



The Circadian Rhythm Story: Past, Present and Future

GoldLab Symposium
Celebrating Science
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May 24, 1995

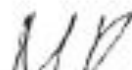
Dr. James Watson
Cold Spring Harbor Laboratory
1 Bungtown Rd.
Cold Spring Harbor, NY 11724

Dear Dr. Watson,

I suspect you have already spoken to Dr. Stewart and heard about the origin of my remarks Saturday morning, namely, the unfortunate misunderstanding between Andrea Stephenson and one of my coorganizers, Jo Ann Wise. Based on this conversation, Jo Ann instructed me to tell the meeting participants on Saturday morning not to leave their possessions in Grace and that the concert was not for us. Jo Ann said her interpretation of the conversation was reinforced by the fact that the concert was not listed in the program/abstract book. Needless to say, I was not present at their conversation and so do not have a first hand record of what transpired between them.

David Stewart and I ran into each other on Saturday afternoon, so I was able to catch the last two thirds of the concert, which was very enjoyable. Your public comments at the outset (which were quoted to me in detail and identically by several in attendance) were undoubtedly based on the assumption that my own Saturday morning remarks were frivolous and in bad taste. However, neither this misunderstanding nor your understandable embarrassment at the consequent lack of attendance justifies insulting me so boldly in public. Even your remarkable scientific and administrative achievements are insufficient license for such abuse.

Sincerely,



Circadian rhythm properties (*circa dia*)

- Not exactly 24hr rhythms
- Function: anticipation (and organization)
- Can entrain to a light cycle. Now a precise 24hr period

The White Rabbit put on his spectacles. "Where shall I begin, please your Majesty?" he asked.

"Begin at the beginning," the King said gravely, "and go on till you come to the end: then stop."



IN THE BEGINNING...

1:3

And God said, Let there be light: and there was light.

1:4

And God saw the light, that it was good: and God divided the light from the darkness.

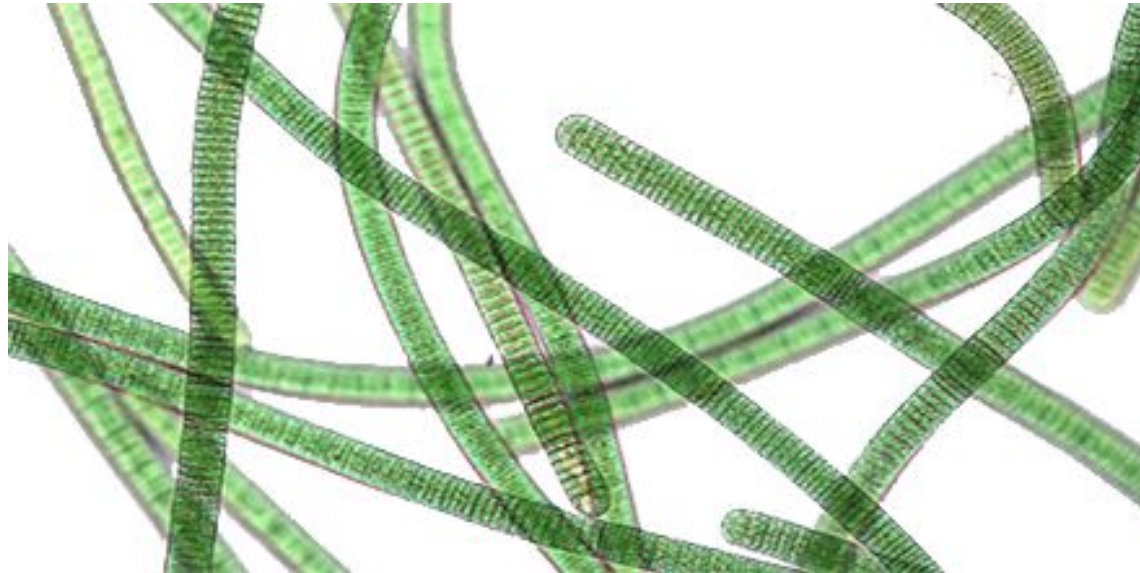
1:5

And God called the light Day, and the darkness he called Night. And the evening and the morning were the first day.

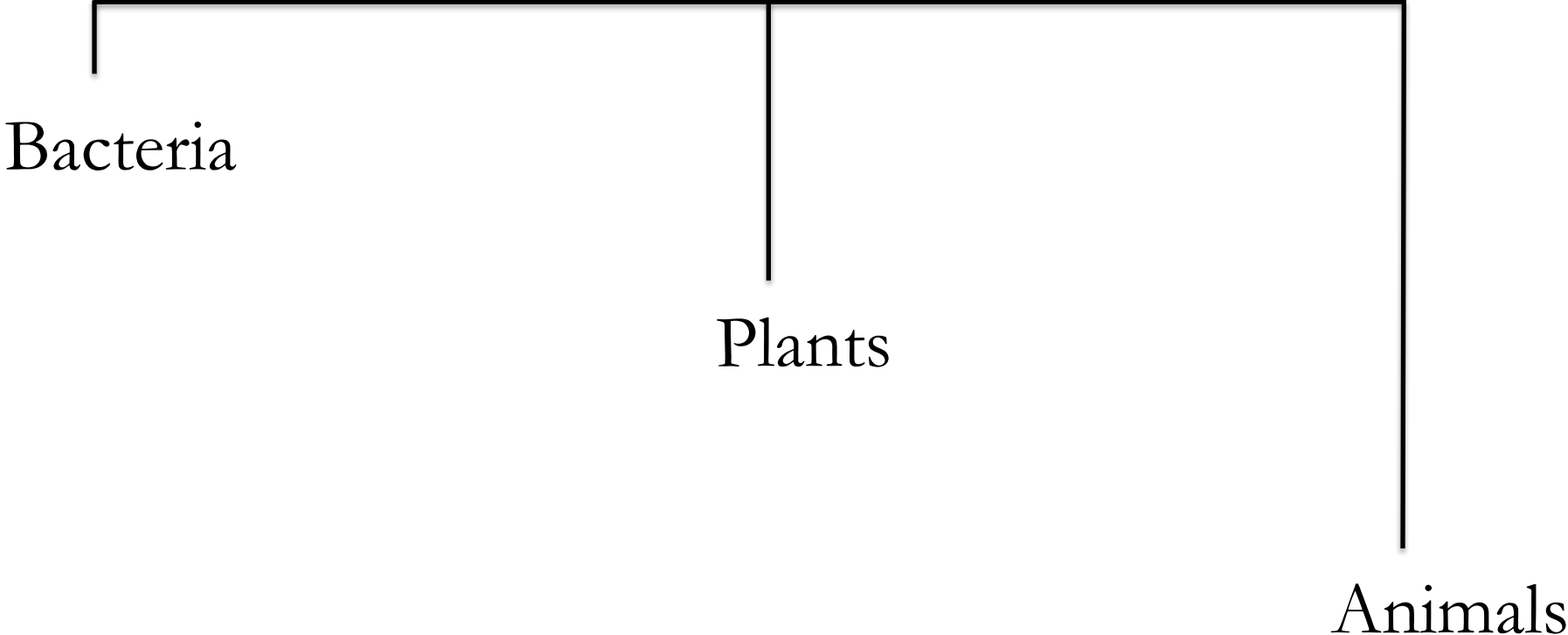
Circadian rhythms arose long ago as adaptations to the rotation of the earth



Oldest known clock is in Cyanobacteria:
oxygenation of the atmosphere > 2
billion years ago



Circadian clocks are very different in different kingdoms,
Indicating multiple origins during this more than 1.5
billion years of evolution



A curious astronomer ponders self-sustaining circadian rhythms



de Mairan observes that plant leaves exhibit the same patterns of movement in constant darkness that they do in a normal day/night cycle. (1729)



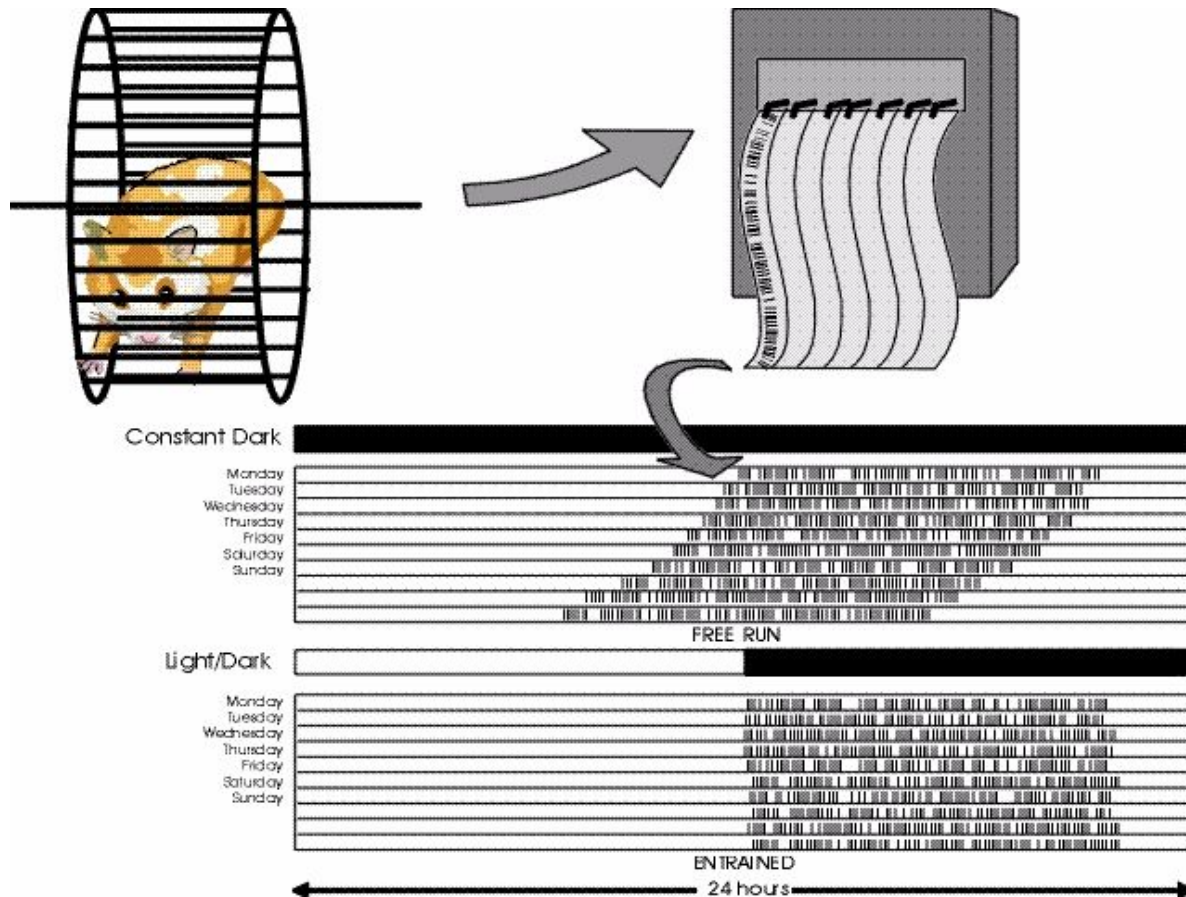
Scientific Progress

(quote from Sydney Brenner)

- “Progress in science depends on new techniques, new discoveries and new ideas, probably in that order.”

Locomotor activity is a remarkable circadian/behavioral assay (“a discovery...”)

“phenotype, phenotype, phenotype”

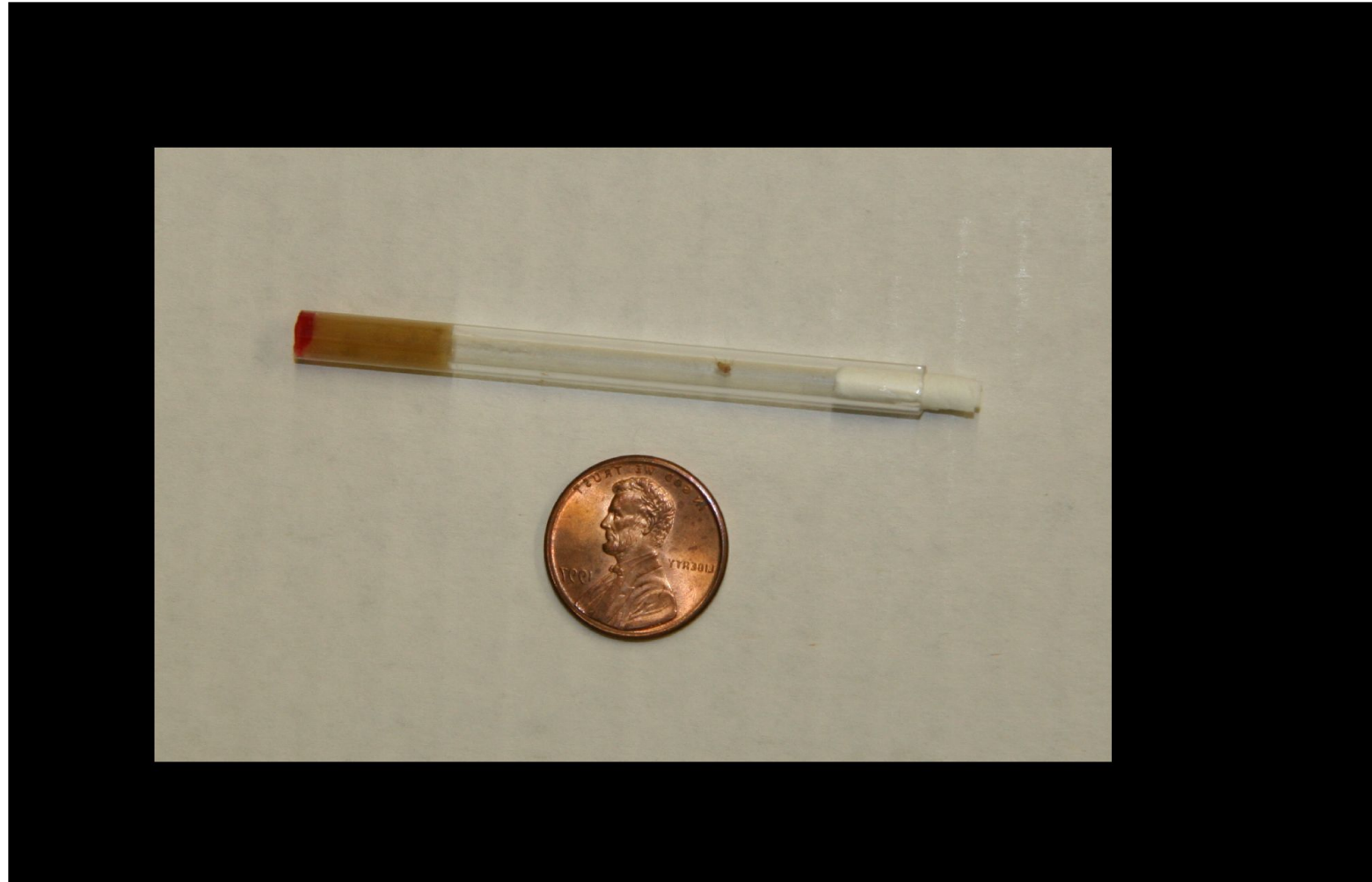


Can assay and select an individual animal

Free-running period
<24 hours

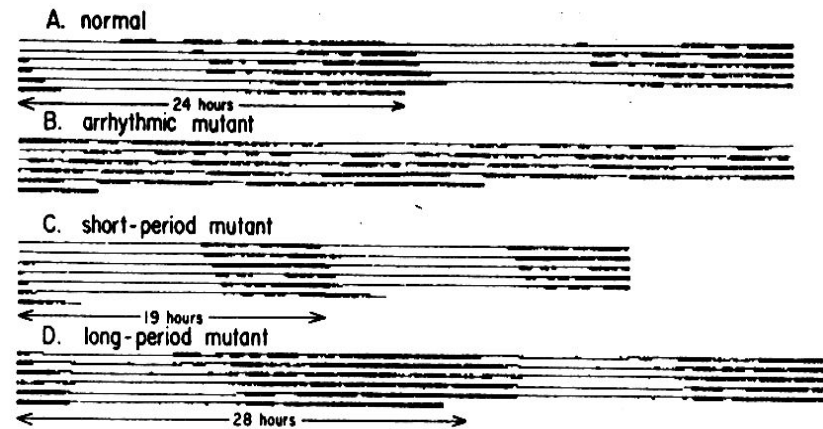
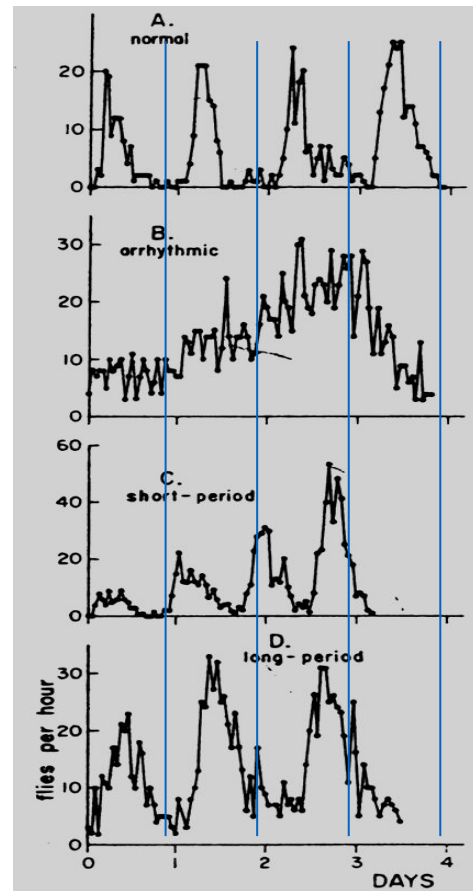
Entrained period
exactly 24 hours

Drosophila locomotor Activity



The beginning of the modern era for animal clocks: the wonderful *Drosophila period (per)* mutants

Konopka and Benzer (1971)



Why Mutants? Why Genetics?

- A mutant is a potential entrée into a mysterious process. What causes the phenomenon? What is the machine that keeps time (the quartz crystal)?
- Different than “you vs me” and a genes/environment debate.

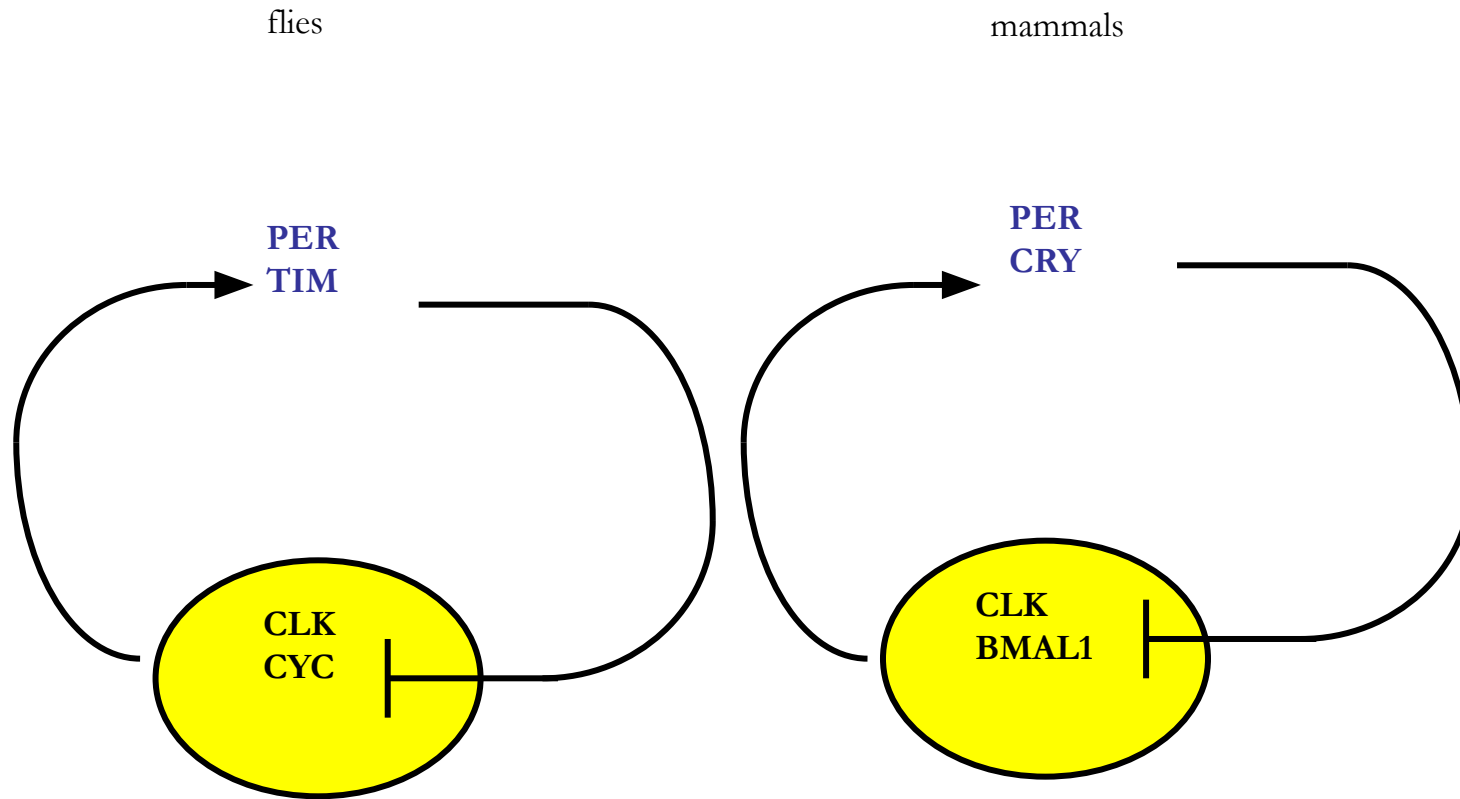
Why Mutants? Why Genetics?

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- Different than “you vs me” and a genes/environment debate.

Hall and Rosbash labs at Brandeis
and
Young lab at Rockefeller

in the 80s and 90s

The circadian transcriptional feedback loop is nearly identical in all animals (1998-2021)

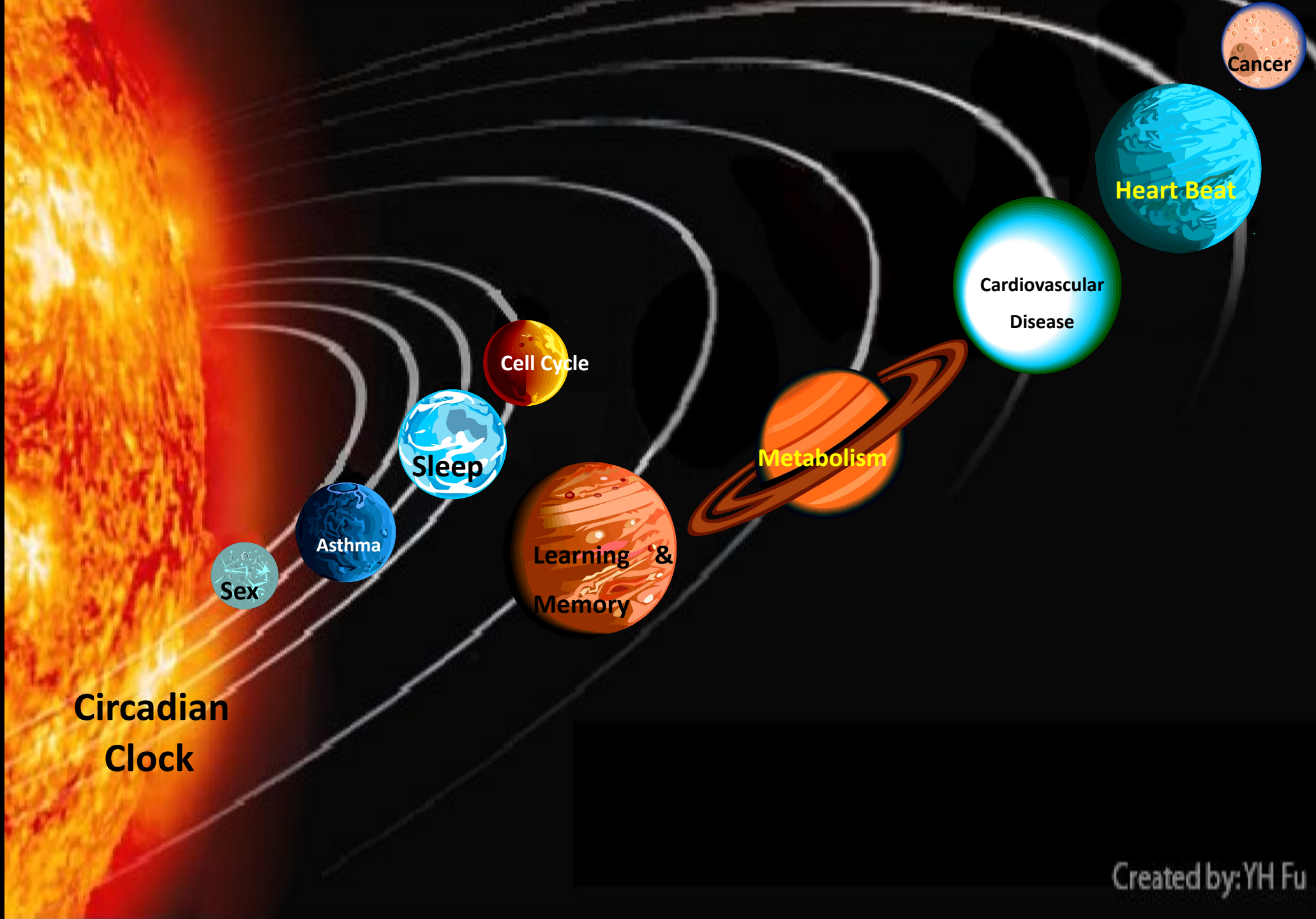


Timekeeping also Involves Important Post-transcriptional Regulation

First Challenge for the Future: (basic science)

- What accounts for the timing? Why ca. 24 hours?
What is/are the rate-limiting step(s)?
- How does temperature compensation work?
- Requires biochemistry and structure.

Second Challenge for the Future: Leveraging Circadian Rhythm Knowledge to Improve Human Health

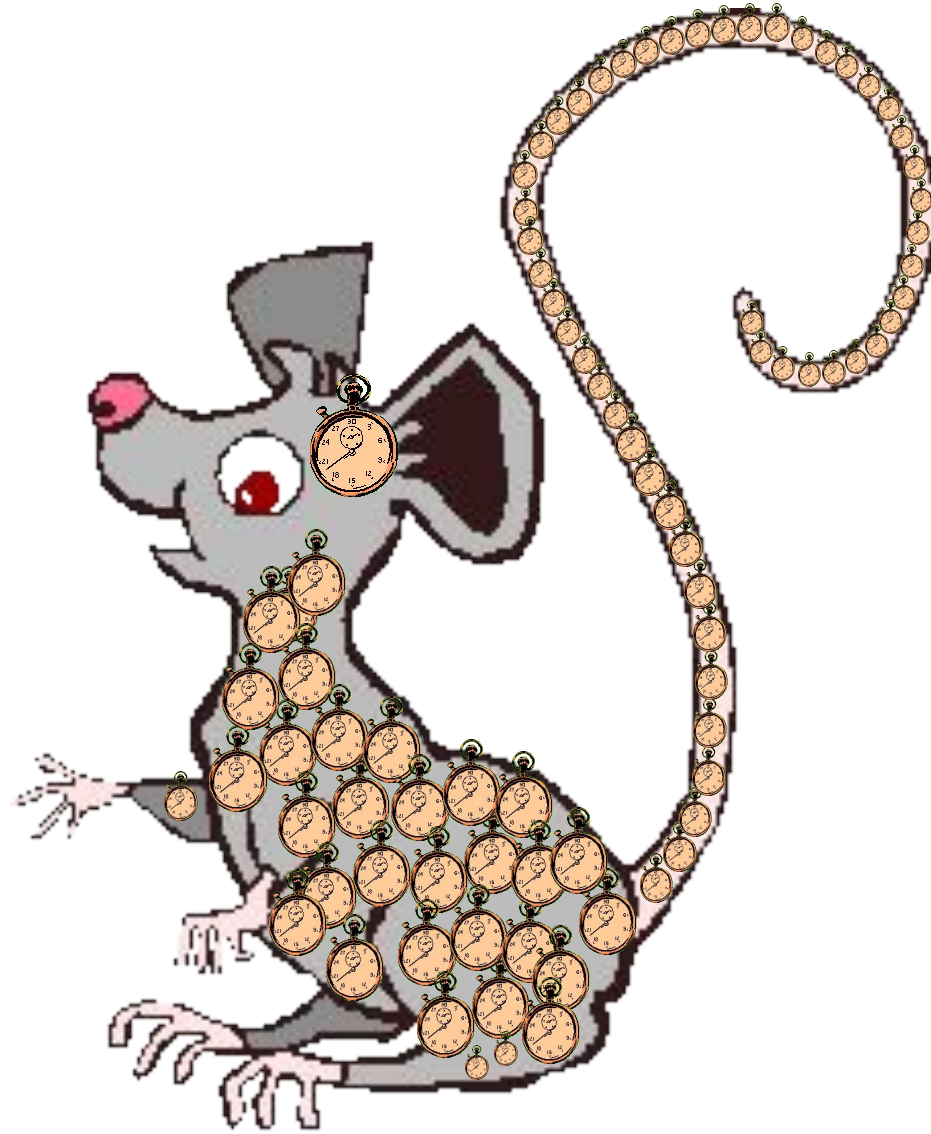


**Circadian
Clock**

Why do circadian rhythms affect so much of human physiology?

- The core circadian clock regulates the cycling of hundreds-thousands of mRNAs in each cell/tissue where it is present...

And the core clock is almost ubiquitous



As a consequence, a large fraction ($>70\%$) of mammalian genes are expressed rhythmically in at least one tissue/cell type

Hence the broad effect on all aspects of physiology

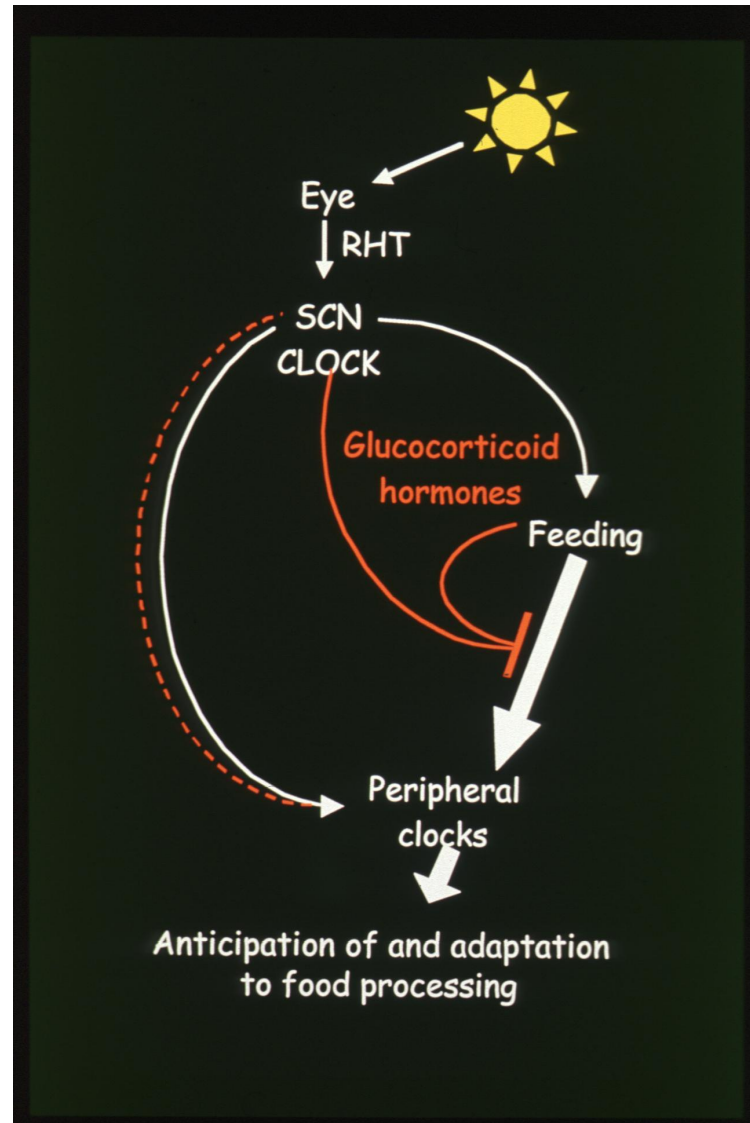
What are some human disorders/considerations?

- Metabolic Diseases, e.g., Diabetes.
- Sleep Disorders.
- Drug Efficacy. Pharmacokinetics. Medicine...
- Seasonal Affective Disorders (Depression?)
- Shiftwork.
- Jet Lag.

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Food metabolites also entrain peripheral oscillators



2012 Cell Metabolism
Article

**Time-Restricted Feeding without
Reducing
Caloric Intake Prevents Metabolic
Diseases**

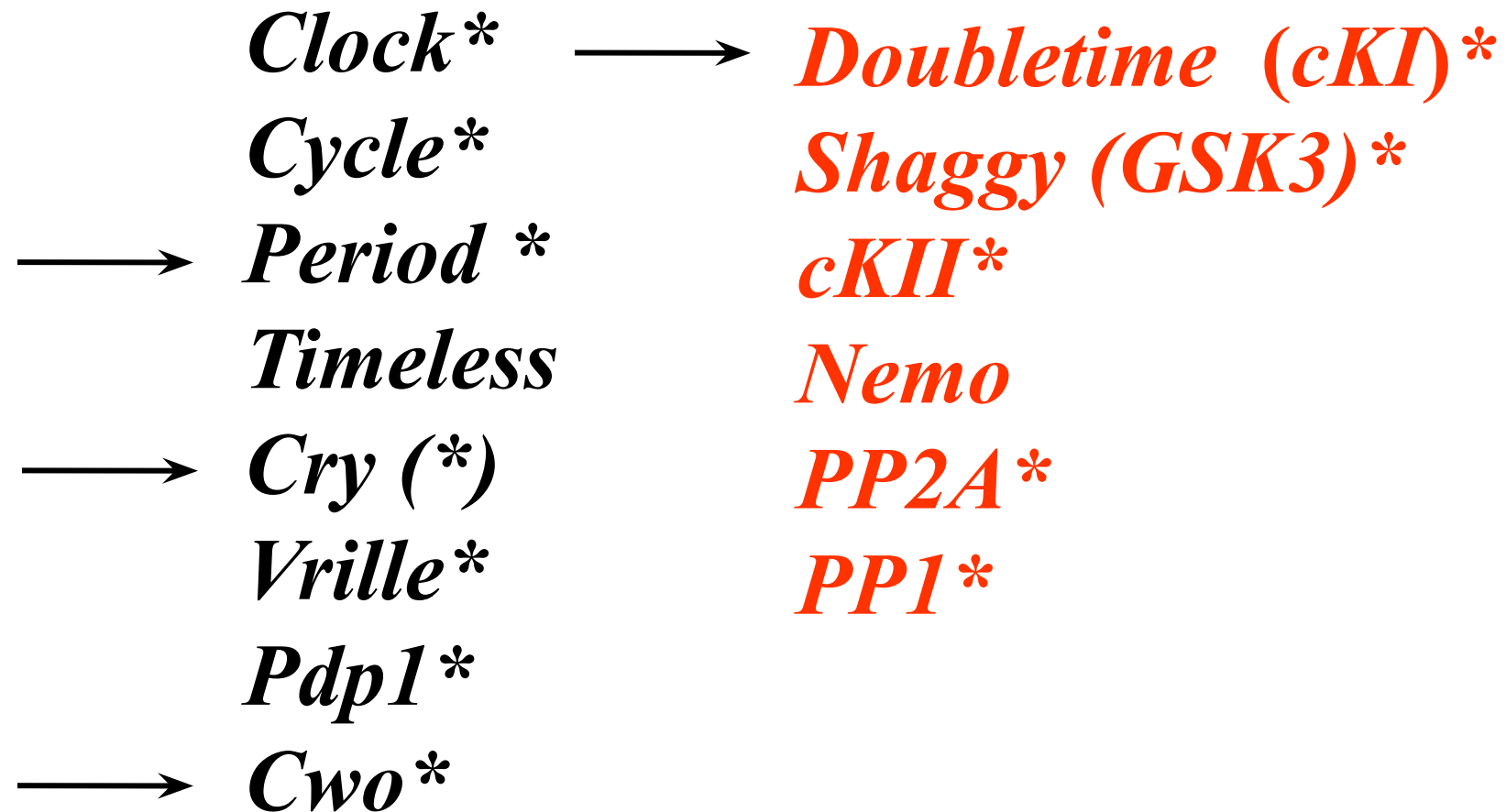
in Mice Fed a High-Fat Diet
Megumi Hatori,^{1,4} and Satchidananda
Panda^{1,*}

What are some human disorders/considerations?

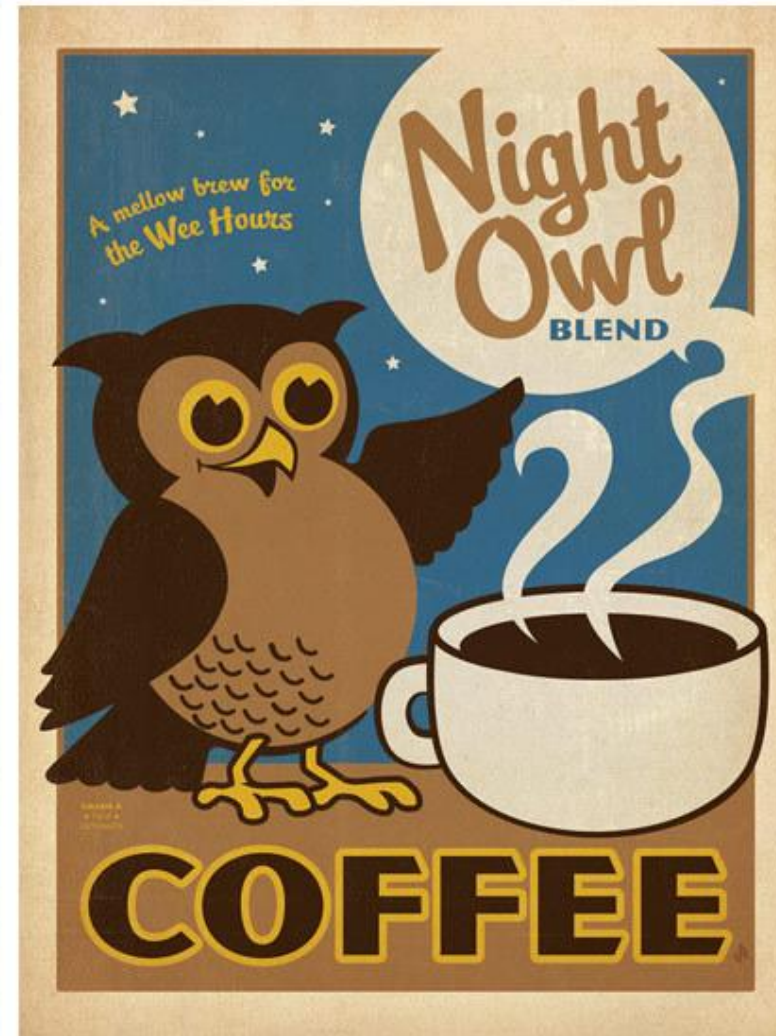
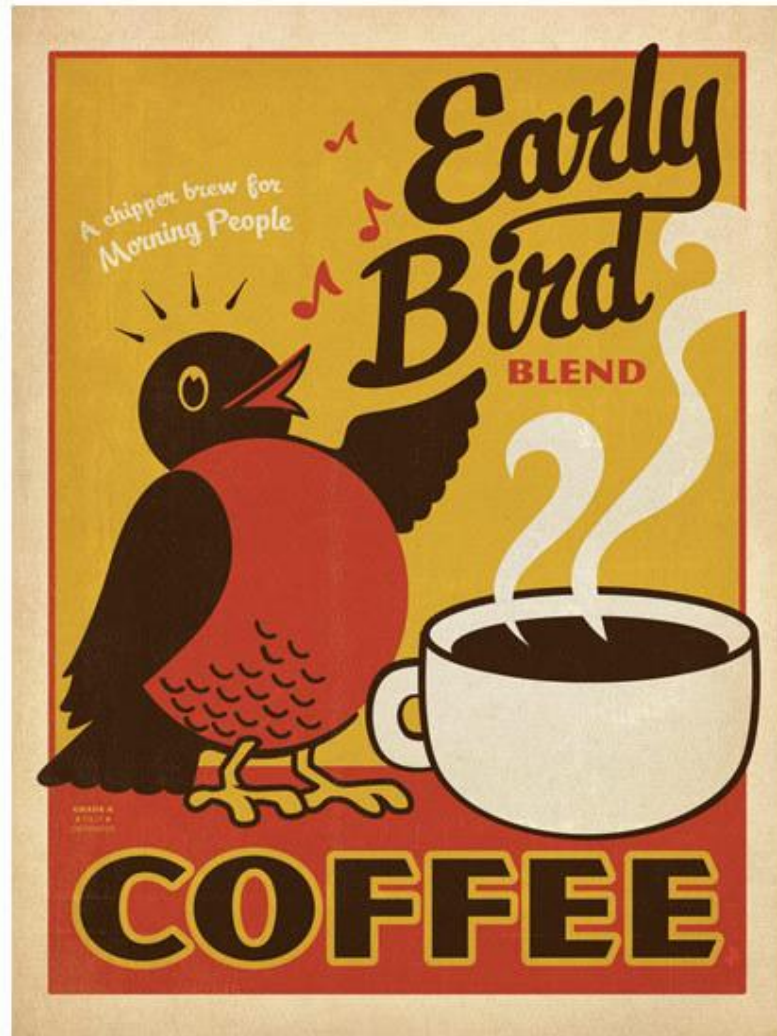
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- **Sleep Disorders.**
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Mutants/Variants of the Human Versions of Four *Drosophila* Clock Genes Cause Human Sleep Syndromes

(ASPS/ DSPS; Mendelian extreme chronotype disorders)



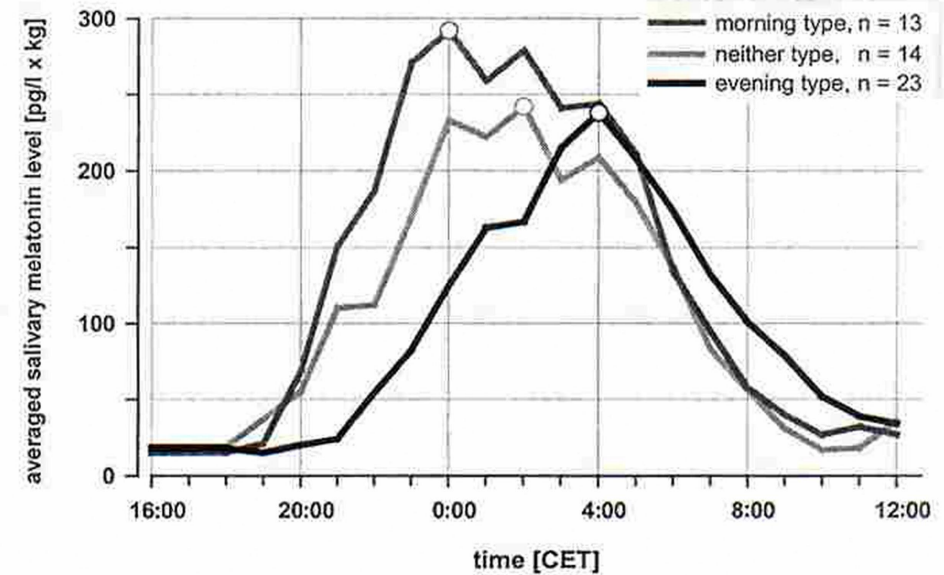
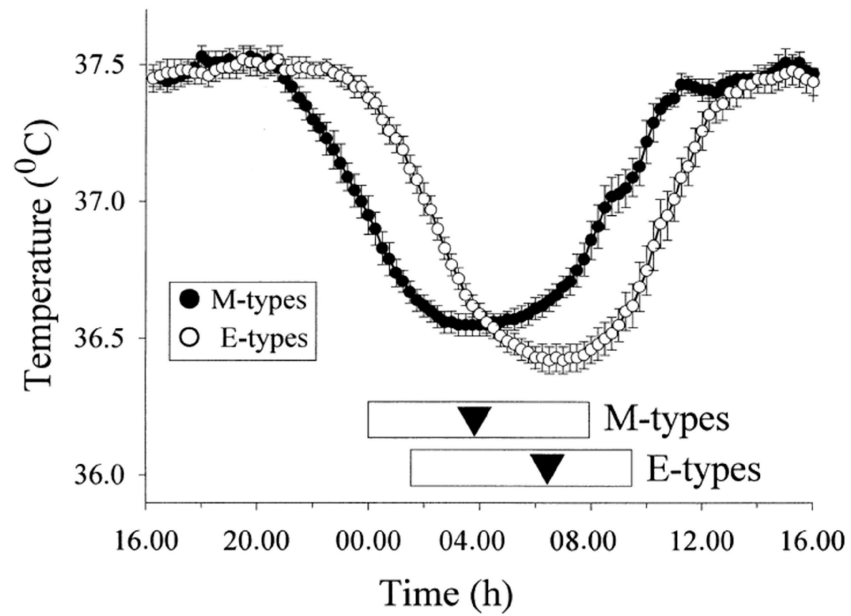
Early Birds, Night Owls (Chronotype) and Social Jet Lag



How to measure chronotype

- Questionnaire
- Activity monitoring
- Lab – constant routine and/or forced desynchrony: temperature and/or melatonin

Body Temperature and salivary melatonin rhythms are phased advanced in Horne-Östberg morning-types.



Why Mutants? Why Genetics?

- A mutant is a potential entrée into a mysterious process. What causes the phenomenon? What is the machine that keeps time (the quartz crystal)?
- **Now let's consider “you vs me” and genes/environment causes.**

Chronotype is heritable.

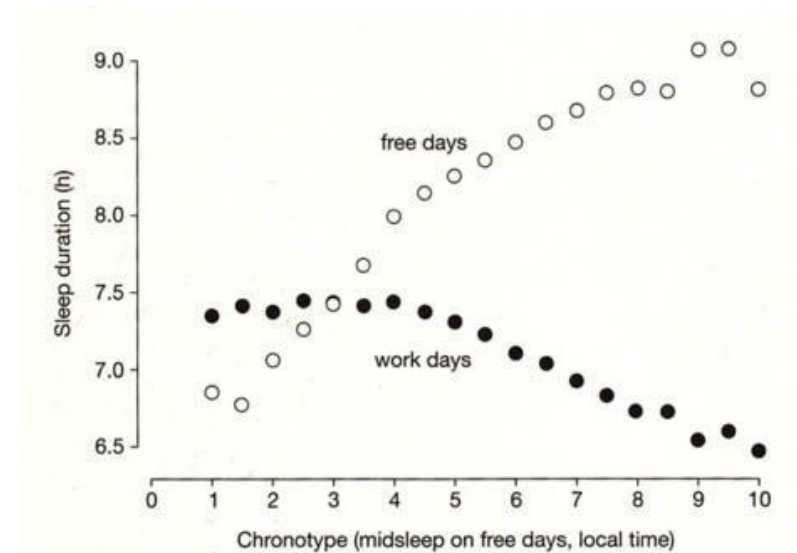
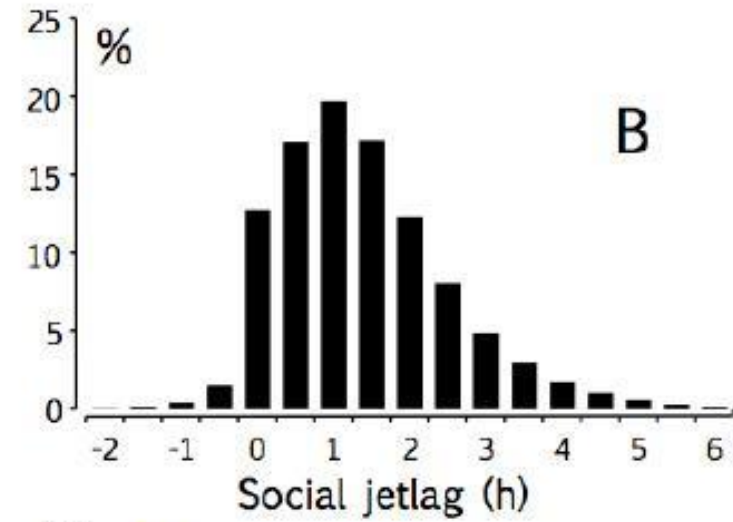
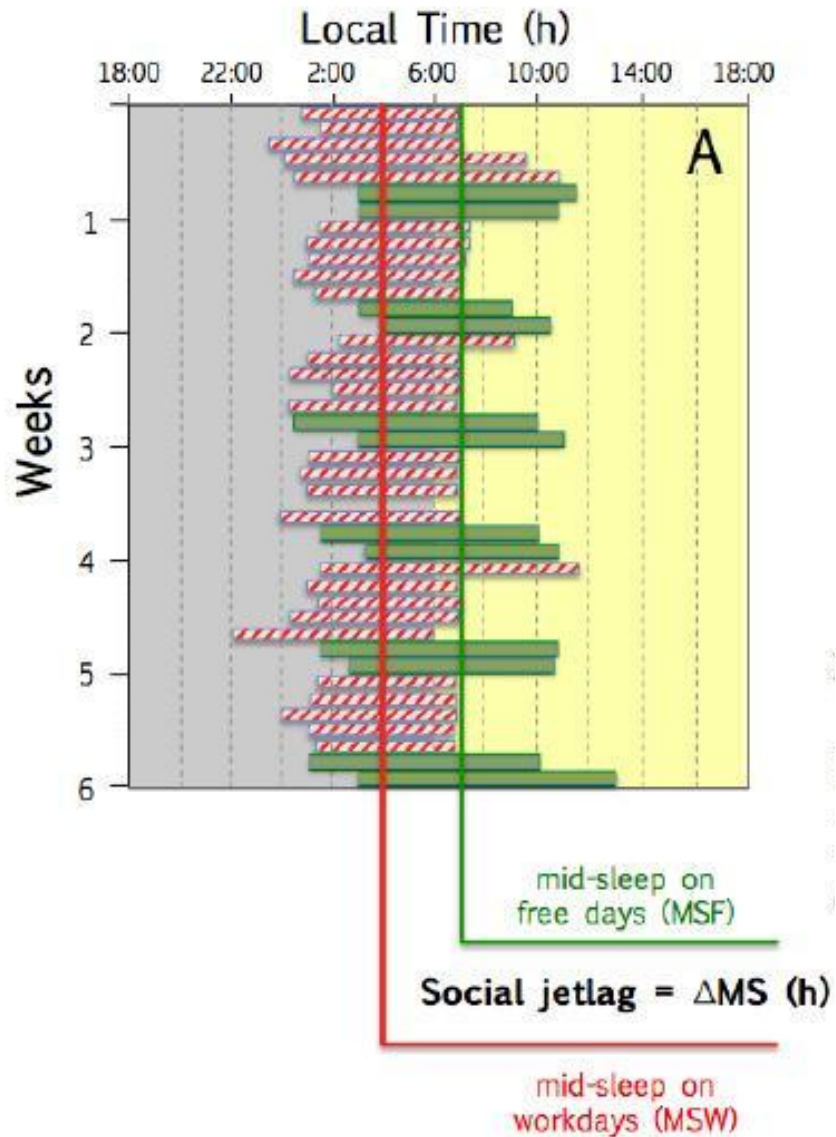
Table 3 Pairwise polychoric correlations (and no. pairs) for diurnal type (including four categories) among twin pairs by zygosity, age and sex

	<i>Monozygotic</i>	<i>Dizygotic</i>
Males aged		
24–34	0.467 (572)	0.087 (1296)
35–49	0.490 (420)	0.185 (979)
50 and older	0.288 (237)	0.120 (492)
All	0.472 (1229)	0.182 (2767)
Females aged		
24–34	0.458 (774)	0.136 (1452)
35–49	0.538 (495)	0.052 (1013)
50 and older	0.501 (338)	0.064 (685)
All	0.516 (1607)	0.128 (3150)
All subjects aged		
24–34	0.461 (1346)	0.115 (2748)
35–49	0.513 (915)	0.116 (1992)
50 and older	0.412 (575)	0.087 (1177)
All	0.497 (2836)	0.153 (5917)

Genes, the UK Biobank and Chronotype

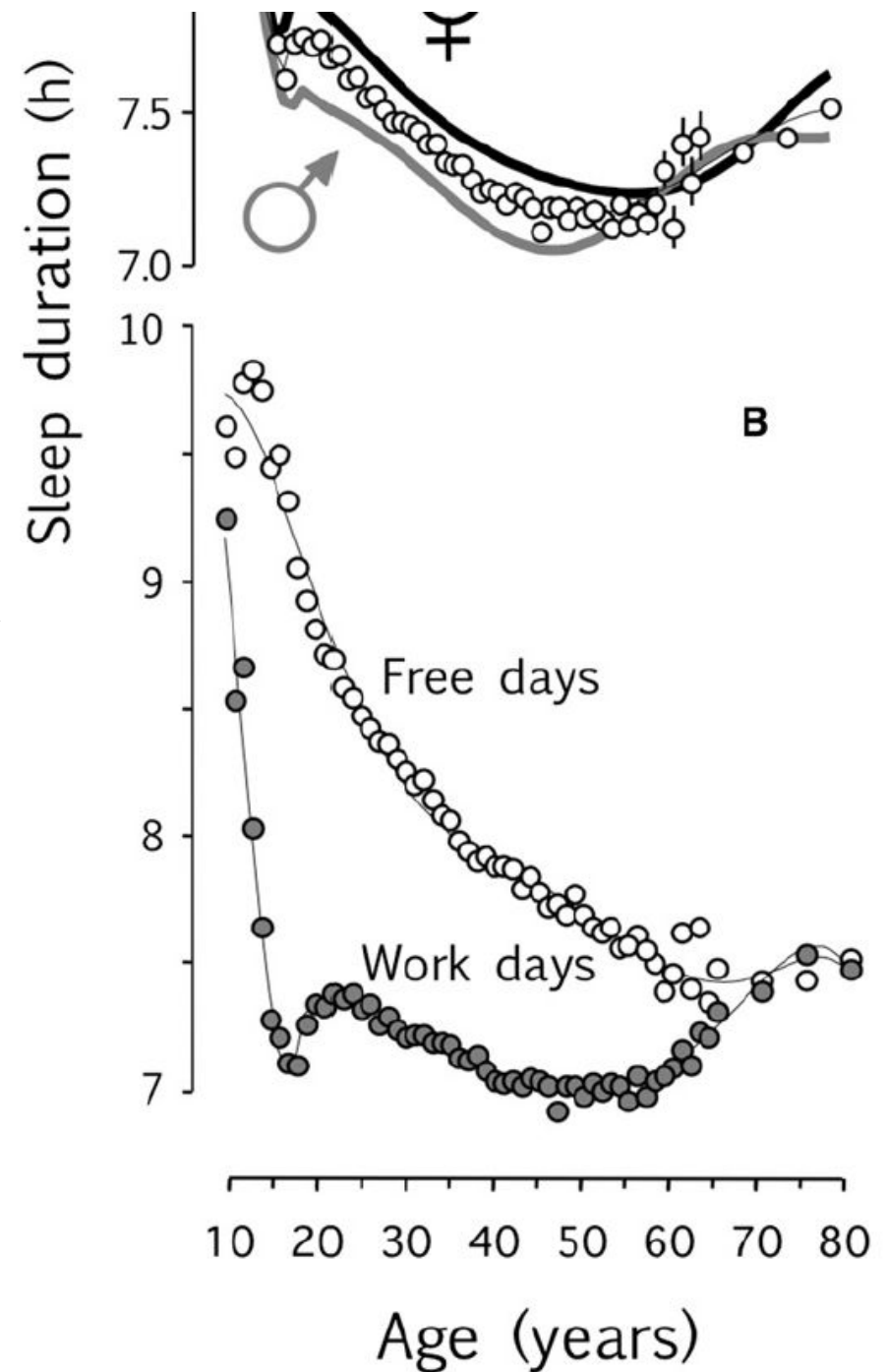
- 2019 Nature Communications:
- Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms
- Many genes contribute to chronotype (known, unknown)

Social Jet Lag (SJM) of an owl



Social Jetlag is Maximal During Teenage Years

Like Jetlag but chronic. Every week. Flying west on Friday
And east on Monday.



The whole world is sleep-deprived or living “anti-natura”

- Alarm clocks
- Sleep latency tests and falling asleep
- Highway accidents – falling asleep >> alcohol
- Not enough light in the daytime and too much at night: sunlight vs indoor lighting
- We now live with 3 clocks: sun, body (circadian), social

The regulation of sleep

Circadian Regulation

Homeostatic Regulation



Third Challenge for the Future:

Understanding the Basic Science of Sleep and Improving Human Sleep

- Why do we Sleep? What is the Conserved Function(s) of Sleep.
- Where/What is Keeping Track of Sleep Need? How does Sleep Homeostasis Work?

Flies really sleep and like we do! Perhaps they will do for sleep research what they have done for circadian rhythms.

A period of quiescence associated with a species specific posture

An increase in arousal threshold

Quick reversibility to wakefulness

Homeostasis

Conserved signaling pathways

Conserved function of neurotransmitters

Conserved effects of hypnotic/stimulant drugs

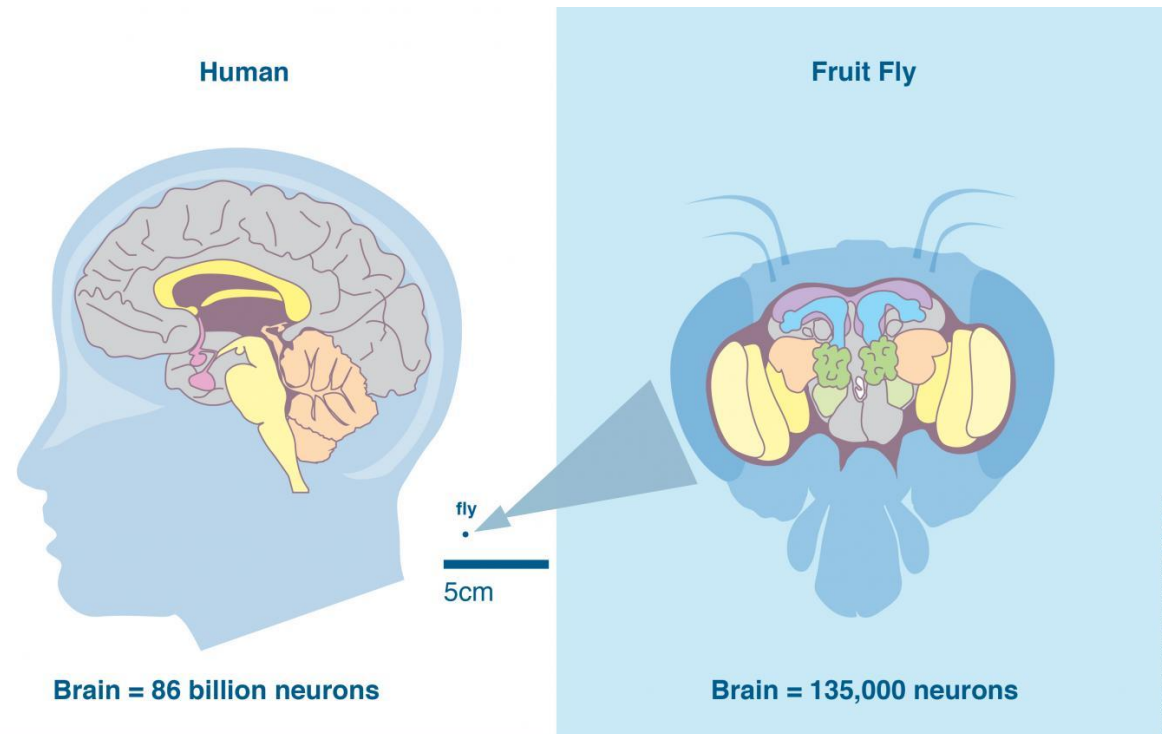
Interactions with the circadian clock



Flies have more generally a sophisticated behavioral repertoire

- Sleep and Activity
- Learning
- Memory
- Aggression
- Motivation
- Mating and courtship
- Addiction
- ...

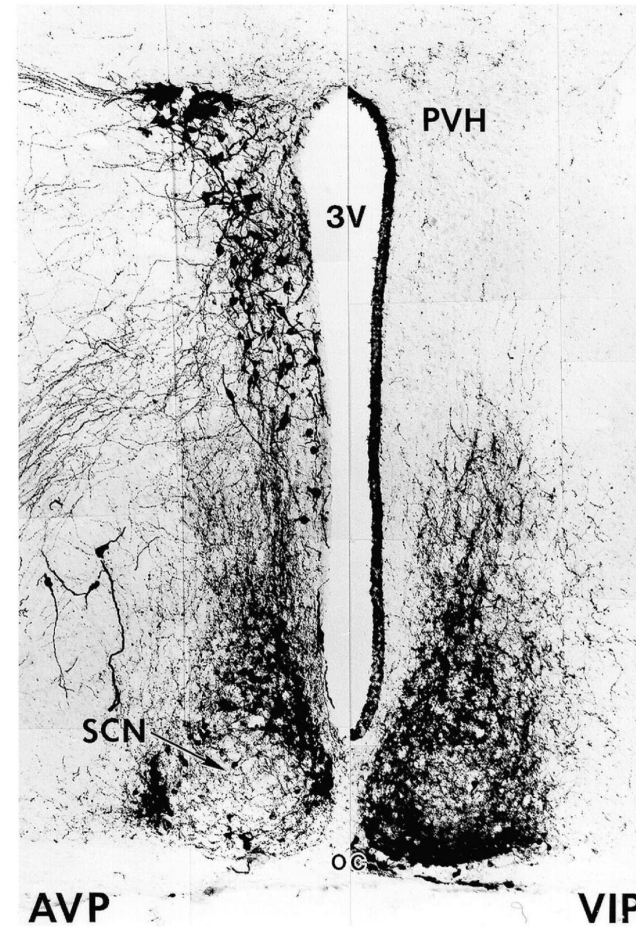
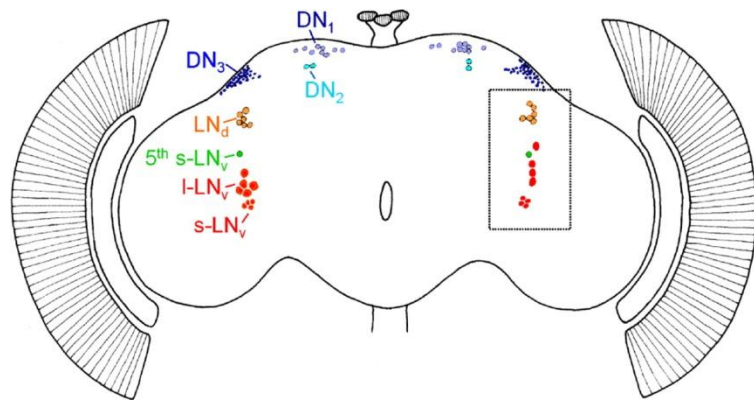
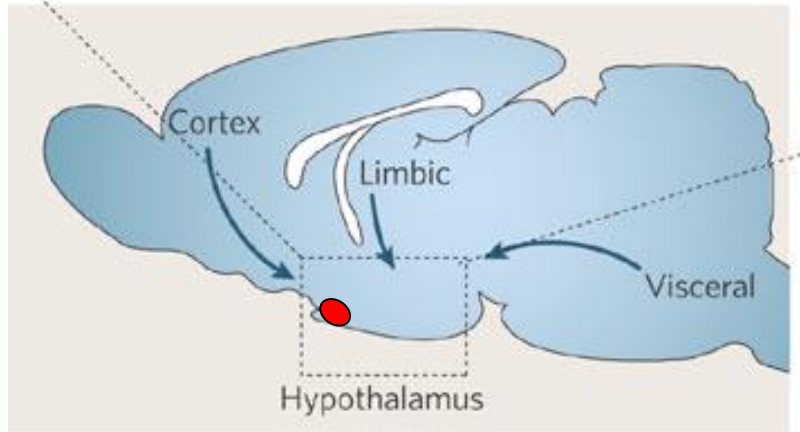
Drosophila does all this with about 100,000 brain neurons,
a million times fewer than the human brain



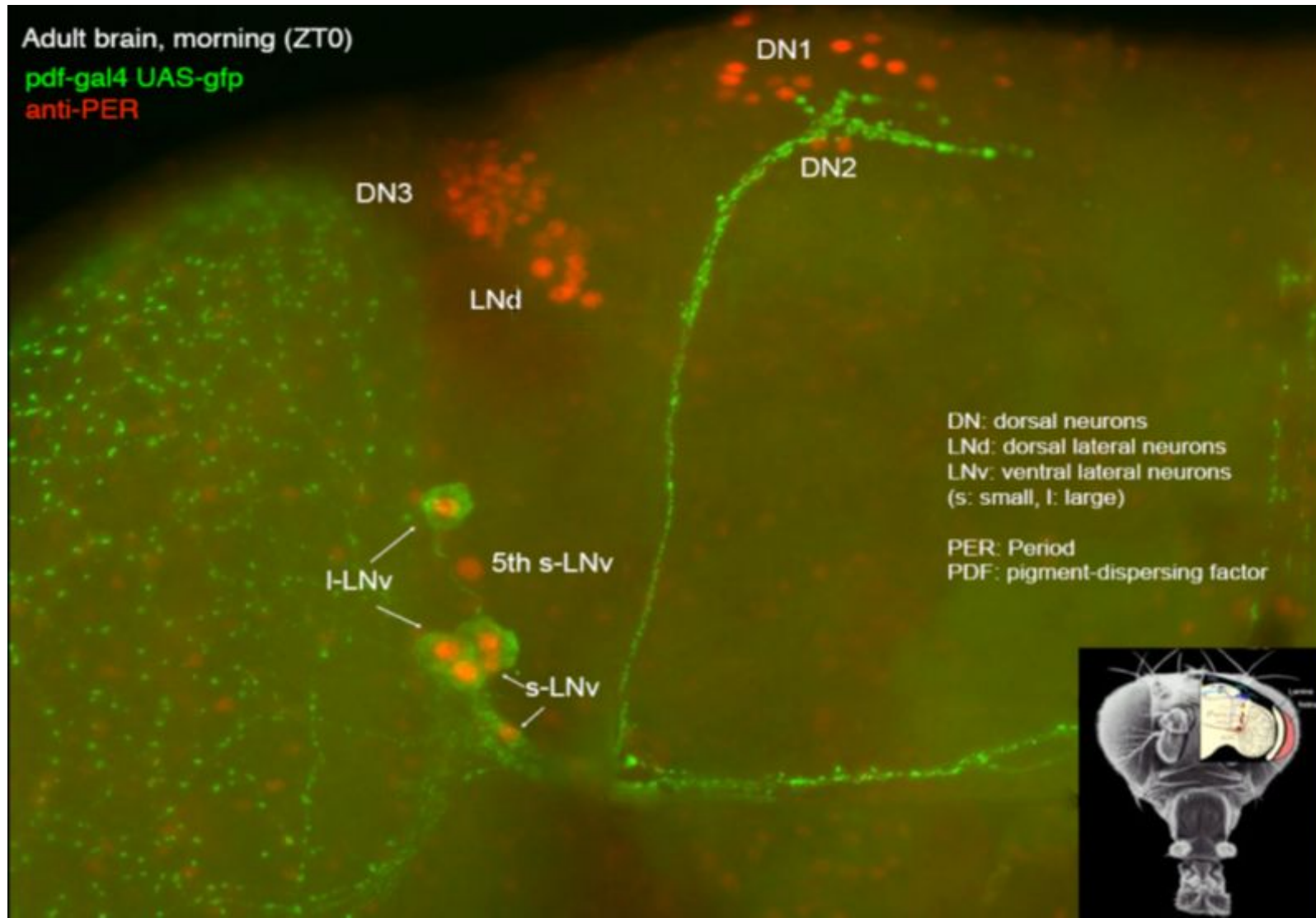
“Fruit flies share nearly 60% of our genes, so the neural circuits in their brains – despite the huge size difference – are likely to be similar to ours. A model of the fruit fly brain – which is achievable – will tell us a lot about the human brain.” Daniel Coca, University of Sheffield

The *Drosophila* circadian network is also much simpler than the mammalian SCN

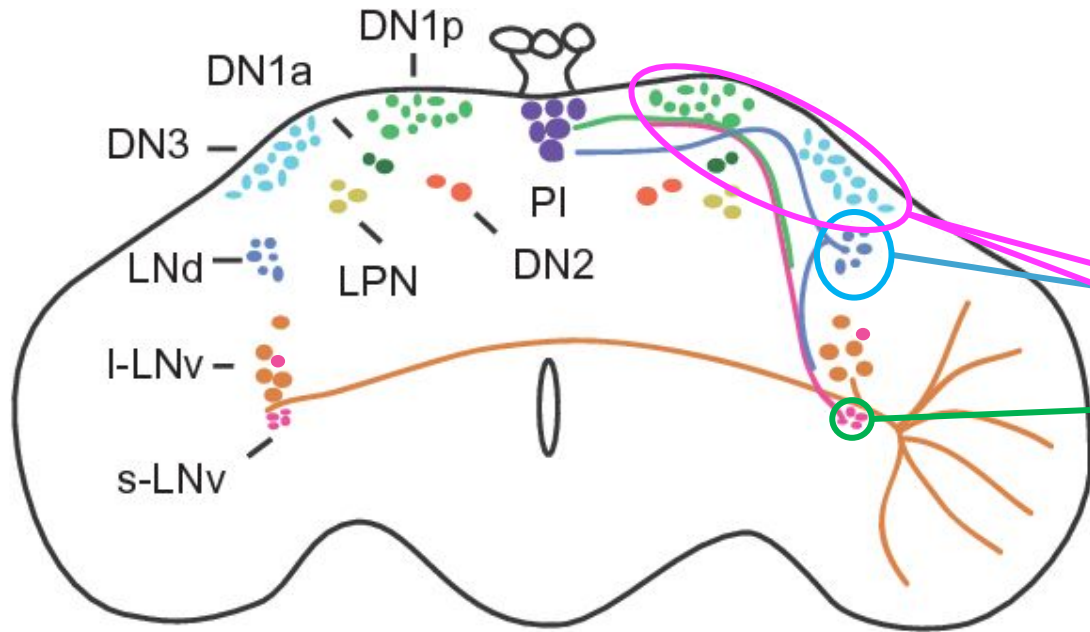
Fly: 125-150 neurons
SCN: 20,000 neurons



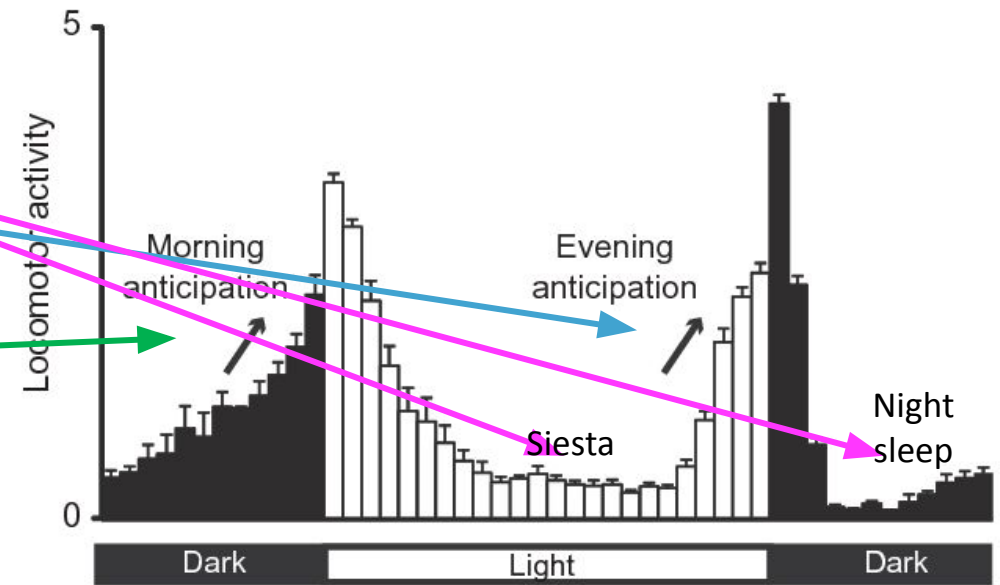
The ~75 pairs of *Drosophila* central brain clock neurons (red)



Many discrete subsets of circadian neurons are linked to specific behavioral features



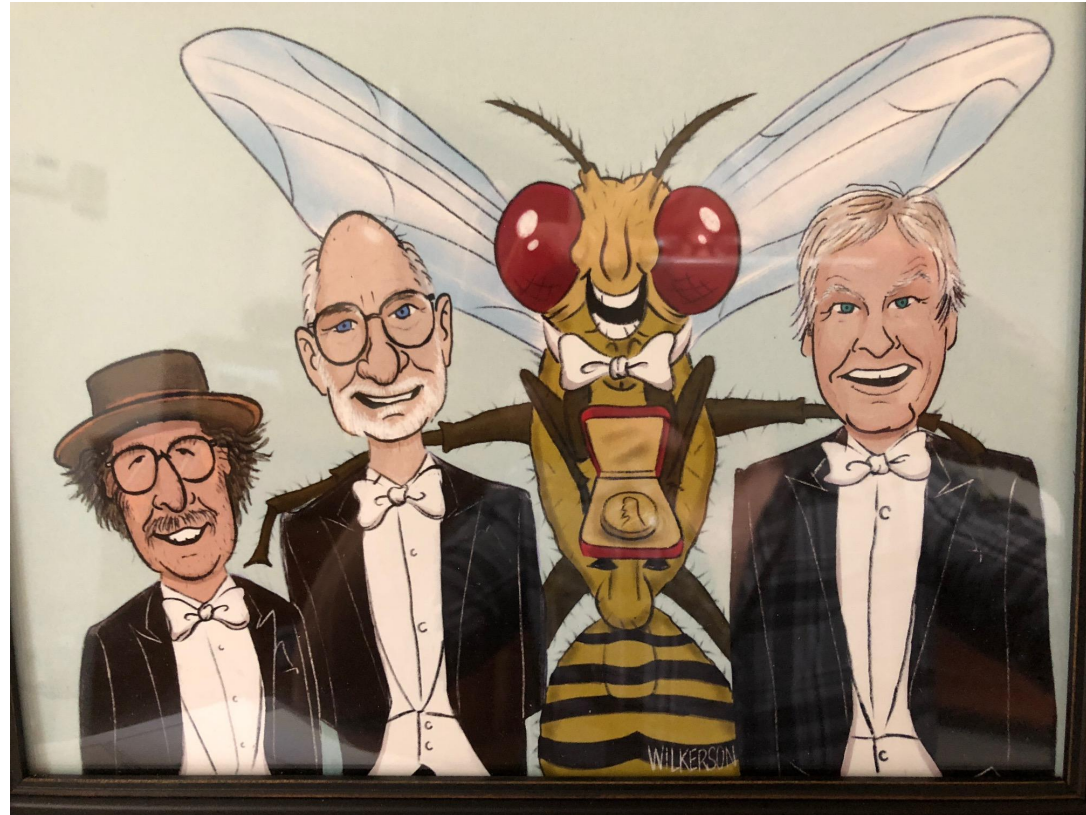
~75 circadian neurons per hemisphere



Flourakis and Allada, 2015

A homage to model organisms and the nobel [sic] fruit fly:
The 2017 Nobel Prize in Physiology or Medicine should
have/could have had a fourth recipient

(fifth fruit fly prize)



Nobel Banquet: 1300 People



Current lab members (Brandeis University and HHMI)

- Kate Abruzzi
- Xihuimin Dai
- Nico Herndon
- Jasmine Le
- Dylan Ma
- Nick Petersen
- Melina Perez Torres
- Corrie Ratner
- Shlesha Richhariya
- Matthias Schlichting
- Daniel Shin
- Albert Yu

The accidents of life: Brandeis, genetics, Jeff Hall and circadian rhythms



Why Mutants? Why Genetics?

- A mutant is a potential entrée into a mysterious process. What causes the phenomenon? What is the machine that keeps time (the quartz crystal)?
- **Different than “you vs me” and genes/environment causes.**

genes and environment=genes and accidents (stochastic events)

Agency and Empathy

*That's All
Folks!*

