families, as well as rods (Fig. 1). For example, whereas most  
174 mammals have only LWS and SWS1, many teleost fish, amphibians, reptiles and  
175 birds have the full ancient complement. Animals that live in dim conditions or in open  
176 water, including various fish, penguins, burrowing snakes and nocturnal mammals,  
177 typically have fewer spectral photoreceptor types (Bowmaker 2008, Davies et al.  
178 2012). Groups that have reduced their cone-complement to but a single class, or  
179 even none, include marine mammals, like whales and seals, as well as many sharks  
180 (Griebel 2002, Griebel & Peichl 2003, Meredith et al. 2013, Theiss et al. 2012), and  
181 also smaller terrestrial species like beavers or racoons (Peichl 2005). In teleosts and  
182 primates the number of opsin genes is increased by gene duplication (Chinen et al.

2003, Nathans et al. 1986). Having multiple opsin genes fish vary pigment expression ontogenetically, sometimes under control of the ambient illumination (Shand et al. 2008, Spady et al. 2006). Normally there are no more than four spectral types of cone in a given retina, each expressing a cone typical opsin gene: L cones (“red”, R, LWS opsin), M cones (“green”, G, MWS/RH2 opsin), S cones (“blue”, B, SWS2 opsin) and UV cones (“ultraviolet”, UV, SWS1 opsin). A notable exception is bird/reptile double cones, which express LWS opsin. Finally, vertebrate rods (RH1 opsin) can also contribute to color vision (Part 2), and a second type of rod found in some amphibians (Korenyak & Govardovskii 2013, Yovanovich et al. 2017).



192

193 **Figure 1 – Photoreceptor lineages.** The ancient photoreceptor complement present in jawless  
 194 ancestral vertebrates (leftmost) gave rise to the photoreceptor complements present in jawed  
 195 vertebrates today (right). Along the way, different lineages added or lost types of  
 196 photoreceptors at different timepoints. Rods (beige), L-cones (red), M-cones (green), S-cones  
 197 (blue), UV-cones (purple), “blue” rods (light blue), “double-cones” (yellow). Photoreceptor (PR)  
 198 complements shown depict the typical maximal diversity in a lineage – often individual groups  
 199 use fewer.

200

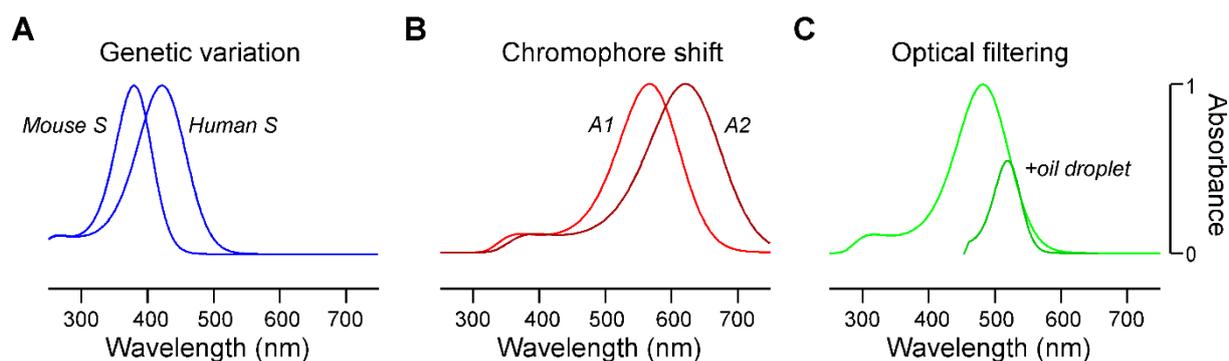
## 201 Spectrally tuning a receptor

202 While vertebrates inherited the four main opsin families from jawless fish (Collin et al.  
203 2009), they now use varied mechanisms to tune their photoreceptors to suit their  
204 lifestyle and habitat. These include (i) genetic changes to the opsin sequence itself,  
205 (ii) changing the chromophore, (iii) co-expression of multiple opsins in individual  
206 photoreceptors, and (iv) the addition of spectral filters.

207 In each of the main opsin families amino-acid residues at a few key sites around the  
208 binding pocket can vary the pigment's peak sensitivity ( $\lambda_{\max}$ ) by up to 80 nm (Fig.  
209 2a), and vertebrate visual pigments cover the visible spectrum with  $\lambda_{\max}$  as follows:  
210 LWS: 490–565 nm, RH2: 480–535 nm, SWS2: 410–490 nm and SWS1: 355–  
211 440 nm (Bowmaker 2008, Yokoyama 2000). Some freshwater fish and amphibians  
212 extend the LWS peak to around 620 nm by replacing the retinal (A1) chromophore  
213 with 3-4 dehydroretinal (A2) (Fig. 2b) (Bowmaker 2008, Enright et al. 2015, Loew &  
214 Dartnall 1976). Using this chromophore shift to control spectral sensitivity allows  
215 individuals to control spectral tuning, for example to follow seasonal or migratory  
216 variation in the light environment. Alternatively, some species co-express more than  
217 one opsin in individual photoreceptors to adjust their spectral tuning (Dalton et al.  
218 2014).

219 Next, although photoreceptor spectral sensitivities depend primarily on their opsin  
220 and chromophore, they are modified by spectral absorption in the ocular media. For  
221 example, some fish corneas transmit UV while others absorb short wavelengths  
222 (Siebeck & Marshall 2001). Spectral filtering is however most significant in those  
223 groups whose cone inner segments contain colored oil droplets, namely a lungfish,  
224 birds and certain reptiles, including freshwater turtles and lizards (Appudurai et al.  
225 2016, Hart 2001, Loew et al. 2002) (Fig. 2c).

226



227

228 **Figure 2 – Opsin Tuning. A, Opsins of the same lineage can exhibit different spectral peaks**  
229 **due to differences in the opsin gene sequence – here illustrated for SWS-opsins of mice and**  
230 **men. B, Depending on the chromophore used, the same opsin can exhibit different spectral**  
231 **tunings – here illustrated for a zebrafish LWS opsin using either 11-cis-retinal (A1) or 11-cis-**  
232 **3,4-didehydroretinal (A2). C, Addition of filtering media such as oil droplets can further be**  
233 **used to shape a photoreceptor’s spectral absorbance, here illustrated in for an avian M-cone.**

234

### 235 *Receptor specialisation and retinal mosaics*

236 The array of photoreceptors in the vertebrate retina has to sample both spatial and  
237 spectral signals, and so should reflect the compromises between these roles that suit  
238 animals’ particular needs, as well as developmental constraints (Rister & Desplan  
239 2011). The following examples from primates, fish, birds and reptiles illustrate some  
240 of the organisational principles in photoreceptor function and mosaics in these major  
241 vertebrate groups. Part 2 looks further at the particular cases of mouse and larval  
242 zebrafish in relation to their retinal circuitry.

243

#### 244 1. Old world monkeys

245 Old-world monkeys are trichromats with opsin spectral sensitivity maxima at about  
246 440 nm (in S/blue cones), 554 nm (in M/green cones) and 565 nm (in L/red cones).  
247 As elaborated below (Part 2) this cone-complement produces to two classical  
248 spectral channels: the “ancient” blue-yellow axis and a primate-specific red-green  
249 axis. A further distinction is made between chromatic and luminance mechanisms  
250 (Lee et al. 1990, Livingstone & Hubel 1988, Mullen & Losada 1994). Primates are  
251 unusual because the red-green system evolved from the dichromatic ancestral  
252 mammalian LWS system by the acquisition of separate L and M cones, without  
253 commensurate change in retinal anatomy (Mollon 1989). Wiring of L and M cone  
254 outputs is largely non-selective (See Section 2) (Field et al. 2010), and they are  
255 integrated to produce a luminance signal which serves many aspects of vision,  
256 notably by the parasol ganglion cells, which project to the magno-cellular layers of  
257 the lateral geniculate nucleus (LGN). Here, spectral sensitivity differences of the  
258 inputs are of no benefit and may corrupt the luminance signal (Gegenfurtner & Kiper  
259 2003, Lee et al. 1990, Osorio et al. 1998). In parallel, chromatic information is  
260 transmitted via ‘blue-yellow’ opponent ganglion cells (Dacey 2000, Dacey & Lee

261 1994), and 'red or green' midget ganglion cells which project to the parvocellular  
262 layers of the LGN (Derrington et al. 1984, Gegenfurtner & Kiper 2003, Lee et al.  
263 2017) (Fig. 3a,b). The midget system, probably evolved as a primate specialisation  
264 for spatial acuity, transmits single L and M cone outputs to the brain, where they are  
265 integrated by activity dependent plasticity (Doi et al. 2003, Mollon 1989, Wachtler et  
266 al. 2007), without specific retinal circuits to separate luminance and red-green  
267 chromatic signals. The mosaic of L and M cones is random (Roorda & Williams  
268 1999), but in macaque the S cone array is semiregular (Martin & Grunert 1999).  
269 Darwin might have been pleased that anatomically our red-green system seems  
270 poorly designed. So far as we know such an arrangement is not present in any other  
271 vertebrate visual system, where it is usual to find orderly receptor mosaics driving  
272 specialised retinal circuits.

273

## 274 2. Goldfish, zebrafish and triggerfish

275 Goldfish and zebrafish belong to the carp family (*Cyprinidae*). Adults have four  
276 spectral types of cones arranged in a regular mosaic (Engström 1963) with  
277 alternating rows of double cones with Red (LWS) and Green (MWS) members, and  
278 Blue (SWS2) and UV (SWS1) single cones, giving twice as many Red and Green  
279 cones as Blue and UV (Allison et al., Raymond et al. 1993). In goldfish,  
280 spectrophotometry of cone outer segments gives respective sensitivity maxima  
281 of 623 nm, 537 nm, 447 nm and 356 nm (Palacios et al. 1998). Zebrafish have  
282 shorter wavelength peaks at about 565 nm, 477 nm, 415 nm and 360 nm (Meier et  
283 al. 2018), but gene duplication allows these fish – like many others – to express  
284 different variants in a given cone (Bowmaker 2008, Chinen et al. 2003, Parry et al.  
285 2005).

286 The presence of four types of cone pigment does not automatically entail  
287 tetrachromatic color vision – which requires that four primaries are needed to match  
288 any spectrum, but (Neumeyer 1992) showed that a mixture of four monochromatic  
289 lights was needed for goldfish to match a white (spectrally flat) light. She also found  
290 evidence for three separate chromatic opponent mechanisms by training to single  
291 monochromatic lights and testing the intensity ratio of pairs of monochromatic light  
292 needed for the fish to make a match. Further, tests under low photopic adapting  
293 illumination for discrimination of monochromatic lights ( $\delta\lambda$ ) wavelength also suggest

294 that goldfish are tetrachromats with sensitivity maxima at about 415 nm, 500 nm and  
295 605 nm (Neumeyer 1986). The long wavelength sensitivity maximum is lost at  
296 illumination intensities in the middle of the human mesopic range (Neumeyer &  
297 Arnold 1989), when the fish fail to discriminate between 555 nm and 663 nm,  
298 implying that signals of the two members of the double cone become functionally  
299 coupled. Similarly, zebrafish retain separate double-cone R and G signals in the  
300 inner retina (Zimmermann et al. 2018), but their optomotor (movement) response  
301 appears to sum R and G signals (Orger & Baier 2005). It is however not clear  
302 whether the red+green tuning of the optomotor response is indicative of a general  
303 luminance system akin to that in primates. In the fishes natural environment, the  
304 main source of optic flow information) is the long-wavelength biased ventral visual  
305 field, but the inner retina of larval zebrafish also has several systems with ‘fully’  
306 achromatic responses that involve all four spectral receptors, rather than ‘just’ red  
307 and green (Zimmermann et al. 2018). Notably, unlike adults, but like in many other  
308 vertebrates, larval zebrafish have different density distributions of photoreceptor  
309 types in different parts of their eye, presumably to capitalise on different wavelength  
310 composition in natural light and different behavioural demands across their large  
311 visual field (Zimmermann et al. 2018).

312 Not all fish are tetrachromats. For example, the triggerfish *Rhinecanthus aculeatus*  
313 has three types of photopigment in two types of cones: single cones with a peak  
314 sensitivity at 413 nm, and double cones which have two outer segments with  
315 sensitivity maxima at about 480 nm and 528 nm (Cheney et al. 2013, Pignatelli et al.  
316 2010). Color discrimination tests find that triggerfish are trichromats (Champ et al.  
317 2016), implying that as in the cyprinids this species retains separate double-cone R  
318 and G signals.

319

### 320 3. Birds and Reptiles

321 Birds and many reptiles have four types of single cone and one type of double cone,  
322 each of which is associated with a specific type of oil droplet that acts as a spectral  
323 filter by cutting off wavelengths below a certain value (Wilby & Roberts 2017). This  
324 filtering narrows spectral tuning of the receptor, at the cost of absolute sensitivity  
325 (Hart & Vorobyev 2005) (Fig. 2c). Each single-cone type contains a photopigment  
326 belonging to one of the four main vertebrate opsin families (Fig. 1) (Bowmaker et al.

1997, Hart & Hunt 2007, Toomey et al. 2015), with two main forms of the UV (SWS1) opsin giving peak sensitivities at about either 365 nm or 410 nm (Kram et al. 2010, Ödeen & Håstad 2003, Wilkie et al. 2000). Bird photoreceptor spectral sensitivities *in vivo* are normally estimated by modelling the sensitivity based on the opsin and oil droplet absorption functions (Hart & Vorobyev 2005, Toomey et al. 2016), which predicts  $\lambda_{\max}$  values of 365 nm or 410 nm (SWS1, UV or violet), 440 nm-475 nm (SWS2, blue), 545 nm (MWS, green) and 605 nm (LWS, red). The UV type SWS1 receptors are associated with shorter wavelength SWS2 receptors, whereas the MWS receptor peaks vary little between species. The double cones contain LWS pigments and oil droplets which gives them a spectral sensitivity much like that of human L (red) photoreceptors.

The cone mosaic in the chicken (and other birds) is orderly but less regular than that of fish. The mosaic is consistent with a model where each cone type forms a fairly regular hexagonal array that is independent of each of the other four types (Jiao et al. 2014, Kram et al. 2010). The densities of these arrays differ between cone types. In chicken, double cones represent about 40% of the total, and of the remainder densities fall in the order LWS>MWS>SWS>V/UVS, with the density of LWS cones being about two to four times that of the V/UVS (Hart 2001). There is however substantial variation between species, and across position in the visual field (Hart 2001).

Behavioural tests of color discrimination thresholds in pigeons, parrots and chickens suggest that, like goldfish, birds have tetrachromatic color vision based on the outputs of the four single cones (Goldsmith & Butler 2003, Olsson et al. 2015, Vorobyev & Osorio 1998). Tests with stimuli designed to reveal interactions between specific pairs of cones likewise imply that chickens have three spectral opponent mechanisms which compare UV vs. S, S vs. (L+M) and L vs. M cones, which is consistent with tetrachromacy (Osorio et al. 1999). Whereas fish double cones contribute to color vision, bird double cones may serve an achromatic system which is used for form and motion vision, resembling the primate luminance pathway (Jones & Osorio 2004). This conclusion is however open to question, for example the fovea of the Harris hawk (*Parabuteo unicinctus*) is free of double cones but has a high spatial acuity and poor color vision (Potier et al. 2018). Similarly, the high acuity lower facing frontal visual field in pigeons, where the birds peck for food, is

360 dominated by red cones and is probably predominantly luminance sensitive (Remy &  
361 Emmerton 1989, Vorobyev & Osorio 1998).

362 The retinal organisation and receptor spectral sensitivities of anole lizards are  
363 essentially identical to those of birds (Bowmaker et al. 2005, Loew et al. 2002),  
364 suggesting that this organisation evolved in the common ancestor of the two main  
365 lineages of living reptiles. Tests of wavelength discrimination by the freshwater turtle  
366 (*Pseudemys scripta*) suggests that, as in birds, four spectral receptor types  
367 contribute to color vision (Arnold & Neumeyer 1987, Zana et al. 2001).

368

### 369 *Principles of spectral coding*

370 Before turning to the physiology of these systems in the vertebrate retina it is useful  
371 to look briefly at underlying principles of spectral coding by photoreceptors, and then  
372 chromatic opponency in the retina

373 When Young suggested that ideally color vision should have an 'infinite' number of  
374 spectrally tuned receptors he was unaware of the nature of the spectral stimuli in the  
375 natural world. To operate efficiently any coding system should be matched to the  
376 characteristics of the signals that it encodes (Barlow 1961, Simoncelli & Olshausen  
377 2001). It follows that the specific set of receptors in a given eye should depend upon  
378 the characteristics of the spectra that the animal needs to discriminate. In practice  
379 the reflectance spectra of natural materials vary smoothly with wavelength, and this  
380 lack of 'spectral detail' means that three receptors capture a large proportion of the  
381 available spectral information (Maloney 1986, Vorobyev et al. 1997). In addition, the  
382 spectra of many biological pigments tends to vary more at long than at short  
383 wavelengths. Consequently, primate trichromacy may in fact be close to the ideal for  
384 discrimination fruit and leaves (Osorio & Vorobyev 1996), with the small spectral  
385 separation of the L and M receptors well suited to capturing this specific type of  
386 spectral information. Similarly, avian color vision with four (single) cone types  
387 narrowed by colored oil droplets is well suited to discriminating amongst the  
388 reflectance spectra of feathers, which can have more spectral variation than most  
389 objects (Osorio & Ham 2002, Vorobyev et al. 1998).

390 Given a set of receptors that are suitably tuned to measure variation in natural  
391 spectra, how should their signals then be encoded by the second-stage of color

392 vision? Having broadly tuned spectral receptors to sample smoothly varying spectral  
393 reflectance functions means that outputs of different spectral receptor are highly  
394 correlated (Barlow 1982, Maloney 1986, Srinivasan et al. 1982). A general principle  
395 of early stages of visual processing is to remove redundancy in neural signals  
396 caused by statistical correlations of this kind (Atick et al. 1992, Buchsbaum &  
397 Gottschalk 1983). Thus, lateral inhibition, which produces the centre-surround  
398 receptive fields of many retinal neurons can be understood as a means of removing  
399 spatial correlation (Srinivasan et al. 1982). In the spectral domain at a basic level,  
400 correlations in the signal received by distinct spectral cones are removed before any  
401 extraction of spectral information. In the retina, this is implemented by (“color”)-  
402 opponent wiring. Beyond the requirement for some type of chromatic opponency  
403 Buchsbaum and Gottschalk (Buchsbaum & Gottschalk 1983) pointed out that for a  
404 retina with  $n$  spectral photoreceptors decorrelation is - under broad assumptions -  
405 achieved by  $n$  mechanisms with spectral responses such that one has no zero-  
406 crossings (i.e. responses have the same sign to all wavelengths), the second has  
407 one zero crossing (i.e. responses to short wavelengths are of the opposite sign to  
408 those to long wavelengths) and the third has two zero-crossings (i.e. responses to  
409 medium wavelengths of the opposite sign to those to short and long wavelengths),  
410 and so forth. It follows that mechanisms which simply transmit the outputs of a single  
411 cone types independently, or multiple signals that have the same number of zero  
412 crossings (e.g. B+G vs. R, or G vs R) are likely to be partly redundant.

413

## 414 **Part 2: Retinal circuits for color vision.**

415 For photoreceptors we have strong basis for understanding the function and diversity  
416 of animal color vision. Behavioural studies show also that the ‘second stage’ of color  
417 processing, involving retinal circuits, is both necessary and sufficient to preserve the  
418 spectral information in the photoreceptors, and that there are distinct chromatic and  
419 achromatic/luminance mechanisms (e.g. (Vorobyev & Osorio 1998)), but reveal little  
420 about specific chromatic mechanisms. To understand how spectral information is  
421 used within the retina and beyond research is now combining single synapse-  
422 resolution anatomy with direct physiological study. Key questions are: (i) what is the  
423 number and nature of opponent mechanisms that compare the outputs of different  
424 spectral receptor types, (ii) how is chromatic- and luminance-information

425 represented, (iii) how do retinal mechanisms contribute to color constancy, and finally  
426 (iv) to what extent do different receptor types contribute to distinct retinal pathways.  
427 We will now look at the picture that is emerging from this work.

428

#### 429 *Color opponency in the outer retina*

430 In general, opponency refers to a neural computation that compares the activity in  
431 sets of neurons with different tuning to a given stimulus parameter – for example  
432 spatial location or wavelength of sound or of light. For color vision, since a single  
433 detector cannot differentiate a shift in wavelength from a change in intensity, retinal  
434 color or chromatic opponency requires a comparison between at least two spectral  
435 receptor types (Hurvich & Jameson 1957, Krauskopf et al. 1982).

436 In the vertebrate retina color-opponency typically begins through interactions  
437 between the photoreceptors themselves, where inhibitory connections are mediated  
438 by horizontal cells (Chapot et al. 2017b, Perlman et al. 2009). These large and highly  
439 interconnected outer retinal neurons communicate bidirectionally with photoreceptor  
440 synapses, which are known as pedicles. Typically, glutamate release from a  
441 photoreceptor's pedicle depolarises the horizontal cell, which by a variety of  
442 mechanisms then negatively feeds back onto the same pedicle (feedback) as well as  
443 to the pedicles of other cones (feedforward) (Thoreson et al. 2008, Twig et al. 2003).  
444 Thereby, cones connected via horizontal cells inhibit each other, and since horizontal  
445 cells can be electrically coupled, to form a dense functional network (Becker et al.  
446 1998, Cook & Becker 1995), these interactions may occur over wide spatial scales.  
447 This general mechanism establishes color-opponent response properties already at  
448 the visual system's first synapse. Since two receptors cannot occupy the same  
449 retinal location, any form of color-opponency inevitably has a spatial component. In  
450 fact, horizontal cells not only set-up opponency in wavelength and space (lateral  
451 inhibition), but also decorrelate neural signals in time. For this, horizontal cell  
452 interactions with photoreceptors use a wide range of synaptic and other mechanisms  
453 to act over different spatial, temporal and chromatic scales (Chapot et al. 2017a,  
454 Jackman et al. 2011, Kamermans et al. 2001, Kemmler et al. 2014, Verweij et al.  
455 1996) including a wealth of feedback mechanisms that remain confined to the level  
456 of a single pedicle. While it remains largely unclear how local and global horizontal  
457 cell interactions exist in parallel (or how switching functions might work), any purely

458 local interactions by definition cannot transmit signals to neighbouring cones,  
459 meaning that color opponency can only be built using global-scale interactions. This  
460 global spectral response of a horizontal cell (HC) type, which is readily measured  
461 from its soma (Connaughton & Nelson 2010, Kamermans et al. 1991), depends on  
462 the specific cone connections made (Dacheux & Raviola 1982, Goodchild et al.  
463 1996, Li et al. 2009) as well as the type and gain of each connection (Baden et al.  
464 2013, Breuninger et al. 2011, Chapot et al. 2017a).

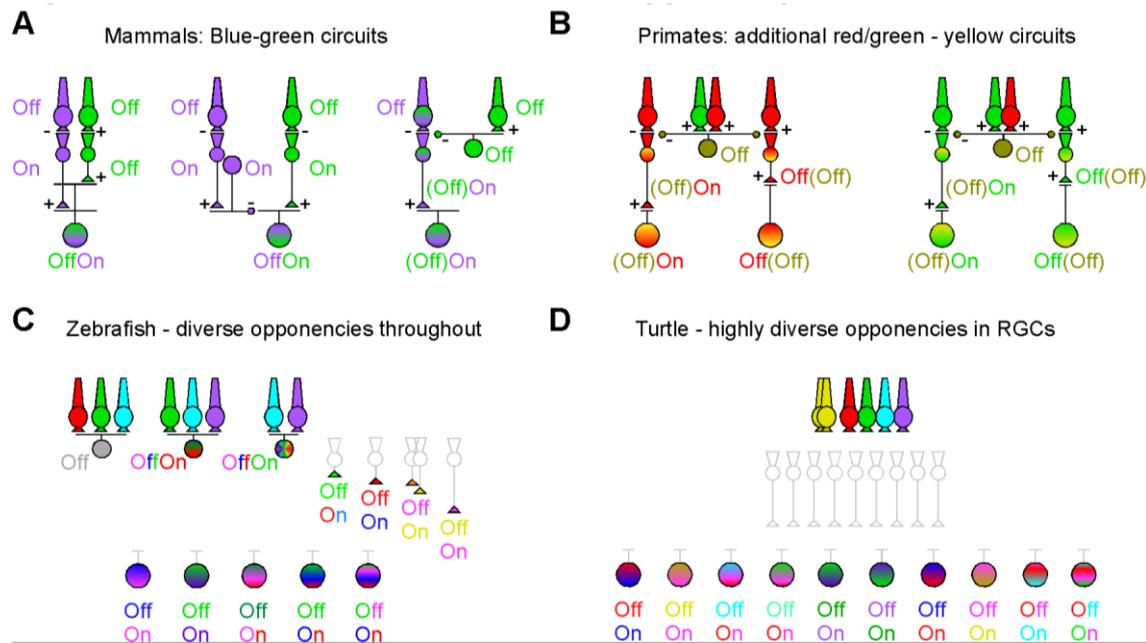
465 Many species, especially those with more than two spectral cone types, feature  
466 multiple types of HCs with distinct, cone-selective connectivity patterns and  
467 correspondingly complex chromatic properties (Connaughton & Nelson 2010,  
468 Kamermans et al. 1991, Packer et al. 2010). As a result, different cone types receive  
469 different spectral-contrast surround inhibition. For example, zebrafish have at least  
470 three cone-selective and one rod-selective HCs with spectrally mono-, bi- and  
471 triphasic response properties (Meier et al. 2018) (Fig. 3c). More simply, primates use  
472 a specific HC type to set up a yellow (R + G dominated) surround in blue cones  
473 (Crook et al. 2011, Neitz & Neitz 2011, Packer et al. 2010), and rabbit use a similar  
474 circuit (Mills et al. 2014) (Fig. 3a). However, how the multitude of horizontal cell  
475 connectivity patterns and feedback functions operate to serve - or even interfere with  
476 - chromatic processing in the outer retina remains poorly understood in most  
477 vertebrate groups.

478

#### 479 *Inner retina and brain projections.*

480 Beyond spectral opponency at the level of photoreceptors, vertebrates dedicate  
481 substantial neural resources to chromatic coding in inner retinal networks (Baden et  
482 al. 2018, Dacey 1999, Euler et al. 2014, Jacobs 2008, Neitz & Neitz 2011). The  
483 complexity of such pathways varies depending on the animal's photoreceptor  
484 complement, but many follow common wiring principles that directly emerge from the  
485 necessity of differentially combining two or more spectral input pathways. For  
486 example, one key circuit motif takes two different "spectrally-pure" bipolar cell  
487 pathways and differentially pools their signals in a postsynaptic ganglion cell, such  
488 that one bipolar cell pathway excites the ganglion cell, while the other inhibits it (Fig.  
489 3a) (Dacey & Lee 1994, Mills et al. 2014). The result is a color opponent ganglion  
490 cell whose spectral tuning is driven by the tuning of the specific bipolar cell pathways

491 that it combines. A well-studied example of such a circuit forms part of the ancient  
492 mammalian “blue-green system” (i.e. S vs L/M cone) which is conserved across  
493 mice, guinea pigs (Yin et al. 2009), ground squirrels (Sher & DeVries 2012) and  
494 rabbits (Mills et al. 2014) all the way to primates (Dacey & Lee 1994). For some  
495 species, including mice, ground squirrel, rabbits, guinea pigs and various primates,  
496 key anatomical connections are known. For example, mice have only one type of  
497 chromatically pure ‘blue<sup>ON</sup>’ bipolar cell dubbed Type 9 (Behrens et al. 2016,  
498 Breuninger et al. 2011), which makes specific dendritic contacts only with blue  
499 cones, thereby ensuring a blue-centre response. Mouse type 9 bipolar cells, like all  
500 mammalian On-bipolar cells, express metabotropic glutamate receptor mGluR6 on  
501 their dendrites, which results in a sign-inversion of the blue<sup>OFF</sup> cone signal into a  
502 blue<sup>ON</sup> signal at the level of the bipolar cell (reviewed in (Euler et al. 2014)).  
503 Accordingly, type 9 bipolar cells provide a blue<sup>ON</sup> center response to their direct  
504 postsynaptic partners. Green<sup>OFF</sup> antagonism to this blue mechanism is provided by  
505 another type of bipolar cell, perhaps the green-cone-biased Type 1 Off bipolar cell  
506 (Behrens et al. 2016). While the specific putative retinal ganglion- and/or amacrine  
507 cells completing such a circuit remain elusive in mouse, such cells are known in  
508 rabbits, guinea pigs and primates (Dacey & Lee 1994, Mills et al. 2014, Sher &  
509 DeVries 2012, Yin et al. 2009). For example, in primates, the small bistratified RGC  
510 selectively collects blue<sup>ON</sup> and red/green<sup>OFF</sup> inputs from different bipolar cells across  
511 its two respective dendritic arbours in the inner plexiform layer of the retina (Calkins  
512 et al. 1998, Crook et al. 2009, Dacey & Lee 1994, Zrenner & Gouras 1981). Notably,  
513 some mammals such as the cone-dominated ground squirrel use at least two green-  
514 cone selective BCs - an On and an Off variant (Li & DeVries 2006) - to give  
515 additional options for building color opponent ganglion cells (Fig. 3a).



516

517

518 **Figure 3 – Circuit Motifs for Retinal Color Opponency.** A, blue-green (S-M) opponent circuits in  
 519 mammals. Blue- and green-cone selective On- and Off-bipolar cells, respectively, can be  
 520 differentially combined via a bistratified retinal ganglion cell (left). Similarly, sign inversion can  
 521 occur via an S-On amacrine cell leading onto a monostratified retinal ganglion cell (centre).  
 522 Moreover, sign inversion can occur in the outer retina via a green-dominated horizontal cell  
 523 feeding into a blue-selective bipolar cell pathway (right). Reviewed in (Neitz & Neitz 2011). B,  
 524 Primates can build red-yellow (left) or green-yellow (right) opponent midget circuits by pooling  
 525 a red-green non-selective surround into individual red- or green cones by way of a horizontal  
 526 cell. Reviewed in (Dacey 1996, Neitz & Neitz 2011). C, Zebrafish use at least three types of  
 527 cone-selective horizontal cells to differentially pool across their tetrachromatic cone-  
 528 complement. From here, retinal bipolar cells build diverse color-opponent responses at the  
 529 level of their presynaptic terminals in the inner retina, and retinal ganglion cells show diverse  
 530 and often complex chromatic opponencies. However, beyond photoreceptor connectivity  
 531 patterns (see below) the specific functional and anatomical circuit principles that generate  
 532 many of these responses are largely unknown. Reviewed in (Meier et al. 2018). D, Turtles are  
 533 reported to combine their five cone-types into highly diverse retinal output channels that carry  
 534 at least 12 color opponent signals to the brain (Rocha et al. 2008), but knowledge on the  
 535 chromatic basis of turtle inner retinal circuits remains sparse.

536

### 537 *Case studies of retinal circuits*

538 The precise anatomical and functional wiring motifs for retinal color opponent circuits  
 539 remain little known in all but a few species, notably primates, mice and zebrafish,  
 540 each of which has specific retinal specialisations, and at times ‘unusual solutions’

541 that need to be considered when aiming to synthesise known details of their circuits  
542 into a bigger picture. Here, we offer a brief introduction to some of these  
543 peculiarities.

544

#### 545 *Color processing in the peculiar retina of mice*

546 Like all sensory systems, the mouse retina is exquisitely adapted to the mouse's  
547 sensory-ecological niche. As a crepuscular species that spends much time  
548 underground, mice are often active in the dim light, and rods make up >90% of all  
549 mouse photoreceptors - a proportion similar to that in primates including humans.  
550 Nonetheless, mice have a well-developed dichromatic cone system based on a UV  
551 cone ( $\lambda_{\max}$  360 nm) and an M cone ( $\lambda_{\max}$  508 nm) (Nikonov et al. 2006). As in  
552 primates, long-wavelength (M) cones outnumber short-wavelength (blue/UV) ones  
553 by over 10:1 (Wässle et al. 2009). In view of the greater abundance of green photons  
554 compared to blue/UV in natural light (Párraga et al. 1998), this makes sense, and  
555 much mouse vision uses a predominant green-driven luminance signal. The  
556 preponderance of green cones means that for color vision it is very important to build  
557 cone-selective circuits for the sparse blue system, but less important for the green  
558 system. Assuming equal gain of green and blue cone inputs (but see (Baden et al.  
559 2013, Breuninger et al. 2011)) any randomly connecting bipolar- or horizontal cell will  
560 be green biased, simply because there are more green cones. This situation is  
561 complicated by a distinctive feature of the mouse retina: the dorso-ventral blue-green  
562 S-opsin co-expression gradient in "genetic M-cones" (Applebury et al. 2000, Baden  
563 et al. 2013, Roehlich et al. 1994, Szél et al. 1992). The ventral mouse retina, which  
564 views the sky, is dominated by M-cones that co-express both M- and S-opsins.  
565 Indeed, direct spectral sensitivity recordings from ventral co-expressing presumed  
566 M-cones reveal a short wavelength bias (Baden et al. 2013, Chapot et al. 2017a),  
567 implying that that the S-opsin co-expression is dominant, converting M-cones into  
568 'functional S-cones'. Importantly, this co-expression ceases approximately at the  
569 visual horizon, leaving the dorsal retina - looking at the ground - with 'pure' green  
570 cones, expressing the LWS opsin interspersed with 'pure' blue cones.

571 The opsin co-expression gradient has several functional consequences for mouse  
572 color vision. Perhaps most importantly, the standard blue-green opponent system  
573 cannot work in the ventral retina as it does in the dorsal retina. At the very least, the

574 green signal is contaminated by enhanced blue sensitivity, and more likely the green  
575 component will be almost abolished. Given only traditional cone circuits, the ventral  
576 mouse retina would be color blind, but behavioural evidence is to the contrary  
577 (Denman et al. 2018). In fact, the mouse retina seems to use “green” rods to build  
578 opponency against the S-biased ventral M-cones (see below).

579 Next, an interesting type of spectral opponency arises at the boundary between the  
580 blue-dominated ventral retina and the green-dominated dorsal retina. Here large-field  
581 retinal ganglion cells that span both zones almost invariably receive a chromatically  
582 mixed input signal, which leads to centre-surround chromatic antagonism in ganglion  
583 cells near the visual horizon, without the need for any wiring specificity (Chang et al.  
584 2013).

585 Overall, mice probably use a subset of the mammalian inner retinal pathways for  
586 color vision in their dorsal retina of those which have been characterized in other  
587 rodents, lagomorphs and primates. The presence of the opsin gradient markedly  
588 complicates things at the horizon and beyond but opens opportunities for exploiting  
589 chromatic contrasts by non-traditional circuit motifs. How these peculiarities translate  
590 to the brain and behaviour remains largely unclear (but see (Denman et al. 2018,  
591 Tan et al. 2015)). Notably, opsin co-expression gradients occur widely in terrestrial  
592 animals (e.g. (Sison-Mangus 2006)), and amongst mammals occur in species as  
593 diverse as hamsters and hyenas (Peichl 2005). A common feature of these  
594 seemingly disparate species is their need to survey the open sky for birds – be it for  
595 predator detection for the hamster or allowing the hyena to predict the location of  
596 prey or carrion by spotting vultures. In mice, in addition to shifting the spectral  
597 sensitivity of genetic M-cones ventral retina, S-opsin co-expression boosts the  
598 detection of achromatic dark contrasts (such as the silhouette of a bird in the sky)  
599 (Baden et al. 2013). Similar mechanisms may also be beneficial to hyenas and  
600 hamsters.

601

602 *Color processing in the peculiar retina of trichromatic primates.*

603 Next to mice, most knowledge about the retinal basis for vertebrate color vision is  
604 from trichromatic primates including humans (Dacey 1996, Neitz & Neitz 2011). Like  
605 many reptiles and birds and some fish, primates use a specialised acute zone or  
606 fovea for high spatial-acuity vision. As with the opsin co-expression gradient in mice,

607 the primate fovea engenders a range of behavioural and circuit peculiarities. First,  
608 since the fovea is only a degree or so across but allows much higher spatial acuity  
609 than the rest of the retina, foveated species use specialised eye-movement  
610 strategies which result in neuronal and attentional oversampling of the visual world at  
611 the fovea (Duncan & Boynton 2003), but, S-cones are absent from the *area centralis*  
612 (Roorda & Williams 1999). Consequently, any blue contribution to' chromatic  
613 contrasts at the fixation point relies on interpolation, which gives rise to a wealth of  
614 popular perceptual illusions. Outside the fovea, primates, like most mammals, have a  
615 low blue-cone density alongside a much higher green/red density (Martin & Grunert  
616 1999) to compute long-versus-short chromatic contrasts along a blue-yellow axis.  
617 The cone-connectivity patterns of primate bipolar cells are broadly similar to those of  
618 mice, including the presence of an S-cone selective On-bipolar cell (Boycott &  
619 Wässle 1991, Dacey 1996), but unlike in mice, blue-yellow chromatic circuits are  
620 well-characterised for retinal ganglion cells (Calkins et al. 1998, Chichilnisky & Baylor  
621 1999, Dacey 1996, 2000; Neitz & Neitz 2011). This exquisite account from primates,  
622 which is complemented by findings in a range of lagomorphs and rodents (see  
623 above) dominates the literature about short-versus-long wavelength retinal circuits in  
624 vertebrates. While this work provides a solid foundation for blue-green/yellow circuit-  
625 motifs in mammals, it is less clear to what extent this translates to non-mammalian  
626 groups.

627 Second, perhaps the most peculiar aspect of trichromatic primate color vision is their  
628 green (M) cone. Primate M cone opsin derives from an evolutionarily recent LWS-  
629 opsin gene-duplication (Mollon 1989, Nathans 1999), which leads to a fundamental  
630 wiring problem. Retinal circuits cannot easily distinguish primate L from M cones (but  
631 see (Field et al. 2010)), and thus lack developmentally programmed red- or green-  
632 only bipolar cell channels. Instead, chromatic selectivity depends on the presence or  
633 'midget' bipolar- and ganglion cells (Kolb & Marshak 2003), which receive their  
634 centre input from a single cone. The surround in turn is spectrally non-selective  
635 between red and green. This single-cone-centre wiring motif produces four types of  
636 opponent midget signals, red<sup>ON</sup>-yellow<sup>OFF</sup>, green<sup>ON</sup>-yellow<sup>OFF</sup>, yellow<sup>ON</sup>-red<sup>OFF</sup> and  
637 yellow<sup>ON</sup>-green<sup>OFF</sup> (Fig. 3b), and cone-'clumping' (Hofer et al. 2005) means that this  
638 same motif can extend beyond the foveal centre (Martin et al. 2001). However, this  
639 strategy defers the disambiguation of red and green signals to the cortex, which

640 could generate chromatic selective neurons by activity dependent plasticity  
641 mechanisms (Doi et al. 2003, Wachtler et al. 2007). As such, unlike other cone-  
642 opponent mechanisms, key circuits underlying our ability to distinguish “red” from  
643 “green” lie beyond the retina. Interestingly, introducing an additional red-opsin into  
644 some mouse green cones leads to apparent trichromatic vision at the behavioural  
645 level (Jacobs et al. 2007, Smallwood et al. 2003) (but see (Makous 2007)).

646

### 647 *Color processing in non-mammalian vertebrates*

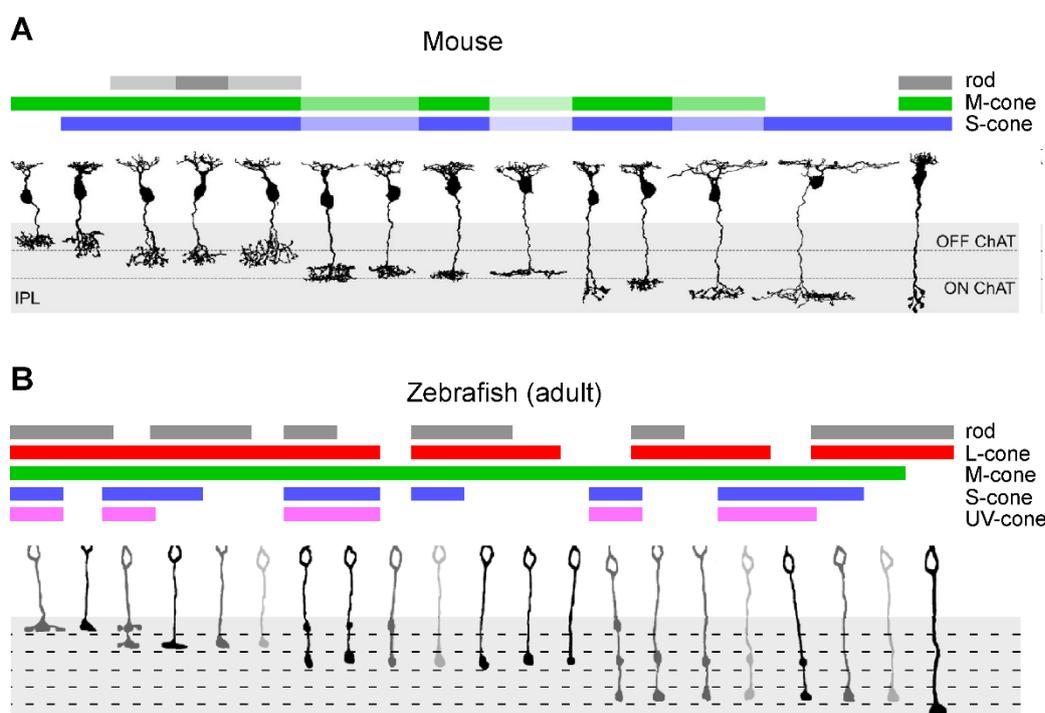
648 As we have seen, vertebrates opsins belong to for main families which evolved  
649 some 500 million years ago in jawless fish (Collin et al. 2009). Retinal circuitry  
650 probably has a similarly conservative *bauplan*, perhaps including chromatic  
651 opponent pathways, such as the mammalian blue<sup>ON</sup> system. However so far  
652 knowledge of this aspect of retinal processing is mainly limited to work in teleost fish  
653 - notably the cyprinids zebrafish and goldfish, and rainbow trout, e.g. (Meier et al.  
654 2018), [Fig. 3c](#) -, reptiles (mostly turtles, [Fig. 3d](#): (Arnold & Neumeyer 1987, Rocha et  
655 al. 2008, Ventura et al. 2001, Zana et al. 2001)) and amphibians (Werblin & Dowling  
656 1969). The vast majority of this work has probed retinal function by single-cell  
657 electrophysiological techniques, which provide detail on single neurons, but have not  
658 delivered a comprehensive overview of retinal channels for color vision of any one  
659 retina. As such although there are some key studies of the retinal basis of vertebrate  
660 color vision (D’Orazi et al. 2016, Li et al. 2009), a coherent picture is yet to emerge.

661 Nevertheless, it is clear that species with diverse cone types such as the turtle with  
662 five cone types and the goldfish with four have a retinal complement of chromatic  
663 neurons far exceeding that of mammals - or indeed theoretical prediction (see  
664 above). For example, at least 12 color opponent retinal ganglion cells have been  
665 described in the turtle (*Trachemys scripta*) (Rocha et al. 2008, Ventura et al. 2001)  
666 ([Fig. 3d](#)), while teleosts including goldfish, zebrafish, carp and trout display complex  
667 chromatic responses even at the level of horizontal cells (Connaughton & Nelson  
668 2010, Kamermans et al. 1991, Meier et al. 2018, Twig & Perlman 2004, Twig et al.  
669 2003). Nonetheless, more coherent picture of the retinal basis for color vision is  
670 emerging in at least one tetrachromatic vertebrate: the zebrafish ([Fig. 3c](#)).

671

672 *Color processing in the peculiar retina of zebrafish*

673 Like many shallow-water teleosts, zebrafish use four ancient cone types for color  
 674 vision: red, green, blue and UV, which in adults form a crystalline mosaic with a  
 675 stoichiometry of 2:2:1:1, respectively (Allison et al., Engström 1960). Each cone type  
 676 is genetically distinct, allowing developmentally hardwired retinal circuits (D’Orazi et  
 677 al. 2016, Li et al. 2009) in any of 24 theoretically possible chromatic combinations (or  
 678 81 if differentiating On and Off connections). Yet, partly in line with arguments on  
 679 chromatic redundancy (above), most combinations appear to not be absent. Instead,  
 680 cone-selective wiring appears to be mainly restricted to spectral ‘blocks’ rather than  
 681 ‘jumps’ (Fig. 4). For example, horizontal cell types make selective connections to  
 682 chromatically neighbouring cones (‘blocks’): R+G+B, G+B+U and B+U (Klaassen et  
 683 al. 2016, Song et al. 2008). In contrast wiring “jumps” (e.g. to R+B but skipping G)  
 684 are absent. Bipolar cells follow the same principle (Fig. 4b). For comparison, the two  
 685 cone types of mice and failure to distinguish G and R cones in primates means that  
 686 also these setups by definition must use blocks (‘jumping’ requires at least 3 cones)  
 687 (Fig. 4a). This ‘block-wiring principle’ of retinal chromatic circuits is untested in any  
 688 other group, but it is worth noting that on a functional level, bipolar and retinal  
 689 ganglion cells of non-mammalian species tend to favour long-vs-short wavelength  
 690 computations, consistent with chromatic block-wiring in the outer retina (Rocha et al.  
 691 2008, Zimmermann et al. 2018).



692

693 **Figure 4 – Wiring photoreceptors to bipolar cells. A, The 14 types of bipolar cells of the mouse**  
694 **retina mostly make cone-type non-selective contacts in the outer retina. Only types 1 (left-**  
695 **most) and 9 (2<sup>nd</sup> from right) bipolar cells make selective contacts with M- and S-cones,**  
696 **respectively. Rods are contacted by a subset of Off-bipolar cells and rod bipolar cells.**  
697 **Modified from (Behrens et al. 2016). B, Adult zebrafish have 20+ bipolar cells that make diverse**  
698 **sets of contacts across its four cone- and one rod type in the outer retina. Based on (Li et al.**  
699 **2009).**

700

701 Simply knowing the anatomical wiring is however insufficient for defining chromatic  
702 circuits: After all, opponency requires the combination of differentially tuned  
703 pathways with opposite signs, which are difficult to identify from anatomy alone.  
704 Here, some understanding of the chromatic physiology of the zebrafish retina is  
705 beginning to emerge. Single unit electrophysiological recordings from throughout the  
706 zebrafish retina from horizontal cells to ganglion cells, all reveal a rich complement of  
707 chromatic opponencies (Connaughton & Nelson 2010, 2015; Klaassen et al. 2016,  
708 Torvund et al. 2017).

709

#### 710 *Regional specialisations in juvenile zebrafish retina*

711 Even if retinal circuits for color vision of the adult zebrafish are reasonably typical of  
712 teleosts of similar habitat and lifestyle, whether the same circuitry is present in the  
713 larva remains unknown. Building on the wealth of single-cell physiology from both  
714 adults and larvae, a recent survey used 2-photon calcium imaging to record the  
715 chromatic response properties of some 4,000 larval zebrafish bipolar cells  
716 (Zimmermann et al. 2018). Eight-day post fertilization zebrafish larvae have about  
717 10,000 cones in each retina, and single-synapse resolution functional measurements  
718 can be made *in vivo*, in any part of the eye. The survey revealed that chromatic  
719 processing in the inner retina of larval zebrafish is not only very rich indeed, but  
720 perhaps more intriguingly, differs dramatically across the visual field. For example, at  
721 the visual horizon bipolar cells encode several varieties of mostly short-vs-long  
722 wavelength chromatic opponency while the temporo-ventral retina that views the  
723 world just above the horizon in front of the animal, was dominated by UV<sup>ON</sup>  
724 responses despite the presence of all cone-types in this part of the eye. In addition,  
725 ventral visual circuits, which survey the sky through Snell's window, were all but  
726 color-blind, probably because there is little chromatic information here. This forms an

727 interesting parallel with the mouse, where cone-only dichromacy also disappears  
728 above the horizon.

729 Where present, in larval zebrafish bipolar cells encoding color opponent or  
730 chromatically biased physiologies are systematically distributed into specific layers of  
731 the inner retina. For example, layers 1 and 3 of the dorsal retina were dominated by  
732 RG vs BU and R vs GBU color opponent responses. Accordingly, retinal ganglion  
733 cells that project specifically to these layers should inherit a similar physiology  
734 (Connaughton & Nelson 2015, Meier et al. 2018), thus leading to color opponent  
735 brain projections that are established already at the second synapse of the visual  
736 system. This is corroborated by bipolar recordings in other non-mammalian retinas:  
737 mudpuppies, turtles, goldfish and giant danio (*Devario aequipinnatus*) all have fully  
738 color opponent bipolar cells (Stell 1978, Werblin & Dowling 1969, Wong & Dowling  
739 2005, Yazulla 1976). Clearly much color opponency is already present at the level of  
740 the input to retinal ganglion cells.

741

#### 742 *Rod-based color vision*

743 Rods are generally inactive at high (photopic) light levels, but in mesopic conditions,  
744 when both rod and cone systems are simultaneously active, rod-cone chromatic  
745 antagonism can occur. This co-activity regime of rods and cones may extend to  
746 traditionally photopic levels (Szikra et al. 2014, Tikidji-Hamburyan et al. 2015).  
747 Vertebrate rods express RH1 rhodopsin, which in most species is spectrally similar  
748 to green cones. Accordingly, rod-driven networks can provide green antagonism. In  
749 the ventral mouse retina, this system appears to be exploited by at least one type of  
750 retinal ganglion cell (Joesch & Meister 2016), and it seems likely that further circuits  
751 in both mice and other species use rod signals (Baden et al. 2016, Field et al. 2009,  
752 Reitner et al. 1991). Rod-cone opponency might support some form of color vision in  
753 cone-monochromats such as most sharks, marine mammals and or racoons (Griebel  
754 & Peichl 2003, Oppermann et al. 2016, Peichl 2005, Von Schantz et al. 1997).  
755 However, since most cone-monochromats use green cones which overlap strongly in  
756 spectral sensitivity with rods, it remains unclear how much chromatic contrast might  
757 be available. Beyond building rod-cone opponent networks, some species even  
758 feature two types of spectrally distinct rods, and there is evidence for rod-rod

759 opponency allowing color vision at low light levels (Denton & Wyllie 1955, Hailman  
760 1976, Korenyak & Govardovskii 2013, Yovanovich et al. 2017).

761

762

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772

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