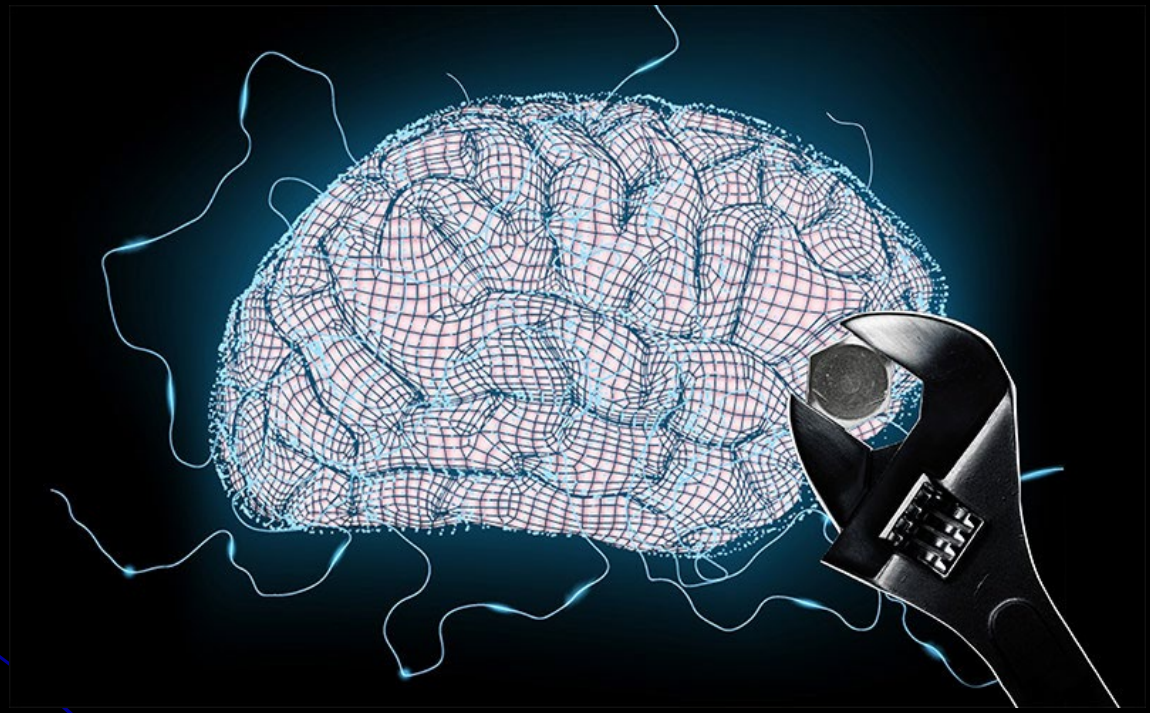
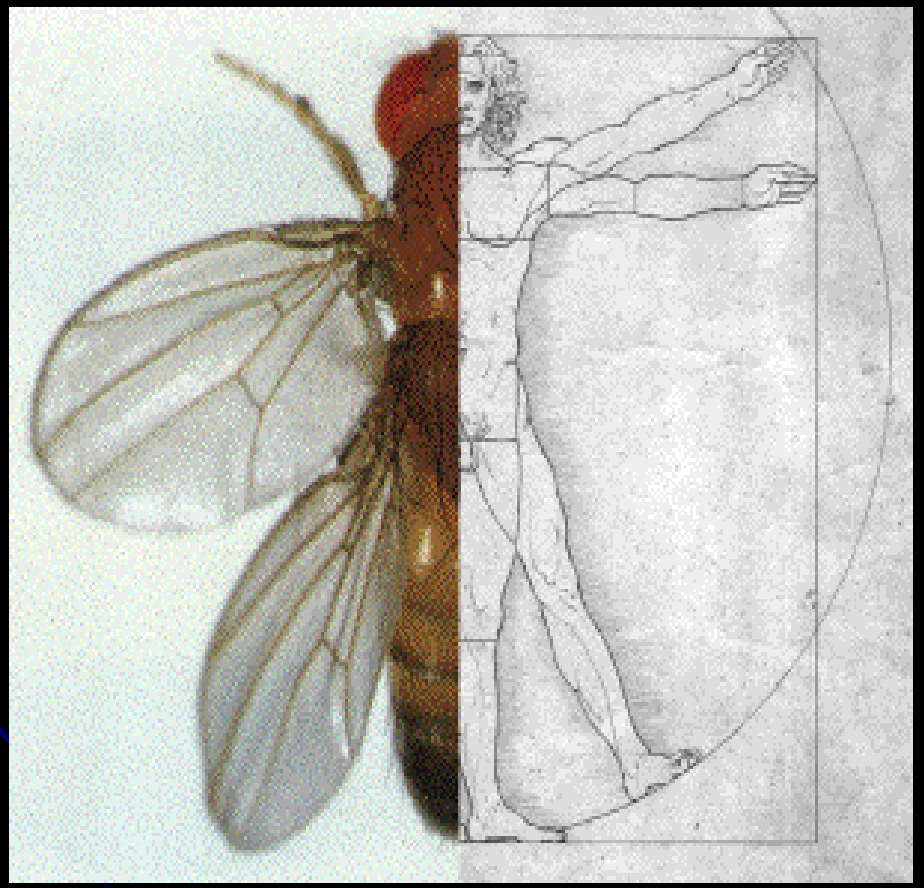
Anything Brains Can do; Sleep Can Make Better



Paul Shaw, PhD
Department of Neuroscience


Campbell's
CONDENSED
A Good Source of 20 Amino Acids!
Primordial
SOUP

My lab uses Drosophila melanogaster (fruitfly) as a model system to understand the function of sleep



Building on a Legacy of Sleep Research

Allan Rechtschaffen
PhD advisor
University of Chicago

Giulio Tononi
Postdoc advisor
The Neurosciences Institute

Chiara Cirelli
Postdoc advisor
The Neurosciences Institute

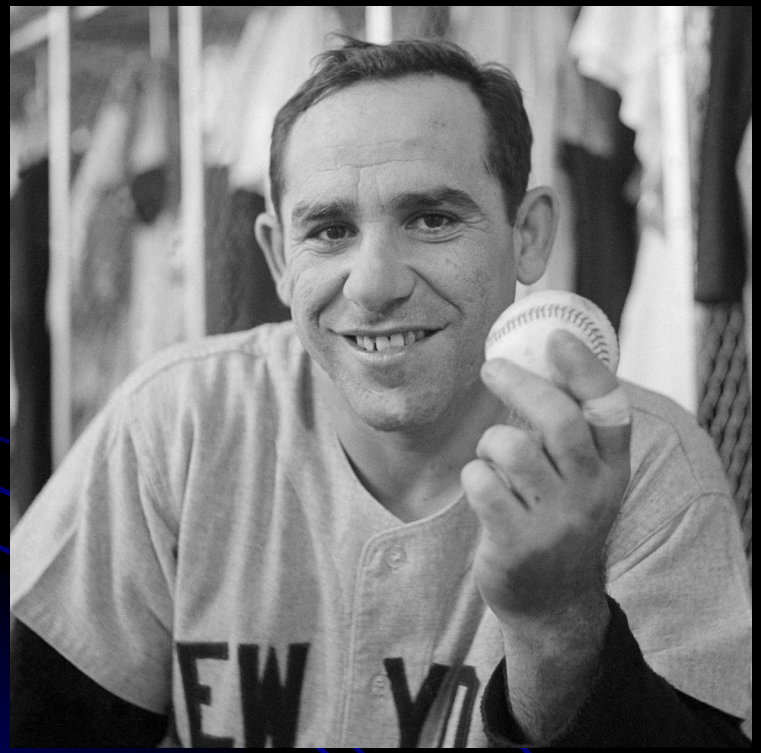
The function of Sleep remains a mystery

- Rest
- Restoration
- Energy conservation
- Important for development
- Erase useless memories
- Adaptive inactivity
- Memory consolidation
- Synaptic Downscaling

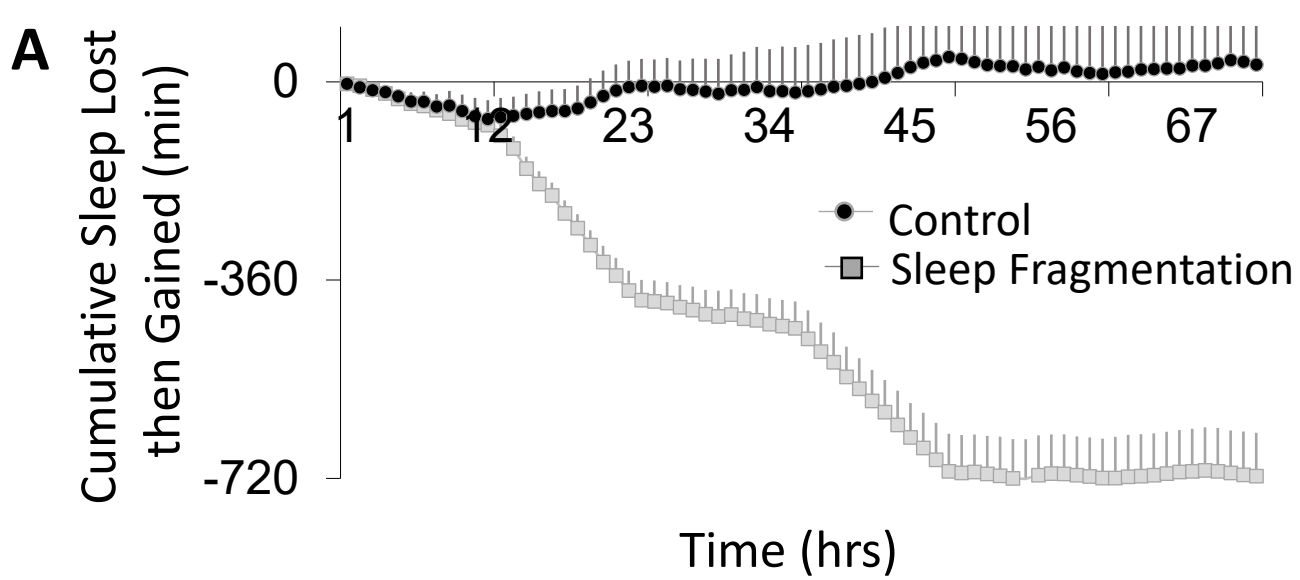
Firsts

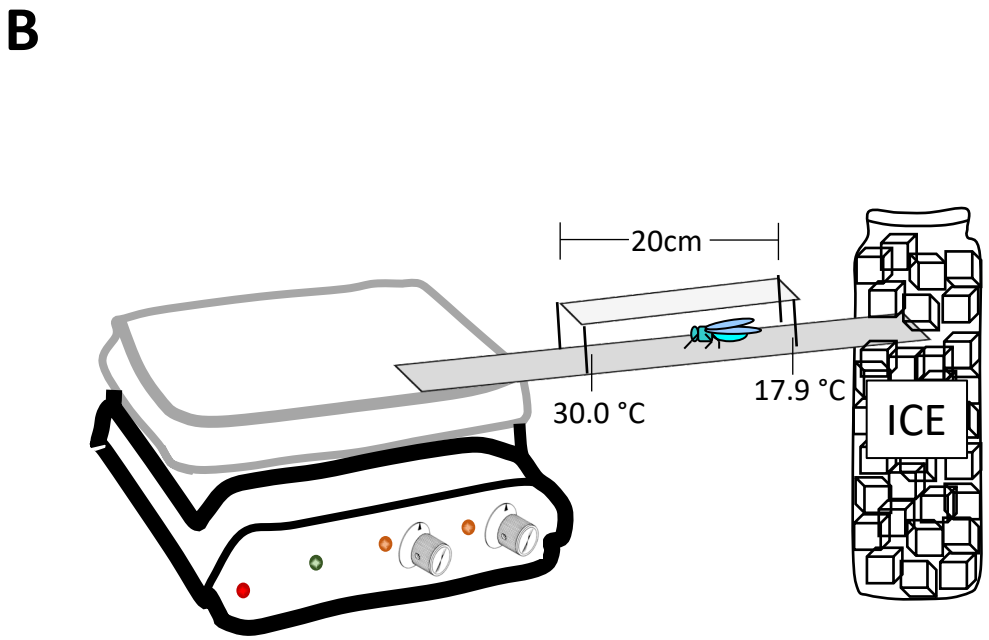
- *Drosophila* sleep
- Sleep deprivation causes lethality in invertebrates
- Salivary biomarkers of sleep loss identified
- Discovery of a bona fide sleep center in flies
- Experimentally enhanced sleep converts STM to LTM
- Hypnotic identified to increase sleep in flies
- Sleep restores memory in extreme memory mutants
- Reversal of Alzheimer's-related memory impairments by sleep
- Sleep counteracts memory loss from brain damage
- Circadian clock enforces memory impairments in disease

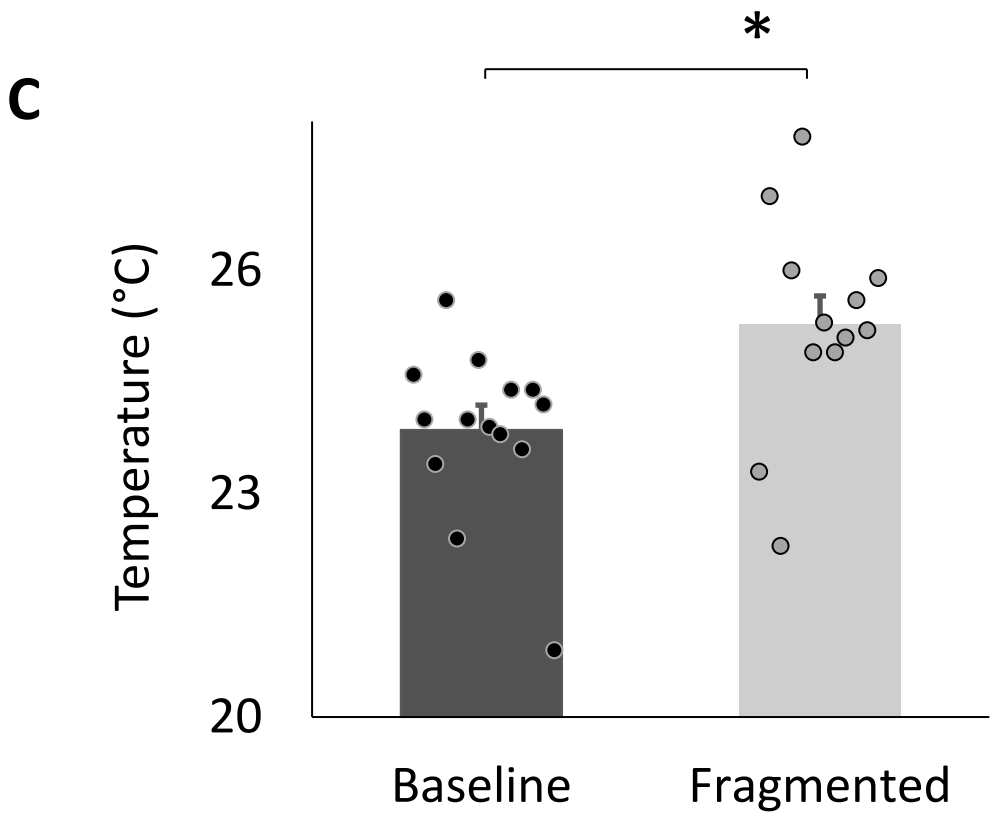
“You can observe a lot just by watching”
-Yogi Berra



“You might be surprised by what you can see just by looking”

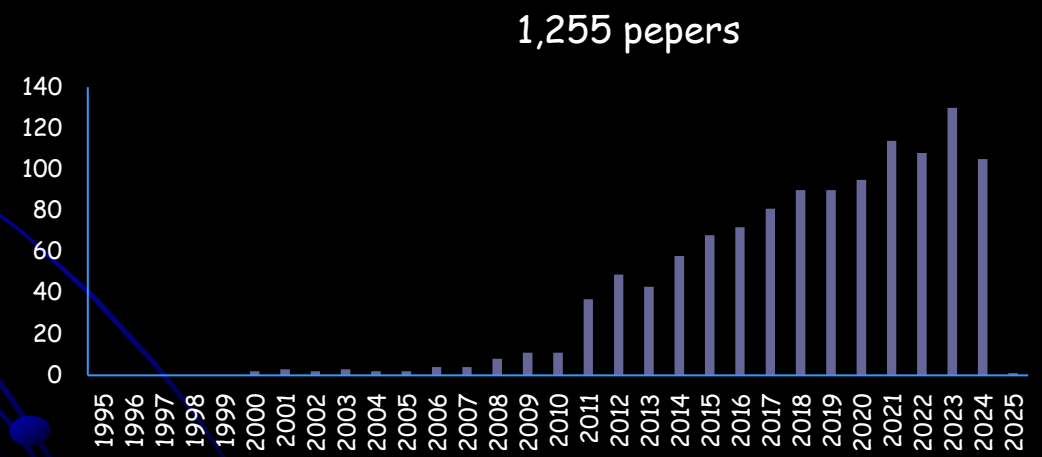

A
Cumulative Sleep Lost then Gained (min)
0
-360
-720
1
12
23
34
45
56
67
Control
Sleep Fragmentation
Time (hrs)


B
20cm
30.0 °C
17.9 °C
ICE


C
*
Temperature (°C)
26
23
20
Baseline
Fragmented

Why is Philanthropy Important to WashU ?

This is not typically how people think about neural circuitry. That being said, everything I just summarized seems mostly right and is interesting and novel (although in and of itself is not sufficient enough for my recommendation for funding).



Biomarkers

- Saliva is readily accessible.
- Collection of Saliva is fast, easy, noninvasive, and requires no special equipment or expertise.
- A large number of diagnostic analytes are known to be present in saliva.

Brainstem nuclei regulating salivary gland activity receive inputs from neural structures in the forebrain that are centers for homeostatic regulation

We have developed genetic and pharmacological tools that allow us to increase sleep on demand.

Inducing Sleep by Remote Control Facilitates Memory Consolidation in *Drosophila*

Jeffrey M. Donlea,[1] Matthew S. Thimgan,[1] Yasuko Suzuki,[1] Laura Gottschalk,[1] Paul J. Shaw[1,*]

Article

Current Biology

Sleep Restores Behavioral Plasticity to *Drosophila* Mutants

Highlights

- We have identified a novel sleep-promoting agent in flies
- Sleep restores STM and LTM to classic memory mutants
- Sleep reverses memory deficits in a *Drosophila* model of Alzheimer's disease

Authors

Stephane Dissel, Veena Angadi, ..., Bruno van Swinderen, Paul J. Shaw

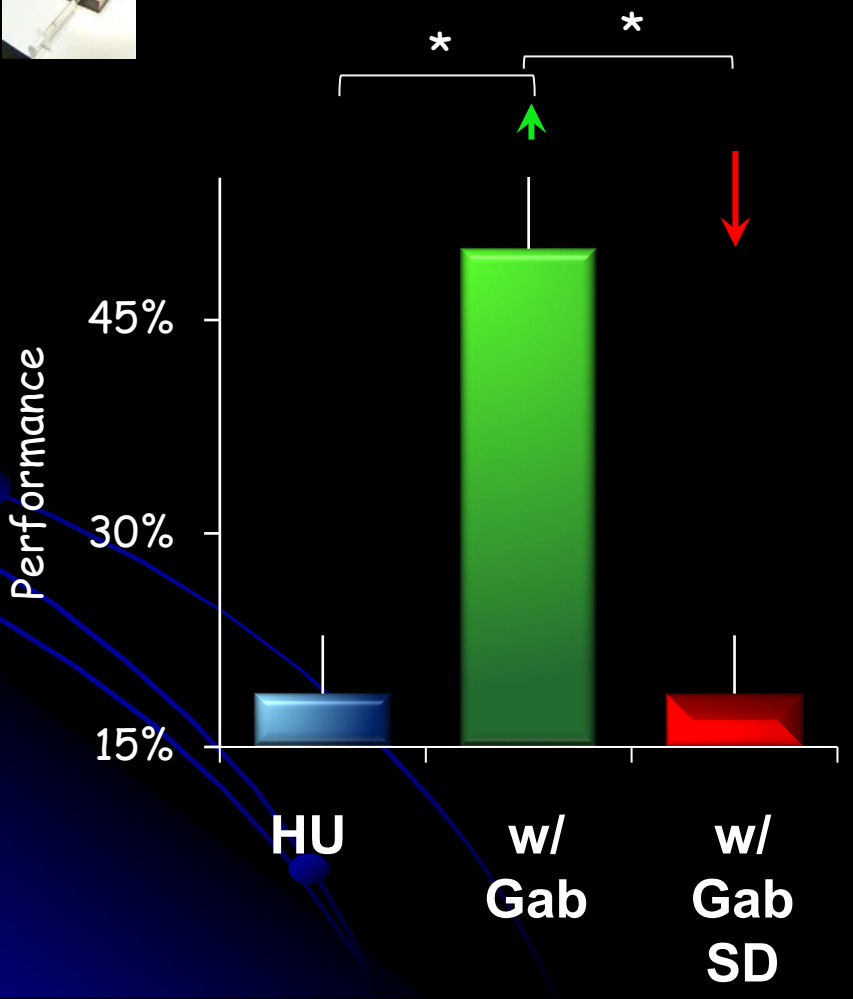
Correspondence

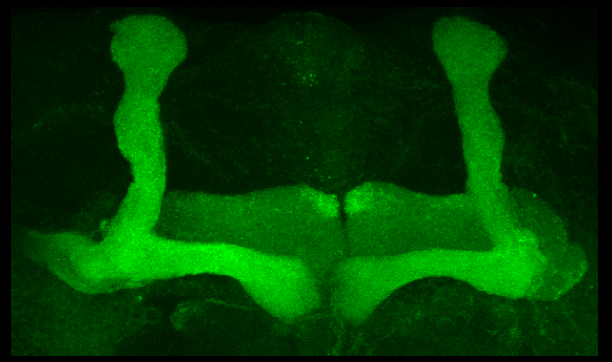
shawp@pcg.wustl.edu

Sleep can "fix" broken brains

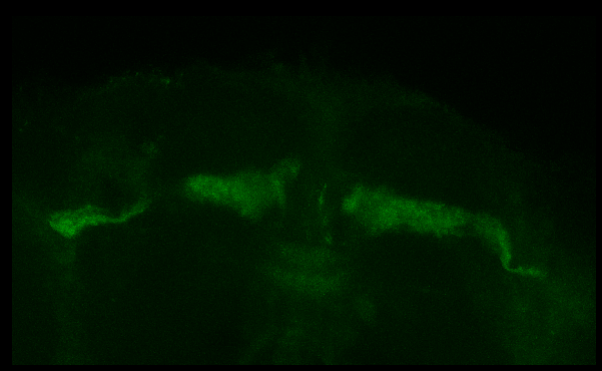
How Broken can they be?

Sleep restores short-term memory to MB-ablated flies



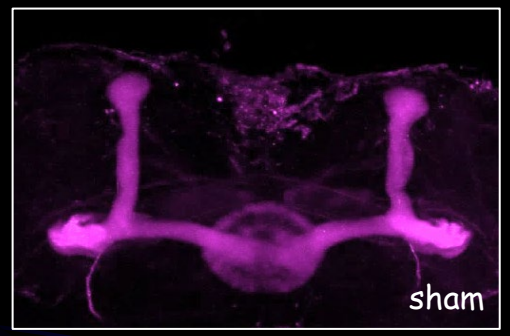


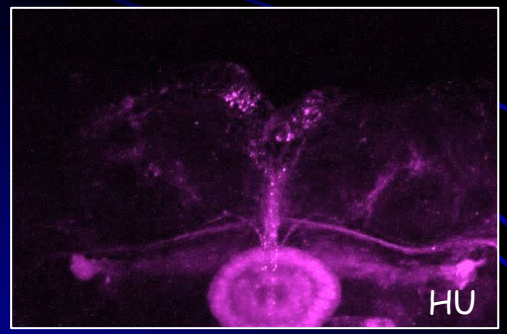
Cs

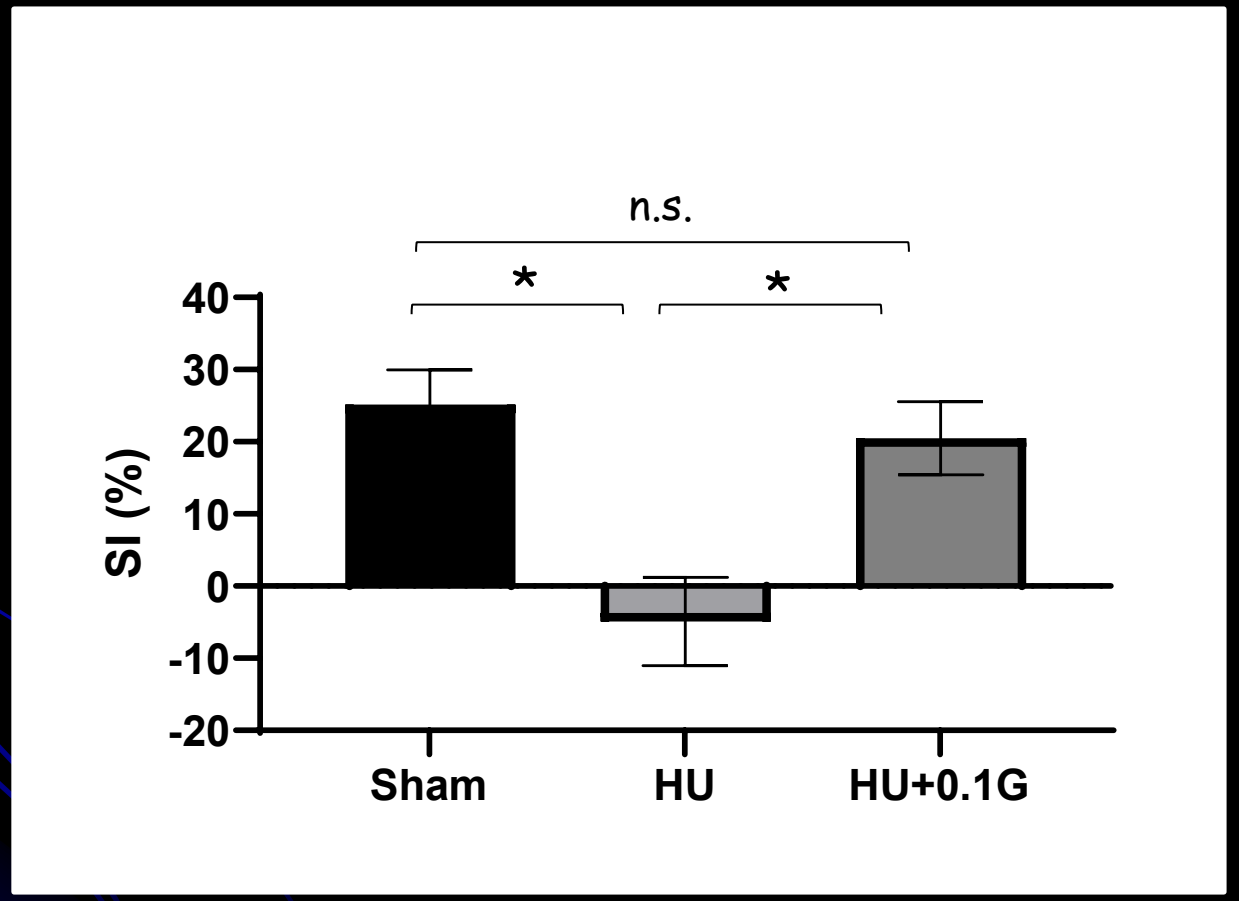


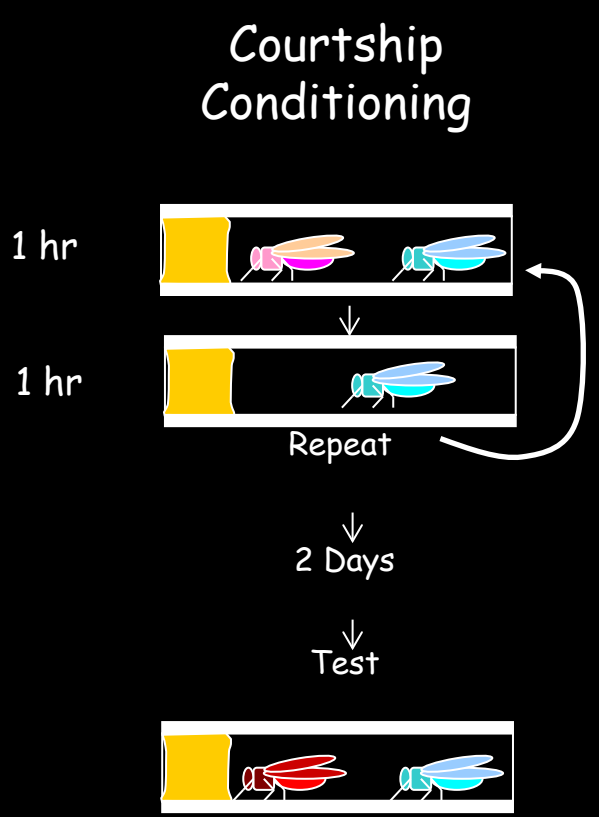
HU

Sleep restores Long-Term Memory to MB-ablated flies

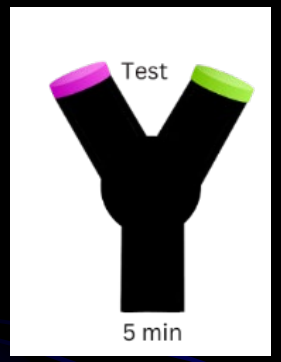


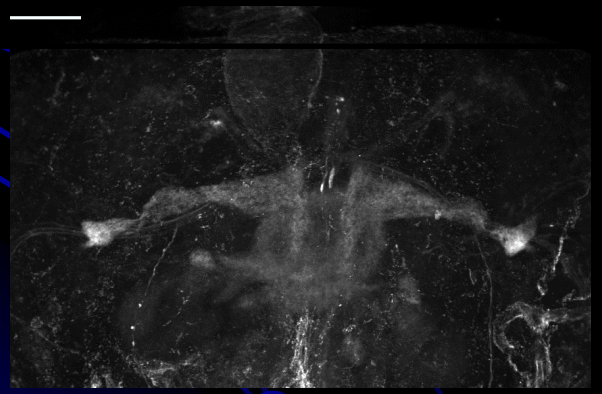


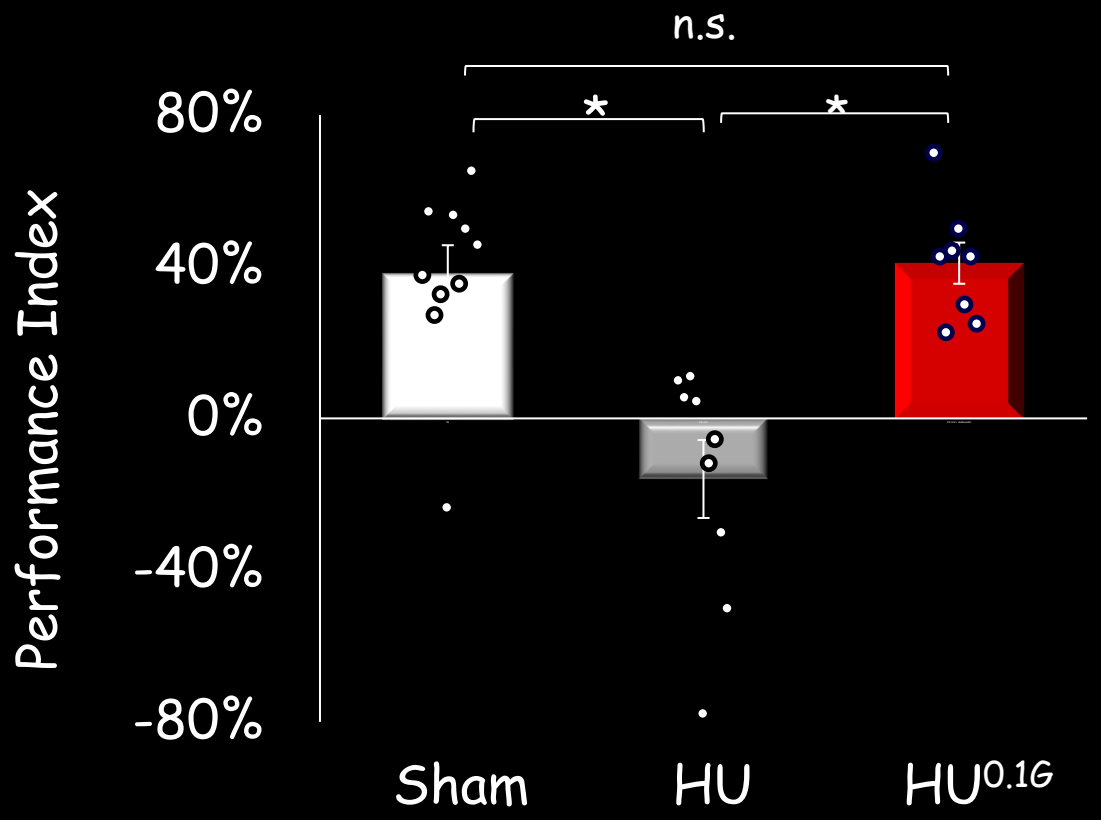




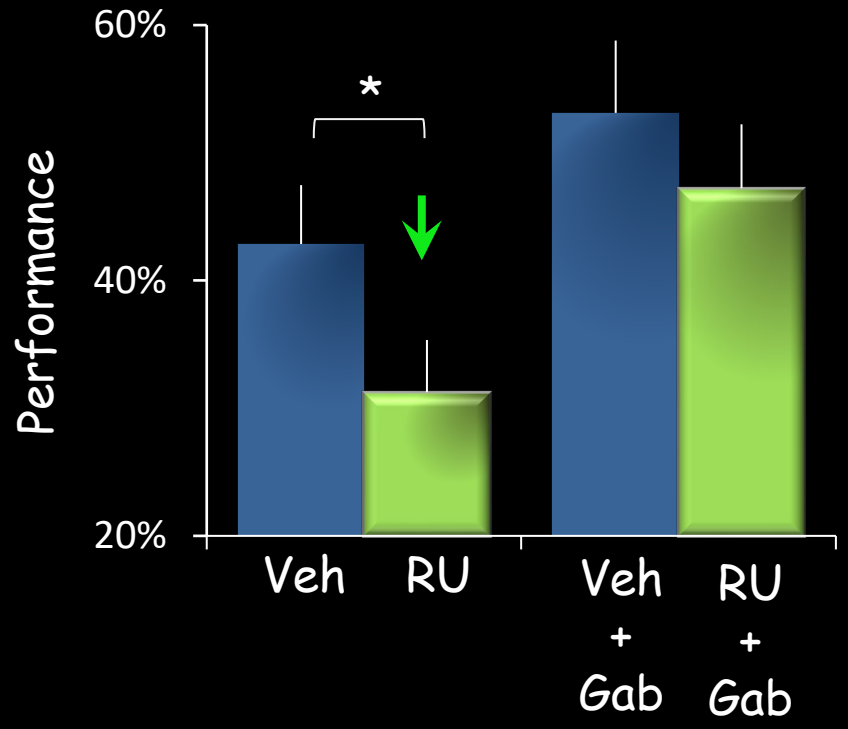
Sleep restores Aversive Olfactory Memory to MB-ablated flies



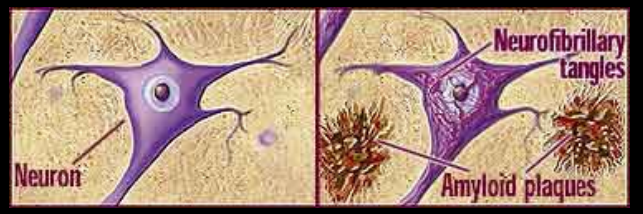


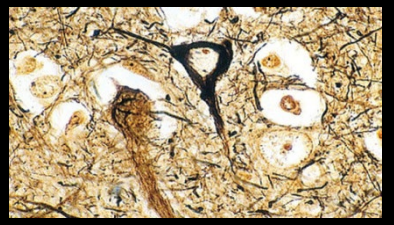


Sleep can restore Short-Term Memory to 14-day old flies expressing human Alzheimer's disease



What about Tau?

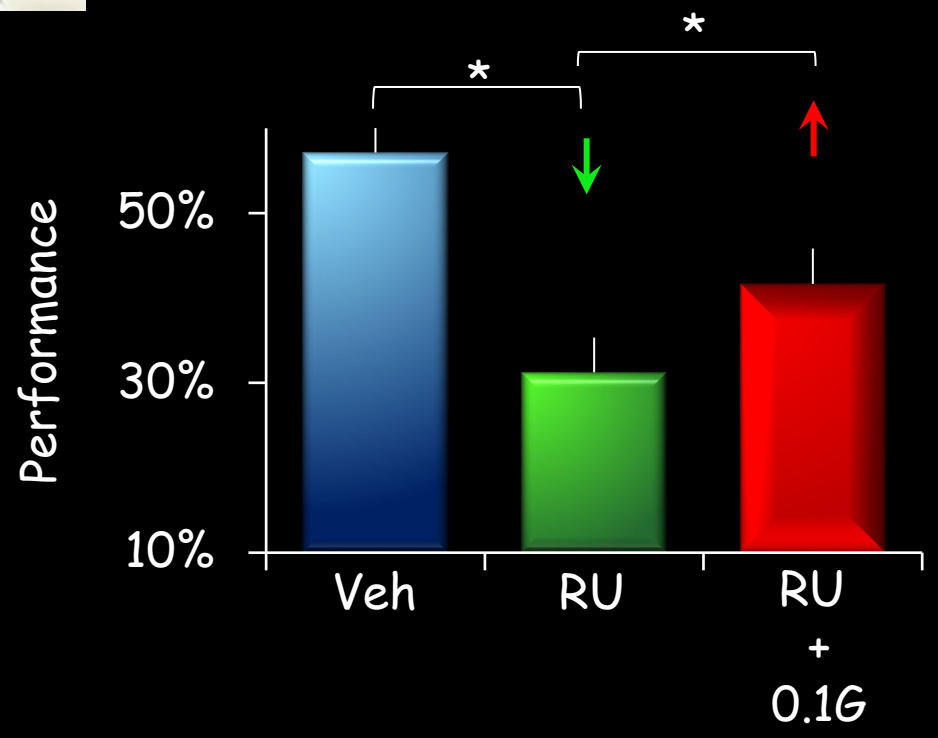




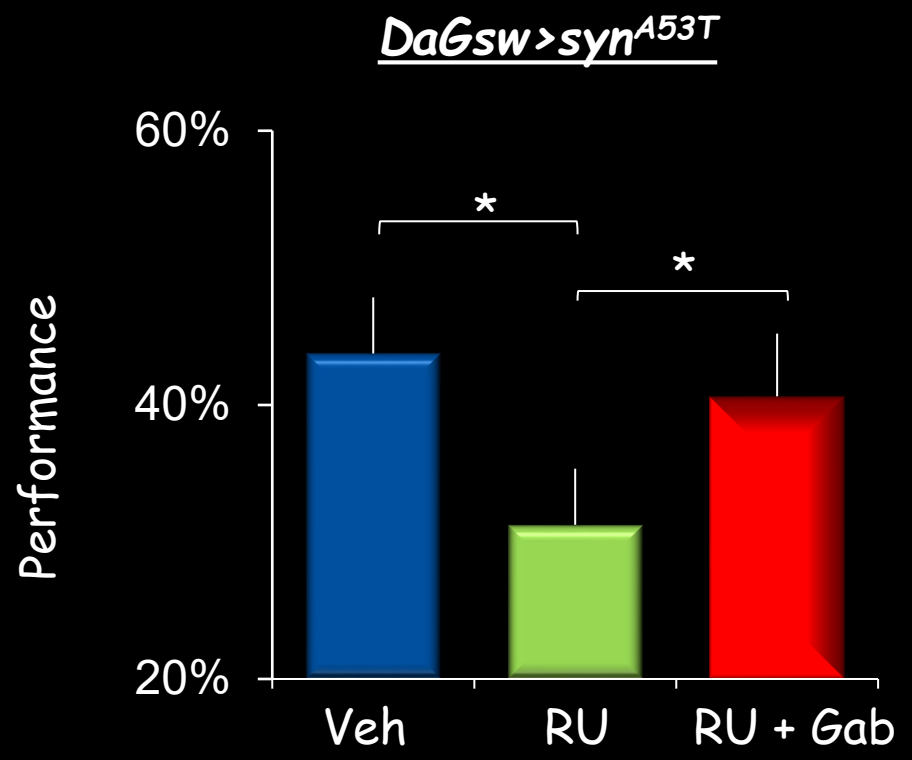
Expression of Alzheimer-Like Pathological Human Tau Induces a Behavioral Motor and Olfactory Learning Deficit in *Drosophila melanogaster*

Cindy Beharry[1], Maria Eugenia Alaniz[1] and Alejandra del Carmen Alonso*
Department of Biology and Center for Developmental Neuroscience, College of Staten Island, Graduate Center, The City University of New York, Staten Island, NY, USA

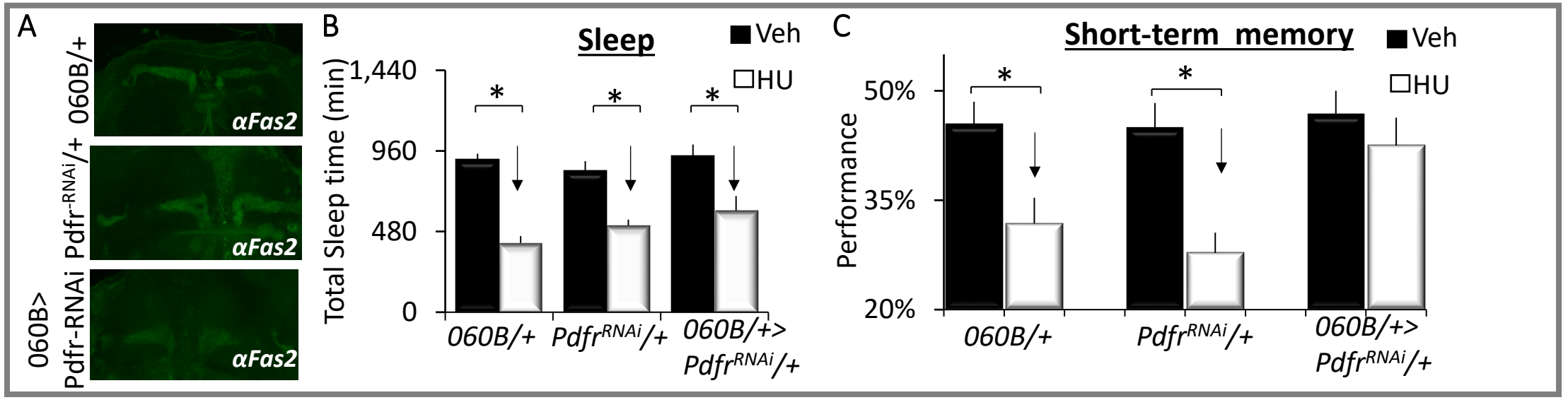
Da-Gsw>UAS-Tau



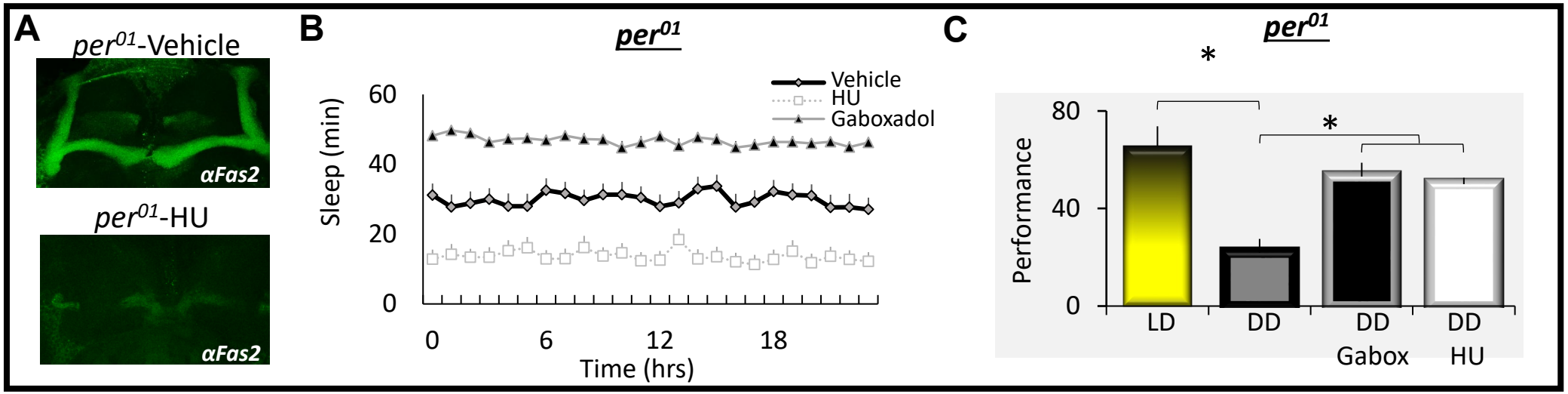
Sleep can reverse cognitive deficits in flies expressing Parkinson's associated genes



Knocking down the Pigment dispersing factor receptor in only 8 neurons prevents STM impairments following MB-ablation

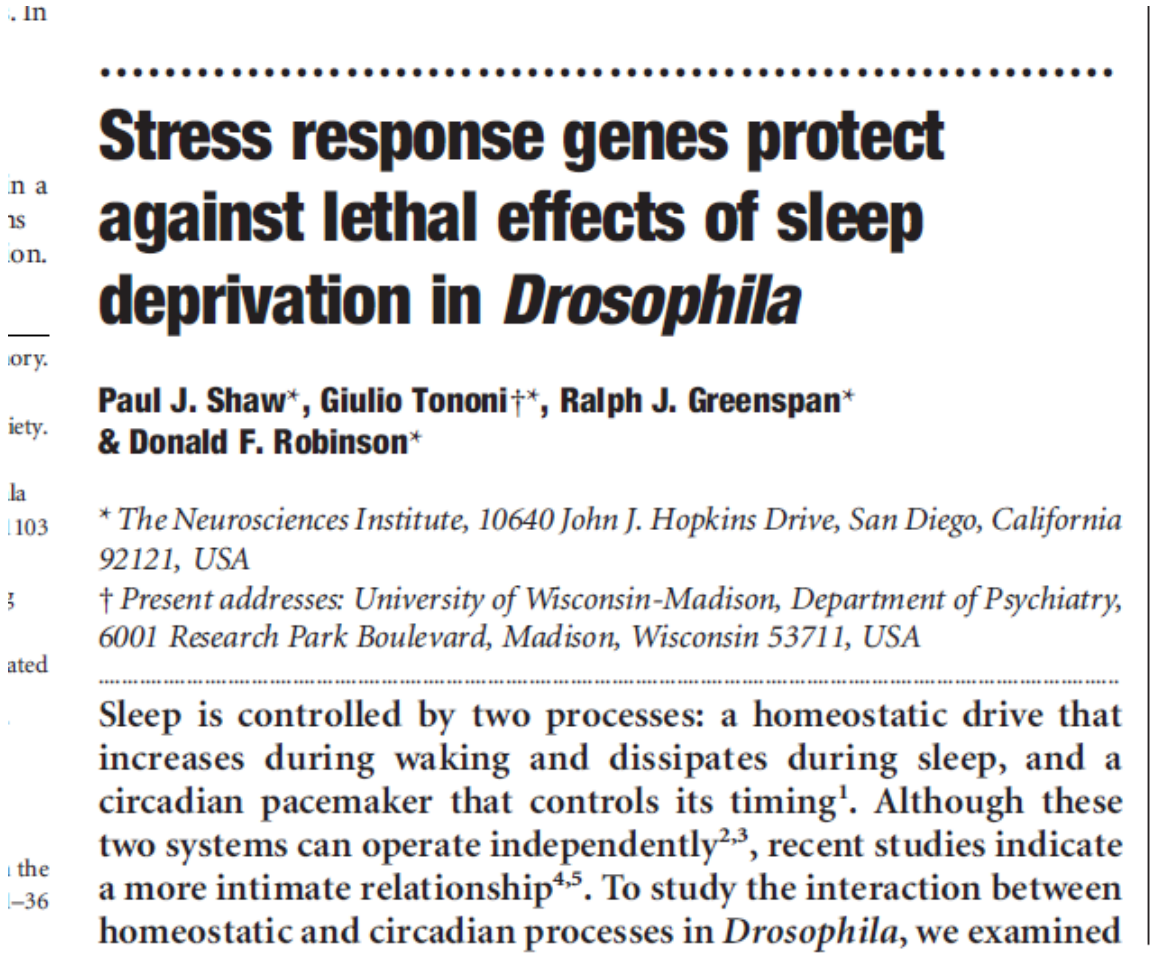


Both Mushroom Body-Ablation and Sleep restore STM to mutants for the canonical clock gene period (*per*^{01}) mutants.



Crisis of Faith:
Sleep does not matter?!!

per^{01} mutants recover from sleep loss 3 times faster than wild-type flies.



Stress response genes protect against lethal effects of sleep deprivation in *Drosophila*

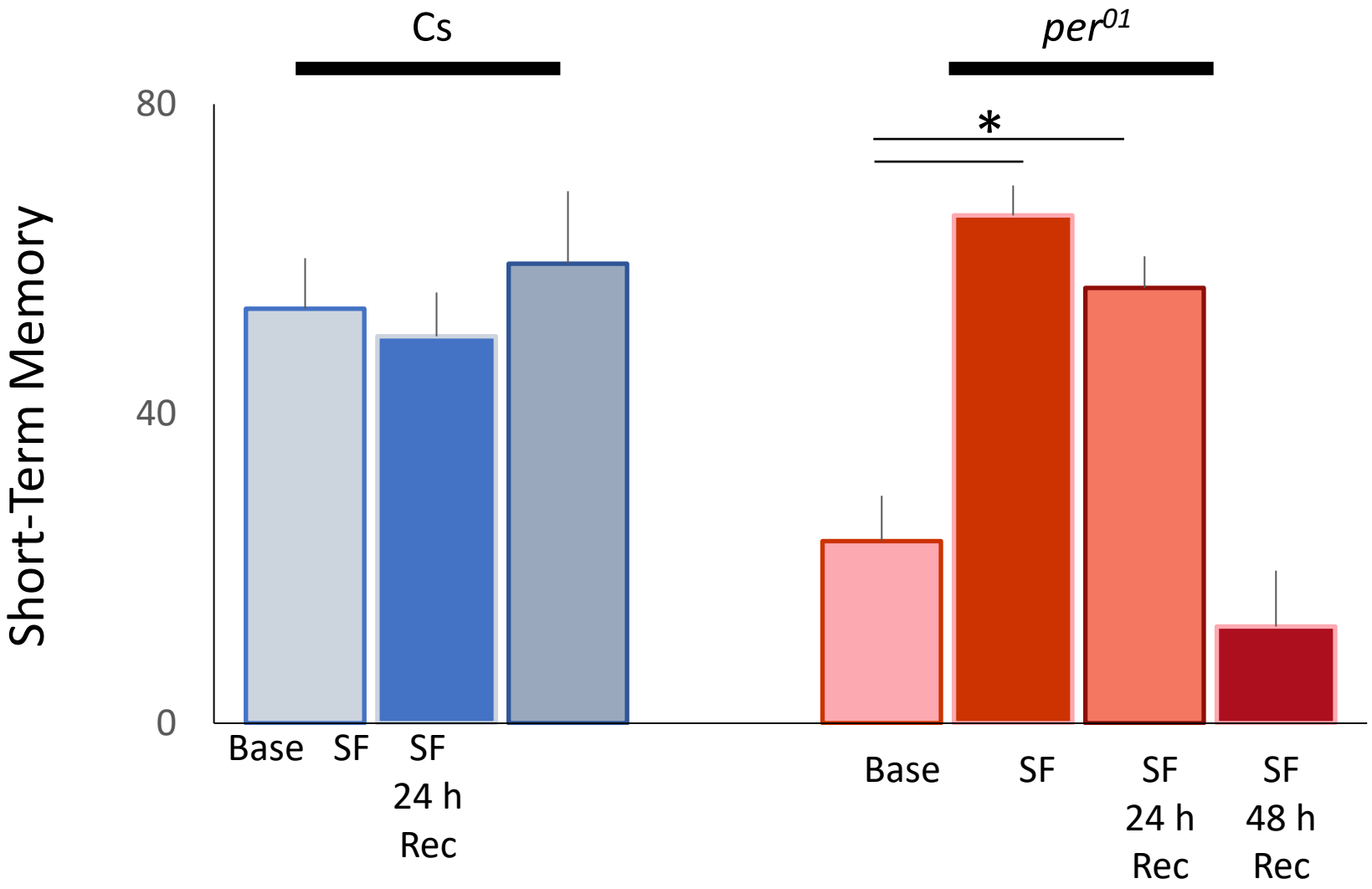
Paul J. Shaw*, Giulio Tononi†*, Ralph J. Greenspan* & Donald F. Robinson*

* *The Neurosciences Institute, 10640 John J. Hopkins Drive, San Diego, California 92121, USA*

† *Present addresses: University of Wisconsin-Madison, Department of Psychiatry, 6001 Research Park Boulevard, Madison, Wisconsin 53711, USA*

Sleep is controlled by two processes: a homeostatic drive that increases during waking and dissipates during sleep, and a circadian pacemaker that controls its timing[1]. Although these two systems can operate independently[2,3], recent studies indicate a more intimate relationship[4,5]. To study the interaction between homeostatic and circadian processes in *Drosophila*, we examined

Sleep Fragmentation Restores STM to per^{01} mutants



Do Flies have Deep Sleep?

SCIENCE ADVANCES | RESEARCH ARTICLE

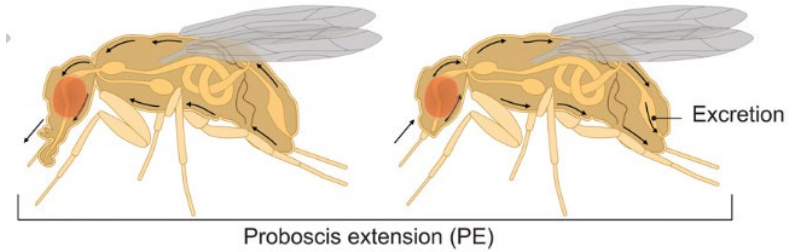
NEUROPHYSIOLOGY

A deep sleep stage in *Drosophila* with a functional role in waste clearance

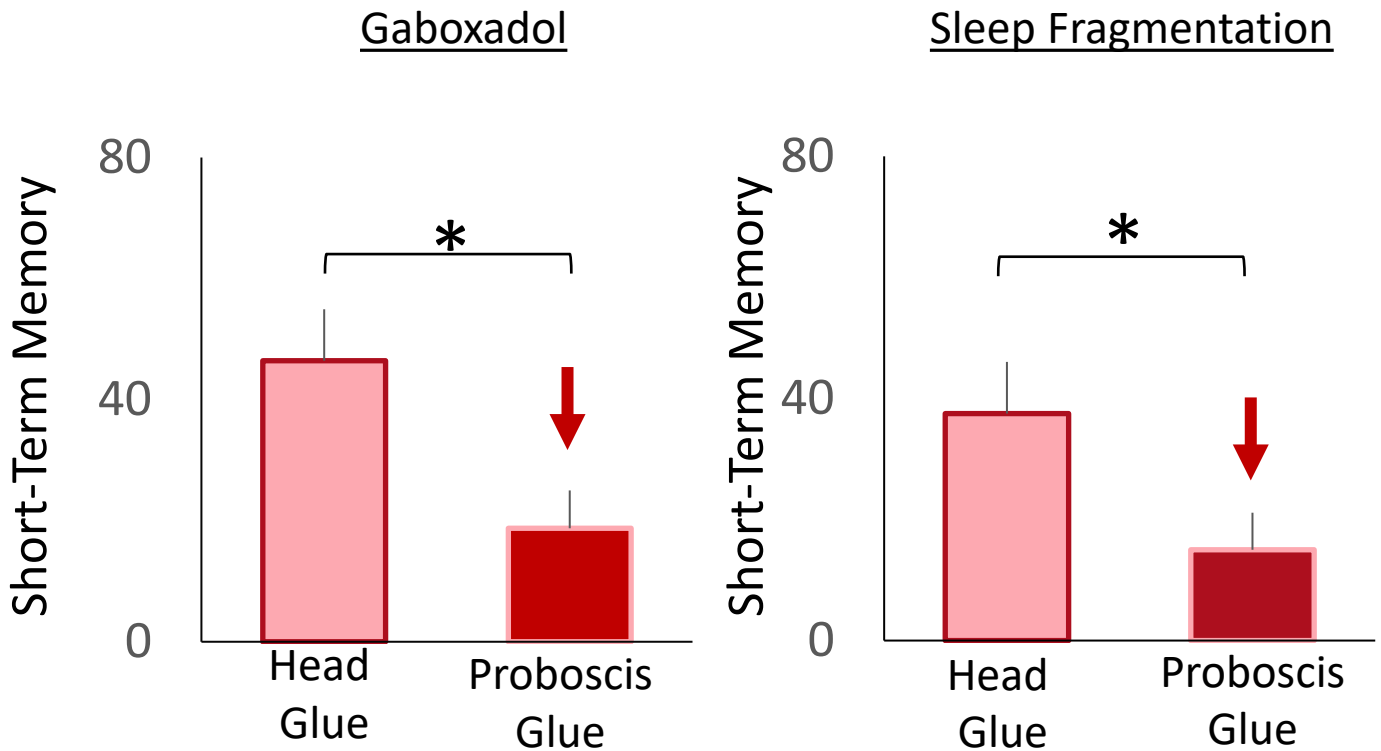
Bart van Alphen[1]*, Evan R. Semenza[1†], Melvyn Yap[2], Bruno van Swinderen[2], Ravi Allada[1]*

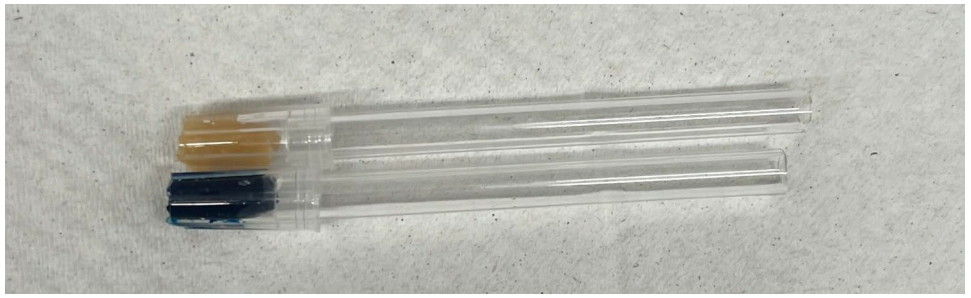
Sleep is a highly conserved state, suggesting that sleep's benefits outweigh the increased vulnerability it brings. Yet, little is known about how sleep fulfills its functions. Here, we used video tracking in tethered flies to identify a discrete deep sleep stage in *Drosophila*, termed proboscis extension sleep, that is defined by repeated stereotyped proboscis extensions and retractions. Proboscis extension sleep is accompanied by highly elevated arousal thresholds and decreased brain activity, indicative of a deep sleep state. Preventing proboscis extensions increases injury-related mortality and reduces waste clearance. Sleep deprivation reduces waste clearance and during subsequent rebound sleep, sleep, proboscis extensions, and waste clearance are increased. Together, these results provide evidence of a discrete deep sleep stage that is linked to a specific function and suggest that waste clearance is a core and ancient function of deep sleep.

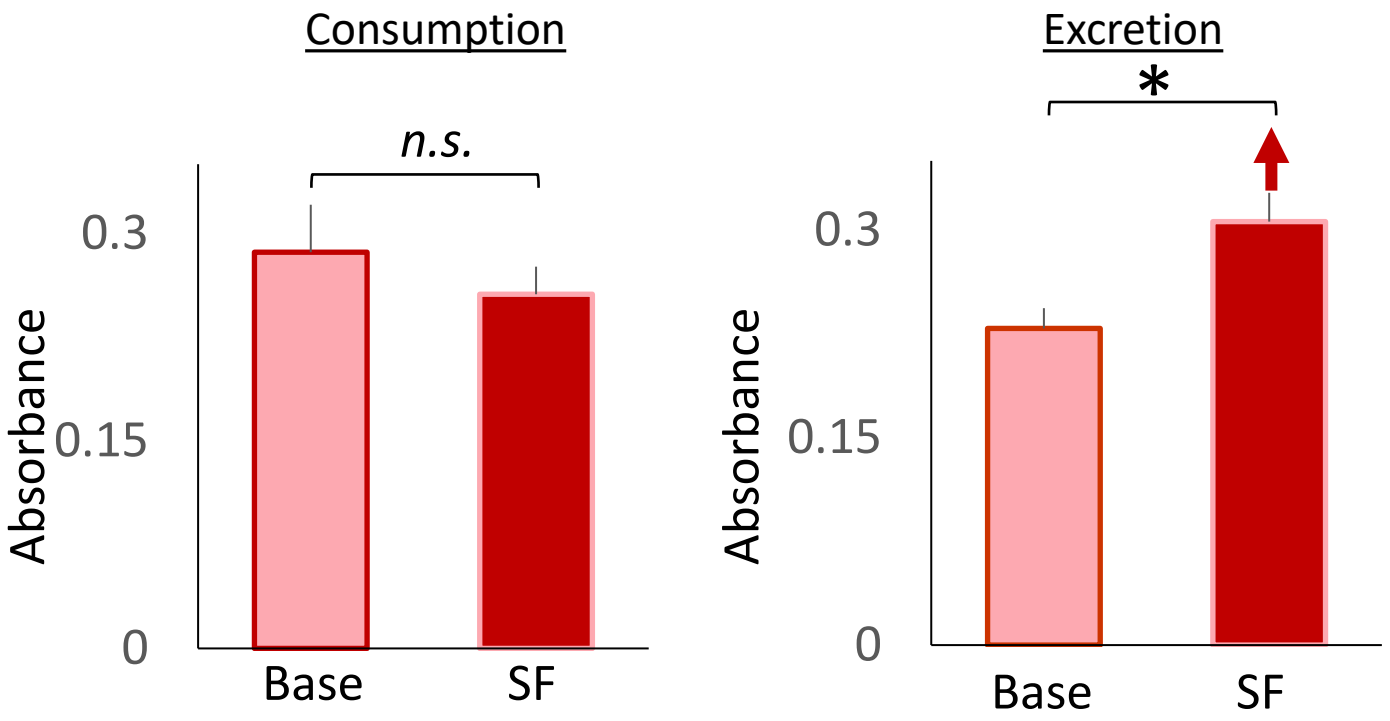
Blocking Proboscis Extension Prevents Memory improvements



VAN ALPHEN ET AL. SCIENCE ADVANCES **20 Jan 2021 Vol 7, Issue 4**






Consumption
n.s.
0.3
0.15
0
Absorbance
Base
SF
Excretion
*
0.3
0.15
0
Absorbance
Base
SF

Collaborators

Washington University

Basic Sleep Research Laboratory

Staying awake so you won't have to

- Stephane Dissel
- Bruno van Swinderen
- Leijuan Cao
- Ellen Morgan
- Denis English
- Zachary Peters Wakefield
- Shohan Shetty,
- Dorothy Chan
- Vincent Duong
- Jeff Donlea
- Hamza Farah
- Chloe McAdams
- Vasilios Loutrianakis
- Melanie Ford
- Lillith Streett
- Erica Periandri
- Zhaoyi Li
- Irene Huang
- Dina Abdala
- Arjan Kalra
- Dorothy Chan
- Lea Sousani
- Brandon Holder

Funding: NINDS, NIA

Is this all hype?