



Diego Rivera

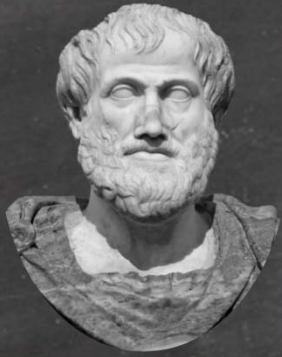
“Sleep is the golden  
chain that ties health  
and our bodies  
together.”

Thomas Dekker

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Mary ET Boyle, Ph. D.

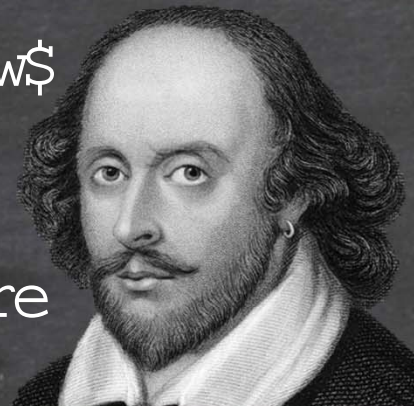
Department of Cognitive Science,  
University of California, San Diego



First, then, this much is clear, that waking and sleep  
appertain to the same part of an animal, inasmuch as they  
are opposites, and sleep is evidently a privation of waking.

Aristotle

Væes gz eoo xsoq wk iqe  
e|ev/ seafe iq wk| erea vw\$  
Z oxog L z ere vœes aqq  
seafe/ vo vz eew wo revw1  
Vkanevseare



Think in the morning.  
Act in the noon.  
Eat in the evening.  
Sleep in the night.

William Blake



350 B.C.

1500's

1700's



Thomas Edison

"We are always hearing people talk about 'loss of sleep' as a calamity. They better call it loss of time, vitality and opportunities."

Photos: Henry Ford Museum

"Sleep is a criminal waste of time  
and a heritage from our cave days."

1800's





Margaret Thatcher

"Sleep is for wimps!"

1980's



A black and white portrait of Bill Clinton. He is looking directly at the camera with a pouting or 'fish face' expression. He has short, light-colored hair and is wearing a dark suit jacket over a white shirt and a patterned tie. The background is dark and textured.

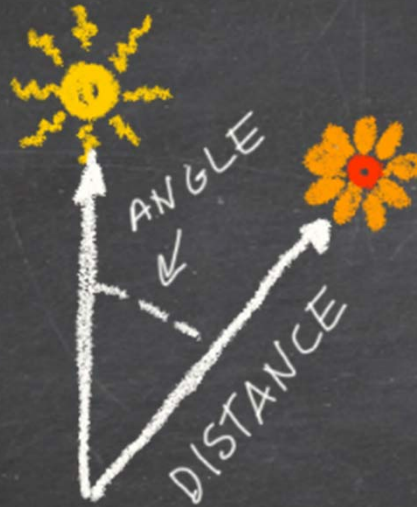
# Bill Clinton

"Every important  
mistake I've made in  
my life, I've made  
because I was too tired."

A horizontal graphic element resembling a film strip. It has a brown, textured background with a series of white, vertical lines along the top edge, mimicking the sprocket holes of a film strip.

1990's

-sleep is essential



imprecise communication

Sleep deprived bees cannot communicate the direction of the food source when they are sleep deprived.

## Sleep deprivation impairs precision of waggle dance signaling in honey bees

Barrett A. Klein<sup>a,1</sup>, Arno Klein<sup>b</sup>, Margaret K. Wray<sup>c</sup>, Ulrich G. Mueller<sup>a</sup>, and Thomas D. Seeley<sup>c</sup>





Sleep deprivation has been indicated as a cause in 7.8 percent of all the Air Force's Class A mishaps (Luna, 2003). Disasters such as Chernobyl, Three Mile Island, Davis-Besse, and Rancho Seco all occurred in the early morning (2:00 a.m. to 4:00 a.m.), a time when sleep deprivation effects are especially powerful, and all involved errors made by people working in groups (Harrison & Horne, 2000). Furthermore, sleep loss was specifically cited as a factor that contributed to the collective human error and poor judgment related to the Space Shuttle Challenger disaster (*Presidential Commission on Space Shuttle Challenger Accident, 1986*).

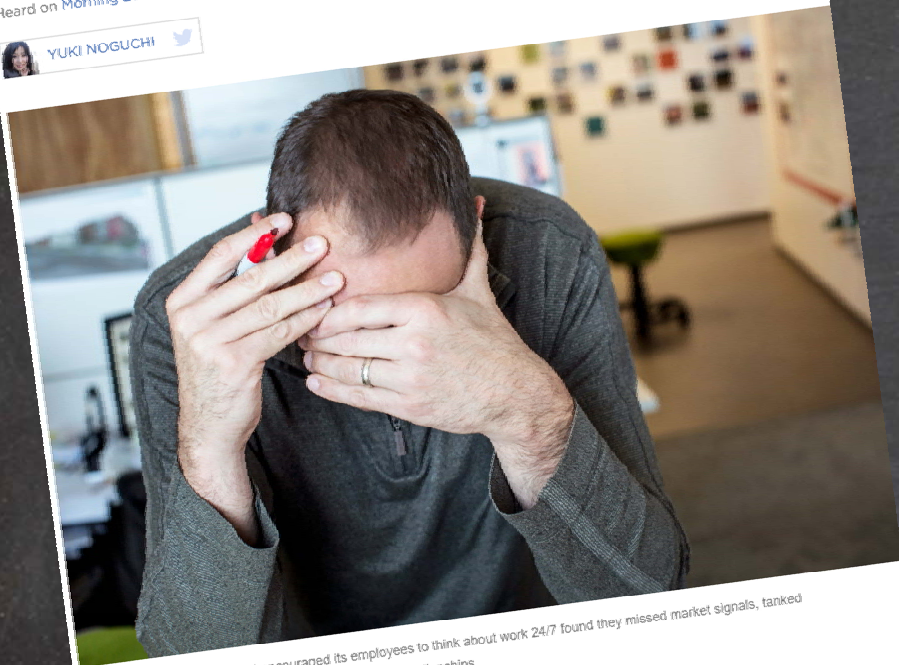


TREATMENTS

## Many Grouchy, Error-Prone Workers Just Need More Sleep

April 26, 2016 · 4:29 AM ET  
Heard on Morning Edition

YUKI NOGUCHI



One Silicon Valley startup that encouraged its employees to think about work 24/7 found they missed market signals, tanked deals and became too irritable to build crucial working relationships.  
Hill Street Studios/Blend Images/Getty Images

Hey! Wake up! Need another cup of coffee?

One Silicon Valley startup that encouraged its employees to think about work 24/7 found they missed market signals, tanked deals and became too irritable to build crucial working relationships.

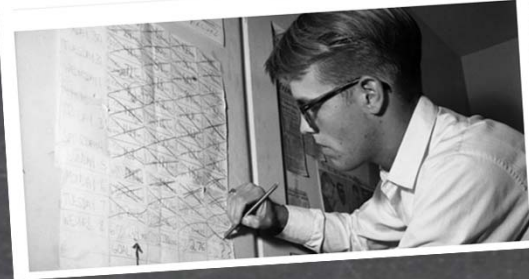
<https://www.npr.org/sections/health-shots/2016/04/26/475287202/many-grouchy-error-prone-workers-just-need-more-sleep>



WHAT HAPPENS  
WHEN WE **DON'T**  
SLEEP?



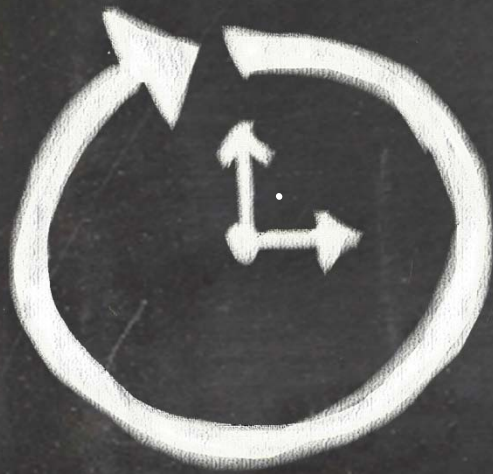
The world's record for the longest sleep deprivation period is 11 days!



1. cognitive & behavioral changes
2. ↓↓ ability to concentrate
3. ↓↓ short-term memory
4. Paranoia & hallucinations



NO SLEEP → COGNITIVE IMPAIRMENT



17-19 HOURS → 0.05 BAC

28 HOURS → 0.1 BAC



*Occup Environ Med* 2000;57:649-655

Moderate sleep deprivation produces impairments in cognitive and motor performance equivalent to legally prescribed levels of alcohol intoxication

A M Williamson, Anne-Marie Feyer



NEW WAY

TO



think

ABOUT

SLEEP



**Sleep is important; our bodies demand it.**



What  
regulates  
sleep?



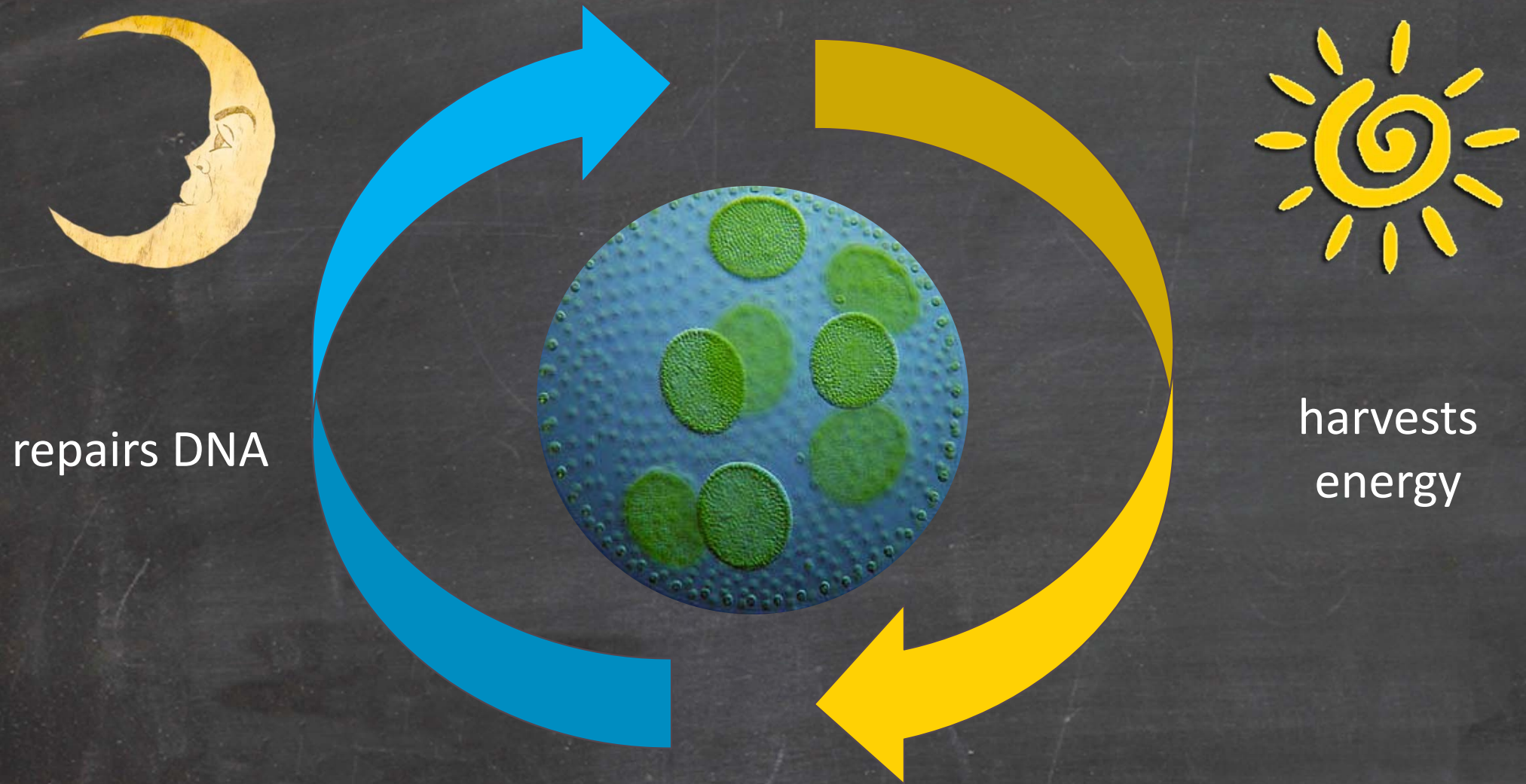


Light & Melatonin  
are the two most  
influential external cues  
that synchronize the  
circadian rhythm

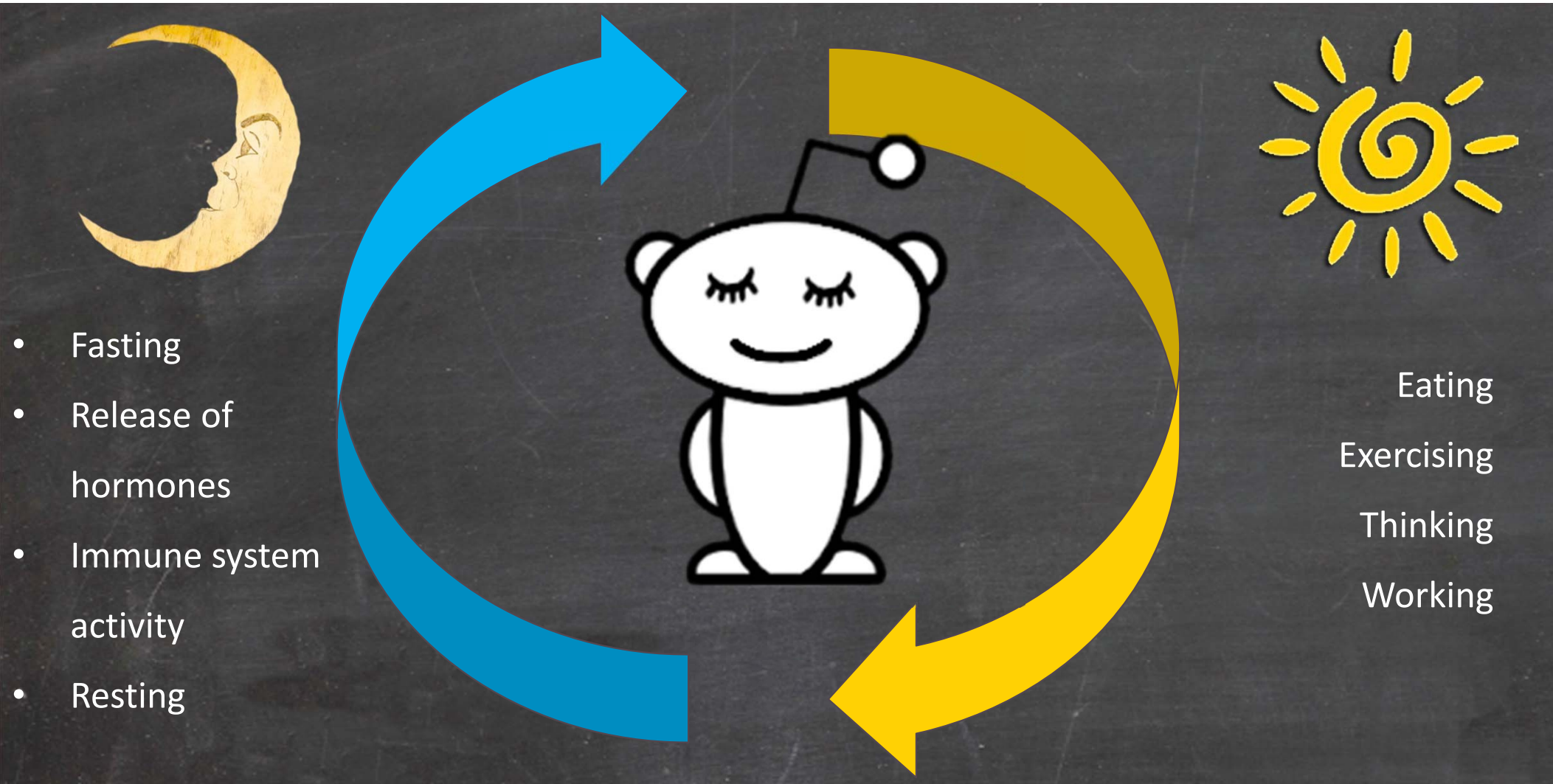
EXTERNAL

*melatonin*

Sleep wake cycle is regulated by the circadian system.



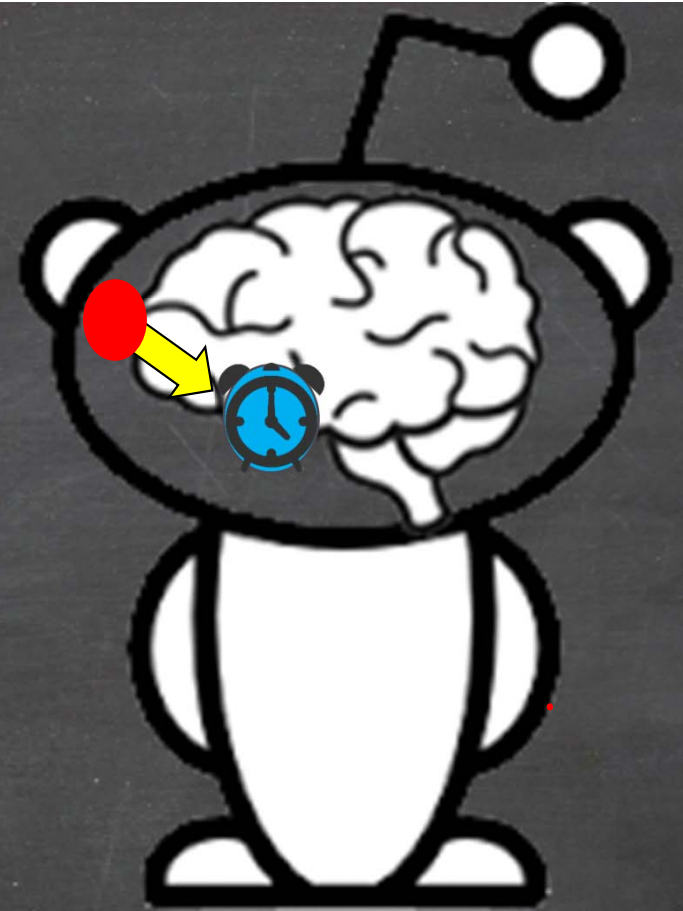
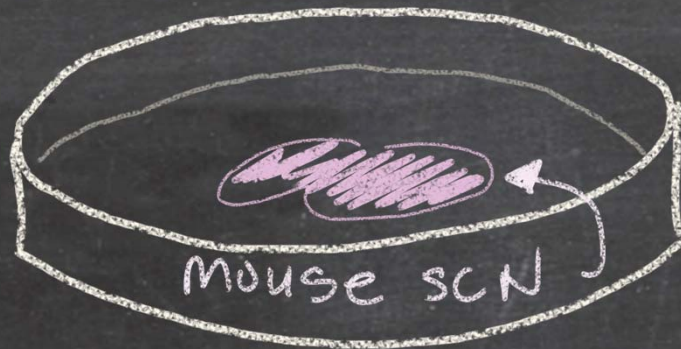
Sleep wake cycle is regulated by the circadian system.



Our metabolic clocks are based on the diurnal rhythm – it is in our genes.



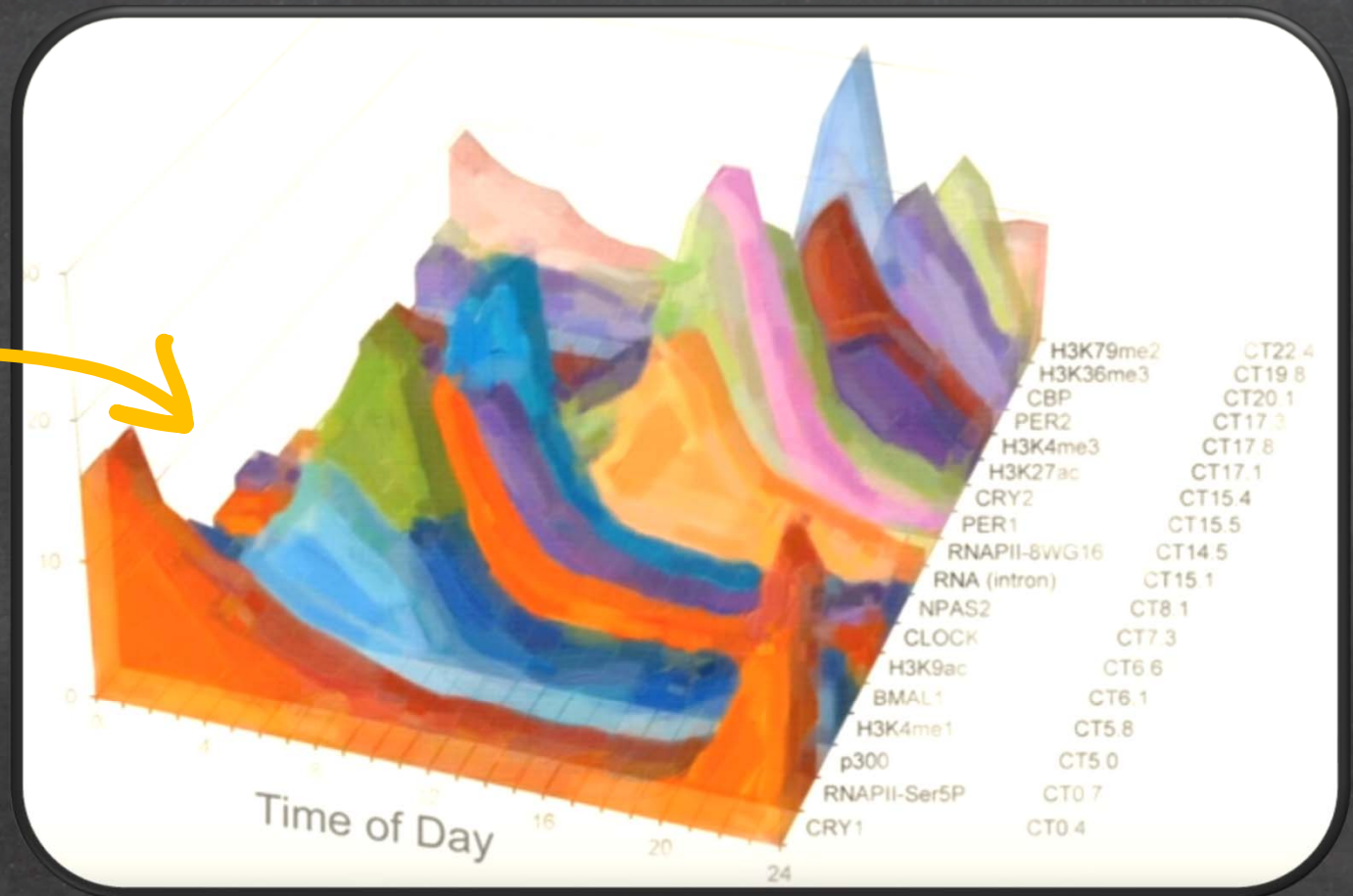
Watch  
brain  
ticking →



Video: J. Takahashi (2013) <https://www.youtube.com/watch?v=ocqn3wYTCRM#>

# Day in the life of a cell 0-24 hours

Genes in  
cells  
cycle on  
and off  
every  
24 hours

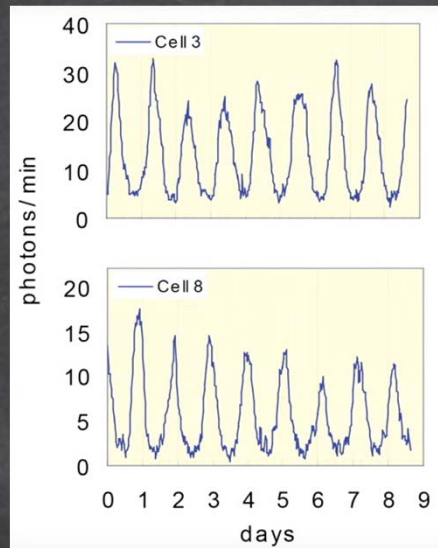




Every cell has it's own clock!

SKIN CELLS

24 HOURS



video recorded for 42 days!



## Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome

Carla S. Möller-Levet, Simon N. Archer, Giselda Bucca, Emma E. Laing, Ana Slak, Renata Kabiljo, June C. Y. Lo, Nayantara Santhi, Malcolm von Schantz, Colin P. Smith, and Derk-Jan Dijk

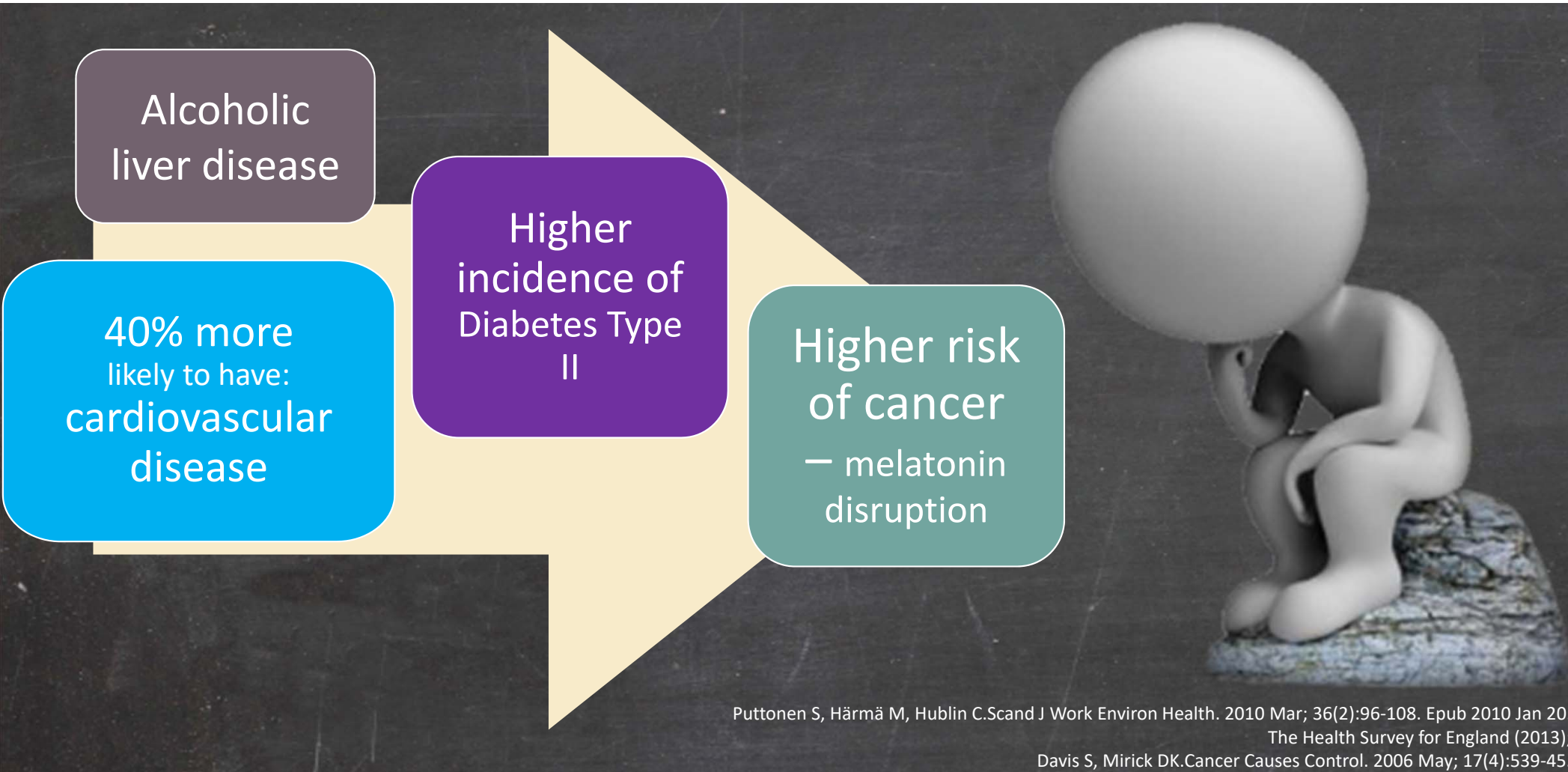
Insufficient sleep and circadian rhythm disruption are associated with negative health outcomes, but the mechanisms involved remain largely unexplored. We show (pp. E1132–E1141) that one wk of insufficient sleep alters gene expression in human blood cells, reduces the amplitude of circadian rhythms in gene expression, and intensifies the effects of subsequent acute total sleep loss on gene expression. The affected genes are involved in chromatin remodeling, regulation of gene expression, and immune and stress responses. The data imply molecular mechanisms mediating the effects of sleep loss on health and highlight the interrelationships between sleep homeostasis, circadian rhythmicity, and metabolism.

One week of insufficient sleep alters gene expression in human blood cells.

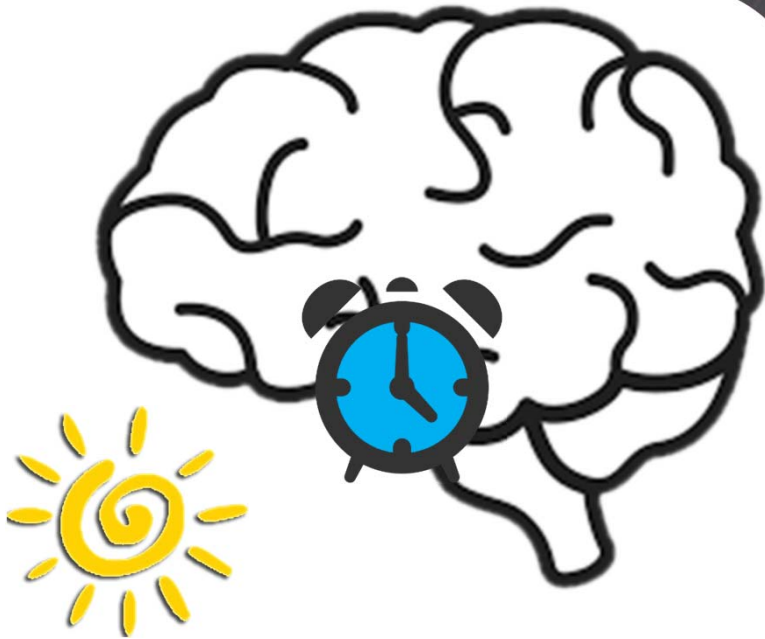
**Intensifies** the effects of subsequent total sleep loss on gene expression

# Immune and stress response

# Shift workers are more prone to developing metabolic disorders







**zeitgeber**

**Food can be a  
zeitgeber for  
the gut.**



intestinal activity and its ability to  
absorb nutrients are dependent on  
the time of day.

**SCN is not the only clock in the body**



**GLUCOSE**

**FAT**



**Cellular response to  
INSULIN is dependent  
on the circadian cycle.**



Johnston, J. (2014) Nutrition Research Reviews, 27, 107–118

**Time of eating has a huge effect on the liver and insulin efficacy**





Insulin-sensitivity is  
dependent on the  
peripheral clock in muscle  
cells.



Johnston, J. (2014) Nutrition Research Reviews, 27, 107–118

Glucose uptake in muscle is dependent on the circadian rhythm.

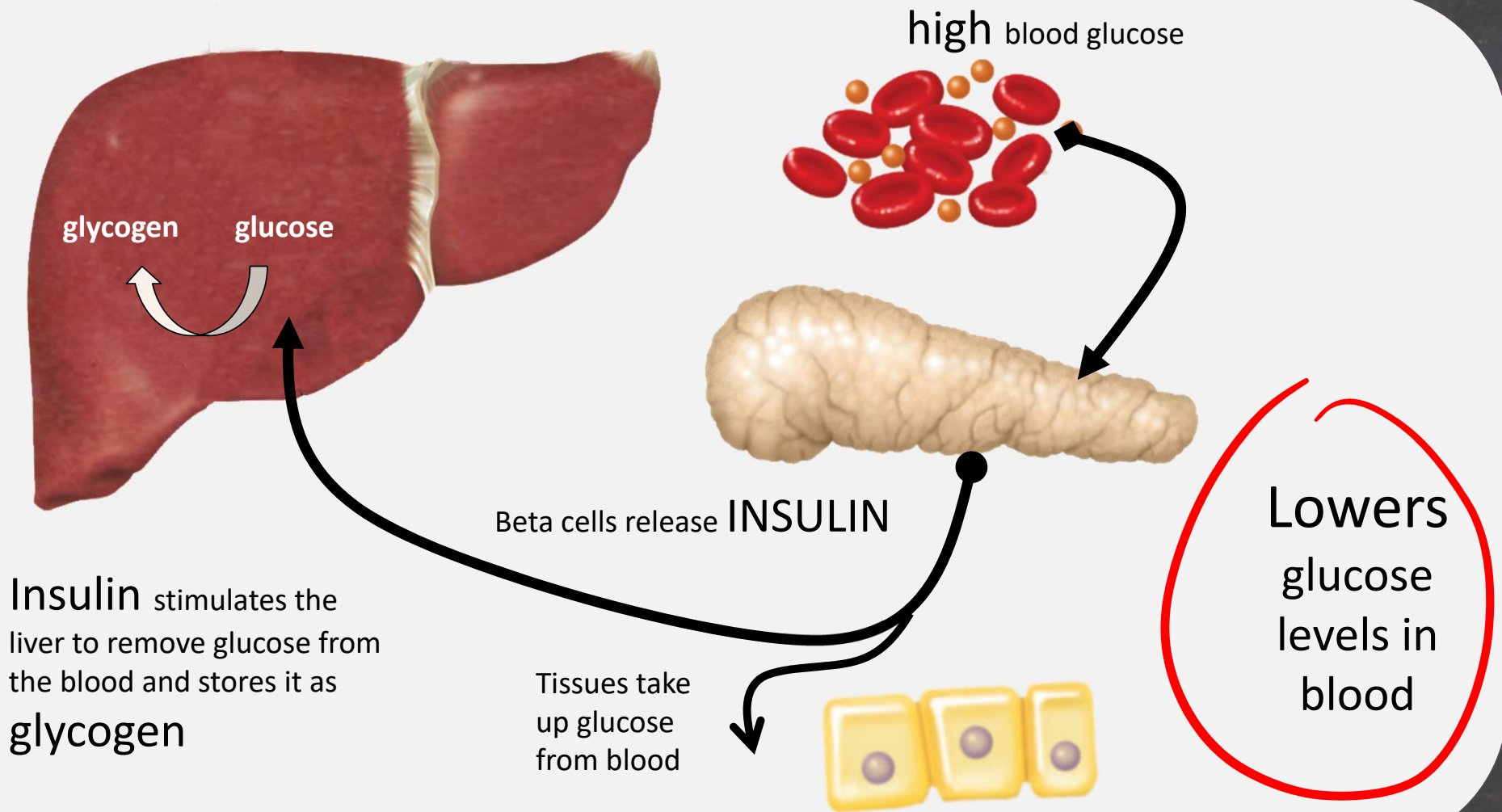
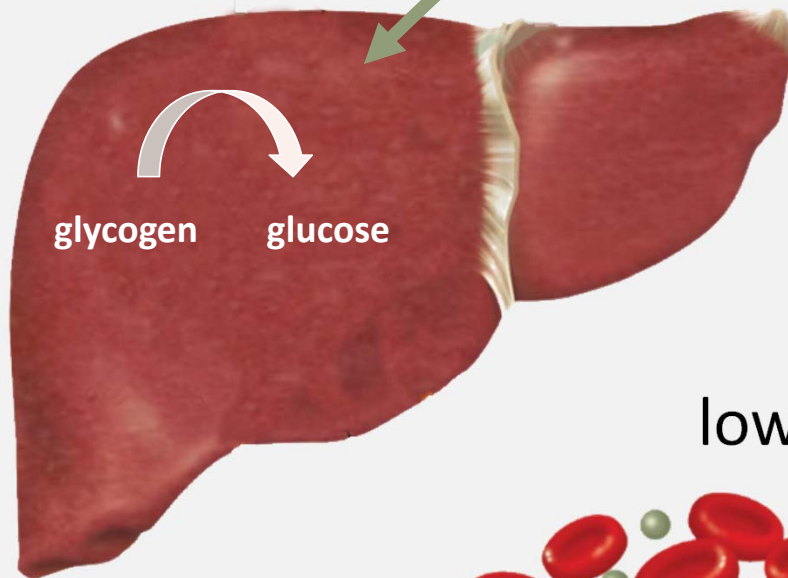


Figure adapted from Kaidanovich-Beilin, O. et al 2012



Glucagon stimulates the conversion of stored glycogen in the liver into glucose.



glycogen      glucose

low blood glucose



Increases  
glucose levels in  
blood

Alpha cells release  
GLUCAGON



Figure adapted from Kaidanovich-Beilin, O. et al 2012

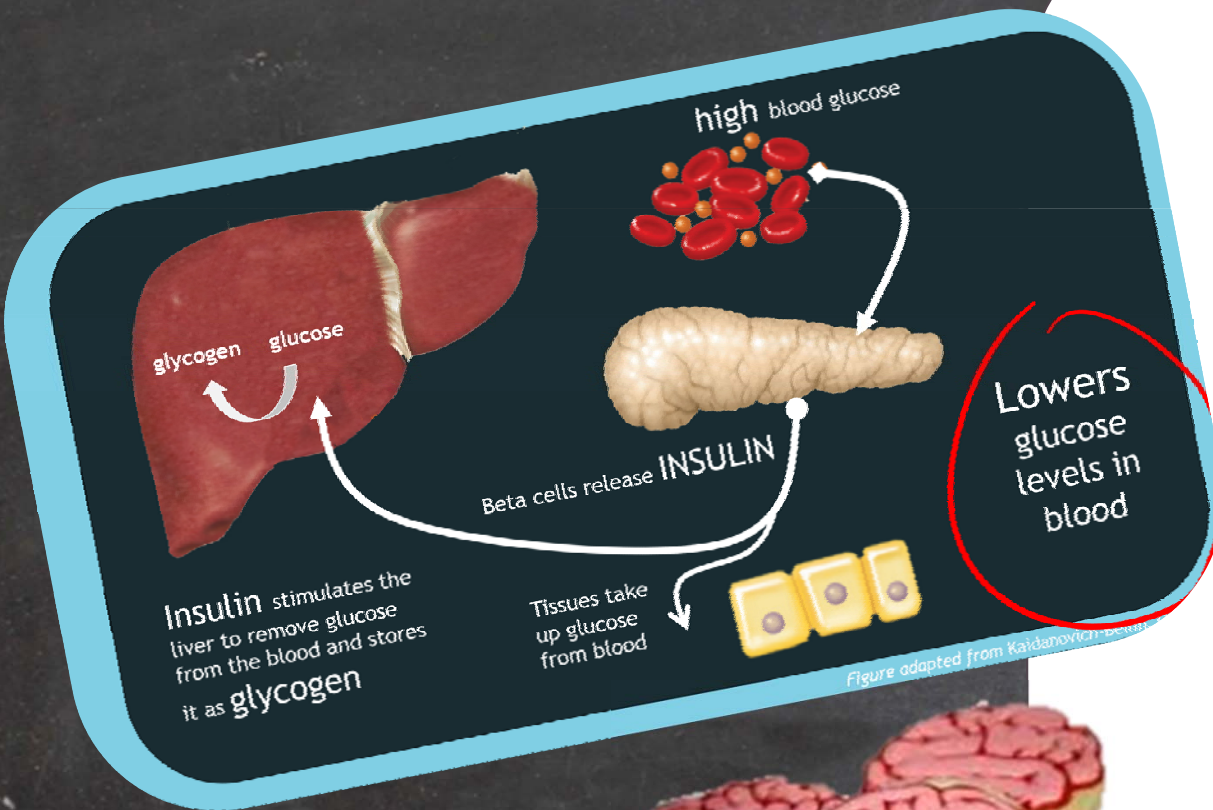
When you eat  
sugar determines  
how your body  
will respond



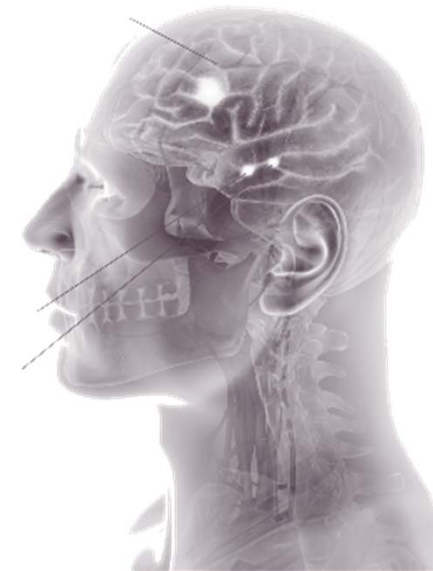
EATING  
SUGAR  
AT NIGHT

→ HIGHER  
BLOOD  
SUGAR





**Insulin activates insulin receptors in the brain → affects feeding behaviors, reward, body metabolism, normal emotion & cognitive behaviors.**



insulin receptors are found throughout the brain – cortex, midbrain and hypothalamus.



The risk of developing Alzheimer's disease is increased by 50 percent in people with diabetes.

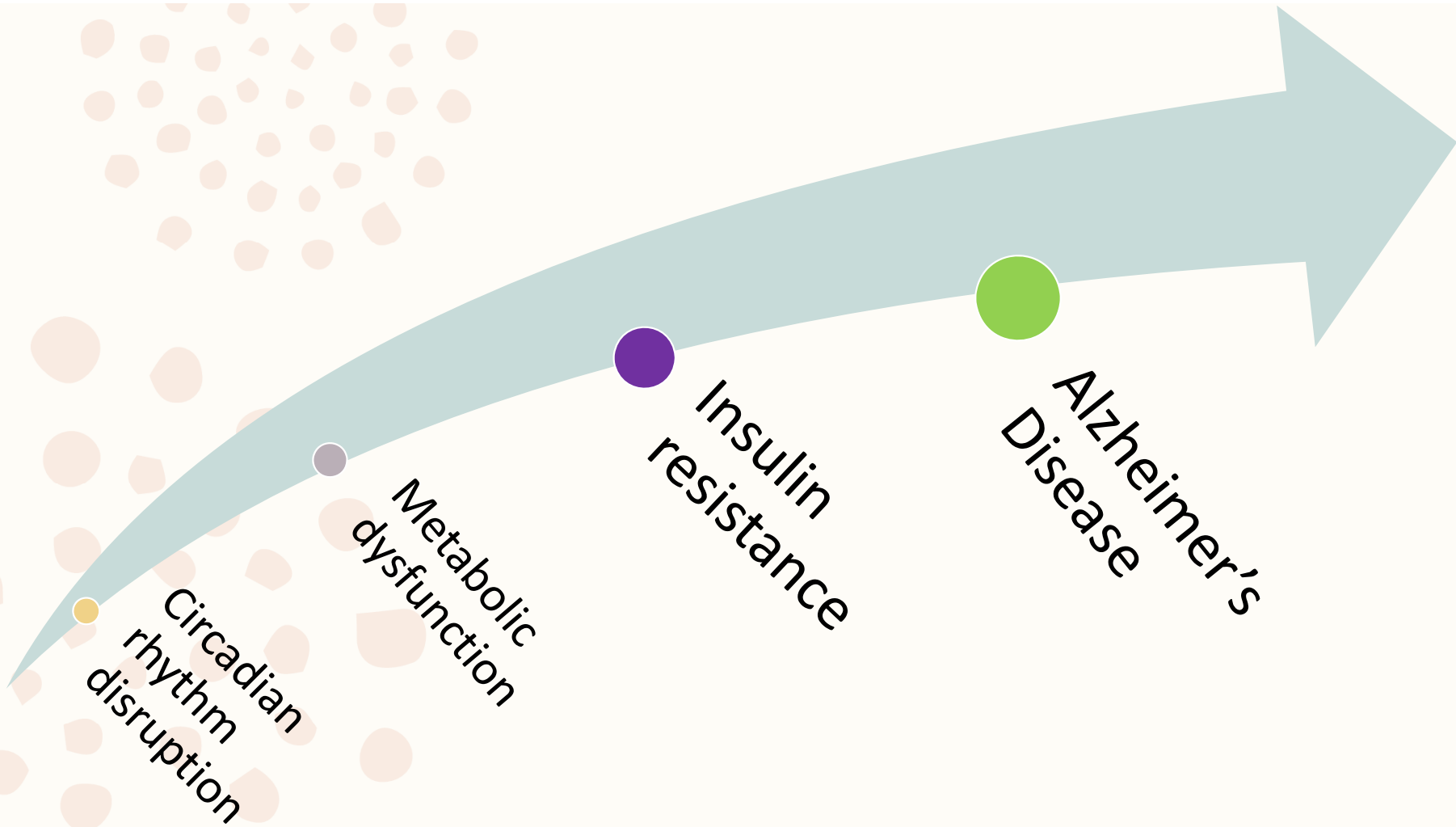
Craft, S. Nat. Rev. Neurol. 8, 360–362 (2012);

**Diabetes is a risk factor for dementia**





PRIVATE COLLECTION/JAMES GOODMAN GALLERY, NEW YORK/BRIDGEMAN ART LIBRARY

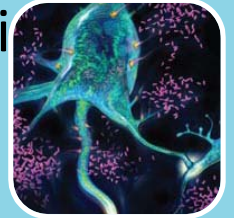


Talbot, K. et al. J. Clin. Invest. 122, 1316–1338 (2012).



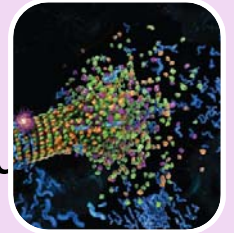
## Amyloid accretion

- 5 – 20 years before diagnosis of Alzheimer's dementia
- damages synapses



## Tau buildup

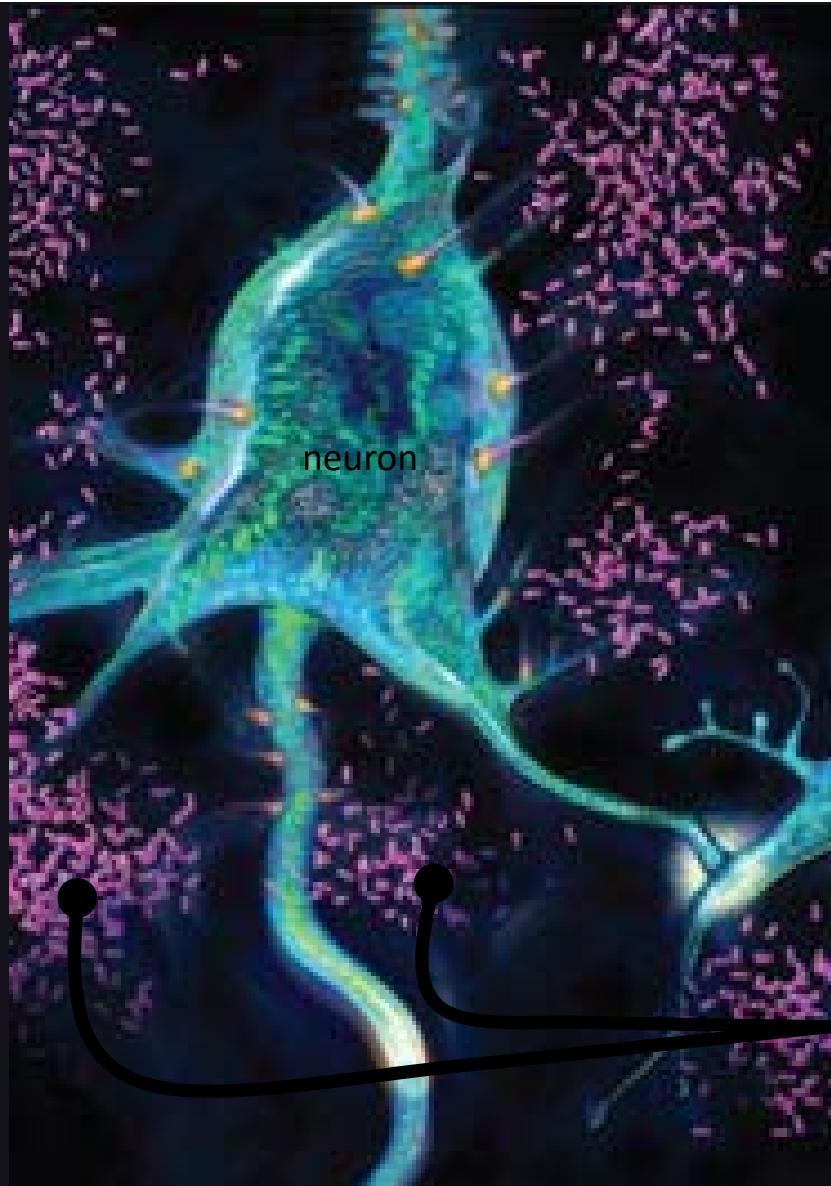
- 1 – 5 years before diagnosis
- Tau protein detaches from the microtubules



## Brain shrinkage

- 1 – 3 years before diagnosis
- Cell death shrinks the brain.





neuron

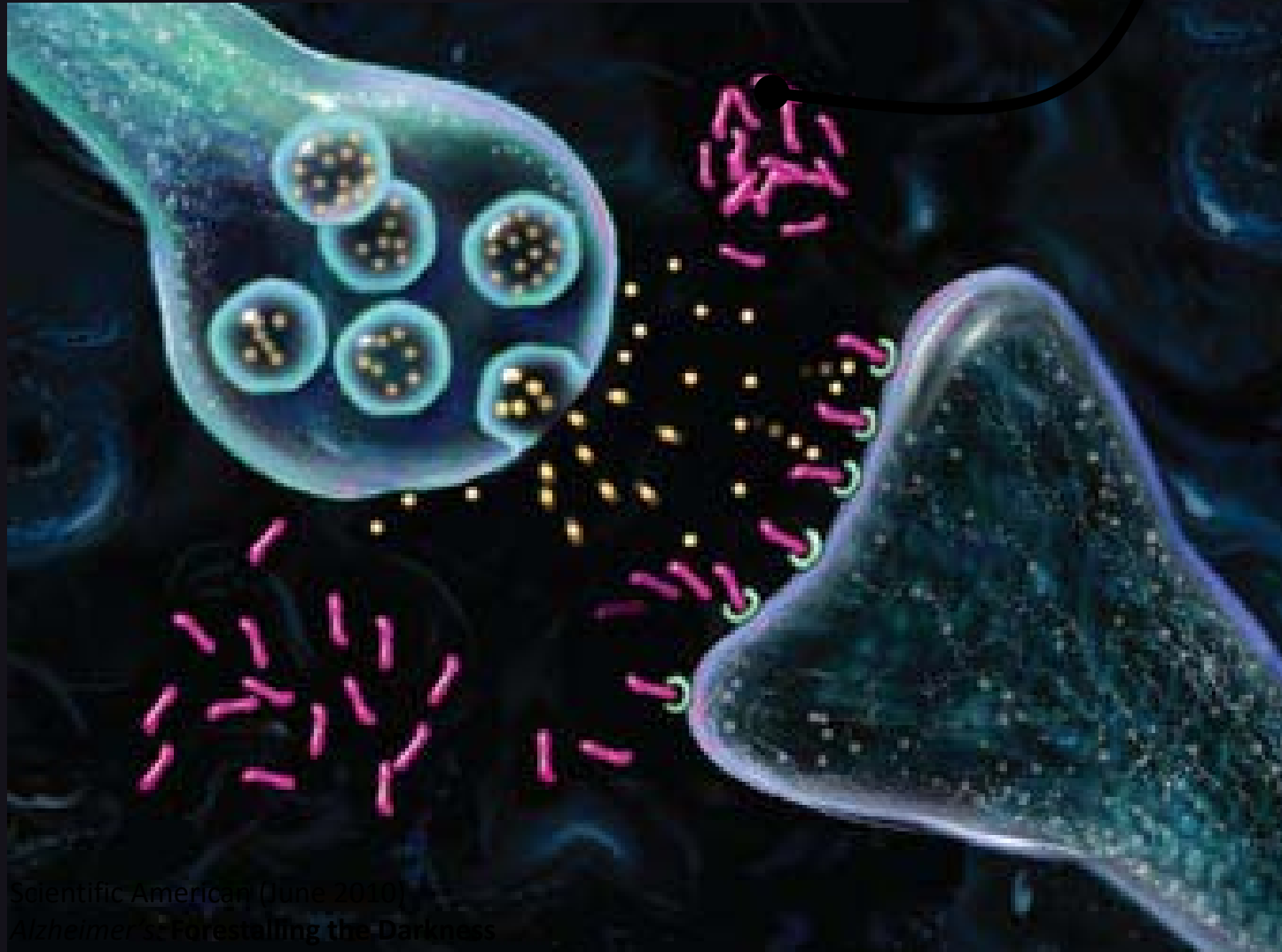
Amyloid Accretion  
5–20 years before diagnosis of  
Alzheimer's dementia

Amyloid-beta plaques

Scientific American (June 2010)  
*Alzheimer's: Forestalling the Darkness*

Amyloid blocks neurotransmitters from reaching the post-synaptic receptors

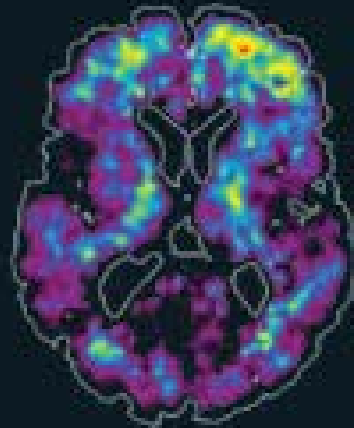
Amyloid-beta plaques



Scientific American (June 2010)  
*Alzheimer's: Foretelling the Darkness*



Baseline

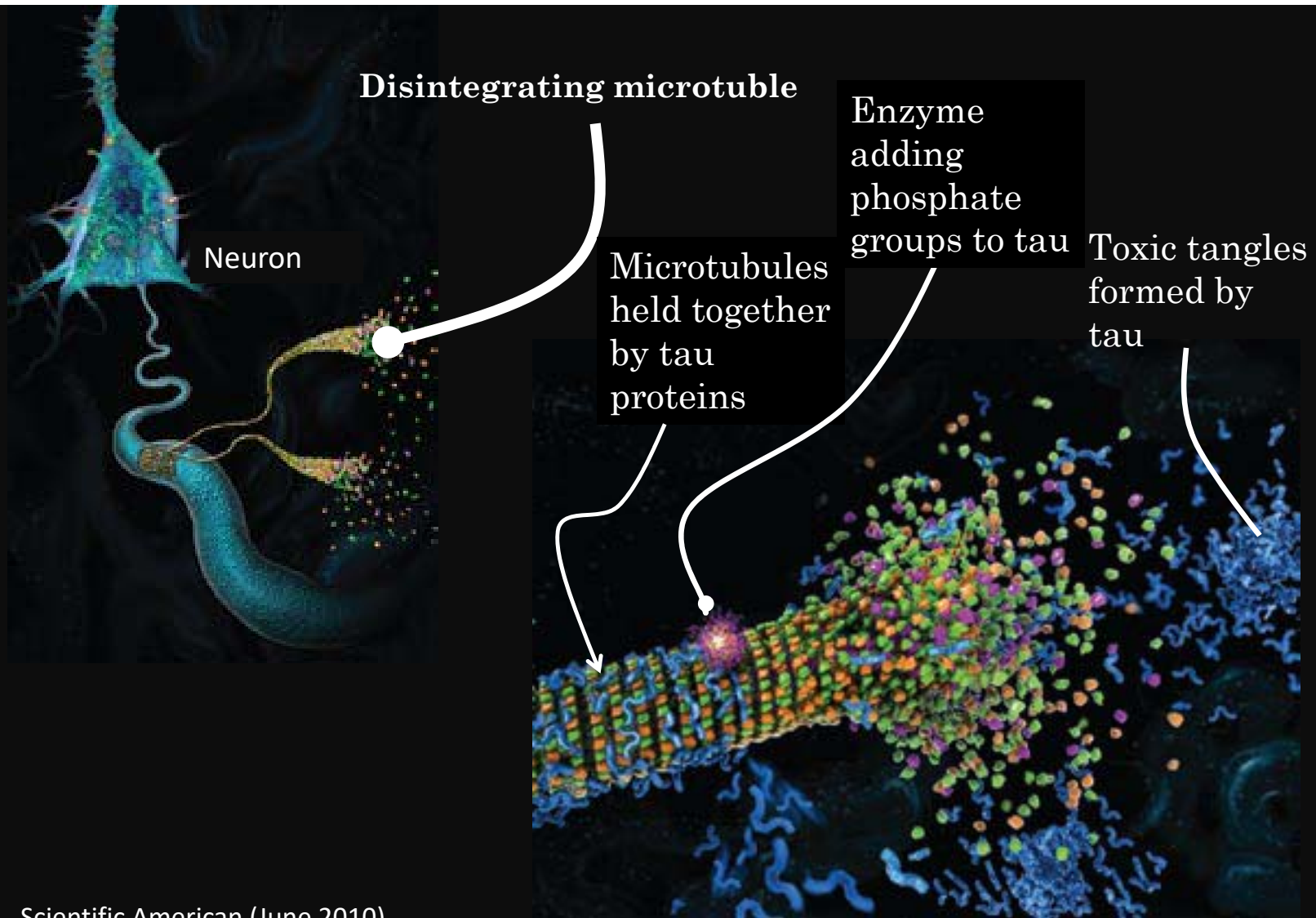


24 months

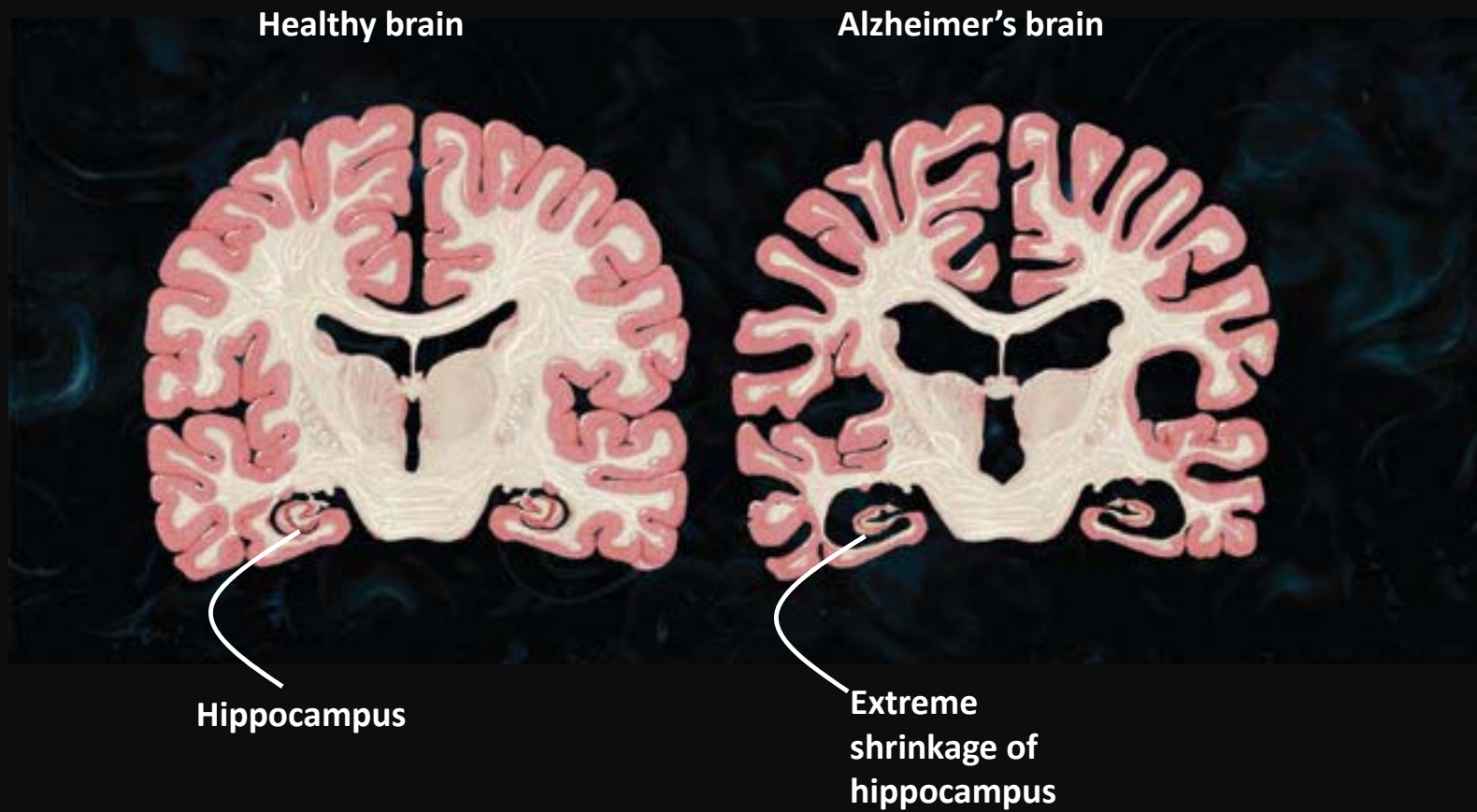


PET scans show increasing retention in the brain's frontal lobes of the amyloid-beta tracer Pittsburgh imaging compound-B (PIB) over the course of two years in a 74-year-old, even while the subject remained cognitively normal.

Scientific American (June 2010)  
*Alzheimer's: Forestalling the Darkness*



Scientific American (June 2010)  
*Alzheimer's: Forestalling the Darkness*



Scientific American (June 2010)  
*Alzheimer's: Forestalling the Darkness*





## High carbohydrate diets and Alzheimer's disease

Samuel T. Henderson\*

High carbohydrate intake worsens cognitive performance and behavior in patients with Alzheimer's disease.

# Hypometabolism:

Decline in glucose metabolism

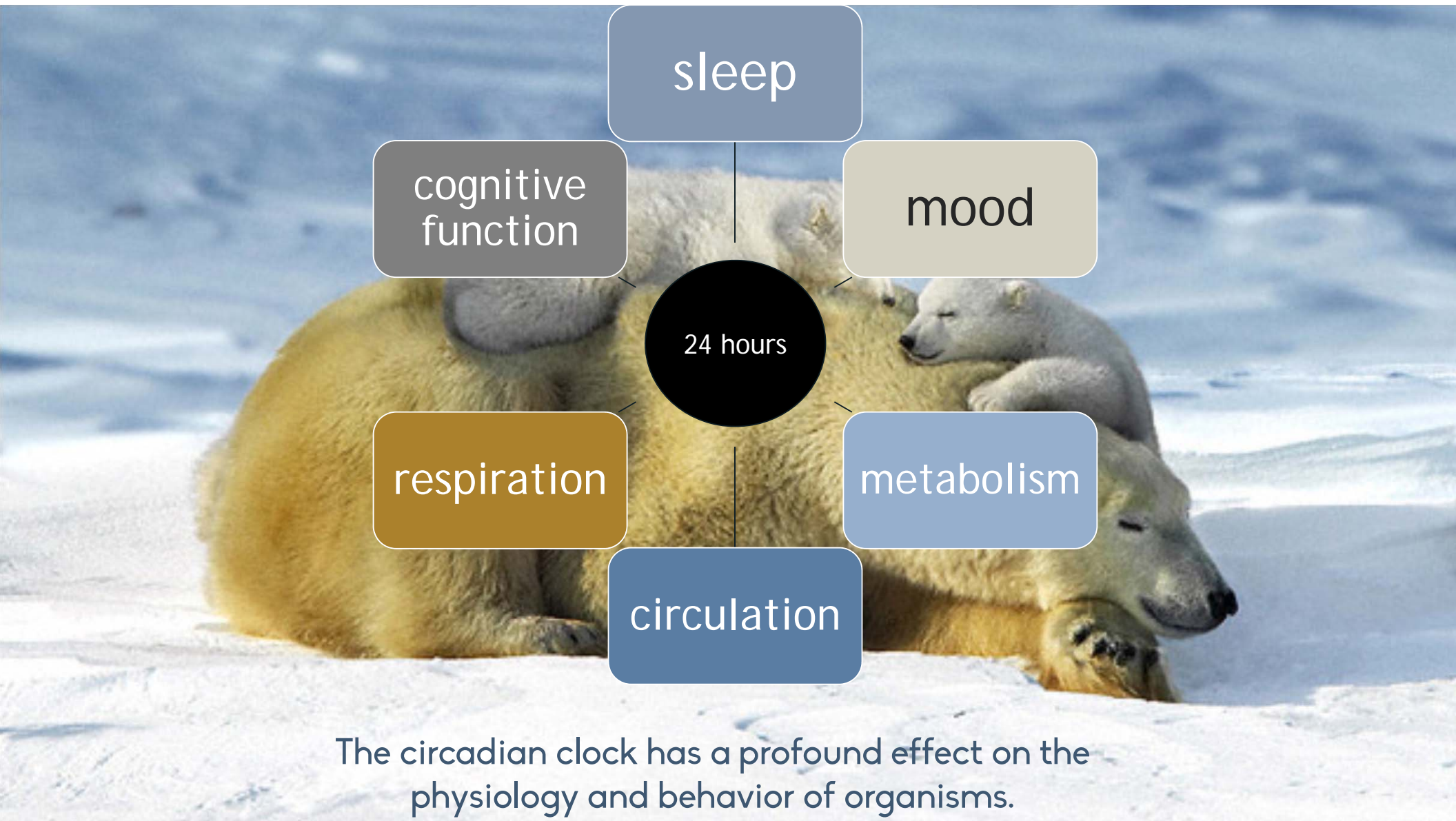
Early feature of AD –  
region specific decline in  
glucose metabolism

Reduction of glucose  
metabolism → reduction  
in function



The circadian clock has a profound effect on the physiology and behavior of organisms.

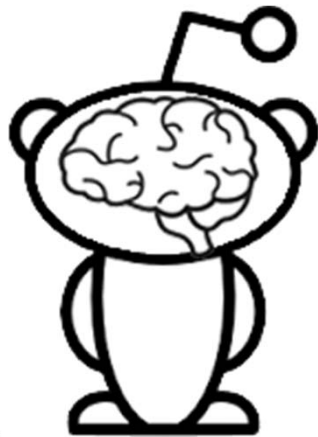




## **A Single Night of Partial Sleep Deprivation Induces Insulin Resistance in Multiple Metabolic Pathways in Healthy Subjects**

Esther Donga, Marieke van Dijk, J. Gert van Dijk, Nienke R. Biermasz, Gert-Jan Lammers, Klaas W. van Kralingen, Eleonara P. M. Corssmit, and Johannes A. Romijn

Departments of Endocrinology and Metabolic Diseases (E.D., M.v.D., N.R.B., E.P.M.C., J.A.R.), Neurology (J.G.v.D., G.-J.L.), and Pulmonology (K.W.v.K.), Leiden University Medical Center, 2300 RC Leiden, The Netherlands



the effect of a single night of  
partial sleep on insulin  
sensitivity

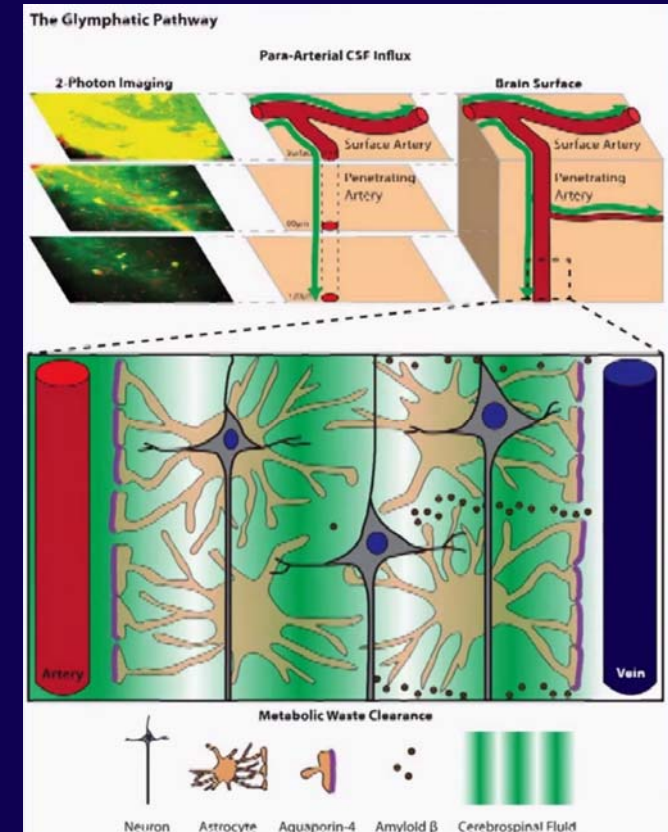
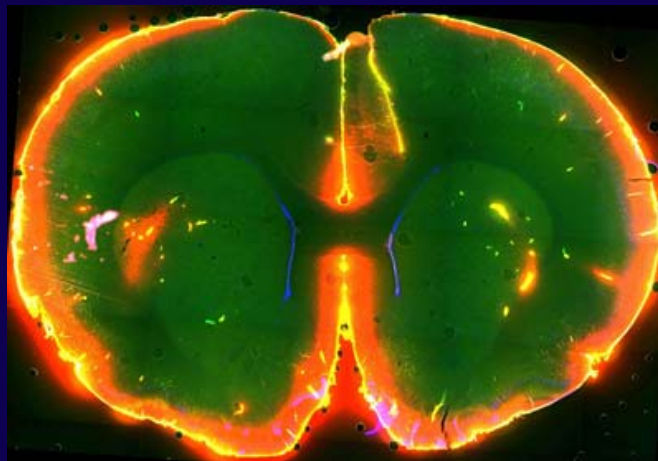




# Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie,<sup>1\*</sup> Hongyi Kang,<sup>1\*</sup> Qiwu Xu,<sup>1</sup> Michael J. Chen,<sup>1</sup> Yonghong Liao,<sup>1</sup> Meenakshisundaram Thiagarajan,<sup>1</sup> John O'Donnell,<sup>1</sup> Daniel J. Christensen,<sup>1</sup> Charles Nicholson,<sup>2</sup> Jeffrey J. Iliff,<sup>1</sup> Takahiro Takano,<sup>1</sup> Rashid Deane,<sup>1</sup> Maiken Nedergaard<sup>1†</sup>

The conservation of sleep across all animal species suggests that sleep serves a vital function. We here report that sleep has a critical function in ensuring metabolic homeostasis. Using real-time assessments of tetramethylammonium diffusion and two-photon imaging in live mice, we show that natural sleep or anesthesia are associated with a 60% increase in the interstitial space, resulting in a striking increase in convective exchange of cerebrospinal fluid with interstitial fluid. In turn, convective fluxes of interstitial fluid increased the rate of  $\beta$ -amyloid clearance during sleep. Thus, the restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate in the awake central nervous system.

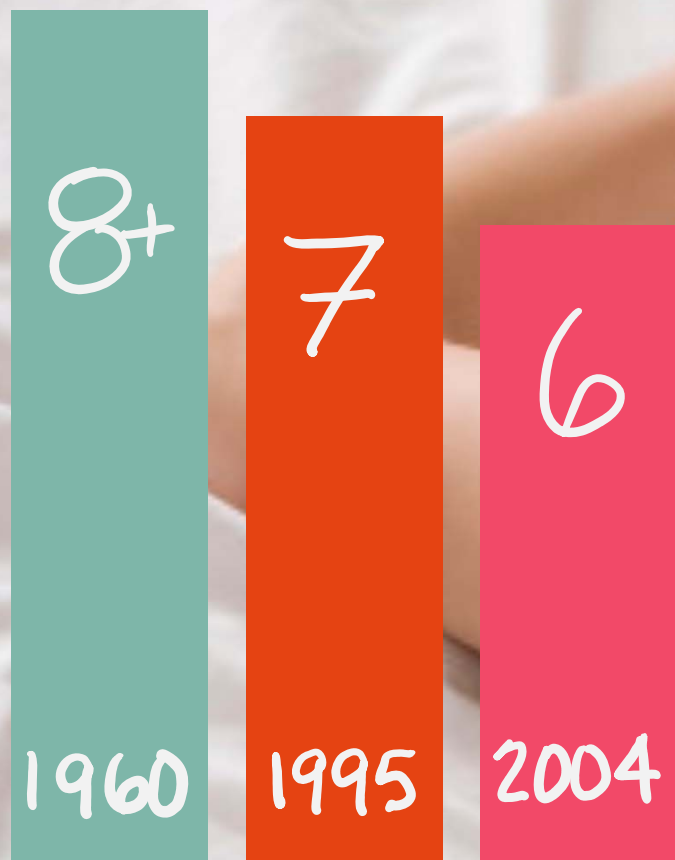


<https://www.youtube.com/watch?v=ci5NMscKJws>



UNIVERSITY *of*  
ROCHESTER  
MEDICAL CENTER

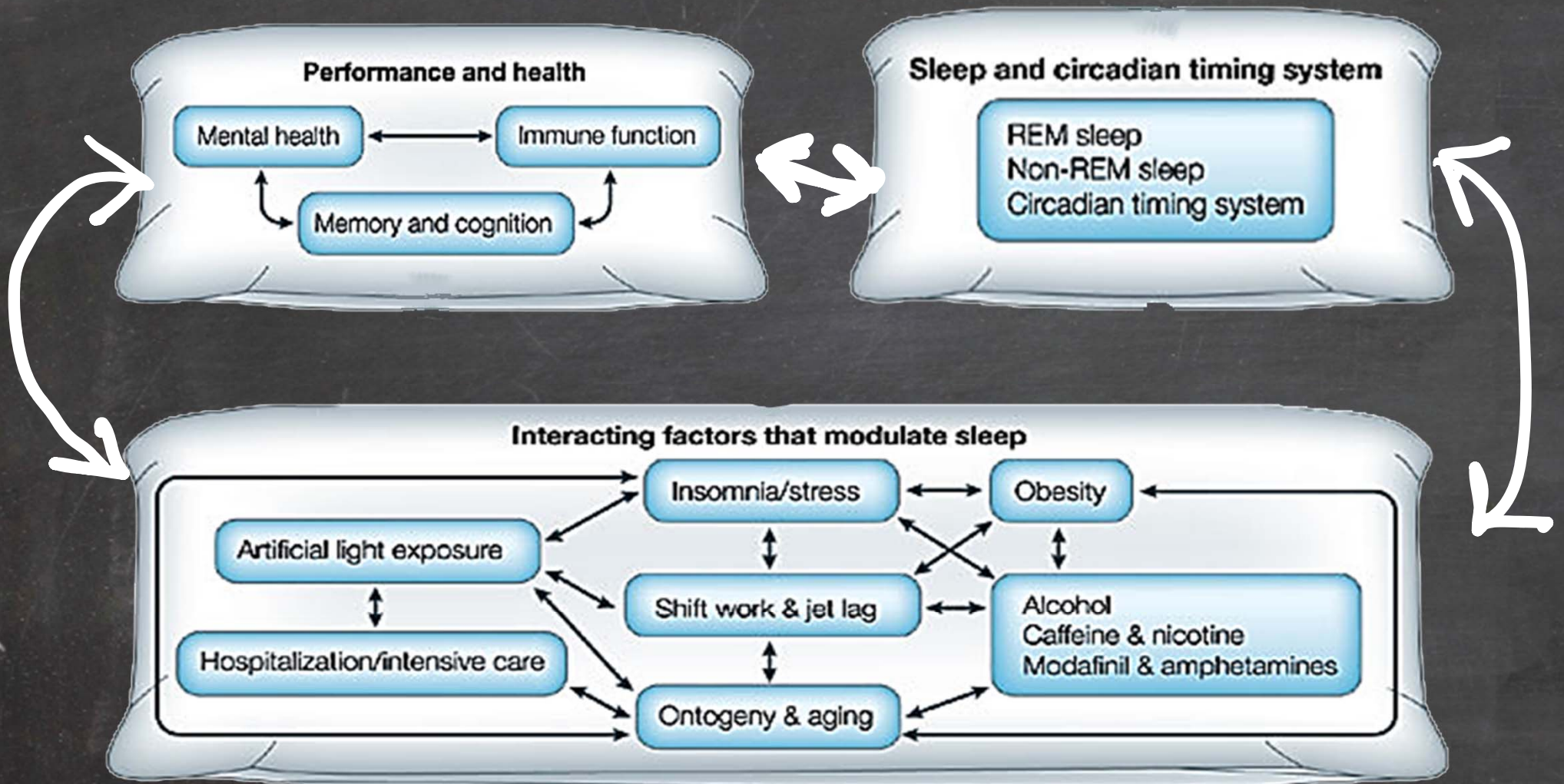
# Average Number of Hours of Sleep per Night



Are you  
getting  
enough sleep?

Kripke, D et al (1979) Arch Gen Psychiatry;  
Gallup Organization (1995), Sleep in America;  
National Center for Health Statistics (1984 & 2004) Morb Mortal Wkly Rep 2005





Adapted from: Nature Neuroscience Reviews

Imagine the  
benefits that would  
await you if you got  
one more hour of  
sleep?



