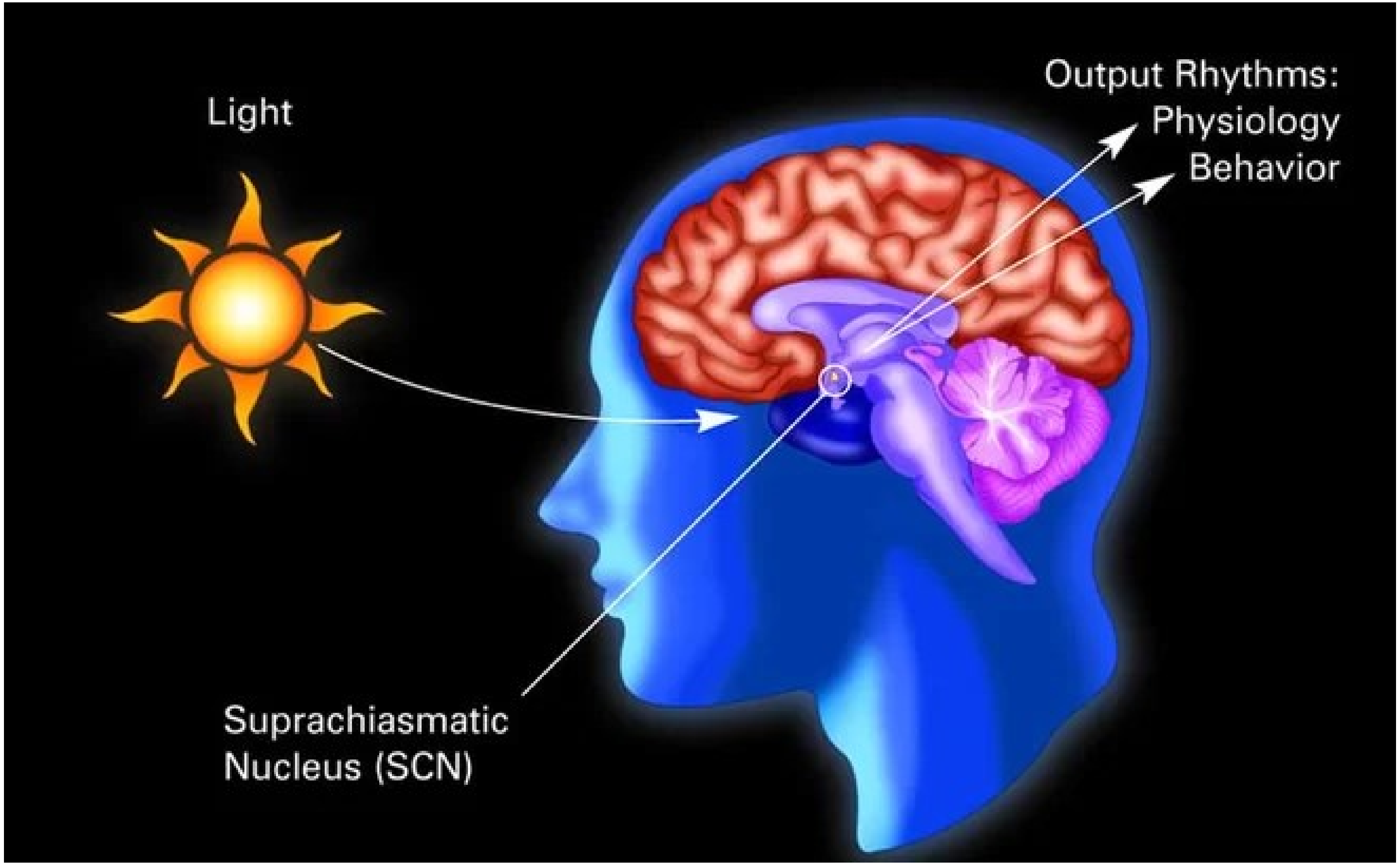
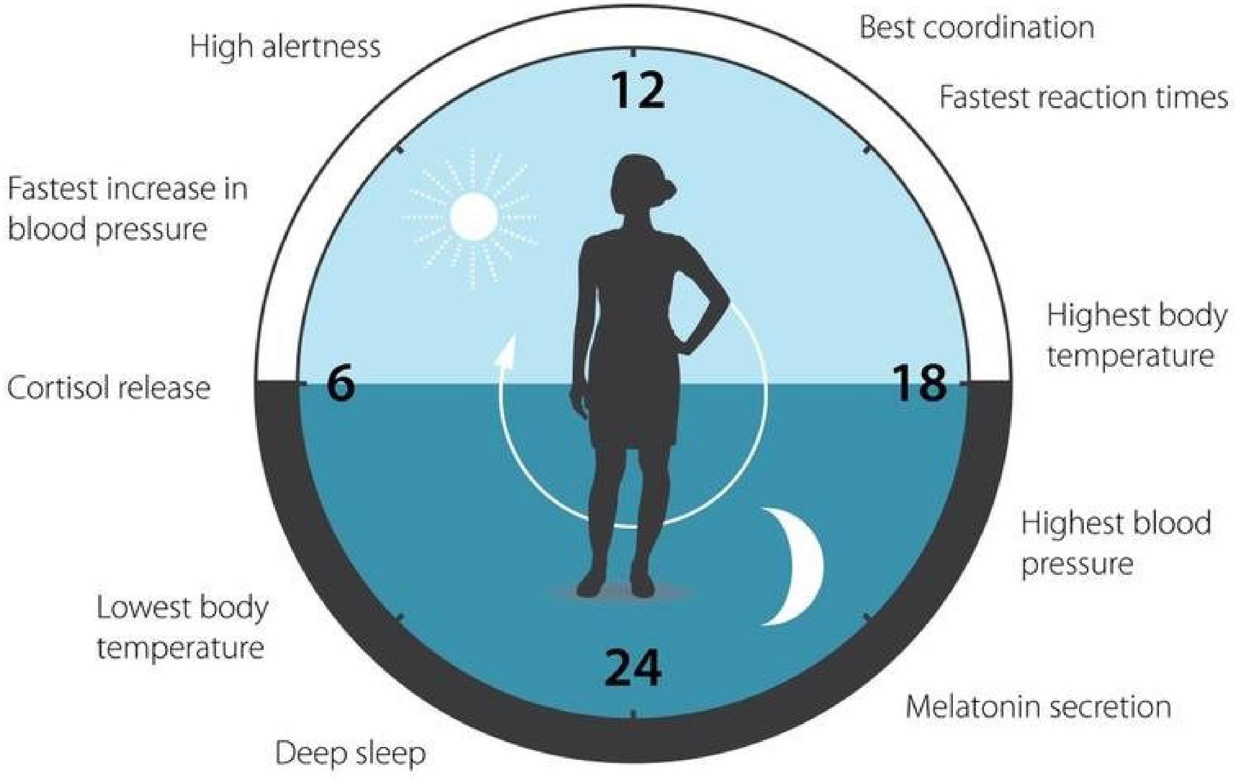
Circadian Rhythms



Controlling the timing of behaviour by anticipating the environment



- Circadian = circa + dium
- Exists in most if not all unicellular and multicellular organisms

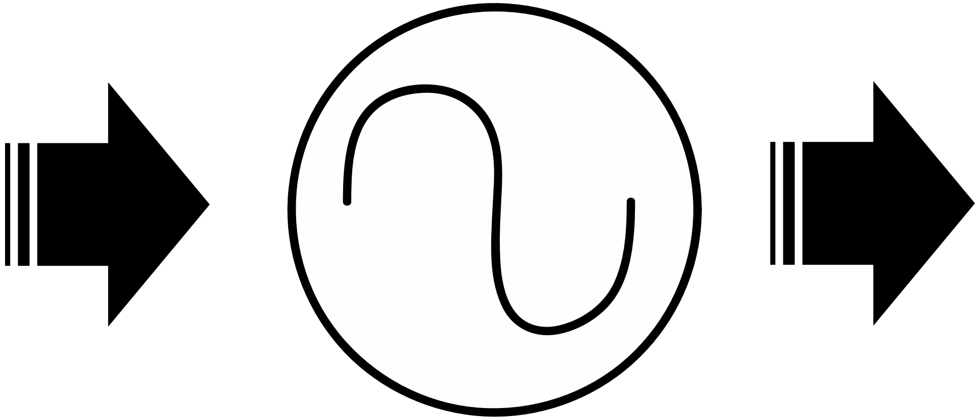
The Circadian Circuit

Environmental Inputs

Light

Temperature

Social Activity



Central Pacemaker

Output Rhythms

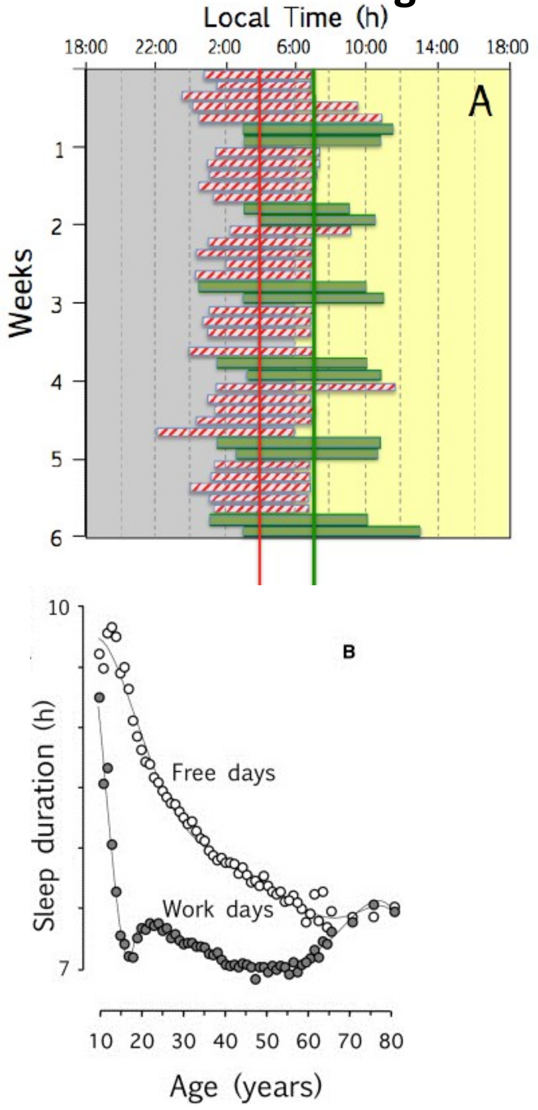
Hormonal Cycles

Rest/Wake

Feeding

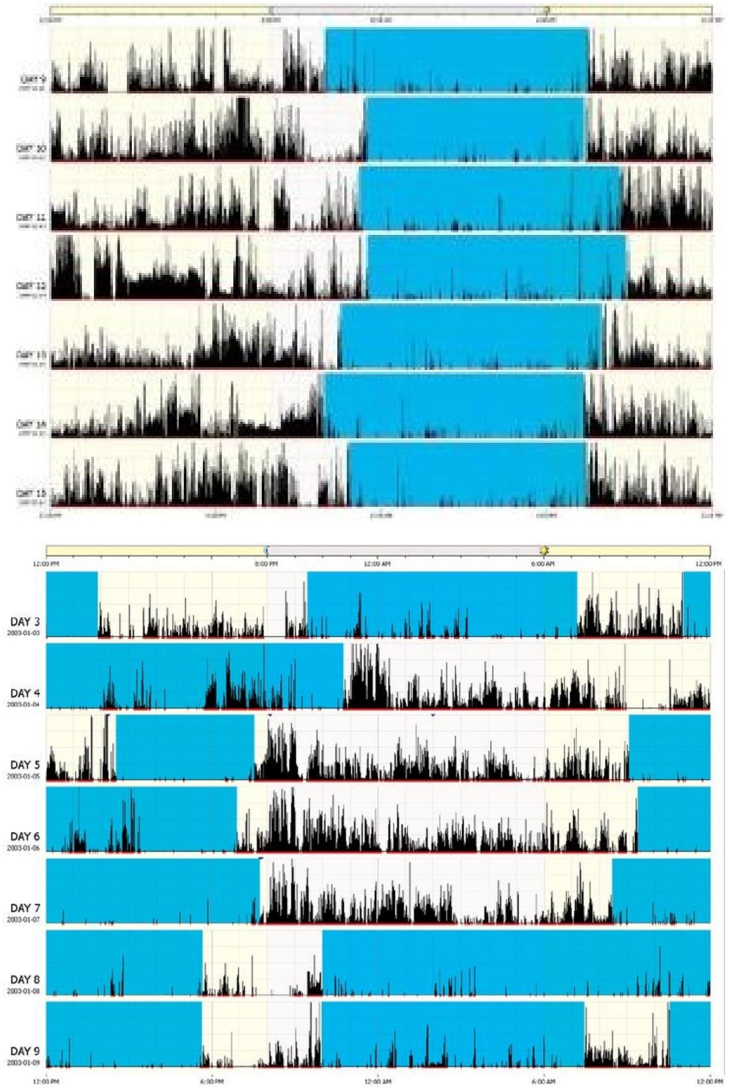
Health consequences of circadian misalignment

Social Jet Lag



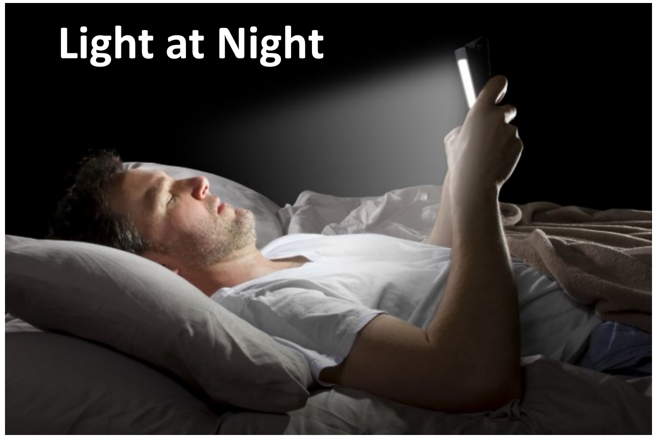
Roenneberg et al. (2012) *Current Biology*

Shift Work

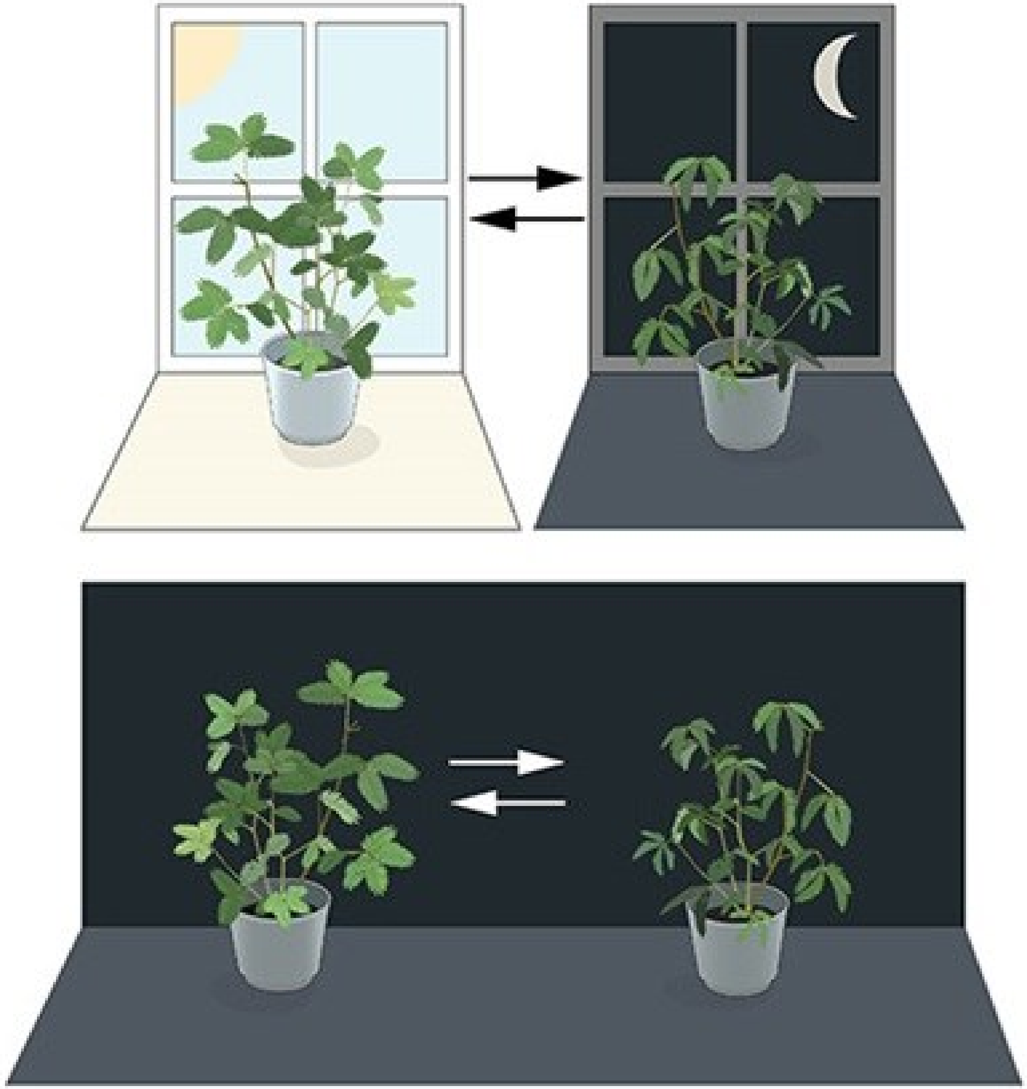


Increased risk of:

- Obesity
- Diabetes
- Cancer
- Mental Illness



Historical Perspective



Jean-Jacques d’Ortous de Mairan
(1678 – 1771)

Hist de l’Acad Royal Sci (Paris), 1729

“…Il est seulement un peu moins marqué lorsqu’on la tient toujours enfermée dans un lieu obscur…”

“The sensitive plant hence perceives the sun without seeing it”

Rhythms in leaf-opening persist even in the absence of sunlight

Historical Perspective

Rat

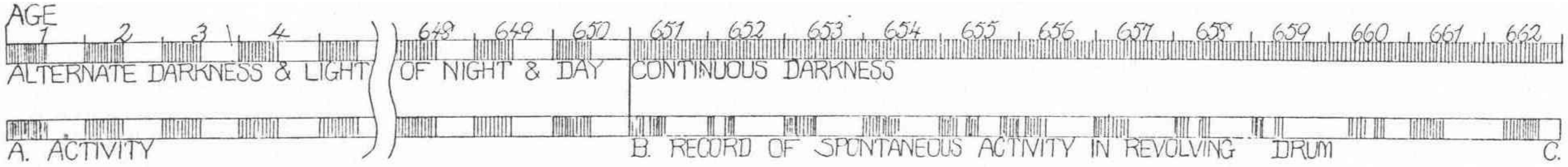


FIG. 19. SCHEMATIC RECORD SHOWING PERSISTENCE OF ACTIVITY RHYTHM AFTER WITHDRAWAL OF ORIGINAL STIMULUS

Comp Psychol Monographs, 1922

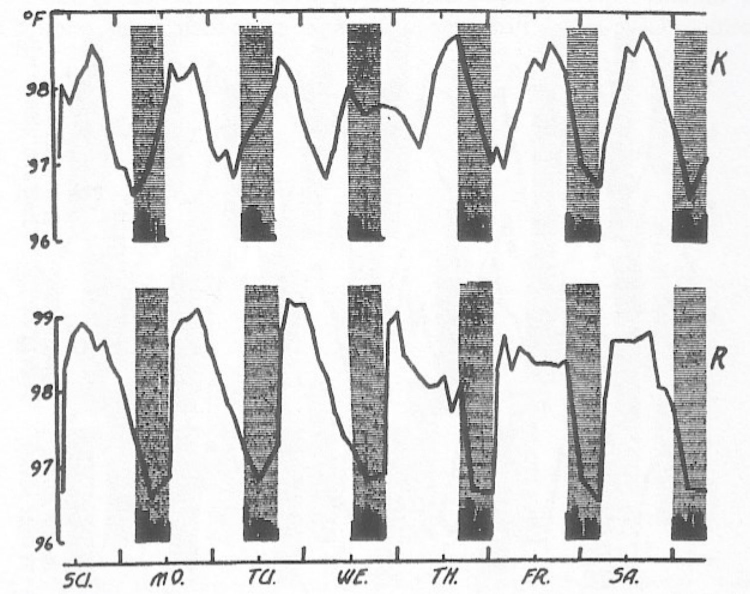
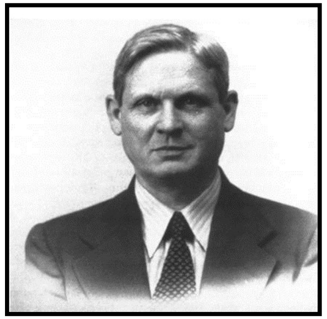


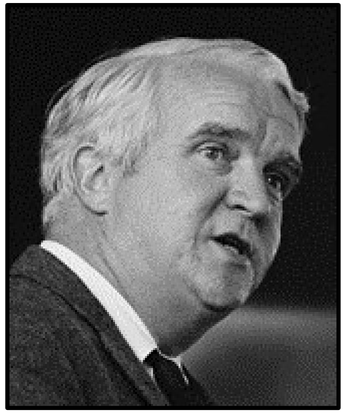
Figure 18.4
Sleep and Wakefulness, 1963



Nathaniel Kleitman
(1895 – 1999)

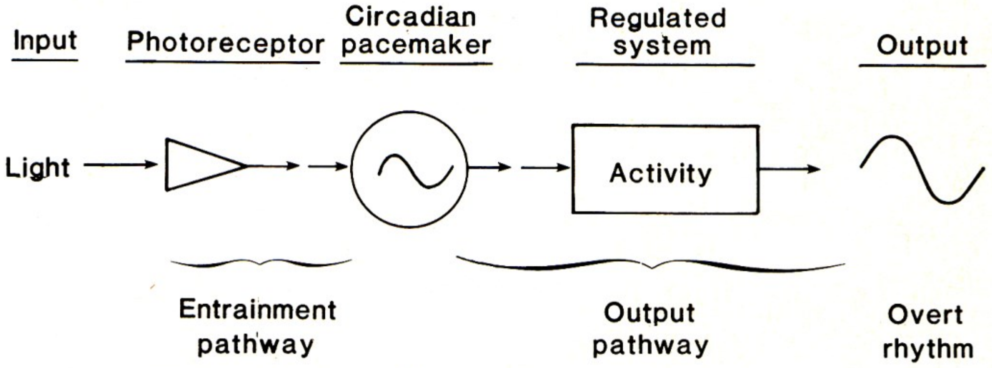
Historical Perspective

'Founders of Chronobiology' 1960



Colin Pittendrigh
(1918 – 1996)

Jürgen Aschoff
(1913 – 1998)



- Conceptual framework of circadian rhythms
- Long before any genes or neural circuits were identified

Cold Spring Harbor Symposium
on Quantitative Biology, Vol. XXV
Biological Clocks

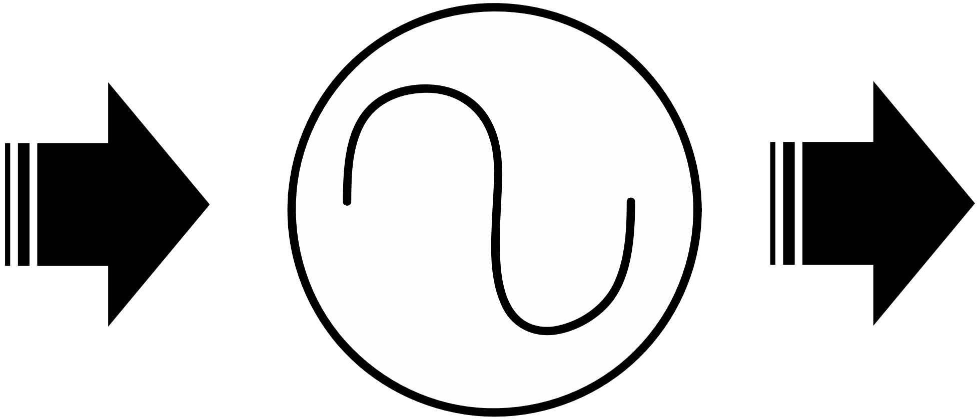
The Circadian Circuit

Environmental Inputs

Light

Temperature

Social Activity



Central Pacemaker

Output Rhythms

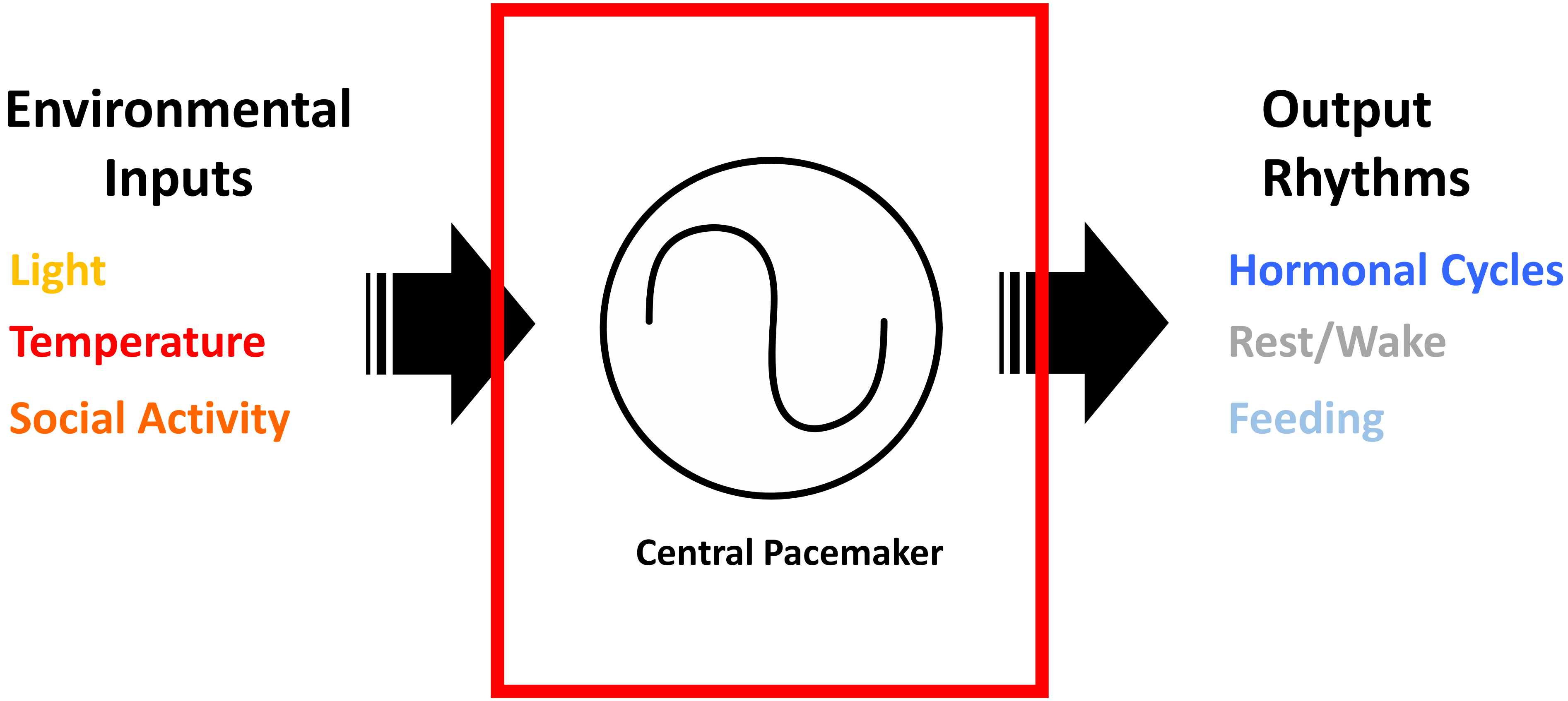
Hormonal Cycles

Rest/Wake

Feeding

What would a circadian pacemaker look like?

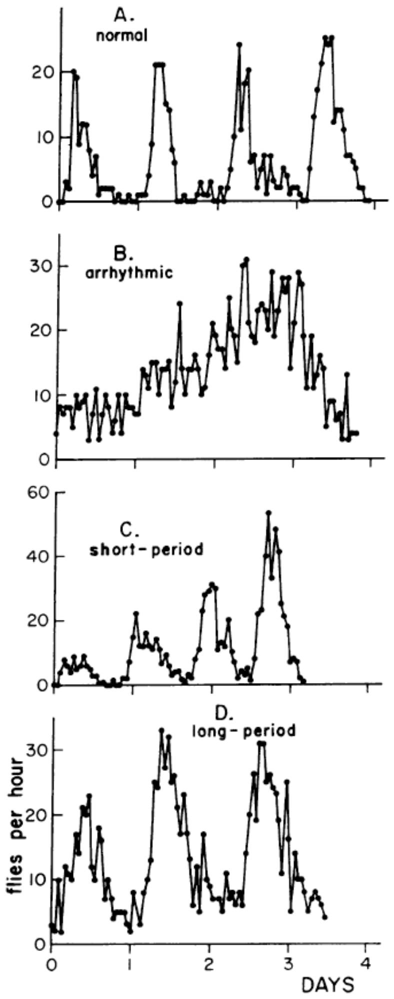
The Circadian Circuit



The Molecular Clock

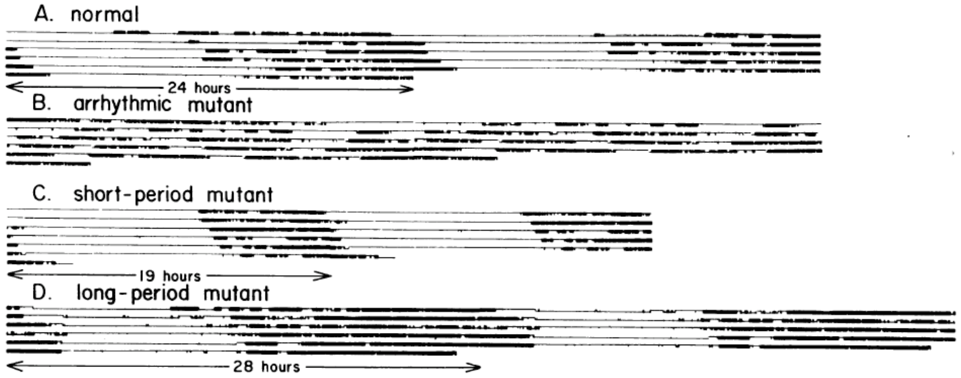
Circadian behaviour has a genetic component

Drosophila period (*per*)

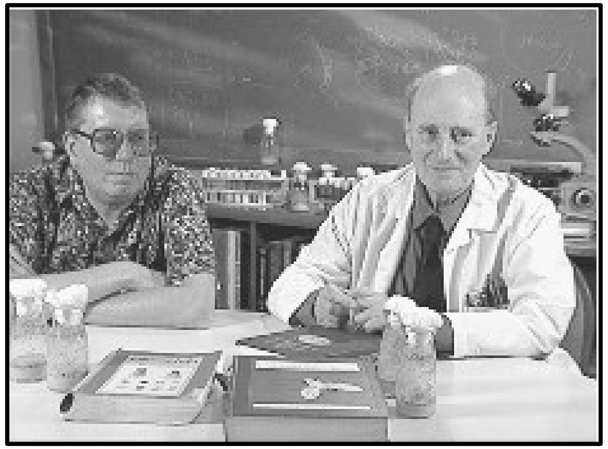


eclosion

locomotion



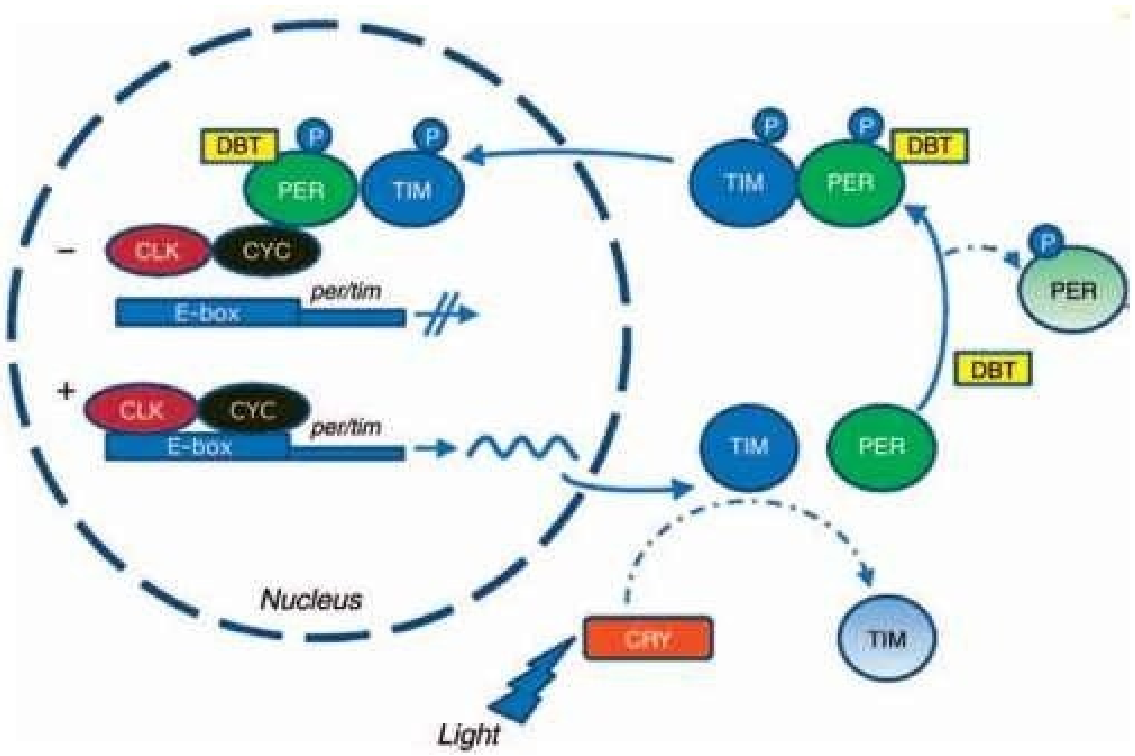
Konopka & Benzer, *PNAS* 68:2112, 1971

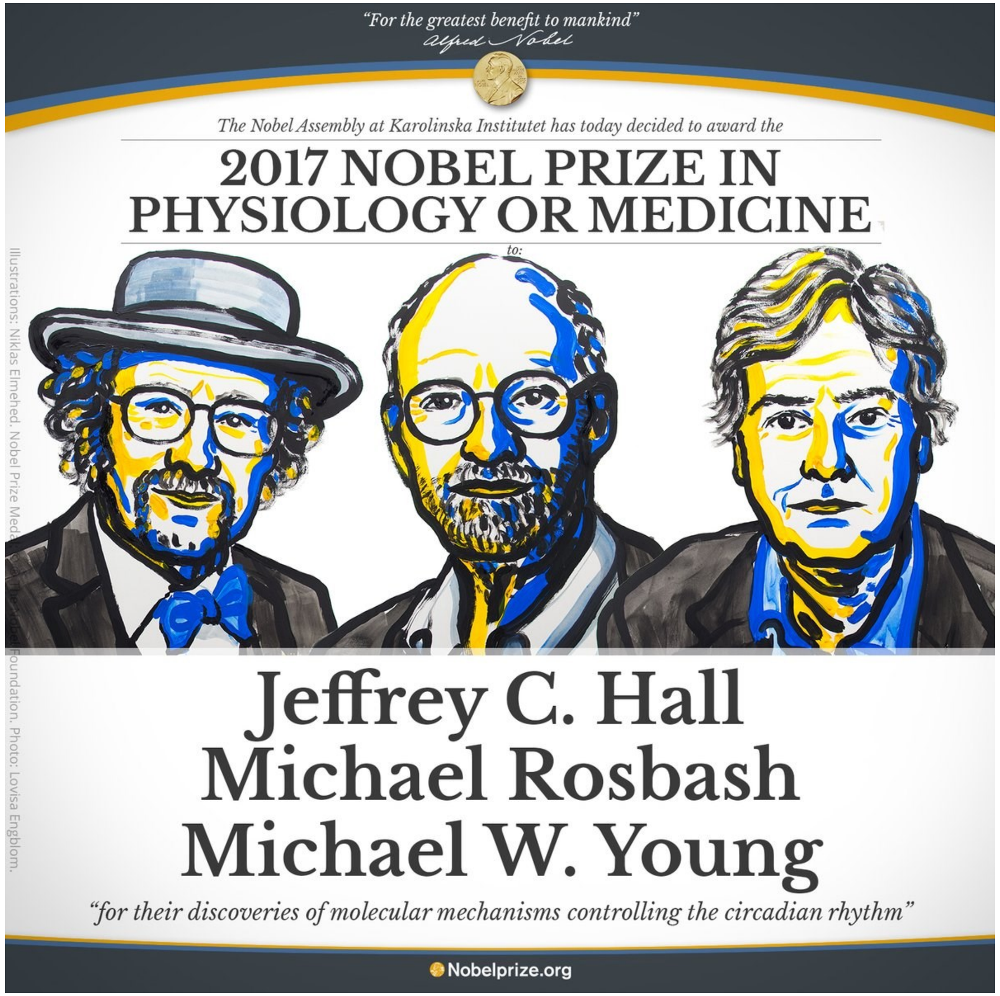


Ron Konopka & Seymour Benzer

Identification of the molecular mechanisms controlling circadian rhythms

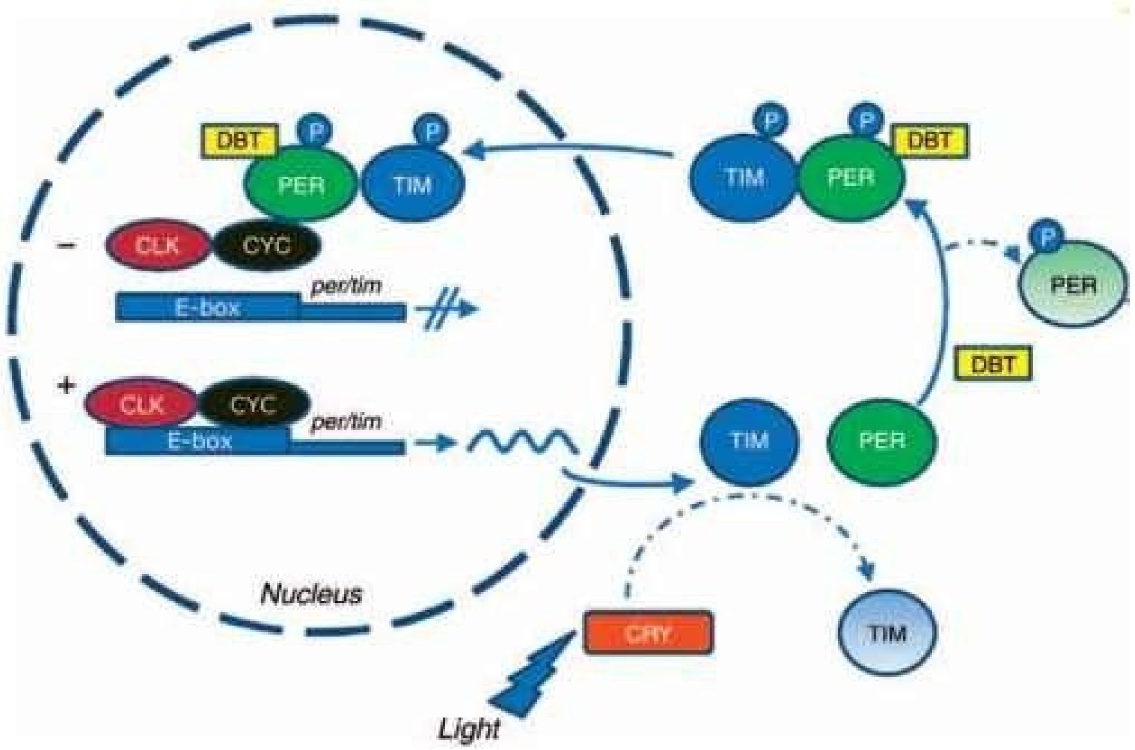
Core clock genes in drosophila





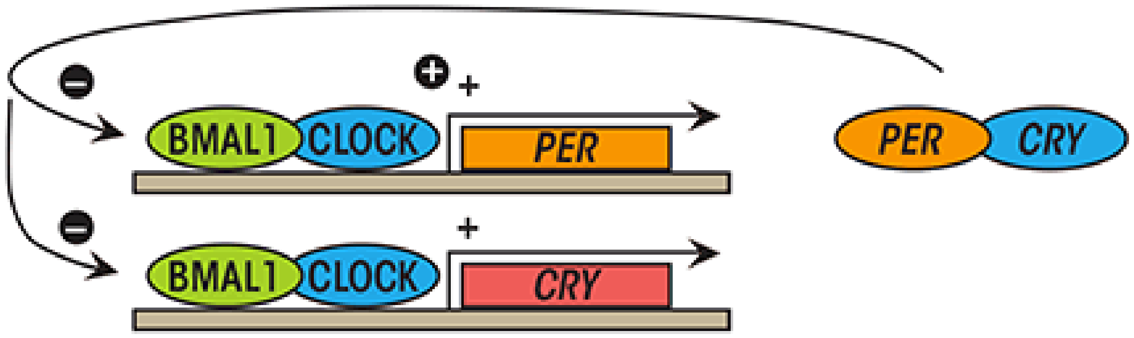
Similar molecular mechanisms generate circadian rhythms in flies and mammals

Core clock genes in drosophila

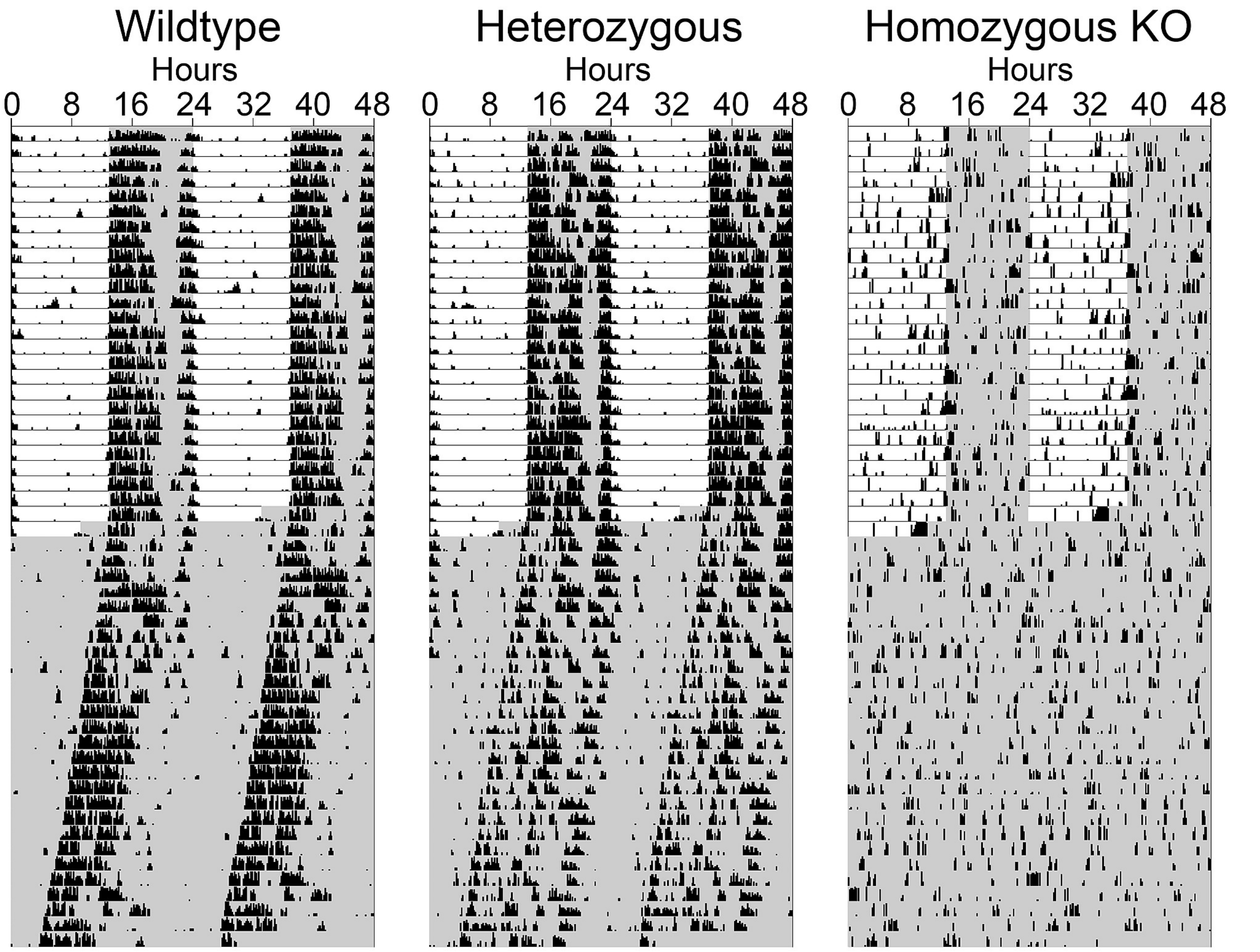


Transcription-translation feedback loop

Core clock genes in mammals



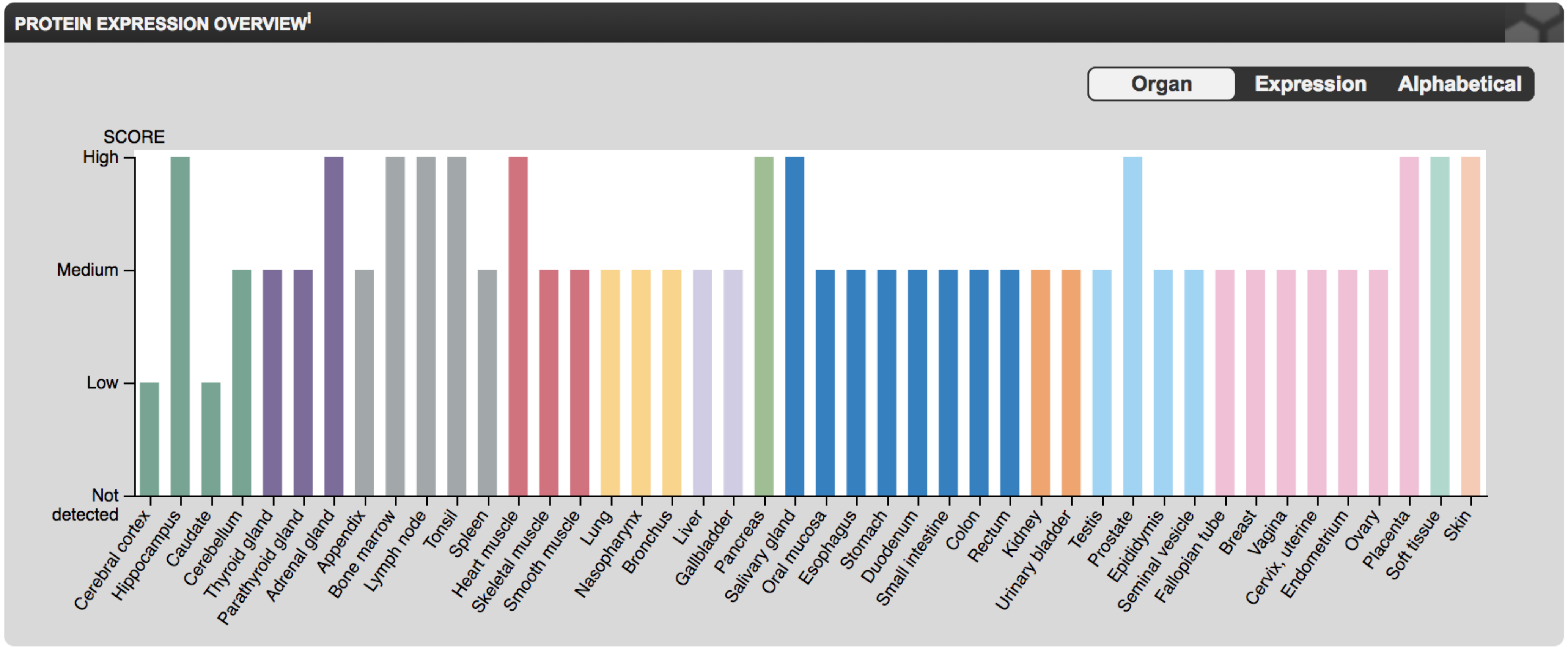
Deleting the circadian clock causes arrhythmicity



- Global Bmal1 KO
- Fully deleting any of the 4 key components of the molecular clock causes behavioural arrhythmicity

The core circadian clock genes are expressed throughout the body

Expression of Bmal1

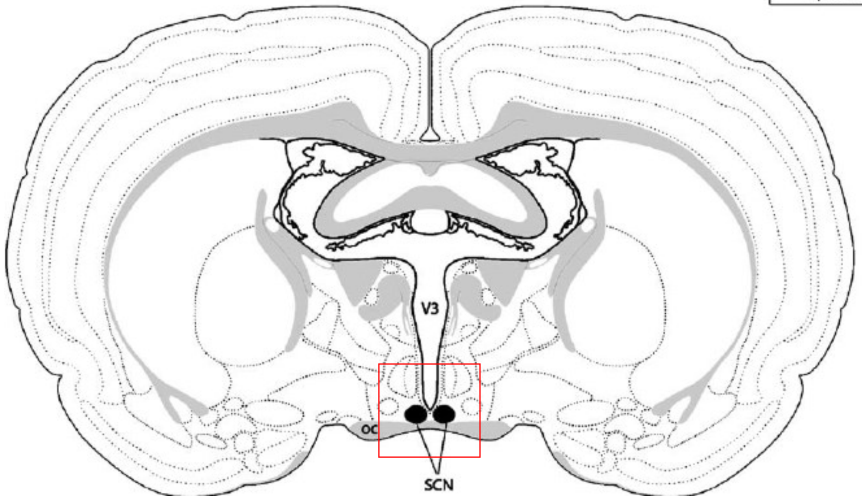


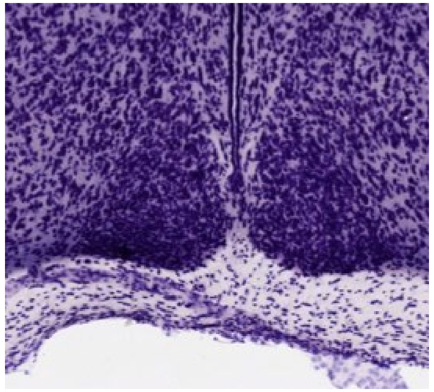
However, one area of the brain was particularly enriched in clock genes

The Master Pacemaker

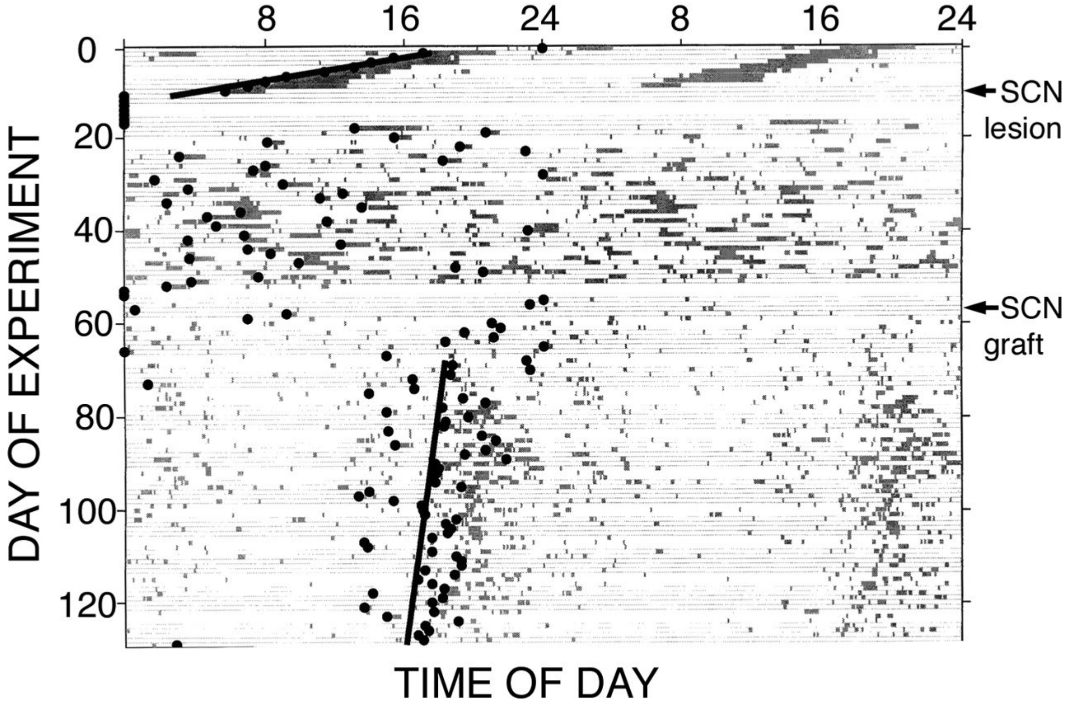
In mammals, the suprachiasmatic nucleus (SCN) is the master circadian pacemaker

(Kriegsfeld & Silver, 2006)



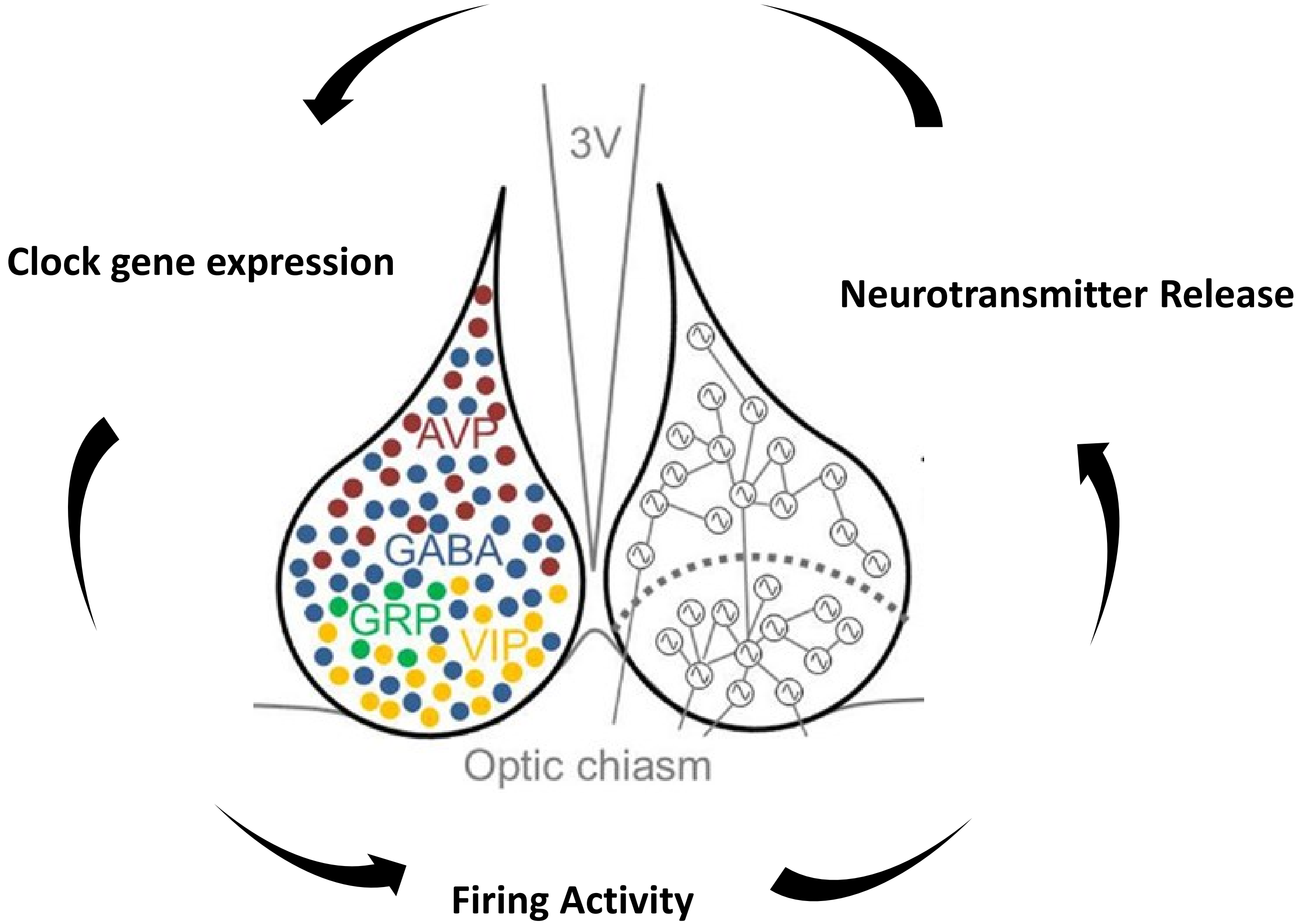


The SCN is necessary and sufficient for circadian rhythms



Guo et al. (2006) *J Neurosci*

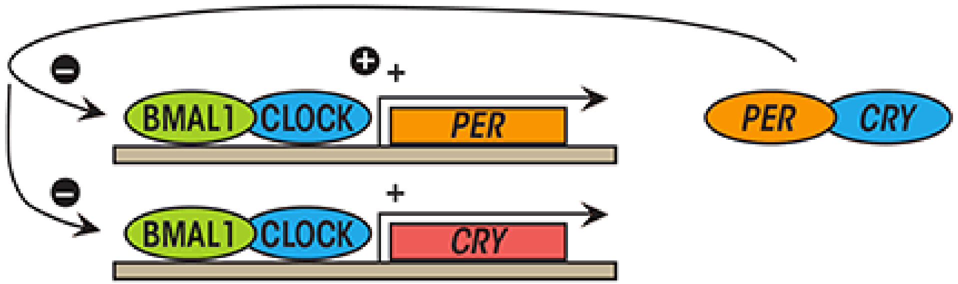
The SCN has self-sustained rhythms in gene expression, firing activity and neurotransmitter release

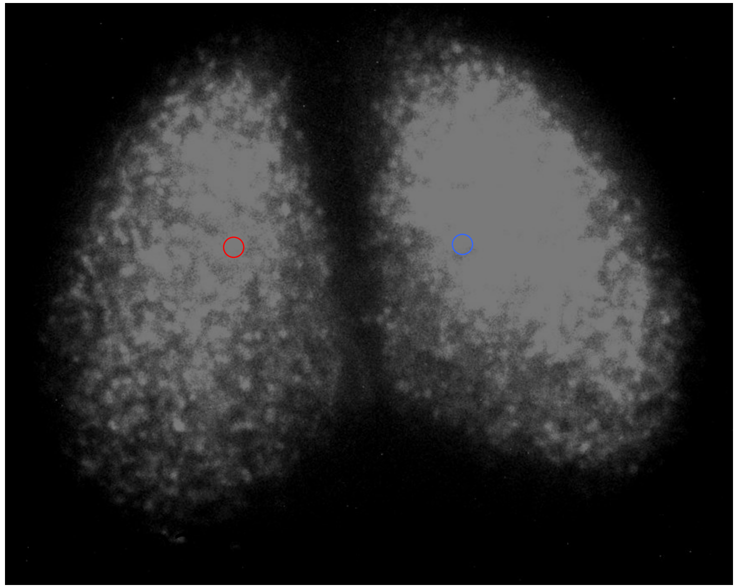


Ramkisoensing and Meijer (2015) *Front. Neurol.*

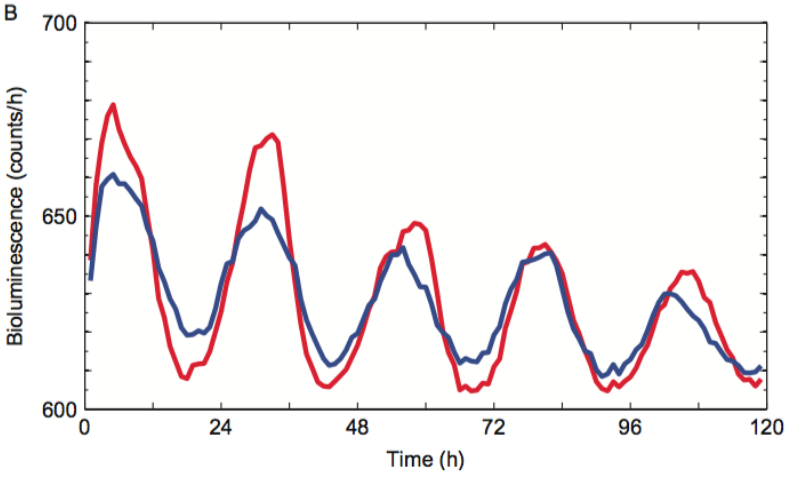
Individual SCN neurons have circadian oscillations in gene expression driven by the 'molecular clock'

Core Clock genes create a ~24-h transcription-translation feedback loop



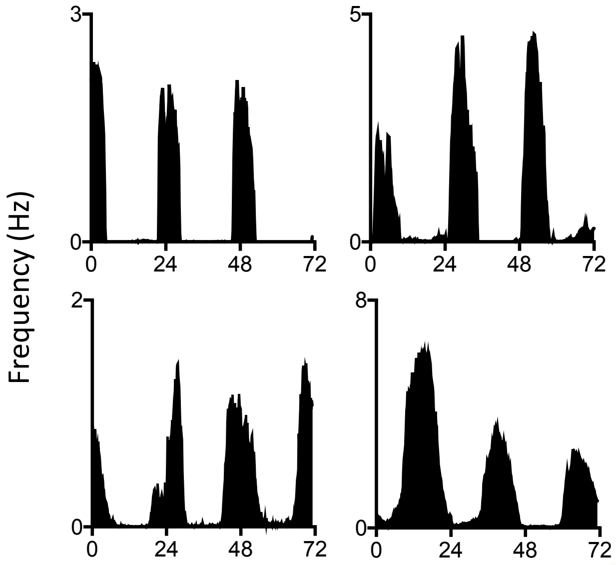


Single-cell rhythms in gene expression

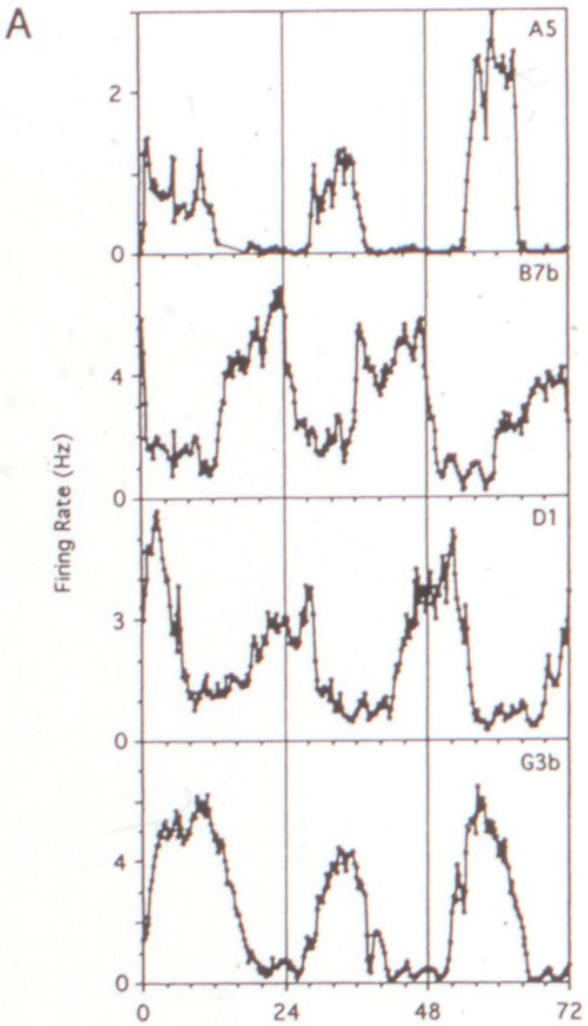


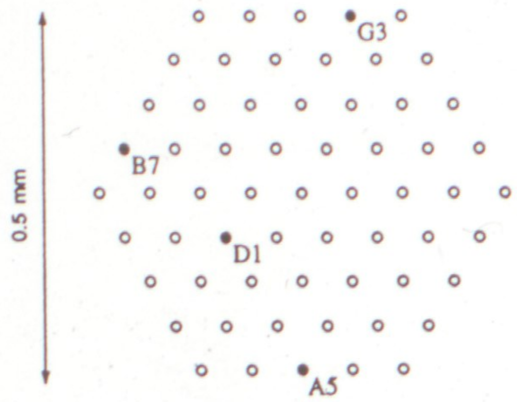
The SCN is Composed of Multiple Autonomous Single-Cell Oscillators

Single-cell rhythms in spontaneous firing activity



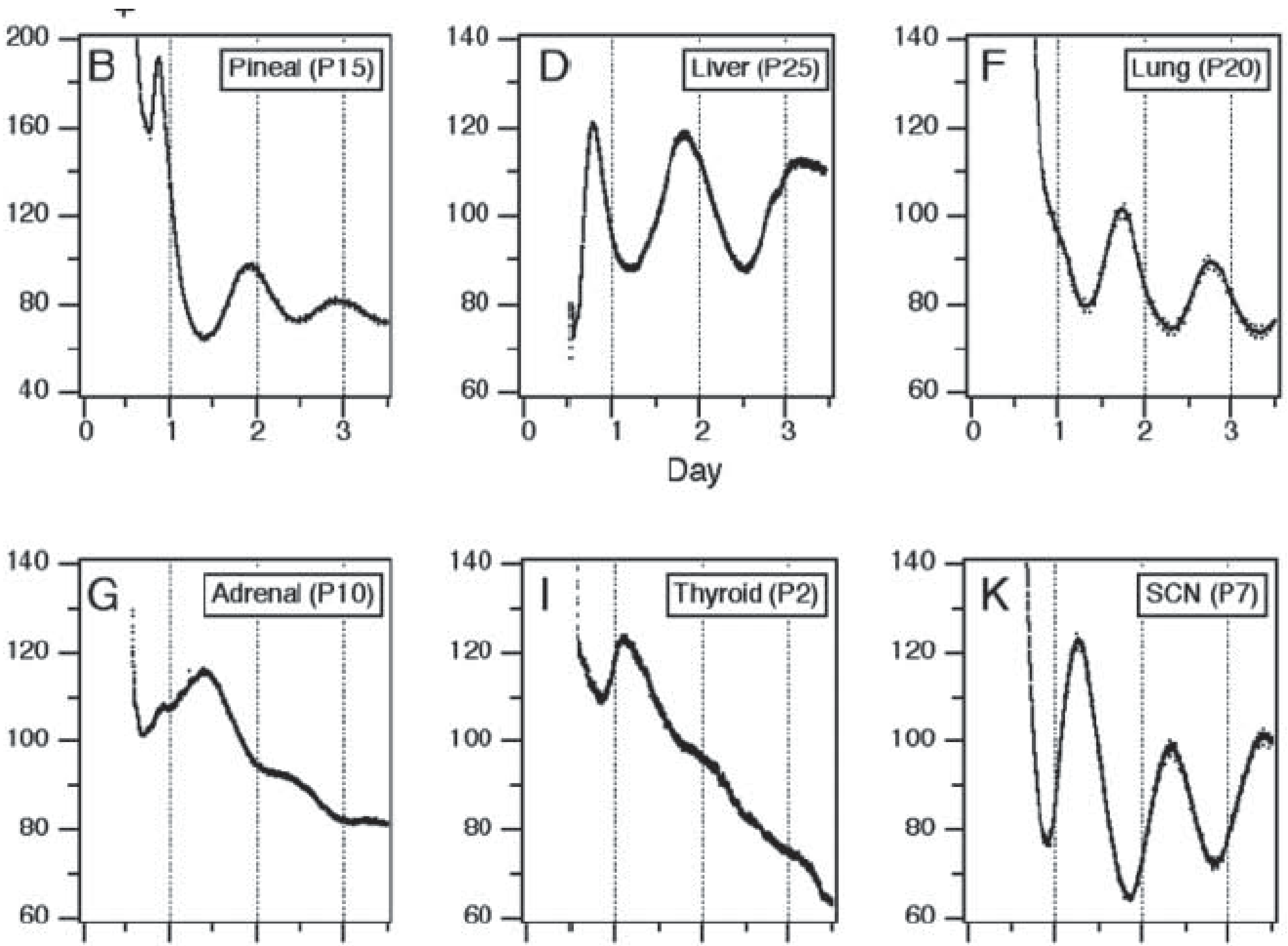
Mazuski et al.





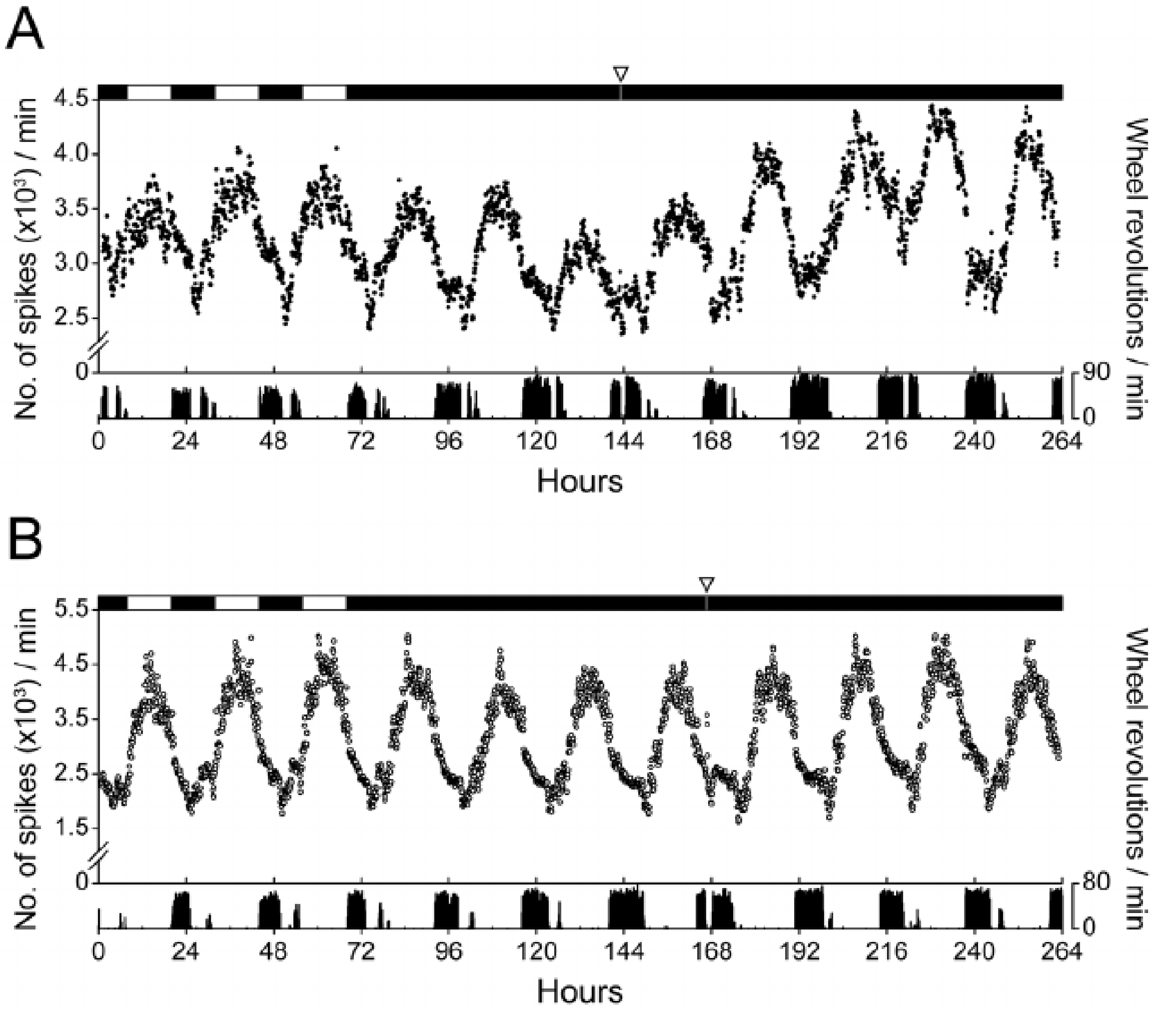
Welsh, Logothetis, Meister, & Reppert, *Neuron* 14:697, 1995

Self-sustained rhythms is a unique feature of the SCN

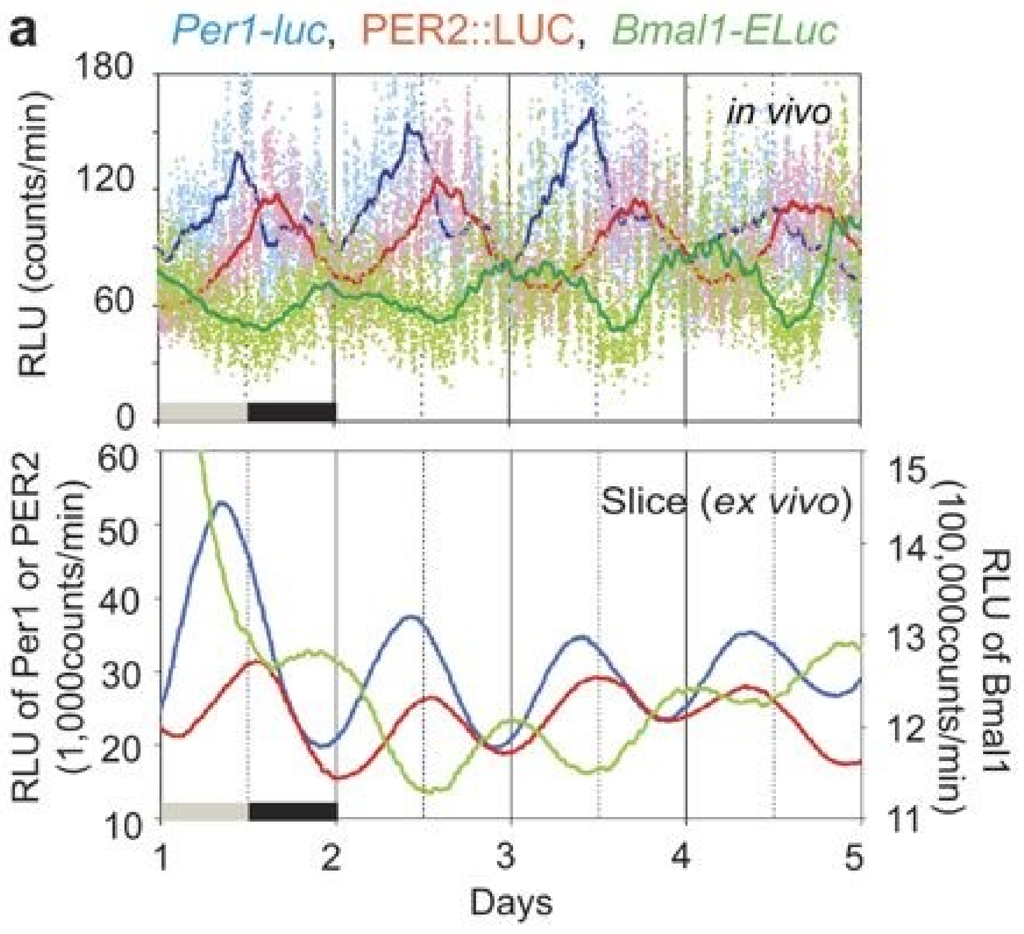


Yamazaki et al (2009) JBR

In vivo rhythms in firing activity and gene expression

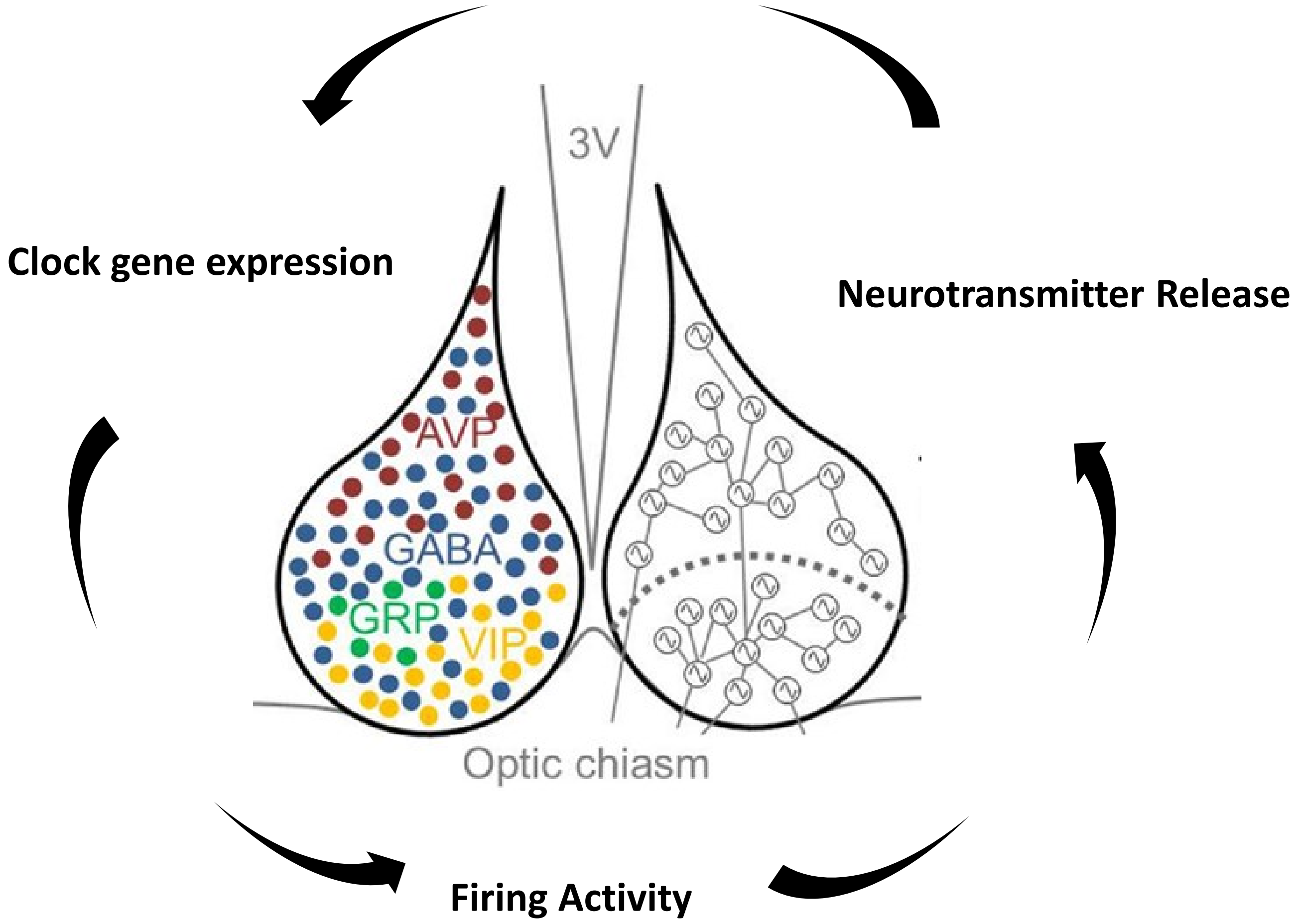


Takasu et al. (2013)



Ono, Honma & Honma (2015)

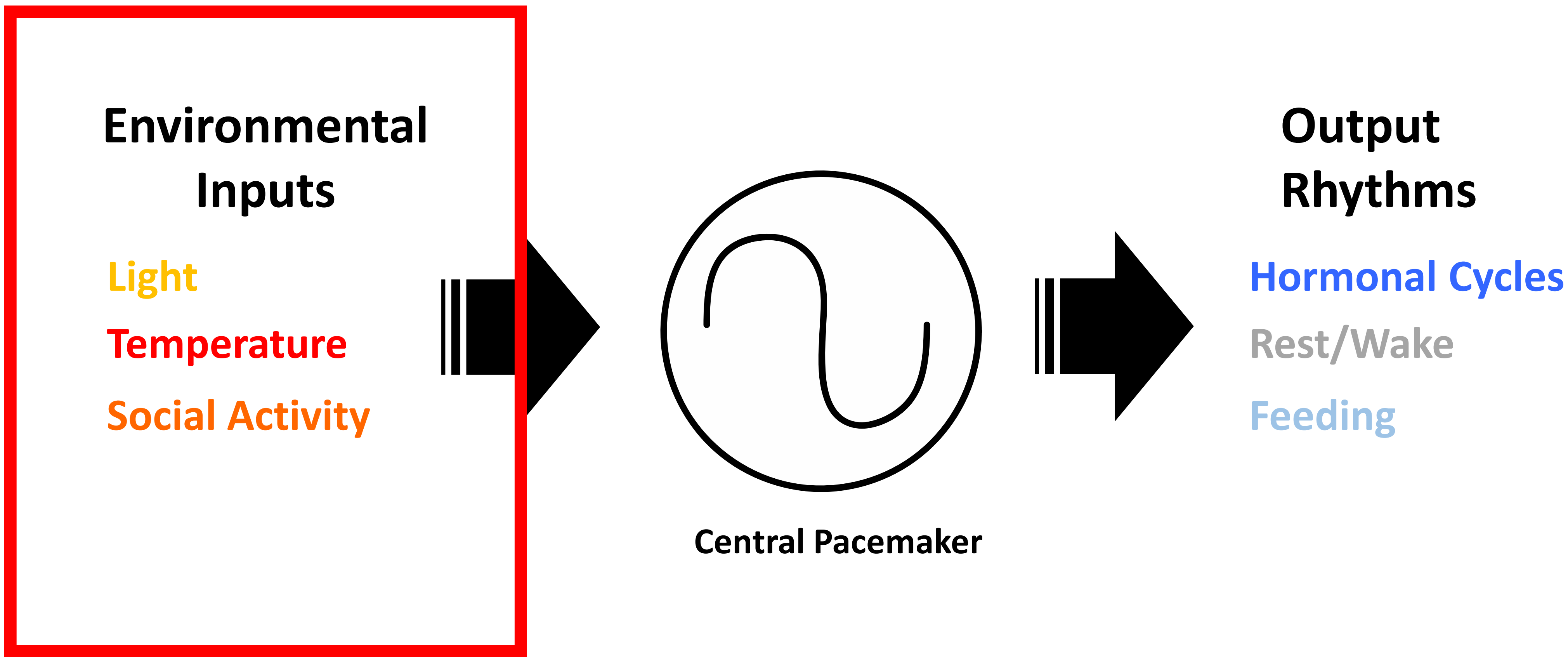
Many open questions remain about SCN function



- How neurons in the SCN respond during different lighting conditions (e.g. seasons) and disease-states (e.g. Alzheimer's)
- How individual SCN neurons couple together?
- **How input information is processed within the SCN**
- **How circadian information is communicated to the rest of the brain**

Ramkisoensing and Meijer (2015) *Front. Neurol.*

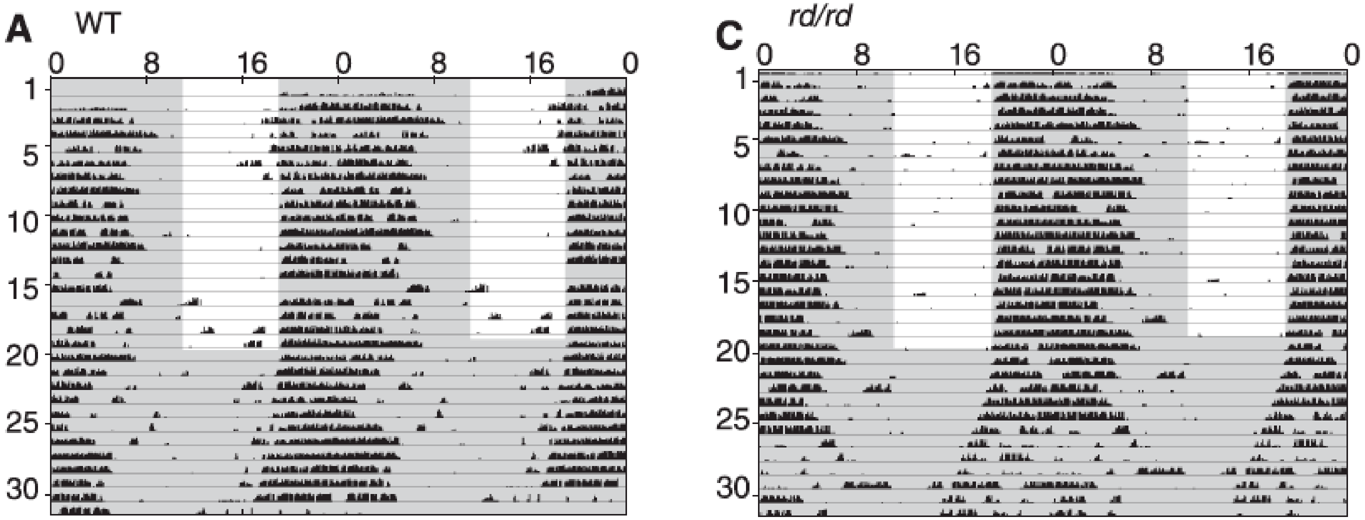
The Circadian Circuit



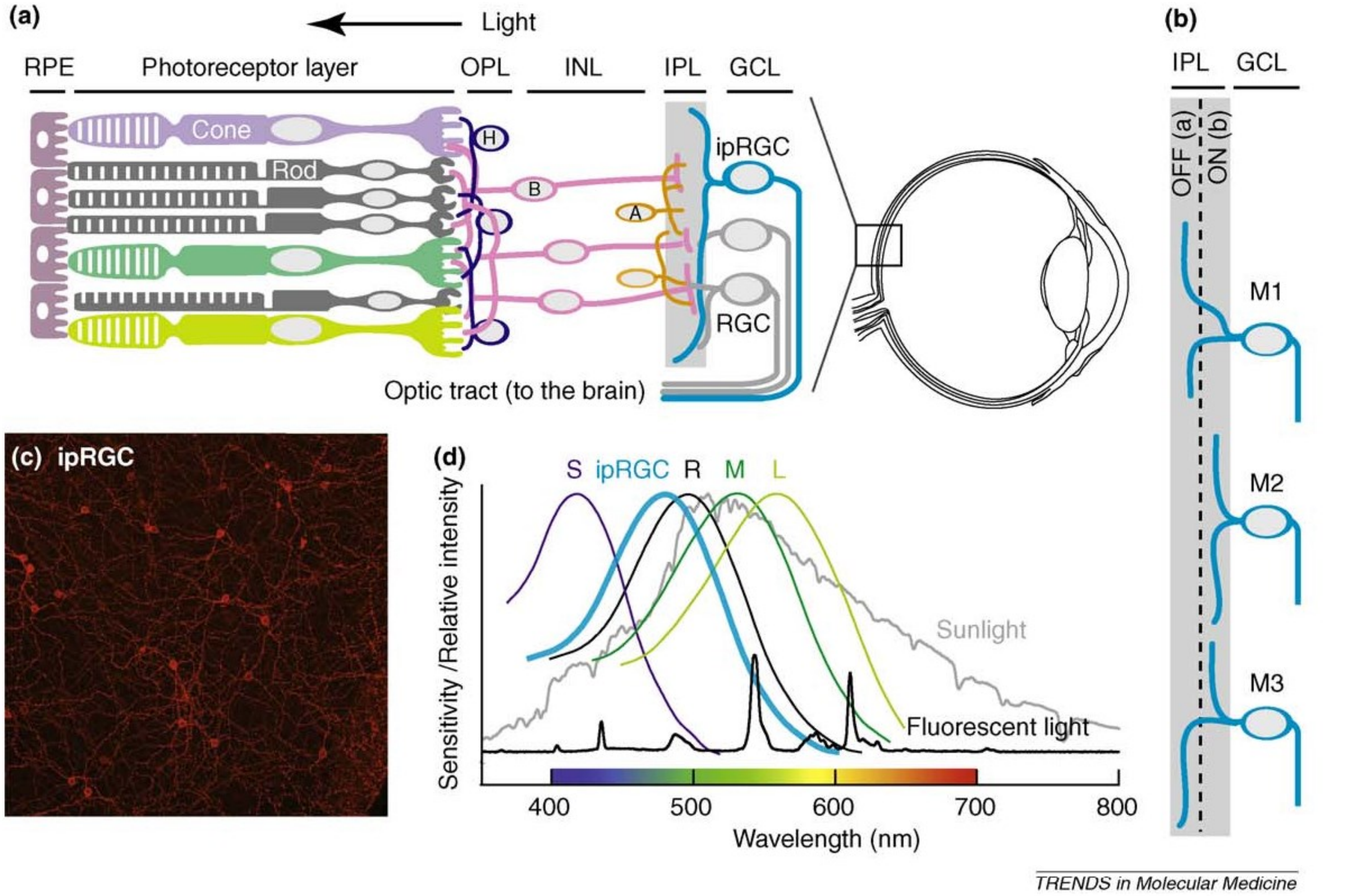
Photic Information

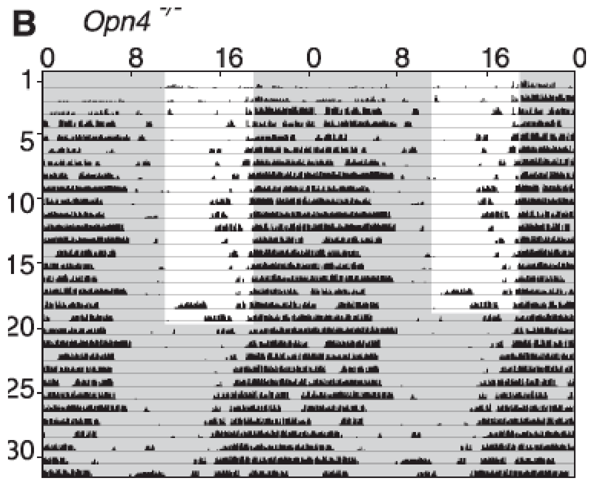
Blocking the input pathway to the SCN should result in a free-running organism

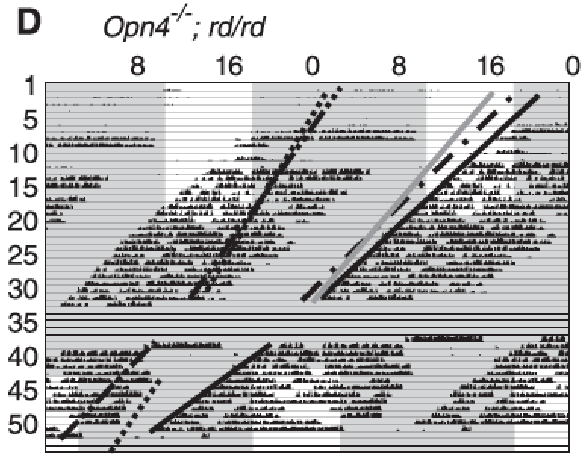
- Ennucleated mice show free-running circadian rhythms
- However, mice that lack both rods and cones show intact circadian rhythms

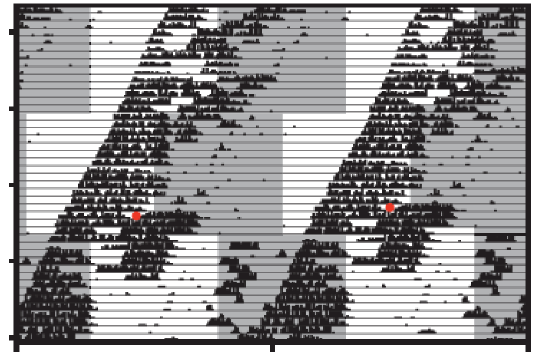


Melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs) are necessary for circadian entrainment

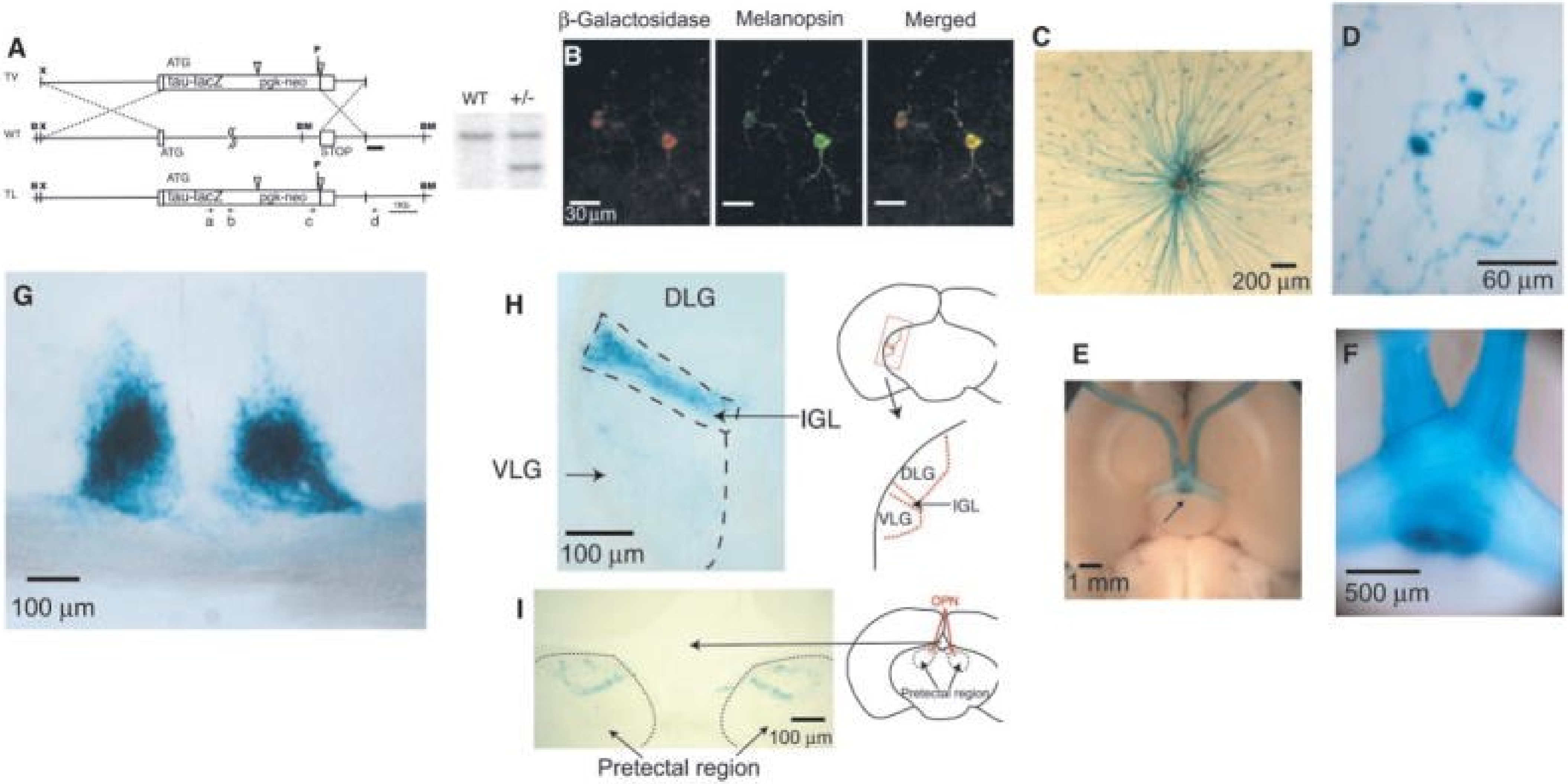








ipRGCs project to the suprachiasmatic nucleus as well as other brain regions



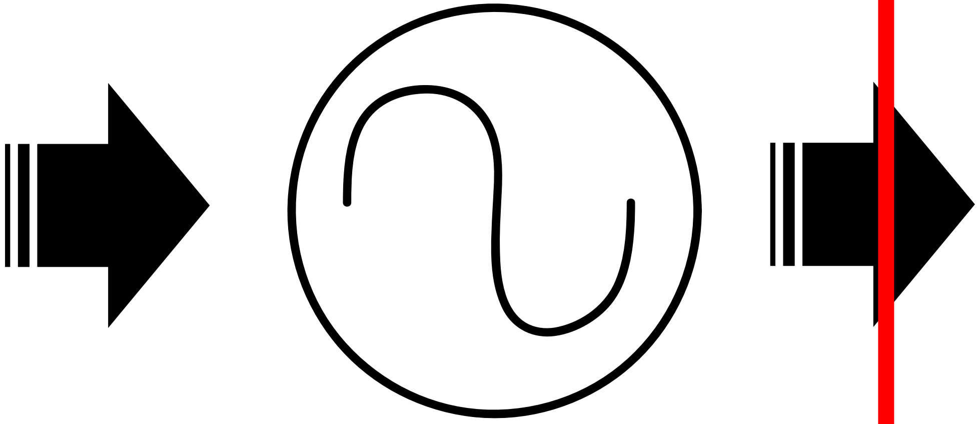
The Circadian Circuit

Environmental Inputs

Light

Temperature

Social Activity



Central Pacemaker

Output Rhythms

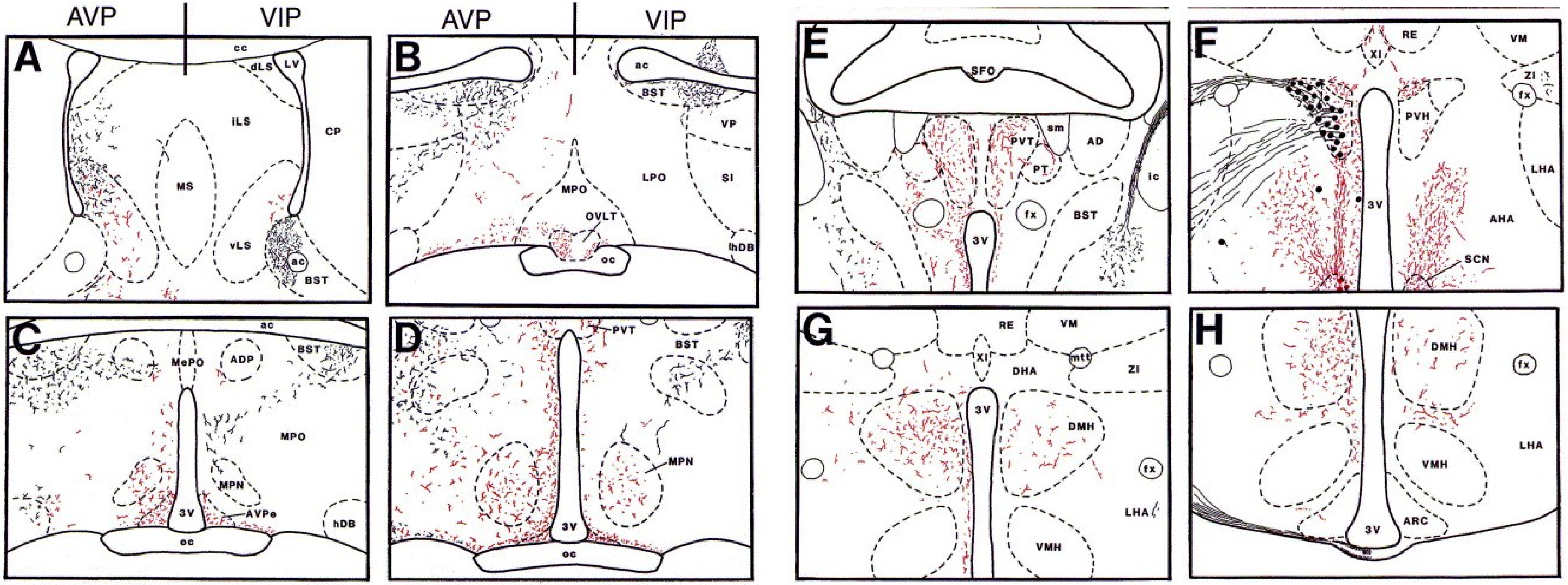
Hormonal Cycles

Rest/Wake

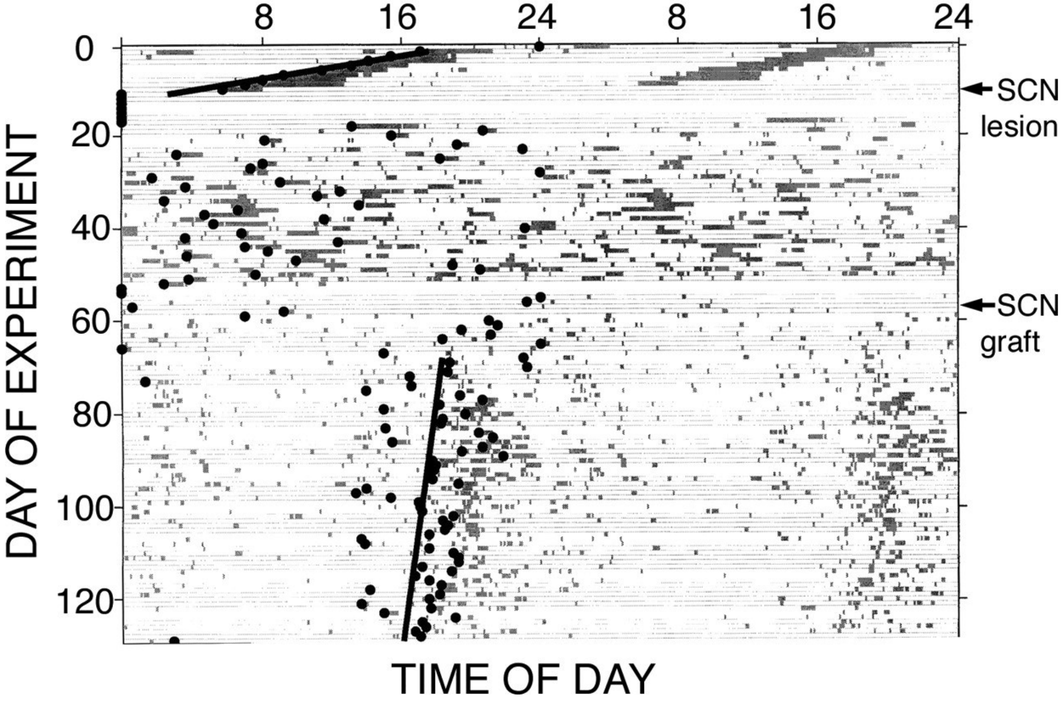
Feeding

How does the SCN communicate circadian information to the rest of the brain?

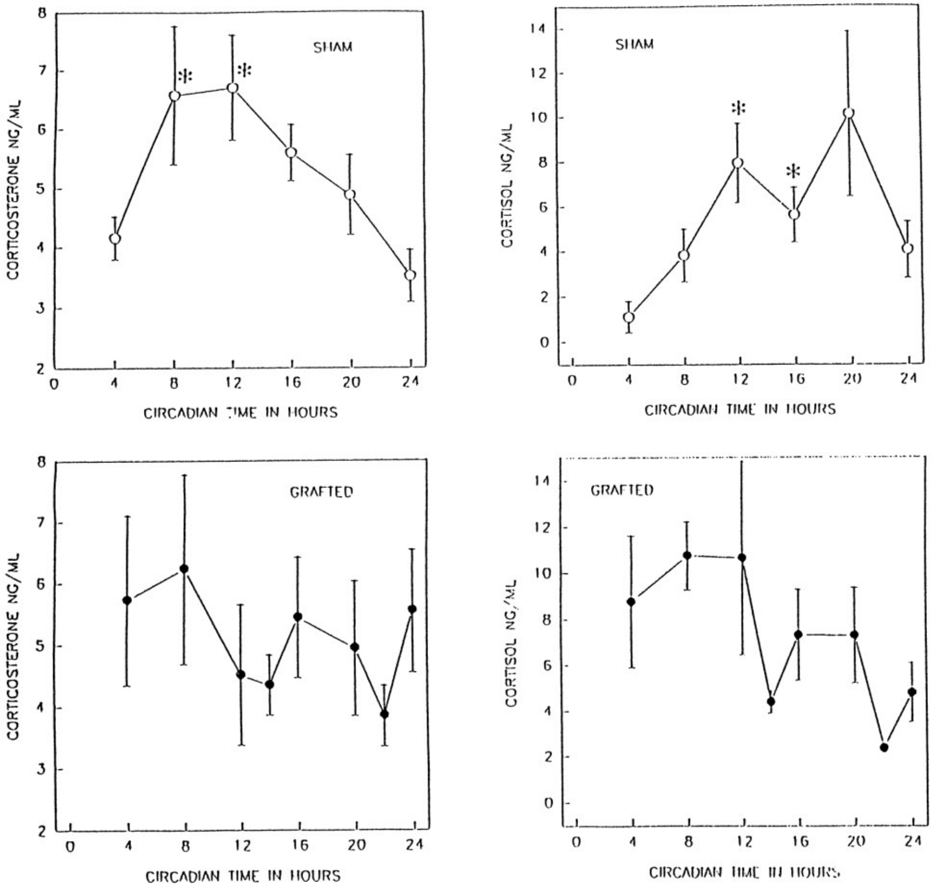
SCN largely innervates hypothalamic areas



SCN transplants only partially recover circadian rhythms

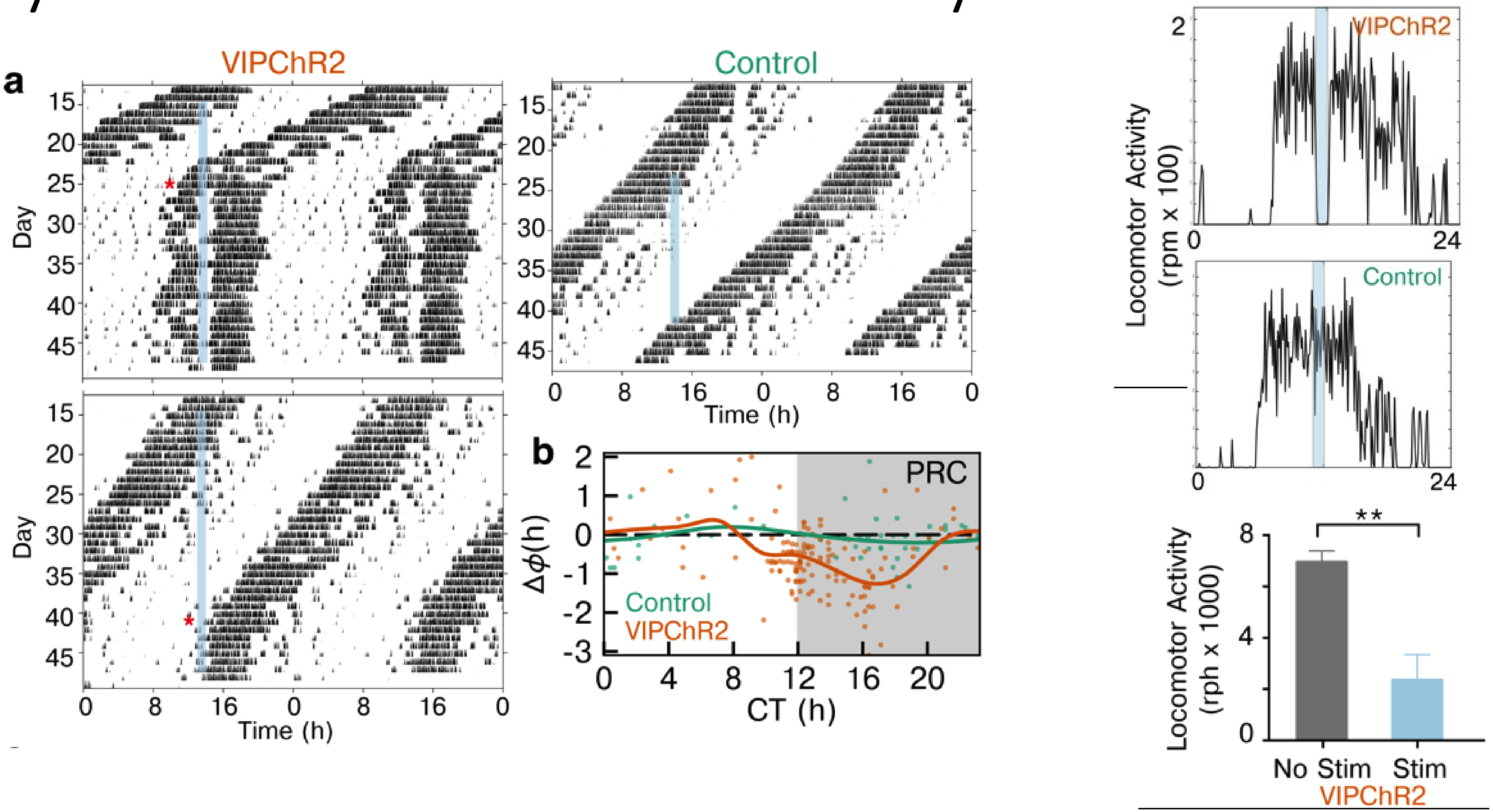


Guo et al. (2006) *J Neurosci*



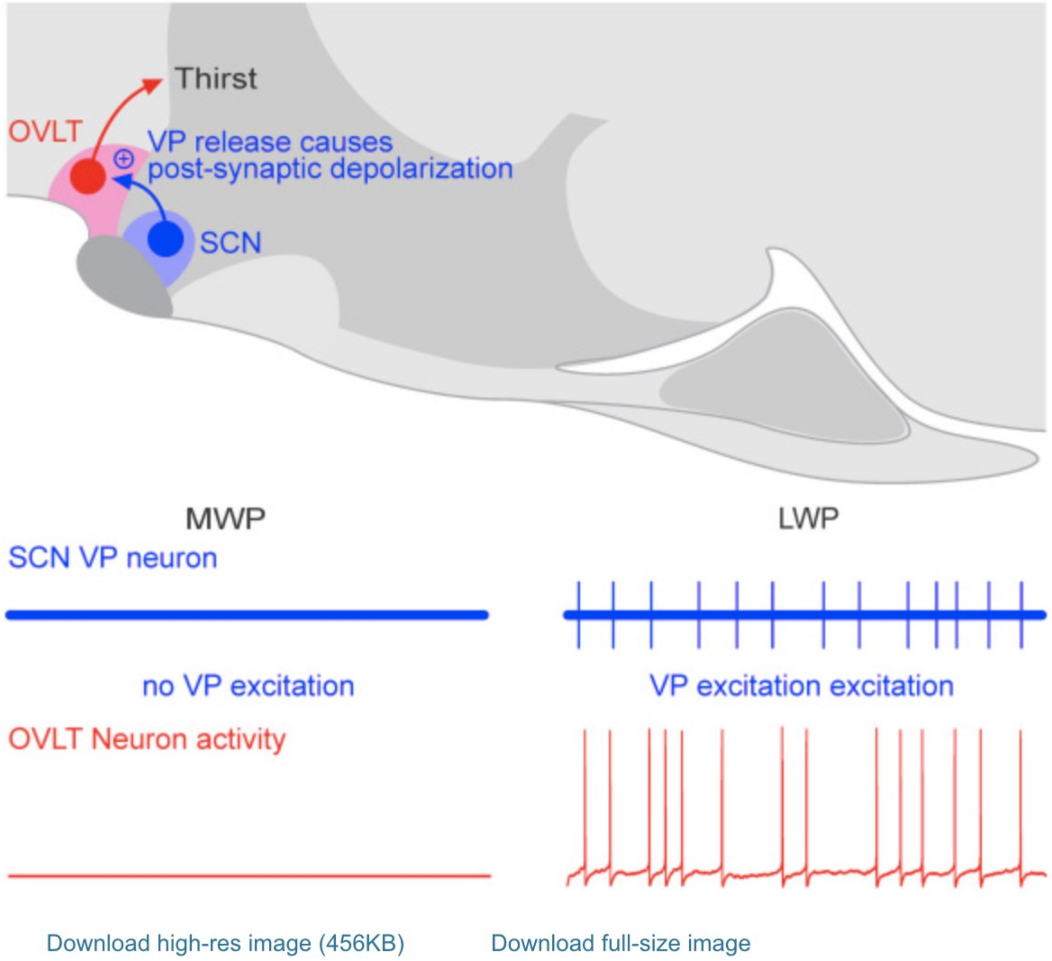
Meyer-Bernstein et al. (1999) *Endocrinology*

Timed firing of SCN can shift circadian rhythms in locomotor activity

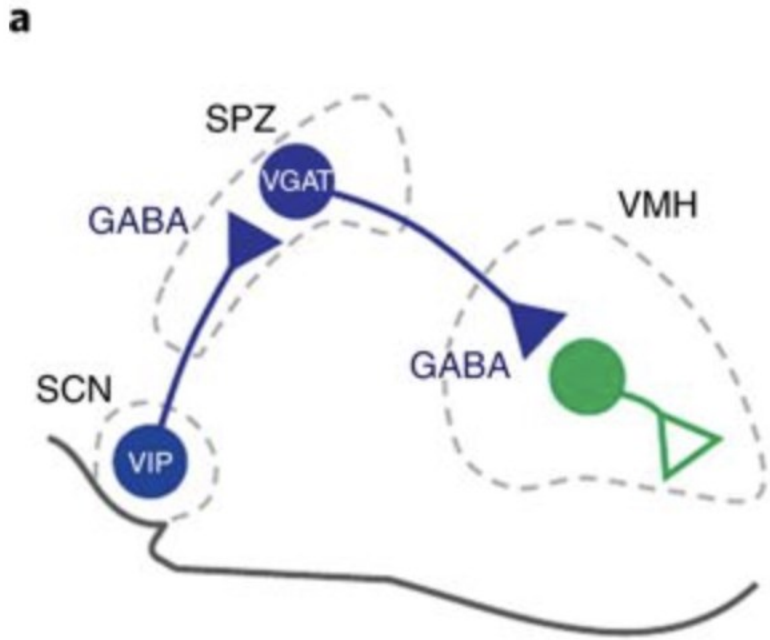


Mazuski et al

SCN circuits that can modulate other behaviours

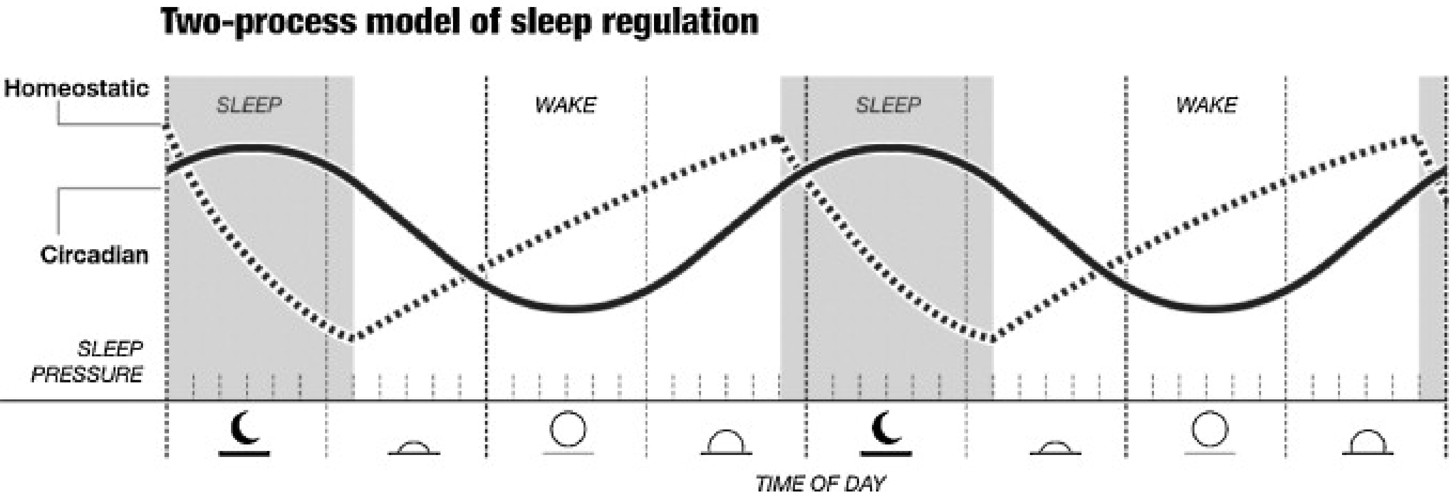


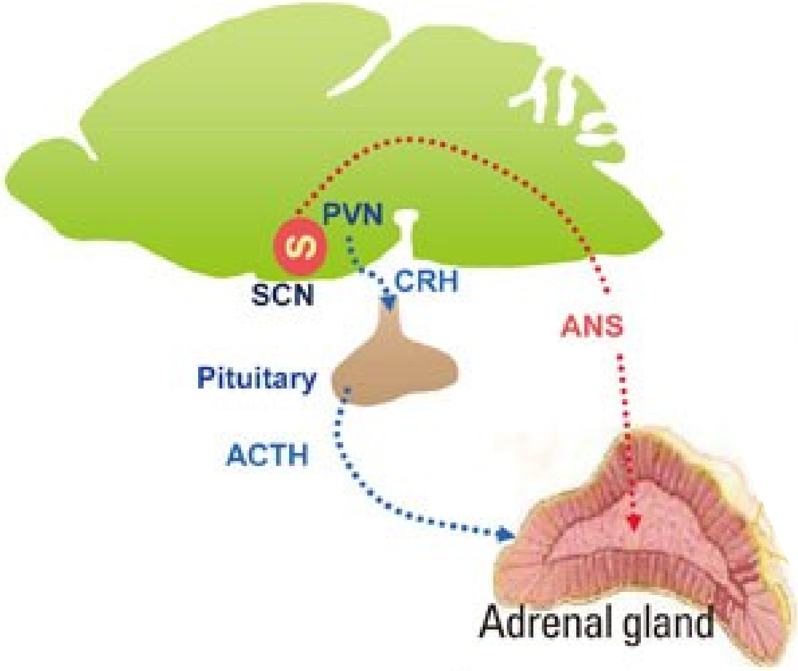
SCN vasopressin neurons can regulate the timing of thirst



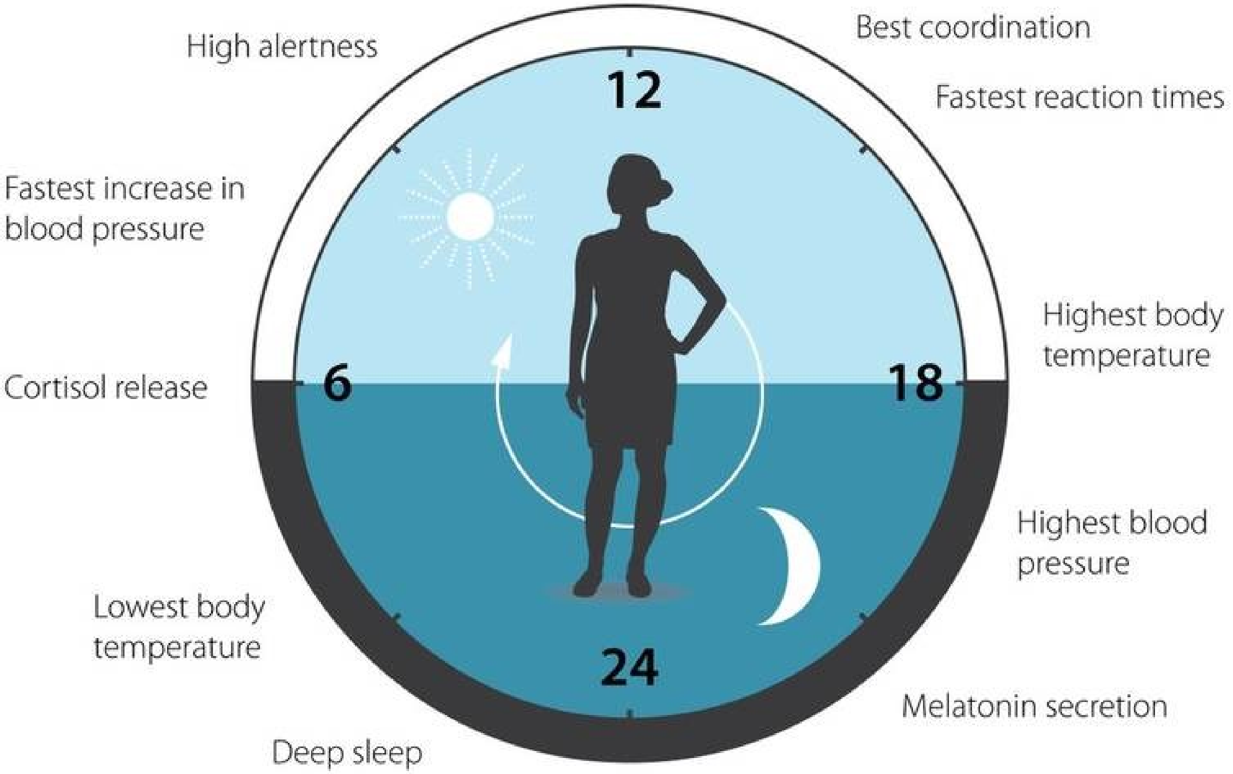
SCN VIP neurons can regulate the timing of aggression

Circadian regulation of key behaviours remains unexplained





Many questions remain about how the SCN communicates timing information



- Diffusable factor, neuronal communication or both?
- What about non-brain areas?
- Differences between diurnal/nocturnal animals?
- How is timing communicated?

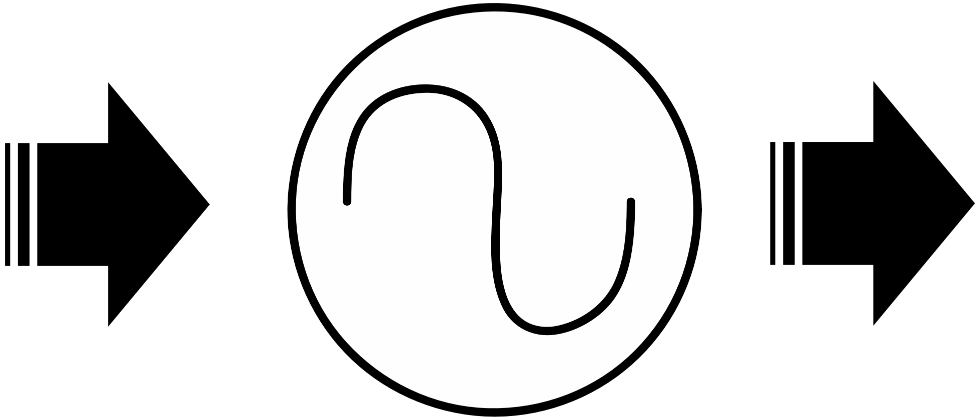
The Circadian Circuit

Environmental Inputs

Light

Temperature

Social Activity



Central Pacemaker

Output Rhythms

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