Alzheimer's Disease

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

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One Hundred Years of Solitude
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BASIC NEURON

- Synapse
- Another Neuron
- SOMA (Cell Body)
- Dendrites (Input)
- Axon (Output)
- Action Potential Signal
- Terminal
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

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

got lactic acid?
When neurons communicate metabolically active neurons release beta amyloidid
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.
WHAT DOES SLEEP

GOT TO DO

WITH ALL THIS ANYWAY

???
SLEEP STAGES

- **DROWSINESS BEGINS**
  - 5-15 minutes
  - Very light sleep
  - Sense of falling is common
  - NREM

- **STABLE SLEEP**
  - 5-15 minutes
  - Light Sleep
  - Body temperature drops
  - Heart rate slows
  - NREM

- **REPAIR**
  - 5-15 minutes each
  - Slow wave sleep (SWS)
  - Stage 4: Delta waves
  - Body repairs itself
  - NREM

- **NEEDED FOR LEARNING**
  - 10 minutes, first cycle
    - (Up to 1 hour in subsequent cycles)
    - Dreaming occurs
    - Brain activity similar to waking levels
    - Rapid Eye Movement (REM)
    - Sleep cycle restarts after REM

**awake**

**REM**

**stage 1**

**stage 2**

**stage 3**

**stage 4**
SLEEP STAGES

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.

- Dementia appeared before she was 50 years old

- 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
Amyloid-\(\beta\) Dynamics Are Regulated by Orexin and the Sleep-Wake Cycle

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Amyloid-\(\beta\) (A\(\beta\)) accumulation in the brain extracellular space is a hallmark of Alzheimer’s disease. The factors regulating this process are only partly understood. A\(\beta\) aggregation is a concentration-dependent process that is likely responsive to changes in brain interstitial fluid (ISF) levels of A\(\beta\). Using in vivo microdialysis in mice, we found that the amount of ISF A\(\beta\) correlated with wakefulness. The amount of ISF A\(\beta\) 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, A\(\beta\) 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.
“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.”

This is what really happens in your brain when you sleep.
CLEANING OCCURS DURING DEEP SLEEP.
BRAIN REMOVES TOXIC WASTE THROUGH THE GLYMPHATIC SYSTEM
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.
NOTE:
GLYMPHATIC SYSTEM CLEARS WASTE BEST DURING DEEP SLEEP.
DAYTIME ➔ NEURONS ➔ DEEP SLEEP

NEURONS SHRINK ↑!
Awake: fluid

Deep sleep:
- Wash debris between neurons
- Neurons shrink

CSF: Cerebral Spinal Fluid
Sleep Drives Metabolite Clearance from the Adult Brain

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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. 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.
Amyloid Accretion
5–20 years before
diagnosis of Alzheimer’s
dementia

Scientific American (June 2010)
Alzheimer’s: Forestalling the Darkness
Amyloid-beta 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.
Disintegrating microtubule

Microtubules held together by tau proteins

Enzyme adding phosphate groups to tau

Toxic tangles formed by tau
Wait, wait, there is more...

Sleep disruption leads to metabolic disruption.

**Insulin**
- Hormone helps store sugar and fat for energy – produced in pancreas.

**Type 1 diabetes**
- When body cannot produce enough insulin

**Type 2 diabetes**
- When body has inadequate insulin response

**Type 3 diabetes?**
- Neurodegenerative diseases? Alzheimer’s, Parkinson’s & Huntington’s
How much can one extra hour of sleep change you?
How much can an extra hour's sleep change you?

The average Briton gets six-and-a-half hours' sleep a night, according to the Sleep Council. Now, volunteers have participated in an unusual experiment to see if this is enough.

It has been claimed for some time that the amount of sleep people get has an average decline 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 stay up late and sleep is seen as a luxury - something you can easily cut back on. After all, what else is there to do in the evening, other than some sports or a job you really love? But while the average amount of sleep we are getting has fallen, the rate of obesity and diabetes has soared. Could the two be connected?

We wanted to see what the effect would be of increasing average sleep to just one hour. So we asked seven volunteers, who normally sleep anywhere between 6 and 8 hours, to be subjects in the University of Surrey’s Sleep Research Centre.

The volunteers were randomly allocated to two groups. One group was asked to sleep for seven-and-a-half hours a night, the other for seven-and-a-half hours. 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 had less than two hours of extra sleep, while the other group slept an extra hour.

While we were willing to see what effect this would have, we also wanted to find out more about what actually happens when we sleep.

In the Sleep Centre, they fitted me up with a simple electroencephalograph, a

Click here to read the article.

Five things that stop a good night’s sleep

http://www.bbc.co.uk/science/0/20427553
STATE OF THE ART REVIEW

NEURODEGENERATIVE DISEASE

Alzheimer’s Disease: The Challenge of the Second Century

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Alzheimer’s disease (AD) was first described a little more than 100 years ago. It is the most common cause of dementia with an estimated prevalence of 30 million people worldwide, a number that is expected to quadruple in 40 years. There currently is no effective treatment that delays the onset or slows the progression of AD. However, major scientific advances in the areas of genetics, biochemistry, cell biology, and neuroscience over the past 25 years have changed the way we think about AD. This review discusses some of the challenges to translating these basic molecular and cellular discoveries into clinical therapies. Current information suggests that if the disease is detected before the onset of overt symptoms, it is possible that treatments based on knowledge of underlying pathogenesis can and will be effective.