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.
melatonin
If the sleep wake cycle is disrupted it can cause metabolic dysregulation. Metabolic disruption can lead to weight gain, obesity, impaired immunity, and 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.
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 blood.

Lowers glucose levels in blood.

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

Alpha cells release GLUCAGON

Figure adapted from Kaidanovich-Beilin, O. et al 2012
Insulin-sensitivity is dependent on the peripheral clock in muscle cells.

Glucose uptake in muscle is dependent on the circadian rhythm.
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);
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 increased, glutamate remained rather unchanged. This depression 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
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

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.

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.

- **Today, 2010**: 80
- **2050**: 2050

... 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.

- **Age 65**: 1%
- **75**: 4%
- **85**: 10%

... 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.

- **2000**: 4.7 million
- **2010**: 5.3 million
- **2030**: 7.9 million

*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.
New York Times, The Vanishing Mind 2010
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]

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.

---