Brain Fitness

What we know about keeping your brain Healthy:
You need to start early

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2019

Aging without dementia is achievable.

- Is dementia an inevitable consequence of aging?
- Is aging without dementia achievable?
- 75% of people do not realize they can reduce the risk of dementia.
- Those who live to be 100 often avoid dementia (30%; males less).
- Dementia is not an inevitable consequence of extreme old ages
- Nearly half of 100 year olds with dementia did not have sufficient brain pathology to explain their cognitive symptoms.
- 30% of very old people who have no dementia or cognitive impairment have moderate-to-high Alzheimer disease.

Aging without dementia is achievable 2

- This suggests that certain compensatory mechanisms (e.g., cognitive reserve or resilience) may play a role in helping people in extreme old ages escape the dementia syndrome.
- Evidence has been accumulating in recent years indicating that the incidence of dementia has declined in Europe and North America, which supports the view that the risk of dementia in late life is modifiable.
- Evidence has emerged that intervention strategies that promote general health, maintain vascular health, and increase cognitive reserve are likely to help preserve cognitive function till late life, thus achieving the goal of aging without dementia.

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.
- While genetics drives vulnerability to Alzheimer's, the way we live earlier in life will determine how normal our cognition remains, and for how long.

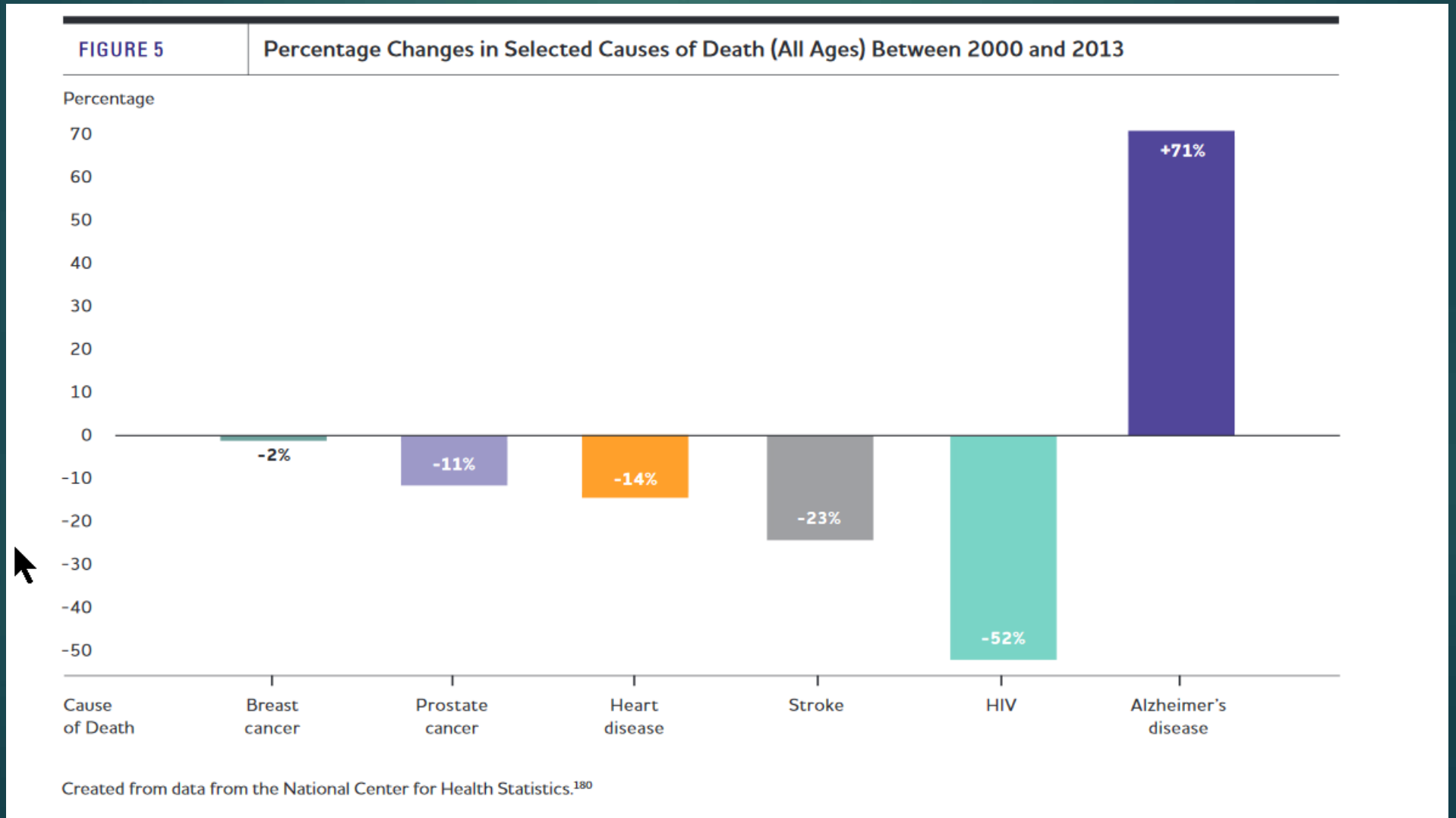
Cognitive decline due to aging

- All cognitive decline in cognitive normals is pathologically driven (CV, Inflammation, etc.); no “normal” aging; all aging is pathological
- Issues are CV risks, oxidative stress, inflammation, genetics, lifestyle, health
- We will never be able to cure late age dementia if people are elderly: too late; too many lost neurons
- Aim: early prevention; don’t want CV, HTN, abnormal BA; want lowest BP without fainting

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

- You cannot change your age or the genes you are born with.
- Major NCD/dementia depends on your lifestyle choices
- Nothing has been shown to prevent Alzheimer's pathology, but there are evidence-based ways to improve and prolong brain functionality, and to reduce the probability of cognitive decline

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



Created from data from the National Center for Health Statistics.[180]

50% of AD risk are Modifiable

- diabetes mellitus and insulin resistance,
- obesity,
- metabolic syndrome,
- hypertension,
- hypercholesterolemia,
- cerebrovascular disease,
- depression,
- psychological and physiologic stress,
- traumatic brain injury,
- sleep-disordered breathing,

- smoking,
- alcohol abuse,
- high blood pressure,
- renal disease,
- alcohol and tobacco use,
- high cholesterol,
- coronary heart disease,
- sedentary life style,
- diet.

Modifiable factors appearing to protect against AD

- cognitive reserve and mental activity,
- educational attainment
- lifelong learning,
- cognitive leisure activities,
- physical activity and exercise,
- social engagement,
- mindfulness and wellness activities,
- optimism and purpose in life,
- healthy diet (fresh fruits and vegetables, whole grains, and lean proteins, and avoiding processed foods)
- omega-3 intake

A review of 19 studies:
crossword puzzles,
card games,
computer use,
arts or crafts,
taking classes,
group discussions,
listening to music.

Dear God,
My prayer for 2018 is for a fat bank account & a thin body.
Please don't mix these up like you did last year.

Chill Out

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

Bigger is better

- An examination of brain tissue (n = 35) has revealed that:
  - Brain cells are significantly bigger in people with high IQ scores than those with lower scores.
  - The dendrites are longer, suggesting that these neurons may be capable of receiving and processing more information.
  - Cells from people with high IQs transmit faster: people with higher IQs tend to have faster reaction times.
  - The properties of brain cells explain about 25% of the differences in IQ. Genes, on the other hand, are thought to account for only around 3 to 7 per cent of the difference.
  - Cause or a consequence of high IQ?

Higher IQ, less dendrites

- Intelligent people tend to have larger brains; predominantly located in parieto-frontal regions.
- Despite their comparatively high number of neurons -- the brains of intelligent people demonstrated less neuronal activity during an IQ test than the brains of less intelligent individuals.
- Intelligent brains possess lean, yet efficient neuronal connections; boast high mental performance at low neuronal activity.
- The more intelligent a person, the fewer dendrites there are in their cerebral cortex; have lower values of dendritic density and arborization
- These results suggest that the neuronal circuitry associated with higher intelligence is organized in a sparse and efficient manner, fostering more directed information processing and less cortical activity during reasoning.

Erhan Genç, et al., 2018

Brain has ability to change: Neuroplasticity

- Neuroplasticity = Physical and chemical brain changes based on experience
- It is the brain's ability to rewire itself or change itself based on new experience
- N = creation of new synapses and dendrites

Experience changes our brains: London Taxi Drivers

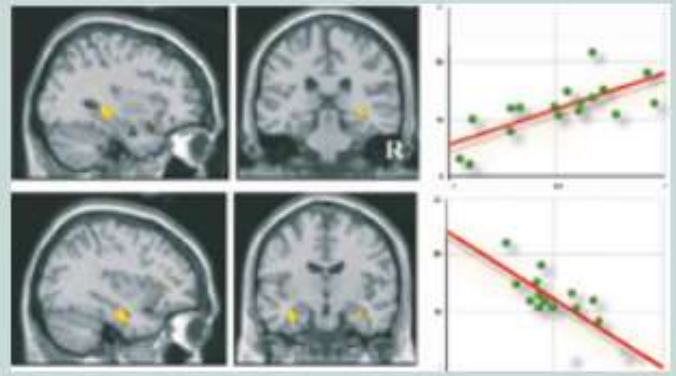
If you lived in London, and wanted to grow your hippocampus, which driving job would you choose?

Knowledge exam: 3 of 10 pass

25,000 streets
1400 landmarks

Study of London Taxi cab drivers (vs. bus drivers): To earn their licenses, cab drivers in training spend three to four years driving around the city on mopeds, memorizing a labyrinth of 25,000 streets within a 10-kilometer radius of Charing Cross train station, as well as thousands of tourist attractions and hot spots. "The Knowledge" exams that only about 50 percent of hopefuls pass.

Larger Right Posterior Hippocampus in London Taxi Drivers:
7% larger, but otherwise normal memory



Christoph Schneider, based on an original from: Maguire EA, Woollett K, Spiers HJ. 2006. London taxi drivers and bus drivers: A structural MRI and neuropsychological analysis. Hippocampus 16:1091-1101.

Enlarged the posterior hippocampus at the expense of the anterior

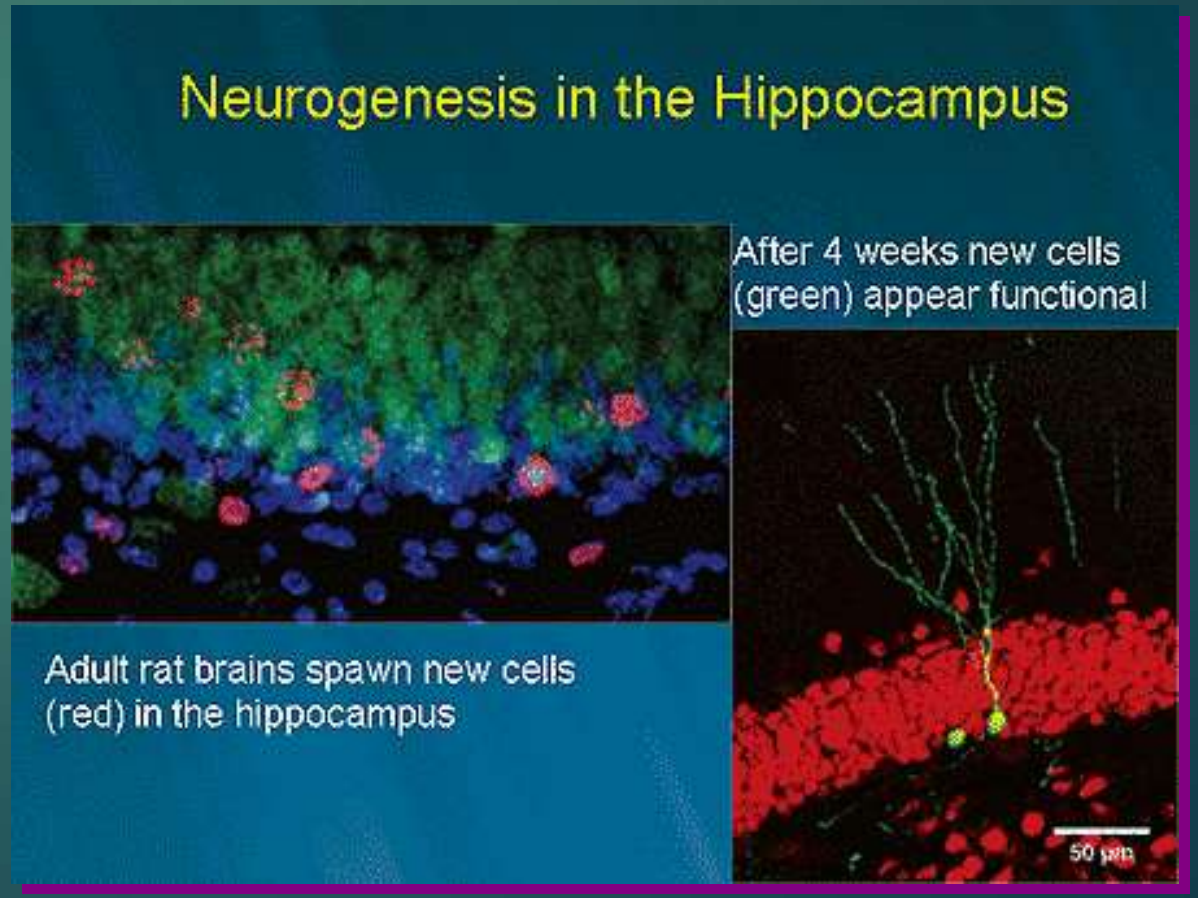
Use it or lose it

- Without use, brain cells are signaled that it is no longer needed
  - Dendrites atrophy
  - Synaptic connections weaken
- Negative neuroplasticity in older adults:
  - “Brain disuse” and sedentary lifestyles
  - 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:
  - Exercise, Sex
  - Calorie restriction
  - Antidepressants
  - THC
- Ways to decrease
  - Depression
  - Sleep deprivation

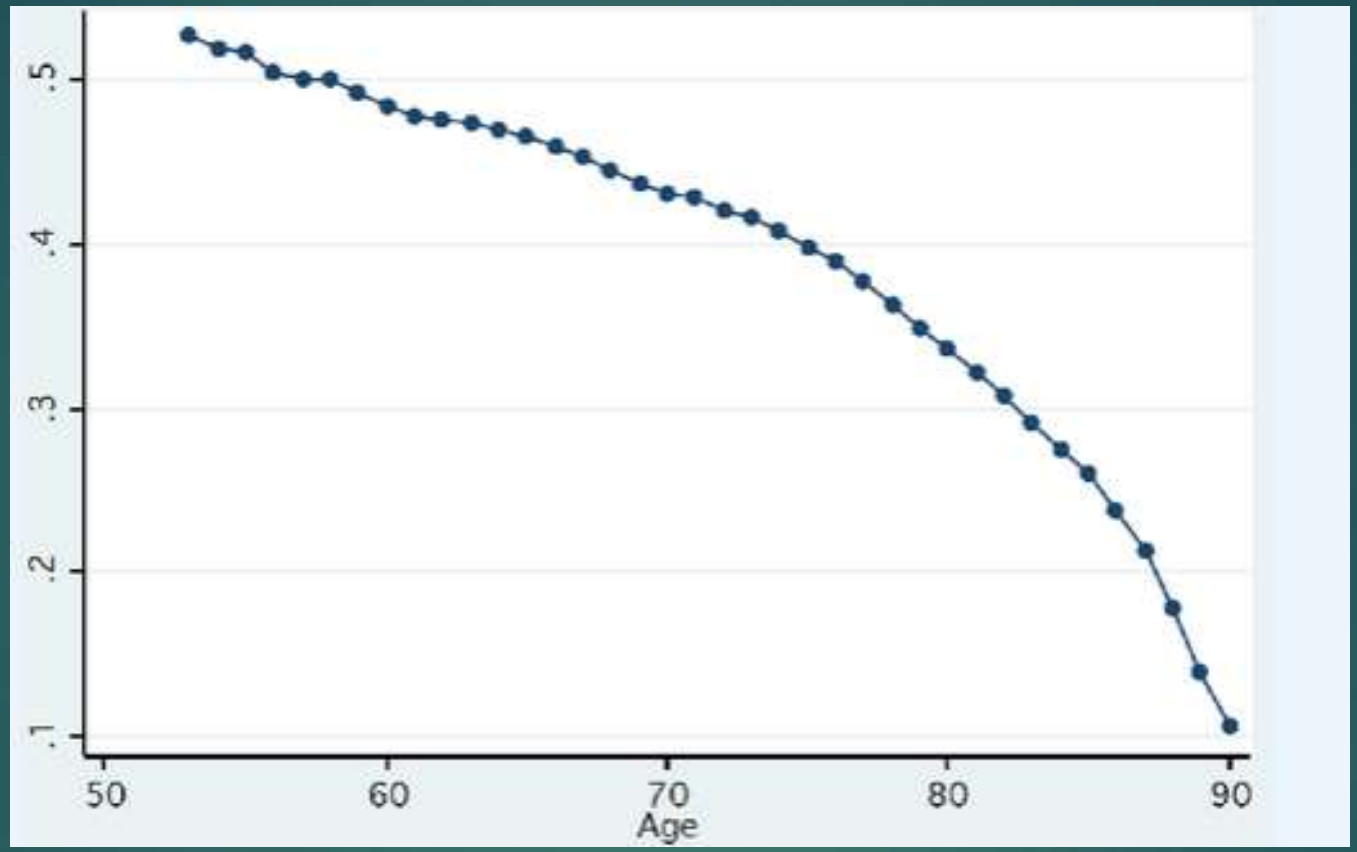


Neuroplasticity can also have negative consequences

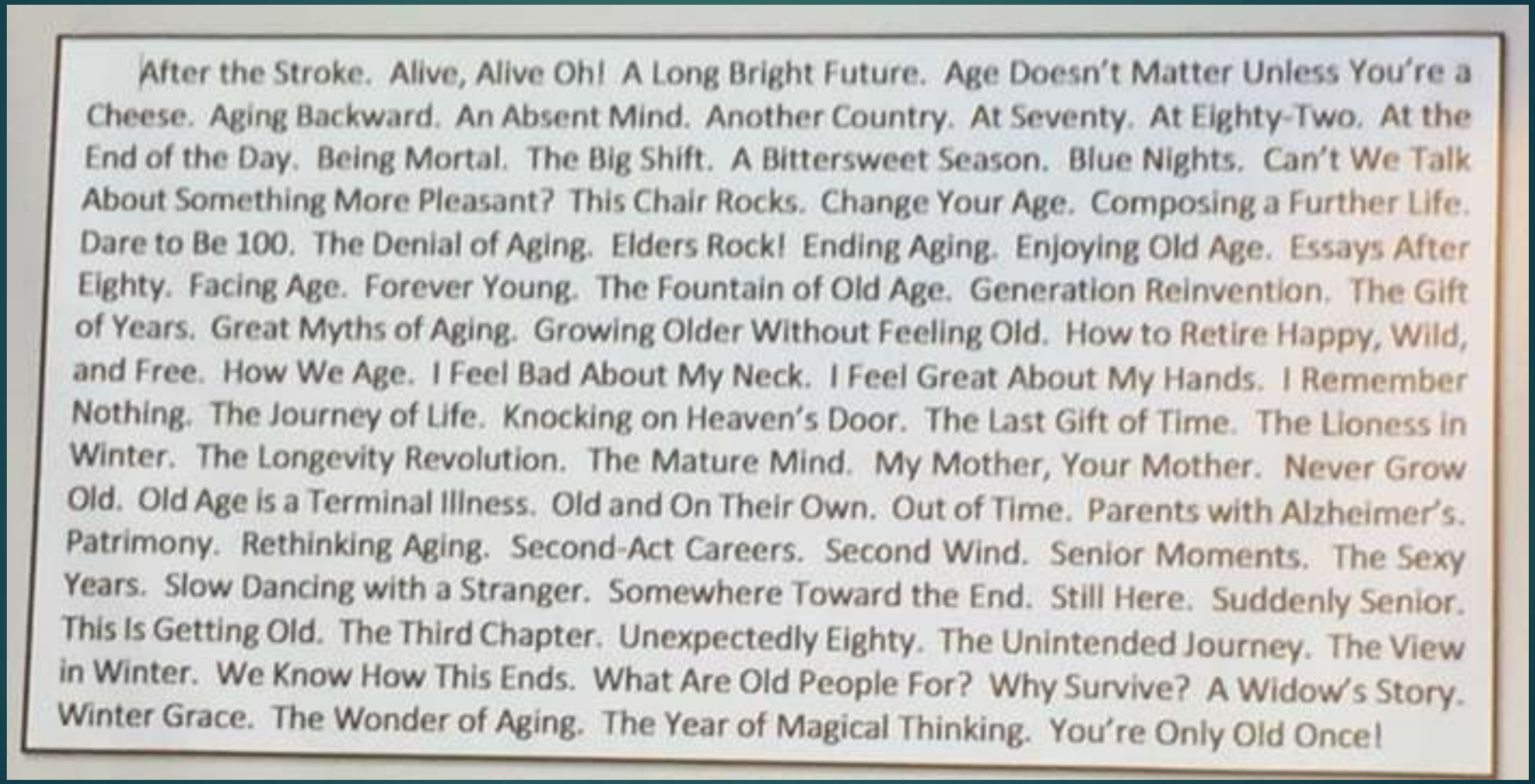
- Negative neuroplasticity in older adults:
  - Reduced brain activity - "Brain disuse" and sedentary lifestyles
  - Negative learning (loss of skills) due to non practice
  - Example: sitting all day in front of TV

Intellectual Ability Declines in Normal Aging

Public Perception of Normal Aging: Major Decline with Age



Old age is always 15 years older than I am



After the Stroke. Alive, Alive Oh! A Long Bright Future. Age Doesn't Matter Unless You're a Cheese. Aging Backward. An Absent Mind. Another Country. At Seventy. At Eighty-Two. At the End of the Day. Being Mortal. The Big Shift. A Bittersweet Season. Blue Nights. Can't We Talk About Something More Pleasant? This Chair Rocks. Change Your Age. Composing a Further Life. Dare to Be 100. The Denial of Aging. Elders Rock! Ending Aging. Enjoying Old Age. Essays After Eighty. Facing Age. Forever Young. The Fountain of Old Age. Generation Reinvention. The Gift of Years. Great Myths of Aging. Growing Older Without Feeling Old. How to Retire Happy, Wild, and Free. How We Age. I Feel Bad About My Neck. I Feel Great About My Hands. I Remember Nothing. The Journey of Life. Knocking on Heaven's Door. The Last Gift of Time. The Lioness in Winter. The Longevity Revolution. The Mature Mind. My Mother, Your Mother. Never Grow Old. Old Age is a Terminal Illness. Old and On Their Own. Out of Time. Parents with Alzheimer's. Patrimony. Rethinking Aging. Second-Act Careers. Second Wind. Senior Moments. The Sexy Years. Slow Dancing with a Stranger. Somewhere Toward the End. Still Here. Suddenly Senior. This Is Getting Old. The Third Chapter. Unexpectedly Eighty. The Unintended Journey. The View in Winter. We Know How This Ends. What Are Old People For? Why Survive? A Widow's Story. Winter Grace. The Wonder of Aging. The Year of Magical Thinking. You're Only Old Once!

Old Age?

From age 70 es, won the Nobel Prize i

Attitude toward aging: Be Positive!

- Seniors who view their own aging as positive live 7.5 years longer than other seniors.
- Those with positive age beliefs are significantly less likely to develop dementia.

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)
- 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

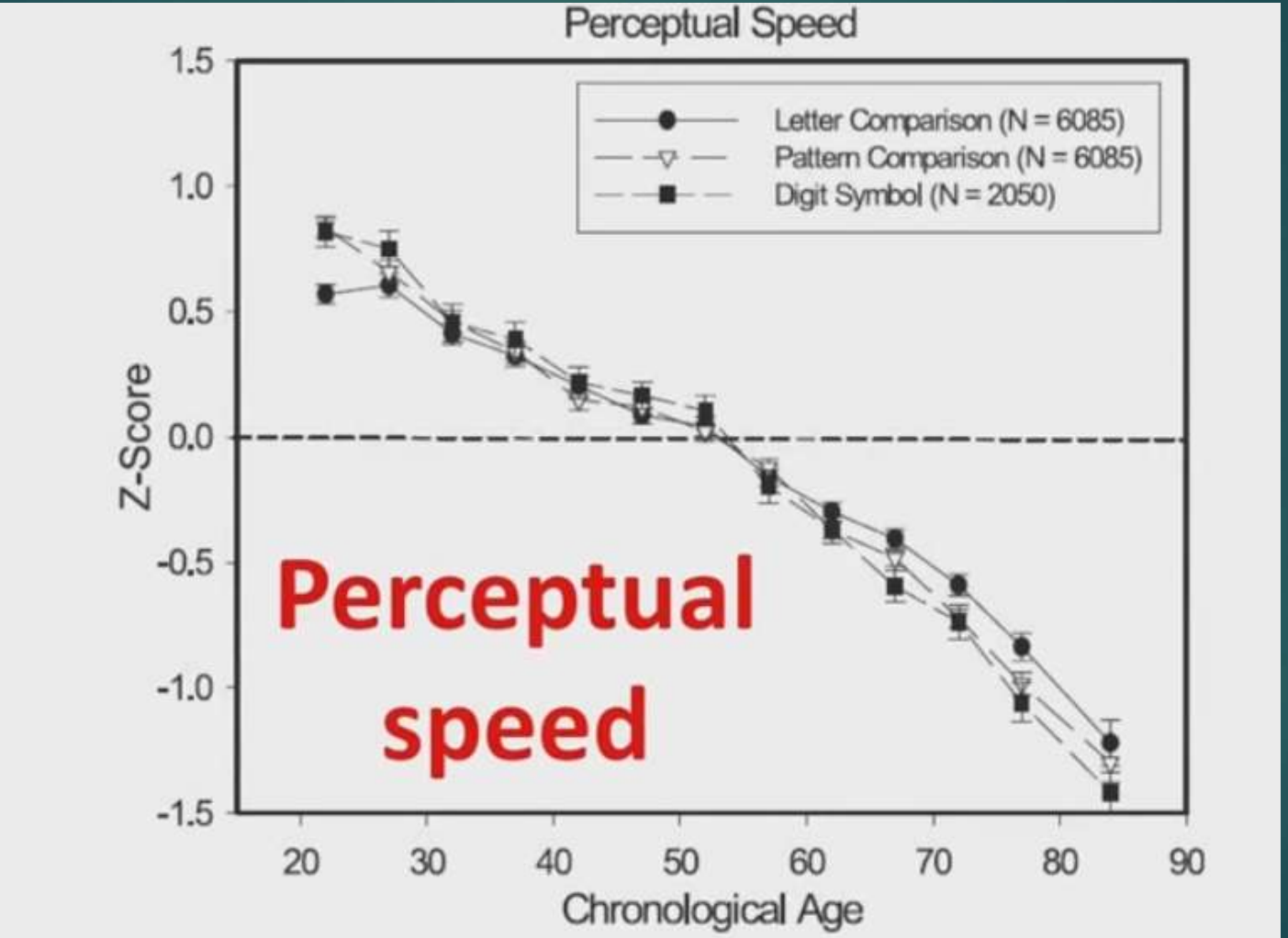
- K. Warner Schaie and Sherry Willis's Seattle Longitudinal Study:
- Reliable decline can be found for all abilities by age 74
- By age 81, average decline is 1 s.d. for most abilities
- Cognitive better from age 40-65 than in our 20s for:
  - Vocabulary
  - Verbal Memory
  - Spatial Orientation
  - 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 ↓ ↓ ↓

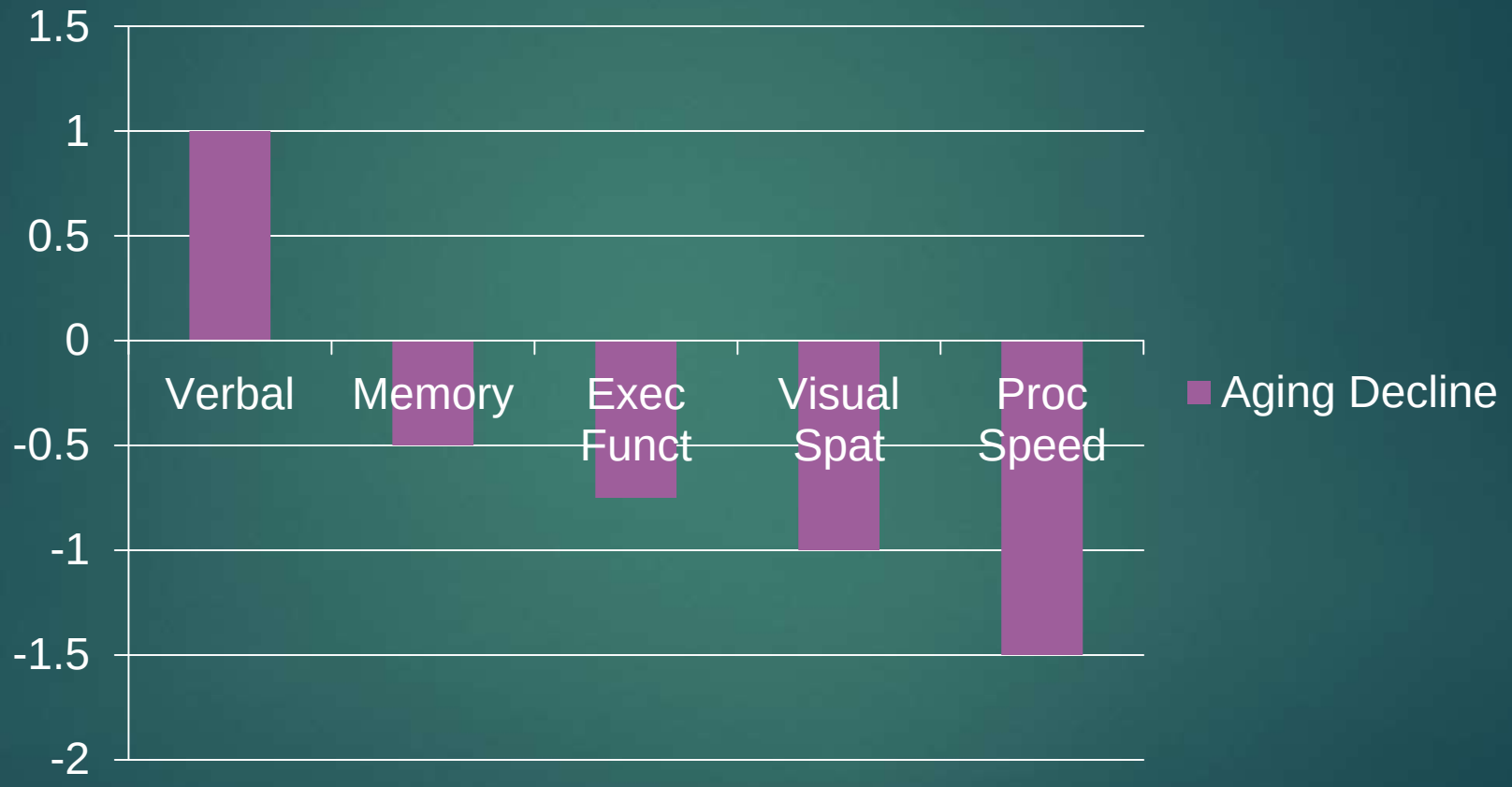
We are all past our peak: 1 ½ s.d. decrease ↓↓↓



Salthouse (2004) *Intelligence*, *32*, 541-561.

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

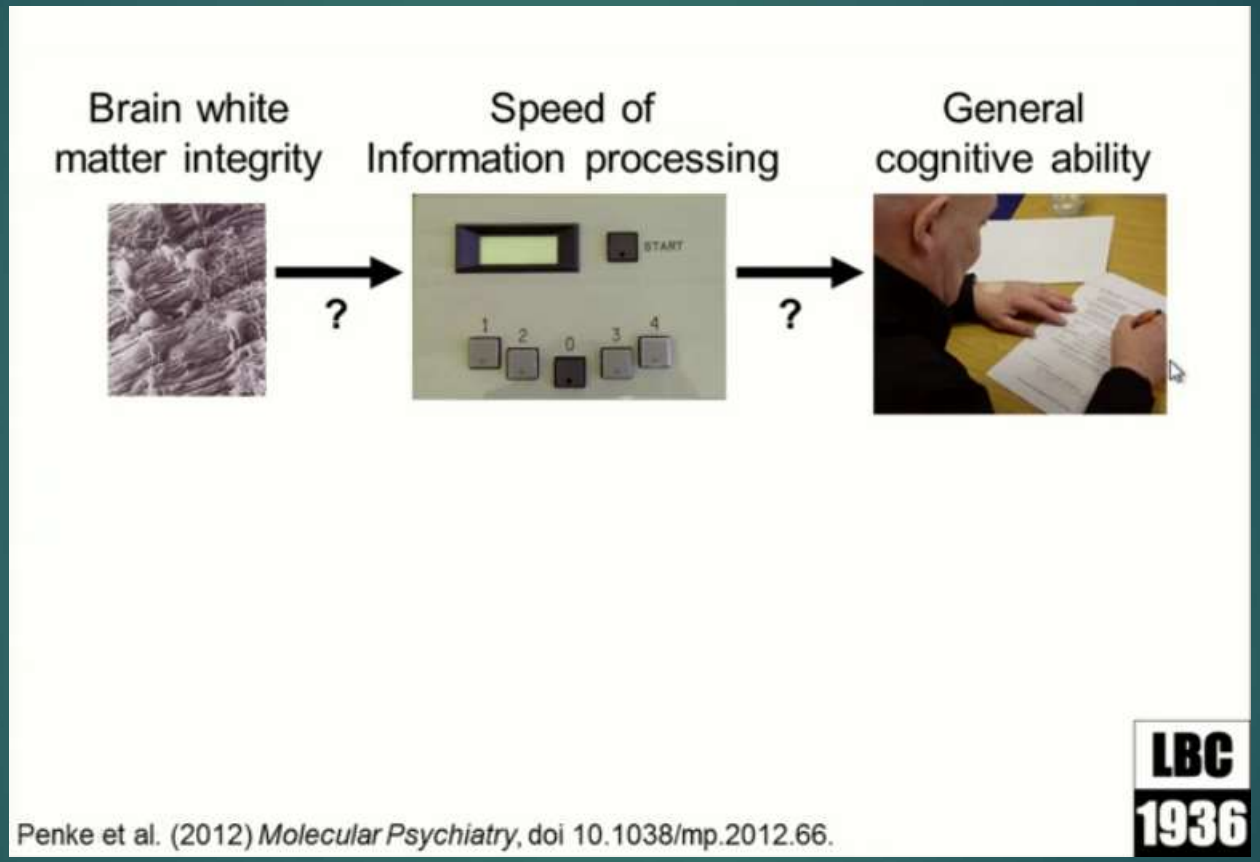
After age 65, we return to this speed!

Lenovo W5307
Intel Core i72. @ 2.70GHz

2500 times faster

Our brain internet (White Matter) counts:

White Matter Health = Faster Processing speed = Good Cognition



Lothian study = the better WM integrity, faster processing speed is, and better cognition is at age 70

Normal Age-Related Changes 2

- Cognitively better with age if:
  - better heart condition & absence of other chronic diseases
  - favorable environment mediated by having more money
  - higher education
  - work that involves complex thinking and social interaction
  - involvement in a complex and intellectually stimulating environment
  - maintenance of high levels of processing speed

- higher intellectual status of spouse: spouse's cognitive ability was protective: lower IQ spouse gets the benefit (lower risk of AD)

Two Different Aging Populations

- Age Unimpaired:
  - Optimally healthy and higher SES:
  - Fewer cognitive changes
- Age Impaired:
  - Typically health (DM↑, HTN↑, obesity↑, cardiac↓):
  -
  - More cognitive deficits

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
- 90+ Study: Past age 90, high blood pressure better than low blood pressure.

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.

Alzheimer's ≠ Major NCD

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

Normals with AD Pathology

- 30% of cognitively normal elderly
  - have intermediate or high levels of Alzheimer's disease in brain (abnormal proteins & synaptic loss)
  - but have no cognitive decline

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 at Univ. of MN

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 had less dementia than those who had worse linguistic ability.
- Early Idea density and grammatical complexity: Idea density predicted AD in 60 years with 80% accuracy. The fewer the number of ideas expressed in those autobiographies the greater the severity of dementia later in life

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 pathology of AD

Cognitive Reserve: what buffers the impact of brain pathology on cognitive function

- Nun's Study Lead to concept of that some people can tolerate brain damage for a longer time without showing intellectual signs of damage.

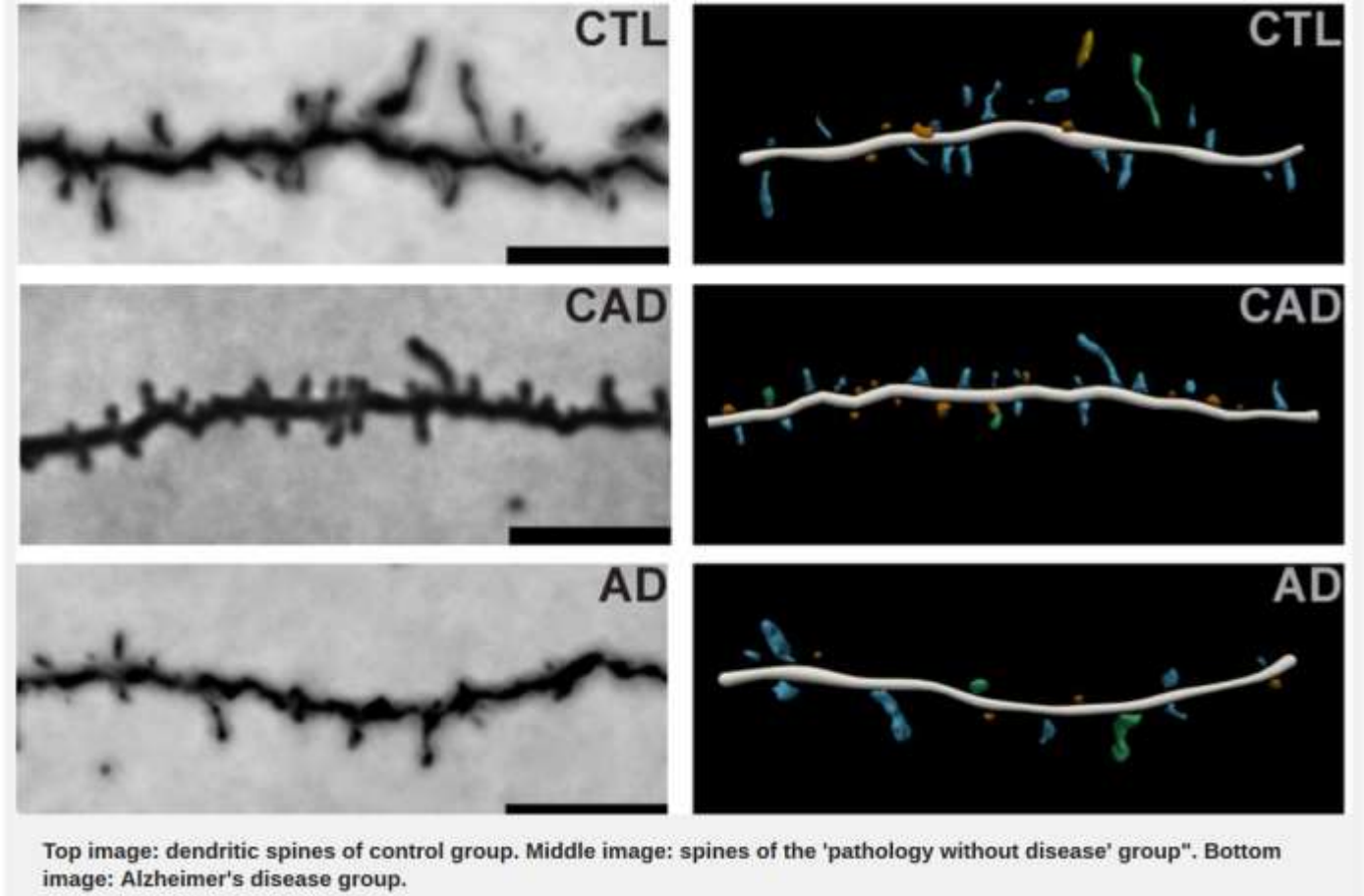
- Cognitive reserve: difference between amount of brain pathology & actual cognitive function

- CR = more synaptic connections, abundance of neuronal connections

- CR benefit: Protective = can have more disease before cognitive decline

- Cost: Once cognitive decline begins, brain decline goes faster (have used up reserve)

Presence of more & larger dendritic spines create a protective effect against AD in people with BA & Tau accumulation



Top image: dendritic spines of control group. Middle image: spines of the 'pathology without disease' group". Bottom image: Alzheimer's disease group.

- Pathology, but no disease
- Longer spines than other 2

Pts with high BA & Tau with no cognitive decline had larger, more numerous dendritic spines than those with dementia,

Jeremy Herskowitz, et al., 2017

Predictors of Cognitive Reserve

- Bigger brain/head circumference
- Higher IQ
- Higher vocabulary level
- Higher education: college degree reduces cognitive decline by up to a decade; The more educated also live longer
- Occupational complexity: Work that involves complex thinking and social interaction
- Higher Social Economic Status
- Regular cognitive activity (reading, crossword puzzles)
- Higher literacy
- Social engagement
- Early-age physical activity
- Better cardiovascular status

Brain networks in Cognitive Reserve: experience changes brain

- Brain networks with more alternative routes between nodes provide more ability of compensation or resilience to brain damages
- Education strengthens brain network reliability in normal aging
- Highly educated subjects with normal cognition had more brain volume than poorly educated subjects
- A form of neuroplasticity or born with better brain?

Proof of Cognitive Reserve: Dementia was decreasing

- 2016 JAMA study, more normative sample: The percent of older US adults with dementia, including Alzheimer's disease, declined from 12% percent in 2000 to 9 percent in 2012, a decrease of nearly 25% (1M people). The decline was even greater in 85+ age group.

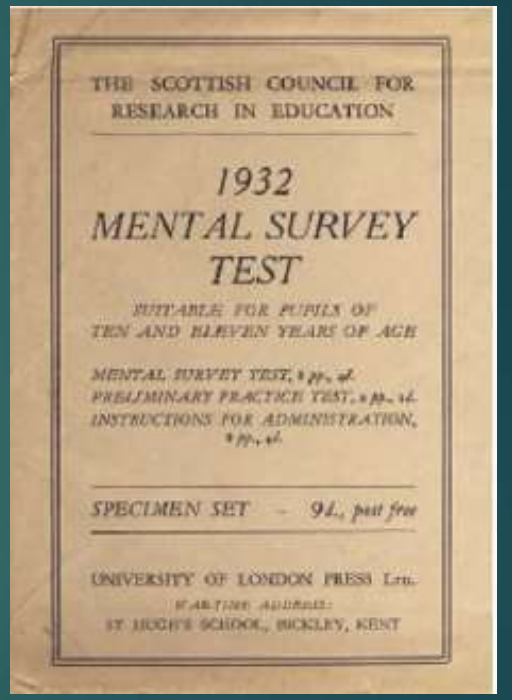
- Increases in education and better control of cardiovascular risk factors as likely contributors to declining dementia risk.

"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 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.
PRELIMINARY PRACTICE TEST, 2 pp. 1d.
INSTRUCTIONS FOR ADMINISTRATION, 8 pp. 4d.

SPECIMEN SET – 9d., post free

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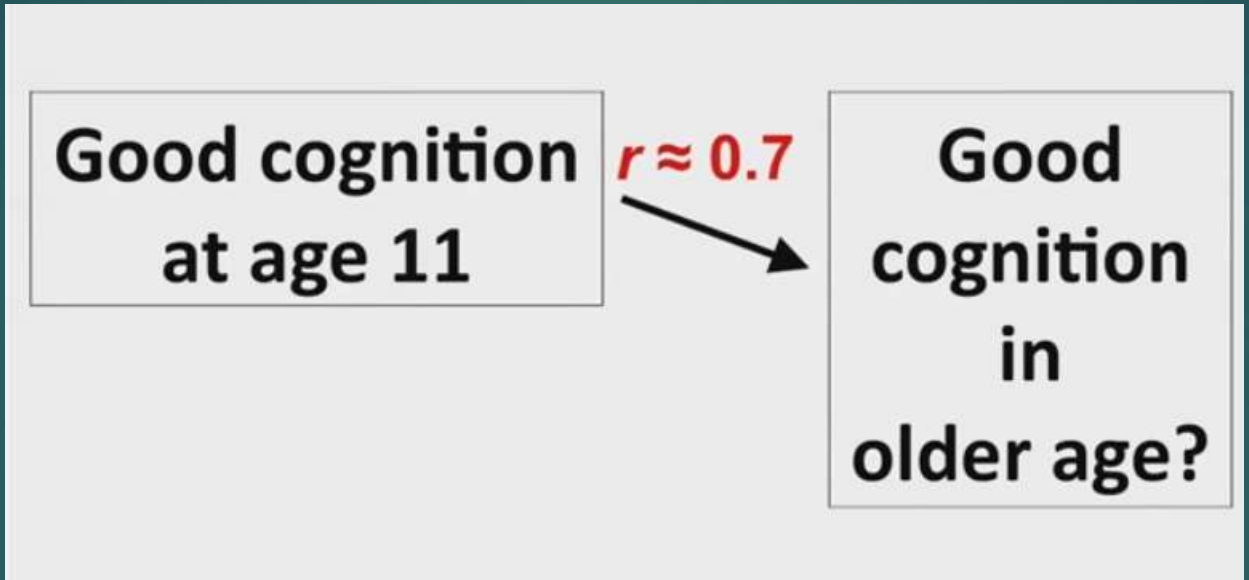
EARLIER ADDRESS:
ST HUGH'S SCHOOL, BICKLEY, KENT

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

Lost, and then Found

Brain you are born with really counts- cognition is stable:

50% of the variance at age 77 is explained by IQ at age 11



But lifestyle matters: those who did not smoke, were physically fit, bilingual, more educated had higher IQ scores at age 77

Abstract problem solving, fast thinking & reaction time declined in all.

Those born with a better brain have initial advantage

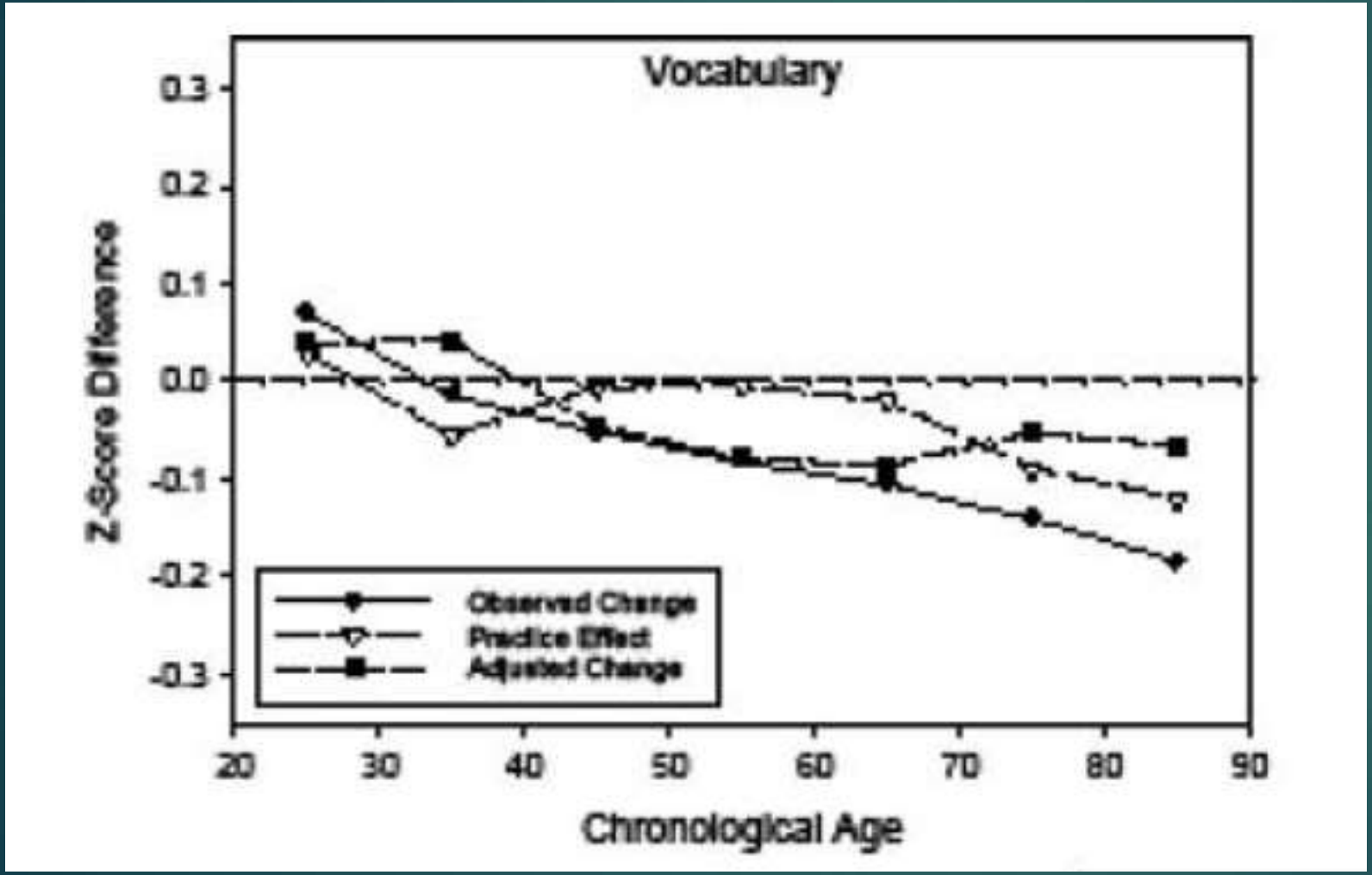
Brains don’t want to be demented

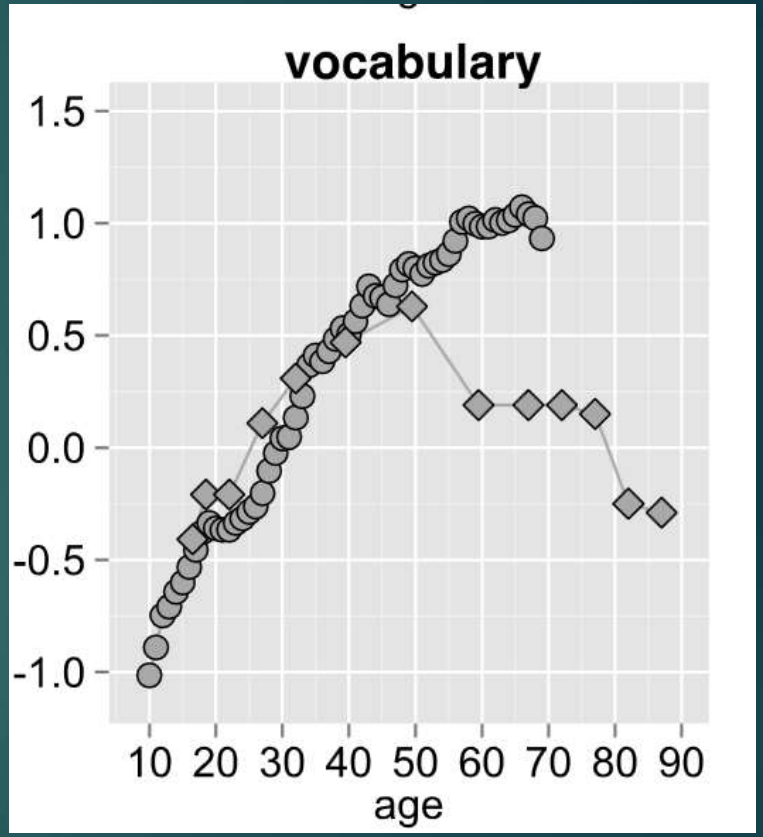
- Decline predictors:
  - Depression ↓
  - Loneliness ↓
  - Anxiety ↓
  - Neuroticism ↓
  - Kidney disease ↓

Resilience markers:

Education ↑
Social networks ↑
Conscientiousness ↑
Harm avoidance ↑
Good Sleep ↑
Purpose in life ↑
Late life cognitive activity ↑

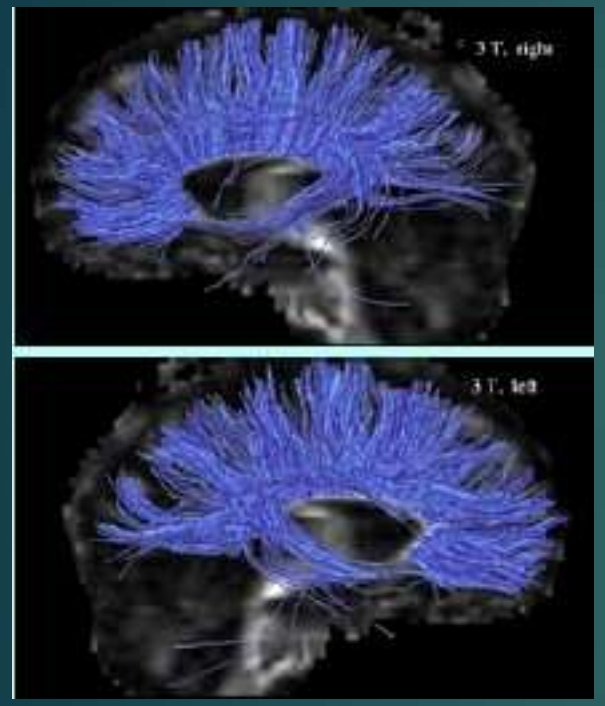
Vocabulary stays relatively intact

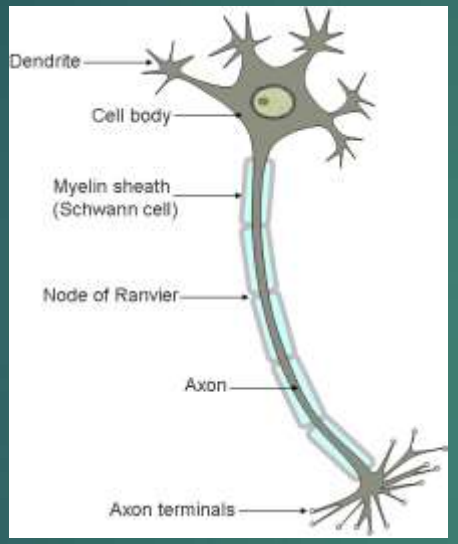


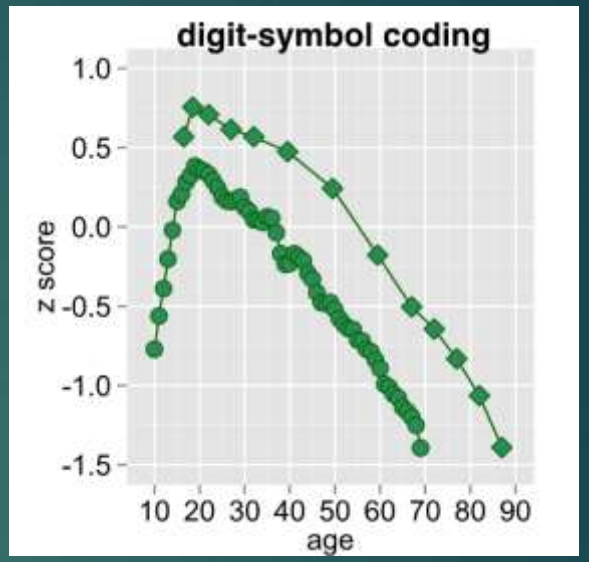


Squares = less than .05 change

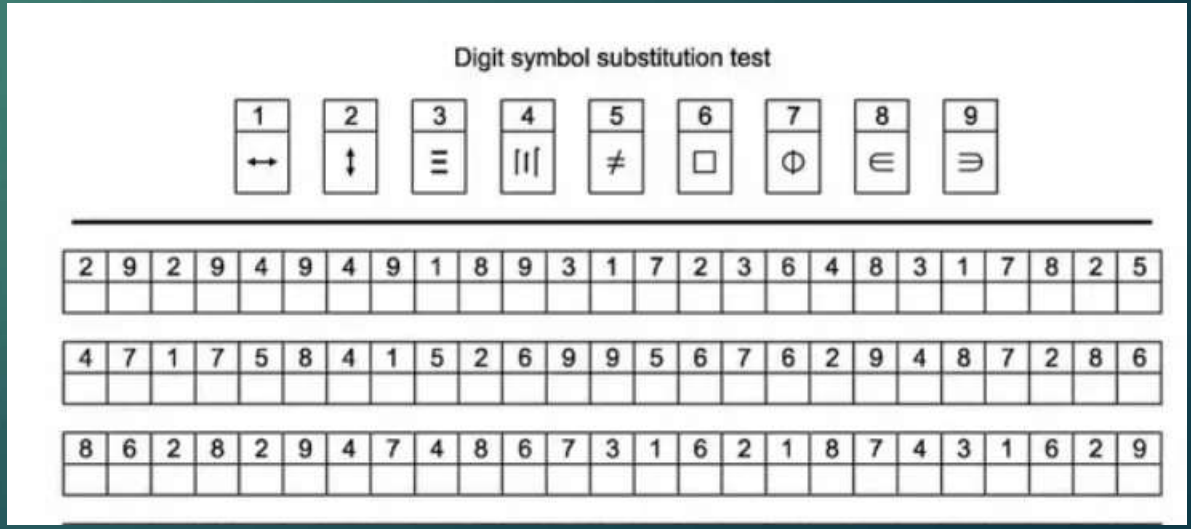
Older are Centrally Slowed: Processing Speed Decreases (3 ms per decade due to WM decline)



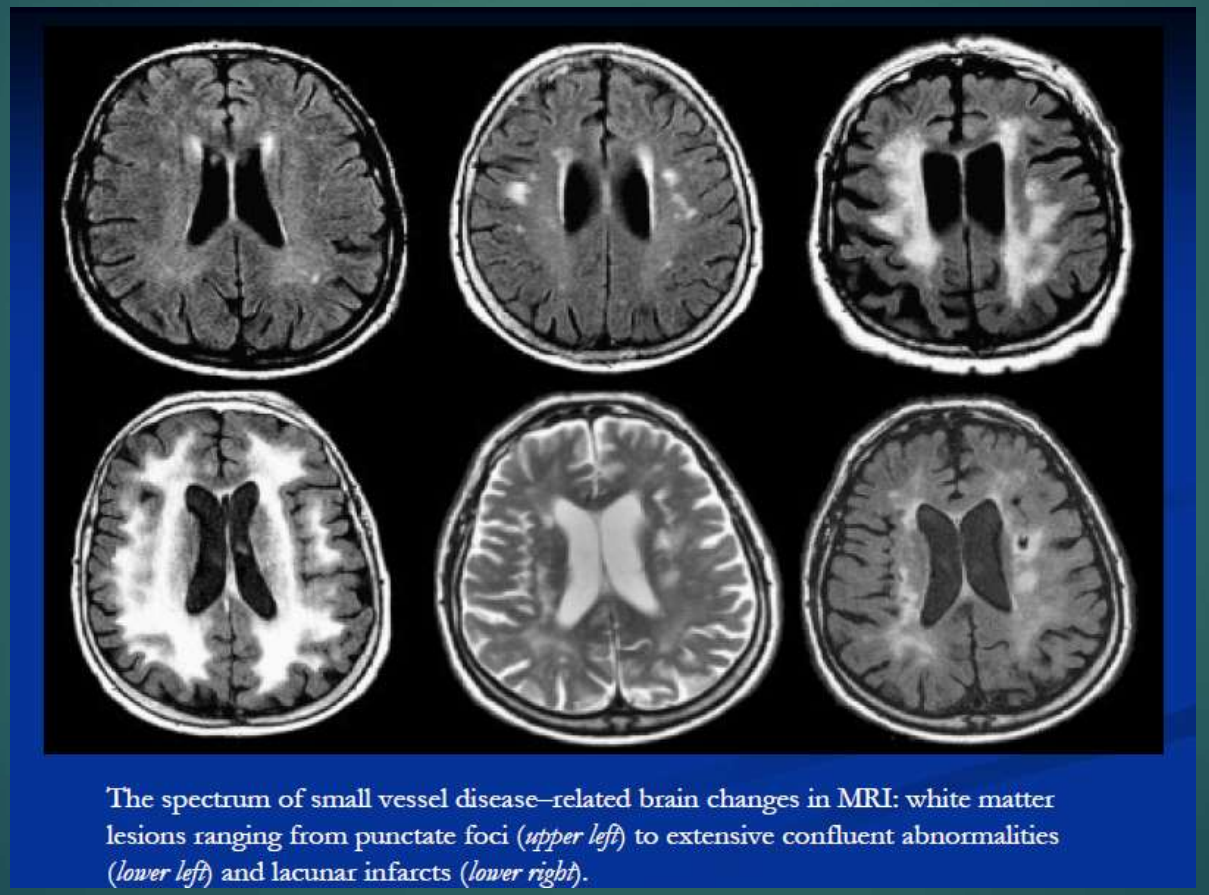




One of reasons naming ability decreases



Mild to Extensive Vascular WM Hyperintensities:
Slower Processing Speed



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

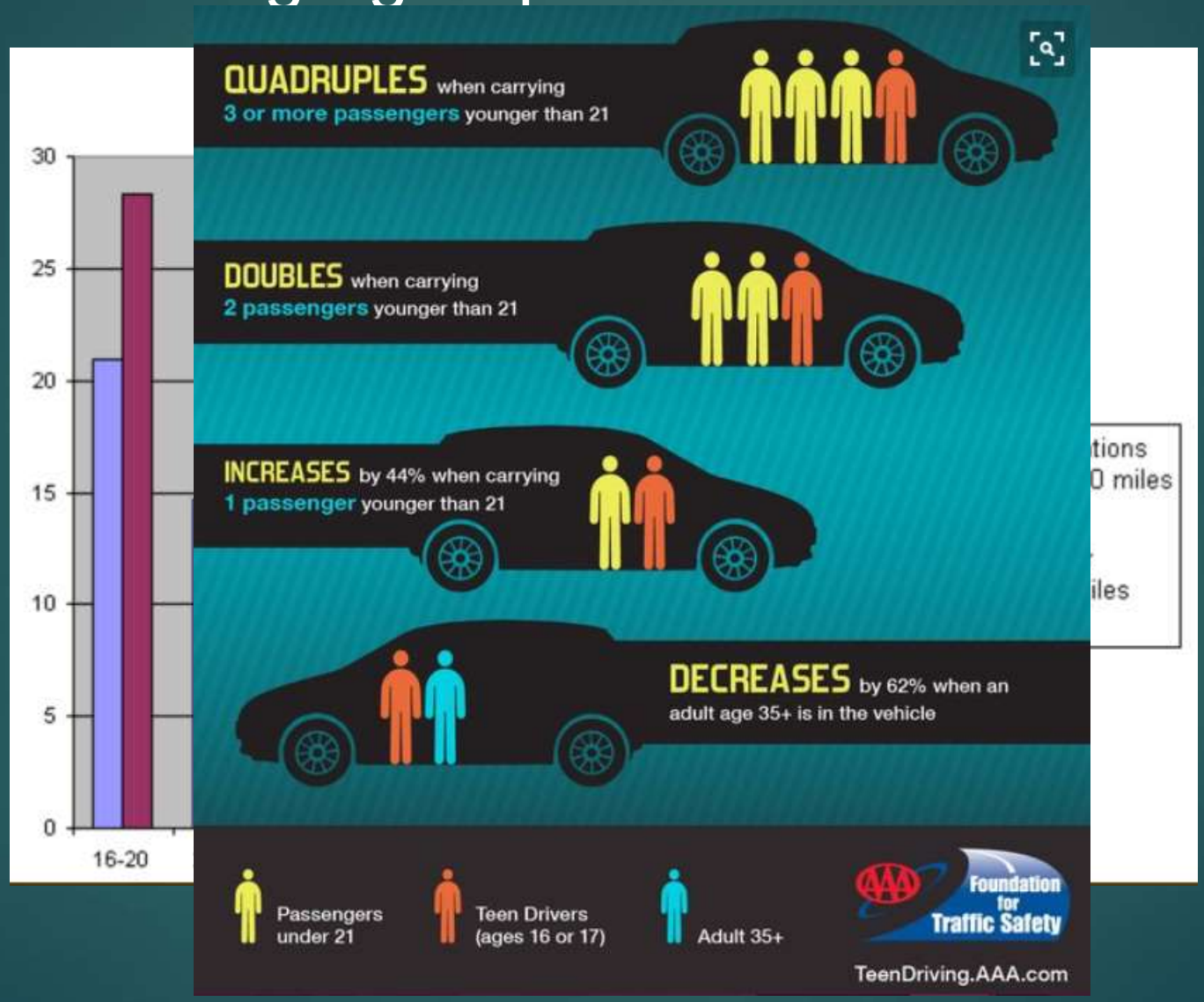
- Attention is like a football team:
  - 1 - need quarterback for focus
  - 2 - a defensive line against distractions.
- As we get older, we lose our defensive line
- Older people are able to pay attention, but have more difficulty inhibiting distractions.
- Older people get age-activated “ADD”

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

Decline in Spontaneous Verbal Free Recall:

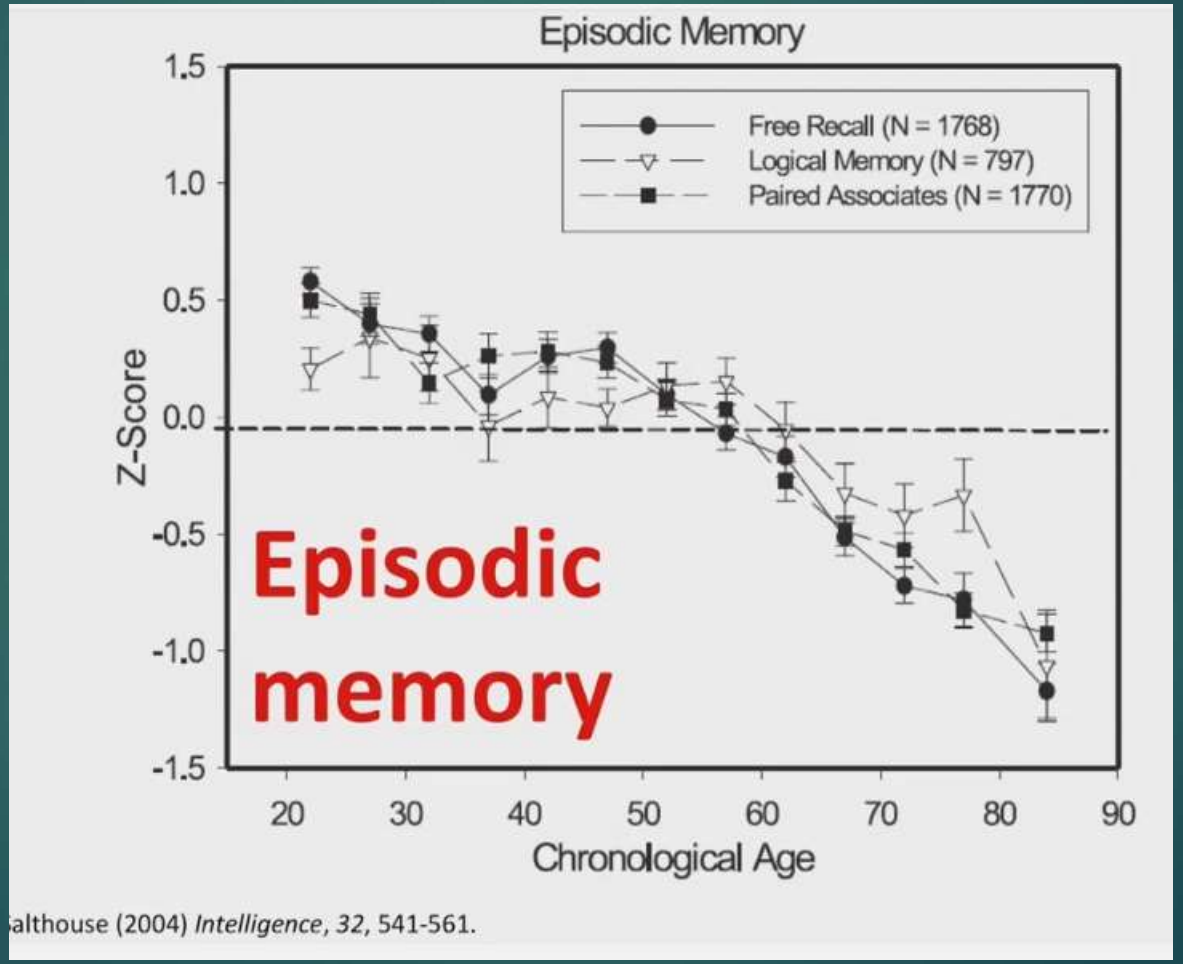
For 1 trial of 16 words:

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

Number of items learned in 1 attempt:

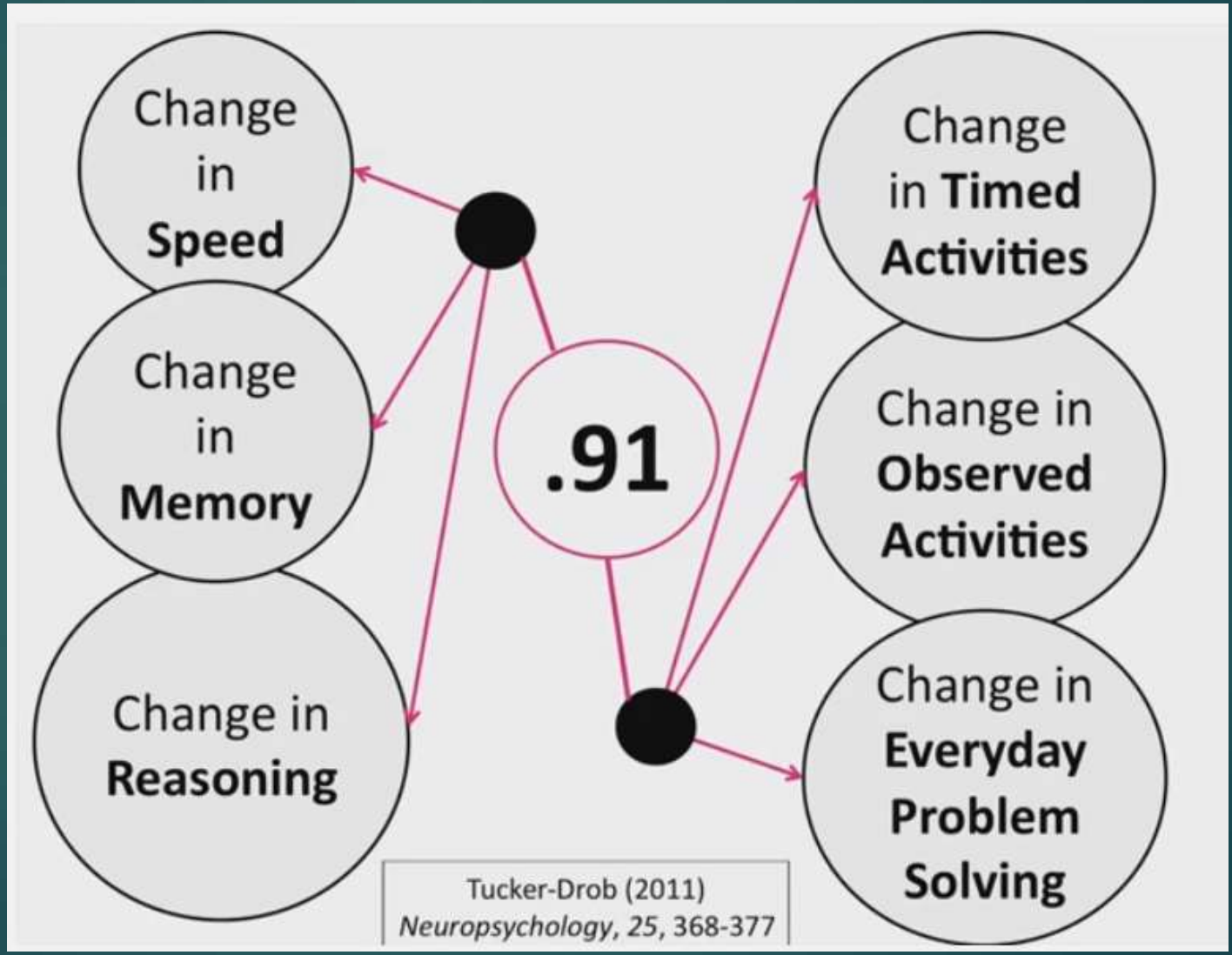
Remember two fewer words every decade past age 40

Episodic Memory: What did you have for breakfast (memory of time & particular fact)

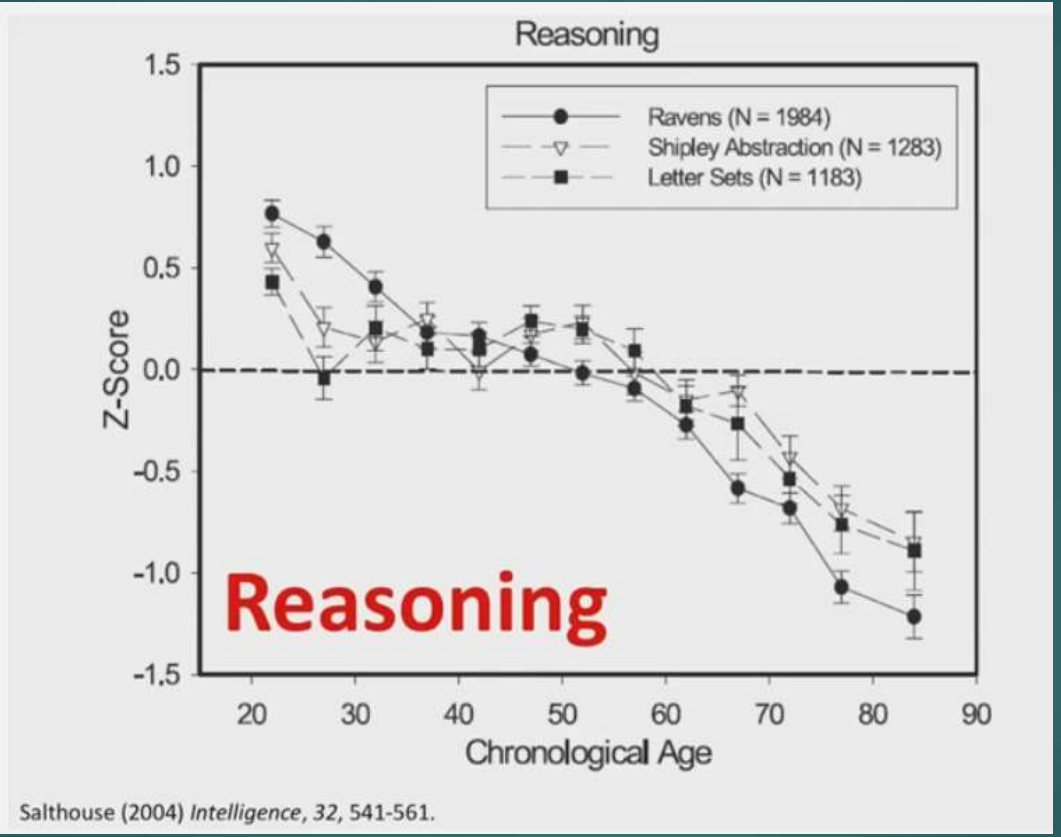


Virginia Longitudinal Study

Tests vs real world: As you decline in 1 ability, you tend to decline in others, both on tests and in real world practical skills



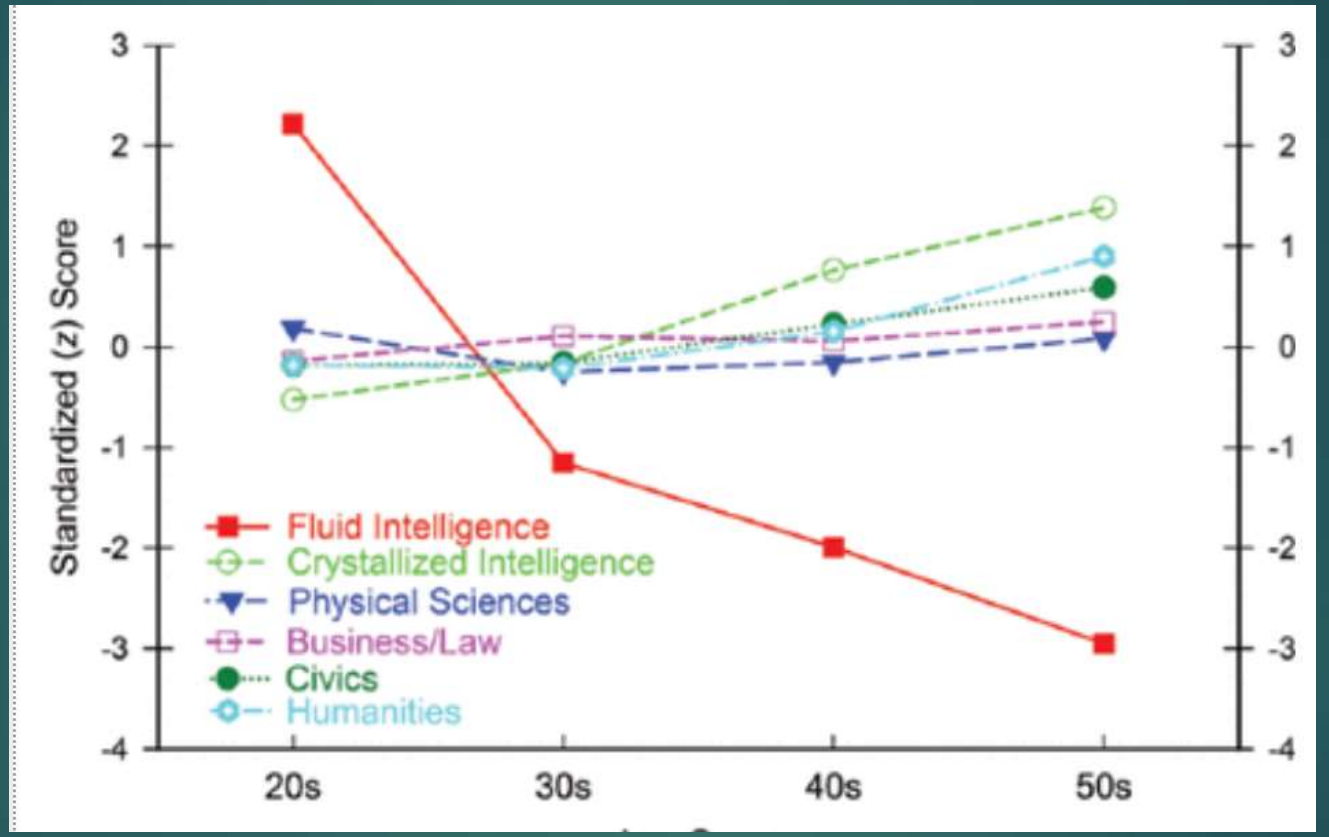
Reasoning: example =
"What completes this number series: 2-4-6-?"



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

Fluid IQ (Problem Solving) declines earlier, Experiential Knowledge declines only after late 70s

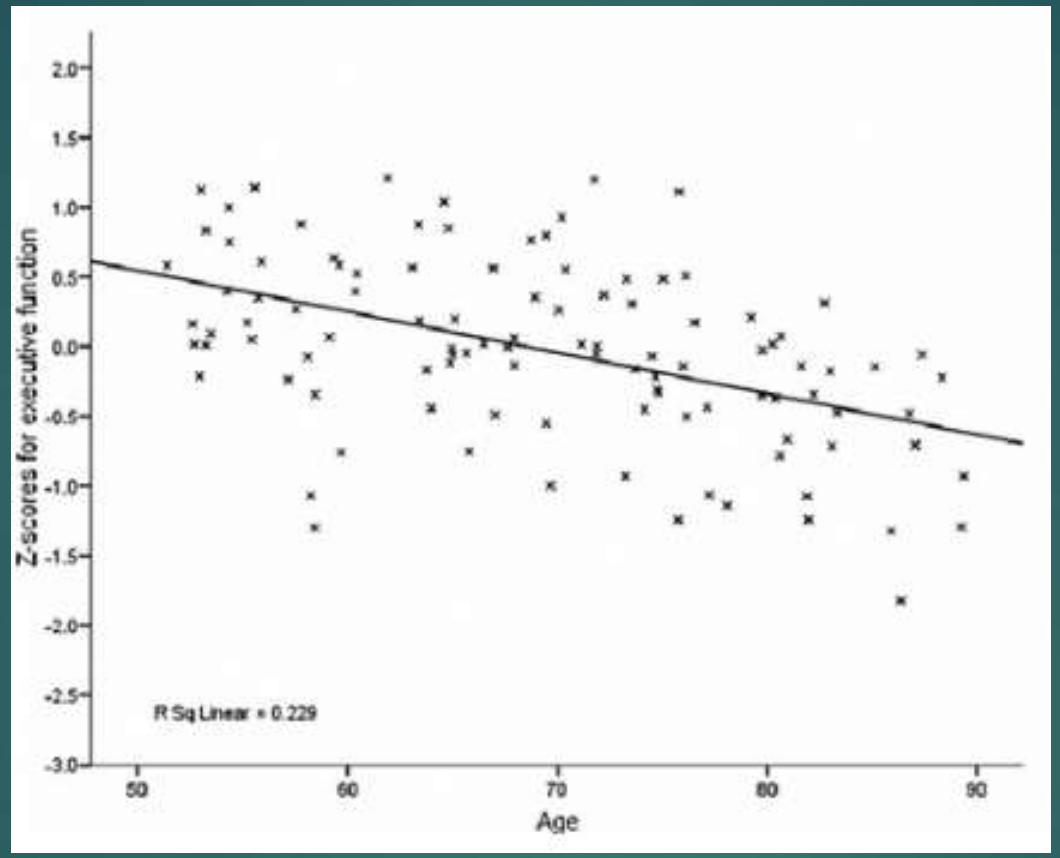
All had a B.A.



In contrast to performance on fluid IQ measures, middle-aged adults performed as well as or better than young adults on nearly all domain-knowledge tests

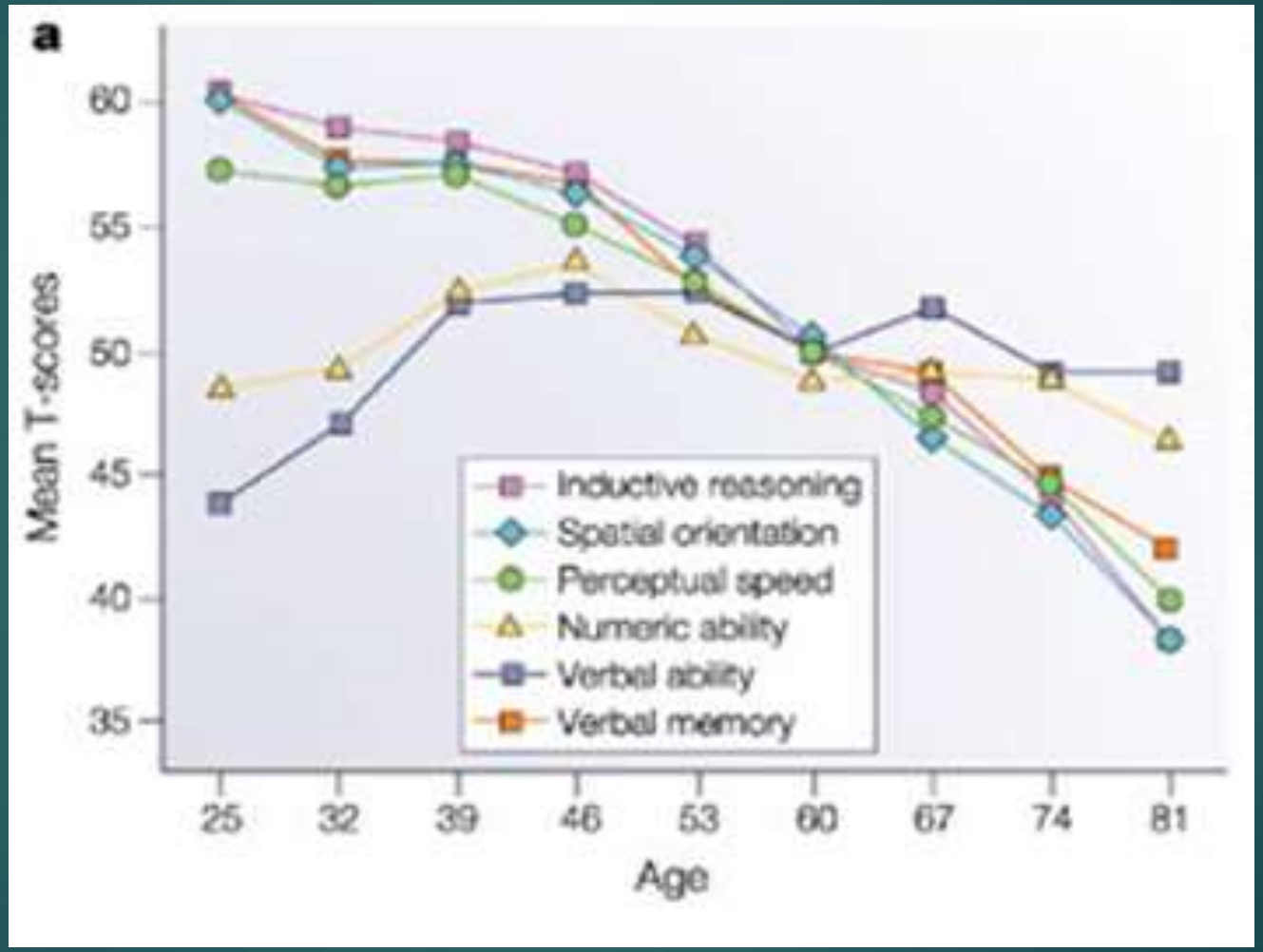
Phillip L. Ackerman, 2014

Executive Functioning (new problem solving, fluid IQ) declines



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

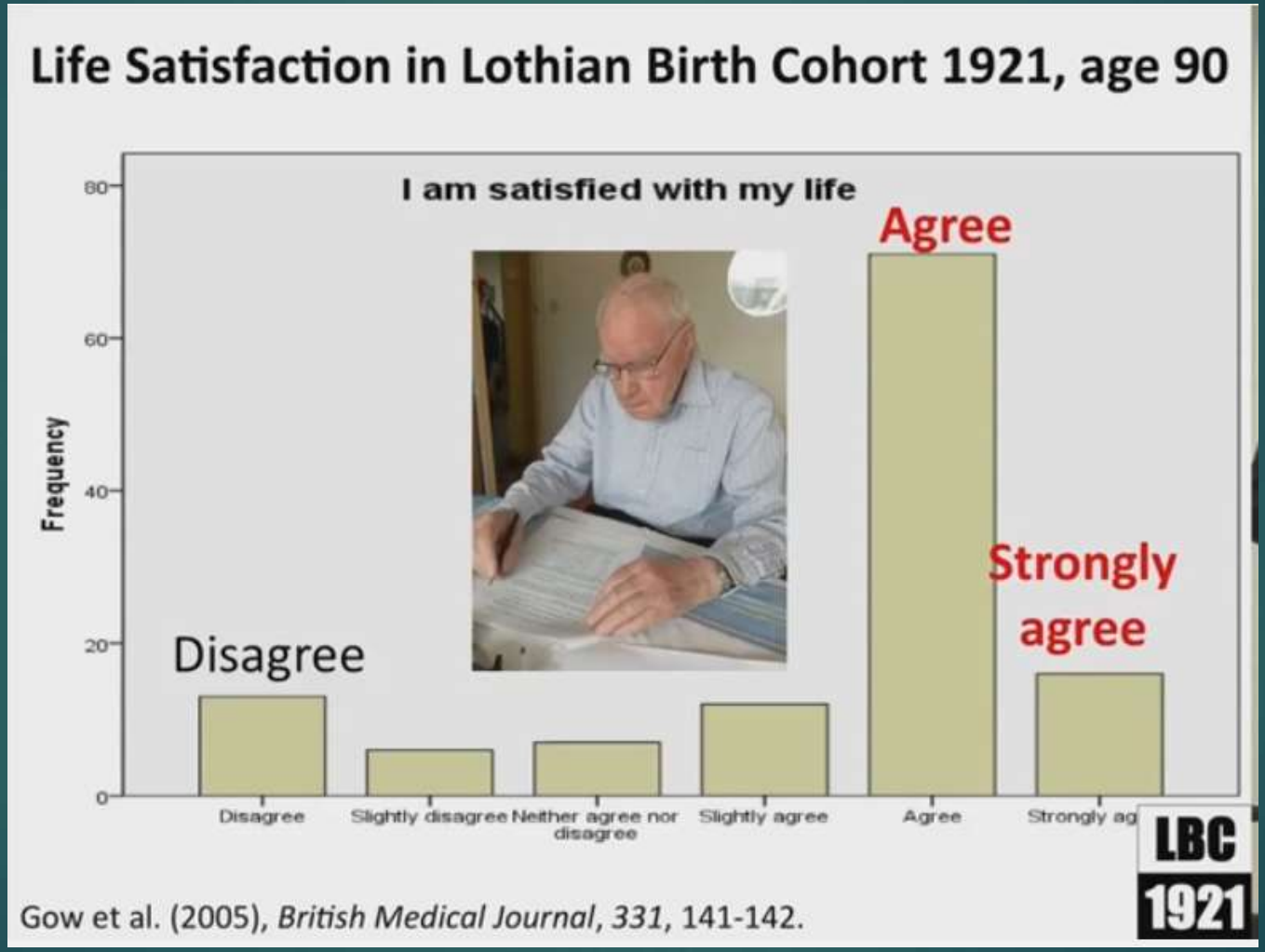
Verbal Ability ok vs. All Else ↓↓; but stay functionally independent



Seattle Longitudinal Study; no practice effect correction

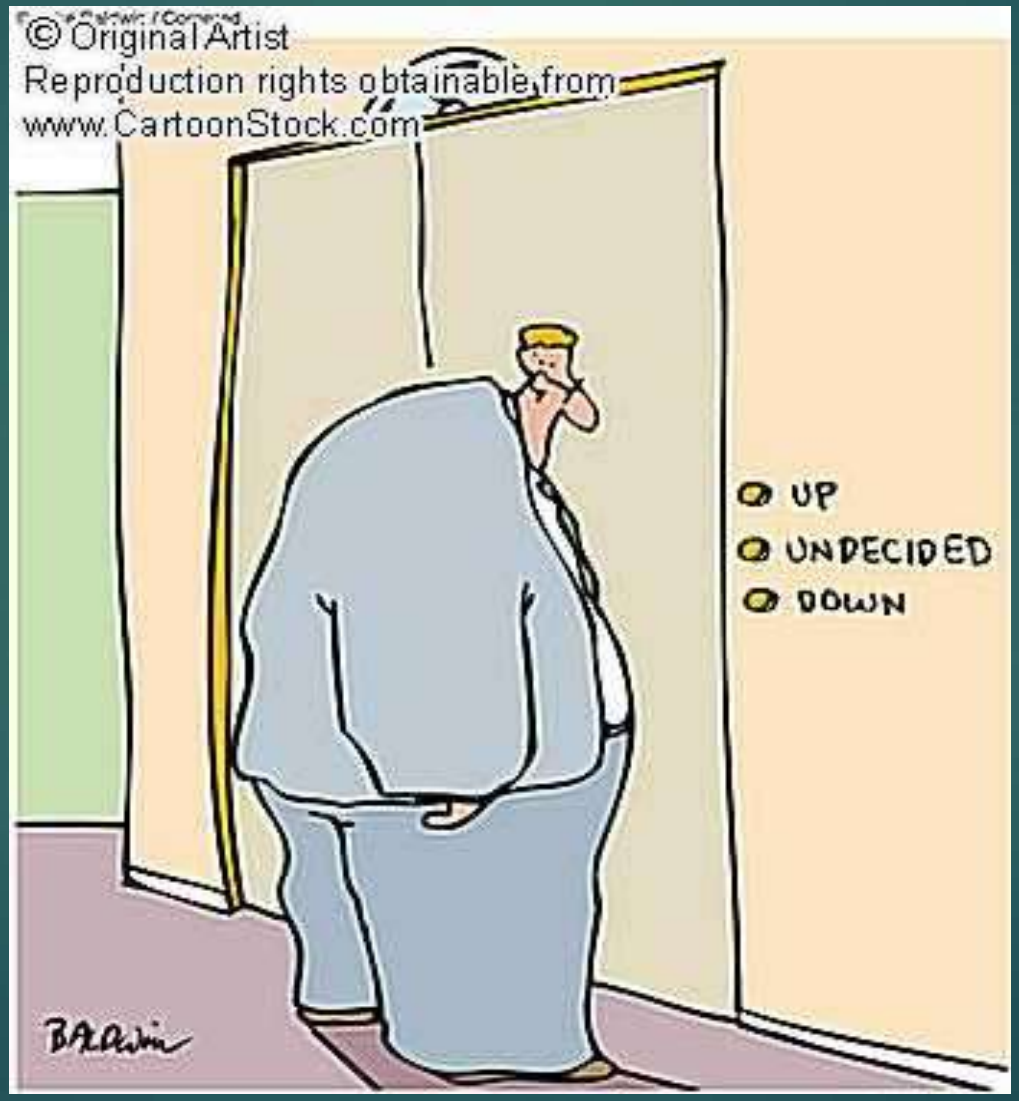
Do you want a young or older pilot?
"Sully" Sullenberger & Hudson River, age 59

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



No correlation between life satisfaction and IQ at age 11

Decision Making



Executive Functioning

- A woman marries 11 men in 10 years. She divorces none of them, none of them die, and she had not committed any crime. How is this possible?

Executive Dysfunction in Major NCD

- Executive ↓ can be independent of Memory ↓

- New changes in behavior:

  personality changes, dysinhibition, hypomania, apathy

Executive Dysfunction in Major NCD 2

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

- If executive functioning is impaired: can't live independently
- Money management decline
- Medication management decline
- Poor geriatric orthopedic & stroke rehabilitation outcome

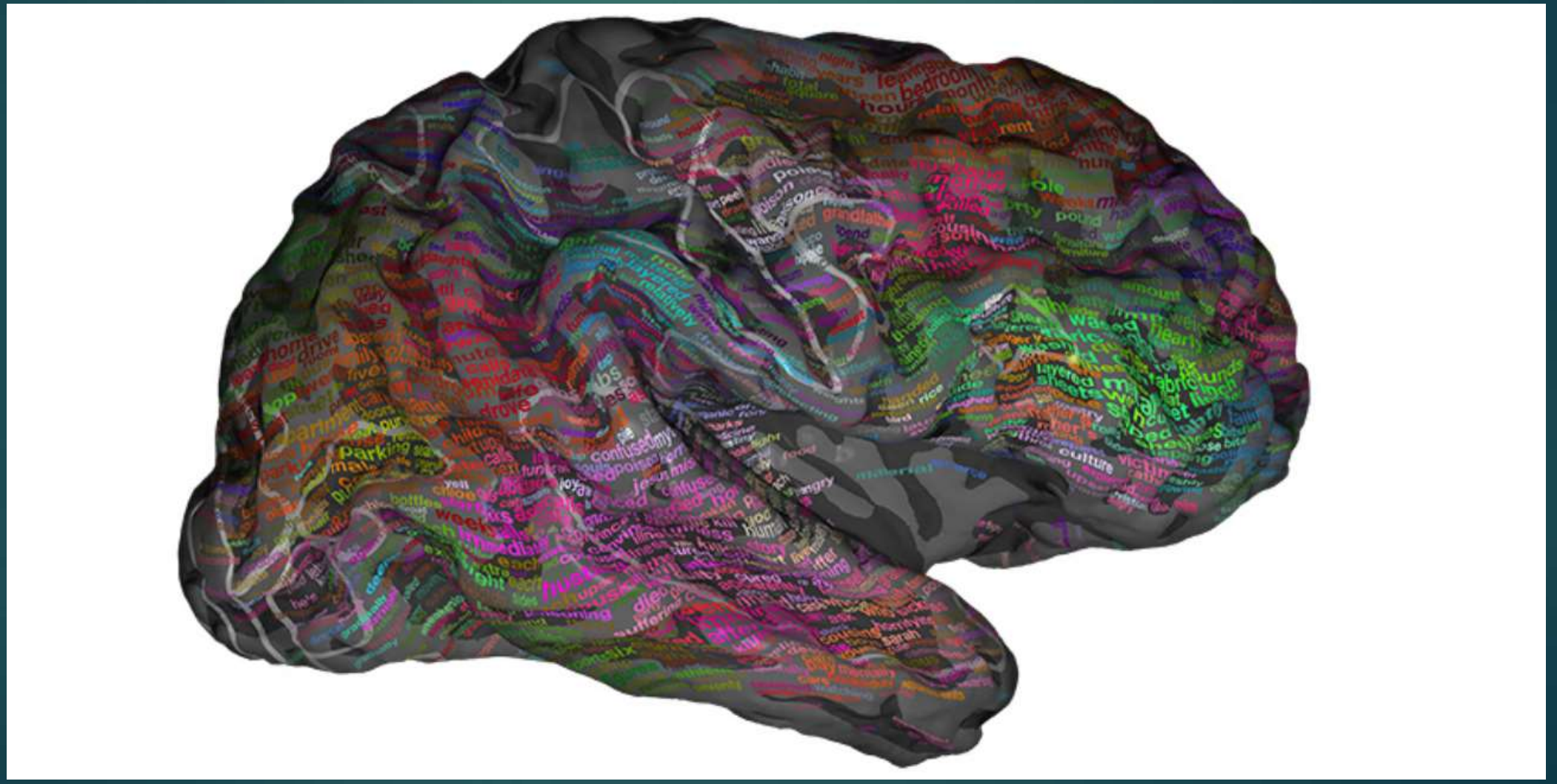
Senility (or Neurodegeneration) Prayer

- 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

Meaning and names in the Brain: Listening to narrative stories – areas activated by meaning



Naming vs. 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

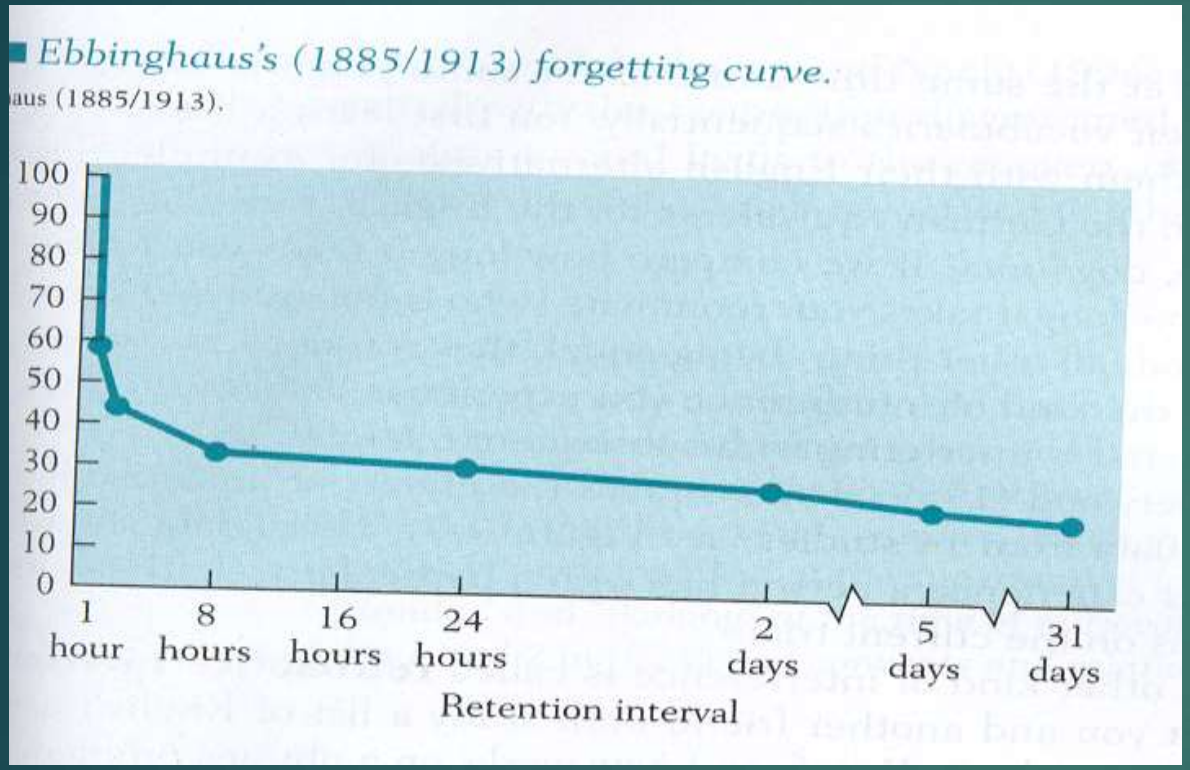
The Nature of Memory

Superman in his later years

Actual Memory Worries in a Mental Aerobics Class

- Forgetting names
- Sudden spelling blanks
- Train of thought: Lose point of what I am saying
- Memory for words, keys, movies, novels
- Why am I in this room
- Tip of tongue
- Driving directions
- Distraction
- Turning off stove, water; locking door

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 .

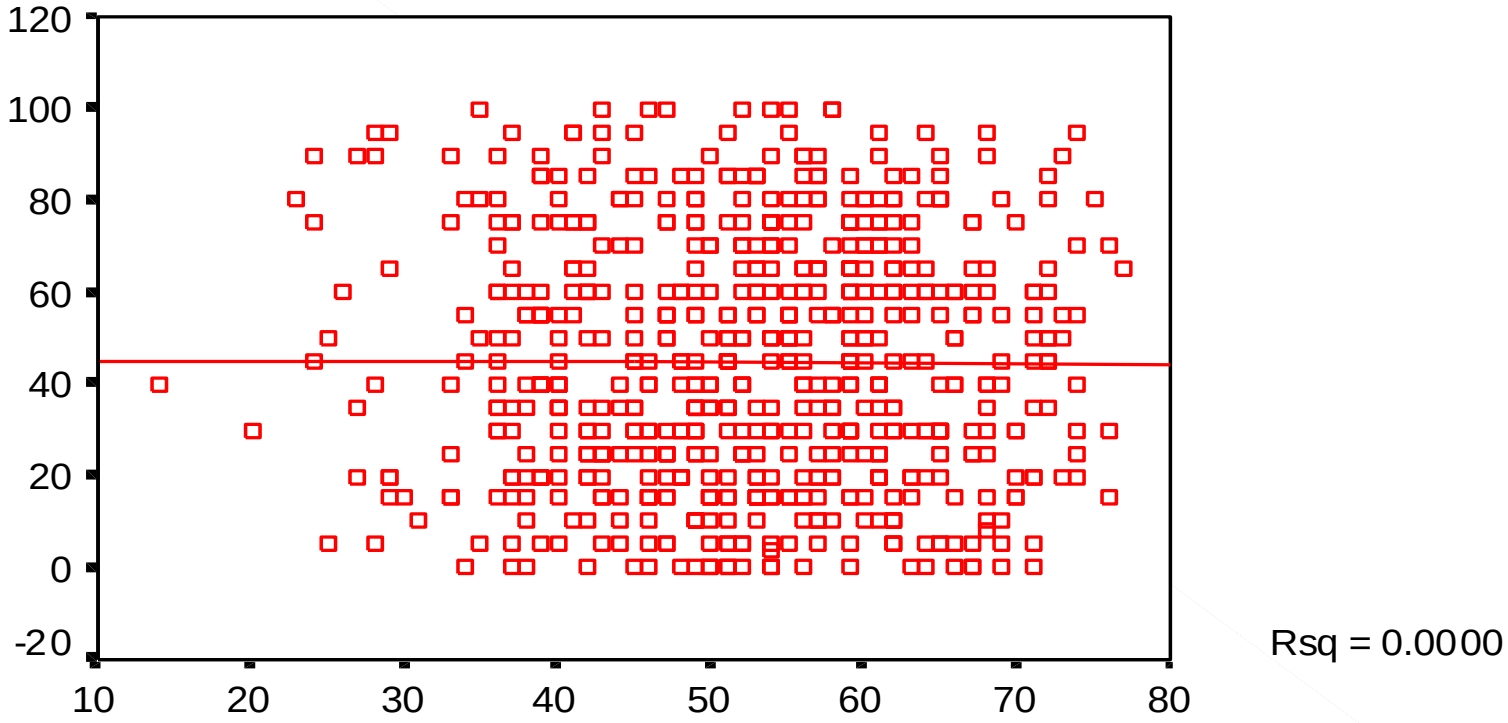
How information is lost over time when there is no attempt to retain it

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%

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 glitches.
- 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

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

1st 3rd

1. Quadriplegia
2. **Major NCD**
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

Rush Study:

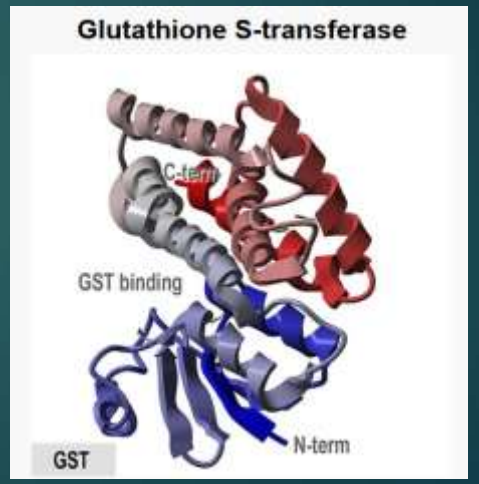
Mixed diseases are the most common cause of dementia.

- Pure AD pathology as the cause of dementia is relatively rare
- People clinically diagnosed with AD have pathologically mixed disorders (AD + VD+ LBD).
- 37% with no cognitive decline/dementia have significant AD
- 41% had cognitive decline and no ND brain disease

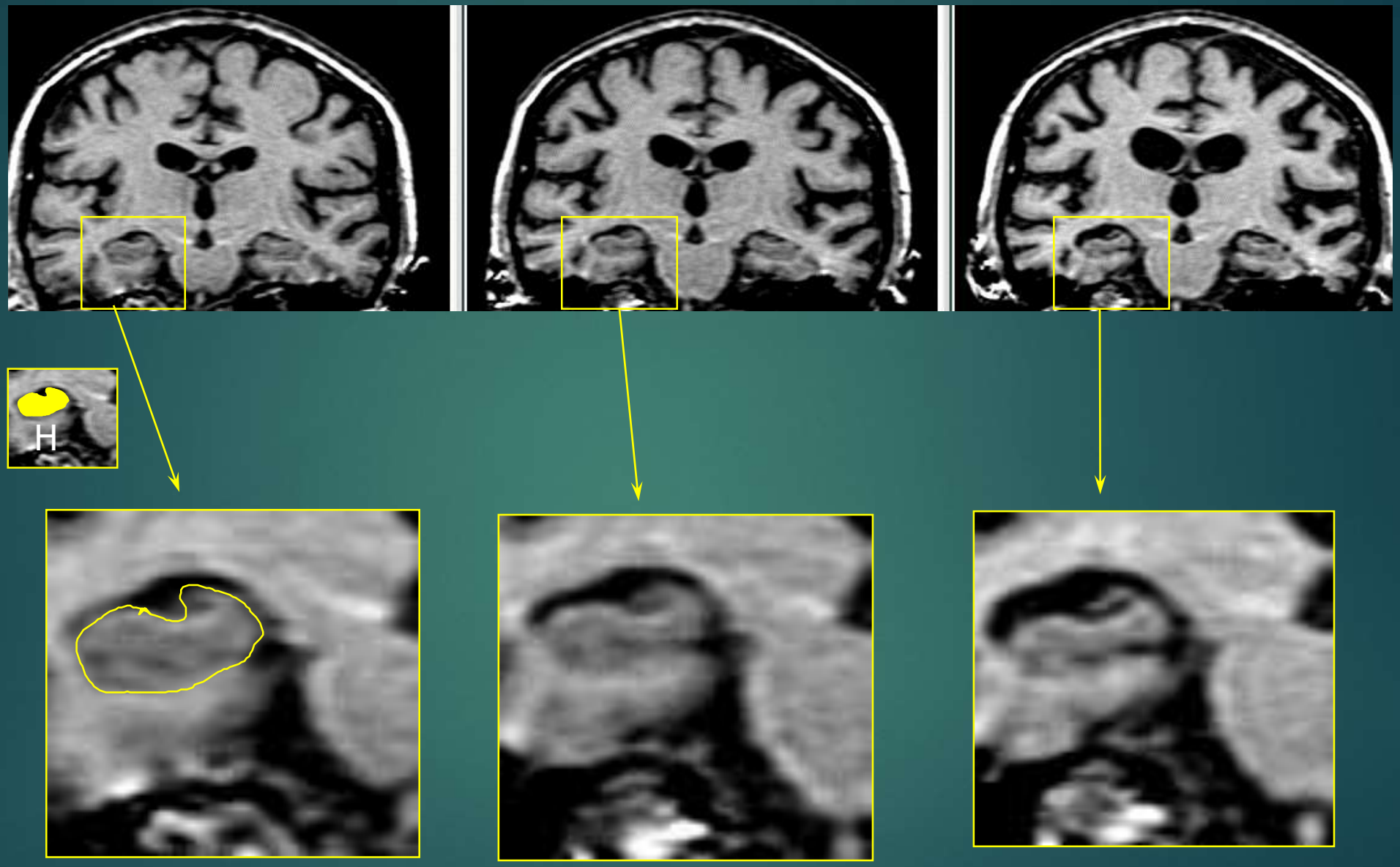
59% Residual Cognitive Decline

- Most of late life cognitive decline is not due to the common neurodegenerative pathologies

- Causation in the residual 59%:
  - Soluble Beta Amyloid
  - A-synuclein
  - TDP-43
  - Hippocampal sclerosis
  - Chronic macro/micro infarcts
  - GSTPI
  - Other pathologies

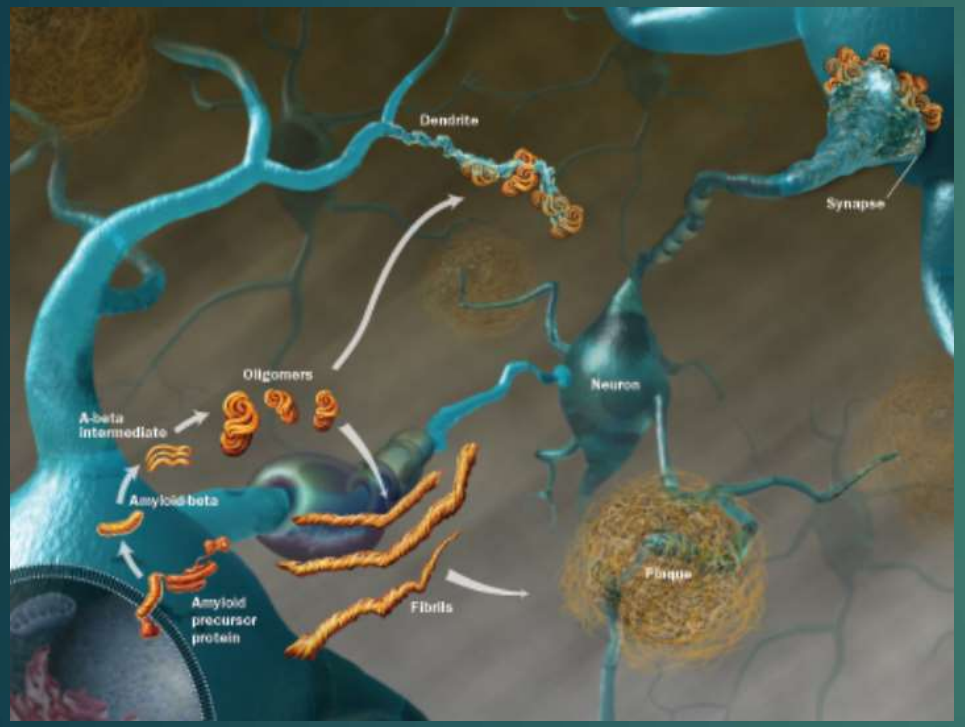


David Bennett UCSF lecture, Oct 2013



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

Current AD Concept: A Beta Amyloid driven tauopathy: abnormal protein Beta Amyloid between cells & Tau inside cells



Amyloid hypothesis:

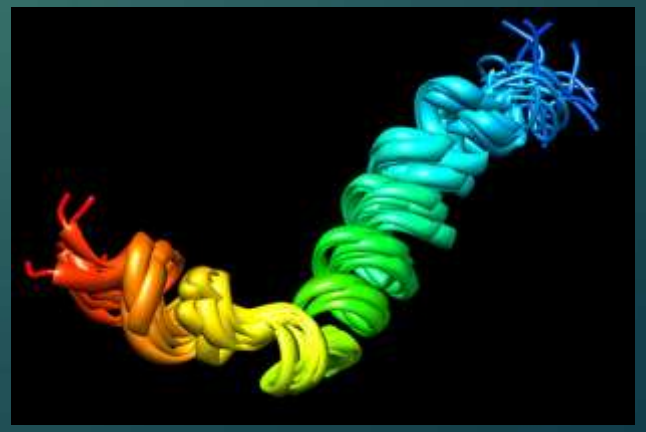
1 - a build-up of BA plaques causes inflammation in the brain,

2 - which spurs increase in Tau,

3 - which disables and then kills brain cells, through neuroinflammation

4 - resulting in cognitive decline.

Aβ is like the match that sets fire to the underbrush, sparking tau tangles, which then start a forest fire of neuroinflammation,



Herpes Virus & Gingivitis and AD

- Aβ42 is an antimicrobial, fighting off bacterial & viral infections in the brain.
- Aβ42 protects neurons and mice from infection by herpes viruses and *P. gingivalis*
- The peptide binds viral particles and rapidly fibrillizes, forming sticky nets.
- As a result, viral infections bring on amyloidosis in AD models within 48 hours.
- Herpes is the most common virus found in AD patients.
- Inhibitors of the bacterium's proteases are in clinical trials.

Biomarkers: AD Tests for predicting future AD pathology

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

- 3 for neurodegeneration
  - Tau in spinal fluid
  - deficits in glucose uptake on FDG-PET
  - and structural MRI (most predictive of Major NCD)

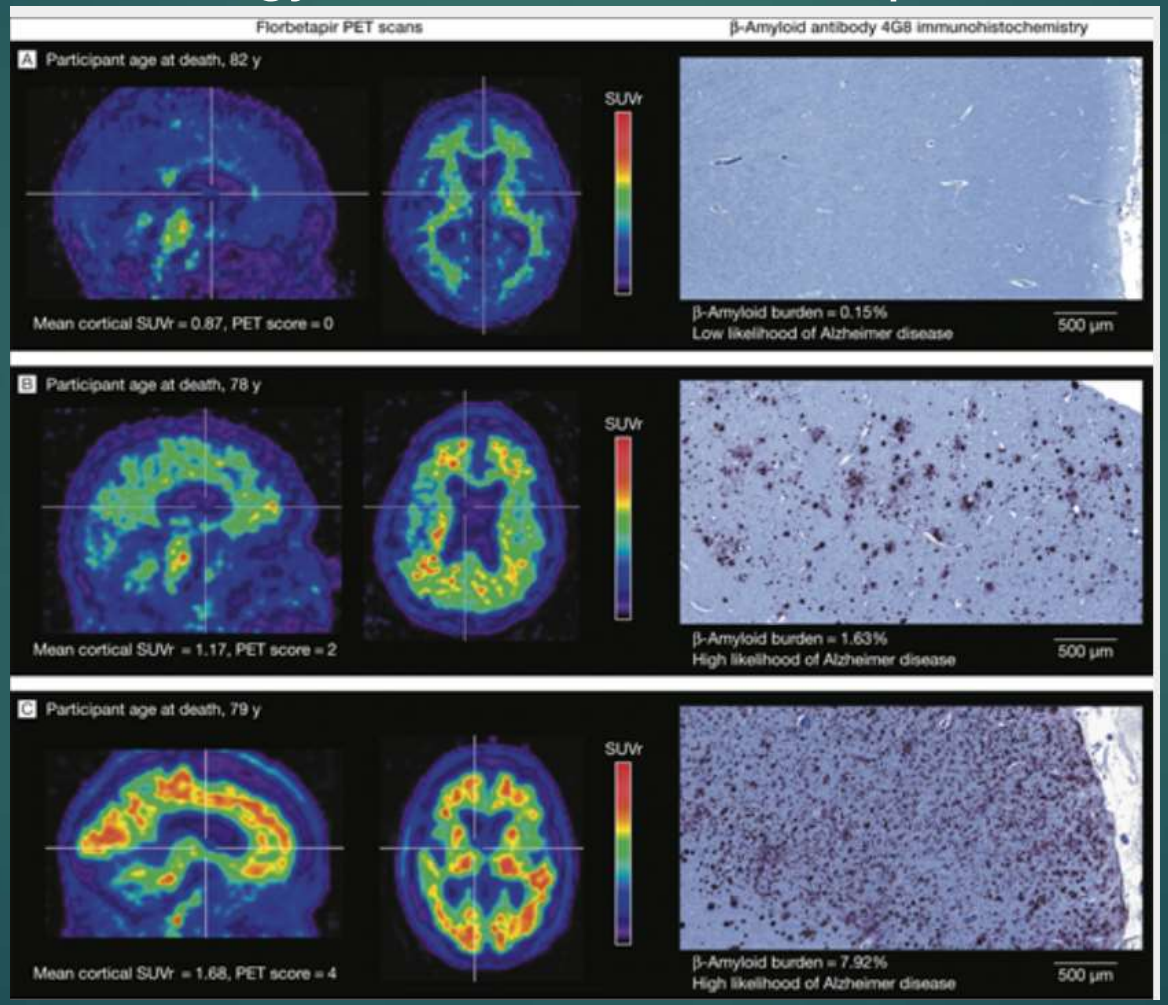
PET= autopsy specificity for Beta Amyloid

Pathology Validation: Florbetapir PET

Normal

Moderate

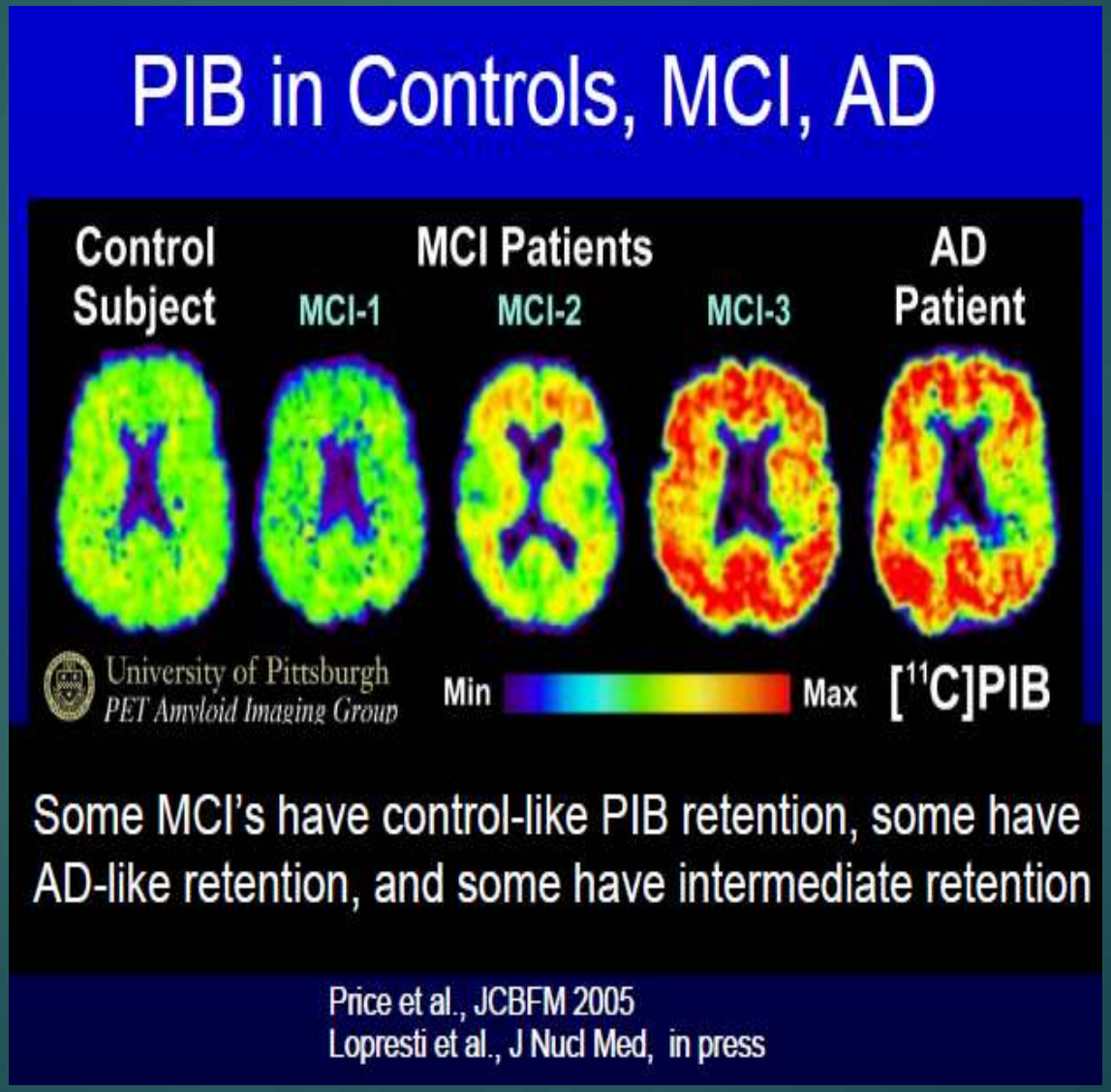
Severe AD



BA on autopsy

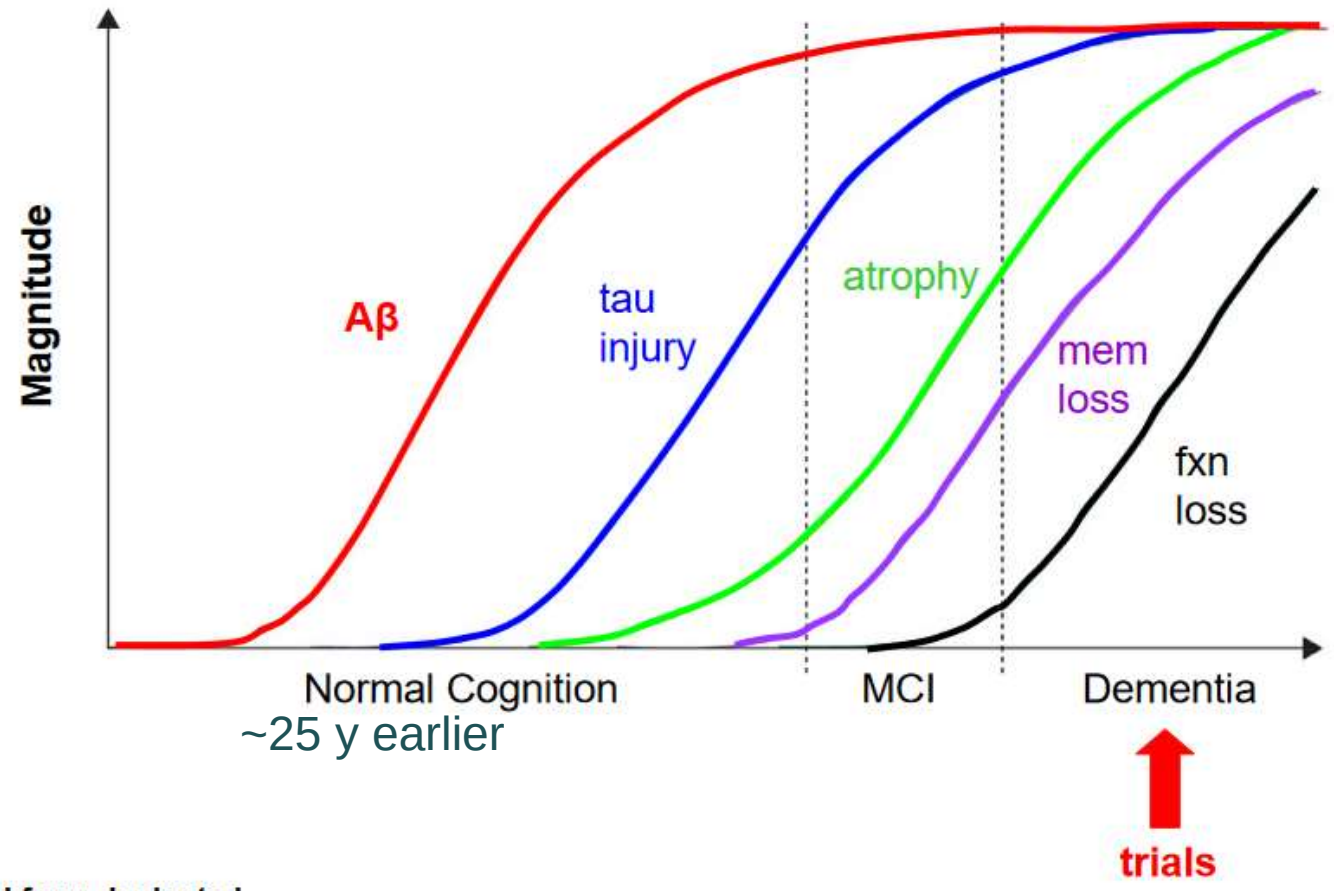
2012 FDA approval study: Dying AD pts: Pet scan and equivalent autopsy findings

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



But not indicative of amount of cognitive decline

Alzheimer's starts well before sxs



Modified from Jack et al
Lancet Neurology 2010

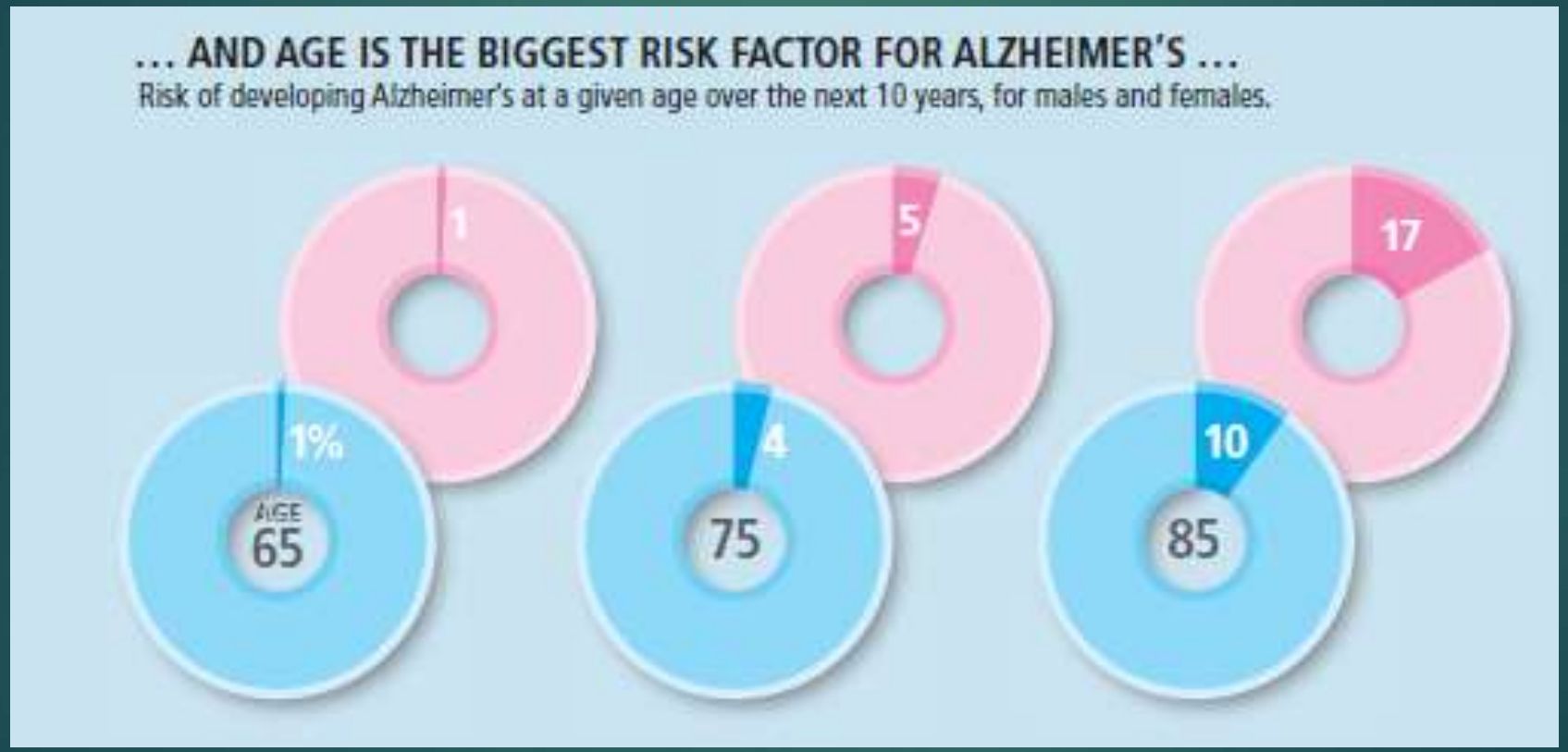
Cognitive Decline in Elderly

- Of all Americans in 2002, aged 71+:
- 65% were cognitively normal
- 21 % had some mild NCD
- 14% had dementia/major NCD
- By age 85, 42% have AD pathology

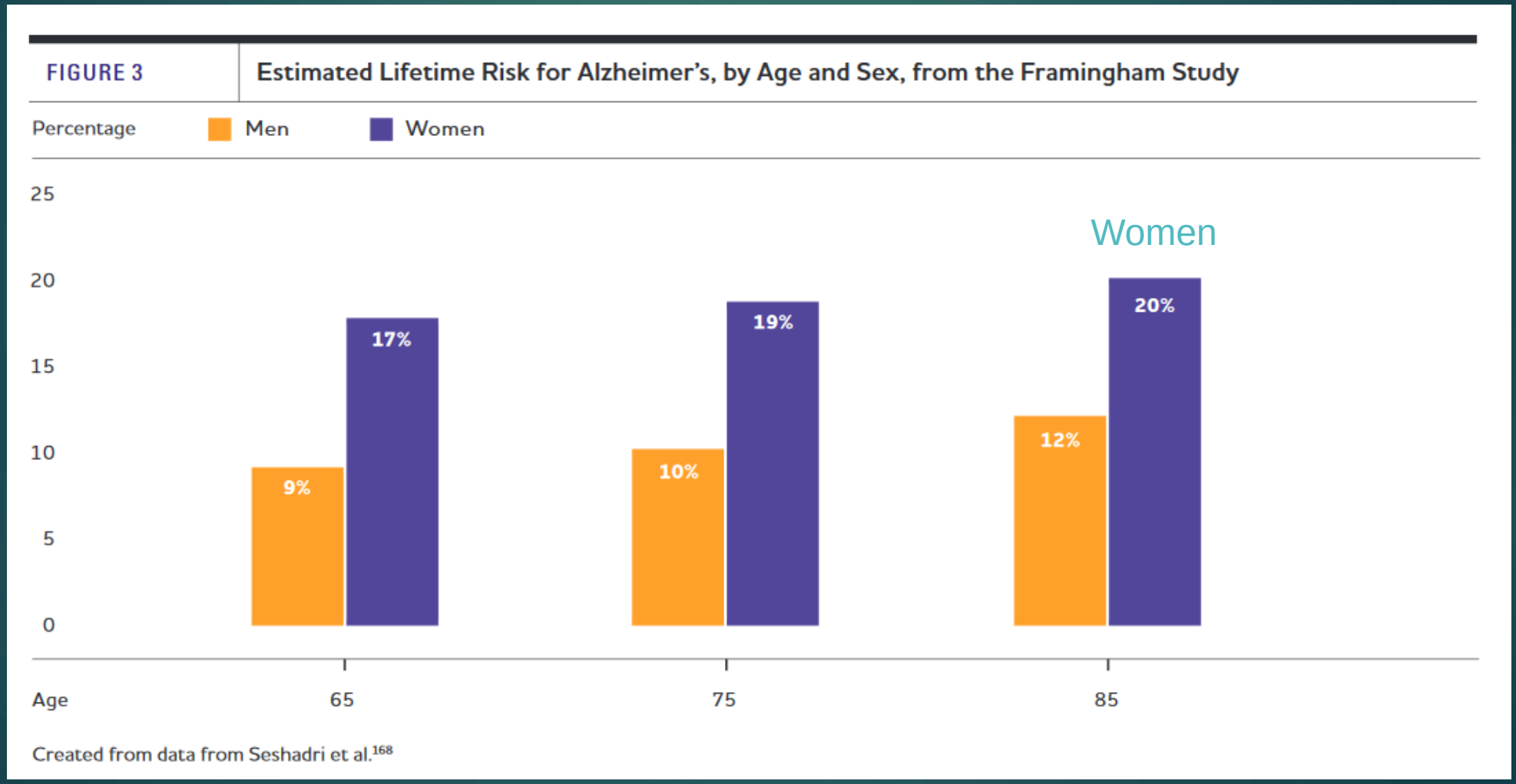
Causes of Accelerated Synaptic Loss→ higher rates of AD

- TBI
- CVA
- HTN
- DM
- High Cholesterol
- Homocystine (red meat)
- Low exercise
- Specific genes (Apoe4, Presenilin 1 & 2)

AD is usually not genetic.
Age is greatest risk factor.
Major NCD doubles every 5 years after 65



AD by sex and older age



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

Good News: Less Major NCD, 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.

146 Disease Modifying Treatment Trials: 99.6% Failure Rate

- AN1792 vaccine: 2003 (Eliminated BA; still major NCD)
- Tramprostate
- Flurizan: 2008
- Bapineuzumab: 2009
- Semagacestat: 2010
- Solanezumab: 2016
- Verubecestat: 2018

- Right TX, wrong stage of disease?

New Research Strategy

- Eventually 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.)

Hope for near future:
Columbian Prevention Study

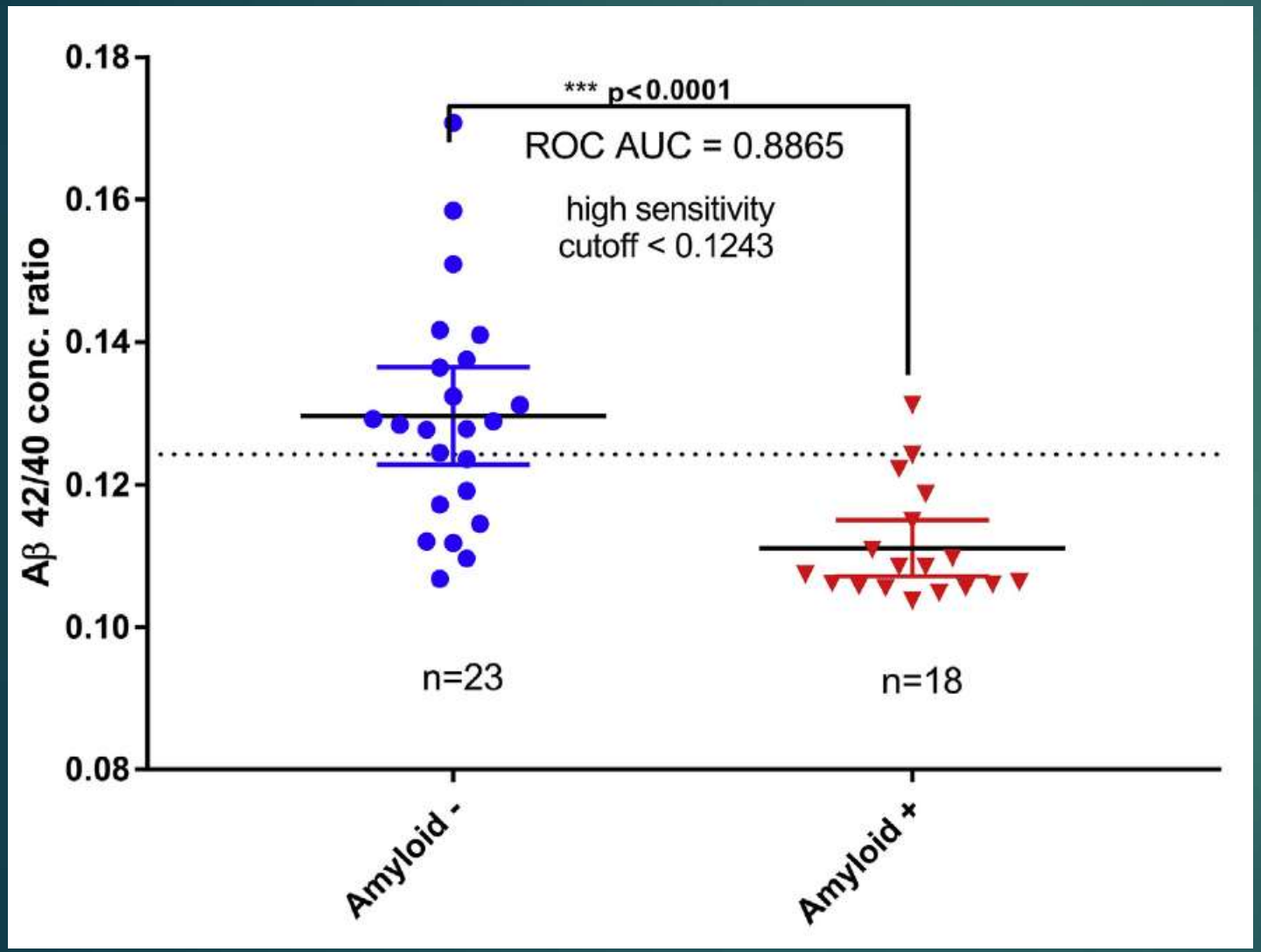
- Eventually treat AD like HTN and heart disease preclinically
- Columbian study: extended clan of 5,000 people who live in Medellín, Colombia with early onset AD
- Family members with a presenilin 1 gene mutation begin showing cognitive impairment around age 45, and full Major NCD around age 51; disease 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

July 2018: Biogen anti-BA drug BAN240

- Announcement of results of Phase 2 results of n = 856:
  - High dose of injectable antibody BAN240 resulted in 30% decline in negative cognitive decline after 18 months
- Not peer-reviewed or FDA review
- Failed Phase 1 in Dec 2017; reanalyzed statistics and continued for 18 months at highest doses

- Second study: keep BP at 120 produces less memory decline.

Blood test for AD is near! Can tell who is BA+.



- Blood plasma level is 50% less in BA +
- An 89% probability that a randomly chosen individual with low plasma Ab42/Ab40 concentration ratio would have amyloidosis
- Correlates with CSF level & BA on PIB PET
- Plasma BA+ level has sufficient specificity to be used as screening test

Ovod, et al., 2017

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

400 miles of blood vessels in human brain.

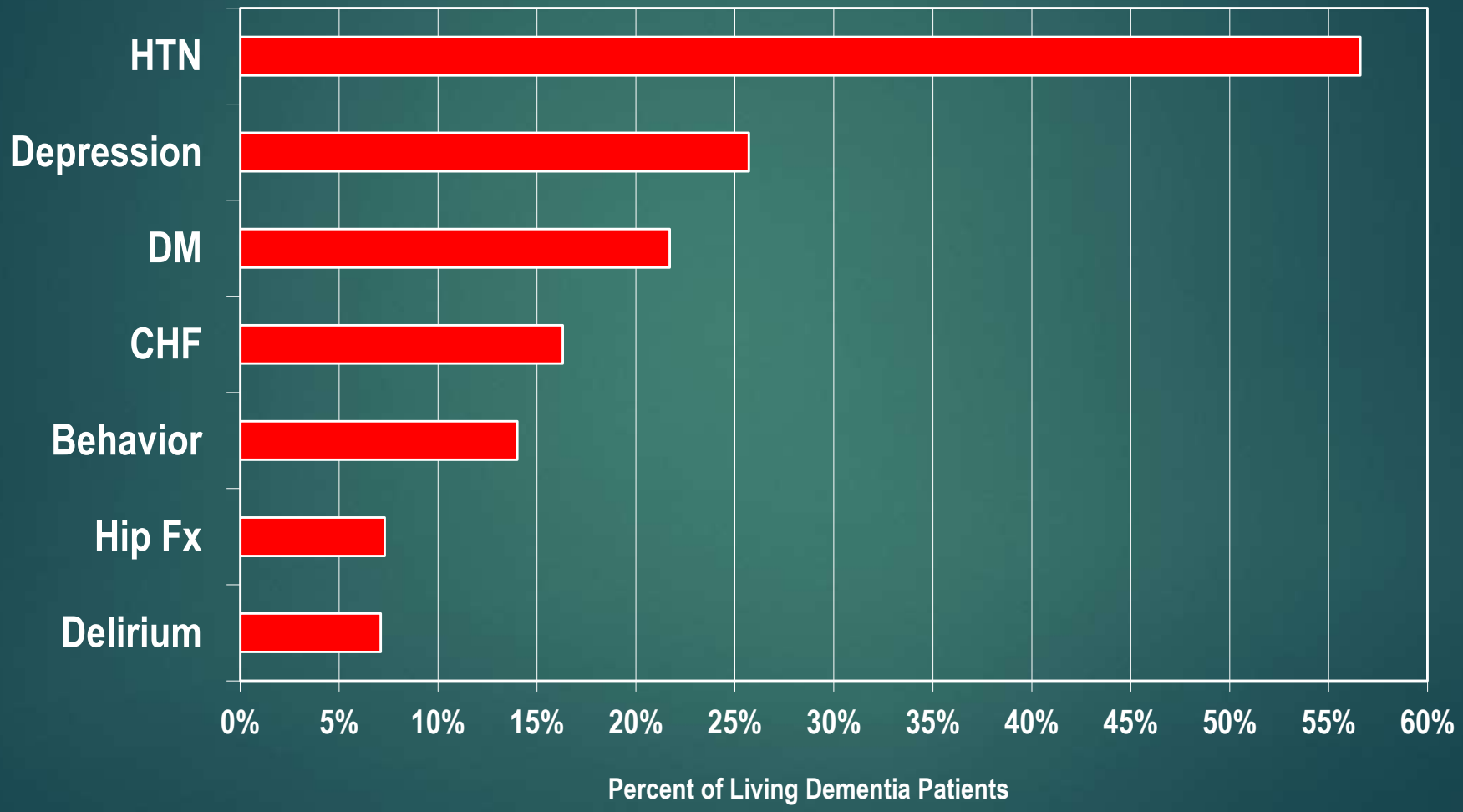
A plastic emulsion was injected into brain vessels and brain tissue was dissolved.

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

BA and midlife CV status

- There is very strong evidence for a relationship between midlife cardiovascular risk factor status and the odds of having BA deposition in the brain
- CV risk factors:
  - smoking,
  - hypertension (high blood pressure)
  - diabetes,
  - high cholesterol,
  - obesity.
- Having even one of these risk factors was associated with about double the odds of brain amyloid deposition, and having two or more was related to about triple the odds

Co-Morbidities of Northern Cal KP Major NCD 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.

Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes

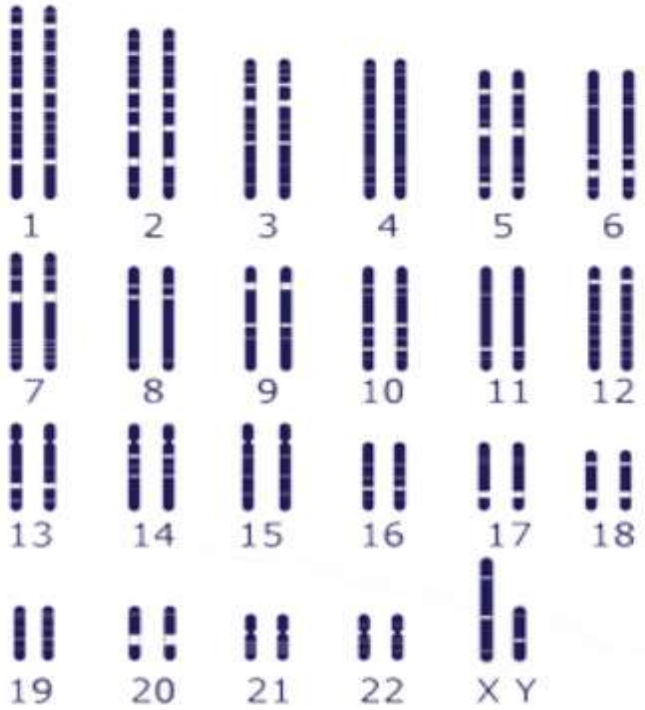
- In 2012, suboptimal intake of dietary factors was associated with an estimated 318, 656 cardiometabolic deaths, representing 45.4% of cardiometabolic deaths.
- The highest proportions of cardiometabolic deaths were estimated to be related to:
  - excess sodium intake (9.5%)
  - insufficient intake of nuts/seeds (8.5%)
  - high intake of processed meats (8.2%)
  - low intake of seafood omega-3 fats (7.8%)
  - low intake of vegetables and fruits (7%).

Renata Micha, et al, JAMA, 2017

Aging = more risky than having a 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 Major NCD

Only 4 Major Genes Implicated in Alzheimer's: 3 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.

Onset: 60-70s

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:
$159

In April, 23andMe started including genetic risk tests for APOE4 and Parkinsonism.

Remember:

- No current treatment for AD

Anti-Major NCD Medications ?

- **The Question:** Are there medications that prevent Major NCDs like Alzheimer's disease?

- **The Verdict:** No Major NCD disease prevention 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; i.e. Aricept.

- But…There are Major NCD modifying behaviors.

Only 5 drugs approved by FDA for AD

Drug name	Brand name	Approved For	FDA Approved
1. donepezil	Aricept	All stages	1996
2. galantamine	Razadyne	Mild to moderate	2001
3. memantine	Namenda	Moderate to severe	2003
4. rivastigmine	Exelon	All stages	2000
5. donepezil and memantine	Namzaric	Moderate to severe	2014

Source: alz.org

None effect the progression of disease

Neuroprotective lifestyles:
26Tips for
Protecting Your Brain
Only 2 red tips are RTC proven

AD pseudomedicines

- Pseudomedicine refers to supplements and medical interventions that exist within the law and are often promoted as scientifically supported treatments, but lack credible efficacy data: dietary supplements to improve cognition and brain health, $3.2-billion industry; do not undergo US Food and Drug Administration (FDA) testing for safety or review for efficacy
- Use of testimony not scientific data
- No known dietary supplement prevents cognitive decline or dementia
  - i.e. TV ads for Prevagen (Quincy Bioscience); FDA warning vs them

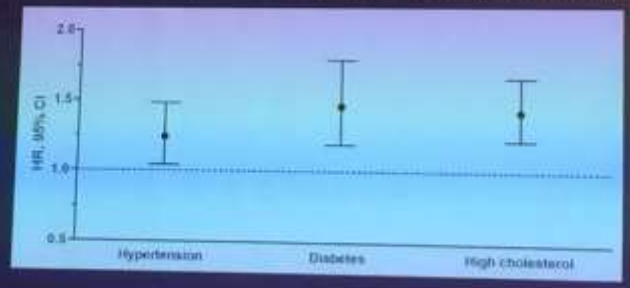
July 2018: Dementia Prevention at Population Level – Kristine Yaffe, UCSF

Risk Factors for Dementia: Strategies with Strong Evidence

- Cardiovascular Risk Factors
- Physical Activity
- Sleep Quality and Sleep Disturbances
- Traumatic Brain Injury (TBI)

Midlife Cardiovascular Risk Factors Increase Risk of Dementia

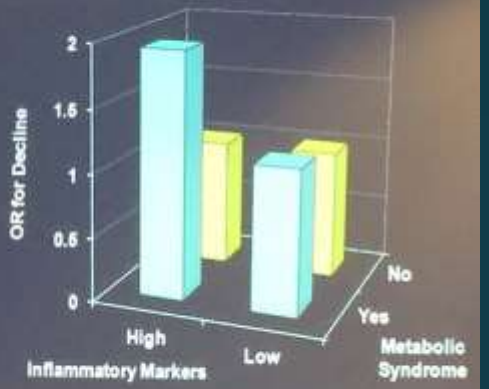
- Cardiovascular risk factors may be "modifiable"
- Control of these risk factors beneficial in multiple organ systems
- Best evidence for mid-life associations
- Dementia is often "mixed" with AD & vascular pathology



Whitmer…Yaffe, *Neurology*, 2004.

Late Life Cardiovascular Risk Factors Increase Risk of Dementia

- Together may be greater than individual components
- Role of inflammation
- Offer strategies to modify as a group



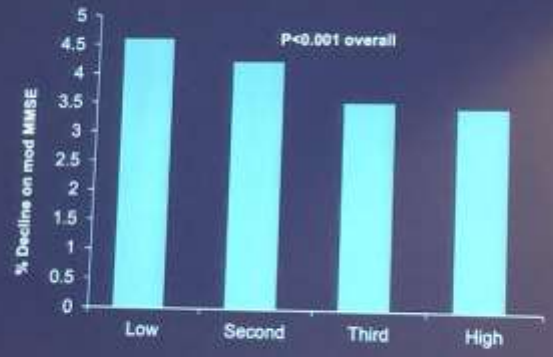
P for interaction = 0.04

Yaffe et al, *JAMA*, 2004.

Cardiovascular Risks: Future Directions

- Hypertension, diabetes, obesity consistently associated with dementia risk, especially at mid-life
- Composite risk factors such as metabolic syndrome suggests ways to target those at especially high risk

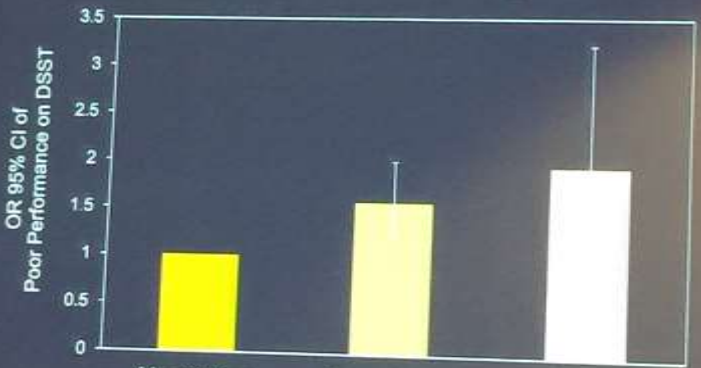
Walking Reduces Risk of Cognitive Decline



More blocks walked associated with less decline

Yaffe et al, *Arch Intern Med*, 2001.

Early Adult Physical Inactivity over 25 Years Linked to Poor Mid-Life Cognition



Hoang…Yaffe, *JAMA Psychiatry*, 2016.

Primary AD Prevention

Potential for Primary AD Prevention

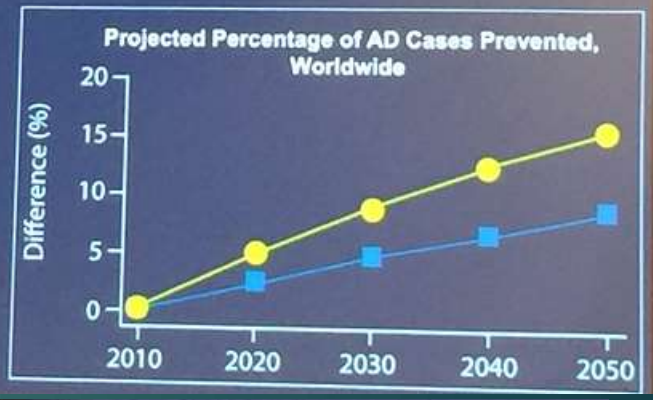
- Estimate impact of risk factor reduction on AD prevalence for 7 modifiable factors
  - Diabetes
  - Mid-life hypertension
  - Mid-life obesity
  - Depression
  - Physical inactivity
  - Low education
  - Smoking
- Population attributable risks (PARs) - estimate proportion of disease caused by a given risk factor
- Calculated using risk factor prevalence & relative risk from most recent/comprehensive literature

Barnes and Yaffe, *Lancet Neurology*, 2011.

Risk Factor Reduction Could Significantly Lower Prevalence of AD, Worldwide

Barnes and Yaffe, *Lancet Neurology*, 2011; Norton...Yaffe et al, *Lancet Neurology*, 2014.

Risk Factor	Population Prevalence	Relative Risk (95% CI)	PAR % (Range)
Physical inactivity	33%	1.8 (1.2, 2.8)	21% (6-37%)
Smoking	21%	1.6 (1.2, 2.2)	11% (3-20%)
Depression	19%	1.7 (1.4, 1.9)	11% (8-15%)
Mid-life hypertension	14%	1.6 (1.2, 2.2)	8% (2-15%)
Mid-life obesity	13%	1.6 (1.3, 1.9)	7% (4-11%)
Low education	13%	1.6 (1.4, 1.9)	7% (4-10%)
Diabetes	10%	1.5 (1.2, 1.8)	5% (2-7%)
Combined (max.)			53%
Combined (adj.)			31%



Multi-domain Alzheimer's Risk Reduction Study (SMARRT)

- Previous multi-domain interventions relatively intensive and all standardized, may be difficult to implement in real-world settings
- NIA R01AG057508 (Multiple PI: Yaffe and Larson)
- Pilot-test multi-domain risk reduction intervention
- Personalized and pragmatic delivered through a U.S. integrated healthcare delivery system
- Leverage advancements in digital health
- Intervention will be over 2 years

SMARRT

2015 *Lancet* first RCT study

- N = 1650; 2 year (2009-2011) Finnish study of ages 60-77;
- FINGER is the first large-scale, longer-term RCT (randomized controlled trial) to assess a multidomain approach to prevent cognitive decline in at-risk elderly people (nutritional guidance, physical exercise, cognitive training, social activities, and management of heart health risk factors (control group received regular health advice);
- Would this lead to a protective effect on cognition?
- There were significant intervention effects on the outcome (overall cognition, executive functioning and processing speed, complex memory tasks), and other secondary outcomes (BMI, dietary habits, and physical activity).
- Outcomes were 25% to 150% better in the intervention group.
- Now 7-year follow up study

Tiia Ngandu, et al., *Lancet*, 2015

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

Marginal gains, not magic bullets

- Effect sizes of findings: how much of a gain does each health behavior give you. Most are small effects.
- Each behavior may contribute only a little, but the total is really important
- Play the numbers; the more, the better
- ****: tips with this sign are behaviors to seriously avoid or seriously engage in

2018: Stay heart fit in Middle Age

- Strive for a healthy middle age.
- 44 year study: Women who scored high on a fitness test in midlife were nearly 90 percent less likely than their moderately fit or unfit peers to develop dementia decades later.
- Fittest women held dementia at bay 10 years longer.
- Underlying poor cardiovascular health partially explained the relationship between fitness and brain health

30 year study: 5 tips that can add decades to life

- Maintaining five healthy habits during adulthood may add more than a decade to life expectancy (14 more years for women; 12 for men)
- 5 habits:
  - not smoking,
  - low body mass index (18.5-24.9 kg/m2),
  - at least 30 minutes or more per day of moderate to vigorous physical activity,
  - moderate alcohol intake (1 per day for women, 2 for men),
  - and a healthy diet
- U.S. women and men who maintained the healthiest lifestyles were 82% less likely to die from cardiovascular disease and 65% less likely to die from cancer
- There was a dose-response relationship between each individual healthy lifestyle behavior and a reduced risk of early death, and that the combination of all five healthy behaviors was linked with the most additional years of life.

Yanping Li, et al., 2018

Lancet 2018 Recommendations:
If we do the following, we can decrease dementia by 30%

- Active treatment of hypertension in middle age (45-65) & older age (65+)
- Increase childhood education
- Exercise
- Social engagement
- Stop smoking
- Reduce hearing loss
- Reduce diabetes and obesity
- Reduce depression

Reduced Dietary Gluten Is Linked to Heart Risk in Non-Celiacs

- Myth that a low-gluten diet is healthy for everyone.
- Limiting whole grains as part of a reduced-gluten diet could actually increase heart attack risk in people without celiac disease
- A study of more than 100,000 men and women revealed that dietary gluten is not associated with heart disease risk in people without celiac disease.
- The findings also suggest that limiting whole grains as part of a low-gluten diet may increase the risk of heart disease in people who do not have celiac disease.

British Birth Cohort Studies: 70 year developmental study

- 70,000 British infants followed since birth, since 1946 & 3 further periods – 6000 research papers, 40 books
- Pick your parents carefully
- Do not be born in poverty
- Poverty predicts multiple long term negative outcomes related to health, longevity, and dementia
- Good engaged parents in early years is protective; daily reading to children predicts escape from poverty
- But persistent poverty trumps good parenting

Join UCSF's Brain Registry

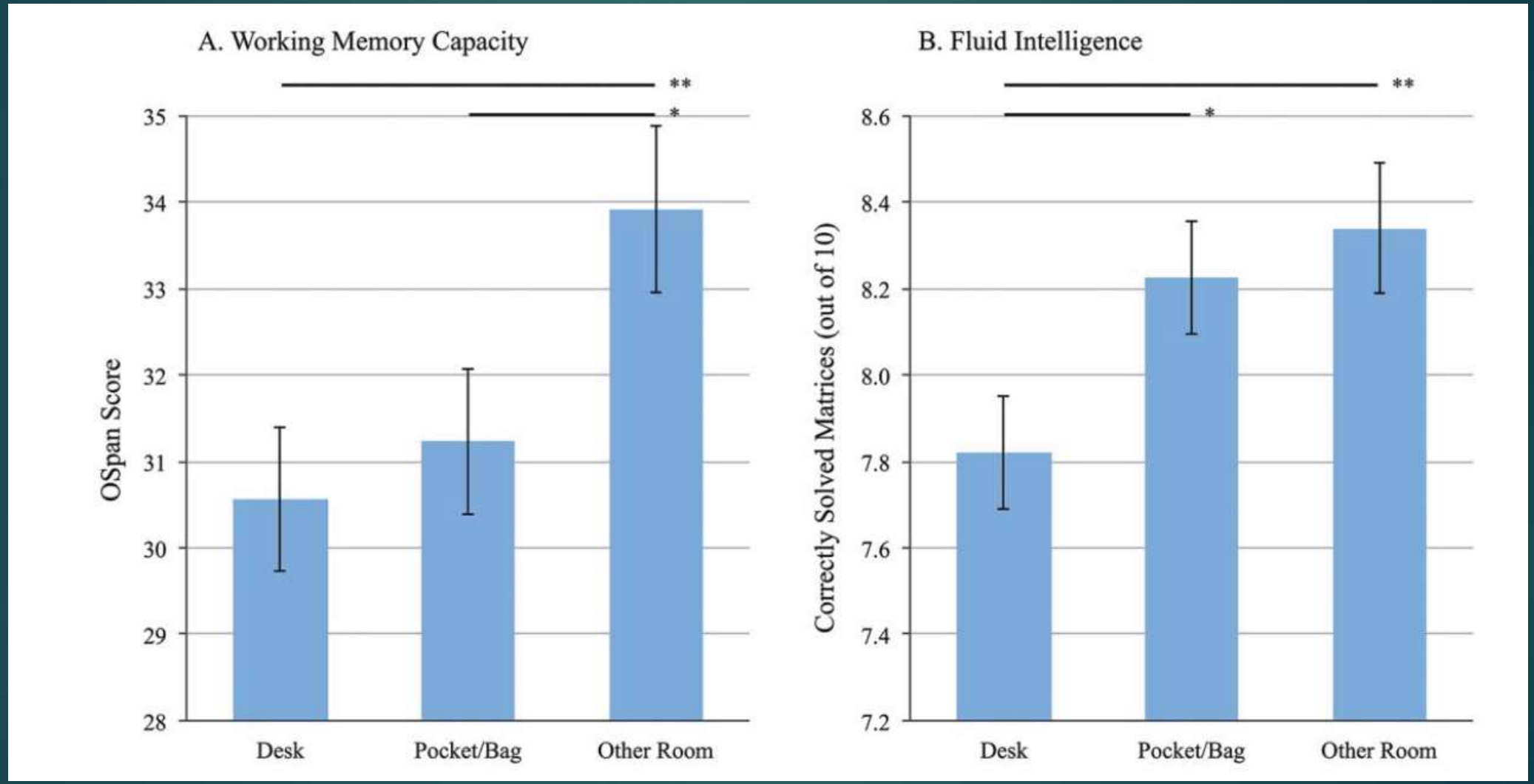
- If you have a computer, join this new research program:
  - http://www.brainhealthregistry.org
- Answer some health questions and play some Lumosity games, which gives them info on your brain functioning.
- They check in with you every 6 months.
- It's easy and you contribute to a very large brain research project. They are building a large pool of potential participants in clinical trials to find cures for brain disorders.
- Join it!!

Absolutely Do This !!!

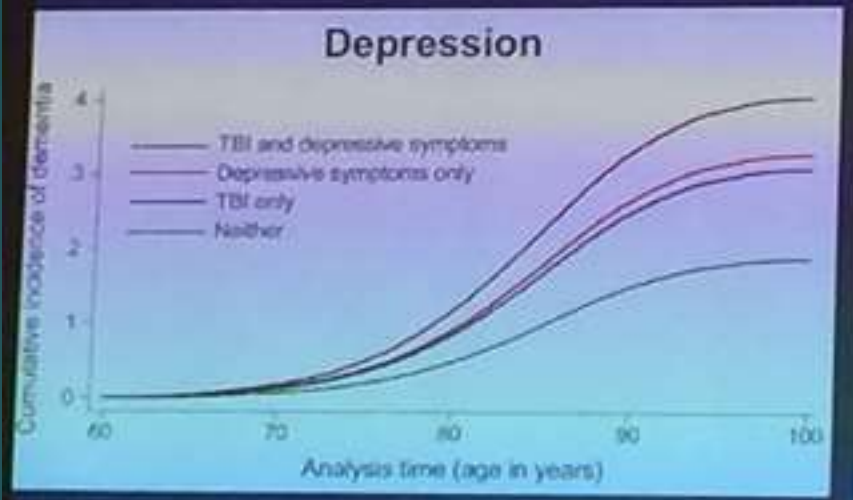
Benefits of reading

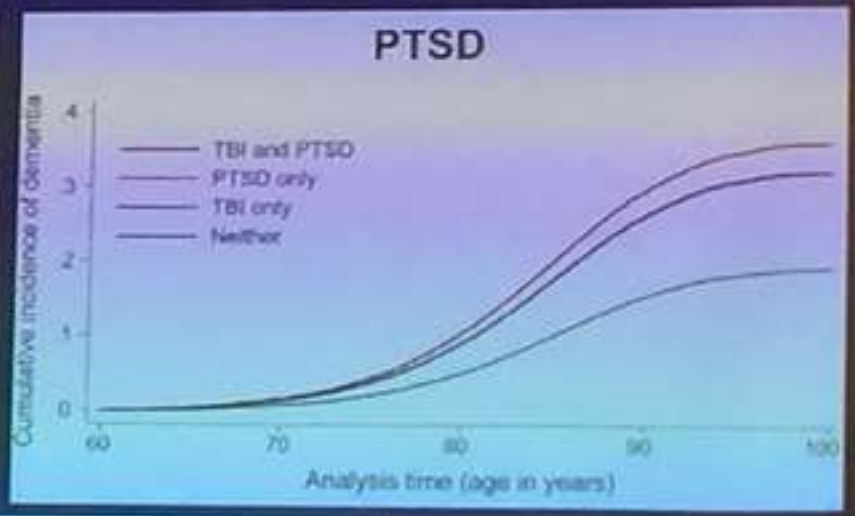
- Makes you more intelligent: As Dr. Seuss once wrote, “The more that you read, the more things you will know. ”
- Reading is a brain workout: Frequent brain exercise was able to lower mental decline by 32 %
- Reading can make you more empathetic. Increases theory of mind.
- 2.5 times less likely to develop dementia
- Reading may reduce stress by as much as 68 %
- Read a real book not e-reader in bed
- 40 % of frequent readers ages six through 10 were read to out loud at home
- Helps to improve & maintain memory function

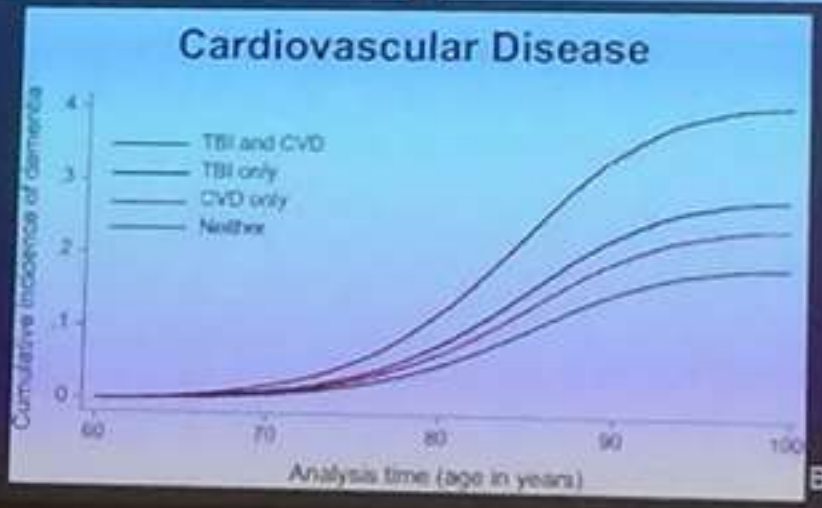
Your IQ test results depend on where your Iphone is!



Comorbidities Have an Additive Effect on Dementia Risk







Barnes...Yaffe. *Neurology*. 2014.

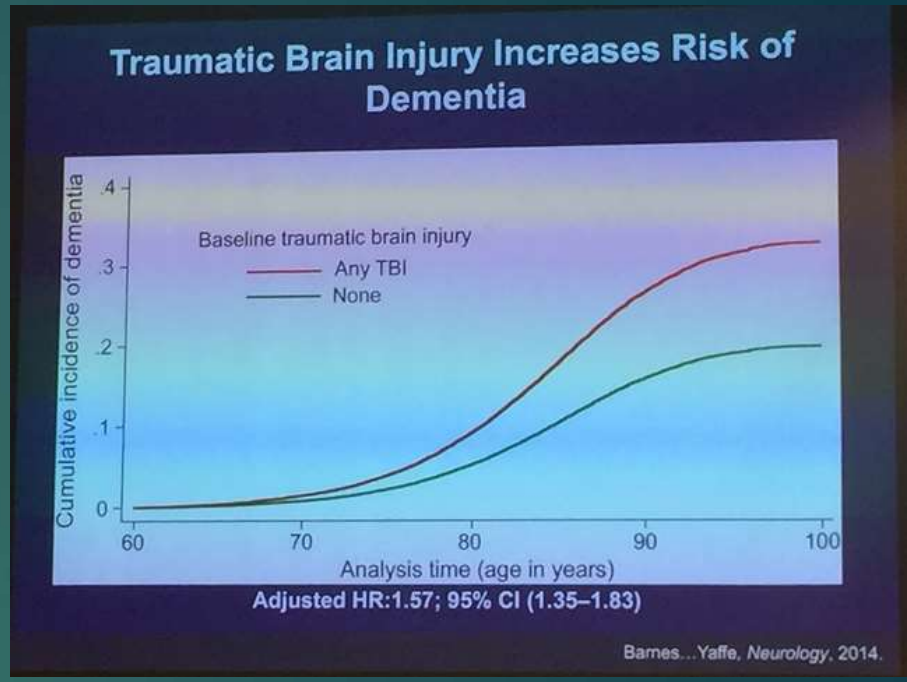
Mere presence of your smartphone reduces cognitive ability; it is a brain drain

- N = 800: place their smartphones either on the desk face down, in their pocket or personal bag, or in another room.
- Mere presence of one's smartphone reduces available cognitive capacity and impairs cognitive functioning, even though people feel they're giving their full attention and focus to the task at hand. As the smartphone becomes more noticeable, participants' available cognitive capacity (available working memory capacity & functional fluid intelligence) decreases.
- Participants with their phones in another room significantly outperformed on cognitive tests those with their phones on the desk.
- Your cognitive capacity is significantly reduced when your smartphone is within reach -- even if it's off.

Adrian F. Ward, et al., 2017

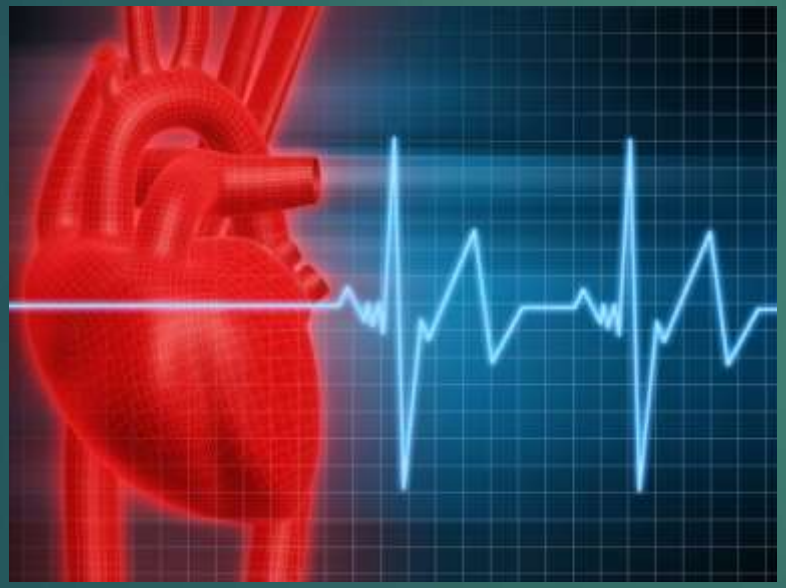
Tip #1: Protect your head!

- Blows to the head increase odds of Major NCD years later.
- Pro football players have 19 times the typical rate of memory-related diseases.
- 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.



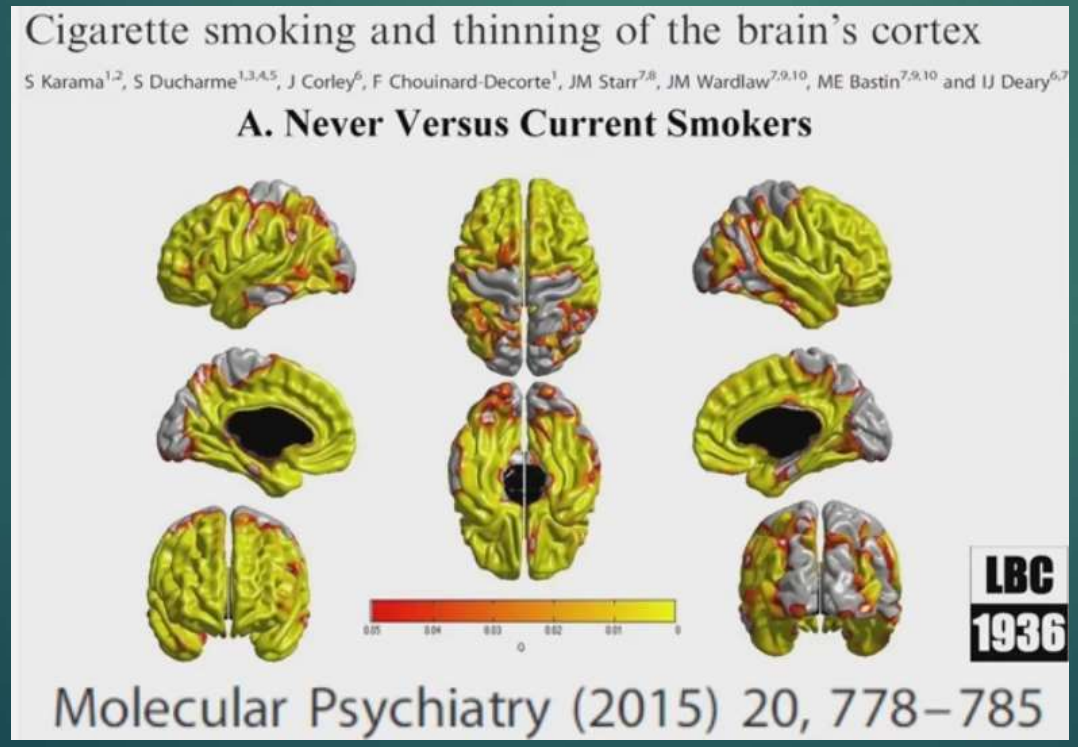
Monitor your vascular numbers; take your antihypertensive and cholesterol meds

Keep your heart fit

- 1 - Get moving: People who exercise regularly have a 30 to 40 percent lower risk of heart disease
- 2 - Eat more plants: 17 percent lower risk of heart disease ; Make plant foods and fish the centerpiece of your meals.
- 3 - Replace saturated fat, such as butter, with olive oil, and other unsaturated oils.
- 4 - Relax
- 5 - Drink alcohol (a little)

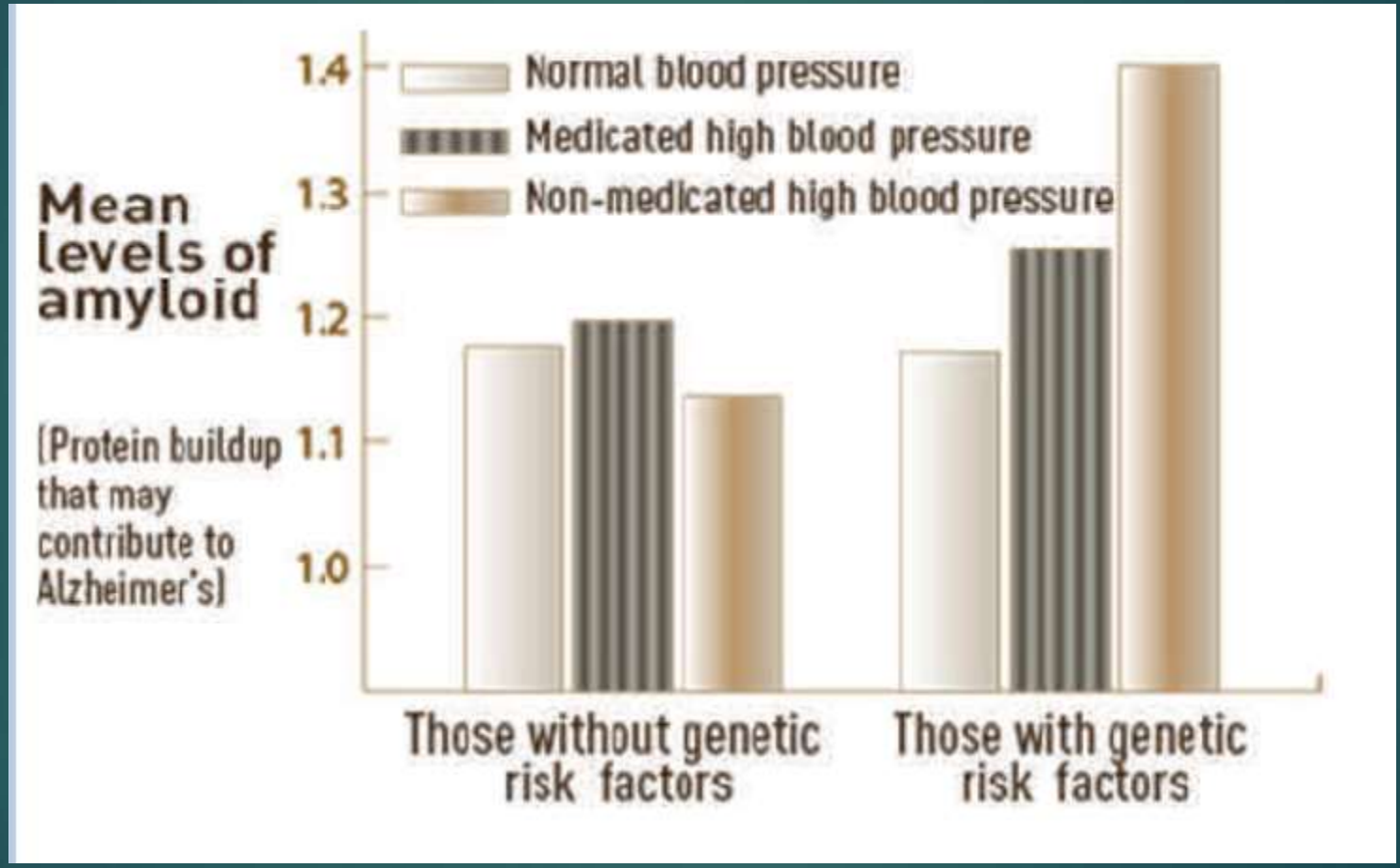
Tip #3: Do not Smoke

- 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.



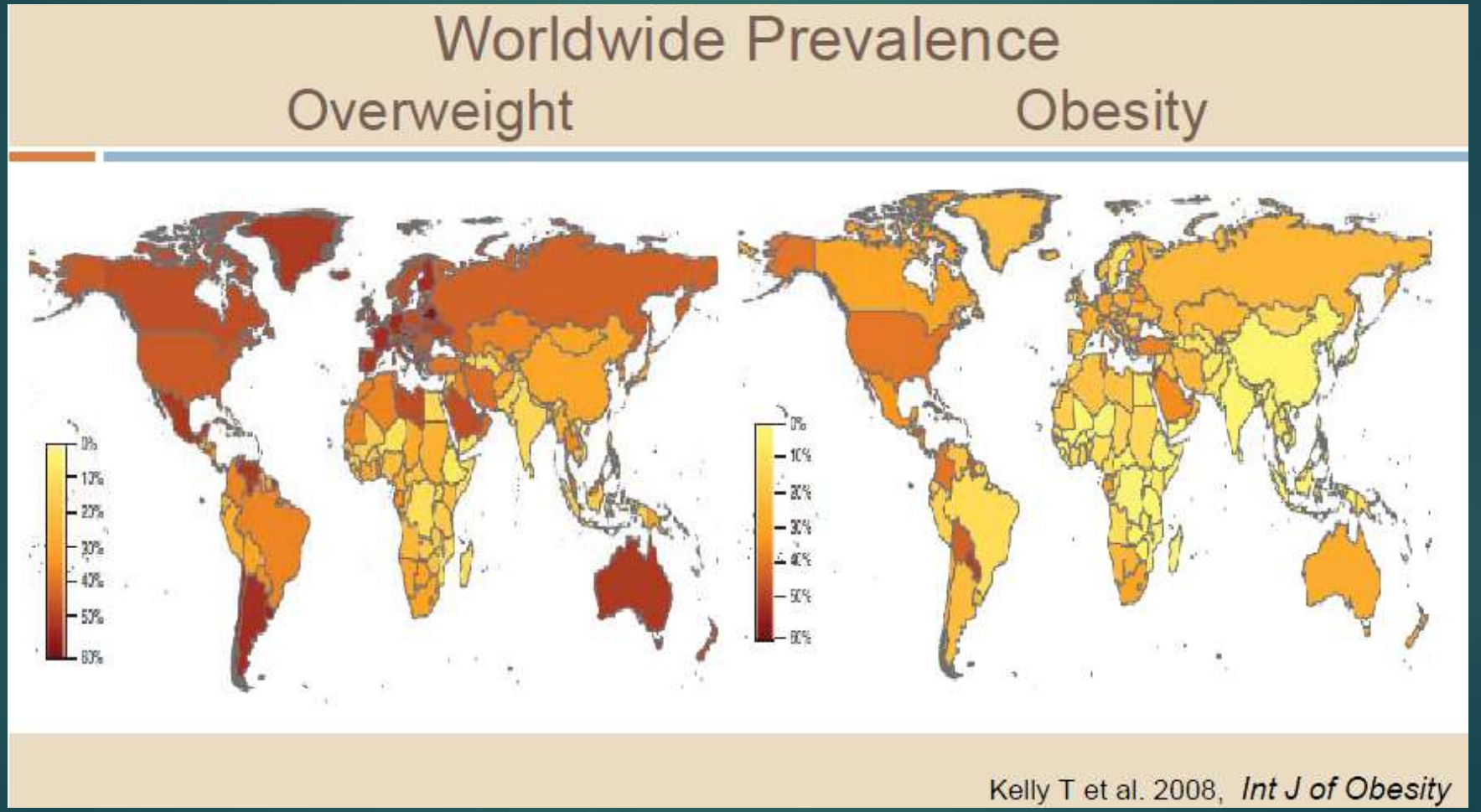
Yellow: thinner cortex in smokers;
If you stop smoking, takes 15-25 years to catch up to thicker cortex

Take your meds: Hypertension Increases Beta Amyloid



Bad news: **** Double APOE4 & non-medicated hypertension

Tip #4: Stay at a normal weight

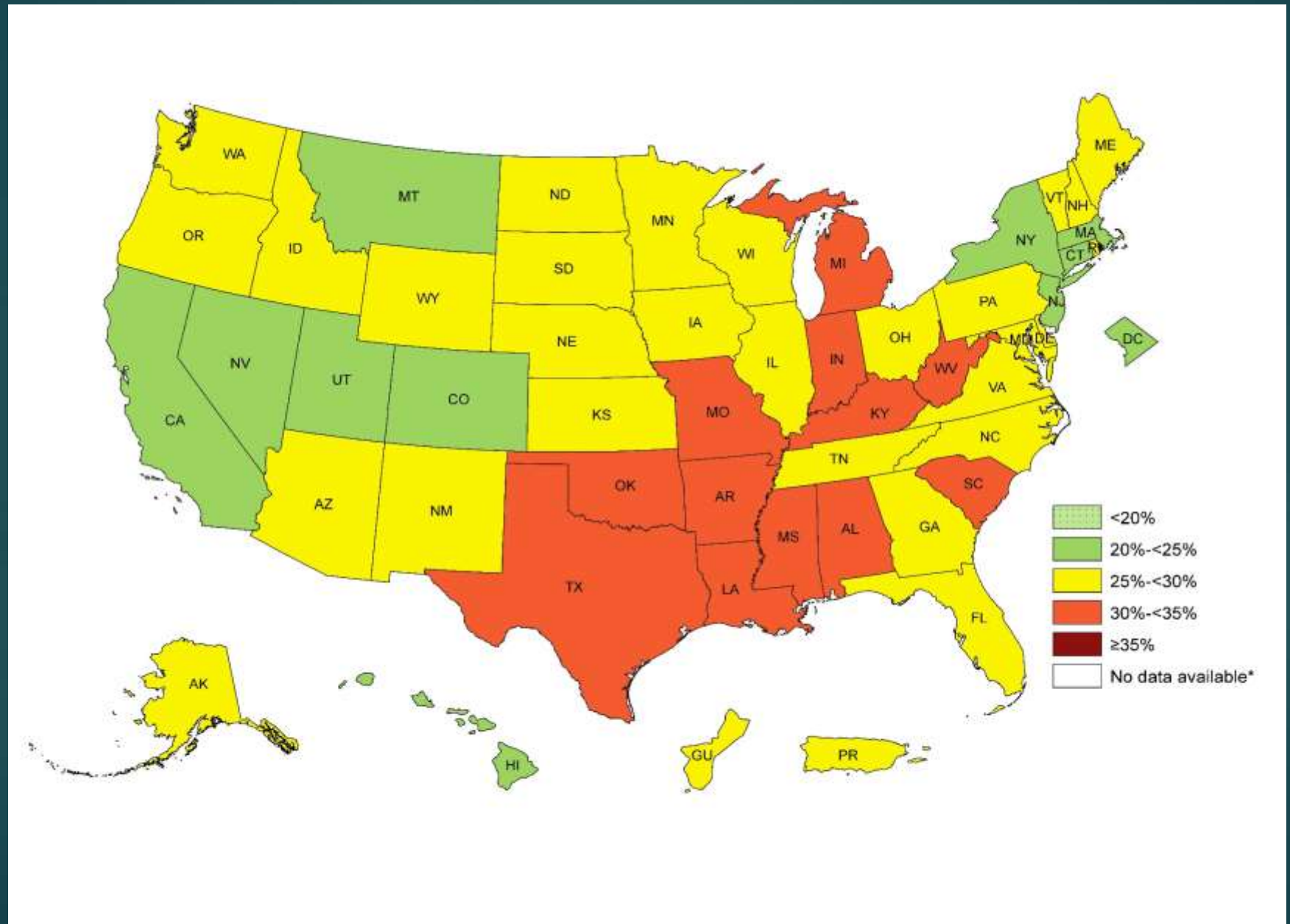


We are overweight

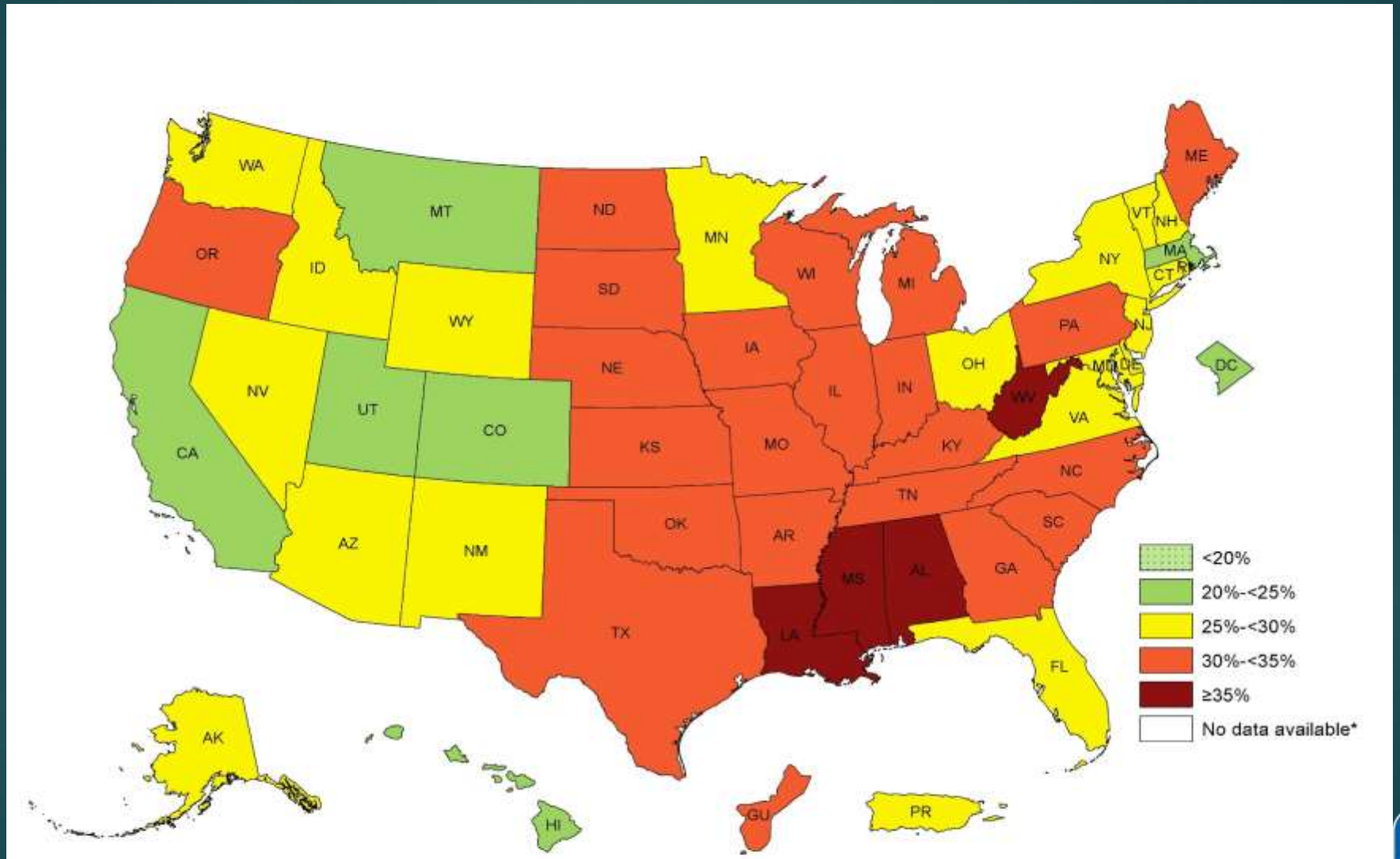
- 75% of U.S. Men & 67% of Women Are Overweight
- 40% of US adults are obese (>30 lbs.); 20% of kids
- Food intake control is method
- Midlife obesity accounts for 7 percent of Alzheimer's cases
- Waist/hip ratio was highly associated with death from CV disease
- Normal-Weight Central Obesity More Deadly Than Just High BMI

Run 1 mile = 100 calories

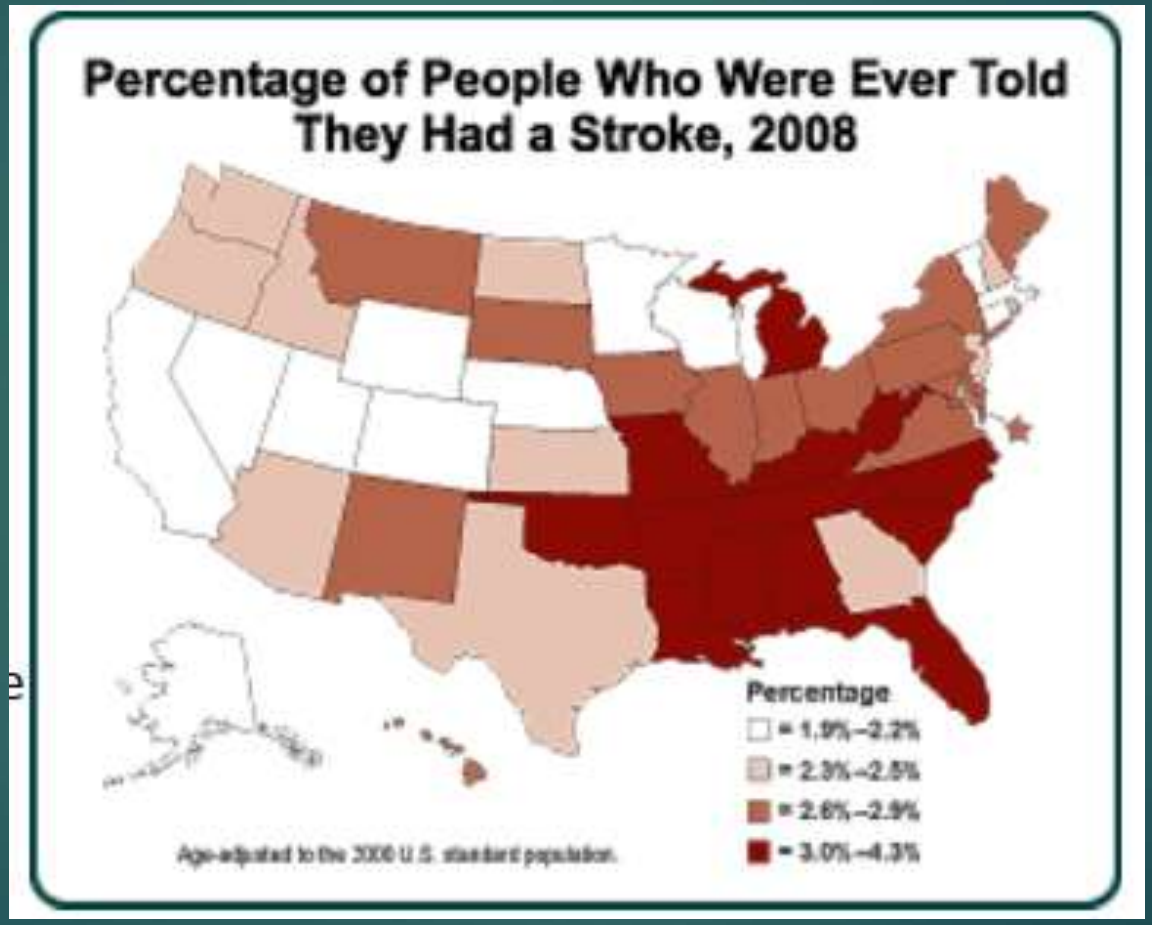
Prevalence of Self-Reported Obesity Among U.S. Adults, 2011



Prevalence of Self-Reported Obesity Among U.S. Adults, 2015

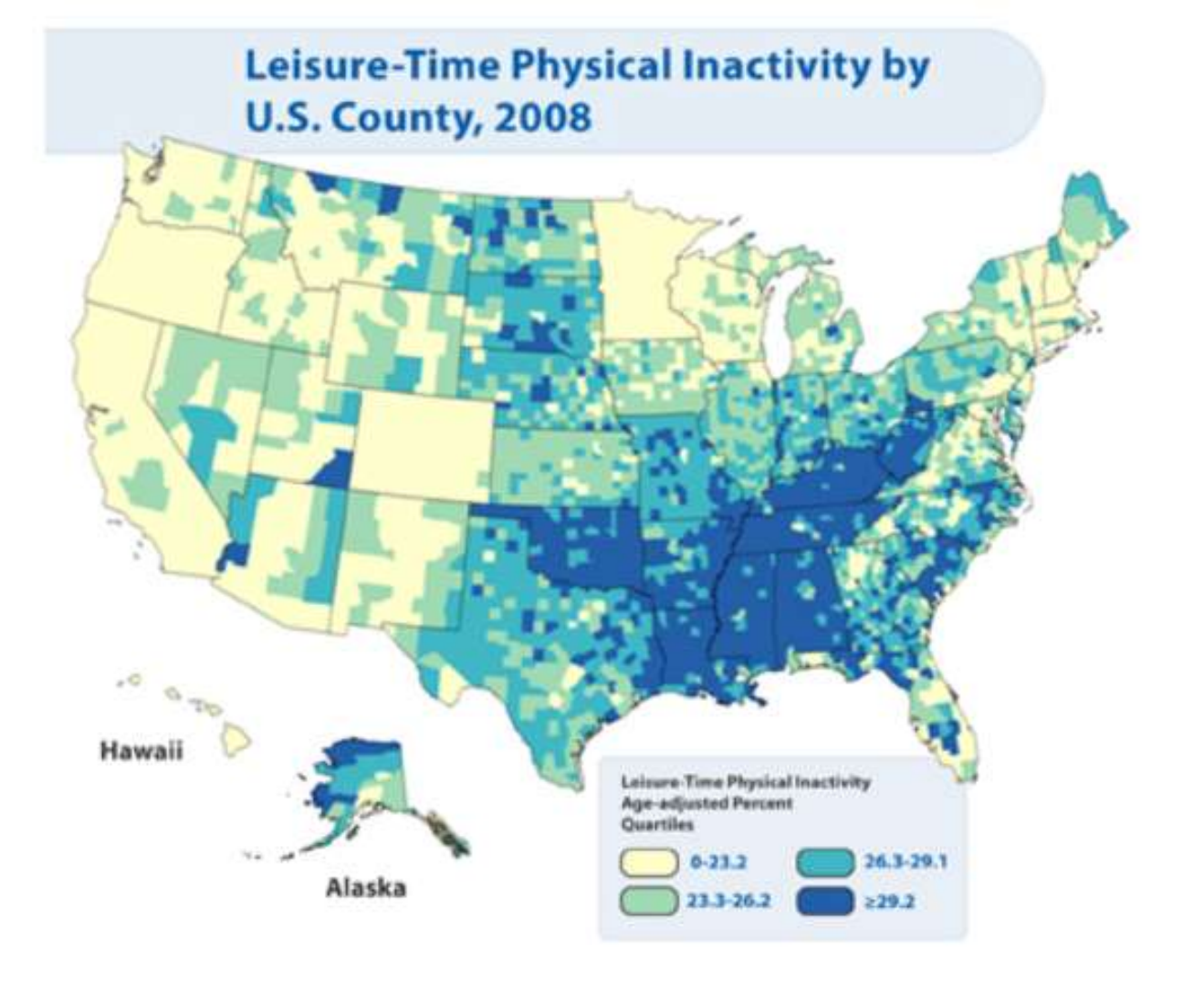


CDC: % Strokes by State



Highly tied to high consumption of fried and processed foods

CDC Physical Inactivity



Most Strokes Can Be Prevented;
1 in 6 People Will Have a Stroke

- Know your personal risk factors: high blood pressure, diabetes, and high blood cholesterol.
- Take your medications faithfully.
- Be physically active and exercise regularly.
- Avoid obesity by keeping to a healthy diet.
- Limit your alcohol consumption.
- Avoid cigarette smoke. If you smoke, seek help to stop.
- Learn to recognize the warning signs of a stroke.

Tip #5: Meditate! Get longer telomeres

- People who meditate regularly have less cognitive decline and brain shrinkage
- 12 minutes a day for two months = improved cognition in seniors with memory problems.
- More mind wandering = shorter telomeres; being present in the moment = longer telomeres

Tip #6: Take Vitamin D or get Sun

- Older do not get enough sunlight
- Low Vitamin D increases cognitive decline
- Aged 65+ 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).
  - Colorectal cancer (22% decline; 30% increase if no Vit D)

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

2017 metaanalysis of coffee

- lower risk for:
  - all cause mortality,
  - cardiovascular mortality,
  - total cancer
  - prostate cancer
  - endometrial cancer
  - Melanoma
  - non-melanoma skin cancer
  - liver cancer
  - type 2 diabetes
  - metabolic syndrome
  - gallstones,
- gout
- renal stones
- liver conditions including hepatic fibrosis, cirrhosis, cirrhosis mortality and chronic liver disease combined.
- Parkinson’s disease
- Depression
- and Alzheimer’s disease

Tea: Less NCD & Stroke

- Tea: less liver disease, depression (3 cups = 37% less), less heart disease
- 2017 Chinese study, n=957, 7 y study: Less NCD with green or black tea drinking only among females & APOE e4 carriers
- 13 year Japanese study, 2013:The more green tea or coffee people drink, the lower their stroke risks (3 cups).

- Green tea drinkers in the study were more likely to exercise

- Red wine and Green Tea: may reduce beta amyloid

L. Feng, et al., 2017

Don’t drink soda: soda is associated with telomere shortness

- Daily consumption of a 20-ounce soda was equivalent to an average of 4.6 years of telomere shortening.
- Equals effect of smoking, or not exercising
- Links that has tied sugary beverages to obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease

Tip #8: Brush and Floss

- Gingival inflammation is associated with cognitive decline.
- Periodontal disease before age 35 quadrupled the odds of Major NCD years later.
- Elderly people who reported brushing their teeth less than once a day were up to 65 percent more likely to develop Major NCD than those who brushed daily.

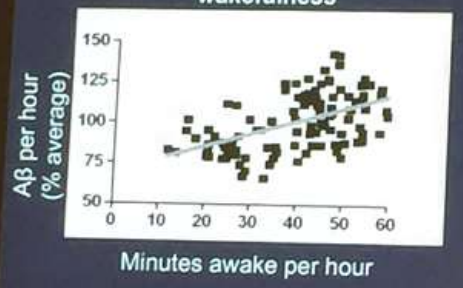
Tip #9: Google! Use the Internet.

- Doing an online search can stimulate your aging brain even more than reading a book

- UCLA's Gary Small: Novice Internet surfers, ages 55 to 78, activated key memory and learning centers in the brain after only a week of Web surfing for an hour a day.

Sleep Linked to Amyloid Production & Clearance

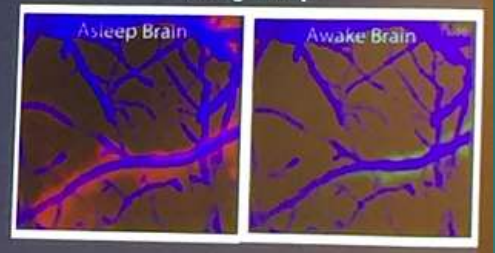
Increased Aβ production during wakefulness



- Brain interstitial (ISF) Aβ level correlates with wakefulness in mice
- Significantly greater Aβ plaque deposition after chronic sleep restriction

Kang et al, *Science*, 2009.

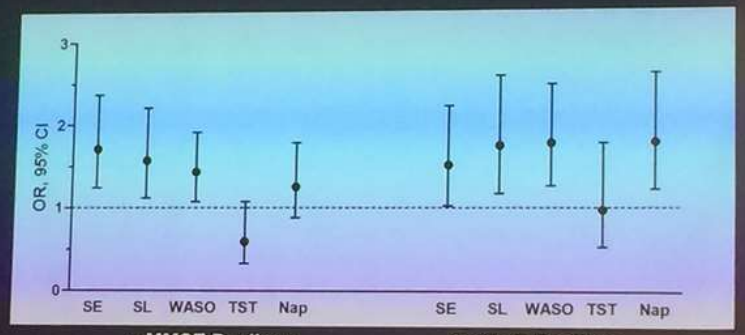
Aβ clearance is increased during sleep



- Cerebrospinal fluid (CSF) flow in asleep (left) and awake (right) brain
- Sleeping mice cleared twice as much Aβ from their brains as conscious mice

Xie et al, *Science*, 2013.

Cognitive Decline is Associated with Poor Sleep Quality



SE: Sleep efficiency <70%, SL: Sleep latency ≥1 hour, WASO: Wake after sleep onset ≥90 min
TST <5 hours, Nap time >2 hours

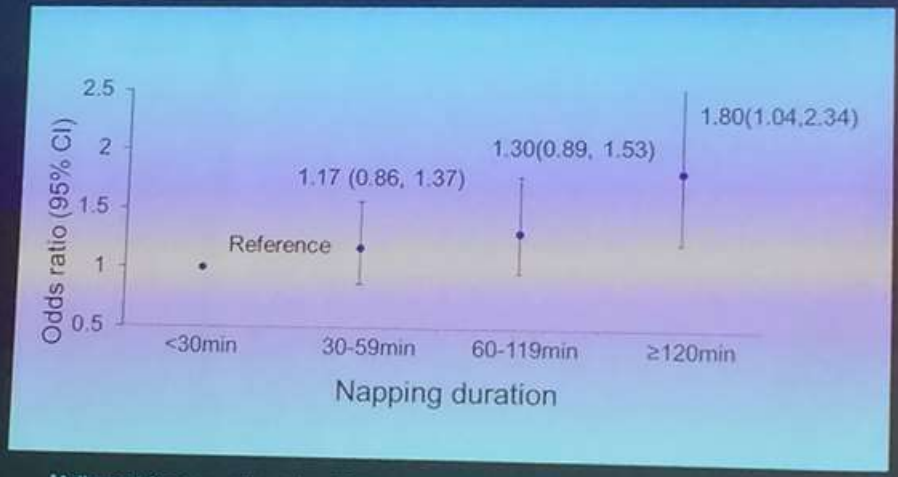
*Adjusted for age, depression, education, history of stroke

Yaffe et al, *Neurology*, 2007.

Sleep and Cognitive Outcomes

- In people with advanced dementia, sleep is disturbed but little information on older adults without dementia
- Unclear direction of causal path or bidirectional
- Does cognitive decline lead to sleep disturbances?
- Do sleep disturbances lead to cognitive decline and dementia?

Napping Duration and Risk of Dementia



*Adjusted for age, education, BMI, smoking, physical activity, depressive symptoms, comorbidities, sleep medication use and baseline global cognition score

Leng...Yaffe, *In Preparation*.

Get Enough Sleep!

Tip #10: 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 Problem? 5 Rules

5 Rules

- 1 Single alarm time rules them all
- 2 Keep it dark
- 3 Keep it cold (65-68 degrees)
- 4 Don’t stay in bed if awake; bed is only for sleep or sex
- 5 No screens

- Avoid or cut down on having daytime naps
- No coffee or alcohol after 3 pm
- Do Cognitive Behavioral Therapy for Insomnia (80% successful)

Why we sleep - Matthew Walker

Sleep apnea increases stroke, cancer, Major NCD & death risk

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

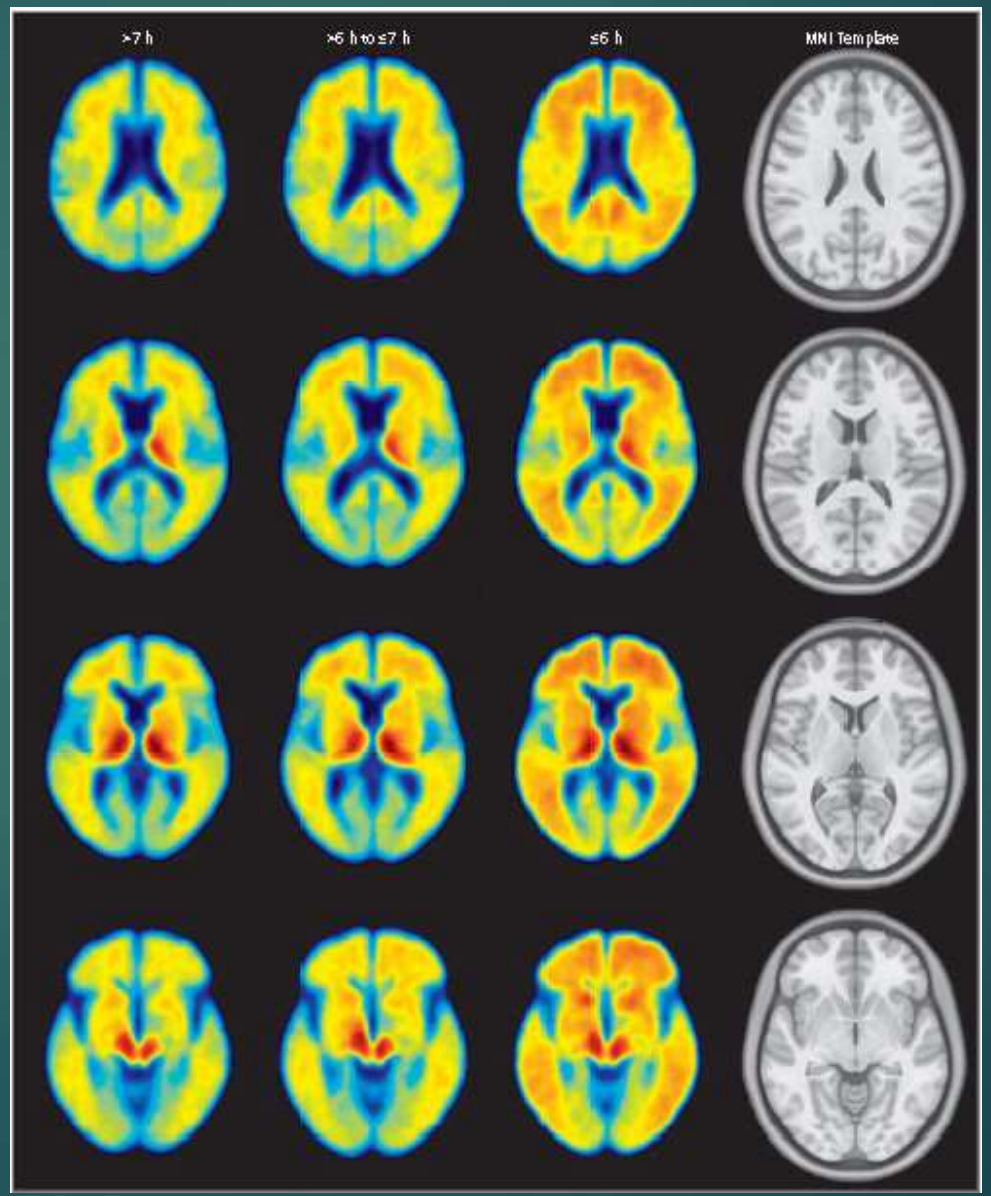
- Moderate to severe sleep apnea triples risk of stroke, cancer, and earlier death

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

Sleep duration, BA, & Alzheimer's

Duration of sleep =

< 6h



Amyloid PET Scans

Reports of shorter sleep duration and poorer sleep quality are associated with greater Aβ burden.

Tip #11: 15 minutes of laughter and smiling

- Laughter & smiling are good for the heart and longevity.

- Benefits:
  - blood vessel relaxation
  - Lower blood pressure
  - Less pain
  - Longer life

Smiling: 250 baseball players photos of 1950s: smile intensity in photographs was linked to longevity.

Smilers lived 7 years longer.

Tip #12: De-stress!

- Chronic stress increases risk of Major NCD
- 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 #13: Eat a little dark chocolate

- Chocolate, red wine, cocoa, and coffee are major dietary flavonoids found in plant-derived foods.

- CV effects: makes arteries more relaxed and flexible

- A high-flavanol intervention was found to enhance memory functioning.

- Increases Dopamine

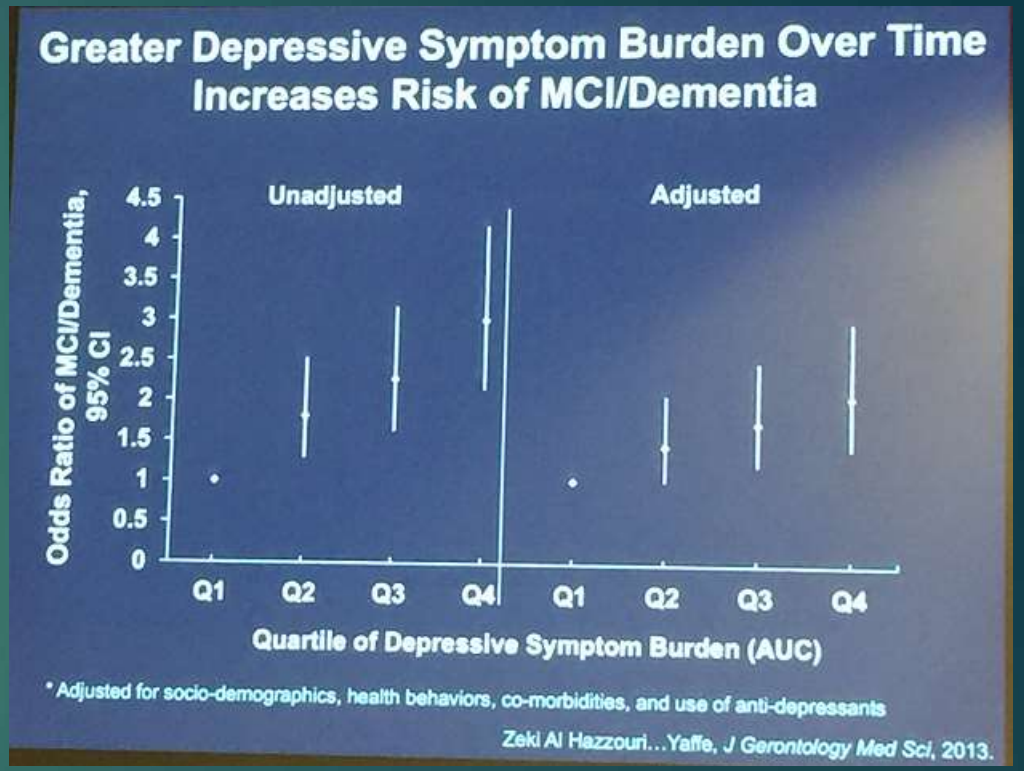
- But correlation between depression and increased chocolate consumption

Tylenol: reduces any type of pain

- Acetaminophen: reduces negative affective responses across a variety of social contexts:
  - reduced self-reports of hurt feelings from social rejection
  - dampened the emotional experience associated with aversive stimuli such as thinking about one's own mortality, and empathy for another person's physical and social pain.
  - reduced affective responses to both negative and positive emotional affect; may selectively dampen affect; reduces affective responses.

Tip #14: Treat Depression

- Depression is a risk factor for Major NCD
- 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 Major NCD



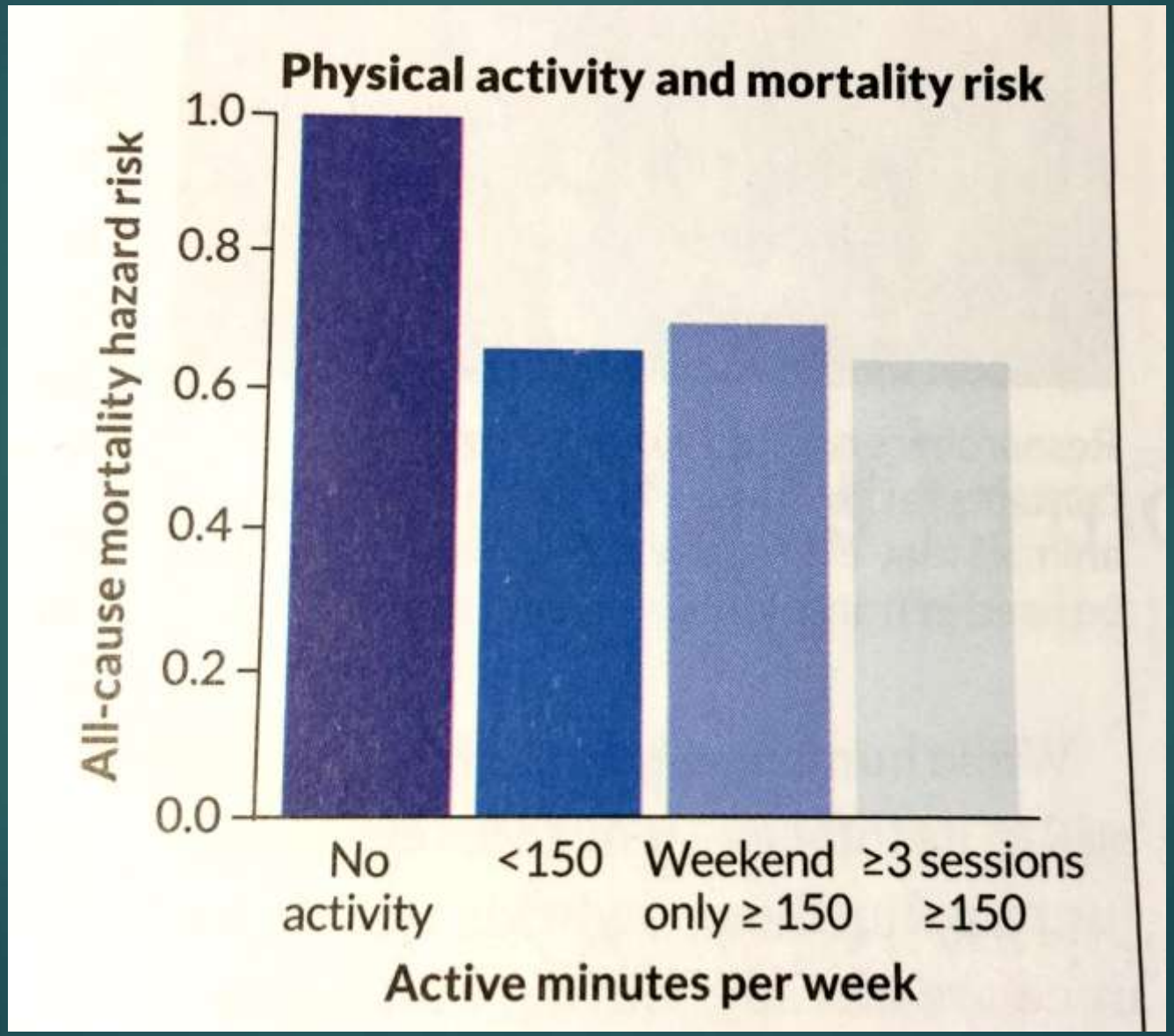
Antidepressants: Increase Hippocampal Volume

Most Important Tip #15: **** Exercise

Keep moving and Keep your wits

- **** Exercise is the single most powerful and best way to reduce the risk of cognitive decline.
- 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; Levels of physical activity correlates with good cognition, regardless of neuropathology.

Physical activity & risk of dying



Higher death rate

Exercise and dementia risk = 40% reduced risk

Exercise – how much?: 30 min/day 5d/week – moderate levels

- 16 studies, highest vs lowest exercise levels: 45% reduced AD risk
  Hamer & Chida, Psychol Med 2009)
- 15 prospective cohort studies, 1-12 yrs f/u: 35-38% reduced risk
  - Low-moderate/high levels exercise (Sofi et al., J Int Med 2011)

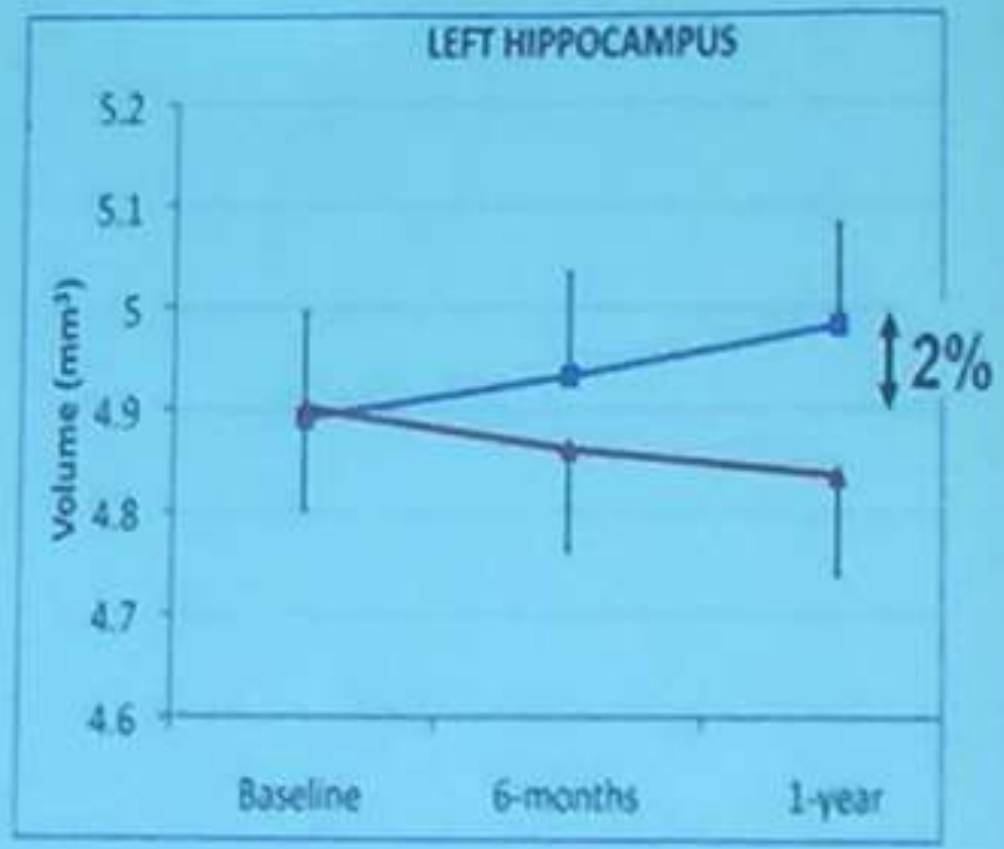
- 17 studies, highest vs lowest exercise levels: 40% reduced AD risk
  (Guure et al. BioMed Res Int 2017)

  - Greater than any current drug effect
  - Decreases BA in bran

Walking – Reversal of Hippocampal Age-related Atrophy

10 ⟶ 40 min/day walk 1 year

hippocampus
1-2%/yr atrophy



Benefits of Exercise

- Reduces risk of cardiovascular disease, stroke, diabetes; increases large LDL molecules, less small LDL
- Prevents certain cancers (breast, colon)
- Improves mood and reduces anxiety
- Builds bones and muscles
- Expands lung capacity
- Reduces inflammation
- Reduces fall and fracture risk
- Keeps weight normal
- Boosts cognitive ability (executive function)
- Increases size of hippocampus; more neurogenesis; more BDNF
- Prolonged sitting (6 hours) cancels many of these

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).

1 hour of vigorous exercise per day

- 1 hour of vigorous exercise per day reduces mortality by 57 %.
- Hour can be broken up throughout the day

- Other 2017 metaanalysis: Running may be the single most effective exercise to increase life expectancy.
- Runners tended to live about three additional years, even if they run slowly or sporadically and smoke, drink or are overweight.
- As little as five minutes of daily running was associated with prolonged life spans

Sitting kills you sooner; even if you exercise

- Average Adult = 55% of their day engaged in sedentary pursuits
- Adults who sat for long stretches at a time -- an hour or more without interruption -- had a greater risk of early death than those who were sedentary for the same total amount of time but got up and moved around more often
- Too much sitting, like smoking, increases the risk of heart disease, diabetes, obesity, cancer, depression, premature death, faster cognitive decline, and thinning in memory regions of the brain.

- Metabolism slows down 90 percent after 30 minutes of sitting. After two hours, good cholesterol drops 20 percent.

Any movement is good: physical activity of any intensity

- people who sat for less than 30 minutes at a time had the lowest risk of early death, suggesting that taking movement breaks every half-hour could lower your risk of death.
- A new study of around 8,000 middle-aged and older adults found that swapping a half-hour of sitting around with physical activity of any intensity or duration cut the risk of early death by as much as 35 percent. The findings highlight the importance of movement -- regardless of its intensity or amount of time spent moving -- for better health.
- replacing just 30 minutes of sitting with low-intensity physical activity would lower the risk of early death by 17 percent; Swapping the same amount of sitting for moderate to vigorous activity would be twice as effective, cutting the risk of early death by 35 percent. The researchers also found that short bursts of activity -- of just a minute or two -- provided a health benefit.

Must use your leg muscles

- New research shows that using the legs, particularly in weight-bearing exercise, sends signals to the brain that are vital for the production of healthy neural cells.
- Limiting physical activity decreased the number of neural stem cells by 70 percent compared to a control group of mice, which were allowed to roam. Both neurons and oligodendrocytes (WM insulation) didn't fully mature when exercise was severely reduced.
- Restricting exercise lowers the amount of oxygen in the body, which creates an anaerobic environment and alters metabolism

Raffaella Adami, et al., 2018

Exercise causes Neurogenesis

- Neurogenesis declines with age; declines with early Major NCD

- Number of new hippocampus neurons is twice that of mice living in standard cages.

Exercise: Best is one you will do

- Exercise ↑, Cognitive ↑
- Reduced Major NCD risk
- Slower hippocampal loss, better executive functioning
- Find an “exercise partner”

Amy Jak, UCSD

90+ Cohort: What helps you live longer

- Alcohol - 1 glass daily
- Caffeine (coffee, cola, chocolate): U shape relationship, 1-2 cups daily
- Weight: your BMI: if 70+, normal or slightly overwgt better; being thin in 80's, higher mortality
- Exercise: minimum of 15 minutes daily; 45 minutes best
- Active leisure & social life: up to 8 hrs a day

Advantages of Bilingualism?: Ongoing science

- Regularly speaking more than one language appears to strengthen skills that boost cognitive reserve
- Bialystok, 2010: Dementia delayed by four years in bilingual people.
- Better executive functioning
- Kenneth Paap, SFSU, 2015 & Claudia von Bastian, 2015 : not true
- New metaanalysis: 83 percent of them found no EF difference between the two groups - a tendency for studies with positive results to have used smaller samples; those using larger samples more likely to find no effect. Conclusion: Publication bias: 68% of positive studies published (in reproducibility crisis in psychological science)
- But Lothian study: Those with higher age 11 IQs were more bilingual; being bilingual increased rate of better cognition at age 70, reducing dementia by 4-5 years; whether you were born bilingual or learned it later did not matter

Bialystok, 2010; Paap, et al., 2015; De Bruin

Tip #16: Drink a little Alcohol?

- Drinking one drink per day correlates with positive health outcomes; drinking more increases heart disease
- If you drink 5 drinks in 2 hours on any day of the week, you are alcoholic!
- Alcohol consumption, particularly of wine, is associated with higher incomes and education levels, which in turn are associated with lower rates of smoking, lower rates of mental illness and better access to health care.
- Heavy drinking increases the risk for death by 31% to 54%.
- Latest 2014 British Study: 2.5 drinks per day produces memory impairment 10 years later
- 2014 study: light and moderate alcohol consumption in older people is associated with higher episodic memory and is linked with larger hippocampal brain volume.

Alcohol and Cancer

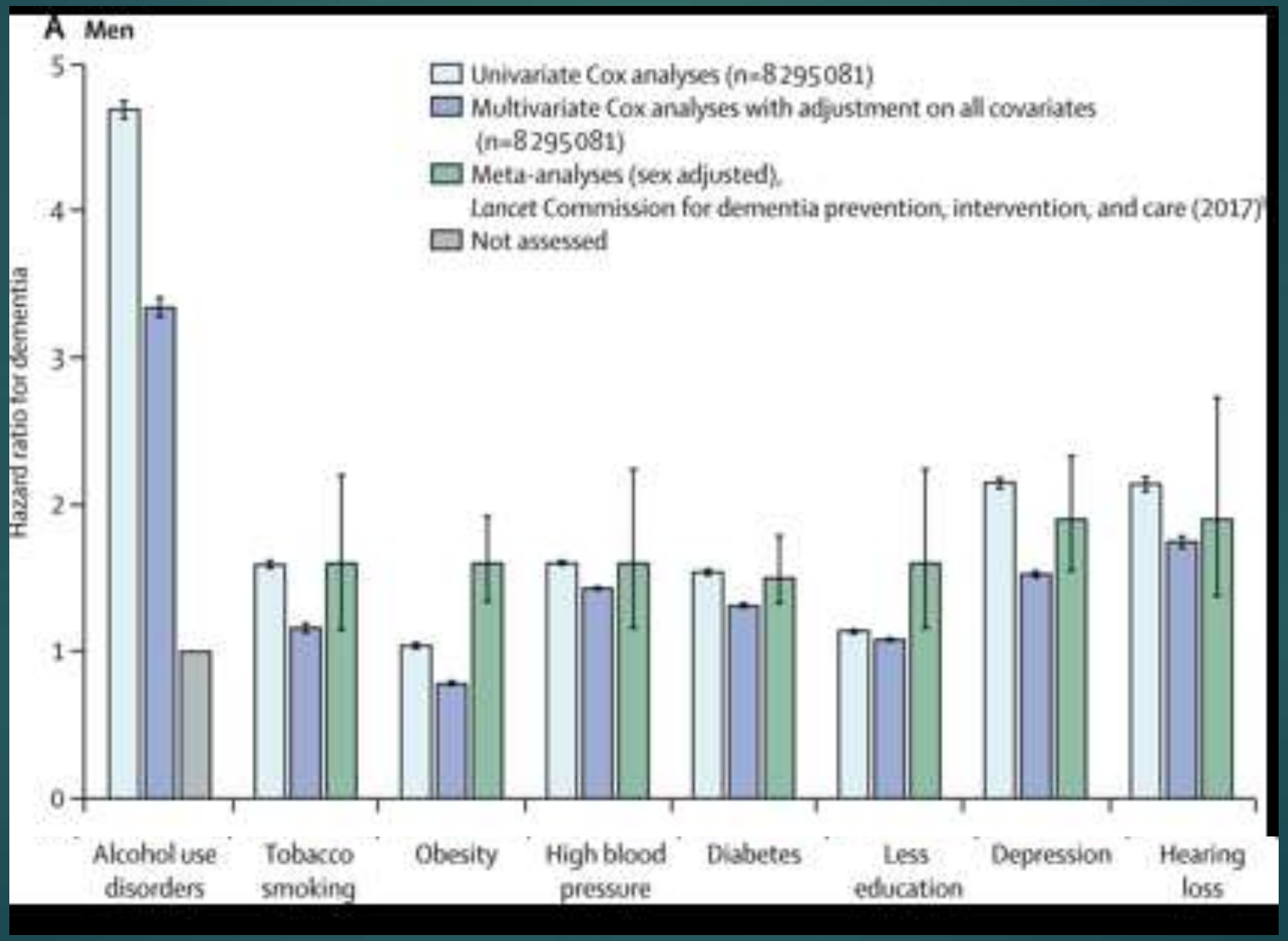
- Alcohol use — whether light, moderate or heavy — increases cancer risk.
- 5 % of cancer deaths can be attributed to alcohol.
- Alcohol consumption is particularly linked to increased risk for breast, colon, esophageal, and head and neck cancers.
- Mortality risk increased among patients with cancer who are moderate drinkers (3 or more per day) or heavy drinkers.

Heavy Drinking 'Strongest' Modifiable Risk Factor for Dementia

- Heavy alcohol consumption is a major risk factor for all types of dementia, but particularly early-onset dementia.
- 2018: n = all hospital admissions in France; 31 million people over a 6-year period; 80% of the 65+ French population; 1 M with dementia; 945 K with AUD
- Risk for dementia was three times greater if the patient had a history of alcohol use disorders (prob. 5+ drinks/day)
- Results suggest that heavy drinking is the strongest potentially modifiable risk factor for dementia that we have ever seen

Michaël Schwarzinger,, et al., 2018

Potentially modifiable risk factors for dementia,
n = 11,000,000



Tip #17: Socialize
Longer life & less cognitive decline

Go dancing

Socialize

- Remain actively engaged with other people
- Decreases risk for Major NCD & increases longevity (= to quitting smoking)

Scientific research says real source of happiness:

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
  - 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 Major NCD & increases longevity (= stopping 2 packs of cigarettes per day effect)

Playing Bridge: Better immune system

M. Diamond: 1.5 hours of bridge playing increased T lymphocytes immune cells

Loneliness kills

- Subjective experience of loneliness (self perceived social isolation) is harmful, not the actual number of social contacts a person has.
- Loneliness kills: isolation is toxic (less happy, health declines earlier in midlife, brain declines sooner, die sooner); 1 in 5 Americans
- Correlated with dementia, probably of CV causation
- Loneliness = 2 packs of cigarettes per day effect
- Need one intimate friend

2017: Association Between Mentally Stimulating Activities in Late Life and MCI Outcome and relation to *APOE* ε4

- 1929 cognitively normal participants 70 years or older were followed for approximately 4 years.
- Computer use, craft activities, social activities, and playing games.
- associated with a decreased risk of MCI.

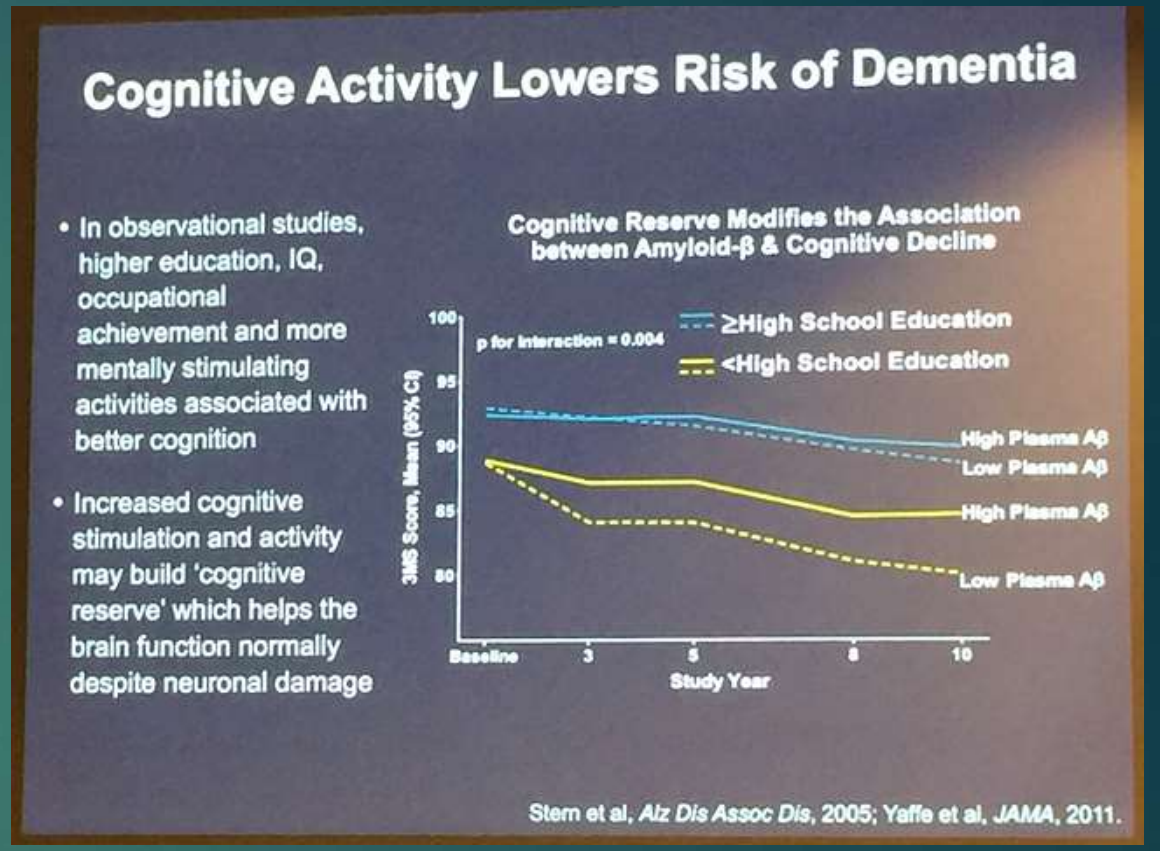
J. Krell-Roesch, et al. JAMA Neuro, 2017

Get a Pet

- Seniors w/ Pets:
  - 36% Less Likely to Report Loneliness;
  - 21% Fewer Doctor Visits
- Seniors with pets are also less likely to exhibit depression, report feelings of loneliness and experience illness.
- But taking care of a pet – feeding, grooming and veterinary care – can be financially and physically burdensome to seniors
- Meals on wheels will feed both

Tip #18: Stay Cognitively Active

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



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

Tip #19: Dance

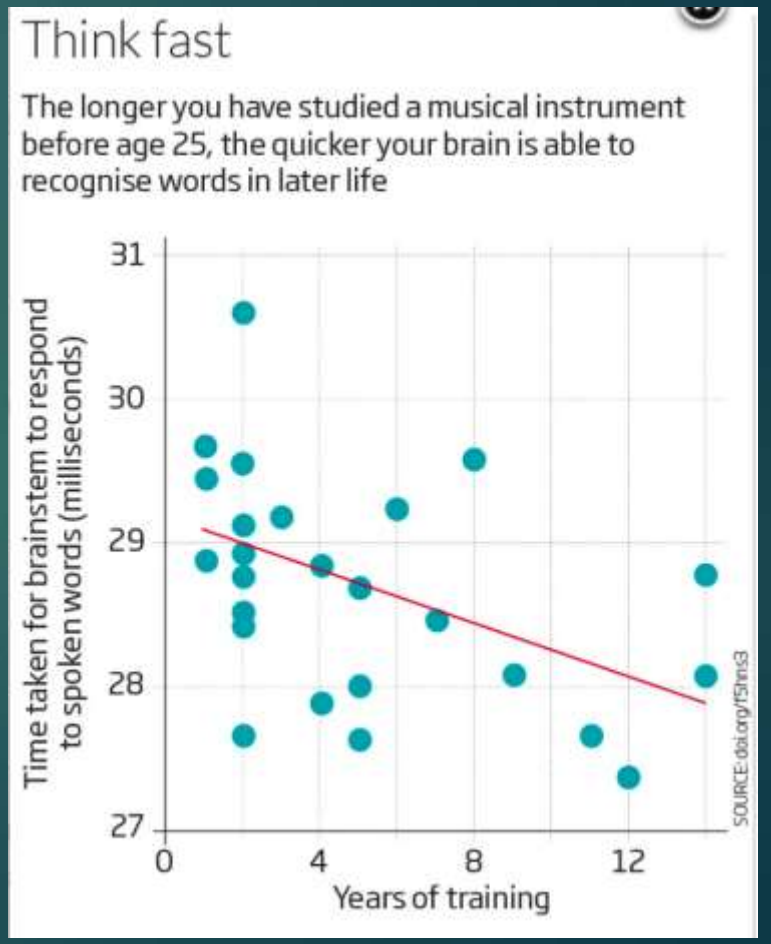
- There is a significantly reduced risk of dementia in older adults who dance frequently.
- Dance increases volume of left HC. Both dance and fitness training can induce hippocampal plasticity in the elderly, but only dance training improves balance capabilities.
- Increased socialization and improved physical functioning
- Improves balance and gait in older adults.

Pumpkin carving, belly dancing, UCSF med school grad, daughter Dr. Maya Vella

Tip #20: Play a Musical Instrument

- 10 years of musical experience = better nonverbal memory, naming, and executive functioning in advanced age relative to nonmusicians.

- It is never too late to be musically active.



Hanna-Pladdy & MacKay, 2011.

Tip #21: You are what you eat: Eat like a Greek or Swede

- Mediterranean diet:
  - high plant foods (vegetables, fruits, legumes, and cereals);
  - high intake of olive/vegetable 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

Mediterranean Diet: many benefits

- Associated with:
  - longer survival,
  - reduced obesity,
  - reduced diabetes,
  - reduced risk of CV or cancer death,
  - reduced risk of neurodegenerative disease: ~20% risk reduction
- 36% fewer strokes
-
- Significantly reduces Metabolic Syndrome

Extra-virgin Olive Oil in mice

- Extra-virgin Olive Oil in mice significantly reduced BA and Tau and increased memory functioning

- Eating nuts, seeds, and oils could serve as an alternative to fish and fish oils in terms of providing neuroprotective omega-3

Olive oil vs. Canola oil

- Good: Alzheimer mice fed a diet enriched with extra-virgin olive oil had reduced levels of BA plaques and tau and experienced memory improvement.
- Bad: Consumption of 1 T daily of canola oil in the diet produced worsened memory, worsened learning ability and weight gain in mice which model Alzheimer's disease.
- Canola oil-treated animals had greatly reduced levels of beneficial BA 40; showed increased formation of BA42 and decreased synaptic connections and increased memory impairment

Tip #22: Eat fish

- Fish twice a week better at reducing heart attacks & strokes than dietary supplements of Omega 3 fish oil
- Algae/green grass source crucial
- Preserves telomere lengths in (best longevity predictor)

Current Lothian Study Conclusions

Red = bright kids do all of them; they are related to cognition at age 70, but do not cause it

Green = positive correlation with older age cognition

Omega 3: Positive & Negative

- Always better to get it from fish than supplements
- Omega 3 Fish Oil:
  - lower levels of Beta amyloid & Major NCD risk
  - larger left frontal area, better fluid IQ & memory
- But DHA 1000mg 2x/day had no effect on AD
- Caution for men: High intake of omega-3 fats linked to 40% increased prostate cancer risk in men

Brasky et al., JNCI, 2013

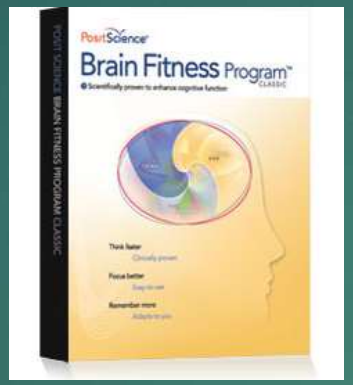
Tip #23: Keep learning

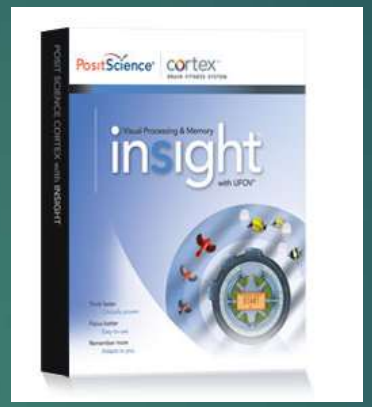
- Hope Levy SFCC classes
- Local Universities:
  - Fromm Institute at USF,
  - OLLI at SF State: Charlie's 6 week class in January
  - CLIR,
  - OSHER
- Road Scholars
- Lifelong Learning Institutes
- Local Senior Centers
- SeniorNet OASIS Institutes (volunteer)
- Shepherd's Centers of America
- Senior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

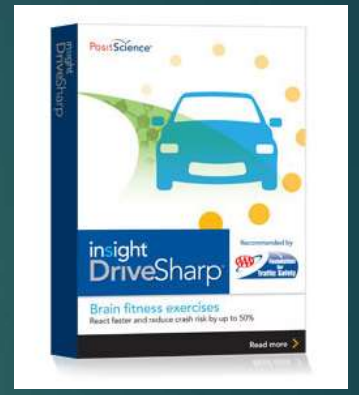
Neurobics: Brain Training Computer Products

25% of adults age 40+ believe that the best way to maintain or improve brain health is to play so-called “brain games” like Lumosity; there is little scientific evidence to support this belief.

NeuroActive



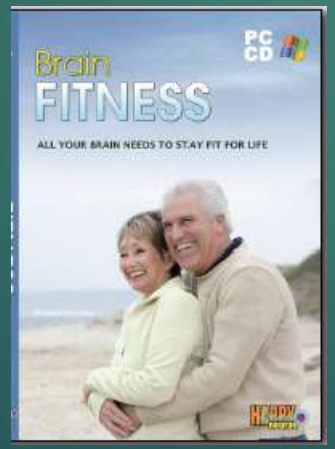




Posit Science

CogniFit
PERSONAL COACH
MindFit
BRAIN POWER FITNESS

Mindfit



Happy Neuron

Lumosity

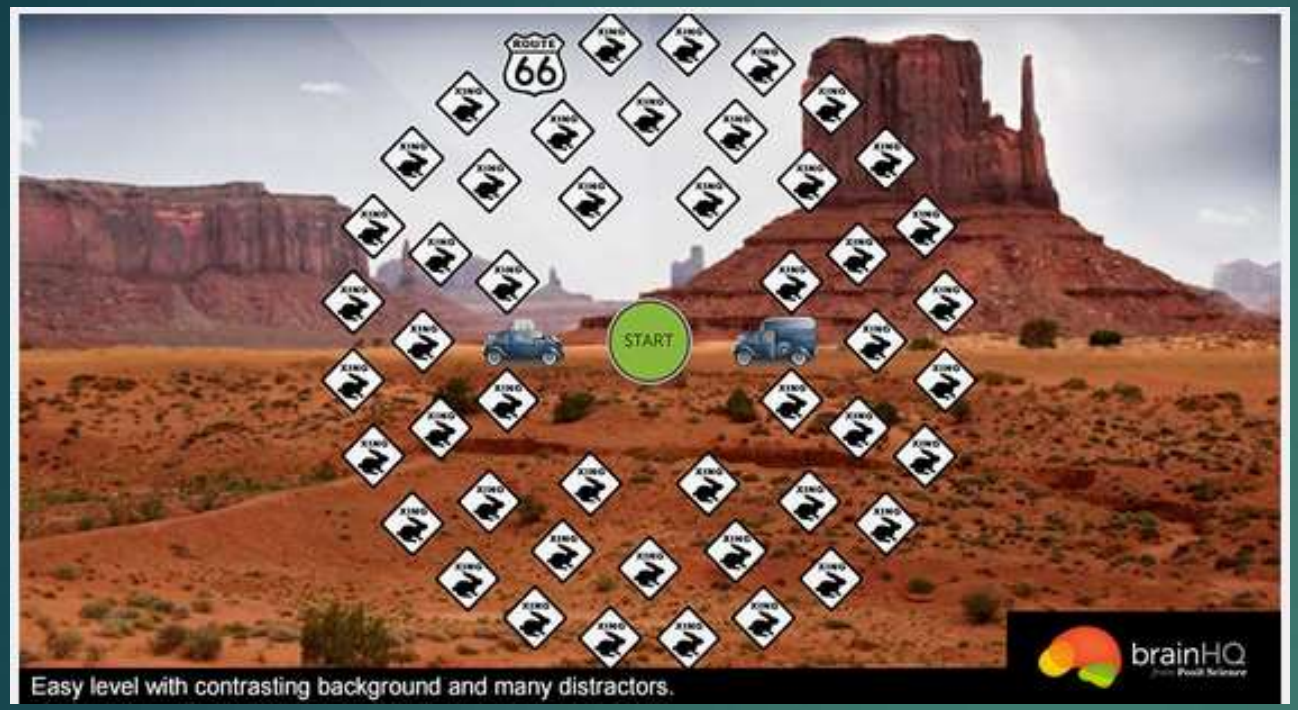
Brain Websites

- Dakim: http://www.dakim.com
- Brainmetrix: http://www.brainmetrix.com/mind.htm
- Lumosity: http://www.lumosity.com/k/brain-train
- Brain Training Games: www.braintraininggames.net
- Miniclip: www.miniclip.com
- Mindsparke: www.mindsparke.com
- Cambridge Brain Sciences: www.cambridgebrainsciences.com

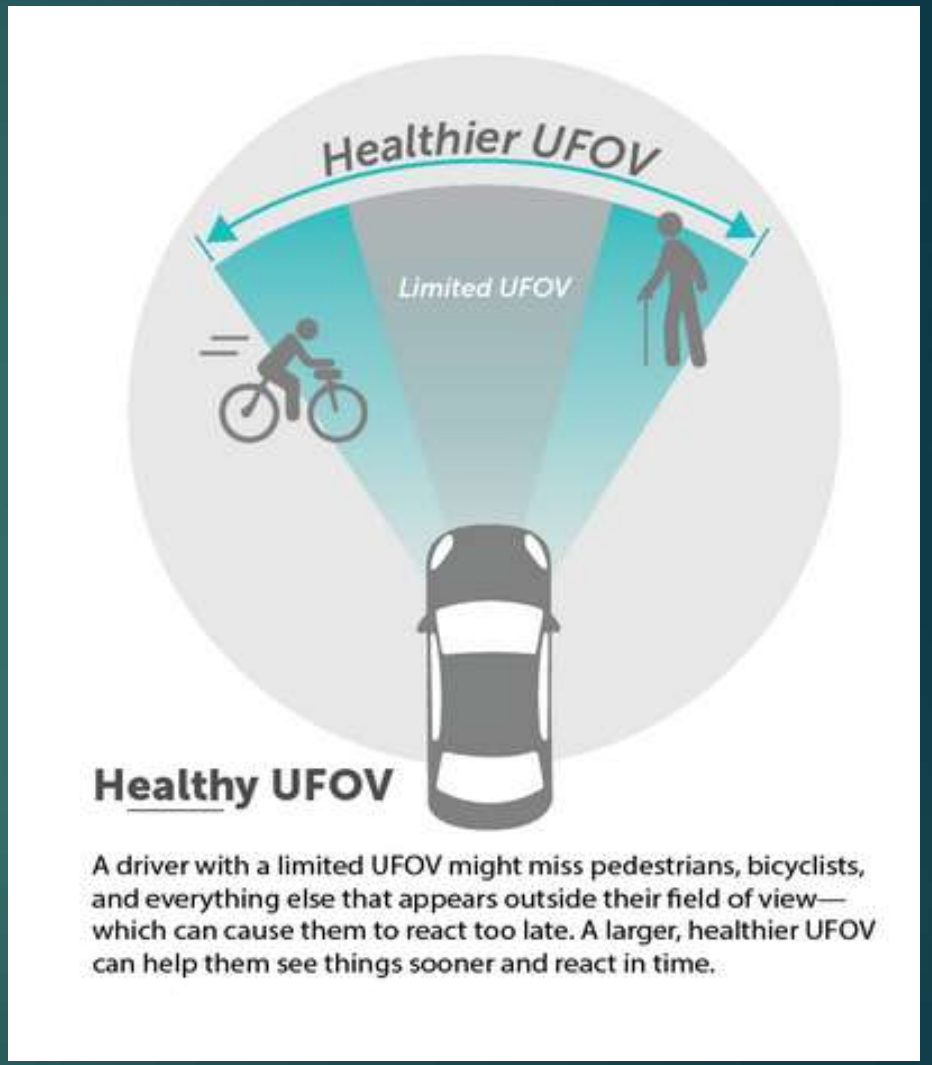
Digital Brain Fitness tools

- BrainBaseline: A free mobile app featuring dozens of cognitive tests that can be retaken over time, and that facilitate self-monitoring; www.brainbaseline.com/.
- BrainHQ: A Web-based cognitive training program that includes Useful Field of View (UFOV) training (UFOV is an important component of safe driving); www.brainhq.com/
- Cogniciti: A free Web-based cognitive assessment designed to measure whether the test taker's cognition is within a normal range given their age, or warrants a visit to the doctor; www.cogniciti.com/.
- CogniFit Senior Driver: A Web-based cognitive training program that assesses and trains for ten driving-related cognitive skills; https://lifestore.aol.com/category/online-learning/cognifit-senior-driver.
- HeartMath Inner Balance: A mobile Heart Rate Variability (HRV) sensor designed to help measure and regulate physiological stress; www.heartmath.com/innerbalance/.

BrainHQ: Posit Science – definite positive research: Useful Field of View



Double Decision program



Adam Gazzaley of UCSF: Project: Evo

Software-based method to measure and improve a key system of executive function known as "interference processing." FDA medical device approach

NIH 10 year ACTIVE study

- Older adults who engaged in brain training drills retained measurable benefits up to 10 years later.
- 10 sessions, each lasting about 60 to 70 minutes over five to six weeks: by Posit Science)
  - 74% of those who participated in reasoning exercises and information-processing drills
  - 71 % of speed-trained participants still displayed those abilities a decade later

- No such difference was observed in memory skills

Sharon Tennstedt, et al., 2013

DTC neurotechnologies: Unclear Efficacy, Potential Harms

- Direct to consumer neurotechnologies: Marketed for the purpose of modulating cognition or a variety of affective and mental states, a growing ecosystem of neurotechnology products is being sold direct to consumers (DTC)
- Offering individuals the prospect of monitoring and manipulating a range of brain functions from memory to mental health, the major product categories are neuromonitoring devices, cognitive training applications, neurostimulation devices, and mental health apps.
- Questions have been raised about whether
  - devices that deliver transcranial direct current stimulation (tDCS) can improve cognitive performance
  - whether cognitive gains from brain-training games are generalizable
  - whether the behavioral effects of EEG neurofeedback and mental health apps are due to placebo.

- See psyberguide.org/apps/

Brain Training: Current Conclusions

- Brain-training programs do indeed produce short-term, highly specific improvements in the task at hand, but most do not produce generalized improvements to overall intelligence, memory, attention, or other cognitive ability.

- The real benefit: expose yourself to a variety of problem-solving skills throughout the day--and not necessarily on the computer.

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 #24: Be Passionate!: Have a Purpose in Life

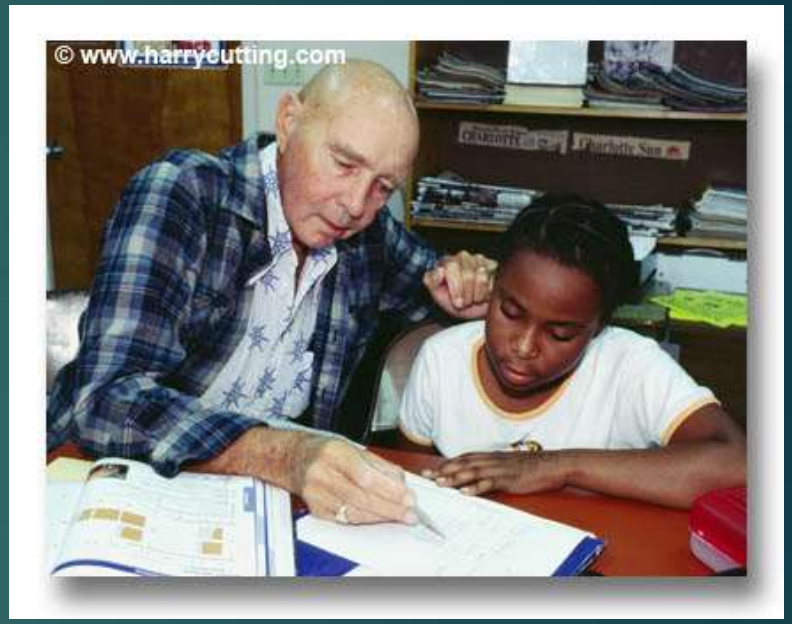
- Purpose in life (psychological tendency to derive meaning from life's experiences and possess a sense of intentionality and goal directedness)

- 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 #25: 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 #26: 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
- 77% of Adults Aged 60 to 69 Have Hearing Loss—Only ~20% of People Who Would Benefit from Hearing Aids Have Ever Use One

- 30% of higher risk of dementia: cognitive impairment were linearly associated with the severity of an individual's baseline hearing loss

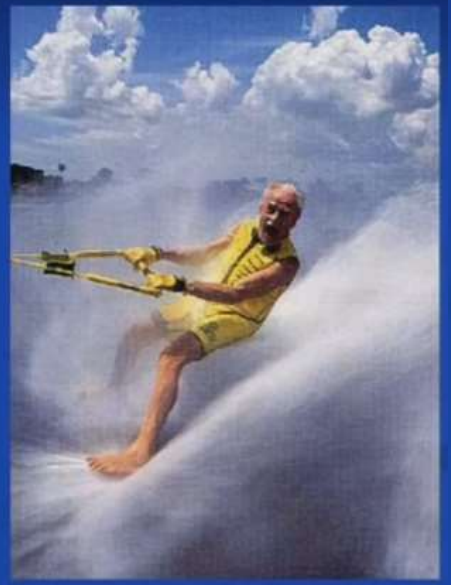
- Poor hearing and vision reduce neuroplasticity

- Get good hearing aides and glasses!!

Be An Active Learner!

If you want the 1-step program…

USE IT
OR
LOSE IT!



General Recommendations

- Manage your medical “numbers” (cholesterol count, blood pressure level, blood glucose level, and weight)
- Take blood pressure, cholesterol, and/or diabetes medications as prescribed. 3 percent of Alzheimer's cases are linked to diabetes
- Eat a Mediterranean diet rich in leafy and bright-colored vegetables, folic acid, antioxidants, and omega-3 fatty acids. Avoid omega-6 fats like butter and processed oils.
- Get aerobic exercise at least two to three times per week.

Recommendations 2

- Cognitive exercise is equally vital -- rather than staying entrenched in a routine; Try new things and do familiar things in novel ways.
- Maintain social and family relationships: isolation is “a huge risk factor for AD.”
- Manage mental health issues such as anxiety, stress, and depression -- all of these can adversely affect memory.
- Avoid excess alcohol, as it can hamper memory formation.

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

Best: Exercise & Socialize

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."

THIS is why we visit museums.
Art is life.

Keep a Young Mind:
All is possible

Hang On!

Einstein

“He who can no longer pause to wonder and stand rapt in awe, is as good as dead.”

Major NCD Self Test

- Johns Hopkins Memory Survey:

- http://www.alzcast.org/memorysurvey/

Good sites

- http://www.mempowered.com/

Contact Info

- Charles J. Vella, PhD
- www.charlesjvellaphd.com
- charlesvella@comcast.net
- 415-939-6175

As the Vulcans say…

Live long and prosper!