2020
Vella Family
Pumpkins

Passionate pumpkin carving 10-year old daughters grow up to have good brains, high IQs, and graduate from UCSF School of Medicine in 2015 & 5th year Fellowship in 2021. She was just hired as a cardiothoracic Radiologist at UCSF. Yeah Maya!! Proud Dad!

Neurocognitive Disorders due to Neurodegenerative Disorders

Alzheimer's, FTD, Vascular, & Lewy Body & Subcortical Diseases

Charles J. Vella, PhD

2021

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Test your knowledge

- Alzheimer's is a normal part of aging.
- Alzheimer's is a progressive brain disease.
- People younger than age 50 can get Alzheimer's.
- Family history is greatest risk factor for Alzheimer's
- Dementia/NCD is the same thing as a neurodegenerative disease.
- There are drugs to treat the progression of AD

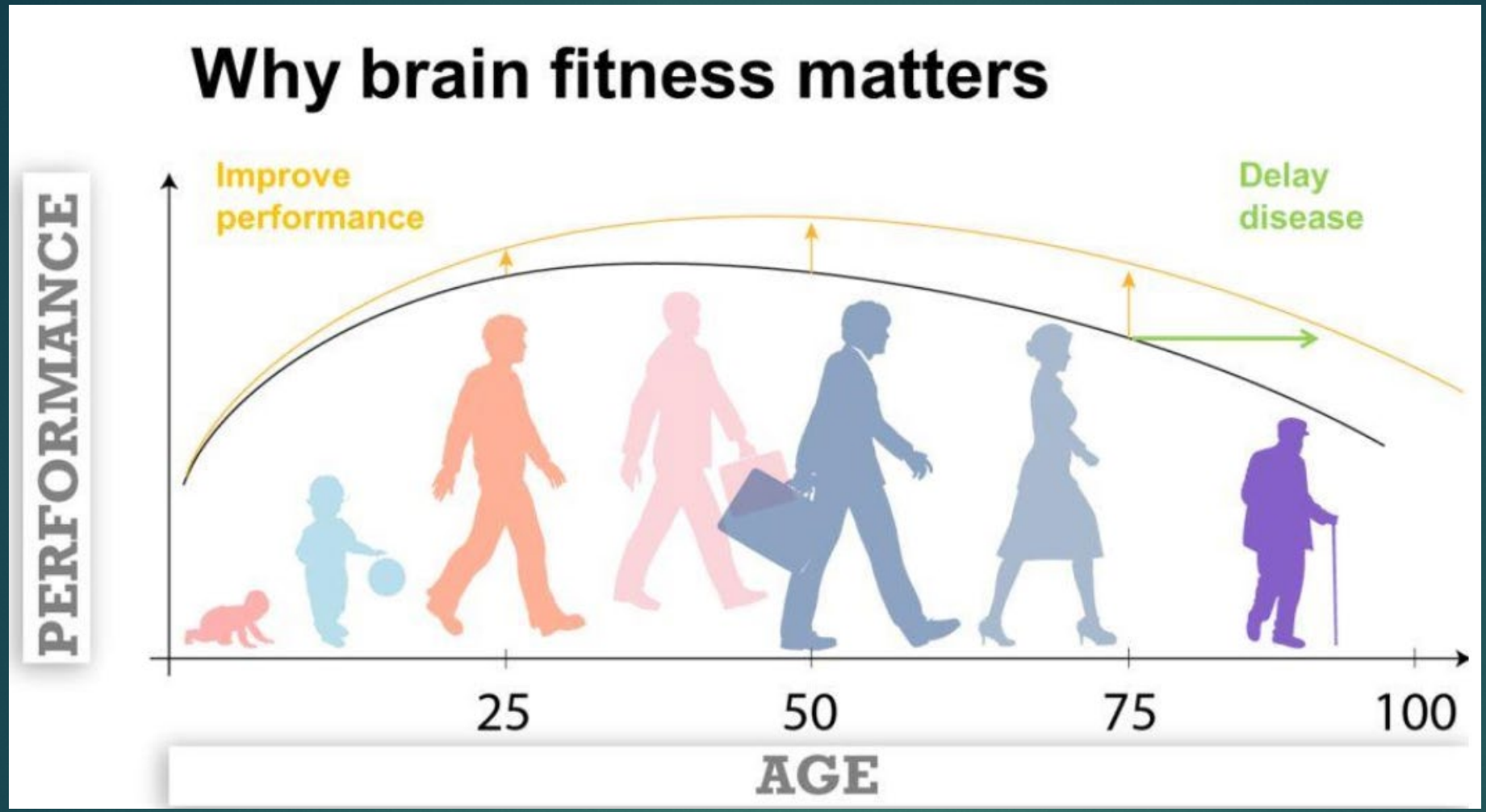
Required reading: Explanation of major symptomology of the dementias and basic questionnaire

California Dept. of Public Health, Chronic Disease Control Branch, Alzheimer's Disease Resources for Families and Health Professionals

Assessment of Cognitive Complaints Toolkit for Alzheimer's Disease

- https://www.cdph.ca.gov/Programs/CCDPHP/DCDIC/CDCB/Pages/AlzheimersDiseaseResources.aspx
- The Assessment of Cognitive Complaints Toolkit for Alzheimer's Disease (PDF, 2.19 MB)
- The Assessment of Cognitive Complaints Toolkit for Alzheimer's Disease Instruction Manual (PDF, 2 MB)

- Best way to question patients to confirm dementia diagnosis: memorize all the questions!!



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

Intellectual Ability Declines in Normal Aging

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.
- The estimated proportion of the general population aged 60 and over with dementia at a given time is between 5-8%.
- 75% of people do not realize they can reduce the risk of dementia.

Old Age?

From age 70 es, won the Nobel Prize i

Age-related cognitive impairments

- Cognitive health span does not currently match human lifespan.
- 16 million people in the USA are living with cognitive impairment, and more than 1.6 million of these individuals will develop Alzheimer's disease (AD) annually.
- But the majority of older adults—~ 85%—will not develop dementia in their lifetime.
- Nevertheless, many individuals in their 60s and older will experience a range of age-related cognitive impairments that contribute to decreased quality of life and that have important socioeconomic consequences

Medications to watch out for in the elderly

- **Beers List: Potentially Inappropriate Drugs for Elderly:** http://www.empr.com/clinical-charts/beers-list-potentially-inappropriate-drugs-for-elderly/article/125908/
- Screening Tool for Older Persons' Prescriptions (STOPP) criteria: https://www.ngna.org/_resources/documentation/chapter/carolina_mountain/STARTandSTOPP.pdf
  - Very little data for drug effects in age 70+ in general
  - Docusate (Colace) stool softener: does not work
  - Proton pump inhibitors (PPIs) for reflux (Prilosec, Nexium, Prevacid) - dementia
  - Statins without heart hx, esp. 80+
  - Benzodiazepines – falls, cognitive decline
  - Beta blockers (atenolol)

Medications to watch out for 2

- Antimuscarinics for urinary incontinence (oxybutynin) – high anticholinergic effects
- Cholinesterase inhibitors (Aricept): side effects – pacemakers, urinary incontinence
- Muscle relaxants for the back
- OTC Supplements, i.e. multivitamins (Expensive pee)

Life-long Cognitive Declines

- Tend to decline during the entire adult lifespan:
  - Processing speed
  - Working memory
  - Episodic memory

- These show linear life-long declines with no evidence for accelerated decline in the later decades in normals

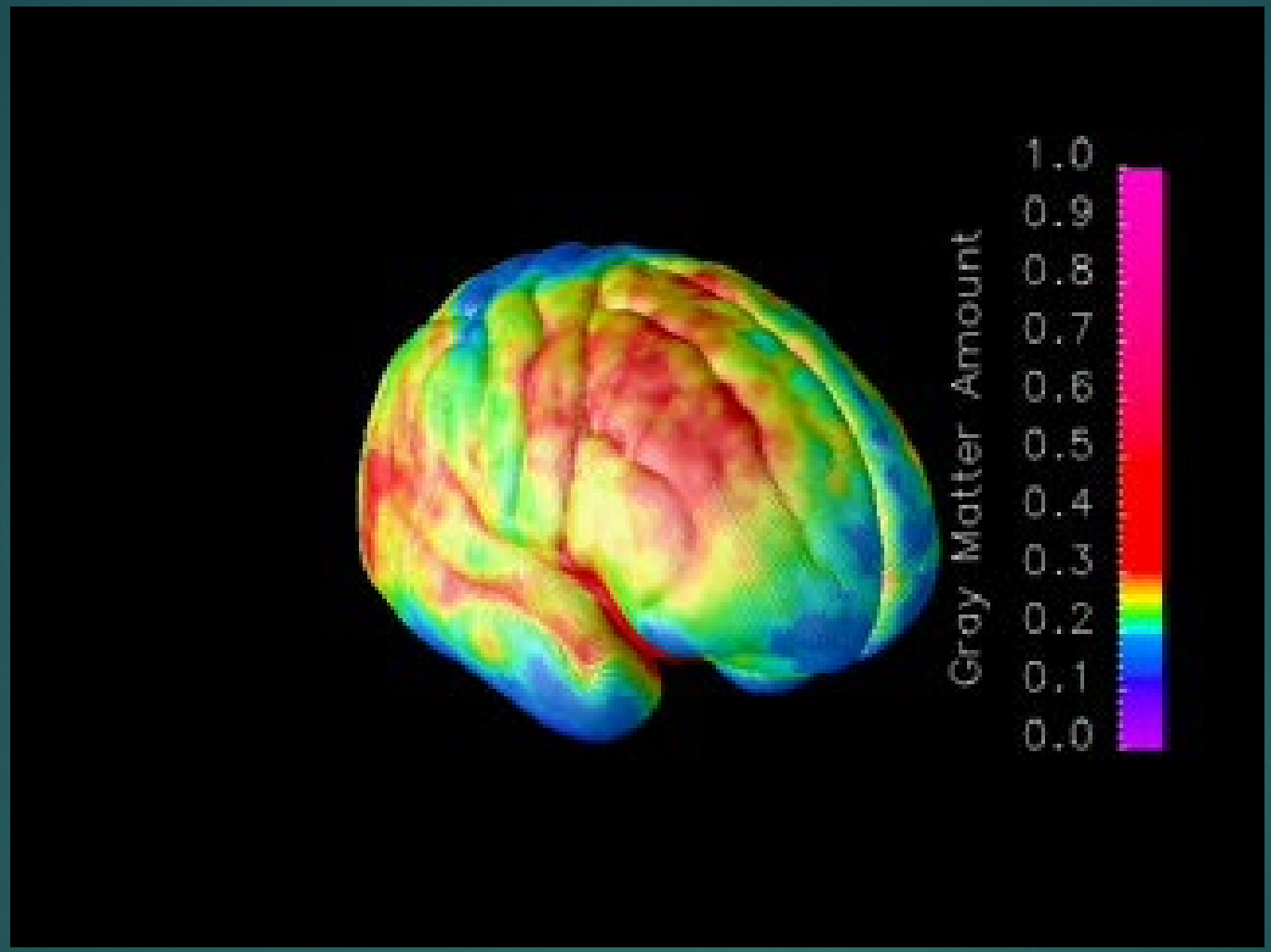
Late life cognitive declines

- Procedural memory and experiential knowledge show no age related decline
- Vocabulary and semantic knowledge are stable
- But words that you do not use regularly will disappear
- Any accelerated declines are due to the influence of disease processes.

Stable Cognitive Abilities

- Cognitive abilities unchanged throughout life:
  - Autobiographical memory
  - Theory of mind tasks (attribution of mental states to other individuals)
  - Emotional processing
  - Behavioral memory
  - Recognition/familiarity memory (I know I know that)

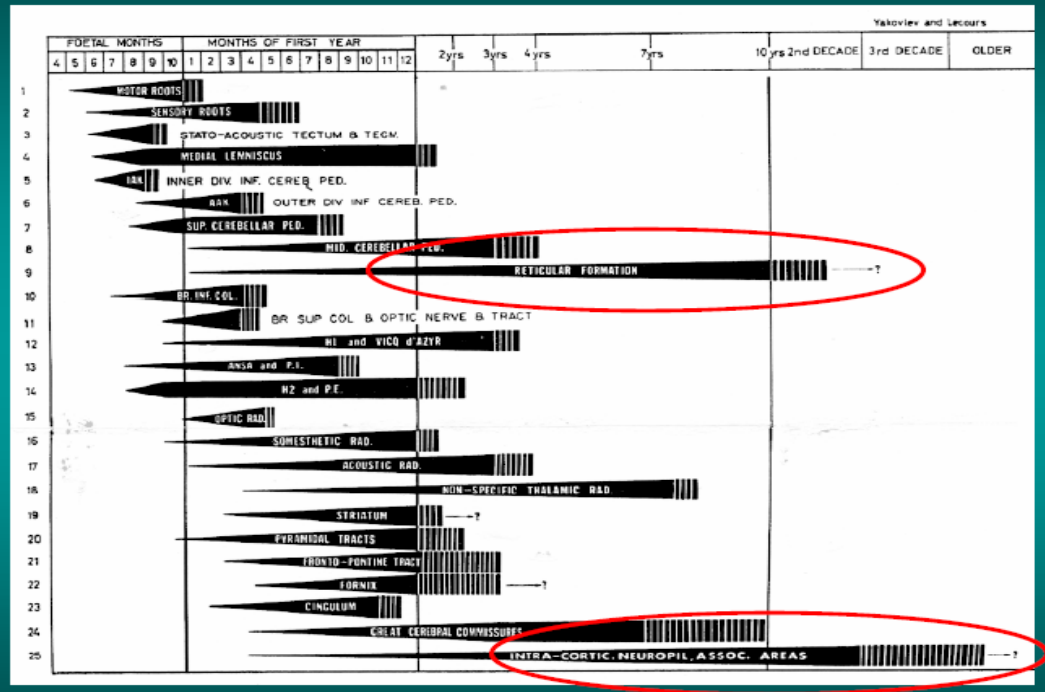
Normal Teen Brain: cortical pruning, age 5 to 21



Lose 50% of all synaptic connections;
Motor areas first, frontal last to develop

Myelin Sheets on Axons Mature Slowly in Frontal Lobes; may increase into 30s.

Regional Maturation: Myelogenetic Cycles



Taken from Yakovlev & Lecours, The Myelogenetic Cycles

Amount of white matter (axon interconnections) distinguishes us from primates, not size of prefrontal lobes. Creates "greater bandwidth" and processing speed. Einstein had more white matter, not neurons.

Yakovlev & Lecours 1967

Neuronal Changes with Age

- Lower volumes of grey matter, not from cell death, but rather from lower synaptic densities
- More atrophy in prefrontal and hippocampal areas
- PFC undergoes the largest age related volumetric changes in adulthood:
  - decline of about 5% per decade after the age of 20.
  - largest declines in volume are in lateral regions of the PFC (vs. inferior PFC in AD).

Neuronal Changes 2

- Hippocampus in normals:
  - Entorhinal cortex and CA1 region are preserved in normal aging
  - Dentate gyrus and Subiculum show age-related declines in normal individuals (opposite pattern in AD)

- Amygdala is less active in older adults in response to emotionally negative stimuli, but exhibits similar activity in emotionally positive stimuli

Cognitive Changes: Lower Executive Functioning

- Older adults experience greater difficulty than younger adults in performing executive processes:
  - Either a failure to activate PFC regions
  - Or increased activation of PFC regions under relatively easy conditions

- Physical exercise has robust effects for executive-control processes.

Longitudinal Studies of cognition in normals

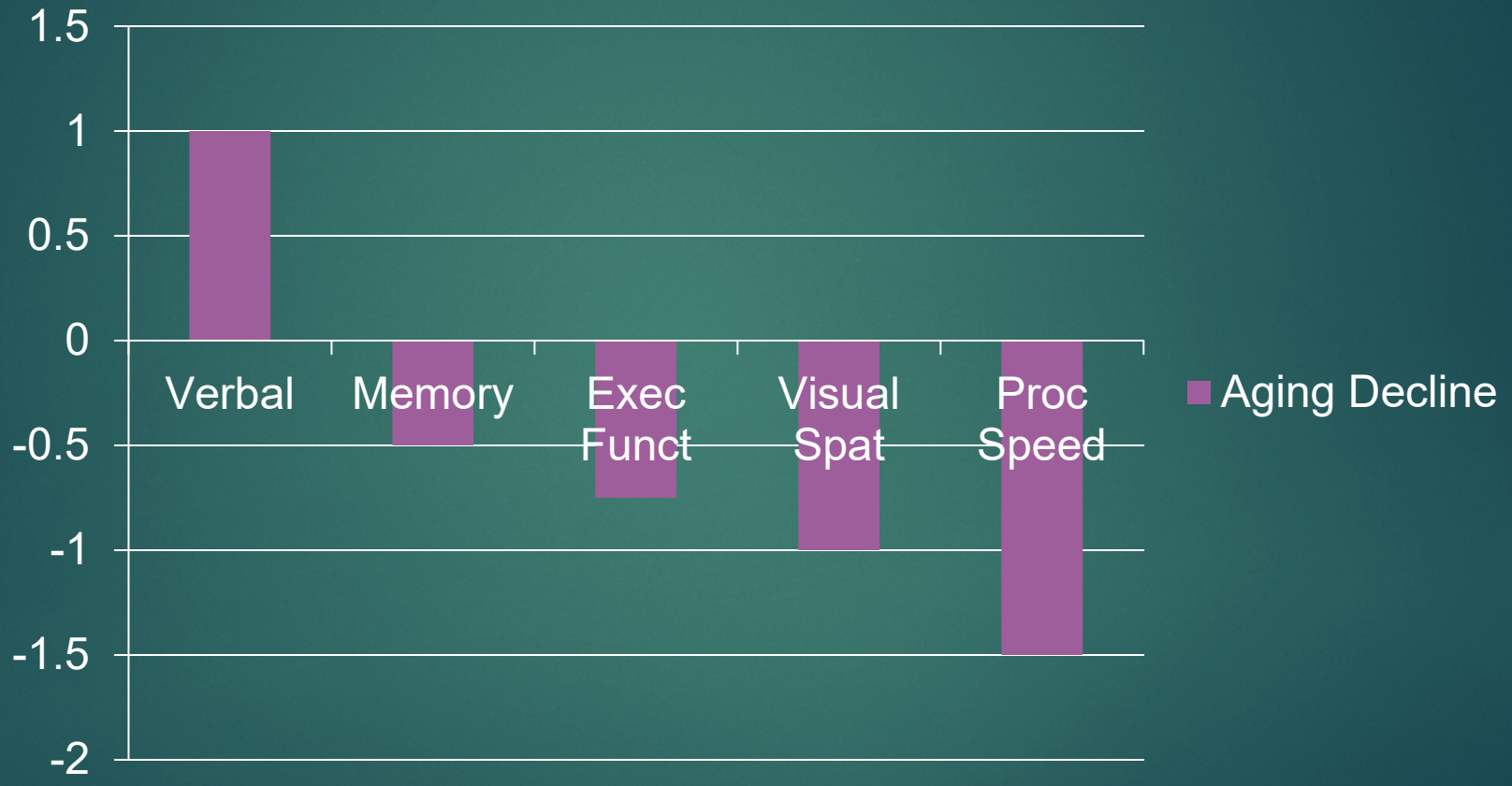
- K. Warner Schaie and Sherry Willis's Seattle Longitudinal Study: n = 5676
- Whitehall Study of British Civil Servants: n = 18,000; Whitehall II: n = 10,308 women and men
- Joshua K. Hartshorne, 2015: n = 48,537, Web-based and in-person testing
- The Nun Study: n = 678 (Religious = homogenous populations)
- The Religious Order Study: n = 1350 (40 groups; 94% autopsy rate)
- Rush Memory and Aging Project: n = 1,850

Normal Age-Related Changes in Cognitive Abilities

Seattle Longitudinal Study: After age 65:

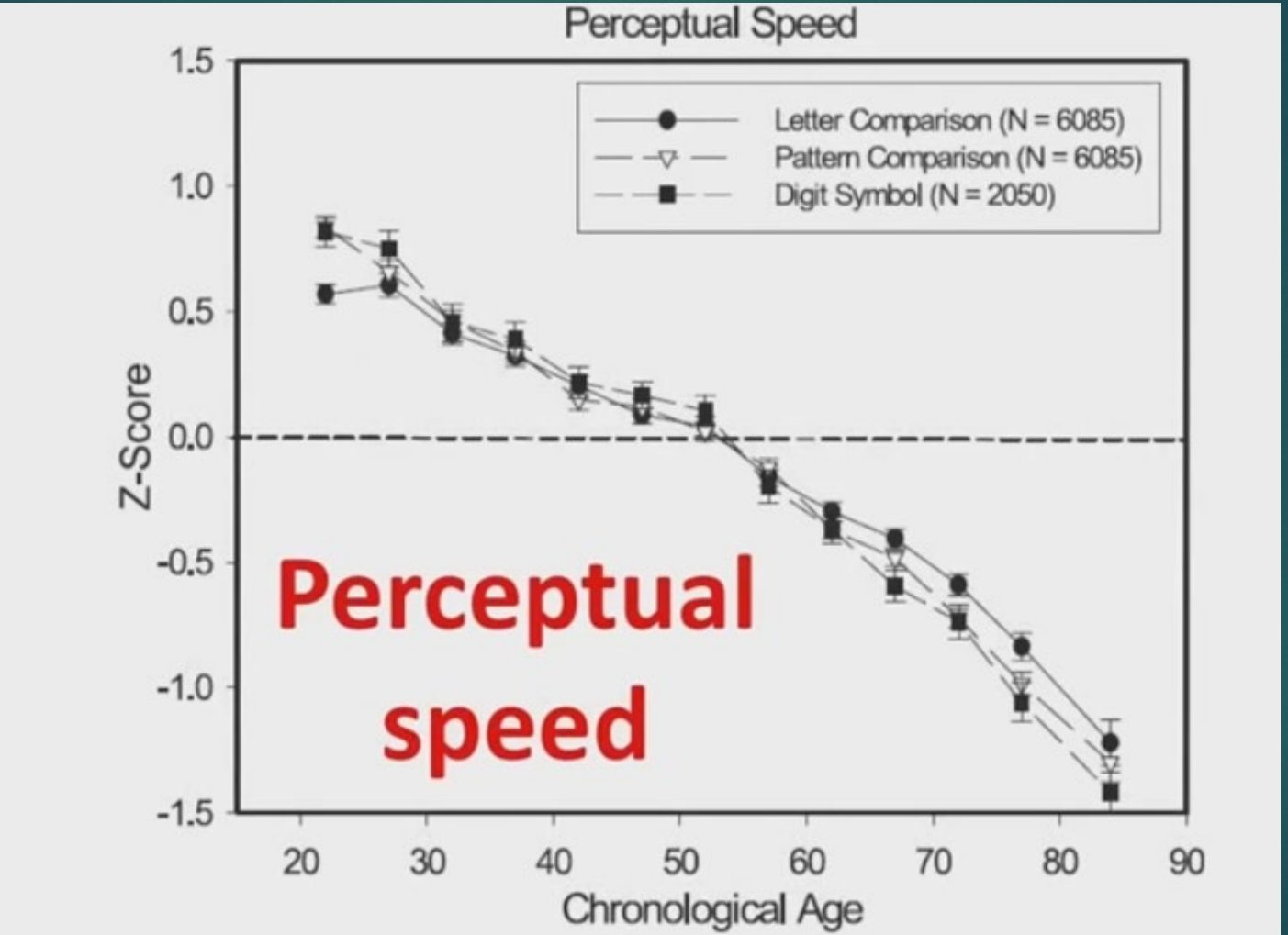
- Verbal Knowledge intact; difficulty with name retrieval, particularly the names of those we've not seen in a while
- Memory Ability = ½ s.d. decrease ↓
- Spatial Ability = 1 s.d. decrease ↓ ↓
- Perceptual speed = 1 ½ s.d. decrease ↓ ↓ ↓

Normal Aging Cognitive Decline
in the absence of brain pathology



Based on Schaie and Salthouse

We all lose PS: 1 ½ s.d. decrease ↓↓↓



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

Tale of Two Computers: Speed ↑↑↑

My 1982 IBM Computer
Intel 8088 chip @ 4.77 MHz

After age 65, we return to this speed!

2019 Lenovo ThinkPad P51
Intel Core i72. @ 2.70GHz

2500 times faster

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
- What is good for your heart is good for your brain
- 90+ Study: Past age 90, high blood pressure better than low blood pressure.

Alzheimer's ≠ Major NCD

- 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 pathology (abnormal proteins & synaptic loss)
  - meet neuropathologic criteria for AD
  - but have no cognitive decline

Souls go to God; Brains to Lab

Sister Matthia from the Nun Study

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

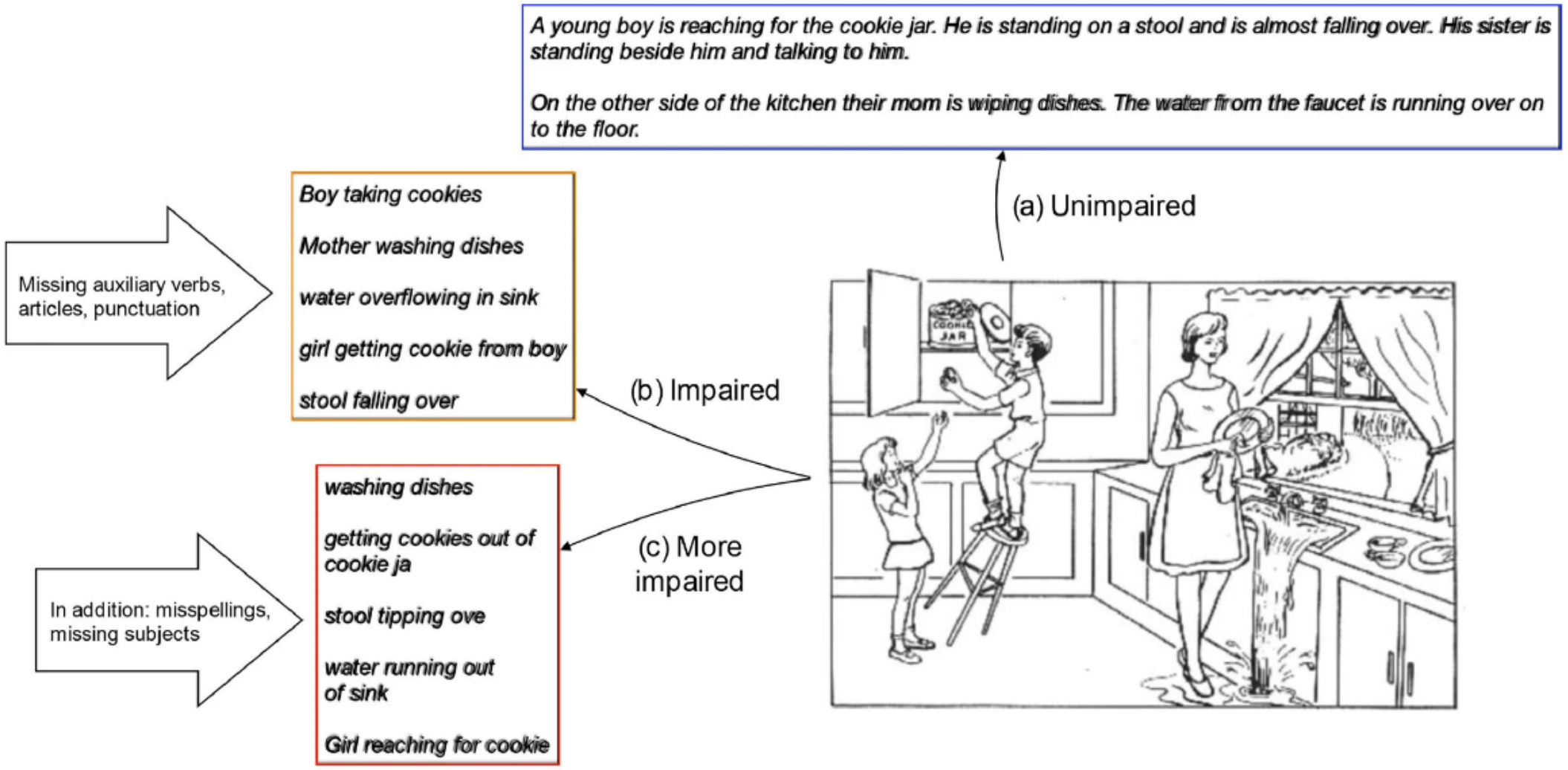
Aging with Grace, Snowdon; Snowdon et al, 2000

Nun's Brains: Preserved for Science at Univ. of MN

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

- Sister Helen: I was born in Éclair, Wisconsin on May 24, 1913 and was baptized at St. James Church.
- Sister Emma: It was about half past midnight between February 28 and 29 of the leap year 1912 when I began to live and to die as the third child of my mother whose maiden name is Hilda Hoffman and my father Otto Schmidt.
- Women with early richer vocabularies and grammatical complexity had less dementia than those who had worse linguistic ability.
- Early Idea density and grammatical complexity: Early 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

2021: AI predicts 10 years earlier who gets AD



Examples from the Framingham Heart Study, including (a) an unimpaired sample, (b) an impaired sample showing telegraphic speech and lack of punctuation and (c) an even more impaired sample showing in addition significant misspellings and minimal grammatic complexity. Elif Eyigoz et al., The Lancet 2020

Cookie Jar

- FTD: Early in the course of that disease, there are changes in the pace of the patients' speech, with pauses distributed seemingly at random. Word usage changes, too — patients use fewer abstract words.

Alzheimer disease without NCD/dementia: Sister Bernadette

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

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

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

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

- CR = more synaptic connections, abundance of dendrites

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

Predictors of Cognitive Reserve

- Bigger brain/head circumference (more neurons)
- Higher IQ
- Higher vocabulary level
- Higher education: college degree reduces cognitive decline by up to a decade; the more educated also live longer
- Occupational complexity: Work that involves complex thinking and social interaction
- Higher Social Economic Status

Predictors of Cognitive Reserve

- Regular cognitive activity (reading, crossword puzzles, plays)
- Higher literacy
- Social engagement
- Early-age physical activity
- Better cardiovascular status
- Having a partner with higher intellectual ability: partner's cognitive ability was protective: lower IQ partner gets the benefit (lower risk of AD)

Correlates of preserved cognition in NDAN

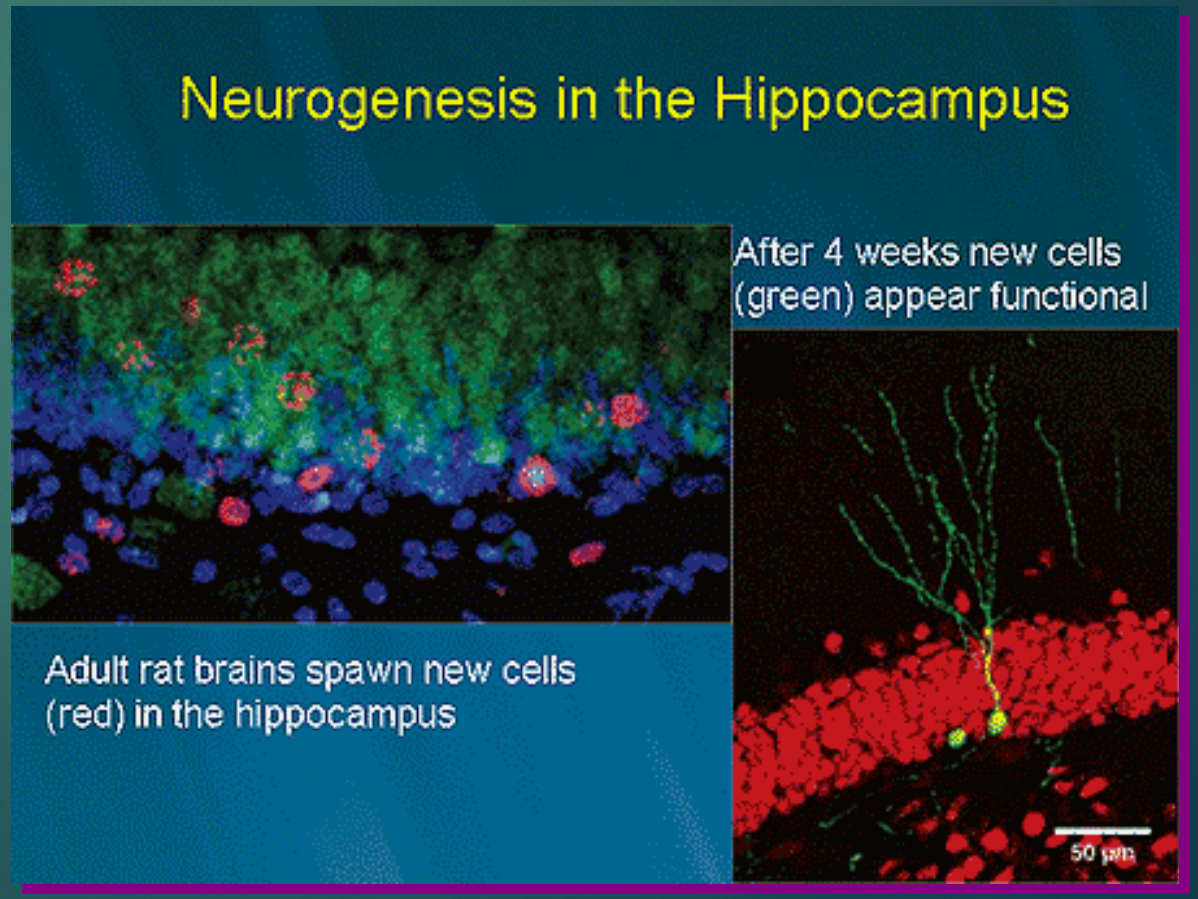
- Some atrophy is present, the progression rate is consistent with normal aging
- Larger global and regional grey matter volumes
- Total brain and hippocampal volume are greater.
- Higher number of synapses and enlargement of neuronal nuclei
- Increased insulin sensitivity; Increased levels of BDNF
- Reduced neuroinflammation
- Post synaptic resistance to amyloid-β (15 proteins different from AD)

Olga Zolochevska* and Giulio Taglialatela, 2016

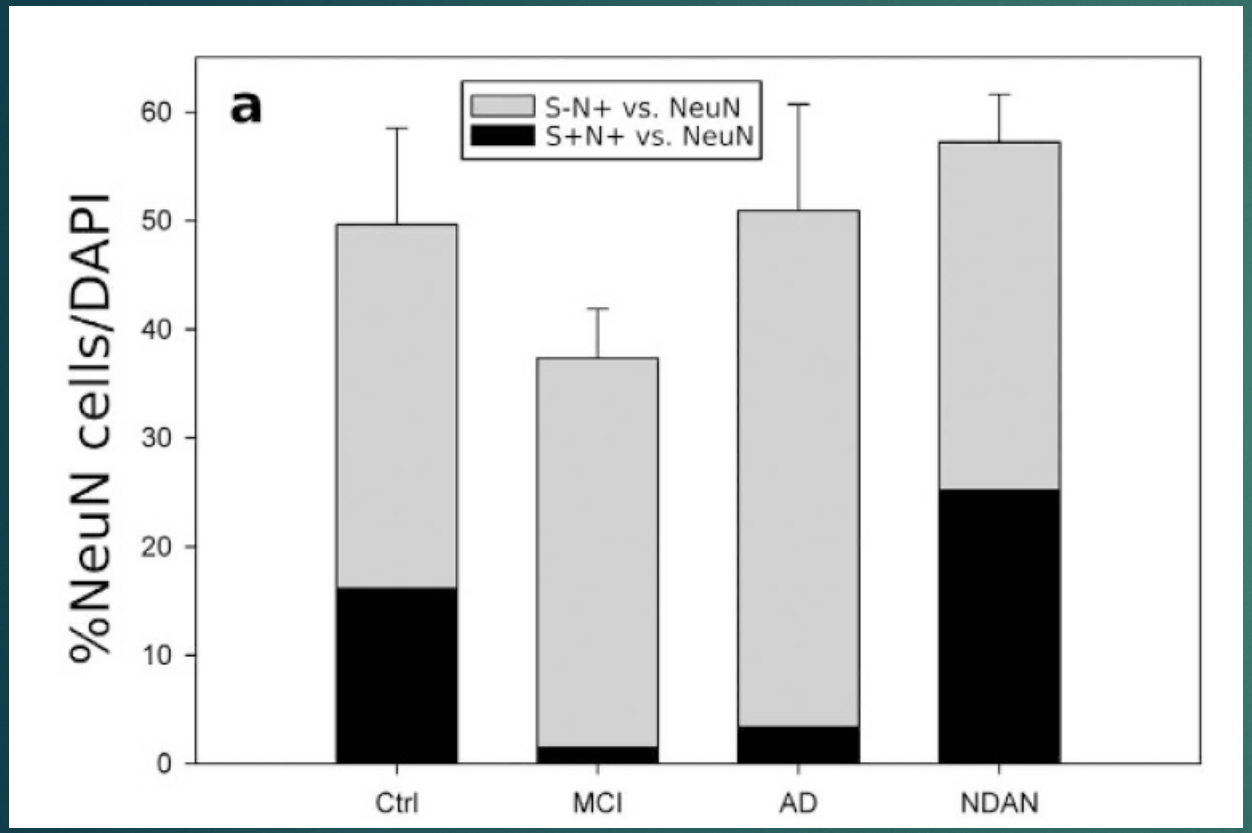
Neurogenesis = New brain cells

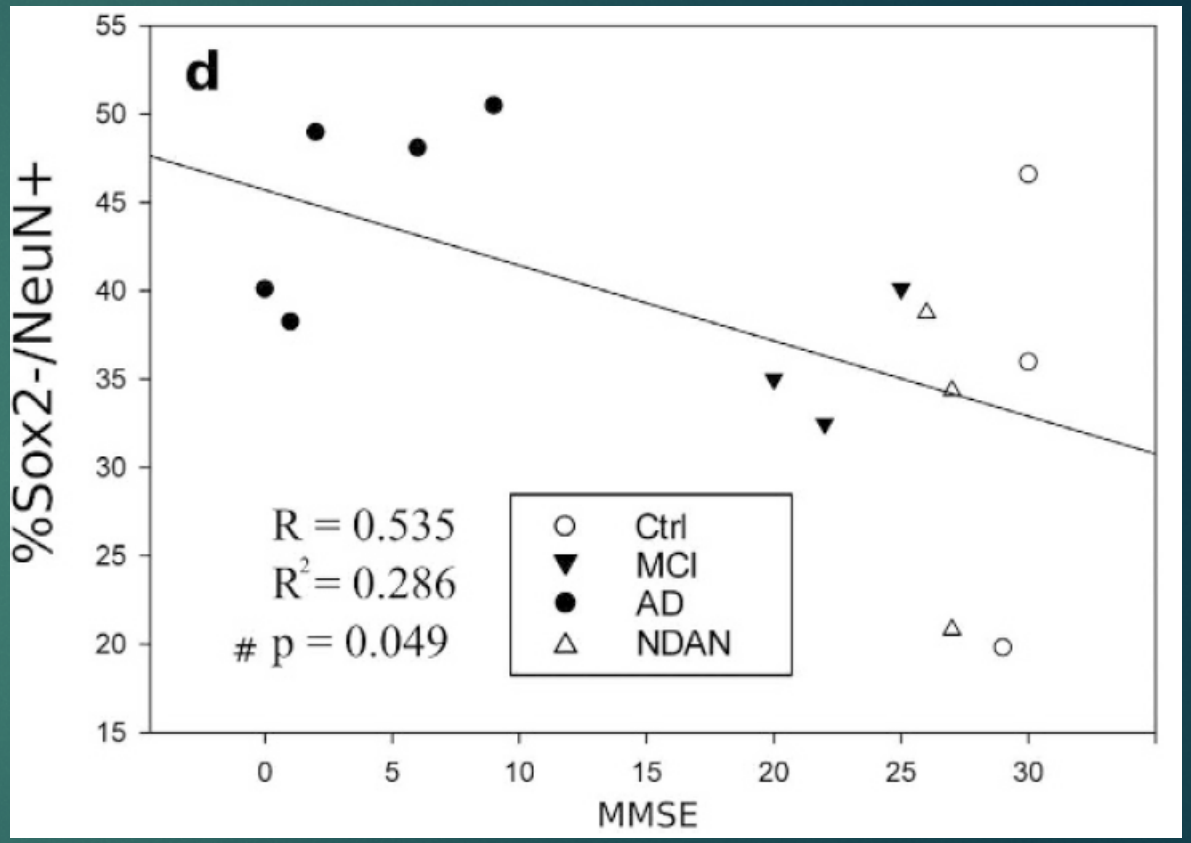
- Neurogenesis: growth of new neurons in the adult brain; Stem cells can become new adult neurons; 1,400 cells a day, esp. in dentate gyrus of hippocampus

- Ways to increase:
  - Exercise, Sex
  - Calorie restriction
  - Antidepressants
  - THC
- Ways to decrease
  - Depression
  - Sleep deprivation
  - Alzheimer's



Non-Demented with AD's Neuropathology (NDAN): have preserved levels of neurogenesis; more matured stem cells in Dentate Gyrus of hippocampus on autopsy (AD & NDAN = both Braak 6 level of BA)





Sustained neurogenesis in the DG of NDAN subjects is an important factor mediating their ability to evade dementia in spite of the presence of a degree of neuropathology (plaques and tangles) usually associated with clinically manifest AD.

David Briley, et al., 2016

Proof of Cognitive Reserve: Dementia was decreasing

- 2016 JAMA study: 2000 to 2012
  - 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% (1 M 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.

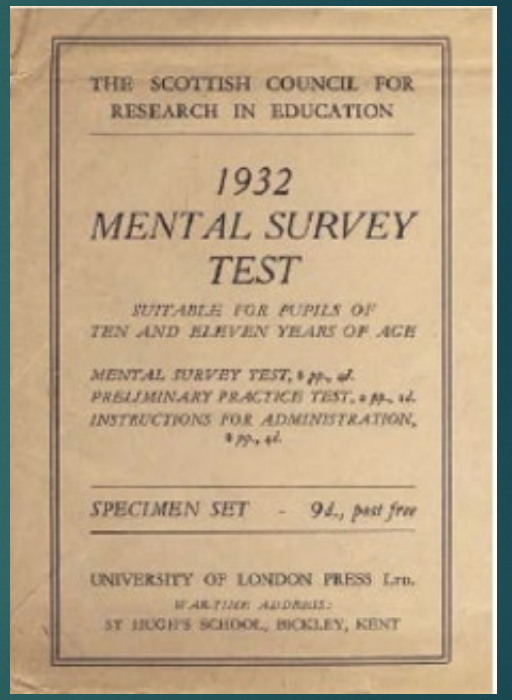
"Old age is like everything else.
To make a success of it, you've got to start young."

Fred Astaire
(1899-1987)

Many factors in early life can determine dementia risk in old age.

Lothian Study Scotland: all of Scotland's 1921-born population = 87,498 children; Fear of European immigration = pollute Scottish IQ

Study participants alive in 2011



THE SCOTTISH COUNCIL FOR RESEARCH IN EDUCATION

1932
MENTAL SURVEY TEST

SUITABLE FOR PUPILS OF TEN AND ELEVEN YEARS OF AGE

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

SPECIMEN SET - 9d., post free

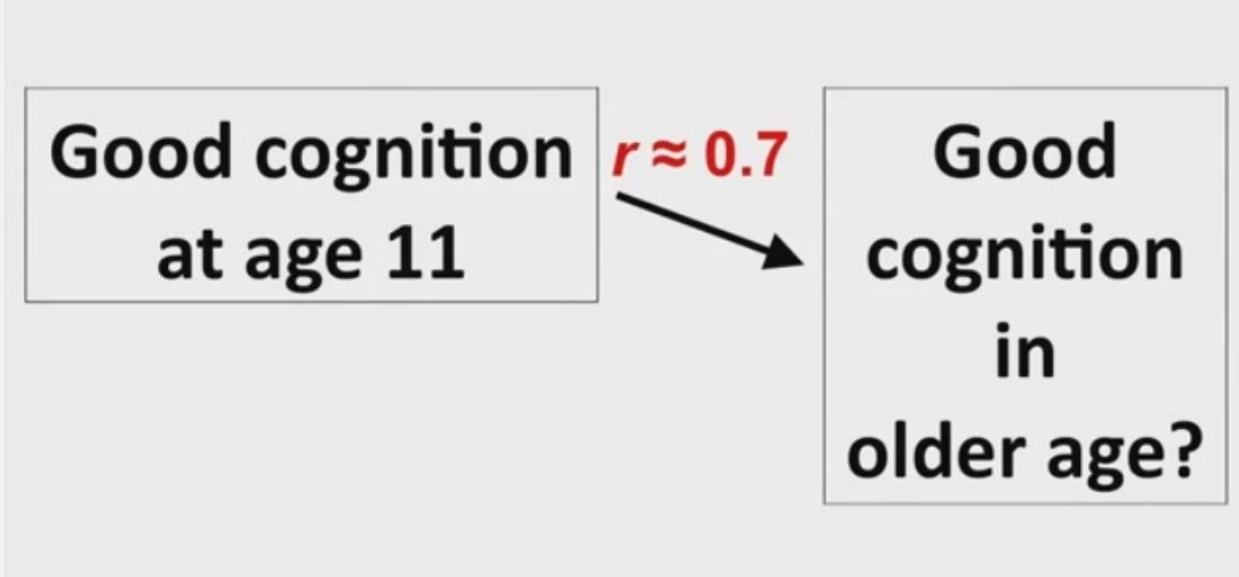
UNIVERSITY OF LONDON PRESS Ltd.
WARTIME ADDRESS:
ST HUGH'S SCHOOL, BICKLEY, KENT

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

Lost, and then Found

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

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



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

Those born with a better brain have initial and long term advantage

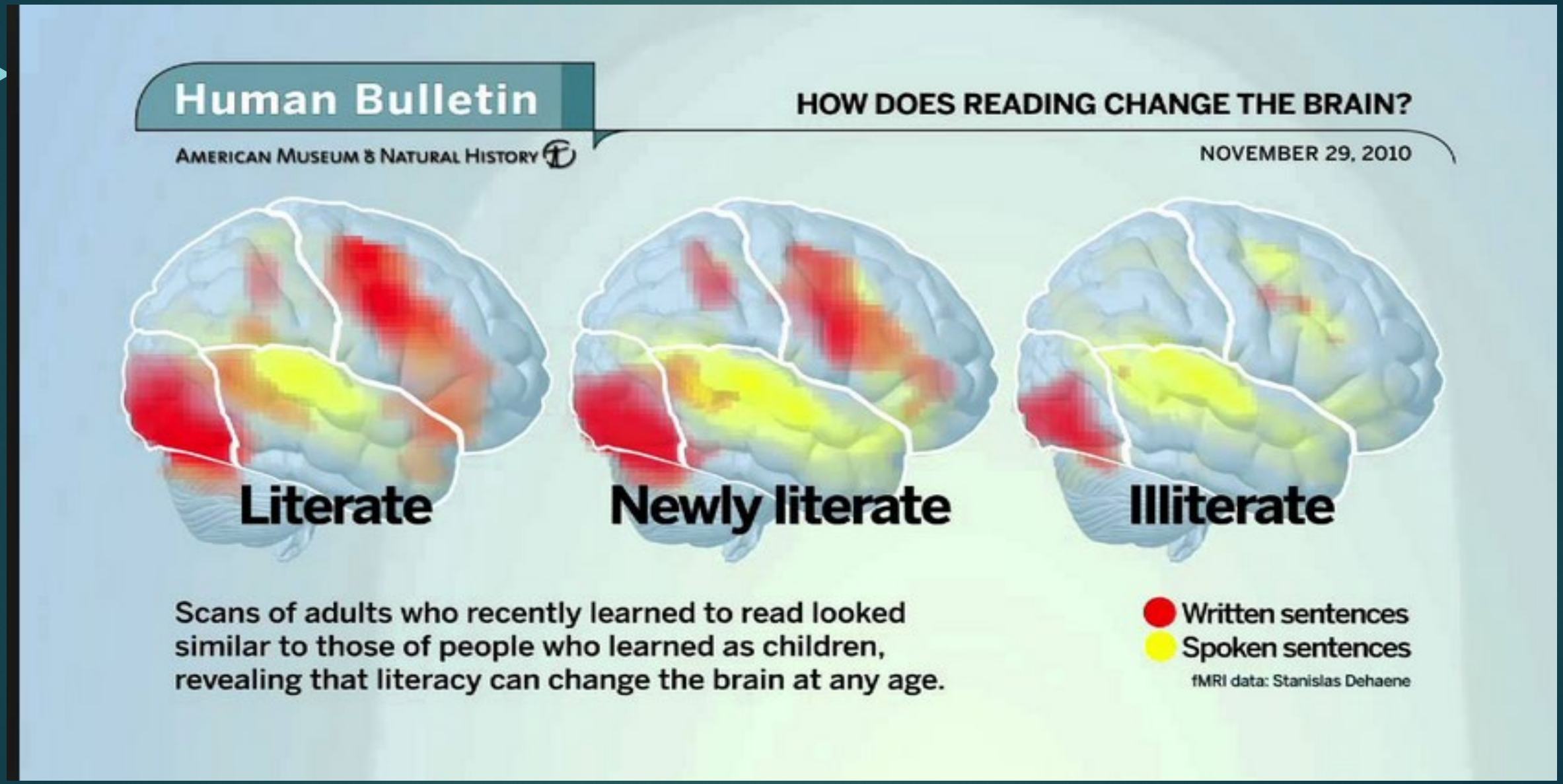
Low early-life cognitive ability is an early marker of dementia risk in later life

- 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 their 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

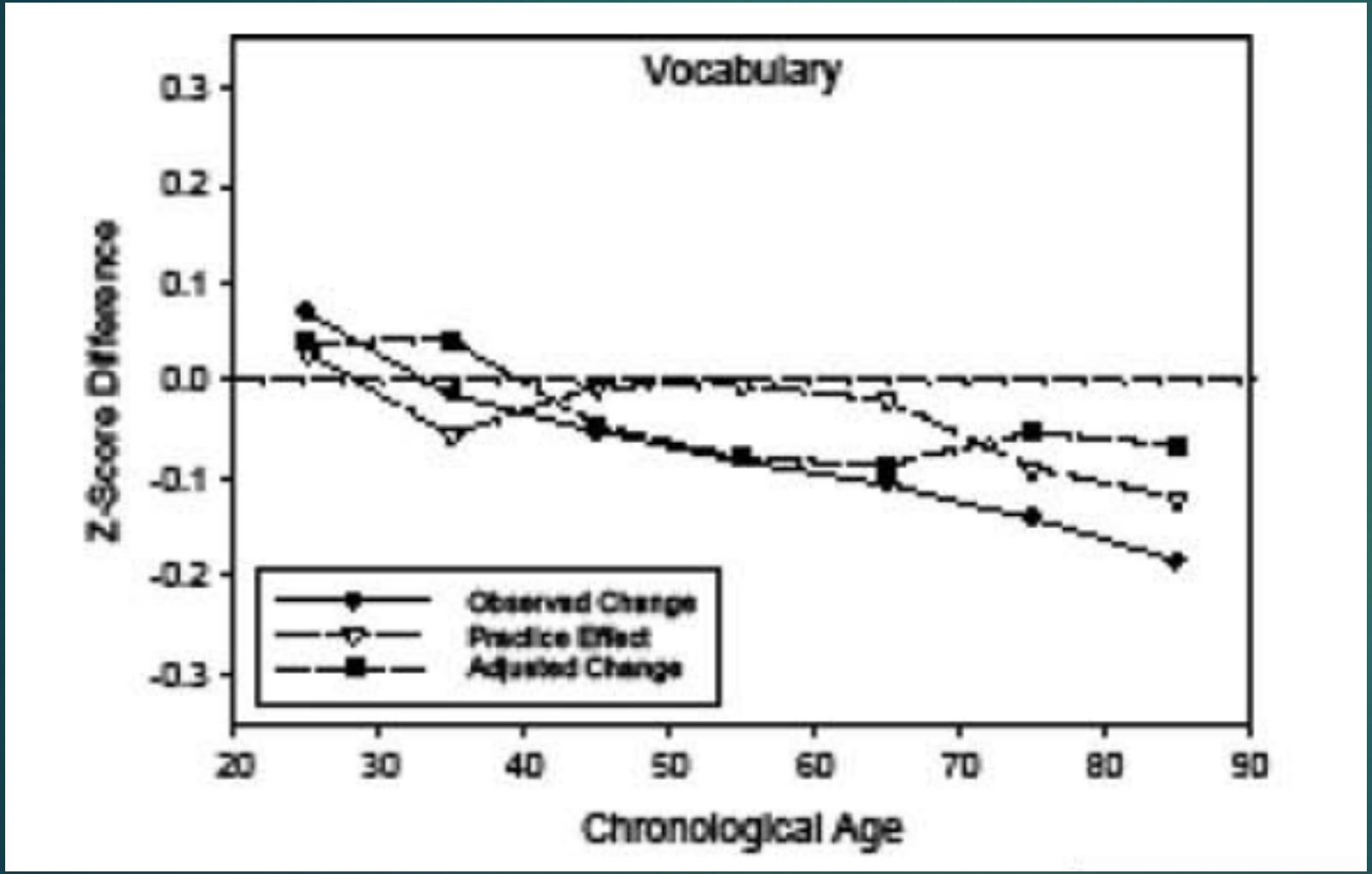
Reading

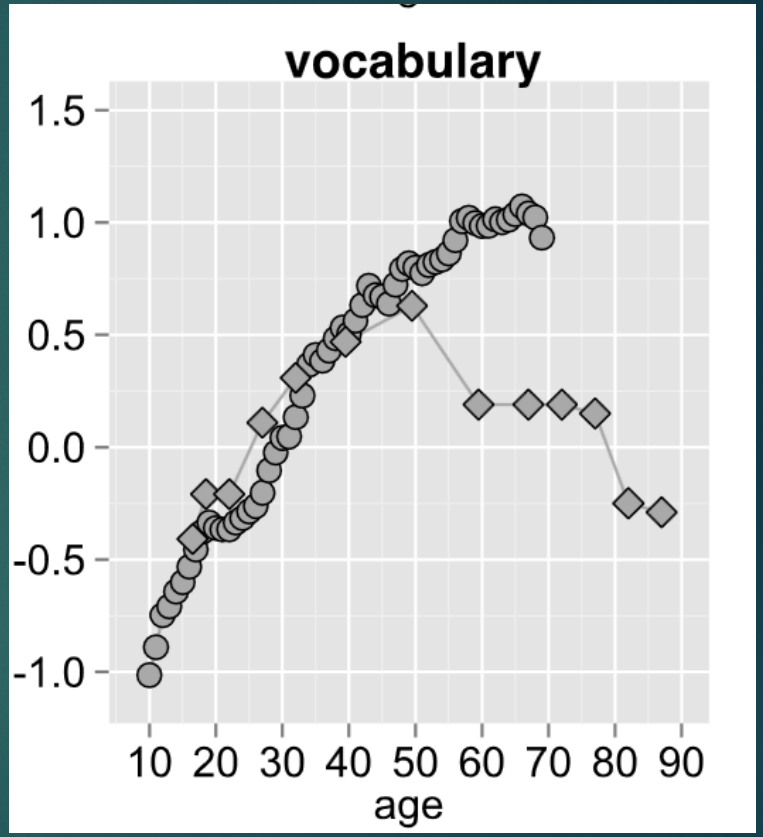

Human Bulletin
American Museum of Natural History
HOW DOES READING CHANGE THE BRAIN?
NOVEMBER 29, 2010
Literate
Newly literate
Illiterate
Scans of adults who recently learned to read looked similar to those of people who learned as children, revealing that literacy can change the brain at any age.
Written sentences
Spoken sentences
fMRI data: Stanislas Dehaene

Dementia risk factors

- The failure to complete more than eight years of school — is childhood's most potent risk factor for developing dementia.
- This alone is responsible for 8% of one's lifetime risk for the disease. That makes lack of education a more powerful driver than the ApoE-e4 gene variant, which is responsible for 7% of its incidence.
- 9% of lifetime risk for dementia lies with hearing loss during midlife
- 20% most economically deprived older adults were 50% more likely to develop dementia than the 20% least deprived adults.

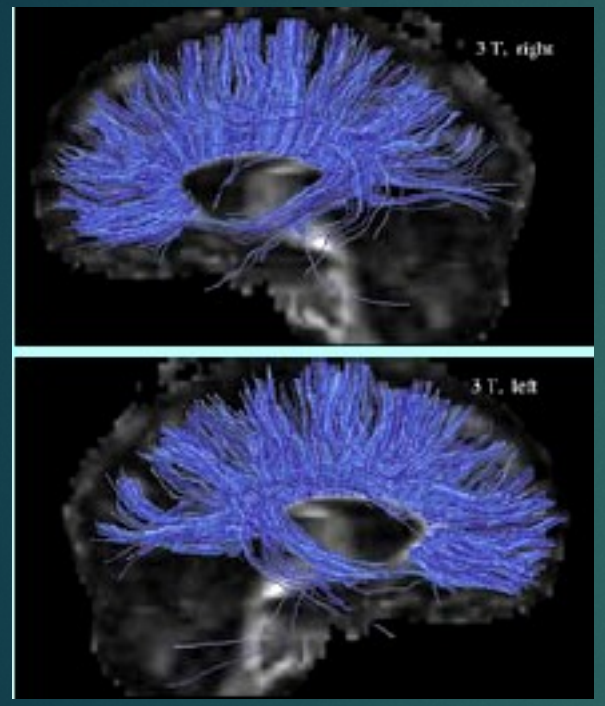
Vocabulary stays relatively intact

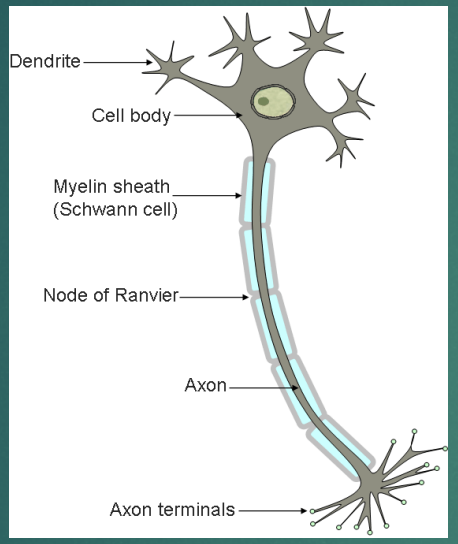


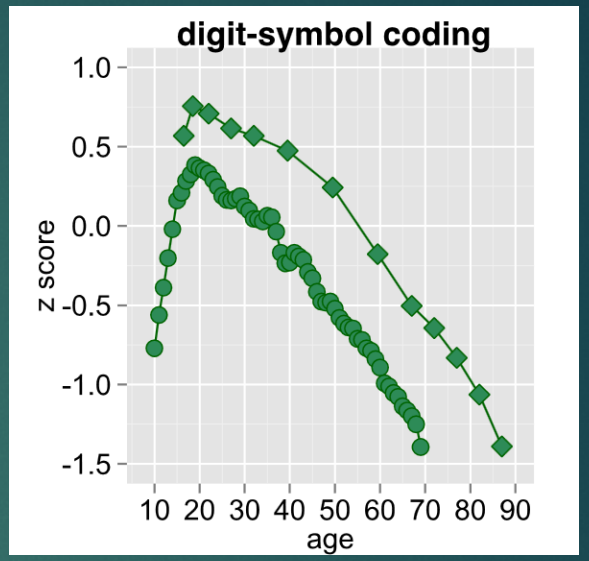


Squares = less than .05 change

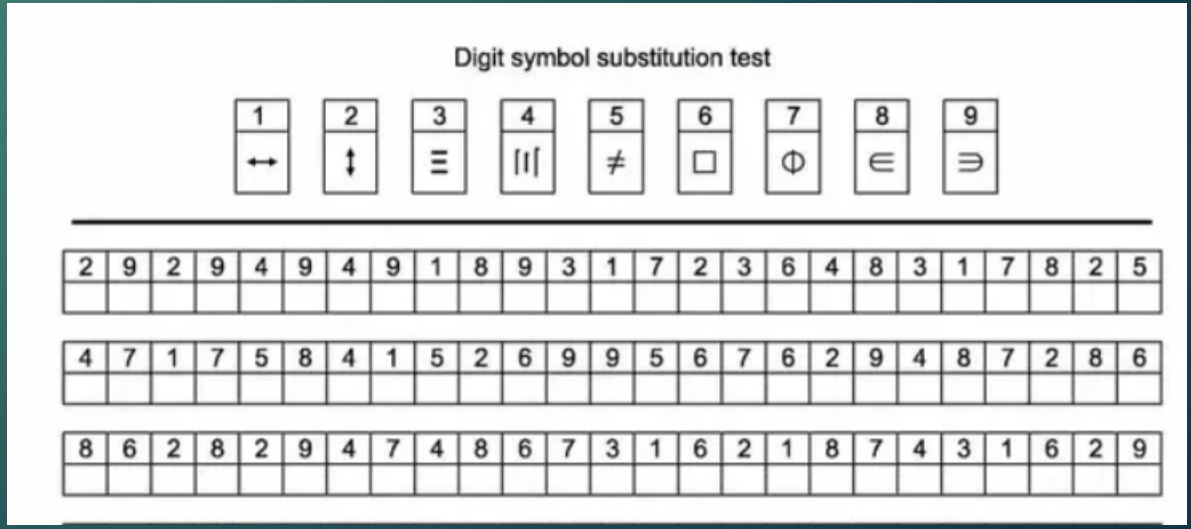
Older are Centrally Slowed: Processing Speed Decreases (3 ms per decade due to WM decline)



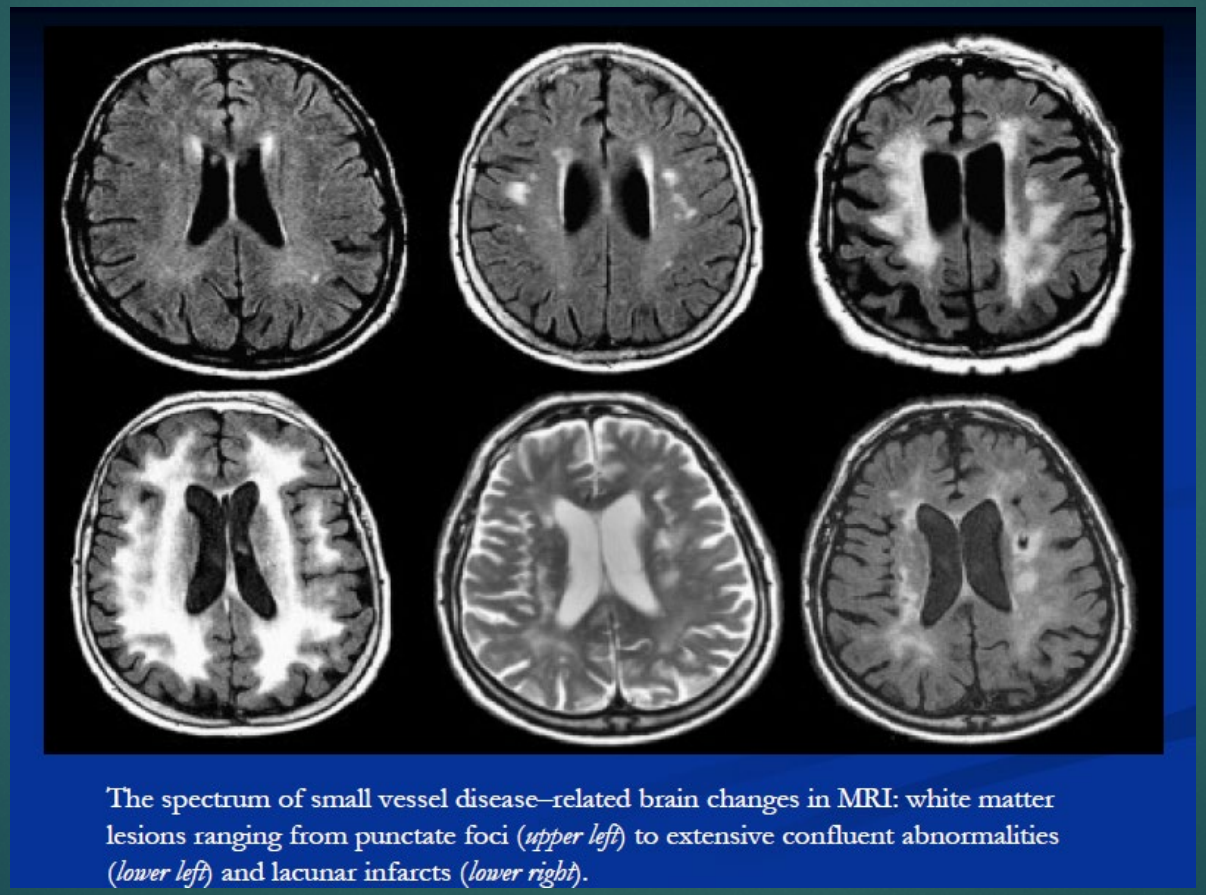




One of reasons naming ability decreases

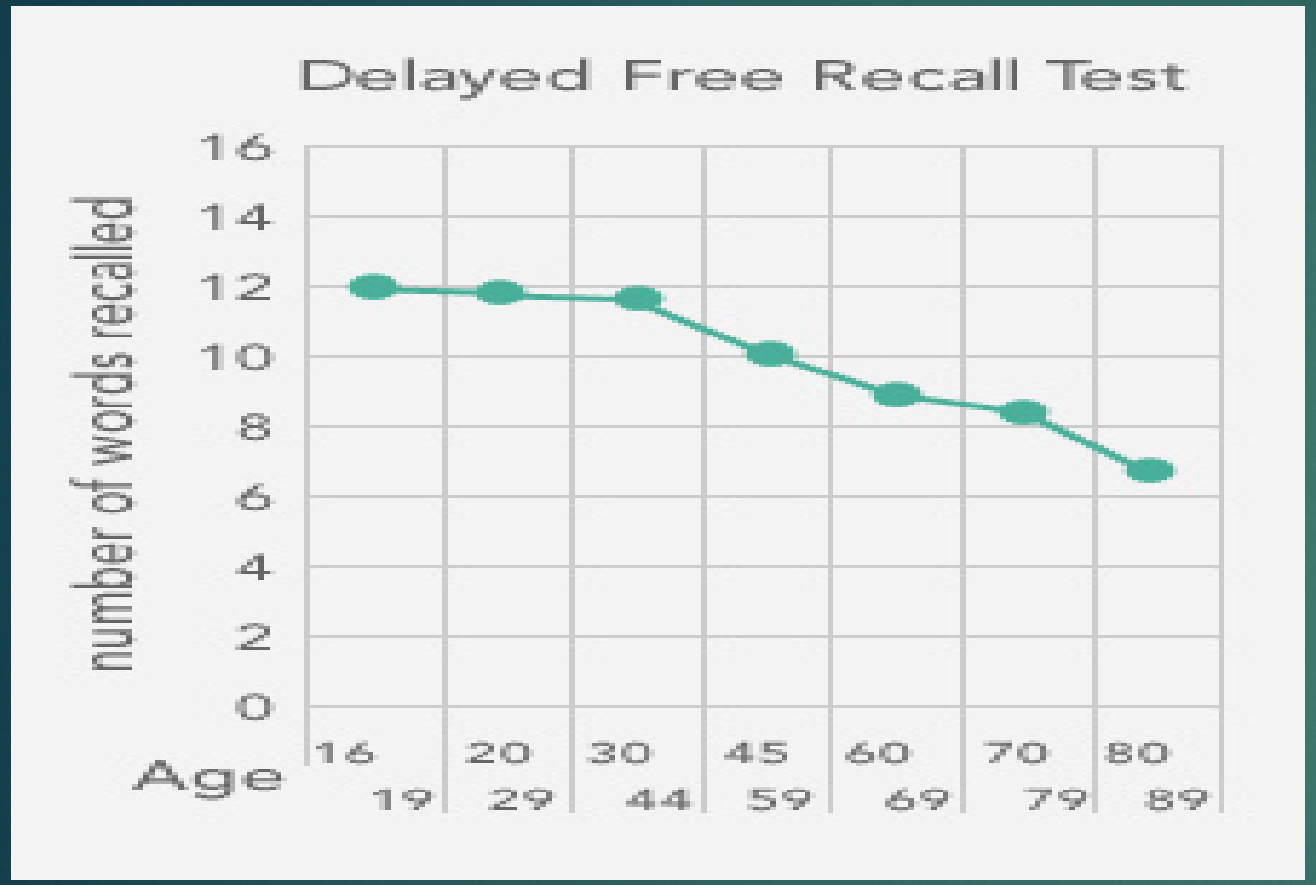


Mild to Extensive Vascular WM Hyperintensities: Slower Processing Speed



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

Spontaneous Verbal Free Recall Decline:



CVLT: For 1 trial of 16 words:

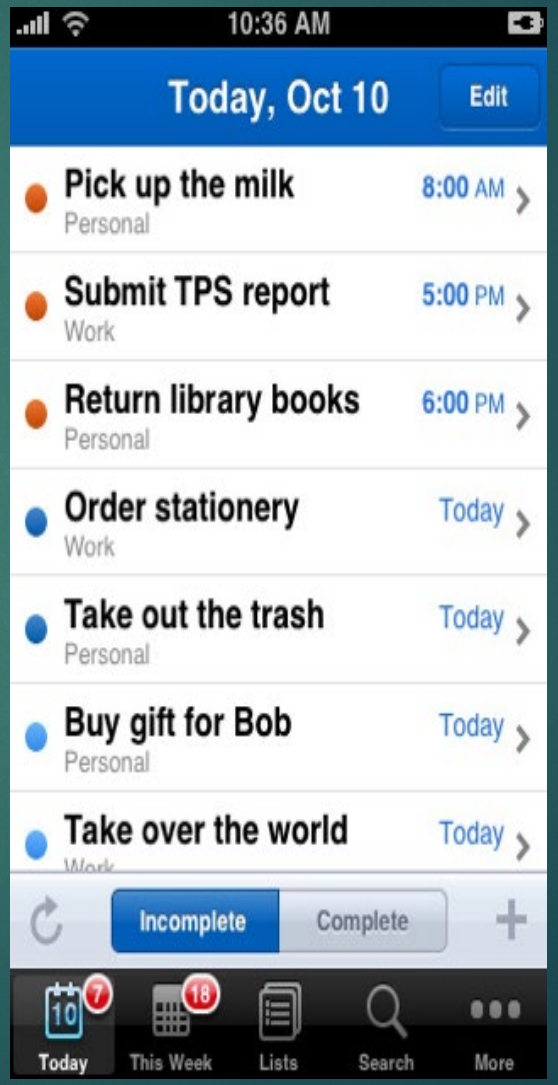
- 12 items retrieved at age 20
- 7 items at age 80

Number of items learned in 1 attempt:

Remember two fewer words every decade past age 40

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

Left hand lever moves paper up and to left edge

Behavioral Memory

Normal Memory vs. Real Memory Deficit Types

- Memory Encoding (hippocampus) works fine for input & output
- Given 16 new words 5 times, you recall 12 at half an hour
- New & old memories are equally accessible
- Recognition/Cuing helps

Encoding Failure:
Tape recorder is off

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

Retrieval Failure:
Trouble finding your memory

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

Attention

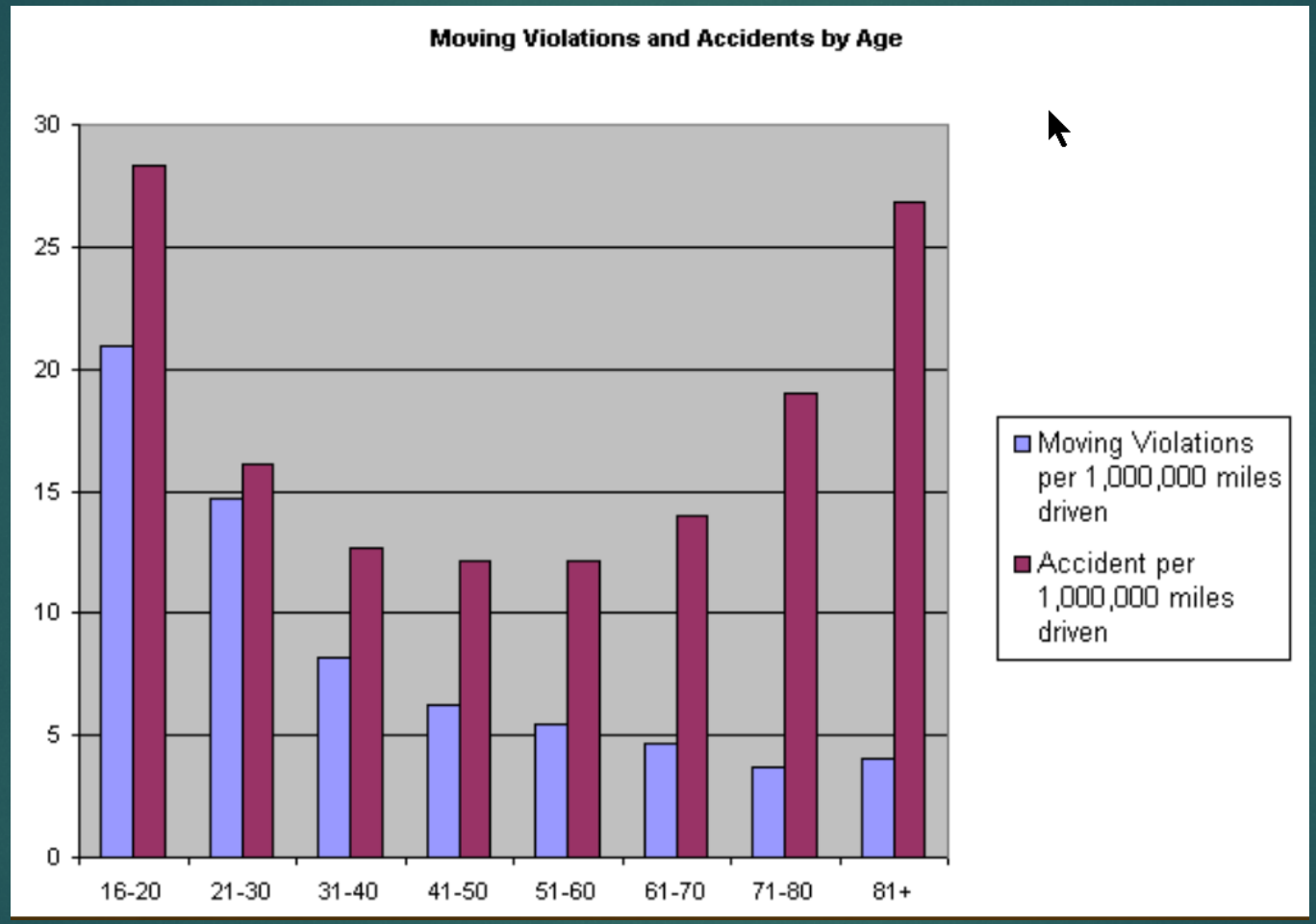
- Attention is like a football team:
  - 1 - need quarterback for focus
  - 2 - a defensive line against distractions.
- As we get older, we lose our defensive line
- Older people are able to pay attention, but have more difficulty inhibiting distractions.
- Older people get age-activated “ADD”

Cautionary tale…

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

  - Not screaming like the other passengers in his car.

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

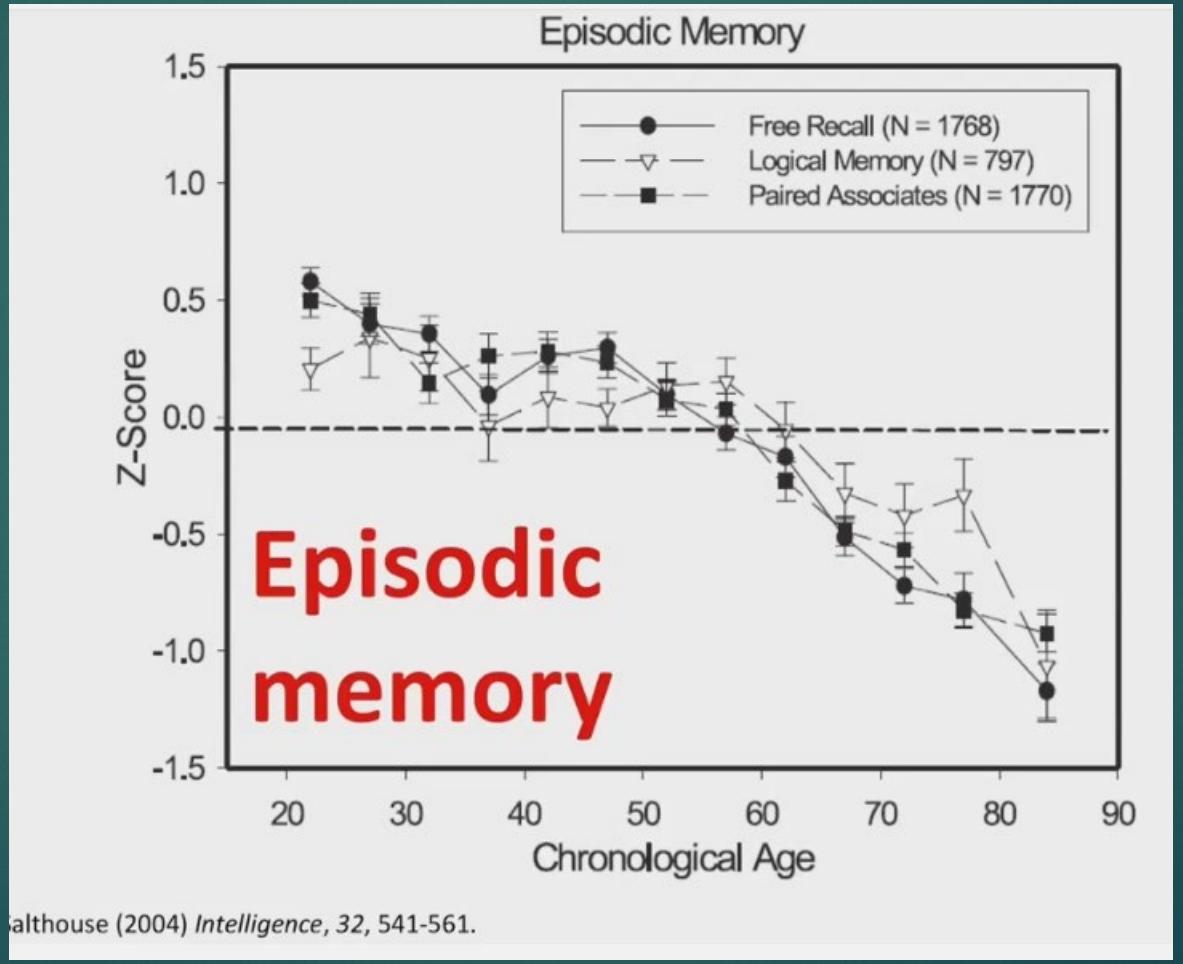


But teenagers kill more people in accidents.

Teens: Impulsivity & Alcohol ↑↑

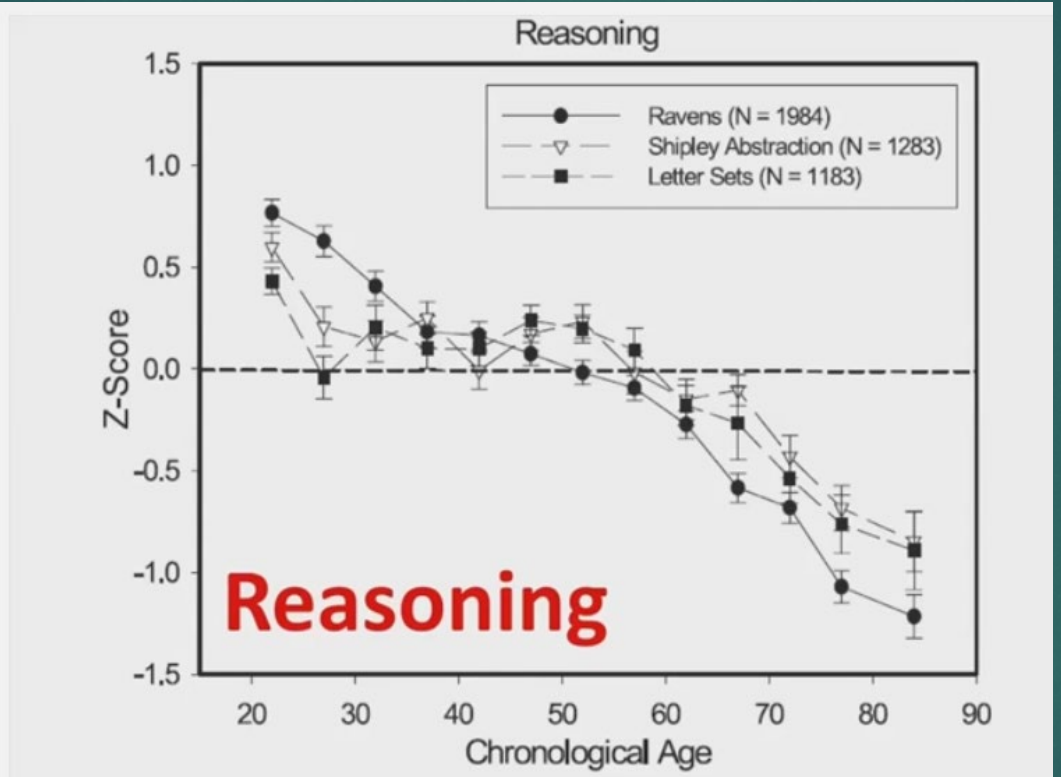
Seniors: Sensory & Processing Speed Declines

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



Virginia Longitudinal Study

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

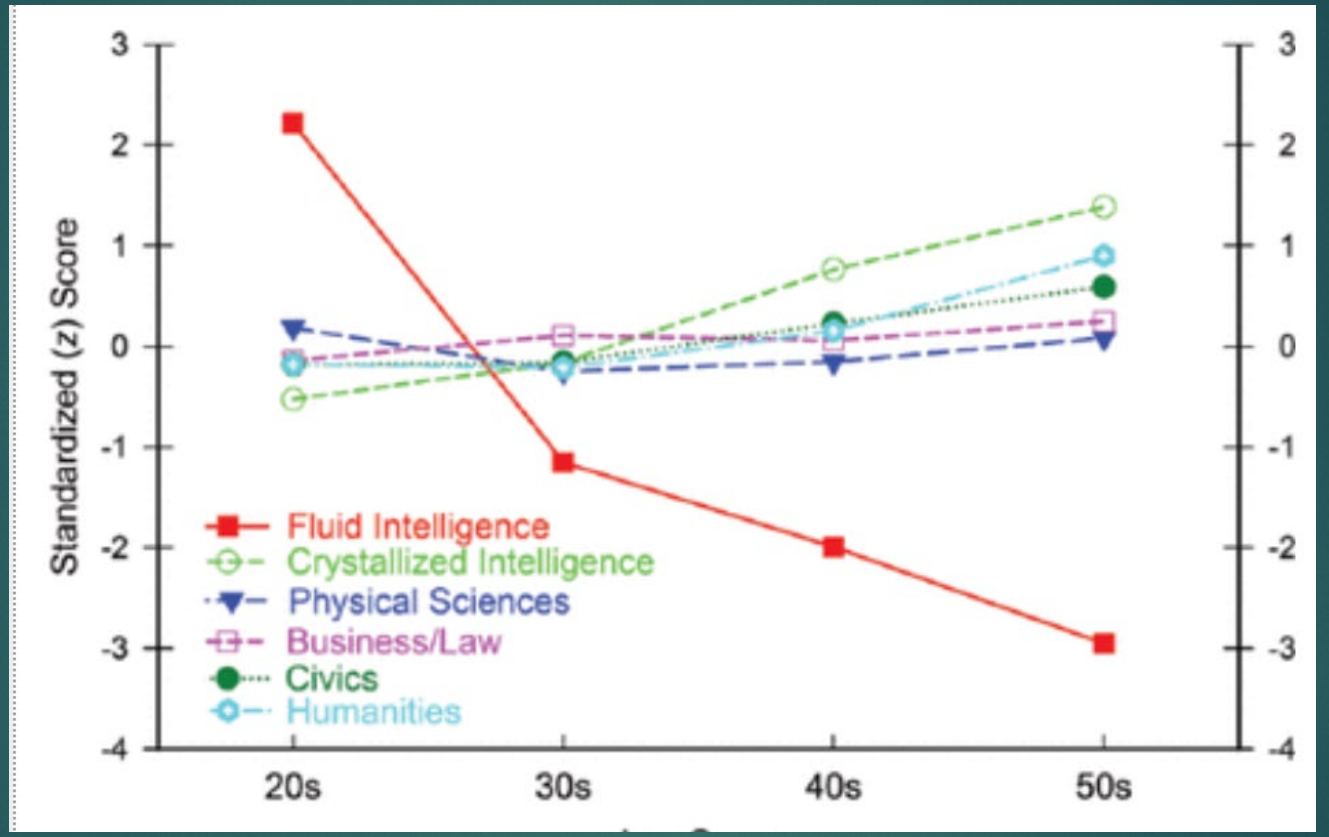


Salthouse (2004) *Intelligence*, *32*, 541-561.

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

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

All had a B.A.



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

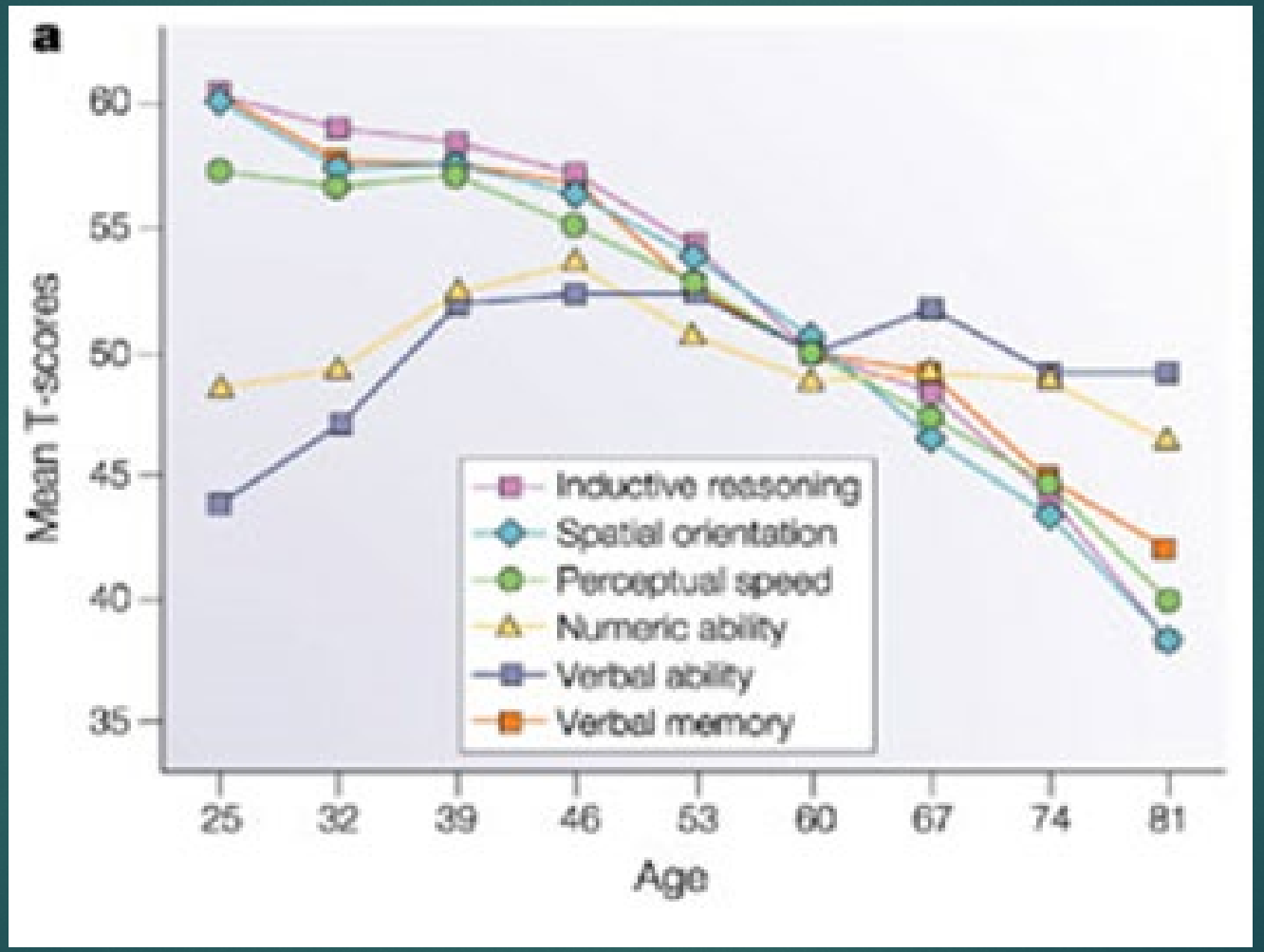
Phillip L. Ackerman, 2014

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

This is normal aging.

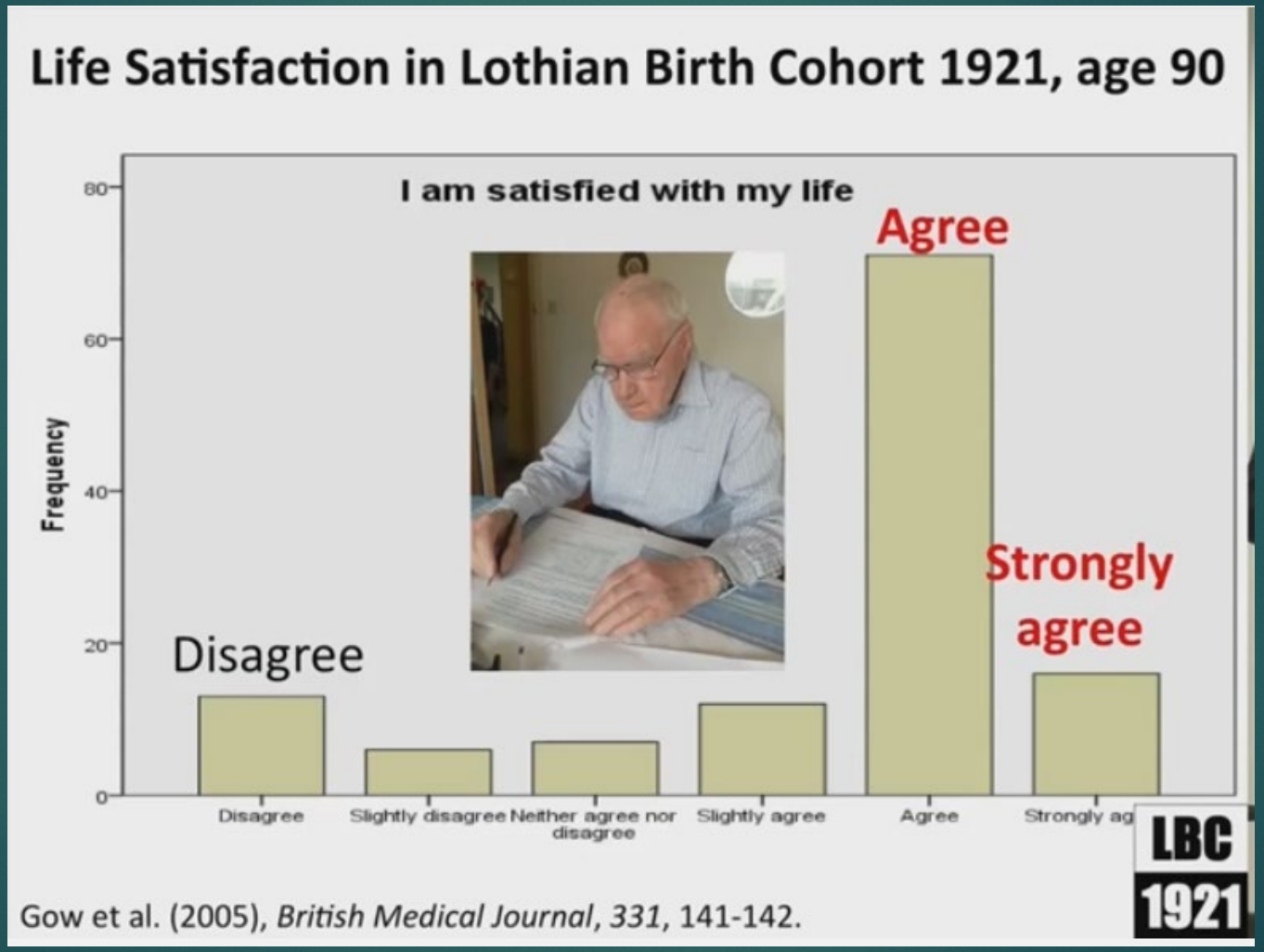
Not AD.

Do not freak out



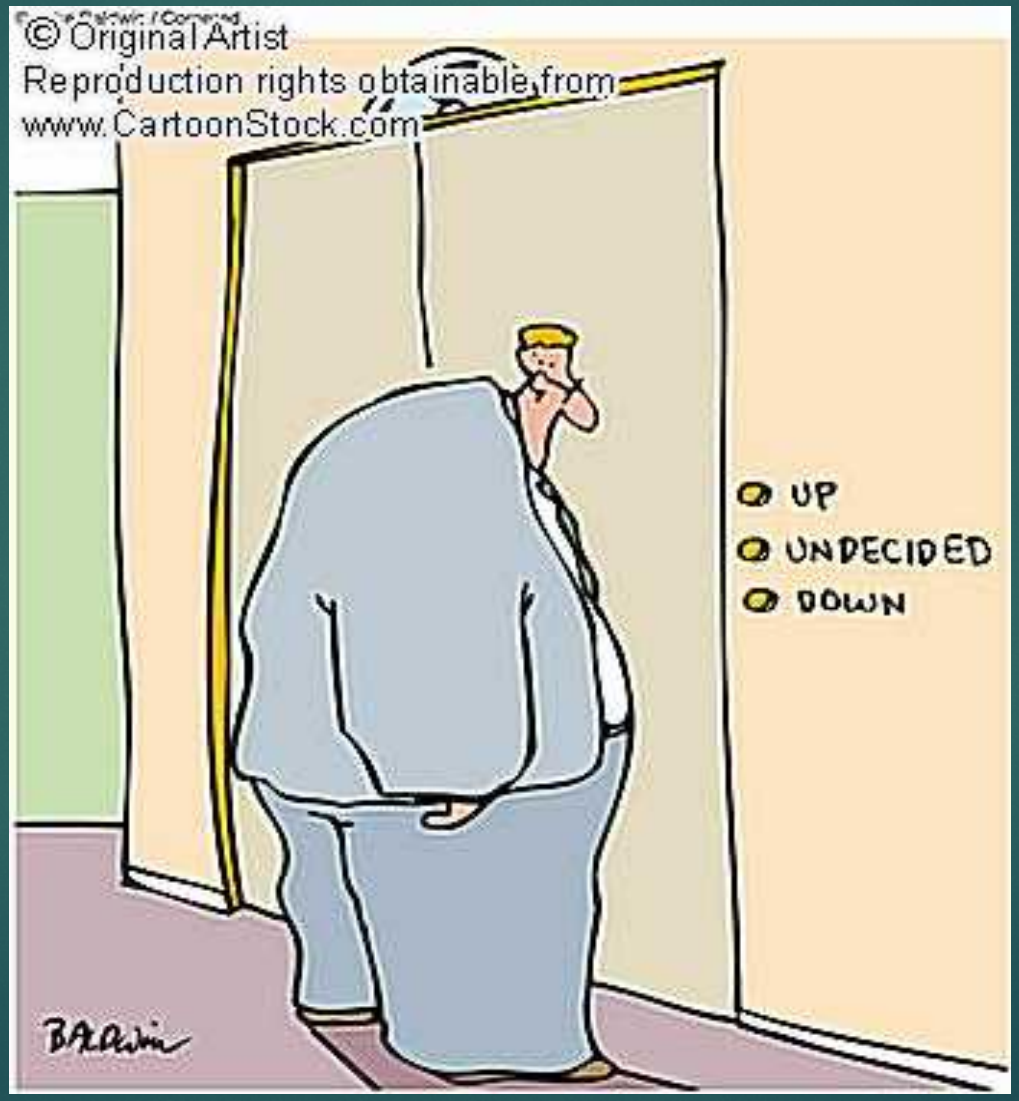
Seattle Longitudinal Study; no practice effect correction

Life is not all about cognitive ability: most people 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 they have a problem ("I can drive; I can live alone")
- Executive dysfunction associated with:
  - Functional decline
  - Increased need for care/supervision
- Executive ↓ correlates with decline in independent functioning (inability to use phone, letter, finances, meal prep)

Executive Deficit Predicts:

- Significant Executive ↓ requires Adult Protective Service referral
- If executive functioning is impaired: can't live independently
- Money management decline
- Medication management decline
- Poor geriatric orthopedic & stroke rehabilitation outcome

Normal Aging Effects on NP Testing: Require Age corrections

- Older individuals perform more poorly on NP tests
- Most NP tests correct for age
- WAIS age corrections for motor & nonverbal subtests
- Speed ↓: motoric, perceptual, central processing slowing; PIQ ↓
- Visual Spatial ↓: perceptual processing, complex visual ↓; perceptual judgment, figure copy
- Explicit/Declarative Memory ↓: Spont. Recall ↓, Recognition normal
- Executive Functioning ↓: rapid set shift ↓, abstraction (WCST, Category Test.) ↓

Age adjustments

- Age adjustments required in most cognitive tests
- WMS norms: 70-74 yo scores are 50% lower than 35-44 y.o.; more nonverbal ↓
- Every 6-8 years of age decreases scores by ½ σ, visual > verbal
- Every additional 4 y education, memory score increases by ½ σ

Other Cognitive Changes

- Mayo, ’95: Lots of cognitive scatter with age (WAIS, WMS, AVLT factors):

- Normal testing variability:
  - 37-53% of normals had 1 σ ↓ factor discrepancy;
  - 20 % had 2 σ ↓

- Score discrepancies common
- 4-year retest: scale pairs shift in normals; Alzheimer’s had steady ↓
- Normals have positive practice effects; AD does not

2020 study: Is sitting always bad for your mind?

- A new study of older adults suggests that some sedentariness isn't all bad, so long as basic physical activity benchmarks are being met.

- Association between sensor-measured physical activity and cognitive performance in a sample of 228 healthy older adults, aged 60 to 80.

- Adults who engaged in more moderate-to-vigorous activity had better speed, memory, and reasoning abilities (fluid IQ, declines with age).

- The adults who spent more time sedentary performed better on vocabulary and reasoning tasks (crystalized IQ, increase with age).

Agnieszka Z. Burzynska, et al., 2020

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

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 like
- And the eyesight to tell the difference.

Ten Commandments for Brain Fitness

I. Choose thy parents wisely (For brain genes & IQ)
II. Exercise 150 minutes per week.
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; treat sleep apnea
VIII. Drink 1 drink of alcohol per day
IX. Manage your stress effectively
X. Don’t text or use cell phone while driving.

First population-based studies of variation in dementia by marital status in the United States.

- N = 15 K
- All unmarried groups, including the cohabiting, divorced/separated, widowed, and never married, had significantly higher odds of developing dementia
- For divorced/separated and widowed respondents, the differences in the odds of dementia relative to married respondents were greater among men than among women.

That Naming Problem

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

Simple AD test: 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

DSM-5 Neurocognitive Disorders

- Delirium
- Mild neurocognitive disorder
  (old MCI, Cog Disorder NOS)
- Major neurocognitive disorder
  (old dementia)

DSM - 5

- No more “Dementia” in DSM-5
- New Dx: Neurocognitive Disorder (NCD), mild or major
- Focus on decline (rather than deficit) from a previous level of performance.
- Cognition, not just Memory, central
- NCD: covers any form of cognitive decline from any brain disorder, i.e. TBI or AD

DSM-5: Delirium

- A. Disturbance in attention and awareness
- B. Develops over a short period of time (hrs/days), change from baseline, tends to fluctuate
- C. Disturbance in cognition
- D. A & C not better explained by another NCD, or coma
- E. Evidence that disturbance is direct physiological consequence of a medical condition, substance intoxication or withdrawal

Delirium

- Disturbance of consciousness (attention/awareness):
  - attention deficit is core feature

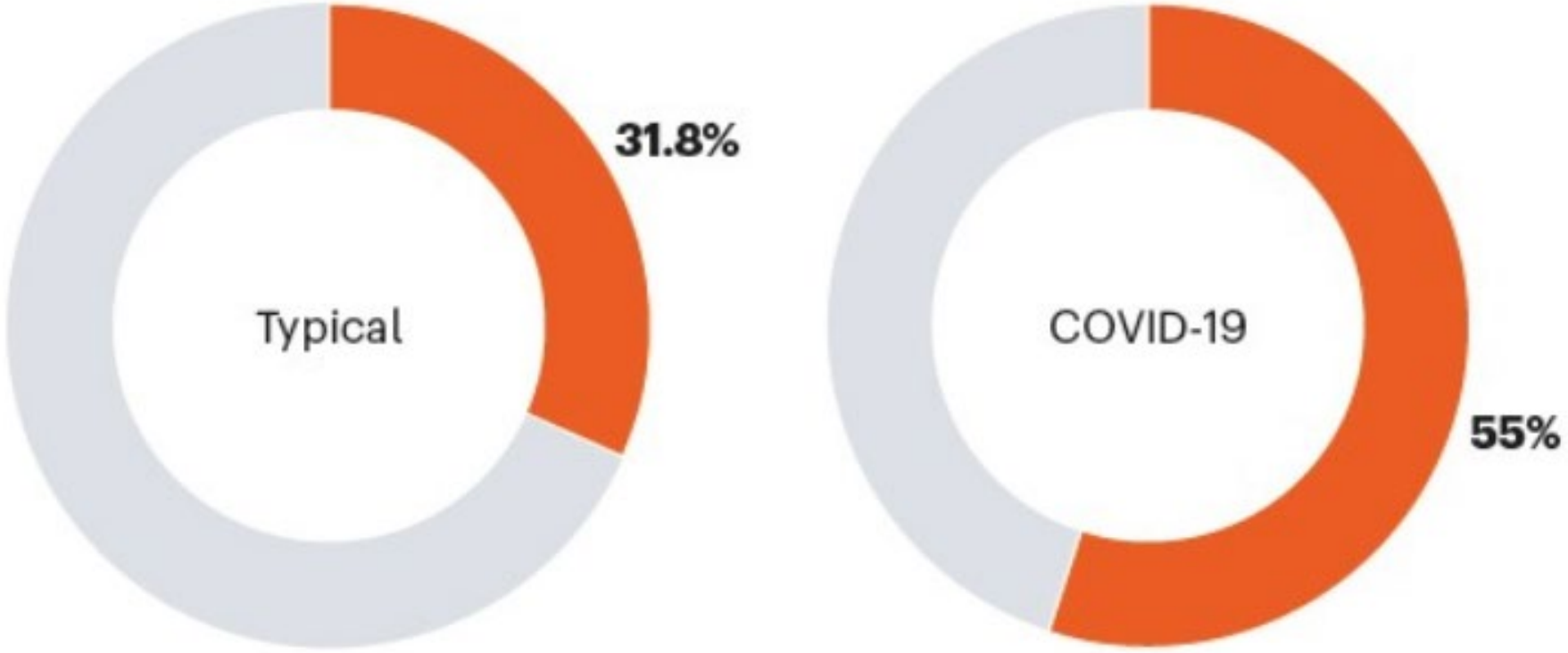
- Fluctuation in sleep/wake cycle; worse at night
- Amnestic for episode
- Cognitive/perceptual changes (hallucinations (often visual), illusions, paranoia)
- Psychomotor ↓↑

Delirium = effect of an MI

- Delirium is the most common complication in hospitalized older people
- Mortality in hospitalized delirium is high; up to 40% with delirium die within a year.
- Statistically having delirium = having a heart attack in mortality risk: Once delirium occurs, the same percentage of individuals die from it as die from a heart attack

HOW COMMON IS DELIRIUM?

Typically, almost one-third of people who are critically ill will have an episode of delirium; for COVID-19, the proportion rises to more than half.



Delirium and Dementia

- Long-term studies have revealed that a single episode of delirium can increase the risk of developing dementia years later, and accelerate rates of cognitive decline in those who already have the condition.
- The reverse is also true: having dementia makes someone more likely to develop delirium
- Underlying biological causes are inflammation and an imbalance in neurotransmitters — chemical messengers such as dopamine and acetylcholine.
- 70% of those with delirium symptoms eventually recover completely.
- In the 30% who don't, however, an episode of delirium predicts a downward spiral over a period of months that leads to profound cognitive impairment, even to symptoms of dementia.
- 28% of older adults with COVID-19 have delirium when they present to the emergency department

Delirium

- A 2020 meta-analysis of 23 studies showed that delirium during a hospital stay was associated with 2.3 times greater odds of developing dementia.
- And work by a team of Brazilian scientists showed that, in a group of 309 people with an average age of 78 years, 32% of those who developed delirium in hospital progressed to having dementia, compared with just 16% of those who did not become delirious

- 40% reduction in delirium = (Hospital Elder Life Programme), which focus on reducing sedation, even during mechanical ventilation, paying close attention to nutrition and hydration, and ensuring the presence of family members to help reassure and orient patients.

Postsurgical Delirium

- Delirium is common in Postoperative intensive care units (ICU) admissions

- Delirium occurred in 43%:
  - 68% hypoactive,
  - 31%mixed,
  - 1.4% hyperactive motor subtypes

- Hypoactive delirium is the most common subtype and is associated with worse prognosis (6-month mortality, 1 in 3 patients, secondary to pulmonary emboli)

Robinson, 2010

Hypoactive Delirium

- Hypoactive delirium:
  - sluggish and lethargic
  - onset is sudden,
  - fluctuating level of consciousness. Need light in day, dark at night.

- Patient is often perceived to be depressed. Psychiatric consultation is often requested to treat the patient for depression.

- Delirium is unrecognized in 60 percent of patients who experience it, esp. hypoactive version

Anticholinergic Syndrome (ACS): Mad as a hatter lyric

Hat-making in 19th century included mercurous nitrate, used in curing felt = mercury poisoning; ACS = follow the ingestion of a wide variety of prescription and over-the-counter medications

- hot as a hare = high temperature
- red as a beet = vasodilation
- dry as a bone = decreased mucus, dry mouth, constipation
- blind as a bat = blurred vision
- mad as a hatter = hallucinations, delirium

Medications: urinary meds (bladder antimuscarinics), atrophine, tricyclics, anti-parkinsonian, antihistamines, haldol, digoxin; Elderly usage: 8% to 37%.

Anticholinergic (Acetylcholine inhibition) effects

Possible effects in the central nervous system resemble those associated with delirium, and may include:

Ataxia; loss of coordination
Decreased mucus production in the nose and throat
Dry mouth
Cessation of perspiration; leading to hot, red skin
Increased body temperature
Pupil dilation; therefore photophobia
Blurred vision
Double vision (diplopia)
Increased heart rate (tachycardia)
Urinary retention
Diminished bowel movement
Shaking

Anticholinergic effects

- All bladder control meds are anticholinergic
  - Bethanechol hydrochloride (Urecholine)
  - Propantheline
  - Oxybutynin (Ditropan XL, Gelnique, Oxytrol)
  - Tolterodine tartrate (Detrol, Detrol LA)
  - Trospium (Sanctura, Sanctura XR)

- Can worsen cognitive status of patients with Alzheimer disease and may blunt the effects of cholinesterase inhibitors like Aricept.

- Higher rates of long-term functional decline are associated with concurrent use of cholinesterase inhibitors (Aricept) and bladder cholinergic drugs (oxybutynin, tolterodine)

What is Neurocognitive Disorder (NCD)?

Neurocognitive Disorder (NCD):

- Not a disease
- A diagnosis by a professional clinician
- A decline in a set of cognitive symptoms
- Caused by a variety of conditions.

What is a neurodegenerative disease?

- An acquired neuropathological disease
- Eventually causes global decline of cognitive and emotional functions and personality.
- Due to a neurodegenerative disease (AD, FTD, etc.)
- Person has a mild or major NCD; they are not “demented”

NCD: DSM 5 -- 6 Cognitive Domains

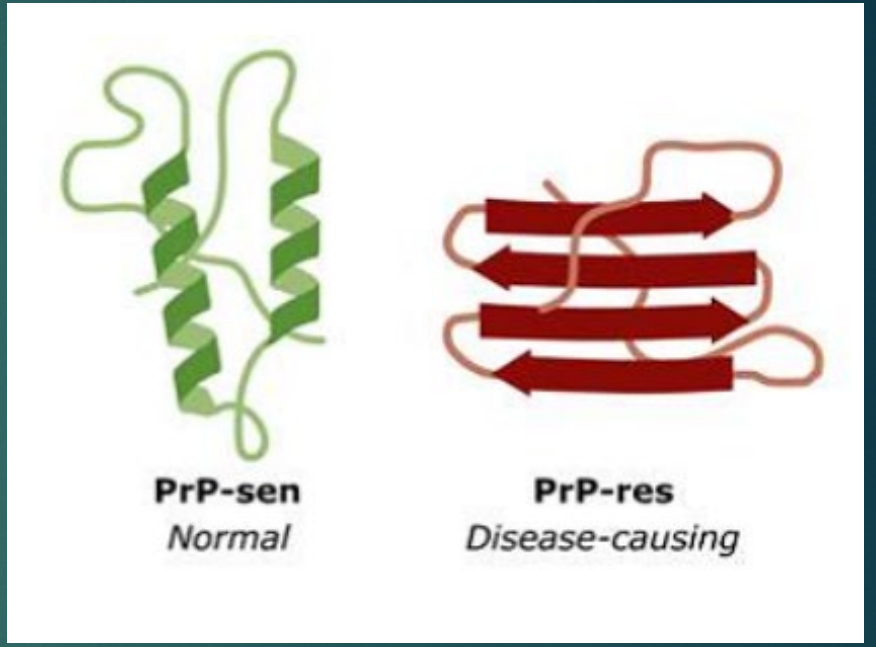
- Complex Attention (Sustained, selective divided)
- Executive Function (Planning, decision making, working memory, feedback/error utilization, overriding habits/inhibition, cognitive flexibility)
- Learning and memory
- Language (expressive, grammar/syntax, receptive)

NCD: Cognitive Domains 2

- Perceptual-motor (visual, visoconstructional, perceptual-motor, praxis, gnosis)
- Social cognition (recognition of emotions, theory of mind)

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

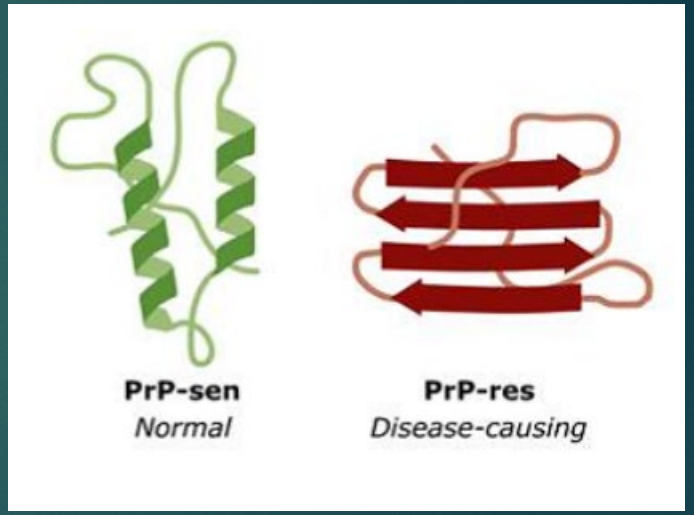


Mechanisms in Neurodegeneration

- Aggregation (clumping) of misfolded proteins
- Early synaptic loss (beginning of clinical sxs)
- Neuronal loss

Neurodegenerative Diseases

- All have abnormal protein aggregate that kills cells
- All have uncommon genetic and sporadic common forms
- All have
  - Preclinical phase
  - Early symptom phase, i.e. mild NCD
  - Symptomatic phase, i.e. major NCD
- NDs often do not come in pure form
  - Vascular & Alzheimer's
  - Parkinson's develop AD features and vice versa



Pathology in cognitively normal elders

- N = 467 normals without NCD at autopsy:
  - 82% had beta amyloid,
  - 100% had tangles,
  - 29% had macroscopic infarcts,
  - 25% had microinfarcts,
  - 6% had neocortical Lewy bodies

P. Boyle, et al., 2013

Molecular Bases of NDs

Type	Causative Molecule
Alzheimer's	AB42, Tau
FTD	Ubiquitin, Tau, TDP-43
ALS	Ubiquitin2, TDP-43
Parkinson's	a-synuclein
Huntington's	Intranuclear inclusion, Huntington's protein
ECT	Tau
JCD	Prion, spongiosus

Differential Diagnosis of Neurodegenerative Diseases:
Different First Symptoms

- AD – Memory (no encoding) (70%)
- FTD – Behavioral impulsivity, loss of empathy, executive loss, language
- VaD – Apathy, processing speed & executive deficits
- LBD – Visual hallucinations, delusional misidentification, Parkinsonism, delirium
- PDD – Motor problems, depression, hallucinations
- CJD – Involuntary motor
- SubCD – Slowing, executive deficits

What is the most common cause of cognitive decline with aging?

- 1 – Alzheimer’s Disease (AD)
- 2 – Cardiovascular Disease (CV)
- 3 – Lewy Body Disease (LBD)
- 4 – Mixed causation

Cognitive Decline with Age:
Heterogeneity of Pathology

- Most Common Cause of Cognitive Decline in Aging: Mixed pathology
- Pure AD pathology as the cause is relatively rare.
- In Major NCD Dx: AD, CVD, LBD = 90% of causation
- In all cognitive decline dxs:
  - AD (34%), CVD, LBD = 41%
  - Residual decline = 59%

David Bennett lecture, Oct 2013; Boyle PA, et al., 2013

Other 59% Residual Cognitive Decline

- Much of late life cognitive decline is not due to common neurodegenerative pathology

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

- GSTPI protein (Glutathione *S*-transferase) (an antioxidant toxic cleanser in the cells) = 5% of all variability of residual cognitive decline

Causes of Adult Onset NCD (not exhaustive list)

Primary Degenerations

Alzheimer's disease (70% of cases)
NCD with Lewy Bodies (LBD)
Pick's disease
Frontal lobe NCD
Vascular

Parkinson's Disease
Huntington's Chorea
Progressive supranuclear palsy
Spinocerebellar degenerations
Progressive myoclonic epilepsy

Multiple cortical infarcts
Cranial arthritis
Cerebral arteritides (PAN, SLE)
Chronic subdural
AV malformations and giant aneurysms
Hyperviscosity syndromes
Thrombotic thrombocytopenic purpura
Angiopathies
CADASIL (hereditary strokes)

Causes of Adult Onset NCD 2

Inherited Metabolic and Storage disorders & Neoplasms

Porphyria
Wilson's Disease

Mitochondrial cytopathies

Meningiomas
Gliomas
Metastases
Lymphomas

Infections & inflammation, Metabolic, Toxic, Etc

Syphilis

Viral encephalitis
AIDS

Progressive multifocal leucoencephalopathy
Subacute sclerosing panencephalitis
Behcet's Syndrome
Meningitis
Multiple Sclerosis
Sarcoidosis
Whipple's disease

Causes of Adult Onset NCD 3

Disseminated encephalomyelitis

Creutzfeldt-Jakob

Hypothyroidism

Hypo and hypercalcaemia
Uraemia
Dialysis NCD
Alcoholic NCD
Vitamin B12 deficiency
Pellagra
Malabsorption syndrome
Drugs, poisons and heavy metals
Post irradiation /aquaduct stenosis
Dementia pugilistica

Traumatic Brain Injury
Normal pressure hydrocephalus
COPD and Carbon monoxide

	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 neu-ron disease	Alien limb, unilateral dystonia	Falls, supra-nuclear 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 atro-phy, small hippocam-pal volumes	Cortical or subcortical white mat-ter lesions on MRI	Possible global atrophy	Atrophy in frontal and temporal lobes	Asymmetrical parietal and frontal atrophy	Midbrain atrophy	Left fron-to-insular or anterior temporal atrophy

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

Mild Neurocognitive Disorder (old MCI)

Specify whether due to (AD, FTD, LBD, VD, etc.)

Specify with or without behavioral disturbance

NP Testing: - 1 to -2 s.d. (3 to 16th %tile)

- Petersen:
- Some with mild NCD go on to develop major NCD.
- Some with mild NCD do not progress to major NCD.
- Some with mild NCD at one point in time later revert to normal cognitive status.

Petersen et al.,1999, 2008; DSM-5

Mild NCD: Tx

- **American Academy of Neurology:**
  - No evidence exists to support pharmacologic treatments (cholinesterase inhibitors) for Mild NCD.
  - What is single most important recommendation to make to patient?
  - Exercise training (6 months) should always be recommended & is likely to improve cognitive measures

Mild NCD

- Possible Prodromal AD in elderly
- Assessment: Need subjective experience of cognitive difficulty; collateral corroboration; objective NP evidence
- ** No significant functional effects; still capable of independent living
- Only 50% progress to AD
- Identify if amnestic or not; if amnestic, 99% AD progression;
- Can also be due to depression, polypharmacy, ETOH

Impaired Financial ADL in Mild NCD

- Amnestic Mild NCD subjects impaired relative to controls in:
  - Cash transactions
  - Bank statement management (fail to calculate the balance)
  - Bill payment
  - Overall financial capacity
  - Can write out the check correctly but fail to calculate the balance after making the transaction.

Griffith et al., Neurology, 2003; 60: 449-457

Mild NCD

- Peterson Study: 1,969 subjects without NCD, 329 subjects had Mild NCD, 70-89 years old on October 1, 2004

- 16% of community elderly subjects are affected by Mild NCD

- Amnestic Mild NCD is the most common type.

- Higher among:
  - never married
  - ApoE genotype.
  - lower years of education.

Peterson, et al., 2010

Differentiation of
Mild NCD vs. normal aging

- Misplacing things and word/name recall difficulty is probably normal.
- No correlation between naming deficit & episodic memory deficit
- Mild NCD: forget more important info (appts, phone conversations, recent events); noticeable to people close to patient
- MMSE not sensitive; MoCA will catch Mild NCD
- Rule out depression, medication effects
- Note if present: slow gait and loss of olfaction recognition (an agnosia)

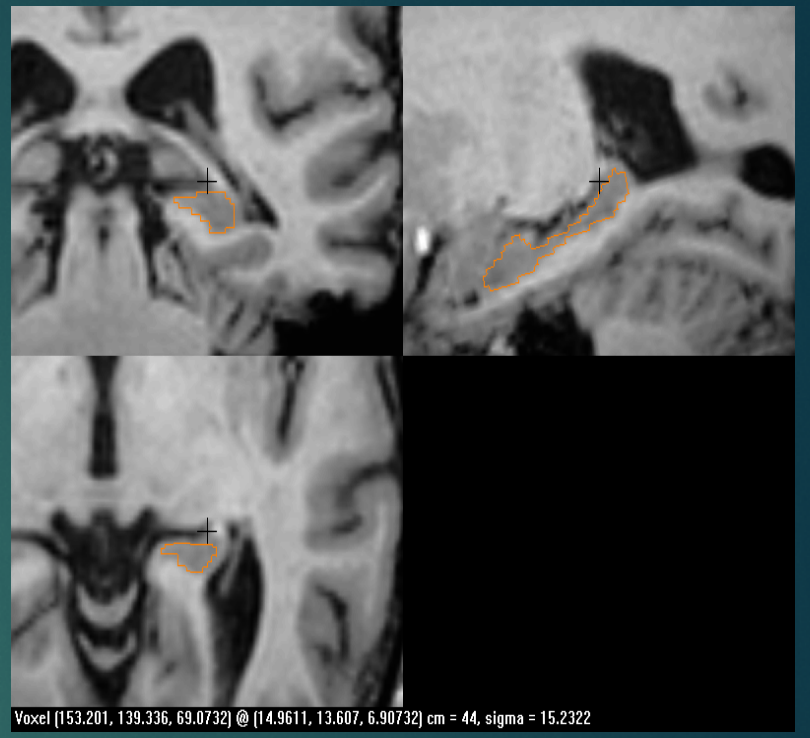
Mild NCD progression prediction

- Larger ventricles
- FDG-PET: temporal parietal hypometabolism (11 x higher in next 2 years)
- Low AB42 and high Tau in CSF
- PIB –PET detection of AB42 in brain (but remember autopsy AB presence in normal cognitive)

Best AD Conversion Predictors

- Hippocampal volume
- ApoE 4 allele frequency
- CSF proteins (AB-42, total tau, hyperphosphorylated tau [p-tau181p])
- Glucose metabolism (FDG-PET)
- Subjects with Mild NCD who had abnormal results on both FDG-PET and episodic memory were 12 times more likely to convert to AD

Hippocampal Volume Decline



Risk of converting to AD

- 9% - Hippocampal Volume ≥ 50th percentile
- 26% - Hippocampal Volume between 1st and 50th %ile
- 50% - Hippocampal Volume below 1st percentile
- Hippocampus becomes hyperactive in response

Jack, C (2004)

Mild NCD management

- Many causes of Mild NCD, i.e. TBI, depression, AD
- Don’t say or diagnose Alzheimer’s!
  - No certainty of progression (unless significant memory deficit).
  - Need for reassessment in 1-2 years.
- Aricept/Namenda do not stop progression of AD
- Always recommend exercise for 150 minutes per week

DSM: Major Neurocognitive Disorder

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

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

DSM-5: Major or Mild NCD due to Alzheimer's Disease 2

- For Mild NCD:
  - Probable AD diagnosed if
    - evidence of causative AD genetic mutation from family hx or genetic testing
  - Possible AD if
    - no genetic evidence and all 3 of following present:
      - Memory decline
      - Progressive gradual decline in cognition
      - No evidence of mixed etiology

- D. Not better explained by CV disease, etc.

NCD due to Alzheimer's Disease

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

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

- CJV: "Possible AD" will become new dx norm for neuropsychologists; NCD due to multiple etiologies being most likely

Neurodegeneration Fiction & Fact

- Degenerative disorders begin with changes in cognition or movement?
- Most start with a psychiatric prodrome that is the key to early intervention
- Psychiatric symptoms lack scientific relevance to dementia?
- These symptoms are key to the understanding dementia
- Mood, anxiety, withdrawal are a reaction to the illness?
- These changes reflects anatomy/chemistry of disease
- Psychiatric symptoms in neurodegeneration irrelevant to typical psychiatric disorders
- Bruce Miller: They are the roadmap for understanding mood, emotion psychosis, compulsions, etc.

Psychiatric Syndromes in Dementia

- Bipolar
- Antisocial personality
- Schizophrenia
- Borderline personality
- Schizoaffective disorder
- Depression/anxiety
- Borderline

- Conversion
- Addiction
- Body dysmorphic disorder
- Schizotypal
- Schizoidal
- OCD

NPS: neuropsychiatric symptoms

- Neuropsychiatric symptoms (NPS) have been viewed as “non-cognitive” symptoms of dementia (also known as Behavioral and Psychological Symptoms of Dementia (BPSD)).
- They include impairments of mood, anxiety, drive, perception, sleep, appetite, as well as behavioral disturbances such as agitation or aggression.
- NPS have been described since Alois Alzheimer’s index case of Auguste D, who presented initially with emotional distress and delusions of infidelity, followed by cognitive impairment.
- NPS are common in dementia with prevalence rates of up to 97%, increasing with time after diagnosis.

NPS: neuropsychiatric symptoms

- NPS are associated with
  - faster cognitive decline and
  - accelerated progression to severe dementia or death,
  - higher rates of institutionalization,
  - greater functional impairment,
  - greater caregiver stress,
  - worse quality of life, and
  - higher burden of neuropathological markers of dementia.

- NPS are often present at the time of dementia diagnosis, and for some they precede the onset of cognitive symptoms

- Most commonly used rating scales for NPS are the informant-rated Neuropsychiatric Inventory Questionnaire (NPI-Q), and the interview-based NPI

Psychiatric manifestations of Neurodegeneration (ND)

- Every ND disorder begins with psychiatric symptoms: MDD, Anxiety, Neuroticism
- Psych & ND: Not 2 boxes, not either-or diagnosis

- Late life onset depression is often a product of Vascular or AD dementia
- AD does not start with memory disorder, but with psychiatric sxs

- Psych manifestations of ND are the disease, not the reaction to it;
  - Belief that mood disorder (MD) is a reaction to ND disorder is wrong; it reflects onset of disease, i.e. Huntington's = 2x depression & suicide
- Mood changes begin before awareness of ND
- Early changes in brainstem reticular core is cause of psychiatric sxs in ND disorders

Bruce Miller, UCSF, 2019

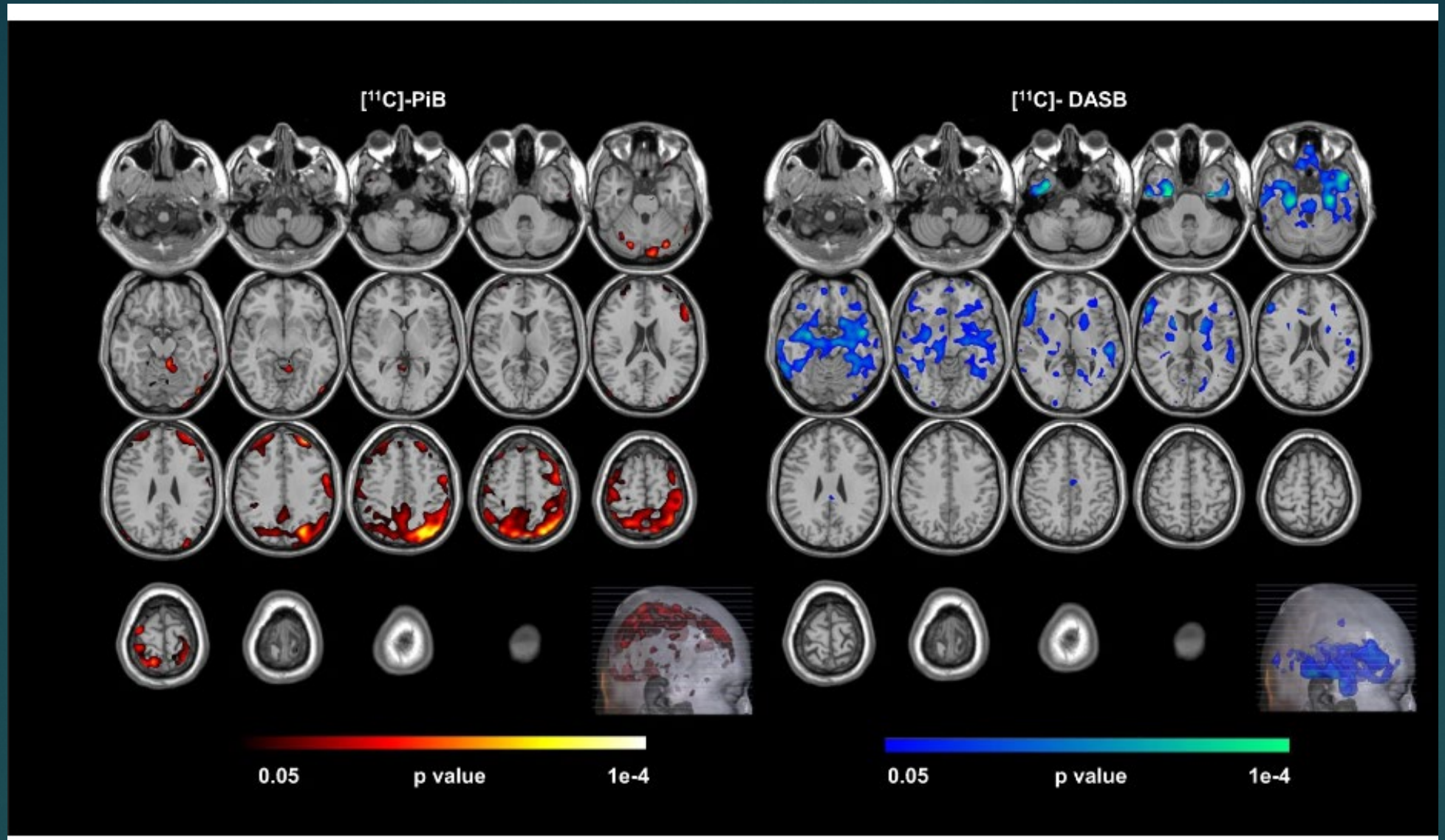
Late Life Depression

- Depression in late-life is associated with increased risk of cognitive decline and development of all-cause dementia. Antidepressant treatments, developed for the treatment of younger patients, are effective in only half of patients in late-life

- Hypotheses were proven that a spatial covariance pattern of higher beta-amyloid (Aβ) and lower serotonin transporter availability (5-HTT) in frontal, temporal, and parietal cortical regions would distinguish LLD patients from healthy controls and the expression of this pattern would be associated with greater depressive symptoms.

- Greater expression of the combined pattern, as well as both Aβ and 5-HTT patterns, was correlated with greater depressive symptoms.

BA



Higher beta-amyloid (left, hot colored areas) and lower serotonin transporter availability (right, cool colored areas) was observed in Late-Life Depressed (LLD) Patients than in normal controls, applying the Monte-Carlo Simulation Method (uncorrected $P = 0.005$).

Serotonin

Barnes, Yaffe, 2012: Psych. Syndromes → Dementia

Psychiatric Syndromes, Particularly Late in Life, Increase Risk for Dementia

- 13,535 patients, Kaiser Permanente
  - 14% midlife depressive symptoms (45–60)
  - 9% late life symptoms (60–75)
- Midlife symptoms increased risk of dementia by 20%
- Late life symptoms increased risk by 70%

Table 2. Depressive Symptoms and Risk of All-Cause Dementia

	All-Cause Dementia		
Depressive Symptoms	No. (%) of Subjects	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
None	2026 (20.7)	1.00 [Reference]	1.00 [Reference]
Midlife only	450 (23.5)	1.22 (1.10-1.35)	1.19 (1.07-1.32)
Late life only	389 (31.4)	1.69 (1.51-1.88)	1.72 (1.54-1.92)
Midlife and late life	181 (31.5)	1.80 (1.54-2.09)	1.77 (1.52-2.06)

Barnes, Yaffe et al, Arch Gen Psychiatry, 2012

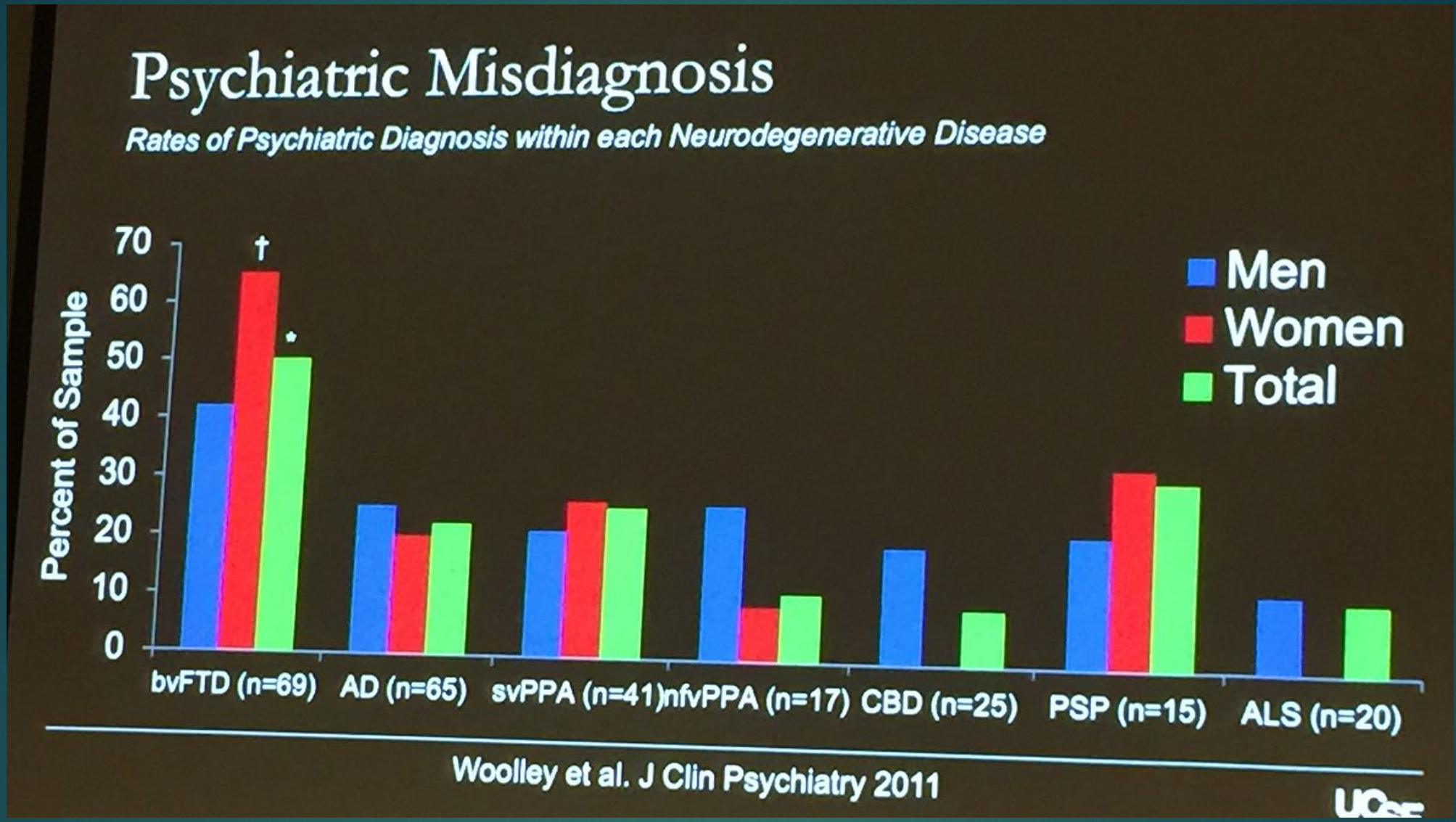
MDD increases risk and precedes onset of ND dementia

Psychiatric Manifestation of ND

- Early changes in brainstem reticular core is cause of psychiatric sxs in ND disorders
- Parkinsonism: anxiety and depressive disorders are initial sxs in more than 50%
- PD: can have most ferocious depression and anxiety syndromes prior to movement disorder
- AD: early changes in emotions accompany AD, esp. depression & anxiety; those with these changes have worse cognition & more rapid decline

Psychiatric Manifestation of ND

- Adults with higher neuroticism at a single time point in midlife are at higher risk of late-onset AD. Normal adults show decreasing neuroticism in large longitudinal studies.
- Antidepressant use is linked to lower levels of Beta Amyloid in brain
- Need to treat both psych. Sxs and ND: use antidepressants

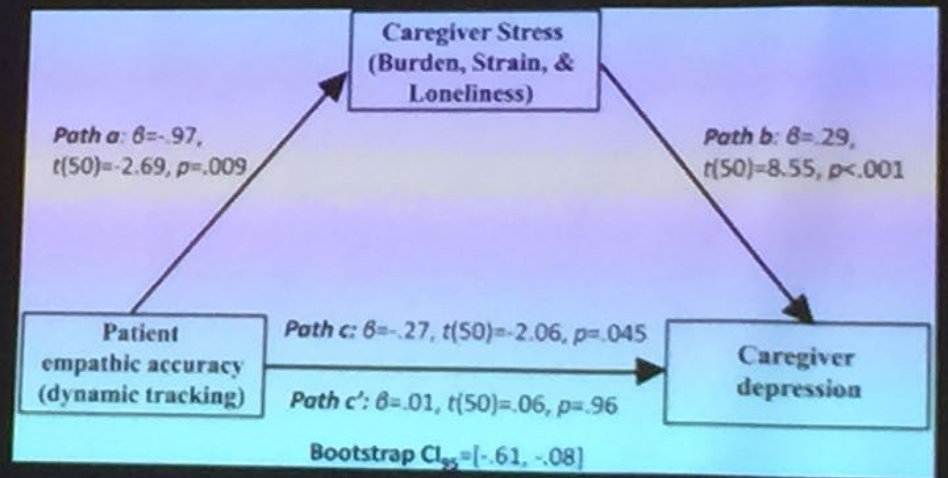


FTD is frequently misdiagnosed as Psychiatric; 70% of women

Empathic Accuracy Deficits in Pts with NDD

Association with Caregiver Depression

- Lower empathic accuracy in ND patients associated with greater depressive symptoms in their caregivers
- Associations between patient empathic accuracy and caregiver depressive symptoms found when accuracy was measured by caregiver report or dynamic tracking task
- Patients' ability to recognize specific emotions not associated with caregiver depressive symptoms
- The association between lower patient empathic accuracy and greater caregiver depressive symptoms was accounted for by increased loneliness, burden, and strain in caregivers



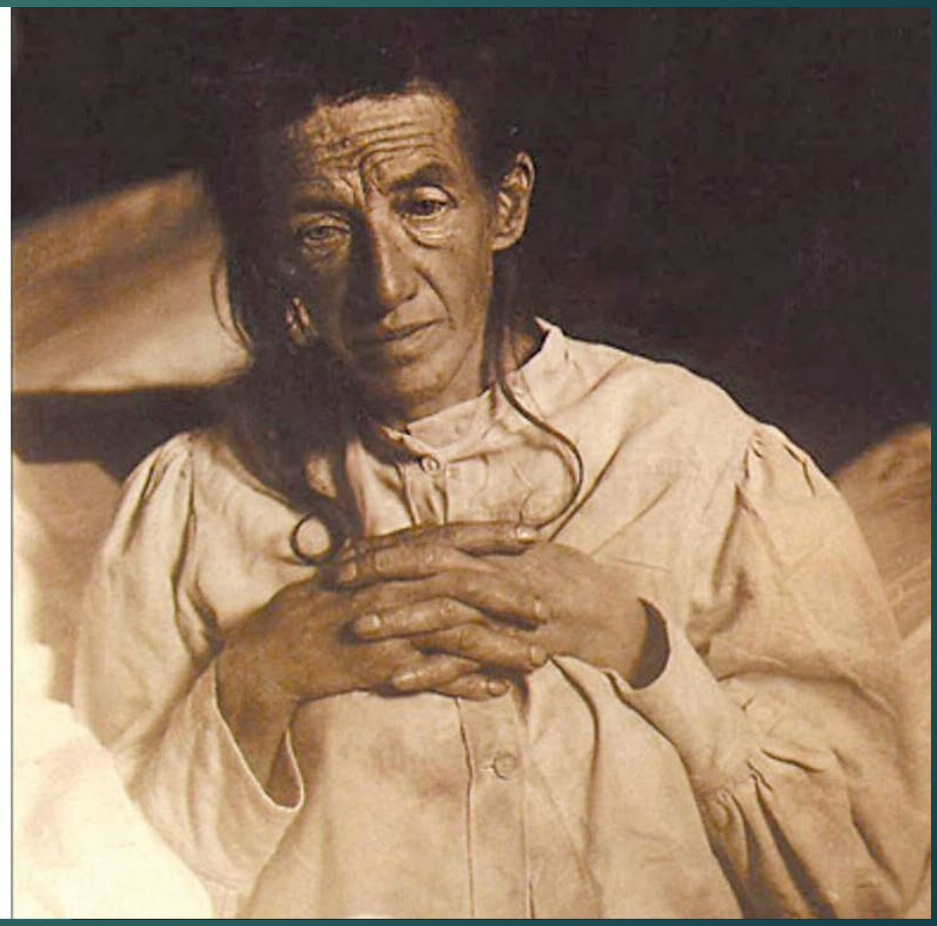
Brown CL, Lwi SJ, Goodkind MS, Rankin KP, Merrilees J, Miller BL, Levenson RW, 2018

UCSF

Lower empathy in ND pts associated with greater depression in caregivers

Alzheimer’s Disease

Alois Alzheimer, 1864-1915: Auguste Deter, 1850-1906: first diagnosis of AD, 1901



Auguste Deter: 1st dx of dementia, 1901

Emil Kraepelin was the first to use Alzheimer's name in association with dementia in the eighth edition of his textbook of Psychiatry

AD Prevalence

- AD = Most common form of major NCD (70%)
- Increases with age in exponential fashion with every 5 years post 65
- 5-10% in 7th decade; 25%+ thereafter
- US census AD diagnosed: 65-74 yo – 7%; 75-84 – 53%; 85+ - 40%
- Majority of mild amnestic NCD = due to AD
- Survival after diagnosis: 10 years (but up to 20)
- Death most commonly due to aspiration (foreign matter into the lungs)

DSM-5, 2013

Alzheimer’s Disease

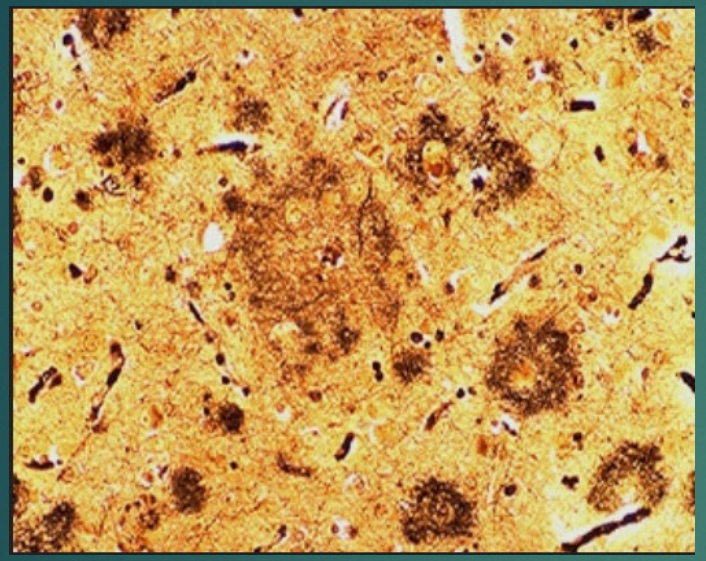
- Sixth leading cause of death; 100,000/yr of >65; 4 million affected
- Every 72 seconds, someone develops Alzheimer's disease.
- 5.7 million people with AD
- 50% of nursing home population

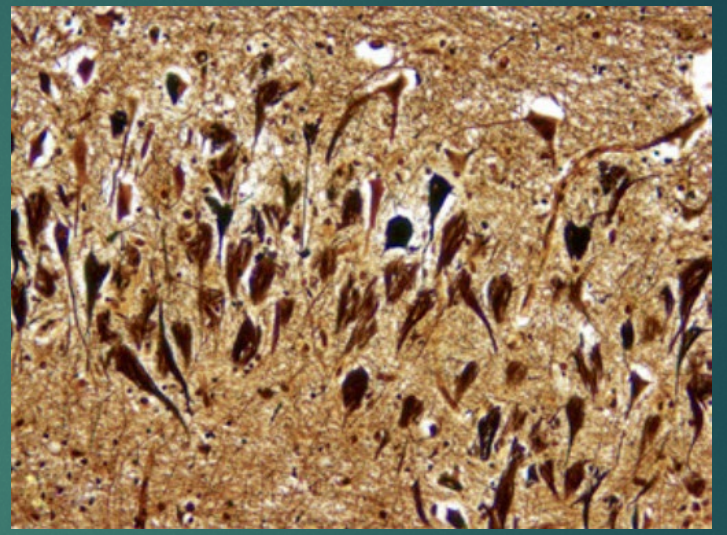
Chenjie Xia, et al., JAMA, 2017

Causation

- Causation of AD:
  - Current theory: amyloid-beta 42 (AB42),Tau protein accumulation, & neuroinflammation which produce synaptic and neuronal damages
  - BA normally is an antimicrobial; part of immune system
  - Newer viral theory =
    - herpes simplex virus type 1 (HSV1) in brain with APOE-ε4
    - Bacteria Porphyromonas gingivalis
- Neurofibrillary changes (tau) more highly correlated with NCD than beta-amyloid

Causation: AD Pathology + Neuroinflammation

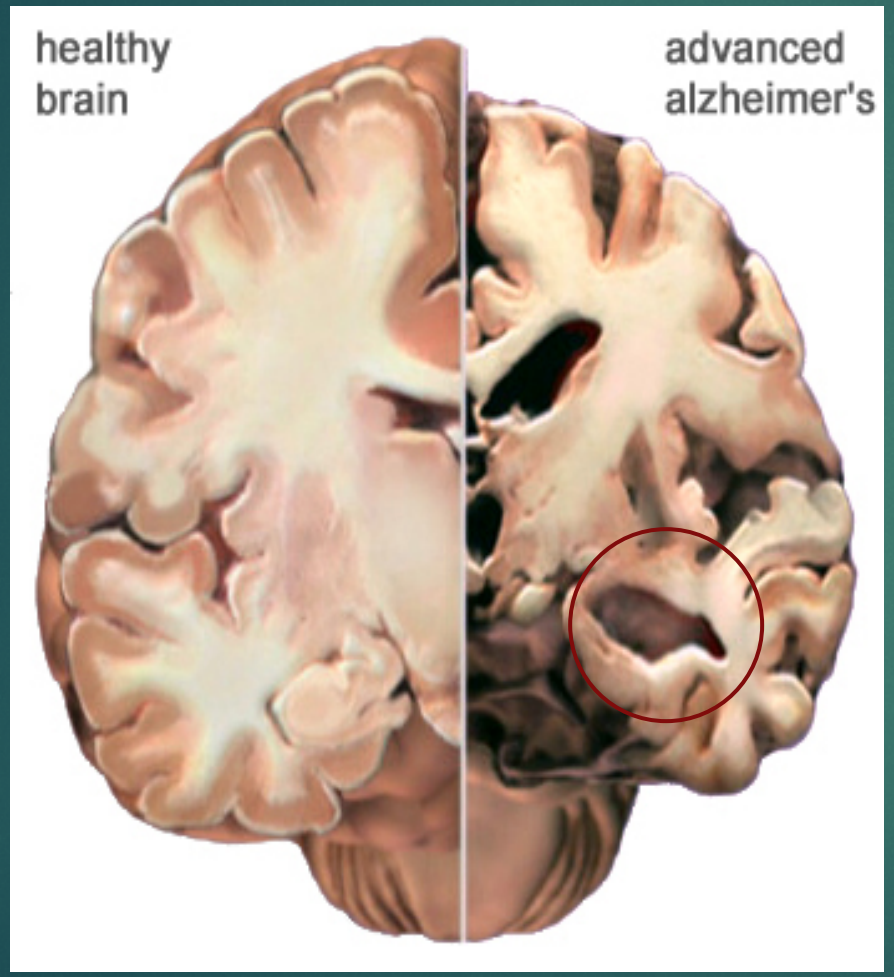




Amyloid Plaques:
- Extra-cellular
- Amyloid-B (AB)

Neurofibrillary Tangles
- Intra-cellular
- Tau

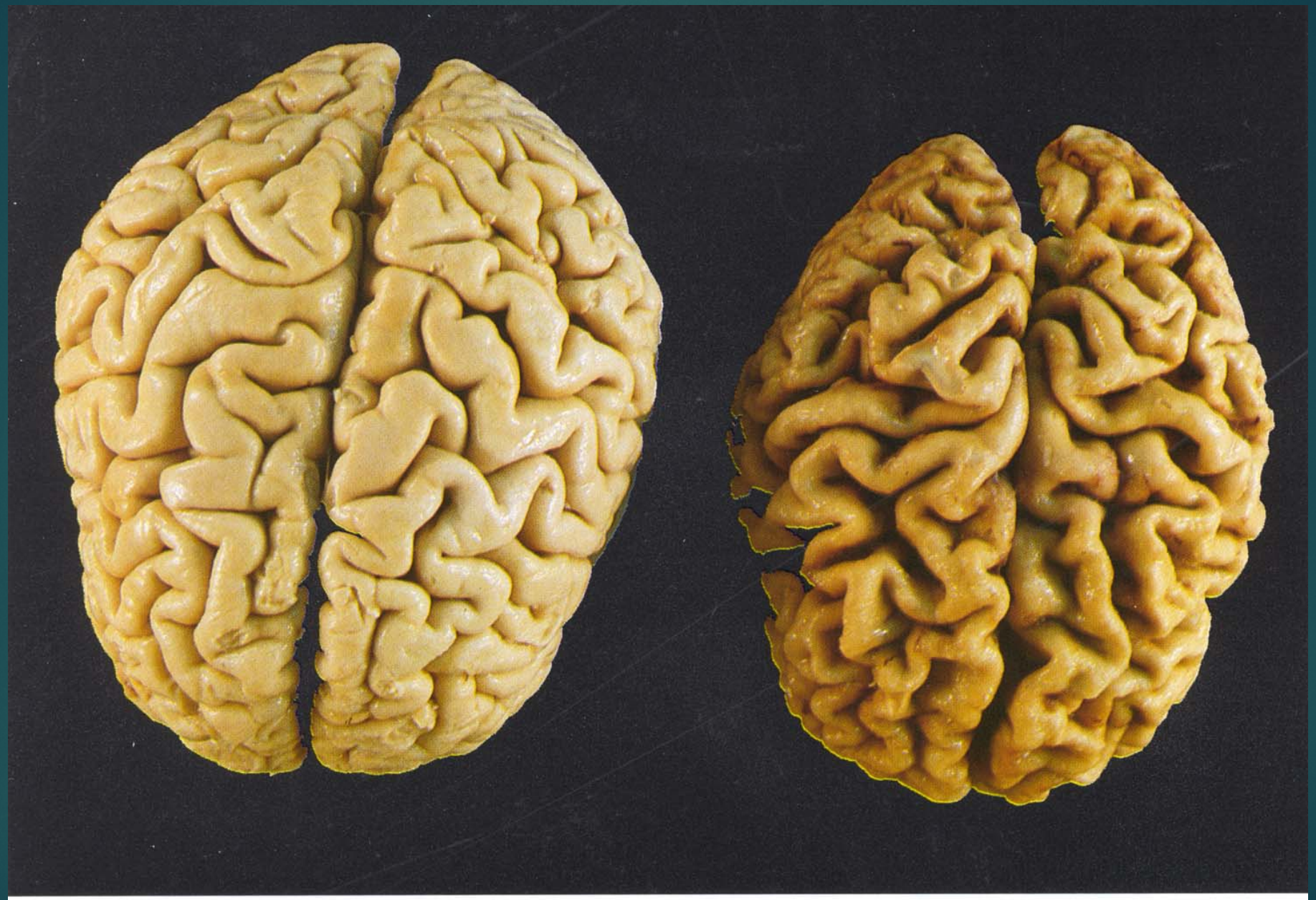
Neuropathology of Alzheimer's



1 Atrophy: loss of synapses & dendritic spines

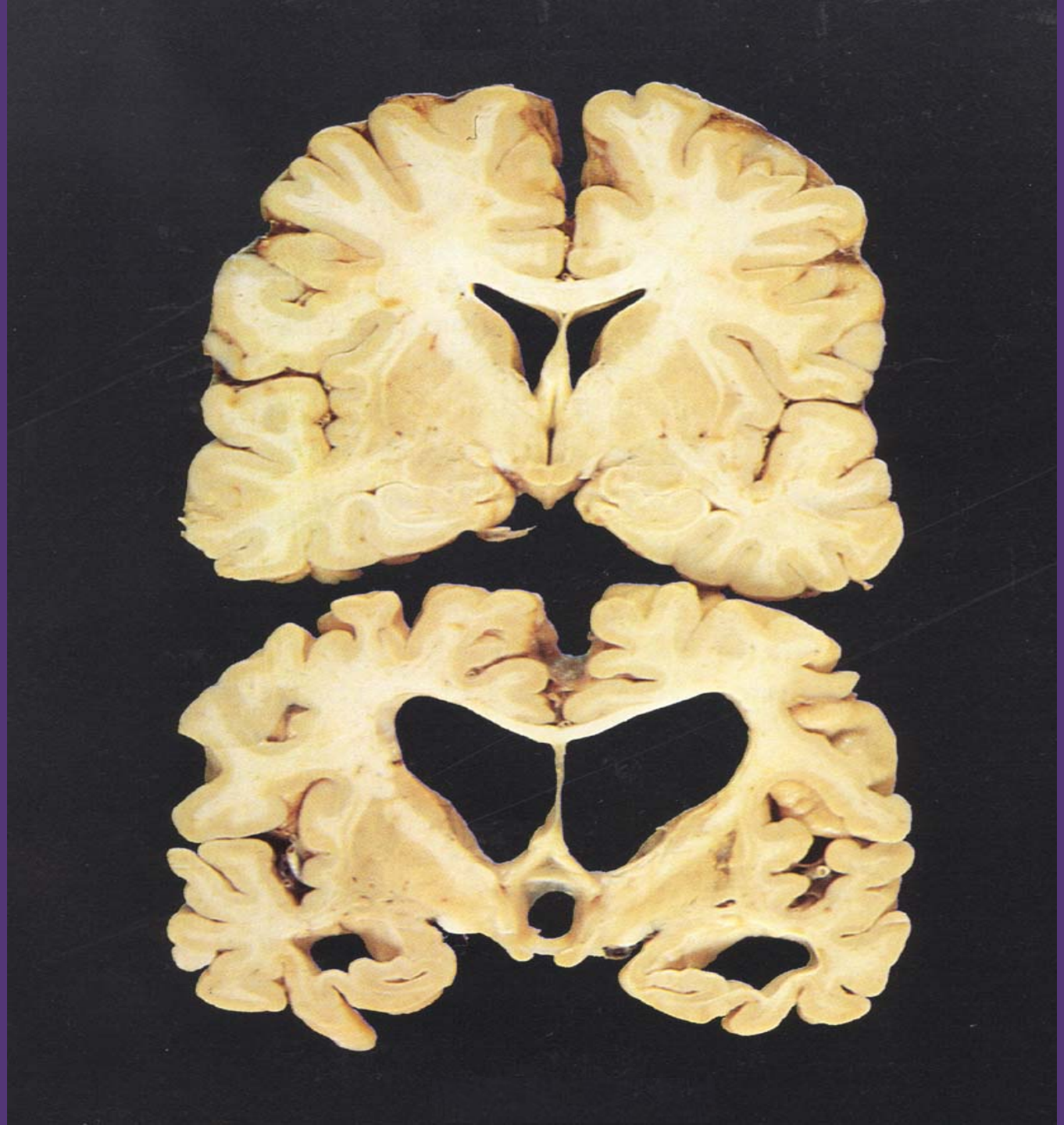
2 Enlarged Ventricles

3 Reduced Hippocampal Volume



Normal

Alzheimer



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

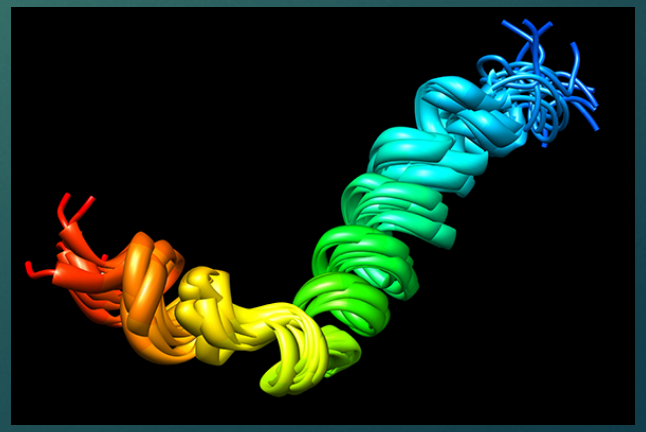
Amyloid hypothesis:

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

2 - which spurs increase in Tau,

3 - which disables and then kills brain cells,

4 - resulting in cognitive decline.



Neuropathology of AD

- Atrophy (neuronal loss) and ventricular dilation:

- Neuron and synaptic loss: 1st in temporal/hippocampus, temporal/parietal hypometabolism, nucleus basalis, cholinergic neurons, locus coerulus of midbrain, then frontal

- Neuritic (amyloid) plaques ↑ (neurons): beta amyloid

- Neurofibrillary tangles ↑ (axons): tau protein in tubules glue up:
  - Entorhinal & transentorhinal,
  - then Hippocampus,
  - then association areas

Cascade of cognitive decline

- Normals: Unlike episodic personal memory, which decreases with age, semantic/word meaning memory tends to increase with healthy aging.

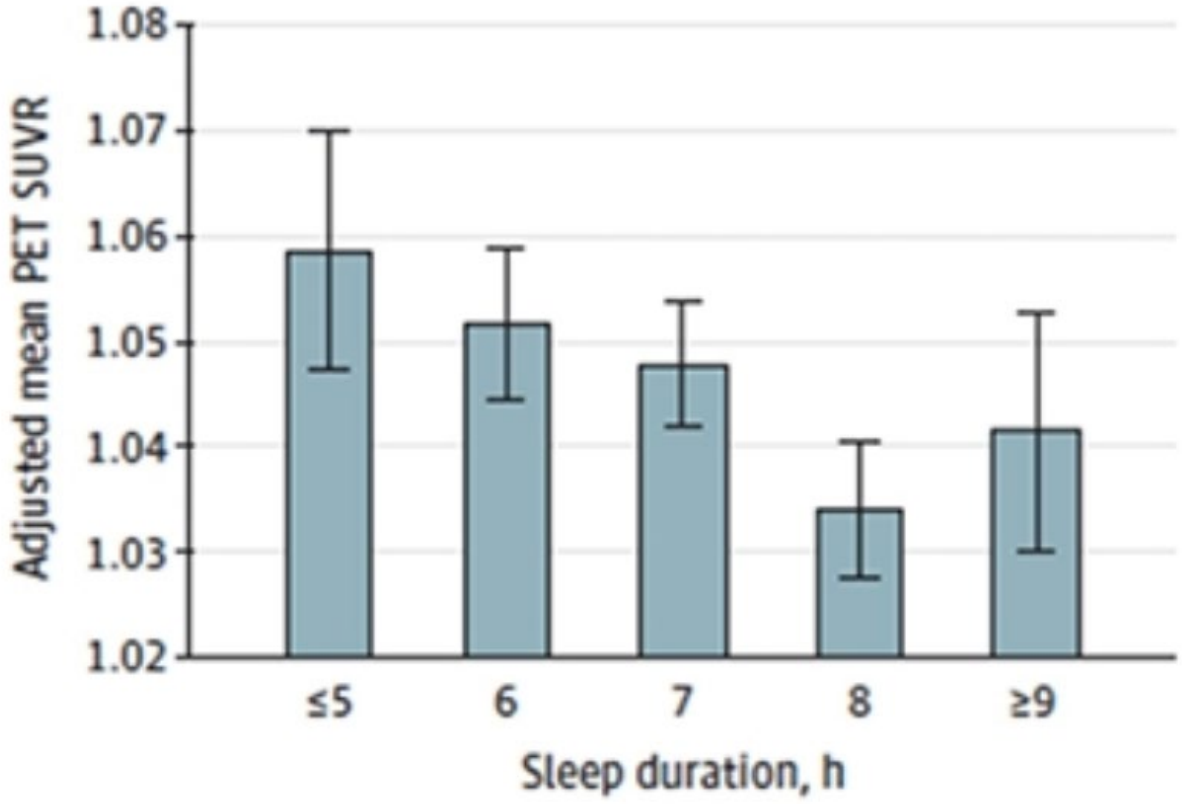
- Alzheimer's:
  - Episodic memory begins to decline first,
  - then processing speed,
  - executive function,
  - and lastly semantic memory

- Tau increase is what produces memory disorder.

Beta Amyloid (AB42) and Tau are the Probable Causes of AD

- Two forms of AB: AB40 and pathological AB42
- Greater amount of AB40 with increasing age and being APOe4 carrier
- Normal function: AB is antimicrobial (part of innate immune system)
- Normals turn over the amount of AB 3 x daily and Tau (especially during deep sleep)
- BA loads the gun & pulls the trigger, and Tau is the bullet.
- Tau does not spread from Temporal lobe until enough BA accumulates.

Less Sleep = more BA plaque



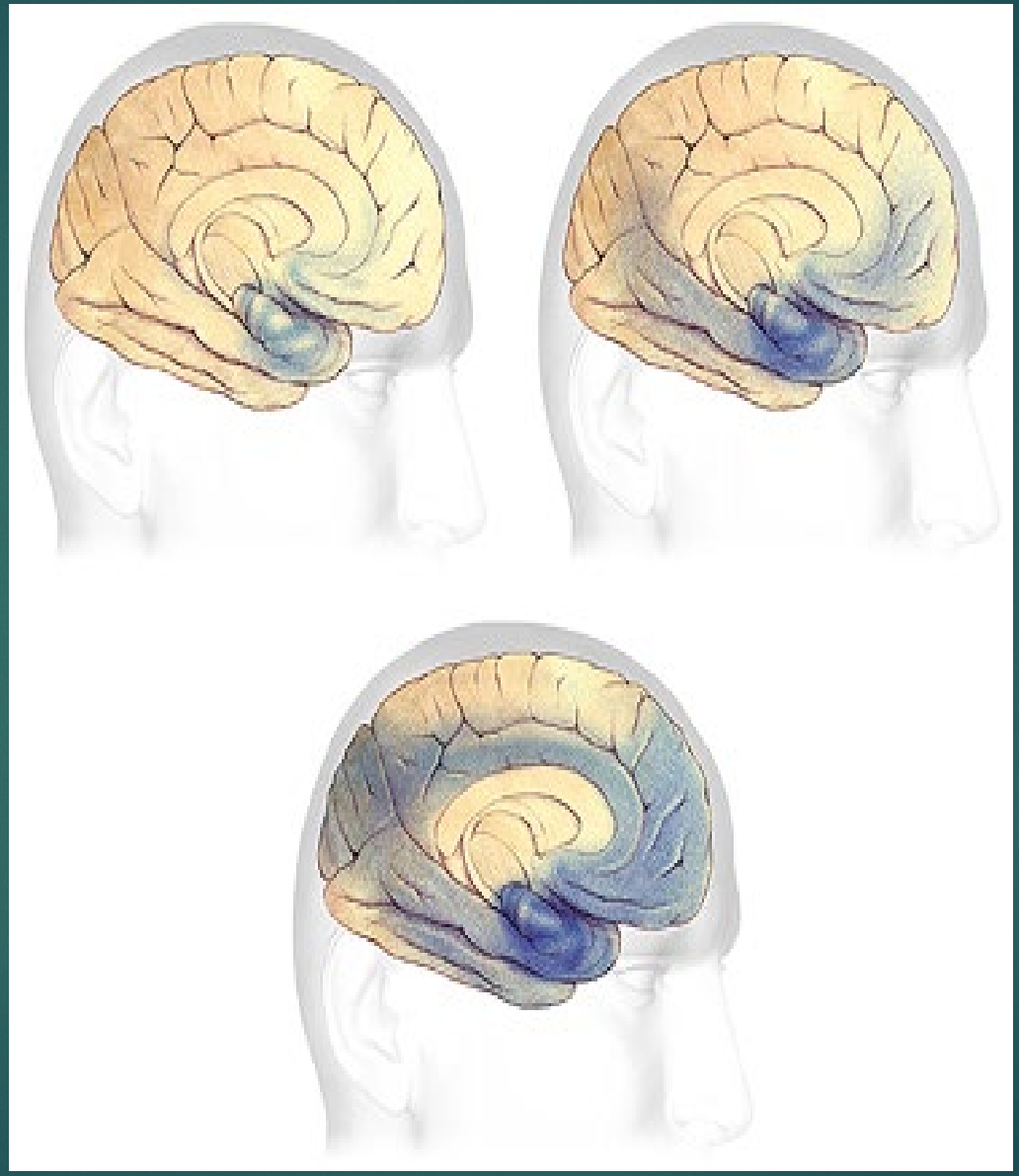
Less Sleep More Plaque. *Amyloid burden correlated with hours of sleep per night. [Courtesy of Winer et al., JAMA Neurology, 2021.]*

Clinical presentation, neuropathology and NP deficits in early familial vs. late AD

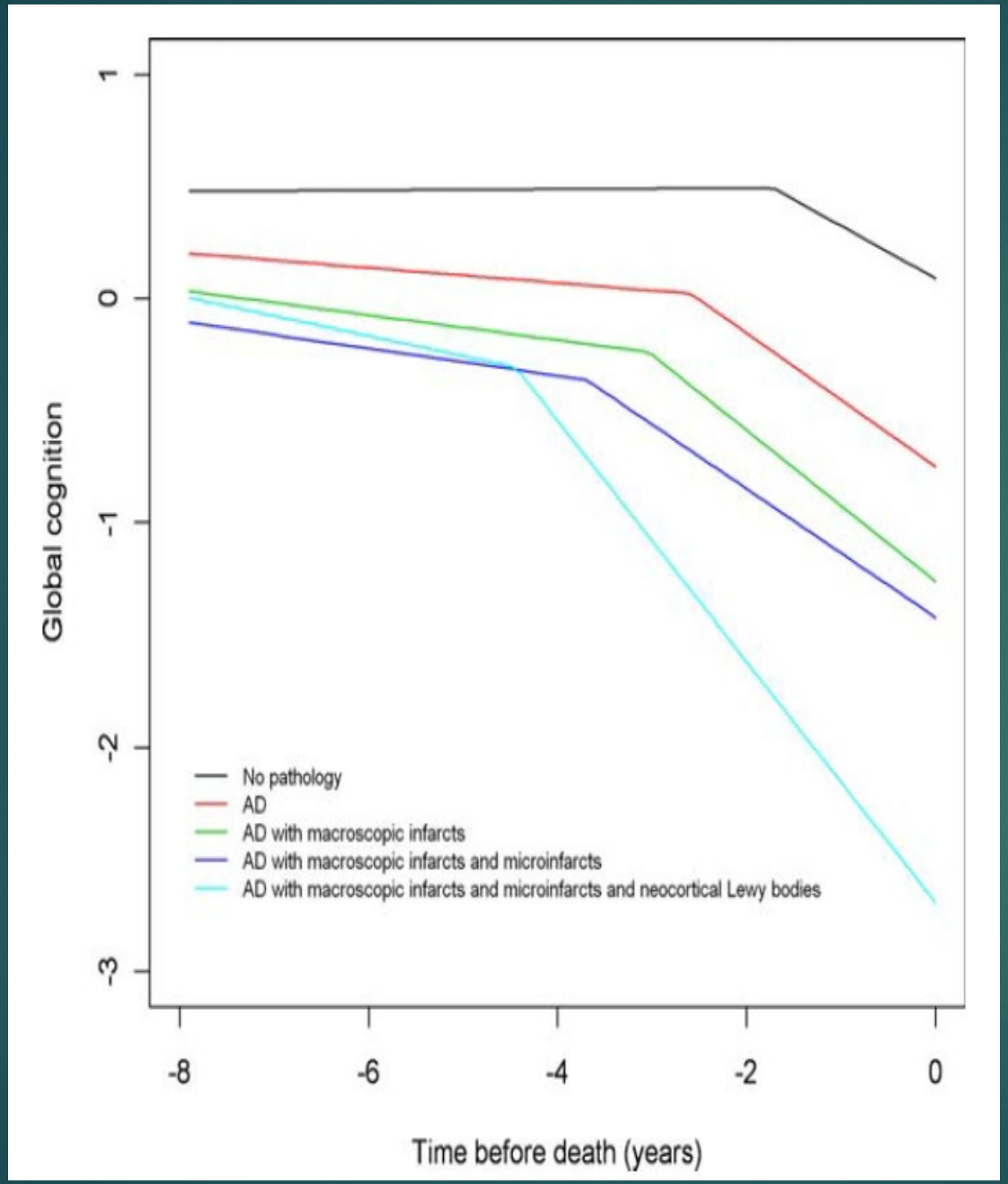
- Sporadic, age related, late-onset AD
  - 90% of all AD; slight female>male
  - higher frequency of ApoE-e4 alleles in late onset
  - slower progression
  - memory, visualspatial and language deficits
  - functional deficits present later

- Familial/genetic, early-onset AD
  - more severe pathology
  - faster progression
  - apraxia, language and attention deficits
  - early on, memory is relatively preserved
  - functional deficits earlier
  - earlier NCD in a family, more likely to inherit

AD Progression



More pathologies, worse cognitive outcome



Normal

AD

AD + VaD

AD & LBD

P. Boyle et al., 2013

Core AD issue: No new memory recorder

- Encoding Deficit: memory encoding does not work
- Do not encode new information
- Core difference: cuing does not help
- Their brain has stopped recording
- The record machine is permanently broken.

AD Symptoms

- Proportion of First Symptoms:

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

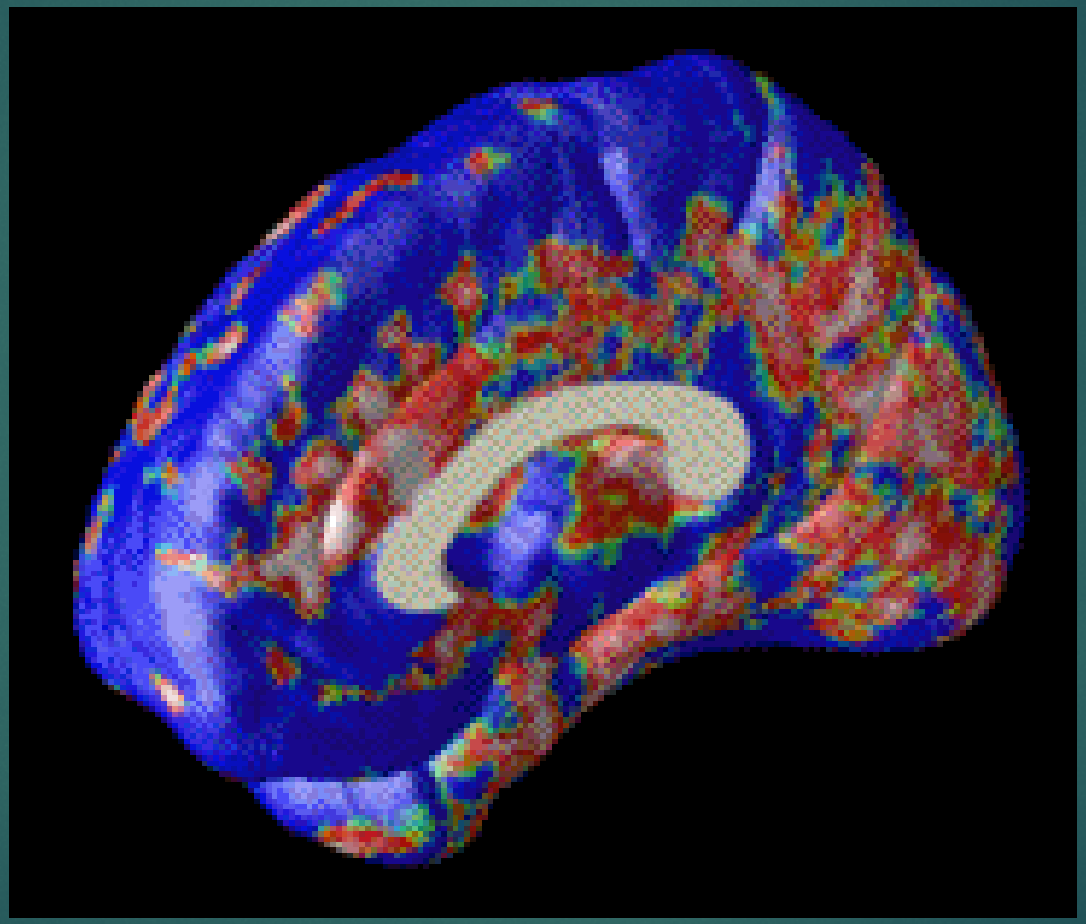
Family Home behavior description:

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

Wandering

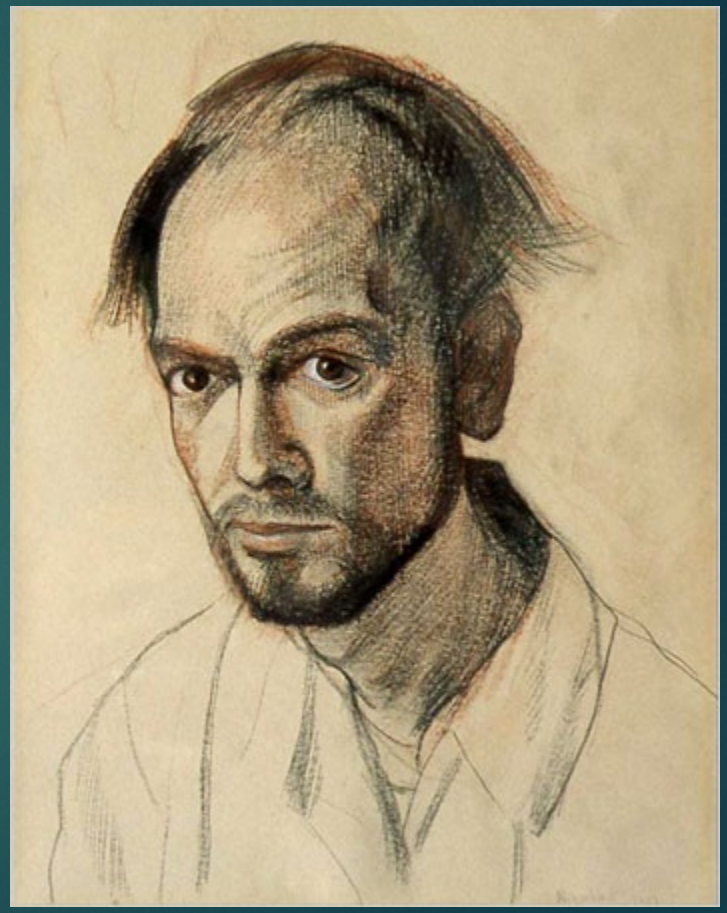
- 50 percent of people who wander will suffer serious injury or death if they are not found within 24 hours.
- MedicAlert® + Alzheimer's Association Safe Return® is a nationwide identification program
- Comfort Zone® and Comfort Zone Check-In® allows families to monitor a person with dementia's whereabouts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

Progression in Alzheimer: 18 Months



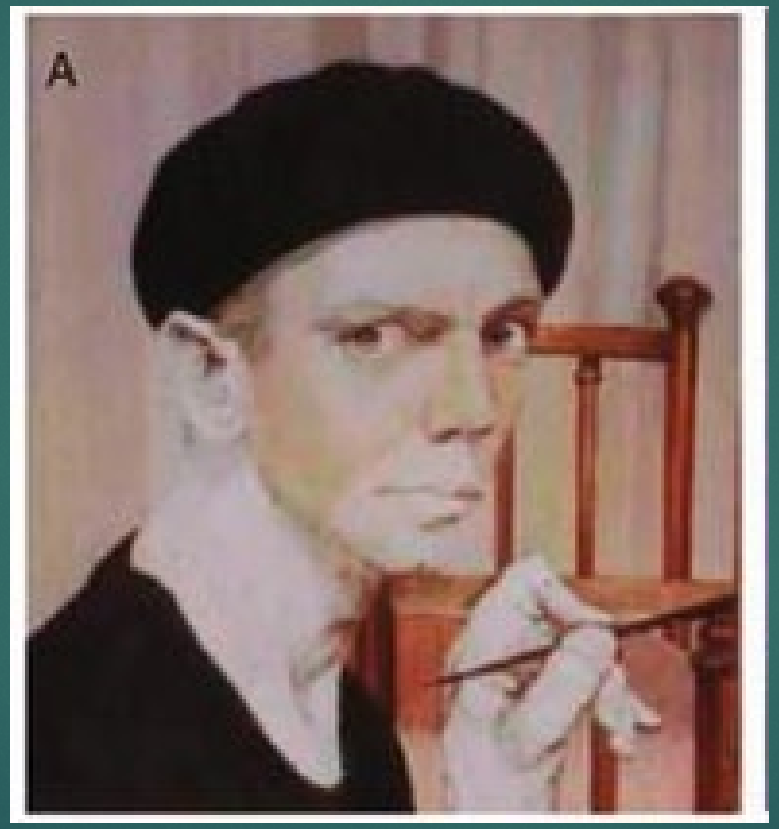
P. Thompson, UCLA, 2002

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

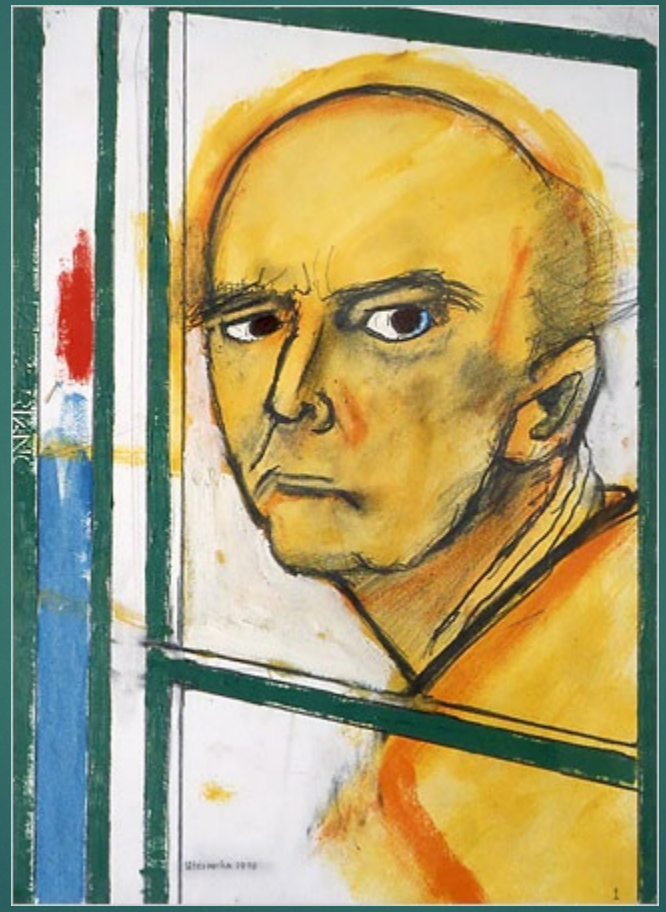


1967

1977, age 40

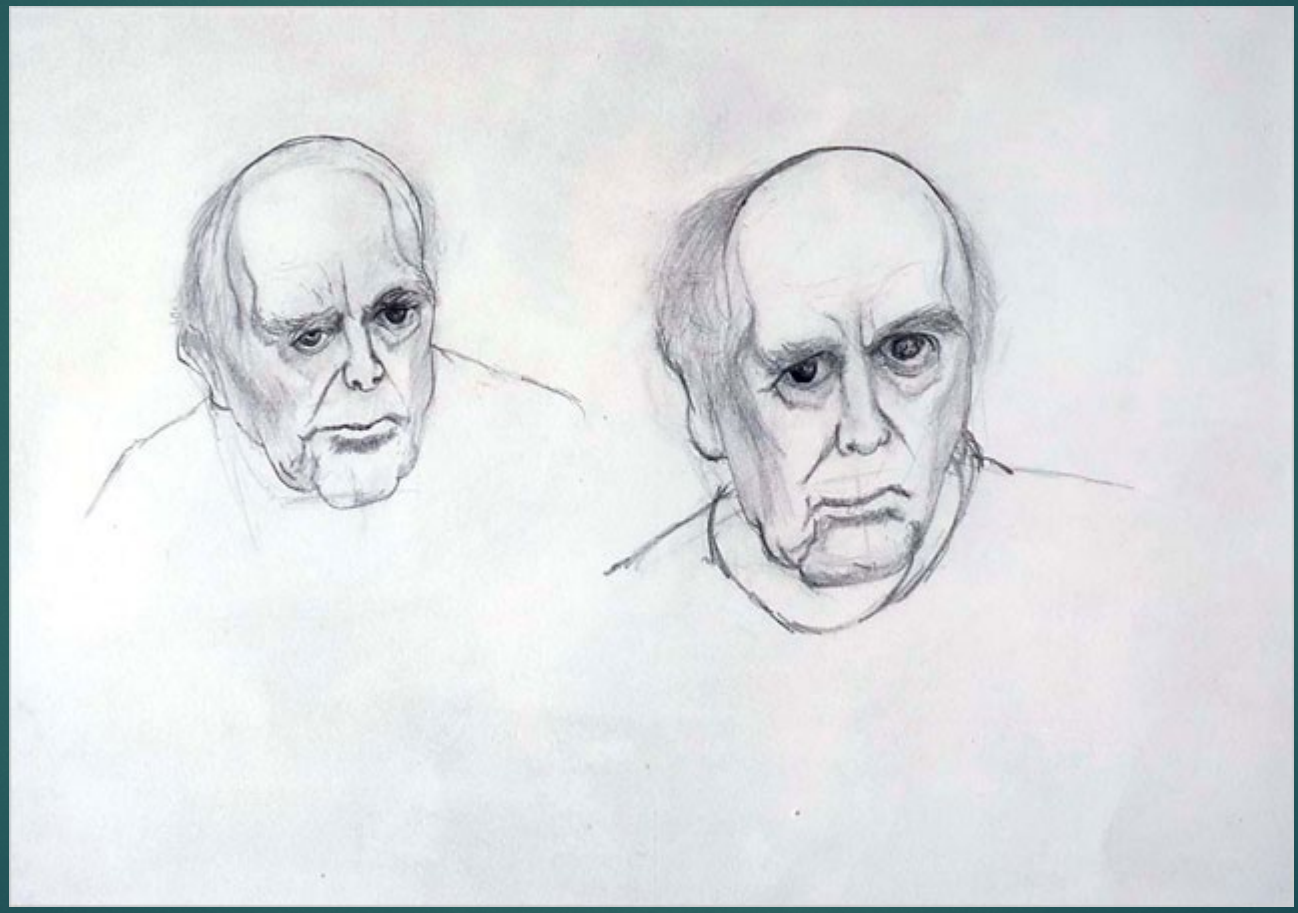


Self Portrait: 1996, age 63

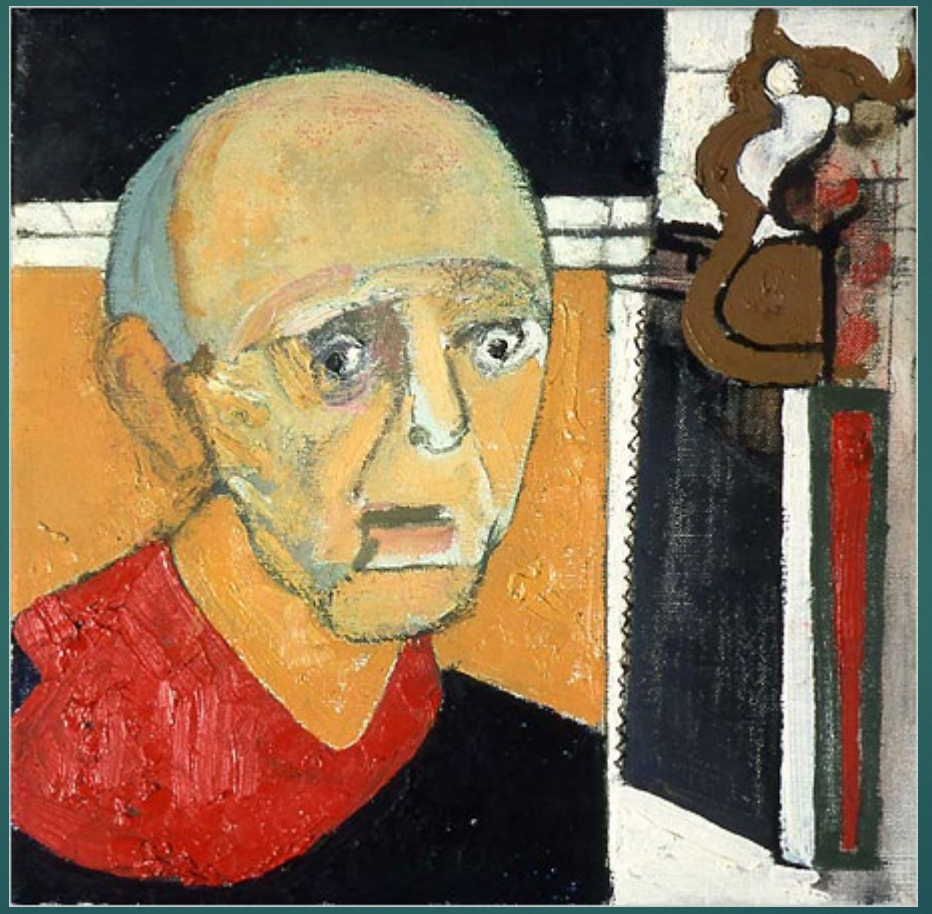


Self Portrait: 1996

Self Portrait: 1996

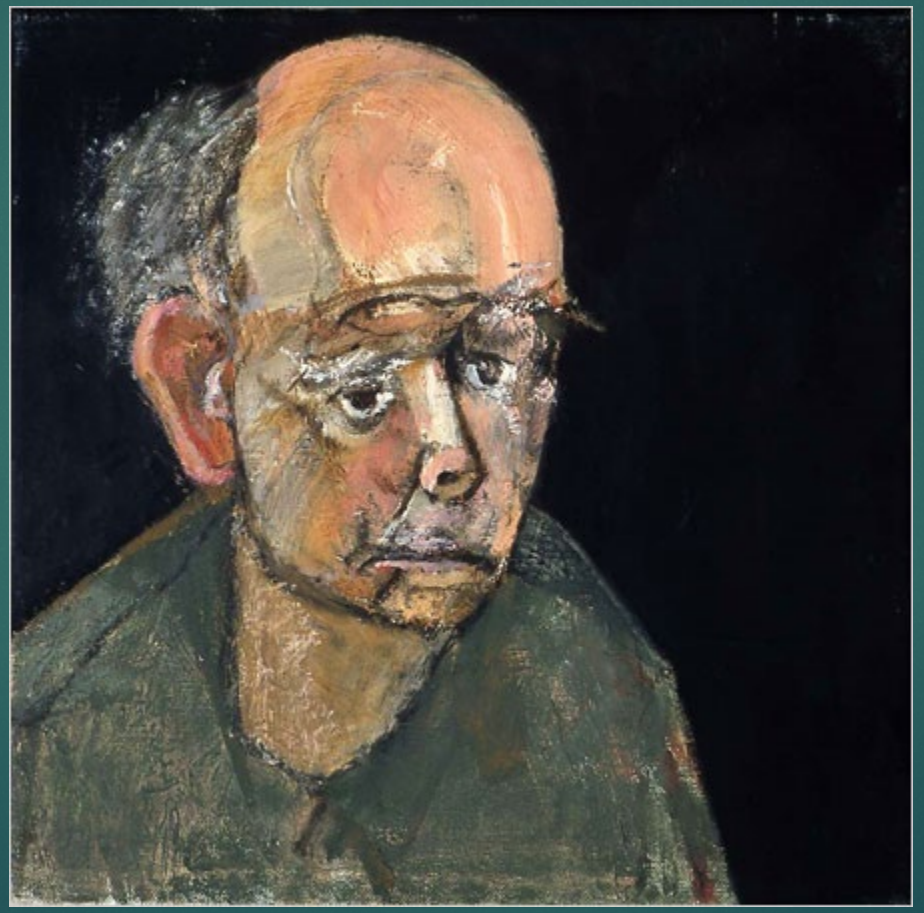


Self Portrait: 1997

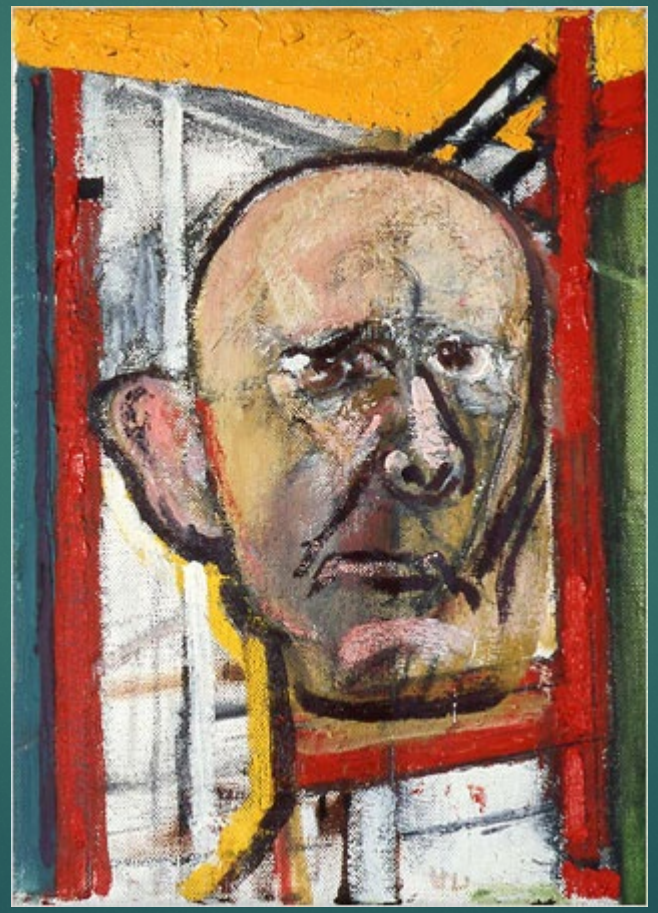


Decides to donate his body to science

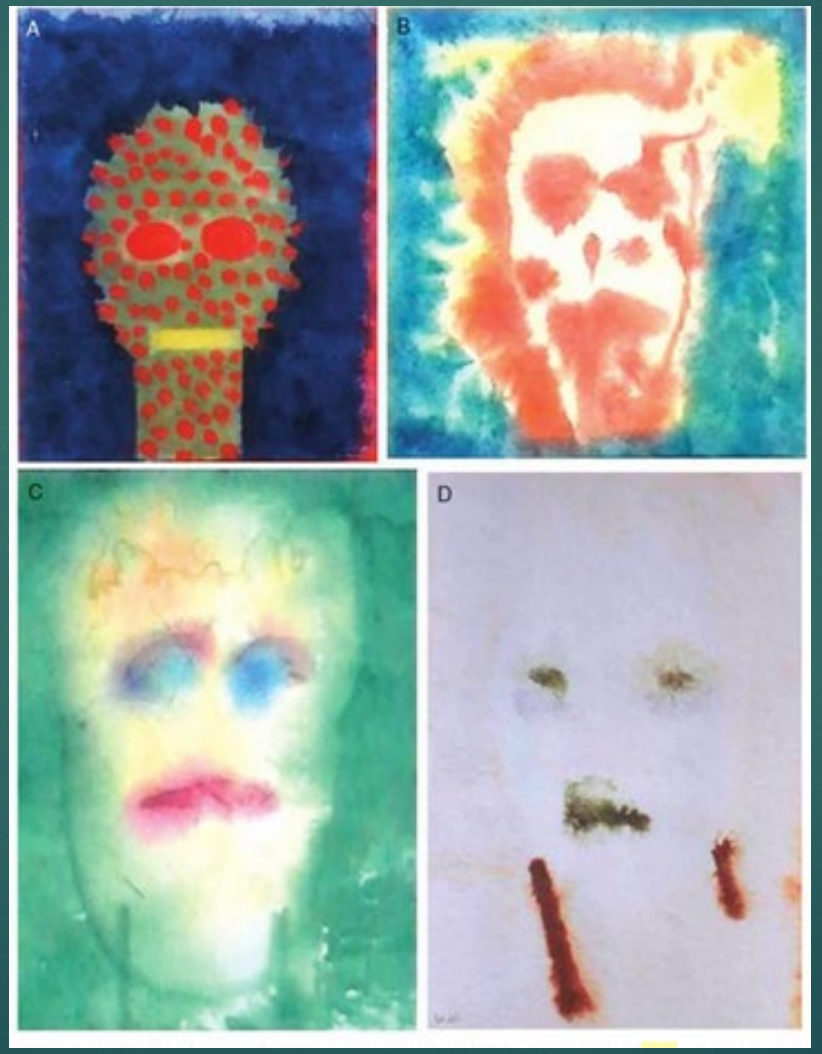
Self Portrait: 1997



Self Portrait: 1998



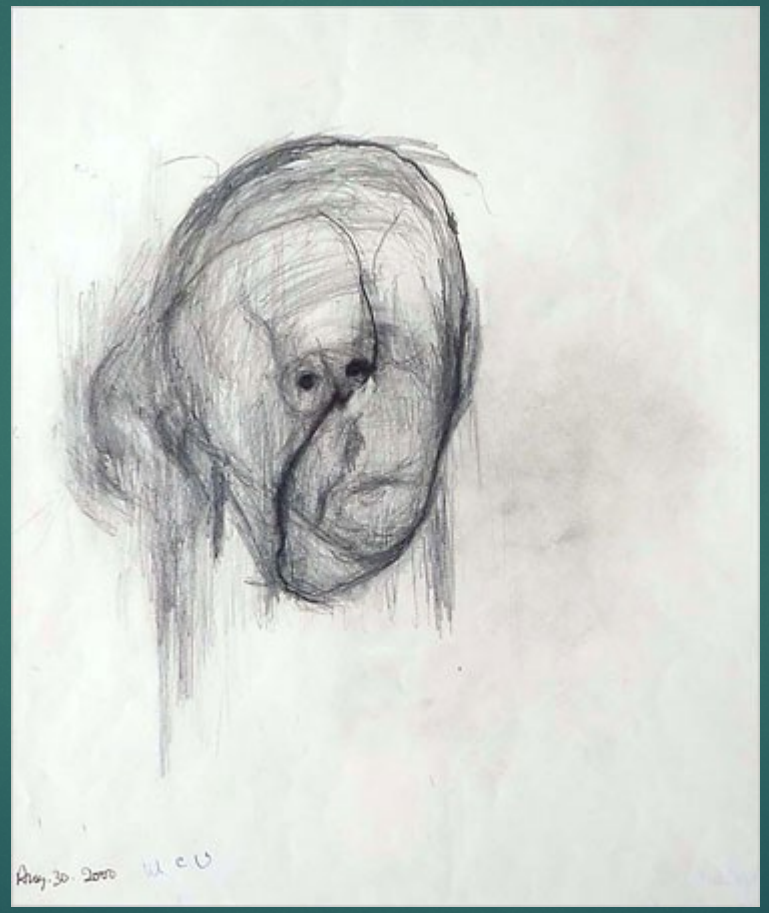
1998, Age 65



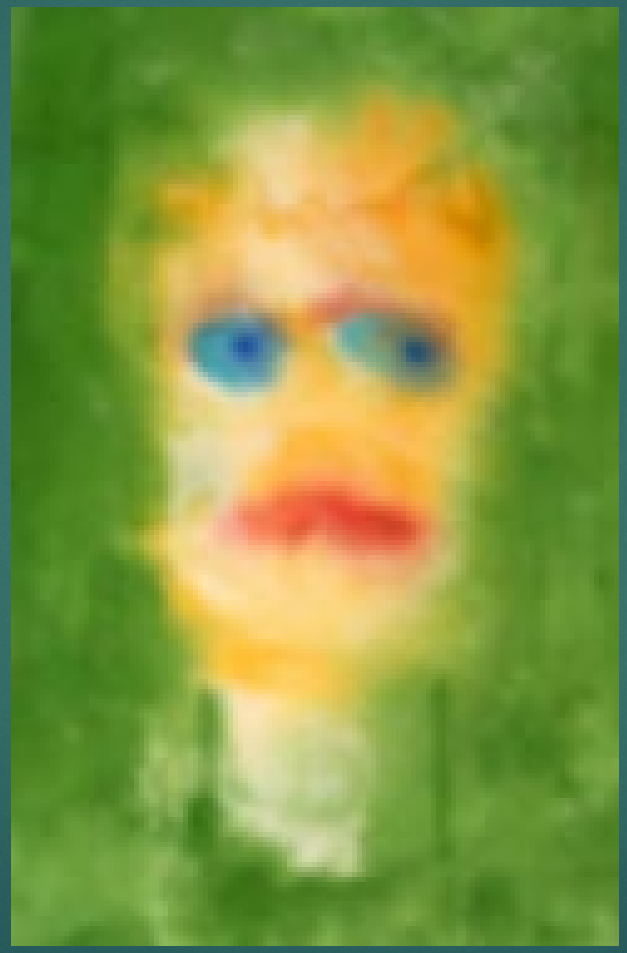
Self Portrait: 1999

2 years to complete

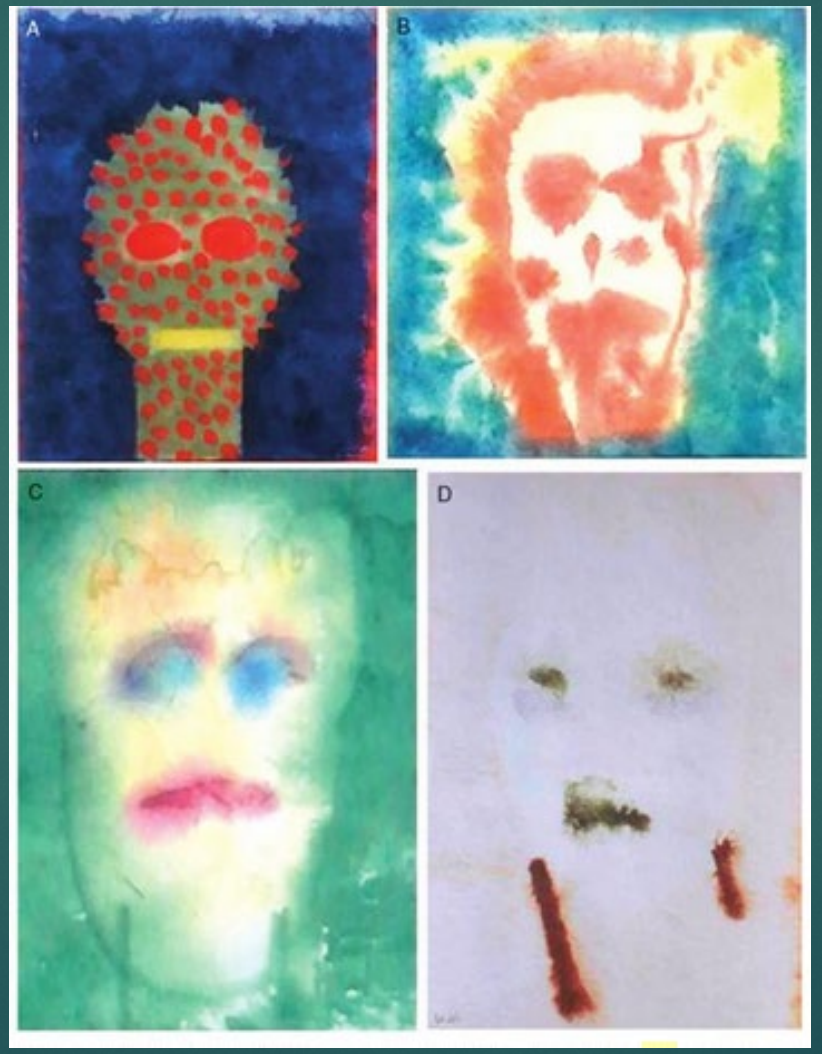
Self Portrait: 2000



Self Portrait 2000+

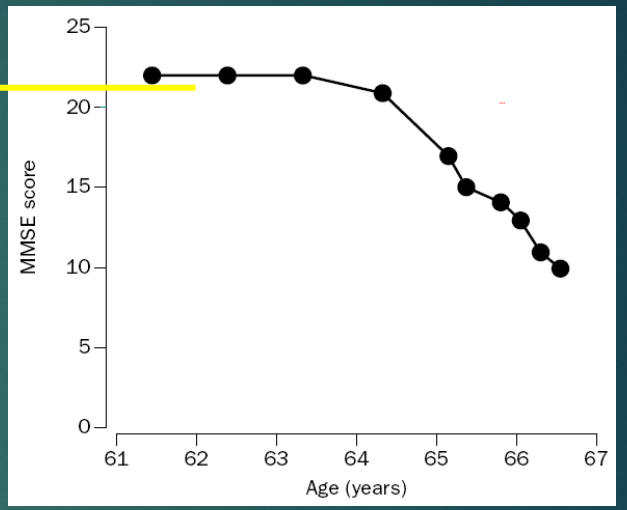


1998, Age 65



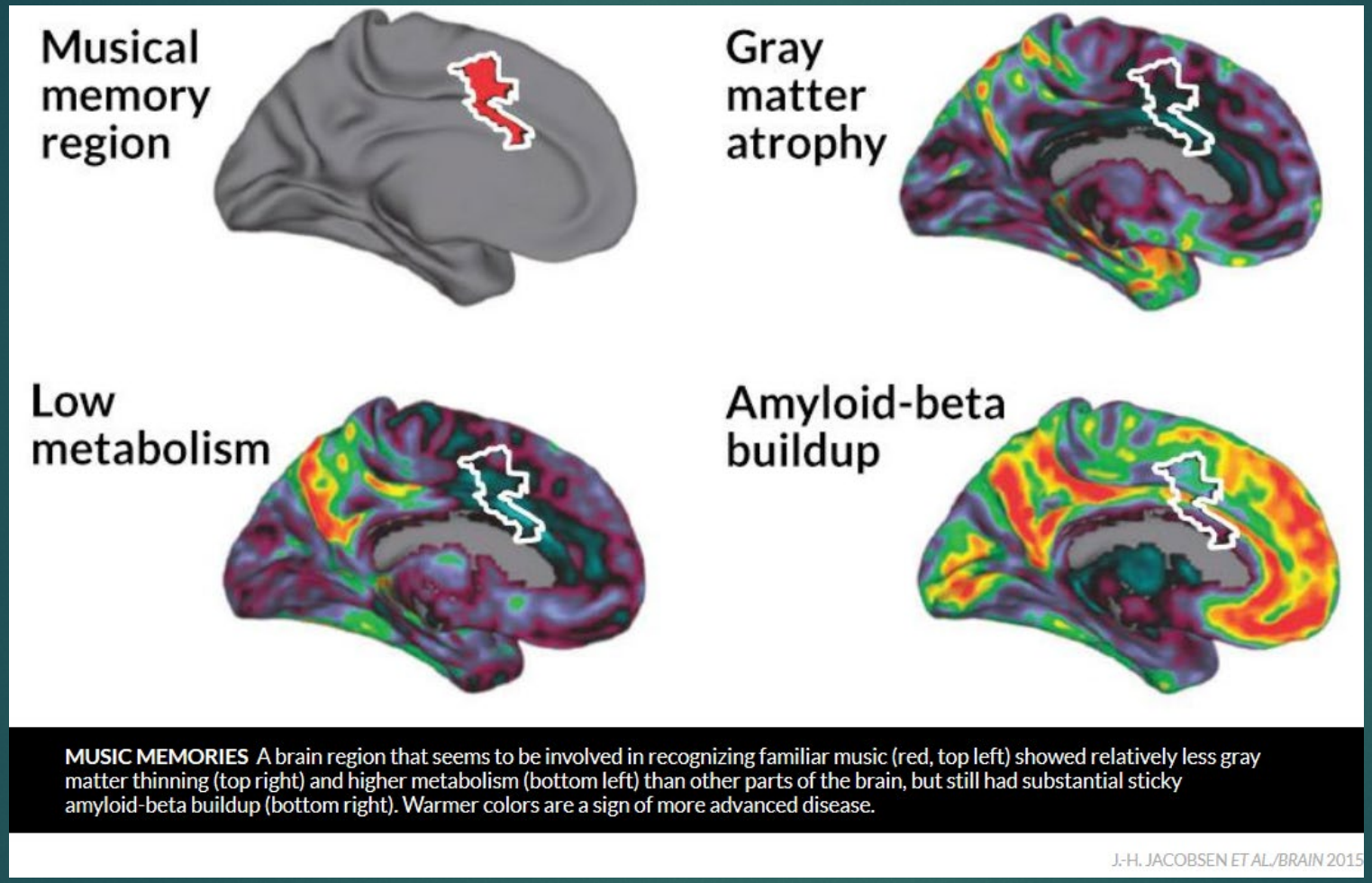
William Untermohlen –self-portraits correlate with cognitive decline

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



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

Music memory survives in Alzheimer's Disease



Familiar music seems to boost autobiographical memories in people with AD:
Recent Tony Bennett and Lady Gaga concert; no memory function, but all his songs ok

AD Pathology, EF deficit, Olfaction

- AD pathology is endemic in old age; most do not have NCD
- Mixed pathologies are the rule: 40-60% of diagnosed AD cases have ischemic lesions &/or Lewy Bodies
- Memory ↓ always precedes Executive↓ in AD
- Executive ↓ with intact olfaction is not AD
- Olfactory ↓ in AD: not anosmia (inability to smell), but agnostic for odor ID: odor recognition ↓ not odor detection

Royall, 2007

AD Underdiagnosed

- Early Alzheimer's disease is subtle – it is easy for family members and physicians to miss the initial signs and symptoms
- Need collateral information
- Less than 50% of AD patients are diagnosed
  - Estimates are that 25% to 50% of cases remain undiagnosed
  - PCPs miss up to 91% of mild AD
  - Only 10-15% receive acetylcholinesterase inhibitors

Evans DA. Milbank Quarterly. 1990; 68:267-289; Valcour et al, 2000

Late-Life Dementia Risk Index:
15 items

• Age 75-79	1	Factors
• Age 80-100	2	Age
• Low 3MS (≤ 87)	2	
• Low DSST (low education)	2	Education
• Low BMI <18.5	2	Weight/Frail
• ≥ 1 APOE allele	1	Genetics
• MRI WM disease	1	
• MRI Large Ventricles	1	
• Internal carotid thick > 2 mm	1	CVascular
• Hx coronary bypass	1	
• Time to put on/button shirt > 45s	1	Motor Speed
• No alcohol consumption	1	Alcohol
• Range	0-15	

- Accurately stratified older adults into those with low, moderate, and high risk of developing dementia.

Deborah Barnes, et al., 2007

Neuropsychology of AD

- Memory deficit (hallmark): impaired free recall not normalized by cueing
  - AD: lower on all memory indices
  - encoding ↓ ↓
  - rapid forgetting ↑ (new info lost in less than 5 minutes)
  - intrusions ↑ (esp. on cued recall), Novel intrusions

- Impaired recognition memory is major differentiation from other NCDs:
  - Cueing ↓ ↓

- Later, impaired executive function:
  - problem solving ↓ (TMT-B, WCST, CAT)

Typical Alzheimer's CVLT 3

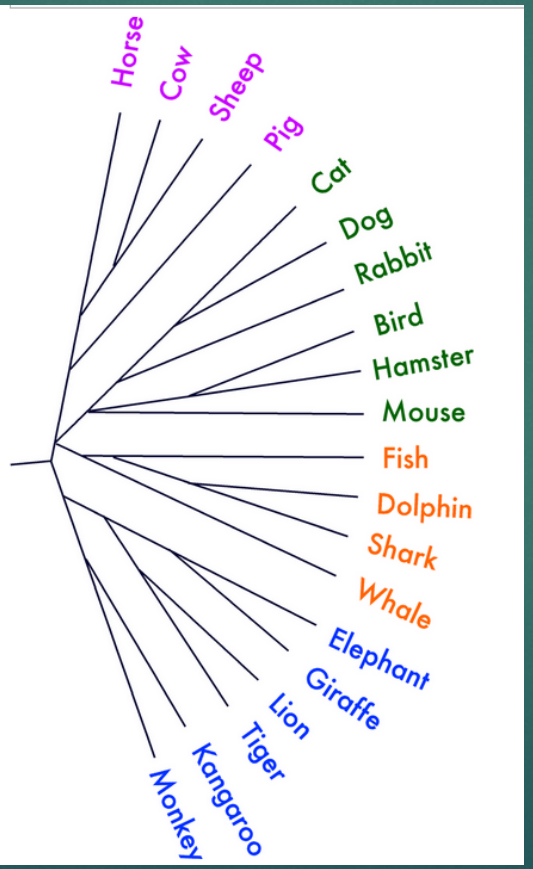
	# words	SS	
Trial 1 – 16 words	1	-3	
Trial 5	5	-3	
Short Delay	2	-4	
Long Delay	0	-4	
Long Delay/Cue	0	-4	
Sem. Clustering	1	-1	
Recency Region	62%	+5	
Cued Recall Intrus	15	+5	
Recognition Hits	6	-4	
False Positives	5	+2 (Yes bias)	
Discriminability		-4	
All Novel recognition & intrusion scores			High

Decline in temporal lobe Semantic Knowledge

Phonemic:

Sin
Super
Sober
Salient
Sugar
Salt
Sincere
Sinister

Semantic (category) ↓ ↓ :



- Semantic (animal, categorical naming) (temporal lobe)
- Is worse than
- phonemic (words beginning with “S”) (frontal lobe)

Verbal Fluency in FTD vs AD

- AD: diminished semantic/category fluency where letter fluency is intact.
- FTD: worse on both letter and semantic category fluency
- Letter fluency (FAS/Cowat): more intact frontal executive process for organized lexical search strategy.
- Semantic fluency: accesses more impaired temporal semantic/factual neural networks

K. Rascovsky, 2010

Neuropsychology of AD 2

- Intact behavioral memory until late
- Social skills spared (hallmark)
- Impaired visuospatial skills (5-10% first symptom)
- Psychiatric: delusions (19%), paranoia, hallucinations (14%)
- Lack of insight, blandness, passivity
- Later: aphasia, agnosia, apraxia

Symptom Validity testing: Worse WMT and lower CVLT score correlation

Mean WMT	N#	SDFR	LDFR
91-100%	745	10.7	11.2
81-90%	206	8.3	8.9
71-80%	105	7.8	8.2
61-70%	61	7.4	7.3
51-60%	50	5.8	5.5
<=50%	34	4.4	3.3

But check dementia algorithm

Green, 2006

Neuropsychologists can now make a fairly accurate diagnosis of Alzheimer's while someone is alive

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

- ~85% accurate diagnosis

Subtle language changes in MCI and AD

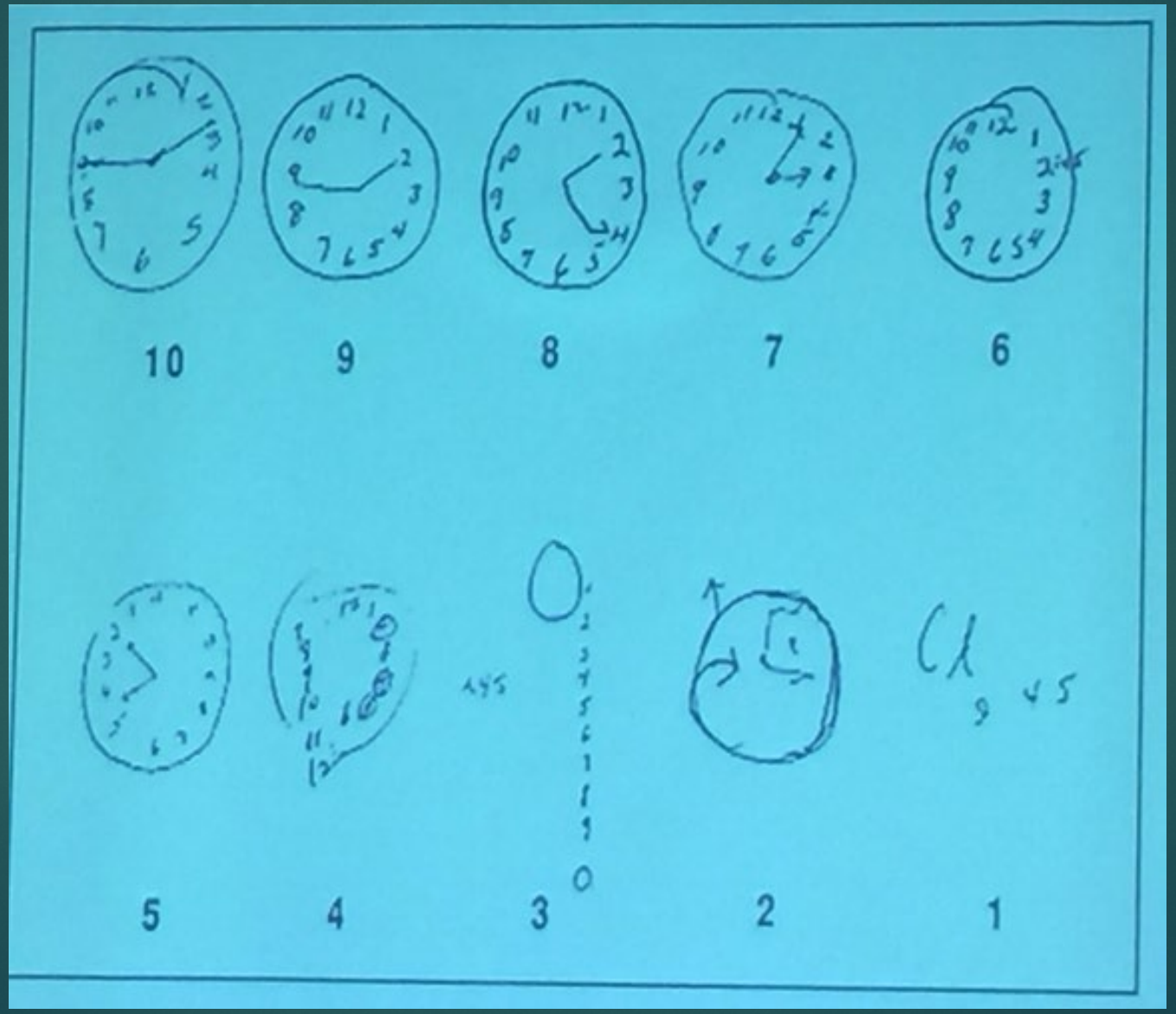
- Rambling and long-winded anecdotes could be an early sign of Alzheimer's disease, more than a decade before meeting the threshold for an Alzheimer's diagnosis.
- Vocabulary in novelist Iris Murdoch's later works, which showed signs of Alzheimer's years before her diagnosis, and the increasingly repetitive and vague phrasing in Agatha Christie's final novels
- Striking changes in Ronald Reagan's speech over the course of his presidency: started to have a decline in the number of unique words with repetitions of statements over time. "[He] started using more fillers, more empty phrases, like 'thing' or 'something' or things like 'basically' or 'actually' or 'well'."
- Worsening "verbal imprecision" was the key, rather than being verbose

Language Decline Progression

- Decreased word list; verbal imprecision
- Word finding pauses
- Lexical anomia
- Transcortical aphasia (fluent, intact repetition)/Wernicke’s
- Palilalia (verbal repetitions)
- Muteness

Clock drawing in AD patient over several years

Loss of visual spatial ability

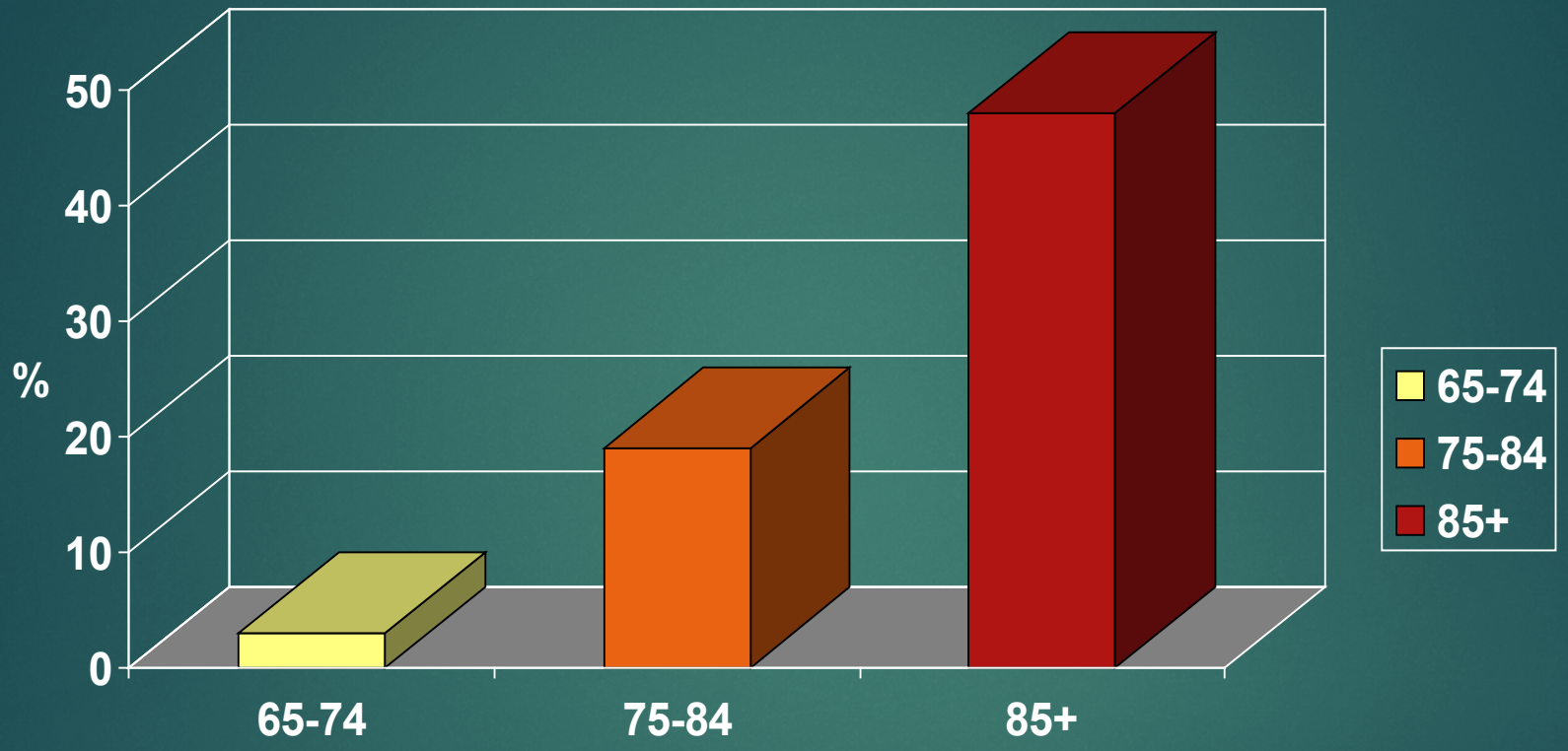


Down's & AD

- Almost all adult Down's Syndrome (extra chromosome 21) develop Alzheimer's
- By age 65, up to 75% of people with Down syndrome have Major NCD due to Alzheimer's.
- They have same genetic pathway: APP, amyloid precursor protein, on 21st chromosome.

Prevalence of Alzheimer's Disease by Age

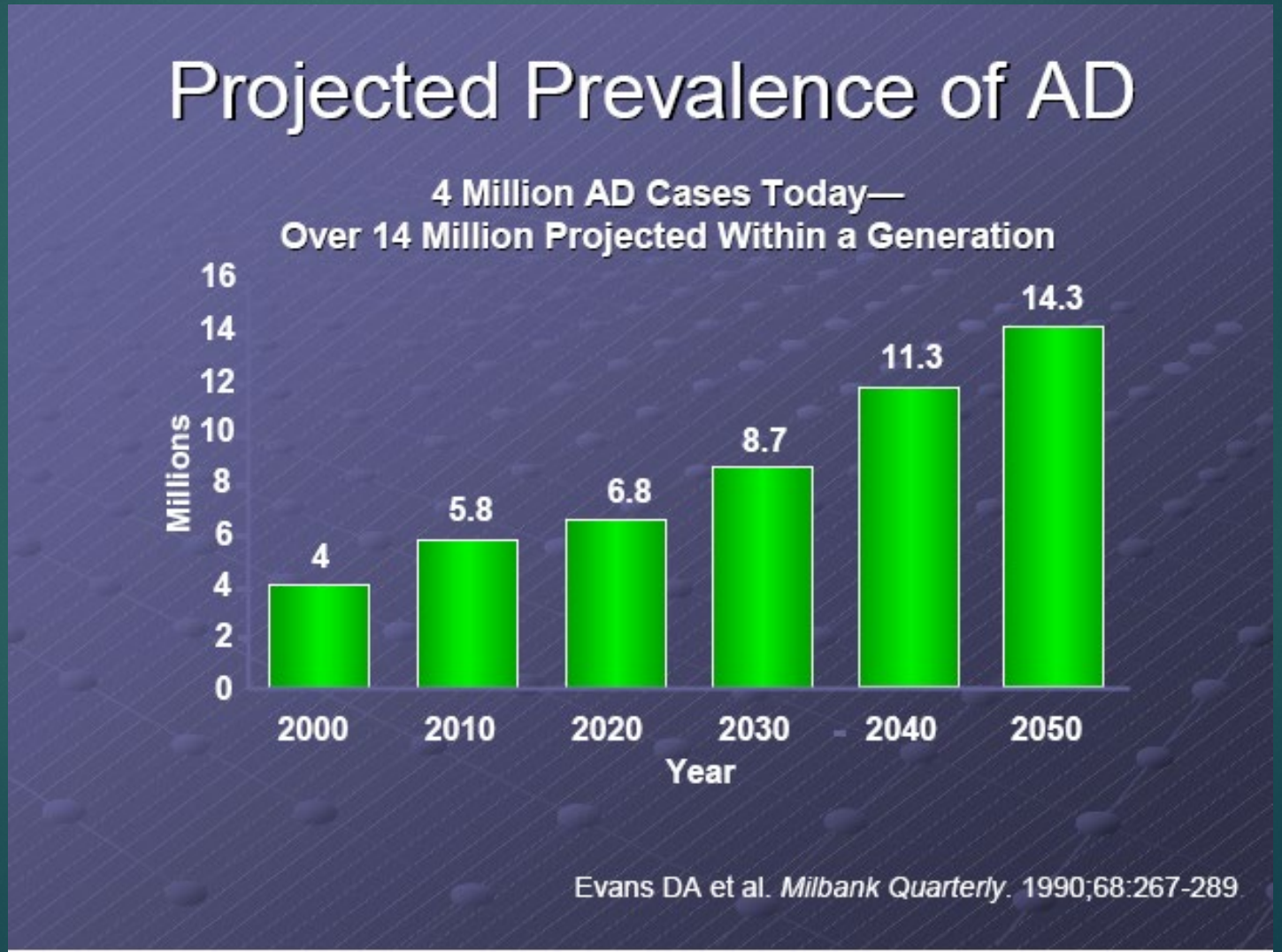
1% at age 60, doubles every five years.



Age, not genetics, is primary risk factor in AD

Evans, D.A. et al. (1989). Journal of the American Medical Association. Vol. 262: 2251-2256.

By 2050, AD will become the major public health issue; May bankrupt Medicare



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: (recent study: more in PD)
- Lower Cognitive Reserve: Reduced cognitive and physical activity throughout life
- Vascular disease: HTN, cholesterol, diabetes, tobacco, obesity, heart disease

Higher NCD Risk & Ethnicity: Life experience factors

- Higher NCD Risk
  - Age 65+ Hispanics have 1.5 x higher rate of AD
  - African Americans have 2 x higher rate of AD
  - 2/3rds of Americans with AD are women

- Higher rates of hypertension & diabetes in Hispanics and African Americans

- Higher rates of low education, low quality of education, low income, rural living (all risk factors for AD)

ADAMS & WHICAP studies

Higher Risk factors

- Newer Studies: Higher dementia risk accounted for by lower childhood SES, adult literacy, and exercise

- Kaiser study: Black decedents with AD dementia are more likely to have mixed brain pathologies compared with age-, sex-, education-, and cognition-matched white decedents with AD dementia.

Mixed Pathology is the norm in autopsy cases

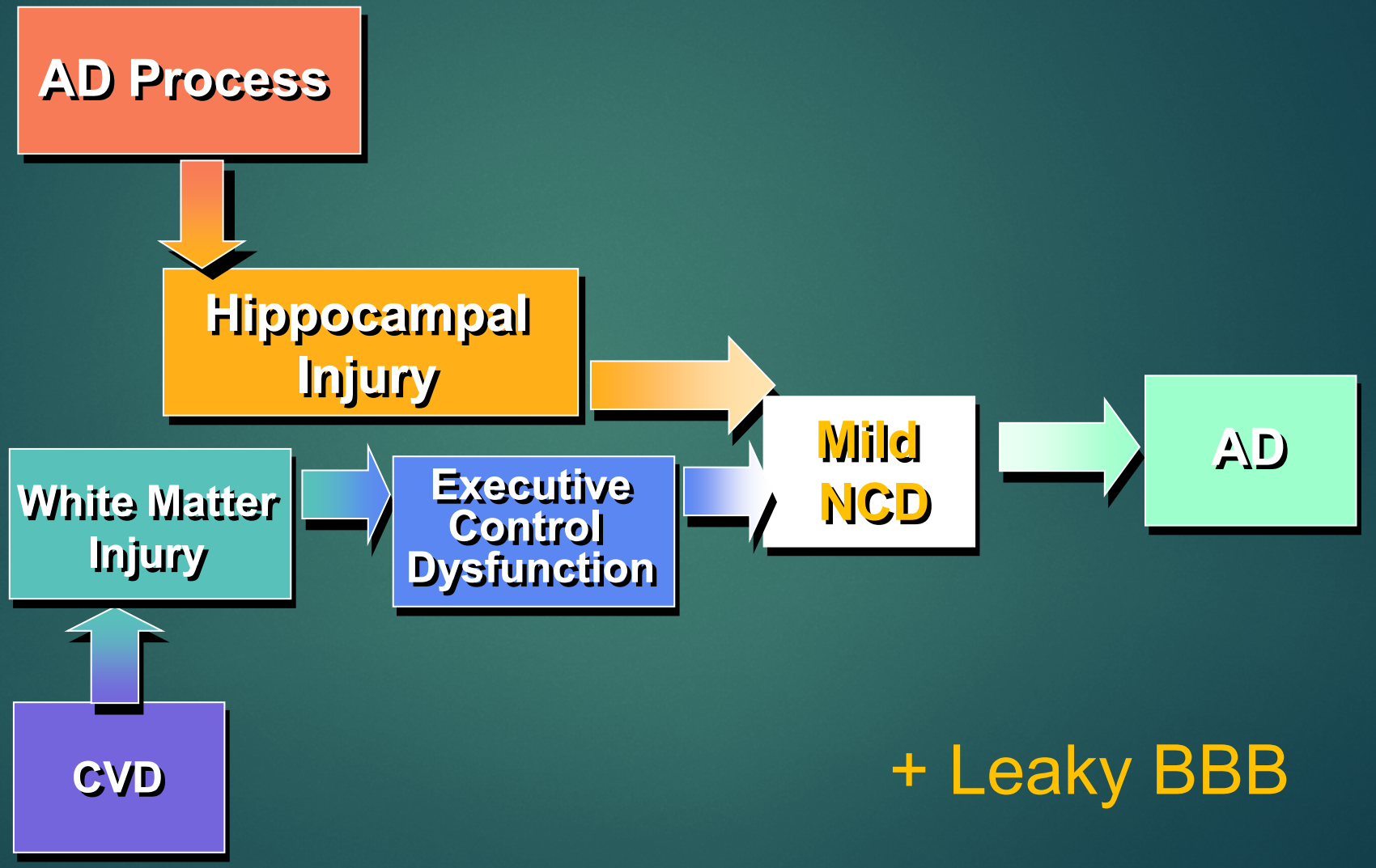
- Long-range study of 3,400 men and women in the Seattle ACT program

- In the autopsied brains of people who had experienced cognitive decline and major NCD:
  - AD pathology: 45 %
  - Small vessel disease: 33 %
  - Lewy bodies: 10 %

- Small vessel damage is the cumulative effect of multiple small strokes & auto dysregulation of blood vessels caused by hypertension and diabetes

Montine, 2008

Combined Role of CVD and AD in mild and major NCD



DSM5 diagnosis is too late for TX– Need Earlier Biomarkers

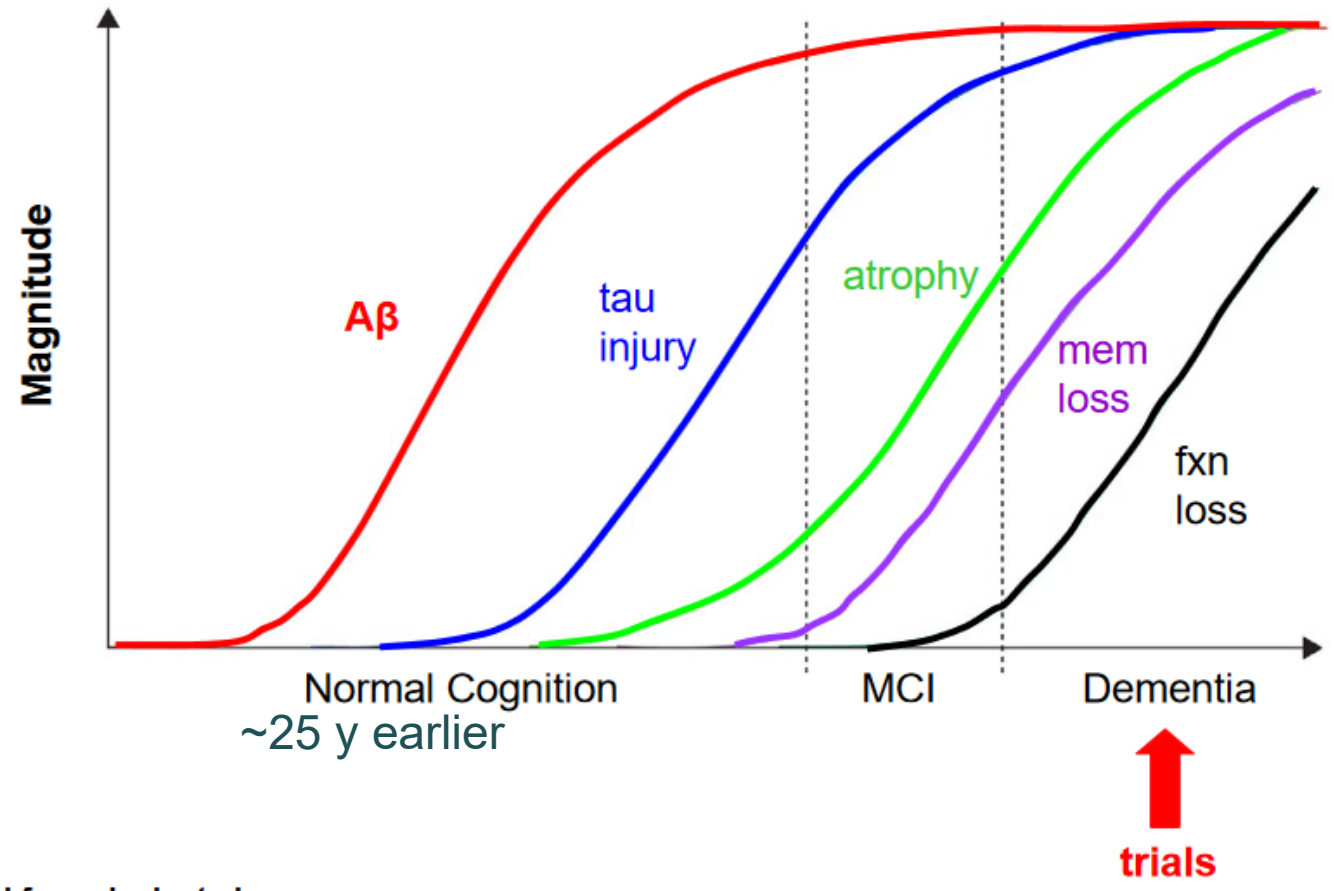
- Biomarkers are variables (physiological, biochemical, anatomical) that:
  - can be measured while person is alive and
  - indicate specific features of disease-related pathological changes.

- Used to predict conversion from Mild NCD to Major NCD/AD.

- Prediction studies show that individuals destined to develop AD can be identified earlier in the disease course

- DSM5 is too late: the clinical diagnosis of AD requires the presence of Major NCD (too many dead neurons by then)

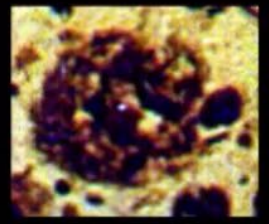
Alzheimer's starts well before sxs

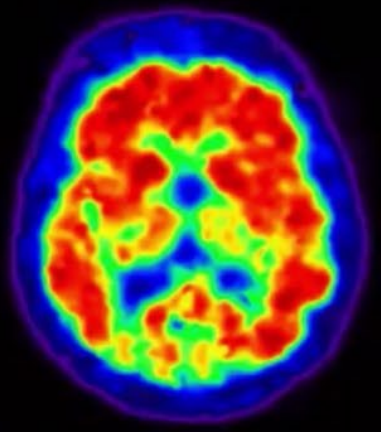


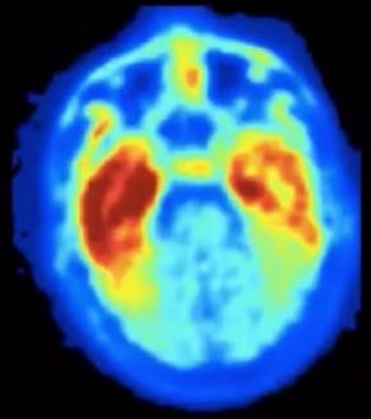
Modified from Jack et al
Lancet Neurology 2010

NP Testing

Aβ and Tau Biomarkers







Late 1990s
CSF Aβ, Tau, p-Tau

Mid 2000s
Amyloid PET ^{11}C-PIB

Mid 2010s
Tau PET ^{18}F-FTP

2020s
Plasma Aβ, Tau, p-Tau

Read these foundational articles

1) Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Clifford R Jack Jr, et al., Lancet Neurol 2010; 9: 119–28*

2) Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Clifford R Jack Jr, et al., Lancet Neurol. 2013 Feb;12(2):207-16.

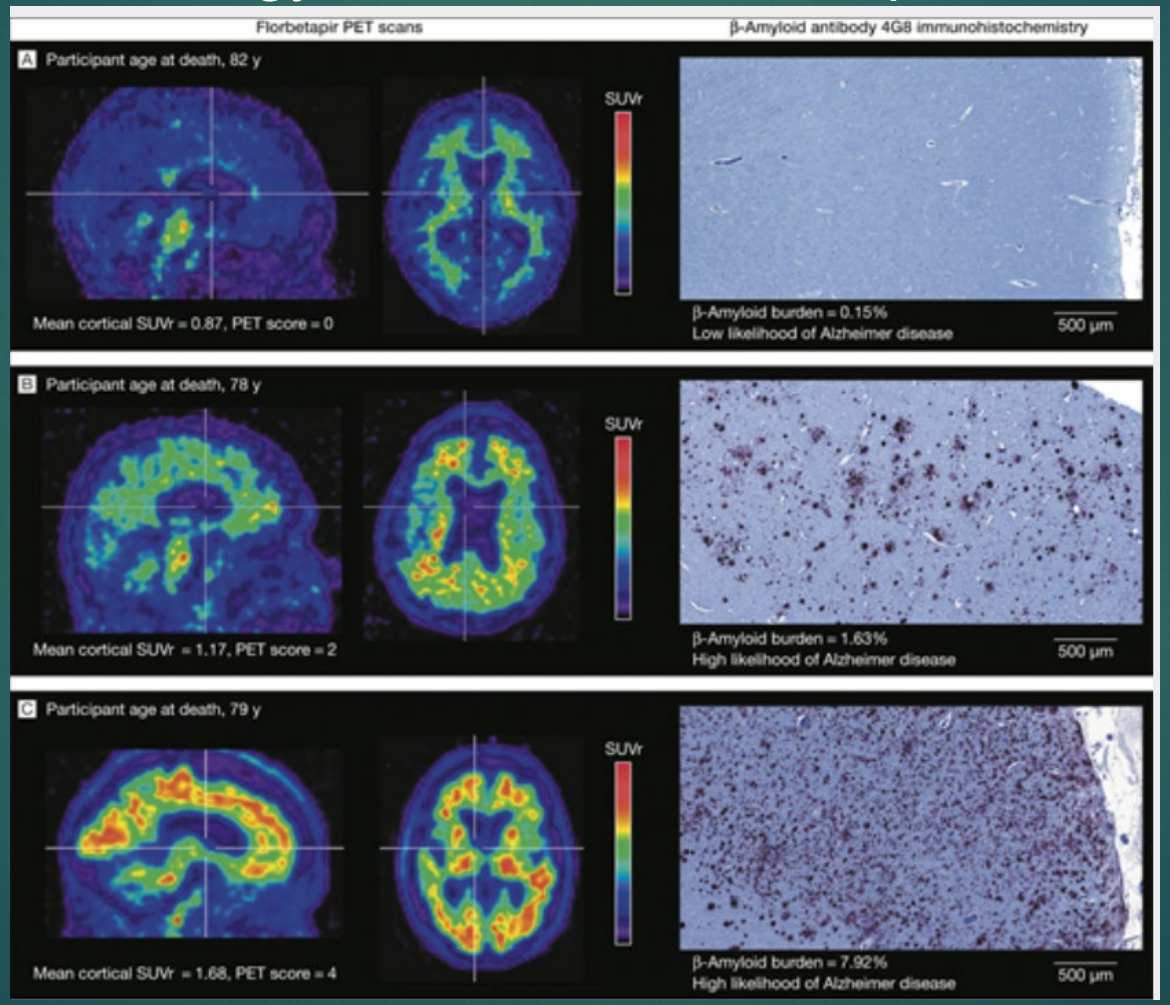
PET of BA = autopsy specificity

Pathology Validation: Florbetapir PET

Normal

Moderate

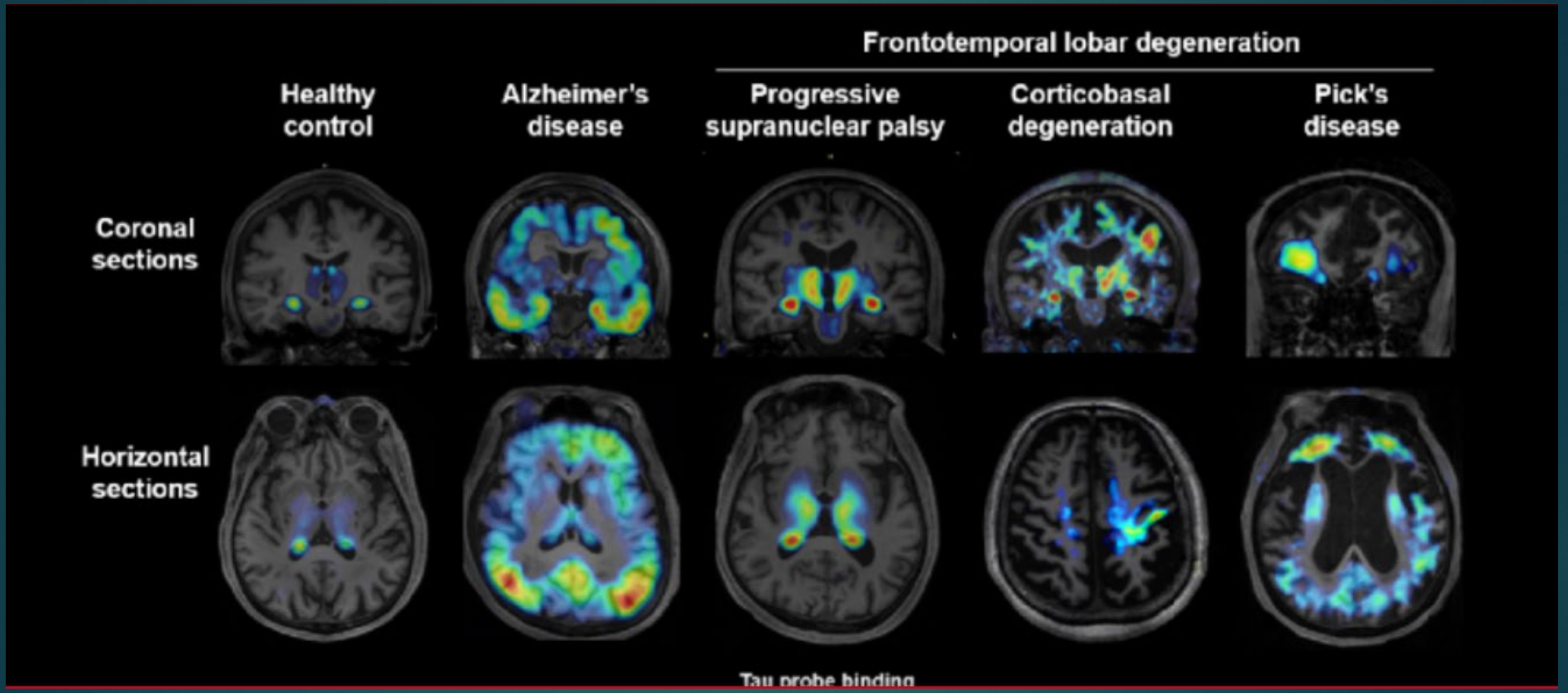
Severe AD

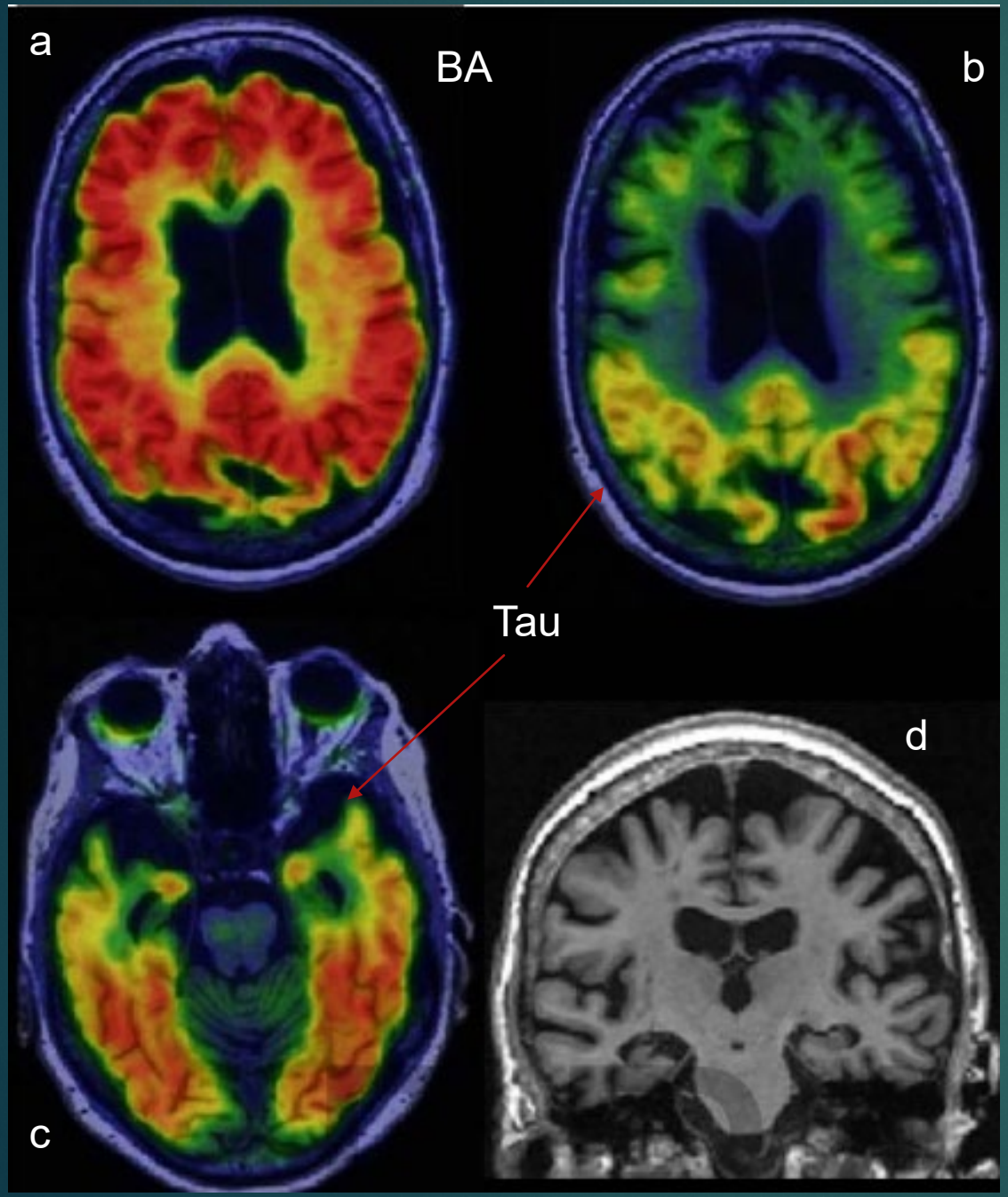


2012 FDA approval study

Dying AD pts: Pet scan of BA and equivalent autopsy findings

Tau Binding in various NDs





PET: Alzheimer's disease with dementia

75 yo woman with amnestic multi-domain dementia.

Abnormal amyloid PET (a),

tau PET (b, c)

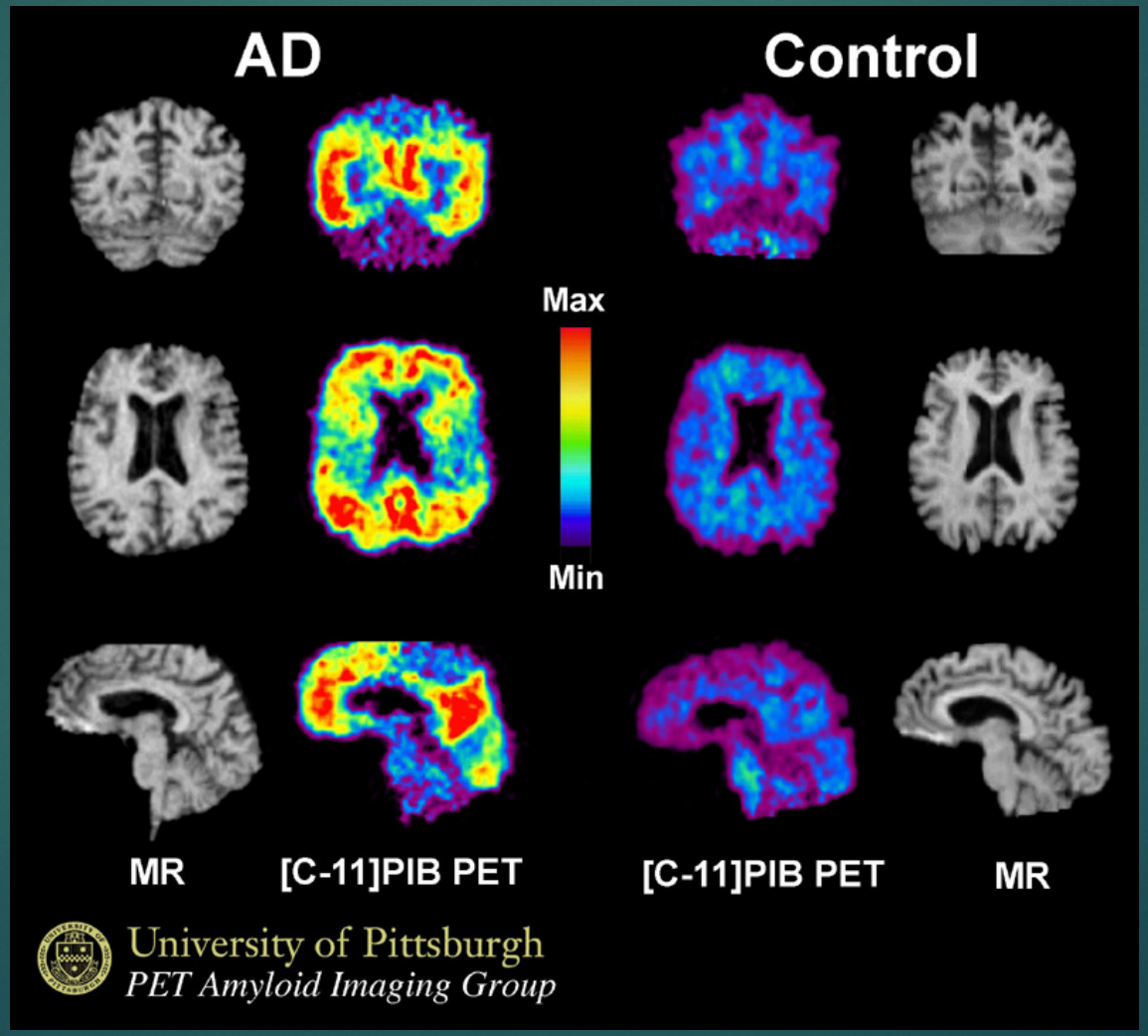
and atrophy on MRI (d).

.

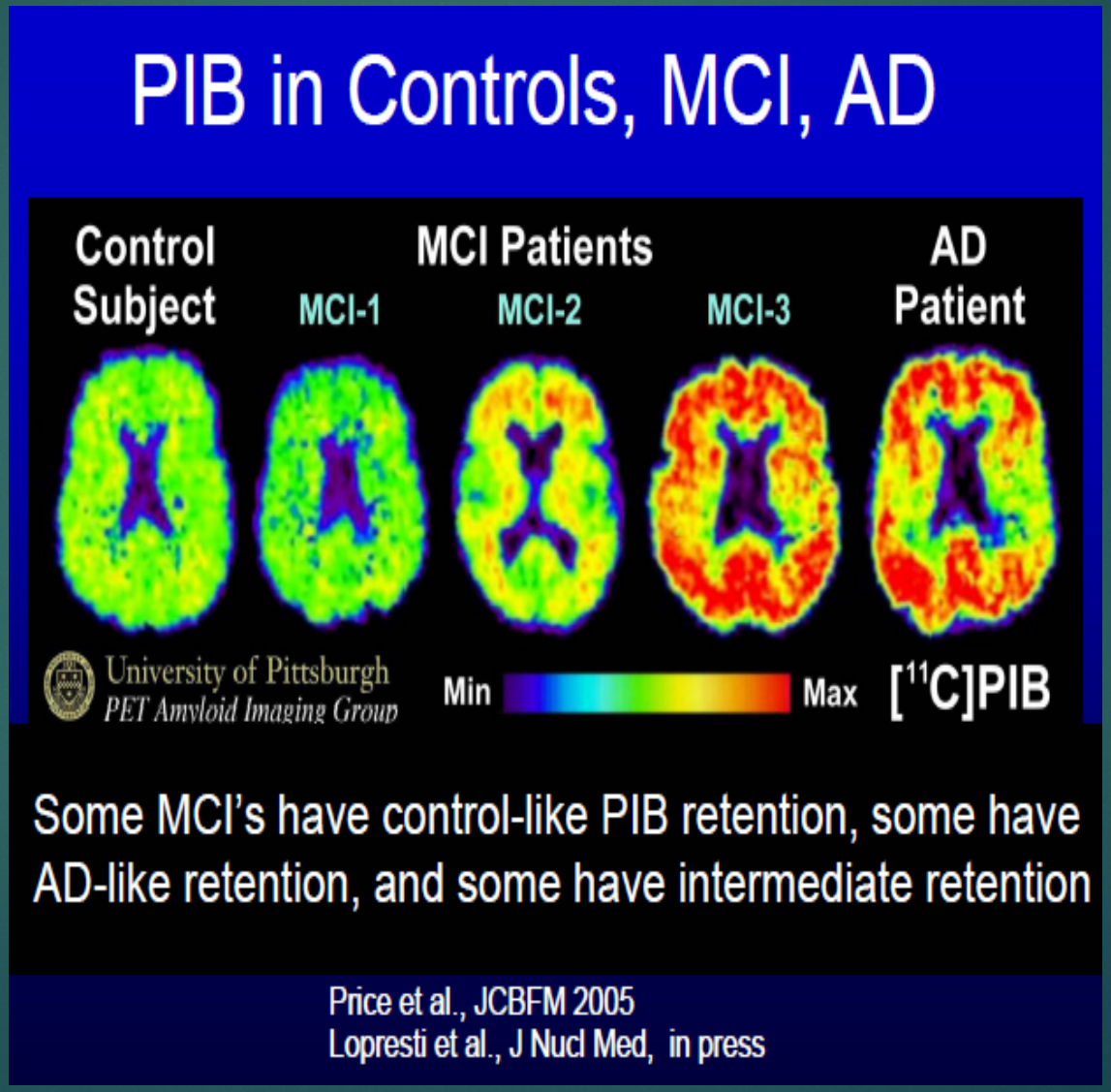
Biomarkers

- CSF Aß and Tau
- Clinically available new assay with autopsy validation
- Amyloid PET
- Head-to-head comparison with FDG-PET in autopsy-confirmed
- Appropriate Use Criteria (amyloid PET and CSF)
- Tau PET
- Autopsy study -> FDA approval
- Differential diagnosis and prognosis
- Blood-based biomarkers
- Plasma Aß, p-Tau and NfL
- AD biomarkers in drug development
- Anti-Aß monoclonal antibodies: aducanumab and donanemab

Pittsburg B Compound (& Amvid) labels Beta Amyloid Plaques on PET: AD vs. Normals

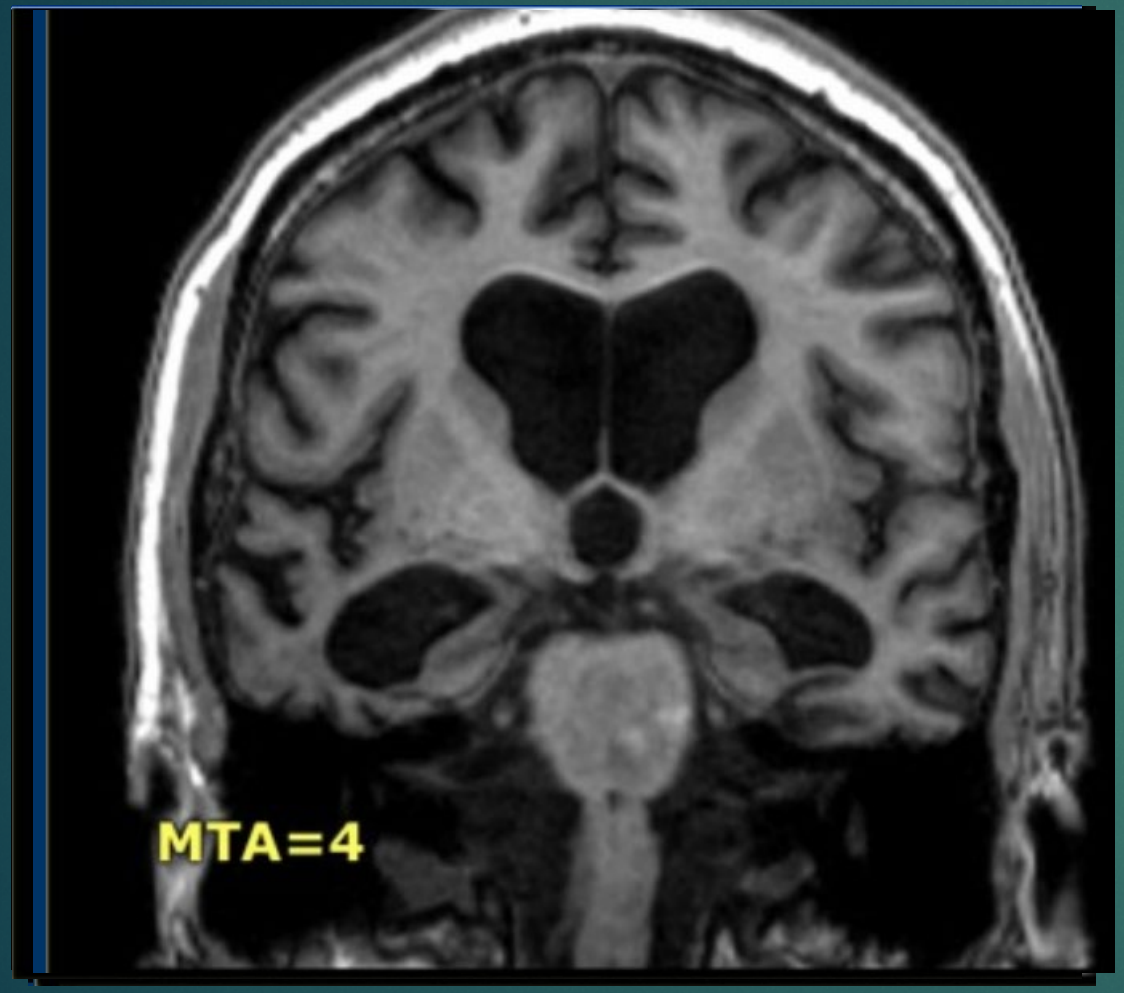


PIB-PET (radioactive): Beta Amyloid in Normal to AD



No correlation to cognitive decline; 30% of high BA are cognitive normal

Medial Temporal Atrophy



Here you can scroll through the images for examples of MTA score 0-4.

- score 0: no atrophy
- score 1: only widening of choroid fissure
- score 2: also widening of temporal horn of lateral ventricle
- score 3: moderate loss of hippocampal volume (decrease in height)
- score 4: severe volume loss of hippocampus

< 75 years: score 2 or more is abnormal.
> 75 years: score 3 or more is abnormal.

2020: FDA-cleared quantitative volumetric analysis program – Neuroreader™.

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 begin to develop 20-30 years before the earliest clinical symptoms occur.

- Therefore need to treat at beginning, not end, of the disease.

- Need biomarkers.

New Research Strategy

- Eventually treat AD like HTN and heart disease:
  - start treating after early dx based on biomarkers
  - But still need to identify medications and long term effects

- Need to consider AD as lifestyle disease
  - reduce risk by increasing education, exercise, take care of heart, etc.

AD Timeline to Major NCD due to AD: 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)

IDEAS study: clinical effect of doing biomarkers

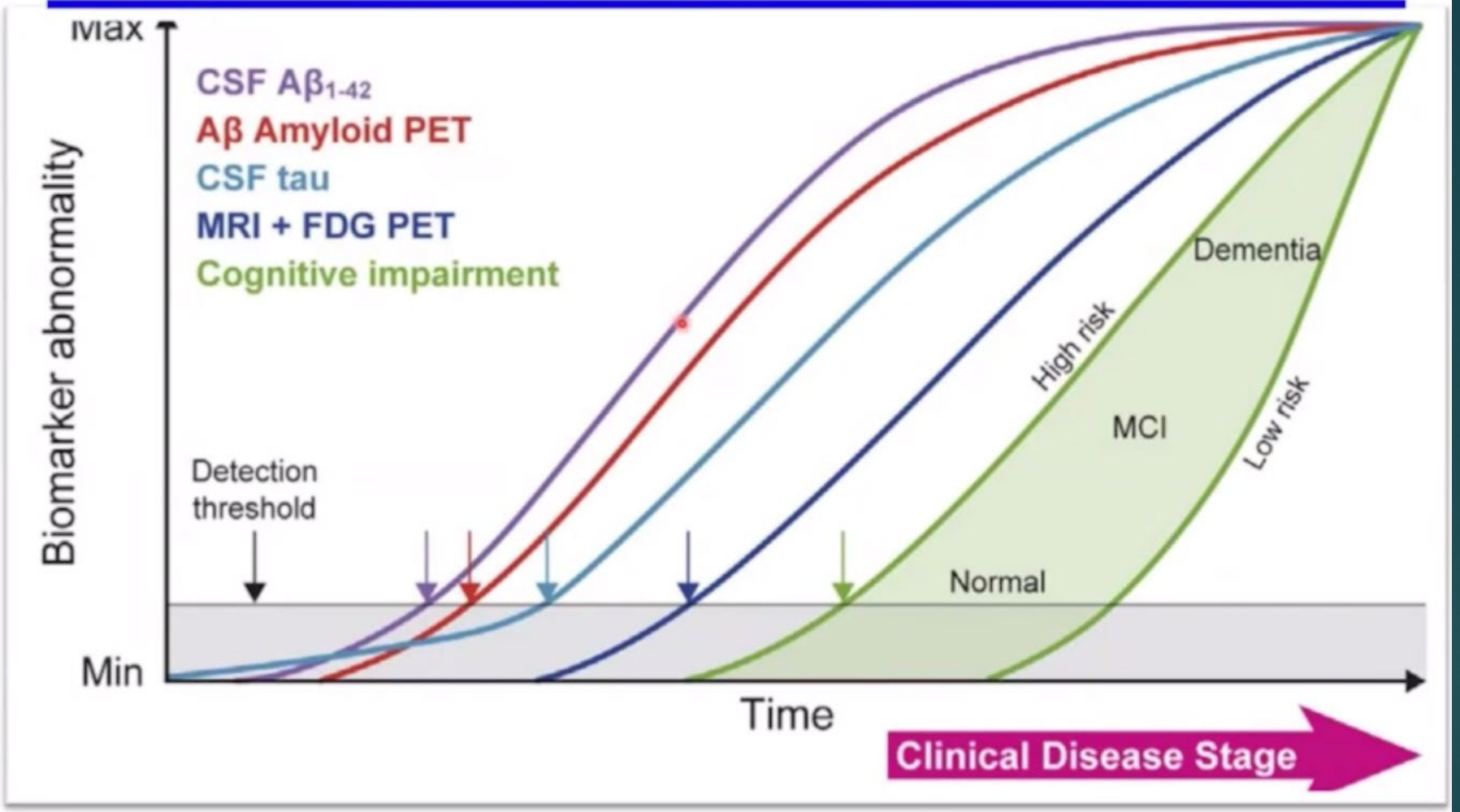
- Clinical impact of BA PET on MD practice: because Medicare does not pay for PET
- Having a negative BA PET scan rules out AD (60% of MDs changed medications in MCI/Dem Tx; 25% changed dx from AD to nonAD);
- If positive BA PET, less useful in diagnosing AD (because of 30% cog normal with high BA)
- High Tau PET in presence of high BA predicts memory and cognitive decline
- Plasma measures are probably the future of early dx, not 4 PET scans (which need Mass spectrometry and fast processing
- Finding: in APOe4 with MCI, Aricept does help
- CSF significant for AD: low BA42, high T, high p-T

G. Rabinovici, et al., 2019

Biomarkers: AD Tests of future

- 2 for brain Aβ plaque deposition
  - CSF Aβ42
  - PET amyloid imaging, using Pittsburgh Compound B (PIB);
    - Negative scan excludes AD
    - best for identification of non-AD (MDs dropped AD dx from 73% to 15% when informed of low BA PET data
- 3 for neurodegeneration
  - CSF tau
  - deficits in glucose uptake on FDG-PET
  - and structural MRI (most predictive of Major NCD)

Trials in disease stage context



At what disease stage would removing Aβ be beneficial?

Kang J-H, et al.
Alzheimer's & Dementia, 2015

First AD blood test: www.precivityad.com/

- The first blood test to determine whether a patient has Alzheimer's disease is now available in most US states, the company C_2N Diagnostics announced October 29, 2010.

- The PrecivityAD™ blood test: The C_2N test relies on the ratio of two isoforms of the amyloid-β protein, Aβ42 and Aβ40, combined with the presence of isoforms of apolipoprotein E (ApoE): Amyloid Probability Score (APS), 0-100

- A study in 686 patients with cognitive impairment found that those with scores above a certain cutoff point had a positive amyloid PET scan 92 percent of the time, while those with scores below a certain cutoff had a 77 percent chance of having a negative result on the PET scan.

First blood test

- Price: $1250: not certified yet in CA, MD, PA, RI, NY
- Screening and enrollment represents up to fifty percent of the cost of clinical trials in Alzheimer's disease, and one Phase 3 trial costs three to four hundred million dollars,
- Game changer

Biomarkers are not yet clinical measures

- Currently used for research, not clinical measures, except at research hospitals
- CSF biomarker tests considered less reliable than amyloid PET
- No widely accepted normative databases of scan results
- Prognostic uncertainty of amyloid imaging: A positive scan (more BA) indicates a higher risk for AD but is not diagnostic.
- Best currently is structural MRI and Spinal CSF

Cognitive Decline in Elderly

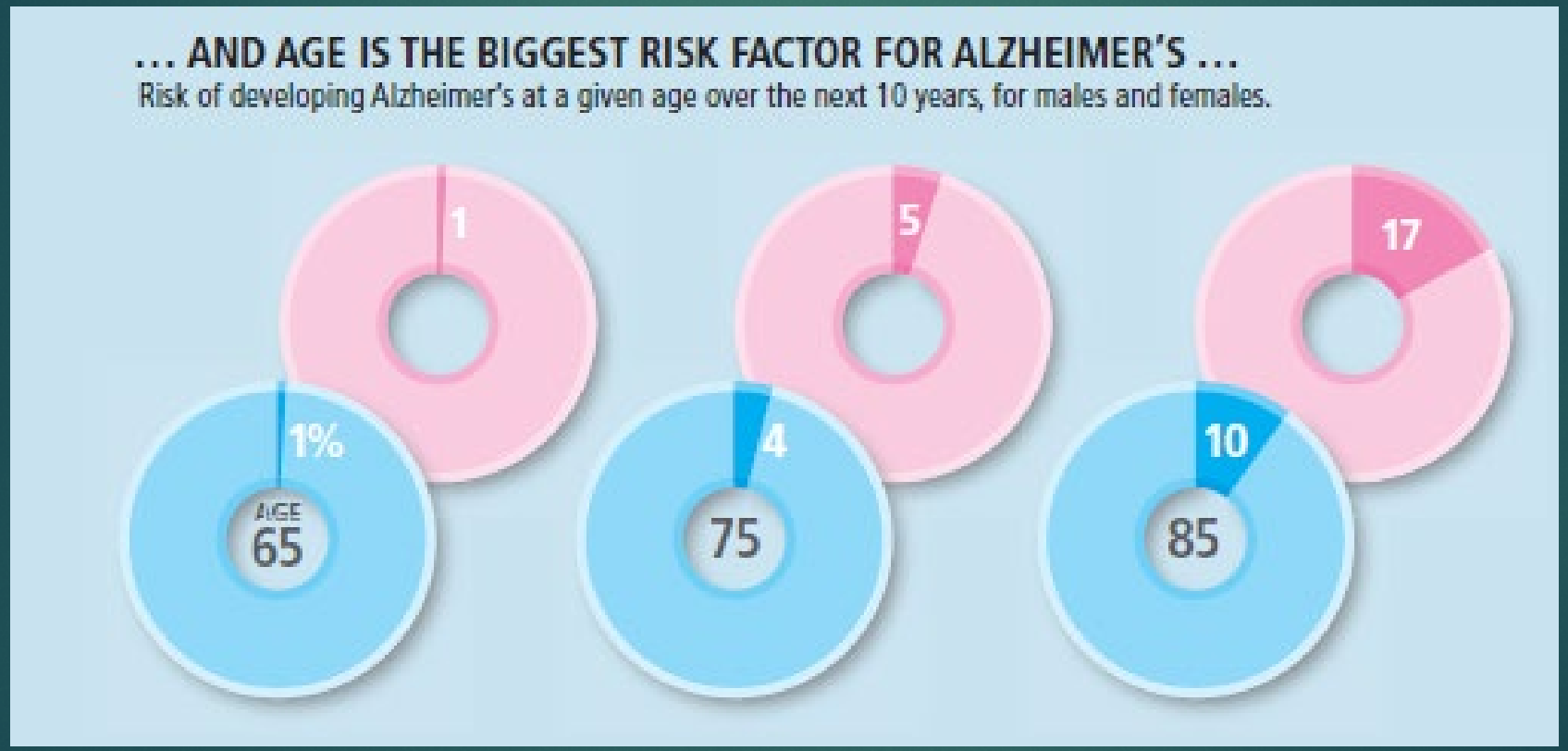
- Of all Americans in 2002, aged 71+:
- 65% were cognitively normal
- 21% had some mild NCD
- 14% had dementia/major NCD

All causes of Accelerated Synaptic Loss→ higher rates of AD

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

AD is usually not genetic. Age is greatest risk factor.

Major NCD doubles every 5 years after 65



Being Female

Women are the epicenter of AD crisis

- A woman's AD risk at age 65 is 1 in 6, compared with nearly 1 in 11 for a man.
- Women in their 60s are twice as likely to develop AD as they are to develop breast cancer. 2/3rds of AD pts are women
- Not do to longer life than men
- Women with shorter-than-average reproductive periods are at a markedly increased risk for dementia; reduced exposure to the neuroprotective effects of estradiol,
- More likely to be caregivers of those with Alzheimer's: More than 3 in 5 unpaid Alzheimer's caregivers are women

2020 Stanford Study: Women at higher risk

- ApoE4 is a key risk factor for Alzheimer's disease, with a single copy of ApoE4 increasing that risk twofold or fourfold. Carrying two copies confers 10 times the risk of Alzheimer's.

- Among healthy older controls, having one copy of the ApoE4 variant confers a substantial Alzheimer's disease risk in women, but not in men

- Female ApoE4 carriers are more at risk for Alzheimer's than male carriers are

- Brain connectivity in the ApoE4 men does not differ much from normal. But connectivity in ApoE4 women does differ from normal.

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
- This trend will be overwhelmed by increases in NCD brought on by:
  - population aging and
  - negative health trends such as diabetes and obesity – fast food.

Family History of AD

- Familial early-onset AD: only 2–5% of all AD cases.
- APOe4: timing gene in AD: get late onset AD 10 years earlier
-
- The ε4 variant of the APOE gene accounts for about 50% of the heritability of late-onset AD.
- Family history status is associated with earlier onset of preclinical pathologic AD

154 Disease Modifying Treatment Trials in elder AD: 99% Failure Rate

- AN1792 vaccine: 2003 (Eliminated BA; still major NCD)
- Tramprostate
- Flurizan: 2008
- Bapineuzumab: 2009
- Semagacestat: 2010
- Solanezumab: 2016
- Verubecestat: 2018
- CREAD I and 2 (Crenezumab): 2019
- Aducanumab: 2020

- Right TX, wrong stage of disease? Or Type of Tx does not work?

AD Drug Trials

- Classical AD Drug trials have almost exclusively sought to use antibodies targeted toward BA and Tau to try to attack and clear the misfolded forms or mop up soluble forms, or to inhibit enzymes responsible for generating these peptides.

- Still 130 Trials in progress

- Newer research: roles of vasculature, immunology, and neuroinflammation as well as lifestyle and environment in Alzheimer's disease; development of biomarkers and diagnostic tests to monitor disease presence and progression, plasma/blood tests

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

AUGUST 26, 2021

Revisiting FDA Approval of Aducanumab

G. Caleb Alexander, M.D., David S. Knopman, M.D., Scott S. Emerson, M.D., Ph.D., Bruce Ovbiagele, M.D., Richard J. Kryscio, Ph.D., Joel S. Perlmutter, M.D., and Aaron S. Kesselheim, M.D., J.D.

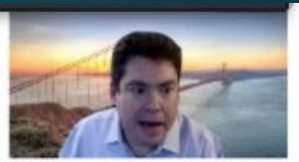
Controversy and Progress in Alzheimer's Disease — FDA Approval of Aducanumab

Gil D. Rabinovici, M.D.

CORRESPONDENCE

An Appropriate Use of Accelerated Approval — Aducanumab for Alzheimer's Disease

Billy Dunn, M.D.
Peter Stein, M.D.
Robert Temple, M.D.
Patrizia Cavazzoni, M.D.
U.S. Food and Drug Administration
Silver Spring, MD



Meme credit: Lawren VandeVrede MD PhD, UCSF

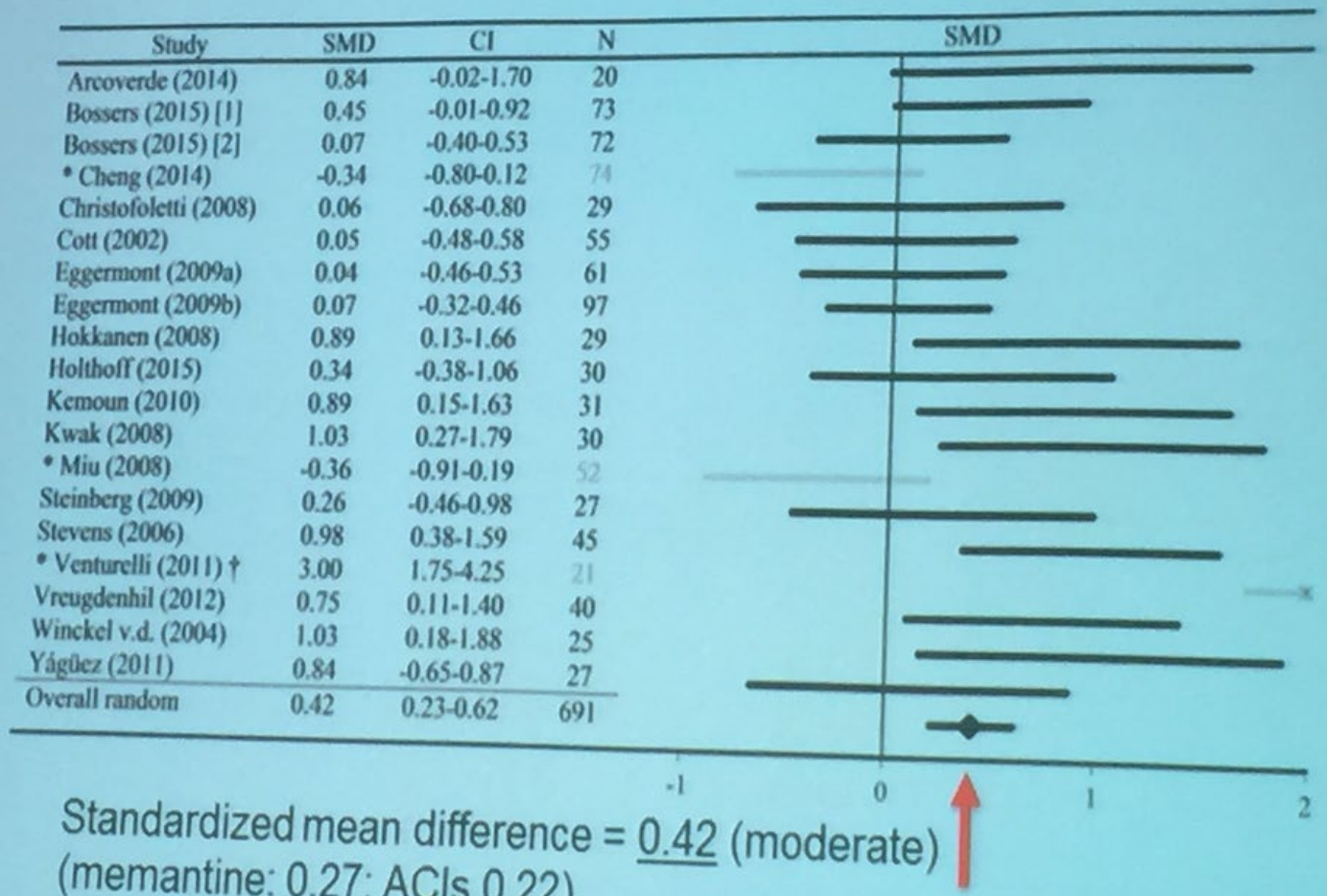
Amyloid hypothesis

- No anti-amyloid treatments tested in trials to date, even those that moved Aβ biomarkers in the expected direction, have meaningfully improved clinical outcomes.
- BACE inhibitors worsened cognition.
- Immunotherapies that lower tau in the CSF have not yet helped people with primary tauopathies.
- Ditto for drugs to boost urate, a protective marker linked to Parkinson's.
- A trial of an antisense oligonucleotide that reduces huntingtin in the CSF recently failed because it held more risk than benefit.
- Are scientists putting too much faith in the cherished assumption that treating even a well-substantiated biomarker of disease will benefit the patient?
- Part of the problem stems from not really understanding the basic pathogenesis of the disease

Physical activity effects on cognitive measures in dementia: RCT meta-analysis

Mean: 183 min/week, aerobic vs social activity (AD + non-AD)

Study	SMD	CI	N
Arcoverde (2014)	0.84	-0.02-1.70	20
Bossers (2015) [1]	0.45	-0.01-0.92	73
Bossers (2015) [2]	0.07	-0.40-0.53	72
* Cheng (2014)	-0.34	-0.80-0.12	74
Christofoletti (2008)	0.06	-0.68-0.80	29
Cott (2002)	0.05	-0.48-0.58	55
Eggermont (2009a)	0.04	-0.46-0.53	61
Eggermont (2009b)	0.07	-0.32-0.46	97
Hokkanen (2008)	0.89	0.13-1.66	29
Holthoff (2015)	0.34	-0.38-1.06	30
Kemoun (2010)	0.89	0.15-1.63	31
Kwak (2008)	1.03	0.27-1.79	30
* Miu (2008)	-0.36	-0.91-0.19	52
Steinberg (2009)	0.26	-0.46-0.98	27
Stevens (2006)	0.98	0.38-1.59	45
* Venturelli (2011) †	3.00	1.75-4.25	21
Vreugdenhil (2012)	0.75	0.11-1.40	40
Winckel v.d. (2004)	1.03	0.18-1.88	25
Yágüez (2011)	0.84	-0.65-0.87	27
Overall random	0.42	0.23-0.62	691



Standardized mean difference = 0.42 (moderate)
(memantine: 0.27; ACIs 0.22)

Groot et al, Aging Res Reviews 2016

Mediterranean Diet

Systematic reviews longitudinal and prospective trials: MedDiet and cognition

13/18 longitudinal studies associated with :

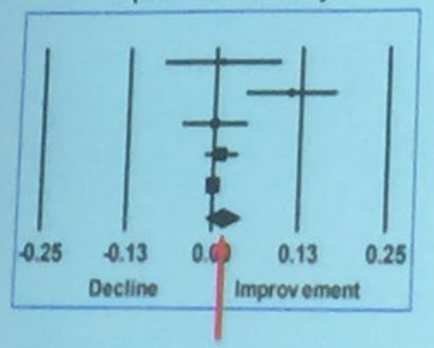
- slowed decline
- decrease conversion to AD
- improved cog fxn: memory, executive, visual

Hardman et al Front in Nutr 2016

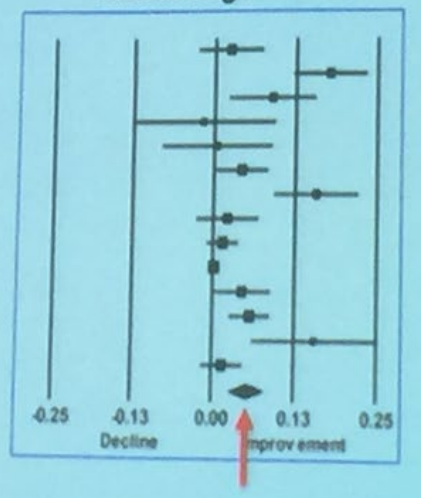
→ ~20% risk reduction

Meta-analysis and review of 15 cohort studies:

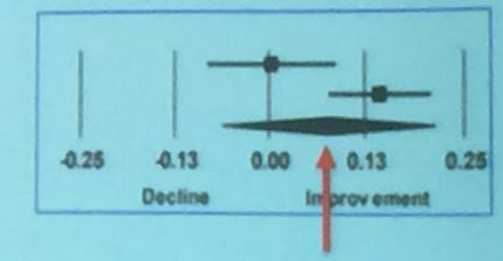
Episodic memory



Global cognition



Semantic memory



Loughrey et al
Adv Nutr 2017

Lowering BP to 120
Reduces mild and
Major NCD

Systolic Blood Pressure Intervention Trial
SPRINT

Lowering sys BP to 120: improved cardiac, stroke and renal outcomes

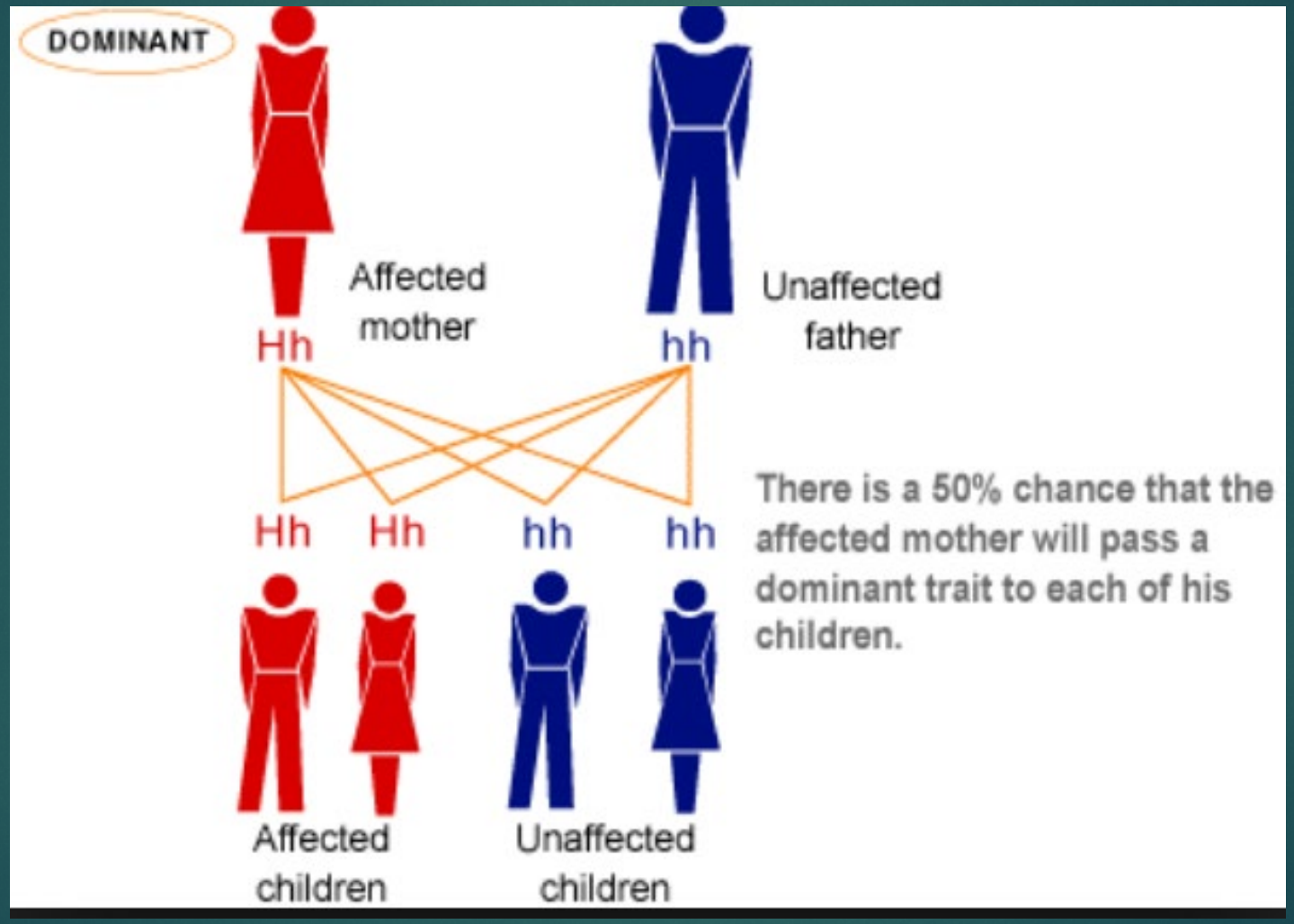
19% less likely develop MCI; 15% less likely develop combined MCI-dementia

Reduced MCI risk (14.6 vs 18.3 cases per 1000 person-years; HR, 0.81) Reduced combined MCI-dementia (20.2 vs 24.1 cases per 1000 person-years; HR, 0.85). Dementia endpoint did not reach significance.

dementia incidence

JAMA 2019

Very Rare Genetic Alzheimer's disease is inherited in an autosomal dominant fashion (in only 450 families)



Mendelian rare: only 450 families with mendelian forms of Alzheimer's disease in the world; only 1-5% of AD

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%

Alzheimer's Genetics

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

Risk Genes

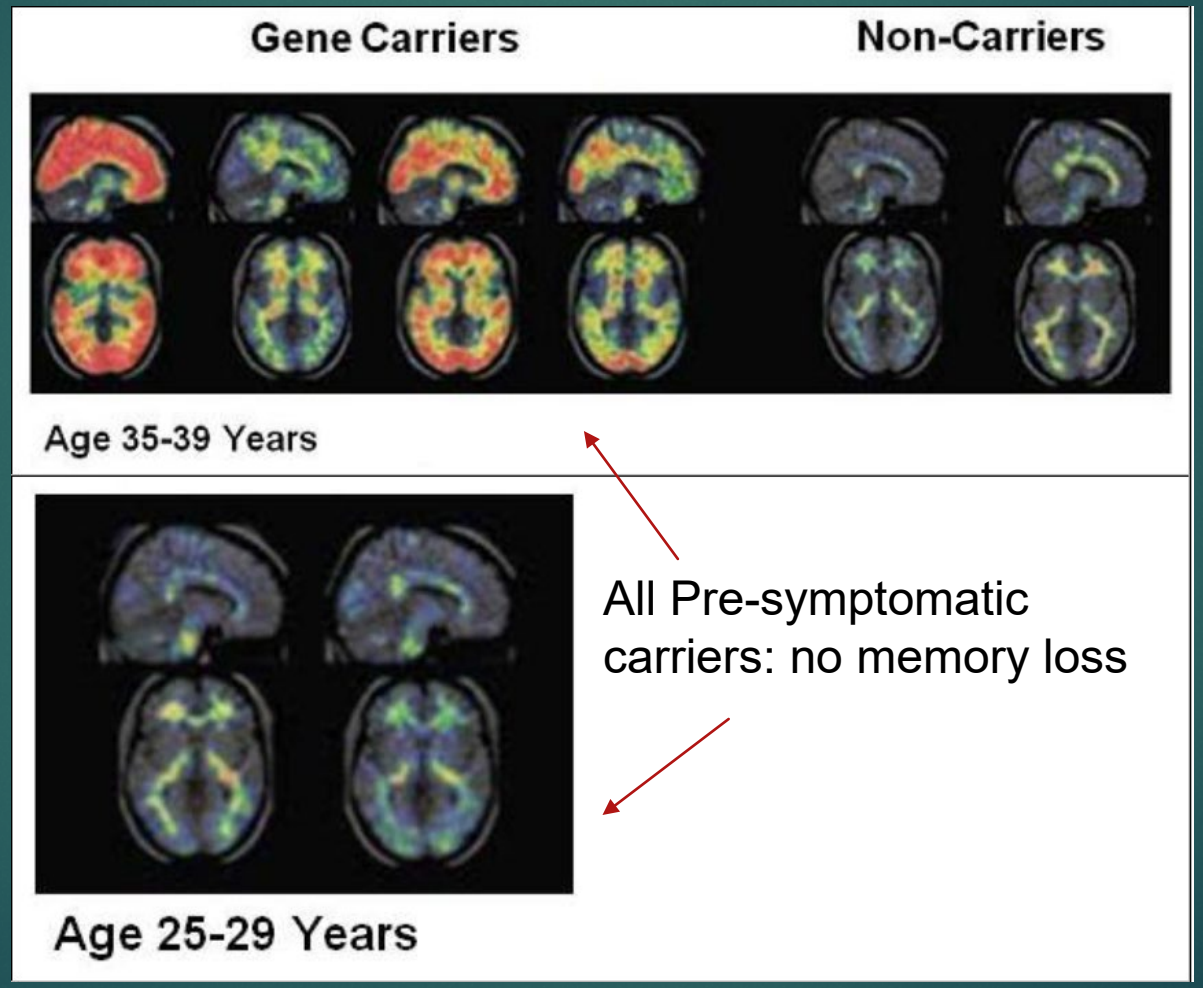
- No single causal genetic mutation has been identified for most common form of AD: non-genetic, late-onset Alzheimer disease (90%+)
- 2 types of genes in AD
- Risk genes: increase in risk of developing AD, but does not guarantee it, i.e. APOe4
- Deterministic genes: rare, but guaranteed risk; mendelian dominant genes, i.e. Presenilin

Early-onset familial Alzheimer's disease genes (Onset < age 60)

- Deterministic genes in Familial AD (FAD):
  - 3 Causative Mendelian Genes = 1% of all AD;
  - autosomal dominant (50%) transmission;
  - early onset, age 40-50s; ~450 families in world:
    - Presenilin 1 (PS1) (chromosome 14) – most common
    - Presenilin 2 (PS2) (chromosome 1)
    - Amyloid Precursor Protein (APP) (chromosome 21)
  - All 3 AD genes (+ APOe4) create excessive accumulation of Aβ peptide

Ken Kosik, 2021: Colombia: Early onset Alzheimer's clus

Antioquia, Colombia Family:
Amyloid Deposition in Genetic (Presenilin 1) AD



Mild NCD: median age 44; Major NCD: median age 49

Hope for near future:
Colombian Prevention Study

- Eventually treat AD like HTN and heart disease preclinically

- Colombian study: extended clan of 5,000 people who live in Antioquia, Colombia with early onset AD

- N = 242; 5 year trial; Genentech drug, Crenezumab injection every 2 weeks; massive pre and post testing

- Data in 2022

Aliria Rosa Piedrahita de Villegas , 1943-2020: Massive BA, no Tau

- Colombian women with family hx of Presinilin 1 and massive BA in her brain but without buildup of Tau.
- Highest levels of amyloid ever seen; only 1 year of education; two copies of APOE3
- Normally family gets dementia in 40s, she only developed mild sxs before her cancer death at age 77. Still cooked her own meals and bathed herself, and had no trouble recalling words like “neuroscience” and “coronavirus.”
- Homozygous APOE3-Christchurch (R136S) mutation protects a presenilin 1 (*PSEN1)* mutation carrier from developing Alzheimer’s disease until her seventies. Both APOE3 copies have a mutation called Christchurch; those with only 1 copy get AD early; her 4 kids have only 1 copy;; mutation is in an area of the gene binds with a sugar-protein compound that is involved in spreading tau; with mutation, no binding
- low-density lipoprotein receptor-related protein 1 (LRP1) controls the spread of tau.

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:
- UCSF 2011 study: Need to reduce:
- 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

Does Brain Development in Childhood Set the Stage for Dementia?

- Early life brain differences shape the susceptibility to neurodegenerative disease later on:
  - connection between early learning problems and dementia?

- Learning disabilities, esp. dyslexia, are over-represented among patients with primary progressive aphasia (PPA) and with posterior cortical atrophy (PCA).

- There is connection between learning disability and the logopenic variant of PPA (lvPPA) (5x higher), but not with the semantic PPA or non-fluent variants

Risk: ApoE4

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

- Has a gene-dose effect on risk and age of onset for AD

- The majority of *ApoE* carriers (25% of US) never develop AD.
  - 3 alleles –
    - ApoE2 (significantly lowers AD risk, 8% of population),
    - ApoE3 (most common, 78%),
    - ApoE4 (14% -- harmful); in 40% of AD pts

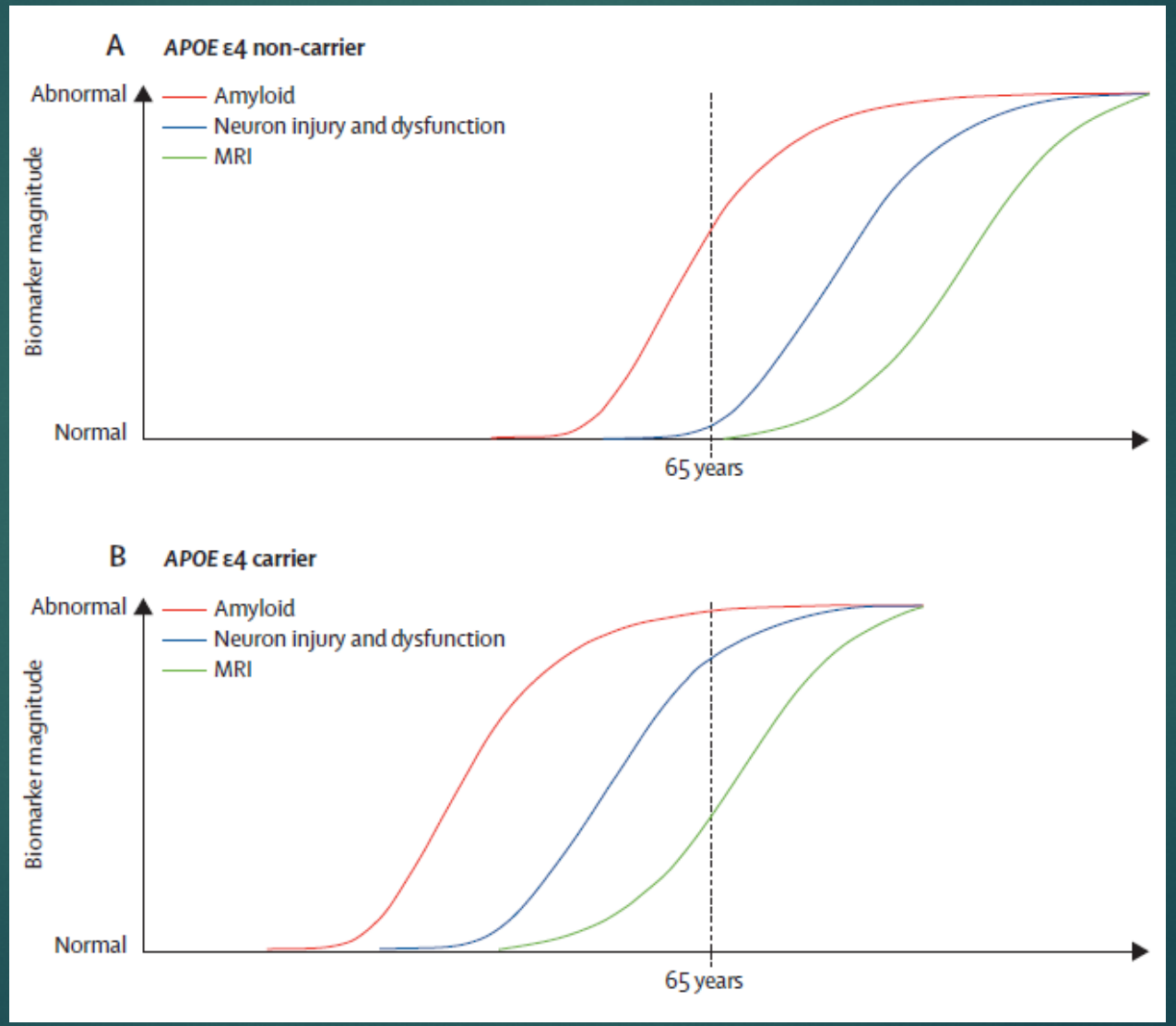
Effects of ApoE4

- Linked to reduced removal of Aβ and greater amyloid deposition
- Timing gene: Associated with earlier age of onset of AD (in 60-70s, not 80-90s)
- 65–80% of all AD patients have at least one APOe4 allele
- Having 1 copy confers a substantial AD risk for women (2x greater), but not for men
- APOE4 is linked to damaging the blood-brain barrier
- ApoE4 testing now included in 23andme kit

Timing of APOE4 effect on AD onset:
no gene (later onset) vs. gene present (earlier onset)

No APOE4

APOE4 = Earlier Onset



Age 65

ApoE4: Negatively affects many conditions

- Affects the age of onset, progression, or severity of (unrelated to BA load):
  - atherosclerosis,
  - AD,
  - impaired cognitive function,
  - reduced hippocampal volume,
  - HIV,
  - faster disease progression in MS,
  - unfavorable outcome after TBI,
  - ischemic CVD,
  - sleep apnea,
  - accelerated telomere shortening,
  - reduced neurite outgrowth,
  - Down's, LBD, Delirium, FTD, VAD, WM lesions, PD, ALS, stroke, post chemo

Klotho KL-VS variant: Ying to ApoE4 Yang

- *Klotho (KL)* is an age regulating protein (named after the Greek goddess who spins the thread of life) which is associated with greater brain volume and cognitive enhancement; its overexpression extends lifespan. Effects synaptic plasticity. Increases brain cognitive reserve, longevity

- Heterozygous (only 1 copy) is better (2 gums up cell): associated with longevity, global cognitive enhancement. Some 25% of Americans are heterozygous for the protective klotho variant

- Klotho enhances learning and memory. Klotho levels fall with age and in AD

- Higher levels are also tied to large cerebral cortex volume, strong functional connectivity, and better cognition.

- KL-VS Associated with:
  - Greater GM volume in Right DLPFC (Area 46) , independent of age (neurodevelopmental, counters decline) and Enhanced executive function

Jennifer Yokoyama, 2014

23andMe:
$99/199

In April, 2019, 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; 3% North African; 2% sub-Saharan African; 2% Ashkenazi Jew; 2.7% Neanderthal (223 variants); double APOE 3; Klotho variant

Remember: No current treatment for AD
Support: https://www.apoe4.info/wp/

Start here next time

Latest Memory Cure

Phillip's
Milk of Amnesia

for people who can't remember shit.

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

Driving & NP Testing

- Road-test performance is significantly related to a number of executive and visual attention measures
- Clock Drawing Test, Trails B test, Digit Symbol
- Correlate with poor driving outcomes in older adults with NCD (e.g., increased crash rates, impaired performance in driving simulations and performance-based road tests).
- Andrea Piatt: if you can't drive a one ounce pencil in an 8.5 X 11 space without errors or going too slowly, what would make one think they can drive a 3000 pound machine at 50 mph in a 10 foot lane?

1st Network: DMN and AD

- AD corresponds to the "Default Mode Network"
- DMN: task-related deactivation across fMRI studies; task free or task negative network
- In patients with Alzheimer disease (AD), the pattern of amyloid accumulation tracks to hub areas of DMN

1st Network: DMN and AD

- Disruption of this network even in the resting state is a marker for early AD.
- Prominent medial temporal/hippocampus, posterior cingulate (PCC)/precuneus, and lateral temporoparietal, and dorsal raphe nucleus atrophy.
- Episodic memory dysfunction

Rare Behavioral-dysexecutive variant of AD

- Predominant behavioral & executive deficits with major AD pathology
- Rare syndrome: 2% per year of UCSF referrals
- 2 groups:
  - behavioral (bvAD) type
  - cognitive/EF (deAD) type
  - worse EF in both; more EF than typical AD; bvAD: memory worse, like typical AD
- Age = ~65; 73% male; MMSE =23/>18; APOe4= 60%; worse EF than memory/VS
- First sxs: Cog = 90%; Cog & beh = 20%; Behav only=20%
- Medical: HTN, 35%; depression, 25%; TBI, 20%

Rik Ossenkopple, 2014 UCSF lecture

Alzheimer's Association Key Resources

We're available wherever and whenever you need reliable information and support.

- On the phone – 24/7 Helpline, 800.272.3900
- Online – alz.org
- In communities nationwide – alz.org/CRF

Flu and pneumonia vaccinations reduce AD risk

- Two studies:
- Regular flu vaccinations after age 60 reduces AD risk by 17%; earlier the better; 1 year delay reduced effect by 9%
- Pneumonia vaccination after age 60 reduces AD risk by 30%
- Theories that bacterial and viral infections of the brain may be part of AD causation
- Studies were correlational: unclear if the shots are themselves protective, or correlate with other health behaviors.
- Another study found that people with AD are twice as likely to die after a serious infection

LATE:
Limbic-predominant age-related TDP-43 encephalopathy

LATE: Alzheimer's Mimic

- An 86-year-old woman develops classic amnestic symptoms of Alzheimer's disease in her last years of life, but upon autopsy, her brain bears only a modest amount of Aβ plaques and tau tangles. Instead, TDP-43 inclusions crowd her limbic regions.

- LATE: Limbic-predominant age-related TDP-43 encephalopathy

- A new form of dementia that "mimics" the symptoms of Alzheimer's; LATE is present in >20% (up to 50%) of individuals past age 80 years

- LATE is caused by a buildup of TDP-43, not BA and Tau

Peter T. Nelson, et al., 2019

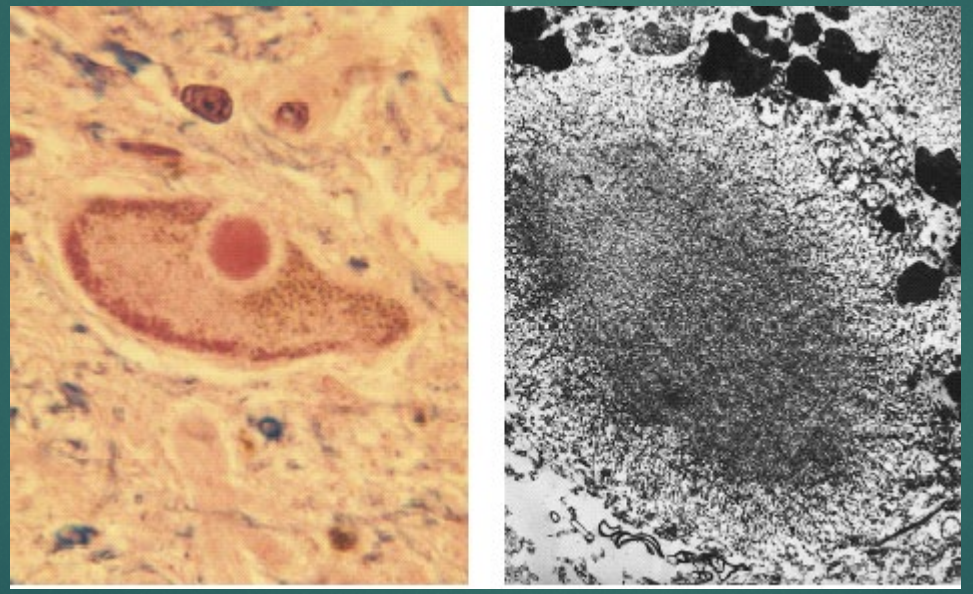
Neurocognitive features: OK verbal fluency, severe memory deficit

- LATE distinctive neurocognitive features: OK verbal fluency, severe memory deficit
- Pts with relatively 'pure' LATE (lacking severe comorbid pathologies) tend to have a more gradual clinical decline compared to those with 'pure' AD.
- In contrast, those with comorbid AD and LATE showed faster decline and more severe cognitive impairment
- Prominent impairment in episodic memory, but other cognitive domains and global cognitive status were also commonly affected especially in the later disease stages.
- Episodic memory wanes early, other cognitive domains later.

The Other Dementias

Dementia with Lewy Bodies (LBD)

Lewy bodies:
Hallmark of PD, but not cause



DSM-5: Major or Mild NCD with Lewy Bodies

- Meet criteria for major or mild NCD
- Insidious onset & gradual progression
- Probable: meets 2 core features or 1 suggestive
- Possible: meets only 1 core or suggestive feature
- Core diagnostic features:
  - Fluctuating cognition with pronounced variations in attention & alertness
  - Recurrent well formed & detailed visual hallucinations
  - Spontaneous motor features of parkinsonism (be it slowness of movement, tremor, or rigidity), with onset after cognition decline
  - REM Sleep Behavior Disorder

Pathology of LBD

- Neuropathology of both AD and Parkinsonism
- Presence of increased Lewy Body (intraneuronal cytoplasmic) inclusions in cortical regions and substantia nigra; NCD possible without AD pathology
- Causation: alpha-synuclein and beta amyloid
- Neurotransmitter: profound deficits in:
  - Acetylcholine (Nucleus Basilis) ↓
  - Dopamine (Substantia Nigra) ↓
- Onset ~55, duration 12-13 years

Lewy Body NCD

- ~15% of all NCD, 1 in 7, 800T in US; only 1 in 3 diagnosed
- Causes significantly greater functional disturbance than AD
- Care costs 2x AD
- 25% of LBD caregivers rate LBD as worse than death
- 80% of people with LBD received a diagnosis for a different cognitive, movement or psychiatric disorder before ultimately learning they had Lewy Body NCD (LBD)

Bostrom, 2007, Alz Dis Ass

EPS symptoms (rigidity, bradykinesia)

- Extrapyramidal Sxs:
  - rigidity
  - Bradykinesia (slow movement)
  - gait
  - Frontal release signs (grasp reflexes)
  - myoclonus are common in moderate to severe AD (use Klonopin)

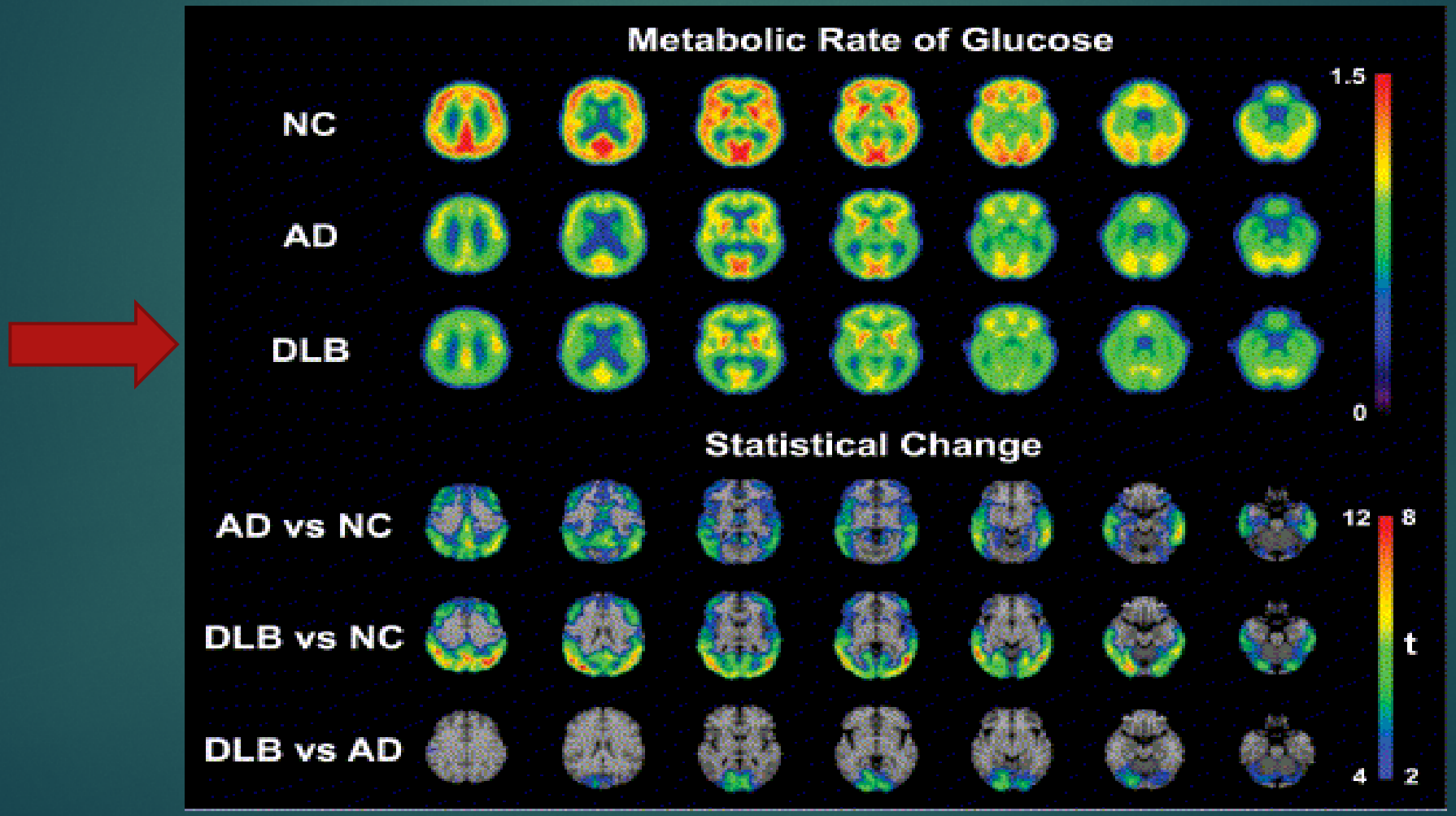
- Early EPS symptoms means it is not AD

- If Early EPS = either LBD, PD, CBD

LBD predictors

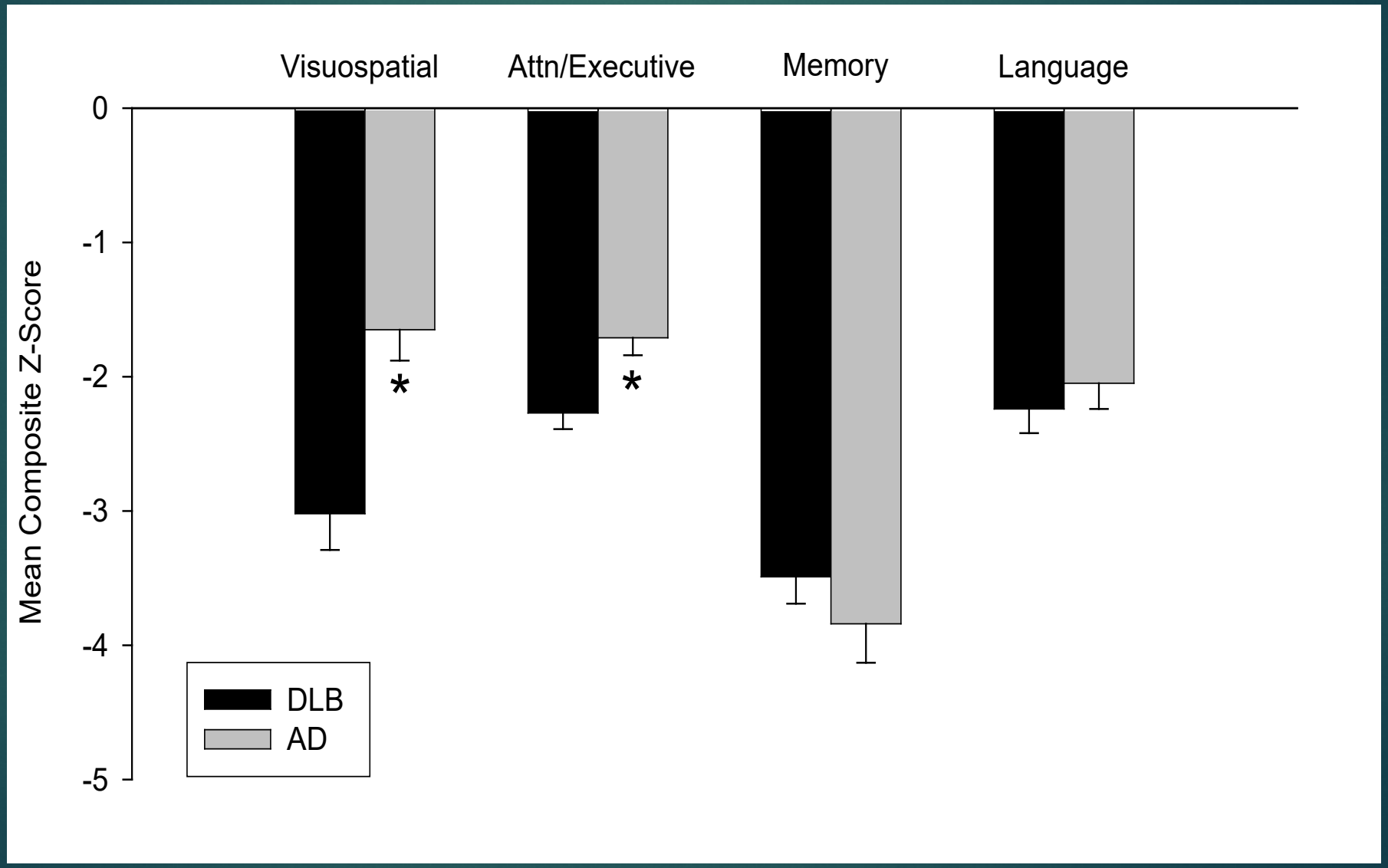
- Male
- Any EPS (resting tremor, bradykinesia)
- Cognitive fluctuation
- Visual Hallucination
- Neuroleptic sensitivity
- Depression
- Sleep disturbance
- Myoclonus
- Auditory Hallucinations
- REM sleep disorder

Occipital (visual) cortex hypometabolism is worse in LBD than in AD



Gilman et al., 2007

Cognitive Profiles in AD vs. LBD: VS & EF↓



Visuospatial Deficits: Predictor of Bad News?

Visuospatial Deficits:

- May predispose patients for visual hallucinations (Mosimann et al., 2004; Hamilton et al., 2009)
- Can differentiate LBD from AD with 80% sensitivity and 90% specificity (Ferman et al., 2006)
- May predict the rate of cognitive decline in LBD patients (Hamilton et al., 2008)

ADHD →→ Lewy Body NCD

• 360 patients with degenerative NCD and 149 healthy controls, matched by age, sex and education. The NCD patients comprised 109 people with NCD with Lewy bodies (LBD) and 251 with Alzheimer's.
•
• Adults who suffer from attention-deficit and hyperactivity disorder (ADHD) are three times more likely to develop LBD

• 48 per cent of patients with LBD had adult ADHD.

• More than three times the 15 per cent rate found in both the control group and the group with Alzheimer's.

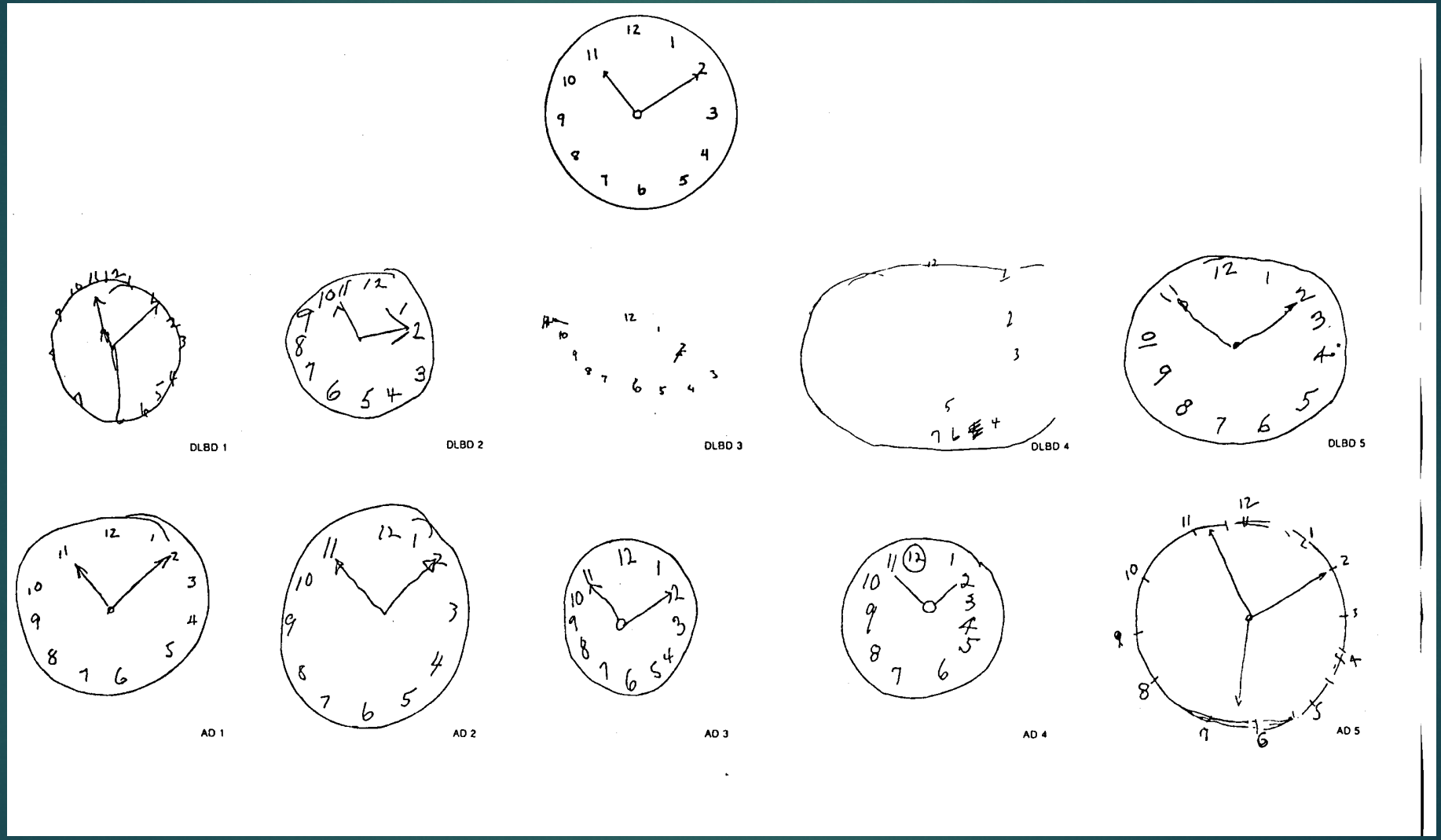
• Impulsivity and hyperactivity were significantly higher in the LBD group than the Alzheimer's group and the control group (measuring 14.7, 5.9 and 6.4 respectively on the Wender Utah Rating Scale).

Angel Golimstok, 2010

LBD (top) vs. AD Clock copies: LBD worse

LBD

AD



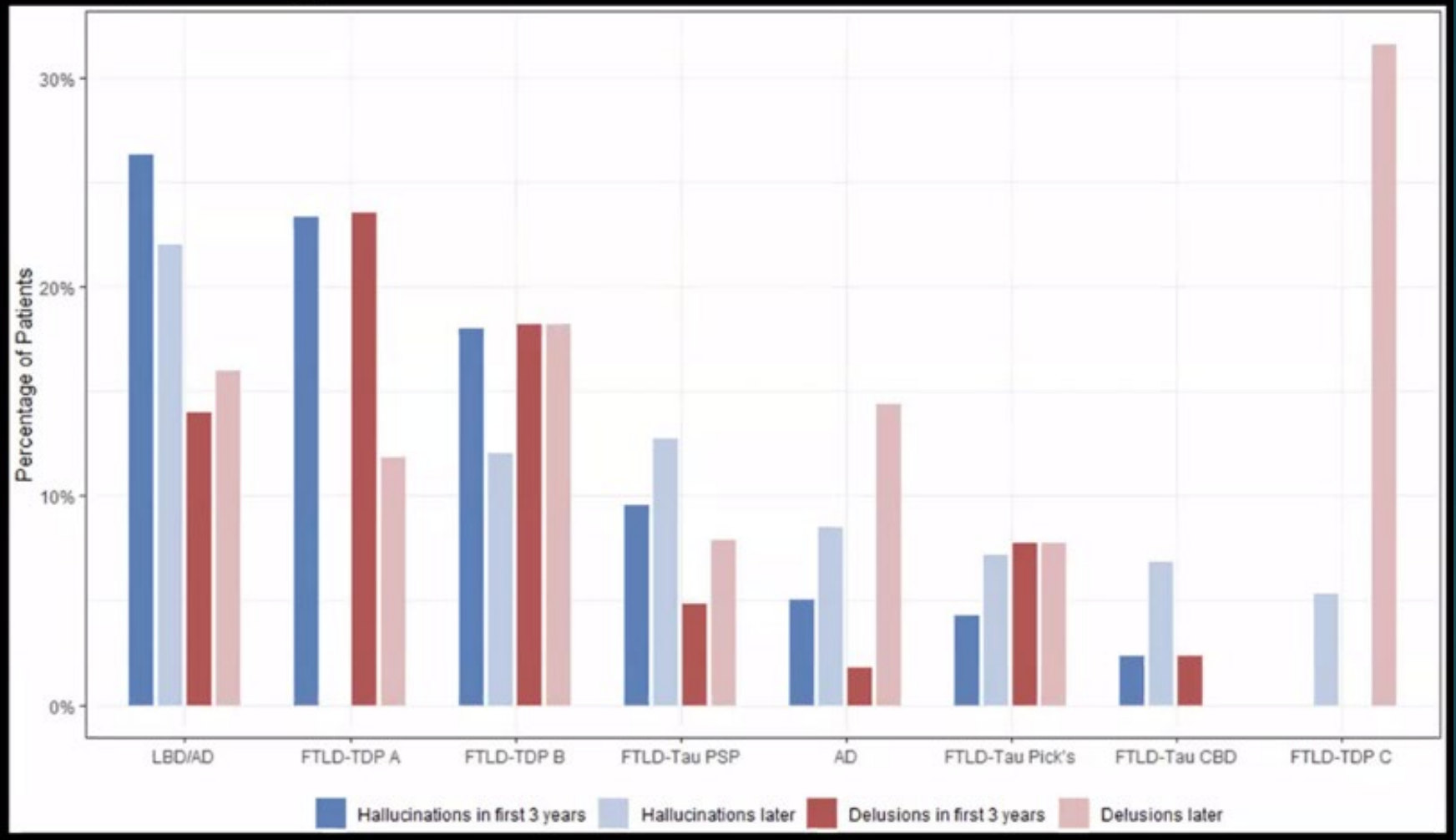
Visual Hallucinations in LBD

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

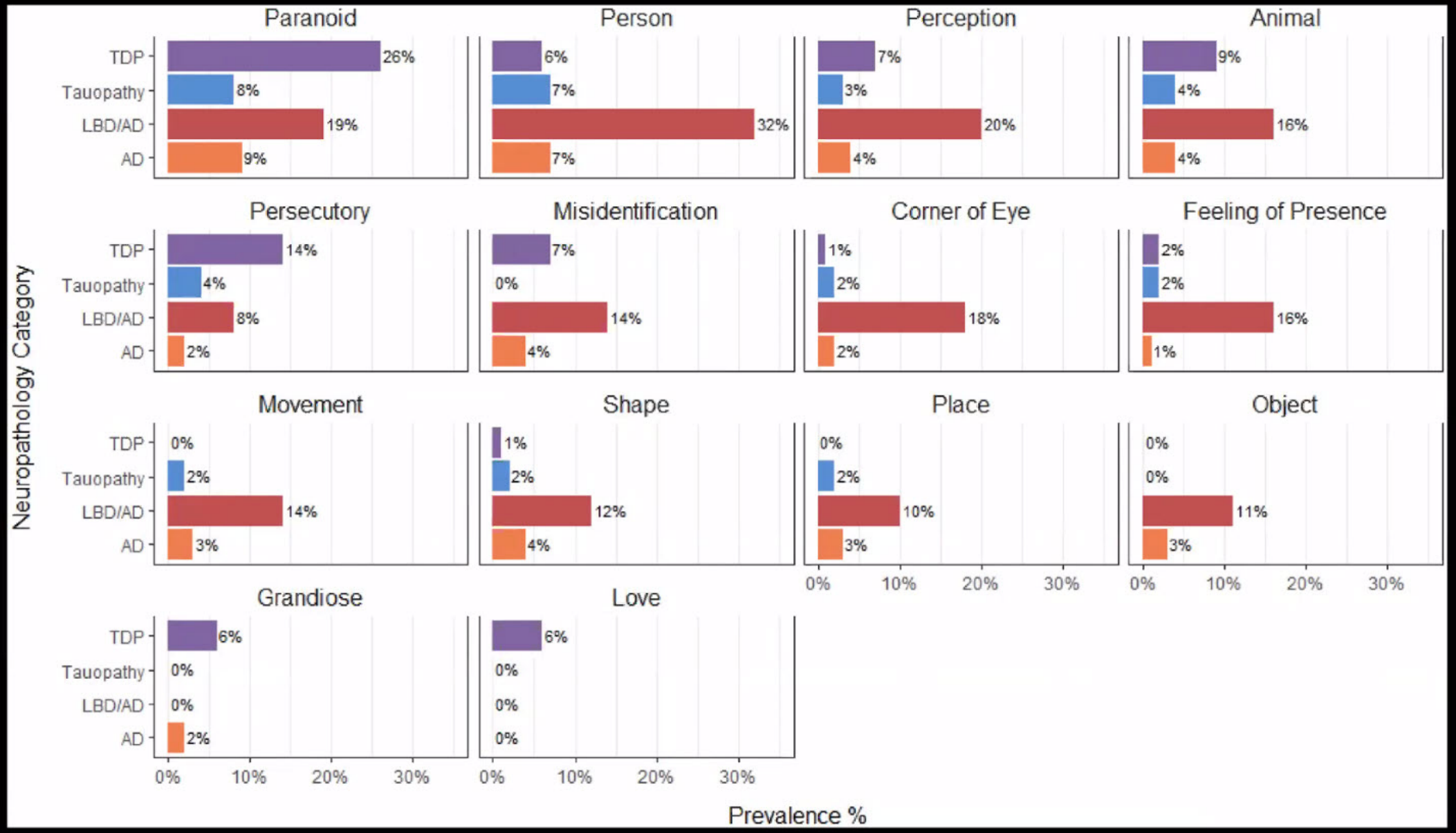
Cases with well-formed visual hallucinations had high densities of LB in the amygdala and parahippocampus, with early hallucinations relating to higher densities in parahippocampal and inferior temporal cortices.

Frequency of Psychotic Symptoms

Across Neuropathological Cohorts



Psychosis Subtypes by Major Pathology

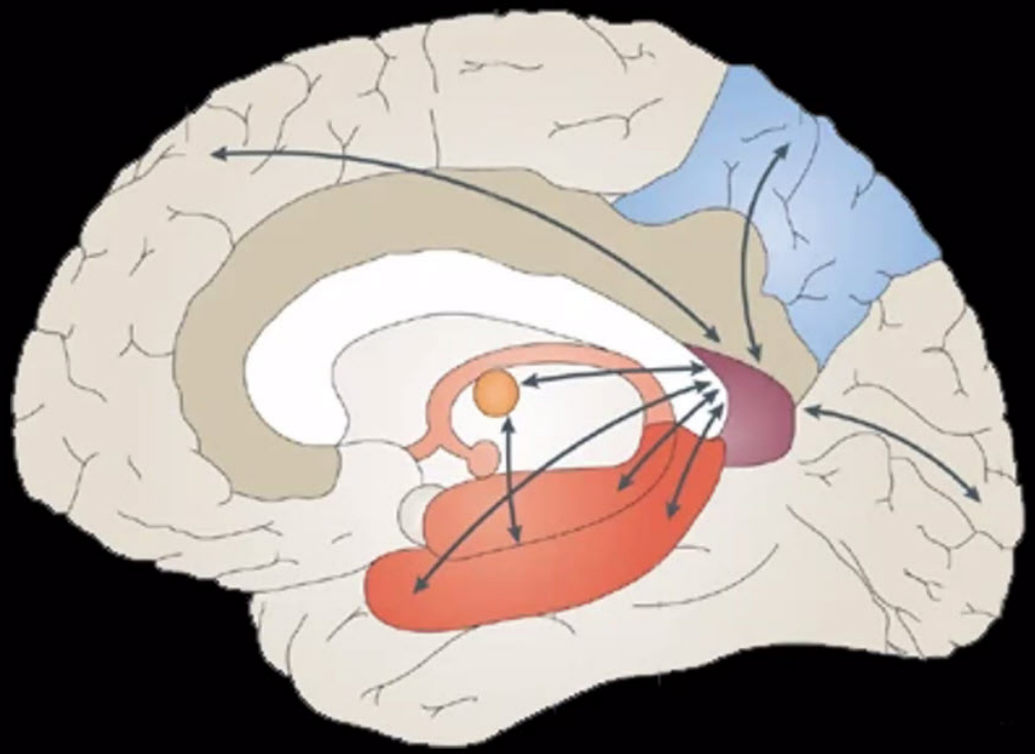


Different Delusions with Different Dementias

- **DLB Dysfunction**
- Capgras syndrome
- Reduplicative paramnesia
- Nocturnal visitors
  - People
  - Animals
- **FTD Dysfunction**
- ■ Grandiose delusions
  - “I am wealthy”
  - “I won the lottery”
  - “I am friends with famous people”

Capgras Syndrome

The false belief that a loved one has been replaced by an impostor

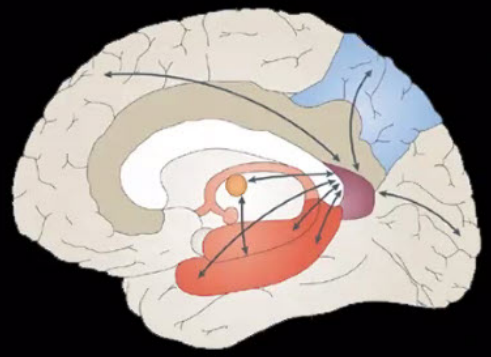


Vann, Aggleton & Maguire. *Nat Rev Neurosci* 2009.

Two-Hit Hypothesis for Capgras Syndrome

DLB Dysfunction

- Retrosplenial cortex (familiarity)
- Right frontal cortex (belief evaluation)
- Fusiform gyrus (face information)
- Frontal brain circuitry (credibility)



Vann, Aggleton & Maguire.
Nat Rev Neurosci 2009.

FTD Dysfunction

- Frontal brain circuitry (credibility)

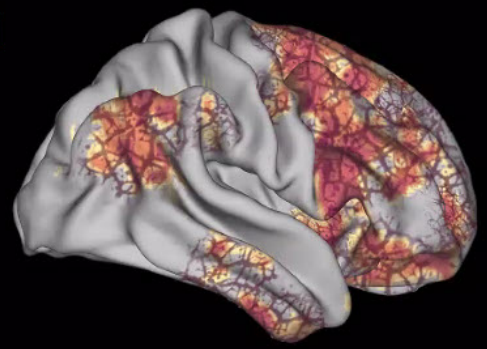


Image courtesy of Amy Wolf

Hallucinations in AD

- Alzheimer's:
  - hallucinations in 20% at 1 year and 51% at 4 years;
  - visual hallucinations in 30%
  - delusions in AD: 36%
  - severity of cognitive decline a major predictor of above

- VHs in AD: later onset & and occur with greater cognitive impairment and a more advanced stage of the dementia.

Visual Hallucinations in LBD

- LBD has significantly higher sxs:
  - visual hallucinations (70%)
  - delusions (56%)
  - delusional misidentification (50%)

- PD:
  - hallucinations in 40% of patients
  - sensation of a presence (person), a sideways passage (commonly of an animal) or illusions were present in 26%
  - formed visual hallucinations in 22%
  - auditory hallucinations were present in 10%

Visual Hallucinations in LBD

- VHs onset earlier in LBD compared to AD.
- If VHs in first 5 years: odds are 5 x greater for autopsy-confirmed LBD and not AD.
- Types of VH images:
  - fully formed adults or children in 84%,
  - animals or insects in 37%
  - objects in 39%
  - unformed images, such as fire, smoke, water and designs occurred in less than 12% in both LBD and AD.

T.J. Ferman, et al., 2012

Charles Bonnet Syndrome:
Pts with visual loss

- Experience of complex visual hallucinations in ~17% of patients with visual loss (cataracts, central vision loss due to macular degeneration or peripheral vision loss from glaucoma)
- First described by Charles Bonnet in 1760 in his 89-year-old grandfather
- Usually are "lilliputian" (everything smaller).
- The most common hallucination is of faces or cartoons; sudden appearance & disappearance
- Know that the hallucinations are not real
- Reassure that they are not crazy; SSRIs may help
- Also an auditory version of this syndrome

LBD NCD: Faster decline

- 226 autopsied, community based : 126 had LB pathology (56%), 44% in neocortex
- Cognitive decline:
  - LBD alone > AD with LBD > AD
- LDB has more rapid cognitive decline
- Worse on TMTB, Story memory

Leverenz, 2008

PD vs LBD

- Parkinson's pts hallucinate due to the side-effects of ***medication***
- Hallucinations are the early signs of DLB.

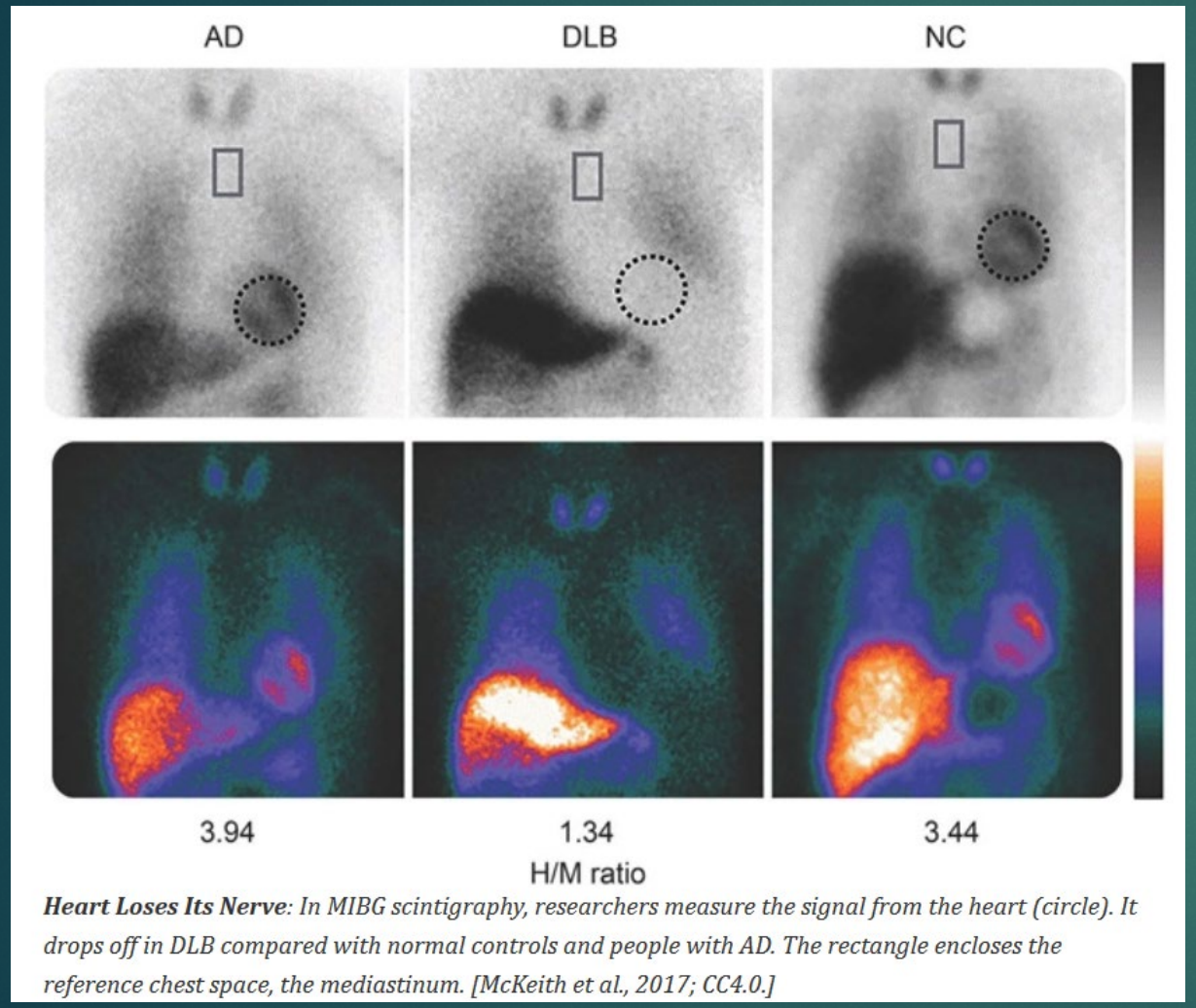
- In a nutshell:
  - people who present motor difficulties before cognitive impairment are diagnosed with Parkinson's
  - those that hallucinate before motor symptoms often have dementia with Lewy bodies.

LBD NCD: Faster decline

- 226 autopsied, community based : 126 had LB pathology (56%), 44% in neocortex
- Cognitive decline:
  - LBD alone > AD with LBD > AD
- LDB has more rapid cognitive decline
- Worse on TMTB, Story memory

Leverenz, 2008

Decline in heart signal in LBD – request nuclear medicine consult



***Heart Loses Its Nerve**: In MIBG scintigraphy, researchers measure the signal from the heart (circle). It drops off in DLB compared with normal controls and people with AD. The rectangle encloses the reference chest space, the mediastinum. [McKeith et al., 2017; CC4.0.]*

- Now a core feature: iodine-123-metaiodobenzylguanidine (MIBG) myocardial scintigraphy;
- This type of imaging visualizes the amount of postganglionic sympathetic innervation to the heart, which plummets in LBD
- sensitivity and specificity of 69 and 87 percent for distinguishing LBD from AD

2017: Neurology diagnosis recommendations 2

- LBD patients respond differently to medications used in AD and PD
- LBD tends to progress and lead to death faster than AD or PD, so a correct diagnosis helps families plan.
- Cholinesterase inhibitors appear to improve LBD patients' cognition, activities of daily living, and global function
- Avoid prescribing antipsychotics to these patients, as they can have severe adverse reactions.
- Avoid dopaminergic drugs (L-Dopa, etc.), used widely and effectively in PD, can cause psychosis in LBD patients, though some may tolerate minimal doses.

LBD Clinical Presentation 1

- Progressive NCD
- "One year rule" between onset of NCD and PD sx:
  - If NCD in 1st year, dx LBD;
  - If NCD later, dx PD;
  - Idiopathic PD takes 5-10 years before NCD develops
- Day to day fluctuations in attention; episodic confusion; easy to tip into sudden delirium
- Changes in arousal (sleep 20-30 hours)
- PD symptoms: axial (head and neck), not tremor

LBD Clinical Presentation 2

- Parkinsonism actually begins with a loss of smell (see Robin Williams)

- REM Behavior Syndrome years before NCD (loss of motor paralysis in REM: move in dreams, physically act out their dreams by kicking, screaming and even harming themselves and others lying next to them); (see **Mike Birbiglia - Sleepwalk with me film)**
- RBD is common in LBD; 75% patients act out their dreams while sleeping, often years before the onset of other symptoms. RBD now is a core clinical features of LBD
- People diagnosed with REM sleep disorder are 18% more likely to develop a neurodegenerative disease like NCD or Parkinson within five years of their diagnosis, and 52% more likely after 12 years.
- 56% of PD or LBD (compared to AD, 2%)

R. Postuma , Neurology, 2008

Bizket: REM Sleep Disorder

LBD predictors: 65% in 3 years

- Moving or vocalizing in bed during REM (80% develop LBD)
- Shouting out during a nightmare
- Abnormal color vision, loss of smell & motor sxs
- Struggling to balance a checkbook
- Weak sense of smell
- Hallucinations
- Chronic constipation

LBD Clinical Presentation

- Neuroleptic (antipsychotic drug) sensitivity (fatal) and increased anticholinergic sensitivity (delirium)
- Severe neuroleptic sensitivity: induce Parkinson-like side-effects or Neuromalignant syndrome (high fever, sweating, unstable blood pressure, stupor, muscular rigidity, and autonomic dysfunction)
- Underdiagnosed: Clinical diagnosis of LBD in only 49% of cases confirmed at autopsy

Neuropsychology of LBD

- Severe visuospatial and visuoconstructional deficits > AD
- Executive and attention deficits > AD
- Severely impaired verbal fluency (both semantic & phonemic)
- Relatively intact memory: poor retrieval rather than rapid forgetting

Memory & VS ability: AD vs. LBD

- Memory deficits precede diagnosable AD by two or more years
- Earliest AD symptoms of AD: memory loss with rapid forgetting
- AD: Loss of semantic knowledge measured by tests such as confrontation naming and category fluency occurs early in the course
- Short-term memory tends to be better with LBD, especially with Aricept or Exelon.
- Severe early visuospatial dysfunction is suggestive of LBD

Differences between AD and LBD

- PD symptoms are LBD, not AD;
  - greater rigidity and fewer tremors;
  - falls more common with LBD.
- Cognitive fluctuations are LBD, not AD.
- LBD: more severe visuospatial, visuoperceptual, and visuoconstructive problems.

Differences between AD and LBD 2

- More men seem to have LBD, while more women are prone to AD.
- Rapid Eye Movement (REM) sleep disorder is more common in LBD
- LBD: more hypersensitive to medications than either AD or PD patients.
  - Anti-psychotics drugs may work or may cause irreversible damage; could be fatal in long term.

Use Aricept for Visual Hallucinations in LBD

- Acetylcholinesterase inhibitors, such as donepezil (Aricept) and Namenda, are licensed to treat mild to moderate Alzheimer's disease.

- They can also be used to treat people with dementia with Lewy bodies, and can be particularly effective at treating visual hallucinations.

- They work by delaying the breakdown of the neurotransmitter acetylcholine by inhibiting the enzyme acetylcholinesterase.

Frontotemporal Dementia (FTD)

FTD

- A mysterious set of neurodegenerative diseases
- It can start with:
  - theft by a previously law-abiding citizen,
  - sexual misconduct by a hitherto faithful spouse
  - halting speech or a blank stare at a simple sentence, overeating,
  - odd misperceptions of pain or cold
- Frontotemporal dementia (FTD) usually ends in the mute, bed-bound misery of advanced dementia, and death.

The Varieties of FTD

- FTD is an umbrella term for:
  - A diverse set of diseases that are all marked by
  - atrophy starting somewhere in the frontal or temporal lobe of the brain,
  - often unilateral.

- But, FTD is heterogeneous at every level—the clinical presentations, the underlying neuropathology, the neural networks that become dysfunctional, and the genes that cause the havoc.

- FTD is a spectrum of diseases that stretches toward parkinsonian symptoms on one end and amyotrophic lateral sclerosis (ALS) on the other.

7 Current FTD subtypes

- bvFTD: behavioral variant FTD
- svPPA: Semantic Progressive Primary Aphasia
- nfvPPA: Nonfluent variant PPA
- lvPPA: Logopenic variant PPA
- FTD-MND: FTD Motor Neuron Disease
- CBS: Corticobasal Syndrome
- PSP: Progressive Supranuclear Palsy

Frontotemporal NCD

- A. NCD criteria met; B. Insidious and gradual progression
- C. Either 1 or 2:
  - 1. Behavioral variant
    - A. 3 or more of following behavioral sxs:
      - 1 Behavioral disinhibition
      - 2 Apathy or inertia
      - 3 Loss of sympathy or empathy
      - 4 Perseverative, stereotyped or compulsive/ritualistic behavior
      - 5 Hyperorality and dietary changes
    - B. Prominent decline in social cognition and/or executive abilities

Frontotemporal NCD

- 2. Language variant
  - A. Prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension

- D. Relative sparing of learning & memory and perceptual-motor function

- E. Not better caused by another syndrome

Frontotemporal NCD

- Probable FT NCD: if either of following is present; otherwise Possible FTNCD
  - 1 Evidence of causative FT NCD genetic mutation, from either family history or genetic testing
  - 2 Evidence of disproportionate frontal and/or temporal lobe involvement from neuroimaging

- Possible FT NCD: if no evidence of genetic mutation, & no neuroimaging

Frontotemporal NCD (FTD)

- Prevalence: 4th most common cortical NCD, (10% of NCDs)

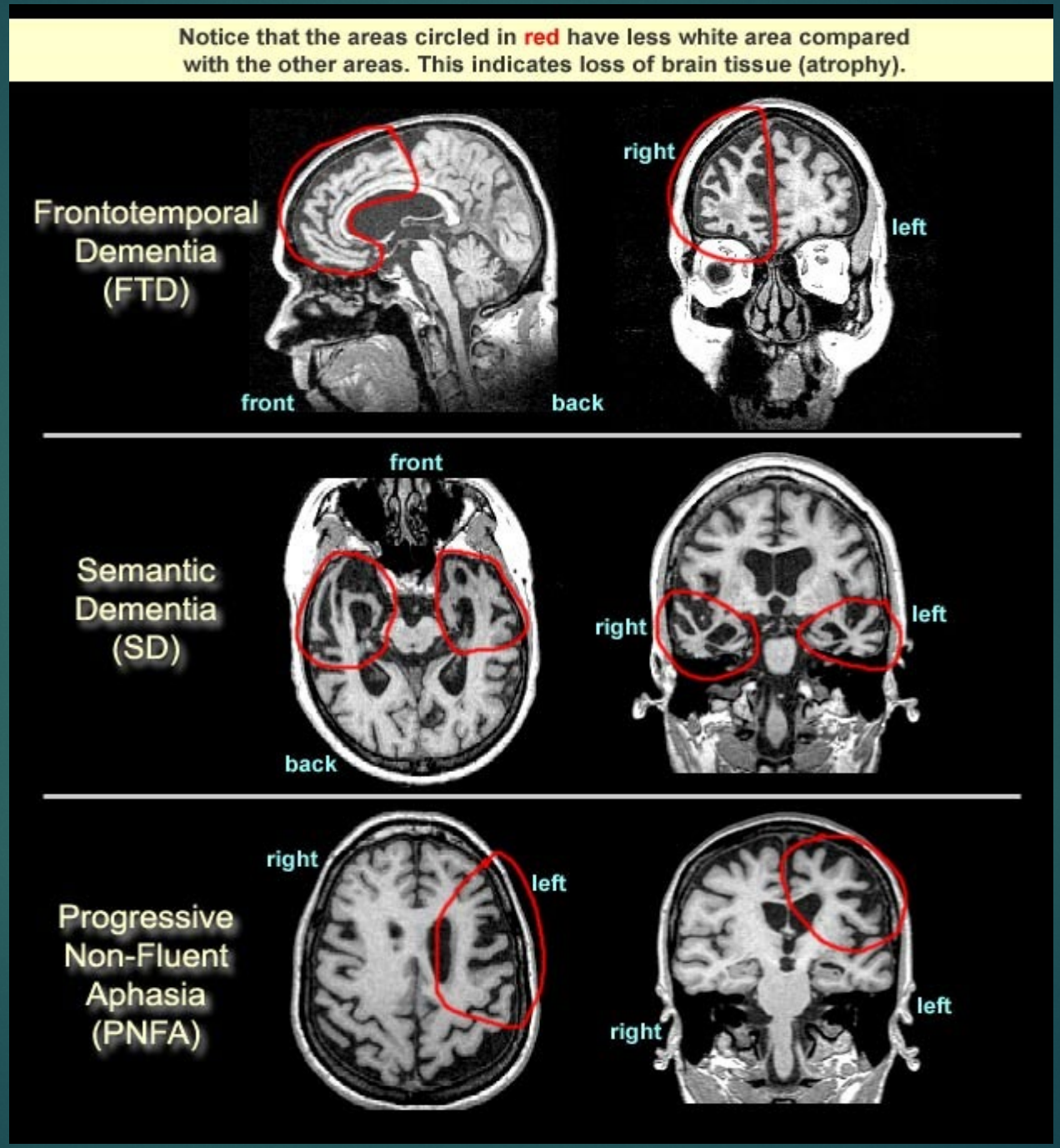
- Deficits in behavior and cognition began to show five to 10 years after brain atrophy, a few years prior to the estimated age of onset.

- Pathology: progressive often unilateral, degeneration of:
  - the anterior cingulate (apathy, empathy, beh. initiative),
  - dorsolateral frontal (executive deficits),
  - orbital basal frontal (disinhibition),
  - temporal lobes (language)

  - frontal atrophy & hypoperfusion, 80% gliosis, bilateral amygdala degeneration
  - tau inclusions in tangles
  - Serotonin ↓

Miller B L, Cummings J L, et al., Neurology 41:1374-1382, 1991

Notice that the areas circled in red have less white area compared with the other areas. This indicates loss of brain tissue (atrophy).



FTD Common Features

- Onset before age 65 (35-70)
- Positive family history of similar disorder in 1st degree relative in 50%
- Show up in Psychiatry not medicine; decline in social conduct; most difficult for families
- Presentation of a progressive language or behavioral disorder

FTD Common Features

- No amnesia or marked visuospatial deficit
- Later alteration in attention, initiation, executive functioning
- Often asymmetrical
- Apathy, change in eating habits, and disinhibition are great distinguishing factors between psychiatric disease and bvFTD

C9orf72

Benussi et al., JAMA Network Open, 2021

	C9orf72	Disease duration, y						
		0	2	4	6	8	10	12
Behavioral symptoms	Disinhibition	51.7%	52.0%[c]	64.9%	74.3%[a]	75.0%	90.0%	95.8%
	Apathy	51.7%	68.0%	81.9%	82.4%	80.6%	86.4%	87.5%
	Loss of empathy	48.3%	58.7%	75.5%	81.1%	80.6%	95.5%	95.8%
	Compulsive behavior	34.5%	36.0%[c]	53.2[c]	67.6%	61.1%	59.1%[c]	75.0%
	Hyperorality	27.6%	36.0%[a]	58.5%	71.6%	63.9%	77.3%	87.5%
Neuropsychiatric	Hallucinations	10.3%[a]	22.7%[a]	33.0%	33.8%	41.7%[c]	54.5%[c]	41.7%
	Delusions	6.9%	16.0%	30.9%	37.8%	38.9%	36.4%	33.3%
	Depression	37.9%	44.0%	37.2%	27.0%	27.8%	27.3%	20.8%[a]
	Anxiety	27.6%	41.3%	43.6%	41.9%	55.6%	50.0%	50.0%

GRN

GRN		Disease duration, y						
		0	2	4	6	8	10	12
Behavioral symptoms	Disinhibition	38.2%[c]	48.8%[c]	52.4%[c]	38.7%[b,c]	47.6%	100%	100%
	Apathy	67.6%	79.8%	84.1%	74.2%	81.0%	100%	100%
	Loss of empathy	58.8%	64.3%	68.3%	67.7%	71.4%	80.0%	66.7%
	Compulsive behavior	20.6%[c]	35.7%[c]	47.6%[c]	51.6%	52.4%	80.0%	100%
	Hyperorality	55.9%	60.7%[b]	65.1%	64.5%	61.9%	80.0%	100%
Neuropsychiatric	Hallucinations	11.8%	7.1%[b]	11.1%[b]	32.3%	28.6%	20.0%	0.0%
	Delusions	11.8%	13.1%	15.9%	16.1%	19.0%	40.0%	0.0%
	Depression	47.1%	46.4%	42.9%	25.8%	23.8%	60.0%	100%[b]
	Anxiety	44.1%	50.0%	55.6%	41.9%	23.8%	40.0%	100%

MAPT

MAPT		Disease duration, y						
		0	2	4	6	8	10	12
Behavioral symptoms	Disinhibition	85.7%[a]	79.4%[a,b]	79.3%[a]	82.6%[a]	81.0%	91.7%	100%
	Apathy	78.6%	76.5%	75.9%	73.9%	76.2%	91.7%	100%
	Loss of empathy	64.3%	64.7%	69.0%	73.9%	76.2%	91.7%	100%
	Compulsive behavior	64.3%[a]	70.6%[a,b]	79.3%[a,b]	73.9%	76.2%	100%[b]	100%
	Hyperorality	42.9%	47.1%	55.2%	73.9%	81.0%	91.7%	100%
Neuropsychiatric	Hallucinations	0.0%	2.9%	10.3%	13.0%	4.8%[b]	0.0%[b]	11.1%
	Delusions	0.0%	2.9%	13.8%	21.7%	23.8%	33.3%	33.3%
	Depression	42.9%	35.3%	27.6%	26.1%	38.1%	50.0%	33.3%
	Anxiety	35.7%	35.3%	31.0%	43.5%	57.1%	66.7%	77.8%

Different genetic paths for NP sxs

- Patients with MAPT variants had the most—and the most severe—behavioral disturbances, especially disinhibition and compulsion. Some began to have neuropsychiatric episodes, with anxiety and depression most common among MAPT and GRN carriers, and hallucinations among C9ORF72 carriers. How severe these were, and how that changed over a person's progression, also differed between the genetic forms. For example, while participants with C9ORF72 expansions became steadily less depressed in their late stages, depression grew more profound in GRN carriers. This suggests that individuals go down different symptom trajectories in the different genetic forms of the disease.

First symptom

- Apathy was the most common initial symptom, followed by disinhibition, memory impairment, and language problems.
- Strikingly, even relatives who carried the same mutation often had different first symptoms. Even so, some themes emerged. For example, MAPT mutation carriers tended to lose normal social inhibitions first, while GRN carriers first tended to stumble over language. During the preclinical stage, i.e., in presymptomatic carriers, people with tau mutations were more likely to be moody and wake up a lot at night, while C9ORF72 mutation carriers were slightly more likely to become socially awkward or show odd behaviors, and GRN carriers seemed to have trouble with everyday skills, such as cooking, using appliances, or paying bills.
- People without a known family history of FTD typically do not find their way to a neurologist until the disease has progressed well into the symptomatic stage. Instead, the mood and behavior problems drive people to therapists, marriage counselors, or psychiatrists. Like the nurse (with unrecognized FTD) who one day asked a patient to lend her cash, many people with FTD have a history of losing their jobs due to odd behavior or inefficiency at work.

Demographics

- Mean age onset = age 60 +/- 10 years; 50% < 60

- Of all FTD pts:
  - bvFTD: 56%
  - Sem var PPA: 19%
  - PNFA: 25%

- 65% male

- FTD+ALS (37% autosomal dominant; 59% family hx)

B. Miller, 2007

Demographics 2

- 15% develop:
  - MND (motor neuron disease) (amyotrophic lateral sclerosis) (i.e. Stephen Hawkings)
  - PSP (progressive supranuclear palsy)
  - CBS (corticobasal syndrome)

- Survival post dx:
  - FTD – 3.1 years
  - Sem var PPA – 5. 3 years

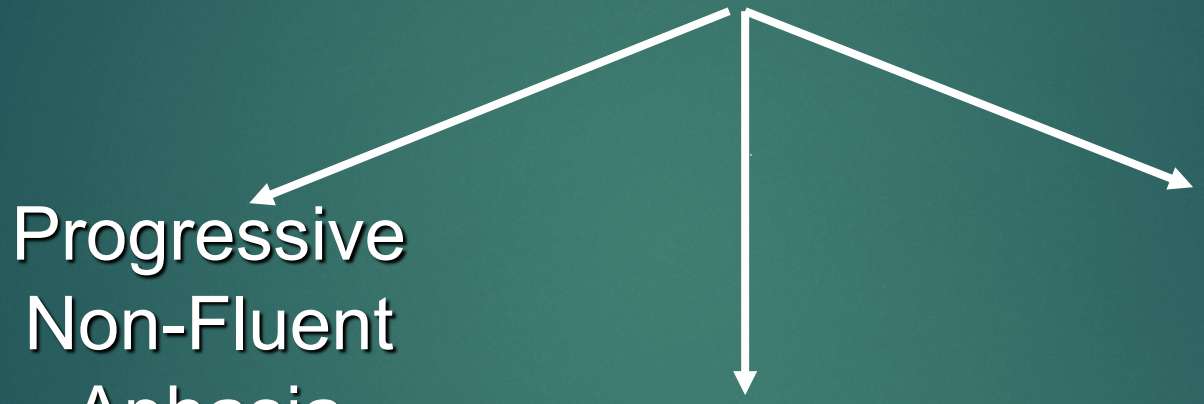
FTD is genetic

- FTD is 50% genetic
- Up to 50 percent of all cases have a family history
- 10 to 30 percent are autosomal-dominant.
- Mutations in the genes for MAPT (tau), progranulin, and C9ORF72 (40%) account for a majority of familial cases
- But more genes continue to be implicated in FTD overall, i.e. VPS13C, Hox

Misdiagnosis of FTD

- 28% of patients with a neurodegenerative disease received a prior psychiatric diagnosis.
- Depression is the most common psychiatric diagnosis in all groups.
- BvFTD patients received a prior psychiatric diagnosis significantly more often (51%) than patients with Alzheimer's disease (23%), semantic NCD (24%), or progressive nonfluent aphasia (12%)
- Often misdiagnoses as bipolar disorder or schizophrenia

Frontotemporal NCD
Unilateral Localization



Progressive Non-Fluent Aphasia

(nfvPPA)

Social/Executive (bvFTD)

svPPA

Left Frontal

Right Frontal

Left Temporal

Primary Progressive Aphasia-AD

- When compared to the typical amnestic form of AD (DAT-AD), the form of AD that causes PPA (PPA-AD) is characterized by asymmetric cortical atrophy of the language-dominant (usually left) hemisphere, leftward predominance of neurofibrillary tangles (NFT), no association with ApoE4 as a risk factor, lesser frequency of limbic TDP-43, and closer linkage to familial dyslexia (Mesulam et al., 2021).
- In some cases, the language cortices have more NFT than limbic areas but in others it is the ratio of cortical-to-limbic NFT that is increased even when the medial temporal NFT density is at Braak stages 5-6.
- Only few PPA-AD cases are “hippocampal sparing” (Murray et al., 2011) postmortem, but most do have leftward asymmetry of NFT density (Gefen et al., 2012; Mesulam et al., 2021). What is remarkable is the preservation of memory in PPA-AD even when the postmortem shows typical NFT densities at Braak stages 5-6 (Mesulam et al., 2021).

bvFTD: A Social Disease

- Loss of empathy
- A defunct “sarcasm radar”
- No embarrassment
- Inappropriate touch, familiarity
- 50% arrested or do antisocial behavior
- Silly antisocial: take off clothes, urinate in public
- At work: Embezzlement, insults
- Compulsions: need to touch, shoplift, counting
- Alienation from family
- Divorce
- Legal & financial problems
- Addiction

Social deficits in FTD

- Wear slippers with fancy evening clothes
- Ordering 3 different dinners because they all taste good
- Walking into traffic without concern
- Spending $700T on credit cards and not know what you spent it on
- Void of emotions
- Current moment is all important
- Changes in a person's sense of humor may be an early warning sign of FTD
- No embarrassment (ACC↓↓)

Relationship Turmoil and Empathy in FTD

- Across all patients, empathy loss is associated with marital dissolution
- Marital dissolution and infidelity significantly greater in bvFTD group compared to other FTD and AD
- Lower empathic accuracy in ND patients associated with greater depressive sxs in their caregivers
- Caregiver burden predicted by bvFTD anatomy; Right anterior atrophy: Divorce! Less empathy, more burden

Takeda & Perry et al., in prep.

Caregiver Health Study

- 162 patients or healthy controls
  - 35 Alzheimer's disease
  - 32 Behavioral variant FTD
  - 15 Nonfluent variant FTD
  - 23 Semantic variant FTD
  - 17 Corticobasal Syndrome
  - 17 Progressive Supranuclear Palsy
  - 23 Healthy Controls

- 162 caregivers or study partners

- 83% spouses
- 63 years old
- 56% female
- 88% White American

Measures:

- Structural MRI
- MMSE (cognitive functioning)
- CDR (disease severity)
- NPI (Neuropsychiatric Inventory)

Measures:

- SCL-90 (Psychopathology)
- SF-36 (Global Health)

Hua, Wells, Haase, Chen, Rosen, Miller, Levenson (accepted)
Dementia and Geriatric Cognitive Disorders

Caregiver burden predicted by bvFTD anatomy;
Less empathy, more burden

Empathic Accuracy Deficits in Pts with NDD Associated with Caregiver Depression

- Lower empathic accuracy in ND patients associated with greater depressive sxs in their caregivers
- This association was accounted for by increased loneliness, burden and strain in caregivers

Brown, et al., 2018

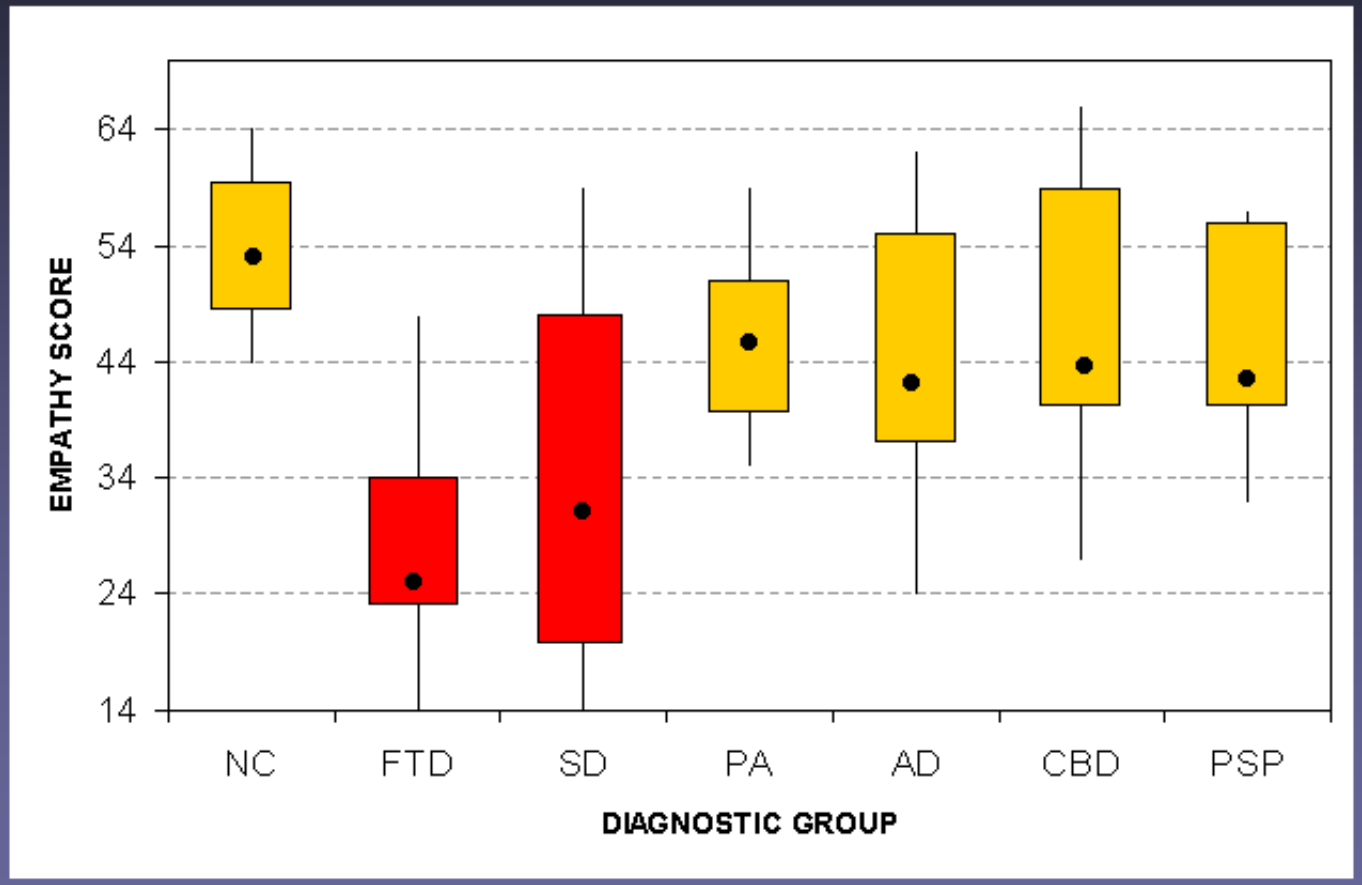
Less embarrassment = ACC↓↓

- bvFTD:
  - fewer changes in facial expression or autonomic responses while watching themselves than other people did
  - less embarrassment or self-consciousness;
  - while they watch a heart-warming scene from a movie, no empathic response

- blunted self-consciousness correlated with atrophy in the anterior cingulate cortex, another key hub in the salience network.

(Sturm et al., 2013)

Measuring social cognition: empathy



(Rankin et al., Brain, 2006)

Regions where empathy score positively correlates with tissue density

(Analysis significant after FWE correction at p<0.05)

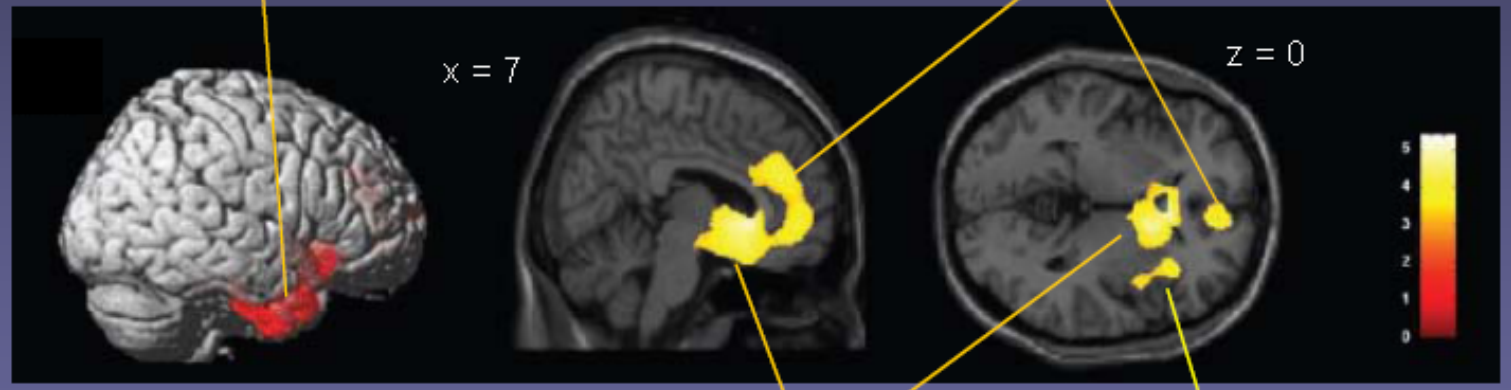
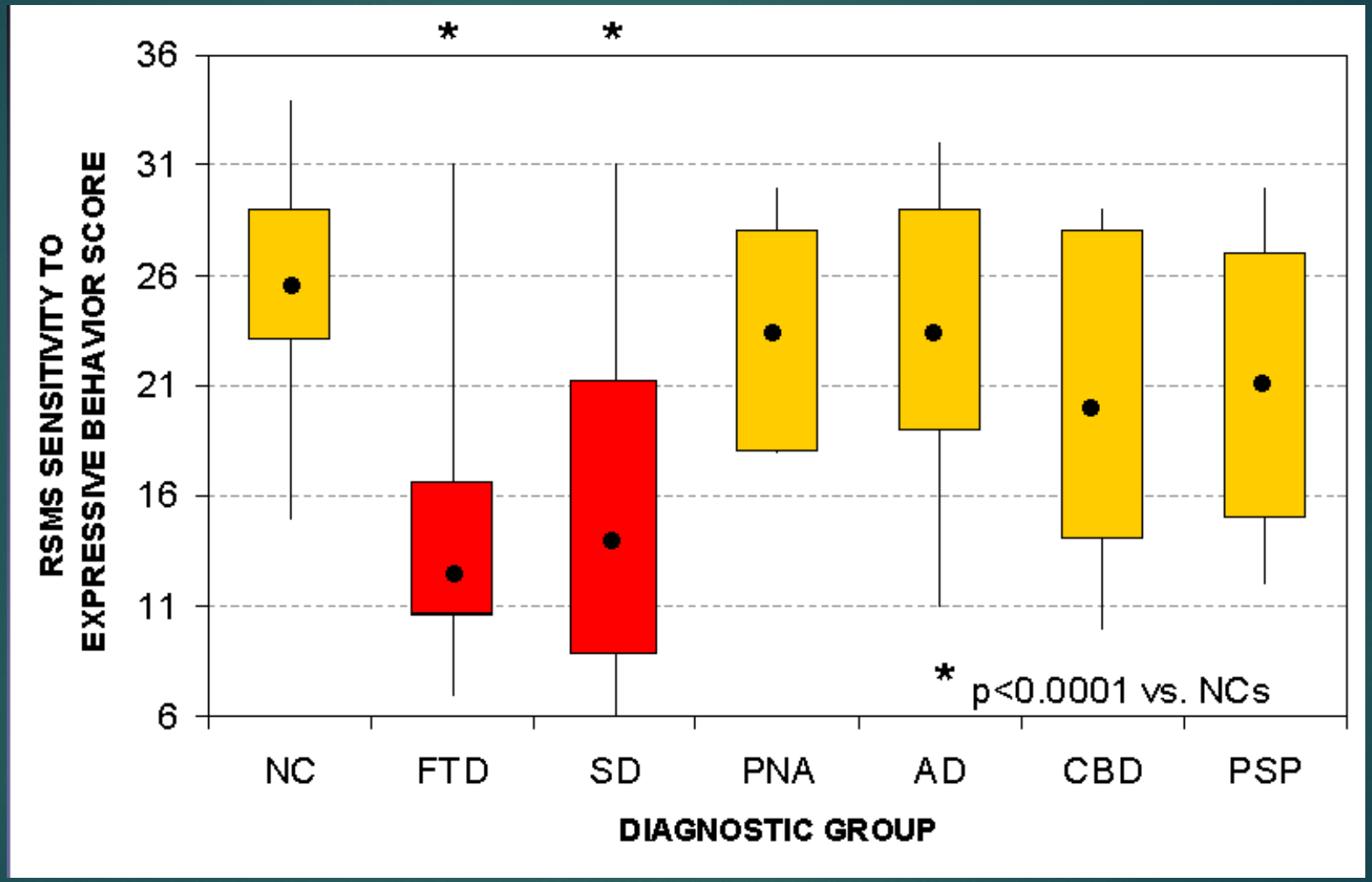


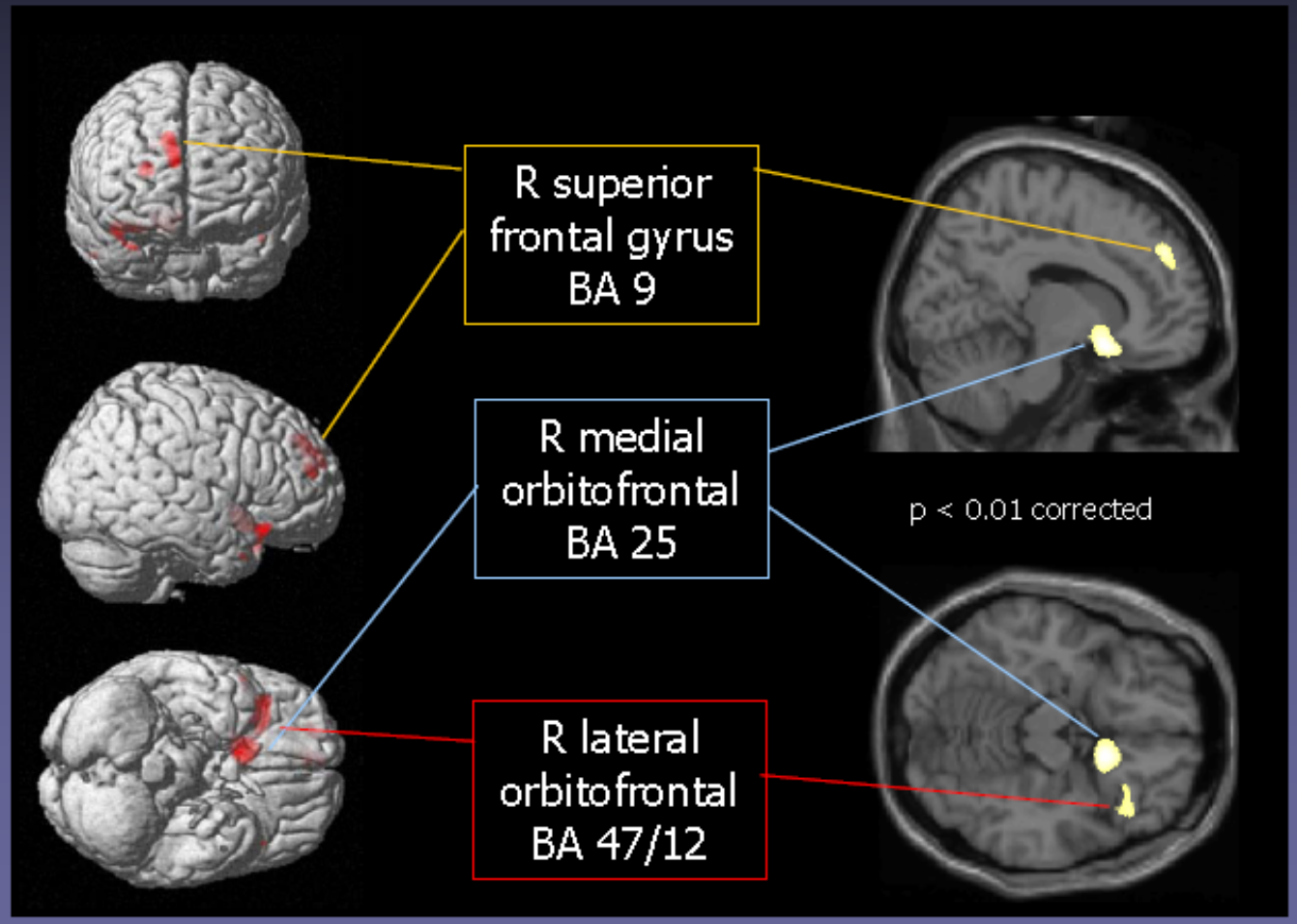
Figure threshold: p<0.001 uncorrected

(Rankin et al., Brain, 2006)

Self Monitoring Scale



Regions where social self-monitoring score positively correlates with tissue density

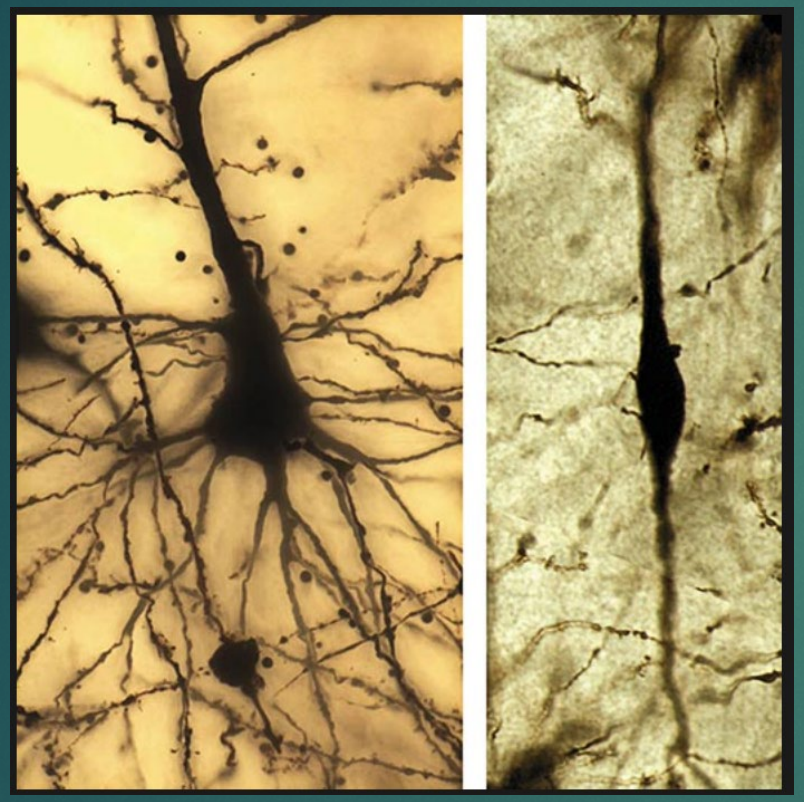


Frontal Temporal NCD

- All FTD phenomena share:
  - Presenile presentation
  - Incipient course of degeneration of the frontotemporal lobes
  - Normal EEG
  - No pronounced white matter alterations

B. Miller, 2007; Seeley, 2008

Von Economo Neurons:
Brain Cells for Socializing?



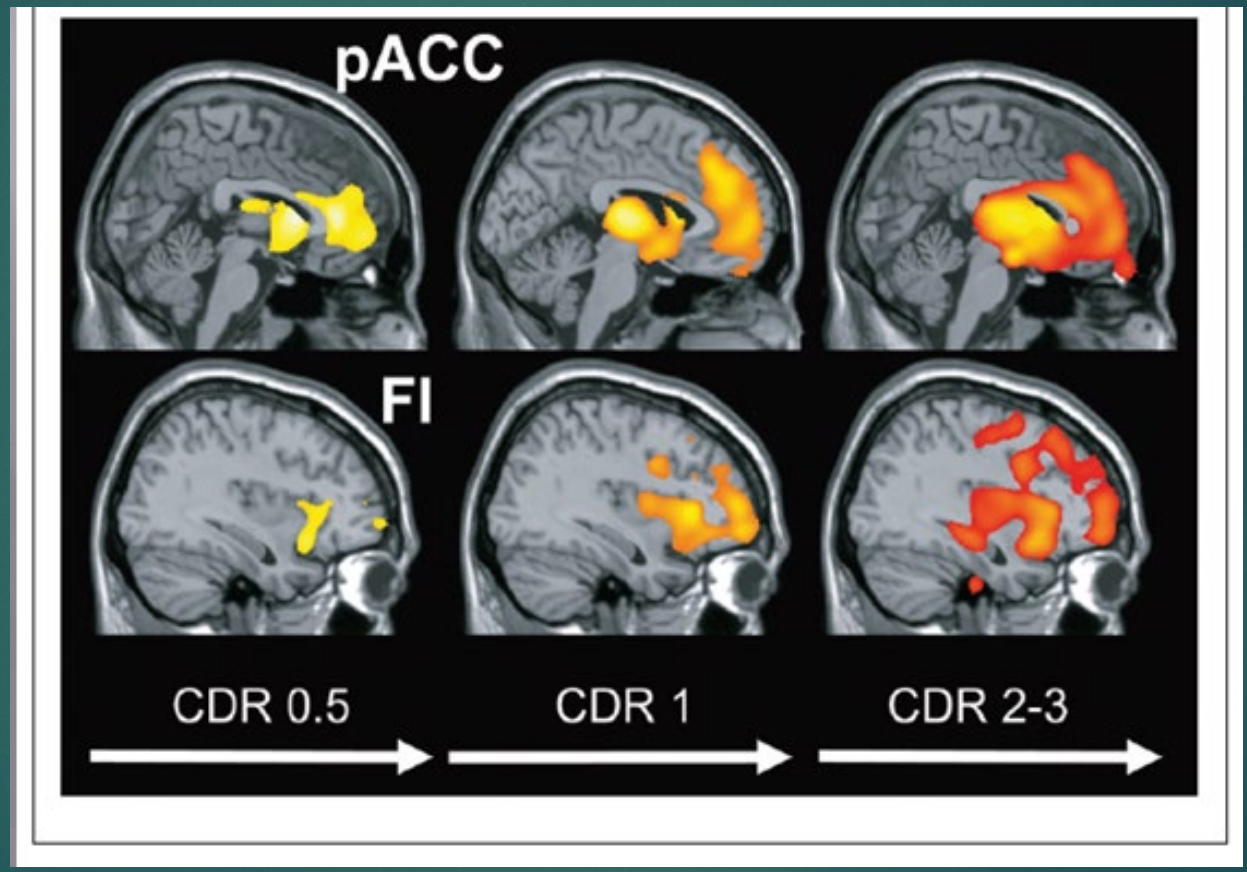
A focal concentration of VENs in Anterior cingulate and Frontal Insula distinguishes large-brained, highly social mammals (primates, elephants, cetaceans) from other mammalian species.

(Allman et al., 2010; Hakeem et al., 2009; Hof and Van der Gucht 2007; Nimchinsky et al., 1999; Rose 1928)

Location of FTD degeneration

- Von Economo & Fork neurons are primary site of degeneration in pACC and Frontal Insula
- FTD: 70 percent of VENs destroyed
- VEN & Fork neuron degeneration predicts overall behavioral symptom severity in FTD & NPI impulsivity
- More R than L

bvFTD degeneration: (emotional) Salience Network (Right pACC and FI)



W. Seeley, J. Zhou, and E. Kim, 2011

Core Brain Networks Underlying Feeling Emotions

Salience Network: Alertness to socioemotional cues

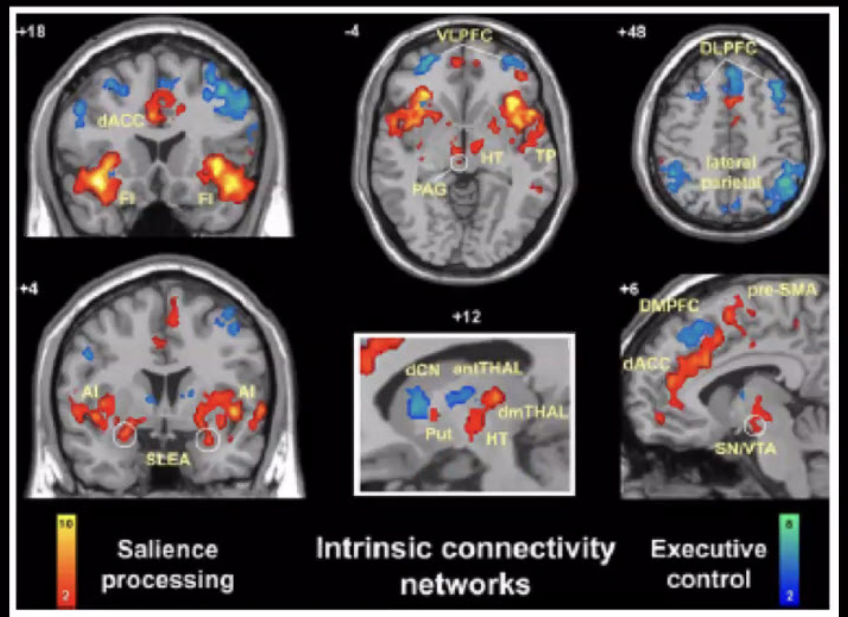


Figure 2. Separable intrinsic connectivity networks revealed by independent component analysis. The salience network (red-orange colorbar) is anchored by paralimbic anterior cingulate and frontoinsular cortices and features extensive connectivity with subcortical and limbic structures. In the executive-control network (blue-green colorbar), the dorsolateral frontal and parietal neocortices are linked, with more selective subcortical coupling. Functional images are displayed as in Figure 1. AI, Anterior insula; antTHAL, anterior thalamus; dCN, dorsal caudate nucleus; dmTHAL, dorsomedial thalamus; DMPFC, dorsomedial prefrontal cortex; HT, hypothalamus; PAG, periaqueductal gray; Put, putamen; SLEA, sublenticular extended amygdala; SN/VTA, substantia nigra/ventral tegmental area; TP, temporal pole; VLPFC, ventrolateral prefrontal cortex.

Why is the SN important for feeling?

Decides what is important for the organism

- Integrates pre-processed sensory data from the environment with visceral "markers" help organism quickly attend to and allocate resources to what is important
- Safety, health, and survival
- For social animals, survival involves achieving and maintaining adequate social status and support

Tuning of network is important:

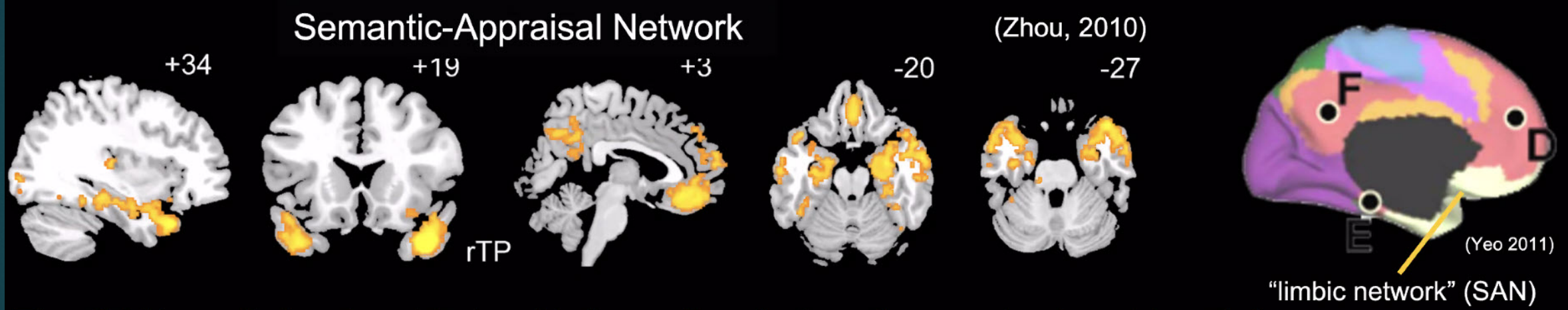
- SN connectivity too high = anxiety (Seeley, 2007)
- SN connectivity too low = socially insensitive, poor social skills (Toller 2018)

Cingulo-insular network:

- anterior insula
- anterior cingulate
- lateral orbitofrontal
- amygdala
- thalamus
- peri-aqueductal gray

Core Brain Networks Underlying Knowledge

Semantic Appraisal Network: Emotional tuning of semantic information



The SAN mediates two kinds of information (primarily acquired, not innate):

1. learned knowledge about the world (semantics)
   - anterior temporal lobes (medial seed)

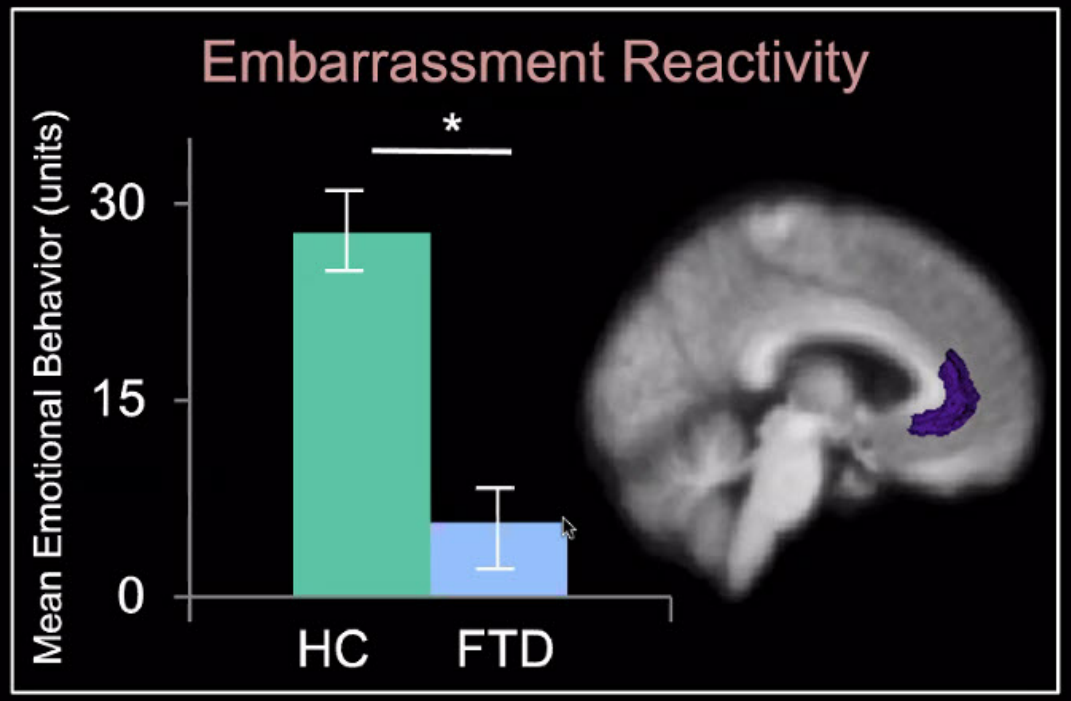
2. acquired personal likes/dislikes (evaluations)
   - subgenual cingulate cortex
   - ventral striatum (caudate & nucleus accumbens)

Profound loss of pleasure related to FTD

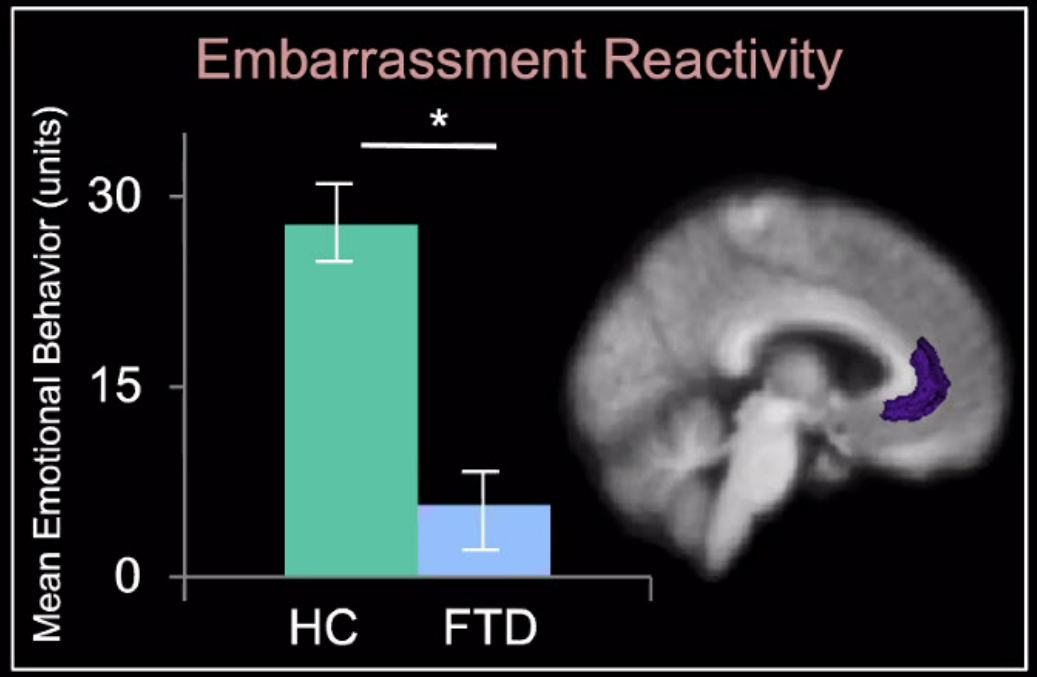
- Loss of pleasure has been revealed as a key feature in early-onset dementia (FTD), in contrast to Alzheimer's disease. - Scans showed grey matter deterioration in the pleasure system of the brain.
- There is degeneration in frontal and striatal areas of the brain related to diminished reward-seeking, in patients with frontotemporal dementia (FTD).
- importance of considering anhedonia as a primary presenting feature of FTD

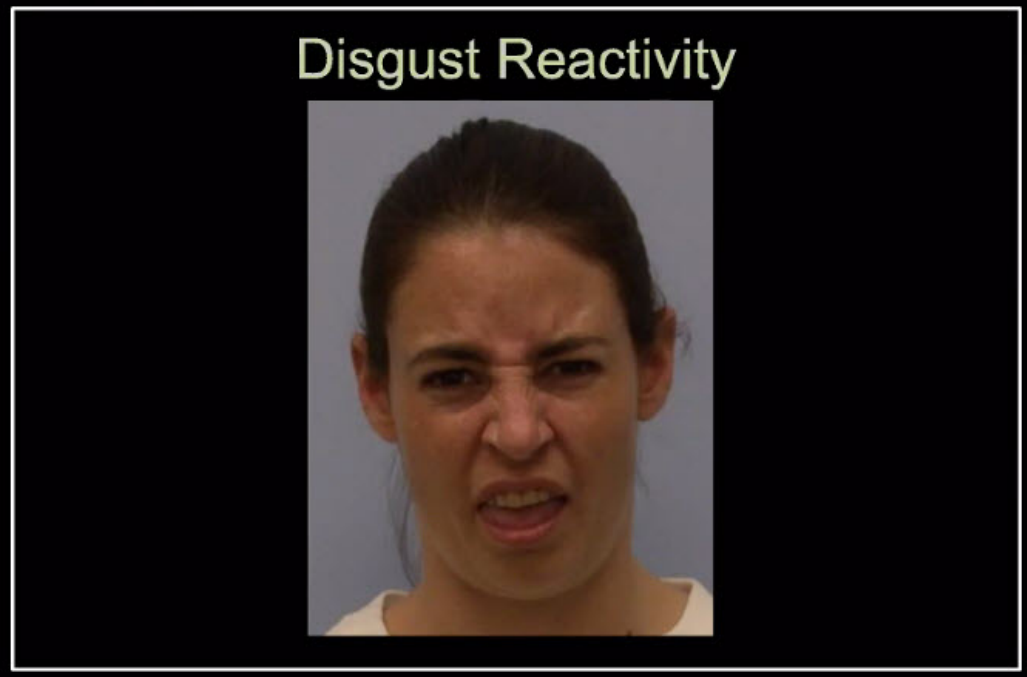
Cherie Strikwerda-Brown, et al., 2021

Autonomic Deficits in bvFTD

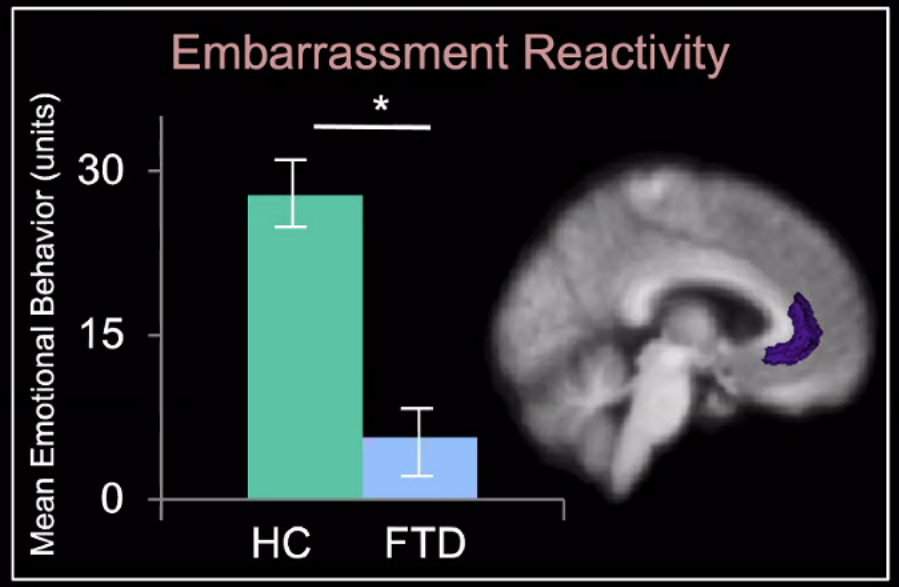


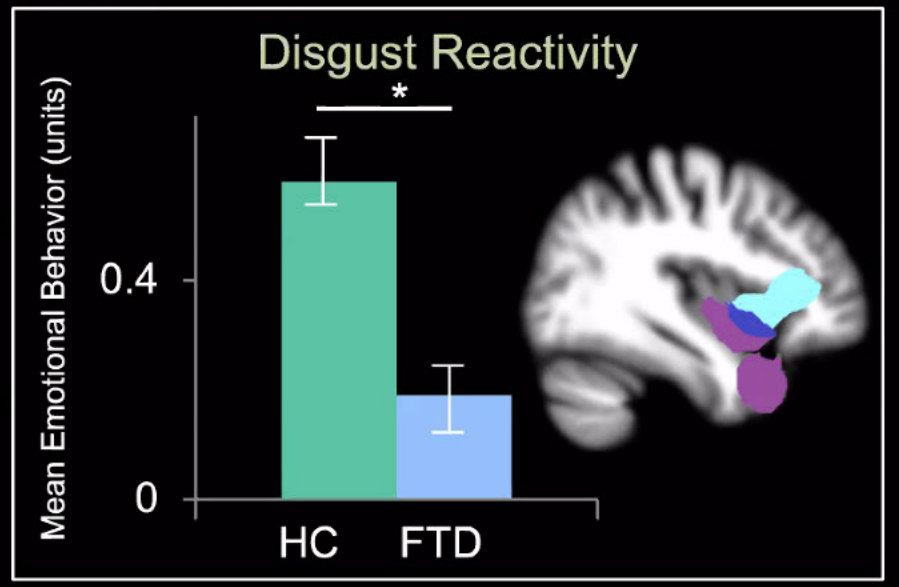
Autonomic Deficits in bvFTD





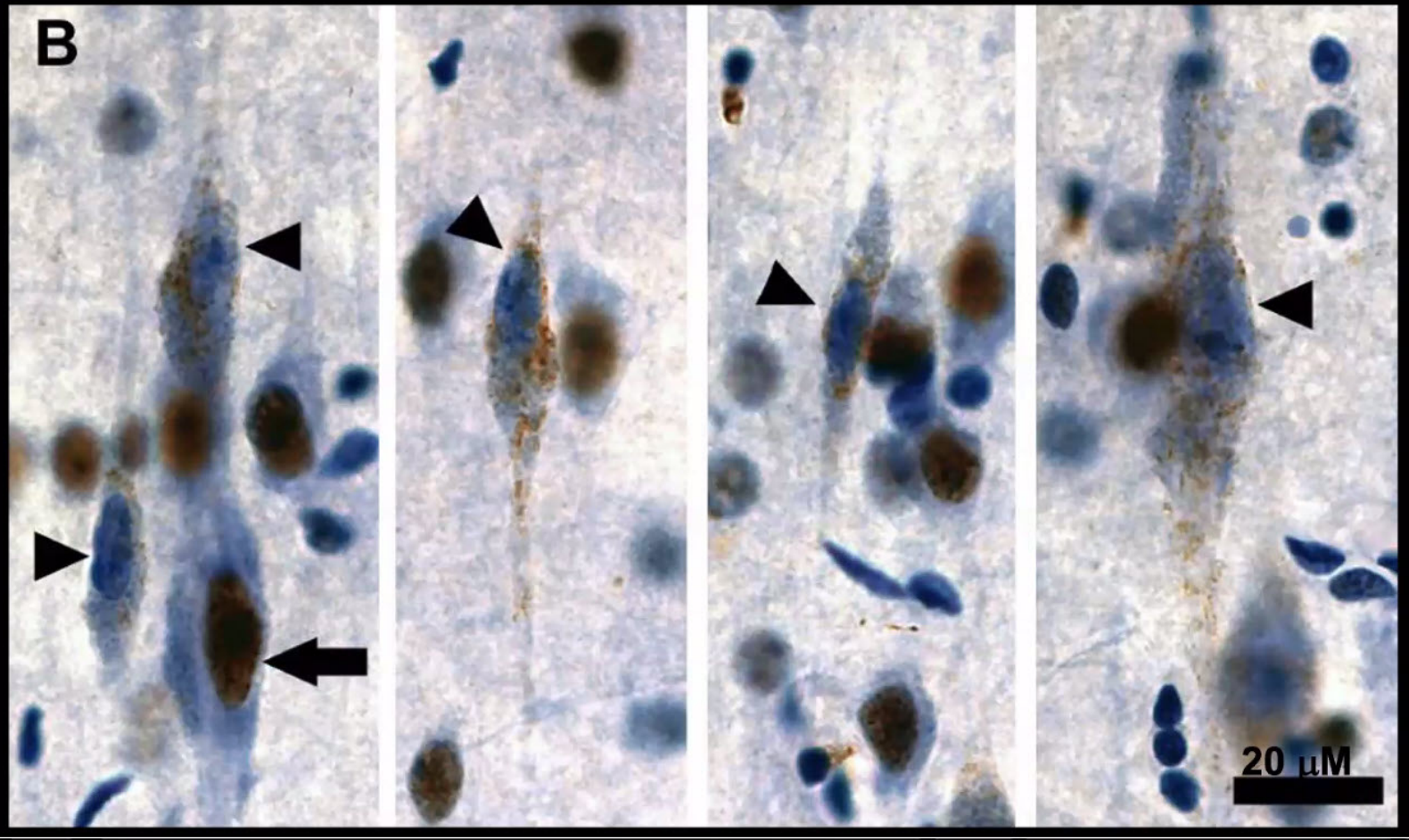
Autonomic Deficits in bvFTD

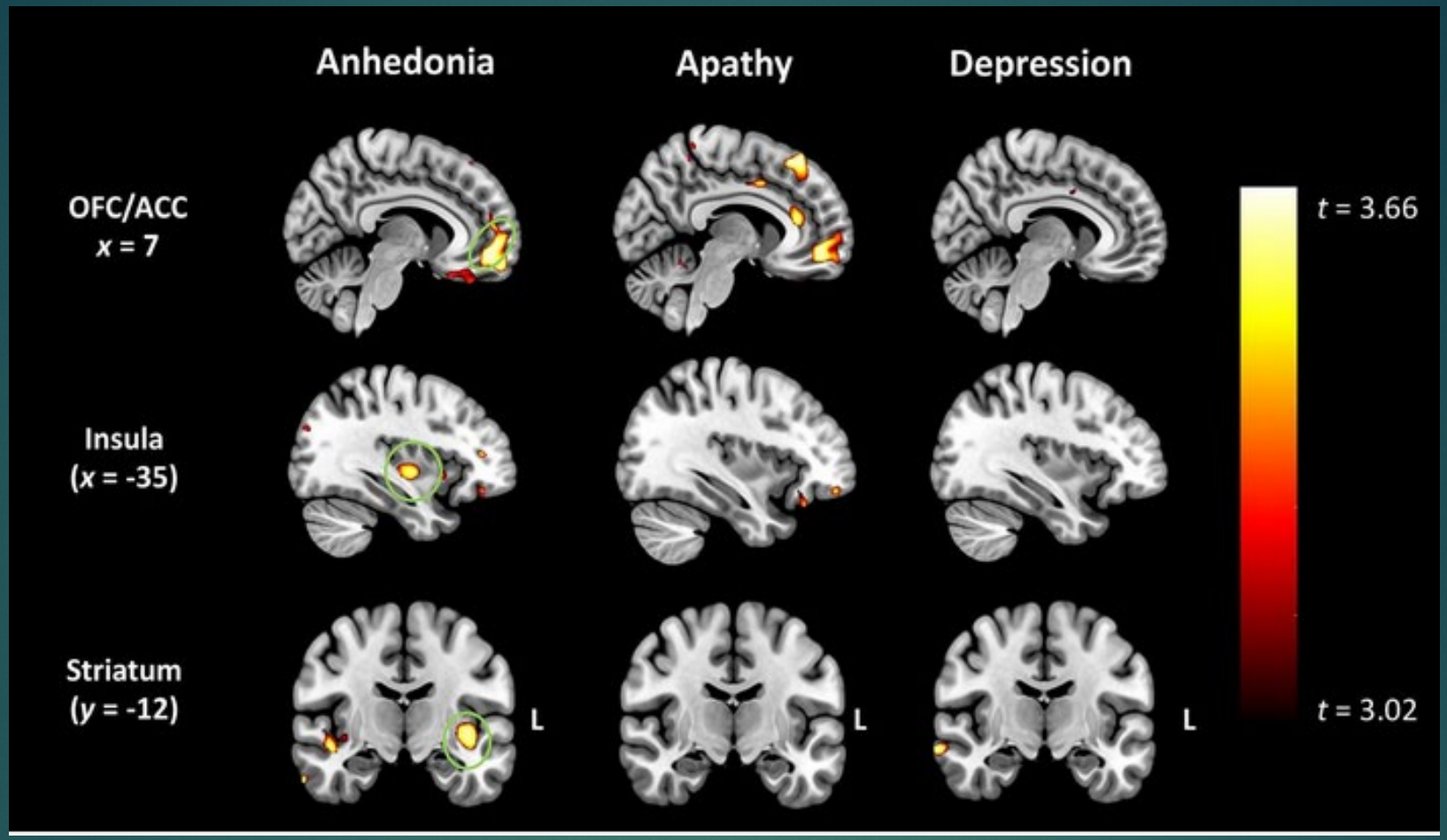




Early FTD: Speckled TDP-43 Inclusions

Right FI, FTLD-MND, Broe Stage 1





Neuroimaging findings show grey matter intensity decreases related to anhedonia, apathy and depression. Anhedonia in FTD was related to degeneration of the regions circled in green, which are 'hedonic hotspots' (related to reward-seeking) in the brain.

Pain & Temperature & Insula

- FTD respond to music, humor, art, and even sarcasm, in an off manner.

- Early abnormalities in their ability to feel or process pain or changes in temperature: All patients with disturbed temperature or pain awareness had atrophy in their right posterior insula

- People with semantic dementia tended to have exaggerated responses, often complaining of cold or pain, for example.

Sarcasm & Reading Emotions ↓↓

- A defunct “sarcasm radar” correlated with decreased integrity of the uncinate fasciculus, a white-matter tract that connects regions of the limbic system to those in the cortex.

- A patient’s inability to read emotions in others correlated with an erosion of white-matter tracts emanating from the thalamus and the fornix.

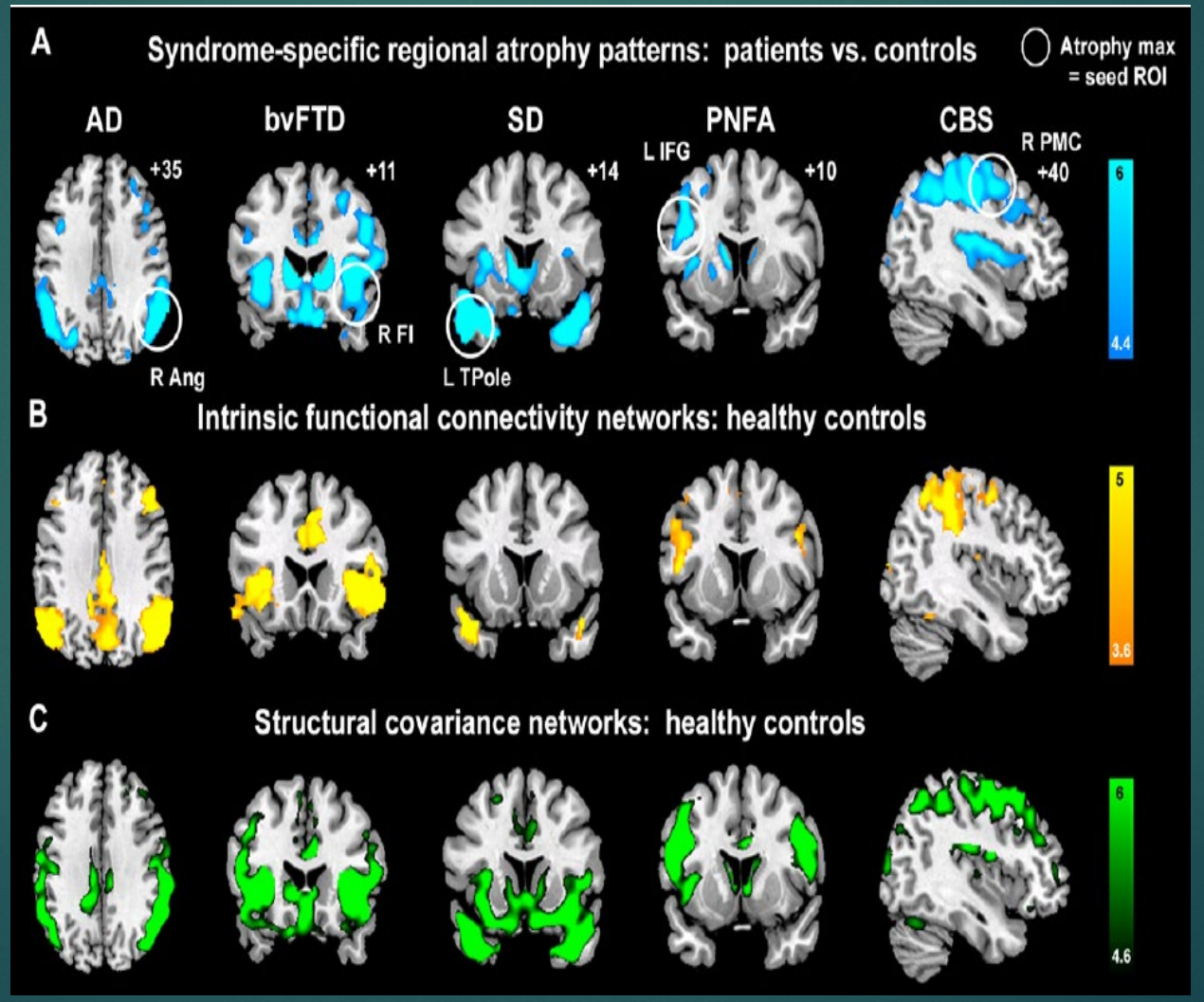
- FTD respond to music, humor, art, and even sarcasm, in an off manner.

- Early abnormalities in their ability to feel or process pain or changes in temperature

AD & 4 FTD+: Syndrome-Specific Regional Atrophy Patterns: can diagnose based on which connectivity system atrophies

Atrophy location

Normals



SN and DMN Networks

- Salience Network (FI & dorsalACC); correlates with anxiety
- DMN inversely related to SN: lesion of either one affects other
- AD decreases DMN & increases SN connectivity
- The right Salience Network targeted in bvFTD: lost in early bvFTD

SN and DMN Networks

- Loss of contextual appropriateness of a behavior

- Know social norms, but can't follow them; acquired sociopathy, social dysdecorum
  - Pick nose publicly, ask age, massage in church, inappropriate jokes, tell end of movie, tell you are fat

Semantic variant Progressive Primary Aphasia

- Semantic var PPA affects left semantic network; shows progressive atrophy in early-stage PPA language disorder

- Loss of what things are: loss of word and object meaning, i.e. what is a cat

4th Network: PNFA – Progressive nonfluent aphasia

- Nonfluent, effortful, and agrammatic speech
- The PNFA-targeted left language network
- Language and motor systems that enable speech fluency

Early FTD symptoms

- FTD starts with behavioral decline long before cognitive decline
- Early bvFTD affects social ability/Salience Network:
  - Insula, Anterior Cingulate, VM Orbital Frontal, Frontal Pole
- But not cognitive DLPF (until much later); NP tests look normal in early bvFTD
- Become socially ostracized
- Loss of facial recognition

FTD Syndromes Progression: Similar end

- In most patients, first symptoms involved semantics, behavior, or both.
  - Semantic loss begins with anomia, word-finding difficulties, and repetitive speech,
  - Early behavioral syndrome is characterized by emotional distance, irritability, and disruption of physiologic drives (sleep, appetite, libido).
  - After an average of 3 years, patients also develop whichever of the two initial syndromes--semantic or behavioral--that they lacked at onset.

(Rascovsky et al., 2011; Khan et al., 2012).

FTD Common Features

- Onset before age 65 (35-70)
- Positive family history of similar disorder in 1st degree relative in 50%
- Show up in Psychiatry not medicine; decline in social conduct; most difficult for families
- Presentation of a progressive language or behavioral disorder
- No amnesia or marked visuospatial deficit
- Later alteration in attention, initiation, executive functioning
- Often asymmetrical
- Apathy, change in eating habits, and disinhibition are great distinguishing factors between psychiatric disease and bvFTD

FTD Neuropsych Profile

- Deficits in executive tasks

- Relative sparing of episodic memory
  - Preservation of episodic memory relative to executive dysfunction;

- Relative sparing of visuospatial skills

- Exhibits significant functional decline: cannot maintain gainful employment or live independently.
- Compulsively binged/carbo loading, consuming large quantities of food after reporting appropriate satiety.

Evidence

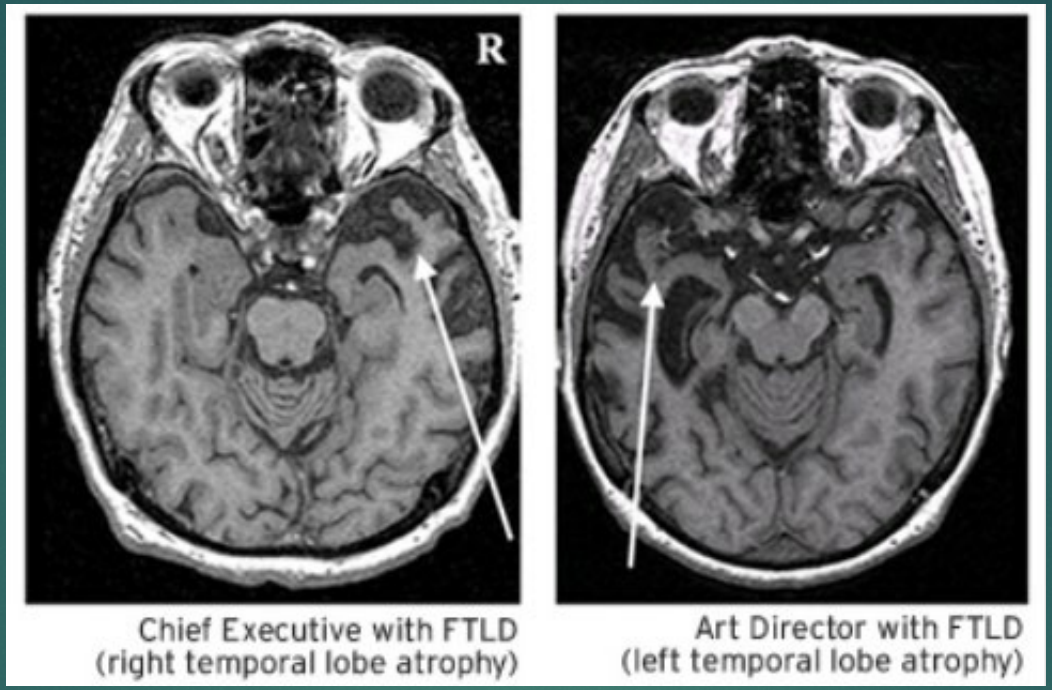
- C. Imaging & genetic results consistent with bvFTD:
  - Frontal and/or anterior temporal atrophy on MRI or CT
  - Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT
  - Autosomal dominant bvFTD may be caused by mutations in several genes,

Sxs Progression

- bvFTD: addictive behaviors, personality change (submissive or disagreeable), decrease concern for others, overeating, apathy

- svPPA:
  - Left sided: word finding (often names)
  - Right sided: recognition of facial emotion, familiar faces, empathy decreased

Prior Occupation may predict side of atrophy



Patients with professions rated highly for verbal skills, such as school principals, had greater tissue loss on the right side of the brain, whereas those rated low for verbal skills, such as flight engineers, had greater tissue loss on the left side of the brain..

"The disease appeared to attack the side of the brain that was the least used in the patient's professional life

Nathan Spreng, 2010

Proportion of First Symptoms

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

Use of Profanity in FTD

- Tell me as many words beginning with the letter F.
- Words produced during FAS letter fluency testing were reviewed, and instances of the use of "fuck," "ass," and "shit" and other words felt to be inappropriate were sought.
- 19% patients with FTD generated the word "fuck" during the "F" trial as opposed to none of 38 patients with AD
- Patients who said "fuck" had diagnoses of either behavioral variant FTD (3/15), progressive nonfluent aphasia (2/8), or semantic variant PPA (1/3).

Ringman, et al., 2010

Neuropsychology of FTD

- Memory: semantic ↓, intrusions & false + ↑
- Attention: ↓
- Executive: ↓
- Boone: Right vs. Left FTD

  (82% asymmetry):

  Right ↓: emotional klg ↓, PIQ ↓,

  Design Fluency ↓, WCST ↓,

  Facial emotion. ↓

  Left ↓ : VIQ ↓, FAS ↓, BNT ↓, Stroop ↓

Treatment of FTD

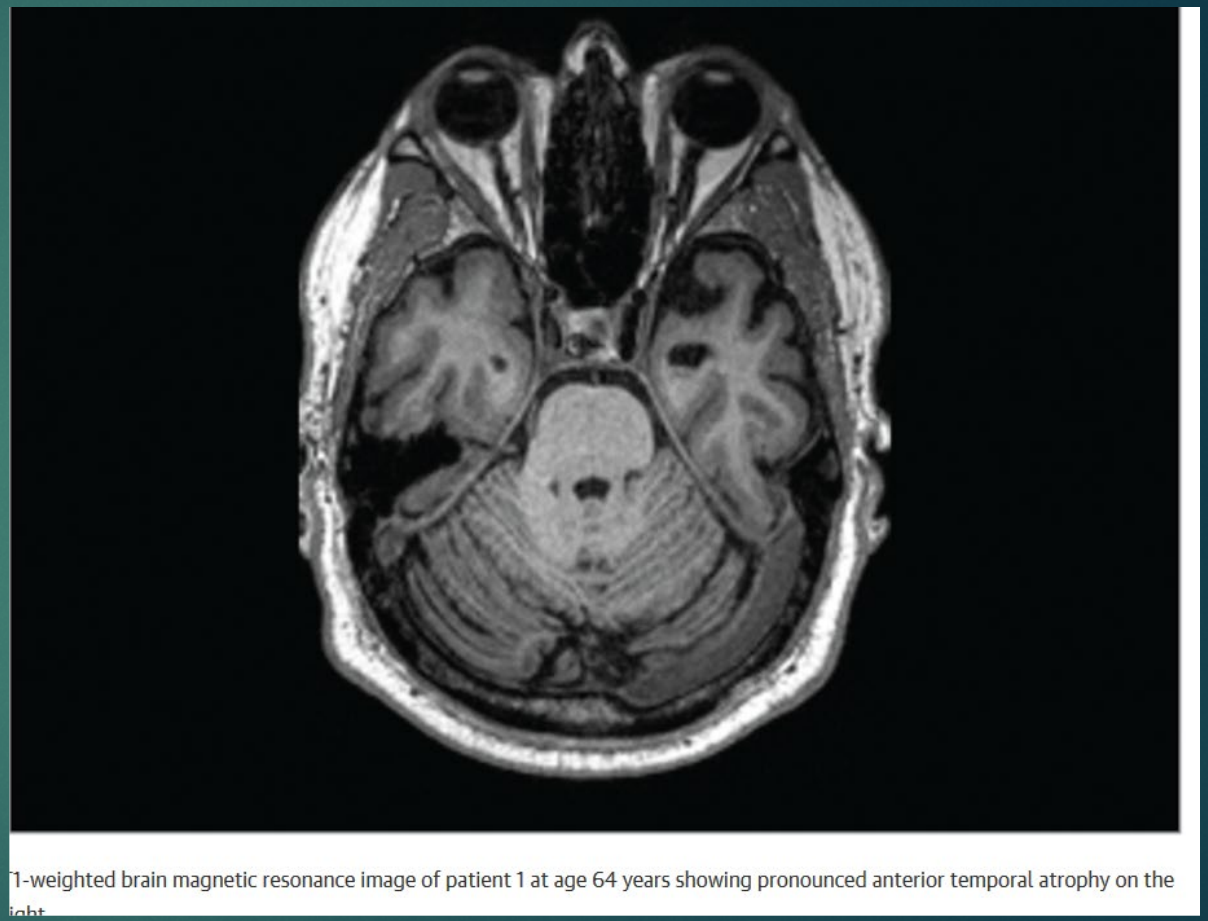
- No drugs approved specifically for FTLD exist.
- Rather, some patients with behavioral symptoms take antidepressants with modest success
- Patients with parkinsonian symptoms often are prescribed levodopa, but typically do not respond to it.

Criminality

- Common manifestations of criminal behavior in the bvFTD group
  - bvFTD: theft, traffic violations, sexual advances, trespassing, and public urination
  - AD: commonly committed traffic violations, often related to cognitive impairment.

- The appearance of new-onset criminal behavior in an adult should elicit a search for frontal and anterior temporal brain disease and for dementing disorders.

Artistic flowering: patients with FTD who experience a sudden onset increase in artistic creativity

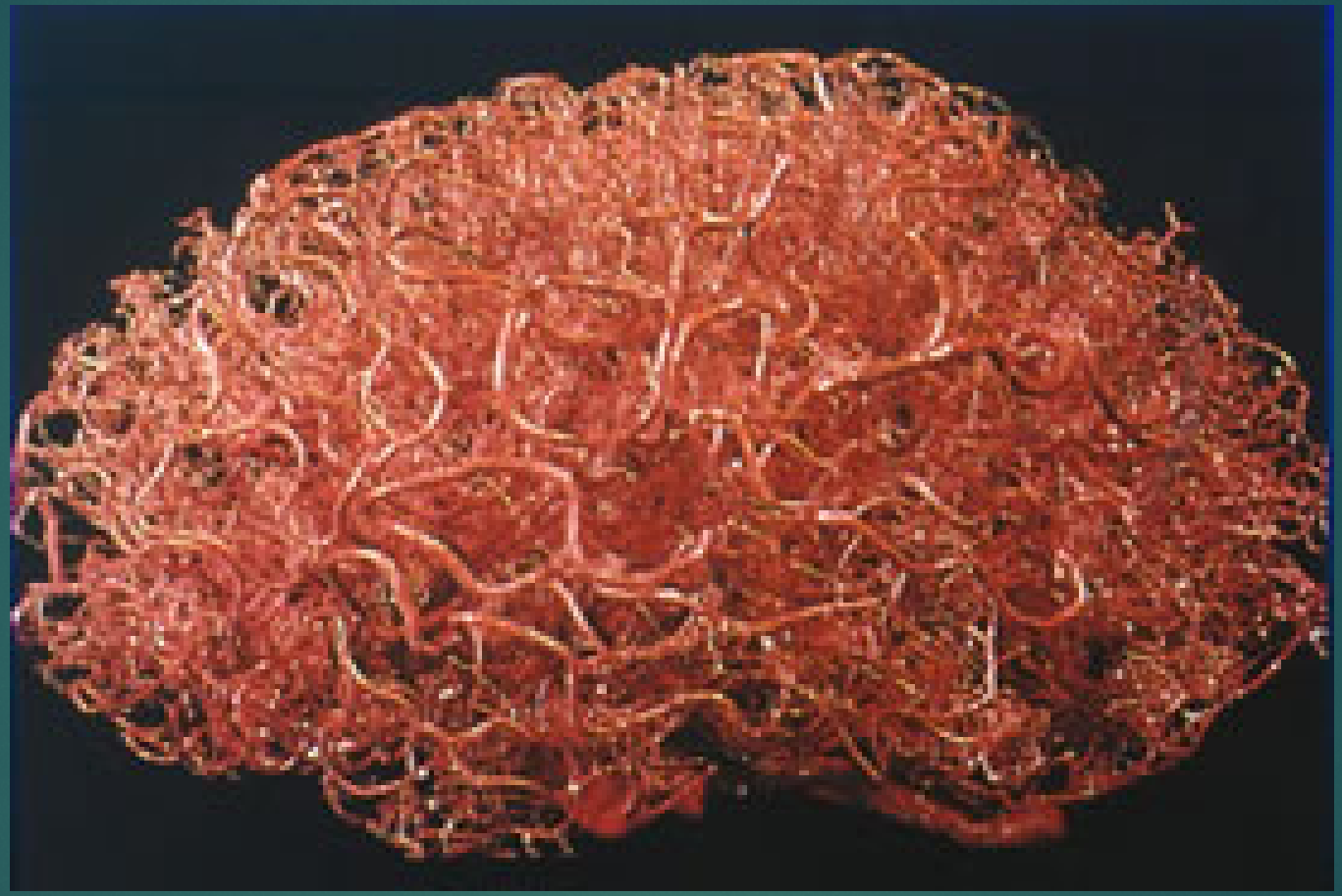


T1-weighted brain magnetic resonance image of patient 1 at age 64 years showing pronounced anterior temporal atrophy on the right

Michael G. Erkkinen, et al., JAMA, 2018

Vascular NCD

Small and Large Vessel Vascular Supply



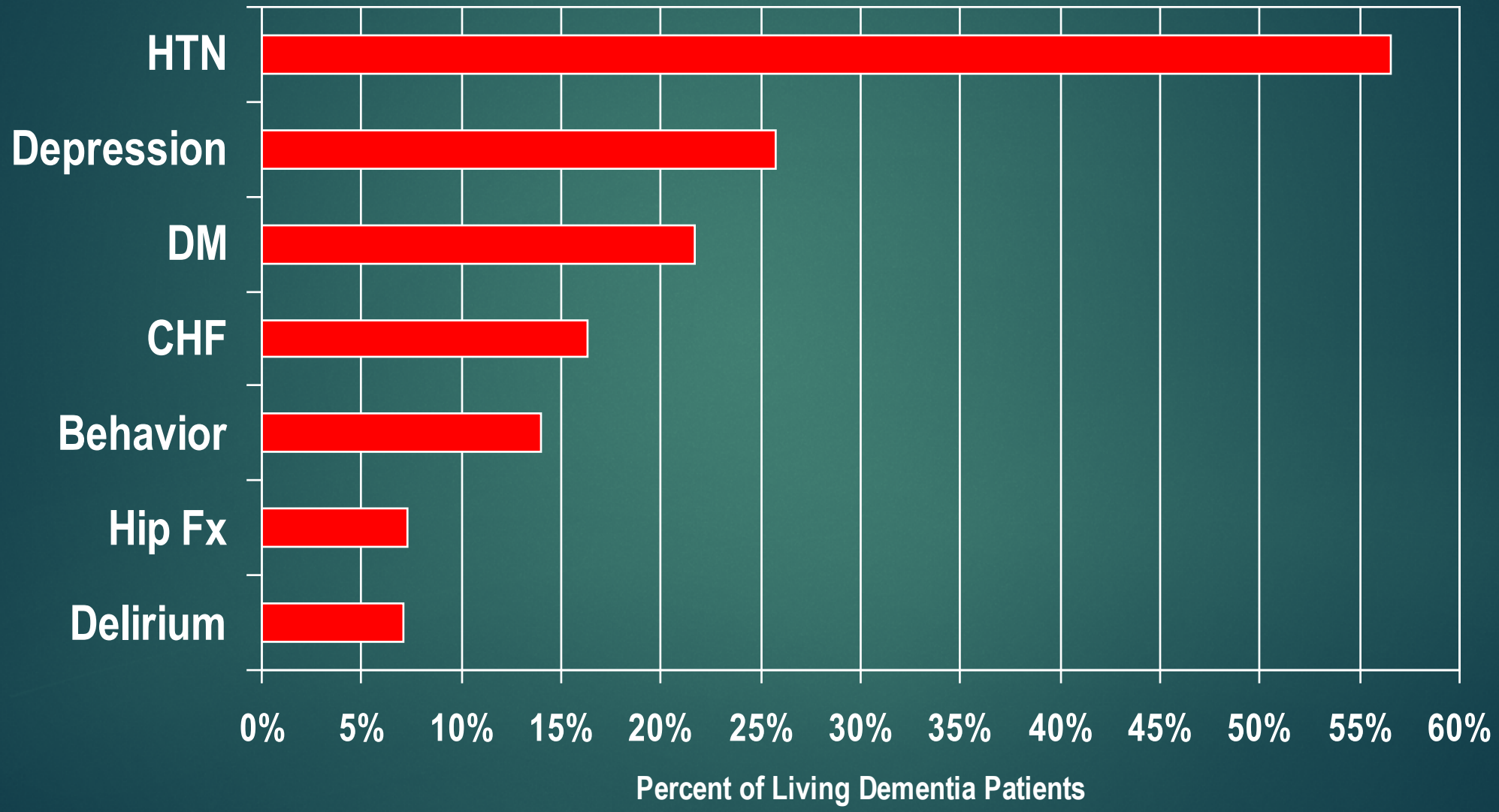
Why what is good for the heart is good for the brain:
400 miles of blood vessels

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

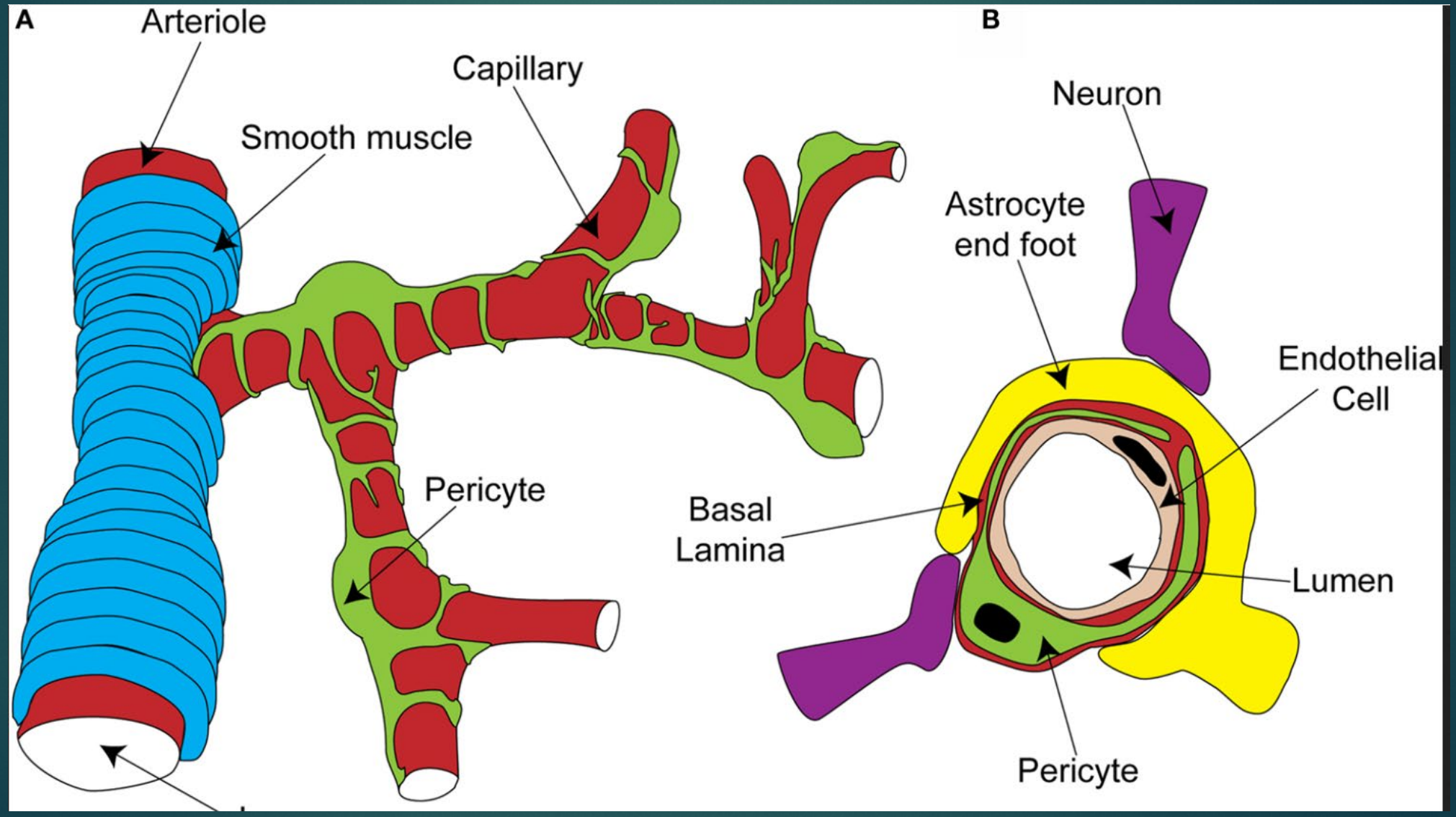
Vascular NCD

- A. Meet NCD criteria
- B. Clinical features consistent with vascular etiology:
  - Onset of cognitive deficits temporally related to 1 or more cardiovascular events
  - Evidence for decline is prominent in complex attention, processing speed, and frontal-executive function
- C. Evidence of the presence of CV disease from history, physical exam, or neuroimaging
- D. Not better explained by other syndrome

Co-Morbidities of NorCal NCD Pts



Pericyte: contractile cells on the capillary wall. Pericytes can modulate capillary diameter & blood flow in response to neuronal activity by constriction



Pericytes, BBB, & APOe4

- Pericyte loss causes white matter dysfunction
- Dangerous leaks: BBB woes in the aging human hippocampus
- Apolipoprotein E (*APOE*) and brain vasculature damage

Hypertension is the curse of the brain

- Hypertension slowly disables the brain's micro vessels, rendering them unfit to adjust blood flow to suit the brain's needs.
- It raises the risk of stroke.
- Impairs the brain's ability to locally increase perfusion where the brain is most active, leading to cognitive decline.
- Reduced cerebrovascular blood flow is directly related to mortality—it is as if the brain is running out of breath

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

Post-Stroke Dementia

- Post-Stroke Dementia doubles risk of dementia in decades after stroke
- More severe the stroke, greater the dementia risk: 30% in 6 m to 5 y period
- Especially hemorrhagic stroke
- Hypothesis: stroke causes chronic autoimmune inflammation which leads to dementia; a stroke induced immunodepression
- Those with immune state activation, have greater MoCA decline
- Cognitive impairment is common after stroke: 53% decline in PS, 45% in memory, 62% in 1 cognitive domain

Concept of NCD

- VD is comorbid with most AD
- After age, Vascular disease is largest risk factor for NCD
- The earliest cognitive manifestations of CV disease are changes in executive function
- MMSE systematically biased the literature in favor of the ascertainment of Alzheimer disease and to the exclusion of vascular disorders.

Diagnostic features of VaD

- History of TIAs (Transient Ischemic Attacks)
- History of vascular risk factors (HTN, CAD, CHF, DM, hyperlipidemia, carotid stenosis, lupus, obesity)
- Two types:
  - Multi-infarct – ischemic, large vessel infarcts
  - Subcortical white matter disease – white matter lesions, small vessel infarcts (Binswanger's)

Meta-analysis: Vascular Mild NCD

- The most common cause of vascular cognitive impairment is cerebral small vessel disease leading to diffuse subcortical white matter lesions.
- The greatest impairment was in processing speed, and the least affected being working memory and visuospatial construction.
- VD MCI show greater deficits in processing speed & executive functioning, while those with nv-MCI exhibited a greater relative deficit in delayed memory.

Brandon P. Vasquez & Konstantine K. Zakzanis, 2014

Neuropsychology of Vascular Dementia

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

Neuropsychology of Vascular Dementia 2

- Relative to AD, VD patients show:
  - poorer verbal fluency,
  - better free recall,
  - fewer intrusion errors
  - better recognition memory.

Treatments

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.

Current AD Drug Therapies

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

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

NCD Treatments

- Cholinesterase inhibitors (acetylcholine deficit; cholinergic enhancers) – Aricept, Exelon, Reminyl;
- Improves attention, ADLs: Inhibitors basically increase the availability of intrasynaptic acetylcholine
- Aricept or Exelon if hallucinations in AD or LBD
- Aricept: 1 year sig. diff. from placebo; no diff. at 3 years; prefrontal activation on SPECT; cost = generic Aricept, Donepezil, for $110 a year
- Memantine (Namenda): Glutamate channel blocker; only for AD
- Combination of Aricept & Namenda appears to work best

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:
  - having permanent pacemakers implanted
  - 18 per cent increased risk of hip fractures.

NCD Treatments 2

- All medications for treatment of behavior problems in AD are off label usage
- Avoid anticholinergics; benzos (cog ↓↓, hip fx, falls = shot of whiskey)
- All antipsychotics in AD have black box warning: increase CVA, stroke, death; all are sedative; Risperidone for behavioral agitation
- Best for agitation: Dextromethorphan (in cough syrups) – glutamate inhibitor
- Pimavanserin (Nuplazid) (1st non dopaminergic antipsychotic)– for PD or LBD psychosis
- No meds for hypersexuality (except for pillow clothes; zipper in back)

NCD Treatments 2

- AD:
  - Belsomra, in patients with mild to moderate AD, prolongs slumber, with more overall sleep time and shorter bouts of nighttime wakefulness than placebo
- CVD:
  - aspirin, HTN medications
  - Be careful with Aricept (11 deaths in n=974 study of vascular NCD)

- LBD:

- No anti-psychotics (induce Parkinsonian sxs; sudden death)
- Avoid anticholinergics (induce delirium)
- Use anti-cholinesterase (Aricept) (reduces visual halluc.)
- SSRIs help reduce hallucinations

NCD Treatments 3

- FTD: serotonergic deficit
  - (marked loss of postsynaptic serotonin)
  - Avoid Aricept (agitates) or Namenda
  - Try SSRIs or Trazodone: reduces irritability & compulsions
  - Behavioral management
  - PNFA: speech therapy, SSRI for depression

- The long-term use of antipsychotic medications in patients with Alzheimer's disease - appears to nearly doubles rate of death after one year;
- No FDA approval for any antipsychotic in major NCD

Prion Disorders:

Transmissible Spongiform Encephalopathy (TSE)

&

Creutzfeldt-Jakob NCD (CJD)

Prion: abnormally folded protein

Normal function of prions is memory consolidation

NCD Due to Prion Disease

- A. NCD criteria met
- B. Insidious onset & rapid progression of impairment common
- C. Motor features of prion disease present (myoclonus, ataxia, or biomarker evidence)
- D. NCD not due to another condition

TSE

- Non-Human:
  - Scrapie in sheep, Mink, Deer/Elk (Wasting Disease)
  - Cattle (Bovine Spongiform Encephalopathy = Mad Cow Disease)

- Human (same polypeptide; shape determines which neurons killed):
  - Kuru (New Guinea, endocannabilism, wives cook brain; eye infections)
  - Creutzfeldt-Jacob Disease (CJD) (Slovakia, Sephardic Jews) (cortex)
  - Gerstmann-Straussler-Scheinker Disease (GSS) (cerebellum)
  - Fatal Familial Insomnia (FFI) (thalamus)

Transmissible Spongiform Encephalopathy (TSE) 4

- Use Universal Precautions
- **Iatrogenic:**

- Infection via: corneal transplant, neurosurgery, dura mater graft (cadaver), growth hormone (cadaver), gonadotrophin, EEG needles

- Onset: 9-16 years post infection; 15 year onset for subcutaneous injection

- Hard to kill: ineffective: steam autoclave, benzene, ethanol, formaldehyde, radiation

Creutzfeldt-Jakob NCD (CJD)

- Prevalence: 1% of NCD, 1 in a million
- 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 (20-90); 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)
- "Alzheimer's in fast forward"

Symptoms of CJD

- Triad of symptoms:
  - NCD,
  - Involuntary movements (esp. myoclonus),
  - Specific EEG activity (periodic sharp, often triphasic, discharges of .5-2 Hz)

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

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

Chronic Traumatic Encephalopathy

Chronic Traumatic Encephalopathy

- TBI is risk factor for NCD
- Long term effects of 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 NCD
- Motor neuron disease (ALS) in some

Ann Mckay, New England VA Neuropathology Lab

CTE starts in high school

- 60,000 concussions per year in high school football
- Owen Thomas, 21 yo; suicided; 12 years of hs and college football; no concussions; CTE visible on slide
- 2009 Purdue study: 2 hs football teams; helmet sensors; no concussions in 1 year season
  - Subconcussive syndrome: more hits, more (50%) cognitive decline during season
- 2017 Jama (Mez, et al.,): CTE in 87% of donated brains (177/202) (48/53 college; 111/112 NFL); retrospective; sickest NFL players
- Major research problem: no normative data; comorbidities (opiates, Etoh, growth hormones, etc.)
- Need prospective studies

Subcortical NCDs

Subcortical NCDs

- Huntington's
- Parkinson's
- Progressive Supernuclear Palsy
- HIV
- Multiple Sclerosis
- Severe Depression

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

Cortical vs. Subcortical NCDs

Cortical	Subcortical
Alzheimer's	**Parkinson's, Huntington's, HIV**
Storage/Encoding Memory Deficit	Recognition > Spontaneous Recall Retrieval problem
Rapid rate of forgetting	Normal rate of forgetting
Intrusions	Normal
Semantic Knowledge decreases Animal worse than Letter fluency	Normal Letter fluency worse than Animal
Procedural/Implicit Memory WNL	Impaired

Neuropsychology of Subcortical NCDs

- Retrieval memory pattern: normal recognition memory
- Reduced processing speed
- Executive dysfunction
- Motoric deficits
- Impaired procedural memory

Parkinson's Disease

- Prevalence: 1% of > 65; males > females
- Causation: Lewy bodies in substantia nigra are pathologic hallmark
- Symptoms: akinesia (loss of motor initiation), tremor (resting, pill rolling), rigidity, paucity of movement, bradykinesia (slow), postural instability, gait abnormal
- NCD: 18-41% of PD; later the motor onset, higher NCD
- Often die of problems related to swallowing
- TX: Carbidopa/Levodopa (Sinemet®)

Parkinson’s Cognitive Decline

- The disease begins on average around age 60 and the risk of Parkinson's increases with age.
- About one-third to one-half of Parkinson's sufferers exhibit some signs of cognitive impairment at the time they are diagnosed, but over time virtually all patients will experience substantial cognitive decline.
- The motor symptoms of Parkinson's appear to be caused by decreased amounts of dopamine.
- Deficits in planning, making decisions and controlling their emotions, and often exhibit changes in personality as a result; not necessarily memory.

Parkinson's Disease:

- Over treatment of PD with dopamine agonists is known to induce abnormal economic decision-making, including compulsive gambling.
- Typical Cognitive Profile:
  - Retention of Problem Solving Abilities with only fluctuations in attention and processing speed
  - Intact learning and memory, although rapid retrieval is compromised
  - Visuoperceptual abilities may be variable
- Typical Emotional Profile:
  - Depressive symptoms reported or may appear
  - May appear apathetic or report apathetic symptoms.

Parkinson's Disease 2

- Motor disability: uncorrelated with cognition; correlated with depression
- Classic picture: facial expressiveness ↓, depression, cognitive slowing, VS & executive ↓, impaired free recall/normal recognition
- Memory: subcortical profile

  impaired free recall and normal recognition

  List learning < story learning

  Semantic coding ↓

  Mixed procedural memory: ok mirror reading; poor temporal order

Huntington's Disease

- Genetics: 50% autosomal dominant (chromosome 4 gene); 2 per 100 thousand
- Causation: atrophy of neostriatum (esp. caudate nucleus)
- Disruption of frontal-striatal circuits
- Onset: late 30-40s; 15-20 years duration
- Symptoms: behavioral and personality changes first; choreoform movements, mood ↓, subcortical cognitive decline
- Xenazine: 1st Treatment: shown to decrease chorea in the short-term, it also showed slight worsening in mood, cognition, rigidity, and functional capacity in clinical trials

Neuropsychology of Huntington's

- Severe executive deficit
- Attention deficit
- Free recall deficit; normal recognition
- Procedural memory impaired

Depression

- Wells, 1979:

  Pseudodementia of Depression

- Comordity with NCDs:

  AD 17-31%

  PD 50-90%

  IVD 30-50%

- Depression in the elderly is often early manifestation of NCD (35-79%), especially “vegetative” sxs

Depression is risk factor for Alzheimer’s

- Early life depression increases risk for Alzheimer's disease
- But depression does not increase during the early stages of Alzheimer's disease, refuting the idea that the Alzheimer's causes the depression, as some claim.
- 503 men and women, aged 60 to 90 at the study start and free of NCD. All were participants in the Rotterdam Scan Study After a six-year follow-up, 33 people developed NCD; 134 of the participants had a history of depression (88 early onset, 46 late).

Breteler, Neurology, 2008

No Depression in Alzheimer’s

- Numerous observational studies have found higher levels of depressive symptoms in old age to be associated with increased incidence of Alzheimer's disease and Mild NCD

- Data from the Rush Religious Orders Study, a cohort of 917 older Catholic clergy without NCD at study onset; 190 major NCD

- Depression is truly a risk factor for Alzheimer's disease rather than a subtle early sign of its underlying pathology. This study found no evidence of an increase in depressive symptoms during the prodromal phase before the clinical diagnosis of Alzheimer's disease.

Wilson, Arch Gen Psy, 2008

Depressive Behavioral Symptoms in Testing

- Use symptom validity test (Word Memory Test) to assess effort in depressed; if ok WMT, ok NP profile
- Lack of congruence between behavioral capabilities and cognitive deficits
- Lack of dressing apraxia; aphasia, agnosia, topographic disorientation
- Reversibility of cognitive deficits

Depression vs. NCD

Test Feature	Depression	NCD
Frequent task reminder	Unusual	Needed
Memory complaint	Extreme *	Infrequent
Rate of forgetting	Normal	Rapid
Incidental Memory	Intact	Impaired
Task effort	Poor *	Good
Memory cueing	Helpful	Unhelpful
“Don’t Know” comment	Usual *	Unusual
Recognition Memory	Intact	Impaired
Digit Span	>5	<5

Language variants of FTD

Next 54 slides

Progressive Primary Aphasia: PPA

- The other main form of FTD, primary progressive aphasia (PPA), starts with:
  - problems understanding speech (the semantic variant)
  - Or deficit in generating speech (the nonfluent or agrammatic form).

- Certain developmental language disabilities may render the brain's language network less resilient. Childhood dyslexia may make the brain more prone to logopenic subtype of PPA later in life.

Primary Progressive Aphasia

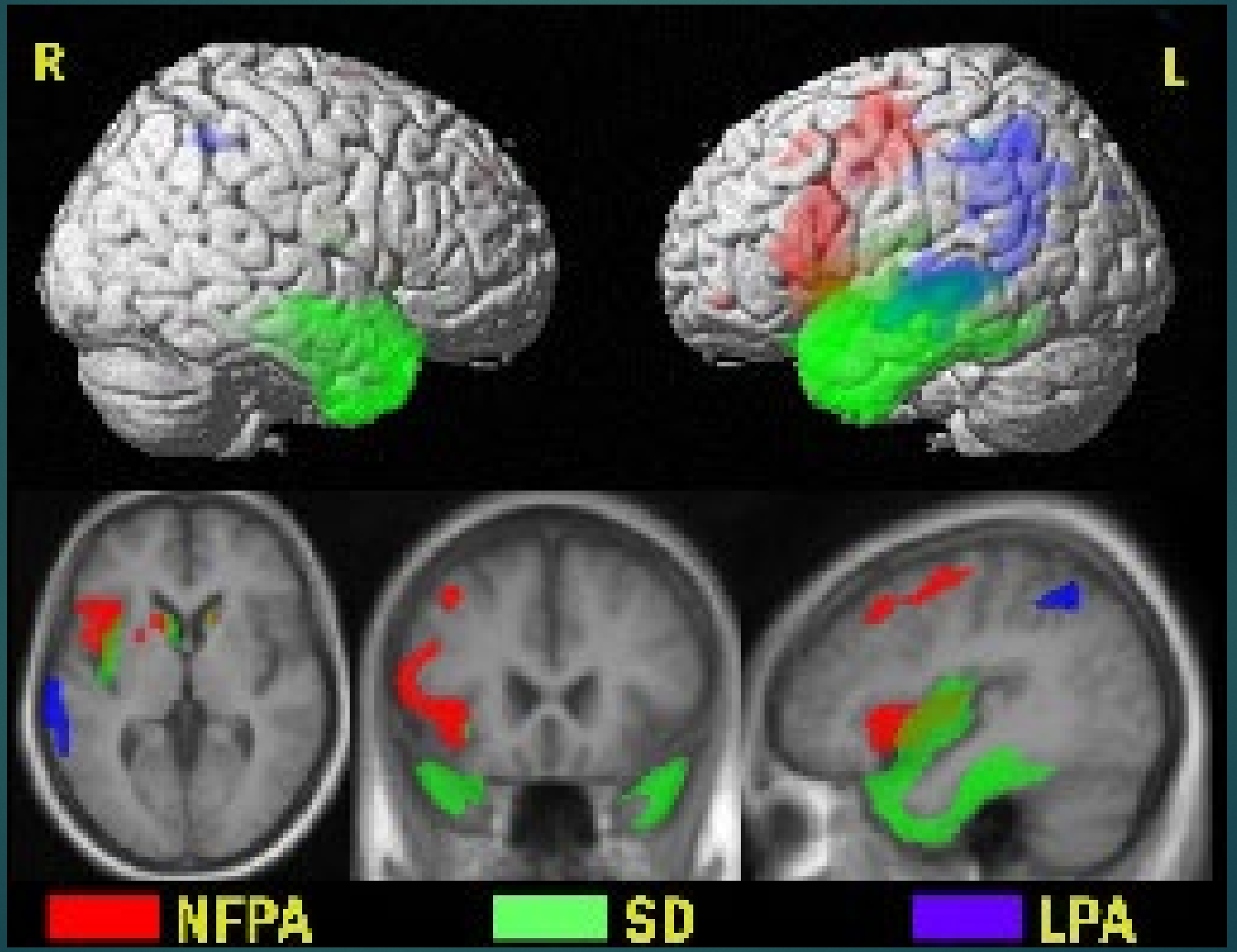
3 Subtypes of Primary Progressive Aphasia (PPA)

- Nonfluent/Agrammatic PPA
  - Formerly Progressive Non-Fluent Aphasia
- Semantic Variant PPA
  - Formerly Semantic Dementia
- Logopenic Progressive Aphasia

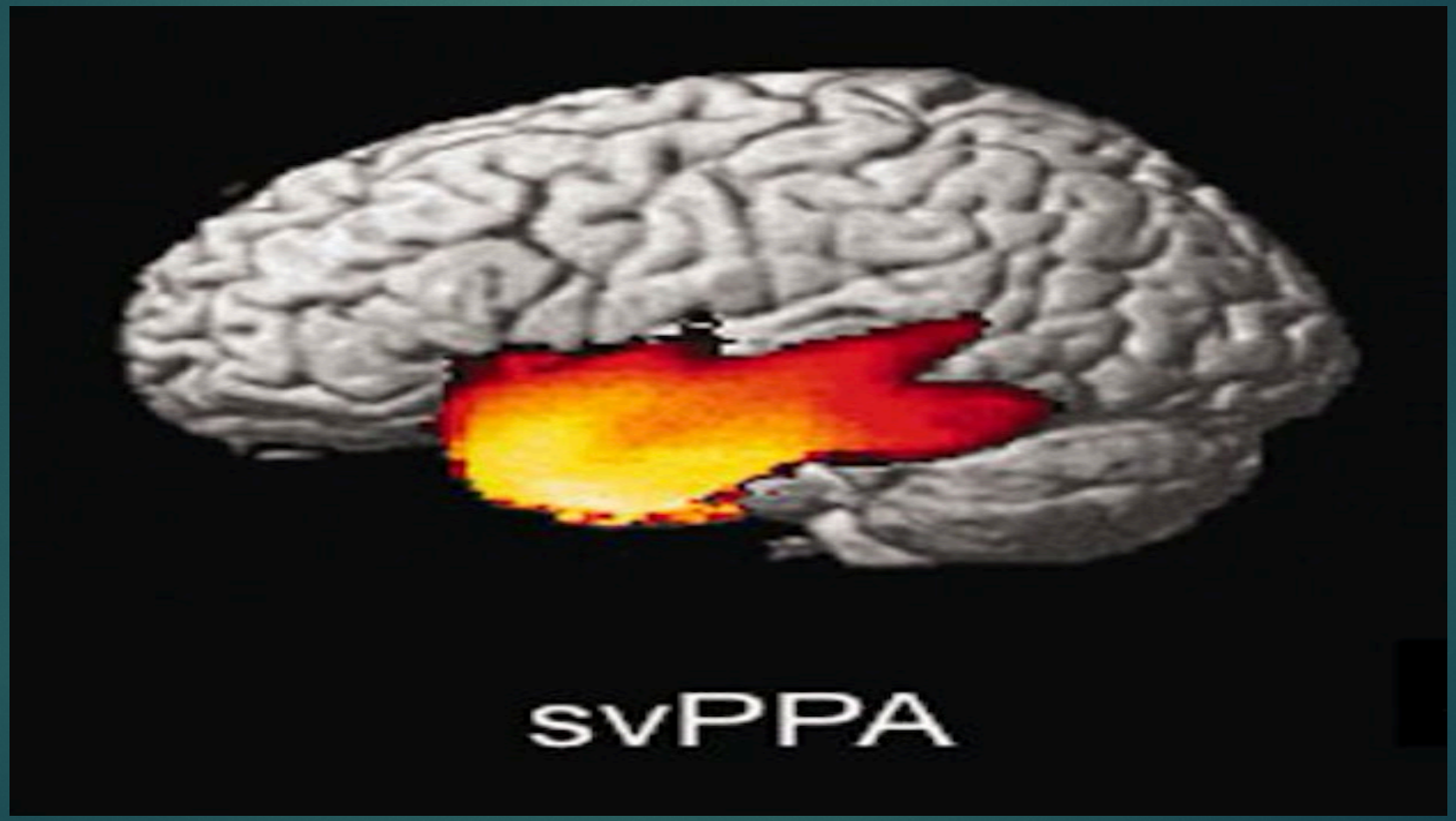
PPA: 3 varieties

- svPPA: Loss of semantic meaning
- nfvPPA: Nonfluent PA: speech apraxia, processing complex syntax deficit → FTD type pathology (L inferior F, insula)
- Logopenic: phonologic paraphasias -- AD

FMRI: NFPA, Sem var PPA, LPA



svPPA = temporal lobe



Neary Criteria for Semantic variant PPA

- Progressive fluent language disorder
- Loss of word meaning
- Semantic paraphasias
- And/or progressive perceptual disorder with prosopagnosia or visual agnosia

Asymmetric degeneration of R or L temporal

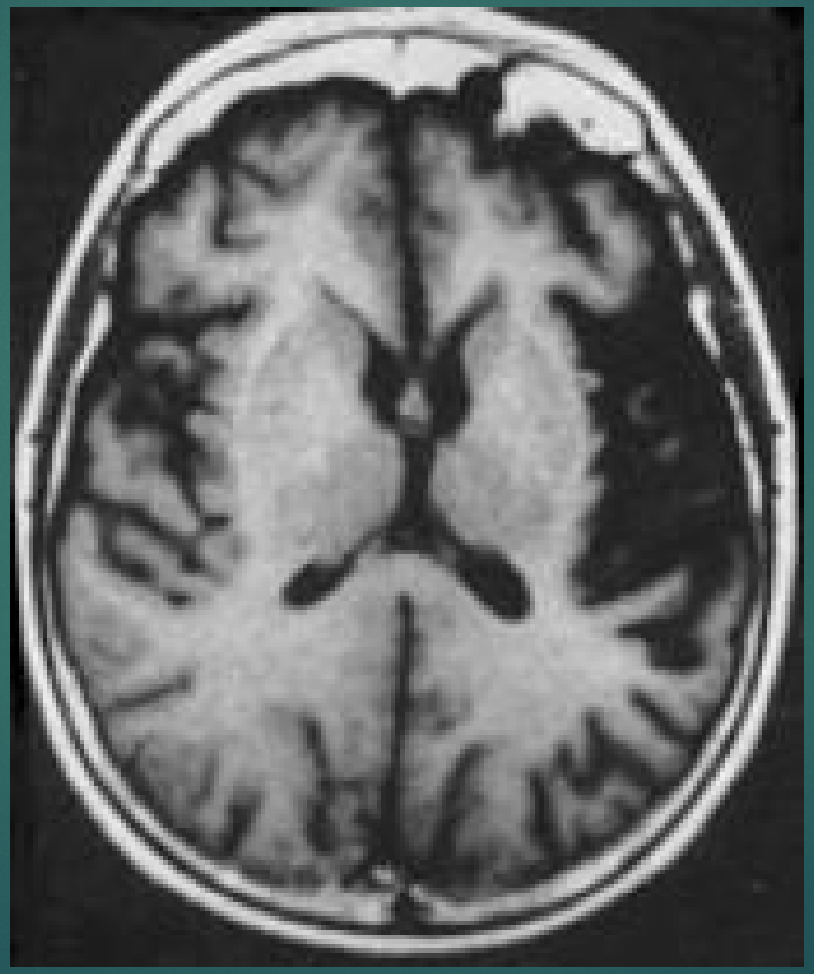
Semantic variant PPA (svPPA) 1

- Language disorder: impaired understanding of word meaning, object identity (visual agnosia), picture meaning
  - progressive, fluent, empty spontaneous speech
  - loss of word meaning: poor naming and comprehension
  - semantic paraphasias
- Anomia 1st, then word meaning loss, klg of what things are (recognition of sounds, smells) ↓ ↓ ↓

Semantic variant PPA 2

- Perceptual disorder
  - Prosopagnosia (inability to recognize faces)
  - Associative agnosia (visual object agnosia; inability to recognize, with intact perception) i.e. tennis ball
- Memory intact
- Focal anterior, bilateral temporal atrophy, > L
- Ubiquitin-positive but tau-negative inclusions. Identical to those in amyotrophic lateral sclerosis (motor neuron disease), but none in brainstem or spinal cord motor neurons.

Primary Progressive Aphasia



Left

Semantic variant PPA 3

- Left anterior temporal FTD:
  - dissociation between marked single-word and object knowledge deficits,
  - but sparing of phonology and fluency

- Semantic meaning loss → comprehension ↓
- Severe word finding ↓ (BNT, fluency)
- Loss of word recognition on Picture Vocabulary
- Memory ↓, long sentence memory ↓

Semantic Variant PPA 3

- General knowledge ↓
- Surface dyslexia (cannot recognize a word as a whole), poor object klg
- Spared repetition, motor speech
- Speech is fluent; awareness of deficit

- If R Temp, face recognition ↓

- Damage to the major superior and inferior temporal white matter connections of the left hemisphere (inferior longitudinal fasciculus. & arcuate and uncinate fasciculi) with relative sparing of the fronto-parietal superior longitudinal fasciculus.

NP Testing of Semantic variant PPA

- BNT (15 item): < 5
- Draw a word ↓, i.e. cat, duck
- Color in animal picture ↓, i.e. brown frog
- Echoic memory buffer ↓
- Digits Backwards ↓
- Trails, design copy ok

svPPA

- Anomia = Defining feature of svPPA
  - Unavailable content words (specific nouns, verbs, adjectives) are replaced and surrounded by speech that is correctly pronounced and has normal grammatical structure.
  - Syntax is often simplified

- Word retrieval deficit not a word finding problem; rather a loss of semantic knowledge.

- Lower-frequency words are replaced by more general and higher-frequency words
  - Zebra becomes “horse,” “animal,” and eventually “thing”

svPPA

Anomia

- Simple Test
  - Ask patient to repeat a long, unusual word such as “hippopotamus” or “chrysanthemum” and then to define it
    - Repetition is almost always normal and rapid
    - Definition will be generalized, lacking detail, and sometimes completely uninformative
- Object use is also impaired, although not initially
  - Patients typically function normally with everyday objects at home, but show impairment on formal tests

svPPA

Behavior and Personality Change

- Degraded social functioning
  - Emotional Withdrawal
  - Depression
  - Disinhibition
  - Apathy
  - Irritability
  - Difficulty understanding the things people do and say

svPPA

Behavior and Personality Change

- Changes in Eating Behavior
  - Restriction of food preferences rather than the overeating in bvFTD
  - Exacerbation of a sweet tooth
- Loss of physiological drives is common
  - Poor appetite
  - Weight Loss
  - Decreased Libido
- New sense of religiosity and/or eccentricity of dress have been reported

svPPA

- Stereotyped interests often looking similar to obsessions are prominent but delayed feature
  - Patients with left-predominant svPPA often become fixated on objects like coins or buttons or visual arts
  - Patients with right-predominant svPPA often become fixated on letters, words, and symbols (e.g. word puzzles, writing notes, poetry)

svPPA

- Deficits in person recognition often occur at some stage in the disease (Thompson et al., 2003)
- Right predominant may *present* with a profound difficulty in recognizing and naming people
- Regardless of side dominance there is a cross-modal loss of person knowledge involving face, name, and/or voice recognition

svPPA

Maintained Skills

- Orientation
- Recall of recent life events
- Visuospatial and topographical abilities
- Complex hobbies (e.g. sports games)

svPPA: Neuropsychological Findings

- Impaired semantic memory
  - Object/Picture Naming
  - Category Fluency
  - Generation of verbal definitions to words and pictures

- Progression of anomia
  - Substitution of similar category coordinate
    - Zebra -> Giraffe
  - Then higher-familiarity member of category
    - Zebra -> Horse
  - Then superordinate category name
    - Zebra -> Animal
  - Then vague circumlocution, often with personal content
    - Zebra -> It's one of those things, I saw them on the television last night
  - Then inability to say anything
    - Zebra -> I don't know

svPPA

Neuropsychological Findings

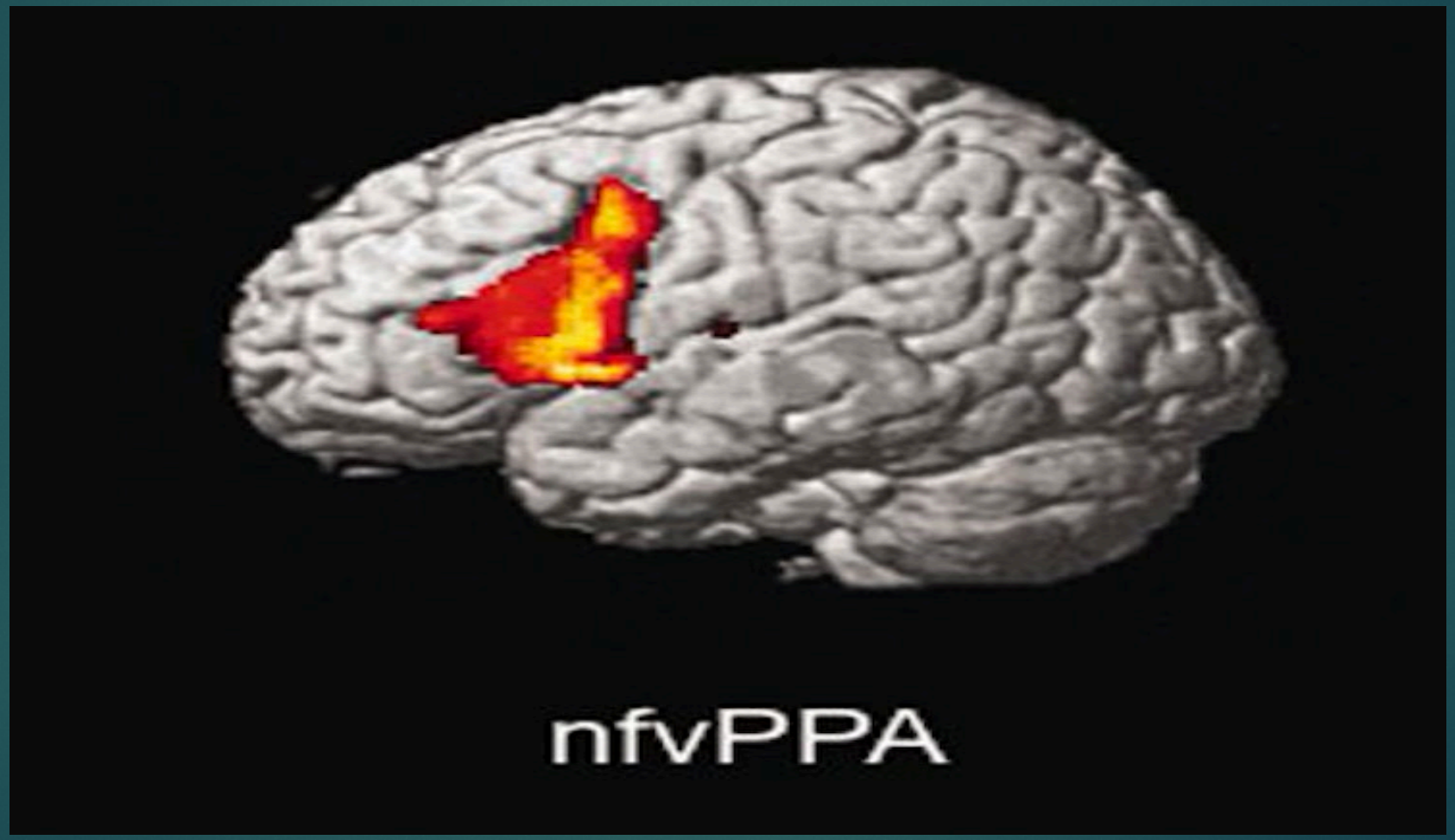
- Verbal anterograde memory (story memory, list learning) is impaired as a result of poor semantic knowledge that can't be encoded

- Differential between Alzheimer's Disease:
  - Autobiographical memory
    - AD - impaired memory for recent life events but preserved autobiographical memory for earlier phases of their lives (Nestor et al., 2002)
    - svPPA - memory for remote autobiographical events is most vulnerable (Piolino et al., 2003; Westmacott et al., 2004)

svPPA: Structural and Functional Imaging

- Focal, often asymmetric (L>R) atrophy of the anterior temporal lobe (Hodges et al., 1992)
- Temporopolar and perirhinal cortices most affected (Rosen et al., 2002)
- Degree of anterior temporal atrophy correlates with extent of semantic impairment (Davies et al., 2004)
- Left hippocampus is typically as atrophied as AD if not more when matched for disease duration (Davies et al., 2004)
- Amygdala is consistently involved and linked to emotional recognition impairments

Nonfluent PPA



Nonfluent Primary Progressive Aphasia

- Disorder of speech production ↓ (expressive language deficit)
- Language disorder is primary deficit for first 2 years
- Non-fluent spontaneous speech with 1 of the following:
  - Phonemic paraphasias - errors in which the incorrect sound is used within a word (e.g. ‘tittle’ for ‘little,’ or ‘label’ for ‘table’)
  - Anomia - naming deficits that cause long pauses during spontaneous speech or the selection of a word
  - Agrammatism - omission or inappropriate use of grammatical words such as articles, prepositions, and auxiliary verbs
- Relatively spared word comprehension
- Other possible features: stuttering, oral apraxia, impaired repitition, alexia, agraphia, early preservation of word meaning, late mutism
- Focal Left Temporal atrophy, hypometabolism

Mesulam, Annals of Neur., 1986

Nonfluent PPA

Clinical Features

- Nonfluent speech - hesitant, effortful production with reduced speaking rate; Speech is generally slow, halting, and effortful
- Patients often complain of articulation or word-finding problems
- Memory, visuospatial, and judgment spared, at least initially
- It is the most common PPA (Mesulam & Weintrob, 1992; Mesulam et al., 2003)
- CBD is most common pathology (Gorno-Tempini et al., 2004; Kertesz 2005)
- Nonfluent PPA more likely to be female and isolated language problems will occur for 4 years before other symptoms begin

Nonfluent PPA

Clinical Features

- Often starts with anomia and progresses to non-fluency
- “Broca’s-like-aphasia”
- Patients will use a simplified sentence and decreased phrase length
- Speech is slow and apraxia of speech and/or stuttering are common complaints
- Anomia thought to be a problem of speech production rather than semantic loss

Nonfluent PPA

Clinical Features

- As the disease progresses patients can show symptoms of executive dysfunction
  - Poor thought organization
  - Severe frustration
  - Depression
  - Mild disinhibition

Nonfluent PPA: Neuroimaging

- Left frontal hypometabolism as measured by PET (Grossman et al., 1998; Nestor et al., 2003)
- Atrophy found in the left inferior and middle frontal gyri, motor cortex, premotor cortex, and anterior insula regions (Nestor et al., 2003; Gorno-Tempini et al., 2004)
- Left greater than right atrophy is well documented, bilateral damage is common (Westbury & Bub, 1997)

Nonfluent PPA

Neurological Evaluation

- Mild motor symptoms are present usually in the right hand or right side of the body (Kertesz et al., 2003; Kertesz & Munoz, 2004)
- Diffuse motor slowing
- Reduced dexterity
- Mild Rigidity

Nonfluent PPA

Neurological Evaluation

- Limb apraxia (deficits when carrying out purposeful movement) is common and along with acalculia can be present early in the disease (Neary et al., 1998)
- Impaired ideomotor apraxia (inability to correctly imitate hand gestures and voluntarily mime tool use) is consistent with disruption to a left parietofrontal network (Joshi et al., 2003)
- Buccofacial apraxia and dysarthria can be present (Grossman et al., 1996)

Nonfluent PPA

Pathology

- Tauopathies are the most common: CBD, FTLD, PSP, argyrophilic grain disease (Kertesz et al., 2005; Josephs et al., 2006; Knibb et al., 2006)

- Despite distinct clinical presentation, a growing number of reports suggest that as much as 30% of nonfluent PPA caused by AD pathology (Knibb et al., 2006)

Nonfluent PPA

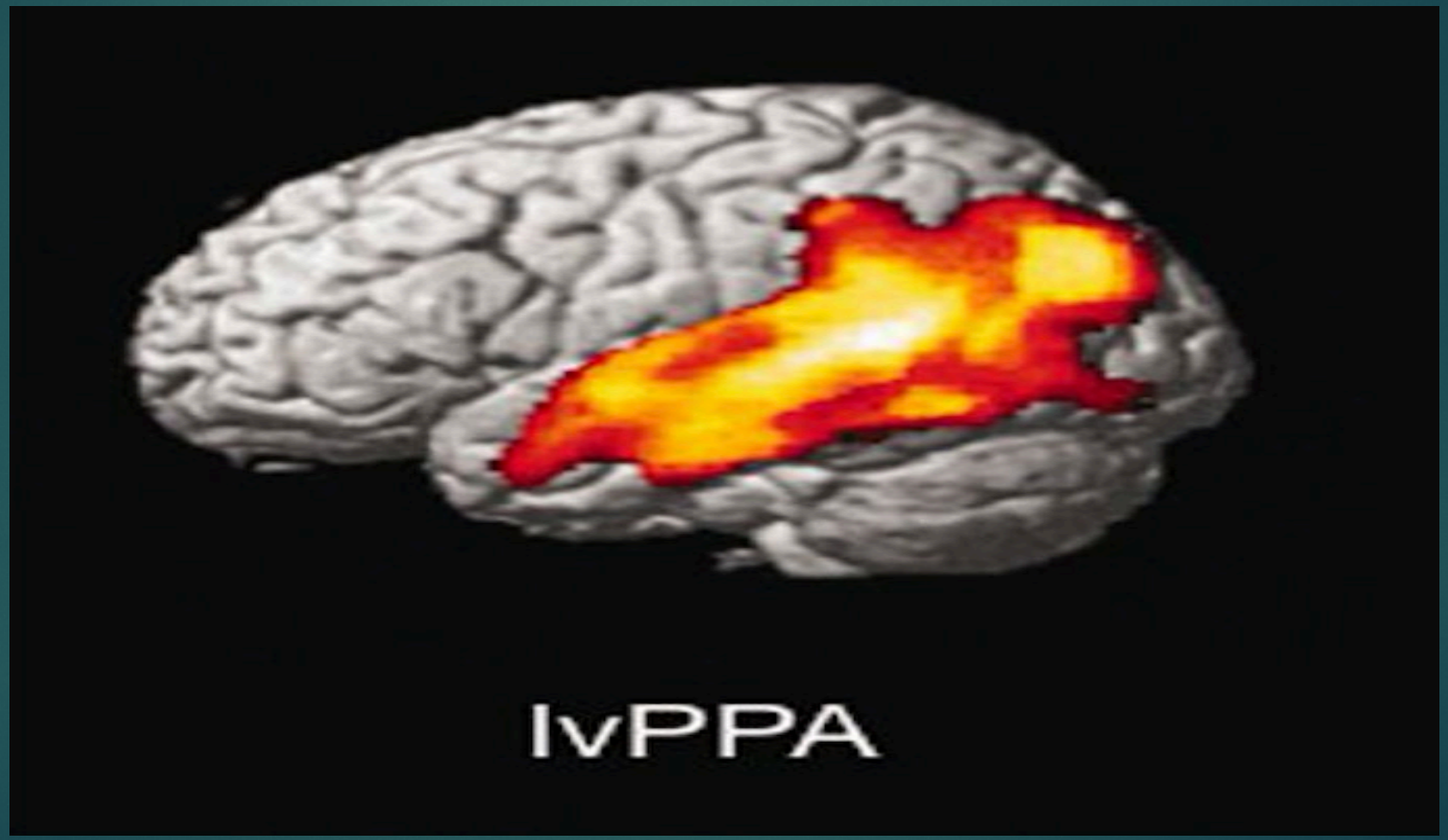
Demographics

- Nonfluent PPA have a later age of onset (ave. 63 y) than svPPA and bvFTD
  - Nonfluent PPA - 63-years-old
  - bvFTD - 58-years-old
  - svPPA - 59-years-old

Treatment Options

- Work with a speech-language pathologist
- Use of augmentative/alternative communication devices (e.g. talking computers)

Logopenic PPA



Logopenic PPA: Word Finding deficit

Clinical Features

- The presenting feature in people with logopenic PPA is deterioration in their ability to retrieve words.
- Spontaneous speech is at slow rate with frequent pauses due to significant word-finding problems; hesitant and nonfluent, with islands of good speech
- No agrammatism; good articulation
- Confrontation naming impairment is usually less severe than svPPA and errors are phonological in nature (Gorno-Tempini et al., 2004)

Logopenic PPA

- **Word retrieval or word-finding;** retain the underlying meaning of words.
- **A slow rate of speech** with frequent pauses due to difficulty finding the right words; the mechanics or motor skills needed to produce speech are not affected.
- **Sentence and phrase repetition is impaired**, but **repetition of single words is spared.**
- **Reading and writing abilities** may be preserved longer than speech, but these eventually decline, as well.
- Over time, **impaired comprehension** of long or complex verbal information, due to problems with working memory (auditory attention span).
- **Mutism** eventually develops with progression.
- **Difficulty swallowing** may develop late in the course of illness.

Logopenic PPA

Clinical Features

- Sentence and phrase repetition is characteristically impaired while reproduction of short, single words can be spared
- This can also cause problems with sentence comprehension, which is influenced by length than grammatical complexity
- Phonologic paraphasias in spontaneous speech and naming
- Sound substitutions are usually well articulated, without distortions
- Lack of agrammatic errors, preservation of articulation, and prosody

Logopenic PPA

Neuroanatomy

- Left temporoparietal junction area (i.e. posterior temporal, supramarginal, and angular gyri)

- AD pathology most common underlying pathology

- ApoE4 Haplotype
  - LPA - 67%
  - svPPA - 0%
  - Nonfluent PPA - 20%

NCD Risk Factors

Risk & Protective Factors for NCD

Increase risk

- Low exercise
- High cholesterol, low HDL
- Type II diabetes
- High saturated fat
- Inflammation
- Low fish/DHA
- High blood pressure
- High Homocystine

Possible Protection

- Exercise (walk >2 miles/day)
- Statins-Lipitor trial positive
- Folate
- Curcumin (Turmeric)
- Polyphenols: High Fruits & Veggies, Juices
- ? Red wine & modest alcohol

Resources

- UCSF Memory Clinic & Research
- Family Caregiver Alliance:

180 Montgomery St, Ste 1100,
San Francisco, CA 94104

phone: (415) 434.3388
(800) 445.8106
fax: (415) 434.3508
info@caregiver.org

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