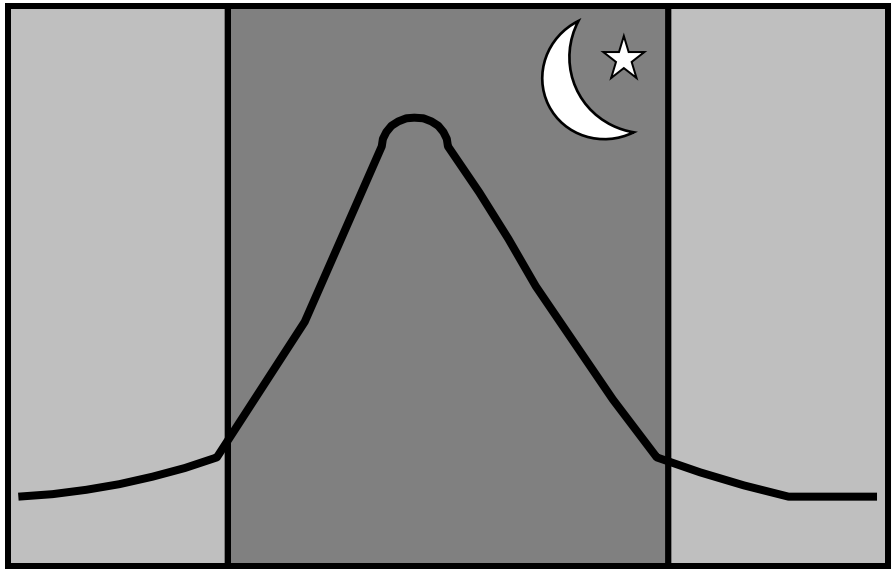
Biological rhythms



Sleep/wake cycles
Locomotor activity
Cognitive abilities
Reaction time
Body temperature
Metabolism
Hormone secretion
Enzymatic activities
Gene expression

→ Biological clock

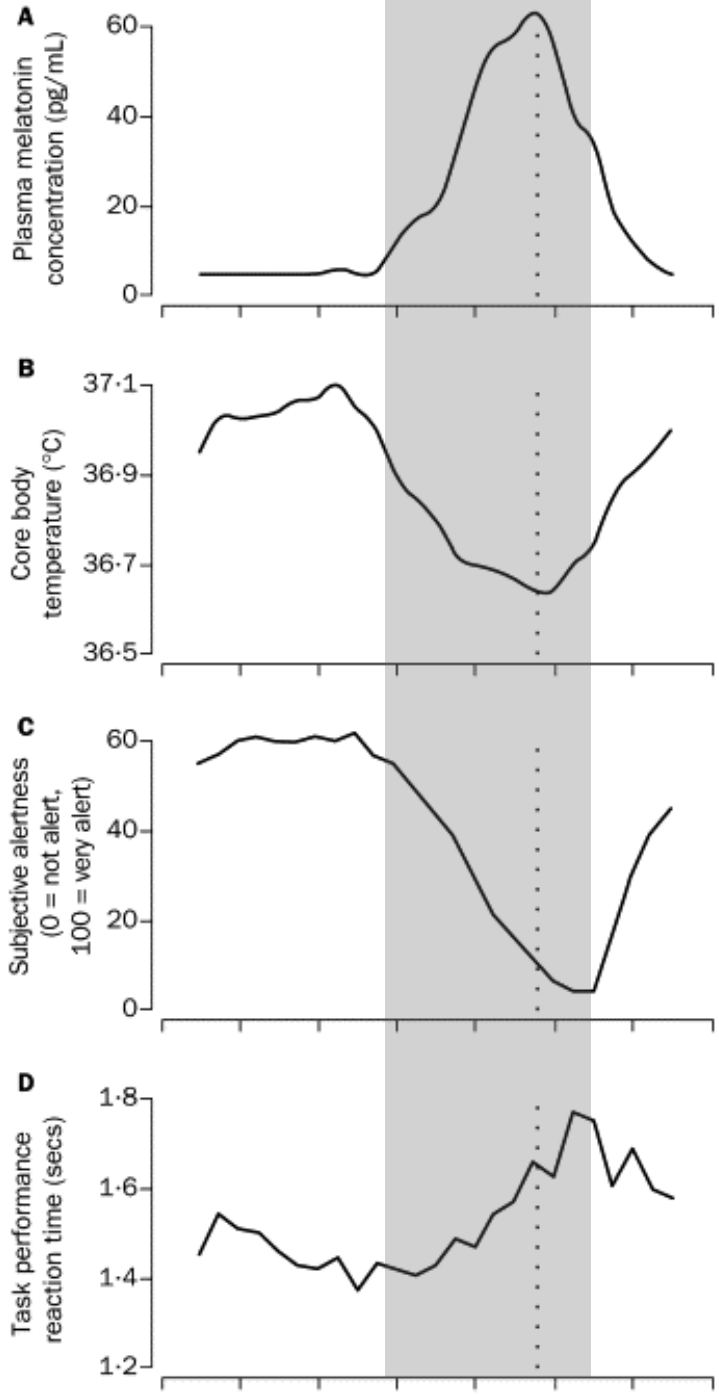
Why?

Who cares?

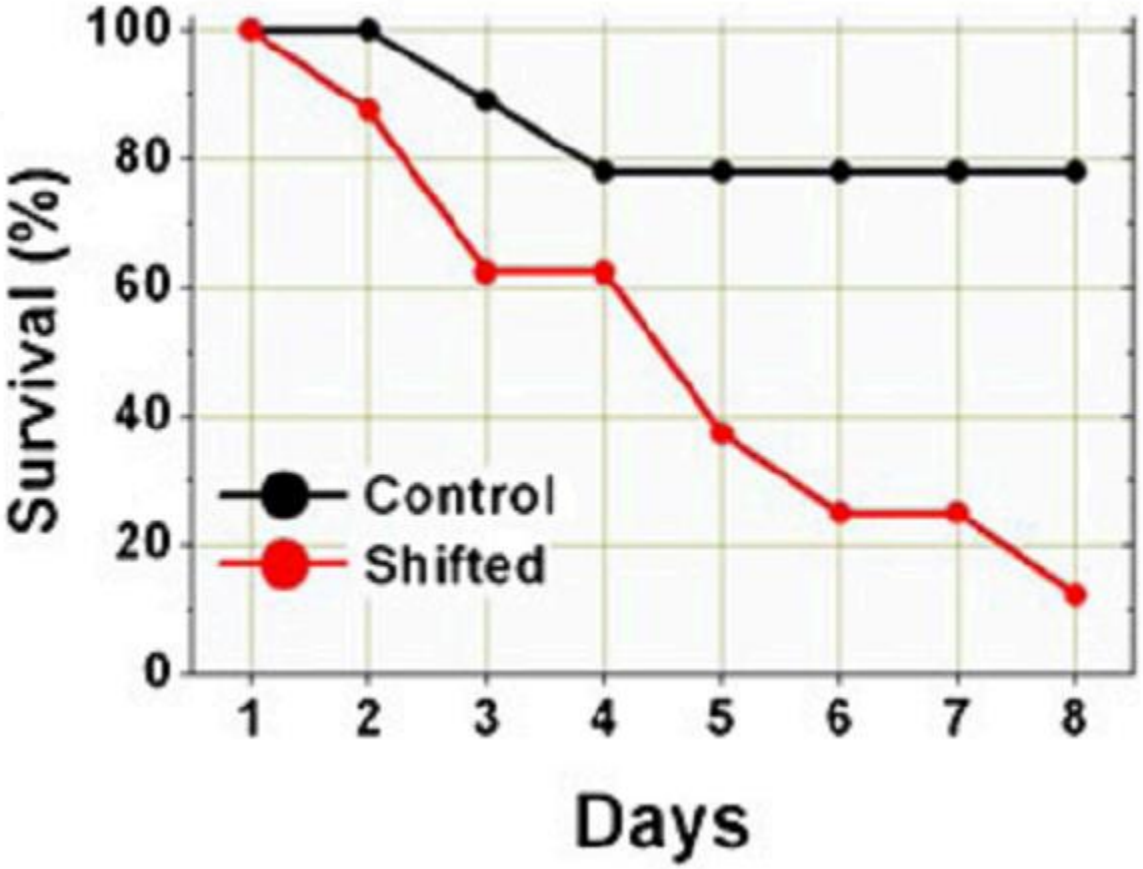
Research Importance

Medical importance: time of treatment, time of symptoms, synchronization of rhythms

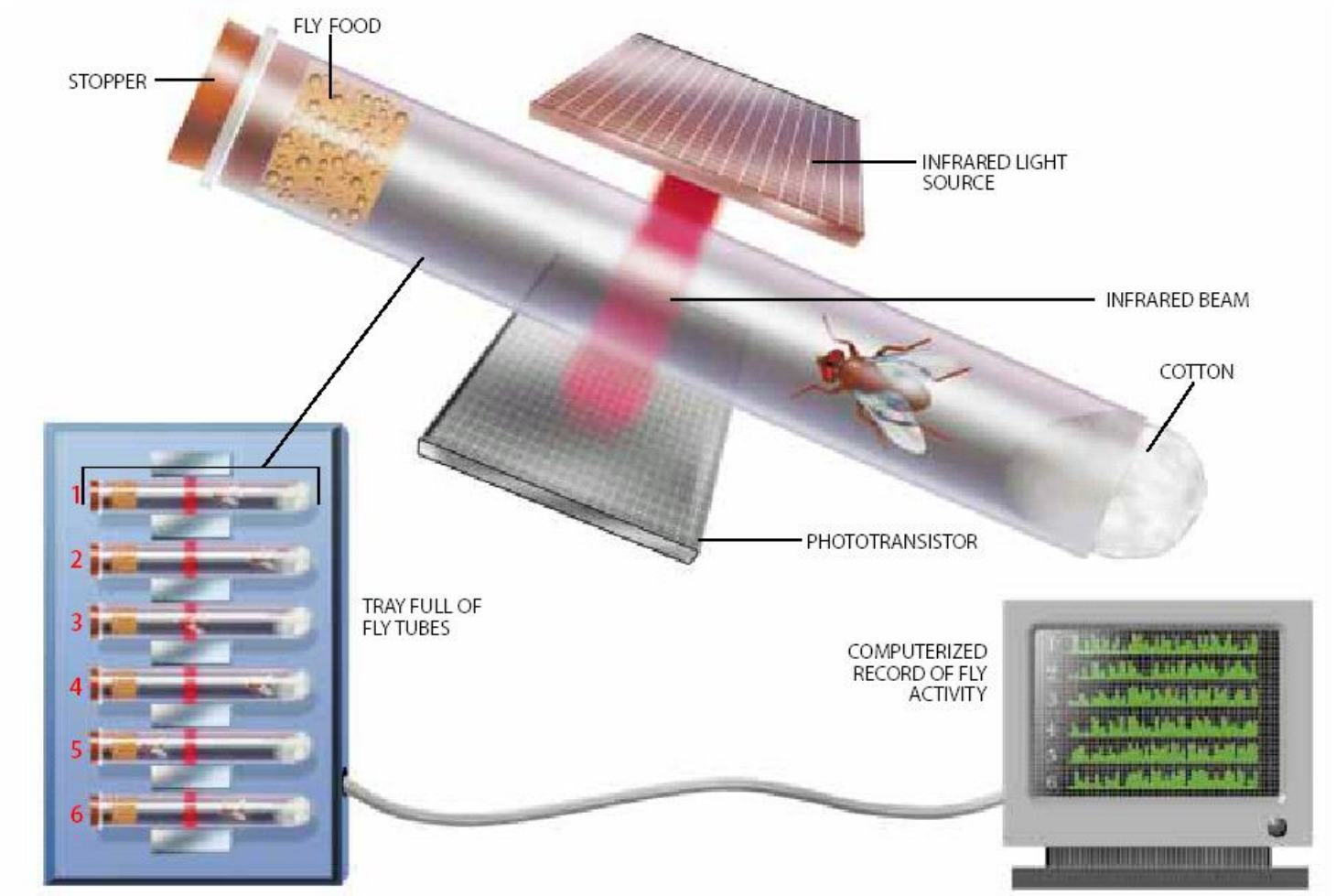
Economical importance: accidents, efficiency.


A
Plasma melatonin concentration (pg/mL)
60
40
20
0
B
Core body temperature (°C)
37·1
36·9
36·7
36·5
C
Subjective alertness (0 = not alert, 100 = very alert)
60
40
20
0
D
Task performance reaction time (secs)
1·8
1·6
1·4
1·2

“Shift workers” mice are less resistant to Lipopolysaccharides (LPS)-induced endotoxemic shock



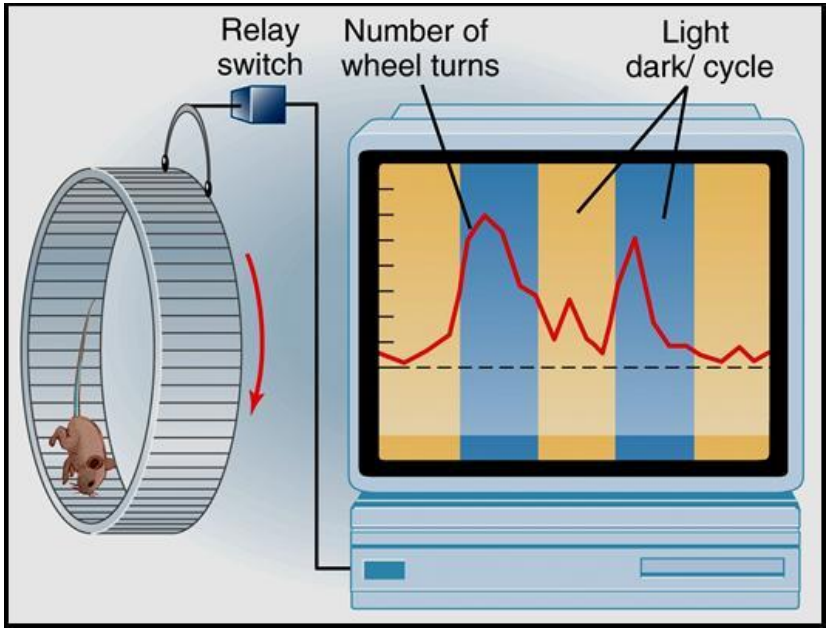
Castanon-Cervantes et al., 2010


FLY FOOD
STOPPER
INFRARED LIGHT SOURCE
INFRARED BEAM
COTTON
PHOTOTRANSISTOR
1
2
3
4
5
6
TRAY FULL OF FLY TUBES
COMPUTERIZED RECORD OF FLY ACTIVITY

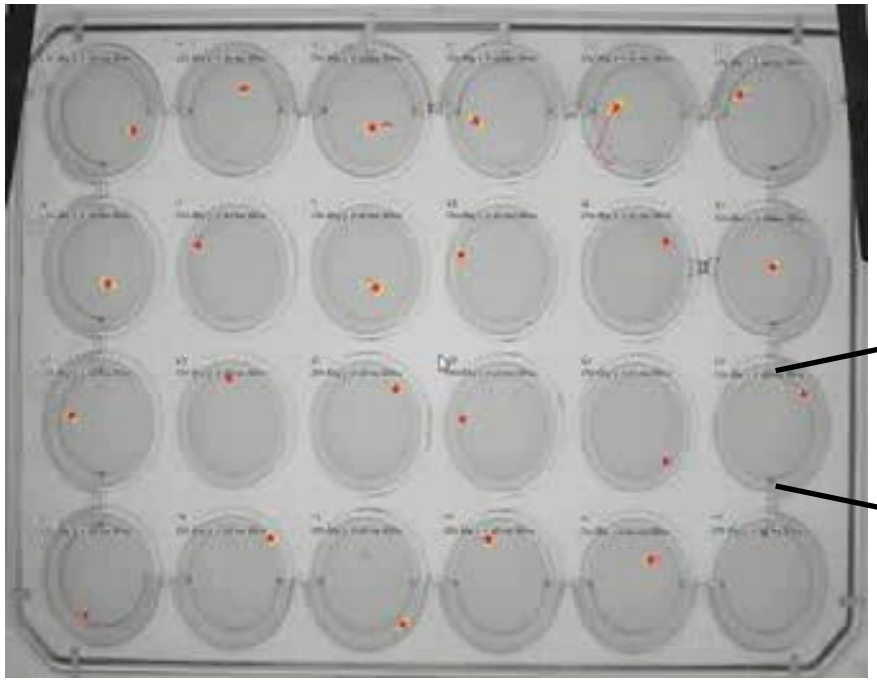
Monitoring circadian rhythms of activity in rodents.

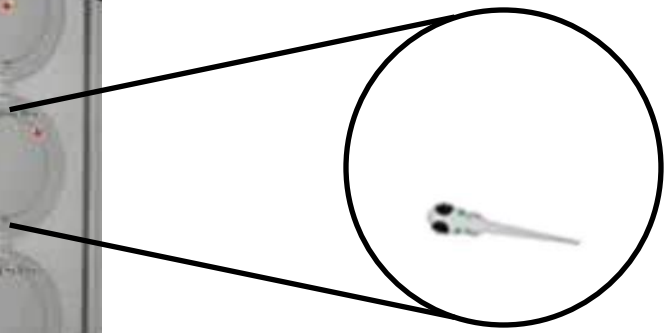
Actogram, the secret hand-shake of chronobiologists

Free running

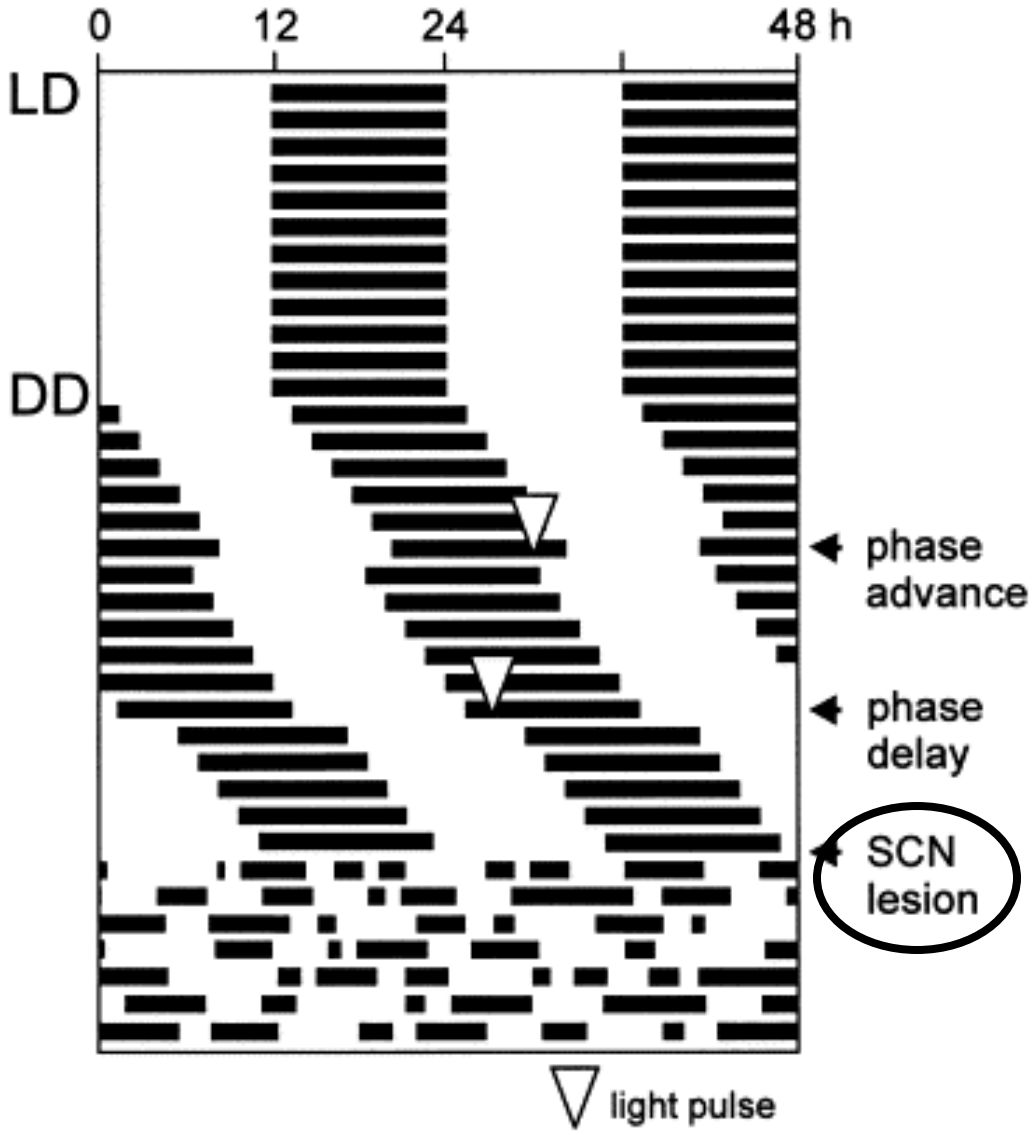


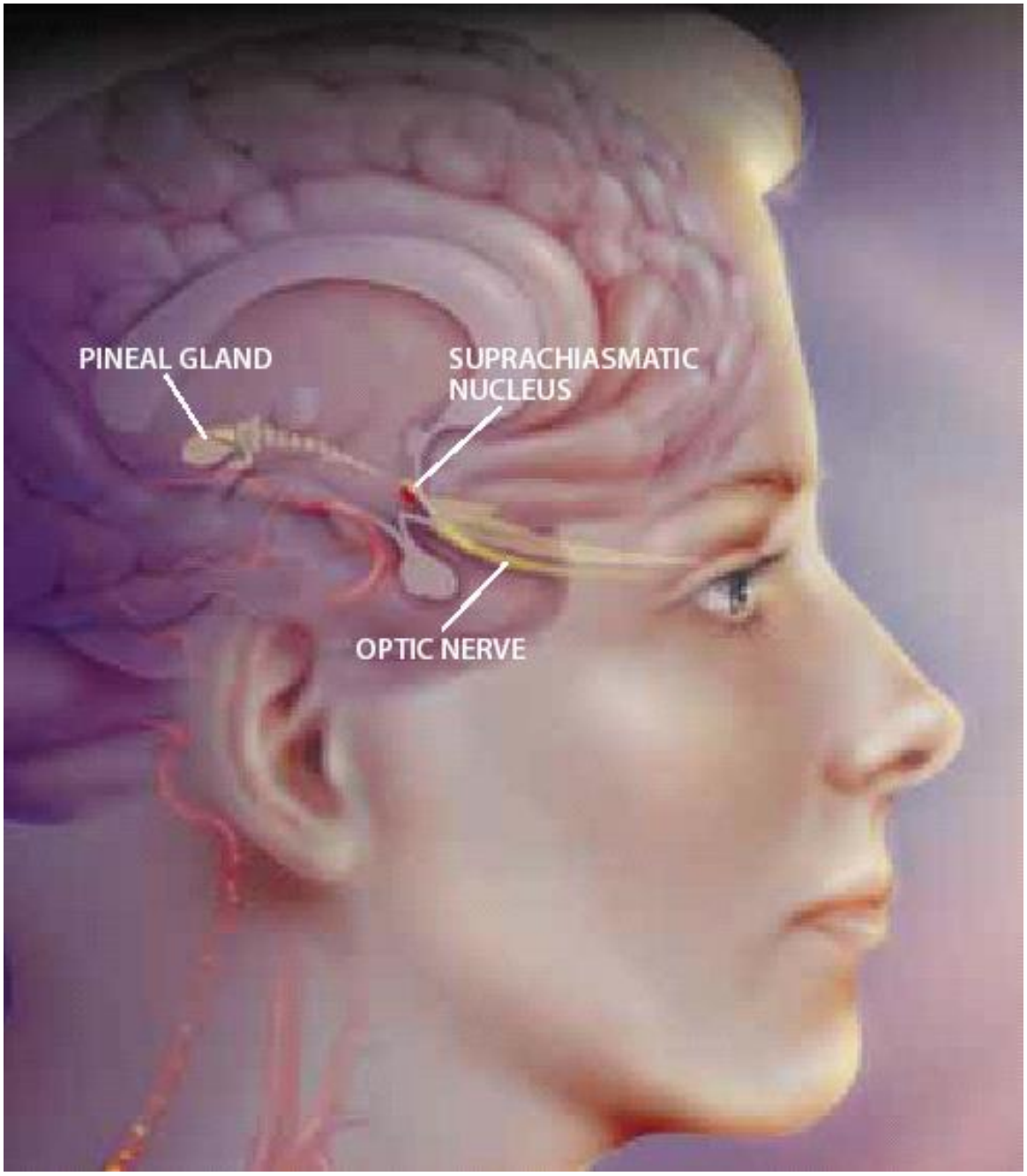
Monitoring circadian rhythms of activity in zebrafish



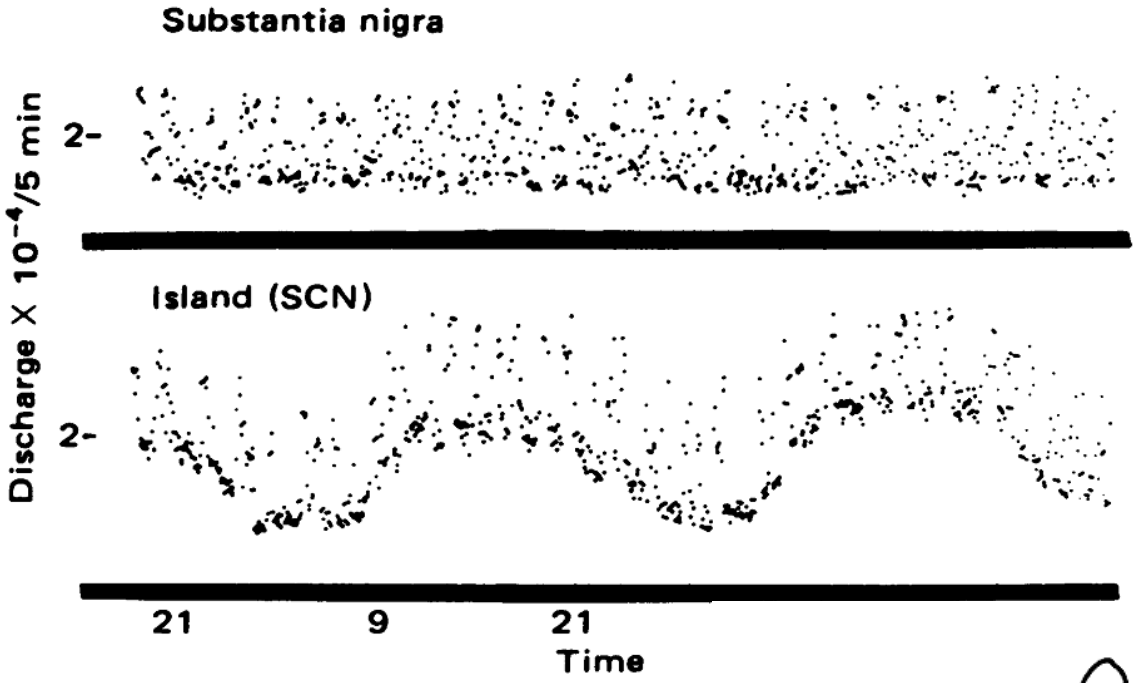


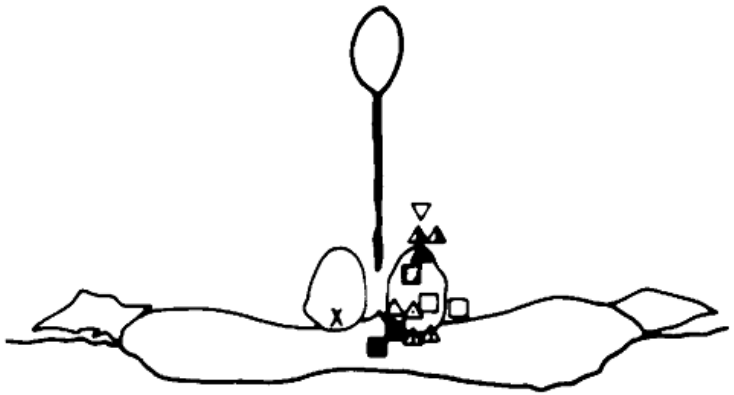
DanioVision, Noldus


0
12
24
48 h
LD
DD
phase advance
phase delay
SCN lesion
light pulse


PINEAL GLAND
SUPRACHIASMATIC NUCLEUS
OPTIC NERVE

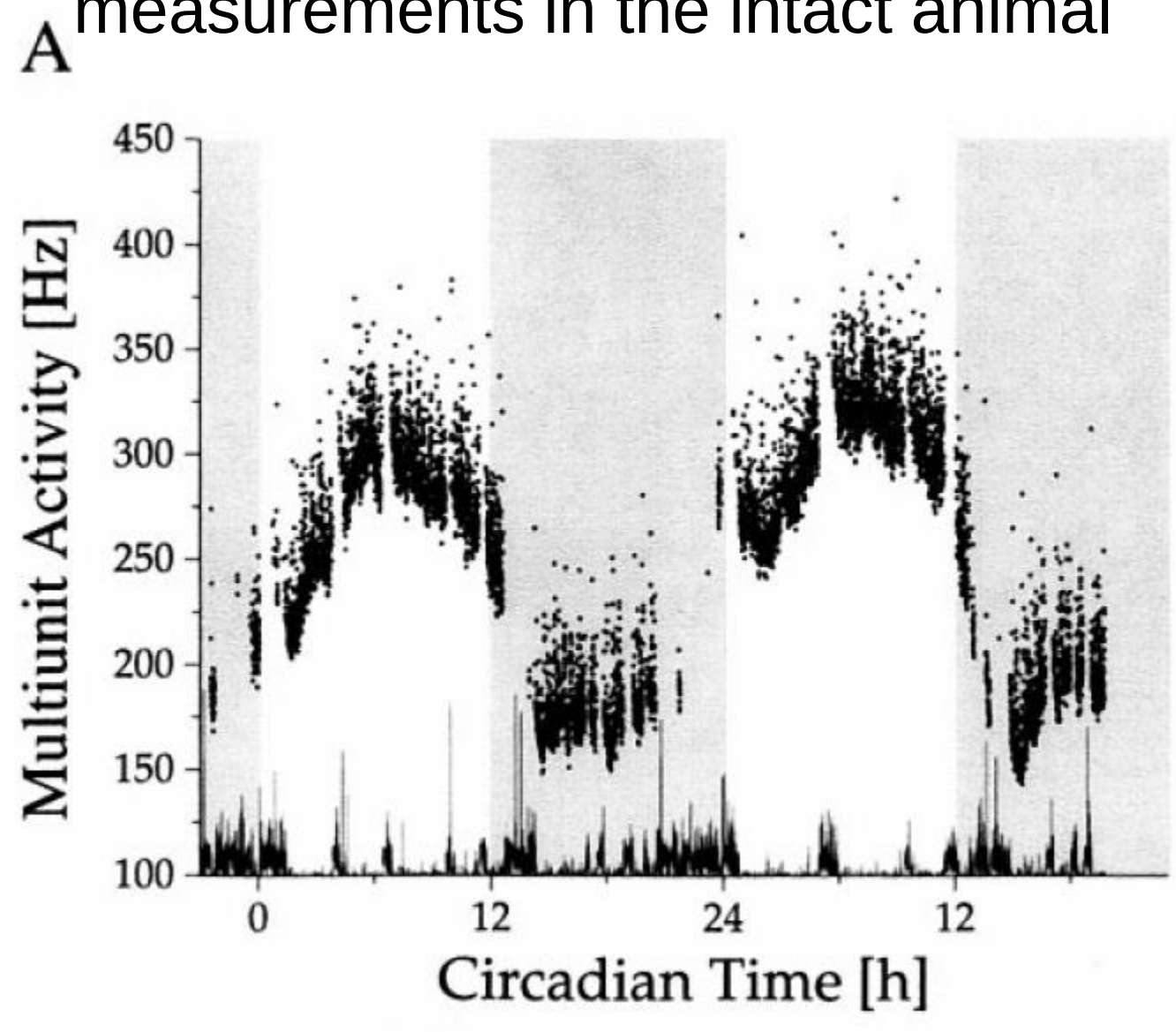
Rhythms of firing rate in the SCN, measurements in the intact animal





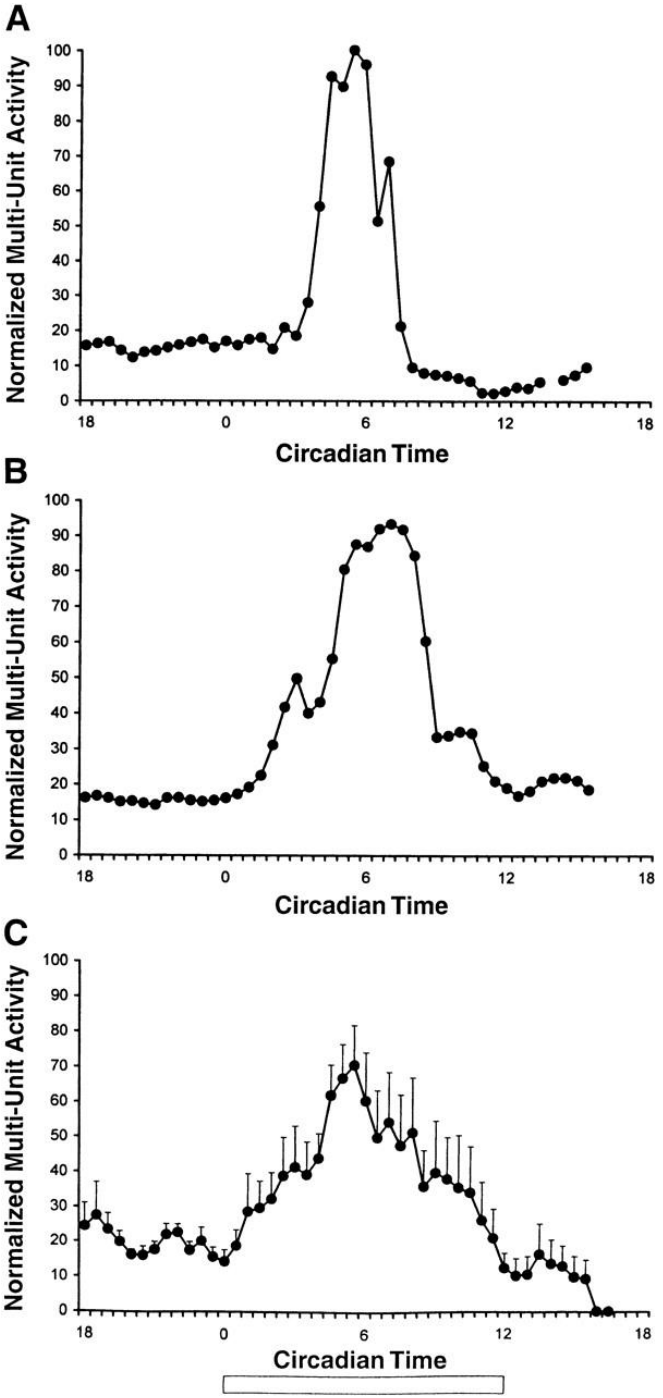
Inouye & Kawamuram 1979

Rhythms of firing rate in the SCN, measurements in the intact animal



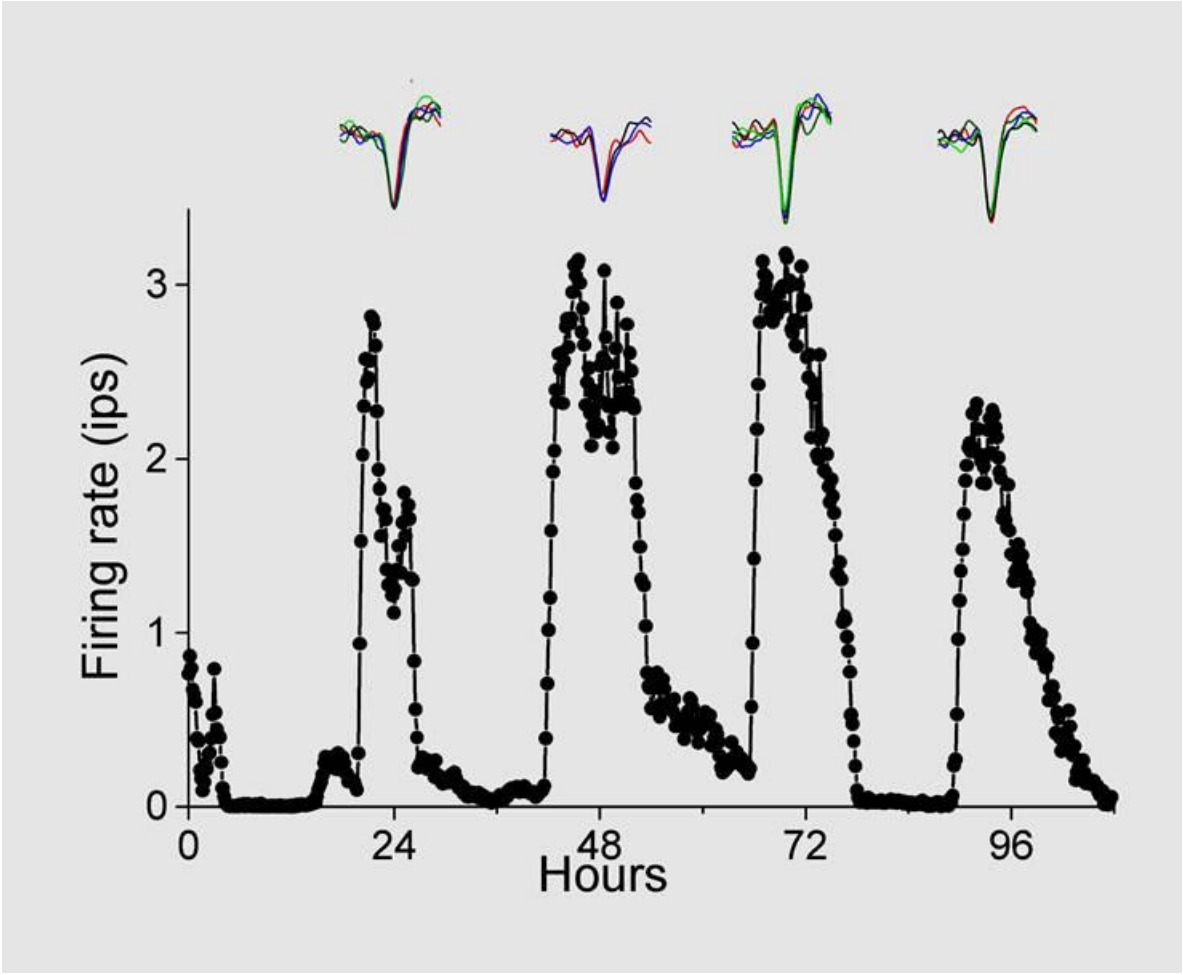
Meijer et al., 1998

Rhythms of firing rate in the SCN, measurements in tissue culture

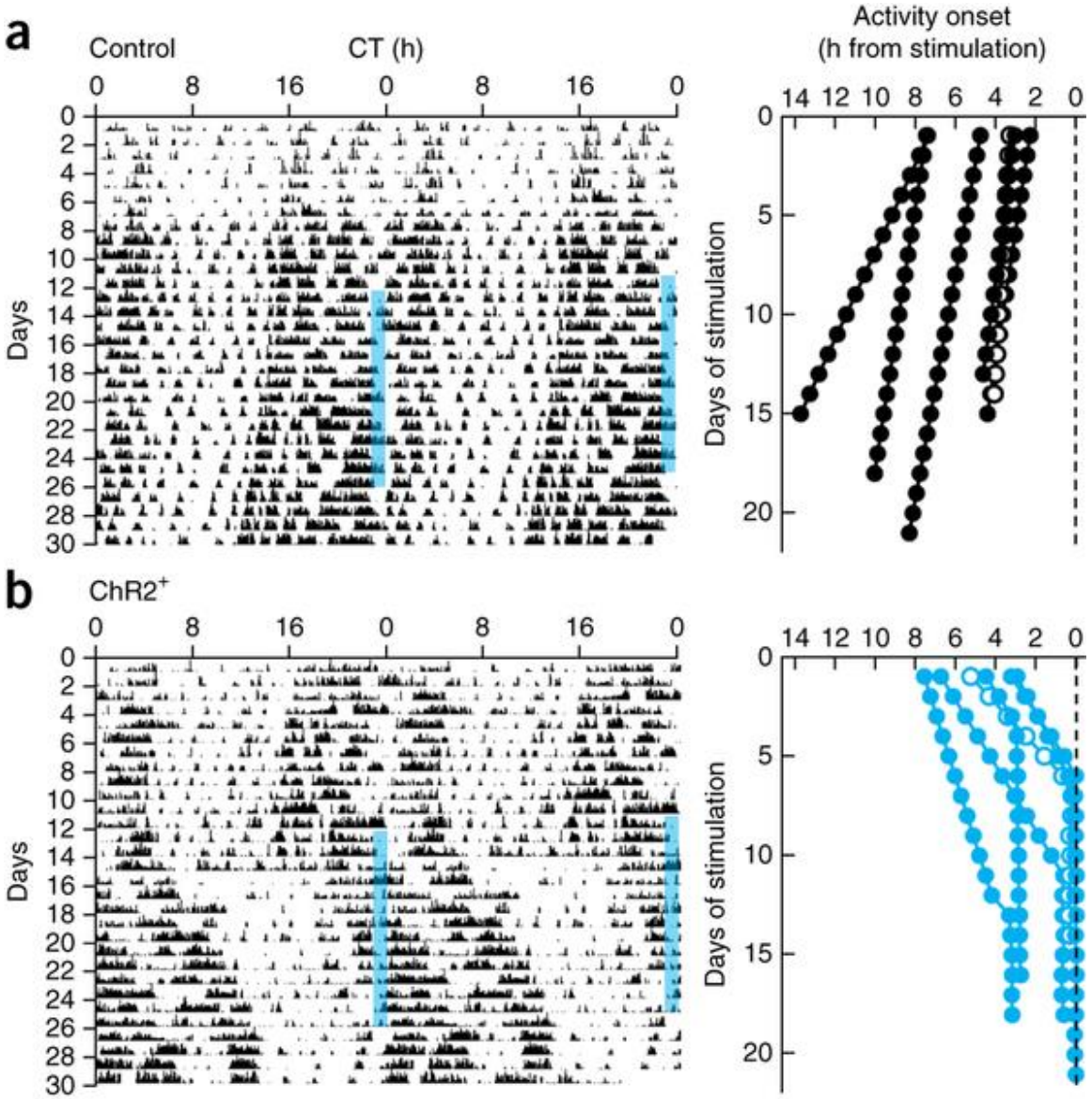


Mrugala et al., 2000

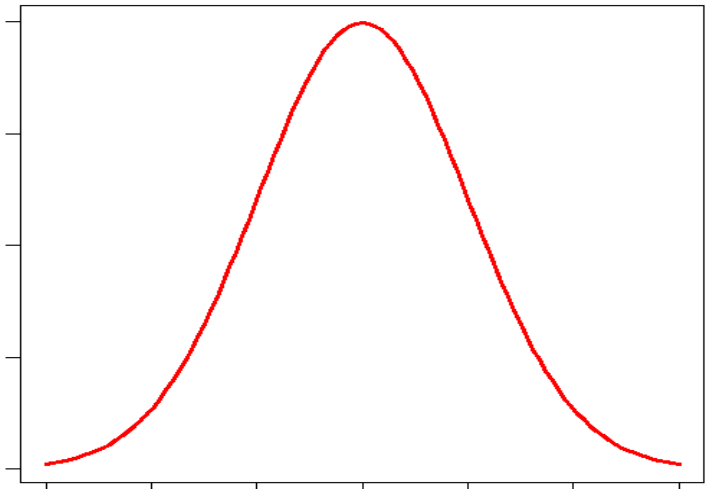
Rhythms of firing rate in the SCN, measurements in SCN cell culture

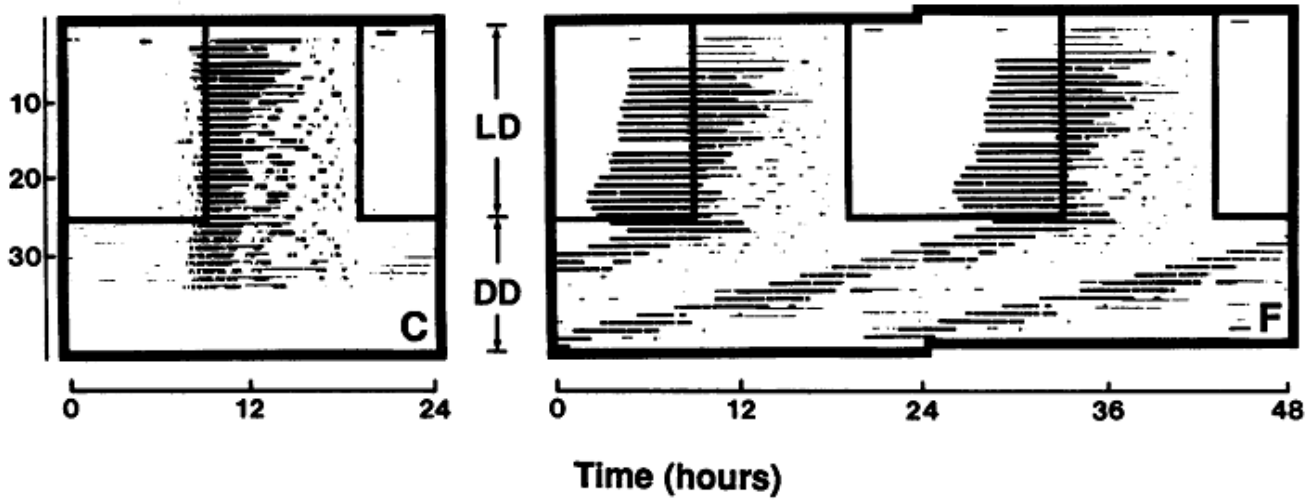


Optogenetic-stimulation of the SCN entrains rhythmic locomotor activity

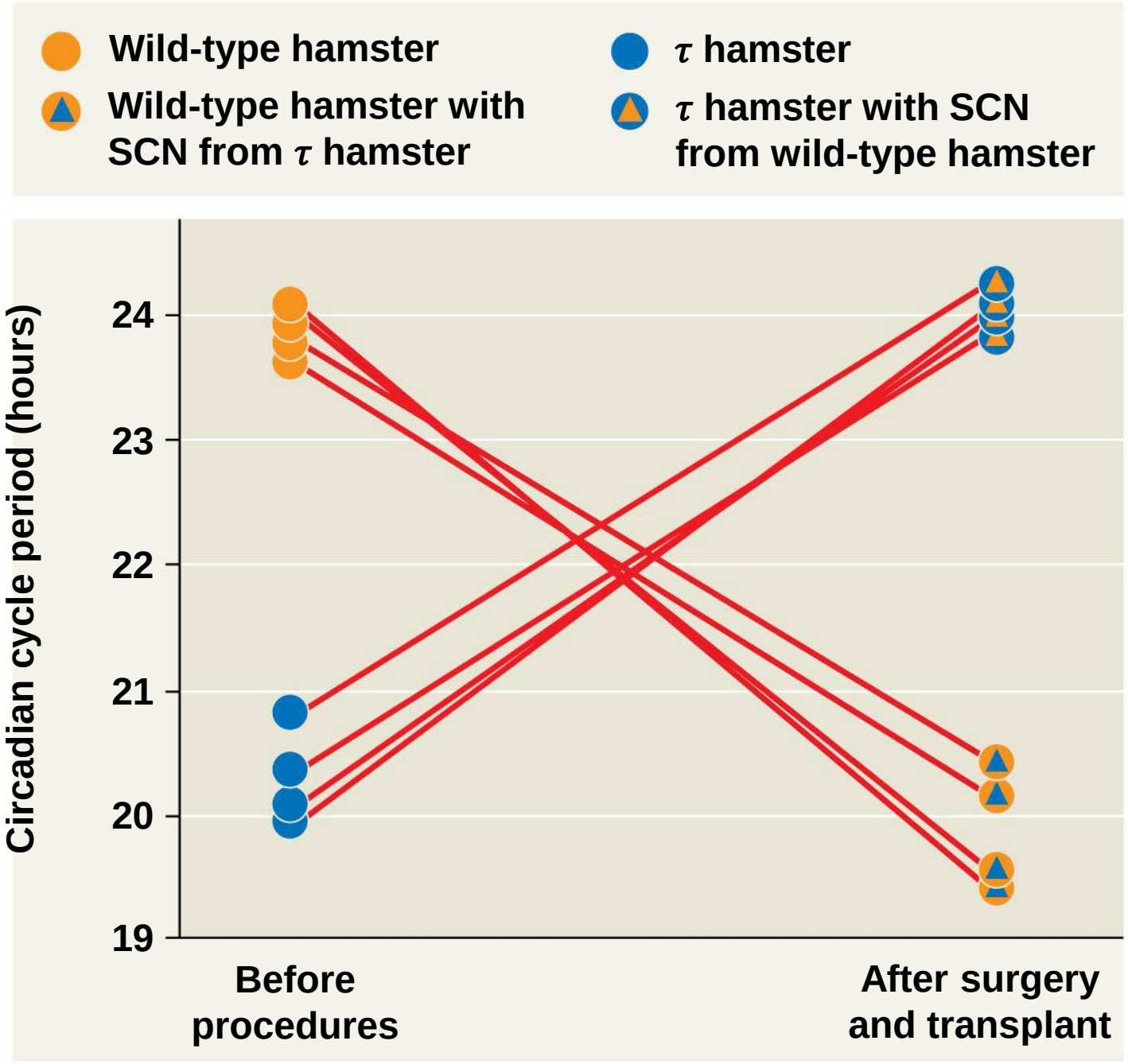


Mike Menaker





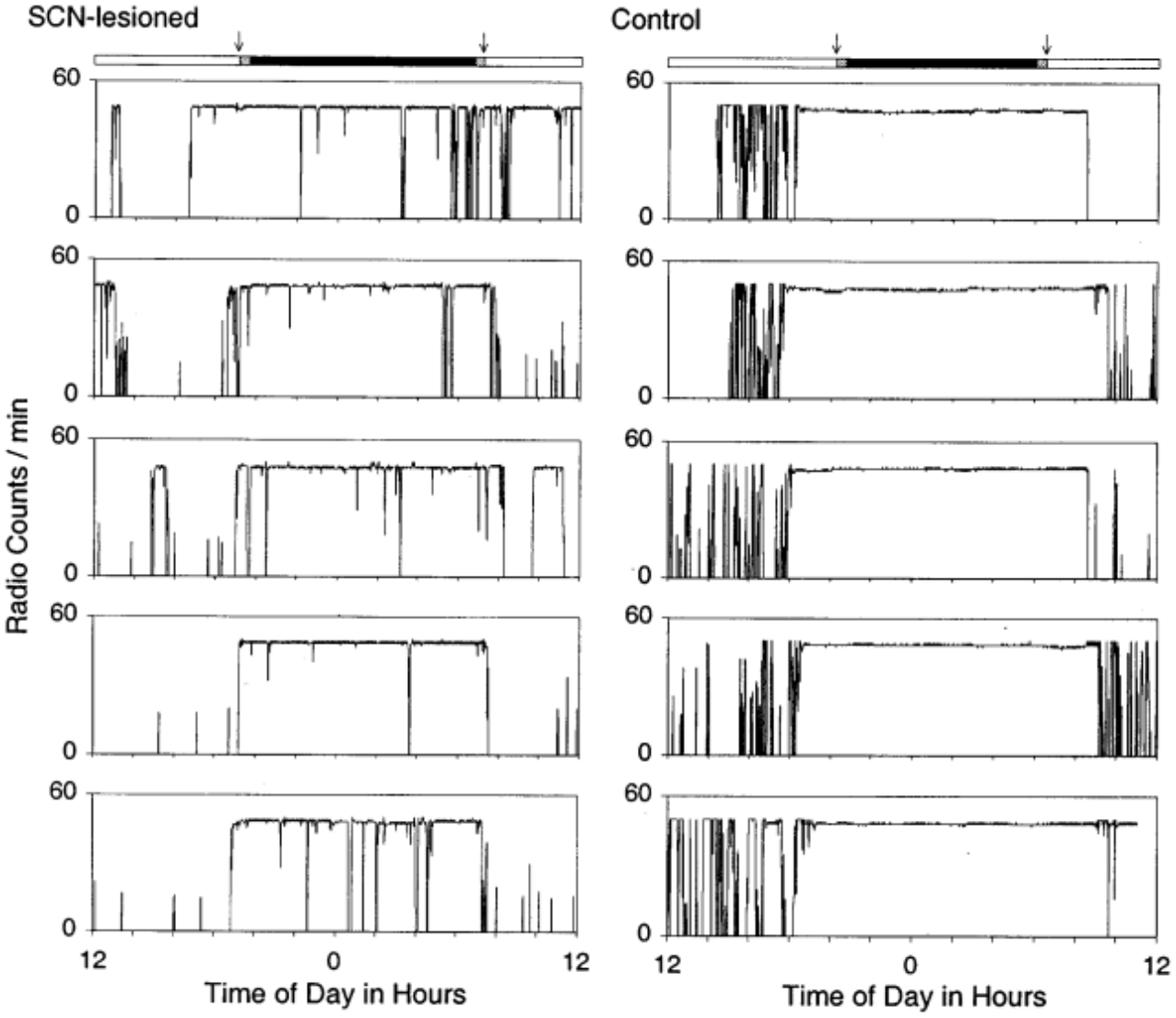
Ralph et al., 1990


Wild-type hamster
Wild-type hamster with SCN from τ hamster
τ hamster
τ hamster with SCN from wild-type hamster
Circadian cycle period (hours)
24
23
22
21
20
19
Before procedures
After surgery and transplant

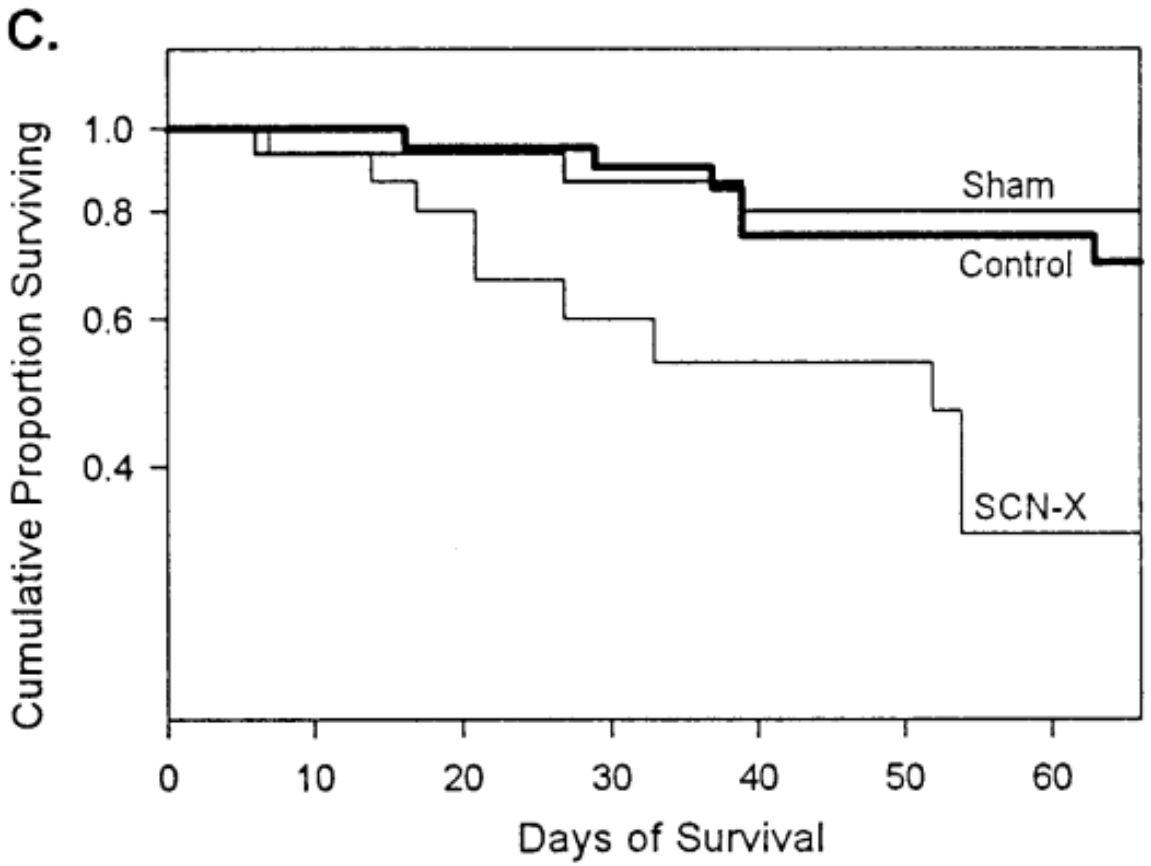
What are the evidence that the SCN is the central pacemaker (or central clock)?

- SCN lesion led to loss of rhythms
- SCN neurons have an intrinsic clock
- Stimulation of SCN neurons synchronized rhythms
- An implanted SCN dictates the rhythm

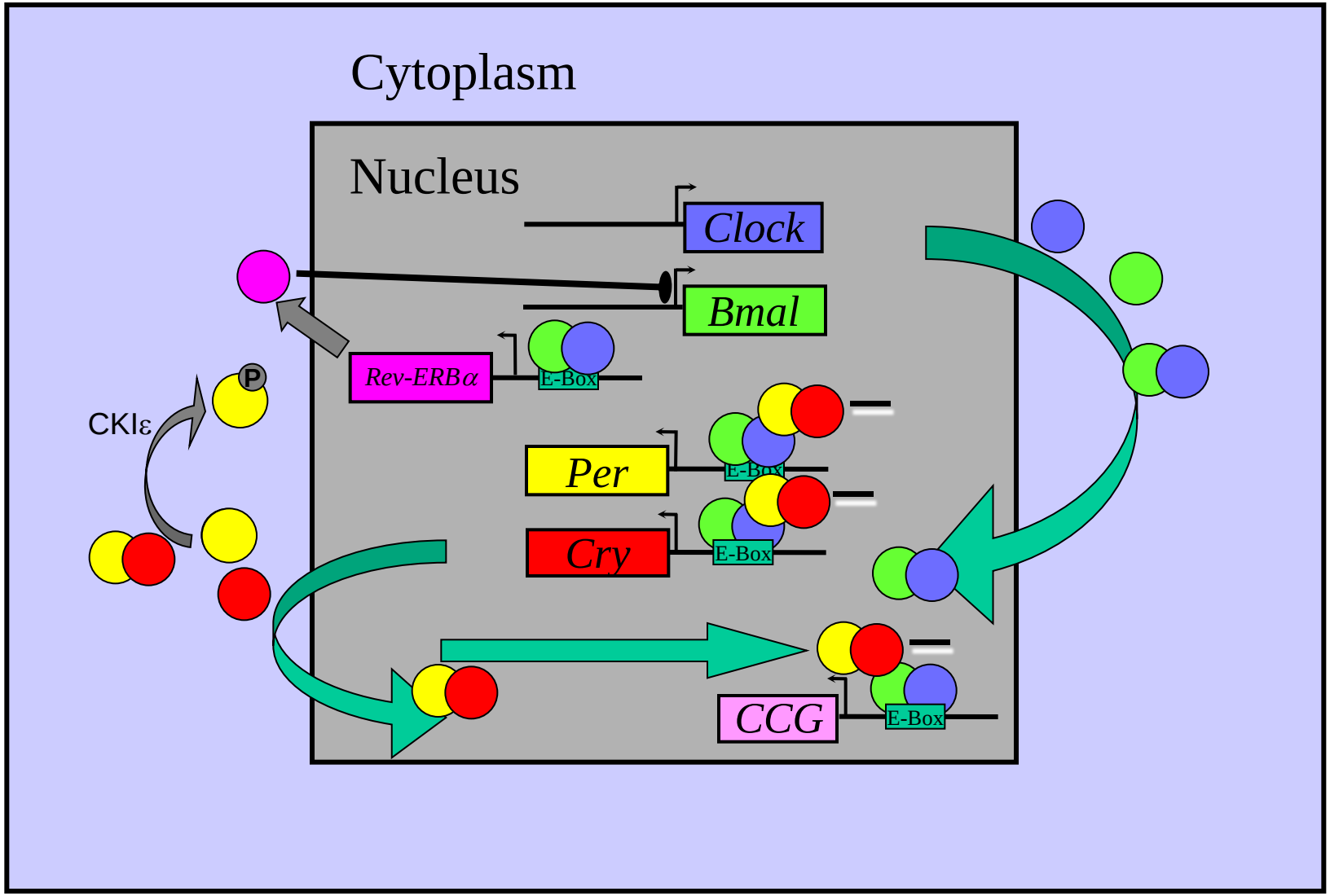
How important is the SCN?
A wild experiment


SCN-lesioned
Control
Radio Counts / min
60
0
12
0
12
Time of Day in Hours

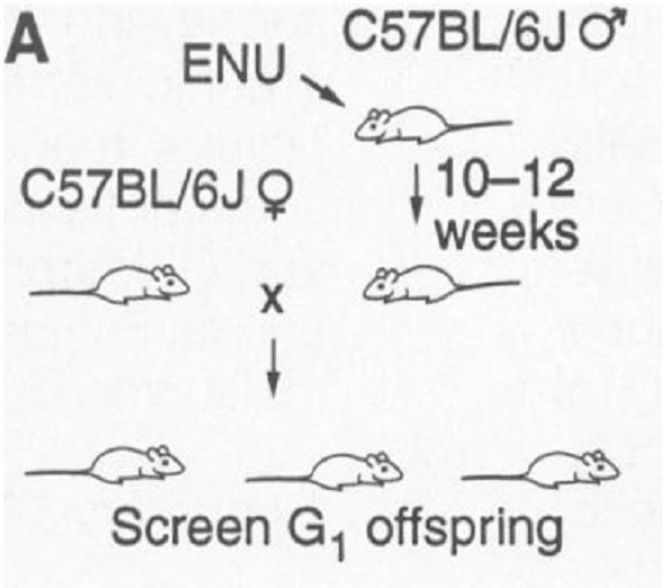
SCN-lesioned animals did not survive well

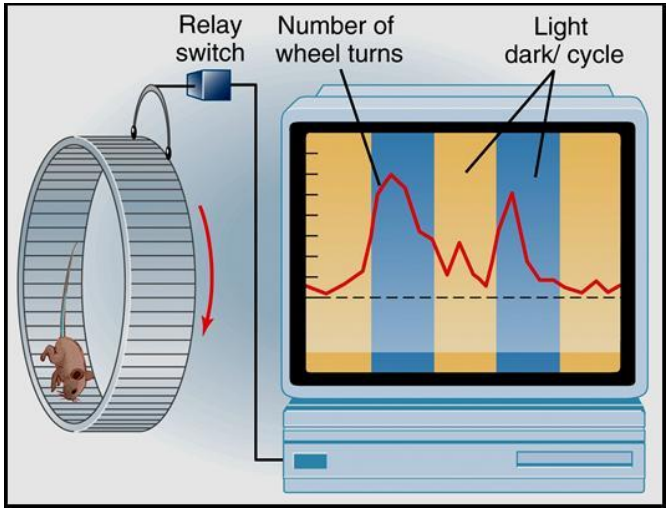


Molecular oscillator based on a transcription feedback loops

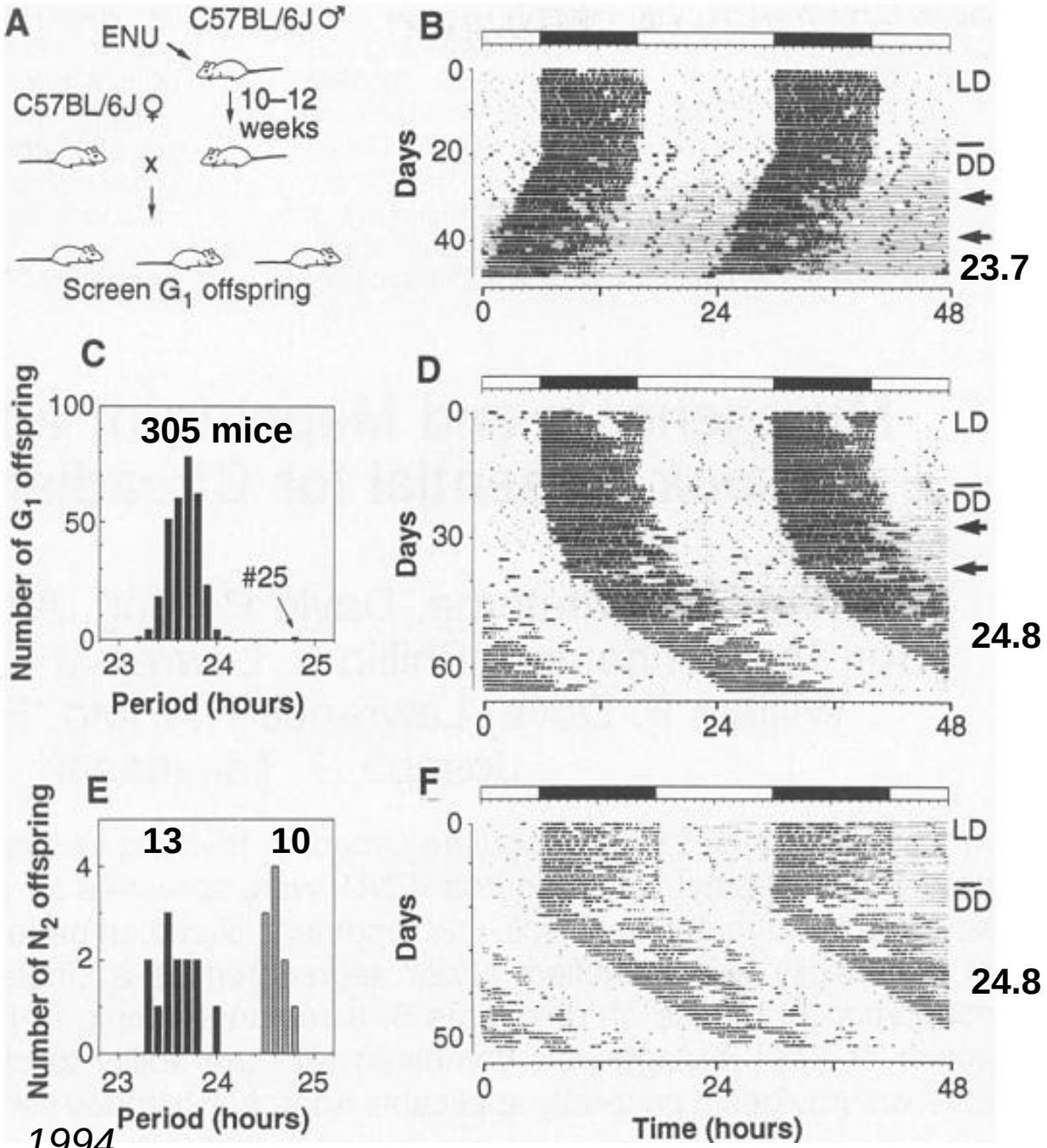


Searching for circadian clock mutant in mammals, ***clock***

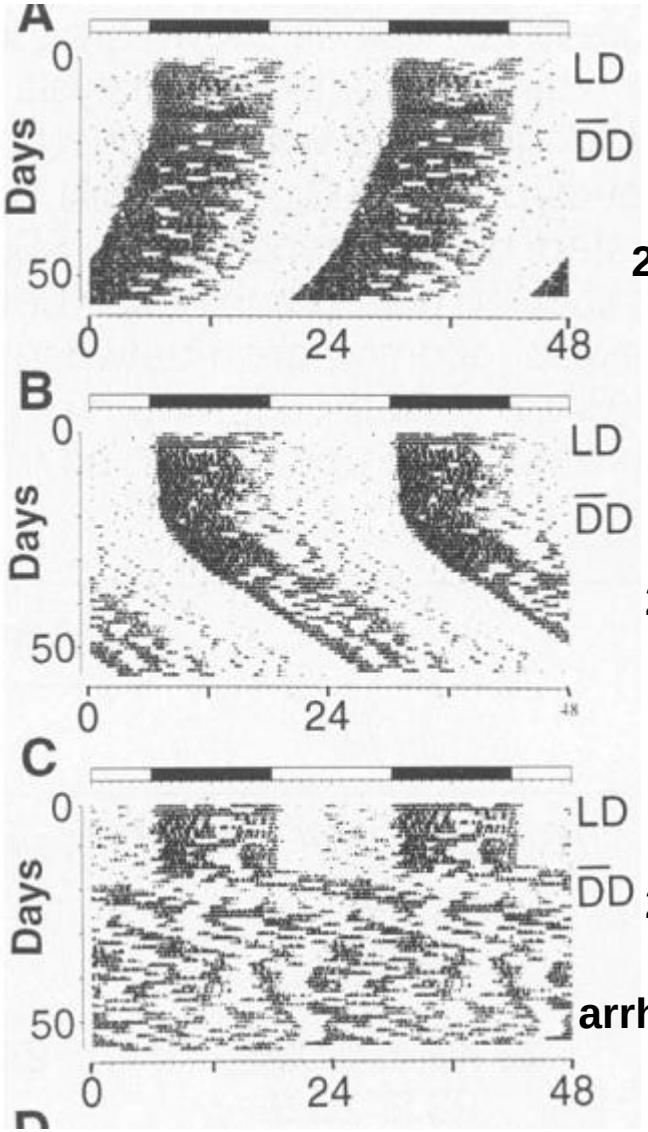




Vitaterna et al., 1994



Vitaterna et al., 1994



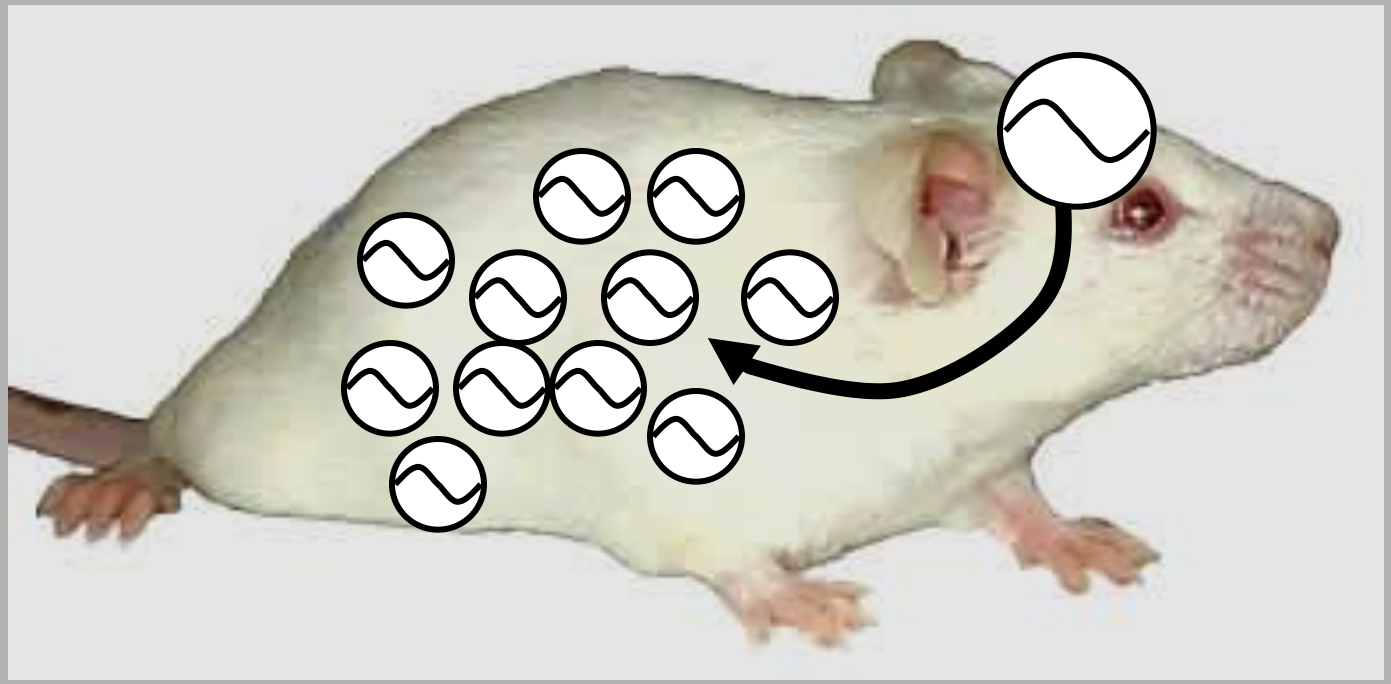
+/+ **23.6**

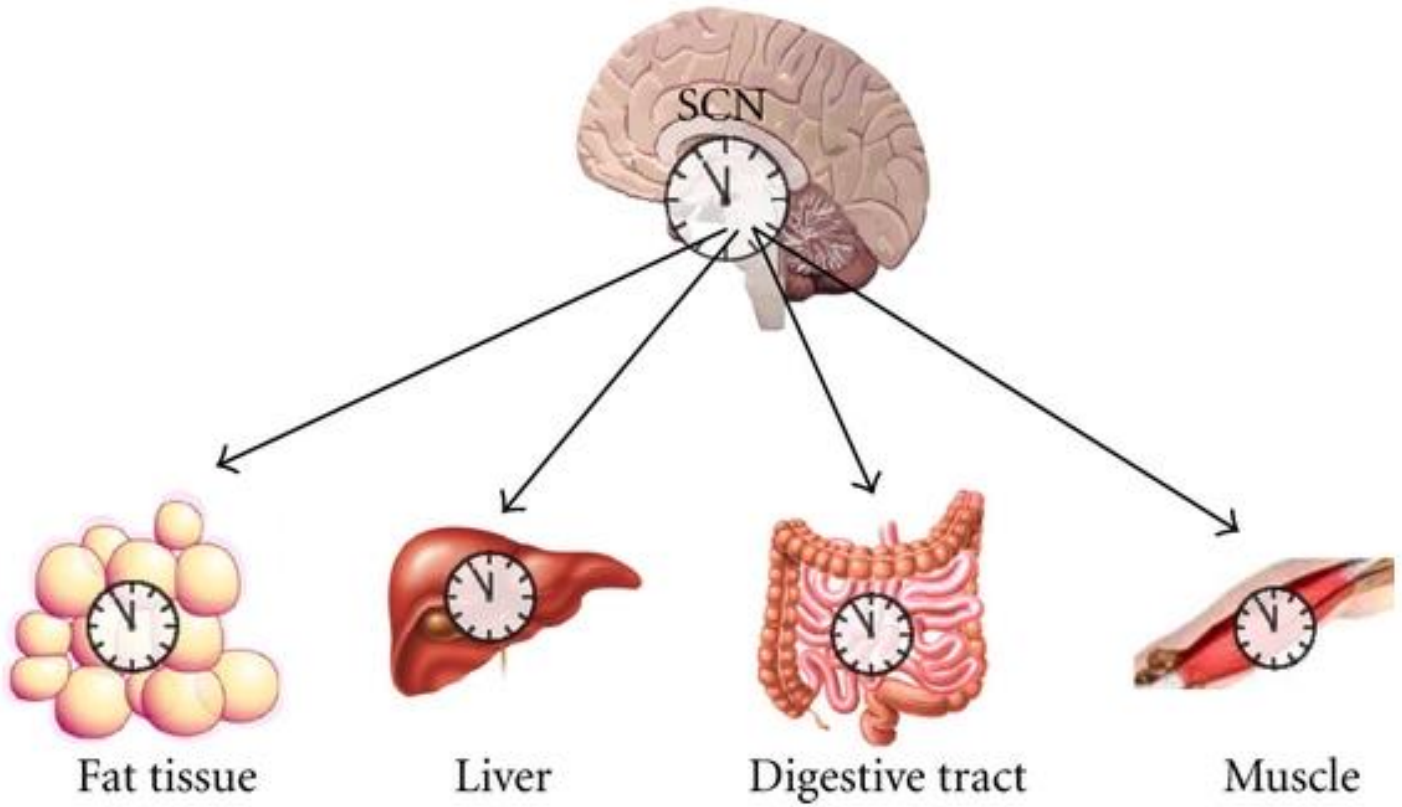
+/- **24.8**

-/- **27.1**

arrhythmic

Vitaterna et al., 1994




SCN
Fat tissue
Liver
Digestive tract
Muscle

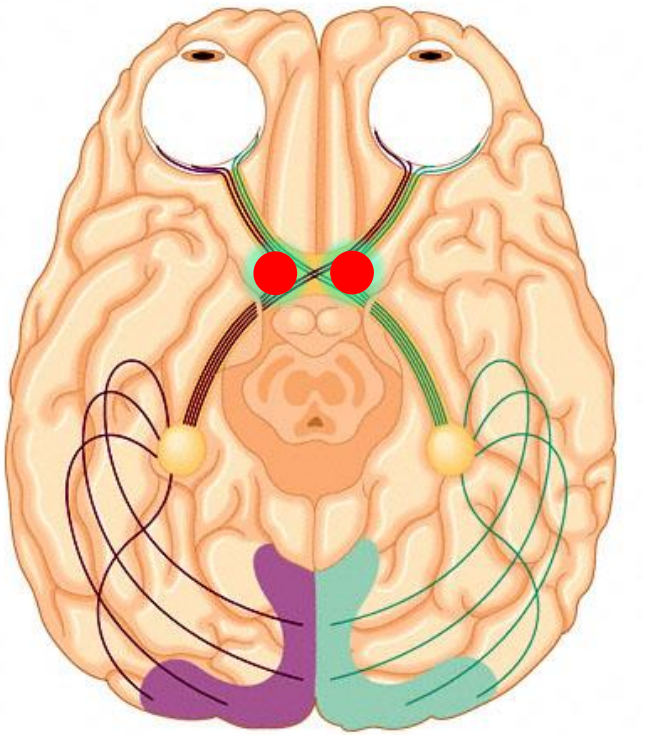
What would the phenotype as a result of:

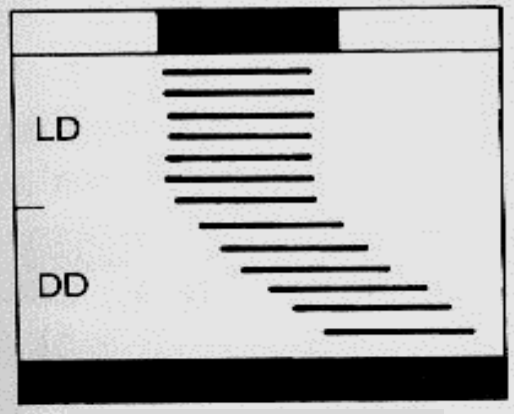
SCN lesion

Removal of the eyes

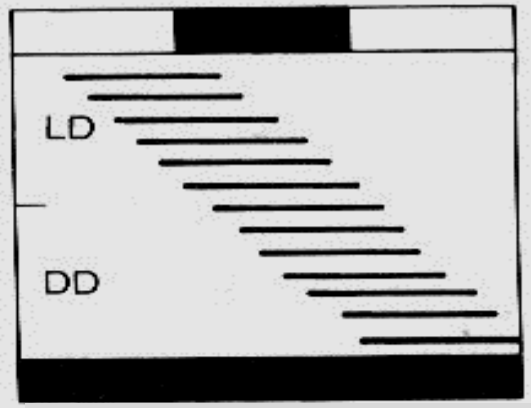
Pre-chiasm dissection of the optic nerve

Post-chiasm dissection of the optic nerve

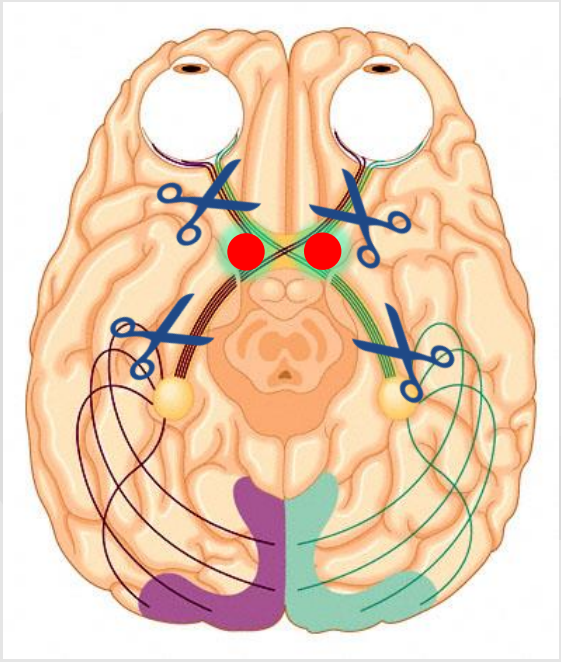




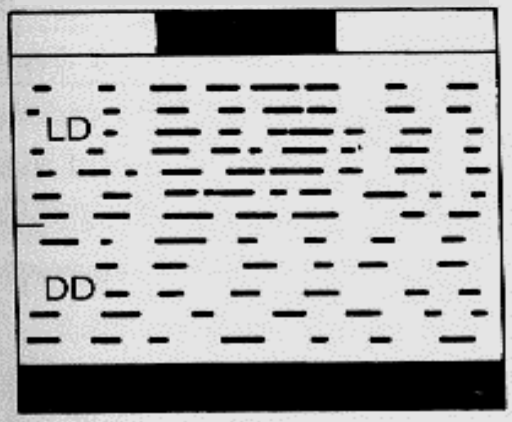
No manipulation



Pre-chiasmatic dissection of the optic nerve

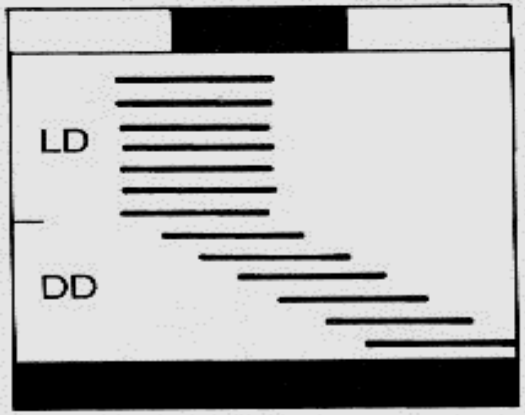


SCN lesion

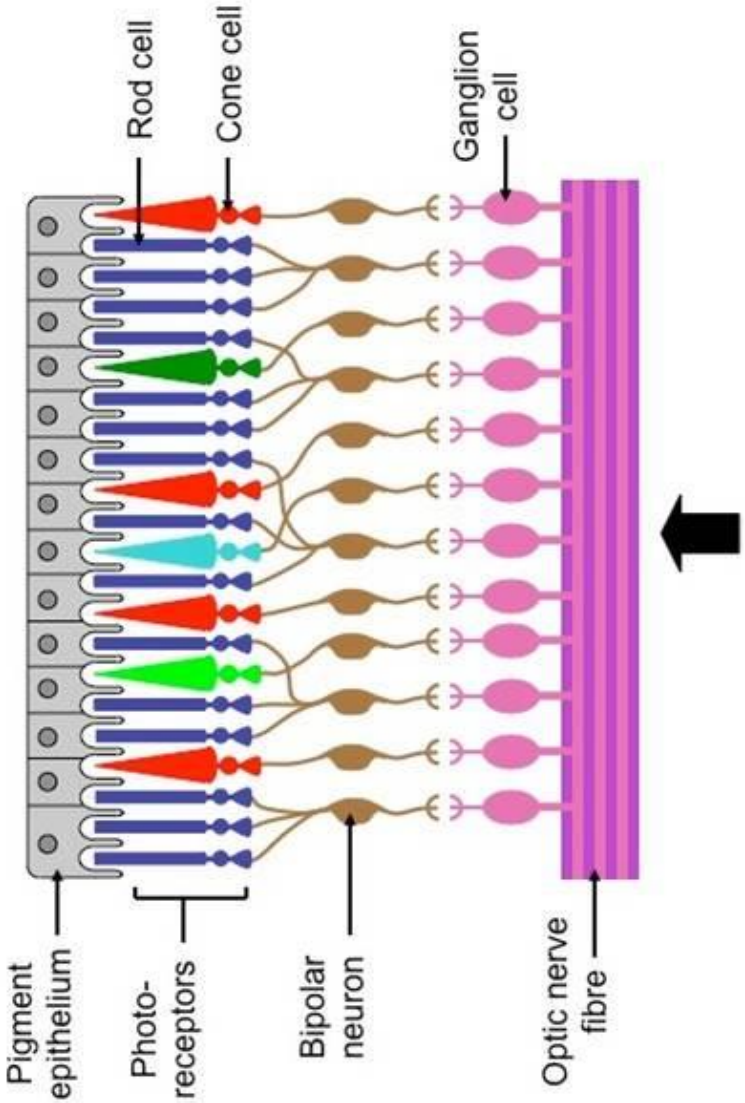


(c)

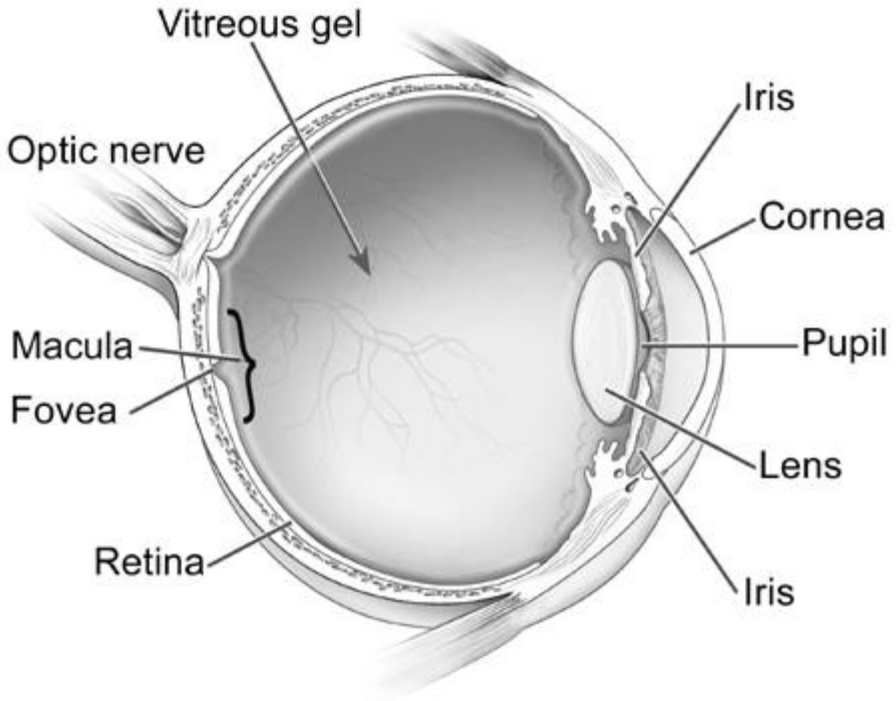
Post-chiasmatic dissection of the optic nerve

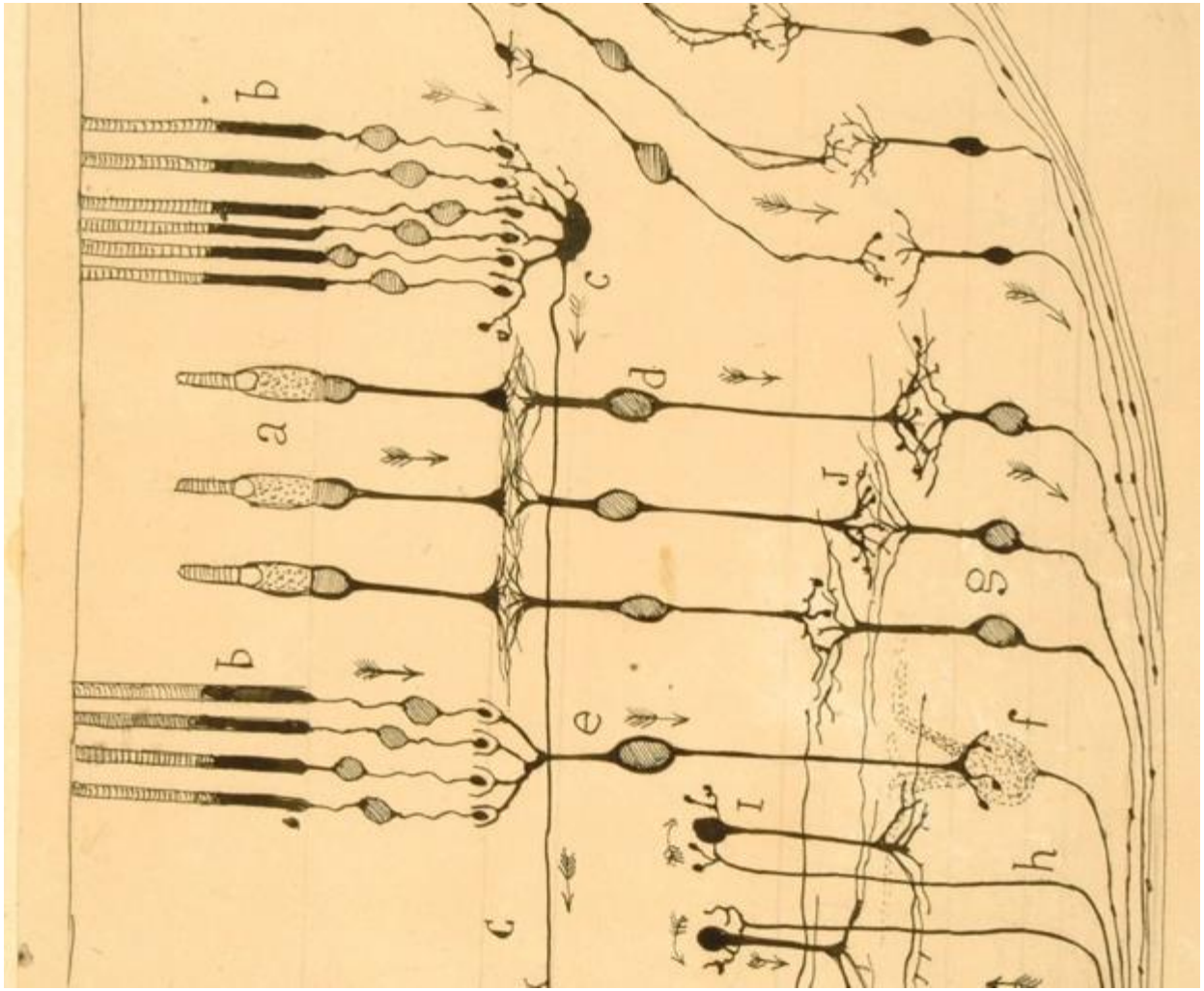


(d)

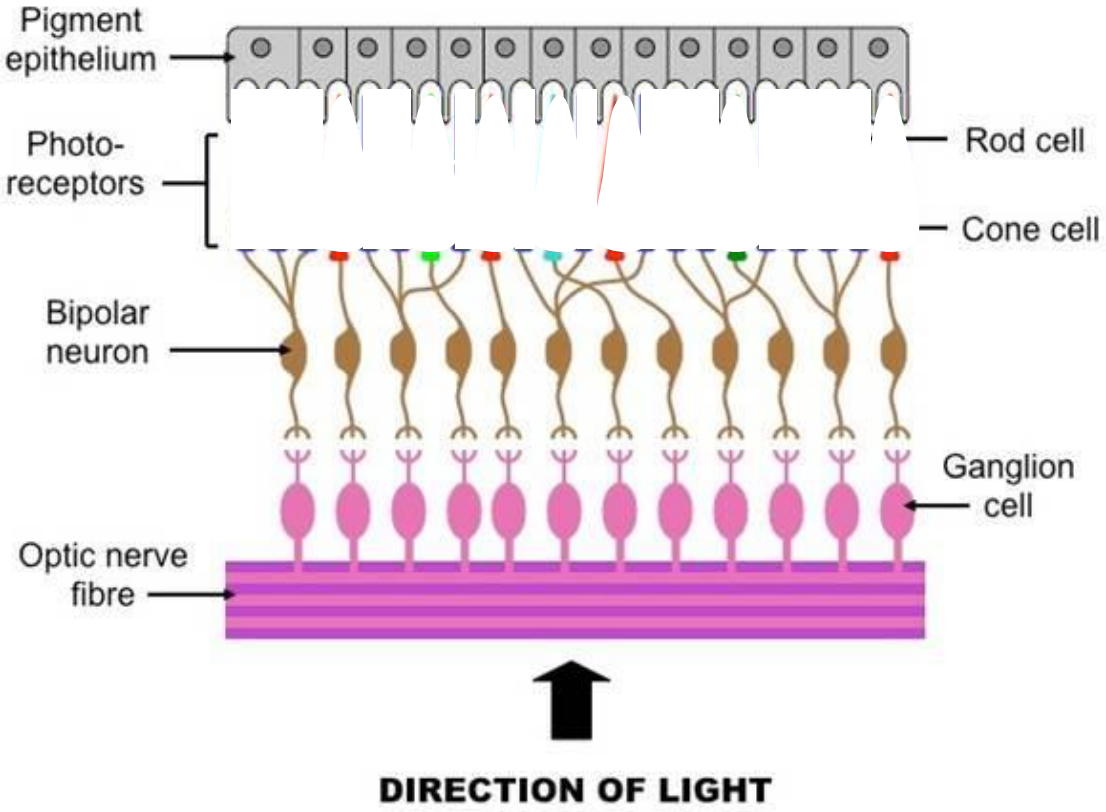


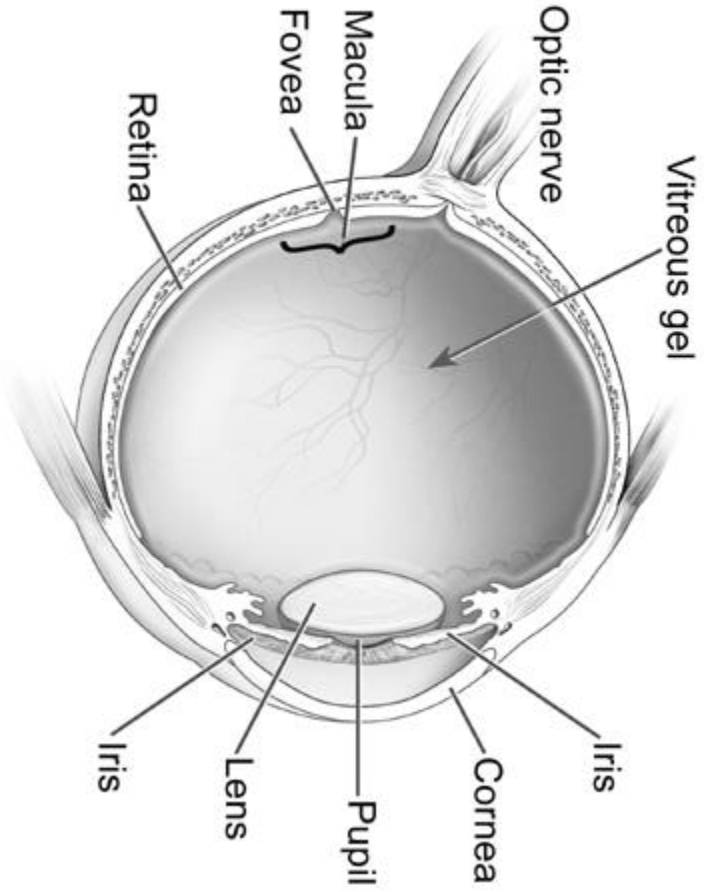
DIRECTION OF LIGHT





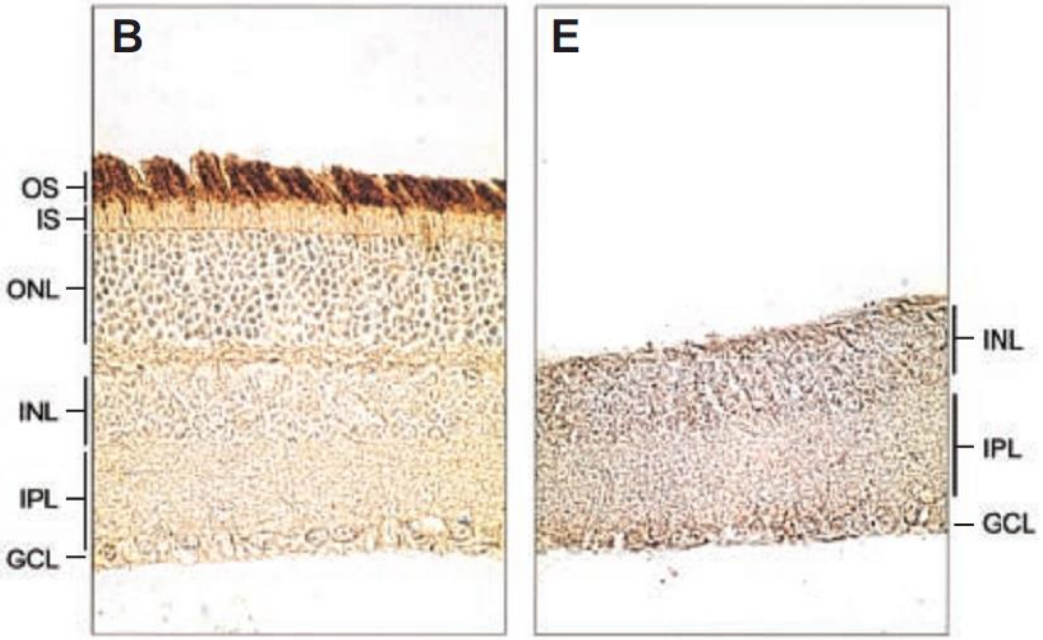
Cajal 1894

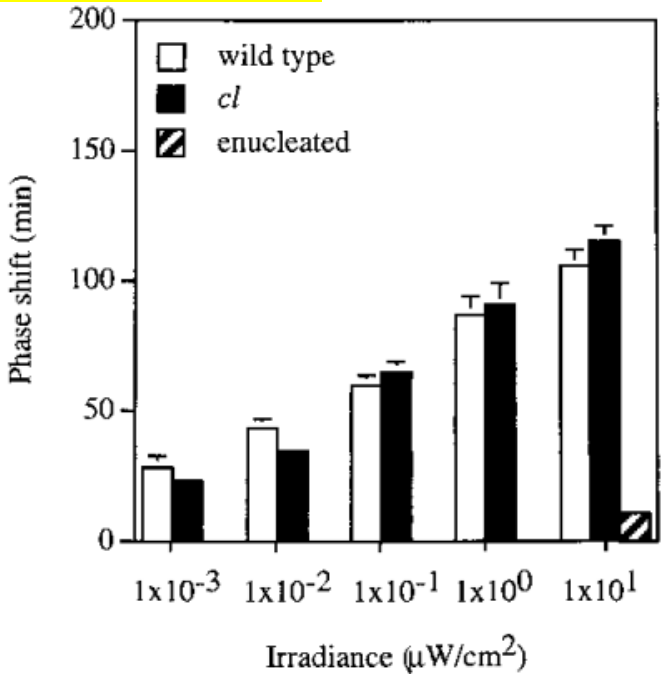

Pigment epithelium
Photo-receptors
Rod cell
Cone cell
Bipolar neuron
Ganglion cell
Optic nerve fibre
DIRECTION OF LIGHT

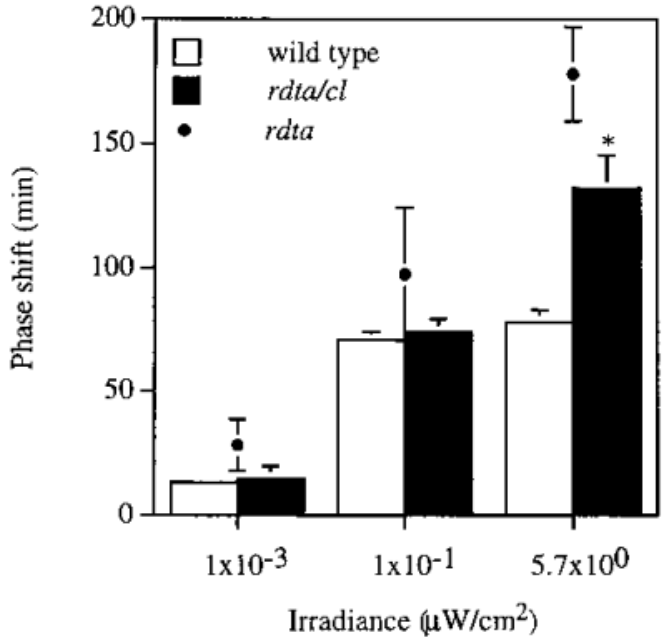

Retina
Fovea
Macula
Optic nerve
Vitreous gel
Iris
Lens
Pupil
Cornea
Iris

Genetic ablation of both rods and cones using diphtheria toxin did not affect light-induced phase shifts

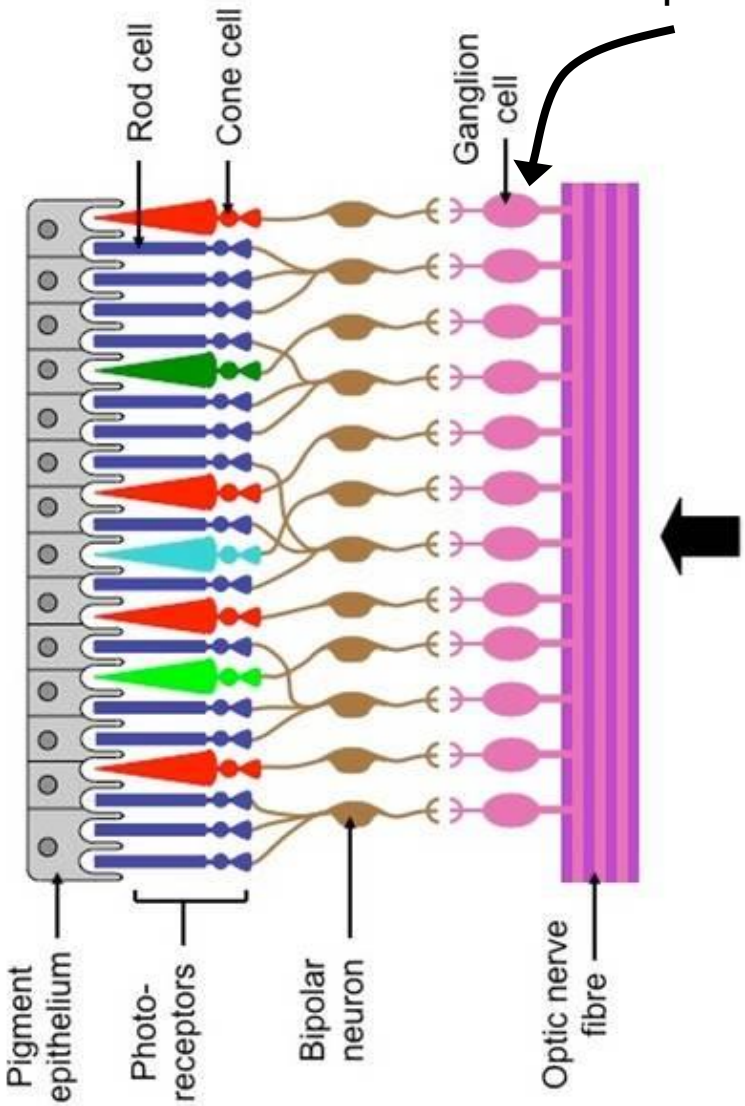
"The eye contains additional photoreceptors that regulate the circadian clock."
Freedman et al, 1999

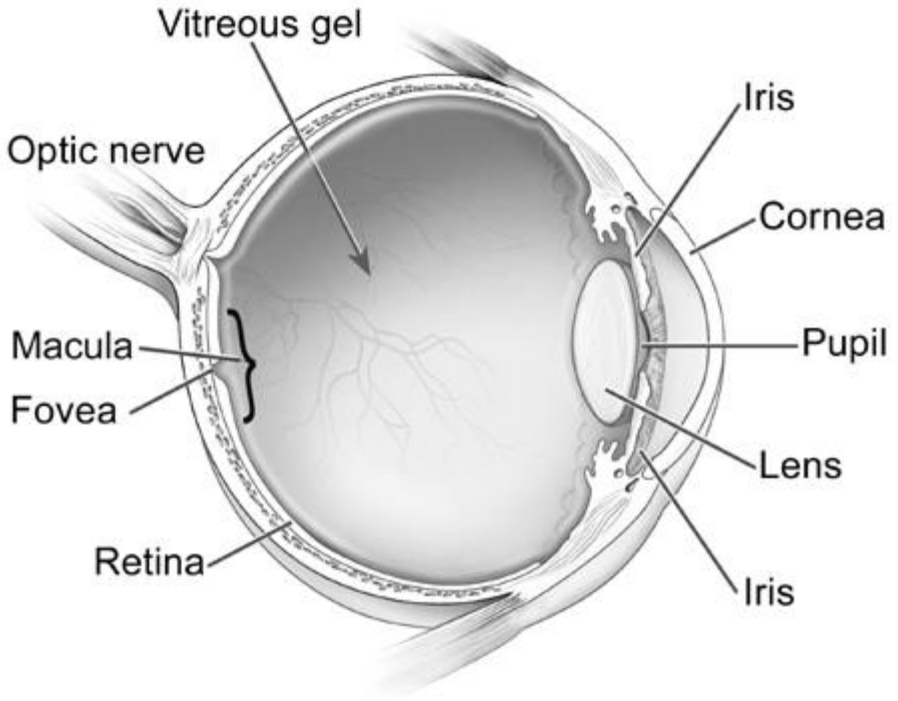




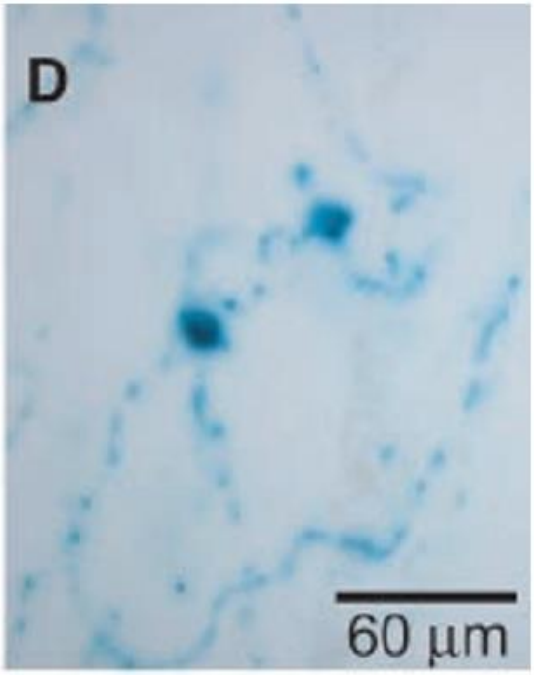


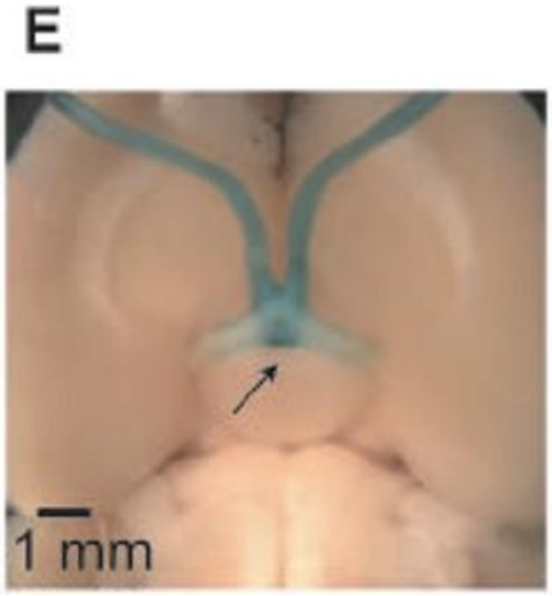
ipRGC - intrinsically photosensitive retinal ganglion cells express melanopsin

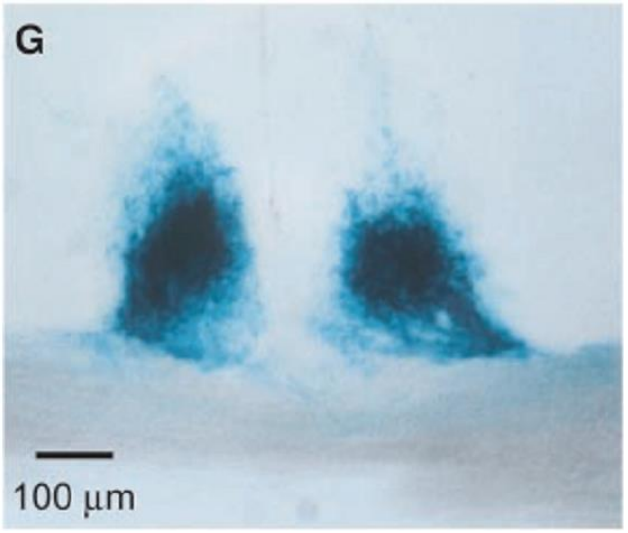




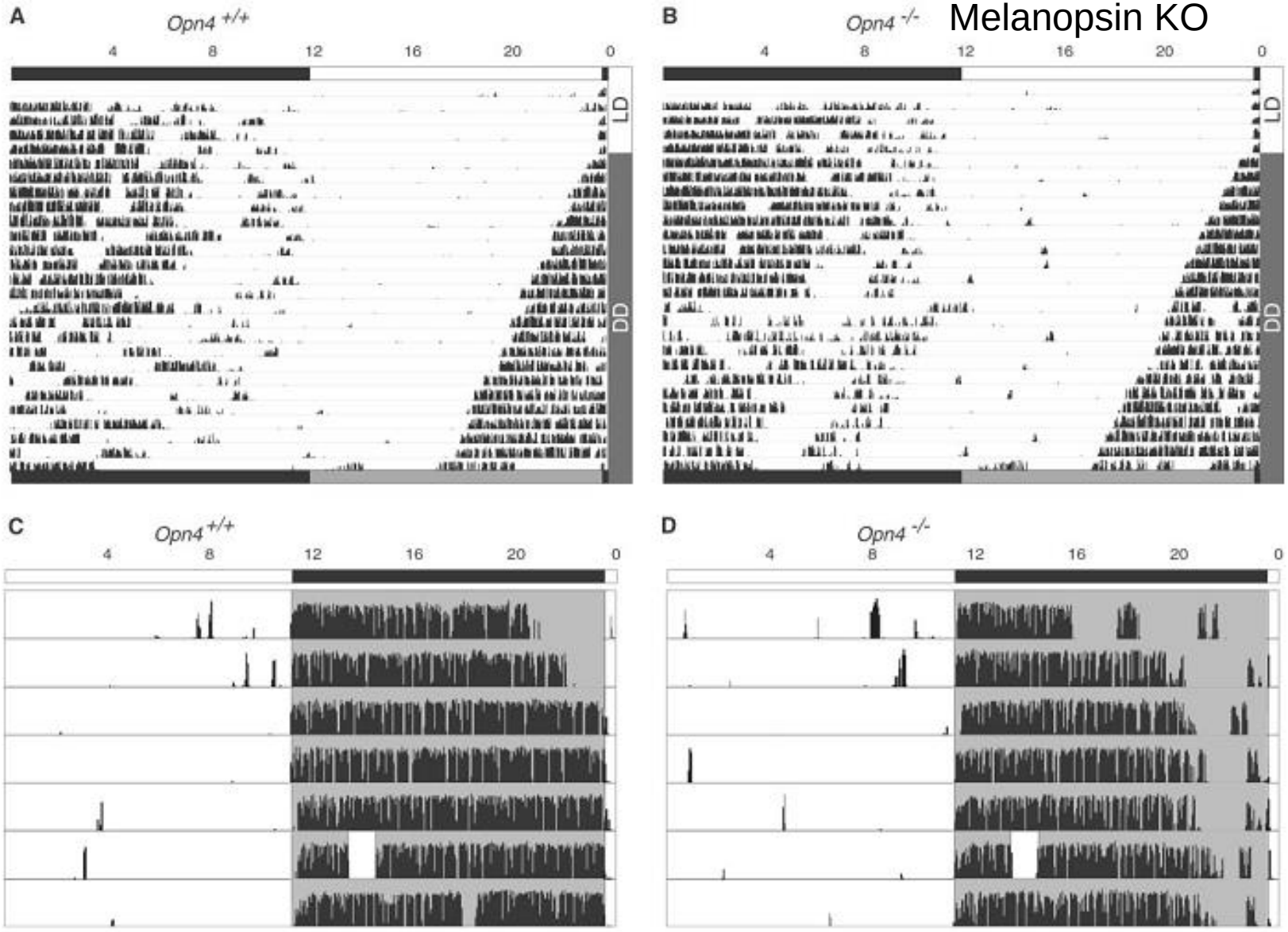
Transgenic mice expressing x-gal under the control of the melanopsin gene





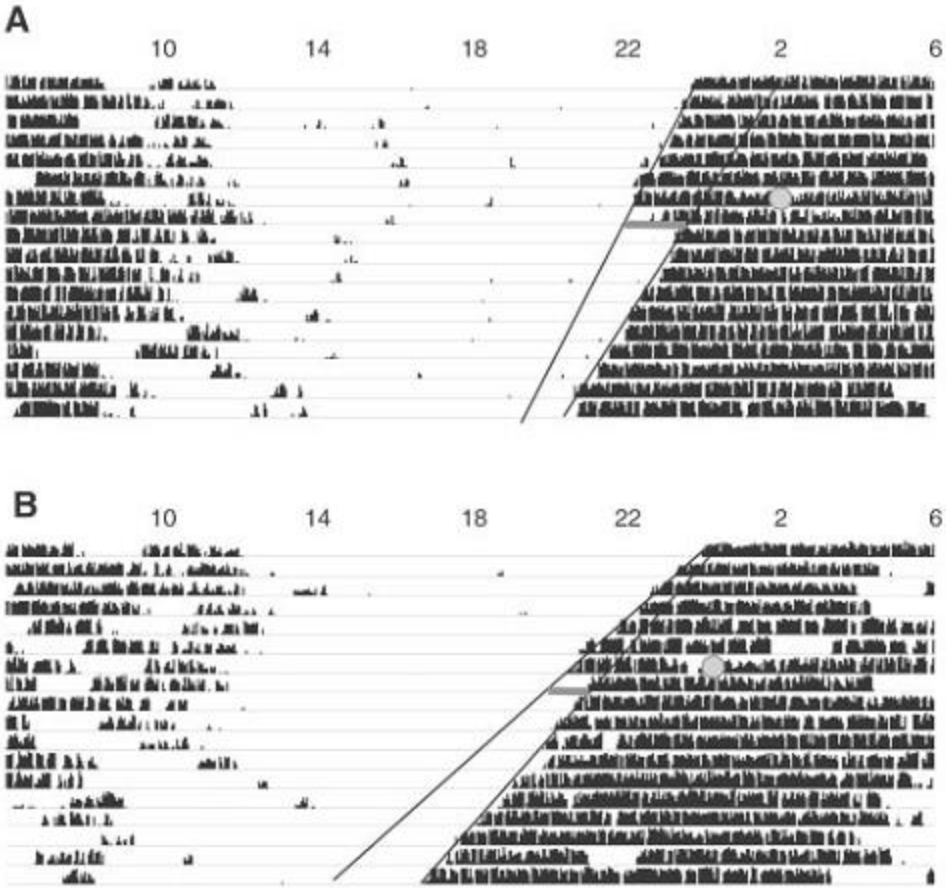


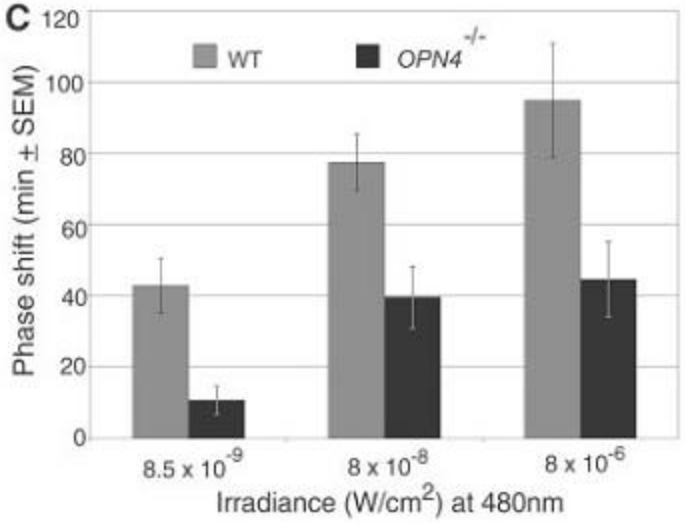
Hattar et al, 2002



No effect of melanopsin KO

Panda et al, 2002

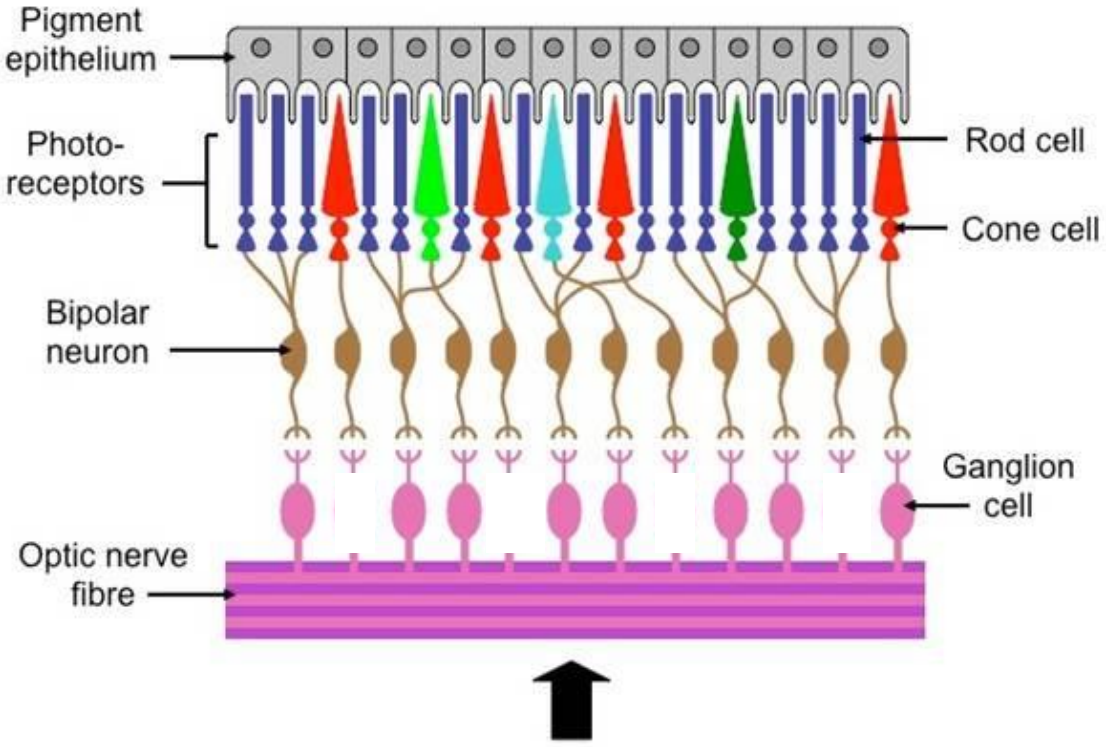


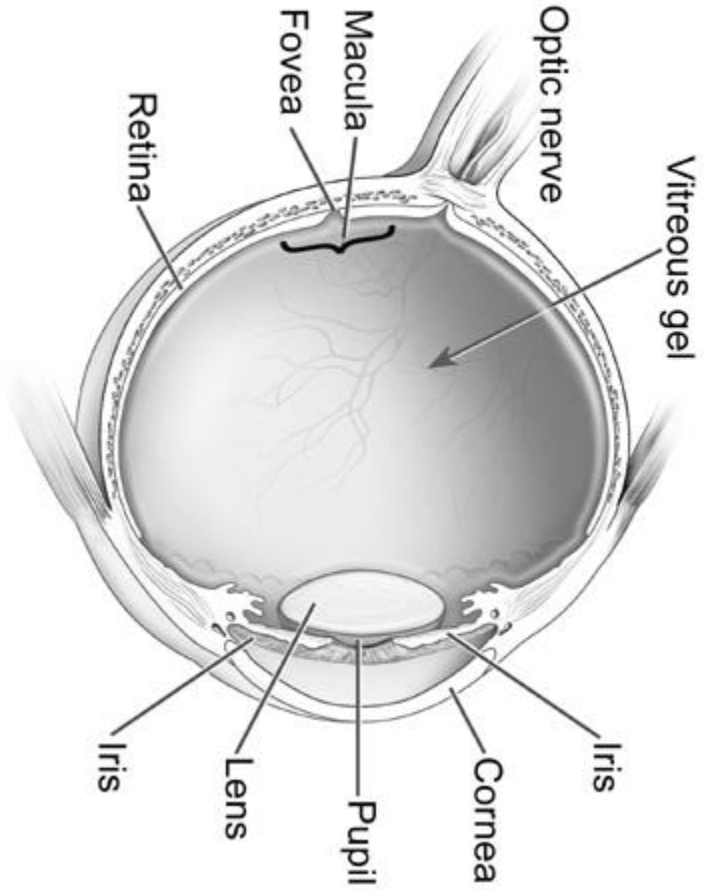


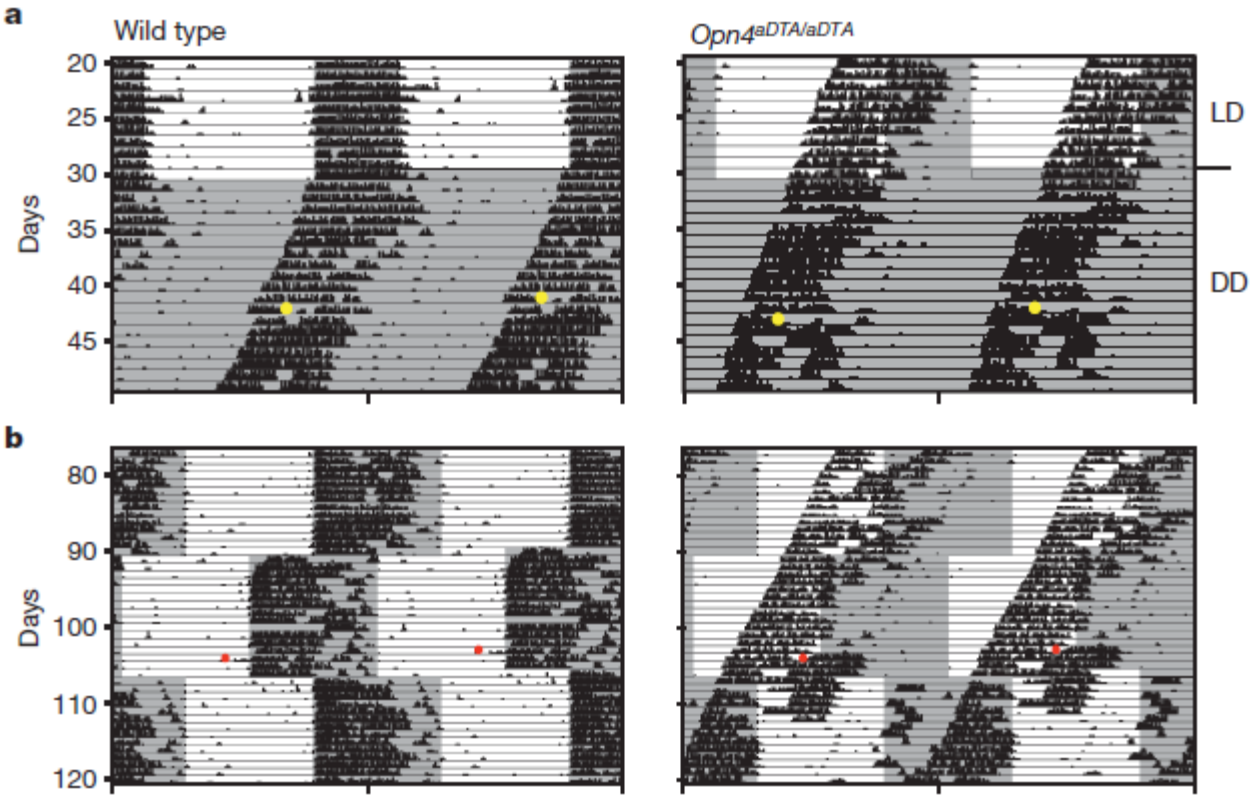
←480 nm 15 min.

Some effect of melanopsin KO

Panda et al, 2002


Pigment epithelium
Photo-receptors
Rod cell
Cone cell
Bipolar neuron
Ganglion cell
Optic nerve fibre
DIRECTION OF LIGHT

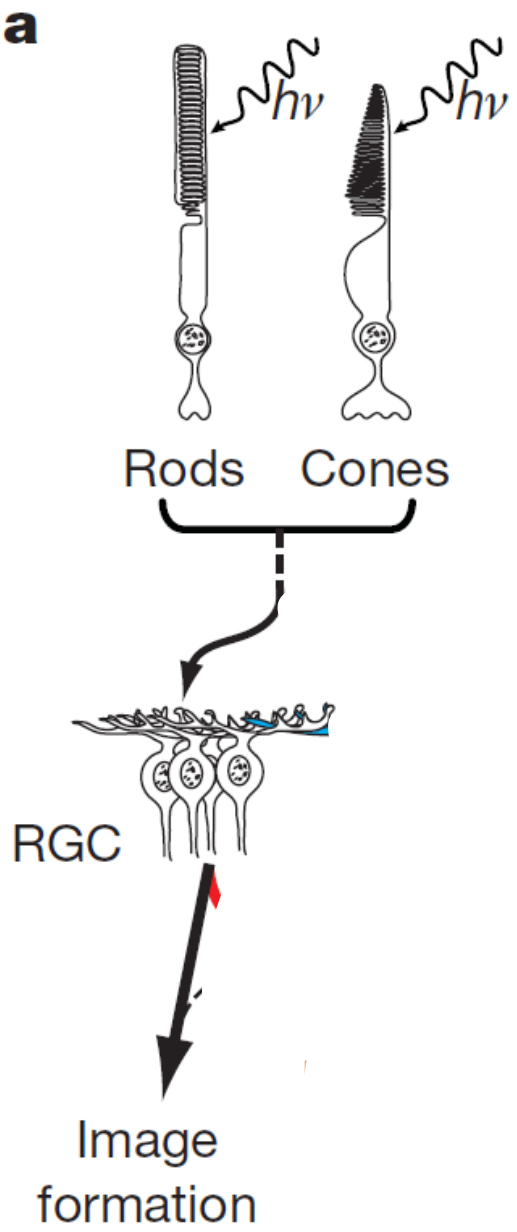

Retina
Fovea
Macula
Optic nerve
Vitreous gel
Iris
Lens
Pupil
Cornea
Iris



Major effect of ablation of the ipRGCs (the intrinsically photosensitive retinal ganglion cells that express melanopsin)

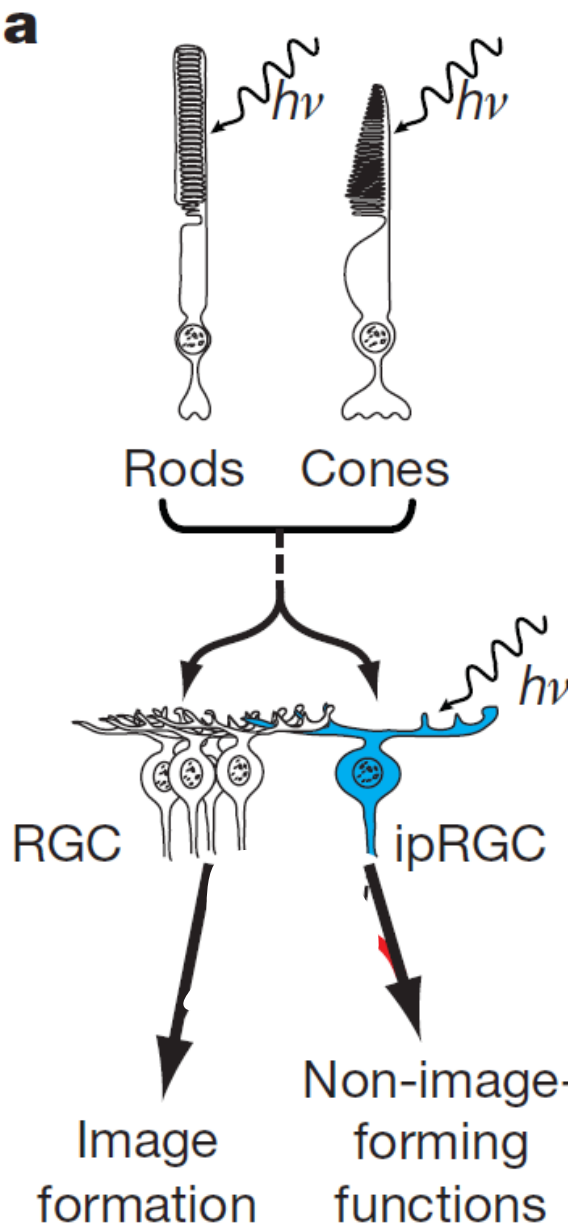
Guler et al, 2008

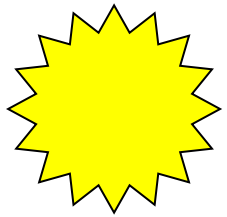
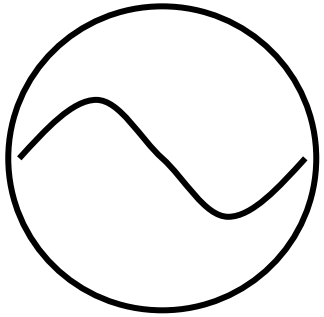
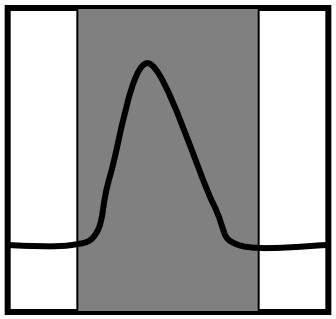
RGC - retinal ganglion cells



RGC - retinal ganglion cells

ipRGC - intrinsically photosensitive retinal ganglion cells



Light input	Oscillator	Output rhythm
		
ipRGC	**SCN**	**Circadian rhythms**
Also: Feeding Activity Social interaction	Independent Light-entrained	Sleep/wake cycles Locomotor activity Cognitive abilities Reaction time Body temperature Metabolism Hormone secretion Enzymatic activities Gene expression