# AN OVERVIEW OF ALZHEIMER'S DISEASE

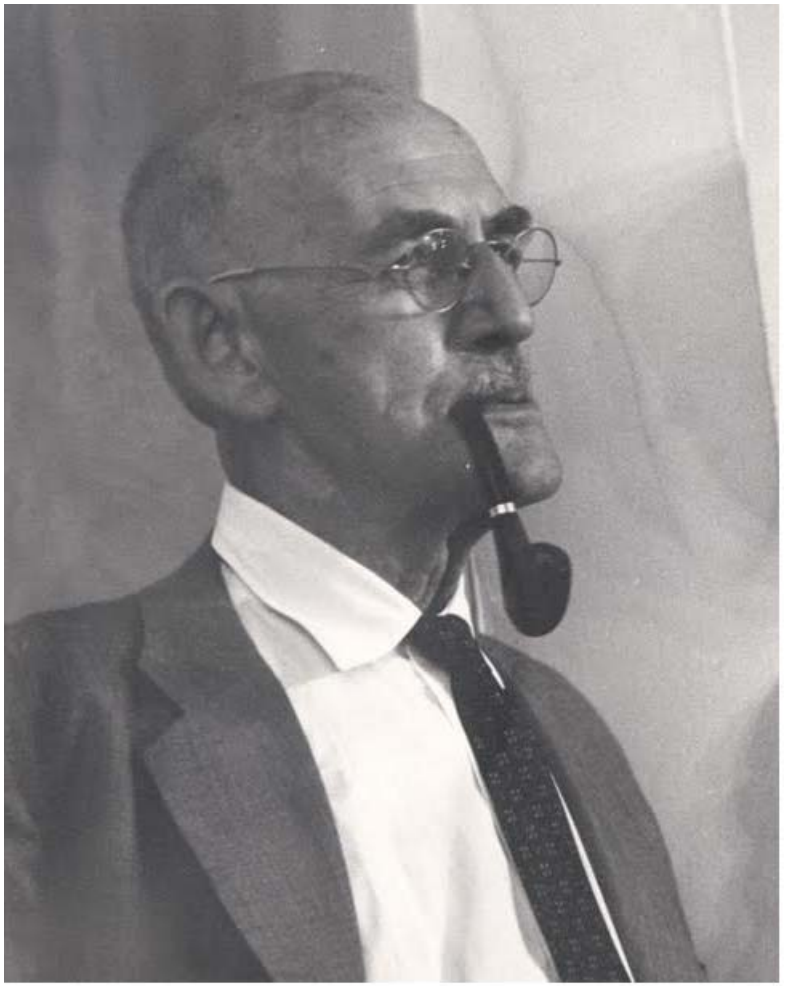
MGMC Grand Rounds

May 10, 2017

Ames, Iowa

# A TALE OF TWO BRAINS

Auguste Deter died age 51 in 1906. Diagnosed in 1901.
Index case of Alzheimer's disease.



George Bishop, Neurophysiologist at Washington University. 1889-1973.
No dementia but copious brain amyloid.

# ALZHEIMER'S IS ONE TYPE OF DEMENTIA.

- Vascular dementia
- Toxic/metabolic dementias-alcohol, B12
- Infectious disease-damage from encephalitis
- Immune mediated-MS
- Genetic disorders-mitochondrial diseases
- Normal pressure hydrocephalus
- Head trauma-Traumatic Brain Injury

# DEFINITIONS

- Dementia—memory impairment plus 1 or more other domains of behavior and cognition that renders the patient unable to function independently.
- Mild cognitive impairment– Impairment in some cognitive sphere but patient is still able to function independently.
- Preclinical---no clinical signs but evidence of damage to the brain from a degenerative process.
- What is healthy-normal cognitive aging(Morris, 2014, Institute of Medicine, 2015)

# DEMENTIA AND FUNCTION

- How do you define function?
- J Gerontol. 1982; 37(3):323-329
- In the past 4 weeks trouble with:

1. Paying bill.
2. handling business affairs
3. shop alone
4. play a game
5. cook
6. follow current events
7. follow a book or show
8. directions and driving
9. remember appointments

# DEMENTIA-REVERSIBLE?

- 68 yr old woman on a trip she failed to recognise a family member. Former financial officier lives alone.
- Evaluation is normal but MMSE=23/30(2009)
- In 2012 followup MMSE=28/30
- ?Etoh, OSA.

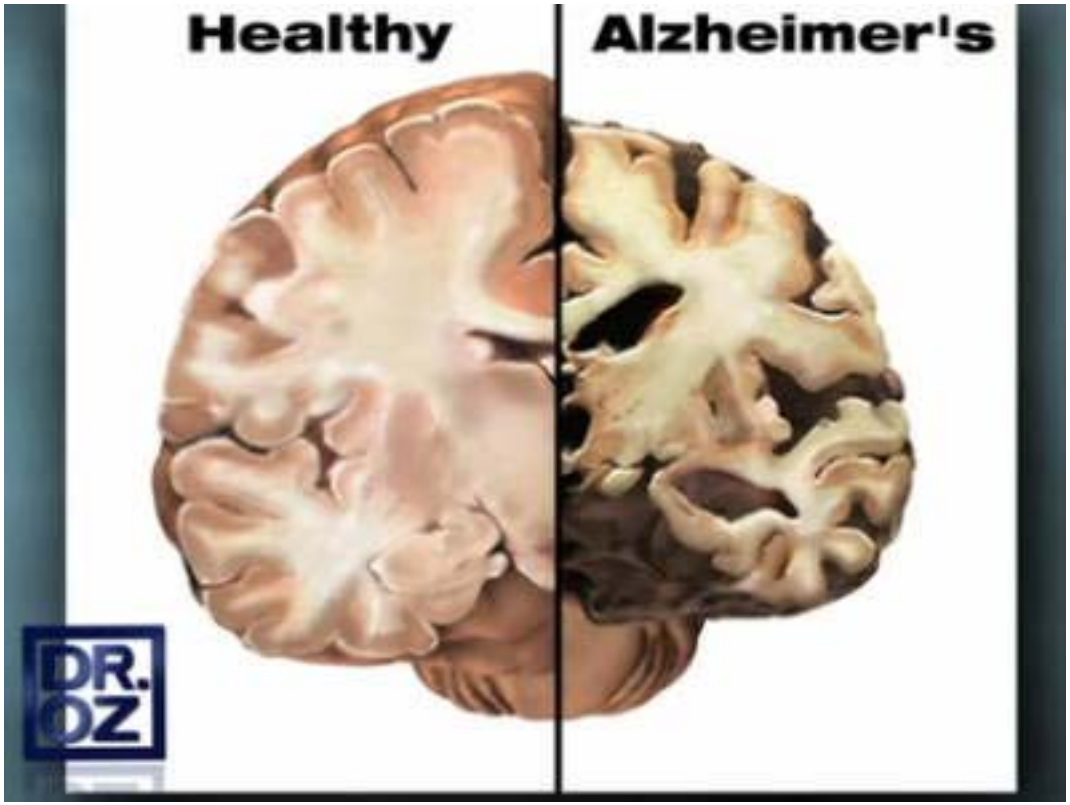
# MILD COGNITIVE IMPAIRMENT

- About 10% of men>woman develop MCI after age 65.
- About 10% per year proceed on to dementia
- About 15% of MCI revert back to normal for a time.
- Obviously a fluid condition but a convenient concept.

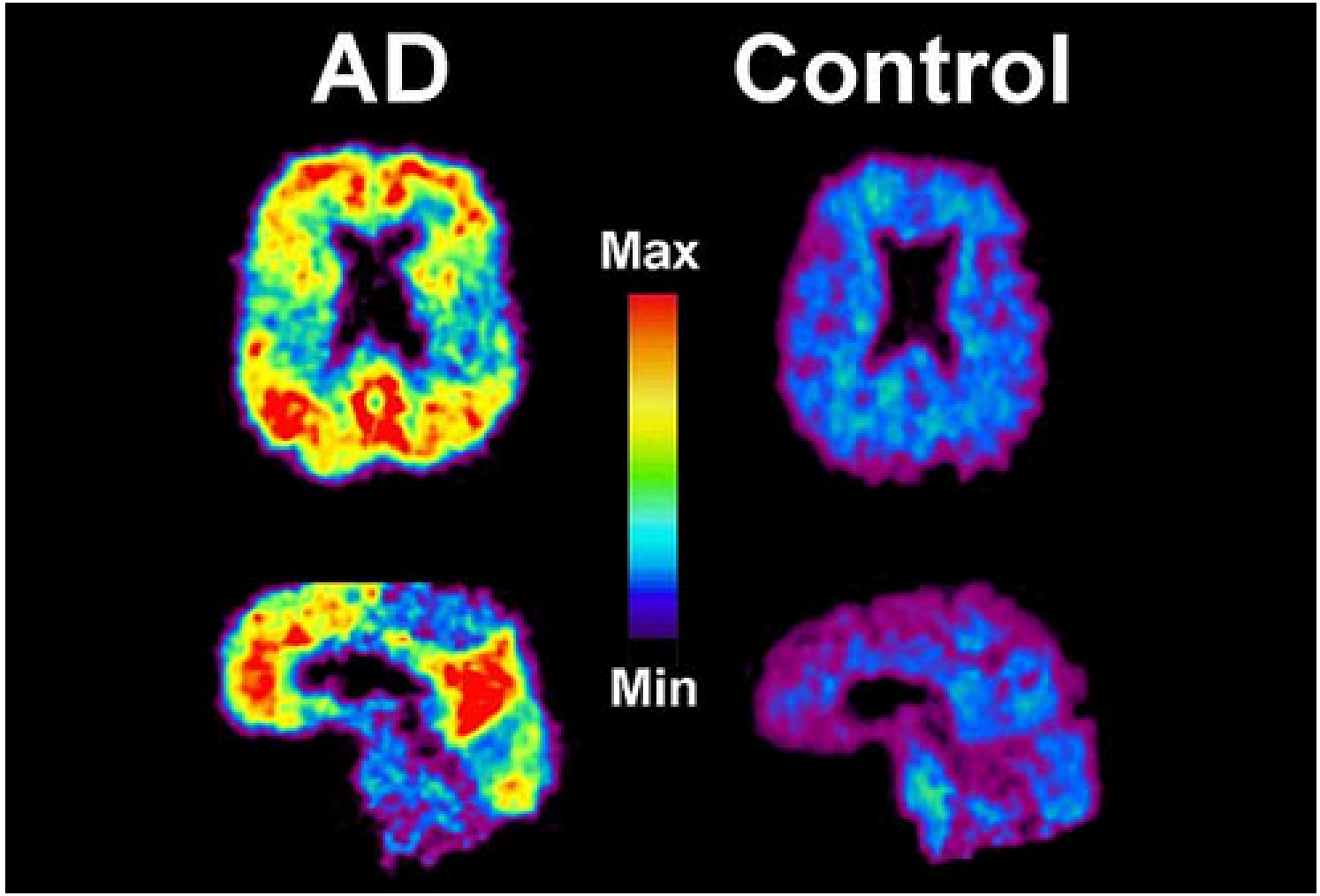
# ALZHEIMER'S DISEASE—NUMBERS

- Prevalence—5.4 million
- Incidence– 53/1000(65-74), 170/1000(74-85)
- Half of all greater than 85 ?
- Women>men (1.5 increase risk)
- Cost– 200 billion per year
- 6th leading cause of death
- Only major disease category increasing

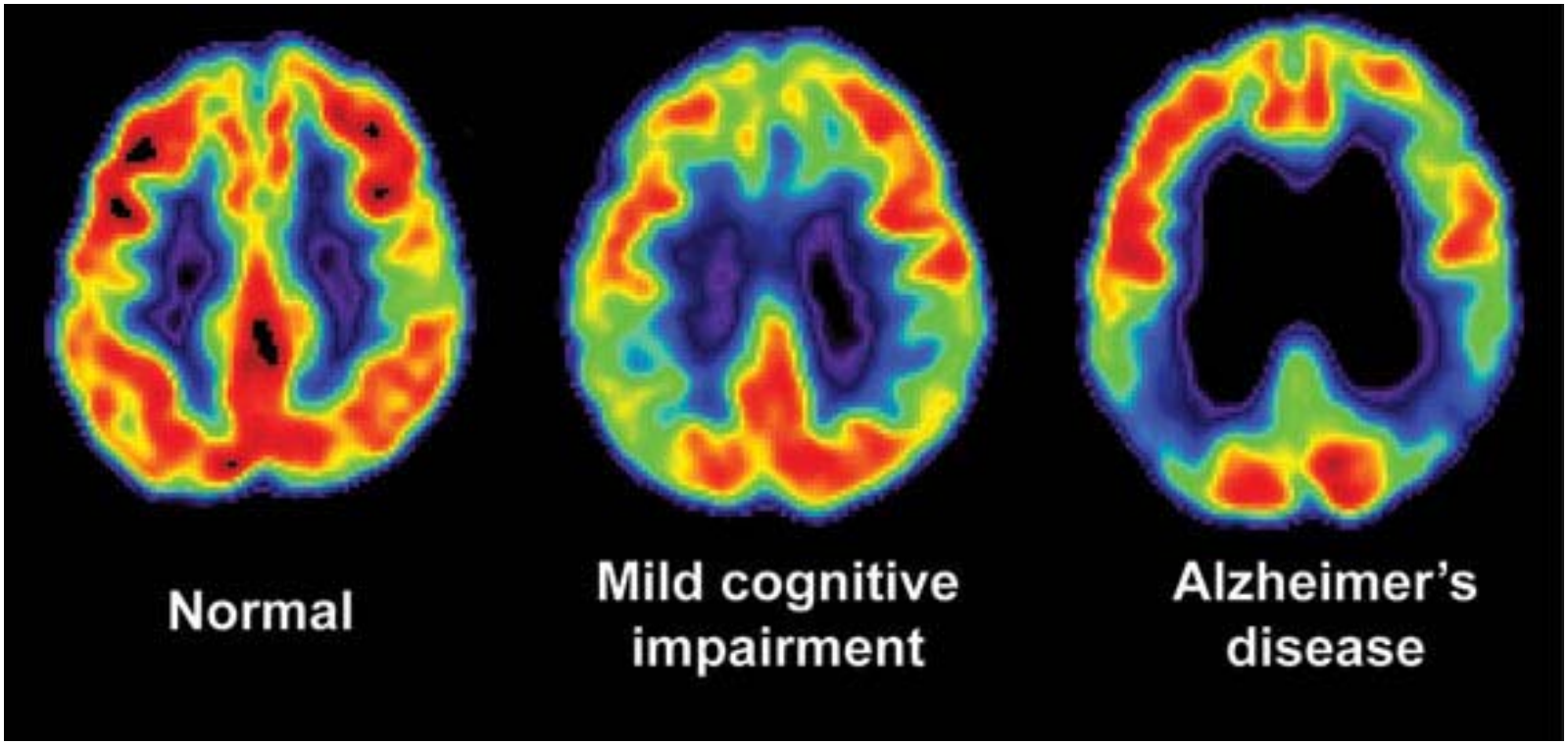
# ALZHEIMER'S DISEASE



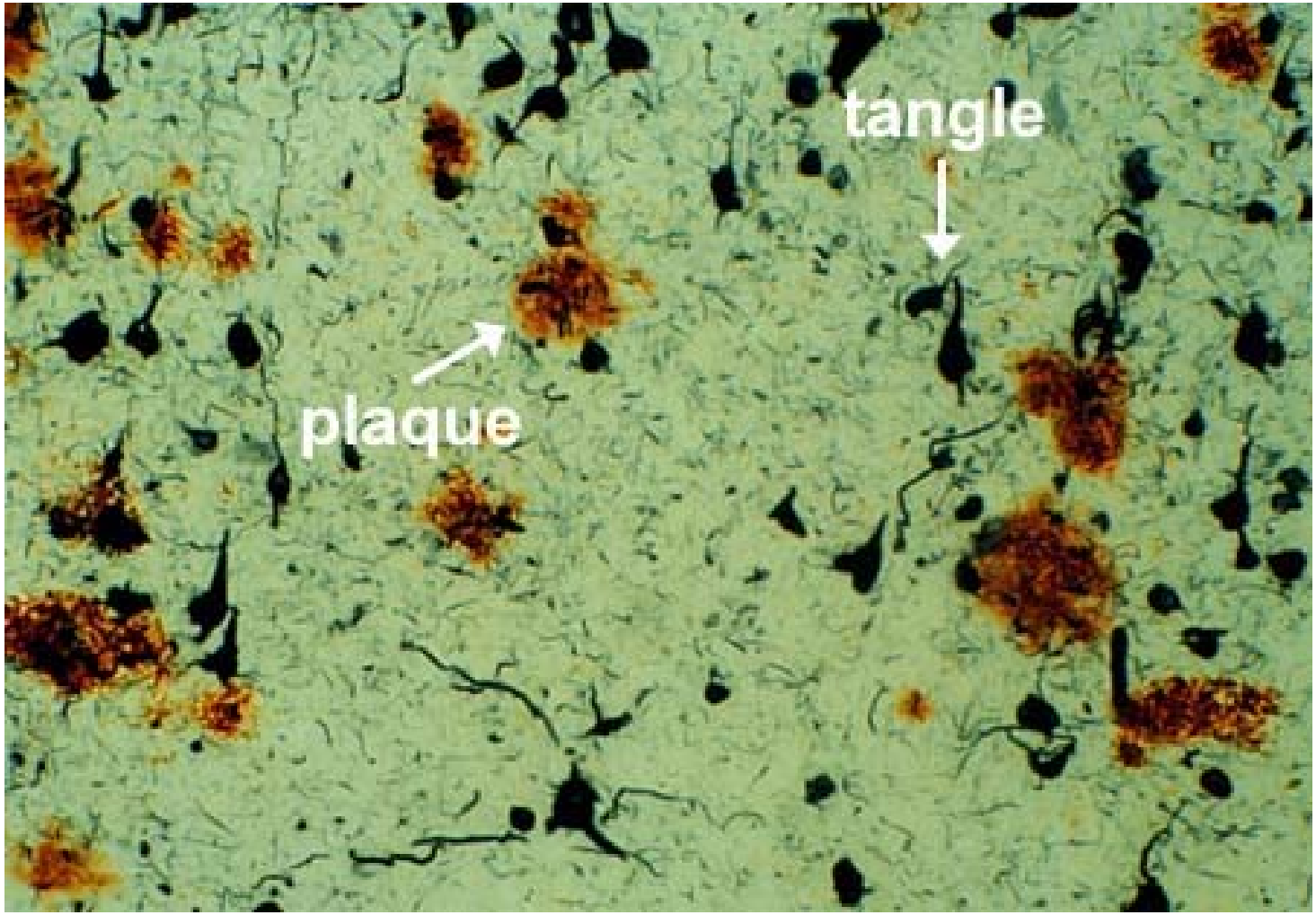
# DEPOSITION OF AMYLOID

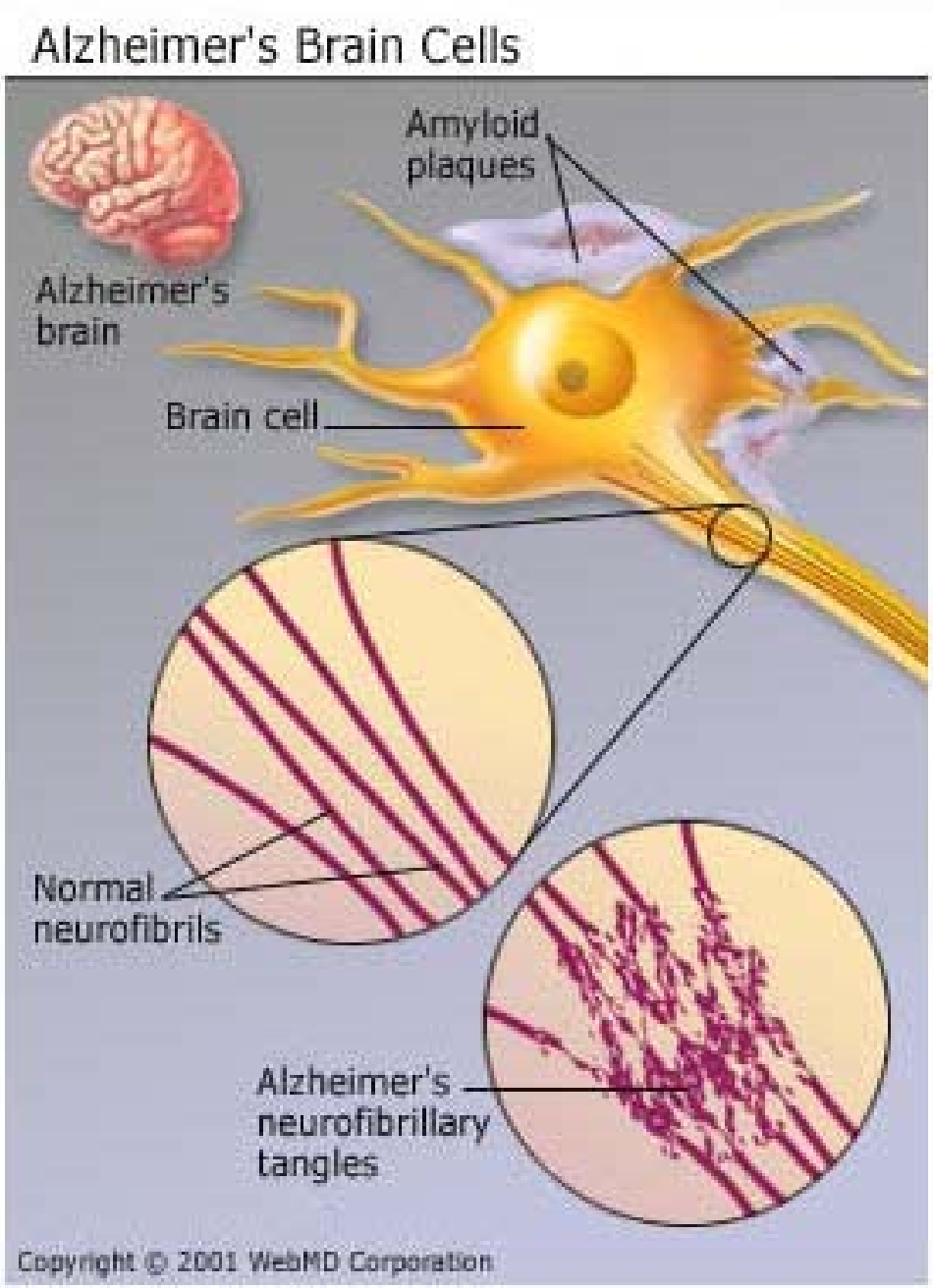


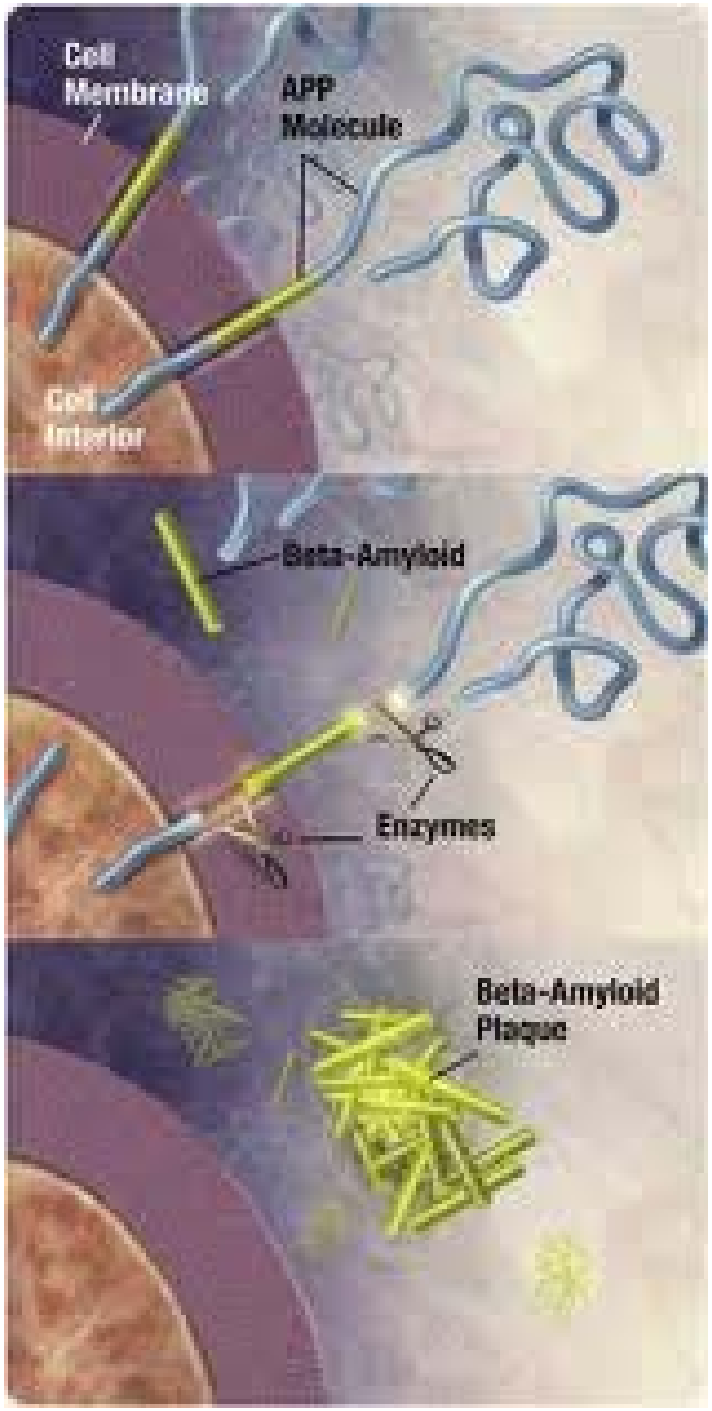
# PROGRESSIVE LOSS OF METABOLISM



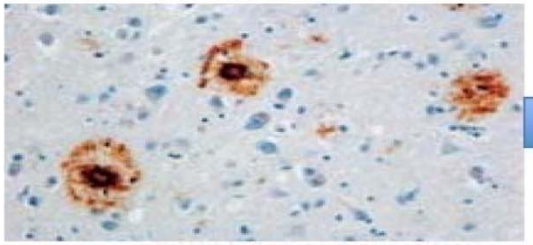
# ALZHEIMER'S PATHOLOGY

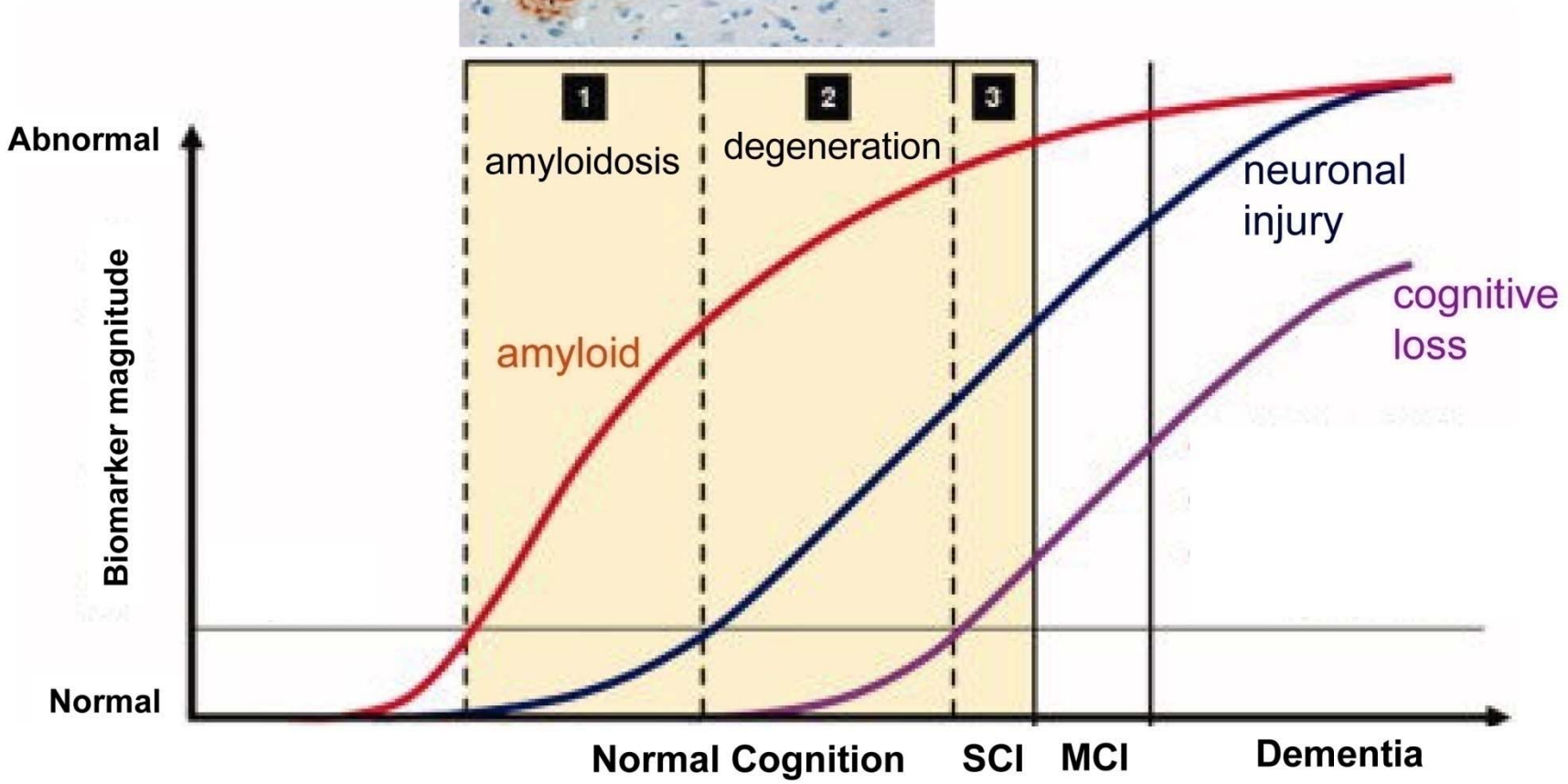



Alzheimer's Brain Cells
Amyloid plaques
Alzheimer's brain
Brain cell
Normal neurofibrils
Alzheimer's neurofibrillary tangles
Copyright © 2001 WebMD Corporation


Cell Membrane
APP Molecule
Cell Interior
Beta-Amyloid
Enzymes
Beta-Amyloid Plaque

# Alzheimer's Starts Before Symptoms



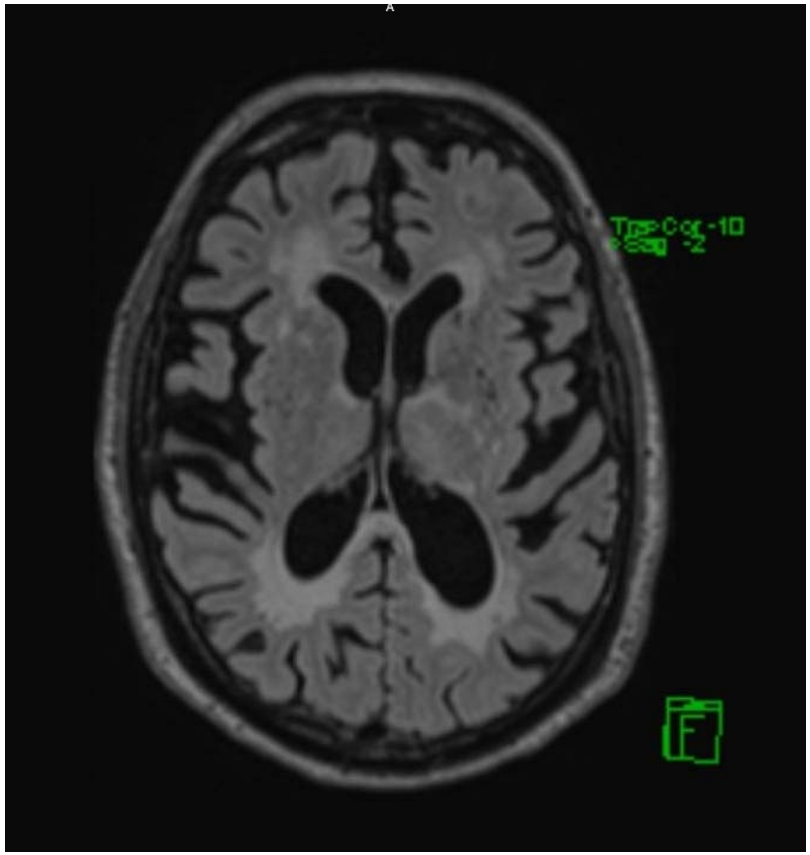


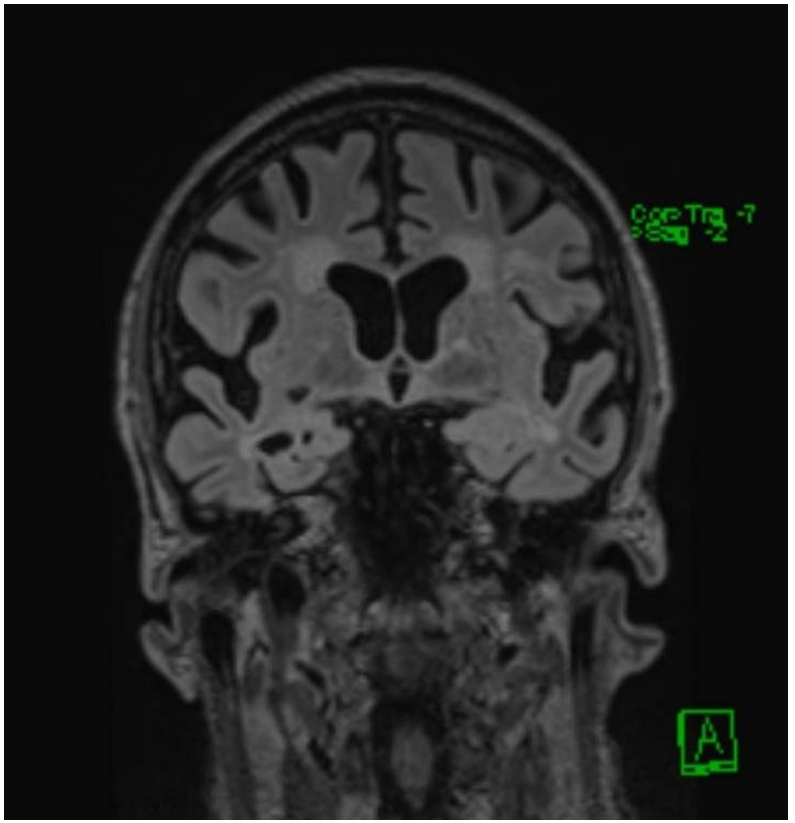

Modified from Jack et al Ann Neurol 2012

# PROBLEMS WITH THE THEORY

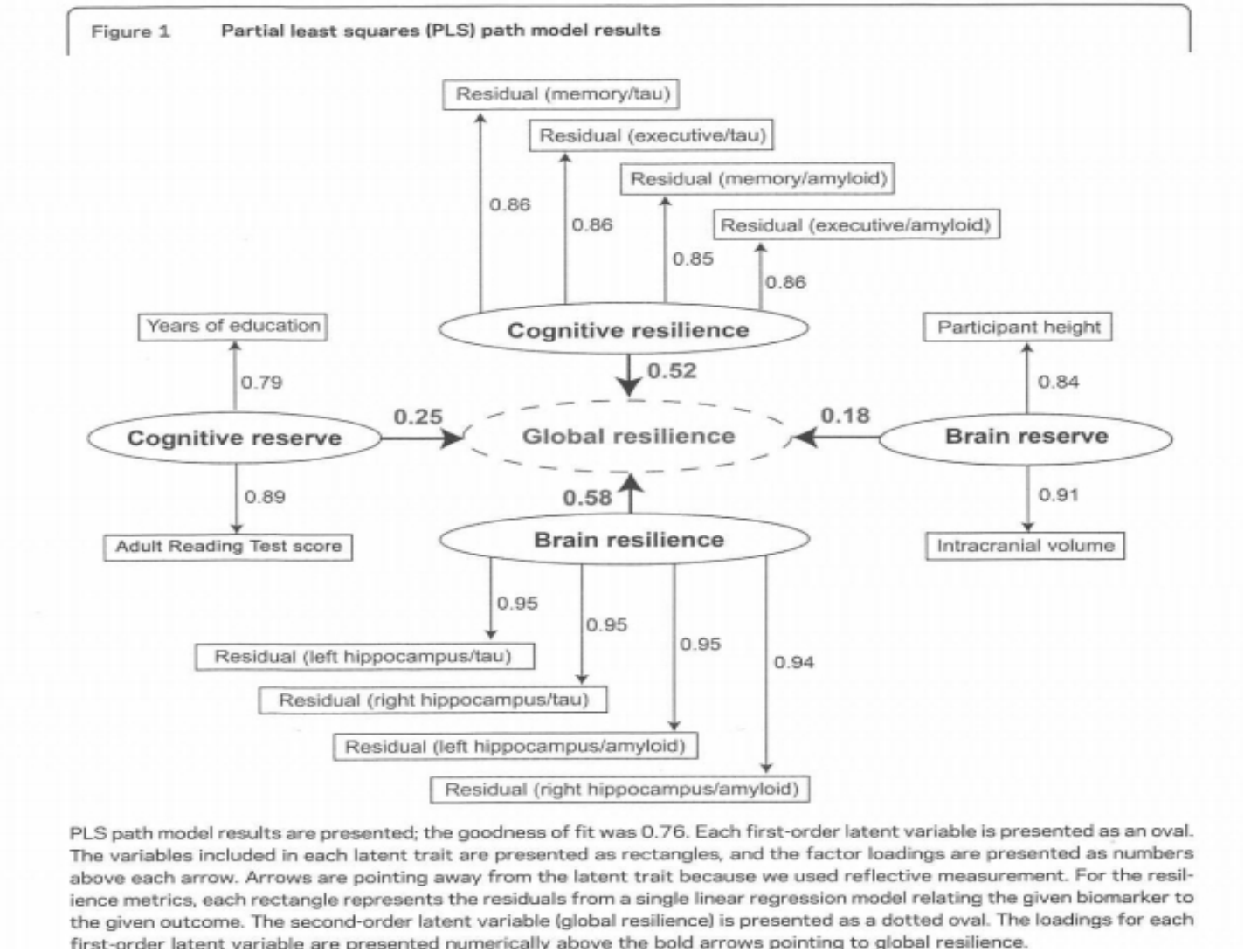
- No clear benefit from removing amyloid
- NeuroDegeneration(ND) - cell death proceeds beyond amyloid. ND as important as amyloid. Effects are synergistic.
- How do tau, amyloid, TDP-43, glucose utilization, ND interact and relate? Amyloid not Neuro 2014;82:1768
- Neuron death brought on by all these problems acting synergistically and spread prion like thru the connectome. JAMA Neuro 2014; 71:505

# VOLUME? A BISHOP STORY?





# VARIABLES IN COGNITION



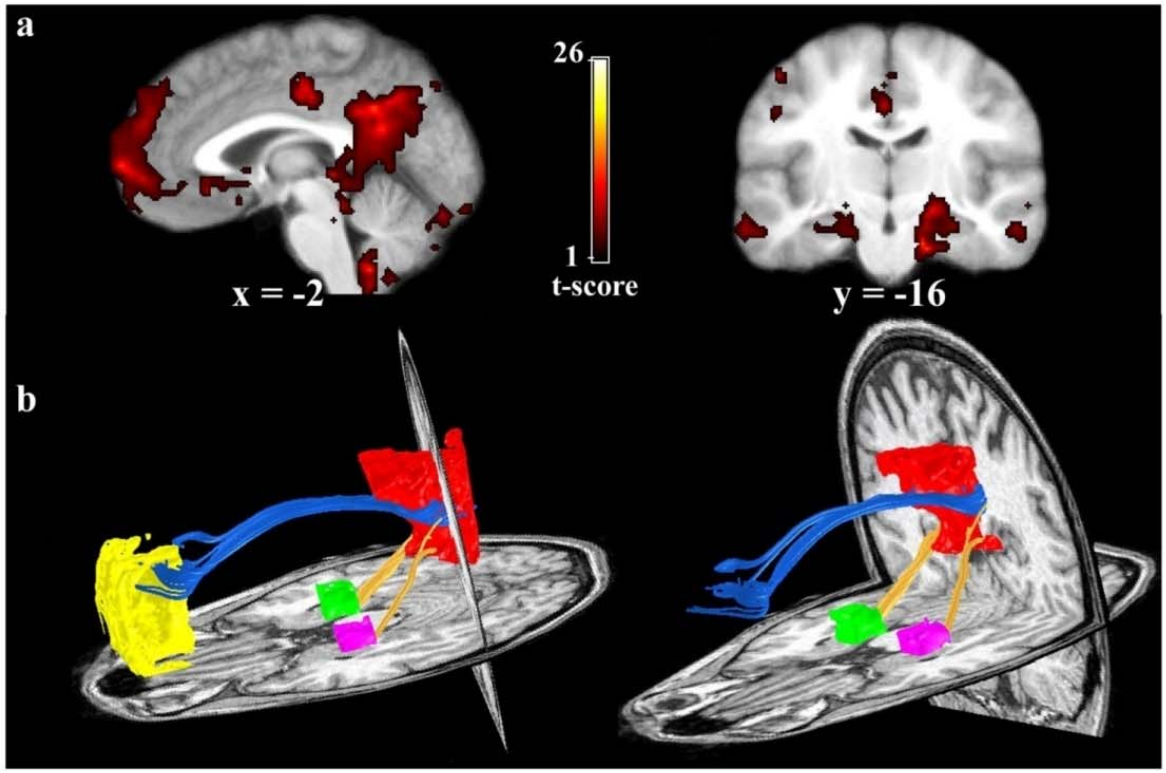

PLS path model results are presented; the goodness of fit was 0.76. Each first-order latent variable is presented as an oval. The variables included in each latent trait are presented as rectangles, and the factor loadings are presented as numbers above each arrow. Arrows are pointing away from the latent trait because we used reflective measurement. For the resilience metrics, each rectangle represents the residuals from a single linear regression model relating the given biomarker to the given outcome. The second-order latent variable (global resilience) is presented as a dotted oval. The loadings for each first-order latent variable are presented numerically above the bold arrows pointing to global resilience.

# THE CONNECTOME

- Neural networks; Default mode network
- DMN-mind wandering (try not to spend too much time there-meditation?)
- Neurons that play together fray together. ?Repetitive firing a problem
- Decline of neural networks is associated with cognitive decline.
- Alzheimer's as a network disease
- Last network(adolescence) is first to go

# CONNECTOME

## Functional Connectivity Reflects Structural Connectivity

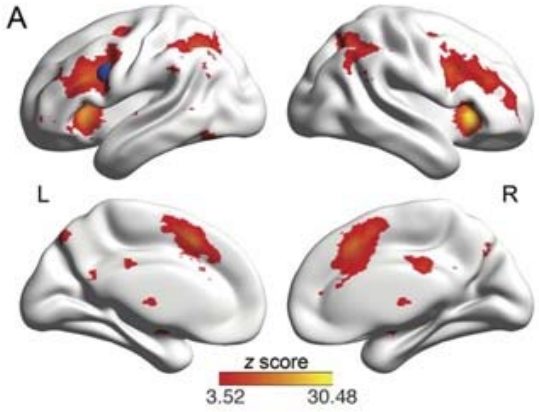



Greicius et al., *Cer Cortex*, 2008

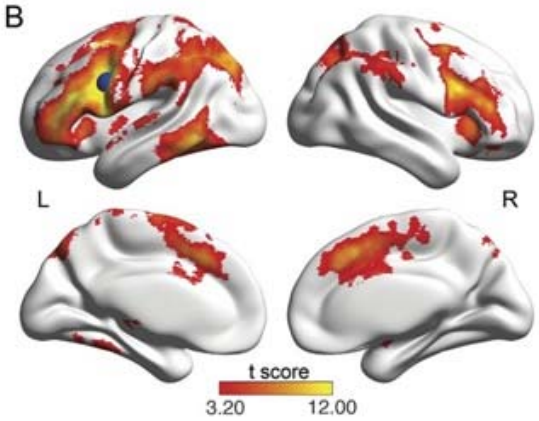
# COGNITIVE RESERVE ANATOMY

- Strength of Left Frontal Cortex connectivity correlates to cognitive reserve. Neurology 2017; 88: 1054-1061

# LEFT FRONTAL CORTEX AND COGNITIVE RESERVE




Meta-analysis: fMRI activation - cognitive control

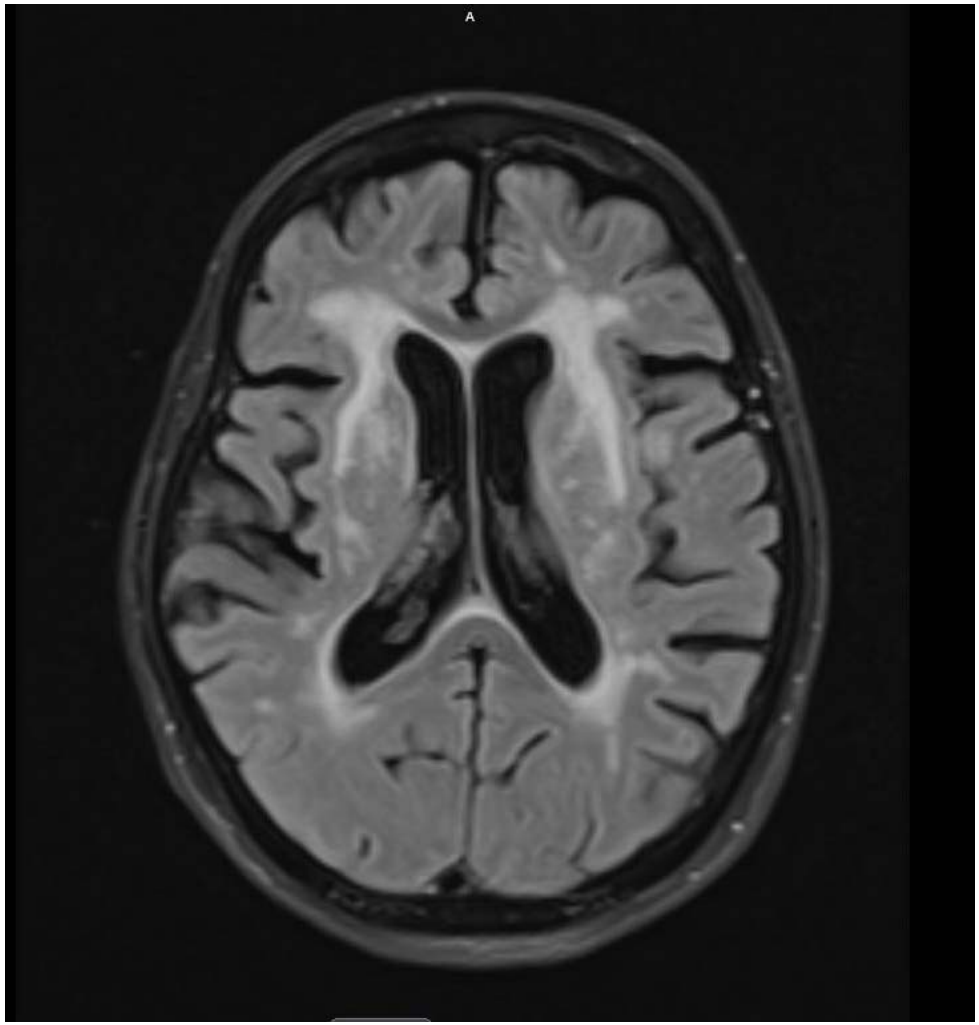



LFC seed-based connectivity in MCI (ADNI)

# OTHER IDEAS BEYOND AMYLOID

- Vascular issues
- Neuroinflammation
- Infection
- Aging gone bad
- Neurodegenerative disorders are disorders of our innate immunity.
- Amyloid beta peptides entrap microbes.

# VASCULAR DEMENTIA



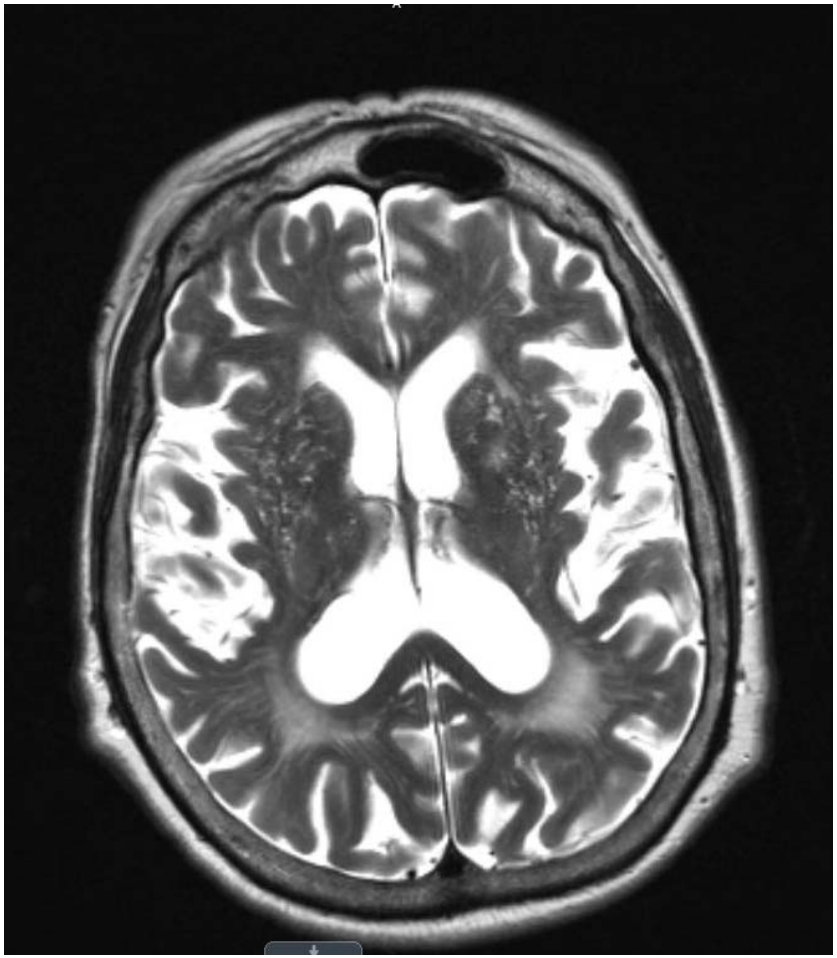
# VASCULAR UPDATE

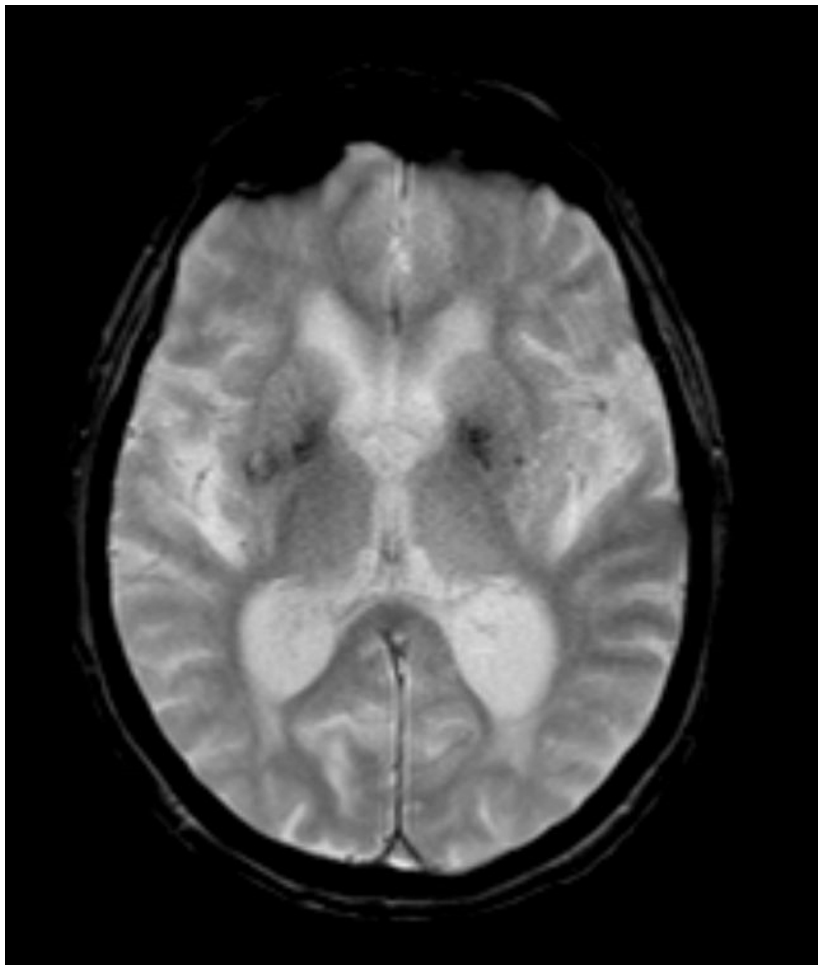
- Small vessel infarcts bad; makes more amyloid
- Variety of small vessel problems (Neuro 2012)
- Amyloid in small blood vessels really bad
- Most AD have a vascular component
- HTN midlife and later have distinct damages
- Controlling BP reduces damage Neuro 2013;81:888, JAMA Neuro; 2014;71:10

# CLINICAL CHARACTERISTICS

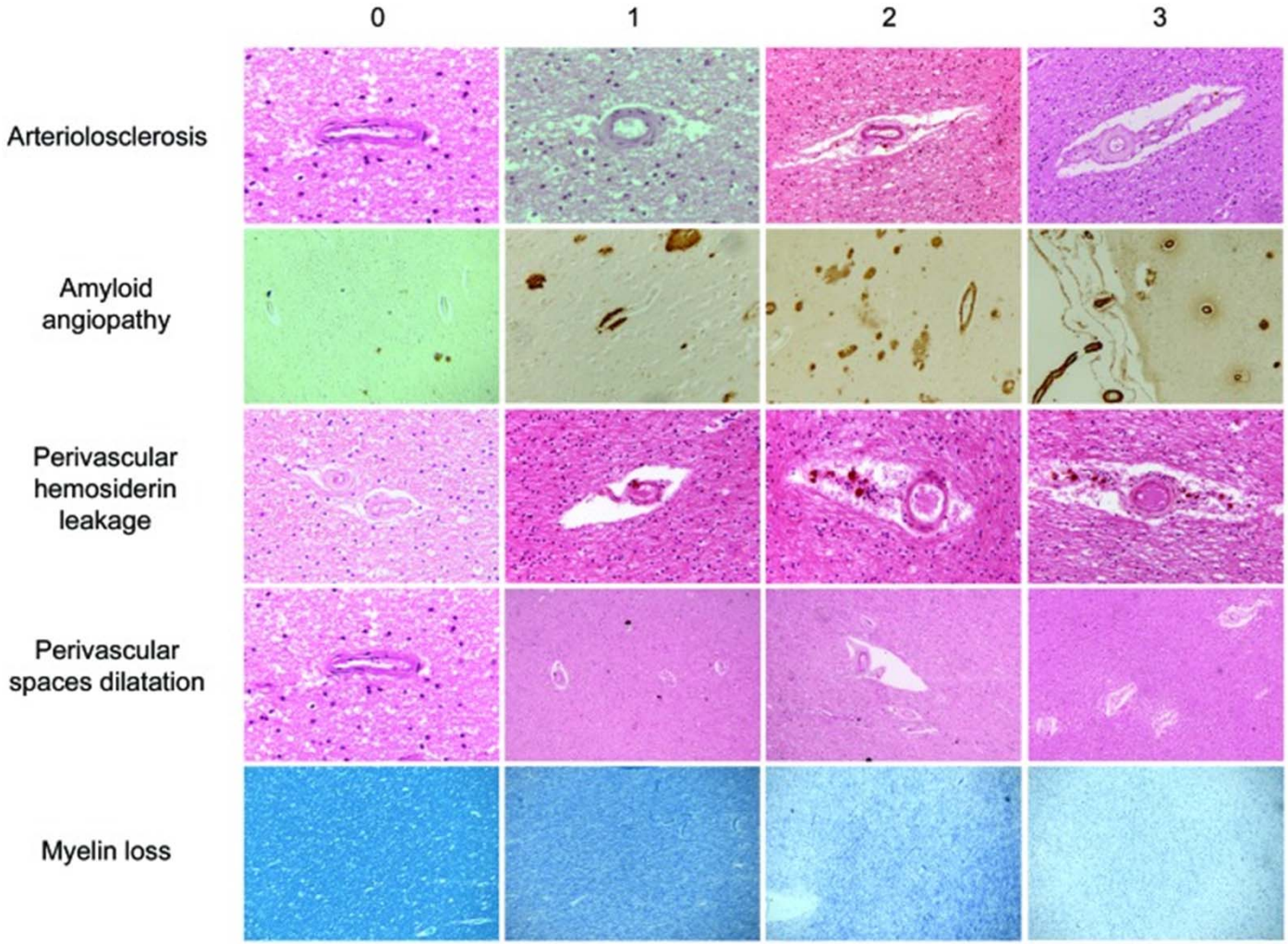
| TABLE 3: CLINICAL FEATURES DISTINGUISHING VASCULAR DEMENTIA FROM AD | | |
|---|---|---|
| | **Vascular Dementia** | **Alzheimer's disease** |
| Cognitive Symptoms | Psychomotor slowing | Short-term memory deficits |
| | Complex attention deficits | Word-fining difficulty |
| | Executive function deficits | Visuospatial deficits |
| | Memory retrieval deficits | Memory encoding deficits |
| Neuropsychiatric features | Apathy, depression | Loss of insight |
| | Hallucinations, delirium | Delusions |
| Other clinical features | Focal neurologic signs | No focal signs |
| | Parkinsonism | |

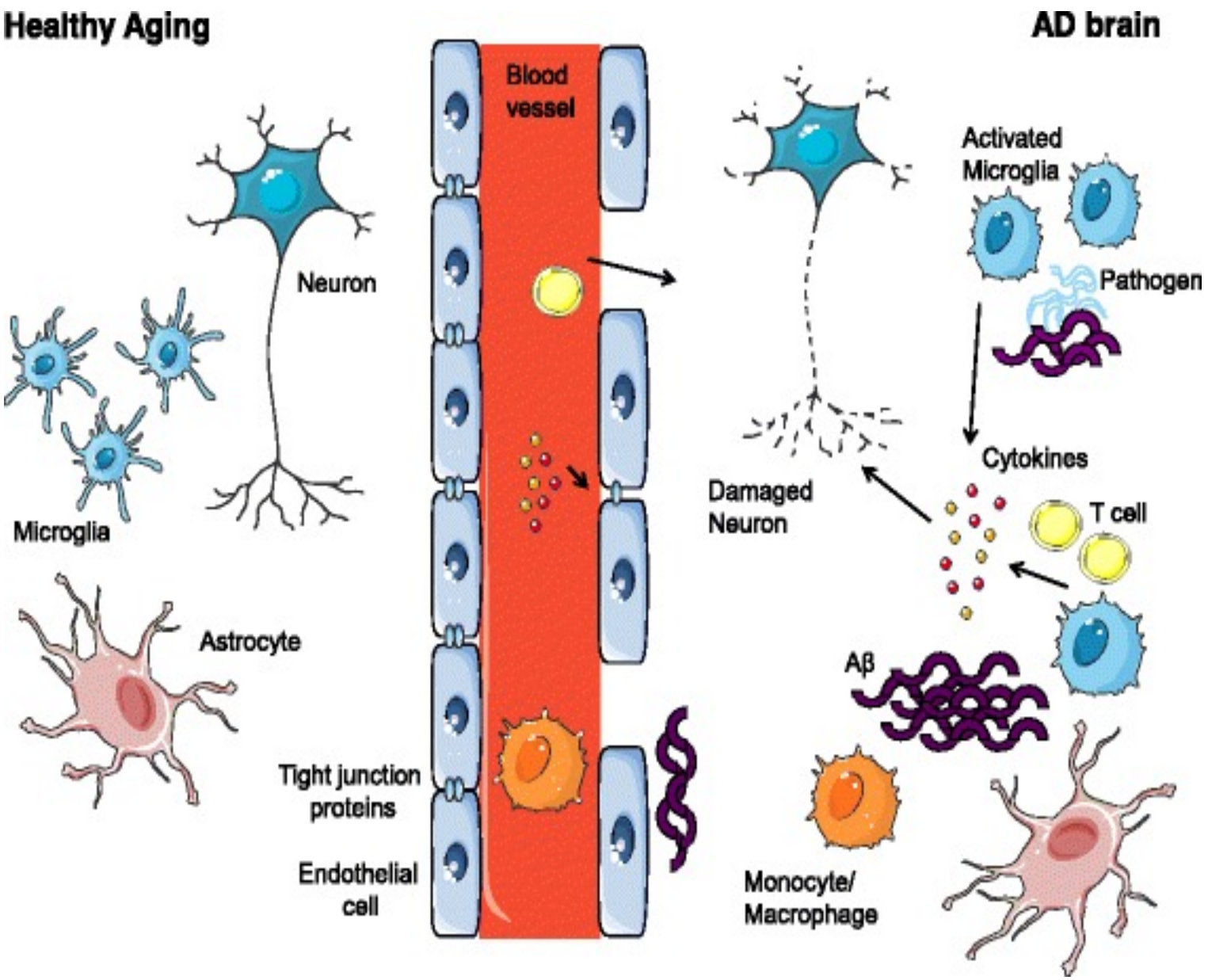
# MRI PATHOLOGY



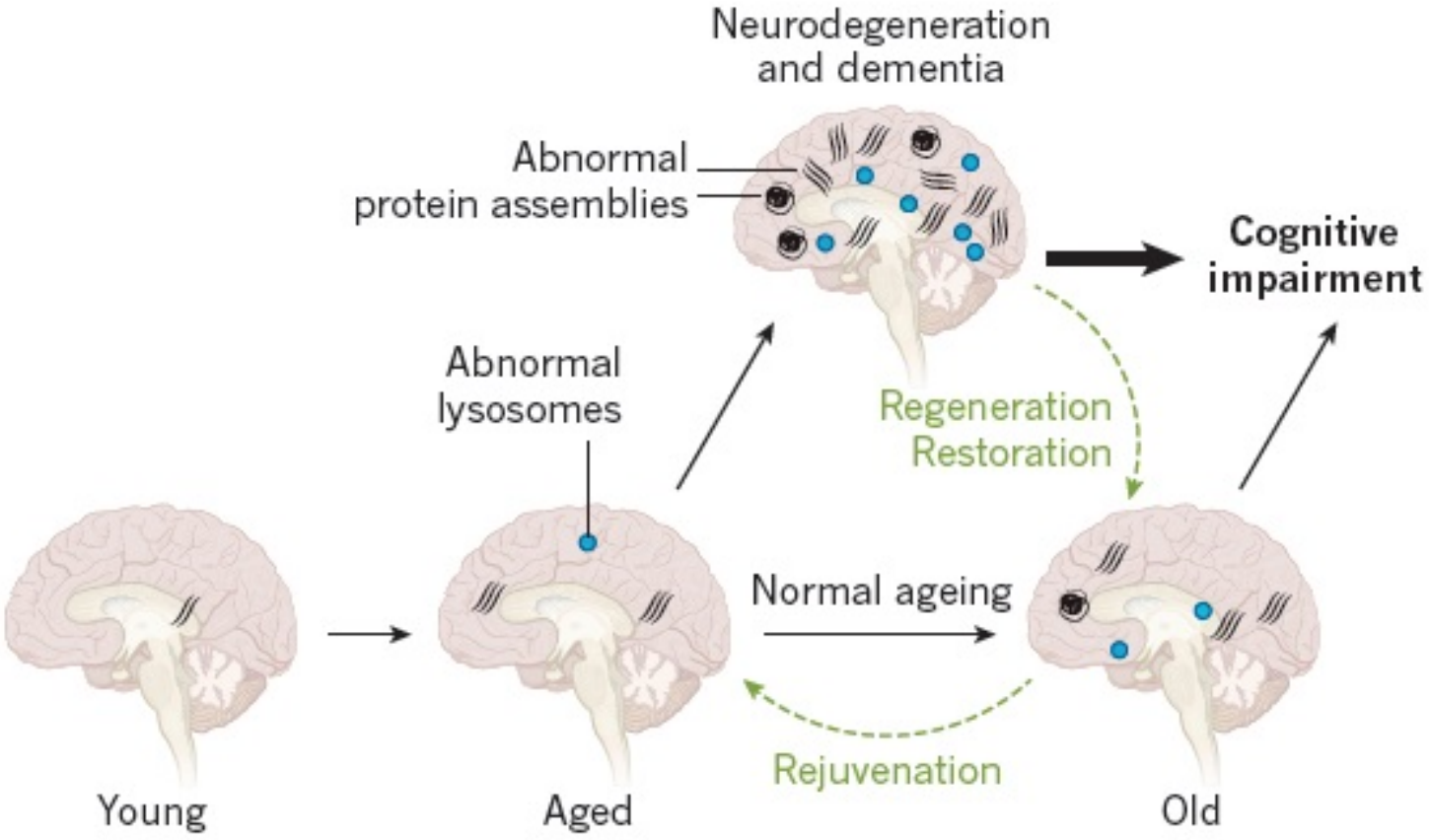


# VARIETIES OF SMALL VESSEL D.

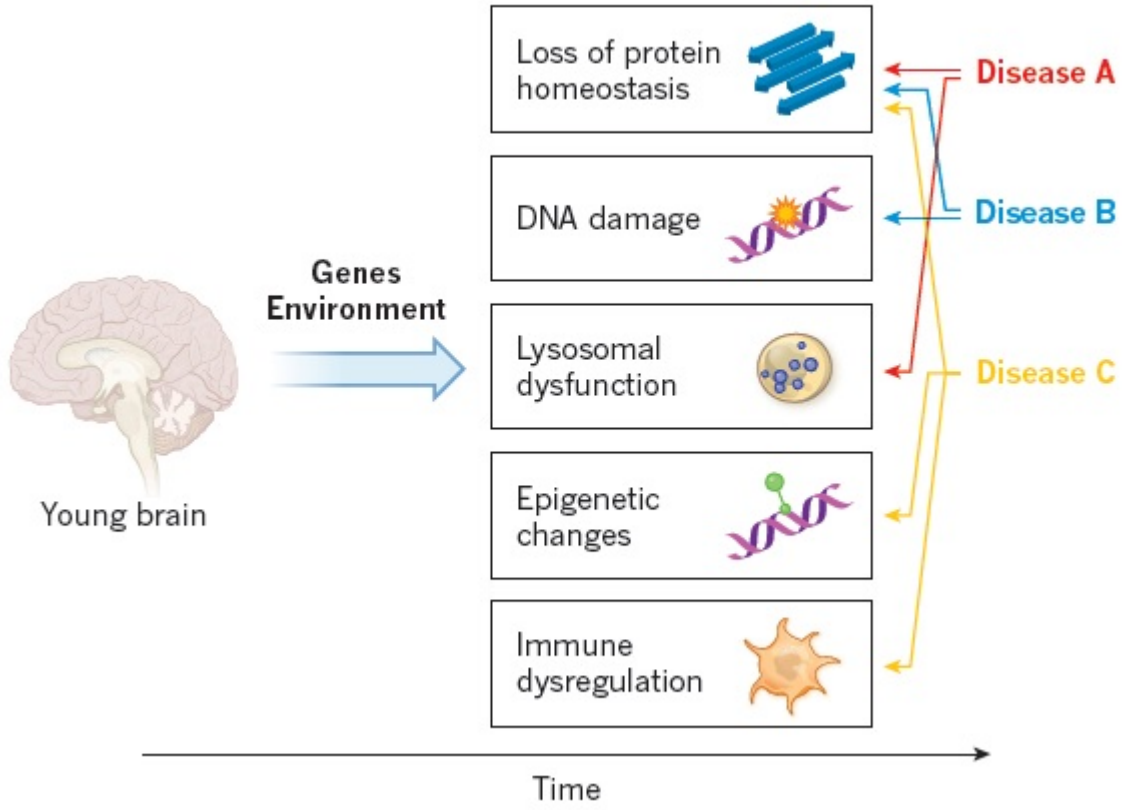



Healthy Aging
AD brain
Blood vessel
Neuron
Microglia
Astrocyte
Tight junction proteins
Endothelial cell
Activated Microglia
Pathogen
Cytokines
Damaged Neuron
T cell
Aβ
Monocyte/ Macrophage

# AD-AGING BREAKING BAD?



# LOTS OF VULNERABILITIES



# ALZHEIMER PATHOPHYSIOLOGY?

- Bad arterioles lead to leaking.
- Bad bugs or toxins get into brain.
- Neuroinflammation.
- Amyloid produced to protect.
- Amyloid insufficient or not cleared or out of control.
- Neurons die and tau fragments appear.
- Tau spreads like a prion

# PRION LIKE SPREAD?

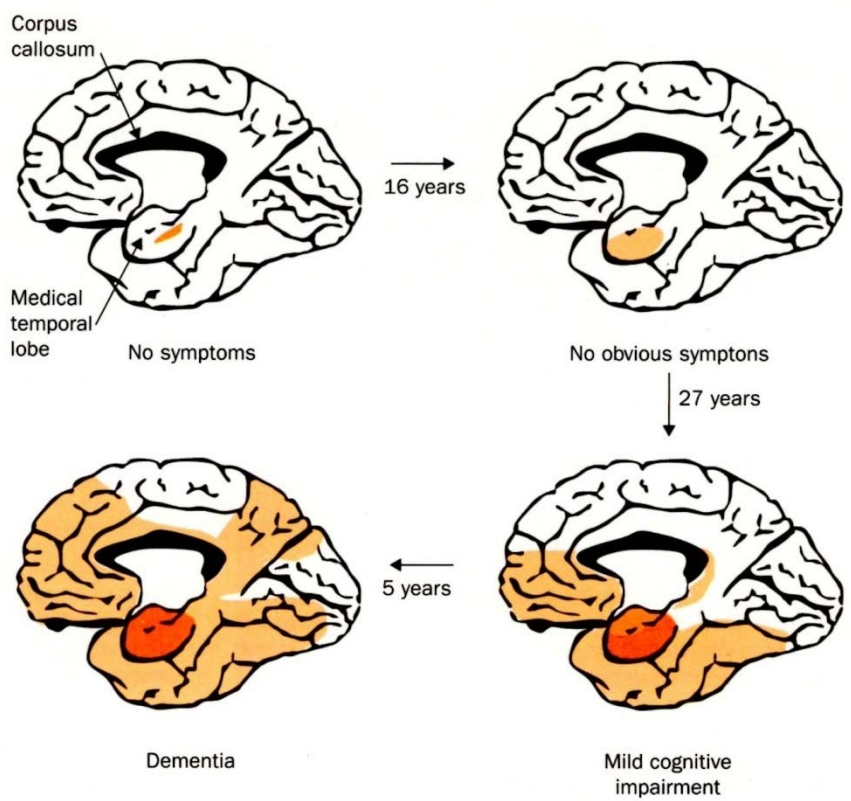
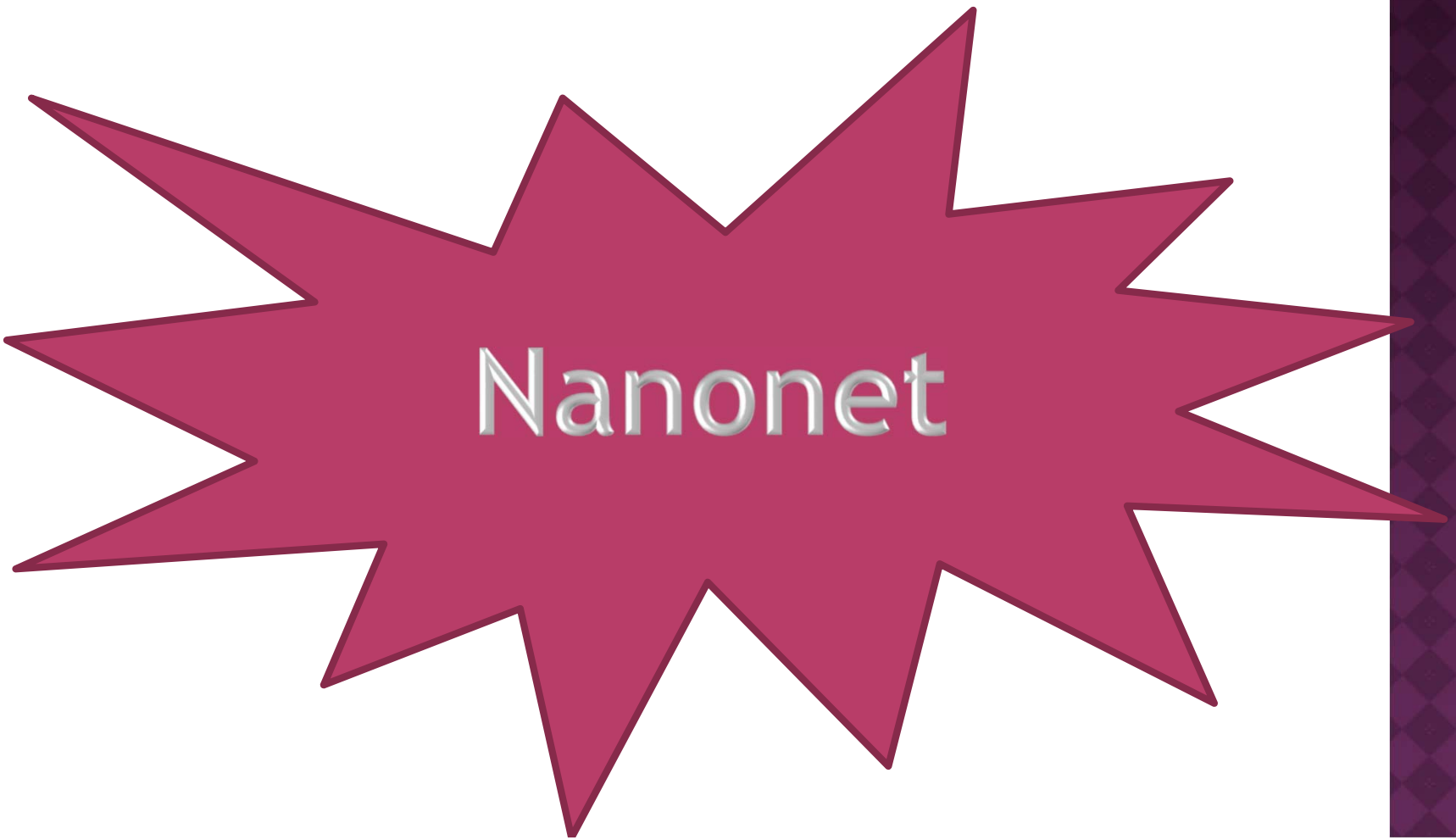
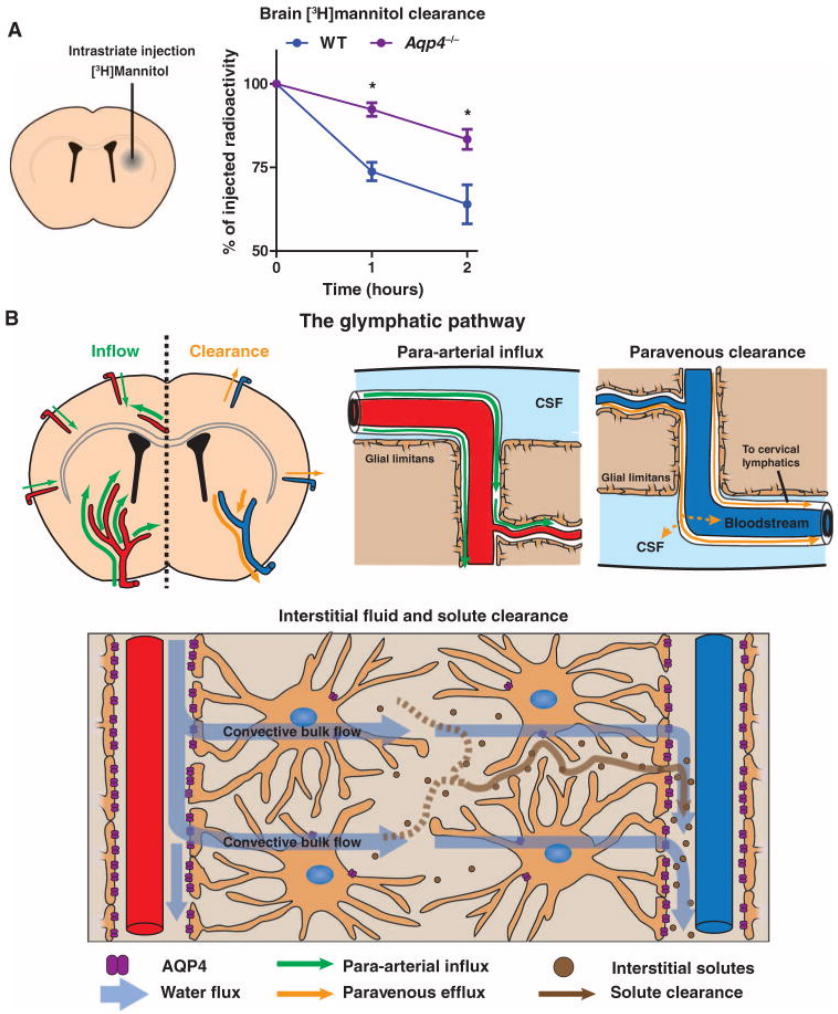


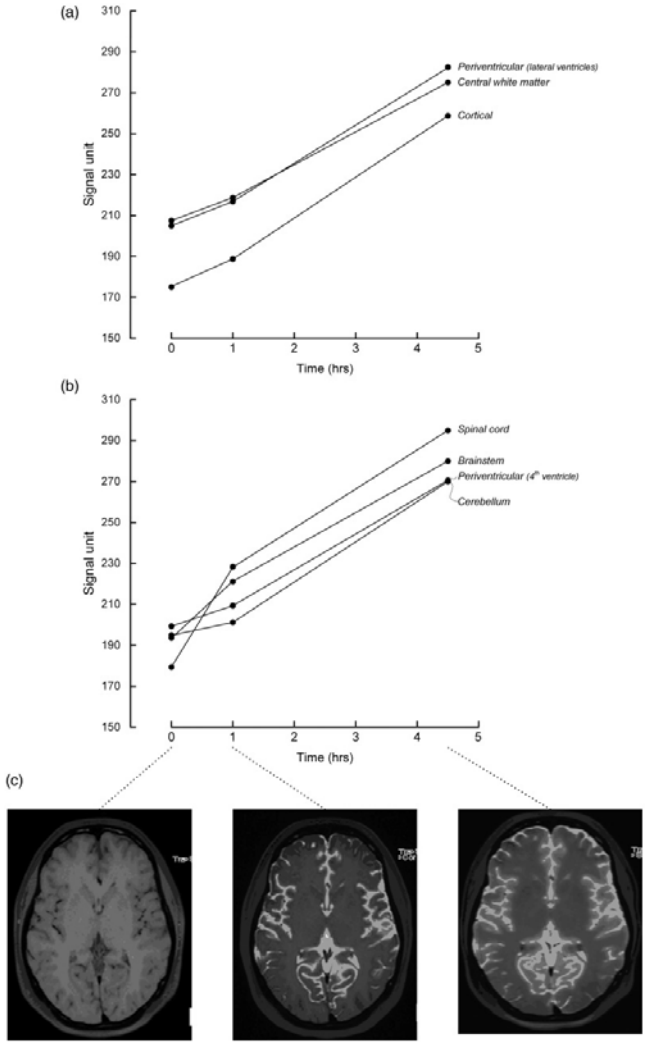

Figure 4: **Sagittal view of medial aspect of cerebral cortex showing postulated spatial sequence of spread of pathology in Alzheimer's disease from medial temporal lobe to sensory association cortices.**
The postulated temporal sequence is also shown indicating the prolonged incubation period of this disease. The depth of colour is in proportion to the density of pathology. Reproduced with permission from Smith DA, *Proc Natl Acad Sci* 2002; **99:** 4135–37.

# WORD OF THE DAY!



# GLYMPHATICS- CLEARANCE?



NEURAL WASTE DISPOSAL

# Clearing the Head

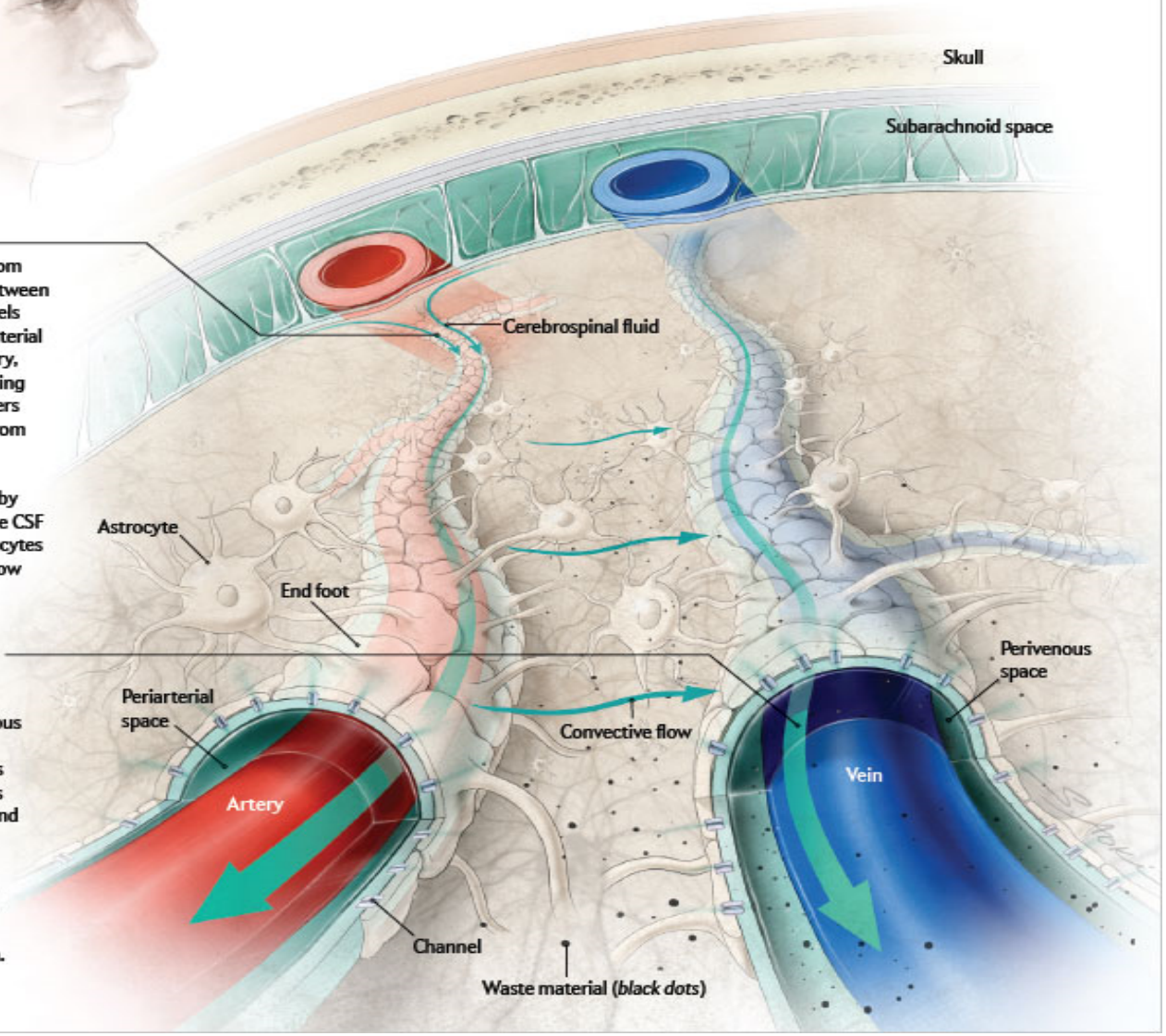
An intricate system of vessels—the glymphatic system—snakes throughout the brain, carrying fluid that rids the organ of discarded proteins and other wastes that can clump together and turn toxic if left in place. The protein fragments known as beta-amyloid peptides, which are present in Alzheimer's disease, are examples of the cellular detritus cleared through the drainage system, mostly during sleep.

## Incoming Fluid

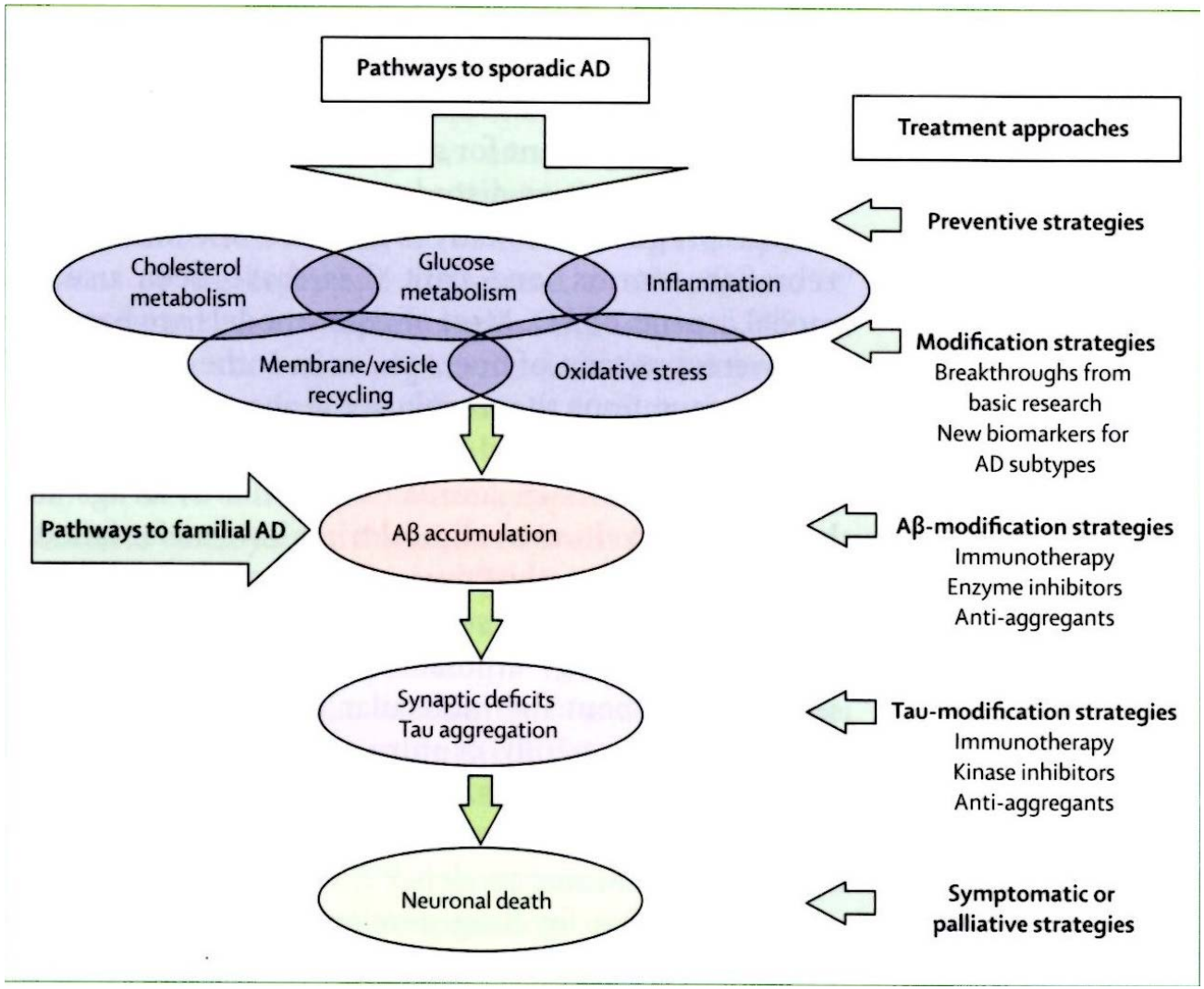
Cerebrospinal fluid (CSF) from the subarachnoid space, between the skull and the brain, travels through a cavity (the periarterial space) surrounding an artery, propelled along by the pulsing of blood flow. This fluid enters tiny channels that extend from the cavity into cells called astrocytes, whose end feet form the periarterial space by encircling blood vessels. The CSF then moves out of the astrocytes and travels by convective flow through brain tissue.

## Outgoing Wastes

The fluid, having picked up wastes from brain tissue, is transported to the perivenous space, which surrounds a network of veins that drains blood from the brain. In this cavity, the fluid passes around progressively larger veins that eventually reach the neck (*detail of brain above*). The wastes then move into the lymphatic system and eventually the bloodstream.



# TREATMENT THEORY



# PREVENTION

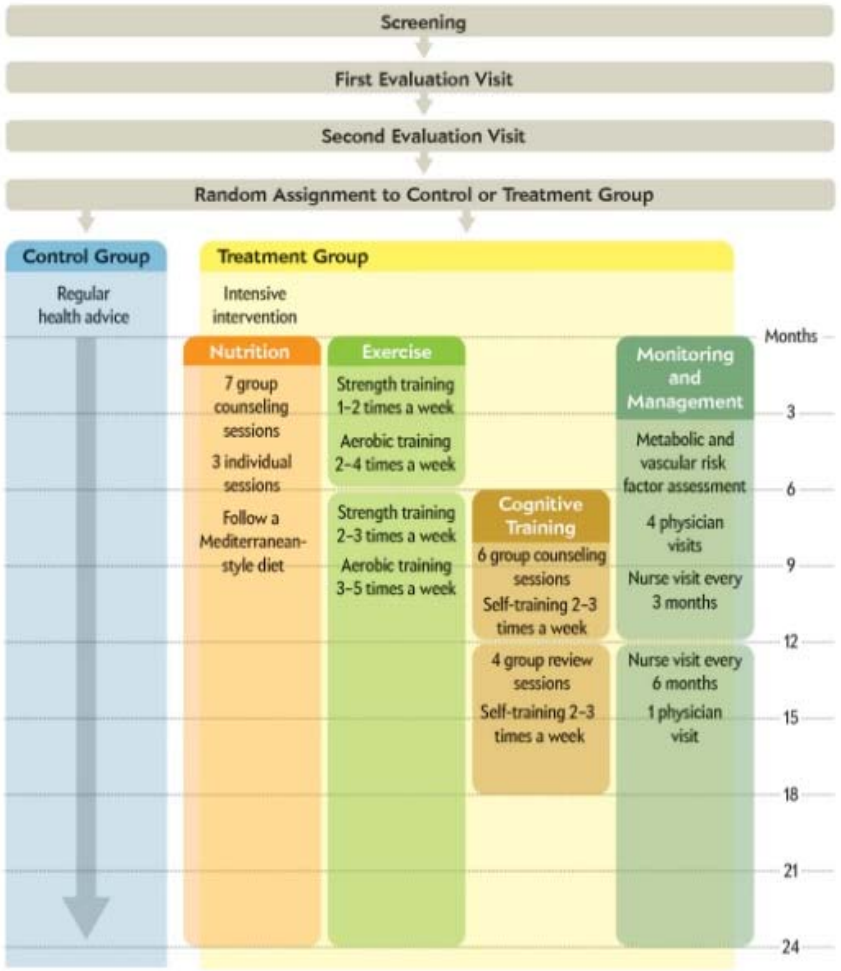
- Level of education attainment is protective. Even in grade school performance(JAMA 2002, NEJM 2003, Brain 2010)
- Occupational complexity is protective (Neuro 2014)
- Read, write, games slow rate of cognitive decline (Neuro 2013)-"idea density"
- Cognitive Reserve(differential preservation) refers to adaptive strategies-due to NE input?
- Brain Reserve (preserved differentiation) refers to your anatomy; synaptic density

# FINGER TRIAL-SLOW DEMENTIA

TRIAL DESIGN

## FINGERing Dementia

Between 2009 and 2011 a clinical trial—the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)—enrolled 1,260 men and women between the ages of 60 and 77. Of that number, 629 were randomly assigned to a control group, and 631 were directed to a treatment group. All of those recruited in both groups had a slightly higher risk for dementia. Members of the treatment group were then directed to follow a regimen of diet, exercise and cognitive training. They received nurse visits, initially every three months, and visited physicians five times during the two-year course of the trial to check on how well they were able to follow recommendations. Control group participants, in contrast, received only basic health advice during two physician visits.

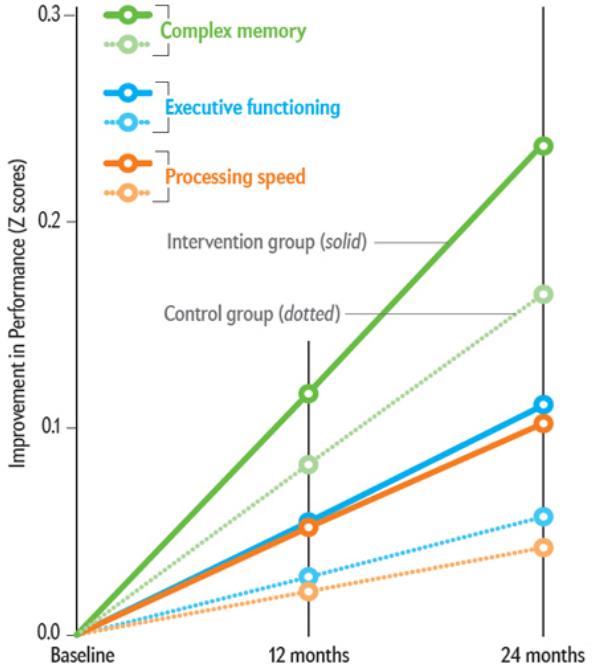


# FINGER TRIAL-RESULTS

TRIAL RESULTS

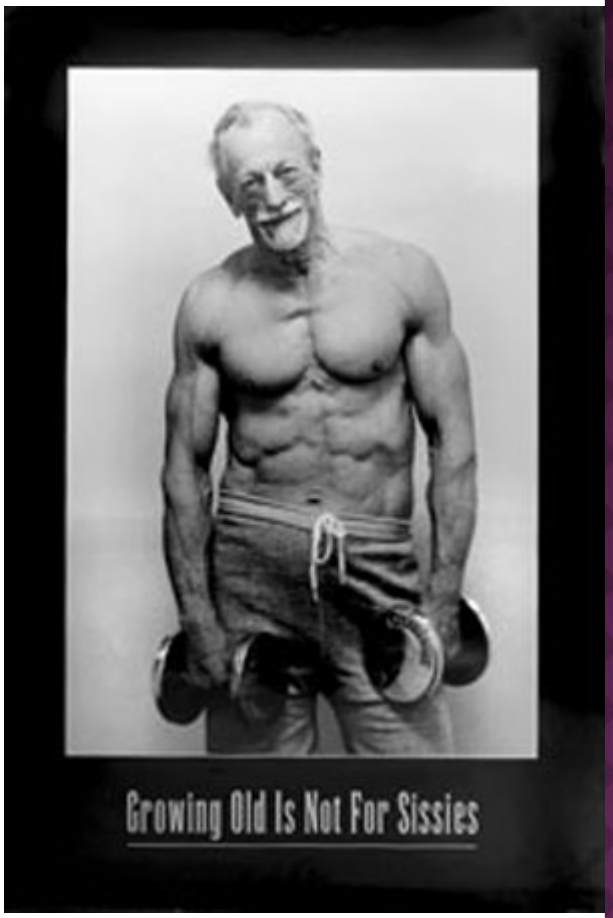
## Getting Better

FINGER trial participants in both the treatment and control groups improved on various cognitive measures of memory, executive functioning and mental-processing speed. But the treatment group had better scores after 24 months than the control group did.



# THE CURE

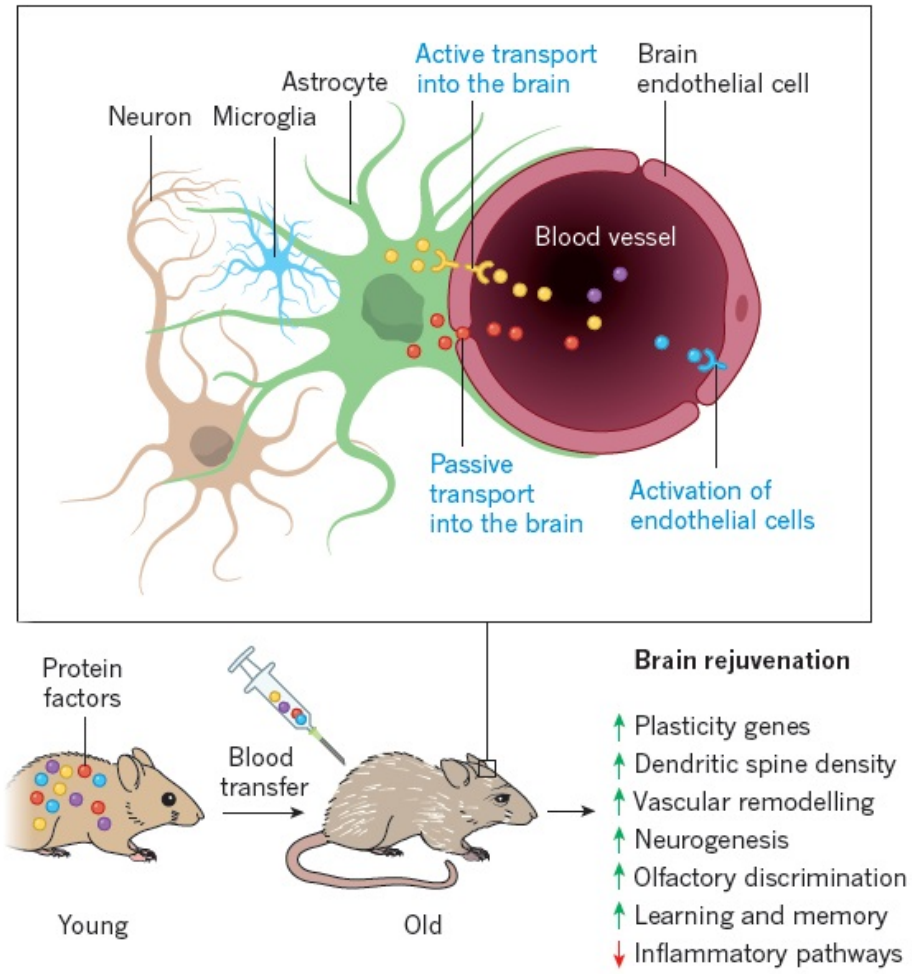
- EXERCISE !!!!!



# THE CURE: EXERCISE

- Midlife fitness reduces risk by 36%. All markers reduced(amyloid, glucose, atrophy) Neuro 2014; 83:1753)
- Decline with MCI or Alz is reduced
- Vascular dementia?
- BP variability, carotid stiffness, microvascular white matter changes.
- MET, VO2, 80% of max HR
- Huff and puff.

# YOUNG BLOOD?




Wyss-Coray; Nature:180-186; 11/10/2016

# FDA APPROVED DRUGS

- Acetylcholine esterase inhibitors means more acetylcholine and better neuronal communication. Donepezil, rivastigmine.
- Memantine helps the neurotransmitter glutamate
- They help a failing brain work better and help keep patients at home longer.
- NOT treatment for the underlying disease.

# CONCLUSION

- EXERCISE
- STAY MENTALLY ACTIVE-Complex tasks
- You can adapt to brain aging-individualize
- STAY TUNED.

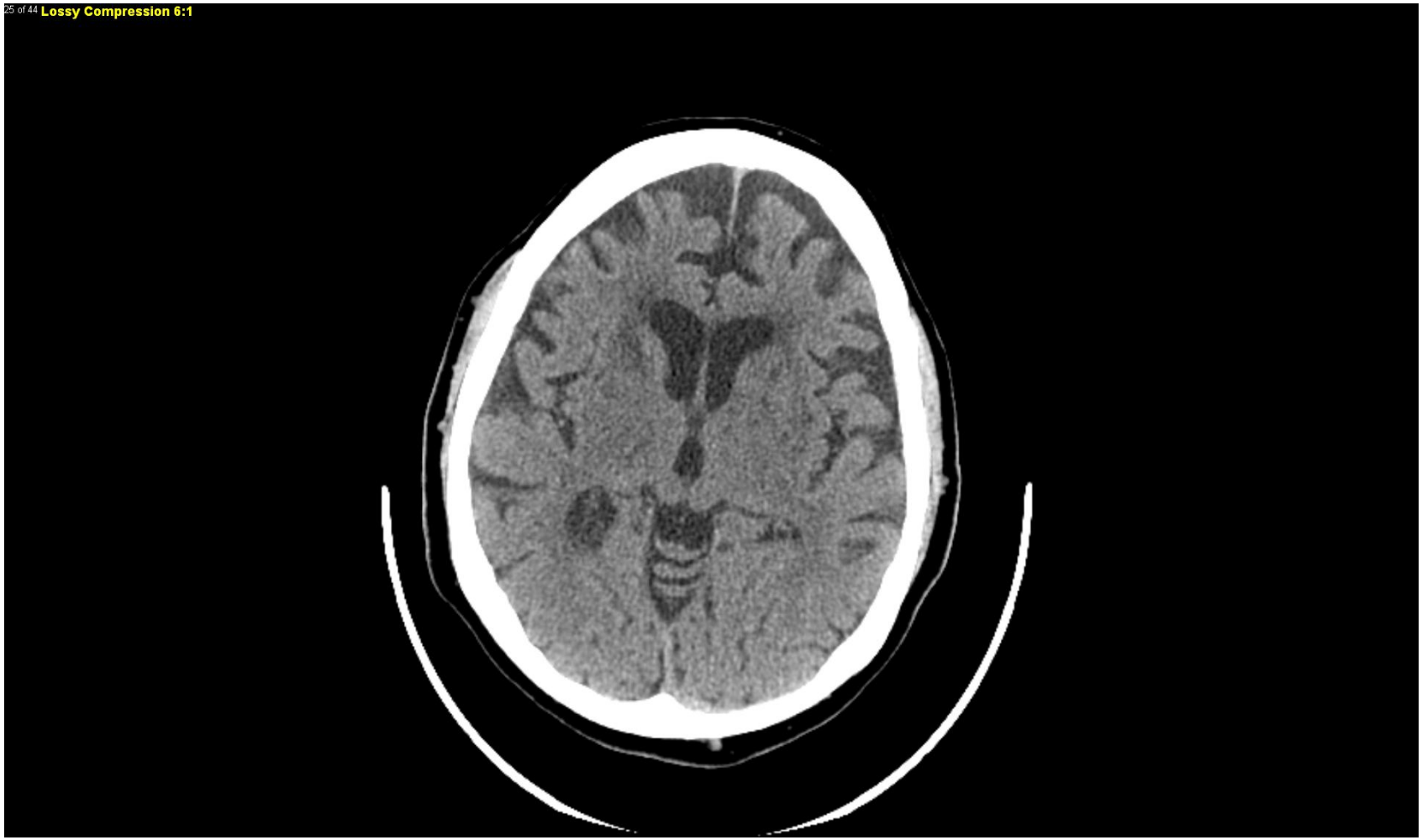
eat curry and don’t be grumpy

- Thanks
- Questions?

# IMPLICATION?

- Maybe each variable will need to addressed separately?
- Insulin-like GF-1 and glucose and atrophy
- Acitretin (alpha secretase promoter) to cleave amyloid precursor better and less B-amyloid.
- Tau or intracellular demise. Nothing brewing except this may be how AD spreads(prion)
- Education and cognitive and brain reserve.
- Plasticity and adaptation. TDP-43?

# ATROPHY OR NEURODEGENERATION



# IS ALZHEIMER'S DISEASE AN INFECTION?

- Infectious disease burden correlates to lower mental status scores. Viruses correlate better. Effect modified by EXERCISE. ? Trial of antiviral drugs? (Neuro 2013;80:1209)
- Virus kills neurons and causes inflammation which kills neurons(amyloid). ApoE4 increases herpes infections which increases Alz. JofAlzD 2013
- We get old and immunity not so good.

# PLACEBO

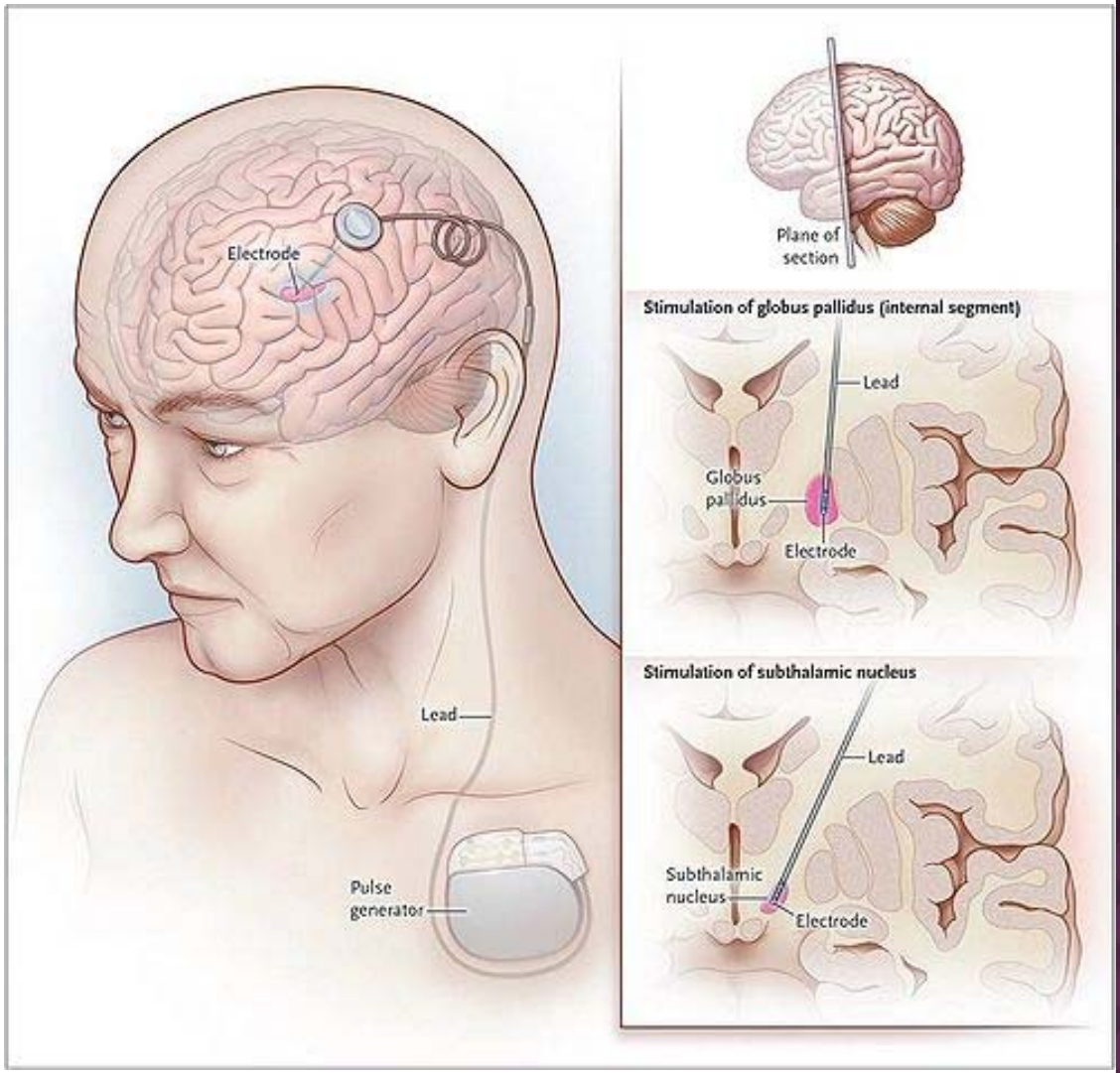
- Do you think better if you have to think better and believe you are thinking better?
- Flight suits and visual acuity-better vision if it is important
- Ellen Langer and NH experiment with 75 y/old
- We are what we think we are?

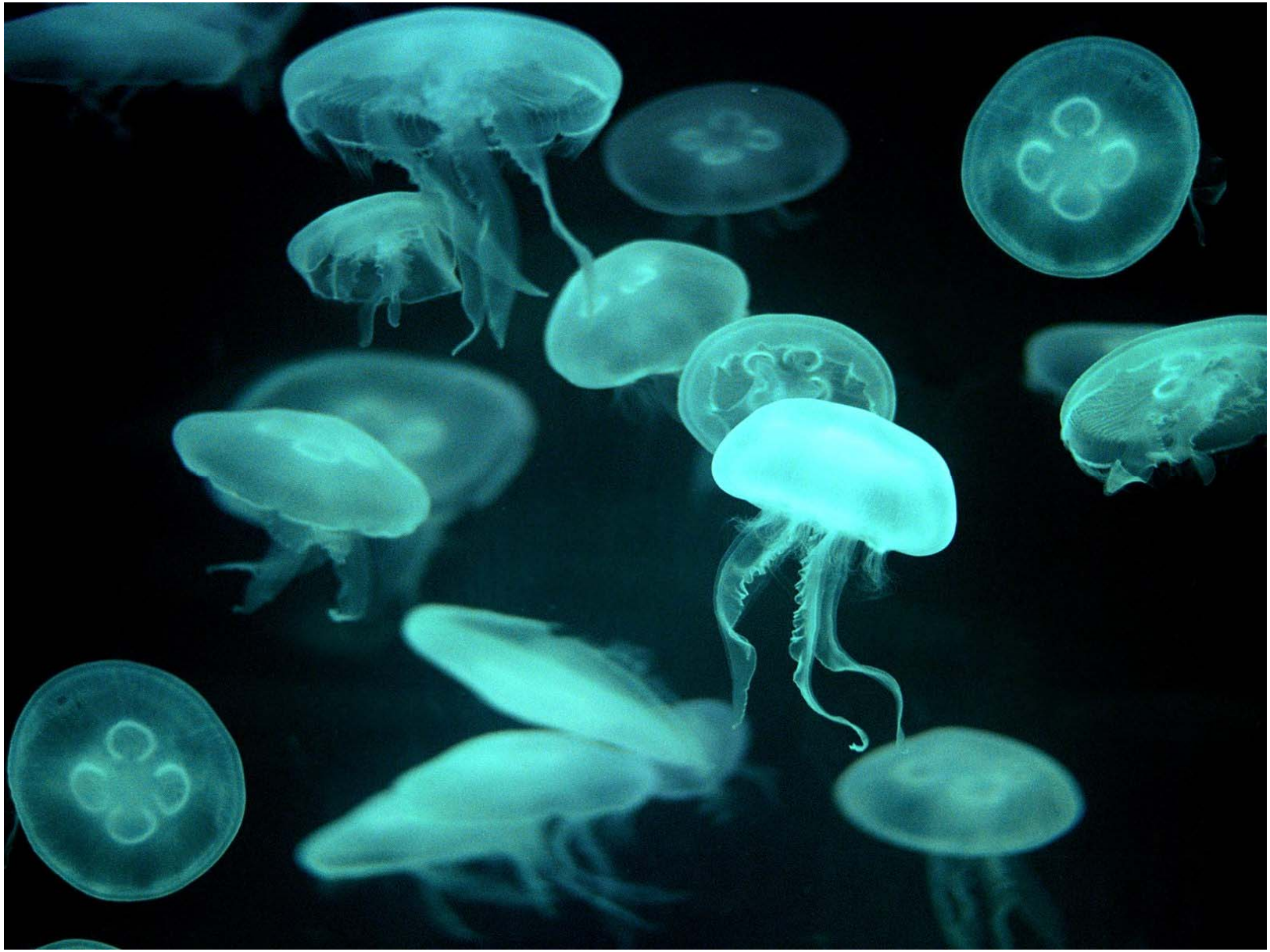
# LET'S ALL GET STONED

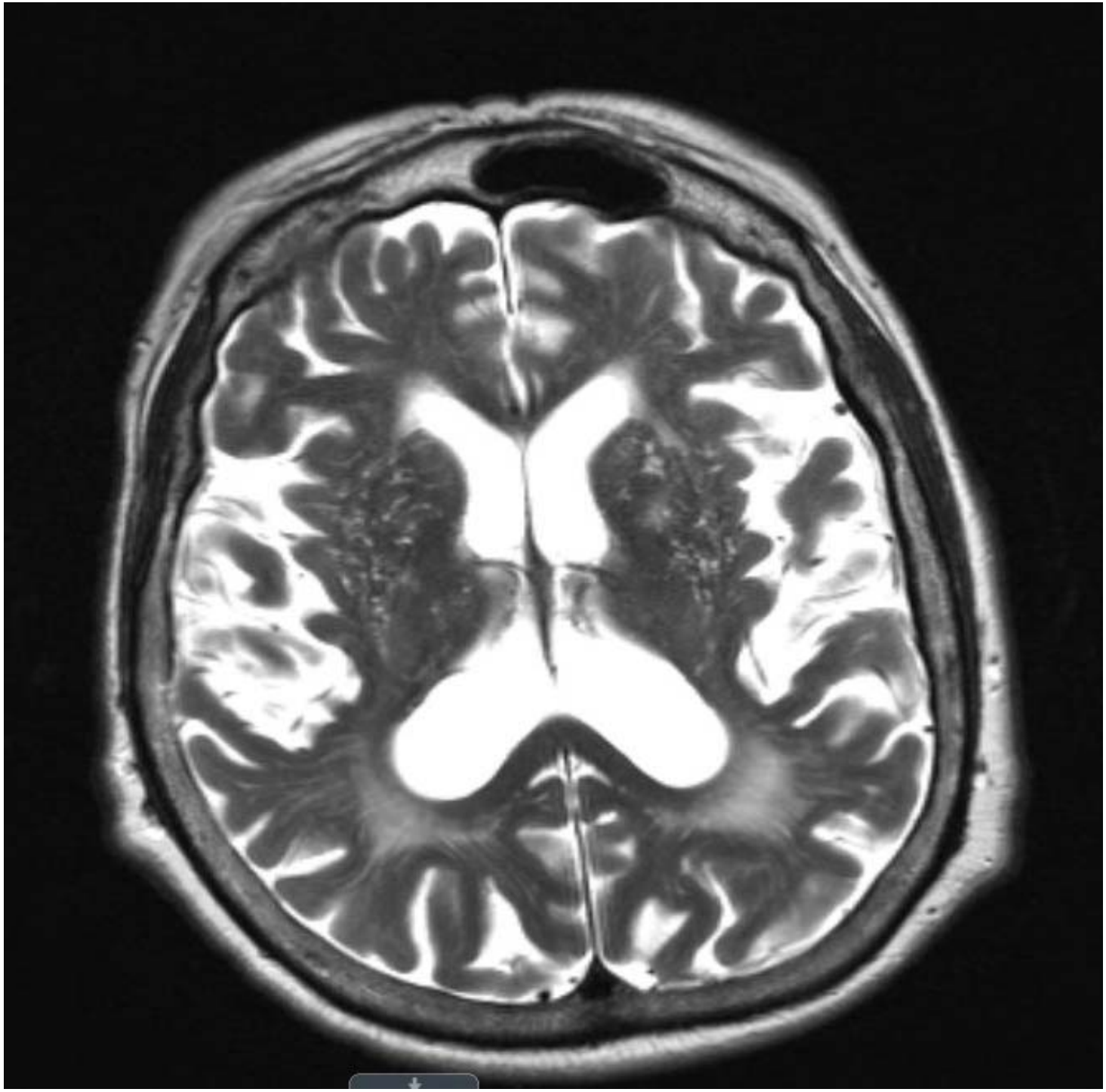
Cao, et al find THC prevents cells from producing Beta amyloid. No amyloid ; no Alzheimer's

# DEEP BRAIN STIMULATION FOR MEMORY

DARPA- UCLA, U of Penn, Johns Hopkins-stimulate the fornix, ento







# PERSONALITY EFFECTS

- Neuroticism-fear, moodiness, envy, loneliness, worry, frustration, jealousy
- Neuroticism midlife increases AD risk Neuro 2014;1538
- Cynical distrust associates with AD Neuro 2014;2205
- Depression associates with AD
- Self reporters of memory complaints have lots of AD pathology even if no impairment.

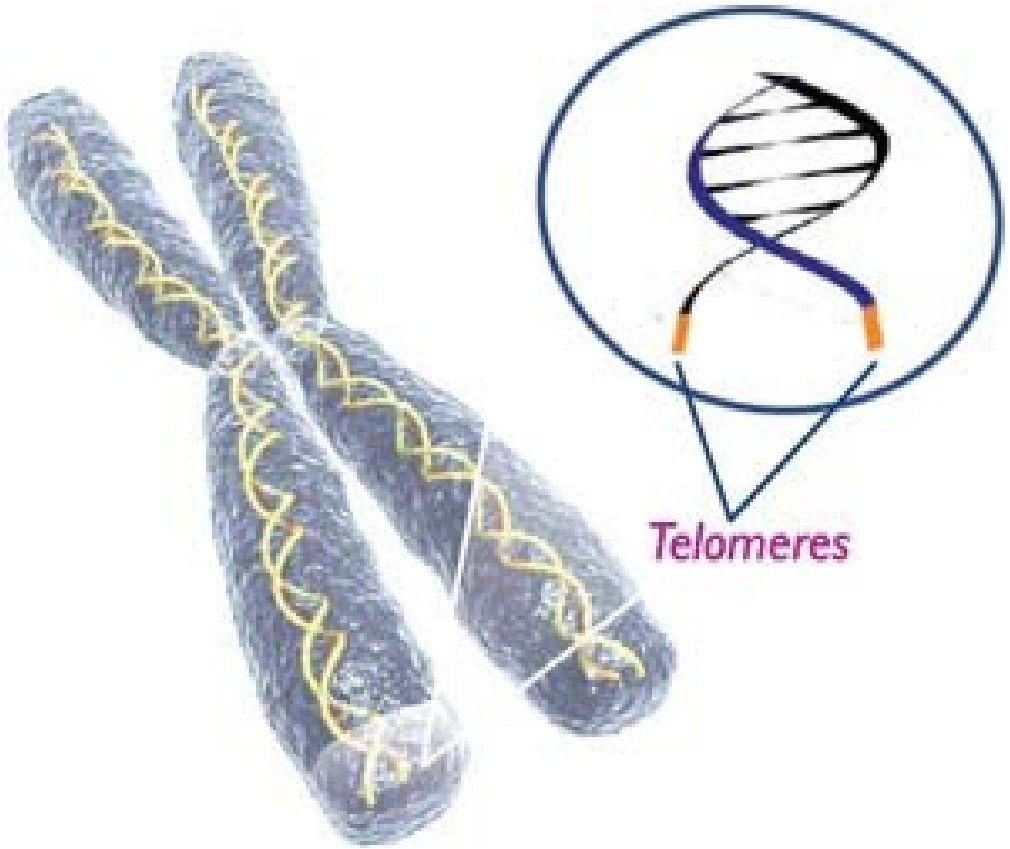
# MEMORY ENHANCERS

- Prevagen- Apoaequorin which controls bioluminescense.
- Clinical studies are pretty weak-in house Groton Maze Learning task.
- FDA unhappy-seizures and strokes-synthetic hence a drug not a supplement.
- ENJOY

# NEW STUFF - FRINGE

- Infection
- Drugs and diet
- Computers and stimulators
- Placebo
- Memory enhancers
- Personality

# TELOMERES



# HEAD TRAUMA

- Head trauma bad
- Traumatic Brain Injury mimics Alz pathologically
- Football concussion have increase BBB
- Increase amyloid in MCI with head trauma
- White matter and cognition change within a season of football
- 2 fold increase in veterans with TBI Neuro 2014;83:312

# TELOMERES AND AGING

- Telomere is the cap of your shoelace
- Short telomere correlates to aging, disease and cerebral atrophy
- There are activities associated with long telomere
- Klotho is a gene that helps synapses/cognition
- REST(repressor element silencing Transfactor)
- Young blood helps old mice think.

# ENVIRONMENT/DIET

- DDT levels higher in people with AD
- Consumption of trans fats associated with memory impairment but ketones good
- Still articles about cooper, aluminum
- UCLA documented improved memory in AD via diet rich in fish and vitamins and lifestyle rich with sleep and exercise. Aging; Sept(2014)
- Finland too! Alz Dement. 2013;9:657-665

# CURCUMIN(TUMERIC) AND ALZ

- India vs USA: Prevalence 4 times less in India for adults aged 70-79
- Score on MMSE better among curry eaters than non eaters.
- MOA?; reduce microglia, reduce inflammatory factors, metal chelation, antioxidant, can disrupt amyloid formation.

  ( Ann Indian Acad Neurol. 2008;11:13-19)

# COMPUTER AVATAR?

Put who you are into a computer and use it as your real brain declines.