“early to bed, early to rise, makes a man healthy, wealthy, and wise”
EARLY TO RISE?
A Nation of Night Owls

The amount of sleep that Americans get has declined by more than an hour a night since the 1940s. The percentage of people saying they usually get this much sleep nightly:

<table>
<thead>
<tr>
<th>Year</th>
<th>3 hours or less</th>
<th>4 hours</th>
<th>5 hours</th>
<th>6 hours</th>
<th>7 hours</th>
<th>8 hours</th>
<th>9 or more</th>
<th>No Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1942</td>
<td>3%</td>
<td>25%</td>
<td>45%</td>
<td>14%</td>
<td>14%</td>
<td>5%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>1990</td>
<td>8%</td>
<td>28%</td>
<td>30%</td>
<td>22%</td>
<td>22%</td>
<td>5%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>2014</td>
<td>17%</td>
<td>25%</td>
<td>27%</td>
<td>26%</td>
<td>26%</td>
<td>6%</td>
<td>6%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Average hours/night:
- 1942: 7.9
- 1990: 6.7
- 2014: 6.7

Sleep and Well-Being

How people scored on the Gallup-Healthways Well-Being Index, by nightly hours of sleep:

<table>
<thead>
<tr>
<th>Sleep Duration</th>
<th>Average Well-Being Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4 hours</td>
<td>51.4</td>
</tr>
<tr>
<td>5 hours</td>
<td>56.5</td>
</tr>
<tr>
<td>6 hours</td>
<td>59.4</td>
</tr>
<tr>
<td>7 hours</td>
<td>64.2</td>
</tr>
<tr>
<td>8 hours</td>
<td>65.7</td>
</tr>
<tr>
<td>9-10 hours</td>
<td>64.7</td>
</tr>
</tbody>
</table>

Note: The well-being index, scored on a scale of 0 to 100, measures five elements of well-being: purpose, social, financial, community and physical.

Source: Gallup phone surveys and Gallup-Healthways Well-Being Index

THE WALL STREET JOURNAL.
Sleep and Alzheimer's Disease

Mary ET Boyle, Ph.D., Department of Cognitive Science, UCSD
Figure from Brain Basics Reading
When neurons are active, they are communicating with other neurons at the synapses.
Communication

WHERE NEURONS COMMUNICATE

synapse
WHEN NEURONS COMMUNICATE

SYNAPSE

METABOLICALLY ACTIVE
WHEN YOU RUN... MUSCLES ARE METABOLICALLY ACTIVE

got lactic acid?
WHEN NEURONS COMMUNICATE

SYNAPSE

METABOLICALLY ACTIVE

NEURONS RELEASE

(\(\beta\)) BETA AMYLOID
Amyloid Precursor Protein (APP)

- Important for growth
- Neuron repair
- APP is a precursor to Aβ (Amyloid Beta)
Aβ is generated by cutting APP in two places by two enzymes: β-secretase and γ-secretase.
Aβ length is between 40 & 42 amino acids.

42 is more toxic.
Alzheimer’s Disease

One of the most frightening and devastating of all neurological disorders is the dementia that can occur in the elderly. The most common form of this illness is Alzheimer’s disease. Rare before age 60 but increasingly prevalent in each decade thereafter, Alzheimer’s affects 5 percent of Americans age 65 to 74 and nearly half of those age 85 and older. As many as 5.3 million Americans have Alzheimer’s. The disease is predicted to affect approximately 14 million individuals in the United States by the year 2050.

The earliest symptoms of Alzheimer’s include forgetfulness, disorientation as to time or place, and difficulty with concentration, calculation, language, and judgment. As the disease progresses, some patients have severe behavioral disturbances and may even become psychotic. In the final stages, the affected individual is incapable of self-care and becomes bedridden. Patients usually die from pneumonia or some other complication of immobility. Alzheimer’s disease is the seventh leading cause of death in the United States and the fifth leading cause of death for Americans aged 65 and older.
In the earliest stages, the clinical diagnosis of possible or probable Alzheimer’s can be made with greater than 80 percent accuracy. As the course of the disease progresses, the accuracy of diagnosis at Alzheimer’s research centers exceeds 90 percent. The diagnosis depends on medical history, physical and neurological examinations, psychological testing, laboratory tests, and brain imaging studies. New brain imaging strategies promise to enable doctors to visualize Alzheimer’s neuropathology during life. At present, however, final confirmation of the diagnosis requires examination of brain tissue, usually obtained at autopsy.
The causes and mechanisms of the brain abnormalities underlying Alzheimer’s are not yet fully understood, but great progress has been made through the study of genetics, biochemistry, and cell biology, as well as the use of experimental treatments. Neuroscientists do know that reductions occur in markers for many neurotransmitters that allow cells to communicate with one another. These include acetylcholine, somatostatin, monoamines, and glutamate. Damage to these neural systems, which are critical for attention, memory, learning, and higher cognitive abilities, is believed to cause the clinical symptoms.

we are now understanding that sleep dysfunction is part of the problem.
Microscopic examination of brain tissue from people who died from Alzheimer’s shows abnormal accumulations of a small fibrillar peptide, termed beta amyloid, in the spaces around synapses. These accumulations of tissue are referred to as neuritic plaques.
Another abnormal clump of proteins, called neurofibrillary tangles, have been identified as a modified form of the protein tau, which is found in the cell bodies of neurons. In all forms of Alzheimer’s, plaques and tangles mostly develop in brain regions important for memory and intellectual functions. New brain imaging strategies that may one day be used for diagnosis use a mildly radioactive chemical marker that shows amyloid plaques and tau tangles in living people.
Early-onset Alzheimer’s disease is a rare, dominantly inherited form of the disease. Recently, scientists have identified Alzheimer’s disease-associated mutations. The gene encoding the amyloid precursor protein (APP) is on chromosome 21. In some families with early-onset Alzheimer’s, mutations have been identified in the presenilin 1 and 2 genes. Genes that cause dominant Alzheimer’s appear to do so by causing beta amyloid plaques to accumulate. Apolipoprotein E (apoE), which influences susceptibility for Alzheimer’s later in life, exists in three forms. The variant known as APOE epsilon 4 is clearly associated with enhanced risk.
Latest Research and Treatments  

Currently approved treatments for Alzheimer's disease do not modify the course of the disease and offer only temporary mitigation of some symptoms, such as agitation, anxiety, unpredictable behavior, sleep disturbances, and depression. Five drugs have been approved by the FDA to treat Alzheimer's. Four prevent the breakdown of acetylcholine, a brain chemical important for memory and thinking. The fifth regulates glutamate, a brain chemical that may cause brain cell death when produced in large amounts. These agents temporarily improve memory deficits and provide some symptomatic relief but do not prevent progression of the disease. Several other approaches, such as antioxidants, are being tested.

An exciting area of research is the introduction of Alzheimer's disease-causing genes in mice. These mice, carrying mutant genes linked to inherited Alzheimer's, develop behavioral abnormalities and some of the microscopic changes in tissue structure that occur in humans. It is hoped that these mouse models will prove useful for studying the mechanisms of the disease and testing novel therapies, although appropriate caution must be taken. Experimental therapies in models of other neurodegenerative diseases — amyotrophic lateral sclerosis, for example — have been effective in mice with the disease but not in humans.

Researchers have begun to modulate the actions of genes that play critical roles in the production of amyloid in animal models. These genes encode beta and gamma secretases, which cut amyloid peptide from a larger protein. The amyloid peptide is then released from the neuron into the space around synapses, where it can accumulate and form Alzheimer's disease plaques. Amyloid-destroying enzymes, known as alpha secretases, break up the amyloid peptide, preventing amyloid accumulation. Anti-amyloid therapies for Alzheimer's aim either to remove existing amyloid or decrease production of new amyloid.
Within the past three to five years, greater appreciation has developed for the surprisingly important roles that diet and lifestyle play in determining risk for Alzheimer’s disease. Cognitive activity, physical activity, and heart-healthy diets lower the risk for Alzheimer’s, while obesity, high blood pressure, high cholesterol, metabolic syndrome, and diabetes raise the risk. Some evidence indicates that successful management of these cardiovascular risks can delay the onset or slow the progression of dementia.
Alzheimer's disease primarily affects the hippocampus and cortex regions of the brain, probably by damaging and destroying the connections between brain cells and later by causing cell death. Although initial symptoms are minor, this damage leads to impairments in learning, memory, and thinking and is eventually fatal. [Credit: Adapted and reprinted with permission from the Alzheimer's Association. © 2008 Alzheimer's Association.]
Function and toxicity of amyloid beta and recent therapeutic interventions targeting amyloid beta in Alzheimer’s disease

K. Rajasekhar, Malabika Chakrabarti and T. Govindaraju*

Amyloidogenesis has been implicated in a broad spectrum of diseases in which amyloid protein is invariably misfolded and deposited in cells and organs. Alzheimer’s disease is one of the most devastating ailments among amyloidogenesis induced dementia. The amyloid beta (Aβ) peptide derived from amyloid precursor protein (APP) is misfolded and deposited as plaques in the brain, which are said to be the hallmark of Alzheimer’s disease. In normal brains physiological concentration of the Aβ peptide has been indicated to be involved in modulating neurogenesis and synaptic plasticity. However, excess Aβ production, its aggregation and deposition deleteriously affect a large number of biologically important pathways leading to neuronal cell death. Targeting Aβ production, Aβ aggregation or its clearance from the brain has been an active area of research for preventing or curing AD. Our Feature Article intends to detail the aggregation mechanism, the physiological role of the Aβ peptide, elaborate its toxic effects, and outline the different classes of molecules designed in the last two years to inhibit amyloidogenic APP processing, Aβ oligomerization or fibrillogenesis and to modulate different pathways for active clearance of Aβ from the brain.
Amyloid Cascade Hypothesis

The deposition of Aβ peptide clumps (plaque) drive AD pathology.

Aggregation
AMYLOID CASCADE
HYPOTHESIS

The deposition of Aβ peptide clumps (plaque) drive AD pathology. Aggregation

ALZHEIMER'S DISEASE

this is not the whole story...

Aβ is a crucial step in AD.
Recall,
disrupts communication
WHAT DOES SLEEP
GOT TO DO
WITH ALL THIS ANYWAY
???
RECALL:

insight: dementia is physical

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

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.”

dementia appeared before she was 50 years old

http://en.wikipedia.org/wiki/Auguste_Deter
As you may painfully know: Sleep gets more difficult the older you get. Older adults are less able, on average, to obtain as much sleep, or as restorative a sleep, as young adults. The problem gets so bad that by our 80s, the lack of sleep can have major health ramifications, though we don’t always notice.

Older adults face a number of challenges. The first is a reduction in the quantity and quality of deep sleep—the stage that beneficially overhauls your cardiovascular, immune and metabolic systems and refreshes learning and memory abilities. As you enter your 30s and 40s, your deep-sleep brain waves become smaller, less powerful and fewer in number. Reductions in deep-sleep quality increase your risk of heart attacks, obesity and stroke, as well as the buildup of a toxic brain protein—called beta amyloid—that is linked to Alzheimer’s disease.

Passing into your mid- to late-40s, age will have stripped you of 60% to 70% of the deep sleep you were enjoying as a teen. By the time you reach age 70, you will have lost 80% to 90% of your youthful, restorative deep sleep.
Stages of Sleep

REM

Rapid Eye Movement

NREM

Non-Rapid Eye Movement
SLEEP STAGES

**Awake**

- **Stage 1**
  - Duration: 5-15 minutes
  - Description: Very light sleep
  - Characteristics: Sense of falling is common
  - Type: NREM

- **Stage 2**
  - Duration: 5-15 minutes
  - Description: Light Sleep
  - Characteristics: Body temperature drops, Heart rate slows
  - Type: NREM

- **Stages 3 & 4**
  - Duration: 5-15 minutes each
  - Description: Slow wave sleep (SWS)
  - Characteristics: Stage 4: Delta waves, Body repairs itself
  - Type: NREM

**REM**

- **Stage 3 & 4**
  - Duration: 10 minutes, first cycle
  - Description: Dreaming occurs
  - Characteristics: Brain activity similar to waking levels
  - Type: Rapid Eye Movement (REM)

- **Stage 1**
  - Description: Sleep cycle restarts after REM
  - Type: NREM

**Drowsiness Begins**

**Stable Sleep**

**Repair**

**Needed for Learning**
SLEEP STAGES

- 11 pm: awake, REM
- 1 am: stage 1
- 3 am: stage 2
- 5 am: stage 3
- 7 am: stage 4

This is what really happens in your brain when you sleep.
CLEANING OCCURS DURING DEEP SLEEP.
“Furthermore, relatively short-term (3 weeks) sleep deprivation markedly accelerated amyloid plaque deposition in amyloid precursor protein transgenic mice.

Thus, sleep-wake behavior is linked to Aβ levels, and abnormal sleep may be linked to AD pathogenesis.”

Brain removes toxic waste through the glymphatic system.
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 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.
NOTE: GLYMPHATIC SYSTEM CLEARS WASTE BEST DURING DEEP SLEEP!
DAYTIME

NEURONS

DEEP SLEEP

NEURONS SHRINK
Awake

Fluid

Neurons

CSF: Cerebral Spinal Fluid

Deep Sleep

Fluid

Wash Debris Between Neurons

Neurons Shrink ↑!
Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie,1*, Hongyi Kang,1* Qiwu Xu,2 Michael J. Chen,1 Yonghong Liao,1 Meinakshisundaram Thiyagarajan,2 John O’Donnell,2 Daniel J. Christensen,2 Charles Nicholson,2 Jeffrey J. Iliff,1 Takahiro Takano,2 Rashid Deane,1 Maiken Nedergaard*1

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.
Sleep disturbances may precede the onset of neurodegenerative diseases.

In some cases, by decades!

Sleep changes are part of the normal aging process.
Sleep changes are part of the normal aging process.

1. Increased sleep fragmentation
2. Nighttime awakenings
3. Increased daytime sleep
"The older you are, the worse you sleep."
1st: Arousal System

THALAMUS

ACH

ACH = Acetylcholine
Cholinergic (ACH) neurons in the brainstem activate the thalamus.
THALAMUS ALERTS CORTEX TO INCOMING IMPORTANT INFORMATION

BIG IDEA: GATE TO ALERTNESS
These neurons:

1. Fire fastest during wakefulness & REM sleep.
2. Not so active during NREM sleep.
2nd:
Arousal System

Orexin
Serotonin
Noradrenaline (Norepinephrine)
These neurons:

1. Fire fastest when awake
2. Slow down during NREM
3. Stop during REM
Lesions in the arousal system → produce profound sleepiness &/or coma.
What drives sleepiness?
ventrolateral preoptic area

VLPO
What activates VLPO?

(What makes your brain sleepy?)
As you think & work, you need energy. ATP $\Rightarrow$ ADP $\Rightarrow$ AMP $\Rightarrow$ Adenosine
ATP $\xrightarrow{P}$ ADP $\xrightarrow{P}$ AMP $\xrightarrow{P}$ Adenosine

When you have ↑↑ adenosine levels, you are tired!
ATP $\rightarrow$ ADP $\rightarrow$ AMP $\rightarrow$ ADENOSINE

When you have ↑↑ adenosine levels you are tired!

* ADENOSINE SECRETION REFLECTS BRAIN ACTIVITY

* ADENOSINE LEVELS RISE DURING WAKEFULNESS
ATP $\rightarrow$ ADP $\rightarrow$ AMP $\rightarrow$ ADENOSINE

When you have ↑↑ adenosine levels you are tired!

ADENOSINE BINDS TO VLPO AREA $\rightarrow$ SLEEP

ADENOSINE LEVELS DECLINE DURING SLEEP
ATP → ADP → AMP → Adenosine

When you have ↑↑ adenosine levels, you are tired!

Note: Coffee

✓ Caffeine interferes with adenosine binding
Lesion VLPO?

→ insomnia
  - sleep for a few hours per day

- people are extremely tired

→ but find it difficult to sleep.
VLPO:

(*) are active during Sleep
VLPO inhibits arousal system during sleep
VLPO; helps to control REM sleep states

* Helps to transition to sleep via histamine neurons
Ventral lateral preoptic area (VLPO)

INHIBIT

norepinephrine

AROUSAL SYSTEM

DREXIN

norepinephrine (noradrenaline)
Flip-Flop Switch

Sleep inhibits arousal

Arousal inhibits sleep

Inhibit
Alzheimer's Disease characteristics:

- Chronic Neurodegeneration
- Dementia: most common
- Short-term memory loss
Amyloid-β (Aβ) accumulation in the brain extracellular space is a hallmark of Alzheimer’s disease. The factors regulating this process are only partly understood. Aβ aggregation is a concentration-dependent process that is likely responsive to changes in brain interstitial fluid (ISF) levels of Aβ. Using in vivo microdialysis in mice, we found that the amount of ISF Aβ correlated with wakefulness. The amount of ISF Aβ also significantly increased during acute sleep deprivation and during orexin infusion, but decreased with infusion of a dual orexin receptor antagonist. Chronic sleep restriction significantly increased, and a dual orexin receptor antagonist decreased, Aβ plaque formation in amyloid precursor protein transgenic mice. Thus, the sleep-wake cycle and orexin may play a role in the pathogenesis of Alzheimer’s disease.
The second hallmark of altered sleep as we age is fragmentation. The older we get, the more frequently we wake up throughout the night. Causes include body pain and a weakened bladder. Reducing fluid intake in the evening can help the latter, but it isn’t a cure-all.
Mechanisms linking circadian clocks, sleep, and neurodegeneration

Erik S. Musiek* and David M. Holtzman

Disruptions of normal circadian rhythms and sleep cycles are consequences of aging and can profoundly affect health. Accumulating evidence indicates that circadian and sleep disturbances, which have long been considered symptoms of many neurodegenerative conditions, may actually drive pathogenesis early in the course of these diseases. In this Review, we explore potential cellular and molecular mechanisms linking circadian dysfunction and sleep loss to neurodegenerative diseases, with a focus on Alzheimer’s disease. We examine the interplay between central and peripheral circadian rhythms, circadian clock gene function, and sleep in maintaining brain homeostasis, and discuss therapeutic implications. The circadian clock and sleep can influence a number of key processes involved in neurodegeneration, suggesting that these systems might be manipulated to promote healthy brain aging.
Be Happy
Get enough Sleep!