Sleep Cycle Shift and its effects on Cognitive Function
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.
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. Zeitgeber intestinal activity and its ability to absorb nutrients are dependent on the time of day. Food can be a zeitgeber for the gut.
Time of eating has a huge effect on the liver and insulin efficacy.
High blood glucose

Beta cells release INSULIN

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

Tissues take up glucose from blood.

Lowers glucose levels in blood.

Figure adapted from Kaidanovich-Beilin, O. et al. 201
Glucagon stimulates the conversion of stored glycogen in the liver into glucose. Alpha cells release GLUCAGON which 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.
Time of eating affects gut bacteria
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

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 in excess, glutamate remained rather unchanged. This suggests increased intracellular accumulation 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.

Mary ET Boyle, Ph. D.
Department of Cognitive Science
UCSD
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.”

Dementia appeared before she was 50 years old.

insight:
- Dementia is physical
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.

<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>
</tr>
</tbody>
</table>

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.

Javier San Pedro Gómez
Lived into his 70s

Maria Luisa Chavarriaga Mejía
Suspected carrier of the Paisa mutation

Mauricio
Common ancestor of Carlos Alberto and Blanca Nelly

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

Note: the chart has been simplified and does not show all children or descendants.

TODAY Carlos Alberto Villegas, his wife and their siblings descend from a common ancestor, circled above, who had the Paisa mutation.

Carlos Alberto, 53. Onset of memory problems at 41.

María Ely, 61 (his sister) 48 at onset.

Darío, 55 (his brother) 47 at onset.

Odells, 50 (his brother) 46 at onset.

Blanca Nelly, 41 (his wife) Currently no symptoms.

William, 48 (her brother) 45 at onset.

Gladys, 36 (her sister) Too afraid to have children.

Liliana, 29 (her sister) Terrified of any memory lapse.

Two sisters show early symptoms but deny it.

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
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)

- amyloid precursor protein (APP) on Chromosome 21
- presenilin-1 (PS1) on Chromosome 14
- presenilin-2 (PS2) on Chromosome 1

Accounts for most eFAD

these are deterministic mutations

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

Not autosomal dominant (ApoE)
ApoE4

ApoE4 is thought to lower the age of onset by a decade

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

these are genetic risk factors

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.

Lessons:
- eFAD
- Test drugs before symptoms

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

Memory:
- 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.

Lifestyle:
- 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 shrinkage
• 1 - 3 years before diagnosis
• Cell death shrinks the brain.
Amyloid Accretion
5–20 years before diagnosis of Alzheimer’s dementia

neuron

Amyloid-beta plaques

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 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
Disintegrating microtubule

Toxic tangles formed by tau

Enzyme adding phosphate groups to tau

Microtubules held together by tau proteins

Neuron

Scientific American (June 2010)
Alzheimer’s: Forestalling the Darkness
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.
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.
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.
**Stage 1**
- 4-5%

**Stage 2**
- 45-55%
- Breathing pattern and heart rate slows. Slight decrease in body temperature.

**Stage 3**
- 4-6%
- Deep sleep begins. Brain begins to generate slow delta waves.

**Stage 4**
- 12-15%

**Stage 5**
- 20-25%
- Rapid eye movement. Brainwaves speed up and dreaming occurs. Muscles relax and heart rate increases. Breathing is rapid and shallow.
This is what really happens in your brain when you sleep.

Figure: Eiko Ojala, NYT
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.

Large (green) and small (red) tracers tagged to soluble proteins in the paravascular cerebrospinal fluid.
Ventricles of the Brain

- Lateral Ventricles
- Interventricular foramen
- Third Ventricle
- Cerebral aqueduct
- Fourth Ventricle
- Central canal

© Buzzle.com
Choroid plexus of third ventricle
Interventricular foramen
Third ventricle
Cerebral aqueduct
Fourth ventricle
Choroid plexus of fourth ventricle
Blood-filled dural space
Pia mater
Subarachnoid space
Arachnoid mater
Dura mater
Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie,1* Hongyi Kang,1* Qiwu Xu,2 Michael J. Chen,1 Yonghong Liao,1 Meenakshisundaram Thiagarajan,3 John O’Donnell,1 Daniel J. Christensen,1 Charles Nicholson,2 Jeffrey J. Iliff,4 Takahiro Takano,2 Rashid Deane,3 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 increase 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 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

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 a problem.

It has been known for some time that the amount of sleep people get has an average variation from week to week. This has happened for a whole range of reasons, not least because we live in a culture where people are encouraged to stay up late and then get up early the next day. However, the average amount of sleep people get varies a lot, with some people getting very little sleep and others getting a lot more. Could the two be connected?

We wanted to see what the effect would be of increasing average sleep by just one hour. We invited seven volunteers, who normally sleep anywhere between six and eight hours, to be studied at the University of Surrey's Sleep Research Centre.

The volunteers were randomly allocated to two groups. One group was asked to sleep for an additional half hour a night, the other group slept an extra hour 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 an extra hour a night went back to their normal sleep pattern, while the other group slept an hour less.

While we were waiting to see what effect this would have, I read an article in the Sunday Times about how sleep affects your body. The article suggested that sleep helps to repair your body, and that lack of sleep can lead to health problems such as obesity and diabetes. Could this be true?

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

Reversed these effects
Dr Michael Mosley takes part in a sleep study
LIGHT ~ CONFUSES BODY CLOCK

NOISE ~ DISTURBS LIGHT SLEEP

WHY CAN'T I SLEEP!?!

BUSY MIND ~ CAN'T FALL ASLEEP

HOT ROOM ~ CONFUSES BODY CLOCK

ALCOHOL ~ DISRUPTS SLEEP

CAFFEINE ~ LESS DEEP SLEEP

HEAVY MEAL ~ HEARTBURN & DISCOMFORT

http://www.bbc.co.uk/science/0/20427553