Sleep Cycle Shift and its effects on Cognitive Function

Mary ET Boyle, Ph. D. • Department of Cognitive Science • UCSD
Sleep wake cycle is regulated by the circadian system.

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.
- 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.
SCN is not the only clock in the body.

Zeitgeber

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.

Cellular response to INSULIN is dependent on the circadian cycle.
Insulin stimulates the liver to remove glucose from the blood and stores it as glycogen. Tissues take up glucose from blood. Beta cells release insulin. Insulin lowers glucose levels in blood.

Figure adapted from Kaidanovich-Beilin, O. et al 2012
Glucagon stimulates the conversion of stored glycogen in the liver into glucose.

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 stimulates the liver to remove glucose from the blood and stores it as glycogen.

Beta cells release insulin, tissues take up glucose from blood, high blood glucose.

Lowers glucose levels in blood.

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

S. Hoyer and R. Nitsch

Department of Pathochemistry and General Neurochemistry, University of Heidelberg, Heidelberg, Federal Republic of Germany

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 whereas glutamate remained rather unchanged. This production in cerebral glucose metabolism.


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Alzheimer's Disease

A mind in darkness awaiting the drink of a gentle color.

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One Hundred Years of Solitude

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

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

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.”

http://en.wikipedia.org/wiki/Auguste_Deter
DEGENERATION GENERATION
The prevalence of Alzheimer’s disease is expected to rise sharply in the United States as its population ages.

THE POPULATION IS AGING...
Millions of people aged 65 and older, living in the U.S.

...AND AGE IS THE BIGGEST RISK FACTOR FOR ALZHEIMER'S...
Risk of developing Alzheimer's at a given age over the next 10 years, for males and females.

...SO THE NUMBER OF CASES IS GROWING
Numbers of people diagnosed with Alzheimer's will increase by nearly 50 percent during the next 20 years.
1 dot represents 100,000 people diagnosed with Alzheimer's.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>4.7 million</td>
</tr>
<tr>
<td>2010</td>
<td>5.3 million</td>
</tr>
<tr>
<td>2030</td>
<td>7.9 million</td>
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</tbody>
</table>
EARLY ONSET:

Memories begin failing in one’s 40s, occasionally as early as 32.

By 47, on average, full-blown Alzheimer’s develops.

New York Times, The Vanishing Mind 2010
Over three centuries, many in this lineage of 5,000 people have inherited a single genetic mutation guaranteeing that they will develop Alzheimer's.
A Clouded Inheritance

A group of 25 families in Colombia has inherited a genetic mutation from common ancestors, making members prone to early-onset Alzheimer's.

At right, Alzheimer's cases among the founding members of the clan and some of their early descendants, who number in the thousands today.

**KEY**
- No Alzheimer's
- Suspected cases
- Known cases

**PAISA MUTATION**
The inherited disease is caused by a mutation of the presenilin 1 gene on chromosome 14.

**TODAY**
Carlos Alberto Vilegas, his wife and their siblings descend from a common ancestor, circled above, who had the Paisa mutation.
The Vanishing Mind

In the mountains of northwest Colombia, many members of a sprawling extended family suffer from a genetic mutation that makes them begin to forget in their early 40s. | Related Article
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.

200,000 is the number of people with AD who are younger than 65.

“accounts for less than 1 percent of the 27 million Alzheimer’s cases worldwide documented in 2006”
- 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)

<table>
<thead>
<tr>
<th>Amyloid precursor protein (APP)</th>
<th>Presenilin-1 (PS1)</th>
<th>Presenilin-2 (PS2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome 21</td>
<td>Chromosome 14</td>
<td>Chromosome 1</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Not autosomal dominant (ApoE)</th>
<th>ApoE4 is thought to lower the age of onset by a decade</th>
</tr>
</thead>
</table>

Note: Amyloid-B is cleared from the brain by attaching to ApoE. If it is not attached it can become toxic to the brain.

Brickell, K. L. et al *Arch Neurol.* 2006;63(9):1307-1311
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.

eFAD
Test drugs before symptoms

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.
• 5 - 20 years before diagnosis of Alzheimer’s dementia
• damages synapses

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

• 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
Neuron

Disintegrating microtubule

Microtubules held together by tau proteins

Enzyme adding phosphate groups to tau

Toxic tangles formed by tau
Healthy brain

Alzheimer’s brain

Hippocampus

Extreme shrinkage of hippocampus
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.

Henderson, 2004
ApoE4 protein alters lipid metabolism in a manner similar to high carbohydrate diets. Why?

1. ApoE4 protein alters lipid metabolism in a manner similar to high carbohydrate diets.

2. Prolonged excessive insulin/IGF signaling is toxic to neurons.

Recall, increased risk for LOAD with ApoE4 allele. Why?

Henderson, 2004
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.
Insulin resistance
AD - brain insulin receptors fall as the disease progresses.

ADDLs (amyloid beta-derived diffusible ligands) bind to dendrites - and prevent insulin receptor insertion at the synapse.

Neurons become insulin resistant when there were high levels of ADDLs

Dendrites with high insulin receptors had no bound ADDLs.
“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 → 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.
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

This is what really happens in your brain when you sleep.
Glymphatic 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 clears 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,1,2 Hongyi Kang,2 Qiuwu Xu,3 Michael J. Chen,1 Yonghong Liao,1 Memakshisundaram Thiagarajan,2 John O’Donnell,2 Daniel J. Christensen,1 Charles Nicholson,2 Jeffrey J. Iliff,4 Takahiro Takami,2 Rashid Deane,4 Maiken Nedergaard4†

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

Are you getting enough sleep?

Kripke, D et al (1979) Arch Gen Psychiatry;
Gallup Organization (1995), Sleep in America;
What would happen if you got one more hour of sleep?
Go to this website and read the article.
