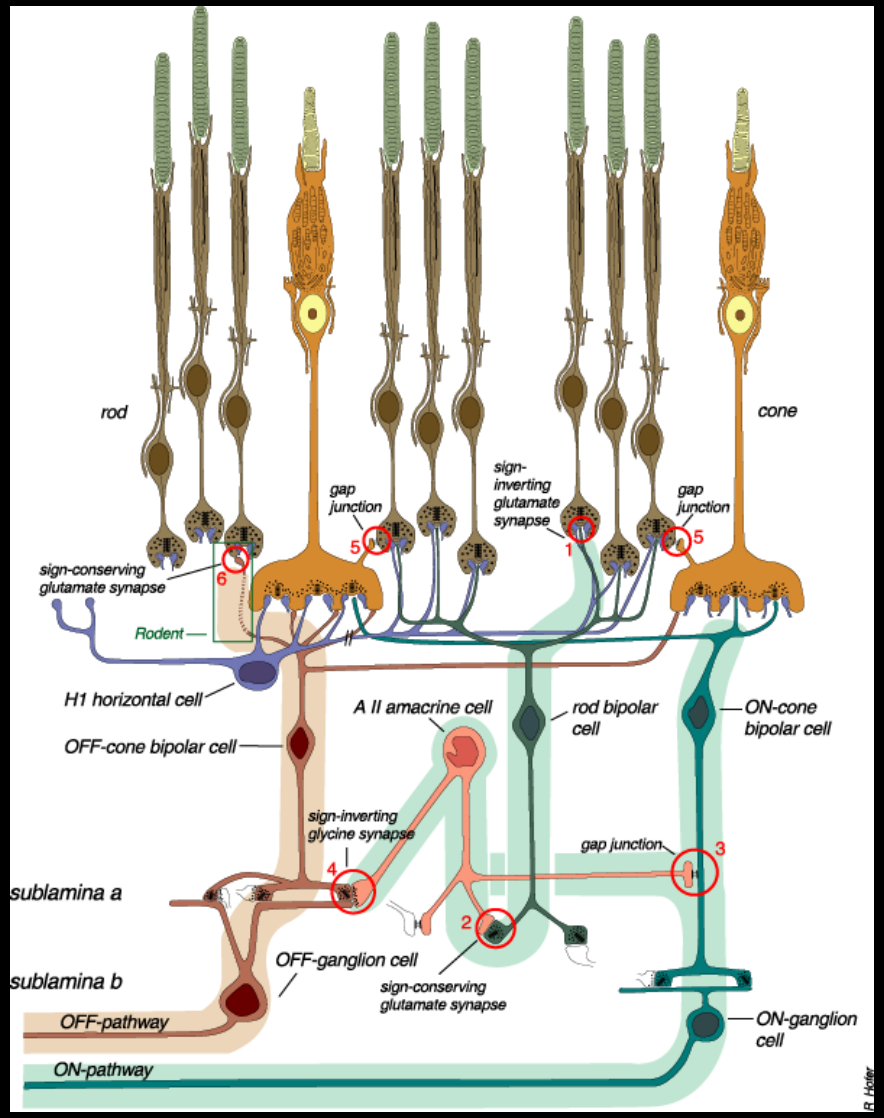
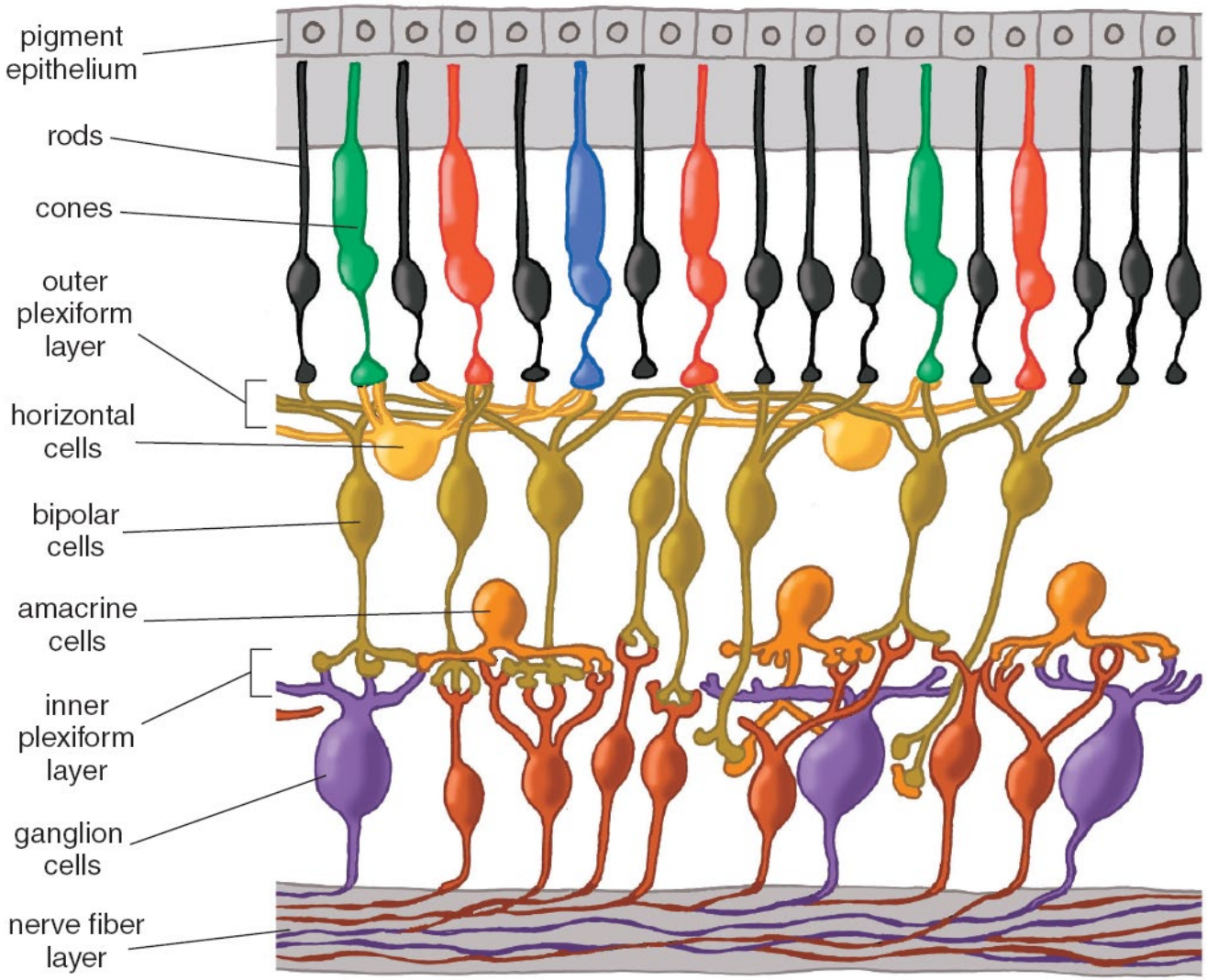
Advanced Retina

Andrew Stockman

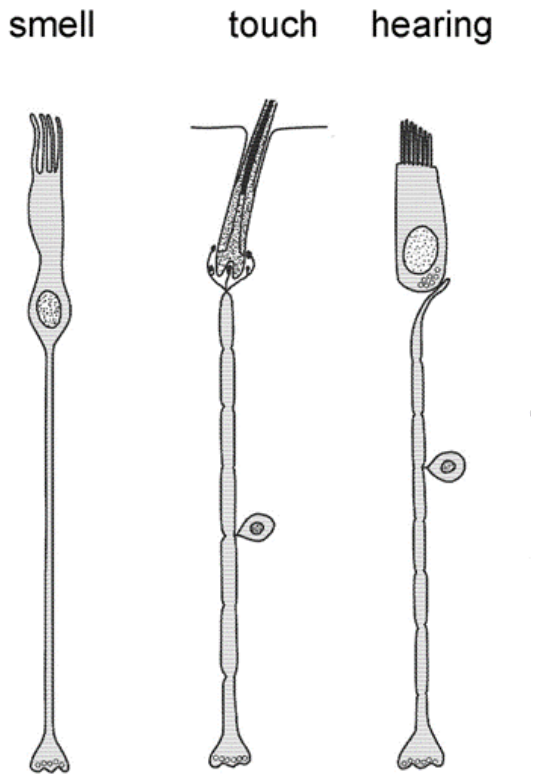
NEUR 0017
Visual Neuroscience



Retinal Circuitry



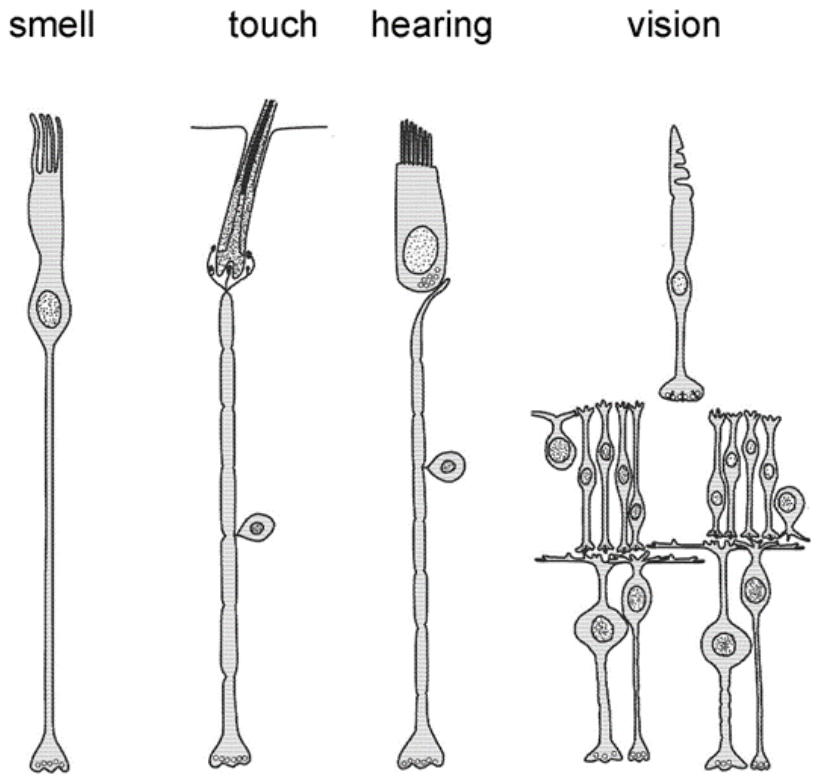
ADVANCED TOPICS

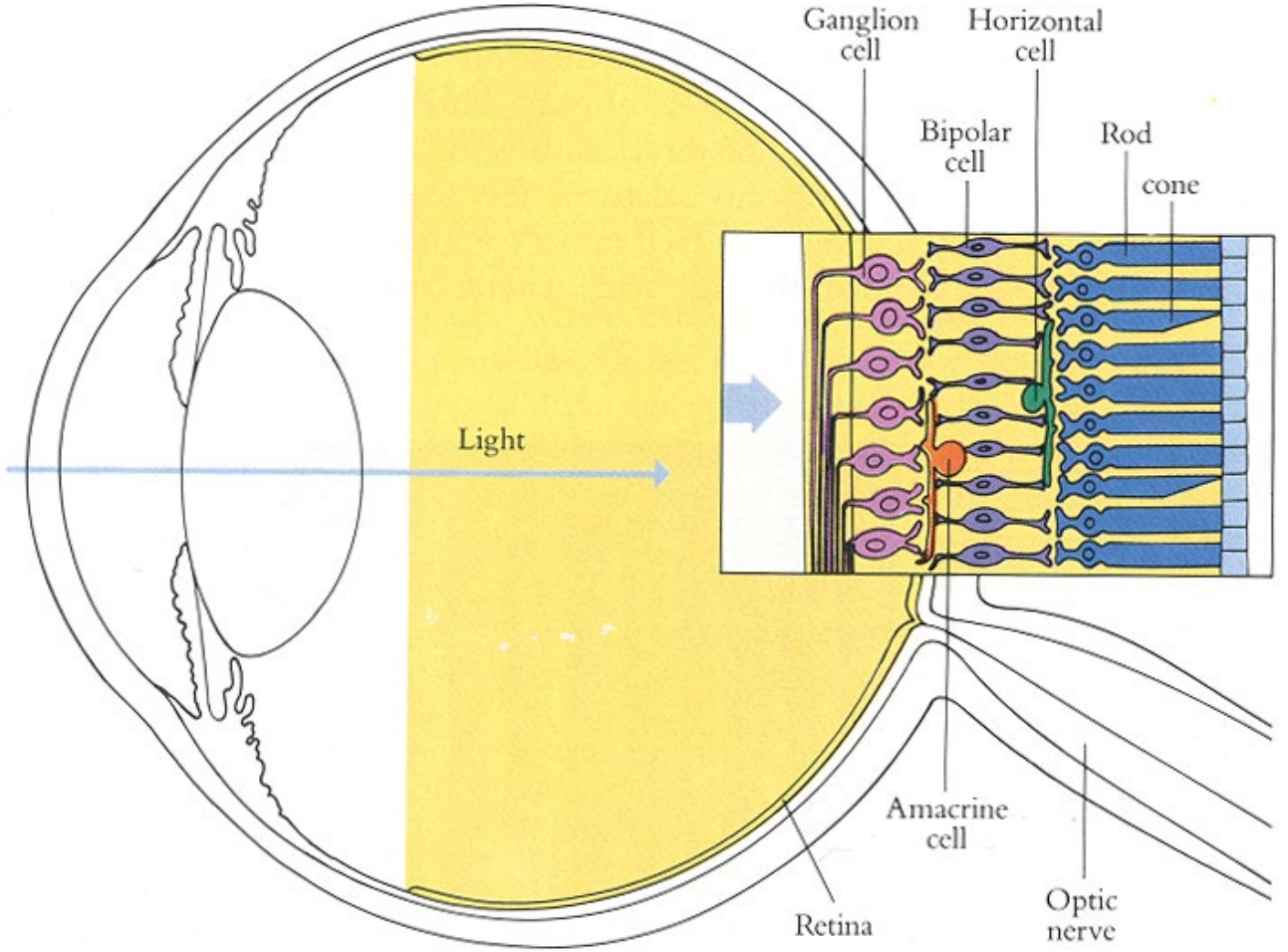


Other sensory receptors transmit action potentials straight to the brain.

Calupa & Werner The Visual Neurosciences

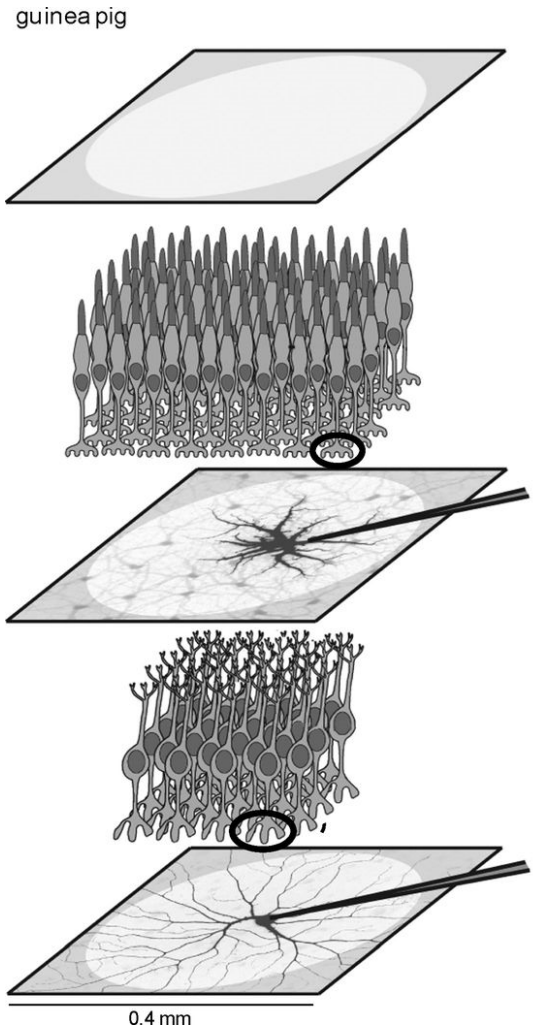
Why does so much processing occur in the retina?





Calupa & Werner The Visual Neurosciences

The retina steps down quantal rates by 10^9



reduce quantal rate **sensitivity loss**

pattern (100 ms)
10^9 light quanta

photoreceptors
10^7 R* quanta **10 x**

cone terminals
10^5 glut quanta
remove high and low frequencies

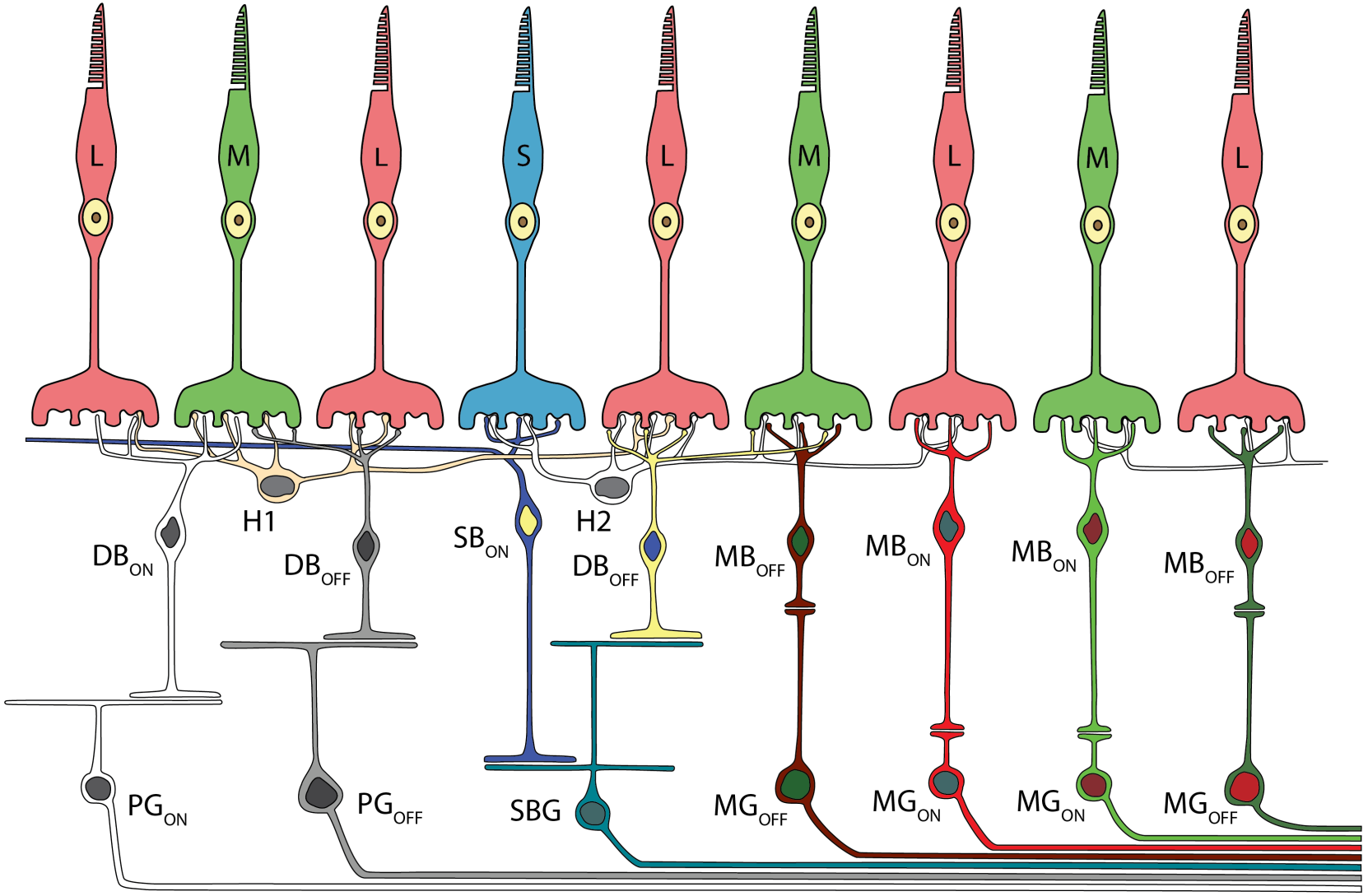
horizontal cell **4 x**
average cone quanta, subtract mean

bipolar terminals
glut quanta
~ 0 tonic
10^2 evoked
initiate sparse coding

ganglion cell
readout bipolar quanta **2.5 x**
~1 spike

Borghuis, Sterling & Smith J Neurosci. 2009; 29: 3045–3058

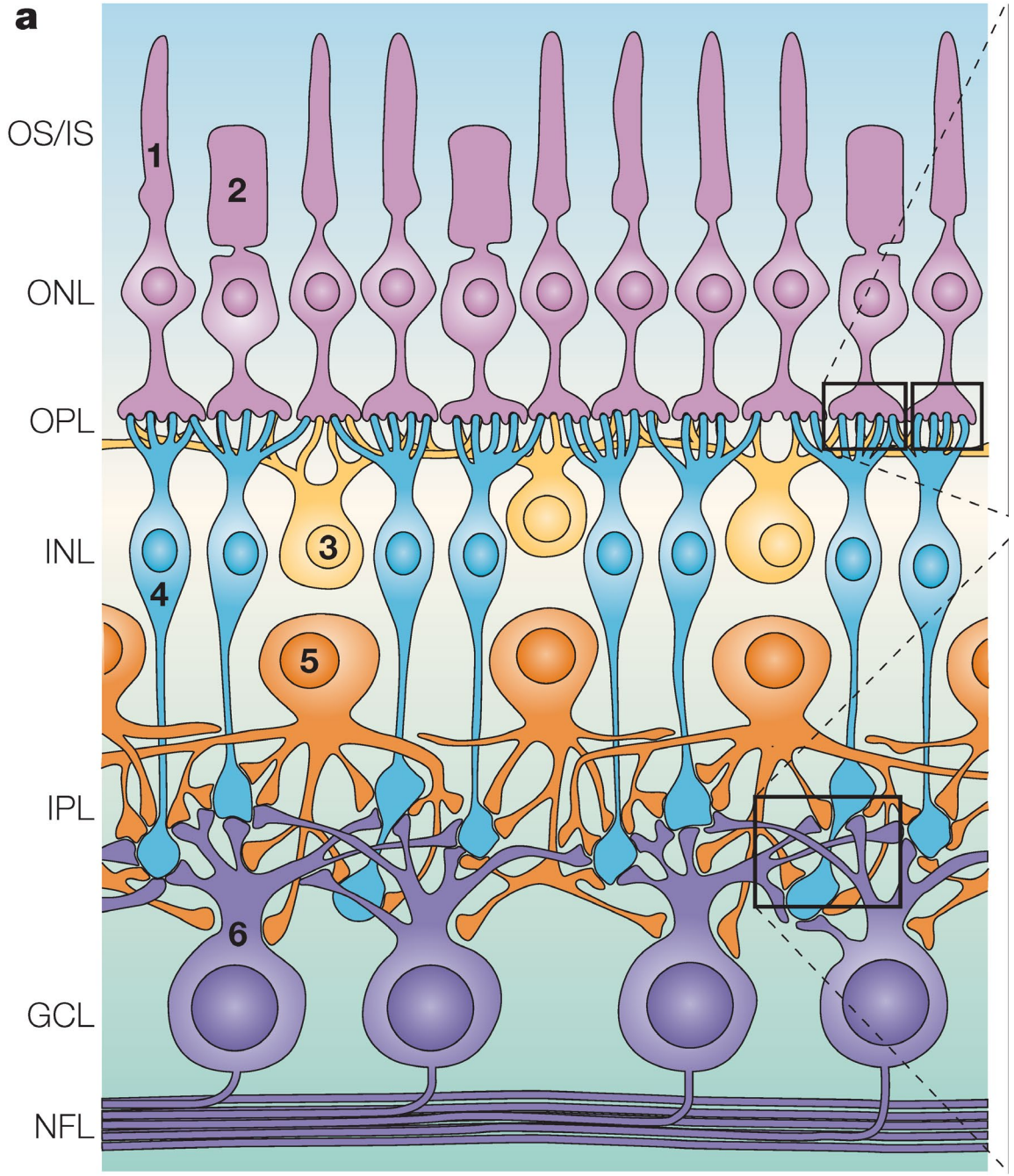
Parallel and serial processing in the retina



PARALLEL PROCESSING IN THE RETINA

Parallel processing in the mammalian retina is established at the synaptic level

(a) Rods (1), cones (2), horizontal cells (3), bipolar cells (4), amacrine cells (5) and retinal ganglion cells (RGCs) (6).



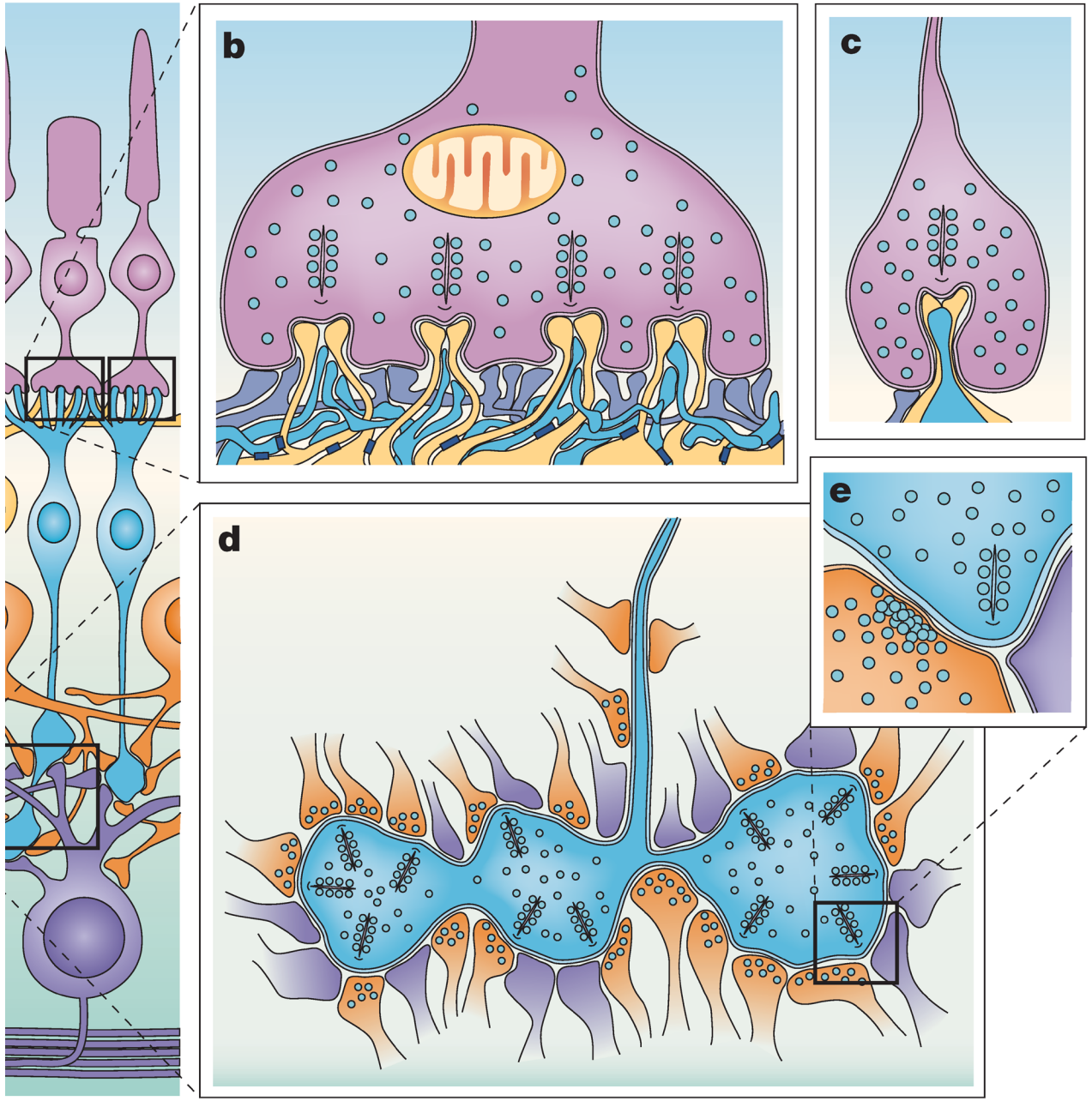
Heinz Wässle *Nature Reviews Neuroscience* 5, 747–757 (2004)

(b) Cone pedicle, the synaptic terminal of cones. Four presynaptic ribbons are apposed to the dendrites of horizontal cells (yellow) and ON cone bipolar cells (blue) in a 'triad'. OFF cone bipolar cell dendrites form contacts at the cone pedicle base (purple).

(c) Rod spherule, the synaptic terminal of rods. The presynaptic ribbon is apposed to the invaginating axons of horizontal cells (yellow) and the dendrites of rod bipolar cells (blue). OFF cone bipolar cell dendrites form contacts at the base (purple).

(d) The axon terminal of a cone bipolar cell (blue) contains up to 50 presynaptic ribbons, and connects to postsynaptic amacrine cell processes (orange) and RGC dendrites (purple).

(e) A magnified view of a bipolar cell ribbon synapse (blue) with an amacrine cell process (orange) and an RGC dendrite (purple) in a “dyad”.

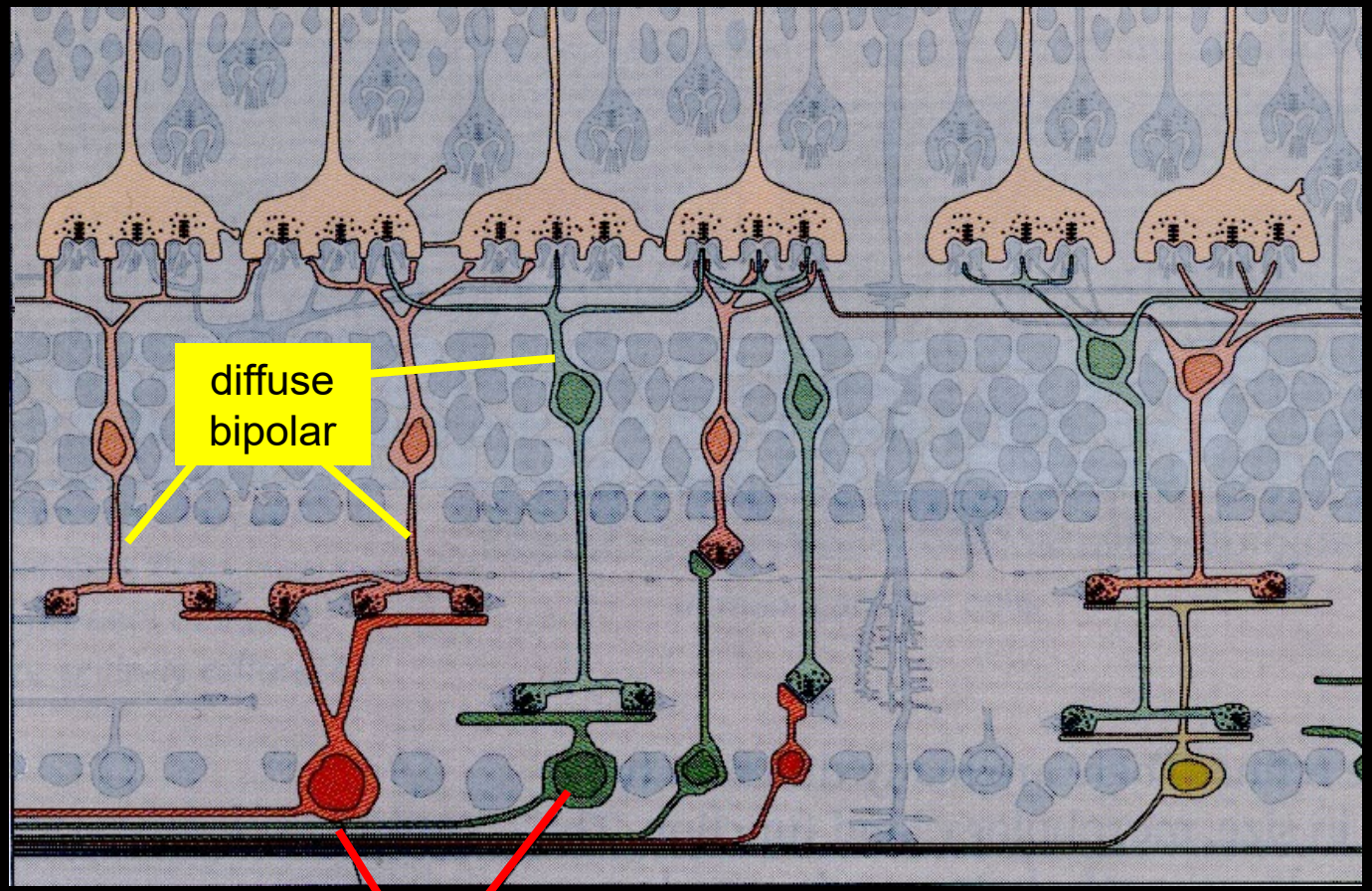


Heinz Wässle *Nature Reviews Neuroscience* 5, 747–757 (2004)

Why do we need parallel pathways from eye to brain?

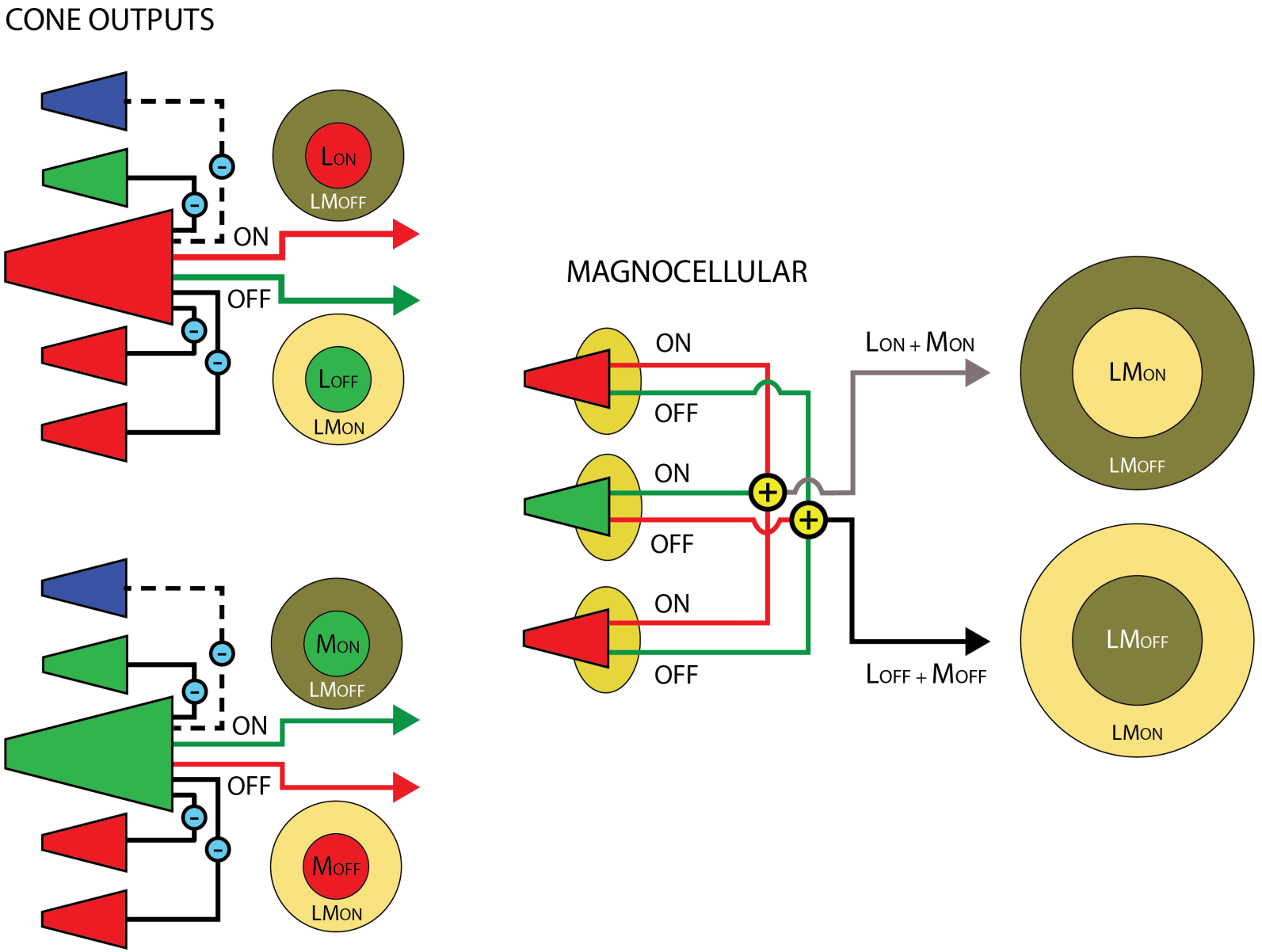
MAGNOCELLULAR

Magnocellular



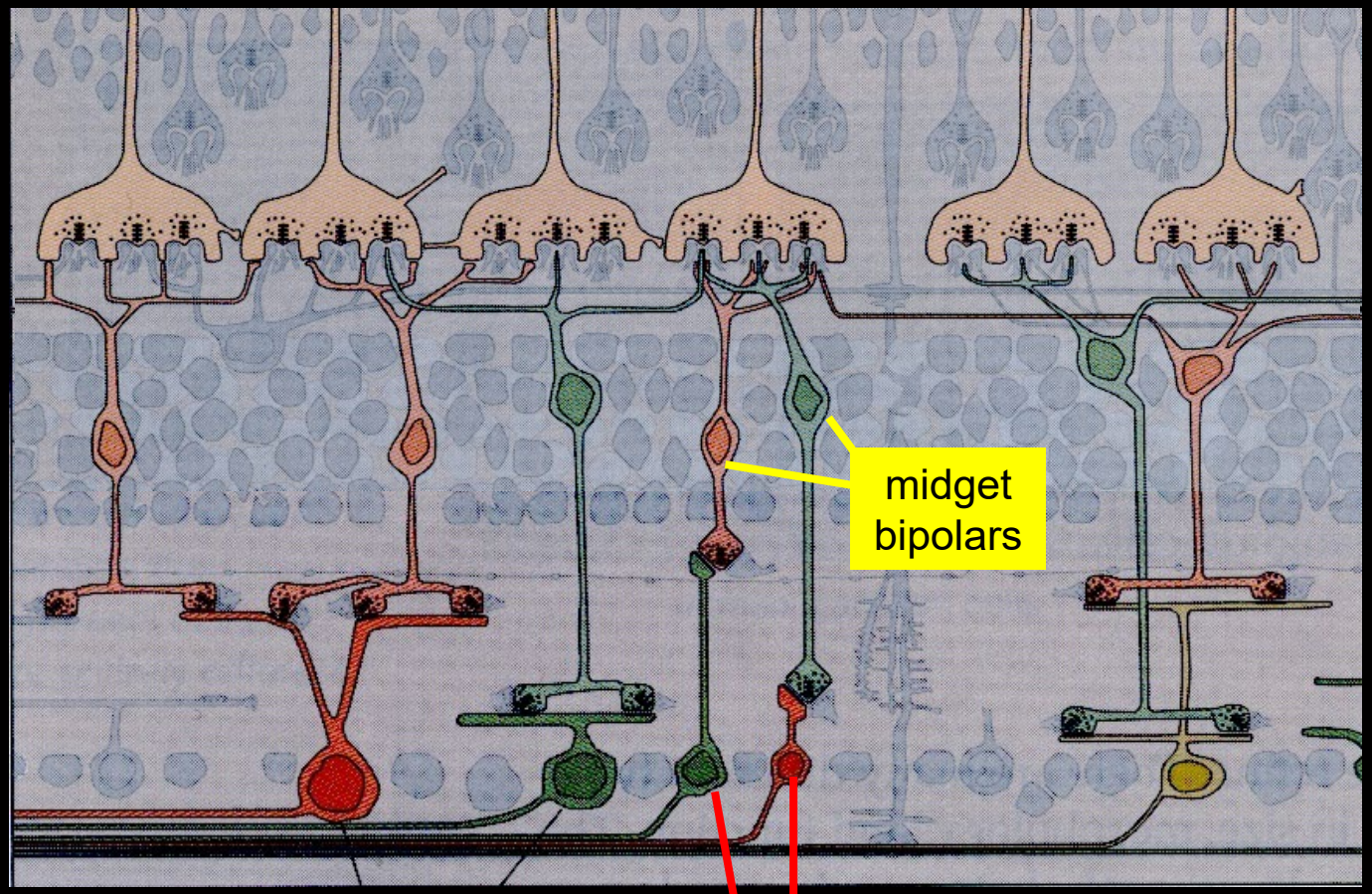
From Rodieck (1998)

Magnocellular



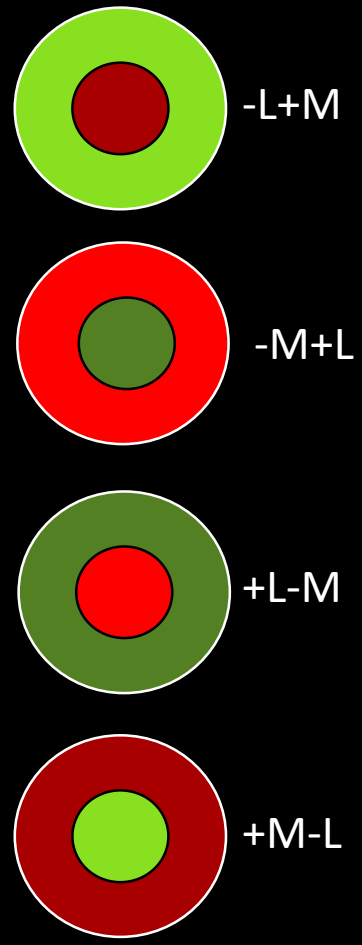
PARVOCELLULAR

Parvocellular



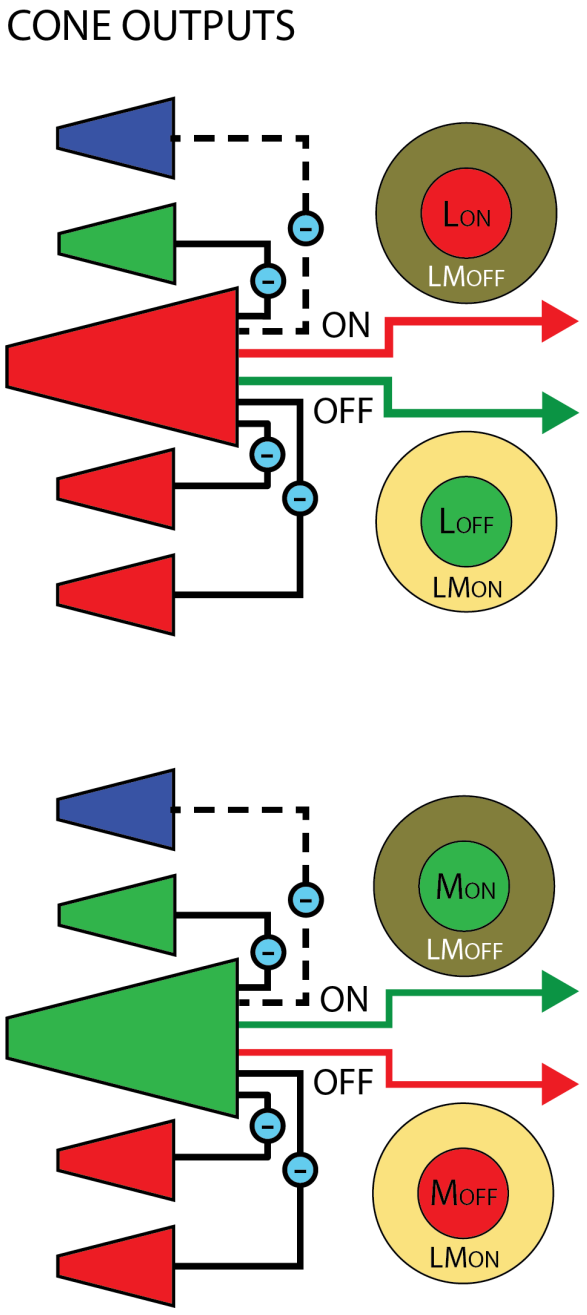
OFF

ON



From Rodieck (1998)

Parvocellular

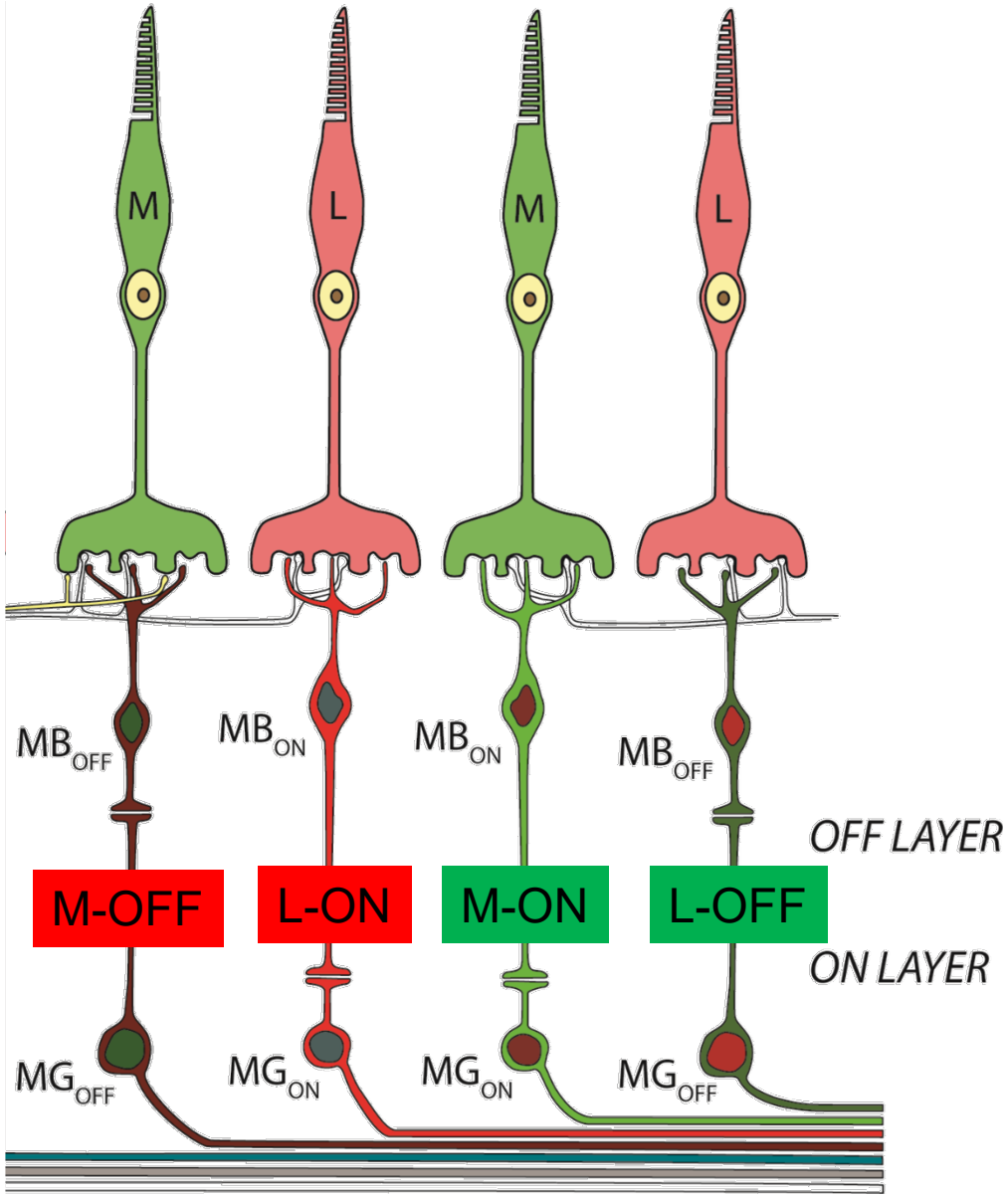


Parvocellular centres

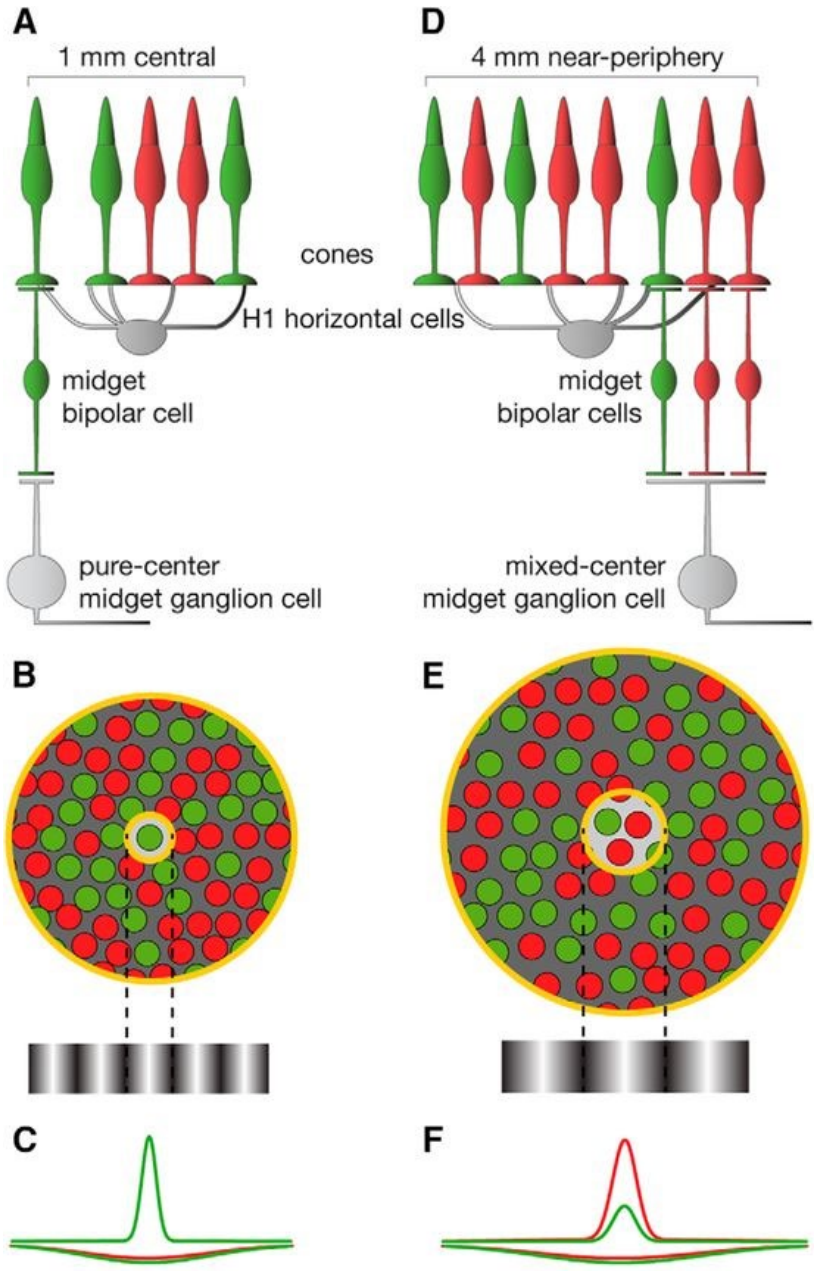
Parvocellular cells in the central retina have a roughly one-to-one cone mapping and are thus inherently colour opponent. The ON and OFF cells half-wave rectify the cone signals into four “chromatic” types...

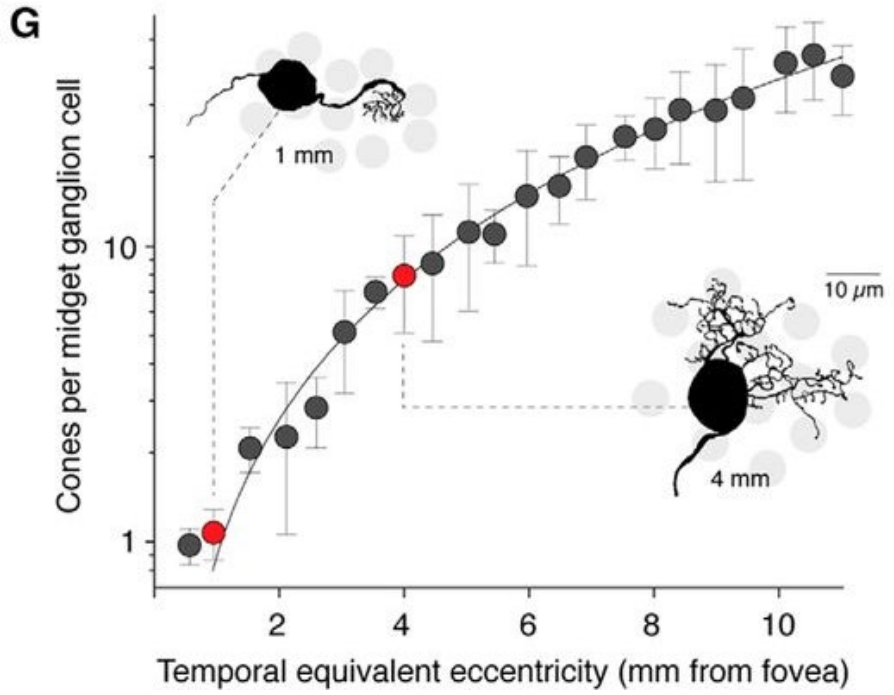
FOUR TYPES

They are “chromatic” simply because the centre has one cone type and the surround has a mixture.



Parvocellular surrounds



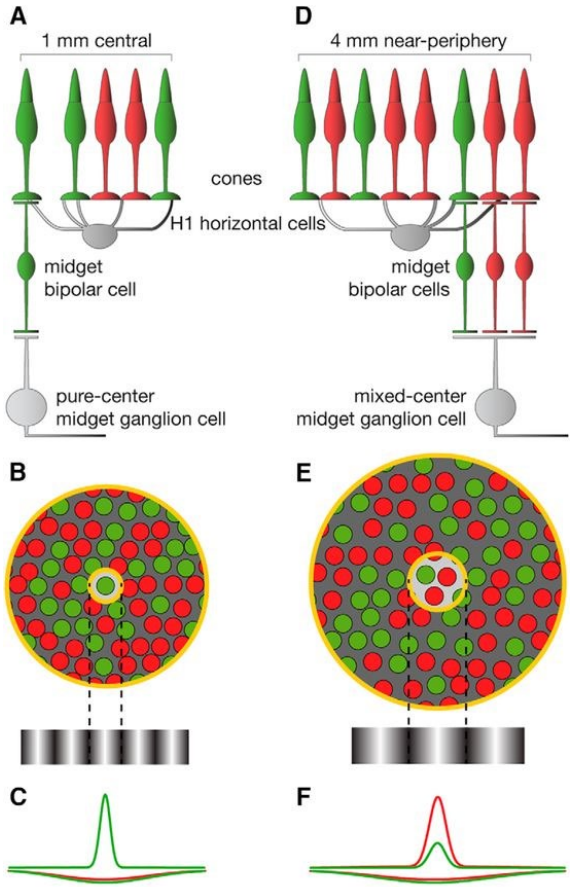


Random cone centre-surround model

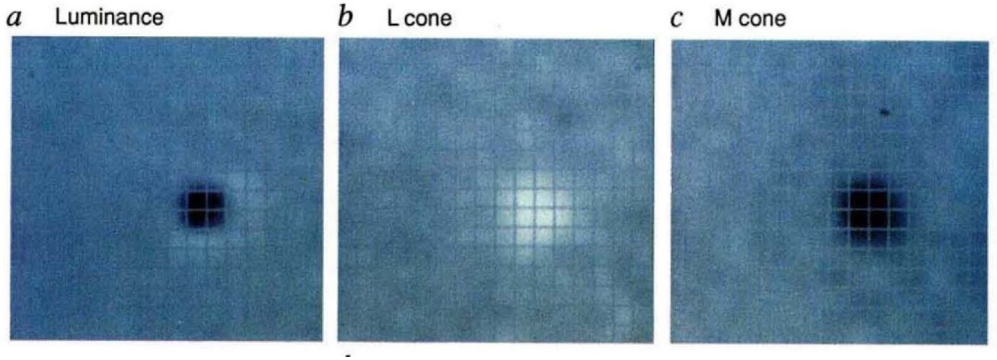
Parvocellular surrounds

Receptive field of green-off / red-on Type I a parvocellular neuron at a stimulus-response interval of 59 ms.

Random cone centre-surround models

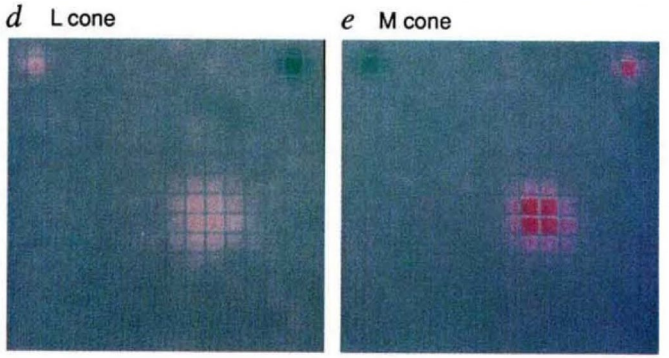


Average stimuli that preceded a response



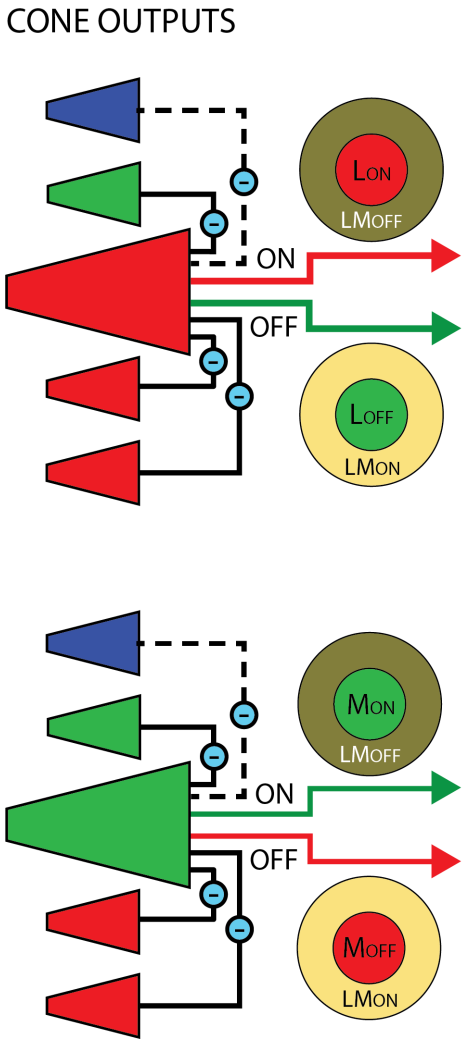
Average “colour” stimuli that preceded a response

Evidence for cone-specific centre-surround models…

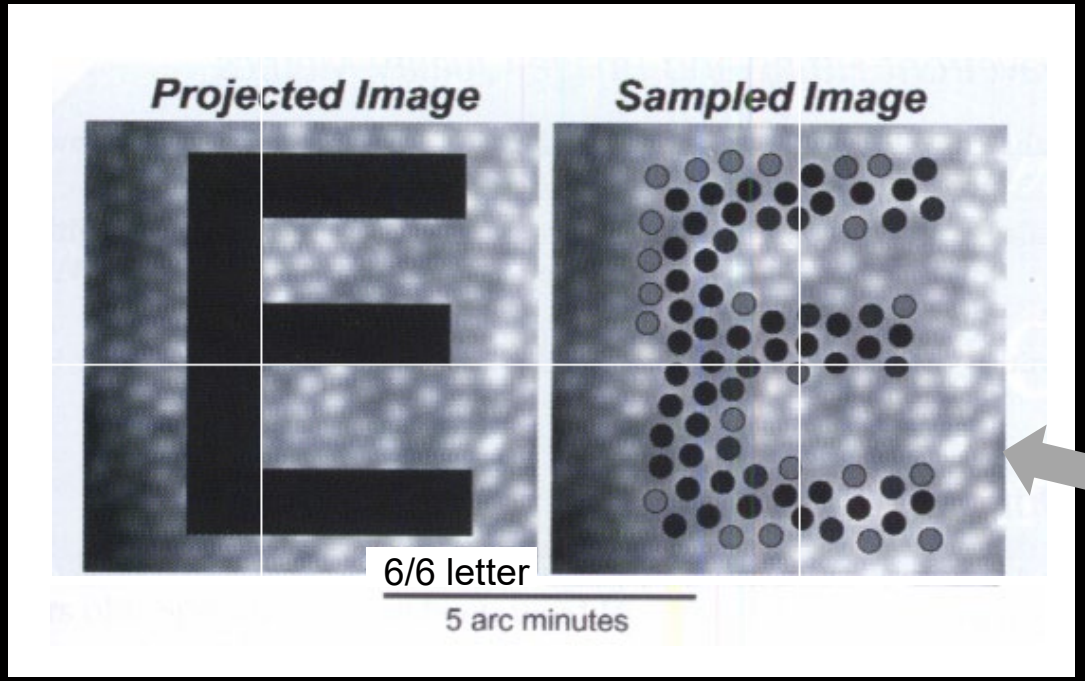


Reid & Shapley (1992)

Parvocellular



The parvocellular pathway isn’t just about colour…



Austin Roorda, 2004

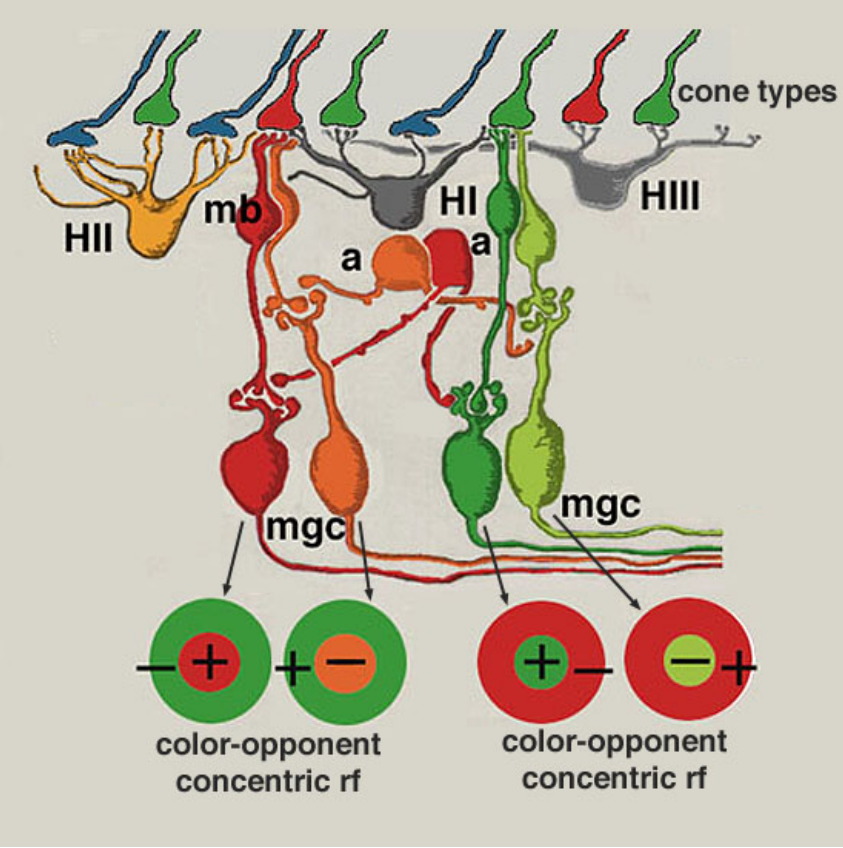
RETINAL CONE ARRAY

To be able to resolve this E, the image must be sampled at enough points.

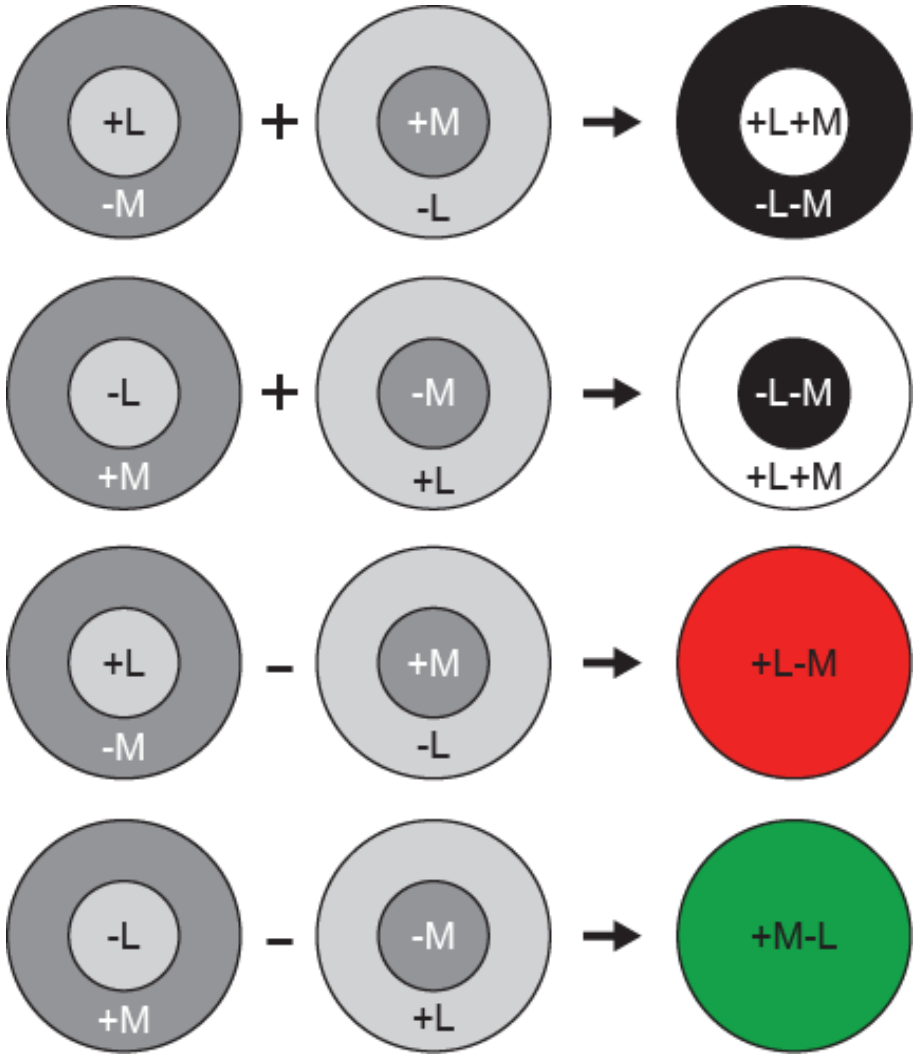
The parvocellular pathway, with its midget one-to-one cone to bipolar to ganglion cell connections, provides enough samples.

The magnocellular pathway, with diffuse bipolar cells, does not.

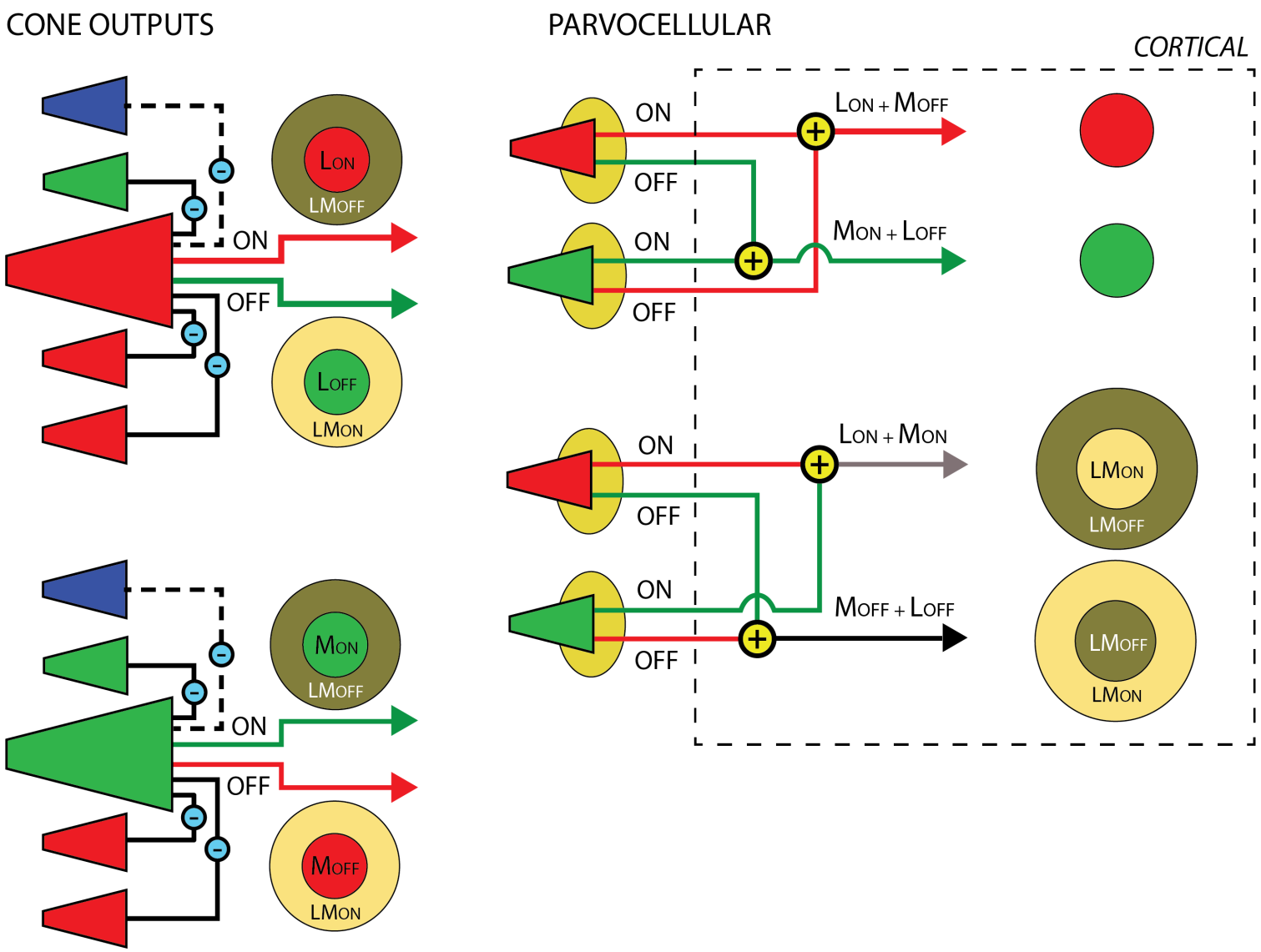
Colour and luminance information are “multiplexed” in the parvocellular pathway



Demultiplexing

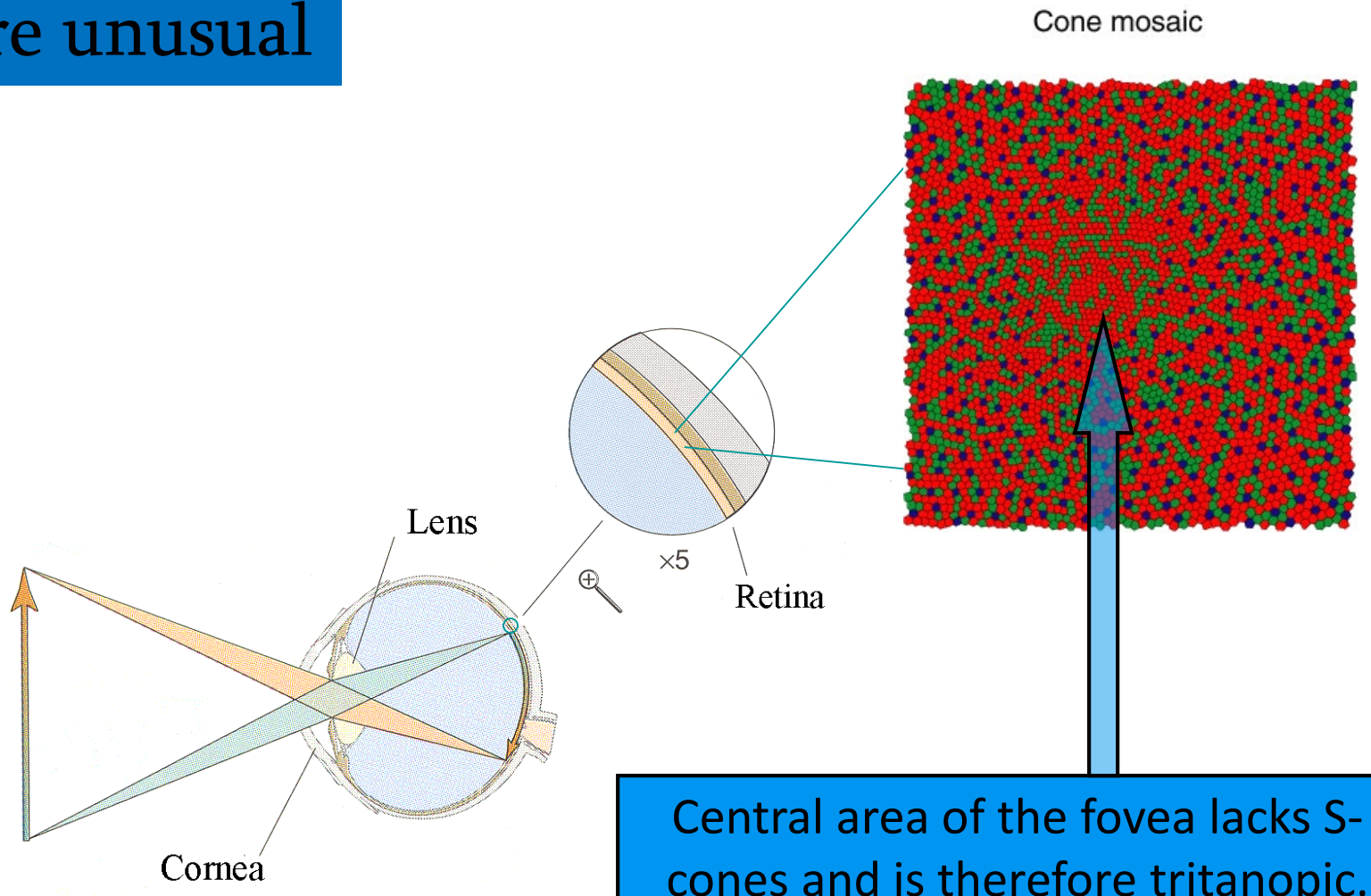


Parvocellular



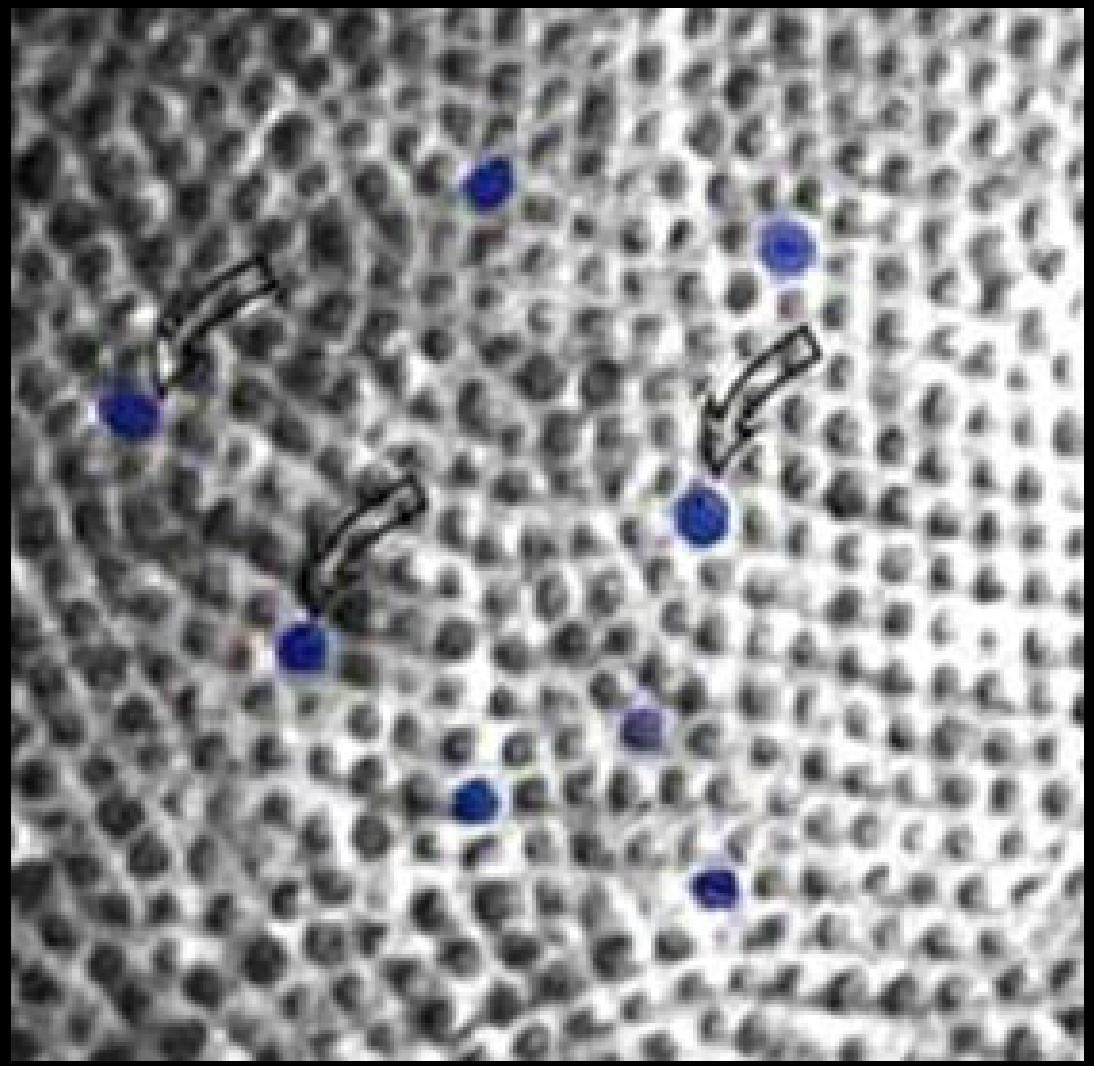
S-CONE (KONIOCELLLAR) PATHWAY

S-cones are unusual



Central area of the fovea lacks S-cones and is therefore tritanopic.

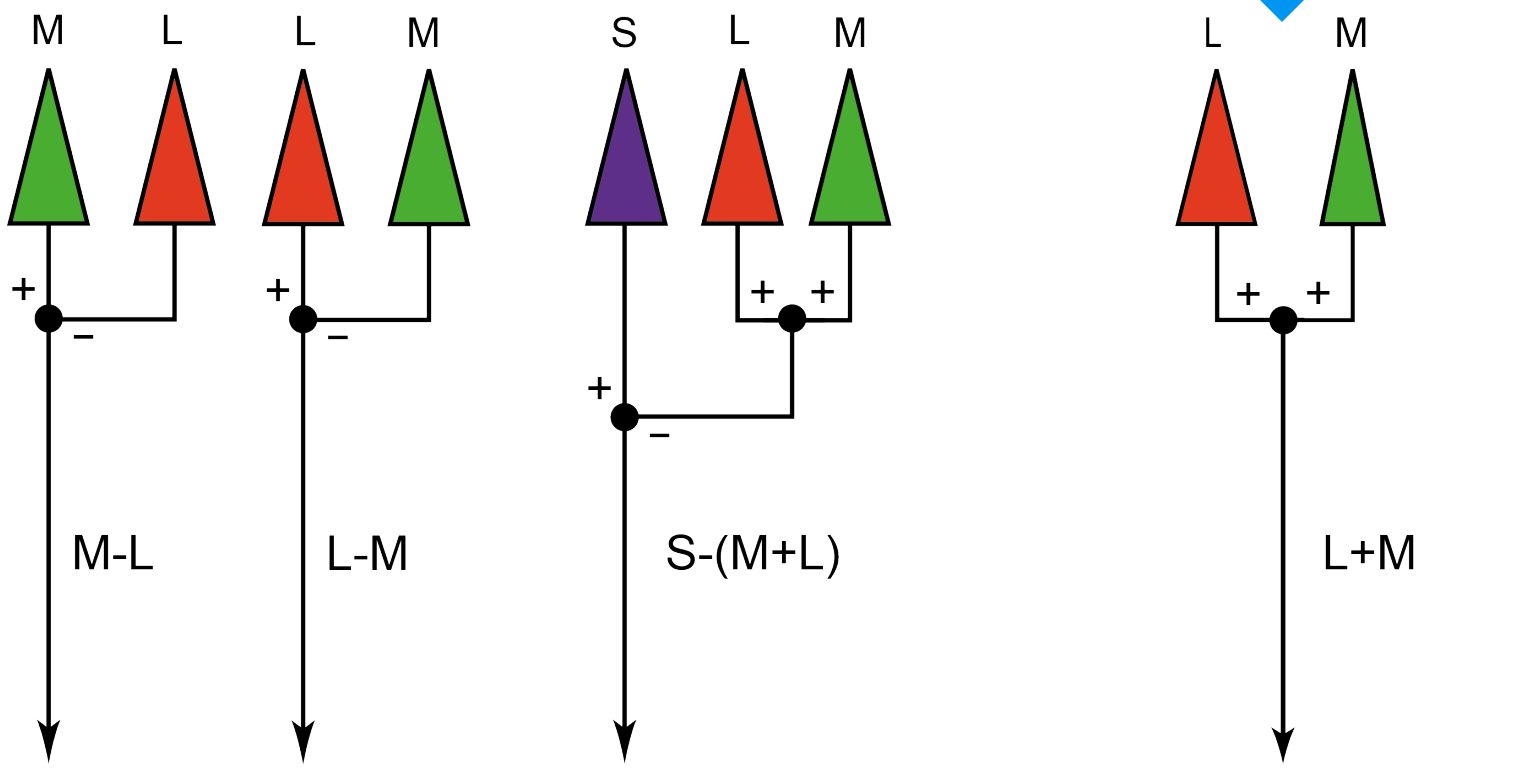
In other retinal regions, the S-cone mosaic is sparse.



S-cones form between 5 and 10% of the cone population.

Curcio et al.

S-cones make little or no contribution to luminance

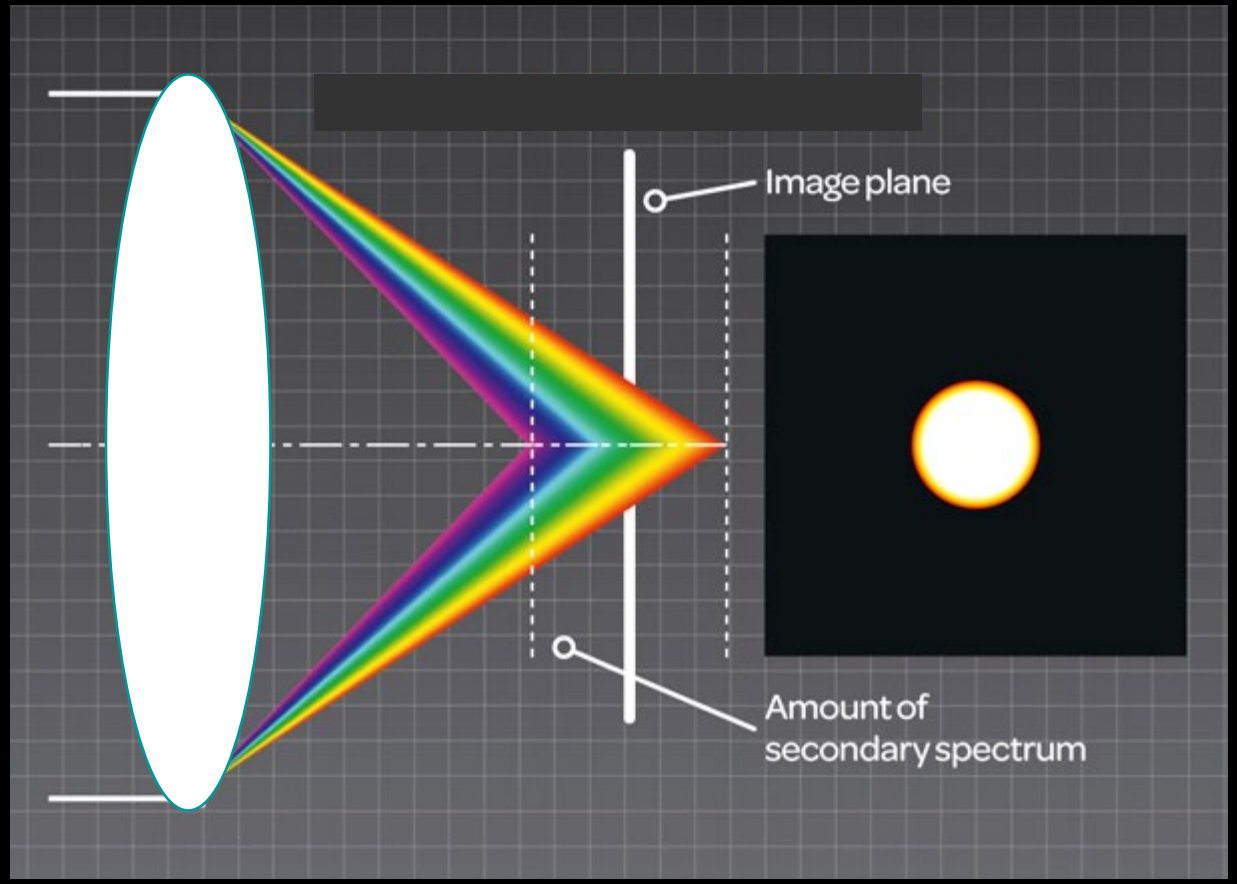


Chromatic pathways

Luminance pathway

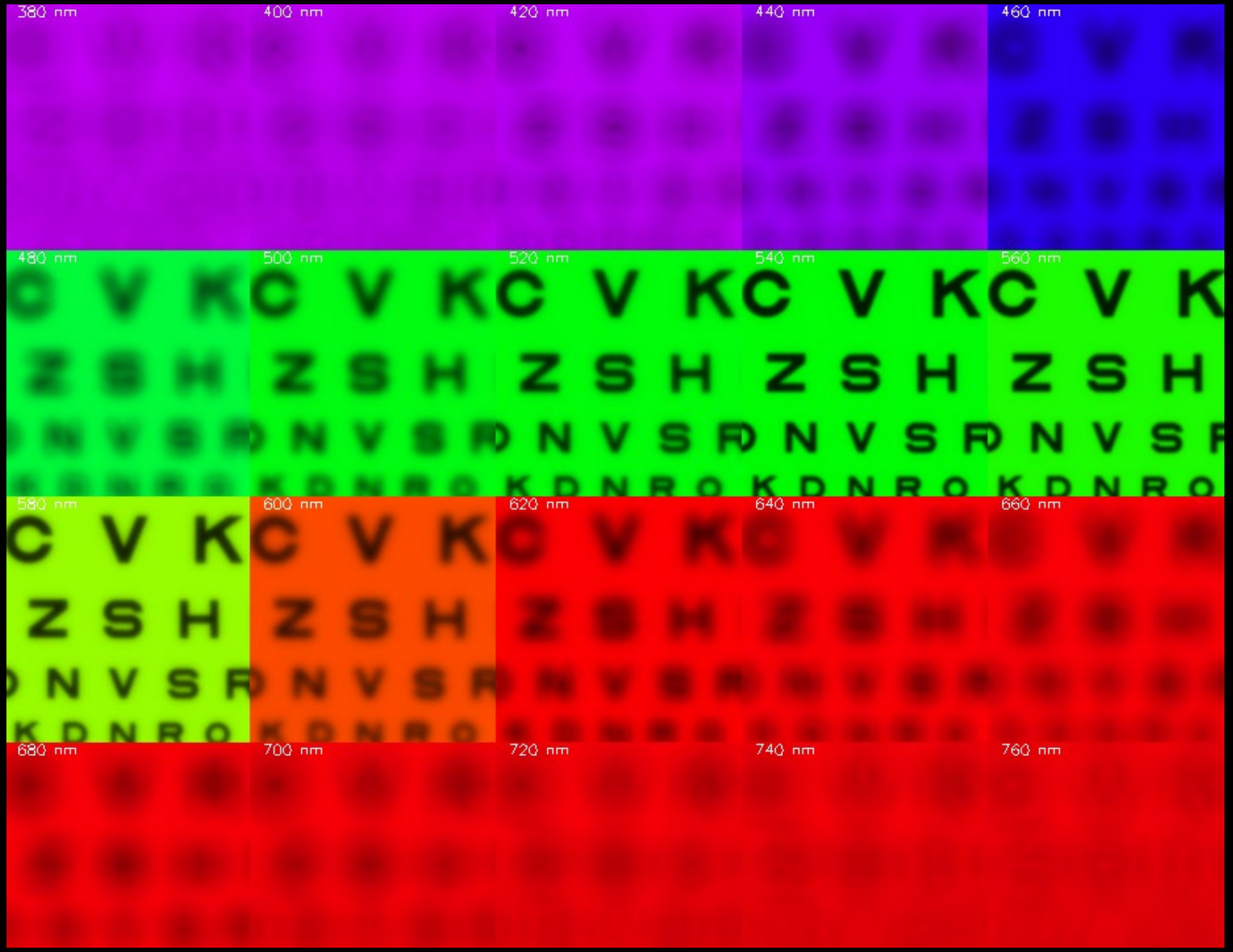
Why have S-cones evolved to be sparse and restricted to chromatic pathways?

Chromatic aberration



Base picture: Digital camera world

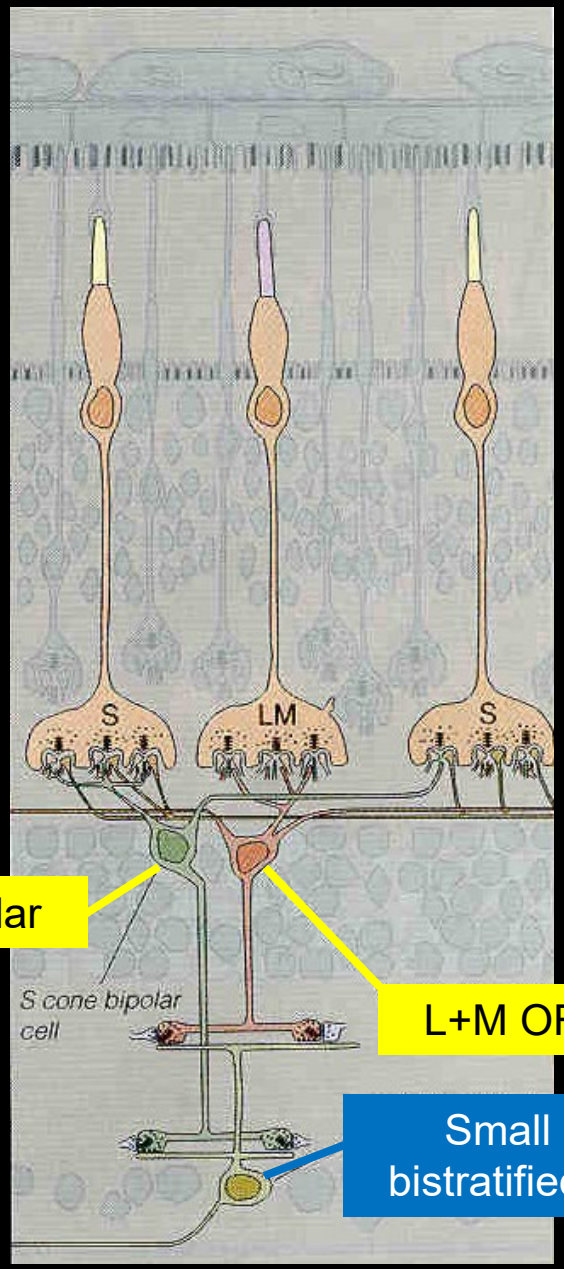
Effect of chromatic blur on eye chart



Jim Schwiegerling

Koniocellular

Primary S-cone pathway
is a separate pathway
through the retina…



S-cone ON bipolar

OFF

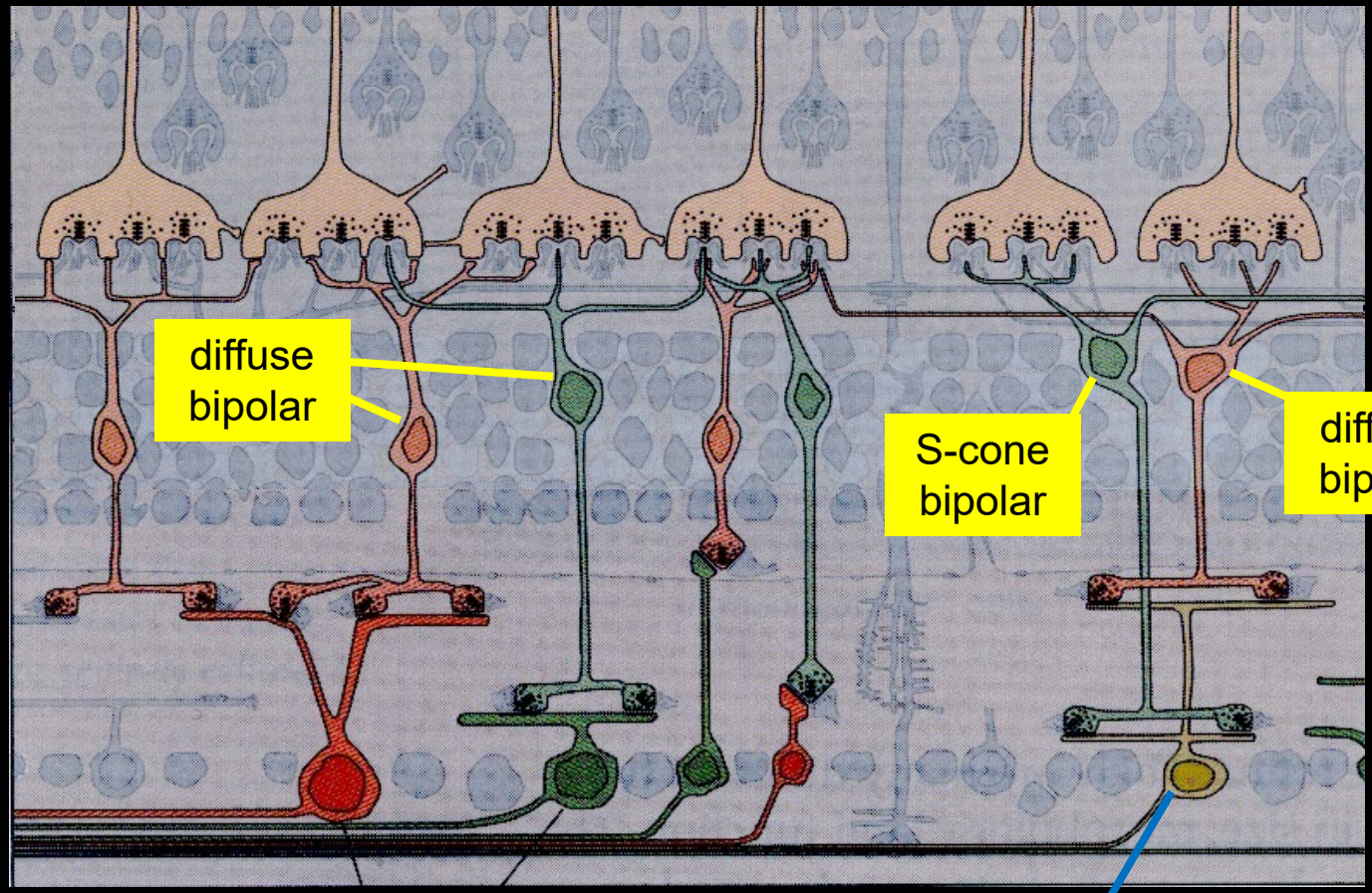
ON

L+M OFF bipolar

Small blue-yellow
bistratified ganglion cell

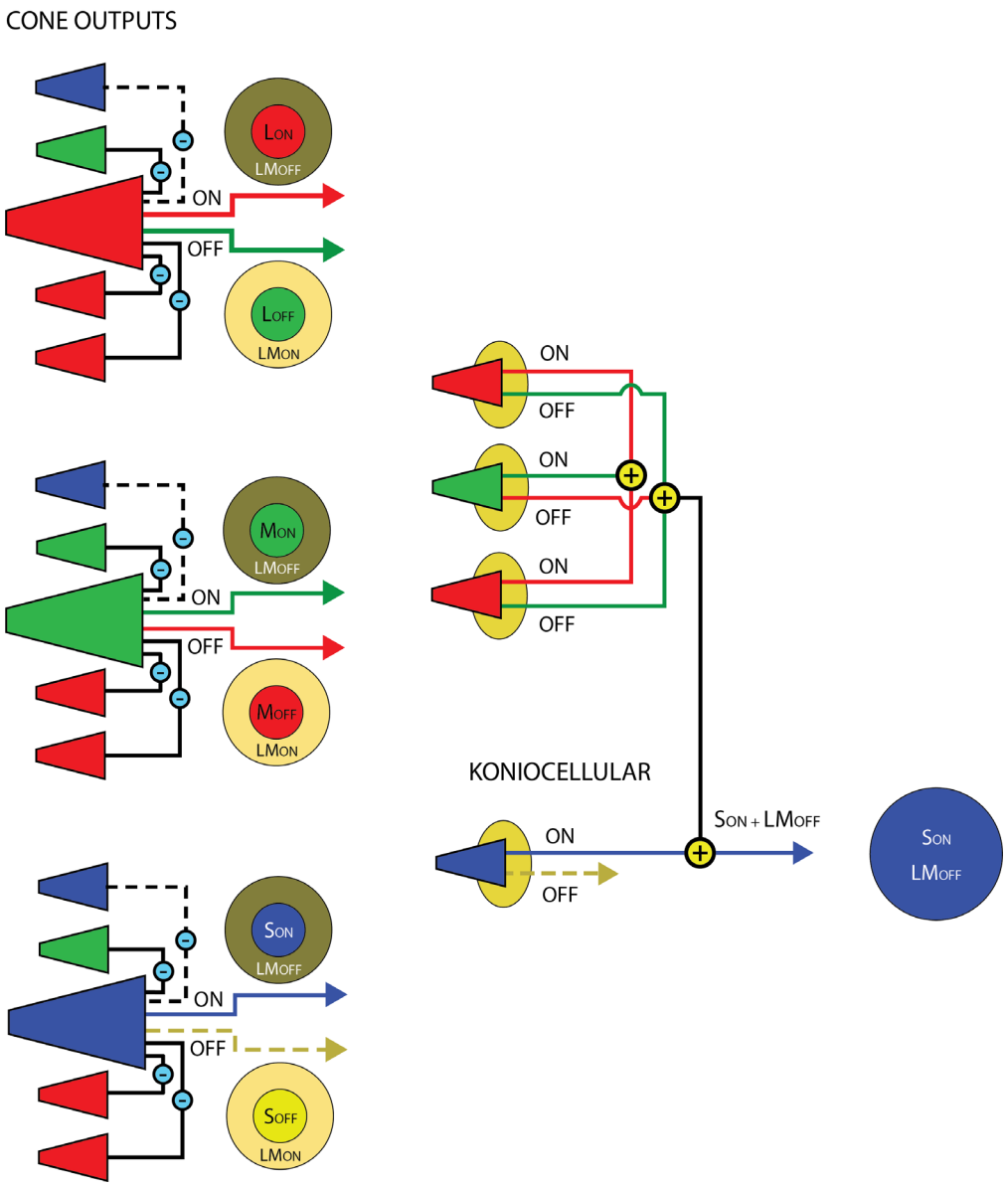
From Rodieck (1998)

Koniocellular

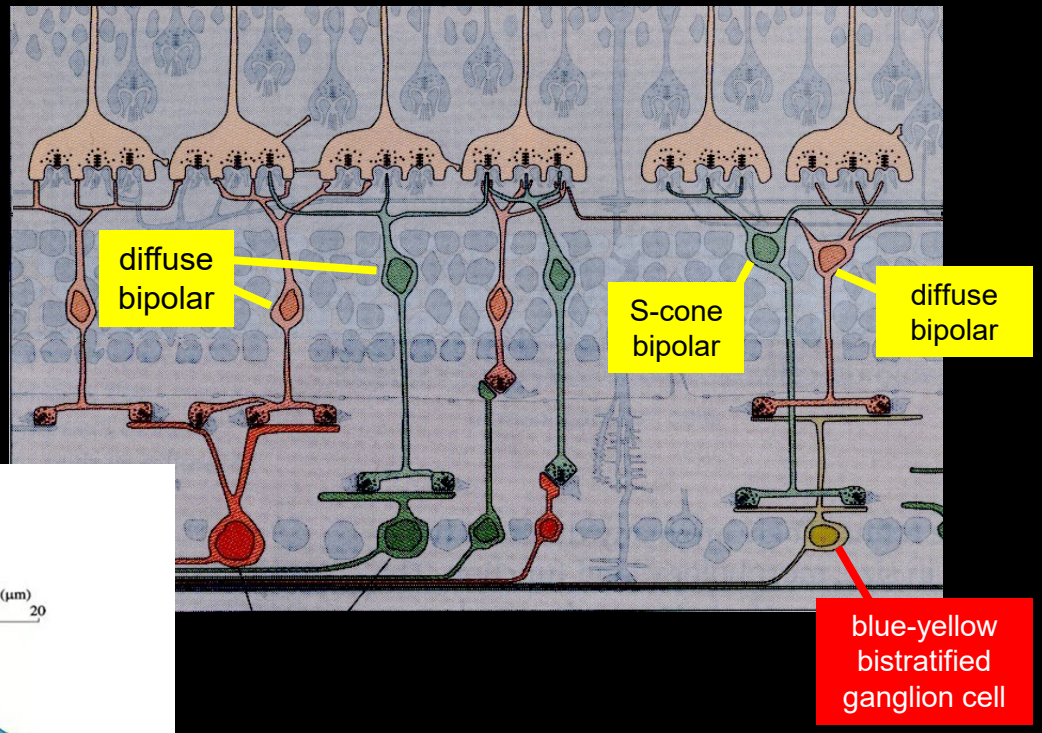


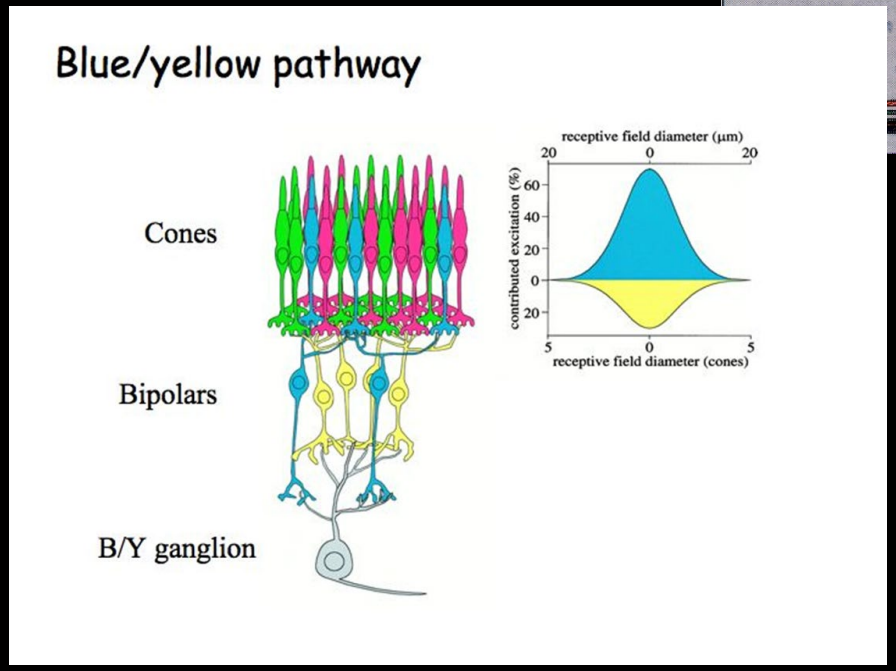
From Rodieck (1998)

Koniocellular



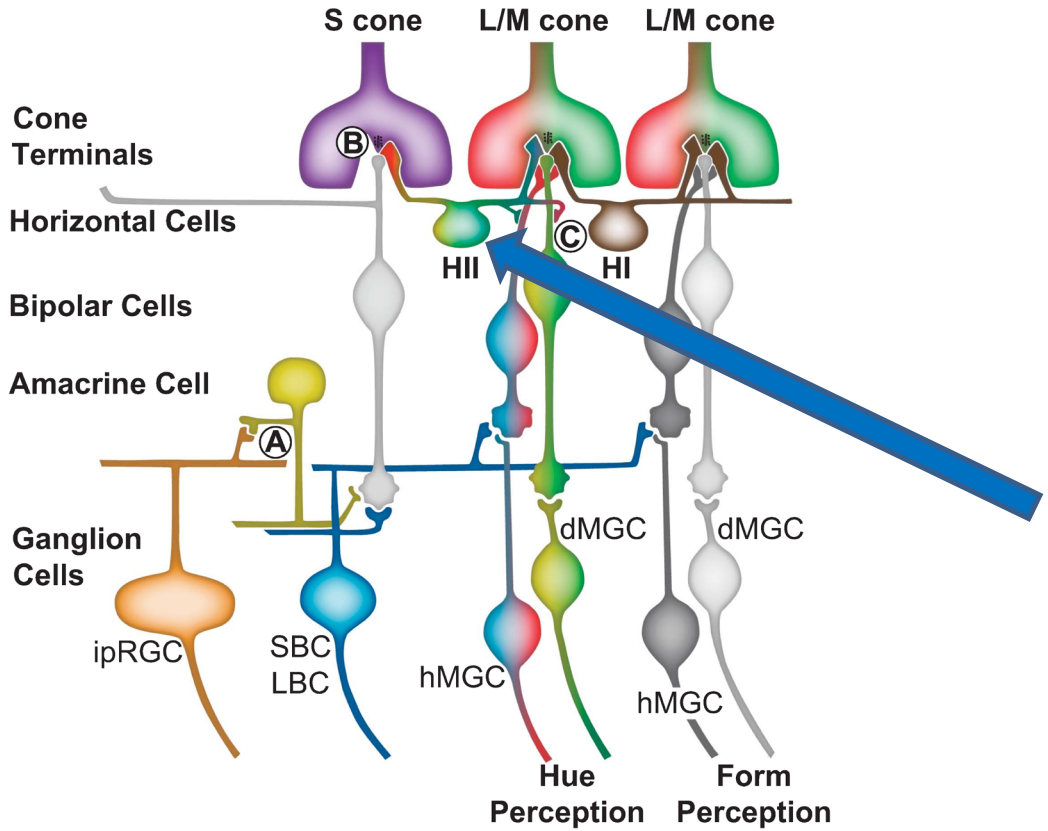
Koniocellular





From Rodieck (1998)

Other S-cone pathways

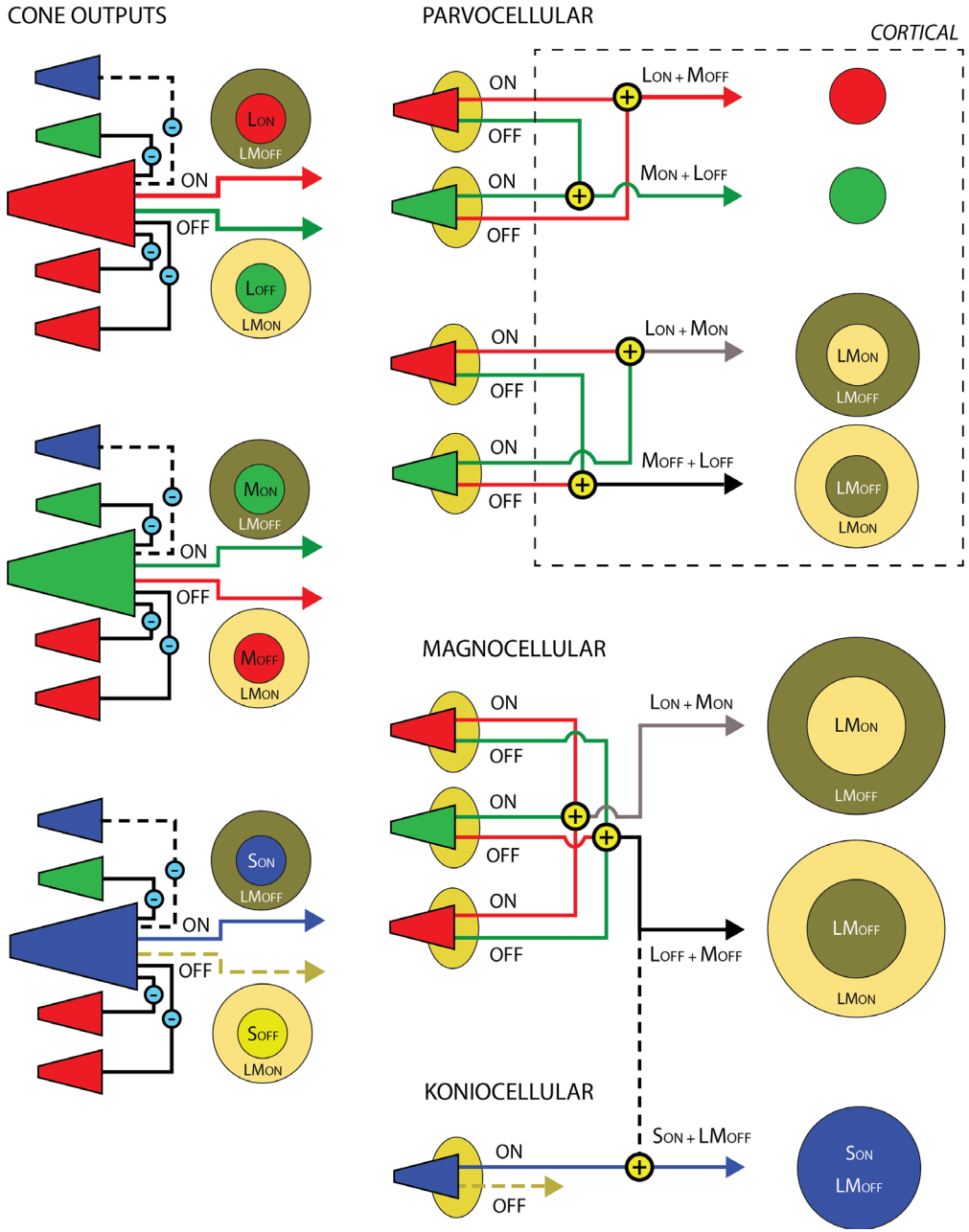


Neitz & Neitz (2107)

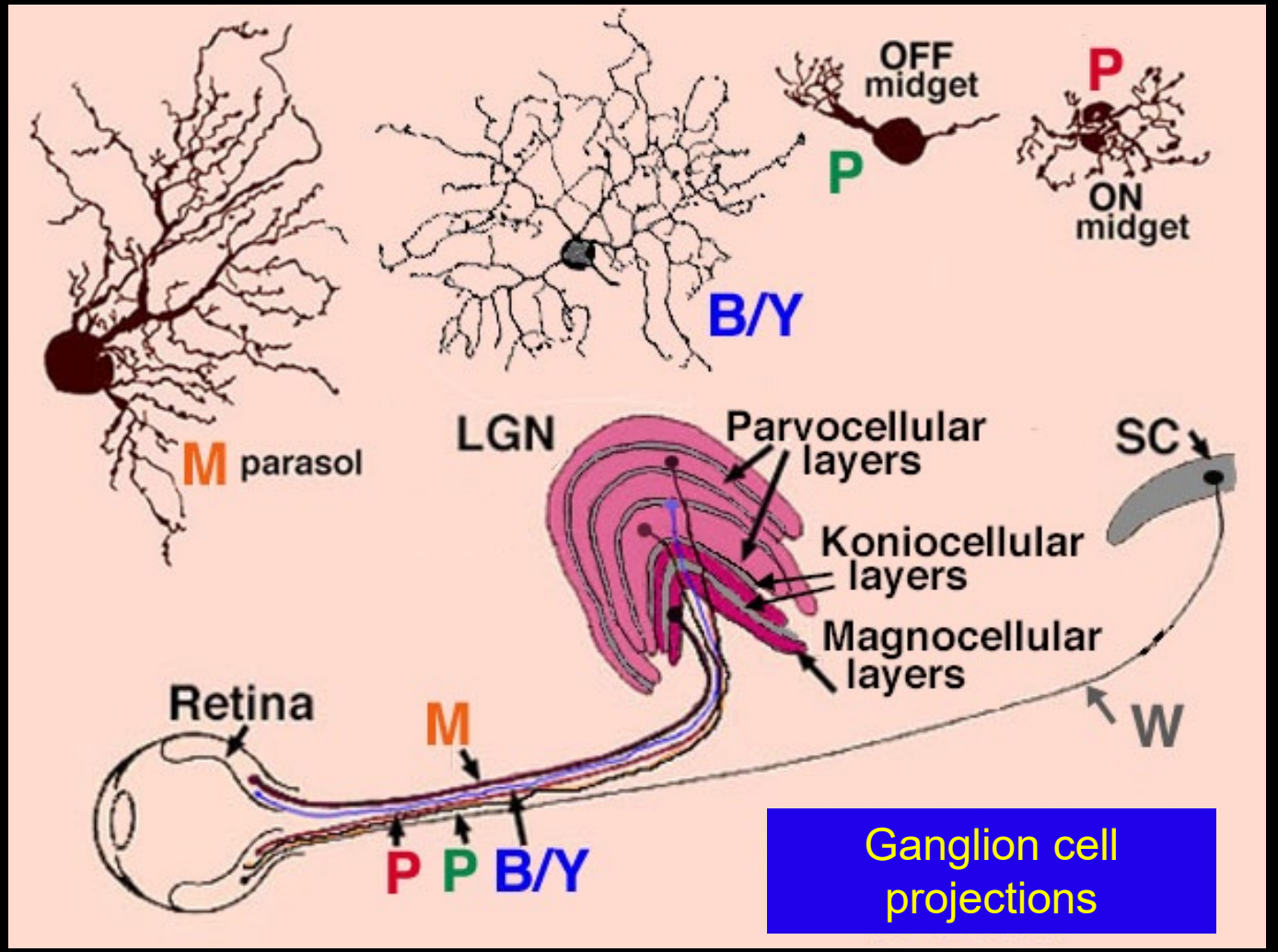
There must also be an OFF S-cone pathway (because, for example, CSNB patients are *not* tritanopic).

Could S-cone signals via horizontal (HII) cells provide S-cone colour signals?

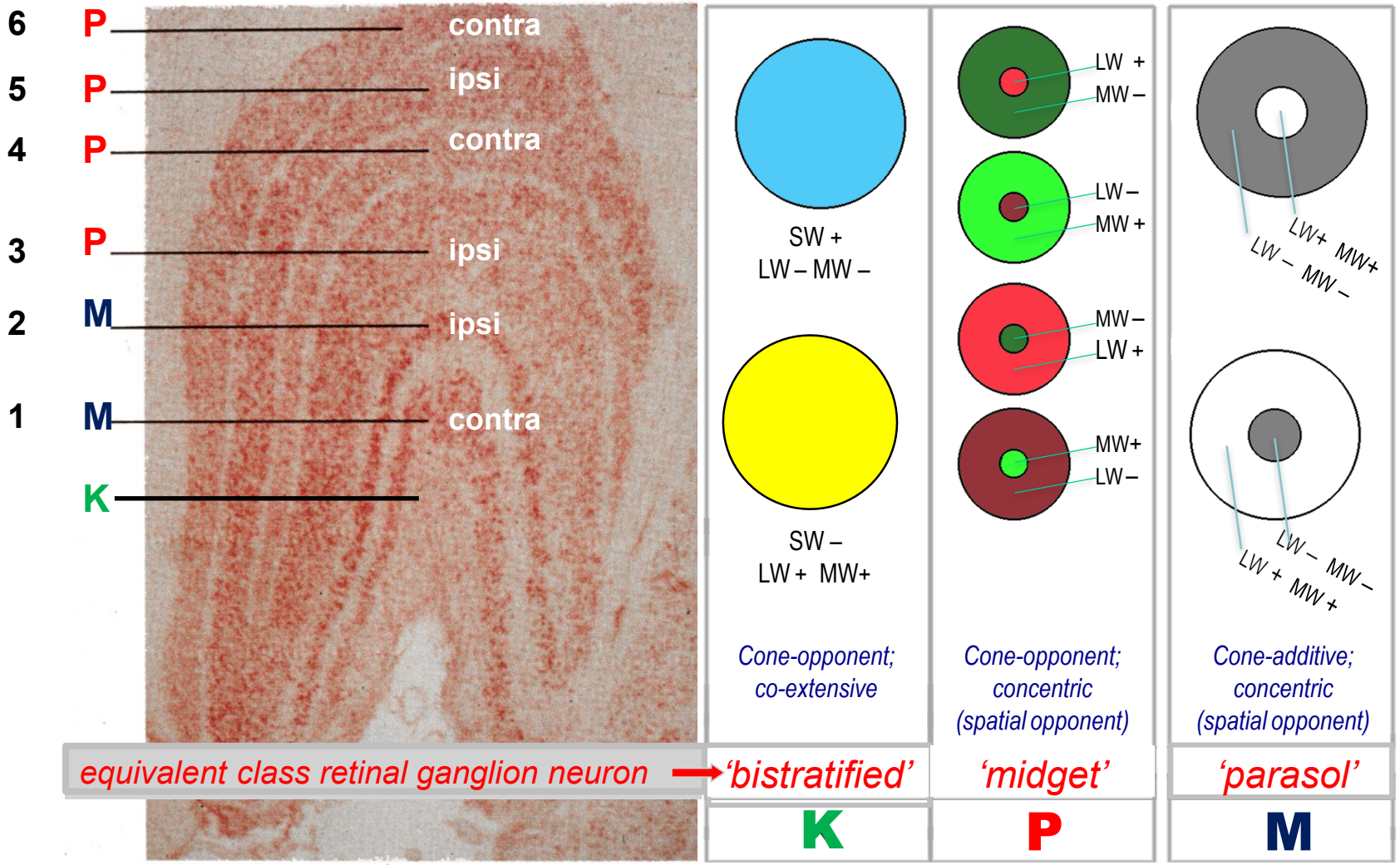
Summary


CONE OUTPUTS
PARVOCELLULAR
CORTICAL
LON
LMOFF
ON
OFF
LOFF
LMON
ON
OFF
LON + MOFF
MON + LOFF
ON
OFF
LON + MON
MOFF + LOFF
LMON
LMOFF
LMOFF
LMON
MON
LMOFF
ON
OFF
MOFF
LMON
MAGNOCELLULAR
SON
LMOFF
ON
OFF
SOFF
LMON
LON + MON
LOFF + MOFF
LMON
LMOFF
LMOFF
LMON
KONIOCELLULAR
SON + LMOFF
SON
LMOFF

Separate projections through the LGN



LGN – receptive field properties of 3 different channels

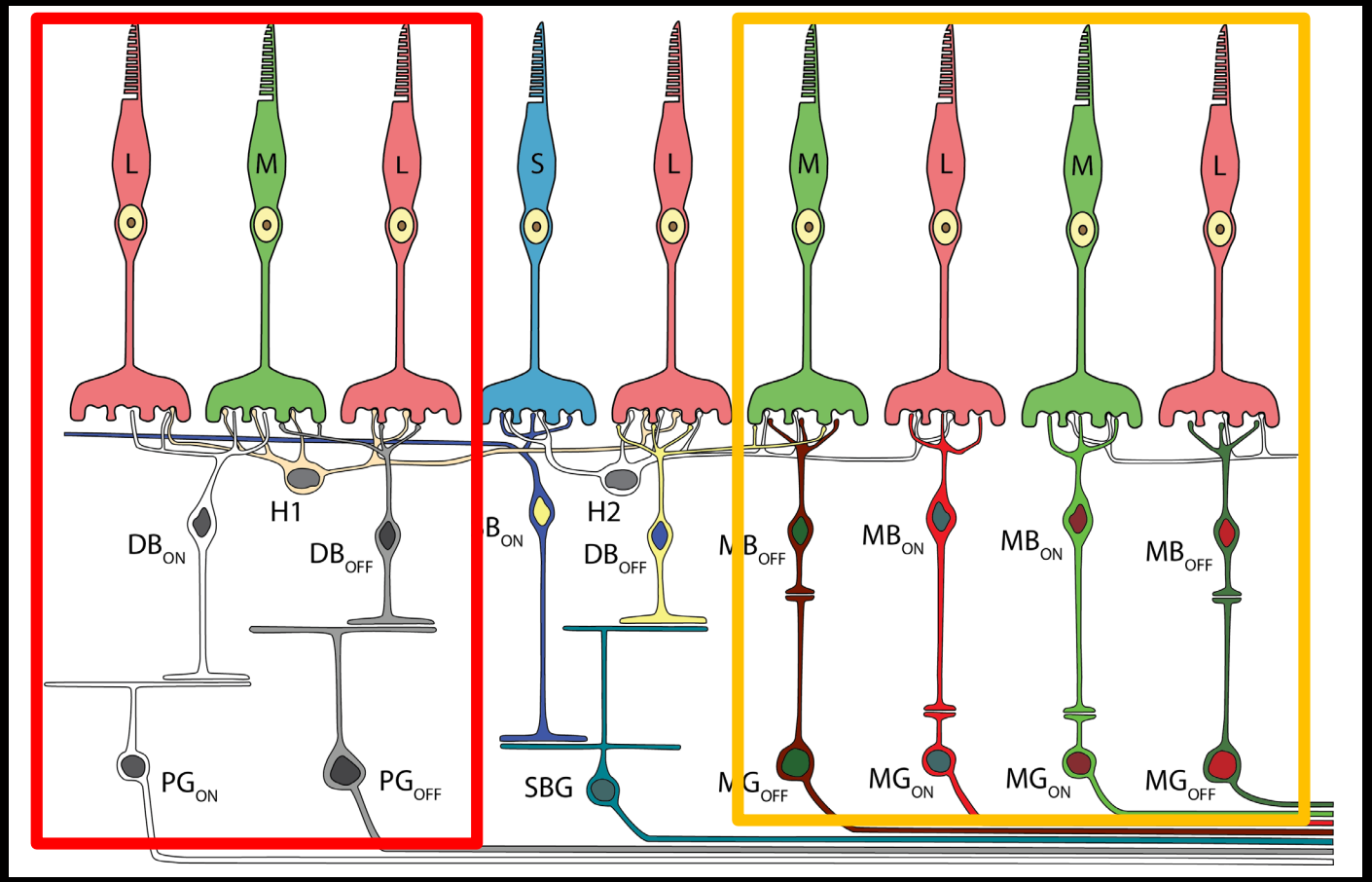


Magnocellular pathway:

- High temporal frequencies (motion/flicker)
- Low spatial frequencies
- Achromatic
- Higher contrast sensitivity

Parvocellular pathway:

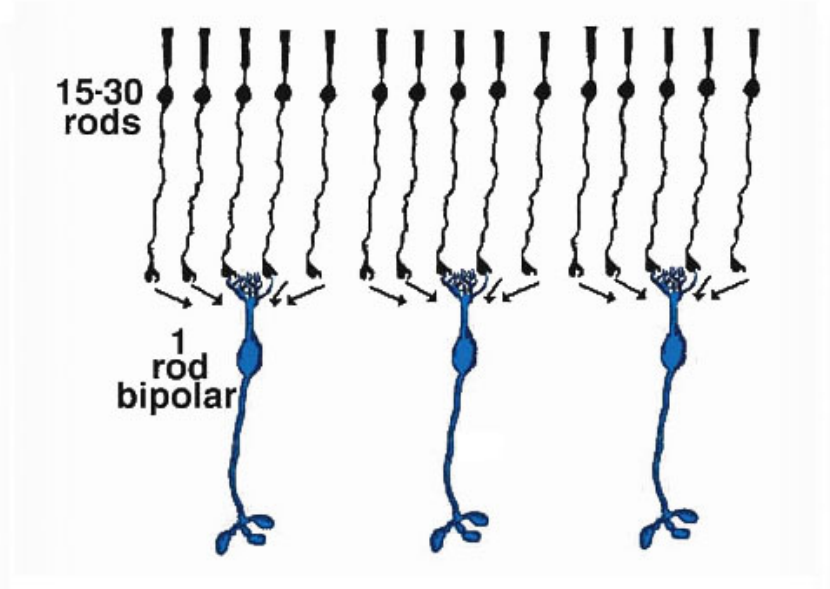
- High spatial frequencies (spatial detail)
- Low temporal frequencies
- Chromatic
- Lower contrast sensitivity



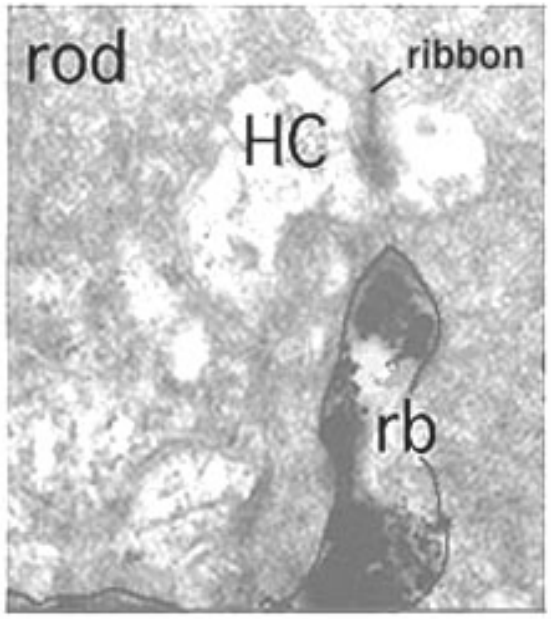
So, why do we have separate pathways from eye to brain?

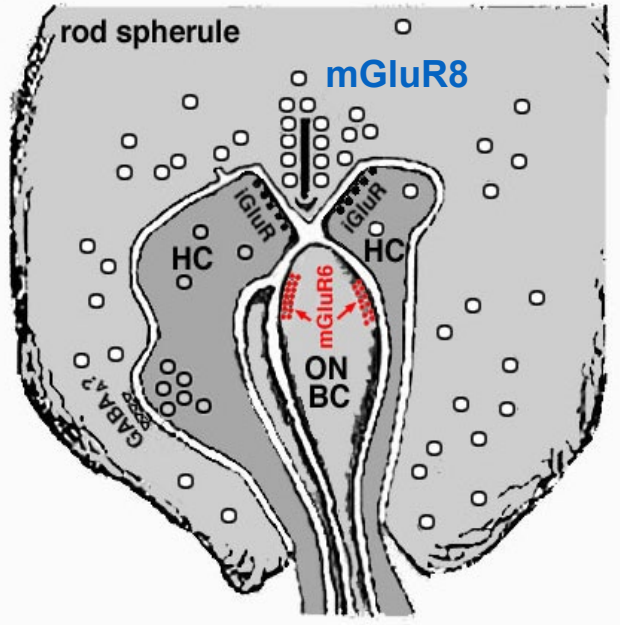
ROD PATHWAY

Rod bipolar cells



Convergence of rods onto rod bipolars



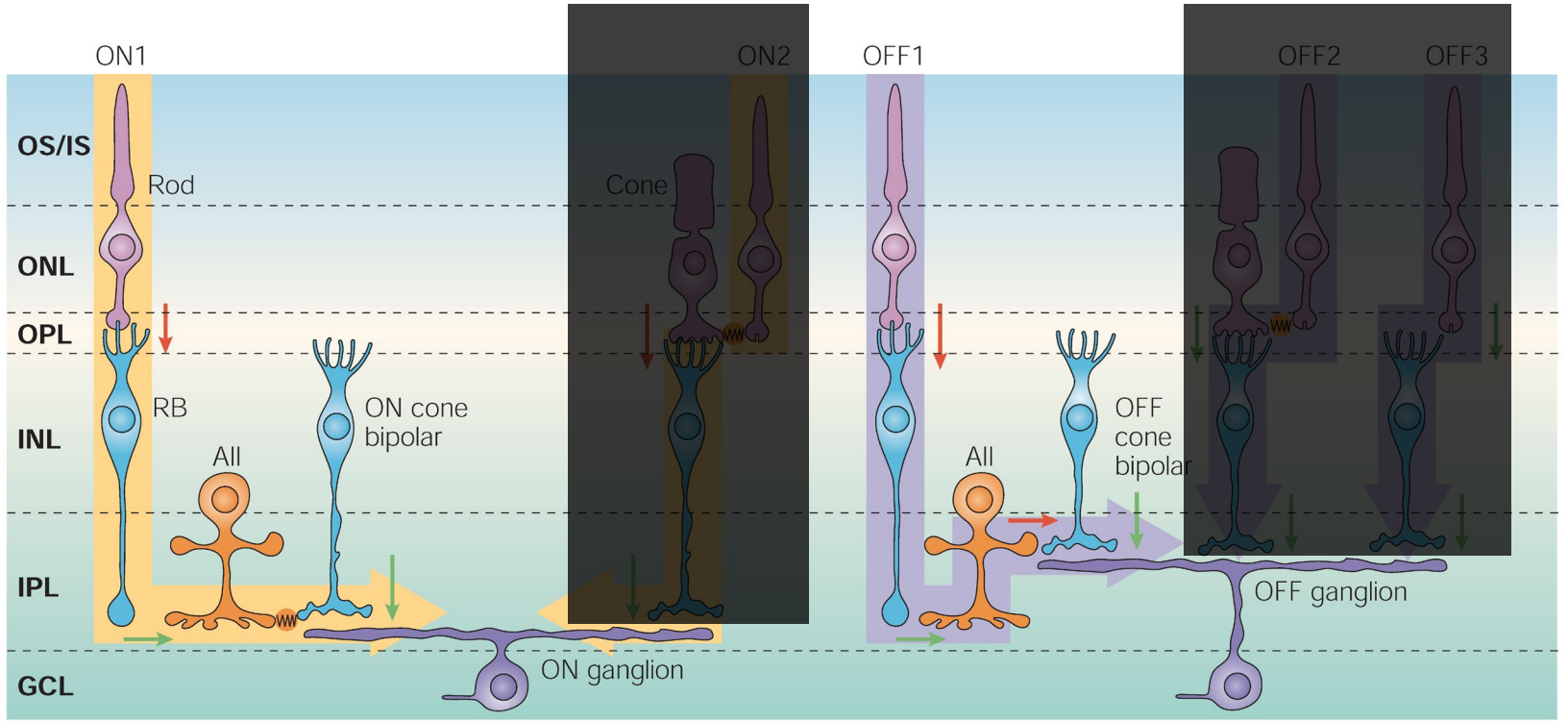


Electron micrograph and schematic of a rod spherule

BC – Bipolar Cell
HC – Horizontal Cell

Only ON cells

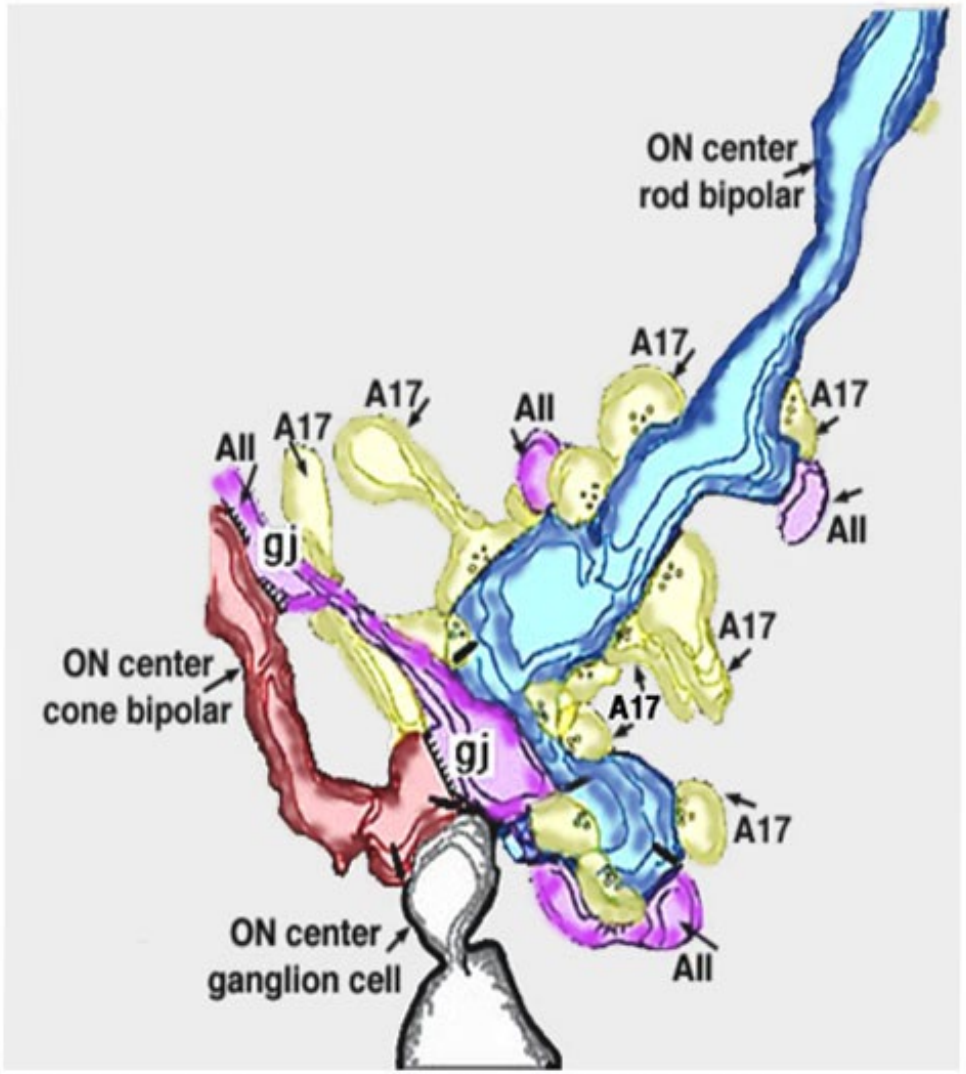
Main rod pathway depends on AII cells



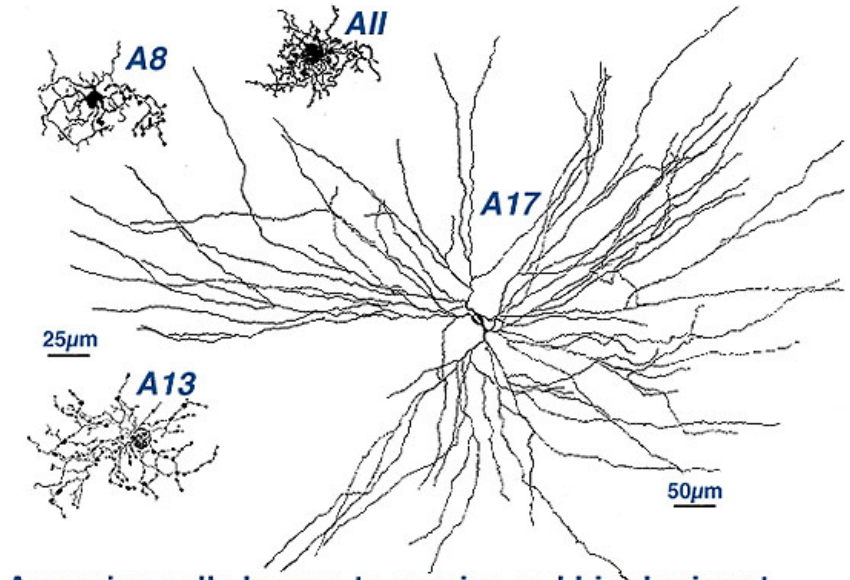
Nature Reviews Neuroscience

AII cells generates and ON and OFF copy of the rod signal

Rod pathways to RGCs

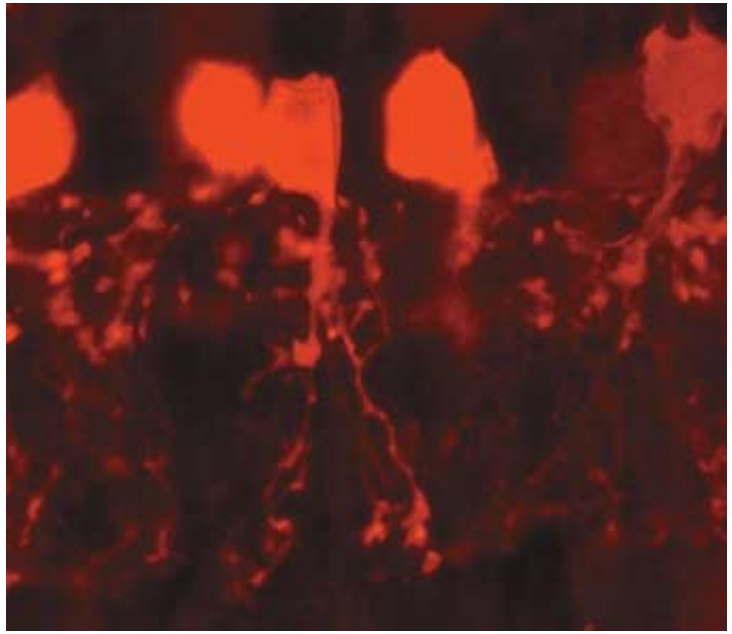


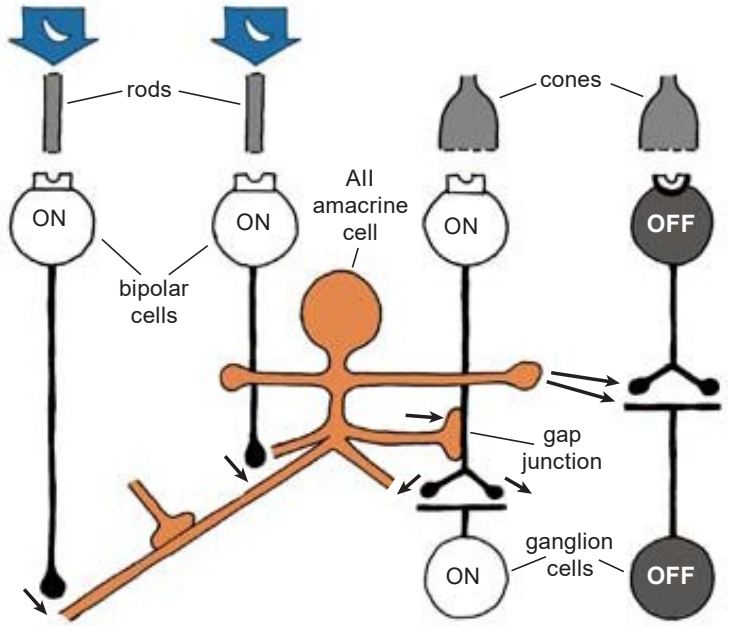
3-D reconstruction from serial electron micrographs of a rod bipolar axon terminal (blue) synapsing upon AII amacrine cell (lilac) and A17 amacrine cell (yellow) profiles. A17 processes make reciprocal synapses. AII amacrine cells make gap junctions on ON center cone bipolar axons.



Amacrine cells known to receive rod bipolar input

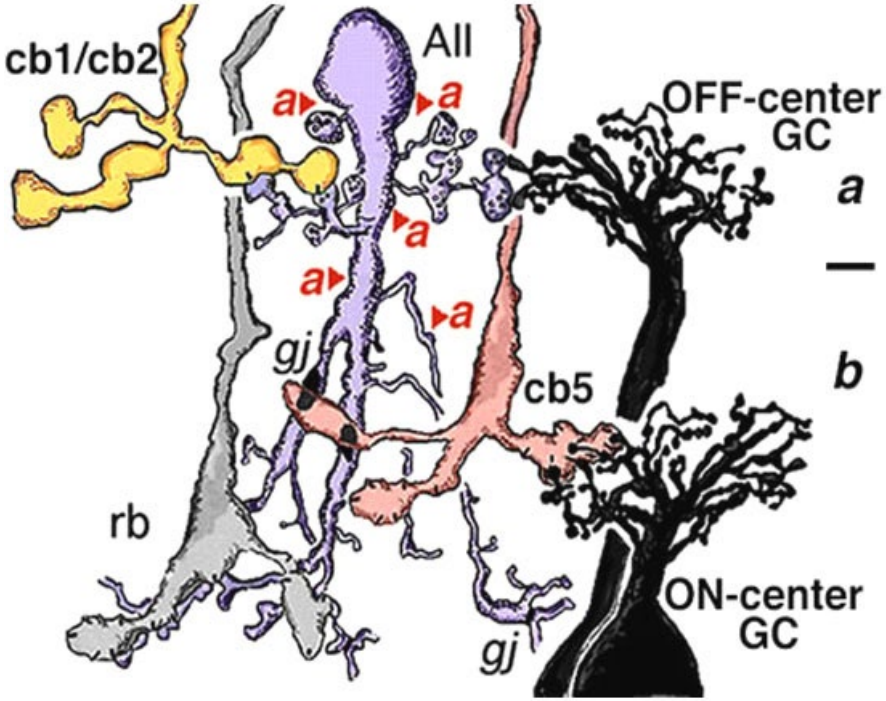
AII amacrine cell





Rod bipolar cells communicate with ganglion cells indirectly using AII amacrine cells. The AII amacrine cells increase the signal under dim lighting conditions by coupling electrically to ON cone bipolar cells (gap junctions) and signalling chemically to OFF cone bipolar cells.

AII cell function



Drawing to show the circuitry of the AII amacrine cell with pre and post synaptic neurons. Sublaminas a and b are indicated.

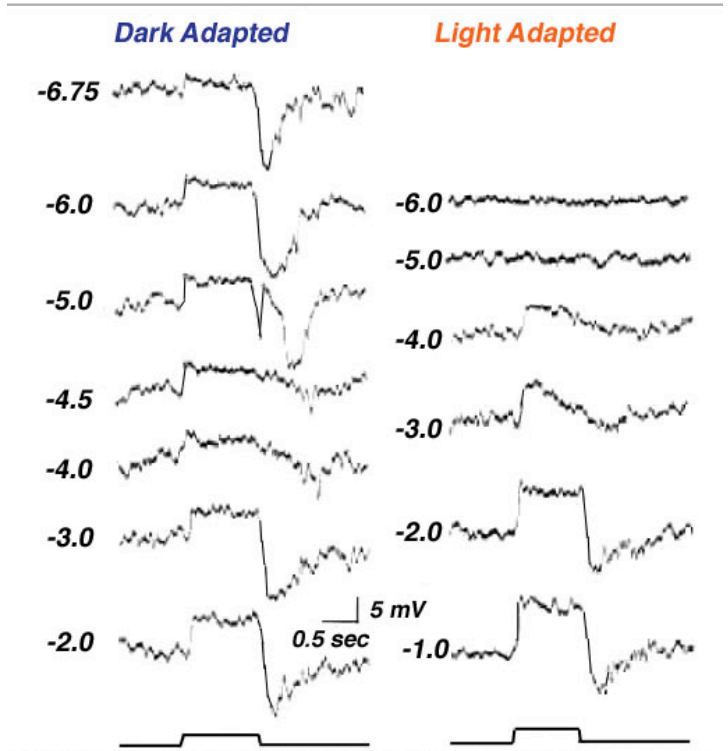
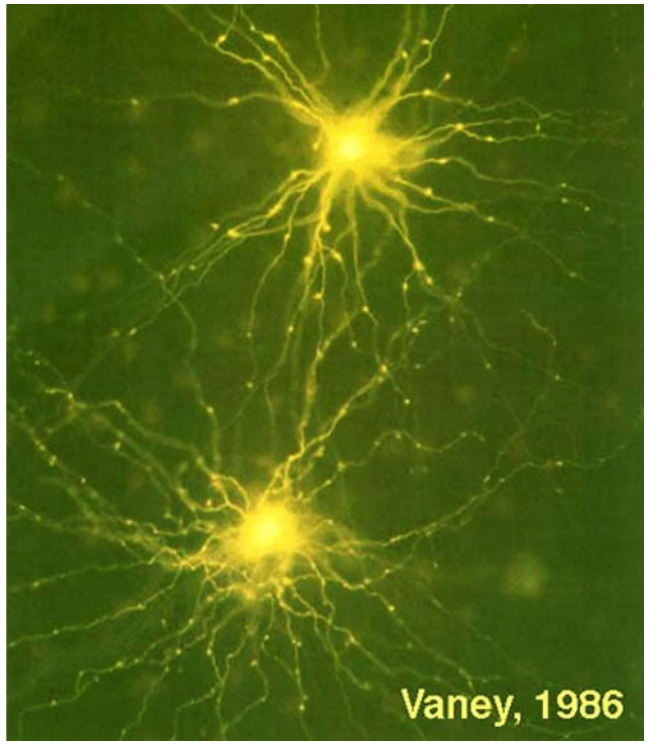
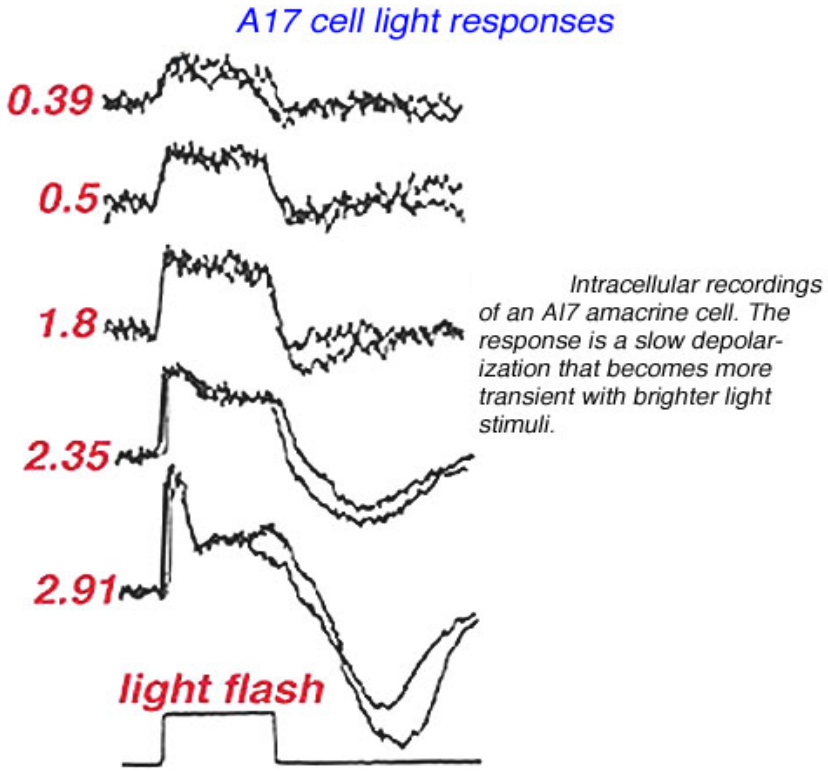


Fig. 8a. In dark-adapted conditions (A, left) an ON-center response was recorded at all light intensities tested (threshold = log -6.75). The amplitude of the ON-center response increased with increasing light intensity until saturation at ~ log -4.5 to log -4.0. An ON-center response was also recorded from light-adapted cells (A, right), though the threshold under these conditions was higher (~ log -4.0). The light-adapted ON-center response also increased with increasing light intensity, but reached saturation (log -1.0 to 0.0) at a higher light intensity than dark-adapted AII's.

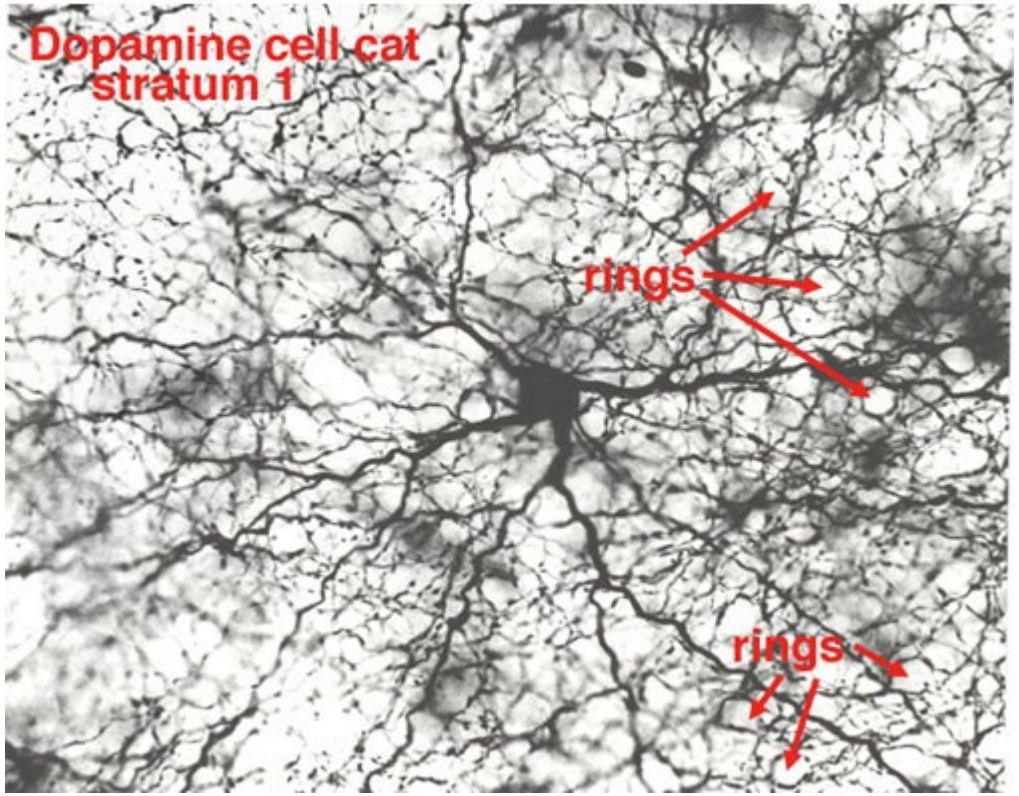
Amacrine Cell Function (A17)





Wide-field *diffuse* amacrine. Large coverage allows it to collect scotopic rod signals from several thousand rod bipolar axons. Its high sensitivity to scotopic conditions (rod driven light intensities) suggests that this amacrine plays a role in converging rod signals from huge areas of retina and to amplify them at very low light intensities (Webvision).

Dopamine containing (A18) cells



Immunostaining for tyrosine hydroxylase. A18 Amacrine cells have overlapping dendrites that form into rings.

Wide-field diffuse amacrine cells that are dopaminergic. Dopamine affects AII coupling.

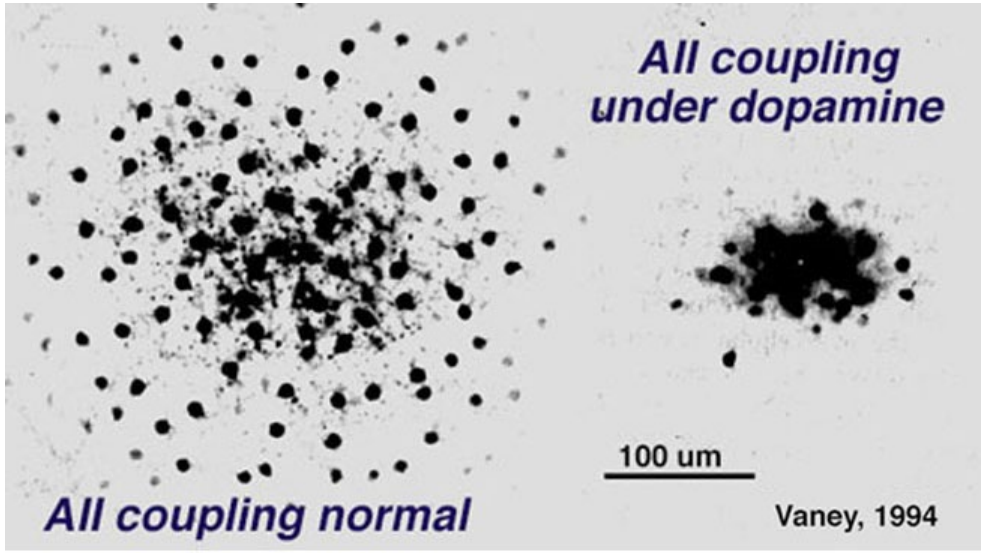
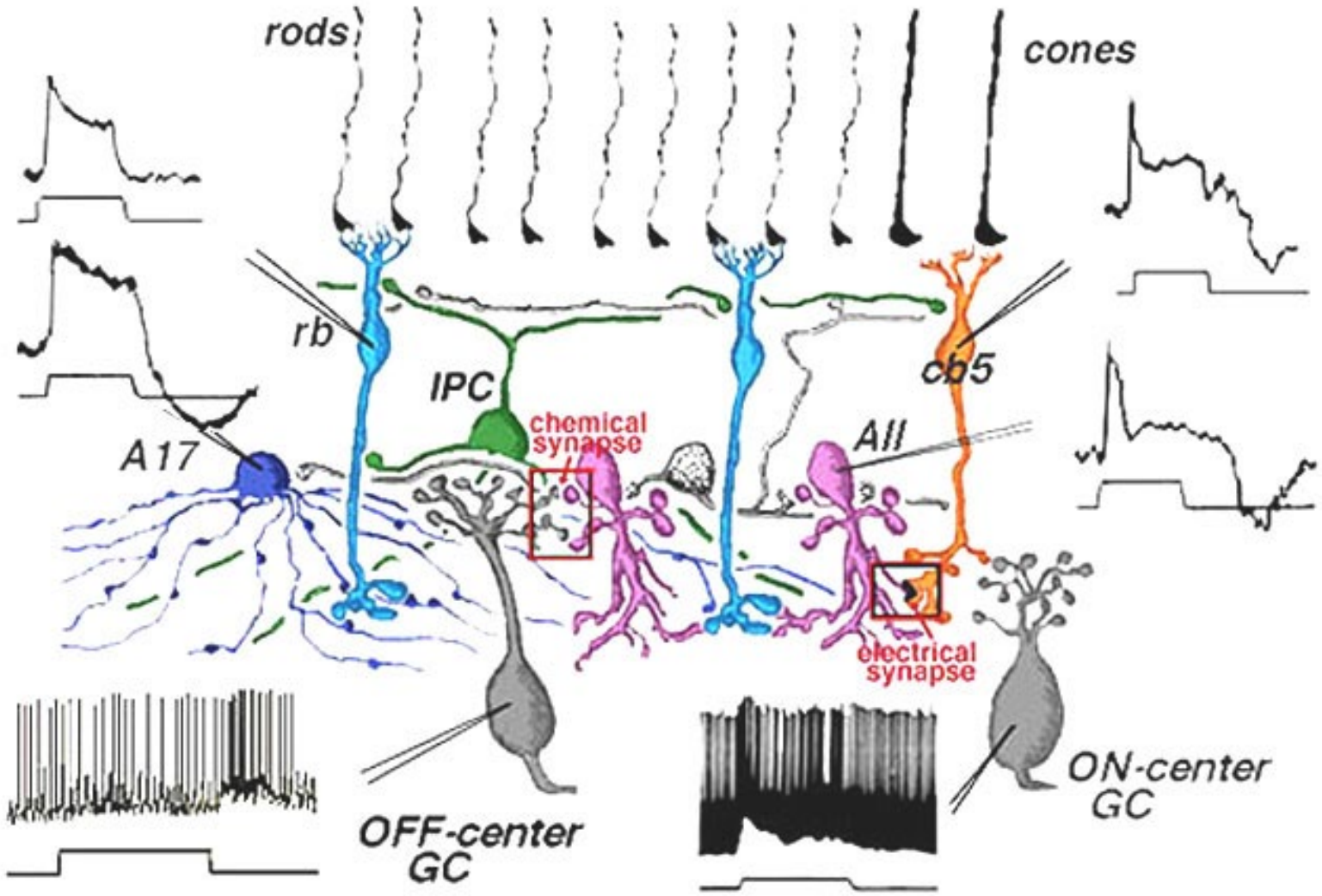
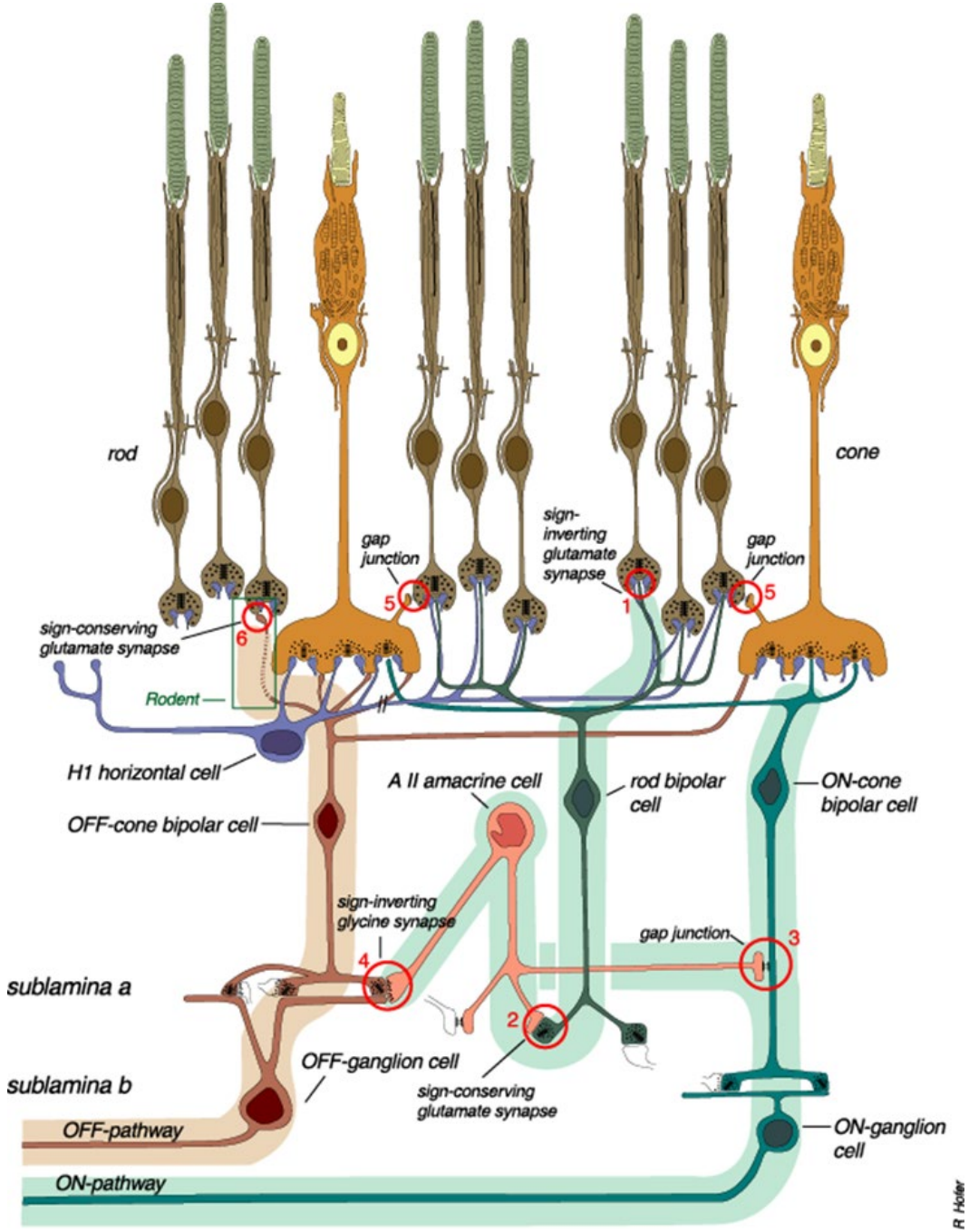


Fig. 34. Effects of dopamine on AII amacrine cell coupling. AII cells are normally coupled extensively, but under the influence of dopamine release, AII cells uncouple.

Summary of main rod-driven pathways

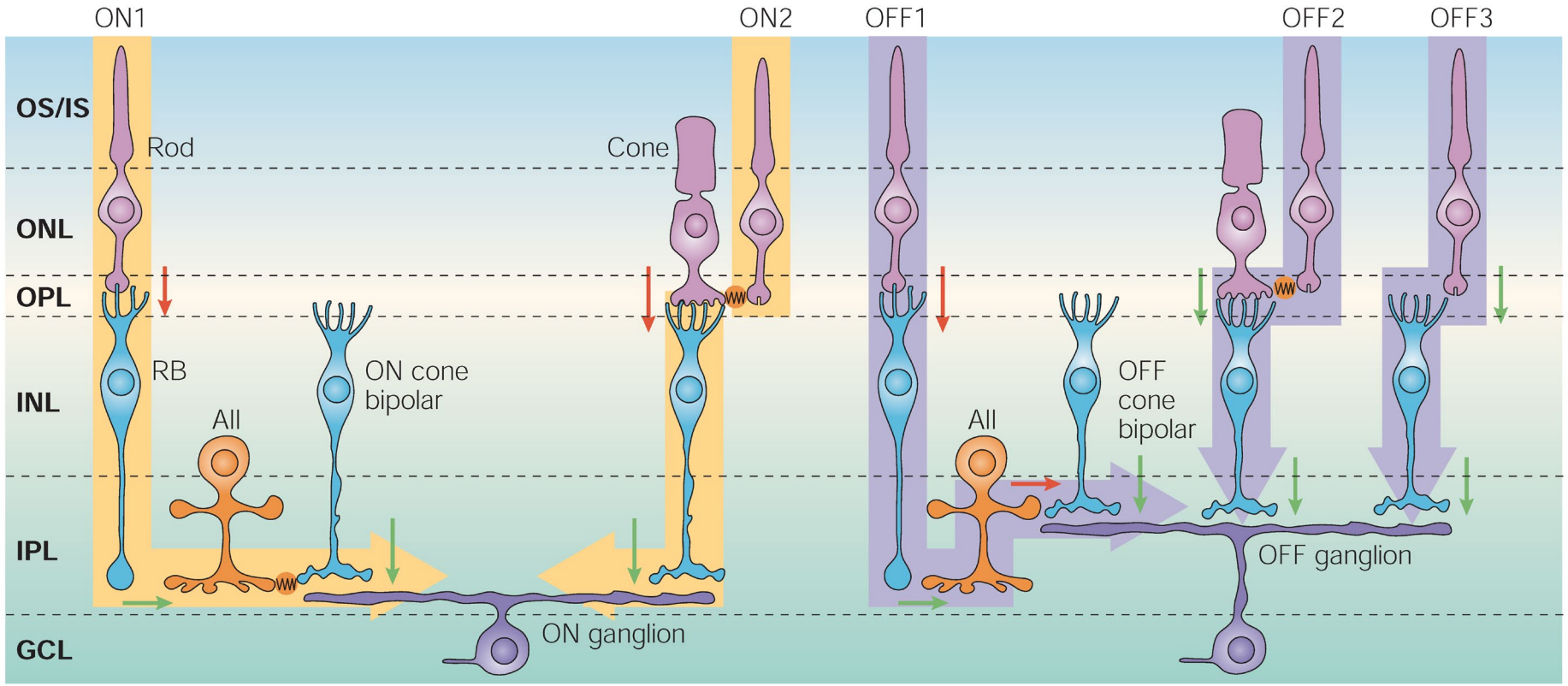


Rod pathways



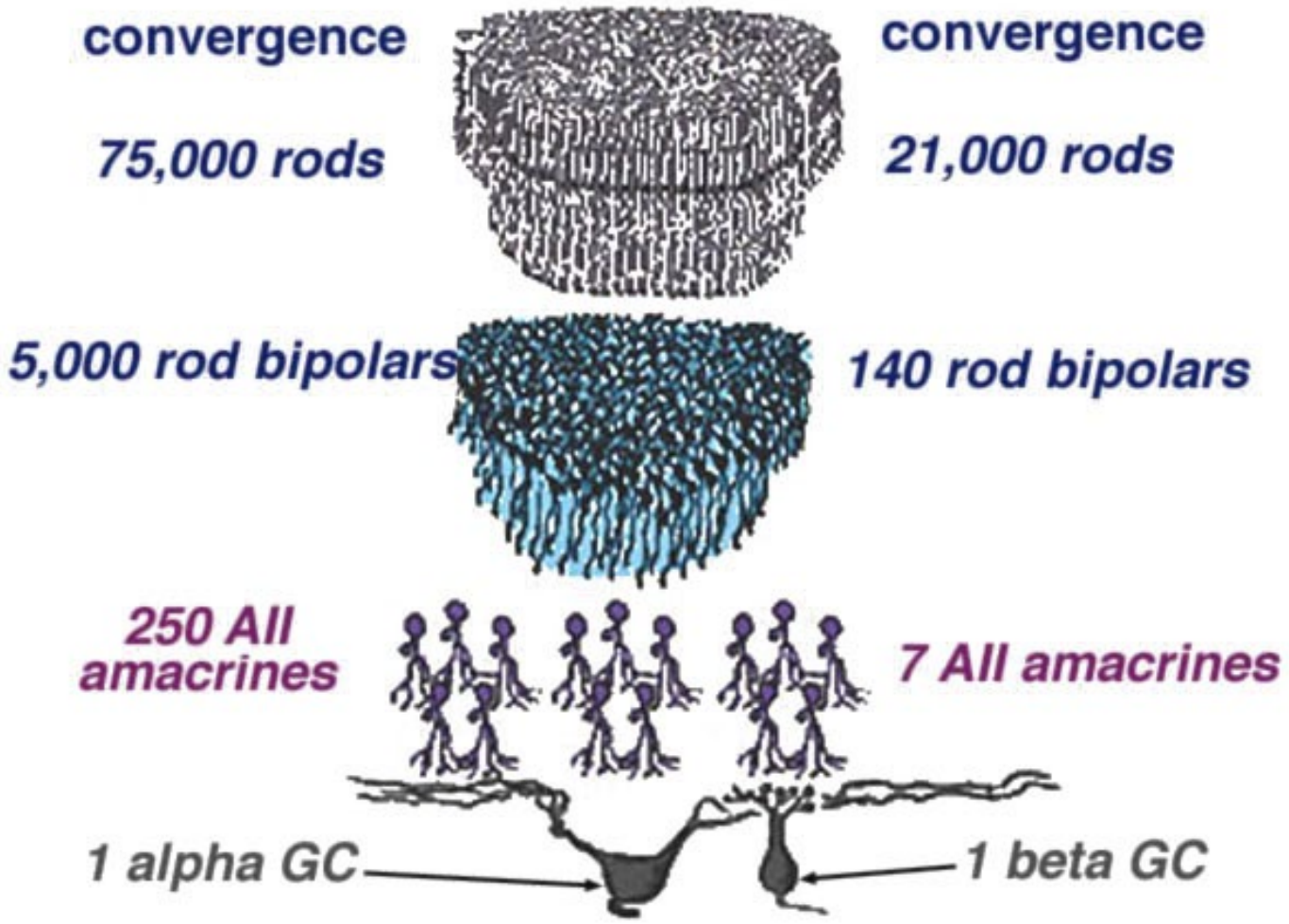
AII rod pathways

AII cells generates and ON and OFF copy of the rod signal



Nature Reviews Neuroscience

Convergence of the rod pathway



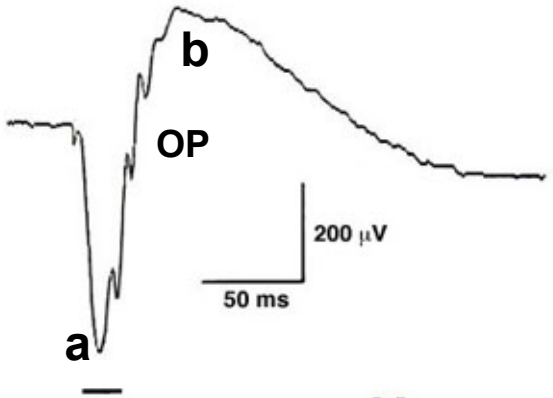
Cat retina

ELECTRORETINOGRAM (ERG)

Electroretinogram

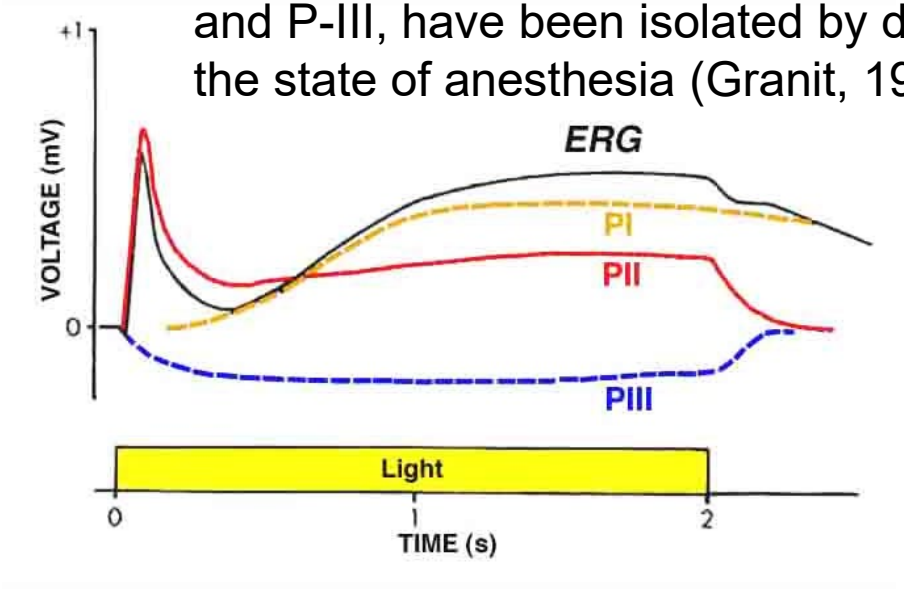
ERG responses of human, in addition to those recorded from other vertebrate species, are characterized by the basic features of a negative a-wave followed by a positive b-wave.

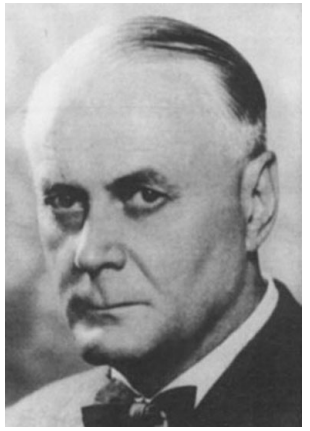
Responses to brief flashes in dark adapted state. Longer stimuli can also evoke a c-wave.



Human

The ERG of a cat in response to a 2 sec light stimulus. The components, P-I, P-II and P-III, have been isolated by deepening the state of anesthesia (Granit, 1933).

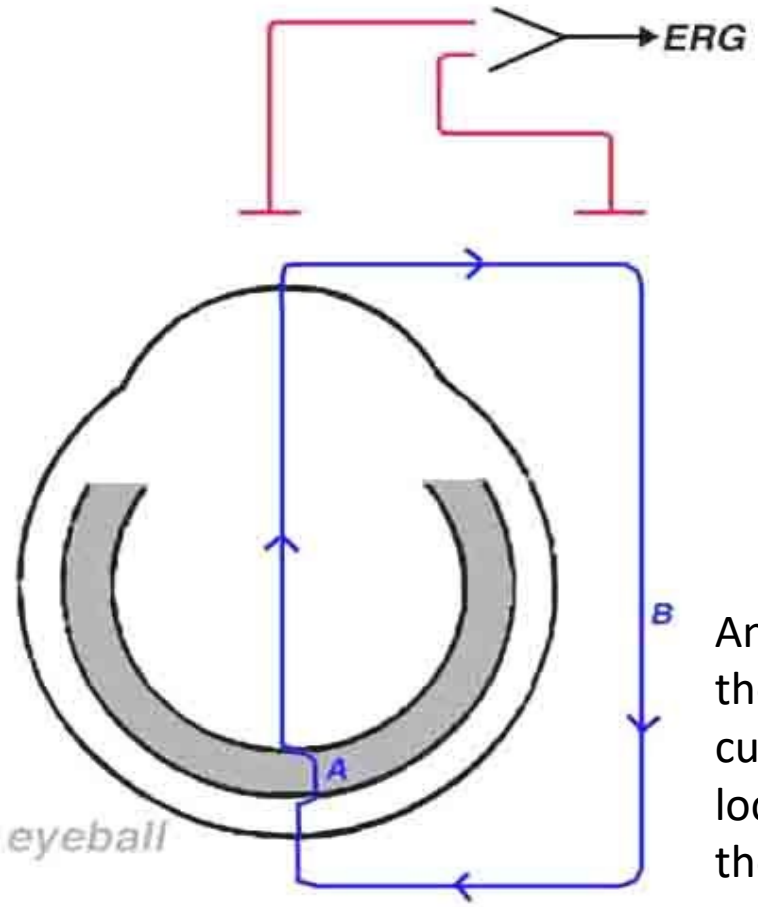


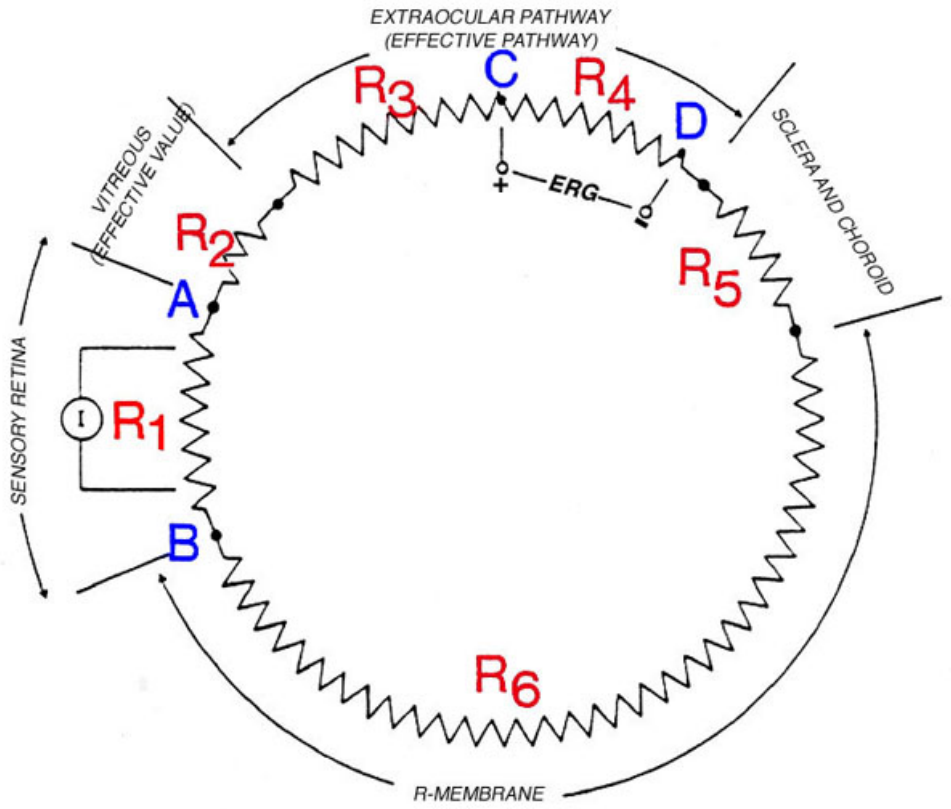


Ragnar Granit, winner of the Nobel Prize for Physiology and Medicine in 1954

Recording the ERG

A schematic representation of the extracellular currents that are formed following light stimulation. Pathway A represents local currents within the retina, while pathway B shows the currents leaving the retina through the vitreous and the cornea and returning to the retina through the choroid and the pigment epithelium.



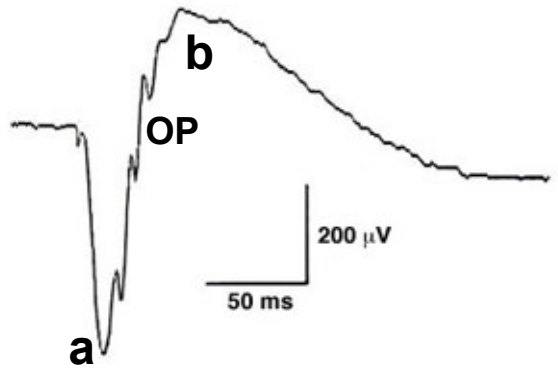


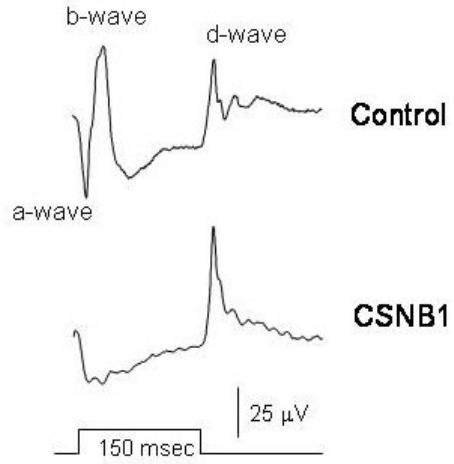
An electrical scheme of the resistances through which currents IA and IB flow when the retina is stimulated with light. The current source I, represents the electrical current that is generated in the retina in response to a light stimulus. Pathway A is the local intra-retinal route of current flow and pathway B is the remote route going from the retina and through the vitreous, lens, cornea, extra-ocular tissues and back to the retina through the sclera, choroid and pigment epithelium.

Cellular Origins of the ERG

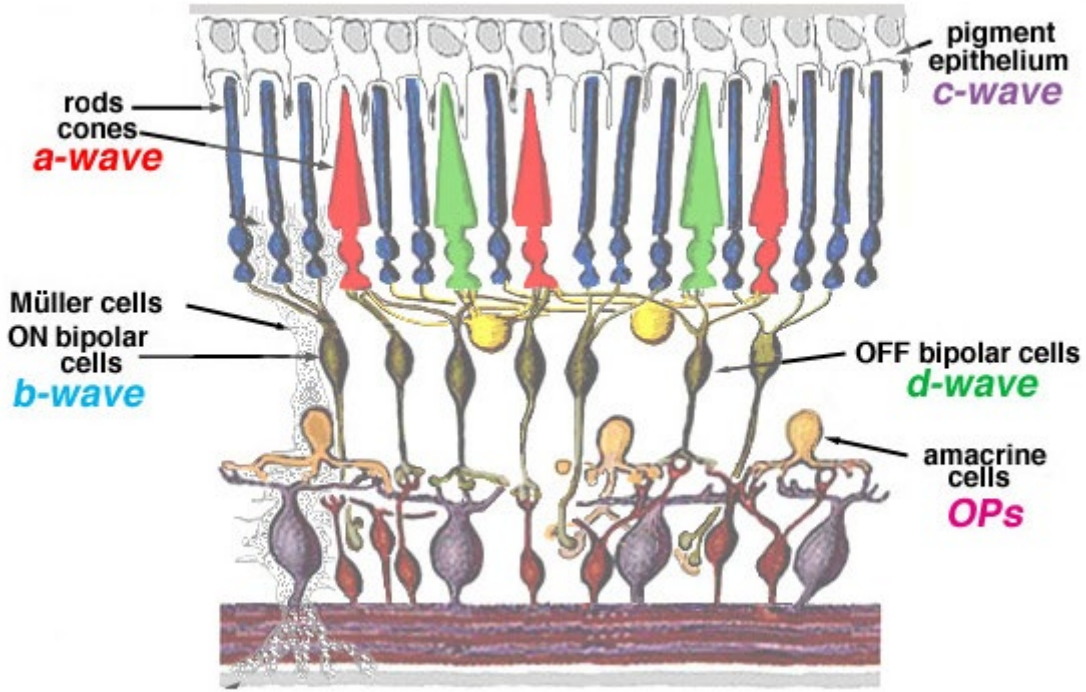
ERG components

- **a-wave**: photoreceptors
- **b-wave**: ON bipolars (+Mueller Cells)
- **c-wave**: pigment epithelium
- **d-wave**: OFF bipolars
- **OP** (oscillatory potentials): amacrine cells

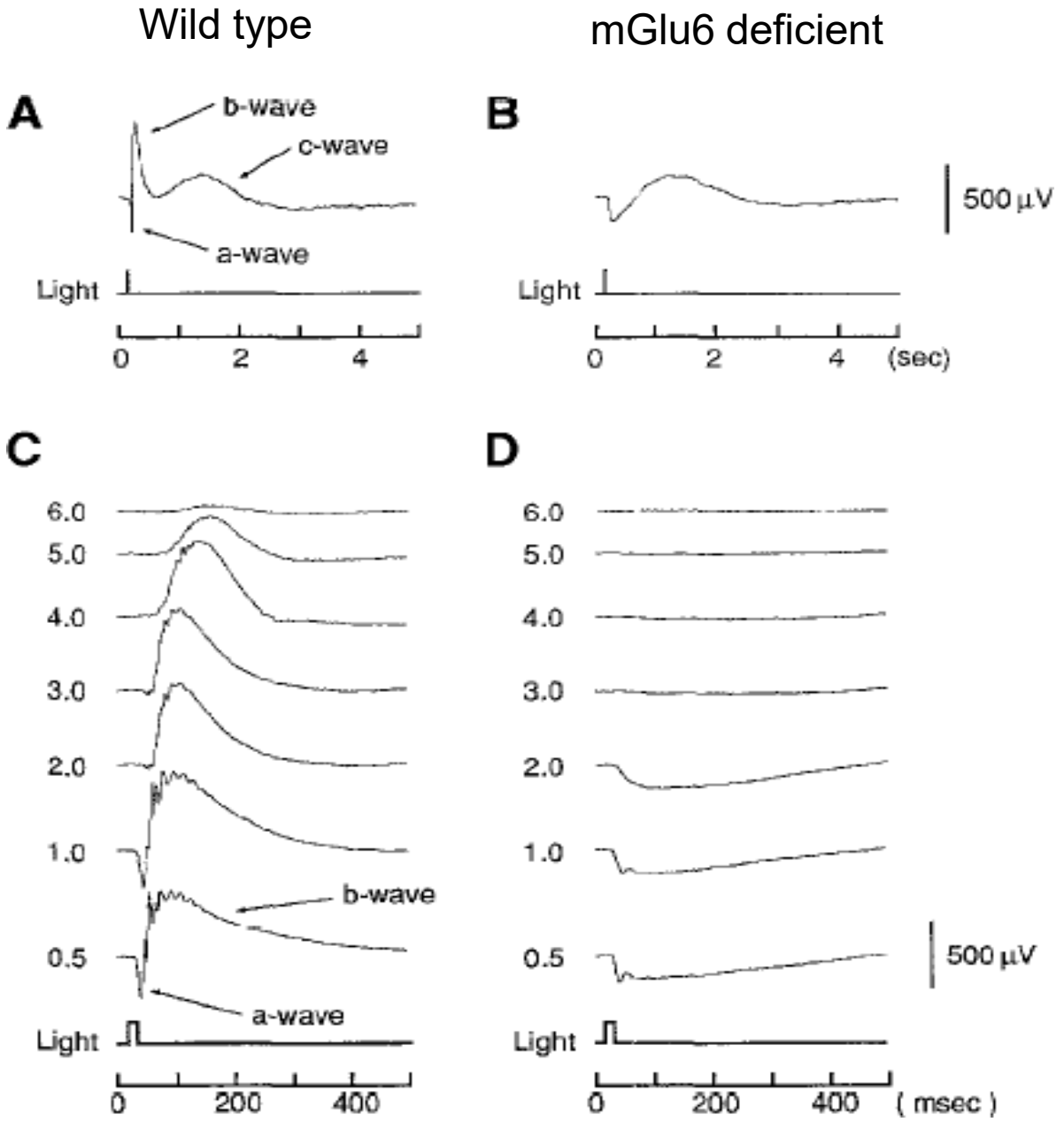




Khan et al., 2004



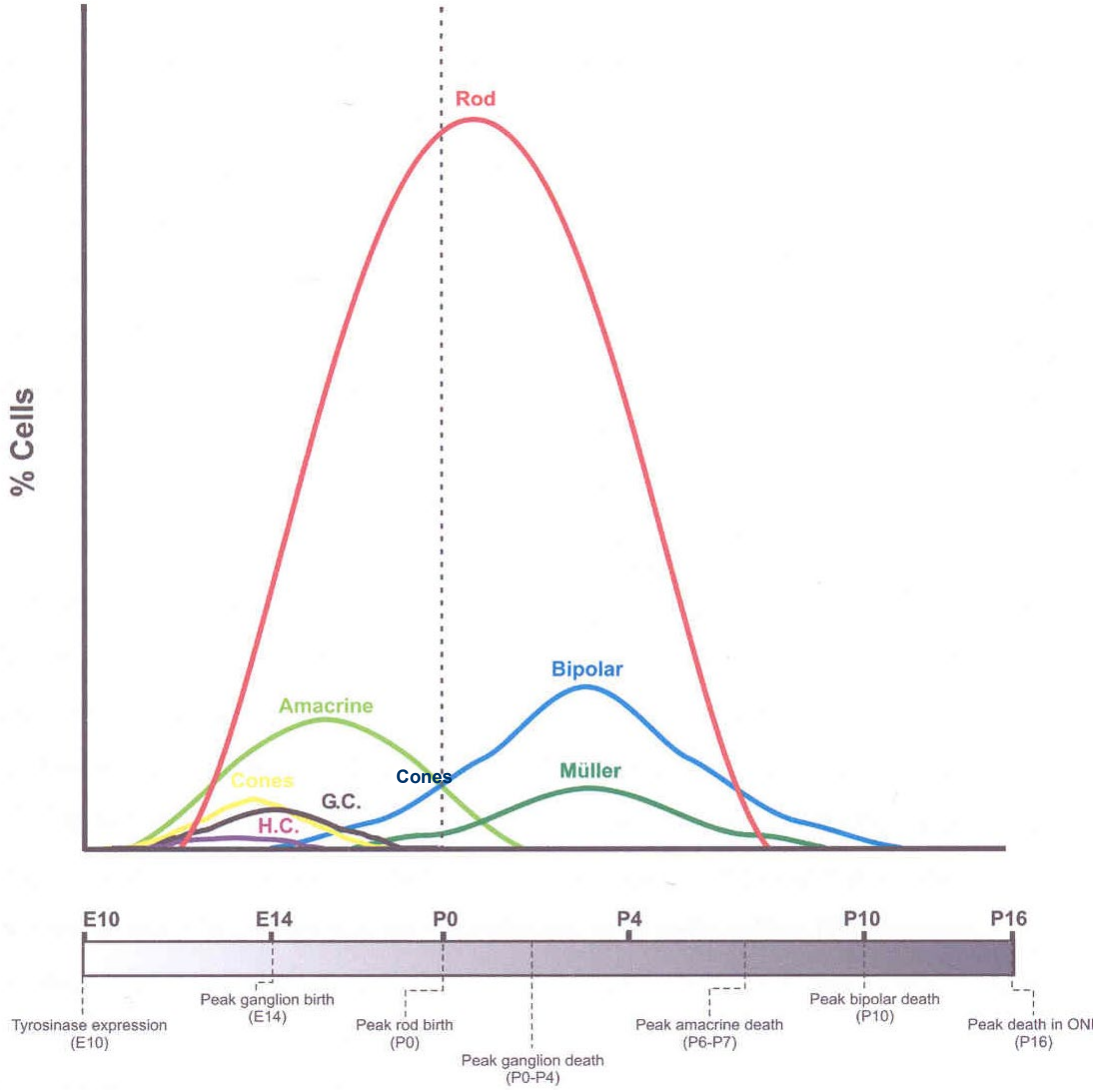
ERG in mGlu6 deficient mice

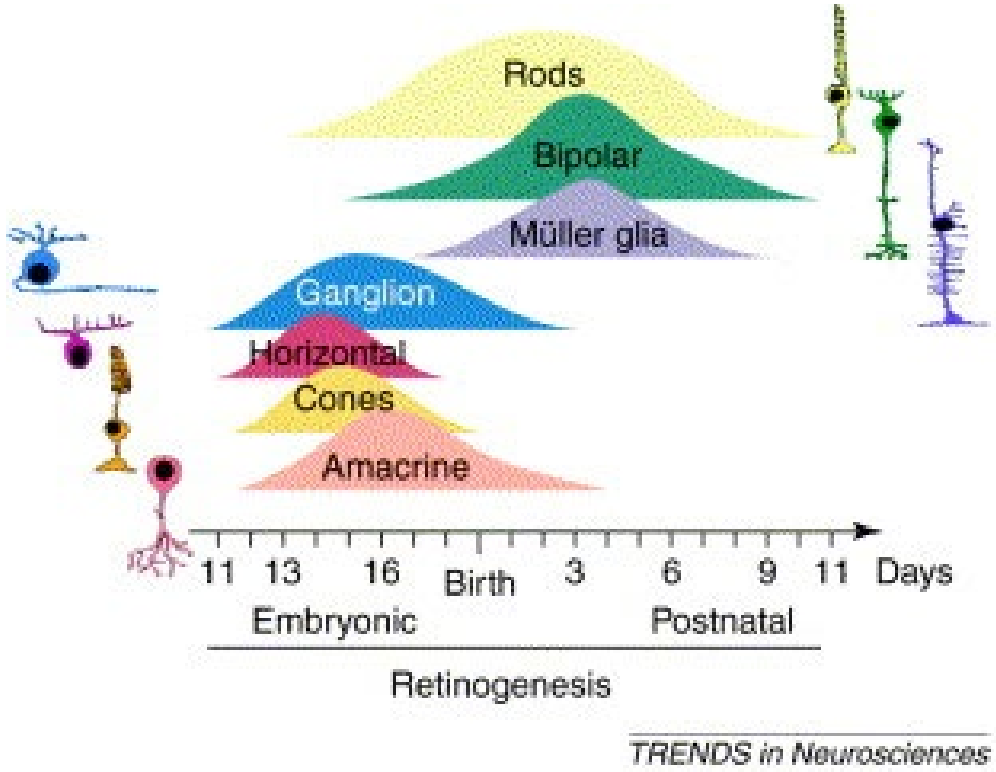


Masu et.al. (1995) *Cell* 80[5], 757-765.

RETINAL DEVELOPMENT

Retinal neurogenesis

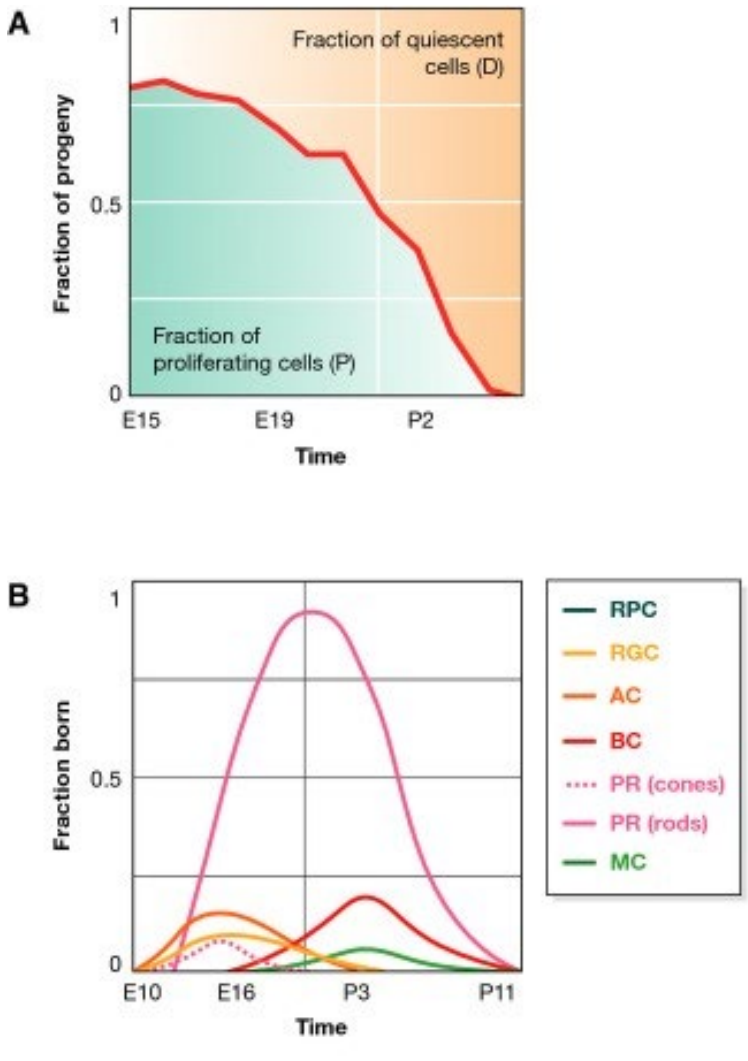




Mouse

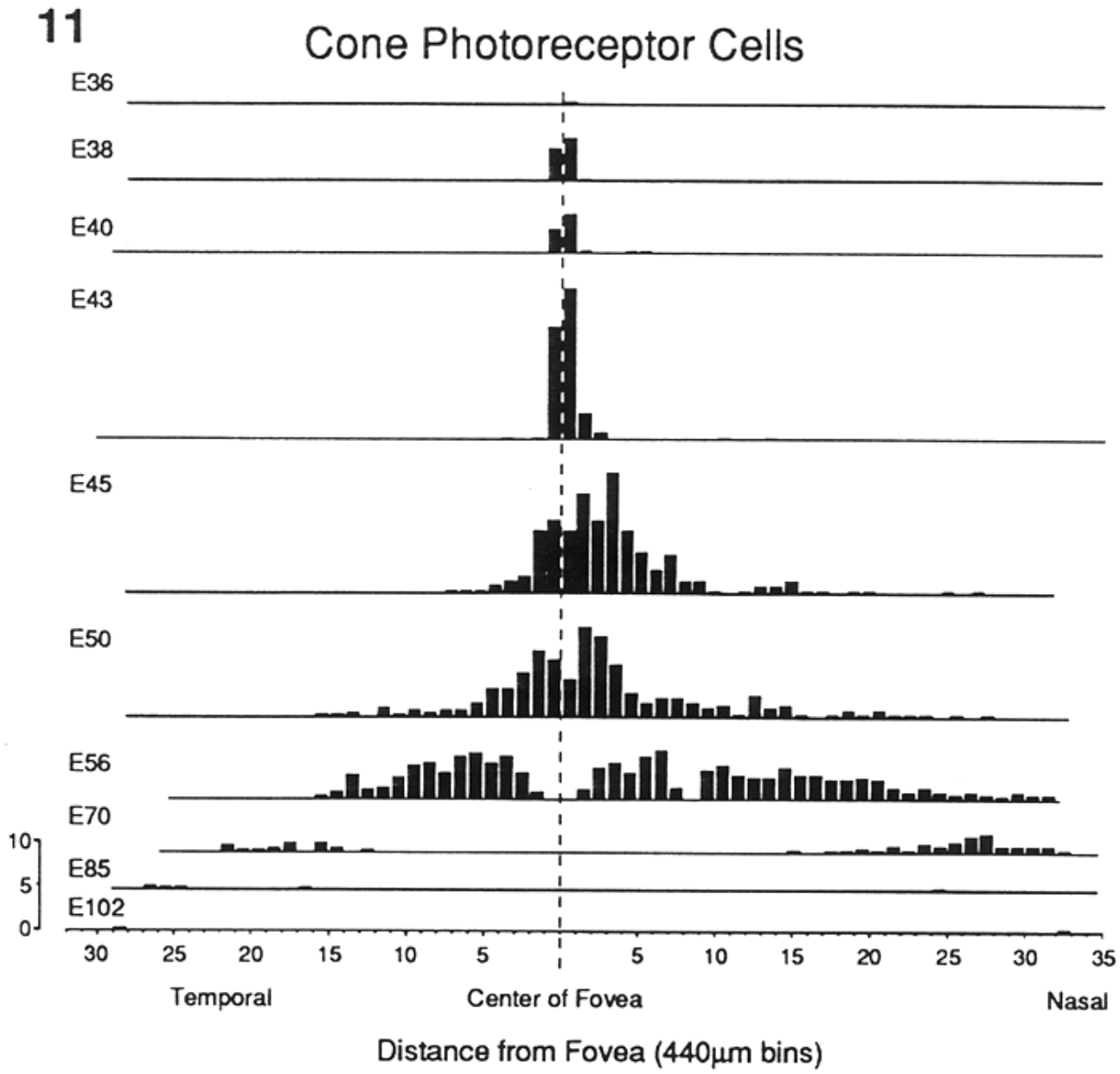
Retinal neurogenesis

(A) During the development of the vertebrate retina, there is an initial phase where most of the divisions lead to progenitor amplification, which then slows down. When individual cells stop dividing, they differentiate and this leads to a link between the different cell types and the growth of the tissue (Livesey & Cepko, 2001).
(B) Throughout retinal development, a reproducible sequence of overlapping temporal windows of specific fate adoption by differentiating cells is established. An early differentiating cell can become a retinal ganglion cell (RGC), a horizontal cell (HC), a rod photoreceptor (PR) or an amacrine cell (AC), whereas if it differentiates later, it can become a bipolar cell (BC), a Müller cell (MC) or a cone PR; that is, there appears to be an overlap between these windows of opportunities (adapted from Cepko et al, 1996).
(C) Recent accurate single-cell tracing assays have unveiled complex lineage compositions in the zebrafish retina development.

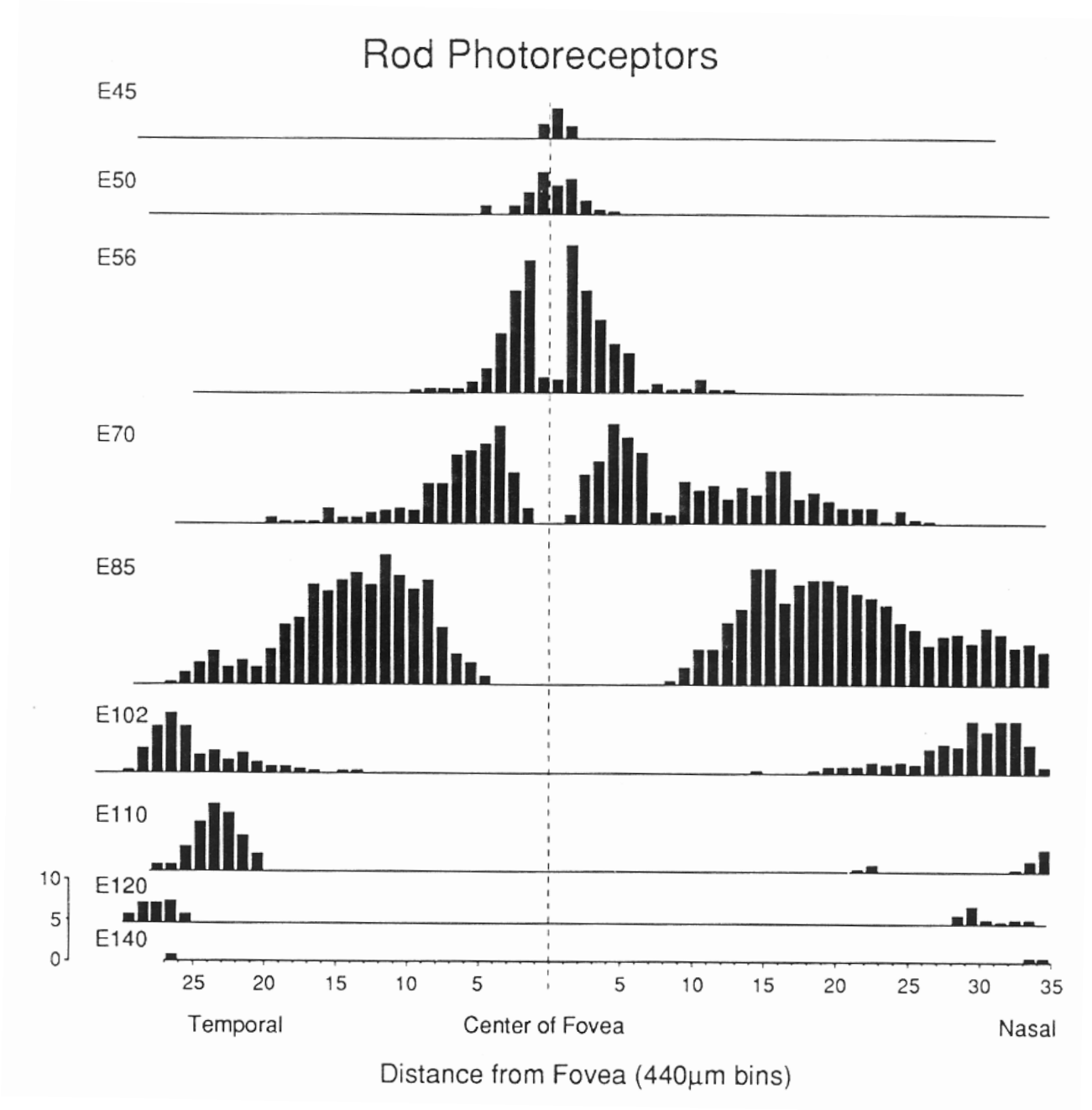


Pau Rué and Alfonso Martinez Arias

Cone neurogenesis



Rod neurogenesis



Circuit assembly

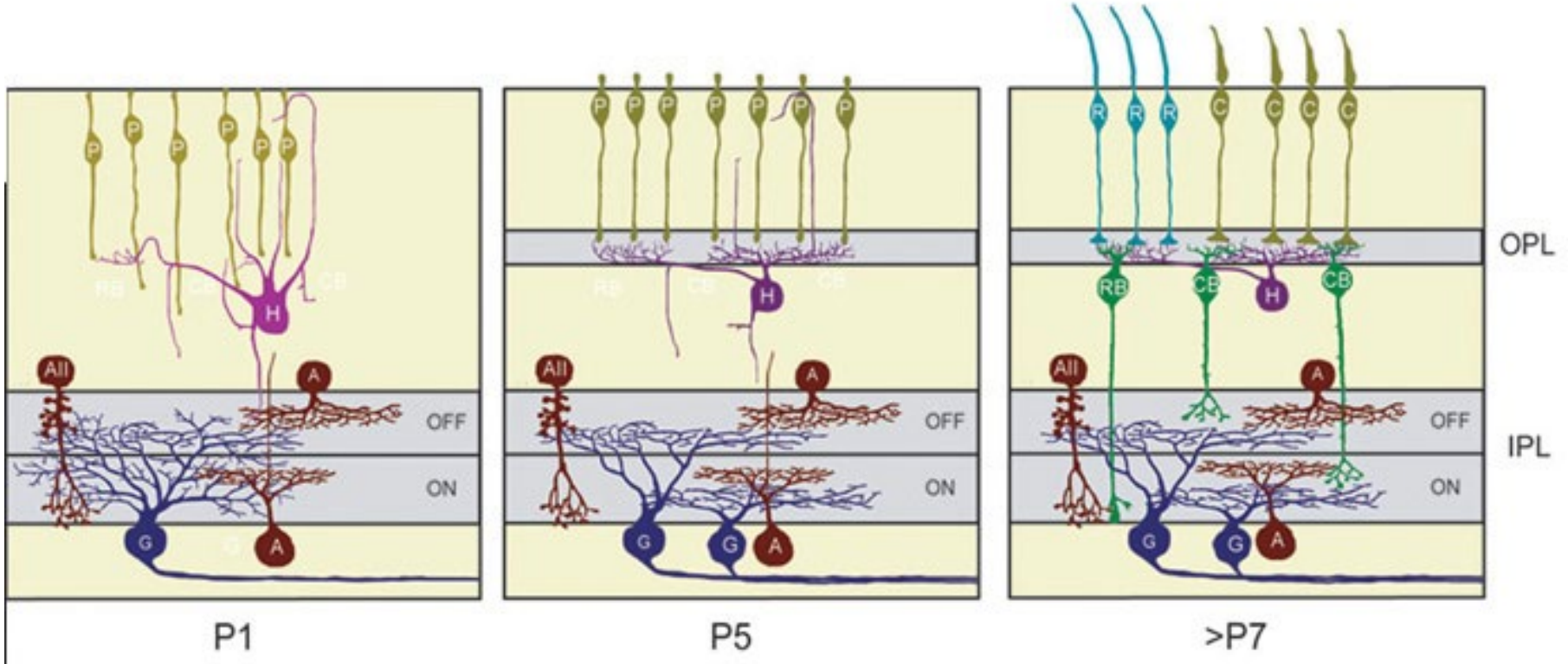


Fig. 2. Schematic showing the sequence of circuit assembly in the vertebrate retina, illustrated for the mouse. P = postnatal day. IPL= inner plexiform layer; OPL= outer plexiform layer.

Circuit assembly

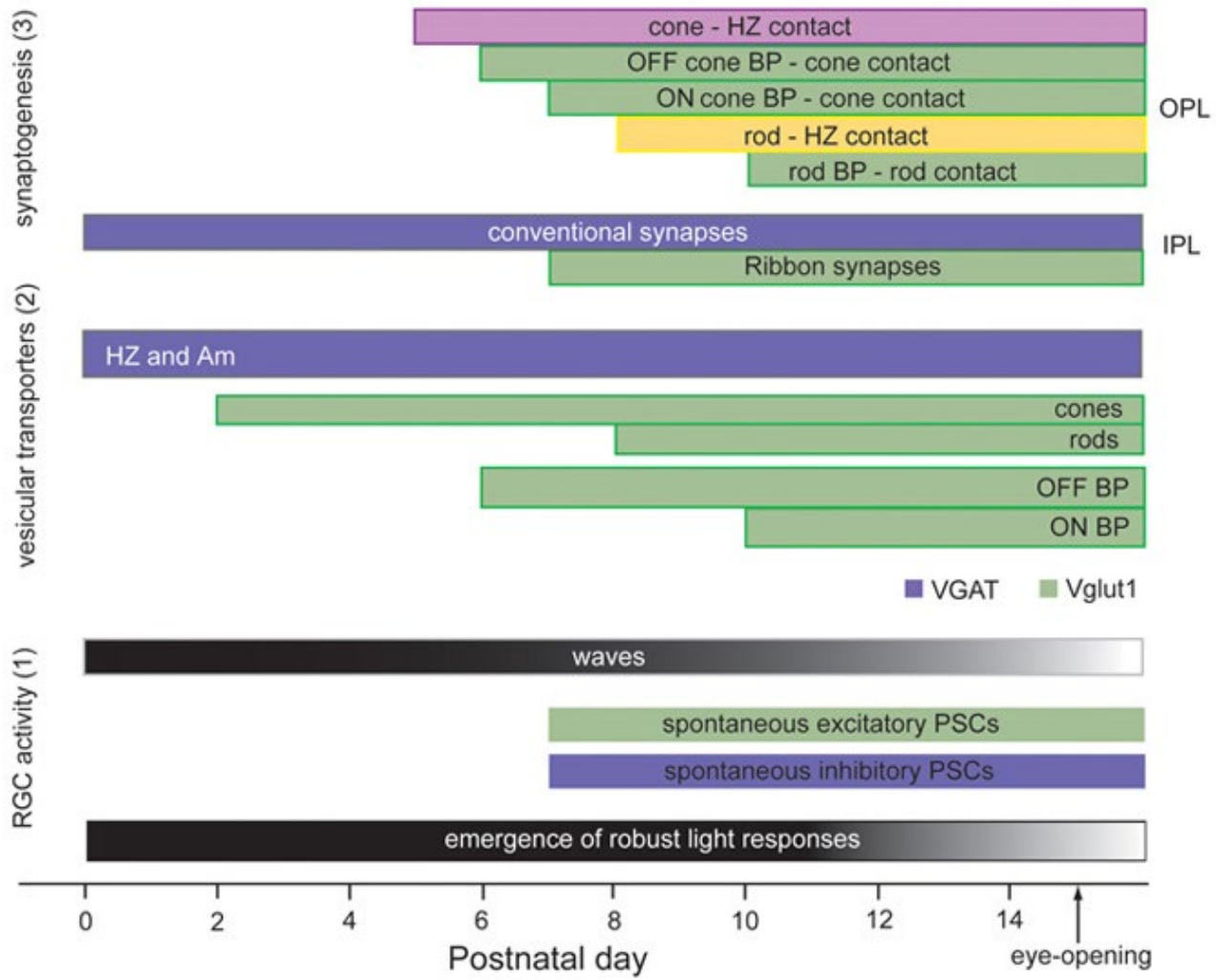
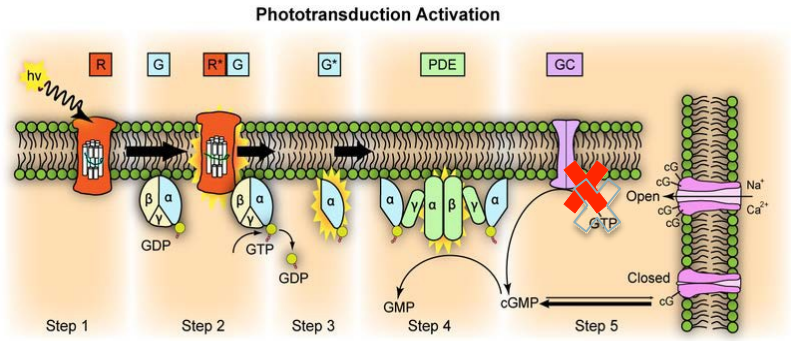


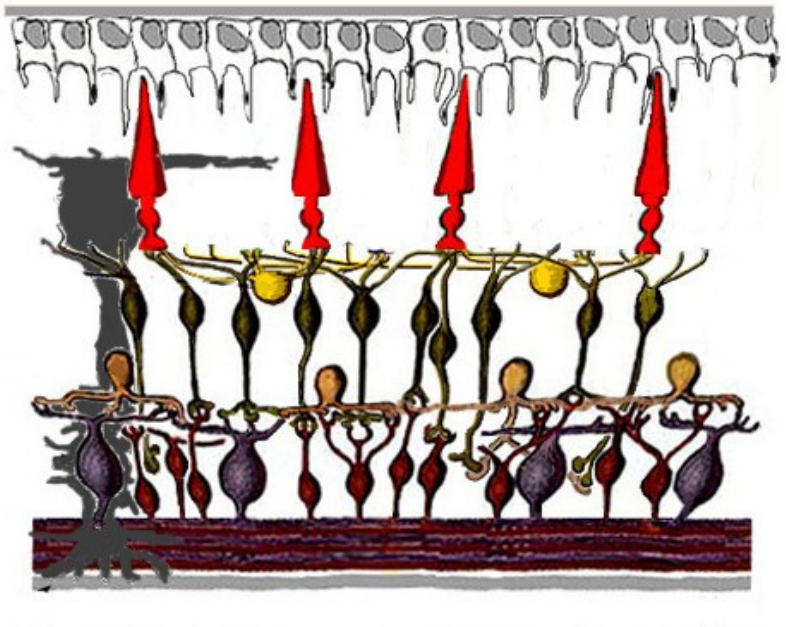
Fig. 18. Summary of key physiological events during circuit assembly and maturation in the mouse retina. (1) Wong, 1999, Johnson et al., 2003; (2) Johnson et al., 2003; Sherry et al., 2003; (3) Olney, 1968; Blanks et al., 1974; Fischer, 1979).

INTRINSICALLY PHOTOSENSITIVE RETINAL GANGLION CELLS

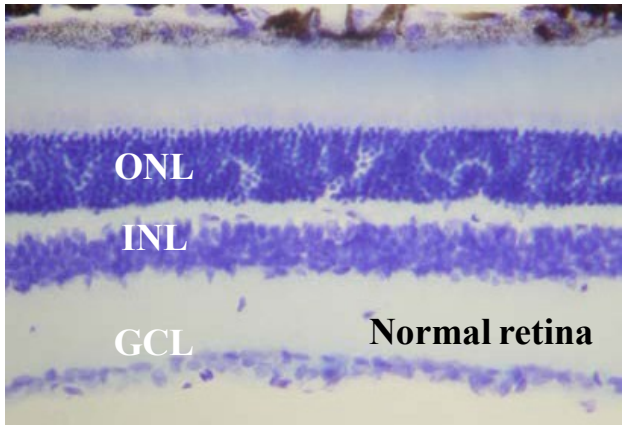
ipRGCs

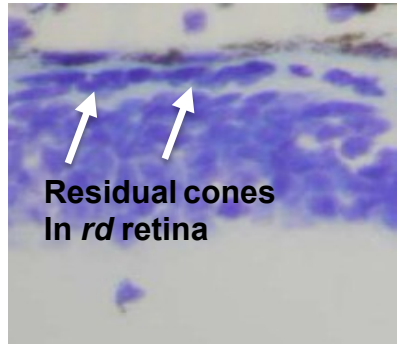
Could there be something that is light-sensitive apart from rods and cones?

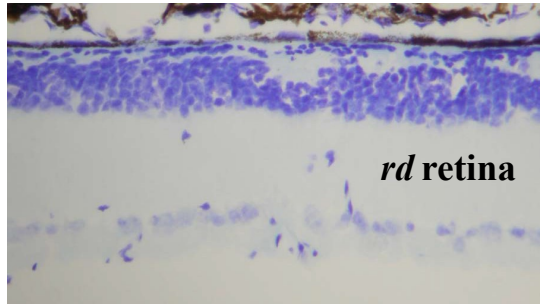




Evidence came from studies of retinal degenerate (*rd*) mice, which have a mutation in the β subunit of rod-specific phosphodiesterase (PDE). This leads to a rapid degeneration of rods followed by a slower loss of cones.





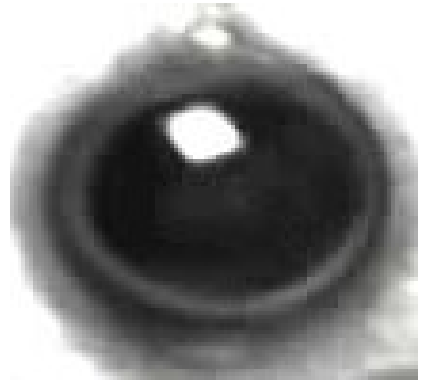


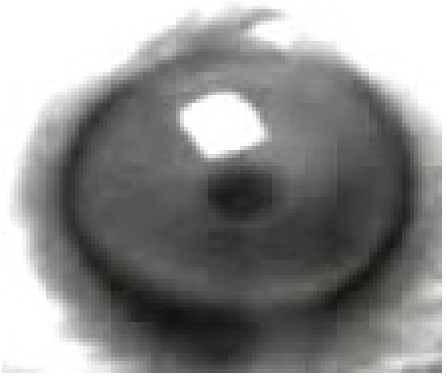
rd mice retain a pupillary light reflex (PLR)

TABLE 1

INDIVIDUAL		EYE	CONDITION OF RETINA	AVERAGE CONTRACTION	TIME OF LATENT PERIOD					TIME OF CONTRACTION					DIAMETER OF PUPIL	
					1	2	3	4	5	1	2	3	4	5	Atropin	Sulfide of eserine
Gray	♀ 28	Left	Normal	1.46–0.616	0.3	0.3	0.3	0.3	0.3	3.0	3.0	3.0	3.0	3.0	2.31	0.231
Black	♂ 23	Left	Normal	1.54–0.539	0.6	0.6	0.6	0.6	0.6	3.0	3.0	3.3	3.3	3.3	2.31	0.099
Black	♂ 23	Right	Normal	1.54–0.539	0.6	0.6	0.6	0.6	0.6	3.0	3.3	3.3	3.3	3.3	2.31	0.099
Gray	♀ 12	Left	Normal	1.54–0.539	0.6	0.6	0.6	0.6	0.6	3.0	3.0	3.6	4.2	4.2	2.31	0.924
Gray	♀ 12	Right	Normal	1.54–0.616	0.6	0.6	0.6	0.6	0.6	4.2	4.2	4.2	5.6	5.6	2.31	0.924
Gray	♀ 13	Left	Normal	1.54–0.616	0.6	0.6	0.6	0.6	0.6	3.6	3.6	3.6	3.6	3.6	2.31	0.385
Gray	♀ 13	Right	Normal	1.54–0.616	0.6	0.6–	0.6	0.6	0.6	3.6	3.0	3.0	3.0	3.0	2.31	0.385
Gray	♀ 10	Left	Normal	1.54–0.693	0.6	0.6	0.6	0.6	0.6	3.0	3.0	3.0	3.0	3.0	2.31	0.154
Gray	♀ 10	Right	Normal	1.54–0.616	0.6	0.6	0.6	0.6	0.6	3.0	3.0	3.0	3.0	3.0	2.31	0.154
Chinchilla	♀ 11	Left	Normal	1.54–0.616	0.6+	0.6	0.6	0.6–	0.6	5.4	5.4	5.4	5.4	6.8	2.16	0.616
Chinchilla	♀ 11	Right	Normal	1.54–0.616	0.6+	0.6+	0.6+	0.6+	0.6+	4.8	5.4	5.4	5.4	5.4	2.16	0.616
Averages				1.53–0.602					0.57					3.73	2.28	0.417
Gray	♀ 31	Left	Rodless	1.54–0.62	2.4	2.4	2.7	2.7	2.4	2.4	2.4	2.1	2.1	1.8	2.31	0.154
Gray	♀ 31	Right	Rodless	1.54–0.62	3.0	3.3	2.7	3.0	3.0	2.4	1.5	1.5	2.1	1.8	2.31	0.154
Black	♂	Left	Rodless	2.31–1.16	3.3	3.6				6.0	6.6	Animal choked to death				
Chinchilla	♀	Left	Rodless	1.39–0.61	1.8	1.8	1.8	2.4	1.8	3.0	3.0	3.0	3.0	3.0	2.70	0.385
Chinchilla	♂	Left	Rodless	1.39–1.16	1.2	1.5	1.8	1.8	1.8	3.0	2.4	2.4	2.4	2.4	2.70	0.308
Brown	♂ 7	Left	Rodless	1.93–1.16	1.8	3.0	3.0	3.0	1.8	3.0	2.0	3.0	3.0	2.0	2.39	0.154
Brown	♂ 7	Right	Rodless	1.93–1.16	0.6	0.6	2.4	1.8	2.4	2.4	3.0	1.8	3.0	2.4	2.39	0.154
Brown	♀ 34	Left	Rodless	1.54–0.77	1.8	3.0	3.0	3.0	3.0	2.4	1.8	2.4	3.0	1.8	2.39	0.365
Brown	♀ 34	Right	Rodless	1.54–0.77	1.8	3.0	3.0	3.0	4.8	3.0	1.8	1.8	2.4	1.8	2.31	0.365
Brown	♀ 6	Left	Rodless	1.54–1.16	1.8	1.2	1.8	0.6	0.6	3.0	1.8	2.4	2.4	3.6	2.39	0.231
Brown	♀ 6	Right	Rodless	1.54–1.16	1.8	1.5	1.2	0.6	0.6	2.4	2.4	2.4	3.6	3.6	2.39	0.231
				1.65–9.40					2.18					2.56	2.43	0.250

All diameters are given in millimeters. All times are given in seconds.

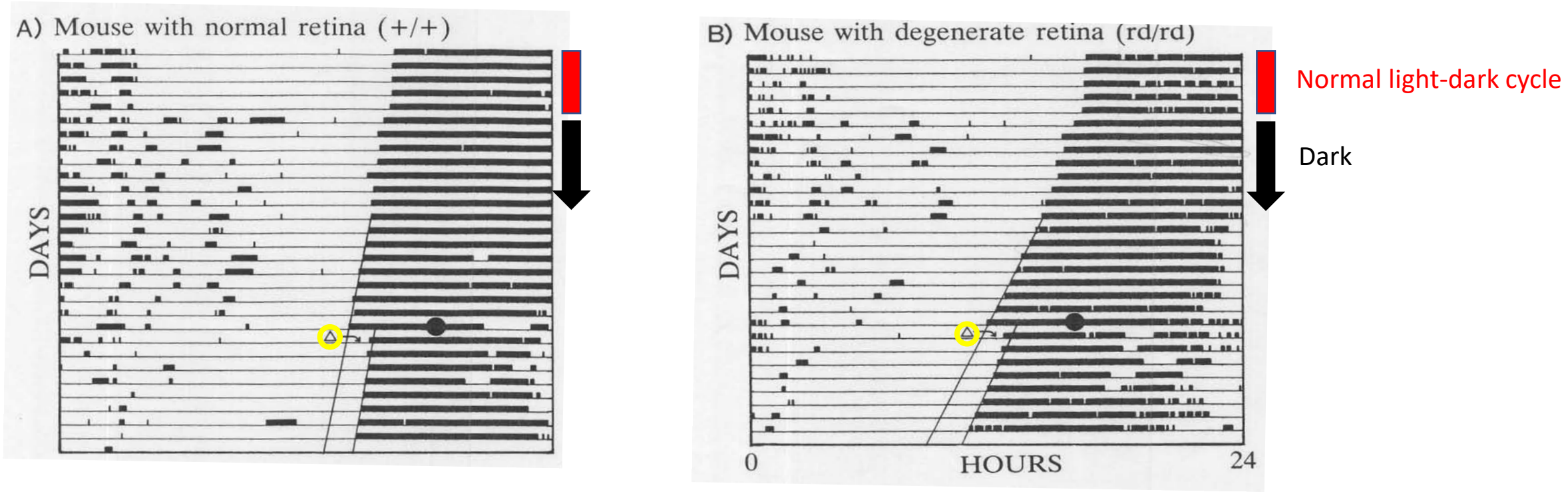




Clyde Keeler noted that rodless animals had a slower and weaker PLR than normals. He concluded that the iris may function independently of vision in rodless animals (based on work in eels from the 1840s) and that the deficits in rodless animals pointed to a regulatory system for iris constriction in normal eyes.

Keeler, (1927) American J. Physiology 81: 107-112.

rd mice retain circadian photoreception

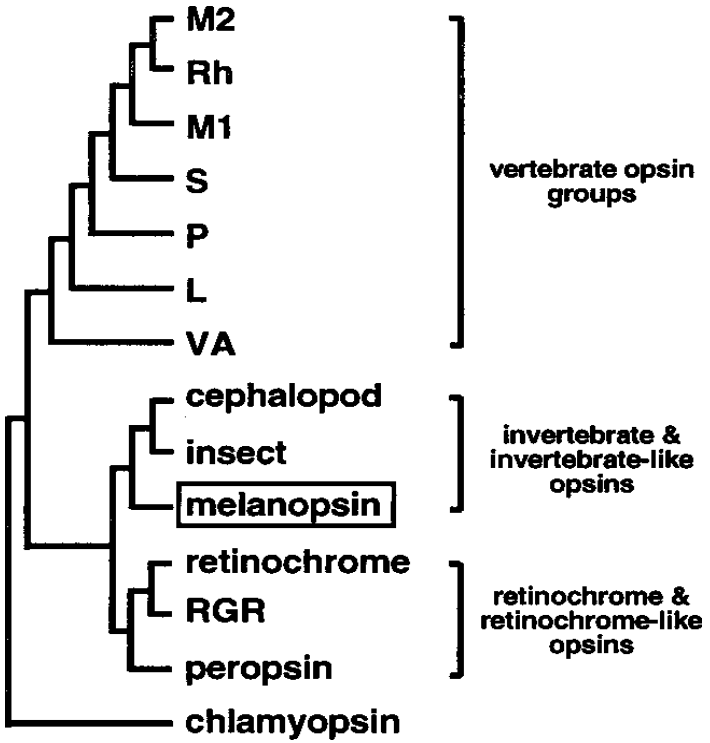


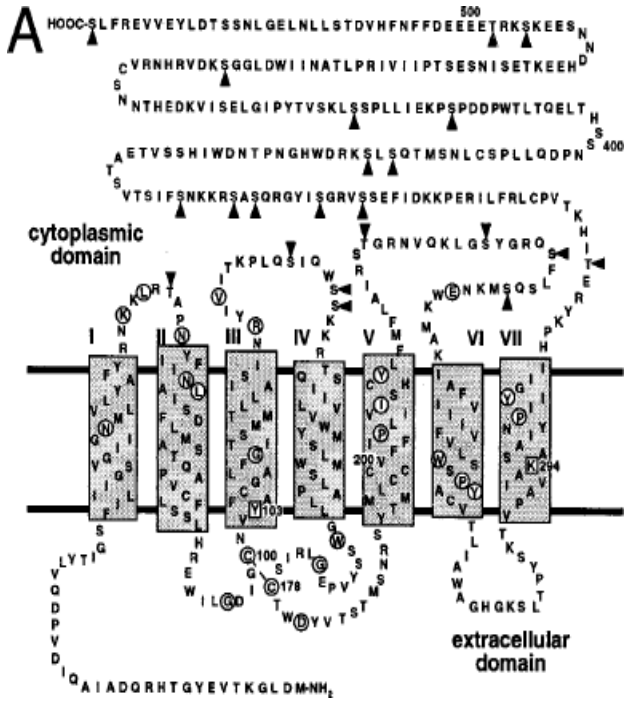
Locomotor activity records for 29 days. 5 days normal light-dark cycle. After 16 days in dark a 15-min pulse of light (●) shifted the dark-light cycle by about 90 minutes (△).

Foster et al., (1991) J. Comp Physiol A 169: 39-50.

Melanopsin

Ignacio Provencio discovered melanopsin in photosensitive dermal melanophores, brain and eye of the African clawed frog





Provencio et al., (1998) *Proc. Natl. Acad. Sci. USA* 95(6) 340-345

ipRGCs

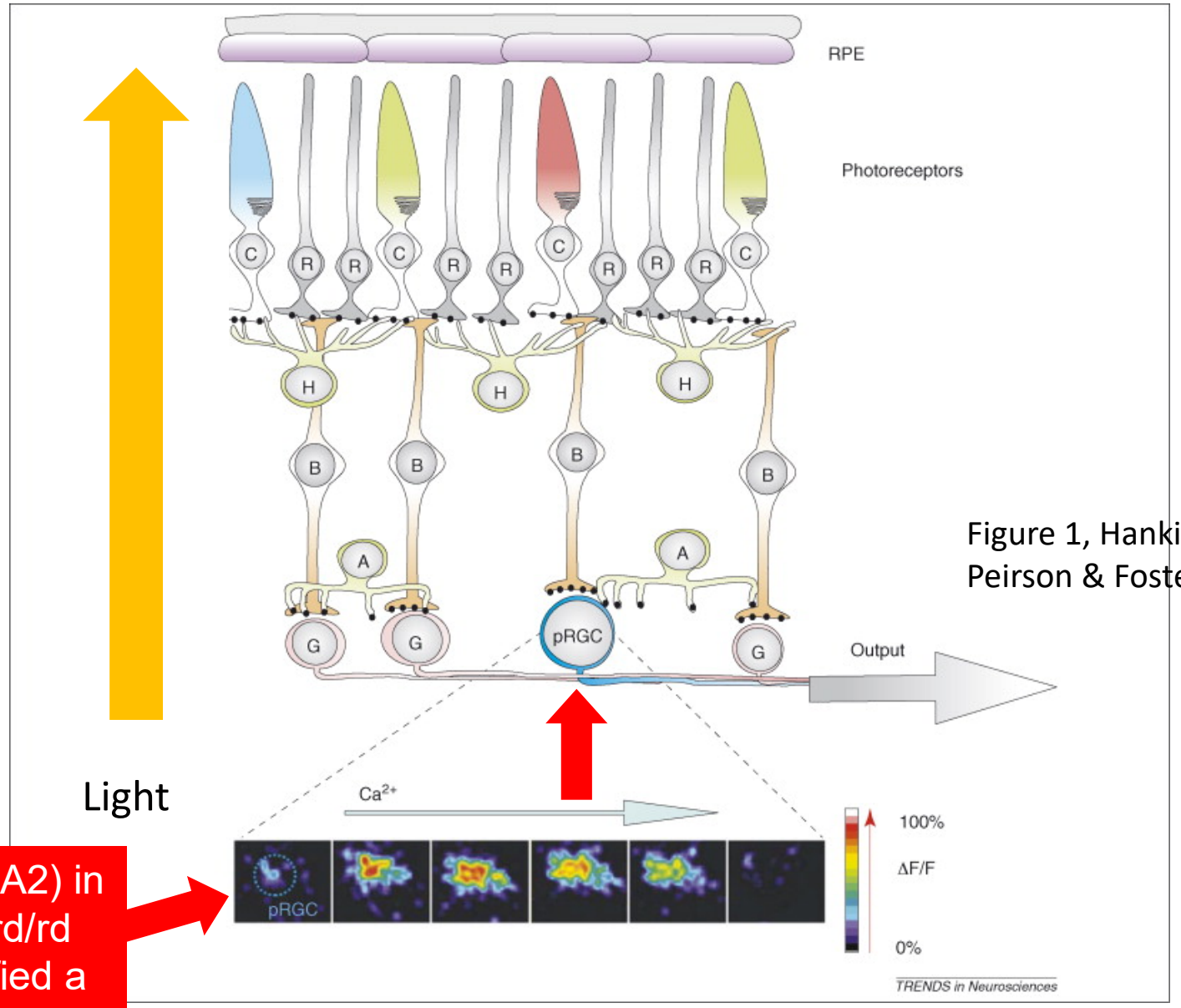


Figure 1, Hankins, Peirson & Foster, 2007

Calcium imaging (FURA2) in the rodless-coneless (rd/rd cl) mouse retina identified a population of pRGCs

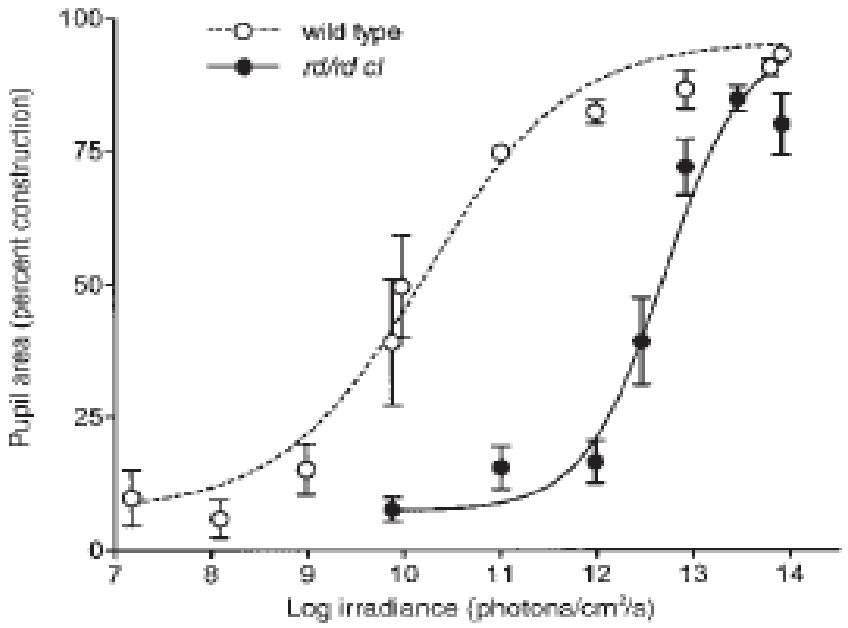
rd/rd cl mice

Foster lab at Imperial College London generated mice lacking rods and cones (*rd/rd cl* mice).

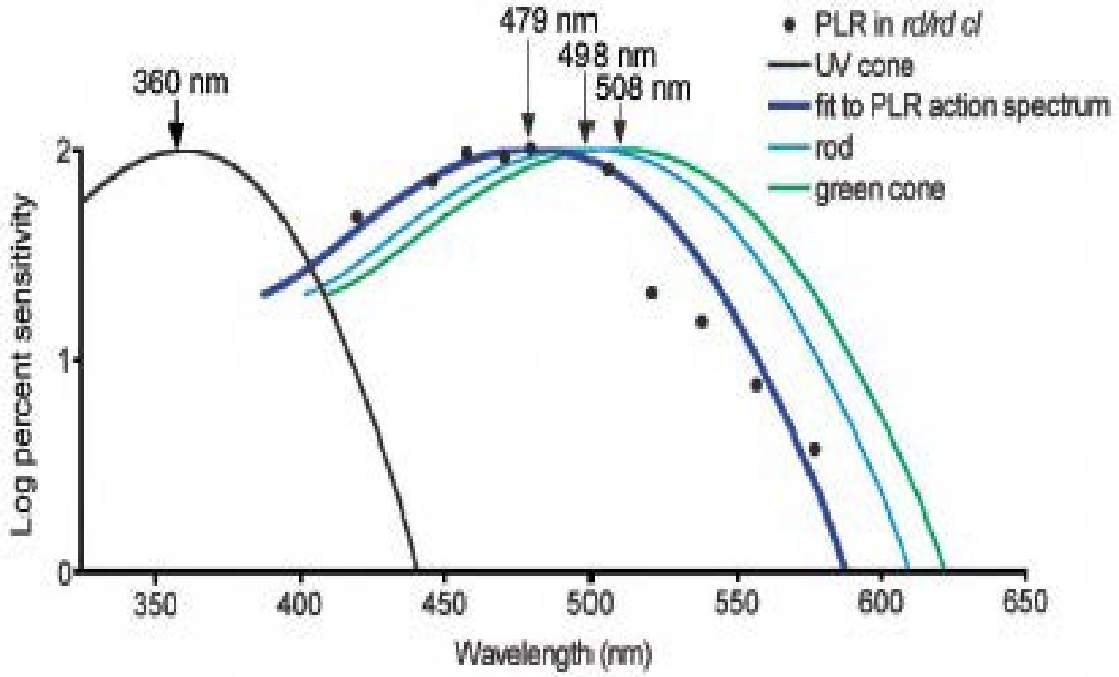
- Following a 15 minute exposure to green light the *rd/rd cl* mice still had:
  - Circadian phase shifting (Freedman et al., **Science** (1999) 284 502-504)
  - Suppression of pineal melatonin (Lucas et al., **Science** (1999) 284 505-507)
- The *rd/rd cl* mice also retain a pupillary light reflex (PLR)
  - Lucas, Douglas and Foster (2001) **Nature Neuroscience** 4(6) 621-626

Melanopsin spectral sensitivity

The spectral properties of this new photoreceptor were defined using the pupillary light response in *rd/rd cl* mice



Irradiance response to
506 nm monochromatic light

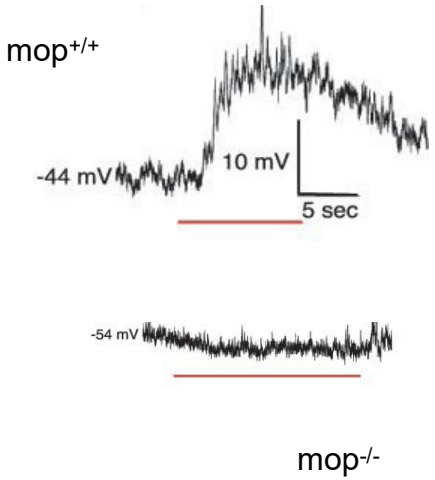


The action spectrum for the unidentified
Photopigment peaks at 479nm (OP^{479})

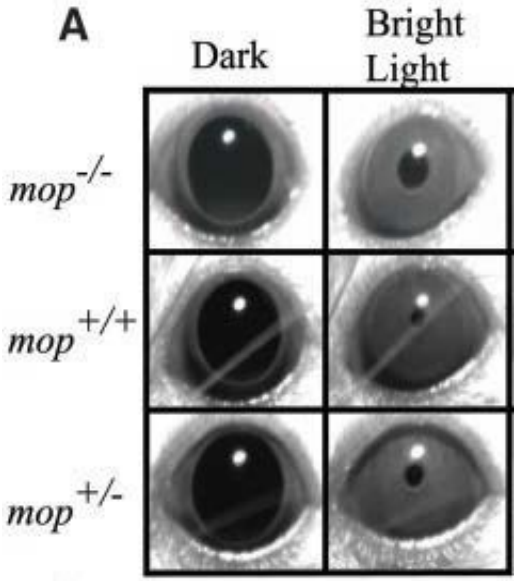
Lucas et al., (2001) *Nature Neuroscience* 4(6) 621-626

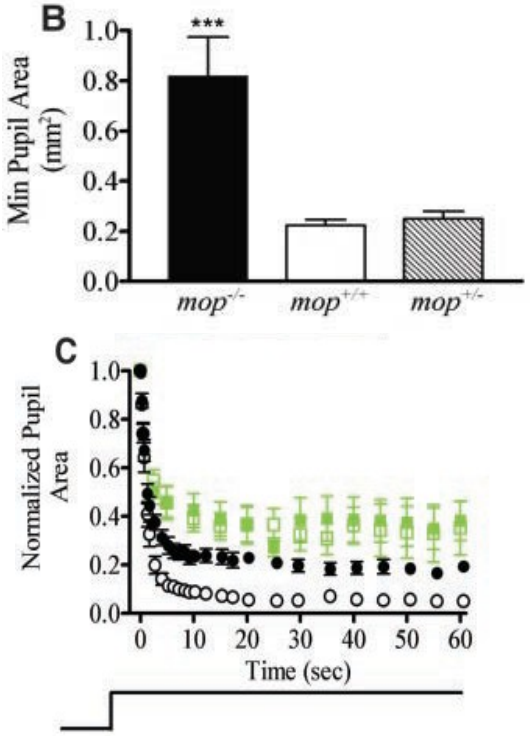
Melanopsin knock-out

Melanopsin-knockout eliminates the intrinsic light response of ipRGCs and reduces the PLR at high irradiance



Electrophysiology



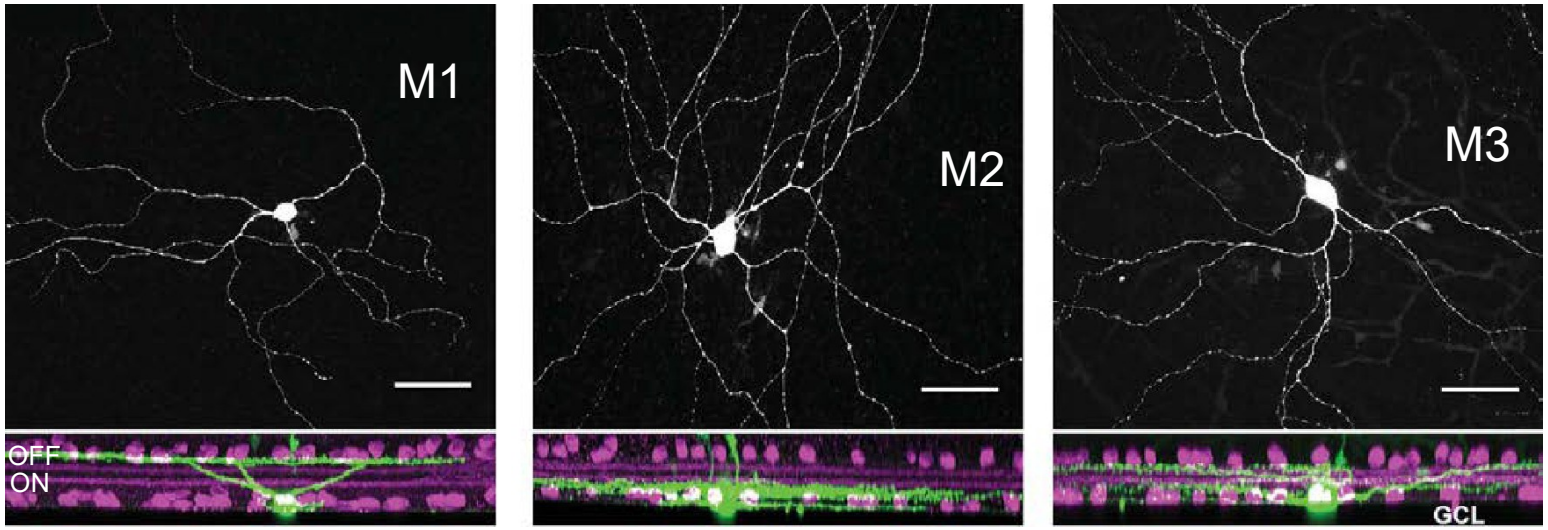


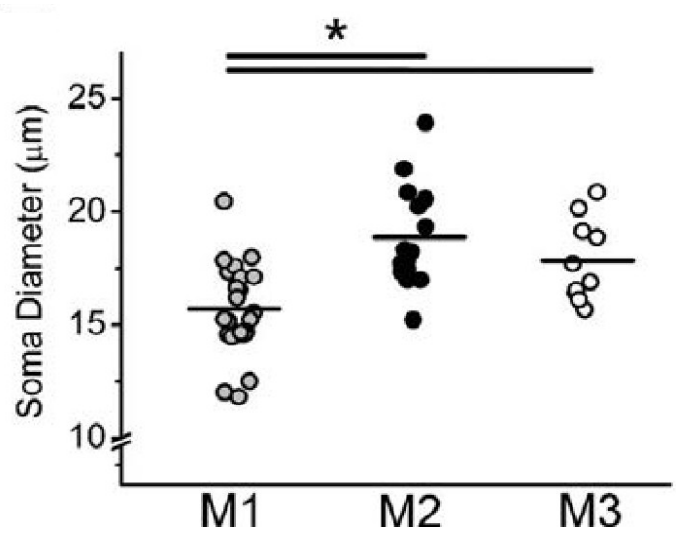
Melanopsin-knockout (*mop*$^{-/-}$) mice were generated, where the ipRGCs remain but lack melanopsin and do not respond intrinsically to light (see intrinsic light responses on the left). As shown in **A** and **B**, unlike wildtype (*mop*$^{+/+}$) and heterozygote (*mop*$^{+/-}$) mice, *mop*$^{-/-}$ mice could not quite achieve a full pupil constriction under bright light (monochromatic 480nm, 145µW cm^2). The *mop*$^{-/-}$ mice can sustain pupillary constriction for 60 seconds like wildtypes (**C**) and can sustain the same level of constriction under low irradiance (0.12µW cm^2, green squares) but not high irradiance (110 µW cm^2, black circles).

Lucas et al., *Science* (2003) 299 245-247

Three types of ipRGCs

Three types of ipRGC were originally distinguished on the basis of dendritic stratification



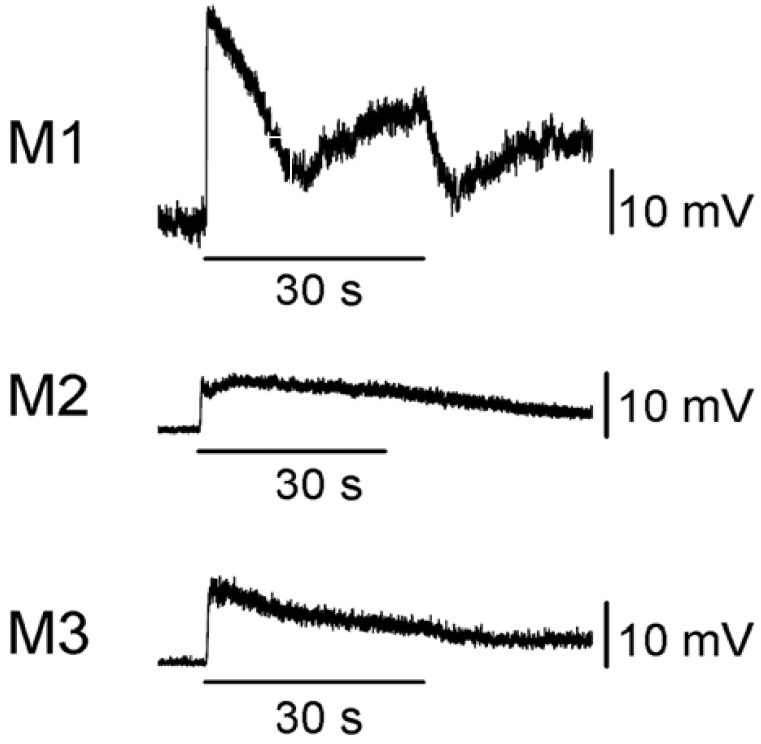


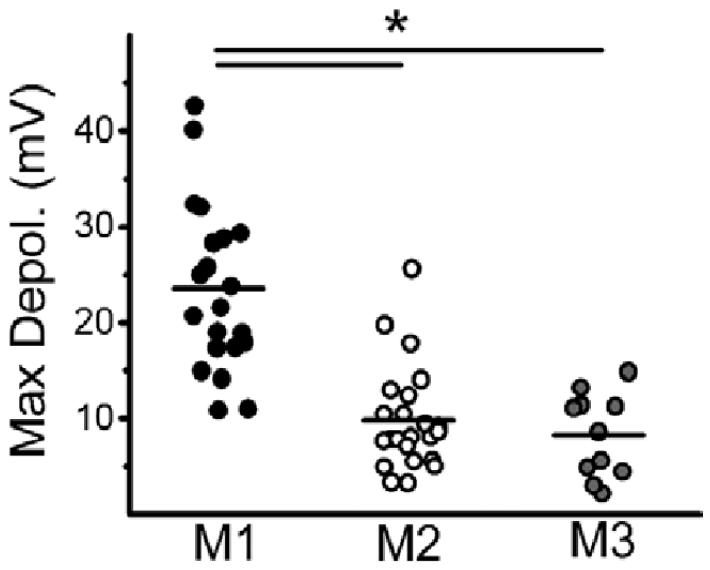
The three types of ipRGC (M1, M2 and M3) are shown in green (filled with neurobiotin), with a marker for cholinergic amacrine cells in magenta (to delineate ON and OFF sub-regions of the inner plexiform layer). The M1 cells (smallest soma diameter) extend dendrites into the OFF subdivision, while M2 cells extend dendrites into the ON subdivision only. M3 cells extend dendrites into both ON and OFF regions

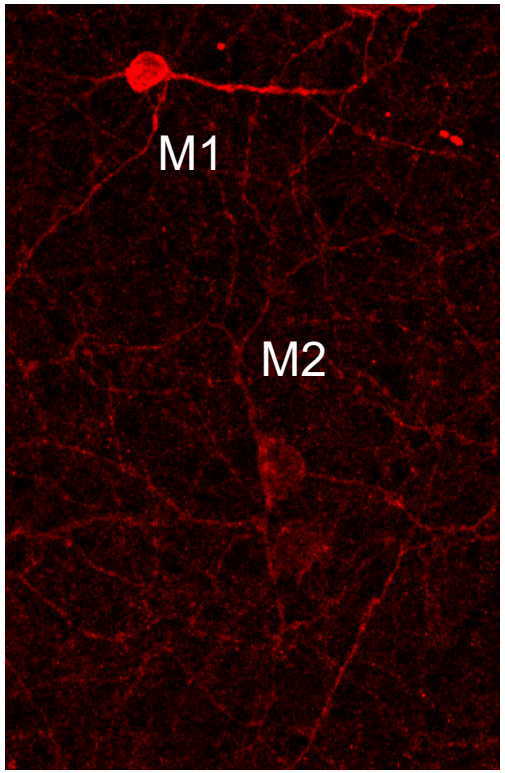
Schmidt and Kofuji J. Comp Neurol. (2011) 5(19) 1492-1504

Three types of ipRGCs

The three different types of ipRGC have distinct electrophysiological responses to light



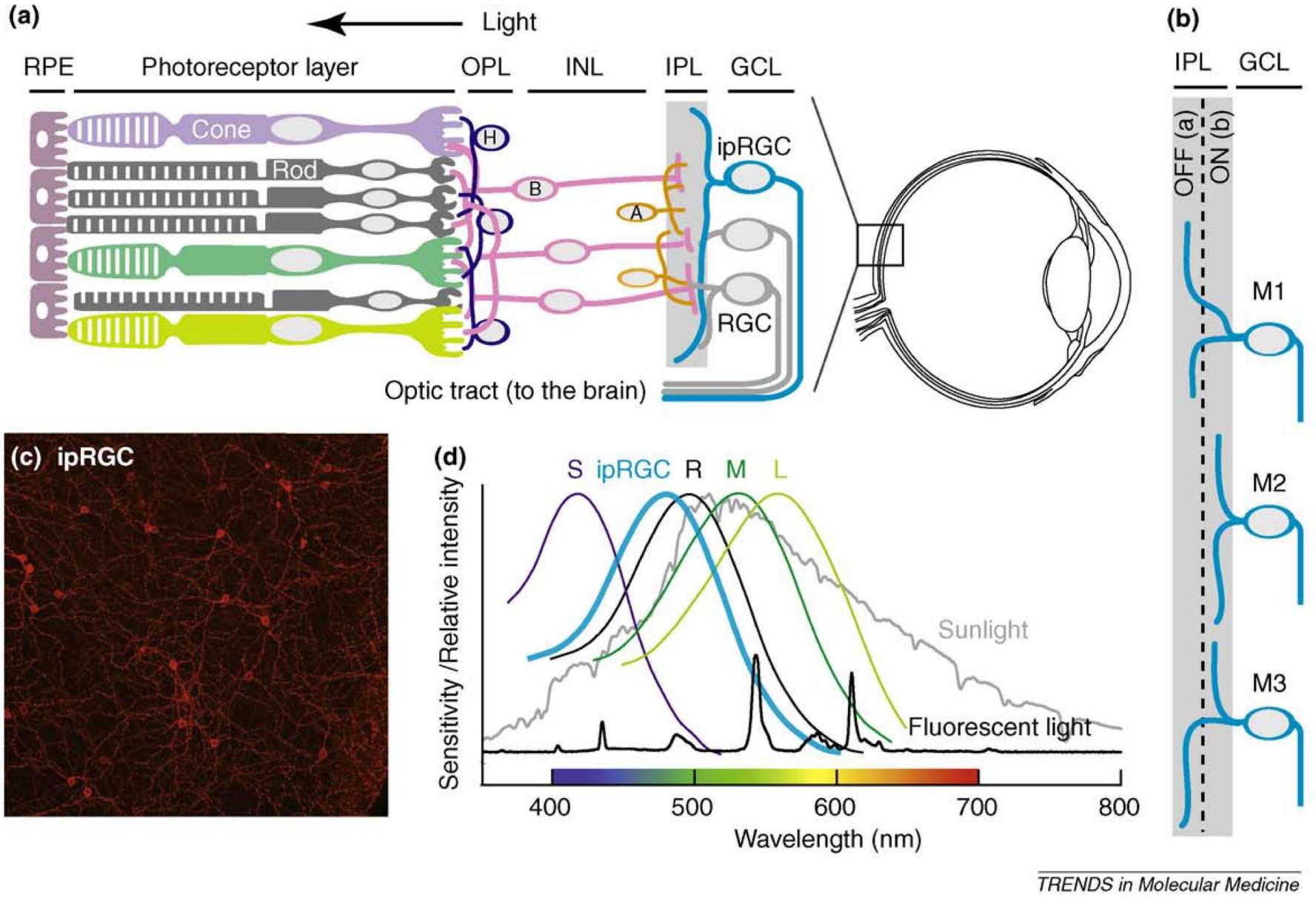




Patch-clamp recordings from ipRGCs in Opn4-EGFP mice (in the presence of synaptic blockade), reveal a stronger depolarisation to bright white light in M1-type cells. This is because M1 ipRGCs contain the highest levels of melanopsin (Opn4, stained red).

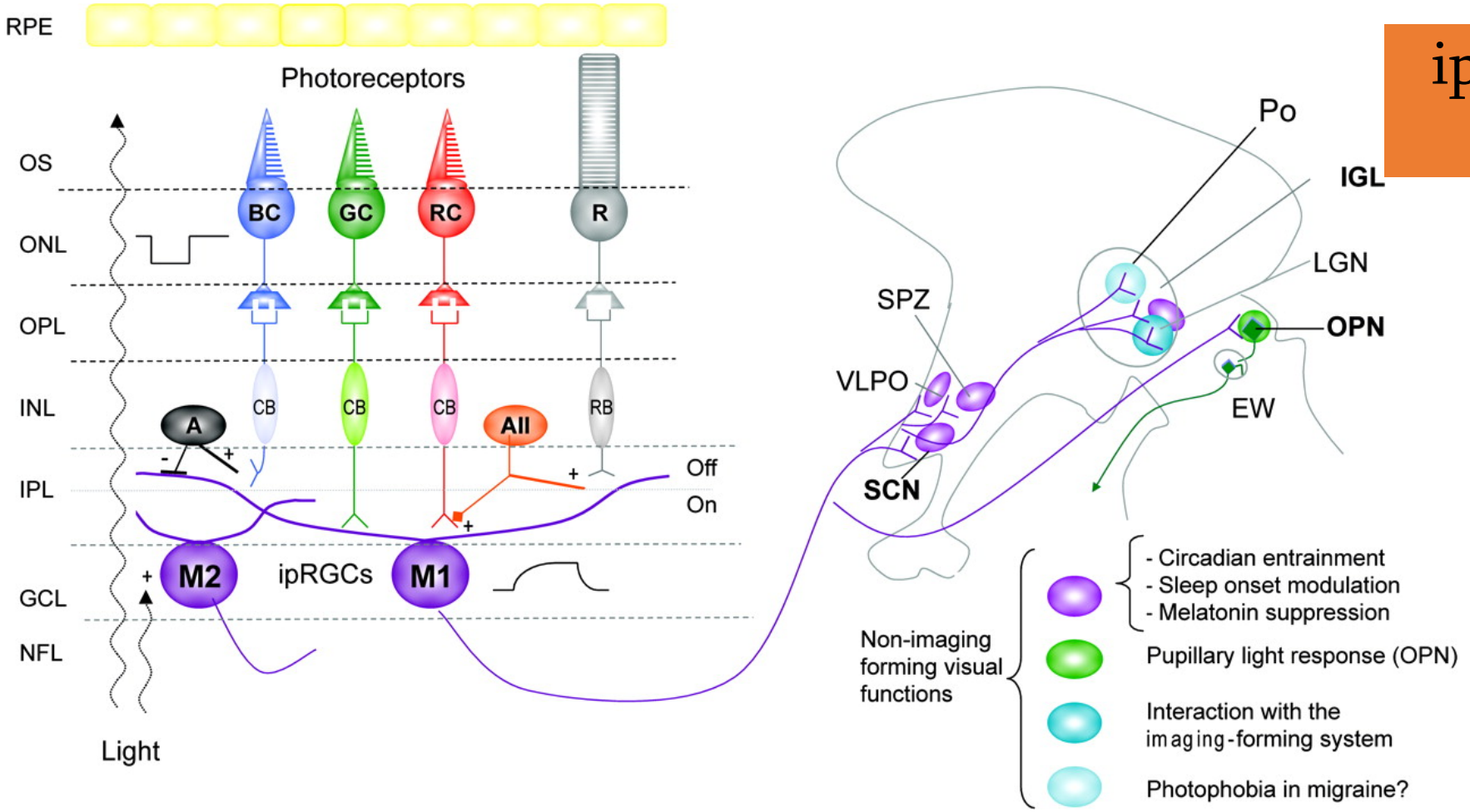
Schmidt and KofujiJ. Comp Neurol. (2011) 5(19) 1492-1504

Summary



TRENDS in Molecular Medicine

ipRGCs sub-cortical projections

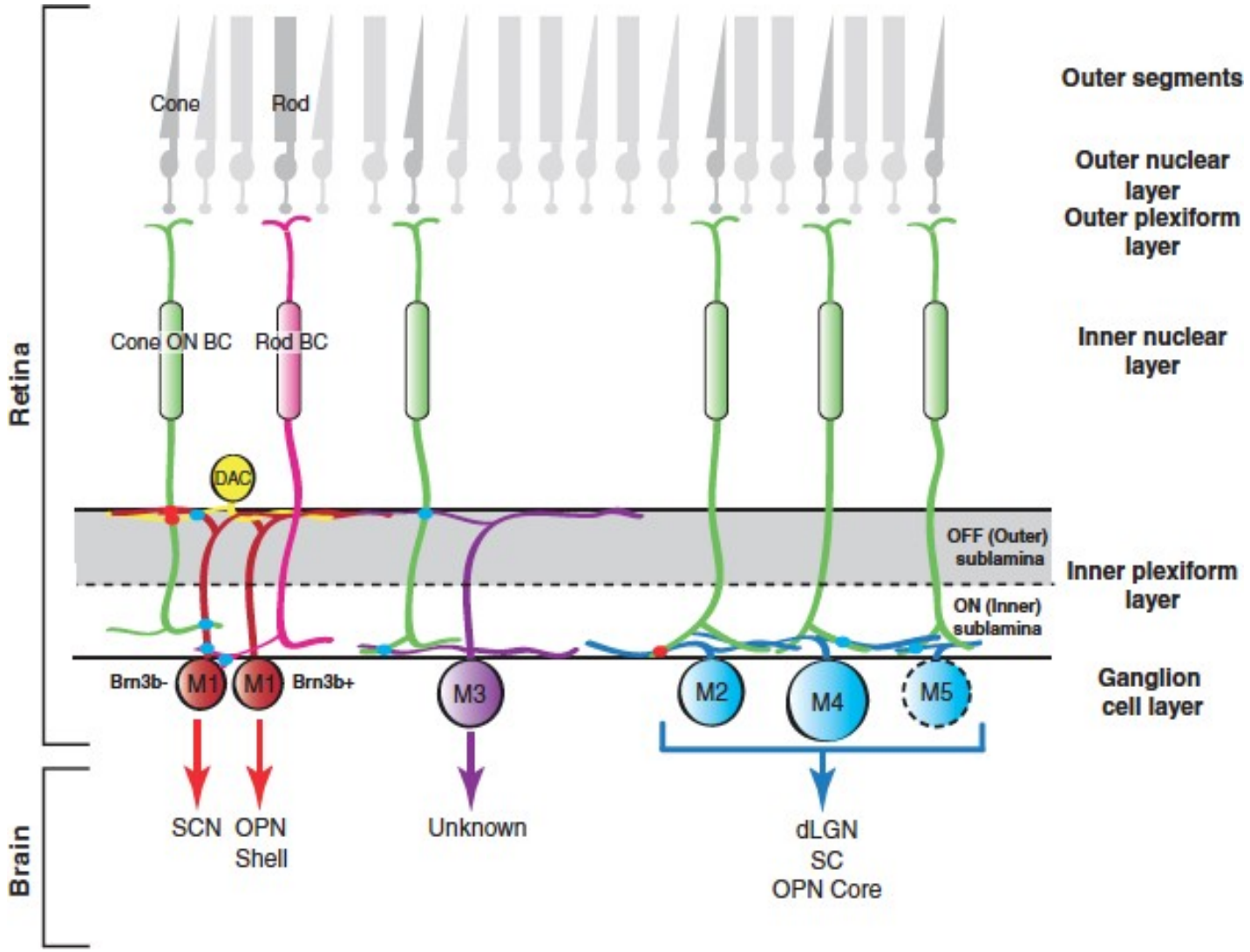


The ipRGCs project to the suprachiasmatic nucleus (SCN), the subparaventricular zone (SPZ), the ventrolateral preoptic area (VLPO), and the intergeniculate leaflet (IGL) of the lateral geniculate nucleus (LGN), which are involved in circadian regulation, and to the olivary pretectal nucleus (OPN), which is a relay of the pupillary light reflex. Projections to the dorsal LGN provide an interface with the imaging-forming system.

Benarroch, 2011

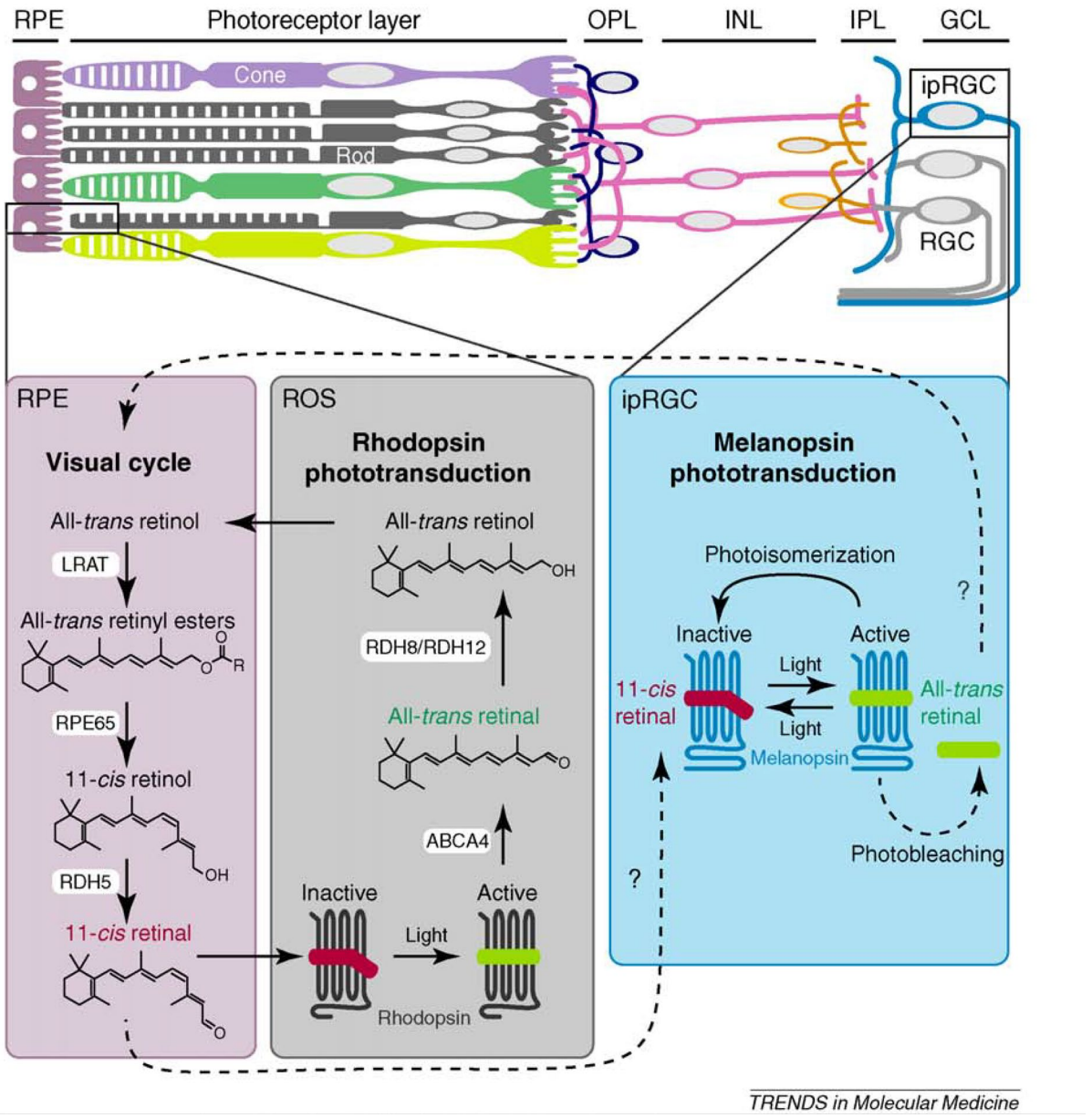
ipRGCs sub-cortical projections

Summary of different ipRGC subtypes and their sub-cortical projections.



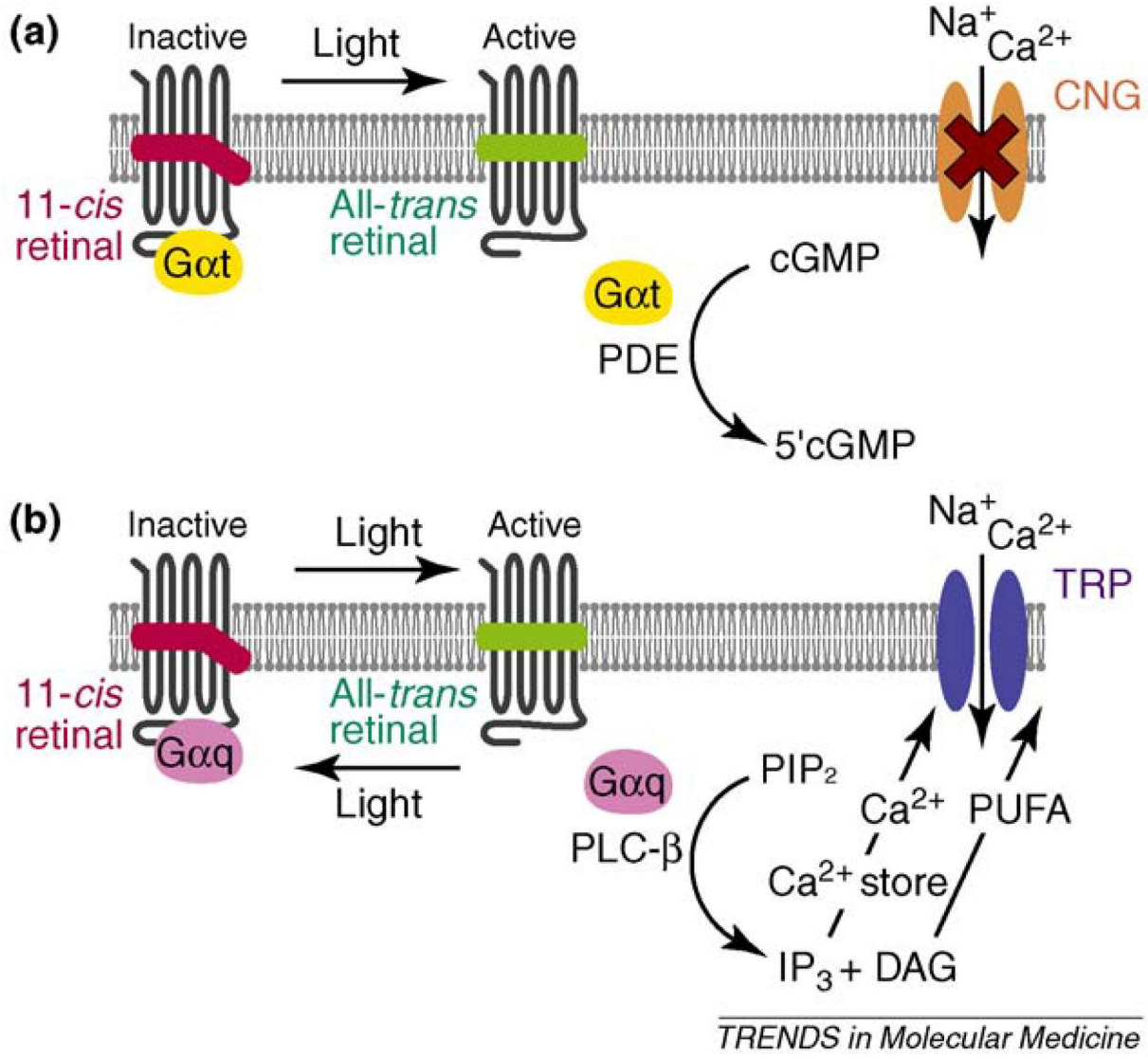
Schmidt et al., TINS (2011) 34(11) 572-80)

Transduction



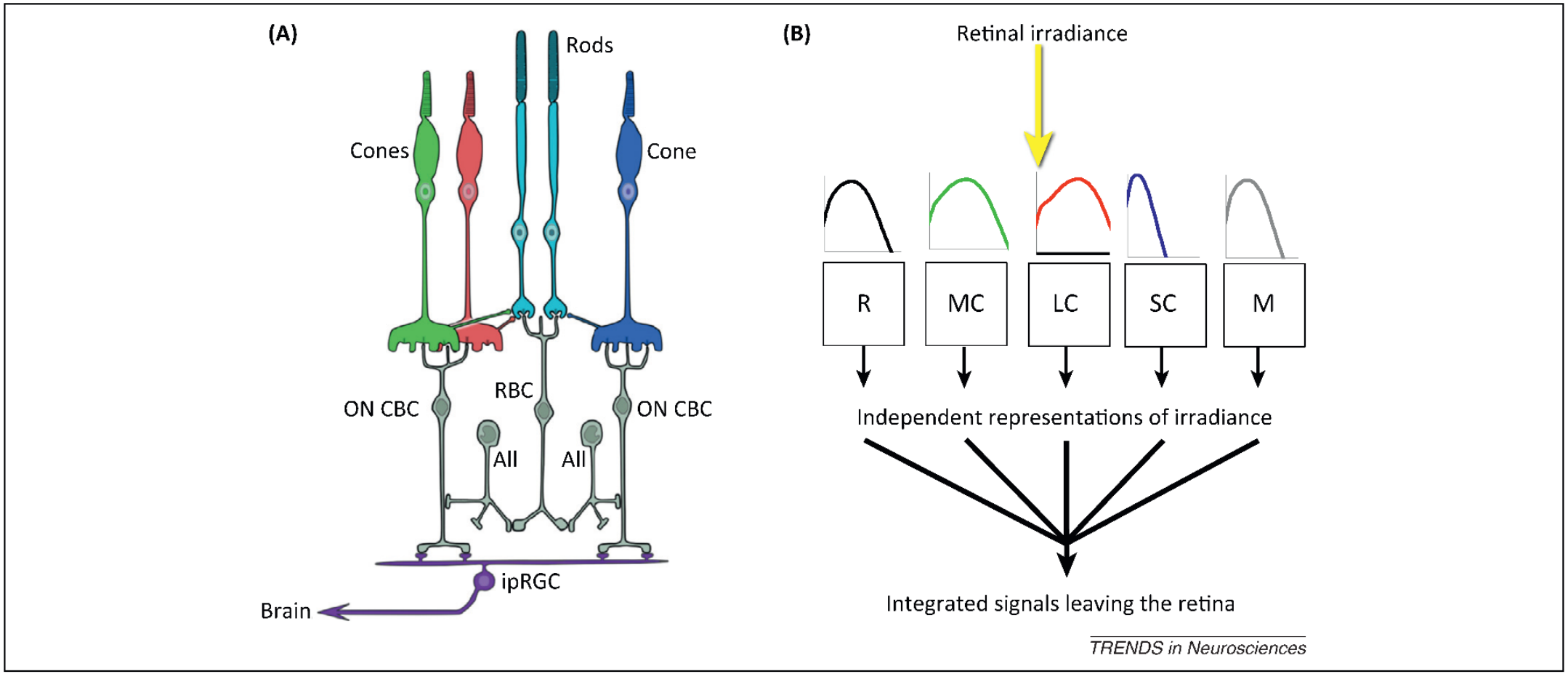
Transduction

Rods and cones hyperpolarize in response to light, but melanopsin-containing ipRGCs depolarize upon light stimulation.



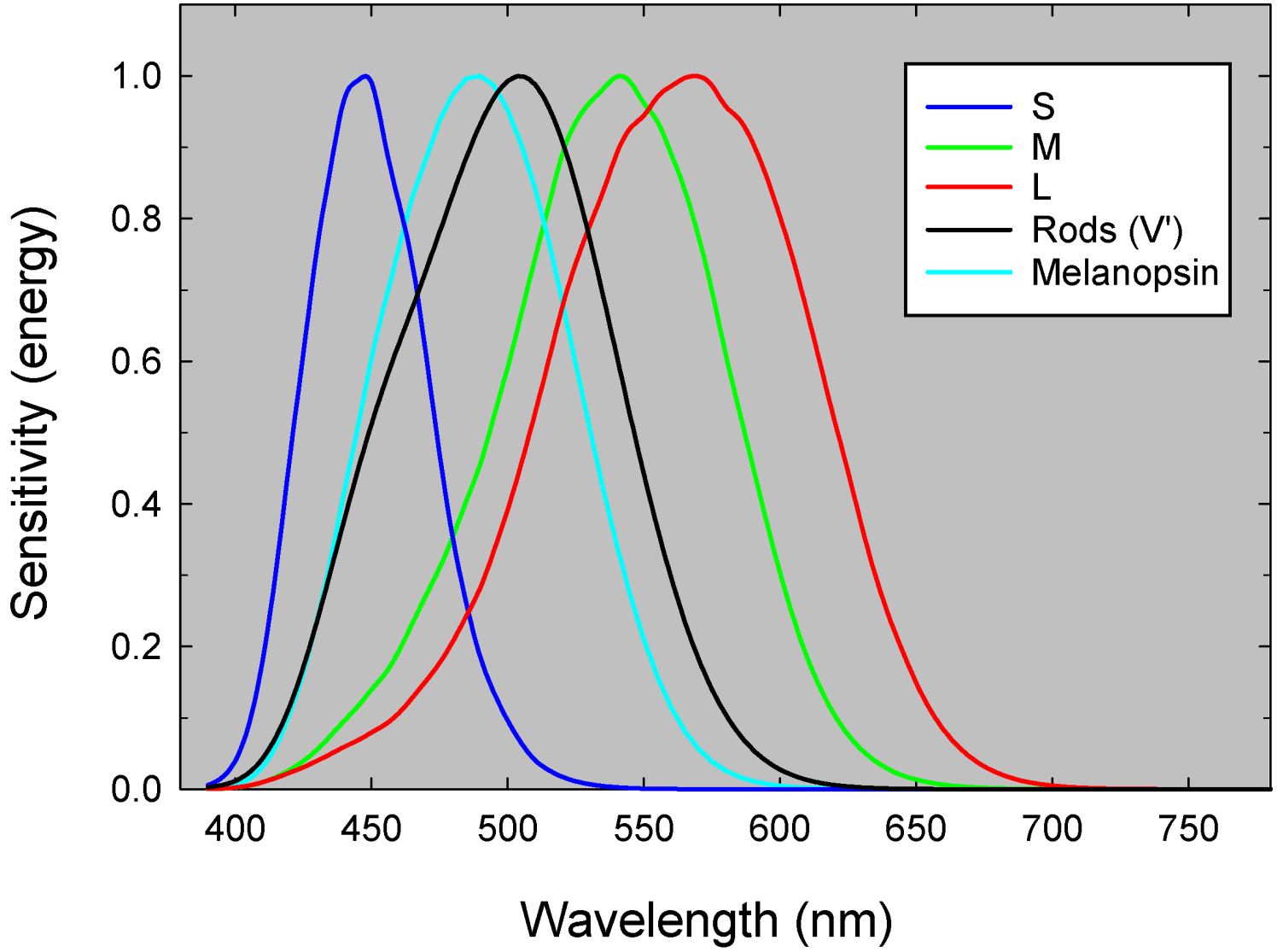
Natural daylight and circadian rhythms

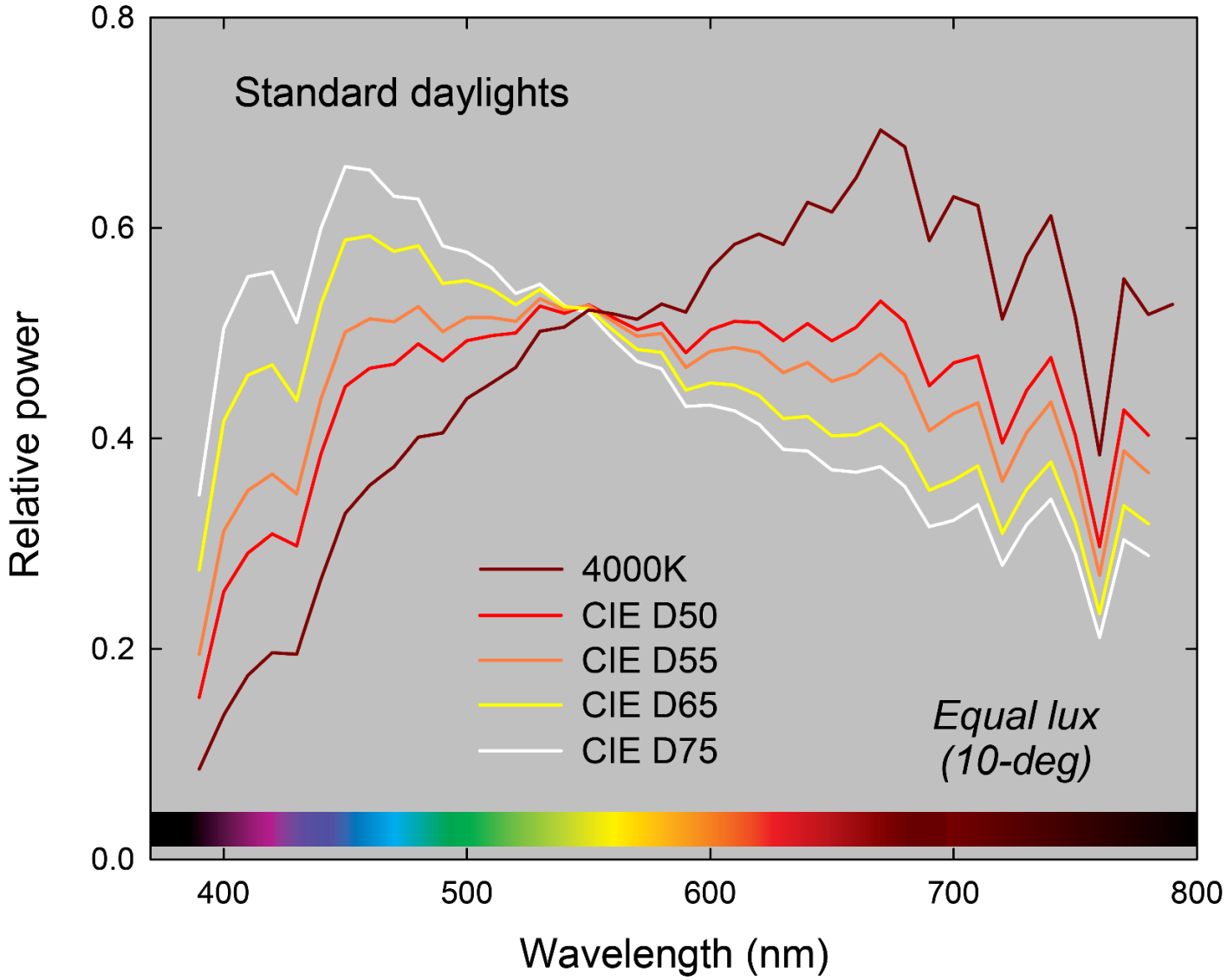
The ipRGCs receive inputs from all other photoreceptor types:



From Lucas et al. (2014). Measuring and using light in the melanopsin age. *Trends Neurosci, 37(1), 1-9.*

Should consider all photoreceptors…




Standard daylights
Relative power
0.0
0.2
0.4
0.6
0.8
400
500
600
700
800
Wavelength (nm)
4000K
CIE D50
CIE D55
CIE D65
CIE D75
Equal lux
(10-deg)

Summary

The melanopsin system mediates several non-image-forming visual functions, including light entrainment of circadian rhythms and pupillary responses to light.

The ipRGCs constitute a small percentage of ganglion cells; in each human eye, up to 3,000 out of ~1.5 million retinal ganglion cells stain positively for melanopsin.