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University of Kentucky College of Medicine, Lexington, KY

ALZHEIMER'S DISEASE & RELATED DISORDERS RESEARCH UPDATE 2012

Disclosures

- I will discuss research findings with unapproved implications for diagnosis and treatment of degenerative brain disease
- Paid Consultant: Lilly
- Contract Research: Baxter, Jannsen, Medivation, Pfizer

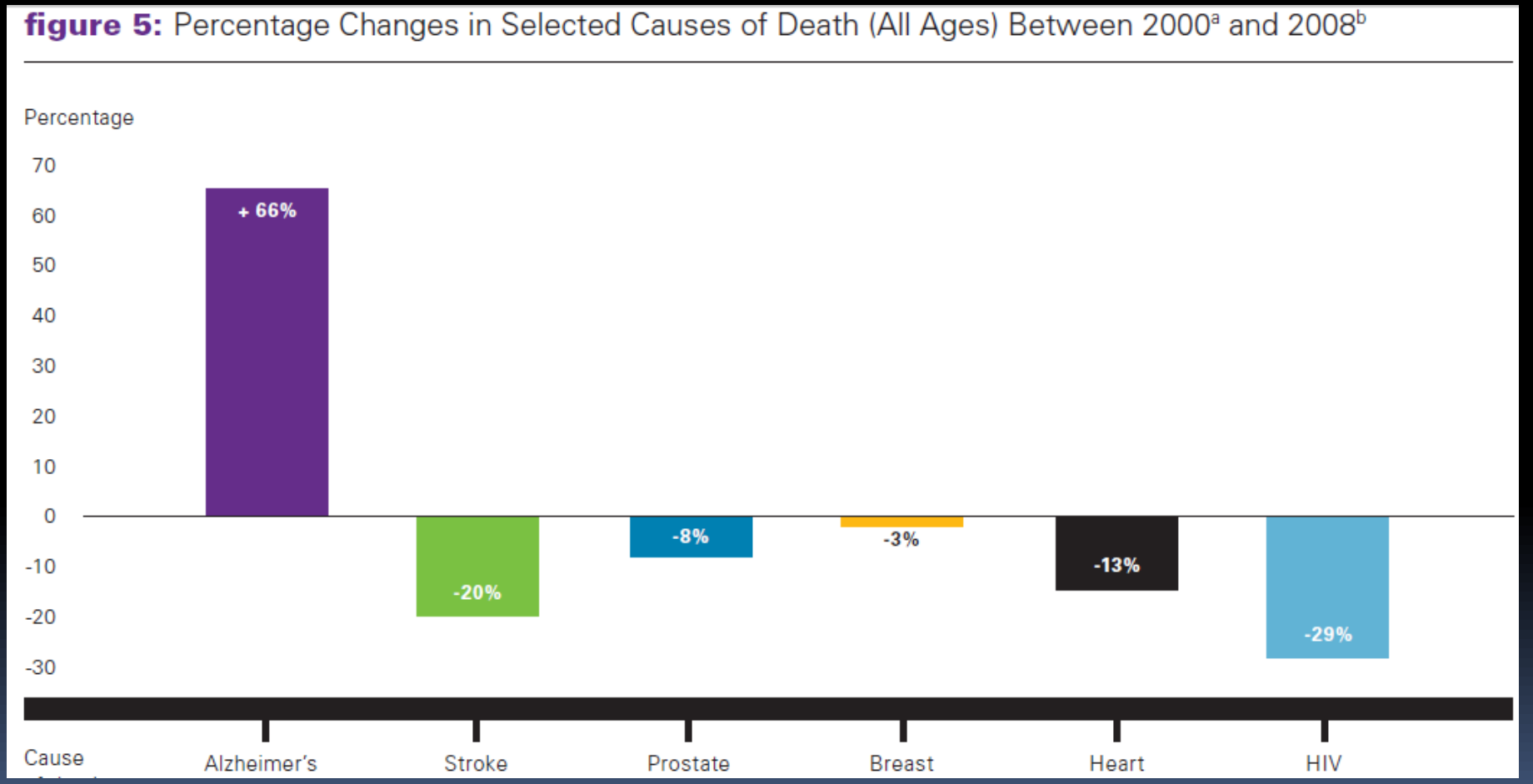
OUTLINE

- Alzheimer's disease
- Vascular dementia
- Frontotemporal dementia
- Normal Aging

Alzheimer’ disease

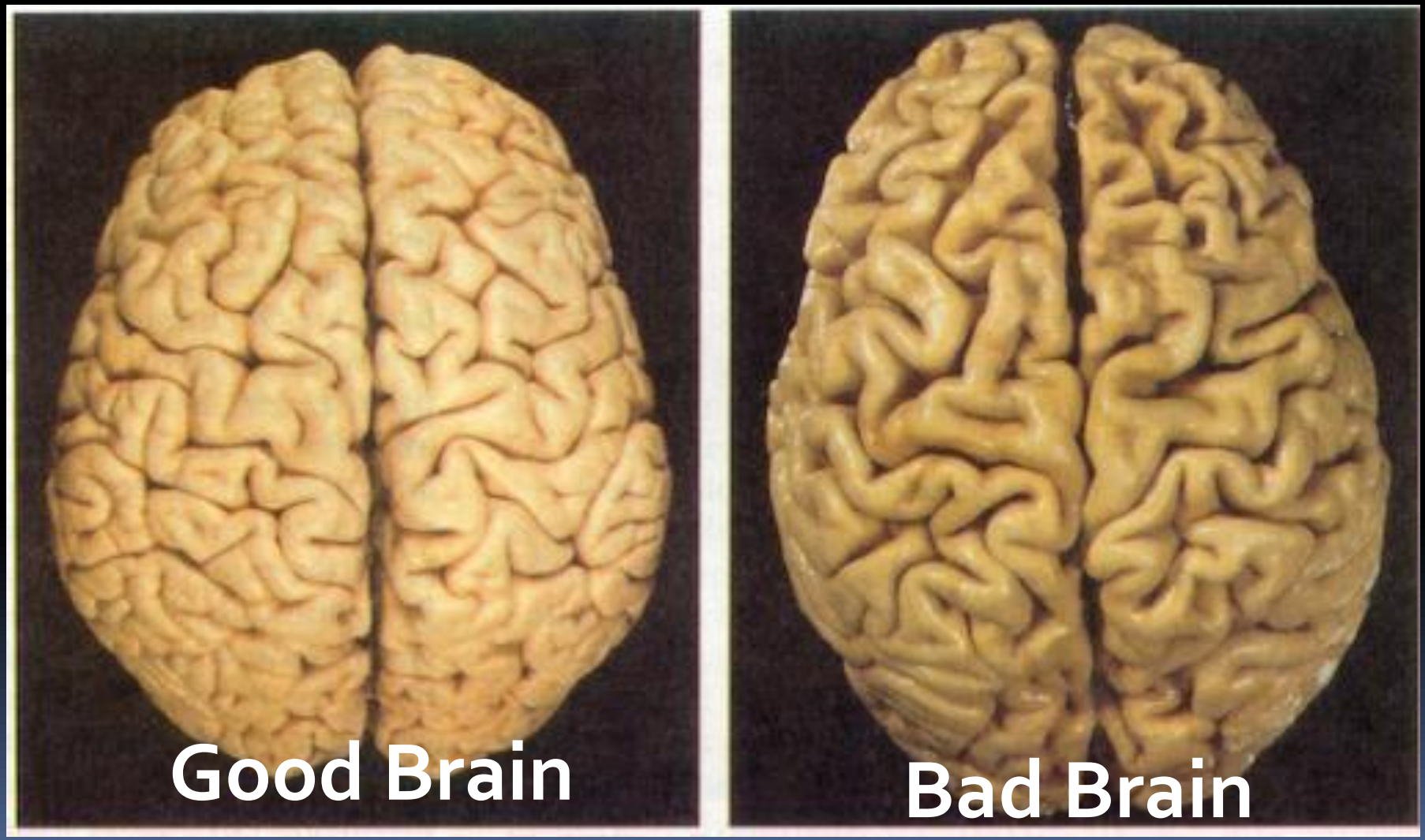
Overview & Research Advances 2012

We really suck at this!



Alzheimer Association Facts & Figures 2011

It all boils down to this…

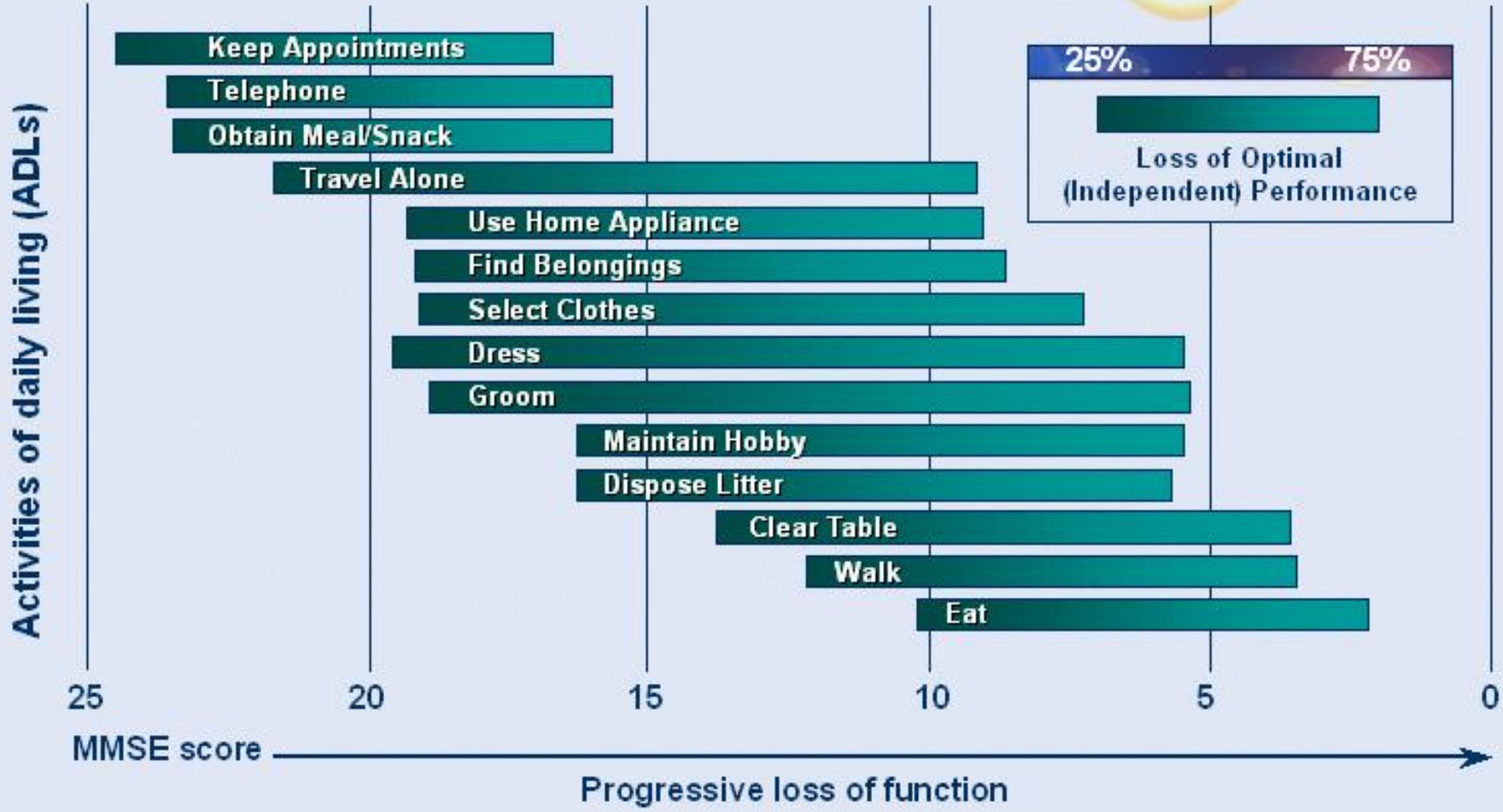


The cost to society…

- For each penny the National Institutes of Health spends on Alzheimer's research, we spend more than $3.50 on caring for people with the condition
- We spend $172 billion a year to care for people with Alzheimer's. By 2020 the cumulative price tag, in current dollars, will be $2 trillion, and by 2050, $20 trillion.
- NIH spends about $3 billion a year on AIDS research, while Alzheimer's, with five times as many victims, receives a mere $469 million.

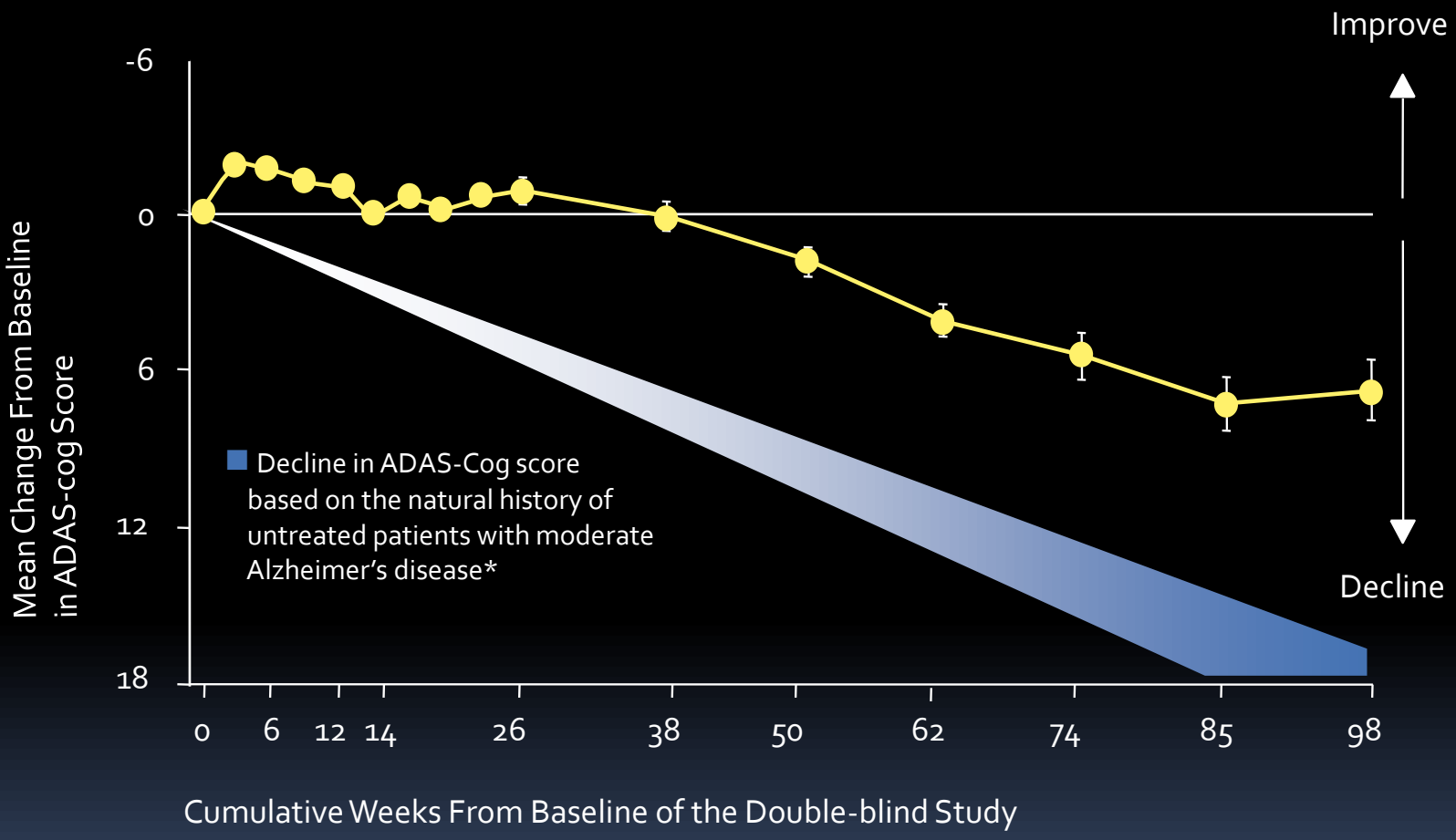
Sandra Day O'Connor

MMSE Scores Correlate With Functional Ability



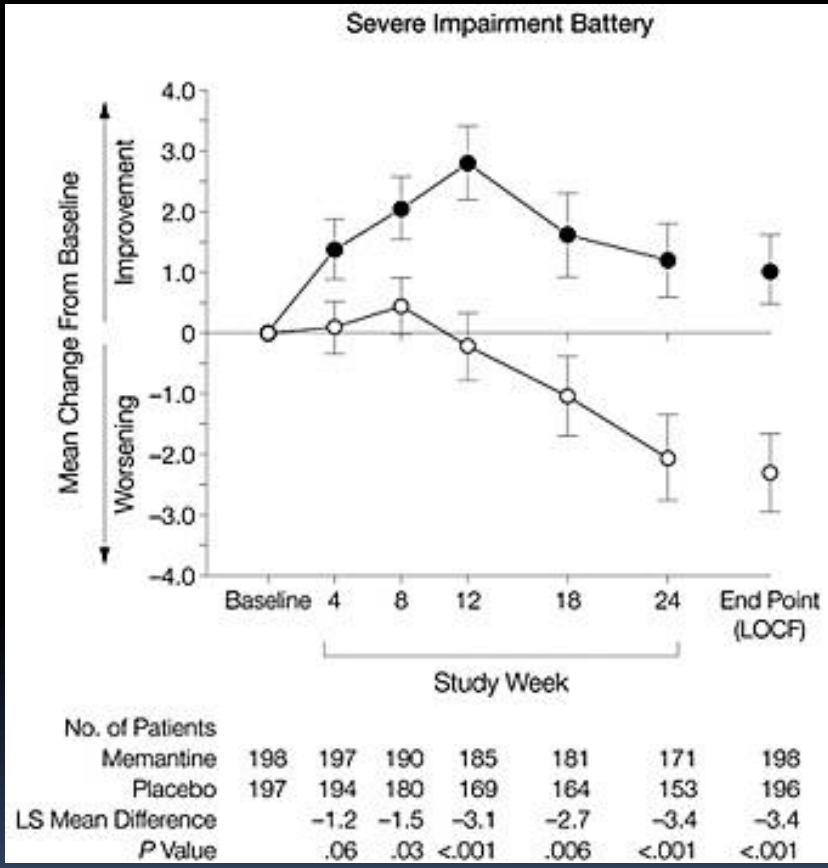
Adapted with permission from Galasko et al. *Eur J Neurol.* 1998;5:S9-S17.

Long-term Effects of Donepezil on Cognition: ADAS-Cog Mean Change From Baseline

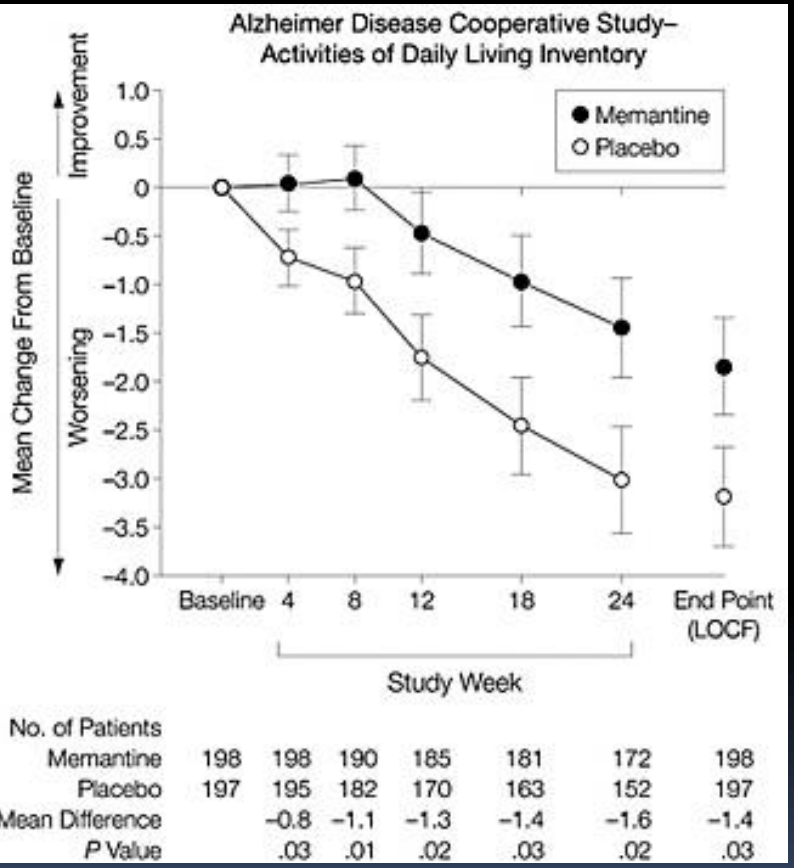


Rogers SL, Friedhoff, LT. *Eur Neuropsychopharmacol*. 1998;8:67-75.
*Stern RG, et al. *Am J Psychiatry*. 1994;151:390-396.

Increased benefit in mod-severe AD adding memantine to AchEI



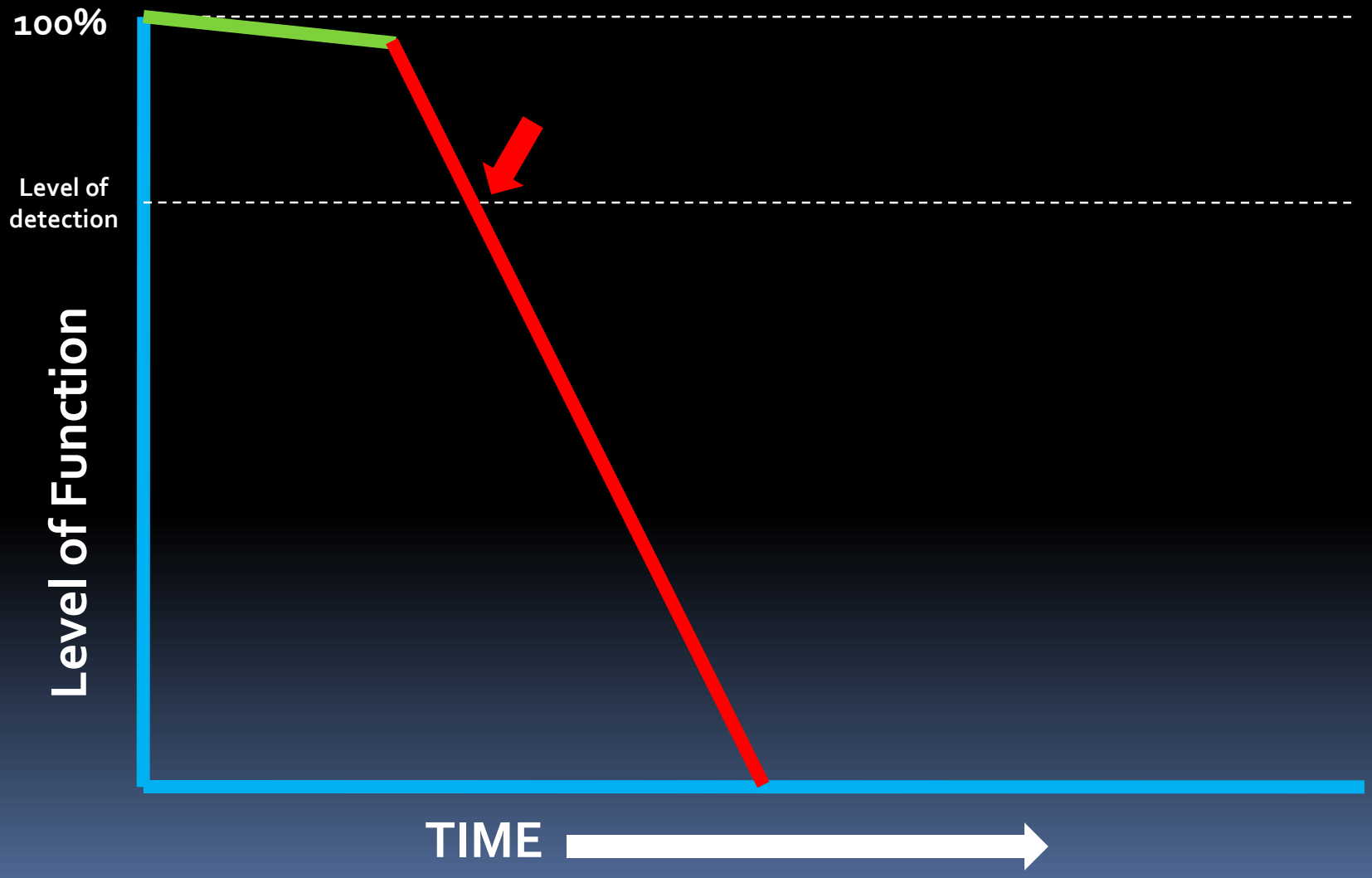
No. of Patients							
Memantine	198	197	190	185	181	171	198
Placebo	197	194	180	169	164	153	196
LS Mean Difference		-1.2	-1.5	-3.1	-2.7	-3.4	-3.4
P Value		.06	.03	<.001	.006	<.001	<.001



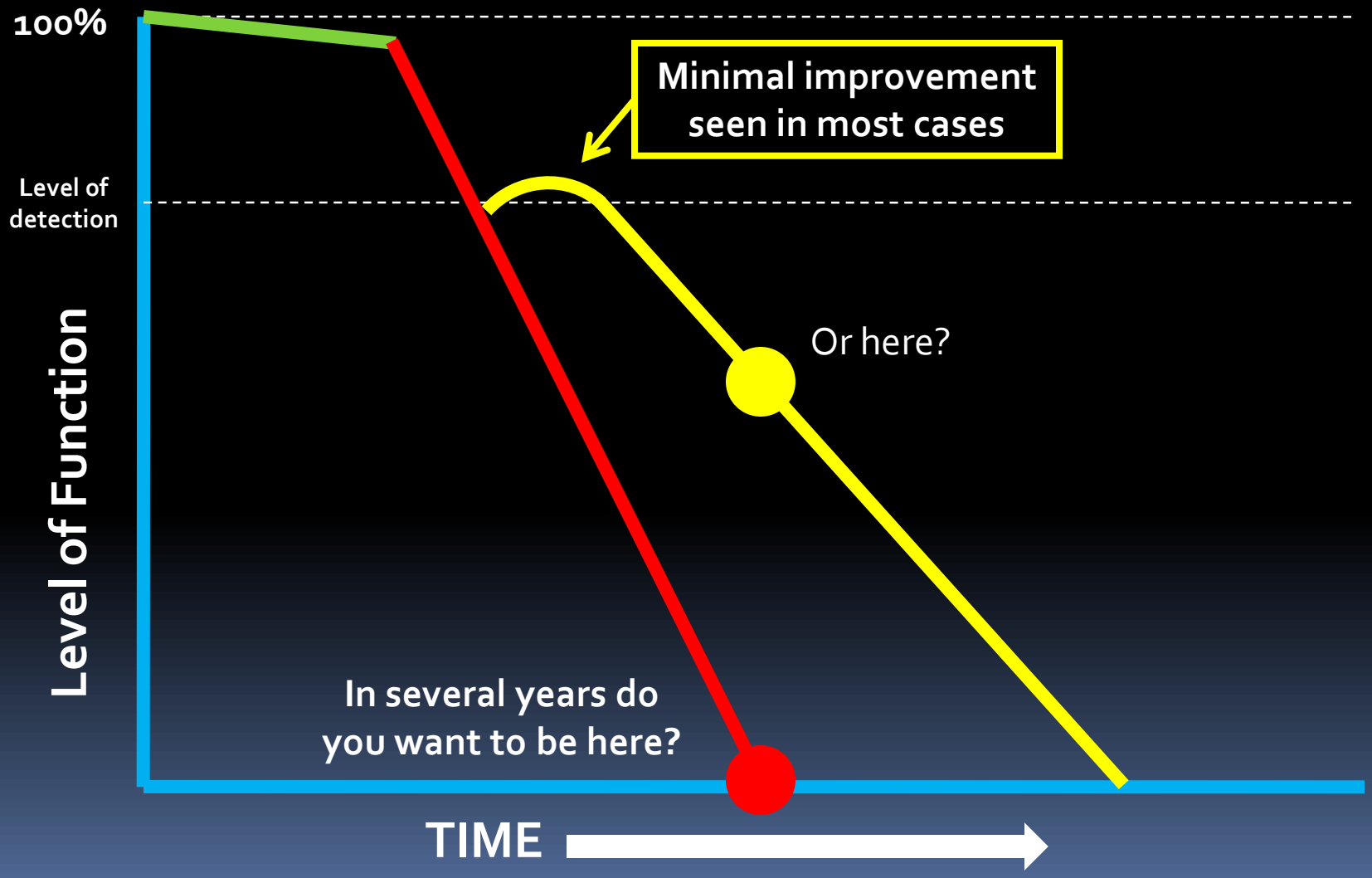
No. of Patients							
Memantine	198	198	190	185	181	172	198
Placebo	197	195	182	170	163	152	197
LS Mean Difference		-0.8	-1.1	-1.3	-1.4	-1.6	-1.4
P Value		.03	.01	.02	.03	.02	.03

Tariot PN. Farlow MR. Grossberg GT. Graham SM. McDonald S. Gergel I. Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA. 291(3):317-24, 2004 Jan 21.*

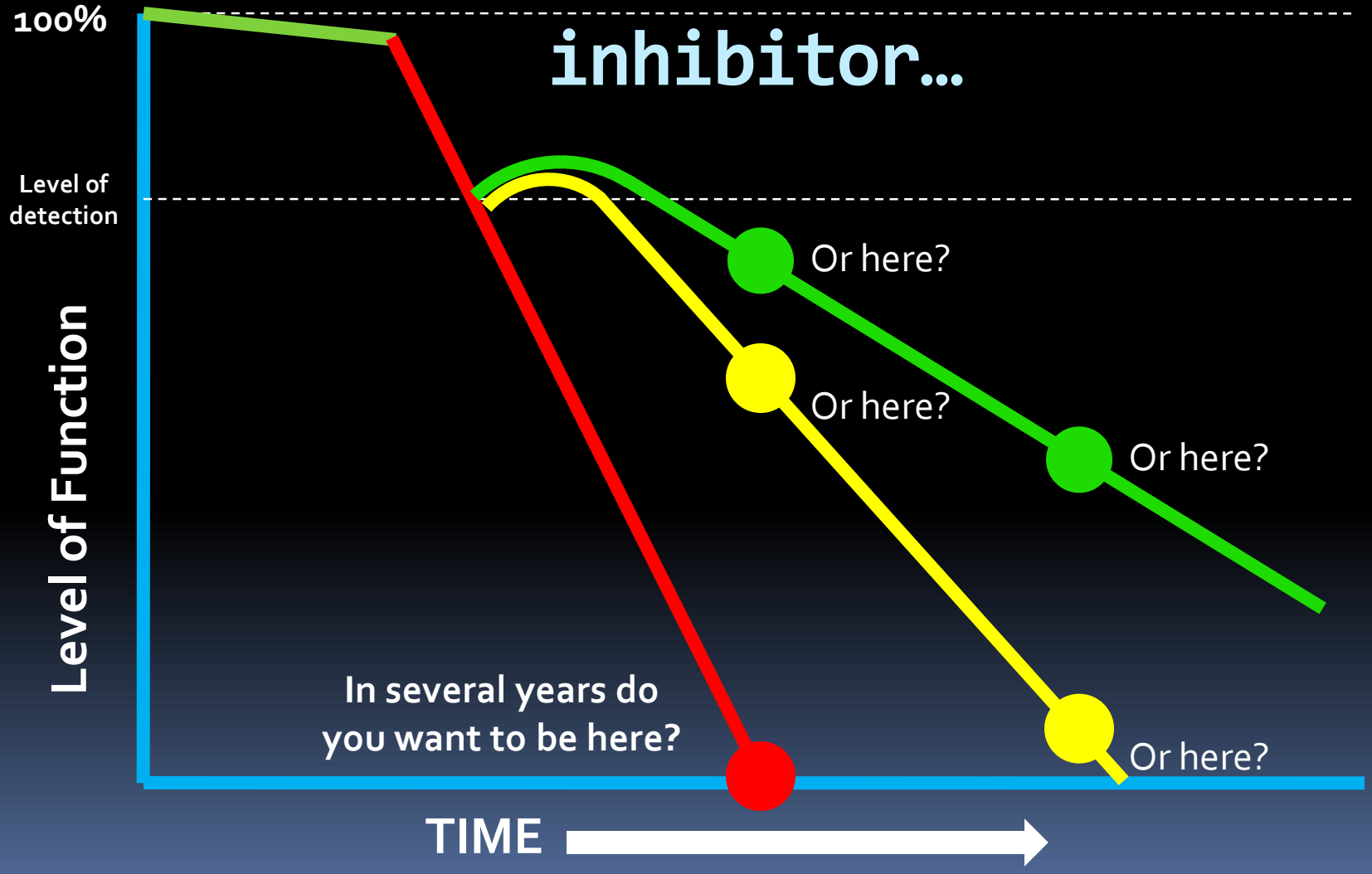
This is Alzheimer's disease untreated



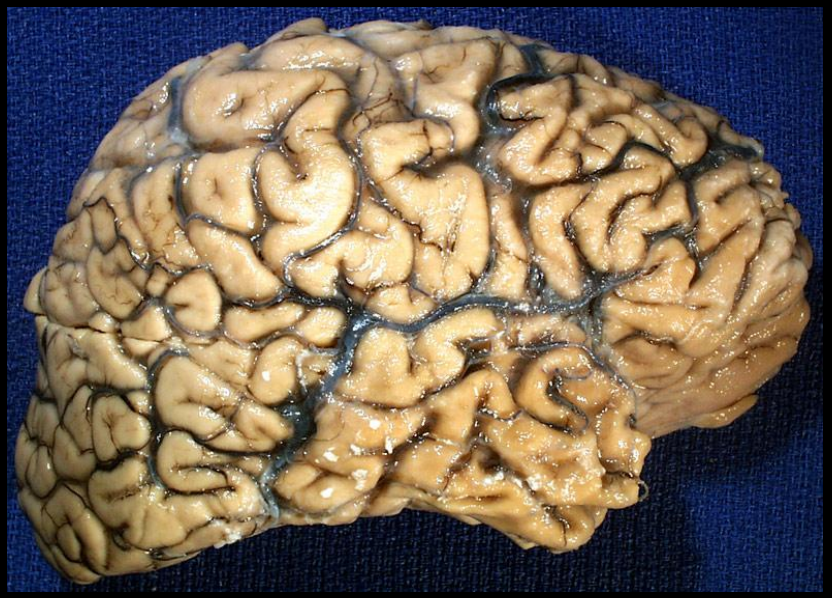
Let's add a cholinesterase inhibitor…

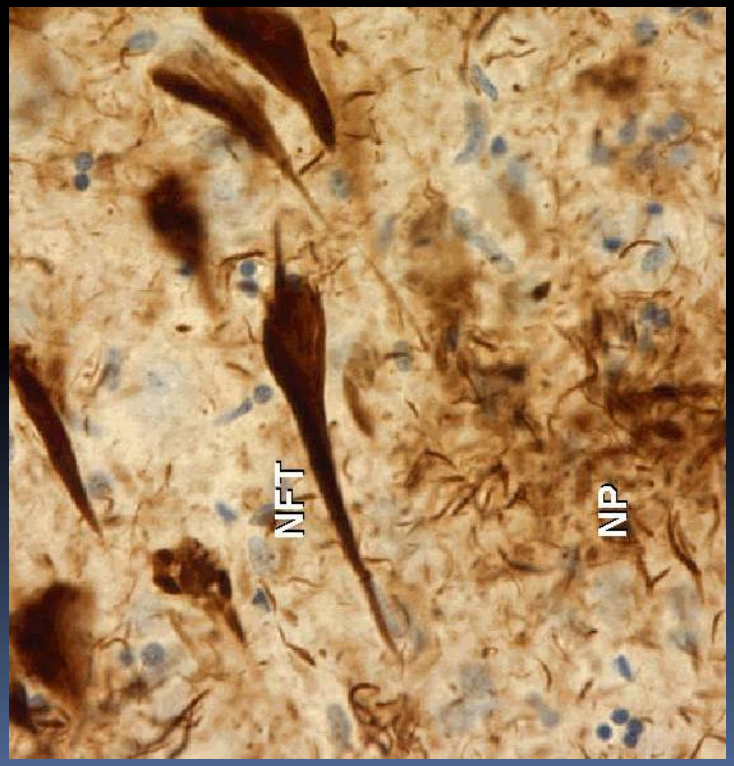


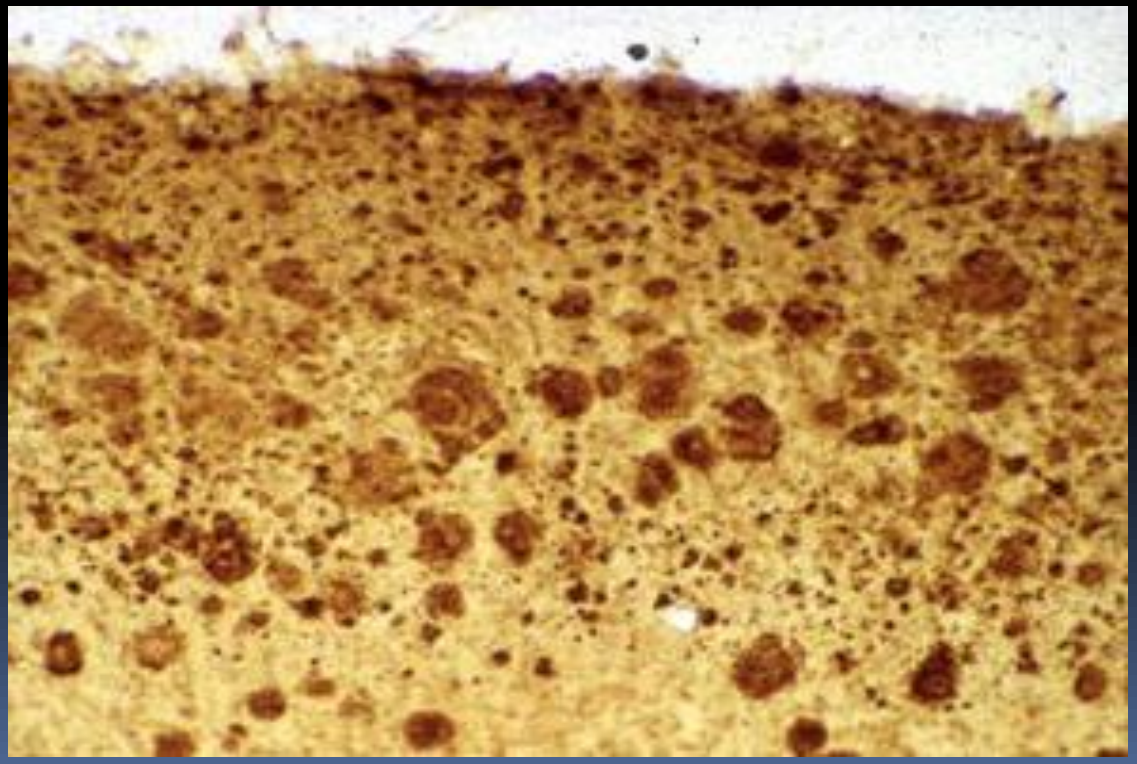
Now let's add a NMDA antagonist to our cholinesterase inhibitor…



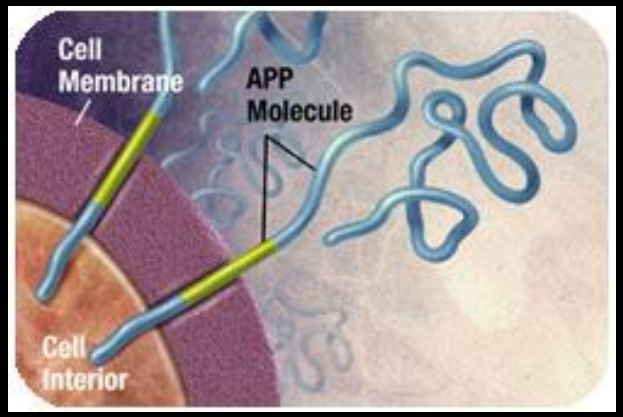
Alzheimer's disease pathology

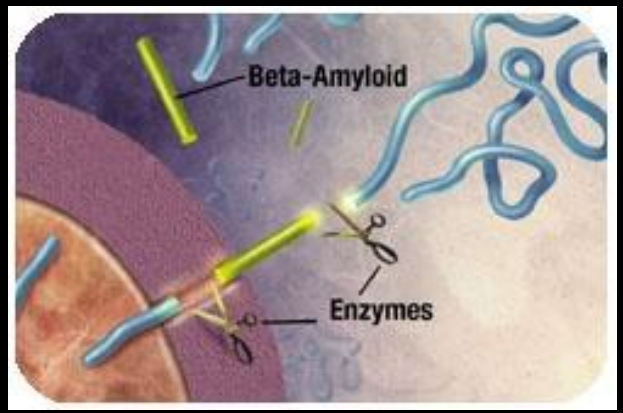


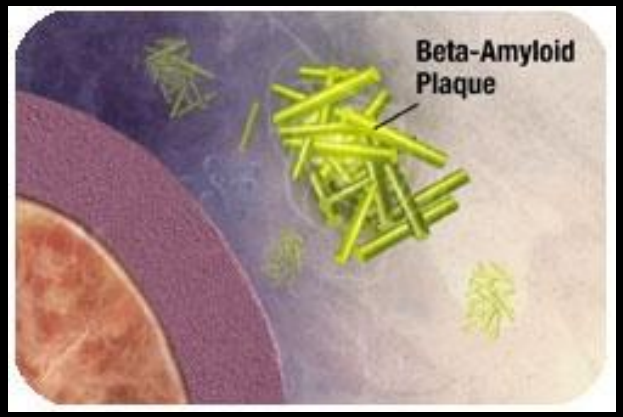




β amyloid is a key player in AD





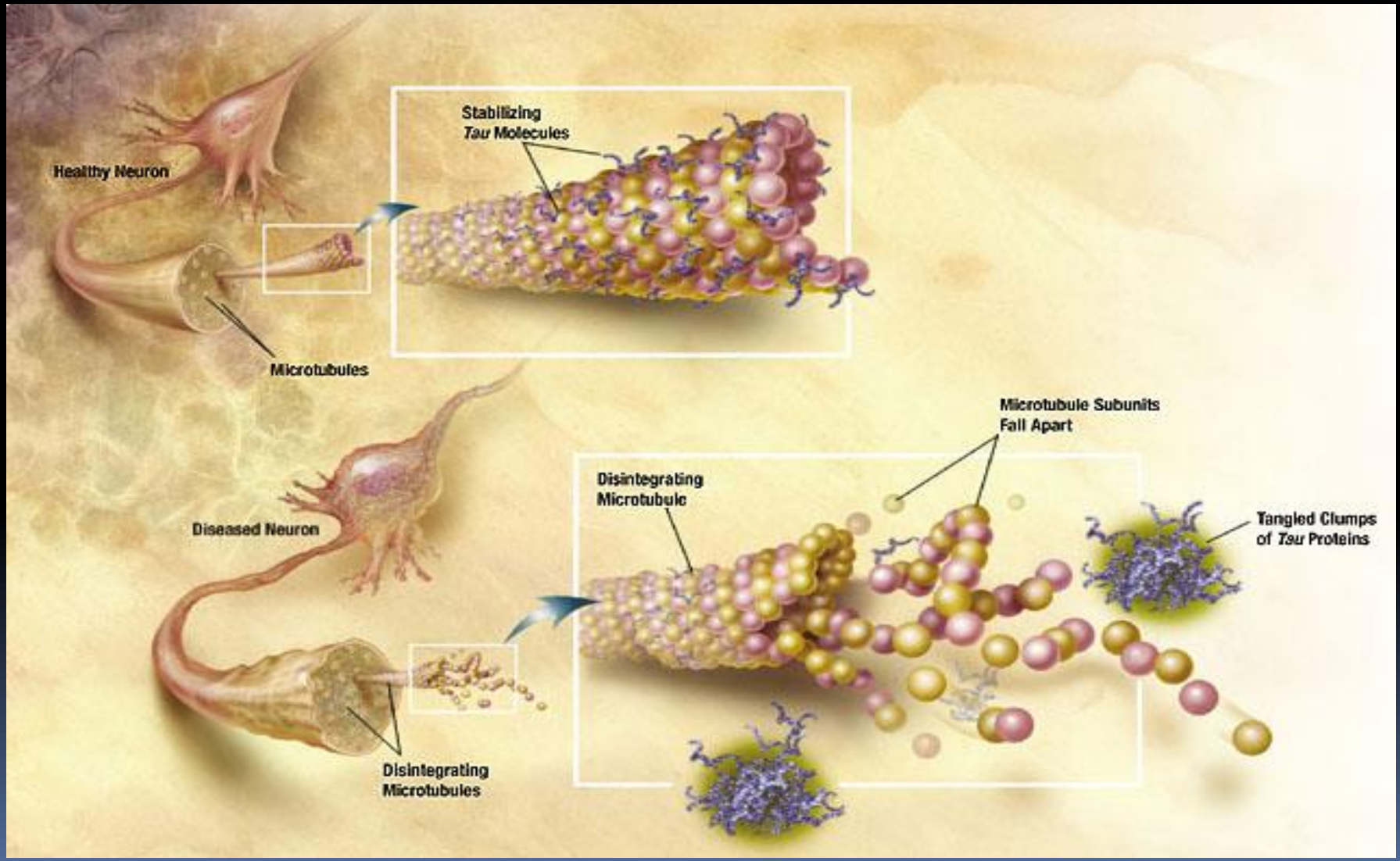


1) APP is a membrane-bound glycoprotein that may serve as a growth factor in injury and repair

2) APP is normally cleaved by α-secretase and β-secretase, but in AD, γ-secretase is active

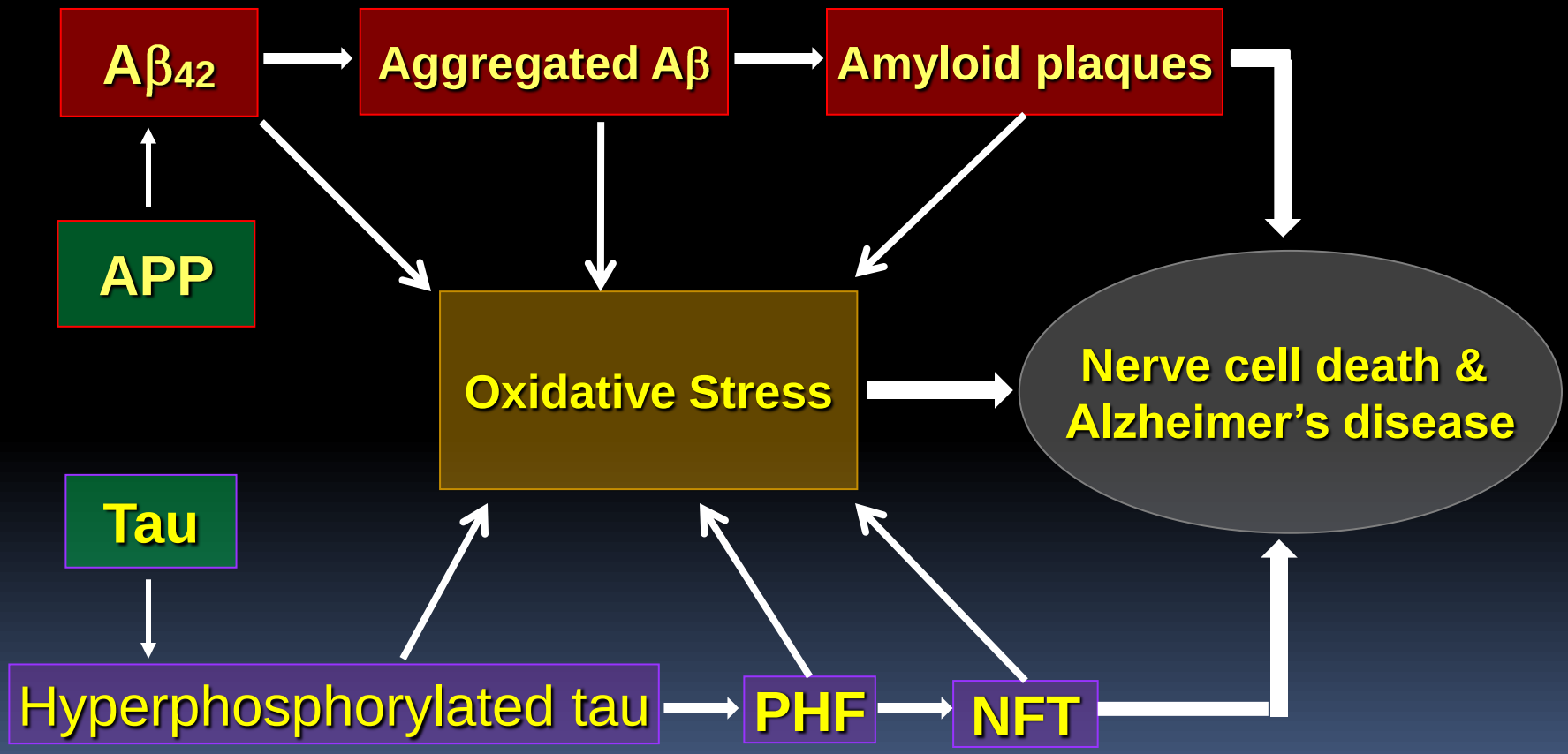
3) β-amyloid is toxic to cells and accumulates in brain tissue as amyloid plaques, a hallmark of the disease

The role of the microtubule-associated protein tau in AD



Oxidative stress is like brain rust or corroded batteries…

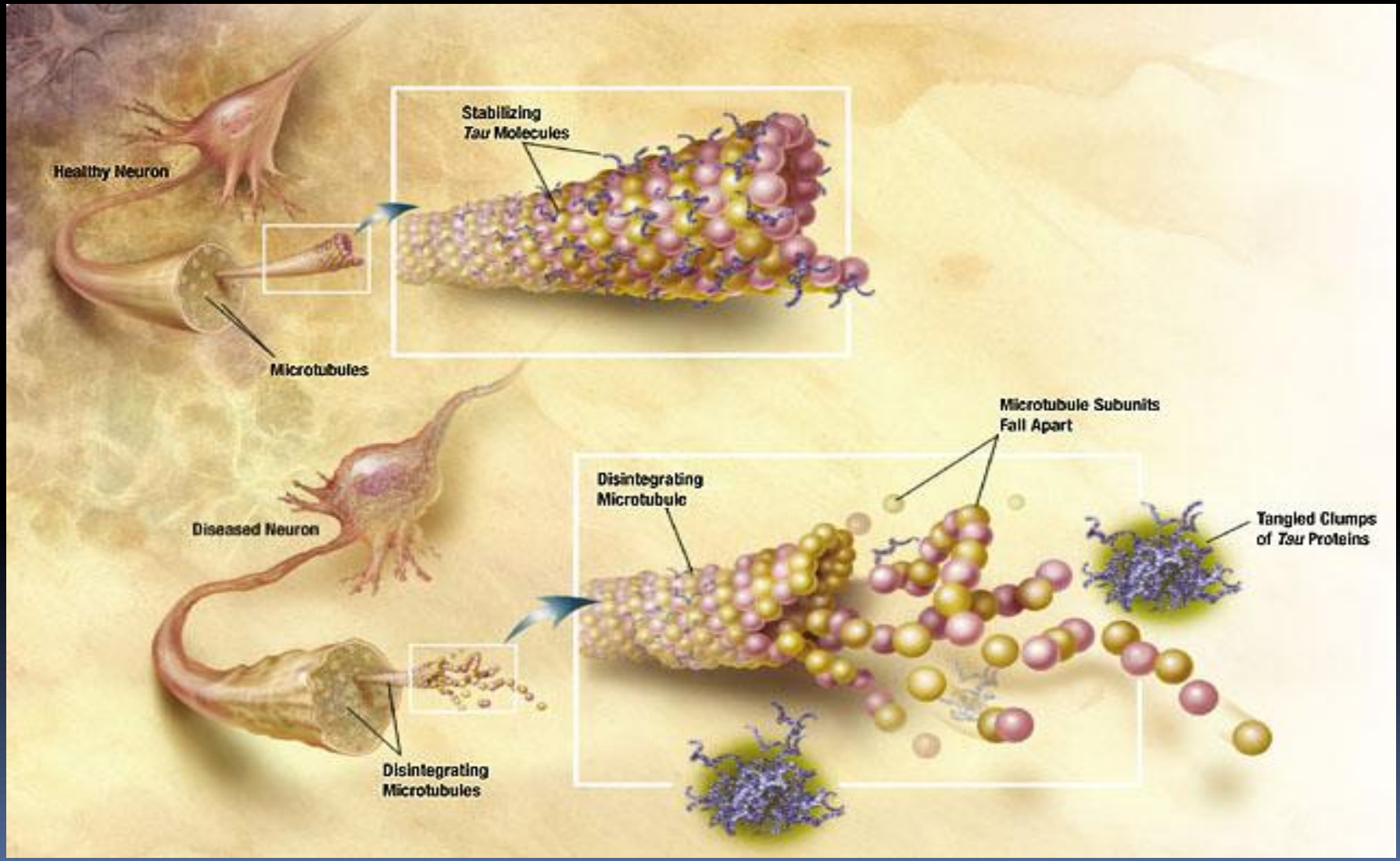
AD Processes and Possible Therapeutic Targets



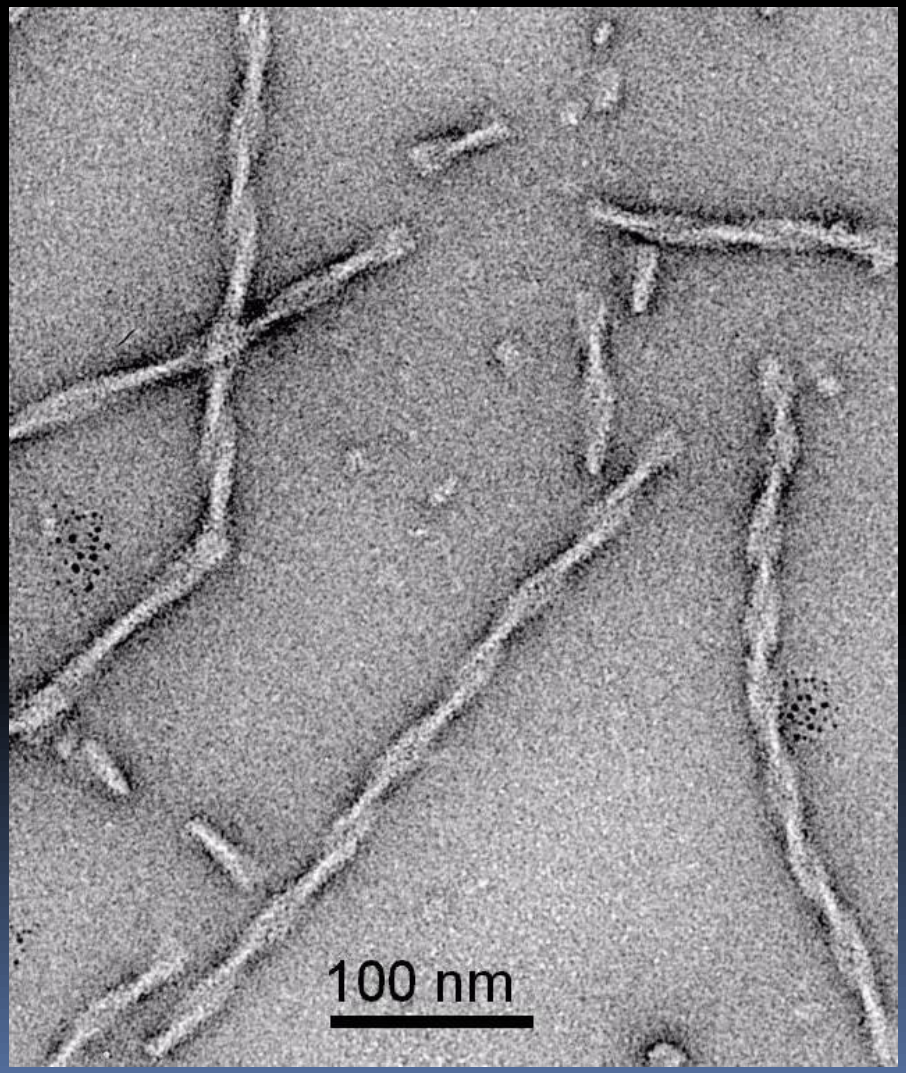
NFTs

Amyloid plaques

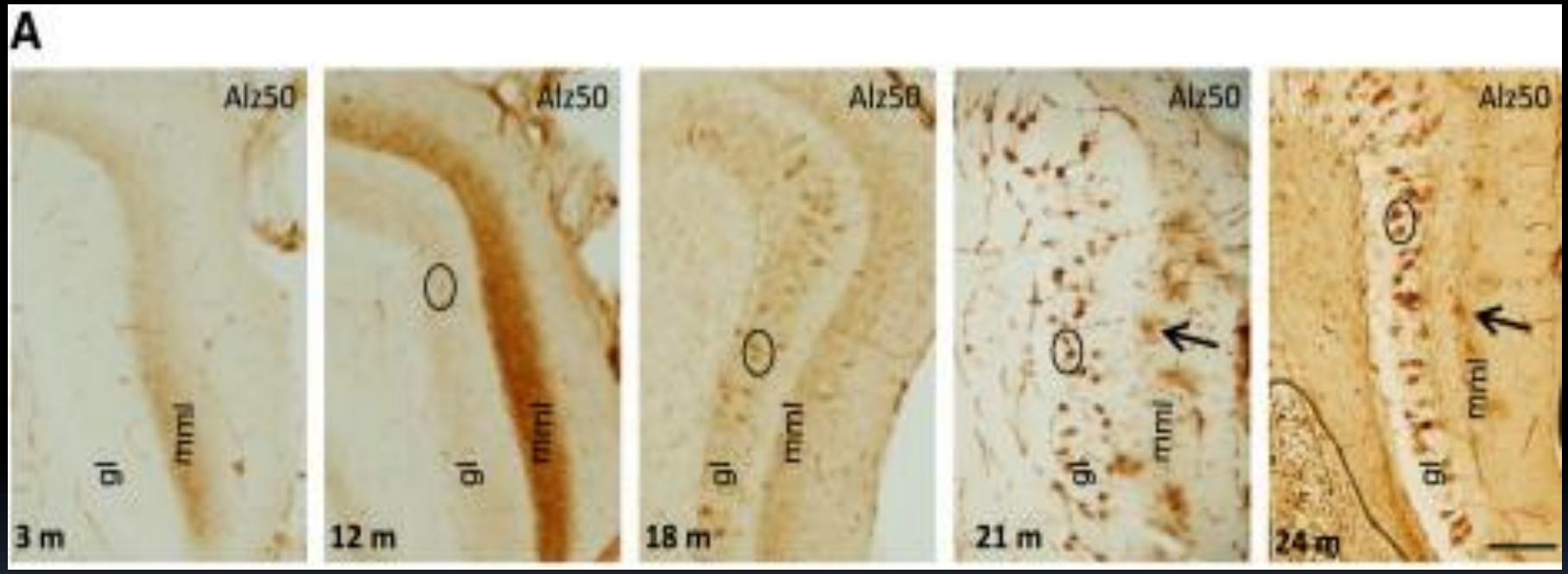
The role of the microtubule-associated protein tau in AD



Neurofibrillary tangles (NFT) & paired helical filaments (PHF)



Neurofibrillary degeneration spreads from nerve cell to nerve cell



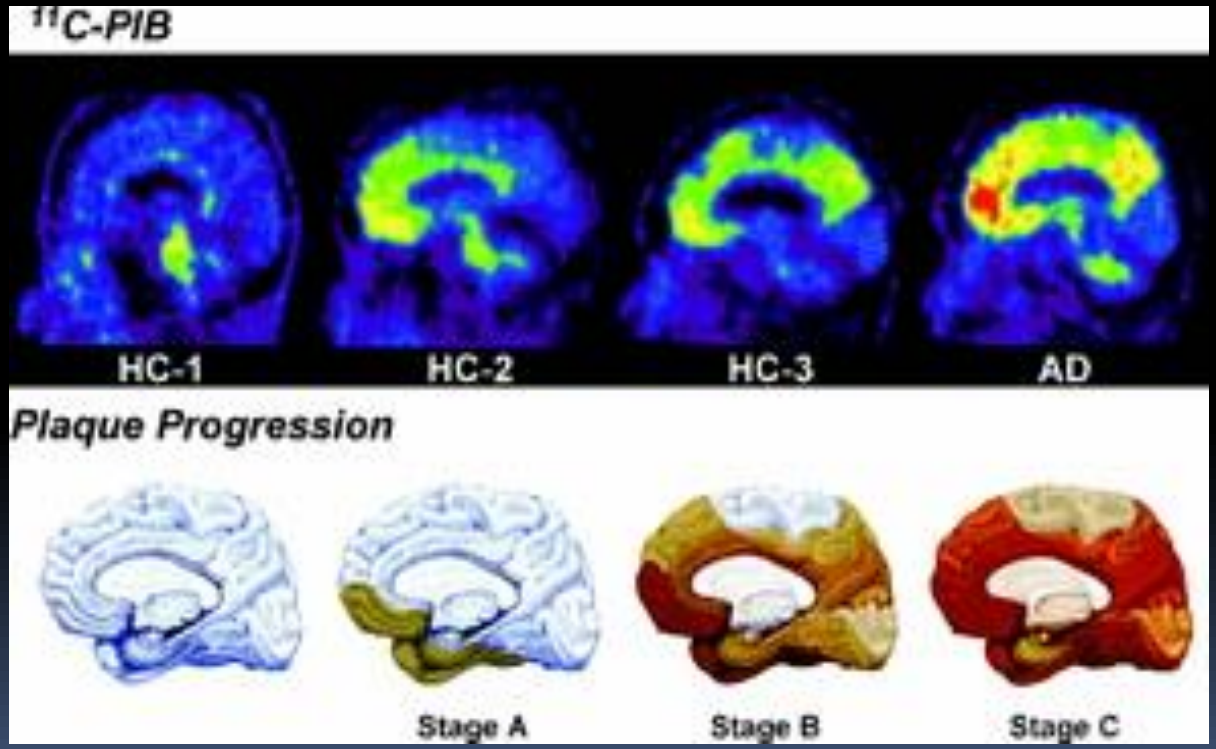
de Calignon et al., Neuron. 2012 Feb 23;73(4):685-97.

Liu et al., PLoS One. 2012;7(2):e31302. Epub 2012 Feb 1

NFTs

Amyloid plaques

Amyvid/AVID-45 approved by FDA for detection of cortical amyloid deposition



Rowe CC et al., Imaging beta-amyloid burden in aging and dementia. Neurology. 2007 May 15;68(20):1718-25.

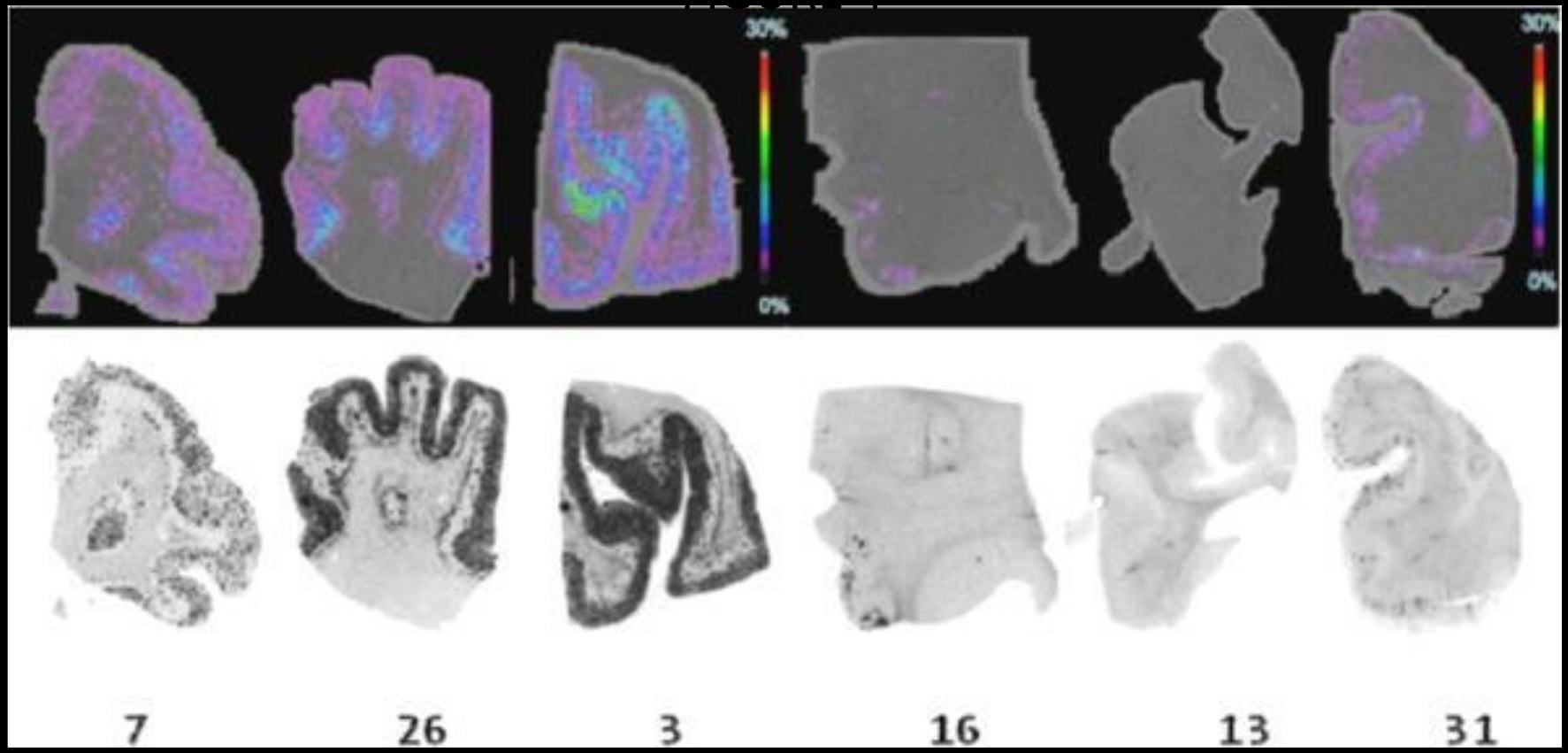


FIGURE 4 . Anti-A[beta] immunohistochemistry with antibody 4G8 and florbetapir F 18 autoradiography on adjacent sections of human brain tissue (numbers correspond to patient numbers in Tables 1 and 2). Top row: parametric maps of A[beta] burden over the entire tissue section generated from PERMITS processing of digitized 4G8 immunohistochemistry data. The spectral color scale shows gray matter amyloid burden per unit area (0% to 30%). Bottom row: florbetapir F 18 autoradiography.

Correlation of Amyloid PET Ligand Florbetapir F 18 Binding With A[beta] Aggregation and Neuritic Plaque Deposition in Postmortem Brain Tissue.
Choi, Seok; Schneider, Julie; Bennett, David; Beach, Thomas; MD, PhD; Bedell, Barry; MD, PhD; Zehntner, Simone; Krautkramer, Michael; BS, MBA; Kung, Hank; Skovronsky, Daniel; MD, PhD; Hefti, Franz; Clark, Christopher

Alzheimer Disease & Associated Disorders. 26(1):8-16, January-March 2012.
DOI: 10.1097/WAD.0b013e31821300bc

FIGURE 1

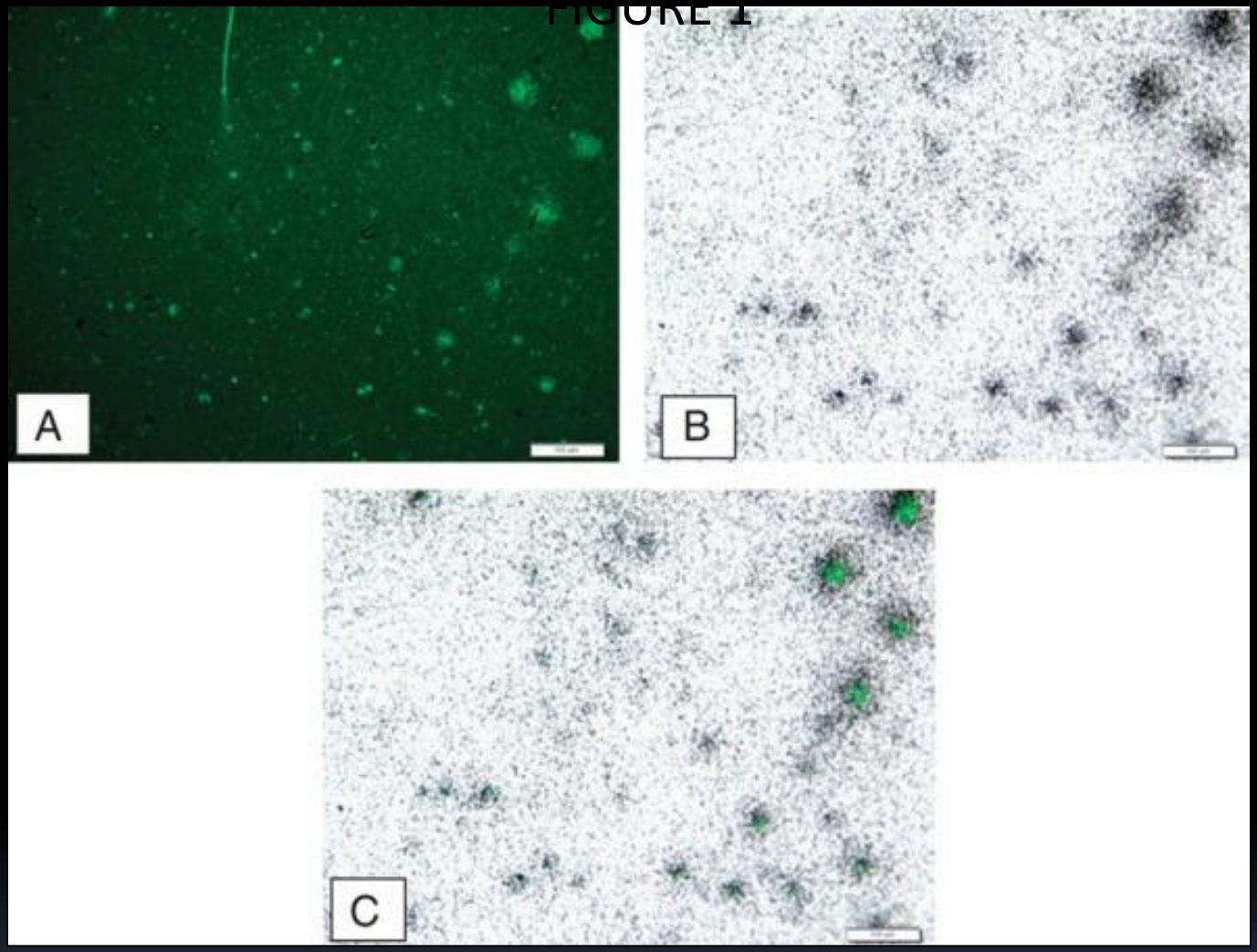


FIGURE 1 . Double-labeling of amyloid plaques with thioflavin S fluorescence microscopy (A) and florbetapir F 18 autoradiography (B). Image (C) shows the 2 figures combined. White bars indicate 100 [mu]m.

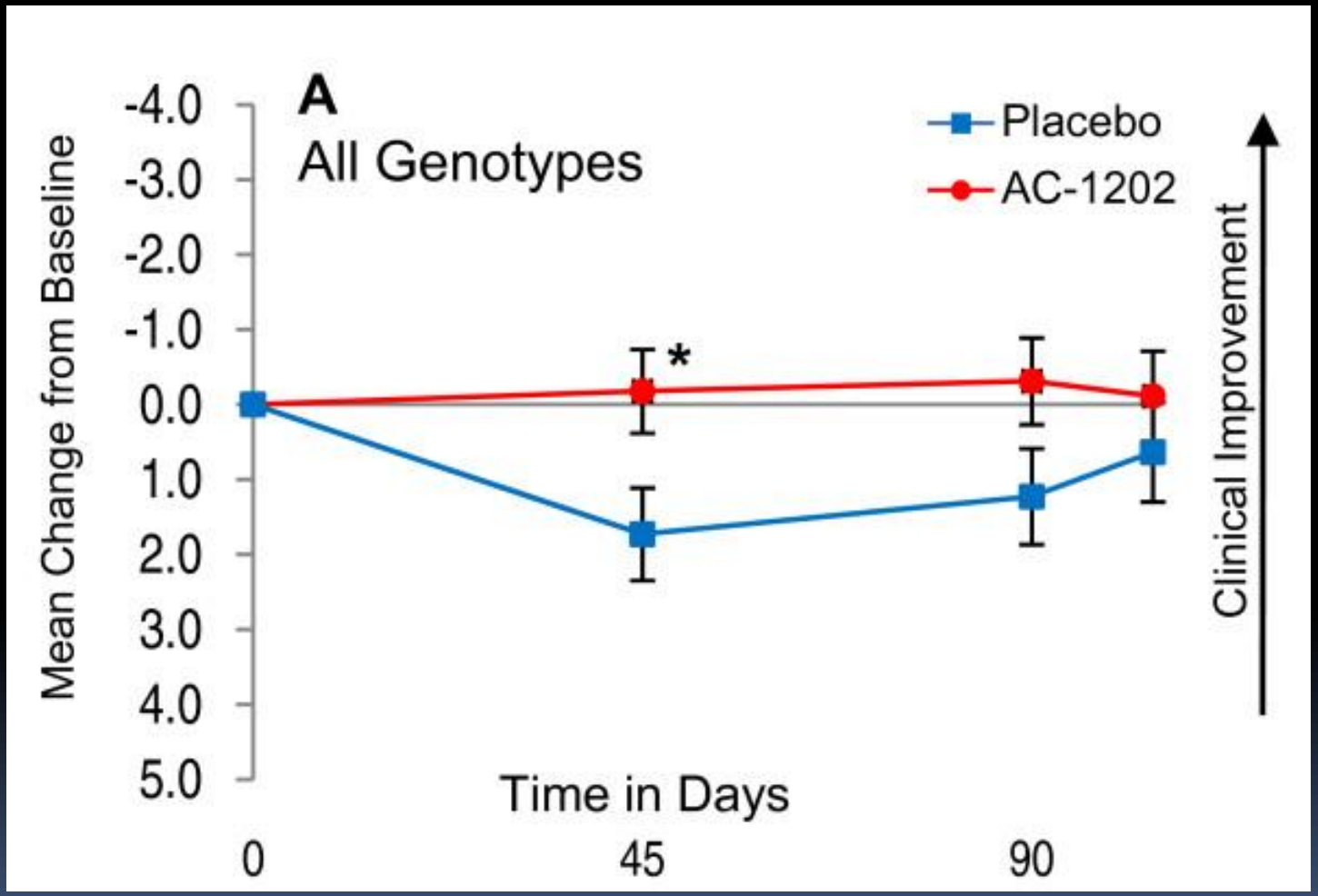
Correlation of Amyloid PET Ligand Florbetapir F 18 Binding With A[beta] Aggregation and Neuritic Plaque Deposition in Postmortem Brain Tissue.

Choi, Seok; Schneider, Julie; Bennett, David; Beach, Thomas; MD, PhD; Bedell, Barry; MD, PhD; Zehntner, Simone; Krautkramer, Michael; BS, MBA; Kung, Hank; Skovronsky, Daniel; MD, PhD; Hefti, Franz; Clark, Christopher

Alzheimer Disease & Associated Disorders. 26(1):8-16, January-March 2012.
DOI: 10.1097/WAD.0b013e31821300bc

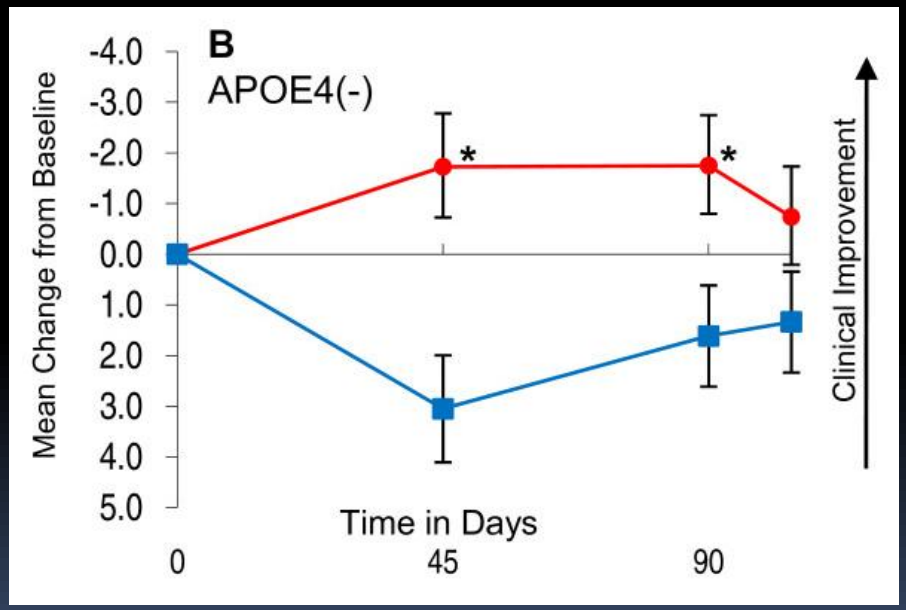
Coconut oil?

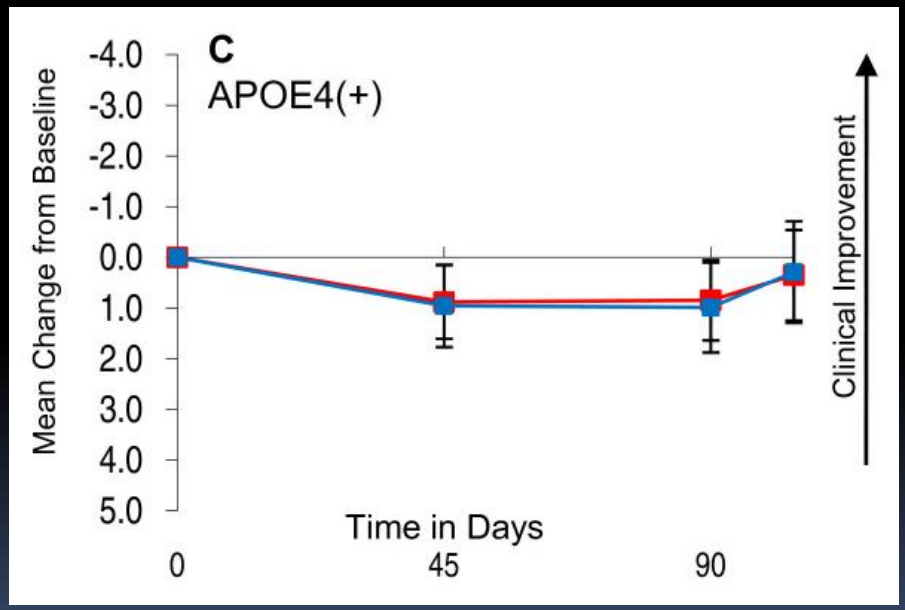
Caprylic acid (Axona™) for AD



Henderson et al., Nutr Metab (Lond). 2009 Aug 10;6:31

The effects are small, seen only in ApoEe4 negative, and short lived





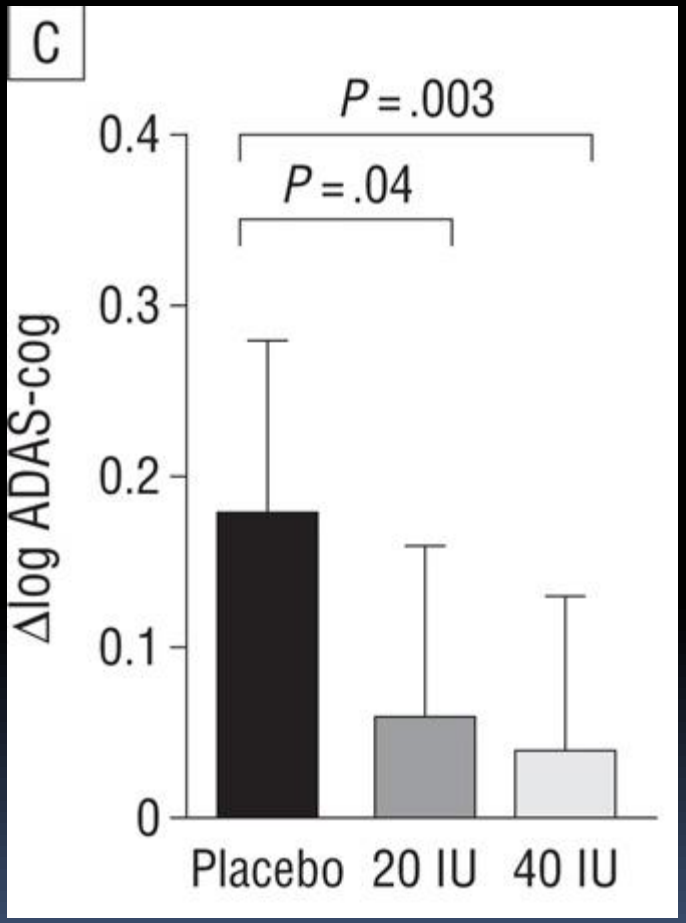
Henderson et al., Nutr Metab (Lond). 2009 Aug 10;6:31

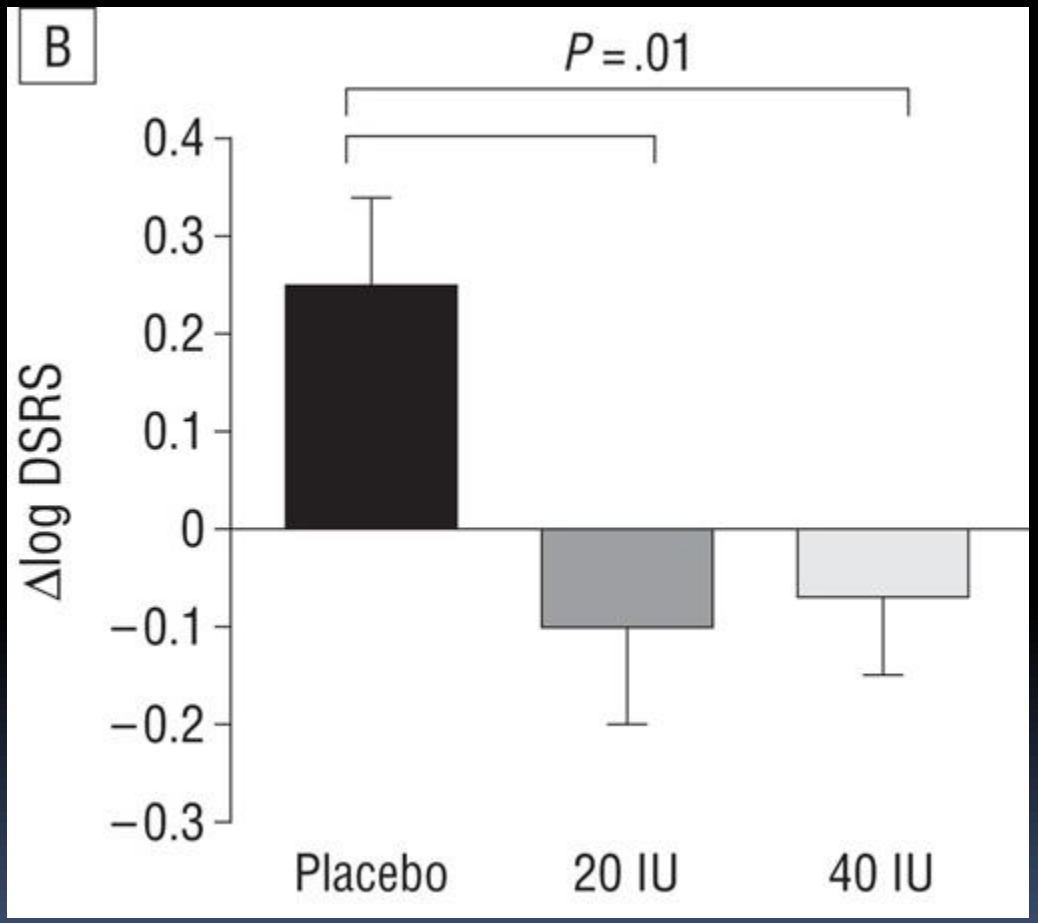
National Alzheimer Project Act (NAPA)

NATIONAL ALZHEIMER'S PROJECT

FROM ACT TO ACTION

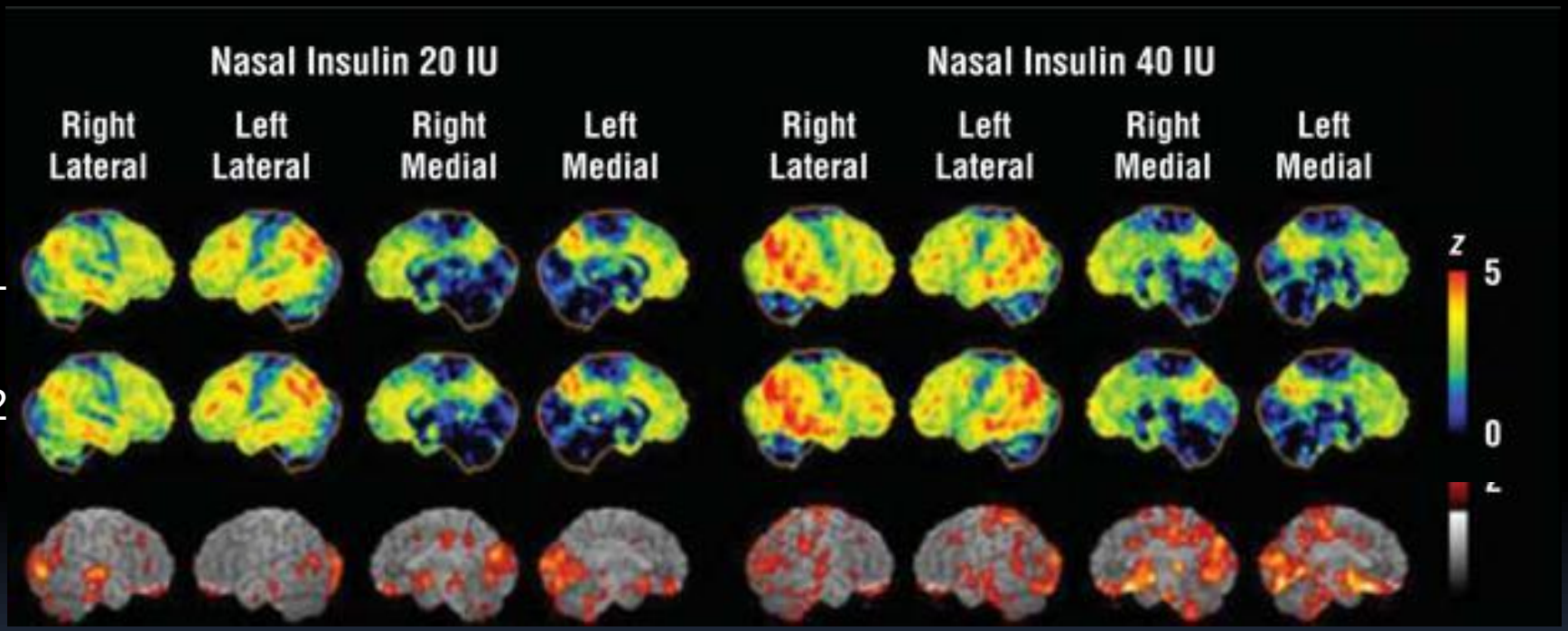
Intranasal insulin for AD





Craft et al., Arch Neurol. 2012 Jan;69(1):29-38. Epub 2011 Sep 12

Intranasal insulin increases brain metabolism by PET



Bottom panel demonstrates increase in metabolism compared to placebo

Craft et al., Arch Neurol. 2012 Jan;69(1):29-38. Epub 2011 Sep 12

Side effects are minimal!

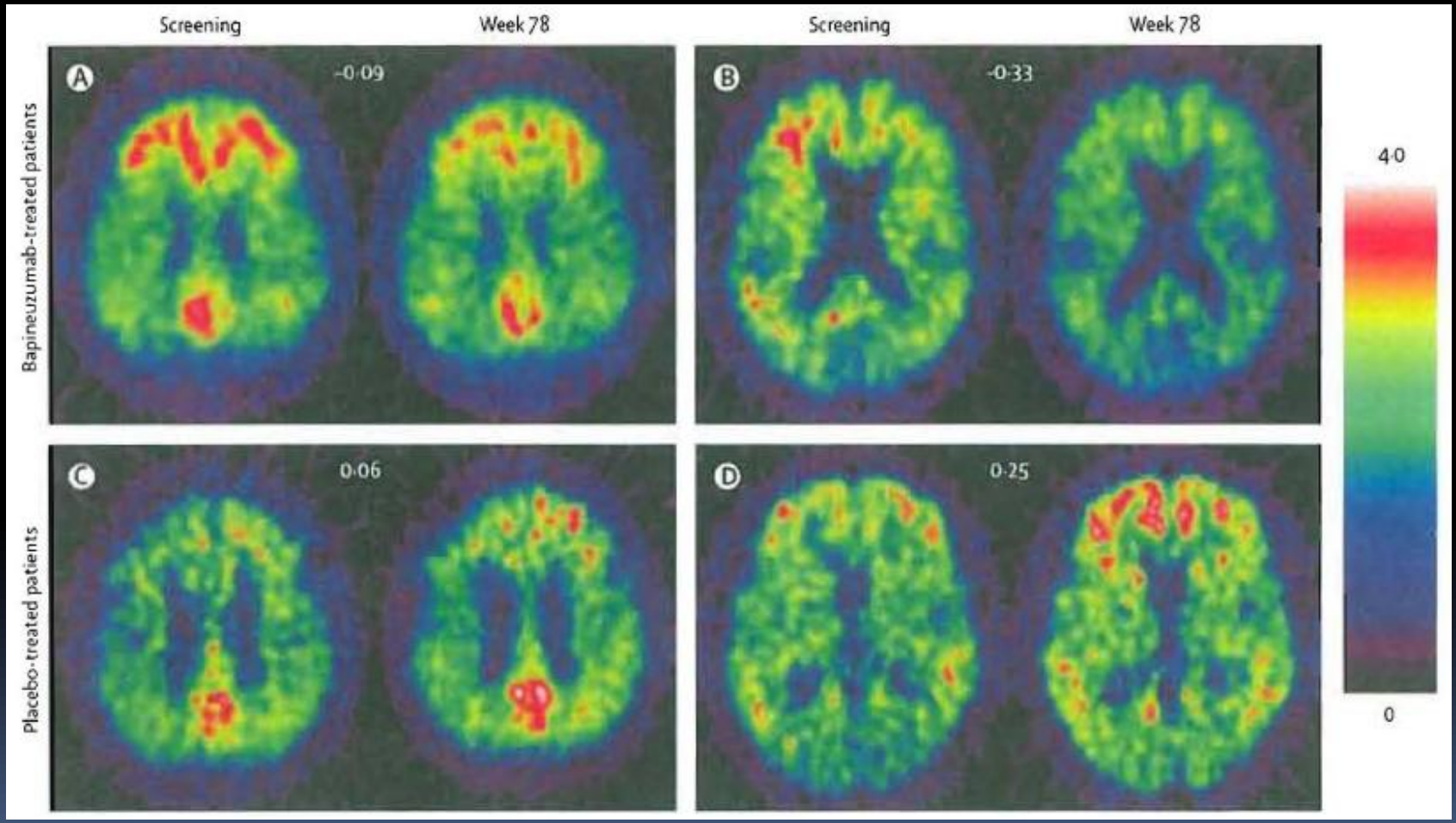
Adverse Event	Treatment Group					
	Placebo		20 IU of Insulin		40 IU of Insulin	
	Events, No.	Sample, %	Events, No.	Sample, %	Events, No.	Sample, %
Light-headedness and/or dizziness	3	10.0	3	8.3	5	13.2
Headache not related to lumbar puncture	1	3.3	4	8.3	2	5.3
Nose bleed	0	0.0	6	8.3	3	2.6
Rhinitis	1	3.3	8	16.7	4	7.9
Upper respiratory tract infection	2	6.7	2	5.6	1	2.6
Fall	2	6.7	1	2.8	1	2.6
Rash	2	6.7	1	2.8	2	2.6
Other	16	46.7	30	58.3	33	60.5
Total	27	56.7	55[a]	72.2	51[b]	68.4

[a] $P < .05$ for comparison of 20-IU dose insulin group vs placebo group.

[b] $P < .10$ for comparison of 40-IU dose insulin group vs placebo group.

Craft et al., Arch Neurol. 2012 Jan;69(1):29-38. Epub 2011 Sep 12

Anti-amyloid treatment reduces cortical amyloid burden

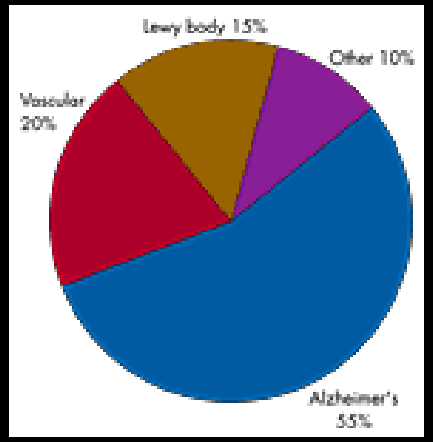


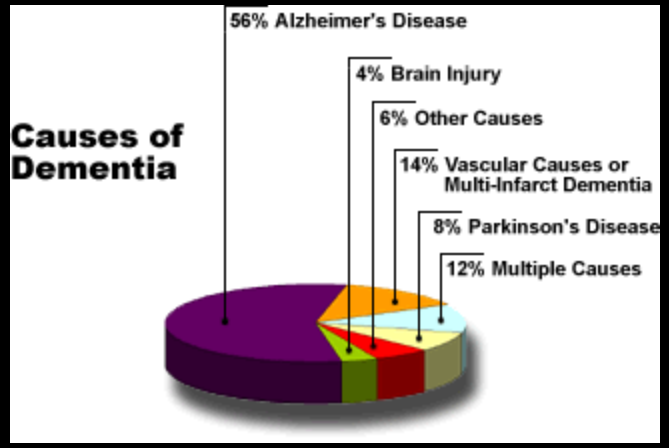
Rinne et al., Lancet Neurol. 2010 Apr;9(4):363-72. Epub 2010 Feb 26.

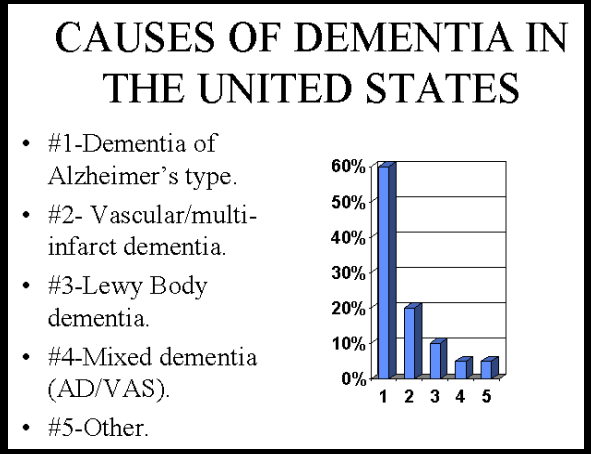
On the horizon…

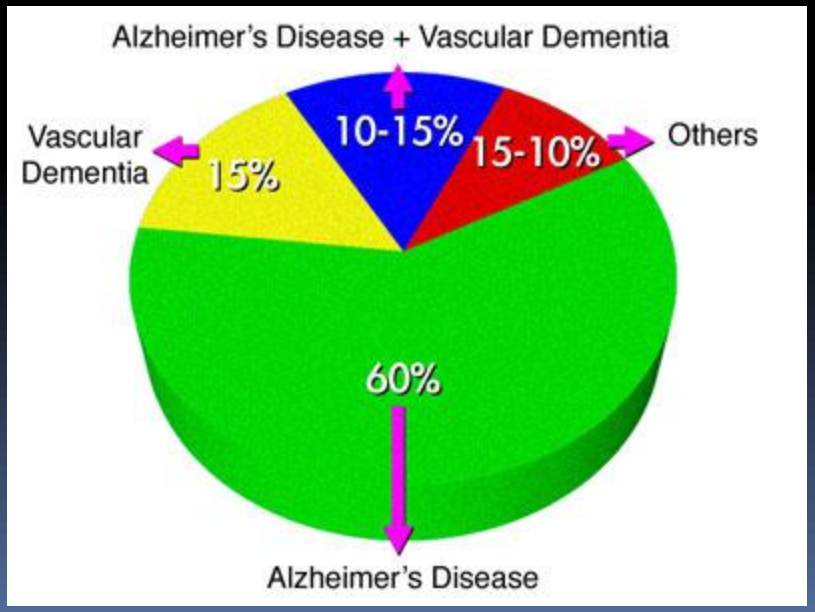
- This fall 2012
  - Bapineuzimab, solineuzimab data scheduled to be presented at the ANA in Boston
- Early 2013
  - IVIG trial data will be released

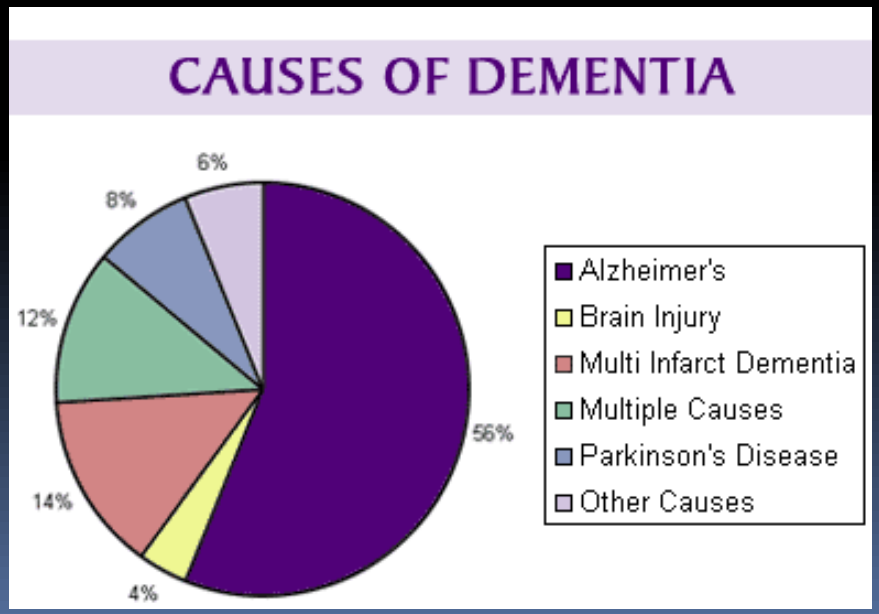
It's clear that dementia is a "mixed bag" of disorders



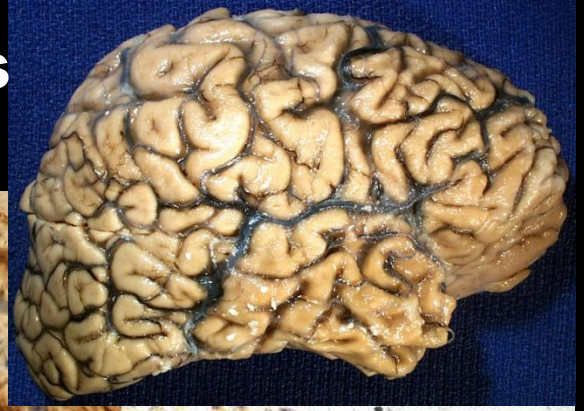


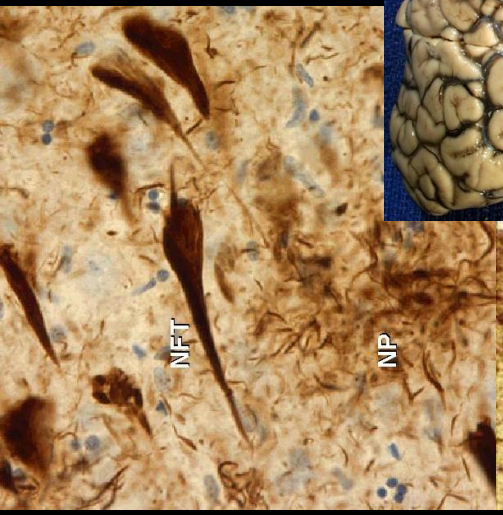


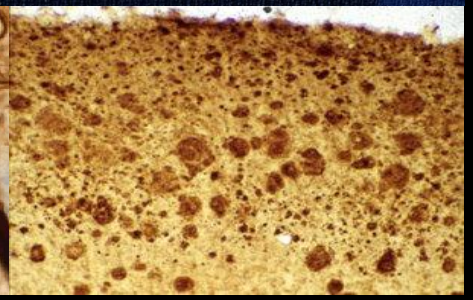




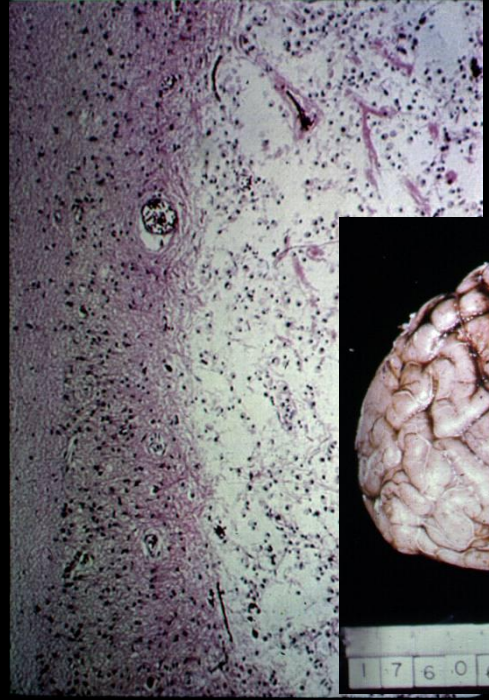
Alzheimer's disease

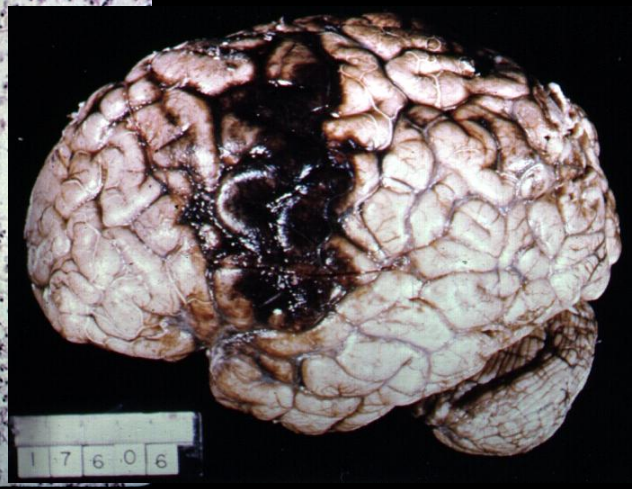




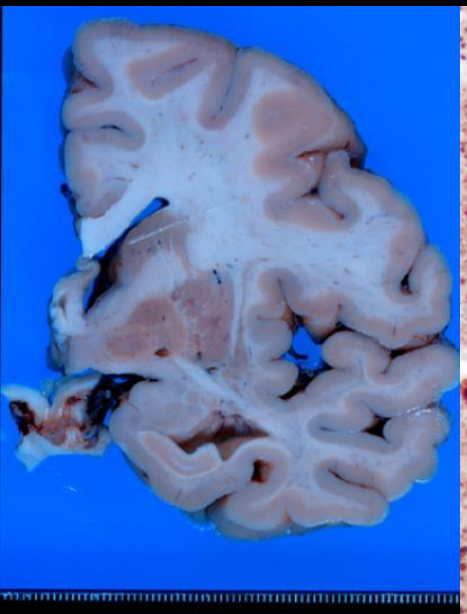


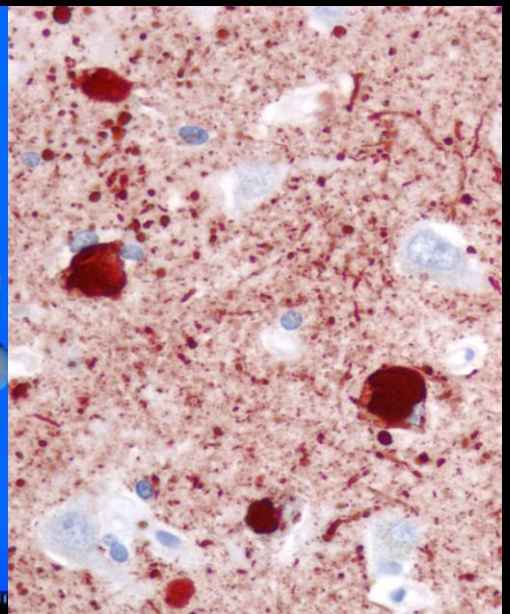
Vascular dementia



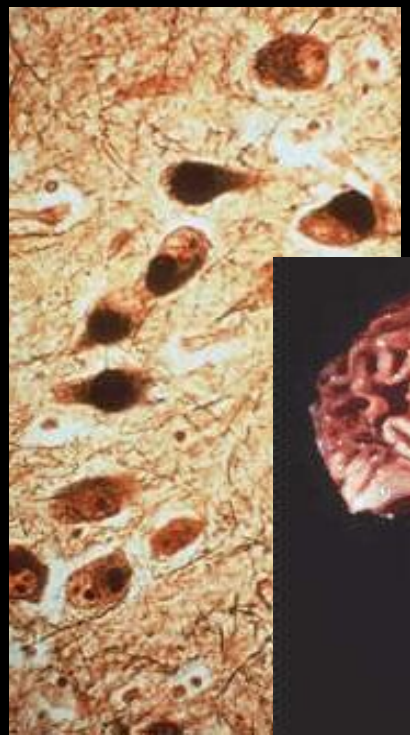


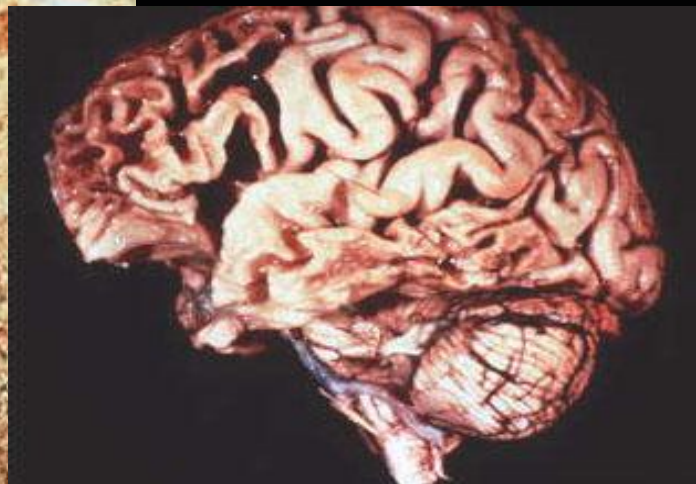
Dementia with Lewy bodies





Frontotemporal dementia

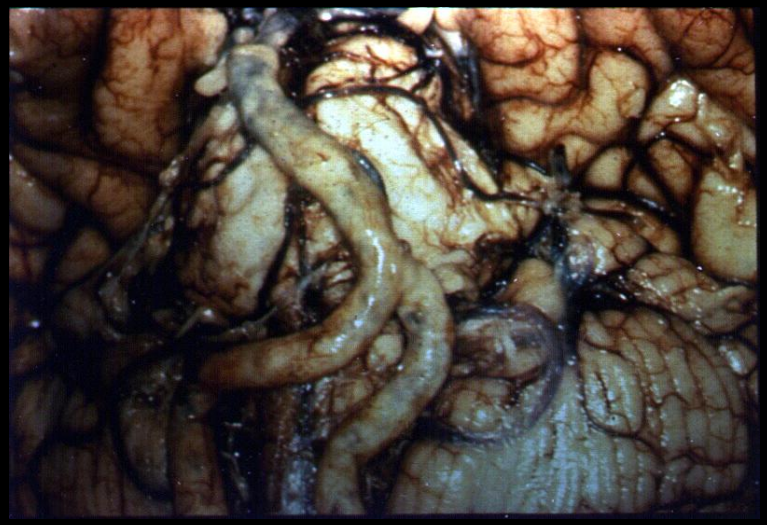


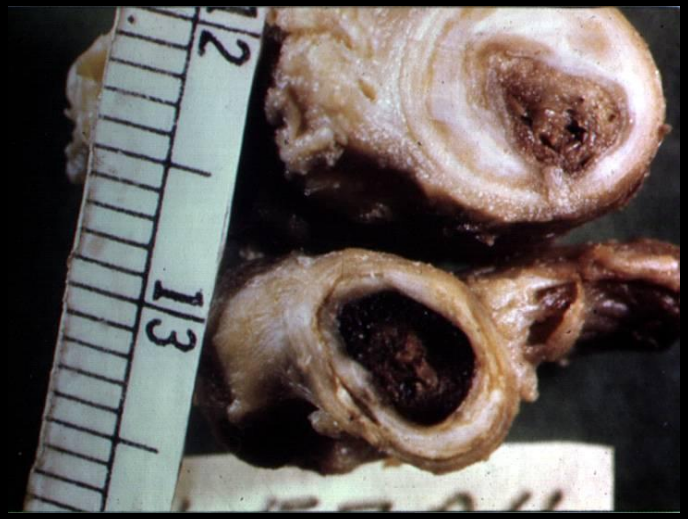


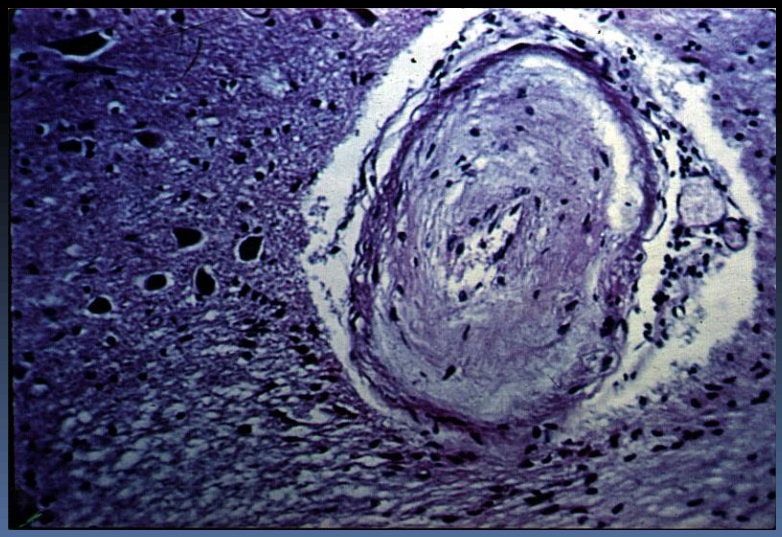
Vascular dementia

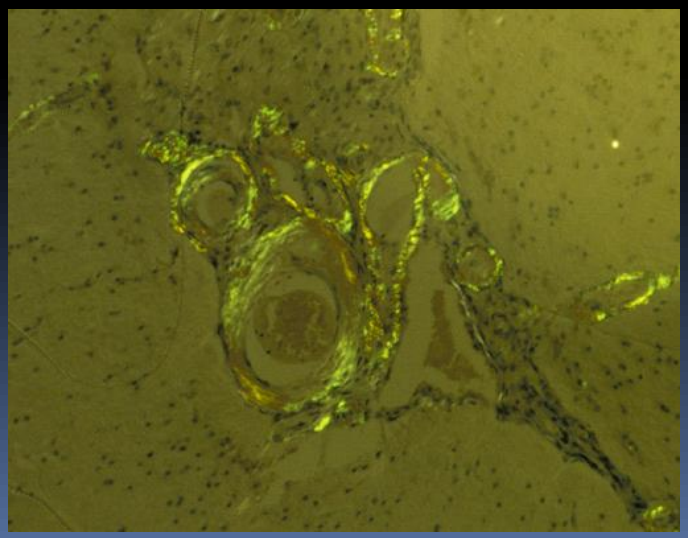
Overview & Research Advances 2012

Vascular Pathology









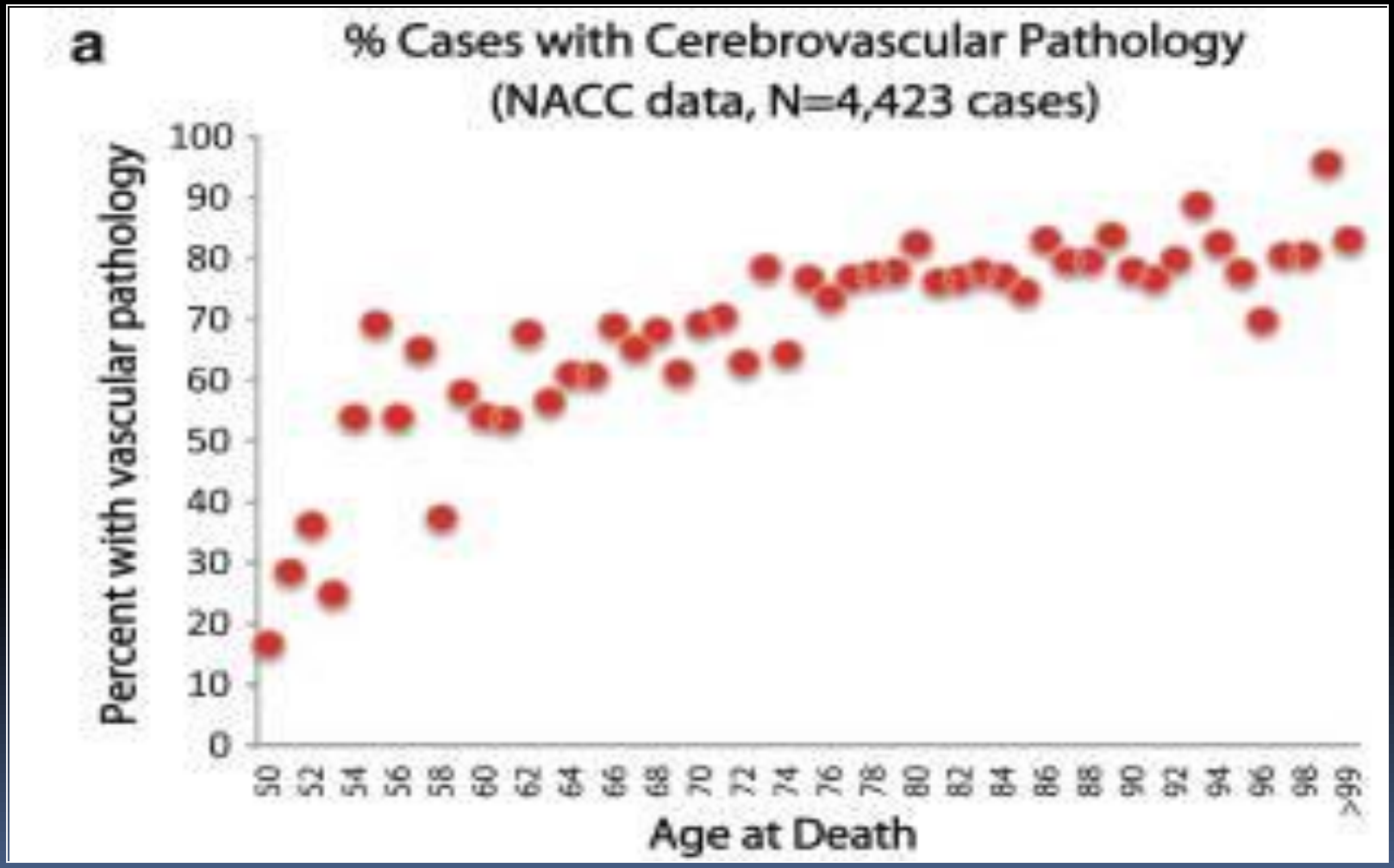
NINDS-AIREN Criteria for VaD

- Clinical Diagnosis of:
  - 1) Dementia
  - 2) Cerebrovascular disease:
    - a) focal neurologic signs (history of stroke not necessary)
    - b) Imaging demonstrating vascular disease
  - 3) Onset of dementia within 3 months of stroke, or abrupt deterioration of cognitive function or stepwise course

*(high specificity 96%, low sensitivity 25%)

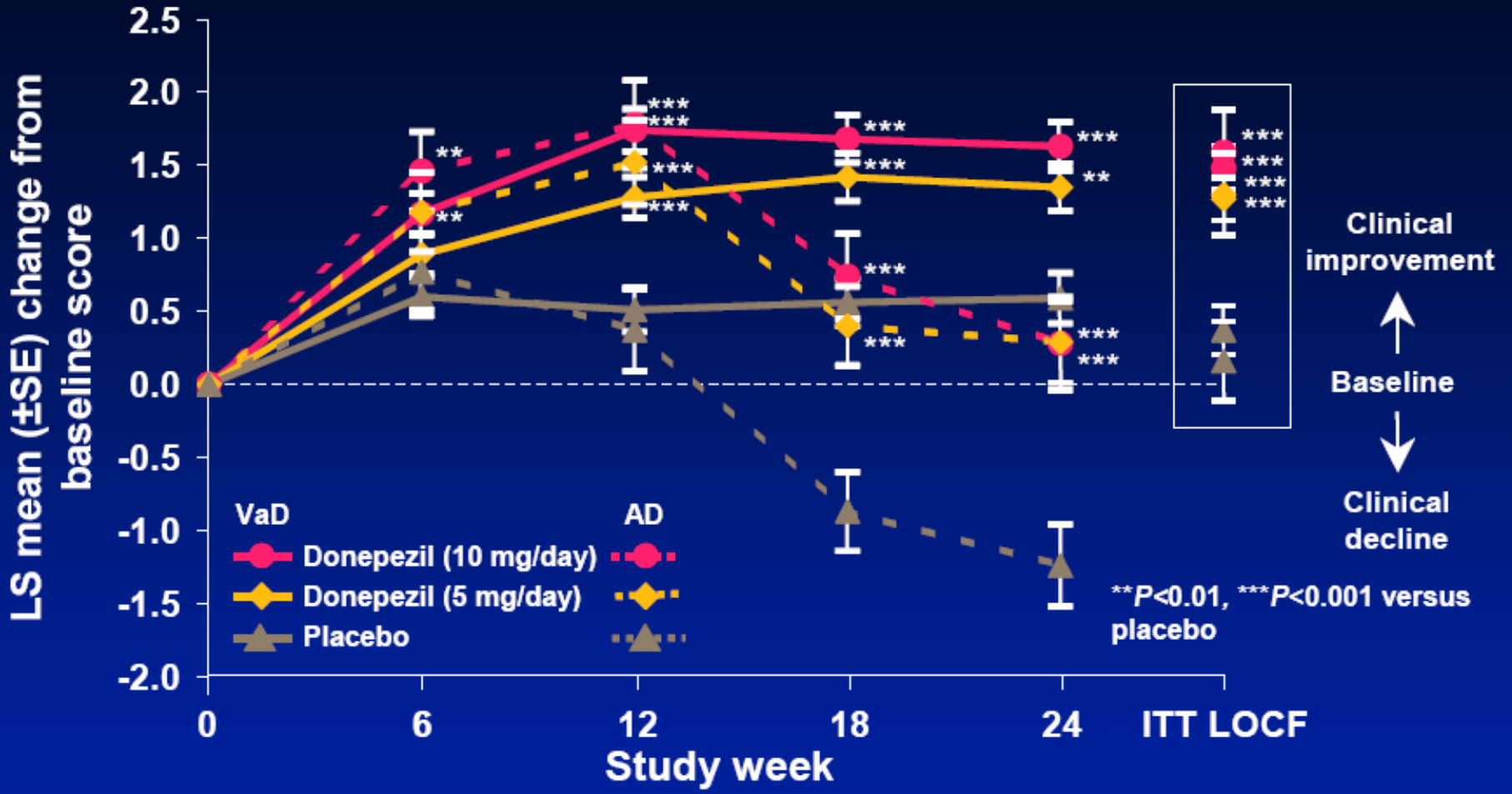
Roman et al, Neurology 1993;43:250-60
*Knopman et al, Arch Neurol 2003;60:569-575

VaD is a major problem with advancing age!



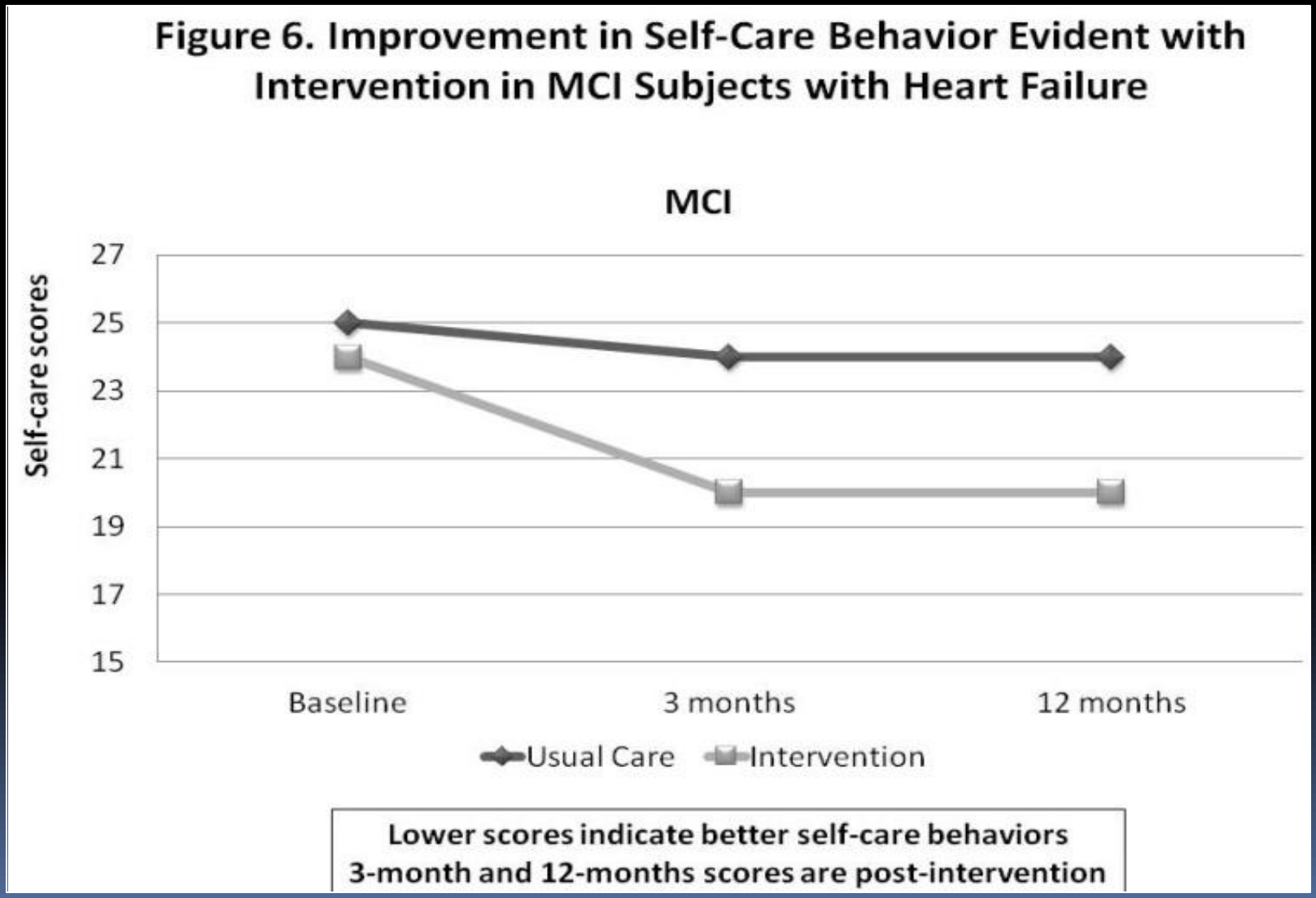
VaD and AD cognitive function

MMSE



Don 10 mg	n= 398/312	388/278	348/255	321/113	309/105	398/312
Don 5 mg	n= 399/349	384/324	363/319	338/135	328/131	397/345
Placebo	n= 381/350	379/327	353/318	339/134	321/133	381/350

Personalized intervention can really help improve things!



Frontotemporal dementia

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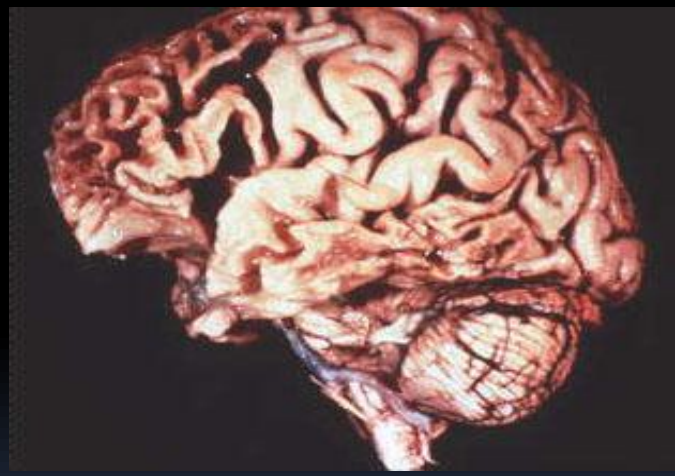
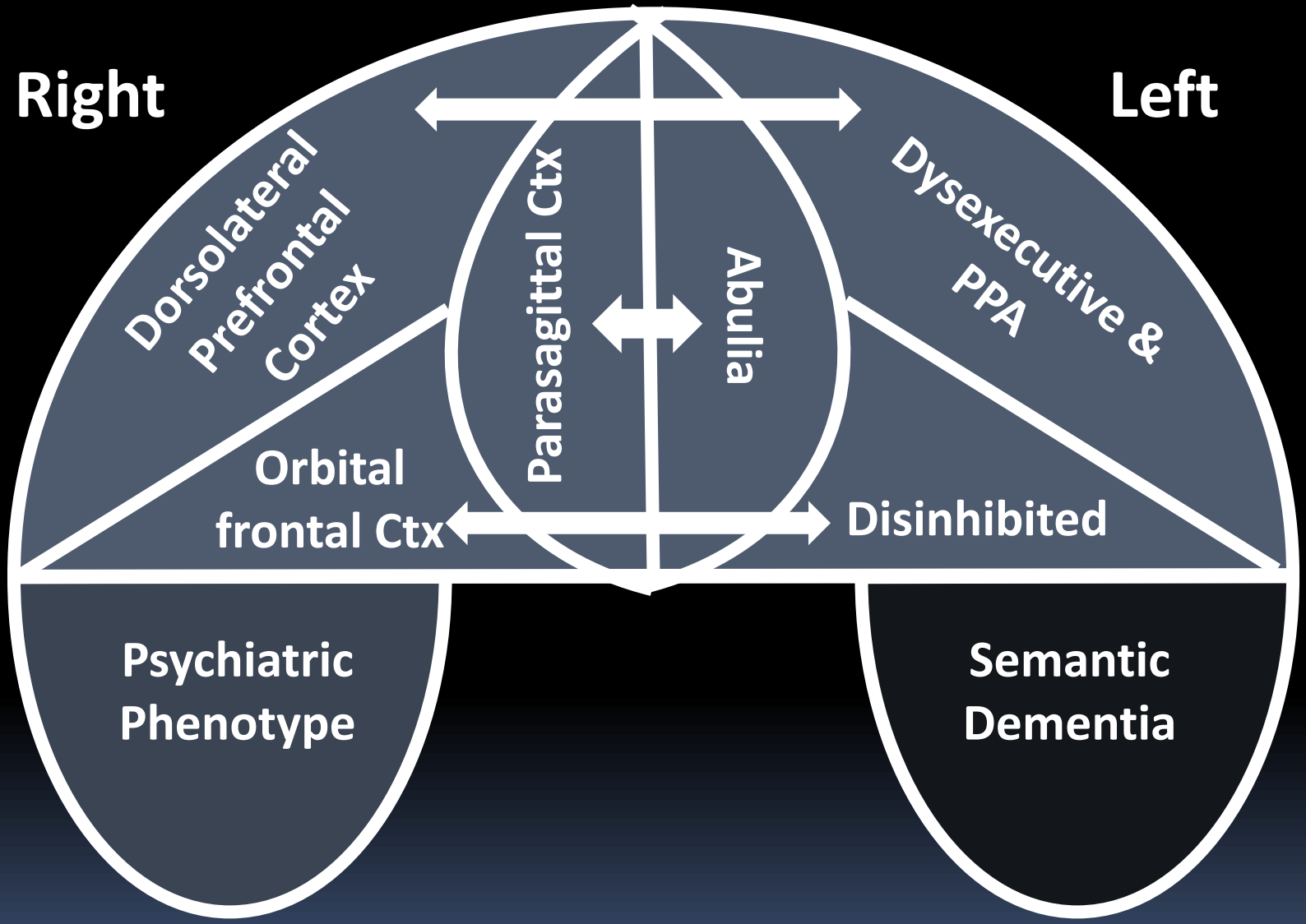
Frontotemporal dementia (NIH working group on FTD)

- Prominent behavioral disorder
  - Loss of interpersonal skills
  - Emotional blunting
  - Perseveration or impersistance

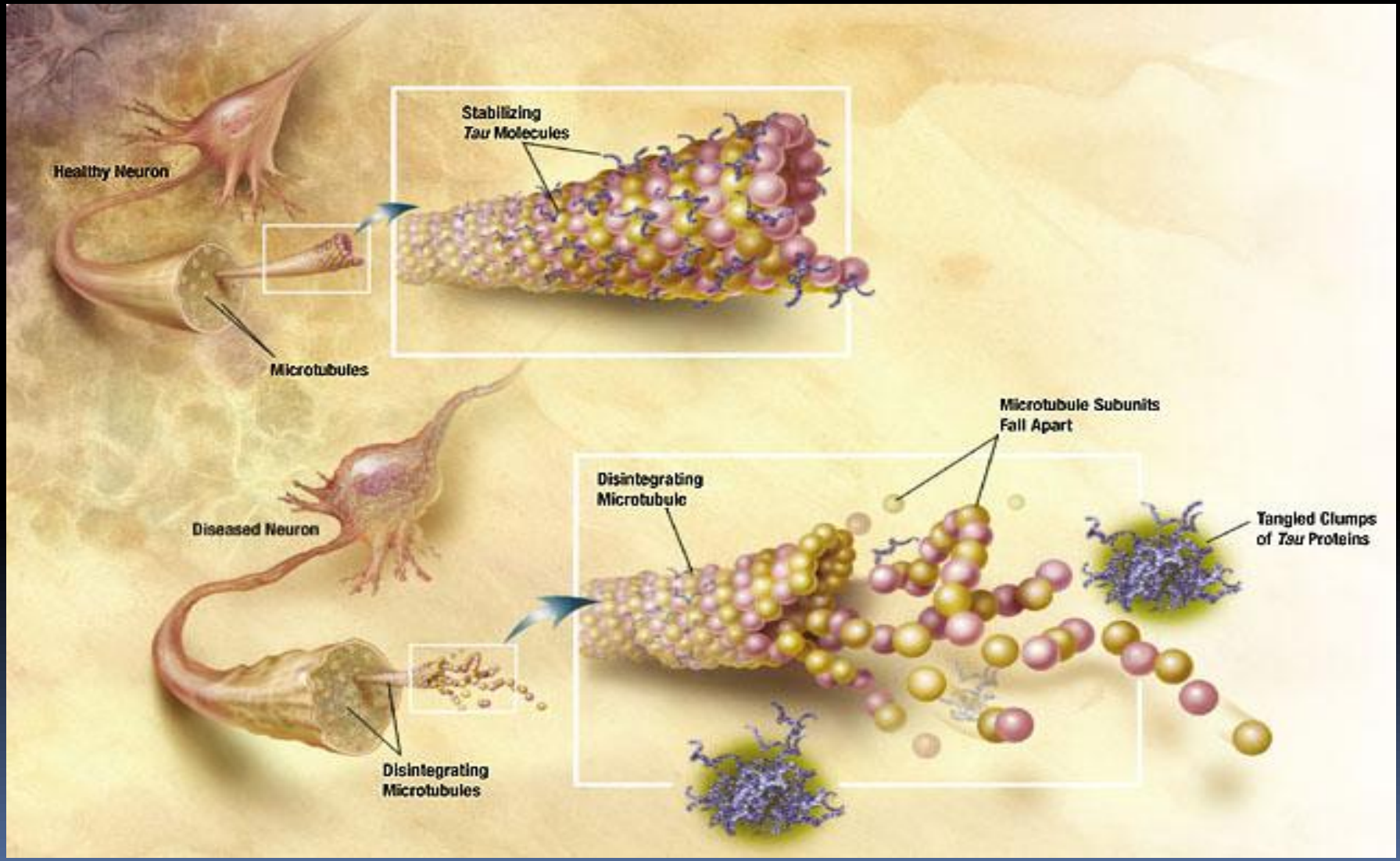
or

- Language involvement
  - Comprehension or fluency
- Cognition typically preserved
- Can be assoc with MND/ALS

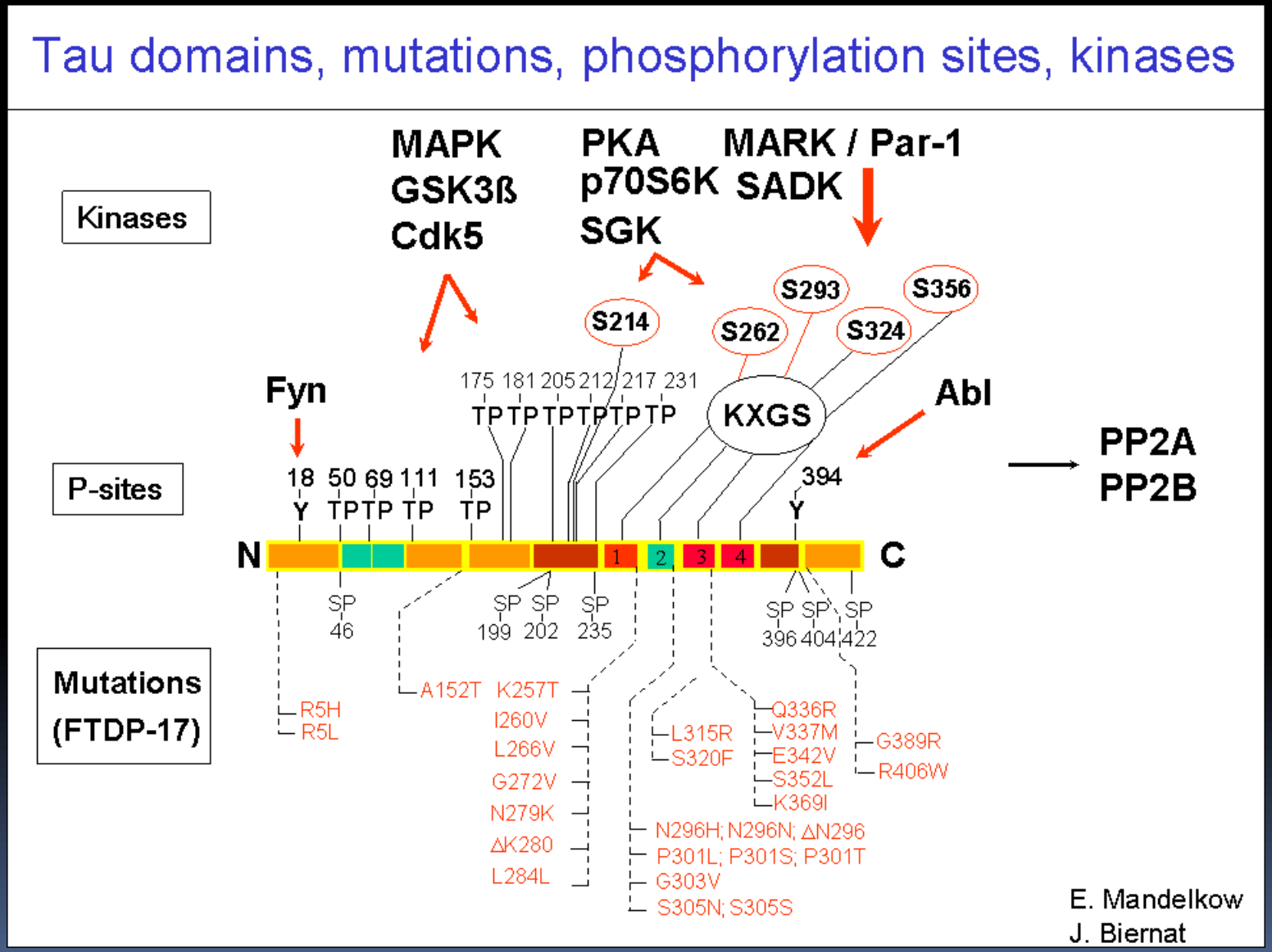



Right
Left
Dorsolateral Prefrontal Cortex
Parasagittal Ctx
Abulia
Dysexecutive & PPA
Orbital frontal Ctx
Disinhibited
Psychiatric Phenotype
Semantic Dementia

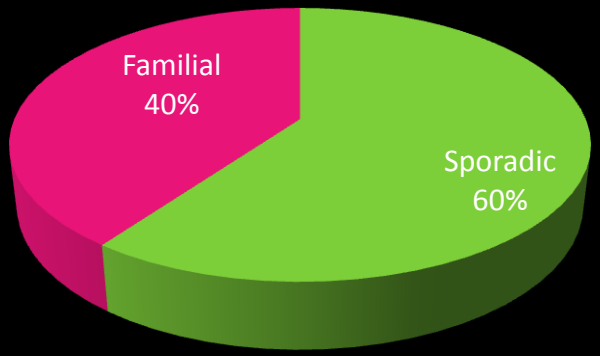
The role of the microtubule-associated protein tau in AD



Tau and FTDP-17

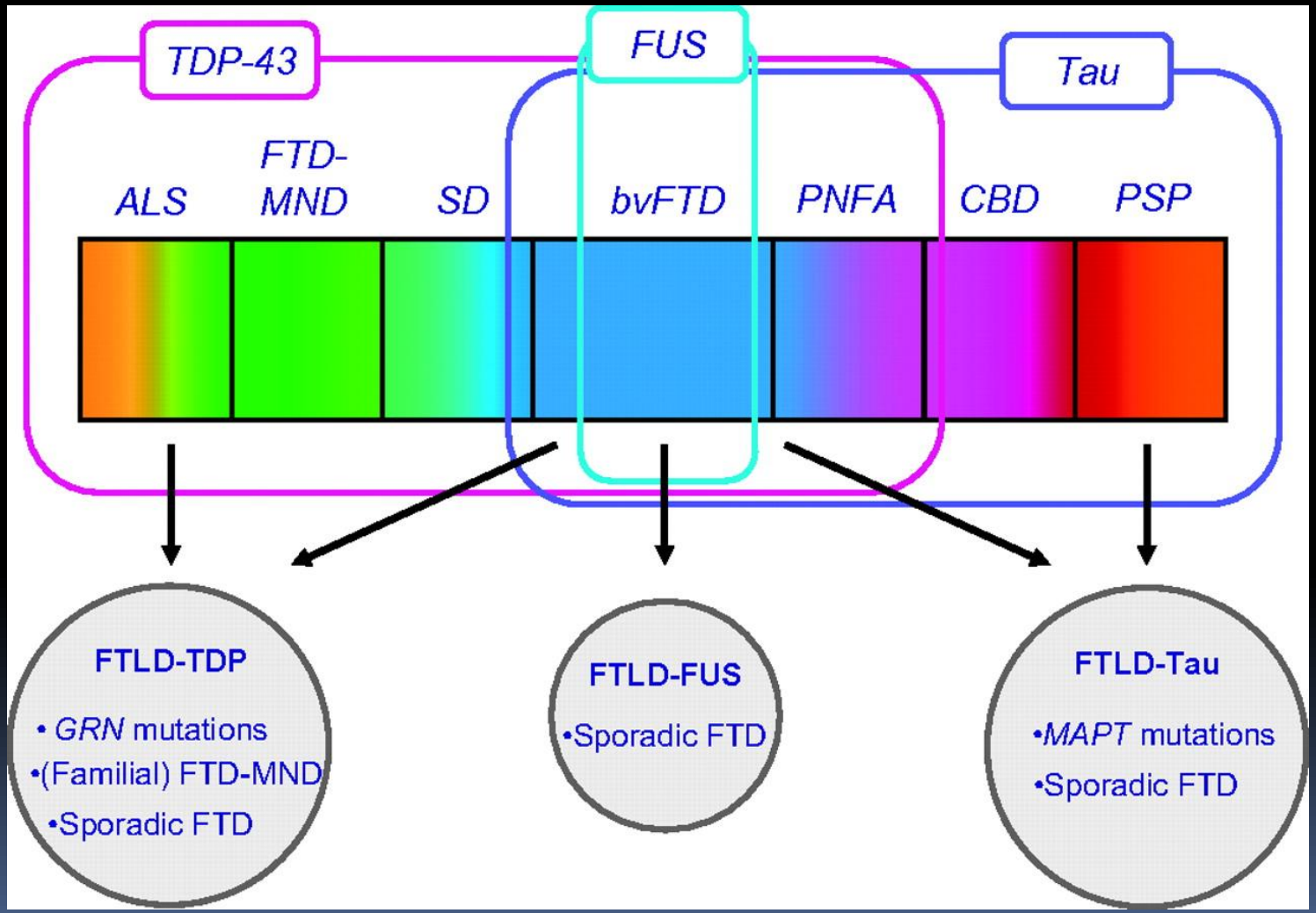


Genetics of FTD



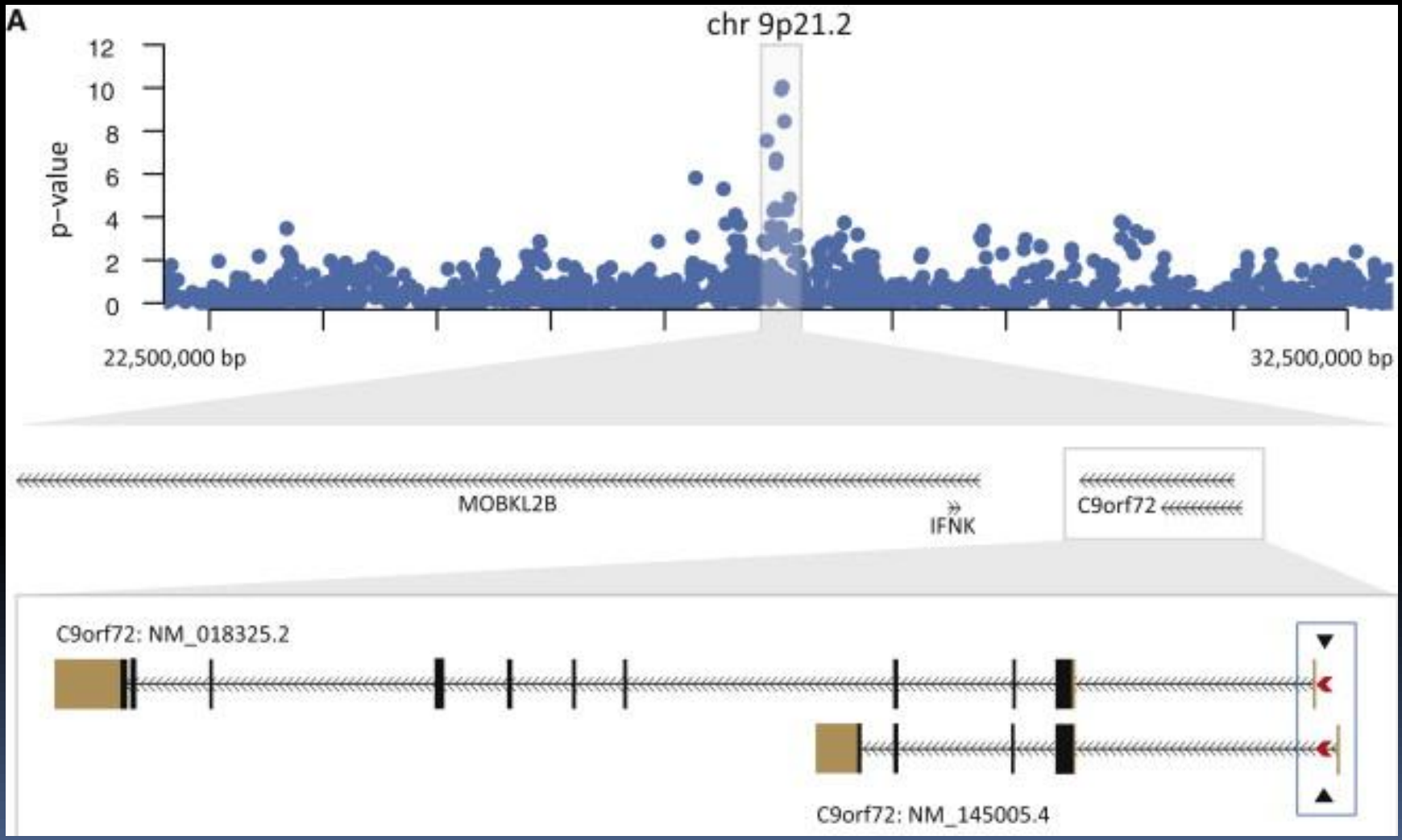
- Genes involved
  - Microtubule-associated protein tau
    - Stabilizes microtubule arrays
  - Progranulin
    - Inflammation, angiogenesis, wound healing
  - Valosin-containing protein
    - FTD-Pagets-myopathy
    - associates with clathrin, and heat-shock protein Hsc70
    - implicated in homotypic membrane fusion and ubiquitin-dependent protein degradation in mitosis
  - CHMP2B-Charged multivesicular body protein 2b
    - Inhibits endosomal trafficking and dendritic spine arborization
  - TDP-43- Tar DNA binding protein-43
    - transcription and splicing regulation, microRNA processing, apoptosis, cell division, stabilization of messenger RNA, and dendritic spines
  - FUS- Fused in sarcoma
    - FET/TET family of multifunctional DNA/RNA binding proteins
    - cell proliferation, DNA repair, transcription regulation, and RNA , microRNA processing, and dendritic spine stabilization

Clinical, genetic and pathological spectrum of frontotemporal lobar degeneration.



Seelaar H et al. J Neurol Neurosurg Psychiatry doi:10.1136/jnnp.2010.212225

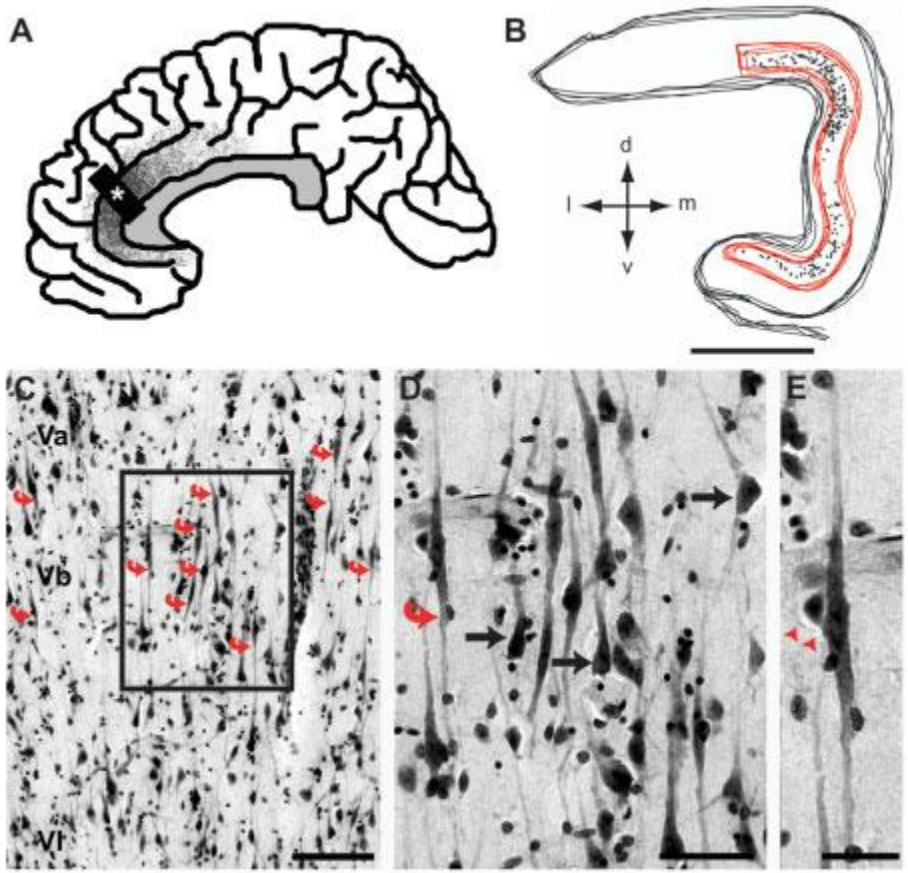
Chromosome 9 mutation causes familial FTD and ALS



Renton et al., Neuron. 2011 Oct 20;72(2):257-68. Epub 2011 Sep 21

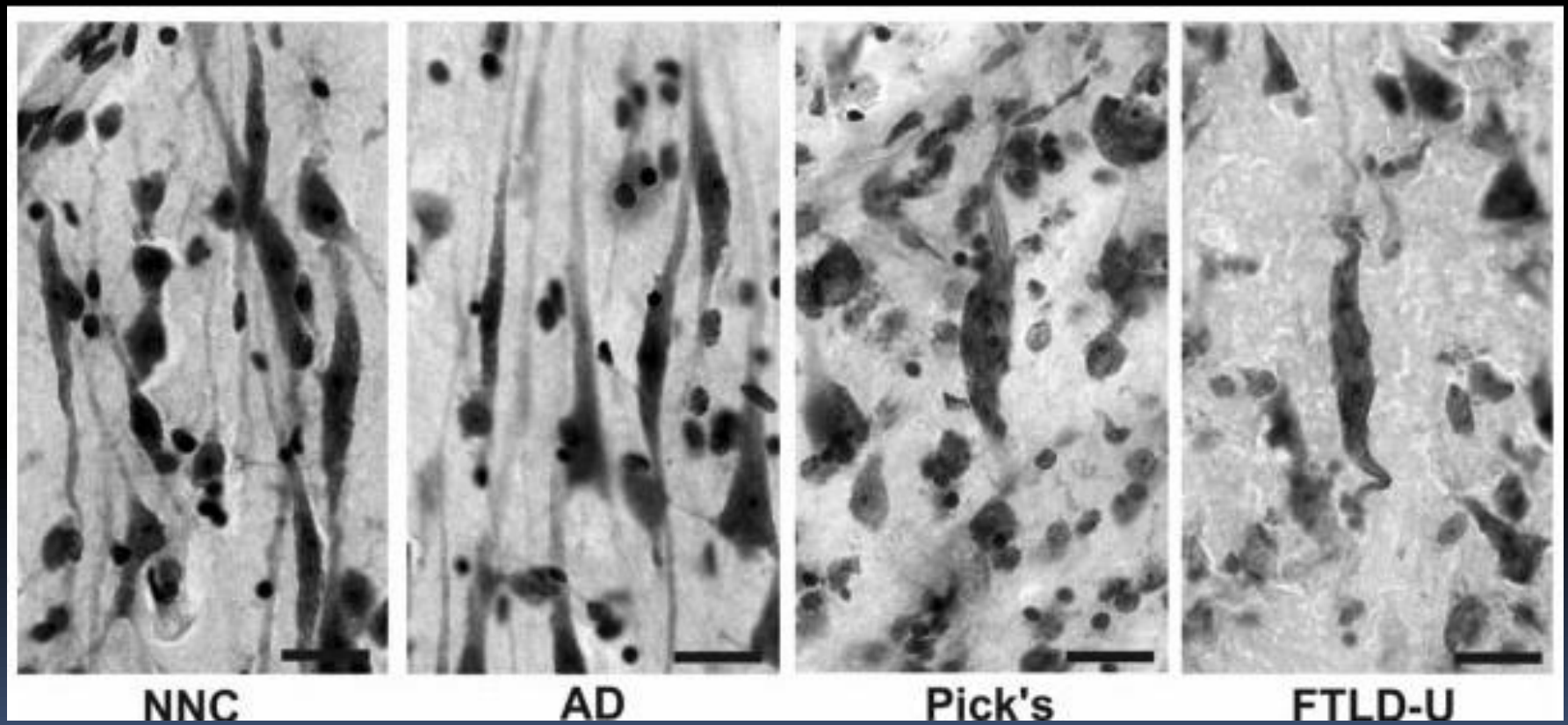
Why behavior? Do other animals get FTD?

Von Economo Neurons are unique to higher order social mammal species



Allman et al., Ann N Y Acad Sci. 2011 Apr;1225:59-71
Seeley et al., Ann Neurol. 2006 Dec;60(6):660-7

The loss of these cells specifically may cause the behaviorally abnormalities in FTD



Seeley et al., Ann Neurol. 2006 Dec;60(6):660-7

Normal Aging

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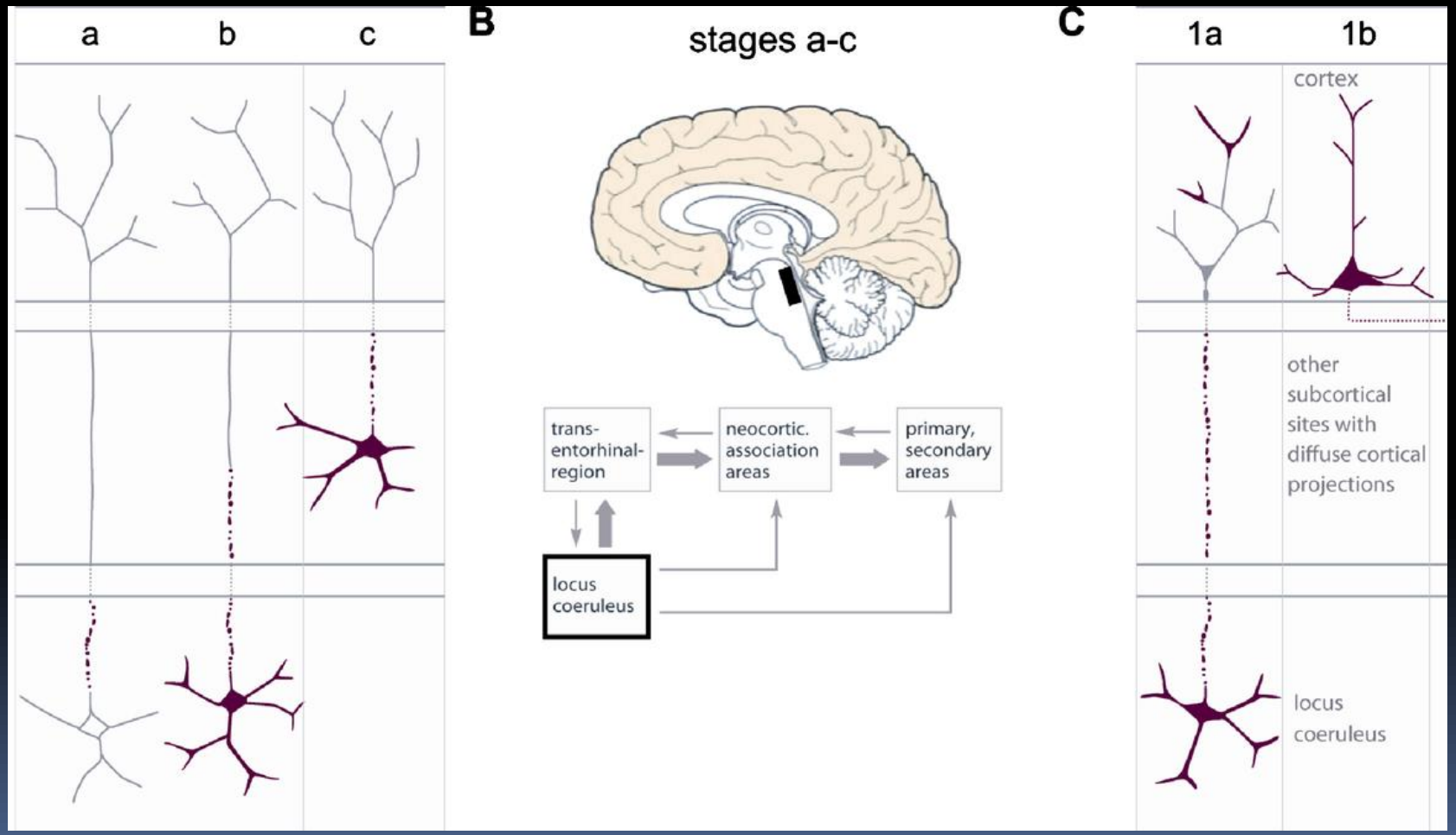
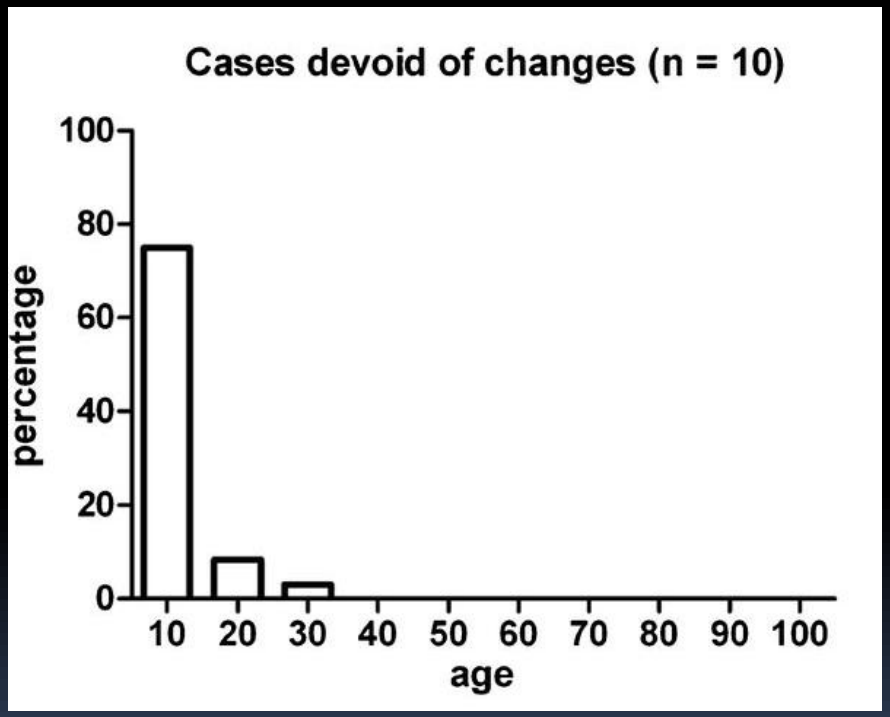
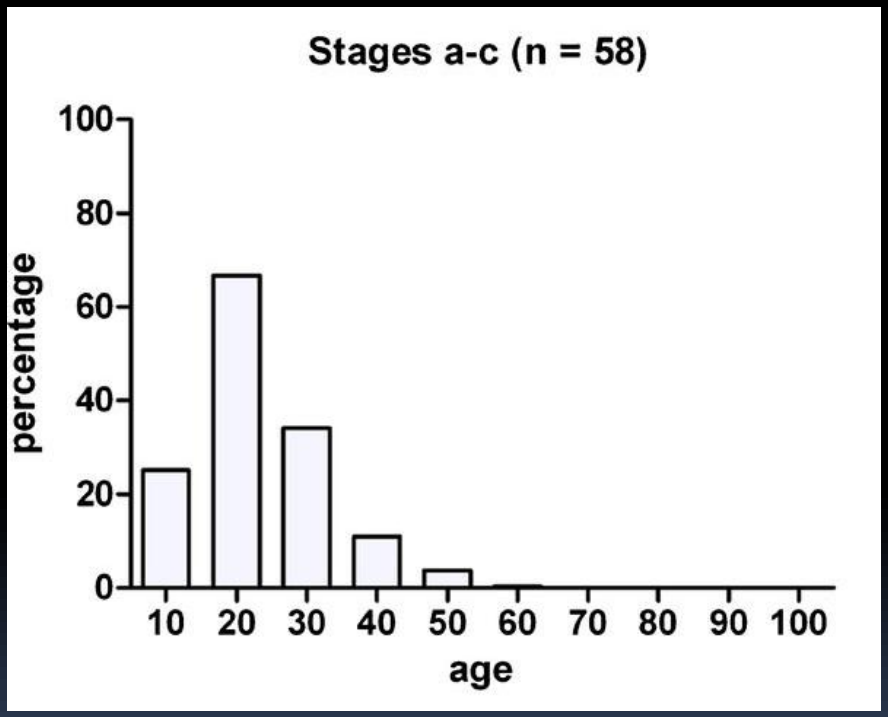
AD starts in the brainstem, as a teenager!



Braak et al., J Neuropathol Exp Neurol. 2011 Nov;70(11):960-9

Can you escape it?

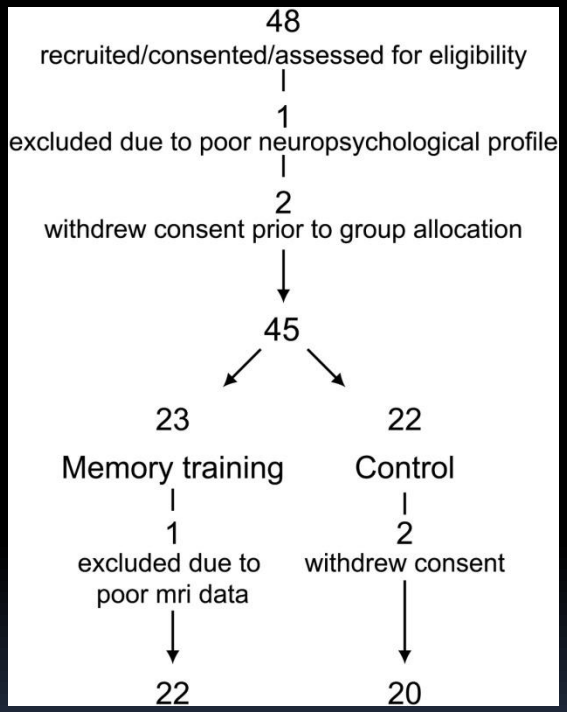




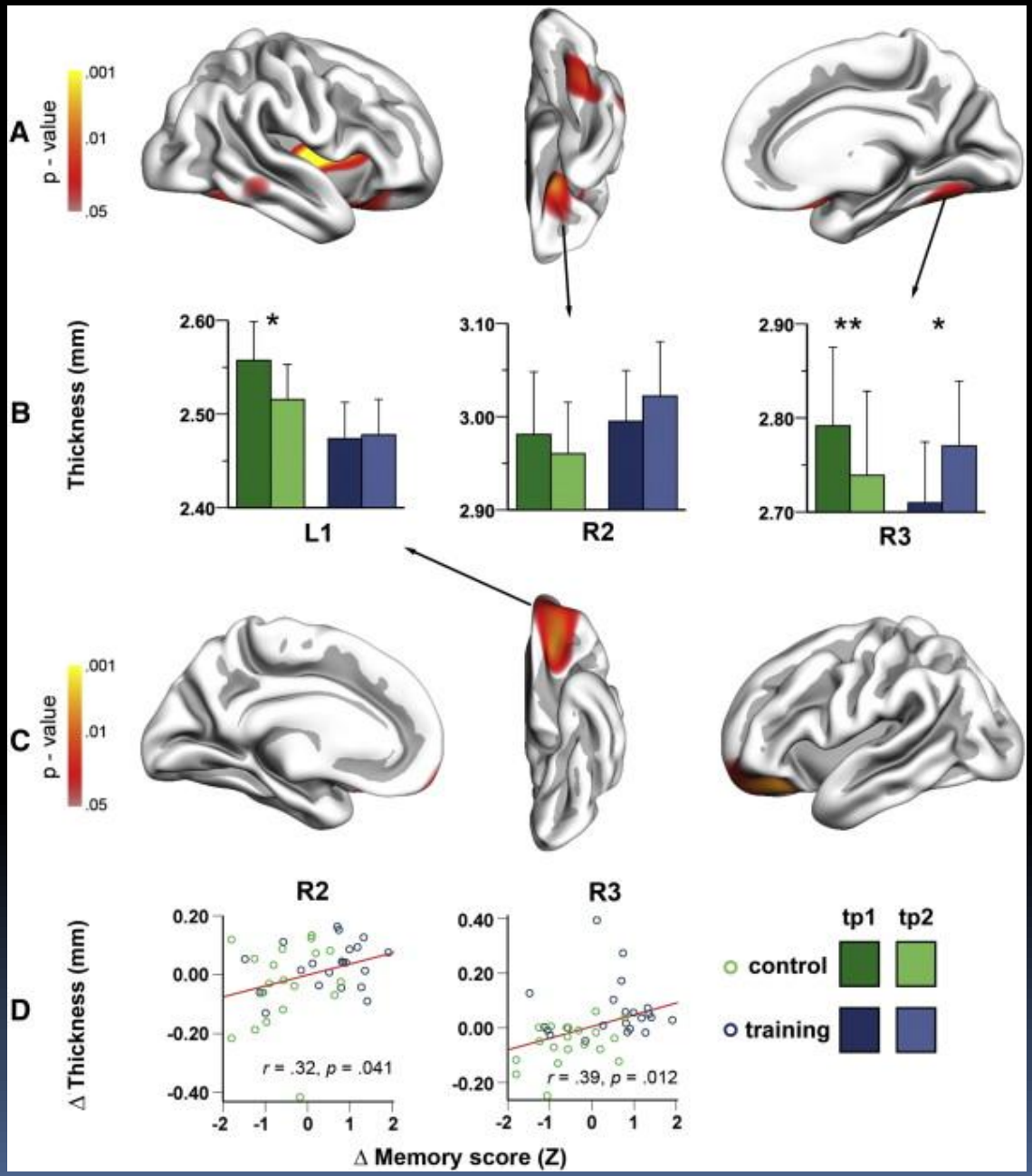
Braak et al., J Neuropathol Exp Neurol. 2011 Nov;70(11):960-9

What can you do about your risk?

Mental exercise

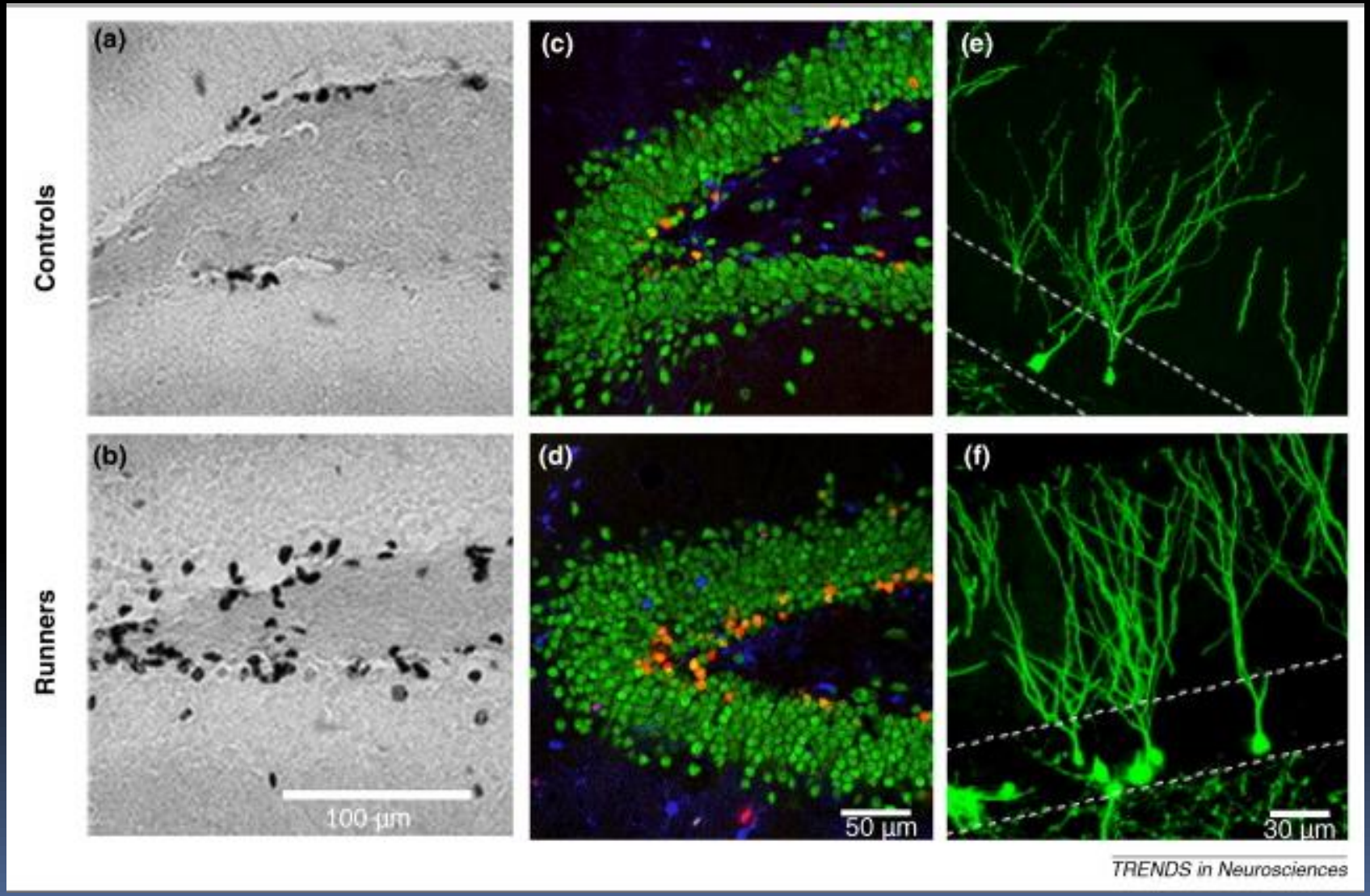


Engvig et al., NeuroImage Volume 52, Issue 4, 1 October 2010, Pages 1667-1676



Physical exercise

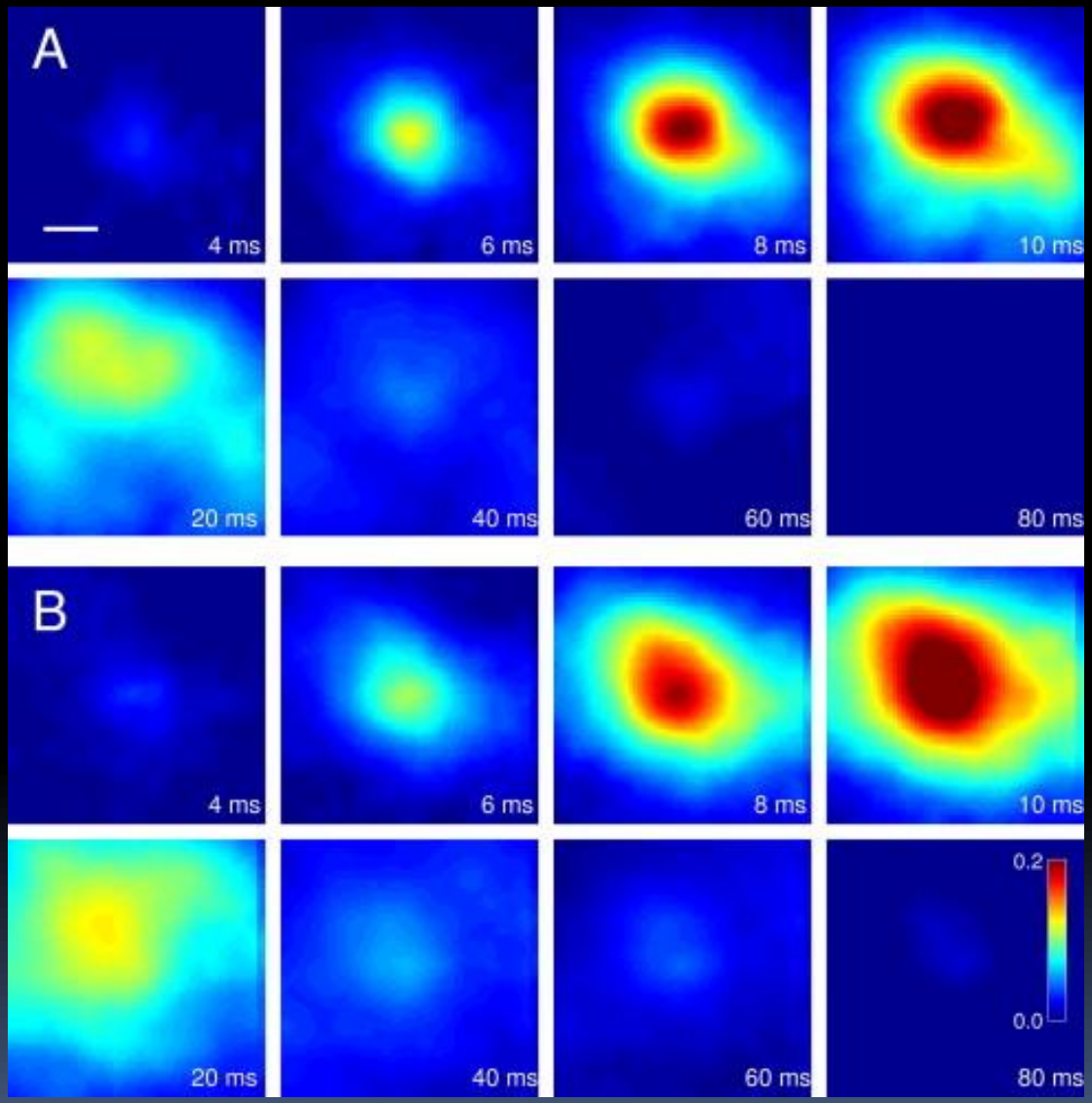
Lazarov et al, Trends Neurosci. 2010 Dec;33(12):569-79



Sensory stimulation

Non-enriched environment: Cortical evoked responses

Enriched environment: Cortical evoked responses



Devonshire et al., Neuroscience. 2010 Oct 13;170(2):662-9

You are what you eat…

A healthy diet can prevent or delay Alzheimer's disease for almost 3 years!

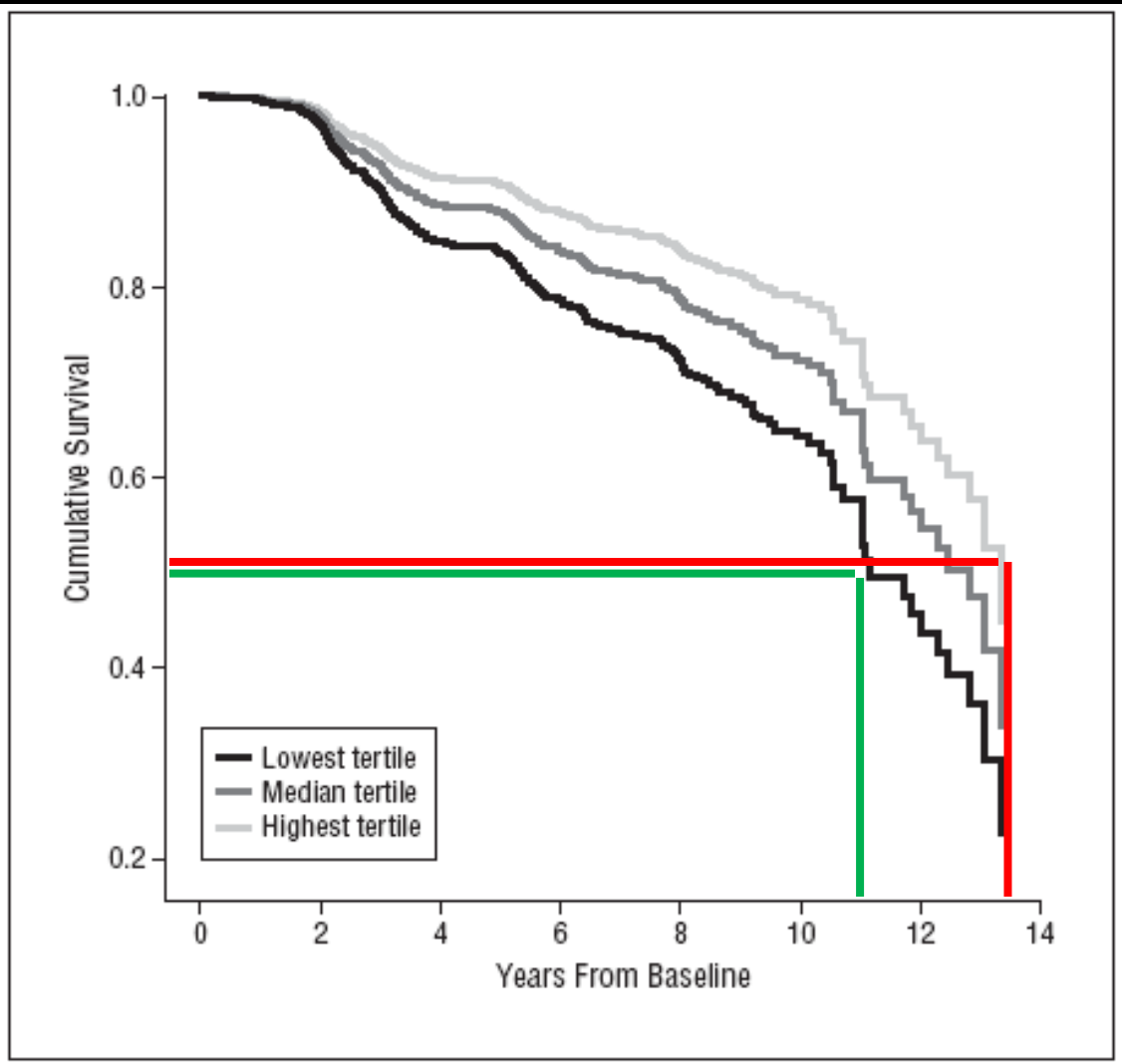
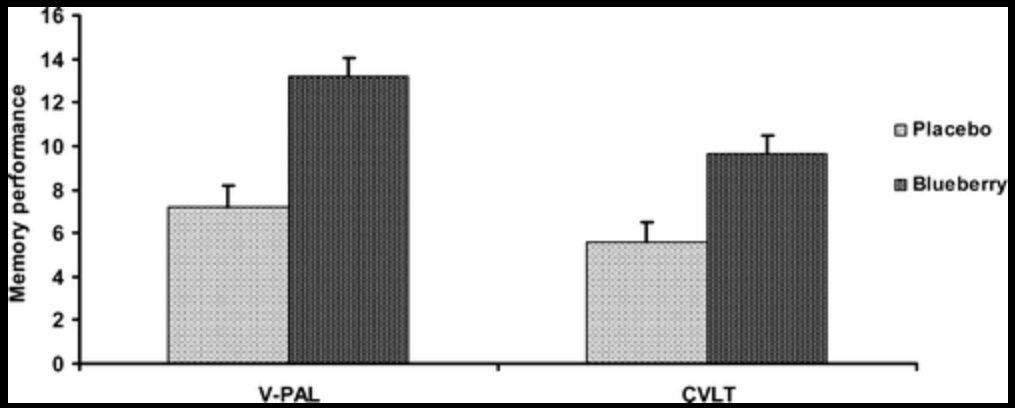


Figure. Survival curves based on Cox analysis comparing cumulative Alzheimer disease incidence in subjects belonging to each dietary pattern (DP) score 2 tertile (*P* for trend <.001). Lowest tertile (black line) corresponds to the lowest adherence to DP 2; median tertile (dark-gray line), to median adherence; and highest tertile (light-gray line), to the highest adherence. The Figure was derived from a crude model that used all subjects (N=2148).

Gu Y, Nieves JW, Stern Y, Luchsinger JA, Scarmeas N. Arch Neurol. 2010 Apr 12.

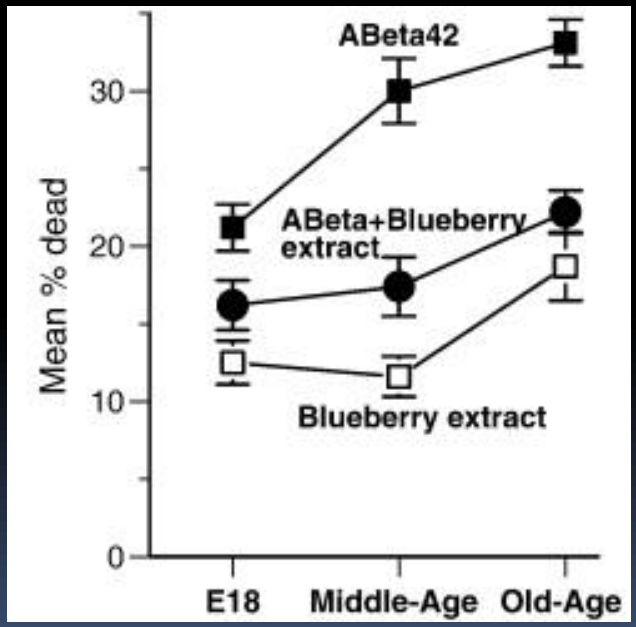
Blueberries and the brain

Blueberries improve memory !

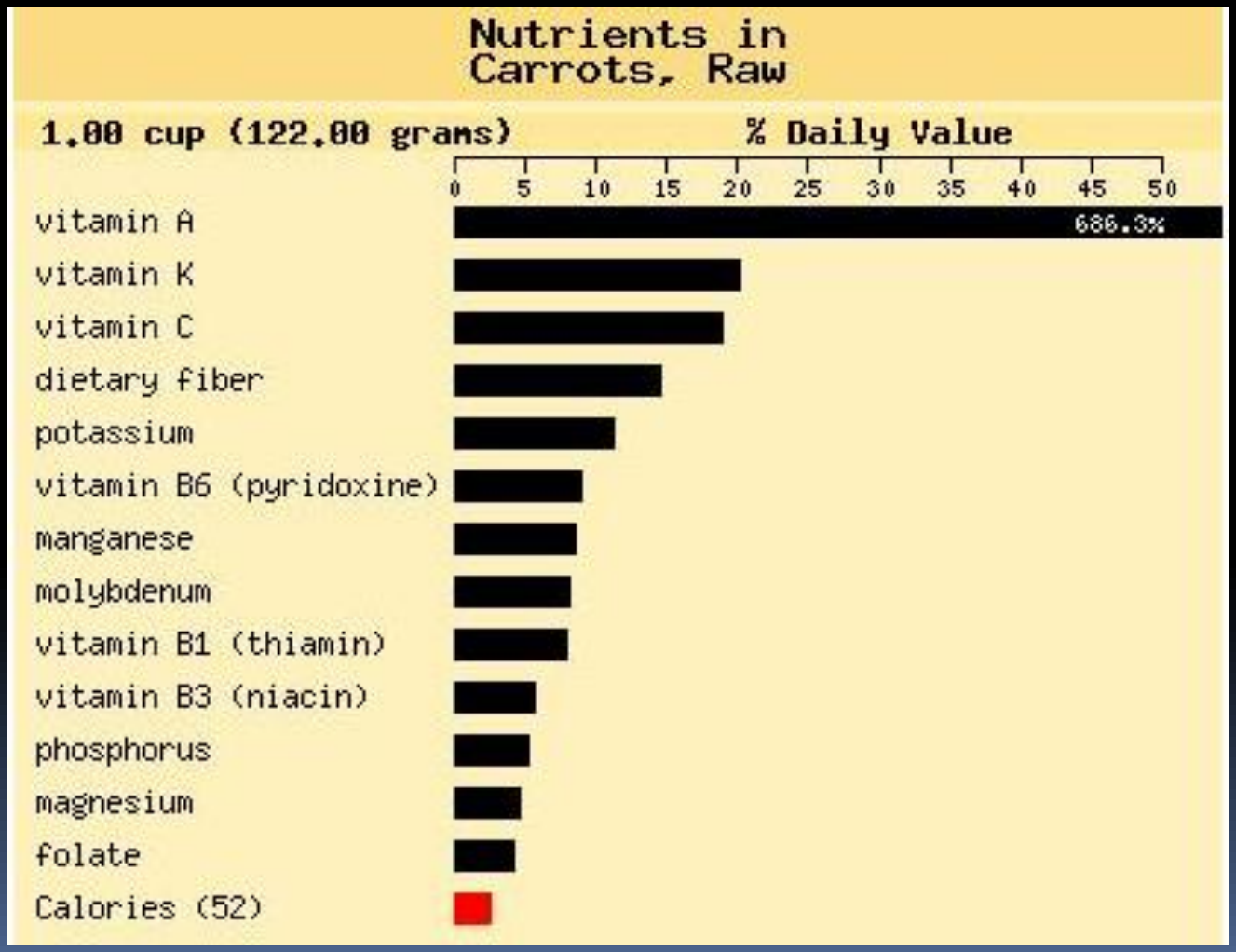


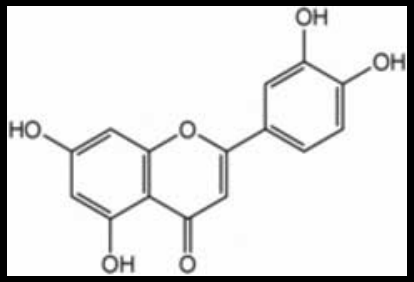
Krikorian et al., J Agric Food Chem. 2010 Apr 14;58(7):3996-4000

Blueberries prevent amyloid toxicity and death of nerve cells



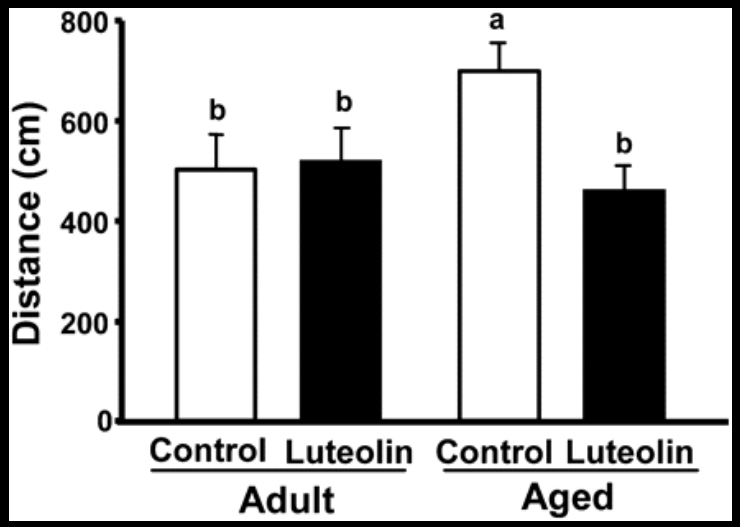
Health benefits of carrots

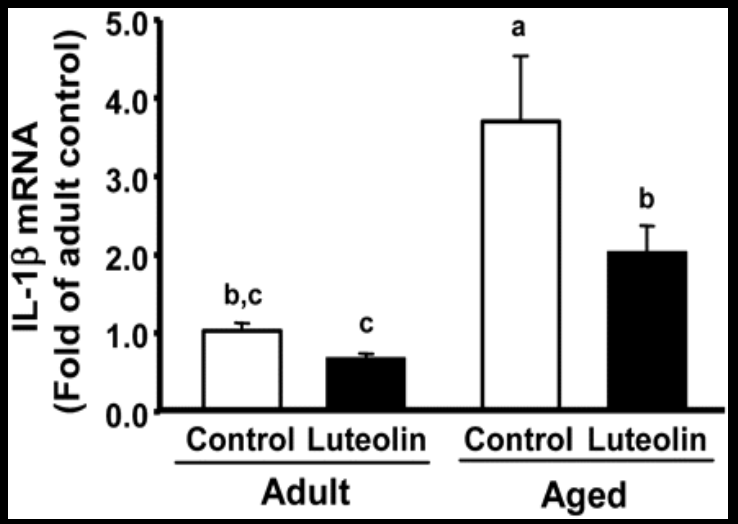




Luteolin is a plant flavonoid found in carrots, parsley, and chamomile tea that promotes brain health!

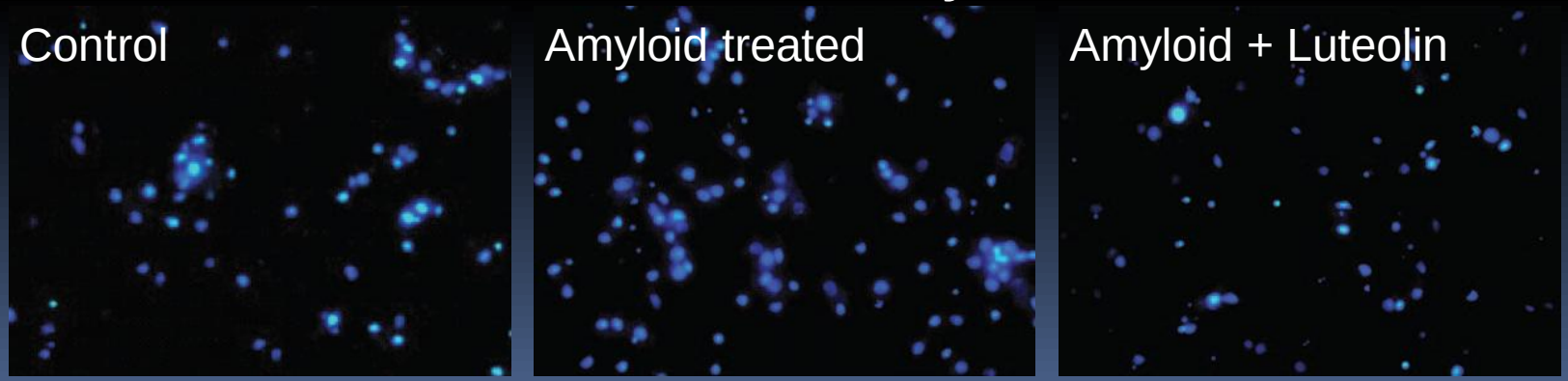
Luteolin (plant flavonoid) improves memory in aged mice and reduces brain inflammation





Jang et al., J Nutr. 2010 Oct;140(10) :1892-8.

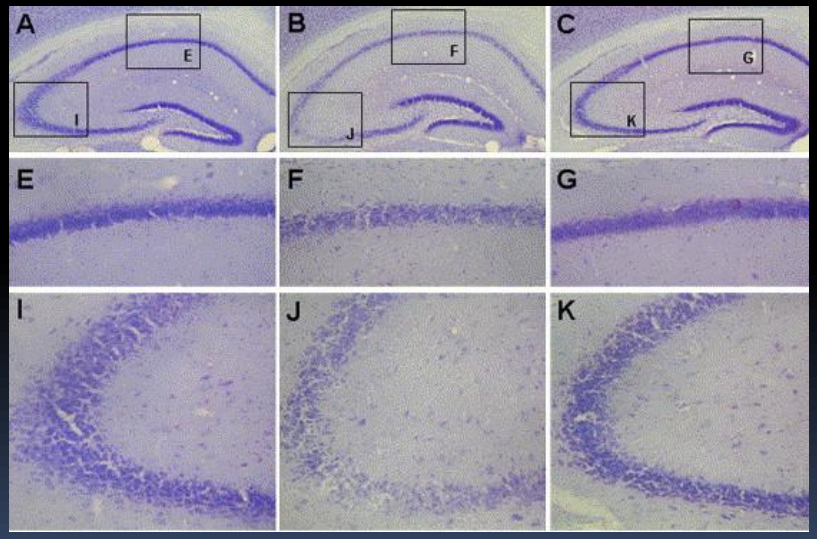
Luteolin prevents nerve cell death caused by toxic Alzheimer amyloid



Cheng et al., Phytother Res. 2010 Jan;24 Suppl 1:S102-8

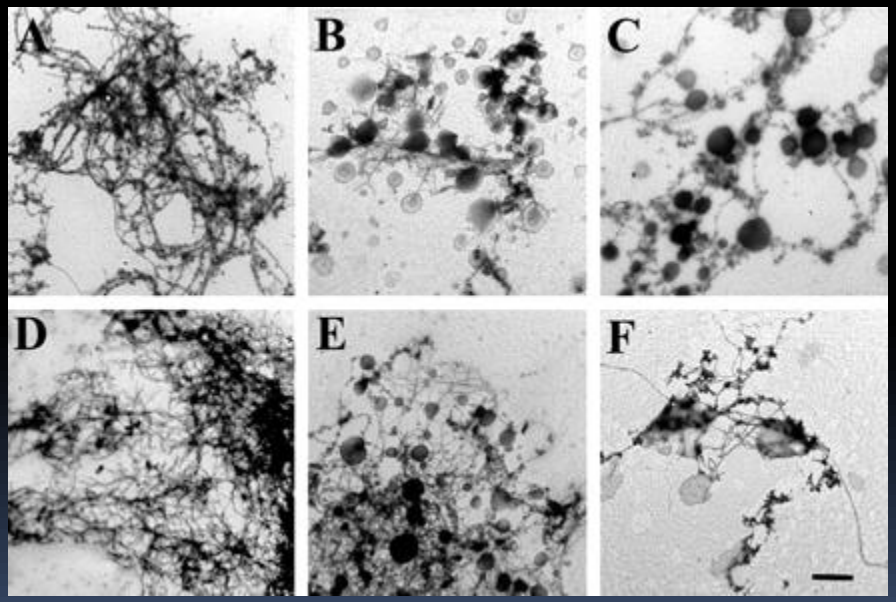
Turmeric and the brain

Curcumin prevents cell death in the hippocampus



Shin et al., Neurosci Lett. 2007 Apr 6;416(1):49-54

Curcumin prevents amyloid fibril formation and also degrades this toxic species



Yang et al., J Biol Chem. 2005 Feb 18;280(7):5892-901

The UK Alzheimer's Disease Center & the Sanders-Brown Center on Aging

We can't win this fight against AD without you!