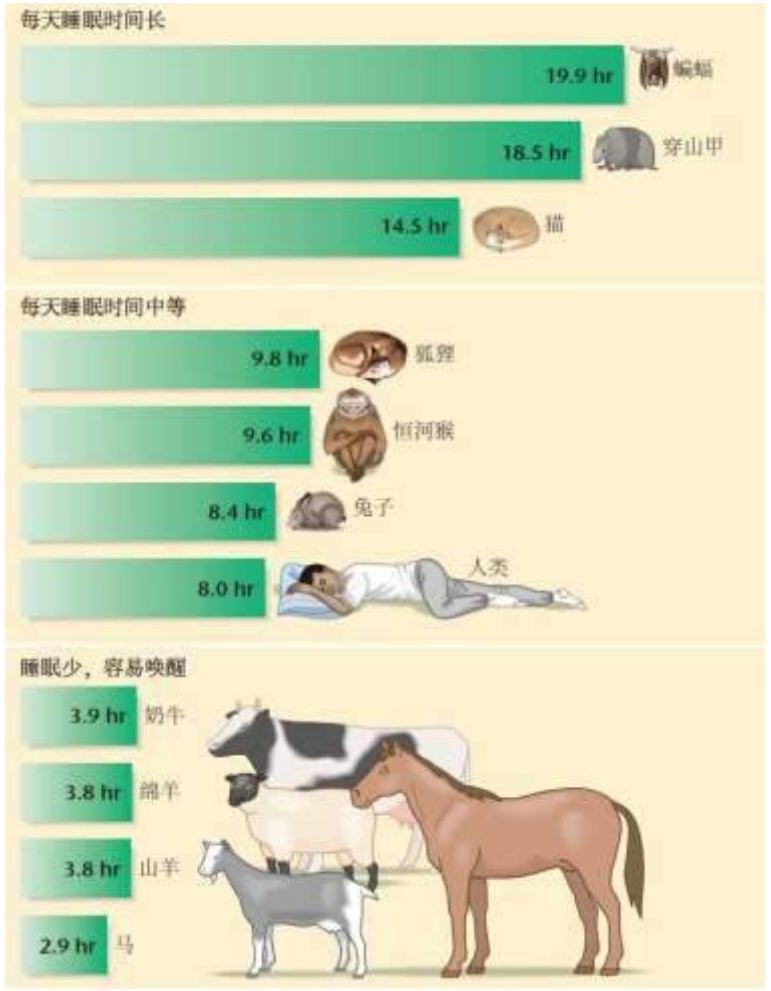
Regulation of sleep in *Drosophila*

邢丽敏 朱寰 王林

2020/06/24

What is the function of sleep?



Ideas about sleep

A. Energy Reserves

B. Theory of restoration and maintenance

C. Theory of functional

Memory consolidation theory

Synaptic homeostasis hypothesis, SHY

Study sleep using fruit flies as a model

Neuron, Vol. 25, 129–138, January, 2000, Copyright ©2000 by Cell Press

Rest in *Drosophila* Is a Sleep-like State

Joan C. Hendricks,* Stefanie M. Finn,
Karen A. Panckeri, Jessica Chavkin, Julie A. Williams,
Amita Sehgal, and Allan I. Pack
Center for Sleep and Respiratory Neurobiology
School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania 19104

study, we present evidence that, according to these criteria, rest in *Drosophila* is a sleep-like state. We also initiated studies to elucidate the relationship of rest behavior to the central clock genes *period* and *timeless*.

Results

Correlates of Sleep and Waking in *Drosophila melanogaster*

Paul J. Shaw, Chiara Cirelli, Ralph J. Greenspan, Giulio Tononi*

- ✓ Clock control
- ✓ Homeostatic response to sleep deprivation
- ✓ Increase arousal threshold during sleep
- ✓ Species specific sleep posture
- ✓ Response to hypnotic/stimulant drugs

Content

- The interaction between sleep and mating behavior in *Drosophila*

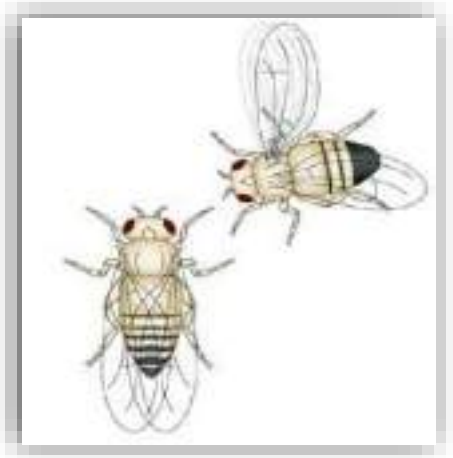
  by XLM

- The neural circuits of sleep

  by ZH

- Homeostatic response to sleep deprivation

  by WL

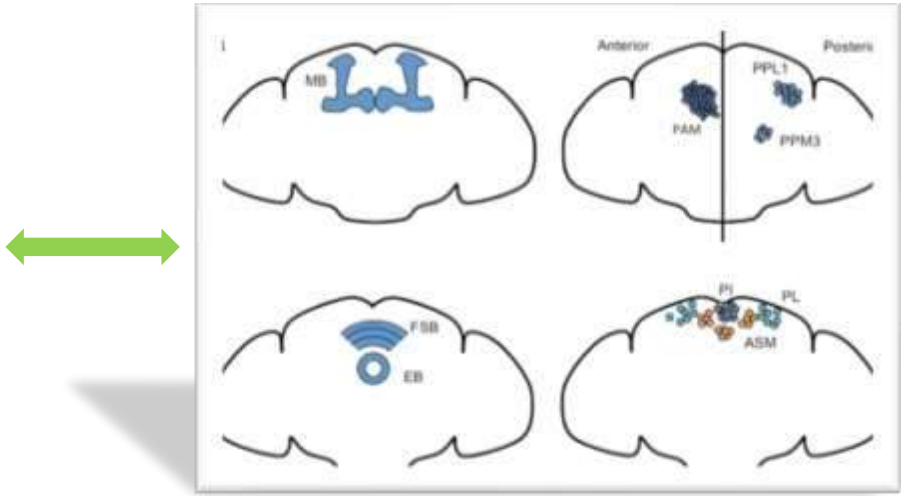


The interaction between sleep and mating behavior in *Drosophila*

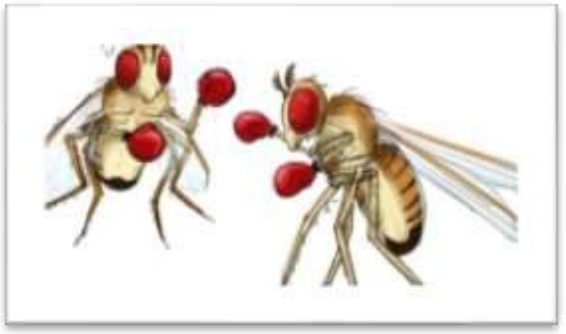
XLM

2020/06/24

- Sexually Aroused Males Suppress Sleep
- Mating Reduces Female Sleep
- Conclusion

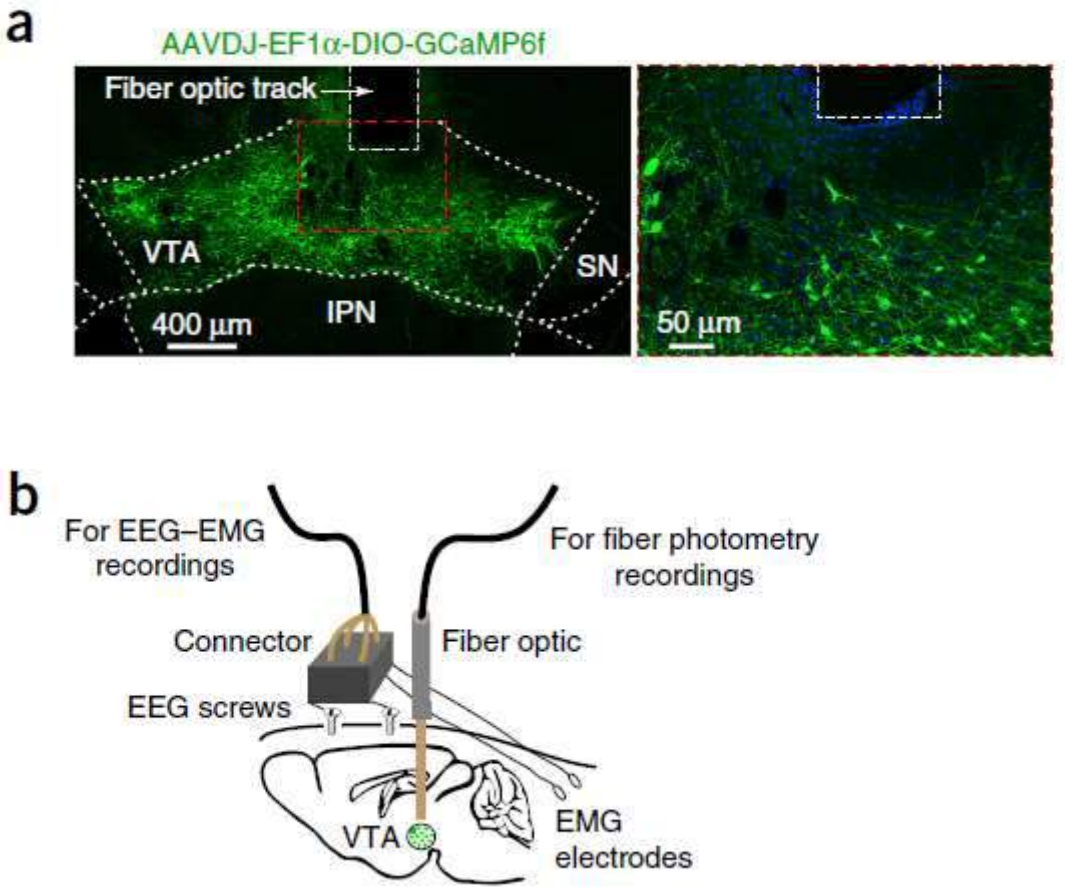


diverse environmental factors



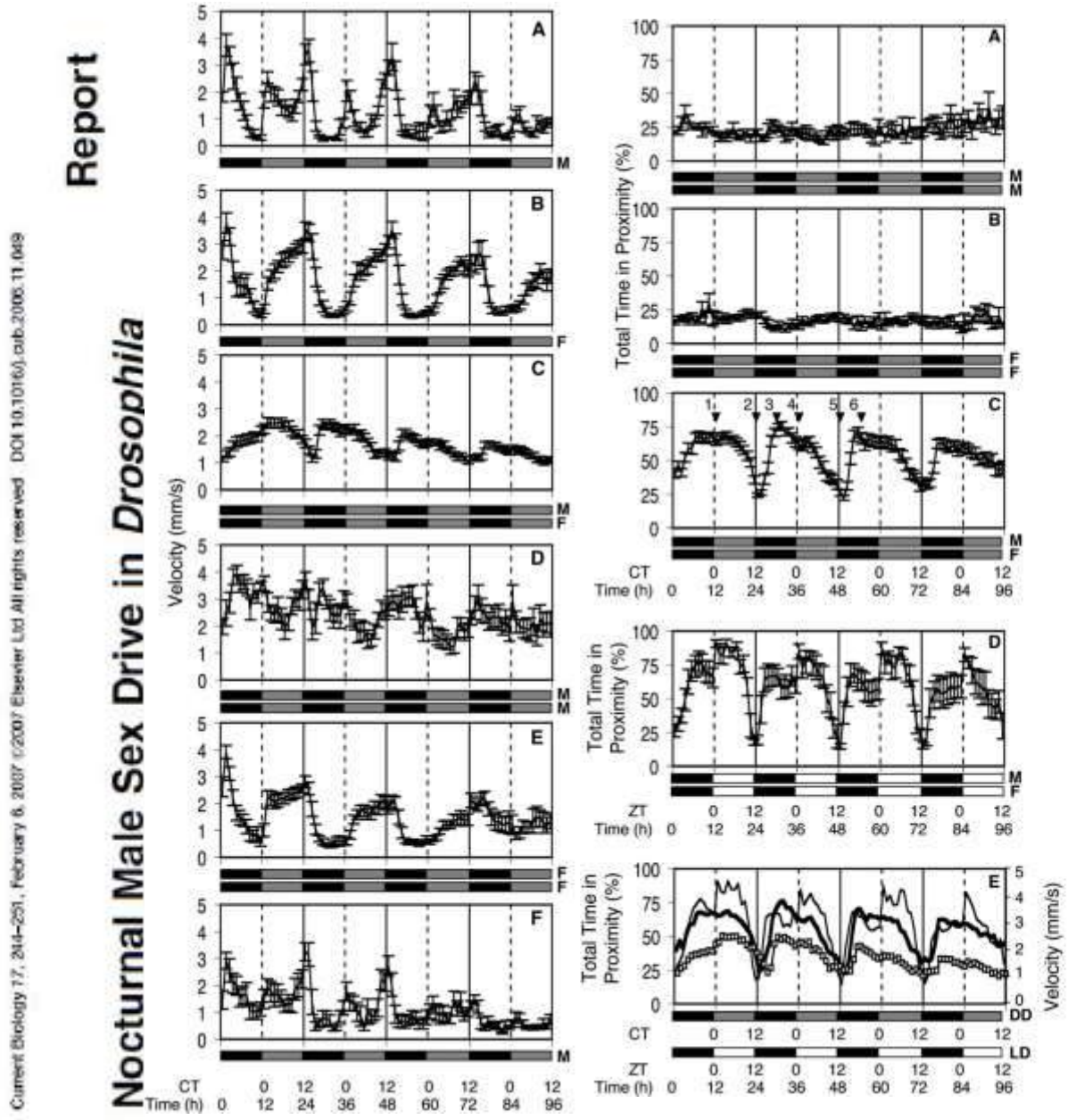
Two clear examples of how sexual arousal and the possibility of mating can regulate sleep

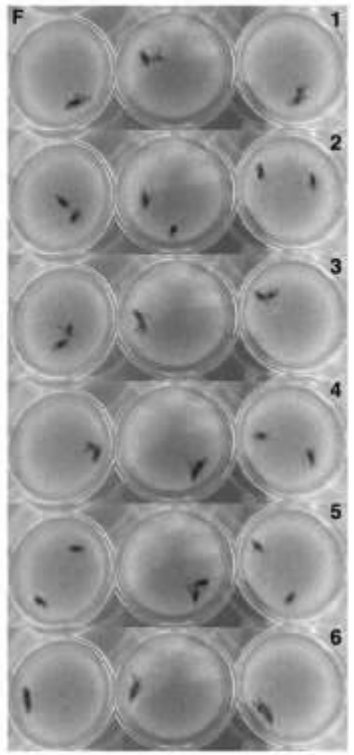
Lesku., *et al*., *Science*. 2012

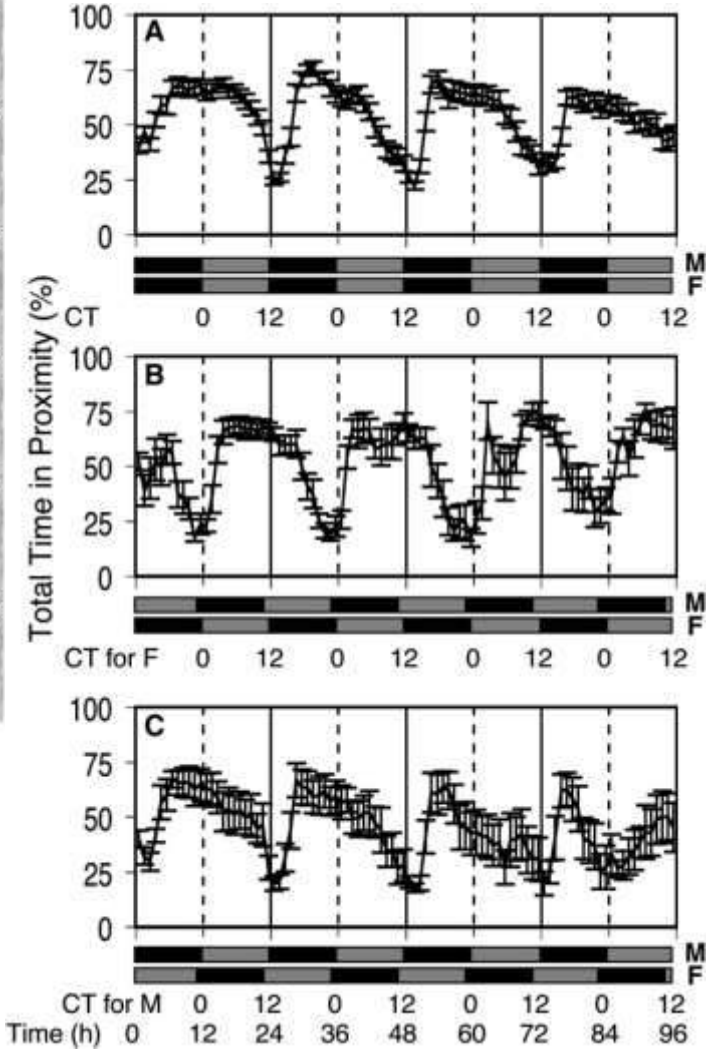


Eban-Rothschild., *et al*., *Nat. Neurosci*. 2016

Male sexual arousal disrupts sleep homeostasis in flies when females are present

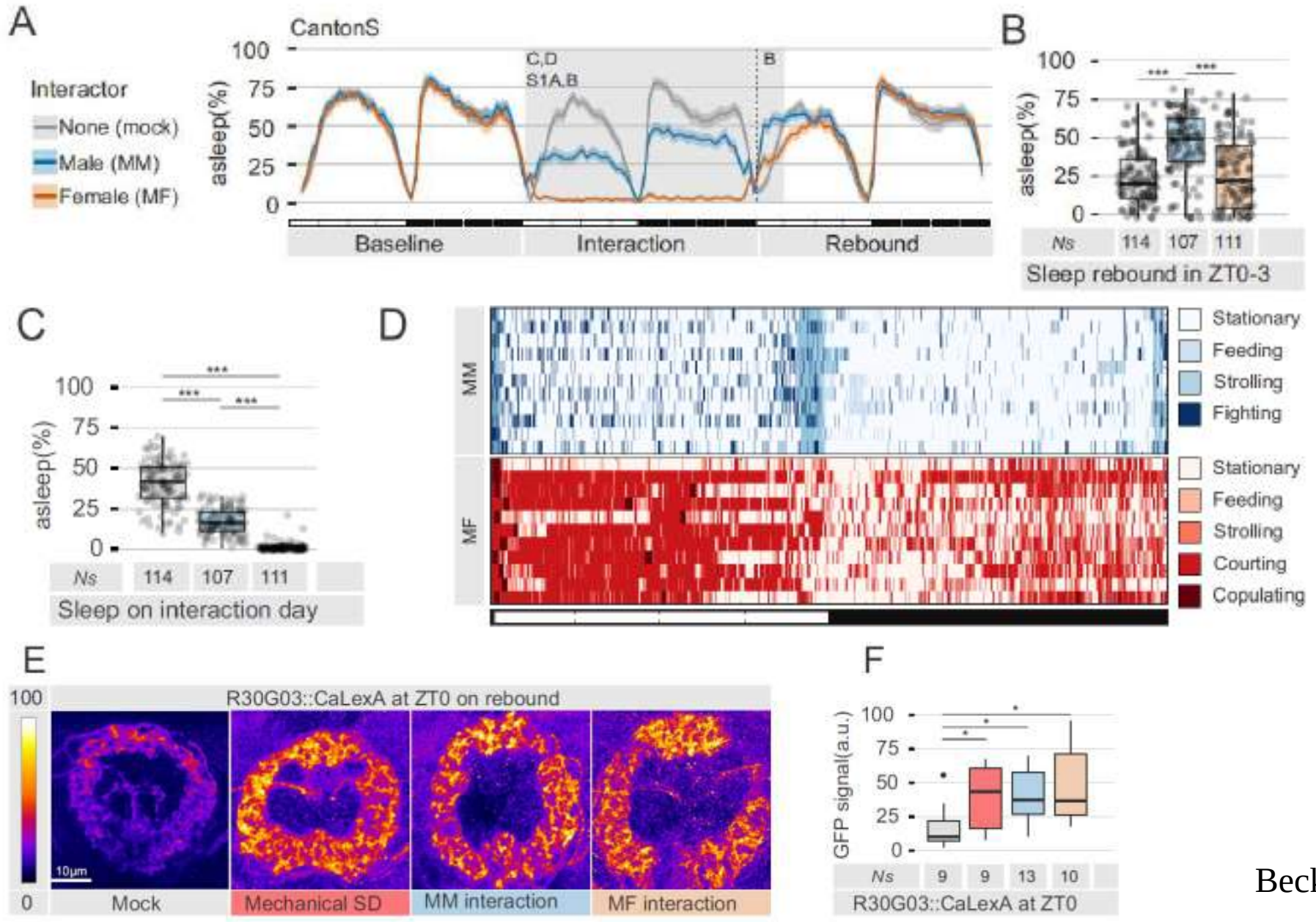






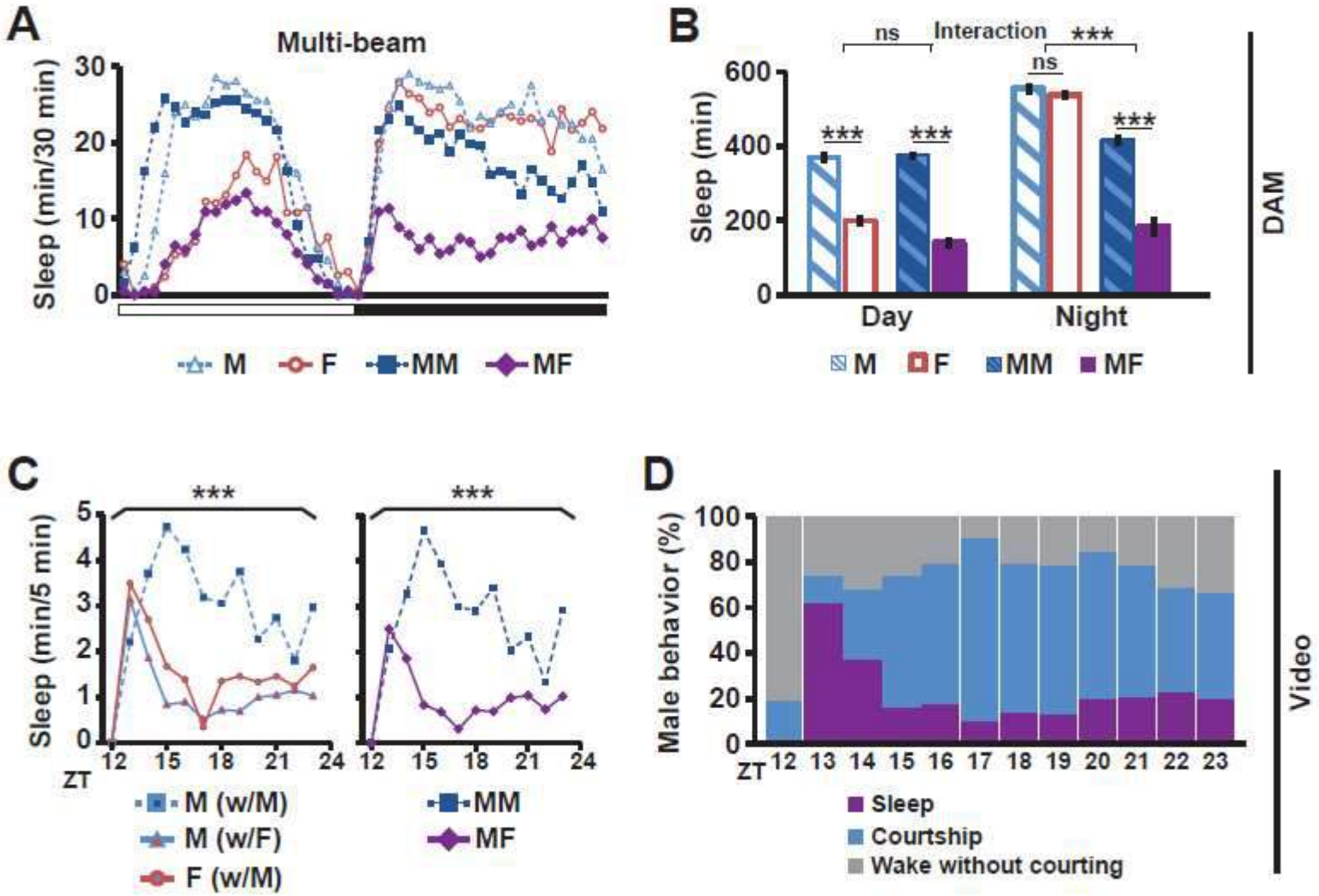
Fujii *et al*., *Curr. Biol*. 2006

The Male-Female interaction led to an even greater deprivation of sleep, but no rebound



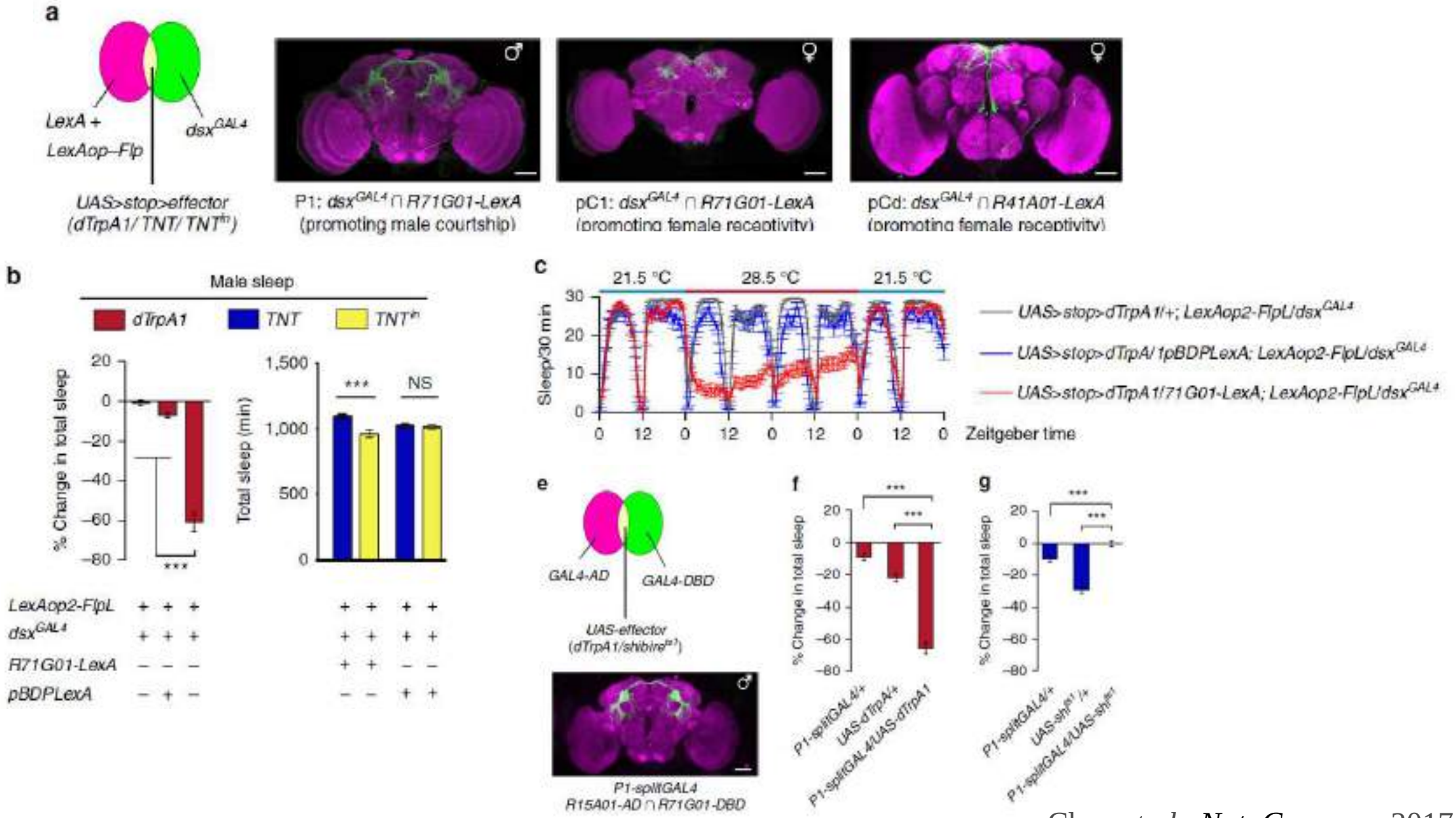
Beckwith *et al.*, *eLife*. 2017

Male flies possess mechanisms for suppressing sleep in the presence of female flies



Machado *et al.*, *eLife*. 2017

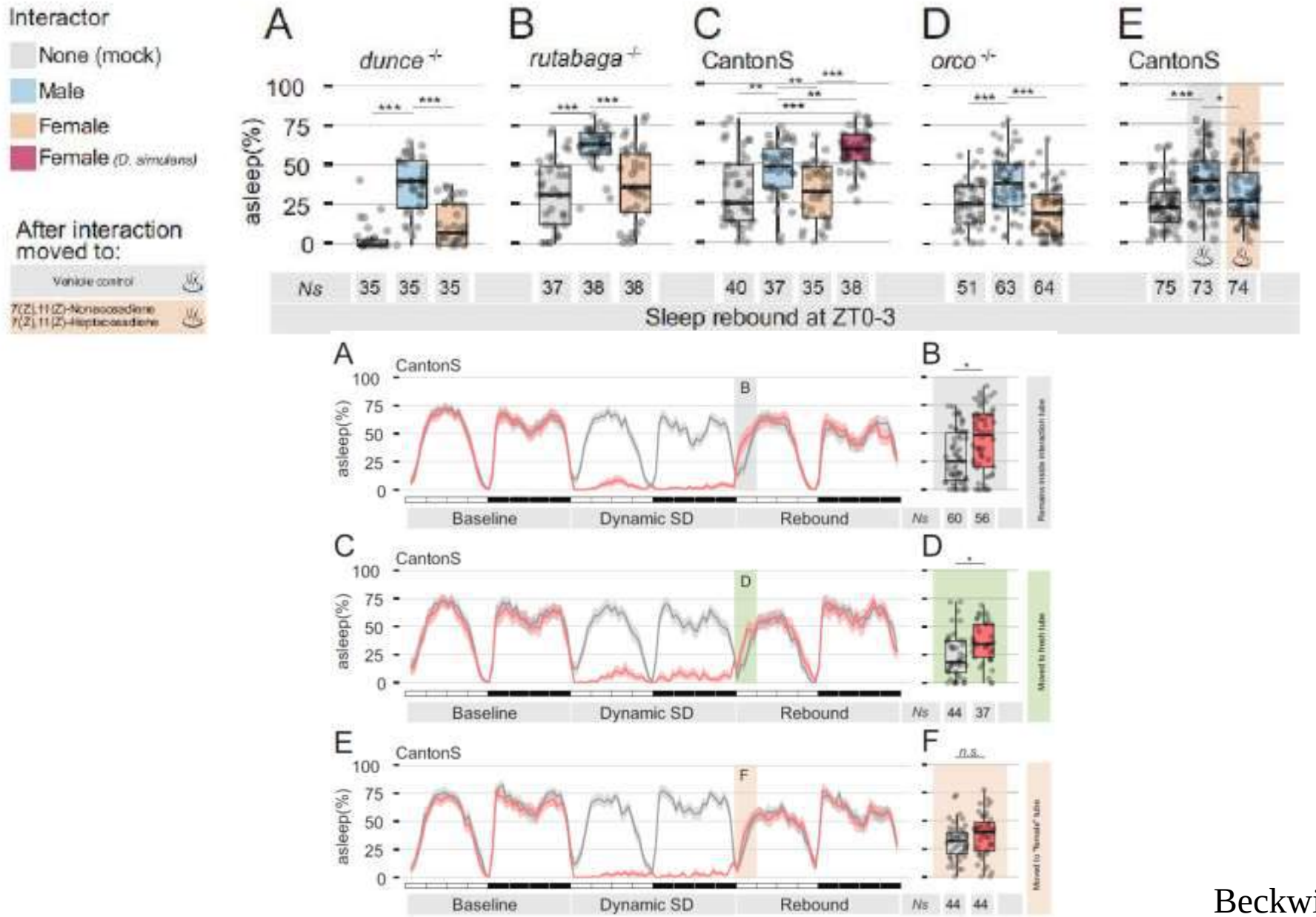
Sleep can be regulated by the sexual arousal circuits in *Drosophila*



Chen *et al.*, *Nat. Commun.* 2017

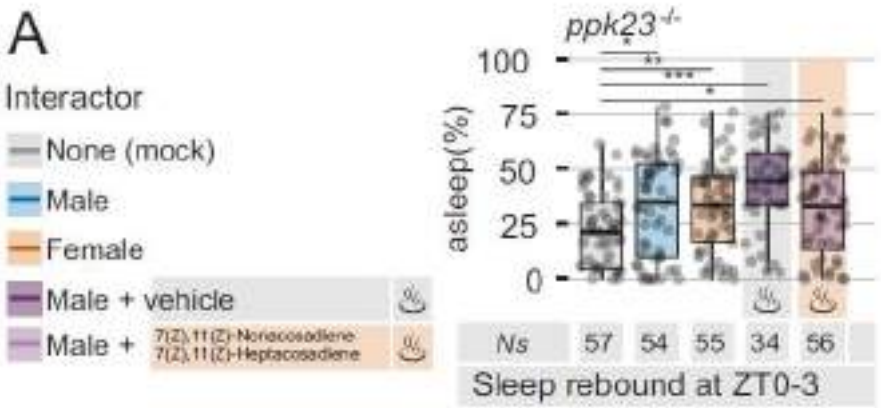
What is involved in regulating abnormal sleep homeostasis and sleep rebound in male *Drosophila*?

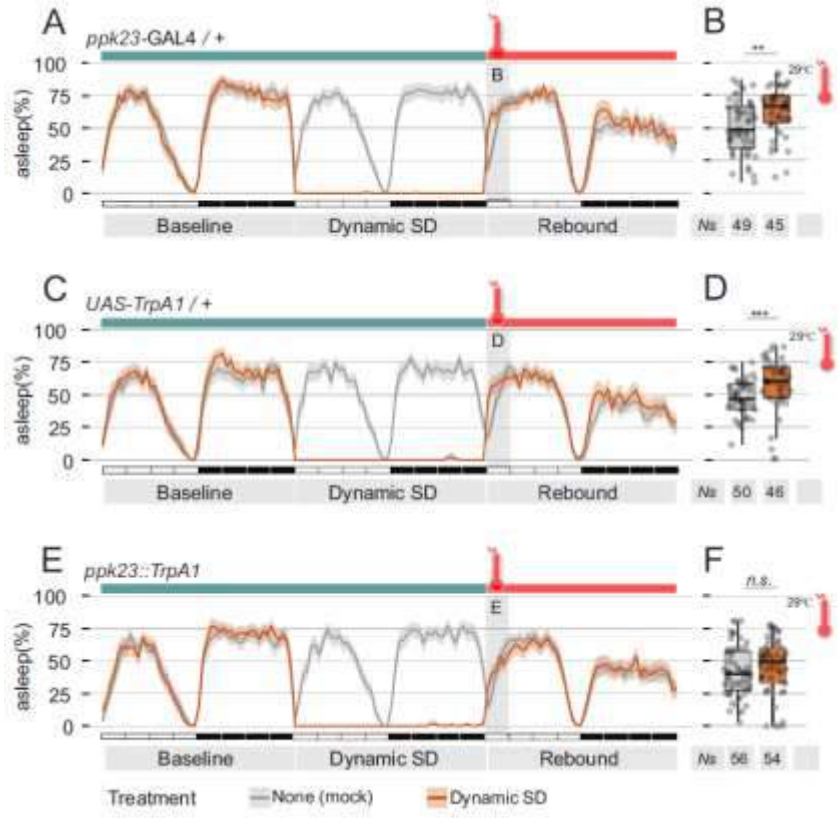
Presence of female pheromones is sufficient to suppress sleep rebound after sleep deprivation

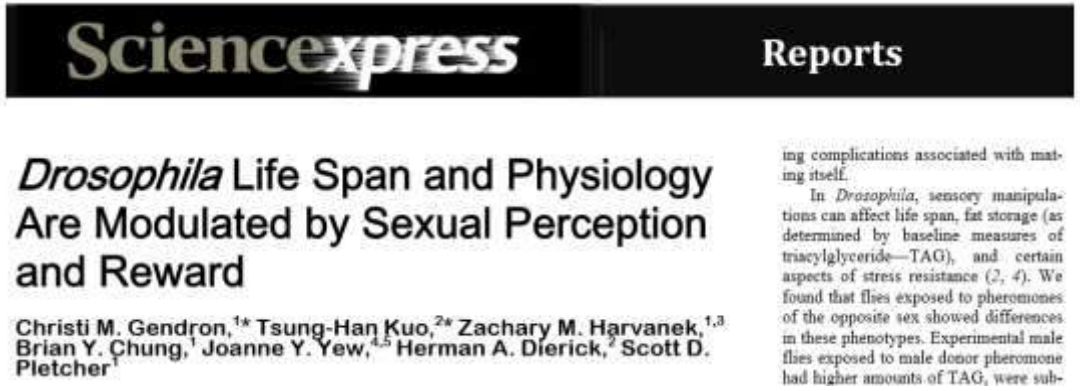


Beckwith *et al.*, *eLife*. 2017

The pheromone receptor Ppk23 is necessary for sleep suppression after sleep deprivation.







Sciencexpress Reports

Drosophila Life Span and Physiology Are Modulated by Sexual Perception and Reward

Christi M. Gendron,[1]* Tsung-Han Kuo,[2]* Zachary M. Harvanek,[1,3] Brian Y. Chung,[1] Joanne Y. Yew,[4,5] Herman A. Dierick,[2] Scott D. Pletcher[1]

ing complications associated with mating itself.

In *Drosophila*, sensory manipulations can affect life span, fat storage (as determined by baseline measures of triacylglyceride—TAG), and certain aspects of stress resistance (*2*, *4*). We found that flies exposed to pheromones of the opposite sex showed differences in these phenotypes. Experimental male flies exposed to male donor pheromone had higher amounts of TAG, were sub-

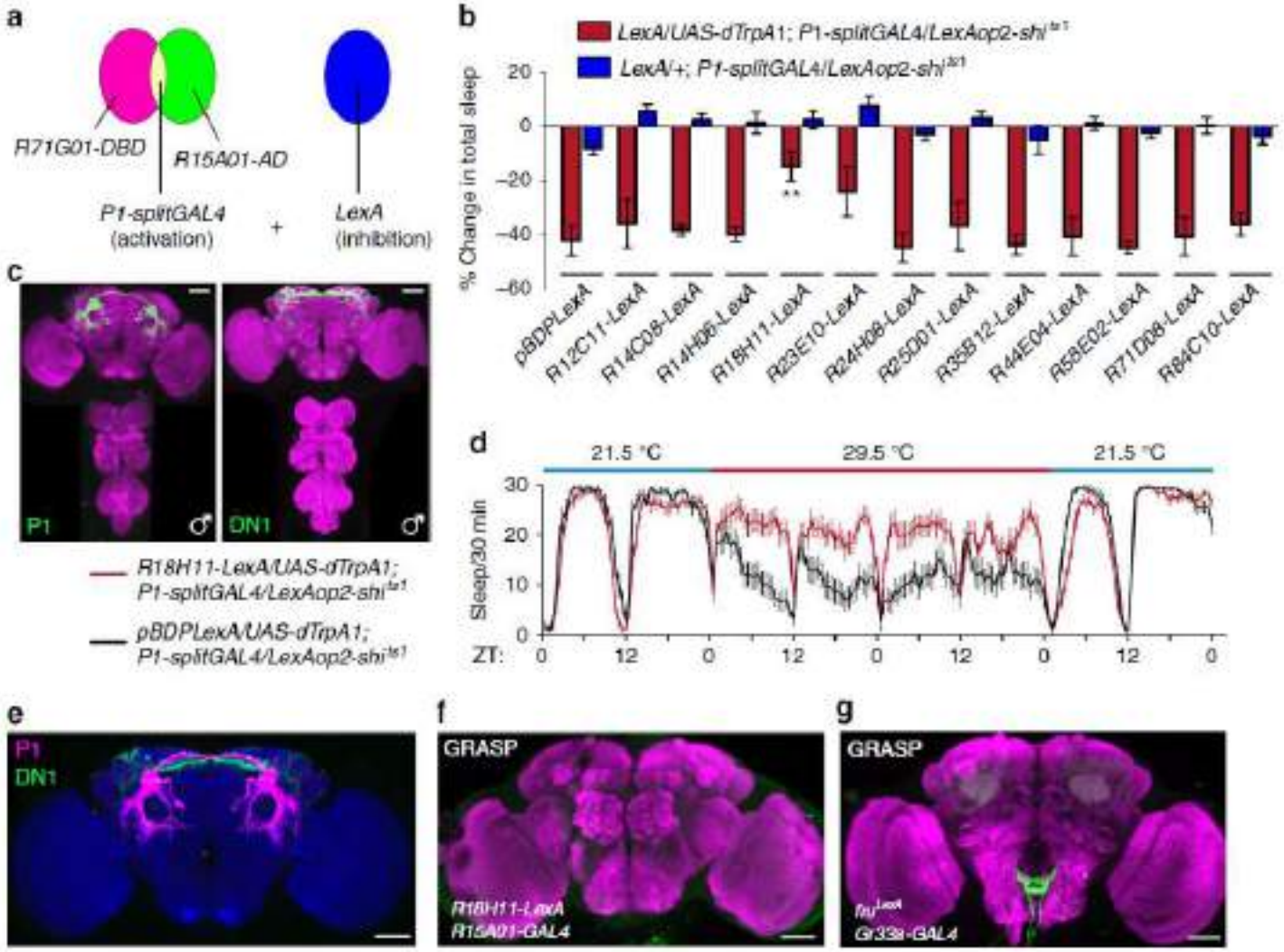
Consequences of ppK23 receptor activation

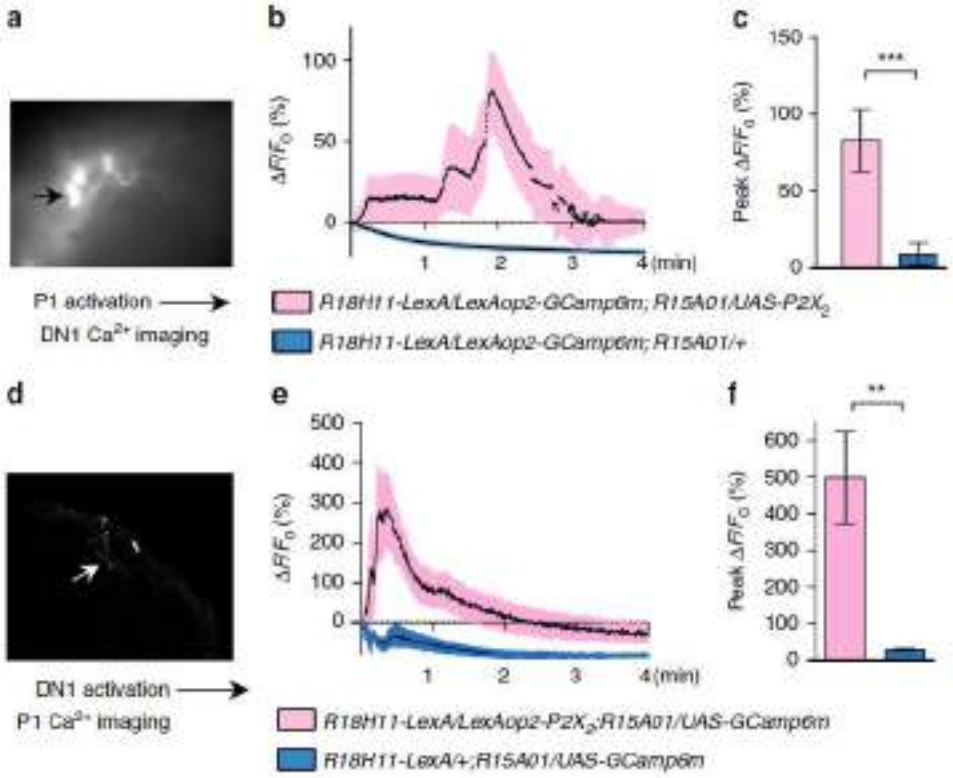
- The loss of triacylglyceride
- An increased susceptibility to stress
- Faster aging
- A significantly higher expression of NPF

?

Courtship and sleep-devoted circuits may interact to balance these competing drives

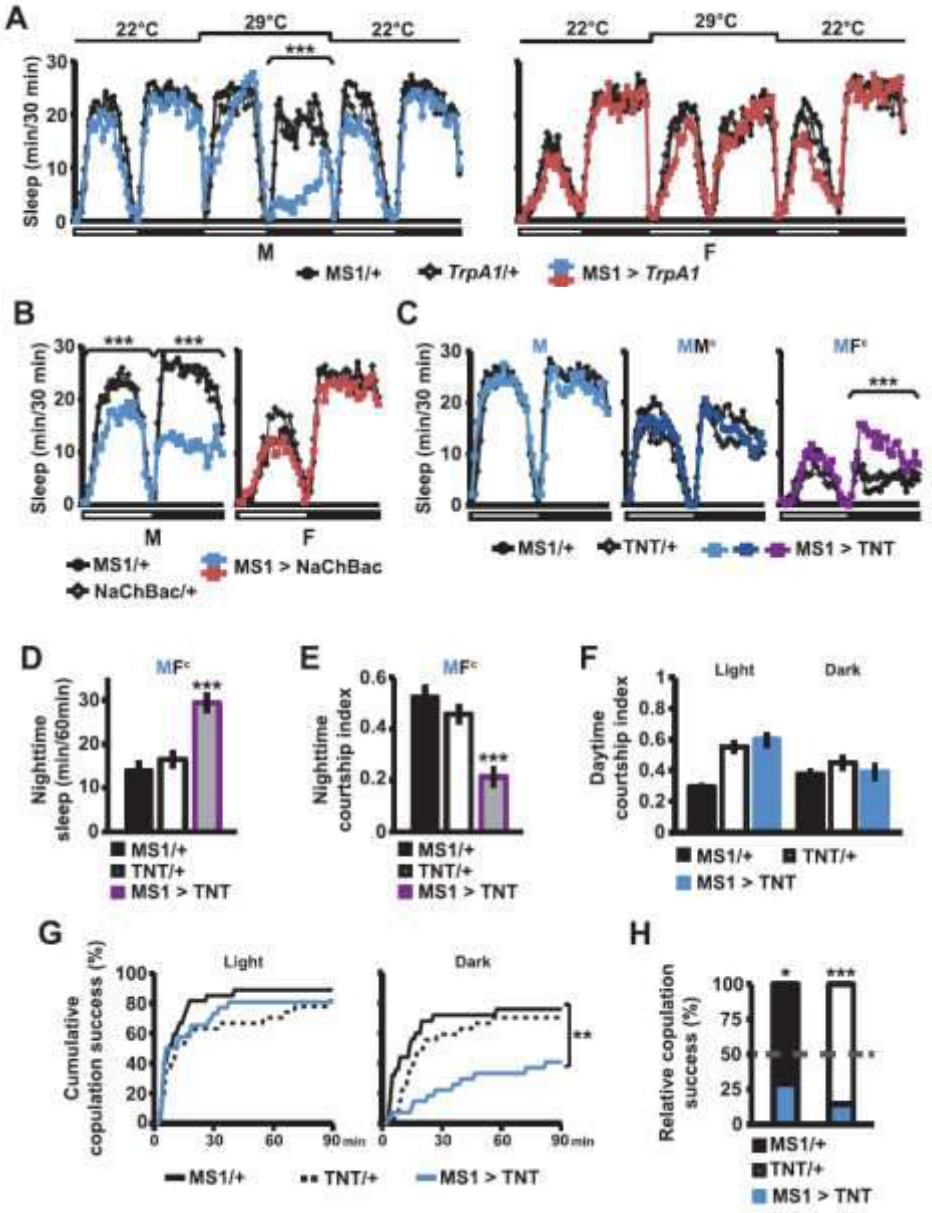
P1 regulates male sleep through DN1 neurons, and form mutually excitatory connections

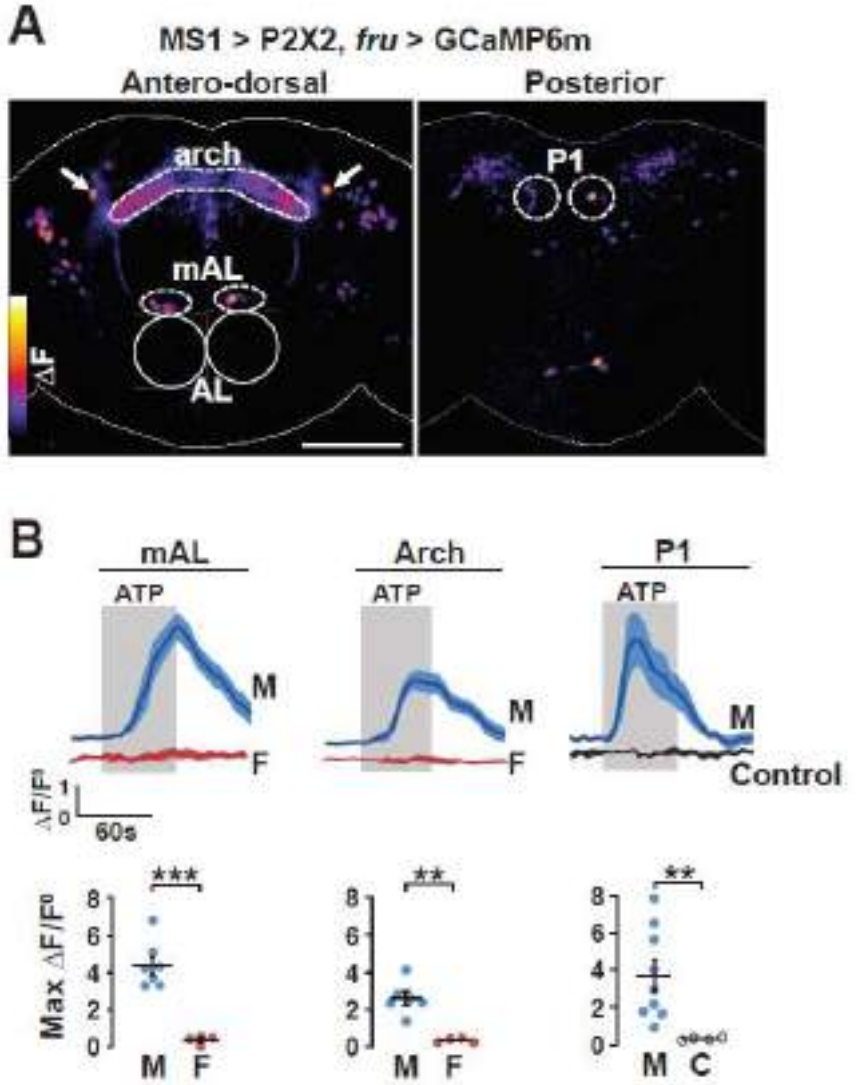




Chen *et al*., *Nat. Commun.* 2017

Octopaminergic neurons Male-Specific One is upstream of the P1 neurons

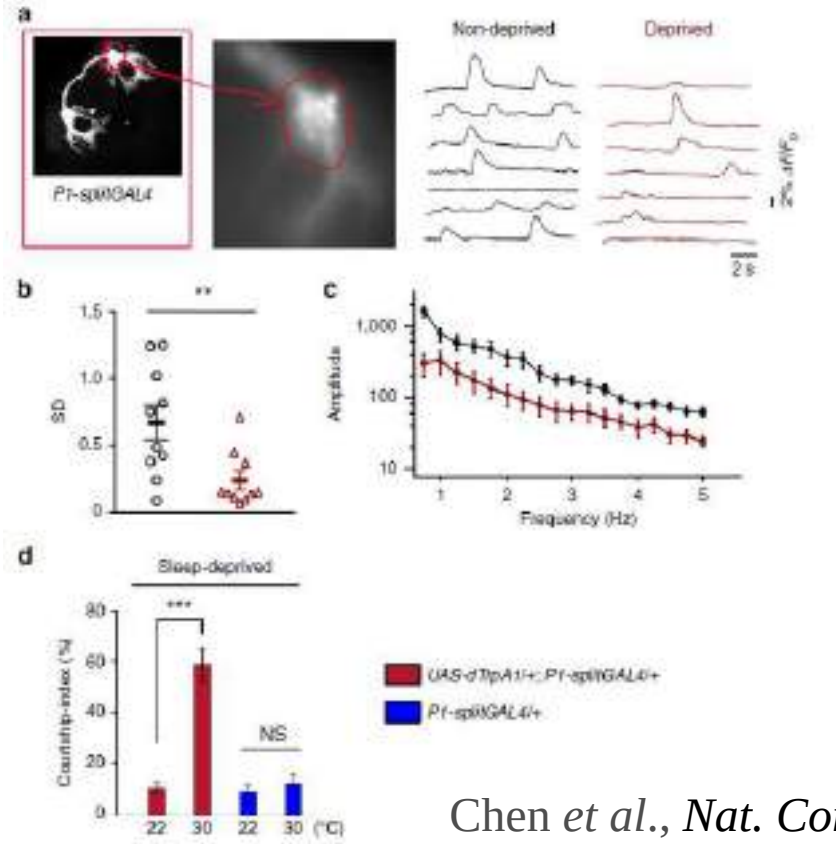




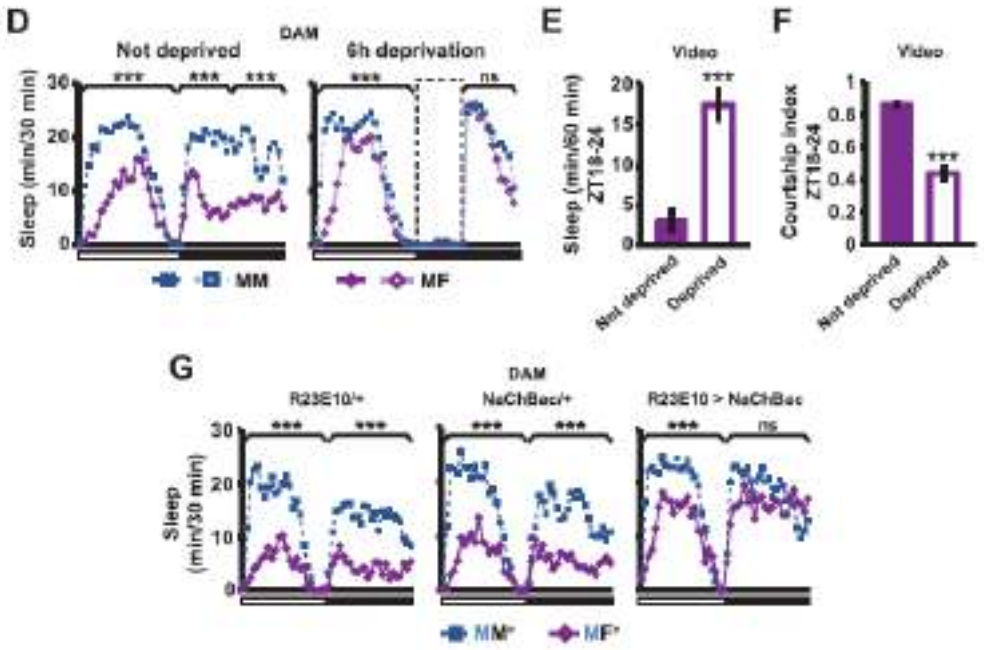
Machado *et al*., *eLife*. 2017

Does sleep in turn affect courtship in male Drosophila?

Excessive sleep deprivation inhibits mating behavior



Chen *et al*., *Nat. Commun*. 2017

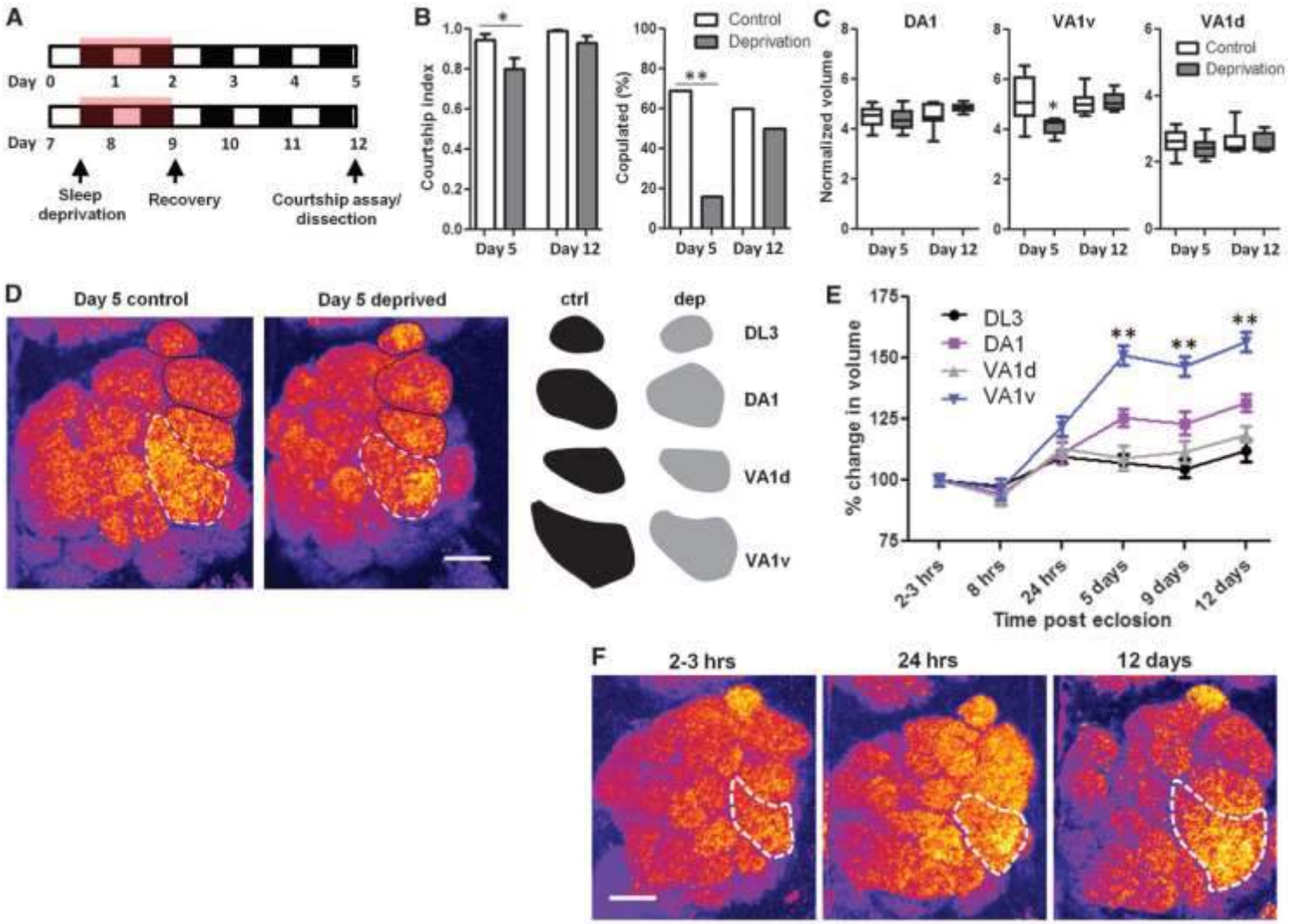


Machado *et al*., *eLife*. 2017

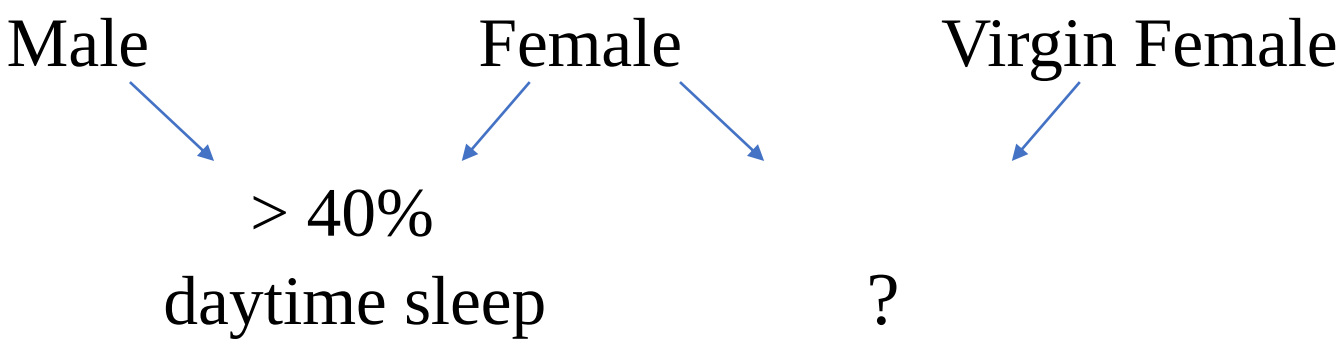
Science
AAAS

A Critical Period of Sleep for Development of Courtship Circuitry and Behavior in *Drosophila*
Matthew S. Kayser *et al.*
Science **344**, 269 (2014);
DOI: 10.1126/science.1250553

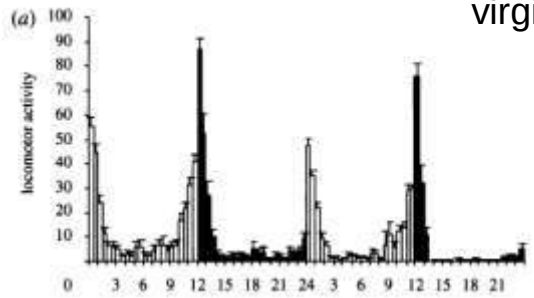
Sleep in young flies is required for courtship behaviors and circuitry development



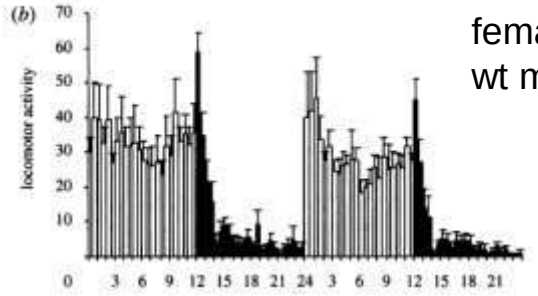
Kayser *et al.*, *Science*. 2014


Male
Female
Virgin Female
> 40%
daytime sleep
?

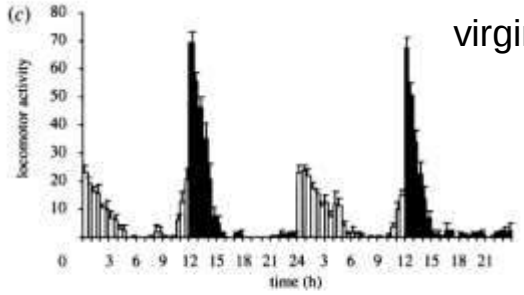
The sex peptide regulates arousal after mating in female *Drosophila*



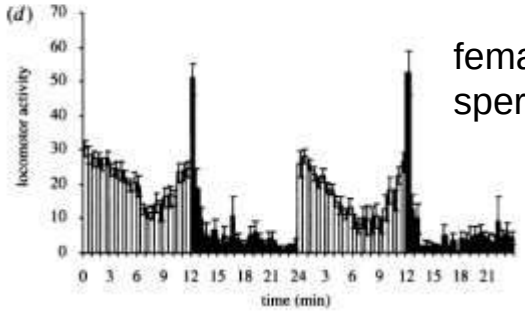
virgin males



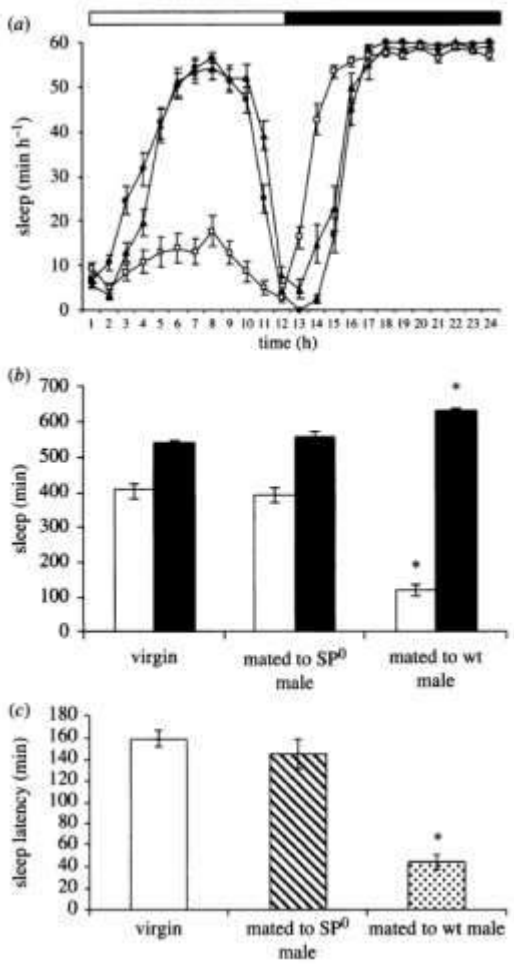
females mated to wt male



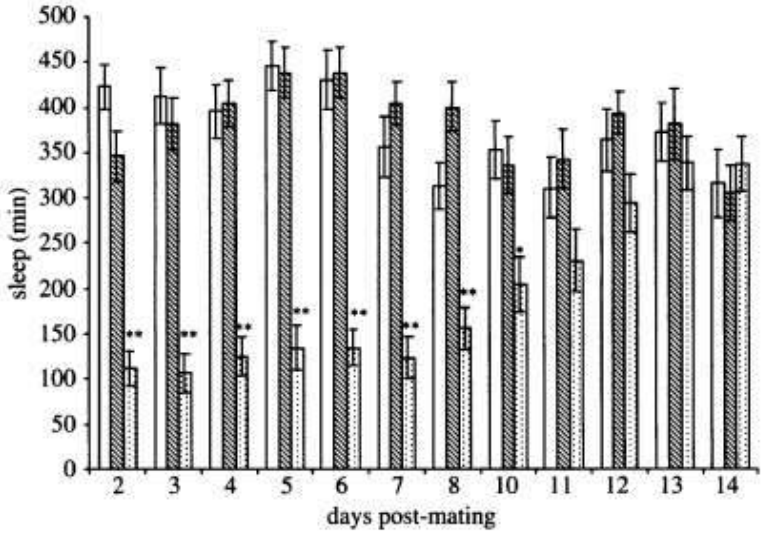
virgin females



females mated to spermless male



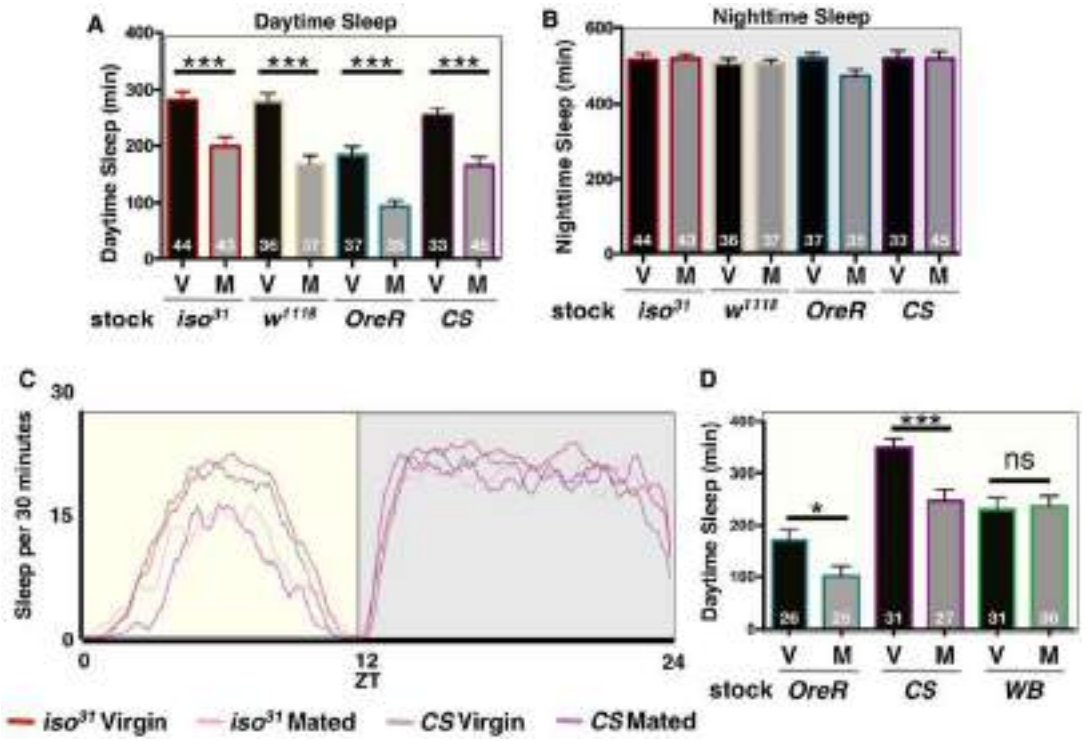
filled circle, virgin;
filled triangle, mated to SP° male;
open square, mated to wt male

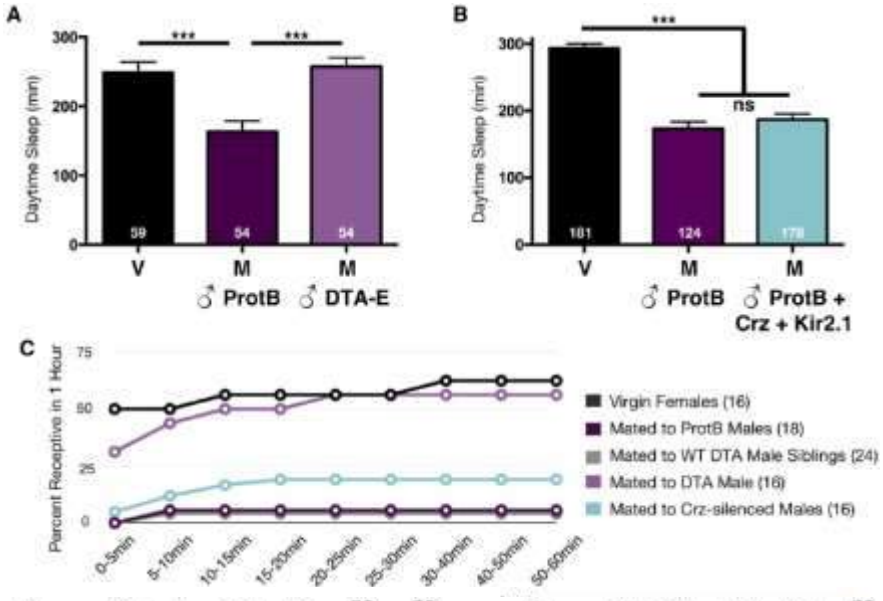


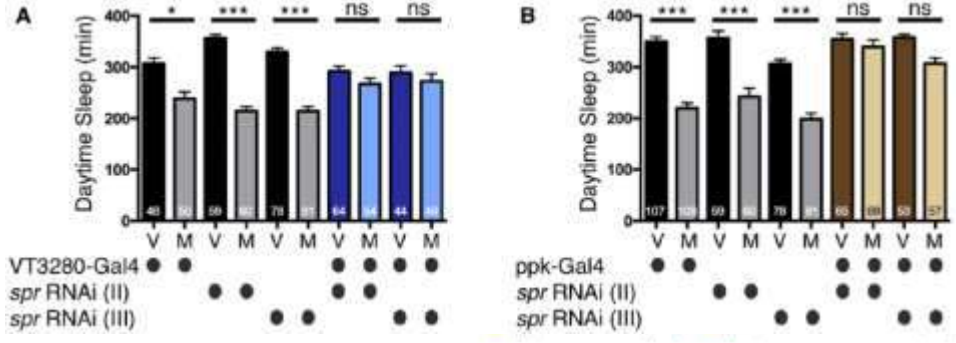
Day: SP inhibits sleep
Night: SP promotes sleep

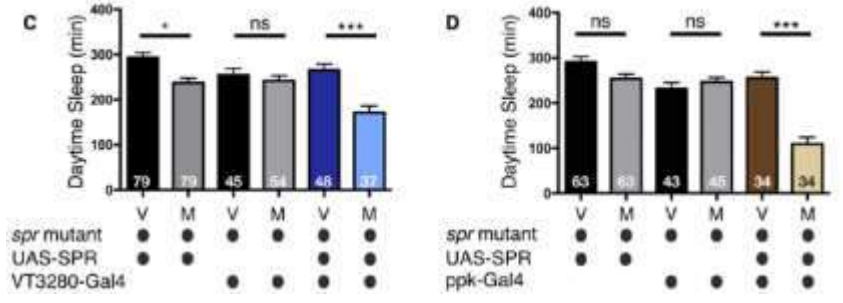
Isaac *et al.*, *Proc. Biol. Sci.* 2010

Sex peptide and Sex peptide receptor contribute to post-mating decreases in female sleep





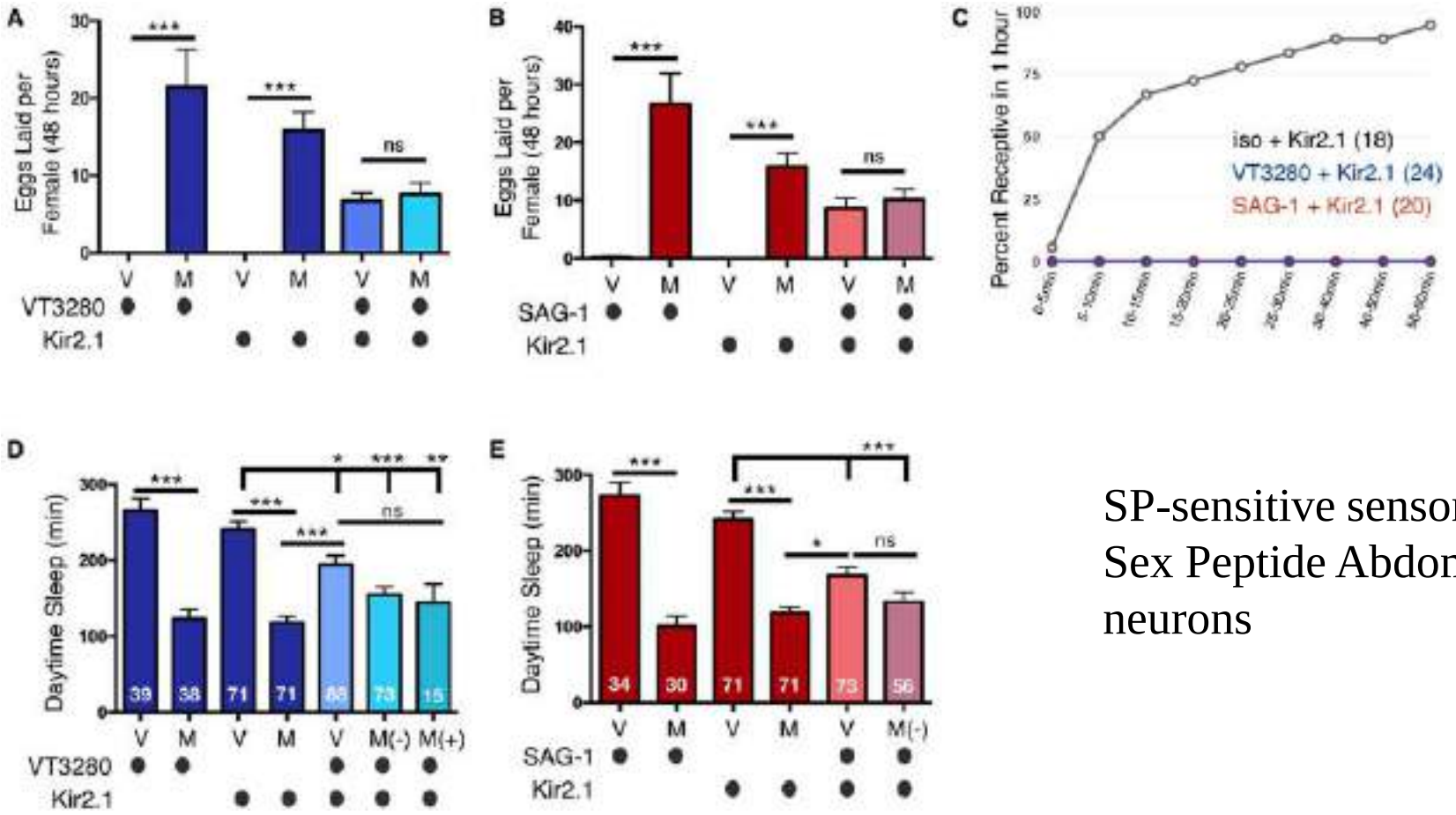




abdominal ganglion: Abg
DTA-E: males fail to produce seminal fluids
Corazonin (crz): silenced males do not transfer sperm
ProtB: GFP-sperm
Sex peptide receptor: SPR

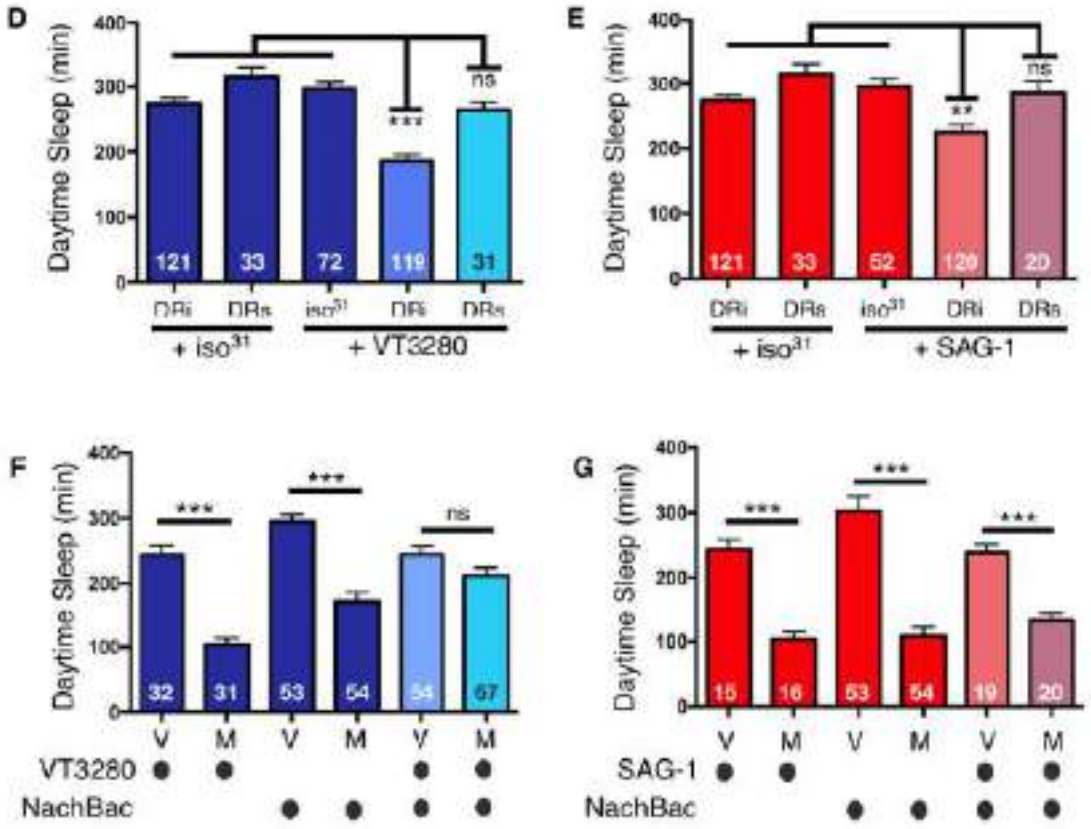
Garbe *et al.*, *J. Biol. Rhythms*. 2016

Chronically silencing the SPSN-SAG post-mating circuit decreases female daytime sleep



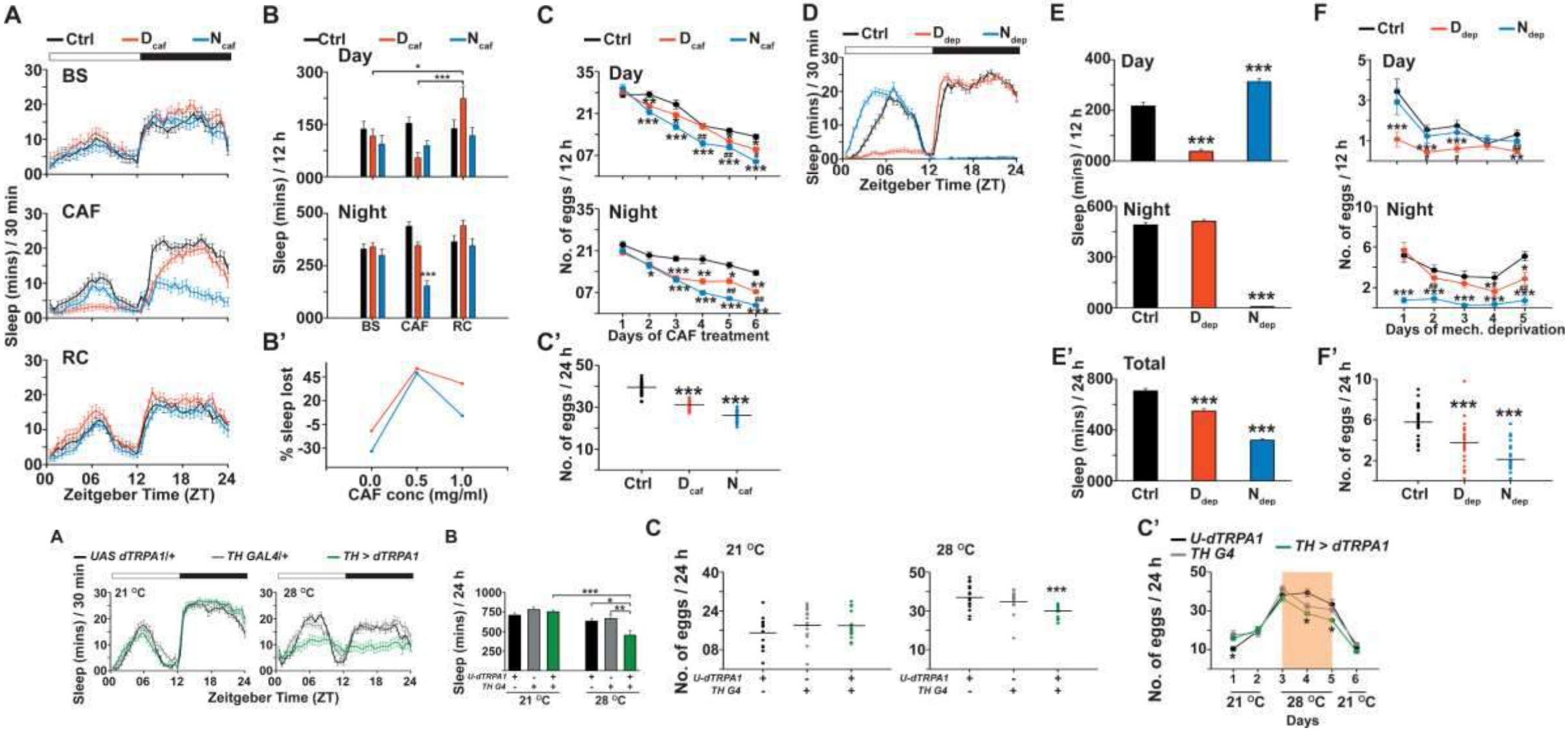
SP-sensitive sensory neurons (SPSN)
Sex Peptide Abdominal Ganglion (SAG) neurons

Acutely silencing the SPSN-SAG post-mating circuit decreases daytime female sleep



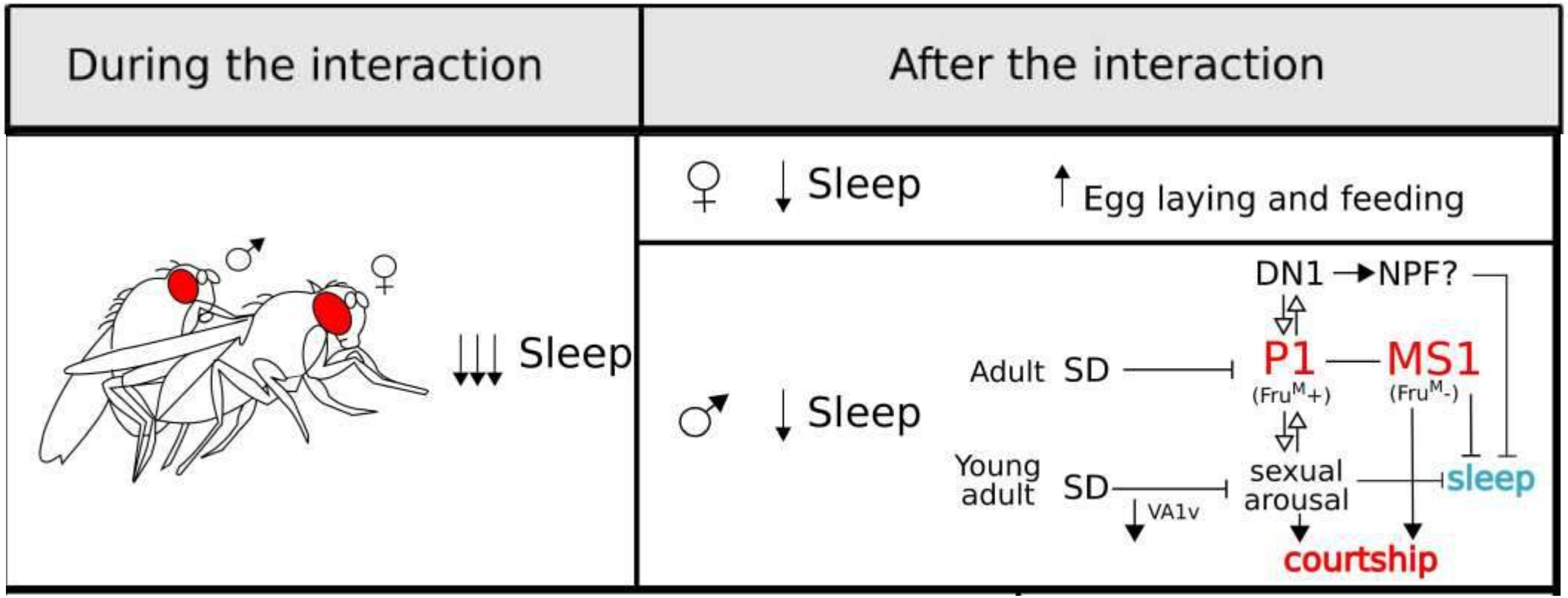
DREADDs [Designer Receptors Exclusively Activated by Designer Drugs]

Sleep deprivation by caffeine and mechanical disturbance of w^{1118} flies results in decrease of egg output



Potdar *et al*. *J. Exp. Biol*. 2018

Conclusion


During the interaction
After the interaction
♀
Sleep
Egg laying and feeding
♂
Sleep
Sleep
DN1
NPF?
Adult
SD
P1
(Fru^{M}+)
MS1
(Fru^{M}-)
Young adult
SD
VA1v
sexual arousal
sleep
courtship

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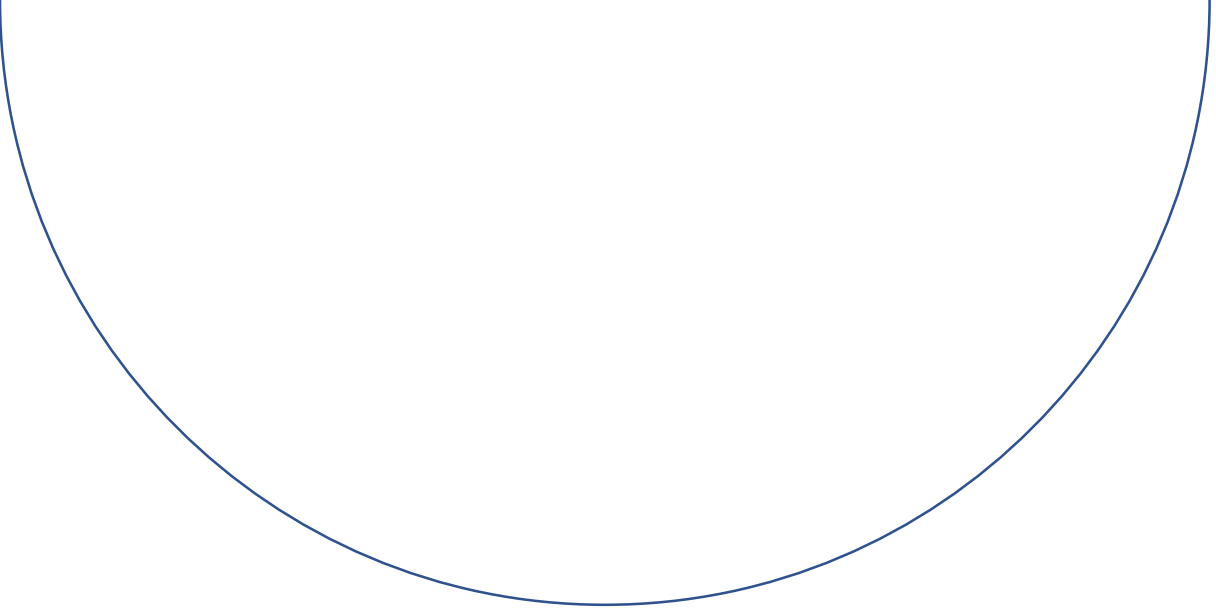
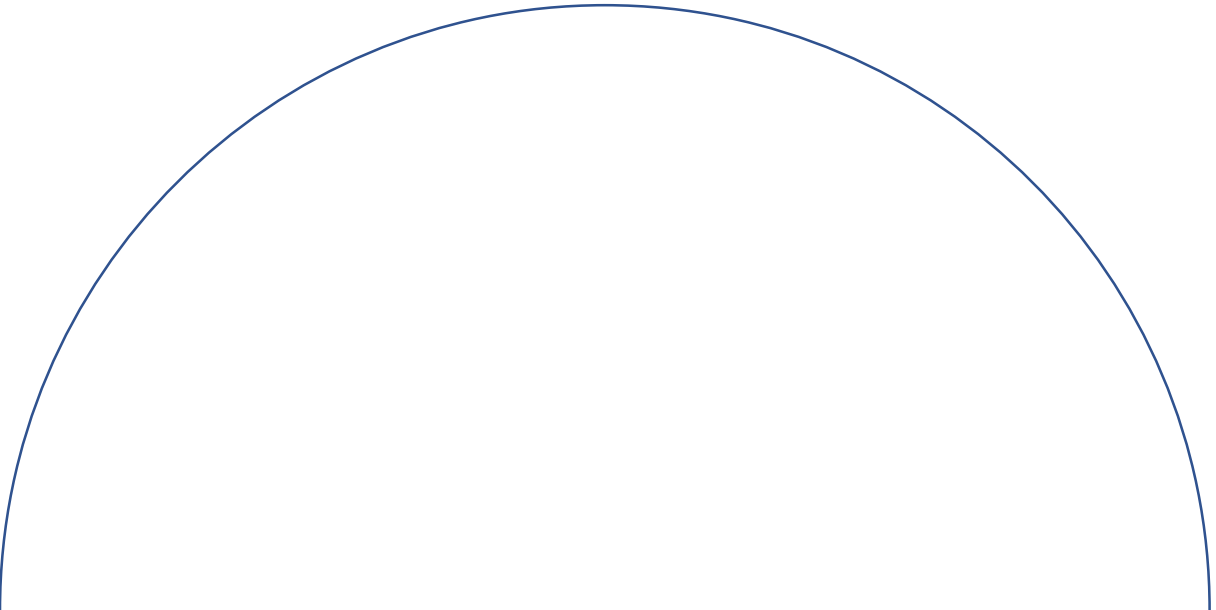
THANKS!





C I R C U I T
for
S L E E P

The clocks

Circuit for circadian cycle

- All of them have *per* expression, most of them have *pdf* expression.
- Their activity depends on time of day.
- LNv，LNd，DN1

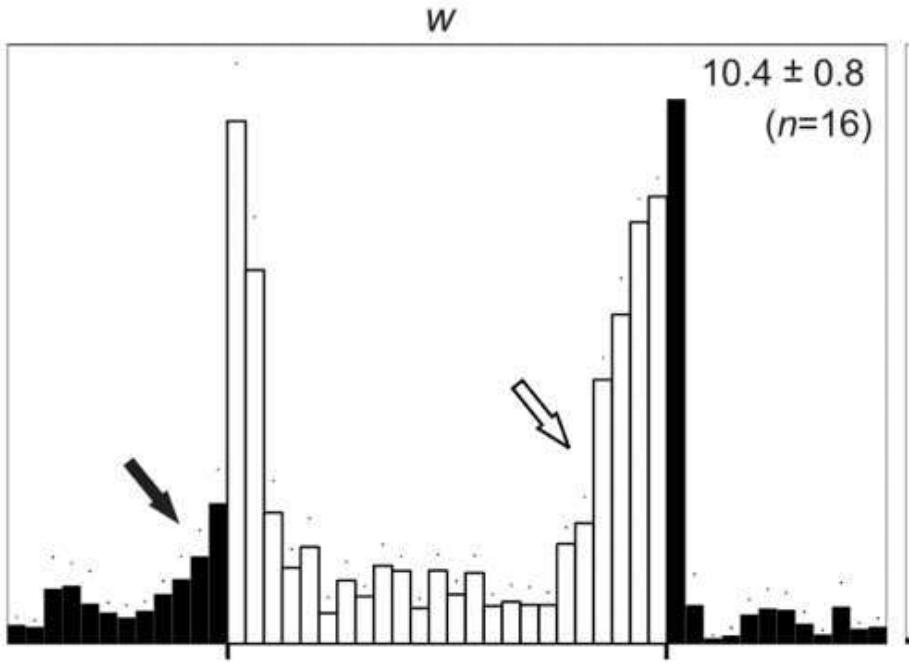
The modulators

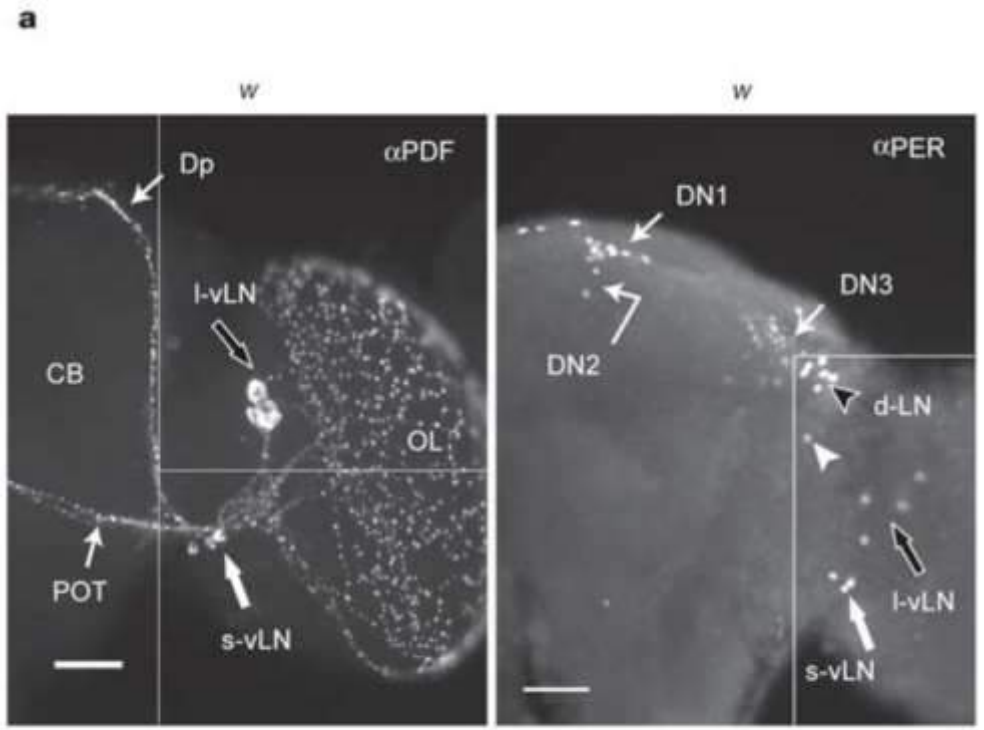
Circuit for sleep homeostasis and other aspects

- Modulate sleep in other dimension like homeostasis, stimulation-responding arousal and sleep drive.
- MB，FB ，EB

2 systems

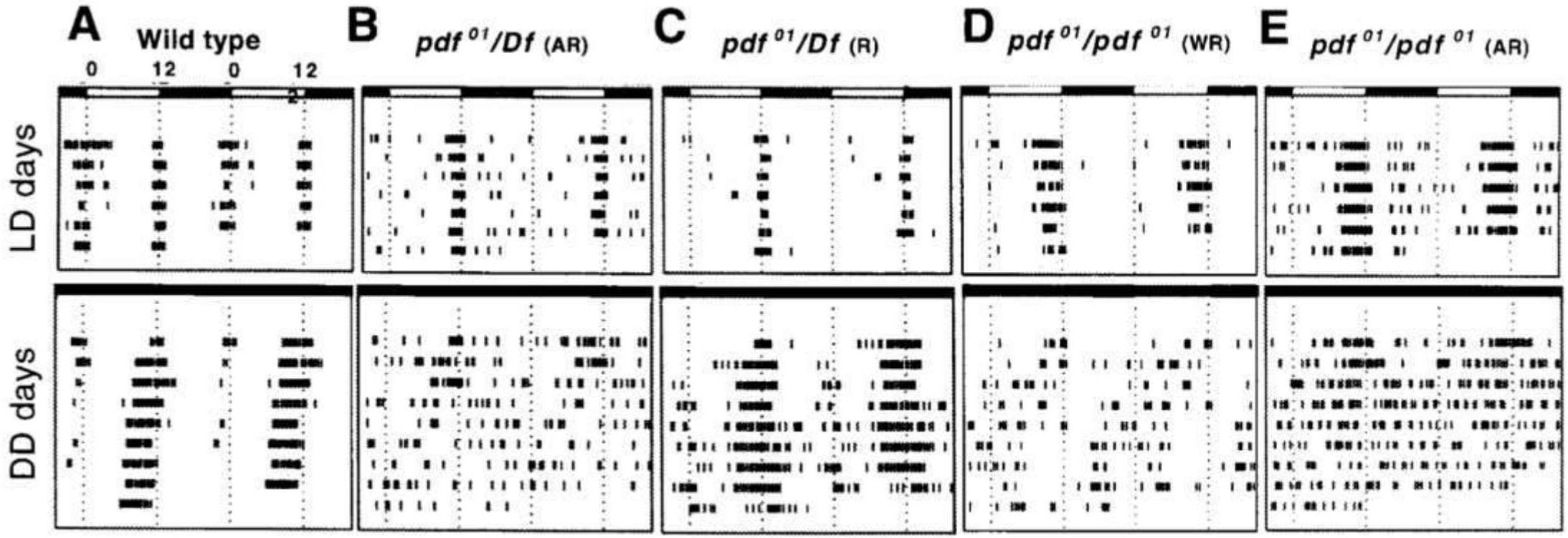
1. the clocks





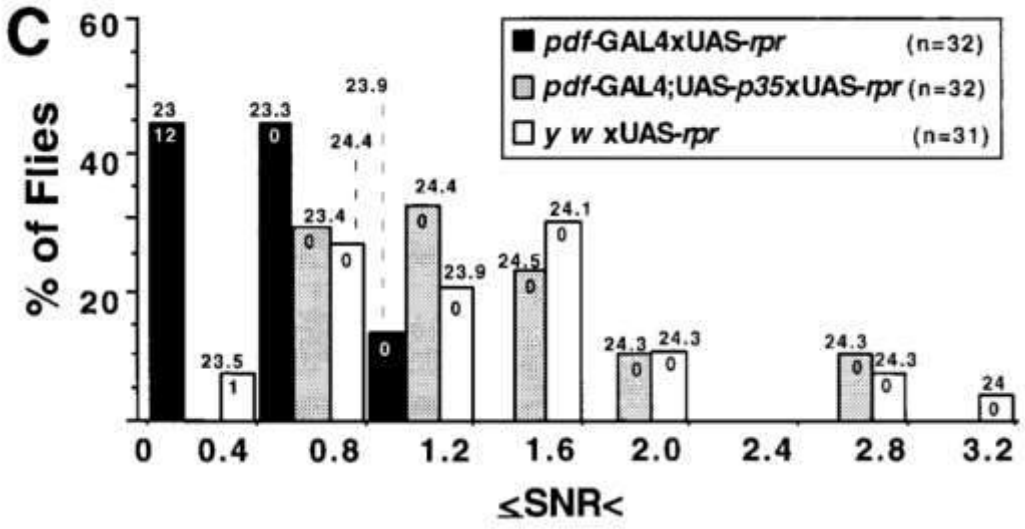
(Grima *et.al* ,2004)

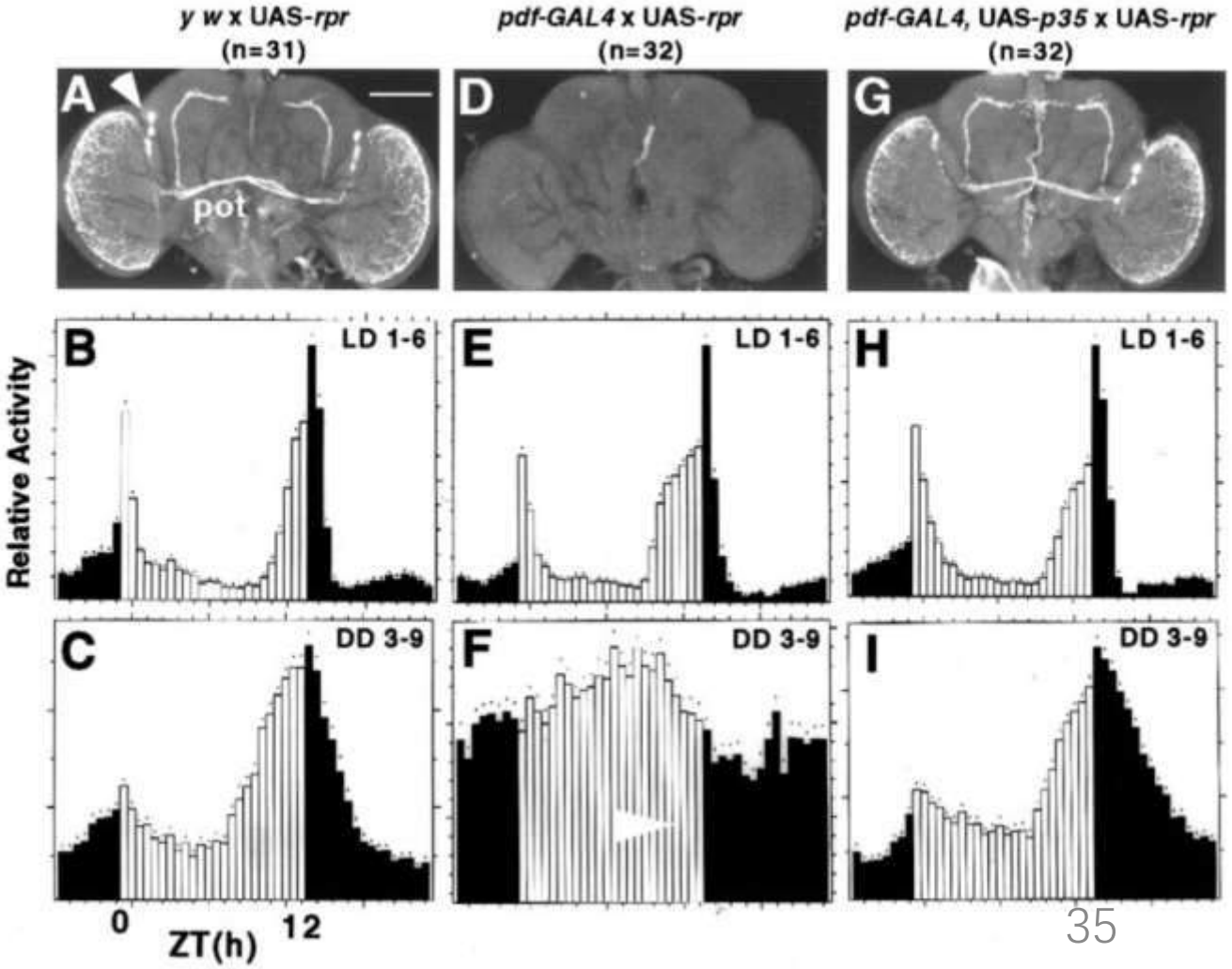
pdf (*pigment dispersing factor*) is responsible for morning locomotive activity



(Renn *et.al* , 1999)

pdf expressing LNvs(Ventral Lateral neurons) are crucial to circadian cycle both in LD and DD

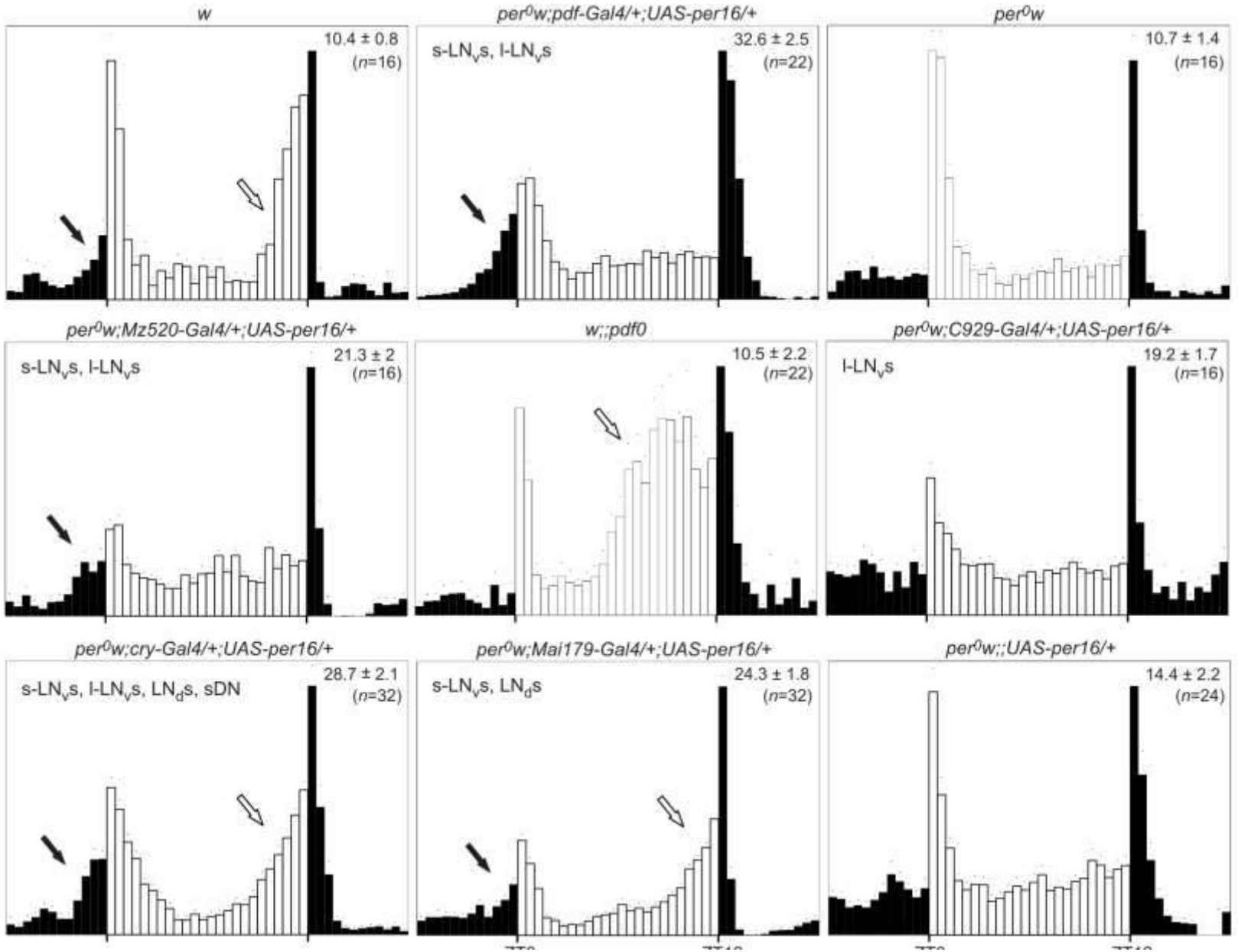




(renn *et.al* , 1999)

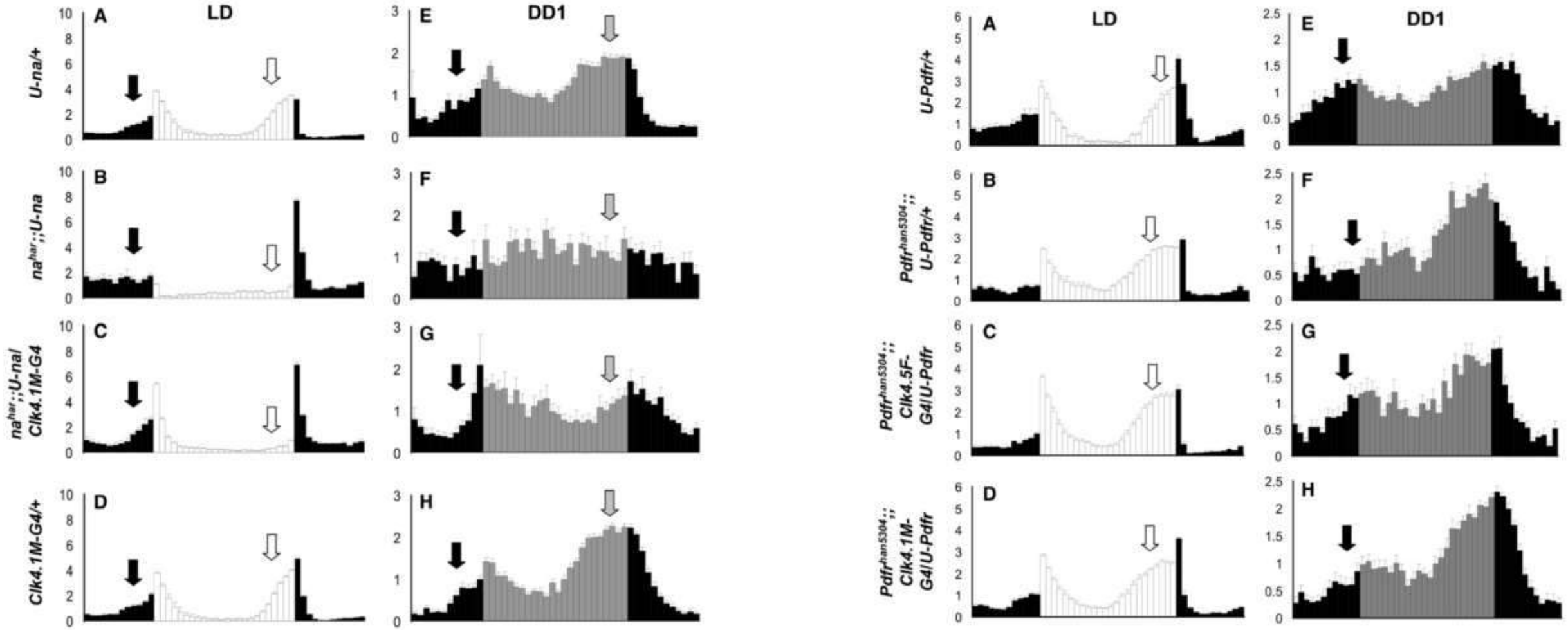
What about evening activity?

PDF-negative LNds (dorsal lateral neurons) are the key to early evening activity.



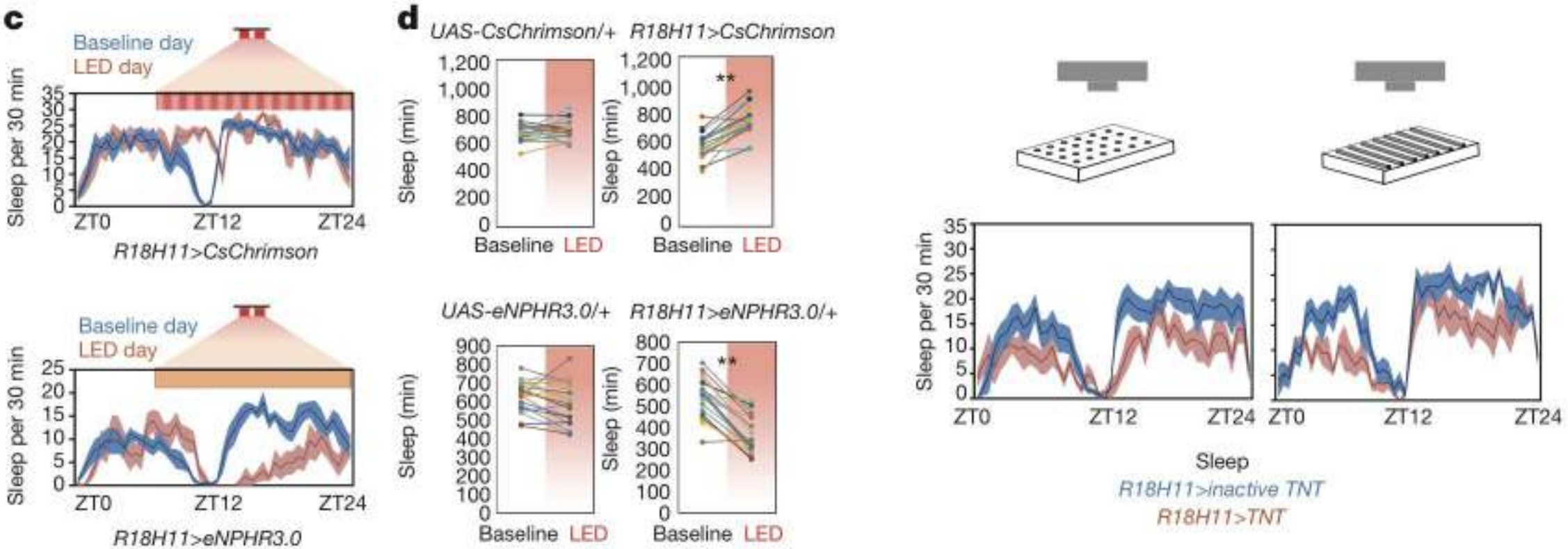
(Grima *et.al* ,2004)

Rescue *na* in DN1 restores light-on arousal response and is sufficient for morning anticipatory behavior



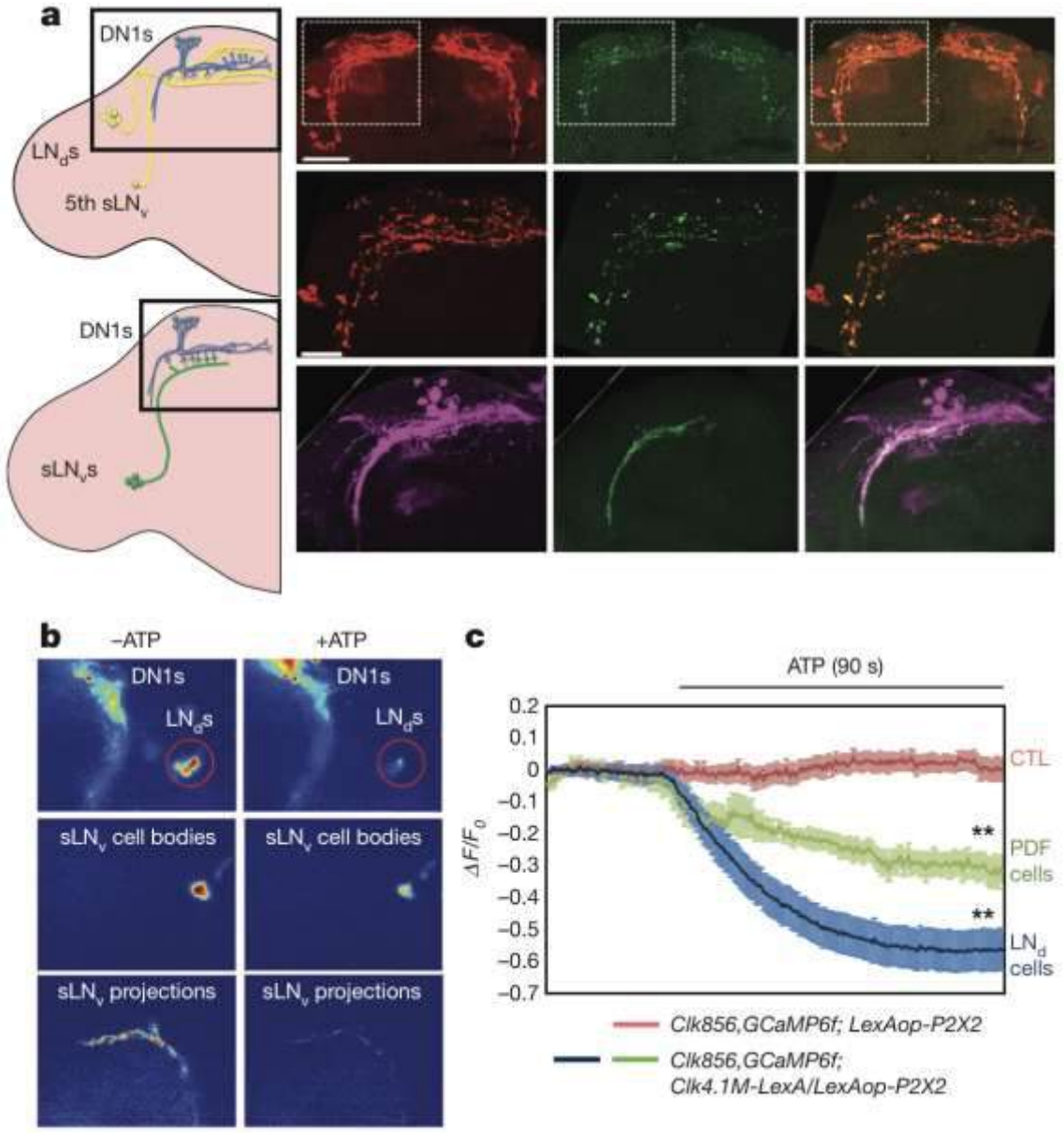
(zhang *et.al* ,2010)

DN1 activation is sleep-promoting



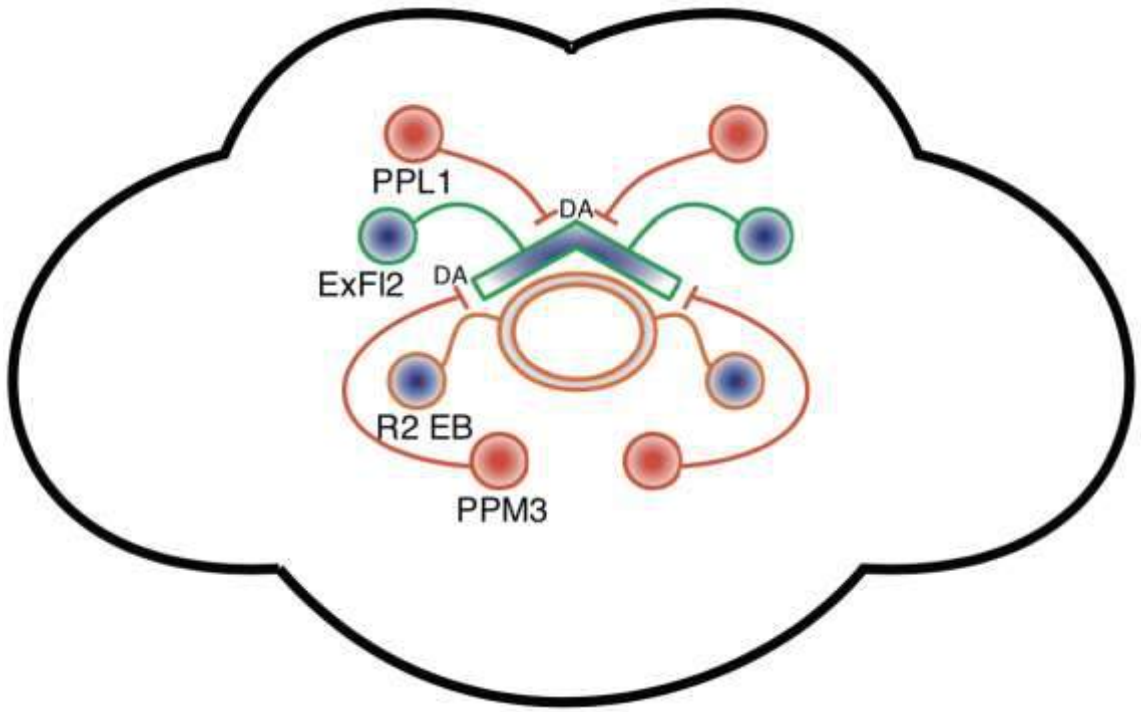
(guo *et.al* 2016)

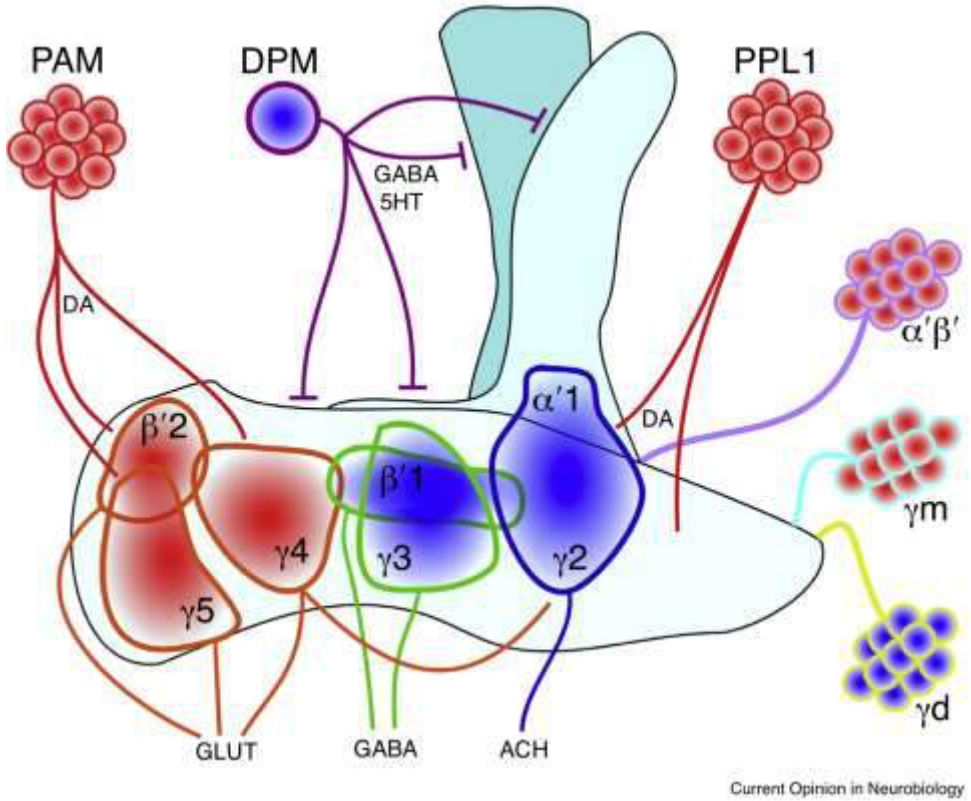
DN1s directly contact and reduce calcium levels of LNds and pdf-cells



(guo *et.al* 2016)

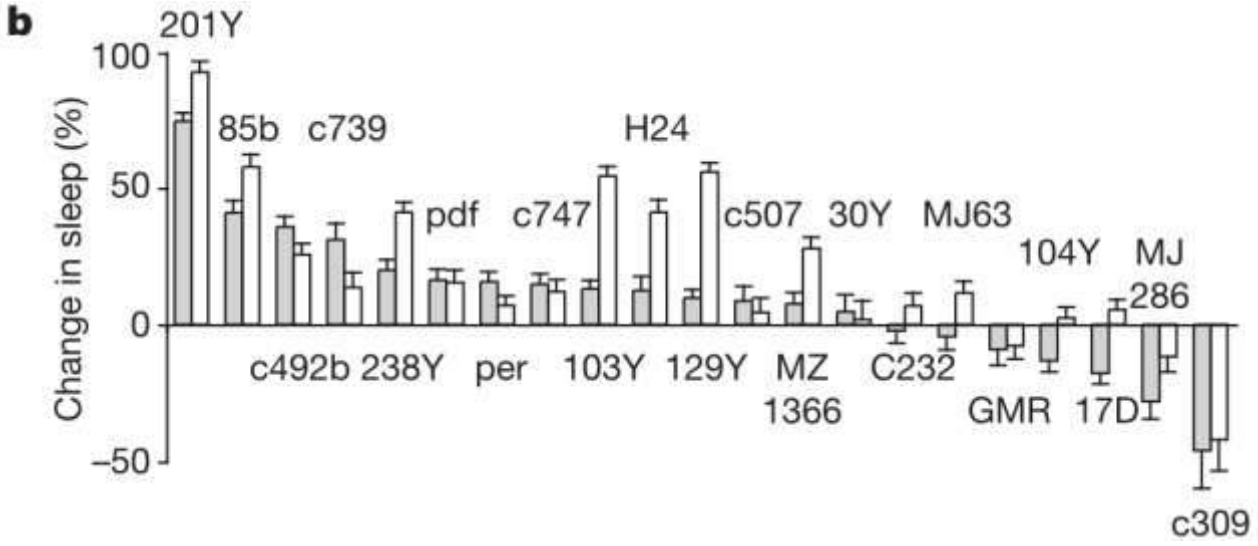
2. the modulators

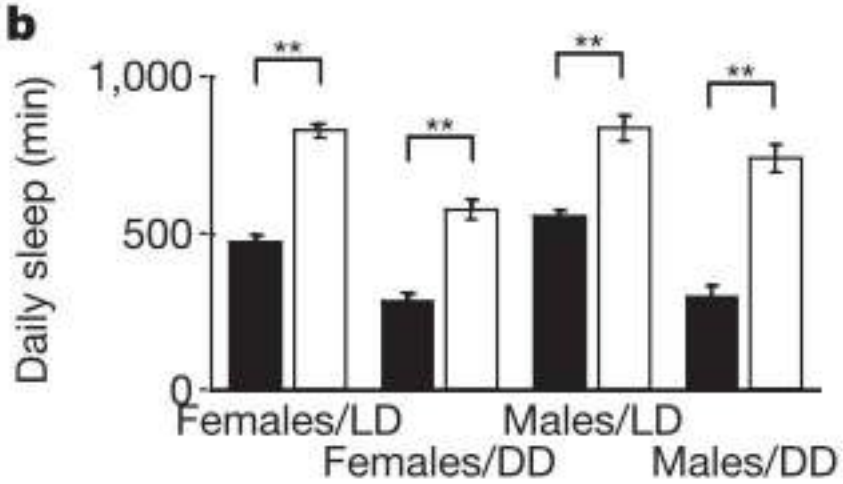


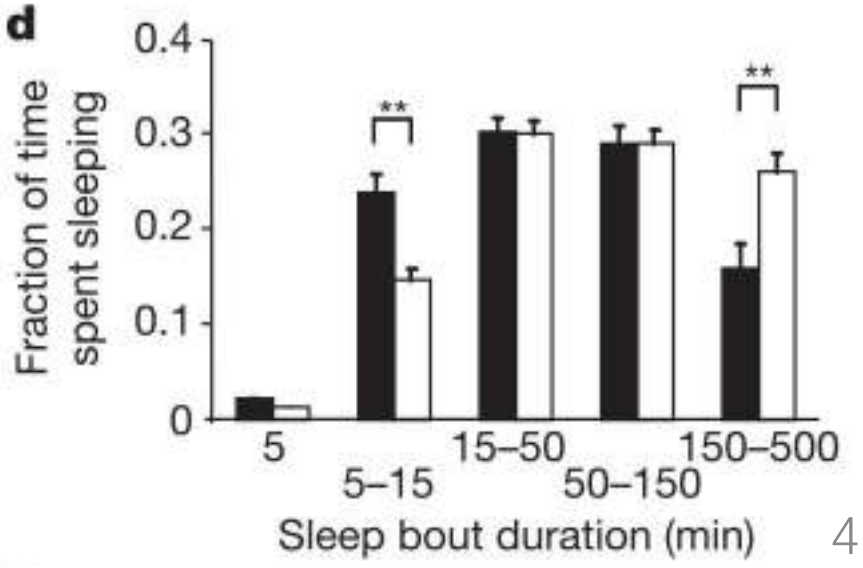


Red for wake-promoting, blue for sleep-promoting (Artiushin *et.al* 2017)

1 MB Inducible expression PKA in MB leads to shorter sleep bout duration and longer sleep accumulation





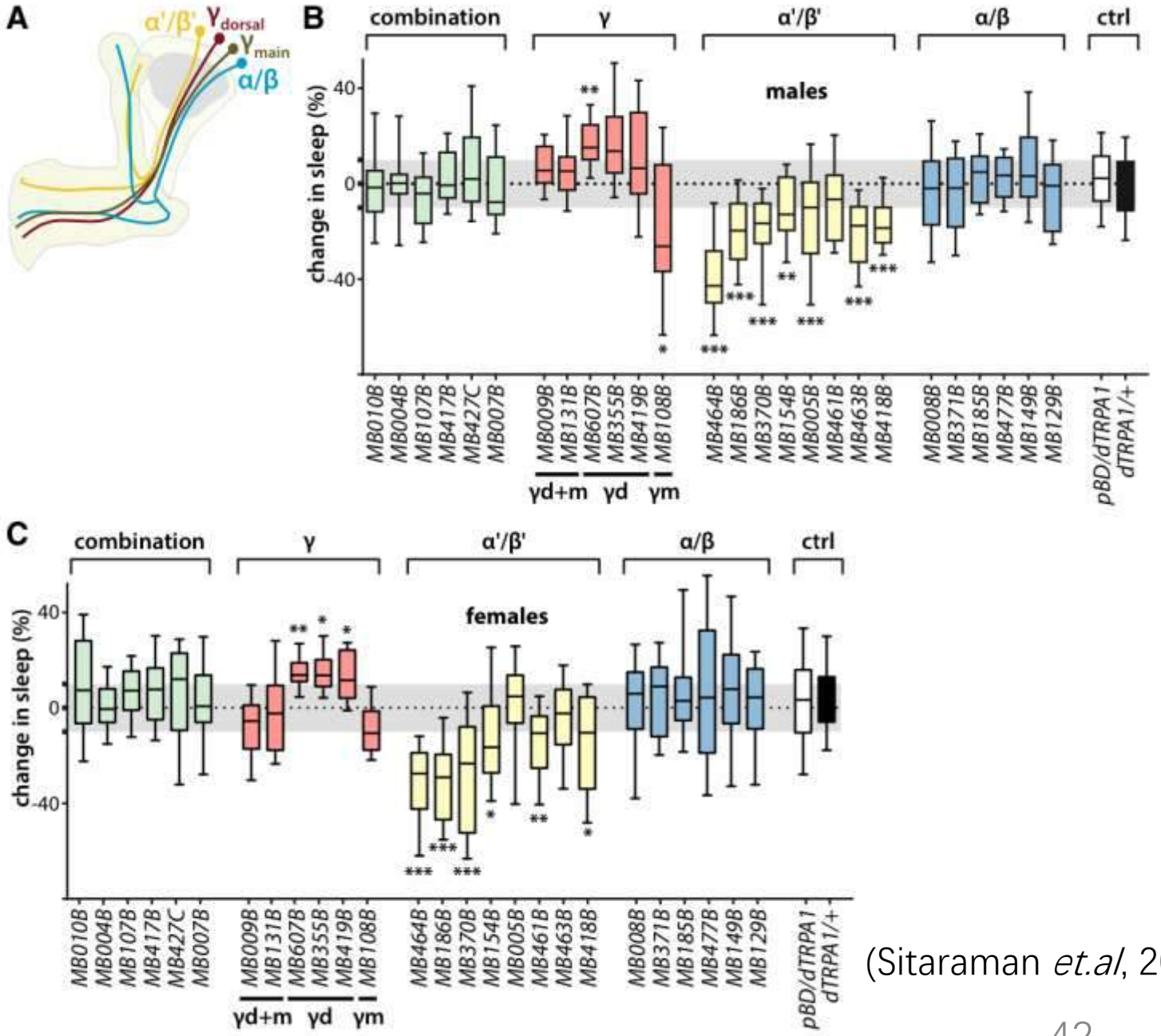


"201Y is expressed largely in the g lobes and the core region of the a/b lobes of the MBs, whereas c309 is expressed in the a/b and g lobes but not in the core region of the a/b lobes ."

(Joiner *et.al* , 2018)

Thermo activation in γ-lobe increases sleep time.

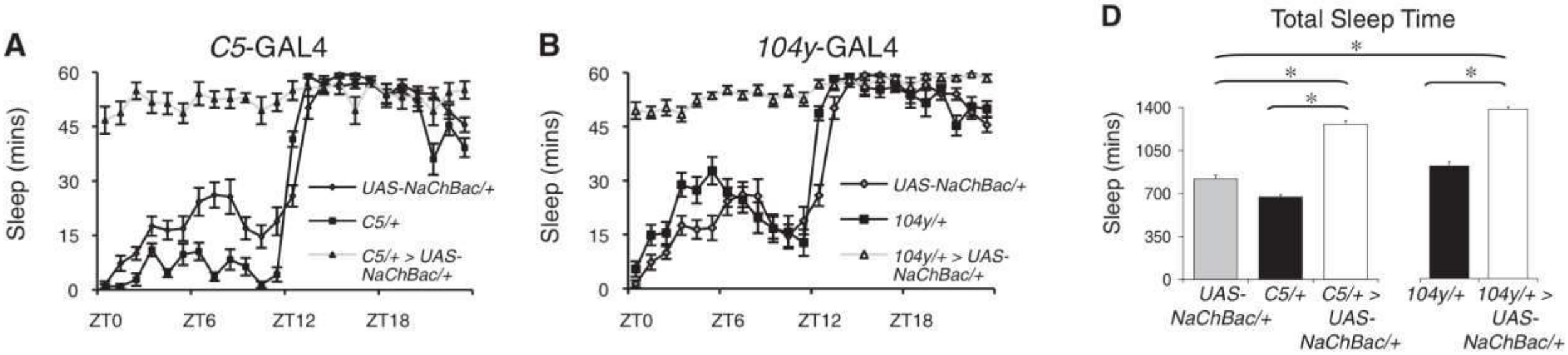
Whereas in α-lobe and β-lobe decreases sleep time.



(Sitaraman *et.al*, 2015)

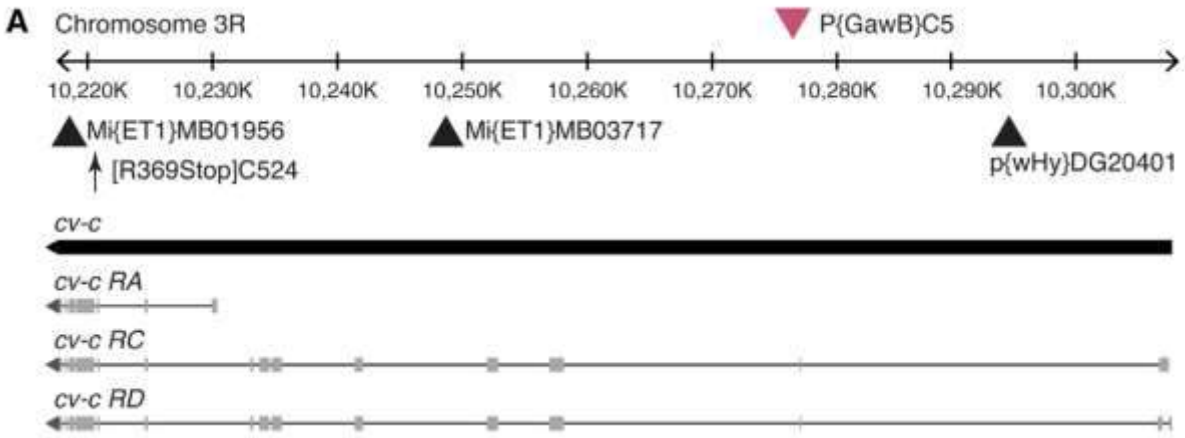
2 FB

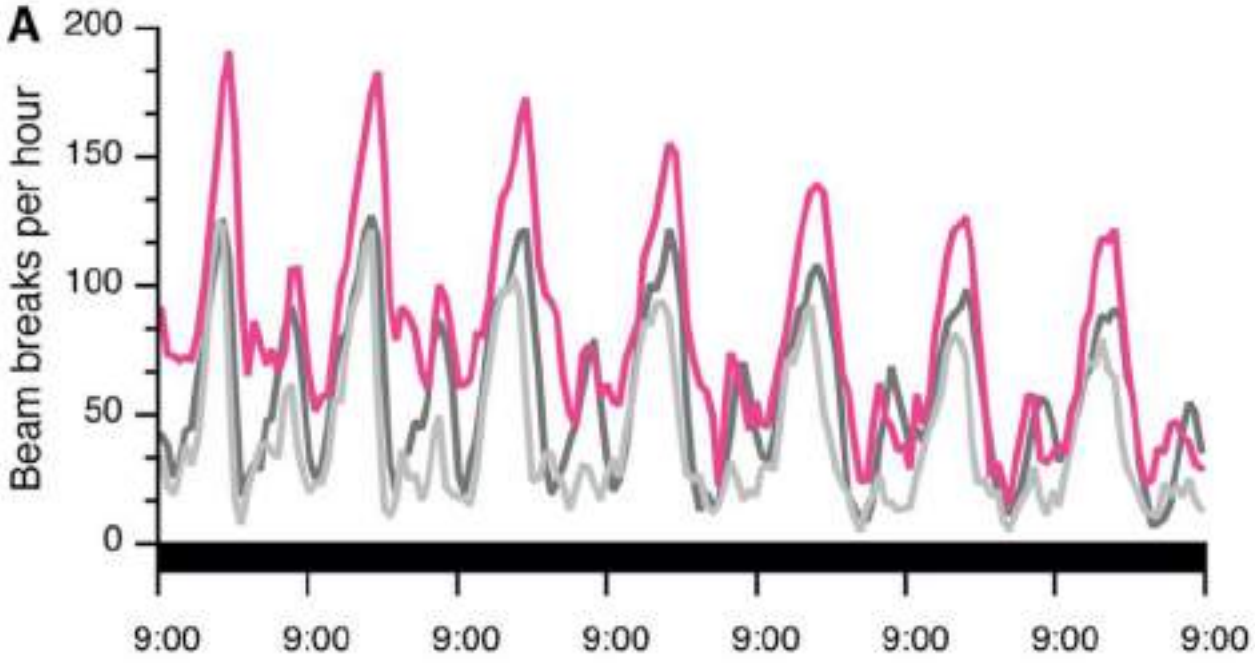
Fan-shaped body activation increases total sleep time

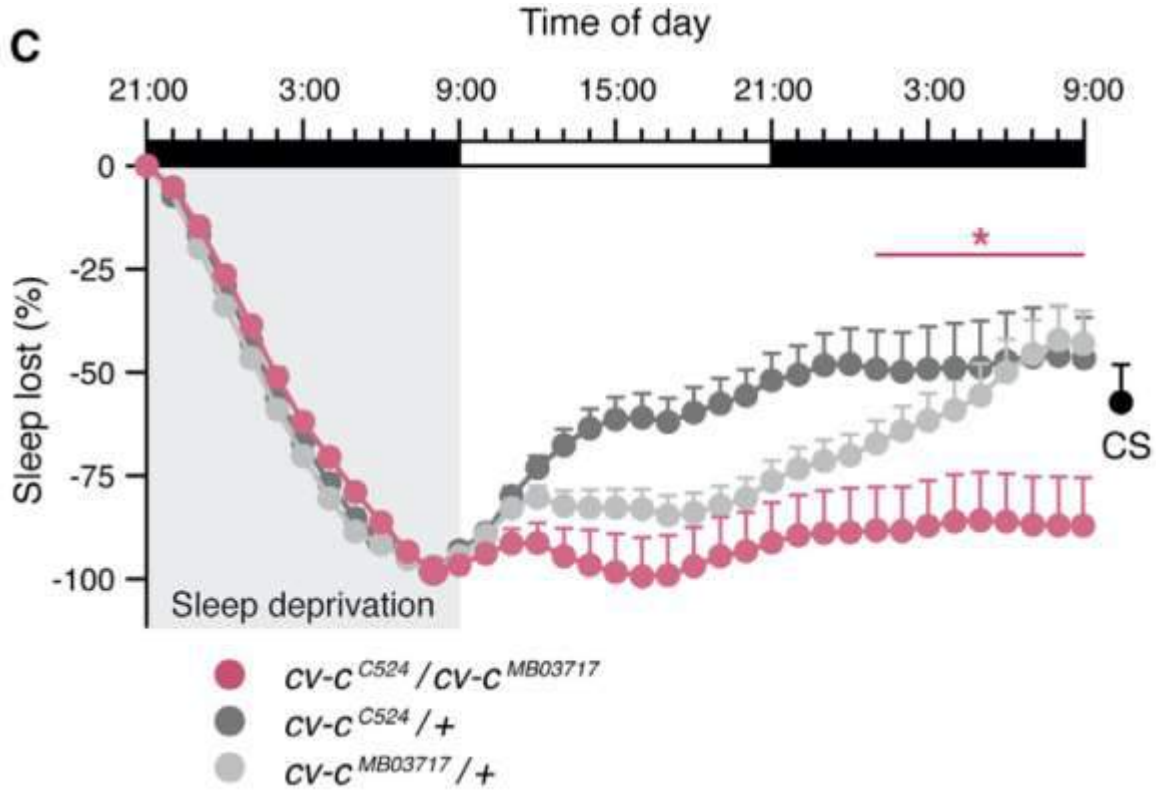


(Donlea *et.al* , 2011)

The P element insertion site of *C5-GAL4* lies in *crossveinless* (*cv-c*) intron
Mutations in *cv-c* impair homeostatic sleep regulation

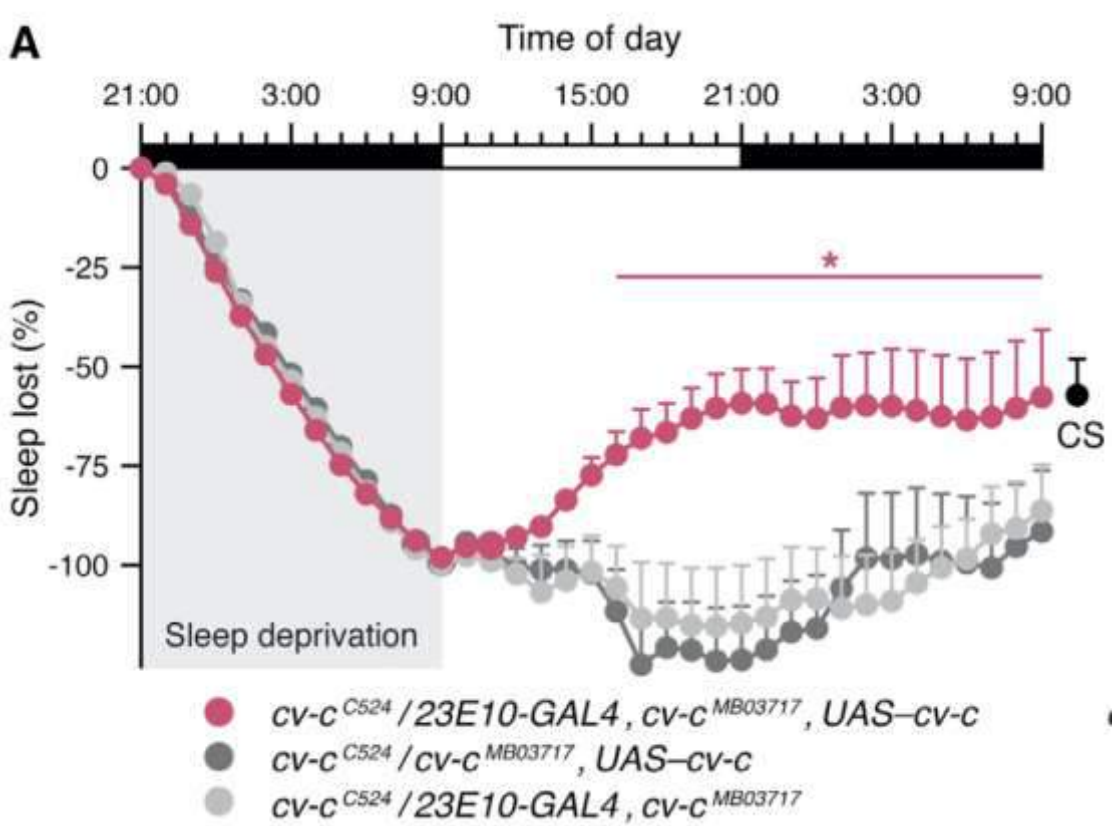


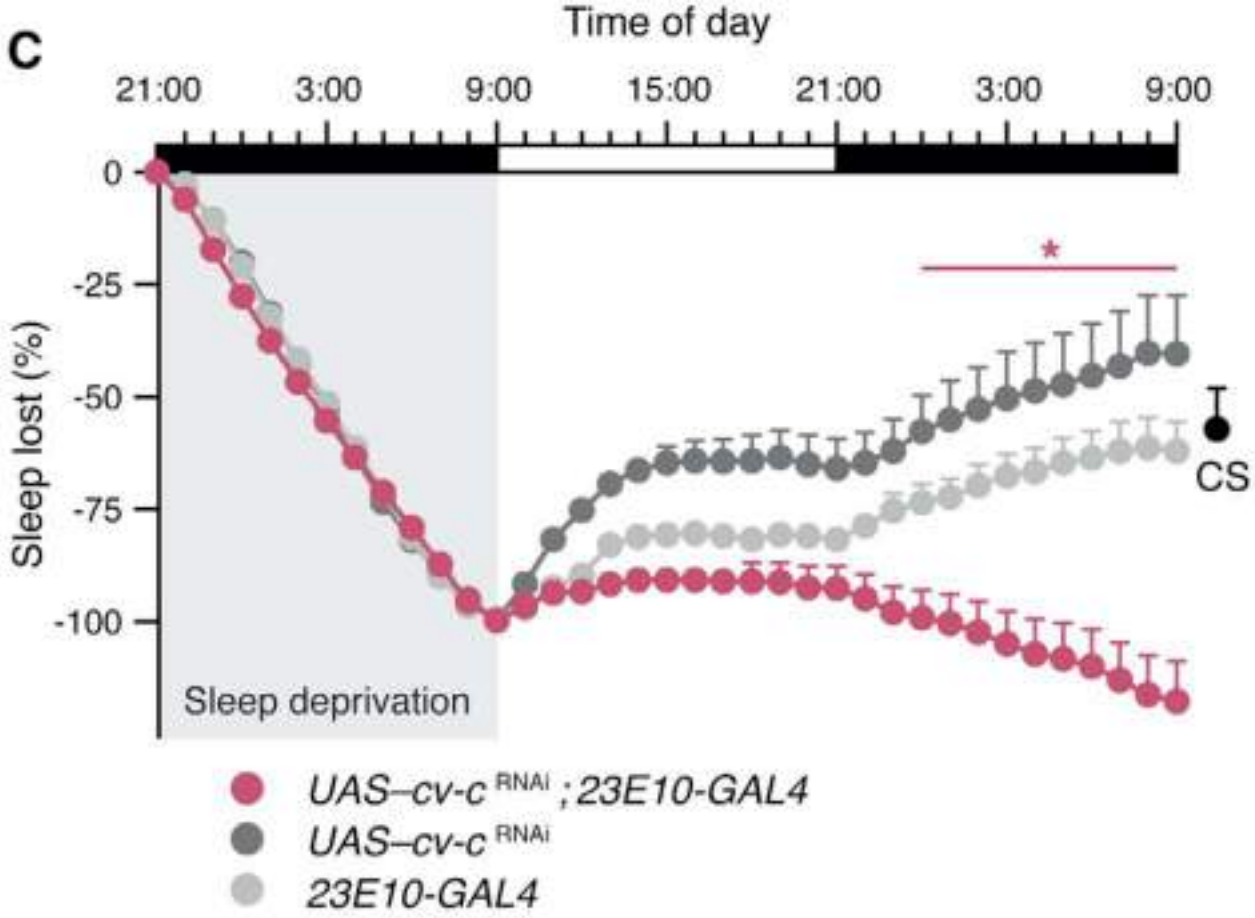




(Donlea *et.al* , 2014)

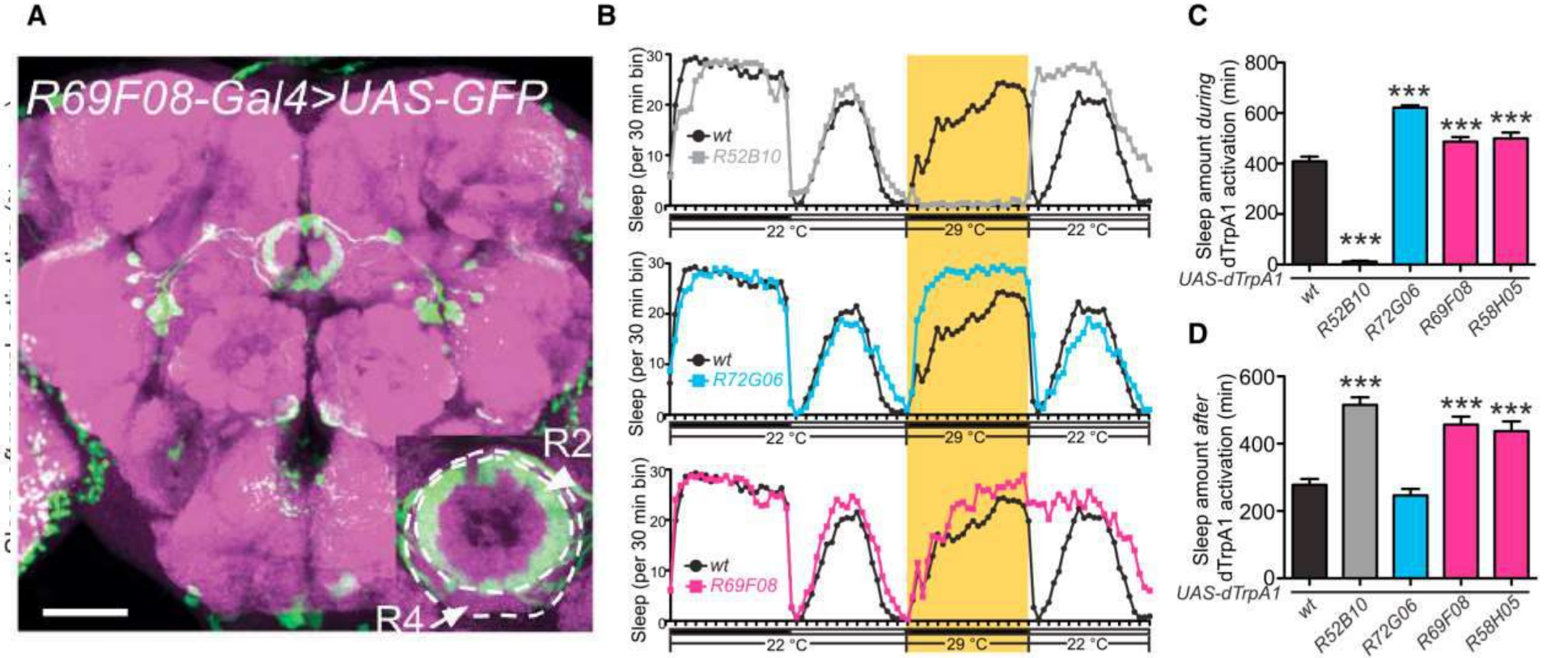
Rescue cv-c in FB restores homeostatic sleep control
And inhibition cv-c in FB impairs sleep rebound after sleep deprivation





(Donlea *et.al* , 2014)

3 EB Activation of R2 Ring Neurons Induces Sleep Drive



(Liu *et.al* ,2016)

summary

	Neurons/ Region	Function in sleep
The clocks	LNvS	Morning locomotive activity
	LNdS, 5th LNvS	Evening locomotive activity
	DN1	Light-on arousal response, Sleep promoting
The modulators	MB	Multiple functions Both sleep-promoting and wake-promoting
	FB	Sleep-promoting , homeostasis after sleep deprivation
	EB	Sleep-promoting Encoding sleep drive

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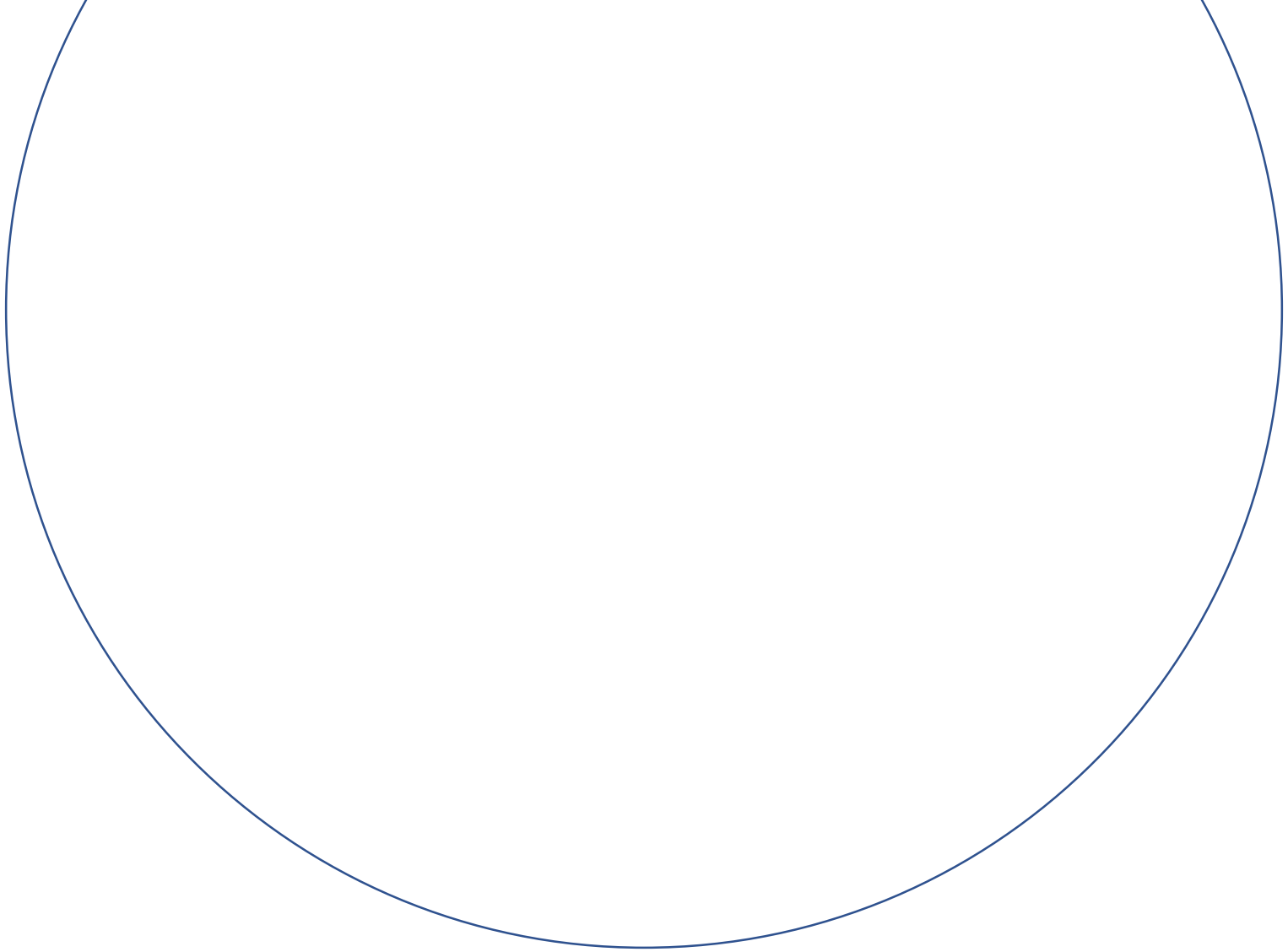
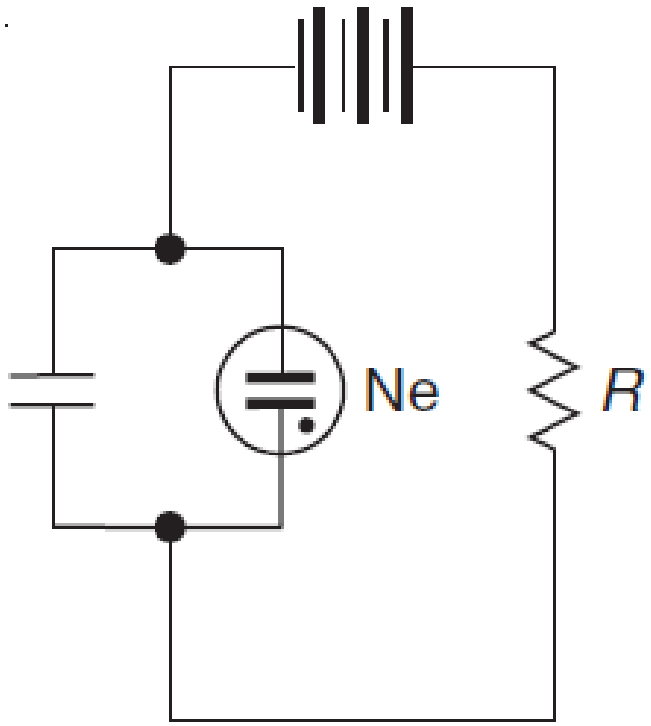
10. Donlea JM, Thimgan MS, Suzuki Y, Gottschalk L, Shaw PJ. Inducing sleep by remote control facilitates memory consolidation in Drosophila. *Science*. 2011;332(6037):1571-1576.



Thanks for Listening

Homeostatic response to sleep deprivation

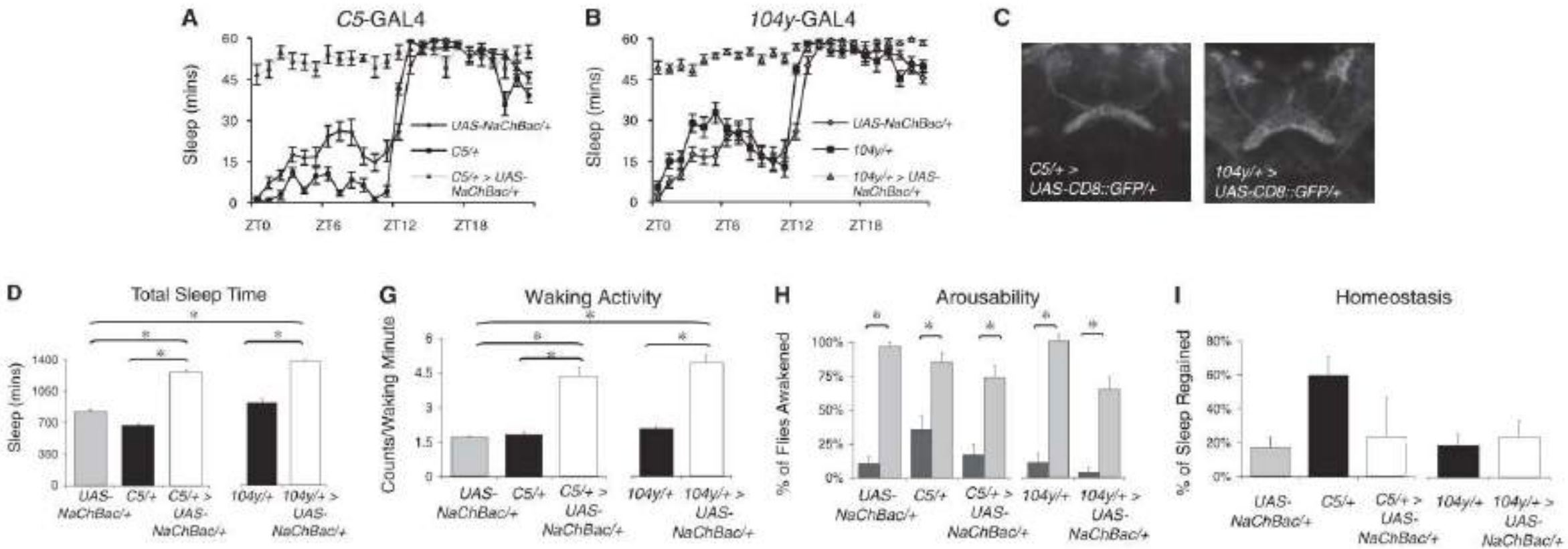


- Sleep homeostasis ensures that flies sleep the proper amount by recovering lost sleep after periods of extended wakefulness.
- Sleep homeostasis is often conceptualized as a continuous build-up of sleep need over periods of wakefulness and dissipation over periods of sleep.

Donlea et al., 2018, Neuron

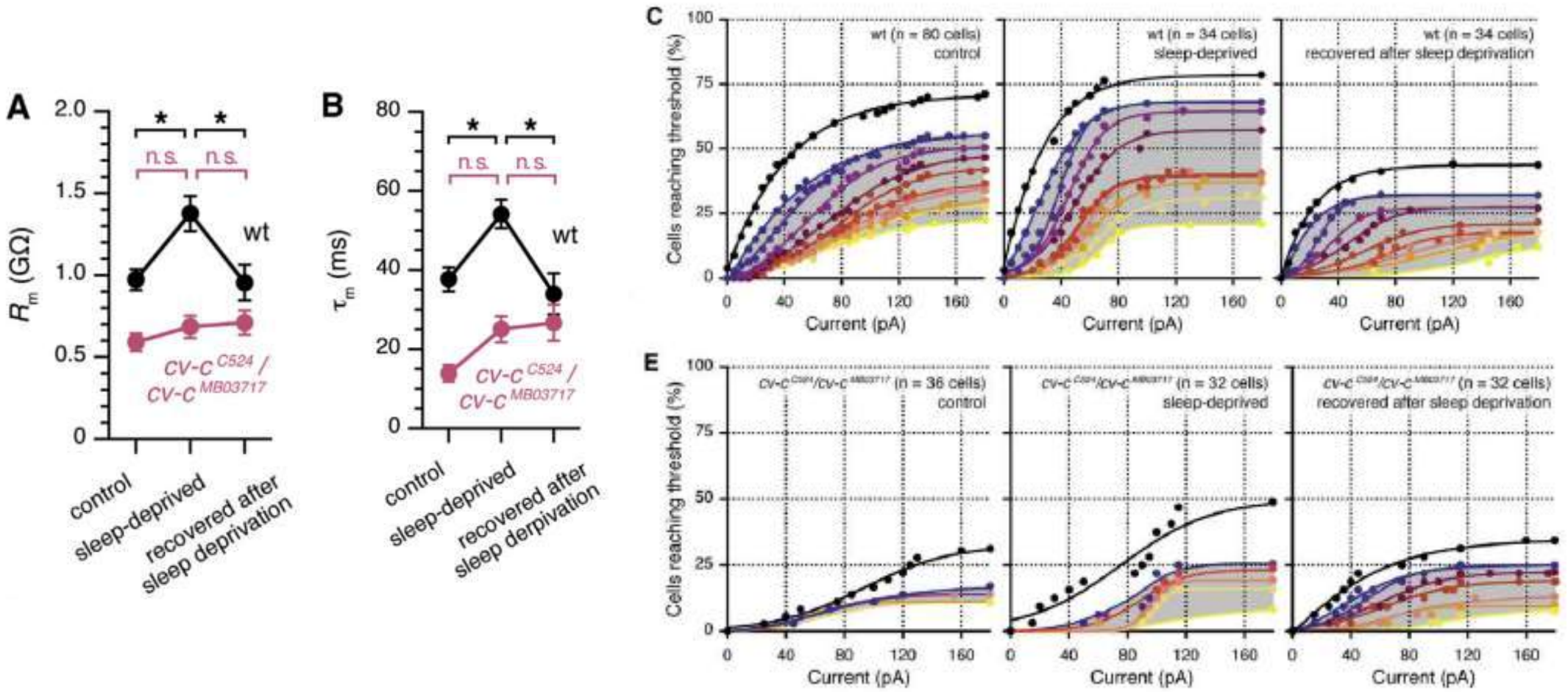
- dFB neurons as a effector to promote sleep
- R2 neurons as a integrator to drive sleep
- An autoregulatory loop

- A cluster of neurons inducing sleep is located at dFB



Donlea et al., 2011,Science

- Sleep deprivation induces excitability of dFB neurons

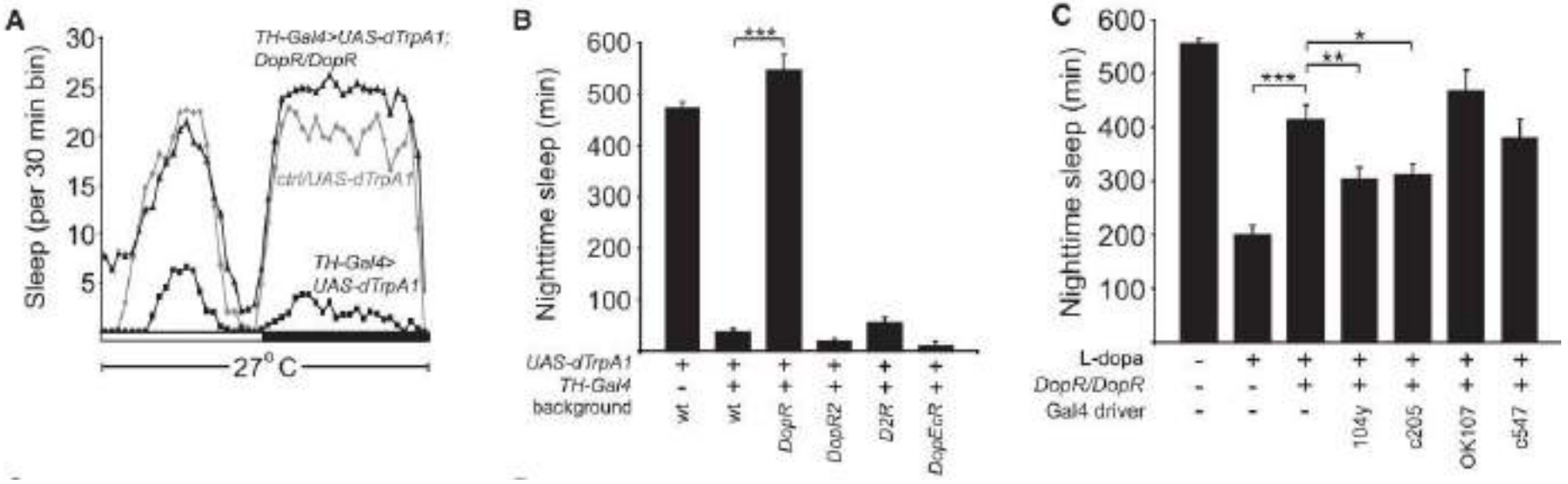


crossveinless-c (cv-c) : Rho-GTPase-activating protein

cv-c mutants exhibit decreased sleep time

Donlea et al., 2014, Neuron

- Dopaminergic Neurons Signal to the Dorsal Fan-Shaped Body to Promote Wakefulness

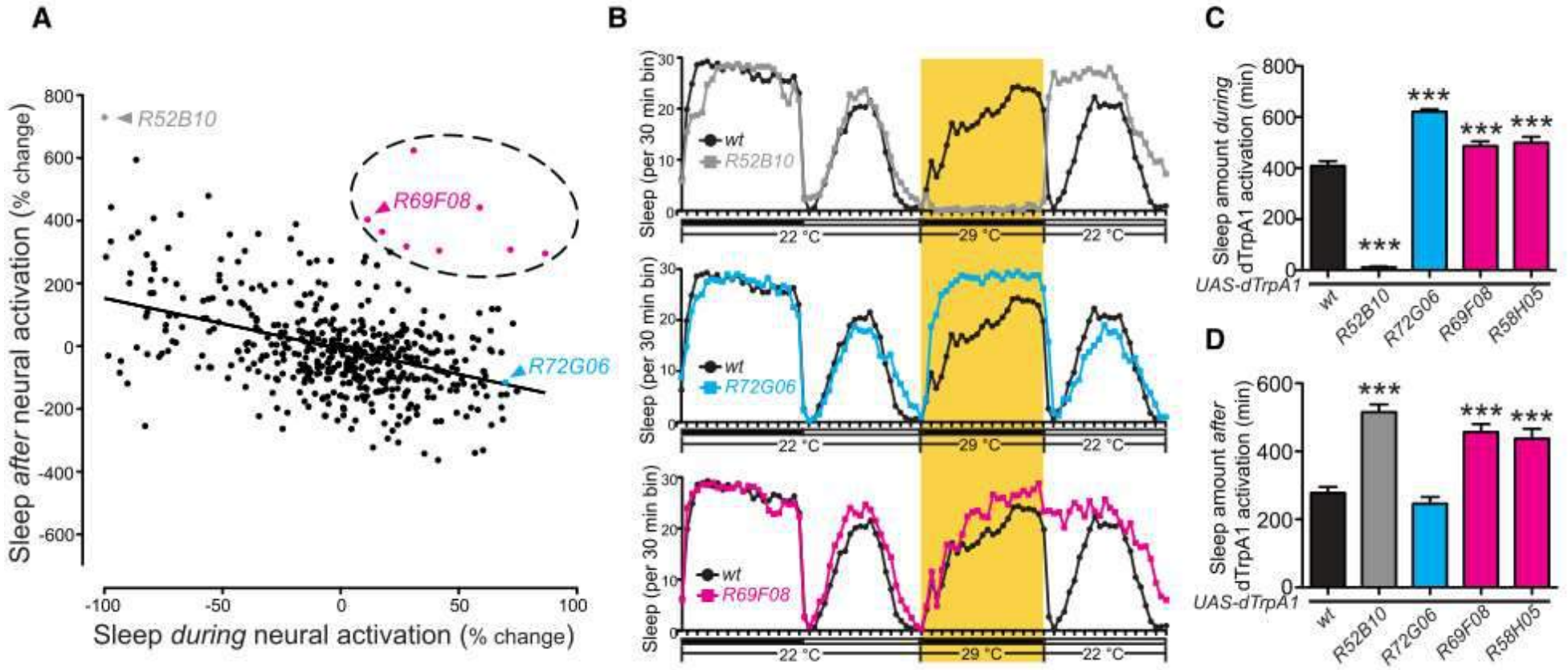


Qili Liu et al., 2011, Current Biology

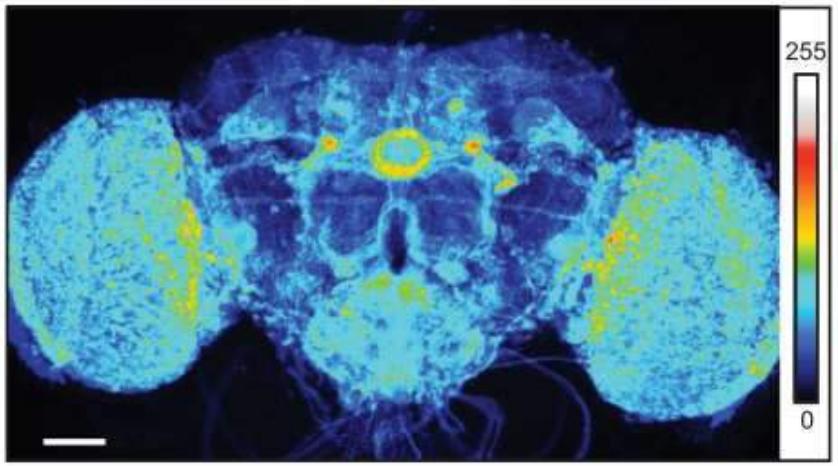
In Drosophila, a crucial component of the machinery for sleep homeostasis is a cluster of neurons innervating the dorsal fan-shaped body (dFB) of the central complex.

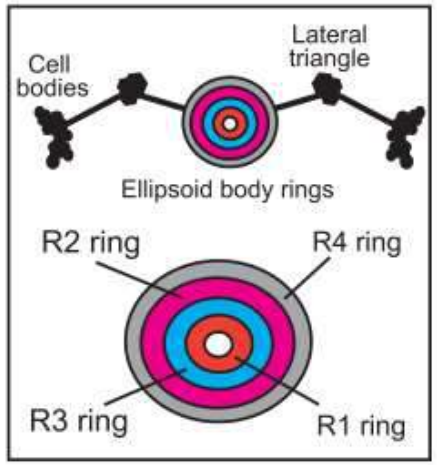
- Artificial activation of these cells induces sleep
- Reductions in excitability cause insomnia.
- dFB neurons in sleep-deprived flies tend to be electrically active.
- dFB neurons in rested flies tend to be electrically silent.

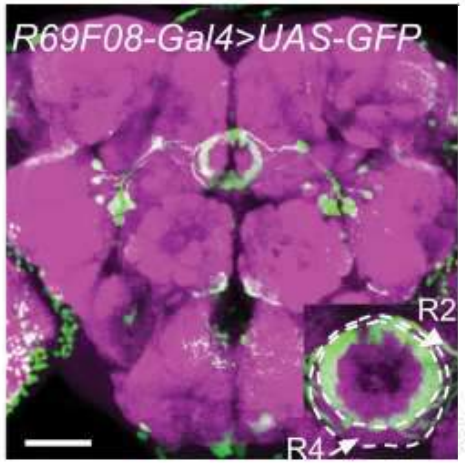
- Identification of a neuronal circuit that induces sleep drive

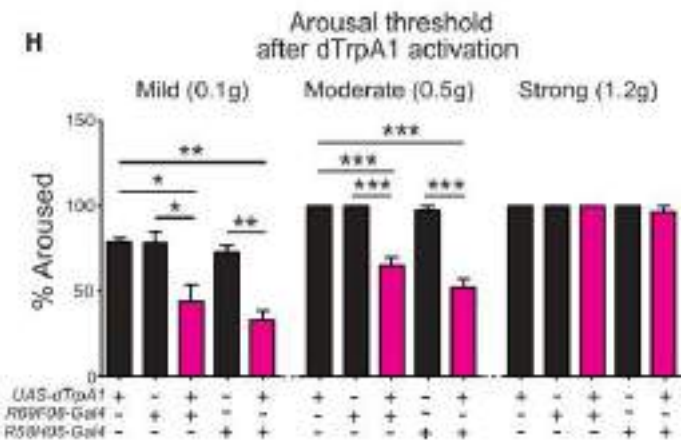


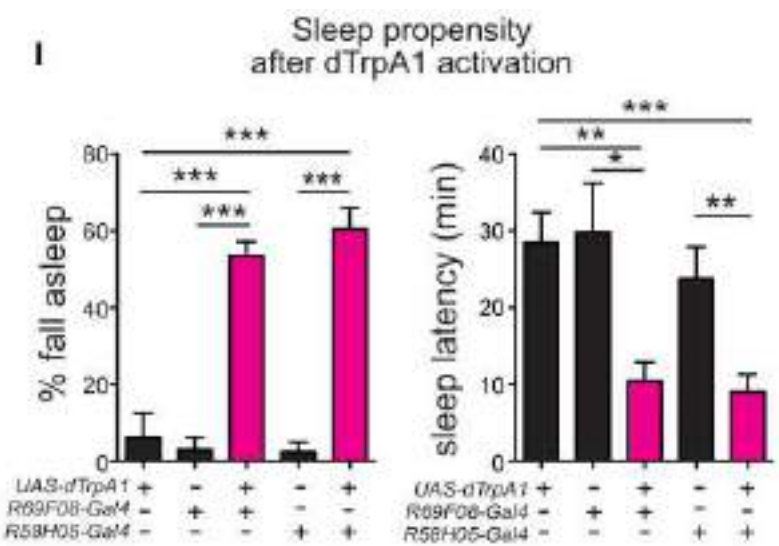
Sha Liu et al,.cell.2016

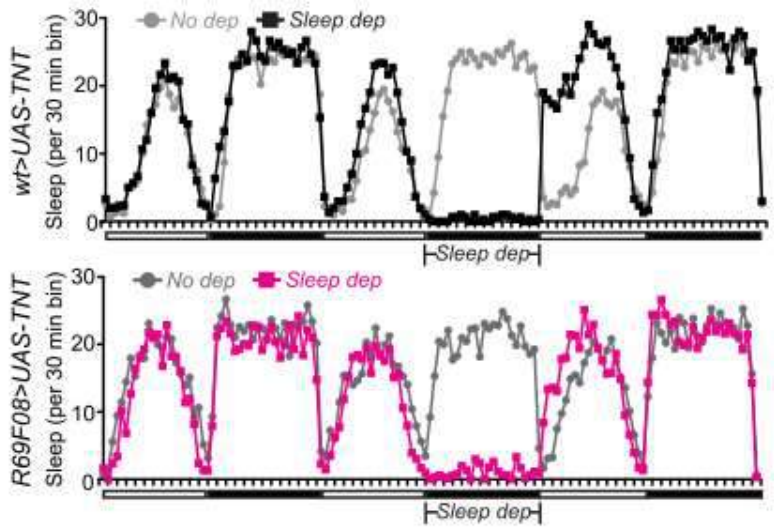


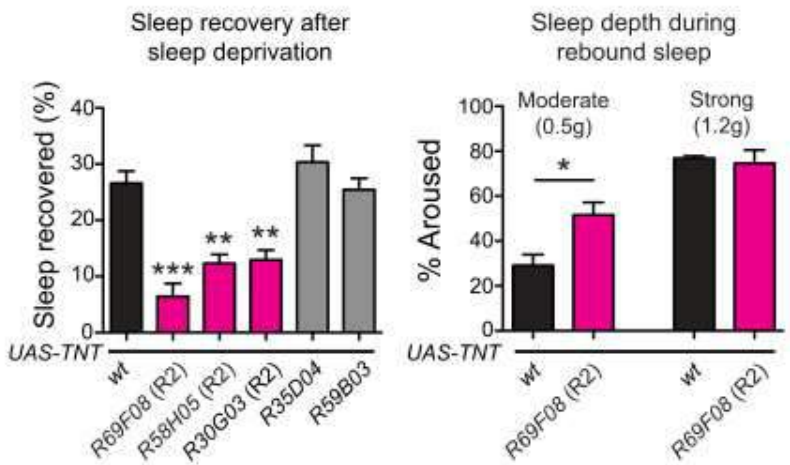






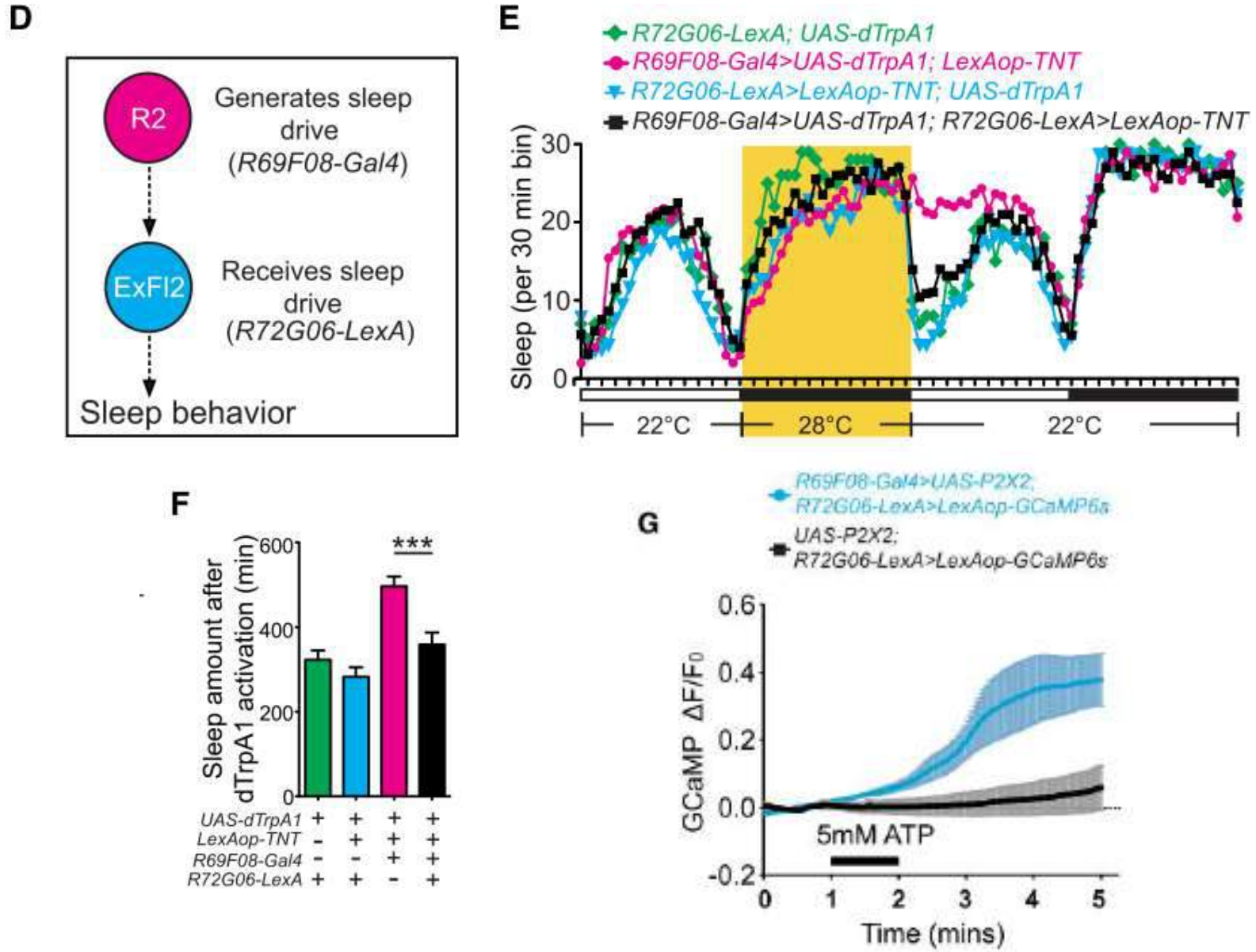




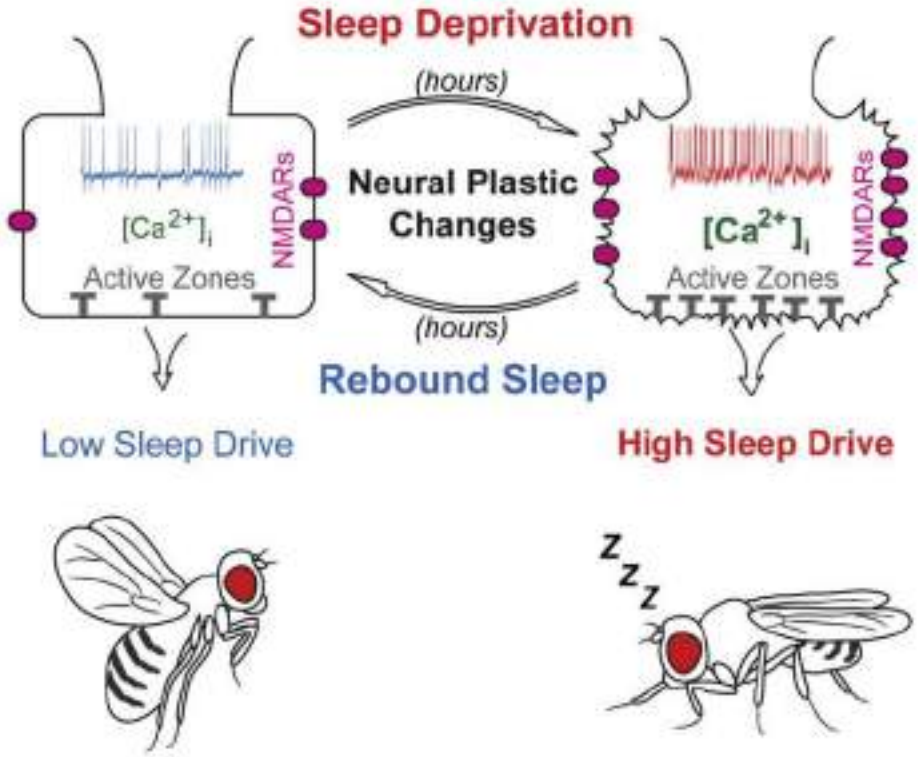


Sha Liu et al,.cell.2016

- R2 neurons act through ExFl2 neurons to regulate sleep homeostasis



Sha Liu et al,.cell.2016



Sha Liu et al,.cell.2016

- A subset of R2 EB neurons is capable of generating sleep drive in Drosophila
- Ca2+levels and measures of synaptic strength in R2 cells correlate with sleep need
- R2 neuron translational profiling reveals increased NMDA receptors with sleep loss
- Manipulating synaptic strength of R2 neurons directly impacts homeostatic sleep drive

CellPress

Neuron
Article

Recurrent Circuitry for Balancing Sleep Need and Sleep

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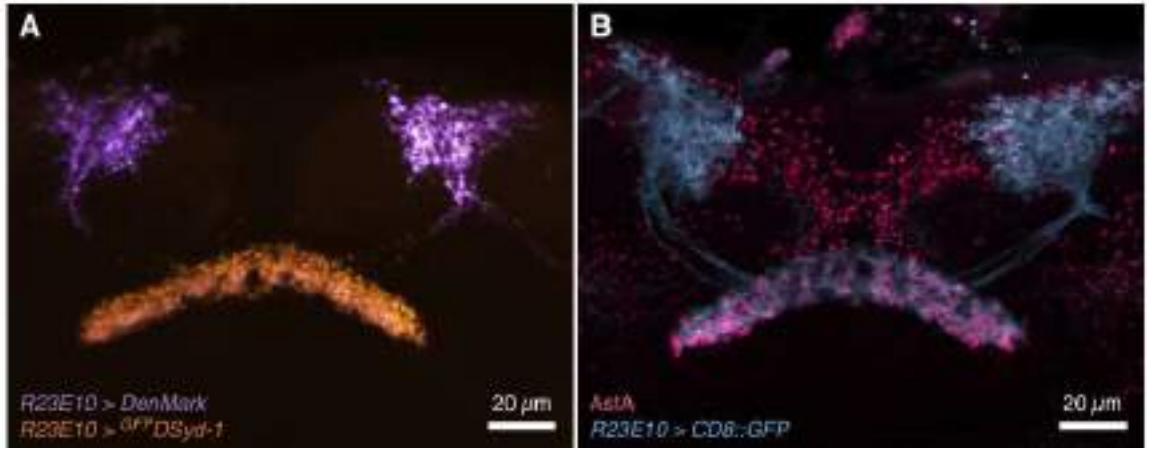
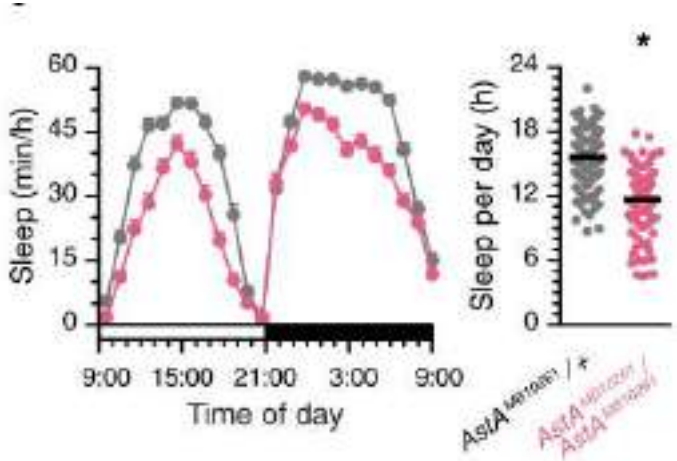
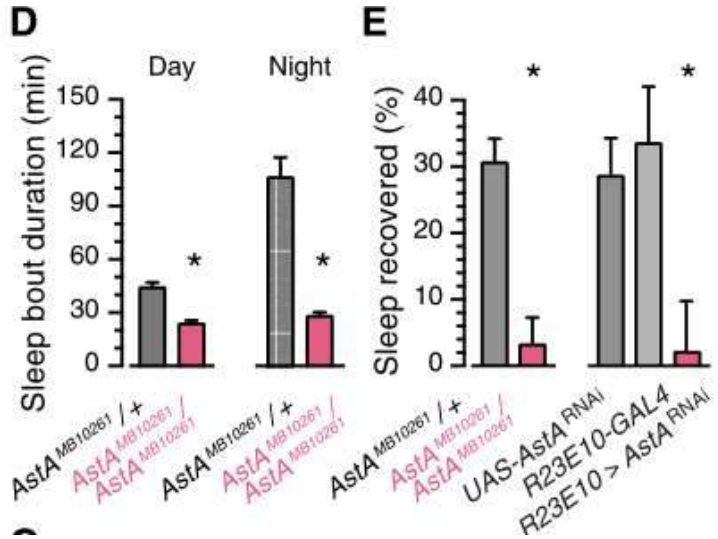
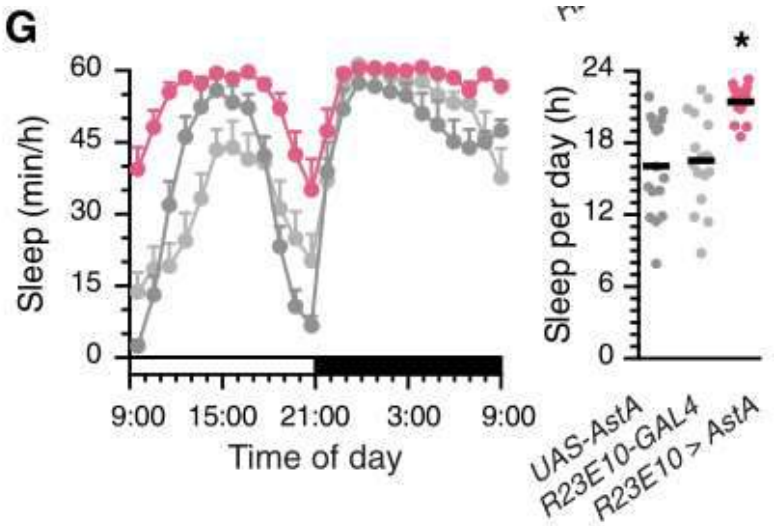
- dFB neurons regulate sleep via AstA

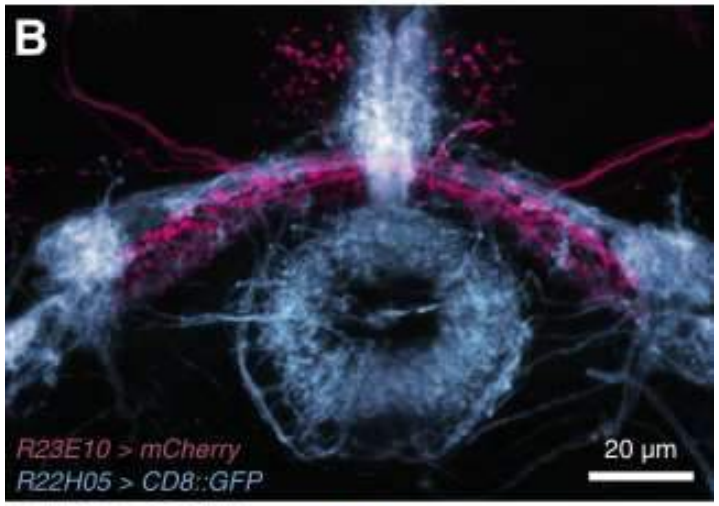


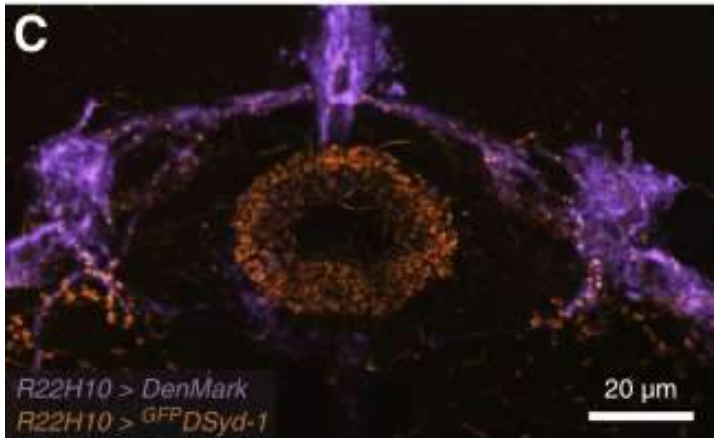


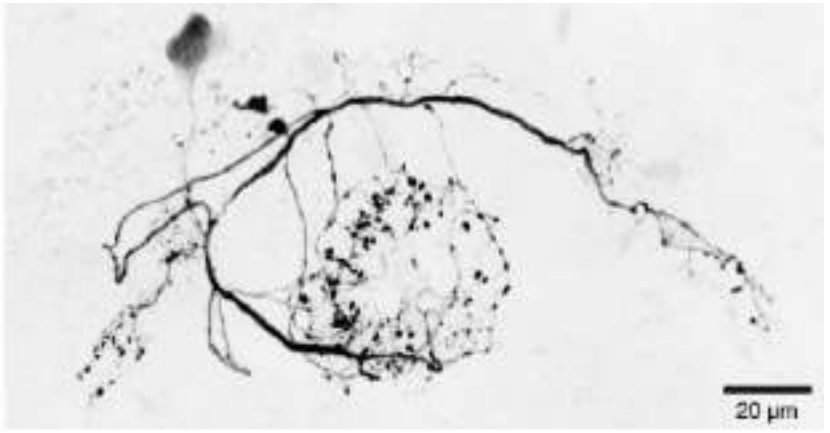


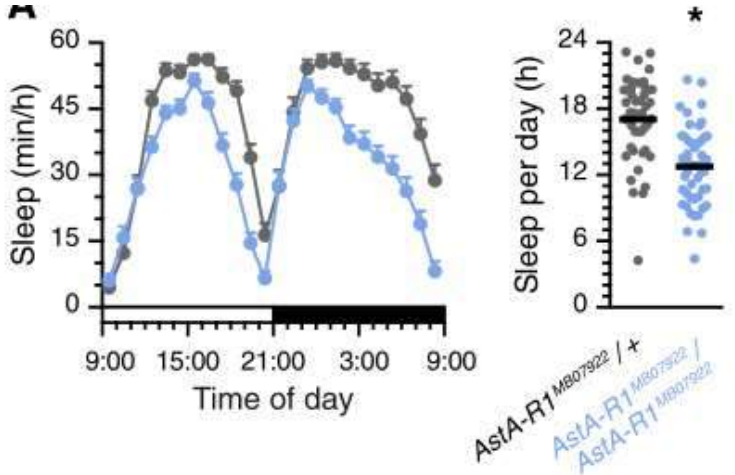


- AstA-R1 Functions in Helicon Cells to Regulate Sleep

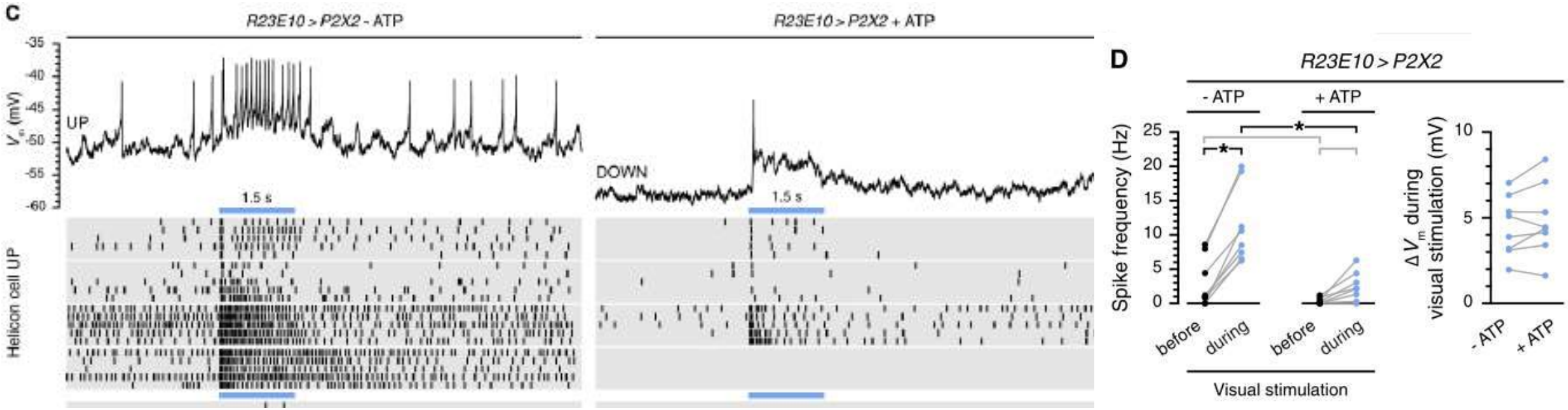




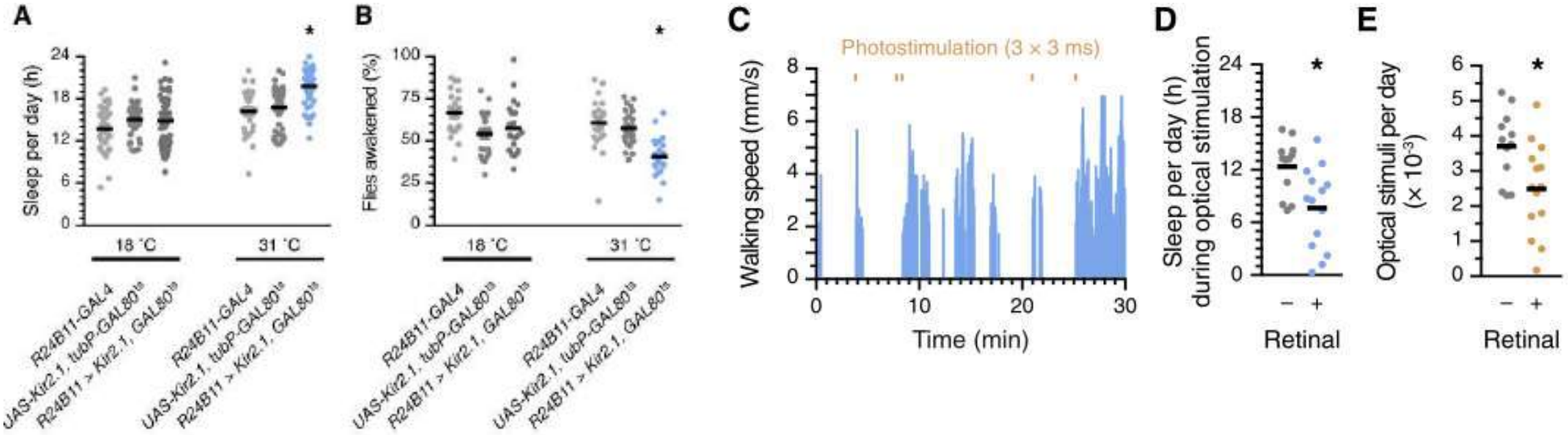




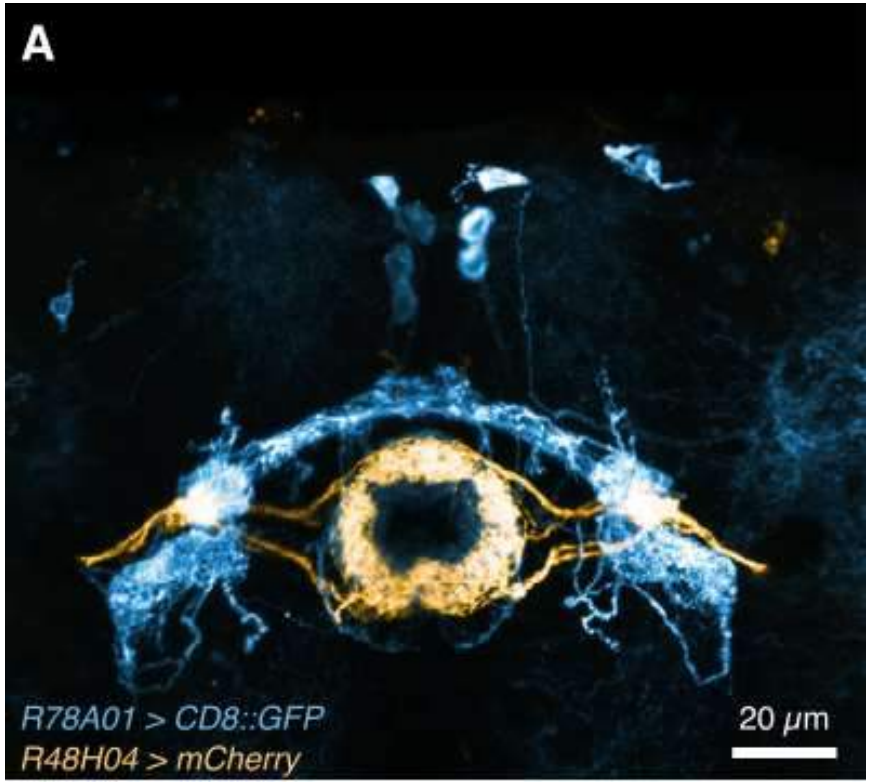
- dFB Neurons Inhibit Helicon Cells and Their Visual Responses

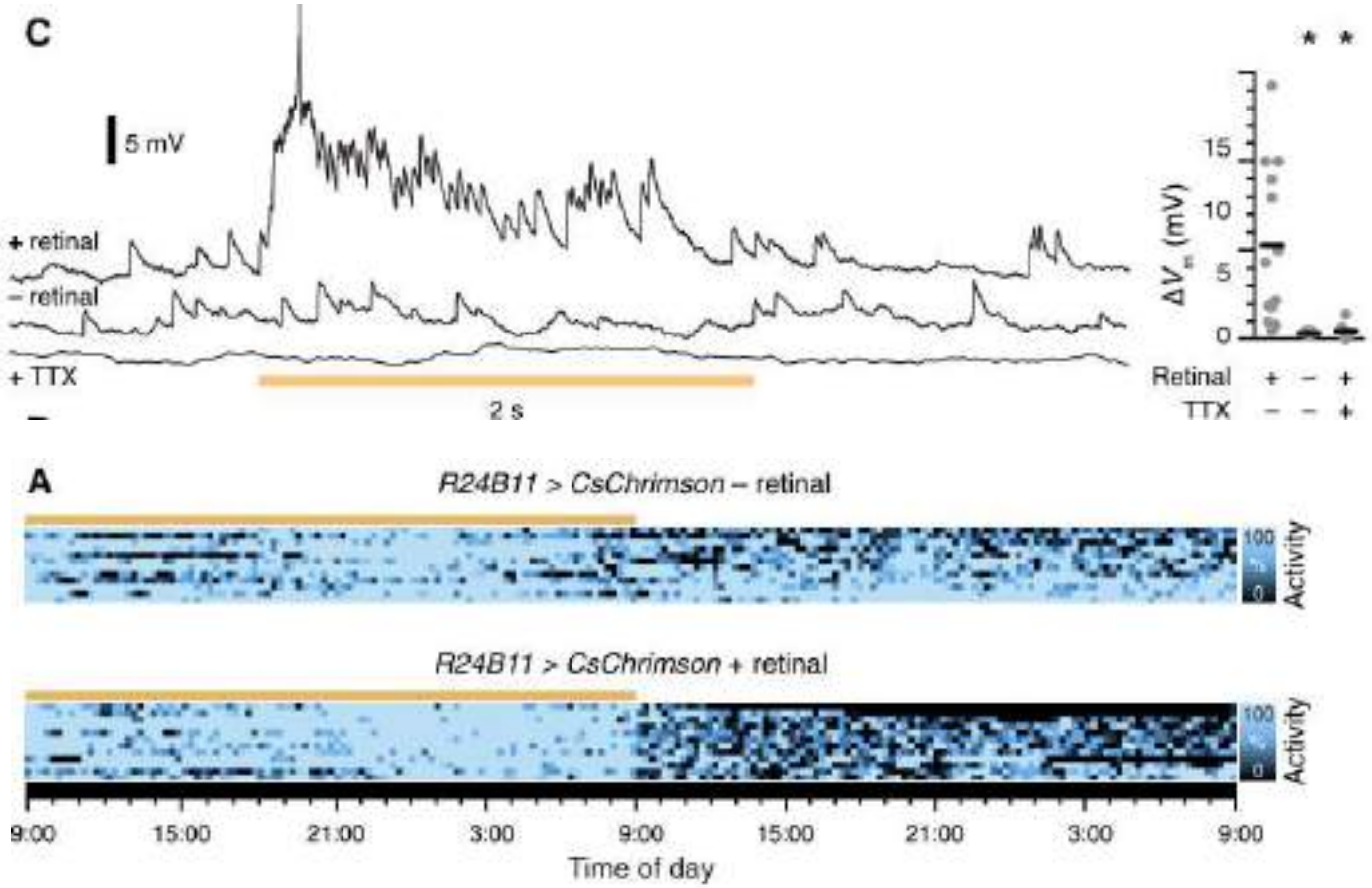


- Helicon cells gate locomotion



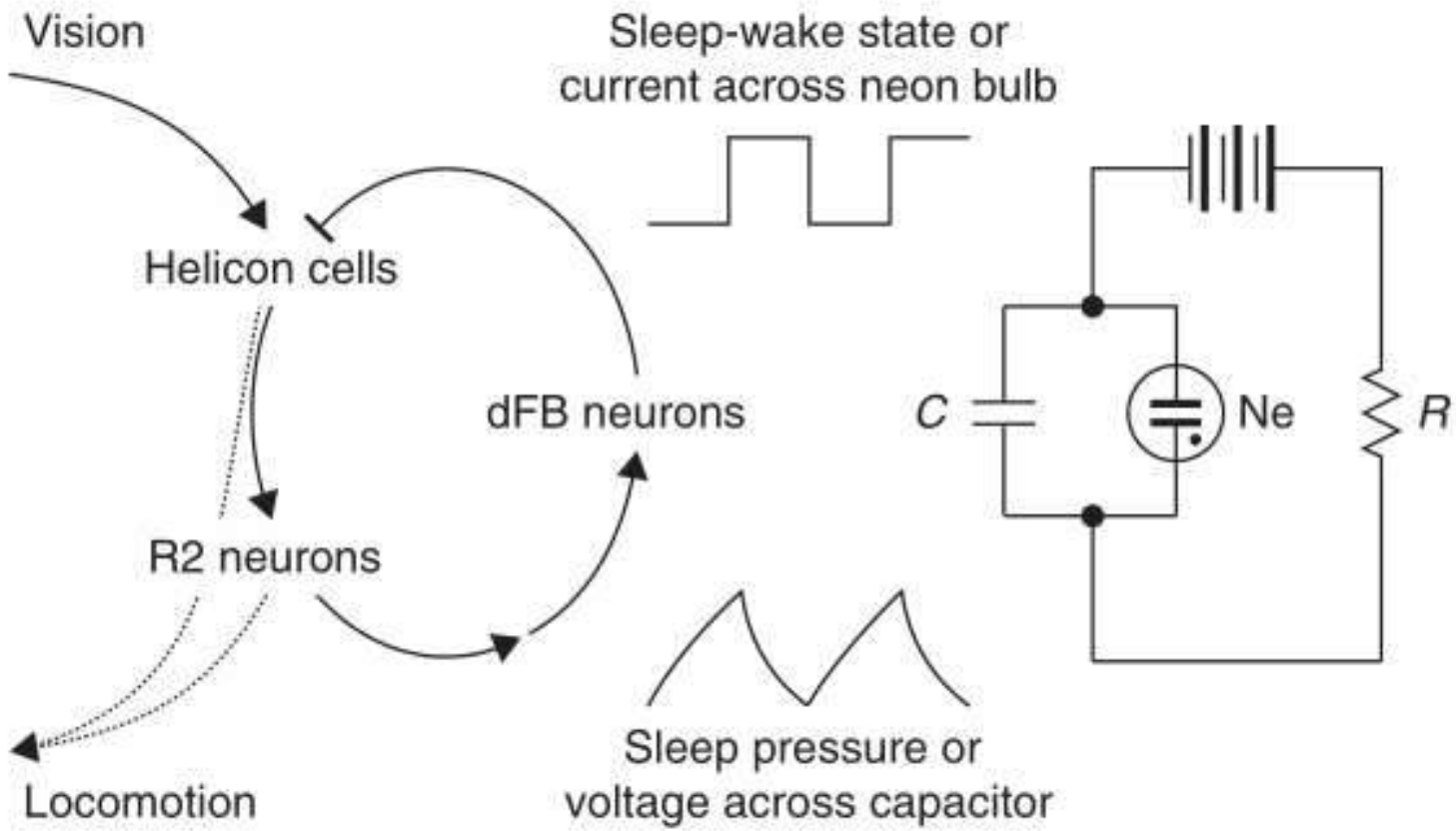
- Helicon Cells Excite R2 Ring Neurons





Helicon cells : R78A01-GAL4 (blue)

R2 neurons : R48H04-LexA (yellow).


Vision
Sleep-wake state or
current across neon bulb
Helicon cells
dFB neurons
C
Ne
R
R2 neurons
Locomotion
Sleep pressure or
voltage across capacitor

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Thank you