

# Circadian Timekeeping and Entrainment in Neuronal Clock Networks



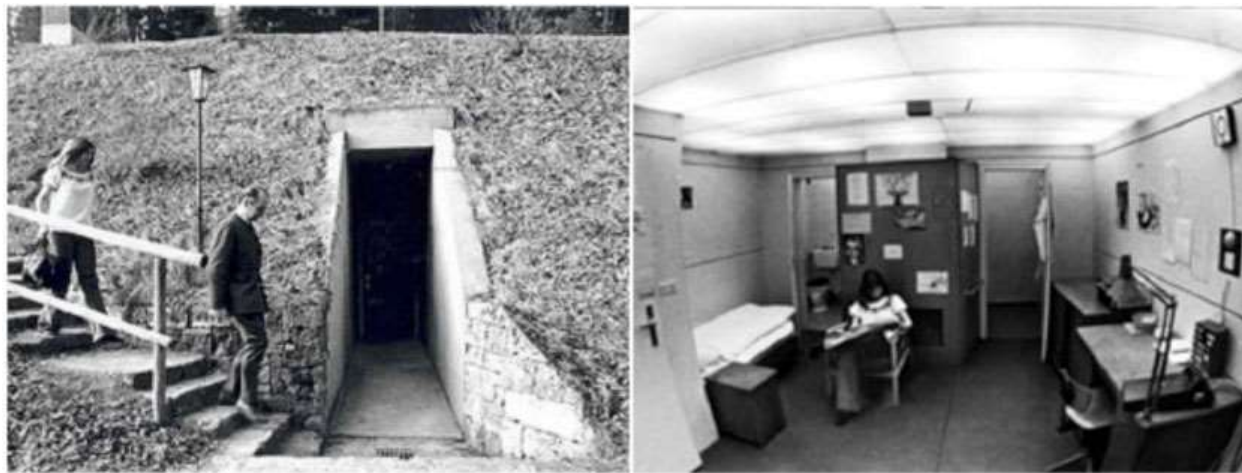
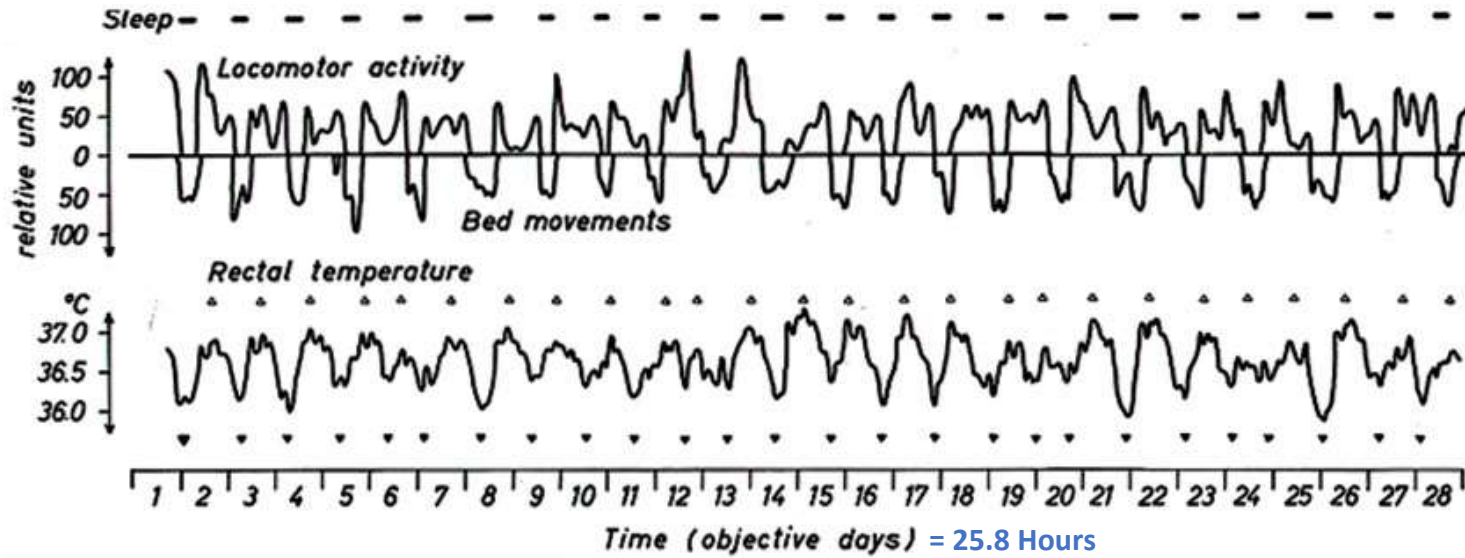
**Orie T. Shafer**

The Advanced Science Research Center, The Graduate Center

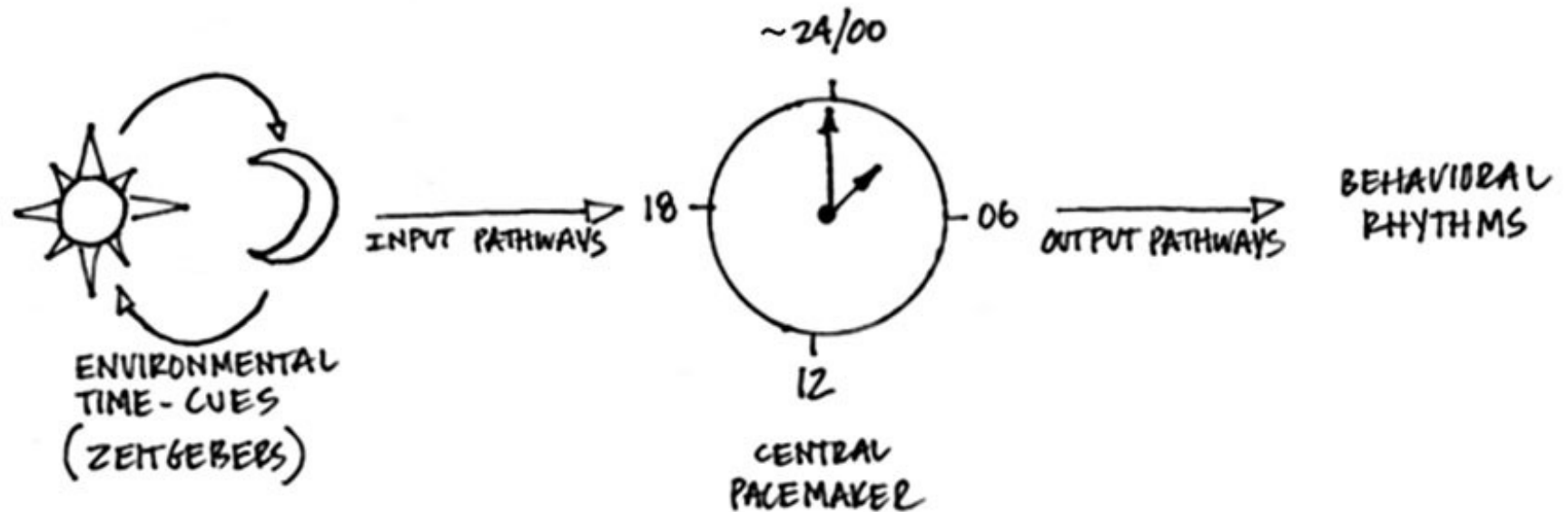
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# Life is a rhythm.

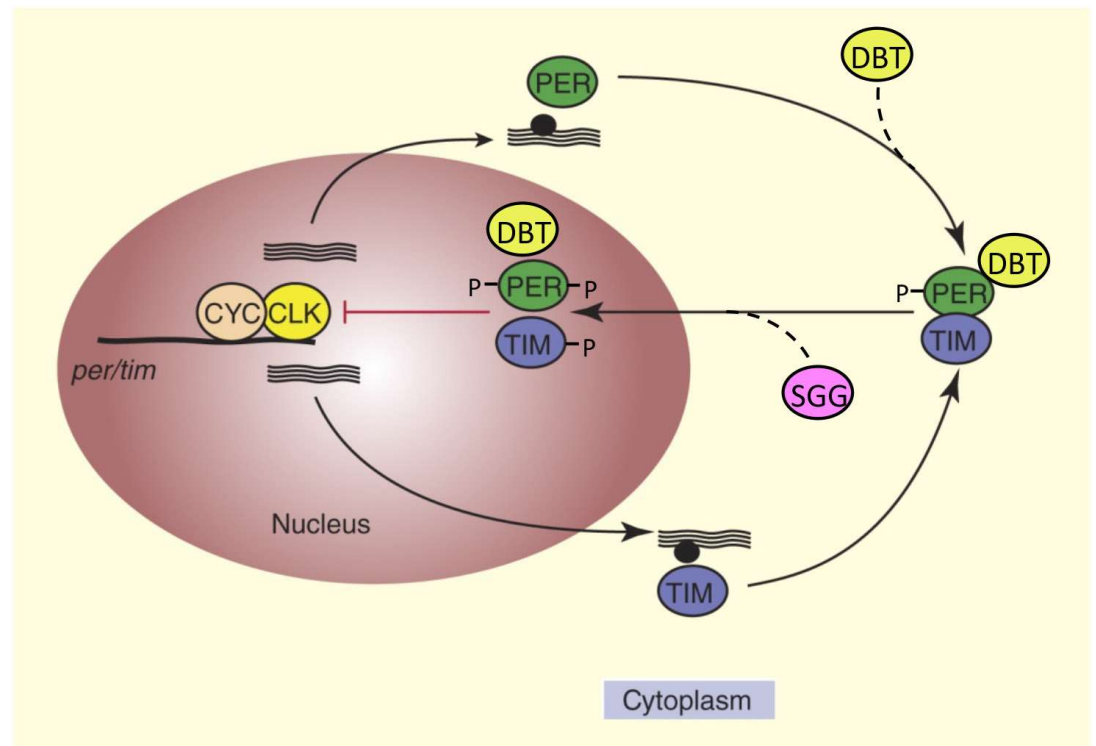


# A Simple Model of the Circadian System

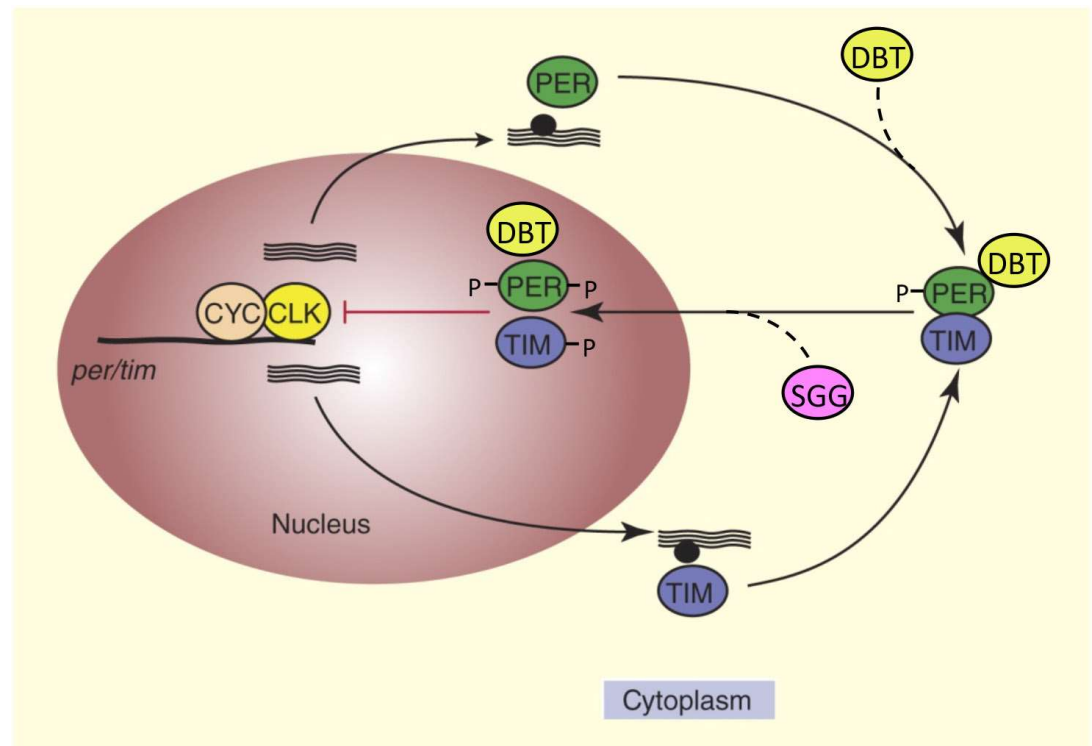
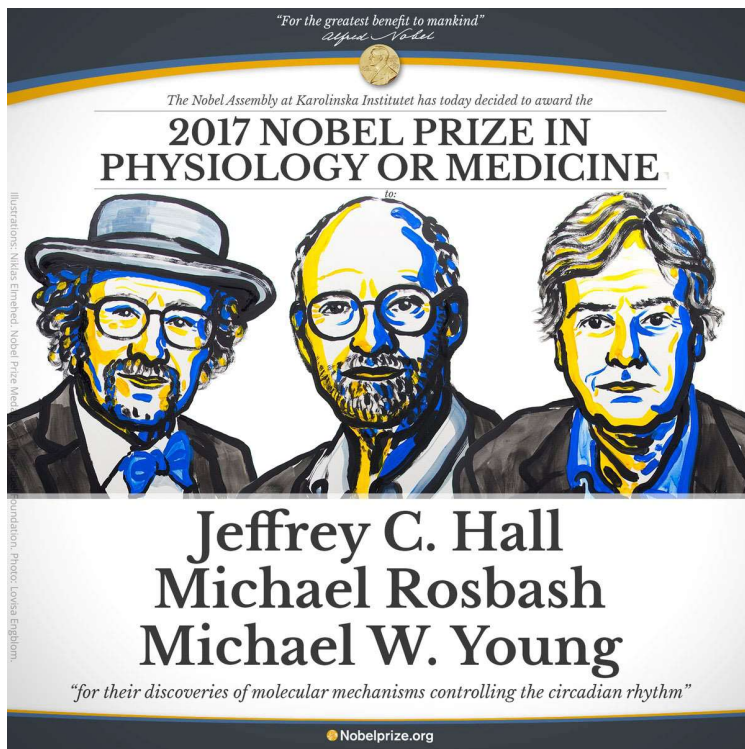


The proper daily timing depends on two phenomena:  
circadian **timekeeping** and **entrainment**.

# *Drosophila* and the Molecular Circadian Clock

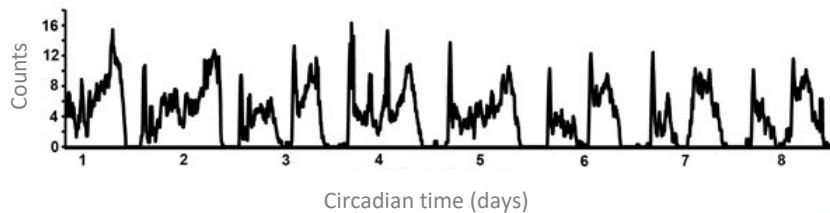


# *Drosophila* and the Molecular Circadian Clock

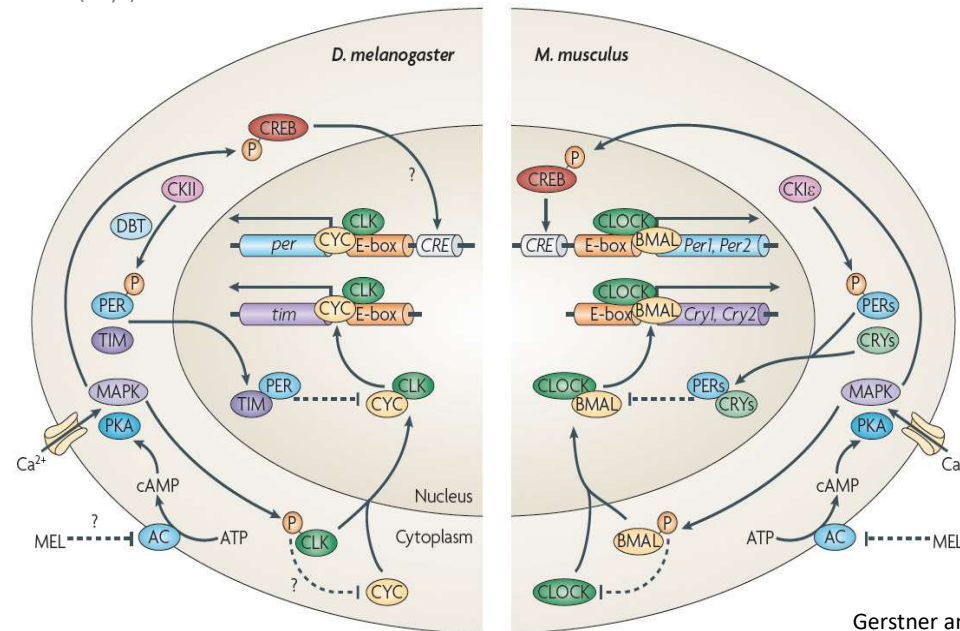
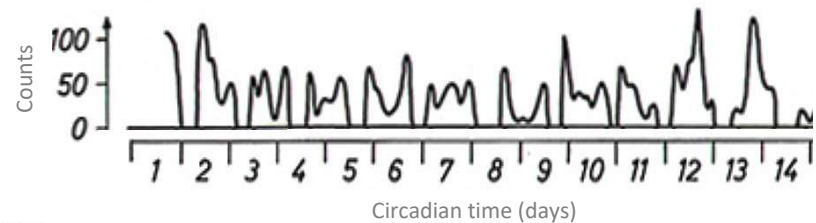


# Behavioral rhythms are driven by molecular rhythms.

## *D. melanogaster*



## *H. sapiens*

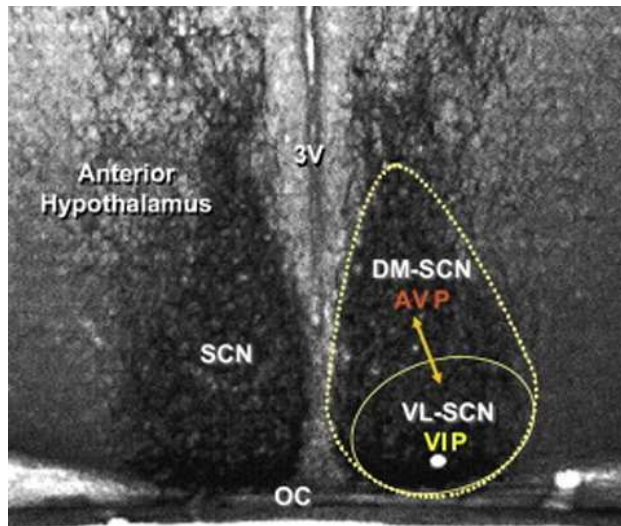
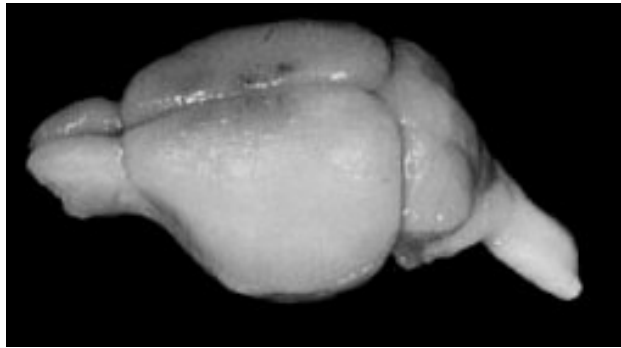


Gerstner and Yin (2010) *Nat. Rev. Neurosci.* 11:577

*Molecular clocks are required in small islands of the brain for behavioral, endocrine, and physiological rhythms.*

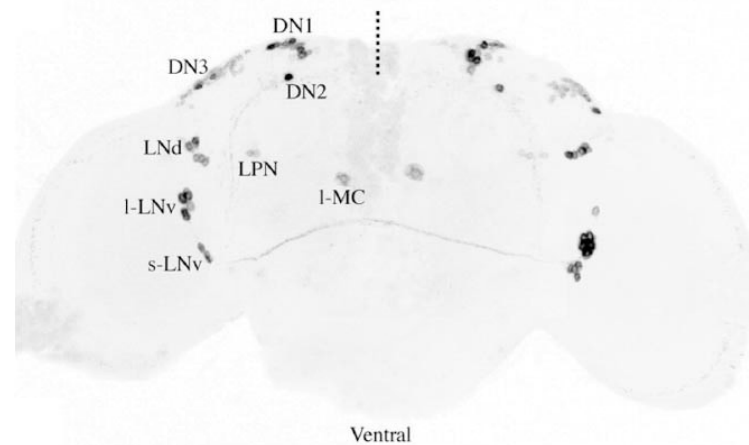
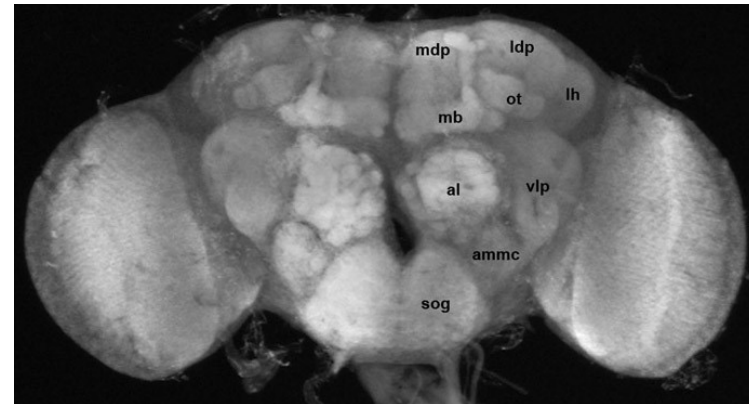
# What is the neuronal basis of circadian timekeeping? How is the circadian clock neuron network organized?

A mouse brain is built of ~75,000,000 neurons.



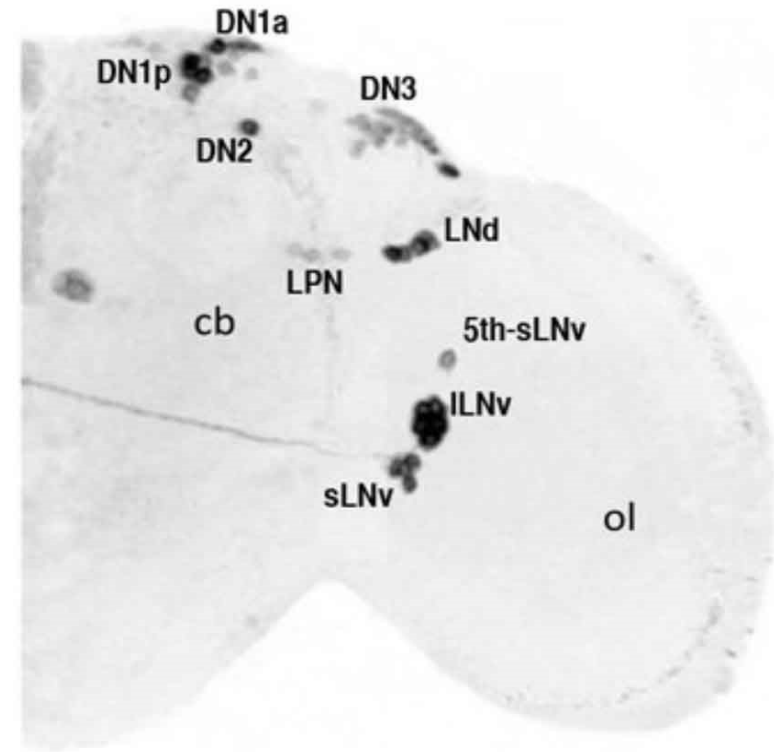
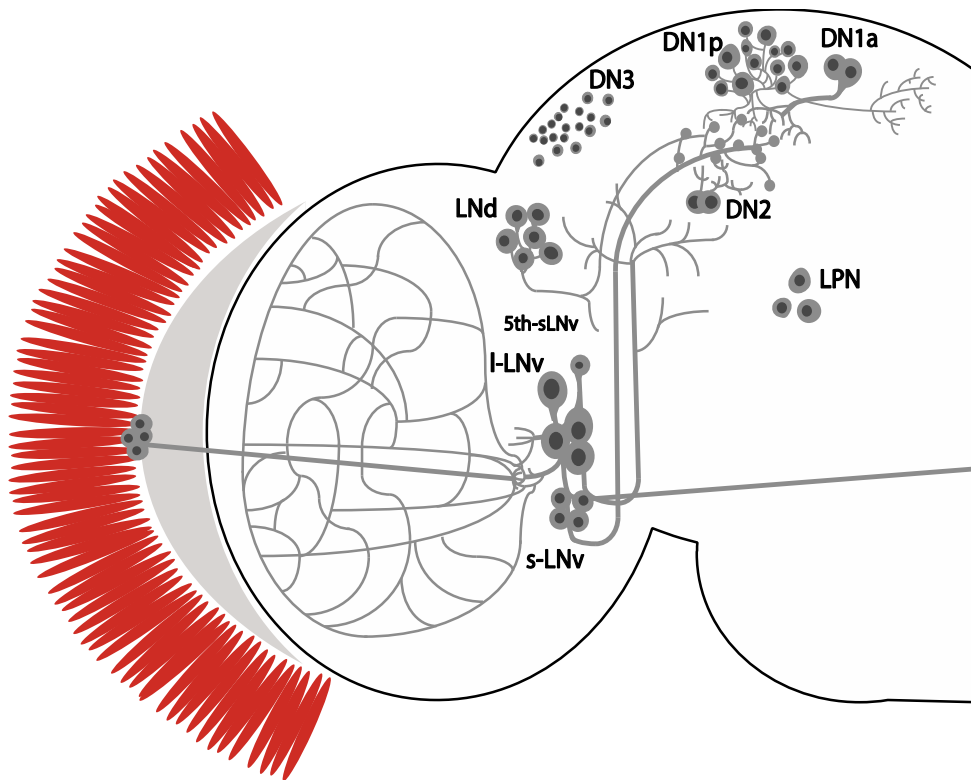
Each suprachiasmatic nucleus comprises  
~20,000 neurons.

The entire fly CNS consists of ~100,000 neurons.



Each hemisphere of the fly brain contains  
~75 "clock neurons."

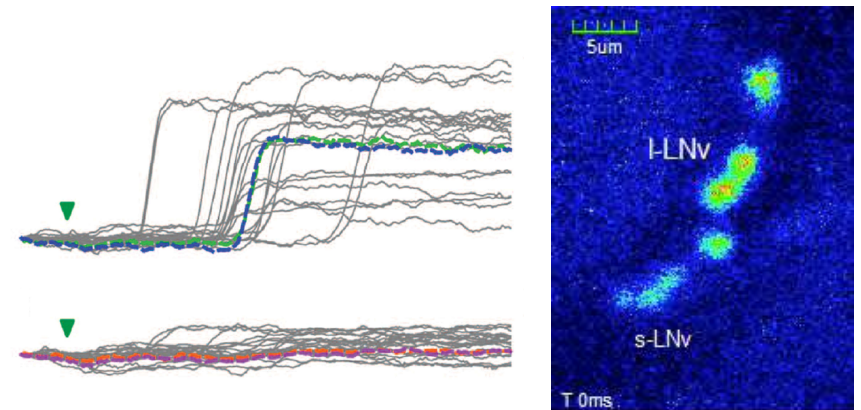
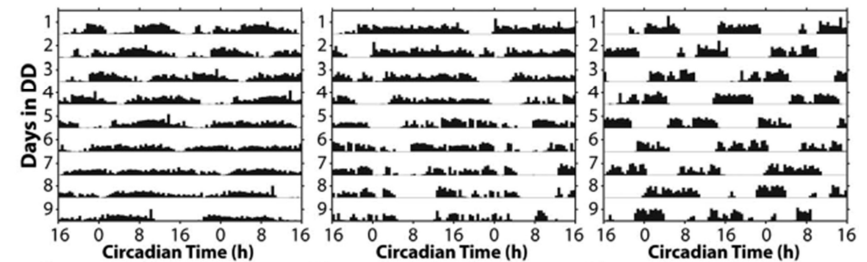
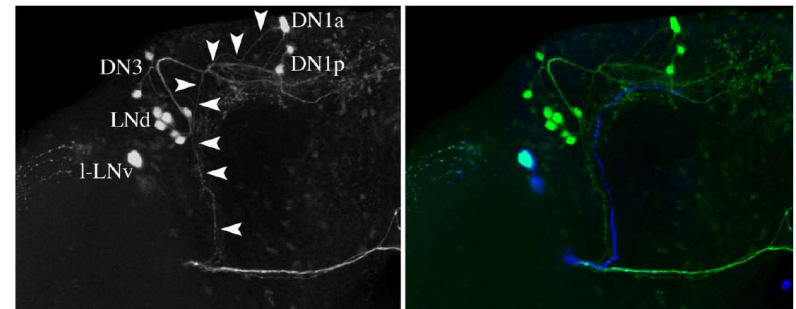
# The Neuronal Clocks of the *Drosophila* Brain: Simplicity, Stereotypy, Genetic Malleability



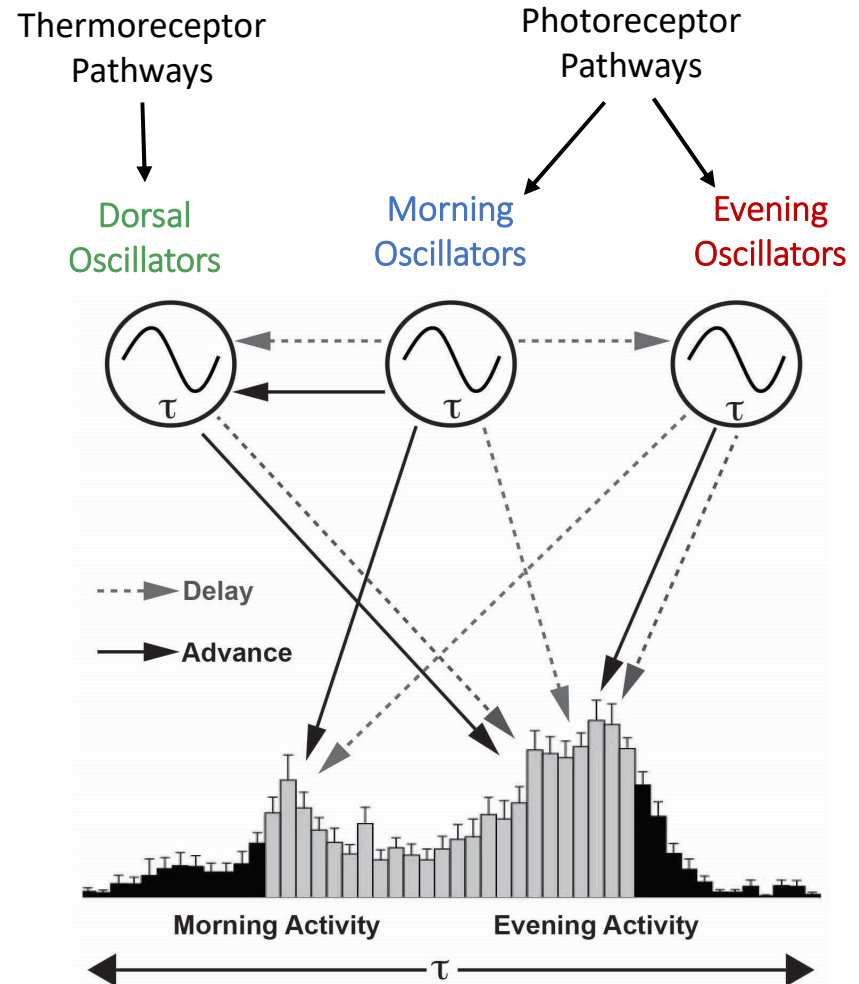
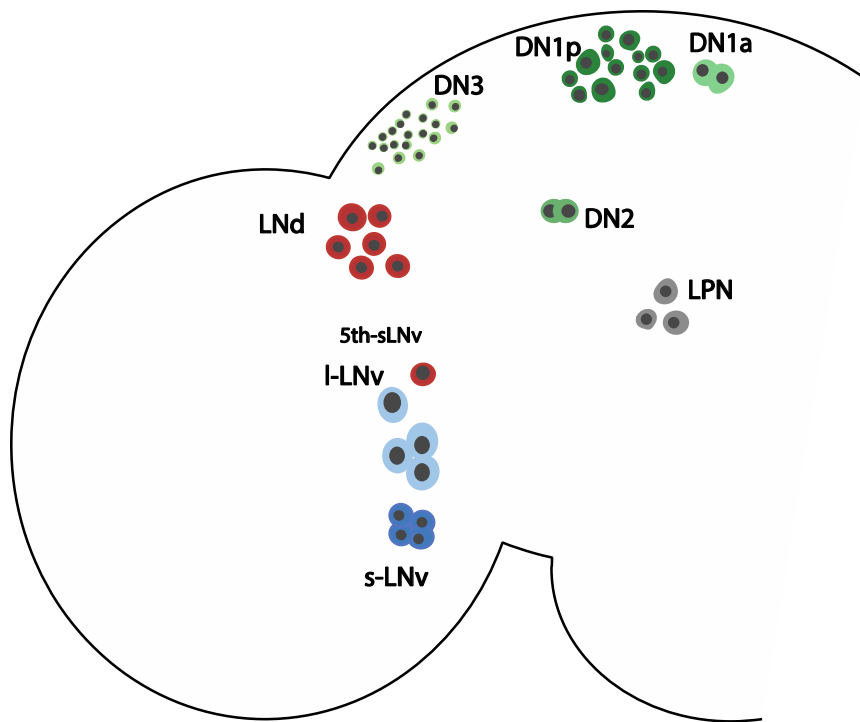


# Network Properties of Circadian Timekeeping in the *Drosophila* brain.

- Cellular Characterization of the Molecular Clock in the Clock Neuron Network
- Anatomical Characterization of the Clock Neuron Network
- Genetic Manipulation of Neuronal Clocks
- Analysis of Sleep/Activity Rhythms and Entrainment
- Live Imaging ( $\text{Ca}^{2+}$  and cAMP) of Clock Neuron Physiology.
- Analysis of Functional Connectivity.



# Network Properties of Circadian Timekeeping and Entrainment in the *Drosophila* Brain



Lelito et al. (2012) *J. Neurophysiol.* 107:2096

Yao et al. (2012) *J. Neurophysiol.* 108:684

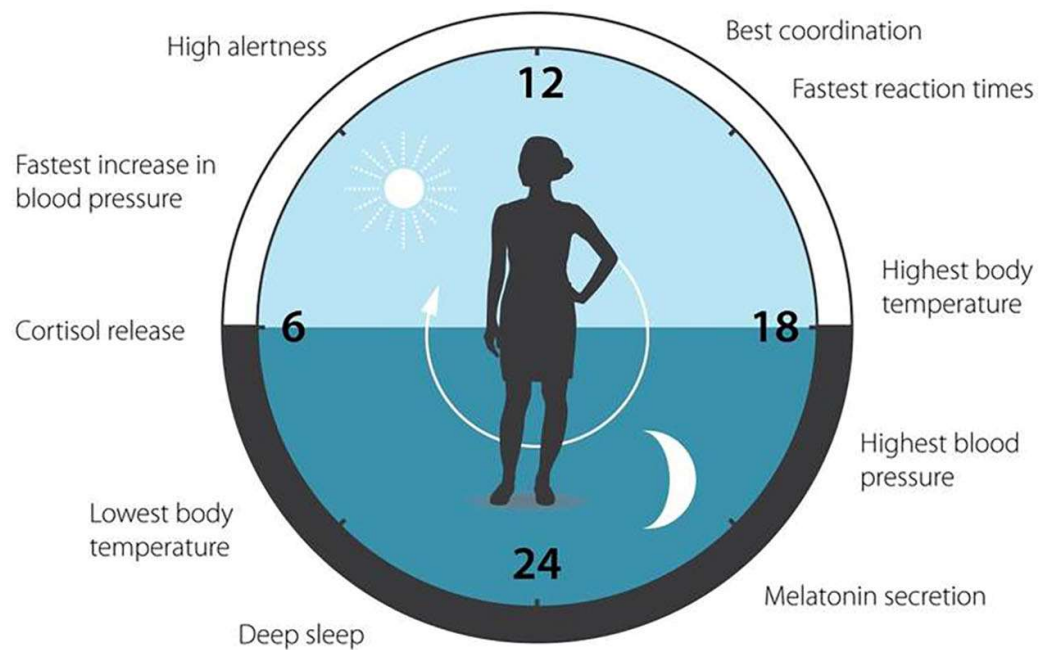
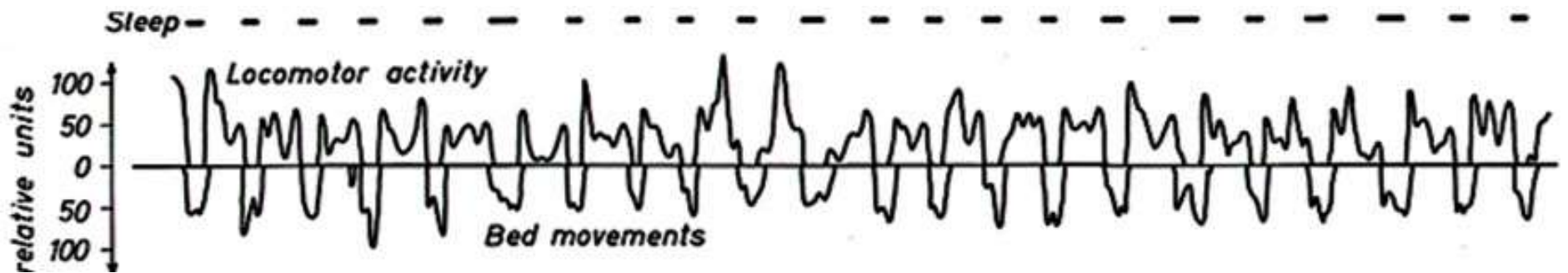
Yao and Shafer (2014) *Science* 343:1516

Yao et al. (2016) *Cell Reports* 17:2873

Schlichting et al. (2016) *J. Neurosci.* 36: 9084

Yadlapalli et al. (2018) *Nature* 555: 98

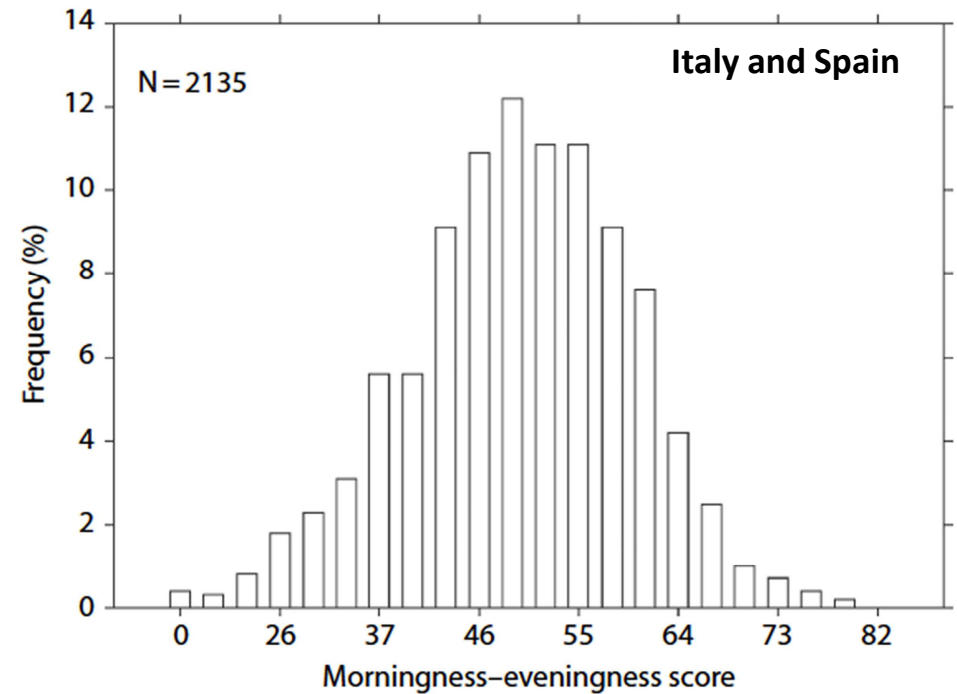
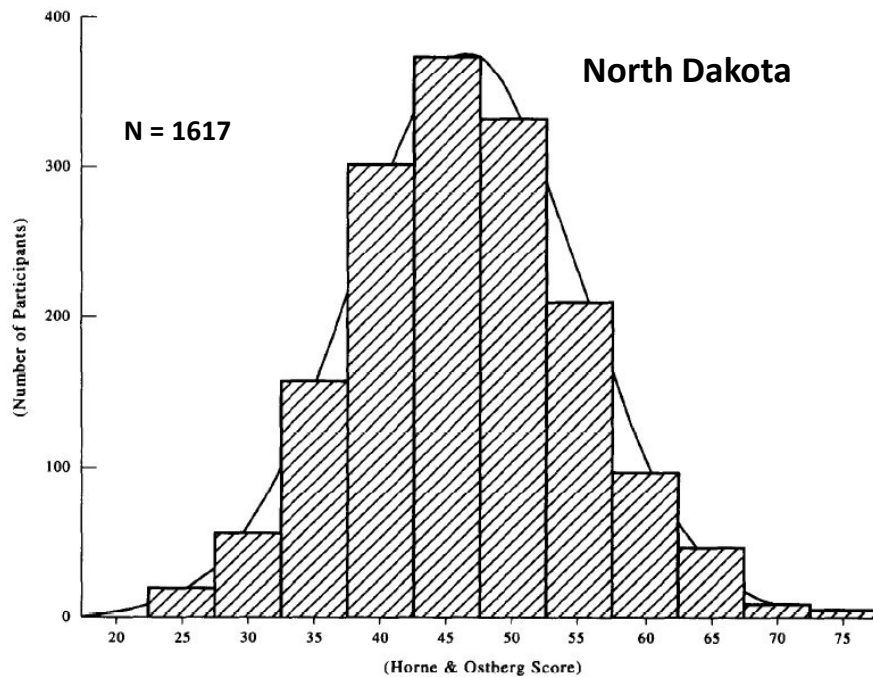
# Human Circadian Rhythms



Humans display significant variation in their phase angle of entrainment.

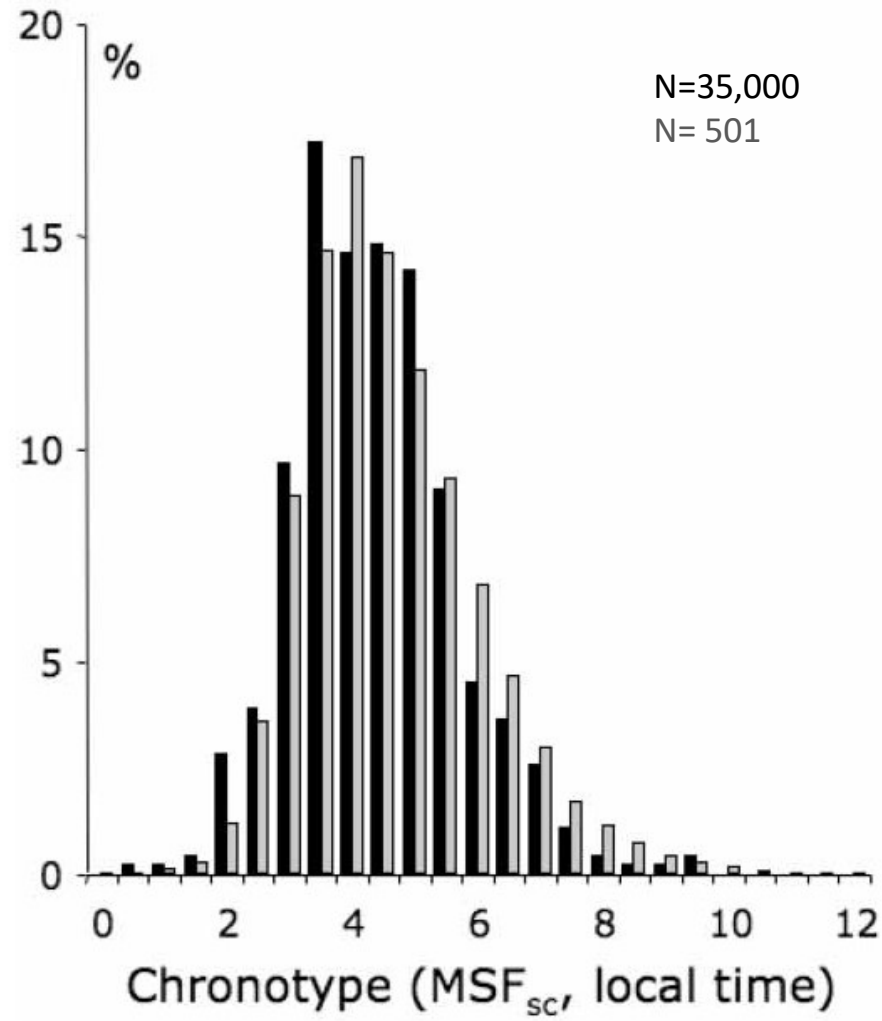


The distribution chronotype is replicable in large samples across cultures.

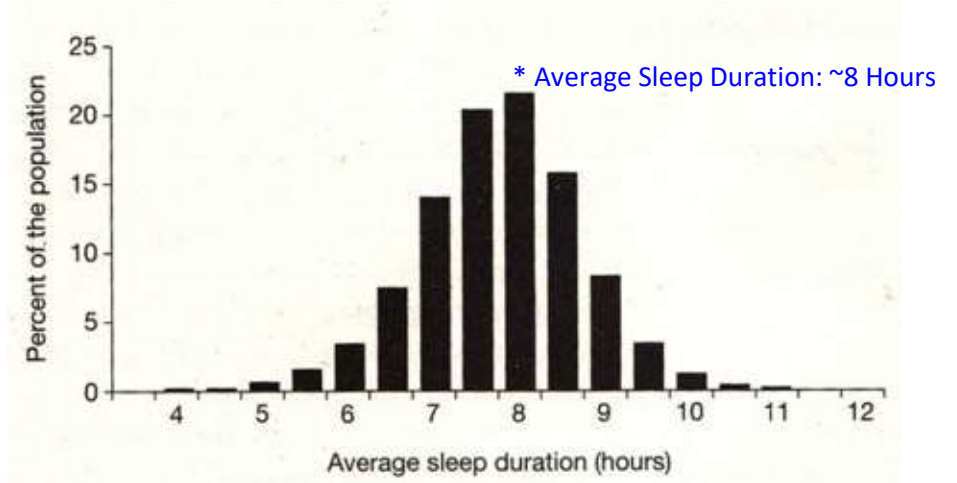
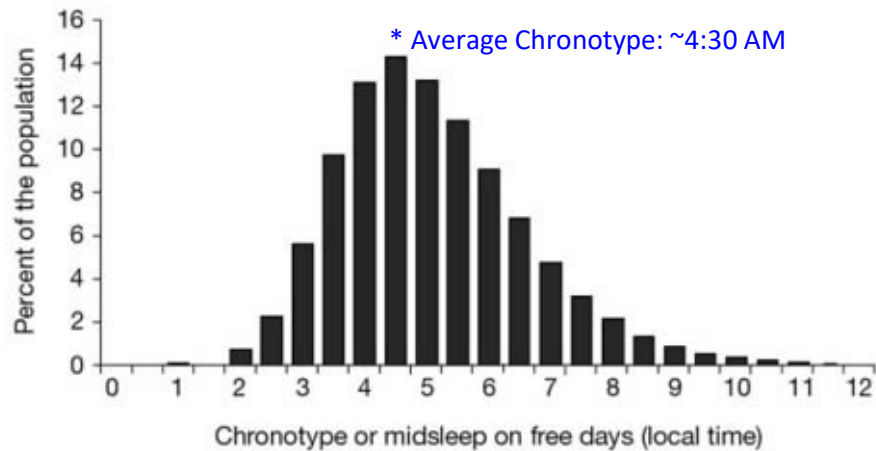


Horne-Östberg Morningness/Eveningness Scores

# Human Chronotypes Using the Midpoint of Sleep on Free Days (MSF)



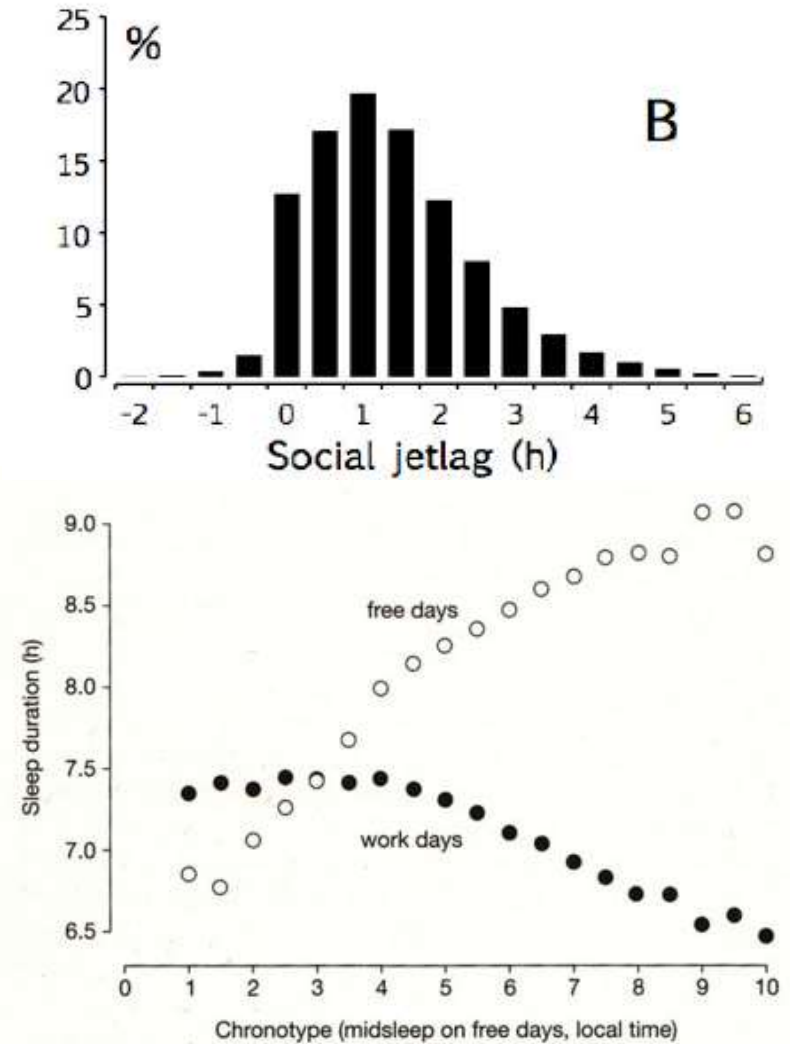
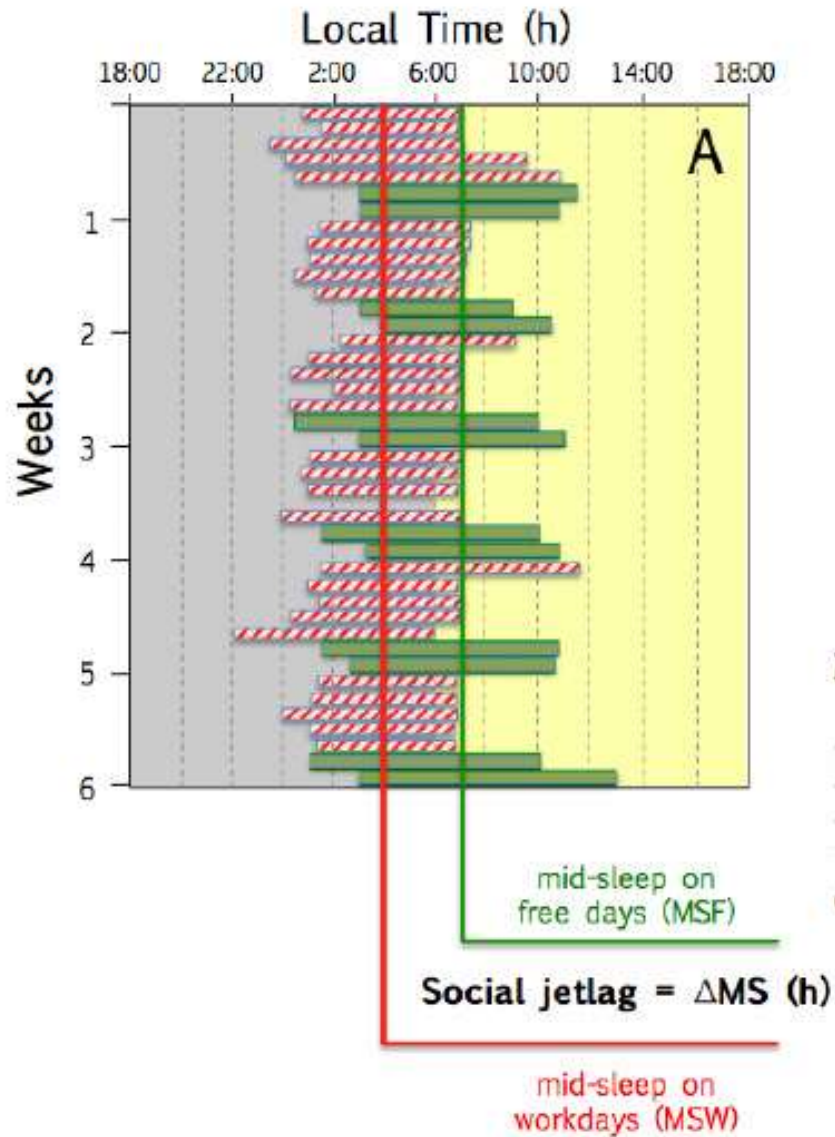
The average work start time in the U.S. is 7:55AM (7:59 for schools).



Average free day sleep starts at 12:30AM and ends at 8:30AM

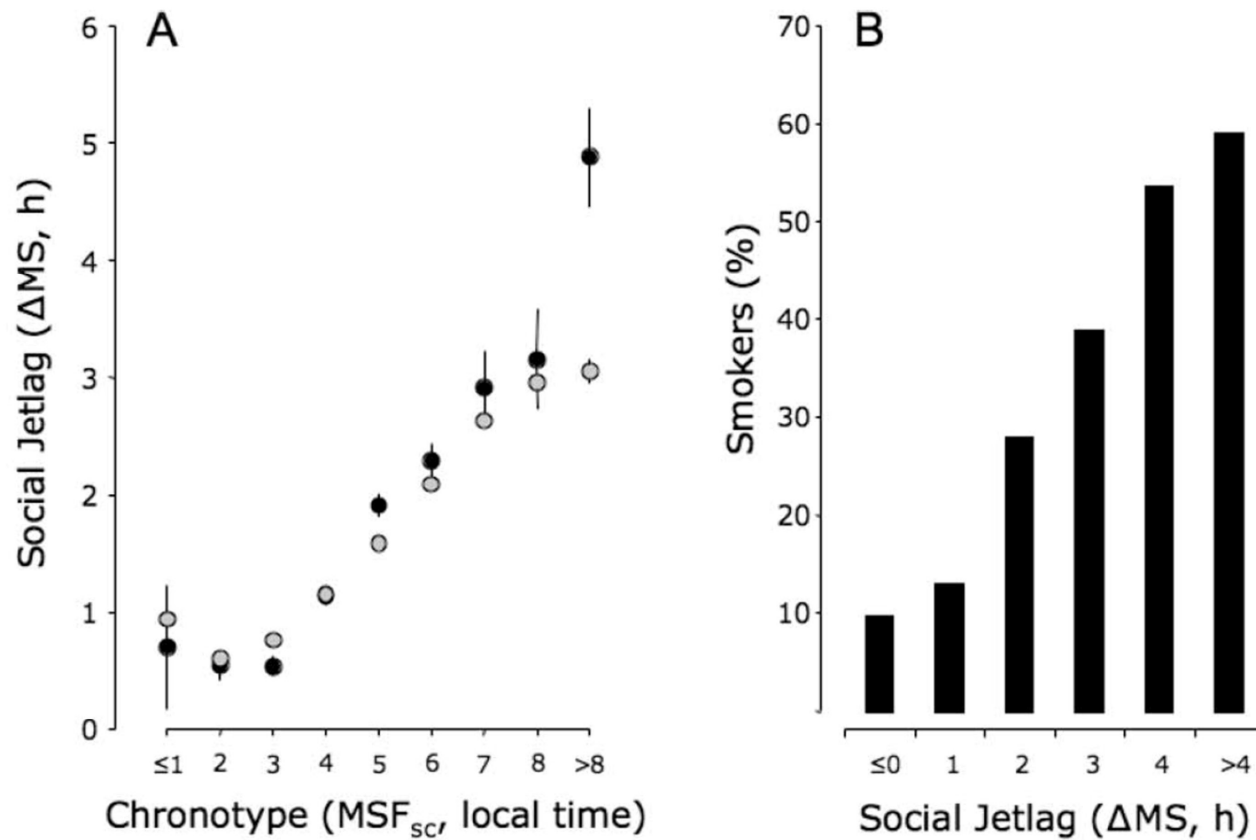
*Whose schedule are we keeping?*

# Social Jet Lag (SJL)

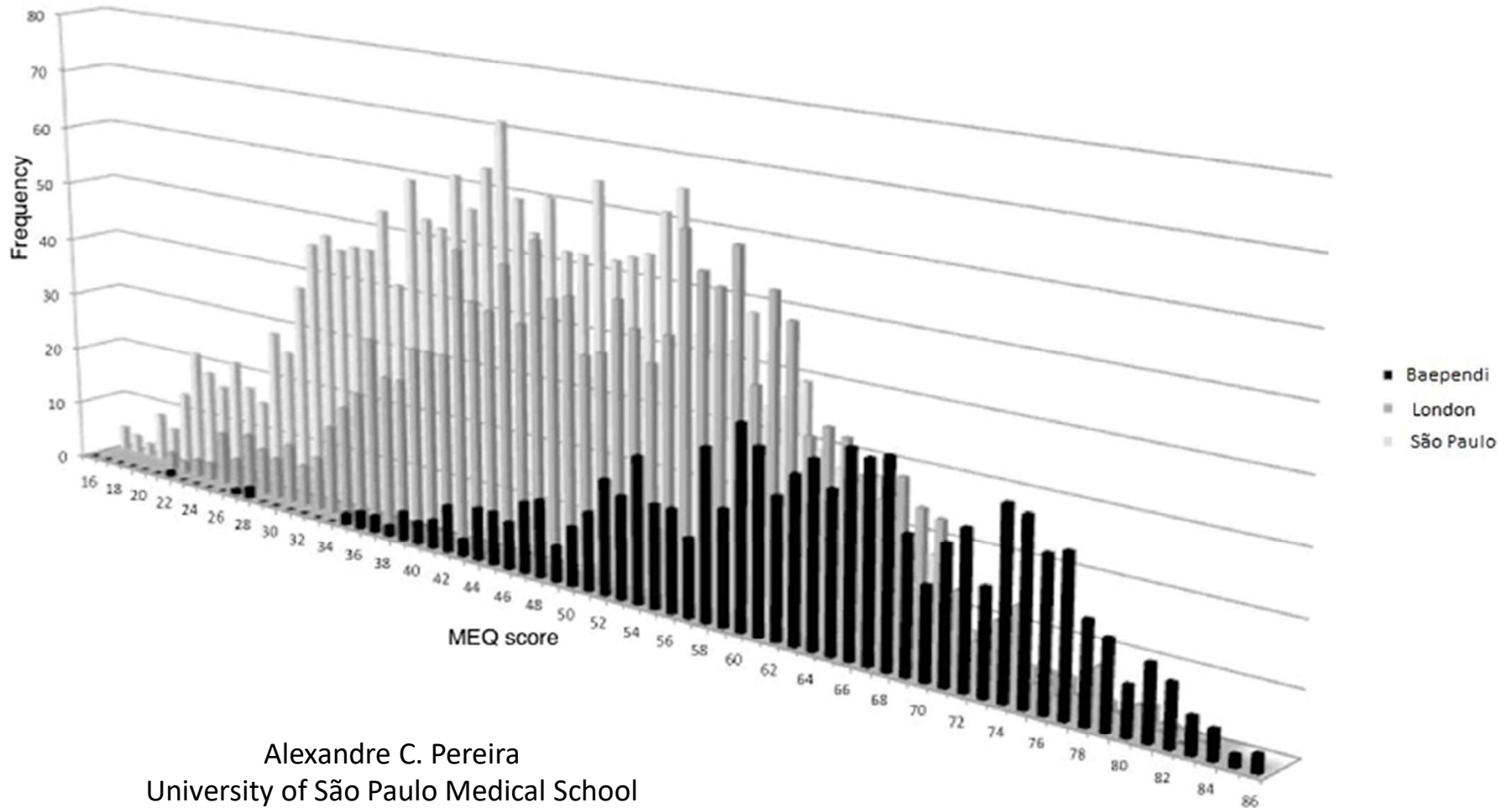




# Late chronotypes experience chronic social jet-lag and its apparent behavioral consequences.

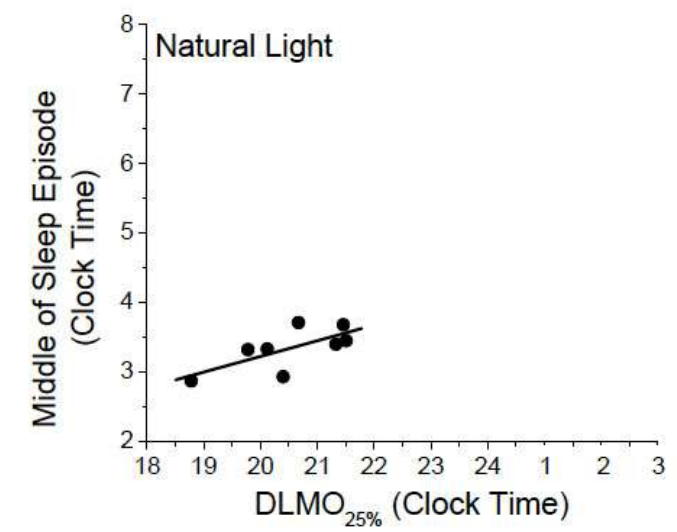
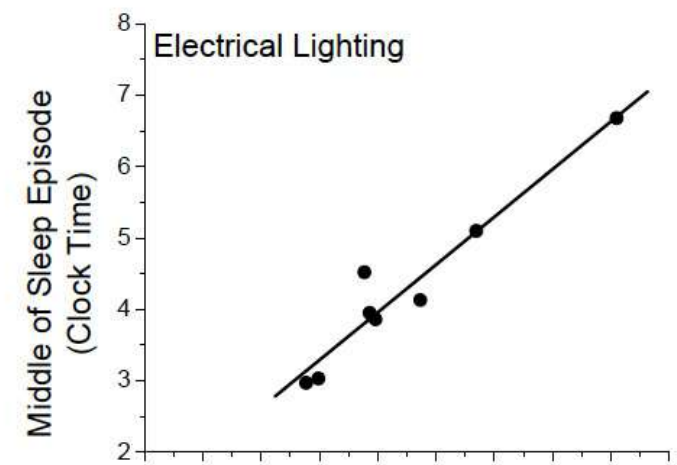
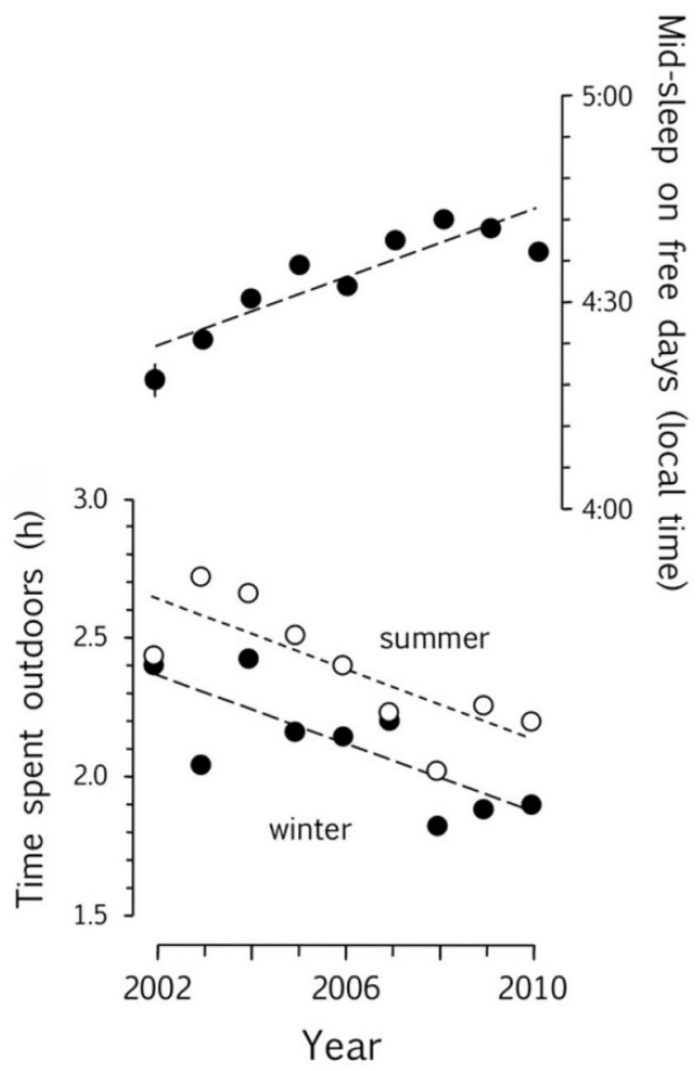


# Chronotype depends on the environmental context.



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University of São Paulo Medical School  
Funded by FAPESP

# The Modern Light Environment and Chronotype



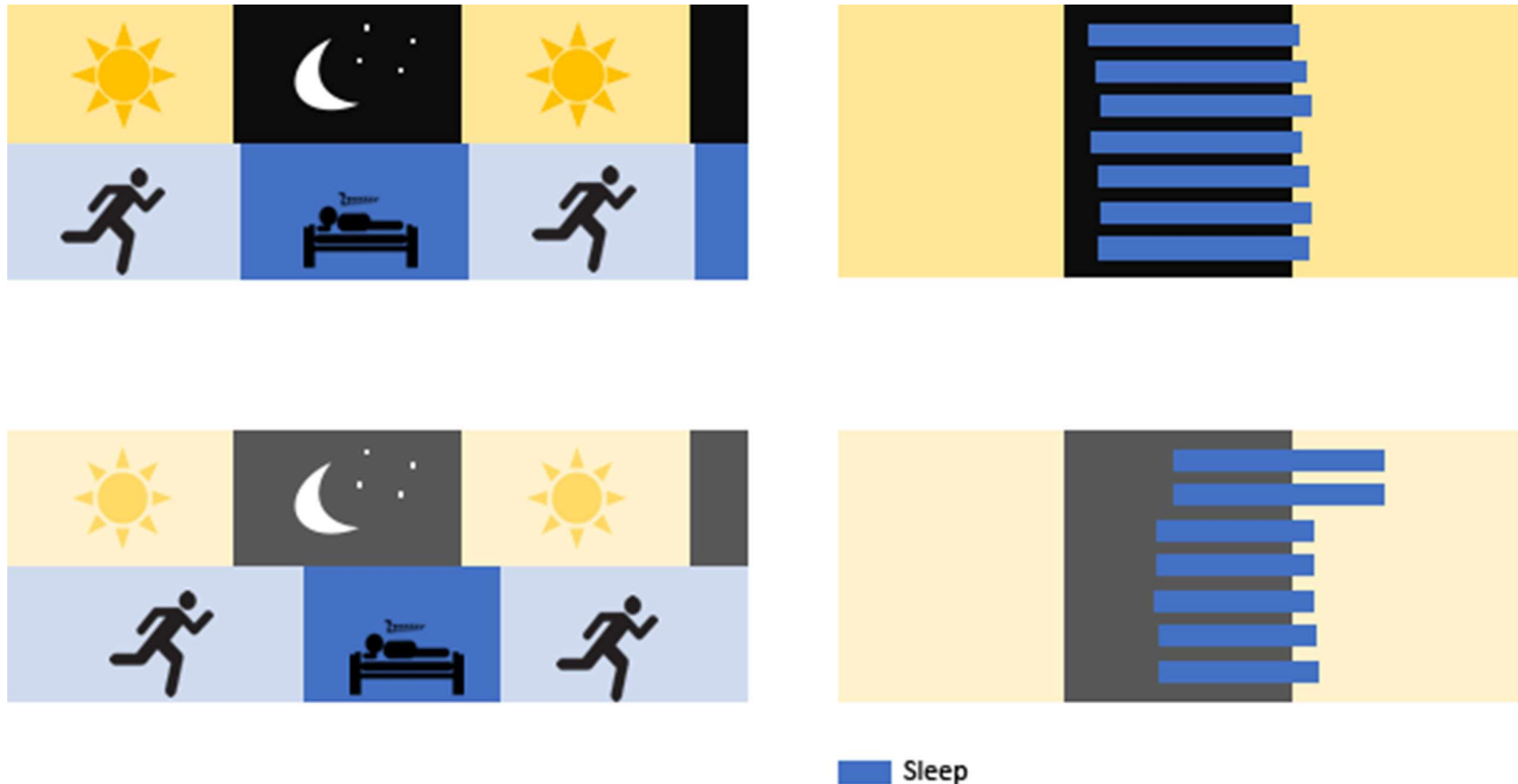
Circadian entrainment rests at the heart of modern circadian dysfunction and its negative health consequences.



*Under ancestral/natural conditions, **two clocks** determined our daily rhythms:  
**The Sun Clock and the Internal Clock***

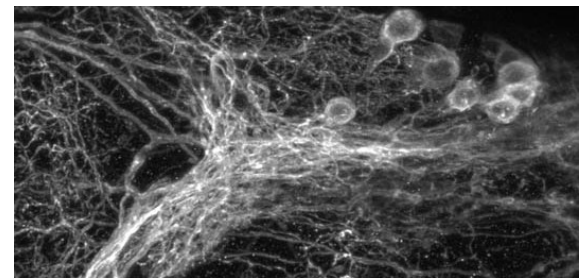
*In modern societies **three clocks** determine our daily rhythms:  
**The Sun Clock, The Internal Clock, and the Social Clock***

Circadian entrainment rests at the heart of modern circadian dysfunction and its negative health consequences.



*In modern societies **three clocks** determine our daily rhythms:  
The **Sun Clock**, The **Internal Clock**, and the **Social Clock***

# Clocks, Entrainment, Light, and Health: A Need for Interdisciplinary Research



The ASRC at CUNY

Environmental Sciences, Photonics,  
Neuroscience, Structural Biology,  
Nanotechnology

