

# Rea (2005,2011) Melatonin suppression model: Upgrade

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## Abstract

abstract placeholder.

*Keywords:* key1, key2

## 1. Introduction

Modification for Rea et al. 2005; 2011.

## 2. Material and methods

### 2.1. Original model

Original model conceptually ( $CS$ , circadian stimulus, Eq. (1)):

$$CS = Melanopsin + Opponent - Rods \quad (1)$$

Melanopsin contribution (Eq. (2)):

$$Melanopsin = a_1 \int M_\lambda P_\lambda d\lambda \triangleleft a_2 \quad (2)$$

S-cone component (blue,  $B$ , Eq. (3)):

$$blue = \int S_\lambda P_\lambda d\lambda \quad (3)$$

L/M-cone component (yellow,  $Y$ , Eq. (4)):

$$yellow = -k \int V_{10\lambda} P_\lambda d\lambda \quad (4)$$

Cone opponent component (blue – yellow,  $B – Y$ , Eq. (5)):

$$Opponent = blue - yellow \quad (5)$$

Rod component (Eq. (6)):

$$Rods = a_3 \left( 1 - e^{-\frac{\int V_{10\lambda} P_\lambda d\lambda}{RodSat}} \right) \quad (6)$$

Original model (Eq. (7)):

$$\begin{aligned} CS &= [ \left( a_1 \int M_\lambda P_\lambda d\lambda \right) \triangleleft a_2 \\ &\quad \times \left( \int S_\lambda P_\lambda d\lambda - k \int V_{10\lambda} P_\lambda d\lambda \right) - b_2 ] \\ &\quad - a_3 \left( 1 - e^{-\frac{\int V_{10\lambda} P_\lambda d\lambda}{RodSat}} \right) \\ \text{for } & \int S_\lambda P_\lambda d\lambda - k \int V_{10\lambda} P_\lambda d\lambda \geq 0 \\ CS &= a_1 \int M_\lambda P_\lambda d\lambda \\ \text{for } & \int S_\lambda P_\lambda d\lambda - k \int V_{10\lambda} P_\lambda d\lambda < 0 \end{aligned} \quad (7)$$

Rod component can be modified to produce smoother transition around spectral cross-over point (Eq. (8)):

$$Rods_{smooth} = Rods \left( 1 - e^{-40[\int S_\lambda P_\lambda d\lambda - k \int V_{10\lambda} P_\lambda d\lambda]} \right) \quad (8)$$

Original model with a smooth transition around spectral “crossover point” (Eq. (10)):

$$\begin{aligned} CS &= [ \left( a_1 \int M_\lambda P_\lambda d\lambda \right) \triangleleft a_2 \\ &\quad \times \left( \int S_\lambda P_\lambda d\lambda - k \int V_{10\lambda} P_\lambda d\lambda \right) - b_2 ] \\ &\quad - a_3 \left( 1 - e^{-\frac{\int V_{10\lambda} P_\lambda d\lambda}{RodSat}} \right) \\ &\quad \times \left( 1 - e^{-40[\int S_\lambda P_\lambda d\lambda - k \int V_{10\lambda} P_\lambda d\lambda]} \right) \end{aligned} \quad (9)$$

$$\begin{aligned} \text{for } & \int S_\lambda P_\lambda d\lambda - k \int V_{10\lambda} P_\lambda d\lambda \geq 0 \\ CS &= a_1 \int M_\lambda P_\lambda d\lambda \\ \text{for } & \int S_\lambda P_\lambda d\lambda - k \int V_{10\lambda} P_\lambda d\lambda < 0 \end{aligned} \quad (10)$$

Circadian light ( $CLA$ ) is defined as following (Rea et al. 2010, Eq. (11)):

$$(11)$$

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### 2.1.1. Model Simulations

Shown in Figure 1 and Figure 2, as discussed.

### 2.1.2. Additional melatonin suppression literature

As with traditional visual system (e.g. [Previc 1990](#), [Corbett and Carrasco 2011](#)) there is evidence for differential visual field responses also in NIF photoreception as shown for melatonin suppression in Table 1. The preference for upper temporal visual field (nasal and lower retina) corresponds roughly to bright sky in real-life evolutionary settings the nasal visual field being attenuated by shadowing nose. Additionally, this suggested preference seems to be in contrast with the spatially uniform distribution (“photoreceptive net”, [Provencio et al. 2002](#)) of mRGCs in retina. This could be interpreted differences either in post-receptor processing after mRGCs, non-homogenous distribution of mRGC subtypes, and/or significant contribution from rod and cone photoreceptors. Similar differential responses on different visual field can be seen with pupillary light reflex (PLR)

## 2.2. “Classical” retinal circuitry

*From Dacey 2000*: “**Macaques** have photoreceptor types with the same spectral tuning as their human counterparts (e.g. [Schnapf et al. 1990](#)) and similar overall visual capacities. Beyond the photoreceptors, as far as has been determined, the cell types and circuits of macaque and human retina are *virtually indistinguishable*, establishing the **macaque retina as an ideal model** for discovering the neural mechanisms at the earliest stages of human trichromatic color vision.”

*From Packer et al. 2010*: “In the primate retina the long (L) and middle (M) cones comprise 90% of the total cone population ([Ahnelt et al., 1987](#); [Curcio et al. 1990](#)) and are thus relatively accessible for physiological study. L and M cones are electrically coupled to each other and to rods via gap junctions over distances of 10–20  $\mu\text{m}$  ([Hornstein et al., 2004, 2005](#)). They also receive inhibitory signals from neighboring L and M cones over much larger distances via an interneuron, the H1 horizontal cell ([Dacey et al. 1996](#); [Packer and Dacey, 2002](#); [Verweij et al., 2003](#)). How these signals are transmitted from horizontal cells to cones is controversial ([Hirasawa and Kaneko, 2003](#); [Davenport et al., 2008](#); [Fahrenfort et al., 2009](#)), but the end target is the modulation of calcium channels in the cone synapse ([Verweij et al., 1996, 2003](#)).

In contrast, primate **short (S) cones** comprise **only 10%** of the cones, and thus physiological recordings from S cones are *rare* ([Baylor et al. 1987](#), [Schnapf et al. 1990](#); [Hornstein et al., 2004](#) **Electrical coupling between red and green cones in primate retina**). Anatomically, **S cones** contact both H2 horizontal cells and rods ([Ahnelt et al., 1990](#); [Dacey et al. 1996](#); [Goodchild et al., 1996](#) **Horizontal cell connections with**

**short-wavelength-sensitive cones in macaque monkey retina**). However, it is **not known** whether these contacts provide input to S cones.”

*From Masland 2012b*: “For rods, cones, horizontal, and bipolar cells, our present census is **pretty definitive**: we can identify the cell types and we can describe them quantitatively. But **amacrine cells** have been enumerated only in the rabbit retina, and **retinal ganglion cells** remain a **struggle**.”

- An initial estimate of 55 cell types in the retina ([Masland 2001b](#)).
- The mammalian retina consists of neurons of >60 distinct types ([Masland 2012b](#))
- ... retinal cell types whose total number, approaching **80**, rivals that of just about any other brain structure. Thus rod photoreceptors subserving scotopic vision, and multiple cone photoreceptor types subserving photopic vision, transmit to at least **10 bipolar** cell types that in turn connect to at least **20 ganglion cell types** and an even greater number of amacrine cell types, estimated at between **30 and 40**. ([Dacey 2000](#))

### 2.2.1. Rods

The 100 million rod photoreceptors appear to be the second most numerous neurons of the human body, after only the cerebellar granule cells ([Masland 2012b](#)).

*From Wässle 2004*: “Like cones, rods release glutamate in darkness and this transmitter **release is reduced** when they are **hyperpolarized by light**. Horizontal cells express ionotropic GluRs at their dendritic tips, in the rod spherule, and rod bipolar cells express the metabotropic receptor mGluR6. Rod bipolar cells — of which there is only one type in any mammalian retina — are depolarized by a light stimulus and are ON-bipolar cells ([Berntson and Taylor 2000](#), [Euler and Masland 2000](#)). Each contacts 20–80 rod spherules, and their axons terminate in the inner IPL, close to the ganglion cell layer. However, rod bipolar cells do not send light signals directly into the ganglion cells but instead **synapse with an AII amacrine cell** ([Famiglietti and Kolb 1976](#), [Raviola and Dacheux 1987](#)) (Figure 3). AII cells, which are also depolarized in response to a light stimulus, **sum the input** from many rod bipolar cells. They form electrical synapses (gap junctions) onto the axon terminals of ON cone bipolar cells (Figure 3, ON1) and inhibitory chemical synapses onto those of OFF cone bipolar cells (Figure 3, OFF1). In turn, these cone bipolar cells synapse onto the ganglion cells. This wiring diagram represents the ‘classical rod pathway’ through the mammalian retina ([DeVries and Baylor 1995](#)). It is the most sensitive pathway and can detect the absorption of a single photon. The **detour** through the AII–cone bipolar cell

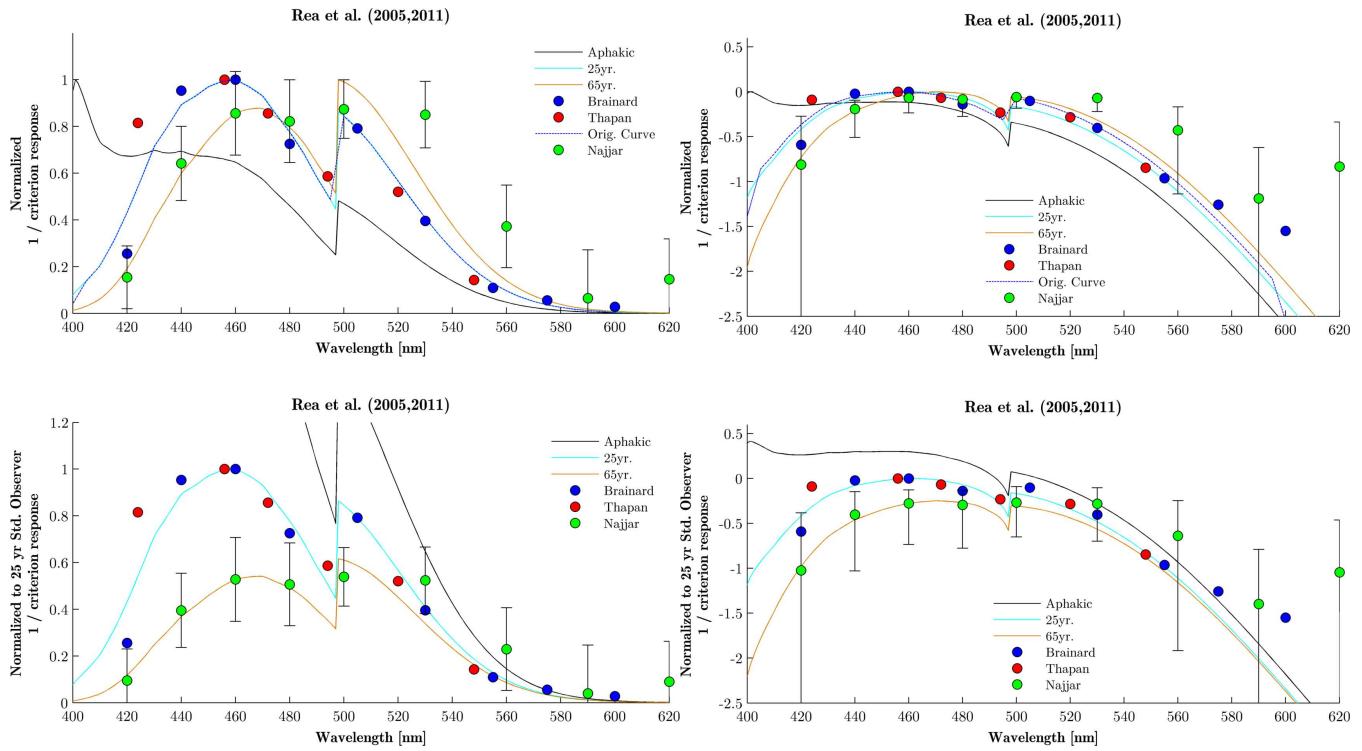


Figure 1: **Model predictions for a monochromatic stimulus** (equal energy with  $hbw=1$  nm) with three different ocular media filtrations (aphakic observer receives equal energy light but the retinal irradiance of 25 yr and 65 yr standard observers are filtered according to the corresponding ocular media models): 1) aphakic observer (black line) with a 25 year standard observer lens removed from tabulated values (<http://www.cvrl.org/>) used in the original implementation (Rea et al. 2005; 2011), 2) the standard observer (blue line) used in the original model (Rea et al. 2005; 2011), 3) the 65 year old standard observer filtered with the ocular media model of van de Kraats and van Norren 2007 using  $age = 65$  years and neutral offset 0.111. The plot **above** is normalized to unity, to give an idea of the spectral shape change involved with ocular media filtration. Whereas the plot **below** is normalized in regard to 25 year standard observer, and should you give the absolute response changes due to ocular media filtration.

The CS model used in the simulation is the sharp transition one of Eq. (7). The melatonin data for young subjects (red and blue points) are from studies of Thapan et al. 2001, Brainard et al. 2001, and the data for elderly subjects (8 subjects,  $59.4 \pm 0.99$ , 10 experimental nights, 1hr exposure, fixed equal photon density of  $3.16 \times 10^{13}$ ,  $hbw=10$  nm interference filters). The points from Najjar are scaled to fit the model prediction at 460 nm.

Table 1: Comparison of studies for spatial sensitivities in NIF-responses focusing on visual field differences in melatonin suppression. (Teikari 2012)

Reference	Measure	Results
Adler et al. 1992	Melatonin suppression	No difference in melatonin suppression between central and peripheral visual field
Gaddy et al. 1992	Melatonin suppression	More light required for lower retinal illumination compared to full retinal exposure
Brainard et al. 1997	Melatonin suppression	Binocular light exposure was more effective than monocular light
Visser et al. 1999	Melatonin suppression	Difference between nasal and lateral areas, but not between the upper and lower areas.
Lasko et al. 1999	Melatonin suppression	Lower half of the human retina (upper visual field) more sensitive
Smith et al. 2002	Melatonin suppression	No difference between lower and upper visual field in the elderly
Glickman et al. 2003	Melatonin suppression	Lower retina (upper visual field) being more sensitive for melatonin suppression.
Rüger et al. 2005	Melatonin suppression	Nasal retina more sensitive than temporal for melatonin suppression
	CBT	No difference between nasal and temporal retina
	Subjective sleepiness (KSS)	No difference between nasal and temporal retina

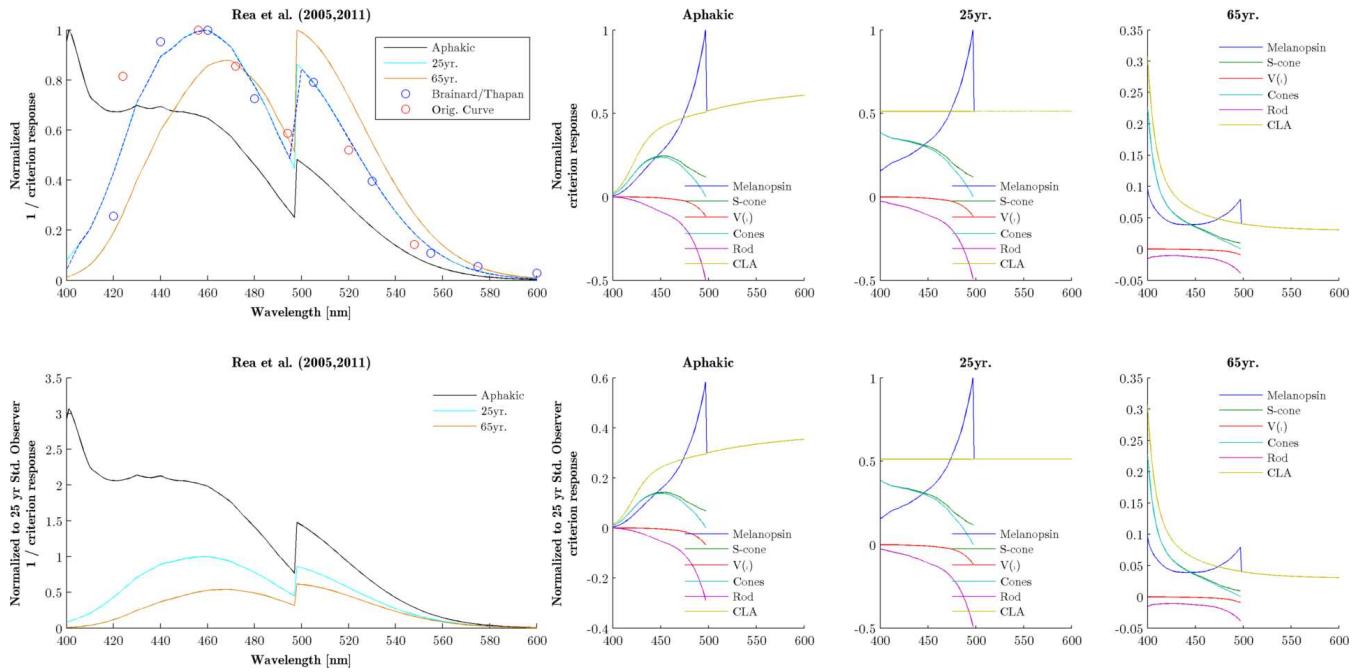


Figure 2: **Model predictions for a monochromat stimulus** (equal energy with  $hbw=1$  nm), the left column as in Figure 1. The three additional column for each ocular media model display the different contributions for CLA (Eq. (11)), Melanopsin (Eq. (2)), S-cones (i.e. blue, Eq. (3)),  $V(\lambda)$  (i.e. yellow, Eq. (4)), Cones (Eq. (5)), and Rods (Eq. (6)). In the row above, all values are normalized to unity (in the 65 years, the peak value is at 380 nm actually and not displayed). In the row below the values are normalized to 25 year observer as in . The component plots are expressed in “criterion responses”, thus the higher the component value, more stimulus is needed on that particular wavelength to produce the criterion response.

loop probably allows the rod pathway to take advantage of the cone bipolar circuitry in the IPL, such as direction-selective wiring or other complex operations.

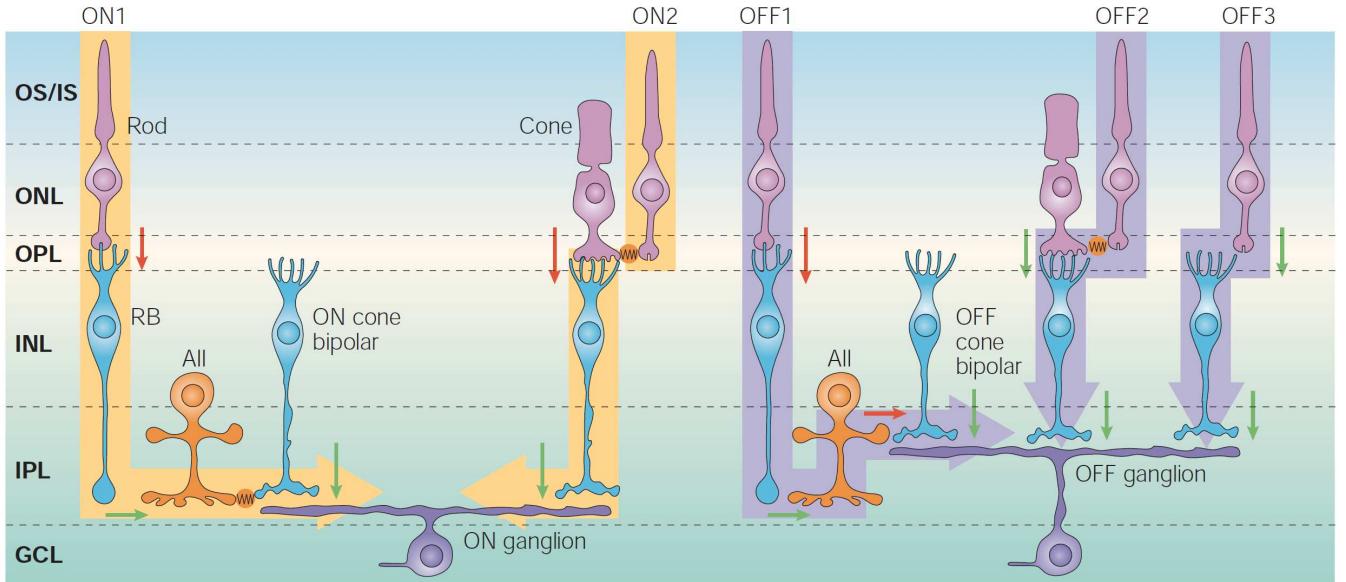
Recent studies have shown that the rod signal can also be transmitted by **alternative routes**. One such route is through gap junctions between rod spherules and cone pedicles (DeVries and Baylor 1995) (Figure 3, ON2, OFF2). In addition, some OFF-cone bipolar cells contact rod spherules directly (Soucy et al. 1998, Hack et al. 1999, Tsukamoto et al. 2001) (Figure 3, OFF3). So, there are at least three circuits for the rod signal, and recent evidence indicates that the different ganglion cells of the mouse retina tap preferentially into one of these circuits (Deans et al. 2002).

#### *Light-driven regeneration in rods*

**From Teikari 2012:** Hubbard and Kropf 2012 was first to show that normal photobleaching could be prevented if additional light was absorbed by the bleaching intermediates, referred as the “**photoreversal**” of bleaching (Williams 1964). Similar phenomenon was observed in early receptor potential (ERP) recordings of a rat, with complete bleaching of rhodopsin abolishing early receptor potential, but being recordable again after a blue light flash (Figure 4B, Cone 1967). The most likely intermediate photoproduct being photoreversed was suggested to be metarhodopsin II, that has a **peak absorbance at ~380 nm** (see Table 2 for intermediate characteristics) with a 1.2 times higher extinction coefficient than rhodopsin (Weale 1967; Bartl and

Vogel 2007). Further rat study *in vivo* by Grimm et al. 2000 estimated the **quantum efficiency of photoisomerization to be roughly ~0.3** (Figure 4A,inset), while demonstrating that light at 550 nm was able to fully bleach the rhodopsin, in contrast to the “rhodopsin-equal” exposure at 403 nm that left significant portion of rhodopsin to the unbleached state (Figure 4A). This blue-enhanced photoreversal was linked to the increased susceptibility for blue-light damage (Grimm et al. 2001).

Additionally, some residual photoregeneration could occur via the putative **retinal G protein-coupled receptor (RGR) photoisomerase pathway** (Chen et al. 2001), with ? showing dim light an **4-fold effect in accelerating rhodopsin regeneration**, although independent of RGR. Authors suggested a plausible candidate for accelerated recovery to be the *light-dependent palmitoylation of sRPE65 to mRPE65*, as palmitoylation of retinal pigment epithelial protein 65 (RPE65) has shown to accelerate the delivery of retinyl esters to the isomerohydrolase (Xue et al. 2004). The authors (?), however did not extend their protocol to include the wavelength-dependent effect of such acceleration making quantification of their findings problematic for our purposes. An equilibrium photoreversal at 1% of the rate of photobleaching (metarhodopsin II and rhodopsin stimulation ratio in response to the used white fluorescent light) was estimated in their study, which was considered being insignificant in practice.

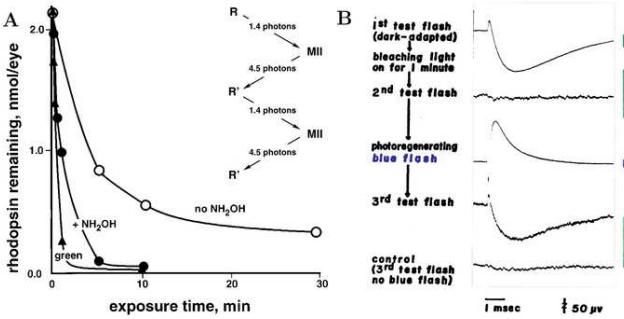


**Figure 3: The rod pathways of the mammalian retina.** The neurons in the mammalian retina have a laminar distribution: OS/IS, outer and inner segments of rods and cones; ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer. The ‘classical’ pathways are ON1 and OFF1. In the **ON1 pathway**, rods are hyperpolarized by light and transfer their signals onto the invaginating dendrites of rod bipolar (RB) cells. RB cells express the glutamate receptor mGluR6, causing a sign inversion at the synapse (red arrow). RB cells are therefore depolarized by light (Raviola and Dacheux 1987). They transfer their signal through a glutamatergic (AMPA;  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) synapse (green arrow) onto AII amacrine cells. AII amacrine cells make gap junctions (electrical synapses expressing connexin-36) with the axons of ON cone bipolar cells, which in turn synapse (green arrow) with ON ganglion cells. In the **OFF1 pathway**, the pathway from rods to AII cells is identical to ON1, but the output of AII cells differs. They make inverting, glycinergic synapses (red arrow) with the axons of OFF cone bipolar cells, which in turn synapse (green arrow) with OFF ganglion cells. In the **ON2 pathway**, the rod signal is transmitted to the cone pedicle through gap junctions (expressing connexin-36) and then follows the cone pathway to the ON ganglion cells. The **OFF2 pathway** is comparable with that of ON2 to the OFF ganglion cells. In the **OFF3 pathway**, OFF cone bipolar cells make direct synaptic contacts with the base of rod spherules and transfer this signal directly onto OFF ganglion cells. These pathways can be pharmacologically dissected and the recent availability of a connexin-36-knockout mouse has shown that different pathways operate under different lighting conditions (Deans et al. 2002). Modified, with permission, from Demb and Pugh Jr. 2002. (Wässle 2004)

**Table 2:** Spectral parameters of rhodopsin and products of its photolysis in *B. bufo* (first row) and *R. temporaria* rods (second row)<sup>a</sup> (Kolesnikov et al. 2003).

	Rh	Meta I	Meta II	Meta III	Retinal	P440	Retinol
$\lambda_{max}$	502 nm	489 503	379 382	479 478	381 381	440 449	325 325
$\epsilon$	1 1	1.09 1.09	1.16 1.16	1.0 1.0	1.05 1.05	0.9 0.9	1.29 1.29
DR	6.4 5.7	6.4 5.7	12.5 14.6	12.5 14.6	0.49 0.5	0.36 0.7	0.41 0.5

<sup>a</sup>  $\lambda_{max}$ , wavelength of maximum absorbance;  $\epsilon$  molar extinction at  $\lambda_{max}$ , with respect to rhodopsin; DR, dichroic ratio Transversal polarization/Longitudinal polarization. In each row, the upper line corresponds to *B. bufo*, and the lower, to *R. temporaria*.  $\lambda_{max}$  for retinal and retinol and  $\epsilon$  for retinol are taken from Knowles et al. 1977.



**Figure 4: Photoreversal of rhodopsin.** **A)** Bleaching of rhodopsin *in vivo* by blue and green light. Eyes of anesthetized rats were exposed to green light ( $\blacktriangle$ , 550 nm), to blue light ( $\circ$ ; 403 nm), or to blue light in the presence of NH<sub>2</sub>OH to inhibit potential photoreversal of bleaching ( $\bullet$ ; 403 nm). rhodopsin disappeared rapidly in green light and in blue light with NH<sub>2</sub>OH, conditions with minimized photoreversal of bleaching. However, in blue light without NH<sub>2</sub>OH, rhodopsin disappeared slowly, despite irradiation with the same photon fluxes as in the other two conditions. **Inset:** Scheme for calculating the total number of photons absorbed by rhodopsin (R) and the photoreversible intermediate, assuming it is metarhodopsin-II (MII). Photoregenerated rhodopsin is shown as R'. The numbers on the arrows indicate the average numbers of photons needed to cause the reactions and reflect the fact that the quantum efficiencies of bleaching and photoreversal are not unity (Grimm et al. 2000). **(B)** Photoregeneration of the ERP in the eye of the albino rat. Both the test flash and the bleaching light consisted of long wavelengths primarily absorbed by rhodopsin. The blue, photoregenerating flash contained wavelengths absorbed by the longer-lived intermediates of the bleaching process. The control trace was obtained from a second eye subjected to the same bleaching exposure and test flashes, but without the blue flash. Temperature, 27°C (Cone 1967).

### 2.2.2. Cones

From Dacey 2000: “A basic property of the cone array critical for ultimately understanding the pathways for luminance and red-green spectral opponency is the relative number and spatial arrangement of L and M cones across the retina. A variety of techniques applied over many years have indirectly suggested a random arrangement and **great variability in the ratio of L to M cones across individuals**. This variability is the most likely explanation for **individual variation in photopic spectral sensitivity** (for review, see Lennie et al. 1993). Direct observations of the two cone types *in situ* have confirmed that the cones are arranged randomly and vary greatly in relative numbers across individuals (Roorda and Williams 1999). Adaptive optics was used to attain the sharpest images ever of the retina and directly view individual cones. These images were then combined with retinal densitometry to identify the photopigment of each cone. Roorda and Williams 1999 found L- to M-cone **ratios** of about **1:1 and 4:1** for two human subjects.”

From Wässle 2004: “Cones respond to a light stimulus with a **graded hyperpolarization**, and release glutamate at their specialized synaptic terminal, the cone pedicle. **Transmitter release is high in darkness** and is reduced by light. The cone pedicle is probably the **most complex synapse** in the CNS (Haverkamp et al. 2000).

It contains between 20 and 50 presynaptic ribbons, each of which is flanked by synaptic vesicles. Invaginations at the ribbons allow horizontal and ON cone bipolar cell dendrites to be inserted. OFF cone bipolar cell contacts are found at the cone pedicle base. Each cone pedicle makes up to 500 contacts, although the number of postsynaptic cells is smaller because each one receives multiple contacts. Two types of horizontal cell and eight types of cone bipolar cell are engaged with every cone pedicle. So, at the first synapse of the retina the light signal is distributed into multiple pathways.

L- and M-cone pedicles are coupled to their immediate neighbours and to rod spherules (the synaptic terminals of rod photoreceptors) through electrical synapses (**gap junctions**) where connexin-36 is expressed. **S-cone pedicles** are only sparsely coupled (Feigenspan et al. 2004, ?, Li and DeVries 2004). This coupling allows the network to **average out the uncorrelated noise** in individual cones, and thereby to improve the response to a light stimulus (Lamb and Simon 1976). ”

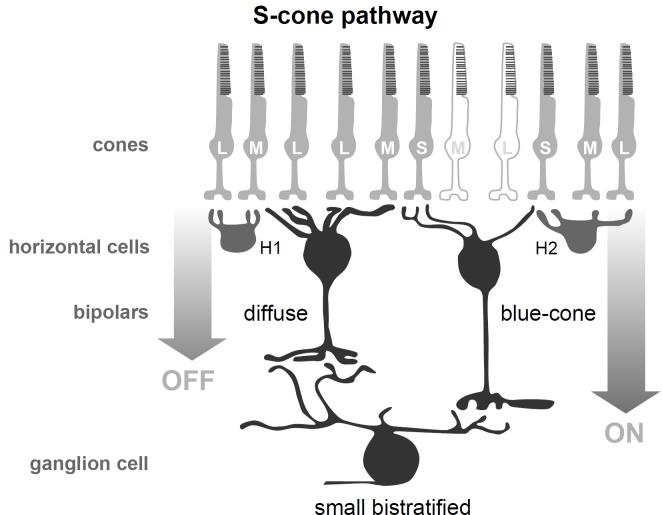
### S-Cones

From Suzuki et al. 1998:

“The present study applied a new technique to separate S- and LM-cone ERG by the use of a light-emitting diode (**LED**) **built-in contact lens electrode**, which provides an intense light with wavelengths of 450 nm and 566 nm (Horiguchi et al. 1995). We recorded the ERGs in **pseudophakic** subjects to avoid the influence of lens yellowing. ... The results of the present study can be understood well by the following explanation taking the theory of Sieving et al. 1994 into consideration. The **age-related changes occur in bipolar cells; off-bipolar cells are more vulnerable than on-bipolar cells**. Therefore, the amplitude of the a-wave is reduced greatly but **reduction in the amplitude of the b-wave is small**. ...

Yoshida and Uji 1976 recorded the S-cone ERG b-wave using yellow light for adaptation and reported that the b-wave in postoperative **aphakic eyes** increased greatly. Thereafter, Machida et al. 1990 compared changes in pseudophakic eyes at various wavelengths (400–600 nm, 14 colors) and concluded that the amplitude of the b-wave in the region below 520 nm changed markedly before and after surgery. ... **Vulnerability of the S-cone system** has been reported psychophysically in many studies (Knoblauch et al. 1987) and the S-cone ERG b-wave actually decreased markedly with aging in the present study using pseudophakic eyes, while the LM-cone ERG b-wave did not show a decrease. However, as mentioned above, the S-cone ERG b-wave derives from *on-bipolar cells*, whereas the LM-cone ERG b-wave is produced by the *interaction of on- and off-bipolar cell response*.”

From Dacey 2000: “Beginning with the identification of the blue-ON bistratified ganglion cell type, the major elements in this **S-cone opponent pathway** were assembled



**Figure 5: Identified cell types and circuitry of the S-cone, blue-ON pathway.** The small bistratified ganglion cell receives synaptic input to the inner stratifying dendrites from a distinct S-cone-contacting bipolar cell, the blue-cone bipolar cell. H2 horizontal cells contact L, M, and S cones and are the probable basis for a surround in the blue-cone bipolar cell and the origin of S- versus (L+M)-cone spectral opponency. The sparse outer stratifying dendrites of the small bistratified ganglion cell receive input from diffuse cone bipolar types that contact L and M cones nonselectively. H1 horizontal cells contact L and M cones and are the probable basis for an inhibitory surround in the diffuse bipolar cell. Combined input from these ON and OFF bipolar cell pathways creates a spatially co-extensive S-ON, OFF (L+M)-opponent receptive field. (Dacey 2000)

rapidly and are summarized in the schema shown in Figure 5. The bistratified dendritic tree of the blue-ON cell suggested a simple but unexpected mechanism for the opponent light response (Dacey and Lee 1994), termed the **ON-OFF pathway hypothesis** (Dacey 1999). This hypothesis proposes that S-ON/L+M-OFF opponency originates **at the level of the excitatory bipolar-ganglion cell** connection by converging an ON S-cone bipolar input and an OFF L+M cone bipolar input to the inner and outer dendritic tiers of the bistratified dendritic tree, respectively. Thus the small bistratified cell would correspond to an ON-OFF cell type, excited in parallel by both an ON- and an OFF-bipolar population. ... result from Dacey et al. 1996 does not completely support the ON-OFF hypothesis but suggests rather that the S-(L+M) **opponency** must already be **present** in the light response of the **blue-cone bipolar cell**."

### 2.2.3. Horizontal cells

From Dacey 1999: "H1 cells hyperpolarize to light across the spectrum and show a spectral sensitivity like that of the **photopic luminosity** function, strongly dominated by L- and M-cone input (Dacheux and Raviola 1990). Two major questions remained **unanswered**. Firstly, does a **second population of H1-like cells** exist that show selectivity in the degree to which they contacted the three cone types, and if so, do these cells show **spectral**

**opponency?** Secondly, what is the **nature of the light response of H2 cells**? Do these cells receive a major physiological input from S-cones as some anatomical data had suggested?

In recordings from now over 200 cells with the characteristic morphology of H1 cells, I have found a single characteristic response to cone isolating stimuli: H1 cells hyperpolarize to light that modulates either the L- or M-cone in isolation, but **do not respond to S-cone** isolating modulation. The spectral sensitivity of the H1 cells as measured with the HMP (heterochromatic modulation photometry; Pokorny et al. 1989) protocol reflected additive input from L- and M-cones and showed a response minimum near the equiluminance. The spectral sensitivity as shown by the HMP data reinforces the anatomical observation that H1 cells draw input indiscriminately from L- and M-cones and show a spectral sensitivity like the photopic luminosity function, VI. Since VI is well characterized by a **1.6 to 1 ratio** in the relative number of the L- and M-cones (or the relative synaptic gain of the two cone types, see e.g. Lennie et al. 1993) the HMP data provides indirect evidence that, **at least in the retinal periphery**, the L- and M-cone mosaic is similarly organized in macaque and human retina. This is consistent with the same conclusion derived from analysis of the spectral sensitivity of M-ganglion cells (Lee et al. 1988), and is discussed further below.

As with the H1 cells, the **H2 horizontal cells** also receive hyperpolarizing input from both L- and M-cone, the null point for these cells in the HMP protocol was similar to that of the H1 cells suggesting that the H2 cell network does not show any preference for selecting L- or M-cone input. Unlike the H1 cells however, the **H2 cells also give a large response to the S-cone stimulus**. The response to S-cone modulation however is also hyperpolarizing so that no spectral opponency is conferred by this additional cone input. ... Even though the **S-cones** make up less than 10% of the cone population they appear to have a **stronger** anatomical, and correspondingly physiological, input to the H2 cells than either the L- or M-cone population.

The **significance** of this S-cone dominated horizontal cell pathway **is not clear** but it raises a problem for understanding the nature of the presumed feedback signal from horizontal cells to cones. Given that the H2 cell contacts L- and M-cones it would be expected that strong S-cone stimulation **should have a depolarizing effect** on the H1 cell via a feedback pathway, but this is **not observed**. The two horizontal cell types therefore may function in parallel with their output primarily feedforward to bipolar cell dendrites. In **sum**, evidence is now strong that the primate, like other mammals, has **two horizontal cell types**; these types are capable of selectively **avoiding** or **seeking out S-cone axon** terminals. However, no selectivity is found for L- or M- cones and all cone inputs to both cell types are hyperpolarizing."

*From Dacey 2000*: “The probable basis for an (L+M)-cone-mediated surround in the blue-cone bipolar cell would be via **negative feedback** from a distinct **horizontal cell type**—the **H2 horizontal cell**—recently shown to be a major component of the S-cone pathway (Dacey et al. 1996). The H2 horizontal cell makes contact with all three cone types, but like the blue-cone bipolar cell, many dendrites **preferentially seek out** and make contact with the **sparse S cones**. The result is that the **light response of the H2 horizontal cell** is driven with **relatively equal strength by L-, M-, and S-cone input**. The H2 horizontal cells could therefore contribute an (L+M)-cone opponent surround to the S cone via a **negative feedback** that would then be conveyed to the blue-cone bipolar cell.

Would an H2 horizontal cell-mediated bipolar surround be of the **appropriate size** to provide for the spatially *coextensive* (L+M)-cone inhibitory field observed in the blue-ON ganglion cell? The **answer** appears to be **yes**. In general, horizontal cells form an electrically coupled *syncytium* that **generates large receptive fields** extending far beyond the extent of the photoreceptor contacts of a single cell. H2 horizontal cells also form a **coupled network**; however, the spatial extent of the H2 horizontal cell receptive field is **relatively small** and comparable in size to the blue-ON ganglion cell receptive field.

A basic question about the retinal basis for a luminance signal is **whether variability in the L- and M-cone mosaic** has a neural representation beyond the cones or whether neural processing can **adjust the relative strengths of L- and M-cone signals** (e.g. Calkins et al. 1998b). If the midget and parasol pathway cells draw randomly from all the L and M cones in their receptive fields, would the physiological balance of the two cone inputs to the receptive field reflect local variability in the L- and M-cone ratio? .. For a large sample of **H1 cells** we found a **striking variability** in L- to M-cone contrast gain ratio with a mean of **1.5:1** (L/L+M) (Figure 12a). This mean value is close to the relative L- and M-cone weights that characterize the photopic luminosity function (Lennie et al. 1993). The large variability from cell to cell was accounted for by systematic variation in L- and M-cone **gain at different retinal locations** and overall variation across different retinas. Both of these sources of variability are now well-documented properties of the cone mosaic itself (Hagstrom et al. 1998, Roorda and Williams 1999) and suggest that the **gain ratios that we measured directly reflect the anatomical cone ratios**. Recent molecular genetic analysis of the L- to M-cone ratios, in pieces of macaque retina in which the physiological gain ratios were measured, strongly supports this conclusion (Deeb et al. 2000).”

*From Wässle 2004*: “Traditionally, it is assumed that horizontal cells release the inhibitory transmitter GABA ( $\gamma$ -aminobutyric acid) and provide **feedback inhibition** at the photoreceptor synaptic terminal. As horizontal cells summate light signals from several cones, such feedback

would cause lateral inhibition, through which a cone’s light response is **reduced by the illumination of neighbouring cones**. This mechanism is thought to **enhance the response to the edges of visual stimuli** and to reduce the response to areas of uniform brightness. However, the GABA-feedback model has recently been **challenged** because of the lack of classical synapses from horizontal cells onto cones, the lack of GABA receptors on mammalian cones and the lack of GABA uptake into horizontal cells from the medium.

Two **alternative hypotheses** of horizontal cell function have been proposed. One assumes that horizontal cells **express connexins** at their processes, which are inserted into cone pedicles and rod spherules (hemigap junctions). Current that flows through the channels formed by the connexins **changes the extracellular potential** in the invaginations and thus **shifts the activation curves** of the cone pedicle Ca<sup>2+</sup> channels. By this mechanism of electrical feedback, horizontal cells could **modulate the glutamate release** from cones and rods (Kamermans et al. 2001).

The **second hypothesis** also postulates modulation of the Ca<sup>2+</sup> channels that regulate the release of glutamate from cones; however, the mechanism responsible is a change in pH within the invagination, caused by voltage-dependent ion transport through the horizontal cell membrane (Hirasawa and Kaneko 2003). There is also evidence that light-dependent release of GABA from horizontal cells provides **feed-forward inhibition** of bipolar cell dendrites. Irrespective of their precise mode of action, horizontal cells sum light responses across a broad region, and subtract it from the local signal. Because horizontal cells are coupled through gap junctions, their receptive fields can be much wider than their dendritic fields (Hombach et al. 2004). Horizontal cell feedback in fish and turtle retinae seems to be cone-specific. However, **no such chromatic organization** of horizontal cell feedback has been observed in the **primate** retina (Dacey et al. 1996).

*From Packer et al. 2010*: “The only known pathway by which **L and M cones could transmit an opponent signal to S cones** is via **H2 horizontal cells** (Dacey et al. 1996). Since H2 horizontal cells receive input from all three cone spectral types (Dacey et al. 1996), the opponent surround of an S cone would be expected to have an S cone component as well. While none was observed, the **lack of a demonstrable contribution from S cones** in the surround may simply reflect our inability to resolve a small inhibitory S cone signal when superimposed on a large excitatory S cone phototransduction signal.

We have determined that **horizontal cell feedback to S cones creates the first stage of blue-yellow opponency** in the primate retina. The maximal response amplitudes of the S cone center and (L+M) cone surround were roughly comparable when recorded at a membrane potential of 40 mV.

The calcium dependence of the opponent yellow sur-

round may help explain the **paradoxical psychophysical** finding that yellow light can increase sensitivity to blue light (“transient tritanopia”) —a flash of blue light becomes less visible when a steady blue background is turned on, but becomes more visible when yellow light is added to the blue background (Pugh and Mollon 1979, Valeton and Norren 1979, Pugh and Larimer 1980, Polden and Mollon 1980, Mollon et al. 1987). The S cone responses we describe here suggest a possible explanation: the blue background **hyperpolarizes S cones**, reducing the slope conductance of the calcium current and **thus reducing synaptic gain**. The addition of **yellow light activates horizontal cell feedback**, increasing the calcium current and its slope conductance, and thereby **restoring synaptic gain** (VanLeeuwen et al. 2009). This explanation would not require contribution from melanopsin, and namely the metamelanopsin contribution (Mure 2009, Teikari 2012).

Our results indicate that **opponent spectral interactions** are created at **two synaptic levels** in the retina. At the **S cone synapse**, horizontal cell feedback creates both blue-yellow chromatic opponency and center-surround spatial opponency. Surprisingly, these large opponent surrounds **are not retained** by S-cone driven ganglion cells where the yellow-OFF and blue-ON fields are more comparable in spatial extent (Solomon et al. 2005, Field et al. 2007, Crook et al. 2009). Why is the spatial opponency of S cones **no longer evident in ganglion cells?**

Both the S-ON and the (L+M)-OFF bipolar cells that comprise the input to the S-cone-driven ganglion cell have themselves opponent (L+M) surrounds, these surrounds reflecting horizontal cell feedback to cones. When signals from the ON- and OFF-bipolar cells are combined by the ganglion cell, the **surrounds would be expected to cancel**, thereby **creating pure chromatic opponency with little spatial opponency** (Crook et al. 2009). These receptive field properties are retained by the downstream neurons of the lateral geniculate nucleus (Wiesel and Hubel 1966, Derrington et al. 1984). Thus it appears that the **main function of yellow opponency** in S cones is **not to create a chromatic signal**, because that function is recapitulated by circuitry in the inner retina, but rather to *estimate and offset average background intensity* and *chromaticity* so as to **optimize transmission of short wavelength signals across the S cone synapse**. The use of presynaptic inhibition to enhance synaptic gain may be a common modulatory mechanism used by the nervous system to counteract synaptic saturation and to optimize synaptic transmission. For example, activation of presynaptic GABA<sub>B</sub> receptors **reduces synaptic depression** in auditory nerve fibers (Brenowitz et al. 1998)

From Masland 2012b: “The large majority of mammals have two types of horizontal cells. Horizontal cells provide **inhibitory feedback** to rods and cones and possibly to the

dendrites of bipolar cells, though this remains controversial (Herrmann et al. 2011). The leading interpretation of this function is that it provides a mechanism of **local gain control** to the retina. The horizontal cell, which has a moderately wide lateral spread and is coupled to its neighbors by gap junctions, measures the **average level of illumination** falling upon a region of the retinal surface. It then subtracts a proportionate value from the output of the photoreceptors. This serves to hold the signal input to the inner retinal circuitry within its operating range, an extremely useful function in a natural world where any scene may contain individual objects with brightness that varies across several orders of magnitude. The signal representing the brightest objects would otherwise dazzle the retina at those locations, just as a bright object in a dim room saturates a **camera’s film or chip**, making it impossible to photograph the bright object at the same time as the dimmer ones.

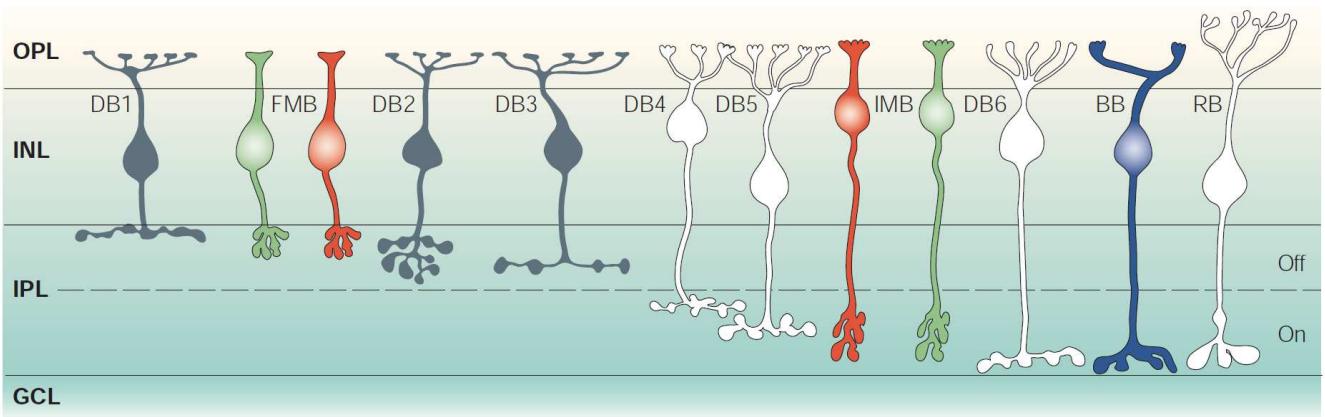
The **synapses** by which horizontal cells provide their feedback signals appear to use both conventional and unconventional mechanisms; they remain a matter of active investigation (Jackman et al. 2011, Klaassen et al. 2011). Taken as morphological populations, however, the **horizontal cells are relatively simple**. They can be stained for a variety of marker proteins in different animals. They, too, have been quantitatively mapped across the retinal surface in many species (Collin 2008). ”

#### 2.2.4. Bipolar cells

From Dacey 1999: “The retinal bipolar cells convey photoreceptor signals to the amacrine and ganglion cells, yet despite this central position in the retinal circuitry, **very little is known** about their responses to light. ... Briefly, primate cone bipolar cells can be divided into **two main classes**: **diffuse** bipolar cells, distinguished by connections to multiple cones; and **midget** bipolar cells, distinguished, over much of the retinal area, by a “private line” connection to a single cone axon terminal. ”

From Wässle 2004: “The axons of OFF and ON cone bipolar cells terminate at different levels (strata) within the IPL: **OFF in the outer half, ON in the inner half**. However, superimposed on this *ON/OFF dichotomy*, further bipolar cell types have been described (Figure 8) and every mammalian retina that has been studied contains at least four types of OFF and four types of ON cone bipolar cell (Ghosh et al. 2004, MacNeil et al. 2004). We are just beginning to understand their functional roles (Freed 2000). ... The preponderance of transient light responses in the middle of the IPL is further supported by the recent finding of **voltage-dependent sodium channels** at the axon terminals of these bipolar cells (Pan and Hu 2000). Such channels would **speed up** the light responses of the bipolar cells.

Most cone bipolar cells contact between five and ten cones (Figure 8, **diffuse bipolar cells**). In the primate retina, in addition to these diffuse types, bipolar cells have



**Figure 6: Bipolar cell types of the primate retina.** The cells were analysed in Golgi-stained whole-mounts and are shown here schematically in a vertical view. Their axons terminate at different levels in the IPL; those terminating in the outer half are putative OFF cone bipolar cells, those terminating in the inner half are ON bipolar cells. **Diffuse bipolar cells** (DB1–DB6) contact — non-selectively — between 5 and 10 L- and M-cone pedicles. Some DB cells also contact S-cone pedicles. Flat midget bipolar (FMB) cells contact a single L- or M-cone and carry a chromatic OFF signal. Recently, an FMB cell connected to S-cone pedicles has been described, but it is not known whether it contributes to the chromatic pathways. Invaginating **midget bipolar** (IMB) cells contact a single L- or M-cone and carry a chromatic ON signal. **Blue cone bipolar** (BB) cells selectively contact 1–5 S-cone pedicles and carry an S-cone ON signal. **Rod bipolar** (RB) cells contact between 6 rod spherules (at the fovea) and 40 (in the periphery) and carry a scotopic ON signal. (Wässle 2004)

been described that contact a single cone pedicle (Figure 8, midget bipolar cells) and that selectively contact S-cone pedicles (Figure 8, blue cone bipolar cells; Kouyama and Marshak 1992a, Calkins 2001). **Blue cone bipolar cells** have also been described in the rat and mouse retina but their circuitry has only been worked out in primates. Here they contact between one and five S-cones at invaginating contacts, so they are ON bipolar cells and transfer an S-cone signal to the innermost part of the IPL.

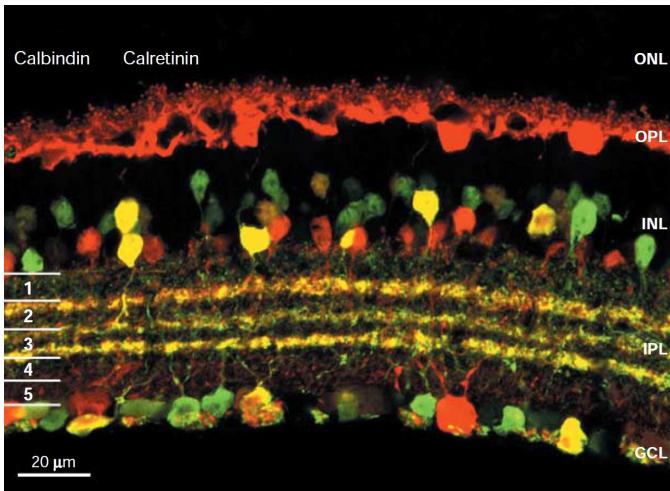
In the **peripheral retina**, the density of cones, bipolar cells and ganglion cells is low, whereas towards the centre of the retina the density of these cells increases steeply. This results in greatly improved spatial resolution (visual acuity) at the **fovea** or central area. Concomitant with the increase in density, the cells' dendritic fields become smaller. During evolution, the spatial resolution of the primate eye and retina has been optimized. To achieve this, a high cone density and a low cone-to-RGC ratio have converged in the '**acuity pathway**'. The anatomic limits for this optimization are reached when each cone is connected through a midget bipolar cell to a midget ganglion cell, establishing a **private line to the brain**. It has been suggested that only after this one-to-one connection in the central retina had evolved, **35 million years ago**, did a subsequent mutation in the L-cone pigment create L- and M-cones of varying proportions at random spatial locations (Boycott and Wässle 1999, Nathans 1999). The midget system of the central retina could transmit this chromatic information to the brain where it could be used, for example, to detect red fruit among green leaves.

This '**midget theory**' of the evolution of trichromacy in primates has its basis in the general pattern of mammalian wiring .. It also explains why mammals other than primates have not evolved trichromacy: their cone bipo-

lar cells sum the signals of several cones and their RGCs sum the signals of many bipolar cells. .. The idea that trichromacy 'piggy-backs' on the high-acuity system of primates also postulates that the midget bipolar cells perform a 'double duty' in visual signalling — **acuity and trichromacy** — an idea that has been promoted for some years (Inglis Jr and Martinez-Uriegas 1983).

However, **other models** for the L- and M-cone selective pathway of the primate retina have also been proposed (Calkins and Sterling 1999). In these models, chromatic bipolar cells contact **several L- and M-cones**: it is postulated that they express ionotropic GluRs (OFF-type) at their contacts with L-cones and metabotropic GluRs (ON-type) at their M-cone contacts. Such cells would be **red OFF/green ON** bipolar cells and similar types have been described in fish and turtle retinae (Haverkamp et al. 1999). So far no evidence has been presented in mammalian retinae, including primates, for such a cone-specific expression of GluRs at bipolar cell dendrites. So, it seems that **diffuse bipolar cells** transmit a **luminosity** signal to the **IPL**, **midget bipolar cells** an L- and M-cone signal and blue cone bipolar cells a S-cone selective signal.

Axons of different bipolar cell types terminate at **different strata** within the **IPL**, where they meet the dendrites of specific ganglion cells (Roska and Werblin 2001, Werblin and Roska 2004) (Figure 6). The IPL is subdivided into **five strata of equal thickness**. In the mouse retina, these strata can be easily defined by immunolabelling the retina for the calcium-binding proteins *calbindin* and *calretinin* (Figure 7), which reveals three densely labelled horizontal bands of processes (Haverkamp and Wässle 2000, Ghosh et al. 2004). The outer band (**stratum 1–2**) contains the processes of the OFF-cholinergic amacrine cells, the dendrites of OFF-alpha cells and the outer dendritic



**Figure 7: Stratification of the inner plexiform layer (IPL).** Vertical section through a mouse retina that was double immunostained for calbindin (red) and calretinin (green) (Haverkamp and Wässle 2000). Horizontal cells and their processes in the outer plexiform layer (OPL) express calbindin only. Amongst the amacrine cells in the inner nuclear layer (INL) and the ganglion cells, different levels of colocalization of calbindin and calretinin can be observed. The labelled dendrites of amacrine and ganglion cells are confined to three narrow bands, segregating four bands of reduced label. This shows that the IPL is precisely stratified and within these strata different aspects of the light signal are processed. GCL, ganglion cell layer; ONL, outer nuclear layer. Reproduced, with permission, from Haverkamp and Wässle 2000. (Wässle 2004)

branches of direction-selective cells. This band is densely packed with synapses and GABA<sub>A</sub> receptors (Brandstätter et al. 1995), and transient light responses and OFF direction-selective responses are ‘calculated’ there (Roska and Werblin 2001). The band in the centre of the IPL (**stratum 2–3**) separates the OFF sublamina (outer) from the ON sublamina (inner). The *polyaxonal amacrine cells* mentioned above ramify in this band, as do two GABA-containing amacrine cells. As well as GABA, these cells contain a neuromodulator (nitric oxide and a catecholamine, respectively). **Their functions are unknown.** The band in the inner IPL (**stratum 3–4**) contains the axon terminals of an ON bipolar cell (Brown and Masland 1999), the processes of the ON-cholinergic amacrine cells, the dendrites of ON-alpha cells and the inner dendritic branches of direction-selective cells. This band is also densely packed with synapses and GABA<sub>A</sub> receptors, providing the circuitry for ON-transient light responses and ON direction-selective responses.”

*From Hoshi et al. 2009:* “The inner plexiform layer (IPL) of the retina is functionally stratified according to the polarity of bipolar cell inputs (Famiglietti et al. 1977, Wässle and Boycott 1991). The response polarity of the **10 –12 types of bipolar cell** is determined by the differential expression of postsynaptic glutamate receptors, in which OFF cone bipolar cells express AMPA/kainate receptors (DeVries 2000) and ramify in **sublamina a** of the IPL, whereas ON bipolar cells express metabotropic glutamate

mGluR6 receptors and descend to **sublamina b** (Nomura et al. 1994). This separation of ON and OFF pathways is a **fundamental principle** of retinal organization. However, dopaminergic amacrine cells (DACs) do not fit neatly into this mold. Most of their dendrites ramify high in the OFF sublayer and receive bipolar input at ribbon synapses, yet they produce an ON response to light (Zhang et al. 2007).

Recently, we have characterized **an unusual bistratified ganglion cell type** whose OFF dendrites return to **sublamina b** to terminate. This ganglion cell spikes only **at light onset** and contains dendritic spines in sublamina a that contact ON bipolar cells as their axons descend through the OFF sublamina. Synaptic ribbons and glutamate receptors are also present at these conjunctions. We found that these bipolar cells also make synaptic contacts in **sublamina a** with DACs and ipRGCs. These novel bipolar cell inputs **break the stratification rules** for the IPL and may account for the **anomalous ON responses** of several postsynaptic targets in the OFF layers of the IPL.

All mammalian retinas contain cells that release the neuromodulator dopamine (Witkovsky 2004). These cells (DACs) can be stained with an antibody to TOH and may comprise **three different subclasses** according to differing physiological responses (Zhang et al. 2007; 2008). There is currently **no evidence for distinct anatomical classes**. Light-driven dopamine release appears **to be driven by ON bipolar cells** because release is blocked by L-APB (Boelen et al. 1998), but the **source of the excitatory drive has never been established.**”

*From Packer et al. 2010:* “Human psychophysical studies indicate that **blue-yellow opponency** is created by neurons that receive opponent signals from S cones versus (L+M) cones (Hurwicz and Jameson, 1957; Krauskopf et al., 1982). One such neuron is the **small bistratified ganglion cell** (Dacey and Lee, 1994). The dendrites of the small bistratified cell stratify in both the ON and OFF portions of the inner plexiform layer, suggesting that the **blue-ON and yellow-OFF** responses reflect synaptic input from **S-ON bipolar cells** and (L+M)-OFF bipolar cells, respectively (Dacey and Lee, 1994; Calkins et al., 1998). However, in a recent study (Field et al. 2007), **both** the blue and yellow responses **were abolished** when the ON pathway was selectively blocked by DL-2-amino-4-phosphono-butyric acid (L-AP4), suggesting that **both the blue and the yellow signals arrive via the S-ON bipolar cell**. Since this bipolar cell contacts S but not L or M cones, it was inferred that the **(L+M) signal was already present in S cones**, and that it **arose from horizontal cell feedback** to S cones. In contrast, a later study found that L-AP4 selectively blocked the S-ON and **spared the (L+M)-OFF responses**, consistent with the (L+M) signal arriving via the (L+M)-OFF bipolar cell (Crook et al. 2009). Thus it **remains uncertain** whether blue-yellow opponency in

the retina arises from **horizontal cell** feedback to cones, from the convergence of ON- and OFF-**bipolar cell inputs** to the ganglion cell, or from some **combination of both.**"

*From Masland 2012b:* "Modern anatomical work and subsequent physiological evidence indicate that the true number of bipolar cell types is about 12 (Figure 8). As a consequence, it is believed that each of the 12 anatomical types of bipolar cell that contacts a given cone transmits to the inner retina a different component extracted from the output of that cone."

The difference between **ON** and **OFF** responses is due to the expression of two classes of glutamate receptor. **OFF bipolar cells** express AMPA and kainate type receptors, which are cation channels opened by glutamate; since photoreceptor cells **hyperpolarize** in response to light, these bipolar cells hyperpolarize in response to light as well, because less glutamate arrives from the cone synapse. **ON bipolar cells** express mGluR6, a metabotropic receptor, which, when glutamate binds to the receptor, leads to closing of the cation channel TRPM1. The receptor is thus **sign inverting**. When light causes less glutamate to be received from the photoreceptor terminal, cation channels open and the cell **depolarizes**.

... Another is a type of bipolar cell that generates  $\text{Na}^+$  action potentials (Figure 9).  $\text{Na}^+$  currents have been known to occur from studies of many retinas, but their functions are unclear (Ichinose and Lukasiewicz 2007). In response to a continually graded noise stimulus (more closely representing a natural scene), they generate **both graded and spiking** responses, the spikes occurring with millisecond precision. It thus appears that this bipolar cell trades the bandwidth inherent in graded signaling for spikes that can elicit a rapid and reliable response in transient-type ganglion cells (Saszik and DeVries 2012)."

### 2.2.5. Amacrine cells

*From Dacey 1999:* "The lack of spectral opponency in the H1 and H2 **horizontal cells** focuses attention on the amacrine cells, the laterally connecting interneurons of the inner retina, as a basis for **cone-opponent** circuitry. ... However, the physiology of mammalian amacrine cells is complex (Masland 1988), and little understood. Given the presence of up to **40 distinct amacrine cell populations**, most of which have yet to be characterized physiologically, the specific role of identified amacrine cell types in an opponent transformation remains an **unsettled and difficult question**."

It is possible to divide the amacrine cells physiologically into **two broad groups**, those cell types that **spike** and those, like the other retinal interneurons, that show only **graded changes** in potential in response to a synaptic input. ... A1 cell body is one of the largest in the amacrine cell layer it was easily targeted for intracellular recording in the *in vitro* retina (Dacey 1989). ... We

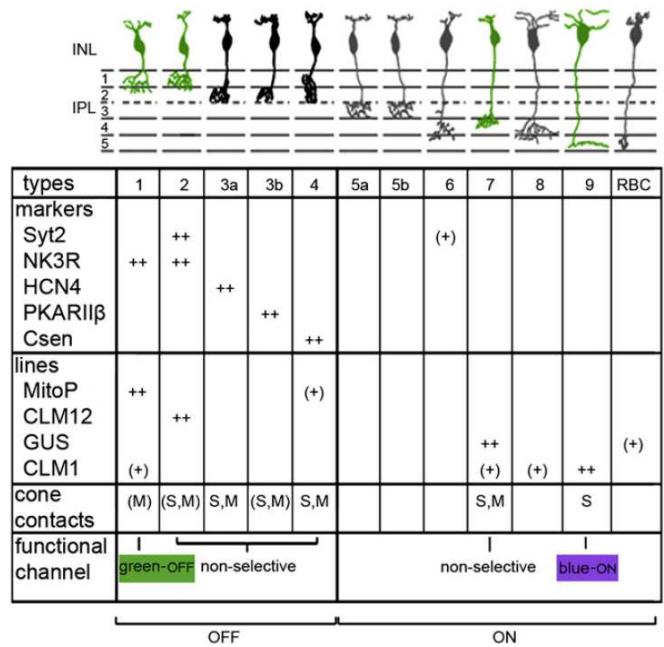


Figure 8: The Types of Bipolar Cells Observed in the Mouse Retina  
Note the different stratification within the inner plexiform layer and the molecular diversity of the cells. Reproduced with permission from Breuninger et al. 2011. (Masland 2012b)

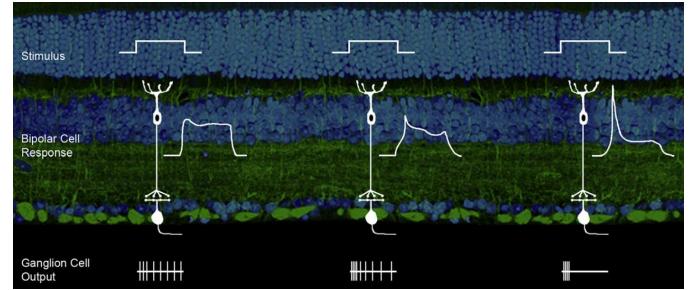


Figure 9: **Bipolar Cells with Different Temporal Properties Give Rise to Ganglion Cells with Different Properties.** For purposes of illustration, the spiking response of the ganglion cells is shown as though it were driven primarily by the bipolar cell, an approximation that ignores the contribution of amacrine cells. It is important to note that *amacrine cells* exert substantial control over the responses to light of the bipolar cells themselves. Amacrine cells have feedback synapses upon the axon terminals of the bipolar cells. The bipolar cells are small and electrotonically compact; as a consequence, the response recorded at the soma of a bipolar cell includes the effects of feedback by amacrine cells to that bipolar cell (see text of Masland 2012b). The stimulus to the bipolar cells was direct injection of current into a connected cone. The responses of bipolar cells are adapted from Saszik and DeVries 2012. Responses of the ganglion cells and bipolar cells are schematic; they do not derive from paired recordings. (Masland 2012b)

found the A1 to truly be a spiking cell, with a phasic ON-OFF discharge. ... This cell type has a spectral sensitivity like the **photopic** luminosity function and is **excluded** from a role in transmitting a cone-type specific inhibitory signal to bipolar cells or ganglion cells.

The AII amacrine is one of the best characterized amacrine types of the mammalian retina. The AII is a bistratified cell, that makes **sign-inverting** inhibitory synapses with cone bipolar cells in the OFF part of the IPL and **sign-conserving** gap junction with cone bipolar cells in the ON portion of the IPL – the AII cell thus “piggy-backs” on the cone bipolar cells to transmit **both ON and OFF rod signals to ganglion cells**. Why then consider the possibility that the AII rod amacrine plays a role in photopically driven cone signal pathways and color coding? Surprisingly the **AII cell also receives significant synaptic input from OFF-cone bipolar cells** (Dacheux and Raviola 1986).

In addition it might be expected that under photopic conditions that bidirectional gap junctions with ON-cone bipolar cell might function to **transmit photopic signals to the AII**. It was possible then that the AII could introduce cone-type selective inhibition into the midget pathway. ... However, after the **rod saturation**, AII cells show a **strong cone driven light response** at light levels 3-4 log units above cone threshold. This response is similar in amplitude to the light response of cone bipolar cells... Responses to cone-isolating stimuli show that, like the A1 amacrine, the **AII cell receives additive input** from L- and M-cones, but **lacks a significant S-cone input** to both the center and the surround of the receptive field.

*From Masland 2012b*: “Amacrine cells occupy a central but inaccessible place in the retinal circuitry. Most are axonless neurons and their lack of a clear polarity makes it hard to recognize the sites of their inputs and outputs. Because of their multiple connectivity, they are hard to conceptualize: they feed back to the bipolar cells that drive them, they synapse upon retinal ganglion cells, and they synapse on each other (Figure 10; Jusuf et al. 2005, Eggers and Lukasiewicz 2011).

An early survey of amacrine cell types counted **29 types** of amacrine cell in the rabbit retina (MacNeil and Masland 1998). ... Second, there was uncertainty about the number of **wide-field amacrine cell types**, which can cover the retina with a very small, absolute number of cells, and thus are rarely encountered. If the traditional definition of a retinal cell type is followed, there would be at least **16 types** of wide-field amacrine cell (Lin and Masland 2006). ... the total number of known amacrine cell types would remain **around 30**.

Second, many amacrine cells—perhaps a majority of the total number—perform some variety of *vertical integration* (the term is meant to contrast with lateral integration, as carried out by horizontal and wide-field amacrine cells). ... This means that they carry ON information into the OFF strata, and vice versa. This is termed **crossover**

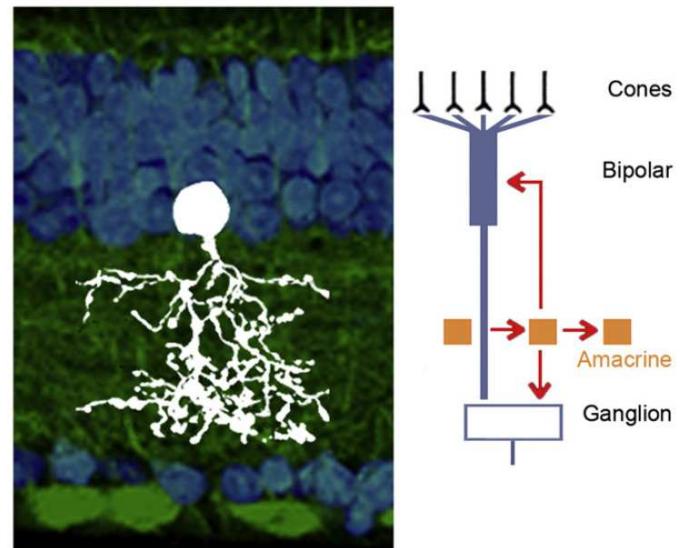


Figure 10: **The Structure and Generalized Connectivity of Narrow Field Amacrine Cells (LEFT)** Type 7 glycinergic amacrine cell of the mouse retina. Note that this cell communicates “vertically,” interconnecting the ON and the OFF layers of the IPL. Cell image is adapted from Menger et al. 1998. **(RIGHT)** Block diagram of amacrine cell pathways. Amacrine cells receive input from bipolar cells and other amacrine cells. They make outputs back upon bipolar cells, to ganglion cells, or to other amacrine cells. Thus amacrine cells participate in *feedback inhibition*, *feed-forward inhibition*, and *lateral inhibition*. A single amacrine cell can have all of these arrangements or a subset of them. ([Masland 2012b](#))

(for the crossing between ON and OFF layers) inhibition (because amacrine cells release GABA or glycine)... but an example is the finding that some **“excitatory” responses** of ganglion cells to light are **actually a release of amacrine mediated inhibition** (Molnar et al. 2009, Sivyer et al. 2010, Werblin 2010, Buldyrev et al. 2012, Demb and Singer 2012, Farajian et al. 2011, Grimes 2012, Nobles et al. 2012)."

#### 2.2.6. Ganglion cells

*From Dacey 2000*: “**Most S-cone opponent** cells identified in extracellular recordings from the retina or the LGN were **blue-ON** cells, receiving excitatory input from S cones, but the existence of a **more rarely recorded S-OFF** opponent cell is also well documented (Valberg et al. 1986). The correspondence of the blue-ON cell with a novel bistratified ganglion cell type raises the question of whether some other non-midget ganglion cell type or types project to the LGN and transmit a blue-OFF signal. **No such novel type** has been observed, and the morphology of an identified **blue-OFF cell has not been identified**. However, each S cone, in addition to its output to the blue-cone bipolar cell, is also connected to a single midget bipolar cell, suggesting that a subset of midget cells in the central retina could transmit a blue-OFF signal.

With surround responses derived from L and M cones via the H2 horizontal cell, like that suggested for the blue-cone bipolar cell, these **S-cone-connected midget**

cells should show blue-OFF/yellow-ON spectral opponency. That a *small proportion* of parafoveal midget cells transmits a blue-OFF signal could explain why these cells are **rarely encountered** by the recording electrode. Blue-OFF midget cells would make up **only a very small proportion** (about 2–3%) of the total midget cell population. In addition, linking the blue-OFF pathway to the midget system suggests a **second anatomical limitation**. Beyond the parafovea, all midget cells begin to receive input from **multiple cones** (Dacey 1993). Thus, any blue-OFF midget cell **should become nonopponent** because S-, L-, and M-cone-connected midget bipolar cells would increasingly converge on a single OFF midget ganglion cell. Thus **only the blue-ON pathway** would have a representation **beyond central vision**. This kind of eccentricity-related asymmetry appears also to be present when comparing the blue-ON pathway with the red-green pathway.

In retinal **periphery**, both the midget and parasol pathways make nonselective connections with all of the L and Mcones in their receptive fields and **lack spectral opponency**. The variability in the relative numbers of L and M cones both locally in the retina and across individual retinæ is reflected in the spectral sensitivities of both cell populations. **Red-green opponency** appears to be a property **restricted** to midget ganglion cells of the **central retina**, where a single cell is dominated by excitatory input from a single cone. ... red-green opponency arises **not from a cone type-selective circuitry but from random connections** of both L and M cones to the midget receptive field (1983, 1993, 1993) (Figure 11). The basis for the **cone type-mixed hypothesis** is that the relative strength of L- versus M-cone input to the receptive field center and surround determines the strength of a red-green opponent signal. In the parafovea, given a greater synaptic strength and input to the receptive field center dominated by a single cone, indiscriminate mixed-cone input to a large weak surround will result in strong red-green opponency (Lennie et al. 1993).

The mixed-cone hypothesis also **predicts** that **red-green opponency** will be **degraded in the retinal periphery** because at eccentricities greater than approximately 7 degrees, midget ganglion cells increase steadily in dendritic field size (e.g. Watanabe & Rodieck 1989 **Parasol and midget ganglion cells of the primate retina**, Dacey 1993), presumably gather input from multiple midget bipolar cells (Milam et al. 1993), (see Figure 11), and are probably driven by input from 30–40 cones. ... These **peripheral midget** ganglion cells (Dacey 1999) receive input from both L and M cones to the receptive field center and surround. Not only do these midget ganglion cells show a **complete lack of red-green opponency**, but they show a spectral sensitivity, like that shown previously for ganglion cells that project via the magnocellular layers of the LGN (e.g. Lee et al. 1988).

The **lack of opponency** in peripheral midget ganglion cells is also present in the physiology of the cone

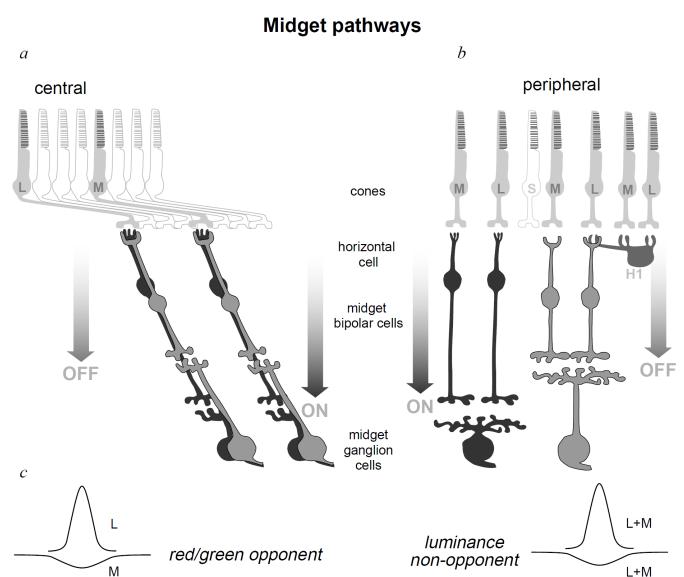


Figure 11: **Cell types and circuits for the L- and M-cone midget pathways in central and peripheral retina.** (a) In the central retina (~0–7 degrees eccentricity) a private line exists in which a single midget ganglion cell receives input from a single midget bipolar cell, which in turn contacts a single cone pedicle (either L or M cone); each cone terminal links to both an ON and an OFF pathway cell. (b) In the peripheral retina, midget ganglion cell dendritic trees enlarge greatly and receive convergent input from a number of midget bipolar cells. (c) In the central retina, receptive fields show strong L- and M- (red-green) cone opponency. In the peripheral retina, larger receptive fields show additive input from L and M cones to receptive field center and surround, lack spectral opponency, and show the spectral sensitivity of cells in the luminance pathway. (Dacey 2000)

**bipolar cells** that generate the midget receptive field. Unlike midget ganglion cells, **midget bipolar cells** maintain the **private-line single-cone connection over most of the retina** (Milam et al. 1993). However, receptive field center size is large relative to that expected from a single cone input, suggesting that **neighboring cones must contribute**, perhaps via *electrical coupling* among bipolar cells. The consequence is that the **receptive field center can show additive input from both L and M cones**. Midget bipolar cells also possess a large and strong receptive field surround that receives combined input from L and M cones. The result is a **nonopponent receptive field** like that observed for midget ganglion cells.

These results support the **mixed-cone hypothesis** in the retinal periphery for both midget ganglion cells and midget bipolar cells and are also compatible with **psychophysical evidence** for a gradual **decline in the sensitivity of red-green color vision** with increasing distance from the fovea (Mullen 1991).

The physiological L:M variability was also present at the next synaptic step (see above for horizontal cells, 2.2.3) at the level of the midget and parasol ganglion cells (Diller et al. 2004) (Figure 12a). In addition, measures of the L- to M-cone contrast gain ratio for single H1, midget, and parasol ganglion cells at the same retinal locations recorded in sequence revealed highly correlated L:M gain ratios for all three cell types (Figure 12b–c), indicating that the **physiological gain set by the anatomical cone ratio is preserved from outer to inner retina** and is identical in both the nonopponent midget and parasol pathways. **What are the implications of these results?** First, both midget and parasol pathways can serve as a neural basis for the photopic luminosity function, at least in the retinal periphery. Second, no special circuitry is devoted to the L- and M cone signals that **adjusts their relative gain** to produce a neural code for **fixed photopic spectral sensitivity** (PT: e.g. Garrigan et al. 2010). This conclusion agrees with **psychophysical measurements** that show similar variability in spectral sensitivity across individuals that can also be directly correlated with the L- to M-cone ratio (Brainard et al. 2000)

From Wässle 2004: “There are at least **10–15 different morphological types of ganglion cell** in any mammalian retina (Masland 2001a, Rockhill et al. 2002). Their main distinguishing features are the size and branching pattern of their dendritic trees, which can be seen in retinal flat mounts. However, it is often difficult to classify ganglion cells by their shapes alone because this can vary across the retina. In the primate retina it has been helpful to label ganglion cells retrogradely through their axonal projections (Dacey et al. 2003). The best way to define and study different ganglion cell types is by applying selective markers that label the whole population of a given type (Wässle and Boycott 1991).

Midget ganglion cells are the most frequently occurring primate ganglion cell type (70–80%; Perry et al. 1984;

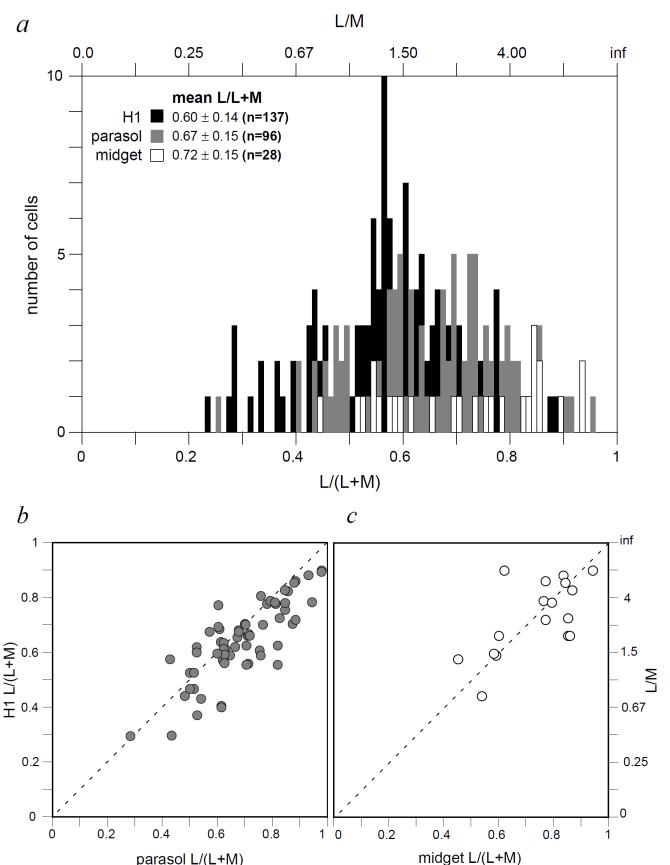


Figure 12: **Relative strength of L- and M-cone input to H1 horizontal, parasol ganglion, and midget ganglion cells of the retinal periphery.** Contrast gains for L- and M-cone signals were measured for stimuli that systematically varied L- and M-cone contrast. (a) Histogram of L- to M-cone gain ratio for H1 horizontal cells, parasol cells, and midget ganglion cells. L:M ratio is variable for all three cell populations. (b–c) For a subset of cells samples L:M ratio was measured for all three cell types in the same retina at the same retinal location. Scatter plots show that L:M gains are closely matched for overlapping H1 horizontal cells and parasol or midget ganglion cells. These and other data discussed in text indicate that variability in the relative numbers of L and M cones can explain the physiological L:M variability. (Dacey 2000)

700'000 - 800'000 out of total of more than million ganglion cells in human retina) and in the central retina their dendritic fields are extremely small, so they contact only a single midget bipolar cell which is connected to a single cone (Kolb and Marshak 2003). They therefore represent the ‘acuity’ system of the primate retina and, as previously mentioned, are the L–M-cone-selective ganglion cells (Dacey 1993).

At the level of the retina, two cone-opponent pathways are classically recognized: a ‘red–green’ pathway, in which L- and M-cones are antagonistic, and a ‘blue–yellow’ pathway, in which S-cones are opposed to a combined L + M-cone signal (Taylor and Vaney 2003). Midget ganglion cells have long been thought to represent the red–green pathway. ... It is possible that midget ganglion cells connect non-selectively to all midget bipolars within their dendritic fields, which would mean that cone selectivity would greatly decline in the retinal periphery (Diller et al. 2004). There is a sharp decline in **human chromatic sensitivity** in the visual **periphery** (Mullen and Kingdom 2002). However, Martin 1998 recorded ganglion cells from the intact eye of the macaque and showed that the strength of L- versus M- opponency across the retinal periphery is identical to that in the fovea. This result would predict selective wiring of midget bipolars and midget ganglion cells in the peripheral retina.

The retinal circuitry associated with the **S-cone signals is quite different**. A distinctive RGC — the **small bistratified ganglion cell** — forms the morphological basis for the ‘blue-ON/yellow-OFF’ opponent pathway (Dacey et al. 2002). These ganglion cells receive a direct input from the **blue cone bipolar** cell at their inner dendritic stratum, providing the S-cone-selective ‘blue’ ON input. At their outer dendritic stratum they also receive a **direct input from diffuse bipolar cells** connected to L- and M- cones, which provides the ‘yellow’ OFF input. Recently, based on retrogradely labelling their axons from the LGN, **two further S-cone-specific RGCs were identified in the primate retina**. One of them receives an **S-cone-selective inhibitory input** and represents a *blue OFF ganglion cell*; the other receives an **S-cone-selective excitatory input** and represents a *blue ON ganglion cell* (Dacey et al. 2002). S-cone-selective RGCs are also found in other mammals, and they represent the primordial dichromatic colour system of the mammalian retina.”

*From Field et al. 2009:* “Among the RGC types in the primate retina, small bistratified cells (SBCs) are of particular interest; they display cone opponent responses appropriate for blue-yellow color vision (Dacey and Lee 1994), they are the fifth most numerous RGC type in the primate (Dacey 2004) and they form a major projection to the koniocellular layers of the lateral geniculate nucleus (LGN) (Szmajda et al. 2008).

It is currently unknown whether **SBCs contribute to scotopic** (rod mediated) vision in addition to their

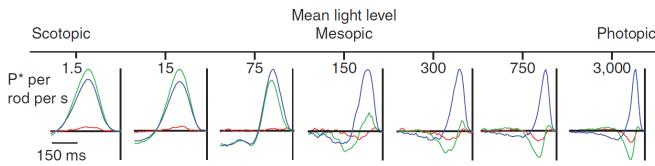
role in photopic (cone mediated) vision. The possibility that SBCs carry rod signals is suggested by psychophysical studies demonstrating perceptual shifts toward blue hues in mesopic (rod and cone mediated) vision (Buck 2004). ... If SBCs **avoid rod input**, it would indicate that a substantial fraction (~10%; Dacey 2004) of the axons in the optic nerve carry no behaviorally relevant signal during night vision. It would also indicate that one function of parallel pathway organization is to specialize certain RGC types for a limited range of light levels. Furthermore, it would suggest that the presynaptic circuitry of SBCs avoids two kinds of rod inputs: **gap junctions between rods and S cones** and gap junctions between **AII amacrine cells and S cone bipolar cells**.

We recorded from nearly complete populations of SBCs with receptive fields that collectively covered the recorded region of retina (Field et al. 2007). **SBCs received rod input with the same ON type response polarity as S cone input**. SBC receptive fields were substantially larger at rod-dominated light levels, revealing a **change in spatial processing in night versus day** vision, as suggested by previous studies (Barlow et al. 1957, Cleland and Levick 1974, Troy et al. 1999). Furthermore, physiological and anatomical experiments indicated that rod signals reach SBCs via a known high-sensitivity pathway; rod signals are conveyed by rod-specific bipolar cells to **AII amacrine cells**, which in turn form gap junctions with ON cone bipolar cells that provide excitatory input to RGCs (Kolb and Famigilietti 1974, Bloomfield and Dacheux 2001).

The presence of robust rod-driven responses at light levels of ~1.0 P\* per rod per s described above suggests that the **high-sensitivity rod pathway** mediated by AII amacrine cells contributes signals to the **presynaptic circuitry of SBCs** (Sharpe and Stockman 1999, Bloomfield and Dacheux 2001, Field et al. 2005). This pathway is thought to dominate visual signaling under low scotopic conditions. However, recent recordings from primate cones (Hornstein et al. 2005) and mouse RGCs (Völgyi et al. 2004) suggest that gap junctions between rods and cones could also provide reliable rod signals at ~1.0 P\* per rod per s.

The above results suggest the presence of gap junctions between AII amacrine cells and S cone bipolar cells, which provide the ON type input to SBCs. However, previous studies have suggested that **AII amacrine cells may avoid forming gap junctions with S cone bipolar cells** (Cohen and Sterling 1990). Therefore, we searched for such contacts by immunolabeling S cone bipolar cells, AII amacrine cells and the connexin 36 protein, which forms the gap junction between AII amacrine cells and other ON-cone bipolar cells (Völgyi et al. 2004) ... Thus, AII amacrine cells appear to make gap junctions with S cone bipolar cells.

We tested for **simultaneous rod and cone input** by measuring SBC light responses across a **range of light levels** (Figure 13). At the highest light levels, SBCs ex-



**Figure 13: Spectral tuning and dynamics of SBC responses depended on light level.** From a single recording of 33 SBCs, the mean spike-triggered average (STA) time courses of the SBCs for the red, green and blue display primaries are shown at seven light levels. The light level increases from left to right. At 3,000 P\* per rod per s, the rods were saturated and the response was mediated by the cones. Photo-isomerization rates for the L, M and S cones were 1,400, 1,200 and 430 P\* per cone per s, respectively. The SBCs exhibited **color opponency**; increments in the blue display primary and decrements in the red and green display primaries tended to precede spikes. At 150 P\* per rod per s, the **spectral tuning** of the SBCs exhibited a **marked change**; the SBCs continued to display color opponent responses, but increments, rather than decrements, in the green display primary tended to precede spikes. At 1.5 P\* per rod per s, the light level was below cone threshold and the spectral tuning of the response was non-opponent, reflecting **pure rod input** to the SBCs. (Field et al. 2009)

hibited a relative sensitivity to the red, green and blue display primaries that was **consistent with a S-ON/(L+M)-OFF** cone-mediated response (Chichilnisky and Baylor 1999, Field et al. 2007). However, between 150 and 300 P\* per rod per s, SBCs exhibited a **marked change in spectral tuning**: increments, rather than decrements, in the green display primary tended to precede spikes. In principle, this change in spectral tuning could be **explained two ways**: a **weakening** of the (L+M)-OFF surround and/or the **inclusion of rod input** with the same sign as S cone input.

In the former case, the sensitivity to the green display primary should approach the value predicted from the spectral sensitivity of the S cones. The expected sensitivity to the green relative to blue display primary for S cones was 0.11. At 150 P\* per rod per s, however, the observed ratio was  $0.35 \pm 0.04$ . Thus, the large sensitivity to increments of the green primary **implies rod input** to the SBCs. Cones must also provide input to SBCs at 150 P\* per rod per s because the response remained color opponent and the spectral tuning of the response did not match that expected from rods. At progressively lower mean light levels, the relative sensitivity to the three display primaries shifted to the values expected from pure rod input. Therefore, **rod and cone signals mix in SBCs** at light levels between  $\sim 75$  and  $\sim 300$  P\* per rod per s.

Furthermore, **human psychophysical and electrotoretinogram** studies suggest that the rod-cone gap junction pathway is **not strongly activated** at light levels of  $< 1$  scotopic Td (Sharpe and Stockman 1999), which corresponds to  $\sim 10$  P\* per rod per s (Lyubarsky et al. 2004). Finally, the present results indicate that connexin-36 is present at appositions of AII amacrine cell dendrites and S cone bipolar cell axon terminals, providing anatomical evidence for the existence of this pathway. However, these

results **do not rule out** the possibility that gap junctions between **rods and S cones** contribute rod signals to SBCs at light levels of  $> 1\text{--}2$  P\* per rod per s. Indeed, **gap junctions between rods and S cones** have been observed in anatomical studies of *primate retina* (*personal communication, S. Massey, University of Texas Health Science Center at Houston*). Also in primates, **rod activation hyperpolarizes S cones**, presumably through gap junctions (*personal communication, J. Schnapf, University of California, San Francisco*). The **relative contribution** of rod-to-cone gap junctions and the AII amacrine cell pathway at mesopic and high scotopic light levels **remains unclear**.

Many studies have highlighted the challenges faced by the visual system at night: a sparse collection of absorbed photons must be detected on a background of substantial cellular and synaptic noise (Field et al. 2005). This, combined with anatomical and physiological observations that AII amacrine cells form synapses with many cone bipolar cell types (Cohen and Sterling 1990, Petrides and Trexler 2008), suggests that **most or all RGC types may participate in scotopic vision**. However, several physiological studies have suggested that **only a fraction** of RGC types may participate in low scotopic vision (Wiesel and Hubel 1966, Cleland and Levick 1974, Lee et al. 1997, Völgyi et al. 2004). ... It remains **unclear** whether these results **will generalize to the central primate retina** (Lee et al. 1997) and whether there are major differences in the divergence of AII amacrine cell signals to various RGC types in primates versus other mammals. Perhaps **surprisingly**, SBCs exhibited a sensitivity under low scotopic conditions that was **qualitatively similar to that of ON parasol cells**. However, our results do not quantitatively compare the signal-to-noise properties of SBCs to those of ON parasol cells or to those of other RGC types, a **comparison** that **will determine** which **RGC types** provide the most reliable signals to the brain when **photons are scarce**.

Furthermore, psychophysical experiments have shown that **rod activation biases** color judgments toward blue hues (Buck 2004) and influences color discriminations involving changes in S cone activation (Knight and Buck 2002, Cao et al. 2008b). **Models explaining** these results **postulate rod input** to SBCs (Buck et al. 2000, Cao et al. 2008b); however, as described above, **previous physiological experiments have largely failed to observe such input**. The **light levels** at which the perceptual effects of rod activation on S cone signals are **maximized** are 2–10 Td (Cao et al. 2008a), corresponding to  $\sim 60\text{--}300$  P\* per rod per s. These values roughly match the light levels for which the **opponent spectral tuning** of SBCs was **most influenced by rod activation** (Figure 13). Thus, the present results may help to explain the psychophysical results. **Activation of the rods**, similarly to **activation of S cones**, results in an increased spike rate in SBCs. Thus, to the **degree that SBC spikes** contribute to the **perception of blue**, rod activation would be expected to

produce a bias toward the perception of blue.”

From Crook et al. 2009: “In the primate retina the small bistratified, “blue-yellow” color-opponent ganglion cell receives parallel ON-depolarizing and OFF-hyperpolarizing inputs from short (S)-wavelength sensitive and combined long (L)- and middle (M)-wavelength sensitive cone photoreceptors, respectively. However, the **synaptic pathways that create S versus LM cone-opponent receptive field structure remain controversial.**

L-AP-4, the mGluR6 receptor agonist and **selective ON pathway blocker, unexpectedly appeared to attenuate both the S-ON and LM-OFF responses** (Dacey et al. 2000, Field et al. 2007, Davenport et al. 2008). These observations, together with recent anatomical (Schein et al., 2004) Evidence that each S cone in macaque fovea drives one narrow-field and several wide-field blue-yellow ganglion cells) and physiological (Packer et al. 2007) evidence for LM surrounds in S cone photoreceptors and reports of center-surround receptive field structure in blue-ON cells (Field et al. 2007), suggested that **S versus LM opponency arises not primarily postsynaptically by convergent ON and OFF bipolar inputs but presynaptically by horizontal cell to S cone feedback.** In such a center-surround model, the small bistratified cells might show **both chromatic and spatially tuned achromatic response components** (Derrington and Lennie 1984, Gouras and Zrenner 1979, Lennie and Movshon 2005). **We hypothesize** that this LM-ON surround normally sums with an LM-OFF surround of the S-ON cone bipolar. The **spatially coextensive blue-yellow receptive field** can then be explained by **summation of parallel excitatory inputs** from S-ON center/LM-OFF surround “blue-cone” bipolar cells with LM-OFF center/LM-ON surround diffuse cone bipolar cells.

Often, the intensity of stimuli used in human **visual psychophysics** or in physiological experiments in the intact primate eye are expressed in units of retinal illuminance, or **Trolands** (Td). To aid comparison with our data, we calculated that for a peripheral cone with an inner segment aperture of  $9 \mu\text{m}$ , **1 Troland (Td) was equivalent to 30 photoisomerizations/s/cone**. For a rod with an inner segment aperture of  $2.5 \mu\text{m}$ , **1 scotopic troland was equivalent to 4 photoisomerizations/s/rod**.

... Below cone threshold, the **light response is converted from an S-ON, LM-OFF response to a rod-ON response.** From cone threshold to rod saturation (between  $10^2$  and  $10^3$  photoisomerizations/cone/s), there is potential for **interaction of the rod-ON input with the S and LM cone inputs.** Given the large difference between the rod and cone signal dynamics, the nature of this interaction would be **dependent on the stimulus temporal frequency** as well as the illuminance level. At  $10^4$  photoisomerizations/cone/s (~333 Td) and above **we assume rods are in saturation;** we believe this is a

safe assumption as psychophysical experiments show that **saturation of primate scotopic vision** begins when a background light **reaches 100 scotopic trolands** (Hayhoe et al. 1976); this is 400 photoisomerizations/cone/s, and is consistent with recordings from individual primate rods (Baylor et al. 1984). We have used stimuli well above this level for all subsequent measurements of cone responses in the small bistratified blue-ON cells.

For the cell shown in the inset to Figure 5C of Crook et al. 2009, the S input latency was **42 ms** and the LM **48 ms**. Across cells, the response to **S cone stimuli showed slightly shorter latencies** than that for LM stimuli (S mean latency  $\pm$  SD =  $40 \pm 3$  ms; LM mean latency  $\pm$  SD =  $46 \pm 3$  ms;  $n = 20$ ) (Fig. 5D). Our data are approximately consistent with those reported from measurements using comparable stimuli made in the intact eye *in vivo* (Yeh et al. 1995). In the study by Yeh et al. 1995, latencies of 35 ms were found for both the S and LM cone driven responses at comparable light levels to those used here.

After **dark adaptation**, rod input to the small bistratified cell is clearly present. The **sign of the rod signal follows that of the S-ON input:** when rod input prevails, the blue-ON yellow-OFF cell **becomes a rod-ON cell.** These results confirm an early observation of strong excitatory rod input to blue-ON cell relay cells recorded in the parvocellular LGN (Virsu et al., 1987 Mesopic spectral responses and the purkinje shift of macaque lateral geniculate nucleus cells), although a more recent study failed to observe a rod signal in blue-ON ganglion cells (Lee et al. 1997). In the **primary rod pathway** the depolarizing AII amacrine cell receives input from the rod bipolar cell and **transmits the rod signal to ON cone bipolar cells** via a sign-conserving gap junction and to OFF cone bipolar cells by a sign-inverting glycinergic synapse (1975, 1988, 1992). The **rod-ON response** of the blue-ON ganglion cell could thus be **mediated by an AII amacrine gap junction** with the blue cone bipolar axon terminal; a preliminary report suggests such a contact is present (Marshak et al., 2009, ARVO abstract). In contrast, our data suggest a **lack of the glycinergic synapse** from the AII cell outer dendrites to the LM-OFF bipolar cell population(s) that are presynaptic to the small bistratified outer dendrites (1997, 1998a).

In this regard, there is **growing evidence** that **certain mammalian bipolar cell types may not participate in the primary rod pathway** (2004, 2008). The degree to which rod signals might be restricted to distinct ON and OFF cone bipolar pathways **remains to be investigated in the primate.** The rod-ON input to the blue-ON cell is consistent with a **large body of human psychophysical data** suggesting that rods interact synergistically with S-cones at mesopic levels to introduce a **blue-bias to color appearance** (for review, 2004). However, the current results **do not exclude a rod-OFF input** that is masked by a larger rod-ON signal or that arises at lower scotopic levels. Experiments that pharmacologically isolate potential ON and OFF components of the rod

signal near threshold are needed to carefully address this question.

Failure of picrotoxin and/or strychnine to significantly modify the S ON or LM OFF response amplitude was also consistent with an excitatory cone bipolar origin for the LM OFF field, and we suggest that amacrine circuitry is not critical for generating S versus LM cone opponency. The majority of synaptic inputs to the small bistratified cell are from amacrine cells, however (Ghosh and Grünert 1999), so the significance of these inputs remains open. There is strong evidence that inner retinal inhibition to some extent works in a push-pull manner to reinforce excitation, and that the OFF pathway, at least for certain ganglion cell types, receives more inhibition from the ON pathway than vice versa (2003, 2007, 2007, 2008). It seems unlikely that the S-ON bipolar would drive such “cross-pathway” amacrine inhibition to the LM-OFF bipolar as this would work against the basic cone opponent response in which S increments reinforce LM decrements. It is possible, however, that disinhibition that arises in LM ON cone bipolar cells reinforces the LM OFF response—although at the high photopic levels and moderate contrasts used here we did not observe a change in the LM OFF response relative to the S ON response after inhibitory block. Whole-cell recordings of blue-ON cells under voltage clamp designed to measure the phase and amplitude of excitatory and inhibitory conductances generated by S and LM selective stimuli are required to directly address this question.

We hypothesize that the S-ON bipolar cell also possesses an LM OFF surround and that under conditions where S-ON and LM-OFF fields are functioning, there is no or little net surround antagonism (Figure 14). The LM-OFF surround of the S-ON bipolar would arise by feedback from H2 horizontal cells, whose processes contact S, L, and M cones. The LM-ON surround of the LM-OFF bipolar would arise by feedback from the H1 horizontal cell that contacts L and M cones nonselectively (Dacey et al. 1996). The light response of the blue-cone bipolar cell (Kouyama and Marshak 1992b) is unknown. However, the S cone already possesses a large opponent surround driven by L and M cones that is likely transmitted to the S-ON bipolar and in turn to the small bistratified ganglion cell.”

*From Masland 2012b:* “...A related example is the retina’s numerical bias toward OFF cells, which mirrors a bias toward darkening events in the natural world (Ratliff et al. 2010). Perhaps this matching to the statistics of natural scenes will provide clues to the response tuning of the many as-yet-unclassified types of retinal ganglion cells.”

*From Percival et al. 2013:* “The most common ganglion cell types in the primate retina are midget and parasol ganglion cells. Midget ganglion cells project to the parvocellular layers of the lateral geniculate nucleus (LGN), and

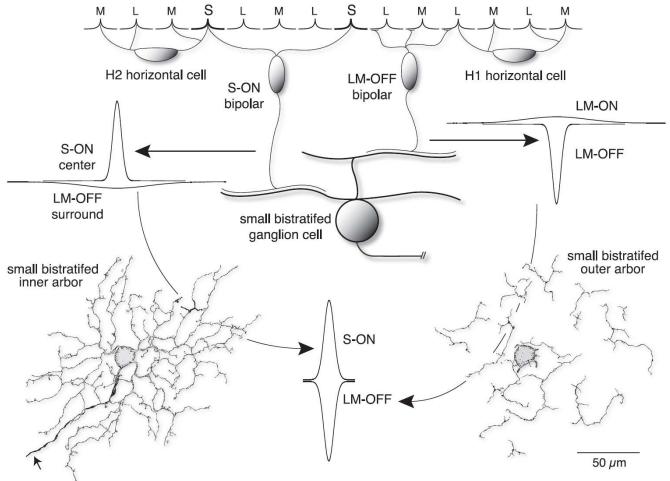


Figure 14: Hypothesized circuitry for the origin of coextensive cone-opponent receptive field structure by summation of S ON and LM OFF cone bipolar inputs with center-surround receptive field structure. The S ON bipolar (left) inherits an LM OFF surround created by H2 horizontal cell feedback to the S cone (Packer et al., 2007), and this receptive field sums at the small bistratified dendritic tree with input from an LM OFF bipolar (right) that shows an LM ON surround created by H1 horizontal cell feedback to L and M cones. Thus, no net surround appears at the ganglion cell leaving spatially restricted, high gain S ON and LM OFF center mechanisms as the basis for a cone-opponent receptive field that lacks center-surround spatial opponency. (Crook et al. 2009)

make up between 45% (Dacey 1993) and 80% of the ganglion cell population in the peripheral retina of macaque (Perry et al. 1984), and up to 95% in the human fovea (Dacey 1993). Parasol ganglion cells project to the magnocellular layers of the LGN, and make up approximately 6–10% of all ganglion cells (Perry et al. 1984, Grünert et al. 1993). The signals flowing through these two afferent pathways form the main thalamic inputs to the primary visual cortex. It is now established that a third visual afferent stream (**koniocellular**) sends signals through the LGN to the primary visual cortex (reviewed by Hendry and Reid 2000). There is evidence from Golgi impregnations (Boycott et al. 1969) and retrograde injections (Cowey and Perry 1980, Perry and Cowey 1984) that koniocellular ganglion cell types are present in the central retina. What remains unclear, however, is whether koniocellular pathways receive input from the cones serving the central-most degrees of the visual field. Alternatively, it is possible that the cones in the rod-free area of the foveola exclusively serve the midget-parvocellular pathway.

Large bistratified cells had very sparsely branching dendritic trees and in this respect resembled the melanopsin-containing ganglion cells (Dacey et al. 2005, Jusuf et al. 2007). However, the dendritic field of large bistratified cells ranged from 83.25 to 106.0  $\mu\text{m}$  in diameter (154–205  $\mu\text{m}$  on the long axis and 53–55  $\mu\text{m}$  on the short axis) and these values were well below the

**diameter of foveal melanopsin-containing ganglion cells** (Figure 15B). Thus, we conclude that these large bistratified cells do not belong to the melanopsin-containing cell type.

In the current study, we found that, in addition to midget and parasol cells, the majority of koniocellular-projecting ganglion cell types previously identified in the **peripheral retina** (Dacey et al. 2003, Szmajda et al. 2008) are **present in the fovea of marmosets**. Thus, we conclude that the organisation of parallel pathways in the foveal retina is not fundamentally different to that in the peripheral retina. The presence and stratification patterns of koniocellular-projecting ganglion cells and DB cell types in the fovea support the view that the same neuronal types interact with the same synaptic partners in the fovea as they do in the peripheral retina (Wässle and Boycott 1991).

The foveal ganglion cells described in the present study included small bistratified, large bistratified, large sparse, broad thorny, narrow thorny, smooth monostratified, and recursive cells. Apart from small bistratified and thorny/garland cells (Calkins et al. 1998a, Calkins and Sterling 2007), **none of these cell types has been described in detail in the fovea previously**. The functional role of koniocellular-projecting cells in the **fovea** is still **unclear** but two reviews have speculated on the putative physiological properties of these cells in the **peripheral retina** (Dacey 2004, Yamada et al. 2005).

In the peripheral retina, small bistratified cells are established to carry **blue-ON/yellow-OFF** signals (Dacey and Lee 1994, Chichilnisky and Baylor 1999, Silveira et al. 1999, Field et al. 2007; 2009, Crook et al. 2009). Similar light responses are expected for foveal small bistratified cells, and consistently electrophysiological recordings of blue-ON cells with foveal receptive fields have been reported in the macaque and marmoset (Tailby et al. 2008b;a). **Large bistratified cells** have not been described previously in the foveal retina. In the **peripheral retina of the human** (Kolb et al. 1992, Peterson and Dacey 2000), macaque (Dacey and Packer 2003, Yamada et al. 2005), and marmoset (Ivanova et al. 2010), these cells lack an elongated dendritic tree. Large bistratified cells in the present study have inner dendrites that stratify close to the middle of the inner plexiform layer. In the peripheral retina, the inner dendrites of large bistratified cells stratify close to the inner dendrites of small bistratified cells (macaque: Dacey et al. 2003; marmoset: Ivanova et al. 2010). Consistently, large bistratified ganglion cells in the peripheral macaque retina have been reported to carry blue-ON/yellow-OFF signals (Dacey et al. 2003).

Together with other ganglion cell types known to be present in the fovea [i.e. the ON and OFF types of melanopsincontaining ganglion cells (Dacey et al. 2005, Jusuf et al. 2007), and the ON and OFF types of midget and parasol cells], in total there are likely to be **at least 15 ganglion cell types in the fovea of diurnal primates**.

Taken together, in the foveal as well as the peripheral

retina, there seem to be a larger number of ganglion cells than bipolar cells, suggesting that specific bipolar types provide input to multiple ganglion cell types. Based on the stratification patterns established for foveal cells in the present study (Figure 16) the following connectivity can be suggested. The **DB1 cells could provide input to the outer stratifying (M1) melanopsin ganglion cells**, which are known to stratify close to the border with the inner nuclear layer (Dacey et al. 2005, Jusuf et al. 2007). ... DB6 cells have potential contact areas with large sparse (Szmajda et al. 2008, Percival et al. 2011) as well as with inner stratifying melanopsin-containing cells (Jusuf et al. 2007, Grünert et al. 2010). Both cell types (large sparse: Dacey and Packer 2003, Szmajda et al. 2006; melanopsin-containing: Dacey et al. 2005) have been implicated with carrying **blue-OFF/yellow-ON** signals. The **DB6 cells** receive their predominant input from medium and long wavelength sensitive cones (Lee and Grünert 2007) and thus could provide the yellow-ON signal.

The responses of small bistratified ('**blue-ON/yellow-OFF**') ganglion cells (Dacey and Lee 1994, Chichilnisky and Baylor 1999, Silveira et al. 1999, Field et al. 2007; 2009, Crook et al. 2009), smooth monostratified ('Y-like') cells (Crook et al. 2008), and melanopsin ('intrinsic photosensitive') cells (Dacey et al. 2005) have been well characterised by direct retinal recordings in the peripheral retina. .. When the results of the current study are added to these previous reports, it seems **highly likely that koniocellular pathways contribute to foveal vision.**"

### 2.3. Updated ipRGC retinal circuitry

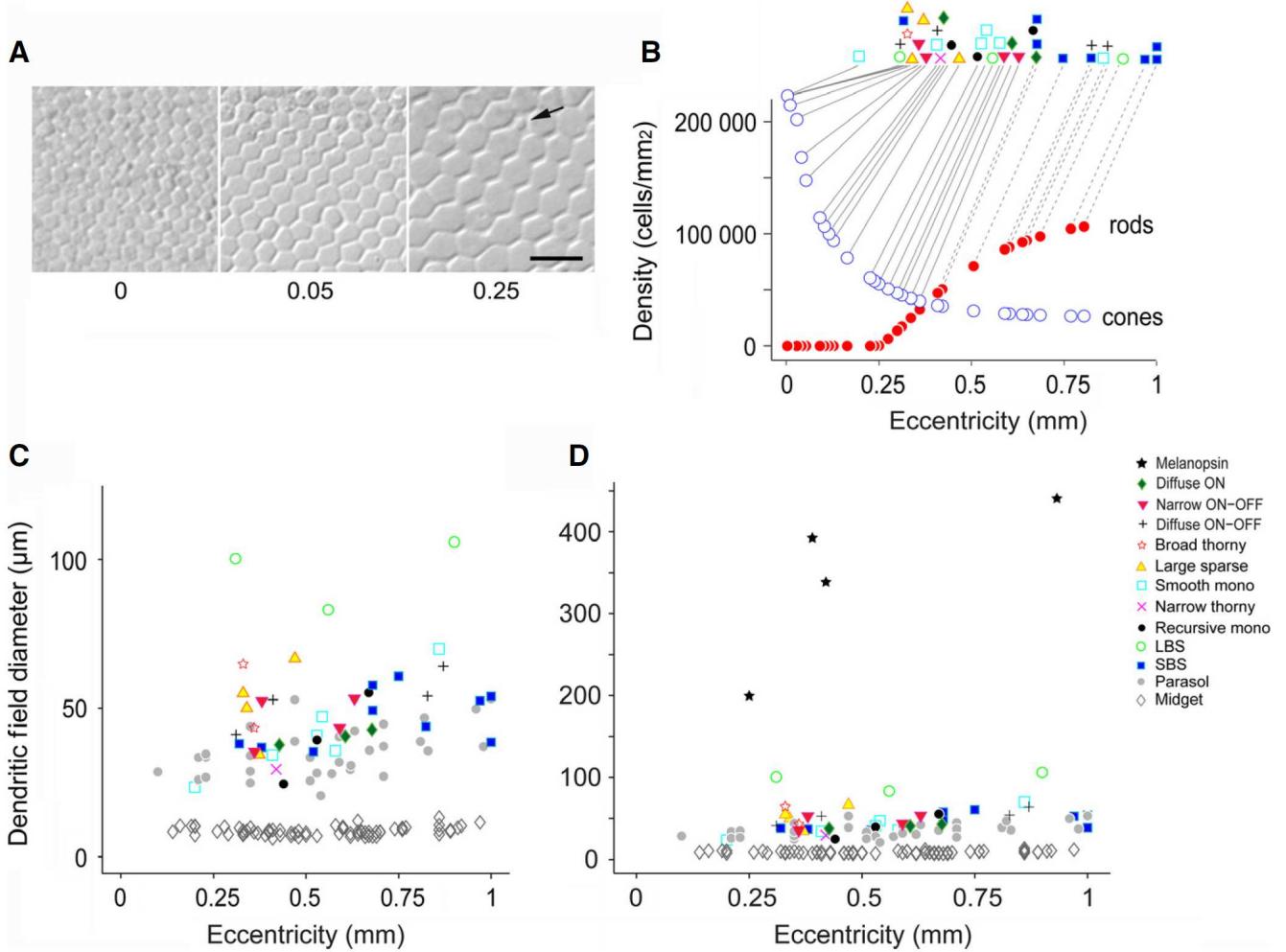
#### 2.3.1. "ipRGC/Melanopsin response"

From Wässle 2004:

"More than 30 years ago, Barlow and Levick 1969 discovered '**luminance units**' by recording extracellularly from the cat retina. These units were extremely **rare** (only *three out of several hundred ganglion cells*) and ON-centre, and their maintained discharge rate monotonically increased with the luminance for at least 5 log units. There is **little doubt** that these luminance units are the **melanopsin-containing cells**. However, it is still unknown whether melanopsin-containing cells also project to the geniculocortical pathway."

From Lucas et al. 2012: "In fact, there is **little direct evidence** that any aspect of mouse photoentrainment **relies upon melanopsin**. Melanopsin knockout mice entrain well to full light cycles over a range of irradiances (Ruby et al. 2002, Panda et al. 2005, Altimus et al. 2010, Morin and Studholme 2011).

Melanopsin's ability to track **dynamic patterns of light** intensity remains largely **unexplored**. A more pertinent issue for the clock is whether melanopsin responds **preferentially** to modulations in irradiance occurring at **particular frequencies**. In fact, sudden increases in irradiance have been reported to induce **anoma-**



**Figure 15: Location and dendritic field diameter of ganglion cells in the central retina of the marmoset.** (A) Micrographs of cone inner segments in the center of the fovea (0) and at 0.05 and 0.25 mm eccentricity. The arrow points to a rod inner segment. Rods are not present at lower eccentricities. (B) Cone and rod densities in the central retina plotted together with the location of koniocellular-projecting ganglion cells from the present study. Rod and cone densities were taken from Wilder et al. 1996. The symbols above the graph show the cell type and position of labeled ganglion cells. The post-receptoral displacements due to Henle's fibres and the sloping processes of bipolar cells are shown as oblique gray lines between the receptor graphs and the position (in the ganglion cell layer) of the labeled cells. (C) Dendritic field diameters of foveal ganglion cells from the marmoset retina. (D) The same data as in A are plotted using a different scale to include melanopsin-containing cells from Jusuf et al. 2007. Data for midget, parasol, small bistratified (SBS) and large sparse ganglion cells include data from previous studies (Ghosh et al. 1996, Szmajda et al. 2008). LBS, large bistratified cell; mono, monostratified. Scale bar, 5 μm. (Percival et al. 2013)

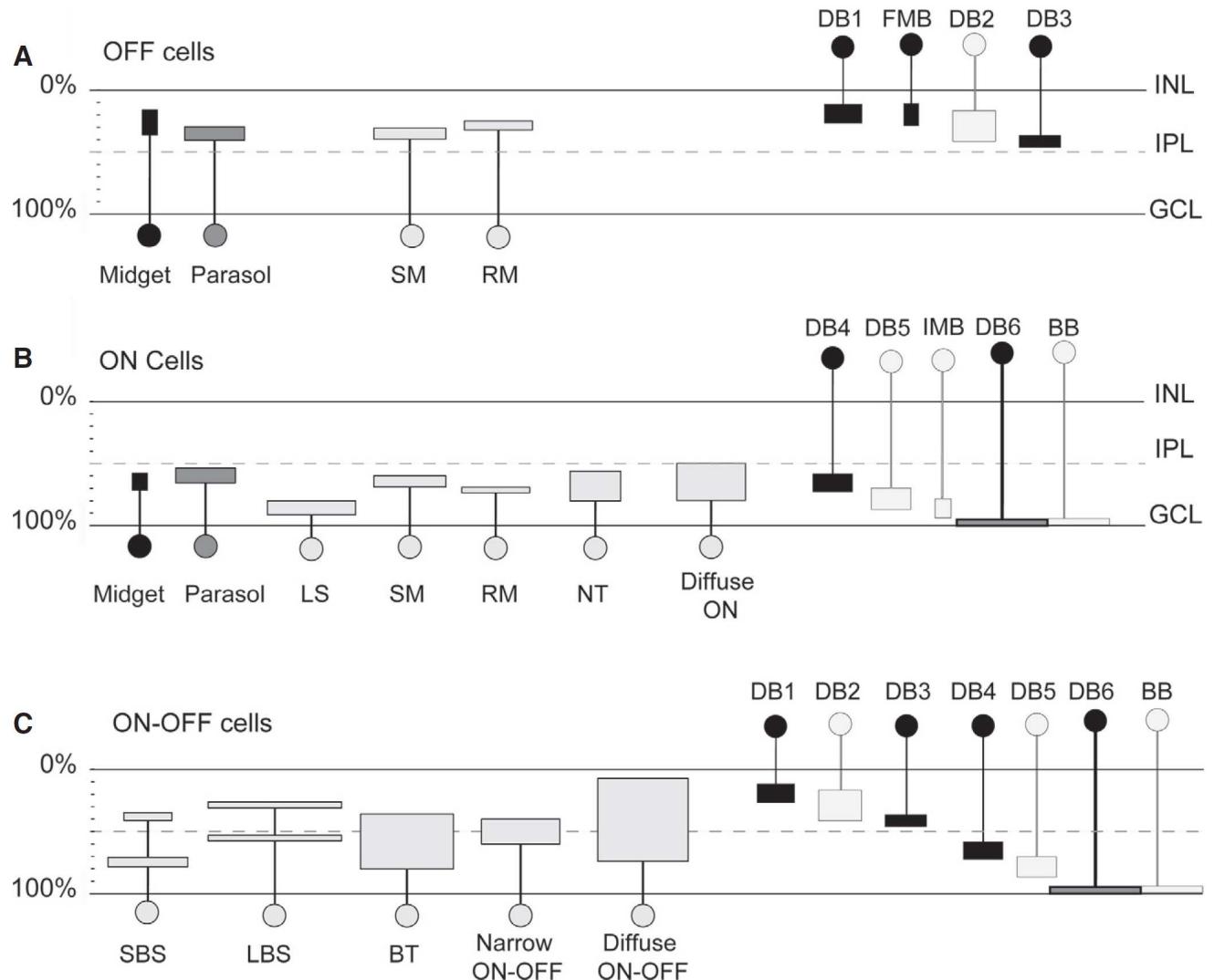


Figure 16: **Summary diagram showing the stratification of the foveal ganglion cell types in the marmoset retina.** The stratification of foveal bipolar cells shown in black was taken from Fig. 11 of [Percival et al. 2013](#). The stratification of the bipolar types shown in gray is modified from [Boycott and Wässle 1991](#). (A) Ganglion and bipolar cells stratifying in the OFF sublamina. (B) Ganglion and bipolar types stratifying in the ON sublamina. (C) Ganglion cell types stratifying in the ON and OFF sublamina together with DB and blue cone bipolar cells. BB, blue cone bipolar; BT, broad thorny; FMB, flat midget bipolar; GCL, ganglion cell layer; IMB; invaginating midget bipolar; INL, inner nuclear layer; IPL, inner plexiform layer; LBS, large bistratified cell; LS, large sparse; NT, narrow thorny; RM, recursive monostratified; SBS, small bistratified cell; SM, smooth monostratified. ([Percival et al. 2013](#))

lously large melanopsin responses, presumably reflecting light adaptation under continuous exposure (Wong et al. 2005). Do melanopsin's **light adaptation** characteristics augment this effect? (Wong et al. 2005, Wong 2012) An answer to that question awaits further study of melanopsin light adaptation and its significance under "**naturalistic**" light exposure profiles. Thus, Nelson and Takahashi 1999 showed that the magnitude of hamster phase shifts were defined by the number of photons encountered, irrespective of whether they appeared in a single long, or up to 100 shorter light pulses ("photon counter"). Such temporal integration is lost for **very short**, very bright, **pulses** (Vidal and Morin 2007), and **melanopsin light adaptation** could contribute to that process."

From Hughes et al. 2012: "Membrane potential is, by definition, a key factor in determining the activation of voltage-gated channels and the progression to **action potential firing**, and as such plays a key role in regulating the excitability and sensitivity of neuronal cells. Single photon responses, that generate small currents of only few pA, are sufficient to induce spike activity in pRGCs (Do et al. 2009) and **spontaneous firing** of pRGCs is observed in the dark (Berson et al. 2002, Tu et al. 2005, Schmidt et al. 2008, Do et al. 2009). From these observations, it appears that the resting membrane potential of pRGCs is tightly regulated and held very close to the threshold for action potential firing."

From Lucas 2013: "One interesting aspect of the melanopsin phototransduction cascade is that it likely has **very high gain**. Do et al. 2009 calculated that photoactivation of a single melanopsin photopigment sets in train such a long lasting activation of the phototransduction cascade that the resultant ipRGC depolarisation has a recordable impact on spike firing. This **high amplification** is thought to *compensate* for the **very small amount of melanopsin** in the retina. ipRGCs lack the specialised membranous discs that rods and cones use to accommodate large amounts of photopigment, and thus must contain proportionally much less opsin. The resultant low probability of photon capture by melanopsin could be important in **limiting the potential of ipRGCs to screen rods and cones**, which lie further down the light path. However, it means that ipRGCs absorb few photons even under relatively bright illumination, and thus require high signal amplification in order to encode physiologically relevant light intensities.

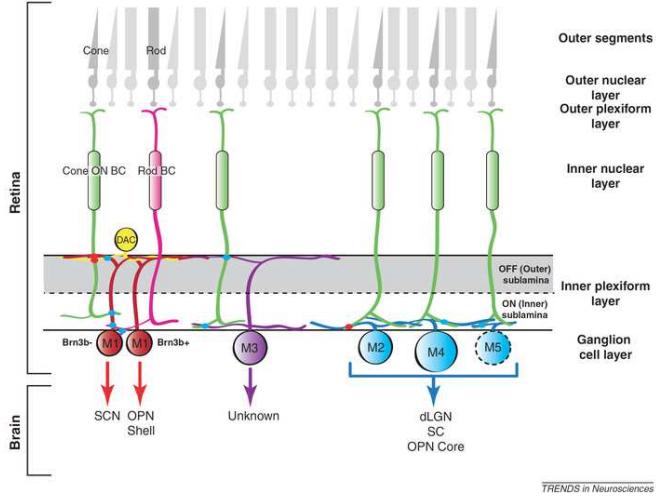
... One **note of caution** here is that much of the behavioural and electrophysiological data giving rise to this model comes from responses recorded to **light pulses applied from darkness**. There has been much less investigation of the ability of ipRGCs (or downstream responses) to track modulations in illuminance under light-adapted conditions. Similarly, our picture of melanopsin's sensory capabilities comes mostly from experiments in which **rod**

**and cone signalling has first been abolished**. However, thanks to its low relative sensitivity, melanopsin will only ever modulate ipRGC activity under conditions in which rod and cone pathways are already providing visual information. Approaches to independently modulate the activity of melanopsin, rod and cone photoreceptors in the **intact retina** (Brown et al. 2012) thus hold the promise of providing a picture of melanopsin's behaviour under more naturalistic conditions and revealing complex interactions between the various photoreceptor signals."

### 2.3.2. ipRGC subtypes

From 2012: Opposed of being one homogeneous group of mRGC as thought initially (Berson et al. 2002; Hattar et al. 2002), recent research indicates that mRGCs consist of several subtypes that are morphologically and physiologically distinct as reviewed by Schmidt et al. 2011. Current knowledge (Schmidt et al. 2011) suggests the existence of six distinct mRGC subtypes referred as M1<sub>Brn3b+</sub>, M1<sub>Brn3b-</sub>, M2, M3, M4 and M5 with the suffix M referring to melanopsin [see for comparison paramorphic pairs in traditional ganglion cells (Famiglietti and Kolb 1976)]. The subtypes can be for example classified either by their **morphology** and **projections** (illustrated in Figure 17); or by their physiology. The most well-characterized subtypes are the M1 mRGCs and the M2 mRGCs. M1 mRGCs were the types originally characterized (Berson et al. 2002), stratifying the outermost sublamina of the IPL and recently further sub-categorized to M1<sub>Brn3b+</sub> and M1<sub>Brn3b-</sub> (based on *Brn3b* marker expression) with differential brain projections (Chen et al. 2011). The M2 mRGCs which stratify in the innermost sublamina of the IPL (Baver et al. 2008, Berson et al. 2010, Schmidt and Kofuji 2009, Schmidt et al. 2008). The bistratified M3 mRGCs, with dendrites in both inner and outer sublaminae, have been only recently characterized (Schmidt and Kofuji 2011). M4 cells have the largest soma of any described mRGC subtype, as well as larger and even more complex dendritic arbors than M2 cells (Ecker et al. 2010). By contrast, M5 mRGCs have small, highly branched arbors arrayed uniformly around the soma (Ecker et al. 2010). In overall, the characteristics of these M4 and M5 are poorly understood compared to other subtypes (Ecker et al. 2010, Schmidt et al. 2011).

Based on the stratification patterns of the mRGC subtypes (M1, OFF; M2, M4 and M5, ON; M3, ON/OFF), the **prediction is that M1 cells would receive synaptic inputs from the OFF pathway**, M2, M4, and M5 cells would receive input from the ON pathway, and M3 cells would receive input from both the ON and OFF pathways. Contrary to this expectation, both ON (i.e. M2), OFF (i.e. M1), and ON-OFF-stratifying (i.e. M3) mRGC subtypes receive **predominantly ON-input** (Pickard et al. 2009, Schmidt and Kofuji 2010), although, a **very weak OFF input to M1 cells** has been reported, but only under pharmacological blockade of amacrine cell inputs (Wong et al. 2007a). Anatomical studies have revealed the source



**Figure 17: Schematic diagram** illustrating the connectivity and location of the five distinct morphological subtypes (M1–M5) of mRGCs and projections to their predominant targets in the brain. For simplicity, M1 mRGCs displaced to the INL [Hattar et al. 2002] are not depicted in this diagram. M1 mRGCs stratify in the OFF sublamina (red); M2, M4, M5, stratify in the ON sublamina (blue); and M3, stratify in the ON and OFF sublamina (purple) of the IPL of the retina. M4 mRGCs have the largest cell body size, and M1 cells have smaller body size than M2–M4 cells [Schmidt and Kofuji 2009, Ecker et al. 2010, Schmidt and Kofuji 2011]. The cell body size of M5 is not known (dotted line). The proportion of ON and OFF stratification in M3 mRGCs varies considerably between cells Schmidt and Kofuji 2011. Recent findings suggest that the M1 subtype consists of two distinct subpopulations that are molecularly defined by the expression of the Brn3b transcription factor [Chen et al. 2011]. Red dots indicate synaptic connections for which both functional and anatomical evidence exists (Belenky et al. 2003, Viney et al. 2007, Dumitrescu et al. 2009, Schmidt and Kofuji 2010, Hoshi et al. 2009). Blue dots indicate synaptic connections for which either functional or anatomical evidence exists [Ostergaard et al. 2007, Zhang et al. 2008, Ecker et al. 2010, Schmidt and Kofuji 2011]. mRGC subtypes project to distinct non-image and image-forming nuclei in the brain [Hattar et al. 2006, Ecker et al. 2010]. M1 cells predominantly project to non-image forming centers such as the suprachiasmatic nucleus (SCN) to control circadian photoentrainment and the shell of the olfactory pretectal nucleus (OPN) to control the pupillary light reflex. M3 brain targets are completely unknown at this time. M2, M4 and M5 are included together because no specific genetic marker exists for a single subtype. Collectively, they project to image-forming areas in the brain such as the lateral geniculate nucleus (LGN) and the superior colliculus (SC), but also to the core of the OPN of which no specific function is assigned to this brain region [Ecker et al. 2010, Brown et al. 2010; ]. Retrograde analysis confirms that M2 cells project minimally to the SCN and strongly to the OPN [Bauer et al. 2008]. Figure from Schmidt et al. 2011

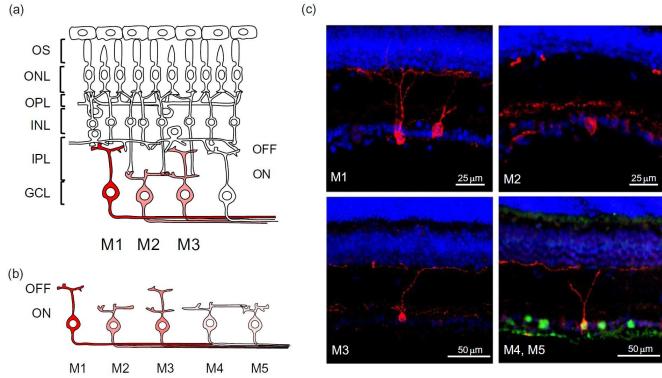
of this unusual synaptic input: ON bipolar cells make *en passant* synapses with M1 mRGC dendrites that stratify within the OFF sublamina of the IPL (Dumitrescu et al. 2009, Hoshi et al. 2009, Grünert et al. 2010). M1 mRGC dendrites also colocalize with dopaminergic amacrine cells (Vugler et al. 2007, Dumitrescu et al. 2009). Dopaminergic amacrine cells were recently implicated in guiding M1 cell dendrites to the OFF layer of the IPL (Matsuoka et al. 2011). Previous observations have also suggested that **mRGCs signal back to dopaminergic amacrine cells** in the **opposite** direction of classical retinal circuits (2008, 2012). The function of this unusual reverse signaling between M1 mRGCs and dopaminergic amacrine cells is **unknown**. The unexpected findings concerning M1 connectivity indicate that mRGC circuitry in the retina is far more complex than previously appreciated (Schmidt et al. 2011).

*From Hughes et al. 2012:* “Since their original description, it has become clear that pRGCs are not a homogeneous population of cells, but instead consist of numerous functionally distinct cell types (Figure 18). ... For **M1** cells, there are **two clear phases** of the light-induced photoresponse. An initial fast-acting transient followed by a smaller more sustained component. The initial **large transient** component to the light response is **absent** from **M2-type pRGCs** (and M3-, M4-, and M5-type pRGCs) that show small but sustained responses (Ecker et al. 2010, Schmidt and Kofuji 2009; 2011). M1 cells increase spike-firing rate with increasing intensities of light (Do et al. 2009), yet M1 cells are prone to *depolarization block* and are only able to fire action potentials at relatively **low rates** (Wong et al. 2007a, Schmidt and Kofuji 2009). In contrast, **M2 cells** are 10-fold less sensitive to light than M1 cells, produce a 10-fold smaller maximum photocurrent and can fire action potentials at **higher frequencies** than M1-type cells (Schmidt and Kofuji 2009, Ecker et al. 2010).”

*From Fox and Guido 2011:* “Since their initial discovery, ipRGCs have been subdivided into five distinct classes, termed M1–M5 ipRGCs. Such classification is based upon melanopsin expression level, dendritic morphology, sensitivity to light, intraretinal circuitry, and the pattern of their projections to retinorecipient nuclei (Figure 19).”

### 2.3.3. Melanopsin spatial distribution

*From Dacey et al. 2005:* “In flat mounts of the entire retina, the melanopsin antisera revealed a morphologically distinct population of **~3,000 retinal ganglion cells** with completely stained cell bodies, dendritic trees and axons (Figure 20a–c). With ,1.5 million ganglion cells in the human retina, the melanopsin-expressing cells comprise only 0.2% of the total. The melanopsin-expressing ganglion cell bodies were big, giving rise to the largest dendritic tree diameters of any primate retinal ganglion cell identified thus far (Dacey et al. 2003) (Figure 20d–f).



**Figure 18: Subtype of melanopsin-expressing pRGC.** (a) Schematic showing the layers and cell types of the mammalian retina, including the melanopsin-expressing photosensitive ganglion cells (pRGCs). (b) Schematic showing the different levels of melanopsin expressed in pRGC subtypes (denoted by intensity of red coloring) and differing patterns of stratification within the inner plexiform layer. (c) Images showing the pRGC subtypes identified in the mouse retina to date. Panels show examples of M1-, M2-, and M3-type pRGCs in wild-type mouse retina stained with an N-terminal melanopsin antibody (shown in red, UF006 antibody) and also M4- and M5-type cells that are only identified via detection of EYFP expression in Opn4-Cre mice (shown in green). In the panel showing M4-and M5-type cells, a melanopsin-immunoreactive M1-type cell is included for comparison (Opn4-Cre mice ([Ecker et al. 2010](#)) were kindly provided by Sammar Hattar, John Hopkins University). Outer segments (OS), outer nuclear layer (ONL), outer plexiform layer (OPL), inner nuclear layer (INL), inner plexiform layer (IPL), ganglion cell layer (GCL). OFF and ON denote the OFF and ON sublaminae of the IPL, respectively. ([Hughes et al. 2012](#))

The long, sparsely branching dendrites produced an extensive meshwork of highly overlapping processes. Cell counts showed a shallow density gradient ranging from  $3\text{--}5 \text{ cells mm}^{-2}$  over much of the retinal periphery to a peak of  $20\text{--}25 \text{ cells mm}^{-2}$  in the parafoveal retina (Figure 20g); in contrast, total ganglion cells reach a peak density of  $\sim 50,000 \text{ cells mm}^{-2}$ . In the central retina, the extremely large dendritic trees of melanopsin-containing ganglion cells spiralled around the foveal pit to form an extensive plexus (Figure 20e). Melanopsin-containing dendrites were localized to two strata: the extreme inner and extreme outer borders of the inner plexiform layer (Figure 20h). Individual cells are principally monostratified, creating two distinct subpopulations that send dendrites to either the inner or the outer stratum. About **60% of the melanopsin-expressing cells were outer-stratifying cells (M1)**, and about 40% had cell bodies displaced to the inner nuclear layer (M1)."

*From Jusuf et al. 2007*: "Like that of other other ganglion cell types in primate retina, the dendritic field size of melanopsin cells increases with the distance from the fovea. In the **fovea**, the dendrites of **melanopsin cells envelop the foveal pit**. The somas of melanopsin-containing cells are located either in the ganglion cell layer or in the inner nuclear layer. Their dendritic processes are located in the inner plexiform layer, either close to the inner nu-

clear layer (S1, outer stratifying, "M1") or close to the ganglion cell layer (S5, inner stratifying, "M2"). The somas of inner-stratifying cells are always located in the ganglion cell layer, whereas outer-stratifying cells have their somas either in the inner nuclear or the ganglion cell layer. Outer-stratifying and inner-stratifying cells share a similar morphology. The large majority of the cells (1141 / 1324, **86%**) were outer-stratifying cells, and **14%** ( $n = 183$ ) were inner-stratifying cells. Most of the outer-stratifying cells (688 / 1141, **60%**) had somas in the inner nuclear layer.

The **dendritic field diameter** was measured for 58 well-labeled melanopsin-containing cells in marmoset retina at various eccentricities (Figure 21). As shown above, no difference can be seen with respect to dendritic field diameter between inner-stratifying and outer-stratifying cells. The dendritic field diameter ranged from about  $200 \mu\text{m}$  to almost  $800 \mu\text{m}$ , and thus is much larger than that of midget, parasol and other wide-field ganglion cell types. Taking the difference in eye size into account, the dendritic field size of melanopsin cells in the marmoset is in the same range as those seen in macaque retina at comparable eccentricities ([Dacey et al. 2005](#)).

In **marmoset retina**, the density of melanopsin somas increases towards the fovea (Figure 22), with a mean peak density of  $15\text{--}17 \text{ cells / mm}^2$  at about 1 mm eccentricity, and decreases with distance from the fovea to a mean of  $6\text{--}7 \text{ cells / mm}^2$  at about 5 mm eccentricity. Thus, melanopsin cells in marmoset retina constitute probably less than 0.2% of the ganglion cell population ([Wilder et al. 1996](#)). Likewise, a low percentage of melanopsin cells has been estimated for Old World primates ([Hannibal and Fahrenkrug 2004](#), [Dacey et al. 2005](#)). In **macaques**, only peripheral retina was analysed. The mean density is  $5 \text{ cells / mm}^2$  at 3.5 mm eccentricity, and this decreases to  $2\text{--}3 \text{ cells mm}^2$  at between 9 and 14 mm eccentricity. These values are comparable to those reported by [Dacey et al. 2005](#). In both species, we found an increased density of melanopsin cells in the far periphery (average  $18 \text{ cells mm}^2$  in marmoset and  $10 \text{ cells / mm}^2$  in macaque) in the nasal / inferior pieces. Such an **increased density in the periphery** has not been reported for other species, and its **significance is not clear**."

#### 2.3.4. Melanopsin adaptation

*From Ichinose and Lukasiewicz 2007*: "Adaptation to the mean intensity of ambient light occurs in rod and cone photoreceptors ([Pugh et al. 1999](#), [Fain et al. 2001](#)) and at sites in the retinal network postsynaptic to photoreceptors (Figure 23) ([Dunn and Rieke 2006](#)). Contrast adaptation occurs in the retinal network but not in photoreceptors ([Smirnakis et al. 1997](#), [Dunn and Rieke 2006](#)).

Figure 24 summarizes how bipolar cell sodium channels contribute ganglion cell light sensitivity at different background light levels. The TTX-sensitive changes in ganglion cell sensitivity are greatest when dopamine levels are thought to be low (dim mesopic) and lowest when

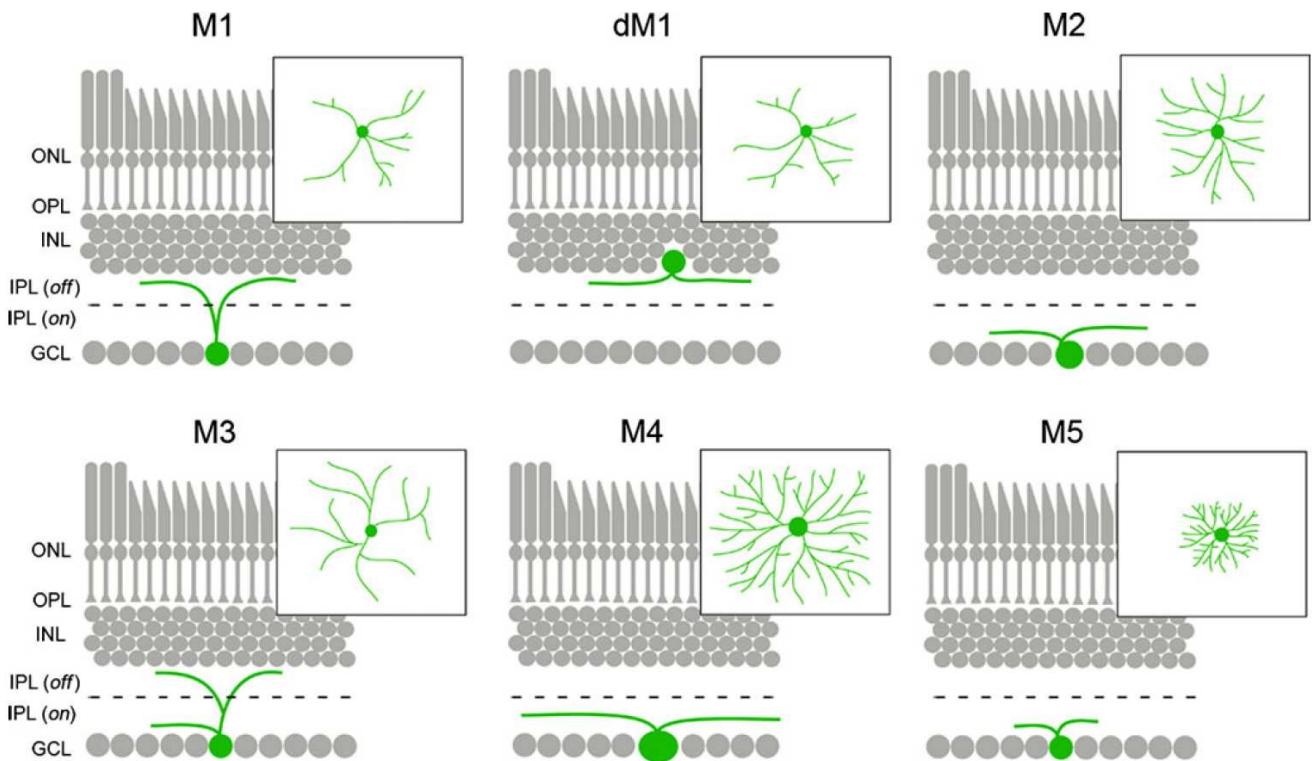
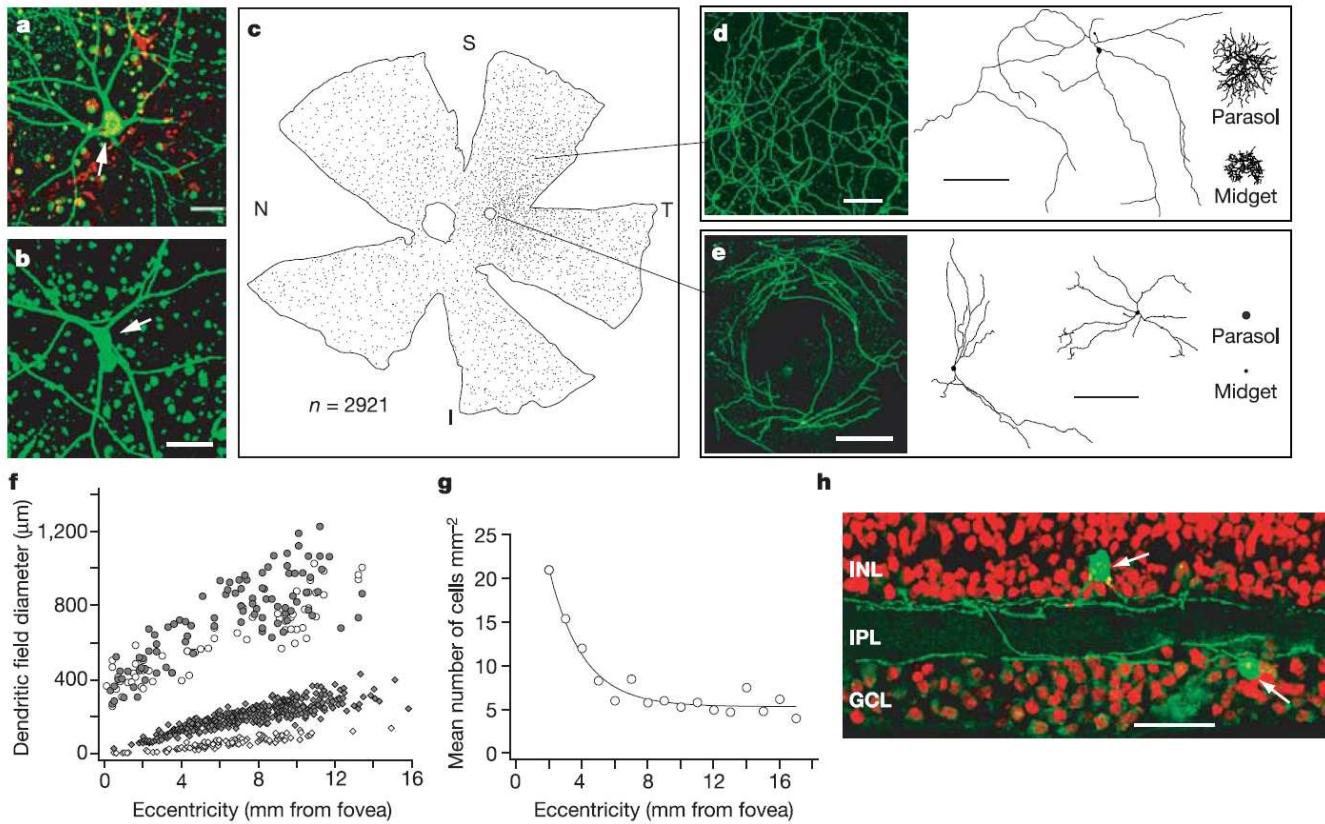
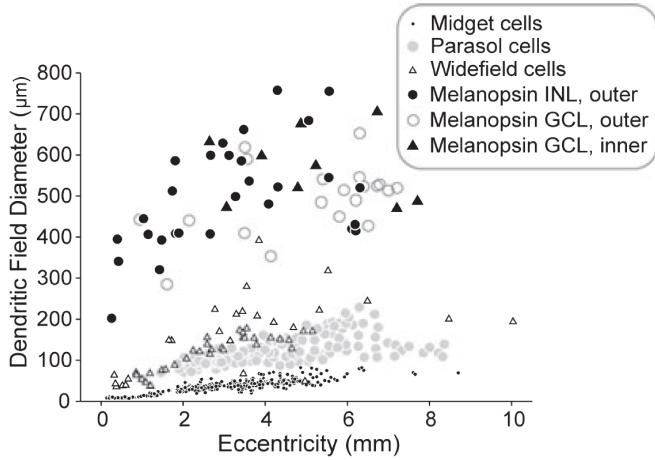


Figure 19: **Morphological differences between classes of ipRGCs.** Stratification of the dendrites of each of the five classes of ipRGCs [and displaced M1 ipRGCs (dM1)] are depicted in retinal crosssections. Insets show the morphology of dendritic arborizations for each class as seen in retinal whole-mount preparations. Black dashed line indicates the division of the inner plexiform layer into ON and OFF divisions of the IPL. ONL outer nuclear layer, OPL outer plexiform layer, INL inner nuclear layer, IPL(off) OFF division of the inner plexiform layer, IPL(on) ON division of the inner plexiform layer. ([Fox and Guido 2011](#))



**Figure 20: Morphology of melanopsin-immunoreactive cells.** **a**, Human cell (arrow); propidium iodide red counterstain. Scale bar, 50  $\mu\text{m}$ . **b**, Macaque cell (arrow). Scale bar, 50  $\mu\text{m}$ . **c**, Macaque retina tracing; dots represent melanopsin cells. T, temporal retina; N, nasal retina; S, superior retina; I, inferior retina. **d**, Melanopsin cells in peripheral retina (left; scale bar, 100  $\mu\text{m}$ ). Tracing of a peripheral HRP-stained giant cell (right; scale bar, 200  $\mu\text{m}$ ). Parasol and midget cells (far right) are shown for comparison. **e**, Melanopsin cells encircling the fovea (left; scale bar, 200  $\mu\text{m}$ ). Tracings of two HRP-stained giant cells ~1–1.5 mm from the fovea (right; scale bar, 200  $\mu\text{m}$ ). Circles (far right) indicate size of foveal parasol and midget cells. **f**, Dendritic field size of melanopsin cells versus eccentricity (inner cells, filled circles,  $n = 93$ ; outer cells, open circles,  $n = 63$ ). Parasol (filled diamonds,  $n = 333$ ) and midget cells (open diamonds,  $n = 93$ ) are shown for comparison. **g**, Mean cell density of melanopsin cells versus eccentricity (total 614 cells in  $78 \times 1 \text{ mm}^2$  samples). **h**, Dendritic arbours (green) of melanopsin cells (arrows) from stacked confocal images of 5 consecutive vertical sections (25  $\mu\text{m}$  thick). The soma of the outer cell is displaced to the inner nuclear layer (INL). GCL, ganglion cell layer; IPL, inner plexiform layer. Scale bar, 50  $\mu\text{m}$ . (Dacey et al. 2005)



**Figure 21: Dendritic field diameter of melanopsin cells in marmoset retina in comparison to other ganglion cell types at different eccentricities.** Outerstratifying cells with somas in the inner nuclear layer ( $n = 29$ ) are labeled: INL, outer. Outerstratifying cells with somas in the ganglion cell layer ( $n = 20$ ) are labeled: GCL, outer. Inner-stratifying cells with somas in the ganglion cell layer ( $n = 9$ ) are labeled: GCL, inner. The data for midget, parasol and other widefield ganglion cell types are from previous studies (Ghosh et al., 1996; Szmajda et al., 2005; Szmajda, Grunert & Martin, unpublished). (Jusuf et al. 2007)

dopamine levels are thought to be high (photopic). Ganglion cell light sensitivity during cone signaling conditions decreases as a function of background light intensity (Figure 24). These findings, along with our observations that **dopamine agonists mimic bright-light conditions**, suggest that increases in dopamine release with increasing light levels are responsible for decreasing ganglion cell sensitivity, modulated by bipolar cell sodium channels.

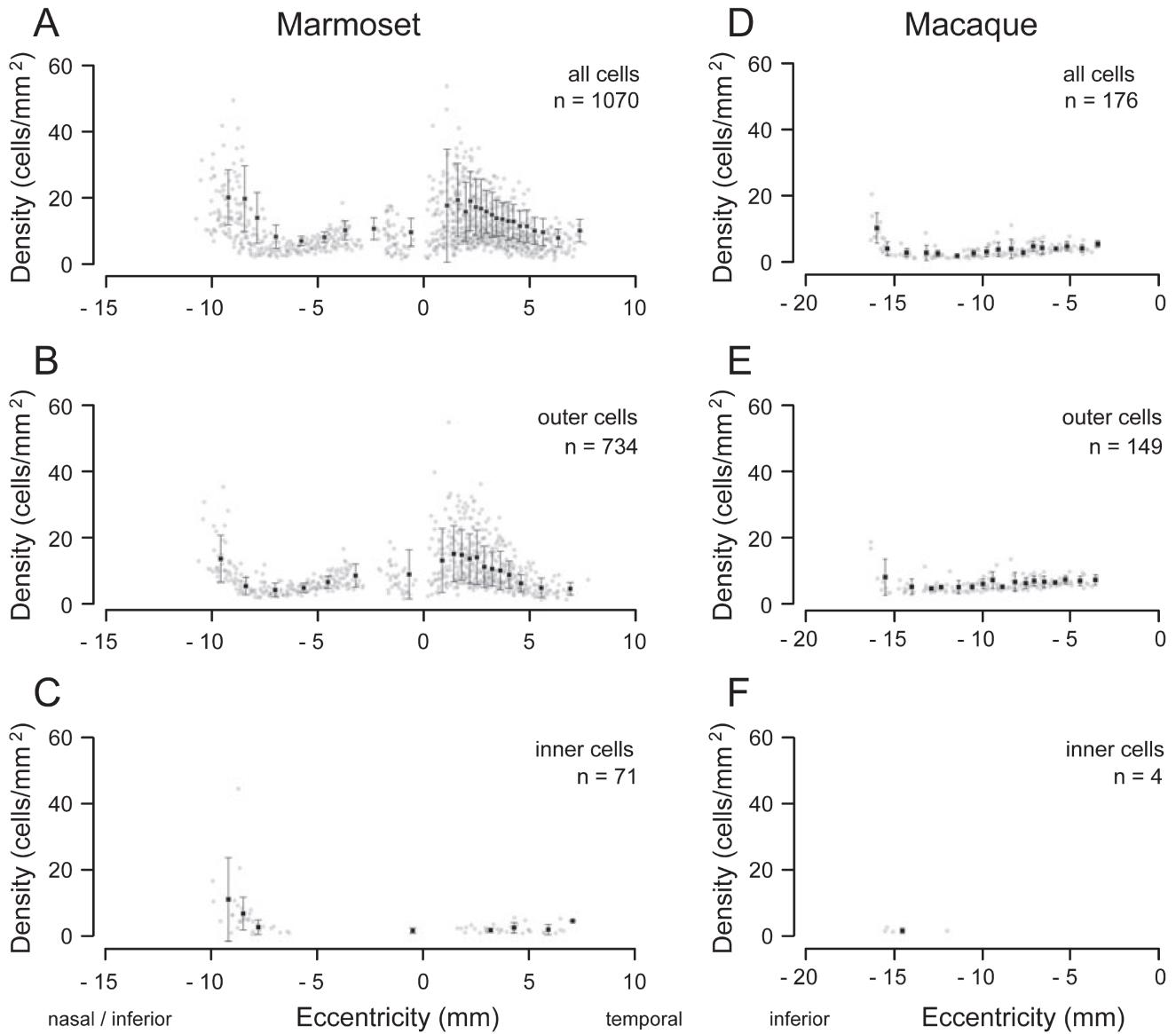
Dopamine modulates voltage-gated sodium channels through diverse mechanisms (Witkovsky 2004). In retinal ganglion cells, dopamine accelerates the rate of entry of sodium channels into an inactivated state and slows their recovery from the inactivated state (Hayashida and Ishida 2004). .. Our findings demonstrate that **sodium channels in bipolar cells** dynamically control retinal sensitivity to mean light and to contrast over a wide range of **ambient light conditions**. In dim-light-adapted conditions, the sodium channels boost retinal sensitivity, whereas in bright-light-adapted conditions, our results strongly suggest that **dopamine suppresses the excitatory effect** of the sodium channels to avoid saturation. We propose that bipolar cell sodium channels contribute to a novel mechanism of **network light adaptation**.”

*From Hughes et al. 2012:* “Interestingly, adaptation and desensitization of pRGC responses have also been reported. Adaptation is evident by **shortening of time to peak** response in response to increasing intensities of light (Do et al. 2009), a **reduction in amplitude** of response following repeated light stimulation (Wong et al. 2005), and **increase in incremental responses** in the presence of steady background illumination (Wong et al. 2005).”

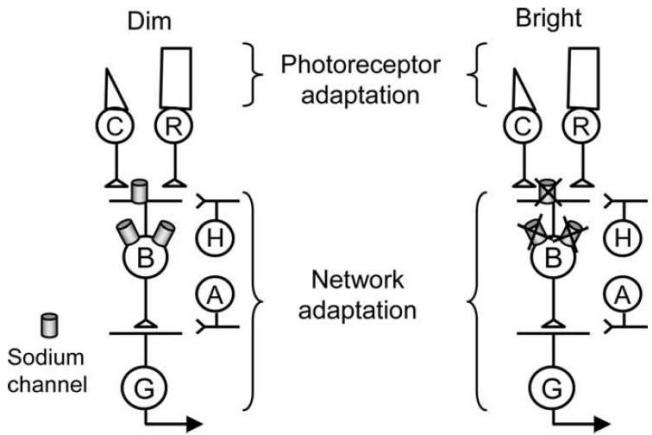
*From Teikari 2012:* The ambient light level varies over 9-10 orders of magnitude in the course of a day, while the post-receptoral spiking neurons have a dynamic range of only 2 log units, the visual system must adjust its sensitivity to the ambient light intensities. Rods and cones can gradually reduce their sensitivity for constant illumination allowing the photoreceptor to respond to further increments in light intensity. This process, termed light adaptation (Thomas and Lamb 1999, Dunn et al. 2007), extends the dynamic range of these receptors by normalizing their sensitivity to the given background light level. The process is complete before spiking neurons get involved. As a result, the ganglion cell signals are more or less independent of the illuminating intensity, but encode the reflectances of objects within the scene (Gollisch and Meister 2010).

The opposite process [note the asymmetry of light-dark adaptation (Reuter 2011)], when in darkness after prolonged exposure to bright light, the photoreceptors gradually recover from light adaptation by regaining sensitivity in a process called dark adaptation (Dowling 1987, Lamb and Pugh 2004). Both in the case of light and dark adaptation, the cones adapt more rapidly than rods, due to their ability either to regenerate the pigment more rapidly for dark adaptation (Hecht 1937, Lamb and Pugh 2004), or to use more elaborate light adaptive schemes (see Pugh et al. 1999, Fain et al. 2001) avoiding electrical saturation at any steady light intensity (Barlow 1972, Lobanova et al. 2010). In addition to simple light intensity adaptation, both vertebrate rods and cones and invertebrate photoreceptors accelerate the responses to dim flashes, enhancing temporal resolution. The time to response peak is shortened in light-adapted photoreceptors and post-stimulus recovery is more rapid and the inverse for dark adaptation (Fuortes and Hodgkin 1964, Baylor and Hodgkin 1974, Fain et al. 2001).

It is unknown whether similar adaptational processes occur in the mRGCs. The operational requirement for non-image forming system differ from those imposed on classical visual system. The classical visual system must be able to respond rapid changes in scene information, in other words detect significant edges and contours for visual perception (Marr and Hildreth 1980, Simoncelli and Olshausen 2001). In contrast, the non-image-forming system requires a stable representation of absolute light intensity. The first evidence to support the existence of both light and dark adaptation in mRGCs came from the study by Wong et al. 2005 done with intact *in vitro* rat retinas under blockade of glutamatergic synaptic transmission (Dolan and Schiller 1994). The kinetics of rat mRGC light adaptation (with a time constant of ~1 min and completion within ~5 min) was found to be somewhat slower than that for rods and cones of various vertebrate species, reported of fully light adapting within anywhere from 1 s to 3 min (Normann and Perlman 1979, Cervetto et al. 1985, Silva et al. 2001, Calvert and Makino 2002). The time constant for dark adaptation was ~3 hr. This is slower than for



**Figure 22: Density of melanopsin cell somas at different eccentricities for marmoset (A–C) and macaque (D–F) retinas.** Each gray dot represents the density derived from a single melanopsin soma and its Voronoi cell. The black squares and bars show the means and standard deviations of binned cells. Eccentricities of temporal pieces have been arbitrarily assigned as positive and those from nasal or inferior pieces as negative. The two pieces from macaque retina did not include the fovea. (A and D) Density derived for melanopsin somas from seven retinal pieces of four marmoset eyes and two inferior pieces of one macaque eye (A, every 40 cells binned; D, every 10 cells binned). (B and E) Density of outer-stratifying cells. Data were obtained from the same retinal pieces, excluding one piece where the outerstratifying and inner-stratifying cells could not be distinguished (B, every 40 cells binned; E, every 10 cells binned). (C and F) Density of inner-stratifying cells (C, every 10 cells binned; F, four cells binned). In macaques 1mm corresponds to an eccentricity of roughly 5 degrees (Crook et al. 2009). (Jusuf et al. 2007)



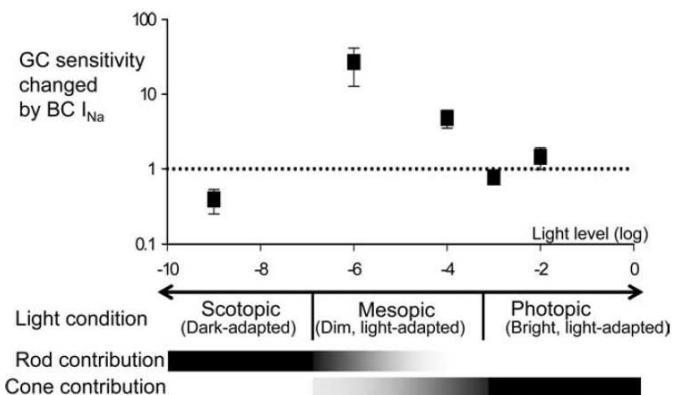
**Figure 23: Schematic of retinal neural network and sites of adaptation.** Voltage-gated sodium channels in bipolar cells contribute to network adaptation in dim (left) but not in bright (right) light conditions. C, Cone photoreceptors; R, rod photoreceptors; B, bipolar cells; G, ganglion cells; H, horizontal cells; A, amacrine cells. (Ichinose and Lukasiewicz 2007)

example the complete dark adaptation of albino rat cone occurring within about 30 min, and the time constant of ~40 min and the steady state full adaptation occurring in about 3 hour for rods of the same animals dark adapted (Perlman 1978, Behn et al. 2003). The same authors extended these findings providing preliminary evidence for light adaptation in mRGCs during a prolonged light exposure of 1 hour (Wong et al. 2011, Wong 2012; the 10h paper was not out yet then).

Behavioral correlates of the mRGC adaptation (Wong et al. 2005) can be found for example from PLR studies, where the PLR gradually regains sensitivity as the duration of dark adaptation after prior exposure to adapting light increases (Ohba and Alpern 1972, Trejo and Cicerone 1982). Increased firing rates evoked by light in SCN cells often decay during steady illumination in a manner suggestive of light adaptation (Aggelopoulos and Meissl 2000). Light adaptation in conventional photoreceptors has been shown to make their intensity-response curves (IRC) shallower, compared to absent light adaptation, thus broadening dynamic ranges of their responses (Baylor and Hodgkin 1974, Matthews et al. 1988). It is plausible that light adaptation in mRGCs likewise serves to enable them to discriminate a wider range of light intensities, e.g., from dawn light to noon light or in longer term, between summer and winter. Furthermore, there has been some evidence suggesting a role for mRGCs in intraretinal processing (Van Gelder 2001, Hankins and Lucas 2002, Zhang et al. 2008; 2012), and the adaptational properties of mRGCs might therefore modulate the adaptational states of other retinal cells.

The human behavioral sensitivity of the non-image forming (NIF) visual system seem to be modulated by not only the ambient light but also by the light history preceding the ambient lights even up to periods of several days (Hébert and Stacia 2002, Smith et al. 2004, Jasser et al. 2006, Rufiange et al. 2007, Beaulieu et al. 2009, Danilenko et al. 2009; 2011, Chang et al. 2011), or by the season (Higuchi et al. 2007, Mathes et al. 2007). It is however unclear at the moment where the observed phenomena originate from.

Study by Hannibal et al. 2002 in albino Wistar rats showed an amount of melanopsin protein varying over 24 h cycle, suggesting either an oscillator or adaptive mechanism driving the amount of melanopsin pigment. Follow-up study by the same group (Hannibal et al. 2005) further supported the findings that the expression of melanopsin protein in the retina of the albino Wistar rat is strongly regulated by light and darkness (10-fold suppression in constant light condition (LL) and a 7.5-fold increase in constant darkness (DD) after 5 d of LL). The up-regulation in DD seemed to be faster and more pronounced than the down-regulation in LL. It was suggested by the authors (Hannibal et al. 2005) that the observed phenomenon reflect a functional adaptation. Adaptation was shown to be morphological [see also for example increased bipolar sprouting in aged mice (Liets et al. 2006)



**Figure 24: The enhancement of ganglion cell (GC) light sensitivity is decreased by increasing adaptation levels.** The enhancement of ganglion cell sensitivity to mean illumination attributed to bipolar cell (BC) sodium channels was plotted as a function of background light (same dataset as in Fig. 6 E). In scotopic conditions, light sensitivity in ganglion cells was not affected by bipolar cell sodium channels. In mesopic, dim-light-adapted conditions, light sensitivity was dramatically enhanced. The enhancement was decreased by increased ambient light levels and was not observed in photopic conditions. The decrease in light sensitivity was attributed to decreased bipolar cell sodium channel contributions and maybe correlated with dopamine release by light adaptation (see Discussion). (Ichinose and Lukasiewicz 2007)

and humans (Eliasieh et al. 2007)] in addition to mere regulation of the protein, melanopsin immunoreactive dendrites form an extensive network during DD, whereas during LL, melanopsin immunoreactivity was limited to the soma and proximal dendrites. The source for the observed adaptation was suggested to be cone-rod driven (Sakamoto et al. 2004, Mathes et al. 2007) more specifically via rod-cone driven dopamine synthesis, dopamine finally regulating melanopsin expression (Sakamoto et al. 2005).

The findings were further supported in a study with three diurnal and 4 nocturnal rodent species (Refinetti 2007), where in four of the species tested (diurnal rodent: degus; and nocturnal rodents: CD-1 mice, Wistar rat and Syrian hamster) phase delays of the running-wheel activity rhythm evoked by 1-h light pulses were several-fold larger after 3 to 4 weeks of exposure to darkness than after a single day. This finding was consistent with previous estimate of full adaptation in the circadian system of rodents taking up to 3 or 4 weeks (Daymude and Refinetti 1999, Refinetti 2001; 2003). Counter-intuitively, dim nighttime illumination have been found to enhance the phase-shifting abilities of following bright light exposure in hamsters (Evans et al. 2009; 2011, Frank et al. 2010) and in humans (Chang et al. 2011). It has been suggested (Mure 2009) that the observed potentiation of the observed response could be due to melanopsin bistability, the dim light penetrating the selectively red-transmitting eyelids (Moseley et al. 1988, Robinson et al. 1991, Ando and Kripke 1996) favoring photoconversion from the M state to the R state (and ensuring maximum pool of photoresponsive melanopsin.

### 2.3.5. Retrograde visual signaling

From Zhang et al. 2008: “Sustained drive from ipRGCs to DA neurons is likely responsible for dopaminergic signaling elicited by steady illumination (Brainard and Morgan 1987) that mediates reconfiguration of the retinal circuits to background light through modulation of retinal networks, neurons, and synapses. Indeed, melanopsin photopigment has been shown to contribute to the modulation of second order neurons in human and mouse retinas (Hankins and Lucas 2002).

The input to sustained DA neurons from ipRGCs was also shown to carry the known input of ON-bipolar cells to ipRGCs (Wong et al. 2007a), reflected as a transient light-induced synaptic current which was blocked by L-AP4 [L-(+)-2-4-amino-4-phosphonobutyric acid].

A parsimonious circuit model for the excitatory influence of ipRGCs on sustained DA neurons (Figure 25) is that glutamate is released from the dendrites of light activated ipRGCs and acts at AMPA/kainate receptors on the costratifying processes of DA neurons in the outermost IPL. This model is consistent with the fact that ipRGCs are glutamatergic (Wong et al. 2007b), that DA neurons express AMPA/kainate receptors (Puopolo et al. 2001), that sustained light responses in DA neurons are blocked by AMPA/kainate receptor antagonists (Zhang et al. 2007). ...

Although ipRGCs have been suggested to make **gap junctional contacts** with other inner retinal neurons (Sekaran et al. 2003), electrical coupling between ipRGCs and DA cells cannot directly mediate the melanopsin signal analyzed here because it is vulnerable to blockade of ionotropic glutamatergic transmission. Recently, **long-latency ON** responses, proposed to be carried by the **retinal OFF channel**, have been described in mouse and zebrafish ganglion cells under circumstances in which the ON channel is genetically or pharmacologically inactivated (Rentería et al. 2006). This mechanism is **unlikely** to underpin the sustained light responses of DA neurons because the OFF channel-mediated GC ON responses are transient and presumably would carry the spectral signature of rod or cone input, not of melanopsin input as observed here.

Retinal **dopamine**, released by DA neurons, modulates the function of all **major classes of retinal neurons**, including photoreceptors and horizontal and bipolar cells in the outer retina (Ichinose and Lukasiewicz 2007). Thus, the excitatory influence of ipRGCs on DA neurons provides a basis for sustained photic signals originating in the innermost layer of the retina to feed back centrifugally to the outer retina, reversing the canonical direction of visual signaling (Figure 25). ”

s

From Zhang et al. 2012: “Ganglion cell photoreceptors are **glutamatergic** and the sustained light responses of retinal dopamine neurons are driven by a glutamatergic mechanism (Zhang et al. 2008). ...

Our results establish that expression of melanopsin photopigment is necessary for the sustained-type light responses in retinal dopamine neurons that are not mediated by rod/cone photoreceptors. Since in the mammalian retina melanopsin is only known to be expressed in ganglion cells, this is strong evidence that the sustained light responses of dopamine neurons are driven by ganglion cell photoreceptors...

The synaptic mechanism for retrograde signaling from ganglion cell photoreceptors to dopamine neurons clearly involves **AMPA-type glutamate receptors**, with the likelihood of a modest contribution by **kainite** receptors as well. The localization of AMPA receptor proteins to dopamine neuron processes apposed to melanopsin-expressing ganglion cell processes supports the physiological role of AMPA receptors in this synaptic mechanism. Both dendrites and recurrent axon collaterals of ganglion cells have previously been shown to be presynaptic elements of synapses in the inner plexiform layer of the retina, establishing **two potential routes** by which retrograde transmission could take place (Dacey 1985, Sakai et al. 1986, Peterson and Dacey 1998).

In the **absence of melanopsin** expression all recorded light responses in DA neurons are **transient** in time-course and blocked by inhibition of rod/cone transmission to ON bipolar cells by LAP4. The proportion of DA cells responding to visible light in *OPN<sup>-/-</sup>* retinas is identical to

the total proportion of both transient and sustained light responses in wild-type retinas (ca. 60%). This is consistent with the notion that sustained **DA neurons receive** both **ON bipolar** and **ipRGC input**. This suggestion is further supported by our previous observations that sustained DA neuron responses exhibit a transient component that is blocked by **inhibition of ON bipolar** cell transmission (Zhang et al. 2008), and anatomical studies suggesting that most DA neurons receive bipolar cell input (Dumitrescu et al. 2009, Hoshi et al. 2009, Contini et al. 2010).

What could be the **function of the retrograde light signaling** pathway in the retina? ... It is striking that ipRGCs provide their sustained input to the **dopaminergic amacrine cells** that are a key retinal neuromodulatory system for **light-adaptation** and for **synchronization** and expression of retinal circadian rhythms (Ruan et al. 2008, Jackson et al. 2012). Indeed, retinal circadian rhythms are disrupted in melanopsin knockout mice and in retinal dopamine knockout mice (Barnard et al. 2006, Jackson et al. 2012). Therefore a single cell class, the ganglion cell photoreceptor, may provide **both upstream** retinal circuits and **downstream** brain circuits with sustained signals encoding luminance.

*From Lucas 2013:* “A couple of potential routes via which ipRGCs could regulate retinal physiology have been described. Pharmacological and anatomical data indicate that ipRGCs are coupled to neighbouring GABAergic amacrine cells (Sekaran et al. 2003, Pérez de Sevilla Müller et al. 2010), and appear to regulate the activity of dopaminergic amacrine cells (although apparently not dopamine release itself, Cameron et al. 2009) via a glutamatergic synapse (Vugler et al. 2007, Zhang et al. 2008). Either of these routes could be used to link ipRGCs to the retinal circadian clock(s) (Guido et al. 2010) and/or to provide more immediate light adaptation of the retinal circuitry.”

### 2.3.6. “Classical rod-cone” contribution

*From Aggelopoulos and Meissl 2000:* “The identity of the photoreceptor type that mediates the responsiveness of the circadian system of rodents to light remains, however, unknown. Involvement of either a cone opsin-based mechanism (Nelson & Takahashi, 1991 Nelson and Takahashi 1991) or **rhodopsin** (Bronstein et al. 1987) has been suggested.

These demonstrated a ubiquitous electrical ‘bistability’ in spontaneous discharge dependent on these two conditions. Figure 26 shows one such neurone with a typical on-excitatory response under scotopic conditions (Figure 26A) changing to an on-excitation followed by off-inhibition under photopic conditions (Figure 26B). Another characteristic aspect of this bistable behaviour was that the spontaneous firing pattern of these neurones changed under the

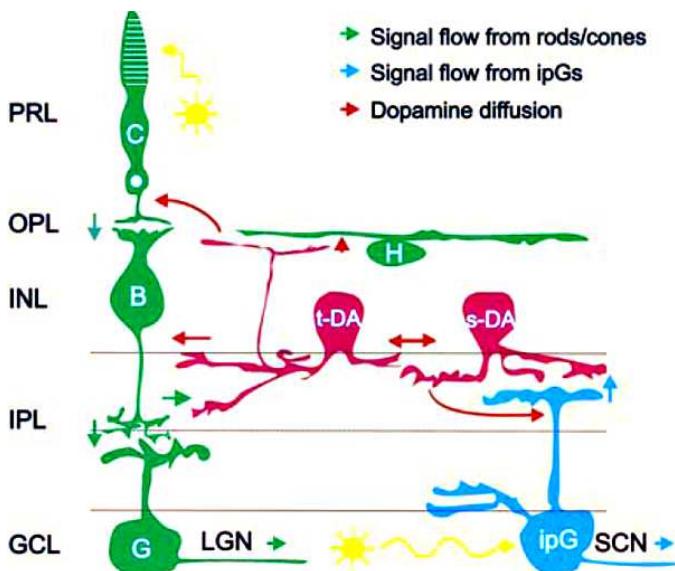
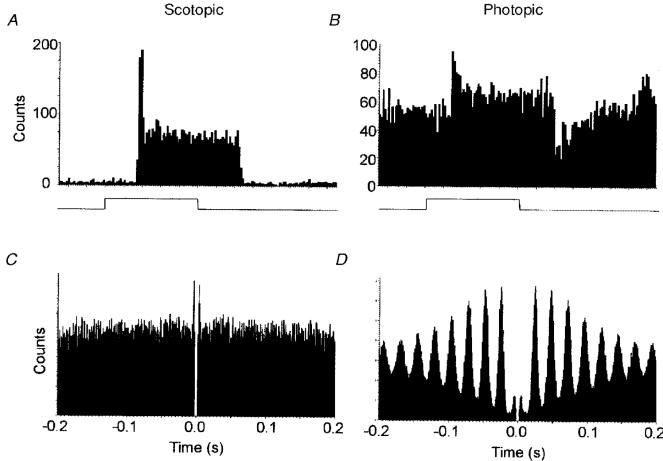


Figure 25: **Neuronal circuit diagram of the light input pathways to dopamine cells in the mammalian retina.** Blue arrows represent the light signalflow from melanopsin ganglion cells to sustained dopamine cells and the SCN; Green arrows: light signal flow from rods/cones to ganglion cells through ON-bipolar cells to transient dopamine cells and the LGN. Red arrows represent the dopamine diffusion to target cells in all retinal layers. Yellow arrows represent light. C, cones; H, horizontal cells; B, ON-type cone bipolar cells; t-DA, transient dopamine cells; s-DA, sustained dopamine cells; G, ganglion cells; ipG, melanopsin-expressing intrinsically photoreceptive ganglion cells; PRL, photoreceptor layer; OPL, outer plexiform layer; INL, inner nuclear layer; IPL, inner plexiform layer; GCL, ganglion cell layer; LGN, lateral geniculate nuclei, the thalamic visual nuclei of the brain that are innervated by conventional ganglion cells; SCN, suprachiasmatic nuclei, the hypothalamic master biological clock nuclei that are innervated by intrinsically photoreceptive ganglion cells. (Zhang et al. 2008)

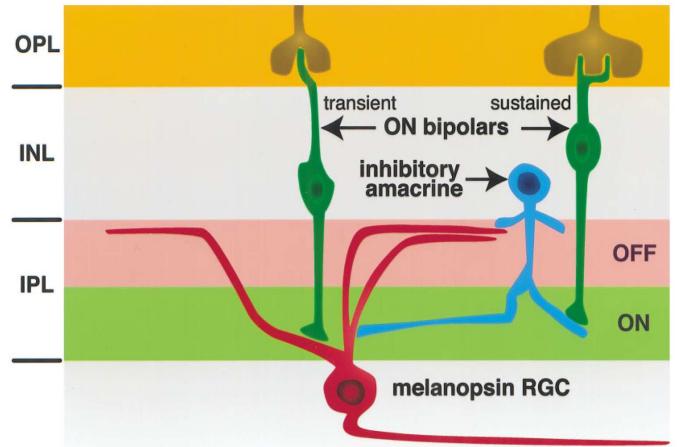


**Figure 26: Discharge patterns in a visually responsive SCN neurone** **A**, under dark adaptation, this neurone had a low firing rate (mean, 0–9 Hz) and responded to a light stimulus (indicated by the square waveform ramp at the lower trace) by an onexcitation that had both transient and sustained components. Average of 60 responses. **B**, under white light adaptation, this neurone showed a typically high spontaneous firing rate (mean, 26 Hz) and responded with an onexcitation followed by an offinhibition. These responses have been averaged over several stimulus presentations. Average of 20 responses. **C**, autocorrelogram under dark adaptation, showing the distribution of neighbouring spikes to every spike sampled. The autocorrelogram of this neurone's spontaneous activity suggests that the electrical discharge pattern was completely random over a 20 min period. **D**, autocorrelogram under light adaptation from the same neurone, showing the patterning of activity at discrete intervals, over a 20 min sampling period. Interspike interval histograms. (Aggelopoulos and Meissl 2000)

two conditions of adaptation. Whereas under dark adaptation the firing of these neurones was totally random (Figure 26C), under photopic conditions all light-responding suprachiasmatic neurones were displaying highly autocorrelated activity, such that a spike had a higher probability of occurring at a certain time after another spike (Figure 26D)."

*From Belenky et al. 2003:* "As described in the current study, the multiple synaptic inputs to photosensitive retinal ganglion cells (i.e., amacrine input to dendrites and ganglion cell perikarya and bipolar input to dendrites exclusively in the ON layer of the IPL) may serve as a structural basis for the excitatory and inhibitory inputs to intrinsically photosensitive retinal ganglion cells. The physiologic data of Berson et al. 2002, Berson 2003, Warren et al. 2003 are included in the summary diagram illustrating the synaptic input to melanopsin ganglion cells (Figure 27).

**Rod bipolars have never been observed to make synaptic contact with ganglion cell bodies or dendrites** (Kolb 1979, Chun et al. 1993), and it is now widely accepted that the transmission of rod signals to ganglion cells is via ON rod bipolar to amacrine type II cells to ON and OFF cone bipolars to ON and OFF ganglion cells (Sharpe and Stockman 1999). .. The **type 9 cone bipo-**



**Figure 27: Schematic diagram outlining the retinal circuitry presynaptic to melanopsin ganglion cells based on morphologic and physiologic data.** Melanopsin retinal ganglion cells (RGC) are located primarily in the ganglion cell layer, with dendrites stratifying in the outer inner plexiform layer (IPL) near the border of the inner nuclear layer (INL). The proximal dendrites receive bipolar cell input in the physiologically defined ON region, and some melanopsin cells show transient ON responses to light stimulation followed by the intrinsic response to light (Berson 2003). Amacrine cell terminals are found in contact with melanopsin dendrites in the ON and OFF regions of the IPL. Physiologic data suggest that amacrine input is inhibitory (GABAergic) and sustained (F. A. Dunn and D. M. Berson, personal communication). The intrinsic photo response of melanopsin ganglion cells may be modified by rod and/or cone signals. OPL, outer plexiform layer. (Belenky et al. 2003)

**lar cell** appears to be a primary candidate for the cell of origin of bipolar terminals on melanopsin ganglion cell somata and dendrites in the inner IPL. Type 9 cone bipolars seem to be *relatively uncommon*, they have a sparsely branched dendritic tree that covers a wide expanse of the outer plexiform layer, and they possess a sparse but large axon terminal system that stratifies mainly in stratum 5 with occasional processes penetrating into the ganglion cell layer (Euler and Wässle 1995).

.. To add to the complexity, perhaps **as many as 20% of the ganglion cells afferent to the SCN do not express melanopsin** and may receive their inputs entirely from the *conventional rod/cone circuits* (Gooley et al. 2001, Sollars et al. 2003), or these cells may use *other potential photopigments* (e.g., cryptochrome, Sancar 2000, Fogle et al. 2011). If the task of retinal input to the SCN is simply to convey the level of ambient illumination, it is unclear why such complex signal processing is required."

*From Viney et al. 2007:* "... Most of the labeled cells in the INL were amacrine and *Müller glia cells*. Only occasionally have we seen labeled bipolar cells. Müller-cell labeling was consistently observed solely near the cell bodies of infected ganglion cells, whereas labeled amacrine cells were scattered concentrically around them... These results suggest that **Müller cells** make *specialized contacts* with ipRGCs but not with ganglion cells that project to the dLGN and subsequently to the V1.

The labeled circuit gave very strong predictions about the **direct**, amacrine-cell-mediated **inhibitory input to type 2 ipRGCs**. .. Because amacrine cells receive excitation from bipolar cells, the reconstructed amacrines must receive excitation **only at light ON**. Most amacrines are inhibitory cells. If the type 2 ipRGCs receive inhibitory input only from the reconstructed amacrines, *inhibition should arrive at light ON but not at light OFF*. Inhibition at light OFF would *suggest a multistratified or bisstratified amacrine cell*, because OFF activity should travel vertically in the IPL from sublamina A to sublamina B (Roska and Werblin 2001). .. The resting membrane voltage was  $\sim 58 \pm 4$  mV ( $n = 8$ ). Inhibition in type 2 ganglion cells was only evoked at light ON ( $n = 10$ ) when the retina was stimulated with a 1 mm diameter white spot, as predicted by the structure of the PRV-labeled local-circuit elements. This finding is in **strong contrast with inhibitory currents** evoked in most other ON ganglion cells in the mammalian retina; in the rabbit retina, **only one type of ON ganglion cell receives inhibition only at light ON**. These results suggest that *type 2 ipRGCs receive a strong, fast inhibitory input at light onset from a single morphological type of amacrine cell*.

**Dopamine** is a neurotransmitter that is in the retina and controls **light adaptation** (Witkovsky 2004). Dopaminergic cells of the mouse retina are *GABAergic* (Gustincich et al. 1997). These cells make conventional synapses and also release neurotransmitters extrasynaptically (Puopolo et al. 2001, Contini and Raviola 2003, Witkovsky 2004). Our study suggests that **dopaminergic cells are in synaptic contact with type 1 ipRGCs**. The synapse between dopaminergic cells and ipRGCs are GABAergic, dopaminergic, or both. It is possible that, similar to the synapse *between dopaminergic cells and AII amacrine cells* (Contini and Raviola 2003), both GABA and dopamine are released, but the postsynaptic receptors are positioned at different distances from the release site. In either case, however, the synaptic contact between interplexiform cells and ipRGCs suggests that the activity of **dopaminergic cells synaptically influences the activity of and/or gene expression in ipRGCs**."

From Oستergaard et al. 2007.: "Electrophysiological studies in **primates** have provided evidence that the ipRGCs receive **inhibitory signals** from short wavelength-sensitive cones and **excitatory input** from rods and medium- and long-wavelength cones (Dacey et al. 2005). This is in accordance with an ultrastructural study in mice showing that melanopsin-expressing ganglion cells located in the ganglion cell layer (GCL) and displaced to the inner nuclear layer (INL) have close contact with amacrine and bipolar cells of unknown phenotype (Belenky et al. 2003).

In the present study, we demonstrated that PKC $\alpha$ /CtBP2-containing **rod bipolar cells most likely make synaptic contact** at GluR4 receptors on **melanopsin-containing cell bodies** and proximal

dendrites. .. The **functional implications** of outer retinal input to the melanopsin-containing RGCs are **unknown**. .. Melanopsin expression is regulated by a circadian clock and by the light/dark cycles.35–37 Input from the classical photoreceptors also seems to influence the expression level of melanopsin. In rats lacking the outer retina because of retinal degeneration (Royal College of Surgeons rats with a defect in the retinal dystrophy gene RCS/N-rdy) cyclic changes in melanopsin mRNA are eliminated (Sakamoto et al. 2004) indicating that rods, cones, or both are involved in the regulation of melanopsin mRNA expression."

From Jusuf et al. 2007.: "The presumed bipolar synapses are found on all dendrites across the entire dendritic tree. .. Consistently, we often observed that some dendritic regions of outer-stratifying cells are located scleral to the first layer of bipolar synapses in the inner plexiform layer. The **low density of presumed bipolar input** to the outer-stratifying cells ("M1") might explain why Belenky et al. 2003 did not detect any bipolar input to outer-stratifying cells using electron microscopy in mouse retina.

Like the presumed bipolar synapses, the presumed amacrine synapses are found on all dendrites across the entire dendritic tree, with some regions that lack colocalized puncta. The **density of presumed amacrine input** to melanopsin cells is **higher than that of bipolar cell input**, suggesting that both inner-stratifying and outer-stratifying melanopsin-containing ganglion cells receive the **majority of their input from amacrine cells**. .. Taken together, bipolar and amacrine input to melanopsin cells appear to be distributed evenly across the dendritic tree, with no difference between proximal and distal processes.

The bipolar input to **outer-stratifying** cells could derive from **DB1 cells** (Boycott and Wässle 1991) and / or giant bistratified bipolar cells, both of which stratify in S1 (Kolb et al. 1992). Because of their axonal stratification and their dendritic connectivity, DB1 cells are thought to be **OFF bipolar cells** (Hopkins and Boycott 1996). They receive the large majority of their input from medium and long-wavelength sensitive cones, with probably only little input from short-wavelength sensitive cones (Hopkins and Boycott 1996). Thus, these cells may carry a **yellow-OFF** signal. Electrophysiological recordings from melanopsin cells in *in vitro* macaque retina showed that these cells have **blue-OFF / yellow-ON** responses mediated by cone photoreceptors (Dacey et al. 2005). If DB1 cells were responsible for transmitting the yellow-OFF signal to outer-stratifying melanopsin-containing cells, this signal would have to be converted to a yellow- ON signal via a **sign-inverting synapse**.

The **blue-OFF** signal could be mediated by a giant bistratified bipolar cell, which has been suggested to selectively contact short-wavelength-sensitive cones, but direct **evidence is still lacking** (Kolb et al. 1997). A third possibility is that a blue-OFF response in outer-stratifying

cells is transmitted via a **broadly stratifying amacrine cell** contacted by **blue (ON) cone bipolar cells** in S5 (Kouyama and Marshak 1992a).

**Inner-stratifying cells** have their dendrites in the same region of the inner plexiform layer as the axons of **DB6**, blue cone bipolar and rod bipolar cells. Thus, these bipolar cell types are possible candidates to provide synaptic input to these cells. However, **rod bipolar cells** are thought to form synapses only onto amacrine cells (Kolb and Famigilietti 1974, Grunert and Martin 1991), and we **did not observe any spatial colocalizations** between PKC-labeled rod bipolar cells and inner-stratifying melanopsin cell processes in a small sample of vertical sections (*unpublished observations*). On the other hand, Dacey et al. 2005 recorded rod-mediated responses from melanopsin cells in macaque retina, and Ostergaard et al. 2007 suggested that rod bipolar cells contact somas and proximal dendrites of melanopsin cells in the ganglion cell layer.

Our finding that the dendrites of inner-stratifying melanopsin-containing ganglion cells are colocalized with the axon terminals of **DB6 cells** suggests that these cells might receive excitatory input from DB6 cells, as has been suggested for macaque retina (Dacey et al. 2006). The DB6 cells are thought to be **ON bipolar cells**, and like all diffuse bipolar cells, receive the large majority of their input from medium / long-wavelength sensitive cones (Hopkins and Boycott 1996, Lee et al. 2004, Lee and Grünert 2007). The DB6 cells could thus be responsible for a yellow-ON response. A **blue-OFF** signal in inner-stratifying melanopsin cells could result from blue (ON) cone bipolar cells forming sign-inverting synapses with the dendrites of melanopsin cells (e.g. via metabotropic glutamate receptors) or **indirectly through inhibitory amacrine cells** (Hemmi et al. 2002, Li and DeVries 2006).

Electrophysiological recordings in macaque retina revealed **two populations** of **blue OFF / yellow ON**-type cells: the melanopsin-containing cells and a large, sparse cell type (Dacey and Packer 2003, Dacey et al. 2005). The melanopsin cell would thus possibly transmit signals for color vision as well as serving nonvisual functions. However, several questions concerning the synaptic circuitry of melanopsin remain open [see Discussion in Wong et al. 2007a]. In particular, it is still unclear how the ON responses are transferred to the cells stratifying in the OFF sublamina."

From Dumitrescu et al. 2009: "A minority of DA cells exhibit sustained ON responses that persist in the presence of L-AP4, apparently because melanopsin-based photoreponses in ipRGCs provide an excitatory drive to these cells through a circuit involving AMPA/kainate receptors (Zhang et al. 2008; 2007). Because the L-AP4-sensitive ON responses persist during blockade of inhibitory transmitter receptors (Zhang et al. 2007) or when inhibitory input is nullified by voltage-clamping at the reversal potential for chloride (Zhang et al. 2008), they cannot be driven by the

OFF channel through a polysynaptic disinhibitory mechanism (see, e.g., Critz and Marc 1992) but must instead be mediated by a direct ON bipolar cell input. It has been speculated that the necessary synaptic contacts from ON bipolar cells might occur on sparse dopaminergic processes in the ON sublayer (Witkovsky 2004), but it is not certain that these processes belong to true dopaminergic cells or that they receive bipolar contacts (Kolb et al. 1990). Thus, both DA and M1 cells receive a paradoxical ON channel input derived from ON bipolar cells that may be mediated in part by synapses lying outside the ON sublayer of the IPL. Because DA cells and M1 cells narrowly costratify in the outermost IPL, they may share a common source of noncanonical ON bipolar input.

Our initial goal was to provide a stringent test for the hypothesized ON channel input to the OFF sublayer by determining whether this input could be detected in M1 and DA cells even when they lacked any dendrites in the ON sublayer. **M1 melanopsin cells with somas displaced into the INL** provide an ideal test case, because their dendrites arborize in S1 but, unlike the conventionally placed M1 cells, do so without traversing the ON sublayer. To our knowledge, **no recordings have been made from displaced M1 cells** in any species. . . . Thus, ON bipolar cells appear to make direct excitatory synaptic contacts with the dendrites of displaced M1 cells in the OFF sublamina of the IPL.

As with displaced M1 cells, murine DA cells have somata located in the INL, so dendrites need not traverse the ON sublayer en route to their main arborization in S1. However, the dendritic stratification of these cells (especially those with ON channel input) has never been adequately characterized, and the sparse arborization of some DA cells in the ON sublayer must be considered a possible locus of ON bipolar input (Kolb et al. 1990, Witkovsky 2004, Zhang et al. 2007). „, This is the **first direct electrophysiological demonstration**, to our knowledge, of **an OFF bipolar cell-driven light response in DA cells**.) Dye filling of these recorded DA cells revealed that all of them were monostratified, with processes confined to the S1 layer of the OFF IPL. We conclude that **both DA and M1 cells receive a paradoxical ON bipolar cell input that does not involve synapses in the ON sublayer of the IPL**.

Both ectopic terminals and *en passant* ribbons of ON bipolar cells appeared to be concentrated **near the INL-IPL border**. To assess this quantitatively, we plotted the laminar position of each ribbon-containing ectopic terminal or *en passant* synapse relative to the boundaries of the IPL, which were easily identified from the distribution of kinesin II-immunoreactive puncta. Both types of presynaptic elements were highly concentrated in the upper half of the OFF sublayer (Figure 28A), corresponding to sublamina S1. Eighty-eight percent (210 of 239) of the ectopic terminals and 63% (312 of 495) of the *en passant* ribbons of ON bipolar axons were located in S1. Density was particularly high in the outermost S1 (95–100% depth), where the

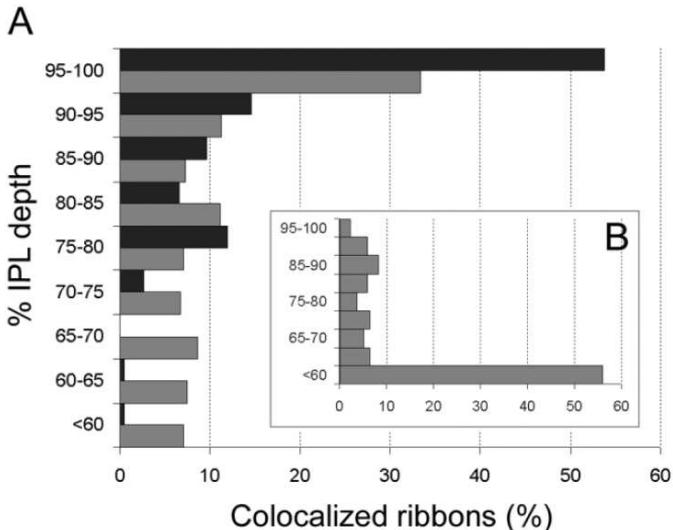


Figure 28: **Ectopic ON bipolar synapses are concentrated near the IPL-INL border, where melanopsin and dopaminergic dendrites ramify.** A: Comparative distribution throughout the OFF IPL of ribbons in ectopic terminals (black bars,  $n = 227$ ) and in smooth axonal shafts (*en passant* synapses; gray bars,  $n = 495$ ) of all ON bipolar cells in the *Grim6-EGFP* retina. Note the peak in density in the vicinity of the IPL-INL border (95–100% depth). B: Similar plot for *en passant* ribbons found only within rod bipolar cell axons ( $n = 218$ ), as identified by PKC immunoreactivity. Note the uniform distribution in depth and absence of a peak near the IPL-INL border. (Dumitrescu et al. 2009)

dendrites of M1 cells and DA cells arborize. This **laminar specificity** provides indirect corroboration for our conclusion that the ribbons in the *en passant* synapses actually lie within ON bipolar axons. If they resulted instead from the occasional overlap of signals (i.e., the erroneous assignment of a ribbon within an adjacent OFF bipolar terminal to an ON bipolar shaft), they **would be expected to be uniformly distributed throughout the OFF sublayer**.

The data presented here would seem to prompt a **revision to the classic view of ON/OFF sublaminar segregation**, first introduced more than 30 years ago (Famiglietti and Kolb 1976). The revised schema would include a thin accessory ON sublayer, lying at the most distal margin of the IPL, adjacent to the INL. In contrast to the classical ON sublayer, this accessory ON sublamina appears not to be strictly segregated from the OFF sublayer...

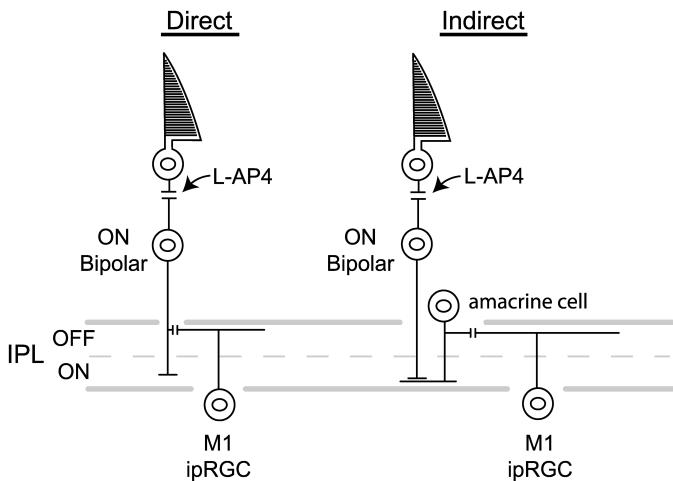
**Rod signals** do appear to drive M1 melanopsin cells (see, e.g., Dacey et al. 2005, Wong et al. 2007a; see also Aggelopoulos and Meissl 2000), but the **circuit by which they do so remains to be established**. Possible circuits include the *primary rod pathway* involving gap junctions between AII amacrine cells and ON cone bipolar terminals, the *secondary rod pathway* involving rod-cone coupling, or *direct contacts from rod bipolar cells* to the proximal dendrites or somata of M1 cells (Ostergaard et al. 2007). . .

We have provided **evidence for sparse ON bipolar inputs to the dendrites of these cells in the OFF**

sublayer. Are these inputs **sufficient** to account for the observed ON responses of these cells? We estimate that there are on average a total of roughly **40 ectopic ON bipolar contacts onto each DA and M1 melanopsin cell**. The estimate for M1 cells is reasonably close to the findings of Jusuf et al. 2007, who reported that M1-like, outer-stratifying melanopsin cells in the marmoset receive, on average, just over **100 ribbon synaptic contacts** in the outer (OFF) IPL; that study did not determine whether these contacts came from ON or OFF bipolar cells. . . *Two ganglion cell types* have total bipolar ribbon contacts that **are at least this low** (Ghosh and Grünert 1999, Eriköz et al. 2008), although both types have much **smaller dendritic fields than the M1 cells**. Before a strong case can be made that a few dozen ribbon contacts are sufficient to account for the observed light-evoked excitatory currents in these cells, **more must be learned about the size of synaptic currents** generated by individual bipolar contacts onto M1 cells and about the passive and active spread of such currents through the M1 dendritic arbor.

It will be of interest to learn whether ON signals transmitted in the accessory ON sublayer **differ functionally** from those in the main ON sublayer. Such differences could arise if the types of cone bipolar cells synapsing in this accessory ON sublayer have **distinctive functional features**. In addition, there might be substantial **functional differences in the amacrine inhibitory influences on bipolar-to-ganglion-cell transmission in this sublayer**. For example, if local tonic amacrine cell inhibition were driven mainly by the OFF channel rather than the ON channel, this might **shield the ectopic ON bipolar synapses** from sustained ON inhibition. Such inhibition has been shown to truncate ON responses passing through the ON sublayer (Roska et al. 1998), so the ON bipolar drive to postsynaptic targets may be relatively more sustained in the accessory ON sublayer than it is in the classical ON sublayer. It is therefore of interest that the **ON channel excitatory synaptic drive to the ipRGCs is substantially more sustained than it is in other ON ganglion cells** (Wong et al. 2007a).“

*From Hoshi et al. 2009:* “ipRGC cells appear to comprise three different types that can stratify in **sublamina a**, **sublamina b**, or stratify narrowly in **both sublaminae** (Viney et al. 2007, Baver et al. 2008). All of these ganglion cells appear to **depolarize to light onset** regardless of their soma location or stratification depth; hence, **they are all ON type ganglion cells**, even if anomalously stratified in sublamina a. . . Approximately **6%** of the descending calbindin-positive bipolar cell axons made contacts with **ipRGCs in sublamina a** when examining large ( $\sim 1 \text{ mm}^2$ ) patches of the retina. Given the **sparseness** of the dendritic fields of the ipRGCs, the **low percentage of contacts is not surprising**. Indeed, if counts are made on  $0.01 \text{ mm}^2$  patches centered on a **soma**, in which the density of processes is higher, the



**Figure 29: ON-bipolar cell input to M1 ipRGCs may be either direct or indirect.** L-AP4 acts at the mGluR6 receptor located on the dendrites of ON-bipolar cells. L-AP4 inhibition of light-induced Fos expression in M1 ipRGCs establishes that this functional channel provides synaptic drive to M1 ipRGCs. However, the results do not differentiate between a direct pathway of ON-bipolar input to M1 ipRGC dendrites in the outer OFF sublamina of the IPL vs an indirect circuit via a potential intervening glutamatergic amacrine cell. (Pickard et al. 2009)

percentage of axonal synapse to ipRGC contacts **rises to 13%**. It may also indicate that contacts are made preferentially close to the somas, perhaps maximizing their influence. It should be emphasized that, despite the low percentage of axons making contact with ipRGCs, **100% of the ipRGCs received such contacts in stratum 1**, as with the DACs.

Together, this set of results suggest that the **axonal ribbons** we have shown may function as **excitatory cone inputs** to ON responding neurons anomalously ramifying in **sublamina a**. Recently, Pickard et al. 2009 demonstrated light-onset-induced c-Fos expression in M1 ipRGCs **even in melanopsin knock-out mice**, i.e., ON inputs originating from traditional photoreceptors are found in these cells whose arbors are wholly contained in sublamina a. Our results provide morphological evidence for their “direct” model (Pickard et al. 2009 their Fig. 3 in Figure 29).

Our results indicate **violation of the canonical division** of the IPL into OFF and ON sublaminae. **Two questions** that naturally arise are as follows: (1) why DACs, which depolarize to light onset, ramify predominantly in the OFF layers, and (2) why *en passant* synapses with **apparent ON polarity occur in the OFF layer**. The answers are **not clear**, but we note that, because DACs regulate outer retinal functions through **paracrine release** of dopamine in the IPL, it would be most efficient for them to be **located as near these targets as practical**. Given this location of the DACs, one possible reason why some ipRGCs ramify in **sublamina a** may be to provide input to the **dopaminergic system** (Zhang et al. 2008).“

*From Grünert et al. 2010:* “In primate, **bipolar input** to both inner (M2) and outer (M1) **melanopsin** cells has been demonstrated in marmoset and macaque retinas (Jusuf et al. 2007), but the bipolar type(s) providing this input **have not been identified**. Bipolar cell types stratifying in the inner third of the inner plexiform layer include rod bipolar, invaginating midget, blue cone bipolar cells, and the diffuse bipolar cell type DB6 (Boycott and Wässle 1991). Rod bipolar cells usually do not contact ganglion cells (Kolb and Famiglietti 1974, Strettoi et al. 1990). Invaginating midget bipolar cells direct their major output to ON midget ganglion cells and amacrine cells (Kolb and Dekorver 1991, Calkins et al. 1994). Blue cone bipolar axons usually form dyads onto an amacrine and a ganglion cells process (Marshak et al. 1990, Kouyama and Marshak 1992a), and the small bistratified cell (blue-ON/yellow-OFF ganglion cell) is probably the major ganglion cell type contacted (Calkins et al. 1998a). Thus, the **most likely bipolar cell type** providing the input to *inner cells* is the **diffuse (ON) cone bipolar cell type DB6** (Jusuf et al. 2007). The main aim of the present study was to analyze the relationship between DB6 cells and inner melanopsin cells.

Recently, two studies of **mouse** and **rabbit** retinas found that **outer stratifying M1 cells** receive *en passant* synapses from descending ON cone bipolar axons (Dumitrescu et al. 2009, Hoshi et al. 2009). This finding, that ON bipolar cells provide output in the OFF sublamina, is *in contrast to the dogma*, which functionally subdivides the inner plexiform layer into an outer (OFF) and inner (ON) sublamina (Famiglietti and Kolb 1976, Nelson et al. 1978). Similarly, contacts between ON bipolar cells and dopaminergic amacrine cells in the OFF sublamina have been identified (Gustincich et al. 1997, Dumitrescu et al. 2009, Hoshi et al. 2009, Contini et al. 2010). The question whether DB6 bipolar axons make contacts with outer stratifying melanopsin cells in primate retina was also addressed in the present study.

In total, we found 44 regions of overlap between DB6 axons and melanopsin dendrites and a total of 34 piccolo IR puncta are located in these regions (77.3%). A lower percentage of puncta (50%) is found when the image is flipped in the horizontal axis. A total of 173 IR puncta are colocalized with DB6 axons, and a total of 102 IR puncta are located close to inner melanopsin dendrites. Thus, in this sample, **19.7% of the output made by DB6 cells** goes to *inner melanopsin cells (M2)* and the synapses formed by DB6 cells make up **33.3% of the input to inner melanopsin cells**. Taken together, these **results indicate** that (i) when DB6 axon terminals overlap with inner dendrites of melanopsin cells, they form synapses in the majority of cases; (ii) inner stratifying melanopsin receives a low percentage (about 30%) of their input from DB6 cells; and (iii) the synapses between DB6 axons and inner melanopsin dendrites make up only a small fraction (about 20%) of the total number of outputs of DB6 axon terminal in S5. Consistently, it has been shown by electron

microscopy that the **large majority of the output from DB6 cells goes to amacrine cells** (Jusuf et al. 2004). Furthermore, regions of close contact have also been detected between DB6 cells and large sparse ganglion cells in marmoset retina (Szmajda et al. 2008).

It has been suggested for rat retina that melanopsin somata located in the ganglion cell layer receive input from **rod bipolar axons** (Ostergaard et al. 2007). ... We found that the varicosities formed by rod bipolar axon terminals are usually located proximally to the dendrites of inner melanopsin cells, whereas the DB6 axon terminals usually are located distally to the inner dendrites. This is consistent with the finding that DB6 axons on average stratify slightly more distal than rod bipolar axons (see also Jusuf et al. 2004). ..... We **did not encounter** melanopsin-labeled ganglion cell somata in our sample of sections and thus **cannot exclude** the possibility that some rod bipolar axon make synapses with onto melanopsin somata as has been shown for rat retina (Ostergaard et al. 2007).

Our findings support and extend our previous studies of marmoset and macaque retinas, which showed that the dendrites of **both outer** (M1) and **inner** (M2) melanopsin cells are colocalized with pre- and postsynaptic markers for bipolar synapses and that both cell types **receive bipolar input** throughout the entire dendritic tree (Jusuf et al. 2007). Our findings are consistent with **electrophysiological recordings** obtained in macaque retina showing that both inner and outer stratifying melanopsin cells have ON-type responses mediated by synaptic inputs from rods and cones (Dacey et al. 2005). .. Consistently, this study and our previous study (Jusuf et al. 2007) **did not find any evidence for rod bipolar** output to melanopsin cells, and rod bipolar axons have been found to contact amacrine cells almost exclusively (Kolb and Famigilietti 1974, Strettoi et al. 1990, Grunert and Martin 1991) (but see Ostergaard et al. 2007).

Thus, piccolo IR puncta, which are located close to inner melanopsin dendrites but are not colocalized with DB6 axon terminals, probably derive from amacrine cells. Consistently, a result from one inner melanopsin cell in marmoset retina indicates that **amacrine input** to these cells occurs at a **higher density than bipolar input** (Jusuf et al. 2007).

Previously we showed that outer melanopsin cells in marmoset and macaque retinas receive bipolar input throughout the entire dendritic tree and discussed the possibility that this input derives from the presumed **OFF bipolar cell type DB1** (Jusuf et al. 2007). Taken together, our results from whole mounts and vertical sections suggest that *en passant* synapses may be formed by **3–4% of the DB6 axons**. This low percentage can be explained with the sparseness of the dendritic tree and the relative low density and small diameter of bipolar axons. Likewise, in rabbit retina, axonal *en passant* synapses with M1 cells were found for about 6% of the calbindin-labeled bipolar cells (Hoshi et al. 2009).

The synapses formed by ON bipolar axons onto den-

drites of M1 cells in the OFF sublamina in mouse and rabbit retinas have been attributed to **specific ON bipolar types**, but the **involvement of other bipolar types** has **not been ruled out** (Dumitrescu et al. 2009, Hoshi et al. 2009). Outer stratifying melanopsin cells in marmoset retina receive an average of two bipolar synapses per 100 lm dendritic length (Jusuf et al. 2007). The low percentage of DB6 axons making potential synapses with outer melanopsin cells found here cannot account for this density, suggesting that in primate, other bipolar cell types are involved in the contacts to outer stratifying melanopsin cells. In addition to **DB6 cells**, least four other ON cone bipolar types and one rod bipolar type are found in primate retina (Boycott and Wässle 1991, Chan et al. 2001). Rod bipolar axons do not make ectopic synapses in mouse retina (Dumitrescu et al. 2009), but **further studies are required** to establish **which other cone bipolar types** may contribute to the bipolar input to outer melanopsin cells and whether this input is responsible for the ON responses found in these cells in primate retina.”

*From Fox and Guido 2011*: “As described above, M1 ipRGCs arborize in the OFF division of the IPL and therefore receive input from OFF-bipolar cells (Figure 30). However, physiological recordings have revealed that these **OFF-bipolar inputs are only weak** (Wong et al. 2007a). Unexpectedly, these same studies demonstrated that M1 ipRGCs receive strong input from ON-bipolar cells, a surprising finding given the dendritic morphology of M1 ipRGCs (Wong et al. 2007a). One possible explanation for this phenomenon is that ON-bipolar cells synapse onto M1 ipRGC somas and dendritic shafts within the ON division of the IPL (Belenky et al. 2003; Figure 30); however, receptive field mapping suggested that ON-bipolar inputs are present throughout entire M1 ipRGC dendritic arbors and not just near their somas (Wong et al. 2007a). More revealing was the **peculiar and remarkable discovery** that a class of ON-bipolar cell synapses onto M1 ipRGC dendrites within the OFF division of the IPL - a finding that **challenges** the prevailing thought that spatial segregation of inputs into ON or OFF divisions of the IPL is critical for the transmission of light stimuli (Hoshi et al. 2009, Dumitrescu et al. 2009, Grünert et al. 2010; see also Contini et al. 2010; Figure 30). The **functional significance** of these unconventional ON-bipolar cell synapses **remains unclear**. Lastly, in addition to receiving information from cone photoreceptors via ON- and OFF-bipolar cells, M1 ipRGCs also receive input from a third type of bipolar cell, **rod bipolar cells**, which are activated by rod photoreceptors (*PT*: in rats, not in primates; ). Synapses from rod bipolar cells have been observed on the soma and proximal dendrites of M1 ipRGCs (Ostergaard et al. 2007; but see Grünert et al. 2010); however, they may also influence ipRGC activity through more conventional pathways that include amacrine cells (Masland 2001b; Figure 30).”

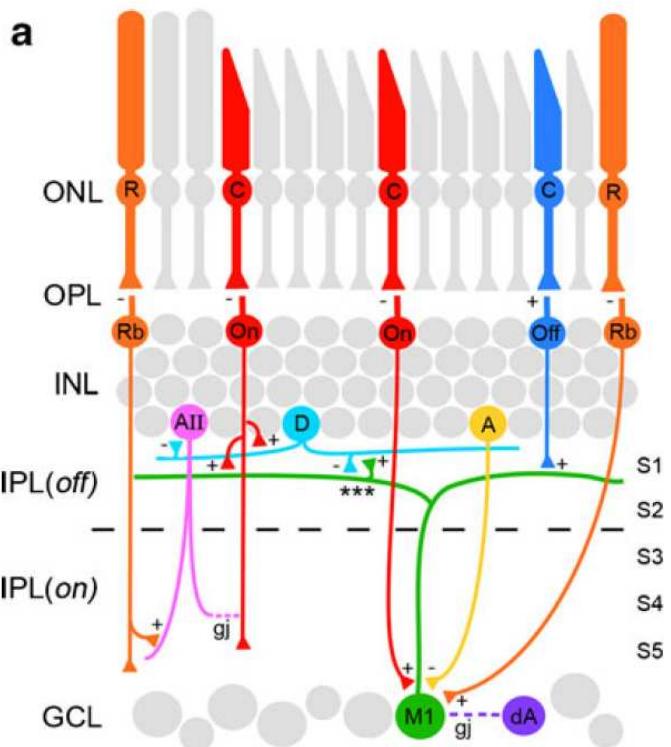


Figure 30: Development of intraretinal circuitry of M1 ipRGCs. A schematic diagram summarizes the synaptic inputs onto M1 ipRGC (M1) dendrites by OFF-bipolar cells (Off), ON-bipolar cells (On), rod bipolar cells (Rb), dopaminergic amacrine cells (D), and inhibitory amacrine cells (A). Rod bipolar cells also exert influence on M1 ipRGC activity indirectly through AII amacrine cell–On bipolar cell circuitry. Gap junction (gj) coupling of M1 ipRGCs and displaced amacrine cells (dA) within the ganglion cell layer (GCL) is depicted with a purple dashed line. Triple asterisks highlight reciprocal connections between dopaminergic amacrine cell and M1 ipRGCs dendrites, which allow M1 ipRGCs to exert influence over neurons in the INL. ‘+’ and ‘-’ denote whether excitatory or inhibitory receptors are present at synaptic sites. (Fox and Guido 2011)

*From Lucas et al. 2012:* “The behavioral data thus reveal that **rods** are a potent influence on the clock not only under very dim conditions, but also at light levels experienced well into the **dawn/dusk transition**. Interestingly, however, this influence is much **less apparent** in **electrophysiological recordings** of light responses in the rodent SCN. Light pulses can evoke large changes in firing (mostly excitatory) in SCN neurones, however this requires relatively high irradiance. Responses are much less pronounced at the **dimmer light** intensities that produce **large behavioral responses** (Meijer et al. 1998; 1992, Brown et al. 2011).

Although rods appear to define circadian responses even at moderate light intensities, at some point they are **expected to saturate** (Wyszecki and Stiles 1982). Under such conditions, the SCN would no longer be able to rely upon them to measure further increases in light intensity. **Cones**, by contrast, can support conventional vision even under the brightest daylight. Could they then compensate for rod saturation in the RHT? In fact, the **role of cones has been (and indeed remains) the hardest to define**.

Nonetheless, anatomical and electrophysiological studies indicate that **cone signals reach the M1 class** of ipRGCs responsible for entrainment (Belenky et al. 2003, Perez-Leon et al. 2006, Ostergaard et al. 2007, Viney et al. 2007, Schmidt et al. 2008, Dumitrescu et al. 2009, Hoshi et al. 2009). Moreover, aspects of the electrophysiological light response of the SCN itself can be attributed to cones on the basis of their spectral sensitivity (Aggelopoulos and Meissl 2000, Brown et al. 2011), indicating that cones are indeed functional components of the light input pathway. What could explain the **apparent contradiction** between the ability of cones to influence behavioral versus electrophysiological endpoints? A closer look at the electrophysiological light responses suggests a **possible answer**. When presented with a simple light pulse, both ipRGCs (Berson et al. 2002, Dacey et al. 2005, Tu et al. 2005, Wong et al. 2007a, Schmidt et al. 2008) and most light responsive SCN neurons (Meijer et al. 1998, Brown et al. 2011) show a transient large increase in firing that relaxes over a few seconds to a lower level of excitation that is sustained over at least tens of seconds of light exposure. These data indicate that cone-dependent excitation is largely restricted to the **first few seconds** of light exposure. If cones activate the RHT only briefly at light onset, that could explain why this photoreceptor class is ill-suited to supporting entrainment to continuous long duration (15 min) light pulses (Mrosovsky and Hattar 2005, Lall et al. 2010).

The **transience** of the cone-derived SCN response to an extended light pulse mirrors to some extent that of the cone itself. Thus, cones respond to such stimuli with an acute high amplitude hyperpolarization that relaxes over time. However, under extended light exposure, cone polarization reaches a “**steady state**” level that is itself dependent upon irradiance (at least at nonbleaching levels; Vale-

ton and van Norren 1983, Schnapf et al. 1990, Burkhardt 1994). In this way, cones can encode both the contrast and irradiance of a light step in transient and steady state phases of their response. The behavioral and electrophysiological evidence reviewed above showing that the clock relies on cones solely to track high frequency changes in irradiance argues that the latter, **steady state** component of the cone response is **actively excluded from the photoentrainment pathway**. Inclusion of further adaptation in the **neural network** bringing cone signals to the clock, as described for other retinal pathways (Dunn et al. 2007), could achieve this goal. ... electrophysiological data indicate that **cone-derived SCN responses** are much reduced during the day and under light adapted conditions (Brown et al. 2011)."

*From Hughes et al. 2012*: "As indicated by the differing location of their dendrites in either the **ON or OFF layers** of the IPL, it is now clear that the pRGC subtypes receive different inputs from the outer retina. **M2-type pRGCs** receive inputs from ON bipolar cells, as might be expected. Interestingly, **M1-type pRGCs** receive *not only OFF inputs* but also **anomalous ON inputs** from synaptic connections with cone ON bipolar cells as their dendrites pass through the ON layer *en route* to the OFF layer of the IPL and also within the OFF layer of the IPL itself (Wong et al. 2007a, Dumitrescu et al. 2009, Hoshi et al. 2009). Indeed, it would appear that despite the pattern of stratification, the **ON pathway** exerts **larger effects** on M1 cells than the **OFF pathway** (Wong et al. 2007a, Schmidt and Kofuji 2010). In addition to contacts with bipolar cells, pRGCs are also known to receive **inhibitory inputs from amacrine cells**, yet again there are cell type-specific differences. **M1 cells** synapse with *dopaminergic amacrine cells* in the OFF layer of the IPL (Ostergaard et al. 2007, Viney et al. 2007, Vugler et al. 2007), whereas **M2-type** cells appear to synapse with a *monostratified amacrine cell type* (Viney et al. 2007).

Photoresponses of **M1 cells** are driven **primarily by melanopsin** function with little influence from synaptic inputs (Schmidt and Kofuji 2009; 2010). By **contrast**, inputs from cone ON bipolar cells represent the **major driving force** behind the generation of photoresponses in **M2-type pRGCs**, with similar photoresponses observed from these cells in the absence of melanopsin expression (Schmidt and Kofuji 2010). Similar observations have been reported for M3-type pRGCs (Schmidt and Kofuji 2011) and are likely also true for M4- and M5-type pRGCs which have even lower levels of melanopsin expression and elicit even smaller photoresponses than M2-type cells. Given the lower levels of innate photosensitivity compared to M1-type cells, it would appear that the functioning of M2-type cells, M3-type cells, and presumably M4- and M5-type cells are **more closely linked to that of the classical photoreceptors compared to M1-type cells**. ... and little is known regarding the specific regions of the brain innervated by M2-, M3-, M4-, or M5-type

pRGCs or the specific functions associated with these cell types.

pRGCs are known to receive **excitatory** synaptic inputs from *bipolar* cells and **inhibitory** inputs from *amacrine* cells (Wong et al. 2007a, Schmidt and Kofuji 2009; 2010; 2011). These inputs influence the membrane potential of pRGCs by the generation of cation- and chloride-based conductances, respectively (Wong et al. 2007a). In **darkness, inhibitory inputs dominate** over excitatory inputs and contribute to setting the resting membrane potential of pRGCs below the threshold for action potential firing (Wong et al. 2007a). However, the nature and influence of these inputs *varies between pRGC subtypes* (Schmidt and Kofuji 2009; 2010; 2011) and would seem to explain in part the differences in resting membrane potential and excitability observed between these cells. However, pRGC subtypes continue to **show differences in resting membrane potential** under conditions where *all synaptic inputs are blocked* (Schmidt and Kofuji 2009; 2010; 2011). Under these conditions, **M1-type cells remain significantly more depolarized** than M2-type cells (and M3- and M4-type cells) and therefore **sit closer to the threshold for action potential firing**. These differences are seemingly the result of intrinsic differences in levels of baseline ion channel activity in these cells. However, the mechanisms which contribute to the intrinsic resting membrane potential of the pRGC subtypes *remain largely unexplored*."

*From Wong 2012*: "Melanopsin is **not required** for *sustained ipRGC responses* to bright light. As shown in Figure 31B, bottom, ganglion-cell photoreceptors could respond continuously for 10 h to the  $7.6 \text{ log quanta } \text{cm}^{-2} \text{s}^{-1}$  constant light. Because this intensity is  $\sim 3$  log units below the melanopsin threshold measured during synaptic blockade (Figure 31D), this result suggested that **synaptic input may be sufficient** to induce sustained ipRGC responses to very dim light.

... However, whereas the light sources used in these studies (Hannibal et al. 2001, Mrosovsky and Hattar 2003, Gooley et al. 2010) were constant, the individual photoreceptors of the animals and human subjects likely experienced **frequent fluctuations** in light intensity. This is because the animals were allowed to move freely in a visually heterogeneous environment and, even though the human subjects were stimulated within *Ganzfeld domes*, they were allowed to **blink their eyes** or even take periodic 10 min breaks from the experiment.

Another important conclusion from this investigation is that **melanopsin is probably not necessary** for generating **sustained ipRGC photoresponses**. Three previous studies showed that 10–15 s light steps below the melanopsin threshold could continuously excite ipRGCs (Dacey et al. 2005, Wong et al. 2007a, Schmidt and Kofuji 2010). ... **rod input** to these ganglion cells is probably sufficient to induce at least 10 h of spiking responses to dim light... An implication of these results is that the neu-

rons driving the ipRGCs' extrinsic photoresponses (i.e., the *outer* retinal photoreceptors and *ON bipolar cells*) are **capable of signaling constant light continuously** for at least 20 min and **potentially even 10 h**, just like the melanopsin phototransduction cascade. This is **somewhat surprising** because both the type-6 metabotropic glutamate receptors on ON bipolar cells and the ionotropic glutamate receptors on ganglion cells exhibit pronounced **desensitization** (Nawy 2004). Desensitization of AMPA/kainate receptors is particularly significant and their responses to glutamate desensitize nearly completely in 1 s (DeVries and Schwartz 1999, Lukasiewicz 2005). The present data suggest that during sustained illumination, even though the glutamate receptors presynaptic to the ipRGCs are probably in a desensitized state, **desensitization of these receptors does not completely inactivate them**, thus allowing very prolonged signaling of light information. By *contrast*, conventional ganglion cells' spiking responses to full-field light last for only up to several seconds (Fig. 1C; Wong et al. 2007a). Presumably, the **rod/cone** photoreceptors' prolonged light responses are **truncated** by the conventional ganglion cells' presynaptic circuits and/or intrinsic properties.

Another line of evidence for **prolonged photic integration** is that at the near-threshold intensity of 10.6 log quanta  $\text{cm}^{-2} \text{s}^{-1}$ , the intrinsic photoresponses of ipRGCs *continued to rise* for 1 h before reaching the peak amplitude (Figure 31D, bottom). The melanopsin response developed significantly faster when stimulus intensity was  $\sim 2$  log units higher, although peak latency was still  $\sim 25$  min (Figure 31D, top). Using responses to single photons, Do et al. 2009 estimated the melanopsin integration time to be only 40 s, far too brief to account for the peak latencies shown in Figure 31D. This short integration time could be partly caused by the fact that Do and colleagues identified ganglion-cell photoreceptors using epifluorescence excitation of fluorescent protein labeling, which severely light-adapted these cells and accelerated their melanopsin response kinetics (Wong et al. 2005).

These reports of prolonged responses (Dacey et al. 2005, Gamlin et al. 2007, Wong et al. 2007a) have led some researchers to assume that the **poststimulus** ipRGC response is **solely due to melanopsin**. However, in response to bright light, I observed pronounced poststimulus spiking even in mouse ipRGCs lacking melanopsin, indicating that, at least under certain conditions, **synaptic input** can contribute to these ganglion cells' postillumination responses. In agreement with this observation, mouse **ON bipolar cells** presumed to contact ipRGCs respond to bright light with a **depolarization that long outlasts the stimulus** (Dumitrescu et al. 2009).

### 2.3.7. S-cone contribution?

From Rea et al. 2005: "Among the three classes of cone photoreceptors, S cones and their neural connections are the most unusual. S cones are usually larger than L and M cones. There are substantially fewer S cones in

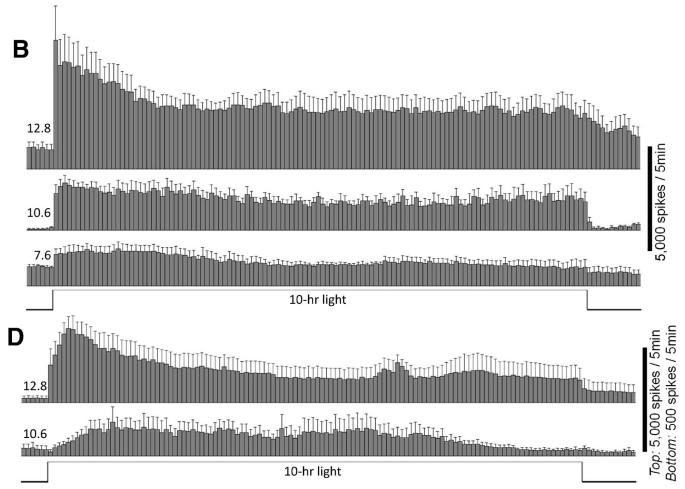


Figure 31: The ipRGCs can spike continuously in response to 10 h step increases in light intensity. B, Averaged spike histograms of all the ipRGCs recorded in normal Ames' medium, with a bin size of 5 min. The number of cells that contributed to these histograms was six for 12.8 log quanta  $\text{cm}^{-2} \text{s}^{-1}$ , three for 10.6 log quanta  $\text{cm}^{-2} \text{s}^{-1}$ , and three for 7.6 log quanta  $\text{cm}^{-2} \text{s}^{-1}$ . D, Averaged spike histograms of all the ipRGCs tested in the presence of *synaptic blockers* to isolate melanopsin photoresponses, with a bin size of 5 min. The number of cells used in these histograms was four for 12.8 log quanta  $\text{cm}^{-2} \text{s}^{-1}$  and four for 10.6 log quanta  $\text{cm}^{-2} \text{s}^{-1}$ . Notice that the response amplitude scale bars are different for the two intensities. (Figure 3 of Wong 2012)

the human retina than L and M cones [5 to 10% of all cones (Dacey 2000)], and they are much more diffusely distributed throughout the retina. In fact, S cones are not found in the central human fovea. .. Dacey and Packer 2003 demonstrated that bistratified RGCs form blue-yellow (b-y) spectrally opponent connections with ON input from S cones and OFF input from the combination of L and M cones. These bistratified RGCs have large dendritic connections in both the ON and OFF sublayers of the IPL (Dacey 2000, Dacey et al. 2003). Furthermore, whereas both L and M cones serve as ON and OFF centers in the midget system, recordings of a y-ON and b-OFF bipolar cell in the S cone pathway are rare (Klug et al. 2003, Dacey et al. 2005). Finally, in contrast to the spatially opponent receptive fields of the midget system, the receptive fields of S cone pathway are relatively large and are not spatially antagonistic (Gouras 2003). Thus, unlike the L and M midget RGCs, the ON and OFF receptive field regions of the b-y bistratified RGCs are spectrally opponent but spatially identical, leading to poor contrast sensitivity (Dacey and Packer 2003)."

From Dacey et al. 2005: "The giant ganglion cells showed cone-driven input and an unexpected response to chromatic stimuli. At mid-photopic levels, a 550-nm light pulse evoked a sustained On response (Figure 32a). Latencies to first spike were  $\sim 30\text{--}40$  ms, typical of cone-mediated ganglion cell signals in primates (Figure 32a inset). Surprisingly, a **sustained On** response was observed for

both morphological cell populations (Figure 32a), showing that the **inner-versus-outer** stratification, normally reflecting a division into On-centre versus Off-centre receptive field categories, **does not apply here**. Furthermore, these cells showed an unusual ‘**colour-opponent**’ receptive field in which an **S cone-mediated Off response** is antagonistic to an (L+M) cone-mediated On response (Figure 32b). Cone-mediated receptive fields were large, approximating the dendritic tree diameter, and they showed spatially overlapping S-Off and (L+M)-On components, with little evidence of the strong inhibitory- surround typical of primate ganglion cells that project to the LGN (Figure 32b, middle inset). When the *in vitro* retina was maintained in total darkness for 10–20 min, **light stimuli in the scotopic range** elicited strong rod-driven responses (Figure 32c). The response was a sustained On-type with the **long latency to spike (~150 ms)** (Figure 32c, inset) and spectral tuning (peak at **502 nm**, data not shown) characteristic of rod-driven input. The rod signal showed high photosensitivity, responding to quantal illuminances as low as  $6\text{--}7 \log \text{quanta cm}^{-2} \text{s}^{-1}$  (or 4–5 log units below the threshold for a cone-mediated response), which is at or near the absolute threshold for human vision (–).

Intrinsic photosensitivity was unmasked in the giant ganglion cells by **pharmacologically blocking rod and cone transmission** to the inner retina. Bath application of **L-AP4** (DL-2-amino-4-phosphono-butyric acid) and **CNQX** (6-cyano-7-nitroquinoxaline-2,3-dione), which block both ionotropic and metabotropic retinal glutamate receptors, completely eliminated the short latency, cone-driven light response at photopic levels. However, long-duration light pulses still elicited a depolarizing voltage response that **grew slowly and declined even more slowly** after stimulus offset (Figure 32d).

Our findings reveal a **fundamental contribution of rod/cone signals** to this circuit in the diurnal primate and at the same time provide the first evidence of a broader role for this pathway in higher visual processing. By combining the rod, cone and inherent photoresponses, the giant ganglion cell pathway can by itself convey signals from all receptor classes known to drive the circadian and pupillomotor systems (Hattar et al. 2003, Lucas et al. 2003). Through **chromatic opponency**, the cone circuitry may have originally evolved to signal the **large spectral changes at dawn and dusk** to the circadian pathway in order to more precisely set the biological clock to the solar day (Mollon and Jordan 1989; PT: dawn/dusk detection in **coral opsins**, see Sweeney et al. 2011). Along the primary visual pathway, neurons with **S-Off and S-On opponent receptive fields** have been previously identified in the LGN (Valberg et al. 1986) and primary visual cortex (Cottaris and De Valois 1998), and are basic components of psychophysical models of human colour vision (Krauskopf et al. 1982). S-On signals originate from at least two novel ganglion cell populations (Dacey and Lee 1994, Dacey et al. 2003), but the ori-

gin of an S-Off signal has remained uncertain (Klug et al. 2003). The giant cells demonstrate that S-Off, like S-On opponency, can also derive from a distinct ganglion cell population. Reciprocally, the sustained, irradiance-encoding signal mediated by the intrinsic light response would presumably also reach primary visual cortex via the LGN. Over 30 years ago, Horace Barlow first called attention to a few exceptional ‘**luminance coding**’ units in the cat’s retina, in which spike rate increased monotonically with increasing irradiance (Barlow and Levick 1969). Similar irradiance-coding units have been recorded in macaque LGN (Marrocco 1975) and primary visual cortex (Kayama et al. 1979), with a **maintained discharge rate** set by the overall level of diffuse illumination. The origin and spectral signature of this higher signal has yet to be determined, but it might arise from the giant cells described here and play a role in the **conscious perception of brightness** (Barlow and Verrillo 1976, Kinoshita and Komatsu 2001).“

*From Johnston et al. 2012:* “... If a green-ON/blue-OFF ganglion cell were built using the same simple strategy, green-ON and blue-OFF bipolar cells would be required. The problem that has been **sitting uncomfortably with vision scientists** is that a bipolar cell responding to decrements in blue light, the **putative blue-OFF**, has not been identified so far. The likely reason is revealed in two recent papers by Chen and Li 2012, Sher and DeVries 2012: the function of the elusive blue-OFF bipolar cell is actually carried out by inverting signals from blue-ON bipolar cells through an inhibitory interneuron, the amacrine cell . . . The resulting circuit explaining the green-ON/blue-OFF response is shown in Figure 33B,C. A **blue-OFF bipolar cell is not needed!**”

Although blue-OFF bipolar cells have not been identified physiologically, absence of evidence does not provide evidence for absence. If they do exist, it may be that they play a role in retinal processes other than classical color opponency. For instance, the retina contains a small percentage of ganglion cells that have an intrinsic sensitivity to light and very large receptive fields. The intrinsically photosensitive ganglion cells also demonstrate blue-OFF responses generated through cones (Dacey et al. 2005). Do these signals travel through **blue-sensitive amacrine cells** or through the elusive **blue-OFF bipolar cell**? And if there are blue-sensitive amacrine cells, might there also be red- or green-sensitive amacrine cells involved in red/green colour opponency? The retina continues to surprise us.”

*From Masland 2012a:* “..For the **blue-Off ganglion cell**, the wiring diagram is more inferential (Figure 33). Because the blue amacrine cell appears to make its main output connections in the deep parts of the retina’s inner synaptic layer, a region dominated by On responses, Chen and Li 2012 propose that the blue amacrine cell synapses on a ganglion cell that branches at that level. This is sup-

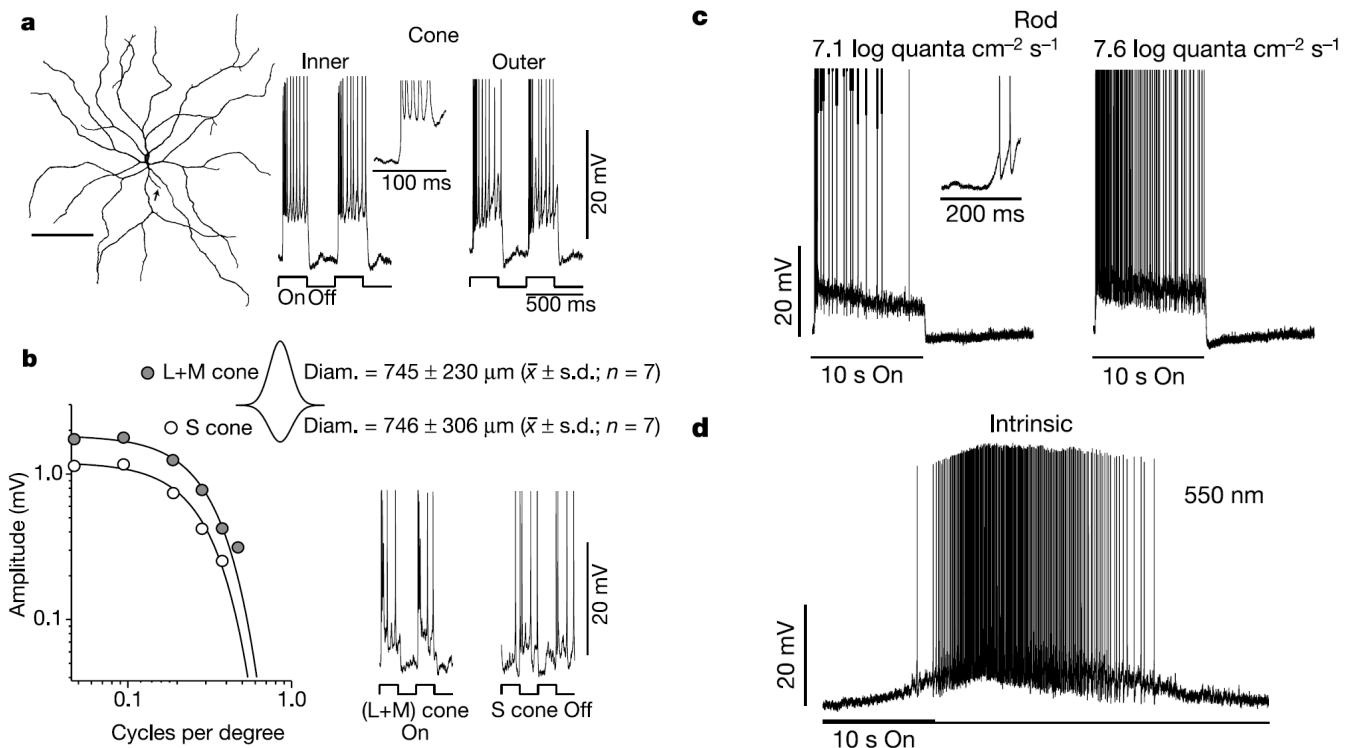
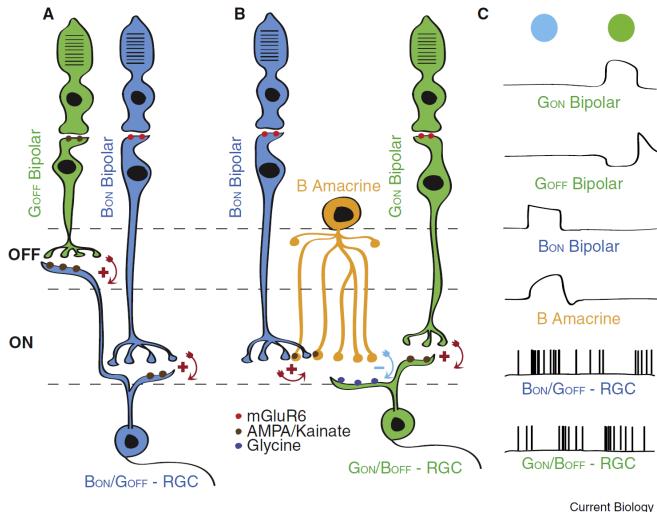


Figure 32: Giant cells show rod and colour-opponent inputs and are inherently photoreceptive. **a**, Tracing of a giant cell (arrow indicates axon; scale bar, 200  $\mu\text{m}$ ). The cell was recorded from and intracellularly filled with Neurobiotin in the *in vitro* retina. Voltage traces (right) show sustained On responses of an inner and an outer cell to a 2-Hz modulated 550-nm, full-field monochromatic light ( $13.5 \log \text{quanta cm}^{-2} \text{s}^{-1}$ ) under photopic conditions. Inset: first 100 ms of voltage response of inner cell; response latency is 38 ms. Stimulus time indicated below voltage traces. **b**, The cell had an (L+M)-On, S-Off opponent receptive field. Plot (left) shows spatial frequency response to drifting gratings used to measure the receptive field; stimuli modulated the L+M cones (dark grey circles) or S cones (white circles) in isolation. Data were fitted with a difference-ofgaussians receptive field model (solid lines). Two-dimensional gaussian profile (middle) summarizes fits for 7 cells. Traces (far right) show responses to (L+M) and S cone isolating stimuli, respectively. **c**, Pure rod-mediated responses elicited by a 550-nm monochromatic pulse at low scotopic levels. Inset: first 200 ms of voltage response at  $7.1 \log \text{quanta cm}^{-2} \text{s}^{-1}$ ; response latency is 147 ms. **d**, L-AP4 and CNQX application block excitatory glutamatergic transmission, revealing a slow, sustained, inherent photoresponse (550-nm light;  $13.5 \log \text{quanta cm}^{-2} \text{s}^{-1}$ ). (Dacey et al. 2005)



**Figure 33: Blue-green color opponency circuits in the retina.** (A) Graphical depiction of the blue-ON/green-OFF pathway. Green-OFF bipolar cells and blue-ON bipolar cells project in the OFF and ON strata of the retinal inner plexiform layer, respectively (dashed lines). The two cell types make excitatory synapses onto a blue-ON/ green-OFF ganglion cell. (B) Graphical depiction of the green-ON/blue-OFF pathway, as described by Sher and DeVries 2012, Chen and Li 2012. In this case a blue-ON bipolar cell provides the inhibitory contribution to the green-ON/blue-OFF ganglion cell through the sign-inverting synapse of the blue-sensitive bipolar cell (B Amacrine). (C) Graphical depiction of the voltage responses to blue and green light for the represented cells. (Johnston et al. 2012)

ported by earlier studies describing blue-Off ganglion cells, which found the dendrites of those ganglion cells to lie in that same On-dominated layer (Yin et al. 2009). Because those layers receive inputs only from On bipolar cells, the **blue-Off ganglion cell is positioned to receive a direct input from green-On bipolar cells**. The blue-Off ganglion cell would therefore balance an inhibitory input received from the blue amacrine cell against excitation received directly from a green-On bipolar cell. The burst of spikes observed at the cessation of a stimulus dominated by blue wavelengths would occur because of rebound excitation **following relief of the ganglion cell's inhibition** by the amacrine cell, a proposal supported by the temporal character of the blue amacrine cell's response to light.

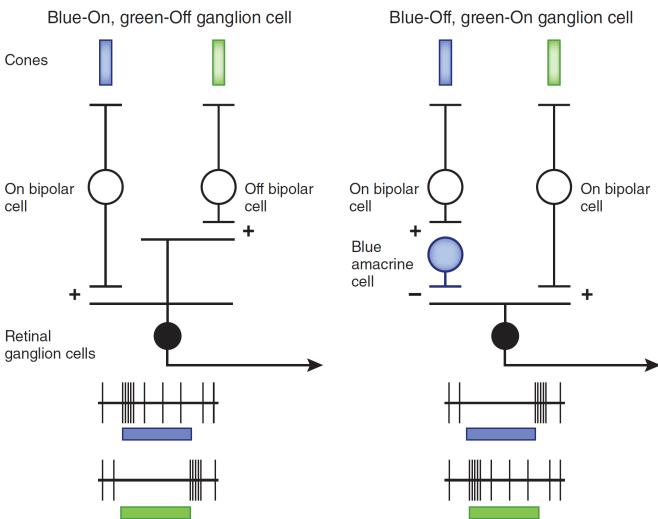
Finally, there is an *alternative*, but *less appealing*, mechanism that both groups note, which is that the **blue amacrine cell**, instead of inhibiting the ganglion cell directly, could **cut off an excitatory input** delivered directly to the ganglion cell by the blue-On bipolar cell. This could occur by **direct inhibition** delivered to the blue-On bipolar cell's axonal terminal. This hypothesis makes it slightly *harder to account for rebound excitation following a blue stimulus*, but it remains a possibility. Perhaps the most pressing current need is for a precise structural identification of the blue-Off ganglion cell; this would resolve the ambiguity by **allowing direct study of the synaptic connectivity between the ganglion cell, its**

afferent bipolar cells and the blue amacrine cell. Another point for future study will be to check the taxonomic generality of the finding. The blue versus green comparison is an **evolutionarily ancient one** (Nathans 1999), and thus far it seems to be very widely conserved across mammalian retinas, but direct confirmation of this assumption would be desirable.

More than a decade has passed since the **extreme diversity of retinal amacrine cells** was documented. These interneurons come in more than 30 structurally distinct cell types (MacNeil and Masland 1998, MacNeil et al. 1999). Their different shapes reflect differing connectivities, which is a strong reason to believe that the **diversity of shapes mirrors a similar diversity of computational tasks**. Direct evidence from recording, however, is still sparse (Pang et al. 2012). The present studies (Chen and Li 2012, Sher and DeVries 2012) are among a very few to examine an individual amacrine cell type systematically. These findings confirm the diversity of function: the **blue amacrine cell indeed has a remarkably specialized role in the retina's signaling**. Although a few amacrine cells, notably the **wide-field cells**, might be grouped as carrying out conceptually similar jobs, it seems increasingly likely that most of the 30 types mediate distinct functions, mirroring the great variety of their structures. In the retina, evolution has constructed a **machine of dazzling intricacy**"

*From Sher and DeVries 2012: . . .* "Recordings from the ganglion cell axons in the ground squirrel optic nerve show an **abundance of S-Off responses**. We used a 512-electrode array to record the spiking activity of hundreds of ganglion cells in the isolated ground squirrel (*Ictidomys tridecemlineatus*) retina. Approximately 90% of ground squirrel photoreceptors are cones, of which 7% are S cones. We classified ganglion cells according to their spike-triggered average (STA) response to a spatiotemporal white noise stimulus in which the red, green and blue monitor primaries were independently modulated. We then used the relative STA response to the monitor primaries to separate the cells receiving mostly M-cone input from those selectively sampling S cones. The former were broadly divided into On and Off center types. The latter consisted of just two distinct ganglion cell types: S-Off/M-On and S-On/M-Off."

"The tight grouping of S-Off/M-On cell STA time courses during simultaneous recordings and regular tiling of their receptive fields support the notion that these cells constitute a distinct type. S-On/M-Off cells also comprised a type by the same criteria. Although the polarities of S-On/M-Off and S-Off/M-On cell responses were opposite, other spatiotemporal properties were similar, including the time courses of their S-cone STA responses and cone-driven receptive field diameters, which were only ~20% larger in S-On/M-Off cells. In addition, the **component S-Off and M-On fields of S-Off/M-On cells were coextensive**, a property shared with pri-



**Figure 34: The retinal circuitry that creates blue-On and blue-Off ganglion cells.** In both cases, a group of bipolar cells selectively contact blue-sensitive cone photoreceptor cells and therefore become blue-sensitive bipolar cells. These are On cells, responding to brightening of the stimulus. In the first case (left), the blue-On bipolar cells synapse directly onto a class of ganglion cells, making them blue-On ganglion cells. In the second case (right), the blue-On bipolar cell is once again the start of the pathway, but the bipolar cell influences the ganglion cell only through an intermediate cell, the blue amacrine cell. Because the amacrine cell makes an inhibitory synapse on the ganglion cell, it inverts the sign on the bipolar cell's On response, creating a blue-Off ganglion cell. In both cases, the blue response is balanced against an opposite effect transmitted from green cones. The final output, a train of action potentials transmitted by the ganglion cell to the brain, is shown below; horizontal bars represent the duration and color of the stimulus. For simplicity, an alternative pathway from the blue amacrine to the ganglion cell via the axon terminal of the ON bipolar cell is not shown here. (Masland 2012a)

mate S-On/(L+M)-Off ganglion cell responses in intracellular recordings.”

We infer that the S-On bipolar cell also signals to a glycinergic amacrine cell, which is predicted to have an S-On response. The **S-On amacrine cell makes a sign-inverting synapse** either directly onto S-Off/M-On ganglion cells or presynaptically onto On bipolar cells that receive input from M and possibly S cones, and which excite S-Off/M-On ganglion cells. Extracellular recordings do not reveal the anatomy of the S-Off/M-On cell, and thus we cannot exclude that it is a type of intrinsically photosensitive retinal ganglion cell, which carries an **S-Off/(M+L)-On** signal under photopic conditions in the primate (Dacey et al. 2005). However, this is unlikely, as intrinsically photosensitive retinal ganglion cells are among the largest ganglion cells in the retina, whereas the receptive fields of ground squirrel S-Off/M-On cells were of average size. This primordial color vision circuit shares features with the sensitive rod pathway, which also contains a single On bipolar cell type. Like the rod pathway, the **S-cone pathway** may use the amplification provided by On bipolar cell transduction. In the case of S-cone circuits, **amplification may serve to compensate for the high M cone-to-S cone ratio in mammalian retinas**. Also, as with the glycinergic AII amacrine cell in the rod pathway, the glycinergic interneuron in the S-Off pathway mediates a form of crossover inhibition between an On bipolar cell and either an Off bipolar or ganglion cell.

*From Chen and Li 2012:* "The presumed role of SCAs (S-cone amacrine cells) in the **S-cone pathway mirrored that of AII amacrine cells in the rod pathway**, which form gap junctions with SCBs and may carry S-cone signals. ...., we wanted to further rule out the possibility that the SCAs in the S-cone pathway were AII cell... We conclude that SCAs are not AII cells, but are instead unique chromatic-selective amacrine cells."

Could SCAs supply a blue-Off signal to blue-Off/green-On ganglion cells? Anatomical descriptions of blue-Off ganglion cells suggest that they are monostratified cells with dendrites ramifying near the inner border of the IPL, matching the stratification of the lower tier of SCA dendrites. Thus, it is possible that SCA varicosities form synapses with dendrites of the blue-Off ganglion cell. Alternatively, SCAs may inhibit green-On bipolar cell terminals, which are presynaptic to the ganglion cell.

Another potential target of SCAs is the intrinsically photosensitive retinal ganglion cell (ipRGC) that, in the primate retina, had **blue-Off/yellow-On** cone responses in addition to intrinsic photosensitivity. Dendrites of ipRGCs ramify at the inner and outer borders of the IPL, co-stratifying with SCA dendrites. If SCAs provide blue-Off inputs to ipRGCs, they could function in the ancient blue-yellow color system that synchronizes the biological clock with the environment by signaling dawn-dusk spectral shifts. In conclusion, our findings **support the exist-**

tence of a color-coding amacrine cell that is well-positioned to provide blue-Off signals in the color pathway of the mammalian retina.

From Jayakumar et al. 2012: “In this context, our findings (J Jayakumar, S Roy, B Dreher, P Martin and T Vidyasagar, *J. Physiol. (Lond.)*, *in press*) are particularly relevant because a recent study on blindsight (Alexander and Cowey 2010) found that in the hemianopic field, S-cone-modulating stimuli were very effective and in one patient presentation of narrow band blue stimuli (427 nm) led to excellent performance but not red stimuli (peaking at 630 nm). Furthermore Alexander and Cowey 2010 found these stimuli were effective only if they came on suddenly rather than slowly. ... Recent psychophysical evidence also suggests that visual attention can be directed better by stimuli activating the blue-yellow opponent pathway than by the red-green opponent pathway (Li et al. 2007). ... that coloured overlays may be helpful in improving reading performance in children with *reading difficulties*. For the small but apparently significant benefits seen for such use of coloured overlays or tinted glasses, a neurophysiological model has been proposed that involves the pathways carrying S-cone signals (Vidyasagar 2005).”

### 2.3.8. Temporal properties of NIF-responses

i.e. the effect of light pulses

### 2.3.9. Mesopic modeling

From Zele et al. 2012: “In primates, small bistratified cells (SBCs) receive ON excitation from S-cones via S-cone (blue) ON-bipolar cells, inhibitory (OFF) input from L- and M-cones via diffuse bipolar cells (Lee et al. 2010), and have low-pass spatiotemporal characteristics to chromatic stimuli (Yeh et al. 1995). Horizontal cell feedback to the S-cone synapse creates chromatic opponency (Packer et al. 2010). Rod inputs to SBCs have the same ON-type polarity response as the S-cone under mesopic illuminations (Field et al. 2009, Crook et al. 2009) and mix with the inhibitory L + M signal (Field et al. 2009). In humans, the precise form of the interaction between rod and S-cone mediated signals is still to be determined. .. In S-cone monochromacy, the results are conflicting, with evidence for linear summation of rod and S-cone inputs to mesopic spectral sensitivity (Blackwell and Blackwell 1961, Pokorny et al. 1970) and complete independence of the rod and S-cone signals (Alpern et al. 1965). In summation studies of pulsed lights, it has been inferred for inhibition (Trezoza 1970), near-complete additivity (Naarendorp et al. 1996), and partial additivity between rod and S-cone signals. ...

The nature of the summation of rod and L- (or M-) cone mediated signals depends on the postreceptoral pathways mediating detection (Kremers and Meierkord 1999). Linear summation can occur when rod and L- (or M-) cone mediated signals are mediated via the same pathway. Probability summation occurs when rod and L- (or M-)

cone signals are mediated via independent pathways (33). The summation characteristics of rods and S-cones have not been systematically studied under conditions that allow controlled examination of the phase relationship between the two photoreceptor types when they have known signal strength.

Probability summation was detected when thresholds were similar for selective rod and S-cone stimulation. These individual differences may depend on factors including the stimulus temporal frequency (Sun et al. 2001) and the relative level of rod and S-cone excitation at the adaptation level. Linear summation of S-cone signals occurs in retinal circuits when the strength of the physiological connections is linearly proportional to the number of anatomically defined synapses (Chichilnisky and Baylor 1999). The generality of that observation (Chichilnisky and Baylor 1999) may not hold under other conditions, including when rods are active, with plastic changes in the physiological strength of cortical circuits (Sterling 1999) and in the presence of interactions. There is evidence from common marmosets that rod-to-cone signal strengths also vary as a function of eccentricity in different ganglion cells types (MC, PC) (Weiss et al. 1998), but this has not been replicated in macaques at the test eccentricities studied (Lee et al. 1997).

The nonlinear reinforcement is an indication for supraddititvity given that thresholds are smaller for simultaneous rod and S-cone modulation than is predicted on the basis of complete additivity. We would not consider this interaction as same-sign additivity because it acts in a similar manner when the two photoreceptor classes are modulated in phase and in counterphase. Therefore, it is indicative of a mechanism that is independent from the opposite-sign additivity found in the phase paradigm. The physiological basis of this nonlinear reinforcement is unclear. The reinforcement is also present in the observer showing probability summation in the phase paradigm and thus rod and S-cone signal transmission in separate postreceptoral pathways gives no possibility for further interactions. This suggests that the nonlinear interaction should occur before the rod and S-cone signals input to the inferred KC and MC pathways, possibly at a photoreceptor level, and may involve gap junctions between rods and cones rather than cone specific horizontal cell syncytium (Dacey et al. 1996). That the nonlinearity is present in the data of all three observers is consistent with this hypothesis.”

## 3. Results

Placeholder

## 4. Discussion

Placeholder

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