Chapter 12
connection: passion, reduced stress and wisdom

Recommended reading: Behave, Robert Saplosky

Why do we benefit from friends and other social ties, from a sense of meaning and control, and from mindfulness?
This is a book about systems aging. Systems approaches work best when the components and interactions are well characterized, and we can ask how they work together as a circuit. In the field of neuro-behavior, however, we are not quite there. So I'll talk about the best understood components that connect mind and body. It's a great field if you want to go into the unknown and discover important biology.

To make mechanistic sense of social ties and longevity, we need to focus on the body's stress response - social ties reduce stress in multiple ways. They protect us from chronic stress that destroys health.

The panic button and its calmers
Let's make friends with brain anatomy. We discussed two brain regions in the Alzheimer section: the seat of memory- the hippocampus, and the seat of reasoning - the prefrontal cortex. Both of these regions provide context and relax the panic button for the brain- the amygdala (Fig 10.15). The amygdala receives input from the senses and compares them to previously learned patterns from times of danger. If this was all, we would jumpscare at any sudden noise. But the hippocampus and prefrontal cortex can give context and say "calm down".

For example if we see a train hurtling towards us the amygdala screams and we get an (appropriate) stress response; if we see a movie of the same train hurtling towards us we enjoy it. Yet people in 1896 seeing the first movie of a train approaching a station had no context that movies are safe probably flinched (Fig 10.14).

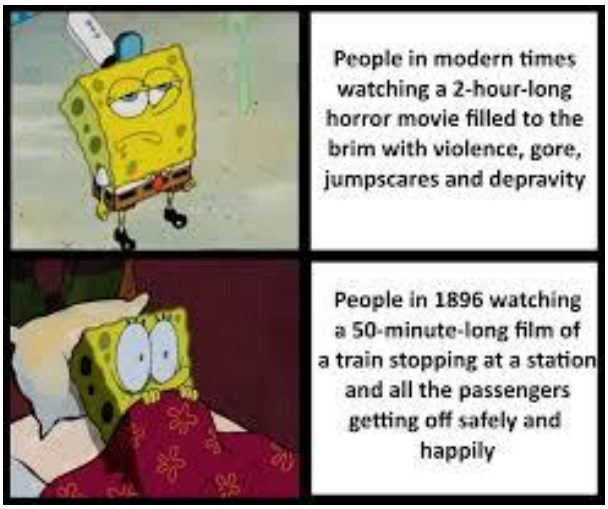


Fig 10.14 Context calms the brain's panic button.

That is also where **meditation, yoga and psychotherapy (CBT)** might work. There is a sequence in the mind- first an event (or body sensation) → we interpret it → and then get an emotional response→ then we act. If we pause and check our interpretation, we have more freedom to choose our response.

Unfortunately most of the time we are on autopilot, and the emotion seems automatic as if we have no choice. We often enter a reactive chain of thoughts (stories) and actions that keeps the stress going.

I recommend meditation, yoga and psychotherapy to everyone, I am greatly helped by them. They can create awareness of the space between event, interpretation (thought), emotion and action. This space gives us more freedom of choice.
Without mindfulness we are doomed to repeat failed behaviors, and thus to reinscribe them, deepening the groove of myelinated neural pathways, making them even more automatic.

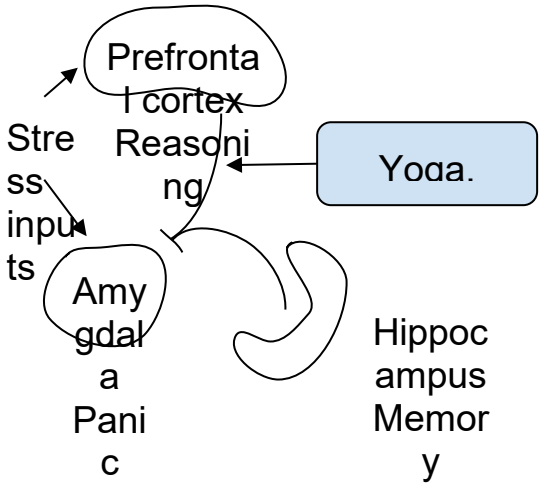


Fig 10.15 Brain regions involved in stress interpretation and panic calming, a simplified view.

The autonomic nervous system stress response acts within seconds
The amygdala signals to the hypothalamus - the brain's thermostat and major interface to the lower 48 states of the body. It is not only triggered by external danger, but also by inner danger - low blood pressure, low sugar, hypoxia, inflammation and other bodily parameters. The hypothalamus activates both a fast and a slow stress response. The fast response (seconds) is by neurons and the slow one (minutes to hours) is by a hormone cascade.

The fast stress response is carried out by the **sympathetic nervous system**, part of the autonomic nervous system, which controls involuntary bodily functions (Fig 10.16). It plays a key role in the "fight or flight" response, preparing the body for emergency situations. When activated, it increases heart rate, dilates pupils, expands airways in the lungs, and redirects blood flow to muscles, all of which help the body respond quickly to threats. At the same time, it slows down non-essential functions like digestion.

The sympathetic system causes the adrenal medulla to secrete adrenaline, and the neurons secrete noradrenaline- two hormones that prepare the body to respond to immediate threats. They rapidly increase heart rate, blood pressure, and energy availability, and focus attention.

I like to think about this as an unavoidable pulse of about 60 sec of sympathetic stress activation when we have an acute stress trigger, potentially followed by relaxation. If we are mindful we can sometimes let this pulse pass, and avoid feeding it with thoughts that incite the flames.

This system is the Yin and works in conjunction with the Yang- the **parasympathetic nervous syste**m, which calms the body and restores balance once the threat has passed.
The parasympathetic nervous system is responsible for the "rest and digest" response. It counteracts the effects of the sympathetic nervous system by slowing the heart rate, constricting the pupils, and stimulating digestion and energy conservation. It helps the body relax, recover, and maintain routine functions.

When we take a nice deep sigh of relief we activate the relaxing parasympathetic nervous system. So let’s take a nice deep sigh of relief:)

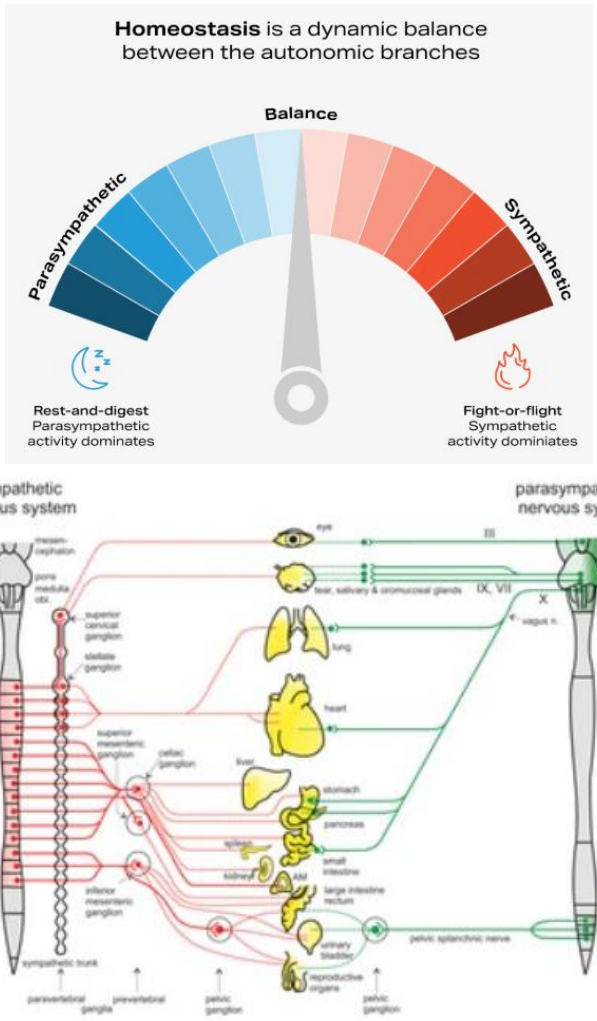


Fig 10.16 the autonomous nervous system has a fight or flight sympathetic arm and a rest and digest parasympathetic arm. They emerge from the spine to activate or relax many organs including the heart, gut and lungs.

The stress hormone cortisol peaks within 20 minutes and readies the body for further stress
The slower arm of the stress response is generated by a hormone cascade called the HPA axis that ends with the hormone cortisol. It is a trip of three steps. The hypothalamus secretes hormone 1 (CRH) that activates the pituitary to secrete hormone 2 (ACTH) along with the natural painkiller and euphoric beta-endorphin, part of the wonderful feeling called "runners high". Hormone 2 stimulates the adrenal gland to make the final hormone 3 - cortisol.

Cortisol regulates important functions that allow the body to manage stress. During acute (brief) stress, cortisol increases glucose availability by promoting the breakdown of fats and proteins, which provides energy for the fight or flight response. It also suppresses non-essential functions like digestion and immune responses to conserve energy for immediate action.

Additionally, cortisol helps control blood pressure by regulating salt and water balance, and it plays a role in enhancing mood and memory.

Cortisol has a circadian rhythm- we get a morning pulse that helps us to have the energy to wake up (for some of us this takes longer than others, author included). It is at its lowest at night.

This axis is helpful for acute stress over hours. But chronic high levels of cortisol over months— as in prolonged psychological stress— have negative effects, including weakened immune function, high blood pressure, and increased risk for anxiety and depression.

Chronic stress shortens lifespan

This system evolved in animals that needed to run from predators and other acute stressors. It's great for us when we need to run to catch a bus or a flight.

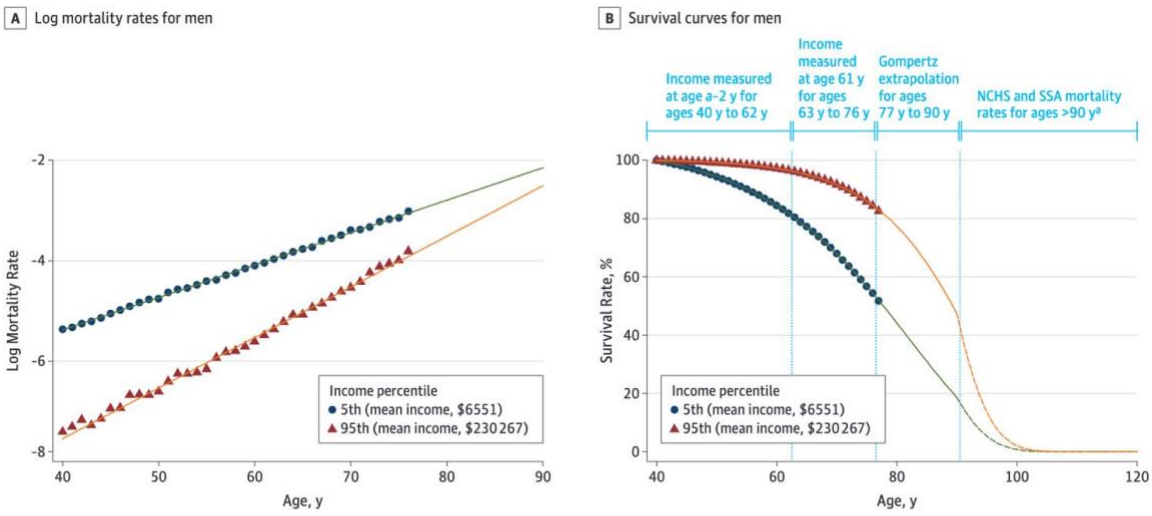
But animals did not have a cerebral cortex, a brain region that can worry about people and things that are not here and now. Humans do, and that is why we can have chronic stress for weeks, months, years, a lifetime. This is reflected in Sapolsky's book title “why zebras don’t get ulcers”.

Here I don't mean stress like an exam period, since we chose to go to university. I mean stress that we didn't choose and we can't escape. For example, people in low socioeconomic status, who have to worry about violence where they live, or are in jobs where they have no control, or need to care for a disabled parent or child with no help, can have chronic stress.

A striking study of stress and social rank showed that Cortisol is higher the lower the rank in the British civil service (the Whitehall study). Death and disease rise in lockstep, despite equal access to healthcare.

That is why **a decade of life often separates the lowest and highest 5% of socioeconomic status ,** defined by income or education (Fig 10.17). The hazard curves show that high income populations have lower hazard, with a low initial intercept but a higher slope. In the houses-and-trucks model this suggests that high income comes with higher threshold Xc- that is, more robustness to a given level of damage x (another possibility is lower noise epsilon). Perhaps the ravages of chronic stress reduce the body's ability to cope with age-related damage.

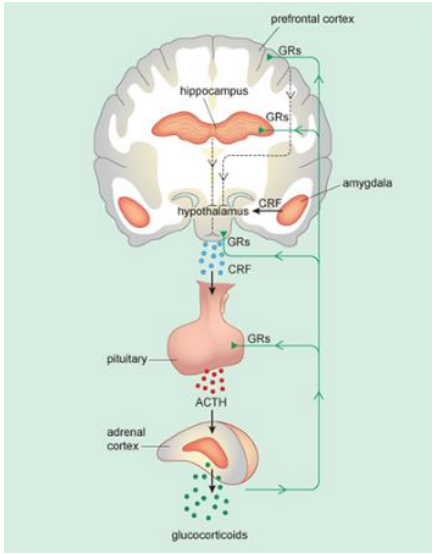
There are differences between countries, but lower socioeconomic status always goes with shorter median lifespan and poorer health. In animal studies, those low in social rank also experience higher cortisol and worse health.



For panels A and B, the data for the scatter points were derived from cross-sectional mortality rates by age using income 2 years prior for men aged 40 to 62 years and cohort mortality rates by year using income observed at age 61 years for men aged 63 to 76 years. Empirical mortality rates were observed until the age of 76 years; therefore, empirical survival rates are observed until the age of 77 years. Solid lines show Gompertz extrapolations through the age of 90 years. In panel B, uniform mortality rates from the National Center for Health Statistics (NCHS) and the Social Security Administration (SSA) were used beyond the age of 90 years. Analogous results for women appear in eFigure 4 in the Supplement.

[a] The mortality rates were constant across income groups.

Fig 10.17 The lowest 5% of people by income die about a decade earlier than the top 5% on average, data for the US.



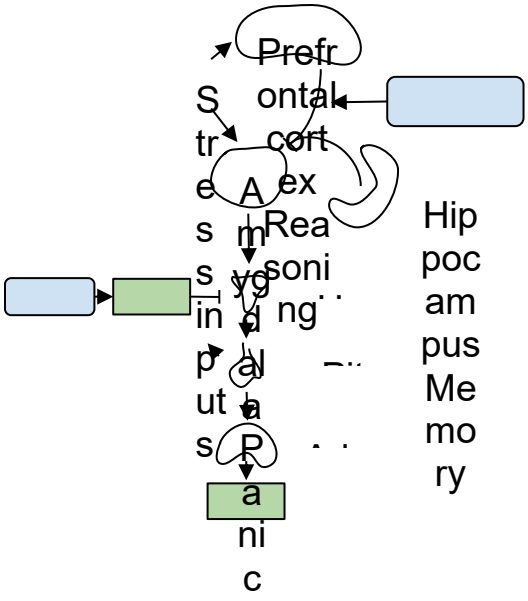


Fig 10.18 simplified view of the brain regions and HPA axis involved in chronic stress.

Chronic stress and elevated cortisol cause diseases

Chronic high cortisol levels caused by prolonged stress can have significant health consequences (Fig 10.19).

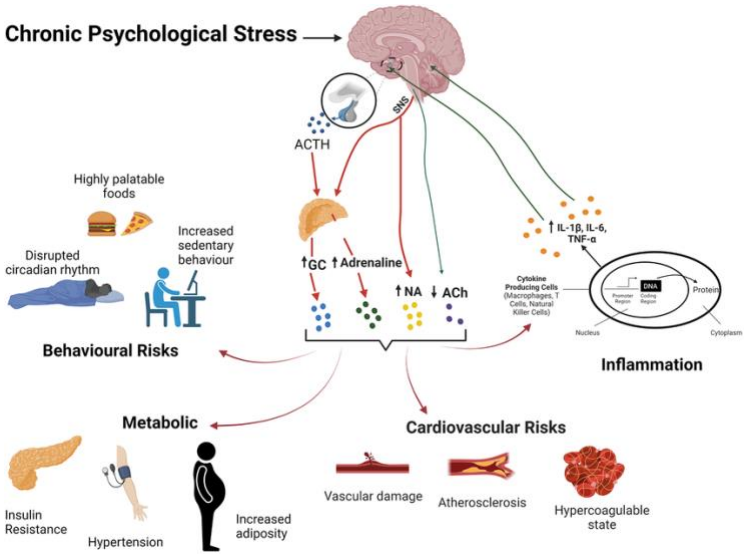


Fig 10.19 Chronic stress and elevated cortisol have a range of destructive effects.

Elevated cortisol promotes visceral fat, causing insulin resistance that drives diabetes. It increases blood lipids and blood pressure, damaging blood vessels - driving cardiovascular diseases.

Cortisol is programmed to delay “non essential functions” like digestion and reproduction, and thus chronic elevated cortisol can disrupt these functions seriously.

Elevated cortisol also suppresses immune responses, making us vulnerable to infections. In a misguided attempt to energy it speeds bone and muscle breakdown, which are deadly at old age. As a wake up signal, elevated cortisol disrupts sleep. This contributes to major depression and anxiety. Half of major depression patients have elevated cortisol. Elevated cortisol causes memory problems by inhibiting hippocampus neuron growth.

On top of all this, it enhances hair loss and thinning skin. Are you convinced yet that chronic stress is bad?

Chronic stress can be managed by lifestyle habits like mindfulness, yoga, or therapy. Regular exercise, a balanced diet, and adequate sleep also reduce chronic stress. Being in nature, listening to music and reading a paper book in bed are favorites of mine.

Let’s take a nice deep sigh of relief.

As another stress reduction tip - stay hydrated. When stressed, drink 10 gulps of water. The physiological reason is that the thirst hormone AVP is a potent amplifier of the HPA axis stimulation. A possible evolutionary role for this is that AVP retains water and raises blood pressure, and is activated when we lose blood- so it makes sense as a stress amplifier.

Depression and high cortisol: More than 1 in 10 older people experience depression. The 3 main causes of depression in older people are poor physical health, social isolation and loss.

One vicious cycle in which chronic stress causes depression is by cortisol gradually degrading the hippocampus, a region that acts to calm the amygdala. This creates a toggle switch situation - low cortisol and high amygdala inhibition (normal mood - euthymic), or high cortisol and low amygdala inhibition. The latter is what happens in major depression in many of the patients.

We developed a mathematical model of depression based on this toggle switch to show how some people are susceptible, and go into depression after months of chronic stress, entering a self sustaining mode of high cortisol (Mizrachi 2023) (Fig 10.20).

A key aspect of this model is the fact that the adrenal gland mass grows over weeks when stress is high, since hormone 2 (ACTH) is its growth factor. People with chronic stress have enlarged adrenal glands. A given stress input now makes more cortisol, because the cortisol factory, the gland, is larger. This creates a “memory” of past stress. This situation makes exiting depression quite challenging . Treatment, such as therapy or ssri pills, needs at least a few weeks in order to help the adrenal mass return to baseline.

For more details on hormone circuits, see my Systems Medicine book, chapters 1-3, or my course ‘hormone circuits’ on my website.

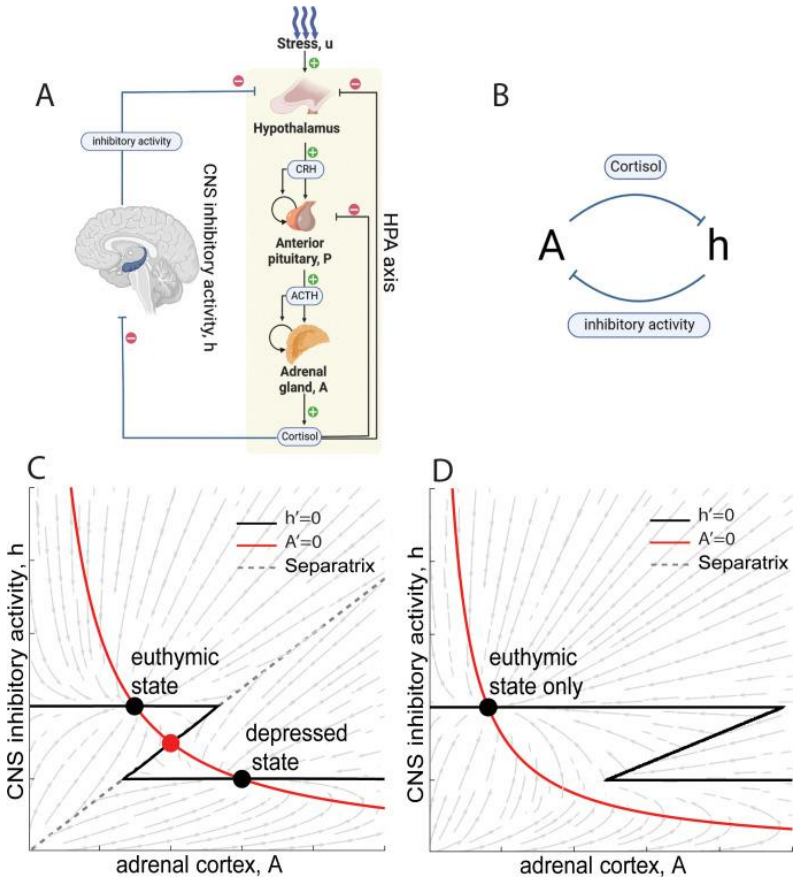


Fig 10.20 Major depression as a toggle switch where cortisol inhibits the brain regions that inhibit cortisol. From Mizrachi et al 2023. A) Schematic of HPA and CNS (central nervous system) interactions in the model B) The model can be summarized as a toggle switch between CNS inhibitory activity h and the adrenal mass, A. CNS inhibits the hypothalamic input and thus leads to a decrease in A. A releases cortisol, which inhibits CNS through the glucocorticoid receptor GR. C) Nullclines show three fixed points in susceptible individuals. Euthymic and depressed states are marked in black dots. D) In non-susceptible individuals there is only one euthymic fixed point. C and D used identical parameters except stress input u = 0.75 and u = 0.4 respectively. An analogous shift between 3 and 1 fixed points can occur when changing the CNS system parameters to represent genetic variants.

Social ties are vital for health and longevity

Friends reduce chronic stress. Social ties prevent loneliness, a major killer at old age. They help the brain produce hormones like oxytocin, which inhibits the HPA pathway and reduces cortisol.

A substantial body of evidence from diverse fields, including epidemiology, psychology, and neuroscience, demonstrates that strong social relationships enhance health and longevity.

One classic study by Holt-Lunstad et al (2010) analyzed 148 studies involving over 300,000 participants. Strong social relationships increased the likelihood of survival by 50%. This effect was comparable to the benefit of smoking cessation, physical activity, or maintaining a healthy weight. Social isolation and loneliness were strong predictors of early death.

Social ties reverse the litany of bad things we mentioned for cortisol- they improve resistance to infections, and reduce cardiovascular disease, cognitive decline, depression and anxiety.

The survival curve shapes of cohorts with high and low social ties suggest that this is a threshold Xc effect.

Prioritizing and maintaining strong social ties is as critical to health as traditional lifestyle factors like exercise, diet, and avoiding smoking.

Oxytocin, often called the "love hormone," reduces stress

One mechanism of the stress-lowering effects of friends involves the hormone Oxytocin. This hormone modulates the physiological and psychological stress response. It is secreted by hypothalamic neurons during childbirth and breastfeeding, in social interactions, and in response to touch.

Oxytocin reduces cortisol levels by inhibiting the two upstream hormones in the HPA axis. In parallel it enhances relaxation by activating the parasympathetic (rest and digest) nervous system. Oxytocin also directly lowers anxiety by dampening the amygdala, making stressful situations feel less overwhelming. This enhances the brain's ability to regulate emotions, contributing to a sense of calm and emotional stability.

Oxytocin also directs positive behavior. It Strengthens Social Support and Connection, promotes trust, empathy, and social bonding, which can help individuals seek and receive social support during stressful times. Particularly in females, oxytocin supports the "tend-and-befriend" stress response, where individuals are more likely to nurture and seek social alliances rather than respond with fight-or-flight.

Positive social interactions, such as hugging, physical touch, or talking with loved ones, increase oxytocin levels. These interactions reduce stress and promote feelings of safety and comfort.

Meaning and control are important for aging well:

A famous study conducted by Ellen Langer and Judith Rodin in 1976 explored how having a sense of control impacts the well-being of elderly residents in a nursing home.

Residents were divided into two groups, one given a plant to care for, and the other given a plant that the staff took care of. The group given responsibility for the plant showed significant improvements in mood, alertness, activity levels, and overall health. They felt more engaged and had a stronger sense of purpose. Eighteen months later, half as many people died in the plant caring group than in the control group in which nurses cared for the plant, 15% compared to 30%, suggesting that psychological agency has a direct impact on physiological survival.

Many other studies show the importance of autonomy, purpose, and engagement in improving quality of life, particularly for the elderly.

Research suggests that losing control or autonomy can negatively impact health and even increase mortality, though it's often indirect and context-dependent. Feelings of helplessness, depression, and reduced purpose in life are all associated with higher mortality risks.

losing control or autonomy—whether through relocation, job stress, or other life changes—can negatively impact health and increase mortality. These findings emphasize the importance of maintaining a sense of purpose and agency for long-term well-being.

There is even evidence that optimism enhances long life. Positivity in young nuns predicts their longevity 70 years later (Fig 10.21)

A good research program would be to isolate the factors, perhaps circulating hormones, that drive longevity in elders with a strong sense of purpose as opposed to the rudderless.

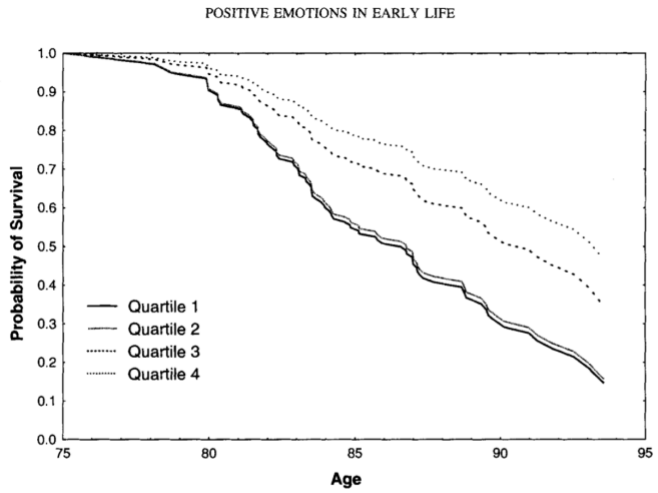


Figure 1. Quartile rankings of the number of positive emotion sentences in autobiographies written in early life and the probability of survival in late life for 180 participants in the Nun Study. (Note that the survival curves for Quartiles 1 and 2 are virtually overlaid on each other.)

Fig 10.21 Nuns with positive emotions in their autobiography written in their 20s have improved survival into their 90s. Note that nuns are relatively homogenous in terms of healthy lifestyle, daily schedule, social support, medical care and spiritual occupation. From:DOi): 10.1037//0022-3514.80.5.804.

Part 4 Wisdom

The wise brain- cognition that improves with old age

Many aspects of cognition get worse with age - such as processing speed and memory. However, there are compensations. Certain aspects of cognition improve with healthy aging - called wise cognition.

For example, fMRI studies show that the connections between the prefrontal cortex and amygdala strengthen with age- and older adults can indeed regulate emotions better. Other studies measure brain activity in tasks that require value based decision making, perspective, empathy, tolerance to ambiguity and so on.

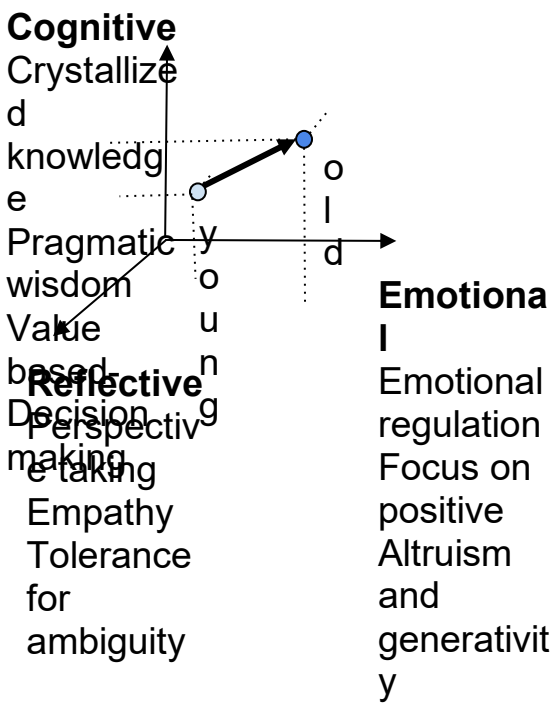


Fig 10.22 Ardelt's three dimensional wisdom model, wise cognition is made of multiple aspects that get better with age on average.

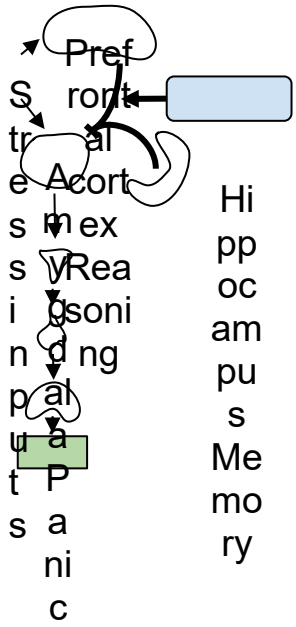


Fig 10.23 The ability to regulate emotions increases with age, in line with fMRI studies that image brain activity and show stronger connections between inhibitory regions and the amygdala on average.

Research has converged on dimensions of wise cognition that tend to improve or remain stable with age. This does not mean that there are no foolish elders. These studies compare *groups* of young and old adults, and they measure the difference in the averages between the groups. Individuals can vary

greatly in temperament and in the life history they experienced. In some senses, the temperament of an old individual is like when they were young, but more so.

1. Emotional Regulation

Older adults as a group are better at managing emotions and maintaining emotional stability. They focus more on positive experiences and emotions, a phenomenon called the positivity bias. Improved emotional regulation is linked to increased life experience and the ability to prioritize meaningful relationships and goals.

2. Perspective-Taking and Empathy

Older adults are better at considering multiple viewpoints and balancing self-interest with the needs of others. This ability is supported by life experience, which helps individuals understand complex social situations.

3. Decision-Making

Older adults excel in value-based decision-making, particularly in scenarios requiring long-term thinking or moral judgment. They tend to prioritize decisions that enhance well-being, relationships, and emotional satisfaction. Their ability to draw on accumulated knowledge and experience enhances decision-making in areas like finance, relationships, and health.

4. Crystallized Intelligence

Crystallized intelligence, which includes knowledge accumulated over a lifetime, remains stable or even improves with age. This form of intelligence supports wise reasoning, problem-solving, and decision-making in familiar contexts.

5. Pragmatic Wisdom

Older adults often develop pragmatic wisdom, the ability to apply knowledge and experience to real-world problems. This includes recognizing the uncertainty of life, accepting diverse perspectives, and focusing on long-term outcomes.

6. Reflective Thinking

Aging enhances the ability to think reflectively and evaluate situations from a broader perspective. Older adults are more likely to consider past experiences, integrate lessons learned, and think holistically about challenges.

7. Altruism and Generativity

Many older adults experience a shift toward generativity, or the desire to give back to future generations. This can manifest as mentoring, volunteering, or sharing life lessons, contributing to a sense of purpose.

8. Tolerance for Ambiguity

With age, people often develop a greater tolerance for uncertainty and complexity. They are better equipped to navigate life’s ambiguities without becoming overwhelmed, a hallmark of wise reasoning.

I like the work of psychologist Erik Erikson (1950), who viewed human development as a sequence of stages, each defined by a conflict that must be resolved to shape a healthy identity. From the foundational "Trust vs. Mistrust" of infancy to the "Generativity" of middle age, every phase builds upon the resolutions of the past. In the final chapter of life, typically beginning after age 65, we encounter the

eighth and ultimate stage: Integrity vs. Despair. "*a retrospective accounting of one's life to date; how much one embraces life as having been well lived, as opposed to regretting missed opportunities,"* Unlike the earlier years focused on accumulation and action, this stage demands a shift toward reflection. The primary task becomes a "life review"—an attempt to find coherence in the timeline of one's existence. Integrity is the acceptance of one's life cycle as something that had to be, a state of wholeness, a feeling of connection to a chain of generations, where the past is accepted without bitterness. The alternative is Despair, the haunting sense that time is now too short to attempt another life or try alternative roads to meaning. Successfully resolving this tension yields wisdom —an informed concern with life itself, even in the face of death.

Why study aging? Should I spend my work life researching longevity and expanding the healthspan?

Why study aging? Is it a good use of my life? I think that research is like voting on what topic you think is fascinating and important. It's making a small contribution to a joint effort to make change and add understanding.

One reason for studying aging is the joy of figuring things out . Deciphering beautiful mechanisms and adding knowledge about something that touches us all. An intellectual adventure.

A second reason is to reduce human disability, dementia and loss - if we could slow Biological Aging and expand the healthspan we would delay hundreds of age related diseases in one fell swoop.

A third reason is economic - reducing age-related diseases will save medical costs, which are highest in the last years of life. These savings are huge, but even larger are the gains from the productivity of each extra year of health. The global dividends are in the tens of trillions per extra year of health. We can use these resources to address the challenges facing humanity.

And finally, I find it appealing to dream about unlocking the potential of wisdom cultivated over a healthier lifespan than ever experienced by humanity.

Some people react negatively to the idea of increasing lifespan because it might cause population growth - true but not a huge effect because the individuals are post reproductive. I find it revealing that no one would raise the same concern about curing cancer, for example, which will also increase the population.

The world population is predicted to plateau at about 11 billion in 2100, after all countries undergo the demographic transition in which women's education leads to reduced childbirth. At steady-state, increasing lifespan would not increase population size but instead raise the fraction of the population which are old.

Imagine a large proportion of wise people participating in civic life, informing decisions with empathy, experience and perspective. Of course not all will be wise, but research suggests that

the majority will be. These healthy active elders are essential to face the challenges ahead and to reach the full potential of being human.

To respect our elders, let's take a nice deep sigh of relief.

For a healthy and meaningful life, let's take one last deep sigh of relief together.

Exercises

1. Consider a population in a steady state where each birth is balanced by a death. At t=0 lifespan increases by 5 years. What will be the transient effect on population size? What will happen to population size at steady state?
2. Construct an SR type model for the Alzheimer mechanism described in this lecture. Suggest parameters that can capture the observed disease free survival curves for familial and Sporadic mutations.
3. Last call for coffee! write equations for the accumulation of adenosine during waking hours and its degradation during sleep. Let caffeine block the adenosine receptor. Write an equation for a sinusoidal wake signal sent by the circadian clock. Sleep occurs when the adenosine receptor signaling minus the wake signaling (by a different receptor) exceeds a threshold. Now write an equation for the amount of caffeine in the body given an input at a given time, and assume a degradation rate of caffeine is 3h in person A and 7h in person B. How late can they drink the coffee and still be asleep by 10:30pm?
4. Read one of the studies mentioned on the wise brain. Give strengths and weaknesses of the study.

The hpa axis and optimal stimulation are flow! Improv can train this! An unpredictable environment is strategic but in a safe playful space leads to flow. This means a book chapter on social including the content of the healthy old age

Function of the Locus Coeruleus (LC)

The locus coeruleus (LC) is a small nucleus in the pons of the brainstem, known for its role in producing norepinephrine (NE) and regulating various physiological and cognitive functions. It has widespread projections throughout the brain and spinal cord.

Key Functions of the Locus Coeruleus:

1. Arousal and Wakefulness

- The LC is the primary source of norepinephrine (NE) in the brain and plays a crucial role in maintaining alertness and attention.

- It helps regulate the sleep-wake cycle, with high activity during wakefulness and minimal activity during deep sleep.

2. Stress and Fight-or-Flight Response

- The LC is activated during stress, triggering the release of norepinephrine, which heightens alertness and prepares the body for action.

- It interacts with the hypothalamic-pituitary-adrenal (HPA) axis, amplifying the stress response.

3. Cognitive Functions (Attention and Memory)

- The LC modulates working memory, learning, and attention by regulating norepinephrine levels in the prefrontal cortex and hippocampus.

- It enhances signal-to-noise ratio in neural circuits, improving focus and cognitive performance.

4. Emotional Regulation and Mood

- Dysfunction of the LC is implicated in depression, anxiety, PTSD, and ADHD, due to its role in emotional processing and stress adaptation.

5. Neuroprotection and Plasticity

- The LC-NE system helps maintain neuronal health, promoting synaptic plasticity and neurotrophic factor release (e.g., BDNF).

- It modulates neuroinflammation, reducing excessive immune responses in the brain.

Aging and Degeneration of the Locus Coeruleus

The LC is one of the earliest brain regions to show age-related degeneration, and its decline is linked to cognitive impairment and neurodegenerative diseases.

1. Neuronal Loss and Degeneration

- The LC experiences progressive neuronal loss with aging, with studies estimating a 30-40% reduction in neurons by old age.

- Neurofibrillary tangles (NFTs) (tau protein accumulations) appear early in the LC, sometimes decades before symptoms of Alzheimer's disease (AD).

2. Reduced Norepinephrine Output

- Aging leads to a decline in norepinephrine production, which impacts cognitive functions such as attention, memory, and emotional regulation.

- Reduced NE also contributes to impaired synaptic plasticity, affecting learning and adaptability.

3. Increased Vulnerability to Neurodegeneration

- The LC is one of the first brain regions affected in neurodegenerative diseases:

- Alzheimer's Disease (AD) → Early tau pathology in the LC precedes cortical involvement.

- Parkinson's Disease (PD) → LC degeneration contributes to non-motor symptoms, such as depression and cognitive decline.

- Lewy Body Dementia (LBD) → LC damage correlates with cognitive impairment and autonomic dysfunction.

4. Impaired Stress Response

- As the LC degenerates, the body's ability to cope with stress declines, leading to increased vulnerability to anxiety and depression in aging.

- Chronic stress and high glucocorticoid (cortisol) levels further accelerate LC neuron loss.

5. Disrupted Sleep-Wake Regulation

- Aging-related LC dysfunction contributes to insomnia and sleep disturbances, due to reduced norepinephrine modulation of the circadian rhythm.

Can LC Degeneration Be Slowed?

There is ongoing research into ways to protect and enhance LC function in aging:

1. Exercise – Physical activity increases norepinephrine levels and promotes neuroprotection.

2. Cognitive Stimulation – Engaging in learning, problem-solving, and social interactions can help maintain LC activity.

3. Diet and Antioxidants – Anti-inflammatory diets rich in polyphenols (e.g., blueberries, green tea) may protect against LC neurodegeneration.

4. Stress Management – Meditation, mindfulness, and relaxation techniques may help preserve norepinephrine function.

5. Pharmacological Approaches – Some research explores norepinephrine-enhancing drugs (e.g.,

Appendix 1

Mechanisms by Which Aging Affects Circadian Rhythm

1. Degeneration of the Suprachiasmatic Nucleus (SCN)

The SCN, located in the hypothalamus, is the body's central circadian clock. It coordinates daily rhythms by receiving light input from the retina and synchronizing peripheral clocks in other tissues. Aging-related changes in the SCN include:

Neuron loss: Reduced number of SCN neurons impairs its ability to generate robust rhythms.

Weakened connectivity: Decline in synaptic connections between SCN neurons reduces its synchronization capacity.

Neurotransmitter changes: Altered levels of signaling molecules like vasoactive intestinal peptide (VIP) and gamma-aminobutyric acid (GABA) disrupt SCN signaling.

2. Reduced Sensitivity to Light Cues

The SCN relies on light signals from the retina to synchronize with the environment. Aging leads to:

Retinal degeneration: Loss of photoreceptors and melanopsin-containing retinal ganglion cells reduces light perception.

Weakened signaling: Reduced transmission of light signals to the SCN diminishes its ability to adjust to environmental light-dark cycles.

3. Changes in Melatonin Production

Melatonin, produced by the pineal gland, is a key hormone that regulates sleep-wake cycles. With aging:

Decreased melatonin levels: Reduced production leads to weaker signals for sleep initiation.

Altered timing: The timing of melatonin release (circadian phase) may shift, contributing to early sleep onset and early morning awakening (advanced sleep phase syndrome).

4. Weakened Peripheral Clocks

Peripheral clocks in tissues like the liver, muscles, and adipose tissue depend on signals from the SCN and other factors like feeding and activity. Aging causes:

Desynchronization: Weaker SCN signals fail to synchronize peripheral clocks effectively.

Metabolic changes: Altered nutrient signaling disrupts peripheral clock function, leading to circadian misalignment.

5. Altered Gene Expression

Aging changes the expression of core clock genes (e.g., CLOCK, BMAL1, PER, CRY) that drive circadian rhythms. Specific changes include:

Reduced amplitude: Flatter oscillations in clock gene expression weaken circadian rhythms.

Phase shifts: Changes in the timing of clock gene expression can desynchronize rhythms.

6. Inflammation and Oxidative Stress

Aging is associated with chronic low-grade inflammation ("inflammaging") and increased oxidative stress, which can impair circadian regulation. Effects on the SCN and peripheral clocks: Inflammatory cytokines and reactive oxygen species disrupt clock gene expression and SCN signaling.

7. Lifestyle and Behavioral Changes

Aging often brings lifestyle changes that can disrupt circadian rhythms, including:

Reduced physical activity.

Less exposure to natural light.

Irregular sleep-wake schedules.

These factors weaken external cues (zeitgebers) that help maintain circadian alignment.

Consequences of Circadian Rhythm Changes with Aging

1. Sleep-Wake Disturbances

Advanced sleep phase syndrome (earlier sleep and wake times).

Insomnia or fragmented sleep.

Reduced total sleep duration and quality.

2. Metabolic Dysregulation

Increased risk of obesity, diabetes, and cardiovascular disease due to circadian misalignment in metabolic tissues.

3. Cognitive Decline

Impaired memory and cognitive function due to disrupted SCN and altered sleep patterns.

4. Mood Disorders

Increased prevalence of depression and anxiety in older adults, partly linked to circadian dysregulation.

Potential Interventions to Support Circadian Rhythms in Aging

Light Therapy: Bright light exposure during the day to strengthen SCN signaling.

Melatonin Supplements: To improve sleep initiation and circadian alignment.

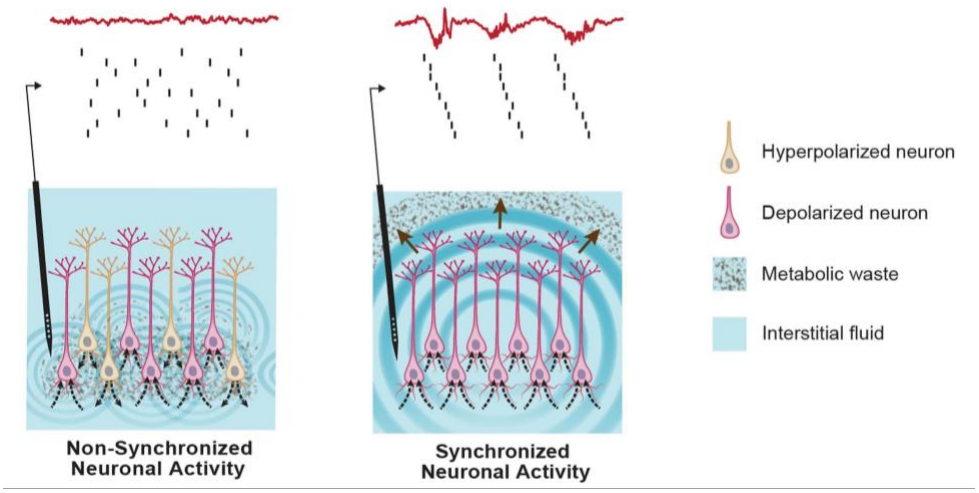
Regular Schedules: Consistent sleep, meal, and activity times to reinforce rhythms.

Physical Activity: Exercise to enhance peripheral clock synchronization.

Dietary Timing: Time-restricted eating to align feeding with circadian cycles.

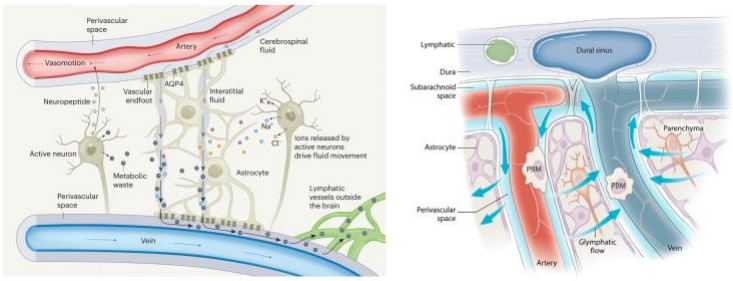
Appendix 2

From eric topol



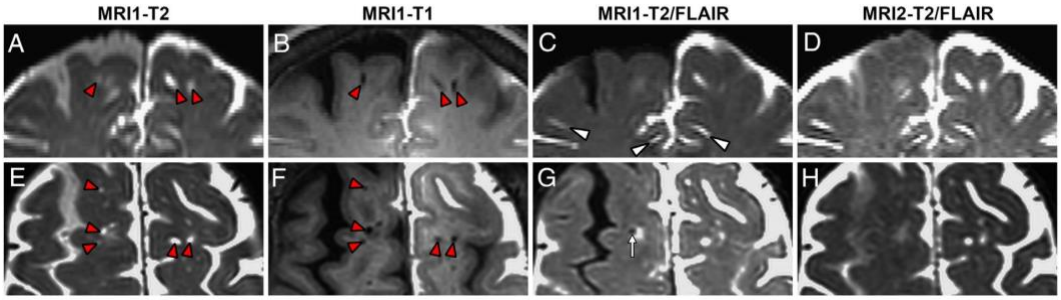
Updating The Glymphatic Mechanisms

The 2 schematics below provide an updated version of our understanding of how glymphatics work. At left, below, you can see key components (neurons, AQP4, neuropeptide, the perivascular space, also known as Virchow-Robin space) with waste material accumulating around the artery (at top), which is subject to vasomotion, and the clearance of the waste material alongside the veins to lymphatics outside the brain (→ meningeal lymphatic vessels and neck lymph nodes). At right, you see the same flow pattern from around arteries to veins to the dural sinus of cerebrospinal fluid. The importance of brain macrophages (parenchymal border macrophages, PBM) is highlighted.



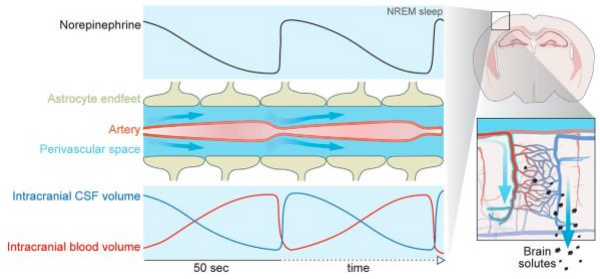
Demonstration in Humans

Until recently, all the work on glymphatics had been done in rodent experimental models. Late in 2024, the first demonstration of glymphatics in humans, among 5 patients undergoing brain surgery with MRI images at two time points, confirmed the presence of this network runing alongside blood vessels in the brain. (The red and white arrows indicate the new appearance of contrast in the 2 sets of paired images below).



The New Study of Glymphatics During Sleep

The pioneer of this field, Maiken Nedergaard, and colleagues, published a new report in *Cell* this week (main Figure schematic below) . This used "flow fiber photometry," a new technique—with surgically mounted electrodes with fiber optic lines for optogenetic tracing—that overrides the problem of previous studies that required anesthesia of mice, and is very different from natural sleep. During non-REM (rapid eye movement) sleep they observed oscillations in the blood brain volume that, with tracing the flow of cerebrospinal fluid, was mediated by norepinephrine levels, serving as a pump. They concluded "we have identified the most important driver of glymphatic flow in non-REM sleep."



Ambien (zolpidem) was assessed for its effect and it suppressed the norepinephrine effect and reduced glymphatic flow. As a cardiologist experienced with the side-effects of sleep disruption from beta blockers, I wouldn't be surprised that their inhibitory effect on norepinephrine is the basis for it.

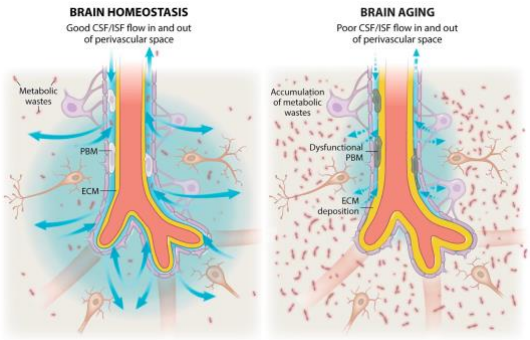
Sleep and Brainwashing

"It's [Sleep] like turning on the dishwasher before you go to bed and waking up with a clean brain" — Maiken Nedergaard

Sleep is the principal driver of glymphatic flow and waste clearance, occurring during the NREM phase of sleep (which includes deep sleep, slow-wave, known as stage N3). Indeed, the totality of evidence backs sleep's major function as waste clearance of the brain through glymphatics. Clearance of toxic proteins, like β-amyloid, are critical to brain health. Back in 2018, PET scanning was used to show that one night of sleep deprivation resulted in substantial increase in β-amyloid accumulation, in regions of the brain linked to Alzheimer's disease. On a chronic basis, several studies have shown that poor sleep is prospectively linked to the risk and progression of Alzheimer's disease. For example, in nearly 8,000 participants with 25-year follow-up, people aged less than 50 or 60 years with 6 hours of sleep or less had a >20% increased risk of developing late-onset dementia. It's also notable that clearance of toxic proteins interacts with our brain immune system (as I reviewed in a recent Ground Truths Guardians of the Brain), invoking another mechanism by which waste induces harm.

Brain Aging and Waste Clearance

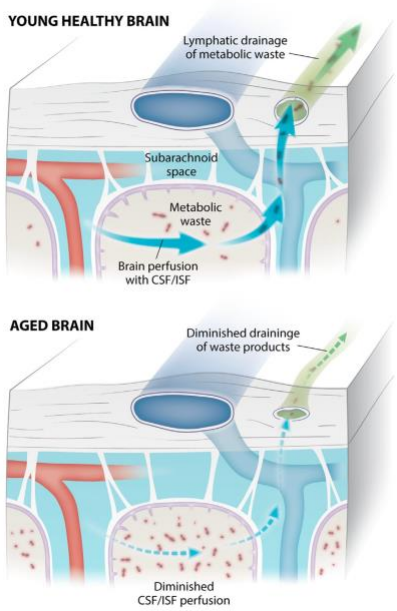
As we age, efficiency of the glymphatics and vascular dynamics decline (ISF-interstitial fluid) and sleep gets disrupted, there are more arousals, less synchronized neural activity, and less NREM stage 3 deep slow-wave sleep. This week there was a new and outstanding review by Jiang-Xie and colleagues from Washington University, St. Louis in the journal Neuron. As you can see from the schematic below, the aging brain accumulates metabolic waste, with deposition of extracellular matrix (ECM) and progressive dysfunction of the parenchymal border macrophages (PBMs). The all leads to buildup of unwanted, molecular waste in the brain. The accumulation of β-amyloid and tau leads to sleep disturbance and dysregulation or circadian rhythm. Reduced non-REM sleep has been linked to the risk of early Alzheimer's disease. This appears to be bidirectional, setting up a vicious loop, since decreased sleep leads to more toxic proteins, and the toxic proteins interfere with sleep.



Further, the exit route of meningeal lymphatics is diminished, as shown below, in the aged brain. This is accompanied by an untoward immune response, with expansion of CD4+ and CD8+ T cells, leading to chronic inflammation in the aged meninges which further impairs the exit route of waste from the brain. In experimental models VEGF-C (vascular endothelial growth

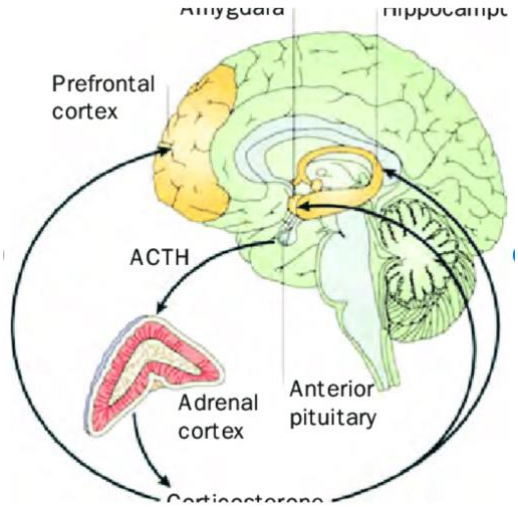
factor) has rejuvenated these meningeal vessels , which makes this a logical target for preventing age-related decline in waste clearance.

All of these features of impaired waste clearance of the aged brain are especially prominent in neurodegenerative diseases, such as Alzheimer's (AD) and Parkinson's (PD) diseases. Instead of the accumulation of β-amyloid and tau for AD, it is alpha-synuclein in PD.



In the last decade a whole body of knowledge has emerged about the brain's drainage system—glymphatics— and the accompanying key components of the system that efficiently rids us of unwanted molecular waste every day. The extensive glymphatic work reviewed here was predominantly accumulated in rodent models since such experiments would not be possible to obtain in people. However, we now have brain organ clocks, as previously reviewed, as a means to determine interventions that slow the pace of brain aging. Finding new ways to promote brainwashing as we age should be considered a high priority to help reduce the toll of neurodegenerative diseases in the future.

Lateral sleep rodents improves glymphatic clearance by about 20%

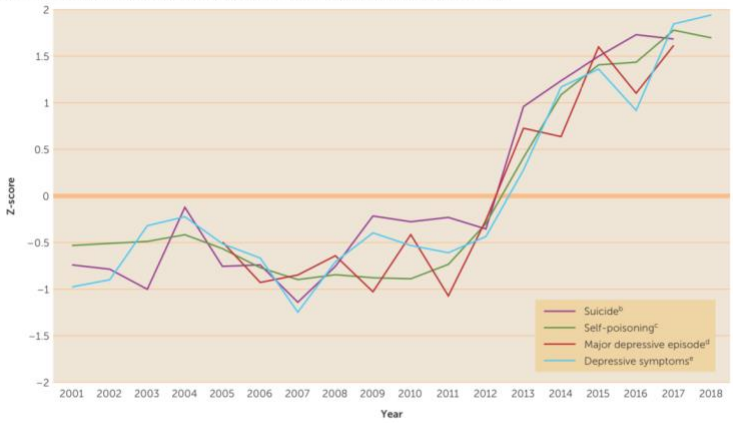


Alzheimer
Disease facts
Fast late incidence
App and presenilin scale
ApoE and trem2 pleiotropic
Model
Habib study and trajectories of aging

Longevity interventions
Compression of sickspan
SR Theory with steepness
Invertebrate data on sickspan
ITP study - candidate drugs
Combinations
Senolytics and senomorohic
Enhanced immune removal- cart and NK
Partial reprogramming
What happens in the fertilised egg?

Social and cognitive longevity
SES and education
Subjective well being
Loneliness and depression
Importance of social ties
The wise brain
Emotional awareness

FIGURE 1. Indicators of poor mental health among U.S. girls and young women, 2001–2018[a]



[a] Standard deviations are within means at the generational level, not at the individual level, and thus should not be used to calculate individual-level effect sizes.
[b] Source: Centers for Disease Control and Prevention. Suicide rates among 12- to 14-year-old girls.
[c] Source: Spiller et al. (14). Self-poisoning among 13- to 15-year-old girls.
[d] Source: Twenge et al. (11). Major depressive episode among 14- to 15-year-old girls.
[e] Sources: Keyes et al. (8) and Twenge et al. (9). Depressive symptoms among eighth-grade girls.

Supporting Research

Grossmann et al. (2010): Studies on wisdom-related reasoning suggest older adults are better at recognizing the limits of their knowledge, resolving conflicts, and promoting social harmony.

Carstensen's Socioemotional Selectivity Theory: Highlights how older adults focus on emotionally meaningful experiences, fostering wisdom in relationships and decision-making.

Ardelt's Three-Dimensional Wisdom Model: Emphasizes the cognitive, reflective, and affective components of wisdom, many of which are strengthened with age.

Several types of experiments and studies demonstrate that older adults can develop a "wiser brain" by showing improvements in emotional regulation, perspective-taking, and decision-making. Here are some key experimental designs and findings:

1. Studies on Emotional Regulation

Experiment: Older and younger adults are exposed to emotional stimuli (e.g., images, videos, or scenarios) while their brain activity is monitored using fMRI.

Findings: Older adults show greater activation in the prefrontal cortex (involved in regulation) and reduced activation in the amygdala (associated with emotional reactivity). This suggests they are better at managing emotional responses and focusing on positive experiences.

Example Study: Carstensen's research on the positivity effect shows that older adults prioritize positive over negative information, indicating emotional wisdom.

2. Social Conflict Resolution Tasks

Experiment: Participants of different ages are presented with real-life social dilemmas (e.g., resolving interpersonal conflicts) and asked to provide solutions.

Findings: Older adults demonstrate more wise reasoning by considering multiple perspectives, acknowledging uncertainty, and focusing on long-term outcomes. Younger participants tend to focus on immediate solutions.

Example Study: Grossmann et al. (2010) showed that older adults excel in tasks measuring wise reasoning, such as balancing self-interest with collective well-being.

3. Decision-Making Under Uncertainty

Experiment: Participants are asked to make decisions in complex, uncertain scenarios (e.g., financial investments or health-related choices) while tracking their thought processes.

Findings: Older adults often rely on crystallized intelligence (accumulated knowledge and experience) to make more balanced and value-based decisions. They may not process information as quickly as younger individuals but make more thoughtful, holistic choices.

Example Study: Studies on intertemporal choice show that older adults are more likely to prioritize long-term benefits over immediate rewards.

4. Perspective-Taking and Empathy Tasks

Experiment: Participants read stories or watch videos about people in challenging situations and are asked to interpret the characters' emotions or motives.

Findings: Older adults show greater empathic accuracy and are better at considering others' viewpoints. This is linked to increased activity in the medial prefrontal cortex, associated with social cognition.

Example Study: Research by Ardelt on the three-dimensional wisdom model (cognitive, reflective, and affective components) highlights older adults' ability to integrate life experiences into empathic understanding.

5. Brain Imaging Studies on Wisdom

Experiment: Using fMRI or EEG, researchers examine brain activity in older and younger adults during tasks requiring wise reasoning, emotional regulation, or problem-solving.

Findings: Older adults show stronger connectivity between the prefrontal cortex (executive function) and limbic system (emotions), suggesting they can better balance emotion and logic. This neural integration supports wisdom-related behaviors.

Example Study: Studies by Meeks and Jeste (2009) highlight the role of the prefrontal cortex and anterior cingulate cortex in wisdom-related brain functions.

6. Life Reflection and Storytelling Tasks

Experiment: Participants are asked to reflect on past experiences, particularly those involving moral dilemmas or personal growth, and analyze their lessons learned.

Findings: Older adults are more likely to express integrative thinking and acceptance of life's uncertainties, both key components of wisdom.

Example Study: Narrative analyses show that older adults emphasize themes of forgiveness, generativity, and the greater good.

7. Longitudinal Studies on Aging and Wisdom

Experiment: Tracking individuals over decades to measure changes in cognitive, emotional, and social skills.

Findings: While fluid intelligence declines with age, wisdom-related traits (e.g., emotional regulation, social reasoning) improve or remain stable, suggesting compensatory mechanisms in the brain.

Example Study: The Berlin Wisdom Paradigm assesses wisdom through open-ended questions, showing that wisdom-related performance peaks in late adulthood.

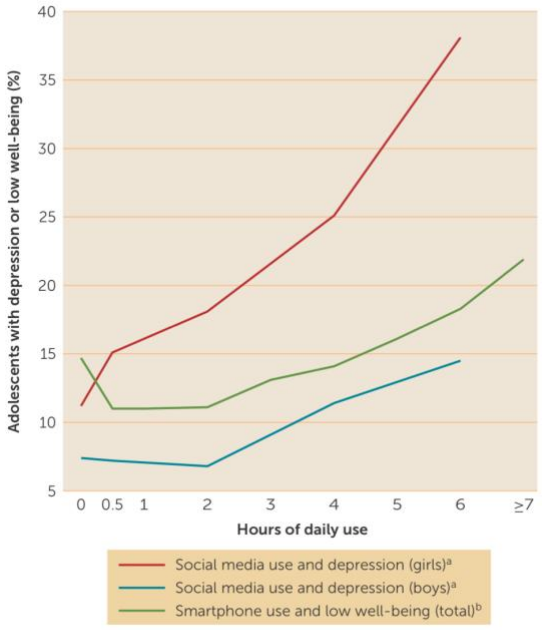
8. Intergenerational Collaboration Experiments

Experiment: Older and younger adults collaborate on problem-solving tasks or creative projects.

Findings: Older adults contribute insights based on experience and perspective-taking, while younger individuals provide novel ideas. This highlights the unique cognitive strengths of older adults in wisdom-related domains.

These experiments collectively show that aging can enhance certain cognitive and emotional abilities tied to wisdom, even as other cognitive functions (like processing speed) decline. This is supported by neuroplasticity, life experience, and emotional growth.

FIGURE 2. Proportion of adolescents with depression or low psychological well-being, by hours a day of social media or smartphone use



[a] Source: Kelly et al. (23).
[b] Source: Przybylski and Weinstein (25) and reanalyzed by Twenge and Campbell (28).