

 The Association  
for Science Education

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# ASE ANNUAL CONFERENCE

# 2-5 JANUARY 2013

## Light, body clocks and sleep - SE13

Friday 4th January 2013

10:15 - 11:00

Location: Palmer, 109

**Russell G. Foster FRS**

Professor of Circadian Neuroscience

Head, Nuffield Laboratory of Ophthalmology

Fellow, Brasenose College

E-mail: [russell.foster@eye.ox.ac.uk](mailto:russell.foster@eye.ox.ac.uk)



## Biology in the real world: Light, body clocks and sleep

- Introduction – The Body Clock
- Light Regulation of The Body Clock
- Time of Day Effects
- Disruption of the Body Clock
- Discussion



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- **Introduction – The Body Clock**
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24h body clocks  
(circadian clocks) and  
sleep processes have  
captured the popular  
imagination.....

**Sometimes...**  
**not always**  
**helpful!**

# Your LIFE

# Time to set your body clock

NATURAL RHYTHMS RULE OUR BODIES AND DICTATE THE BEST TIMES FOR A RANGE OF ACTIVITIES. HERE'S OUR COUNTDOWN!  
BY BETH GIBSON

### 6AM HAVE SEX

It's good news for early birds. "Sex hormones build up overnight, so this is the optimum time to have sex as oestrogen and testosterone levels are at their highest," says Anita Naik, author of *The Lazy Girl's Guide To Good Sex* (Piatkus 799).



### 7.30AM MOISTURISE YOUR SKIN

SKIN gets dehydrated overnight, so moisturise your body in the morning, preferably after a bath or shower when open pores increase absorption.

### 8AM POP A PILL

RESEARCH has shown that women who take the contraceptive pill in the morning are 10 times less likely to forget it.

### 8.30AM TAKE YOUR VITAMINS

THE digestive system works at its peak early in the morning, so by taking your vitamins now the nutrients will be better absorbed.

### 10AM HAVE A BIKINI WAX

OR an injection, or a visit to the dentist – basically, anything with an "ouch" factor. "Pain intensity is at its lowest between 8 and 10am," says Professor Russell

Foster, co-author of *Rhythms of Life* (Profile Books, £5.99). "It's not entirely clear why, but it's probably because pain receptors aren't as alert as they are later in the day."

### 12NOON GIVE A PRESENTATION

INCREASED adrenaline levels help you deal with stressful situations, such as giving a talk. Your voice is also well rested but warmed up, so will sound its best around now.

### 1PM HAVE LUNCH

DON'T be tempted by a late lunch. People buy more high-fat, sugary food between 2 and 3pm because they've missed their body's natural eating slot of 1pm.

### 1.30PM USE YOUR LOAF

LOGICAL reasoning, alertness and short-term memory are at their best at this time, so now's the time to concentrate, negotiate or problem-solve. "The power lunch is a great time to make deals because your mind is at its sharpest," says Professor Foster.

### 2.30PM TAKE IT EASY

"THERE'S a drop in our ability to perform numerical and mind-intensive tasks come the afternoon, regardless of whether we've had anything to eat or drink," says

### AND THE WORST TIME TO...

- DO something painful, such as plucking your eyebrows is after 8pm, as this is when we feel pain most acutely.
- HAVE a big meal is late at night. The later you eat, the more likely you are to gain weight.
- START a car journey is between 4-5am as mental performance is at its worst. Night workers have most accidents at this time.
- EXERCISE is first thing in the morning. The stress hormone cortisol, which can damage the immune system, is at its highest between 6am and 8am. Ah, the perfect excuse for a lie-in...

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THE quality and quantity of men's sperm peaks during this time – it's 35 per cent higher than in the morning. Women are most likely to ovulate between 3pm-7pm, thus making it the perfect time for baby-making.



### 7PM TAKE AN EVENING CLASS

"BETWEEN 6-8pm we get our second wave of alertness and brain-power," says Professor Foster. "Our ability to reason and perform complex tasks is almost as good now as during the morning, so it's an excellent time to do an evening class."

### 8PM HAVE A DRINK

ENZYMES in the liver responsible for breaking down alcohol are at their most effective around now. Make sure you're home from the pub by 10pm though, as your body's ability to cope with booze drops dramatically after that.

### 9.30PM HAVE SEX (AGAIN)

SKIN is at its most sensitive at this time, so if you slept through your 6am alarm call – or even if you didn't – now is the perfect time to catch up on caresses.

### 10PM GO TO SLEEP

RESEARCH by the Body Rhythms Centre found that people who go to bed at 10pm are more alert the following day. "Your body temperature starts to drop around now and your metabolism and heart rate also slow, preparing the body for sleep," says Professor Horne.

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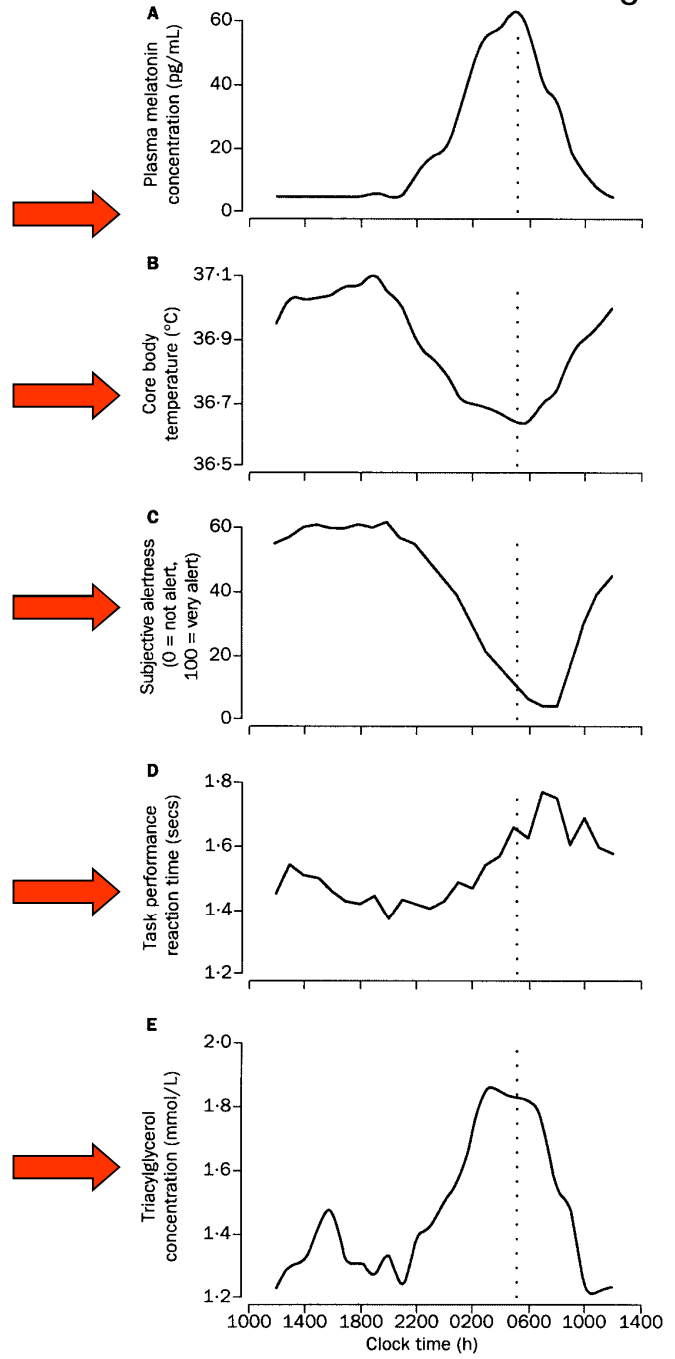
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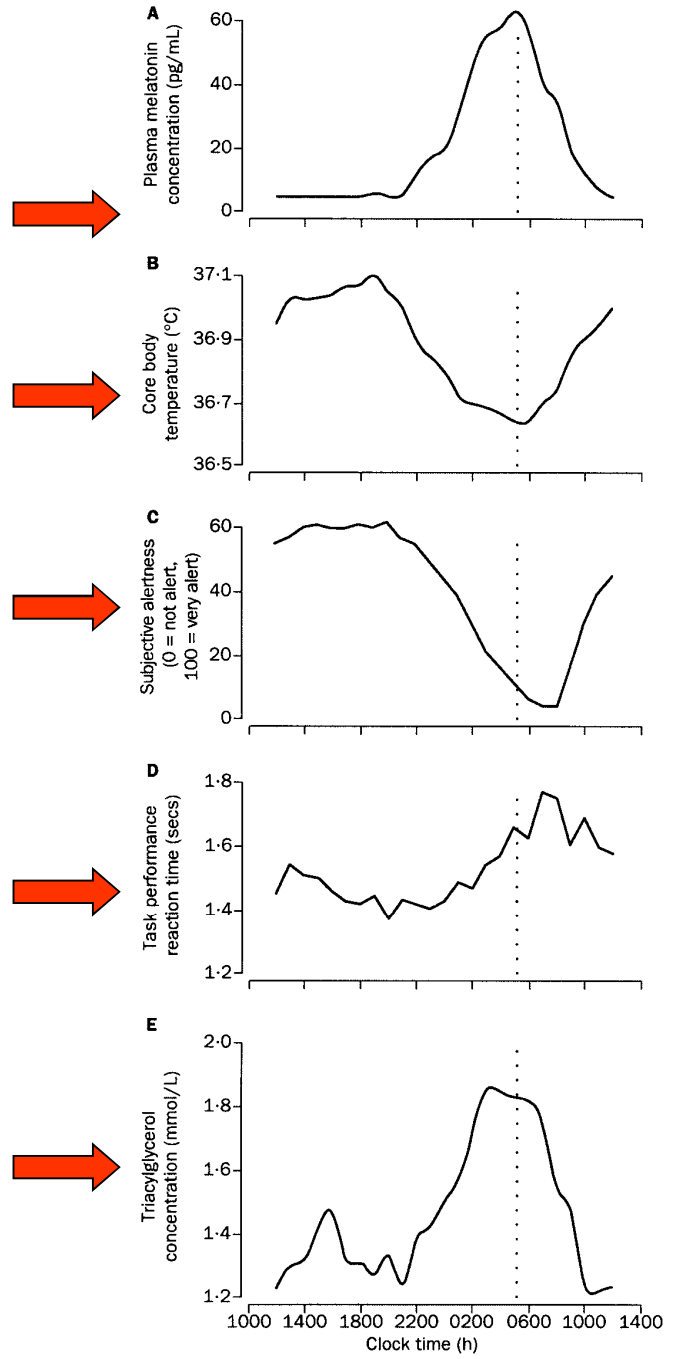
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<i>Rhythmic Changes in Human Physiology and Behaviour</i>	DAY	NIGHT
MELATONIN	LOW	HIGH
BODY TEMPERATURE	HIGH	LOW
ALERTNESS AND COGNITIVE PERFORMANCE	HIGH	LOW
LAPSES IN ATTENTION	LOW	HIGH
CAPACITY TO DIGEST FAT	HIGH	LOW

Base-line Changes

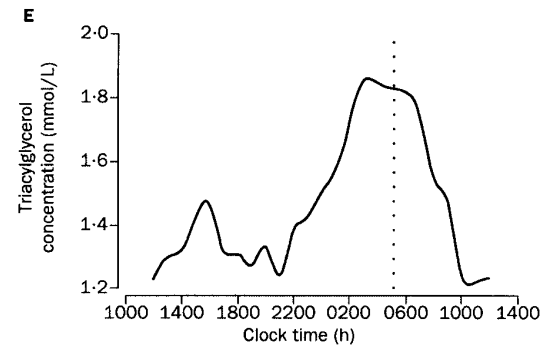
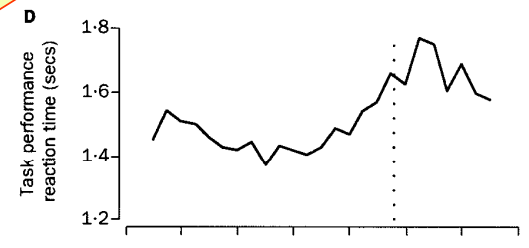
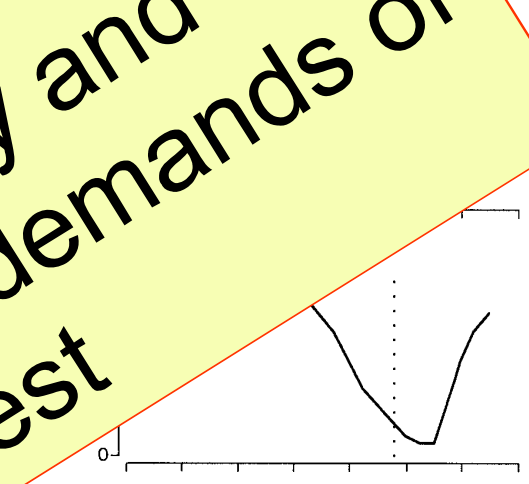


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CORTISOL	HIGH	LOW
BODY TEMPERATURE	HIGH	LOW
GROWTH HORMONE	LOW	HIGH
ALERTNESS AND COGNITIVE PERFORMANCE	HIGH	LOW
CATECHOLAMINES	HIGH	LOW
URINE PRODUCTION	HIGH	LOW
LAPSES IN ATTENTION	LOW	HIGH
SLEEP	LOW	HIGH
MEMORY RECALL	HIGH	LOW
CAPACITY TO DIGEST FAT	HIGH	LOW
MUSCULAR STRENGTH	HIGH	LOW

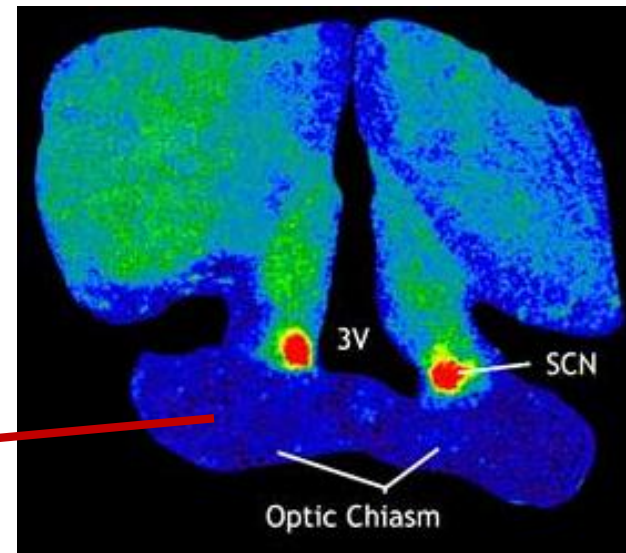
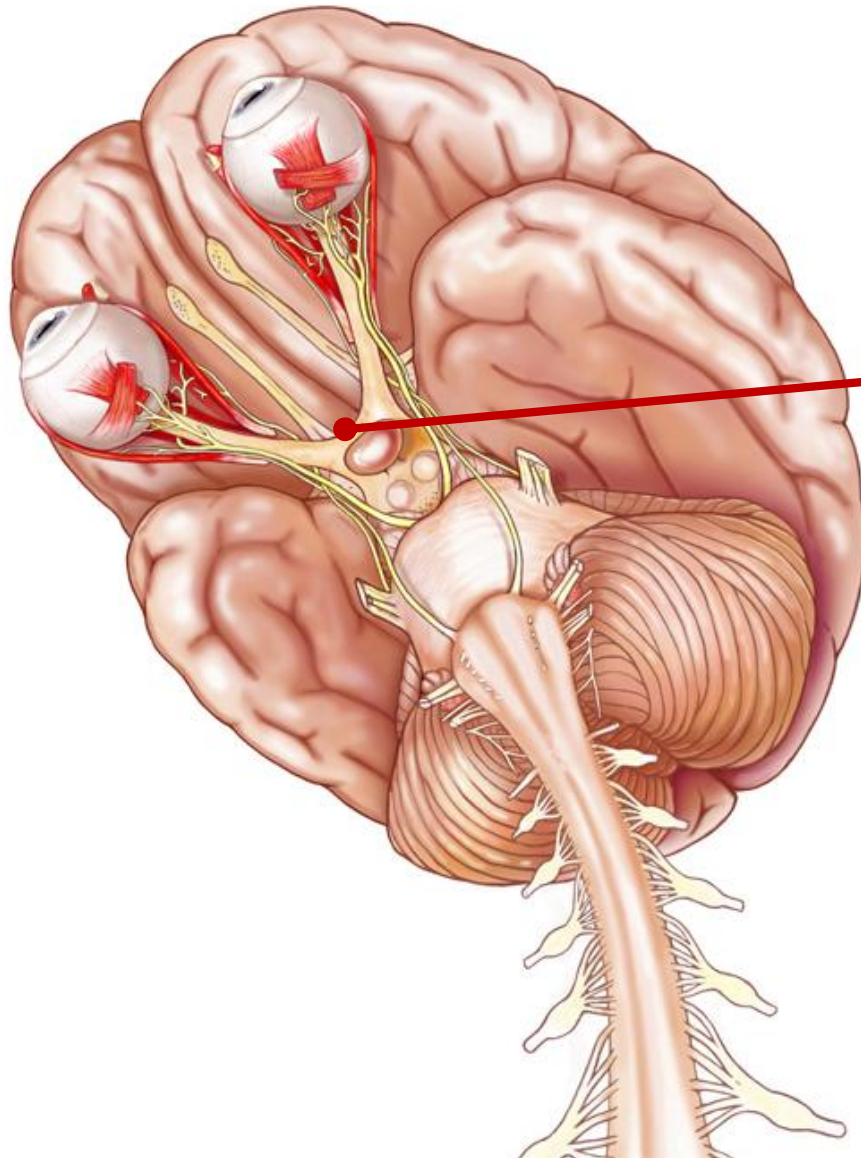


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PERFORMANCE		HIGH	LOW
CATEGORIES			
			HIGH
		HIGH	LOW
	FAT	HIGH	LOW
MUSCLE STRENGTH		HIGH	LOW

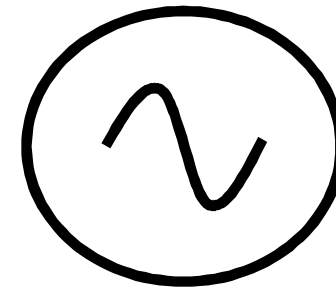
Our biology is highly dynamic and “fine-tunes” physiology and behaviour to the varying demands of activity and rest



# The Circadian System

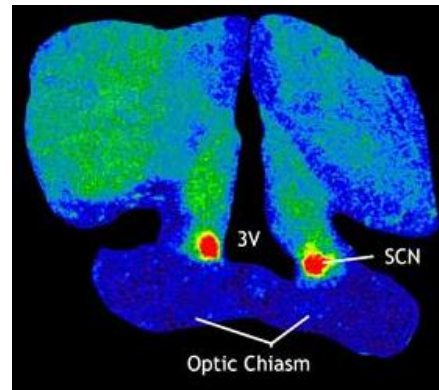


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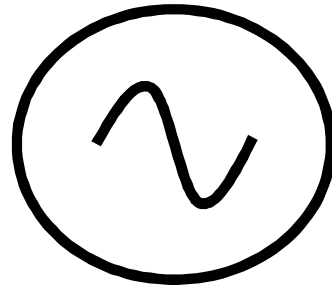


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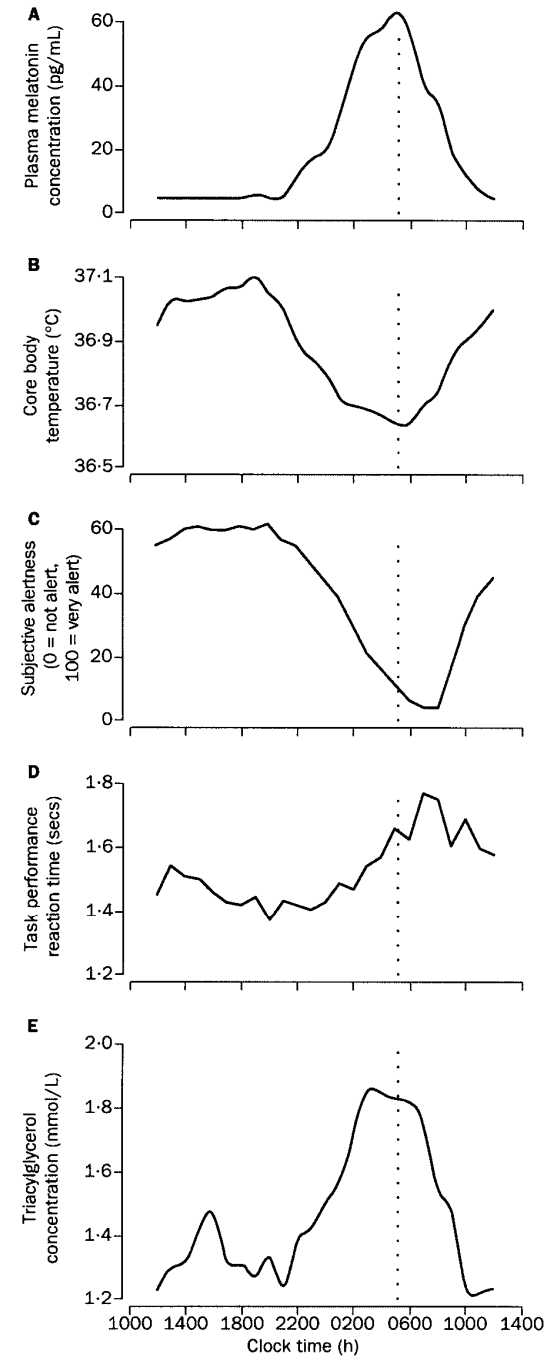
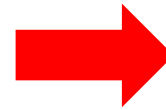
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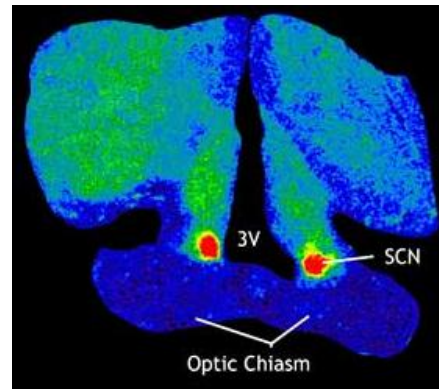
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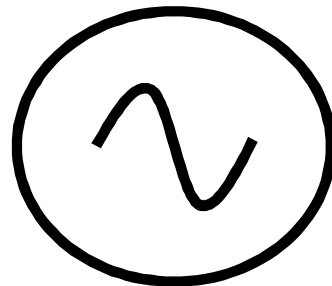
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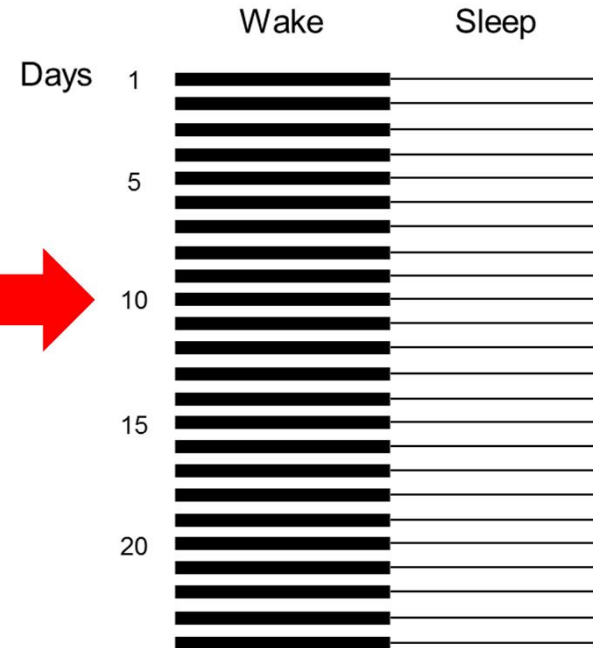


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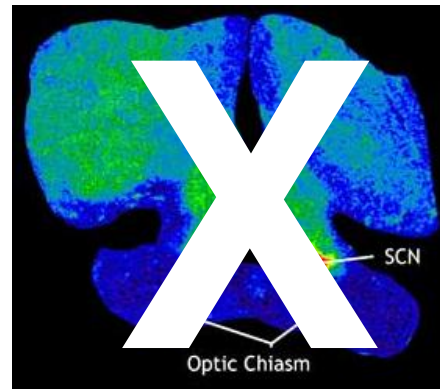
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## Actogram

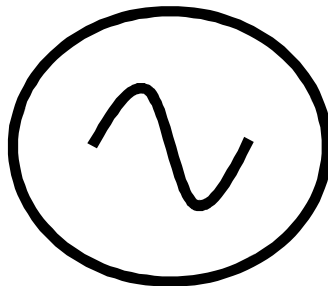


**Rhythmic  
24h**

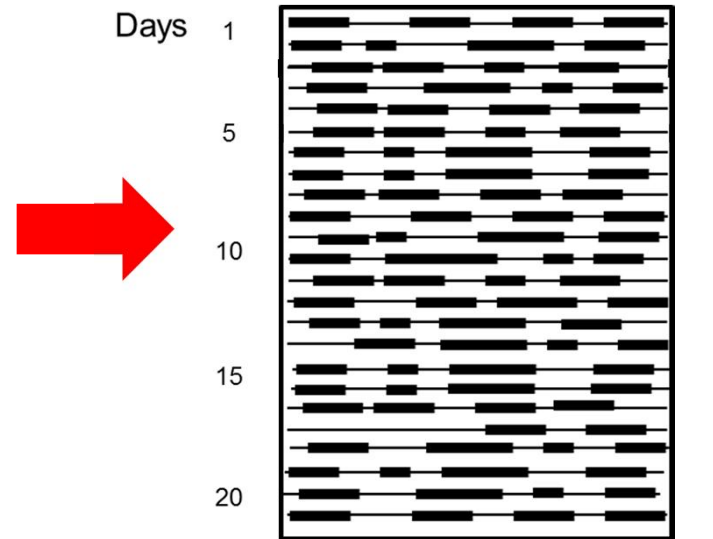
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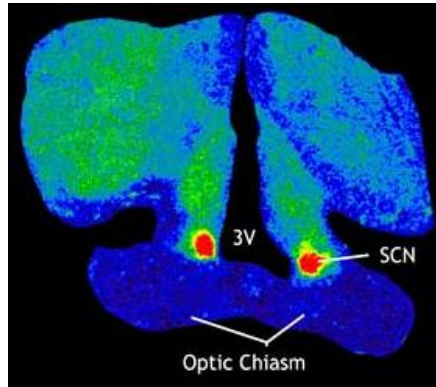
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Arrhythmic Non-24h



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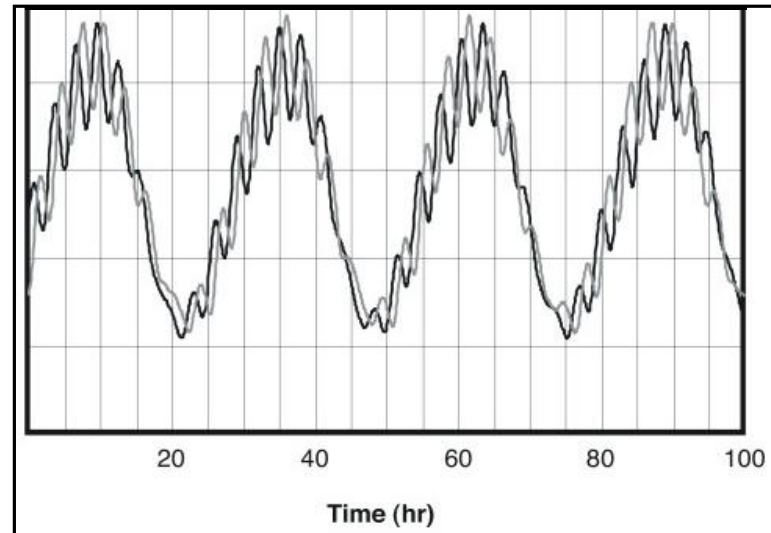


**The clock must be the product of subcellular processes!**

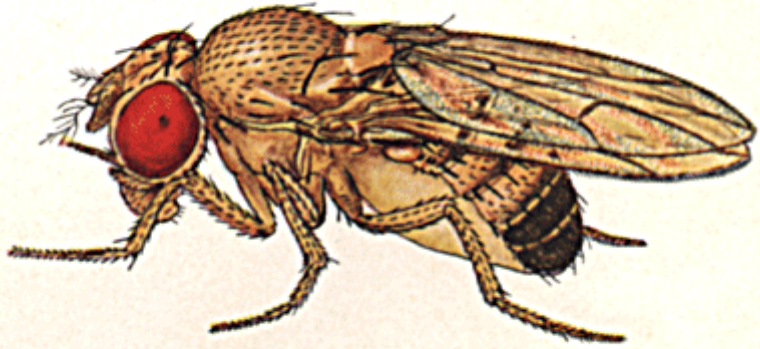
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Suprachiasmatic Nuclei

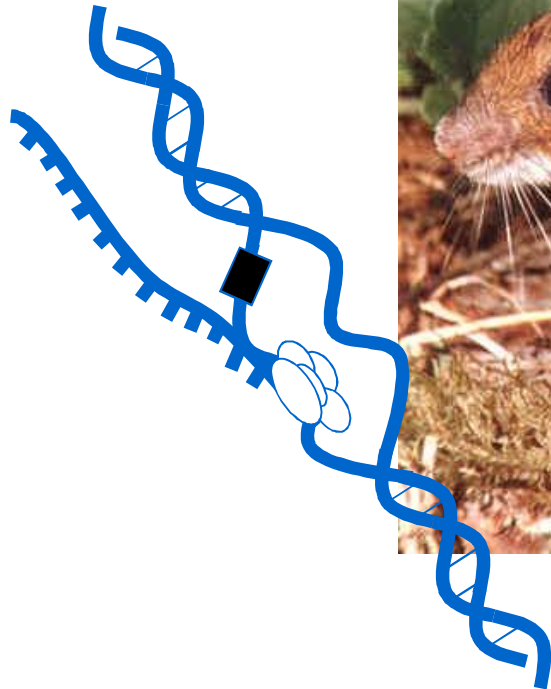
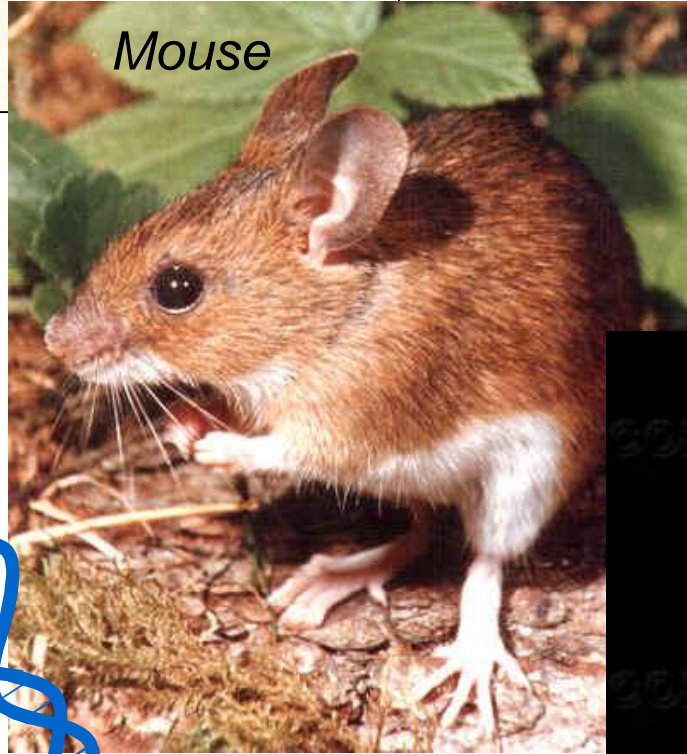


*Drosophila*

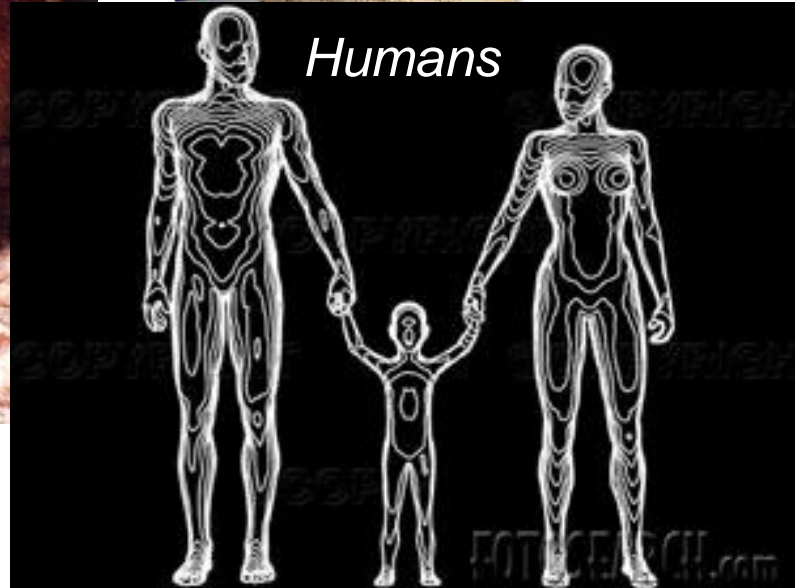


Genome Analysis - the basic building blocks of the molecular clock are conserved between all animals!

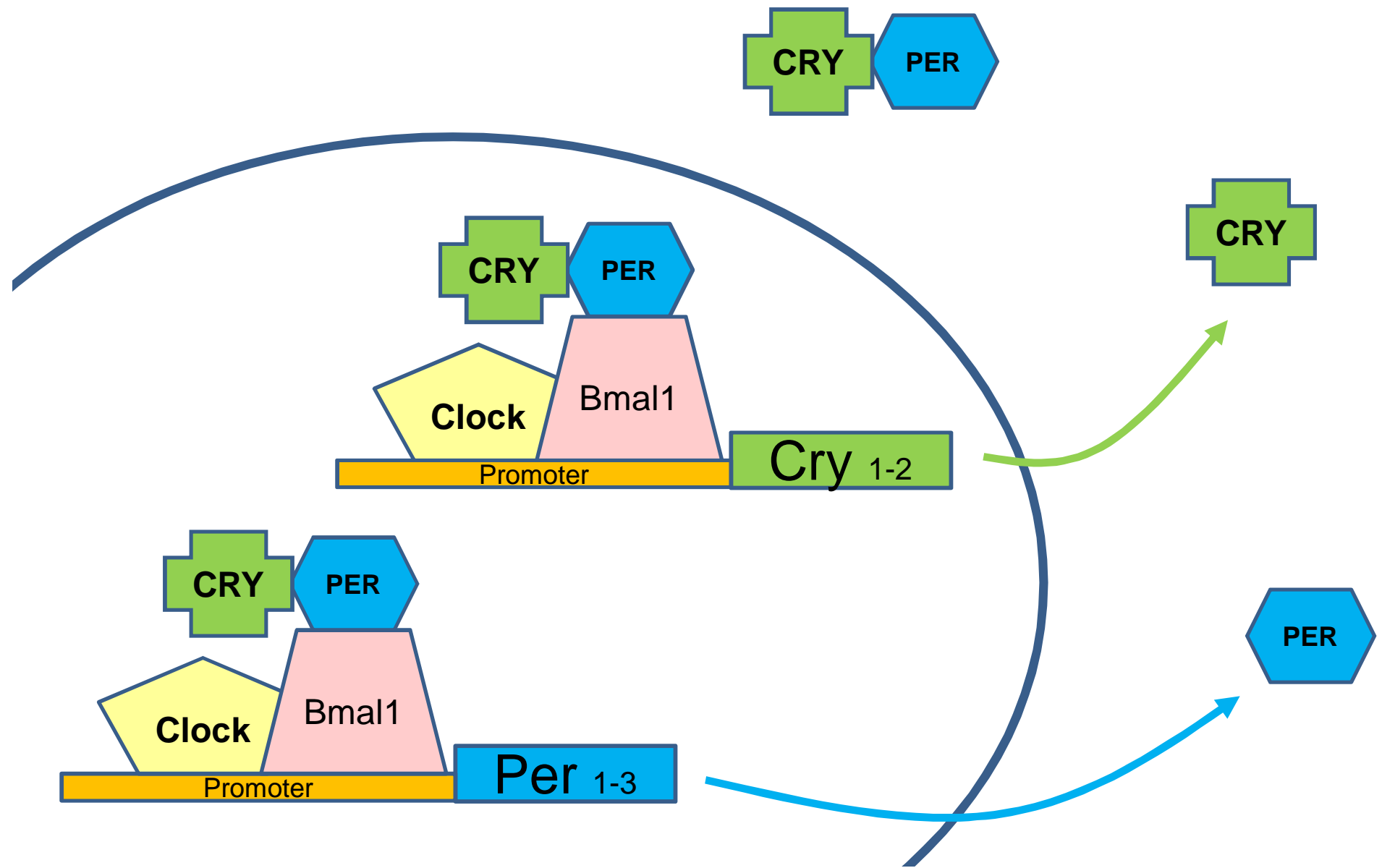
*Mouse*



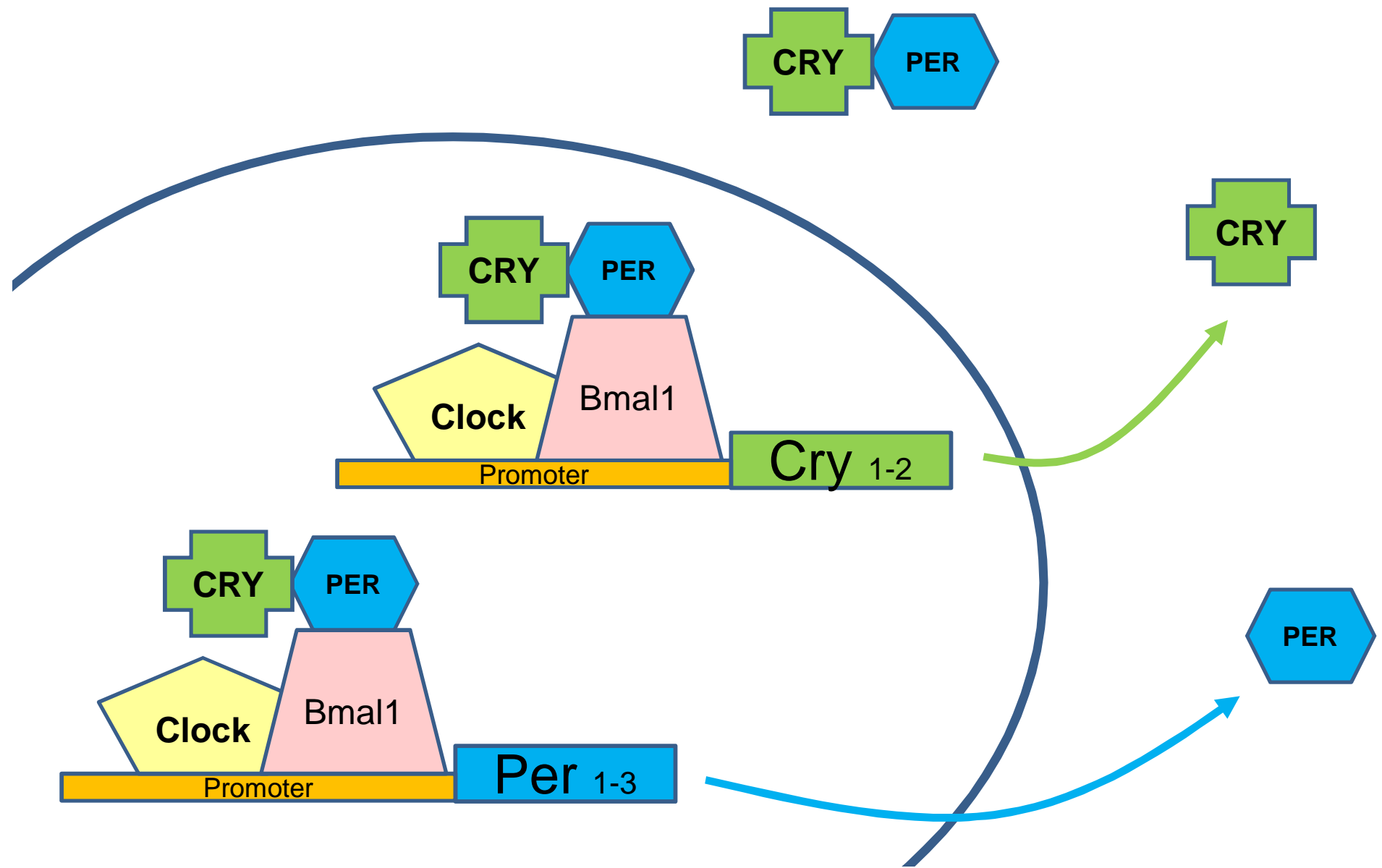
*Humans*



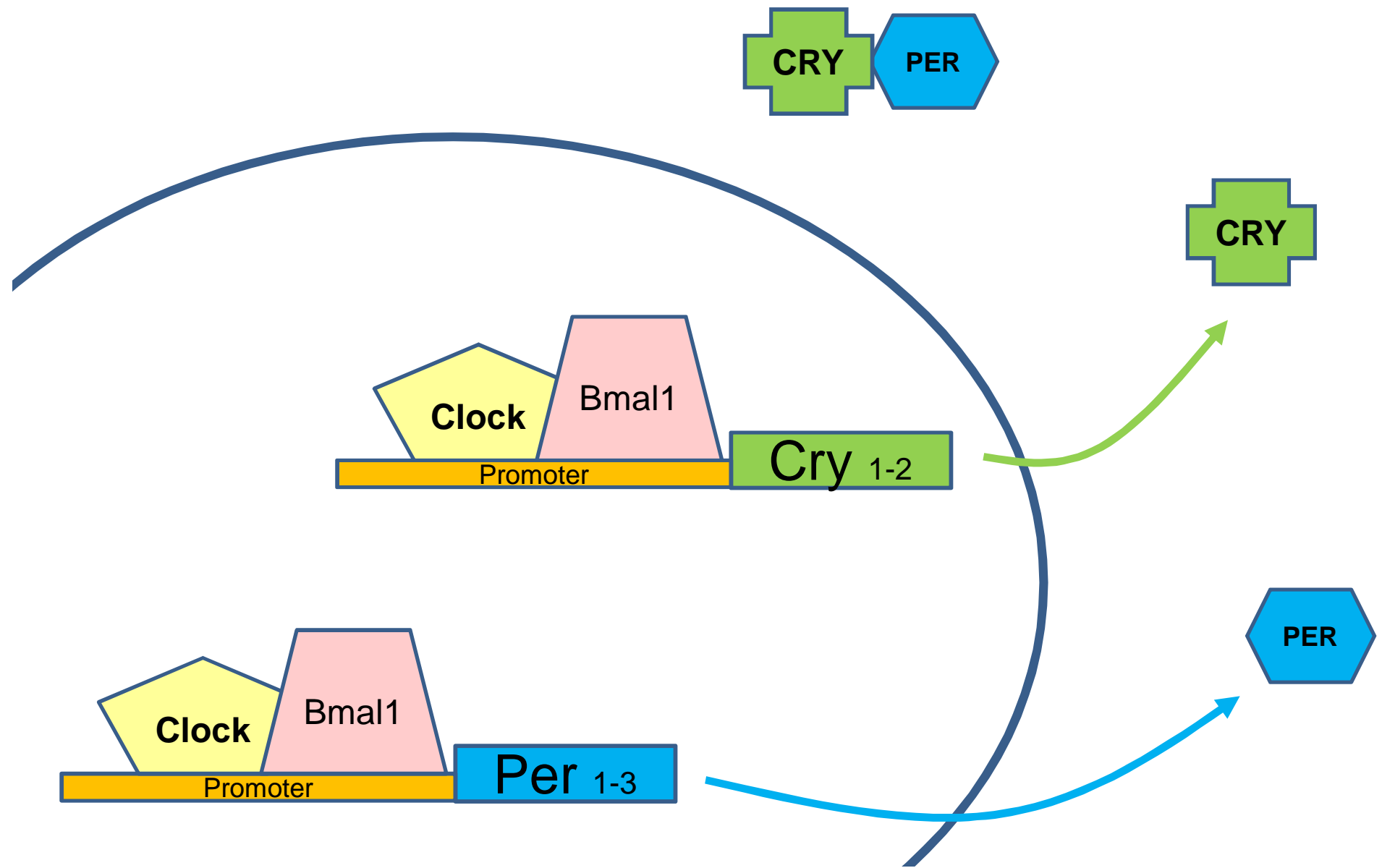
# Molecular Feedback Loop



# Molecular Feedback Loop

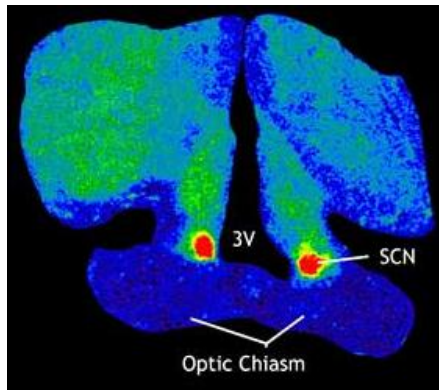


# Molecular Feedback Loop

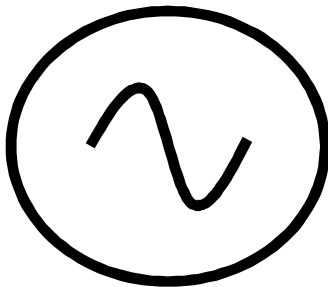


**Circadian  
rhythms don't  
just involve the  
SCN**

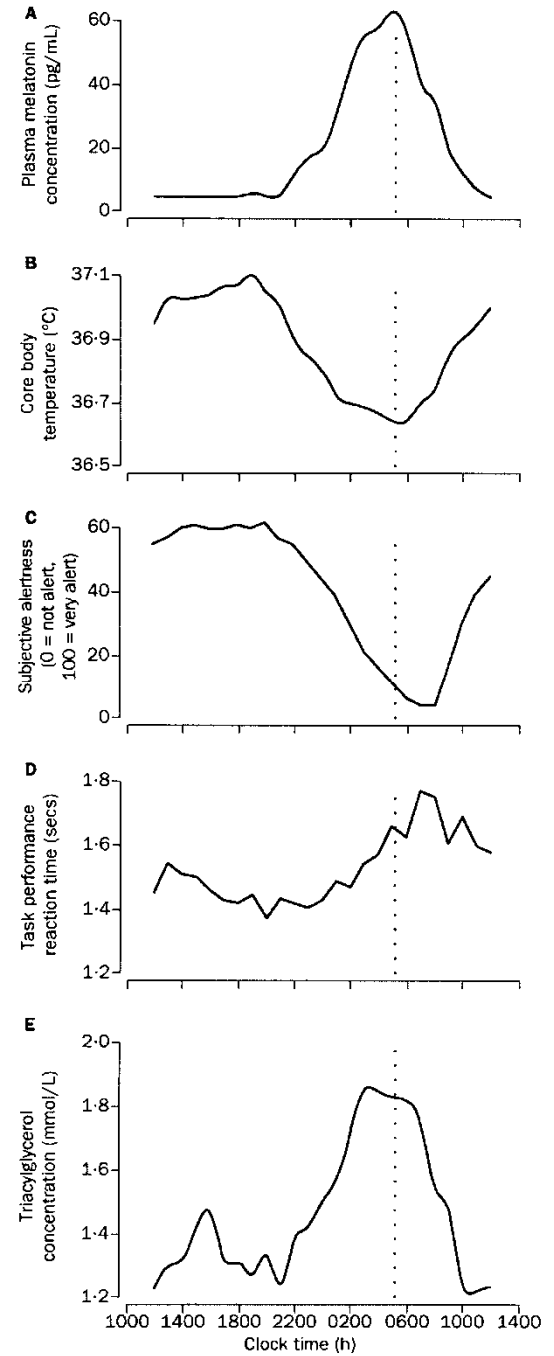
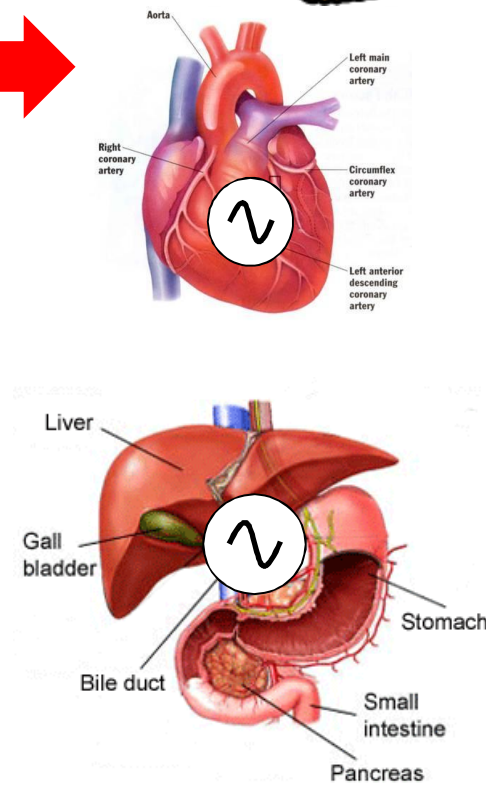
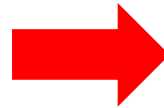
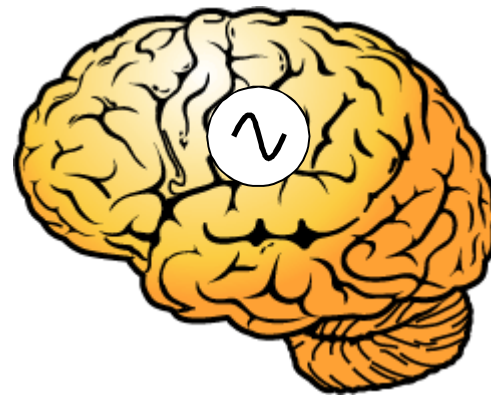
# The Circadian System



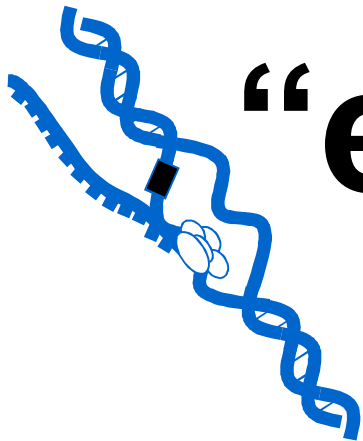
SCN



Suprachiasmatic Nuclei



**Changes in clock  
genes are being  
linked to particular  
“morning” and  
“evening” sleep  
types**

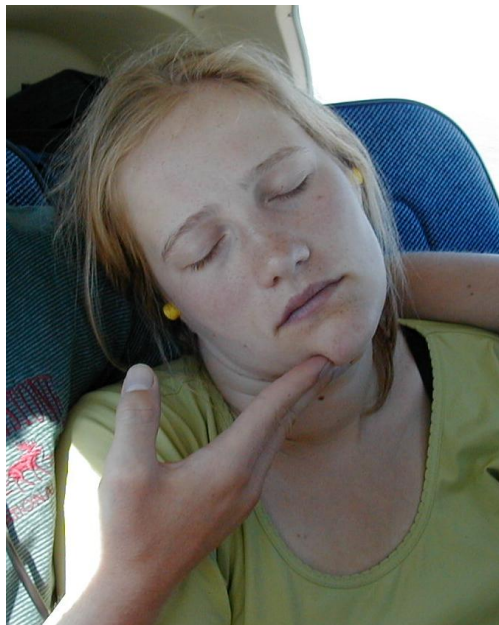




**Perhaps the  
best example  
so far:**

# ***Familial Advanced Sleep Phase Syndrome (FASPS)***

**Grandmother, Daughter,  
Granddaughter:**



# ***Familial Advanced Sleep Phase Syndrome (FASPS)***

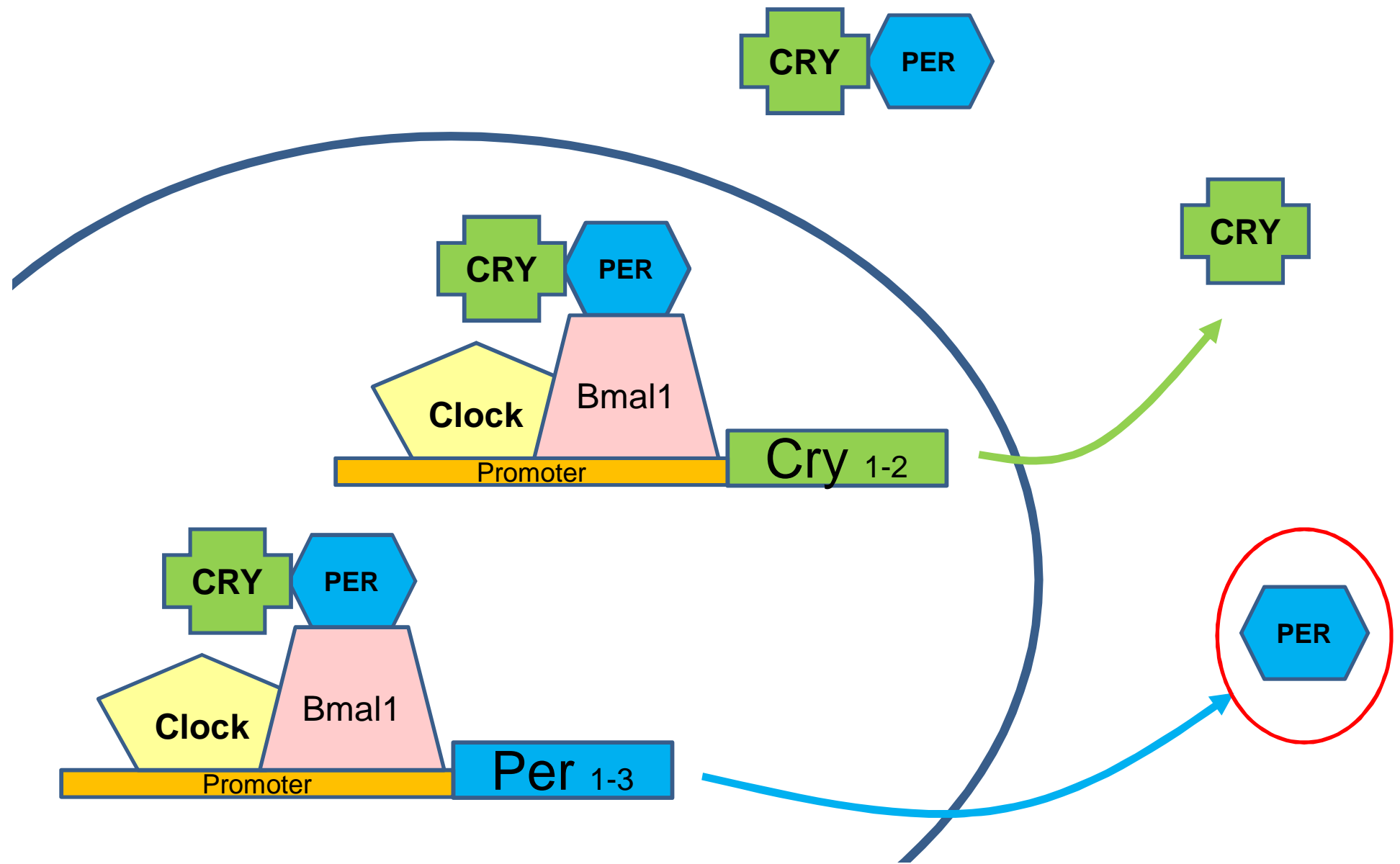
**Grandmother, Daughter,  
Granddaughter:**



**Fall Asleep ~ 19:30**

**Wake ~ 03:30**

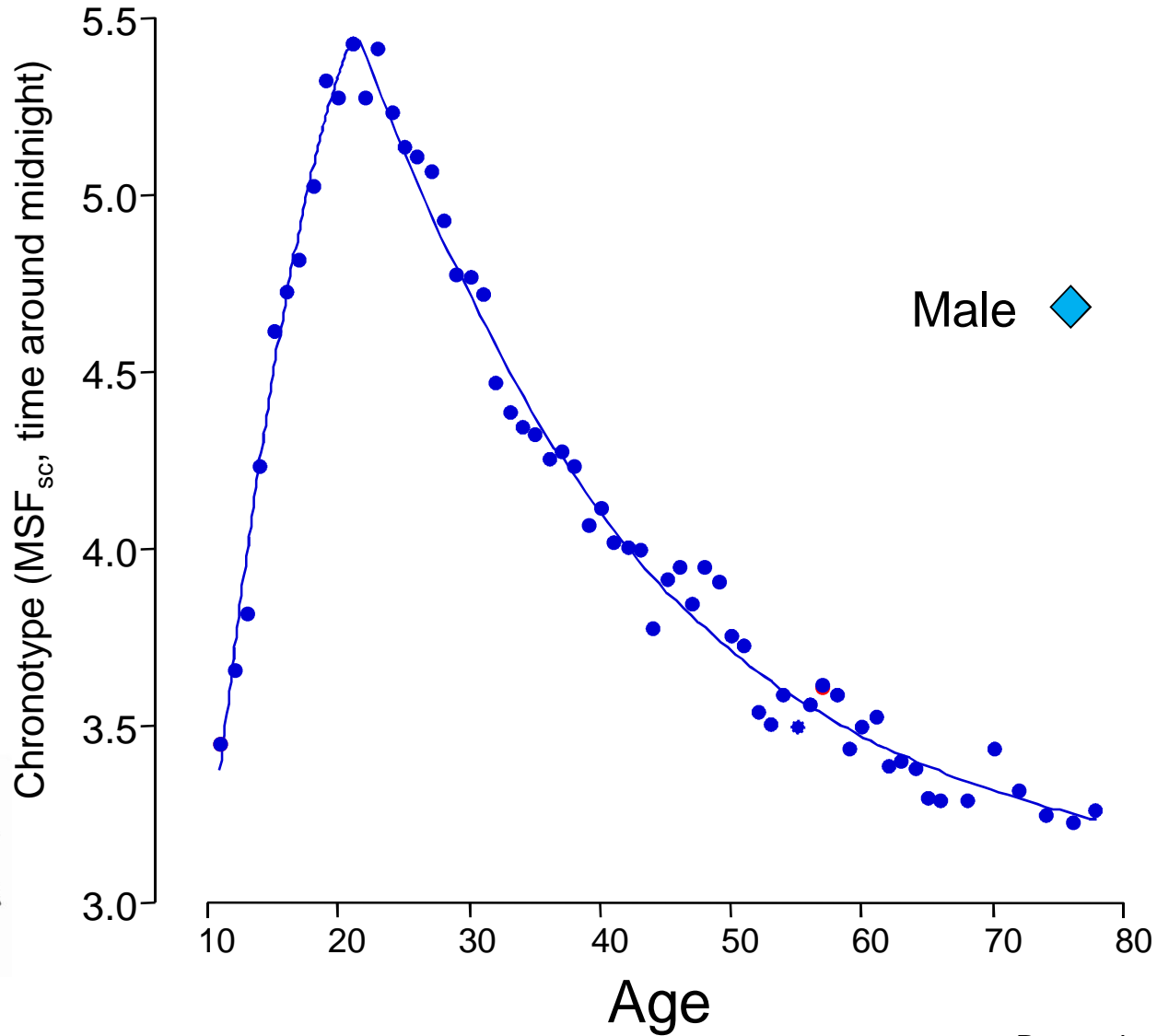
# Molecular Feedback Loop



**Not just genes that  
drive “morning”  
and “evening”  
types – hormones  
too!**

# Morning vs Evening Preference changes with age

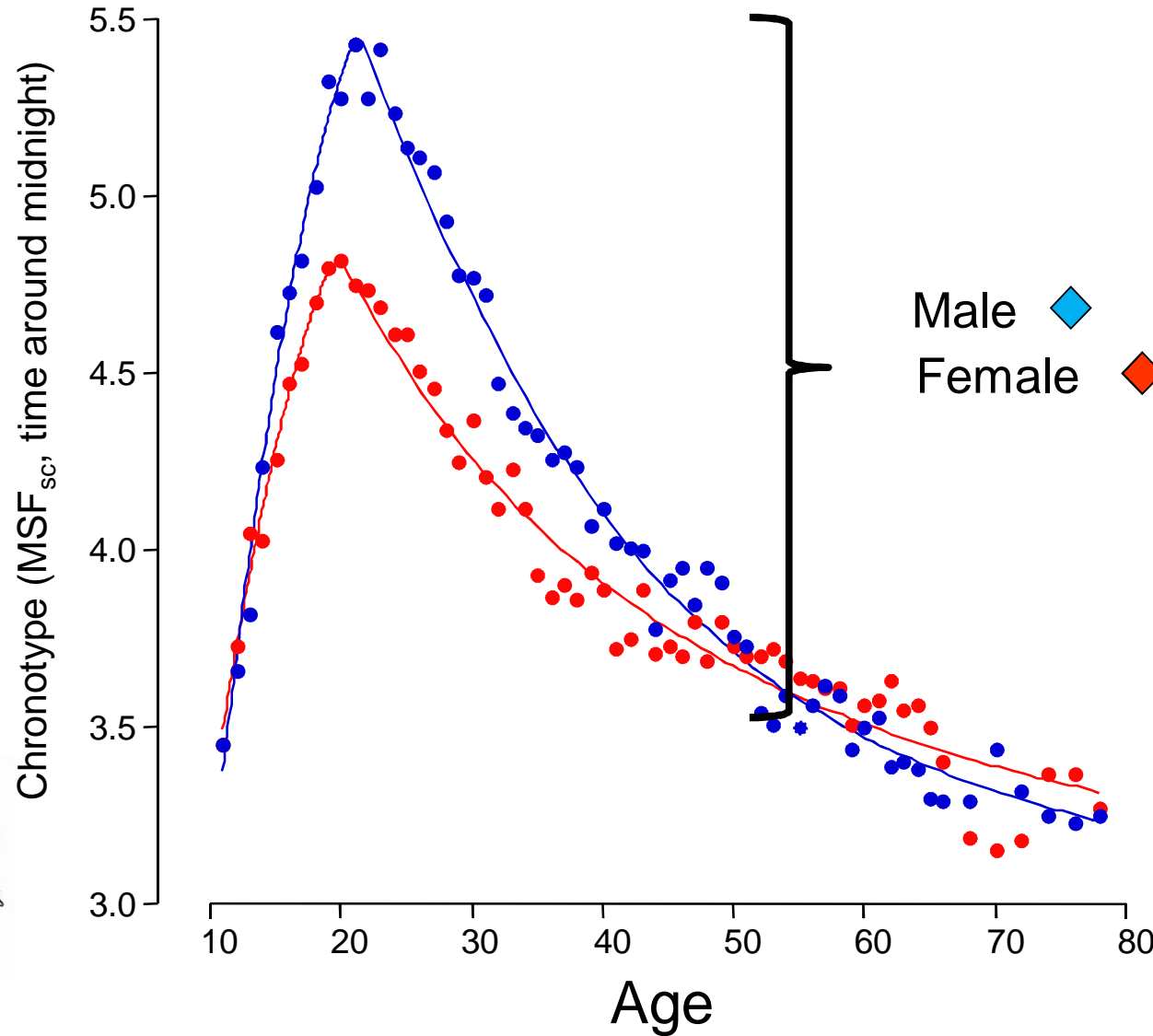
Evening



Morning

# Morning vs Evening Preference changes with age

Evening



Morning

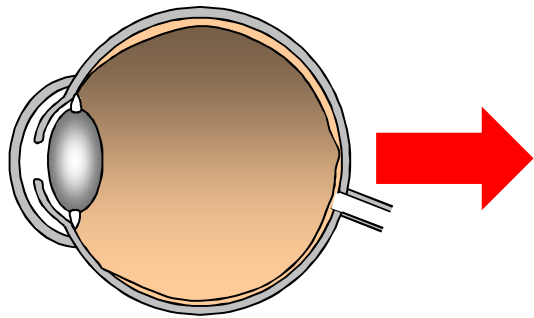
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- Disruption of the Body Clock
- Discussion

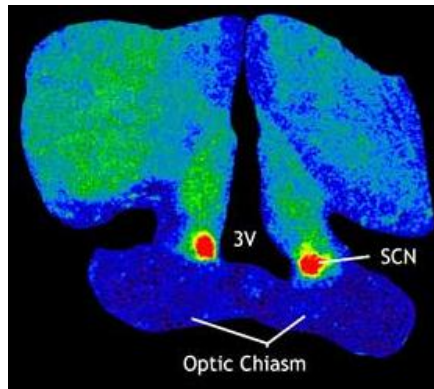




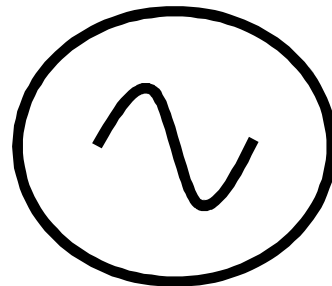
# The Circadian System



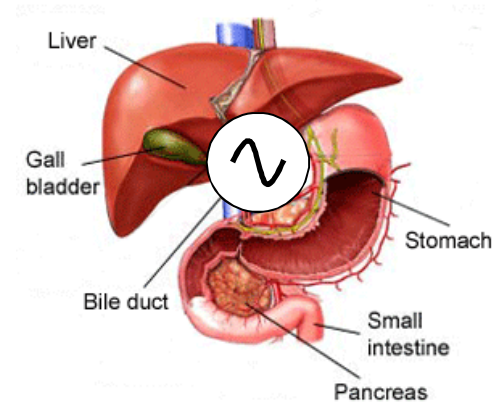
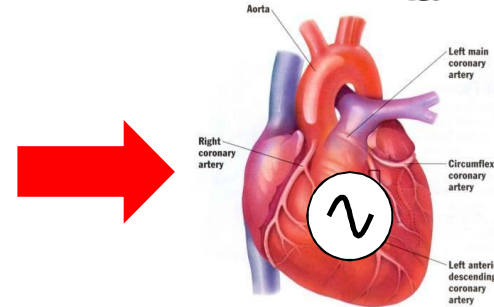
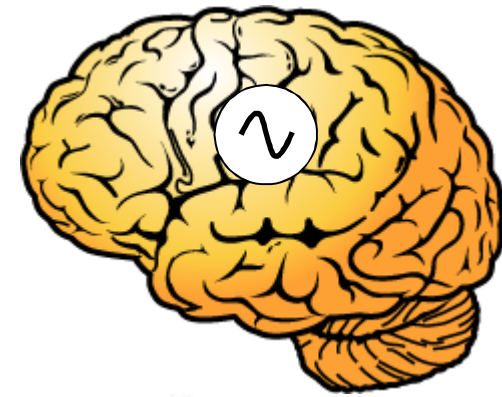
Eye



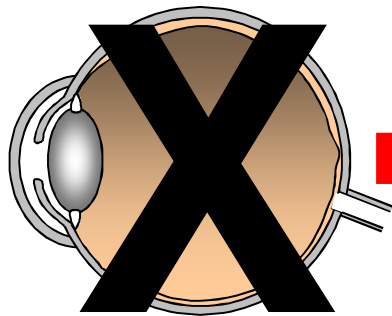
SCN



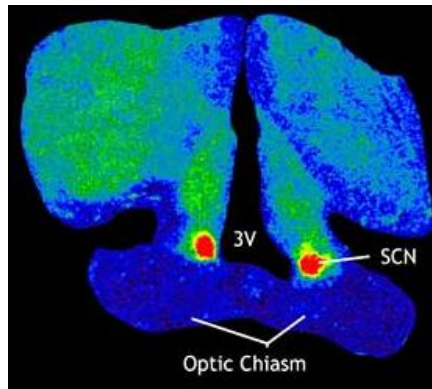
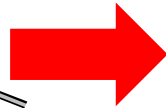
Suprachiasmatic Nuclei



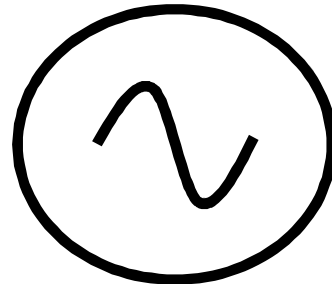
# The Circadian System



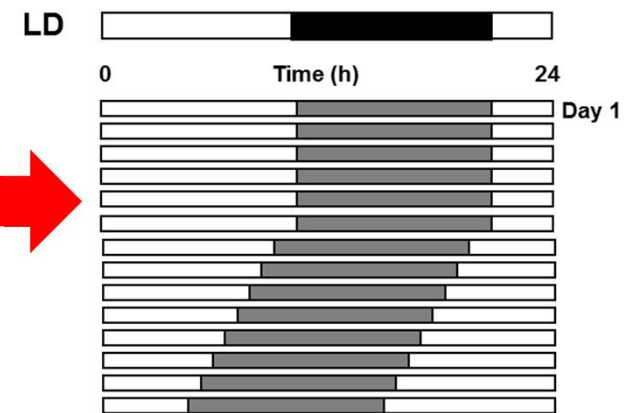
Eye



SCN

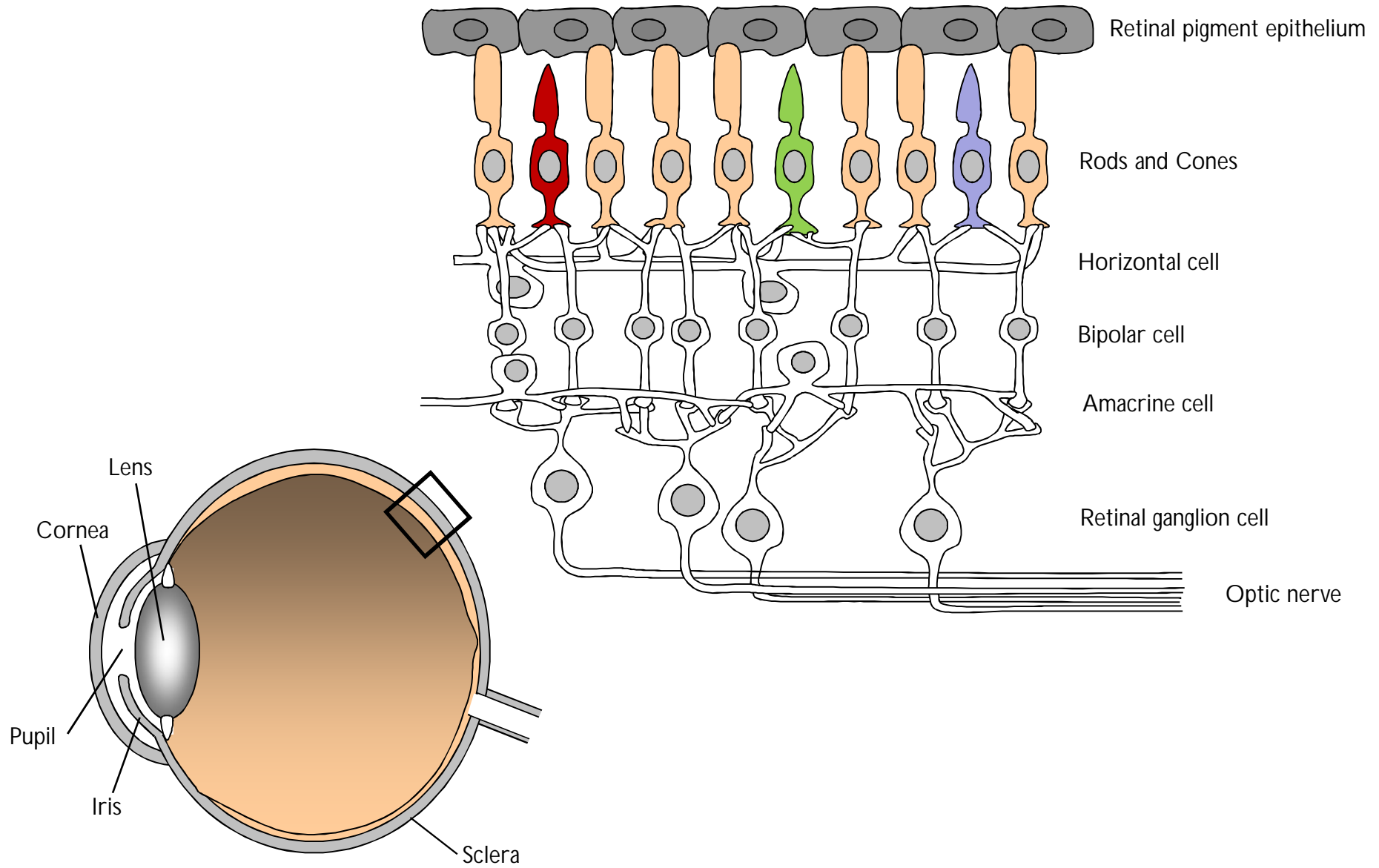


Suprachiasmatic Nuclei



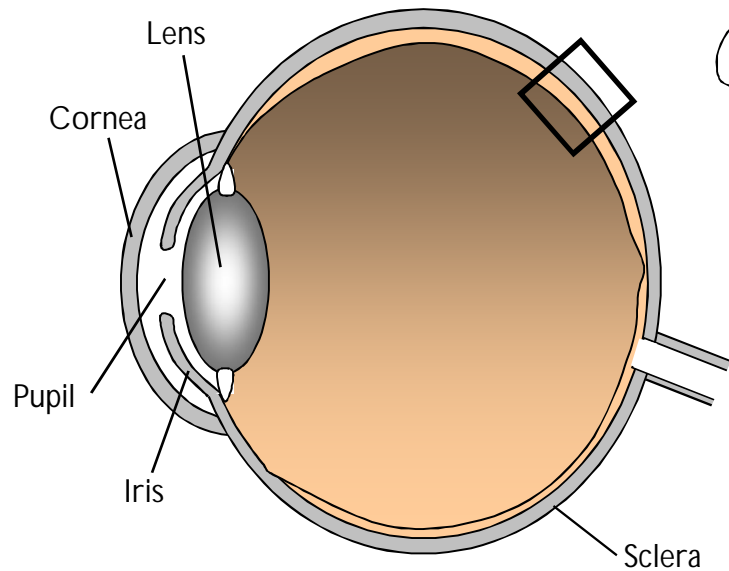
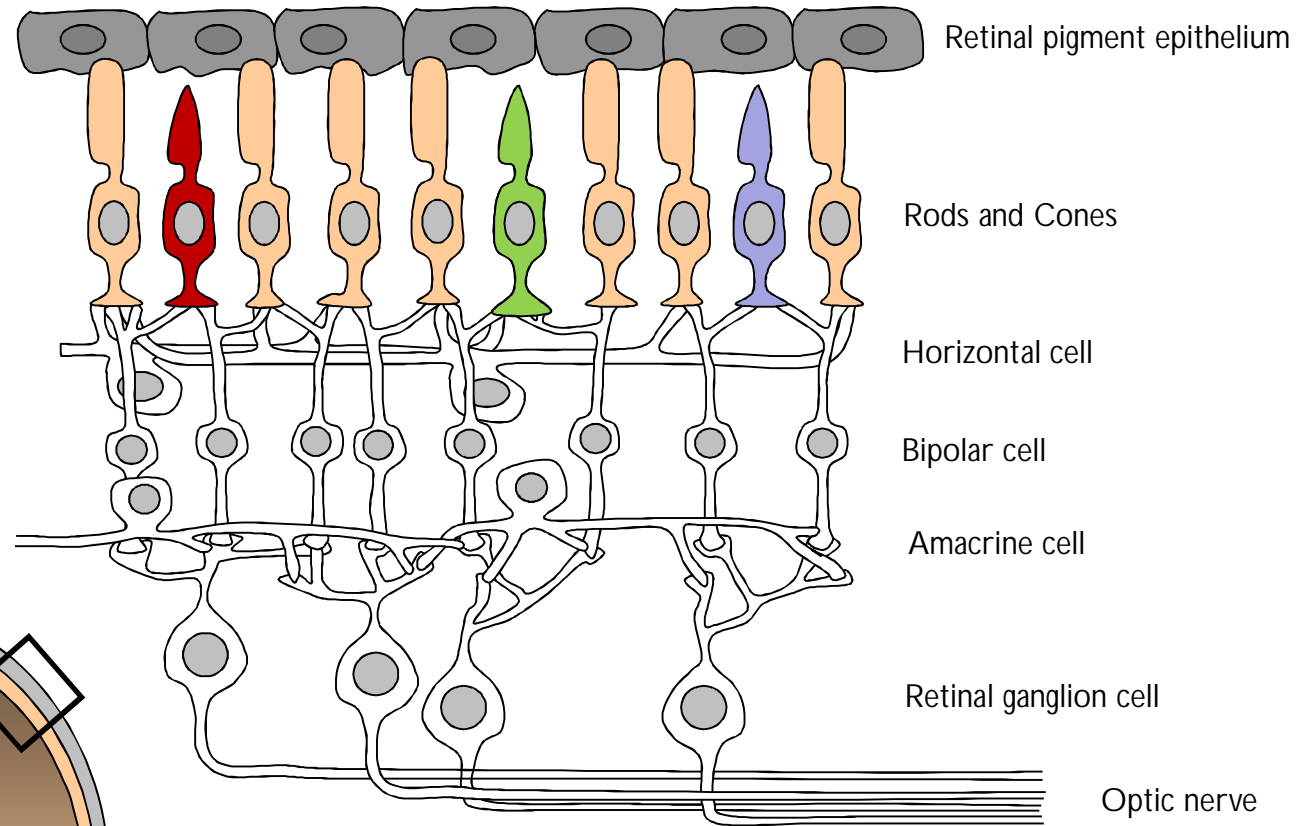
**Freerunning**

# How Does The Eye Regulate Internal Time?



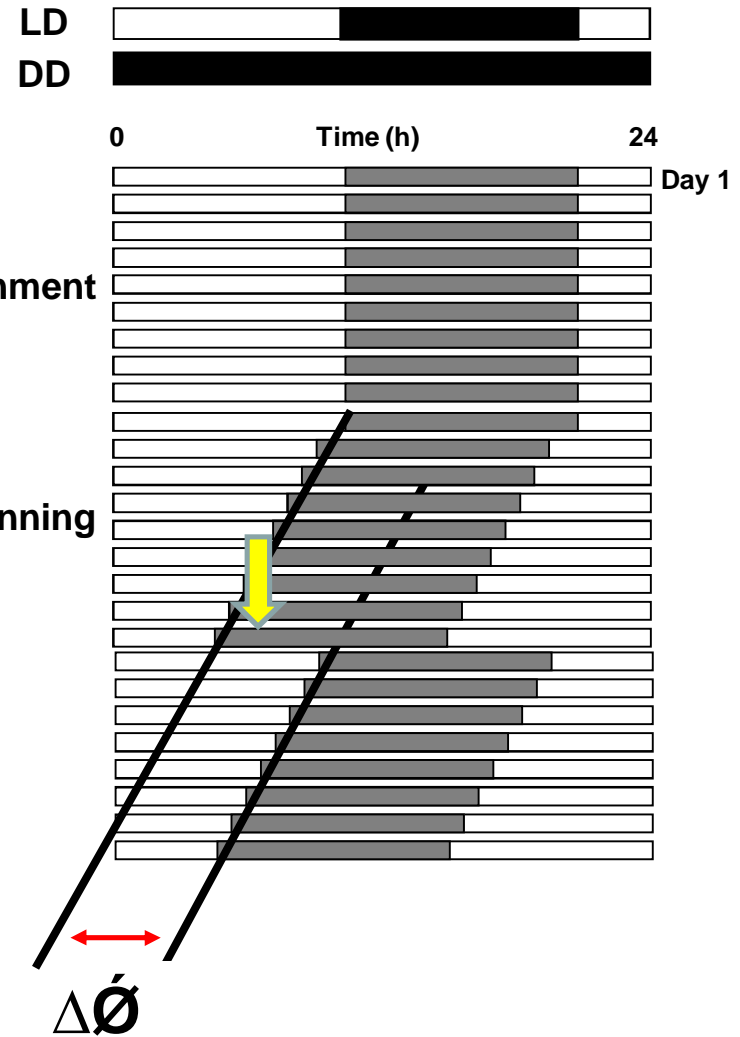
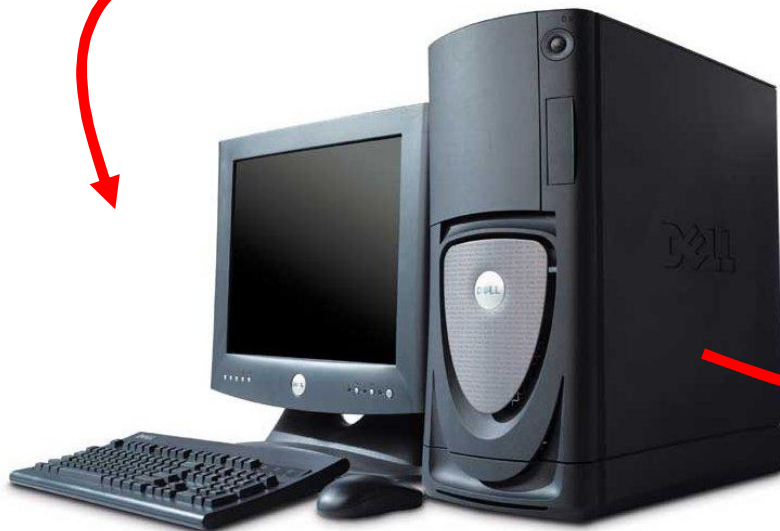
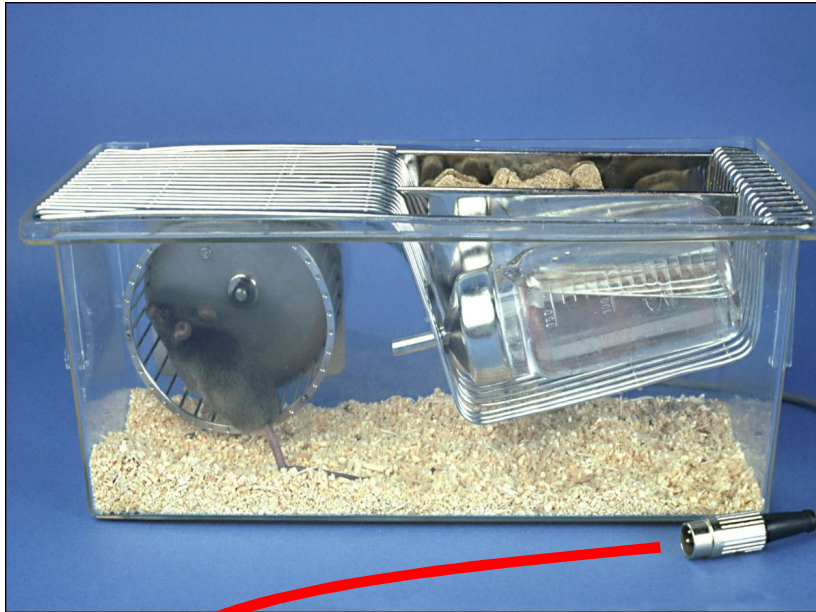
# 1<sup>st</sup> Approach Mutant “blind” mice e.g. *rd/rd* or *rds*

Foster, R. G., Provencio, I., Hudson, D., Fiske, S., De Grip, W. and Menaker, M. (1991). Circadian photoreception in the retinally degenerate mouse (*rd/rd*). *J. Comp. Physiol. [A]* 169, 39-50.

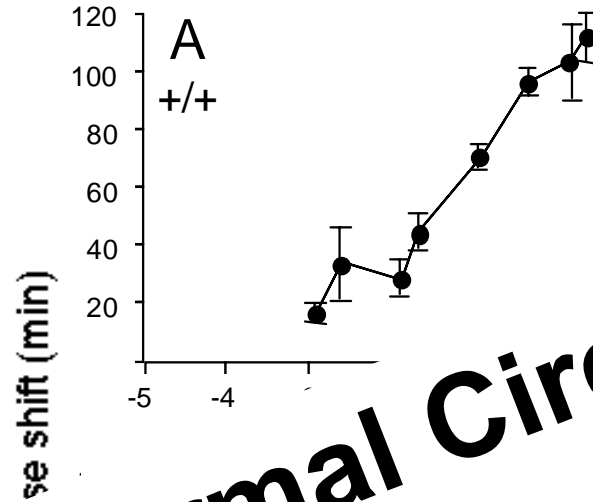
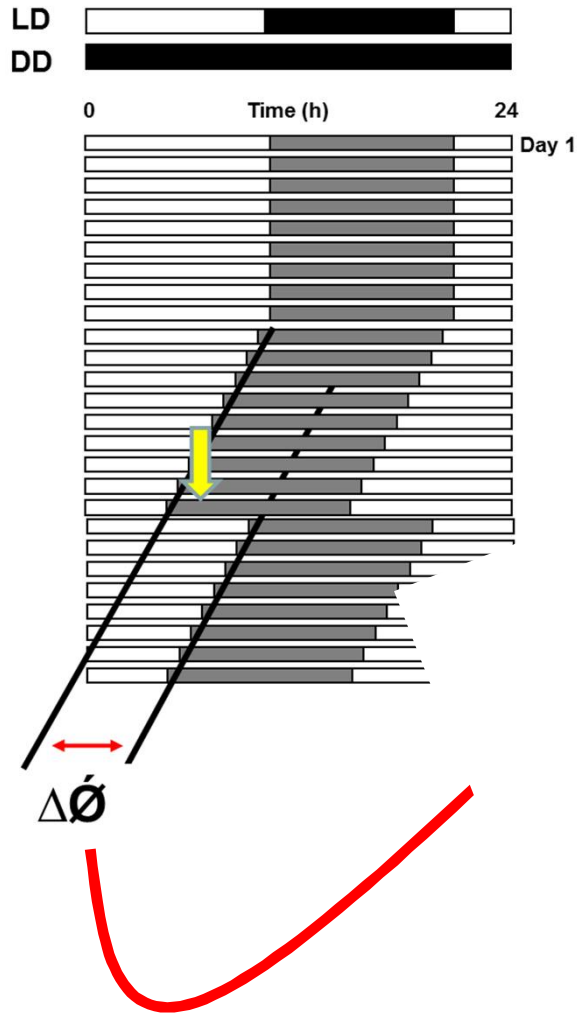


## Visually blind mice

# Wheel Running Behaviour



# The Circadian System



**Normal Circadian Responses to Light!**

Irradiance (log  $\mu\text{W cm}^2$ )

A Mouse can be visually  
blind but not circadian  
blind!

Could there be an  
uncharacterized  
photoreceptor within the eye  
– different from the rods and  
cones?

# Vision Neuroscientists



**NO!**



**NO!**

**NO!**



**Ha Ha!**



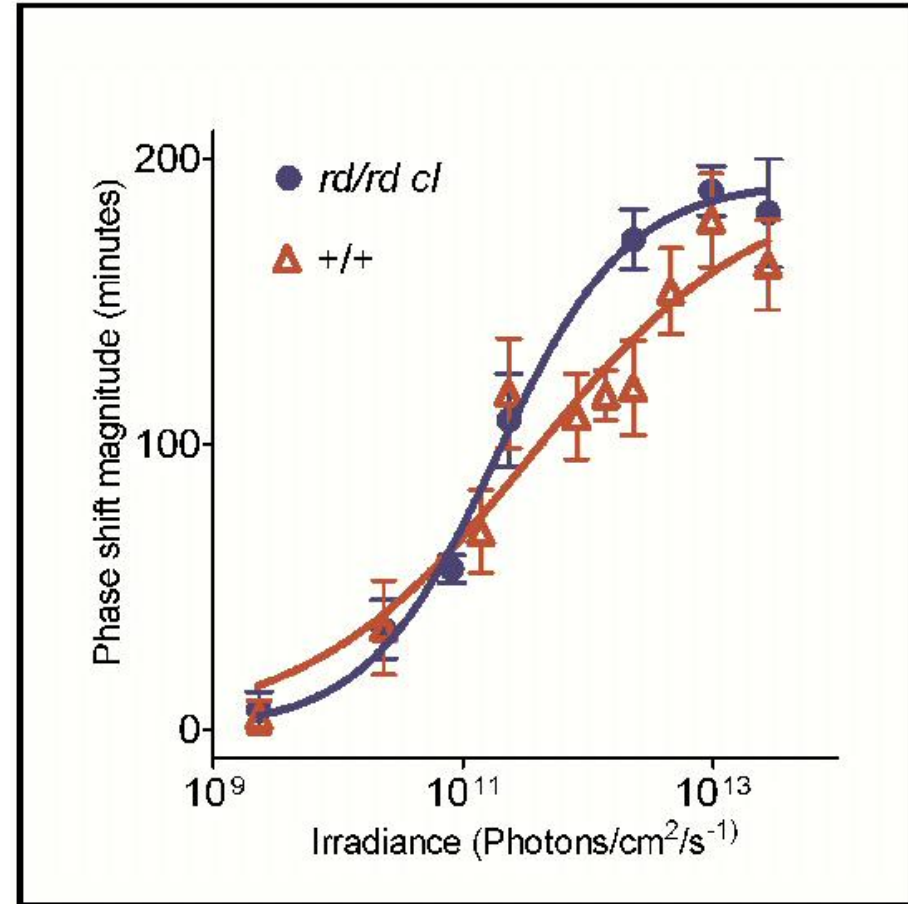
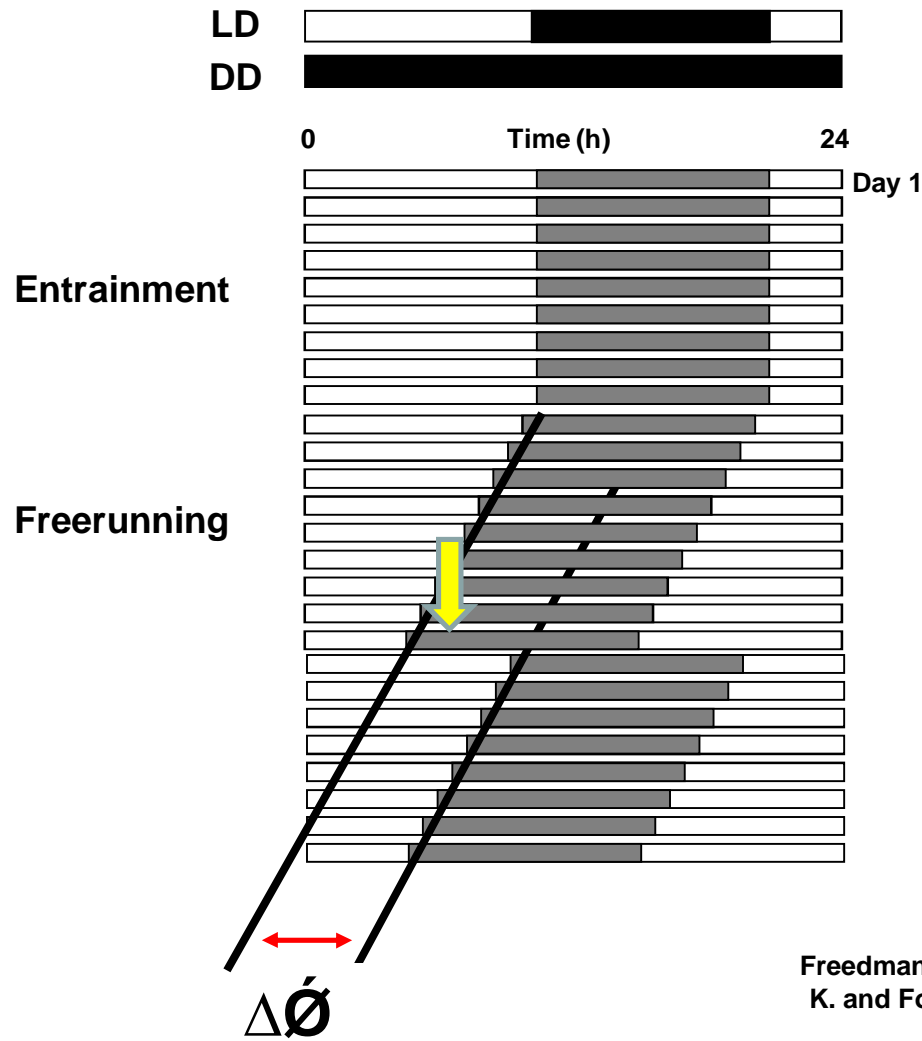


**One *semi-reasonable*  
criticism was....**

***“The circadian system can  
probably maintain normal  
photosensitivity with  
reduced numbers of rods  
and/or cones?”***

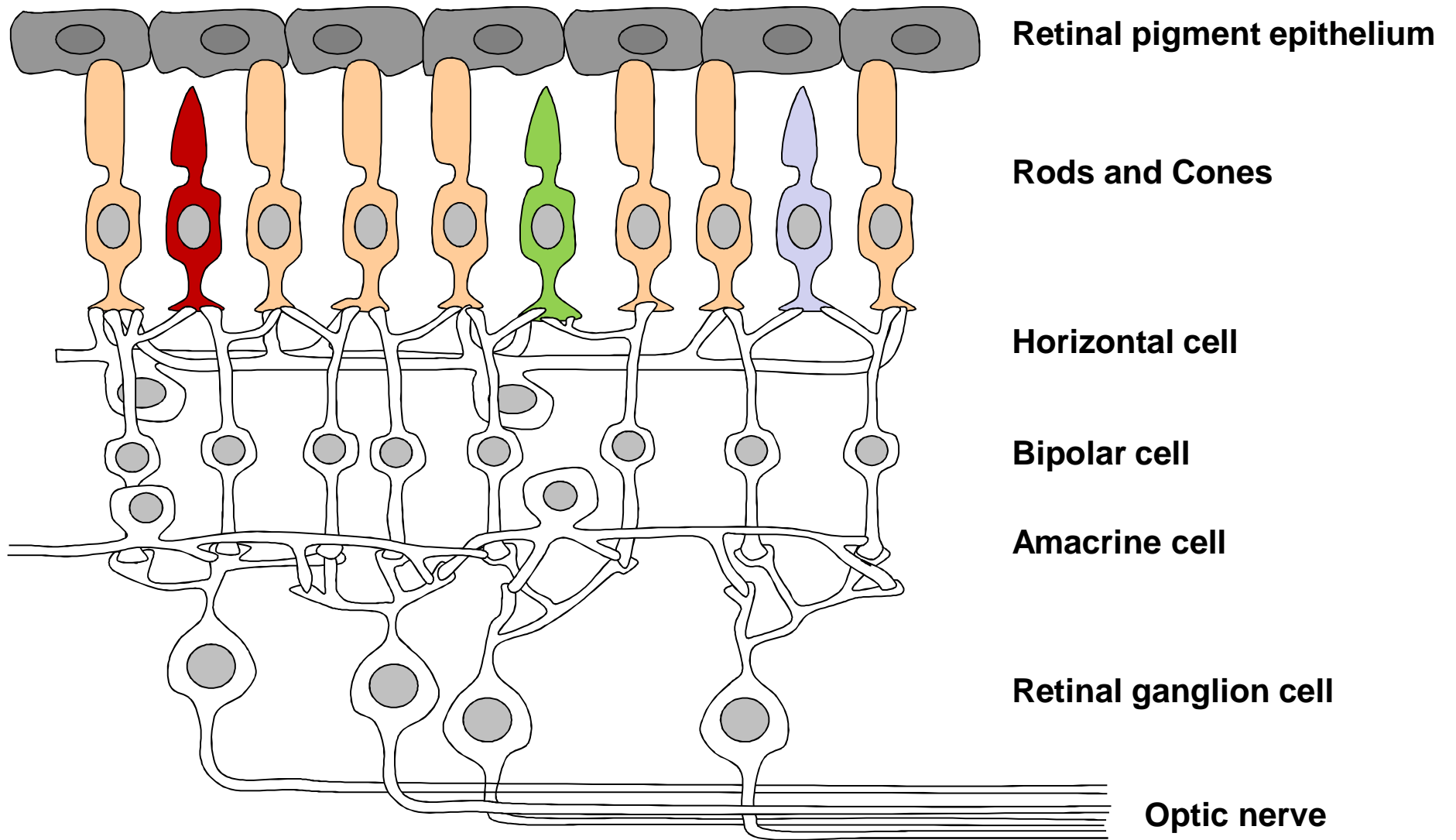


# The Circadian System

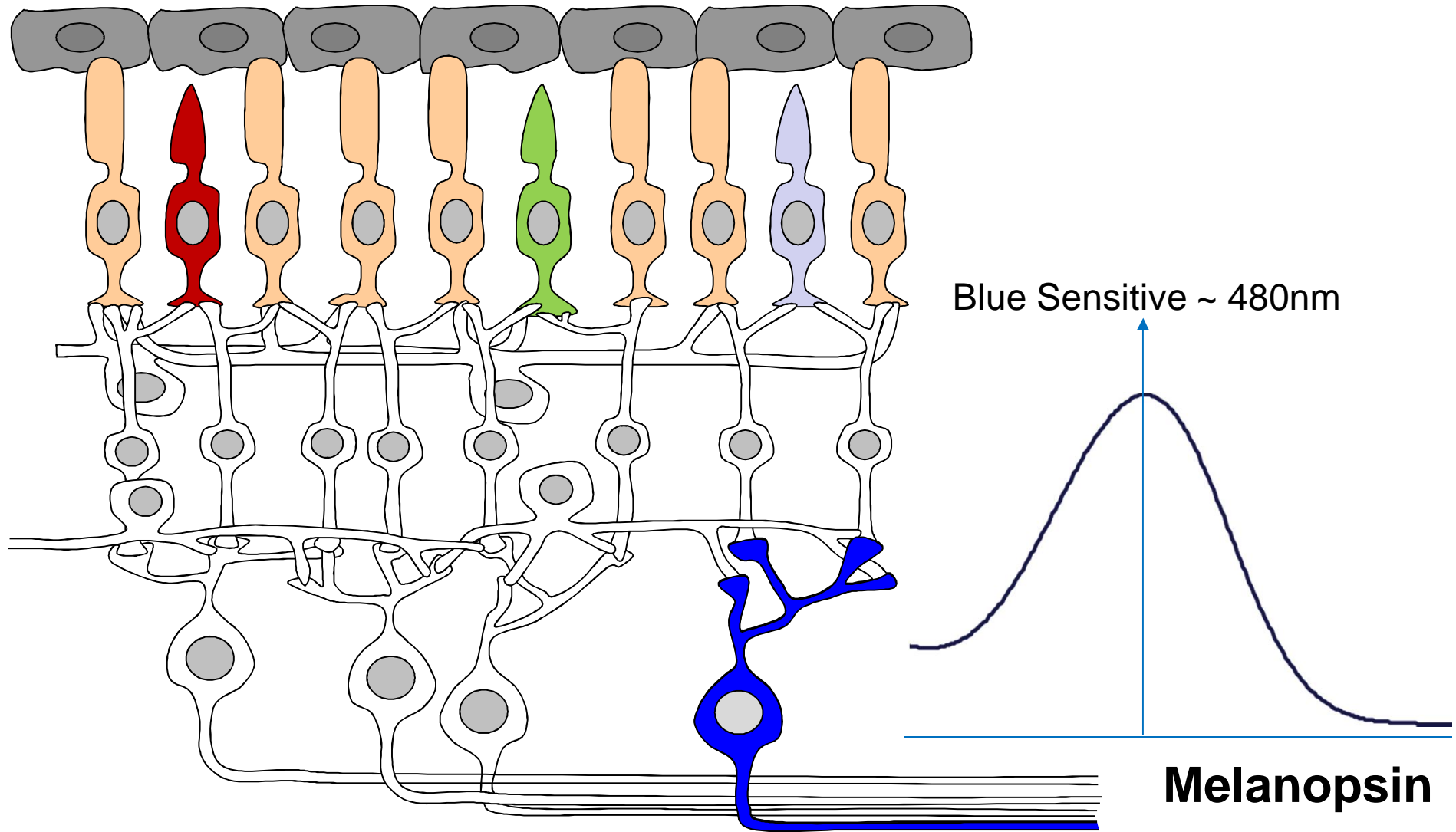


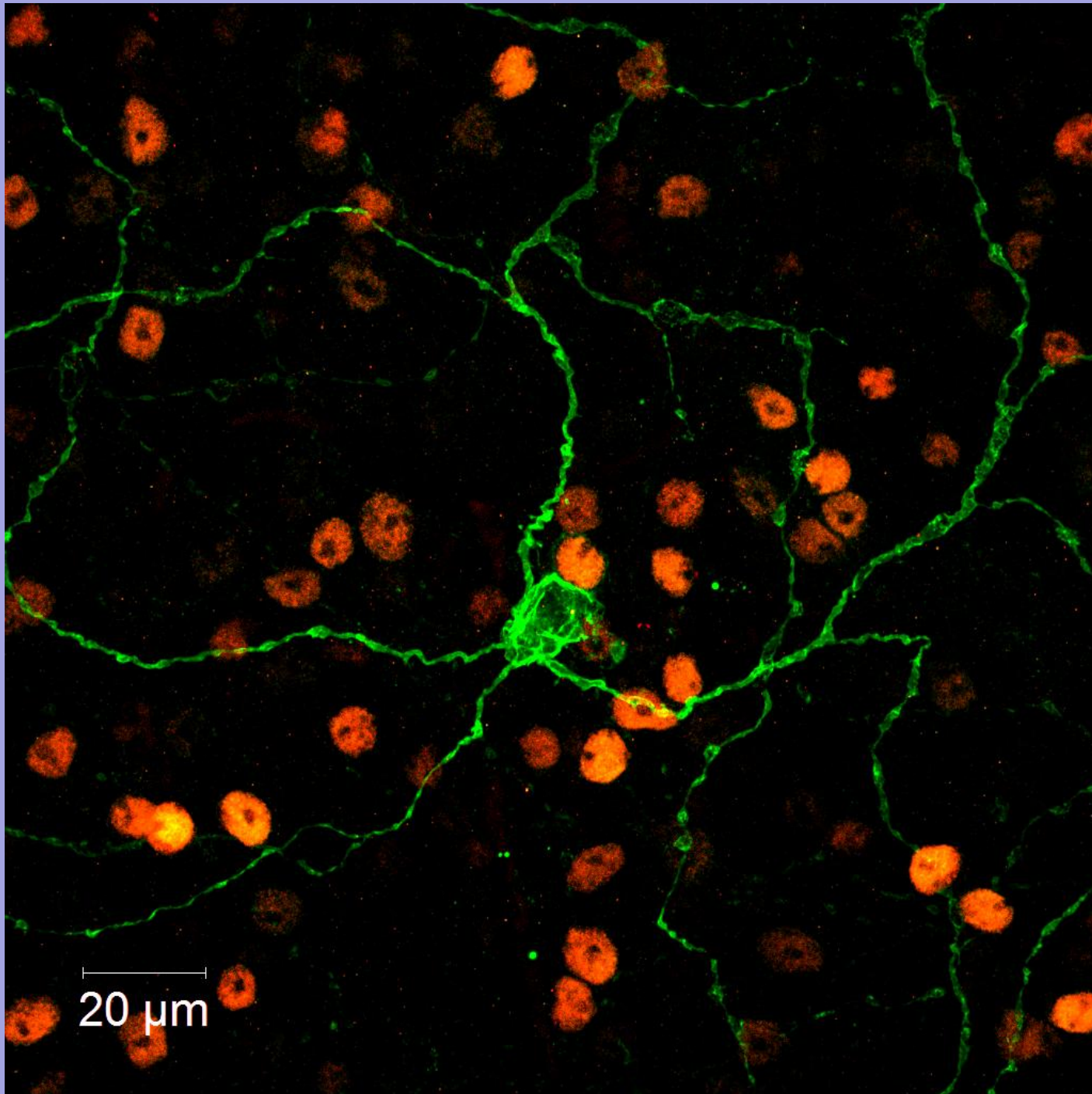
Freedman, M. S., Lucas, R. J., Soni, B., von Schantz, M., Munoz, M., David-Gray, Z. K. and Foster, R. G. (1999). Regulation of mammalian circadian behavior by non-rod, non-cone, ocular photoreceptors. *Science* 284, 502-504.

Lucas, R. J., Freedman, M. S., Munoz, M., Garcia-Fernandez, J. M. and Foster, R. G. (1999). Regulation of the mammalian pineal by non-rod, non-cone, ocular photoreceptors. *Science* 284, 505-507.

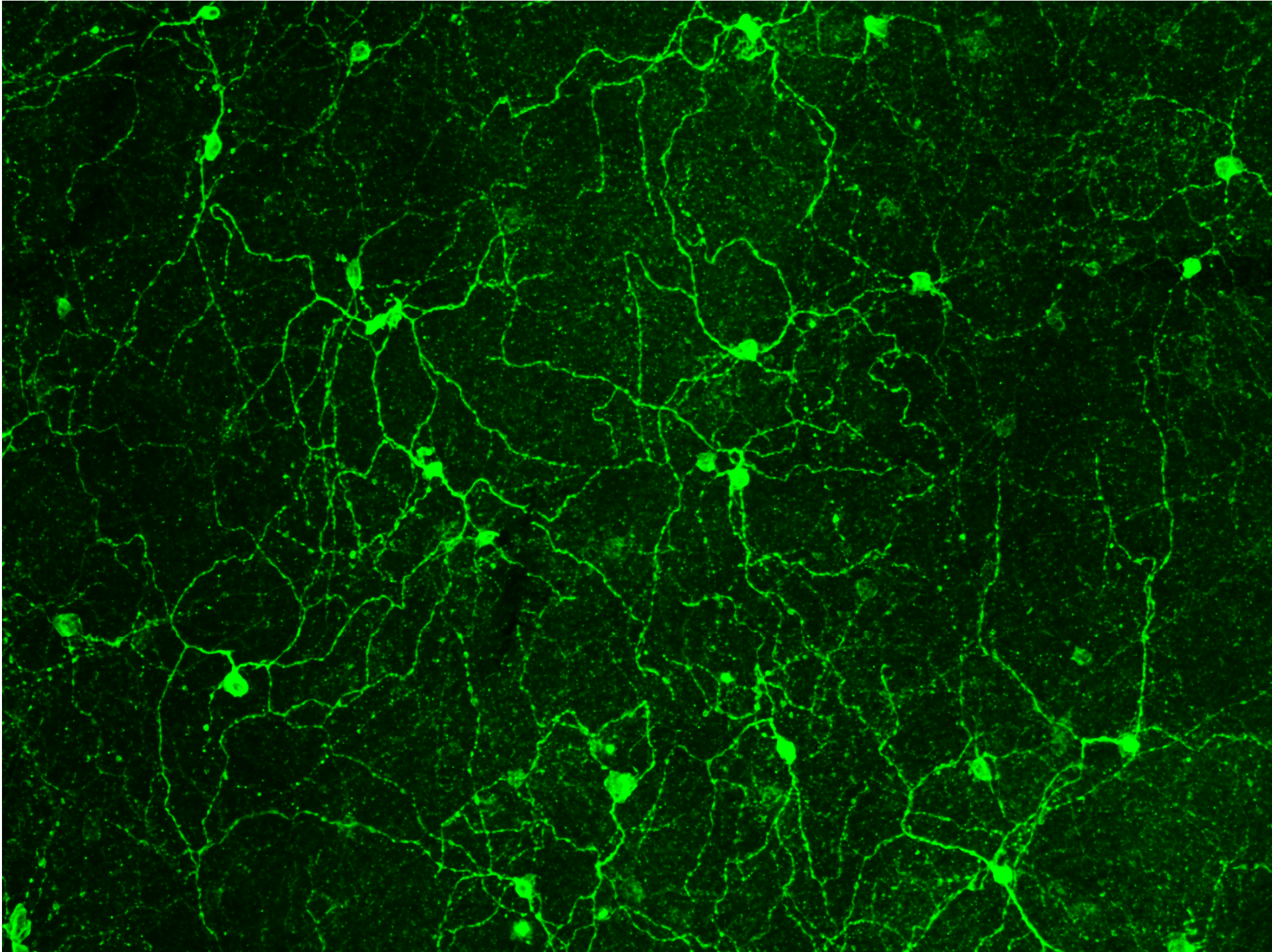


# Photosensitive Retinal Ganglion Cells (pRGCs)

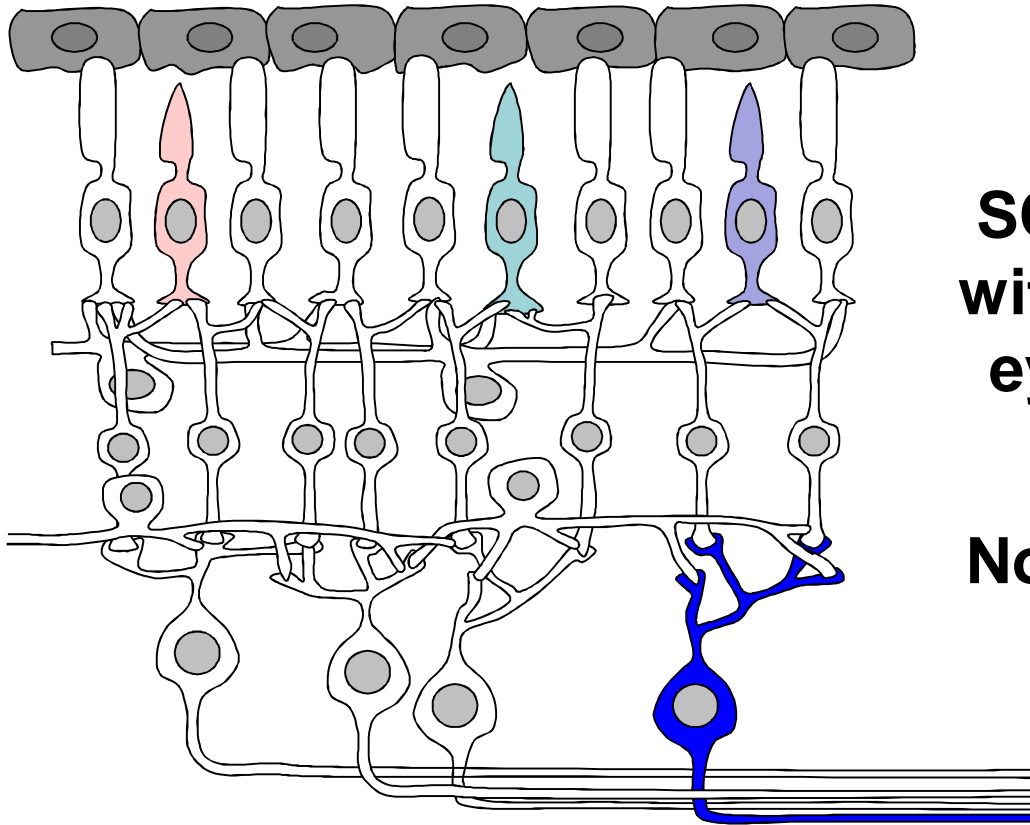




20  $\mu\text{m}$



# Are humans like mice?

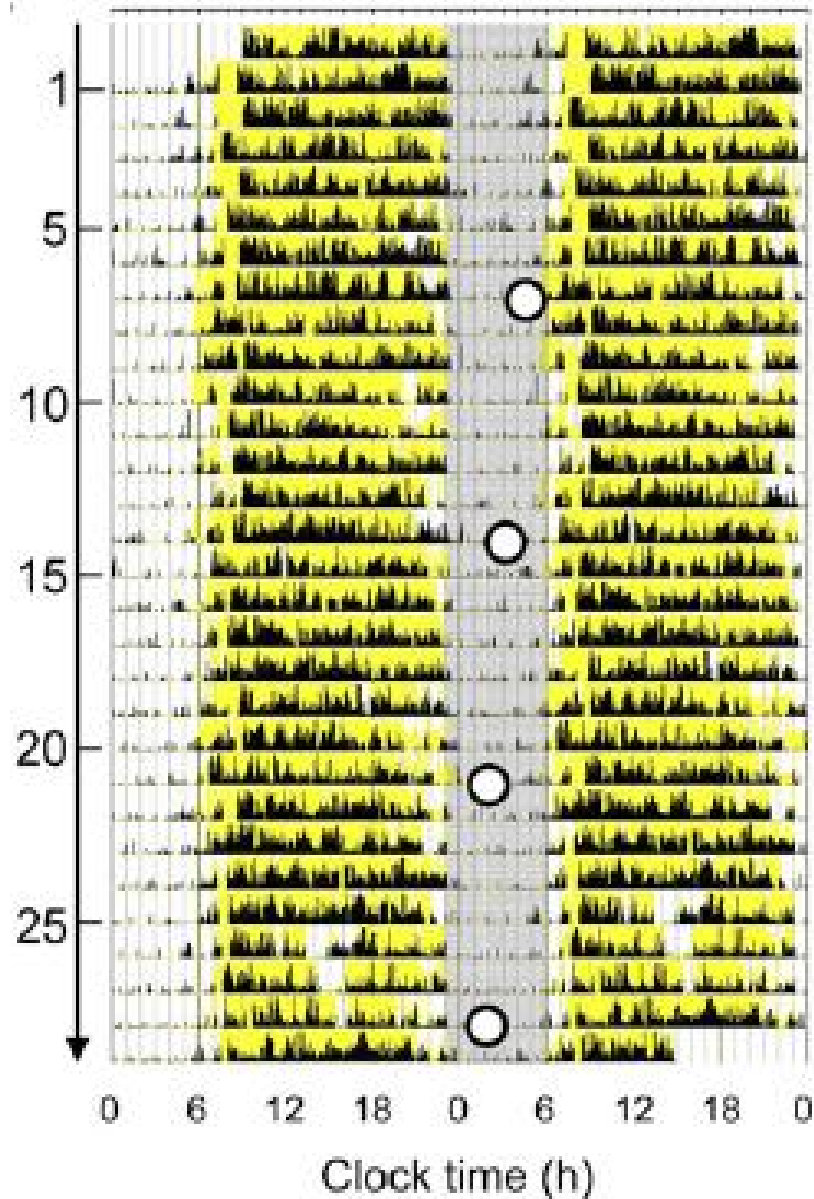


**SC is an 88 year old patient with a genetic disease of the eye resulting in the loss of her rods and cones.**

**No perception of light for 50 year**



# Normal Circadian Rhythms!



**Despite no visual responses, individuals with no rods and cones can regulate their clocks by light!**

**Visual blindness need not  
result in loss of all light  
detection by the eye!**

**But.....sleep and 24h  
rhythm abnormalities  
are ignored in clinical  
ophthalmology**



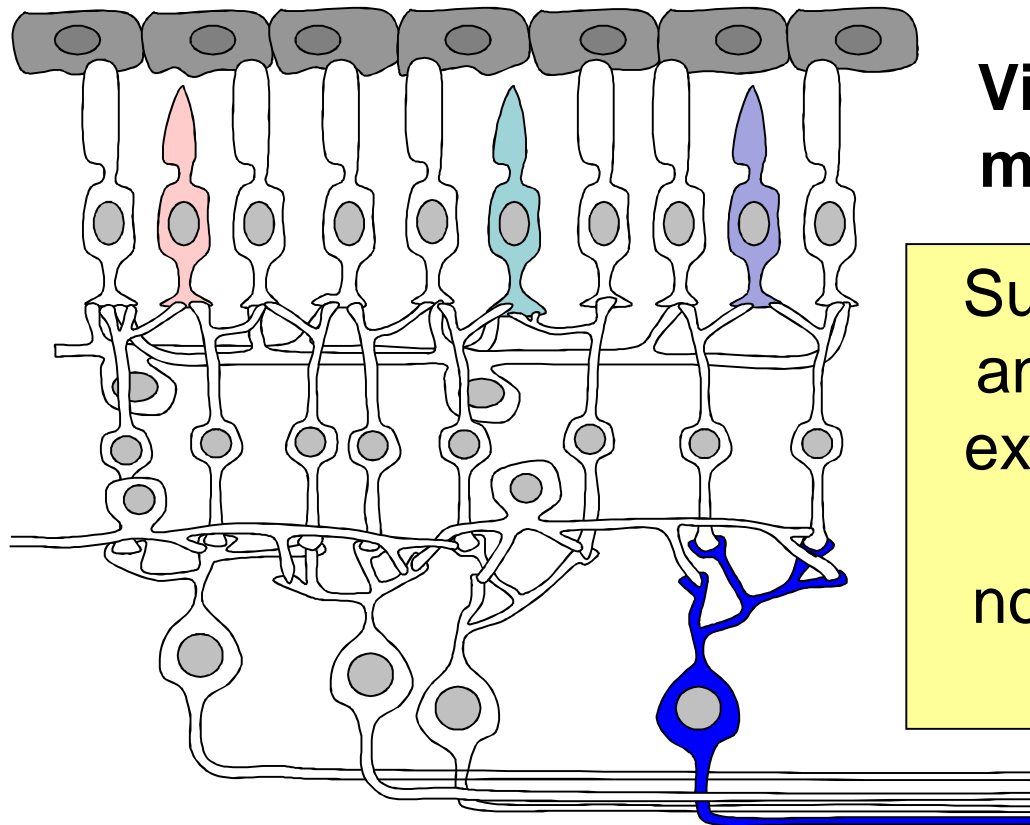
NLO

Nuffield Laboratory of Ophthalmology



Oxford Eye Hospital

**What is the impact  
of ocular disease on  
human sleep/wake  
biology?**



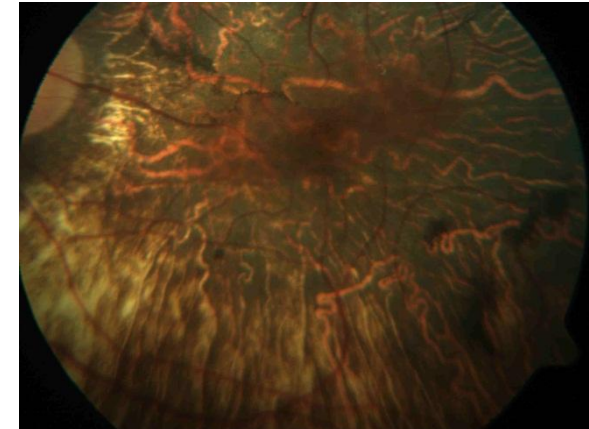
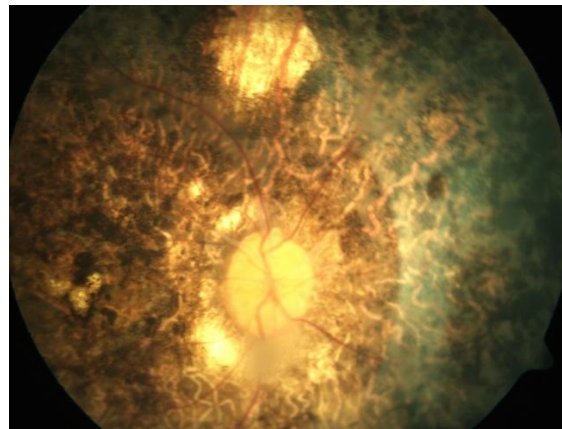
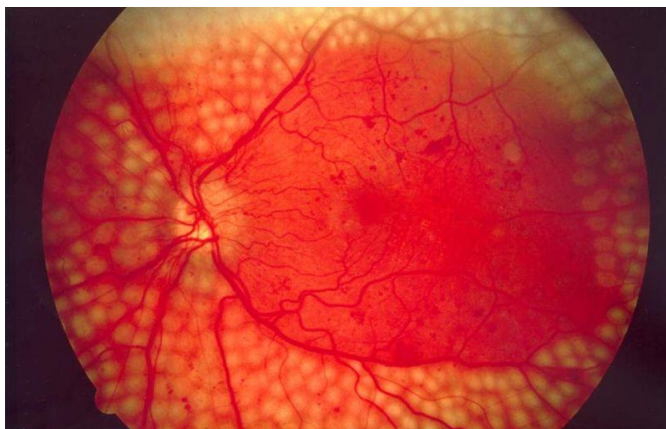
## Visual blindness need not mean complete blindness

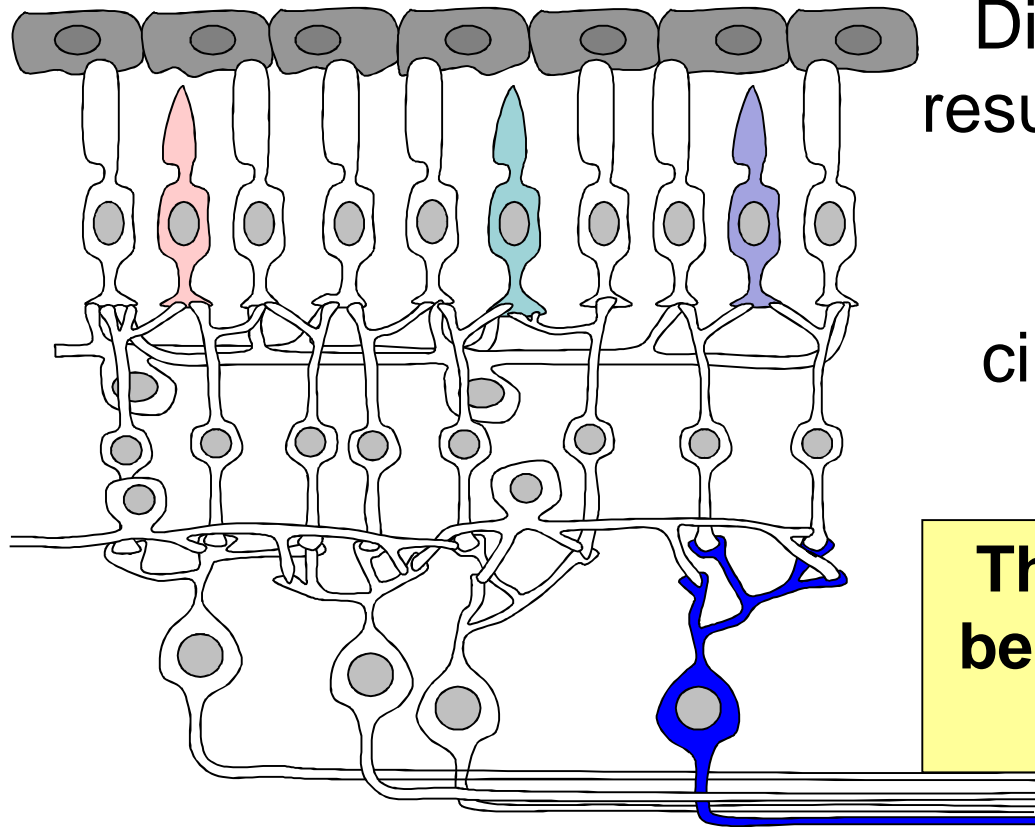
Such individuals have pRGCs and are being encouraged to expose their eyes to sufficient day-time light to maintain normal circadian entrainment and sleep-wake timing

Diabetic retinopathy

Leber congenital amaurosis

Choroideremia





Diseases of the inner retina resulting in retinal ganglion cell death and optic nerve degeneration will inflict circadian rhythm and sleep disruption.

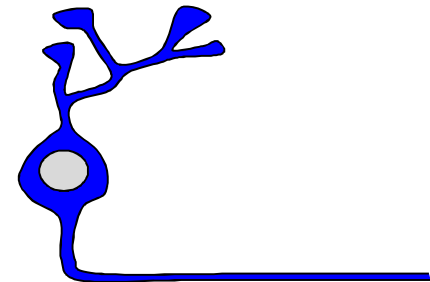
**These individuals are now benefitting from treatments that consolidate sleep**

Normal Optic Nerve

Optic Nerve in glaucoma



- **The clinical diagnosis of ‘complete’ blindness must assess the state of both the visual system and pRGCs.**
- **Eye loss plunges individuals into a world that lacks both vision and a proper sense of time.**
- **Clinical advice in ophthalmology must also incorporate the impact of eye diseases on sleep and circadian timing.**
- **39 Million Blind**
- **285 Million Visually Impaired**
- **246 Million Low Vision**



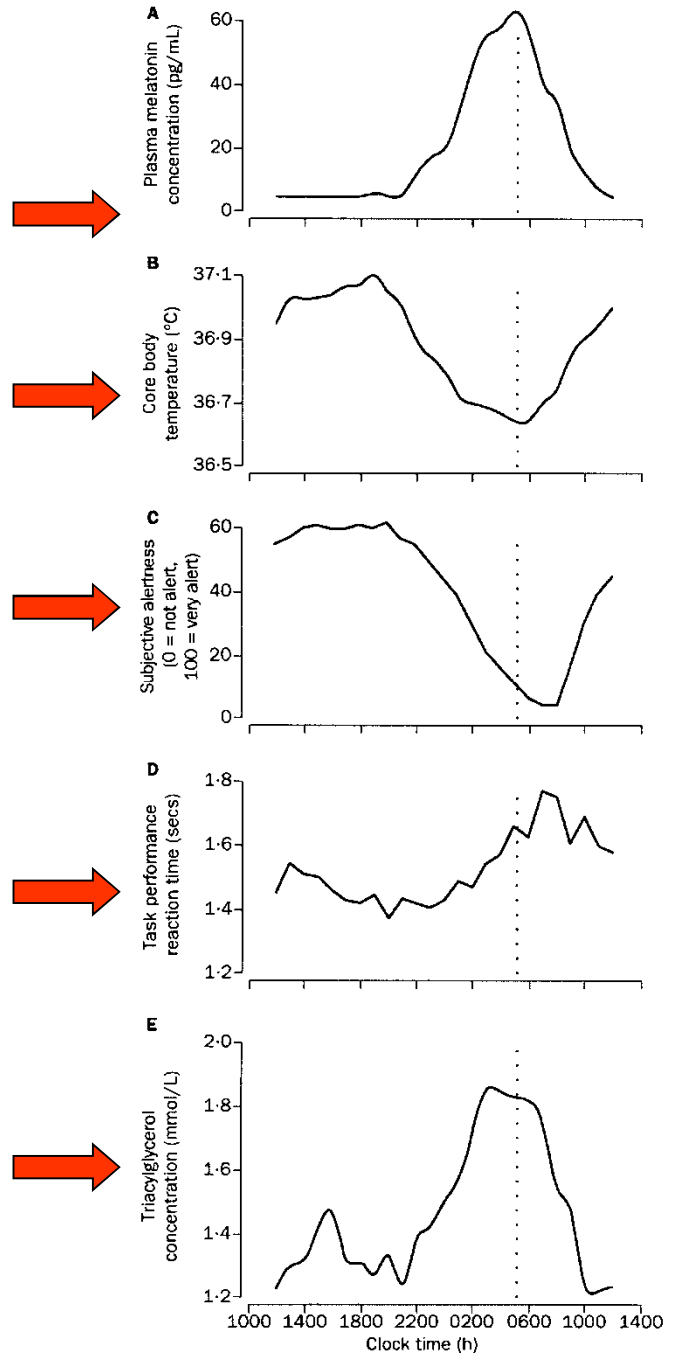
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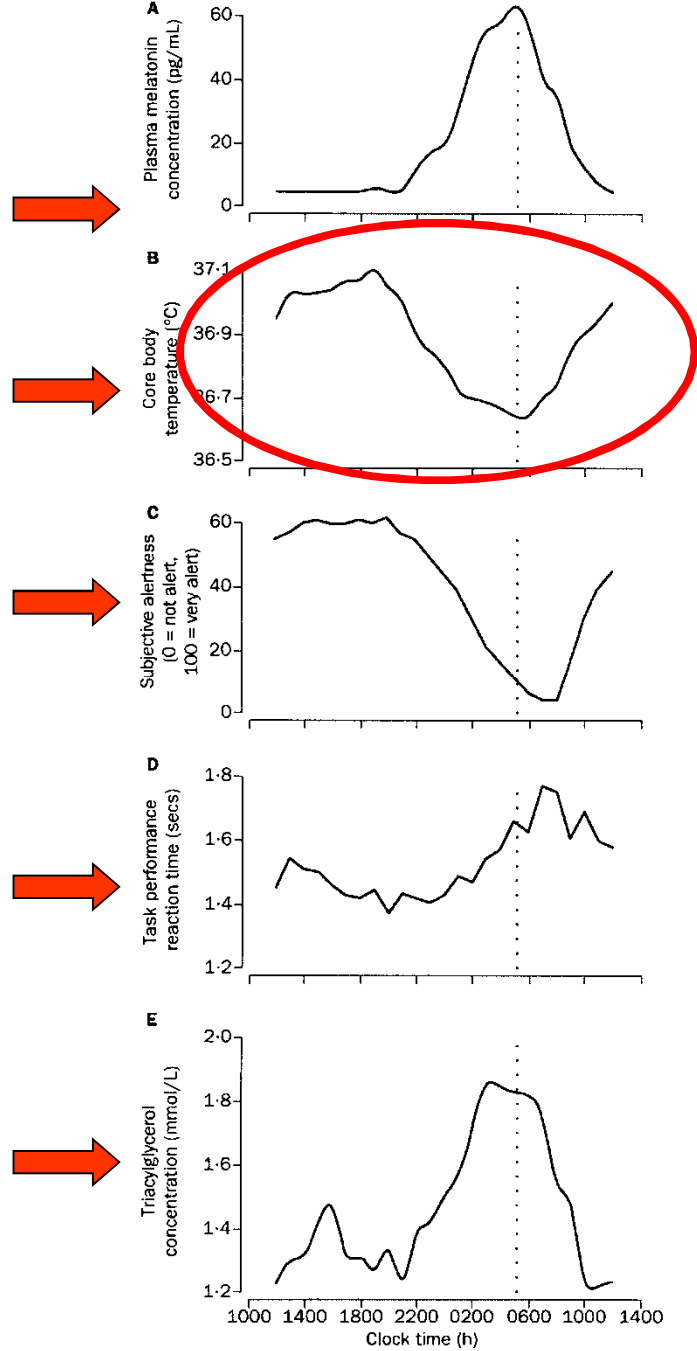


<i>Rhythmic Changes in Human Physiology and Behaviour</i>	DAY	NIGHT
MELATONIN	LOW	HIGH
CORTISOL	HIGH	LOW
BODY TEMPERATURE	HIGH	LOW
GROWTH HORMONE	LOW	HIGH
ALERTNESS AND COGNITIVE PERFORMANCE	HIGH	LOW
CATECHOLAMINES	HIGH	LOW
URINE PRODUCTION	HIGH	LOW
LAPSES IN ATTENTION	LOW	HIGH
SLEEP	LOW	HIGH
MEMORY RECALL	HIGH	LOW
CAPACITY TO DIGEST FAT	HIGH	LOW
MUSCULAR STRENGTH	HIGH	LOW

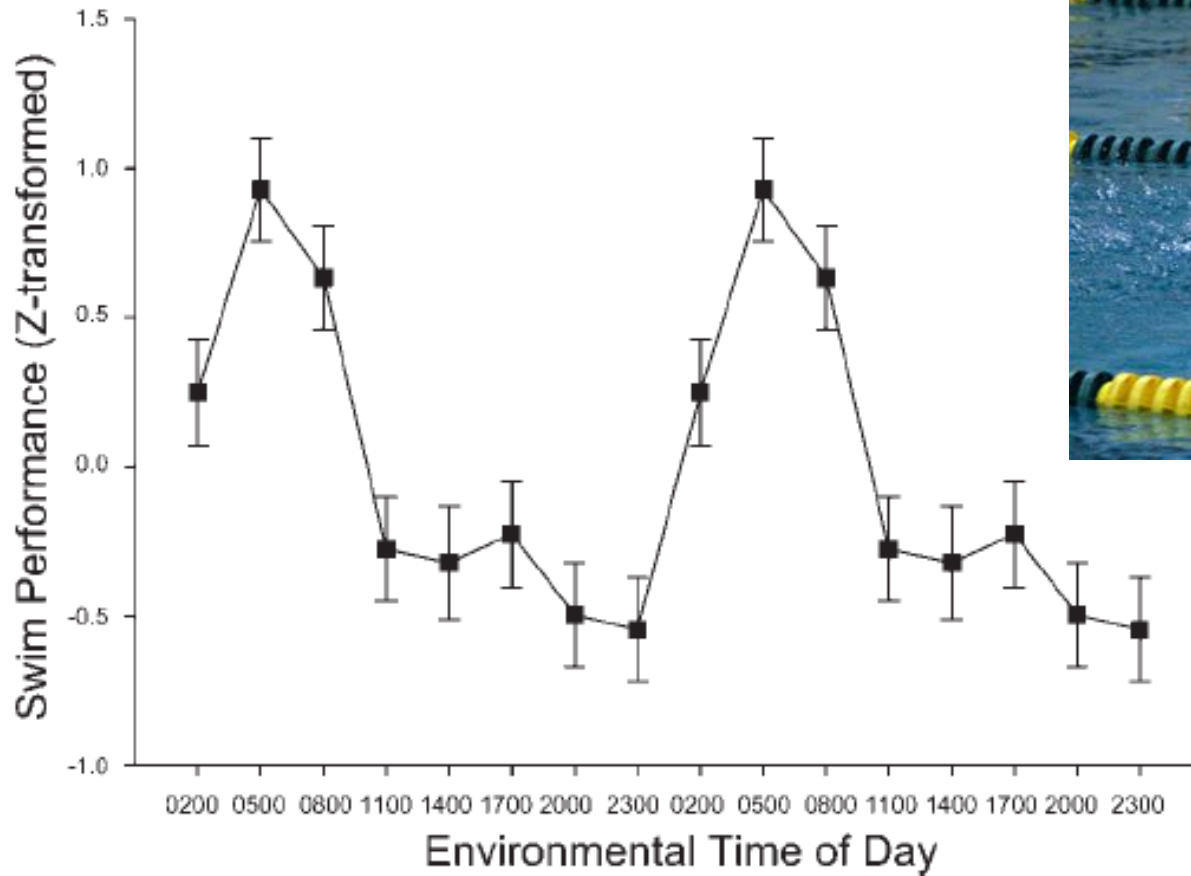


**.....lots of time of day  
effects .....Athletic  
Performance**

<i>Rhythmic Changes in Human Physiology and Behaviour</i>	DAY	NIGHT
MELATONIN	LOW	HIGH
CORTISOL	HIGH	LOW
BODY TEMPERATURE	HIGH	LOW
GROWTH HORMONE	LOW	HIGH
ALERTNESS AND COGNITIVE PERFORMANCE	HIGH	LOW
CATECHOLAMINES	HIGH	LOW
URINE PRODUCTION	HIGH	LOW
LAPSES IN ATTENTION	LOW	HIGH
SLEEP	LOW	HIGH
MEMORY RECALL	HIGH	LOW
CAPACITY TO DIGEST FAT	HIGH	LOW
MUSCULAR STRENGTH	HIGH	LOW



# Athletic Performance



**2.7 second difference  
over 200m**

*J Appl Physiol* 102: 641–649, 2007.  
First published November 9, 2006; doi:10.1152/jappphysiol.00910.2006.

## Circadian variation in swim performance



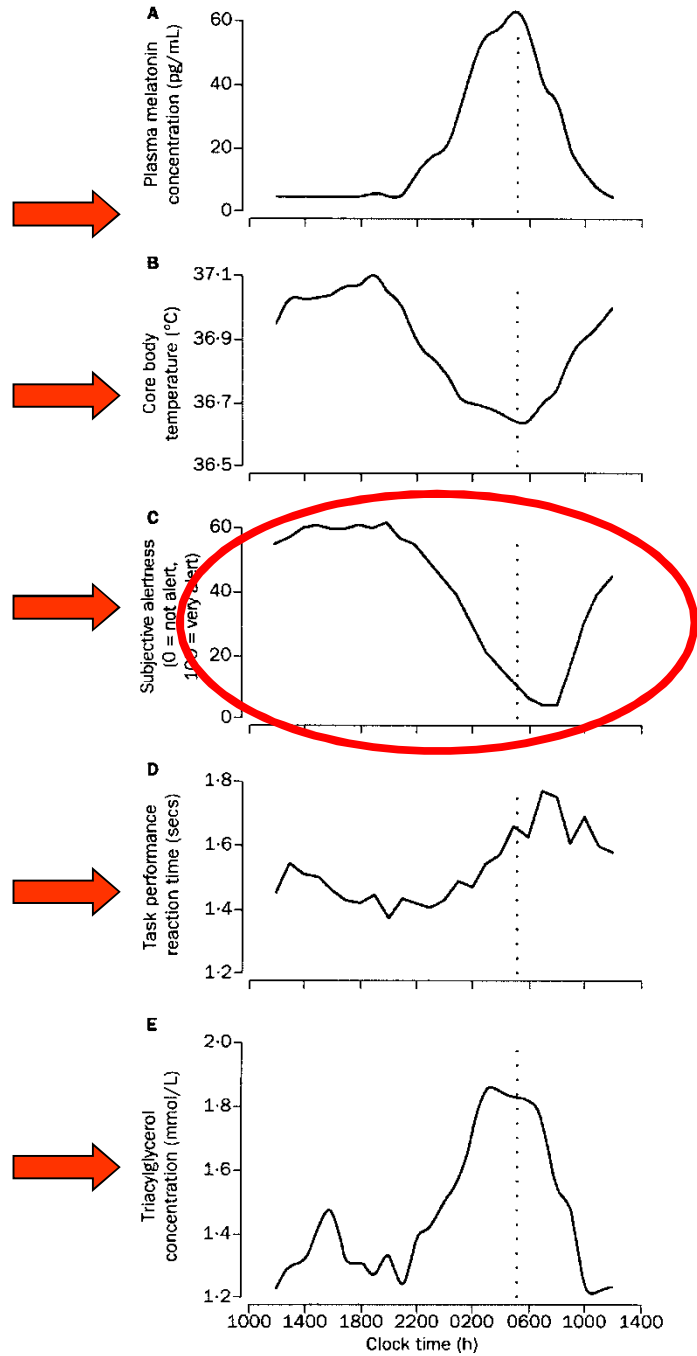
Christopher E. Kline, J. Larry Durstine, J. Mark Davis, Teresa A. Moore,  
Tina M. Devlin, Mark R. Zielinski, and Shawn D. Youngstedt

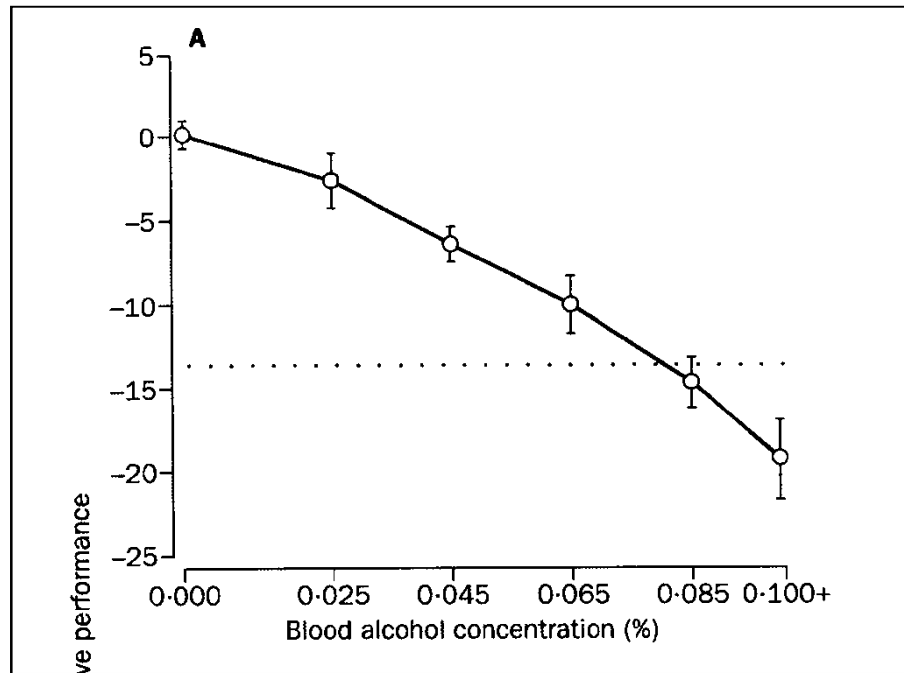
*Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina*

Submitted 17 August 2006; accepted in final form 1 November 2006

**.....lots of time of day  
effects .....cognitive  
abilities**

<i>Rhythmic Changes in Human Physiology and Behaviour</i>	DAY	NIGHT
MELATONIN	LOW	HIGH
CORTISOL	HIGH	LOW
BODY TEMPERATURE	HIGH	LOW
GROWTH HORMONE	LOW	HIGH
ALERTNESS AND COGNITIVE PERFORMANCE	HIGH	LOW
CATECHOLAMINES	HIGH	LOW
URINE PRODUCTION	HIGH	LOW
LAPSES IN ATTENTION	LOW	HIGH
SLEEP	LOW	HIGH
MEMORY RECALL	HIGH	LOW
CAPACITY TO DIGEST FAT	HIGH	LOW
MUSCULAR STRENGTH	HIGH	LOW

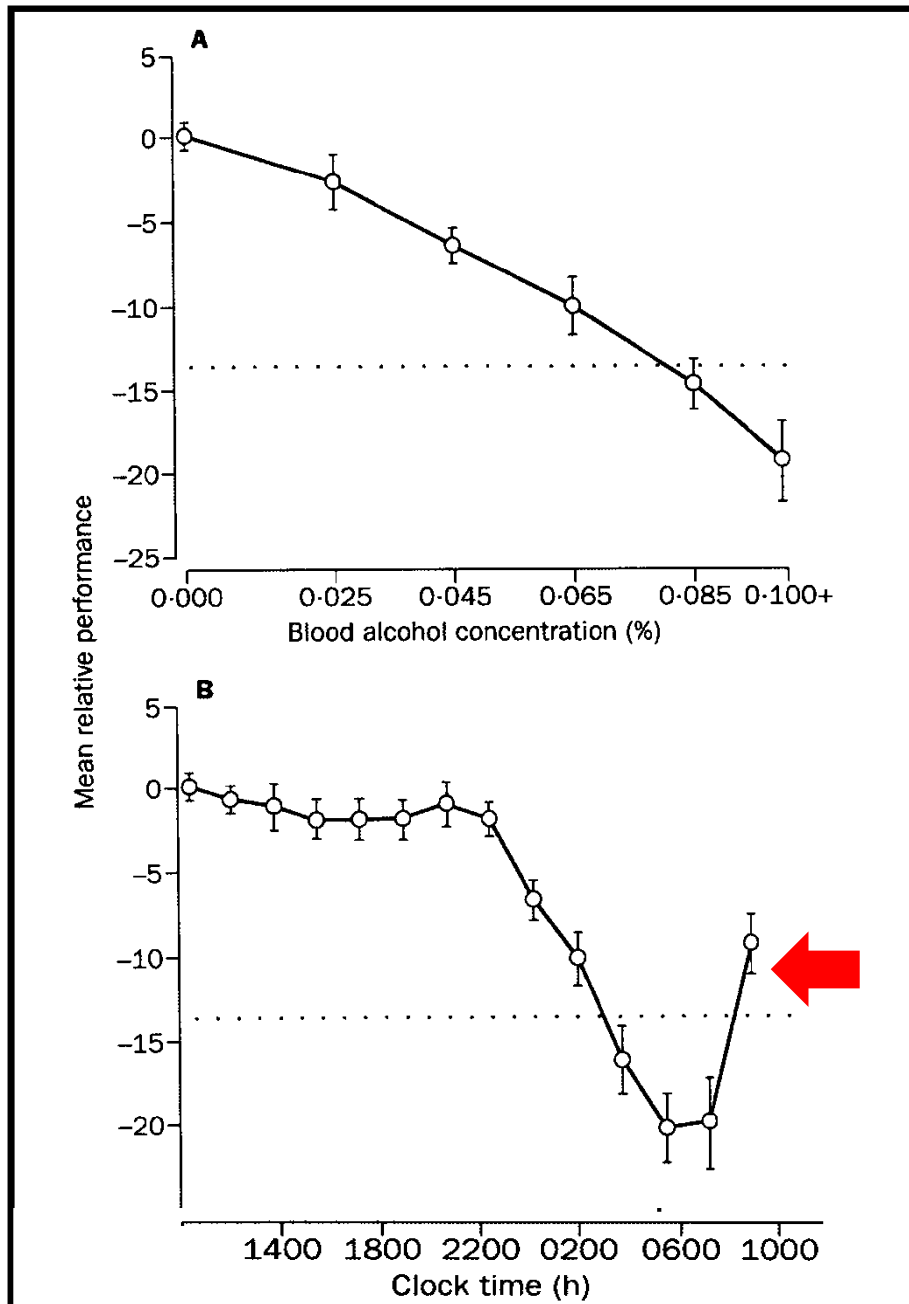




**Comparison of the effect of blood alcohol concentration (BAC) and time of day on task performance.**

The dotted horizontal line is the mean performance at a blood alcohol concentration of 0.08% - the legal limit for driving in the UK.

Lamond and Dawson  
J. Sleep Res. 1999 8: 255-262



**Comparison of the effect of blood alcohol concentration (BAC) and time of day on task performance.**

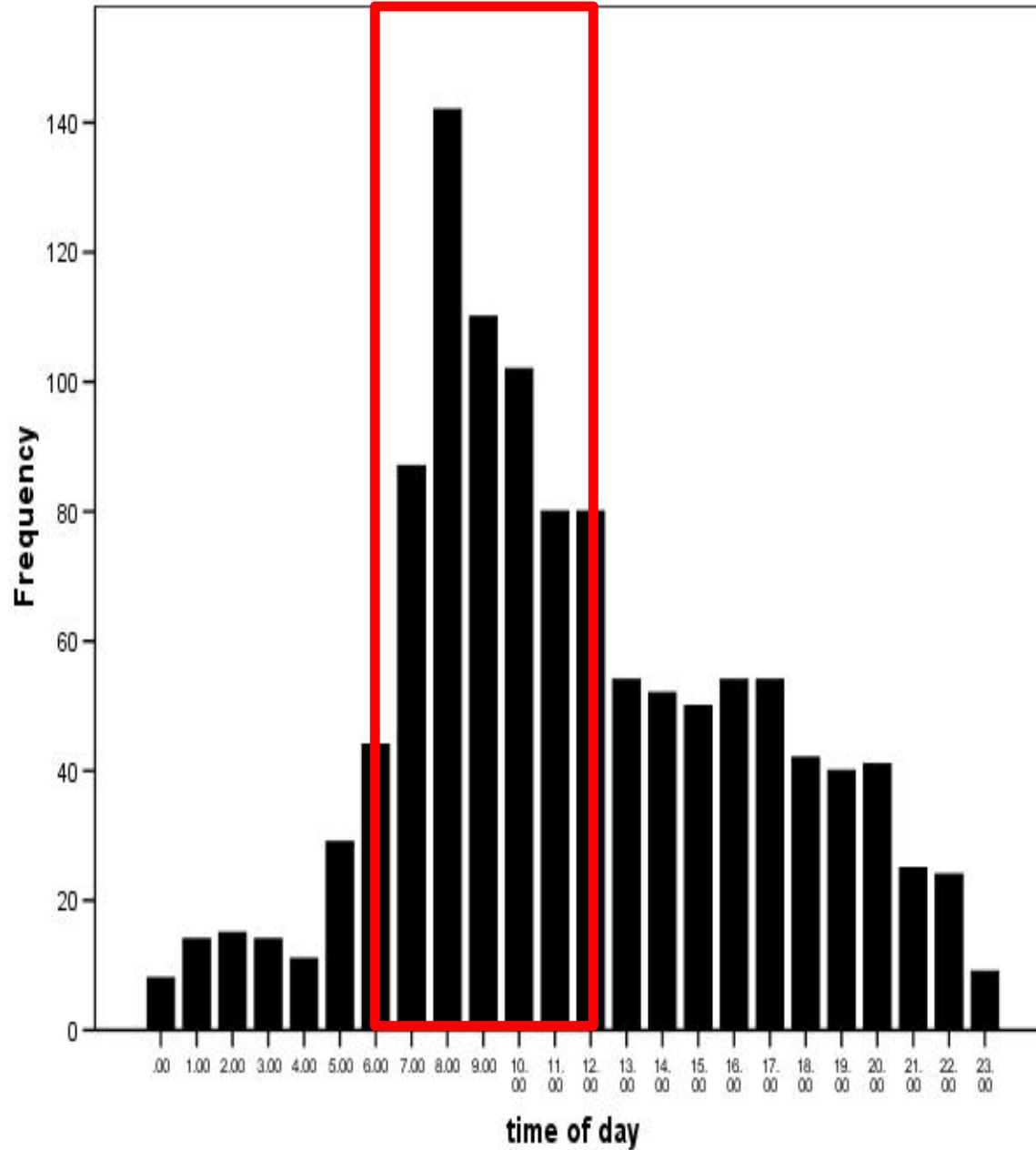
The dotted horizontal line is the mean performance at a blood alcohol concentration of 0.08% - the legal limit for driving in the UK.

Lamond and Dawson  
 J. Sleep Res. 1999 8: 255-262



**.....lots of time of  
day effects .....  
stroke**

# Circadian variation in incidence of stroke



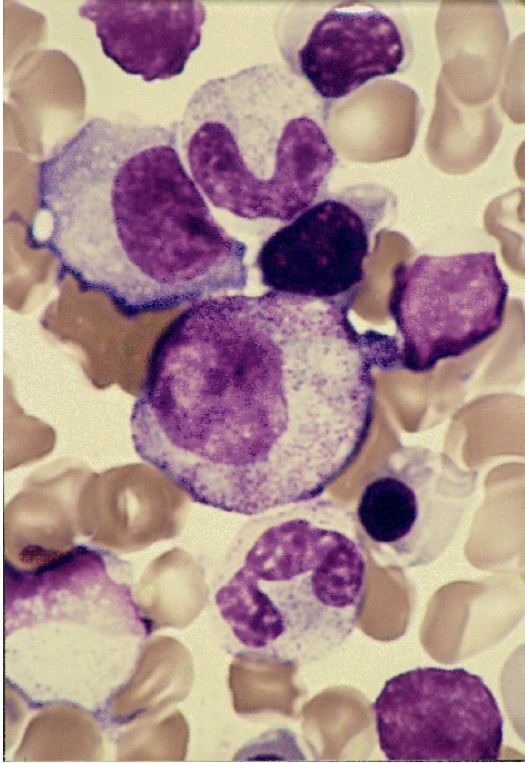
Oxford Vascular Study (Peter M Rothwell )

**.....lots of time of  
day effects .....**  
**drug delivery**

**The right drug at the  
right amount at the  
right time for each  
individual!**

Most drugs and treatments  
are not given on the basis  
of body time – but on the  
basis of convenience  
alone

**But timing matters.....**



## Leukaemia

Disease-free survival rates were compared in 118 children who received chemotherapy (mercaptopurine and methotrexate)

Risk of relapse 2.56 x higher if chemotherapy given in the morning compared to evening.

Rivard GE, Infante-Rivard C, Dresse MF, et al. Circadian time-dependent response of childhood lymphoblastic leukemia to chemotherapy: a long-term follow-up study of survival. *Chronobiol Int* 1993;10(3):201-4

**.....lots of time of  
day effects .....**

**drug testing on  
rats and mice**

# Diurnal Mammal



Delivery





## Diurnal Mammal



Delivery



## Nocturnal Mammal

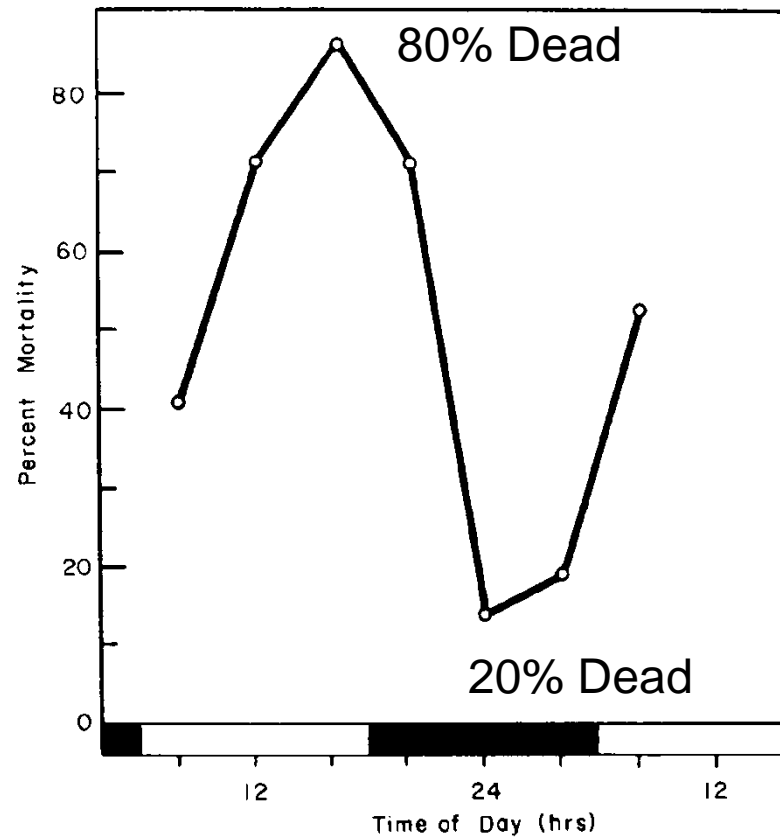


Testing



**Does 12h Matter?**

## Time of day effects: Susceptibility to trauma and toxins



**Fig. 7.10** Susceptibility rhythm of mice to intraperitoneal injections of *E. coli* endotoxin. A dose compatible with survival for most animals at one time of day is highly lethal when injected into comparable mice at a different circadian phase. (After Halberg, 1960.)

**Currently drug testing is performed on nocturnal rodents and extrapolated to a diurnal species such as ourselves.**

**Responses may be very different at different times of the day!**

Exposure to bacterial toxin

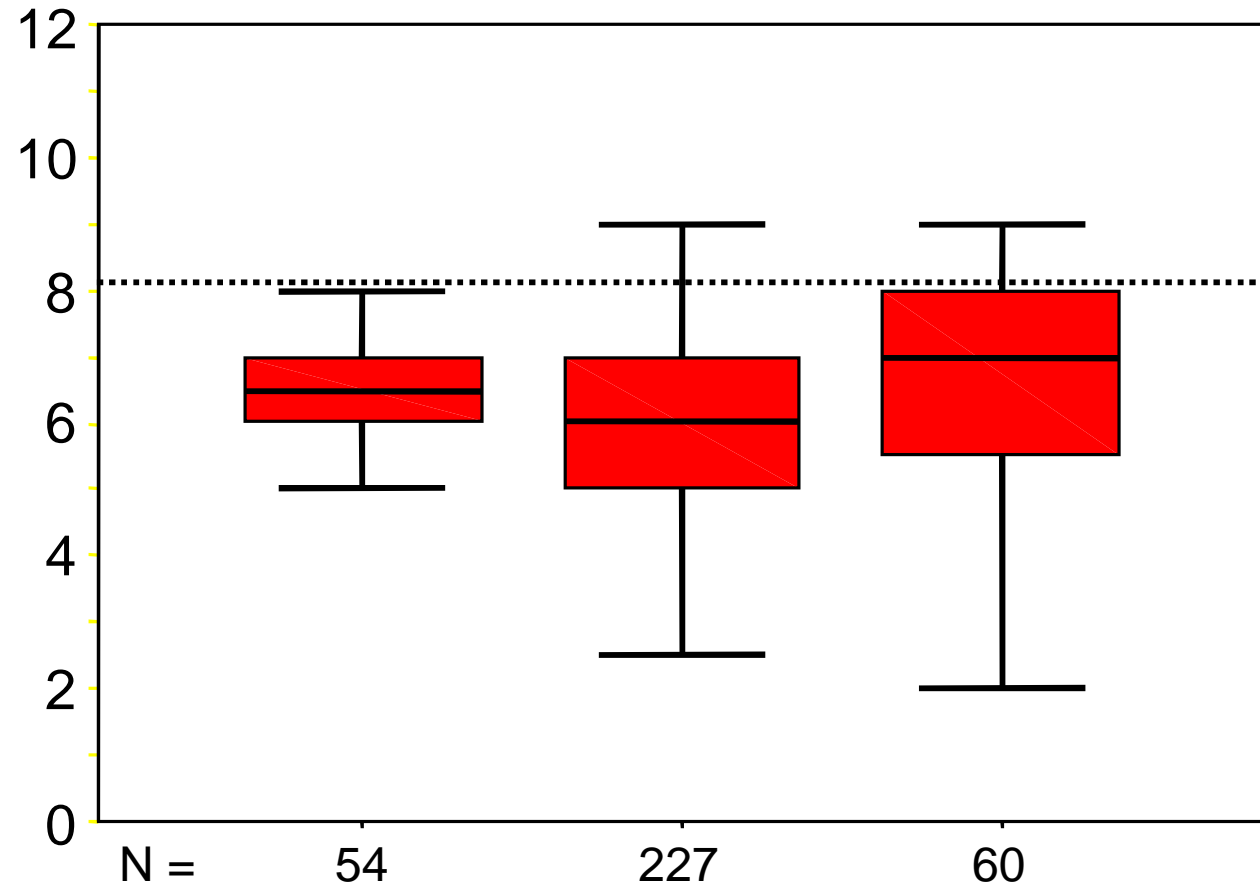
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- **Disruption of the Body Clock**
- Discussion



**Society is  
sleep  
deprived!**

# Self-reported weekday sleep (hours)



University of Chicago  
2001  
Survey Study  
Dr. Eve Van Cauter

18-25

35-50

60-75

Age (years)

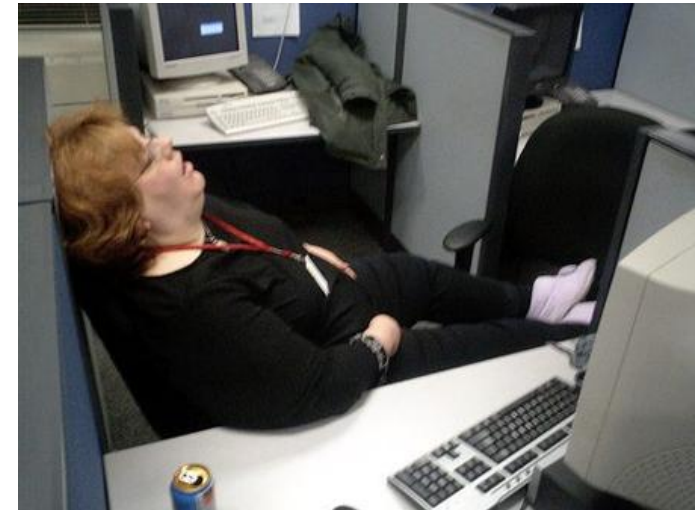
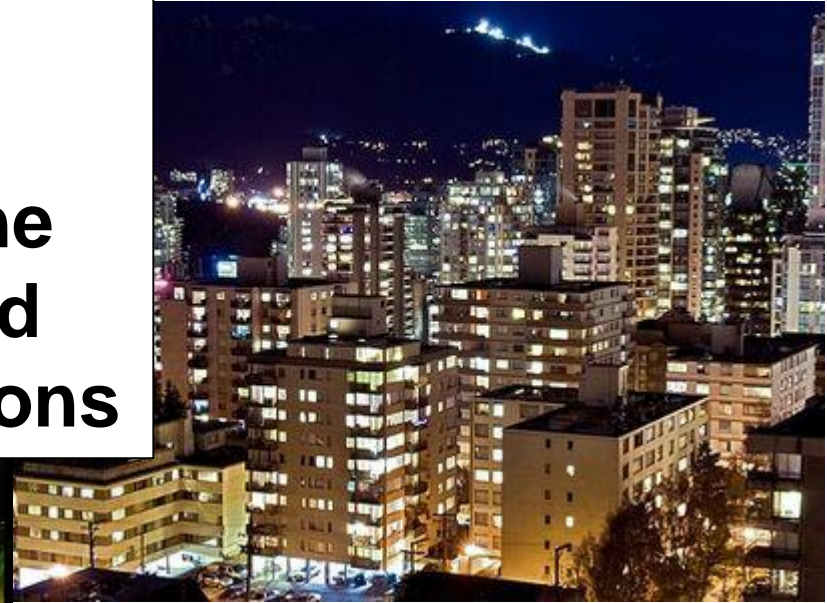
Mary Carskadon at Brown University has shown that, on average, US teenagers are getting about 7.5 hours a night's sleep on school nights, but as many as 25% get fewer than 6.5 hours per night.

Carskadon estimates that to be optimally alert, teenagers need approximately 9 hours of sleep.

**It is even worse  
for shift-  
workers....**



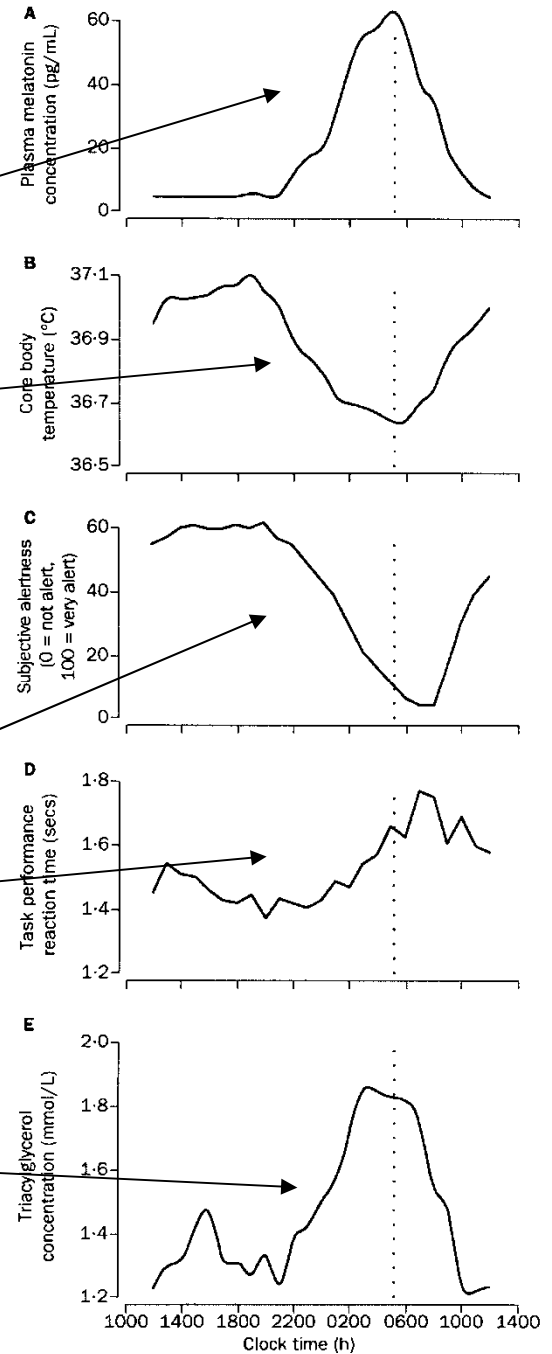
**Night Shift  
> 20% of the  
economy in the  
developed and  
developing nations**



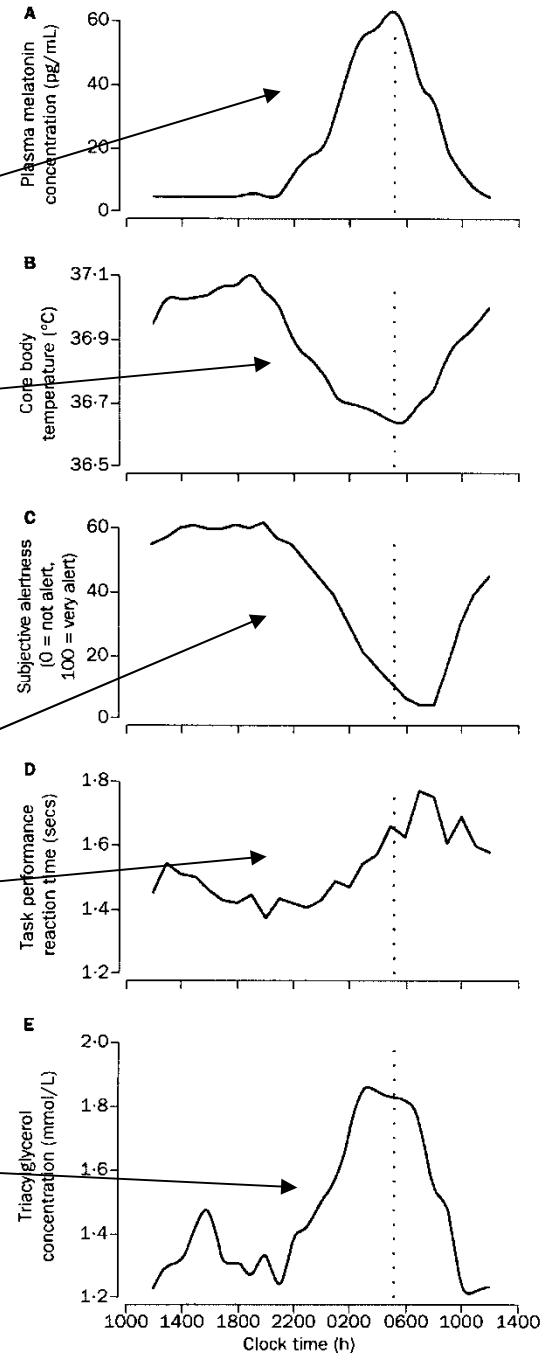
**Most night shift-workers do not shift their physiology in response to the demands of working at night.**

**WHY?**

<i>Rhythmic Changes in Human Physiology and Behaviour</i>	DAY	NIGHT
MELATONIN	LOW	HIGH
CORTISOL	HIGH	LOW
BODY TEMPERATURE	HIGH	LOW
CATECHOLAMINES	HIGH	LOW
URINE PRODUCTION	HIGH	LOW
GROWTH HORMONE	LOW	HIGH
ALERTNESS AND COGNITIVE PERFORMANCE	HIGH	LOW
LAPSES IN ATTENTION	LOW	HIGH
SLEEP	LOW	HIGH
MEMORY RECALL	HIGH	LOW
CAPACITY TO DIGEST FAT	HIGH	LOW
MUSCULAR STRENGTH	HIGH	LOW



<i>Rhythmic Changes in Human Physiology and Behaviour</i>	DAY	NIGHT
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MEMORY RECALL	HIGH	LOW
CAPACITY TO DIGEST FAT	HIGH	LOW
MUSCULAR STRENGTH	HIGH	LOW



**Many night shift-  
workers get 5.5h  
or less sleep  
every 24hs.**

# Consequences of Disrupted Sleep

- **Drowsiness/Microsleeps/Unintended Sleep**
- **Abrupt mood Shifts**
- **Increased irritability**
- **Anxiety and depression**
- **Weight gain**
- **Decreased socialization skills & sense of humor**
- **Decreased motor performance**
- **Decreased cognitive performance**
- **Reduced ability to concentrate & remember**
- **Reduced communication & decision skills**
- **Increased risk-taking**
- **Reduced quality, creativity & productivity**
- **Reduced immunity to disease and viral infection.**
- **Feelings of being chilled**
- **Reduced ability to handle complex tasks or multi-task**

# Night-shift workers in a nuclear power plant.

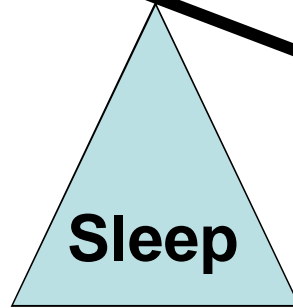
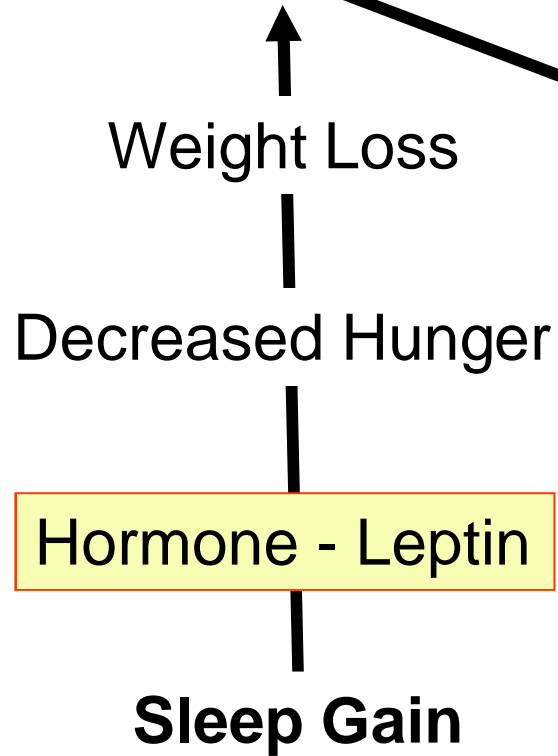
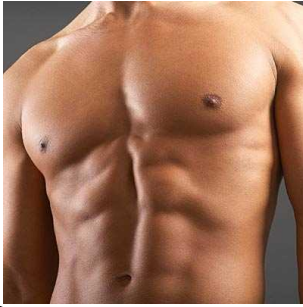
- **60% of workers fall asleep 1/week**
- **25% of workers fall asleep 4-5/week**
- **15% of workers fall asleep 10/week**
  
- **33% of workers admitted that falling asleep had caused a significant error or near-miss once/year**
  
- **All 5 controllers were found asleep – and did not appreciate that they had fallen asleep**





# Consequences of Disrupted Sleep

- Drowsiness/Microsleeps/Unintended Sleep
- Abrupt mood Shifts
- Increased irritability
- Anxiety and depression
- **Weight gain**
- Decreased socialization skills & sense of humor
- Decreased motor performance
- Decreased cognitive performance
- Reduced ability to concentrate & remember
- Reduced communication & decision skills
- Increased risk-taking
- Reduced quality, creativity & productivity
- Reduced immunity to disease and viral infection.
- Feelings of being chilled
- Reduced ability to handle complex tasks or multi-task



**Sleep Loss**

Hormone - Ghrelin

Increased Hunger

Weight Gain  
↓



# Sleep and Calorific Intake

Columbia University:

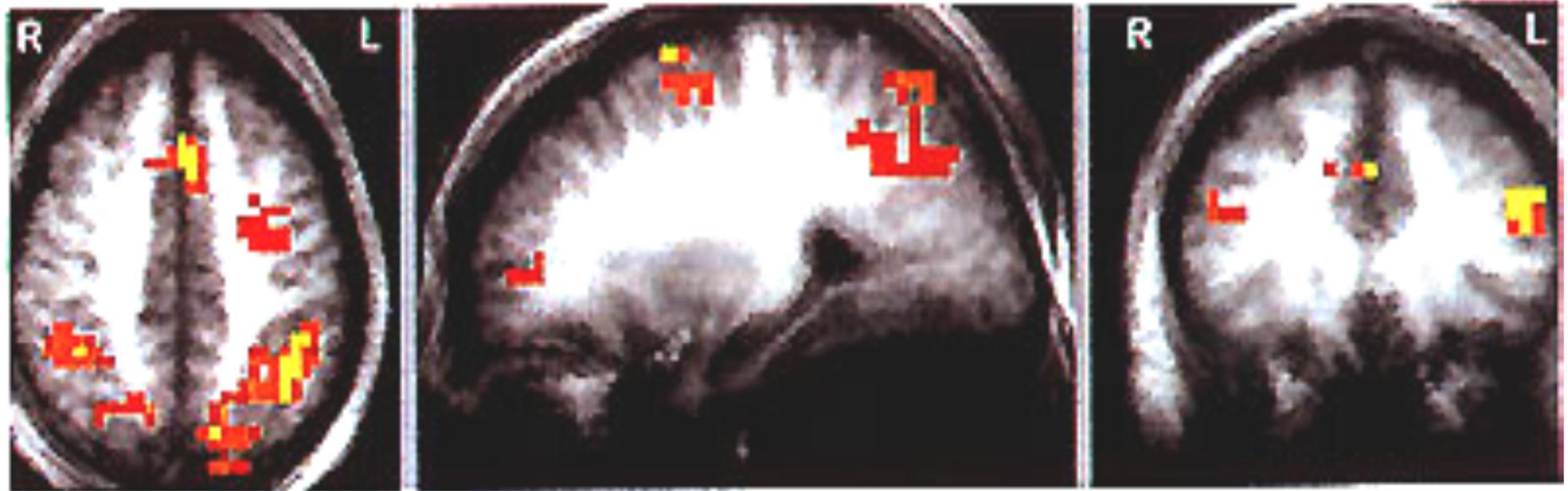
Hours of sleep per night	% likelihood of being obese
< 4h	73%
~ 5h	50%
~ 6h	23%

# Consequences of Disrupted Sleep

- **Drowsiness/Microsleeps/Unintended Sleep**
- **Abrupt mood Shifts**
- **Increased irritability**
- **Anxiety and depression**
- **Weight gain**
- **Decreased socialization skills & sense of humor**
- **Decreased motor performance**
- **Decreased cognitive performance**
- **Reduced ability to concentrate & remember**
- **Reduced communication & decision skills**
- **Increased risk-taking**
- **Reduced quality, creativity & productivity**
- **Reduced immunity to disease and viral infection.**
- **Feelings of being chilled**
- **Reduced ability to handle complex tasks or multi-task**

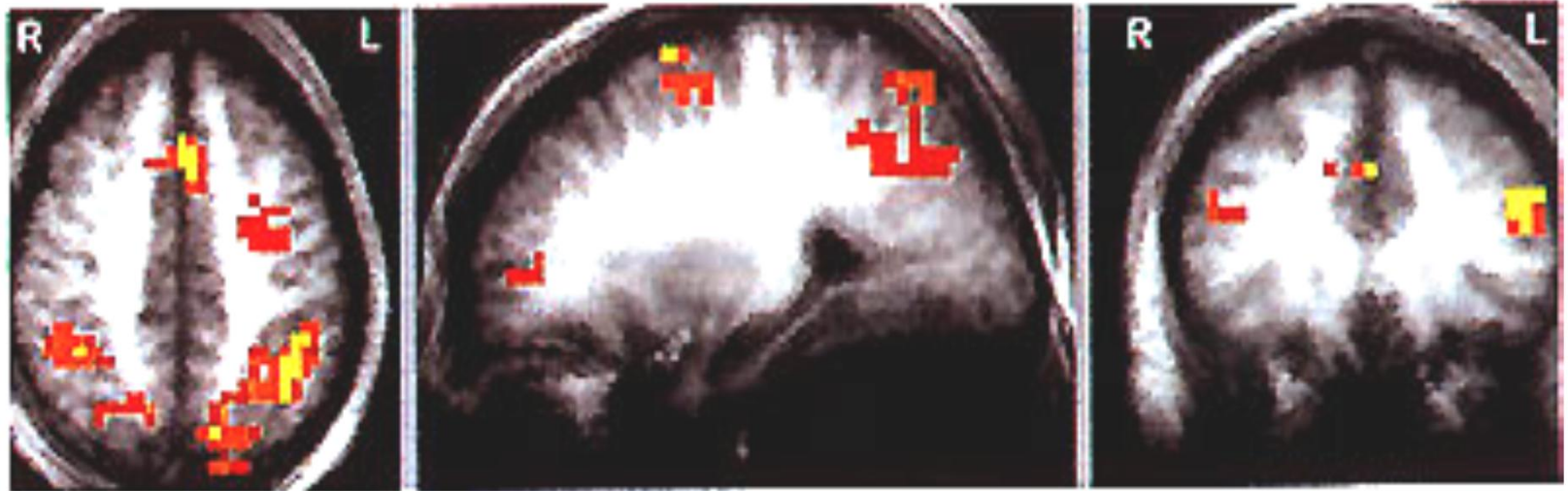
# Effect of sleep deprivation on brain activation while performing mathematical tasks (fMRI)

Rested

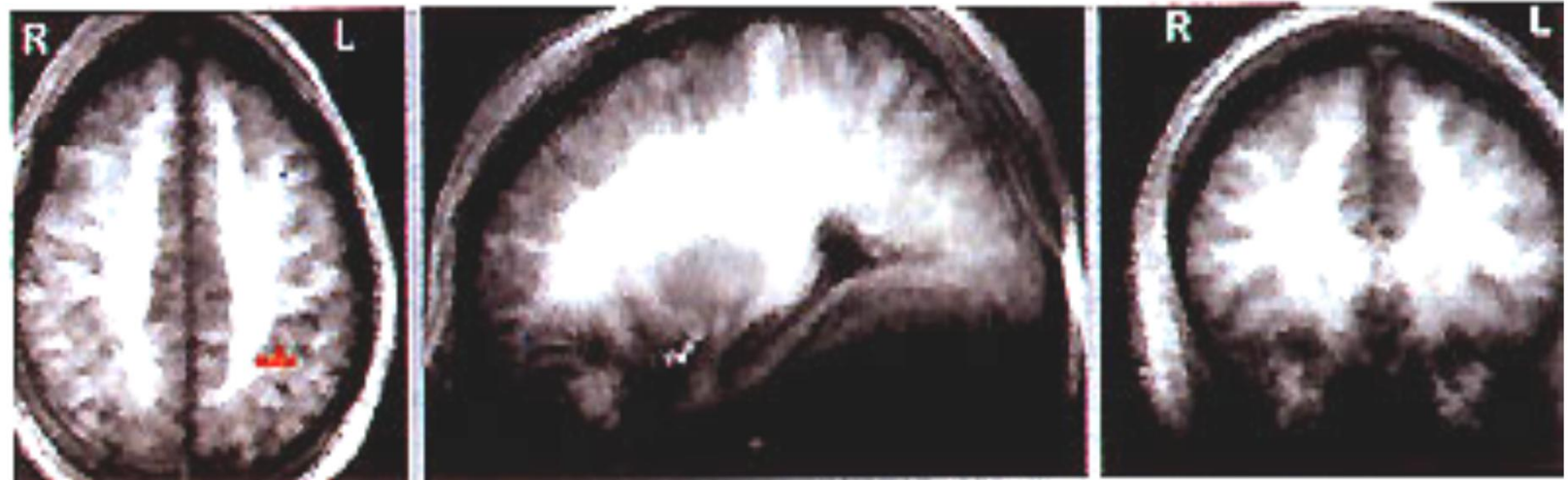


## Effect of sleep deprivation on brain activation while performing mathematical tasks (fMRI)

Rested



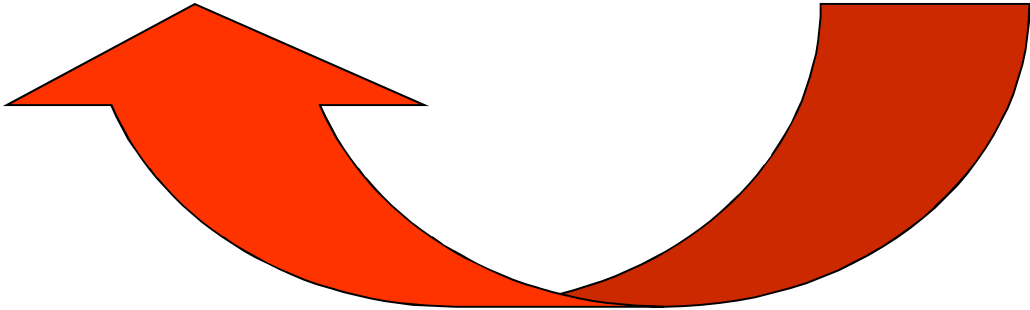
Sleep Deprived



# Consequences of Disrupted Sleep

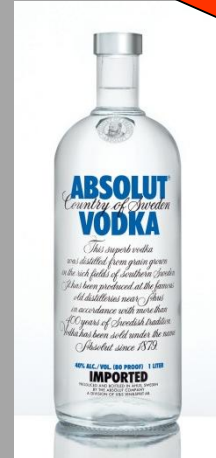
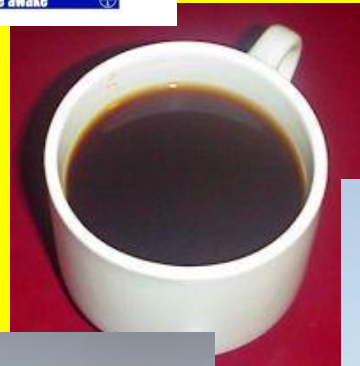
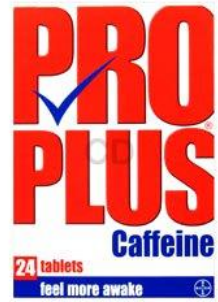
- Drowsiness/Microsleeps/Unintended Sleep
- Abrupt mood Shifts
- Increased irritability
- Anxiety and depression
- Metabolic Problems - Weight gain/loss
- Decreased socialization skills & sense of humor
- Decreased motor performance
- Decreased cognitive performance
- Reduced ability to concentrate & remember
- Reduced communication & decision skills
- **Increased stimulant and sedative use**
- Increased risk-taking
- Reduced creativity & productivity
- Reduced immunity to disease and viral infection.
- Feelings of being chilled
- Reduced ability to multi-task

# Stimulant/Sedation feed-back loop





# Stimulant/Sedation feed-back loop



## Biology in the real world: Light, body clocks and sleep

- Introduction – The Body Clock
- Light Regulation of The Body Clock
- Time of Day Effects
- Disruption of the Body Clock
- Discussion



**Sleep Hygiene!**

# Do

- Go to bed at the same time each day.**
- Get up from bed at the same time each day.**
- Get regular exercise each day, preferably in the morning.**
- Get regular exposure to outdoor or bright lights.**
- Keep the temperature in the bedroom cool.**
- Keep the bedroom quiet when sleeping.**
- Keep the bedroom dark enough to facilitate sleep.**
- Keep feet and hands warm.**

---

# Don't

- Watch television in bed.**
- Work at a computer just before bed**
- Argue just before bed.**
- Have caffeine in the evening.**
- Use alcohol to help you sleep.**
- Go to bed too hungry or too full.**
- Take another person's sleeping pills.**
- Take over-the-counter sleeping pills.**
- Take naps over 20-30 min.**
- Command yourself to go to sleep.**