Biology, Evaluation and Management of Alzheimer's Disease

From Research to Clinical Practice

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Disclosure Declarations
Ranjan Duara, MD

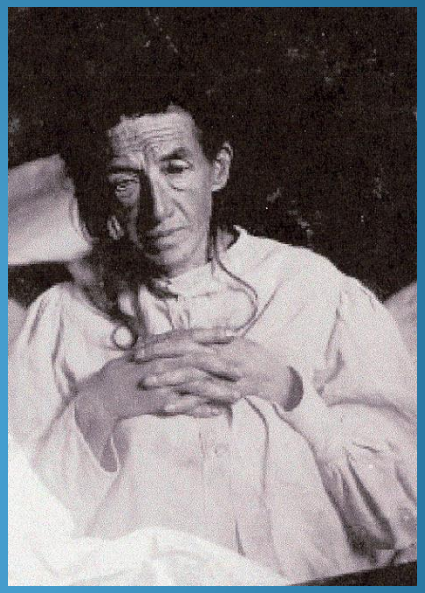
Company	Relationship Description (Name of drug / compound, type of intervention / instrument, etc)	Relationship	Stock and/or ownership rights > $5,000 or 5% interest	Established or potential royalty income	Income in the PAST 12 months of $5,000 or more	Income in the NEXT 12 months of $5,000 or more
Alzheimer's Therapeutic Research Institute	AZD0530 (FYN)in Mild Alzheimer's Disease	Grant / Research Support	No	NA	NA	NA
Avid - Eli Lilly & Company	Amyvid™:Use of AV-45 in ADCS Trials	Grant / Research Support	No	NA	NA	NA
Avid - Eli Lilly & Company	Tau: Tau Imaging AV 1451	Grant / Research Support	No	NA	NA	NA
Eli Lilly & Company	Solanezumab: Anti-Amyloid Trial in Asymptomatic AD (A4 Study)	Grant / Research Support	No	NA	NA	NA
Janssen Research & Development, LLC	JNJ-54861911 in Subjects who are Asymptomatic At Risk for Developing Alzheimer's	Grant / Research Support	No	NA	NA	NA
Medical Learning Group	Speaker's Bureau for Eli Lilly & Company	Consultant or Advisor - Paid DIRECTLY	No	NA	Yes	Yes
Merck & Company	MK-8931: MK-8931-019 in Prodromal Alzheimer's Disease	Grant / Research Support	No	NA	NA	NA
Toyama Chemical Co., Ltd.	TCAD/NOBLE: Toyama Chemical (T-817MA) in Alzheimer's Disease	Grant / Research Support	No	NA	NA	NA
vTv THERAPEUTICS LLC	TTP488: TTP488-301 for Mild Alzheimer's Disease	Grant / Research Support	No	NA	NA	NA

Memories


BACK IN 1952, GASOLINE COST 20 CENTS A GALLON. WHEN YOU PULLED UP TO THE PUMPS, THREE GUYS CAME OUT AND CHECKED YOUR OIL AND YOUR TIRES AND CLEANED YOUR WINDOWS
THIS MUST BE THAT THING THEY CALL "SENILITY"
Dick Dial

Auguste D & Alois Alzheimer

- First patient described - 1907
  - 51 year old woman
  - Memory impairment
  - Hallucinations, delusions, paranoia
  - Agitation
  - Disorientation
- Progression over 5 years
  - At end - fetal position, incontinent, unresponsive



Picture of Auguste D from: Maurer K, Volk S, Gerbaldo H. Auguste D and Alzheimer's disease. Lancet 1997; 349: 1546-49.

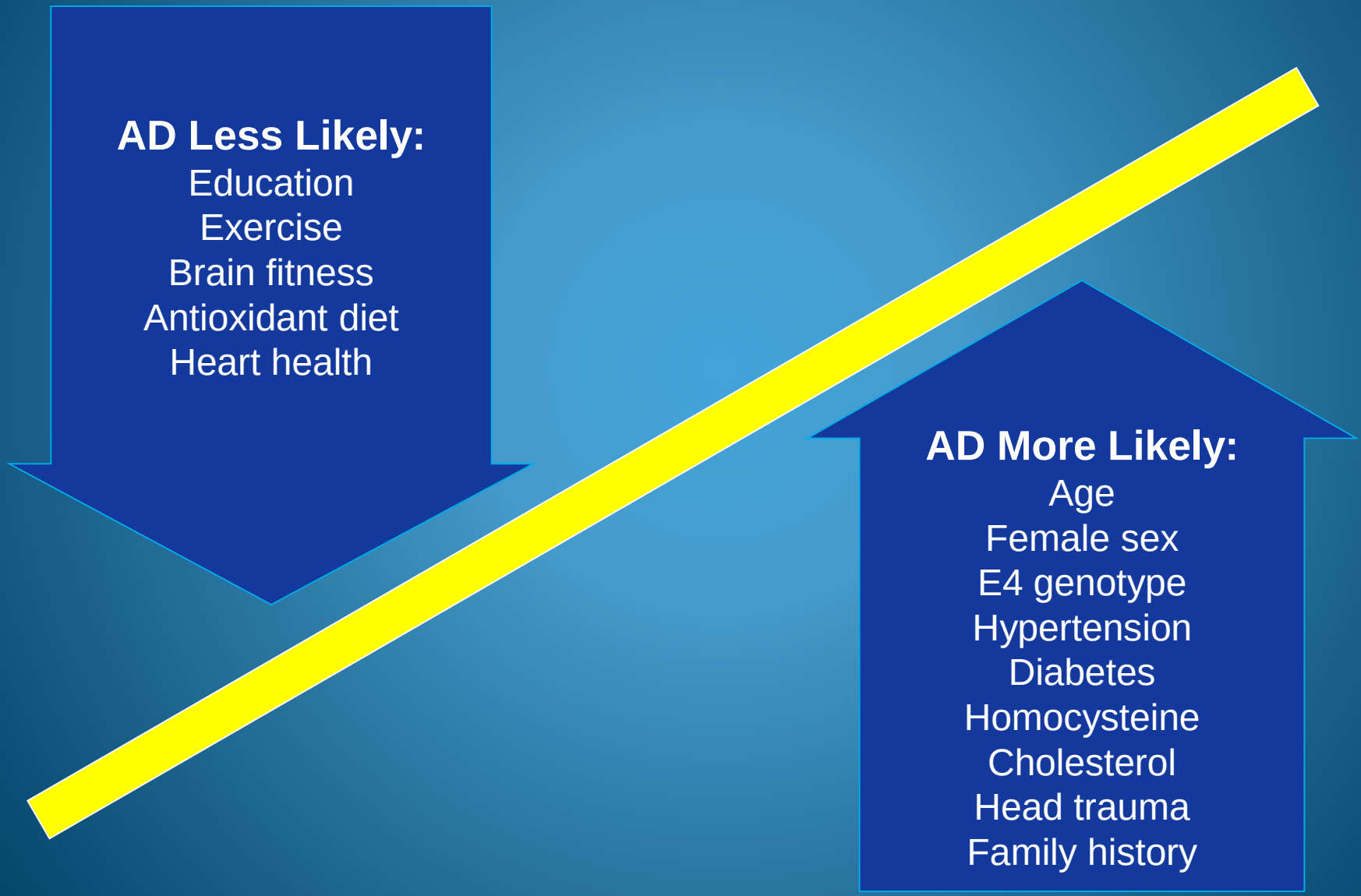
Alzheimer's disease Facts

- First described in a younger persons (50's and 60s) – now known to be the most common cause of dementia in older persons
- ~ 5+ million individuals currently affected in the U.S.
- Alzheimer's affects 50% of people 85 + years of age.
- By 2050 22+ million people will be affected worldwide
- Medical, monetary, and human resources will be severely strained
- New data suggests Alzheimer's is the 3rd most common cause of death (Neurology, 2014)

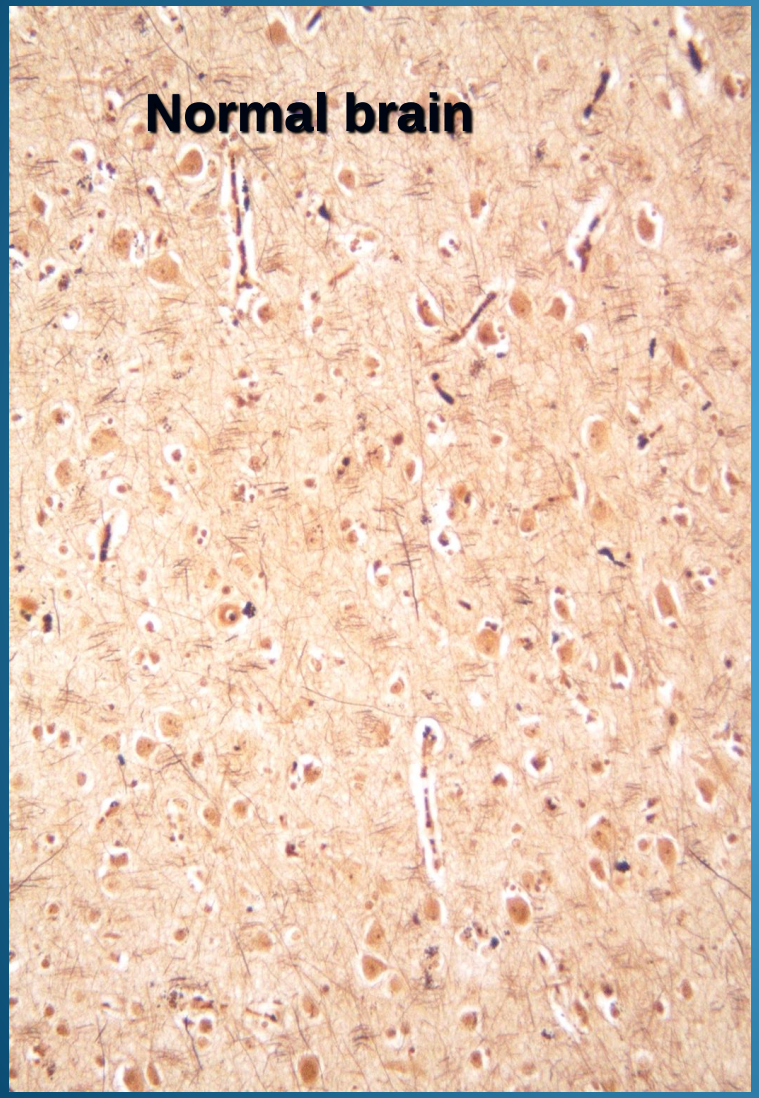
- Genetics contribute to susceptibility
- Early onset AD transmitted as a autosomal dominant trait typically <65 y/o age (esp. presenilin 1 mutation on Chromosome 14; (very rarely Chromosome 1 and Chromosome 21 mutations)
- Majority of cases sporadic (not purely genetic)– but genetic factors play significant role (especially apolipoprotein e4)

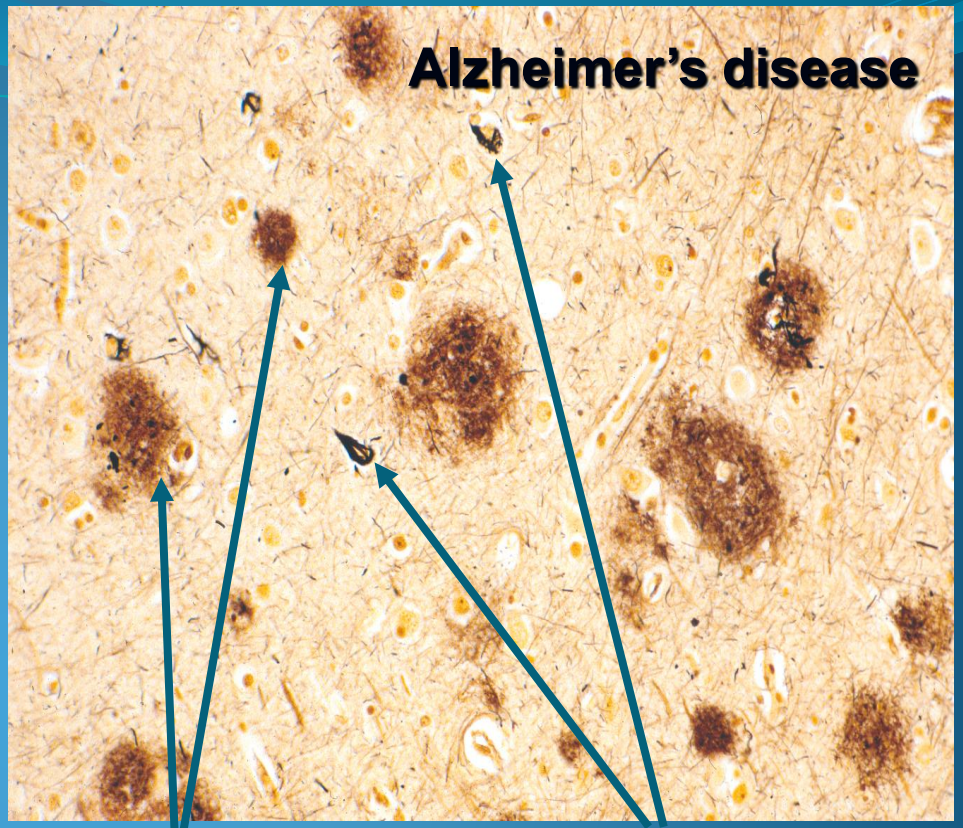
- Non-genetic risk factors important: age – activity, BMI, blood pressure, diabetes, diet, psychosocial factors (e.g., neuroticism, anxiety)

Alzheimer's Disease

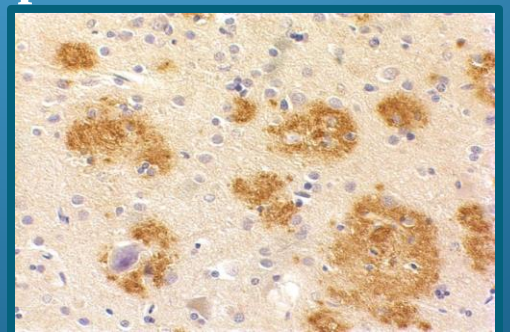


Biology of Alzheimer's

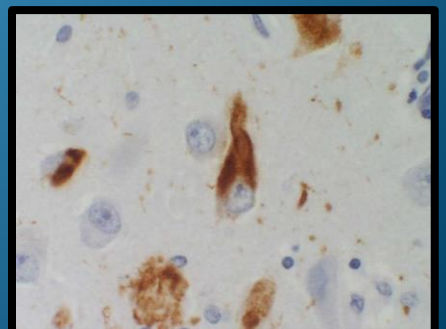




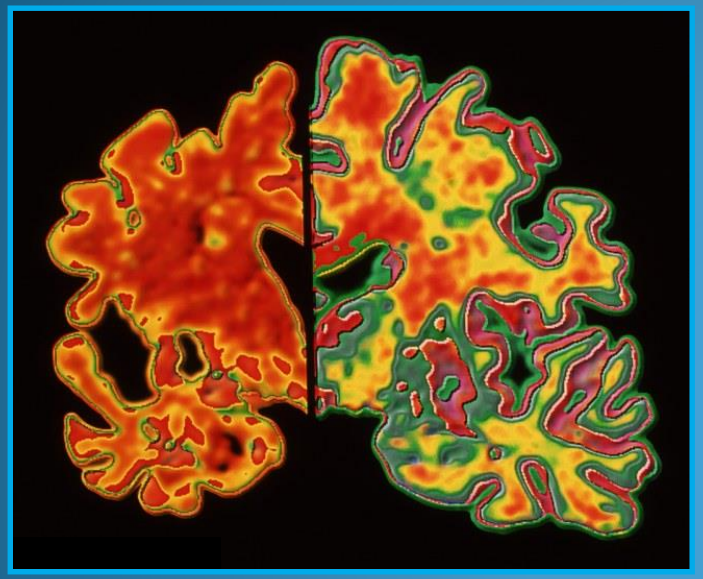
PLAQUES
Amyloid beta protein



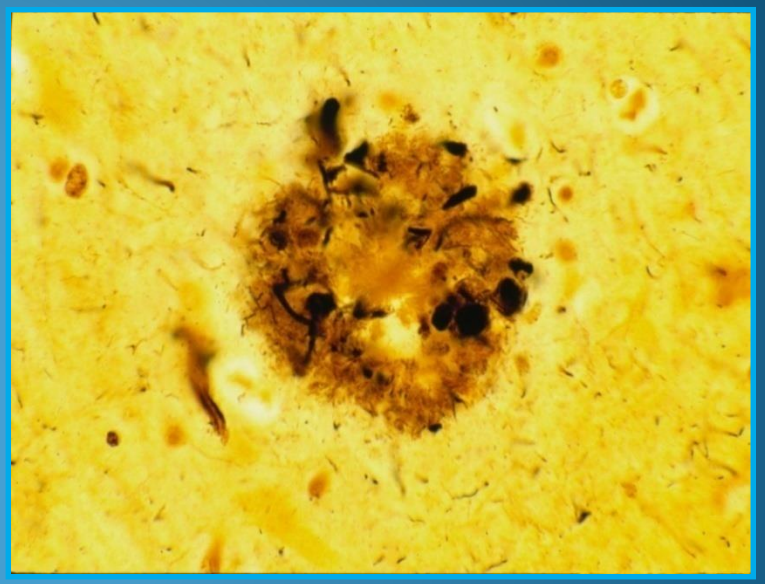
TANGLES
abnormal tau protein



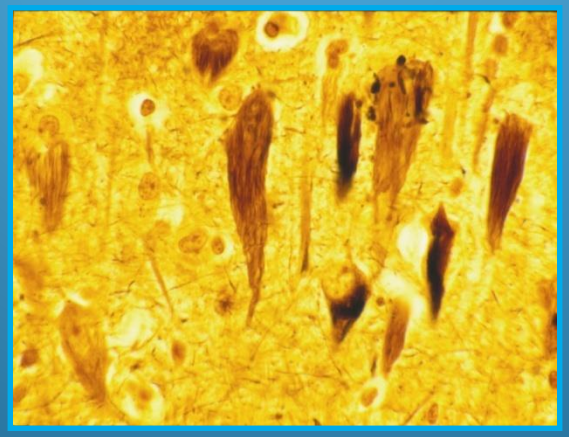
Alzheimer's Disease: Pathology



Brain atrophy



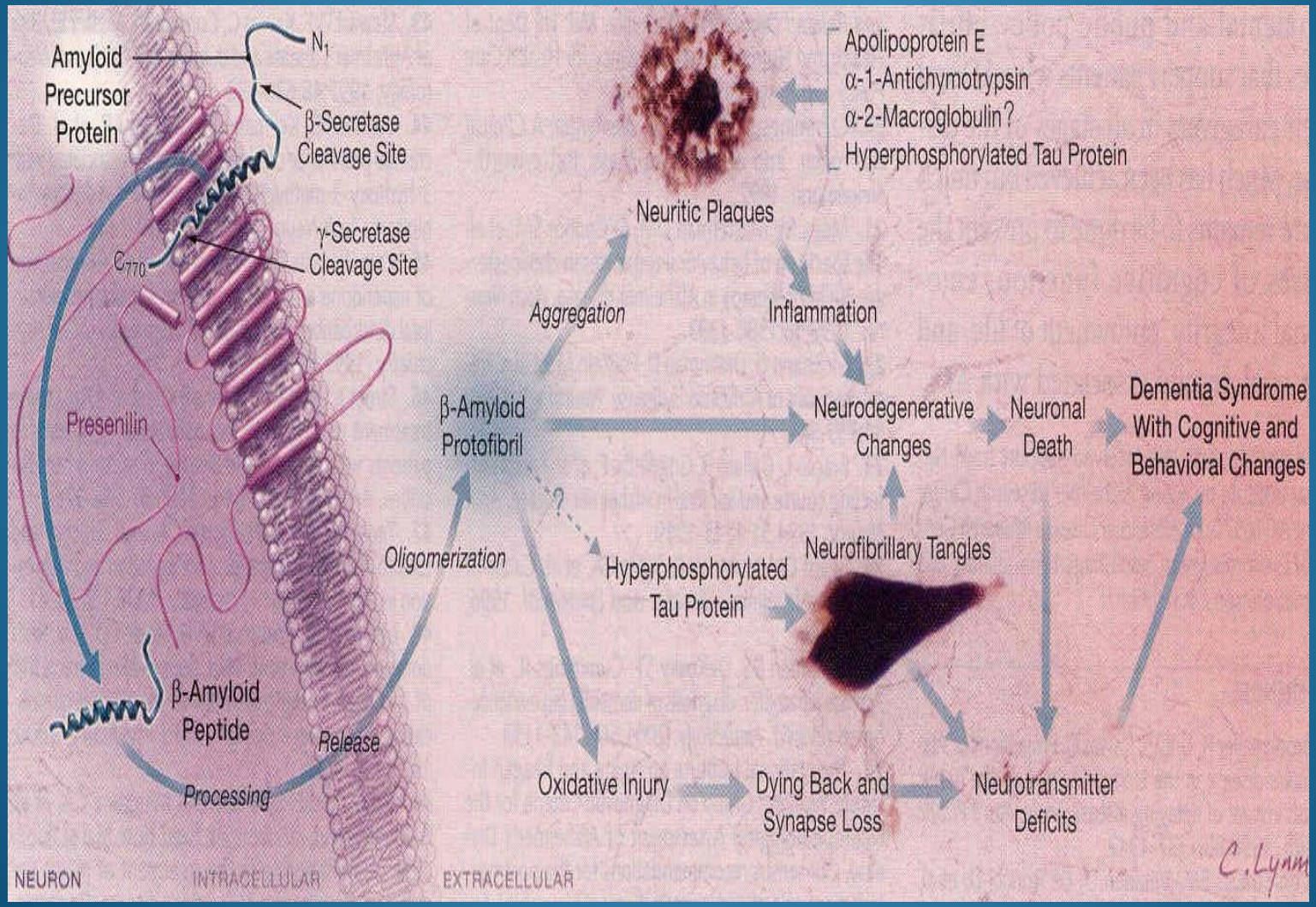
Amyloid plaque



Neurofibrillary tangle

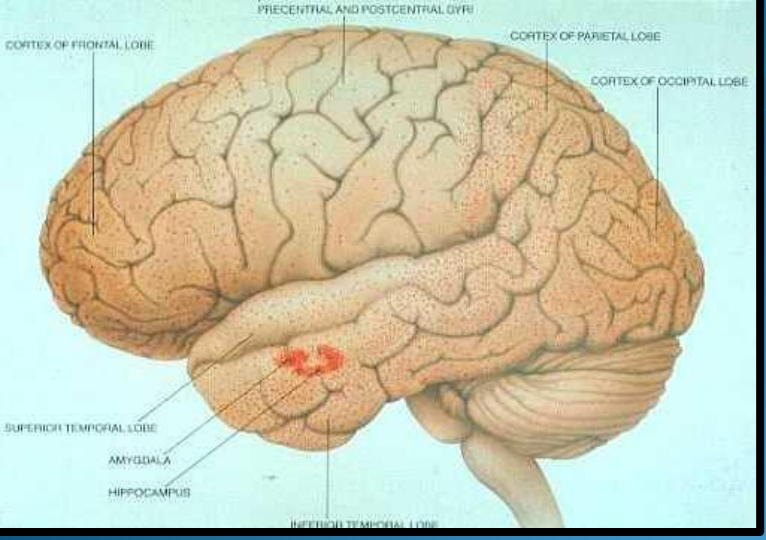
Images courtesy of The Brain Plaques and Tangles That Cause Alzheimer's Disease.
Available at: http://bigthink.com/ideas/the-brain-plaques-and-tangles-that-cause-alzheimers-disease . Accessed October 29, 2012.

- Amyloid Beta protein deposition considered pivotal in Alzheimer's disease process



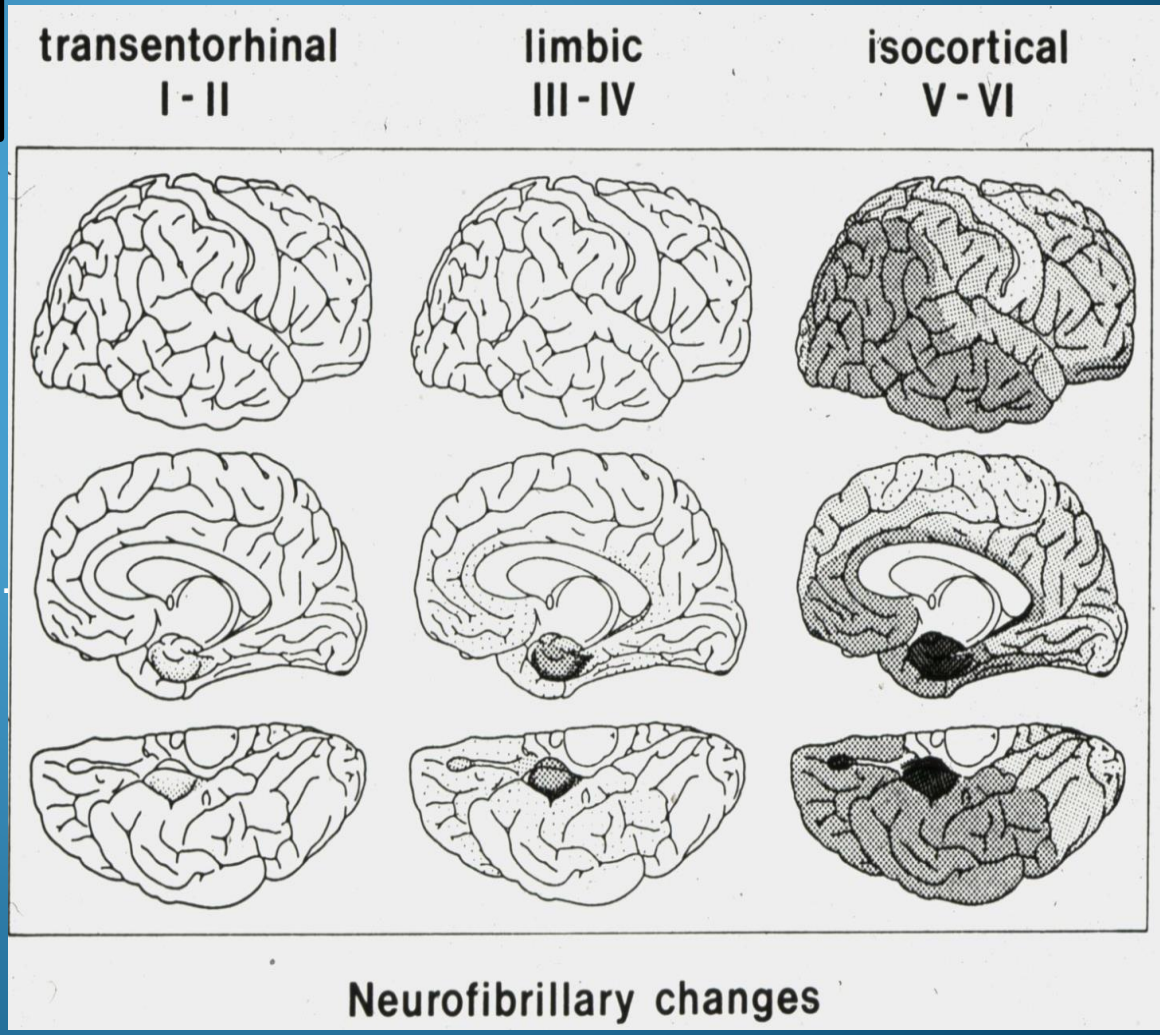
(Cummings JL, JAMA, May 8, 2002)

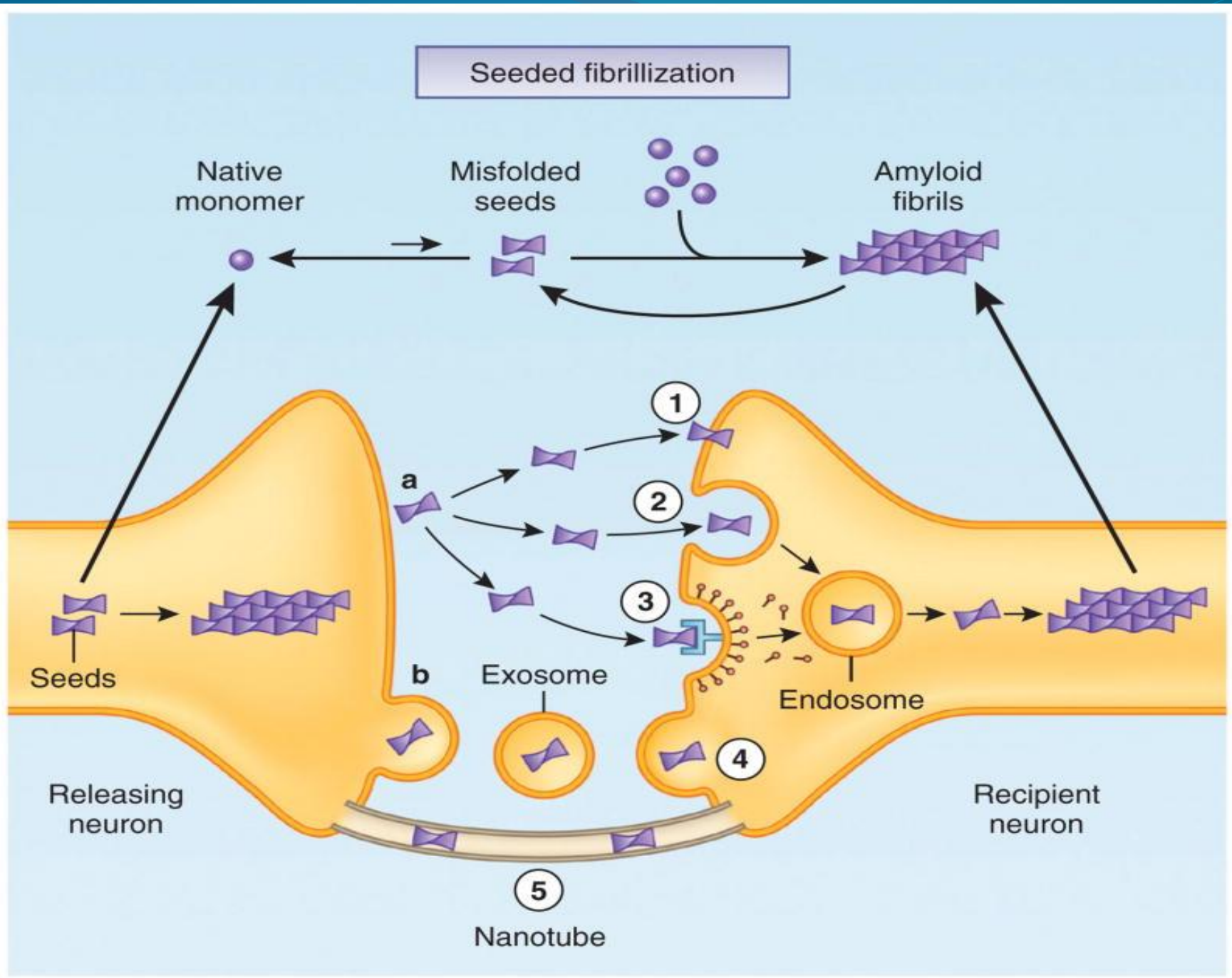
Distribution of amyloid and neurofibrillary pathology in Alzheimer's disease (From Selkoe, DJ, Sci Am, 1991)

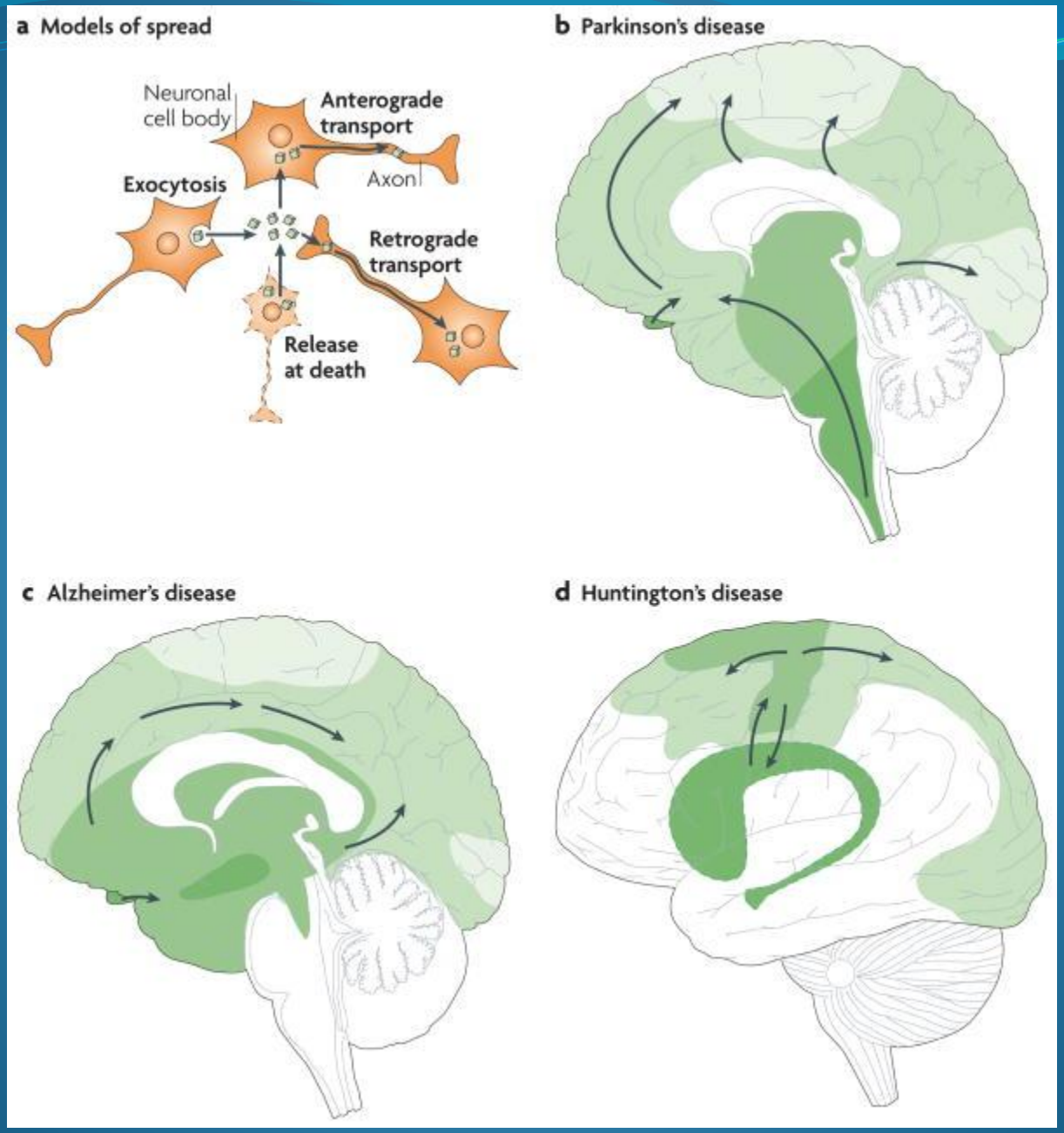


Senile plaque distribution

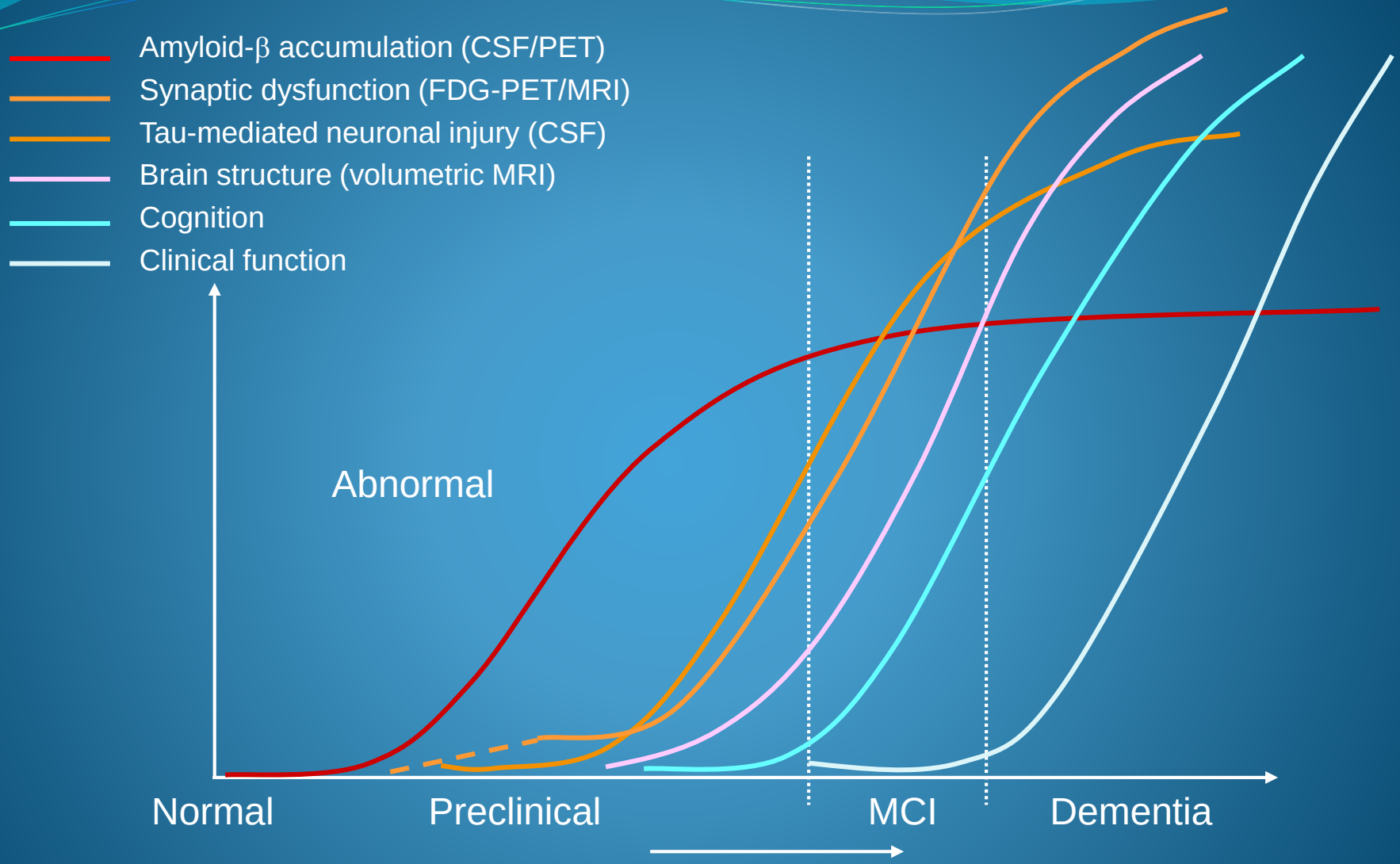
(Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol (Berl) 82: 239-259.)



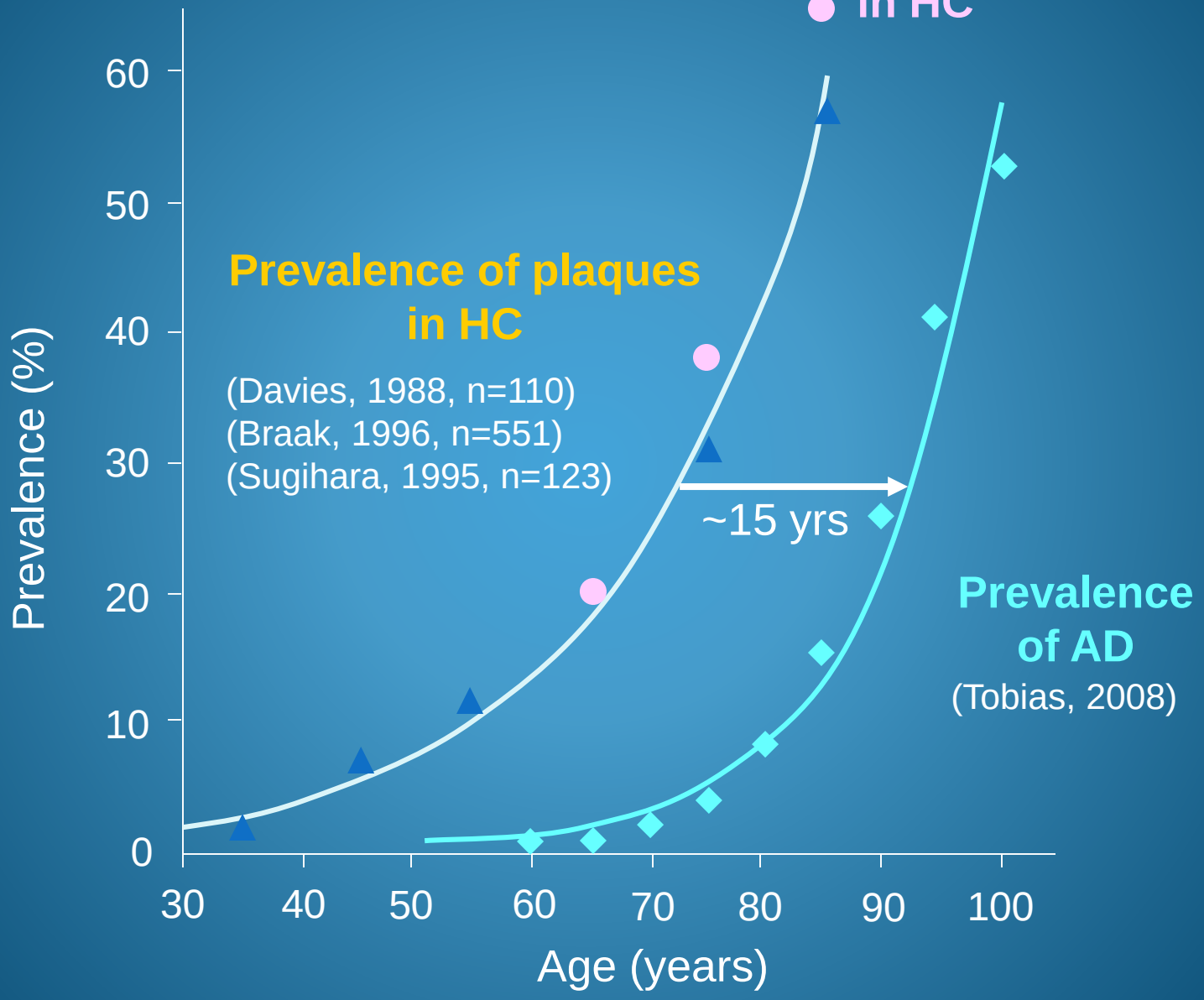

Seeded fibrillization
Native monomer
Misfolded seeds
Amyloid fibrils
1
2
3
4
5
a
b
Seeds
Exosome
Endosome
Releasing neuron
Recipient neuron
Nanotube


a Models of spread
Neuronal cell body
Anterograde transport
Axon
Exocytosis
Retrograde transport
Release at death
b Parkinson's disease
c Alzheimer's disease
d Huntington's disease

Biomarker Changes During AD Progression



R.A. Sperling et al. Alzheimer's & Dementia;(2011) 1-13 [modified]



Rowe et.al. Neurobiol. of Aging 2010;3`:1275-83

Imaging and Diagnosis

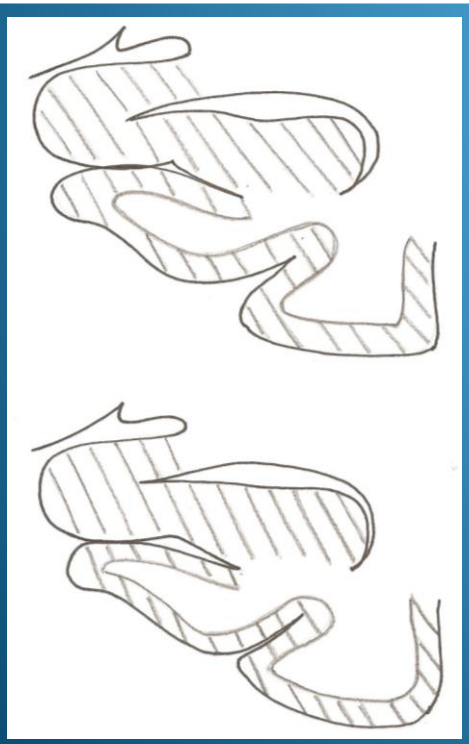
Biomarkers for Assessment of AD Pathology in the Clinic

- Structural
  - Magnetic resonance imaging (MRI)
  - X Ray CT
- Functional
  - Fluorodeoxyglucose positron emission tomography (FDG PET)
  - Functional MRI (fMRI)
- Molecular and biochemical
  - CSF
  - Amyloid PET
  - Tau PET
  - PET markers of Microglial Activation

Medial Temporal Atrophy Rating (HP, ERC, PRC)

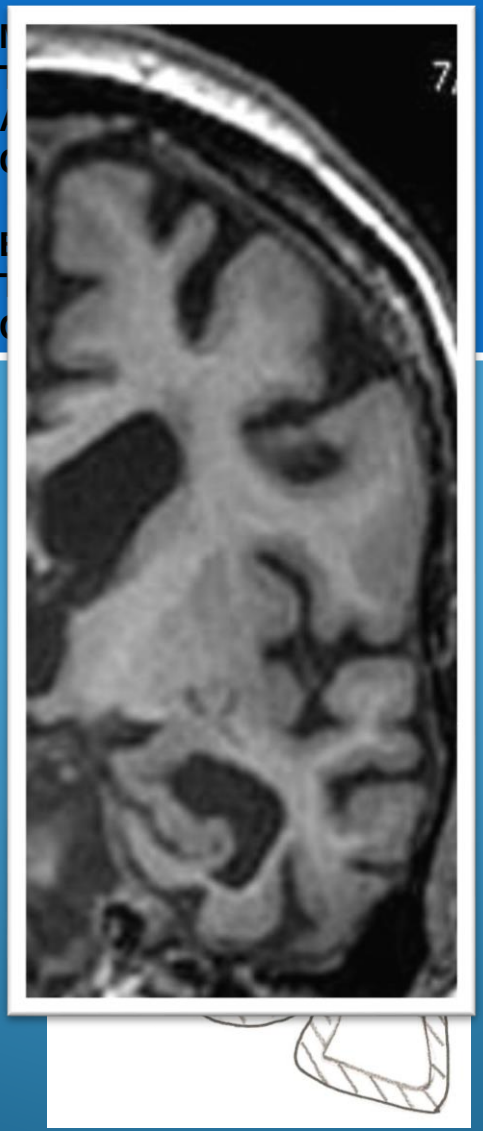
Entorhinal Cortex
Rating = 2 Mild Atrophy

1. **Mild Decrease In Thickness**
   Or
2. **Mild Widening Of Collateral Sulcus**
   Or
3. **Both**



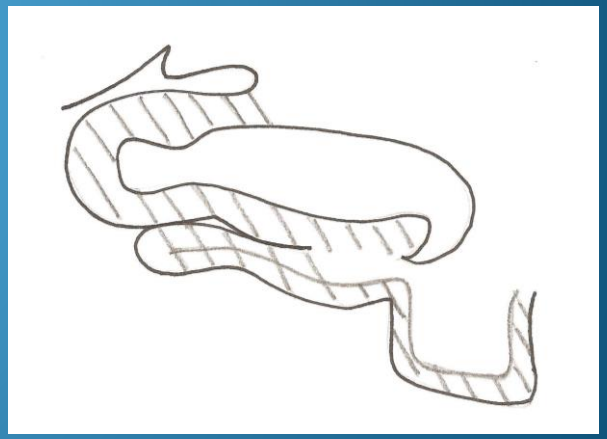
Entorhinal Cortex
Rating = 3 Moderate Atrophy

1. **M**
   T
   A
   C
2. **B**
   T
   C



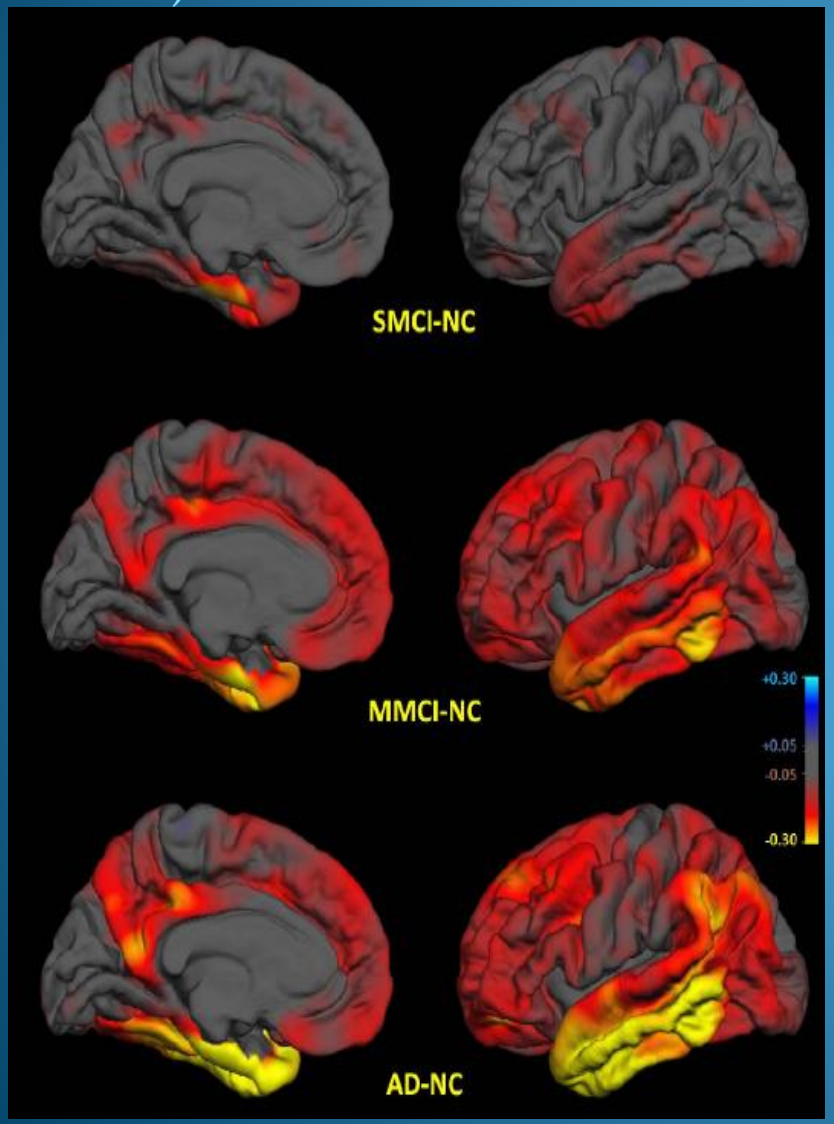
Entorhinal Cortex
Rating = 4 Severe Atrophy

1. **Severe Decrease In Thickness (Even In The Absence Of Widening Of Collateral Sulcus)**
   Or
2. **Both Severe Decrease In Thickness And Widening Of Collateral Sulcus**

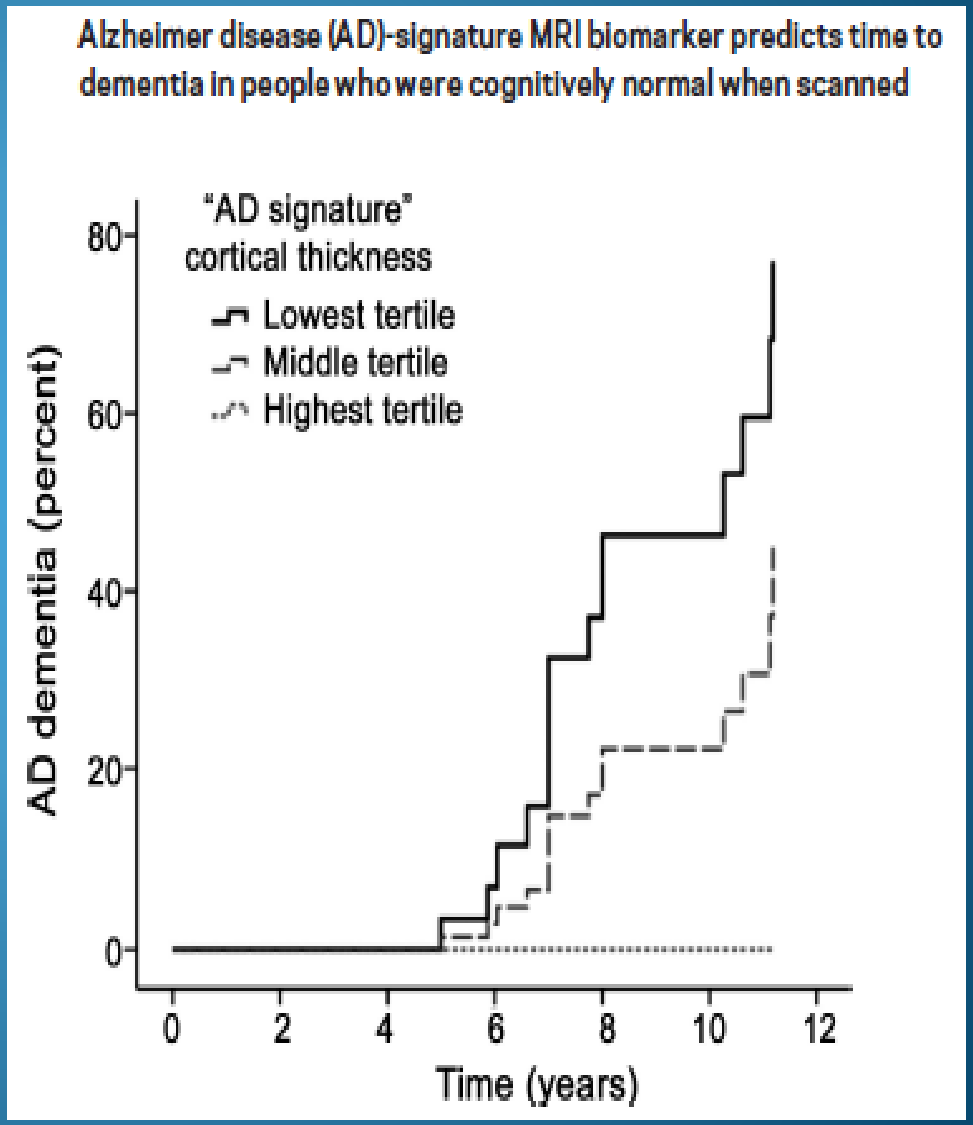


MRI Biomarker and AD Progression

(Reduction in Cortical Thickness Associated with Disease Stage and Future Rate of Decline)



Fennema-Notestine, Fleisher, et al. 2009.



Dickerson B et al. *Neurol.* 2011.

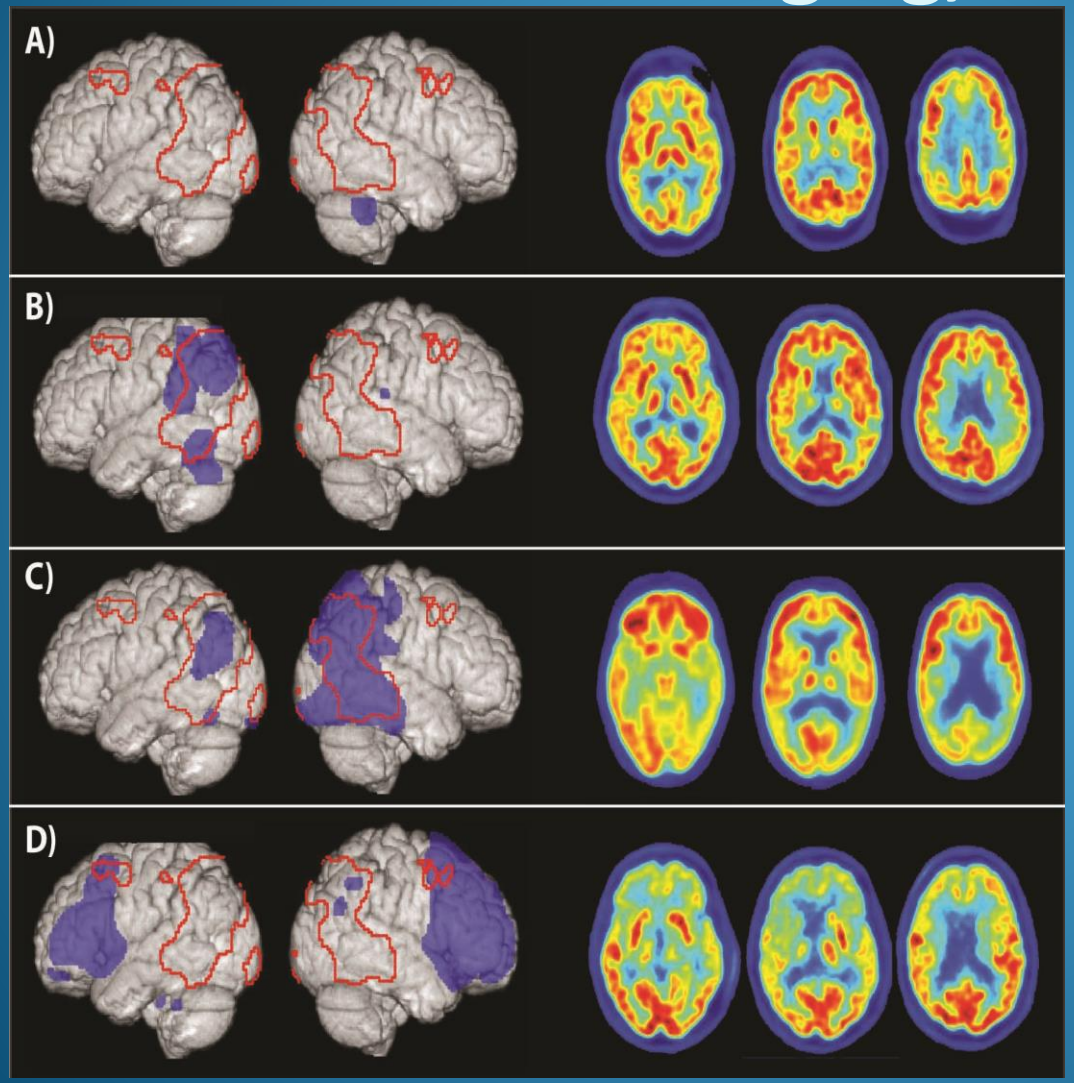
FDG-PET in Normal Aging, MCI, AD and FTD

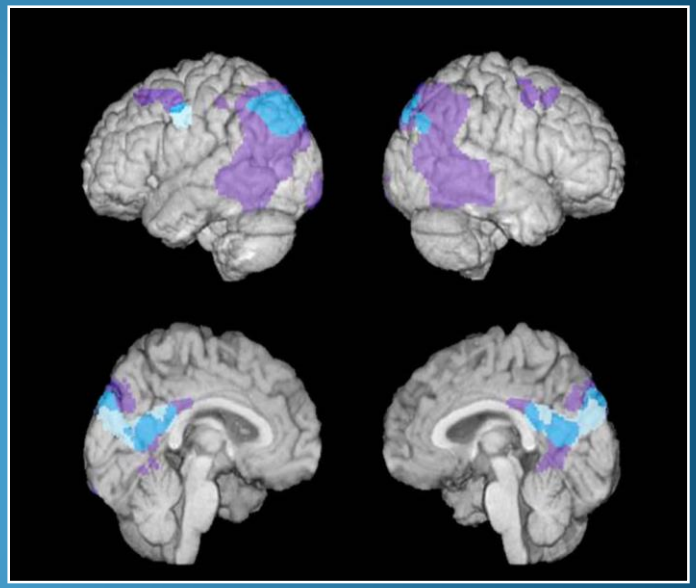
NL

MCI

pAD

fTD





- AD-Dementia

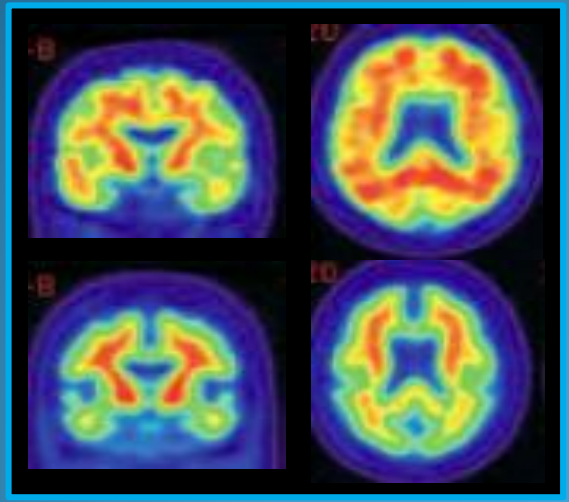
- Cog NL APOE4 carriers

fTD = frontotemporal dementia; pAD = Probable Alzheimer's disease.

[F-18] Amyloid Imaging Tracers

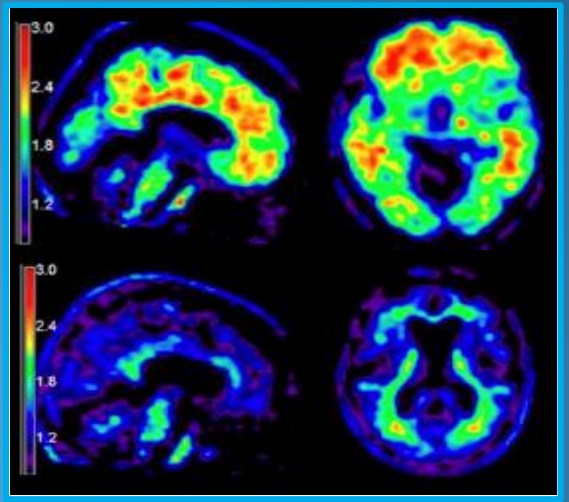
Flutemetamol[1]

AD



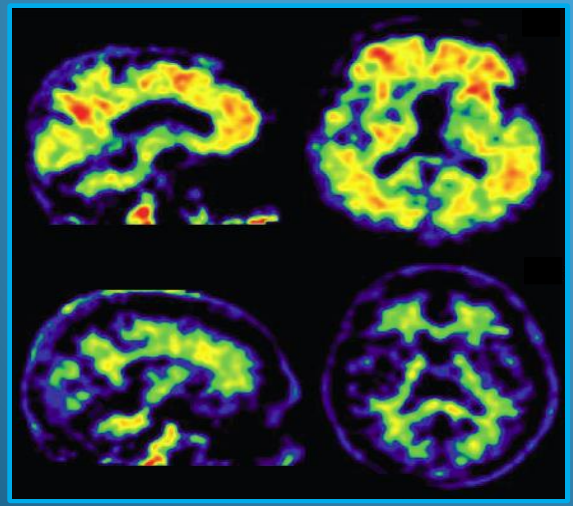
NL

Florbetapir[2]



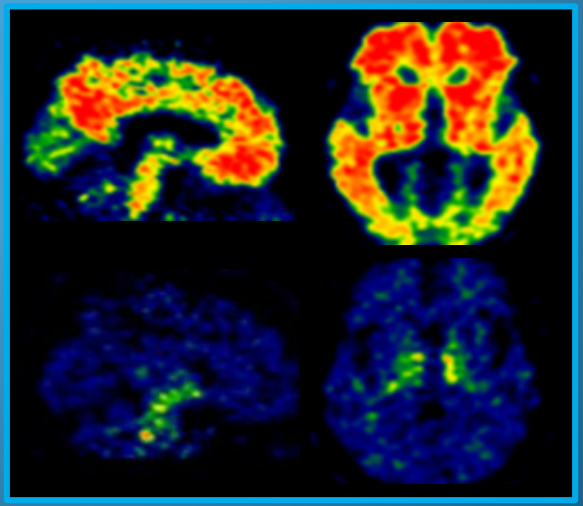
Florbetaben[3]

AD



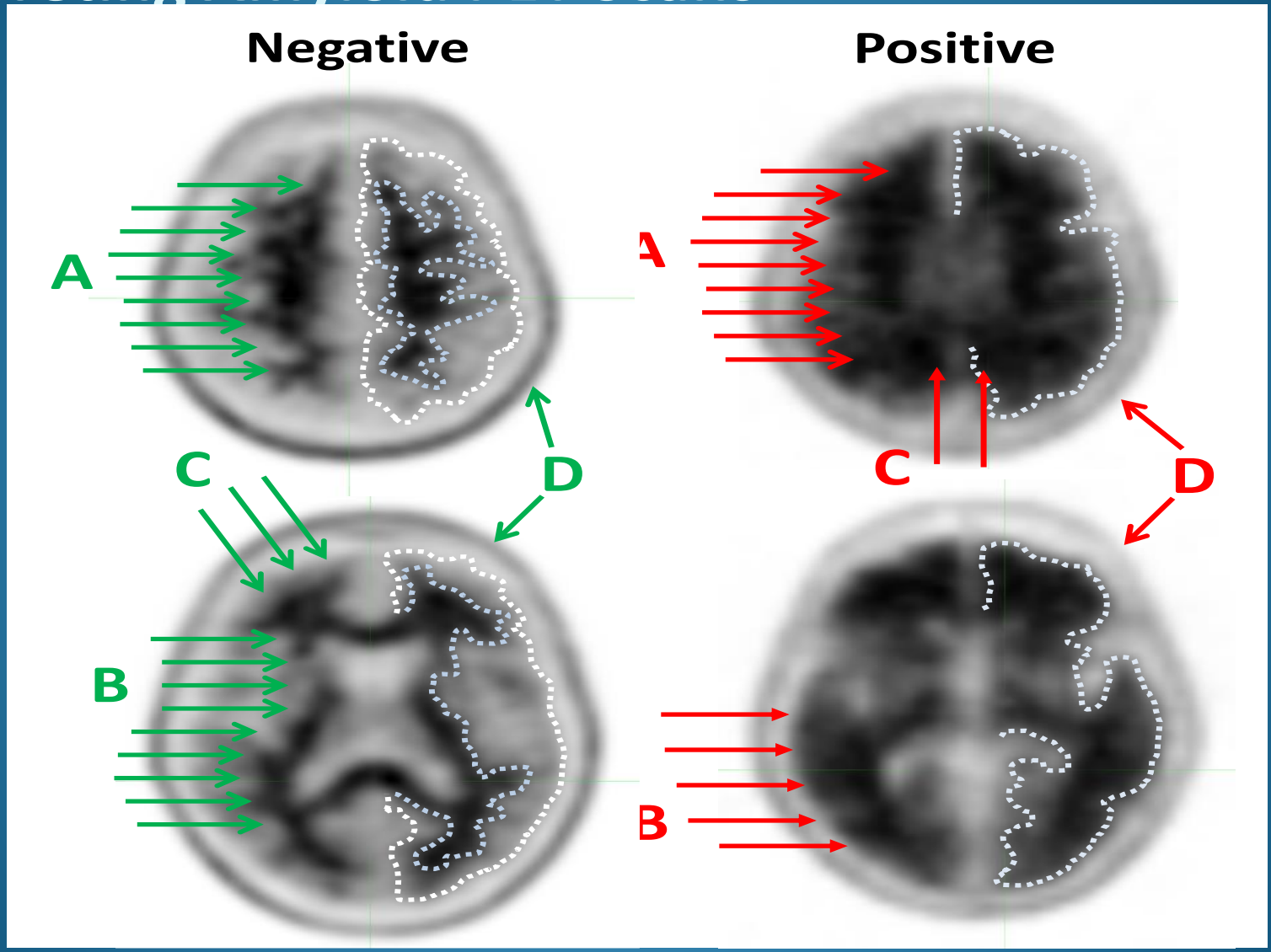
NL

Navidea NAV4694[4]



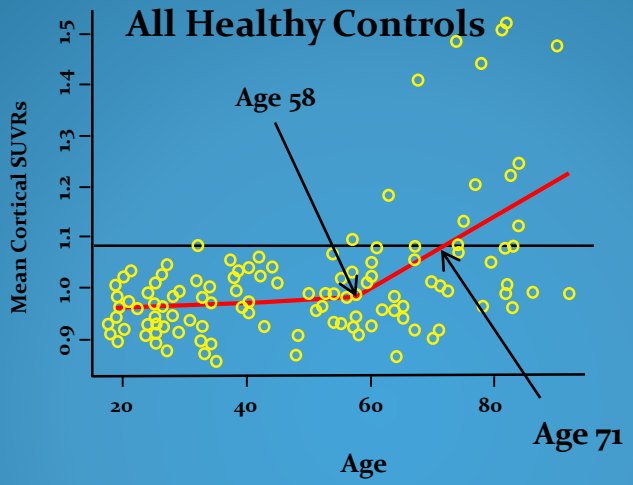
[1]Vandenberghe R et al. *Ann Neurol*. 2010;68:319-329. [2]Barthel H et al. *Lancet Neurol*. 2011;10:424-435. [3]Wong DF et al. *J Nuc Med*. 2010;51:913-920. [4]Chen K et al. *AAIC*. 2012.

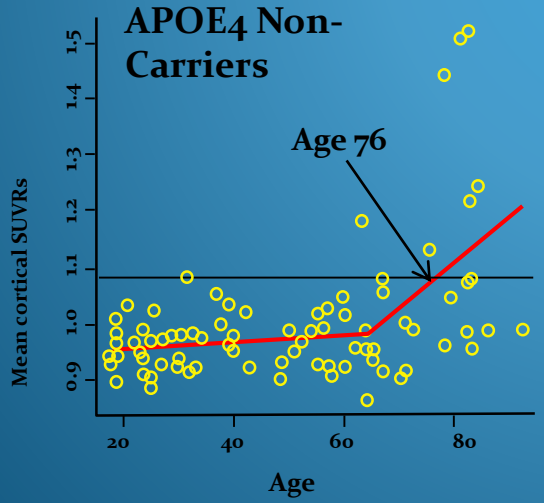
Interpreting Amyloid PET Scans

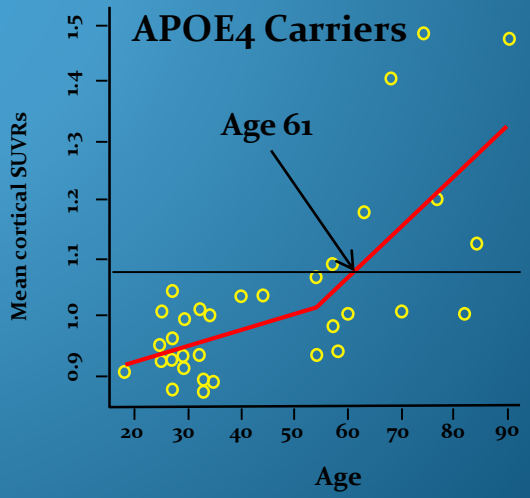


2012 Eli Lilly Prescribing Information, http://pi.lilly.com/us/amyvid-uspi.pdf

APOE4, Age and Amyloid PET

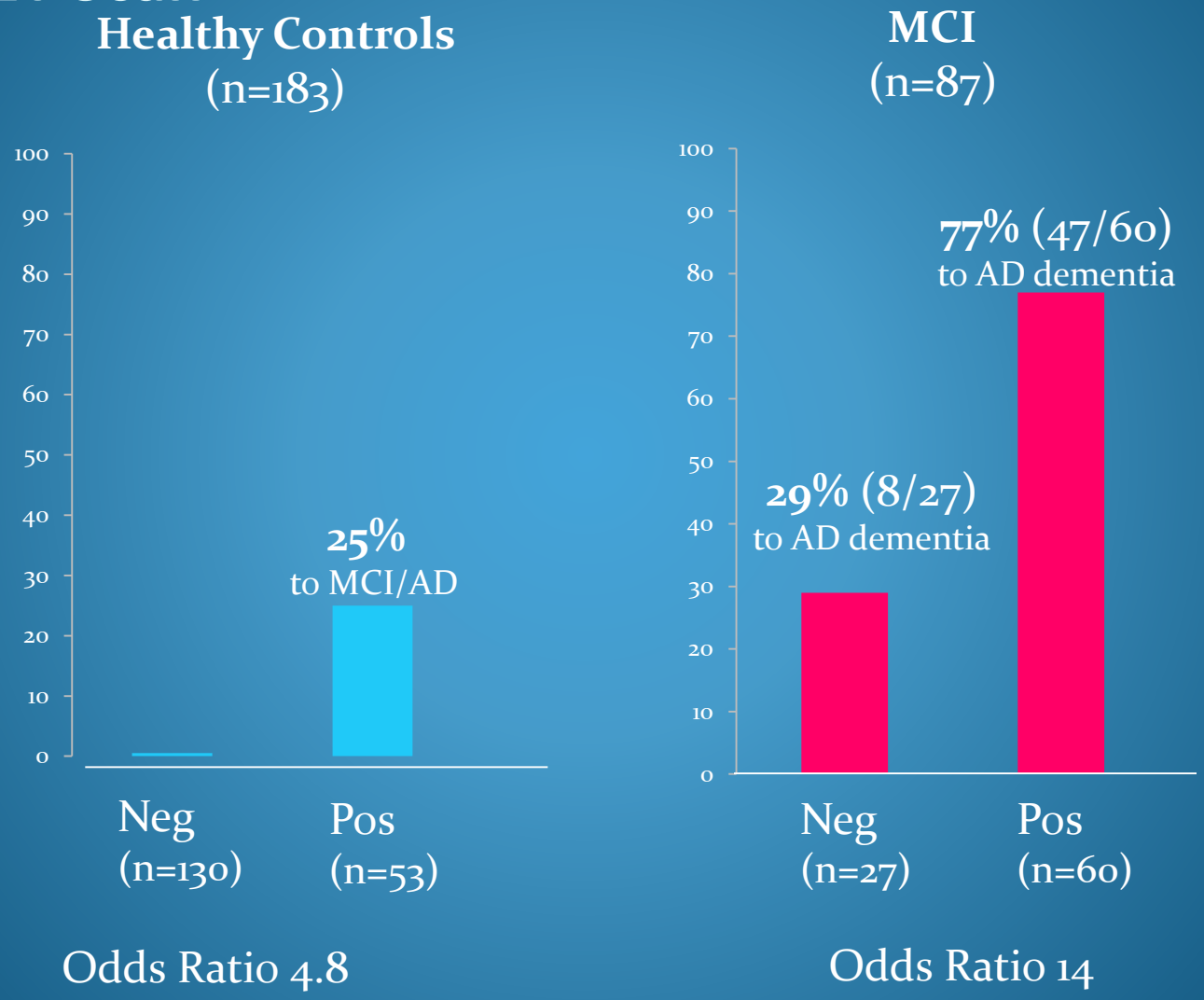




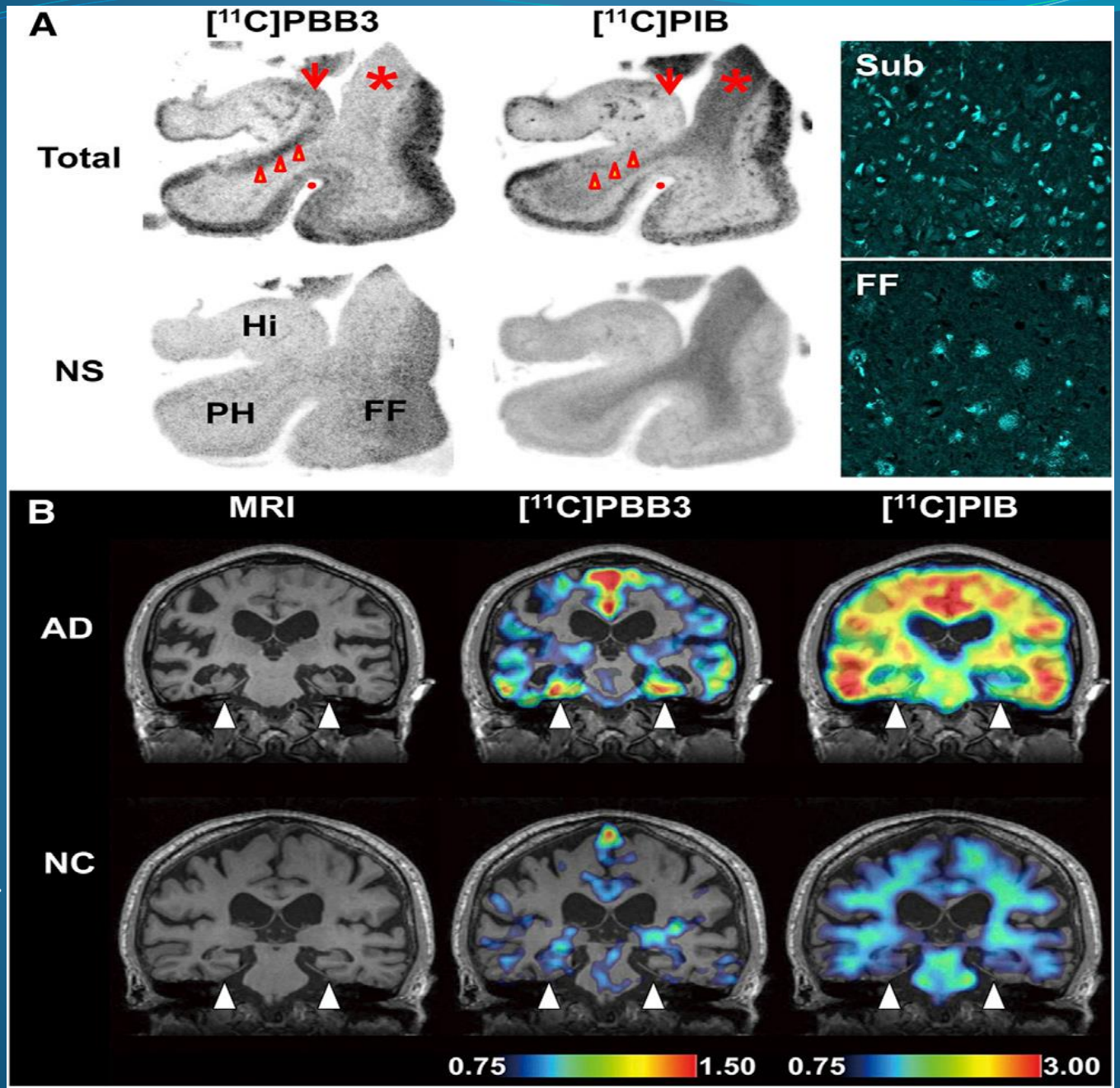


Fleisher AS et al. *Neurobiol Aging*. 2013;34:1-12.

3 year Risk of Progression: Positive vs Negative Amyloid PET Scan



Rowe C. AAIC 2013.



Maruyama M et al. *Neuron*. 2013; 79:1094-1108.

A Case Study

History and Clinical Presentation

- 54yo RHF with gradually progressive cognitive changes
  - Difficulty with judgment and decision-making
  - Social/interpersonal behavior change (withdrawn)
  - Some difficulty with expressive language (i.e., word finding problems)
- Working as psychologist but having some difficulty approximately one year after symptom onset
- General medical history unremarkable; no history of depression
- Negative family history of dementia
- MMSE 29/30; Neurological exam unremarkable;

Case Study - Question 1

Which clinical syndrome is most compatible with this case's history and clinical presentation?

A. Mild Cognitive Impairment (MCI)
B. Dementia
C. Other (e.g., Pseudodementia; Subjective Cognitive Disorder)

Case Study - Question 2

What further tests would be considered part of a standard dementia workup? (select all that apply)

A. Detailed Neurocognitive testing
B. Structural MRI
C. Labs: CBC, CMP, B12, TSH
D. FDG PET
E. Amyloid PET
F. CSF Abeta and Tau

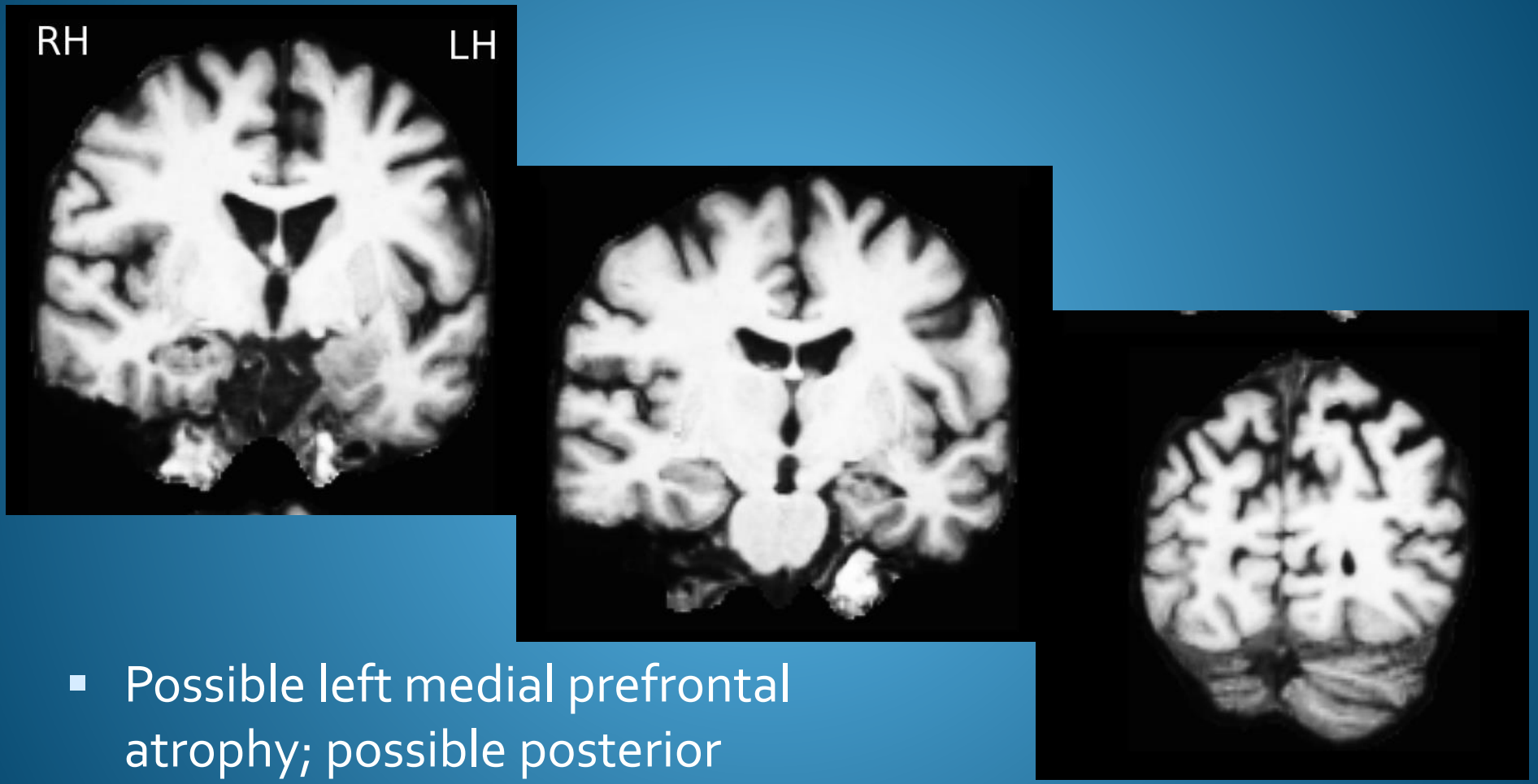
Case Study – Neuropsychological testing

- General observations
  - Flat affect
  - Good effort on tests

- Impairments in
  - Executive function
  - Abstract reasoning
  - Verbal fluency
  - Naming (mild)

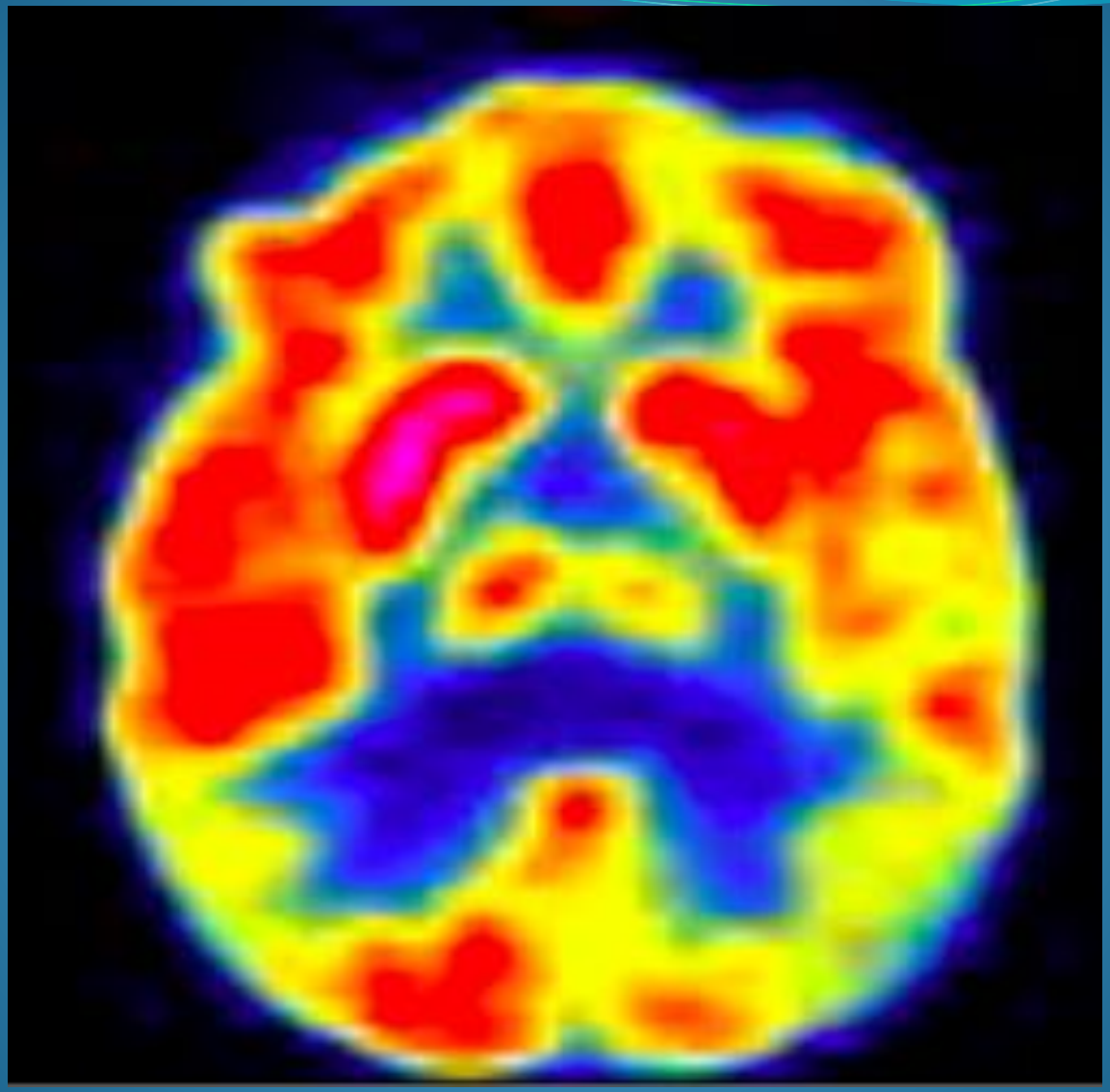
- Relatively preserved
  - Other language abilities
  - Visuospatial abilities
  - Memory

Case #3 – Structural MRI imaging



- Possible left medial prefrontal atrophy; possible posterior parietal atrophy; radiologist was not convinced outside range of normal

Case Study – FDG PET imaging



- Mild bilateral L>R parietal hypometabolism

Case Study - Question 3

What is the clinical diagnosis for this patient?

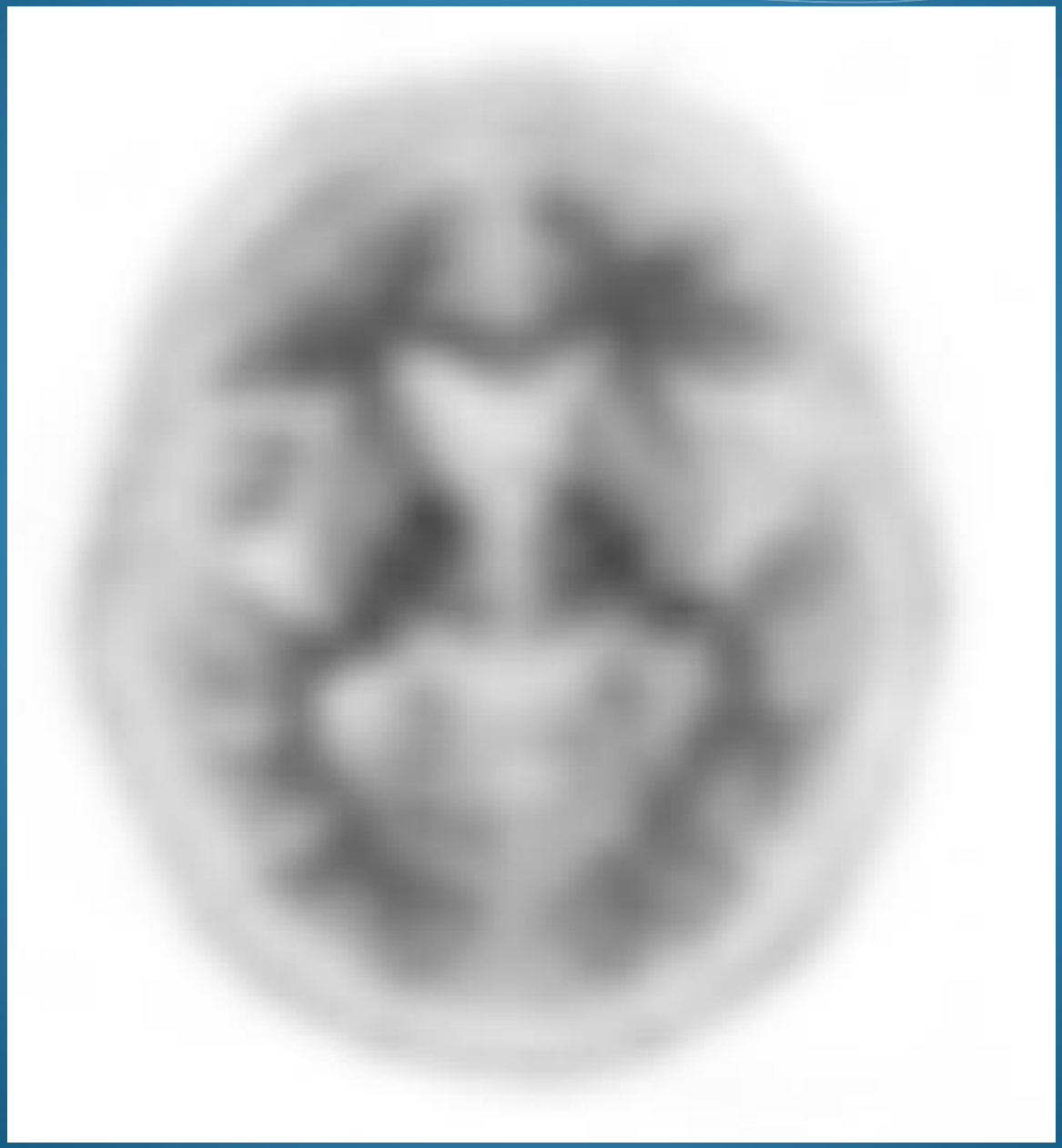
A. Early Alzheimer's Disease
B. Non Alzheimer's Neurodegenerative Etiology
C. Vascular Cognitive Impairment

Case Study – Question 4

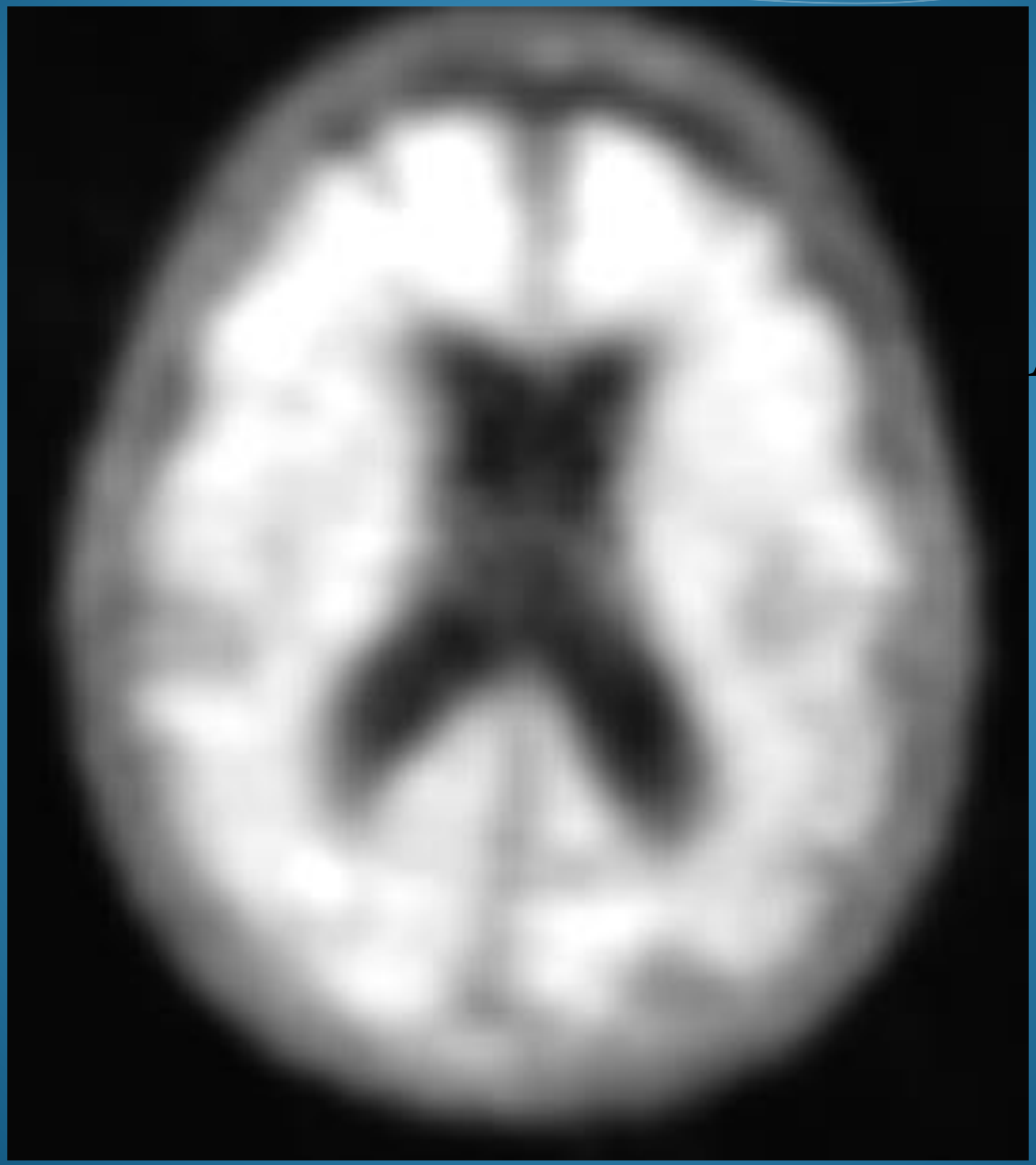
What are the possible diagnoses now?

A. MCI due to AD
B. MCI due to FTD
C. MCI due to Lewy body dementia
D. Still unclear

Amyloid PET scan: Amyloid Negative



Amyloid PET scan: Amyloid Positive



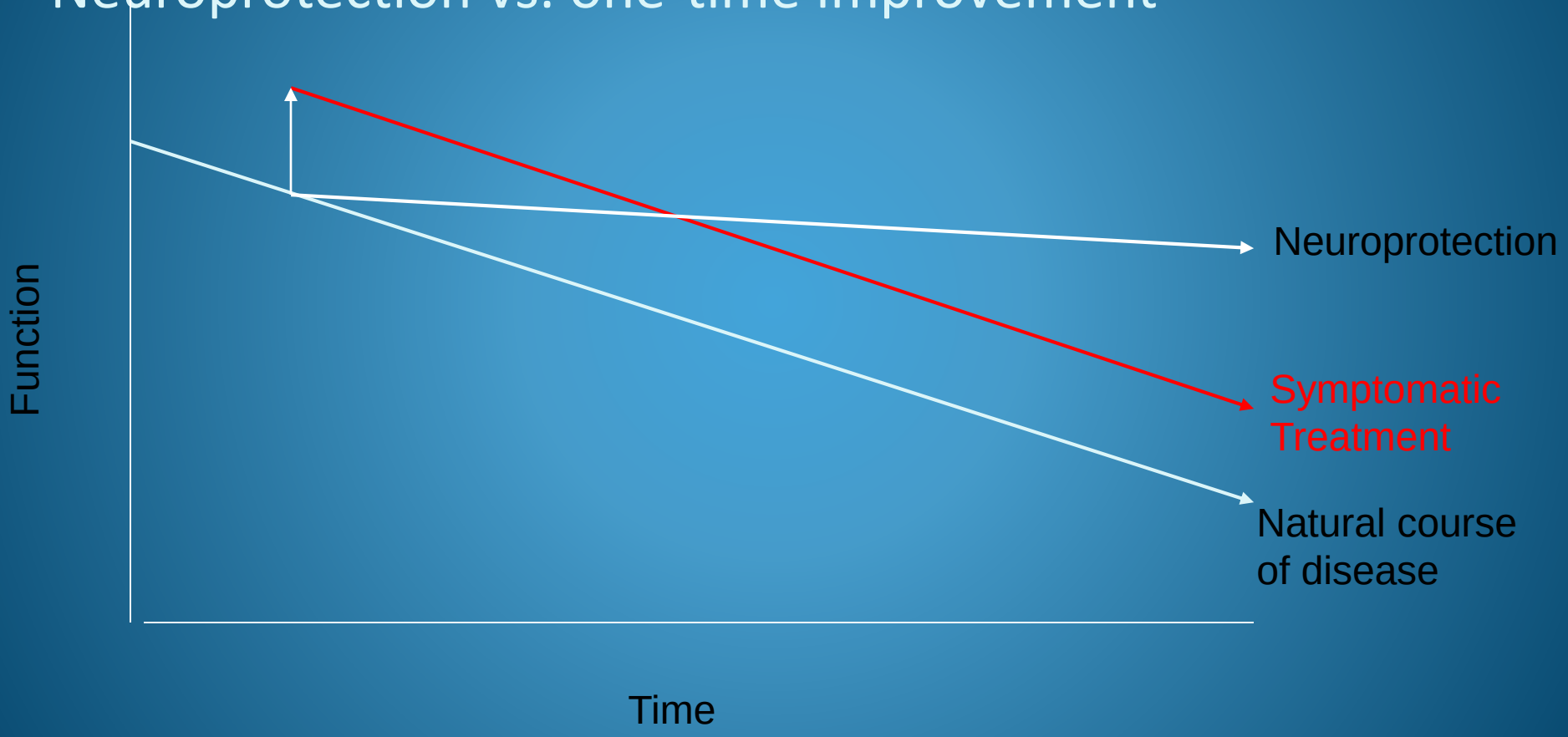
Aβ positive

Achieving Symptom and Disease Modification in Alzheimer's Disease

Recommendations for Possible Prevention

- Control Vascular Risk Factors, esp. HTN and DM)
- Dental Hygiene
- Cognitive/Social Stimulation
- Physical Exercise
- B complex Vit. (B12& B6)
- Vitamin C
- Vitamin E in food
- Eat fish
- Use curry (curcumin)
- Antioxidants
  - Beans
  - Berries
  - Grape juice
  - Pomegranate juice
  - Green tea
- Mediterranean diet
- Quality sleep
  - Treat sleep apnea
- Increase socialization
- Control blood glucose
- Treat anemia

Neuroprotection vs. one-time improvement



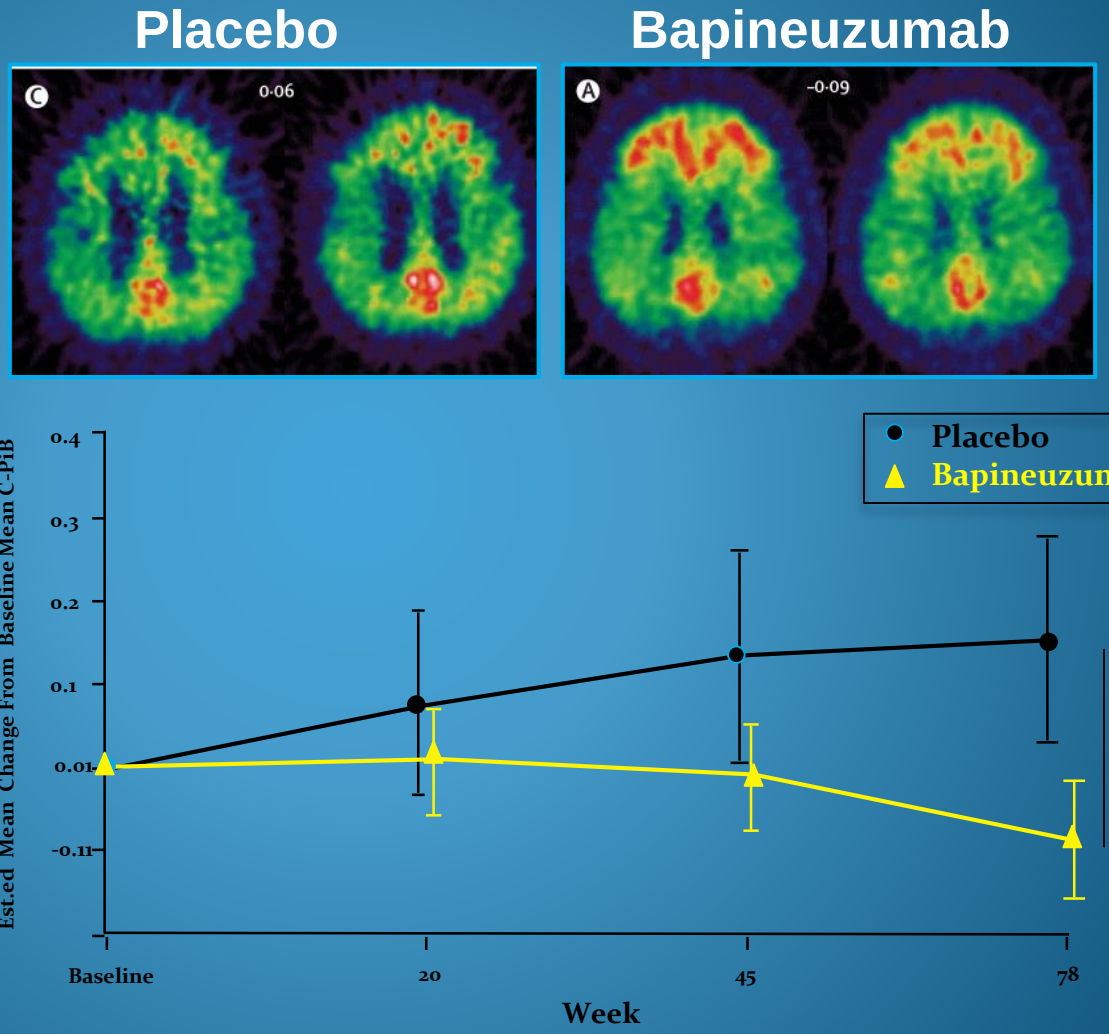
We are still looking for our first Disease Modifying/neuroprotective agent for AD!

Current and Emerging Treatments and Clinical Trials in Alzheimer's Disease

- **Cholinesterase Inhibitors:** ***Donepezil, Rivastigmine & Galantamine***
- **NMDA modulators:** ***Memantine***
- **New symptomatic agents: Nicotinic agonists:** ***MK 7622***
- **Disease-modifying agents**
  - **Anti-amyloid:** ***Solanezumab; Bapineuzemab; Crenezumab***
  - **Anti-tau:** ***Methylthioninium chloride (MTC); Leuko-MTC (TauRx)***
  - **Neuroprotective:** ***Toyoma-817 MA***

Bapineuzumab Clears Plaques in AD

Trial failed to show clinical benefit. About 17% of cohort found not to have amyloid in the brain. **Too little or too late?**



*** Difference between patients in the placebo group and those in the bapineuzumab group at Week 78 = -0.24 (*P* = 0.003).**

Rinne JO et al. *Lancet Neurol.* 2010;9:363-372. Salloway S, et al. N Engl J Med. 2014;370:22-33.

Approved Secondary Prevention Studies

- A4 study: 3 year double blind, 1000 person, Solanezumab study in cognitively normal person who are florbetapir +ve
- DIAN study: 40 per arm, Solanezumab and Gantenerumab vs placebo in unaffected carriers of dominantly inherited genes
- ApoE 44 study: Cognitively normal, 650 person, double blind, agent to be decided
- Colombian kindred study: PSEN1 Paisa mutation using Crenezumab (from Genentech) in asymptomatic carriers

Managements of Behavioral Manifestations of Alzheimer's

Do's

- Look for, Recognize and Rx Precipitating Factors: *(Infection, Pain, Constipation, Hunger/Thirst, Sensory Deprivation, Medication change, Other Medical Conditions, Change in Physical or Social Environment)*
- Reassure, Agree with and Comfort the Patient, "Go with the Flow" *(e.g., with delusions, hallucinations)* Simplify and make Environment Safe
- Educate Caregiver(s) about Precipitating Factors; Encourage Support Groups
- Use SSRIs *(Citalopram, Sertraline)* as first line Rx *(treats anxiety, irritability and depression)*
- Use Non-D2 Antagonist Anti-psychotics *(Quetiapine)*
- Use D2 Antagonists *(e.g., Risperidone)* Use very sparingly
- Use Anticonvulsants *(esp. Lamotrigine)* and Buspar as adjuvants to antipsychotics
- Treat Sleep Disorders *(with Trazodone, Mirtazapine)*
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Managements of Behavioral Manifestations of Alzheimer's

Don'ts

- Don't Confront, Contradict, Offend, Alarm, Challenge or Argue with the Patient (Don't Say: "I already told you that" ; "Don't you remember")
- Avoid Loud Noise and Sudden Movements
- Don't Overstimulate the Patient
- Don't Emphasize Patient's Impairments
- Don't Use Benzodiazepines *(e.g., Lorazepam, Temazepam)* for anxiety, sleep disorder or agitation - Except for very short term use.
- Don't Use Anticholinergics *(Benadryl, Unisom, Hydroxyzine Amitriptyline, Meclizine, Ditropan)*
- Don't Use Haloperidol *(except parentally and for short-term use (in the ER) for very aggressive and violent patients)*

In Summary

- **A realistic goal is to delay or prevent AD in the Preclinical or Early Clinical Stage, and to prevent progression of established Alzheimer's**
- **With a combination of clinical findings and biomarkers we are able to identify those at risk and those who have the disease**
- **Secondary prevention and delaying/ stopping progression may soon become a reality**

Have A Nice Day