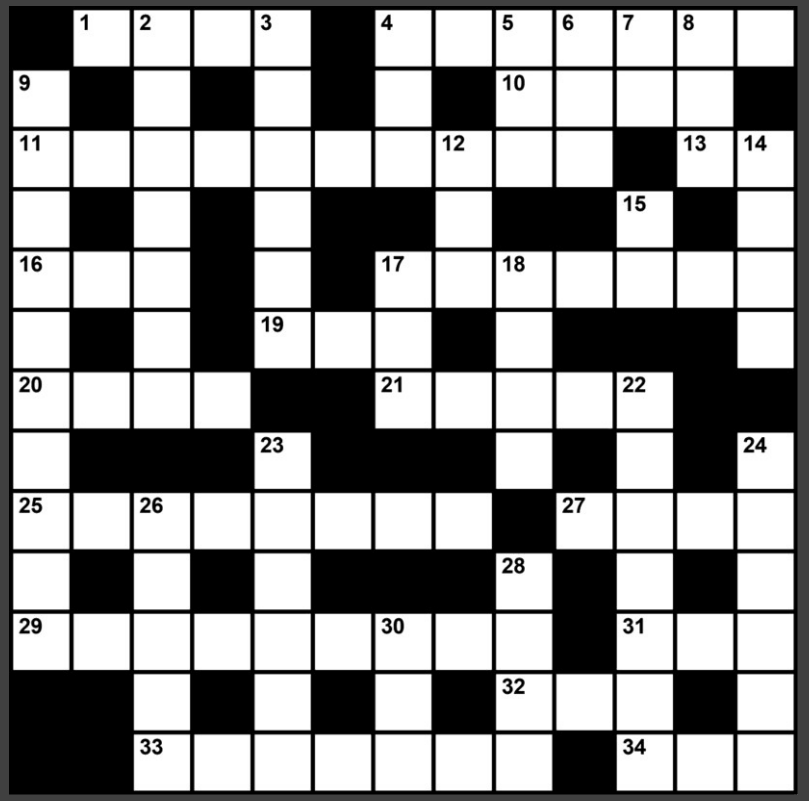


WHY DOING CROSSWORDS IS **NOT** HELPING YOU PREVENT ALZHEIMER'S DISEASE

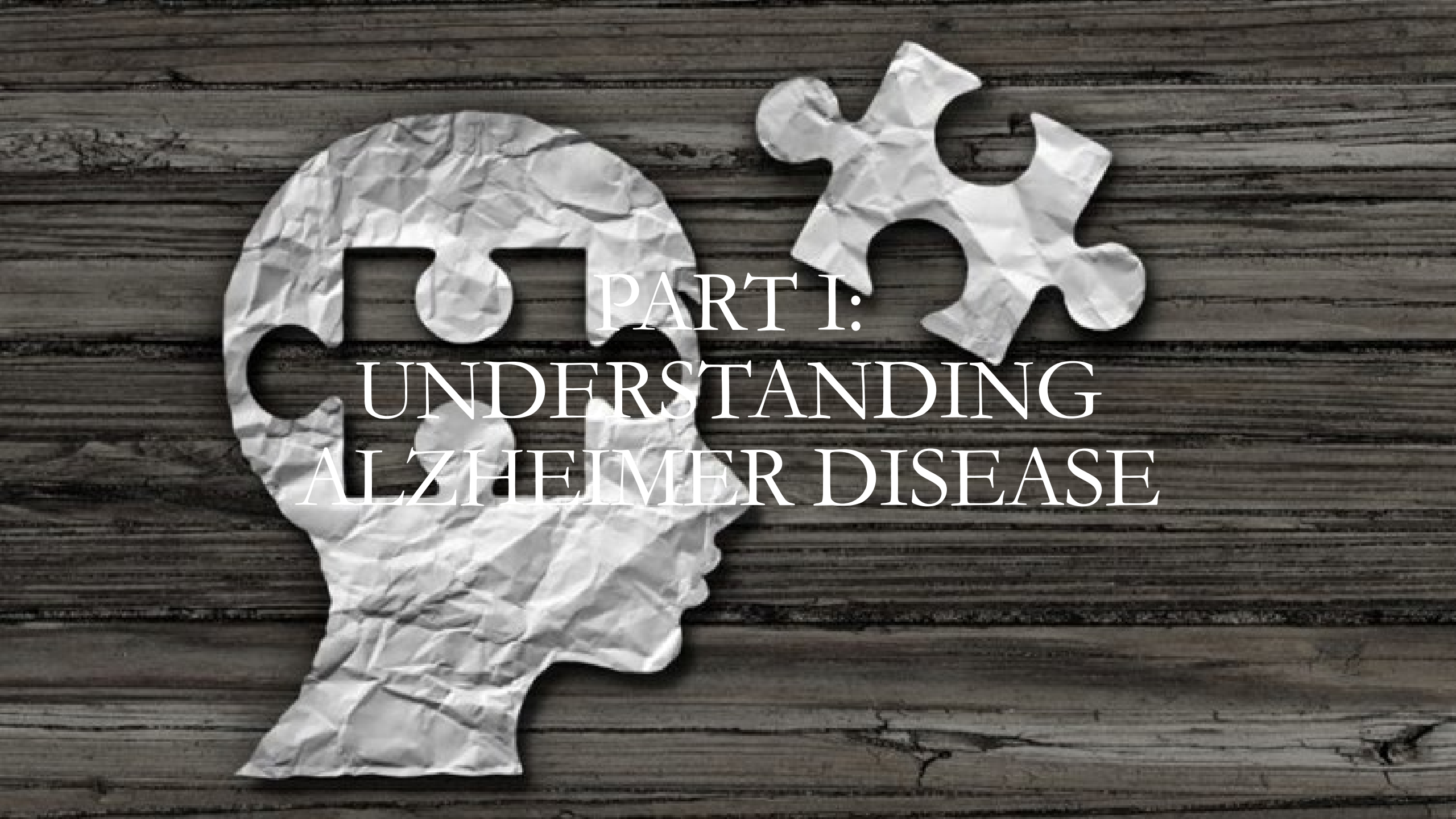
Ashley Thompson, PhD

Overview

<u>Part I: Understanding Alzheimer Disease</u>

- Normal aging VS dementia
- Alzheimer's disease
  - Intro, symptoms, progression and treatment
- What goes on in the brain in AD?
  - Pathology of the disease

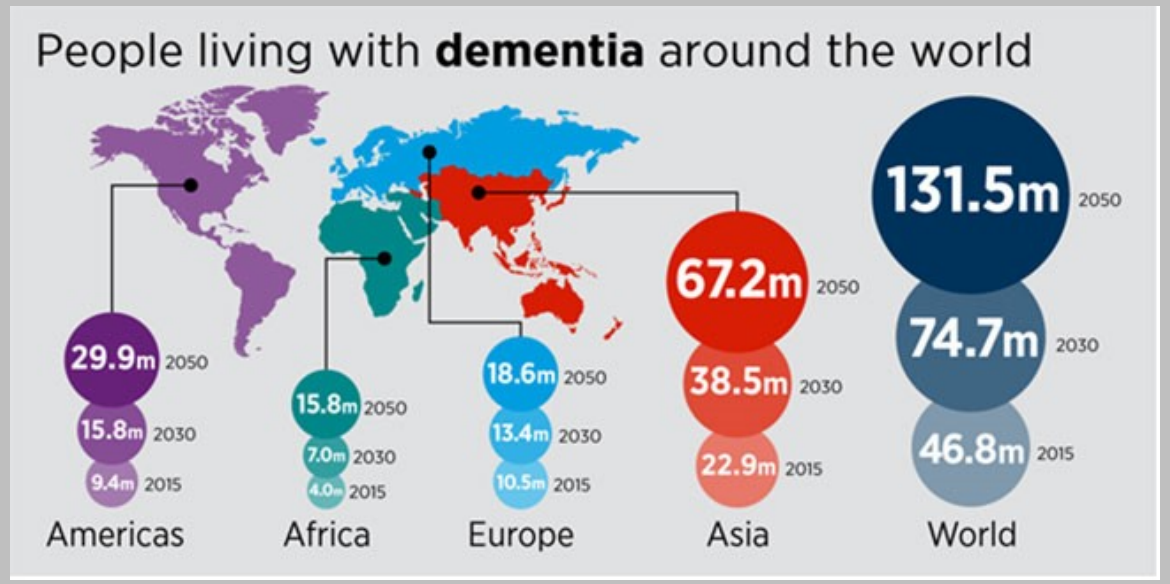
- **<u>Part II: Risks and Prevention: A Balancing Act</u>**
- Risk factors (cumulative, tipping the scale)
- Cognitive reserve
  - The nun study
- How to best protect your brain



PART I: UNDERSTANDING ALZHEIMER DISEASE

Dementia

- **Dementia** refers to a set of symptoms that are caused by disorders that affect the brain
- Symptoms may include memory loss, problems with thinking and problem-solving, and language problems
- Changes in mood or behaviour are also common
- Impairments in these processes are severe enough to affect daily life
- Dementia is progressive (symptoms worsen as more brain cells die)
- **Dementia is not a specific disease**; many diseases *cause* dementia (e.g. Alzheimer disease, Huntington's disease, head trauma, Parkinson's disease, etc)



Alzheimer's Society of Canada, 2017

Normal Aging VS Dementia

- Memory loss is associated with normal aging; however, these problems are caused by ***dysfunctional neurons*** rather than ***dying neurons***
  - This represents the main difference in neuronal pathology between normal aging and dementia
- While both normal aging and dementia target neurons in the hippocampus, different patterns of anatomical dysfunction are observed (different cell populations are affected; Small et al., 2011)
- Almost **40%** of people **over the age of 65** experience some form of memory loss – this is known as **'age-associated memory impairment'**, has no underlying medical cause, and is considered a <u>normal part of the aging process</u>

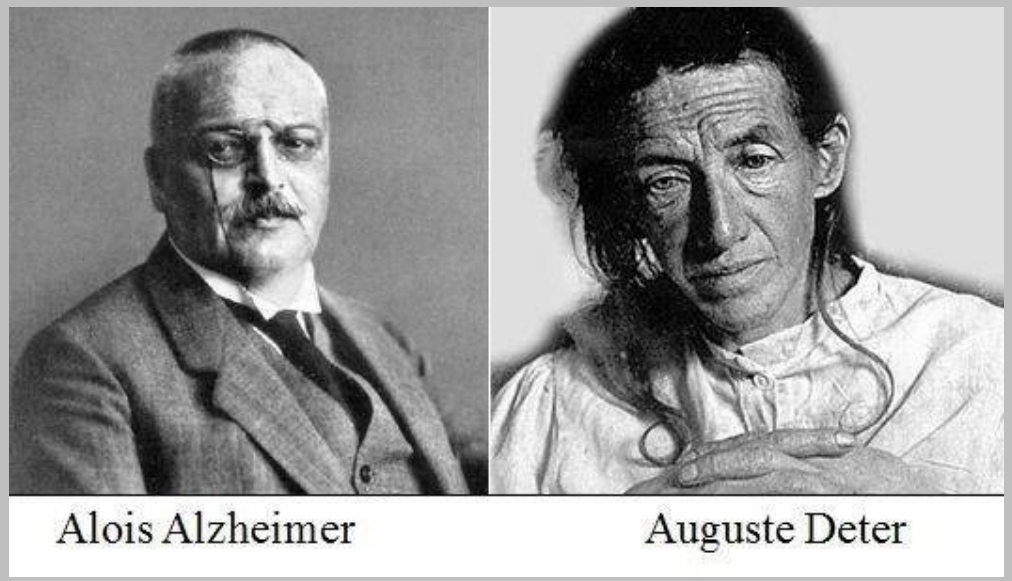
Normal Aging VS Dementia

- Age-associated memory impairment is not the same as Alzheimer disease and other forms of dementia
- Some ways to distinguish the two based on functional abilities

Normal Aging	Dementia
Forgetting details of a conversation or an event that took place last year	Failure to recall details of recent events or conversations
Forgetting names of acquaintances	Not recognizing or knowing good friends and family members
Occasionally having a difficult time finding words	Frequently pauses and word substitutions during a conversation
Individual worries about memory loss, but family members do not	Family worries about memory loss, but individual is not aware of any problems

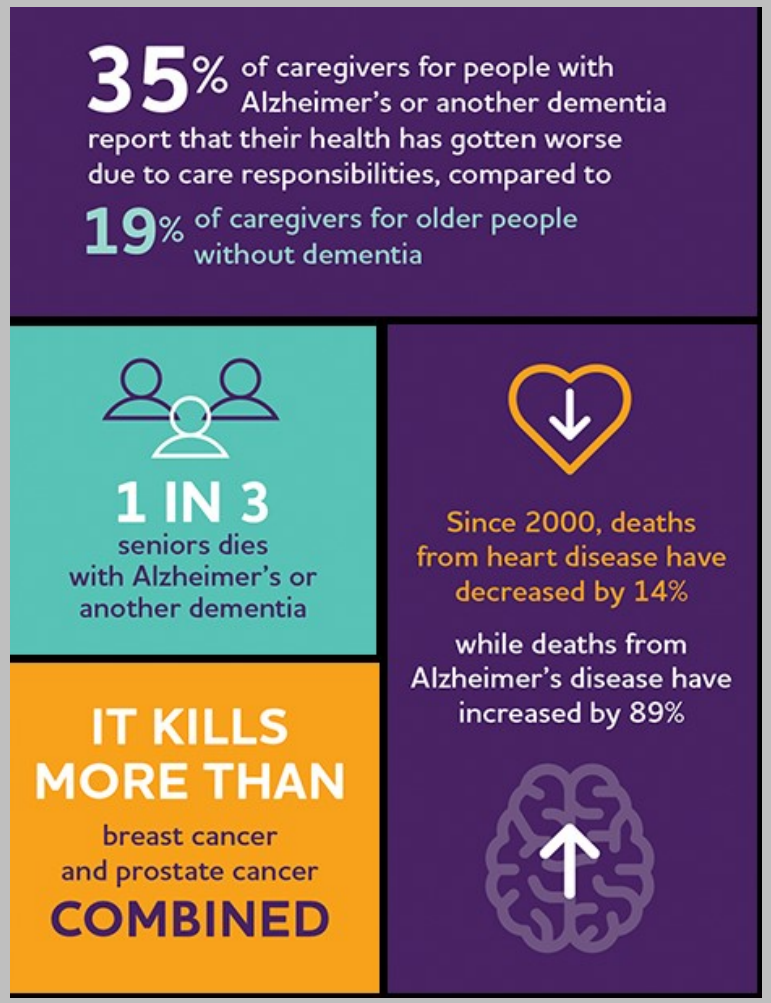
Alzheimer Disease

- First described by Dr. Alois Alzheimer in 1906
  - He followed a patient in an asylum with symptoms including **memory loss, language problems, and unpredictable behaviour**
  - After her death, Alzheimer noticed abnormal clumps and tangled fibers in her brain
  - By 1911, doctors were using Alzheimer's research to base diagnoses – but abnormal protein forming aggregates not identified until 1990s

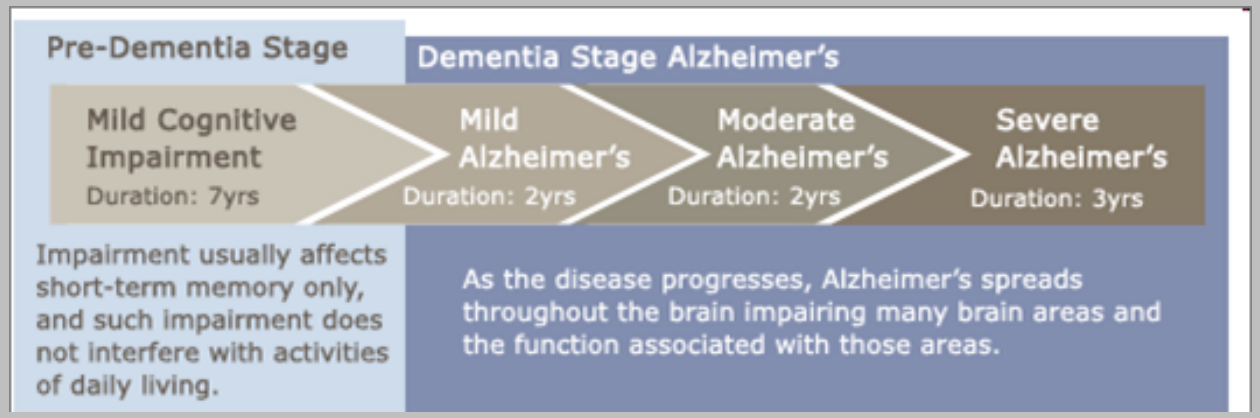


AD: The Stats

- AD is the leading cause of dementia
  - Accounts for 60-80% of cases
- It is a neurodegenerative disease, following a specific pattern of degeneration
- Globally, number of people suffering from dementia estimated around 25 million, and expected to double by 2040
- Of the top 10 leading causes of death in the US, AD is the **only disease** that cannot be prevented, slowed, or cured



AD: Symptoms



- **Mild cognitive impairment (MCI)**
- Refers to memory problems greater than expected for age, but no daily functional impairments observed
  - Older people with MCI at greater risk for developing AD, **but not all do**
- AD progresses in stages – mild, moderate and severe
  - Memory problems usually appear first, but symptoms vary between individuals
  - For many, non-memory aspect of cognition are affected first
    - E.g. word finding, vision/spatial issues, impaired reasoning or judgment

AD: Symptoms

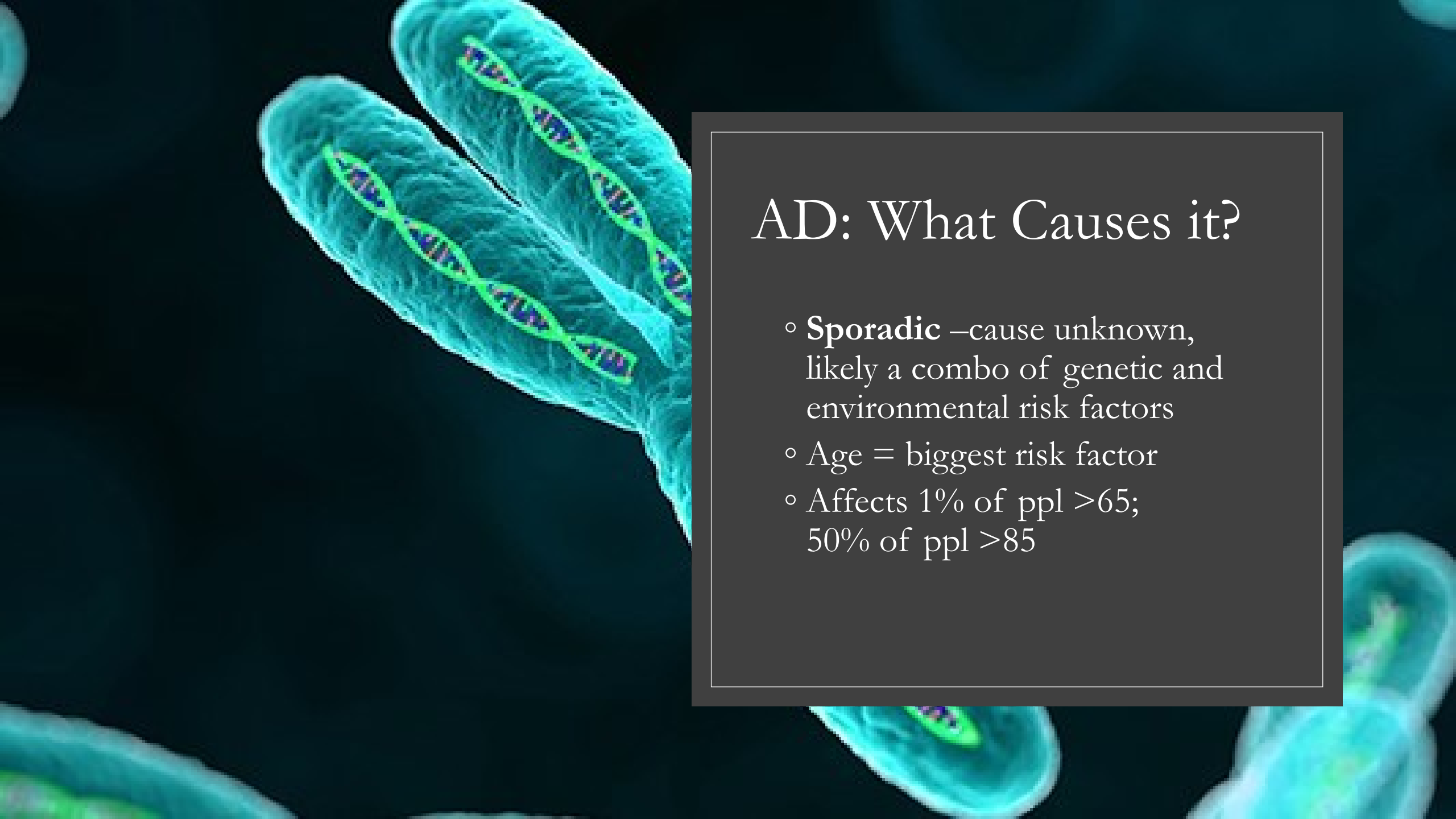
- **Mild AD**: Increasing memory loss, other cognitive difficulties
  - Wandering/getting lost, trouble handling money, repeating questions, taking longer to complete tasks, personality and behavioural changes
  - Apathy, depression
- **Moderate AD**: Involvement of language, reasoning, sensory processing, and conscious thought
  - Memory problems worsen, trouble recognizing friends and family
  - Unable to learn new things, difficulty with multi-step tasks (e.g. getting dressed), or coping with new situations
  - At this stage, people may have hallucinations, delusions and paranoia, and may behave impulsively
- **Severe AD**: Massive cell loss leads to dependence
  - Cannot communicate, bed ridden as body shuts down

AD: Symptoms

- Summary of symptoms clustered by category
  (all are progressive during course of disease)
  - **Cognitive and Functional abilities**
    - Changes in ability to understand, think, remember and communicate
  - **Emotions and Mood**
    - Increased apathy/depressive symptoms (e.g. anhedonia), decreased expression of emotions, withdrawal from social circles/family
  - **Behaviour**
    - Increase in 'out of character' behaviours (e.g. hiding possessions, physical outbursts, restlessness, repeating things)
  - **Physical Abilities**
    - Impairments in coordination and mobility influence individual's ability to perform daily tasks independently (e.g. eating, bathing, dressing)

AD: What Causes it?

- Most of the time, cause is not known (called sporadic or late onset, 90-95% of cases); sometimes, familial link (called early-onset, 5-10% of cases)
  - Late onset – diagnosis after 65
  - Early onset – diagnosis before 65
- **Familial** – some genes have been linked to AD
  - E.g. trisomy 21; Down syndrome

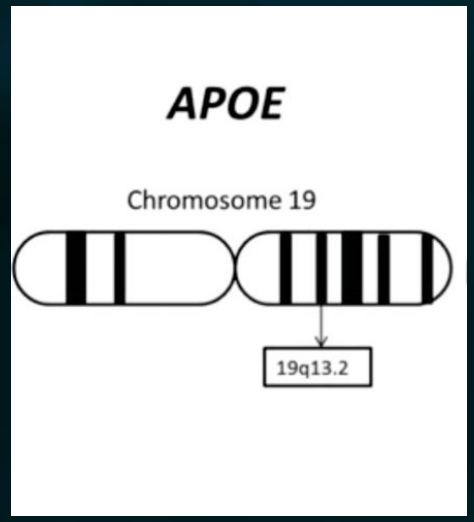


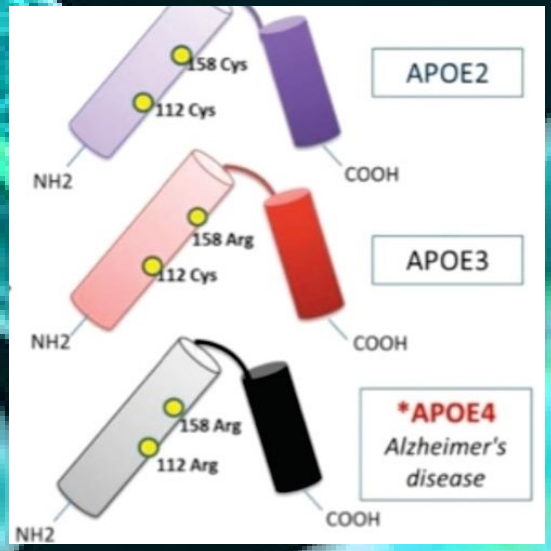
AD: What Causes it?

- **Sporadic** –cause unknown, likely a combo of genetic and environmental risk factors
- Age = biggest risk factor
- Affects 1% of ppl >65; 50% of ppl >85

AD: What Causes it?

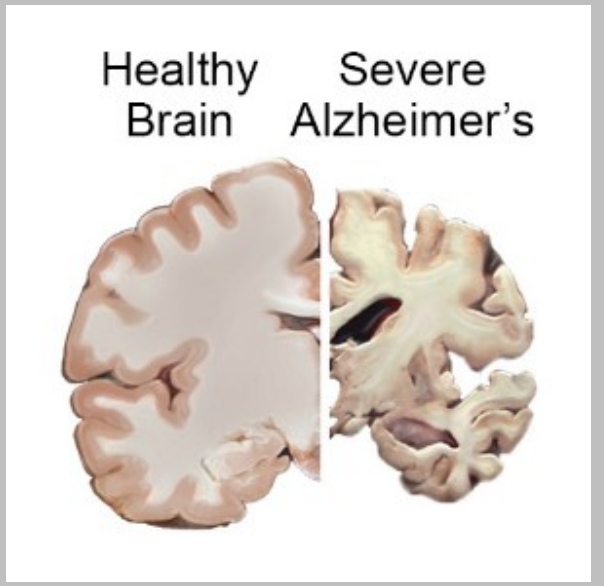
- Gene: There are 3 types of the apolipoprotein E (APOE) gene (e2, e3, and e4)
  - APOE is a protein that helps break down **amyloid-beta (Aβ)**, a major component of the **plaques** seen in AD
  - The e3 version is most common (>50% population has this version)
  - **e4 allele** seems to be **less effective** than **e2** version at breaking down **Aβ**
  - Inheriting 1 e4 allele ↑ risk of developing AD
  - Inheriting 2 e4 alleles ↑ risk even more

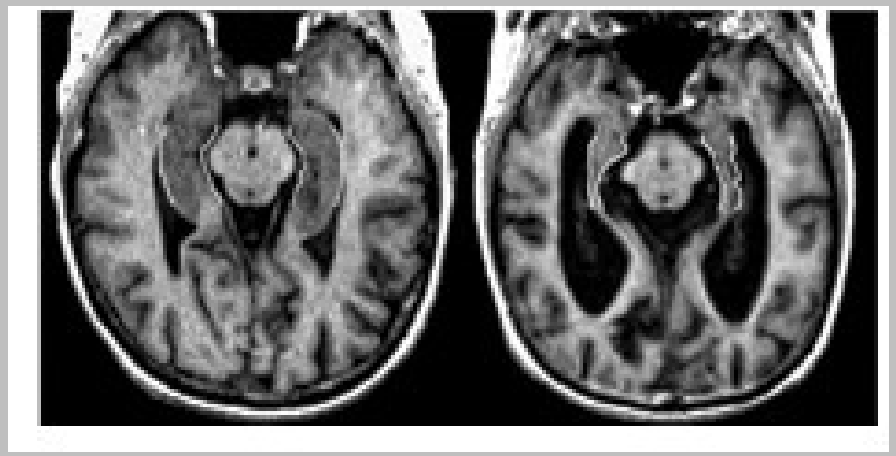




AD Pathology

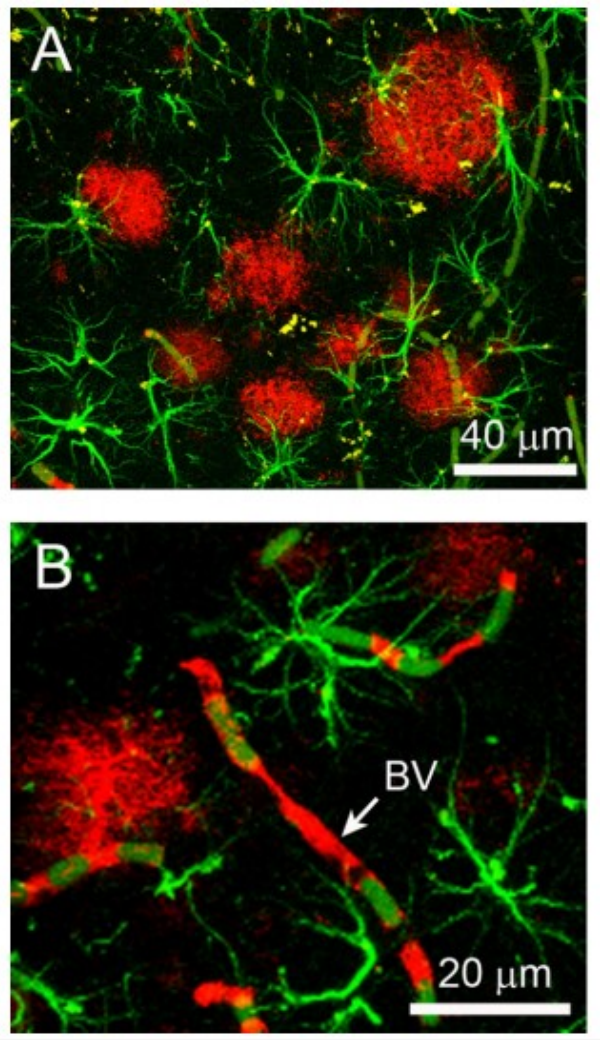
- AD can only be **definitively diagnosed** after death, when patterns of brain damage can be clinically assessed within the context of symptoms patient exhibited
- Neuronal death begins in structures important for **memory and emotion** (e.g. the **hippocampus**), and spreads to the **cortex** (outermost layers of brain) over time
- Brain atrophies (shrinks from cell death), and loss of tissue leads to narrower **gyri**, wider **sulci**, and **enlarged ventricles**





AD Pathology

- Two key pathological features of AD:
  - **Beta-amyloid plaques** (form outside cells)
  - **Neurofibrillary tangles** (form inside cells)
- Beta-amyloid plaques can elicit an immune response by glial cells, and can deposit near blood vessels) – weakens blood vessel wall and increases risk of hemorrhage (rupture of vessel wall)
- Tangles lead to dysfunctional axons, and cells initiate **apoptosis**

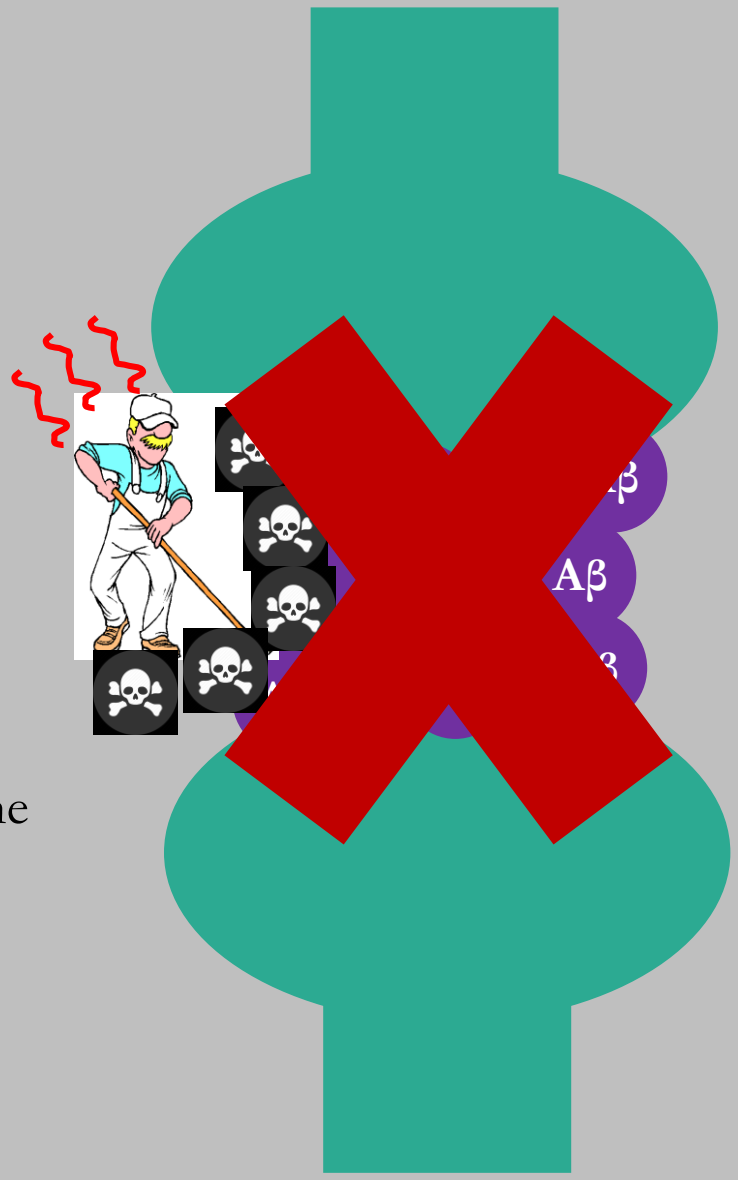


A: Astrogliosis in hippo neurons
B: Aβ deposits near blood vessels

(Verkhratsky et al., 2010)

AD Pathology

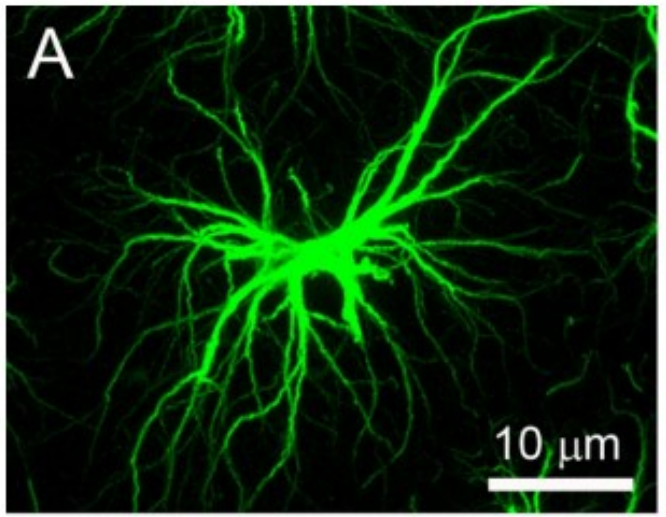
- **Importance of GLIAL CELLS**
- **Beta-amyloid (Aβ)** builds up in the synapse – the place two neurons communicate
- **Microglia** and **astrocytes** – two types of regulatory cells in the brain
  - Once thought to be 'supporting cells' only – we now know they play ACTIVE roles in the health and disease of brain cells.
  - Roles in communication, inflammation and disease, immune response
- **Microglia** normally clean up excess **Aβ** protein that builds up in the **synapse** ('debris clearing' aka janitorial role)
  - However, microglia are also *activated* by excessive plaques
  - They release pro-inflammatory cytokines – causing damage to nearby cells – can even remove synapses (via phagocytosis)



AD Pathology

- **Astrocytes**
- Also involved in janitorial tasks (e.g. clearing Aβ)
- **Important**: astrocytes and microglia talk to each other, which is a factor in how they respond to cellular stress
- Astrocytes become activated later in the disease and add to the inflammatory response
- **Activated (or reactive) astrocytes** have been observed in the brains of patients with AD (Perez-Nievas & Serrano-Pozo, 2018)
- Mouse study (image on the right) – shows loss of branching in astrocytes (B) compared to control animals (A) in the **hippocampus**

(Verkhratsky et al., 2010)



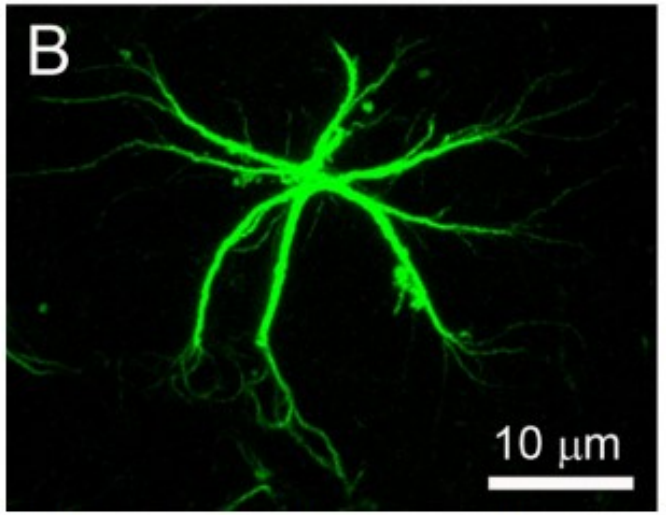


FIG. 2. Confocal micrographs of hippocampal astrocytes non-associated with Aβ plaques in transgenic mice model (3xTg-AD) of Alzheimer's disease. Note the evident astrocytic atrophy in the 3xTg-AD mice (B) when compared to the control animals (A).

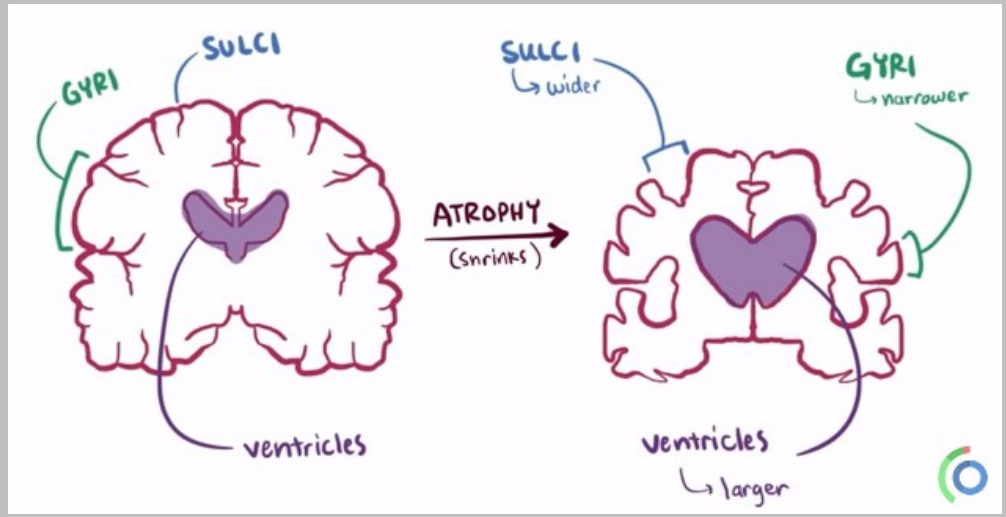
Treatment

- None of currently available pharmacological treatments slow or stop damage to neurons
- Six drugs for AD are FDA approved, and temporarily improve symptoms by increasing NTs in the brain - effectiveness of drugs varies person to person
- Between 2002-2012, 244 drugs for AD were tested in clinical trials
  - Only 1 successfully completed clinical trials and became FDA approved

www.alz.org

Treatment

- Developing effective treatments for AD is challenging
  for a number of reasons:
  - Cost of drug development
  - Time required to observe slowing/changing of disease course in response to treatment
  - Blood brain barrier – getting the drug to the brain



So…

- IS there any GOOD news?
- YES
- We will get to that after the break ☺

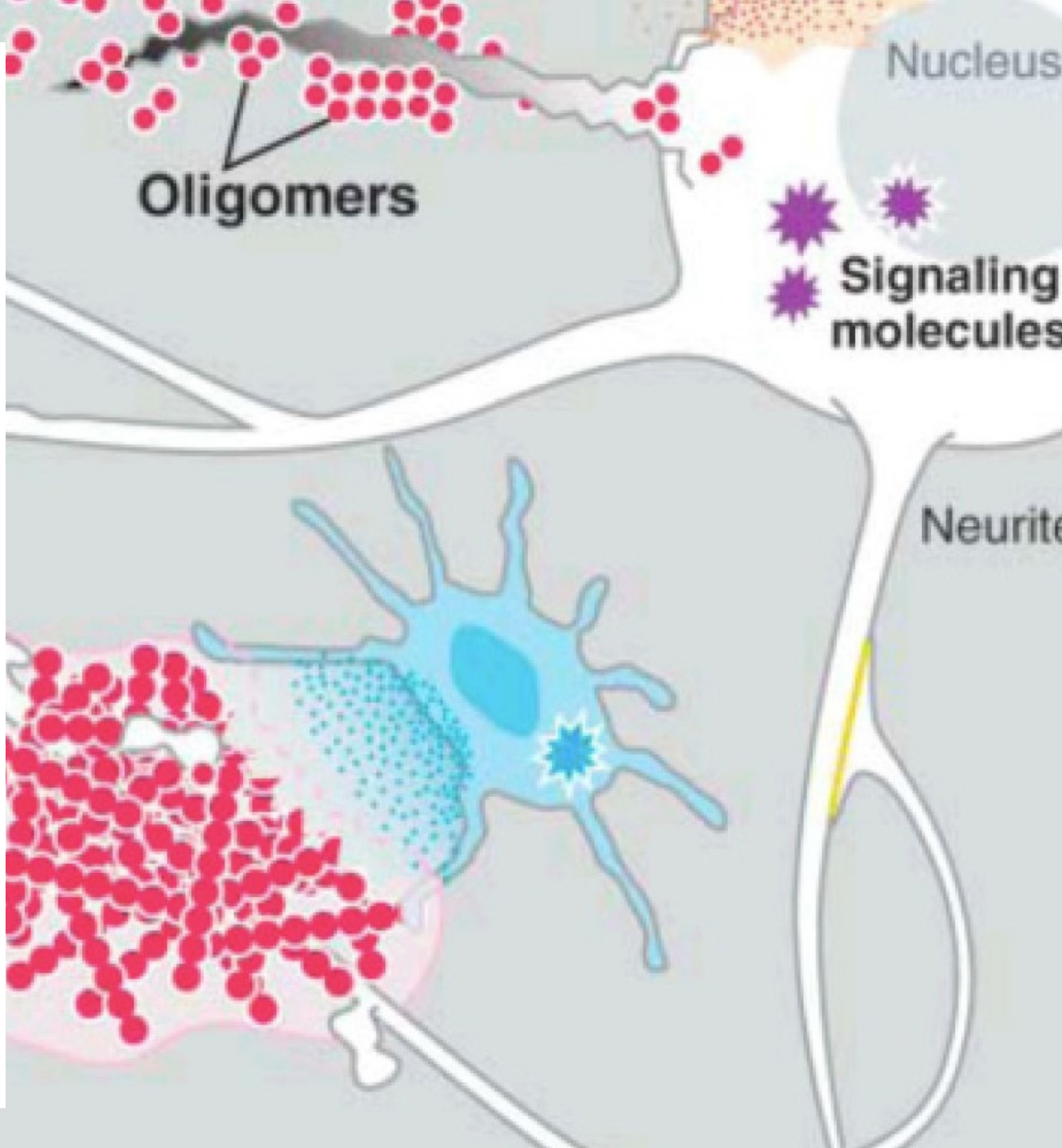
PART II:
RISKS AND PREVENTION:
A BALANCING ACT

Is AD our brain's destiny?

- We all hope to live until old age… but what does that mean for our brains?
- Based on what we have already learned, the reward of living until 85 is a 50% of AD
  - Don't think it will be you?
- One reason Alzheimer's creates so much fear – feeling of helplessness to stop it
  - Is this true, though?
  - Has research given us any hints into how we might protect our brains from AD?

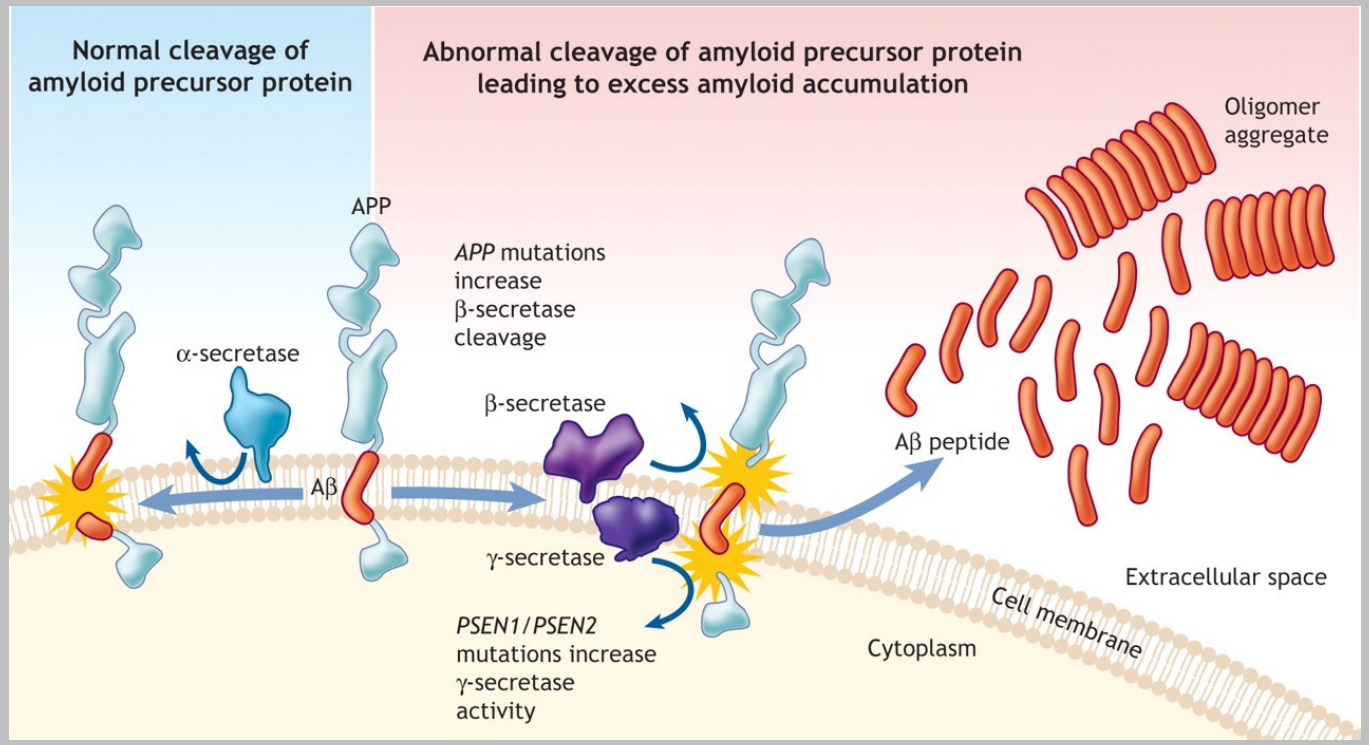
The Synapse and AD

- In Part I, we **discussed the importance of the synapse** (where the amyloid plaques are building up)
- The synapse is important because it is where **chemical communication takes place**
  - We think, feel, hear, and remember here
- We also discussed the **importance of the microglia (i.e. janitor cells)** that clear away accumulated protein/debris in cells
- Microglia clear amyloid-beta from the synapse, but **why is it in the synapse at all?**



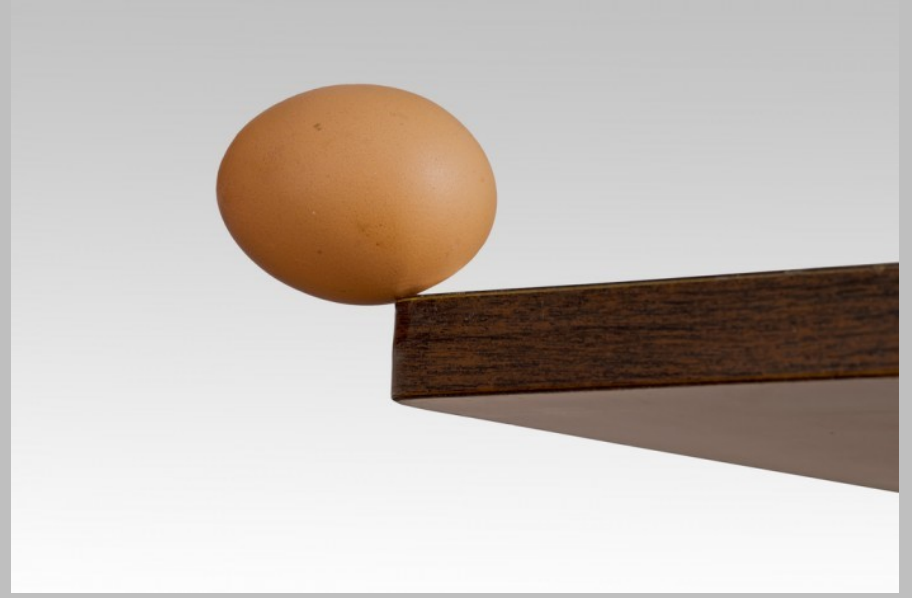
Amyloid-beta build-up

- Amyloid-beta typically released by neurons and can interact with neurons and glial cells
- Important cellular function in the healthy brain, including recovery from injury, communication, and protection from infection – ***this type of amyloid-beta is protective***
- Problems arise when improperly cut protein starts sticking together and forms oligomers, then **plaques**



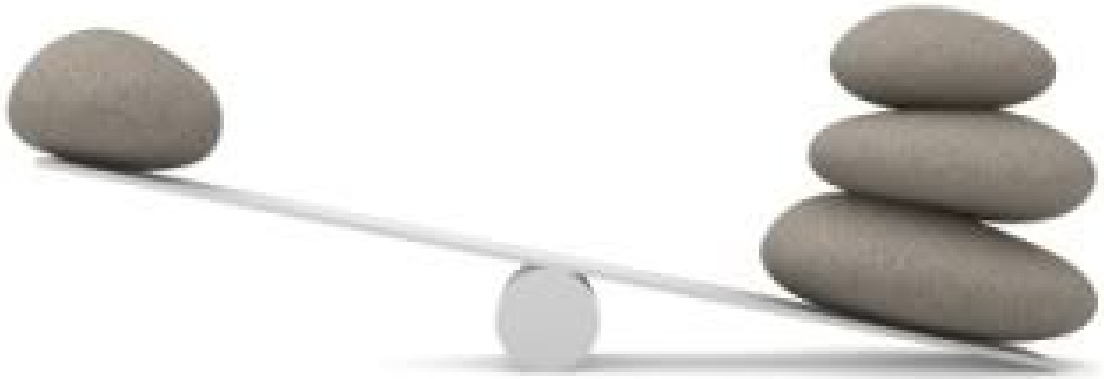
Tipping Point

- Molecular causes of AD under debate, but many believe **pathology** begins when **amyloid-beta begins to accumulate** in the synapse
- Too much released, not enough cleared, or both – starts to get sticky
- Build-up begins in our 40s, but if tipping point is reached, we are symptomatic
- Pre-tipping point memory problems are different from post-tipping point memory problems



Tipping Point

- **PRE-tipping point:**
- Why did I come into this room?
- Where did I leave my keys?
- What is that LinR lecturer's name again?
- These are normal types of forgetting (and in fact, may have nothing to do with memory)
- **POST-tipping point:**
- Finding keys in microwave
- Finding keys and thinking 'what are these for?'



Tipping Point Reached

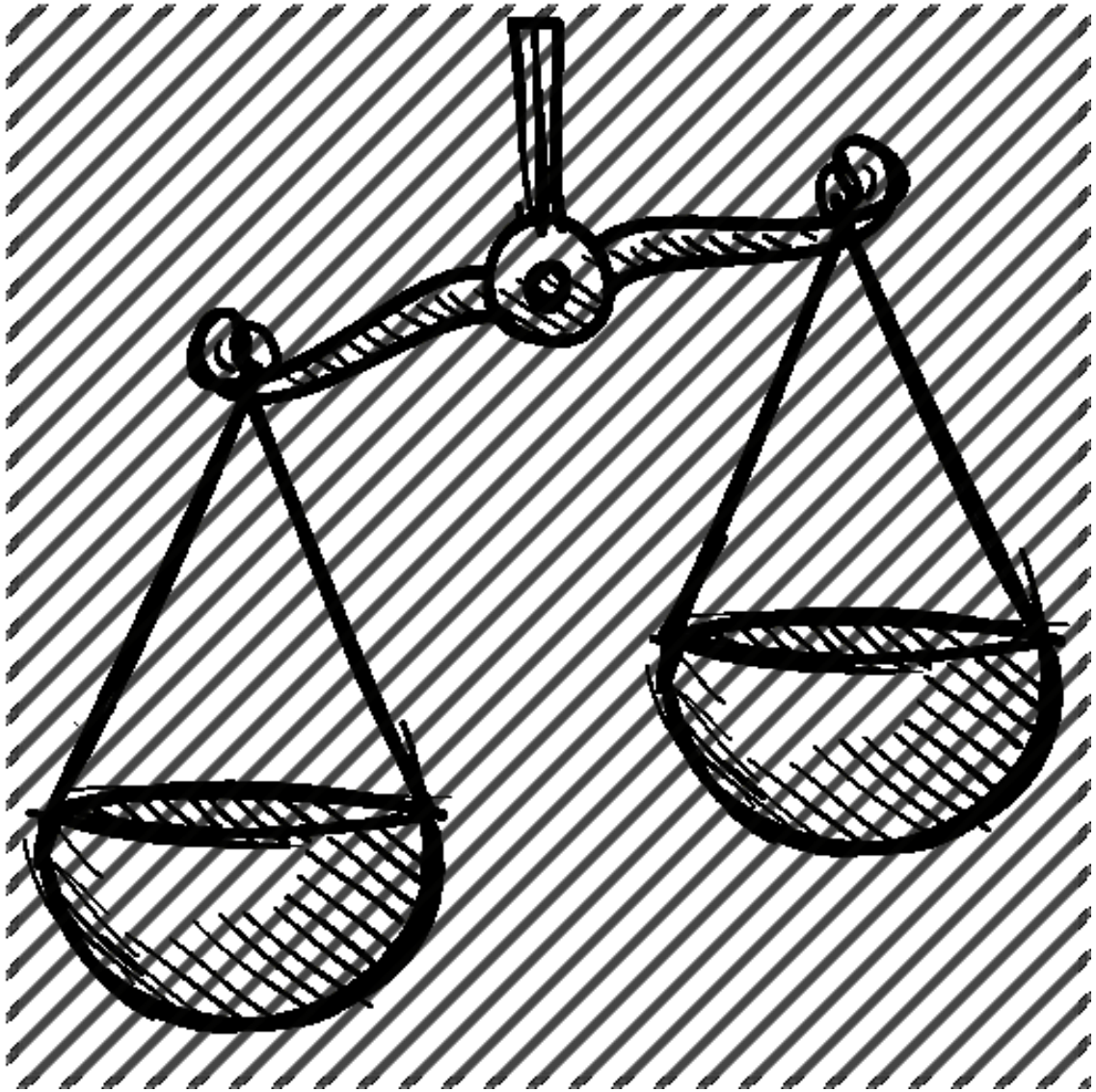
- Microglia are hyperactivated and releasing substances to sound the alarm
  - May even remove the synapse if cells under too much stress
- Tau tangles forming in neurons are choking them off from the inside
- So by mid-stage AD, we have:
  - Extensive inflammatory processes and removal of synapses coordinated by glial cells
  - Cell damage and death (tau tangles, dying neurons)
- YIKES – can we stop this disease?

Preventing Tipping?

- Many scientists focus on preventing build-up of plaques to treat AD
- Prevent the war on synapses by prevent the accumulation of amyloid-beta (meaning the eventual cure will be a preventative drug)
- Recent paper (Shea et al., 2019) developed a **synthetic** protein that **stuck** to **oligomers** and prevented aggregation (tested in cells and animals)
- Even newer research published only a few weeks ago (Ewers et al., 2019) identified a correlation between a protein released by microglia and cognitive decline in over 300 patients with AD (more of this protein led to slower cognitive decline)
- But how can we prevent the tipping point from being reached? Is there anything we have do?

Preventative Drug @ 40?

- Would need to take drug years before symptoms appear
- Possible this is why previous clinical trials have failed
  - If individuals are already symptomatic, too late to prevent Aβ buildup
  - If treatment is attempting to break up oligomers, no use blowing out the match once the forest is ablaze
- BUT there is good news if we are not yet symptomatic – turns out our lifestyle can influence how Aβ accumulates
  - This means there are things we can do to prevent the scales from tipping

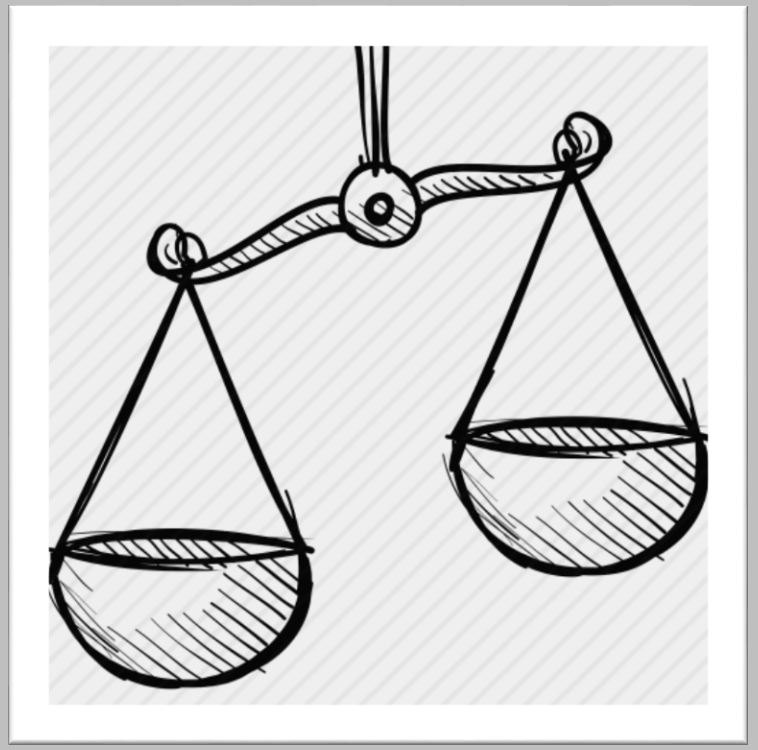


Tipping the Scales

- Think of it as a balance, with risk factors on one side and preventative factors on the other
- If the scale hits the ground, you become symptomatic (develop the disease)
- But how many factors are in your control to hopefully prevent the development of AD?

Tipping the Scales

- **RISKS**
- AGE (e.g. 50-55)
  - You've accumulated some plaques with age
- DNA
  - Some genes alone are enough
  - Most increase risk only APOE4



- **PREVENTATIVE**
- SLEEP
  - Power cleanse for the brain
  - Microglia, toxins in CSF
  - One night of poor sleep ↑ Aβ
  - ↑ Aβ leads to poor sleep - cycle
- CARDIOVASCULAR HEALTH
  - Obesity, smoking, high BP/cholesterol, diabetes all ↑ risk of AD

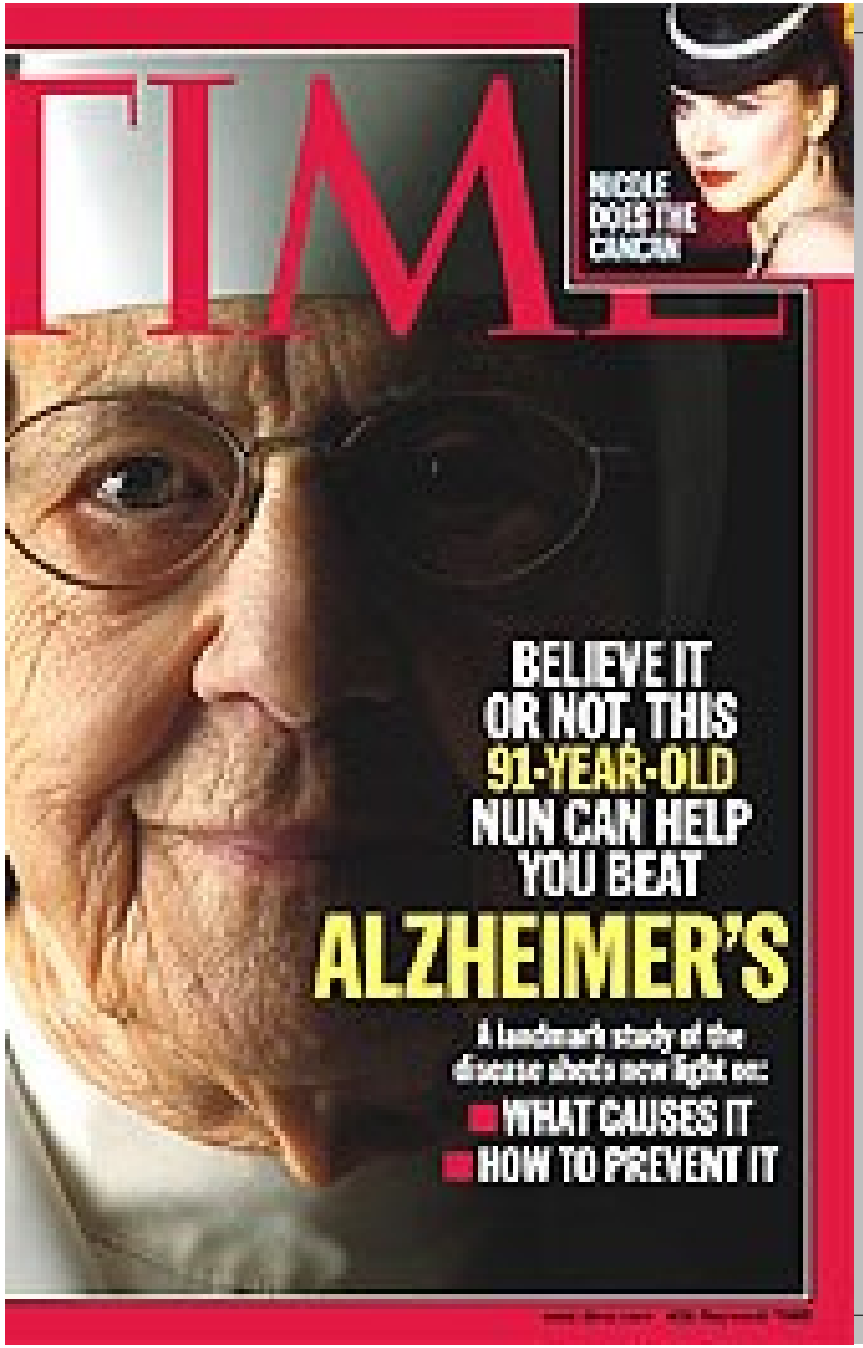
Can't change our age or our genes… so what can we do?

SO – heart-healthy Mediterranean diet and aerobic exercise, 7-8 hours of sleep

What if you haven't done any of this?

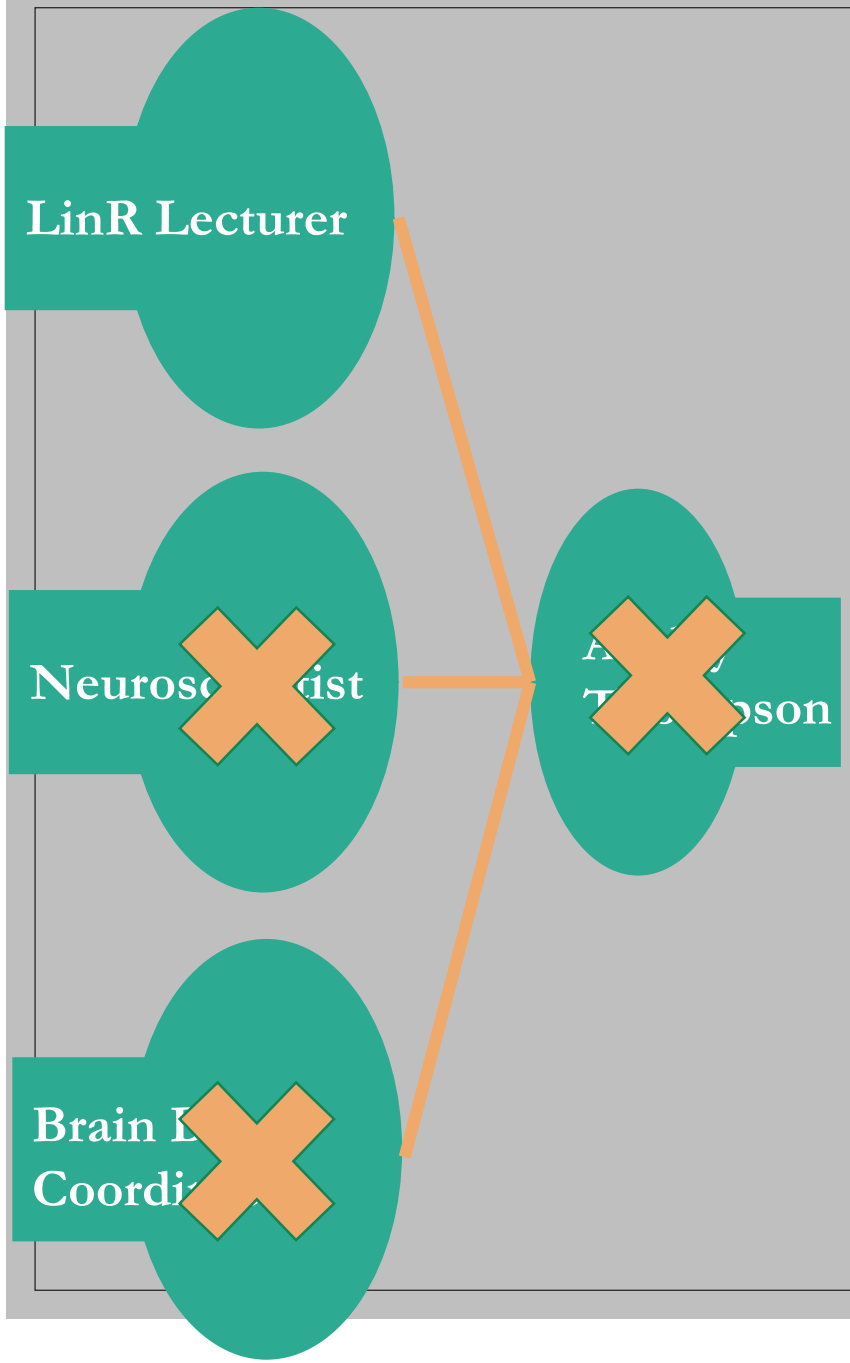
- **YOU**
- In your 60s…
  - Haven't taken good care of body/brain through diet
- Have a couple of genes that increase your risk of AD
- Ran yourself silly for years (poor sleep hygiene)

NOW are you doomed to get AD?
Maybe not!



The Nun Study

- **Ideal group for studying risk factors of dementia – why?**
- Relatively homogenous group with similar lifestyle – typically huge challenge of human research
- Started in the 1980s and is ongoing – more than 700 nuns donated bodies and brains to science in the United States
- In this group, none smoked, none drank excessively, none had partners and each lived a fairly routine, meaningful life
- **At autopsy, several of the nuns' brains showed all physical characteristics of an Alzheimer's diseased brain – yet interestingly, none were symptomatic while alive**



What can we learn from the nun study?

- **COGNITIVE RESERVE**
- Many nuns remain involved in education and service well into old age
- What is cognitive reserve?
- Let's say you only know one thing about me – I'm a neuroscientist
- Lose this connection – lose all memory of me
- Let's say you know a few things about me, though…
- Individuals with more education have lower risk of developing AD – likely due to greater **cognitive reserve**

So what can we do?

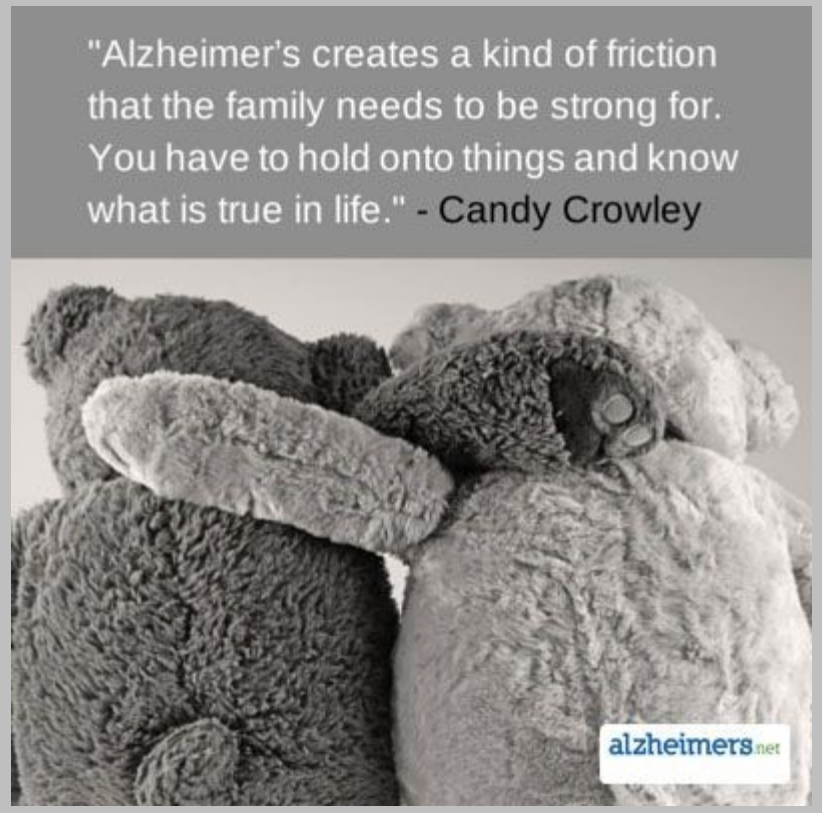
- Activities that create and strengthen new neural connections based on principles of neuroplasticity
  - Behaviours we engage in frequently are like ruts in a road –easier to travel
  - Learning **new things** carves out new pathways (i.e. creates new neural connections) which can be strengthened through **practice**
- **SO: why aren't crosswords helpful in the quest to prevent AD?**
- **We need to engage in activities which are NEW to our brains**
  - Recall task – retrieval of information already there
  - Good news = you're getting better at doing crosswords! ☺

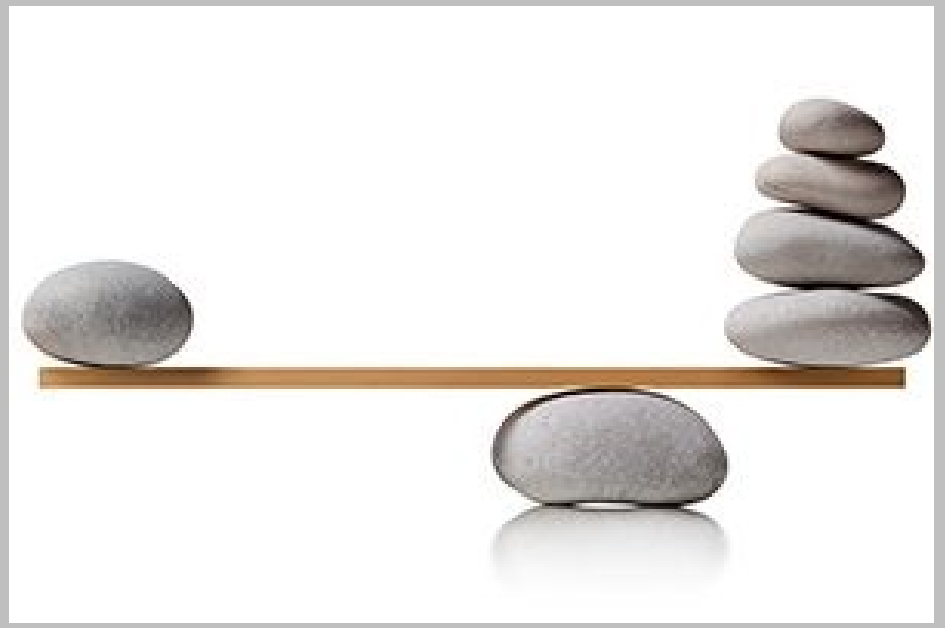
So what can we do?

- **We need to engage in activities which spark the creation of new neural pathways**
  - Learn new things
  - Build cognitive reserve
- **We need to prioritize heart health**
- **We need to be protectors of our sleep**
- **What kinds of 'new' things?**
- Examples are endless since new to you may be different than new for someone else!
- Learn a language, read, cook different foods using recipes, learn a new hobby/craft, dance
- Go to Learning in Retirement lectures = 

Coping with Memory Loss

- Some tips to help cope with memory loss:
  - Keep a routine
  - Organize information (post-its/notes, calendars, reminders for pills/appointments)
  - Put items in safe/same spot (i.e. car keys, phone, wallet)
  - Repeat information when it is learned (e.g. names), and use associations to help recall
  - Tell stories to others
- When interacting with someone with any form of memory loss, remember to be patient, seek support/community, and remember that your own health (both physical and mental) is required to be in a good state for you to care for another





Thank you!