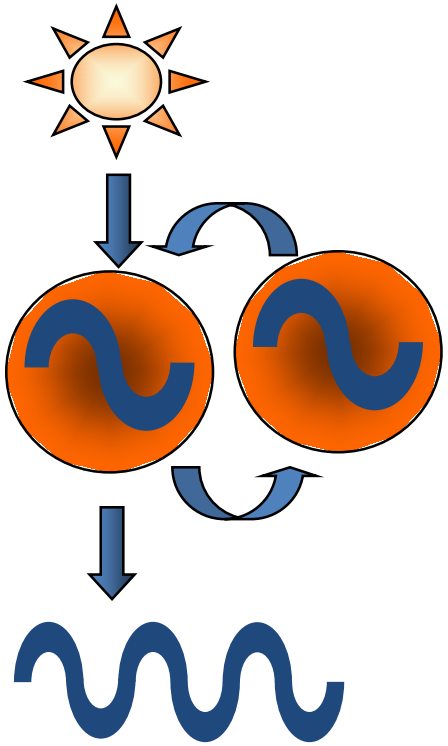
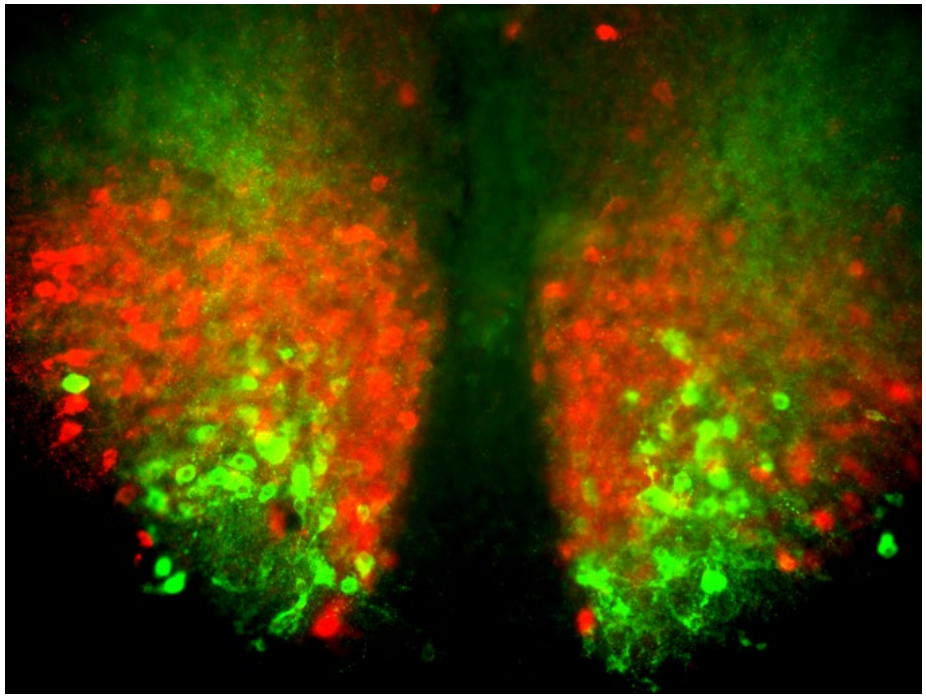
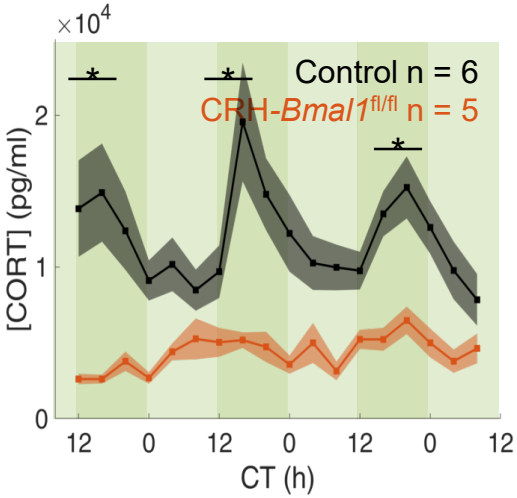
Circadian regulation of wake and sleep







Erik Herzog
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NAS Sleep Workshop
Nov 2, 2022

The **Outline**

- Progress on Process C has outpaced insights into Process S
- The brain functions as a network of circadian cells
- Overlapping maps of neurotransmitter- and neuropeptide-connectivity coordinate daily rhythms in the brain and body

- COI: None

A two-process model for sleep regulation

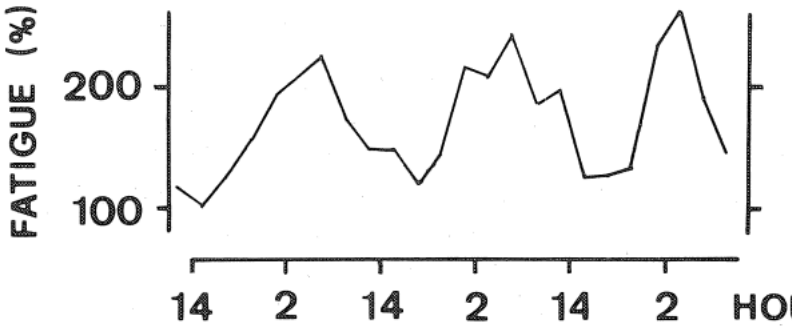
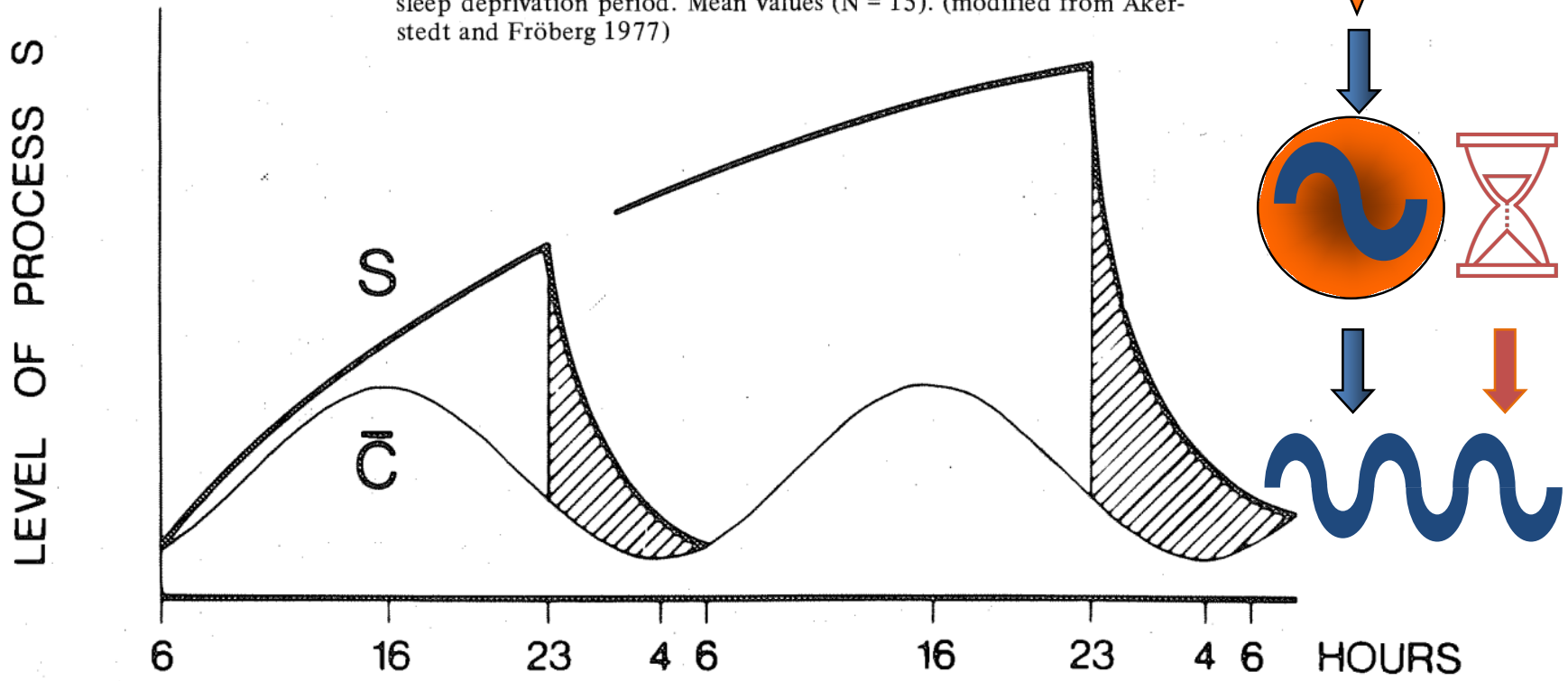


Fig. 3. Fatigue self-ratings obtained at 3-h intervals during a 72-h sleep deprivation period. Mean values (N = 15). (modified from Åkerstedt and Fröberg 1977)

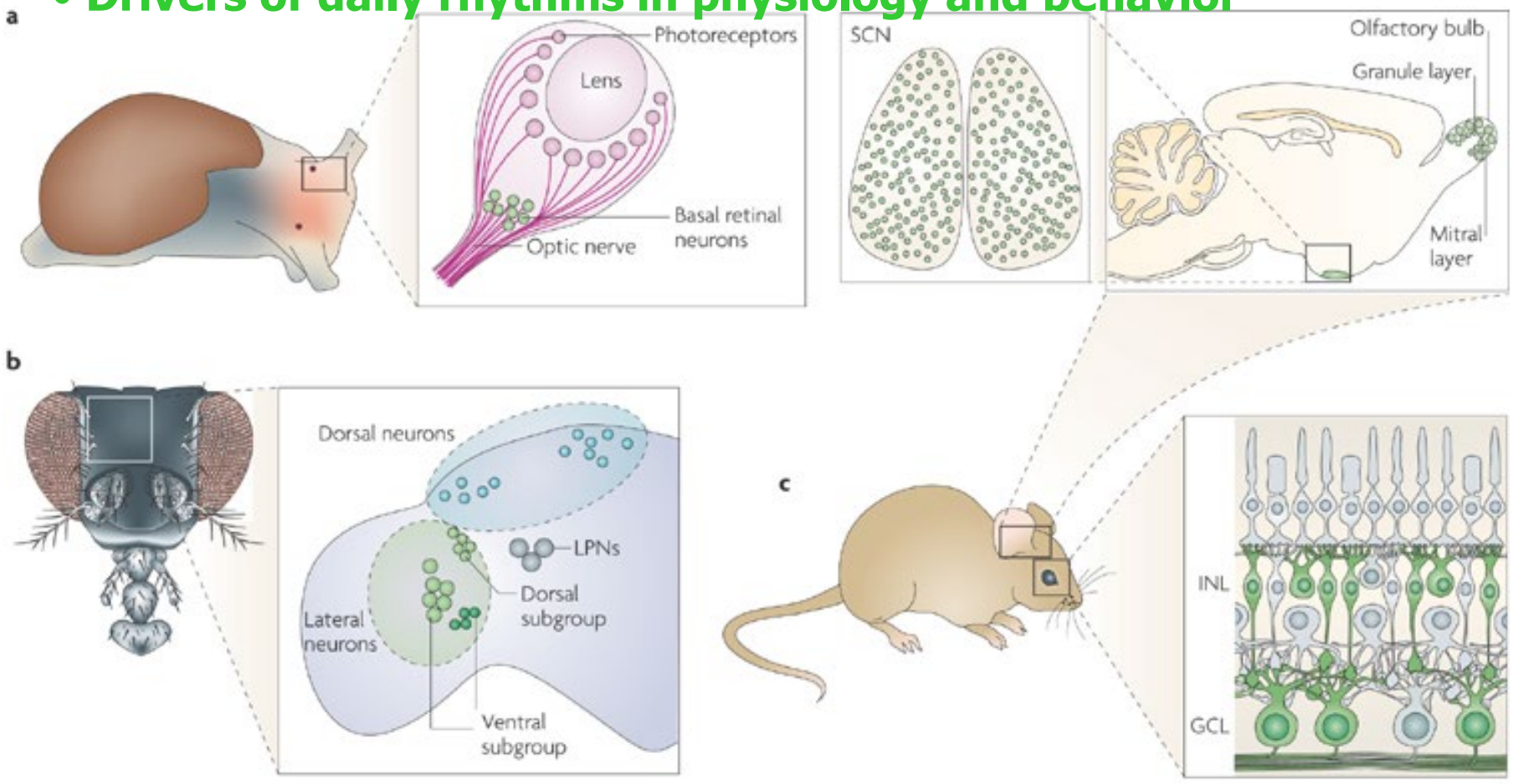


AA Borbély (1982) Hum Neurobiol. Cited by 4995

AA Borbély, S Daan, A Wirz-Justice, T. DeBoer (2016) Journal of Sleep. Cited by 1124

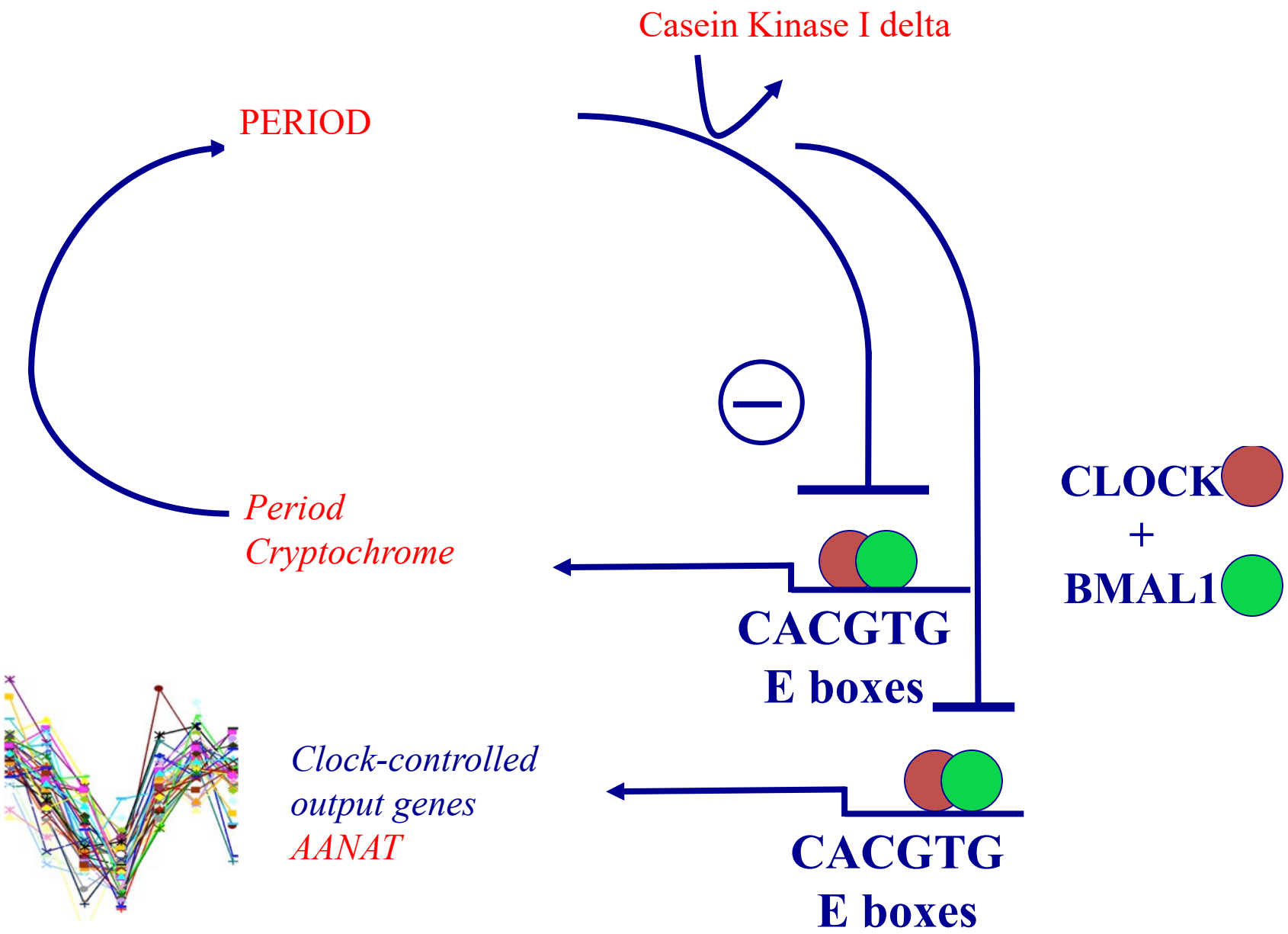
Circadian Pacemakers:

- **Common**
- **Molecular oscillators with a period close to 24 h**
- **Temperature compensated**
- **Light entrained**
- **Drivers of daily rhythms in physiology and behavior**



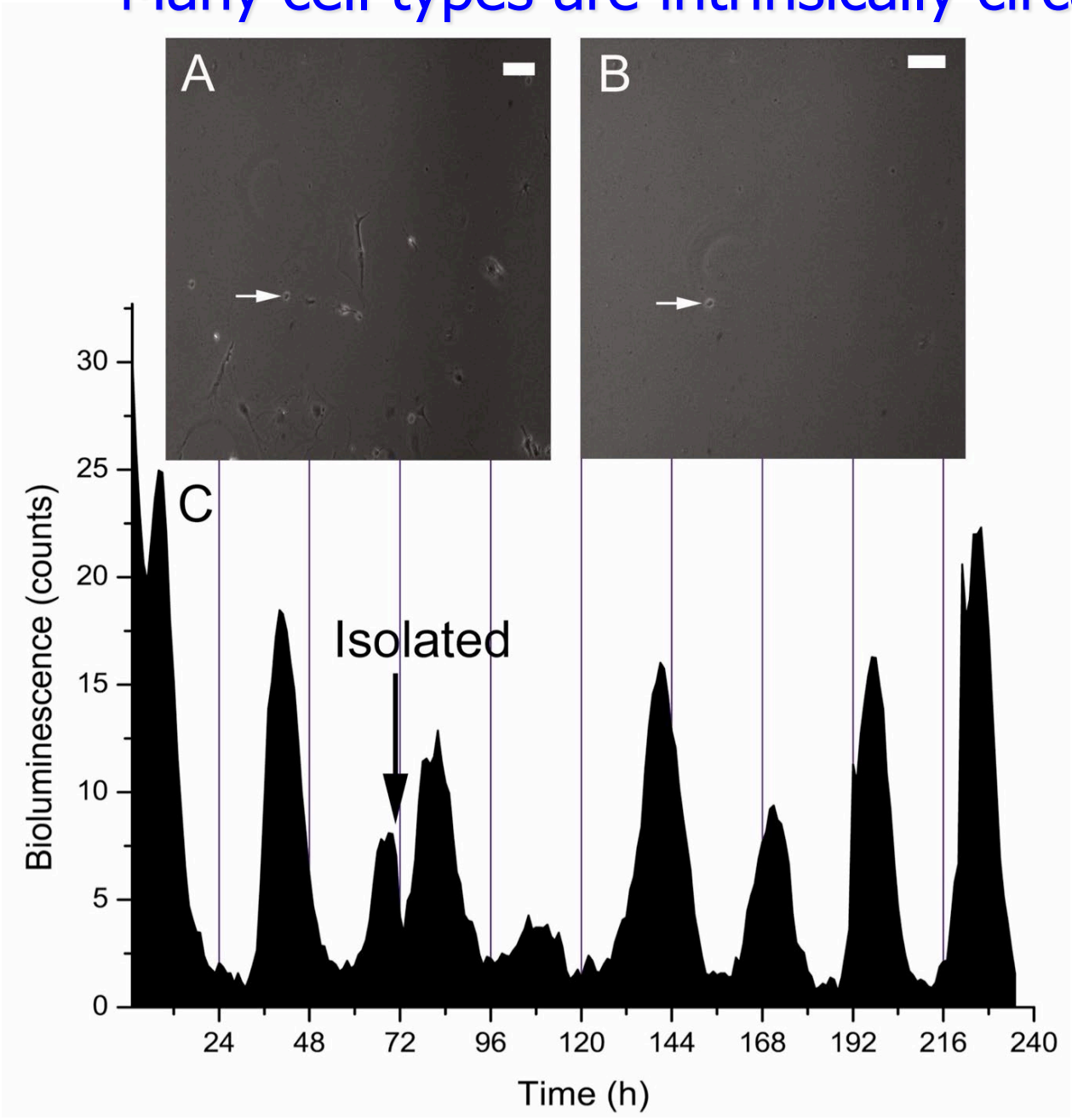
Nature Reviews | Neuroscience

The TTFL: Molecular basis of circadian rhythm generation



Modified from Mick Hastings

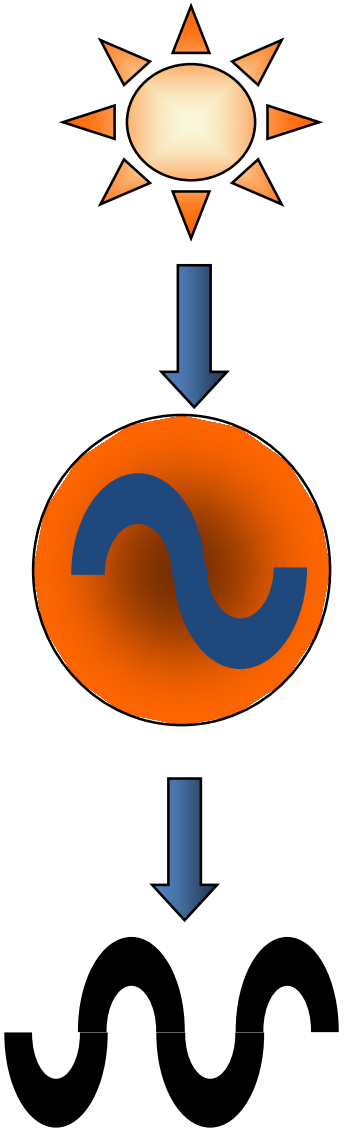
Many cell types are intrinsically circadian



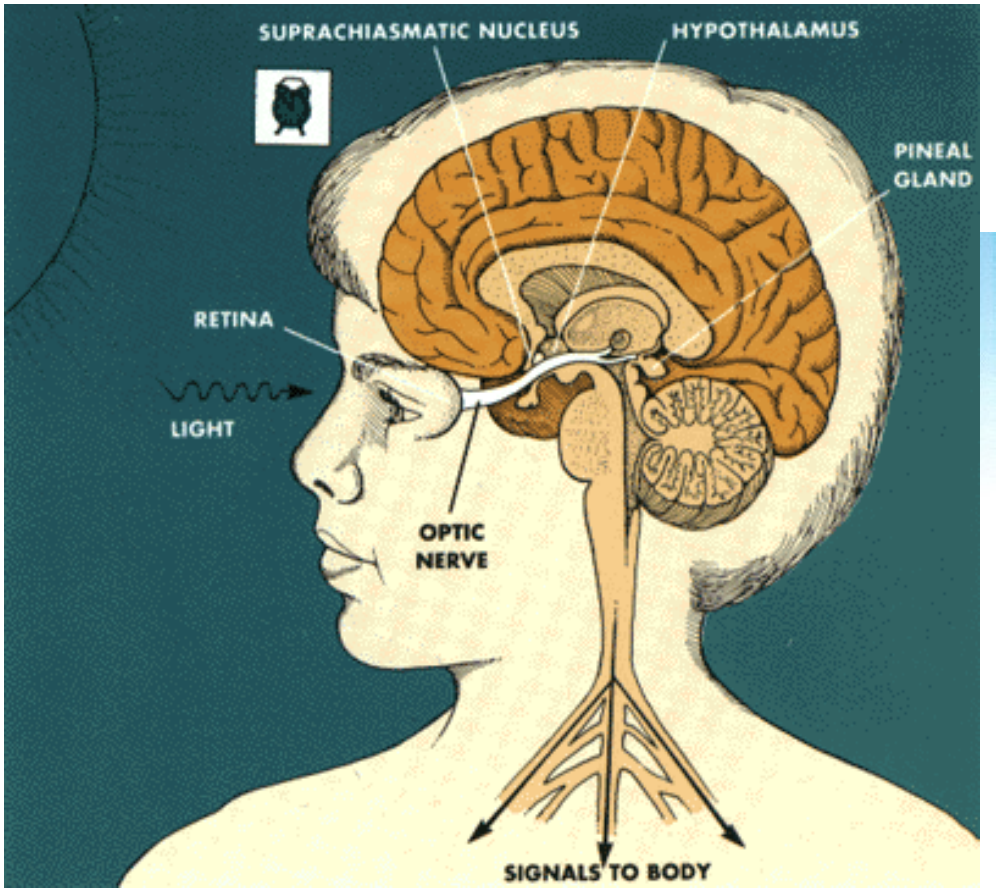
Neurons
Glia
Hepatocytes
Myometrium
Chrondrocytes
…

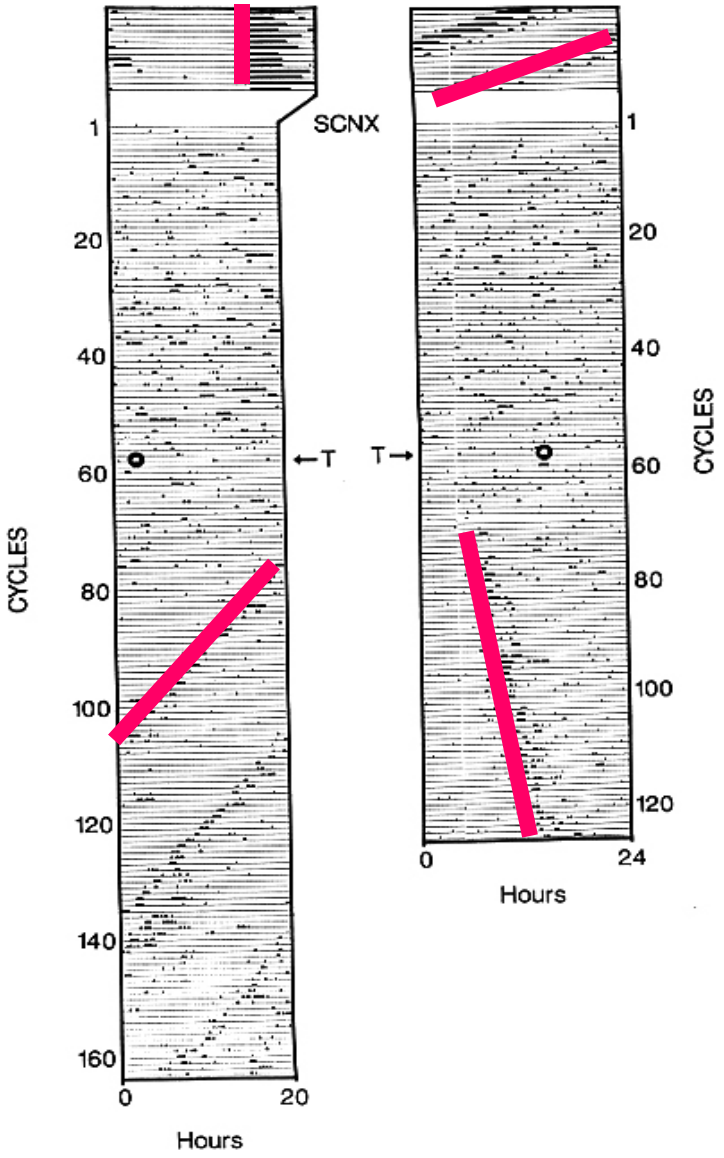
Webb et al. (2009)
PMID 19805326

How do circadian cells regulate the brain and body?



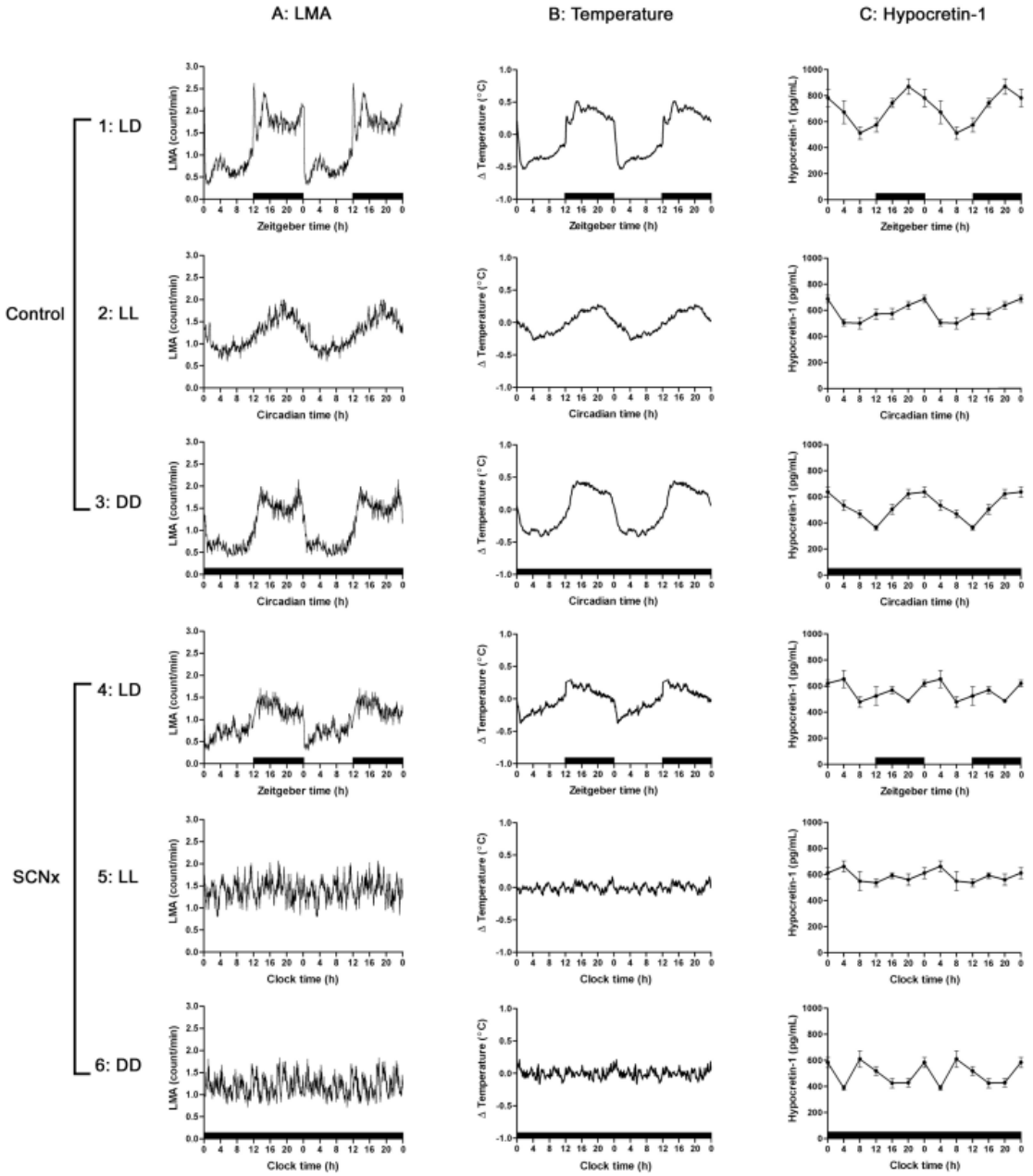
The SCN is a central circadian pacemaker





Ralph et al. (1990) Science

SCN lesions and sleep



Decreased daily rhythms in:

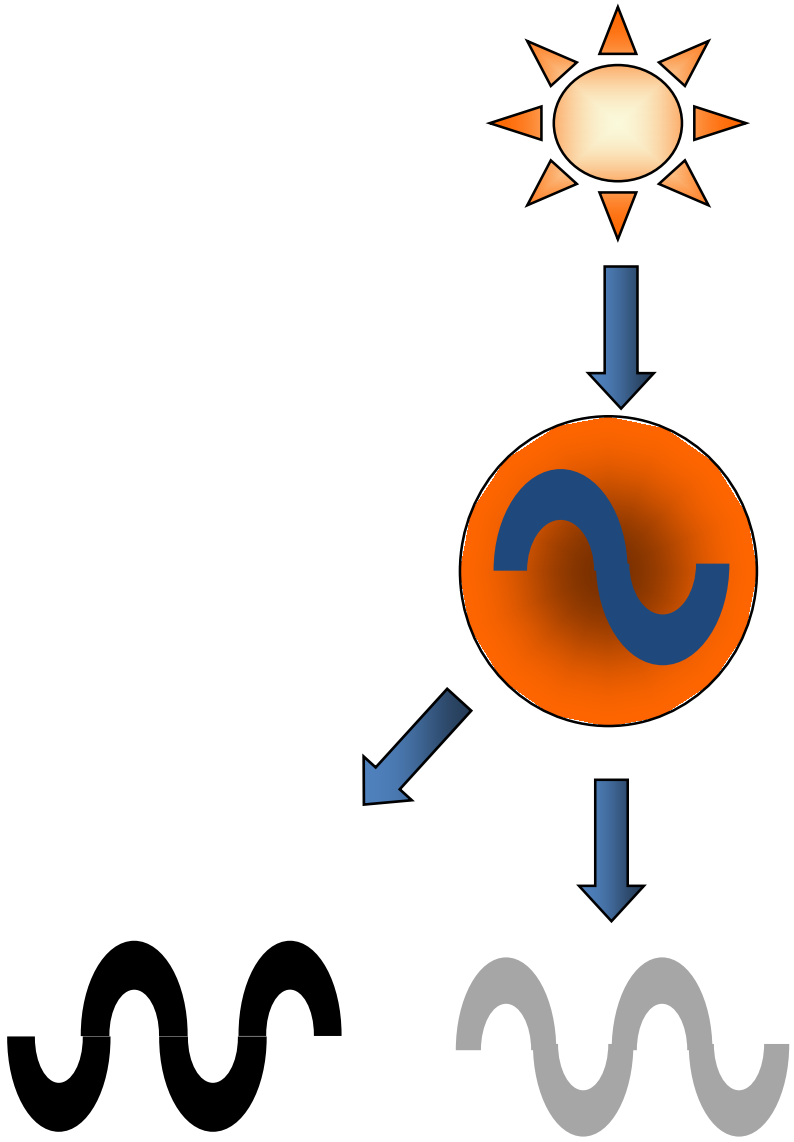
- NREM
- REM
- Siesta
- Glucocorticoid
- Melatonin
- Hypocretin1

Species-specific change in sleep/day:

- no change in rat and mouse
- increased in squirrel monkey

Zhang et al. (2004) Sleep

Mapping circadian circuits to sleep

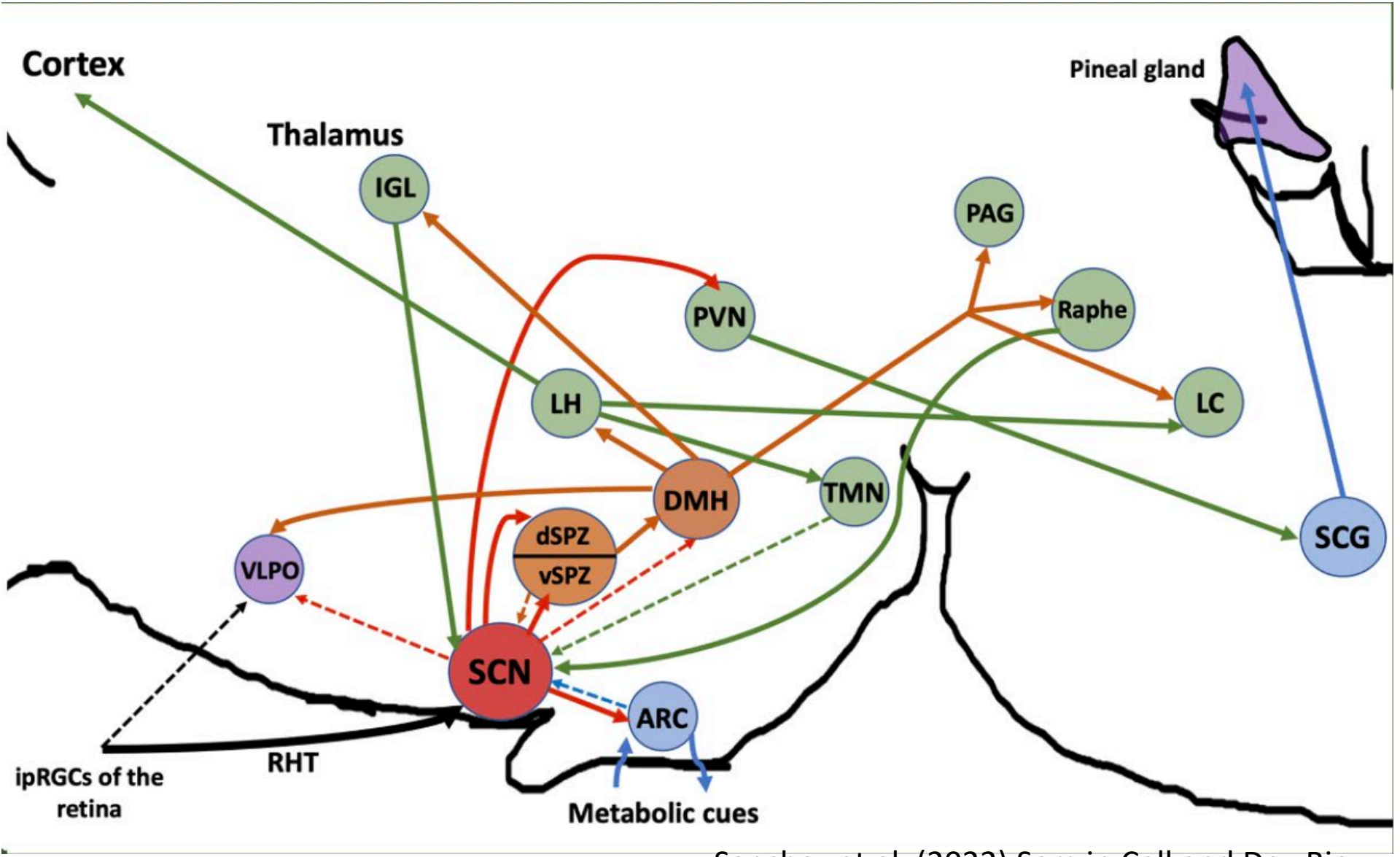


Rods, Cones, Melanopsin cells

Within the SCN

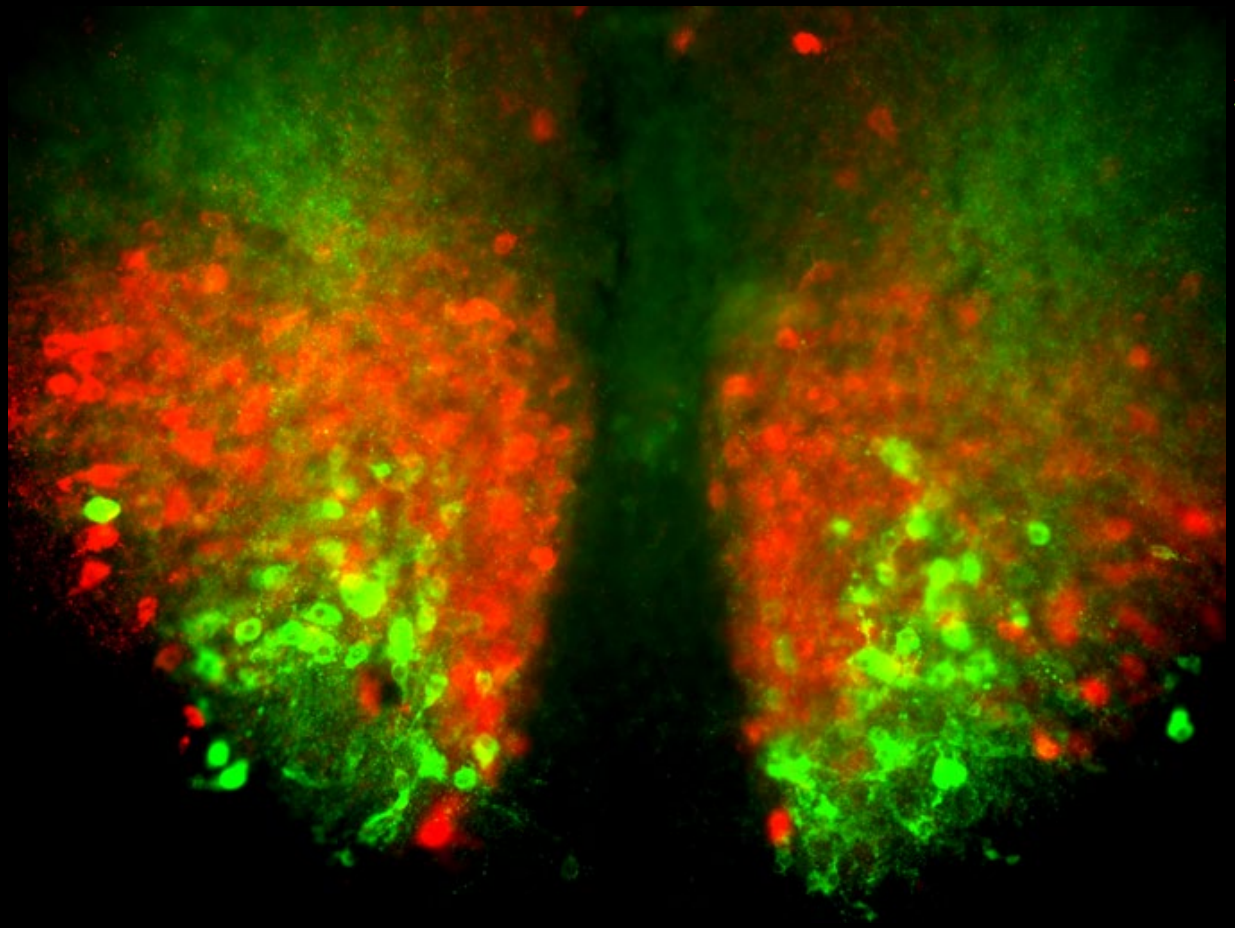
From the SCN

SCN projections to wake and sleep promoting centers

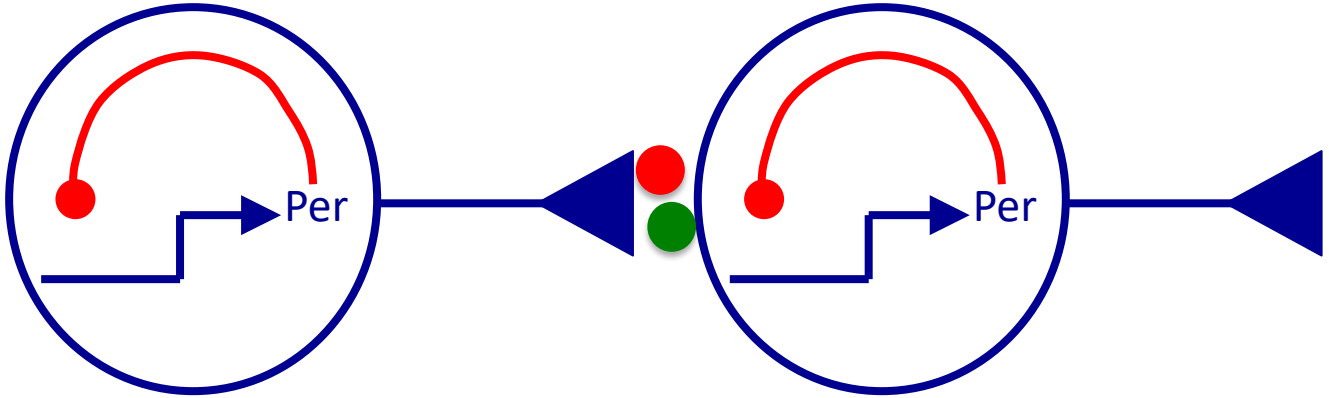


Sanchez et al. (2022) Sem in Cell and Dev Bio

SCN cell types and signals differ in their roles in sleep

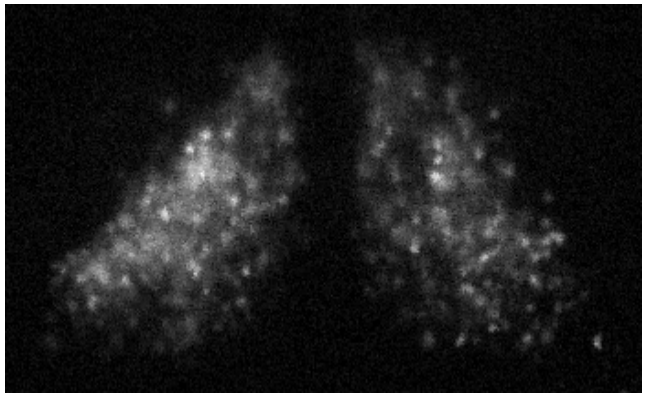


Fast vs. slow SCN signals as sleep regulators



GABA ●

- Opposes sync
- Rapid ↑↓ firing rate
- Sparse



VIP ●

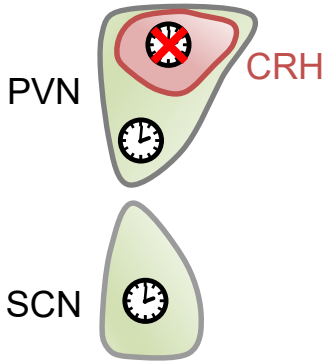
- Synchronizes
- Slow ↑ cAMP
- Topology unknown

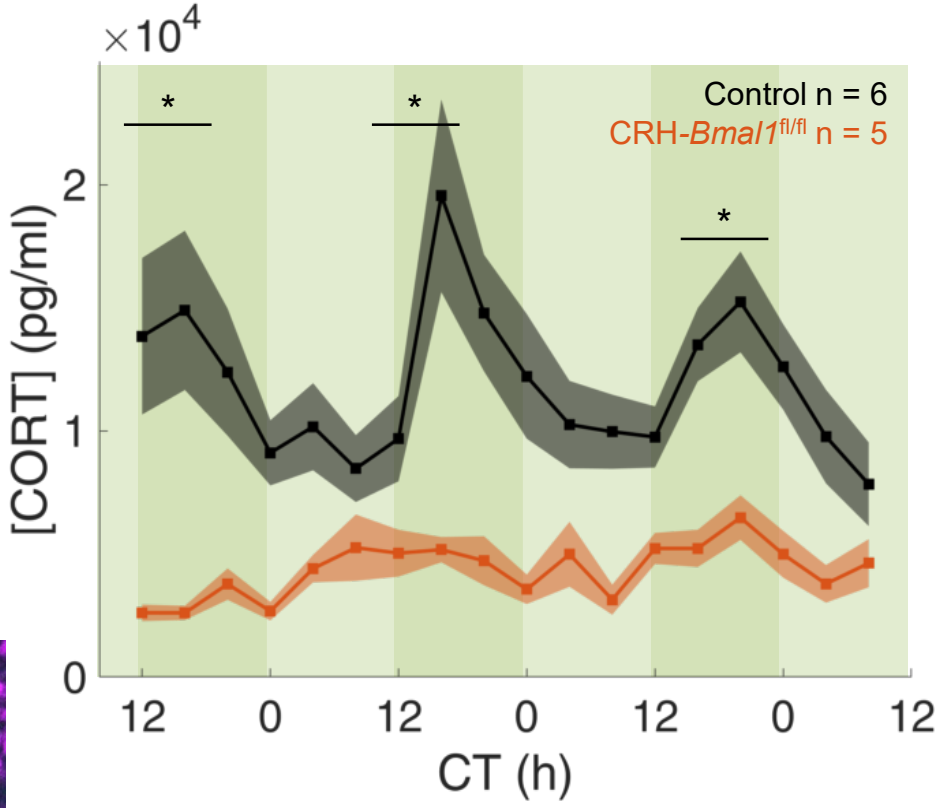
Roles for clock genes in other cell types for daily rhythms

Crh-Cre; *Bmal1*$^{fl/fl}$

Feces

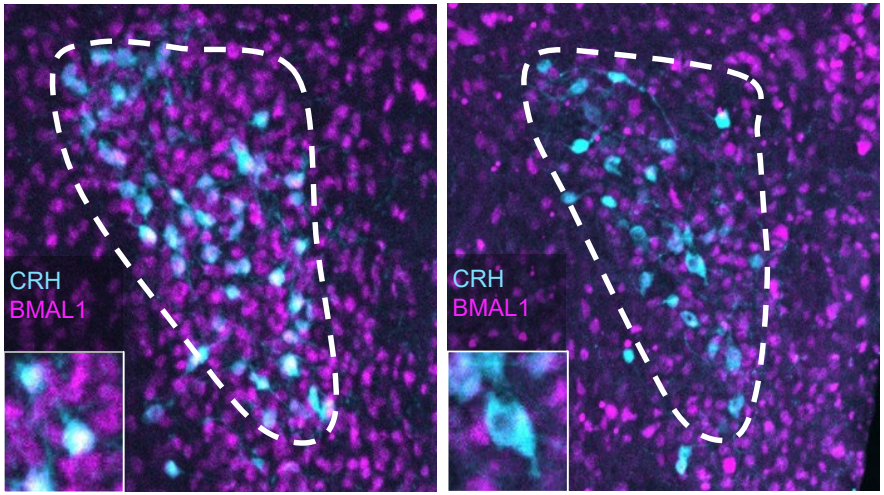
Corticosterone





WT

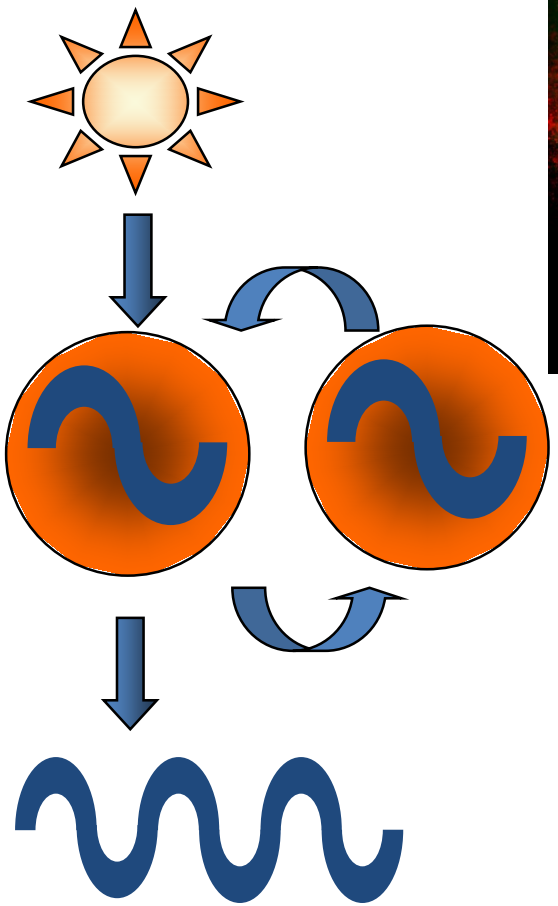
CRH-*Bmal1*$^{fl/fl}$

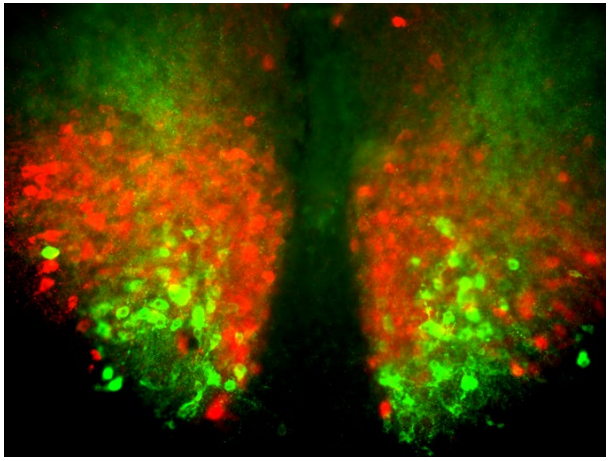


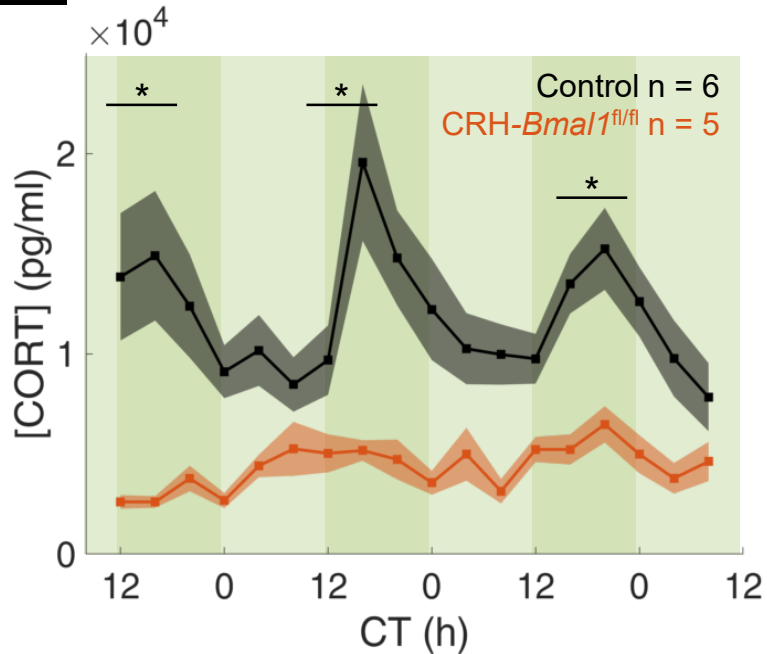
Jones et al (2021) PMID 34599158

Sleep disorders result from circadian disruptions

- GABA and VIP set circadian sync in the SCN
- Clock genes and projections set daily phase and amplitude in brain and body







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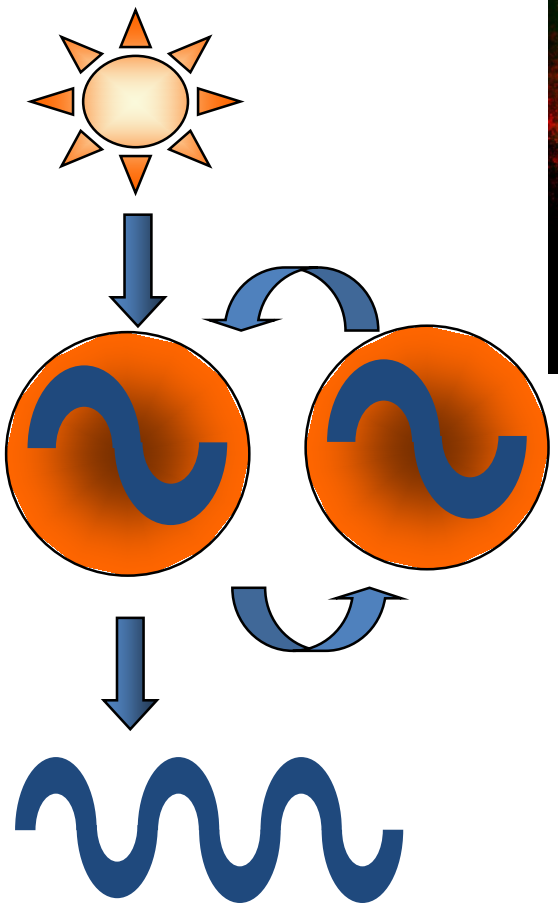

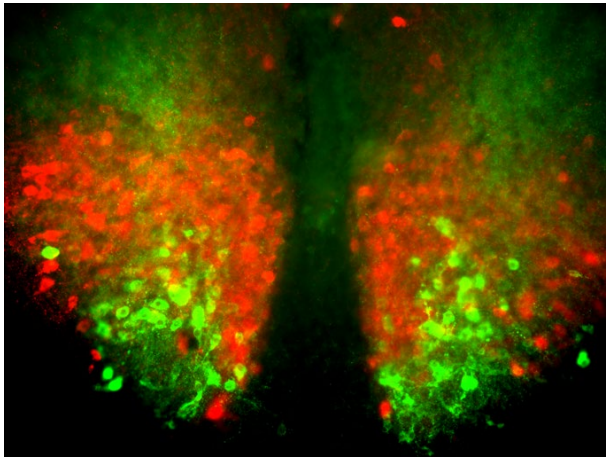

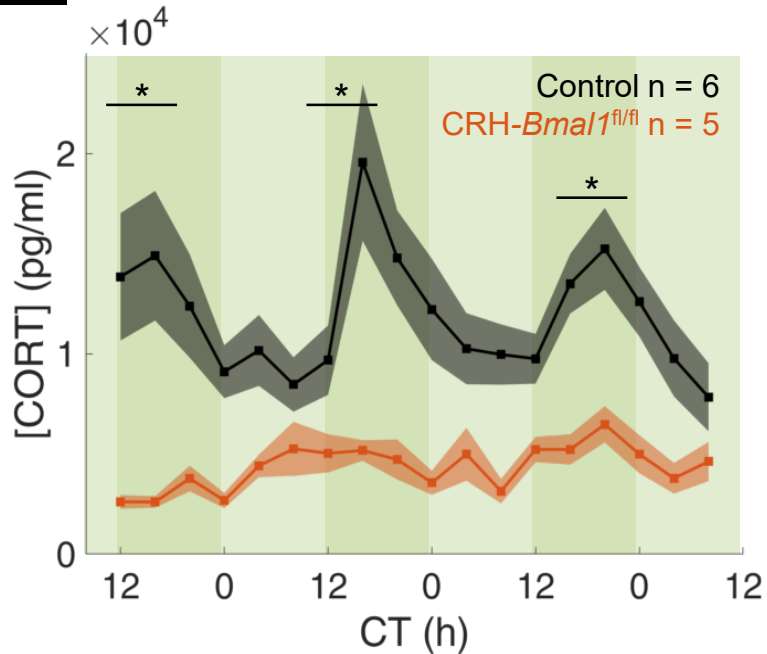

Next steps

- Are all cells and cell types part of a circadian network?
- Is the clock insensitive to sleep need?
- Should we be following tracts or diffusible signals?
- Should we be treating the clock, sleep, and/or the disease?