Brain Fitness

Healthy Cognitive Aging:
Secrets of staying sharp in older age

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Dementia prevention

- Dementia is the greatest global challenge for health and social care of the 21st century.
- It is driven by people living longer.
- The number of people with dementia is increasing globally.
- But dementia is not an inevitable consequence of ageing

The Facts

- Life expectancy is rising due to better healthcare services.
- The number of elderly persons is therefore rising.
- As the risk of dementia increases with increasing age, the number of persons with dementia is also rising.
- 75% of people do not realize they can reduce the risk of dementia.

Aging without dementia is achievable.

- Is dementia an inevitable consequence of aging?
- Is aging without dementia achievable?
- Dementia is not an inevitable consequence of extreme old age

How to Live a Brain Healthy Lifestyle

- This lecture is based on current scientific research.
- We do not know how to prevent Alzheimer’s disease.
- We do know many of the risk factors that contribute to cognitive decline.
- We want to be proactive about brain health & potential risk reduction.
- While age drives vulnerability to Alzheimer's, the way we live earlier in life will determine how normal our cognition remains, and for how long.

Age-related cognitive impairments

- Numerous factors increase risk for age-related cognitive impairments including lifestyle choices such as:
  - diet
  - physical activity
  - quality of social interactions
  - stressors such as chronic illness, bereavement, and depression,
  - peripheral diseases such as heart disease, hypertension, and diabetes,
  - gender and education
  - genetic variants that either exacerbate the effects of these myriad risk factors or are protective of them

Aging without dementia is achievable

- There appear to be certain compensatory mechanisms (e.g., cognitive reserve or resilience) may play a role in helping people in old age escape 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.
- Intervention strategies that promote general health, maintain vascular health, and increase cognitive reserve are likely to help preserve cognitive function until late life, thus achieving the goal of aging without dementia.

Epigenetics

- Long life experience can clearly effect your long term genetic expression

- Exercise, sleep, trauma, aging, stress, disease, and diet have all shown significant epigenetic effects

- Gambia 70-year maternal study: pregnant mother & fetus's 1st trimester access to leafy green vegetables (it was a wet season) vs not (dry season) predicts living to age 90 vs age 65 in that child; key immune gene is left on, which makes it more difficult to fight infections
- 2019 Study – cognition in middle age: Stressful experiences included having a parent with a drinking problem, financial insecurity, legal issues, divorce, being fired from a job, and the death of a child.
- African-Americans reported 60 percent more of these stressful events than white Americans. In white participants, each stressful event added about a year and a half to normal brain aging (reduced processing speed, flexibility). But in African-Americans, each event aged the brain an extra four years.

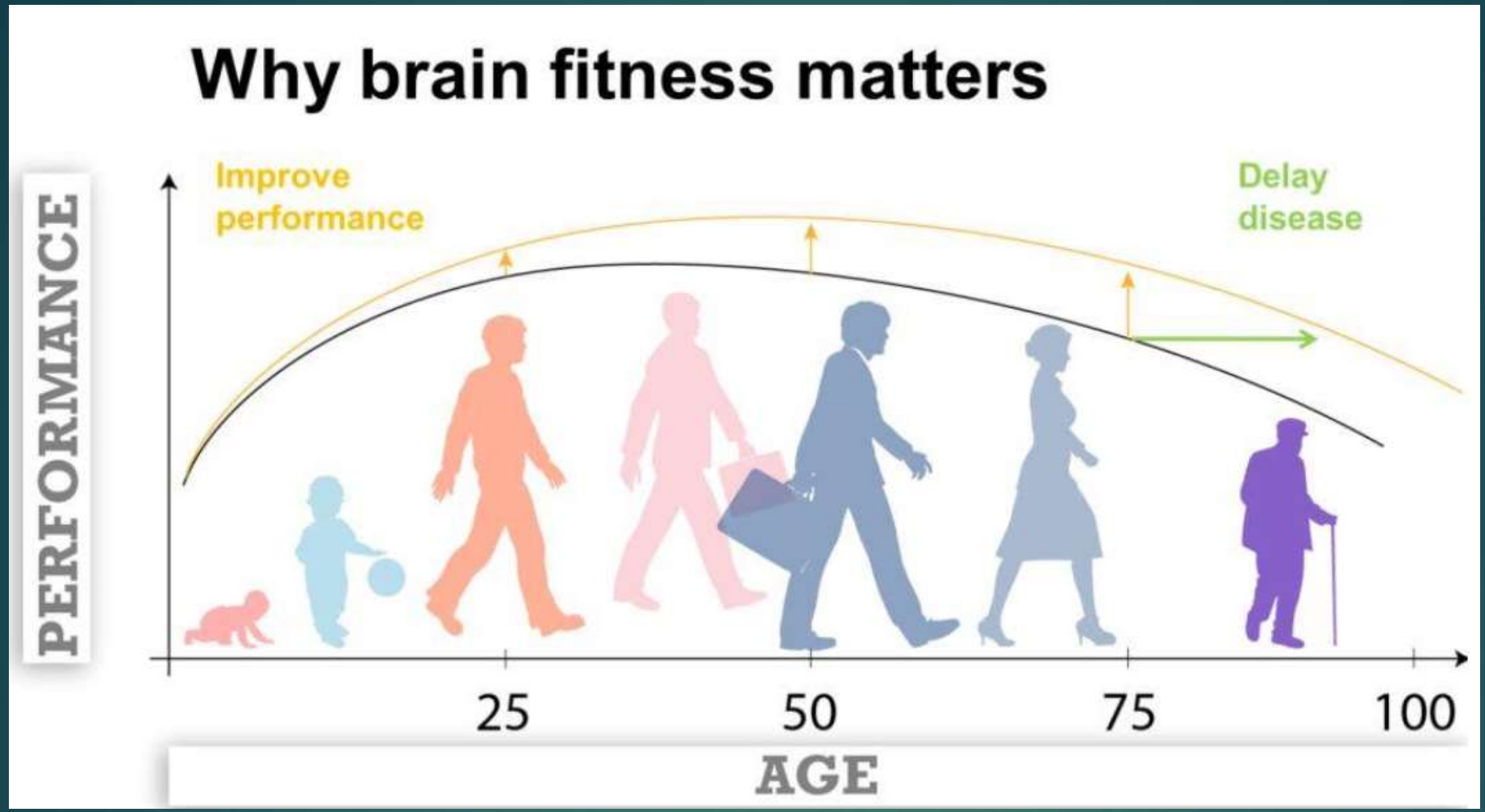
Cognitive decline due to aging

- 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
- It is unlikely that we will be able to cure late-age dementia if people are elderly: it’s too late; too many lost neurons
- Current aim: early prevention; don’t want CV disease, HTN, too much abnormal Beta Amyloid or Tau; want lowest BP without fainting(120/80 or less)

Getting a Major Neurocognitive Disorder is significantly a lifestyle decision

- You cannot change your age or the genes you are born with.

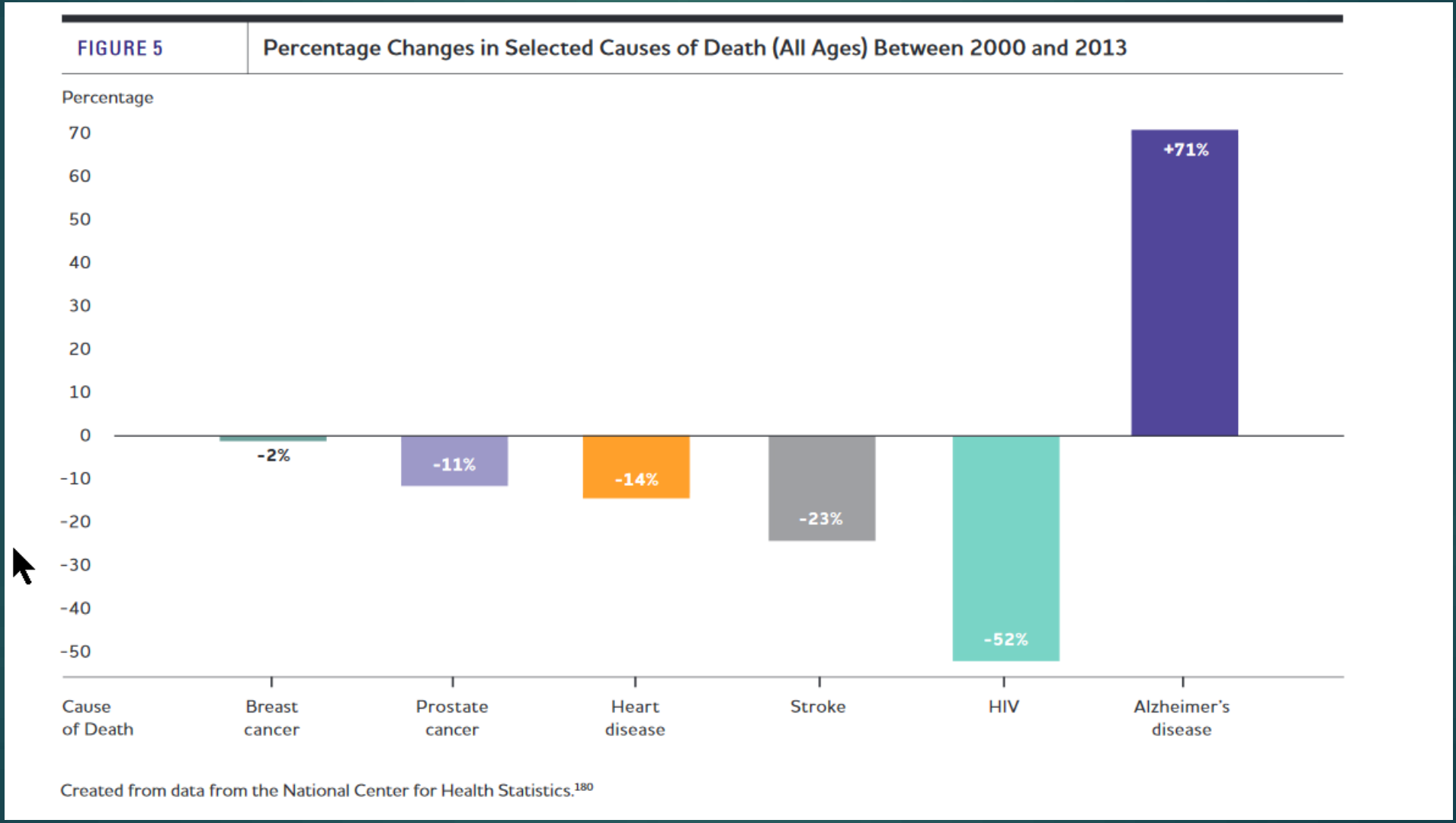
- Major NCD/dementia depends on your lifestyle choices



Target: Delay onset of dementia until after you die

- 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



50% of AD risk is 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
- 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 Goddess,
My prayer for 2019 is for a fat bank account & a thin body.
Please don't mix these up like you did last year.

Use it or lose it

- Use of brain increases neuroplasticity
- Without use, brain cells are signaled that they are no longer needed
  - Dendrites atrophy
  - Synaptic connections weaken

Experience changes our brains: London Taxi Drivers

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

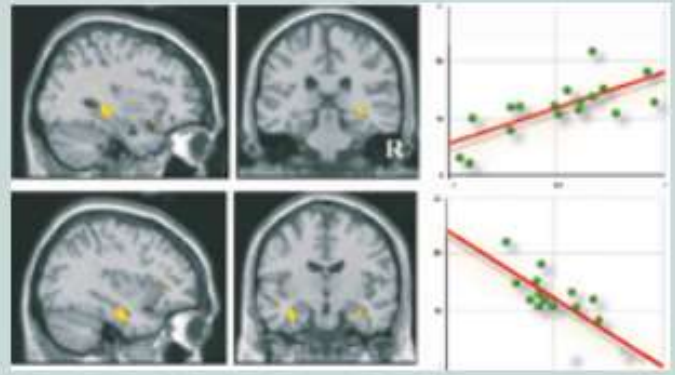
Knowledge exam: 3 of 10 pass

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 (spatial memory), 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

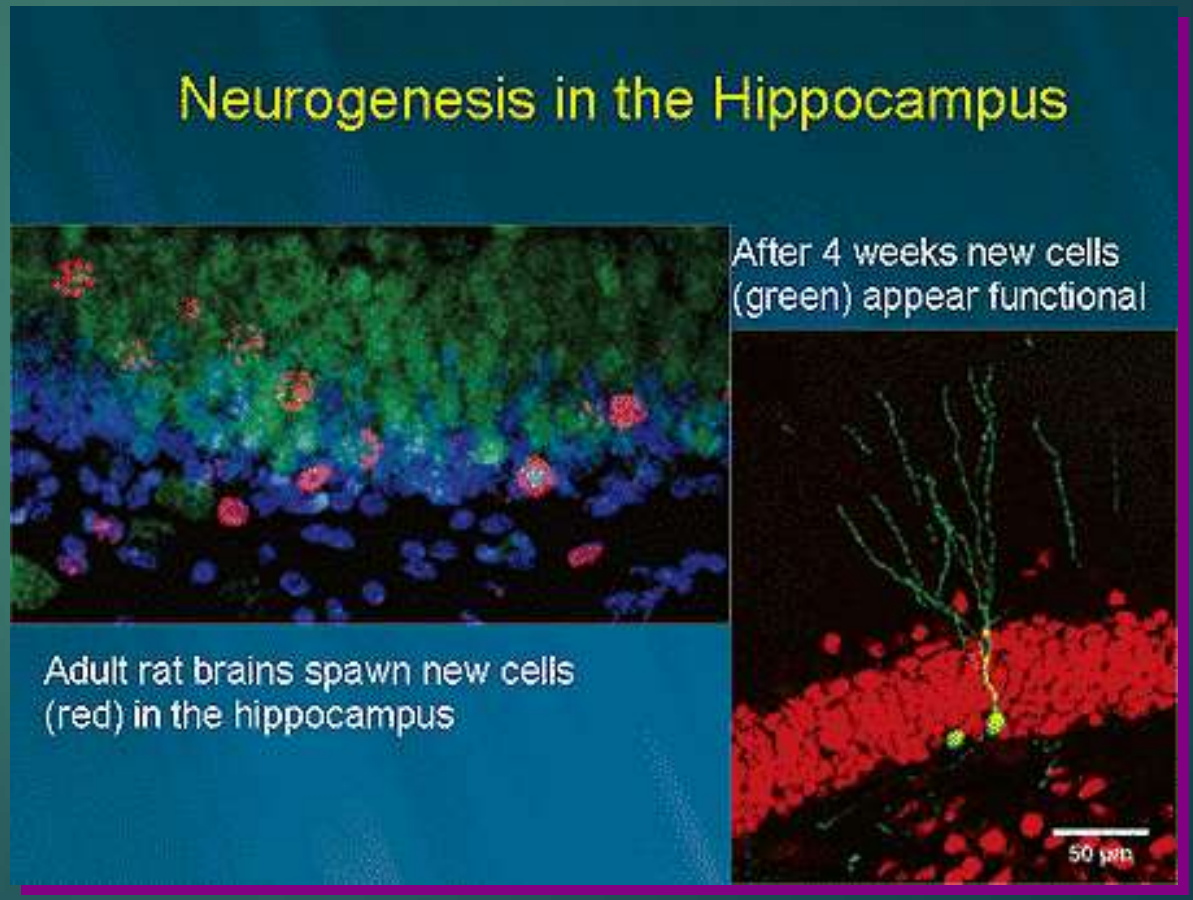
Neuroplasticity can also have negative consequences

- 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

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
  - Alzheimer's



2019: Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in AD patients

- Neurogenesis persists in cognitively healthy people until the end of life but drops off dramatically as soon as Alzheimer's pathology takes hold.
- Healthy brains contain newborn neurons, but the number decline steadily with age.
- Between the ages of 40 and 70, the number of fresh neurons fell from about 40,000 to 30,000 per cubic millimeter. The gradual reduction in new brain cells appears to go hand-in-hand with the cognitive decline that comes with old age.

Intellectual Ability Declines in Normal Aging

Old Age

Isaac Bashevis Singer

From age 7 raphies,

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.

Normal Age-Related Changes in Cognitive Abilities

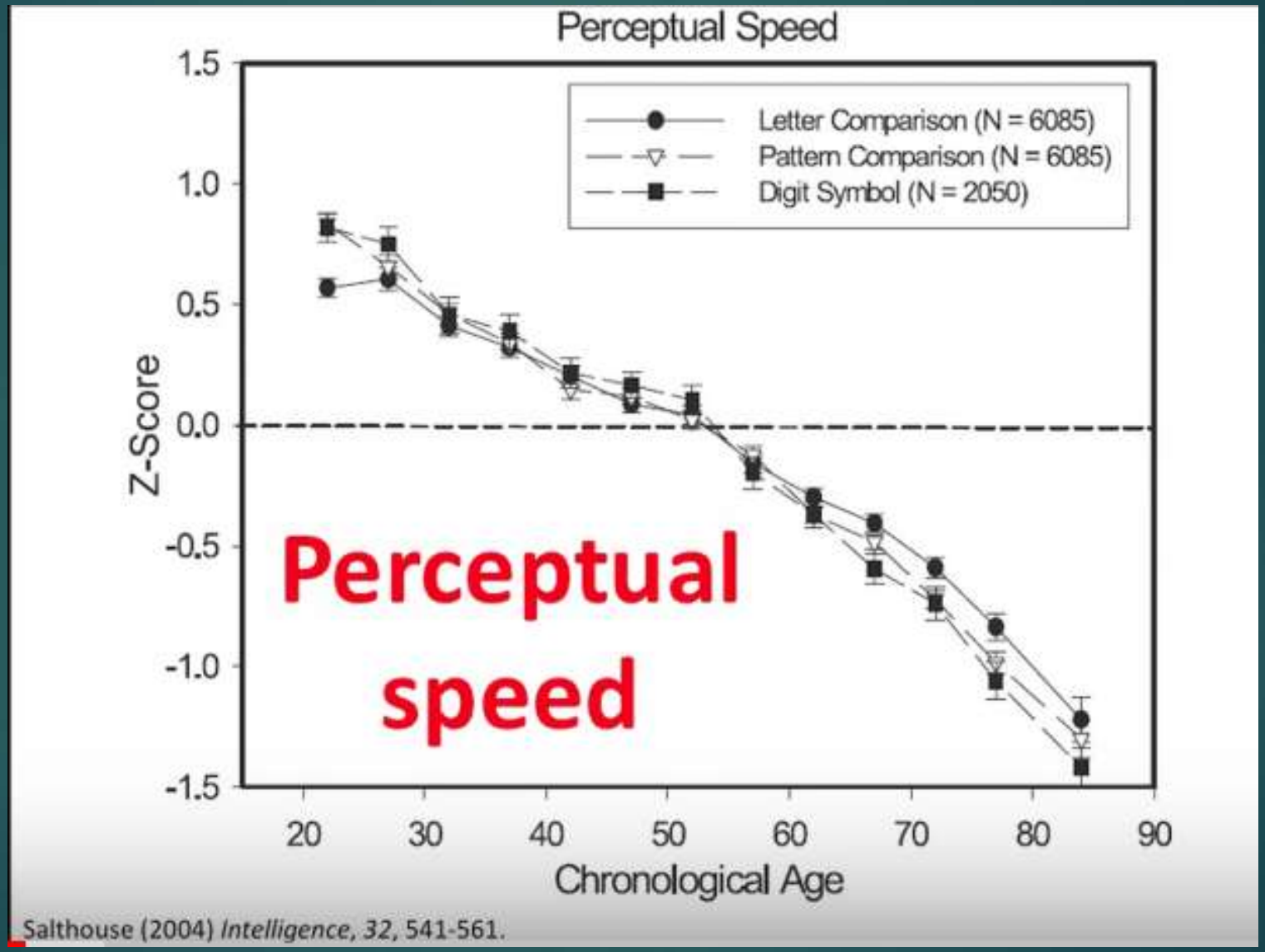
- K. Warner Schaie and Sherry Willis's Seattle Longitudinal Study:
- Reliable decline can be found for all abilities by age 74
- By age 81, average decline is 1 s.d. for most abilities
- Cognitive better from age 40-65 than in our 20s for:
  - Vocabulary
  - Verbal Memory
  - Spatial Orientation
  -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

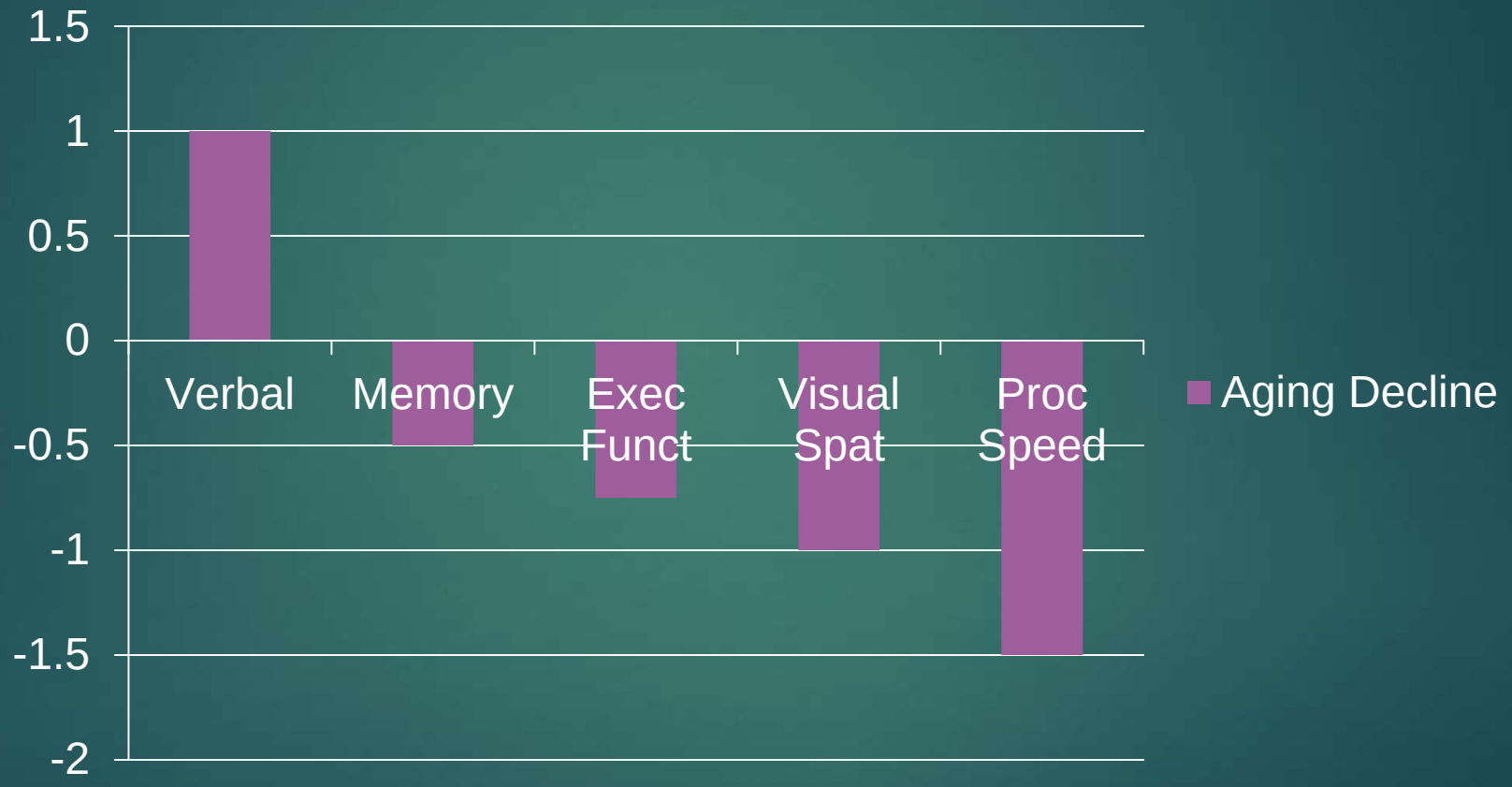
- Verbal Knowledge intact; difficulty with name retrieval, particularly the names of those we've not seen in a while
- Memory Ability = ½ s.d. decrease ↓
- Spatial Ability = 1 s.d. decrease ↓ ↓
- Perceptual speed = 1 ½ s.d. decrease ↓ ↓ ↓

We are all past our age 20 peak: 1 ½ s.d. decrease ↓↓↓



Normal Aging Cognitive Decline

in the absence of brain pathology



Based on Schaie and Salthouse

Tale of Two Computers: Speed ↑↑↑

1982 IBM Computer
Intel 8088 chip @ 4.77 MHz

After age 65, we return to this speed!

Lenovo P71
Intel Xeon E3-1505M @ 3.5 GHz

3000 times faster

Normal Age-Related Changes 2

- Cognitively better with age if:
  - better heart condition & absence of other chronic diseases
  - higher education
  - work that involves complex thinking and social interaction
  - involvement in a complex and intellectually stimulating environment
- 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: 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
- 2019: No obesity paradox: obesity is associated with CV disease at all ages

Age 36

- British Birth Cohort Study, 2019: poor vascular health at age 36 forecasts smaller brains, with more white matter damage, at age 70;
  - more extensive white-matter hyperintensities—a proxy for cerebral small vessel disease;
  - with smaller hippocampal volume
  - Increasing blood pressure between the ages of 36 and 43 correlated with these later-life brain pathologies, but not with Aβ. Vascular factors act through a direct pathway, not via Aβ
  - risk factors, such as smoking, have plummeted since the 1980s, others, including obesity and diabetes, have increased

- Framingham Heart Study: associations between vascular risk at younger ages most strongly associated with late-life brain atrophy

- 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

- Dementia is not a synonym for Alzheimer's
- Alzheimer's Disease = neurodegenerative disease due to increased beta amyloid and tau protein 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 pathology in their brain (abnormal Aβ & Tau proteins & synaptic loss)
  - but have no cognitive decline
- Concept of Cognitive Reserve

Nun Study: Souls go to God; Brains to Lab

Sister Matthia from the Nun Study

- 1986, N=677, School Sisters of Notre Dame
- Age in 2000: 75-103
  - 85% teachers
  - half got major NCD
- Despite lots of BA,
  - 50% = no dementia/NCD

Aging with Grace, Snowdon; Snowdon et al, 2000

Nun's Brains: Preserved for science at Univ. of Minnesota

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.
- Early Idea density (richer vocabularies) 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.
- Early reading exposure is key
- Linguistic aptitude in young adulthood is strongly associated with cognitive decline and AD in women

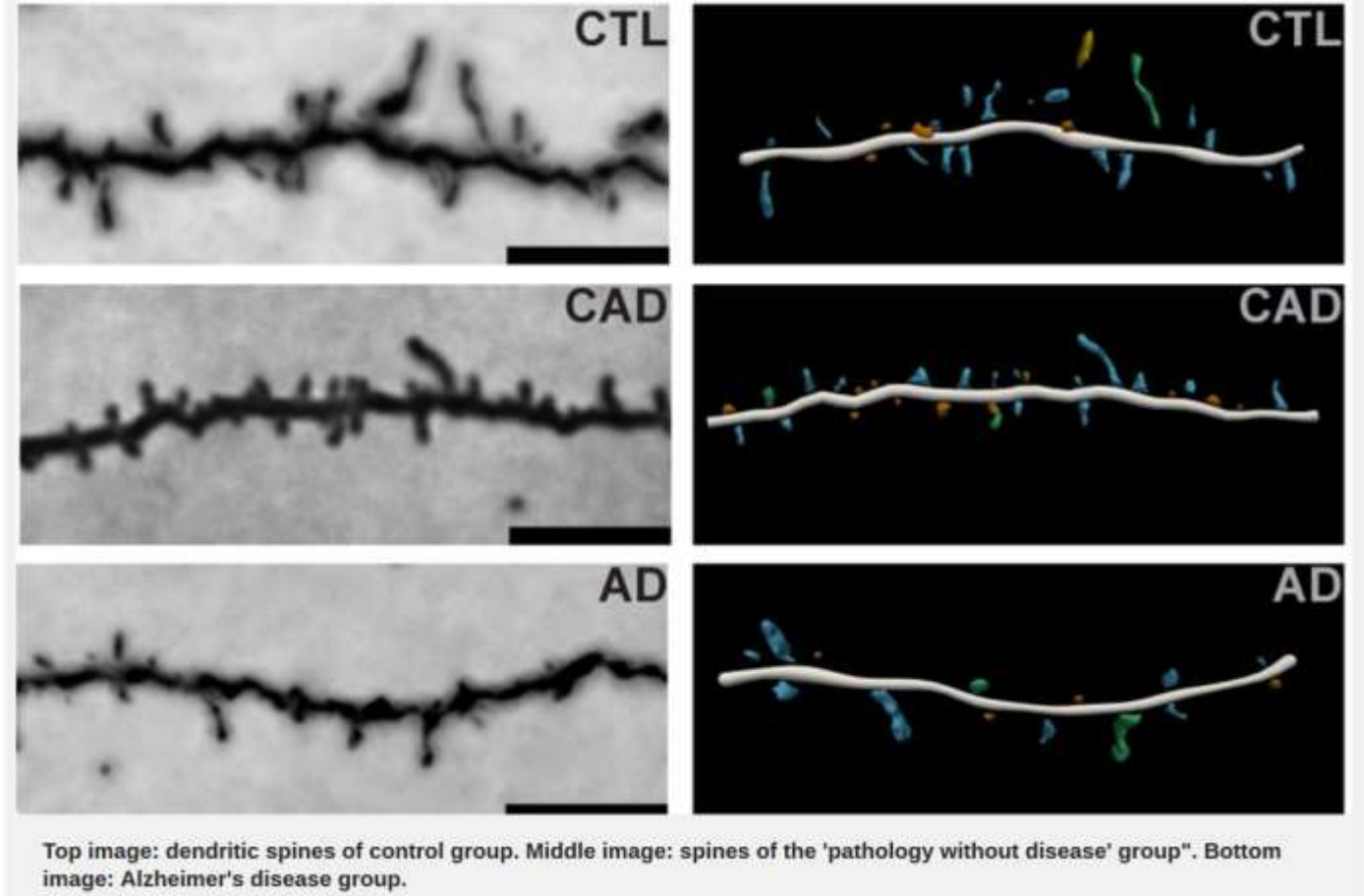
Alzheimer disease without NCD/dementia: Sister Bernadette

- 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 = perfect 30/30 at last 3 testings
  - On autopsy, had worse level of 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 CR: some people can tolerate brain pathology for a longer time without showing intellectual signs of damage.
- Cognitive reserve: difference between amount of brain pathology & actual cognitive function
- CR = more protection vs. Aβ accumulating in synaptic connections,
- CR benefit: Protective = can have more disease before cognitive decline
- Non-Demented with Alzheimer's Neuropathology (NDAN)

Presence of more & larger dendritic spines in people with Aβ & 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 Aβ & 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; also live longer
- Occupational complexity: Work that involves complex thinking and social interaction

Predictors of Cognitive Reserve 2

- Higher Social Economic Status
- Regular cognitive activity (reading, crossword puzzles)
- Higher literacy
- Social engagement
- Early-age physical activity
- Better cardiovascular status

Non-Demented with Alzheimer's Neuropathology (NDAN): synaptic resistance to amyloid beta and tau,

- In NDAN, unlike AD, toxic amyloid-oligomers do not localize to hippocampal postsynaptic densities.
- NDAN show synaptic resistance to amyloid-damage in NDAN
- There were fifteen proteins which comprise the unique proteomic signature of NDAN postsynaptic densities, thus setting them apart from control subjects and AD patients.
- NDAN synapses reject amyloid oligomers
- NDAN individuals have higher rate of neurogenesis in the dentate gyrus
- NDAN are not a pre-AD group

Zolochevska, Olga, et al., 2019

Proof of Cognitive Reserve: Dementia was decreasing

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

- 2018 metaanalysis study: decline in Western high-income countries

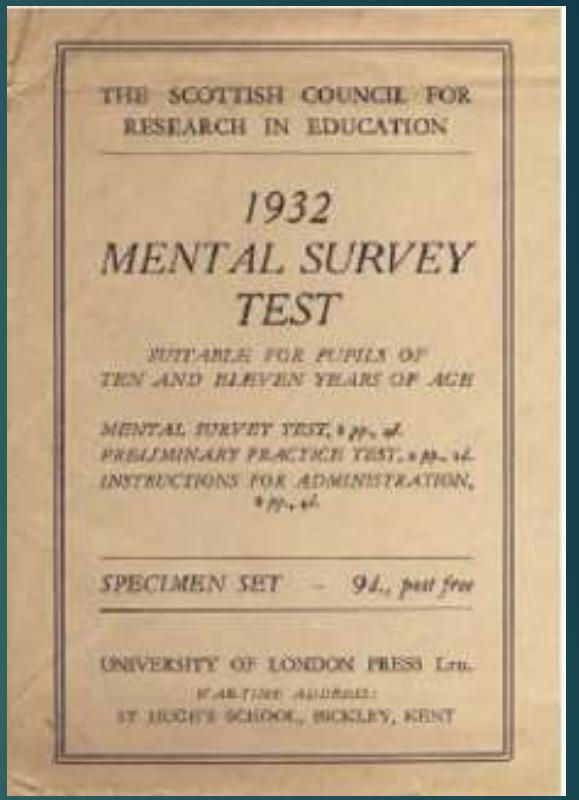
- Increases in education and better control of cardiovascular risk factors as likely contributors to declining dementia risk.

"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

In 1932, tested every Scottish child born in 1921, and again in 1947, every child born in 1936; 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., 9d.
PRELIMINARY PRACTICE TEST, 2 pp., 1d.
INSTRUCTIONS FOR ADMINISTRATION, 8 pp., 9d.

SPECIMEN SET – 9d., post free

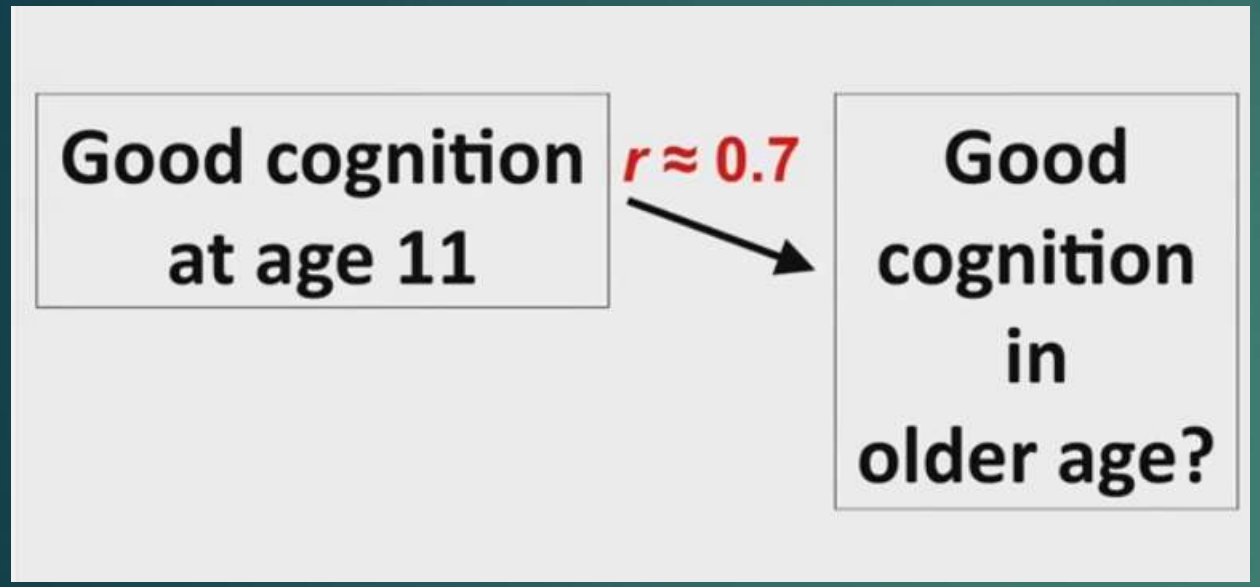
UNIVERSITY OF LONDON PRESS Ltd.
WARTIME ADDRESS:
ST HUGH'S SCHOOL, BICKLEY, KENT

Data rediscovered in 1990s: took test at ages 11 in 1932, then at 79, 87, 90, & 92 in 2013

Stumbling on a gold mine: Data lost for 50 years, and then Found in 1997 in a University of Edinburgh basement.

Tracked 1641 from the two cohorts; 250 scientific publications, based on more than 20,000 hours of cognitive tests and brain scans, done at roughly 2- to 3-year intervals since 2003.

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



Higher IQ is protective against Alzheimer's

25% of changes in cognition from age 11 to 77 is due to genetics;
Genetics controls stability of cognition; less so change of cognition over time (which is changed more by APOe4)

Low early-life cognitive ability is an early marker of dementia risk in later life

- 1960, Project Talent: largest study of US teenagers; 2 and half days of testing at 1353 high schools; 5 % of all students in grades nine through 12 in 1960. Re-contacted in 2009, via the students' 50th high school reunions; review of 2013 Medicare records (aged 66-73 years)

- Higher scores in adolescence predicted a lower incidence of Alzheimer's and related dementias in their 60s and 70s: Adolescent girls who have trouble remembering words and boys with poor/weak mechanical reasoning have increased AD risk (for each SD lower score, 16% increase in AD risk)

Alison R. Huang, et al., 2018

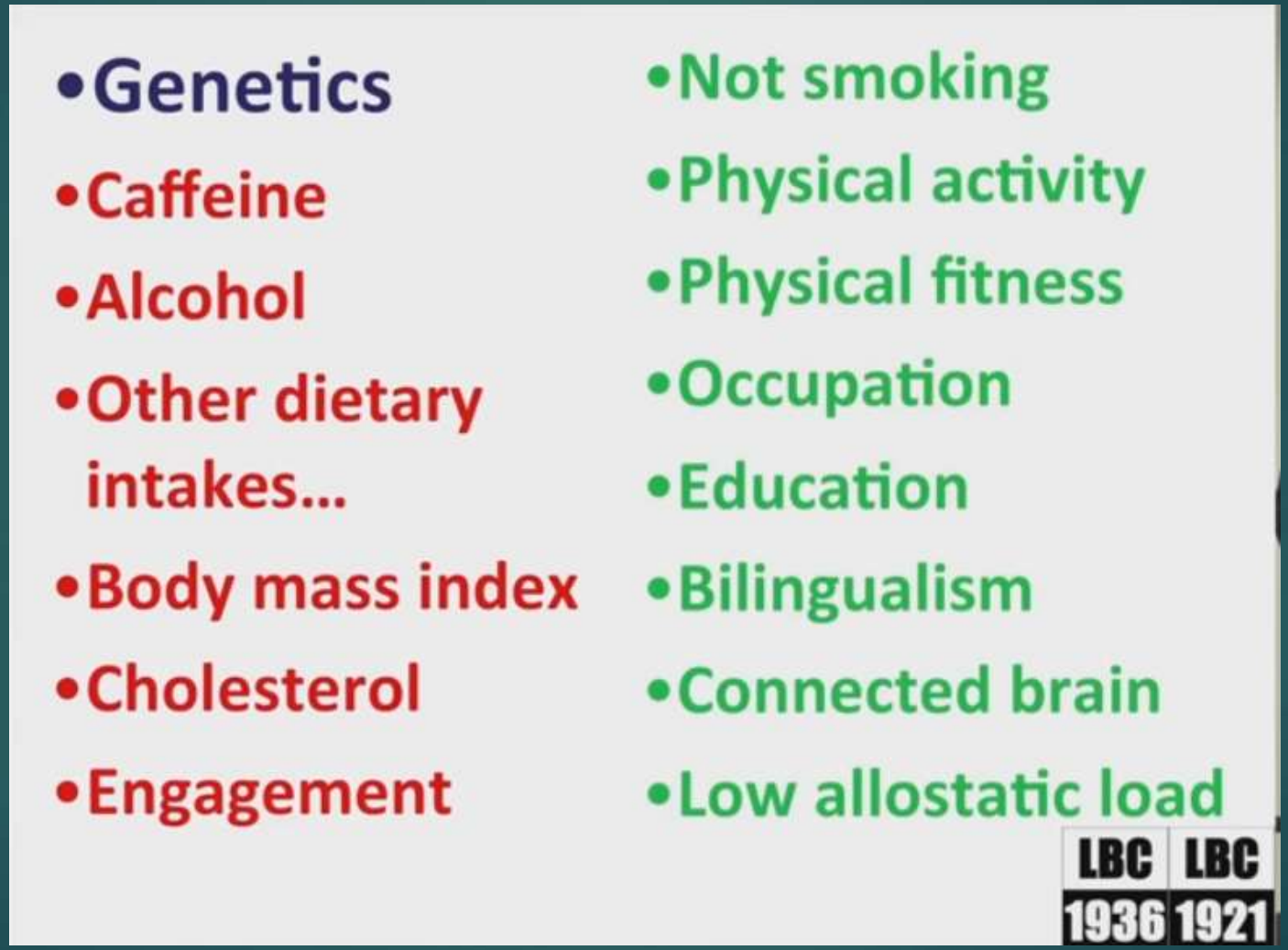
Project Talent: Early life intervention

- Low IQ increased odds for AD for both men and women by 17 %, and poor general academic aptitude by 18%.
- So warning signs for dementia may be discernible as early as adolescence
- Early life performance on cognitive tests could be used to identify potential at-risk populations who might especially benefit from interventions aimed at modifying their dementia risk

Lothian Findings

- Disconnected Brain
  - Bigger brain when young correlates with better cognition at age 70: inside of your skull is size that your brain used to be
  - Less atrophy correlates with better cognition
  - Better white matter connections & less WMHs correlate with better cognition
- Most of our ability in older age is based on cruising on what we already know, not on the cognitive skills that tend to decline
- Life satisfaction is far more than cognition

The Other Possible 50%:



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

1000 children's brains & family income/poverty

- Amount of cortical surface area of brain correlates with IQ
- Study of 1000 children's brains: factor that correlated best with amount of cortical surface area was family income
- Language/vocabulary, avoidance of distraction, self control correlated with family income
- On average, child raised in poverty: 60% lower on cognitive tests, 5x more likely to drop out of high school. Less likely to earn college degree; at age 35, 75x more likely to be poor

Brighter Brains

- Across warm-blooded animals, the number of neurons in the cortex correlates with longevity
- Bigger brains correlate with more intelligence
- BA10 volume and Frontal medial WM volume predicts individual differences in fluid intelligence/problem solving
- Strong age-related decline in fluid intelligence, WM integrity becomes increasingly important for preserved cognitive function with advancing age.
- Extent of the cortical folding is correlated with speed of thought and working memory: smarter people have more-folded brains.
- People with more grey matter in frontal and parietal areas are smarter.

Bigger is better

- An examination of brain tissue (n = 35) has revealed that:
  - High IQ scores correlate with:
    - brain cells are significantly larger
    - bigger cells also have more
    - dendrites are longer: better processing
    - Cells transmit faster: faster reaction times.
  - The properties of brain cells explain about a quarter 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 neuronal activity, less dendrites

- Higher IQ:
  - larger brains; predominantly located in parieto-frontal regions.
  - high number of neurons, 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
- 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

Intelligence Matters More for Brain Reserve, but Education Helps

- Genetic study: intelligence and education are highly correlated
- Intelligent people achieve higher levels of education, but over time, education improves intelligence.
- For each standard deviation (SD) increase in educational attainment, the risk of AD dropped 37%.
- For every one-SD increase in IQ, the risk of AD went down 35%. The influence of educational attainment went away after accounting for intelligence.

Anderson EL, et al., 2018

Intelligence Matters

- The data suggest intelligence is the driving factor behind higher or lower AD risk.
- But more years in school influence the risk of AD by making a person more intelligent
- Education may protect through better cardiovascular health, a known risk factor for AD, since people with more education tend to eat more nutritious food, exercise more, and seek treatment for their cardiovascular disease.

Early life experience and dementia

- Correlation between childhood SES and late life hippocampal size
- Poverty, disadvantage and stressful life events are strongly associated with cognitive problems in middle age and dementia later in life among African-Americans.
- White people's risk of dementia is not affected by their place of birth. But black people are 40 percent more likely to develop dementia if they'd been born in a state with high infant mortality (indicating increased poverty levels)

Dementia risk factors

- The failure to complete more than eight years of school — is childhood's most potent risk factor for developing dementia.
  - 8% of one's lifetime risk for the disease.
  - That makes lack of education a more powerful driver than the ApoE-4 gene variant, which is responsible for 7% of its incidence.

- 20% most economically deprived older adults were 50% more likely to develop dementia than the 20% least deprived adults.

Hearing and cognitive decline

- Hearing loss is not benign. It has been linked to social isolation, depression, cognitive decline, and dementia.
- Age-related hearing loss: two-thirds of those over age 70. However, few adults are tested for hearing loss, and even fewer are treated
- Only 14% of adults with hearing loss in the US wear hearing aids.
- 9% of lifetime risk for dementia lies with hearing loss during midlife.
- Golub et al., 2019 found that for every 10 dB decrease in hearing, there was a significant decrease in cognitive ability
- Hearing loss should be treated. This study suggests the earlier, the better."

Water tank hypothesis

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

Brains don’t want to be impaired

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

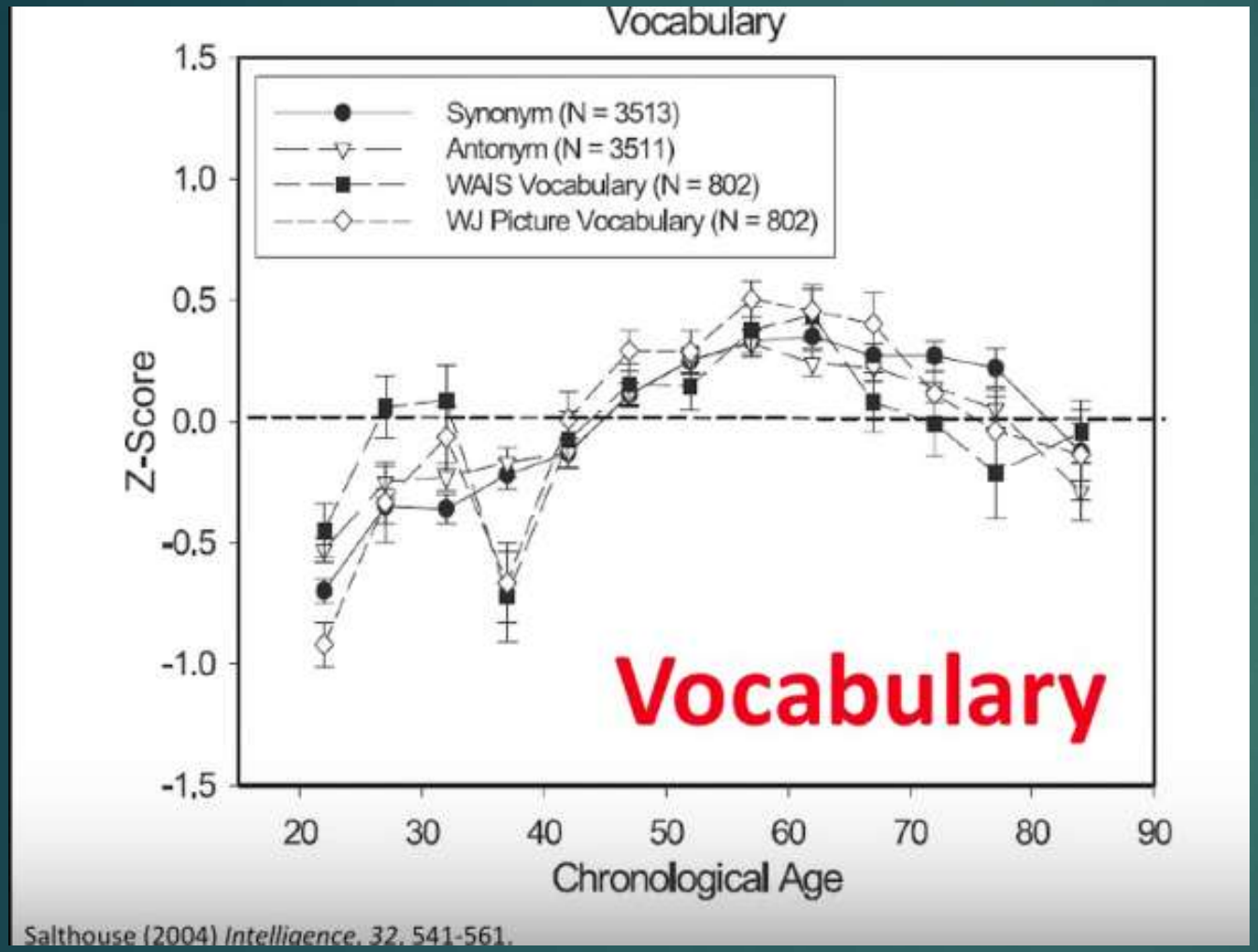
Resilience markers:

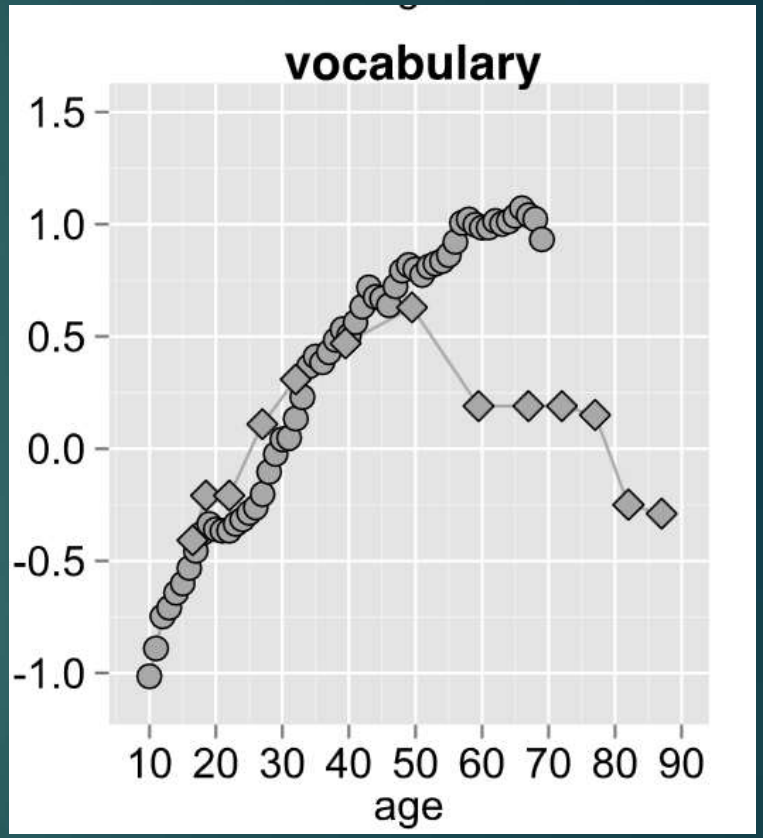
Education ↑
Social networks ↑
Conscientiousness ↑
Harm avoidance ↑
Good Sleep ↑
Purpose in life ↑
Late life cognitive activity ↑

Language ability

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

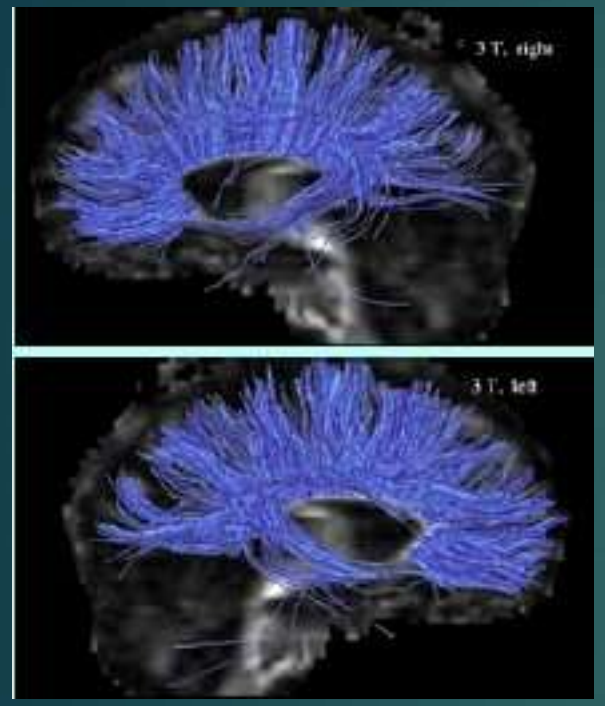
In normal aging: Vocabulary stays relatively intact

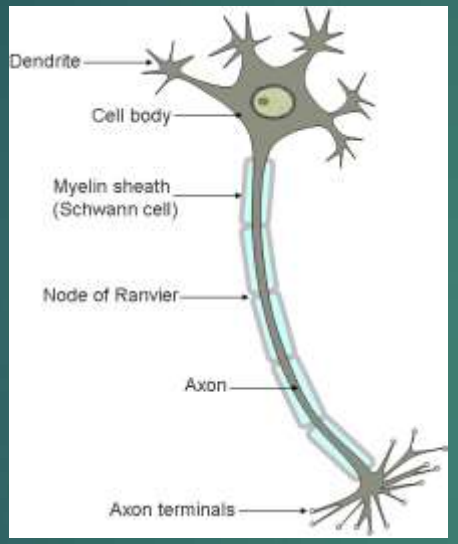


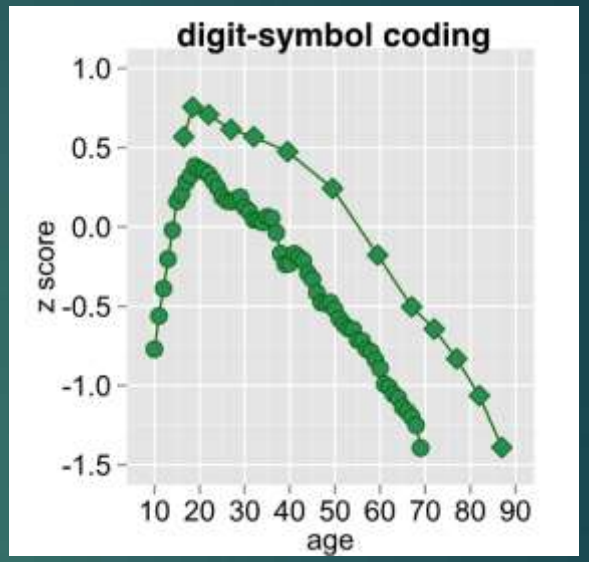


Names, Proper nouns, and rarely used words are first to go. But not Vocabulary.

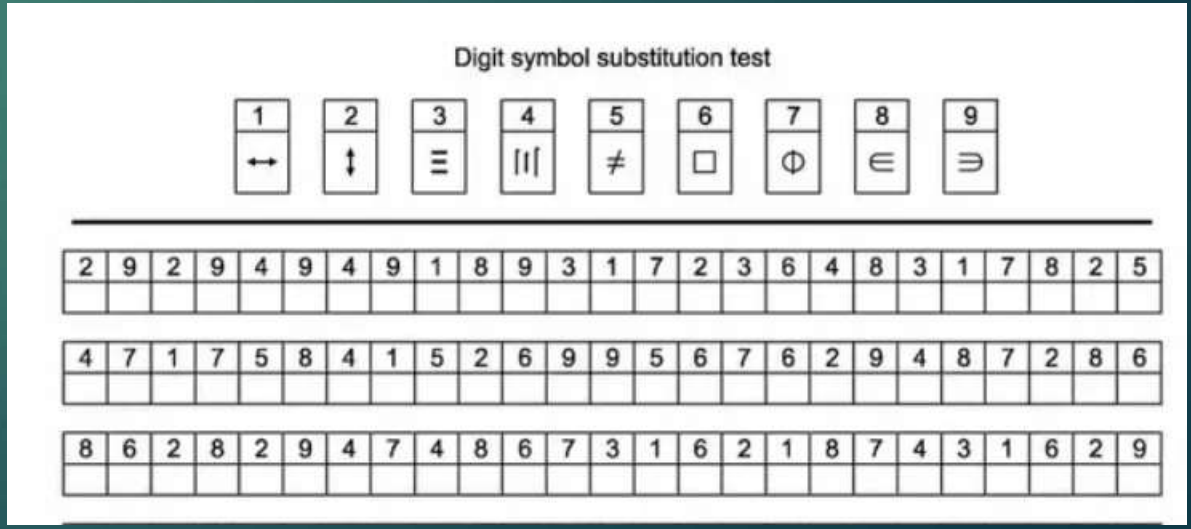
Older are Centrally Slowed: Processing Speed Decreases (3 ms per decade due to WM decline)







One of reasons naming ability decreases



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”

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

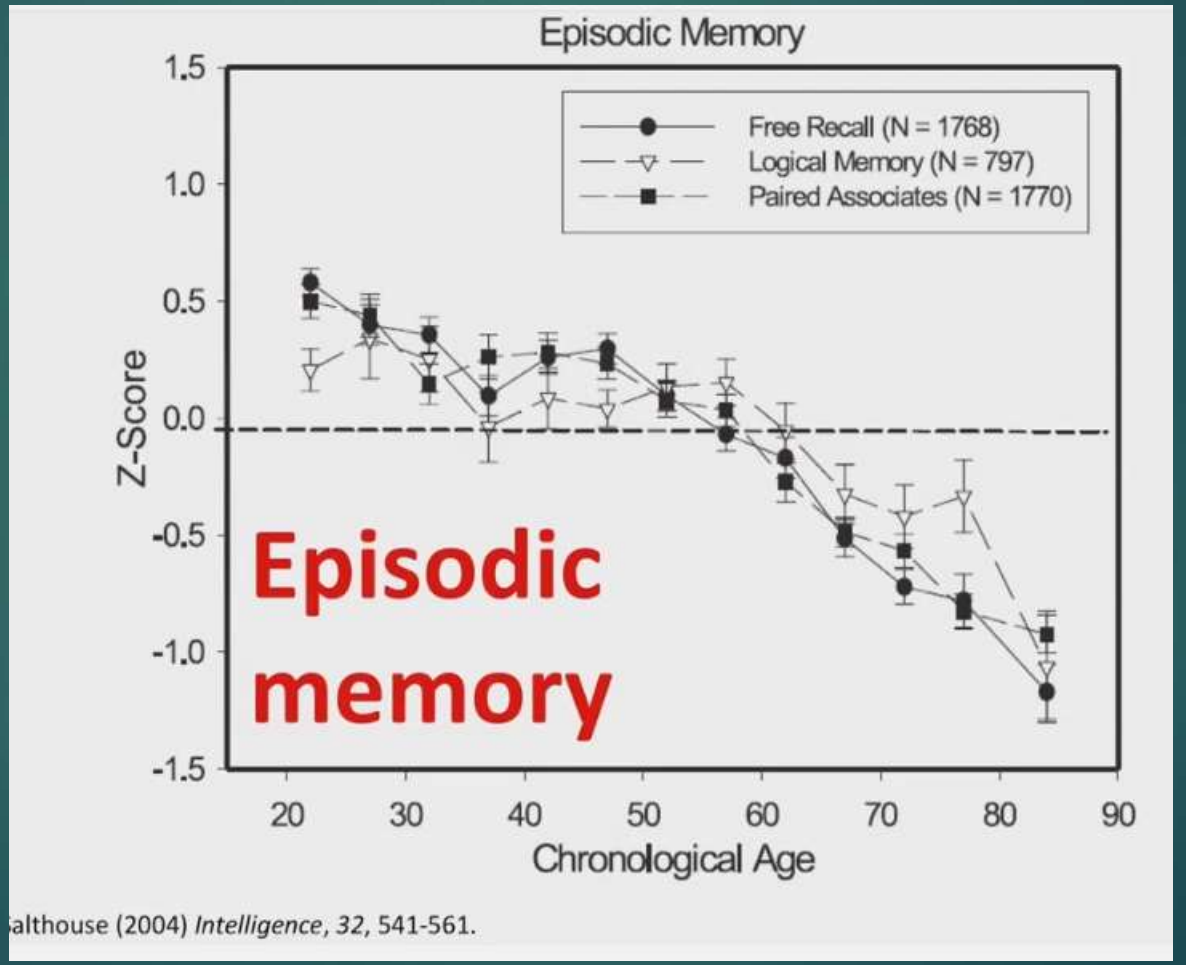
Normal hippocampal atrophy: Get Physical!

- Magnetic resonance-studies indicate an atrophy rate of the hippocampus of 2–3% per decade, which is further accelerated in very old age where there is an annual loss of 1% over the age of 70.

- In animal models physical activity has been identified as a key mechanism that can drive this adult neuroplasticity

- Results reveal that higher cardiorespiratory fitness levels (VO_2 max) are associated with larger hippocampal volumes in late adulthood[1]

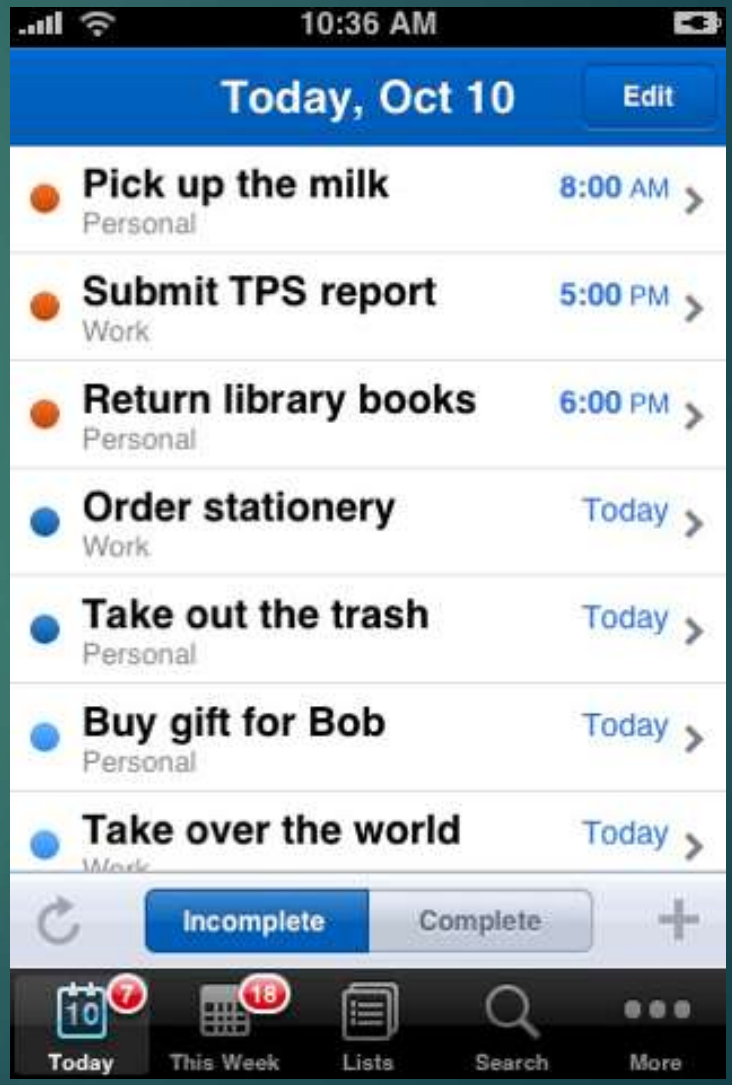
Episodic Memory: What did you have for breakfast (memory of time & particular fact) or who was your first love?



Virginia Longitudinal Study

Prospective Memory
remains normal in real world

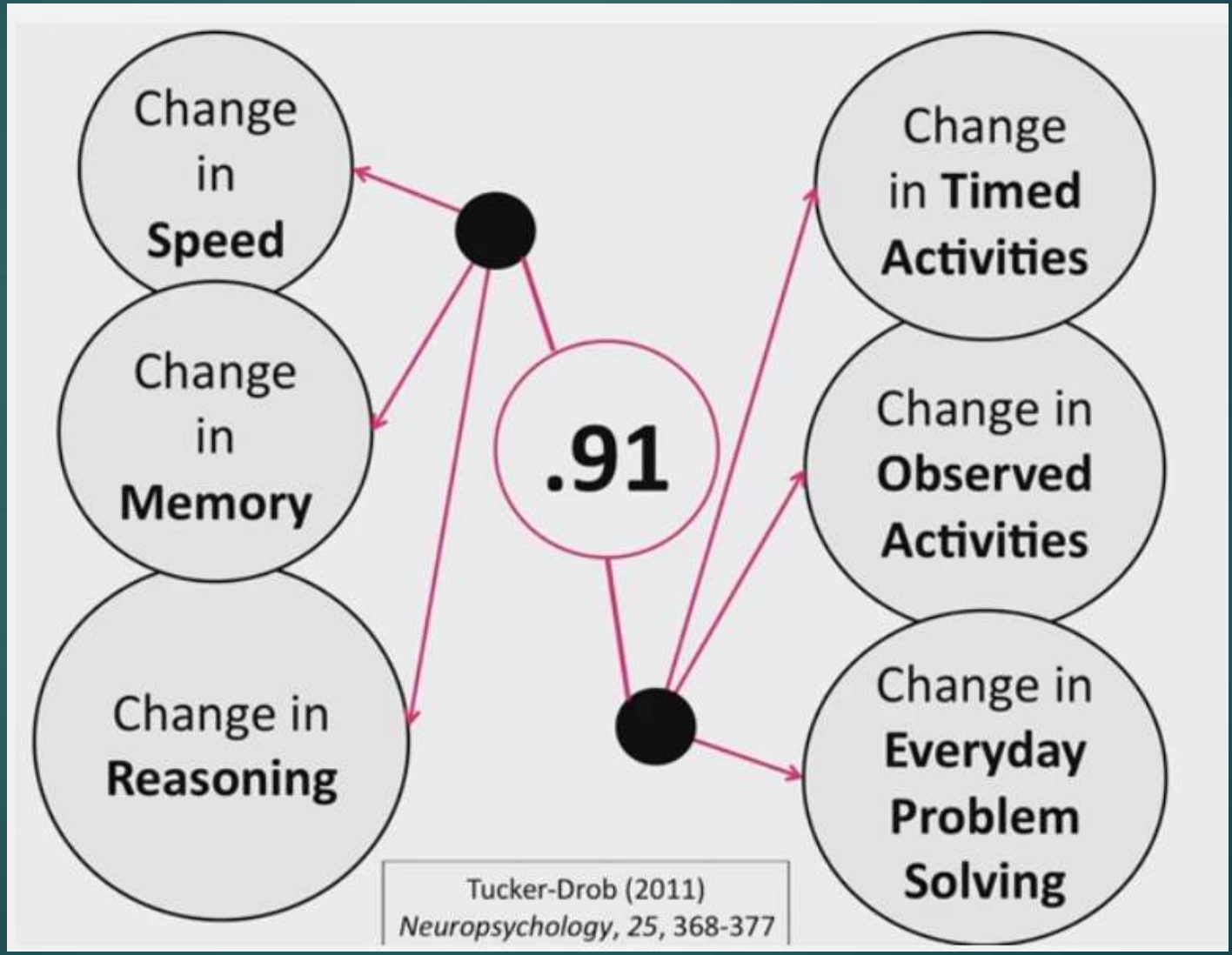
- Remembering to remember
- Intention
- Best predictor of ability to function independently



Tucker-Drob, 2011: Neurocognitive functions and everyday functions change together in old age. Believe tests > self report

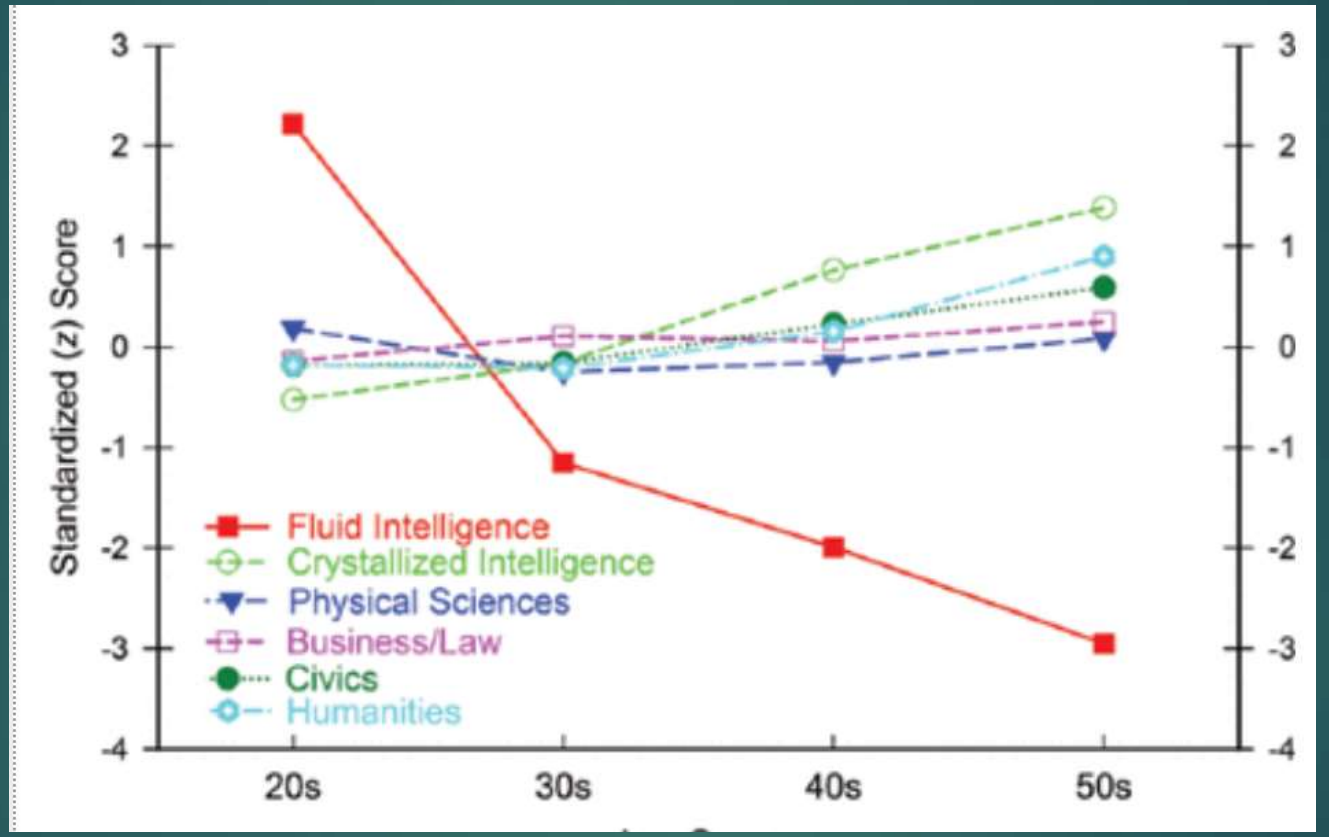
- Neurocognitive functions are known to decline normatively with adult age. Do everyday functions (e.g., paying bills, following medication instructions, making change, looking up telephone numbers in a phone book) also decline?
- Community-based sample of 698 adults (ages 65 to 94 years and living independently at baseline) who were repeatedly measured over five years on neurocognitive tests of executive reasoning, episodic memory, and perceptual speed, and on a number of tasks that adults should be reasonably expected to be able to perform in their day-to-day lives.
- Changes in neurocognitive performance were strongly correlated with individual differences in changes in performance on the everyday tasks. Alternatively, changes in self-reports of everyday functions were only weakly correlated with changes in performance on the neurocognitive tests and the everyday tasks.
- **CONCLUSIONS:** These results together suggest that normative neurocognitive aging has substantial consequences for the daily lives of older adults and that both researchers and clinicians should be cautious when interpreting self-reports of everyday functioning.

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



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

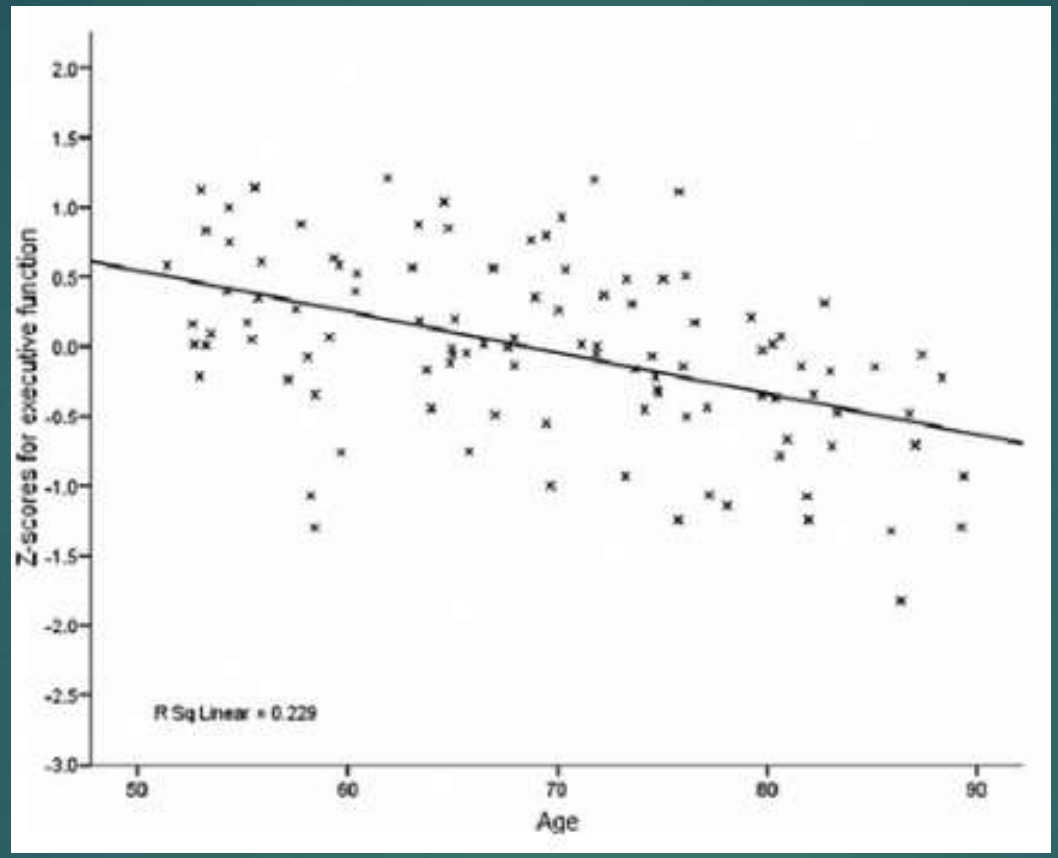
All had a B.A.



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



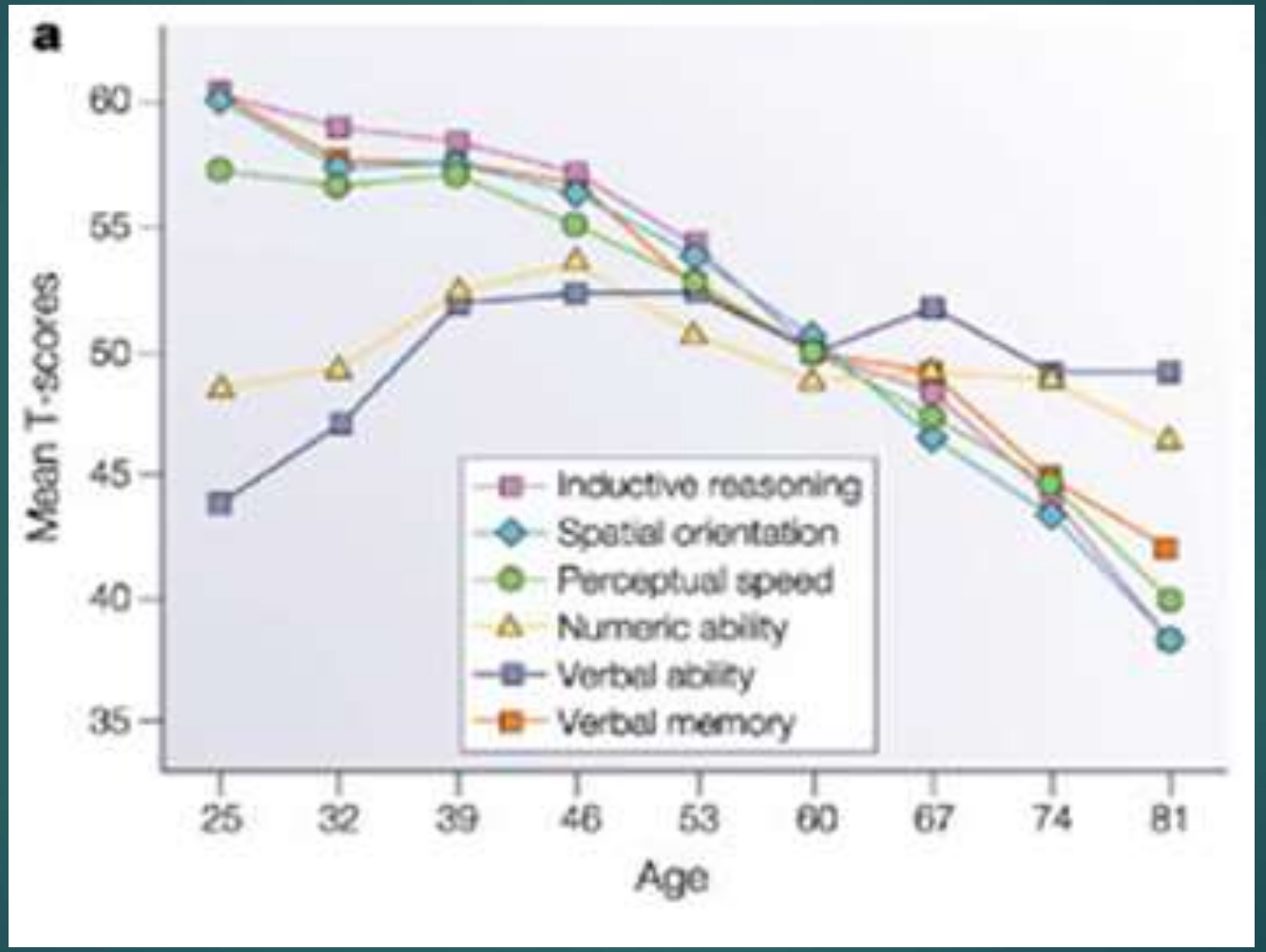
In old age, be prepared to know more than younger people, but not to be as fast in working out new stuff quickly.

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

This is normal aging.

Not AD.

Do not freak out

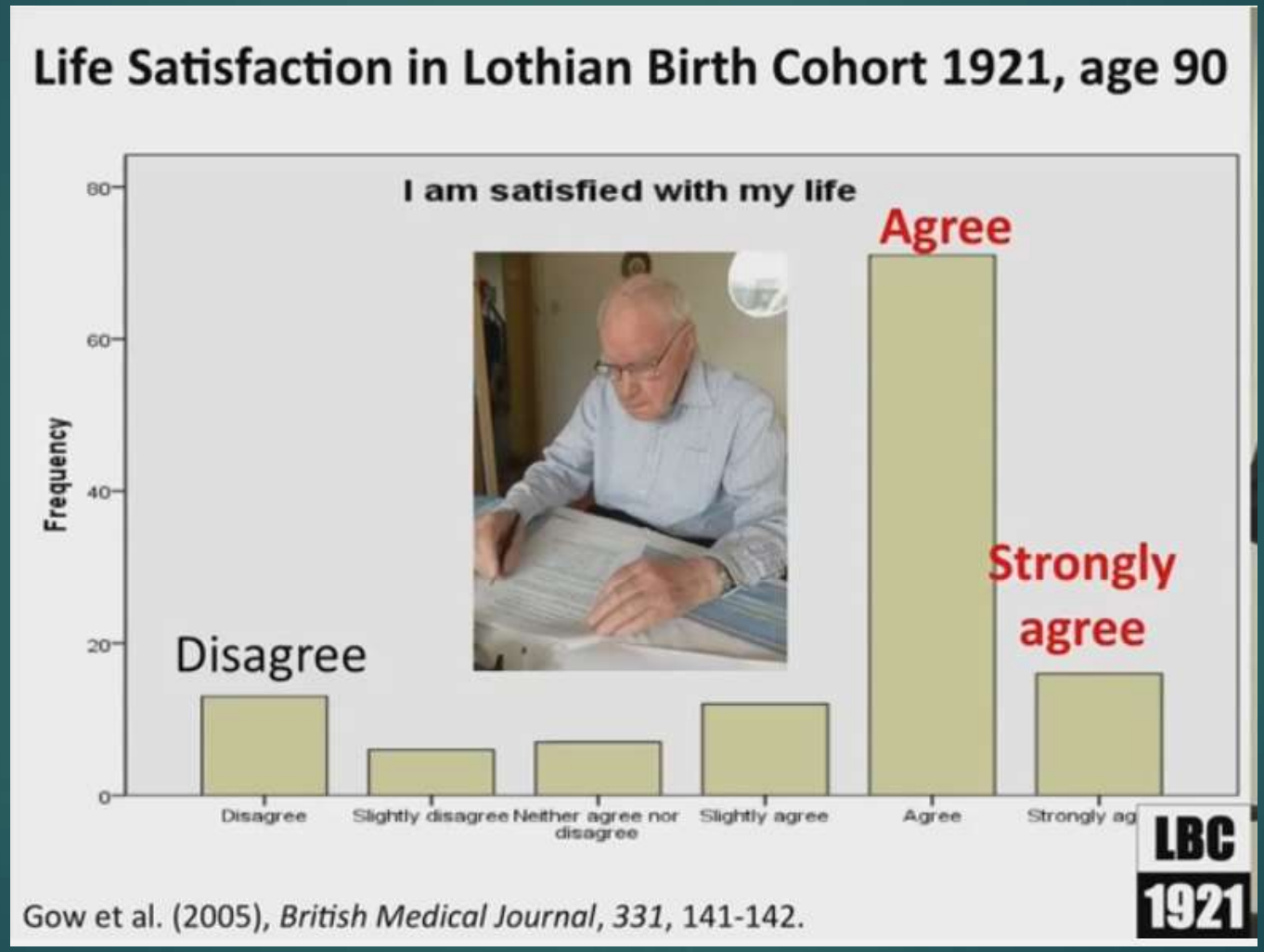


Seattle Longitudinal Study; no practice effect correction

Scottish study of 85-year olds: life is not a bundle of misery

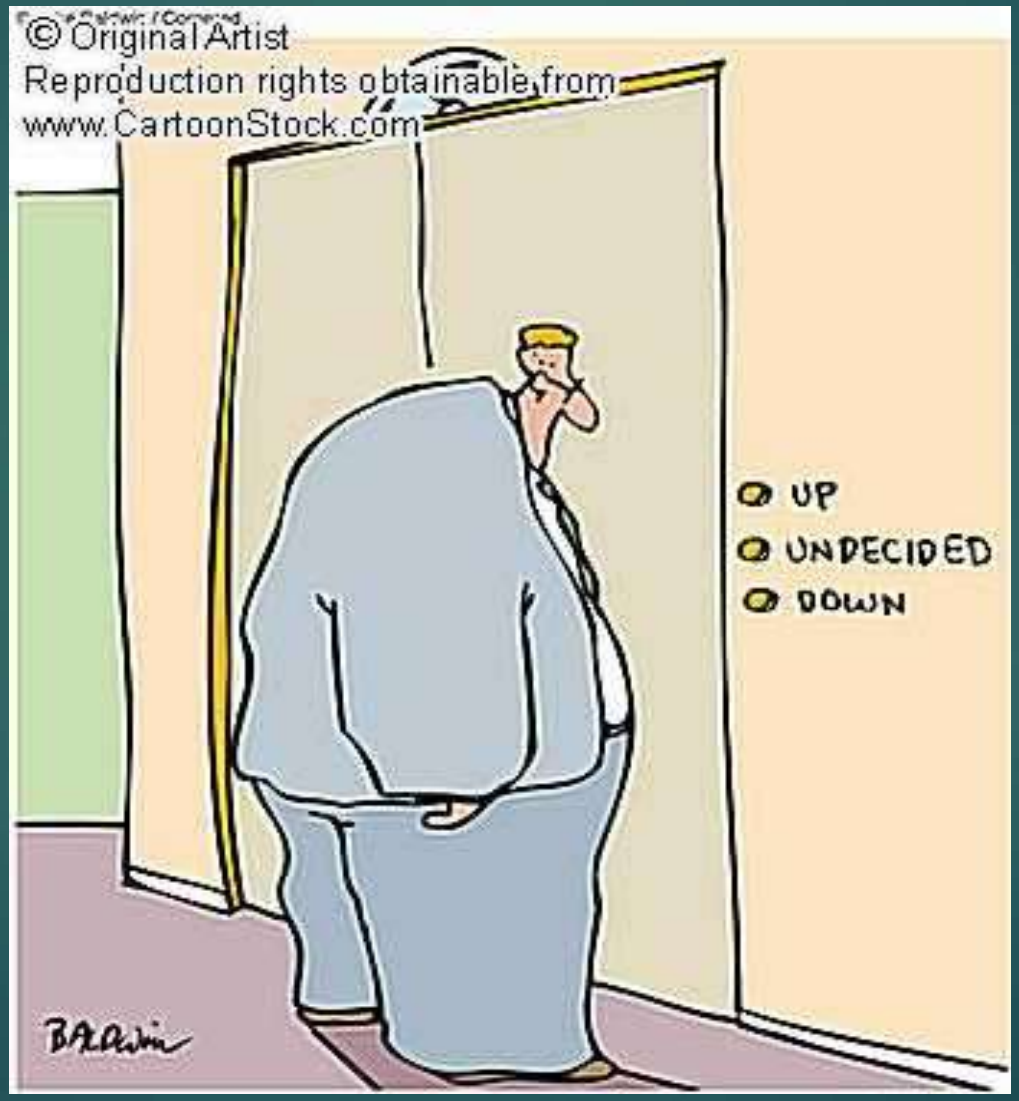
- Illnesses at age 85: none had none; most had 4-5, some 7-8-9
- 78% rated their health as good, very good, excellent
- Only 30% of men and 15% of women had no functional limitation (out of 17 daily living abilities)
- Women live longer but experience more illnesses and have more dependency needs

Life is not all about cognitive ability: most elders 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)

Senility (or Neurodegeneration) Prayer

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

That Naming Problem

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

Naming vs. Recognition

- What is the name of this person?
- Princess Diana

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

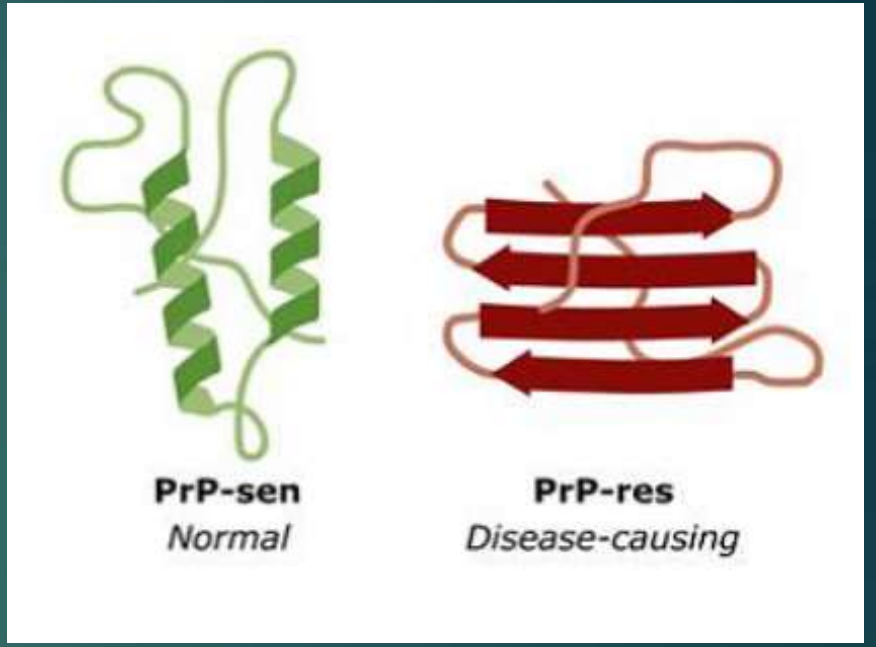
Ranking of MOST-FEARED Disabling Disorders – **14 country study**

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

Neurodegenerative Diseases (NDs)

- Most NDs are abnormal protein folding disorders: AD, PD, Huntington's ALS, Prion, CTE
- No current treatments
- Universally fatal
- By 2040, ND will be 2nd most common cause of death in developing world



Multiple Potential Pathways to Dementia

Lifestyle Factors
- physical activity
- diet
- drug/alcohol abuse

Environmental Factors
- education
- head trauma
- toxins/other

Psychosocial Factors
- depression/anxiety

Aging

Genetic Factors

Sex F>M

Other Medical Risks
- hypertension
- obesity
- stroke
- heart disease
- diabetes
- metabolic
- inflammation
- certain infectious diseases
- certain medications

Health Disparities

***Misfolded Proteins**
- amyloid
- tau
- alpha synuclein
- TDP-43

***Vascular Disorders**
- stroke
- blood vessel diseases

***Other Disorders**

Cognitive Impairment Including Dementia

- Alzheimer's Dementia
- Lewy Body Dementias
- Vascular Dementias
- Frontotemporal Dementias
- Limbic Predominant TDP
- Mixed Dementias
- Other Cognitive Impairment
- Other Dementias

Concept by:
Julie A. Schneider, MD, MS, Rush University &
Roderick A. Corriveau, PhD, NINDS

NIH National Institute of Neurological Disorders and Stroke

	Alzheimer's Disease (AD)	Vascular Dementia (VaD)	Lewy Body Dementia (DLB)	Behavioral Fronto-temporal Dementia (bvFTD)	Corticobasal Degeneration (CBD)	Progressive Supranuclear Palsy (PSP)	FTD Language Variants
Onset	Gradual Usually after age 65	May be sudden or stepwise	Gradual	Gradual, usually before age 65	Gradual, between 60 – 80 (mean 64)	Gradual, between 50 – 80 (mean 63)	Gradual
Causative Protein	Beta amy-loid and tau	N/A	Alpha-synuclein	Tau, TDP-43, FUS	Tau	Tau	TDP-43, tau
Typical First Symptom	Memory difficulties	Depends on ischemia	Varies: hallu-cinations or visuospatial	Behavior or personality changes	Unilateral motor changes	Falls	Language
Cognitive Domains, Symptoms	Memory, language, visuospatial	Depends on anat-omy of ischemia	Memory, visuospatial, fluctuating symptoms	Executive: +/– memory	Executive: +/– memory	Spared memory, frontal subcortical deficits	Language, Loss of knowledge of word meaning
Psychiatric/ Behavioral	Delusions are common	Depression, irritability	Hallucinations, usually visual	Disinhibition, apathy	Disinhibition, apathy	Depression, impulsivity	Compulsions

	Alzheimer's Disease (AD)	Vascular Dementia (VaD)	Lewy Body Dementia (DLB)	Behavioral Fronto-temporal Dementia (bvFTD)	Corticobasal Degeneration (CBD)	Progressive Supranuclear Palsy (PSP)	FTD Language Variants
Motor Symptoms	Rare early, apraxia later	Correlates with location of ischemia	Parkinsonism	Some rare cases with motor neuron disease	Alien limb, unilateral dystonia	Falls, supranuclear gaze palsy, axial rigidity, dysarthria, dysphagia	Effortful speech
Progression	Gradual, over 8 to 10 years	Stepwise with further ischemia	Gradual, but faster than AD	Gradual, but faster than AD	Gradual, motor symptoms	Gradual, mean survival 6 – 9 years	Gradual
Laboratory Tests	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Imaging	Possible global atrophy, small hippocampal volumes	Cortical or subcortical white matter lesions on MRI	Possible global atrophy	Atrophy in frontal and temporal lobes	Asymmetrical parietal and frontal atrophy	Midbrain atrophy	Left fronto-insular or anterior temporal atrophy

Table 1. Brief summary of the major neurodegenerative syndromes that are commonly seen in clinical practice and the main clinical features that distinguish them

200+ Disease Modifying Treatment Trials in elder AD: 99.6% Failure Rate

- AN1792 vaccine: 2003 (Eliminated BA; still major NCD)
- Tramprostate
- Flurizan: 2008
- Bapineuzumab: 2009
- Semagacestat: 2010
- Solanezumab: 2016
- Verubecestat: 2018
- Aducanumab: 2019 (maybe)

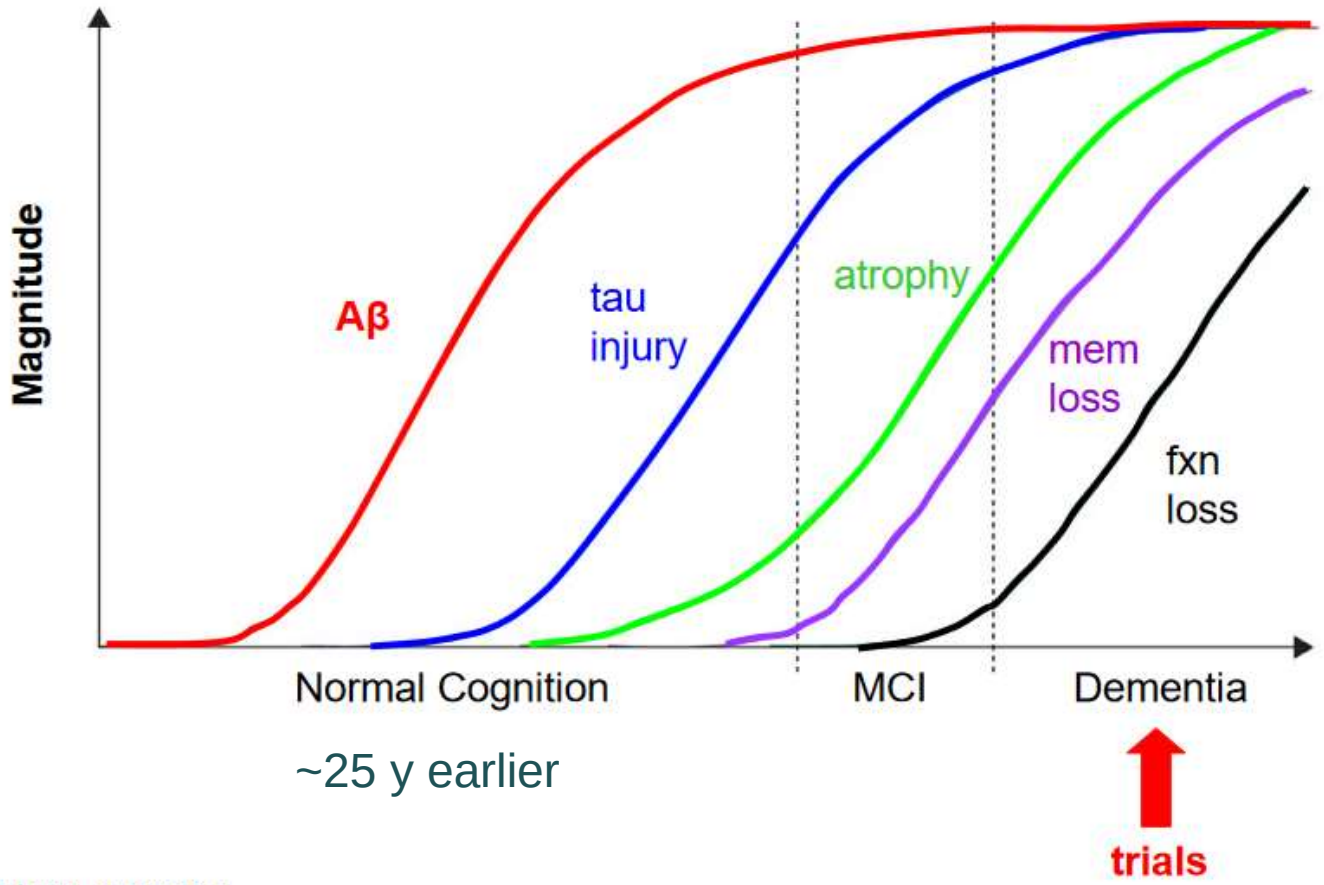
- Right TX, wrong stage of disease? Or wrong theory?

AD Timeline to Major NCD due to AD: 20-30 years before symptoms

- 30 years before, beta-amyloid protein levels in the CSF begin to decline
- 25 years before, beta-amyloid and tau begin to accumulate in the brain. (the earliest sure sign of the disease is in precuneus).

- 19 years before, brain metabolism begins to decline
- 10 years before, the brain begins to shrink due to neuron loss.
- 10 years before, episodic memory is impaired.
- 5 years before, Mild NCD sets in.
- Year 0, Major NCD diagnosis (too late to treat; too many dead neurons)

Alzheimer's starts well before sxs



Modified from Jack et al
Lancet Neurology 2010

So when should anti-BA medications & lifestyle choices start?

Prevention is the New Model of AD Tx
Emerging Model of Preclinical AD

- AD pathological processes and clinical decline occur gradually over several decades before major cognitive sxs occur
- NCD is the end stage of many years of accumulation of these pathological changes.
- These brain changes related to AD begin to develop 20-30 years before the earliest clinical symptoms occur.
- Therefore need to treat at beginning, not end, of the disease.

New Research Strategy

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

2018 National Institute of Aging Research Framework: Towards a Biological Definition of Alzheimer's Disease

- A research framework grounded on a biomarker based definition of AD in living people
- The term "Alzheimer's disease" refers to an aggregate of neuropathologic changes and thus is defined in vivo (while alive) by biomarkers and by post mortem examination, not by clinical symptoms.
- "Alzheimer's disease" = presence of biomarker evidence of both Aβ and pathologic Tau
- These definitions are applied independently from clinical symptoms

Biomarkers: AD Tests for predicting future AD pathology

- 1 for brain PET imaging of Tau deposition, using Flortaucipir
- 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)

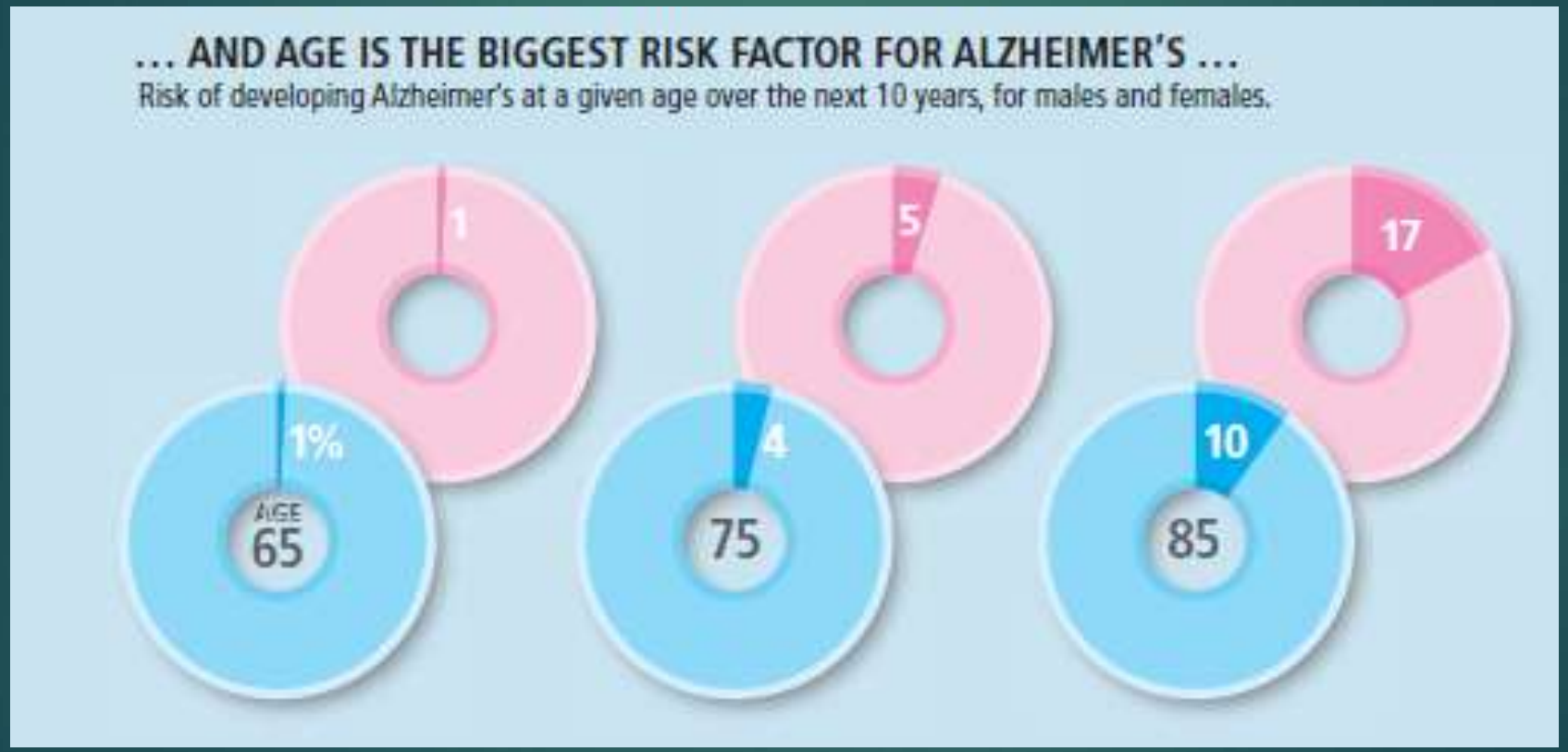
Risk Factors for AD

- Risk factor: i.e. adolescent who drinks 3 beers, then drives without seat belt = at risk; but not certainty
- Age: Prevalence 1% in 60-64; doubles every 5 years; 35-40% in over 85
- Being Female: more virulent AD; independent of being older
- Major TBI
- Reduced cognitive and physical activity throughout life
- Vascular Disease: HTN, cholesterol, diabetes, tobacco, obesity, heart disease; 80% of AD have vascular disease
- Early low IQ and Low childhood school performance

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

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



Women are epicenter of AD

- Alzheimer's dementia risk at age 65: 21% for women, 11% for men.
- 65% of those with living with dementia are women; dementia is the leading cause of death for women in England.

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.

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

400 miles of blood vessels in human brain.

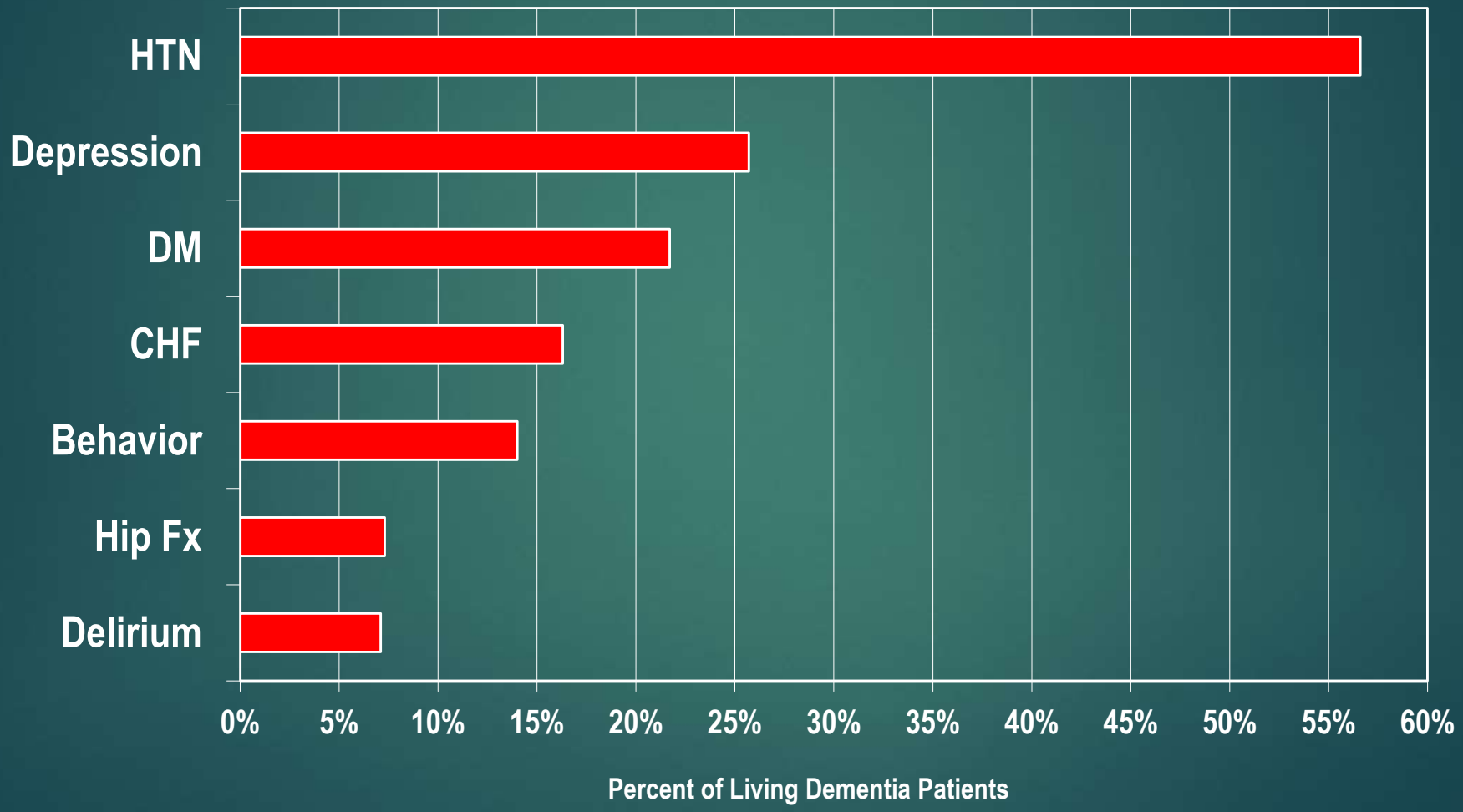
A plastic emulsion was injected into brain vessels and brain tissue was dissolved.

•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 Aβ deposition in the brain
- CV risk factors:
  - hypertension (high blood pressure)
  - smoking
  - high cholesterol
  - diabetes,
  - 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
- Current recommendation for BP: 120/80mmHg to 90/60 blood pressure

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.
- Aβ causes capillary constriction; 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.

Too Little, Too Late? Blood Pressure and Cholesterol Meds Don't Slow Cognitive Decline in 70s

- 2019 HOPE-3 study: For people over 70 who are at intermediate risk of cardiovascular disease, taking blood-pressure- and/or cholesterol-lowering drugs does not slow cognitive decline over six years (in older people who did not yet have high enough blood pressure or cholesterol to warrant taking the medications.)
- Starting treatment that late cannot undo years of cumulative damage done to the brain by slightly elevated blood pressure or cholesterol
- Cardiovascular risk modification needs to start in midlife to confer maximum benefits on late-life cognition

2019 USC: Key is vascular health

- If you're worried about Alzheimer's disease, your best shot at prevention could be maintaining cardiovascular health through exercise and diet and staying on top of conditions such as diabetes and high blood pressure.
- Healthy blood vessels are the key to brain health in old age. Damaged capillaries in the brain may set the stage for Alzheimer's decades before memory problems emerge.
- In some aging brains, the seams between BBB cells loosen, blood vessels become permeable and neurons begin to die.
- Can see the blood vessels leaking, independent of tau and independent of amyloid, when people have cognitive impairment on a mild level. Greater leakage correlates with increased cognitive decline.

CV status: Prevent stroke, heart attack, and dementia

- Don’t smoke
- Control hypertension
- Exercise
- Lower cholesterol
- Watch your diet
- Identify heart disease, esp. afib

- Doing the above, reduces stroke, heart attack, and dementia/AD risk
- Above all, exercise!

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

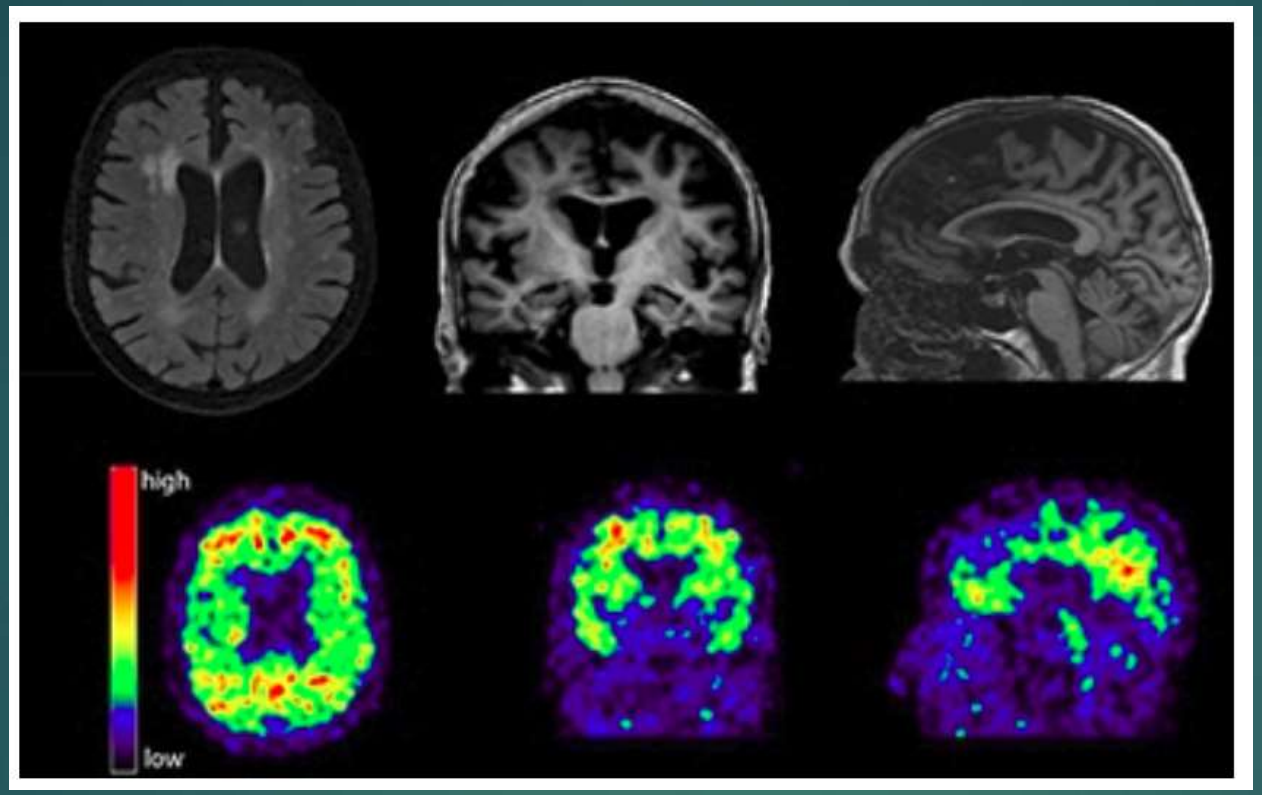
Alzheimer's Genetics

- 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)

Klotho, the good gene allele variant; but on 1, not 2

- The Klotho gene is good to have: longevity and IQ increase
- Benefit from 1 variant allele, not 2
- The klotho variant associated with longevity seems to negate some effects of the ApoE4 allele.
- Among 82 people with this protective klotho variant, ApoE4 carriers accumulated no more brain amyloid than noncarriers.
- Klotho knockout mice live shorter life and have cognitive deficits.
- They have impaired memory, enhanced synaptic plasticity and impaired neurogenesis

The Mutation You Want: It Protects the Brain, Extends Life



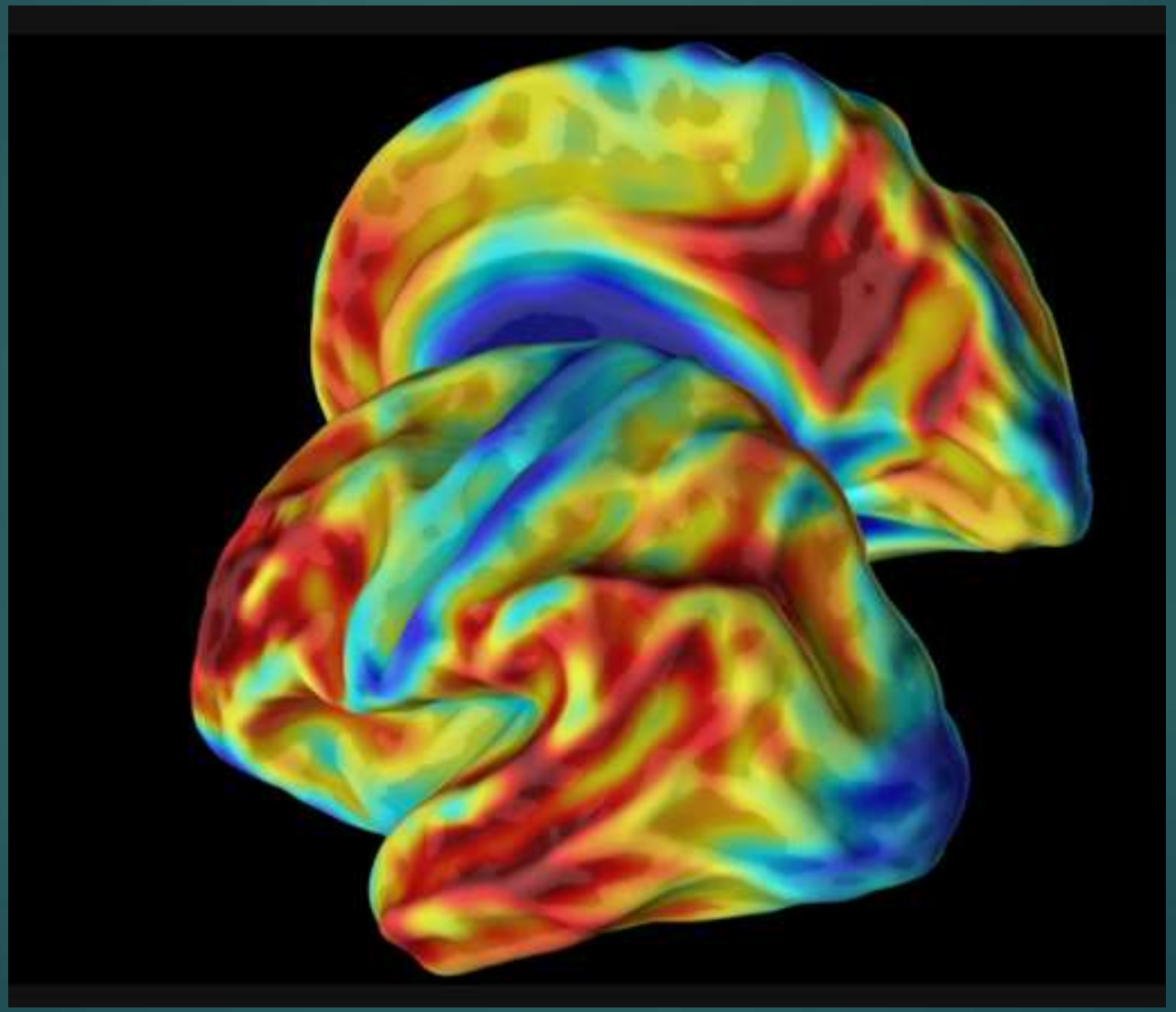
Cognitively Normal. Despite hippocampal and posterior cortical atrophy (top) and amyloid in the precuneus and frontal lobes (bottom), this 102-year-old with double ApoE4 performs normally on all neuropsychological tests. She carries the rs72824905-G variant allele of PLCG2 gene. Unfortunately, it's rare.

Hope for near future: Alzheimer's Prevention Initiative (*API*): Colombian Prevention Study

Map of Colombia.

- Colombian study: extended clan of 5,000 people who live in Antioquia, Colombia with early onset AD
- Family members with a Presenilin 1 gene mutation; disease they call “La Bobera” — “the foolishness”.
- MCI: median age 44; Major NCD: median age 49
- N = 300; 5 year trial; Genentech drug, Crenezumab injection every 2 weeks; massive pre and post testing
- Data in 2021

70 yo woman with massive BA; no dementia; PS1 gene



Unique Colombian Woman with Presenilin 1

- Those with Presenilin 1 in this extended family get familial AD in 40s and die in their 50s. Presenilin-1 increases accumulation of amyloid,
- 76 yo woman from Medellín, Colombia, with PS1 gene has extensive BA but lived for 3 decades without dementia; didn't show the first signs of the disease until her 70s. More amyloid buildup than in any other family member who has been scanned
- She carried two copies of a rare mutation (R136S) in the ApoE3 gene called ApoE3 Christchurch. These mutations helped delay signs of cognitive decline until the woman was in her 70s
- No signs of major damage to neurons; had little tau present in her neurons. This woman's case suggests tau might be the real culprit, not BA; possibility of preventing or treating Alzheimer's by targeting *ApoE*

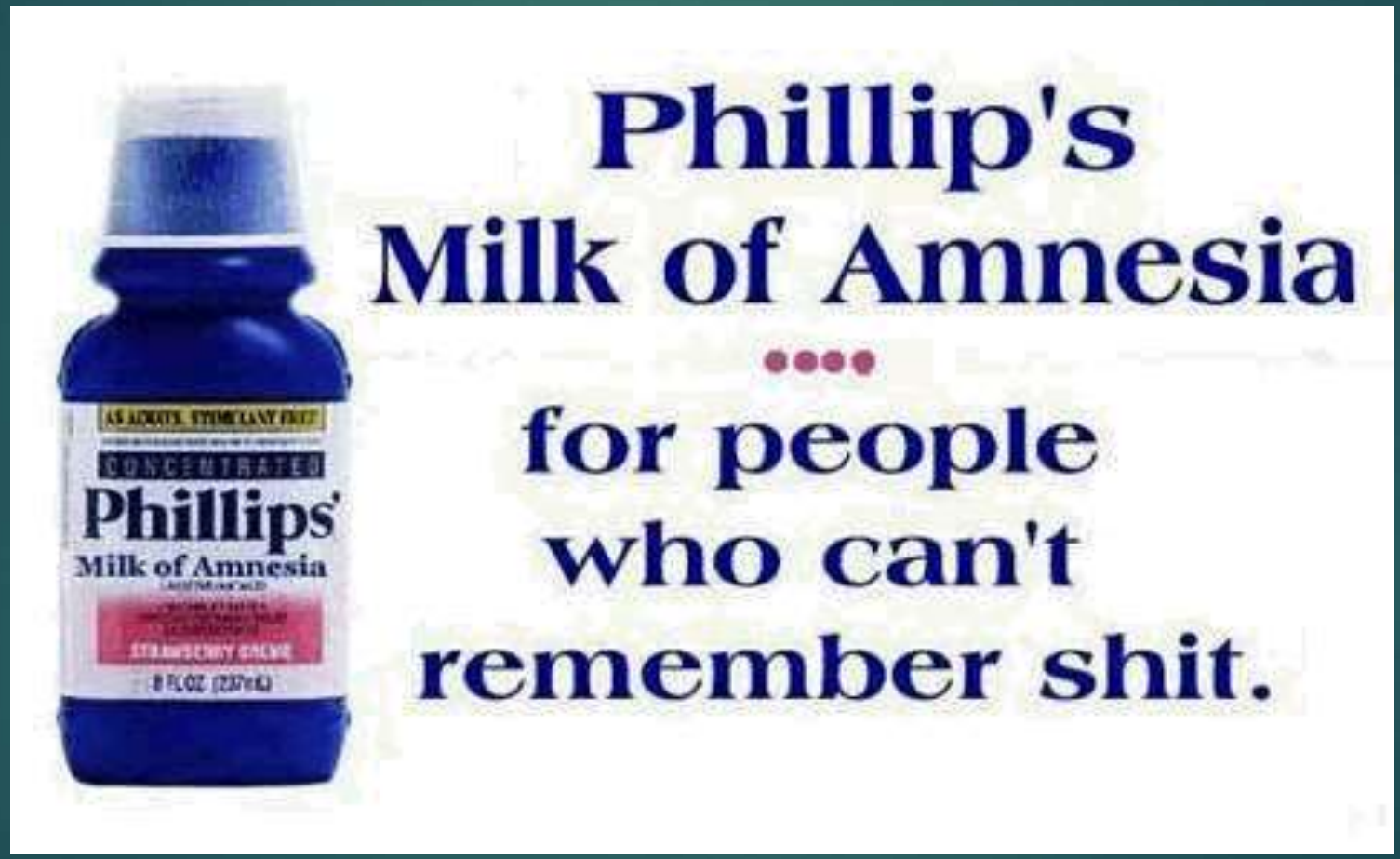
23andMe:
$79/159

In April, 23andMe started including genetic risk tests for AD and Parkinsonism. (ApoE4 allele = rs429358(C) + rs7412(C))

I was born on Malta. My genetic study: 89% Southern European; 1% sub-Saharan African; 5% Ashkenazi Jew; 2.7% Neanderthal; double APOE 3; Klotho variant (longevity, IQ↑)

Remember: No current treatment for AD

Latest Memory Cure



Anti-Major NCD Medications ?

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

- **The Verdict:** There are No Major NCD disease prevention medications.

- But…There are Major NCD modifying behaviors.

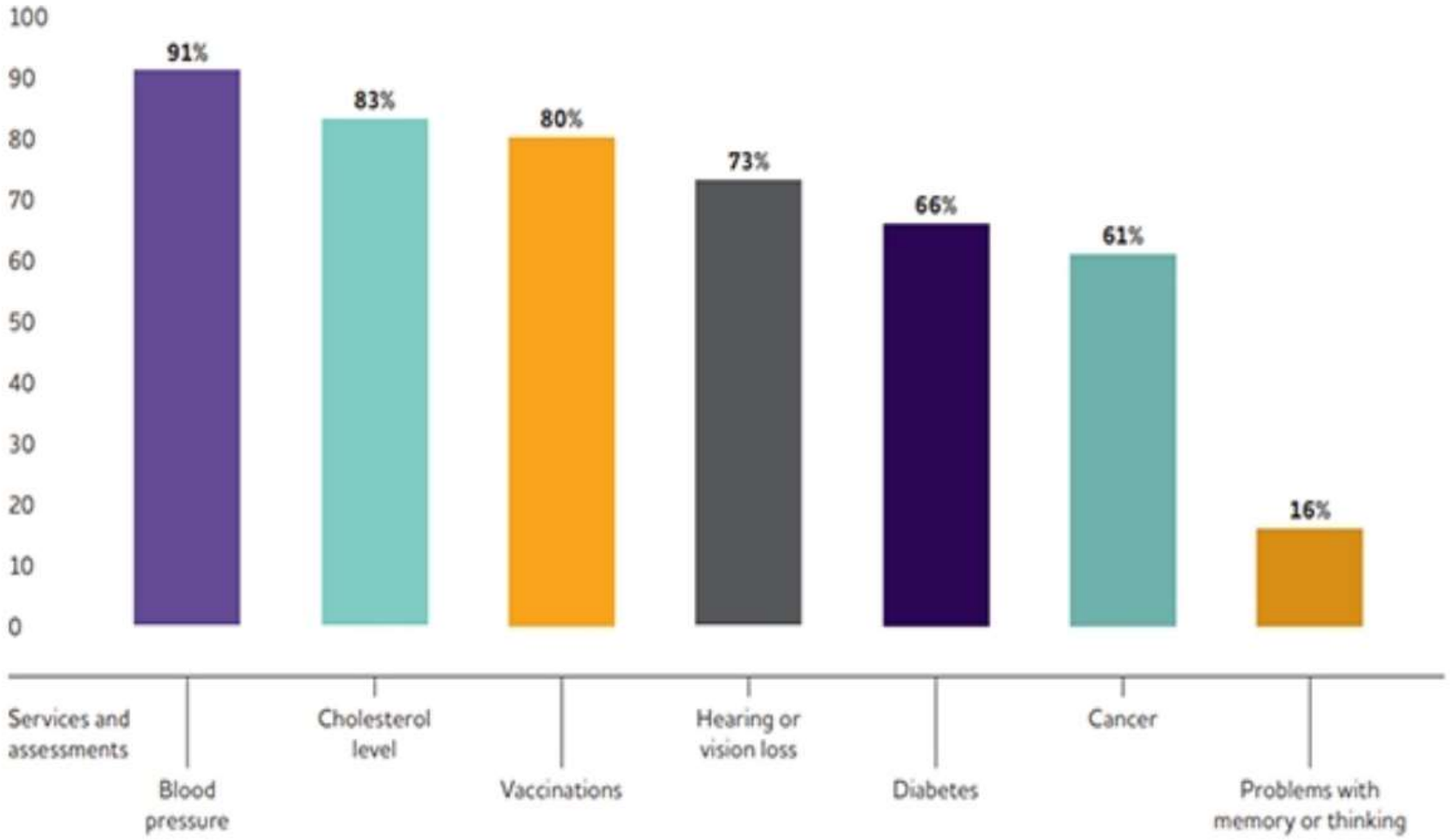
Only 5 drugs approved by FDA for AD

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

Medical screenings: only 16% for cognition



Low Priority. *Few seniors are assessed for memory or thinking (right). [Courtesy of Alzheimer's Association.]*

Brain fitness is a critical part of overall health.

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

Research Caveat

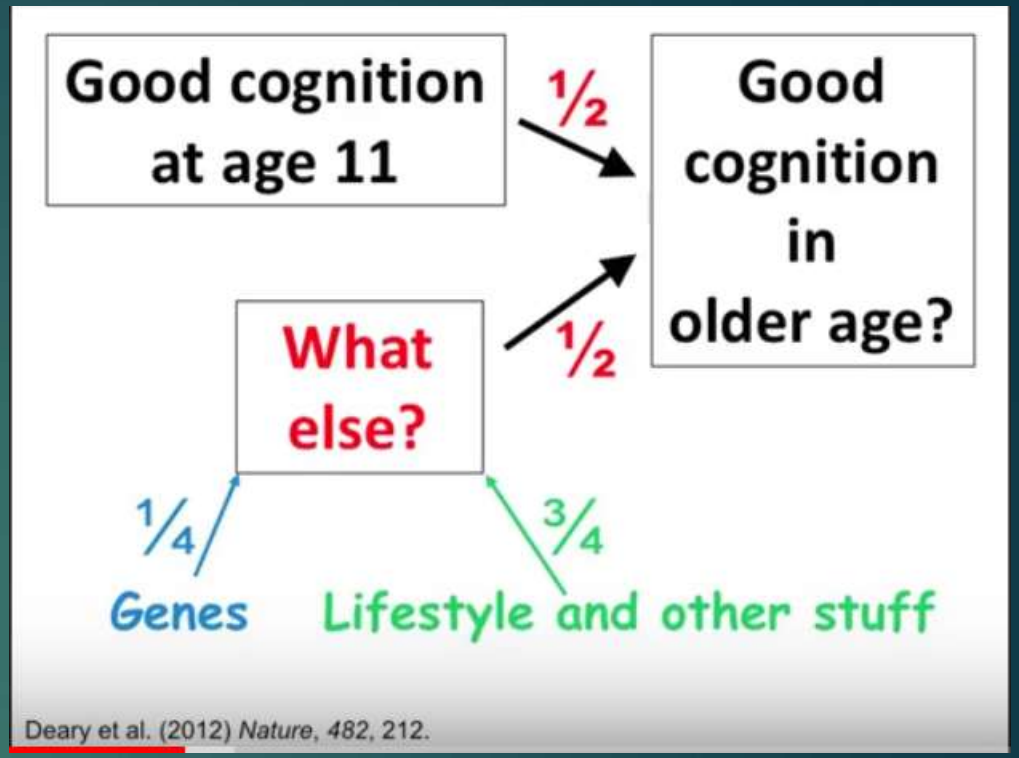
- Majority of studies are observational & correlational, i.e. people who eat chocolate have less CV disease
- Correlation is not causation: gum disease does not cause CV disease, higher plaque in blood vessel does.
- Most studies are cross-sectional (same age cohort), not longitudinal: alcoholics who 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; but more are on the way

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

Lothian Findings

- 50% of cognitive ability at age 70 is there at age 11
- If you want to be smart in old age, start in childhood
- 25% of change in cognitive ability over life is genetic
- 75% is lifestyle and other stuff
- <u>Tendency, but not determination, for smart kids to become smart older adults</u>



Caution from Lothian Study: Confounds & reverse causation

- Confound: murder rates and ice cream sales are highly positively correlated; There is a third variable (hot weather)—a confounding variable—which causes the increase in BOTH ice cream sales AND murder rates
- Lothian Study has concluded that certain variables are confounds: i.e. type of diet, body mass index, caffeine and alcohol consumption. None of those factors seems to have any effect on cognitive skills in the Lothian cohort when childhood intelligence is accounted for.
- Even the effects of social and intellectual activity disappeared when you take into account how bright children were at age 11, possibly because those children are more likely to end up being socially and intellectually engaged.

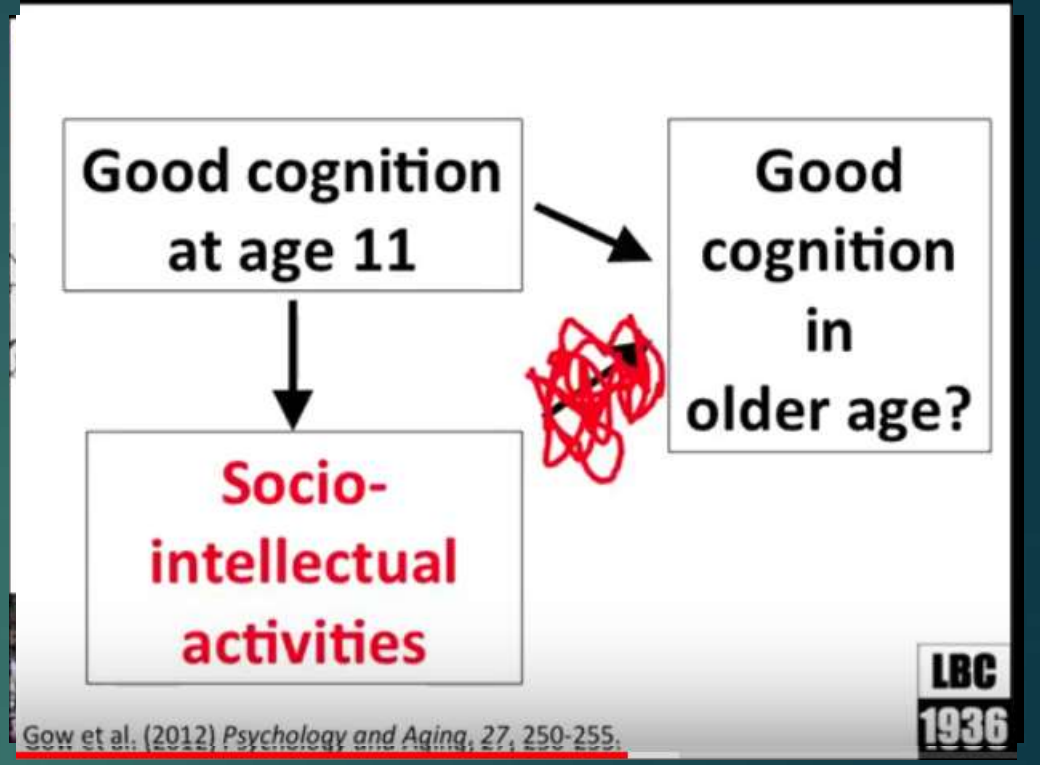
Lothian Findings

- Reverse causation: cause and effect are reversed
- Does diet reduce dementia?
- diet at age 70 are correlated to age 11 cognition: smarter children eat better; eating better does not improve cognition at age 70

- Red variables are red herrings: do not predict age 70 cognition
- Green variables do

Lothian Findings

- Confounding/Reverse Causation: where a disease causes an effect, rather than the other way around.
- Example: correlation between education and dementia was due to more schooling or because the better-educated people were more intelligent to begin with and sought out more schooling
- Study of social & intellectual activities: if you do 1 of these things, you tend to do all the others
- But: intellectual & social activities are correlated with better older cognition, until you account for original cognition; those who are brighter at 11 do more



Lothian Findings

- Green variables = predict better older cognition
- Red variables = red herrings

- Mens sana in corpore sano: physical fitness predicts better cognition; less brain atrophy & better white matter connections
- Marginal gains, not magic bullets: do as many as you can
- Replication, replication

The Brain and Social Connectedness: January 23, 201

GCBH Recommendations on Social Engagement and Brain Health

"The weight of evidence suggests that social engagement helps maintain thinking skills and slows cognitive decline in later life."

Global Council
Brain Healt
A COLLABORATIVE FROM AA

What is the association between sedentary behaviour and cognitive function? A systematic review

Br J Sports Med 2017;**51**:800–811.

Ryan S Falck,[1] Jennifer C Davis,[1] Teresa Liu-Ambrose[1,2]

"Our systematic review provides evidence that limiting sedentary time and concomitantly engaging in regular moderate-to-vigorous physical activity may best promote healthy cognitive ageing."

ody Connection:

ndations on

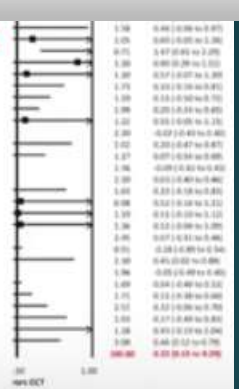
and Brain Health

Global Council on
Brain Health
A COLLABORATIVE FROM AARP

e lifestyle (e.g. walking,
dening, etc.) provides
ealth. Purposeful exercise
cycling, strength training,
ses, etc.) provides benefits

adults, but efficacy varies across cognitive domains... Unsupervised at-home training and training more than three times per week are specifically ineffective."

Lampit et al. (2014)
PLoS Medicine, 11, e1001756.



**** 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, and included:
  - nutritional guidance,
  - physical exercise,
  - cognitive training,
  - social activities,
  - and management of heart health risk factors
  - (control group received regular health advice);

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

FINGER study

- There were significant positive intervention effects on the outcome
  - overall cognition,
  - executive functioning
  - processing speed,
  - complex memory tasks,
  - other secondary outcomes (BMI, dietary habits, and physical activity).
- Outcomes were 25% to 150% better in the intervention group.
- Now 7-year Finnish follow up study
- Alzheimer's Association U.S. Study to Protect Brain Health Through Lifestyle Intervention to Reduce Risk (U.S. POINTER) – 2 year

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 to develop dementia decades later.
- Fittest women held dementia at bay 10 years longer.
- Cardiovascular health partially explained the relationship between fitness and brain health,

Potentially modifiable Risk factors for dementia

- Birth: APOe4 (not modifiable)
- Early age: low education
- Midlife: hearing loss, hypertension, obesity
- Late Life: smoking, depression, physical inactivity, social isolation, diabetes

Livingstone, et al., 2017

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

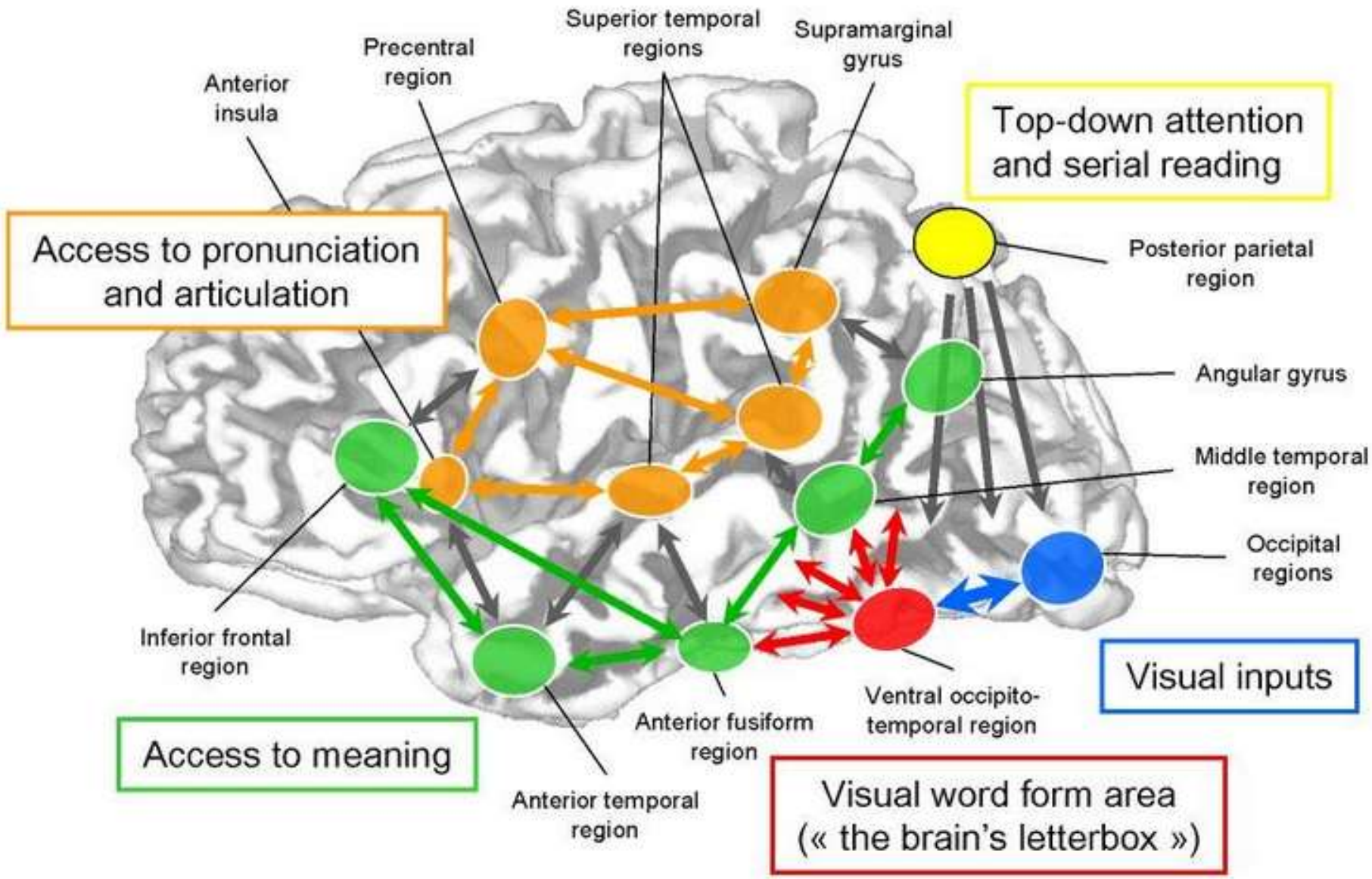
- Myth that a low-gluten diet is healthy for everyone.
- Limiting whole grains as part of a reduced-gluten diet can actually increase heart attack risk in people without celiac disease
- A study of more than 100,000 men and women revealed that dietary gluten is not associated with heart disease risk in people without celiac disease.
- 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.
- Canine dilated cardiomyopathy and dogs eating certain grain-free dog foods (those containing legumes such as peas or lentils, other legume seeds, or potatoes listed as primary ingredients).

Join UCSF's Brain Registry

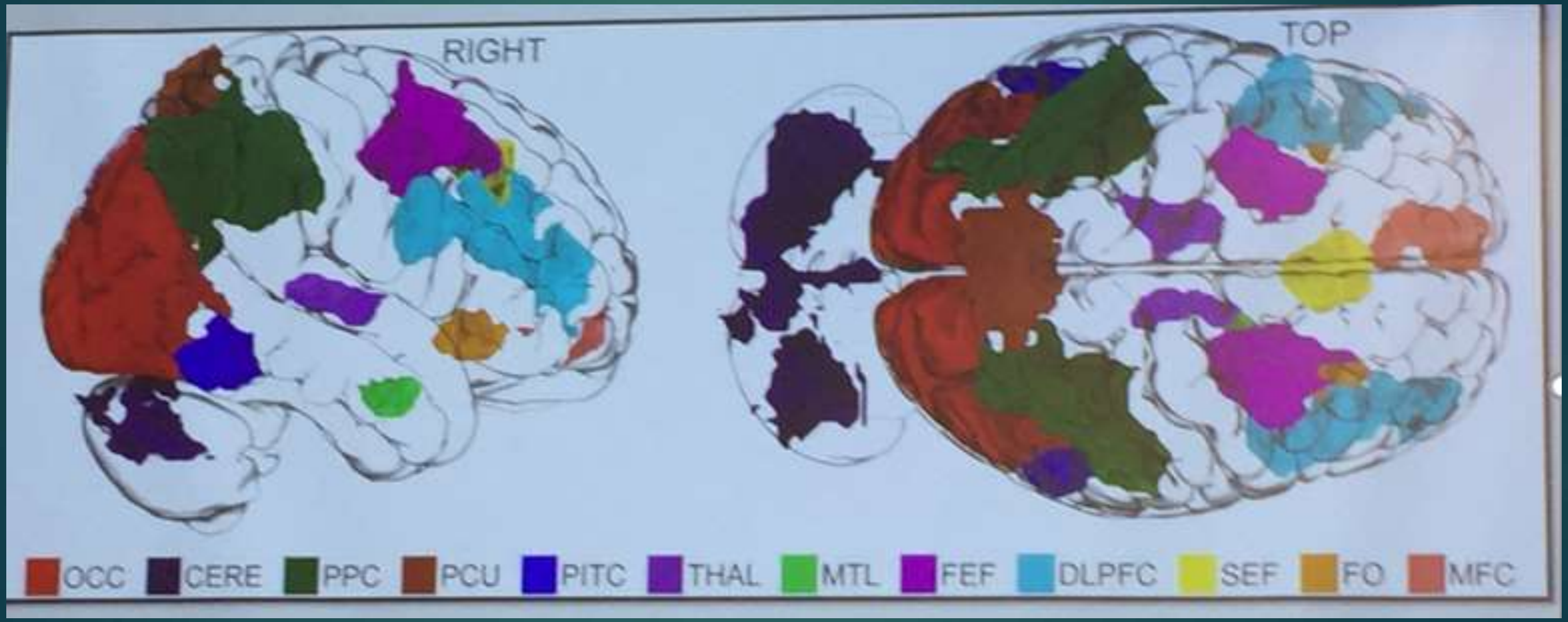
- If you have a computer, join this new research program:
  - http://www.brainhealthregistry.org
- Answer some health questions and play some Lumosity games, which gives them info on your brain functioning.
- They check in with you every 6 months.
- It's easy and you contribute to a very large brain 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 !!!

A modern vision of the cortical networks for reading



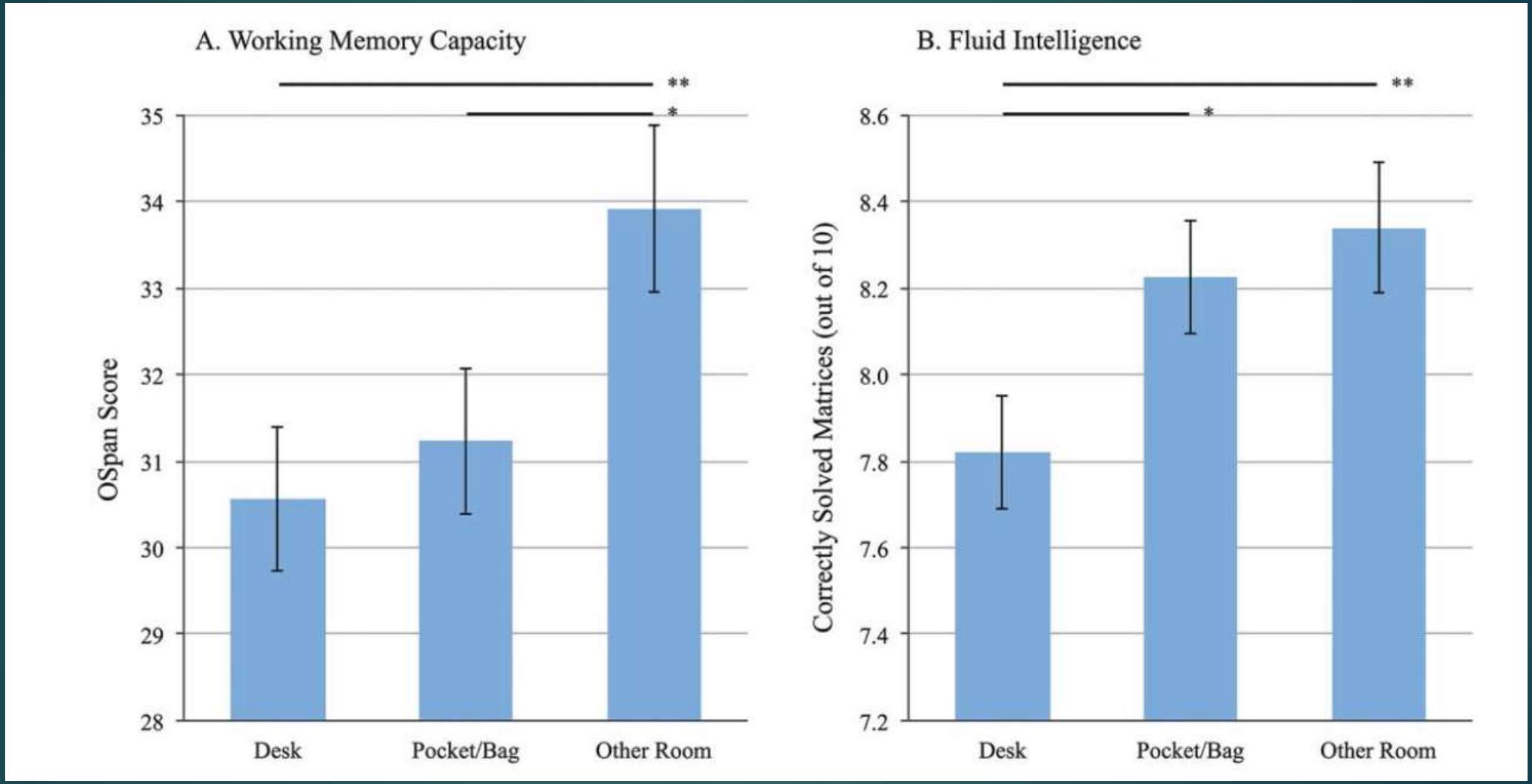
Reading activates more brain areas than any other activity



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 %
- 40 % of frequent readers ages six through 10 were read to out loud at home
- Helps to improve & maintain memory function

Your IQ test performance depends on where your iPhone is!



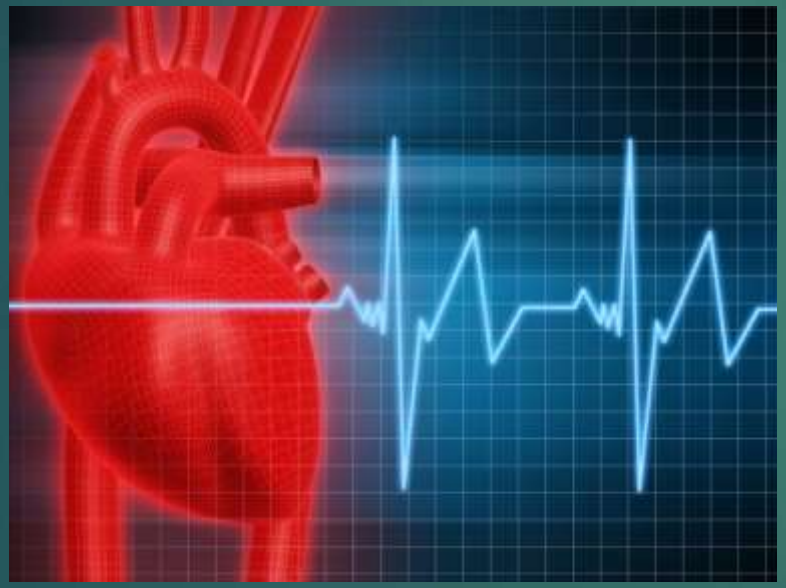
Adrian F. Ward, et al., 2017

Tip #1: Protect your head!

- Blows to the head increase odds of Major NCD years later.
- Falls are leading cause of loss of independence in older individuals
- Wear seat belts and helmets, fall-proof your house, and don't take risks.
- Risky: football, soccer, horseback riding, 2 wheel devices

Tip #2: Protect your Heart

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



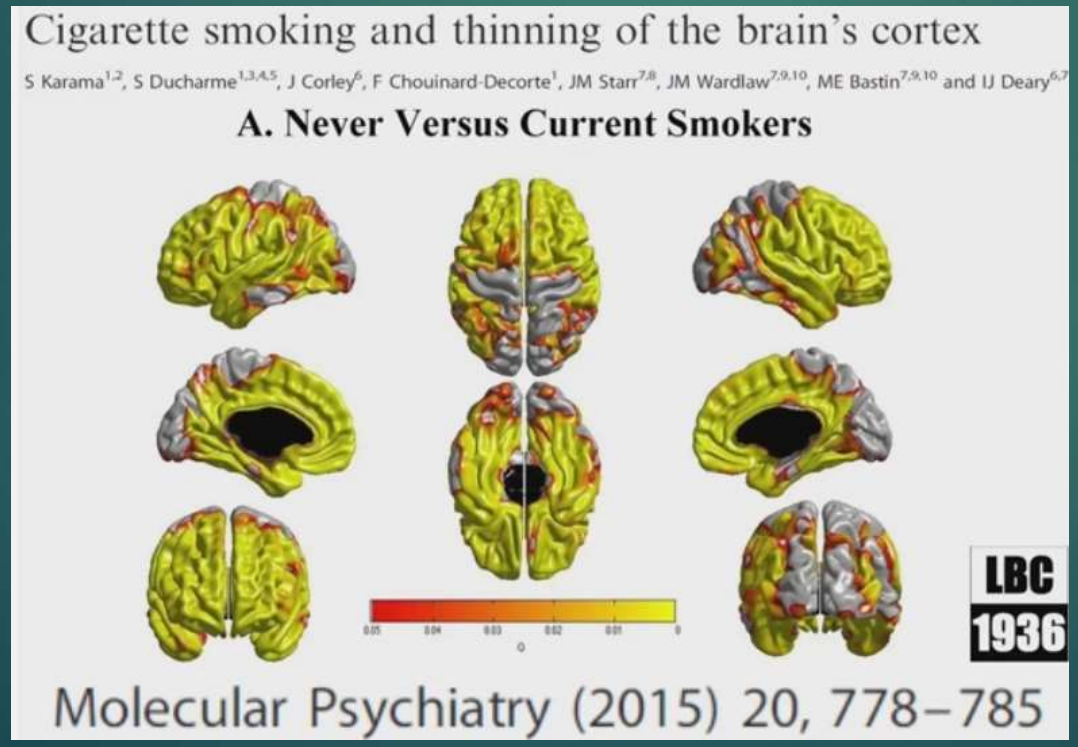
Monitor your vascular numbers; take your antihypertensive and cholesterol meds

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 only a little alcohol

Tip #3: Do not Smoke

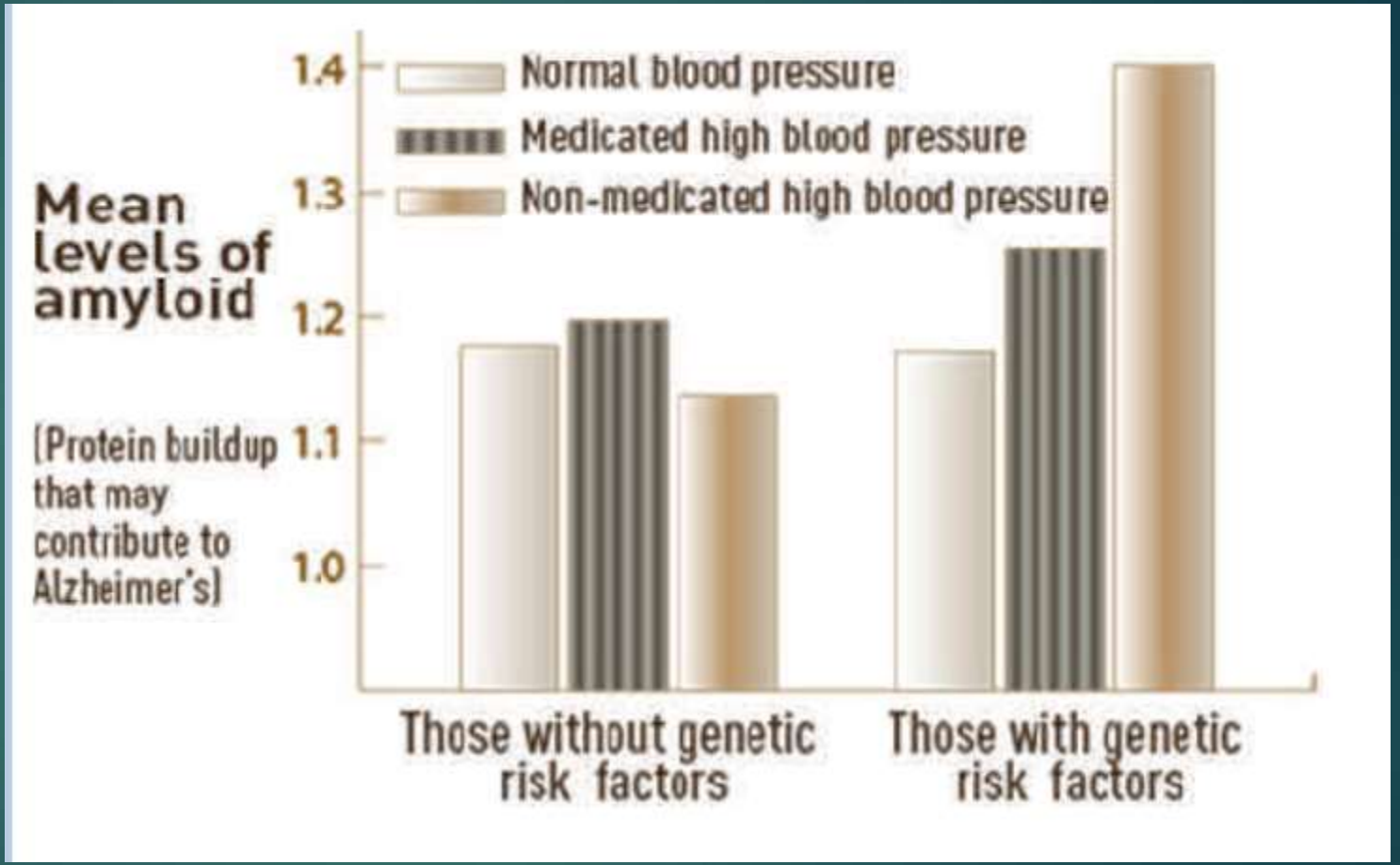
- 6 - **** Quit smoking: Smoking is lethal behavior.
- Smokers are 2 to 4 times more likely to develop heart disease, stroke, and dementia, than nonsmokers. Smoking accounts for 11 percent of Alzheimer's cases; “strong evidence” for raising the risk of cognitive decline.



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

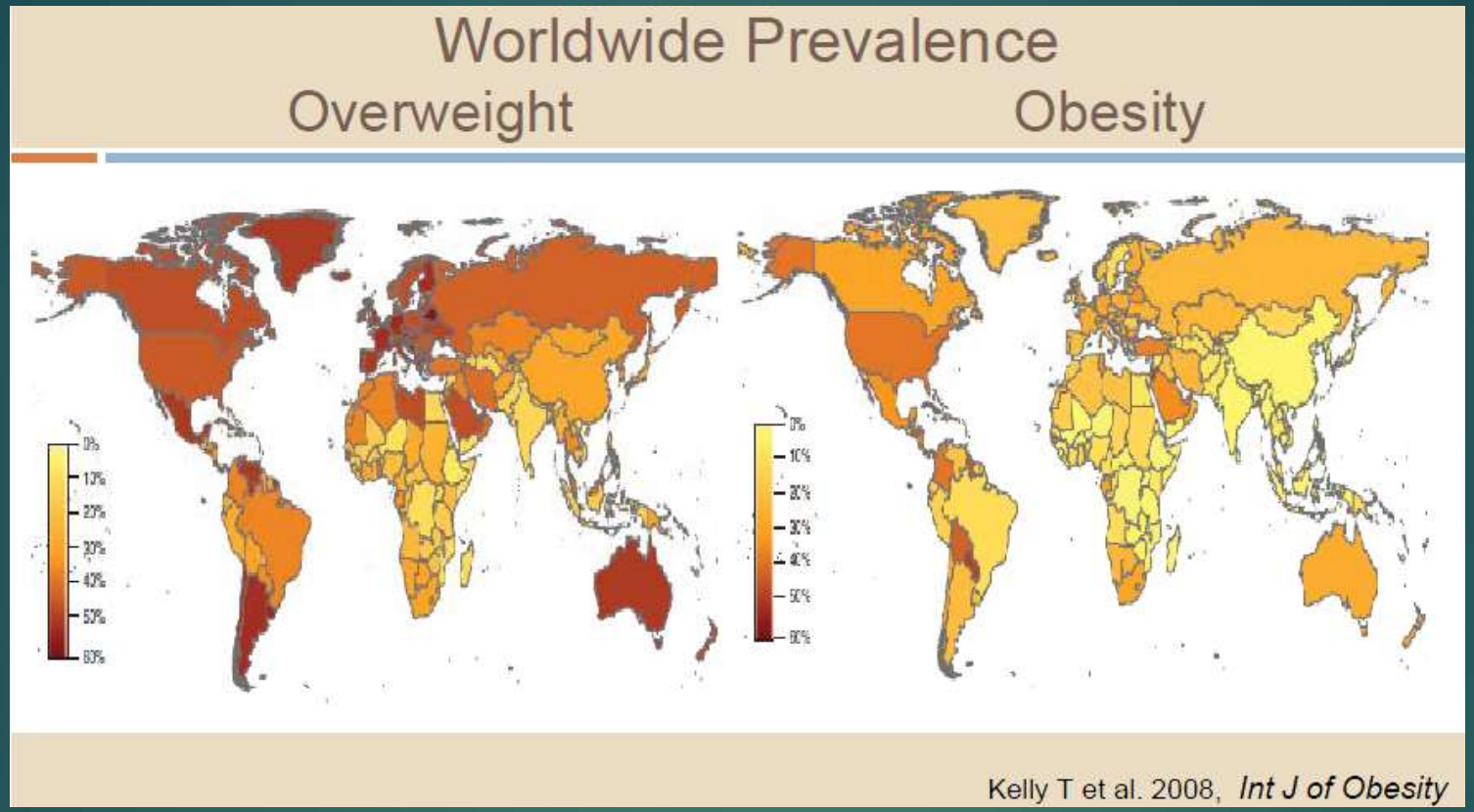
Take your meds: Hypertension Increases Beta Amyloid

$22 on Amazon



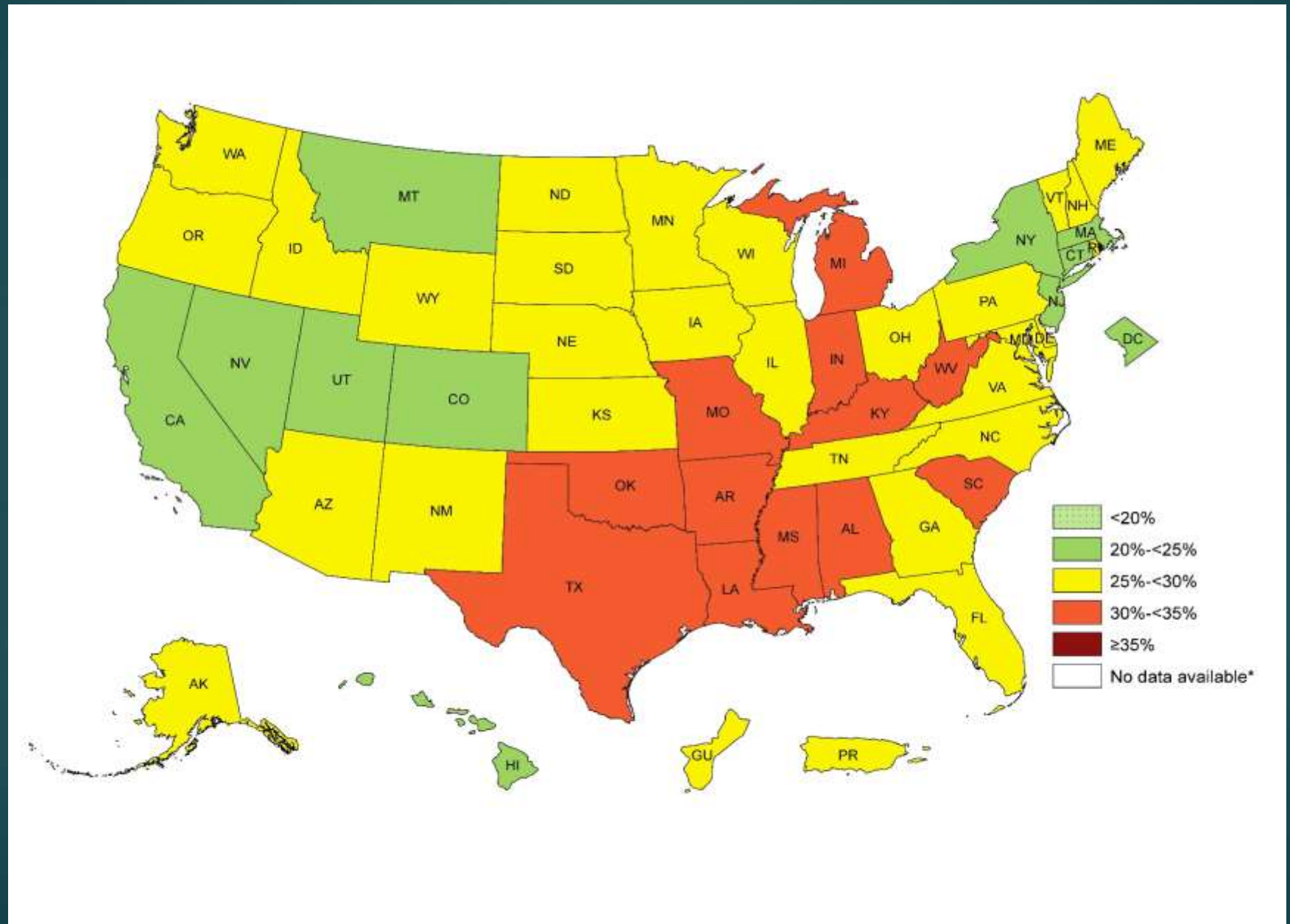
Bad news: **** Double APOE4 & non-medicated hypertension

Tip #4: Stay at a normal weight

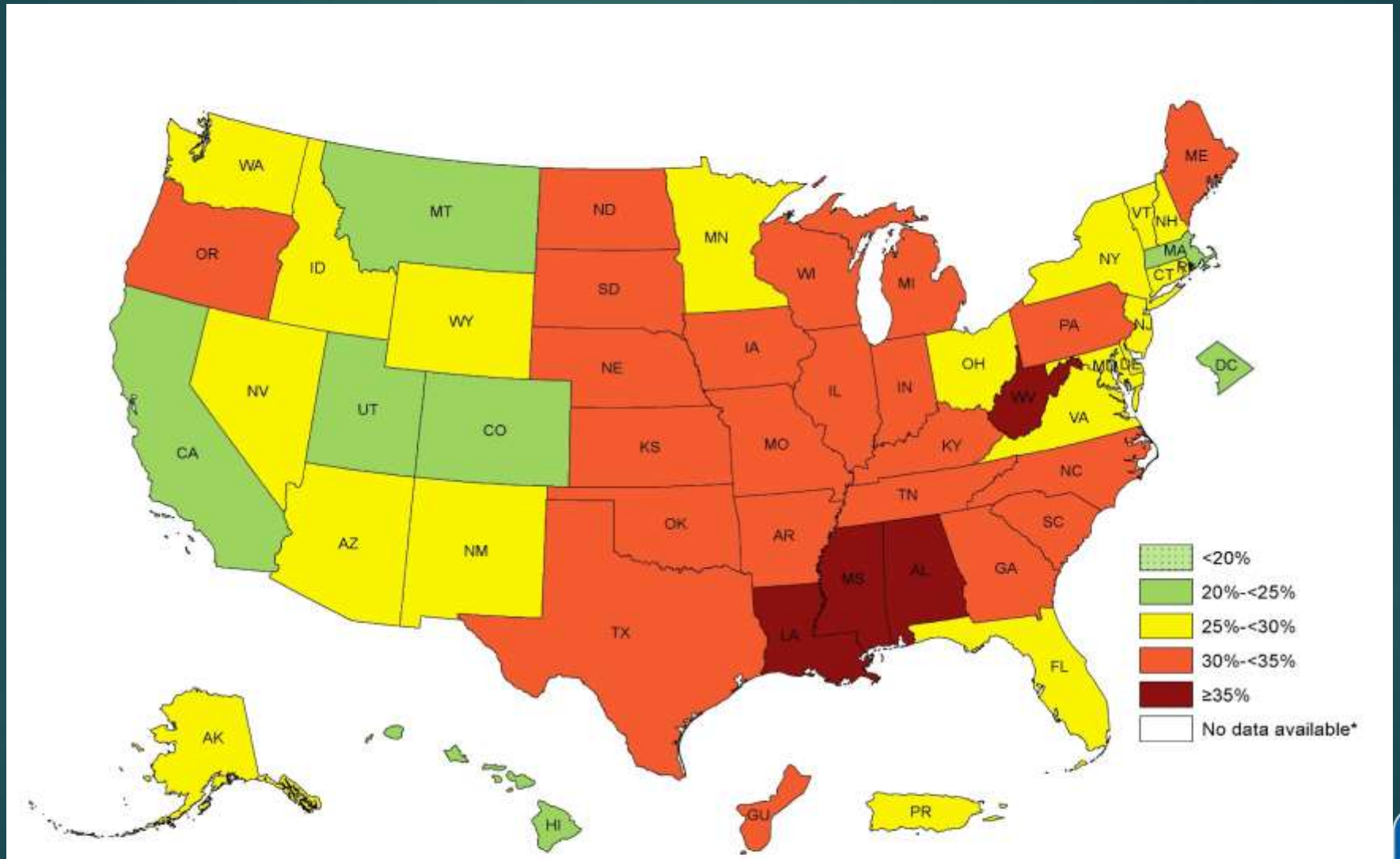


- Midlife obesity accounts for 7 percent of Alzheimer's cases
- Waist/hip ratio was highly associated with death from CV disease
- Normal-Weight Central Obesity More Deadly Than Just High BMI

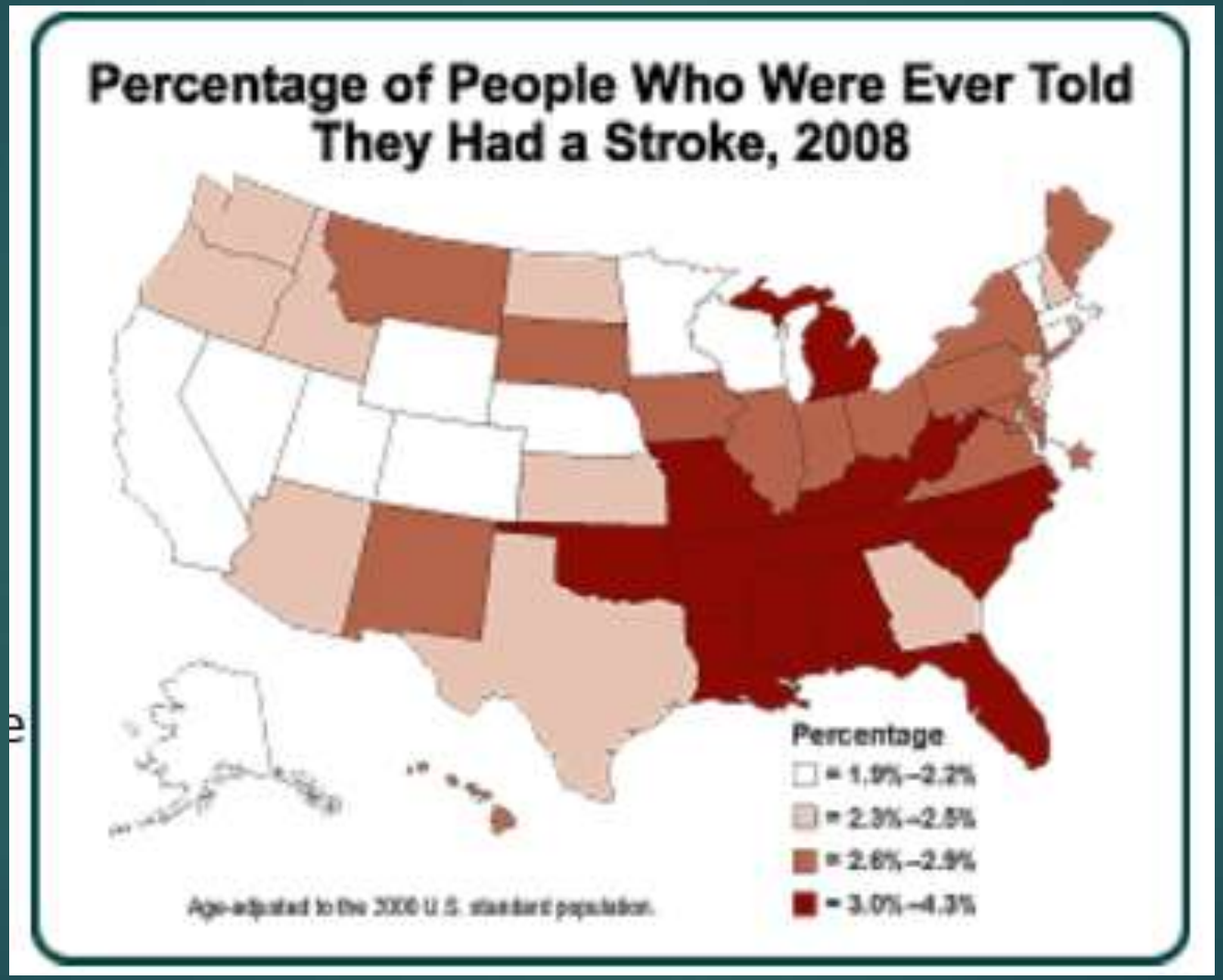
Prevalence of Self-Reported Obesity Among U.S. Adults, 2011



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

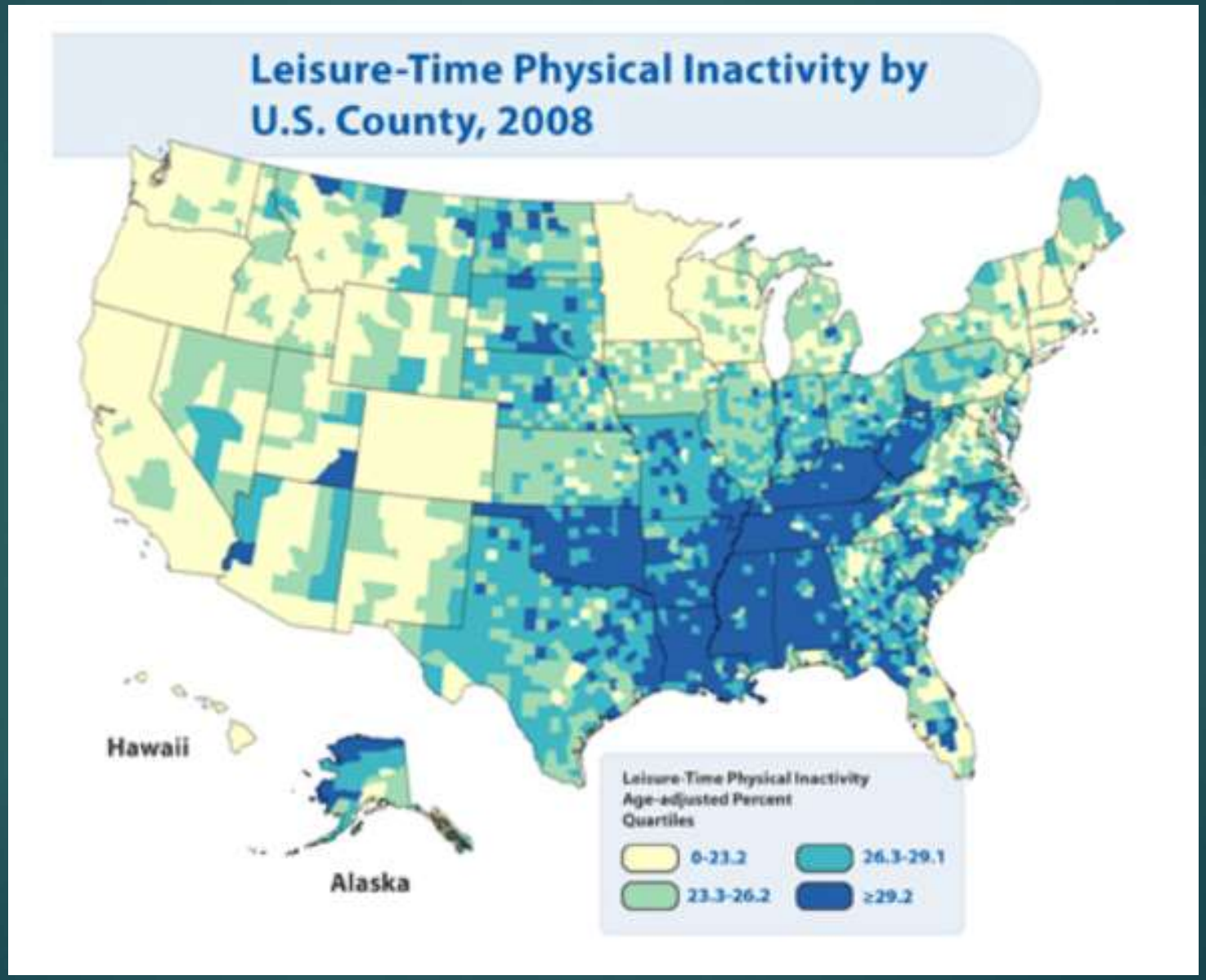


CDC: % Strokes by State



Highly tied to high consumption of fried and processed foods

CDC Physical Inactivity



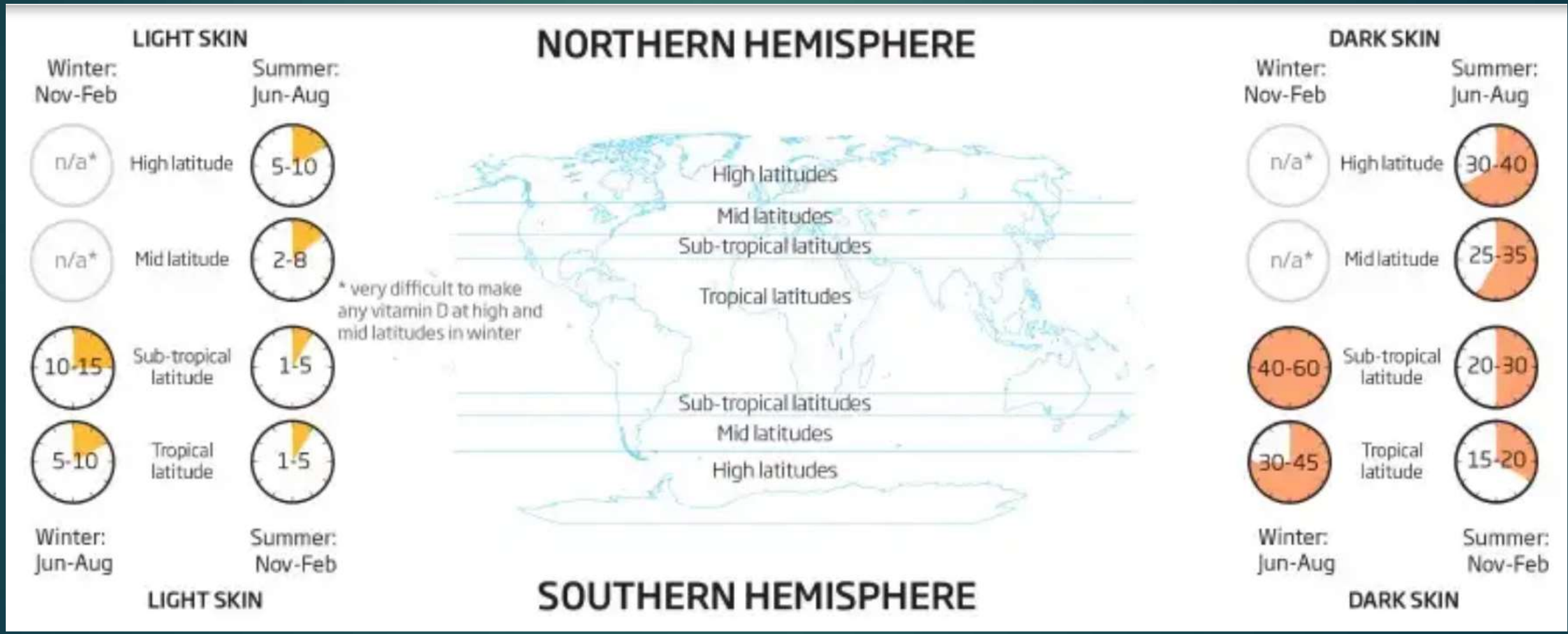
Tip #5: Most Strokes Can Be Prevented;
1 in 6 People Will Have a Stroke

- 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 #6: Take Vitamin D or get Sun (but not thru a window)

- Older do not get enough sunlight
- In elderly, low Vitamin D increases cognitive decline; high Vit D increases life expectancy
- Older need 1000 IUs/day (eat with a fat); Eat fish regularly
- Stroke: The lower the vitamin D level, the more severe the stroke and the poorer the recovery
- Higher Vitamin D associated with a decreased risk of developing:
  - cardiovascular disease (33% reduction)
  - type 2 diabetes (55% reduction)
  - metabolic syndrome (51% reduction).
  - colorectal cancer (22% decline; 30% increase if no Vit D)

In San Francisco, 1-5 minutes at noon in summer; 20-30 minutes if dark skinned, for enough Vit D



Supplements: Wild, Wild West - - No Benefit

- Most supplements are not patented, nor FDA approved.
- There is zero evidence from any reasonably rigorous study that any supplement or dietary aid has any benefit on cognitive function or decline in late life.
- Only reason for a supplement is when patients have a documented deficiency, such as for vitamin B12.
- A recent meta-analysis of vitamin and mineral supplements supports this position, finding no consistent cognitive benefit of supplementation for healthy adults across 28 studies
- Prevagen: do not kill jelly fish for this junk memory aid
- There are currently no cognitive enhancers.

Tip #7: Drink Coffee

- People who drink coffee have:
  - 36% less strokes; less heart disease
  - 20% reduced risk of NCD/dementia (reducing inflammation & beta amyloid)
  - 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
- It didn't matter if the brew was drip grind, decaffeinated or even lowly instant.

2017 meta-analysis 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 and obesity

- 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

- Strokes associated with diet sodas,
- Men who drank the most artificially sweetened beverages on average were heavier, exercised less, consumed more calories, had lower-quality diets, and were more likely to smoke and have a history of diabetes, heart attack, or stroke

AD as “Type 3 Diabetes”: Prediabetes is a risk for cognitive decline

- A high-carb diet, and the attendant high blood sugar, are associated with cognitive decline.

- It’s increasingly looking like Alzheimer’s is another potential side effect of a sugary, Western-style diet.

- People with high blood sugar have a faster rate of cognitive decline than those with normal blood sugar—whether or not their blood-sugar level technically made them diabetic. In other words, the higher the blood sugar, the faster the cognitive decline.

Tip #8: Brush and Floss

- Gingival inflammation in elderly 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: Stay curious. Google! Use the Internet.

- Doing an online search can stimulate your aging brain
- 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.

Tip #10: Get Enough Sleep: 7+ hours

- Brain during sleep:
  - Removes beta amyloid during sleep
  - We sleep to consolidate learning. Sleep is crucial to memory functioning
  - Loss of 1 night of sleep increases Aβ in brain

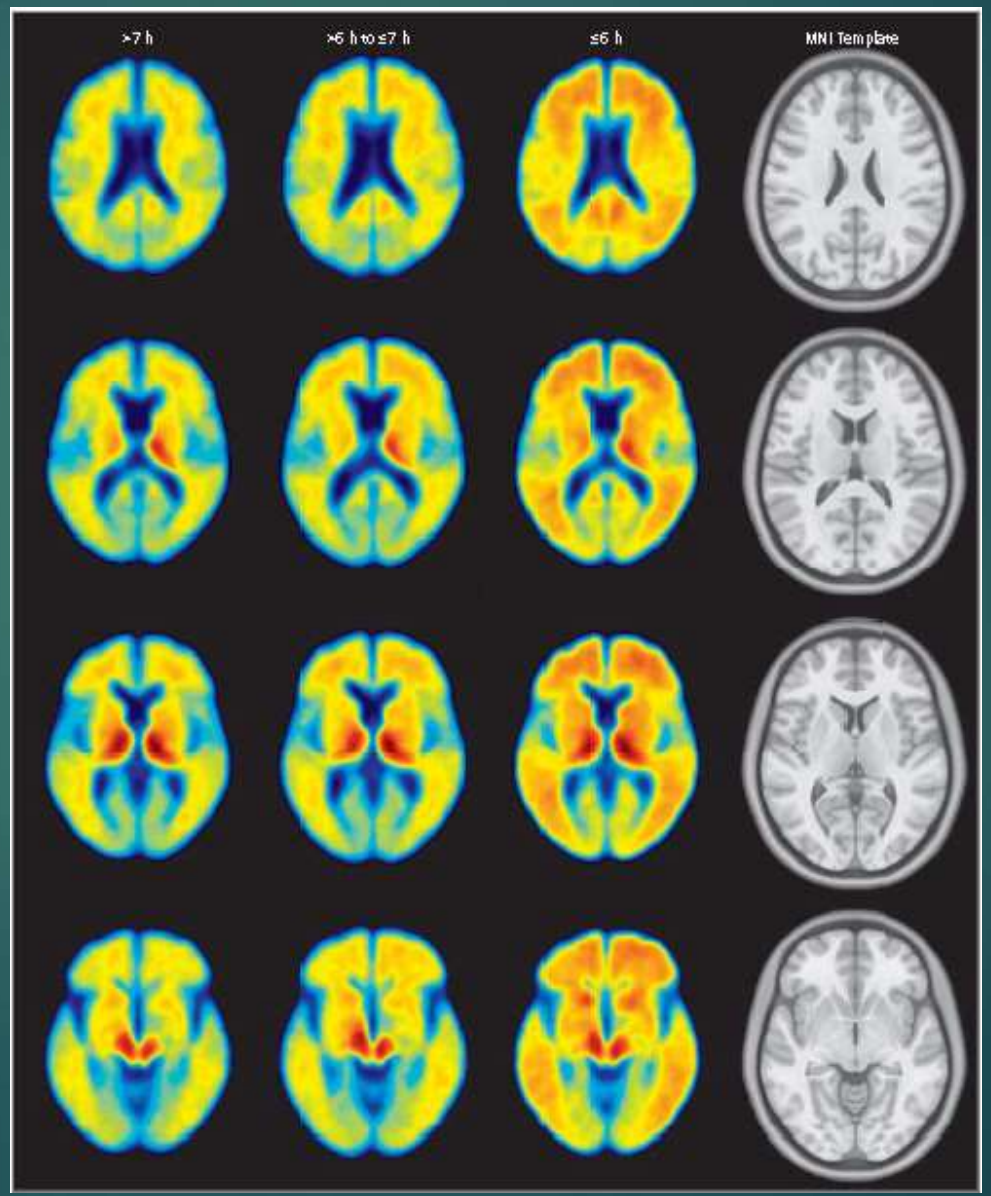
- Lack of sleep:
  - blunts our ability to focus,
  - makes us dangerous drivers
  - can make us eat too much.

- Lower evidence as cause of AD

Sleep 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.

Use of sleeping pills associated with increased dementia risk

- N = 3068 black and white community-dwelling older adults without dementia aged 70 to 79 years
- A total of 147 (4.8%) participants reported taking sleep medications "sometimes" (2 to 4 times per month), and 172 (5.6%) reported taking sleep medications "often" (5 to 15 times monthly) or “almost always" (16 to 30 times monthly).
- Older adults who reported taking sleep medications "often" or "almost always" were 43% more likely to develop dementia; White participants reporting frequent use had a 79% higher dementia risk
- Use of sleep medication may be a risk factor for later cognitive impairment; but not necessarily the cause

Sleep Problem?

5 Rules

- 1 Single alarm time rules them all
- 2 Keep it dark
- 3 Keep it colder (65-68 degrees)
- 4 Don’t stay in bed if awake; bed is only for sleep or sex, not talk or reading
- 5 No screens
- 6 Exercise regularly, but not before sleep

- Avoid or cut down on having daytime naps
- No coffee or alcohol after 3 pm
- Do Cognitive Behavioral Therapy for Insomnia (80% successful)
- Beware of indiscriminate use of sleep medications: no safe sleeping pill, esp. benzos

Why we sleep - Matthew Walker

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

- As sleep apnea increases, so does Major NCD risk
- 2x odds MCI at 5 years (JAMA 2001) & 2x odds dementia at 5 years (PloS One 2013)

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

- There is excellent treatment for apnea: C-pap & B-pap machines
- If you snore significantly, get checked

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

- Smilers lived 7 years longer.

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

Tip #12: De-stress!

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

Tip #13: Eat a little dark chocolate

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

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: **** Regular Physical Exercise

Keep moving and Keep your wits

- Higher levels of any physical activity help ward off an early grave.
- **** 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

2019: Light exercise

- Low-intensity movement—such as leisurely walking, gardening, or even doing household chores—correlated with larger total brain volumes in people over age 50.

- The number of steps taken per day, and time spent engaged in light intensity activity, did associate with brain volume. Participants spent an average of nearly 2.5 hours per day moving in light ways.

- Every hour of light physical activity per day, on average, correlated with a 0.35 percent bigger brain.

Being Physically Active

- Physical activity aids in reducing the risk of myriad diseases, including obesity, type 2 diabetes, cardiovascular disease, dementia, and 8 forms of cancer (bladder, breast, colon, endometrium, esophagus, kidney, lung, and stomach).

- Physical activity improves sleep and physical function, prevents injury from falls, and is beneficial as an adjunct to pain management

- Improves mood, reduces anxiety

- Lowers death rate by 33%

Exercise and dementia risk = 40% reduced risk; only 26% do it

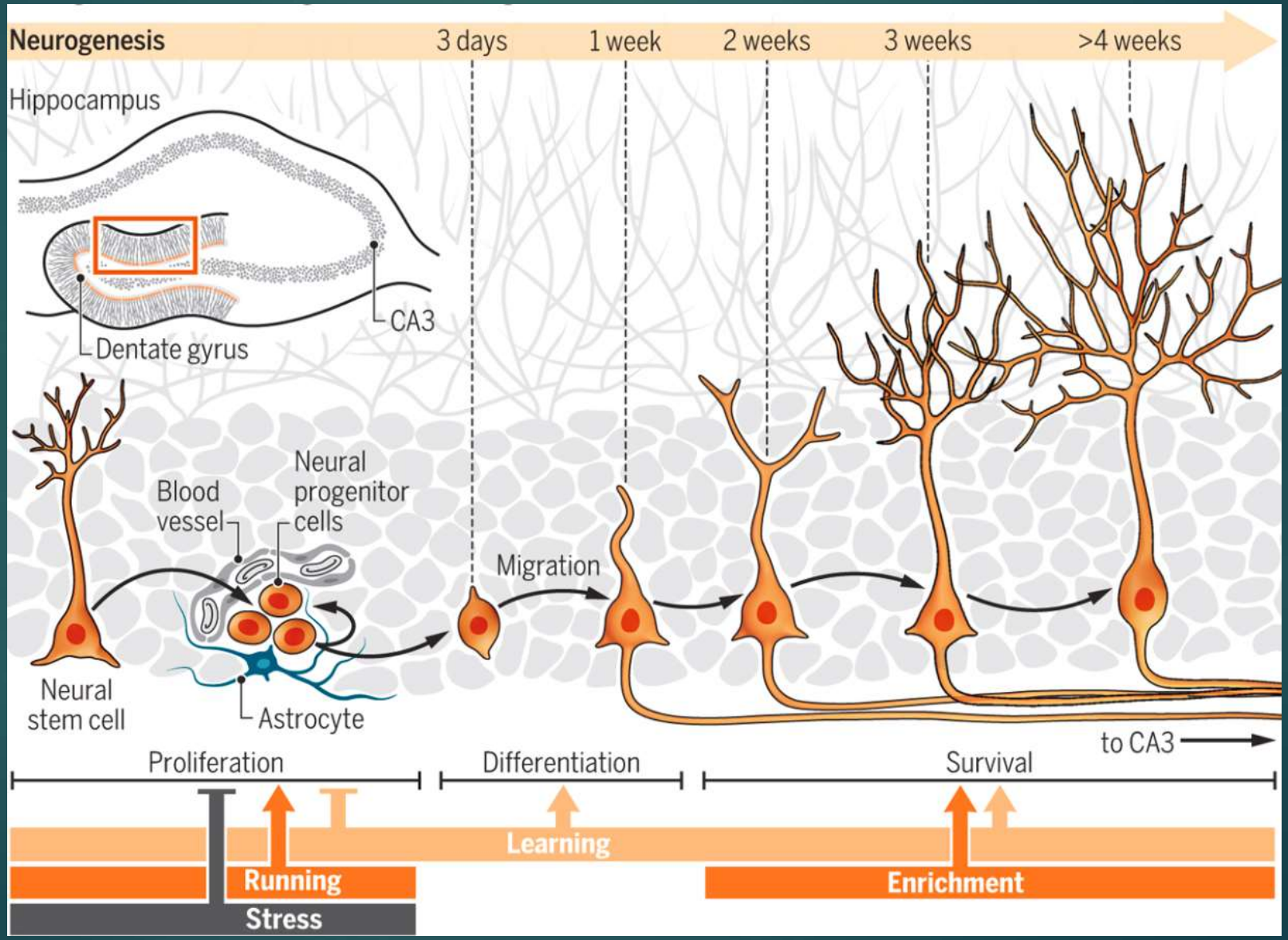
Exercise – how much?: 30 min/day 5d/week

- 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)

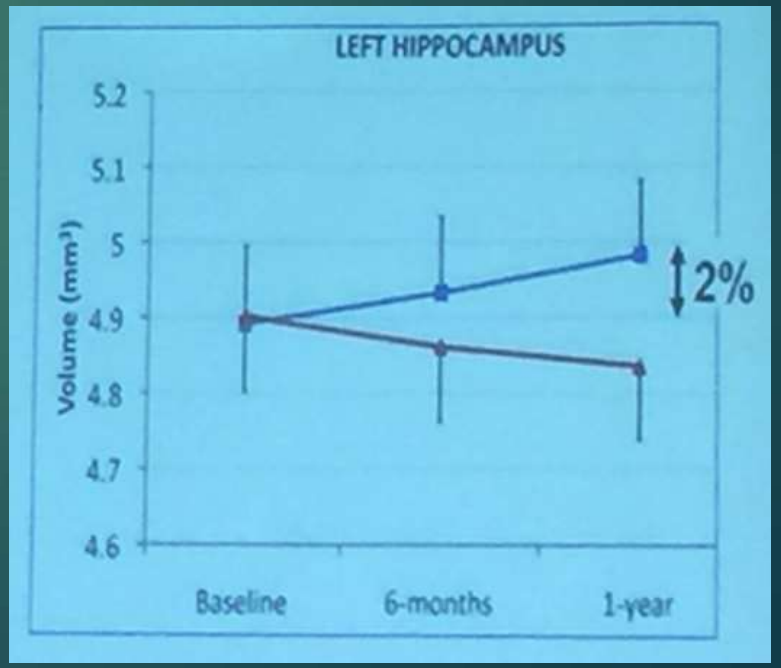
  - Greater effect than any current drug effect
  - Decreases Aβ in brain

Running In rats = neurogenesis



Walking: Reversal of Hippocampal Age-related Atrophy

- Study: 10 to 40 min/day walk for 1 year
- Hippocampus normally loses 1 to 2 % per year
- Walking increased hippocampus by 2%



Multiple 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

Current Recommendations: 150 minutes per week

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

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

Sitting kills you sooner, unless you exercise

- Average Adult = 55% of their day engaged in sedentary pursuits

- 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.
- 13 studies of sitting time and activity levels: sitting for more than 8 hours a day with no physical activity had a risk of dying similar to the risks of dying posed by obesity and smoking (??).
- New analysis = small chance: an excess of around 33 CVD deaths, 27 cancer deaths, and 610 incident cases of diabetes per 100 000 persons per year in people with the highest volumes of sitting. Not same effect as smoking.
- Analysis of data from more than 1 million people found that 60 to 75 minutes of moderately intense physical activity a day countered the effects of too much sitting.

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 debate

- 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??

- Many epi studies: Drinking one drink per day correlates with positive health outcomes

- Drinking more increases heart disease.
- Alcohol use in any amount increases cancer risk.

- If you drink 5 drinks in 2 hours on any day of the week, you are alcoholic! Heavy drinking increases the risk for death by 31% to 54%.
- 2018: n = all hospital admissions in France; 31 million people -- Heavy alcohol consumption is a major risk factor for all types of dementia, but particularly early-onset dementia.

- Lothian Cohort: Alcohol is confound – no effect on old age cognition; it is a general effect of social class (Use of alcohol correlated with higher incomes, education levels, lower rates of smoking, lower rates of mental illness and better access to health care.
- Rather than gaining cognitive benefit from drinking wine when they were older, “people who drank more were already likely to be smart”

No amount of alcohol is good for you

- 2019 study: Moderate drinking of about one or two drinks a day does not protect against stroke; One or two drinks a day is increasing stroke risk by about 10-15%,
- 2018 Lancet: Alcohol, led to 2.8 million deaths in 2016. It was the leading risk factor for premature mortality and disability in the 15 to 49 age group, accounting for 20% of deaths. “Our results show that the safest level of drinking is none.” 27% of cancer deaths in women and 19% in men over 50 were linked to their drinking habits.
- Alcohol use — whether light, moderate or heavy — increases cancer risk.
- 5.5% of global cancer incidence and 5.8% of cancer deaths can be attributed to alcohol.

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:

What makes a good life: social relationships

- Today's Millennials: 80% want to be rich; 50% want to be famous
- Harvard Study of Adult Development: longest developmental study – n =724 men; 60 still alive (in 90s); and continued study of 2000 of their children
- 1938: 2 groups – aged 19: Harvard sophomores (J. F. Kennedy's class) & impoverished Boston adolescents; for 75 years; Boston men ask "why do you want to study me?; Harvard men never asked that; 12 y ago, wives were asked to join; "It's about time!"
- Fundamental finding: good relationships keep us happier & healthier - 3 lessons
  - Social relationships are good for us & loneliness kills – the social are happier, healthier, live longer; opposite for lonely

Social relationships predict longer life

- Quality of relationship is important –
  - constant conflict is bad
  - no affection is toxic & worse than divorce
  - warm relationship is protective; relationship satisfaction at age 50 was best predictor of health at age 80; experience of pain is related to relationship satisfaction

- Good relationships protect our brain; decreases risk for Major NCD & increases longevity (= stopping 2 packs of cigarettes per day effect); Secure attachment (being able to count on the other, even if you bicker a lot) predicts better memory longer

- Adults with adequate social relationships have a 50% greater likelihood of living longer. The greater the extent of the relationships, the lower the risk of mortality.

J. Holt-Lunstad et al., PLoS Med, 2010

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

Get a Pet, if you can afford to

- 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.

Do any of following (or see my website)

- Visit a museum
- Memorize a song
- Exercise your peripheral vision
- Learn a new musical instrument
- Do jigsaw puzzles
- Turn down the TV (listen better)
- Throw & catch a ball; learn to juggle
- Increase difficulty level of crossword/sudoku
- Use your other hand
- Walk on cobblestones
- Learn a new dance or a new language

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 MD, radiologist 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.

- The capacity to enjoy and respond to music outlasts many other cognitive functions; even after spontaneous speech has become difficult, many people can still sing lyrics to songs learned long ago. Even in advanced disease, when happiness is hard to come by, people can respond to music they love.
- Listen to the music you love. Make a playlist of that music.

Hanna-Pladdy & MacKay, 2011.

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

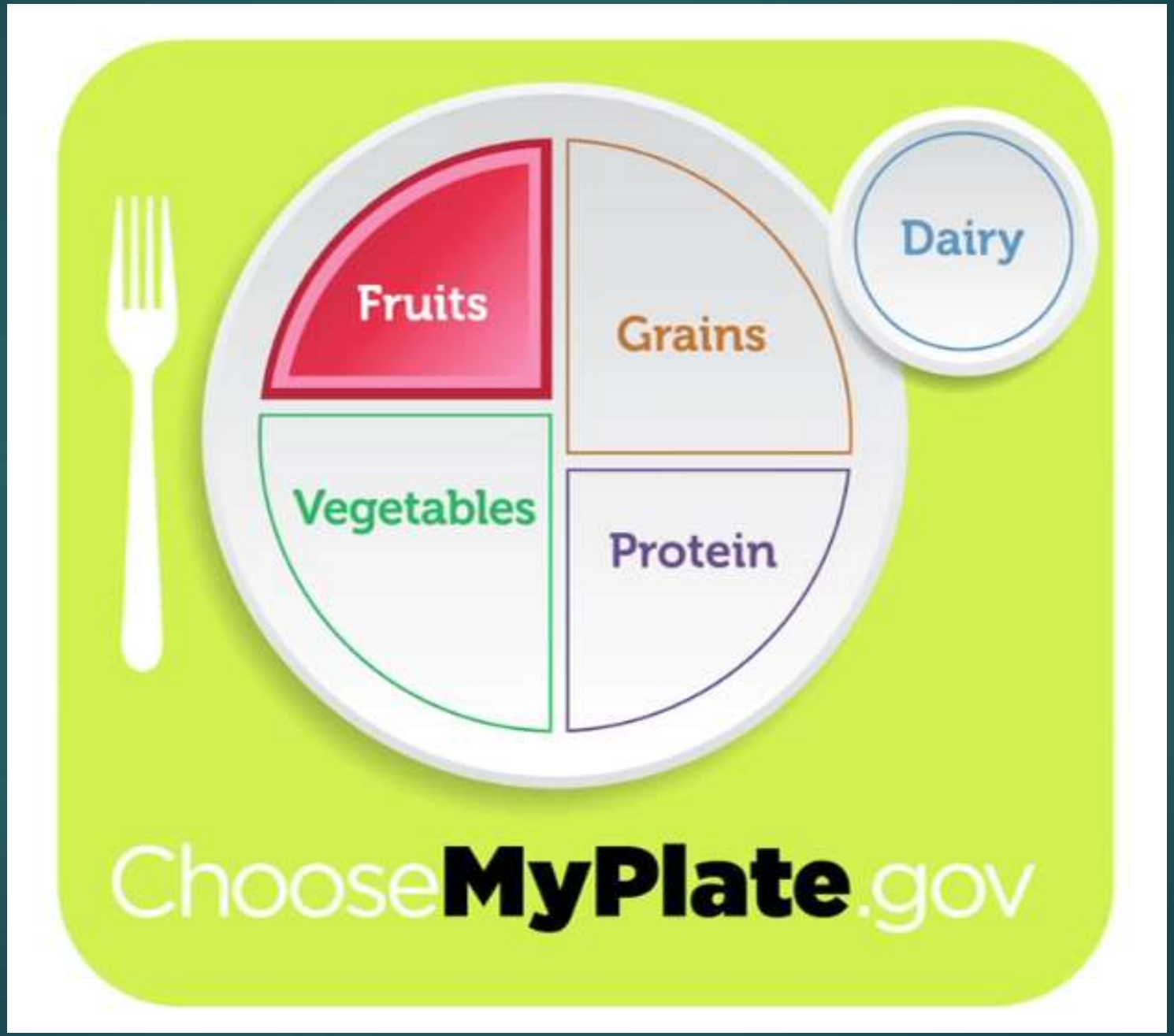
- Mediterranean diet/MIND-DASH:
  - high plant foods (vegetables, fruits, legumes, and cereals);
  - high intake of olive/vegetable oil; low intake of saturated fat, butter;
  - moderate intake of fish and poultry twice a week
  - red meat to no more than a few times a month; low dairy products; using 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

2018 study: Biomarker based nutrients = better brain function

- Higher levels of several key nutrients in the blood correlate with more efficient brain connectivity and performance on cognitive tests in healthy older adults.
- Studied 32 key nutrients in the Mediterranean diet
- Omega-3 fatty acids (in fish, walnuts and Brussels sprouts); omega-6 fatty acids (in flaxseed, pumpkin seeds, pine nuts and pistachios); lycopene (red pigment in tomatoes, watermelon, etc.); alpha- and beta-carotenoids (in sweet potatoes and carrots); riboflavin, folate, and vitamins B and D.
- Higher levels of omega-3 fatty acids paralleled the positive relationship between a healthy frontoparietal network and general intelligence.


Fruits
Grains
Dairy
Vegetables
Protein
ChooseMyPlate.gov

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 (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

- 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

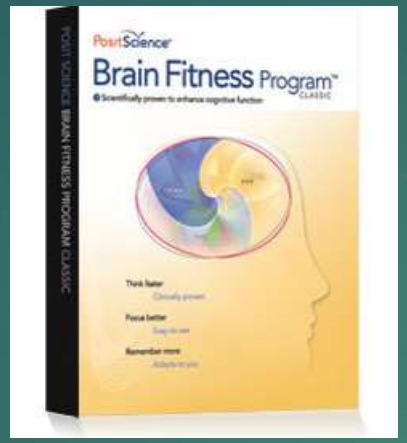
Brasky et al., JNCI, 2013

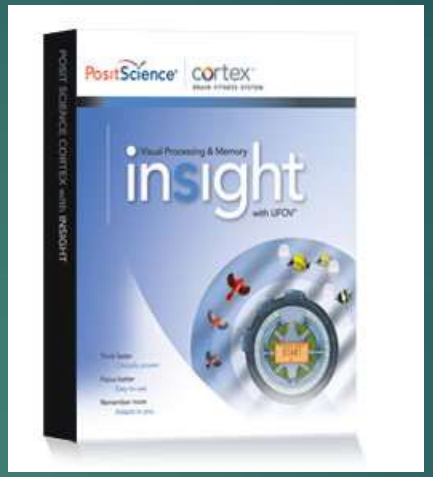
Tip #23: Keep learning

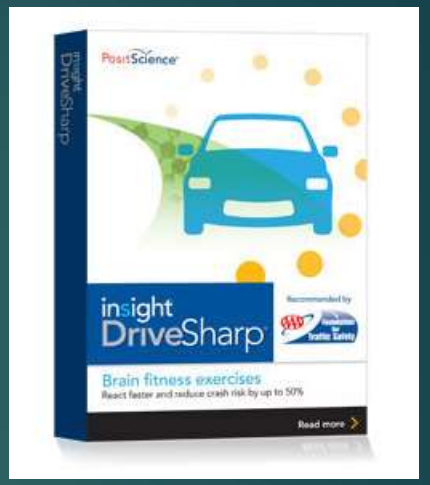
- Hope Levy SFCC classes
- Local Universities:
  - Fromm Institute at USF
  - OLLI at SF State
  - CLIR
  - OSHER
- Road Scholars
- Lifelong Learning Institutes
- Local Senior Centers
- SeniorNet OASIS Institutes (volunteer)
- Shepherd’s Centers of America
- Senior Community Service Employment Program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

Neurobics: Brain Training Computer Products (No endorsement Implied)

NeuroActive





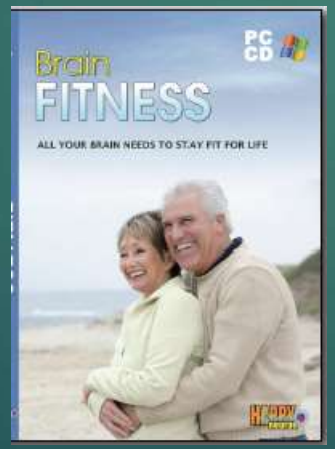


Posit Science

CogniFit
PERSONAL COACH

MindFit
BRAIN POWER FITNESS

Mindfit



Happy Neuron

Lumosity

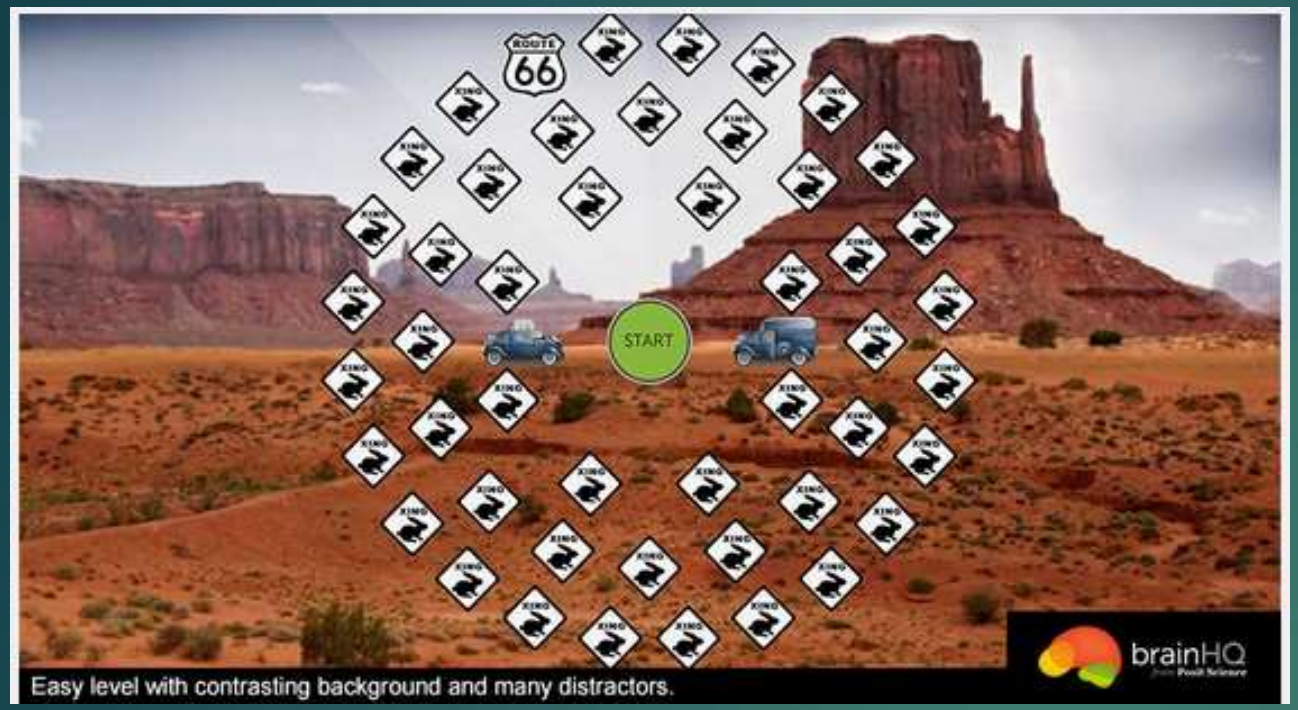
Brain Websites

- 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

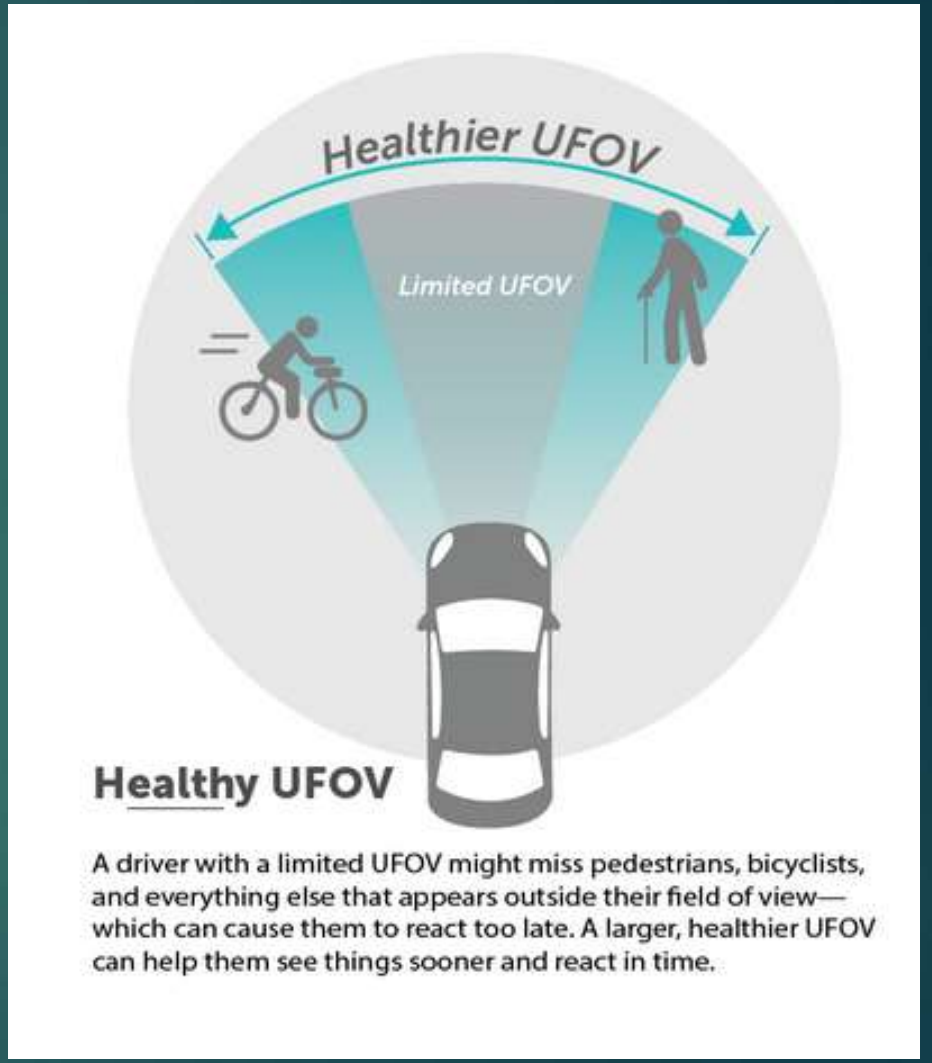
Digital Brain Fitness tools: mobile apps, websites

- 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



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

Speed of processing training results in lower risk of dementia

- 2017: 2,800 initially normal older adults for a decade — brain-training intervention known as "speed-of-processing training" reduced participants' risk of dementia by 29 percent.
- Advanced Cognitive Training in Vital Elderly (ACTIVE) study: Up to 10 training sessions (ten 60–75 minute sessions) were delivered over 6 weeks with up to four sessions of booster training delivered at 11 months and a second set of up to four booster sessions at 35 months; 70% white females aged 73 at baseline; Useful Field of View (BrainHQ, DoubleDecision game)
- Memory and reasoning training did not reduce dementia.
- Each additional speed training session was associated with a 10% lower hazard for dementia
- first study to show that any intervention (behavioral or pharmacologic) can lower risk of dementia.

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 ACTIVE study is lone standout

- 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

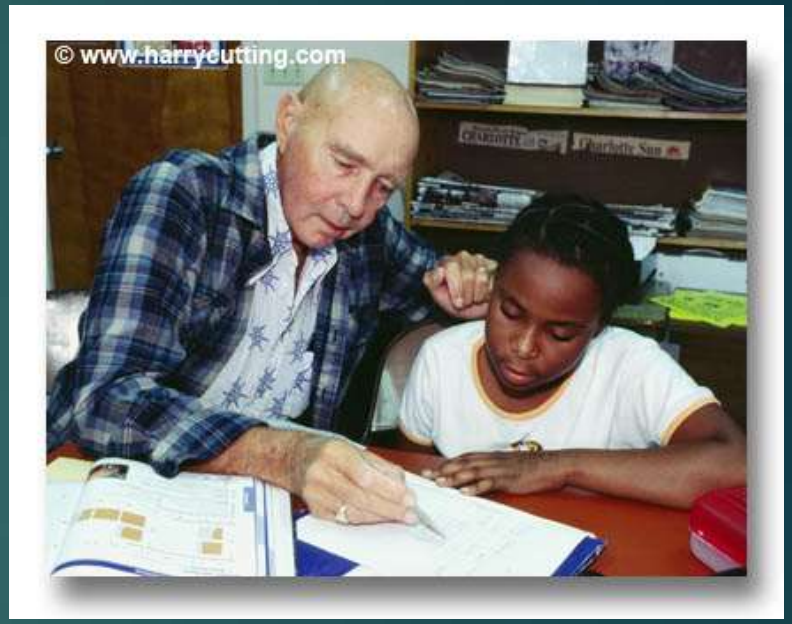
- Purpose in life (psychological tendency to derive meaning from life's experiences and possess a sense of intentionality and goal directedness)

- 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 who would benefit from hearing aids have ever used one (not medically covered and expensive)

- 30% higher risk of dementia with hearing loss: 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!!

Summary: Prevention/Rx Strategies

- No evidence for current AD medications

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

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

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

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

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

Five lifestyle behaviors are key to stopping Alzheimer's

- 2019 Rush Study: n = 2765 over 6 years; 608 developed AD; British study: n = 196,383 over 6 years; 668 developed AD; European sample
- Holding off Alzheimer's: you need a combination of lifestyle habits
- Do 4 out of 5 behaviors:
  - regular exercise (moderate to vigorous, 150 minutes per week)
  - cognitive stimulation 2 or 3 x week (reading the newspaper, visiting the library or playing games such as chess and checkers)
  - brain-healthy diet (MIND diet (Mediterranean-DASH diet)) (leafy green vegetables, beans, olive oil, nuts, poultry; less meat, sweets, fried food)
  - not smoking
  - light to moderate alcohol consumption (1 glass of wine per day)

Five lifestyle behaviors are key to stopping Alzheimer's

- People with high genetic risk and poor health habits are 3 x more likely to develop dementia (1.8% vs 0.6%)
- Over a 6-year period, 60% lower risk of developing Alzheimer's dementia if did 4 of 5 behaviors than those who did 1 or none of behaviors
- In British study, those with APOe4, 50 percent less AD
- Making just one more healthy choice decreased their chance of Alzheimer's by an additional 27 percent.
- Living a healthy lifestyle is associated with a reduced dementia risk, regardless of genetic risk

Five lifestyle behaviors are key to stopping Alzheimer's

- Living a healthy lifestyle is associated with a reduced dementia risk, regardless of genetic risk
- As with heart disease, combating dementia will probably require a "cocktail" approach combining drugs and lifestyle changes.
- Recommendation: consume more leafy green vegetables, replace red meat with poultry, and avoid fried food; also, walk to the grocery store and read books.

30-year mortality study: 5 tips for living longer – usual suspects

- 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 (18-25),
  - 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
- 82% less likely to die from cardiovascular disease and 65% less likely to die from cancer
- Dose-response relationship between each individual healthy lifestyle behavior and a reduced risk of early death

Yanping Li, et al., 2018

Lancet 2018 Recommendations: 9 factors
If we do the following, we can decrease dementia by 35%

- Using population attributable fractions (PAF), the authors estimate that as much as 35% of dementia cases could be prevented by targeting nine modifiable risk factors. But ? of causality.
- 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

Livingston G., et al., 2017

World Health Organization 2019: Good heart, good brain

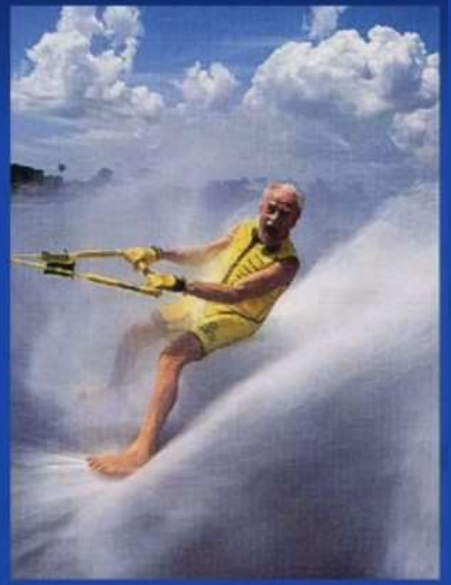
Risk reduction of cognitive decline and dementia

- * Exercise: 150 minutes/week
- * Mediterranean diet
- * Stop Smoking (#1 cause of death globally)
- Reduce Alcohol consumption: (1-women; 2-men, per day)
- Engage in cognitive training
- Be social engaged
- Maintain a normal BMI/weight: (BMI under 25)
- Treat hypertension, high cholesterol, diabetes, depression
- Wear hearing aides
- Don’t use supplements: (B, E, multi vitamins, etc.)

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.”
- Treat 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 Healthy Lifestyle

I. Choose thy parents wisely (For brain genes & IQ)
II. Exercise daily.
III. Minimize risk factors for cerebrovascular disease (HTN, Hyperlipidemia, DM, overweight, smoking)
IV. Eat a Mediterranean Diet
V. Maintain intellectual engagement throughout life
VI. Stay socially engaged with others.
VII. Get sufficiently good quality sleep
VIII. Make sure you have good glasses and hearing aides.
IX. Manage your stress effectively
X. Skip the supplements and buy some good walking shoes.

Brain Fitness by Charlie Vella

- On S Drive:
- 24-page Brain Fitness summary and recommendations by Charlie Vella
- WHO dementia reduction recommendations

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

Exercise

Interact with your friends

Laugh!

Here he is!

Politicians continuing to discuss global warming

Isaac Cordal

George Bernard Shaw

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

we grow old because we stop playing."

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/

As the Vulcans say…

Live long and prosper!

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