Sleep Cycle Shift and its effects on Cognitive Function

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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.
melatonin
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.

- harvests energy
- repairs DNA
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.
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.

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.

Beta cells release INSULIN.

Tissues take up glucose from blood.

High blood glucose lowers glucose levels in blood.

Figure adapted from Kaidanovich-Beilin, O. et al. 2021.
Glucagon stimulates the conversion of stored glycogen in the liver into glucose.

Increases glucose levels in blood

Alpha cells release GLUCAGON

low blood glucose

glycogen glucose

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.
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
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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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 correlation in cerebral glucose
Circadian rhythm disruption

Metabolic dysfunction

Insulin resistance

Alzheimer's Disease

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.

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.

Dementia appeared before she was 50 years old

http://en.wikipedia.org/wiki/Auguste_Deter
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.

Scientific American (June 2010) Alzheimer’s: Forestalling the Darkness
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 Villegas, his wife and their siblings descend from a common ancestor, circled above, who had the Paisa mutation.

Source: University of Antioquia

New York Times, The Vanishing Mind 2010
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

New York Times, The Vanishing Mind 2010
• 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.

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

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

- 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

Accounts for most eFAD

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*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.

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.

• Test drugs before symptoms

• Many recent drug candidates have failed in trials. Perhaps because the drugs were given too late.

• Preventative or delay strategies.

• 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.
• 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
Alzheimer’s: Forestalling the Darkness

Microtubules held together by tau proteins

Enzyme adding phosphate groups to tau

Disintegrating microtuble

Toxic tangles formed by tau

Neuron
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.

Henderson, 2004
Recall, increased risk for LOAD with ApoE4 allele. 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.

Henderson, 2004
with T2D 1.5x 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.
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.
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<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
<th>Stage 5</th>
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<tr>
<td>4-5%</td>
<td>45-55%</td>
<td>4-6%</td>
<td>12-15%</td>
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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.
Ventricles of the Brain

- Lateral Ventricles
- Interventricular foramen
- Third Ventricle
- Cerebral aqueduct
- Fourth Ventricle
- Central canal
Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie,1,3 Hongyi Kang,1,3 Qiwu Xu,2 Michael J. Chen,1 Yonghong Liao,1 Meenakshisundaram Thiagarajan,2 John O'Donnell,2 Daniel J. Christensen,1 Charles Nicholson,2 Jeffrey J. Ruff,2 Takahiro Takano,2 Rashid Deane,2 Maiken Nedergaard1†

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 fluid. In turn, convective fluxes of interstitial fluid increased the rate of β-amyloid clearance fluid. 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
A Single Night of Partial Sleep DeprivationInduces 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

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Average Number of Hours of Sleep per Night

Are you getting enough sleep?

What would happen if you got one more hour of sleep?
How much can an extra hour’s sleep change you?

9 October 2013 Last updated at 04:24 ET

The average Briton gets six and a half hours’ sleep a night, according to the Sleep Council. Michael Mosley took part in an unusual experiment to see if this is enough.

It has been known for some time that the amount of sleep people get has an average influence over the years.

This has happened for a whole range of reasons. Not least because we live in a culture where people are encouraged to think of sleep as a luxury; something you can easily cut back on. After all, that’s what suffers a lot when you get into a rut. But while the average amount of sleep we are getting has fallen, rates of obesity and diabetes have soared. Could the two be connected?

We wanted to see what the effect would be of increasing average sleep by just one hour. So we asked seven volunteers who normally sleep anywhere between six and seven hours to be guided by the University of Surrey’s Sleep Research Centre.

The volunteers were randomly allocated to two groups. One group was asked to sleep for an extra half hour a night; the other group was asked to sleep for seven and a half hours a night. After a week the researchers took blood tests and the volunteers were asked to switch sleep patterns. The group that had been sleeping for seven and a half hours was asked to sleep for six and a half hours.

While we were waiting to see what effect this would have, we sent the John Radcliffe hospital in Oxford to learn more about what actually happens when we sleep.

Activated over 500 genes associated with:
- Inflammation,
- Immune response
- Stress response
- Diabetes
- Cancer risk

Reversed these effects

6.5 hours week1
7.5 hours week2
Dr Michael Mosley takes part in a sleep study