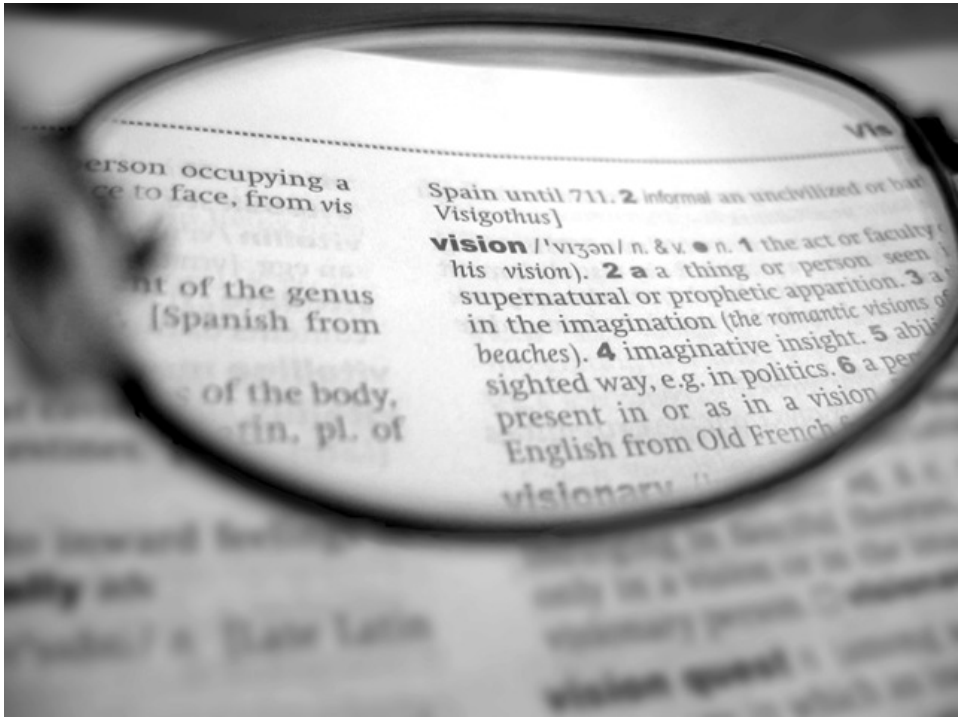
Biological Rhythms:

How Our Eyes Keep Us On Time

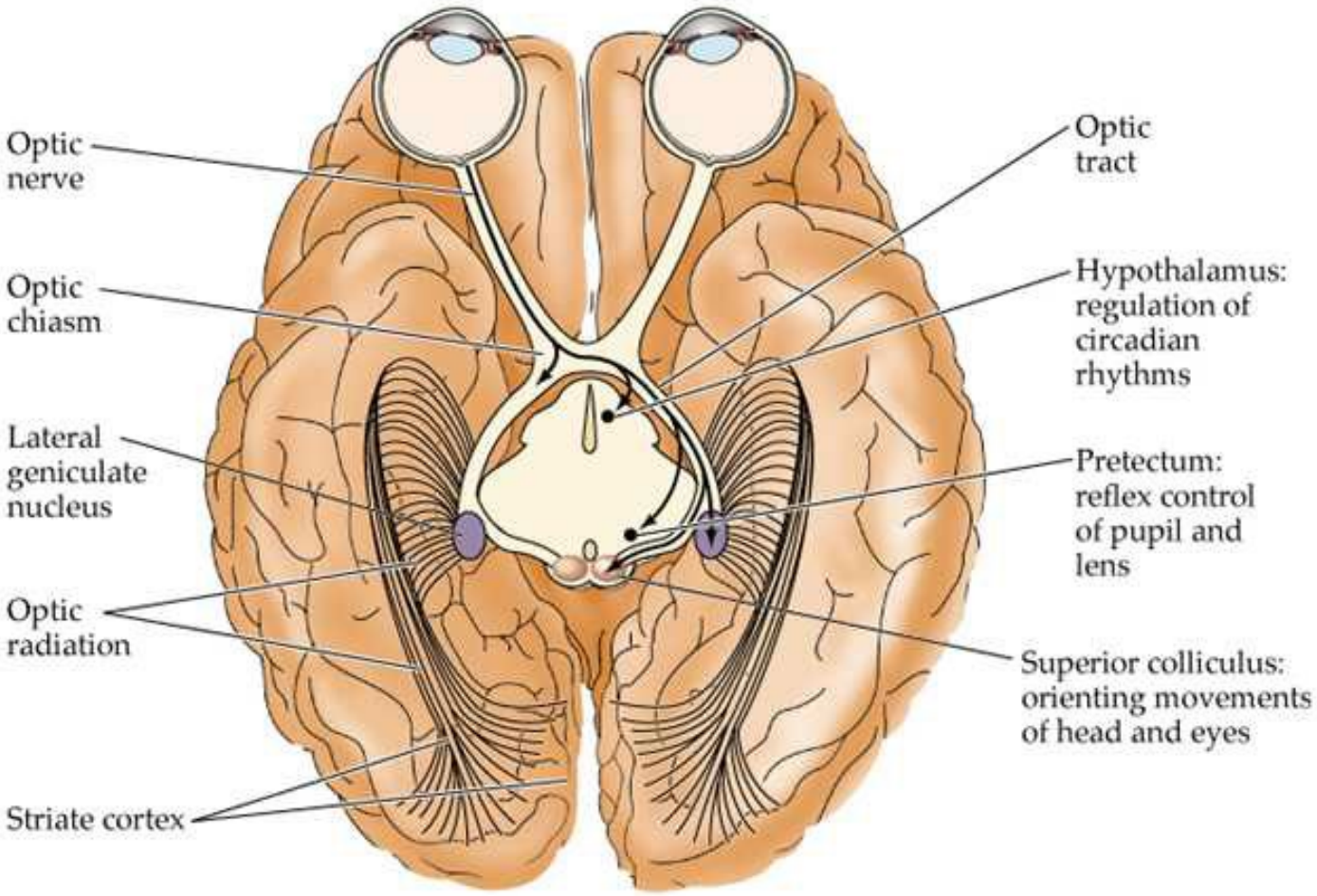
Andrew Hartwick
Hartwick.4@osu.edu

The Ohio State University
College of Optometry

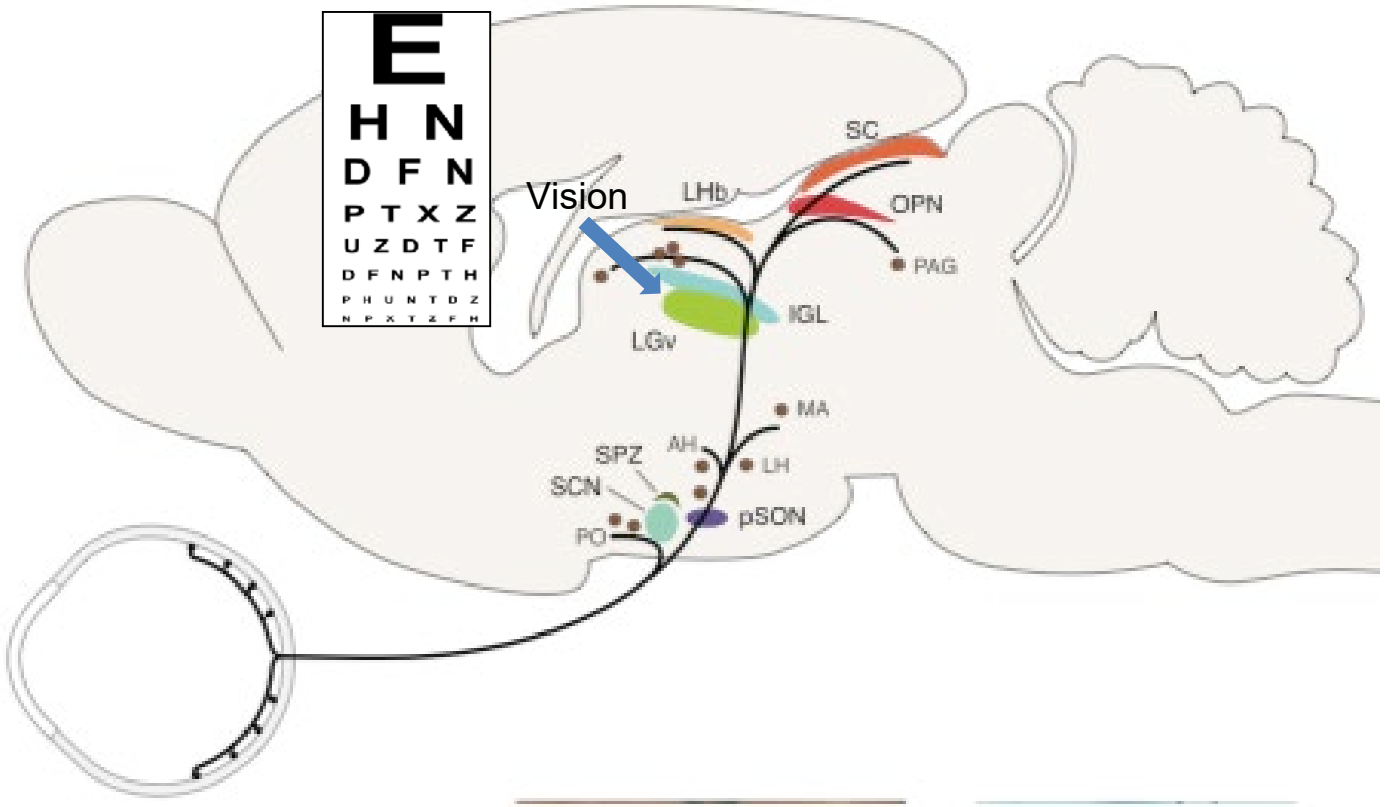
- Regarding the consequences of eye diseases, both clinicians & patients are focused on changes in vision caused by this disease
  - “Doctor, am I going blind?”



- There are other brain targets for RGCs besides the LGN



- ….but by the anatomical projections of RGCs, it's evident that the optic nerve does more than relay visual signals



- Examples of non-LGN targets of RGC axons:
  - Pulvinar
    - Involved in visual attention; hand reaching tasks?
  - Superior Colliculus
    - Saccade generation; reflex head and neck movements to stimuli
  - Lateral Habenula
    - Emotion, pain processing, learning (affected in depression?)
  - Ventrolateral Pre-Optic Nucleus
    - Function:
  - Suprachiasmatic Nucleus
    - Function:
  - Pretectum (Olivary Pretectal Nucleus)
    - Function:

Brain Targets of RGC Axons

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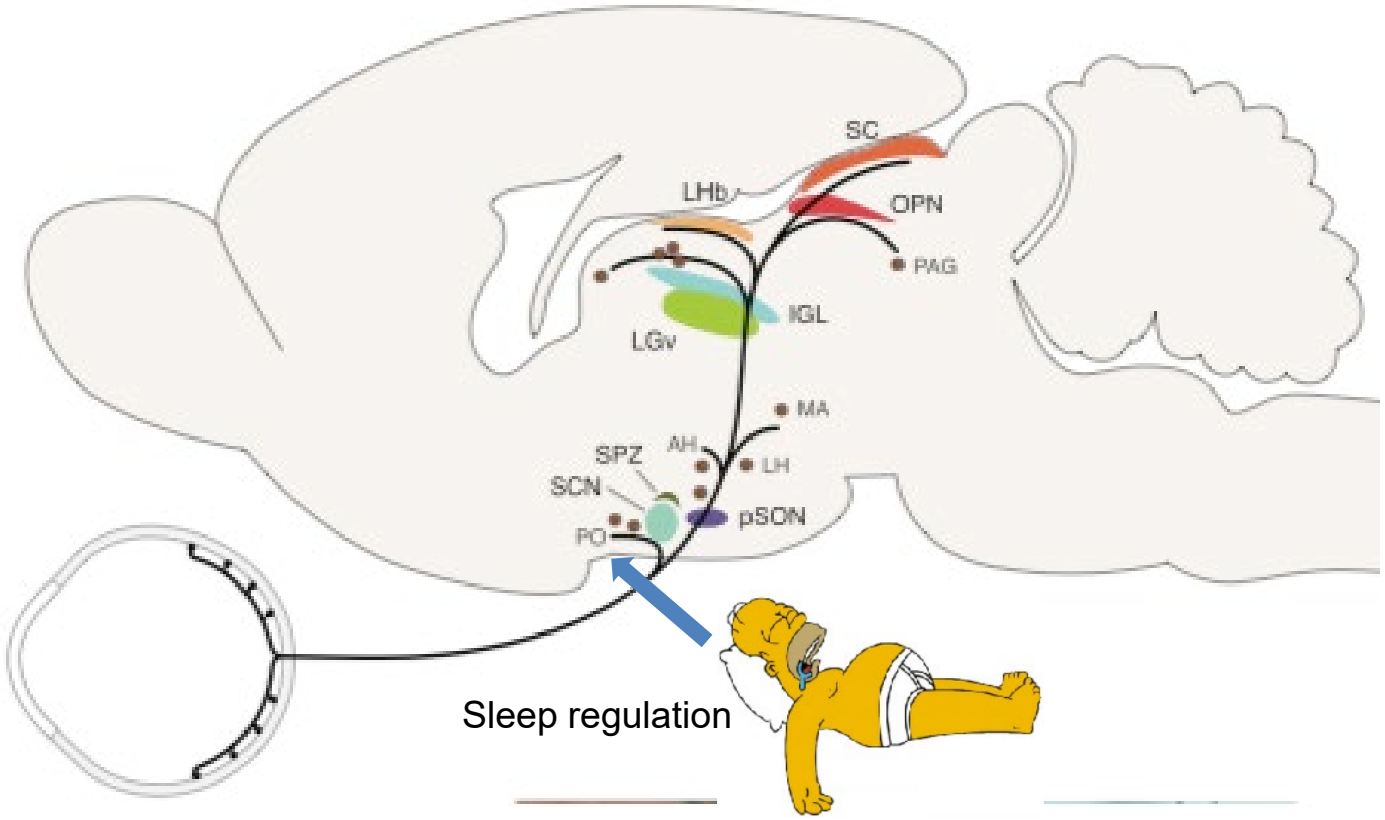

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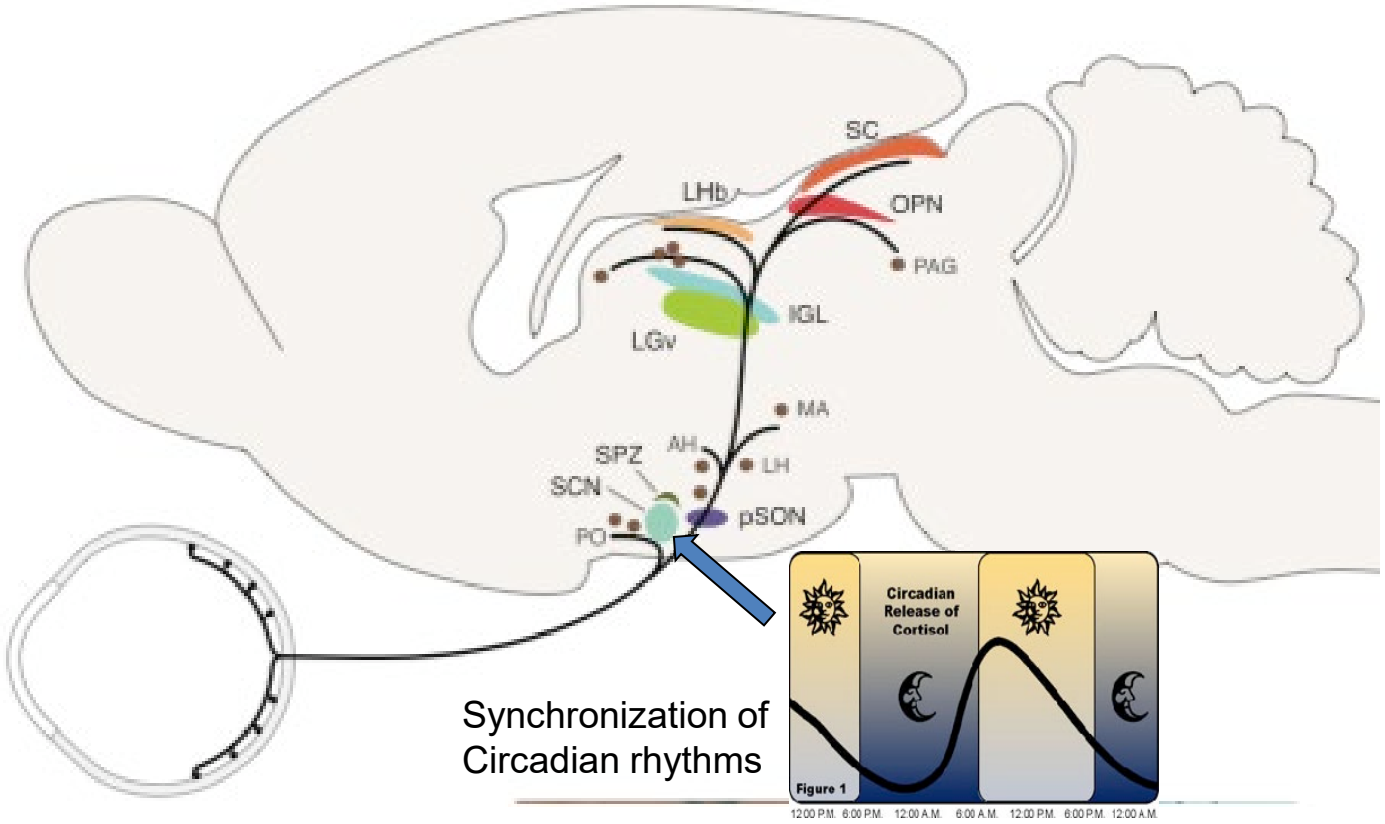

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    - Synchronization of circadian rhythms
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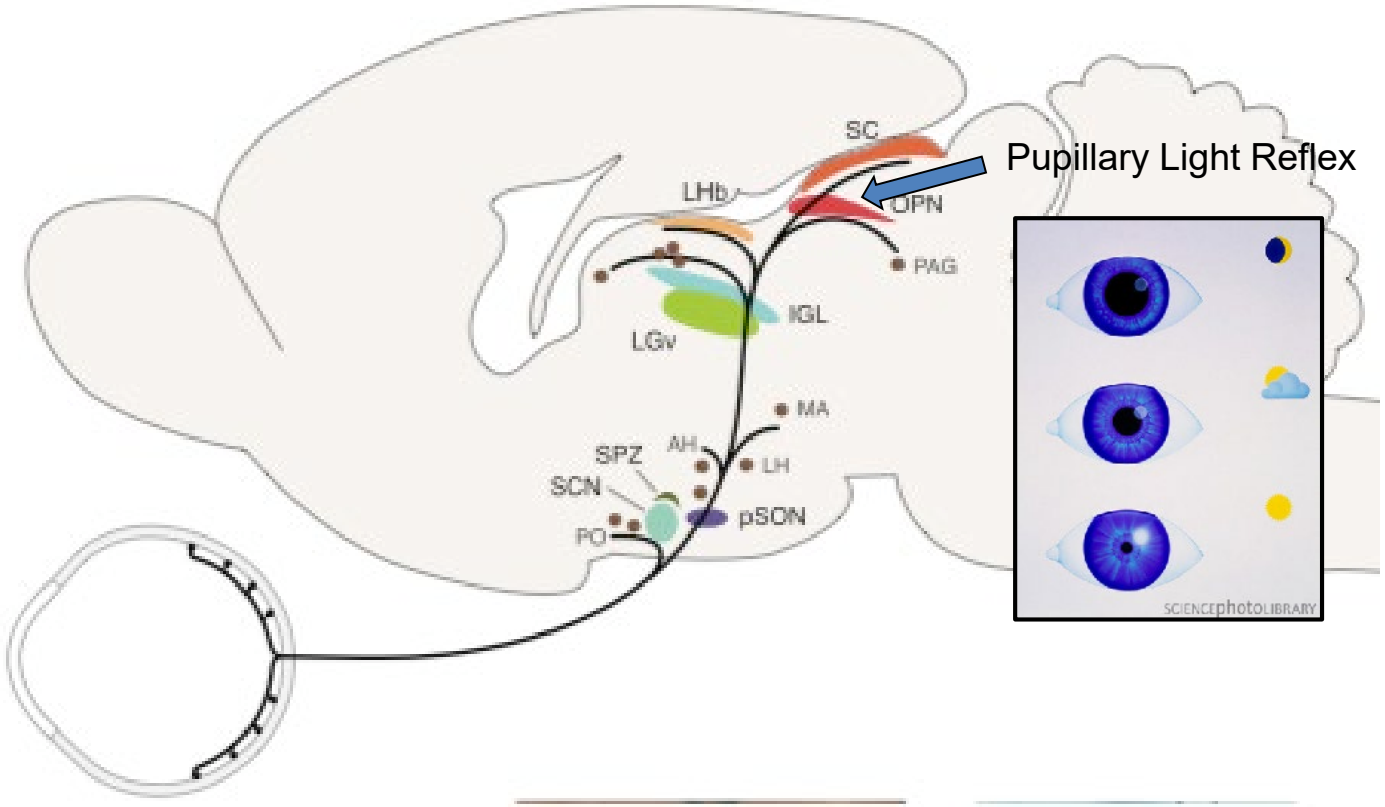

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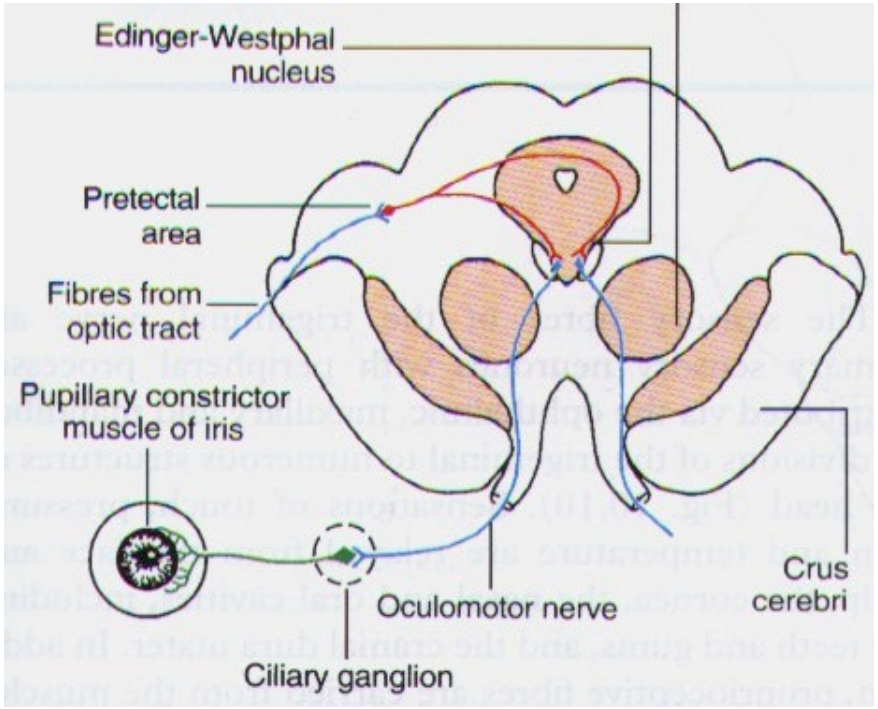
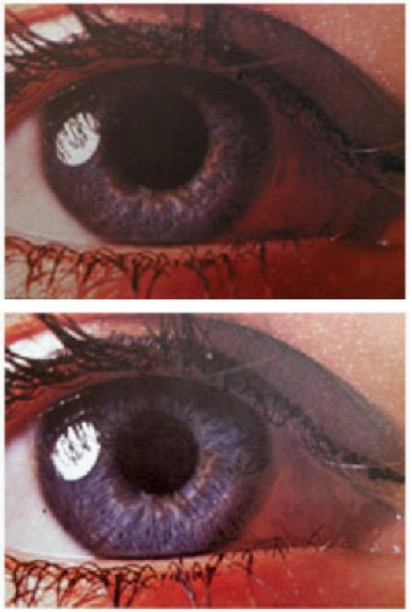
  - Pretectum (Olivary Pretectal Nucleus)
    - Pupillary light reflex

- Neurons from pretectum project bilaterally to Edinger-Westphal nuclei; neurons from E-W nuclei synapse in ciliary ganglion (parasym center)

- Ciliary ganglion neurons synapse on iris constrictor muscle

- Light to one eye stimulates pupil constriction in both eyes

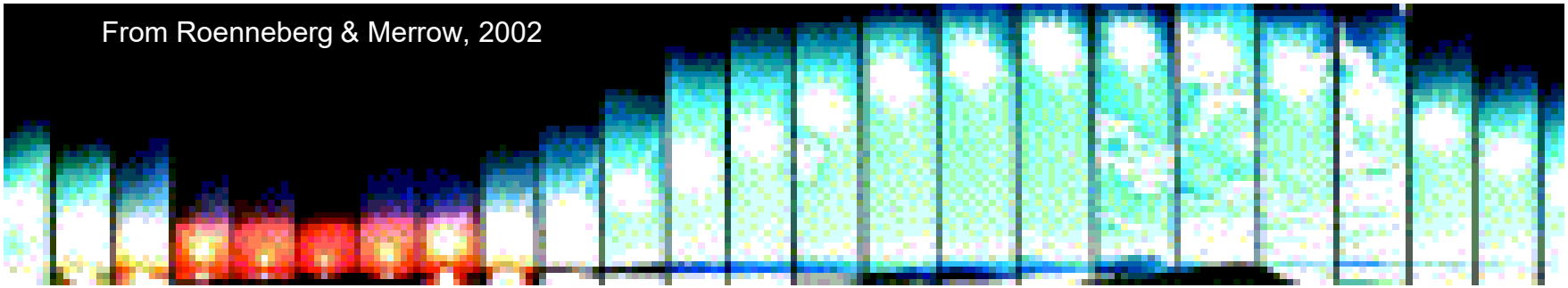


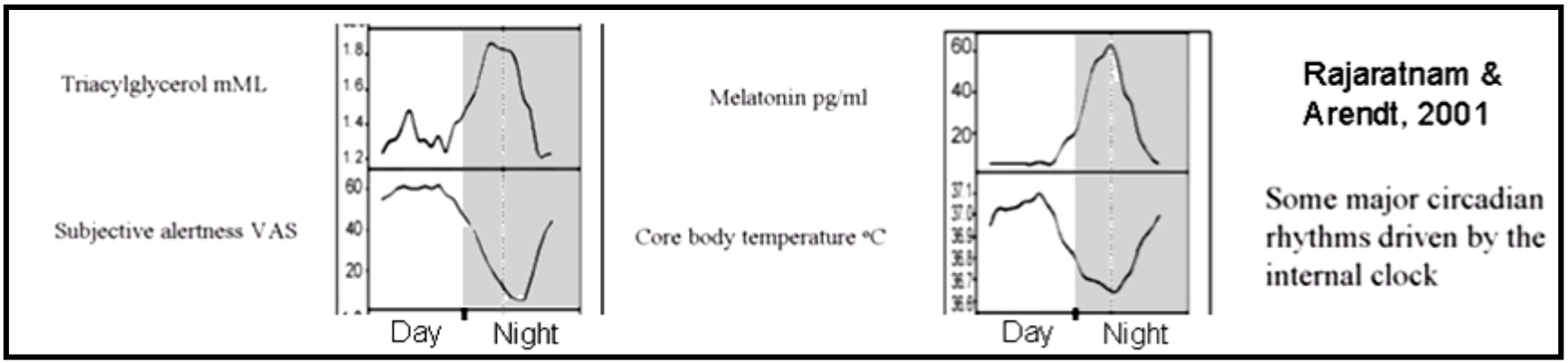


Irradiance Detection by the Eye

- When we think of the eye, we naturally think of its role in sight
  - "Pattern vision"
- In addition to its role in vision, the eye provides the brain with info regarding environmental brightness
  - "Irradiance detection"
- This irradiance information is used to regulate pupil size and our body's circadian rhythms

- Circadian rhythms = patterns of physiology & behavior that have a period of roughly one day
- Ultradian (per<<1 day) & infradian (per>>1 day) rhythms





Symptoms of Disrupted Circadian Rhythms

- If you have flown on a trans-oceanic flight, you probably have experienced at least mild symptoms of “jet lag”
  - Fatigue during the day
  - Inability to fall asleep at night
  - Increased irritability and headaches
  - Digestive issues
  - Decreased ability to concentrate

4:00 pm

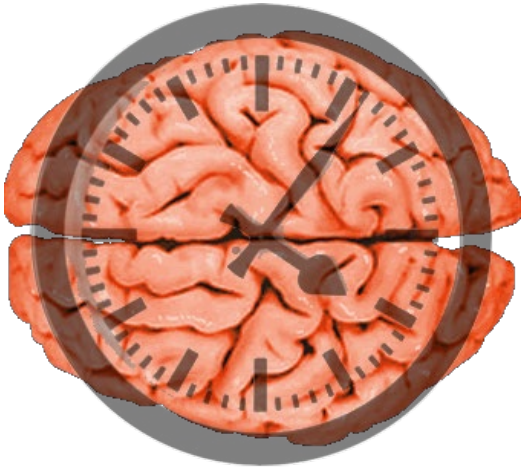
midnight

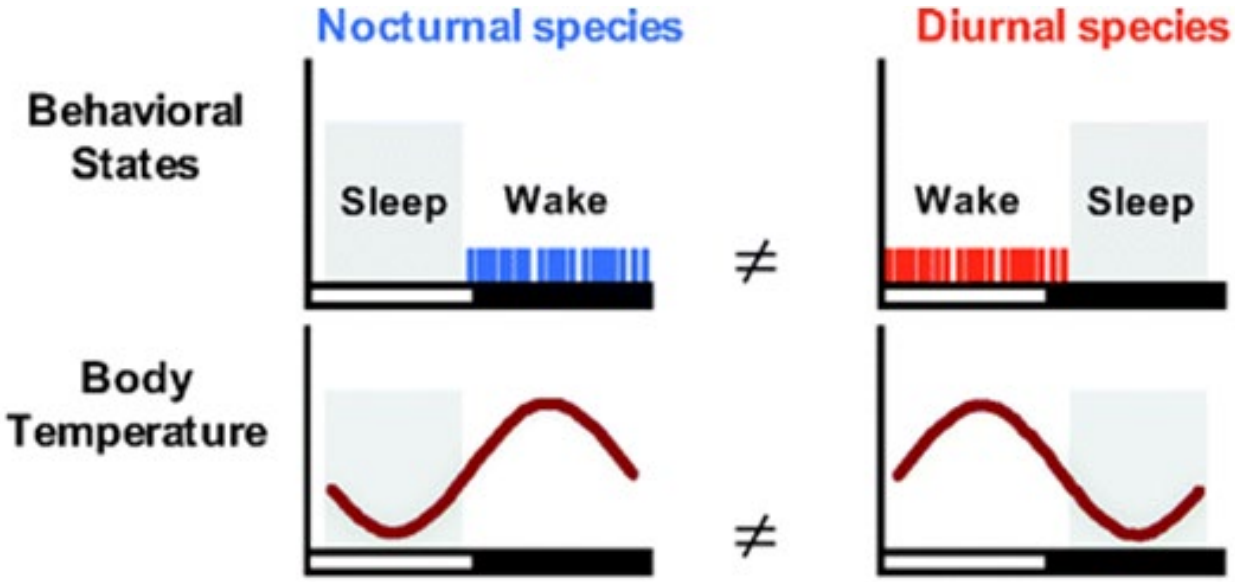
‘Day Outside’ Versus ‘Day Inside’

- The issue with jet lag is that you are suddenly expected to be awake when you are usually still asleep

- A disconnect between external time (the ‘Day Outside’) and the body’s internal time (the ‘Day Inside’)
  - Both ‘Days’ gradually resynchronize (~1 day per time zone crossed)

- Do we really have some sort of internal clock that keeps track of time? If so, why? Where is it? How is it set?

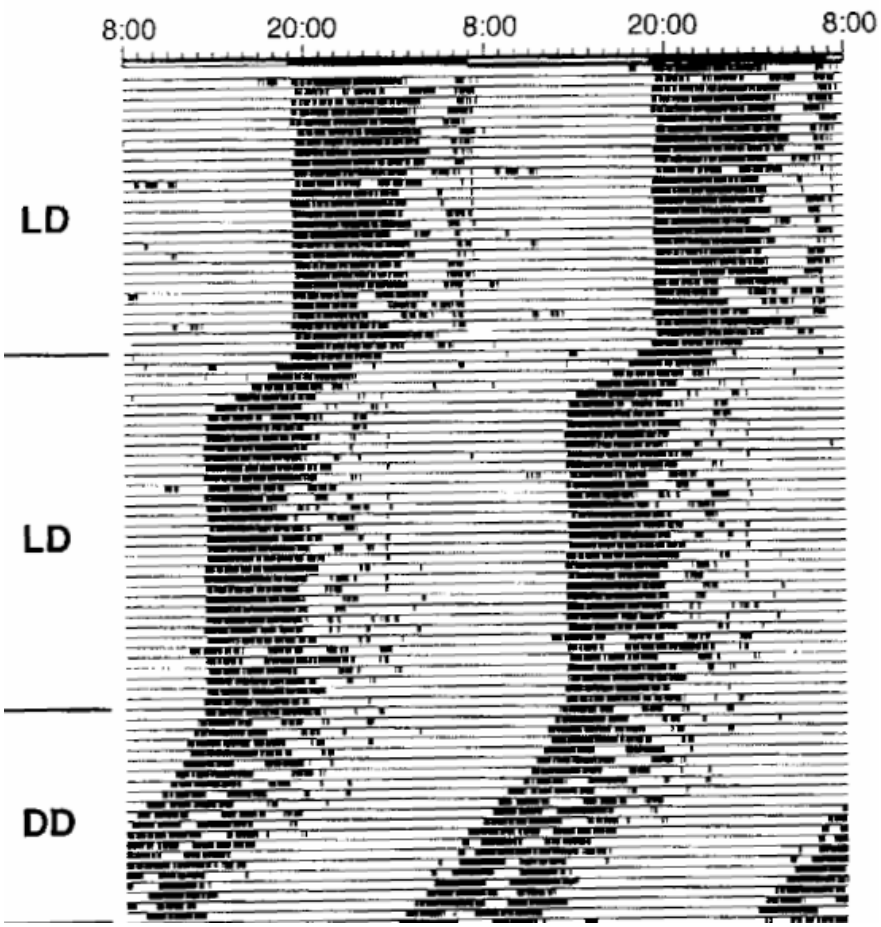


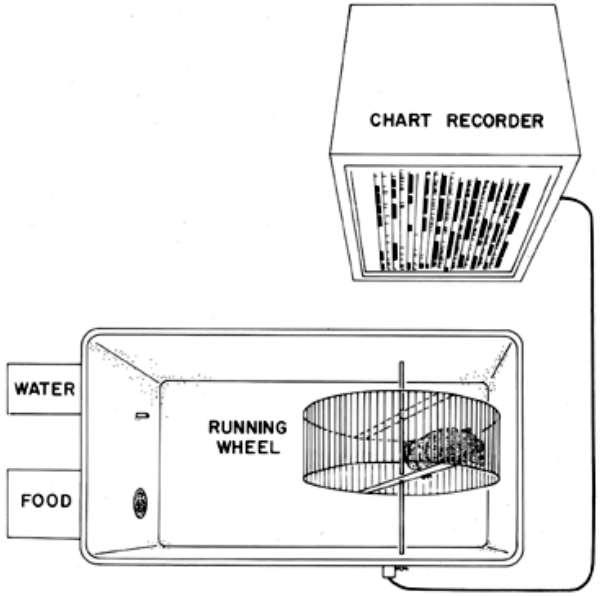


- If daily rhythms of behavior and physiology are controlled by an internal clock, the rhythms should persist under constant environmental conditions (i.e. constant darkness, stable temp)

- 1st evidence for clock in mammals came from looking at activity/rest cycle in mice under constant conditions (M. Johnson, 1939)

- In the lab, locomotor activity is commonly used to monitor circadian behavior in rodents

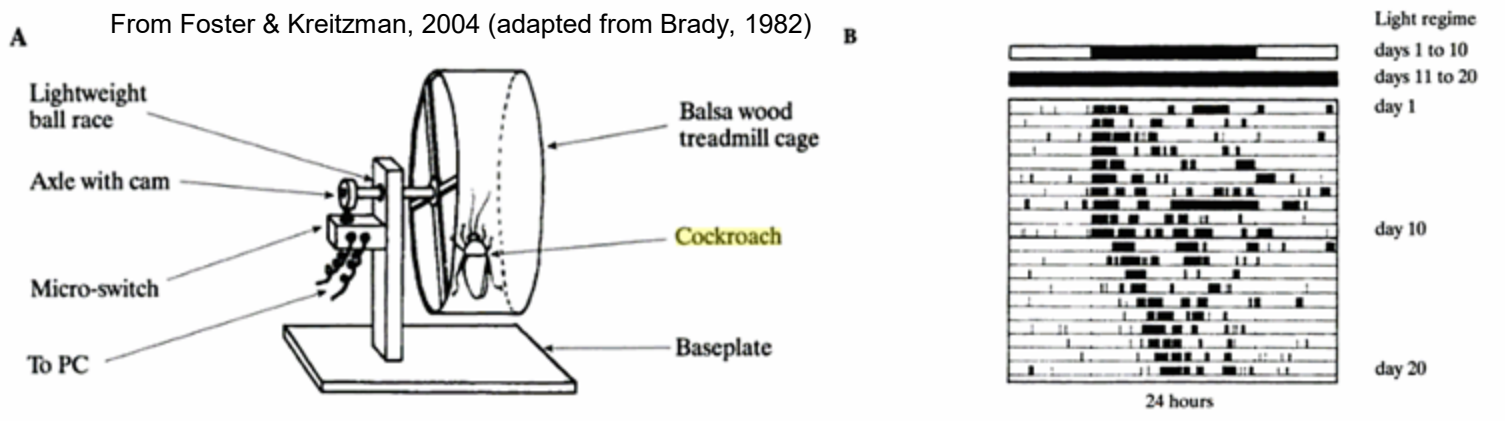




A ~24 hr ‘free-running’ rhythm persists under constant conditions

- Circadian rhythms are found in just about every organism studied
  - Birds, reptiles, insects, worms, plants, and even some algae & bacteria

From Foster & Kreitzman, 2004 (adapted from Brady, 1982)



- For something so universal, there must be a reason…
  - The 24-h rotation of the planet is a constant for all life, so an advantage to anticipate day/night onset

- We live in a world with artificial timing cues, often shielded from the 'Day Outside', so our internal clocks are often masked and ignored

- Research on human volunteers in caves or bunkers have confirmed that humans have rhythms driven by an internal pacemaker

- It appears that the internal 'free-running' rhythms in humans is about ~24.5 h
  - In nocturnal animals like mice, it's usually < 24 h

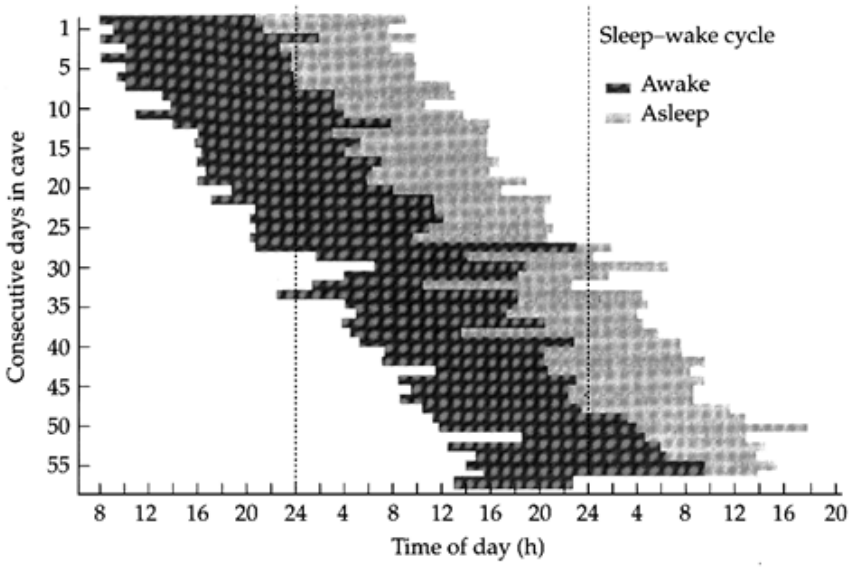
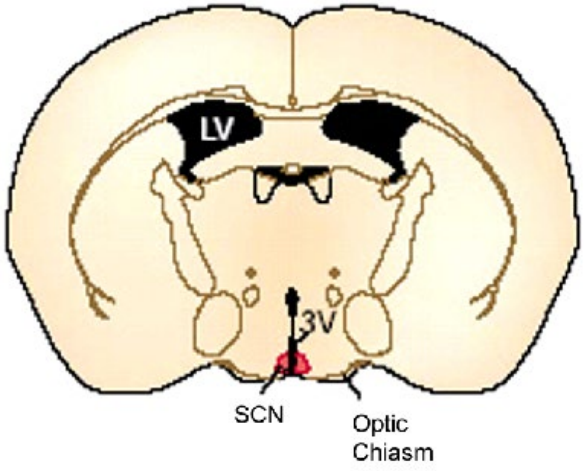


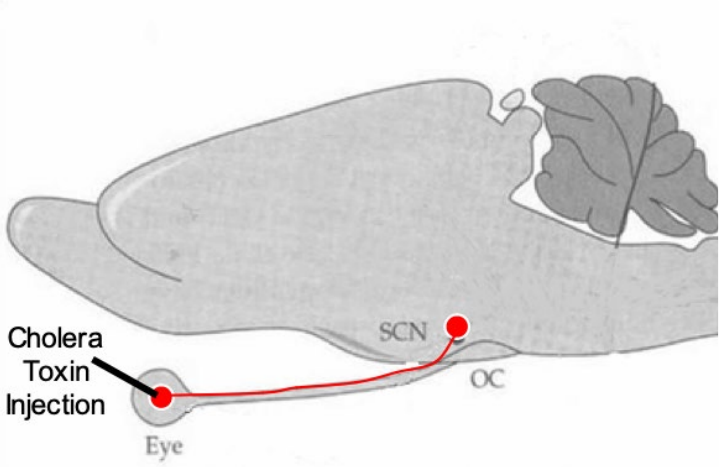
FIGURE 9.4 Body temperature rhythm of an individual living in a deep, lightless cave for 62 days. (From Palmer, 2002.)

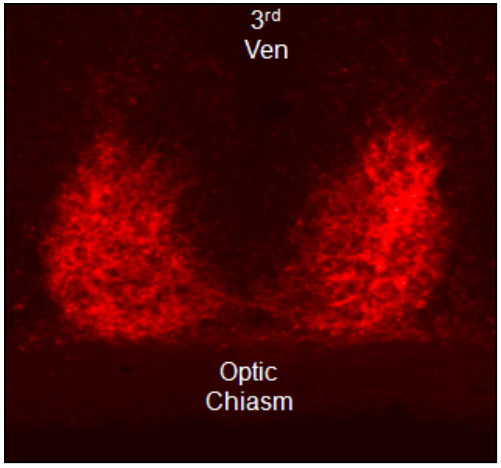
Where's the Clock?

- Lesion experiments narrowed down the location of the clock to the hypothalamus in the brain of rats (Richter, 1967)

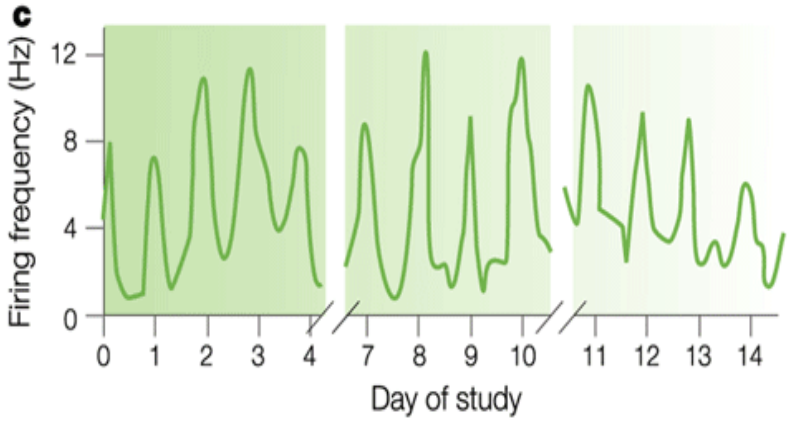
- Then discovered that axons from the retina project to the suprachiasmatic nucleus (SCN) here (Moore & Lenn, 1972)
  - 1-2% of all retinal ganglion cell axons in rodents





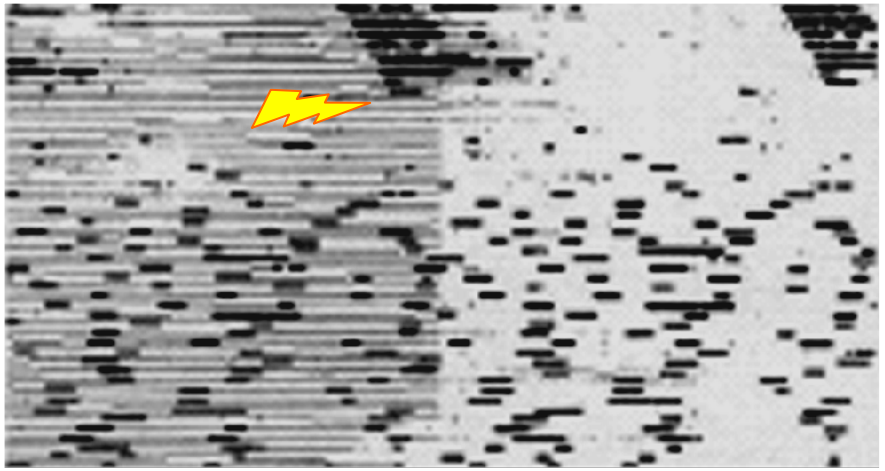


- Evidence gathered from many lesion, transplant, cell culture studies confirmed that SCN is the brain region for the ‘master clock’ of circadian rhythm regulation



Electrical activity from an isolated rat SCN neuron in culture

Hastings et al, 2003; adapted from Liu and Reppert, 2000



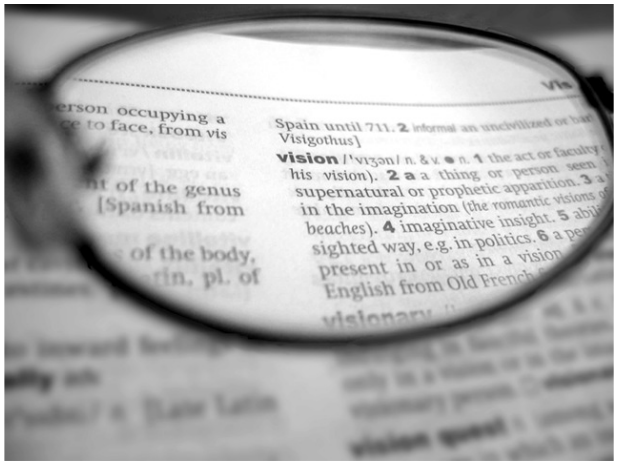
Hamster above in constant darkness

After SCN lesion ( ), hamster becomes arrhythmic

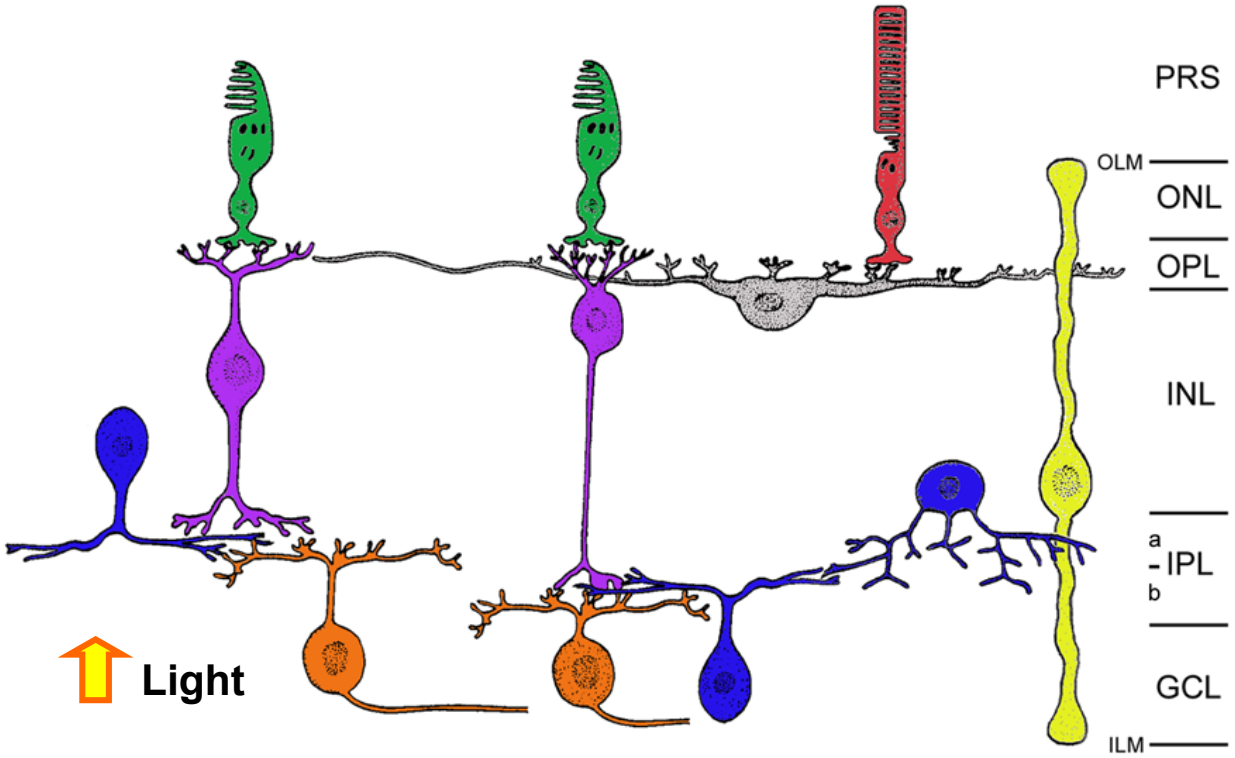
Sollars and Pickard, 1998

How Does the Internal Clock Stay on Time?

- Is the pathway that transfers information about ambient light levels in the environment (irradiance detection) to the brain the same as that for pattern vision?



Relay of Photic Information to the SCN



Rods, Cones

Horizontal Cells

Bipolar Cells

Amacrine Cells

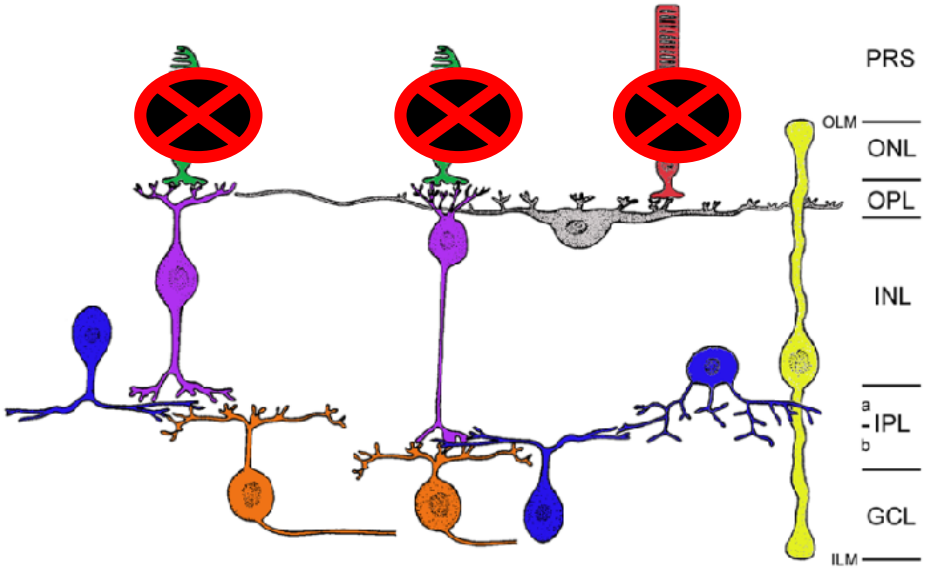
Retinal Ganglion Cells (RGCs)

It was long assumed that the relay of irradiance information to the SCN would be similar to that characterized for the visual pathway

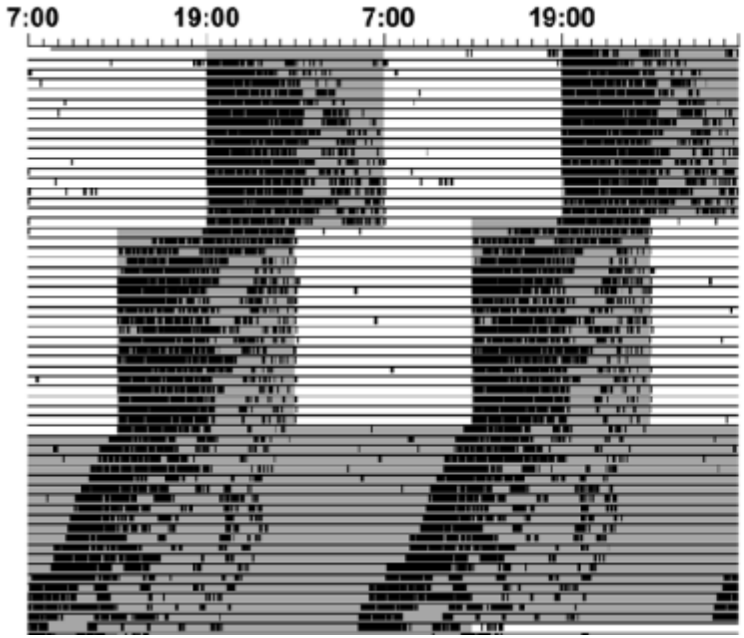
Rods/Cones → Bipolar Cells → RGCs

- With bilateral enucleation, animals do not entrain to the light/dark cycle (they ‘free-run’) (Nelson & Zucker, 1981)
  - Thus, the eye is important…

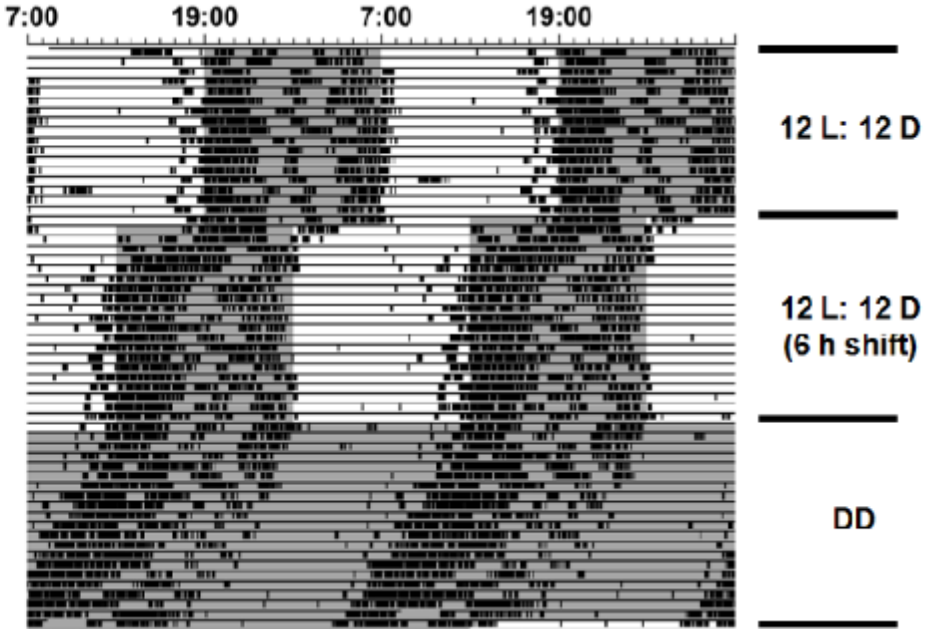
- BUT, work in the ’90s on mice with complete rod/cone loss indicated that these mice still entrain to day/night light cycles



C57BL/6J mice (controls)



GC dKO mice



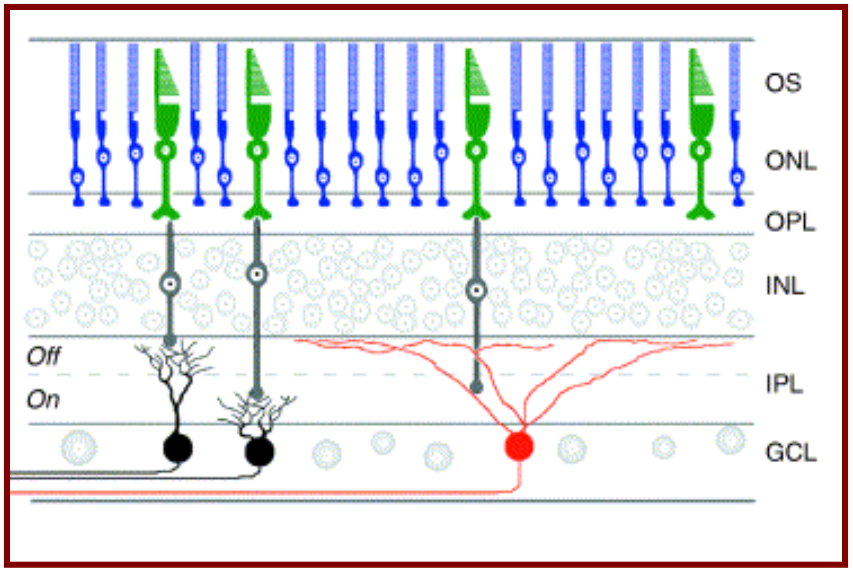
- Mouse on right has guanylate cyclase knocked out, causing all rod/cone function to be eliminated
- Despite being ‘blind’, mice lacking this enzyme still entrain to the daily light/dark cycle

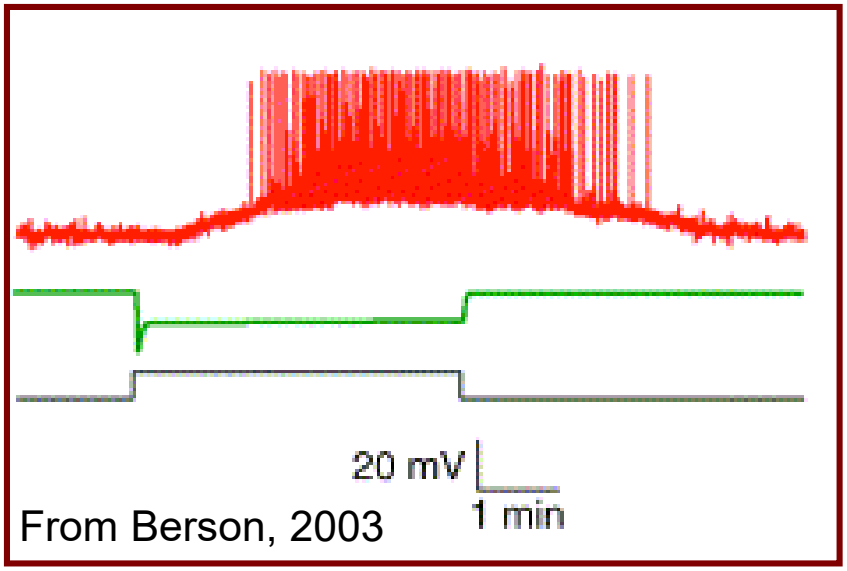
Visually Blind ≠ Circadian Blind

- As work using retinal degenerate mice (or mice with genetically disrupted rod/cone function)…
- Rods/cones are not necessary for irradiance detection

- In accord, some visually blind patients (i.e. with Leber's congenital amaurosis) appear to exhibit normal or near-normal circadian rhythm entrainment
  - Czeisler et al. (1995) N Engl J Med

Intrinsically Photosensitive RGCs (ipRGCs)

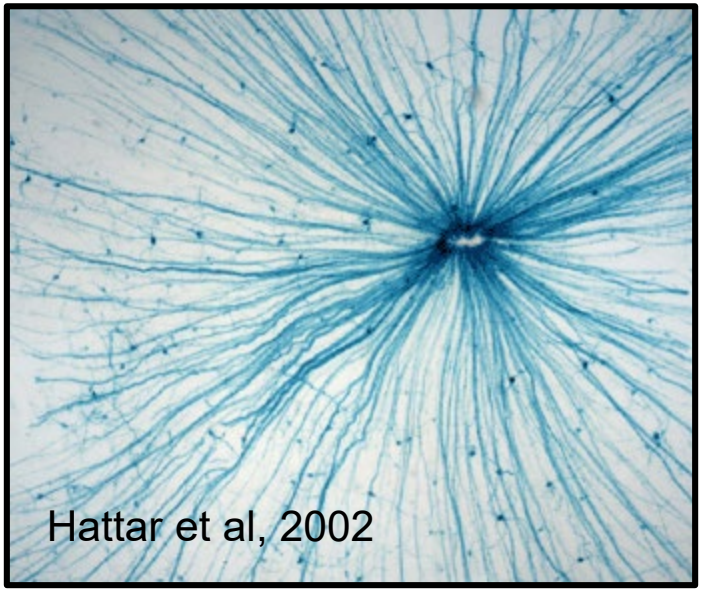


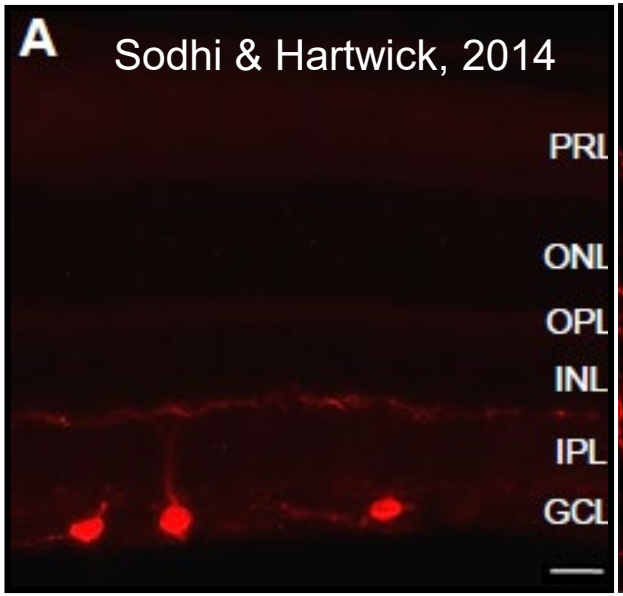


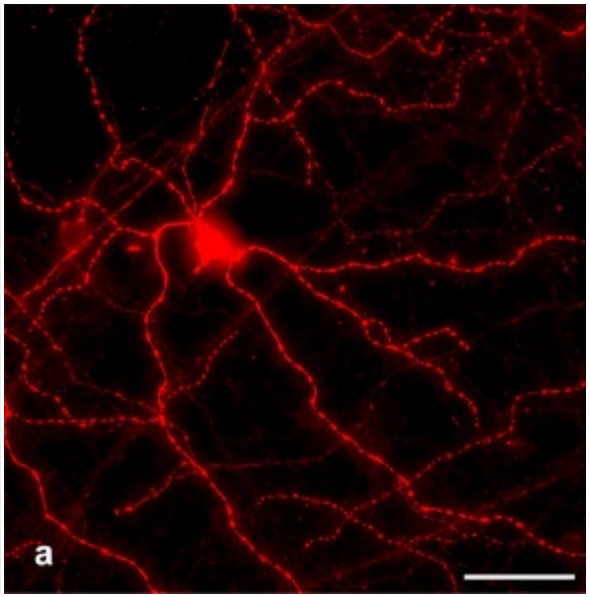
Photoreception is not just for rods and cones any more…

- Berson *et al.* (*Science* 2002) showed that a small subpopulation of RGCs are directly photosensitive
  - Recorded from RGCs that specifically projected to the SCN, the 'master clock' for circadian rhythms

Intrinsically Photosensitive RGCs (ipRGCs)

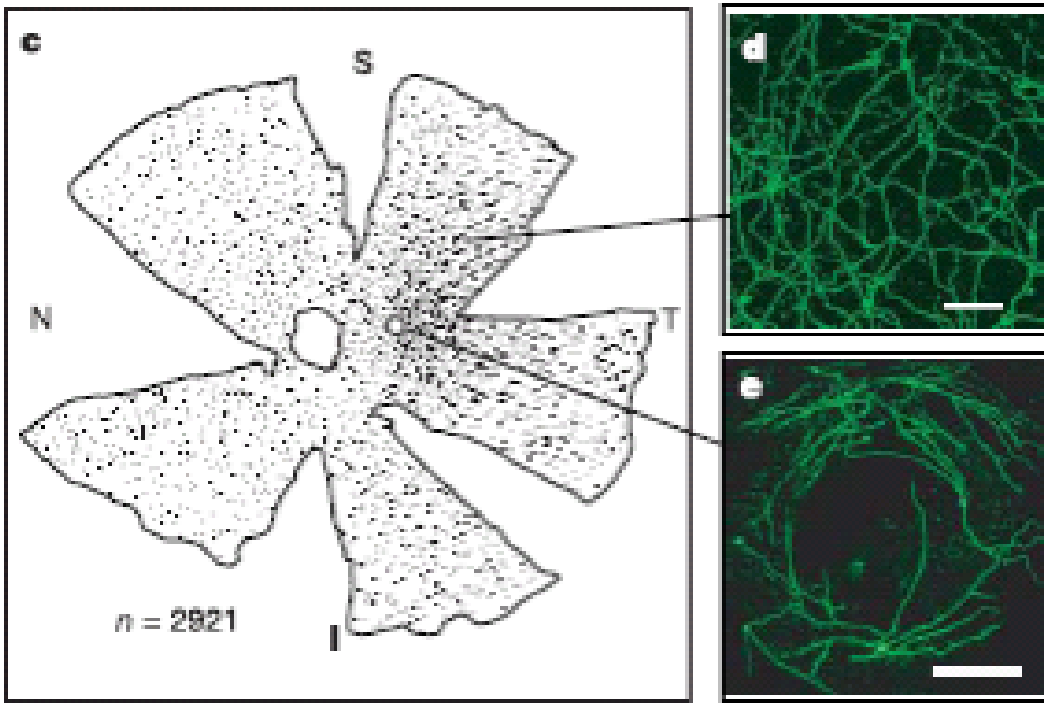






- Hattar *et al.* (*Science* 2002) showed that these ipRGCs express the photopigment melanopsin
- This photopigment had been discovered earlier in frog skin melanophores (Provencio et al, 1998)

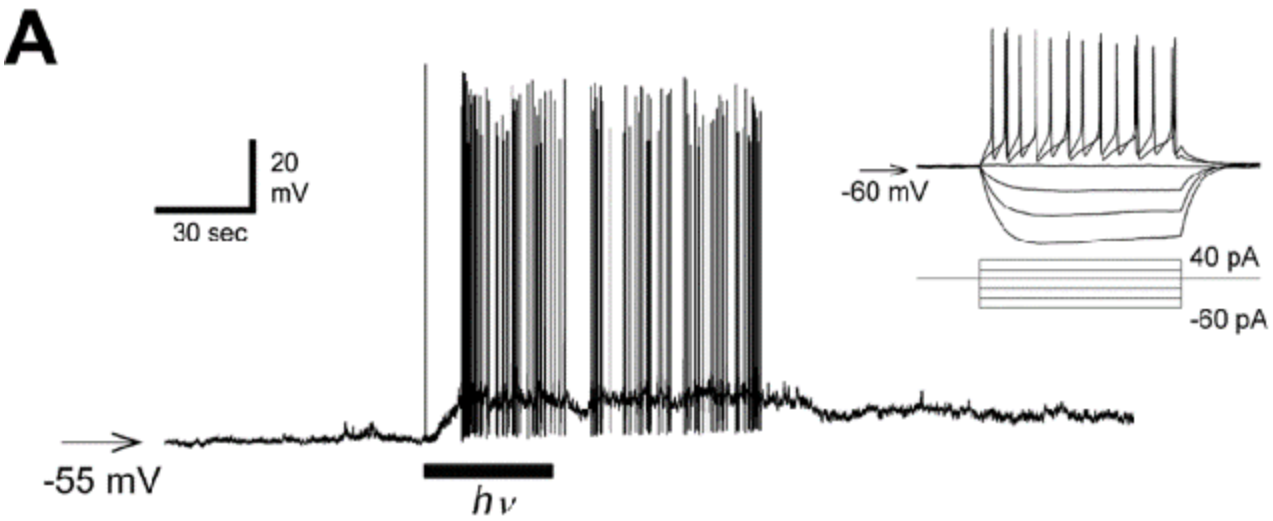
	Rat Retina	Human Retina
Rods & Cones	20,000,000	125,000,000
RGCs	120,000	1,500,000
ipRGCs	2,500 (Hattar *et al,* 2002)	3,000 (Dacey *et al,* 2005)



Monkey retina

(Dacey *et al,* 2005

Melanopsin-Based Light Responses of ipRGCs

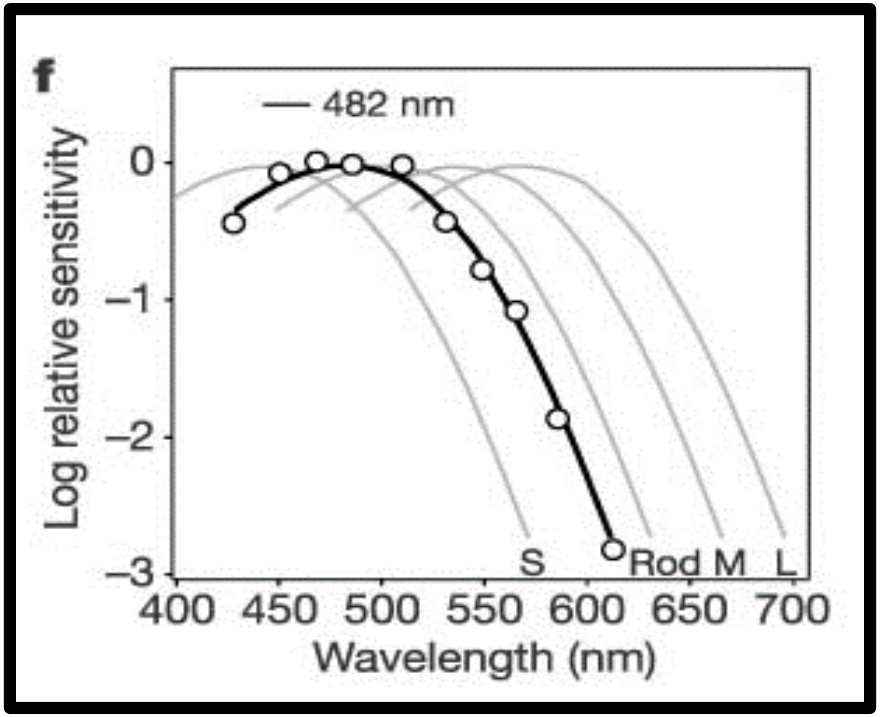


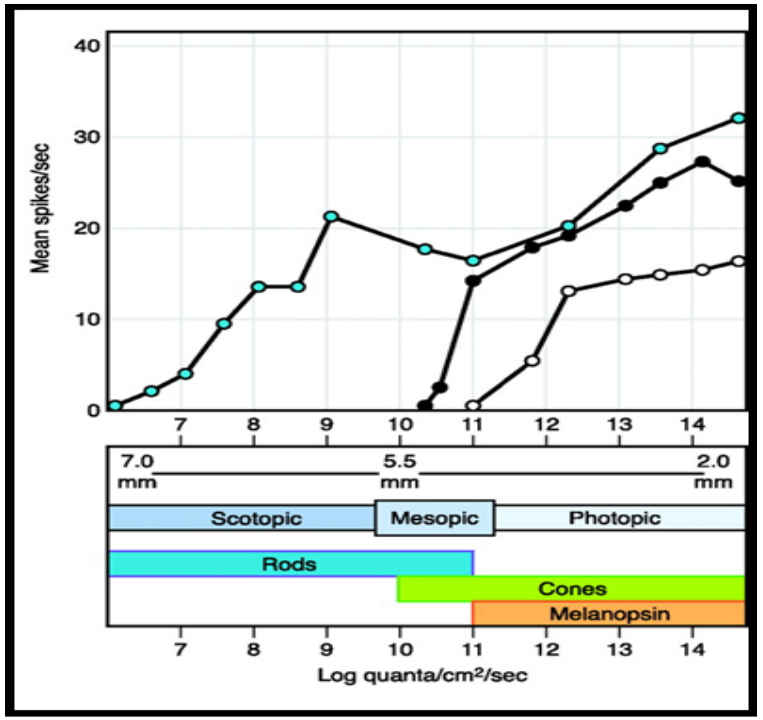
Hartwick et al, J Neurosci, 2007

Light-evoked responses can be recorded from cultured ipRGCs completely isolated from other retinal cell types

ipRGC Spectral & Absolute Sensitivity

Dacey et al, 2005

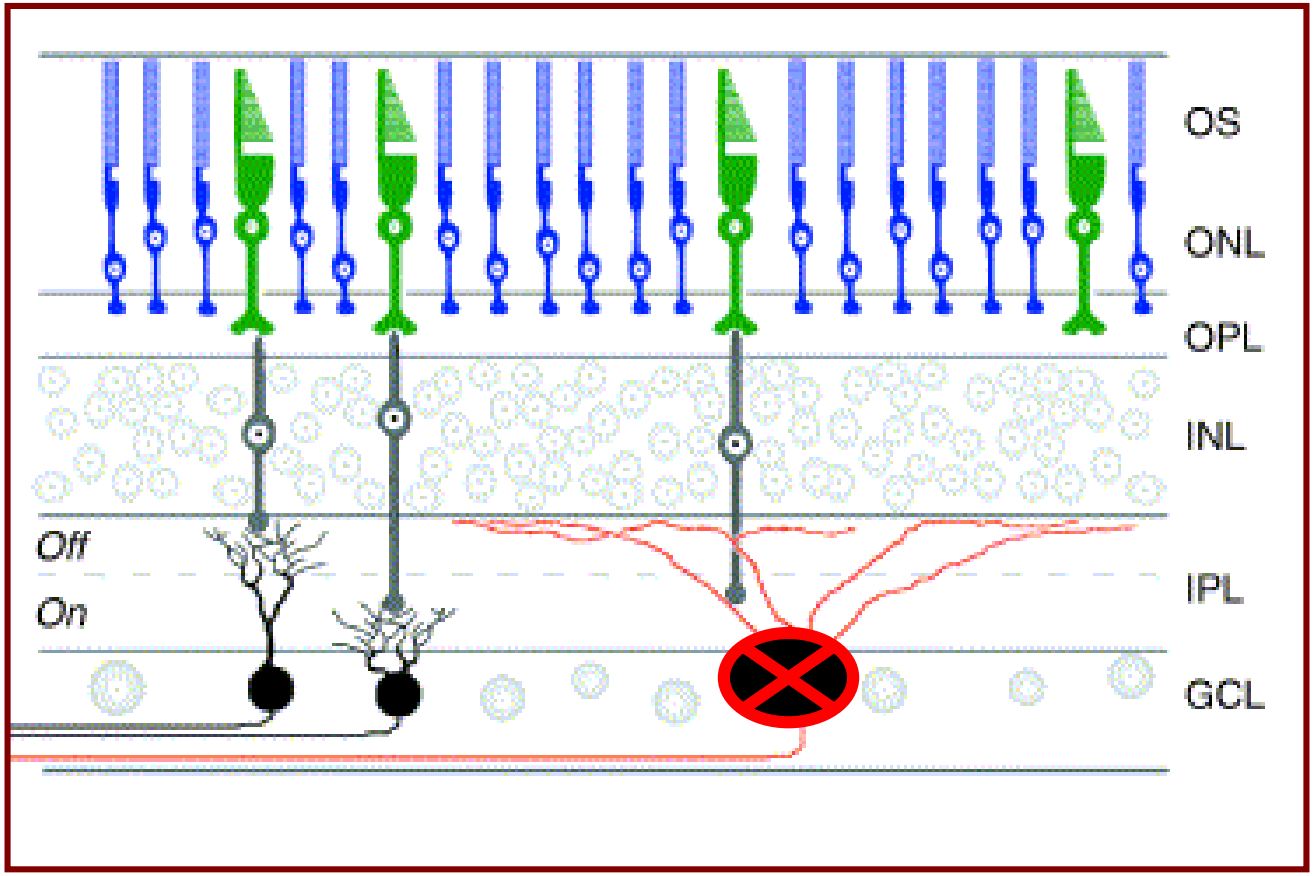




- Peak spectral sensitivity at ~480 nm light

- Threshold irradiance for melanopsin higher (requires brighter light) than that for rod or cone stimulation

- Possible to genetically completely ablate ipRGCs in mice
  - Encode diphtheria toxin receptor with melanopsin gene



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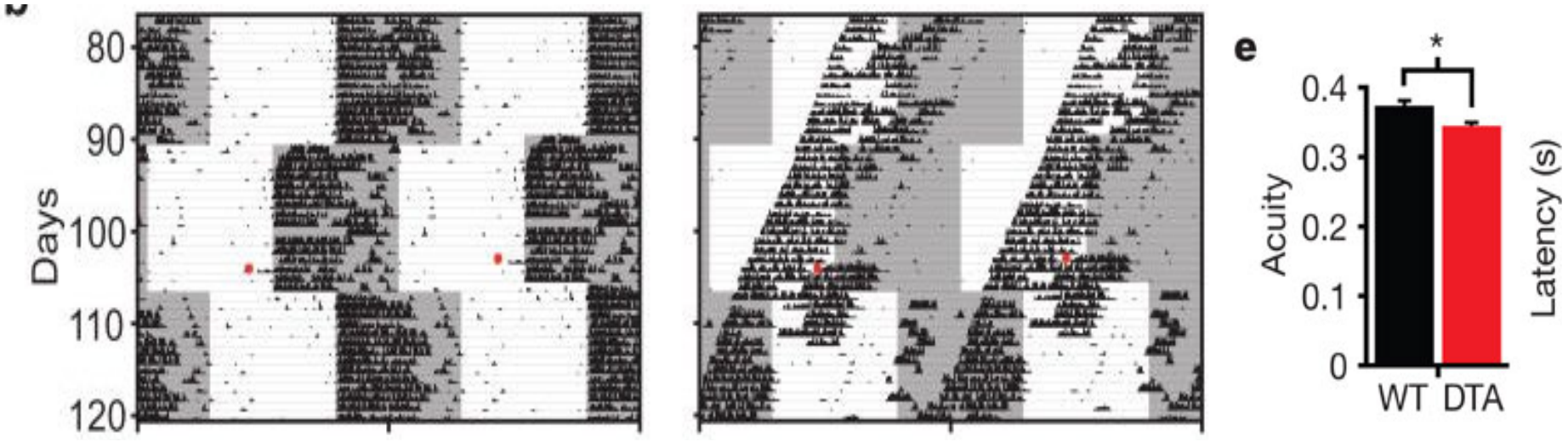
  - Encode diphtheria toxin receptor with melanopsin gene

- These mice are “circadian blind”, not visually blind

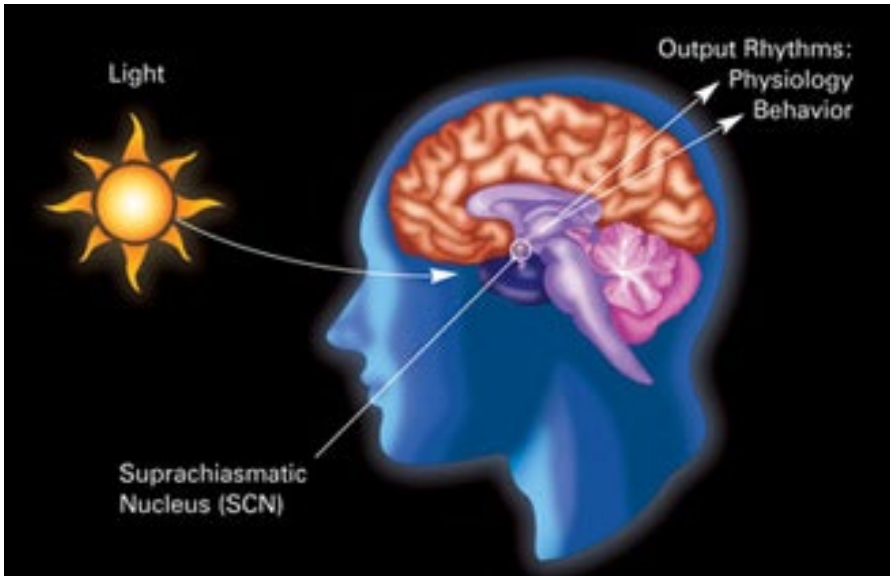


Normal Mice

Mice with no ipRGCs

Guler *et al., Nature* 2008

- Since the discovery of ipRGCs, there has been a major paradigm shift in the understanding of retinal function
  - Pattern vision versus irradiance detection



http://www.nigms.nih.gov/Publications/Factsheet_CircadianRhythms.htm

- What are the potential implications to clinical practice now and in the future?

"Exposure to blue light in the 430 to 480 nm range wakes us up in the morning by signaling the brain to suppress the sleep hormone melatonin and produce the hormone cortisol, which increases wakefulness."

Recall ipRGCs are most sensitive to 480 nm blue light

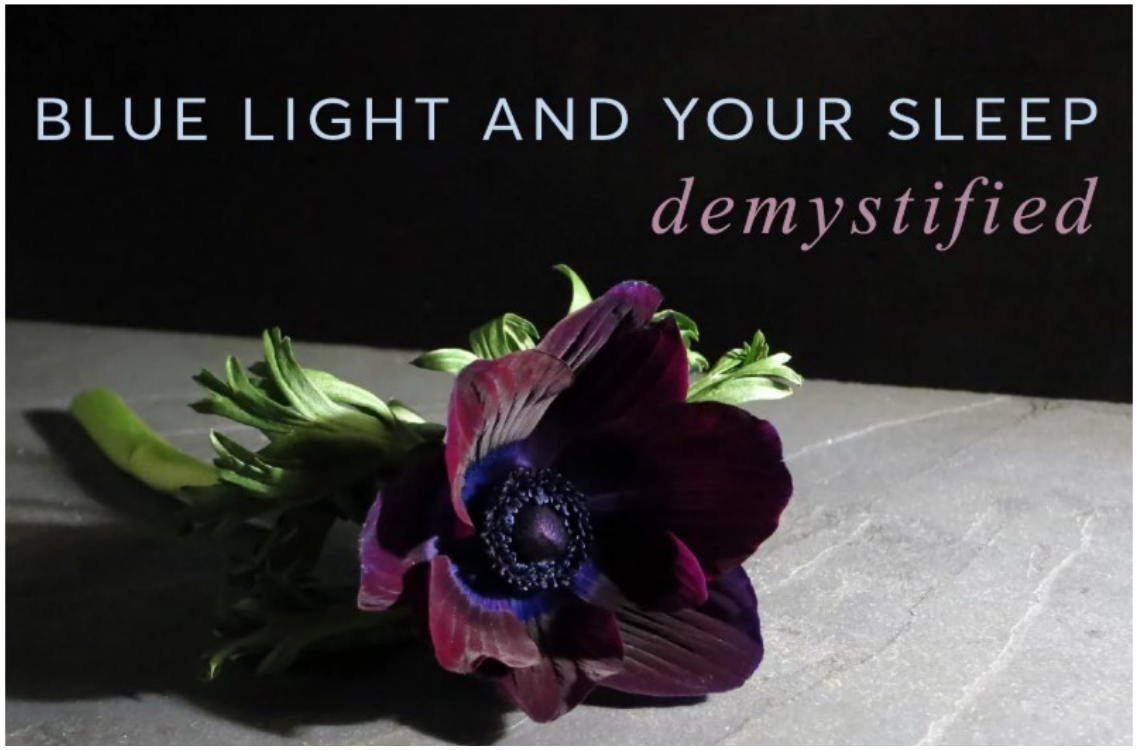
The Perils of Blue Light Exposure?

COMMUNITY // May 22, 2019

Why Is Blue Light Bad for Your Sleep?

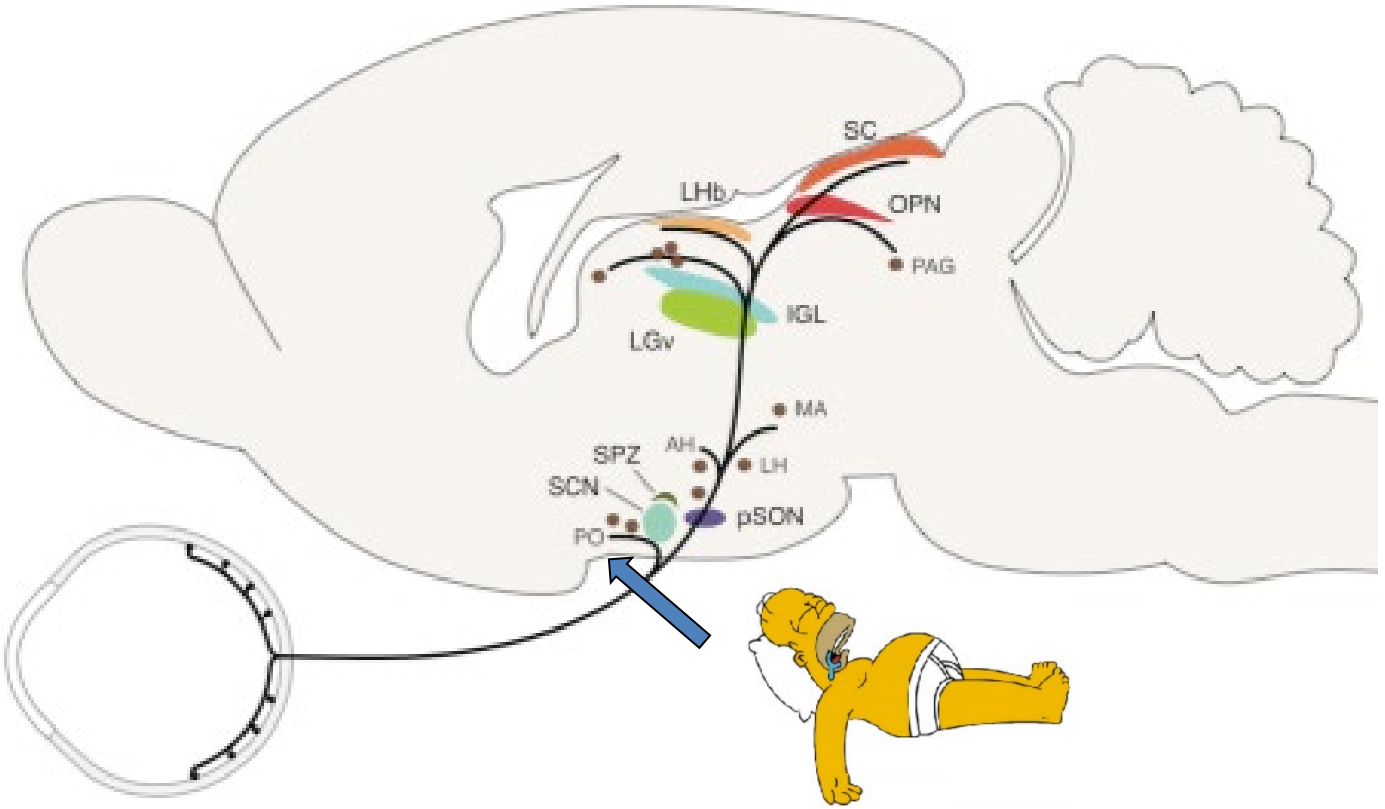
It's more pressing than you think, and here's why

By Casey Gardonio-Foat, Founder, Wink & Rise

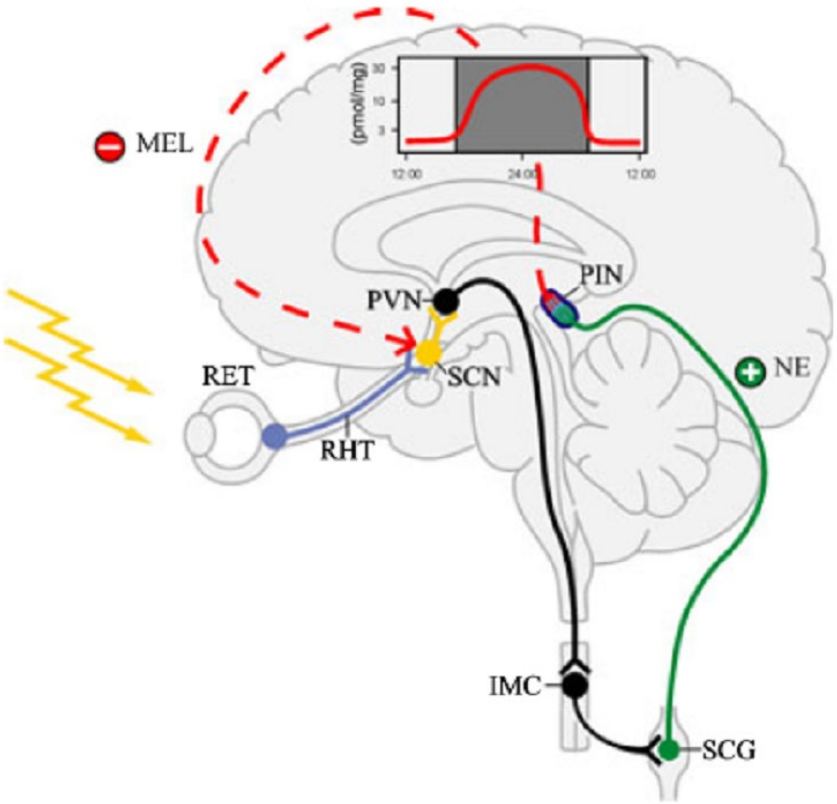


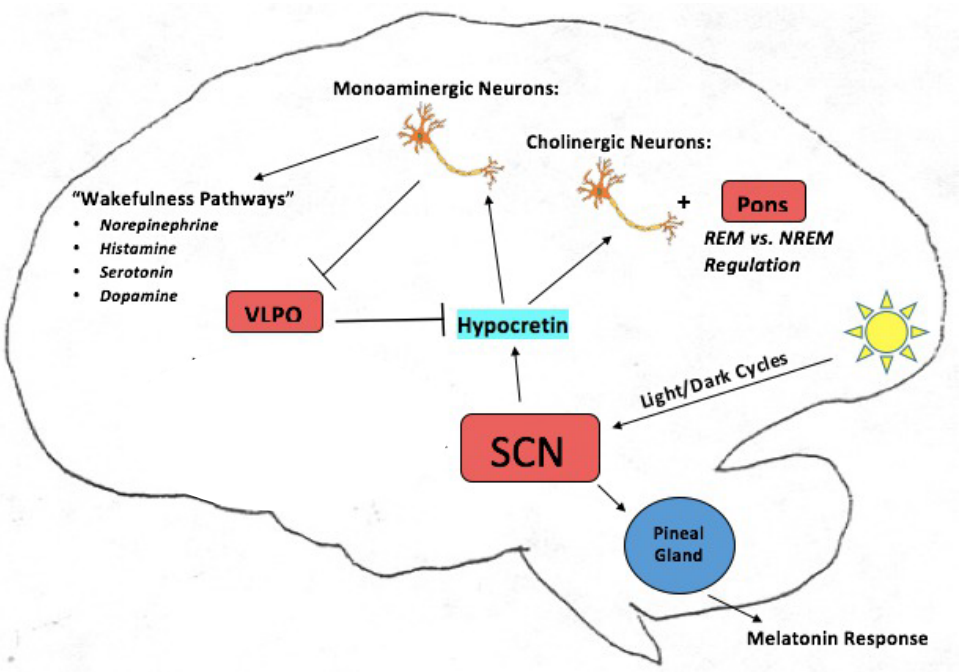
www.thriveglobal.com

- ipRGCs project to a number of non-SCN sites, including ventrolateral pre-optic nucleus (LeGates et al., 2014)
  - Involved in sleep regulation



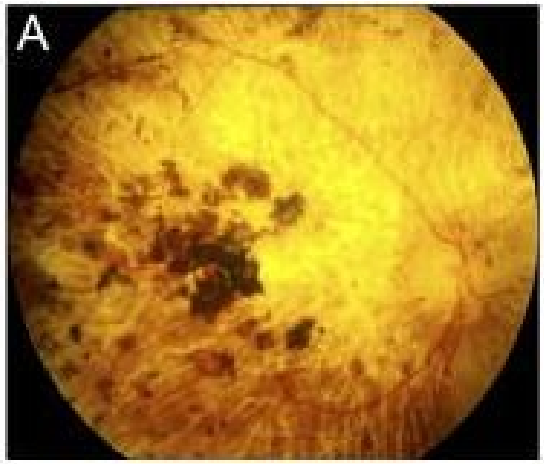
- The light input ipRGCs provide to SCN also play a key role in regulating melatonin release from pineal gland
  - Melatonin helps to promote sleep

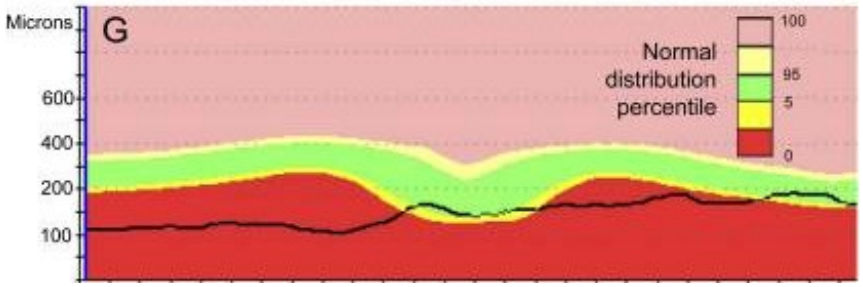




https://sites.tufts.edu/sleep/the-answer/

- Zaidi et al (*Curr Biol* 2007) reported on two patients without light perception
    - Cone-rod dystrophy and retinitis pigmentosa





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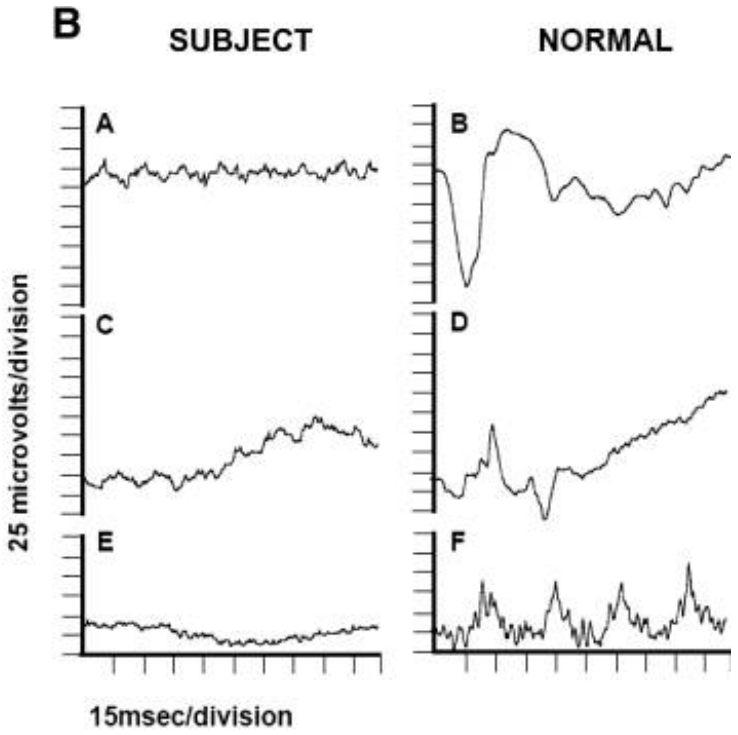
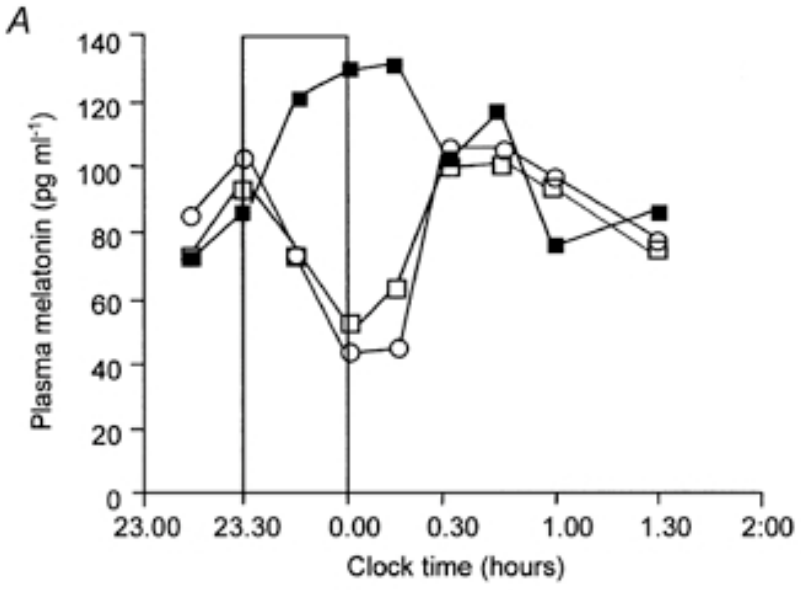
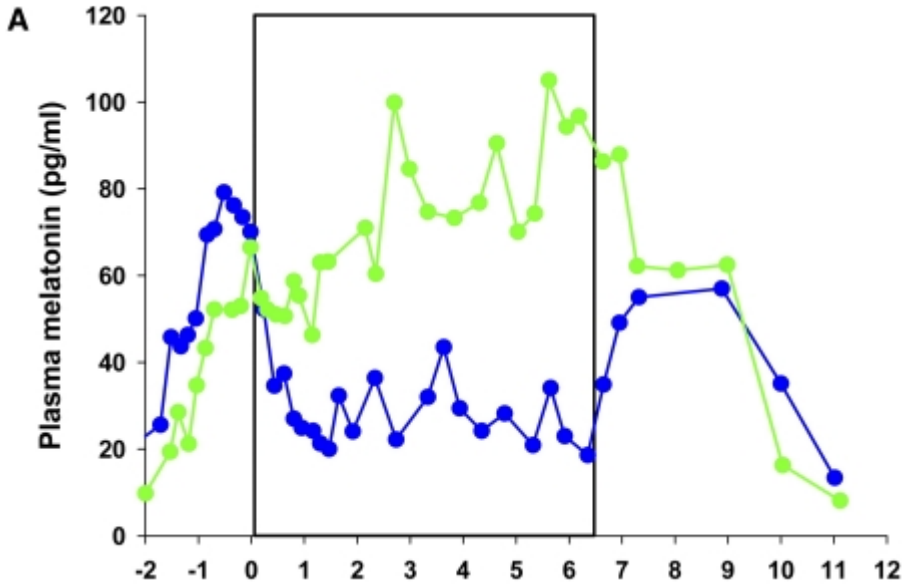


ERG

- Well-known that light suppresses melatonin at night
- In the 2 blind patients, blue light (compared to similarly bright green light) was effective at inhibiting melatonin
  - Supports role for ipRGCs in mediating effect



Melatonin suppression by white light in healthy subjects
Thapan *et al., J Physiol* 2001



Melatonin suppression by blue light in a blind subject
Zaidi *et al., Curr Biol* 2007

Washington
Times-Reporter

Another use for blue blocking glasses: Better sleep

By Leslie Renken
of the Journal Star
Posted May 16, 2019 at 5:26 PM
Updated May 16, 2019 at 7:55 PM

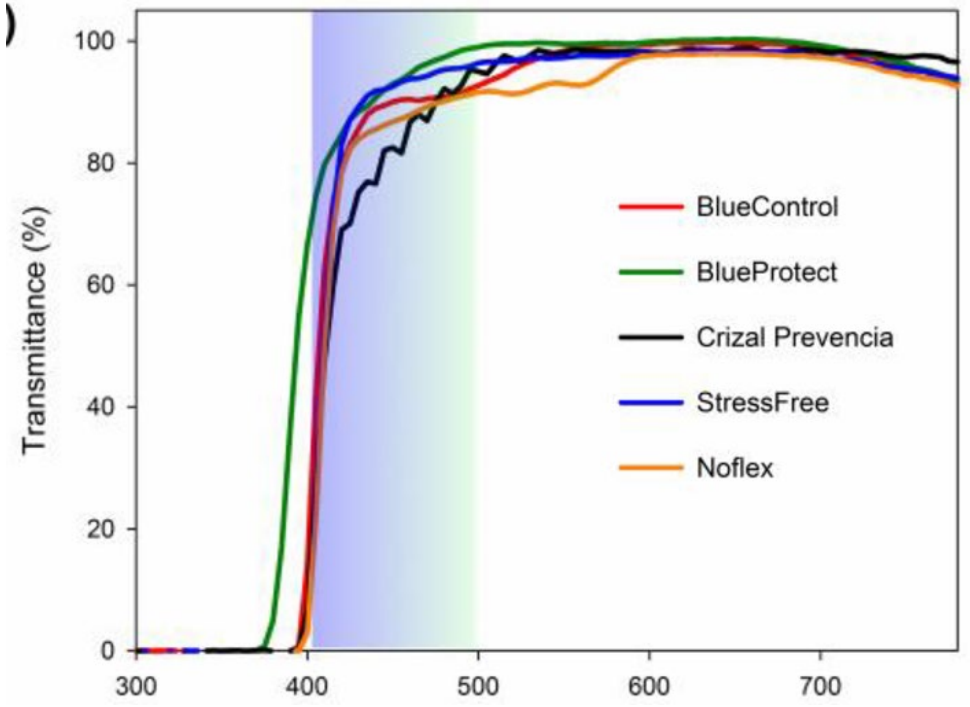
PEORIA — The blue light blocking glasses you purchased to reduce eyestrain may also help you get to sleep faster.

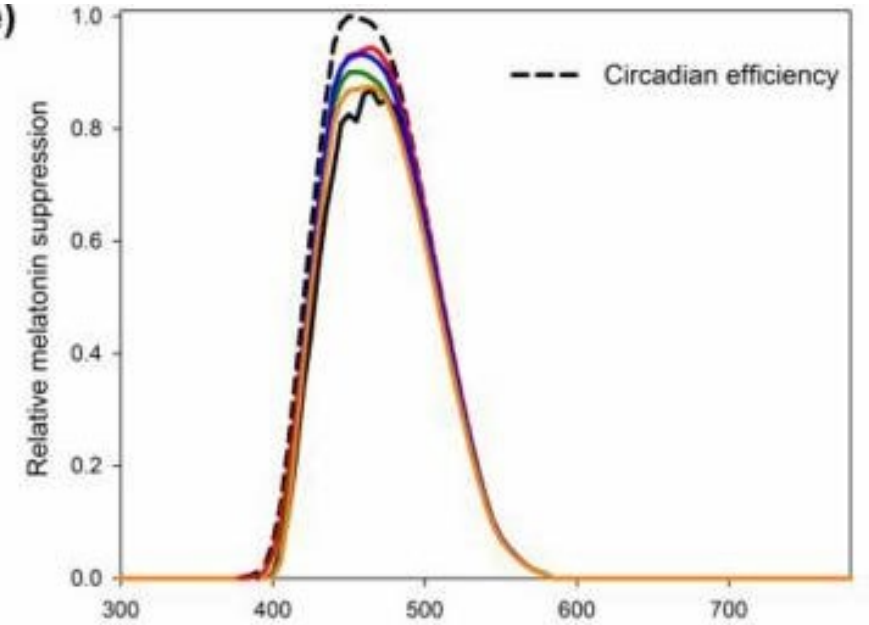
Marketed primarily to prevent eye strain and headaches caused by the blue light coming off computers and other electronic devices, the glasses are being studied by sleep specialists who have long used light regulation as a way to control the production of melatonin, a chemical key to the onset of sleep.

"There are several small studies that hint at those blue blocking glasses being effective (at helping people get to sleep sooner), and the science behind them makes a lot of sense," said Dr. Sarah Zallek, medical director of OSF HealthCare Illinois Neurological Institute Sleep Center.

Light affects the production of melatonin — bright light can suppress it, and dim light allows it to come on. Sleep specialists are now finding that the blue rays in light may play a key role.

- While it's true that these AR coatings selectively filter out some short-wavelength light, it is a relatively small %





Leung TW, Li RW, Kee CS. Blue-Light Filtering Spectacle Lenses: Optical and Clinical Performances. PLoS ONE. 2017;12(1):e0169114.

The effect of blue-light blocking spectacle lenses on visual performance, macular health and the sleep-wake cycle: a systematic review of the literature

John G Lawrenson[1], Christopher C Hull[1] and Laura E Downie[2]

Ophthalmic Physiol Opt. 2017 Nov;37(6):644-654. doi: 10.1111/opo.12406.

A recent meta-analysis of current literature on blue-blocking coatings concluded that there was:

- Lack of properly controlled studies (only 3 so far)
- No convincing evidence, as of yet, that these coatings improve contrast sensitivity, symptoms of eyestrain or sleep quality
- Also no evidence to indicate these lenses conserve macular health (i.e. prevent macular degeneration)

Blue Light-Blocking Lenses (Cutoff Filters)

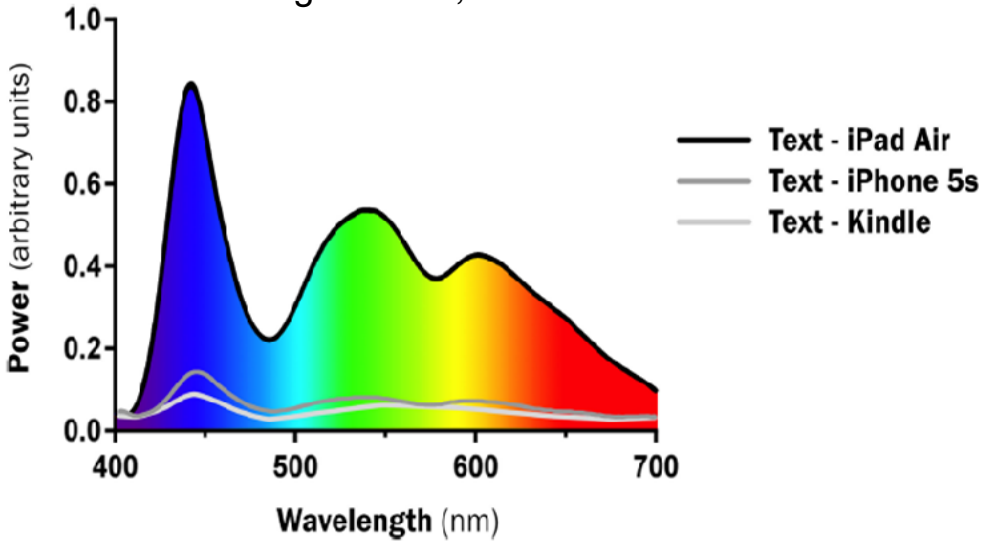
- Schechter et al (J Psychiatr Res, 2018) recently published results from randomized cross-over trial

- 14 insomnia subjects wore clear or amber (blue light cutoff filters) lenses for 2 hrs before bed for 7 days

- Total sleep time increased from 330 to 358 minutes (p=0.035), on average, when the amber lenses worn

- Two caveats:
  - 1) Subjects not masked to treatment (very difficult to do) – bias?
  - 2) Overall # of photons reduced by the amber lenses – would neutral density filters (i.e. sunglasses) have been as effective?

Gringras *et al., Front Public Health* 2015

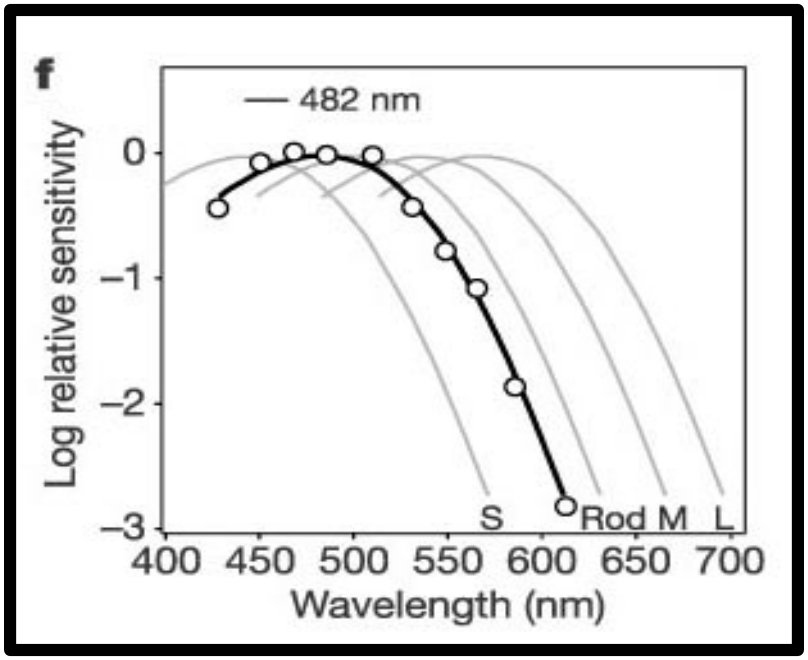


- It's true that electronic devices tend to have screens that are rich in the blue spectrum

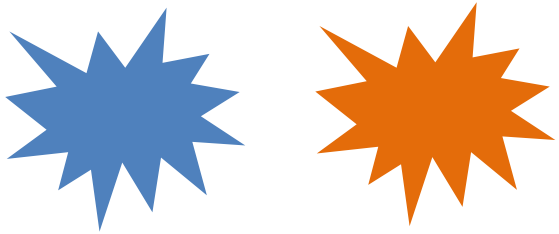
- However, the intensity of the light is as important as the spectral properties…

ipRGC Spectral Sensitivity

Dacey et al, 2005



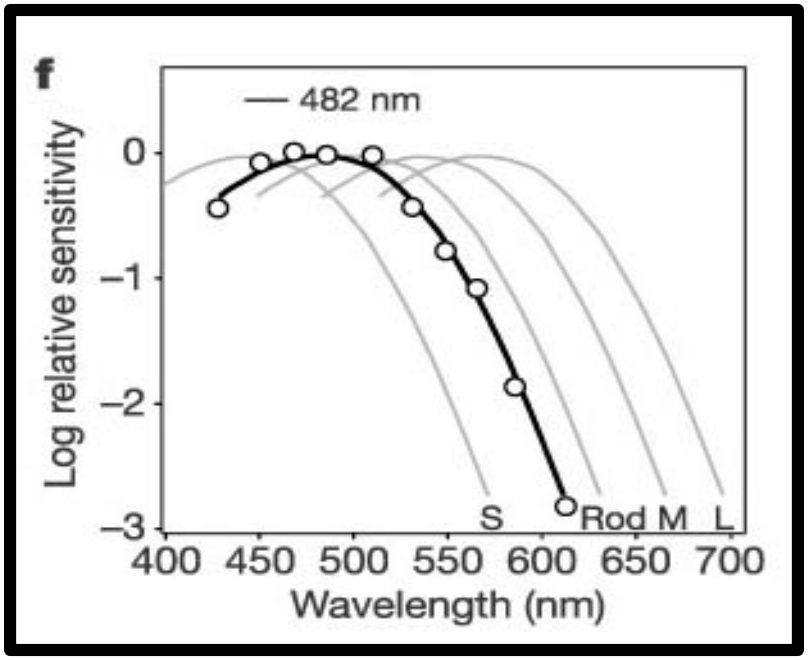
- Note width of spectral sensitivity curve
- ipRGCs are ~100x more sensitive to 480 nm versus 600 nm light



If a blue and orange light are equally bright, the blue light will evoke greater ipRGC stimulation

ipRGC Spectral Sensitivity

Dacey et al, 2005



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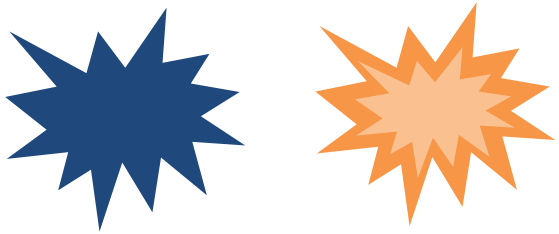
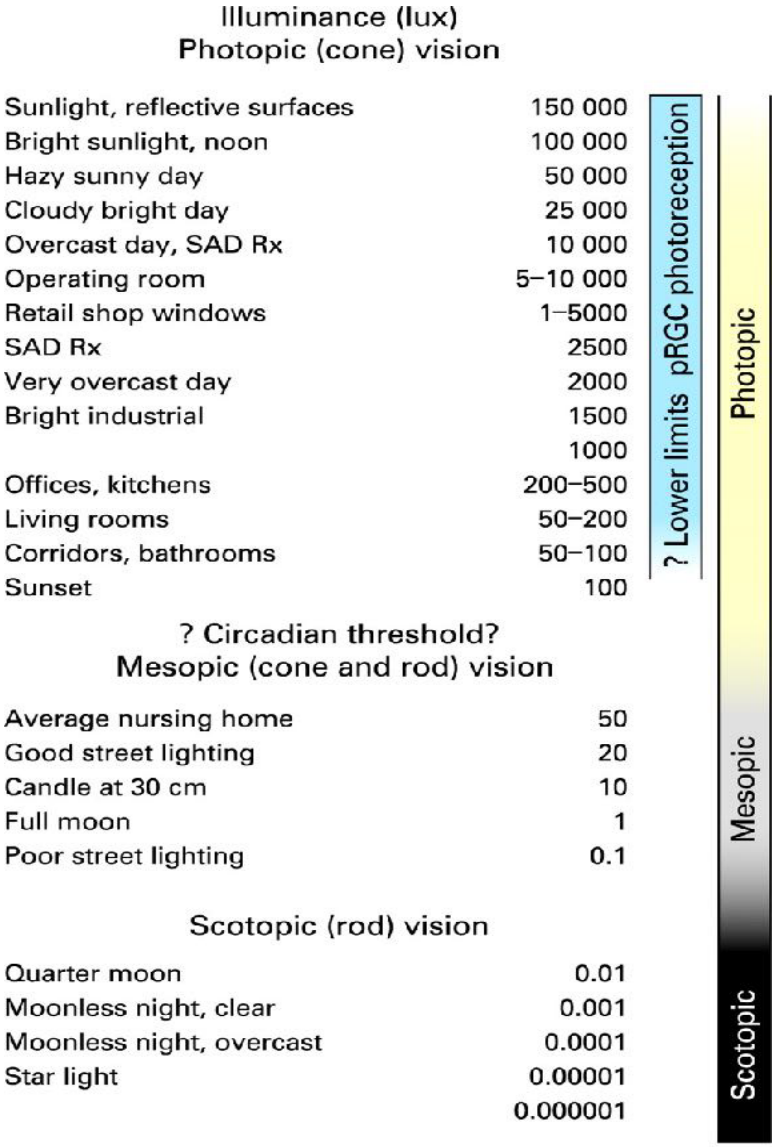


If the orange light is 1000x brighter than the blue, the orange will stimulate ipRGCs more

ipRGCs and Electronic Devices



Turner &Mainster BJO 2008

Gingras et al, 2015

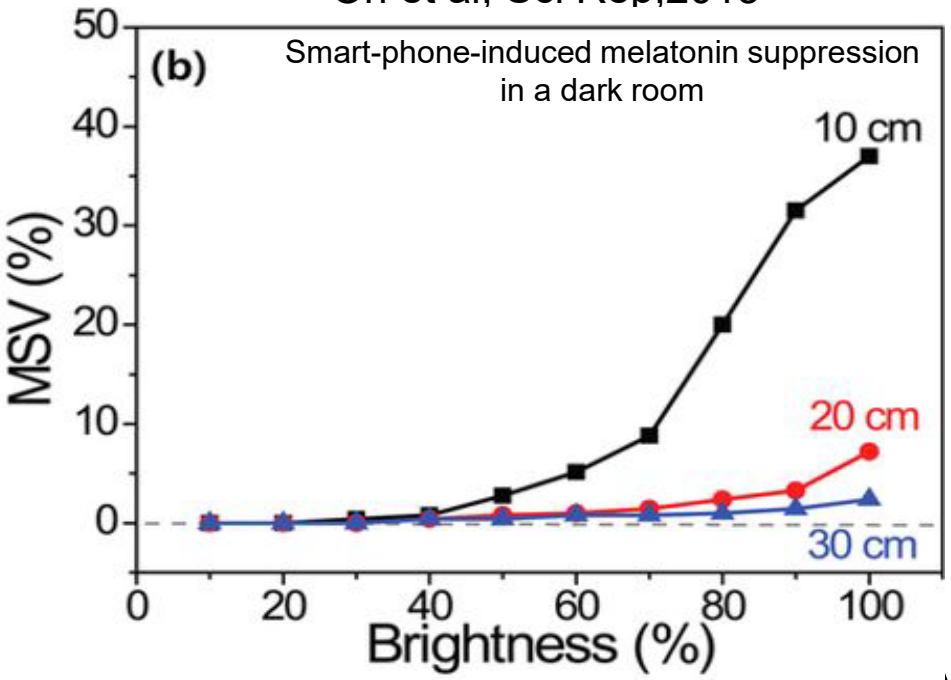
Prefix	Sensitivity	Angry Birds ipad	Angry birds phone
Cyanopic	S cone	244.44	63.03
Melanopic	Melanopsin	176.25	46.49
Rhodopic	Rod	180.07	45.04
Chloropic	M cone	174.03	41.96
Erythropic	L cone	162.66	39.72
Photopic lux	lux	170.42	40.32
Irradiance	μ W/cm^2	60.20	16.40
Photon flux	1/cm^2/s	1.61E+14	4.41E+13
Peak spectral irradiance	nm	445	450

Furthermore, relatively bright lights are needed to stimulate melanopsin

Are electronic devices bright enough?

- Smart phone viewing (Samsung Galaxy 5S in this case) has been shown to suppress melanopsin at night, **IF…**

Oh et al, Sci Rep,2015



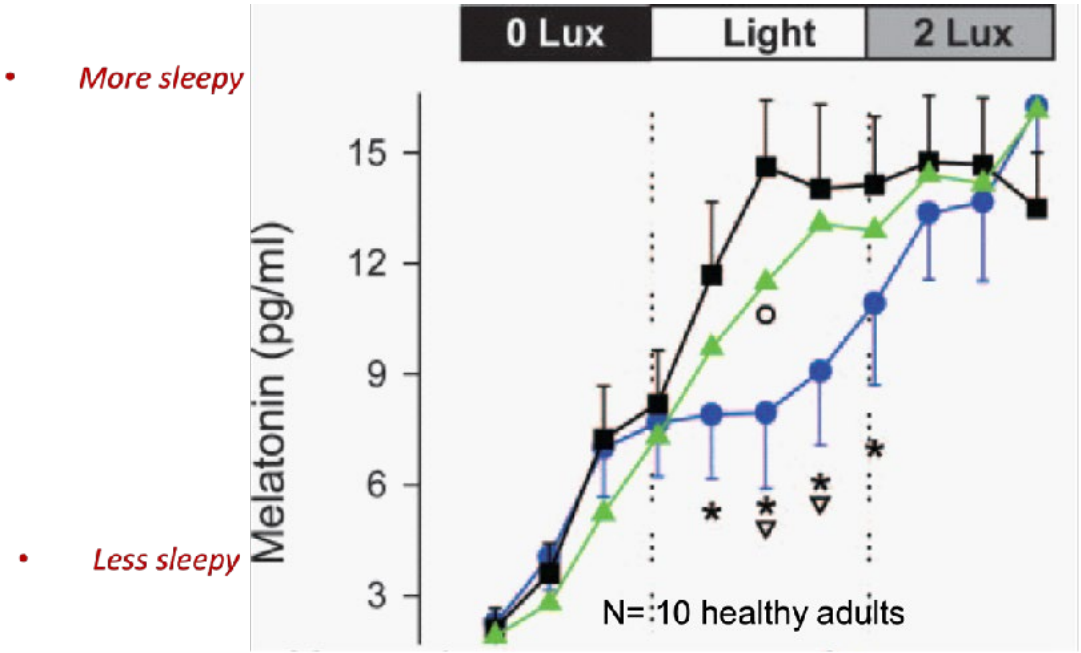
…the phone was held 10 cm away from the eye, the room was dark and the phone brightness was set at maximum

- Therefore, while ipRGCs are most sensitive to blue light
  - They DO NOT ONLY respond to blue light
  - The light needs to be bright enough to reach melanopsin threshold for the intrinsic response

- Taking these caveats into account, decreasing overall light exposure at night (dimming lights) is likely also an effective approach at improving sleep patterns
  - Reducing all light, not just blue light

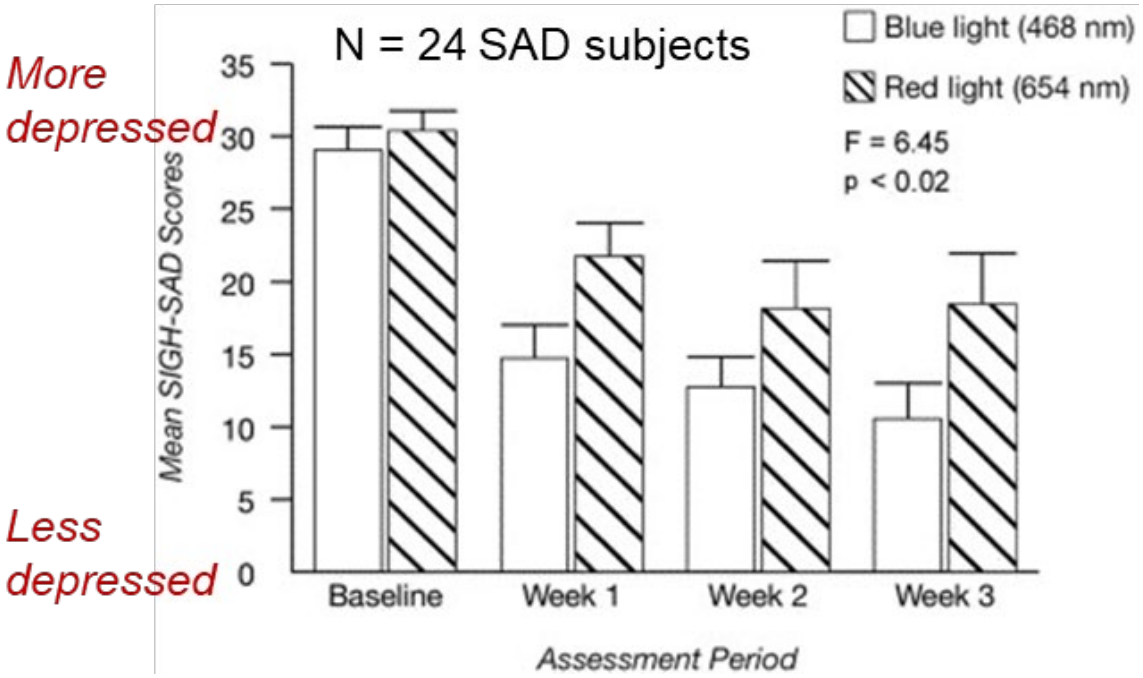
- Although blocking ipRGC stimulation in the evening could help to improve sleep patterns…there are also beneficial effects linked to ipRGC stimulation

- Sometimes, being sleepy in the evening is not desirable
- Blue light (460 nm), of similar brightness to a green light (550 nm) can increase evening alertness
  - Can be important for those that work late/night shifts



Cajochen et al, J Clin Endocrinol Metab,2005

- Blue light therapy given to patients with seasonal affective disorder (SAD) can improve mood more than comparable red light (Glickman et al., Biol Psych 2006)
  - 45 minute treatment every morning for 3 weeks
  - Note effect for red light versus baseline



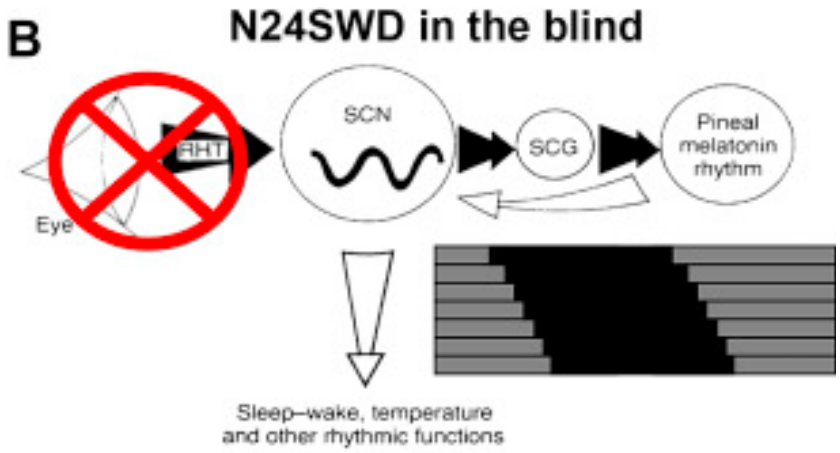
Consequences of Disrupted Circadian Rhythms

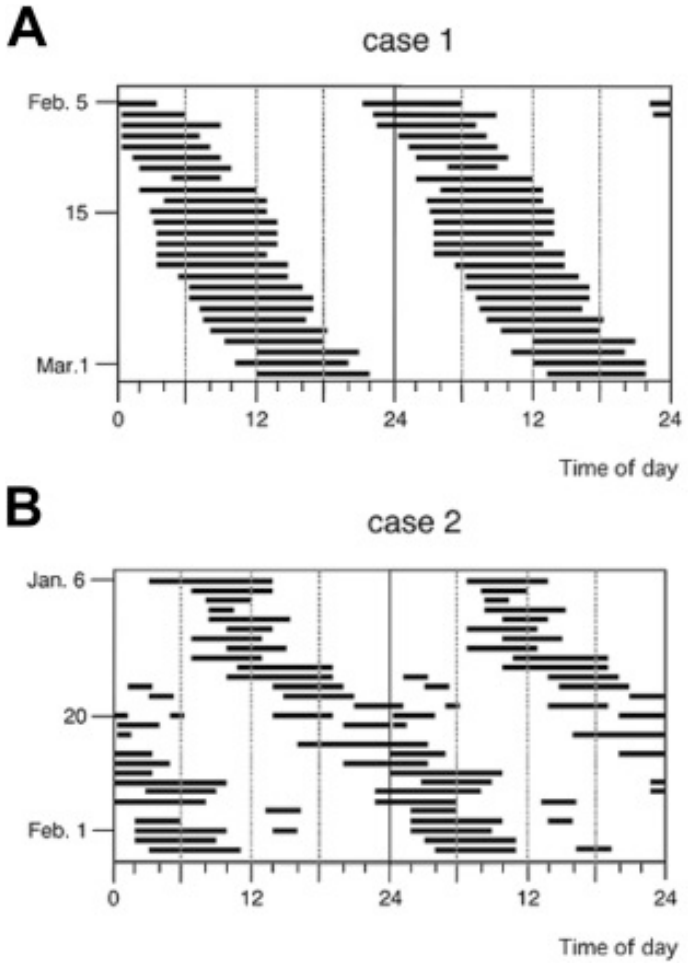
- While some symptoms can be mild and transient…
  - jet lag and shift work malaise

- …some conditions associated with altered circadian rhythms have serious and more chronic consequences
  - Sleep disorders and insomnia
  - Mood disorders, seasonal affective disorder (SAD)
  - Alzheimer's, Schizophrenia

- Non 24-Hour Sleep Wake Disorder in blind patients
  - if rod, cone and ipRGC signals all blocked from SCN (enucleation, bilateral optic neuropathy)

- In N24SWD, the SCN isn't getting input from the eye to synchronize clock so it 'free-runs' with period >24 h





Uchiyama & Lockley, Sleep Med Clin. 2015

On right graph of activity of two case patients with N24SWD

- As indoor lighting is much dimmer than sunlight, light boxes can be used to increase light exposure in the morning
- In addition to evening light avoidance, endogenous melatonin levels can be boosted with oral supplements
  - Can induce sleepiness in some people 1 to 3 hrs after dose
- Tasimelteon is a melatonin receptor agonist that FDA-approved for treatment of Non 24-hour Sleep Wake Disorder

- The premise of chronotherapy is to design dosing regimens for drug therapies that match the body's circadian rhythm of physiology

- "Utilize current treatments more effectively"

- Example: Blood pressure low at night and rises during the morning
  - Heart attacks occur most frequently in the morning
  - Thus, it has been proposed that treatments should strive to lower blood pressure more during the morning than night

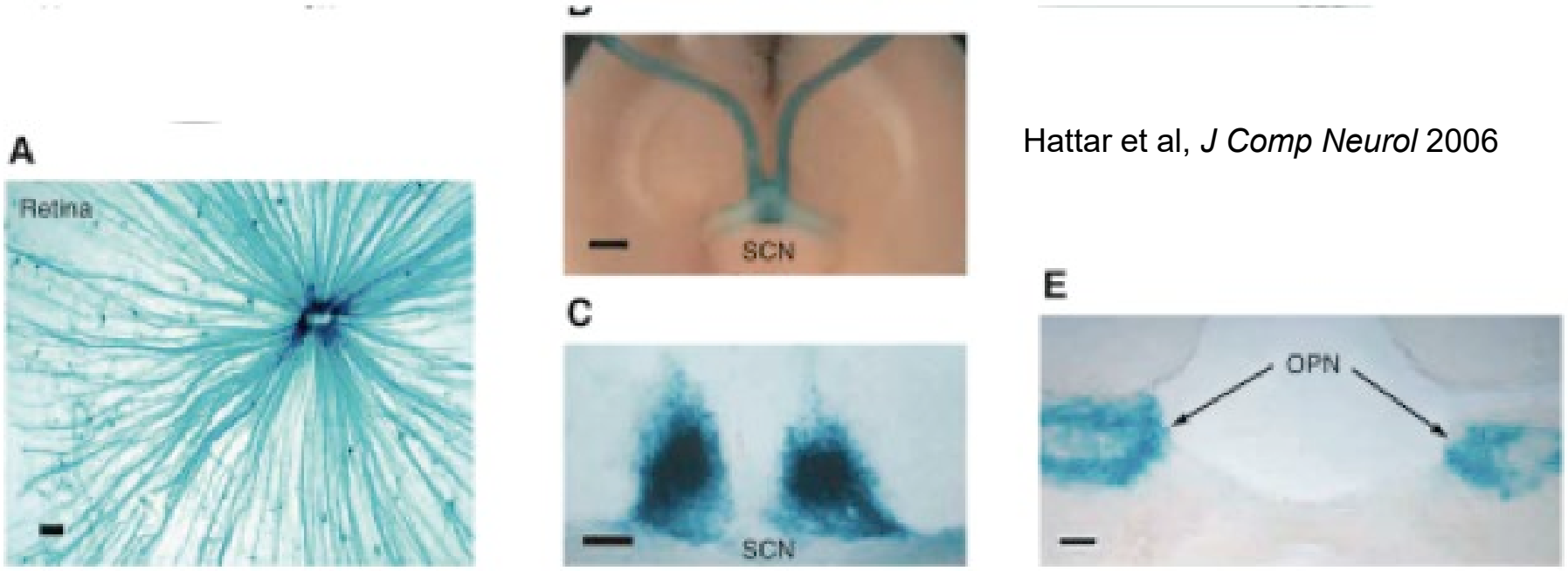
- The premise of chronotherapy is to design dosing regimens for drug therapies that match the body's circadian rhythm of physiology

- "Utilize current treatments more effectively"

- Similar logic could be applied to IOP lowering in glaucoma
  - Some evidence that latanoprost most effective when taken at night versus morning

    (Luu et al., *Clin Pharmacol Ther* 2010)

ipRGCs Project Heavily to Non-Visual Areas



Hattar et al, *J Comp Neurol* 2006

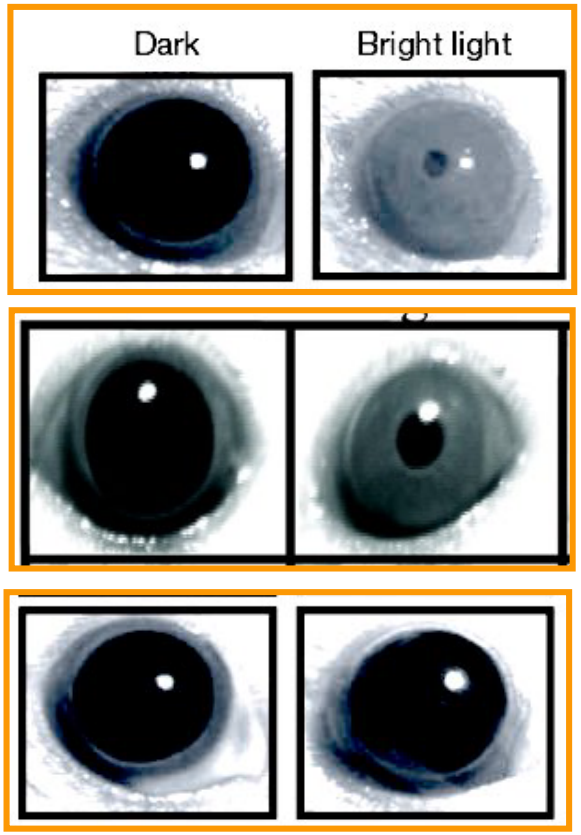
SCN – involved in circadian rhythm regulation

OPN – involved in pupillary light reflex

ipRGCs project to OPN pretectum and contribute to pupillary light reflex *in vivo*

Pupillary Light Reflex

- Redundancy in the PLR circuit
  - Either rods/cones OR ipRGCs can mediate pupil reflexes



Normal mice or mice with rod/cone function knocked out

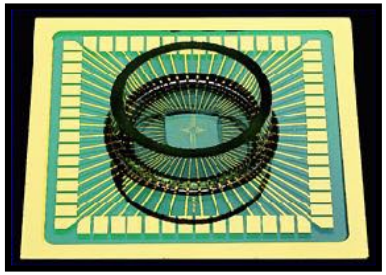
Melanopsin knocked out; rod & cone function unaltered

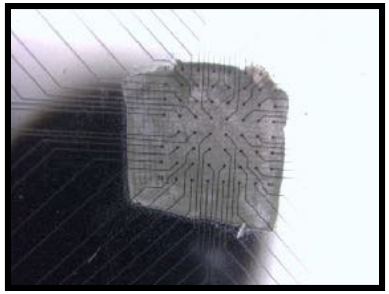
Melanopsin knocked out; rod & cone function knocked out

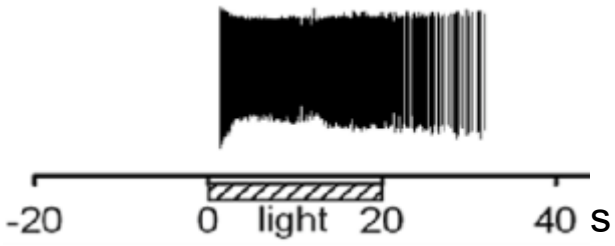
From Lucas et al, 2003; Hattar et al 2003

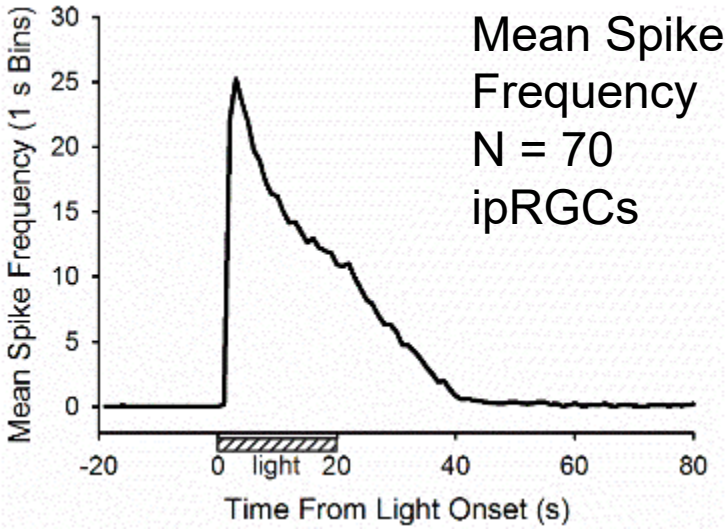
ipRGCs Respond Sluggishly to Light

- ipRGCs exhibit prolonged light responses that persists post-light offset – spiking gradually slows until stopping









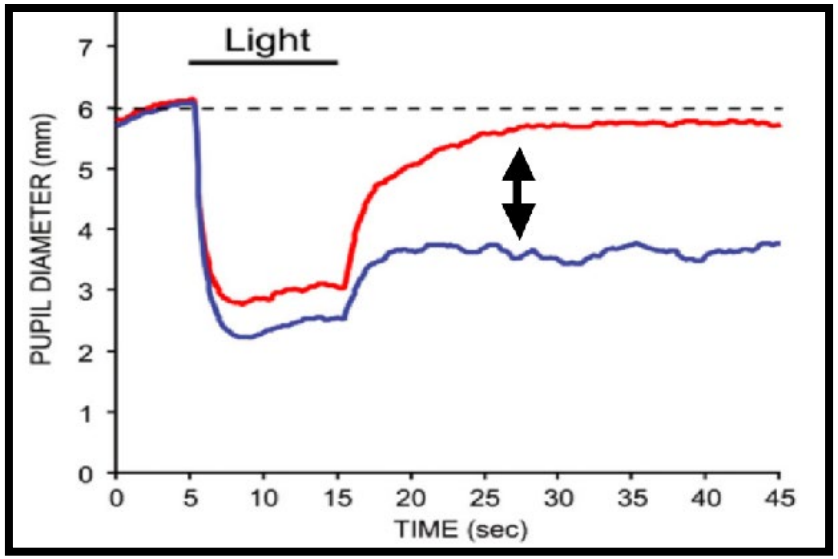
- So, ipRGCs have much worse temporal resolution compared to rods and cones

Sodhi & Hartwick, 2014

ipRGC Contribution to Human Pupil Responses

- In humans, pupil-redilation is longer with blue light stimulation versus red light stimulation – consistent with contribution from sluggish ipRGCs to blue light response

- By blocking rod/cone signaling pharmacologically, Gamlin et al. (2007) showed post-illumination pupil response (PIPR) in primates is melanopsin-mediated



Summary

- Although we seem to live in a 24-hour society, our behavior and physiology, like all animals, exhibits daily rhythms that are generated internally
- The central clock that regulates the timing of these rhythms is located in the suprachiasmatic nucleus in the hypothalamus
- ipRGCs, which are most sensitive to blue light, signal information about ambient light levels to the SCN and play a major role in synchronizing circadian and sleep/wake rhythms
- Understanding biological clocks and associated rhythms can have medical implications in regards to human health and the treatment of certain diseases

- In the future, I believe a bigger role is possible for optometrists in the diagnosis and treatment of disorders that disrupt ‘irradiance detection’ by the eye

- Important to recognize that eye disease could disrupt both pattern vision and irradiance detection in some patients