Systems Aging
Lecture 9 - Alzheimer, Sleep, Stress, Friends and Longevity

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Aging aging aging here and there
*Aging*4 aging everywhere*

Some people seem to think that old age is a disease
But research shows that senior citizens are more at ease
Crystallised knowledge is at its max
Because your brain is wiser
And you don't have to tolerate a phd adviser

Aging aging…

In this lecture we explore the cognitive aspects of aging. We descend to the valley of despair with Alzheimer's disease. Then we ascend, riding on the elephant of health and discuss its remaining two legs - sleep and emotional wellbeing via friends and stress reduction (we already talked about the other two legs nutrition and exercise). We end on a high summit with cognition that *improves* with age- the wise brain.

Part 1 Alzheimer Disease

Healthy aging shows a linear decline in memory and processing speed
In healthy aging our speed and memory decline steadily. The z-scores of computerised tests of processing speed and short or long term memory decline linearly with age. Crystallized knowledge rises, such as knowledge of facts, technical skills and vocabulary, as well as aspects of wise cognition we will return to in the end.

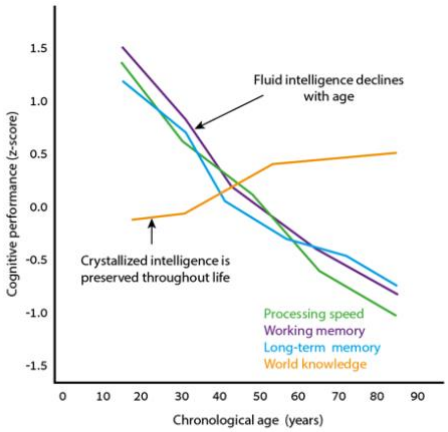


Figure 10.1: Most cognitive functions decline with age. Adapted from (Zamroziewicz and Barbey 2018).

Normal brain ageing shows degeneration in certain areas from age 30-40 and other from age 50 and on

The earliest brain region to show age-related degeneration is the locus coeruleus (LC), a small structure in the brainstem that produces norepinephrine (NE), a chemical important for attention, stress regulation, and memory. Degeneration of the LC can begin as early as the 30s–40s, with progressive neuron loss and the buildup of tau protein, a marker also seen in Alzheimer's disease. As the LC declines, it contributes to reduced alertness, slower cognitive processing, and increased vulnerability to stress, anxiety, and sleep disturbances.

By age 50s–60s, the hippocampus (responsible for memory and learning) and the prefrontal cortex (involved in reasoning, problem-solving, and self-control) begin to shrink. The hippocampus loses neurons and connections needed for forming new memories, leading to increased forgetfulness. The prefrontal cortex, particularly the dorsolateral region, thins out, making it harder to multitask, focus, and make quick decisions. The entorhinal cortex, a key hub between the hippocampus and the rest of the brain, also starts to decline, further impairing memory.

As aging continues into the 60s and beyond, dopamine-producing cells in the striatum decline, slowing reaction time and reducing motivation. The cerebellum shrinks, affecting coordination and balance, making falls more common. Finally, white matter loss reduces the brain's processing speed, weakening communication between different regions. While these changes occur in healthy aging, their progression can be slowed through exercise, cognitive stimulation, and a -healthy diet.

Dementia results in tragic loss of identity

That is healthy aging. Cognition plummets in neurodegenerative diseases, the fourth horseman. Dementia can be caused by several factors such as poor blood supply to the brain -known as

vascular dementia. Much of the research on neurodegeneration is on a single form of dementia that is most common and much feared- Alzheimer's disease . You lose memory and thus much of your identity, and then basic function until disability and death, often by infection. It is a disease that is generally of very old age above 80 - it is the last of the horsemen, the others peak at 65-75, although some Alzheimer cases occur at 60 and before as we shall see.

Two other related diseases are about ten times more rare but still common- Parkinson's disease and Lewy body dementia. They have similar mechanisms and occur in different brain areas- Parkinson's at first related to movement, and Lewy body dementia to executive function.

In a landmark study of hundreds of human brain autopsies, using single cell spatial transcriptomics, Naomi Habib (2024) showed that aging can bifurcate into a healthy aging trajectory or a neurodegeneration trajectory with distinct cell types and inflammatory responses.

Alzheimer incidence rises fast and late and needs its own SR model

Alzheimer caught my attention when we looked at the incidence curves of age related diseases (Katzir 2021). As mentioned in lecture 4, hundreds of age related diseases rise exponentially with similar slopes, 3-8%year.

Alzheimer and prefrontal dementia are the only exceptions, rising more than 15% per year. Whereas Other diseases rise 10-fold in 20 years, Alzheimer's rises 100-fold. This can not be explained by the SR model with the same parameters as other diseases because it would require a disease threshold that is too high, higher than the death threshold. This led to the hypothesis that Alzheimer's has its own driving damage (houses and trucks) distinct from the body's driving damage, and is described by its own SR model with different parameters. Our goal is to find plausible candidates for such a driver.

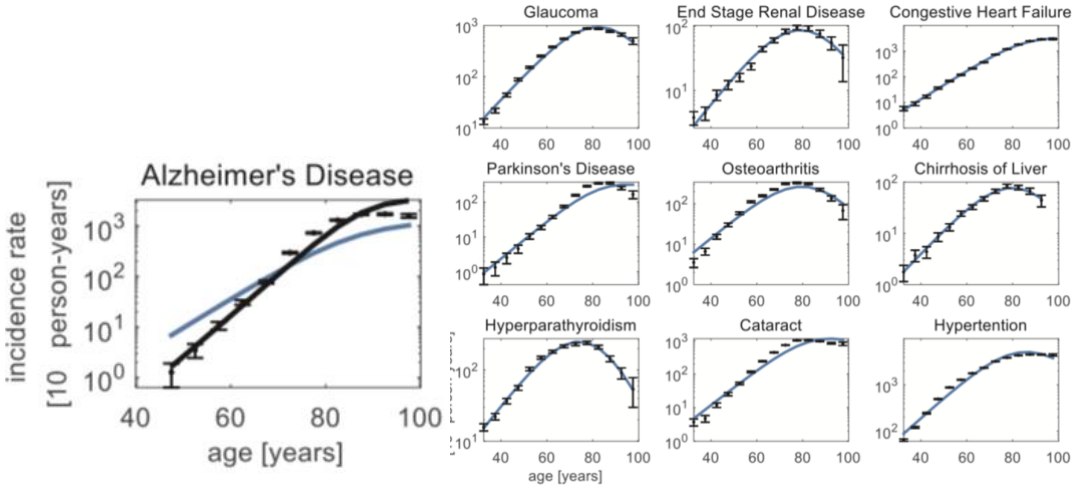


Fig 10.2 Alzheimer disease incidence (black) rises faster than the maximal prediction of the SR model with the parameters that describe all other age related diseases (blue)

Alzheimer involves amyloid beta plaques

Let's start with the basics. Eloise Alzheimer described the disease when he autopsied a patients' brain to find clumps of aggregated protein fragments between the neurons called amyloid plaques. A kind of dental goo. In addition to the amyloid plaques, Neurons died with nasty tangles inside them - another protein aggregate called tau.

Tau tangles and amyloid plaques remain the defining characteristic of the disease. They cause neuroinflammation that shuts down function more widely than each plaque. Destruction begins near the hippocampus- the seat of memory- and rises to the cerebral cortex- the seat of reasoning and recognition.

When imaging amyloid plaques in living people using PET scans became possible, Alzheimer was seen to evolve over decades- first plaques, then tangles that coincide with first mild cognitive symptoms and then worse symptoms. Amyloid can also be detected in the spinal fluid in early stages, and recently a good tau based blood test is improving detection.

At early stages, there are features in common with the yeast mitochondrial mode of death- in neurons in the aging brain, first lysosomes lose acidity, then mitochondria become fragmented and dysfunctional, and then Protein aggregates (amyloid plaques) form. This hints that the Alzheimer driver in neurons might be related to a similar mode to yeast.

The same sequence is seen in other neurodegenerative diseases such as Parkinson's (Alpha synuclein aggregates) and Lewy body dementia- although these diseases have incidence curves that are like other age related diseases.

What is amyloid beta? It is a fragment of a Membrane protein called APP which helps neurons resist stress. When neurons are active they cleave APP by enzymes called gamma and beta secretases. The fragment that is cleaved - called amyloid beta- is exported outside the neuron and is thought to have antimicrobial properties and protective roles at low concentrations. Amyloid beta is normally cleared by the brain's drainage systems called the glymphatic system. With age clearance of the amyloid beta slows down and its concentration rises.

At high concentrations, amyloid beta forms clumps that aggregate into plaques. This aggregation is hypothesised to also have a physiological role to encapsulate microbes and to set off inflammation to fight them.

Unfortunately, in Alzheimer there are too
many plaques that seriously block neuronal connections and cause chronic neuroinflammation. Brain specific cleanup trucks called Microglia attempt to swallow the clumps and plaques, and in doing so they become inflammatory. This is another example of a mechanism which is beneficial in the young but exceeds its usefulness in the old and becomes pathological- antagonistic pleiotropy.

The plaques cause inflammation and nerve damage that incite a neuronal stress response that phosphorylates tau and evolves into tau tangles inside neurons. The tau protein normally holds together the railroad tracks of the neuron - microtubule tracks on which cargo is transported (some neurons are a meter long!). Aggregated tau kills the neuron. Frighteningly, tau aggregates can infect nearby neurons, and thus spread to cause extensive damage. The triggering of tau aggregation near the hippocampus (the seat of memory) is one possible threshold event for irreversible damage and symptom onset.

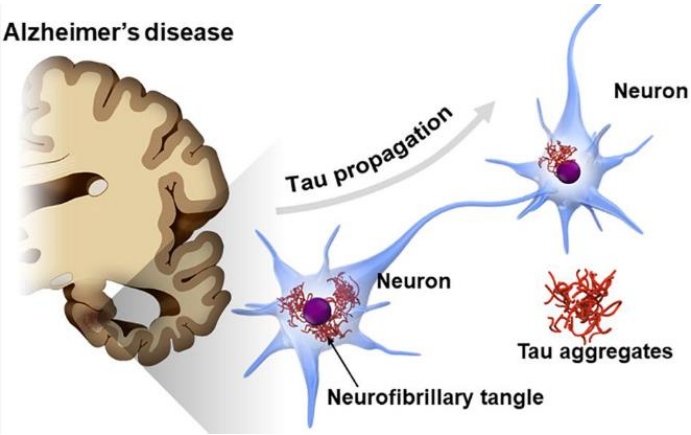


Fig 10.3 Tau tangles can destroy neurons and infect nearby neurons.

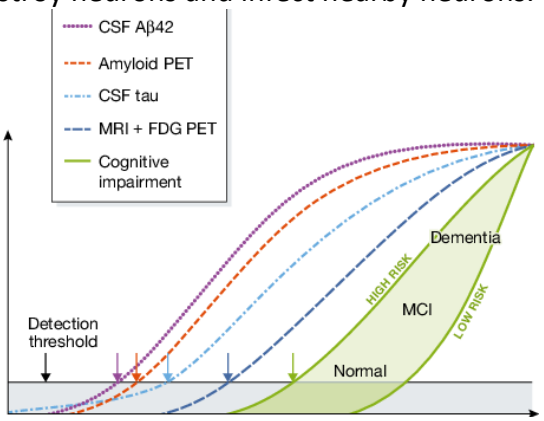


Fig 10.4 Temporal order of biomarkers in Alzheimer's- amyloid beta fragments demented in cerebrospinal fluid (csf), then amyloid plaques, then tau in CSF, and then tau tangles, followed by mild cognitive impairment (MCI) and dementia.
from:http://dx.doi.org/10.15252/emmm.201606210

Familial Alzheimer is caused by rare mutations that increase amyloid beta production

Alzheimer is classified into two kinds - familial and sporadic. Familial Alzheimer has very early onset averaging about 40-50. this early onset form is very heritable- it runs in families such that if one parent has it a child has 50% to inherit (autosomal dominant mutation). Thankfully it is

rare, 0.1% of the cases. Sporadic Alzheimer's accounts for the remaining cases, occurs around age 80 and is less heritable.
Since it runs in families, geneticists quickly zeroed in on the familial Alzheimer genes. And the story is clear - patients have mutations that increase expression of APP or the activity of secretase enzymes that cleave it (known in gene names presenilin 1 and 2 that impact the cutting site of secretase gamma). So elevated plaque production leads to early onset Alzheimer's.
We can analyze the role of these mutations like we did with yeast deletions. Instead of survival curves, we can use disease-free survival curves - take a population that all got Alzheimer's and ask what fraction were disease free (undiagnosed with symptoms) at each age. This curve drops from 100% to zero, and its halfway point is the median onset time. We can compare familial Alzheimer's with a specific gene variant and to the general population that got Alzheimers.
We can see that APP and presenilin mutants have a median onset of 40 years which is much younger than the median onet of 78 in the population. When scaling time by the median onset the curves overlap to a good approximation - scaling. In the SR model (in mammals, not in yeast) scaling means houses- a change in production rate. Similar scaling is seen in different familial presenilin (secretase gamma or beta) mutations.

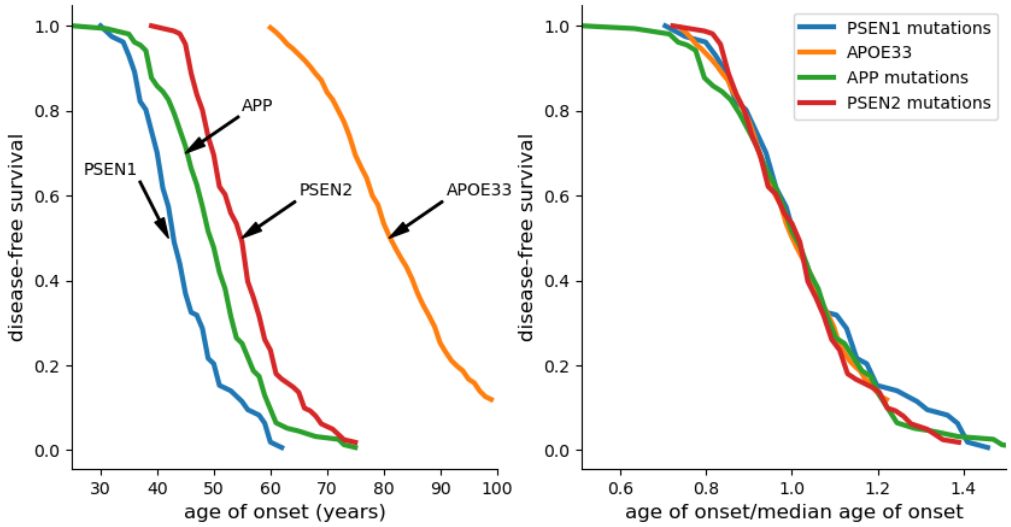


Fig 10.5 The disease free survival for different genetic signatures
We may conclude that the familial genes affect damage production and not damage removal or threshold

This makes sense- amyloid production rate is in the houses, affecting eta. Faster production scales time and causes earlier onset. We can estimate that production in APP variants is about 78/40 ~ 2 times faster than in sporadic Alzheimer's cases.
Another genetic link is in Down syndrome. When the chromosome encoding the APP gene is found in three copies- a trisomy of chromosome 21 that causes Down's syndrome - Alzheimer is a common consequence with mean onset around 50-55, consistent with a 1.5 fold increase in production.

Sporadic Alzheimer is due to APOE4 and many variants of small effect

There are many more genes associated with sporadic alzheimer- the common case of the disease. The prevalence and importance of sporadic Alzheimer led to many large genetic studies on tens of thousands of patients and controls - Genome wide association studies or GWAS. These show one variant of huge effect, another of more minor effect and a multitude of variants of small effect. Let's use the key variants to enrich our understanding of Alzheimer's mechanism in light of the SR model.
The main gene involved is APOE, a protein that binds to lipids - lipids are like oil and don't mix with water, therefore carrying them from place to place in the body requires they bind to APO proteins which have one side that is hydrophobic and sticks to oil, and the other hydrophilic liking water.
APOE is the main lipid transporter in the brain. Other APO proteins like APOB are in LDL 'bad' cholesterol for example which carries lipids in the blood and is involved in atherosclerosis (another kind of plaque that clogs up blood vessels, causing heart attack and stroke).

From: APOE2: protective mechanism and therapeutic implications for Alzheimer's disease

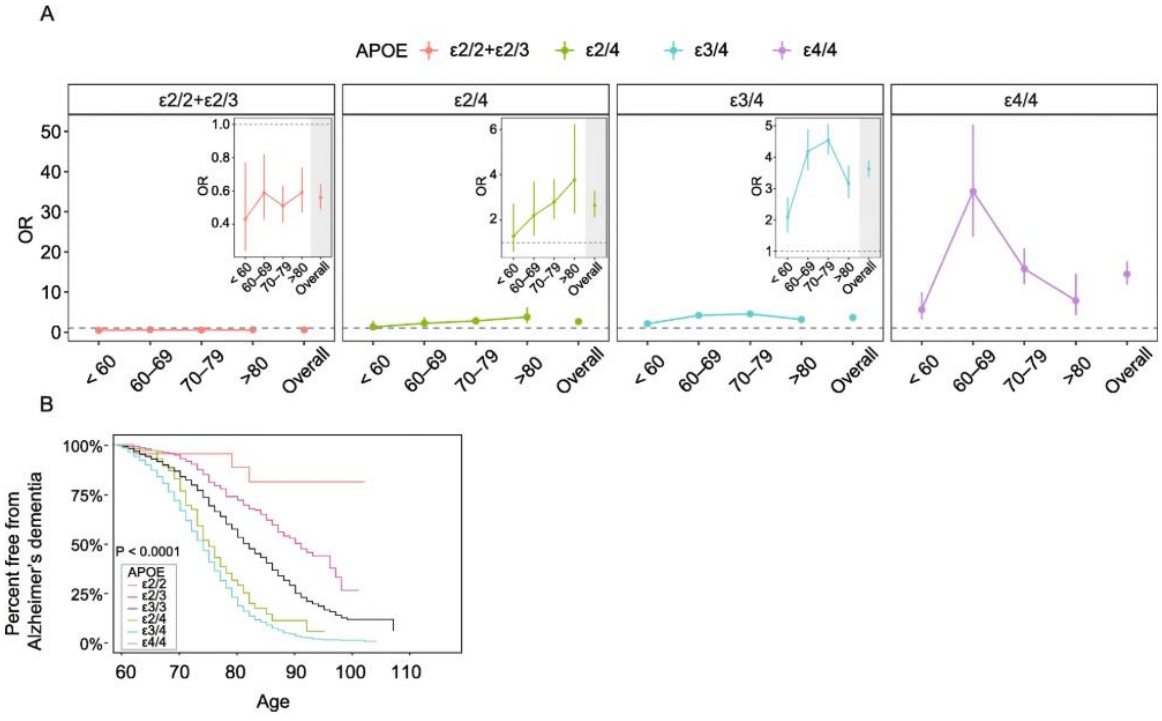


Fig 10.6 Risk of Alzheimer (Odds ratio, OR) in the APOE variants changes with age, source: Genin et al Mol Psych 2011.

APOE comes in three common variants- APOE2,3 and 4. The most common is APOE3, about 70% of the population. APOE2 is protective for Alzheimers -it is rare, but is overrepresented in centenarians. APOE4 is a major risk factor for Alzheimer- most patients carry it. Since we get one copy of a gene from mom and one from dad we can have 6 possible combinations, the most common of which is 3/3. The worst variant 4/4 has about a 10 fold higher risk of

Alzheimer's than the common 3/3 variant! It has almost 30 times more risk for early onset Alzheimer before age 70.
But the effects of APOE4 don't stop there - the 4/4 variant has higher all-cause mortality and risk of heart disease and stroke than the 3/3 allele, and 2/2 is generally protective from death and disease.
So why did evolution not remove the APOE4 variant? Evolutionary thinking is that it must have a beneficial role in some contexts that balances its deadly role. The ancestral gene in primates is actually the APOE4 variant. But what is the protective role? This is unclear.

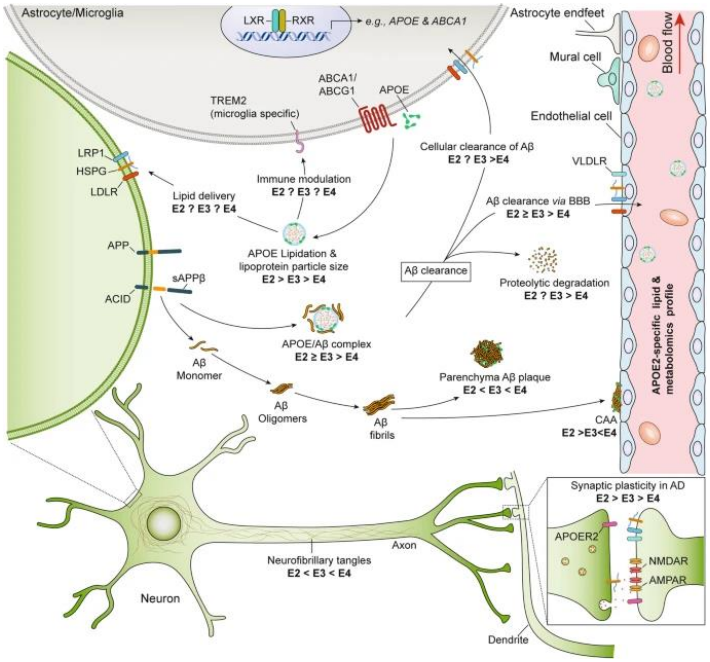


Fig 10.7 The many roles of APOE in removing amyloid plaques, and the relative strength of the three variants APOE2,3 and 4.

Here are the relative risk ratios for Alzheimer's disease (AD) based on APOE genotypes, compared to the baseline risk of ε3/ε3:

Table 10.1 Alzheimer risk of APOE variants relative to the APOE3/3 genotype

APOE2/2	~0.1-0.6x (protective)	Significantly reduced risk; rare genotype (~1% of the population).
2/3	~0.4-0.6x (low risk)	Reduced risk compared to ε3/ε3; common genotype (~10-15%).
3/3	1x (baseline)	Most common genotype (~60% of the population).

2/4	~1.5-2.5x	Moderately increased risk; second most common genotype (~20-25%).
3/4	~2-3x	Moderately increased risk; second most common genotype (~20-25%).
4/4	~8-12x	Highest risk associated with earlier onset of AD (~1-2% of the population).

Notes:

1. Risk varies with age: The impact of APOE ε4 is stronger in individuals aged 65-75 but diminishes in very old age (85+).
2. Gender differences: Women with ε4/ε4 may have slightly higher relative risks than men.
3. Population averages: The lifetime risk of developing AD for the general population is ~10-15%. For ε4/ε4 carriers, this risk increases to ~50-70%, while for ε3/ε4 carriers, it's ~20-30%.

APOE4/4 is **not deterministic for Alzheimers,** but risk is high.

The disease-free survival curves of these variant combinations show that 4/4 has the earliest onset, around 70, and that 2/2 virtually don't get AD.

Using our scaling analysis, we see that unlike the familial mutations, APOE variant survival curves do not scale. In fact they have a somewhat puzzling behavior- 4/4 is short lived and steep. In the SR model no single parameter can do that- short lived is either scaling (high eta) or shallow (low beta,Xc, high epsilon). Never short lived and steep.

This means that APOE4 affects at least two parameters. Moreover these effects are opposite in their impact- it needs to increase eta (more houses, rapid onset), but also to increase Xc (slightly late onset and very steep). It thus needs to have a damaging role (more houses) but also a protective role (higher threshold). This is in harmony with the idea of both bad and good sides of the same variant.

ApoE2 is the opposite- long lived and shallow. Again hinting at two effects (improved clearance at the cost of more inflammatory glia).

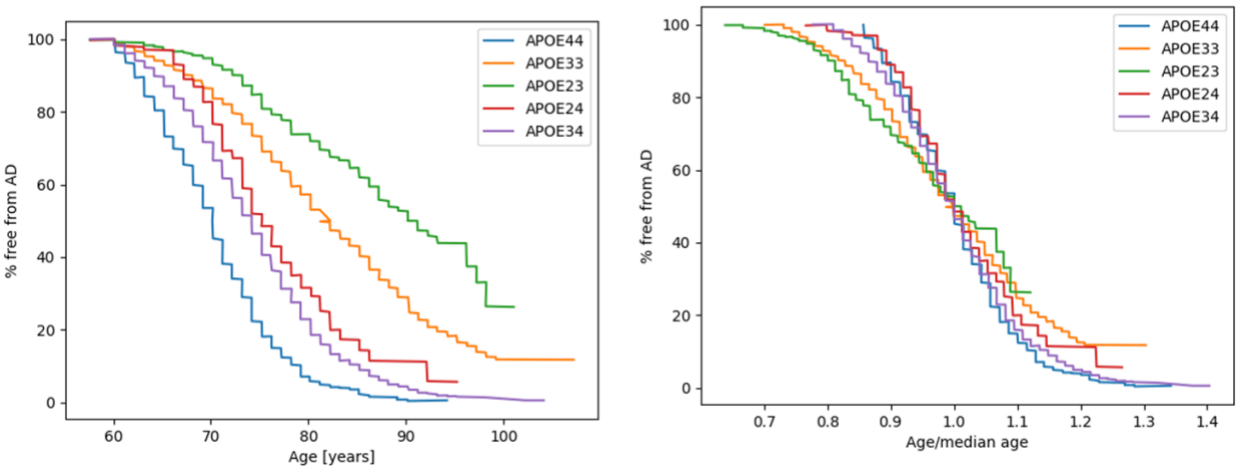


Fig 10.8 Disease free survival curves of the six APOE variant combinations show they do not scale. The shorter the median onset the steeper the curve. This suggests a combination of harmful and protective effects.

In addition to APOE, numerous other genes of smaller effect are implicated in sporadic Alzheimer's disease. many are involved in lipid metabolism, immune response, and amyloid-beta clearance. Some of these genes, like TREM2, ABCA7, and CLU, are important in modulating microglial function and inflammation, which are key contributors to Alzheimer's disease pathology. Some variants are protective even in the presence of AOE4, such as Klotho and CETP, both enriched in centenarians. The interactions between these genes and environmental factors contribute to the complex genetic landscape of Alzheimer's disease.

The second strongest GWAS hit is TREM2, a receptor in glia (the brain's immune cells) that interacts with APOE to clear amyloid beta plaques. The APOE4 variant binds amyloid beta and TREM2 more weakly than APOE3. The disease free survival curve of the TREM2 variant shows rapid onset and steepness-similar to APOE4- suggesting a double edged sword just like APOE4. The double edged sword just to be clear is that the variants APOE4 and TREM2 cause glia to clear less plaque (bad), and hence the glia are less inflammatory (good). We are ready to build a hypothesized mechanism.

Hypothesized SR mechanism for Alzheimer

To sum up what we have learned, we can hypothesize on a candidate SR mechanism for Alzheimer's and why its incidence rate is so different from other age related diseases. In terms of an SR model, it has a different set of house-garbage-trucks with its own threshold. Houses are damaged neurons that cleave APP using beta and gamma secretase to produce amyloid beta.

Why do damaged neurons rise linearly with age? The clues we discussed favor a lysosome-mitochondria mechanism, where more and more neurons have problematic low acidity lysosomes and dysregulated mitochondria causing unfolded protein aggregates. Beta Amyloid is

cleaved into endosomes and when lysosomes are low acidity the toxic amyloid beta fragments are not degraded in the lysosome . Instead They are dumped out of the cell, and cleared by glymphatic flow. The clearance rate slows with age. In total, toxic Ab fragments in the brain found rises with age:

Why do more and more neurons have de acidified lysosomes and endosomes with age ? One possibility is accumulation of a nondegradable mess of crosslinked oxidised proteins, lipids and metals called **lipofuscin**- aka age pigment. It lasts an organism's lifetime and accumulates in non dividing cells, gumming up proton pumps and enzymes in the lysosome.

The garbage x is amyloid beta plaques or oligomers. This is cleared by the glymphatic system and also by glia cells using APOE and TREM2 - the glial cells are the trucks. As more and more neurons are stressed and produce amyloid beta, the trucks become overloaded. When plaques cross a threshold Xd, they generate so much neuroinflammation and other damage that tau tangles are initiated, and travel from neuron to neuron to cause progressive damage, which sets off more amyloid beta in a vicious cycle leading to symptoms.

This SR model can have different rates eta, beta and Xd than the rest-of-the-body SR model, and so can provide the observed rapid rise of Alzheimer's incidence.

The effect of APOE4 and APOE2 variants now becomes more lucid. APOE4 reduces the glia's ability to clear amyloid beta. This decreases the truck's beta, causing a rapid onset and shallow curve. However, overloaded glia cause chronic inflammation- they therefore lower the threshold Xd - it now takes less neuroinflammation from plaques to cause symptoms, because the overloaded glia add to the neuroinflammation. But since APOE4 has less glial uptake of amyloid, it also has less inflammatory glia- and hence a higher Xd than APOE3. This is a protective effect of APOE4 - its reduced glial uptake of garbage protects the trucks from becoming inflammatory.

For the protective allele APOE2 the story is in reverse- better uptake increases beta, but also lowers Xd because the improved uptake causes more inflammatory glia. One obtains the late onset and shallow curves of APOE2.

Therapy and prevention of Alzheimer

Decades of research and tens of billions spent by pharma companies on developing drugs to reduce amyloid plaques led to zero drugs for slowing or preventing Alzheimer. The only available drugs helped manage symptoms - such as certain neurotransmitter inhibitors.

This frustrating situation came to a dramatic climax in 2021 when the FDA approved an antibody that clears plaques, but had no effect on symptoms in clinical trials, despite a 10 out of 11 vote against by the FDA board. Many became unsure of the amyloid beta theory of Alzheimer itself. Perhaps scientists were looking under the lamp but the coin is somewhere else?

But more recently a different plaque-removing antibody - that removes amyloid beta fibrils before they become plaques- has been approved that does slow the rate of early Alzheimer's. The needle is finally moving.
The monoclonal antibody Dananemab approved in 2024 slows disease progression by 35%, and 70% of participants had no visible amyloid after 18 months of treatment.

Prevention is better than treating the disease after it erupts. To prevent Alzheimer's three lifestyle factors emerge. The first is aerobic/strength exercise, which is as always a wonder-drug and reduces Alzheimer's risk by 30%-50%. The second is education and intellectual engagement, probably providing more spare cognitive capacity to delay the worst effects of the disease.
The third, and the focus of the next section, is sleep. Especially deep, slow-wave sleep. Less than 6 hours of sleep over decades raises the risk of Alzheimers by 20-40%.

Part 2 To Sleep, perchance to Dream - Sleep and longevity

Recommended reading - Why we sleep/ Mathew Walker

Sleep… delicious… sometimes fragile… we spend a third of our life snoozing. But we know so little about it. Sleep has been stigmatized as lazy and ineffective - we even market a nap as a Power Nap to make it appealing. That is why it has been underplayed as a health factor until quite recently. It is the third leg of the elephant of health, not less important than nutrition and exercise. If we say “I’ll sleep in the grave” we may do so more rapidly than intended.

The optimum seems to be around 7-8 hours of sleep, and we have a U shaped curve in Fig 10.9 based on objective sleep measures using accelerometers. In the long term, sleeping longer than 9h is often a sign of an underlying health condition. Short sleep in contrast is causative for diseases. If we do not get at least 6 hours of sleep over the long run we are at higher risk of disease and death.

This statement can't be true for everybody. Epidemiological data has its usual biases. Some people seem to need less sleep than others, but it seems that everybody needs at least 4-5h to get enough deep sleep.

Some strains of mice are short sleepers and they seem to have improved brain clearance, as evidenced by reduced alzheimer when crossed with alzheimer model mice.

One of the functions of sleep is to allow the brain to repair and to drain out toxins and aggregates like amyloid beta and tau, through the glymphatic system. This system works mainly during slow-wave sleep. But only this decade it was discovered why and how as I will tell you soon.

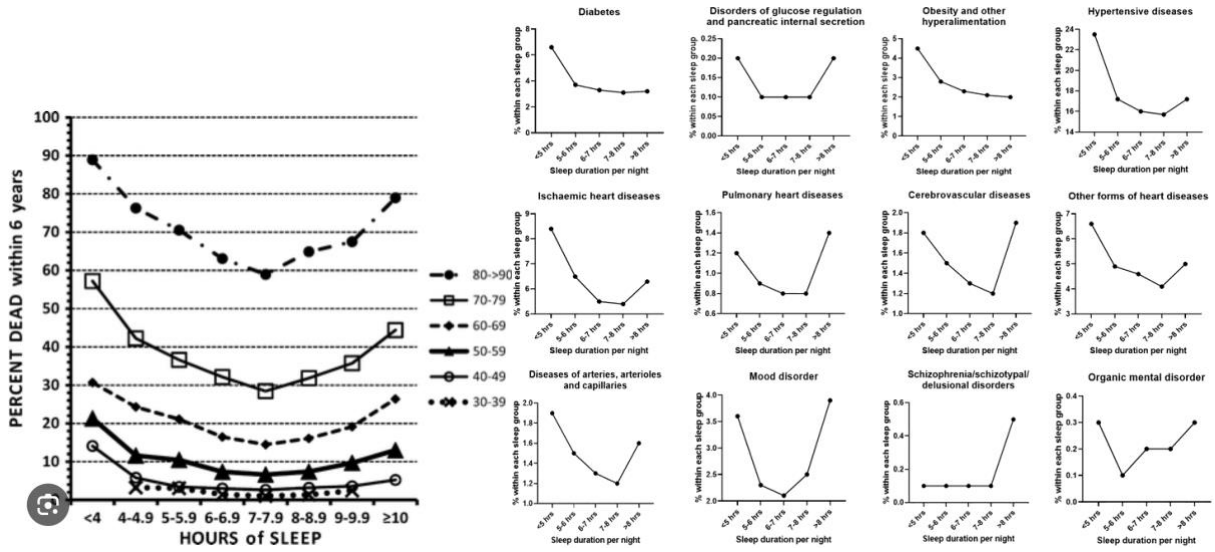
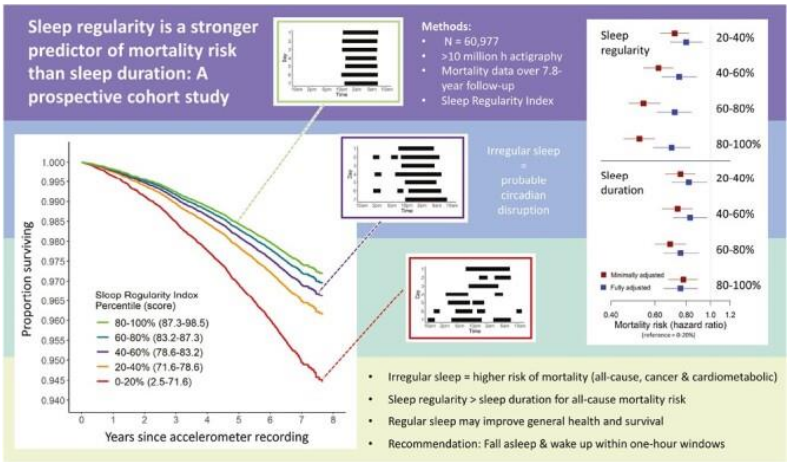


Fig 10.9 six to eight hours of sleep seems optimal for physical And metal health Six to eight hours of sleep, as well as less fragmented sleep, associates with l long-term metabolic and mental health. Data on objective sleep duration were measured using accelerometry. Primary care health records were then obtained from the UK Biobank (n=84,404). Participants (mean age, 62 years) were divided into five groups according to their sleep duration. ICD-10 codes were used for the analysis of primary care data. Wake after sleep onset, activity level during the least active 5 hours and episodes of movement during sleep were analysed as an indication for sleep fragmentation.https://www.researchgate.net/publication/355484130_Exploration_of_Sleep_as_a_Specific_Risk_Factor_for_Poor_Metabolic_and_Mental_Health_A_UK_Biobank_Study_of_84404_Participants?_tp=eyJjb250ZXh0Ijp7ImZpcnN0UGFnZSI6Il9kaXJlY3QiLCJwYWdlIjoiX2RpcmVjdCJ9fQ

Sleep regularity is a stronger predictor of mortality than sleep duration



Does sleep affect houses, trucks threshold or noise?
Why should we care? One reason is curiosity about the relation of sleep and aging.
Another is practical - we saw several interventions that extend mean lifespan by a few years each. What happens if we combine them? Do benefits add up, or are there diminishing returns? , if sleep affects a different parameter than say exercise, they can combine additively. Interventions that act on the same parameter tend to have diminishing returns when combined.

To find out we look, as usual, at survival curve shapes. These curves are from NHANES with survey data on sleep duration and quality, or uk biobank with wearable accelerometry data. Both show that poor sleep is short lived and shallow and regular sleep is long lived and steep, in a way most consistent with noise.

This combines with not findings from the tree of life that noise is linked with trucks. In humans trucks are immune cells removing damage. They work at night , and noise is systemic changes in their activity caused .Therefore , sleep quality - eg the amount of deep nrem - and regularity with respect to the circadian clock- is key. Regular high quality and abundant sleep may reduce noise and increase steepness.
And if exercise raises Xc and sleep quality lowers noise, they should have additive effects - because they work on different parameters, different processes.

Sleep pressure and circadian wake signals
Let's understand sleep better. The urge to sleep is driven by the difference between a sleep pressure signal and a wake signal (Fig 10.10). The sleep pressure is a molecule called adenosine that builds up in the brain when we are awake and is degraded when we sleep.

One hypothesis by Jonathan Kipnis is that sleep pressure is a proxy for dirt in the brain, and cleaning the brain during sleep is one of its main functions. At old age , humans and mice take more naps, and if mice glymphatics are enhanced they take less naps.

Caffeine blocks the adenosine receptor- so sleep pressure may be screaming but the brain doesn't hear it. When caffeine is itself degraded (it has a half life of 3-7 hours) the sleep pressure is revealed.

Note that people differ in their caffeine half life- young have faster clearance than old, and caffeine clearance depends on liver enzyme CYP21A whose gene varies between people - so you can time the last coffee of the day to before early afternoon to be able to sleep.

The wake signal is hormonal (cortisol and other stimulants) driven in a 24h period by the brain's clock- the circadian rhythm. In the morning we get a circadian wakeup call - morning cortisol surge- and adenosine is very low so we wake. At night the circadian signal is low and adenosine is high - we go to sleep

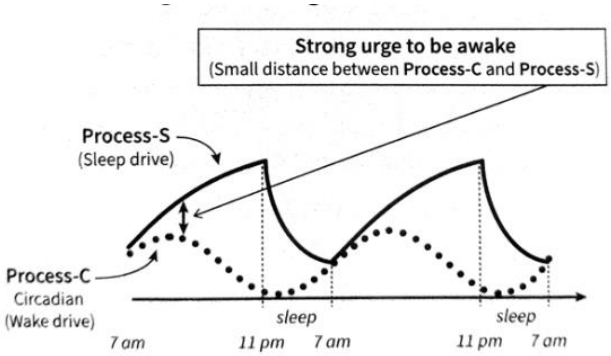


Fig 10.10 The sleep pressure due to brain adenosine rises during wake and is degraded in sleep. The wake signal is circadian and oscillates over 24h. From Why we sleep, Walker

When we pull an all-nighter, we first feel tired and then get a second wind- we feel the wake signal rise in the morning after the sleepless night. But on the second evening of no sleep, the sleep pressure builds up so high that we can't help but fall asleep (Fig 10.11).

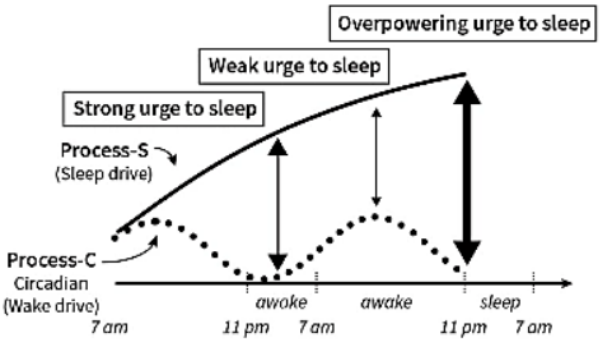


Fig 10.11 After staying awake all night we feel a renewed freshness and then an overpowering urge to sleep. From Why we sleep, Walker

Sleep has a refreshing deep NREM phase and a dreamy REM phase

Sleep cycles: There are two basic types of sleep: rapid eye movement (REM) sleep and non-REM sleep(which has three different stages). Each is linked to specific brain waves and neuronal activity. You cycle through all stages of non-REM and REM sleep several times during a typical night, with increasingly longer, deeper REM periods occurring toward morning. A sleep cycle is the progression through the various stages of non-REM sleep to REM sleep before beginning the progression again with non-REM sleep.

There are generally four to five different sleep cycles during a given night and each one lasts for about 90 to 120 minutes. This cyclical pattern of sleep is called **Sleep architecture**, as represented by a graph called a hypnogram. Typically we see four to five cycles per sleep time of typically 6-8 hours for adults.

One does not go straight from deep sleep to REM sleep, however. Instead, a sleep cycle progresses through the stages of non-REM sleep from light to deep sleep, then in reverse back from deep sleep to light sleep, ending with time in REM sleep before starting over in light sleep again.

A person's sleep time can be thought of as 2 halves. The first half for a majority of people consists mostly of a deeper sleep with sporadic periods of Stage 1 and short REM periods. As the night progresses, the lightest sleep increases with lengthening periods of REM occurring.

Sleep stages A complete sleep cycle progress between 4 different phases (Fgi 10.12):

- non-REM phase
    - Stage 1: the lightest stage of sleep
    - Preparing for deep sleep: Stage 2 and Stage 3:
    - Stage 4: the deep sleep
- REM Phase: the deepest sleep, where dreams occur

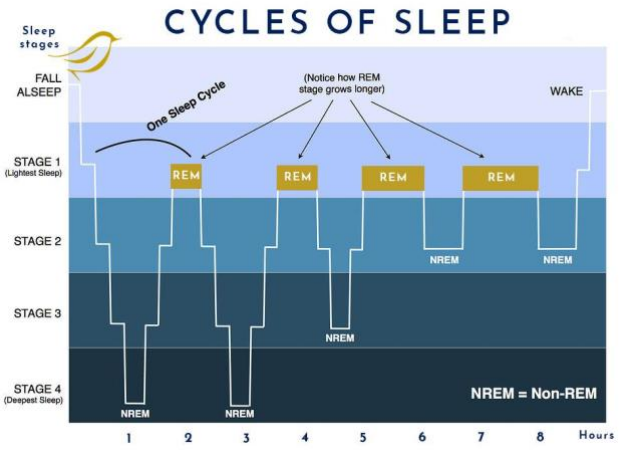


Fig 10.12 Sleep has cycles of several stages, deep NREM occurs in early cycles and REM lengthens in late cycles.

For a majority of people, a sleep cycle begins with a short period of Stage 1 sleep whereby the body begins to relax.

Lightest sleep- stage 1 Light sleep initiates your sleep cycle and acts as a transition to deeper sleep stages. During this stage your muscles begin to relax, your heart rate and breathing slow down, and you wake up easily. During light sleep, you can expect the following:

- muscles relax and may jerk
- respiration slows

- heart rate decreases
- body temperature drops
- sleep begins

Stage 1 is the lightest stage of non-REM sleep. Often defined by the presence of slow eye movements, this drowsy sleep stage can be easily disrupted causing awakenings or arousals. During this short period (lasting several minutes) your brain wave activity begins to slow from that of wake. While drifting in and out of Stage 1, people may occasionally experience sensation of falling,hypnic jerks (called Myoclonus) or abrupt muscle spasms Though arousals or awakenings are prevalent, Stage 1 is important as it allows for the body to enter Stage 2; the first quantifiable stage of NREM sleep.

Preparing for deep sleep- stages 2 and 3: In the second stage, your body starts preparing for deep sleep. Awakenings or arousals do not occur as easily as in Stage 1 sleep and the slow moving eye rolls discontinue. Your heartbeat and breathing slow, and muscles relax even further and your body temperature drops. Brain wave activity slows but is marked by brief bursts of electrical activity. These phases occur for longer periods than Stage 1. For most, they comprises approximately 40-60% of total sleep time

Deep sleep- Stage 4: you are now in deep sleep. Stage 4 is known as deep non-REM sleep. It reduces your sleep drive as it's the most restorative stage of sleep and it occurs in longer periods during the first half of the night. It consists of extremely slow brain waves called delta waves, which are intermixed with smaller, faster brain waves.

If you take a short nap during the day, you're still able to fall asleep at night. But if you take a nap long enough to fall into deep sleep, you have more difficulty falling asleep at night because you reduce your need for sleep.

Awakenings or arousals are rare and often it is difficult to awaken someone in this stage of sleep. People waking up from a deep sleep are disoriented or groggy. Instead Parasomnias (sleepwalking, sleep talking or somniloquy and night terrors) occur during the deepest stage of sleep.

This restorative stage does not last as long as Stage 2+3, lasting between 5-15% of total time asleep for most adults. For children and adolescents deep sleep is much higher in duration.

It is the most rejuvenating and restorative sleep stage, promoting human growth hormone and restores your body and muscles from the stresses of the day. Your immune system also restores itself.

Much less is known about deep sleep than REM sleep. It may be during this stage that the brain also refreshes itself for new learning the following day.

During deep sleep, you can expect the following:

- blood pressure drops
- blood flow increases to muscles
- repair hormones (i.e. growth hormone) are released
- tissue growth and cell repair occurs
- long, slow brain waves
- brain flushes out waste

If it is so good, why is it so short? Tradeoffs may exist- cost of being hard to wake and groggy, and need for additional functions such as information and emotion processing.

Dream sleep- REM Entering the last stage, also called REM sleep(rapid eye movement). , REM is associated with dreaming, memory consolidation, learning, and problem solving

In the REM stage your eyes are closed but move rapidly from side-to-side, due to the intense dream and brain activity you go through in this stage. Your breathing becomes faster and irregular, and your heart rate and blood pressure increase to near waking levels. Your arm and leg muscles become temporarily paralyzed, which prevents you from acting out your dreams. As you age, you sleep less of your time in REM sleep.

In the REM period, you can expect the following:

- respiration increases
- heart rate increases
- temperature regulation is switched off
- brain activity is high; vivid dreams may occur
- body becomes immobile to stop you from acting out dreams
- blood flow increases to genitals

REM can occur at time during the sleep cycle, but on average it begins 90 minutes following sleep onset and is short in duration as it is the first REM period of the night. Following REM, the process resumes starting with periods of Stage 1-4 intermixed before returning to REM again for longer periods of time as sleep time continues

A person typically experiences three to five REM periods throughout sleep time with the longest REM period right before awakening for the day. Awakenings and arousals can occur more easily in REM; being awoken during a REM period can leave one feeling groggy or overly sleepy. Consistent interruptions to REM sleep can lead to a host of potential issues, such as sleep inertia.

Dreaming

Everyone dreams. A French study found that all people do in fact dream, whether they remember their dreams or not. You spend about 2 hours each night dreaming but may not remember most of your dreams. Its exact purpose isn't known, but dreaming may help you process your emotions. Events from the day often invade your thoughts during sleep, and people suffering from stress or anxiety are more likely to have frightening dreams.

Perhaps with the ubiquity of ai we have an analogy for dreaming- hallucinations by a model trained on reality. Like AI training itself to play a video game, dreaming may help train our neural network.

Dreams can be experienced in all stages of sleep but usually are most vivid in REM sleep. Some people dream in color, while others only recall dreams in black and white.

Why deep NREM sleep is crucial to prevent Alzheimer

In 2012, Maiken Nedergaard and her colleagues at the University of Rochester discovered the brain glymphatic pathway, the brain's plumbing system similar to lymphatics in the body (but without lymph nodes), which consists of a network of fluid-filled water channels amd water transporters (specifically aquaporin-4, AQP4, expressed on astrocytes) alongside (para) blood vessels to drain chemical waste, and facilitate movement of cerebrospinal fluid.

In early 2024, 2 *Nature* publications demonstrated that synchronized neurons that occur in deep NREM sleep can activate glymphatic waste clearance. Blocking neuronal firing prevented waste clearance . The best summary for their work, positioning neurons as the master organizers for brain clearance, as articulated by the authors, is: "**neurons that fire together, shower together.**" Gamma stimulation was shown to increase the arterial vasomotion (rhythmic oscillation/movement) and release of neuronal peptide molecules. The neurons that fire together create a rhythmic norepinephrine signal that causes arterial contraction to create a peristaltic pump effect that moves water in the brain and down the glymphatic drain, washing away amyloid beta, tau and other toxins out of the brains casing to the lymph vessels and down to the veins and out.

The impact of non-REM sleep, particularly slow-wave deep sleep, cannot be emphasized enough. Ironically, Ambien, a commonly used drug to help people sleep, backfires and actually suppresses waste disposal. There are likely many other drugs that are either used for sleep aids or are associated with sleep disruption that have similar adverse effects. Ambien, a benzodiazepine like Valium, and other sleep medications have been associated with a heightened risk of Alzheimer's disease and dementia in multiple studies. While this link is not definitive or established as causal, the mechanism may well be the impairment of brainwashing (the vasomotor oscillations and norepinephrine pump function) induced by the medications.

With the elucidation of this pivotal drainage mechanism, it is notable that none of the commonly used sleep medications or supplements have been shown to improve waste clearance, the principal function of sleep. Or promote deep slow- wave sleep *without* important

side effects. We are in desperate need for effective and safe sleep medications that will achieve these objectives.

Recent advances include new sleep medication based on the orexin receptor agonists (Dora). It silences the wake signal, and is reported to be non addictive. One potential non-pharmaceutical technology is non-invasive brain stimulation to promote normal and synchronous neuronal oscillations.

Aging reduces and fragments sleep

A decline in the ability to initiate and maintain sleep is part of the normal ageing process. Older adults commonly experience more fragmented sleep,
shorter sleep duration and more daytime naps. However, some individuals are affected more than others, suggesting other factors may contribute to the inter- individual variability. Existing research recognises the critical role played by gender. Psychosocial influences such as retirement, social isolation and bereavements may also contribute to the increased sleep complaints among older individuals. There is therefore interest in sleep duration as a potential biomarker for healthy or unhealthy ageing and a potentially modifiable risk factor.

Aging alters the circadian rhythm through a combination of changes in the brain's central clock, peripheral clocks, and the signaling pathways that regulate these systems. Aging generally reduces the clock's amplitude and moves it to an earlier phase - a morning chronotype. These changes can disrupt the body's ability to maintain a stable and synchronized daily rhythm, leading to sleep disturbances, metabolic dysregulation, and other age-related health issues.

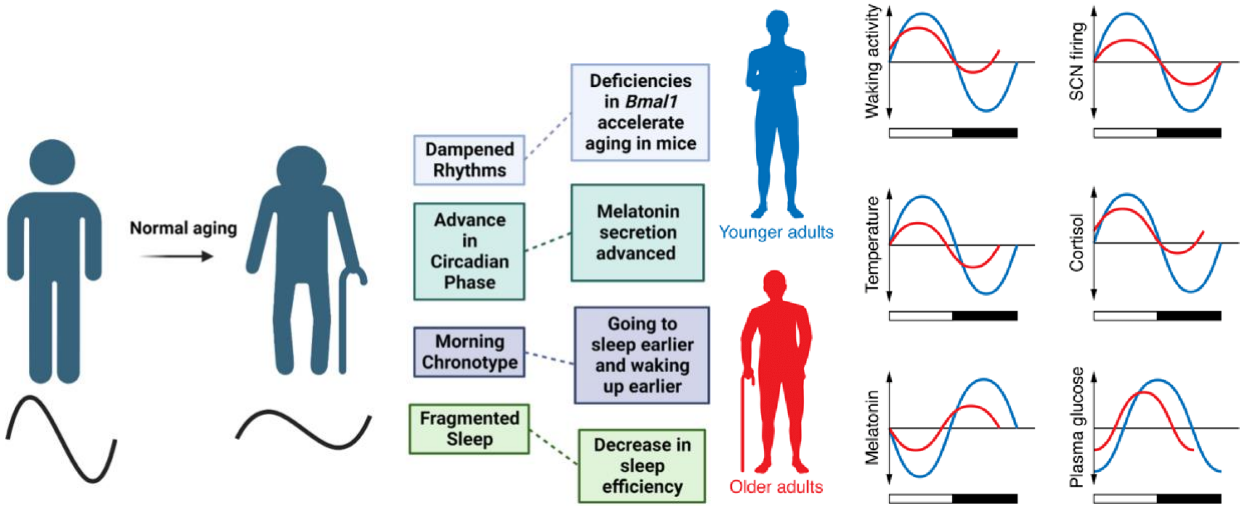


Fig 10.13 Normal aging causes problems with the body's 24h clock called the circadian clock.

Optimize Sleep Quality

Prioritizing sleep is foundational to health. Recommendations include

Consistent Sleep Schedules: give yourself an 8h sleep opportunity. Adhere to regular sleep-wake cycles to reinforce circadian rhythms, optimizing restorative processes and glymphatic activity

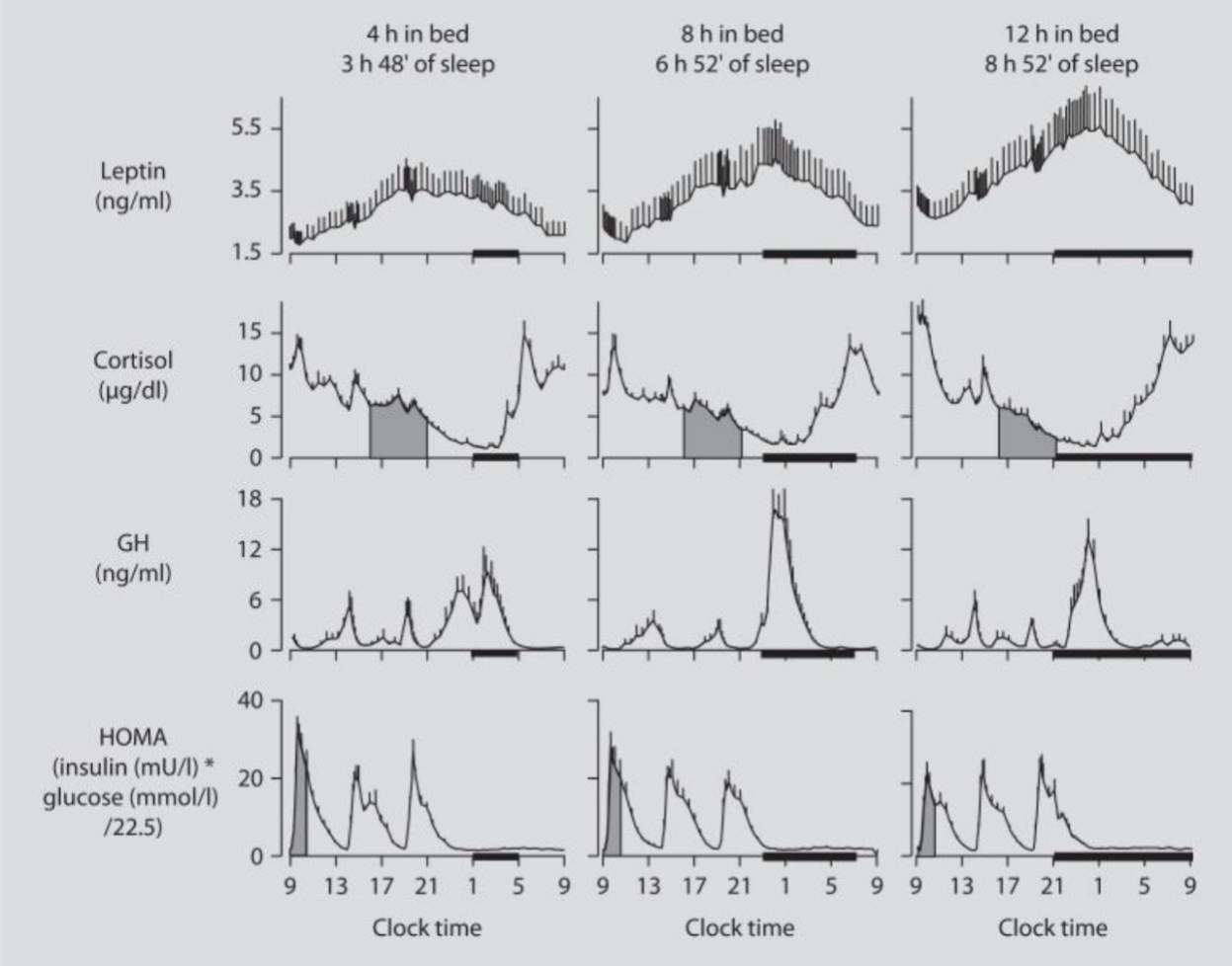
Sleep Environment: A cool, dark, and quiet bedroom facilitates deep, uninterrupted sleep, essential for glymphatic function. After a warm shower the body cools and it's easier to fall asleep.

Pre-Sleep Hygiene: Minimizing screen exposure, alcohol and caffeine intake in the evening supports melatonin production and sleep onset, ensuring optimal rest. Reading a paper book, entering a mental state of gratitude and acceptance.

to promote healthy sleep, the list you are familiar with, including maintaining regularity of bedtime and awakening, exercise, avoidance of late eating close to bedtime, avoidance of alcohol, especially within 3 hours of going to bed, a cool and fully dark bedroom, avoidance of blue light, diagnosing and treating sleep apnea if present, and relaxation training techniques or digital cognitive behavioral therapy.

Sleep Position: research indicates that lateral (side) sleeping positions enhance glymphatic flow compared to supine (back) or prone (stomach) positions. This is from Rodents and is a20% effect. This alignment optimizes CSF dynamics, bolstering waste clearance and exemplifying how subtle behavioral changes might significantly impact brain health. Side sleeping also reduces apnea.

Quiet: new earpods effectively cancel
Out snoring sounds .


4 h in bed
3 h 48' of sleep
8 h in bed
6 h 52' of sleep
12 h in bed
8 h 52' of sleep
Leptin
(ng/ml)
5.5
3.5
1.5
Cortisol
(µg/dl)
15
10
5
0
GH
(ng/ml)
18
12
6
0
HOMA
(insulin (mU/l) *
glucose (mmol/l)
/22.5)
40
20
0
9 13 17 21 1 5 9
Clock time