Sleep Cycle Shift and its effects on Cognitive Function
Organisms have evolved to keep time with the earth’s light and dark cycle.

Circadian clocks allow organisms to predict sunrise and sunset.
Why did organisms evolve timekeeping?

Hypothesis A: multiple circadian clock systems evolved independently

Protect fragile DNA from sun’s UV rays?

Hypothesis B: one clock evolved - to reduce oxygen damage to cells

Reactive Oxygen Species (ROS)
- $\bullet =$ unpaired electrons
- $\text{O}_2^\cdot$ oxygen
- $\text{O}_2^2$ peroxide
- $\text{O}_2^-$ superoxide anion
- $\text{OH}^-$ hydroxyl radical
Light & Melatonin are the two most influential external cues that synchronize the circadian rhythm.
Superchiasmatic Nucleus in the brain is the “master clock” used to coordinate and synchronize most of the body clocks in the periphery.
If the sleep wake cycle is disrupted it can cause metabolic dysregulation.

- Metabolic disruption
- Weight gain, obesity
- Impaired immunity
- Cognitive malfunction

Shift work
Jet lag
Sleep disorders
Poor sleep hygiene
“All-nighters”
Cyanobacteria is a photoautotrophic organism that has a self-sustained circadian rhythm.
Eating
Exercising
Thinking
Working

- Fasting
- Release of hormones
- Immune system activity
- Resting

Our metabolic clocks are based on the diurnal rhythm - it is in our genes.
Shift workers are more prone to developing metabolic disorders

40% more likely to have: cardiovascular disease

Higher incidence of Diabetes Type II

Higher risk of cancer - melatonin disruption


The Health Survey for England (2013); Davis S, Mirick DK. Cancer Causes Control. 2006 May; 17(4):539-45.
Circadian disruption affects multiple organ systems:

“The diagram provides examples of how circadian disruption negatively impacts the brain and the digestive, cardiovascular, and reproductive systems.

Though the diagram displays unidirectional affects, there are various feedback loops that exist within the system and interactions that occur between these systems.”
Obesity and the circadian clock disruption

Disrupted circadian clock increases risk of:

- Obesity
- Diabetes
- Heart disease

It’s not only what you eat but when you eat!

Insulin sensitivity follows circadian clock:

- Other than being nocturnal, mice and men have the same molecular mechanisms underlying circadian rhythm.

- Insulin action follows a 24-hour clock.

- Tissue is resistant to insulin during the fasting phase (night time) and sensitive to insulin during the active phase (day time).

- During inactive phase, glucose is converted to fat.

- During active phase, glucose is used for energy and other tissue building.

No thanks. I read somewhere that late daytime snacking can be bad for your health.

What happens to insulin when the circadian clock is disrupted?

Two approaches:

A

Knock out mice (Bmal1 -/-):

Disrupt circadian clock proteins

Disrupt circadian rhythm

Lights on all day and night

24/7 insulin resistant mode (similar to inactive/fasting phase)

B

Wild type mice


Helps to explain data on night shift workers and obesity

gained more weight, added more fat
zeitgeber

SCN is not the only clock in the body.

Food can be a zeitgeber for the gut.

intestinal activity and its ability to absorb nutrients are dependent on the time of day.
Time of eating has a huge effect on the liver and insulin efficacy.
Insulin stimulates the liver to remove glucose from the blood and stores it as glycogen. Beta cells release insulin. Tissues take up glucose from the blood. High blood glucose levels are lowered. Figure adapted from Kaidanovich-Berlin, O. et al. 20
Glucagon stimulates the conversion of stored glycogen in the liver into glucose.

Alpha cells release GLUCAGON. Increases glucose levels in blood.

Figure adapted from Kaidanovich-Beilin, O. et al. 2012
Glucose uptake in muscle is dependent on the circadian rhythm.

Insulin-sensitivity is dependent on the peripheral clock in muscle cells.
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.
Diabetes is a risk factor for dementia. 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);
Cerebral excess release of neurotransmitter amino acids subsequent to reduced cerebral glucose metabolism in early-onset dementia of Alzheimer type

Short Note

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Accepted November 2, 1988

Summary. A massive cerebral release of amino acids and ammonia was found in early-onset dementia of Alzheimer type. Aspartate and glycine were liberated in high concentrations, whereas glutamate remained rather unchanged. This excess cerebral protein catabolism is due to a 44% reduction in cerebral glucose metabolism. Whereas glutamate and other glucoplastic amino acids may substitute glucose, elevated aspartate may contribute to neuronal damage. The results are discussed with respect to a possible neuronal insulin/insulin receptor deficiency.
• Alzheimer examined Auguste D.'s brain.
• Discovered plaques and tangles.
• At the time it was thought that dementia was normal aging.

insight: dementia is physical

• Alzheimer examined Auguste D.'s brain.
• Discovered plaques and tangles.
• At the time it was thought that dementia was normal aging.

Dementia appeared before she was 50 years old

Auguste showed signs of dementia such as:
- Loss of memory
- Delusions
- Temporary vegetative states

Sleep disturbances:
- Trouble sleeping
- “drag sheets across the house and scream for hours in the middle of the night.”

Case of Auguste D., 50 year old woman in Germany - 1906
• Her disruptive behavior prompted her husband to see Dr. Alois Alzheimer.

http://en.wikipedia.org/wiki/Auguste_Deter
• Early onset familial Alzheimer disease - symptoms can start in 30’s, 40’s or 50’s

• Dominant genetic trait
• One parent had eFAD
• Siblings: 50%

• eFAD and late-onset AD is essentially has the same clinical phenotype - however, they may have different etiologies.

- eFAD is the consequence of mutated genes.
- Late-onset disease is more likely due to a gradual accumulation of age-related malfunctions.

Brickell, K. L. et al Arch Neurol. 2006;63(9):1307-1311
Autosomal dominant forms (eFAD)

- Amyloid precursor protein (APP)
  - Chromosome 21
- Presenilin-1 (PS1)
  - Chromosome 14
- Presenilin-2 (PS2)
  - Chromosome 1

These are deterministic mutations.

Accounts for most eFAD

Brickell, K. L. et al Arch Neurol. 2006;63(9):1307-1311
12 to 15 fold increase risk for AD with two copies of ApoE4

**Note:**
Amyloid-B is cleared from the brain by attaching to ApoE. If it is not attached it can become toxic to the brain.
what increases the risk of 95% of the LOAD?

**amyloid cascade hypothesis**

- peptides generated from APP (amyloid precursor protein) cause AD
- so, reducing the generation or accumulation will treat the disease

**diet hypothesis**

- 1997 William Grant-correlated food consumption with AD worldwide
- found positive correlation between total calories and total fat in the incidence of AD.

Many recent drug candidates have failed in trials. Perhaps because the drugs were given too late. When a person loses their memory - it is too late. The disease has been present for a long time by the time there are symptoms. Preventative or delay strategies.
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 shinkage
- 1 - 3 years before diagnosis
- Cell death shrinks the brain.
Amyloid Accretion
5–20 years before diagnosis of Alzheimer’s dementia

Scientific American (June 2010)
Alzheimer’s: Forestalling the Darkness
Amyloid blocks neurotransmitters from reaching the post-synaptic receptors.
PET scans show increasing retention in the brain’s frontal lobes of the amyloid-beta tracer Pittsburg 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
Disintegrating microtubule

Microtubules held together by tau proteins

Enzyme adding phosphate groups to tau

Toxic tangles formed by tau

Neuron

Scientific American (June 2010)
Alzheimer’s: Forestalling the Darkness
Healthy brain

Alzheimer’s brain

Hippocampus

Extreme shrinkage of hippocampus

Scientific American (June 2010)
Alzheimer’s: Forestalling the Darkness
cascade to AD

• plaques and tangles
  • interact with inflammatory cells in a way that the accumulated plaques and tangles trigger diffuse brain toxicity and neuronal death.

• Measuring amyloid can predict problems even before any mild cognitive impairment (MCI).

• The cognitive decline seems to be triggered when tau protein increases.

• long symptomless amyloid buildup, tau takeover, inflammation and neuron destruction - boom AD.
High carbohydrate intake worsens cognitive performance and behavior in patients with Alzheimer’s disease.
ApoE4 protein alters lipid metabolism in a manner similar to high carbohydrate diets.

Prolonged excessive insulin/IGF signaling is toxic to neurons.

Recall, increased risk for LOAD with ApoE4 allele. Why?
with T2D 2x risk of AD

- Patients on insulin therapy 4x risk for AD
- Insulin degrading Enzyme (IDE) → clears out insulin in the brain
- IDE also clears out excess amyloid (in vitro)
- Therefore - insulin resistance in periphery has an effect centrally and it appears that there might not enough IDE to clear out amyloid-B
- Mice without IDE get dementia
- Elderly people get increased amyloid in CSB when insulin is injected into their veins
- AD is the cause of dementia in 82-91% of T2D - greater than the general population
- Genetic predisposition (ApoE4 allele) for Alzheimer’s have decreased expression of IDE in the hippocampus.
- Combination of the genetic predisposition to Alzheimer’s (carrying the ApoE4 allele) and diabetes could put one at higher risk.
Interaction Between Circadian Rhythm & Metabolic Function

figure: Todd Churin
Shiftwork

Night time light exposure

Decreased melatonin

- Decreased clearance of reactive oxygen species
- Heart disease
- Premature aging
- Cancer

Altered 5HT signaling leading to mood disorders, depression, irritability

Hypothalamic nuclei

- Pancreas, Liver, Adipose tissue

Altered leptin/ghrelin signaling

SCN

Night time eating

Heightened preference/consumption of high fat/sugar diet

Metabolism in “resting” state at night

- Increased adiposity
- Insulin insensitivity
- Increased Body Mass Index

Obesity
- Stroke
- Diabetes
- Heart disease

jet lag syndrome, too

Figure adapted from: Zelinski, E. L. et al (2014) Neuroscience and Biobehavioral Reviews 40:80–101
Signature Hypometabolism in AD

AD patients show regional metabolic reductions involving the parieto-temporal and posterior cingulate cortices, and the frontal areas in advanced disease.

Hypometabolism: Decline in glucose metabolism

- Early feature of AD - region specific decline in glucose metabolism
- Reduction of glucose metabolism \(\rightarrow\) reduction in function
The circadian clock has a profound effect on the physiology and behavior of organisms.
The circadian clock has a profound effect on the physiology and behavior of organisms.

- Sleep
- Mood
- Cognitive function
- Respiration
- Metabolism
- Circulation
A Single Night of Partial Sleep Deprivation Induces Insulin Resistance in Multiple Metabolic Pathways in Healthy Subjects

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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
This is what really happens in your brain when you sleep.
Glympathic System

Throughout most of the body, a complex system of lymphatic vessels is responsible for cleansing the tissues of potentially harmful metabolic waste products, accumulations of soluble proteins and excess interstitial fluid. But astonishingly, the body’s most sensitive tissue—the central nervous system—lacks a lymphatic vasculature. What then accounts for the efficient waste clearance that must occur in order for the neural tissue of our brains to function properly?

This question has puzzled scientists for centuries. Our group believes that understanding how this process functions in the healthy nervous system holds the key to developing treatment options for a wide variety of neurological diseases, especially those characterized by the improper accumulation of misfolded proteins. The breakdown of the brain’s innate clearance system may in fact underlie the pathogenesis of neurodegenerative disorders such as Alzheimer’s, Parkinson’s, and Huntington’s disease, in addition to ALS and chronic traumatic encephalopathy. Past efforts to explain how the brain cleanses parenchymal tissue have suggested that solute and fluid exchange occurs between the interstitial fluid and the cerebrospinal fluid, and that this exchange is driven by diffusion. Yet as many have noted, the distances for diffusion in the brain are too great to explain the highly regulated interstitial environment.
Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie, Hongyi Kang, Qiwu Xu, Michael J. Chen, Yonghong Lian, Meenakshisundaram Thiagarajan, John O’Donnell, Daniel J. Christensen, Charles Nicholson, Jeffrey J. Iliff, Takahiro Takano, Rashid Deane, Maiken Nedergaard

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 β-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
Average Number of Hours of Sleep per Night

<table>
<thead>
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<th>Year</th>
<th>Hours of Sleep</th>
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<tr>
<td>1960</td>
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<tr>
<td>1995</td>
<td>7</td>
</tr>
<tr>
<td>2004</td>
<td>6</td>
</tr>
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</table>

Are you getting enough sleep?

What would happen if you got one more hour of sleep?
Go to this website and read the article.