Understanding Dementia And Alzheimer's Disease

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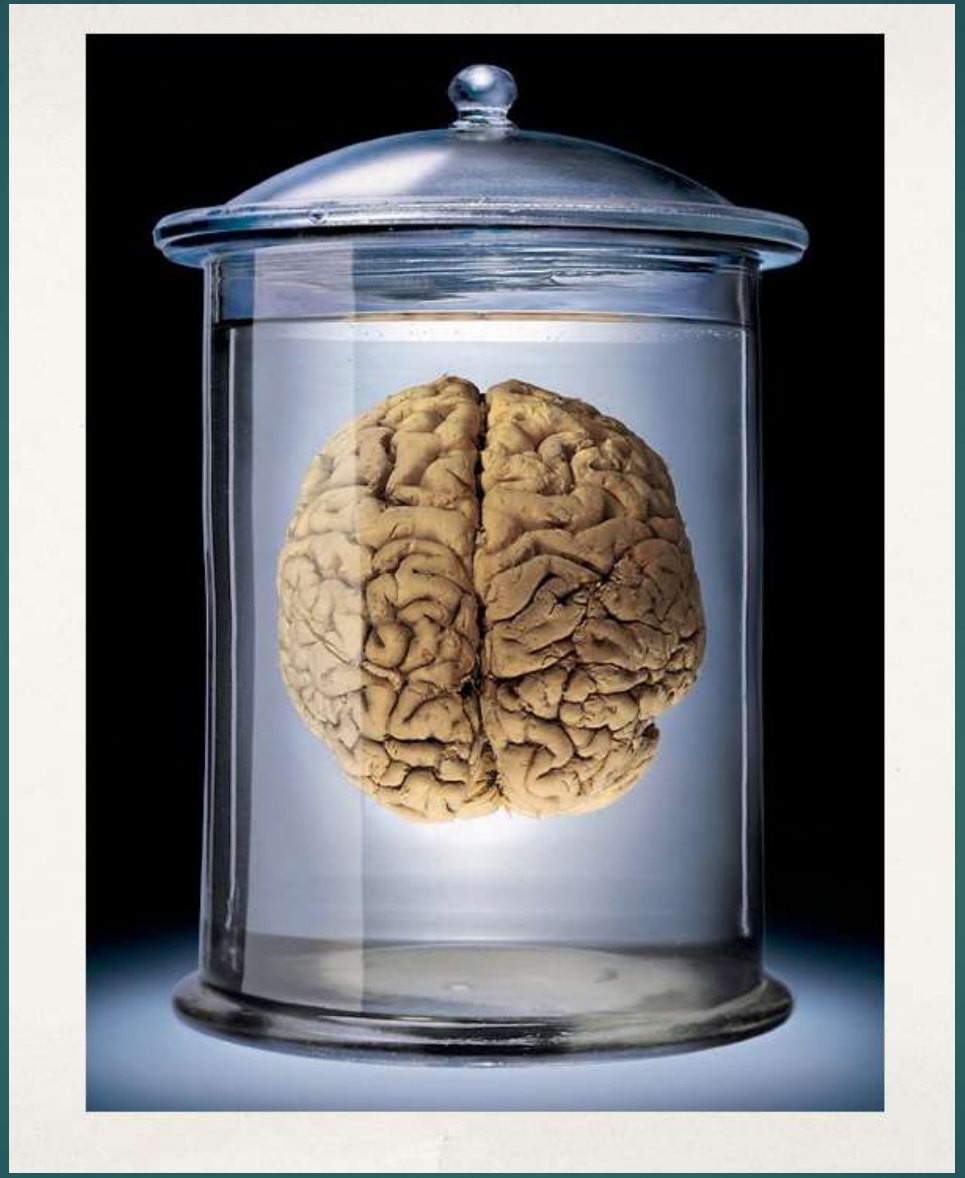
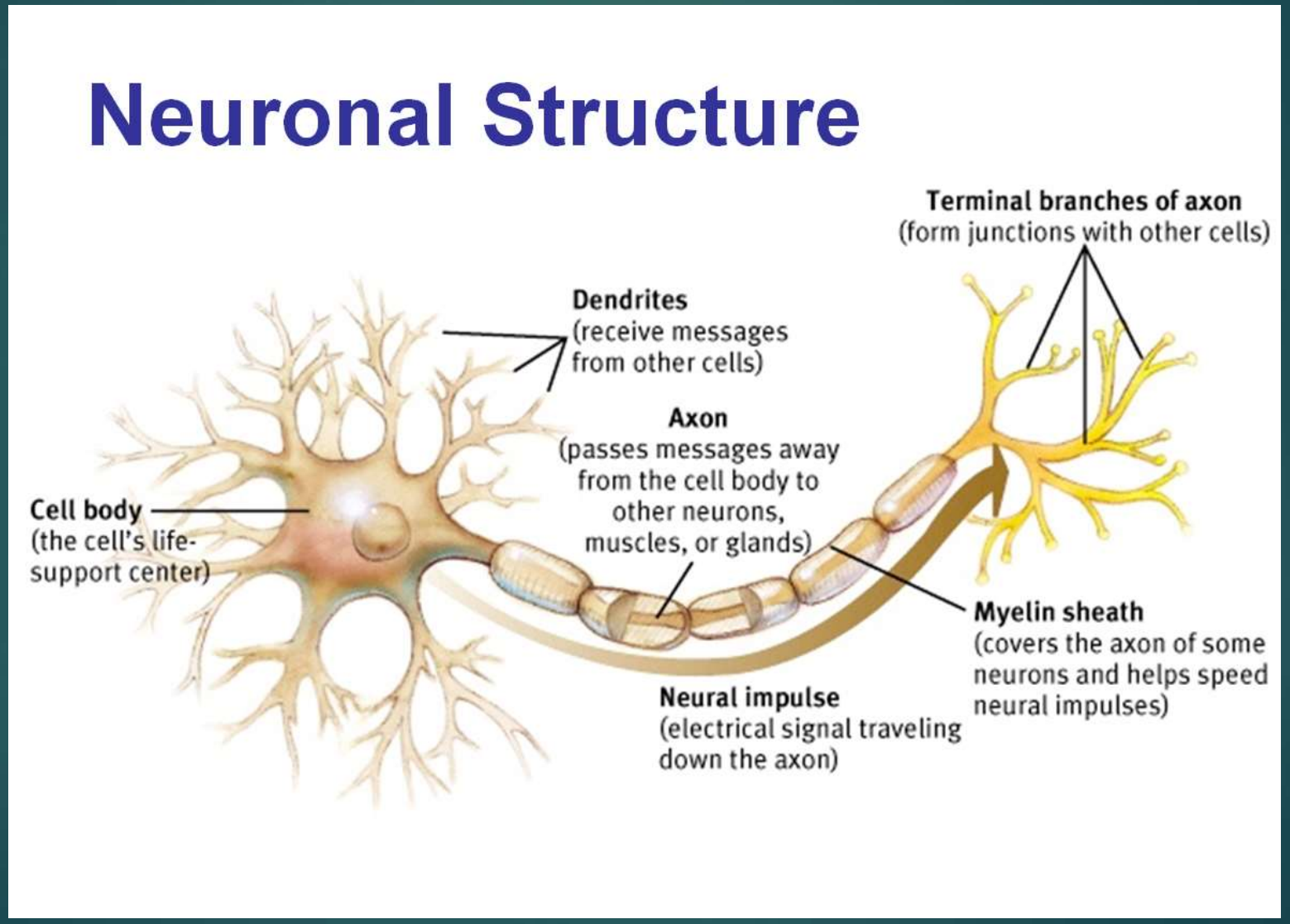
The Brain

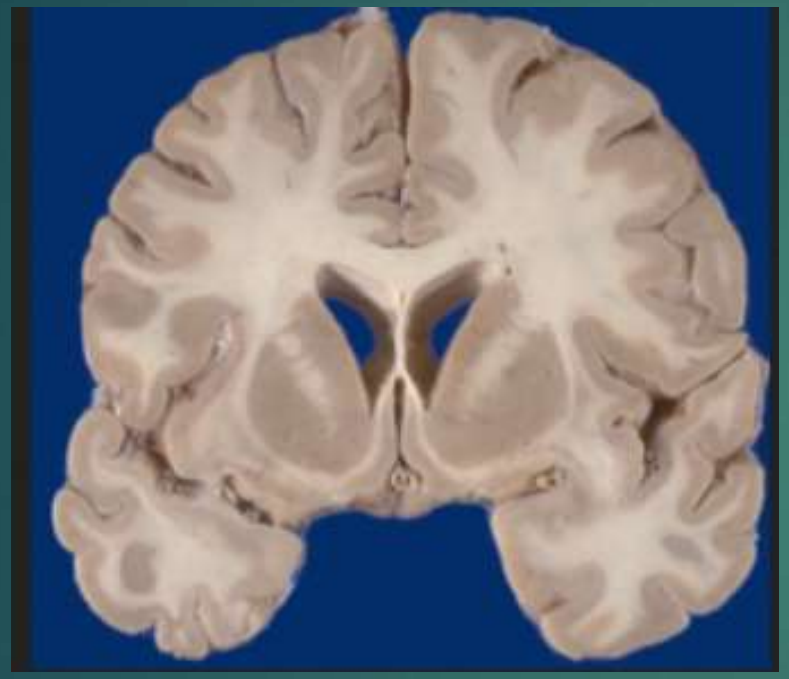


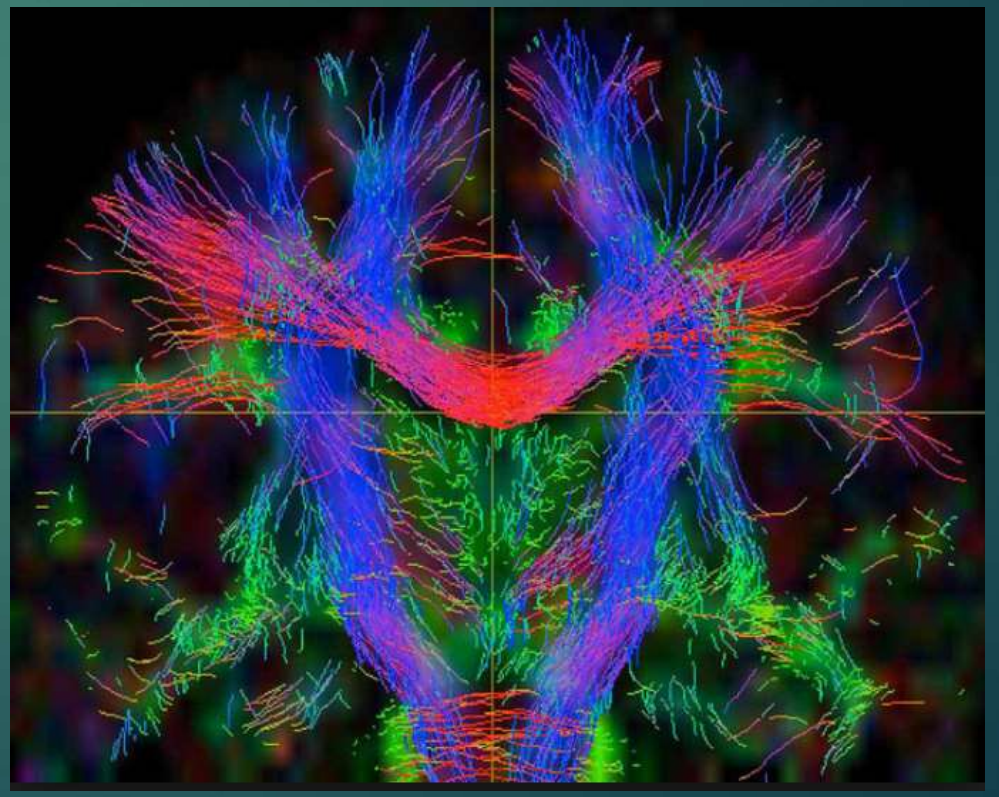
3 pounds: 180 billion brain cells

Neuron


Neuronal Structure
Terminal branches of axon
(form junctions with other cells)
Dendrites
(receive messages
from other cells)
Axon
(passes messages away
from the cell body to
other neurons,
muscles, or glands)
Cell body
(the cell's life-
support center)
Myelin sheath
(covers the axon of some
neurons and helps speed
neural impulses)
Neural impulse
(electrical signal traveling
down the axon)

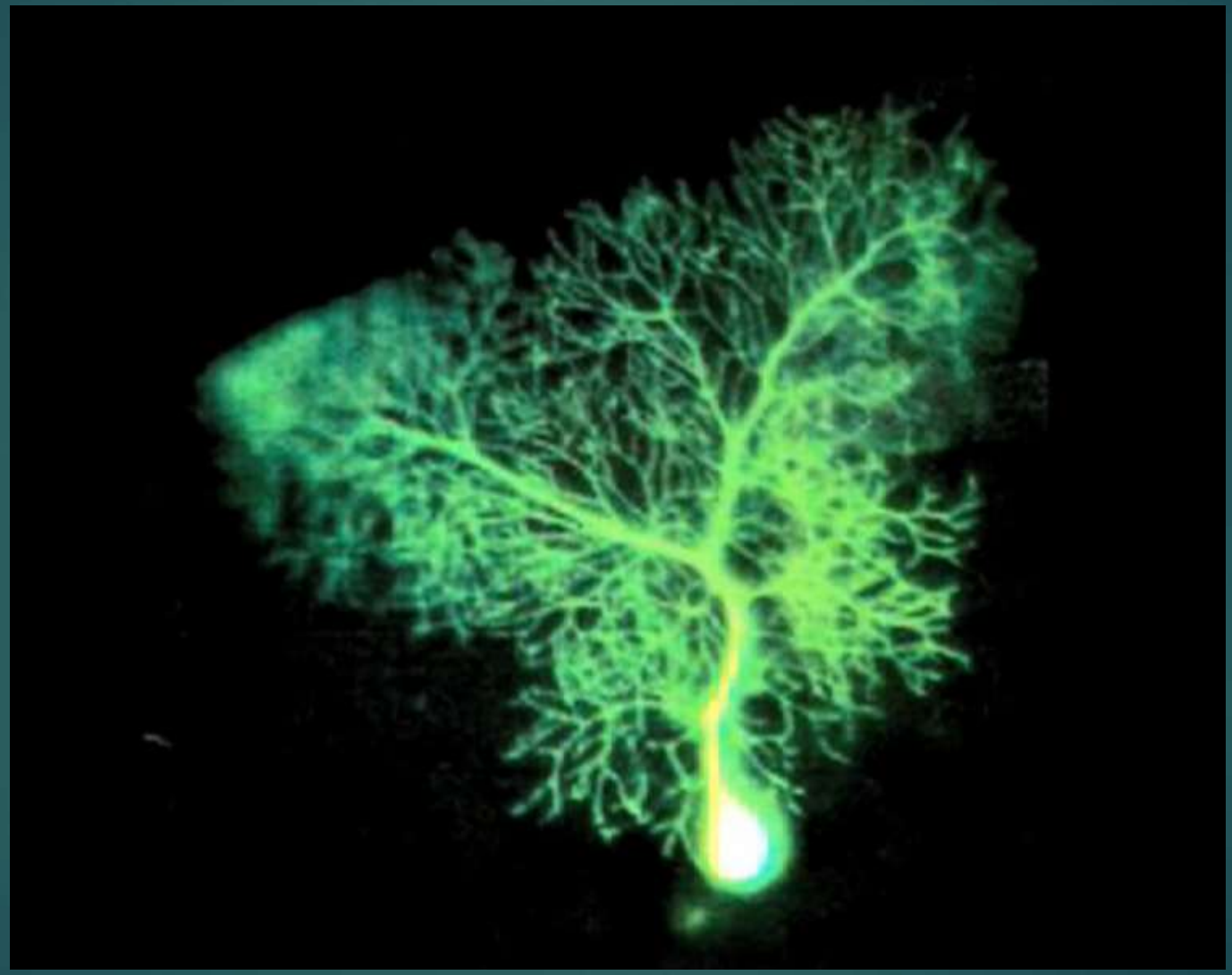
White Matter: Insulation on your neuronal axons





The Internet of your brain:
How fast you process information

1 Neuron: 10,000 connections



Brain Changes with Aging

- Brains shrink 2 % per decade; especially in frontal and hippocampal region
- Cells/dendrites die – 150 grams loss
- Neurotransmitters change – lose half of dopamine
- Increase in beta amyloid plaques
- Vascular abnormality & beta amyloid deposition are tied together
- But great variability in aging in brain; not wholesale neuron loss

The Normal Elderly

Three Major Longitudinal Studies

- K. Warner Schaie and Sherry Willis's Seattle Longitudinal Study
- Whitehall Study of British Civil Servants
- The Nun Study

Normal Age-Related Changes in Cognitive Abilities

- K. Warner Schaie and Sherry Willis's Seattle Longitudinal Study:

- Cognitive better from age 40-65 than in our 20s for:
  - Vocabulary
  - Verbal Memory
  - Spatial Orientation
  - Inductive reasoning

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 ↓ ↓ ↓

Tale of Two Computers: Speed ↓↓↓
Older brain reverts to 1982 speed

1982 IBM Computer
Intel 8088 chip @ 4.77 MHz

Lenovo Thinkpad W530
Intel Core i7-3630QM @ 2.40 GHz
2400 x faster

Normal Age-Related Changes 2

- Cognitively better with age if
  - higher education
  - higher occupation
  - better cardiovascular status

- Spouse's cognitive ability was protective of AD risk: lower IQ spouse gets the benefit, merges toward higher

Whitehall Study, 2012: Cognitive decline begins at age 45

- 10,308 (67% men) British civil servants
- Evidence of cognitive decline at all ages between 45 and 70
- All cognitive scores (reasoning, memory, verbal fluency, vocabulary), except vocabulary, declined in all five age categories (ages 45-49, 50-54, 55-59, 60-64, and 65-70)

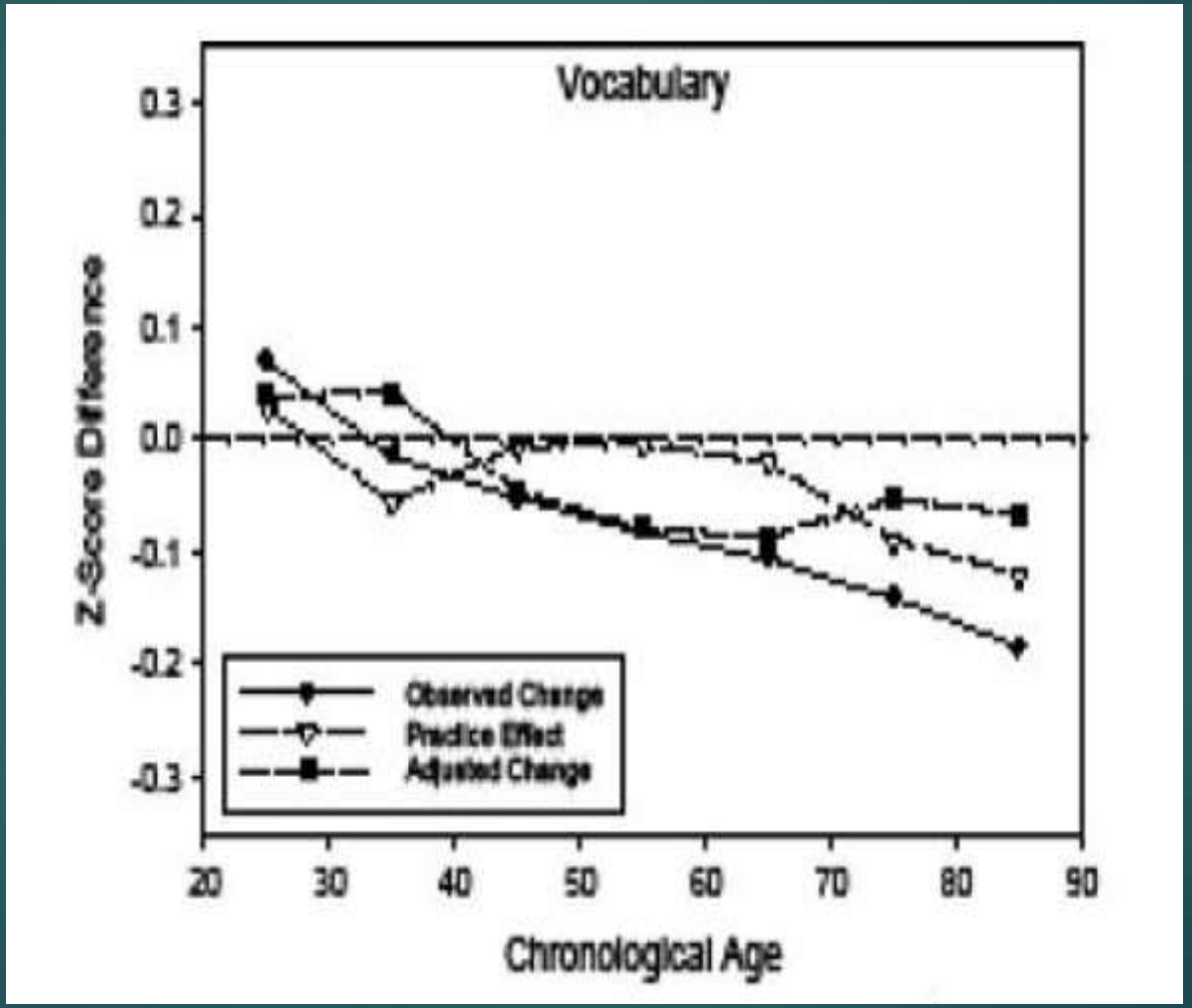
Whitehall Conclusions:
Take care of your heart

- Importance of healthy lifestyles and lowering 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

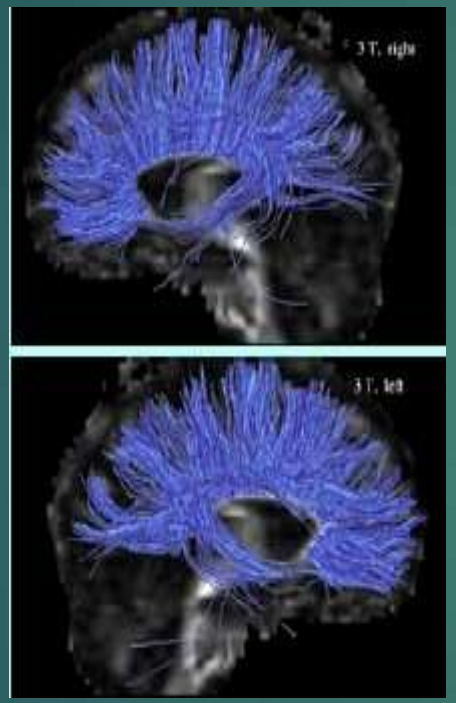
Language

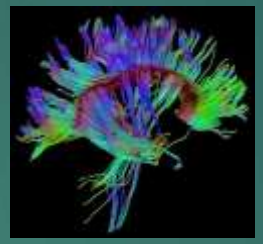
- Advise to Post Docs on Hospital Consults: Do not necessarily believe what patients, who want to go home, tell you
- Language functions are well preserved in elderly
- Vocabulary continues to increase (or may decline slightly)
- Word finding declines (longer to search; due to processing speed)

Vocabulary relatively intact



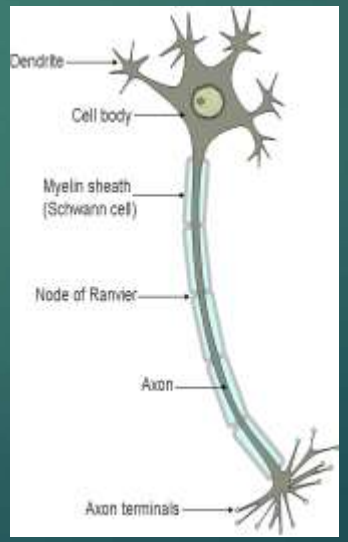
Older are Centrally Slowed: Processing Speed Decreases



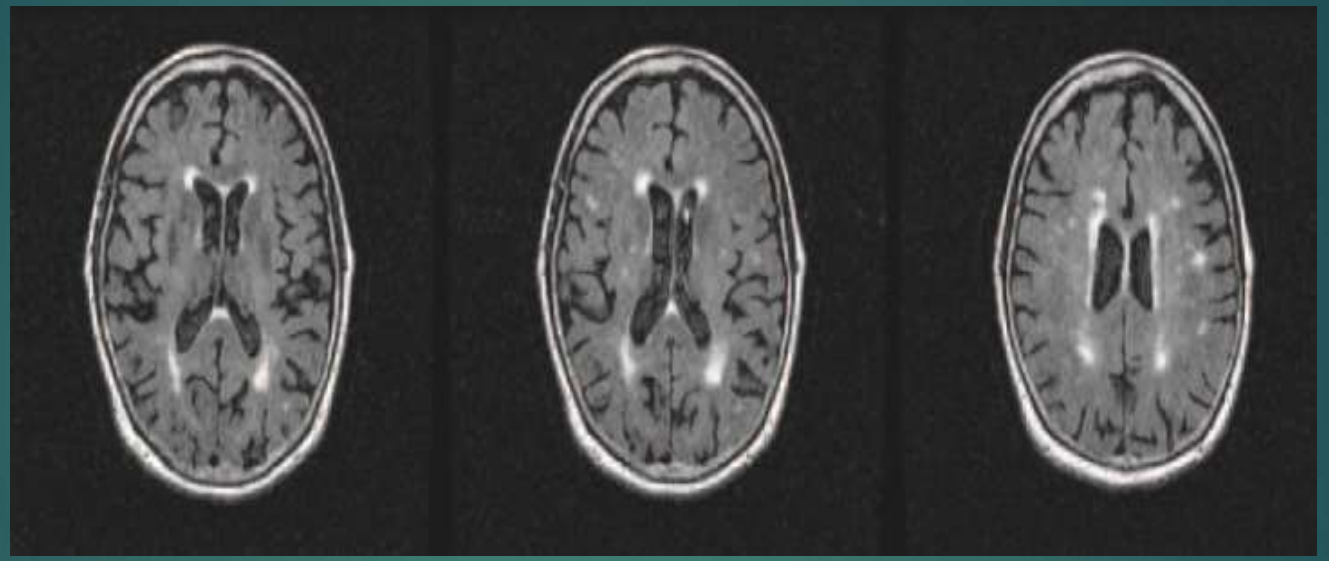


Diffuse Tensor Images of axonal tracts

One of reasons naming ability decreases



White Matter Hyperintensities on MRIs: Small blood vessel damage



Processing speed declines as white matter hyperintensities increase

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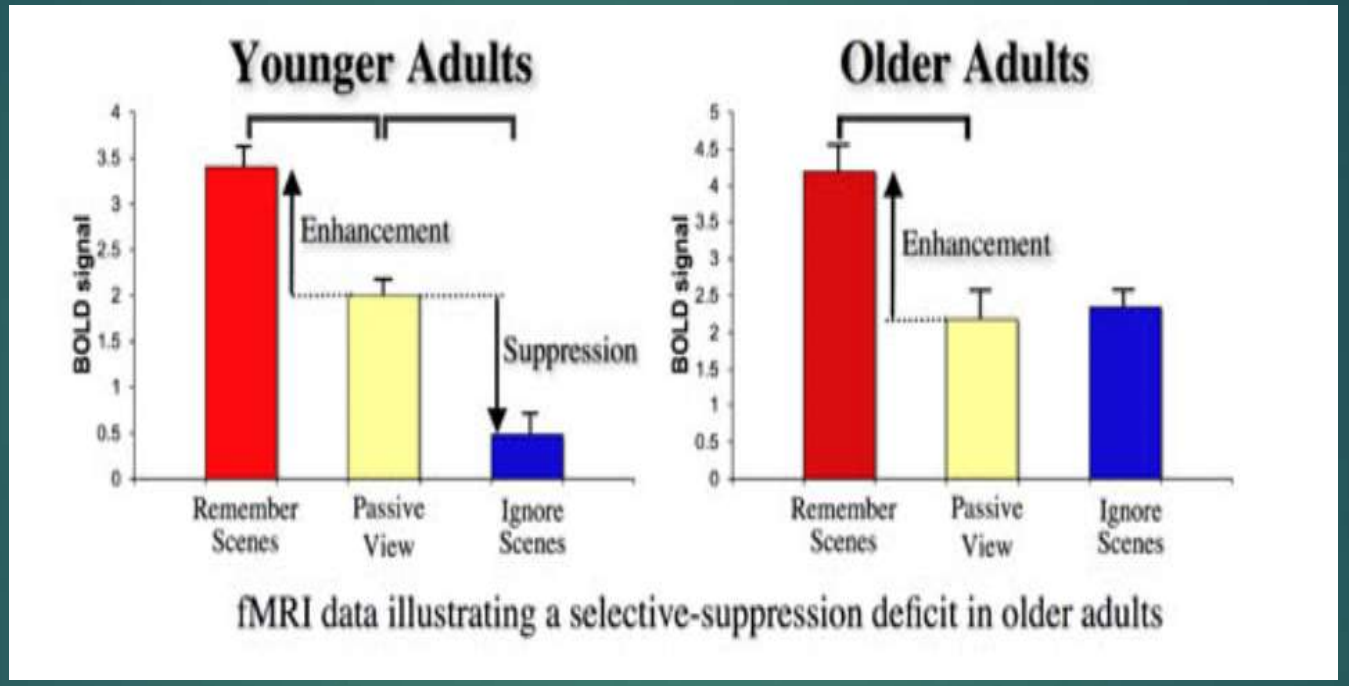
DeCarli, et al., 2005

Samuel Johnson

“The true art of memory is the art of attention”

Ninety percent of remembering is paying attention

Older Adults are more distractible



fMRI data illustrating a selective-suppression deficit in older adults

While healthy older adults (above 60 y.o.) were as effective at enhancing activity for relevant information in visual brain regions as young adults, they were unable to successfully suppress activity for irrelevant information;

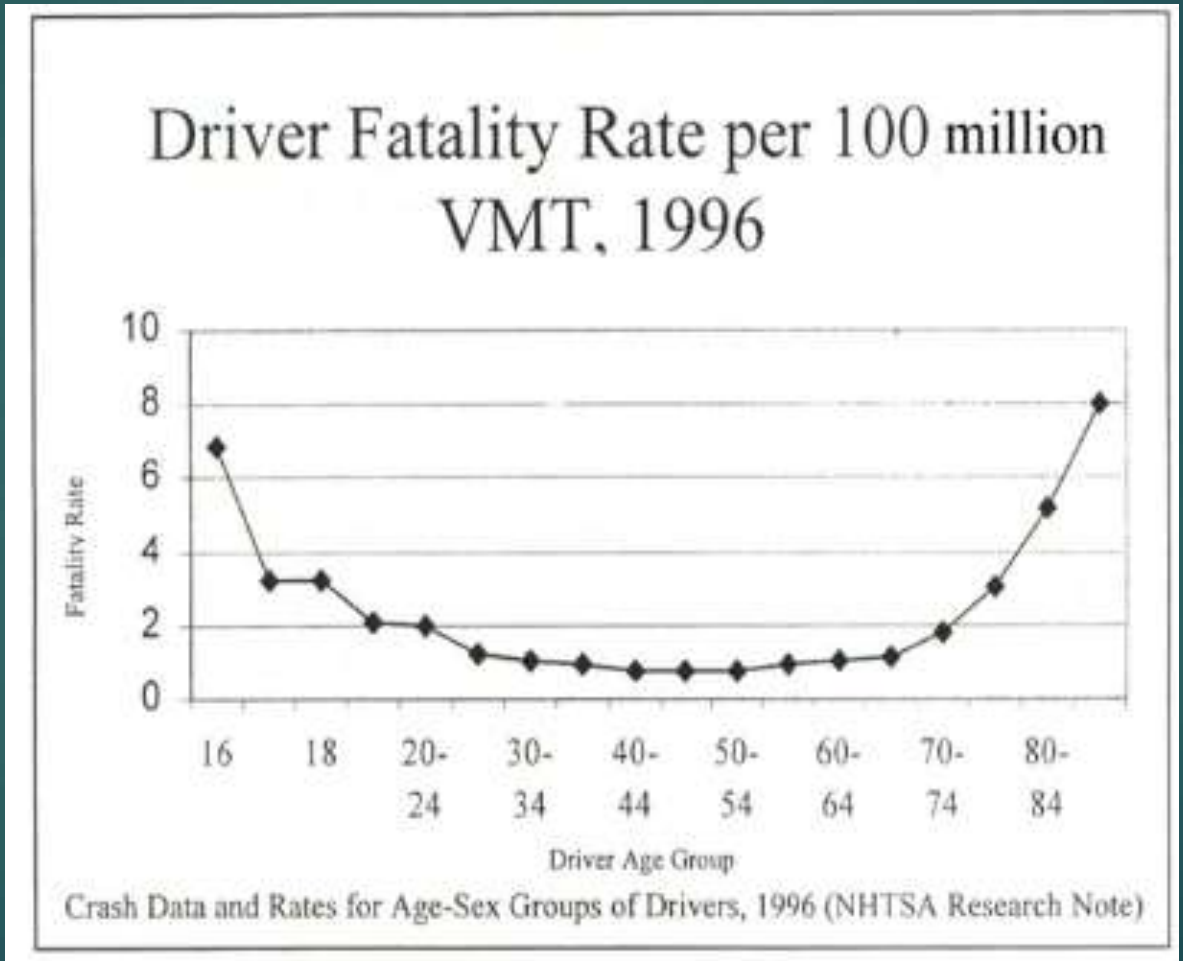
Some older have normal suppression; are less distractible.

Cautionary tale…

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

  - Not screaming like the other passengers in his car.

Driving: Seniors are more fatal than Teenagers



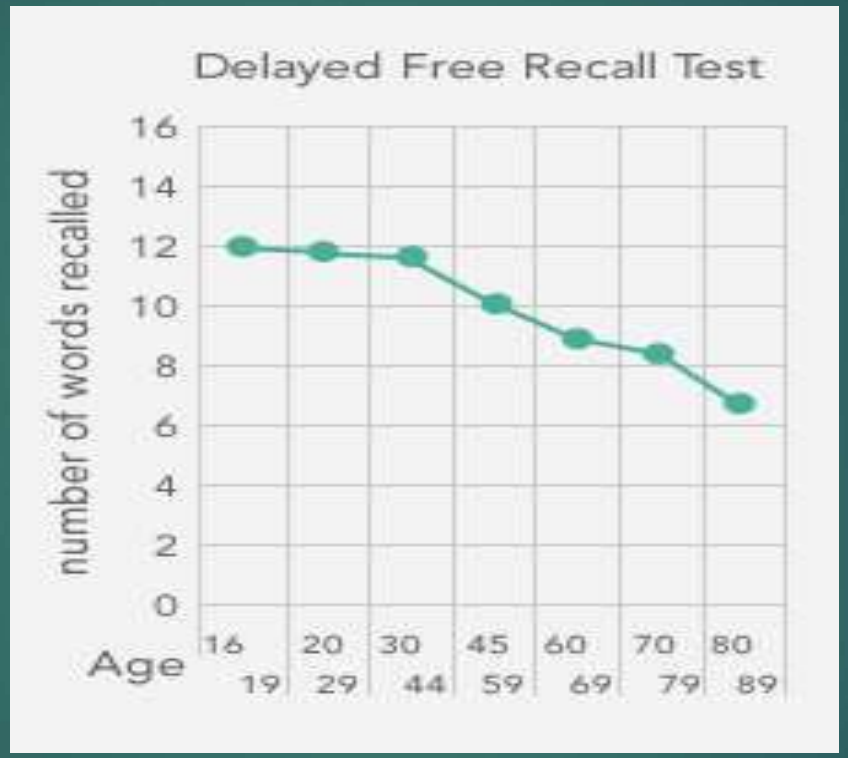
Teens: Impulsivity & Alcohol ↑↑

Seniors: Sensory & Processing Speed Declines

Memory: 2 Women

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

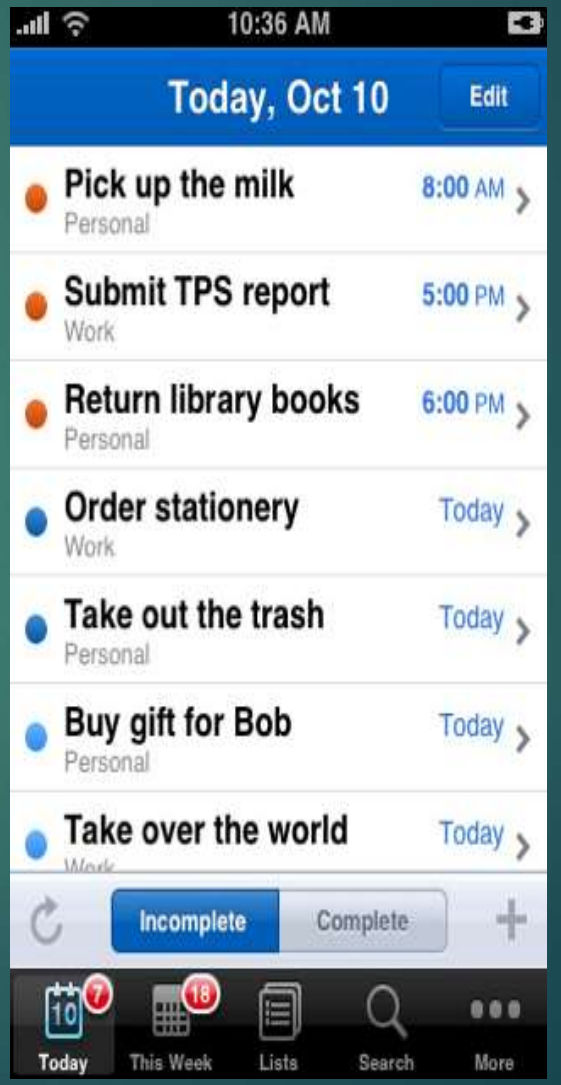
Decline in Spontaneous Verbal Free Recall:
12 items at age 20, 7 items at 80



Number of items learned in 1 attempt

But Prospective Memory remains normal in real world

- Remembering to remember
- Intention



Procedural Memory:

Remembering how to…

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

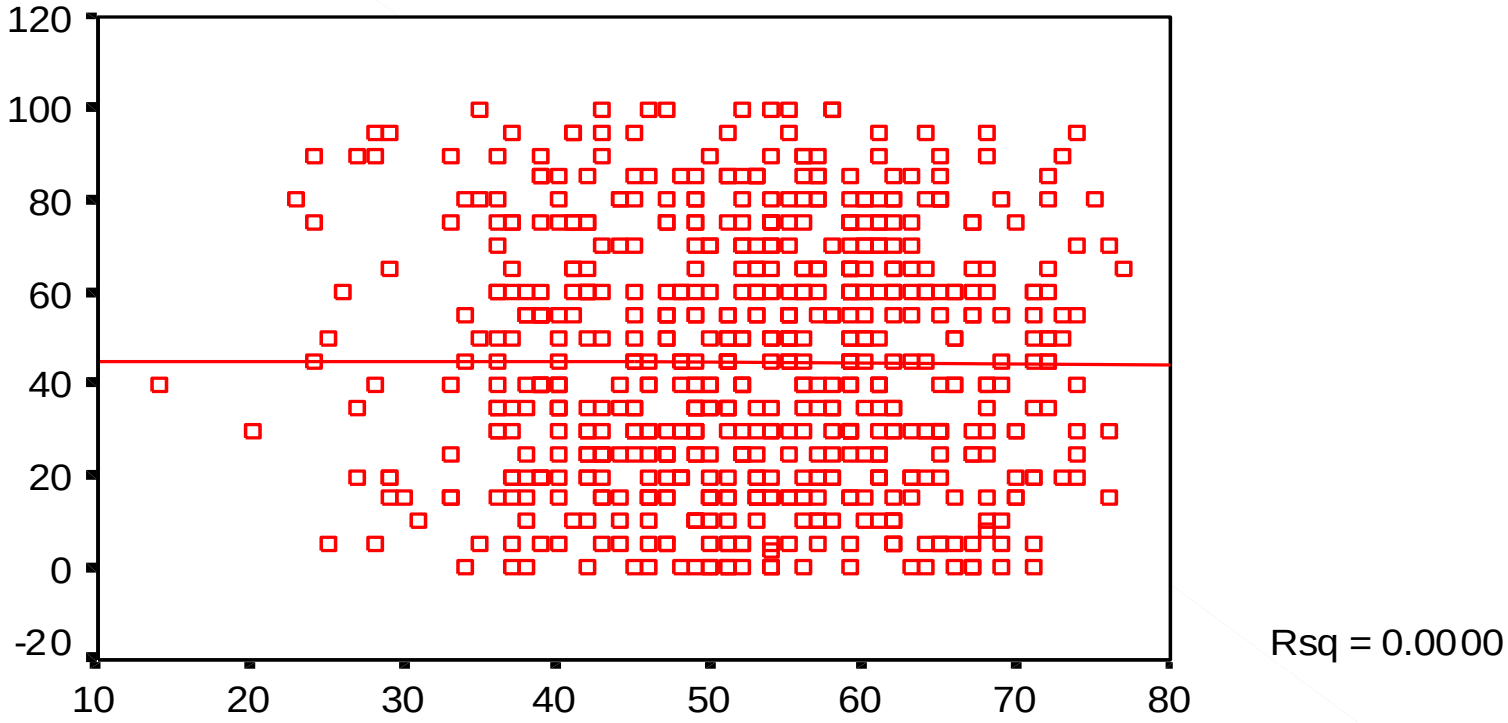
Coming Up Next:
Example of Procedural Memory

- Typewriting skills are procedural memory

Overlearned Memory

Verbal memory complaints versus verbal memory test scores

Zero correlation in 995 cases



Green, 2003

Normal Memory vs. Real Memory Deficit Types

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

Encoding Failure:
Tape recorder is off

- Tape recorder is off: no new input or output
- Poor spontaneous recall and recognition
- Cueing does not help
- Classic problem in Alzheimer's

Retrieval Failure:
Trouble finding your memory

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

All memory decline is caused by brain disease

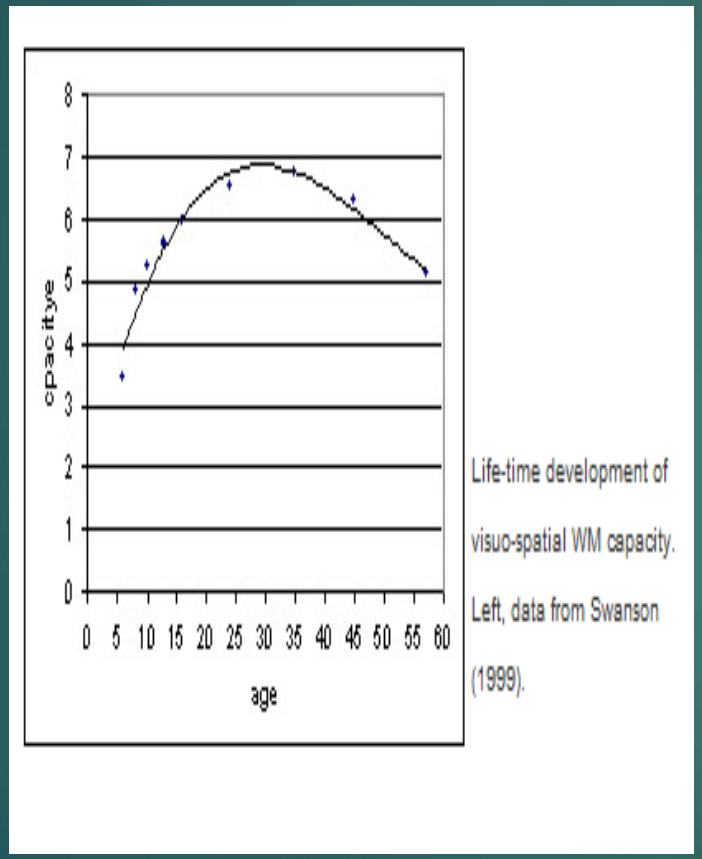
- Brain damage plays a role in virtually all late-life memory loss.
- Tangles, Lewy bodies, and stroke were all related to gradual memory decline. Almost no gradual decline was seen in the absence of tangles.
- Both Lewy bodies and stroke approximately doubled the rate of gradual memory decline.
- Memory decline tended to be gradual until speeding up in the last four to five years of life.

Bennett, 2013

Spatial Ability Declines

- Visual acuity declines with age
- Spatial abilities decline
  - Directions
  - Map reading
  - Longer processing time

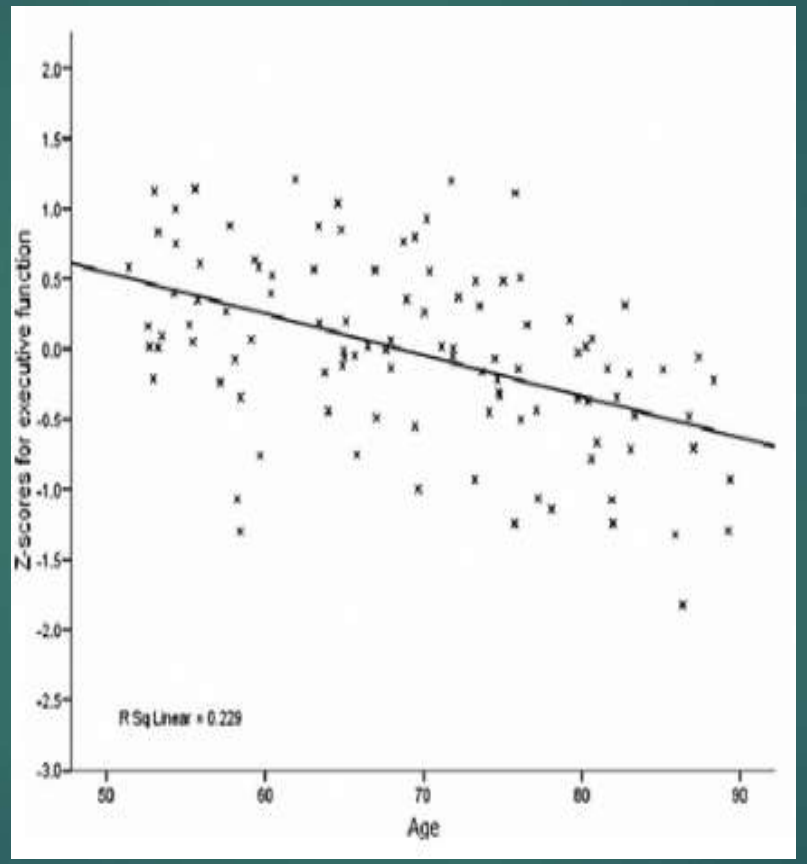
Working Memory (holding a phone number in mind) declines: 7 items down to 5 items



Life-time development of visuo-spatial WM capacity. Left, data from Swanson (1999).

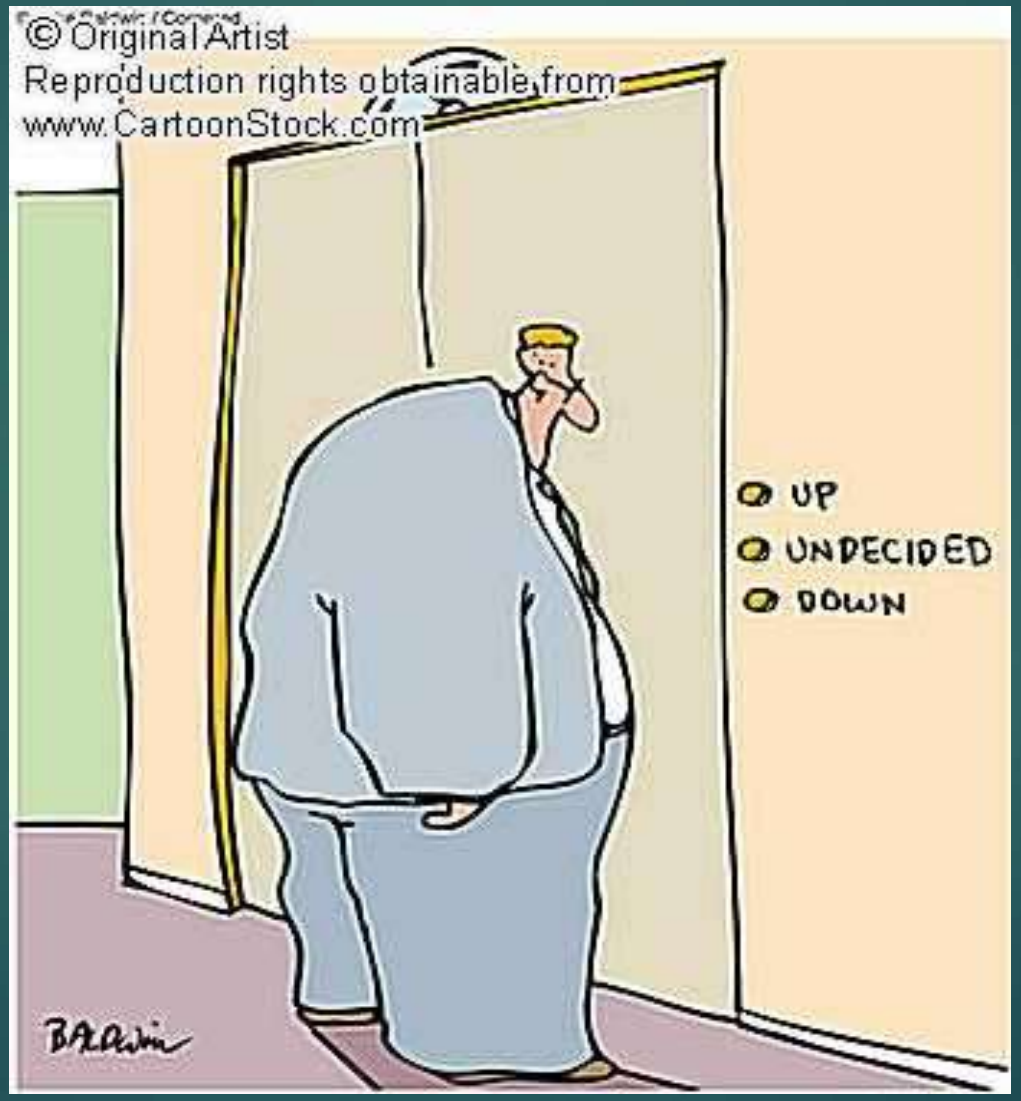
Need to us calculator for math

Executive Functioning (new problem solving, fluid IQ) declines by .5 σ



Mild decline in concept formation;
abstractions become more concrete

Decision Making



Executive Functioning

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

OK Normal Decision Making

- If free of disease that impairs thinking, people are just as good or even better at decision-making than someone younger.

- Healthy older adults show no decline in decision-making.

Executive Dysfunction in Major NCD

- Associated with impairment of prefrontal and frontal-subcortical circuits
- Executive ↓ can be independent of Memory ↓
- New changes in behavior:

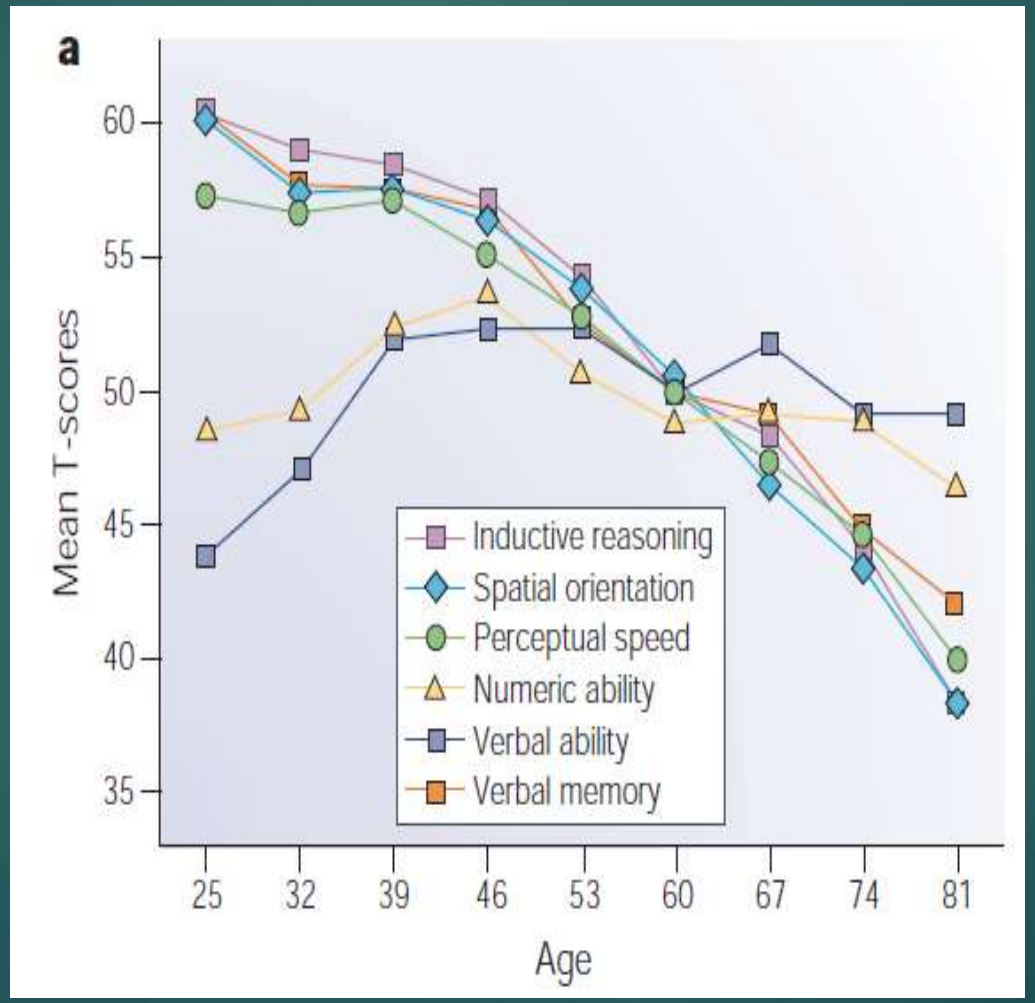
  personality changes, dysinhibition, hypomania, apathy

Executive Deficit Predicts:

- Functional autonomy decline: can't live independently
- Money management decline
- Medication management decline
- Poor geriatric orthopedic & stroke rehabilitation outcome

Seattle Long. Study: Normal Elderly

Verbal Ability ok vs. All Else ↓↓



Best preserved…

- Verbal ability
- Procedural/behavioral memory
- Prospective memory in naturalistic settings

Naming vs. Recognition

- What is name of this person?
- Princess Diana

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

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

- You cannot change your age or the genes you are born with.
- Dementia depends on lifestyle choices
- Santiago Ramon y Cajal: "Every man can, if he so desires, become the sculptor of his own brain."

Dear God,
My prayer for 2016 is for a fat bank account & a thin body.
Please don't mix these up like you did last year.

DSM – 5: Psychiatry's Bible

- No more "Dementia"
- New Dx: Neurocognitive Disorder (NCD), mild or major
- Focus on decline (rather than deficit) from a previous level of performance.
- Cognition, not Memory, central
- NCD: any form of cognitive decline, i.e. TBI

What is dementia (now Major Neurocognitive Disorder)?

Major NCD:

- Not a disease
- A diagnosis by a professional
- A significant cognitive decline, which interferes with ability to function independently
- Can be caused by a variety of illnesses and injuries, i.e. AD, TBI, over-medication, etc.
- Not the same as a neurological disease.

What is Neurodegeneration?

Neurodegenerative disease is an:

- Global deterioration of cognitive and emotional functions and personality.
- Due to an acquired neurodegenerative disease that kills neurons
- Can be caused by a number of neuropathological diseases, i.e. AD

Alzheimer's does not necessarily = Dementia/Major NCD

- Alzheimer's Disease = neurodegenerative disease due to increased beta amyloid & tau presence in your brain
- Dementia= cognitive decline due to anything that affects the brain (neuropathological disorder, TBI, medications, etc.)
- You do not have NCD while you develop Alzheimer's.
- Dementia is the most common final sign of Alzheimer's
- They are not same thing

The Nun Study: Souls to God, Brain to Lab

Sister Matthia Gores, age 104;
4378 students; knit mittens every day;
100 y no dementia;
Braak Stage IV

- David A. Snowdon, epidemiologist, U of Kentucky (*Aging with Grace)*
- 1986, N = 678, School Sisters of Notre Dame; 40 left
- Age 75-103, 85% teachers (85% B.A; 45% MA), half dementia/NCD

Snowdon et al, 2000

Which sentence from a 1 page autobiography, at age 22, predicts NCD/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.
- Difference depends on early exposure to vocabulary and reading comprehension

Read to your kids!

- Pre 4 language & SES:
- Quantity:
  - Low SES: 600 words spoken to child per day
  - High SES: 2100 words spoken to child per day (30 million word difference)
- Idea density depends on vocabulary & reading comprehension; best way to increase both is to read to your children starting early in life

Alzheimer disease without NCD: Sister Bernadette

- Sister Bernadette of Nun's Study:
  - Died at 85 of heart attack; MA, teacher for 40 years; double APOe4
  - One of brightest nuns; died "sharp as a tack" with no signs of dementia; MMSE = 30 of 30 at 3 last testings
  - On autopsy, had massive Alzheimer's pathology (Braak stage 6)
  - Like 30% of Braak stage 5 & 6 nuns
  - Had more grey matter than 90% of other nuns on original MRI
  - A testament to resistance to genetics and pathology of AD

- Despite lots of Beta amyloid, many nuns = no cog sxs; no NCD

Delaying/Preventing Cognitive Decline

- Cognitive Reserve Theory:
- Some people die with AD disease in their brain without ever showing dementia in life
- If we could delay clinical onset of AD, more people would die without showing dementia

Cognitive Reserve

- Cognitive Reserve: Difference between amount of brain pathology & actual cognitive function - can have more pathology before cognitive decline

- Protective Benefit if:
  - Bigger brain/head circumference (more neurons)
  - Higher IQ (more synaptic routes between neurons)
  - Higher education
  - Higher occupation (career complexity with social involvement)
  - More leisure activity
  - Higher literacy

- Cost: Once cognitive decline begins, brain decline goes faster

Lothian Study Scotland

Survivors who took IQ test of 1932

Brain you are born determines the brain with which you end

- Scottish Mental Survey: 1932 & 1947: all 160,000 (now 697) eleven year olds in Scotland took IQ test
- The brain you are born with determines how it will decline in old age: 50% of the difference at age 77 is explained by IQ at age 11 (genetic correlation of .62)
- Early IQ is more powerful predictor of good cognition at age 77 than: alcohol, coffee, BMI, diet, social & intellectual ability
- But lifestyle matters: those who did not smoke, were physically fit, bilingual, more educated had higher IQ scores at age 77

Dreary, et al.

Water tank hypothesis

- Best current science:

- The better your brain is to start with (due to good genes & early environment & 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: your lifestyle choices control the other 50%.

RANKING OF MOST-FEARED DISABLING EFFECTS – 14 country study

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

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

Brains don’t want to be have dementia

- Protective markers:
  - Education
  - Social networks
  - Conscientiousness
  - Harm avoidance
  - Sleep
  - Purpose in life
  - Late life cognitive activity

- Risk markers:
  - Depression
  - Loneliness
  - Anxiety
  - Neuroticism

Good News: Less Cognitive Impairment

- Health and Retirement Study (HRS), a national survey of older Americans: n = 11, 000: over age 70 in 2002 vs. over age 70 in 1993
- Cognitive impairment in this age group went down by 3.5 % between 1993 and 2002 -- from 12.2 percent to 8.7
- Due to more formal education, higher economic status, and better care for risk factors such as high blood pressure, high cholesterol and smoking that can jeopardize their brains.
- The nationwide epidemic of obesity and diabetes will still bring a significant jump in the number of people with Alzheimer's disease over the next few decades

Langa, 2008

Neurodegenerative Disorders

- All have abnormal protein aggregate that kills cells
- All have rare genetic and more common sporadic (unknown reason) forms
- All have
  - Preclinical phase
  - Early symptom phase, i.e. mild NCD
  - Symptomatic phase, i.e. dementia/major NCD
- Major NCDs often do not come in pure form
  - Vascular & Alzheimer’s
  - Parkinson's develop AD features and vice versa

Mild NCD: Mild Cognitive Impairment

1. Memory or Cognitive Complaint severe enough to be noticeable to others
2. Normal everyday functioning
3. Normal General Cognitive Function
4. Abnormal Memory or Cognitive change for age on testing
5. Not major NCD

- Some with MCI go on to develop Major NCD.
- Some with MCI do not progress to Major NCD,
- Some with MCI at one point in time later revert to normal cognitive status.

Petersen et al.,1999

Known Culprits: Molecular Bases of Neurodegenerative Diseases

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

DSM-5 Neurocognitive Disorders

= Dementias

DSM-5: Neurocognitive Disorders

- NCD: The primary clinical deficit is in cognitive function. Only disorders whose core features are cognitive

- Acquired, not developmental: a decline from previous functioning

Mild Neurocognitive Disorder

DSM-5:
Mild Neurocognitive Disorder

1. Modest cognitive decline from previous level of performance in 1 or more cognitive domains
    1. Concern of person, informant, or clinician of a mild cognitive decline
    2. Modest cognitive impairment on NP testing
2. Deficits do not interfere with capacity for independence in everyday activities
3. Not in context of delirium
4. Not explained better by another mental disorder

Major Neurocognitive Disorders = Dementias

Major Neurocognitive Disorder = Dementia

1. Evidence of significant cognitive decline from prior level of performance in 1 or more cognitive domains
    1. Concern of person, informant, or clinician of a significant cognitive decline
    2. Significant cognitive impairment on NP testing
2. ** Deficits interfere in independence in everyday activities

Specify due to what (one of 13: AD, FTD, LBD, VD, etc.)

Specify without or with behavioral disturbance

Specify severity (Mild (IADLS), Moderate (ADLS), Severe (full dependence))

DSM-5: Major or Mild NCD due to Alzheimer's Disease

- A. Criteria for Mild or Major NCD met
- B. There is insidious onset & gradual progression of impairment in 1 or more cognitive domains (2 for Major NCD)
- C. Criteria for Probable or Possible AD
  - For major NCD:
  - Probable AD diagnosed if either of following (otherwise, possible AD)
    - 1. Evidence of causative AD genetic mutation from autosomal dominant family history confirmed by autopsy or genetic testing
    - 2. All 3 present:
      - Memory decline & decline in 1 other cognitive area (hx or serial testing)
      - Progressive gradual decline in cognition
      - No evidence of mixed etiology

Baby Boomer’s risk

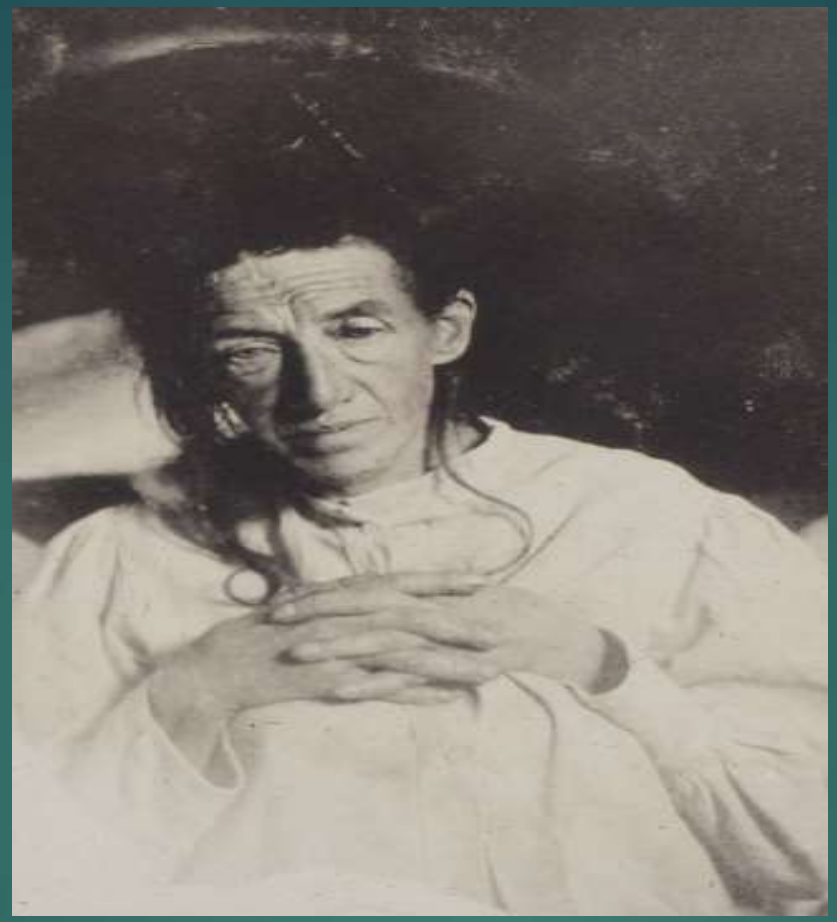
- 10,000 Baby Boomers are turning 65 each day.
- At age 65, a baby boomer has a 1 in 8 (12%) chance of suffering from Alzheimer's disease.
- At age 85 +, 42% will have AD disease in their brains

The Neurodegenerative Disorders

- Alzheimer's Disease
- Lewy-Body Disease
- Vascular Disease
- Frontal Temporal Disease
- Chronic Traumatic Encephalopathy
- Creutzfeldt-Jakob Disease (CJD)

Alois Alzheimer, 1864-1915:
Auguste Deter: 1st dx of dementia, 1901

Auguste D.



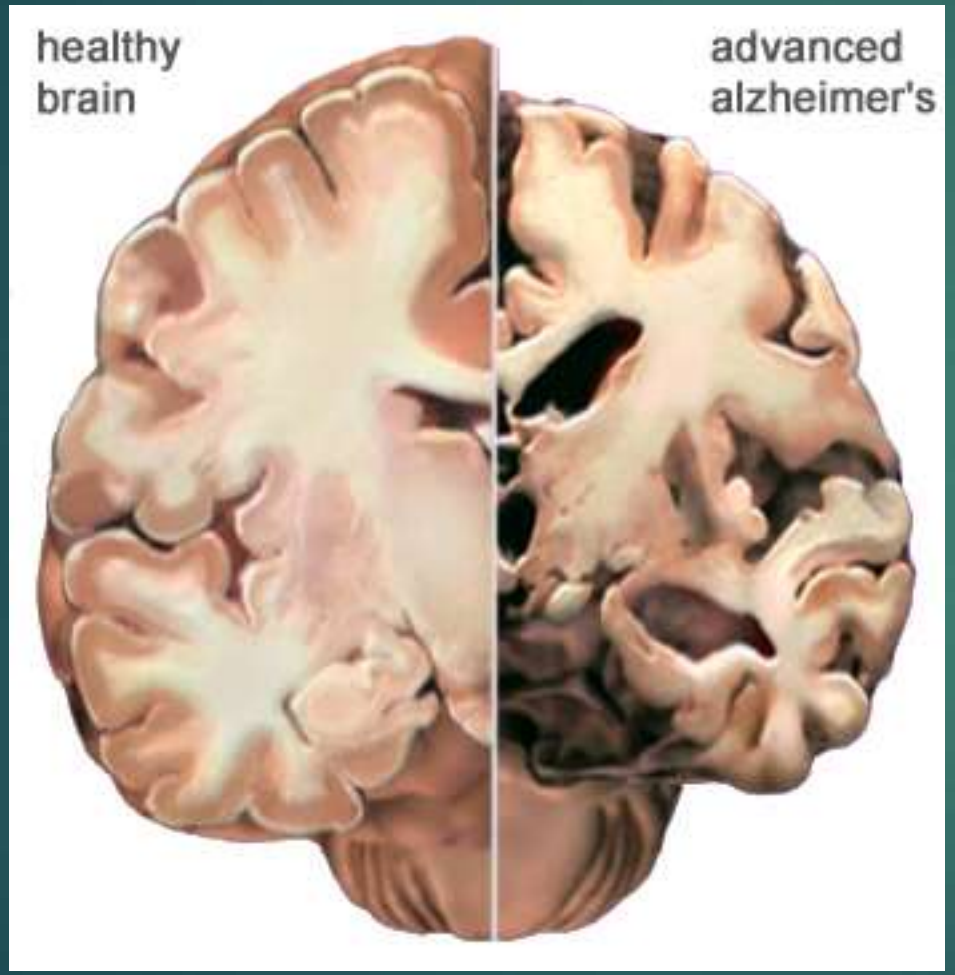
On Nov 25, 1901, Auguste D was admitted to the Frankfurt hospital, where she was examined by Alzheimer. She had a striking cluster of symptoms that included reduced comprehension and memory, as well as aphasia, disorientation, unpredictable behavior, paranoia, auditory hallucinations, and pronounced psychosocial impairment. Her death in Frankfurt was on April 8, 1906

Alzheimer’s Association Estimates

- **5.2 million people** in the United States are living with Alzheimer’s.
- **10 million baby boomers** will develop Alzheimer's in their lifetime.
- Every **71 seconds,** someone develops Alzheimer’s.
- Alzheimer's is the **seventh-leading cause of death**.
- The direct and indirect **costs of Alzheimer's** and other dementias to Medicare, Medicaid and businesses amount to more than **$148 billion** each year.

2008 Alzheimer’s Disease Facts and Figures

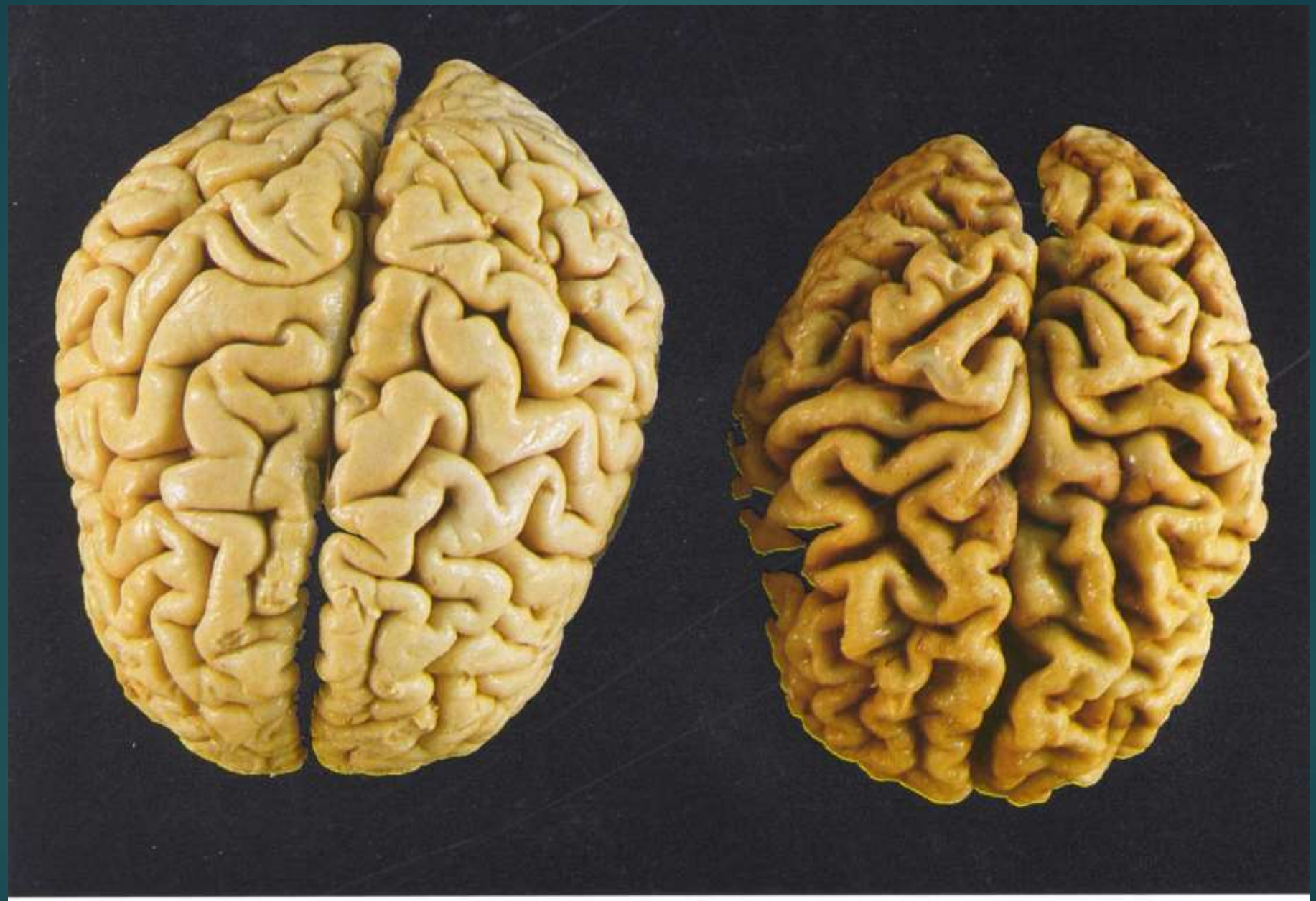
Neuropathology of Alzheimer’s

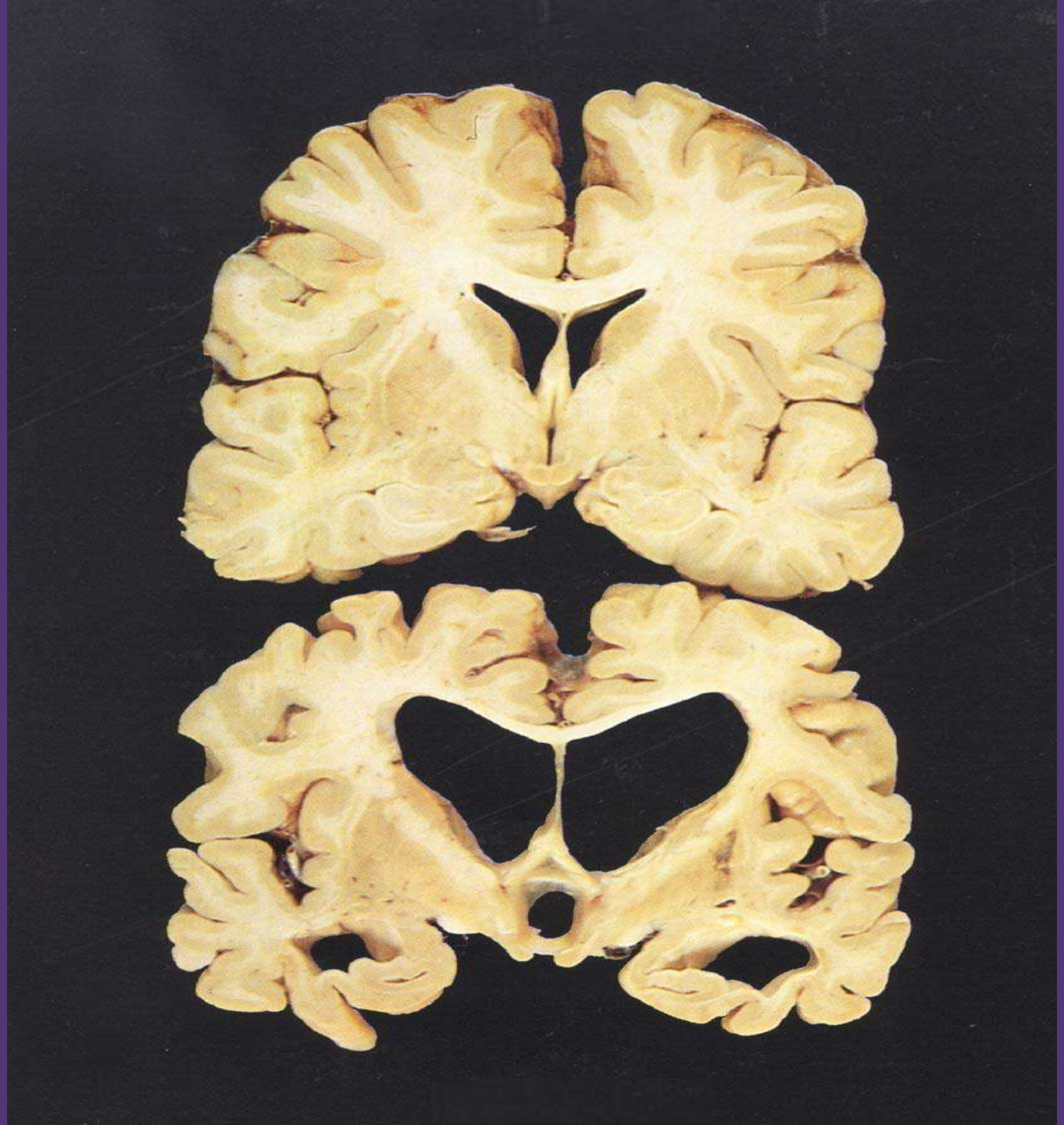


1 Atrophy

2 Enlarged Ventricles

3 Reduced Hippocampal Volume

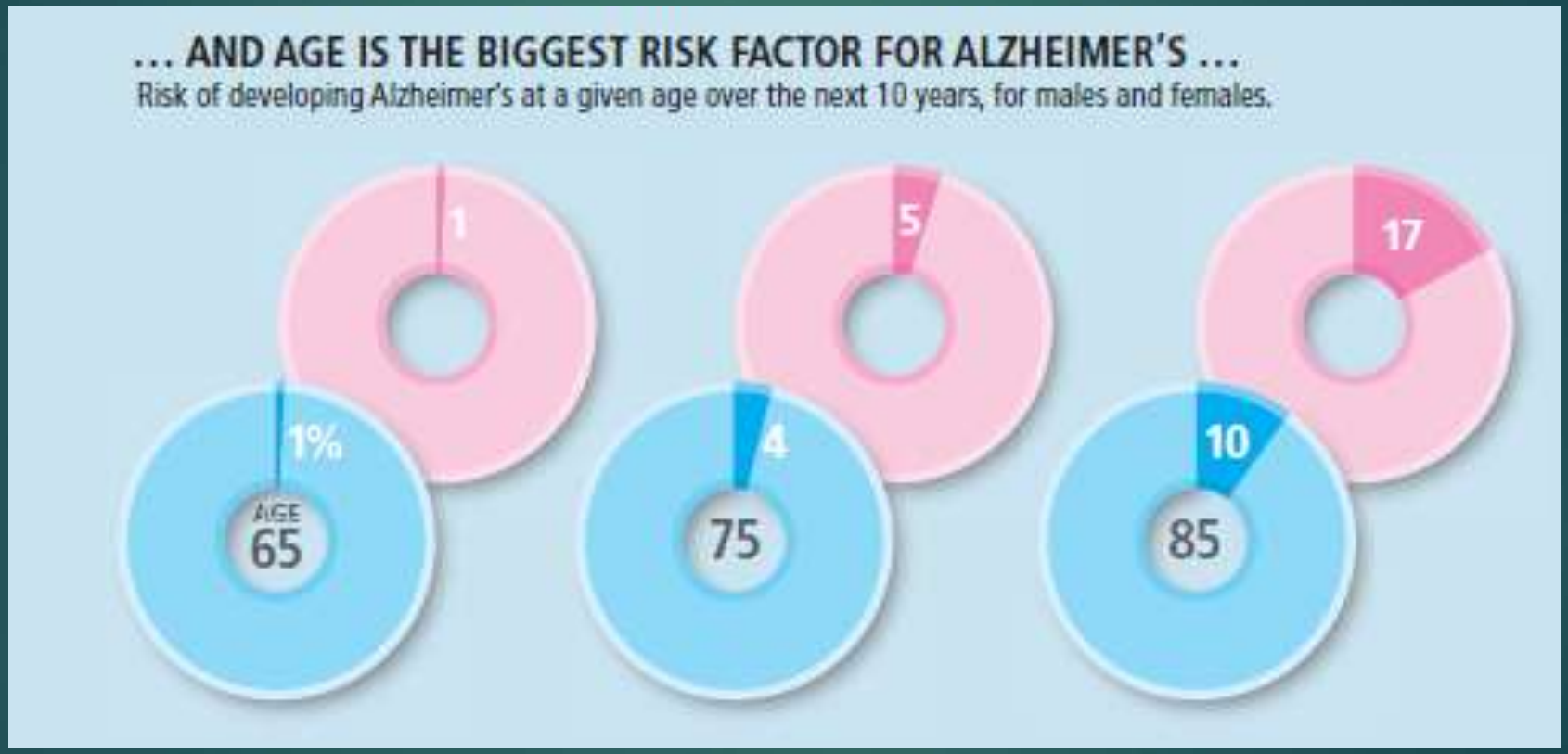

Normal
Alzheimer



Core AD issue:
No tape/CD recorder

- Encoding Deficit: tape recorder does not work
  - (new mouse model: encode, but cannot retrieve)
- People with AD no longer have the ability to remember what's new now; they do not have the ability to remember new life experiences.
- Their brain has stopped recording: cannot tell you what they had for breakfast today
- Stop asking "Do you remember what I said yesterday".

Age, not genetics, is greatest risk factor;
Dementia doubles every 5 years after 65



AD Prevalence

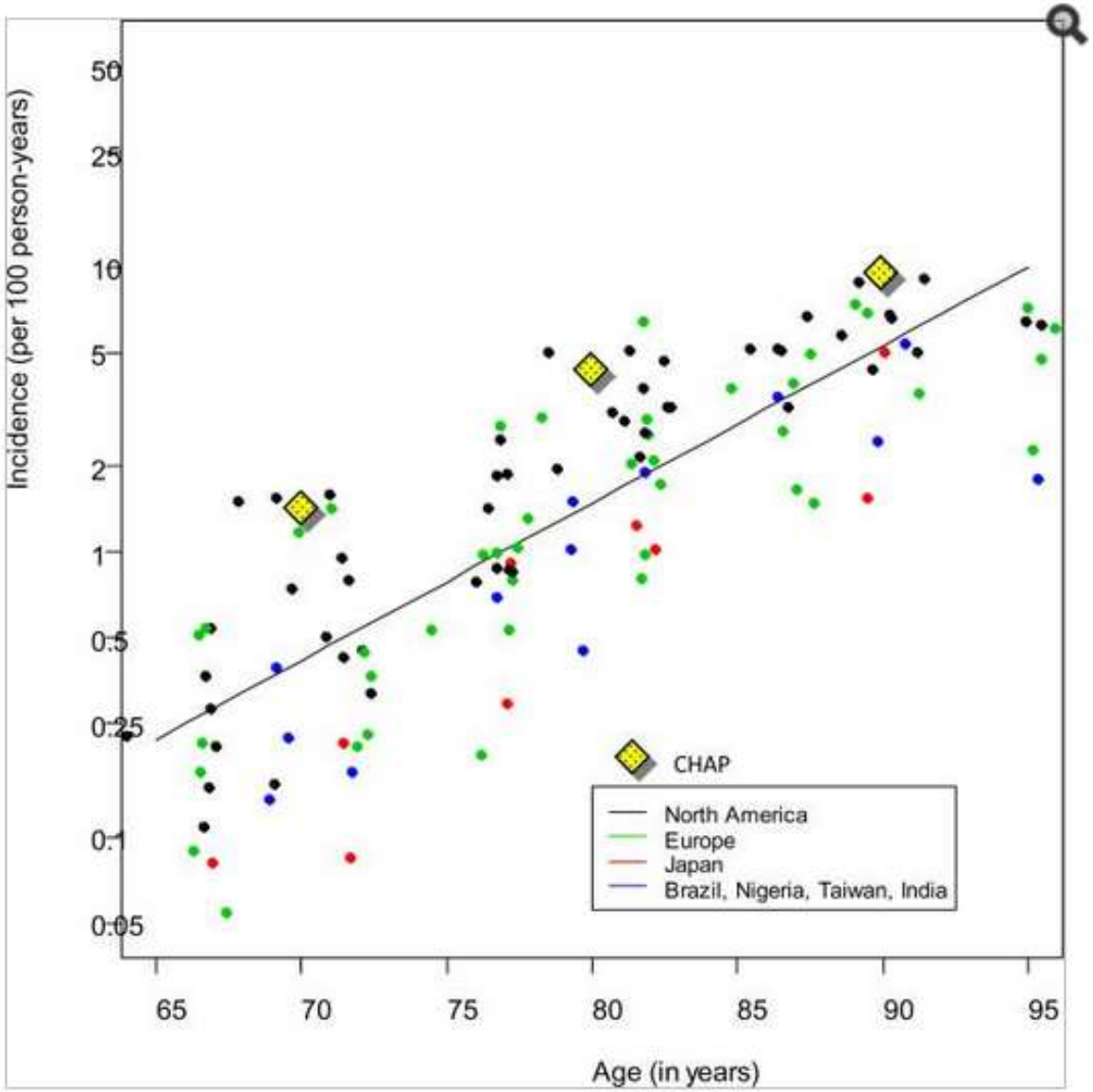
- Most common form of major NCD (70%)
- Increases with age in exponential fashion with every 5 years post 65
- Survival after diagnosis: 10 years (3 to 20 years); death most commonly due to aspiration

DSM-5, 2013

Cognitive Decline in Elderly

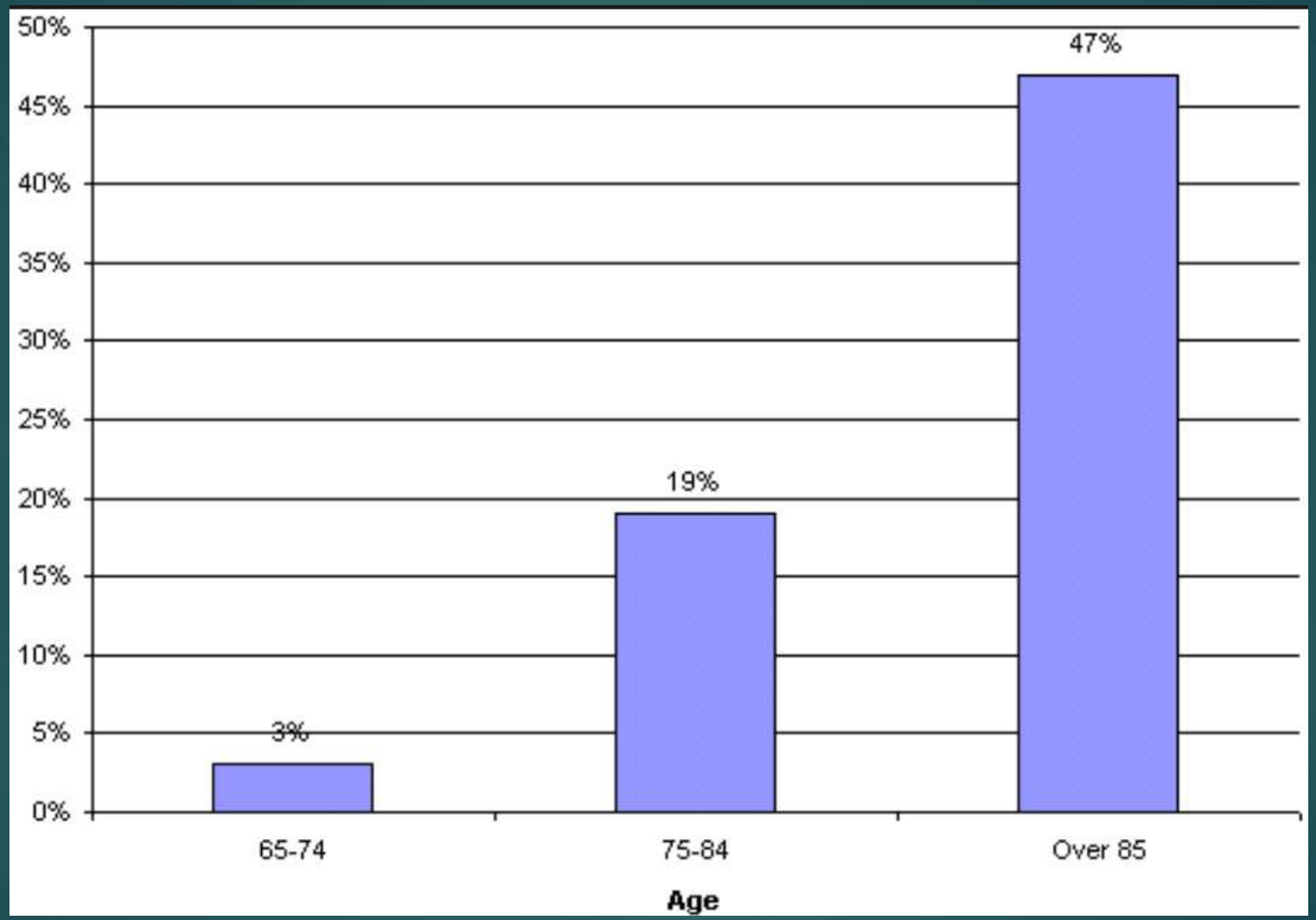
- Of all Americans in 2002, aged 71+:
- 65% were cognitively normal
- 21 % had some mild NCD
- 14% had dementia/major NCD

Alzheimer's disease incidence rates by age



Alzheimer's disease incidence rates from a systematic review [10] and the Chicago Health and Aging Project (CHAP) [13].

Alzheimer's by age



Over 65: 1 in 9 have Alzheimer's

2010 AD Data:

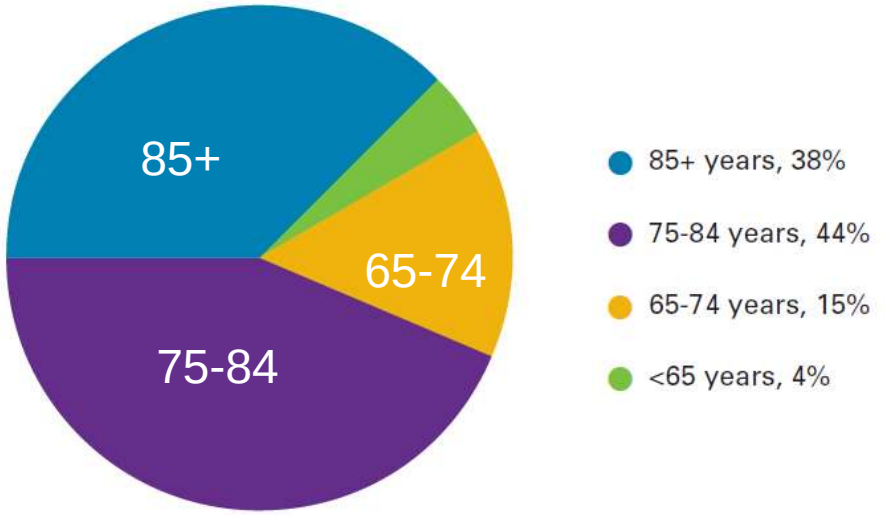
AD = Most common type of dementia; 60-80 % of cases; ~ 50% of these cases involve solely Alzheimer's pathology

82 percent with AD = age 75+

14 % of people age 71+ in the USA have dementia

50% of the estimated 5.2 million Americans with Alzheimer's may not know they have it.

figure 1 Proportion of People With Alzheimer's Disease in the United States by Age



Percentages may not total 100 because of rounding.
Created from data from Hebert et al.[114], A3

2014 Alzheimer's Disease Facts and Figures

Alzheimer's Disease:

- Insidious gradual decline
- Hallmark is memory loss: Encoding deficit; rapid rate of forgetting; poor delayed recall
- Hippocampal loss first: 5% ↓↓ per year
- >67% of pts are at moderate level NCD at first diagnosis

AD Symptoms 1

Proportion of First Symptoms:

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

AD Symptoms 2

- Family Home behavior description:

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

Wandering

- 50 percent of people who wander will suffer serious injury or death if they are not found within 24 hours.
- MedicAlert® + Alzheimer's Association Safe Return® is a nationwide identification program
- Comfort Zone® and Comfort Zone Check-In® allows families to monitor a person with dementia's whereabouts remotely using Web-based location services.
- Paint a bus stop

Alzheimer's Disease

- AD:
  - Fatal,
  - progressive,
  - age-related,
  - irreversible,
  - insidious loss of cognitive ability
  - leading to functional incapacity and death..

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

Women are the epicenter of AD crisis

- A woman's AD risk at age 65 is 1 in 6, compared with nearly 1 in 11 for a man; women with early sxs decline at twice the rate as men (2 pts per year on cognitive tests)

- Women deteriorate twice as fast as men with the condition in both cognitive and functional abilities.

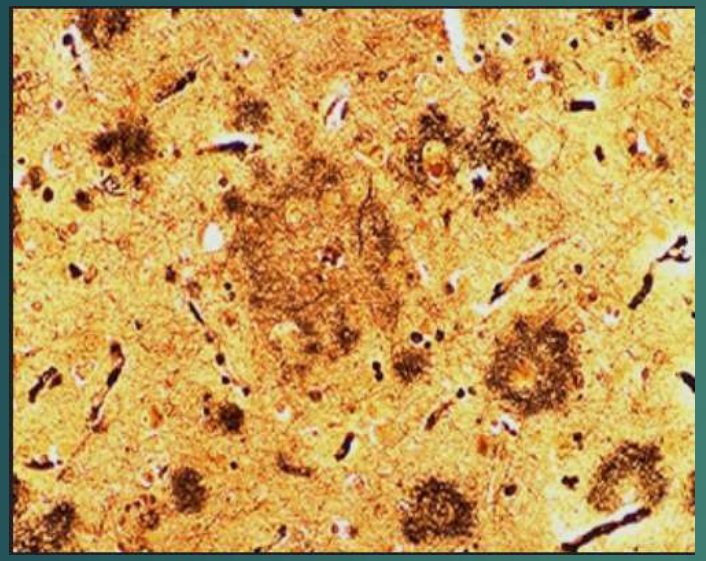
- Women in their 60s are twice as likely to develop AD as they are to develop breast cancer.

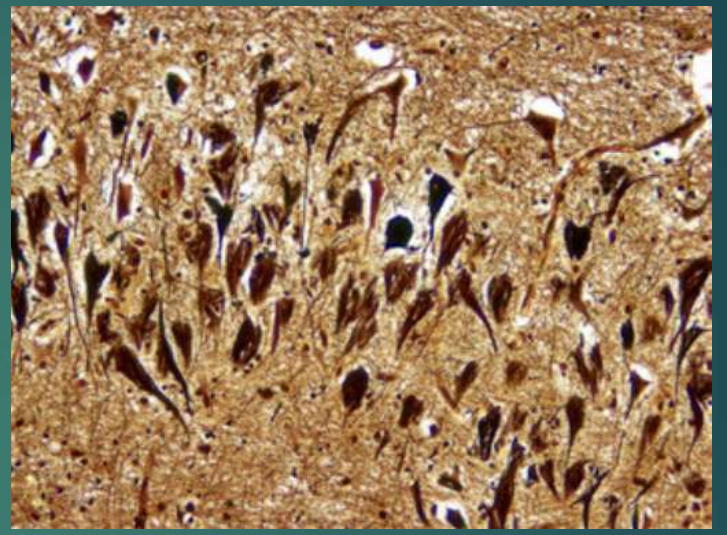
- More likely to be caregivers of those with Alzheimer's: More than 3 in 5 unpaid Alzheimer's caregivers are women

AB42 & Tau are the Probable Cause of Alzheimer’s

- Beta amyloid (abnormal form of the protein) & Tau are the probable cause of Alzheimer's disease
- 35,000 scientific papers on Alzheimer's in last decade
- The leading hypothesis of the cause of Alzheimer's, called the amyloid – tau hypothesis, is centered on the overproduction, or inadequate clearance, in the brain of 2 abnormal proteins: beta amyloid and tau
- Normal function: AB is antimicrobial (part of innate immune system)
- Normals turn over the amount of AB 3 x daily (especially during deep sleep)
- If you can control AB42 & tau, you can control Alzheimer's disease

AD Pathology

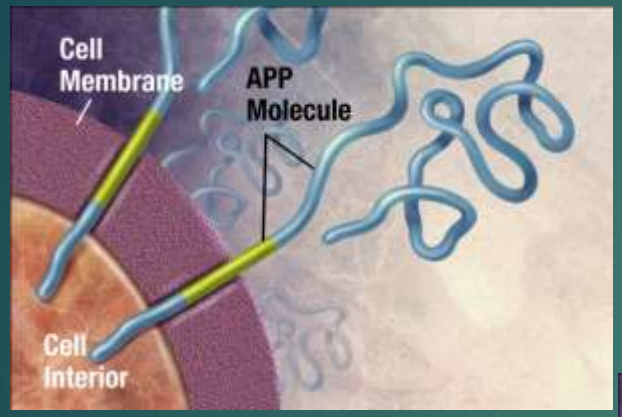


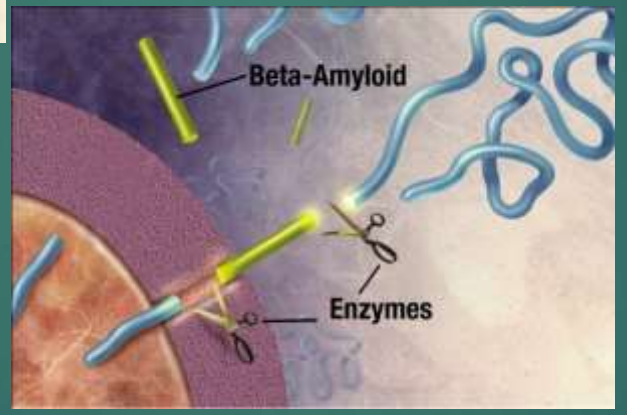


Amyloid Plaques:
- Extra-cellular
- Amyloid-B (AB)

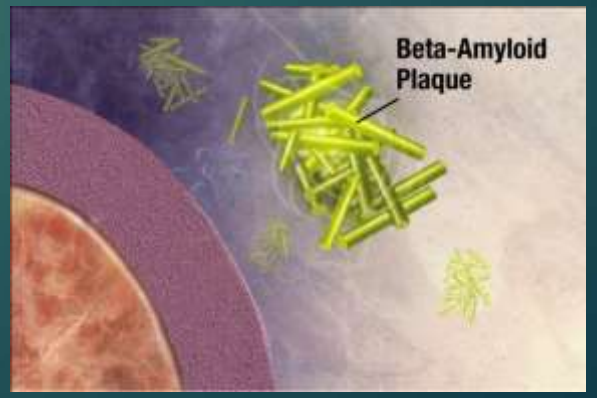
Neurofibrillary Tangles
- Intra-cellular
- Tau

Beta Amyloid

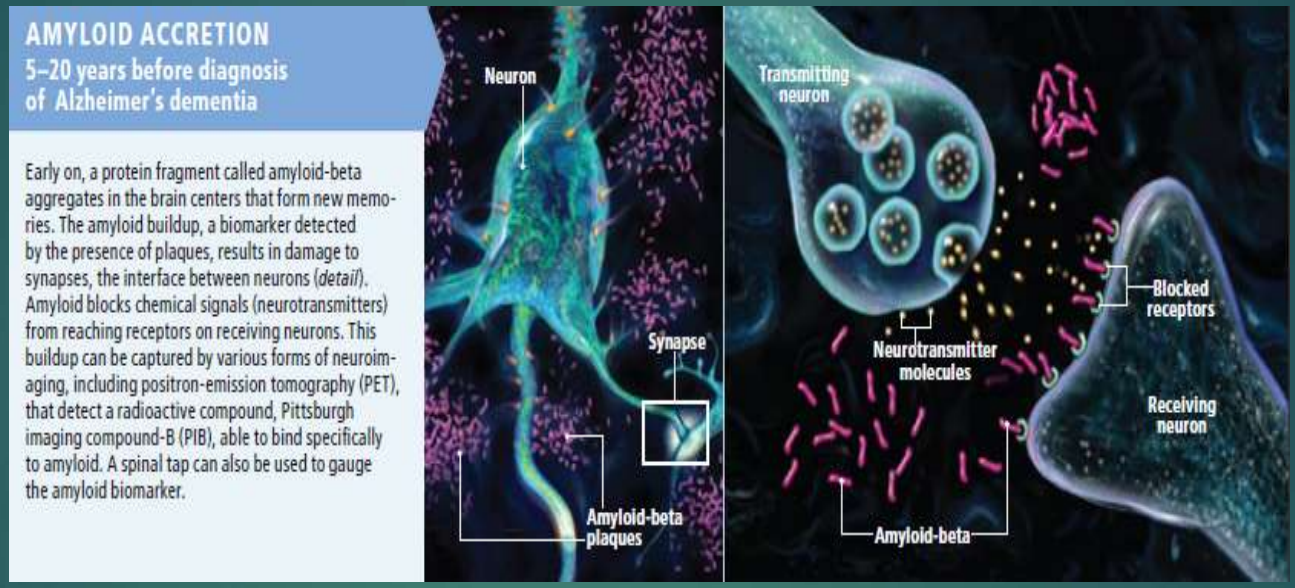


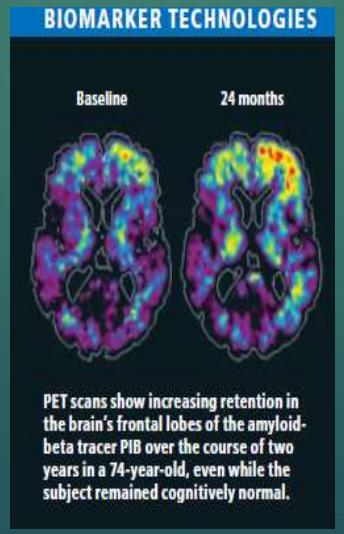


Sticky & neurotoxic



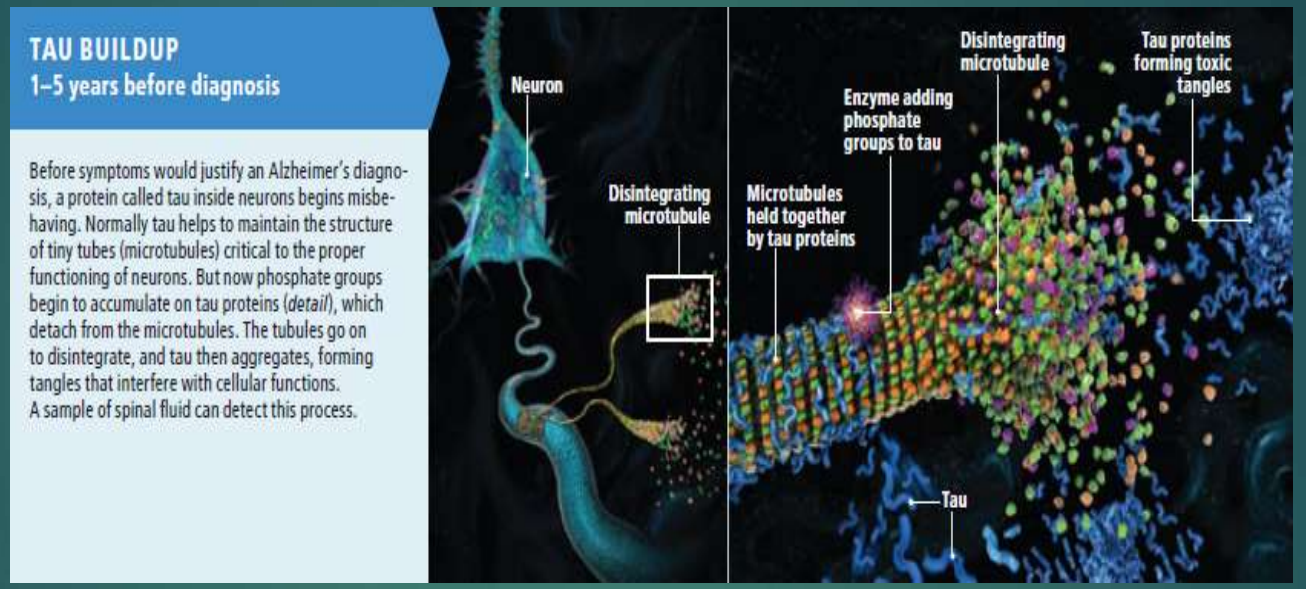
Step 1: Increasing amounts of Beta Amyloid starting 5-20 years before diagnosis



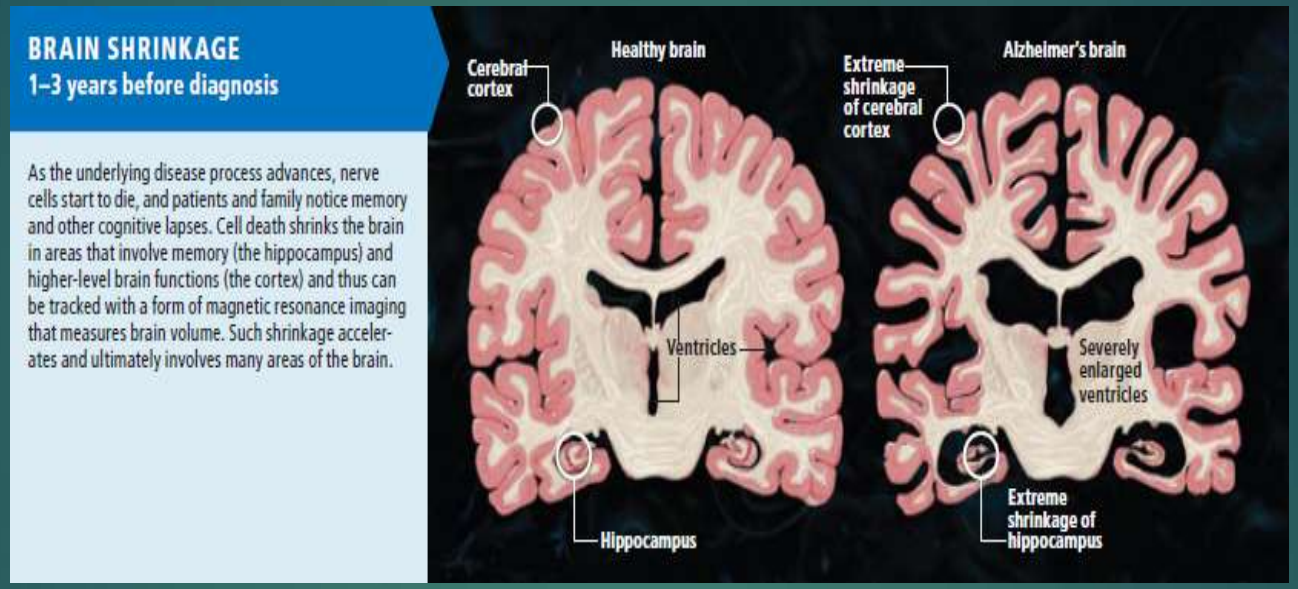


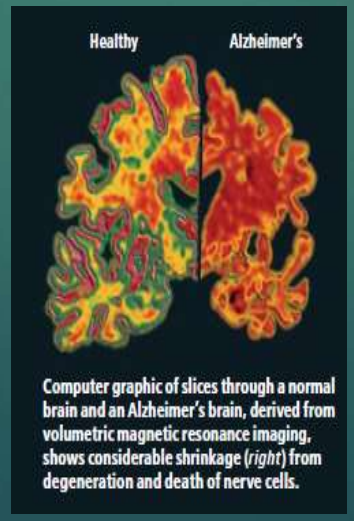
Scientific American, June 2010

Step Two: Tau Buildup – 1-5 years before



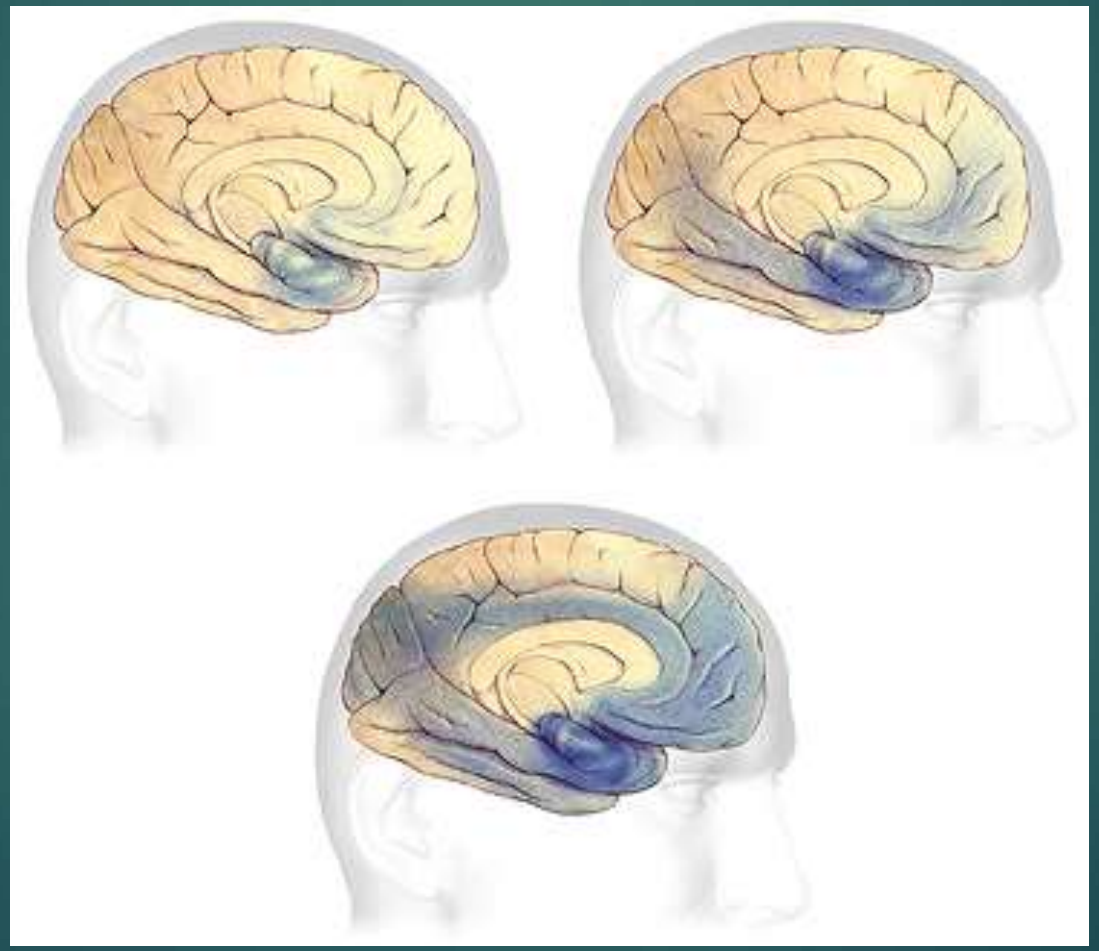
Step Three: Atrophy (Neuron death)

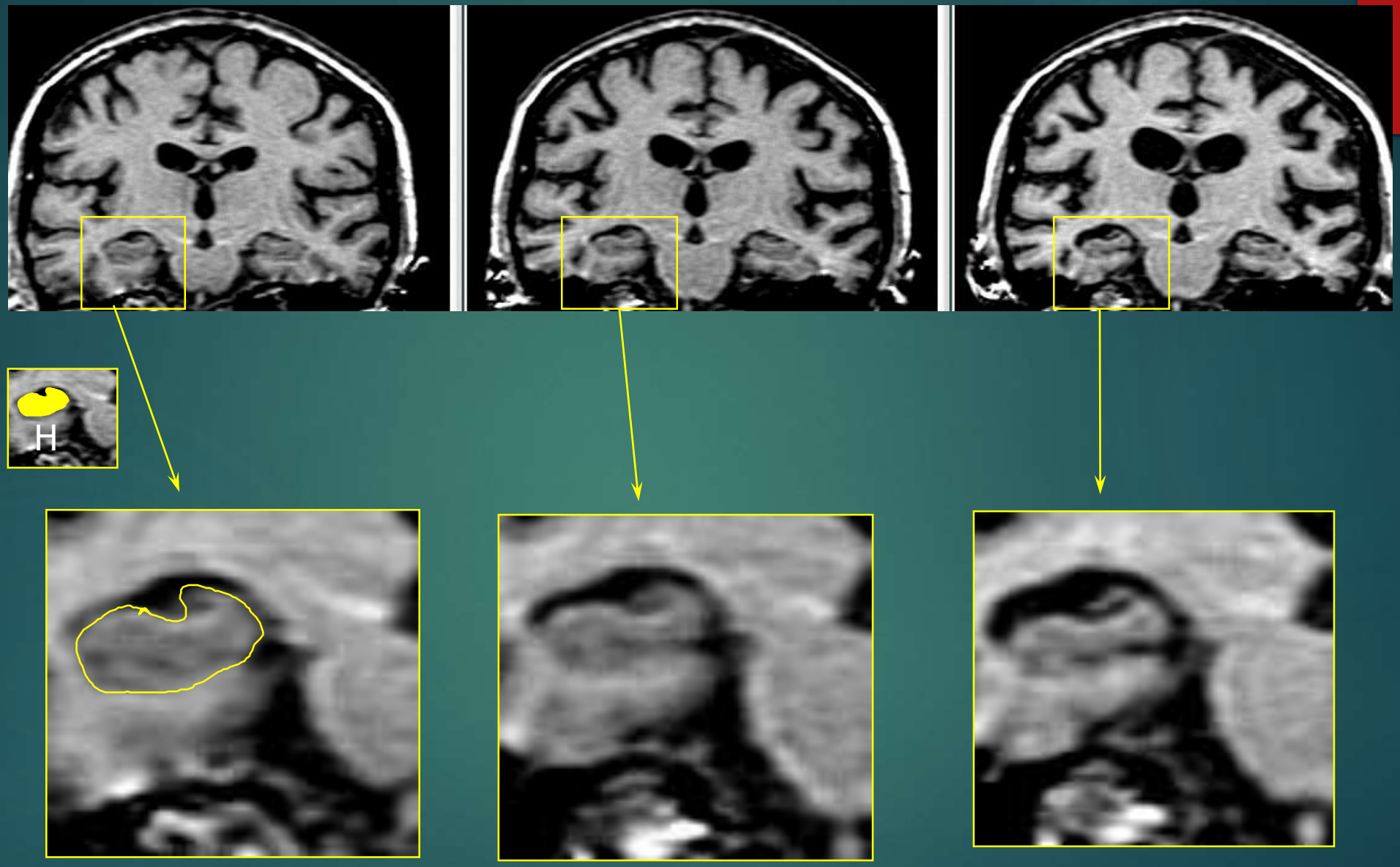




AD Progression in the Brain

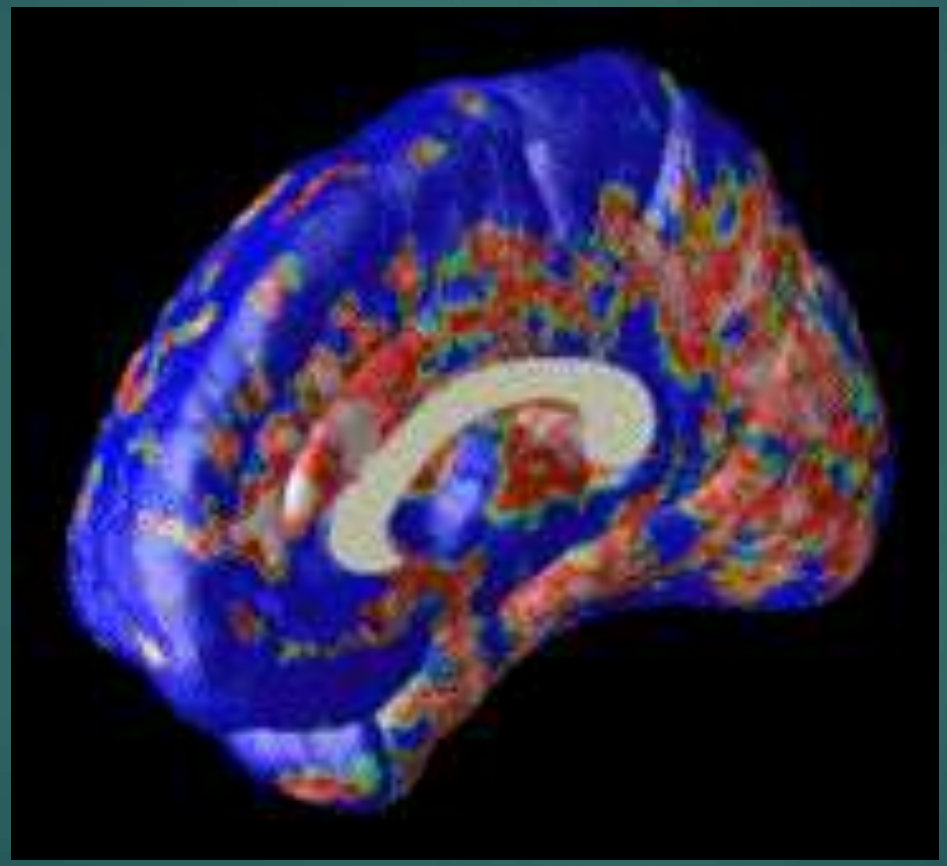
Hippocampus first





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

Alzheimer’s: 18 months of atrophy



Neuron death & atrophy in White areas

Alzheimer's = Most are Not Diagnosed

- Majority Not Diagnosed: Three-quarters of the 36 million people living with AD dementia
- 50% of people with AD do not know they have it.

3 stages of Alzheimer’s

- Preclinical –
  - 25 years or more; asymptomatic beta amyloid (BA) accumulation
  - Evidence of abnormal biomarker patterns, but without signs of cognitive impairment.
  - No clinical dx, may not progress.

- Mild NCD:
  - BA increase + neurodegeneration (dead neurons) + cognitive ↓
  - Diagnosis is made clinically and by exclusion of other causes.

- Alzheimer's Major NCD
  - Significant neurodegeneration (severe neuron death) + severe cognitive symptoms

Older AD less aggressive

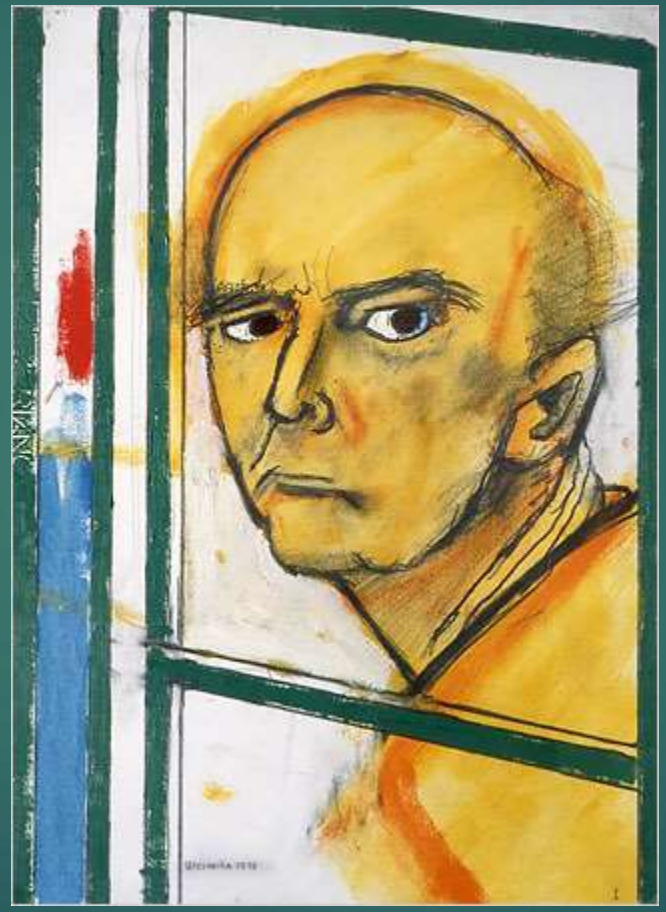
- AD hits hardest among the “younger elderly” – age 60-70s – show faster rates of brain tissue loss and cognitive decline than AD patients 80 years and older.

Dominic Holland, et al., PLOS, 2012

A picture is worth a 1000 words:
Painter William Utermohlen's self-portraits; age 61, AD dx

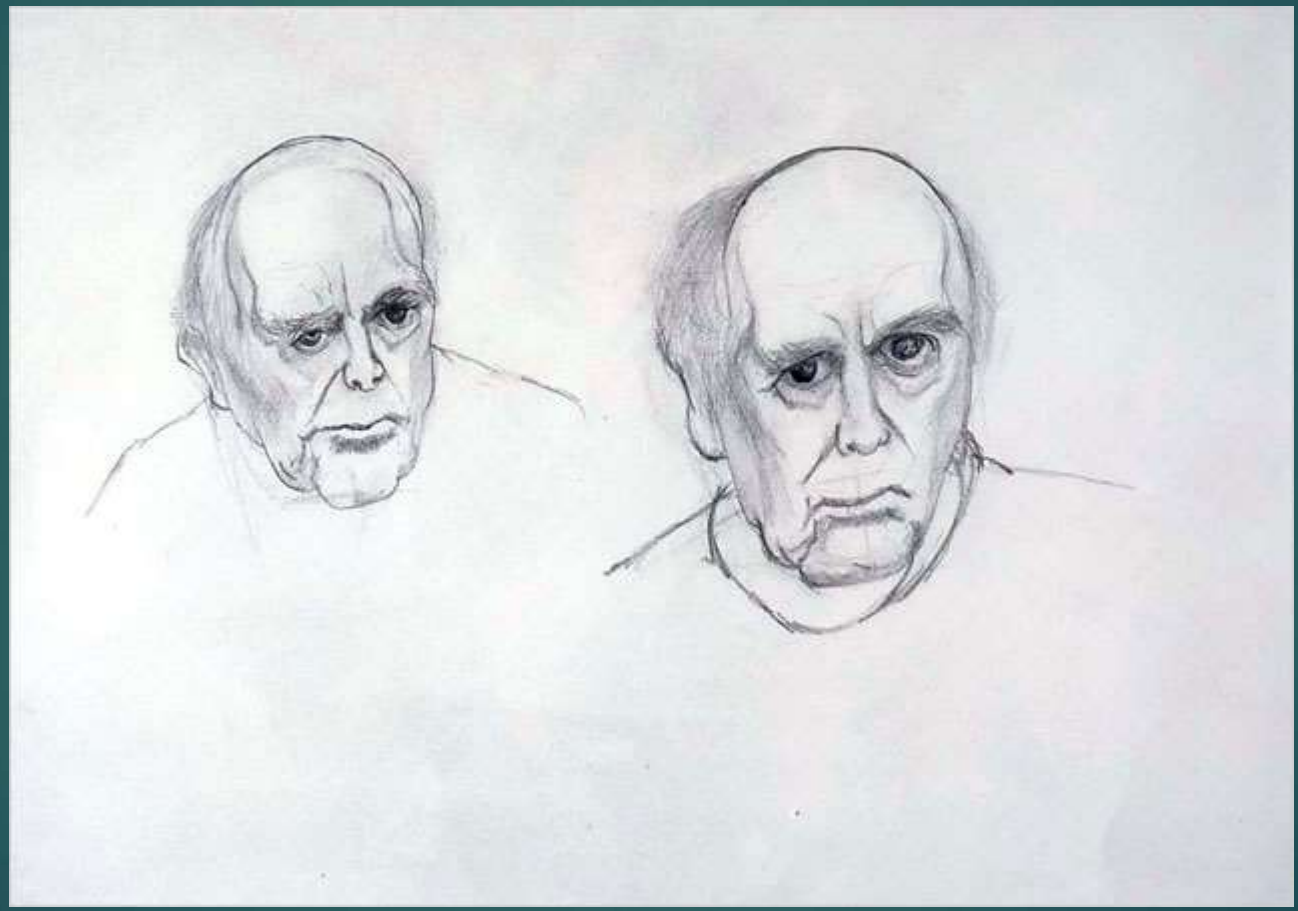
1967

Self Portrait: 1996

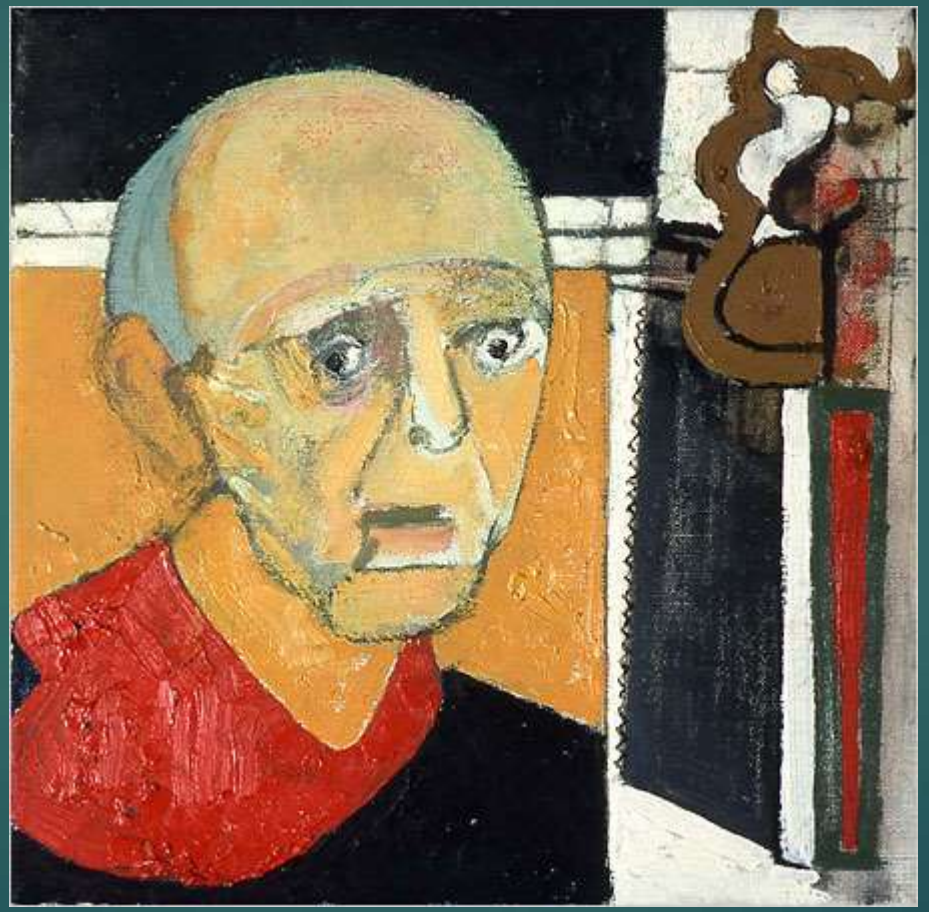


Self Portrait: 1996

Self Portrait: 1996



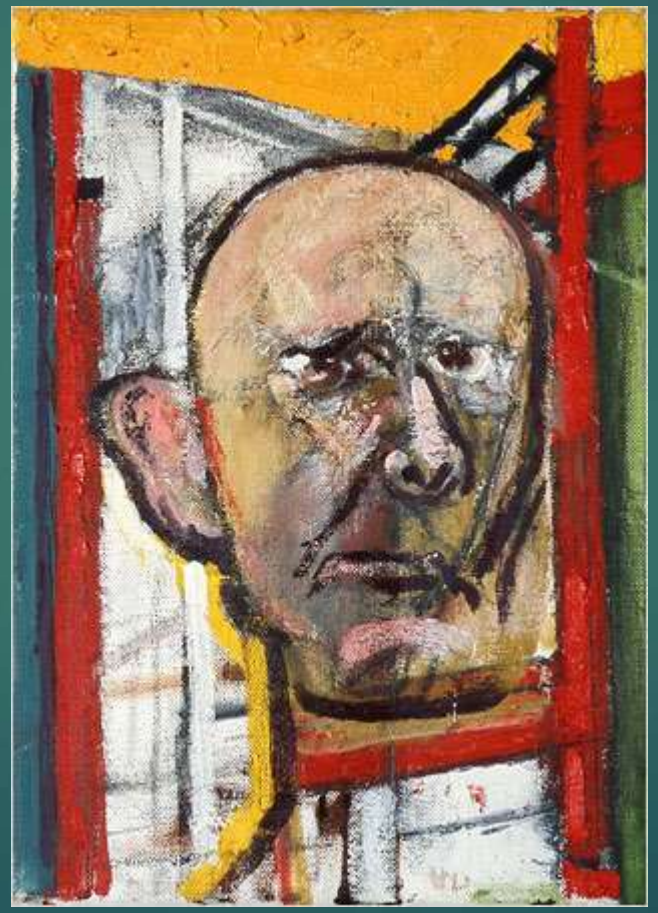
Self Portrait: 1997



Decides to donate his body to science

Self Portrait: 1997

Self Portrait: 1998



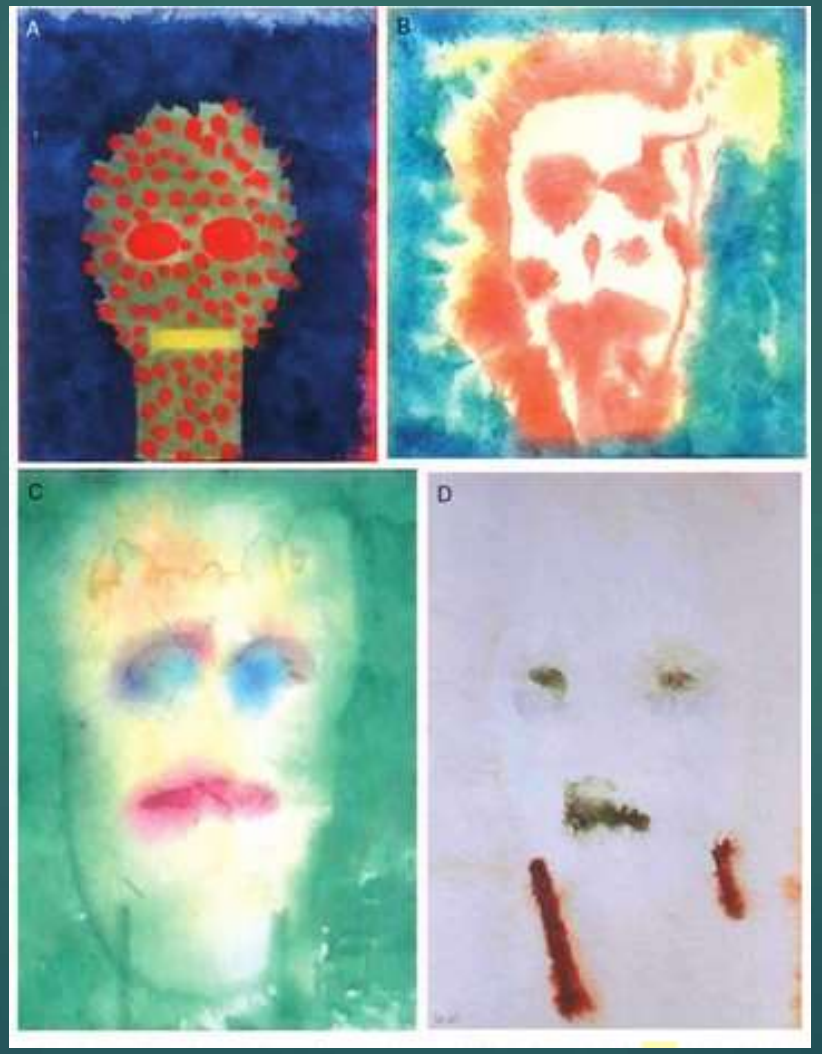
Self Portrait: 1999

2 years to complete

Self Portrait: 2000

Self Portrait 2000+

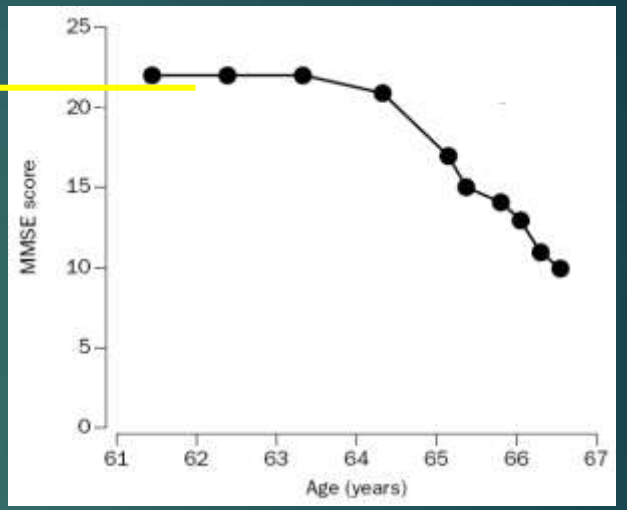
1998, Age 65



Self Portrait 2000+

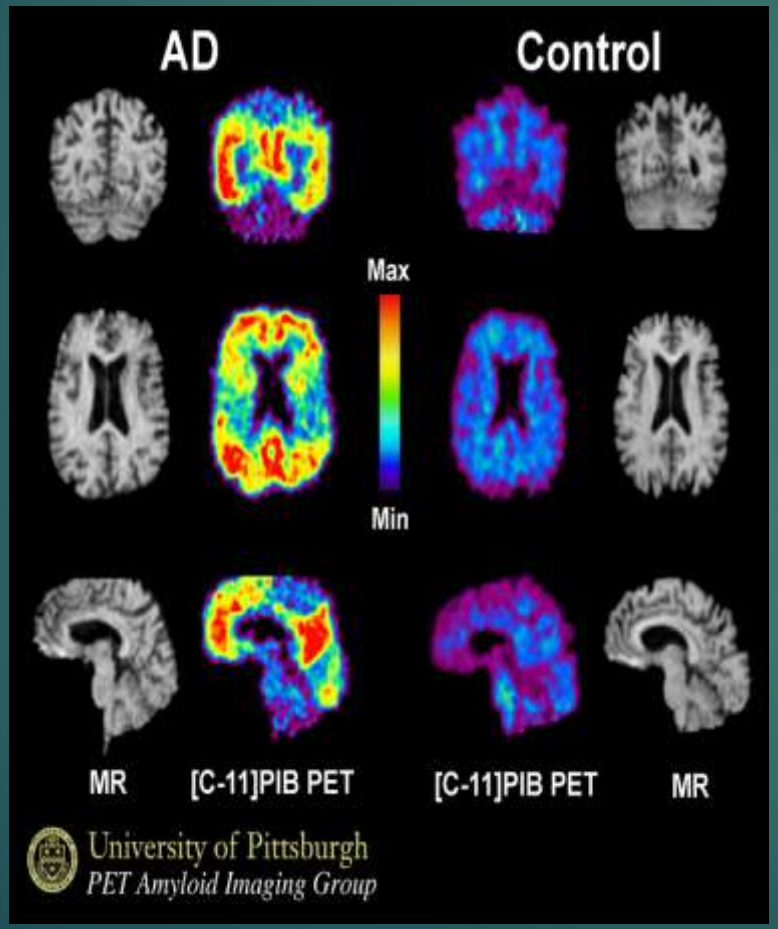
William Untermohlen –self-portraits correlate with cognitive decline

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



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

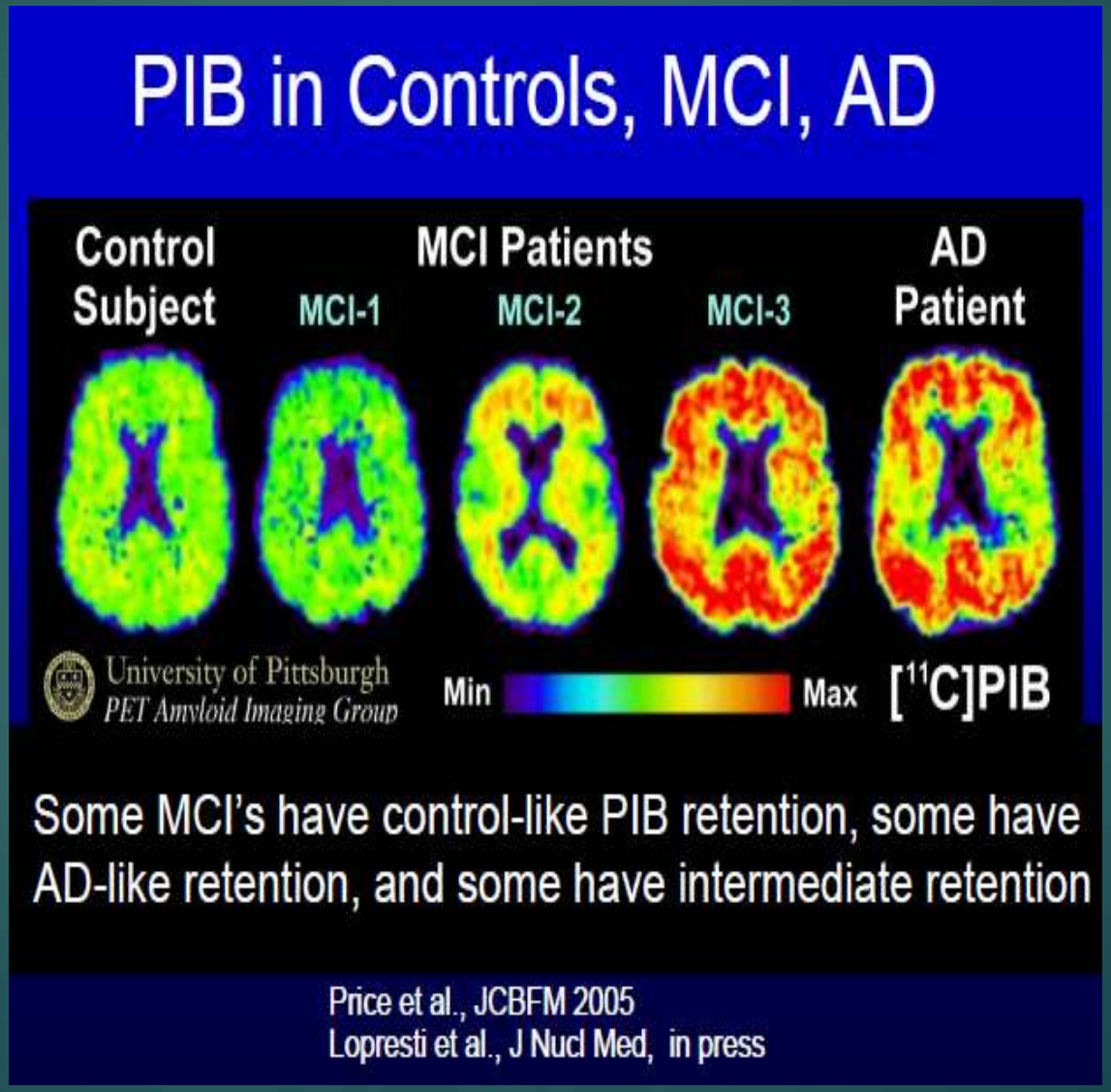
Pittsburg B Compound labels Amyloid Plaques on PET: AD vs. Normals



Carbon 11 as its radioactive tracer. And its half-life is 20 minutes. Researchers have to make it in a cyclotron in the basement of a medical center, quickly attach it to the dye, dash over to a patient lying in a scanner, and inject it.

Does not bind to BA in primates, who do not develop cognitive decline with BA

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



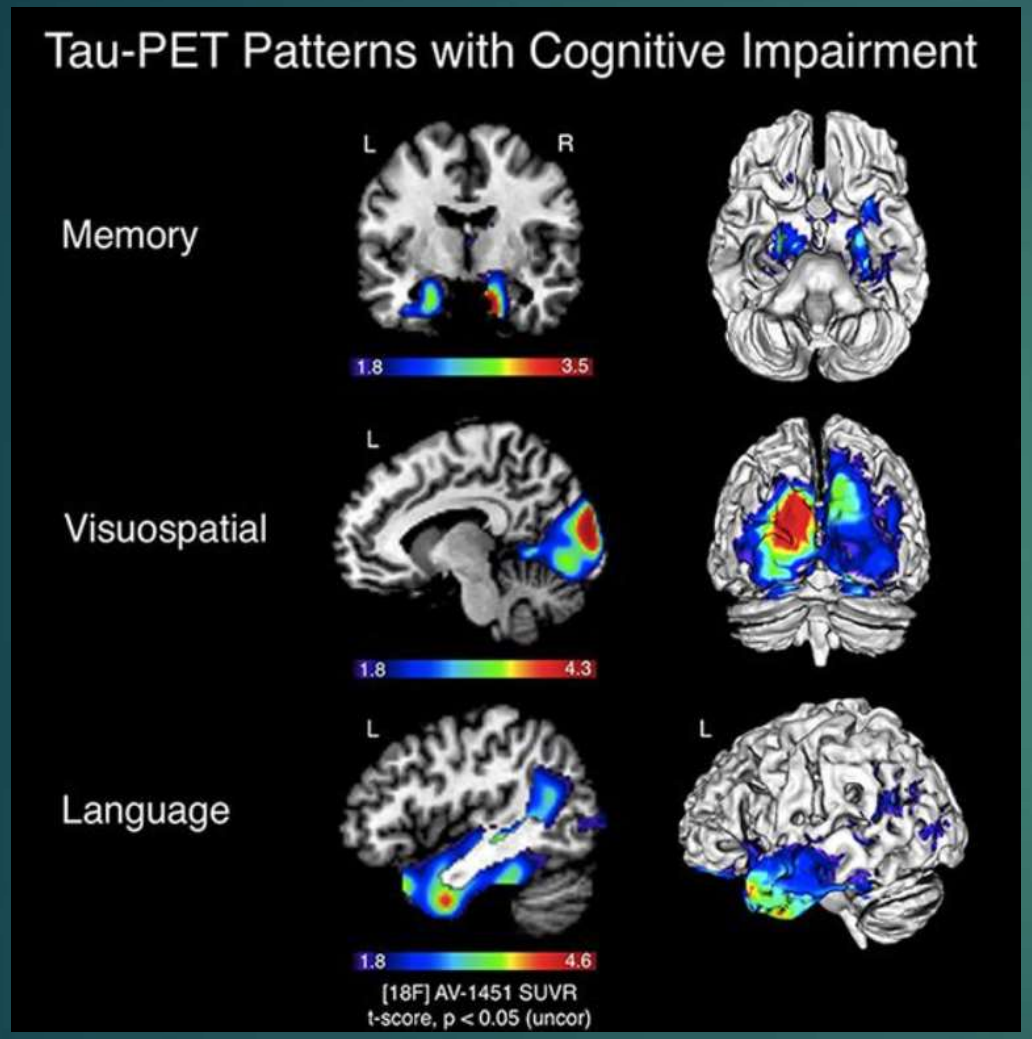
Risk Factors for AD

- Age: Prevalence 1% in 60-64; doubles every 5 years; 35-40% in over 85
- Female: independent of being older
- Family hx: 4x risk if first degree relative (parent/sibling)
- Major TBI ??
- Reduced cognitive and physical activity throughout life
- Vascular: HTN, cholesterol, diabetes, tobacco, obesity, heart disease

Tau = ultimate neuron killer

- In ongoing studies on patients with more advanced disease, the amount of tangles, not amyloid, in each region correlates most closely with neurodegeneration.
- Tau does not spread from Temporal lobe until enough BA accumulates.
- Almost all areas with atrophy contain high tau tangles
- Once tau spreads from hippocampus to cortex, cognition begins to decline.

Tau tracks cognition

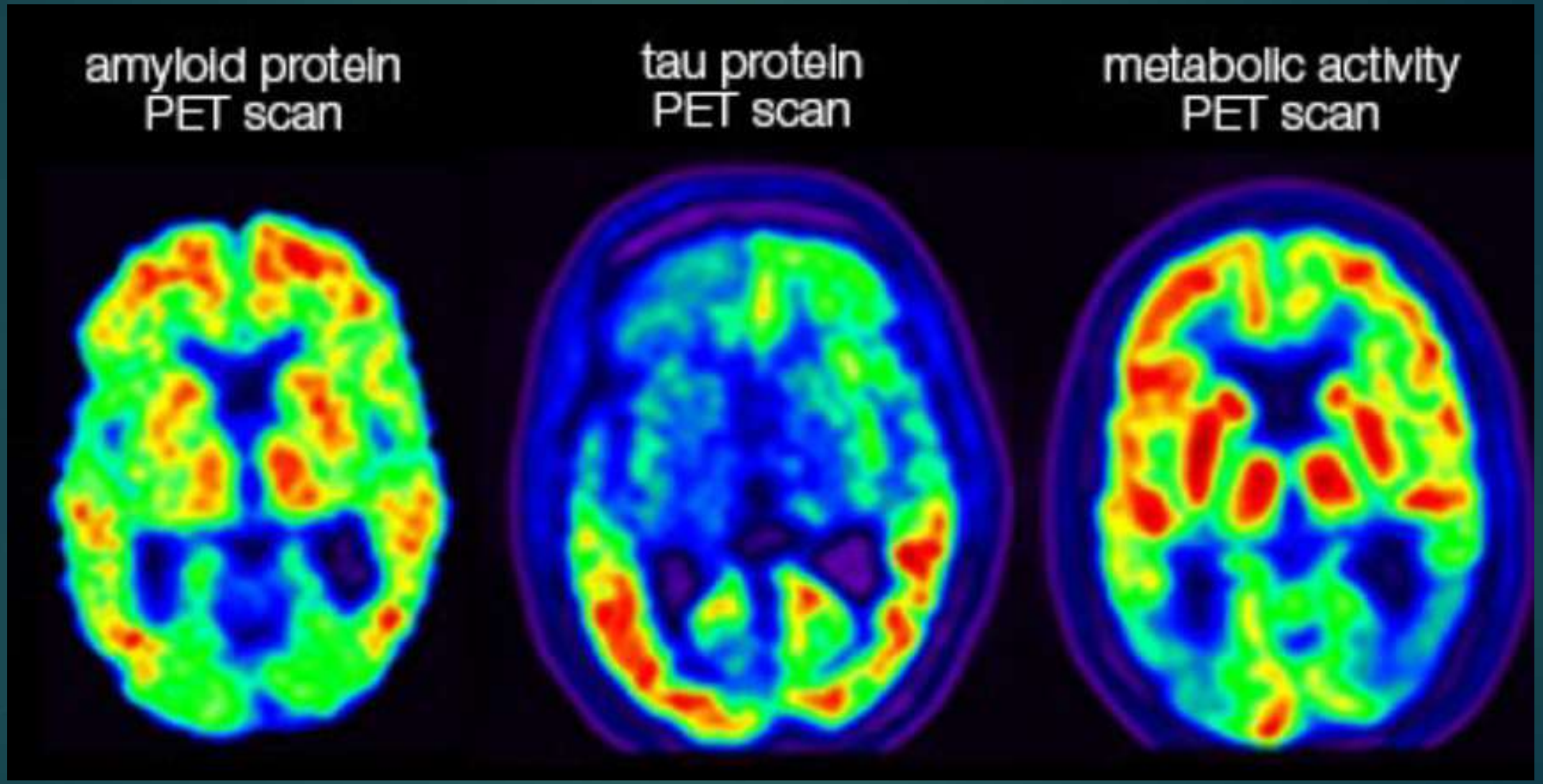


Findings from classic postmortem studies also demonstrate that cognitive state correlates much more strongly with tau tangle than amyloid pathology.

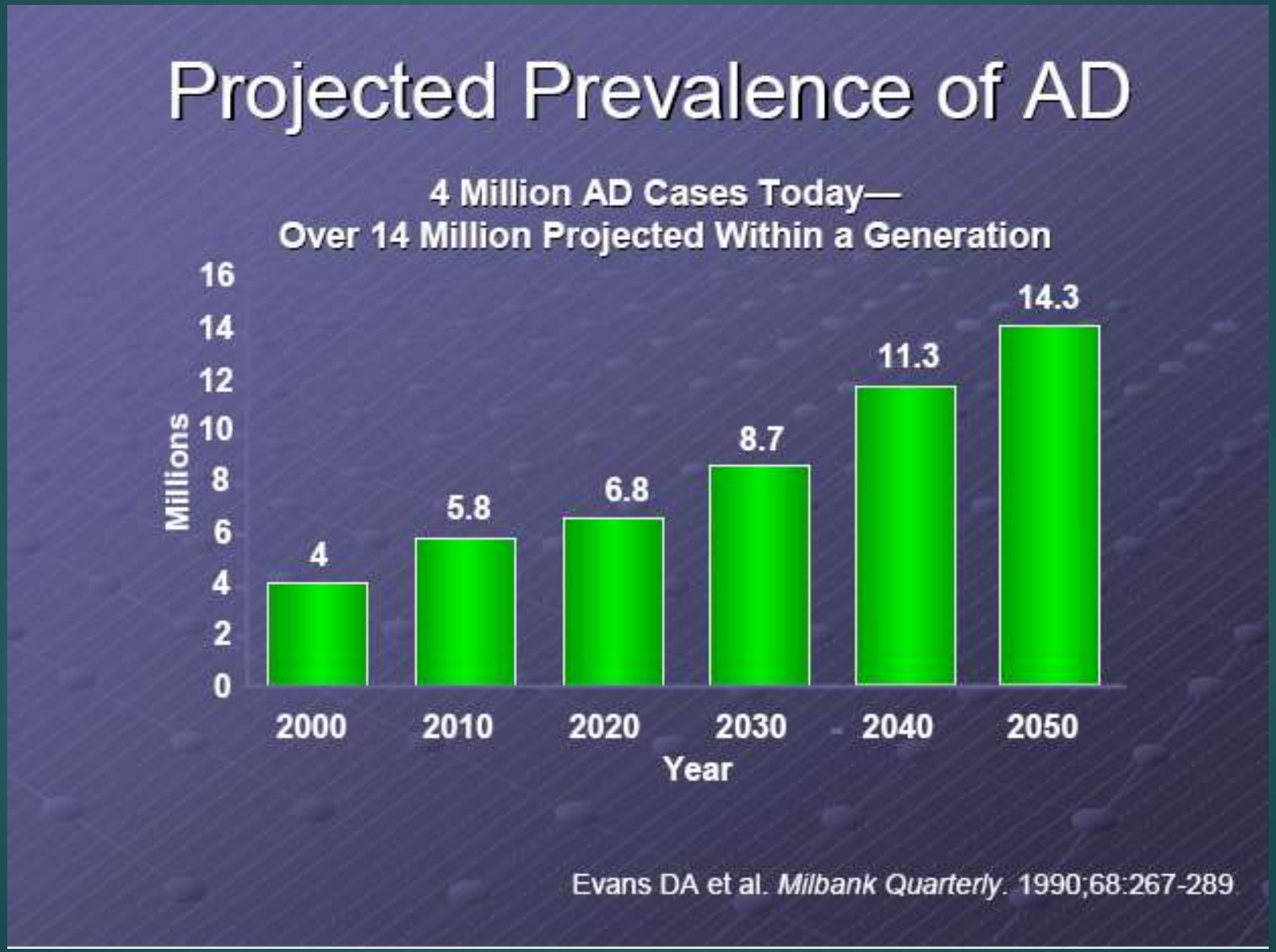
tau deposition also aligns with areas of cortical thinning

[Courtesy of the Rabinovici lab.]

BA loads the gun & pulls the trigger, and Tau is the bullet



Projected Prevalence



New Research Strategy

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

Normals with AD Pathology

- 30% of cognitively normal elderly
  - have some level of AD pathology
  - meet neuropathologic criteria for AD
  - but have no NCD/dementia

New Model of AD Development: Emerging Model of Preclinical AD

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

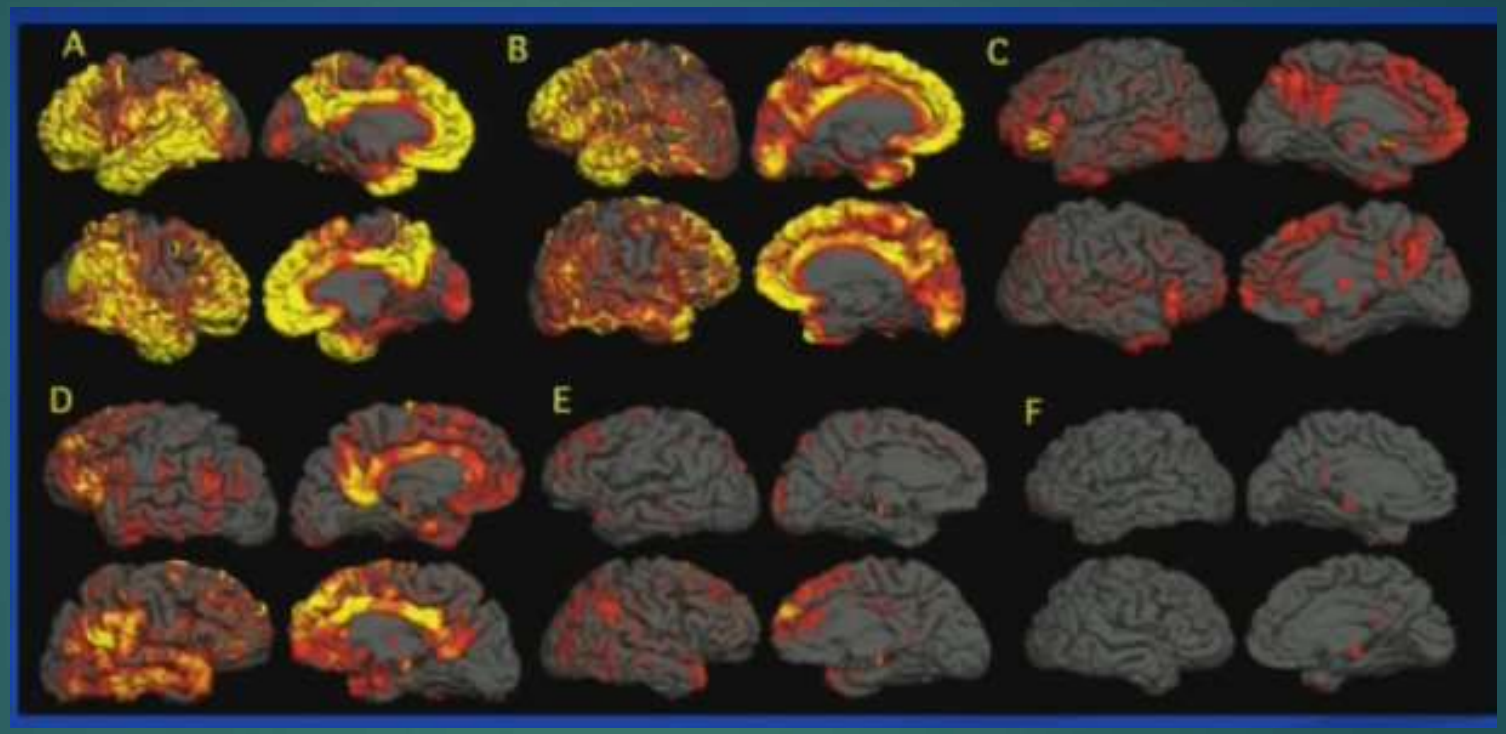
AD Timeline to Major NCD

- 25 years before, beta-amyloid protein levels in the CSF begin to decline
- 15 years before, beta-amyloid begins to accumulate in the brain. (the earliest sure sign of the disease).
- 15 years before, the brain begins to shrink due to neuron loss.
- 10 years before, brain metabolism slows down & episodic memory is impaired.
- 5 years before, Mild NCD sets in.
- Year 0, Major NCD diagnosis (too late to treat; too much neurodegeneration)

PET: Amyloid concentration

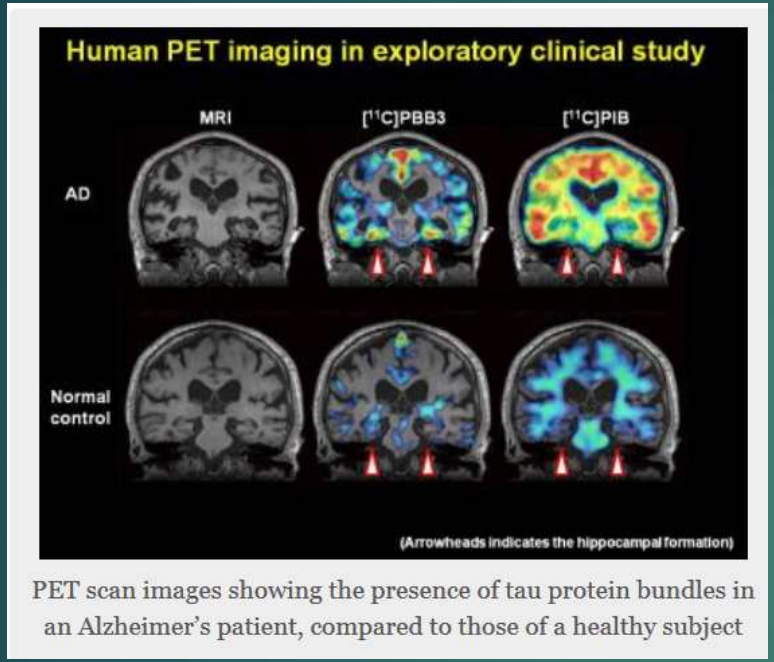
AD

Normal

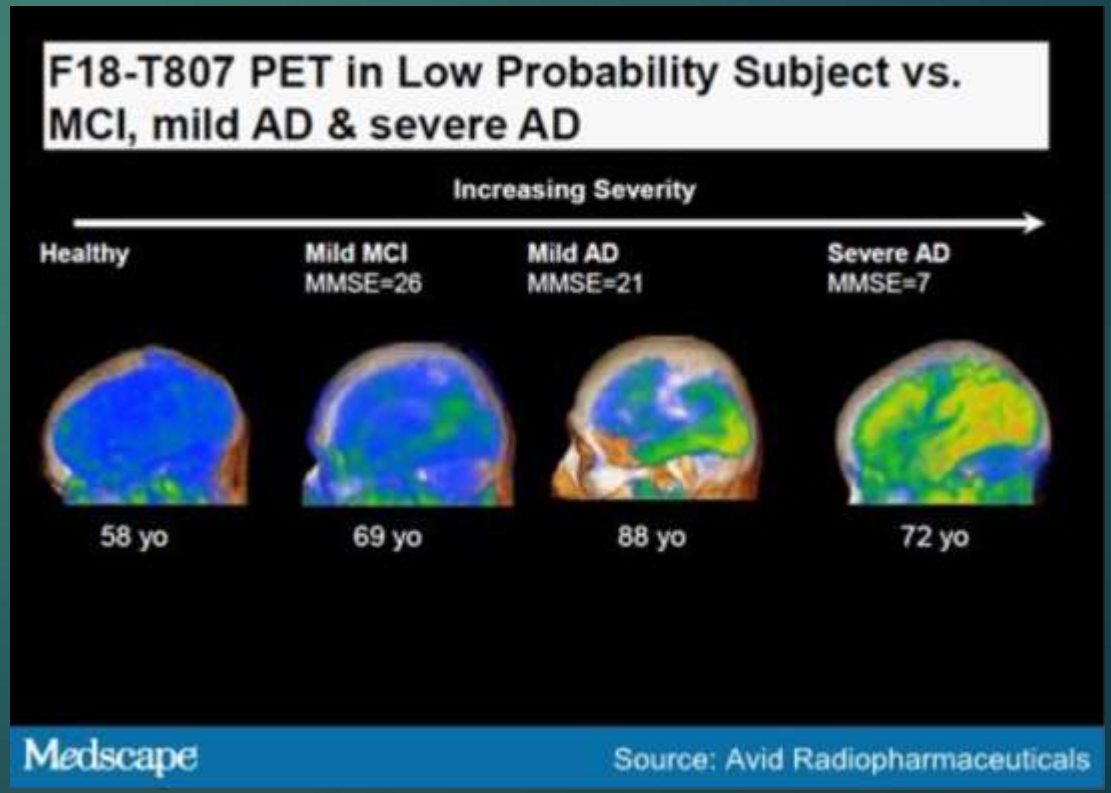


Note that 30% of normals have significant amount of BA, but no NCD

Imaging Tangles: new Tau Pet Scan



PET scan images showing the presence of tau protein bundles in an Alzheimer's patient, compared to those of a healthy subject



2016 Mouse study: Synaptic pruning

- C1q is member of complement cascade, a group of immune system proteins that calls in microglial cells to gobble up synapses and cells.
- Recent research shows the process of synaptic pruning in schizophrenia is triggered by these proteins; basic process that happens in normal adolescent pruning of synapses
- Now in mice, this process seems to spring into action in early stages of AD; injection of oligomeric A-beta caused C1q levels to rise and synapses were destroyed; in mice that lacked C1q, A-beta injections did not harm synapses
- C1q and A-beta are both needed for excessive pruning; both early and late in AD

100+ Alzheimer's Disease Modifying Treatment Trials: 99.6% Failure Rate

- AN1792 vaccine: 2003 (Eliminated BA; still NCD)
- Tramprostate
- Flurizan: 2008
- Bapineuzumab: 2009
- Semagacestat: 2010
- Etc.

- Right TX, wrong stage of disease?

Hope for near future: Columbian Prevention Study

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

Impact of risk factor reduction on AD prevalence

- 50% of the risk factors for Alzheimer's disease are potentially changeable
- Most negative risk factors: reducing them could substantially decrease the number of new cases of AD:
- Low education 19% of cases
- Smoking 14%
- Physical inactivity 13%
- Depression 11%
- Midlife hypertension 5%
- Midlife obesity 2%
- Diabetes 2%

D. Barnes and K. Yaffe,, Lancet Neurology, 2011

Accelerated Synaptic Loss

- TBI
- CVA
- HTN
- DM
- High Cholesterol
- Homocystine (red meat)
- Low exercise
- Specific genes, i.e. ApoE4

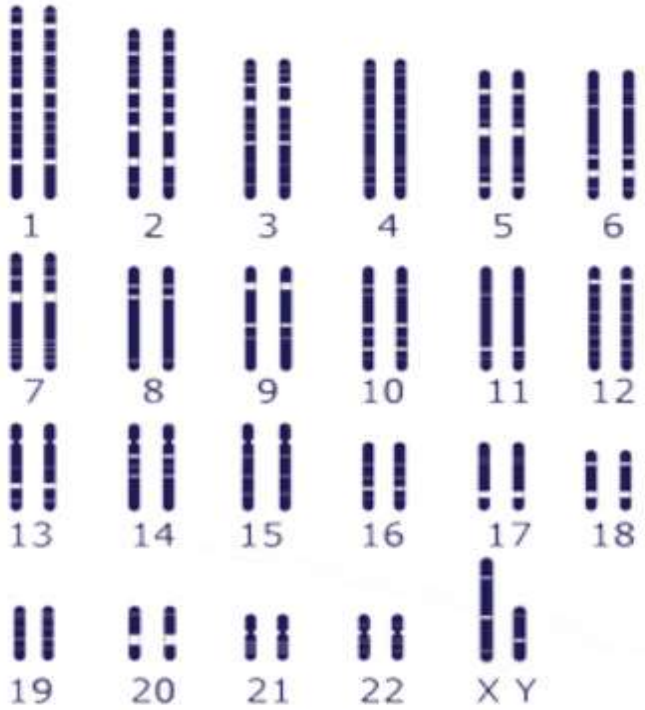
Genetics

- 90%+: sporadic, age related, later onset
- 5-10% genetic/familial

Aging is 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

4 Major Genes Implicated in Alzheimer's:
3 Mendelian (dominant) genes in only 450 families in whole world



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

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

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

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

Youngest Onset: 40s

Onset: 58-59

Onset: 60-70s

Risk: ApoE4

- ApoE4 is the only gene proven to be linked to the common form of non-autosomal-dominant, late-onset AD
- Strongest genetic risk factor for late-onset Alzheimer disease (AD).
- One ApoE4 allele = 4x risk; 2 alleles =12-15x.
- It is a risk factor for earlier AD onset, and general brain decline.

Genetics of Dementia

- "My mother had dementia, do I have 'the gene' and can I test for it?"
- 25% of the general population aged 55 years and older have a family history of major NCD involving a first-degree relative
- Having an AD parent does not necessarily mean there is a mendelian (autosomal dominant) form of major NCD in the family.
- Mendelian rare: only 500 families with mendelian forms of Alzheimer's disease in the world; only 1% of AD

Clement T Loy, et al., 2014

of Apoe4 Alleles and AD Risk: get AD sooner

# Apoe4 Copies	Prevalence	AD Risk	Onset Age
0	73%	20%	84%
1	24%	47%	75%
2	3%	91%	68%

Alzheimer's Genetics

- 95 %: Sporadic (unknown cause) AD with onset later than 65 yo
- 5%: Familial genetic AD, onset 40-50s

- Sporadic: Many genes + environment/lifestyle

- No family hx:
  - Lifetime risk = 15%
  - E4 neg = 9%;
  - E4+ = 30%

- One parent with AD:
  - E3/E3: 30%
  - E3/E4: 45%
  - E4/E4: 60% (& telomere shortening & 6x more likely to buy long term disability insurance)

23andMe.com: $99

- Hundreds of genetic markers,
  - ApoE2/3/4,
  - amount of Neandertal/Denisovan

Lewy Body Disease: 10-15%

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

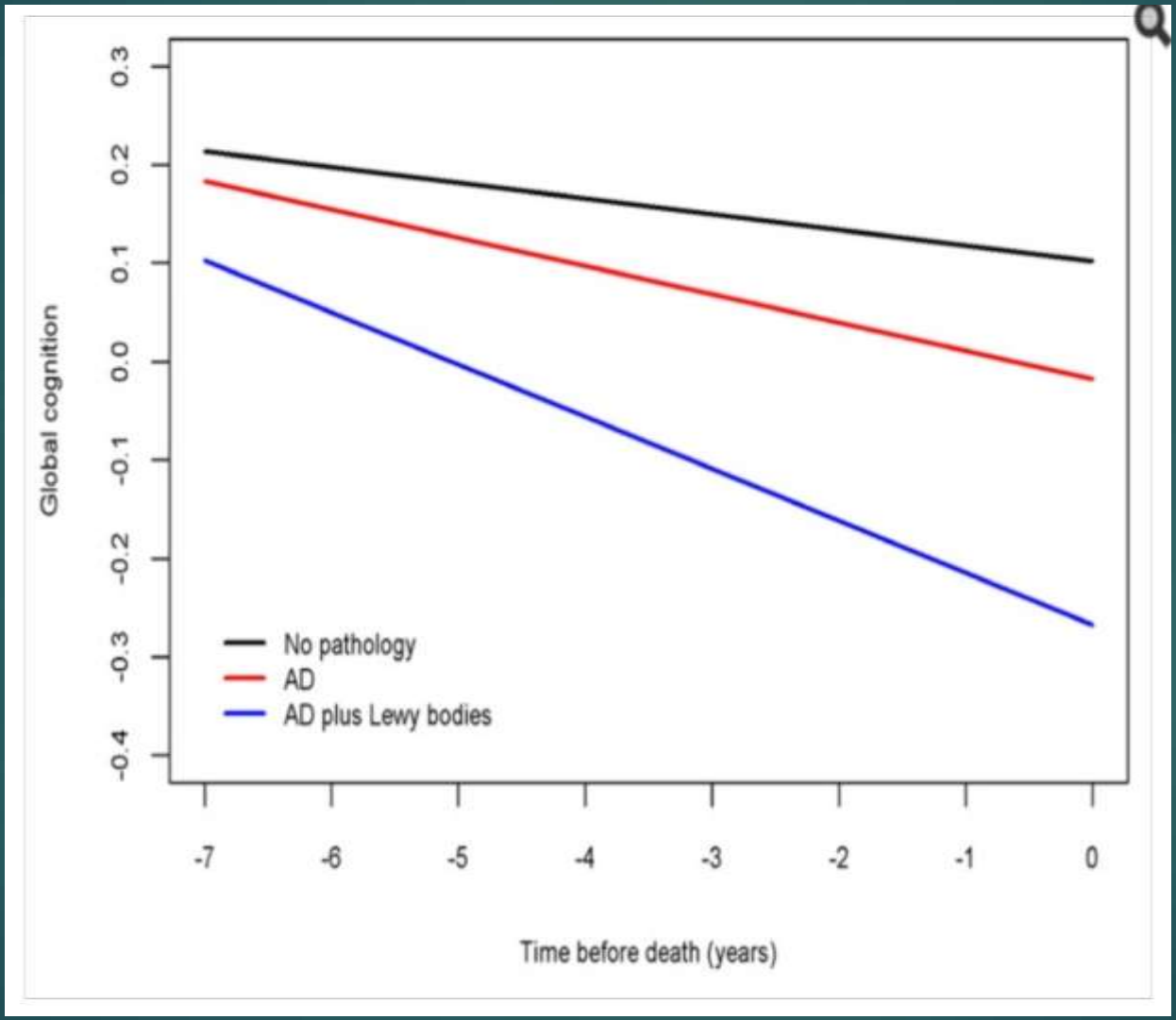
Heyman A et al. *Neurology.* 1999;52:1839-1844.
Ballard CG et al. *Dement Geriatr Cogn Disord*. 1999;10:104-108.

Visual Hallucinations in LBD

- Small Animals
- Little People
- Dwarves
- Odd Creatures
- Animals with hats
- Well-formed landscapes

Cases with well-formed visual hallucinations had high densities of LB in the amygdala and parahippocampus, with early hallucinations relating to higher densities in parahippocampal and inferior temporal cortices.

Worse Cognitive Decline: AD vs. AD + Lewy bodies

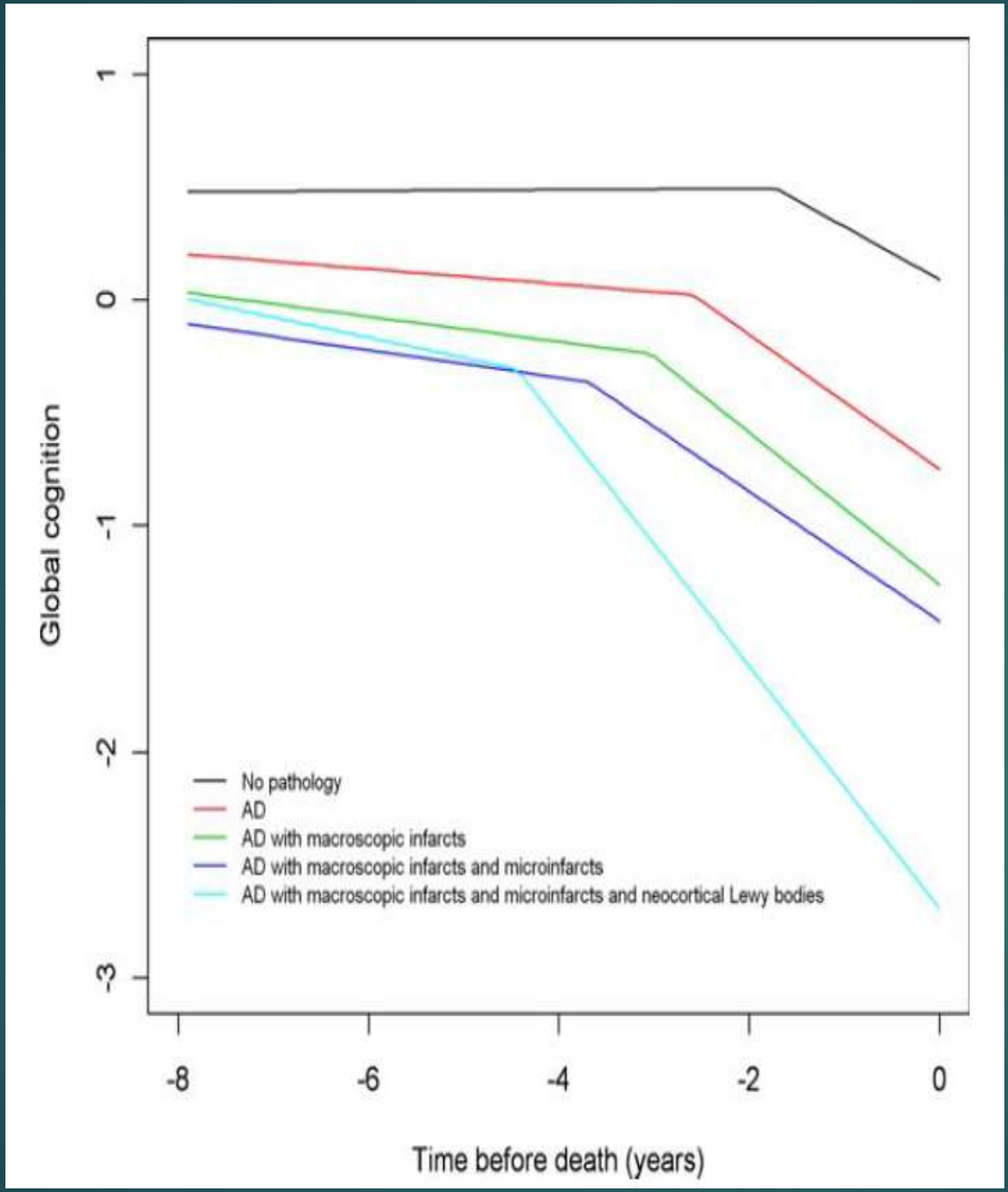


Normals

Alzheimers

AD + Lewy body

P. Boyle, et al., 2013



Normal

AD

AD + VaD

AD & LBD

P. Boyle et al., 2013

Young men’s dreams become old men’s fate

- Rapid Eye Movement (REM) Behavior Disorder
- Loss of normal motor paralysis during REM sleep: physically act out while asleep
- Average 25 (15-50) year onset of REM Behavior Disorder
- 50% develop Parkinson’s or Lewy Body Major NCD

Bizket: REM Sleep Disorder

Why “what is good for the heart is good for the brain”

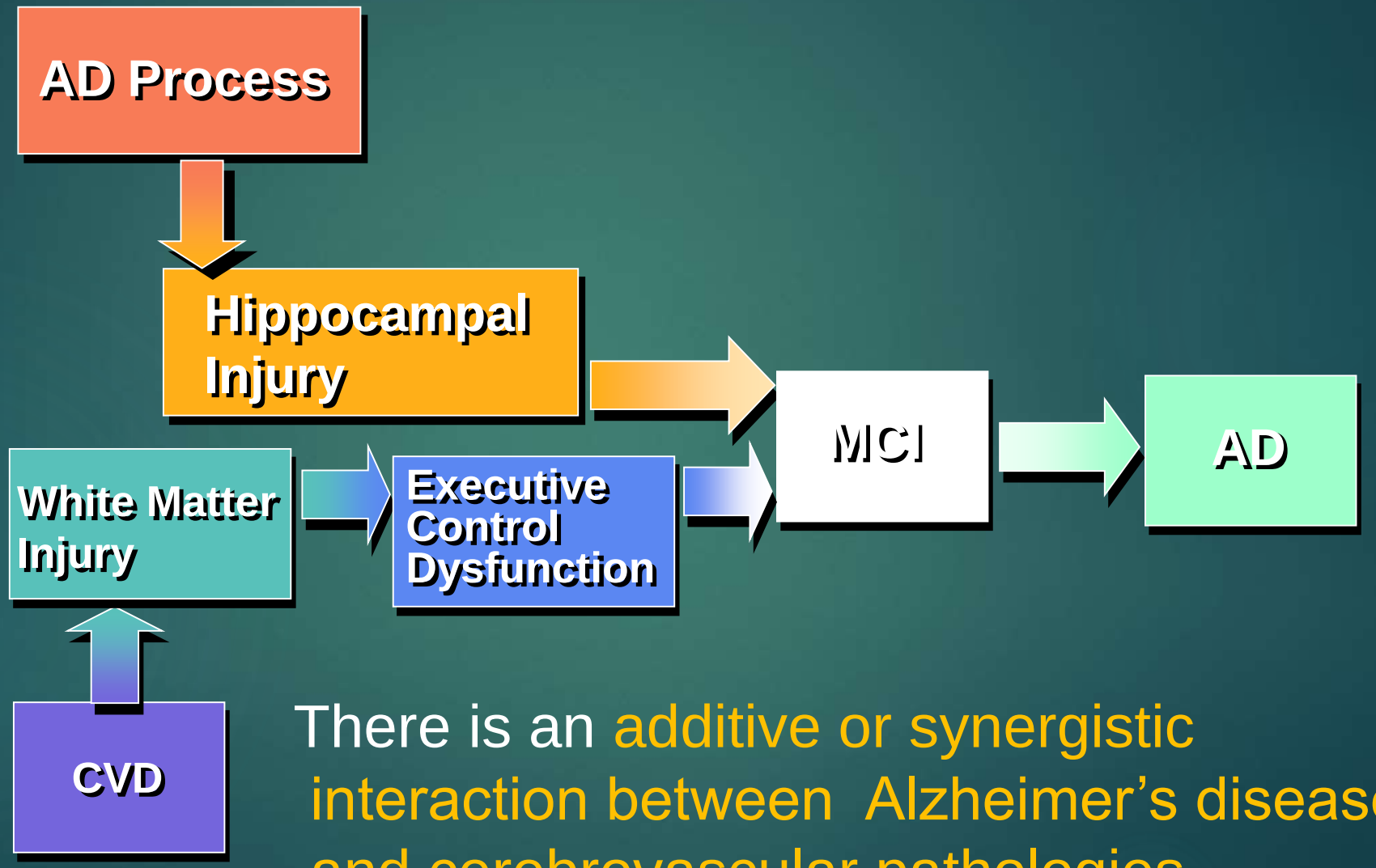
400 miles of blood vessels in human brain.

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

Vascular Disease: 15-25%

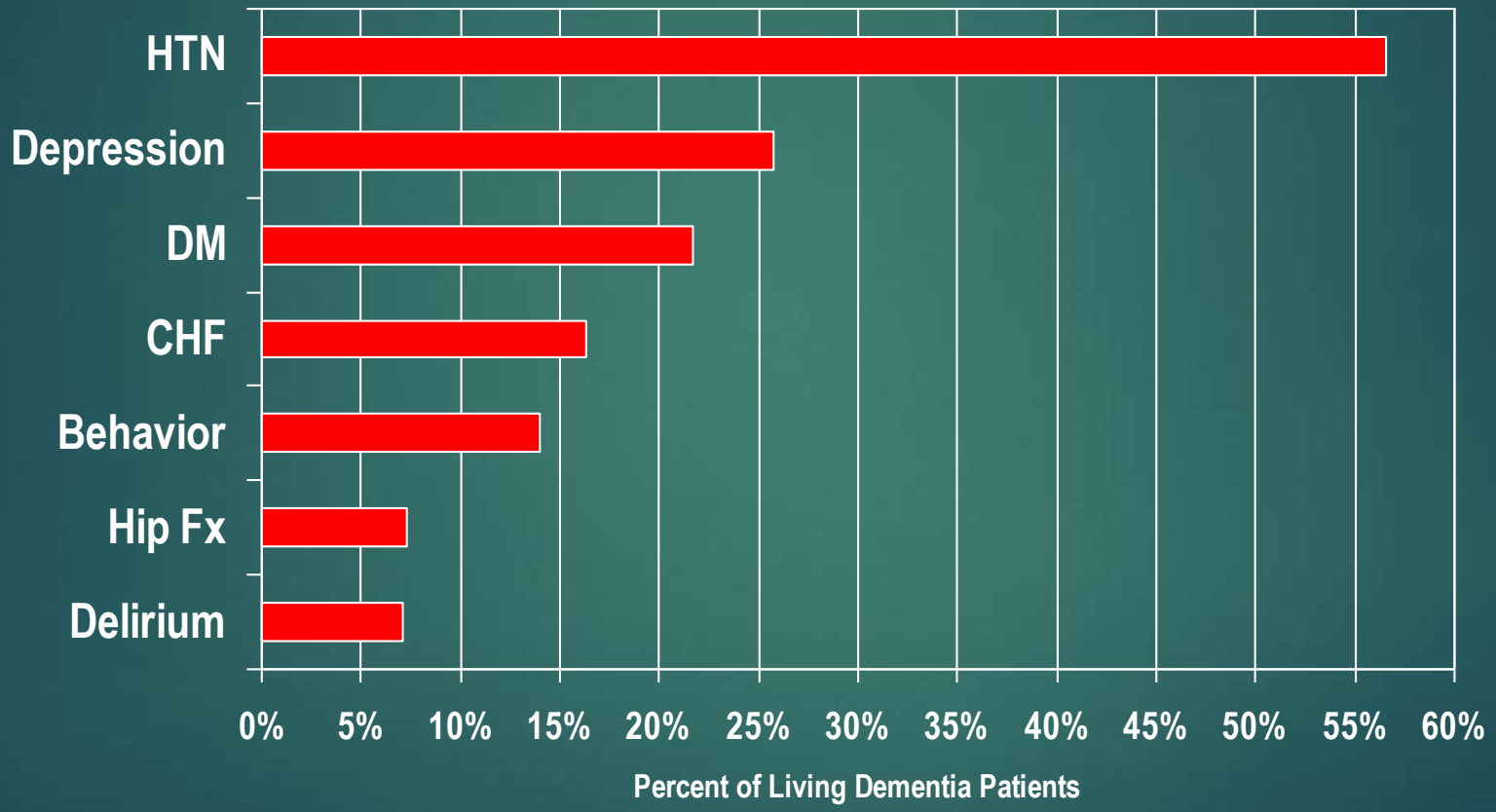
- Capillary autoregulation dysfunction & series of mini strokes
- Abrupt onset, stepwise course
- Focal neurological and neuropsychological deficits
- May or may not include memory deficit
- Major NCD: onset with presence of Alzheimer's

Combined Role of AD and CVD in MCI and Dementia Risk



There is an additive or synergistic interaction between Alzheimer's disease and cerebrovascular pathologies

Co-Morbidities of NorCal KP Dementia Pts; Million chart review



Frontal Temporal Disease: 5-10%

- FTD: Behavioral Sxs precede Neurological presentation
- Personality/Behavioral changes precede memory deficit: disinhibition, agitation, delusion, hallucinations, apathy
- Executive dysfunction: poor judgment, loss of impulse control/disinhibition
- Language Variant: semantic, non-fluent aphasia
- 4 x greater in men; average age: 53

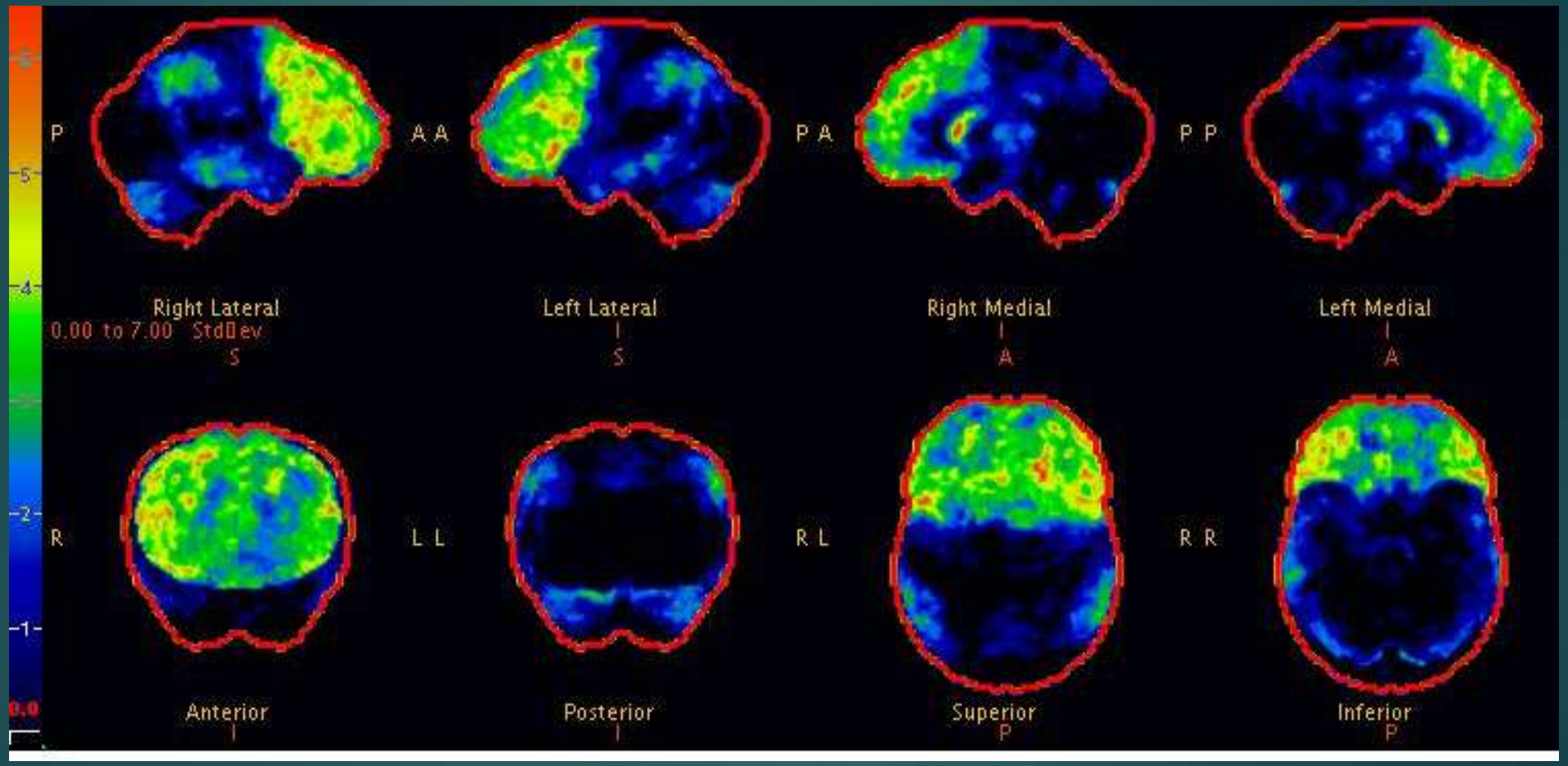
FTD: Proportion of First Symptoms

Behavior	62%
Memory	11%
Language	12%
Executive	11%
Motor	4%

First Symptoms of FTD to appear commonly

Symptom	Examples
Behavioral Disinhibition	Rudeness, hypersexuality, hoarding
Apathy	New “coach potato” habit
Loss of empathy	Insensitivity to others
Perseveration	New obsessions, grinding teeth, humming
	Craving for sweets
Hyperorality	Disorganized at work
EF deficits	

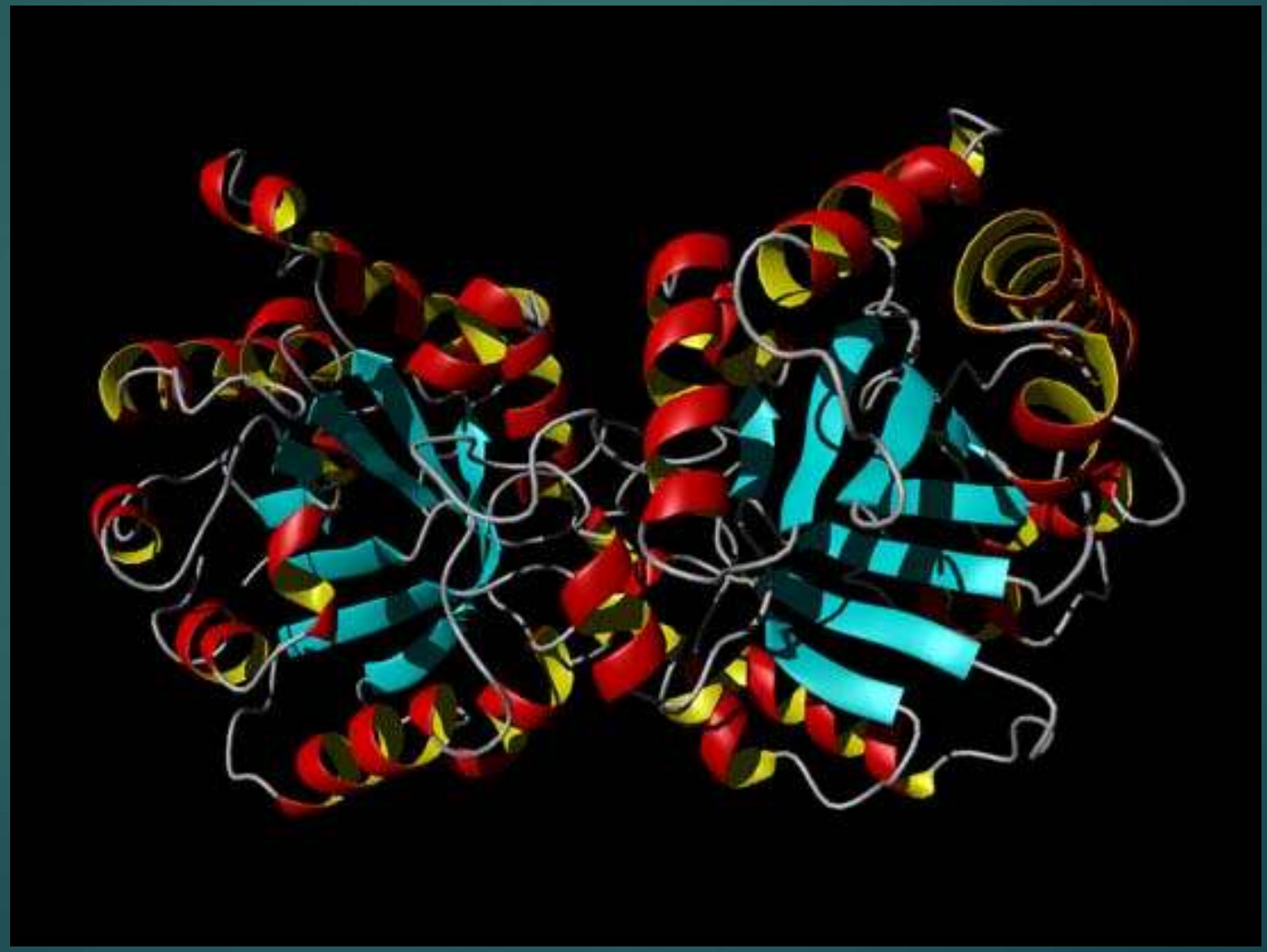
bvFTD Imaging (FDG PET)



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

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

Prion: abnormally folded protein



Creutzfeldt-Jakob Disease (CJD)

- Prevalence: 1% of Major NCD; most rapidly fatal ND
- Causation: infectious prion disorder (abnormal shape changing protein) (Posner, UCSF); very infective (heat does not kill; corneal transplant, human growth factor transmission); Gaba ↓
- Creutzfeldt-Jakob: Historically Eastern European Jewish disorder, in 50's, very rapid (1 year); any age (40-60); 5-15% familial
- Mad Cow Disease (Bovine Spongiform encephalitis): CJD in humans; meat consumption; related, younger (in England: 2 million cows; 156 human cases currently)

Symptoms of CJD

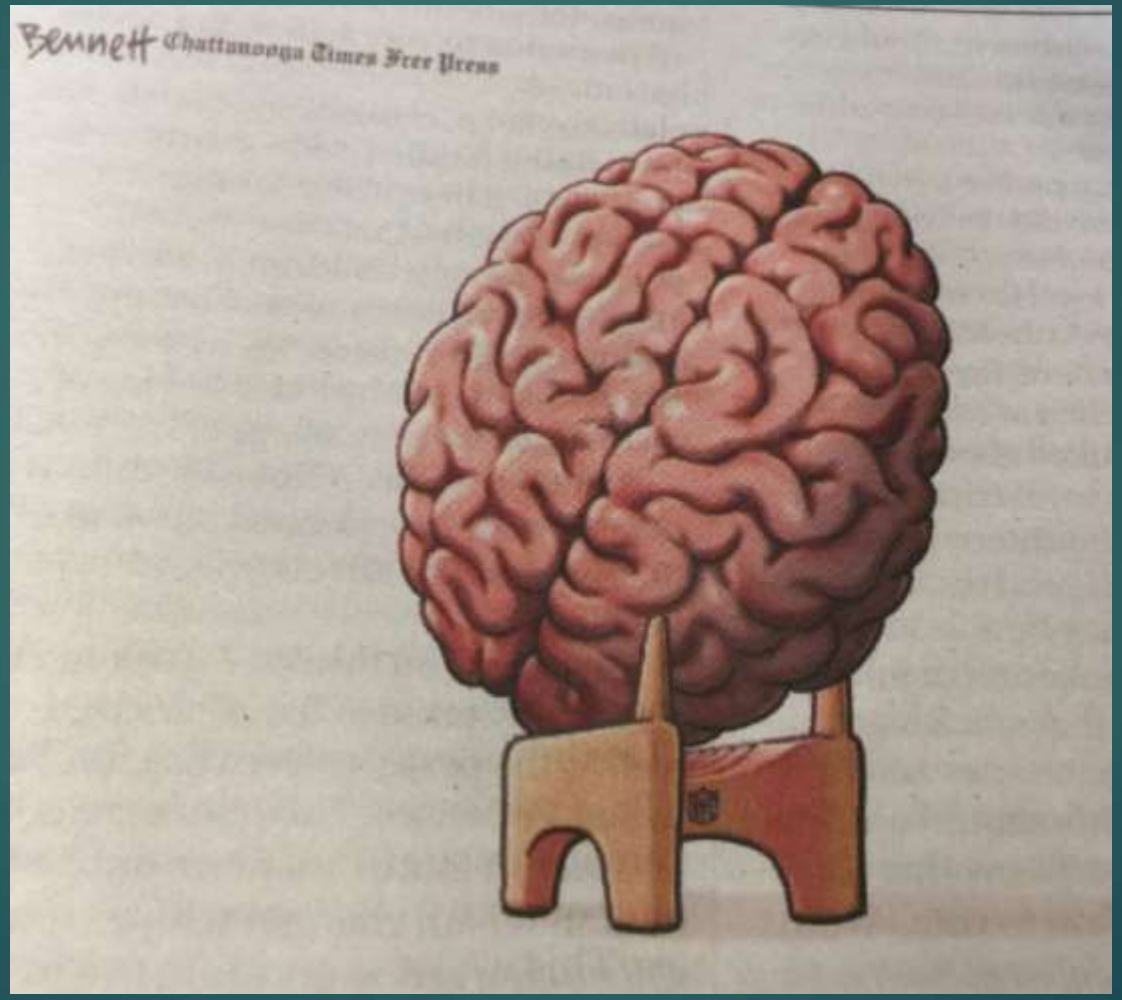
- Triad of symptoms: Dementia, involuntary movements (esp. myoclonus), specific EEG wave

- Prodromal: fatigue, anxiety, appetite/sleep/concentration ↓; then incoordination, altered vision, abnormal gait, rapid Major NCD

- Proportion of First Symptoms:

Motor	30%
Memory	25%
Executive	15%
Language	10%

Don’t Kick Your Brain:
Chronic Traumatic Encephalopathy



NFL Football & Concussions

CONCUSSION

A Must Read for NFL Players

Let's Take Brain Injuries Out of Play

Concussion Facts

Concussion is a *brain injury* that alters the way your brain functions

Concussion can occur from a blow to the head/body:

- following helmet to helmet contact, and / or
- contact with the ground, object or another player

Most concussions occur without being knocked unconscious

Severity of injury depends on many factors and is not known until symptoms resolve and brain function is back to normal

All concussions are not created equally. Each player is different, each injury is different and all injuries should be evaluated by your team medical staff

Concussion Symptoms

Different symptoms can occur and may not show up for several hours. Common symptoms include:

- Confusion
- Headache
- Amnesia / Difficulty remembering
- Balance problems
- Irritability
- Dizziness
- Difficulty concentrating
- Nausea
- Feeling sluggish, foggy or groggy
- Sensitivity to noise
- Sensitivity to light
- Double / fuzzy vision
- Slowed reaction time
- Feeling more emotional
- Sleep disturbances
- Loss of consciousness

Symptoms may worsen with physical or mental exertion (e.g. lifting, computer use, reading)

Why Should I Report My Symptoms?

- Practicing or playing while still experiencing symptoms can prolong the time to recover and return to play.
- Unlike other injuries, there may be significant consequences of "playing through" a concussion. Repetitive brain injury, when not treated promptly and properly may cause permanent damage to your brain.

What Should I Do If I Think I've Had a Concussion?

Report it. Never ignore symptoms even if they appear mild. Look out for your teammates. Tell your Athletic Trainer or Team Physician if you think you or a teammate may have had a concussion.

Get Checked Out. Your team medical staff has your health and well being as its first priority. They will manage your concussions according to NFL / NFLPA Guidelines which include being fully asymptomatic, both at rest and after exertion, having a normal neurologic examination, normal neuropsychological testing, and clearance to play by both the team medical staff and the independent neurologic consultant.

Take Care of Your Brain. According to the CDC*, "traumatic brain injury can cause a wide range of short– or long term changes affecting thinking, sensation, language , or emotions". These changes may lead to problems with memory and communication , personality changes, as well as depression and the early onset of dementia. Concussions and conditions resulting from repeated brain injury can change your life and your family's life forever.

Work smart. Use your head, don't lead with it. Help make our game safer. Other athletes are watching...

*for more information about traumatic brain injury and concussion, go to http://www.cdc.gov/concussion

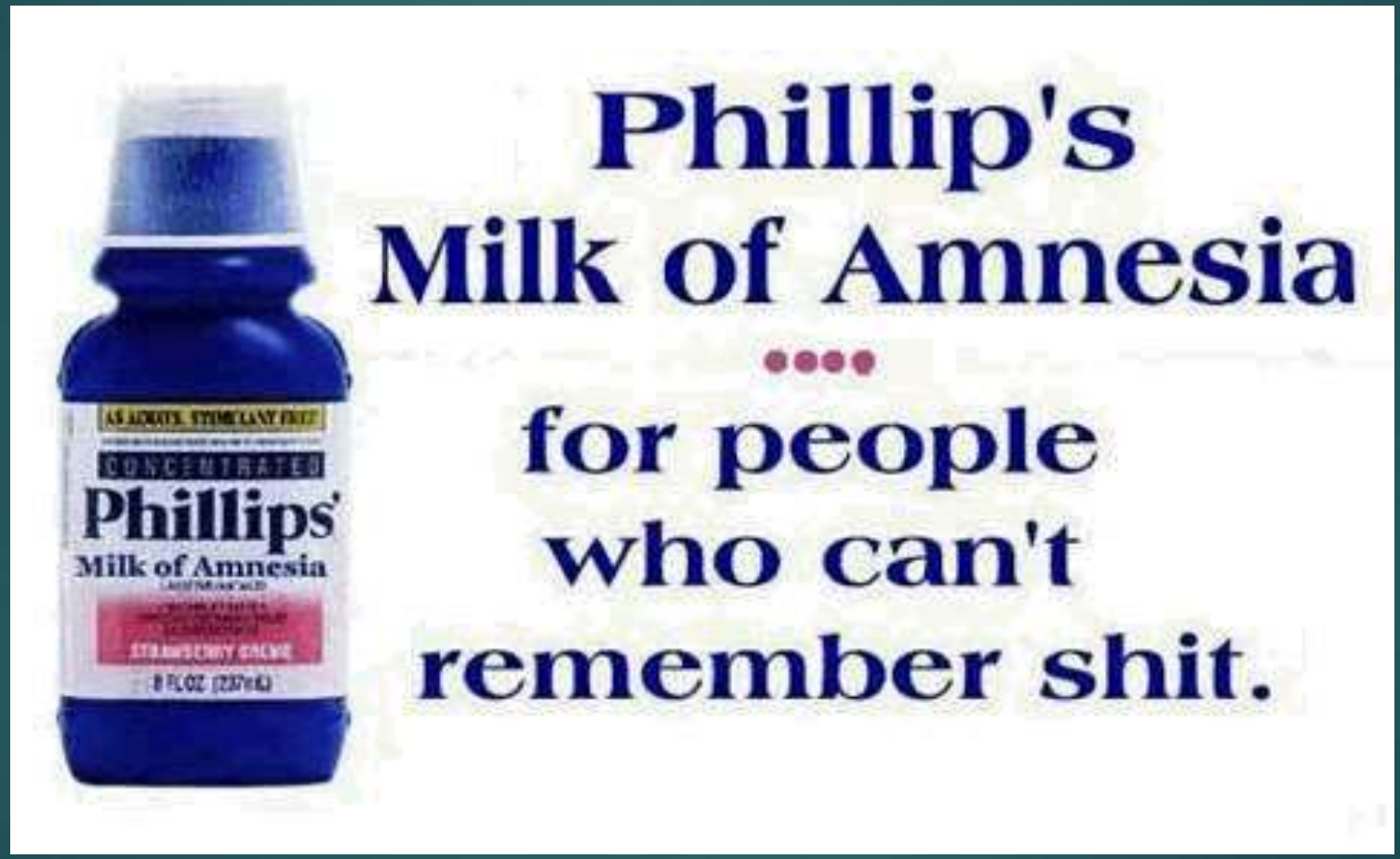
Chronic Traumatic Encephalopathy

- Long term effects of repetitive sports related brain trauma
- Historically dementia pugilistica among boxers
- Caused by Tau & TDP-43 abnormal proteins
- Professional football players, 50% of boxers, wrestlers, military veterans (blast injuries)
- Repeated trauma early in life, end of career; 8 year latency period, then personality & mood & cognitive changes over 17 years, then Major NCD
- Motor neuron disease (ALS) in some i.e. Lou Gehrig ?

Differential Diagnosis of Neurodegenerative Disorders: First Symptom

- AD – Memory (no encoding) (70%)
- FTD – Behavior, executive loss, language
- VaD – Apathy, executive deficits
- DLB – Visual hallucinations, Visual Spatial deficits, Parkinsonism, delirium
- PDD – Motor problems, depression, hallucinations
- CTE - Behavior
- CJD – Involuntary motor

Latest Memory Cure



Anti-Dementia Medications ?

- **The Question:** Are there medications that prevent Major NCDs like Alzheimer's disease?
- **The Verdict:** No Dementia disease prevention medications.
- But…There are Dementia modifying behaviors.

Current AD Drug Therapies: no disease progression prevention

Medication	Dose	Common Adverse Side Effects	Comments
Donepezil (Aricept)	5 mg/day at bedtime with or without food for 4 to 6 weeks; 10 mg/day there-after, if tolerated	Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, muscle cramps, insomnia and vivid dreams	Available in a single daily dose
Rivastigmine (Exelon)	3 mg daily, split into morning and evening doses with meals; dose increased by 3 mg/day every 4 weeks as tolerated, with a max-imum daily dose of 12 mg	Nausea, vomiting, loss of appetite, weight loss, diarrhea, indiges-tion, dizziness, drowsiness, headache, diaphoresis, weakness	Available as a patch
Galantamine (Razadyne)	8 mg daily, split into morning and evening doses with meals; dose increased by 4 mg every 4 weeks, as tolerated, with a maximum daily dose of 16 to 24 mg	Nausea, vomiting, loss of appetite, weight loss, diarrhea, dizziness, headache, fatigue	Available as an extended-release capsule
Memantine (Namenda)	5 mg/day with or without food; dose increased by 5 mg every week, with a maximum daily dose of 20 mg	Constipation, dizziness, headache, pain (nonspecific)	Often used as an adjunct to cholinesterase inhibitors; not recommended alone for treatment of early disease

NCD Treatments

- Cholinesterase inhibitors (acetylcholine deficit; cholinergic enhancers) – Aricept, Exelon, Reminyl;

- Inhibitors basically increase the availability of intrasynaptic acetylcholine; improves attention, ADLs

- Aricept: 1 year sig. diff. from placebo; no diff. at 3 years; prefrontal activation on SPECT; cost = 100 for $196

Aricept: Possible Negative Sxs

- Side effects: diarrhea, muscle
- Hospitalized for fainting almost twice as often as people with NCD who did not receive these drugs.
- Slowed heart-rate (bradycardia) was 69 per cent more common amongst cholinesterase inhibitor users.
- 49 per cent increased chance:
  - of having permanent pacemakers implanted
  - and an 18 per cent increased risk of hip fractures.

Risk Factors for Cognitive Decline:
Need to begin fighting them in your 20's

- Age
- Gender: female
- Hypertension
- Heart Disease
- Diabetes
- Obesity in middle age
- Poor Nutrition
- Chronic Stress
- Poor hearing
- Recurrent Major Depression

Low education
No physical exercise
Sedentary behavior
Smoking
Long term Benzodiazepine use
Social isolation
Neuroticism in women
Mood swings in middle age

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!!

Ten Commandments for Brain Fitness

I. Thou shall exercise daily.

II. Thou shall minimize risk factors for cerebrovascular disease (HTN, Hyperlipidemia, DM, overweight, smoking)

III. Thou shalt eat a Mediterranean Diet

IV. Thou shall choose thy parents wisely

V. Thou shall maintain intellectual engagement throughout life

VI. Thou shall cultivate and sustain friendships and good company

VII. Thou shall obtain restful sleep

VIII. Thou shall enjoy only 1 drink of alcohol

IX. Thou shall manage stress effectively

X. Thou shall not text or use cell phone while driving.

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