Alzheimer's Disease

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Bio: Charles J. Vella, PhD

- Neuropsychologist
- 34 years, Kaiser San Francisco, 1975-2009
  - Chief Psychologist/Manager
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- Neuropsychology Lecturer, 2009-Present

- Download this talk at:
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  - Go to Public Lecture section
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The Facts

- Life expectancy is rising as a result of advances in medical science and the availability of better healthcare services;
- The number of elderly persons is therefore rising.
- As the risk of dementia increases with increasing age, the number of persons with dementia is also rising.
- 75% of people do not realize they can reduce their risk for dementia.

What do you know?

- Does being socially active protect you from developing AD?
- Does being physically inactivate increase your risk of AD?
- Does getting more education protect you from developing AD?
- Does being overweight increase your risk of AD?
- Does smoking increase your risk of AD?
- Can you reduce your risk of cognitive decline?

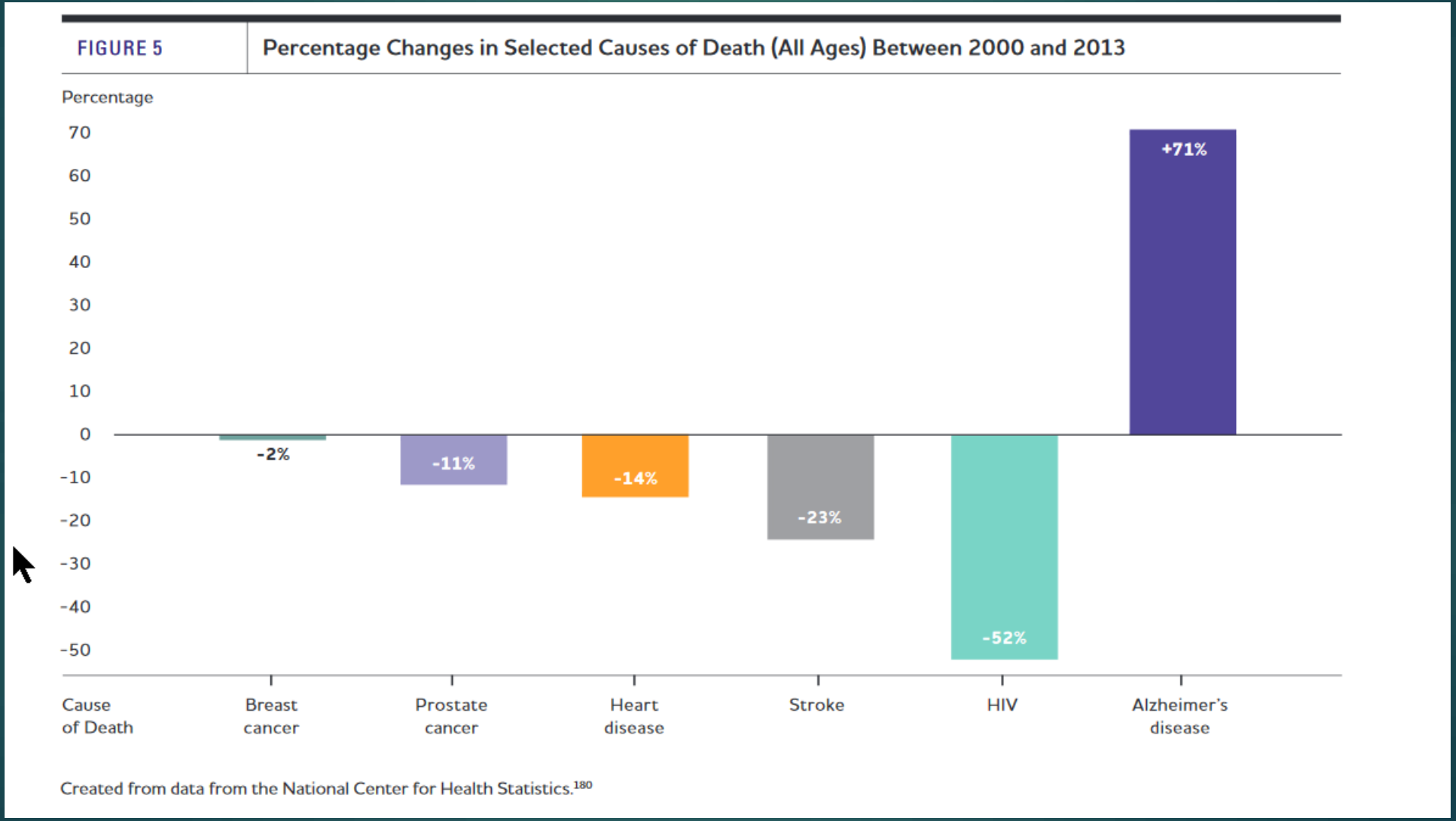
How to Live a Brain Healthy Lifestyle

- Information is based on science and current research.
- We do not know how to prevent Alzheimer's disease.
- We do know some of risk factors that contribute to cognitive decline.
- We want to be proactive about brain health & potential risk reduction.
- The way we live earlier in life will determine how normal our cognition remains, and for how long.

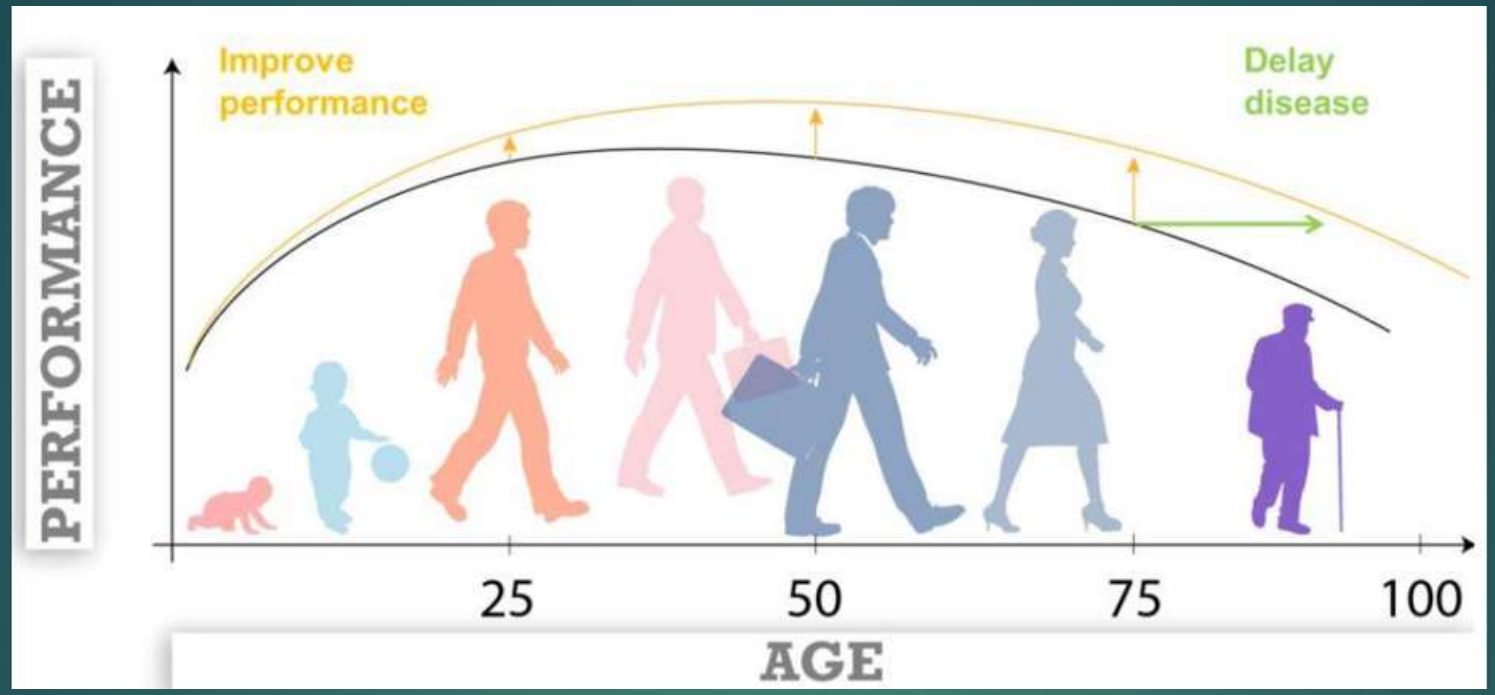
Getting Major Neurocognitive Disorder (Dementia) is partially a lifestyle decision

- You cannot change your age or your genes.
- Dementia depends on your lifestyle choices

We are not paying attention to curing Alzheimer's: deaths from most major medical conditions have declined, but not AD



We need to delay the onset of Alzheimer's



- Nothing has been shown to prevent Alzheimer's pathology, but there are evidence-based ways to improve and prolong brain function, and to reduce the probability of cognitive decline.
- We can't prevent AD from killing people, but we can delay its onset.
- A one-year delay would translate into nine million fewer cases by 2050; a five-year delay would halve the prevalence of dementia globally in that same time period.

Dear God,
My prayer for 2017 is for a fat bank account & a thin body.
Please don't mix these up like you did last year.

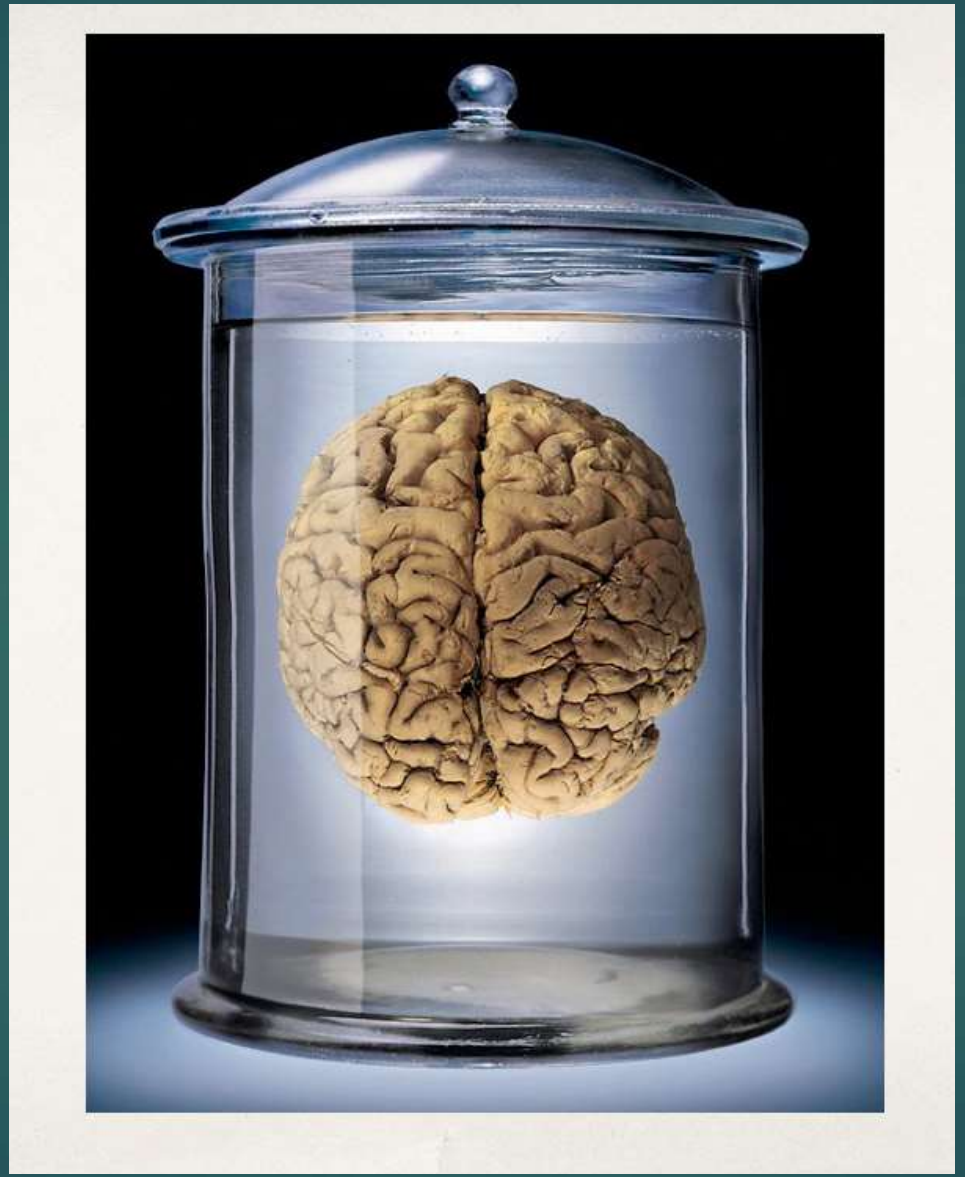
Do you…

- Misplace your keys?
- Miss an appointment?
- Forget the names of people you know well?
- Believe your memory is fading?
- These are not indications of a memory disorder!

Chill Out

- Aging glitches do not necessarily mean you have Alzheimer's disease
- There's a difference between:
  - not remembering where you put the car keys today…
  - And not remembering that you own a car or what a key is.
- Young people lose their keys and they just think they lost their keys.

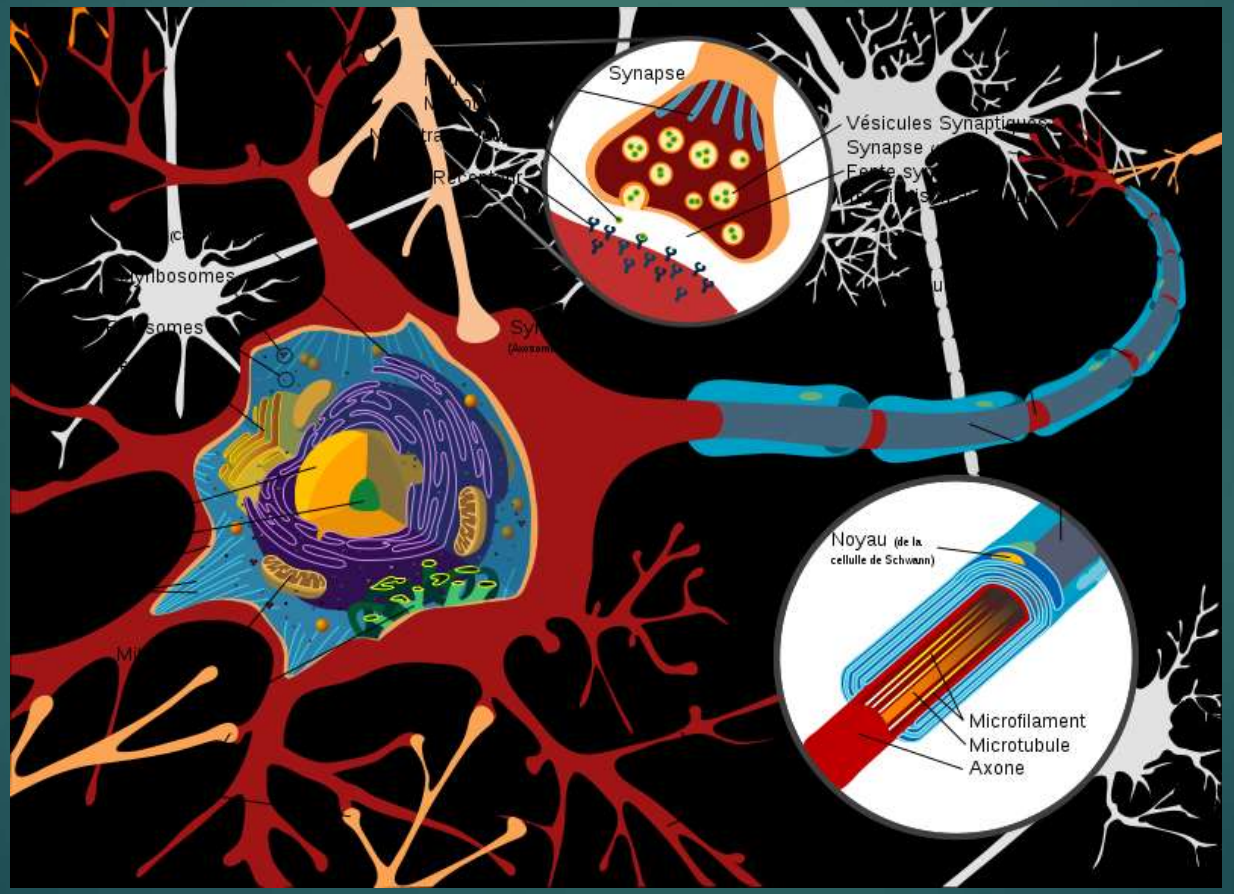
The Brain



3 pounds

Neurons: We have 170 billion brain cells with 10,000 synapses each (10 trillion connections)

Neuron

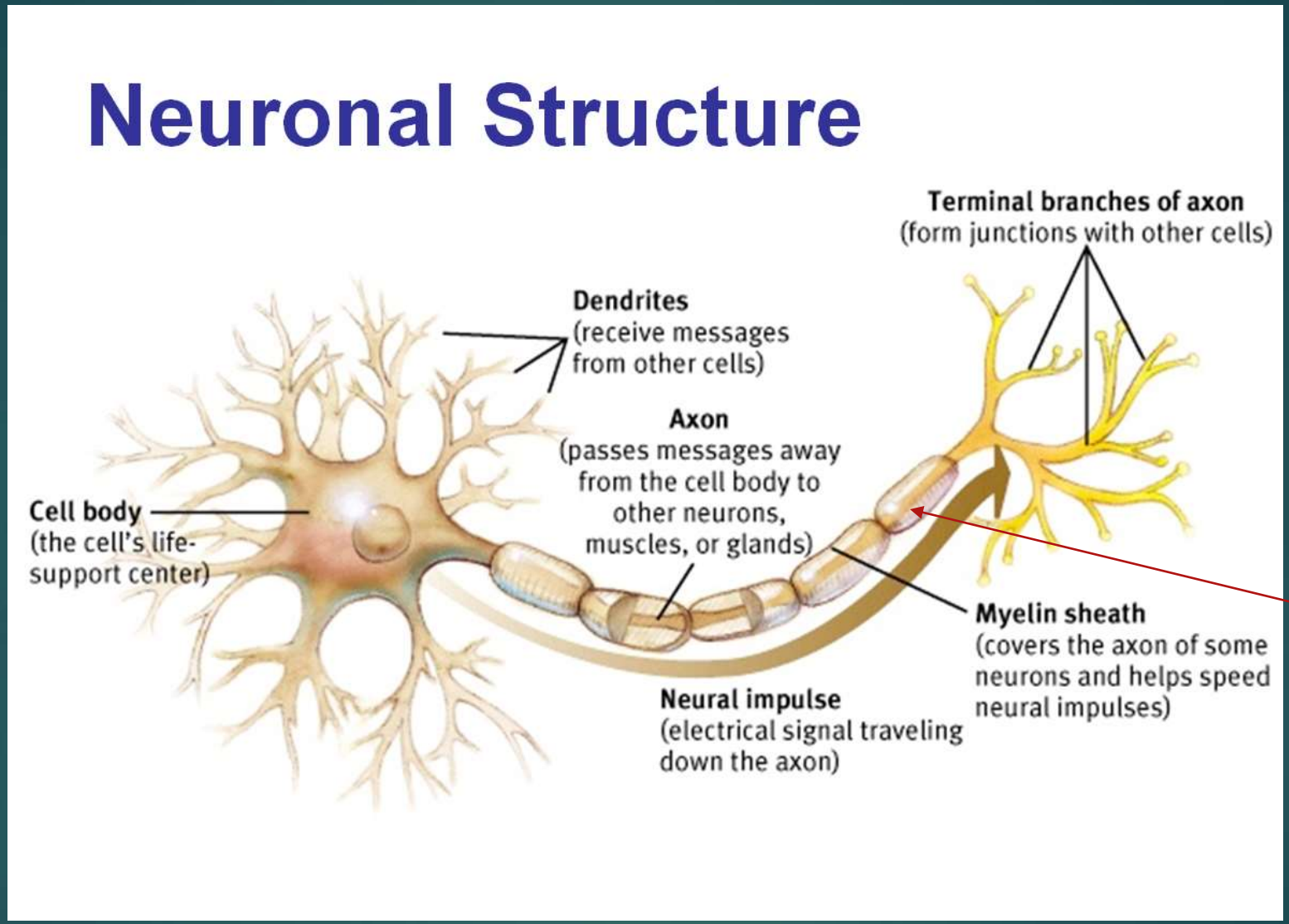


Axon

Dendrites

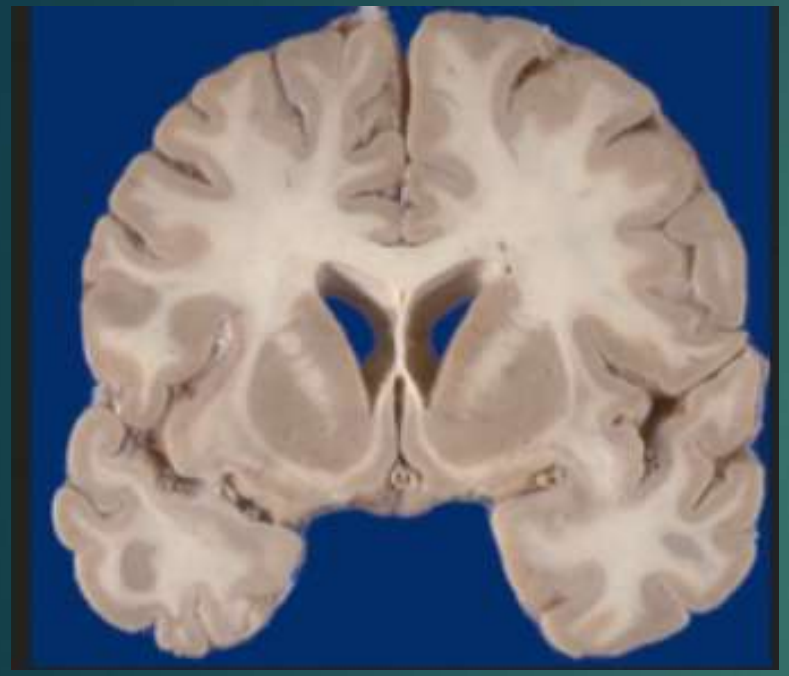
Suzana Herculano-Houzel et al., 2009

Neuron

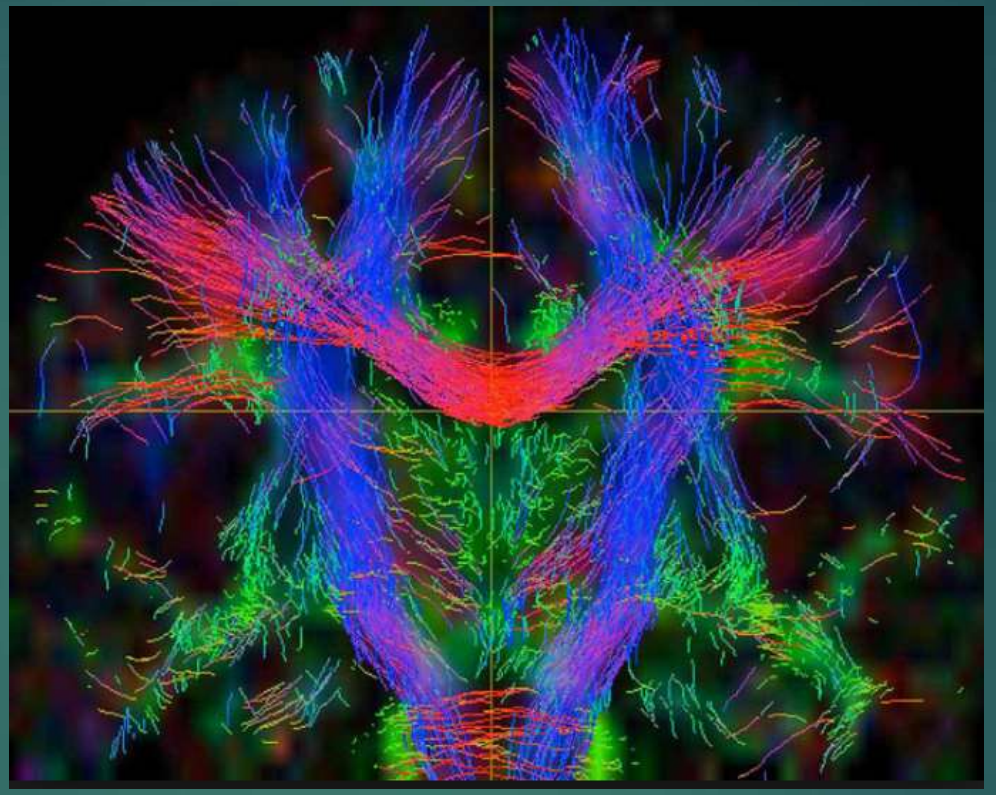


White Matter

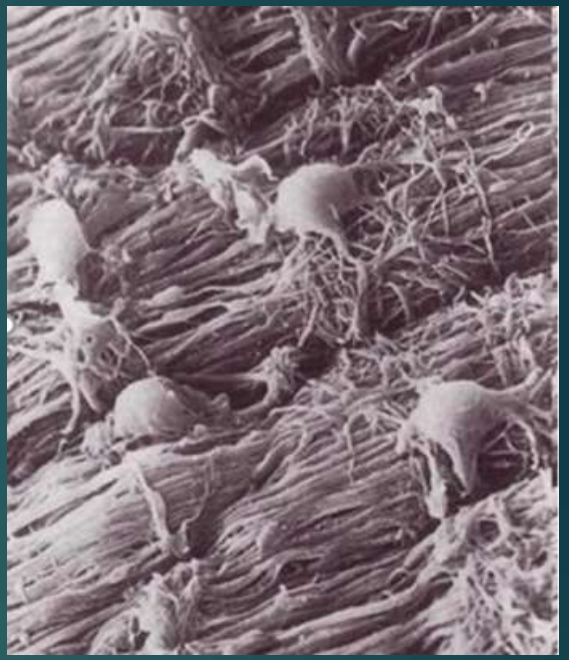
White Matter: Insulation on your Neuronal axons



Brain



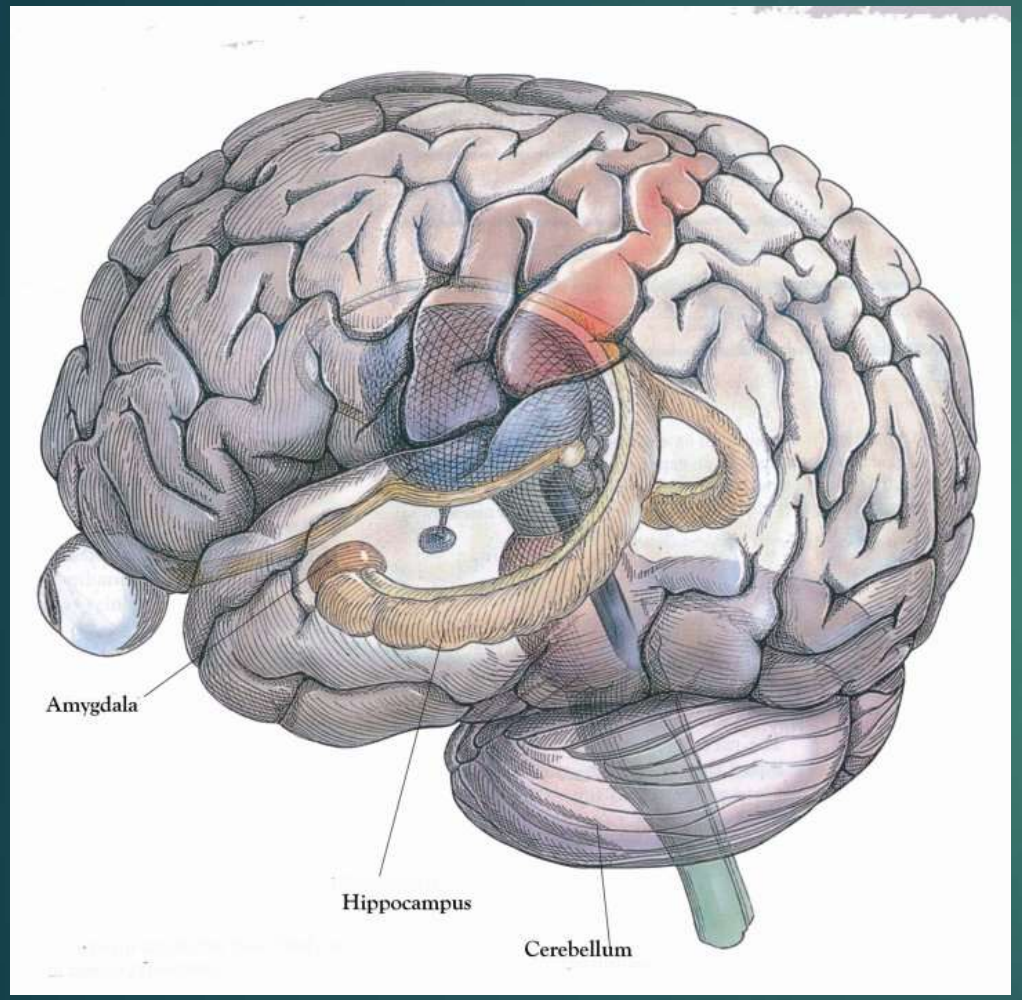
DTI of WM



Electron Microscope of WM

The Internet of your brain: How fast you process information, how fast you think

Hippocampus & Prefrontal Cortex



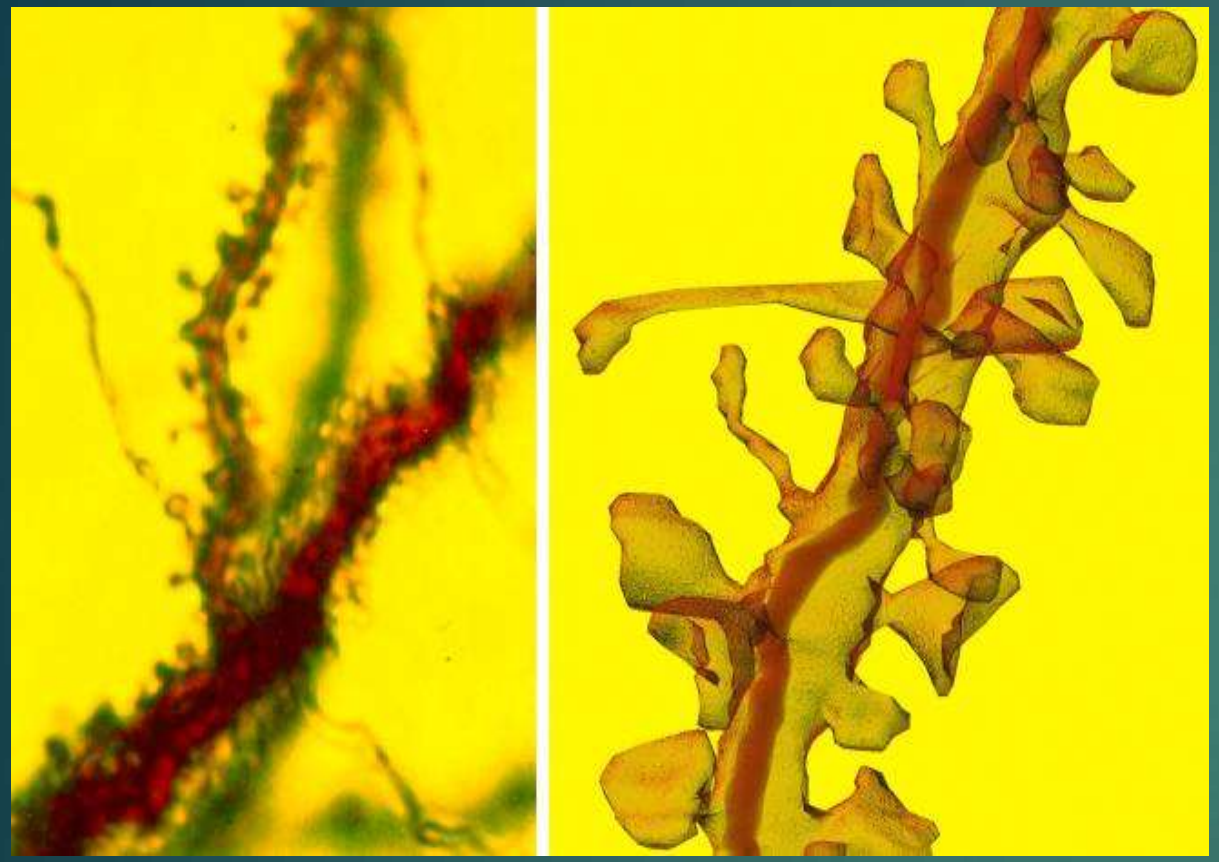
Hippocampus:

- Memory central
- Learning anything new
- Most sensitive to low Oxygen

Prefrontal Cortex

- what makes you a rational adults
- ability to inhibit inappropriate behavior.

Dendrites under Electron Microscope

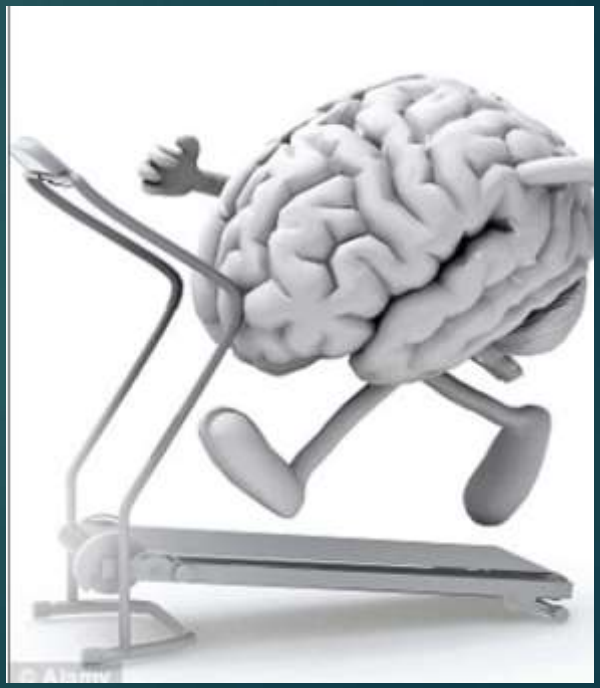


Highly dynamic: can appear in hours to days and also disappear.
60% of cortical spines are permanent; hippocampal spines recycle.

Use it or lose it

- Without use, brain cell is signaled that it is no longer needed
  - Dendrites atrophy
  - Synaptic connections weaken

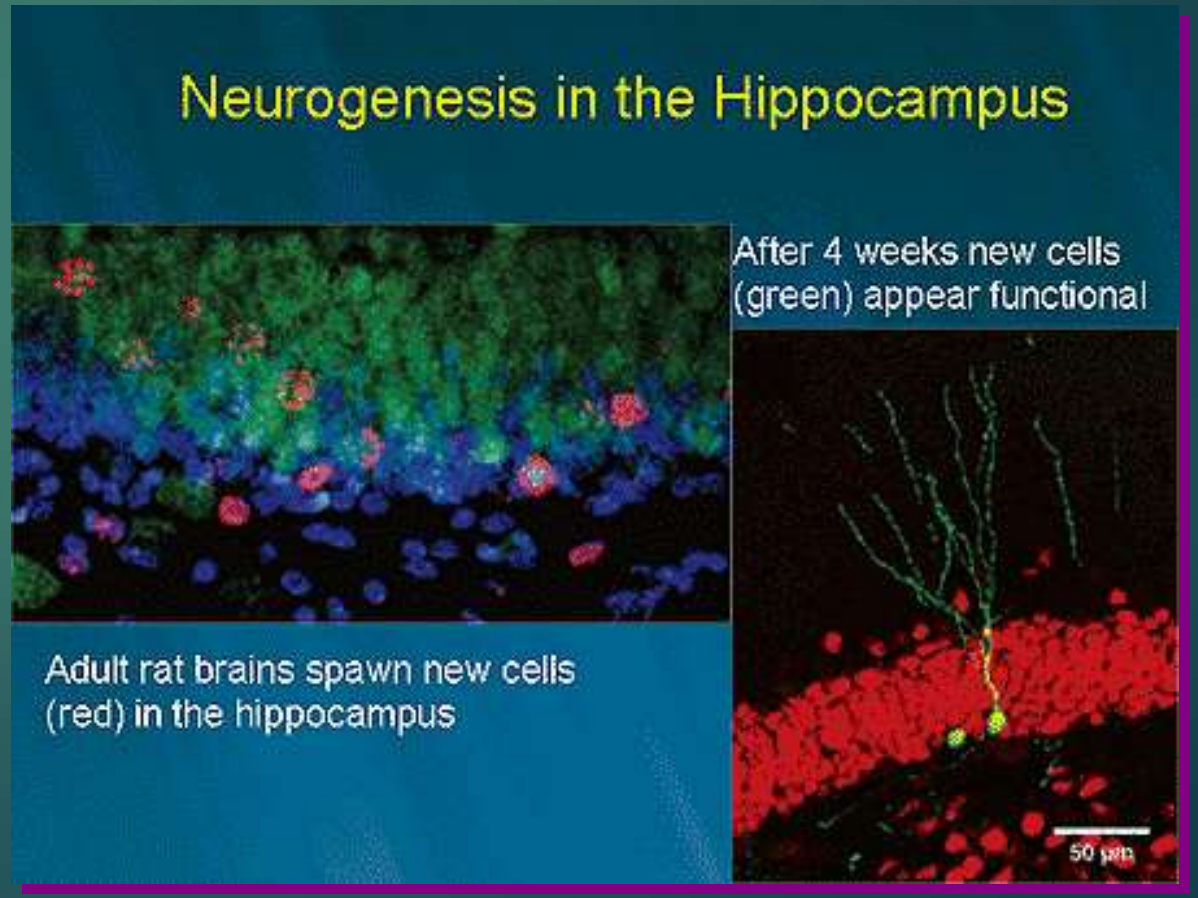
- Negative neuroplasticity in older adults:
  - “Brain disuse”: Loss of skills due to non practice
  - Example: sitting all day in front of TV



Neurogenesis = New brain cells

- Neurogenesis: growth of new neurons in the adult brain; Stem cells can become new adult neurons; 1,400 cells a day, esp. in dentate gyrus of hippocampus

- Ways to increase:
  - Physical exercise
  - Calorie restriction
  - Antidepressants
- Ways to decrease
  - Depression
  - Sleep deprivation



Intellectual Ability Declines in Normal Aging

Not only Forgetfulness

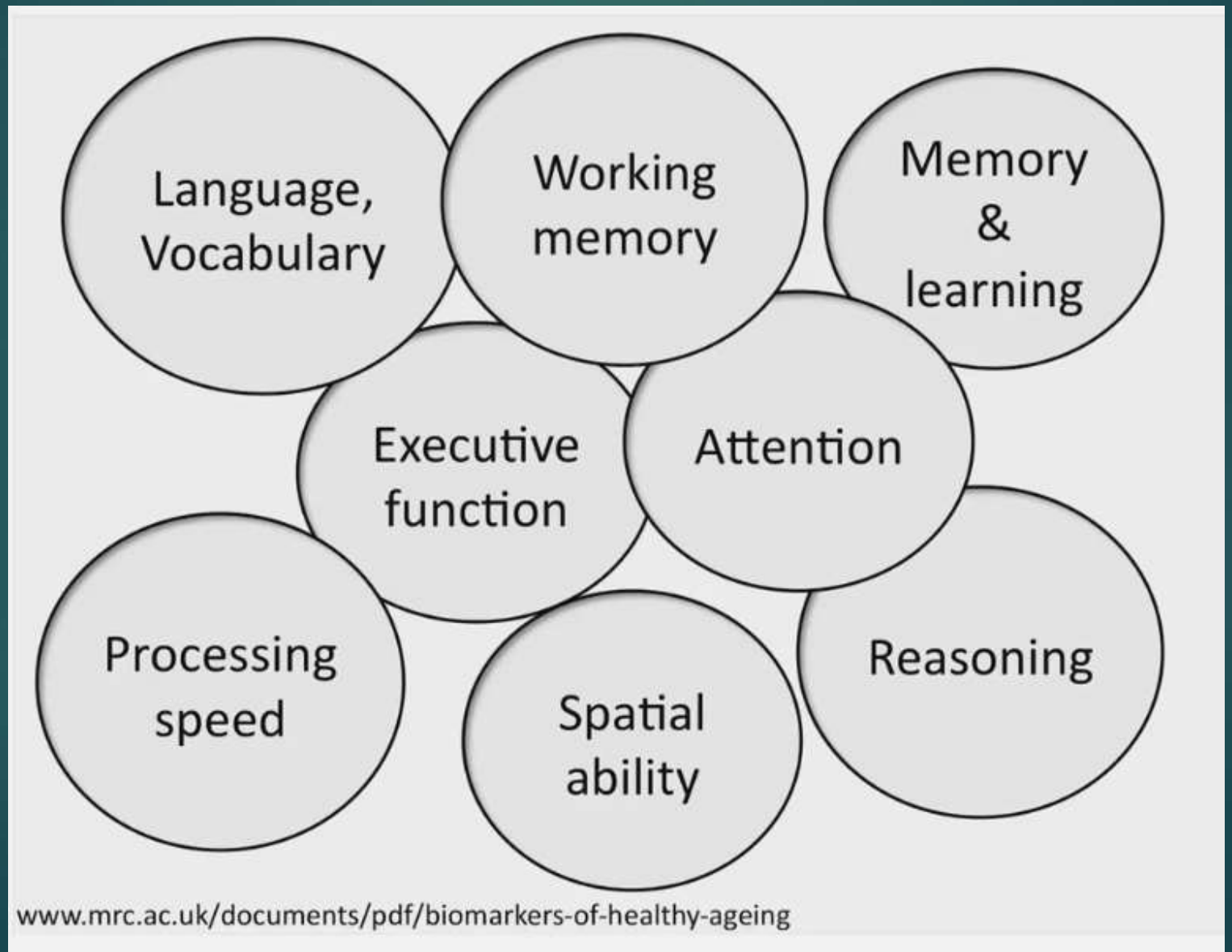
- Older people often worry about whether cognitive glitches are early signs of a neurodegenerative disease, particularly Alzheimer's disease.
- Forgetfulness is often equated with a decline in cognition, and raises issues of ability for independent living and healthy aging.

- There is fear of loss of the ability to live independently (doing finances, following a recipe to cook a meal, and driving)

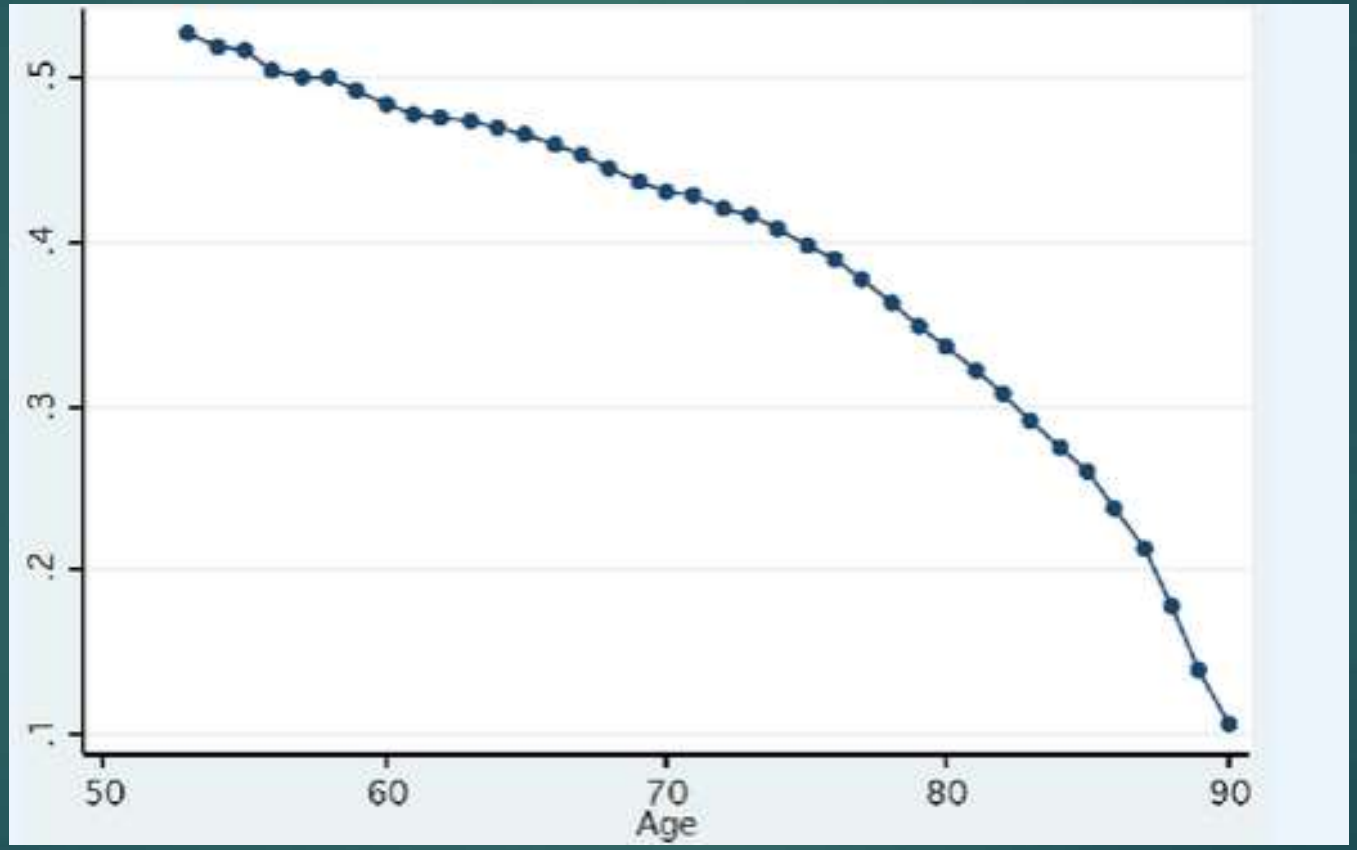
It’s not just Memory: there are 6 Important Cognitive Abilities

- Complex Attention (Sustained, selective divided)
- Executive Function (Planning, decision making, problem solving)
- Learning and memory
- Language (expressive, grammar/syntax, receptive)
- Perception & motor ability (sight, hearing, movement)
- Social cognition (recognition of emotions, theory of mind)

Different Cognitive Skills in Brain:
They do not decline at same time



Public Perception of Normal Aging: Major Decline with Age – Not true



Typical age-related changes

- Typical age-related changes involve:
  - Making a bad decision once in a while
  - Missing an occasional monthly payment
  - Forgetting which day it is and remembering later
  - Sometimes forgetting which word to use
  - Losing things from time to time

Problematic cognitive changes

1. Memory changes that disrupt daily life
2. Challenges in planning or solving problems
3. Difficulty completing familiar tasks
4. Confusion with time or place
5. Trouble with visual images and spatial relationships
6. New problems with words in speaking or writing
7. Misplacing things and losing the ability to retrace steps
8. Decreased or poor judgment
9. Withdrawal from work or social activities
10. Changes in mood and personality

Longitudinal Studies of normals

- K. Warner Schaie and Sherry Willis's Seattle Longitudinal Study: n = 5676
- Whitehall Study of British Civil Servants: n = 18,000; Whitehall II: n = 10,308 women and men
- The Nun Study: n = 678 (Religious = homogenous populations)
- Atherosclerosis Risk in Communities (ARIC)
- The Religious Order Study: n = 1350 (40 groups; 94% autopsy rate)
- Rush Memory and Aging Project: n = 1,850

Normal Age-Related Changes in Cognitive Abilities

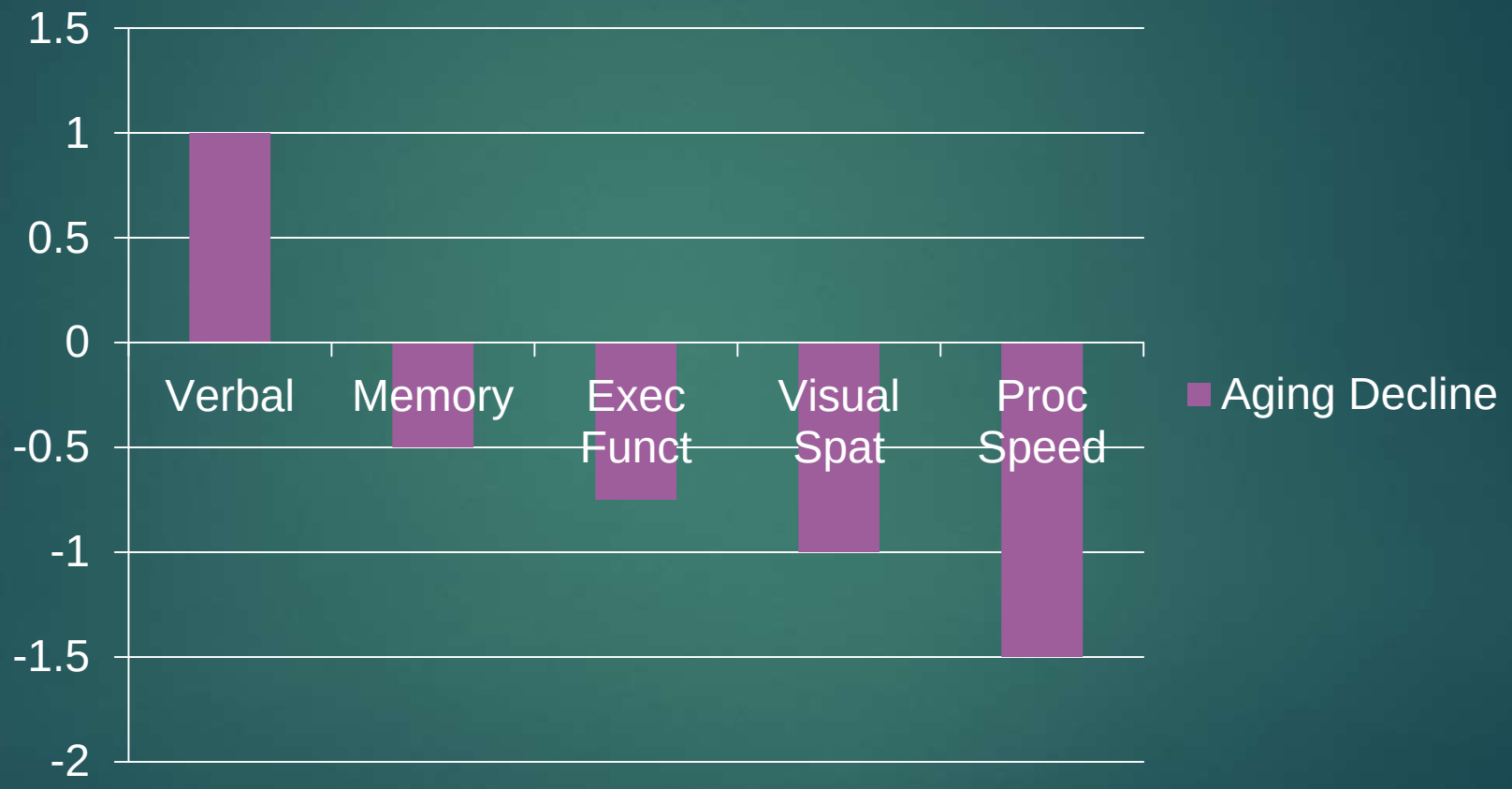
- K. Warner Schaie and Sherry Willis's Seattle Longitudinal Study:
- Reliable decline can be found for all abilities by 74 years of age
- Cognitive better from age 40-65 than in our 20s for:
  - Vocabulary
  - Verbal Memory
  - Spatial Orientation
  - Inductive reasoning (Drawing a general conclusion based on a limited set of observations)

Normal Age-Related Changes in Cognitive Abilities

Seattle Longitudinal Study: After age 65:

- Verbal Knowledge intact; difficulty with name retrieval, particularly the names of those we've not seen in a while
- Memory Ability = ½ s.d. decrease ↓
- Spatial Ability = 1 s.d. decrease ↓ ↓
- Perceptual speed = 1 ½ s.d. decrease ↓ ↓ ↓

Normal Aging Cognitive Decline in the absence of brain pathology



Based on Schaie and Salthouse

Tale of Two Computers: Speed ↑↑↑

1982 IBM Computer
Intel 8088 chip @ 4.77 MHz

After age 65, we return to this speed!

Lenovo W5307
Intel Core i72. @ 2.70GHz

2500 times faster

Whitehall Conclusions: social position influences disease.
Take care of your heart

- Importance of healthy lifestyles and cardiovascular risk factors.
- Mid-life levels of obesity, hypertension, and high cholesterol seem to be more important than at older ages.
- What is good for your heart is good for your brain

Atherosclerosis Risk in Communities (ARIC) cohort: 1980s

- Longitudinal Study (since 1987) 15,792 middle-aged participants who hailed from different counties in Maryland, North Carolina, Mississippi, and Minnesota; 30% African Americans
- What factors recorded in the late 1980s affected dementia risk in the following decades. 10% developed dementia
- Findings: vascular problems in midlife create risk for dementia
  - Age and ApoE were strongest risk factors for dementia.
  - Low education boosted risk by 60%;
  - AA had 30% higher risk; higher incidence of dementias other than AD; higher rates of hypertension & diabetes

What to do?

- Medical school professor says to his medical class:

- Imagine you begin to lose your memory and your thinking begins to become more clouded.
- What would you do?

Medical student responds:
I guess I would have to transfer to law school.

What is Neurodegenerative disease?

A neurodegenerative disease is an:

- Acquired brain disease that kills brain cells
- Caused by abnormal proteins in the brain
- Causes dementia
- Is fatal

What is dementia (now Major Neurocognitive Disorder)?

Dementia:

- Not a disease
- A diagnosis by MD or PhD
- A decline in cognitive symptoms affecting ability to live independently
- Caused by a variety of illnesses and injuries.
- Not the same as a neurological disease.

Terminology

- “Dementia”:
  - Decline in cognitive ability from prior level
  - To interfere with independent functioning
  - Mild (MCI, mild NCD) vs. Major (Dementia, Major NCD) versions
-
- Alzheimer’s Disease = neurodegenerative disease

Alzheimer's ≠ Dementia

- Alzheimer's Disease = neurodegenerative disease due to increased beta amyloid presence in your brain
- Dementia = cognitive decline
- You do not have dementia while you develop Alzheimer's.
- Dementia is the most common final sign of Alzheimer's
- They are not same thing

Normals with AD Pathology who have no dementia

- 30% of cognitively normal elderly
  - have intermediate or high levels of Alzheimer's disease (abnormal proteins & synaptic loss)
  - meet neuropathologic criteria for AD
  - but have no cognitive decline; no dementia

Souls go to God; Brains to Lab

Sister Matthia from the Nun Study

- 1986, N=677, School Sisters of Notre Dame; 8 subjects left; the youngest is 100. In total, 600 brains have been collected.
- Age 75-103, 85% teachers, half got NCD
- Despite lots of BA, 50% = no sxs; no dementia/NCD

Aging with Grace, Snowdon; Snowdon et al, 2000

Nun’s Brains: Preserved for Science

Which sentence from a 1 page autobiography, at age 22, predicts dementia & AD ~60 years later?

- Sister Helen: I was born in Éclair, Wisconsin on May 24, 1913 and was baptized at St. James Church.
- Sister Emma: It was about half past midnight between February 28 and 29 of the leap year 1912 when I began to live and to die as the third child of my mother whose maiden name is Hilda Hoffman and my father Otto Schmidt.
- Women with richer vocabularies and grammatical complexity when young had less dementia than those who had less of these
- Lower Idea density and grammatical complexity predicted AD in 60 years with 80% accuracy. Best way to increase idea density is reading!!
- First evidence that your young brain has effect on your old brain.

Alzheimer disease without NCD/dementia: Sister Bernadette

- Sister Bernadette of Nun's Study:
  - Died at 85 of heart attack; MA, teacher for 40 years; double APOe4
  - One of brightest nuns; died "sharp as a tack" with no signs of dementia; MMSE = 30 at 3 testings
  - On autopsy, had massive Alzheimer's pathology (Braak stage 6)
  - Had more grey matter than 90% of other nuns on original MRI (better brain to begin with)
  - A testament to resistance to genetics and AD disease

Nun's Study Lead to concept of Cognitive Reserve

- Cognitive reserve: difference between amount of brain pathology & actual cognitive function
- CR = more synaptic connections, abundance of neuronal connections
- Benefit: Protective (can have more disease before cognitive decline):
  - Bigger brain/head circumference
  - Higher IQ
  - Higher education: The more educated live longer and have less dementia
  - Occupational complexity: Work that involves complex thinking and social interaction
  - Regular cognitive activity (reading, crossword puzzles)
  - Better cardiovascular condition
  - Higher literacy
  - Social engagement

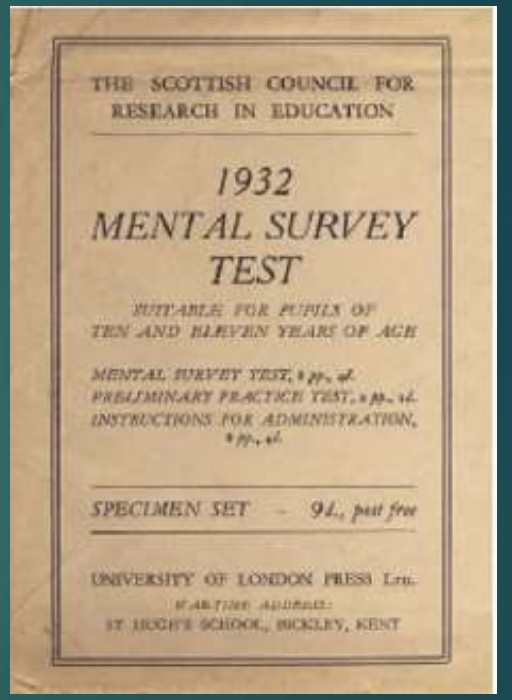
- A form of experience based neuroplasticity or born with better brain?

"Old age is like
everything else.
To make a success of it,
you've got to start
young."

Fred Astaire
(1899-1987)

Lothian Study Scotland: all of Scotland's 1921-born 11 year old population = 87,498 children; Fear of immigration

Study participants alive in 2011



THE SCOTTISH COUNCIL FOR RESEARCH IN EDUCATION

1932
MENTAL SURVEY TEST

SUITABLE FOR PUPILS OF TEN AND ELEVEN YEARS OF AGE

MENTAL SURVEY TEST, 8 pp. 4d.
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SPECIMEN SET – 9d., post free

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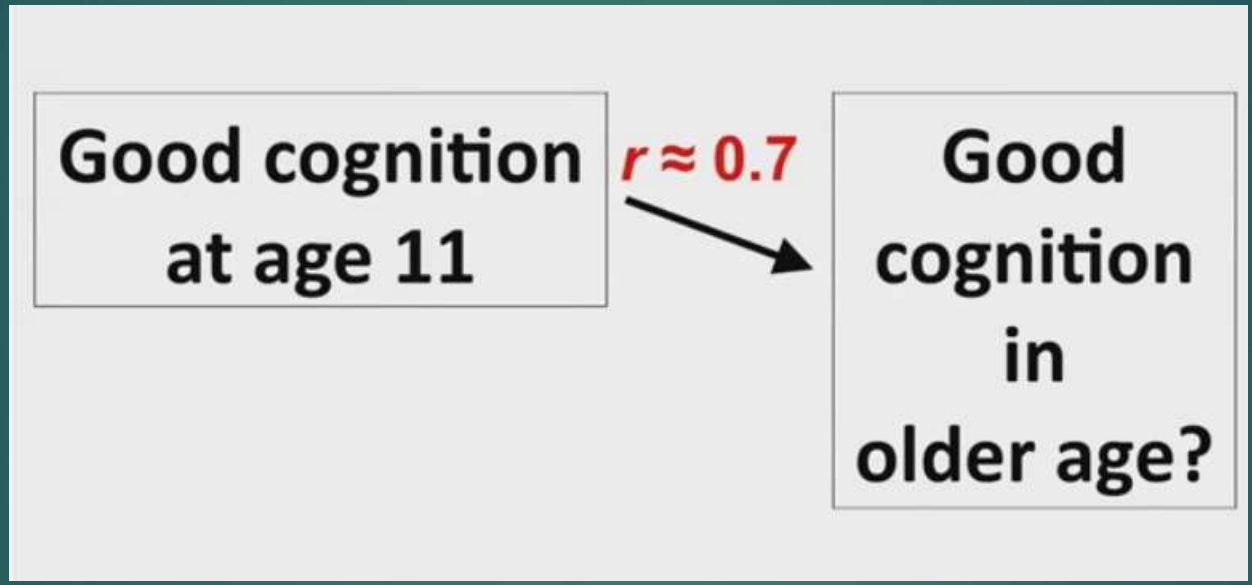
Data rediscovered in 1990s: took test at ages 11, & 79, 87 & 90

Data was lost for 50 years, and then found

Brain you are born with really counts- cognition is stable:
50% of the variance at age 77 is explained by your IQ at age 11



25% of changes in cognition from age 11 to 77 is due to genetics

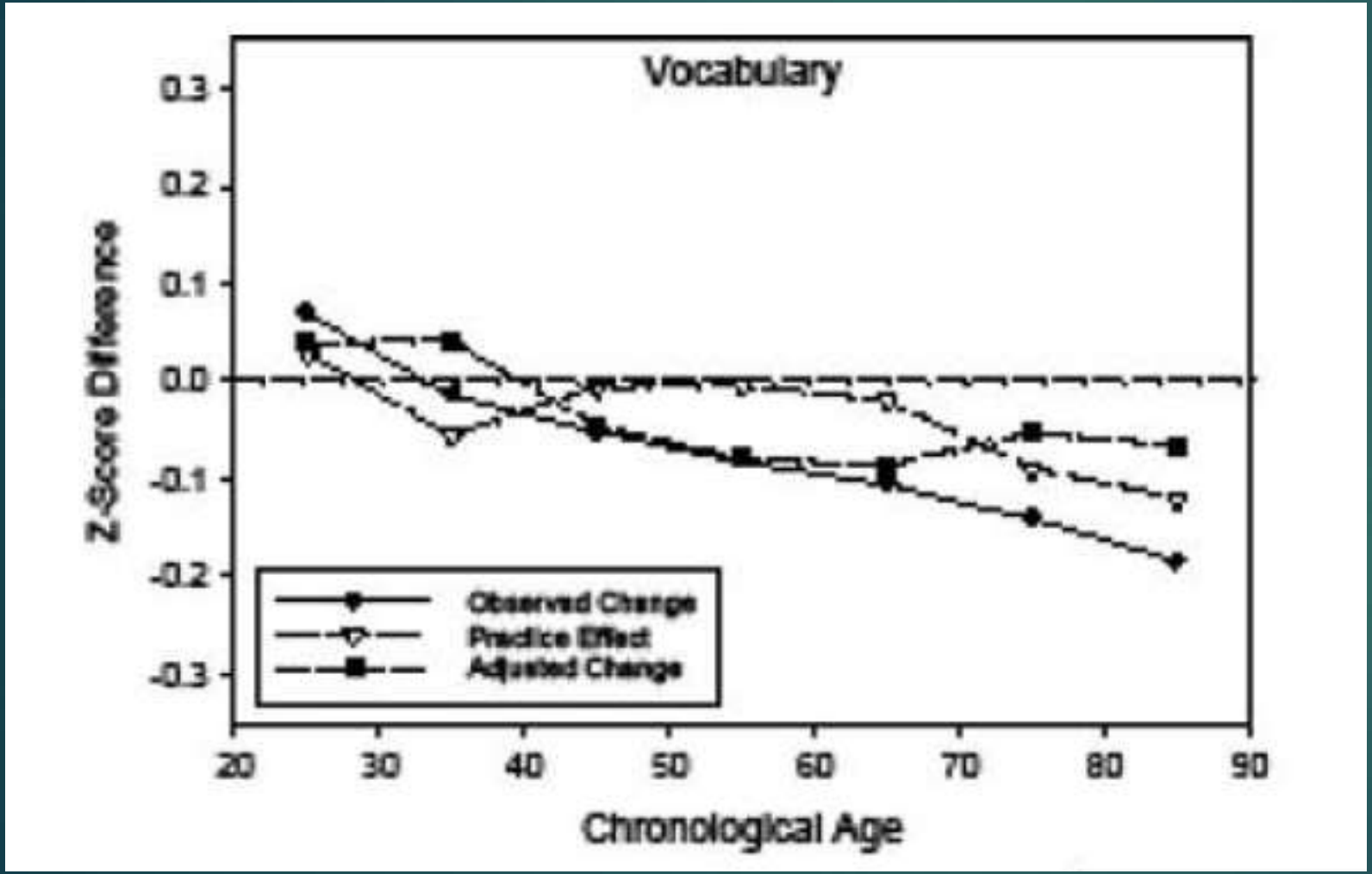
Dr. Vella's Water tank hypothesis of Cognitive Reserve

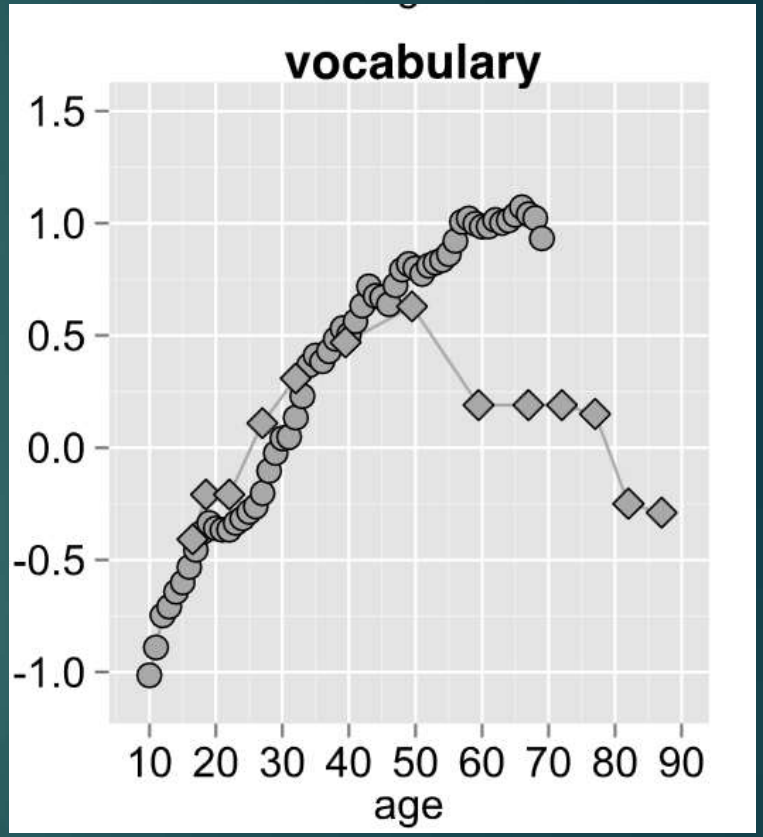
- Think of Cognitive Reserve as amount of water in your water tank
- The better your brain is to start with (due to good genes & early environment & better IQ), the more cognitive reserve you have to lose to neurodegeneration.
- The more you start out with in your tank, the longer it takes to empty it.
- Original brain is 50% of whole amount; your lifestyle choices control the other 50%.

Language ability

- Advise to Post Docs: Do not necessarily believe what pt tells you; all older patients want to leave hospital and therefore lie.
- Many language functions well preserved
- Vocabulary continues to increase (or may decline slightly)
- Word finding declines (longer to search; due to processing speed)
- But all other abilities may be impaired; need to test these.

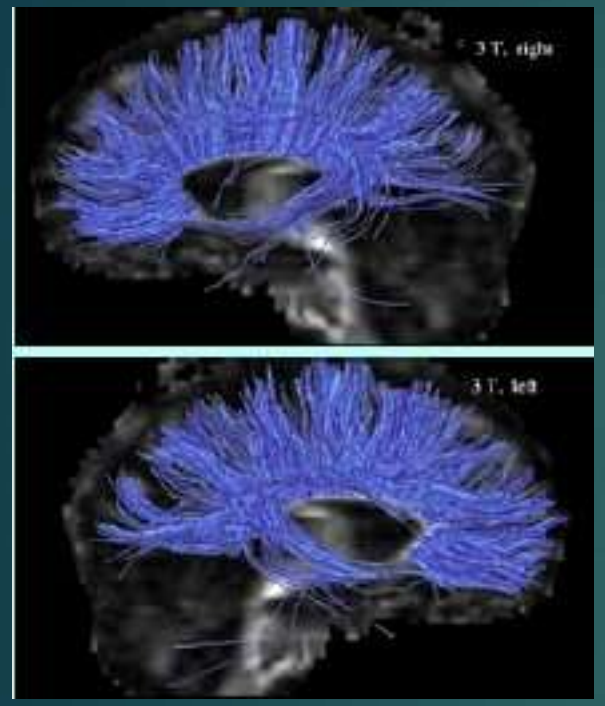
Vocabulary stays relatively intact

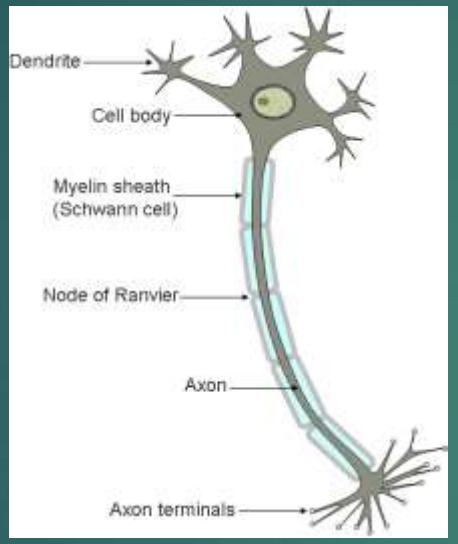


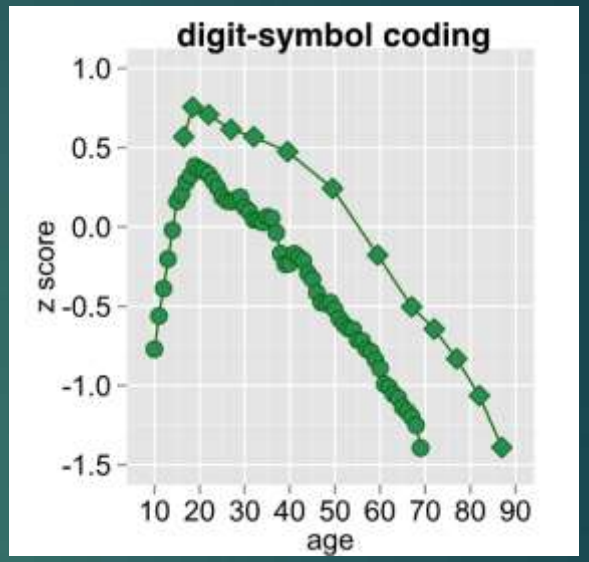


Squares = less than .05 change

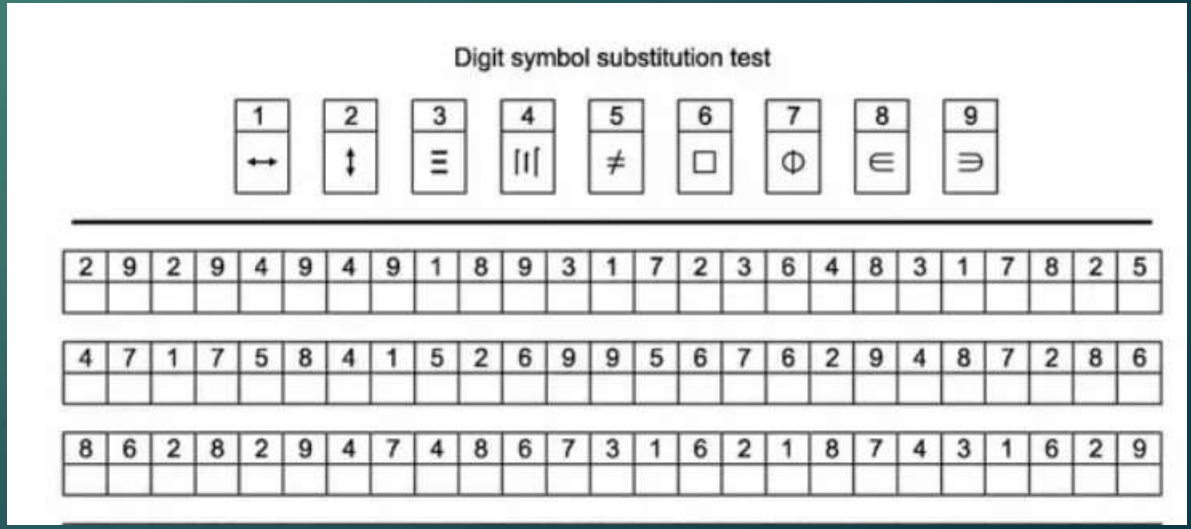
Older are Centrally Slowed: Processing Speed Decreases
(3 ms per decade due to WM decline)



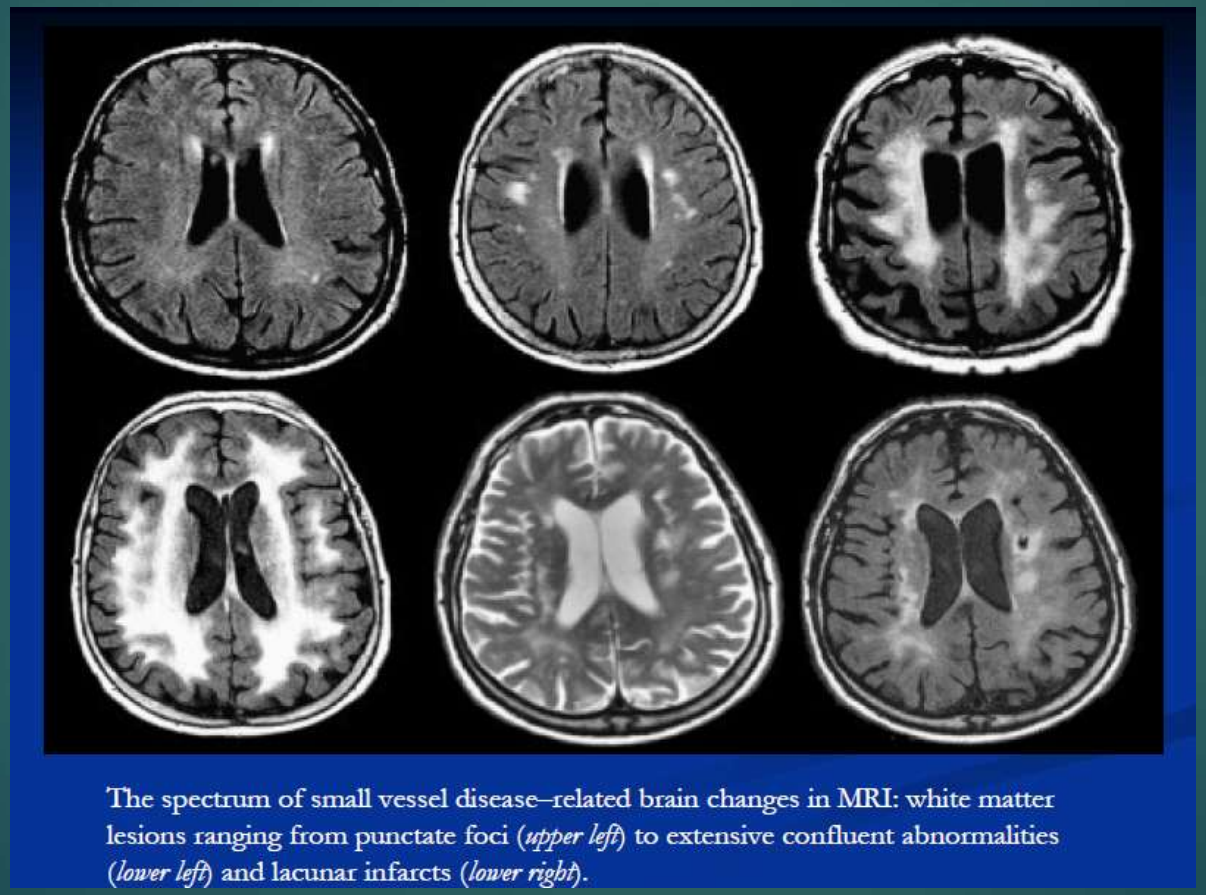




One of reasons naming ability decreases



Mild to Extensive Vascular Hyperintensities (WM damage) = Slower Processing Speed (how fast you think) depends on white matter integrity



The spectrum of small vessel disease–related brain changes in MRI: white matter lesions ranging from punctate foci (*upper left*) to extensive confluent abnormalities (*lower left*) and lacunar infarcts (*lower right*).

Attention

- Attention is like a football team:
  - 1 - need quarterback for focus
  - 2 - a defensive line against distractions.

- As we get older, we lose our defensive line; we become more distractible

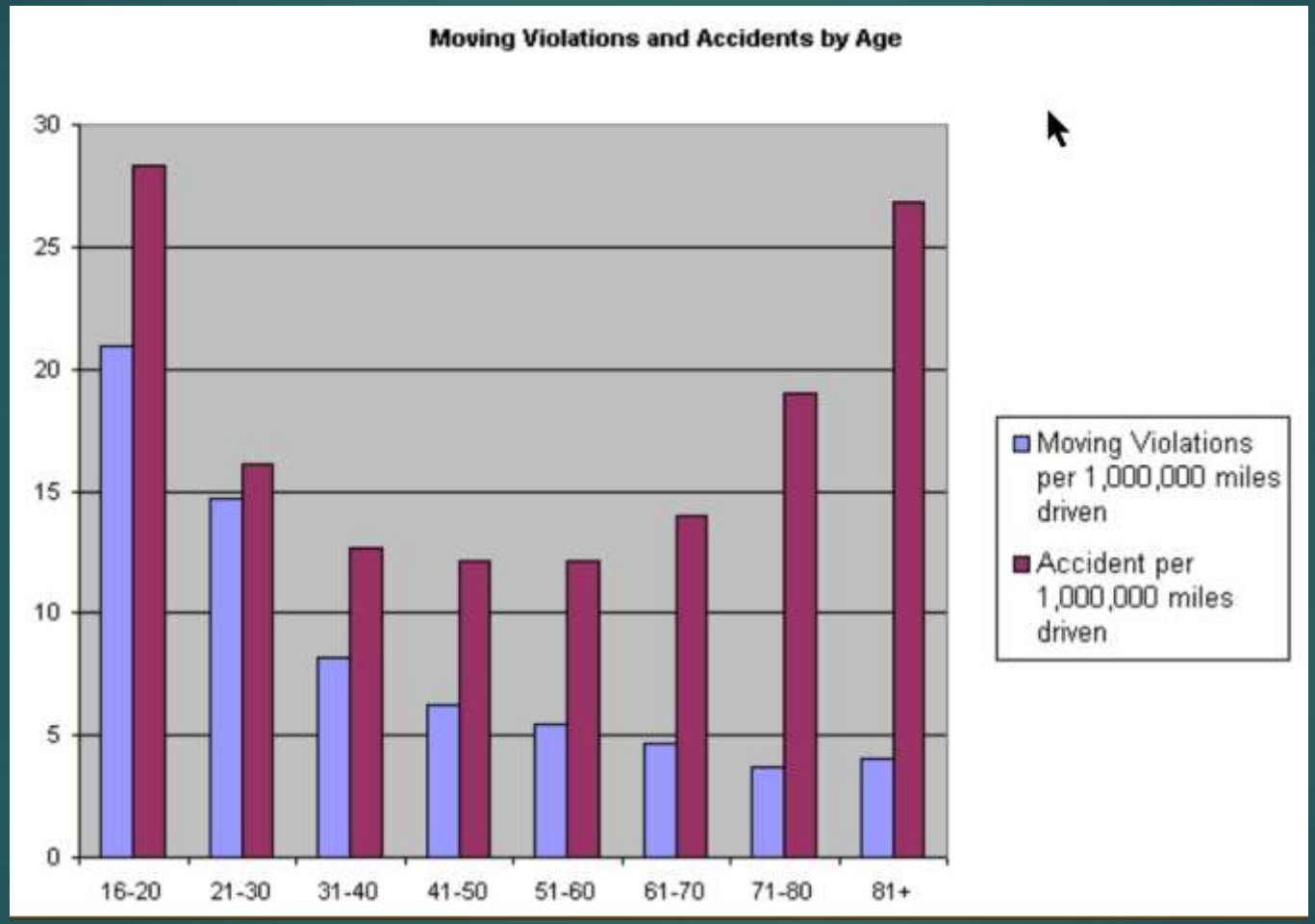
- Older people get age-activated “ADD”

Cautionary tale…

- When I die I want to go peaceably in my sleep, like my grandfather did…

  - Not screaming like the other passengers in his car.

Driving: Seniors have more fatal crashes per miles driven than almost any other age group



But teenagers kill more people in accidents.

Teens: Impulsivity & Alcohol ↑↑

Seniors: Sensory & Processing Speed Declines

Memory: 2 Women

- Two very old friends sitting together
- One says “I feel so embarrassed, but could you tell me your name. I just seem to have forgotten it. I must be getting old.
- Friend answers, “Do you need to know the answer now or can I have a day or two.”

Decline in Spontaneous Verbal Free Recall:

For 1 trial of 16 words:

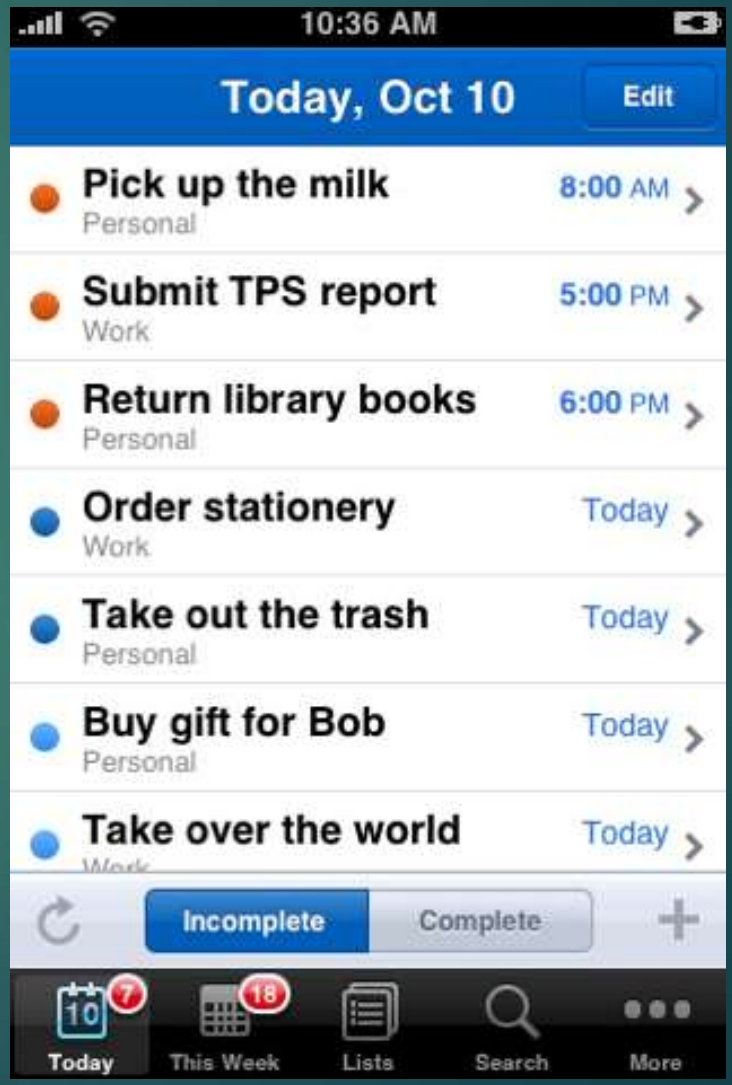
- 12 items recalled at age 20
- 7 items at age 80

Number of items learned in 1 attempt:
We Remember two fewer words every decade past age 40

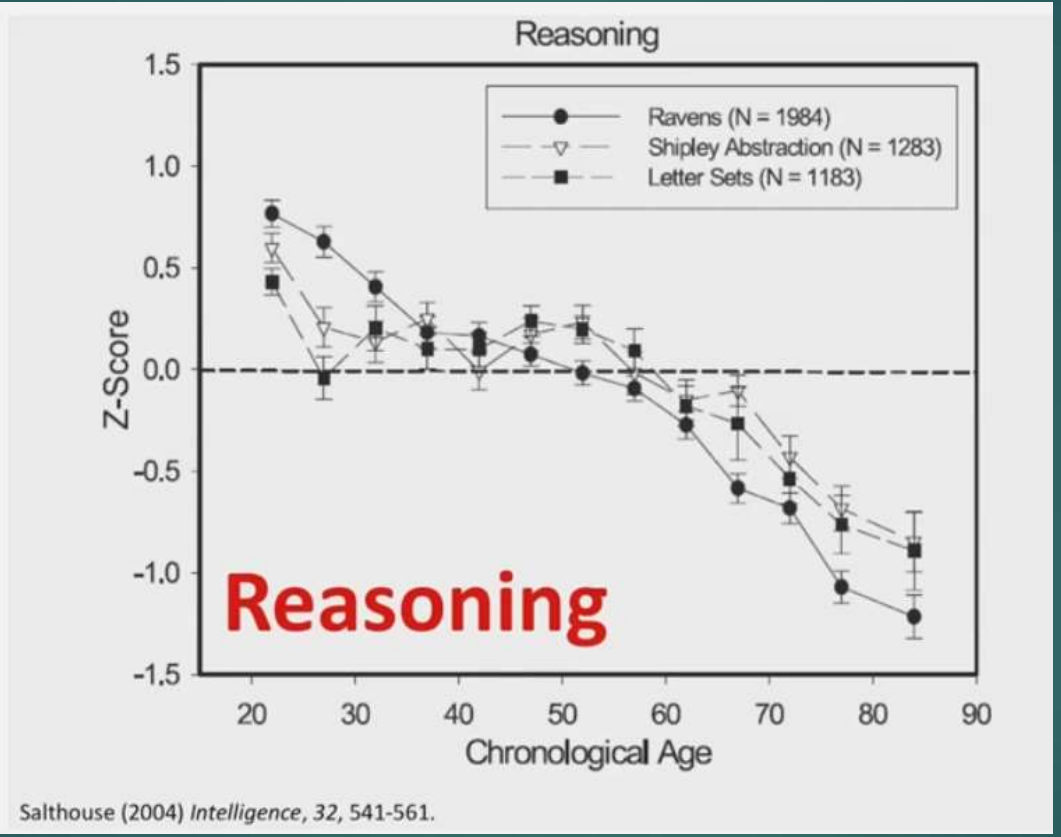
Prospective Memory
remains normal in real world

- Remembering to remember
- Intention

Best predictor of ability to live independently

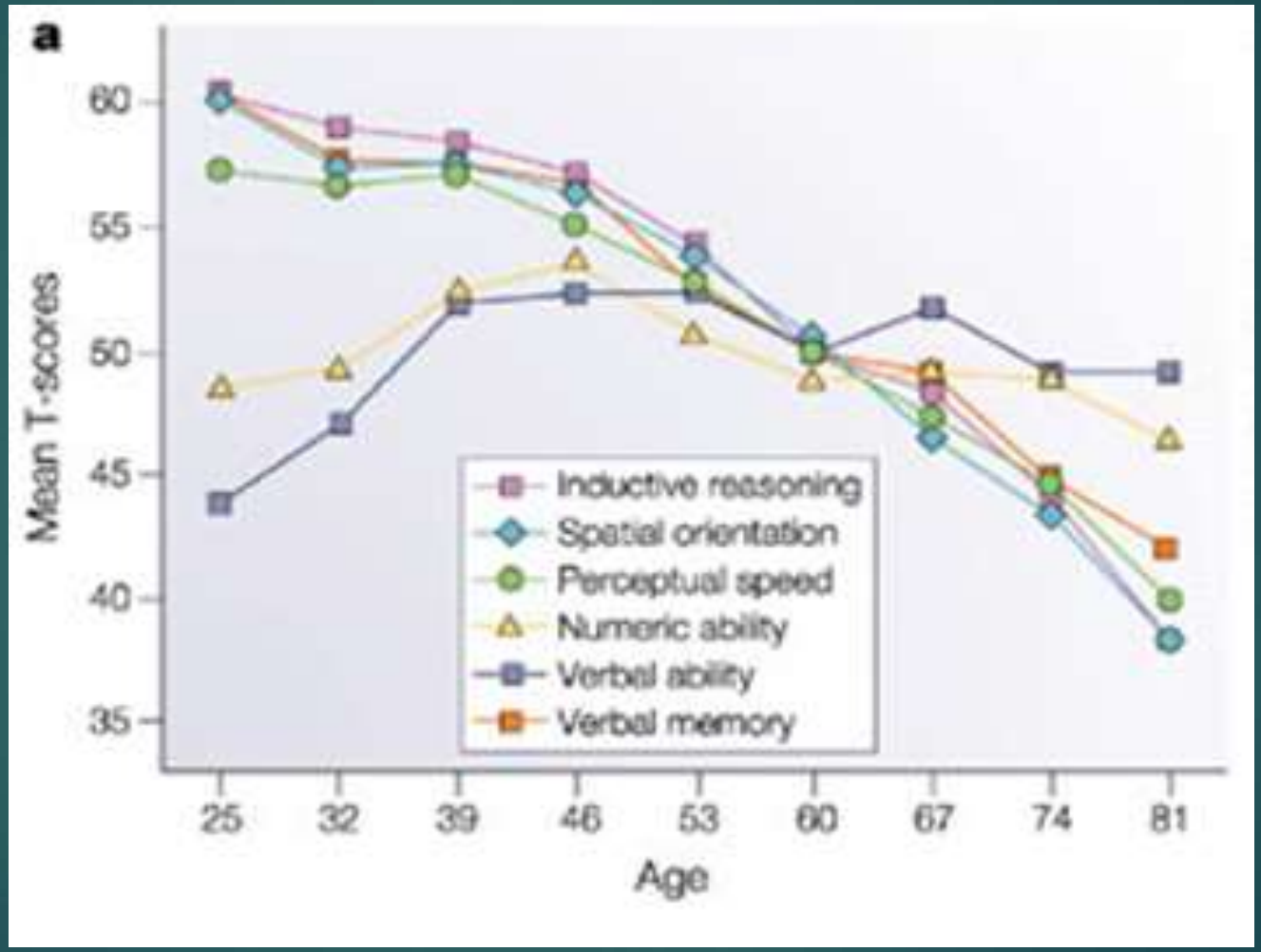


Reasoning/Problem Solving: example =
"What completes this number series: 2-4-6-?"



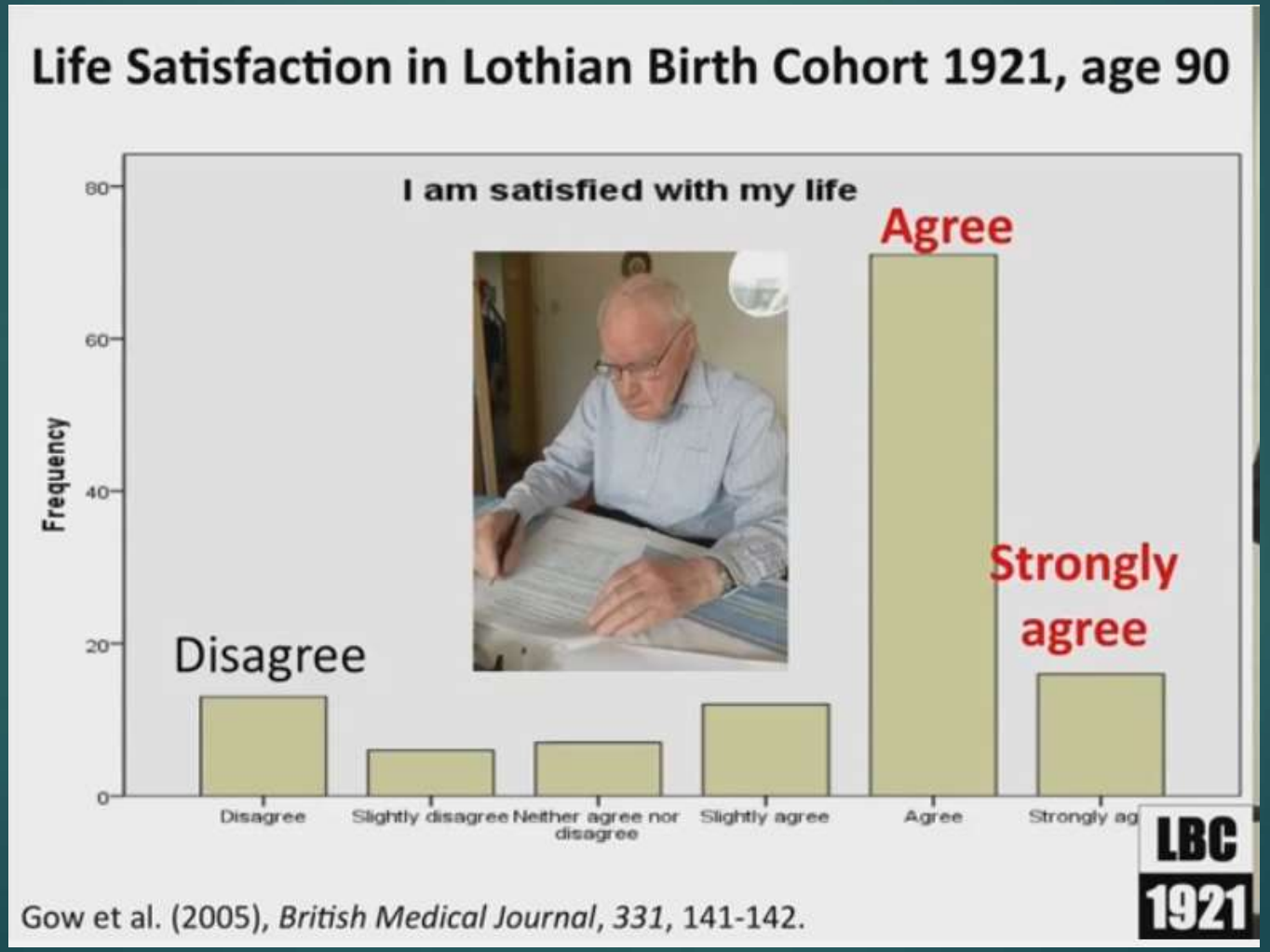
In old age, be prepared to know more than younger people, but not to be as fast in working out new stuff quickly.

Summary of Normal Age Related Decline: Verbal Ability ok vs. All Else ↓↓; but stay functionally independent



Seattle Longitudinal Study; no practice effect correction

Life is not all about cognitive ability: most elderly report being satisfied with their lives



Executive Functioning = Problem Solving

- EF = Applying knowledge toward real world goal directed behavior
- Impairments in EF thus have serious consequences
- Executive functioning examples:
  - Self monitoring behavior
  - Anticipate consequence of action
  - Disregard erroneous strategies
  - Inhibit automatic but inappropriate response
  - Comply with treatment
  - Do something when needed (not just know how to do it)

Executive Dysfunction in Dementia

- Executive ↓ can be independent of Memory ↓
  - Older person with poor EF is more dangerous than one with poor memory

- Neurogenic denial of deficit: Do not know you have a problem ("I can drive; I can live alone")

- Cannot assess risk

Executive Dysfunction in Dementia 2

- Executive dysfunction associated with:
  - Functional decline
  - Increased need for care

- Executive ↓ correlates with decline in independent functioning (inability to use phone, letter, finances, meal prep)

Executive Deficit Predicts:

- Inability to live independently
- Money management decline
- Medication management decline
- Poor geriatric orthopedic & stroke rehabilitation outcome

Senility (or Neurodegeneration) Prayer

- God, Grant me the senility to forget the people I never liked anyway
- The good fortune to run into the ones I do
- And the eyesight to tell the difference.

That Naming Problem:

Inability to come up with a name
is not correlated with memory loss

Naming vs. Memory Recognition

- What is name of this person?
- Princess Diana

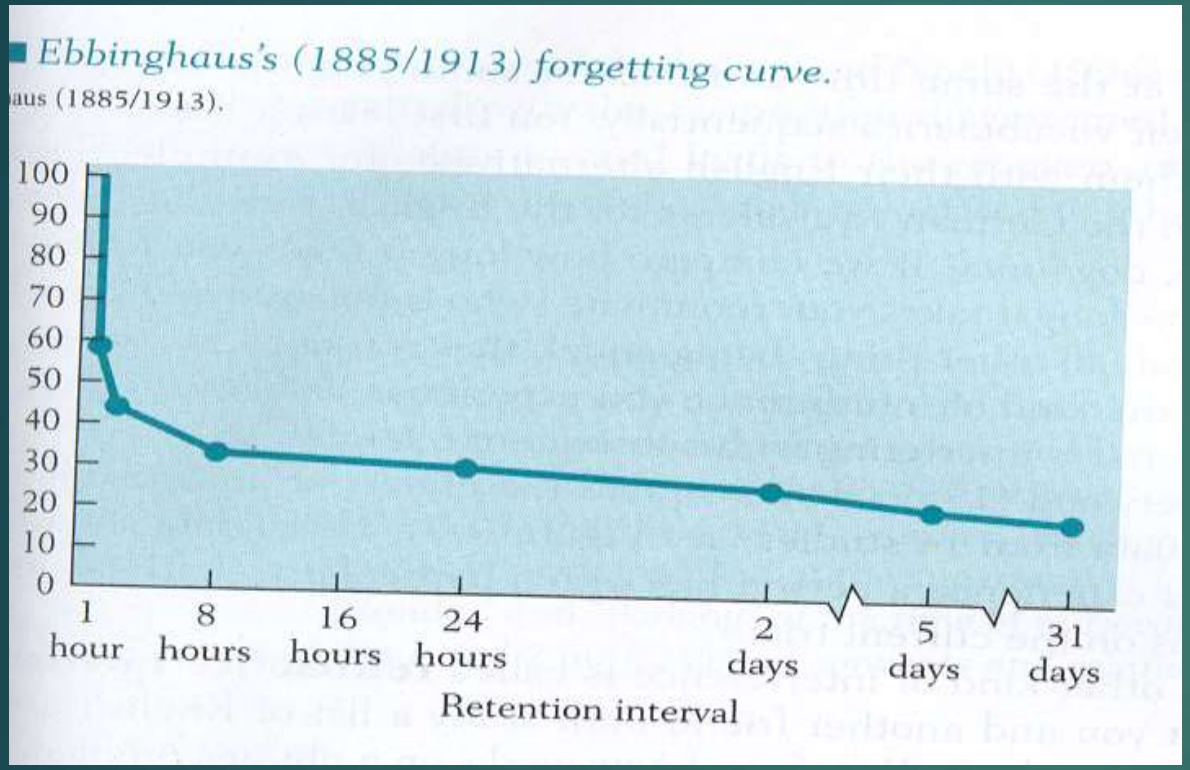
- State several facts about this person
- Married Prince Charles
- Mother of William & Harry
- Died in car crash

The Nature of Memory

Things People Normally Forget

“Forgetting Symptom”	Percentage
Telephone numbers	58%
People’s names	48%
Where car is parked	32%
Lose car keys	31%
Groceries	28%
Reason for entering room	27%
Directions	24%
Appointments	20%

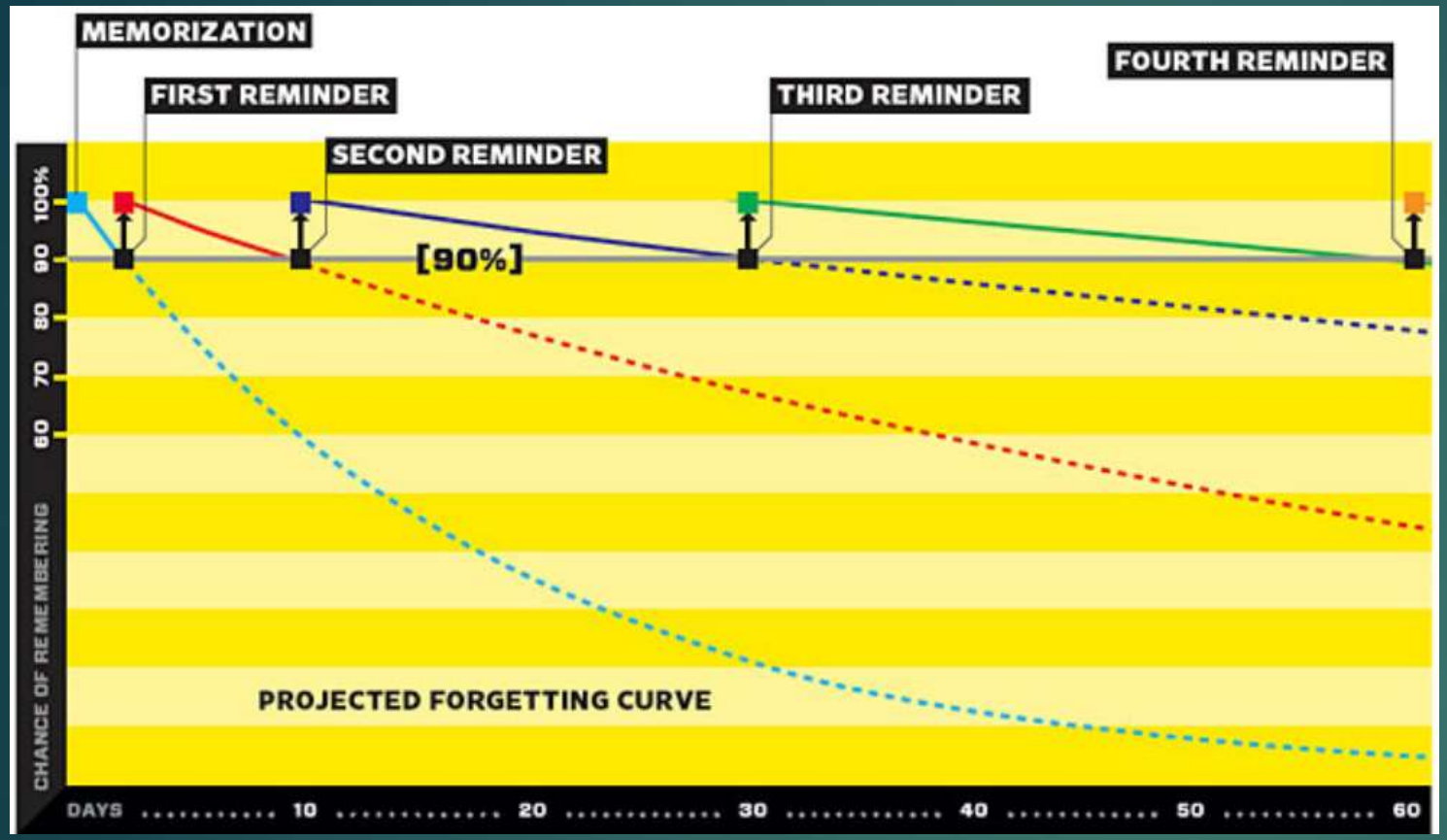
Forgetting Curve:
Time reduces Recall



The Forgetting curve: people forget:
42% after 20 min
56% after one hour,
64% after about 9 hours,
67% after one day,
72% after 2 days,
75% after 6 days
79% after 31 days .

How information is lost over time when there is no attempt to retain it

Tip: Rehearsal is most powerful way to retain memory



Learn 10 new Spanish words:
Repeat today
In 10 Days
In 1 months
In 2 months

= 90% retention

Spacing out repetitions significantly improves retention.

5 Types of Memory

- Explicit (Factual knowledge) Memory - Who is Cleopatra?
- Episodic (Personal) Memory – First person I kissed
- Working (Brief, Temporary) Memory - telephone number
- Prospective Memory - remember to remember later
- Procedural (How to…) Memory – behavioral repetition

Procedural/Behavioral Memory:
Remembering how to…

- Skills, habits: tennis, piano, typing
- Playing a musical instrument
- Playing sports
- Riding a bicycle, driving a car
- Reading mirror-reversed word
- Playing Chess, bridge
- Interpersonal Skills, Therapy behavior
- Longest lasting

Coming Up Next:
Example of Behavioral Memory

- Typewriting skills are behavioral memory

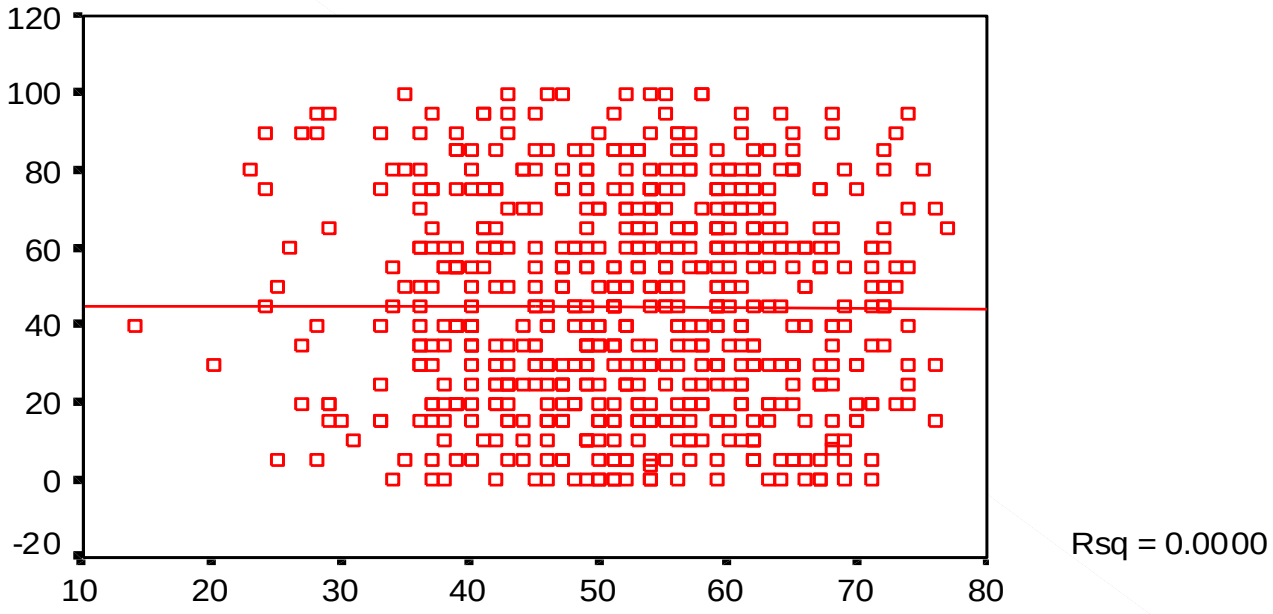
Behavioral Memory

Complaining about memory does not mean you have a memory disorder!

Verbal memory complaints versus

verbal memory test scores

Zero correlation in 995 cases



Green, 2003

Memory Worry

- A memory glitch does not mean you have a memory disorder
- Most memory glitches are attentional issue.
- Most Alzheimer's patients rarely know they have a memory disorder; due to it's insidious onset
- If you or a partner are concerned about your memory, tell your doctor; get tested by a neuropsychologist

Normal Memory vs. Real Memory Deficit Types

- Normal:
- Tape recorder works fine for input & output
- Given 16 new words 5 times, you recall 12 at half an hour
- New & old memories are equally accessible

Encoding Failure: Tape recorder is off

- Tape recorder: no new input or output
- No new memory formation because no new encoding
- Poor spontaneous recall and recognition
- Cueing does not help
- Types: TBI, Alzheimer's, Down’s

Retrieval Failure: Trouble finding your memory

- Tape recorder works fine; output of memories that exist is slower
- Poor spontaneous recall: poor 1-3 items on spontaneous recall,
- Normal recognition (cueing helps)
- Some normals, depression, subcortical Dementias (Korsakoff syndrome, chronic alcohol abuse, Parkinson's, MS, HIV)

Ranking of MOST-FEARED Disabling Disorders – **14 country study**

1st 3rd

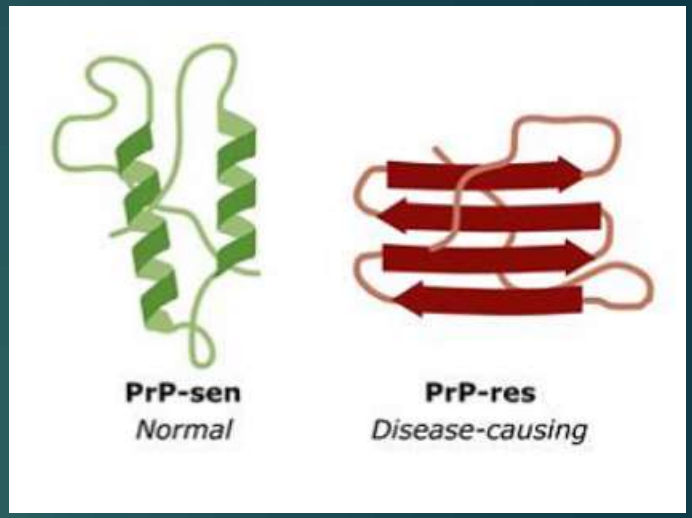
1. Quadriplegia
2. **Dementia**
3. Active psychosis
4. Paraplegia
5. Blindness
6. Major depression
7. Drug dependence
8. HIV infection
9. Alcoholism
10. Total deafness
11. Mild mental retardation
12. Incontinence
13. Below-knee amputation
14. Rheumatoid arthritis
15. Severe migraine
16. Infertility
17. Vitiligo on the face

Bedirhan et al. **Lancet** vol 354, 111-115, 1999

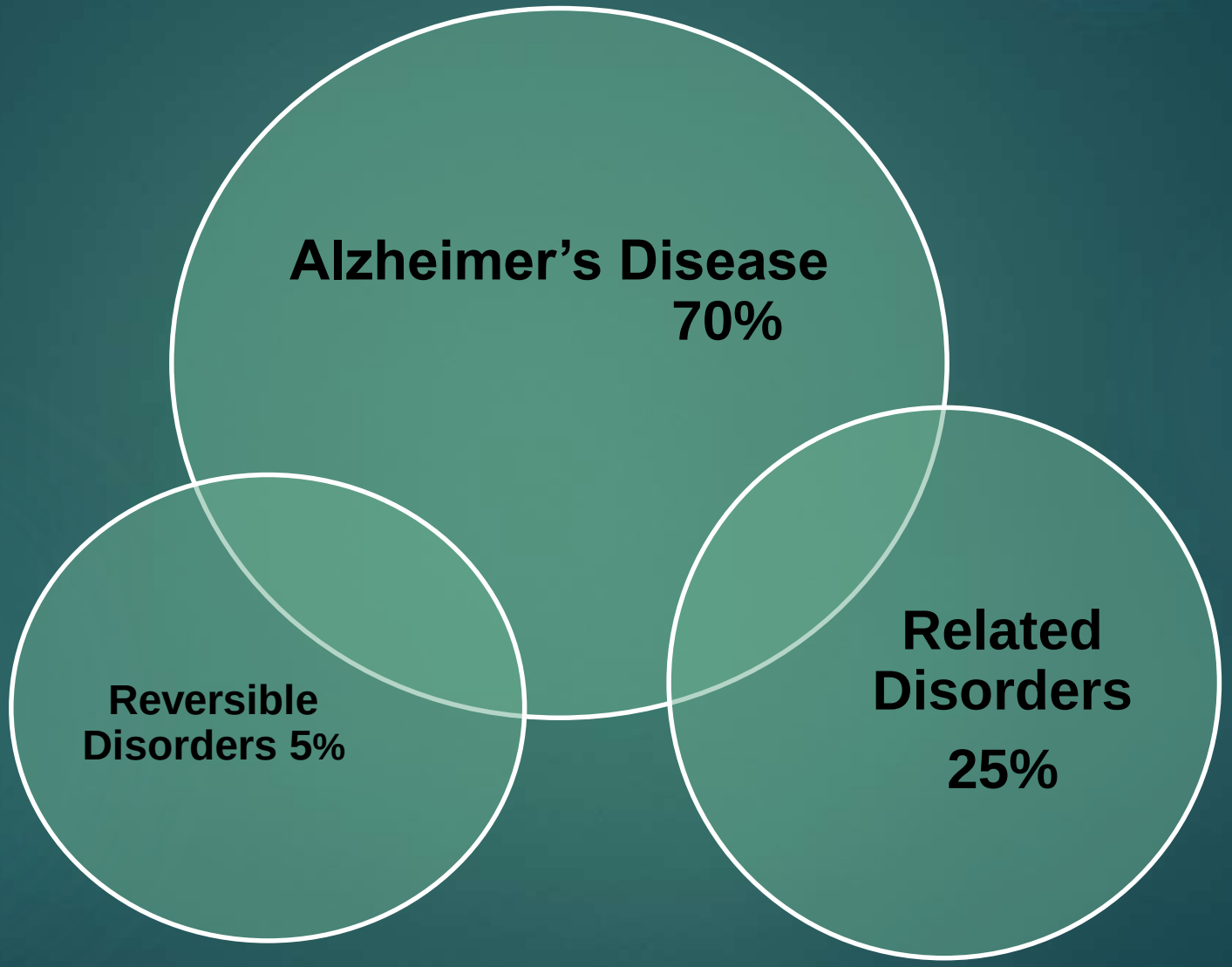
Neurodegenerative Diseases

- Most NDs are abnormal protein folding disorders: AD, PD, Huntington's ALS, Prion, CTE

- By 2040, ND will be 2nd most common cause of death in developing world



Causes of Dementia



Mild Cognitive Impairment

- Significant cognitive decline that show up on MS tests
- Not severe enough to affect ability to live independently
- Increases risk of developing Alzheimer’s disease

Difference between Mild NCD vs. normal aging

- Misplacing things and word/name recall difficulty is probably normal
- No correlation between naming deficit & episodic memory deficit
- Mild NCD: forget more important info (appts, phone conversations, recent events); noticeable to people close to patient
- Rule out depression, medication effects

Dr. Alois Alzheimer, 1864-1915:

1901: First diagnosed patient with Alzheimer's, Auguste Deter.

Auguste Deter

Her brain

51 y.o. woman; 1st sx of pathological jealousy of husband,
"I have lost myself," then rapid decline with amnesia

What is Alzheimer’s disease?

- is a neurodegenerative brain disease
- It is progressive
- is the most common form of dementia
- has no cure
- is eventually fatal
- has been diagnosed every 70 seconds;
- over 5 million Americans have it
- 50% do not know they have it

Neurodegenerative Disorders

- All have abnormal protein aggregate that kills cells
- All have rare genetic and more common sporadic (unknown reason) forms
- All have
  - Preclinical, no symptom, phase
  - Early symptom phase, i.e. mild NCD
  - Symptomatic phase, i.e. Dementia/major NCD
- NDs do not come in pure form
  - Most have both Vascular & Alzheimer’s
  - Parkinson's develop AD features and vice versa

Two types of genetic AD (early vs. late onset AD)

- Age related, late-onset AD (> age 65)
  - 90% of all AD; female>male
  - slower progression
  - memory, visualspatial and language deficits
  - functional deficits present later
  - higher frequency of ApoE-e4 alleles in late onset

- Rare Familial/genetic, early-onset AD (< age 65)
  - more severe pathology
  - faster progression
  - apraxia, language and attention deficits
  - early on, memory is relatively preserved
  - functional deficits earlier
  - earlier the dementia in a family, more likely to inherit

Molecular Bases of Major Neurodegenerative Diseases

Type	Molecule/Abnormal Proteins
Alzheimer's	AB42, Tau
FTD	Ubiquitin, Tau, TDP-43
ALS	Ubiquitin inclusion, TDP-43
Parkinson's	a-synuclein
Huntington's	Intranuclear inclusion, Huntington's protein
JCD	Prion, spongiosus
CTE	Tau, TDP-43

Most common first symptom of 5 neurodegenerative disorders

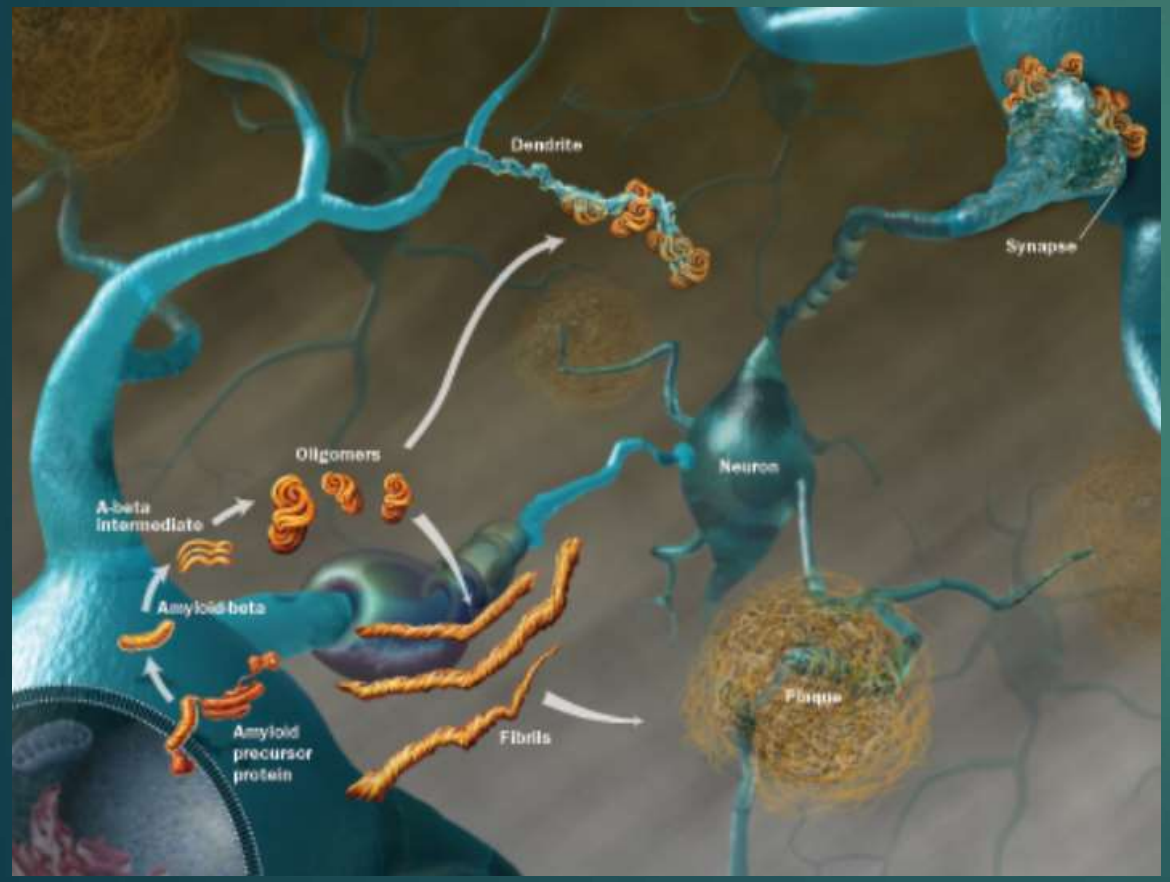
- AD = No new memory encoding; no new learning
- PD = motor deficit
- LBD = visual hallucination
- VD = hypoperfusion; stroke
- FTD = impaired social behavior or language deficit

Rush Study:

Mixed diseases are the most common cause of dementia.

- People clinically diagnosed with AD have pathologically mixed disorders (AD + VD+ LBD).
- 37% with no cognitive decline/dementia had significant AD disease
- 41% had cognitive decline and no ND brain disease

Current AD Concept: A BA driven tauopathy: BA loads the gun & pulls the trigger, and Tau is the bullet; abnormal protein Beta Amyloid between cells & Tau inside cells



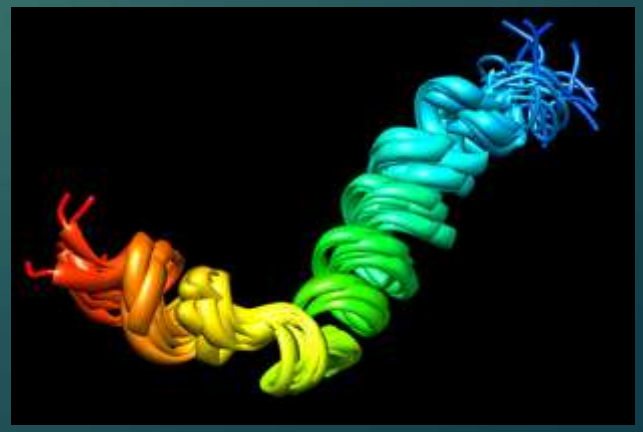
Amyloid hypothesis:

1 - a build-up of BA plaques causes inflammation in the brain,

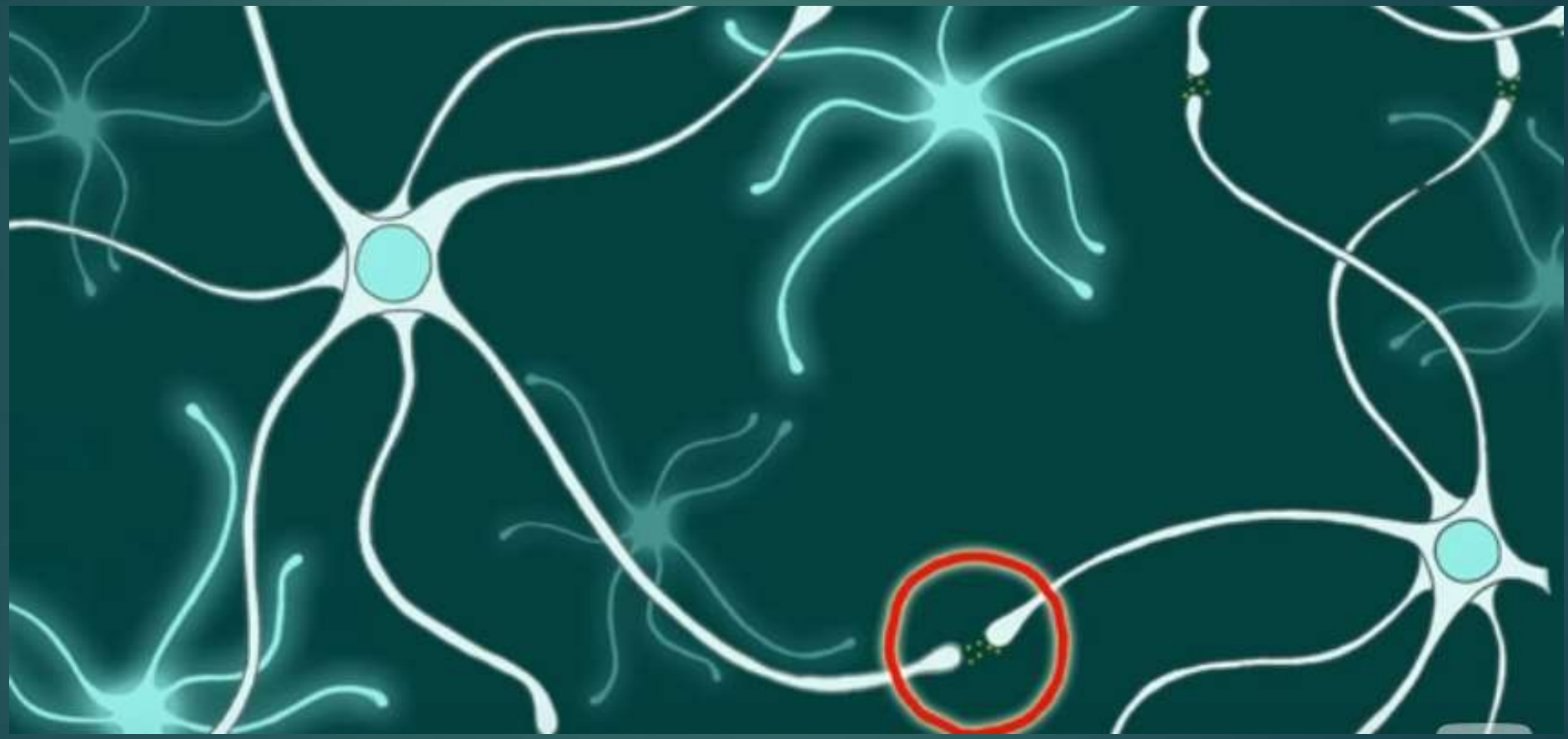
2 - which spurs increase in Tau,

3 - which disables and then kills brain cells,

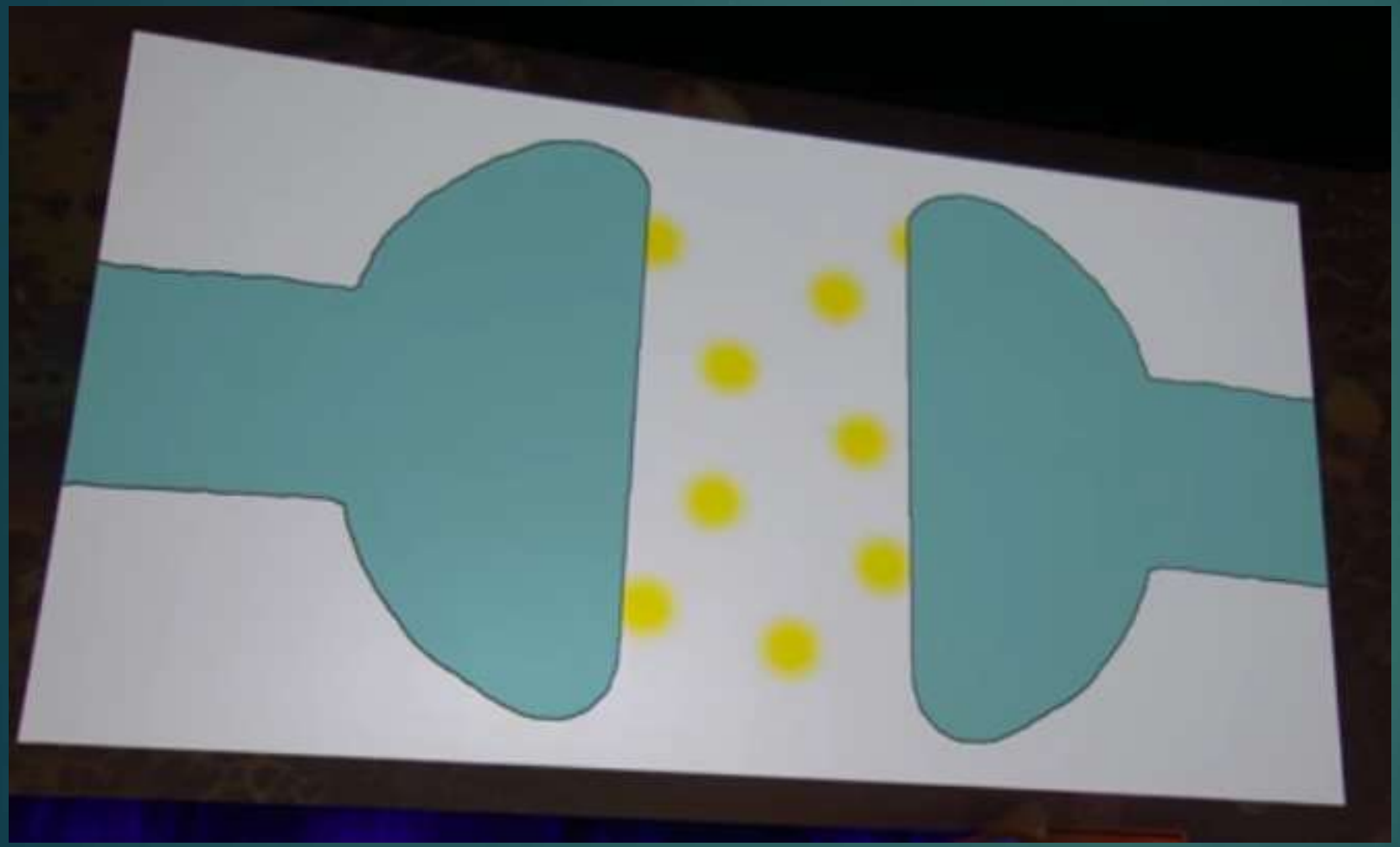
4 - resulting in cognitive decline.

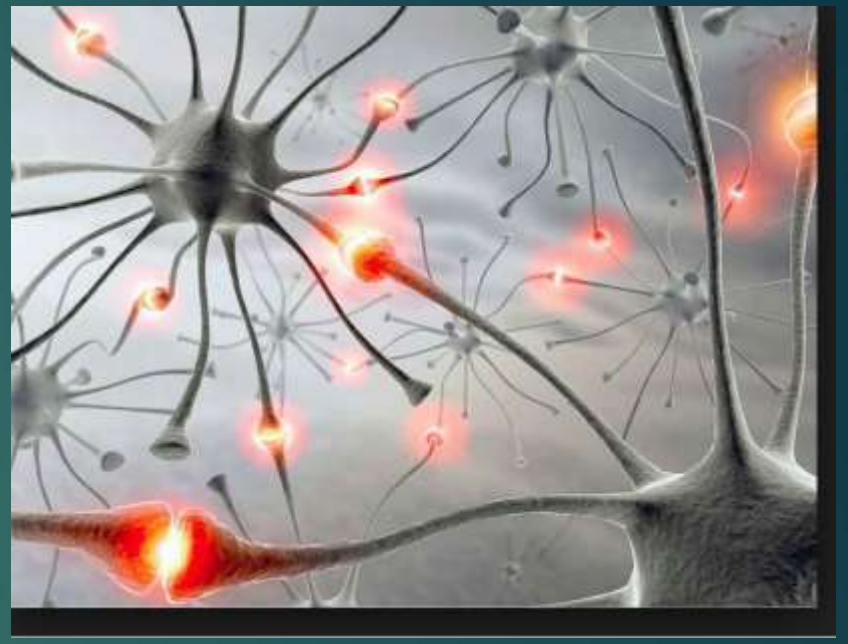


Synapse: connection between neurons, site of neurochemical communication (how brain cells communicate)

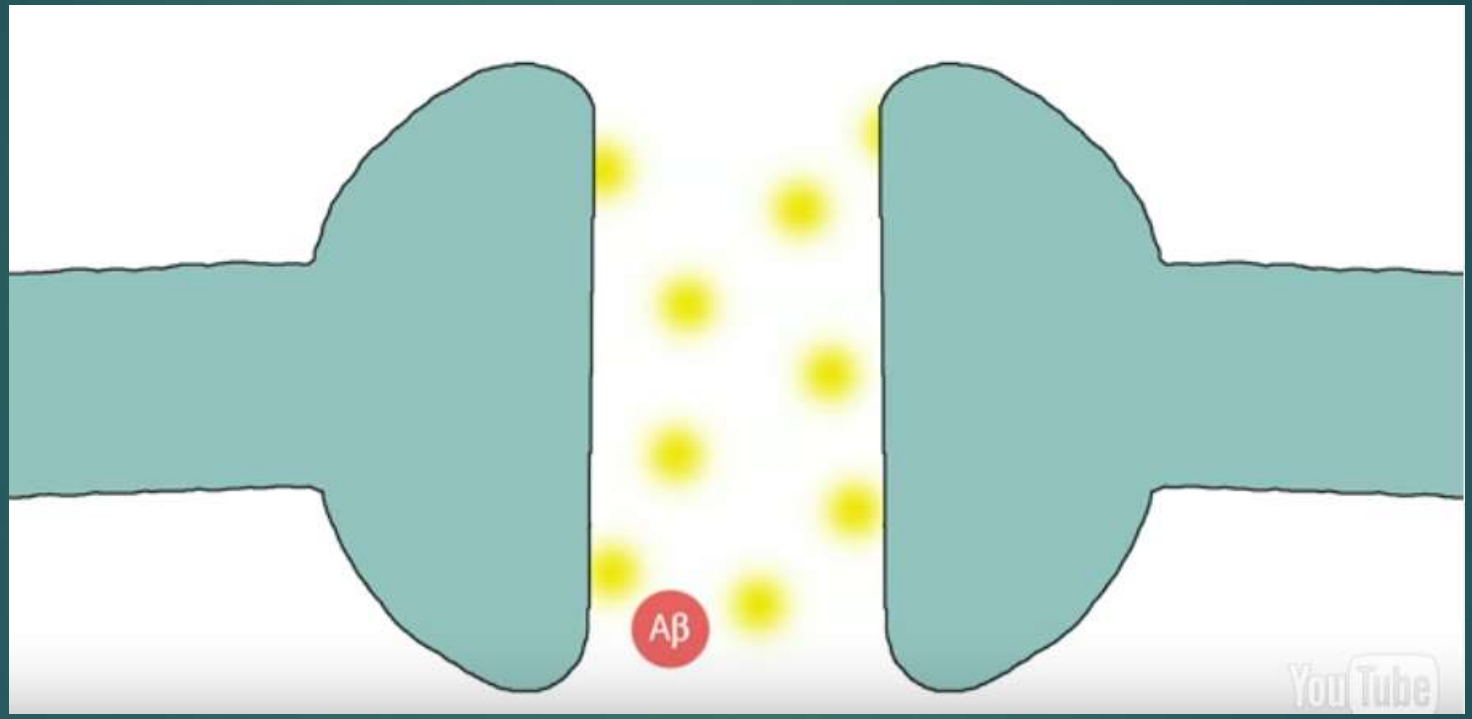


Synapse: transmission of chemical neurotransmitters

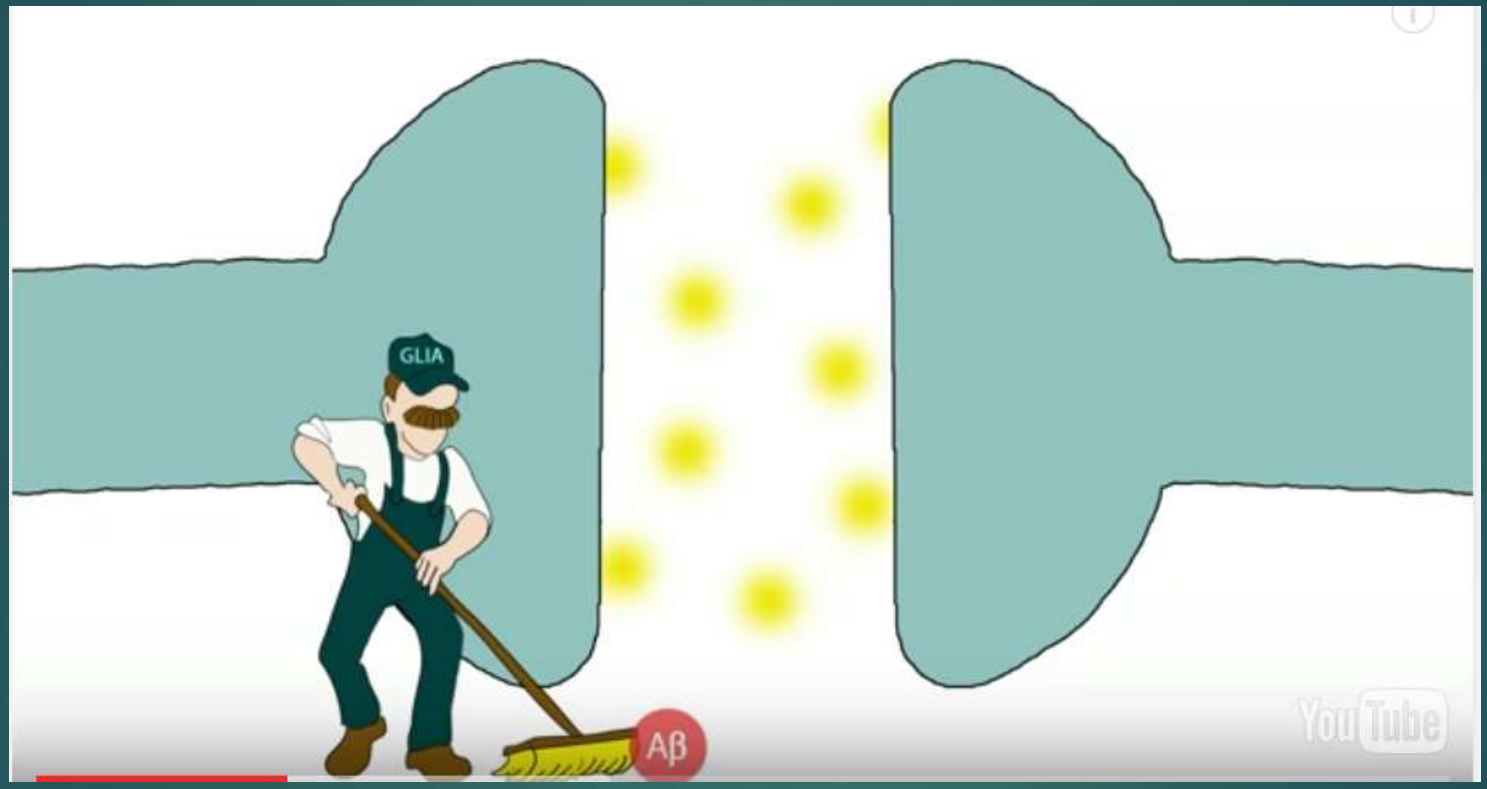




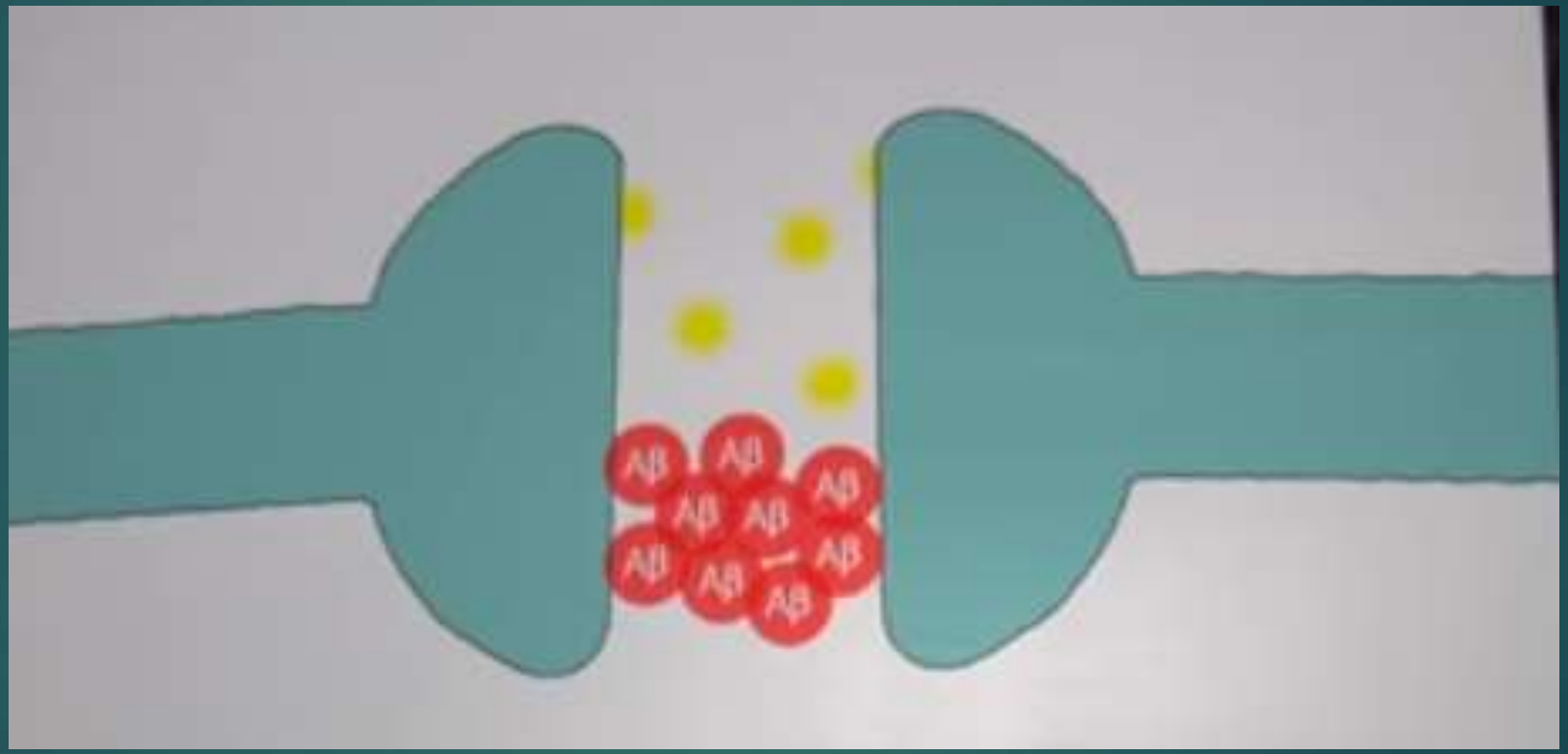
Synaptic transmission of neurotransmitters, including abnormal peptide Beta amyloid



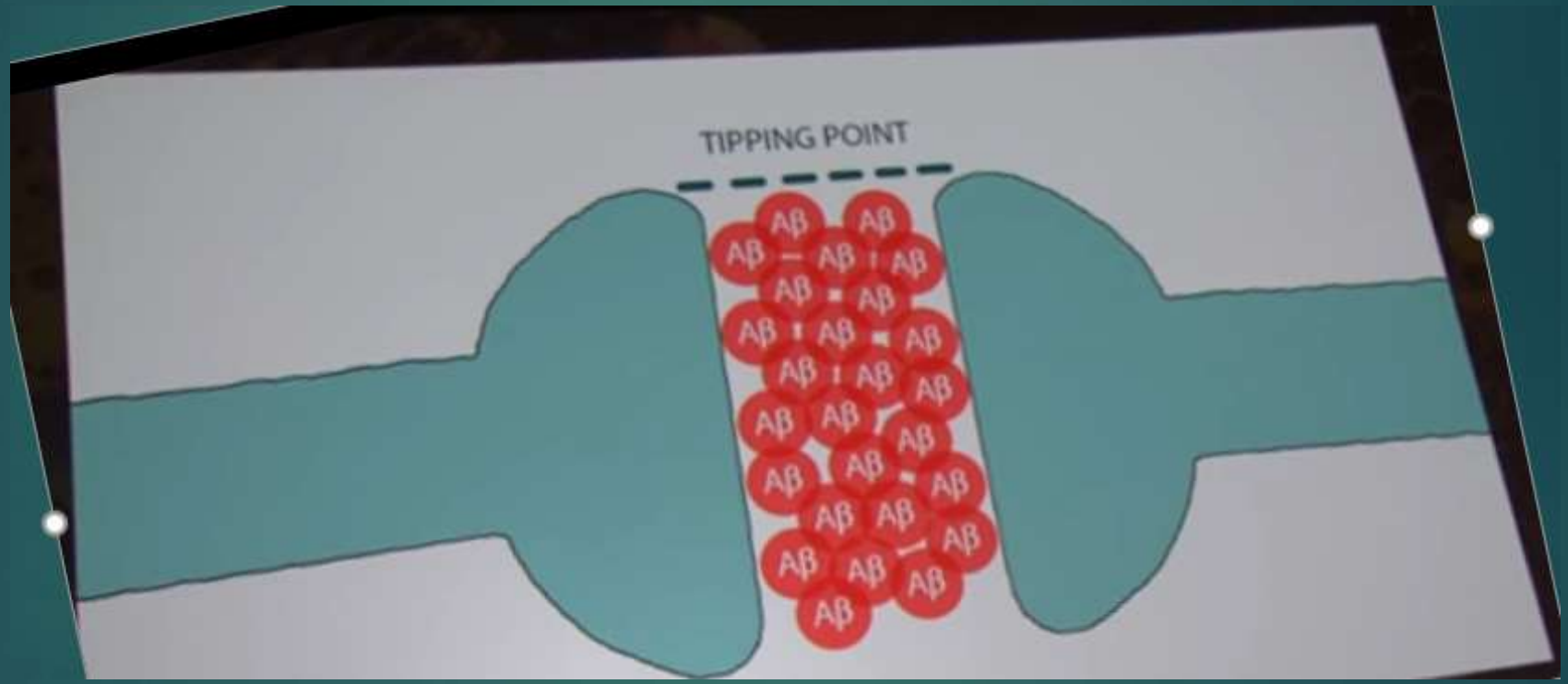
Normally microglia clear away excess Beta Amyloid (during late night deep sleep)



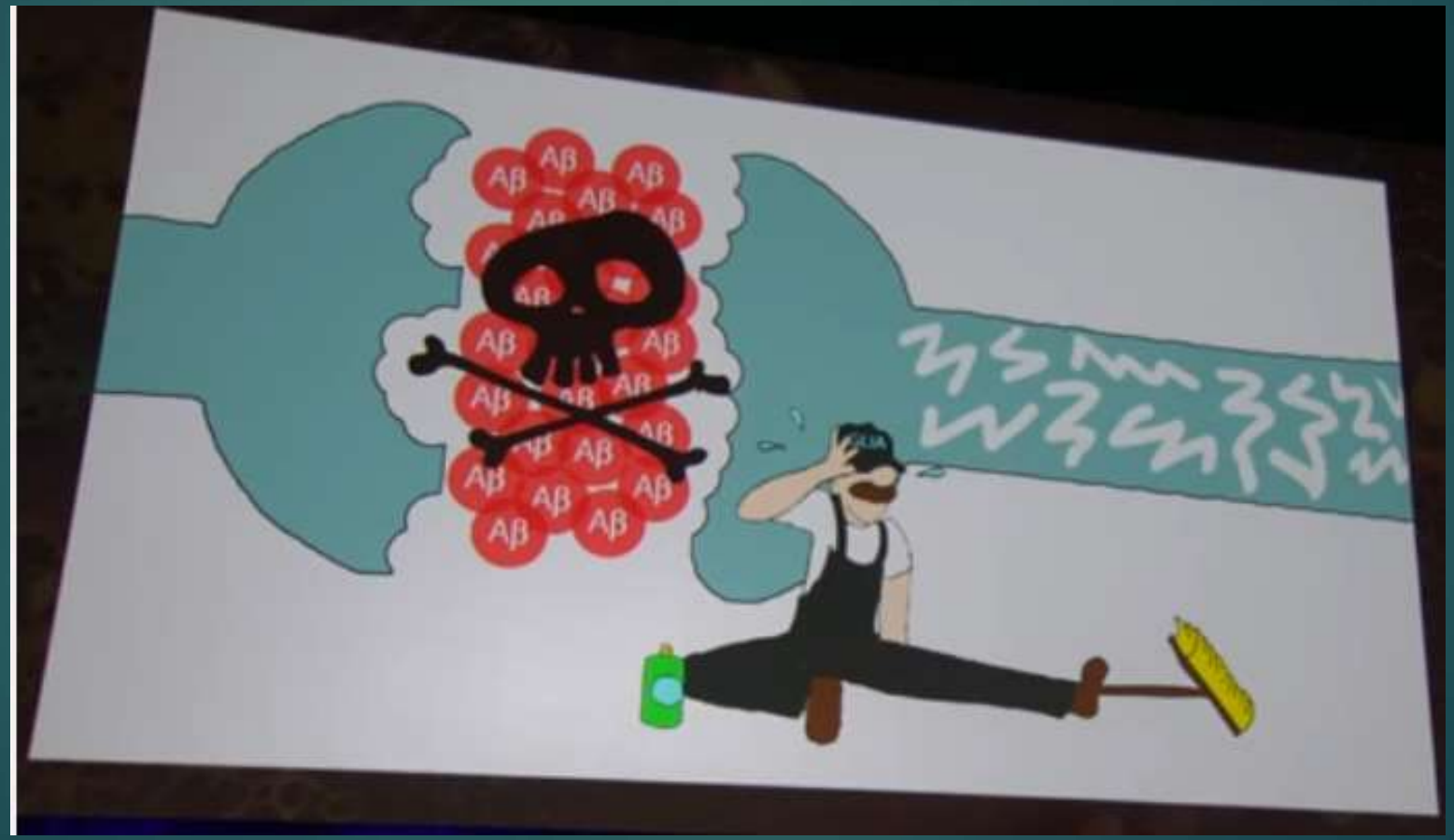
AD is triggered when there is too much abnormal BA; these combine into a sticky mass called a plaque which is toxic; by age 40, 50% of us have these plaques



Takes 15-20 years before BA amount reaches a tipping point which triggers a molecular cascade that creates cognitive symptoms



After tipping point, microglia janitor cells go into overdrive, creating inflammation and cellular damage, & begin to clear away synapses; trigger tau protein to beginning killing cells



New Treatment strategy

- Develop medications that reduce BA before the tipping point happens
- If BA where a match, it can light a forest fire in your brain killing many of your brain cells
- We need to blow out match, before forest fire occurs

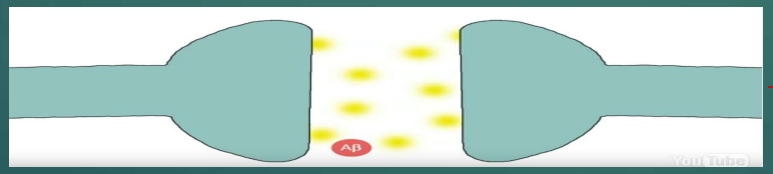
With more Cognitive Reserve, will still have some functioning synapses in brain's fight against Beta Amyloid

Neuropsychologist

Worked for Kaiser

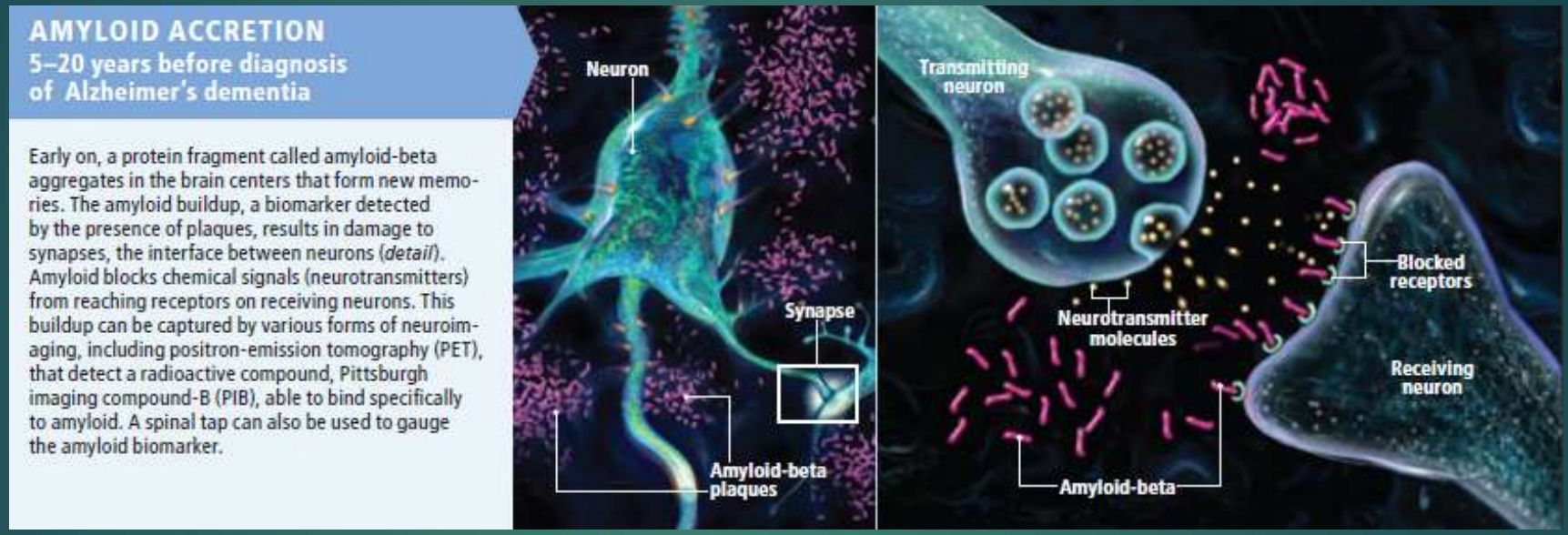
Pumpkin Carver

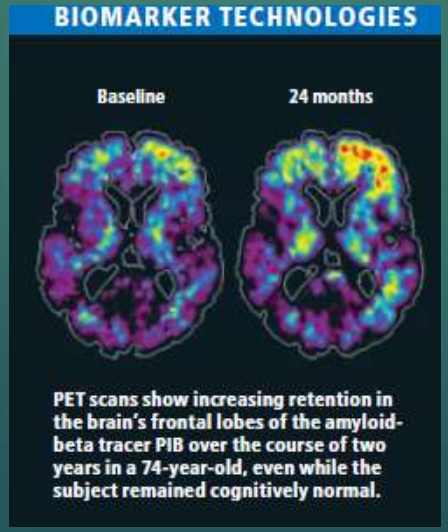
Docent at Academy of Science



Dr. Charles Vella's name

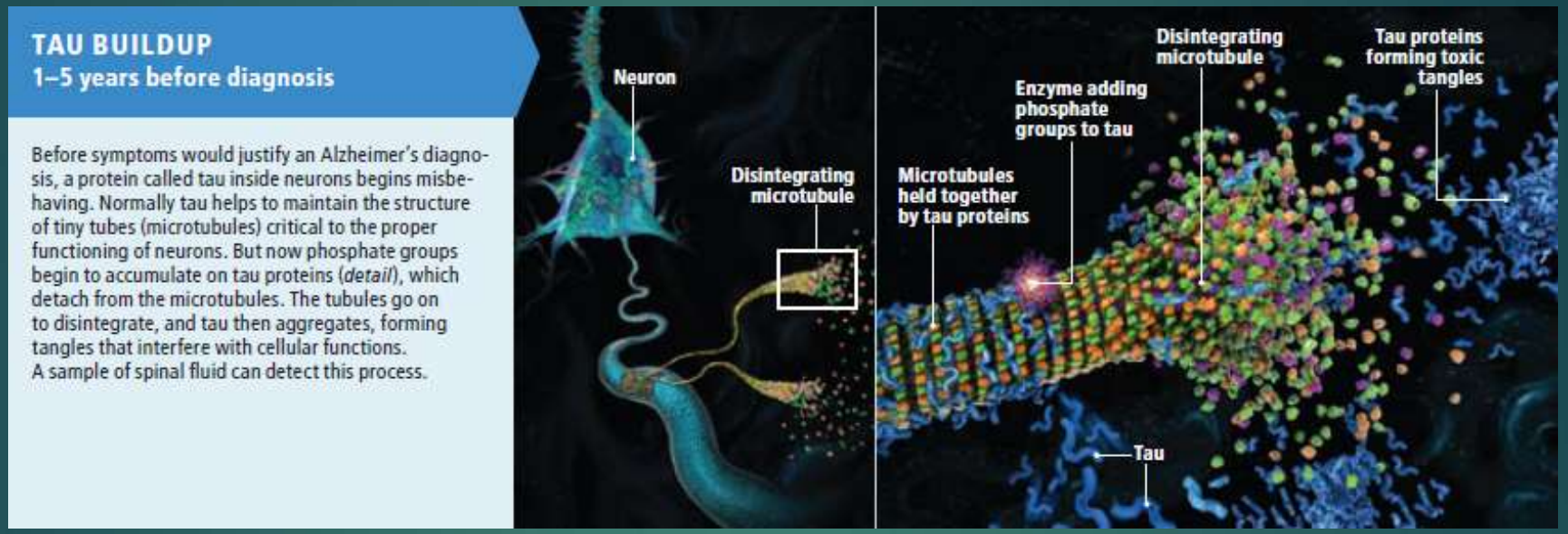
Step 1: Increasing amounts of Beta Amyloid starting 5-20 years before diagnosis

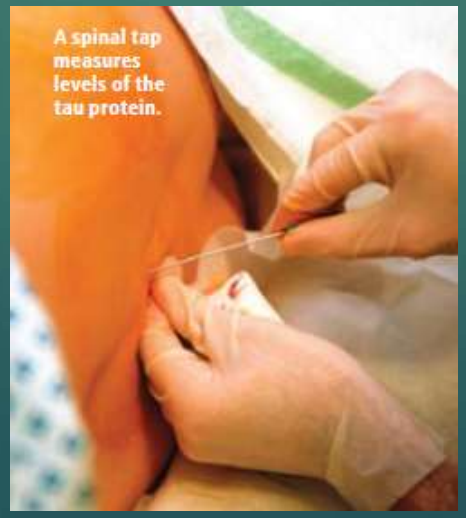




Scientific American, June 2010

Step Two: Tau Buildup – 1-5 years before

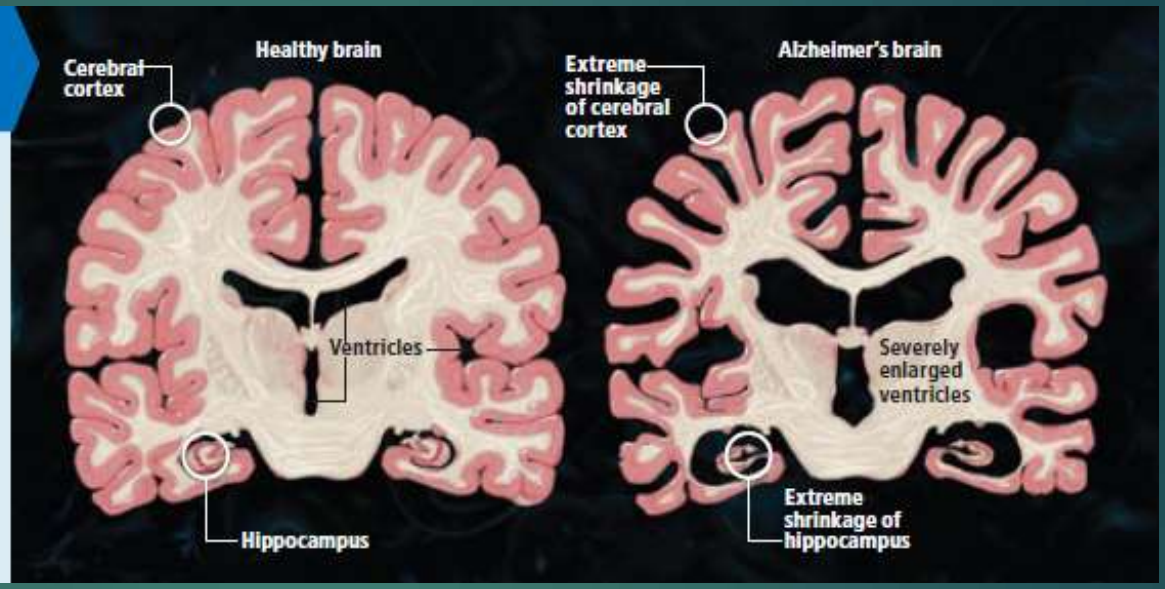


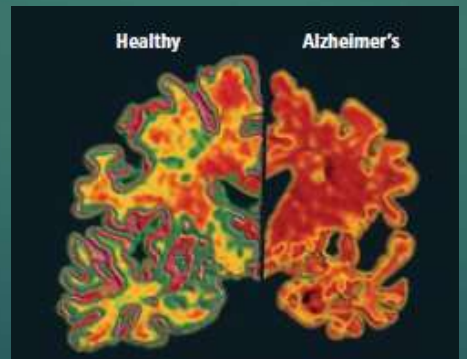


Step Three: Atrophy (Neuron death)

BRAIN SHRINKAGE
1–3 years before diagnosis

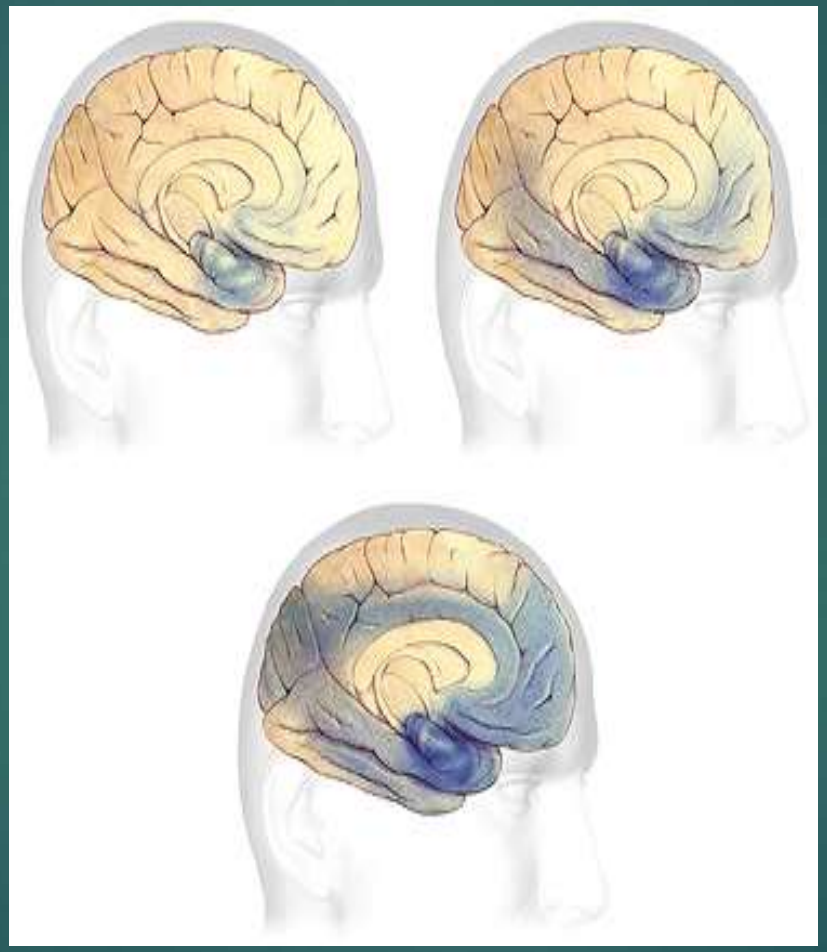
As the underlying disease process advances, nerve cells start to die, and patients and family notice memory and other cognitive lapses. Cell death shrinks the brain in areas that involve memory (the hippocampus) and higher-level brain functions (the cortex) and thus can be tracked with a form of magnetic resonance imaging that measures brain volume. Such shrinkage accelerates and ultimately involves many areas of the brain.





Computer graphic of slices through a normal brain and an Alzheimer's brain, derived from volumetric magnetic resonance imaging, shows considerable shrinkage (*right*) from degeneration and death of nerve cells.

AD Progression



In the presence of Aβ pathology, Nucleus Basalis of Meynert degeneration led to EC degeneration, which triggered memory problems.

Stages of AD

- Early Stage
  - Recent memory loss
  - Difficulty managing money, driving, or handling social situations
- Middle Stage
  - Difficulty with language
  - Problems keeping track of personal items
  - May need help with grooming
- Late Stage
  - Long- and short-term memory affected
  - Needs care around the clock

DSM5: Major Neurocognitive Disorder/Dementia

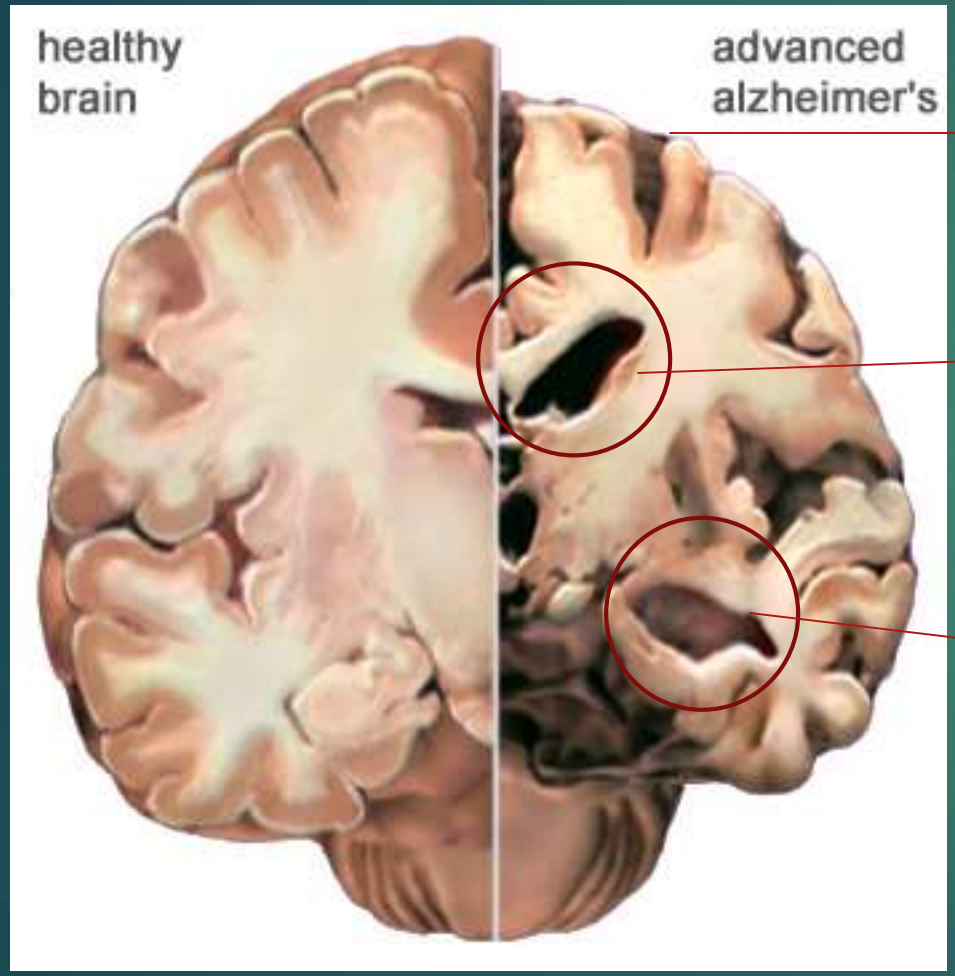
1. Evidence of significant cognitive decline from prior level of performance in 1 or more cognitive domains
    1. Concern of person, informant, or clinician of a significant cognitive decline
    2. Significant cognitive impairment on NP testing (-2 s.d. (below 3rd %tile)
2. ** Deficits interfere in independence in everyday activities

NCD due to Alzheimer's Disease

- Fatal, progressive, age-related, irreversible, insidious loss of cognitive ability

- Specify: 80% of dementia due to AD have behavioral disturbance in Moderate Major NCD: psychotic, irritability, agitation, wandering common; sudden development of belief that someone is stealing from them.

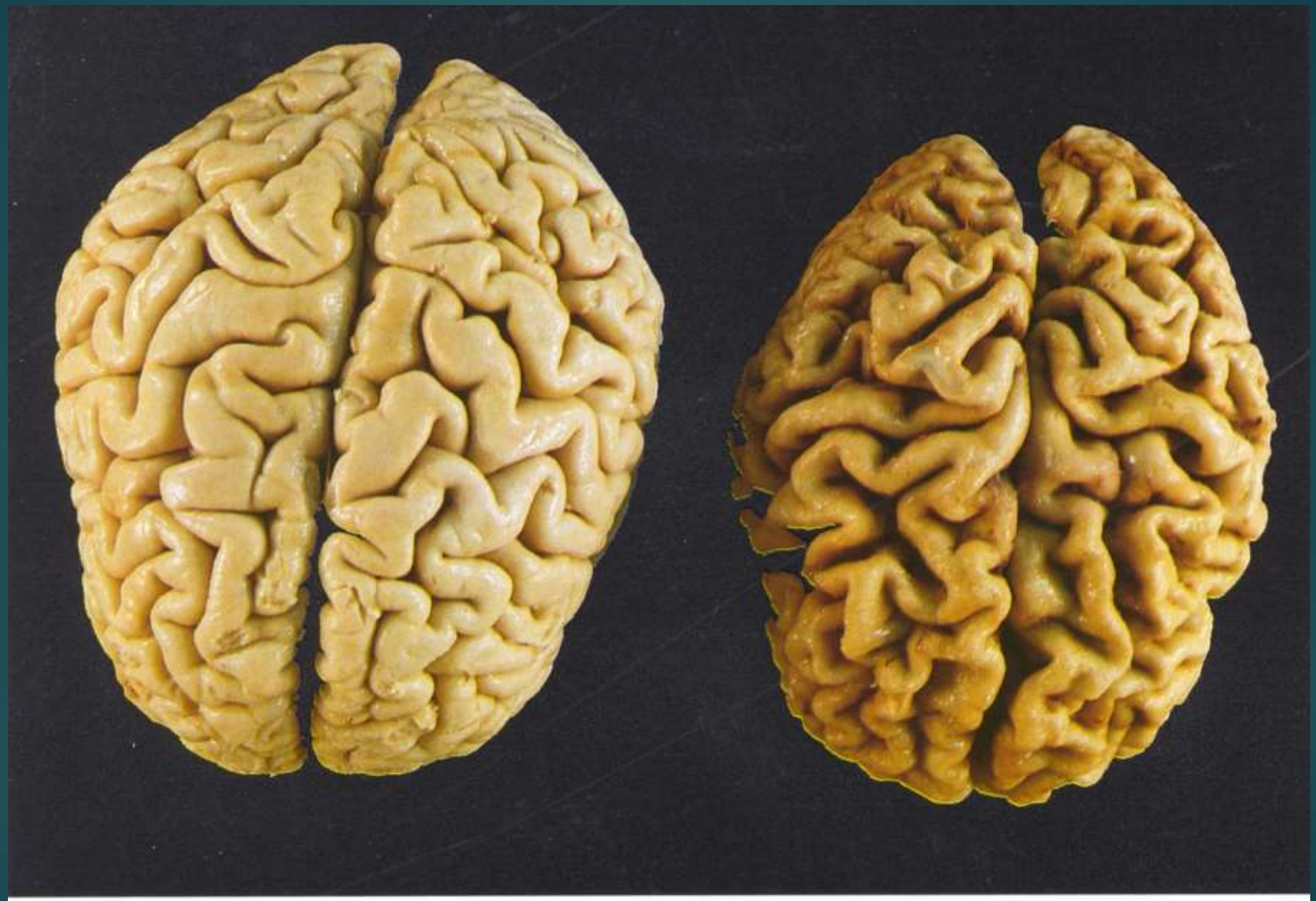
Neuropathology of Alzheimer’s: What goes wrong

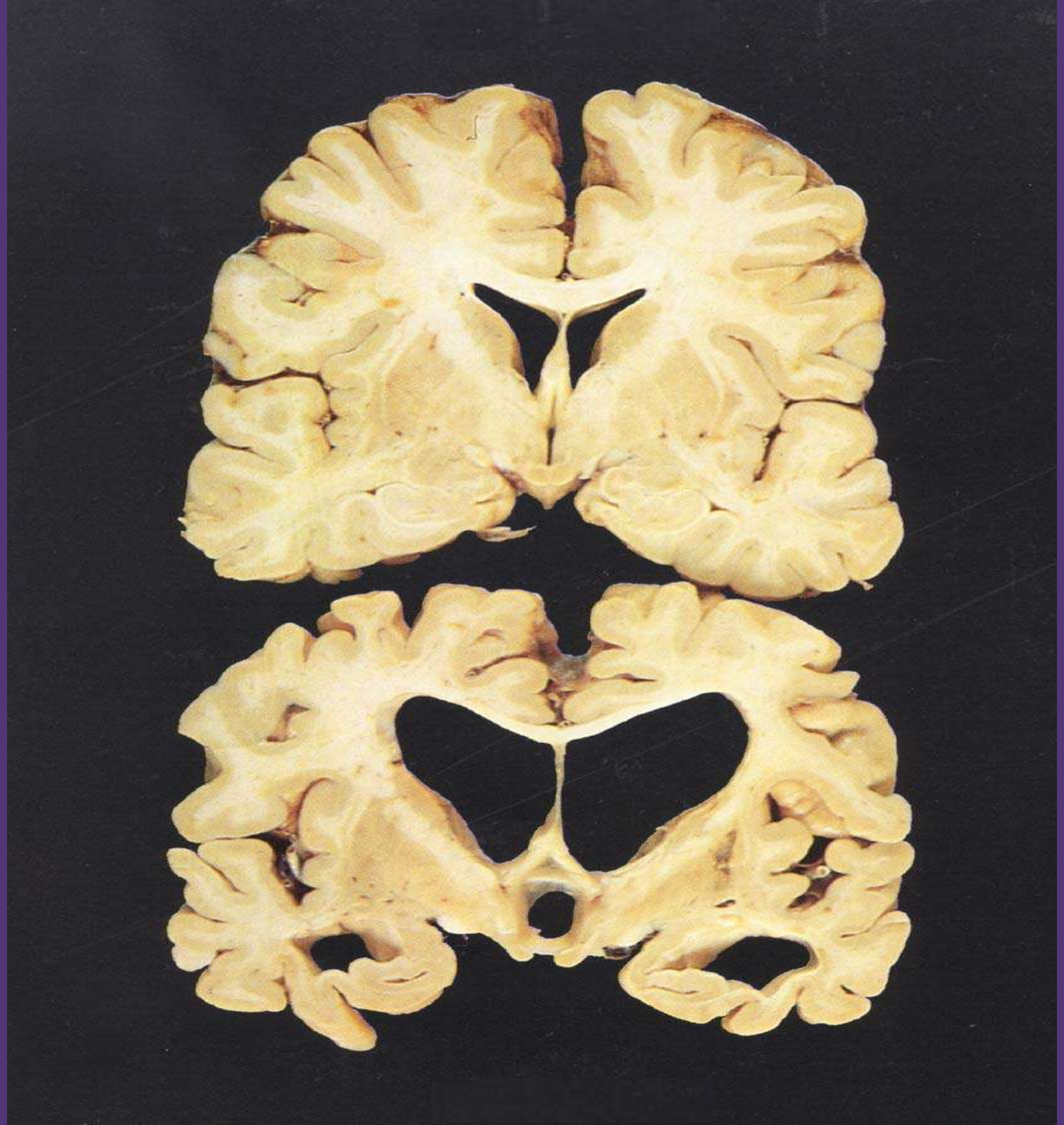


1 Atrophy: loss of neurons, volume

2 Enlarged Ventricles

3 Reduced Hippocampal Volume


Normal
Alzheimer



Alzheimer's Pathology

Plaques & tangles

Blood vessels change

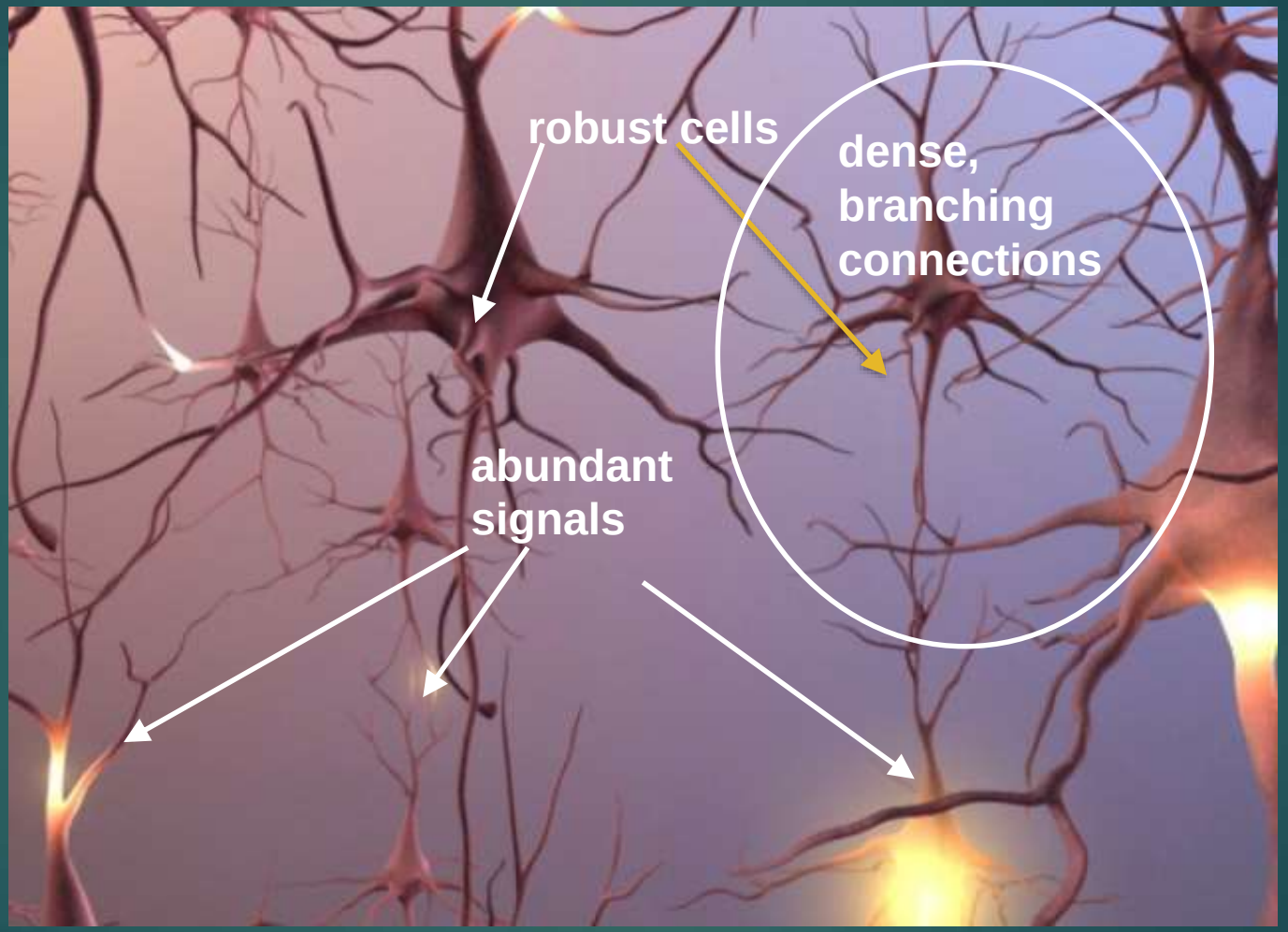
Overlap of stroke & Vascular Dementia & AD

Widespread inflammation

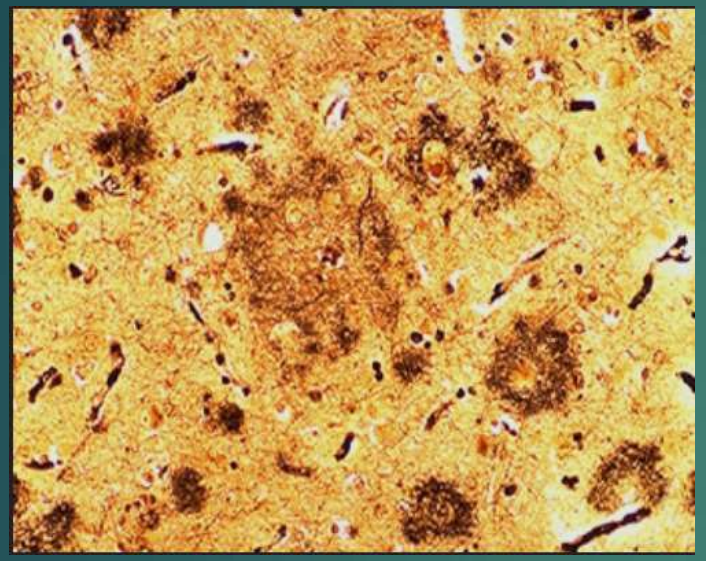
Disruption of critical cell processes

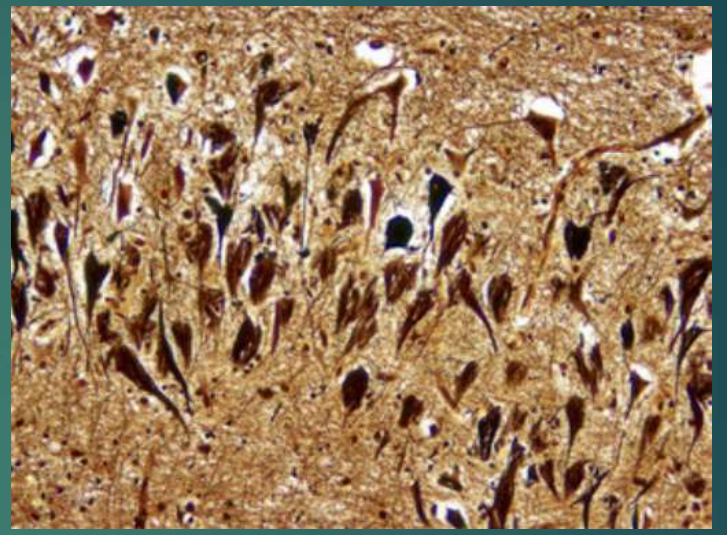
Triggers Pruning

Healthy neurons



AD Pathology





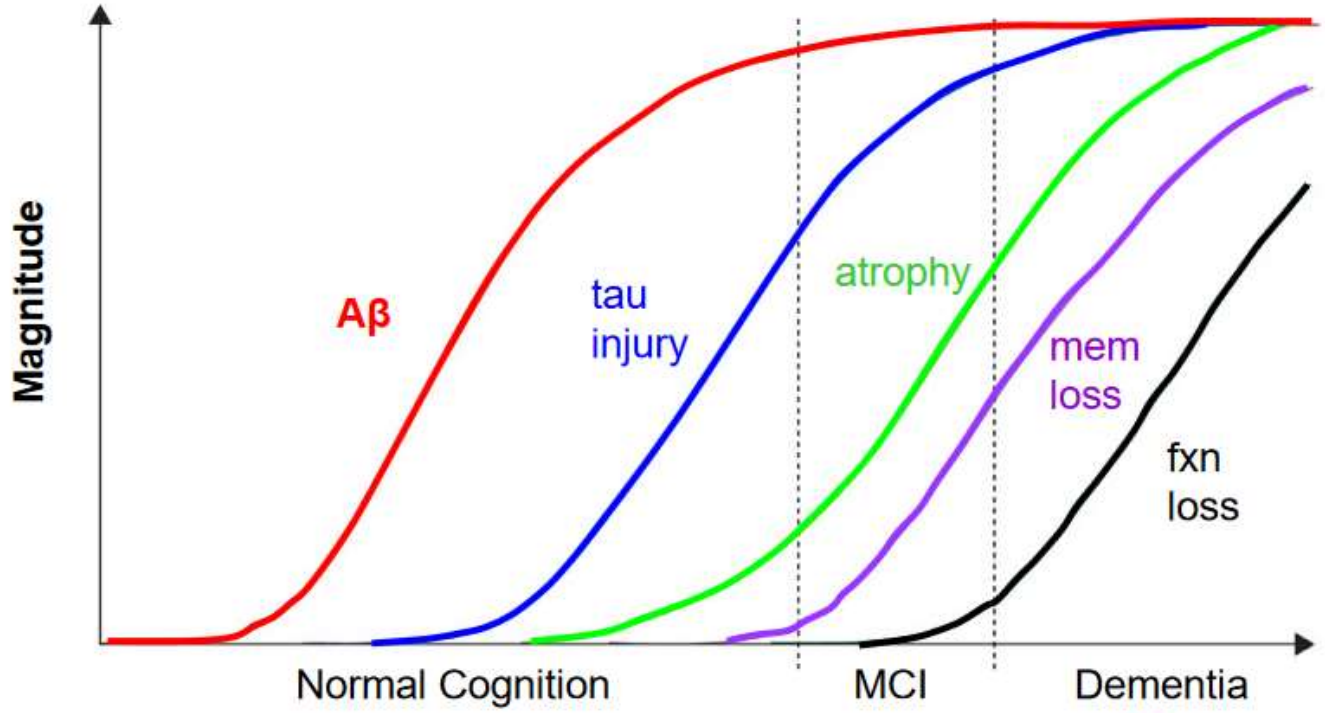
Amyloid Plaques:
- Extra-cellular
- Amyloid-B (AB)

Neurofibrillary Tangles
- Intra-cellular
- Tau

New Model of AD Development:
Emerging Model of Preclinical AD

- AD pathological processes and clinical decline occur gradually
- Dementia is the end stage of many years of accumulation of these pathological changes.
- These changes begin to develop decades before the earliest clinical symptoms occur.

Alzheimer's starts well before sxs



~25 y earlier

Clinical disease progression

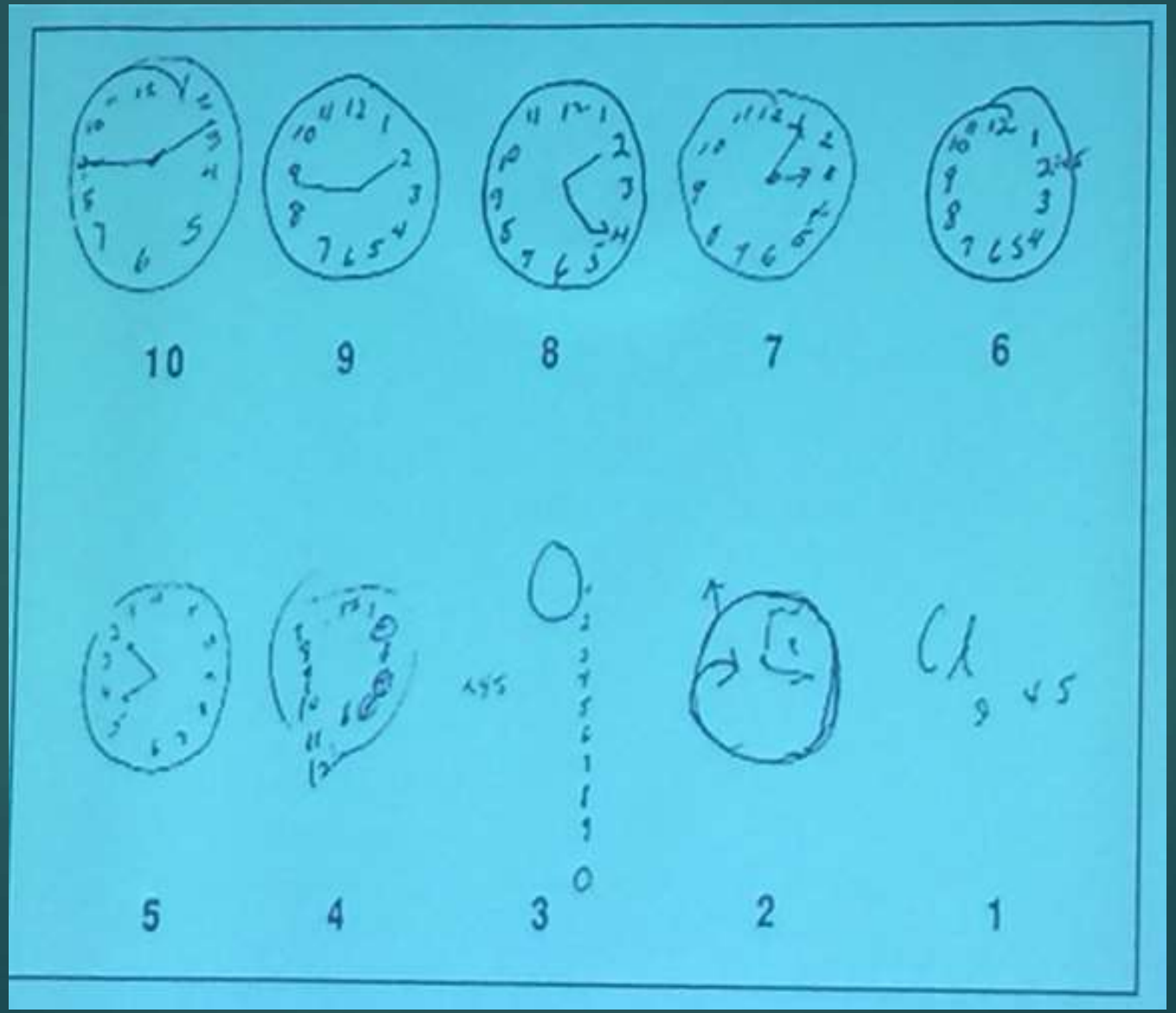
trials

Modified from Jack et al
Lancet Neurology 2010

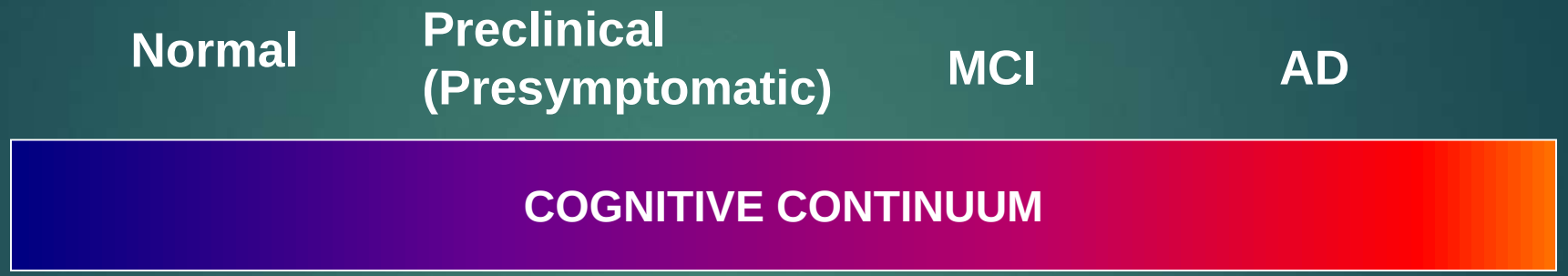
Past Medic Research

Clock drawing in AD patient over several years

Loss of visual spatial ability



We need earlier AD diagnosis, so intervention starts as early as possible



- Thinking effectively but more slowly
- Forgetting a name or appointment but remembering later
- Occasionally misplacing things

Risk factors, but no symptoms:

- APOE-e4 gene
- Multiple protein or gene "barcodes"
- Family history
- High levels of tau or amyloid in CSF or blood

- Subjective problem in memory or another cognitive domain, corroborated by an informant and measurable on tests
- Normal overall cognition and ADLs

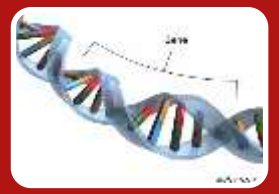
- Clear deficits in 2 or more core cognitive domains (memory, language, problem solving, visual interpretation)
- ADLs affected

Making an accurate diagnosis of Alzheimer's

- History
- Physical exam
- Neuropsychological exam
- Brain MRI
- Blood: B12, thyroid, others

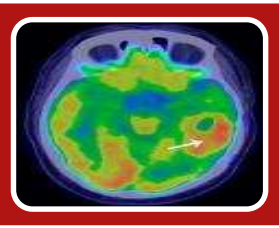
- ~85% accurate diagnosis before death

Early Identification



Genetic Testing

Women: 1 Apoe4 = 4x risk; 2 Apoe4= 8-12x risk; Men: 1 = 1.5x; 2 = 8x risk
Alz Assoc = don't test; preexisting cond



Brain Scans (PET & MRI) – Amyvid

Both for BA & Tau; still experimental; but BA does not mean dementia

Cerebral Spinal Fluid Aßeta

Very low AB & high tau in spinal fluid is negative

Biomarkers

Medical test that predicts AD

Biomarkers: AD Tests of future

- 2 for brain Aβ plaque deposition
  - CSF Aβ42
  - PET amyloid imaging, using Pittsburgh Compound B (PIB)

- 3 for neurodegeneration
  - CSF tau
  - deficits in glucose uptake on FDG-PET
  - and structural MRI (most predictive of Dementia)

Biomarkers are not yet clinical measures

- Research, not clinical measures, except at research hospitals
- Best currently is structural MRI
- Issues of adverse psychological effects of biomarker knowledge

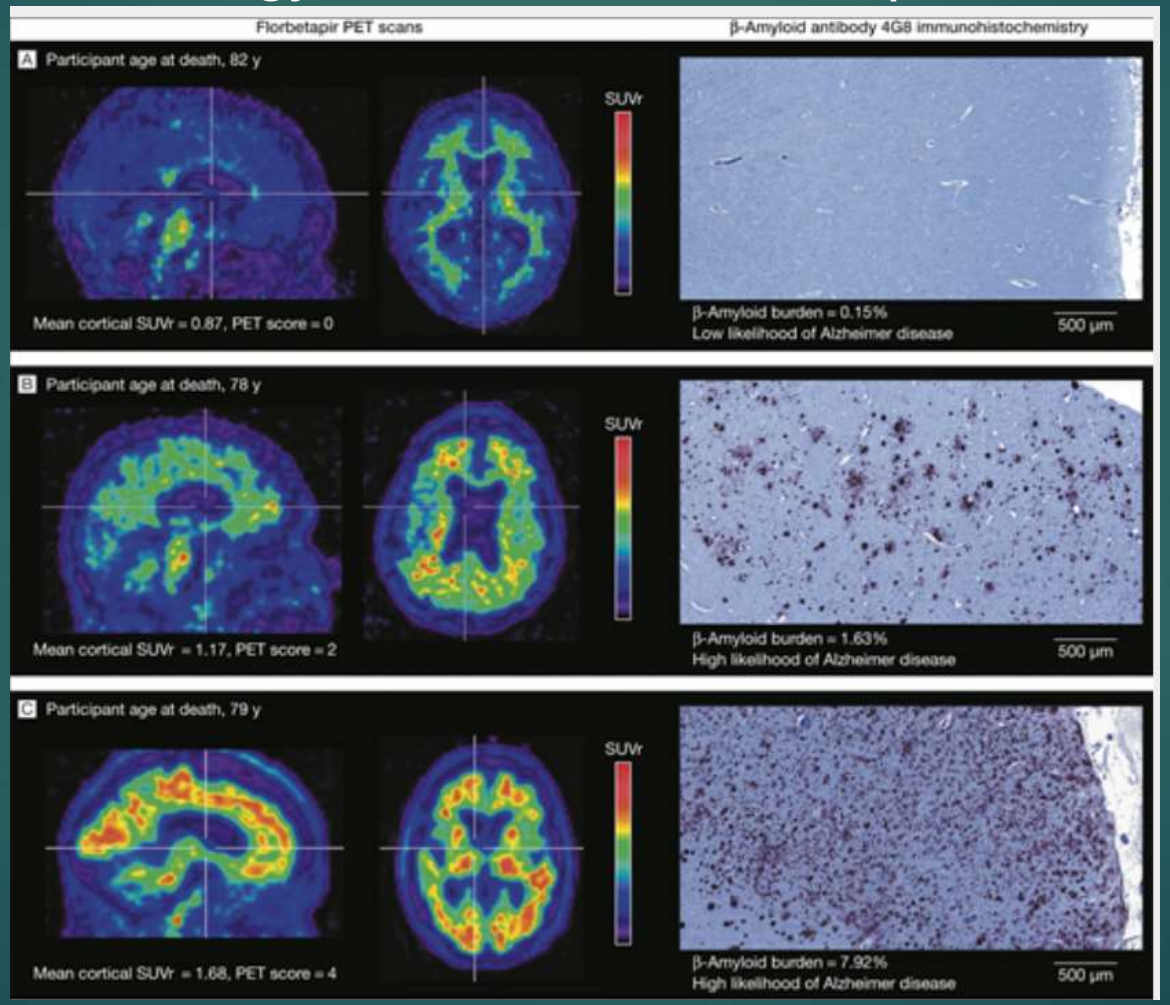
PET= autopsy specificity for Beta Amyloid

Pathology Validation: Florbetapir PET

Normal

Moderate

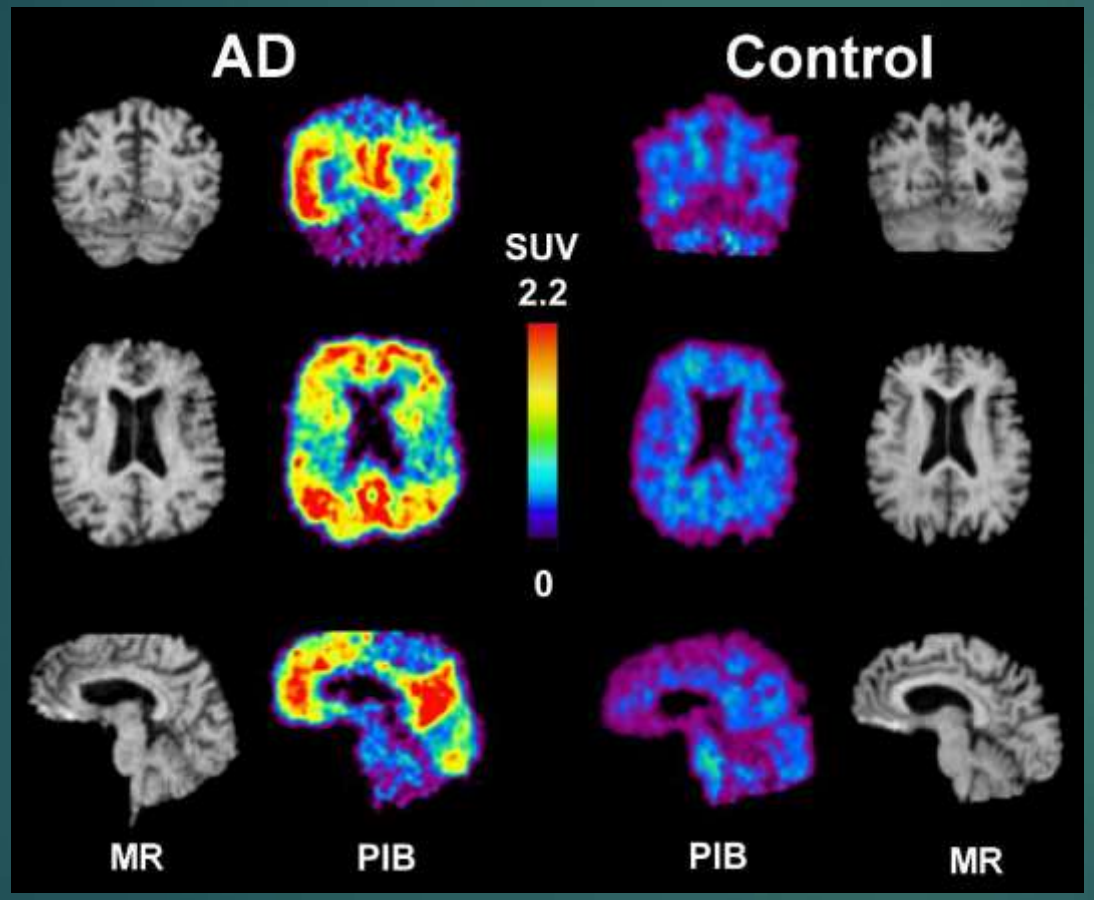
Severe AD



BA on autopsy

2012 FDA approval study: Dying AD pts: Pet scan and equivalent autopsy findings

PIB beta-amyloid imaging agent added to the Alzheimer's Disease Neuroimaging Initiative (ADNI)

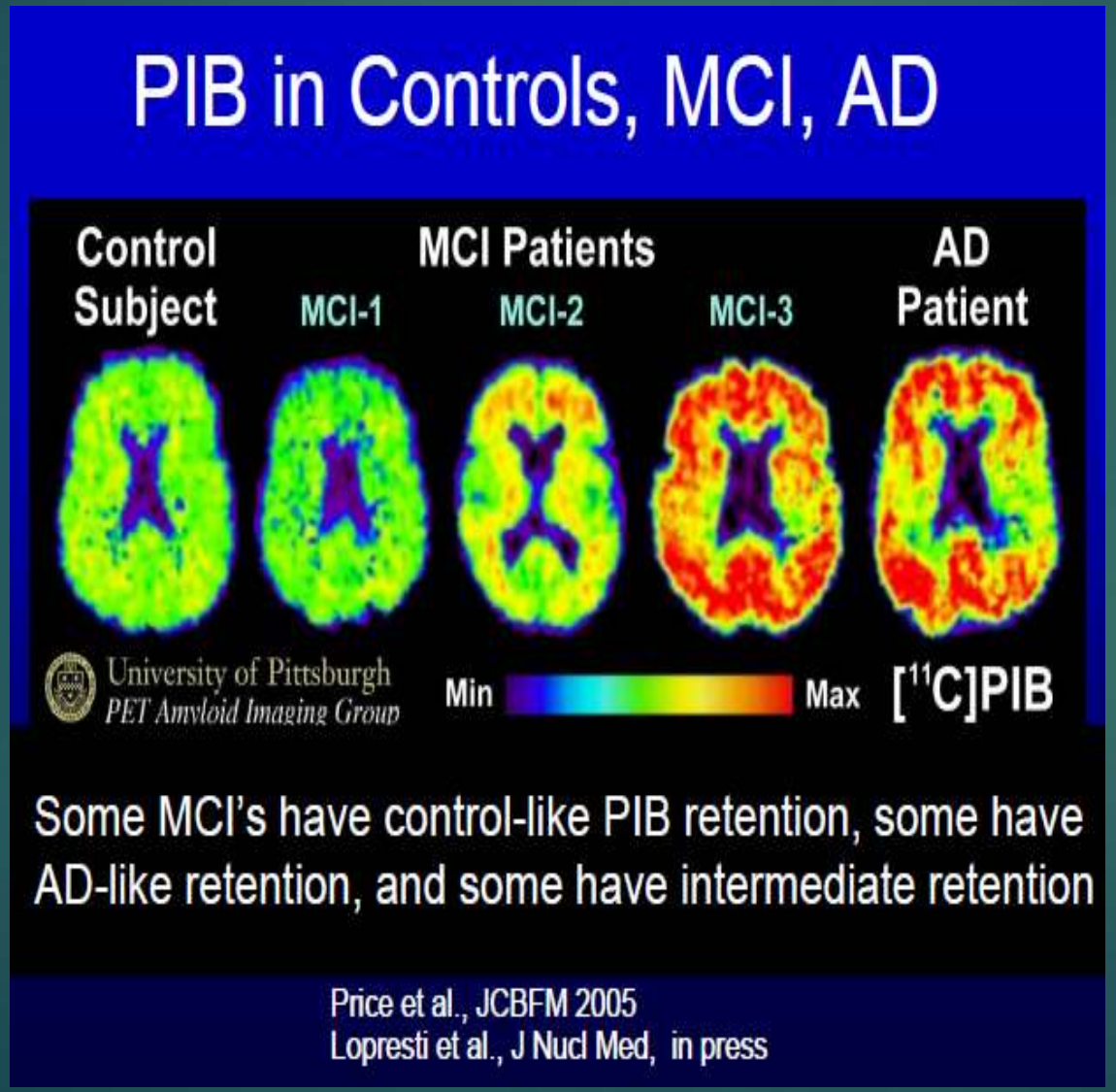


RED = maximum uptake

VIOLET = minimum uptake

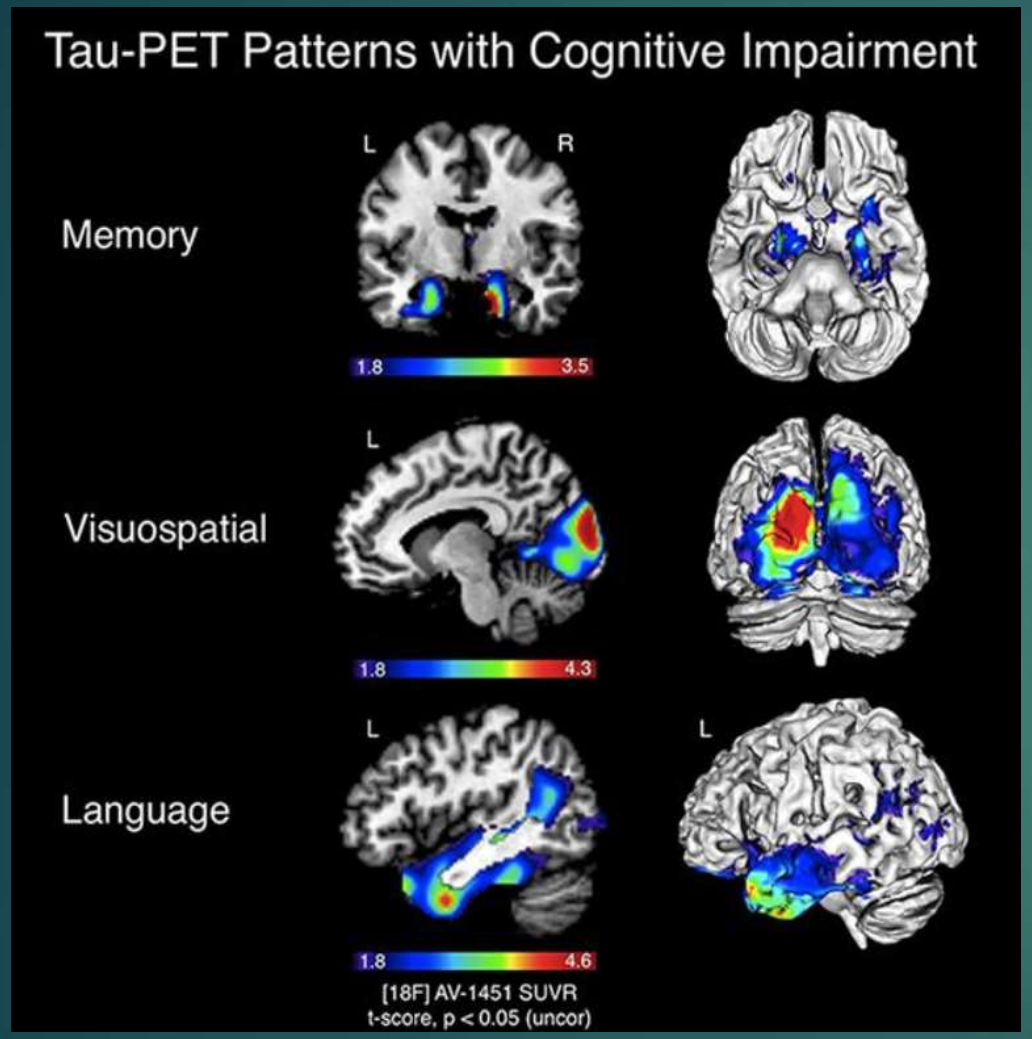
Physicians changed medications or recommendations for patients in two-thirds of 4000 cases; diagnoses shifted dramatically, esp. for non-AD dx

PIB-PET (radioactive): Beta Amyloid in Normal to AD



But does not necessarily correlate with dementia

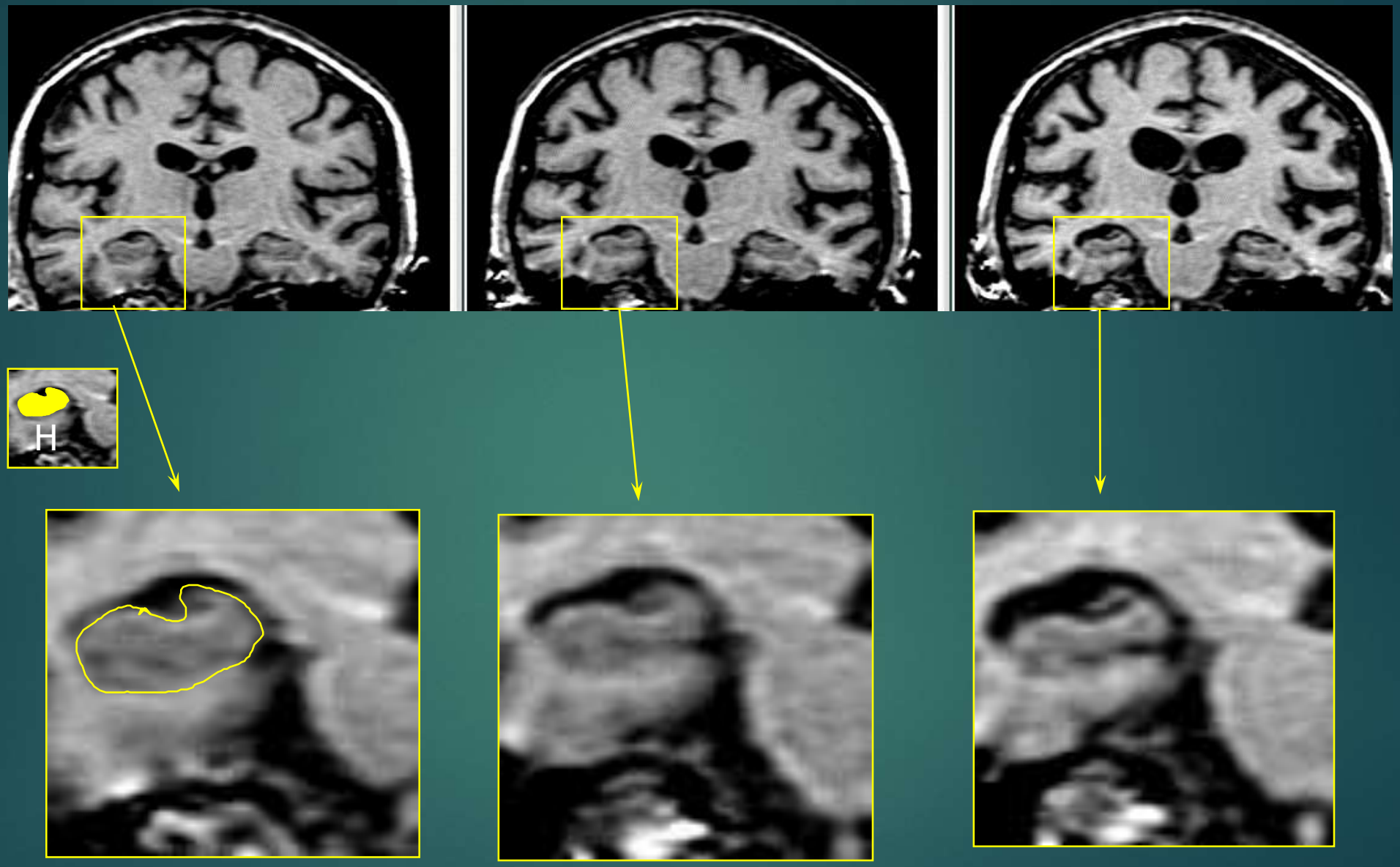
Tau tracks cognition



Findings from classic postmortem studies also demonstrate that cognitive state correlates much more strongly with tau tangle than amyloid plaques.

Tau deposition also aligns with areas of cortical thinning

[Courtesy of the Rabinovici lab.]



Hippocampal Atrophy: Serial coronal MRI of an individual with initially mild AD

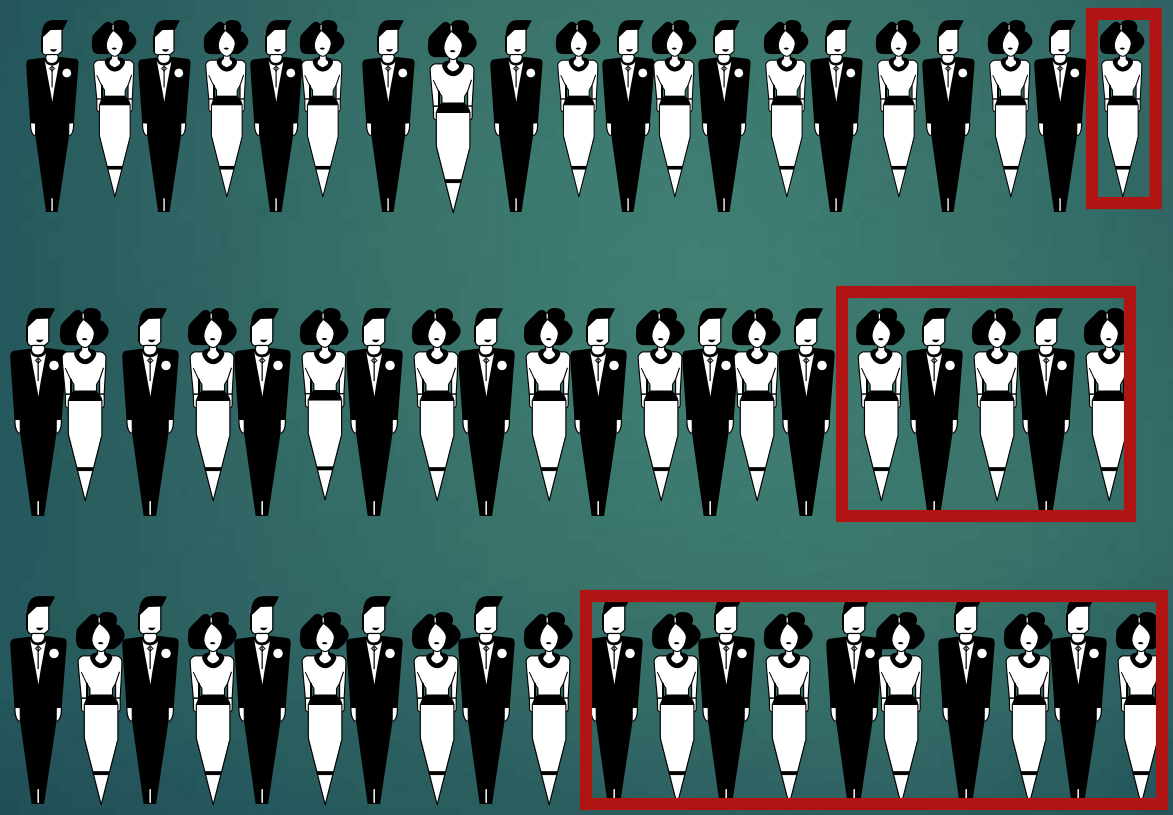
AD Timeline to Dementia due to AD: 25 years before symptoms

- 25 years before, beta-amyloid protein levels in the CSF
- 15 years before, beta-amyloid can be detected in the brain. (the earliest sure sign of the disease).
- 15 years before, the brain begins to shrink. Neurons begin to die.
- 10 years before, brain metabolism slows down & episodic memory is impaired.
- 5 years before, cognitive impairment sets in.
- Today = Year 0, diagnosis of Dementia

Cognitive Decline in Elderly

- Of all Americans in 2002, aged 71+:
- 65% were cognitively normal
- 21 % had some mild NCD
- 14% had Major NCD/Dementia

Age is the biggest risk factor for AD



AGE	AD
65-74	2%
	300,000
75-84	19%
	2.4 million
85+	42%
	2.2 million

Dementia doubles every 5 years after 65

Causes of Accelerated Synaptic Loss→ higher rates of AD

- Age
- Being female
- Down’s syndrome
- Significant Traumatic Brain Injury
- Cardiovascular disease: 80% of AD have vascular disease
- Hypertension
- Diabetes
- High Cholesterol
- Homocysteine (due to too much red meat)
- Reduced cognitive and physical activity throughout life
- Specific genes (Apoe4, Presenilin 1 & 2)

Higher NCD Risk & Ethnicity: Disease & Life experience factors

- Original Studies: Age 65+ African Americans & Hispanics have 2 x higher rate of AD
- Higher rates of hypertension, diabetes; Higher rates of low education, low quality of education, low income, rural living (all risk factors for AD)
- Newer Studies: Higher dementia risk accounted for by childhood SES, adult literacy, and exercise
- Kaiser study: AAs decedents with AD dementia are more likely to have mixed brain pathologies compared with age-, sex-, education-, and cognition-matched white decedents with AD dementia.

ADAMS & WHICAP studies

Women are the epicenter of AD crisis

- A woman's AD risk at age 65 is 1 in 6, compared with nearly 1 in 11 for a man.
- Women in their 60s are twice as likely to develop AD as they are to develop breast cancer.
- More likely to be caregivers of those with Alzheimer's: More than 3 in 5 unpaid Alzheimer's caregivers are women

2017 Study: Gender effects AD

- Women with APOe4 genes face a 10-year window when they have a greater chance of developing the disease than men with similar genetic risks.
- White men and white women aged 55 to 85 with APOe4 have similar odds for developing Alzheimer's except from 65 to 75 years old, when the risk appears to jump for women.
- Menopause and plummeting estrogen levels, which on average begins at 51, may account for the difference
- 65% of the more than 5 million Americans now living with Alzheimer's disease are female.

Good News: Less Dementia, but…

- Incidence of dementia has declined gradually over the past 40 years in higher income developed nations
- Due to better education and CV health effects
- These incidence declines will be overwhelmed by increases in NCD brought on by population aging and negative health trends such as diabetes and obesity.

Major Neurodegenerative Disorders

- Alzheimer’s Disease
- Lewy-Body Disease
- Vascular Disease
- Frontal Temporal Disease
- Chronic Traumatic Encephalopathy

Alzheimer's Disease: 70% of Neurodegenerative diseases

- Insidious gradual decline
- Hallmark is memory loss: Encoding deficit; rapid rate of forgetting; poor delayed recall; Hippocampal loss first: 5% ↓↓ per year
- >67% of pts are at moderate level NCD at first diagnosis
- AD is a fatal disorder, inevitably progressive and terminates in cognitive and functional incapacity and death.

Core AD issue: No new memories

No tape/CD recorder

- Encoding Deficit: tape recorder does not work
- People with AD no longer have the ability to remember what's new; they do not have the ability to remember new life experiences.
- No person with AD can tell you what they had for breakfast
- Their brain has stopped recording
- The record machine is permanently broken.

AD Symptoms

- Proportion of First Symptoms:

Memory	55%
Language	15%
Visual Spatial	13%
Executive	13%
Behavioral	4%

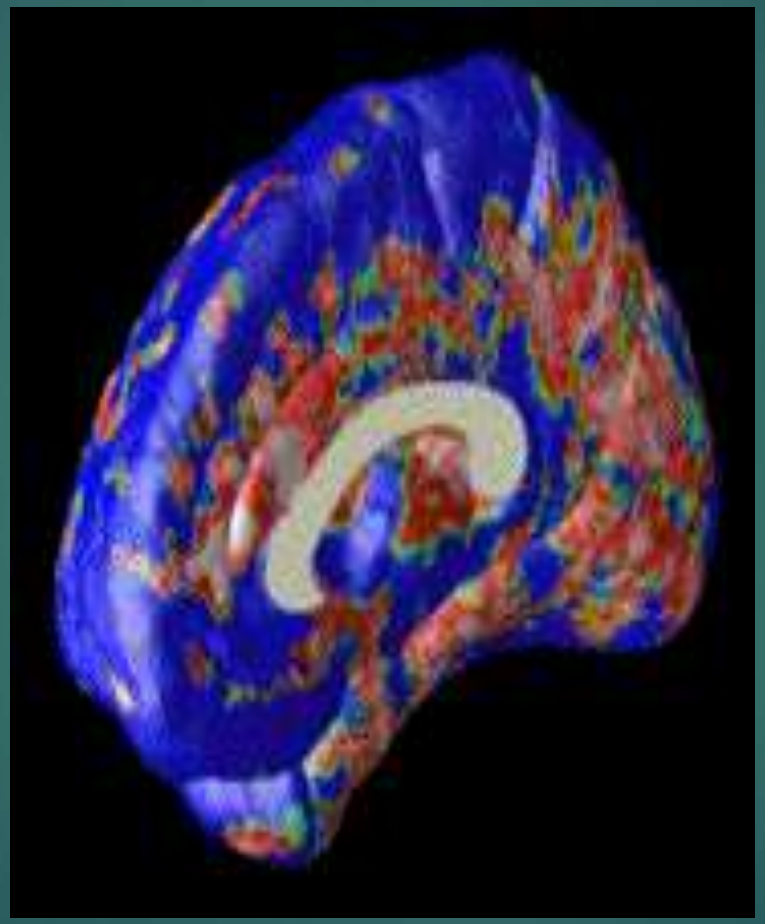
- Family Home behavior description:

- Question Repetitions	70%
- Agitation	66%
- Dependent	56%
- Incontinence	43%
- Dressing difficulty	41%
- Wandering	40%

Alzheimer's = Most are Not Diagnosed

- Not Diagnosed: 75% of the 36 million people living with Dementia
- 50% of people with AD do not know they have it.

Progression in Alzheimer: 18 Months

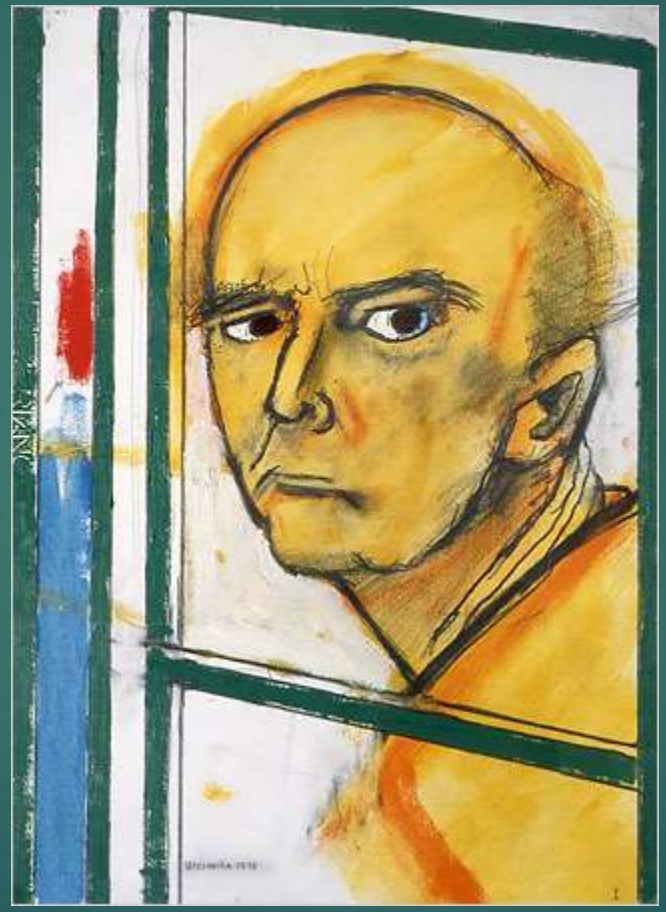


P. Thompson, UCLA, 2002

A picture is worth a 1000 words:
Painter William Utermohlen's self-portraits; (1934-2007)

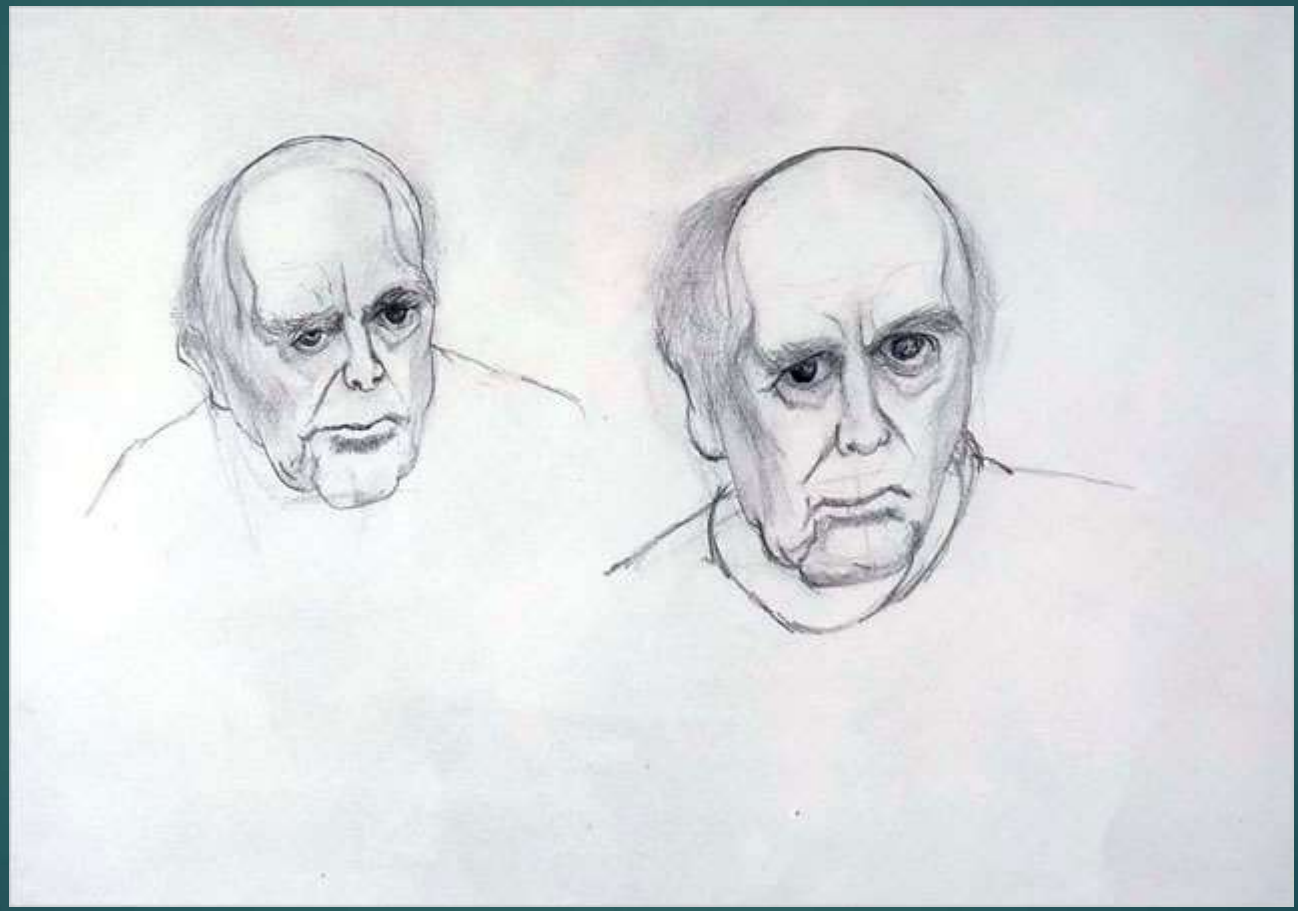
1967

Self Portrait: 1996

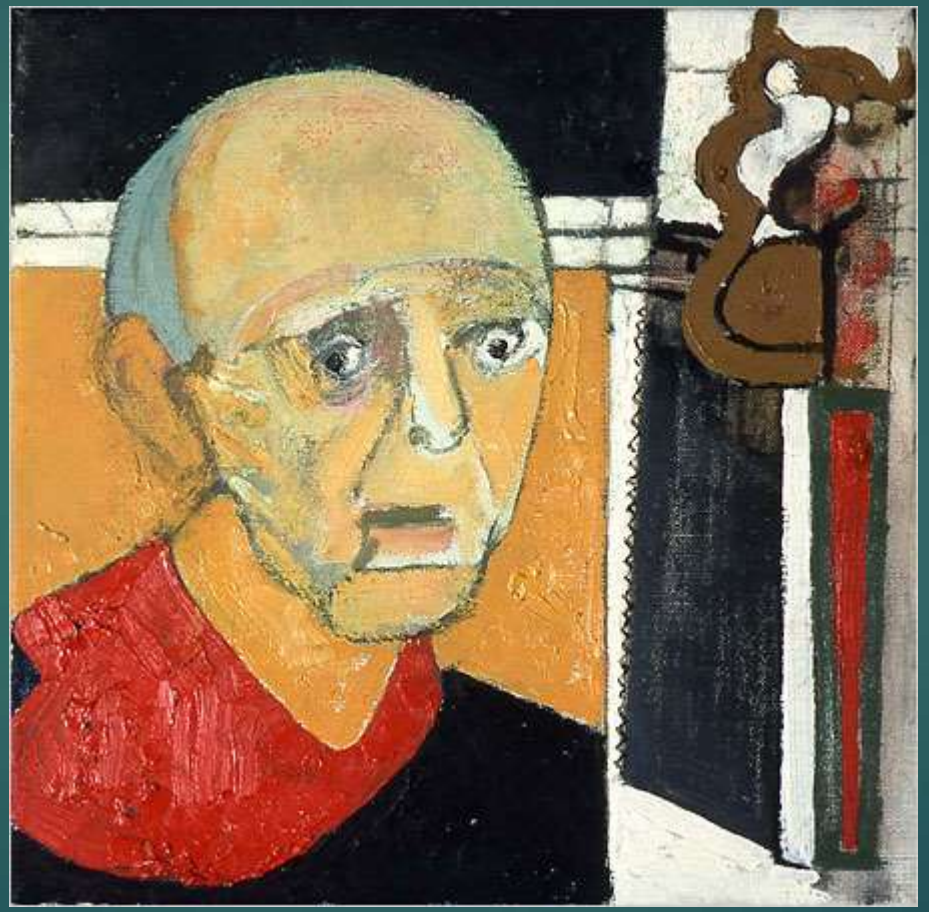


Self Portrait: 1996

Self Portrait: 1996



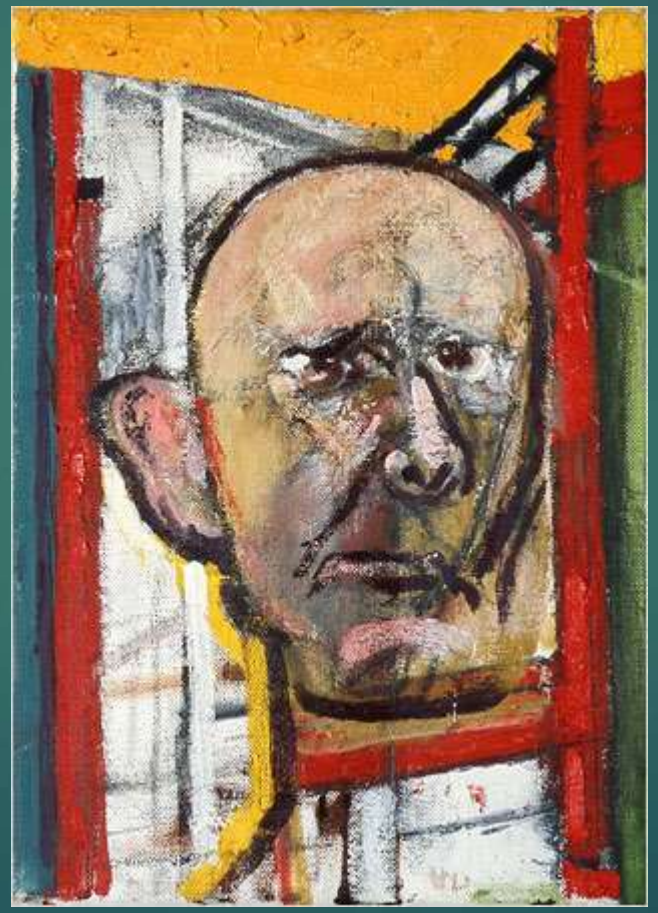
Self Portrait: 1997



Decides to donate his body to science

Self Portrait: 1997

Self Portrait: 1998



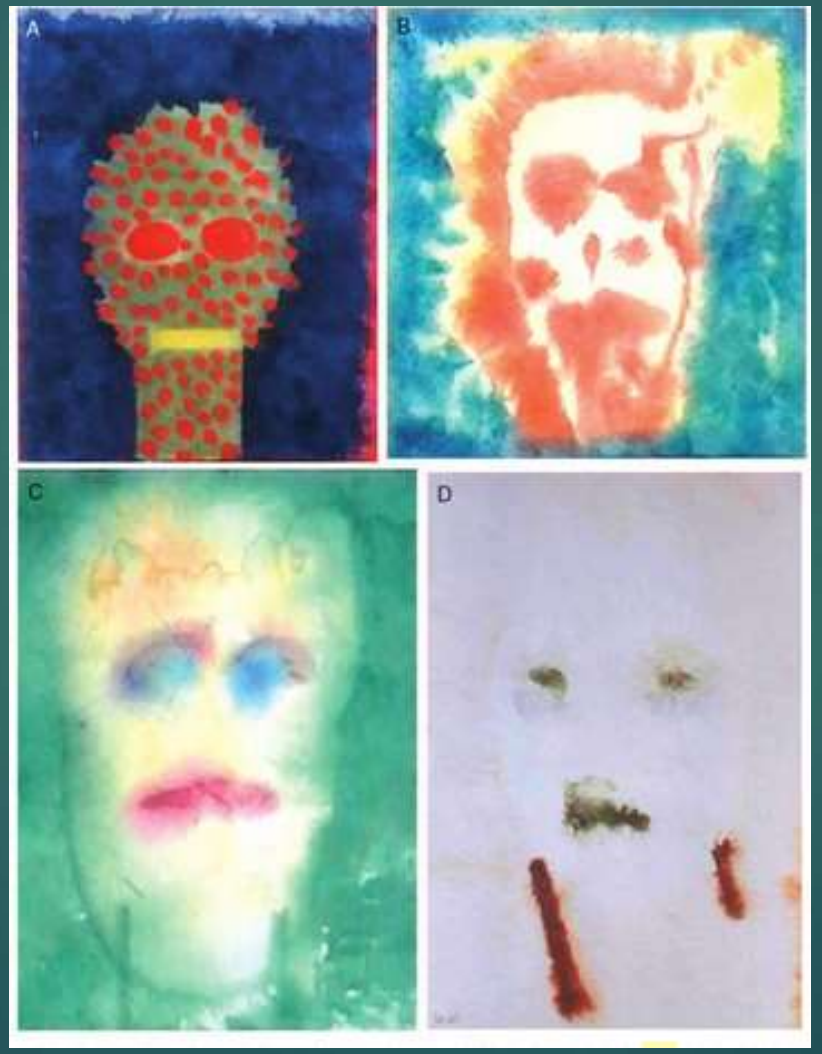
Self Portrait: 1999

2 years to complete

Self Portrait: 2000

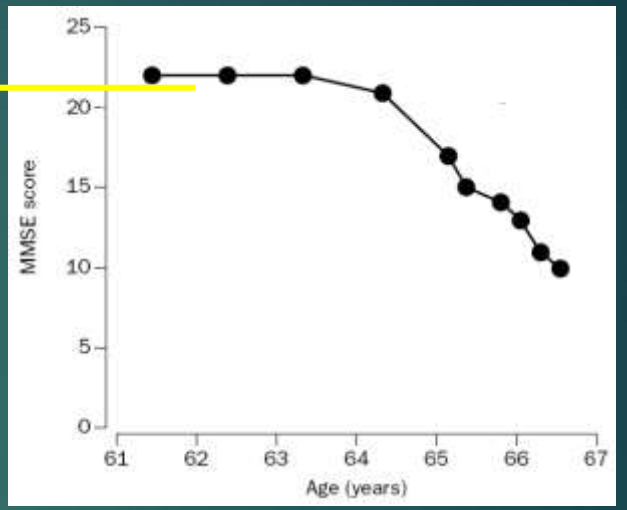
Self Portrait 2000+

1998, Age 65



William Untermohlen –self-portraits correlate with cognitive decline

Figure 3: **Self-portrait series**
Painted at age 60 years (A), at 62 years (B), at 63 years (C), and at 64 years (D). Pencil drawing at age 66 years (E). Abstract self-portrait painted at age 65 years (F).



Crutch SJ, Isaacs R, Rossor MN. Some workmen can blame their tool: artistic changes in an individual with Alzheimer disease. Lancet, 2001, 357:2129

Experimental treatments

Mab = Monoclonal Antibody

Aducanumab 1st to reduce cognitive decline; dose dependent

Very expensive drug (probably > 40k/year)

Immune Targets
Aducanumab
Bapineuzumab - Solanezumab - Crenezumab – 2?
Gantenerumab - 3
Anti-inflammatories

Brain Cell Supports
Signal modulators – Grow or die
Supplements: Nourish AD study (Caprylic acid)
Beta-secretase inhibitors
Tau targeting drugs

Other – FDA Approved ??
Nasal Insulin
Cancer drugs
Deep brain stimulation

All phase 3 studies using antibodies to get rid of Amyloid Beta in AD pts have failed to slow cognitive decline; so now Pre AD strategy

123+ Disease Modifying Treatment Trials: 99.6% Failure Rate

- AN1792 vaccine: 2003 (Eliminated BA; still Dementia)
- Tramprostate
- Flurizan: 2008
- Bapineuzumab: 2009
- Semagacestat: 2010
- Solanezumab: 2016

Failed Phase III Trials

- Ginkgo biloba
- NSAIDs (Ibuprofen, Naproxen)
- Phenserine
- Statins
- Tarenflurbil
- Xaliproden
- Tramiprosate
- Flurizan
- Dimebon

Aricept
Namenda
Estrogen
Prednisone
Valproate
Vitamin A
DHA/Omega 3

Semagacestat : (gamma secretase; worsened cognitive symptoms + skin cancer)

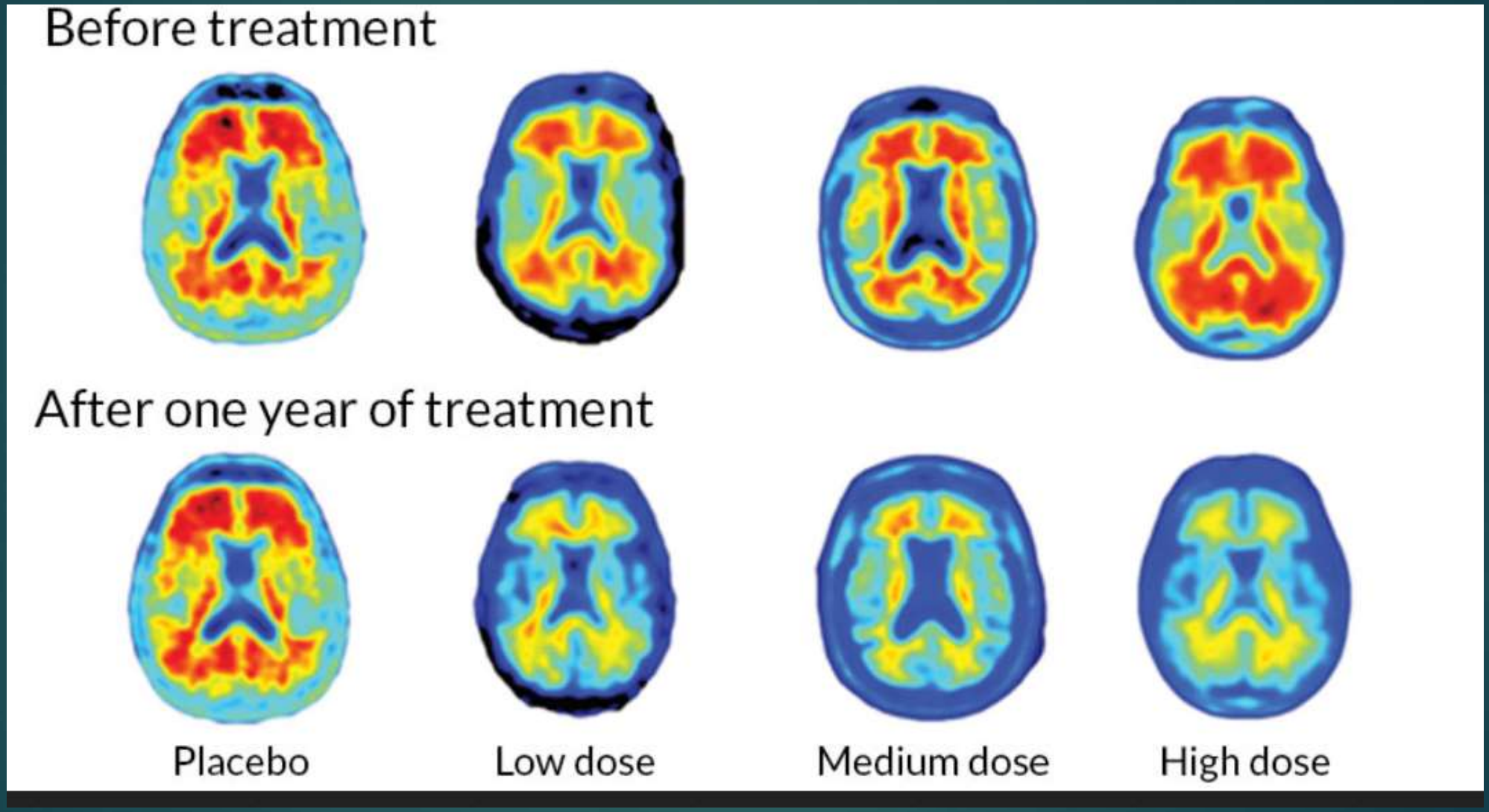
Why Failures

- Don’t actually know the cause of AD
- Difficulty getting medication to cross blood brain barrier
- Treatment is too late in course of disease, i.e. after neuron death
- Treatment is too broad (effects all Beta Amyloid, not just AB42)
- Right TX, wrong stage of disease

New Research Strategy

- Treat AD like HTN and heart disease: start treating after early dx based on biomarkers
- AD as lifestyle disease (reduce risk by increasing education, exercise, take care of heart, etc.)

Aducanumab study



Aducanumab study

- Small study: 165 patients
- Phase 2 study
- Biogen's Aducanumab: dose-dependently reduced amyloid
- After one year, the highest dose appeared to have totally reduced cortical amyloid
- Slowed cognitive decline
- Now larger study

- But in Nov 2016, large solanezumab study with MCI failed.

Hope for near future:
Columbian Prevention Study

- Eventually treat AD like HTN and heart disease preclinically
- Columbian study: extended clan of 5,000 people who live in Medellín, Colombia with early onset AD
- Family members with a presenilin 1 gene mutation begin showing cognitive impairment around age 45, and full Dementia around age 51; disease they call La Bobera — the foolishness.
- N = 300; 5 year trial; Genentech drug, Crenezumab injection every 2 weeks; massive pre and post testing
- Also Dominantly Inherited Alzheimer Network (DIAN)
- Data in 2020

Current Research Summary

- No current disease modifying treatment for individuals with current AD
- Disease-modifying therapy likely to be modestly beneficial in mild AD
- Early detection; Ultimately, we will screen/diagnosis AD neurobiology using biomarkers (e.g. amyloid imaging)
- Very early treatment will maximize benefits
- Potential issues: effect of 30 years on new medications; high cost

Lewy Body Disease

Lewy Body Variant Disease: 10-15%

- Alzheimer's cognitive + Parkinson's motor systems (no tremor)
- Presenting with visual hallucinations (fully formed), lucid periods, movement disorders, falls or syncope
- Visual Spatial deficits
- Predicted by REM Behavior Sleep Disorder
- Fluctuations in functioning: confusion, sleepiness, inattention, incoherent speech, task difficulty

Heyman A et al. *Neurology.* 1999;52:1839-1844.
Ballard CG et al. *Dement Geriatr Cogn Disord*. 1999;10:104-108.

NCD due to Vascular Disease

Why "what is good for the heart is good for the brain"

400 miles of blood vessels in human brain.

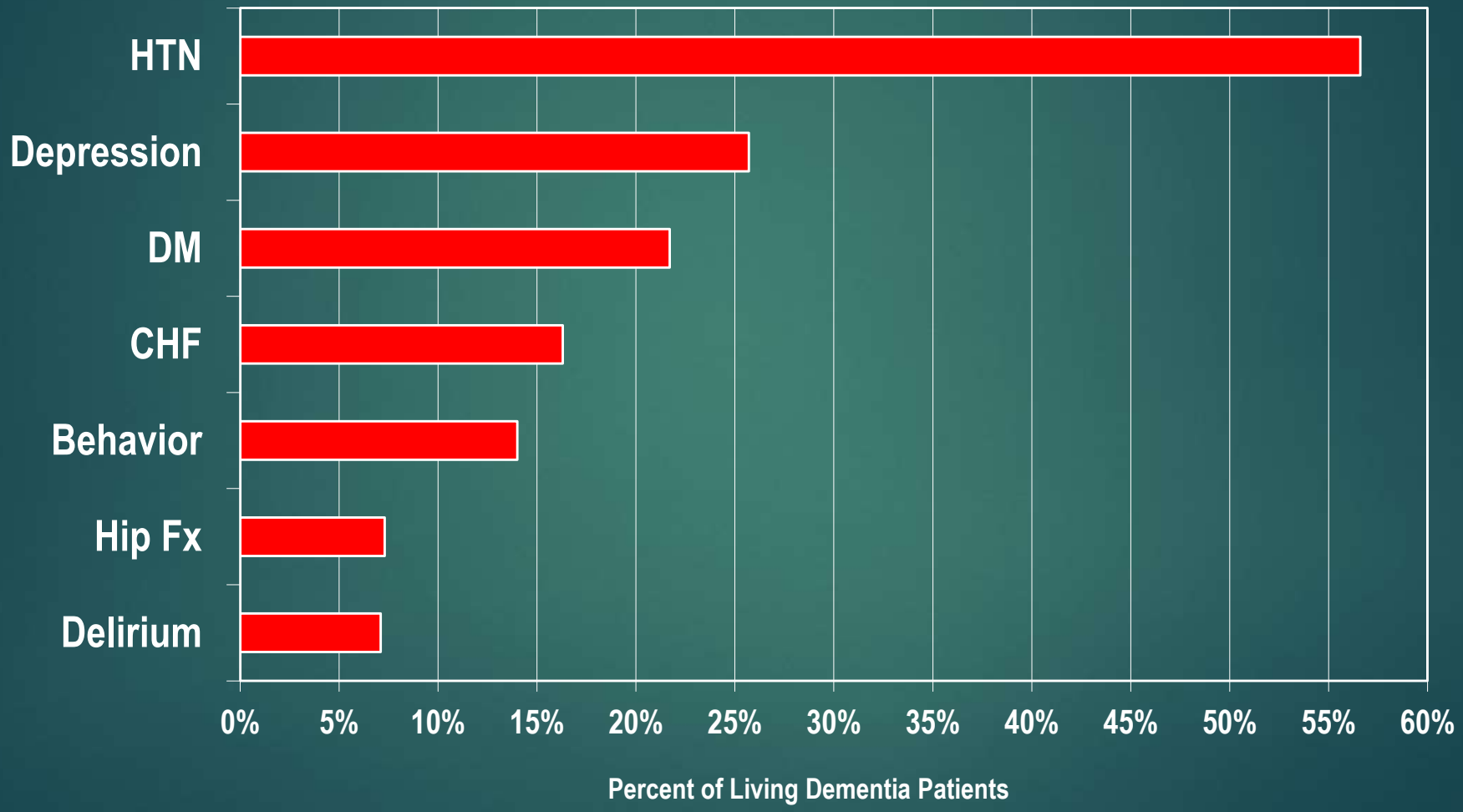
A plastic emulsion was injected into brain vessels and brain tissue was dissolved.

•Zlokovic & Apuzzo, *Neurosurgery,* 43(4):877-878, 1998.

Vascular Disease: 15%

- Vascular disease is largest risk factor for NCD after age; VD is comorbid with most AD; AD pathology and strokes have an additive effect on the odds of dementia
- Blood vessels lose ability to consistently supply glucose and oxygen to neurons
- Series of mini strokes, hypertension
- Focal neurological and neuropsychological deficits; May or may not include memory deficit

Co-Morbidities of Northern Cal KP Dementia Pts



Hypertension is the curse of the brain: brain runs out of breath

- Hypertension slowly disables the brain's micro vessels, rendering them unfit to adjust blood flow to suit the brain's needs.
- Raises the risk of stroke.
- 8 percent of Alzheimer's cases are linked to mid-life hypertension
- Impairs the brain's ability to locally increase perfusion where the brain is most active, leading to cognitive decline.
- Need lowest BP without fainting, until late 80s.

Cognitive deficits in Vascular Dementia

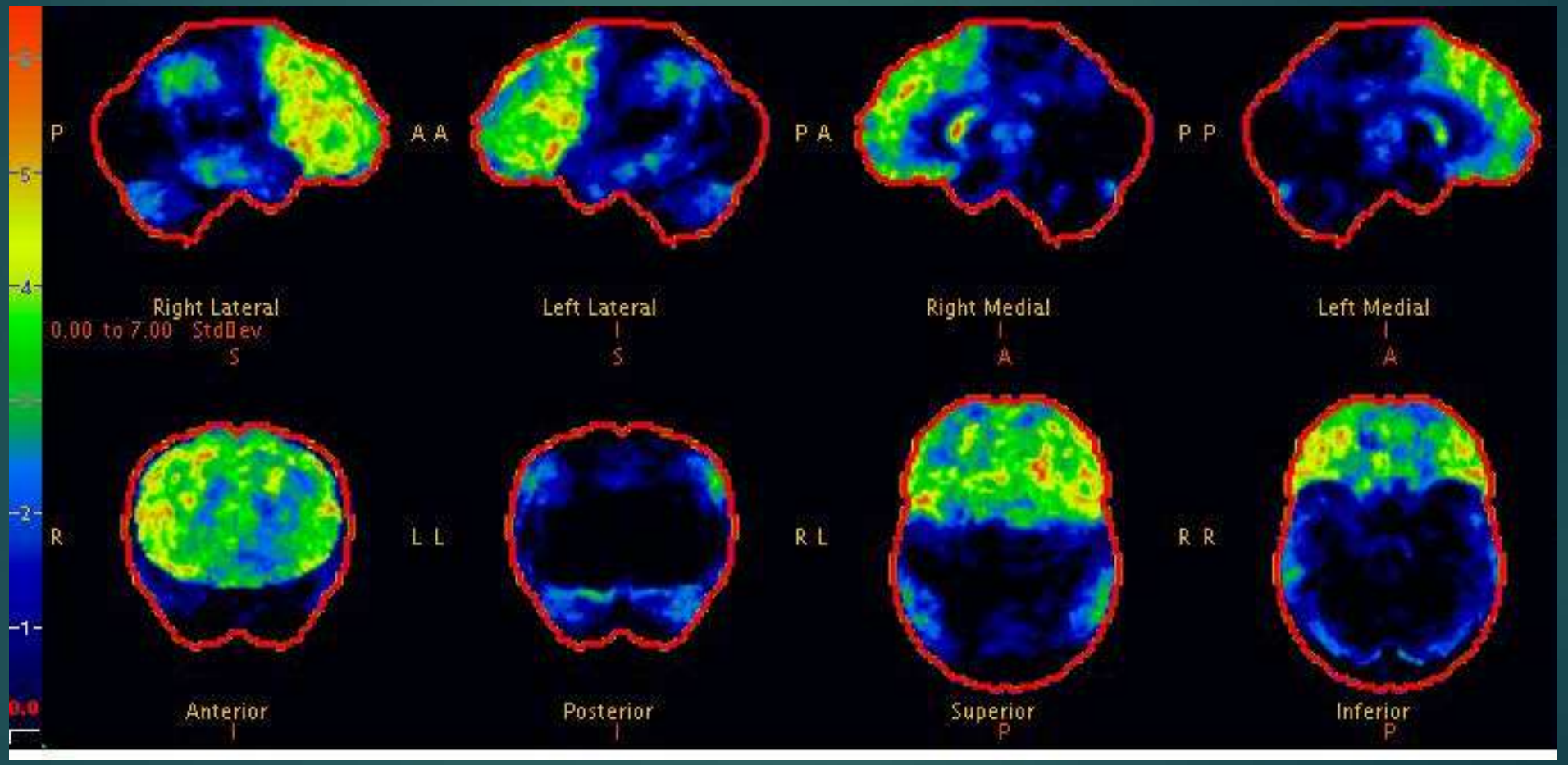
- ** Slowed processing speed
- ** Executive dysfunction
- Memory deficits not necessarily prominent; marked by poor retrieval, normal recognition

Frontal Temporal Disease

Frontal Temporal Disease: 5-10%

- Social Disorder: Personality/Behavioral changes precede memory deficit: disinhibition, agitation, delusion, hallucinations, apathy
- Loss of empathy; disregard social conventions
- Executive dysfunction: poor judgment, loss of impulse control/disinhibition
- Language Variant: semantic, non-fluent aphasia
- 4 x greater in men; average age: 53
- FTD is highly genetic.

bvFTD Imaging (FDG PET)



Subcortical Diseases: Parkinson's, Huntington's, HIV, MS

- White Matter & Prefrontal Disorders
- Slow processing speed
- Motor problems
- Memory Retrieval:
  - Impaired free recall, but normal recognition
  - Cueing helps
- Executive Dysfunction
- Sustained attention decline
- Visual spatial/PIQ decline

Differential Diagnosis of Neurodegenerative Disorders: First Symptom

- AD – Memory (no encoding) (70%)
- FTD – Behavior, executive loss, language
- VD – Apathy, executive deficits
- LBD – Visual hallucinations, Visual Spatial deficits, Parkinsonism, delirium

Aging is more risky than having single Parent with AD

- The risk to a person who has a first-degree relative (parent or sibling) with late-onset Alzheimer disease is just slightly higher than the risk in the general population
- Risk for AD doubles every 5 years post age 65
- 95 % will reach the age of 75 without developing Dementia

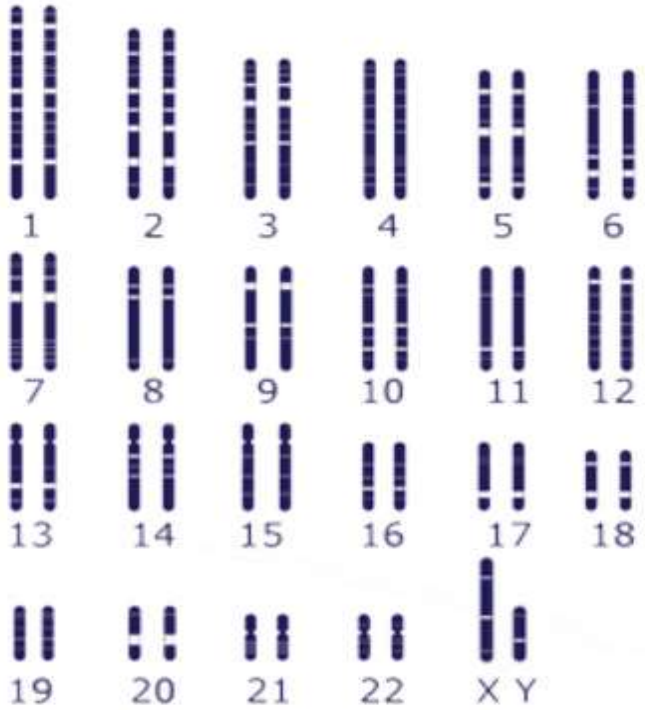
Genes that predispose to AD

- Causative/Mendelian dominant (only 450 families worldwide):
  - Amyloid Precursor Protein (APP)
  - Presenilin 1 (PS1)
  - Presenilin 2 (PS2)

- Risk factor:
  - Apolipoprotein E (APOE4): lowers age of onset

All four AD genes create excessive accumulation of Aβ peptide

Only 4 Major Genes Implicated in Alzheimer's: First 3 genes in only 450 families in whole world



Amyloid precursor protein (APP), discovered in 1987, is the first gene with mutations found to cause an inherited form of Alzheimer's.

10-15%

Presenilin-1 (PS-1), identified in 1992, is the second gene with mutations found to cause early-onset of Alzheimer's. Variations in this gene are the most common cause of early-onset Alzheimer's.

20-79%;
Youngest Onset: 40s

Presenilin-2 (PS-2), 1993, is the third gene with mutations found to cause early-onset Alzheimer's.

Very rare; Onset: 58-59

Apolipoprotein E-e4 (APOE4), 1993, is the first gene variation found to increase risk of Alzheimer's and remains the risk gene with the greatest known impact. Having this mutation, however, does not mean that a person will develop the disease.

25%: Earlier Onset: 60-70s

Risk: ApoE4

- ApoE4 is the major known genetic risk factor for the development of late-onset AD and has a gene-dose effect on risk and age of onset.

- ApoE4 is the only gene proven to be linked to the common form of non-autosomal-dominant, late-onset AD

- The majority of *ApoE* carriers (25% of US) never develop AD.
  - 3 alleles (types/versions)–
    - ApoE2 (lowers AD risk, 5-10% of population),
    - ApoE3 (most common, 50-70%),
    - ApoE4 (10-15%, harmful)

Alzheimer's Genetics

- Approximately 25% of all AD is familial (i.e., ≥2 persons in a family have AD)
- 95 %: Sporadic (unknown cause) age-related AD with onset later than 65 yo
- 5%: Familial genetic AD, onset before age 60
- No family hx:
  - Lifetime risk = 15%
  - E4 neg = 9%
  - E4+ = 30%
- One parent with AD:
  - E3/E3: 30%
  - E3/E4: 45%
  - E4/E4: 60% (1% of normals & 19% of the familial AD; also telomere shortening)

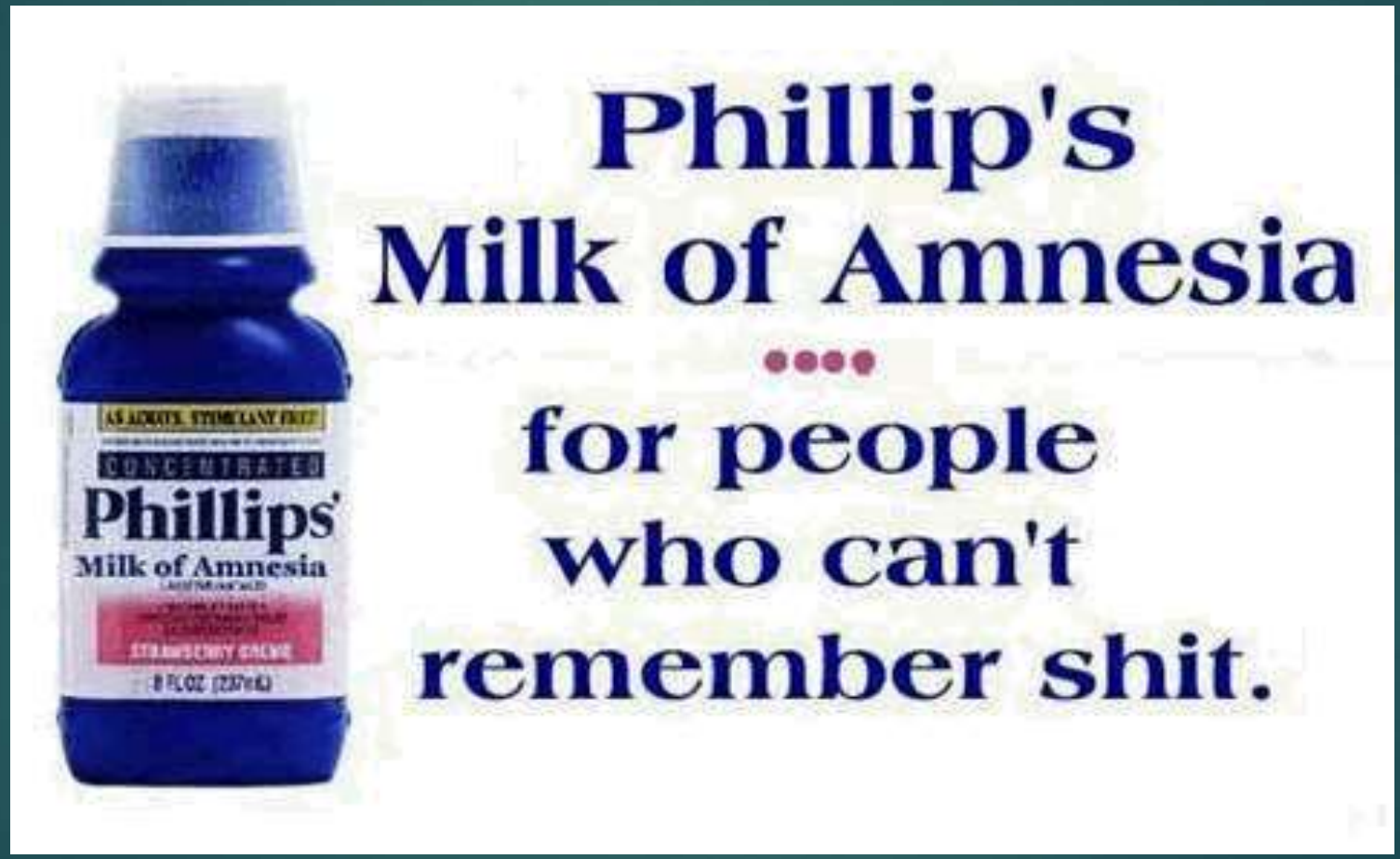
23andMe: $199

In April, 23andMe will have genetic tests for AD and Parkinsonism.

My genetic study: double APOE 3; 1% sub-Saharan African; 0.2% Ashkenazi Jewish; 2.7% Neanderthal

Remember: <u>No current treatment for AD</u>

Latest Memory Cure



Anti-Dementia Medications ?

- **The Question:** Are there medications that prevent Dementias like Alzheimer's disease?
- **The Verdict:** No Dementia disease prevention medications. If brain cells start dying, there is no cure!
- Prevagen? Coconut oil? = hoaxes!!
- But…There are Dementia modifying behaviors.

FDA Approved Therapies

Cholinesterase Inhibitors

- Donepezil (Aricept)
- Galantamine (Reminyl, Razadyne)
- Rivastigmine (Exelon)

NO!

NMDA Receptor Antagonist

- Memantine (Namenda)

Caprylic triglyceride (Axona)
FDA- "medical food"

FDA Approved Medications

- **Symptomatic versus Disease-Modifying Treatments:** Symptomatic treatments simply relieve symptoms associated with a disease. They do not affect the underlying cause of the disease;

- Current Alzheimer's drugs boost signaling among neurons but do not stop cell death
  - 1st 3 treat Acetylcholine deficit In Alzheimer's;
  - Next 2 decrease overexcitement of cells;
  - Better taken together;
  - Effect is temporary; circa 3 years
  - Do not improve memory
  - Do not slow the disease process

Lancet, 2017: Risk reduction targets

- Mid-life hearing loss: 9 %;
- Failing to complete secondary (high-school and above) education: 8 %;
- Smoking: 6 %;
- Failing to seek early treatment for depression: 4 %;
- Physical inactivity: 3 %;
- Social isolation: 2 %;
- High blood pressure: 2 %;
- Obesity: 1 %;
- Type 2 diabetes: 1 %.
- All told, the potential risk reduction adds up to 36 %
- Dementia selectively affects the old and frail, women and the socioeconomically and educationally disadvantaged.

10 Ways to Love Your Brain – actions for brain health

- Break a Sweat
- Hit the Books
- Butt Out
- Follow Your Heart
- Heads Up!
- Fuel up Right
- Catch some ZZZs
- Take Care of Your Mental Health
- Buddy Up
- Stump Yourself

Neuroprotective lifestyles: Tips for Protecting Your Brain

Research Caveat

- Majority of studies are observational & correlational, i.e. people who eat chocolate have less CV disease
- Correlation is not causation: gum disease does not cause CV disease, higher plaque in blood vessel does.
- Most studies are cross-sectional (same age cohort), not longitudinal: alcoholics who have cirrhosis
- There are few double blind, randomized, control studies of factors that reduce risk factors for Alzheimer's and cognitive decline.
- Only 2 of current 26 tips are RTC proven

Join UCSF's Brain Registry & Alzheimer's Association's TrialMatch

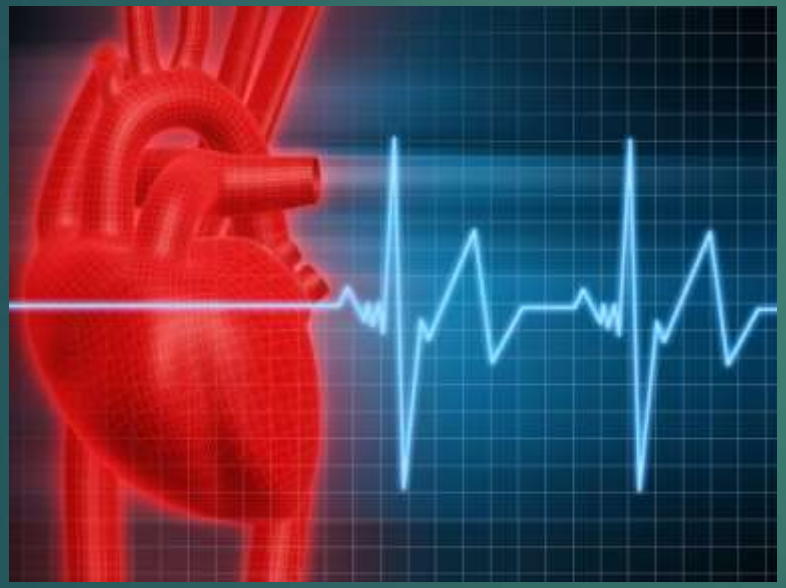
- If you have a computer, join this new research program:
  - http://www.brainhealthregistry.org
  - http://www.alz.org/research/clinical_trials/find_clinical_trials_trialmatch.asp
- Join them!!

Tip #1: Protect your head!

- Blows to the head increase odds of Dementia years later.
- Alzheimer's risk is 4x more common in elderly who suffer a head injury,
- Wear seat belts and helmets, fall-proof your house, and don't take risks.

Tip #2: Protect your Heart

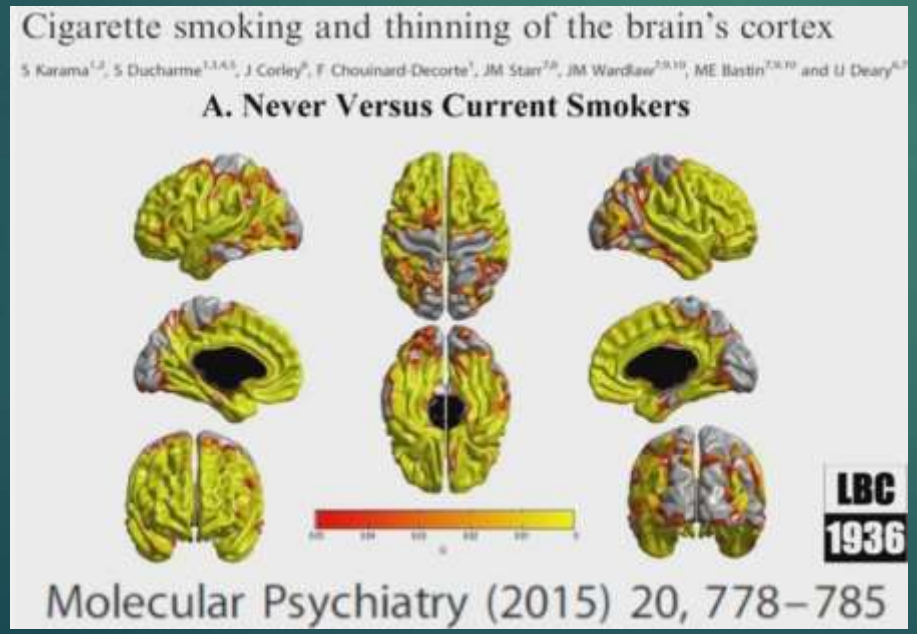
What is bad for your heart is bad for your brain.



Monitor your vascular numbers; take your antihypertensive and cholesterol meds

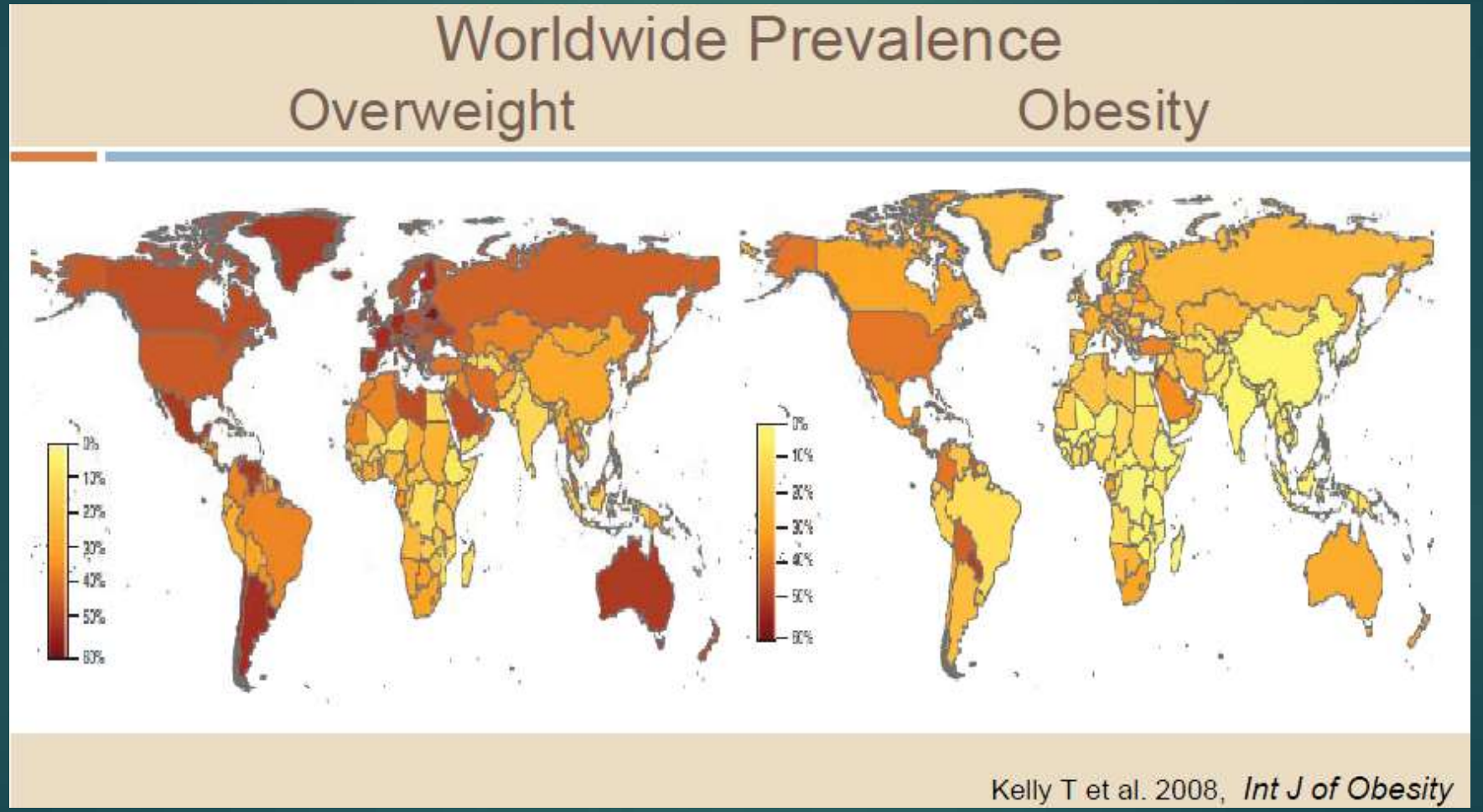
Tip #2a: Do not Smoke

- 6 - **** Quit smoking: Smoking is lethal behavior.
- Smokers are 2 to 4 times more likely to develop heart disease, stroke, and dementia, than nonsmokers.
- Smoking accounts for 11 percent of Alzheimer's cases; “strong evidence” for raising the risk of cognitive decline.



Yellow: thinner cortex in smokers;
If you stop smoking, takes 15-25 years to catch up to thicker cortex

Tip #3: Stay at a normal weight



Tip #4: Take Vitamin D or get Sun

- Older do not get enough sunlight
- Low Vitamin D increases cognitive decline
- Older need 1000 IUs/day (eat with a fat); Eat fish regularly
- Stroke: The lower the vitamin D level, the more severe the stroke and the poorer the recovery
- Higher Vitamin D associated with a decreased risk of developing:
  - cardiovascular disease (33% reduction)
  - type 2 diabetes (55% reduction)
  - metabolic syndrome (51% reduction).

Tip #7: Drink Coffee

- People who drink coffee have:
  - 36% less strokes; less heart disease
  - reduced risk of NCD/dementia (reducing inflammation & beta amyloid); reduces Alzheimer's risk by 20%
  - reduced cancer risk (50% less recurrent breast cancer, prostate cancer, 72% less liver cancer)
  - lower risk of tinnitus in women; lower risk of liver disease
  - lower type 2 diabetes (21-33% less)
  - appears to protect against depression (15% less), Parkinson’s (25% less)
  - More muscle force
  - People who drink two or more cups of coffee a day live longer, 10% less mortality
- 1 to 4 cup per day effect.
- Not for: pregnant women, those with sleep problems
- Lothian study: reverse causation for cognitive decline

Tip #8: Get Enough Sleep

- Brain during sleep:
  - Removes beta amyloid during sleep
  - We sleep to learn. Sleep is crucial to memory functioning
  - Loss of 1 night of sleep increases amount of BA in brain

- Lack of sleep:
  - blunts our ability to focus,
  - makes us dangerous drivers
  - can make us eat too much.

- Lower evidence as cause of AD

Sleep apnea increases stroke, cancer, Dementia & death risk

- As sleep apnea increases, so does Dementia risk
- 1.9x odds MCI at 5 years (JAMA 2001)
- 1.7x odds dementia at 5 years (PloS One 2013)

- Moderate to severe sleep apnea triples risk of stroke, cancer, and earlier death

- There is treatment for apnea: C-pap & B-pap machines

Tip #9: De-stress!

- Chronic stress increases risk of Dementia
- Take a deep breath, expanding your belly. Pause. Exhale slowly to the count of five. Repeat four times.
- Increases levels of “stress hormones” (adrenaline, cortisol)
- High cortisol levels kill hippocampal cells

Tip #10: Treat Depression

- Depression is a risk factor for Dementia
- 15 percent of Alzheimer's cases may stem from depression
- Depression turns off neurogenesis
- Anti-depression TX (either medication or Cognitive Behavioral Therapy or ECT) turns on neurogenesis and reduces risk of Dementia

Antidepressants: Increase Hippocampal Volume

Most Important Tip #11: **** Exercise

Keep moving and Keep your wits

- **** Exercise is the single most powerful and best way to reduce the risk of cognitive decline (~40% reduced risk)
- Not enough physical activity is the number one preventable factor that contributes to Alzheimer's cases
- Aerobic exercise keeps your heart fit and increases the size of hippocampus
- 20 + studies: strong evidence for increasing cognitive function

Current Recommendations

- A – 150 minutes of moderate-intensity aerobic exercise (AHA)
  - 30 minutes of moderate activity (brisk walk; breath hard; can still talk) 5 times a week
  - Or 75 minutes of vigorous activity (jogging)

- B - 20 minutes of muscle strengthening (resistance) activity 2 x a week that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders, and arms).

Sitting kills you sooner; even if you exercise

- Adults = 55% of their day engaged in sedentary pursuits

- Link between extended sitting &/or watching TV to poor health: faster cognitive decline, higher risk of heart disease, diabetes, obesity, cancer, and depression, as well as muscle and joint problems.
- Metabolism slows down 90 percent after 30 minutes of sitting. After two hours, good cholesterol drops 20 percent.

Scientific research says real source of happiness:

Tip #12: Socialize

- 75 year prospective study (724 men; 60 still alive; & 2000 children; 4 directors) – Harvard Study of Adult Development: Longest Prospective Study
- Conclusion: Good relationships keep us happier and healthier
  - Loneliness kills: isolation is toxic (less happy, health declines earlier in midlife, brain declines sooner, die sooner); 1 in 5 Americans
  - Quality of close relationships count; living in conflict with no affection is toxic, & worse than divorce; warm relationships are protective
  - Being in securely attached relationship (you can depend on the other, even if bicker a lot) in your 80s is protective of brain and memory functioning
  - Decreases risk for Dementia & increases longevity (= stopping 2 packs of cigarettes per day effect)

Tip #13: Stay Cognitively Active

- Risk of Dementia is lower with:
  - More educational activities
  - More mentally stimulating activities
  - More leisure activities

Stern, et al., 2005, Alz. Dis. Assoc. Dis.

Tip #14: You are what you eat: Eat like a Greek

- Mediterranean diet:
  - high plant foods (vegetables, fruits, legumes, and cereals);
  - high intake of olive/canola oil; low intake of saturated fat, butter;
  - moderate intake of fish and poultry twice a week
  - red meat to no more than a few times a month; low dairy products; using herbs and spices instead of salt to flavor foods
  - wine in moderation, normally with meals.
- Associated with more exercise & sociability
- Reverse Causation in Scottish Study: no relation to NCD

Diets

- Mediterranean and the Dietary Approaches to Stop Hypertension (DASH) diets:
- both of which reduce risk for hypertension, diabetes, heart attack, and stroke by
- limiting red meat, butter and margarine, cheese, pastries, and sweets, and fried or fast foods,
- incorporating vegetables, especially leafy greens, along with nuts, berries, beans, whole grains, fish, poultry, olive oil, and wine.

Tip #15: Keep learning

- **Hope Levy SFCC classes**
- **Local Universities:**
  - **Fromm Institute at USF,**
  - **OLLI at SF State: Charlie's 6 week class in January**
  - **CLIR,**
  - **OSHER**
- **Road Scholars**
- **Lifelong Learning Institutes**
- **Local Senior Centers**
- **SeniorNet OASIS Institutes (volunteer)**
- **Shepherd's Centers of America**
- **Senior Community Service Employment Program (SCSEP)**

Computer Cognitive Training: Current Conclusions

- Cannot repair or restore neurons
- Transfer of computerized training is still controversial and being researched.
- Not a disease modifying intervention
- CT is not a substitute for exercise, CV medications, or socializing
- Every hour spent alone at the computer is an hour not spent hiking, learning a new language, inventing a new recipe, or playing with your grandkids.

Tip #16: Be Passionate!: Have a Purpose in Life

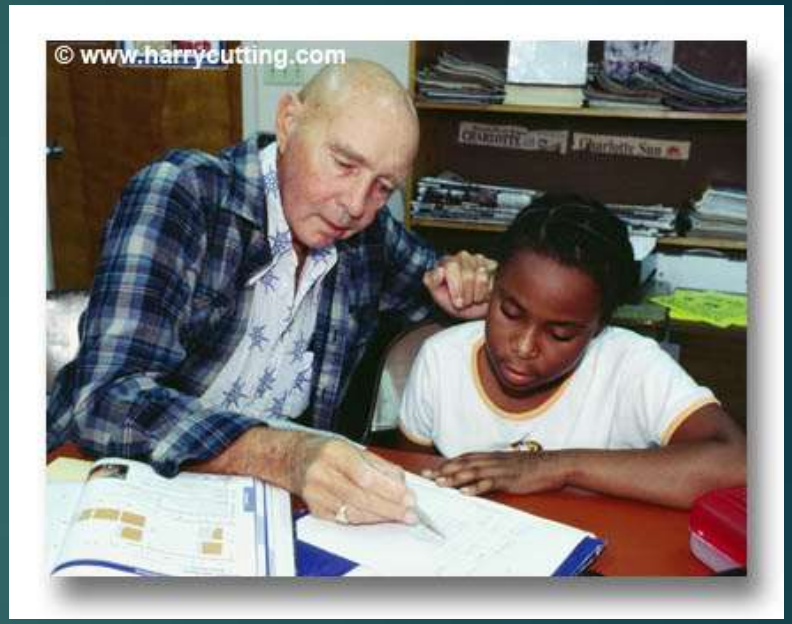
- Purpose in life (psychological tendency to derive meaning from life's experiences and possess a sense of intentionality and goal directedness)

- Greater purpose in life is associated with:
  - 2x reduced risk of AD and MCI
  - exhibit better cognitive function
  - less disability
  - have better mental health
  - live longer.

P. Boyle, et al., 2012

Tip #17: Volunteering is Win-Win: You live longer

- Meta-analysis: Helping others yields health benefits for the helper.
- Volunteering reduces mortality risk by 25%.
- Seniors who tutor young children in reading and math have slower cognitive decline



Tip #18: Hearing and Vision loss

- 1 in 3 people older than 60 has significant hearing loss, but most older adults wait five to 15 years before they seek help
- 30% of higher risk of dementia: cognitive impairment were linearly associated with the severity of an individual's baseline hearing loss
- Good hearing and vision are primary ways you stimulate your neurons.
- Poor hearing and vision reduce neuroplasticity
- Get good hearing aides and glasses!!

Summary: Prevention/Rx Strategies

- No evidence for current medications

- Physical exercise:
  - Lots epi studies ~40% risk decline
  - Multiple RCTs
  - Goal: 30 min/5 days

- Sleep: Early epi,
  - ~25% increased risk?
  - No RCTs

- Diet:
  - Lots epi ~20% risk decline
  - Supplements: O3FAs, Vit D

- Cognitive exercise:
  - No clear epi
  - Effects on Exec Fxn
  - No risk reduction

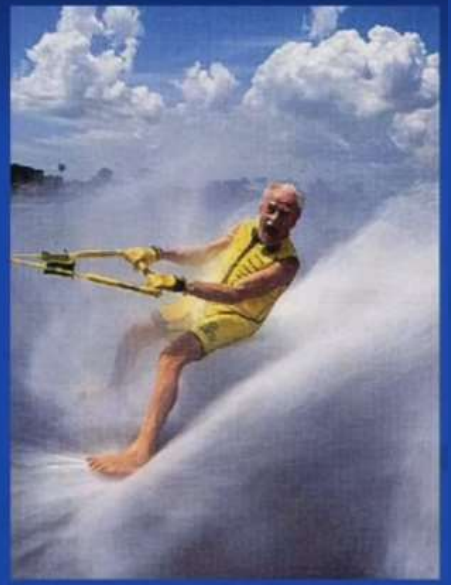
Future: combination approaches:
(FINGER – Finnish Geriatric Intervention Study)

Protect through a Lifestyle Intervention to Reduce Risk (U.S. POINTER), Laura Baker

Be An Active Learner!

If you want the 1-step program…

USE IT
OR
LOSE IT!



Ten Commandments for Brain Fitness

I. Choose thy parents wisely (For brain genes & IQ)

II. Minimize risk factors for cerebrovascular disease (HTN, Hyperlipidemia, DM, overweight, smoking)

III. Eat a Mediterranean Diet

IV. Exercise daily.

V. Maintain intellectual engagement throughout life

VI. Stay socially engaged with others.

VII. Get sufficiently good quality sleep

VIII. Drink 1 drink of alcohol per day

IX. Manage your stress effectively

X. Don’t text or use cell phone while driving.

Please support Alzheimer's Association

- Nationwide 24-hour Helpline
  - Whether you need information or just want to talk, call us at 1.800.272.3900
- www.alz.org
  - Web site is a rich resource of evidence-based content related to Alzheimer's and Dementia
- 2017 Alzheimer's Disease Facts and Figures
  - https://www.alz.org/documents_custom/2017-facts-and-figures.pdf

Helpful Resources

Great websites

- www.alz.org
- www.alzforum.org
- www.alzheimers.org

Best: Exercise & Socialize

Interact with your friends

Laugh!

Here he is!

Politicians continuing to discuss global warming

Isaac Cordal

George Bernard Shaw

"We don't stop playing because we grow old;

we grow old because we stop playing."

As the Vulcans say…

Live long and prosper!

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