Alzheimer's Disease (AD)

- Common age of onset of AD: 70s and 80s. Can also occur in one's 50s or 60s, and the diagnosis of dementia continues to rise exponentially after 90 years of age.[1]
- Subtle short-term memory loss
  - Progresses over 8 to 10 years to involve language, visual-spatial skills, and other cognitive functions
- Patients may be unaware of changes and need a caregiver to relate changes. They may also have some awareness (especially with biomarker positivity) at or before onset.[2]
- Noncognitive symptoms very common throughout course and in conjunction with early memory loss
  - Depression, anxiety, agitation, paranoia

1. Corrada MM. *Ann Neurol*. 2010 Jan;67(1):114-121.
2. van Harten AC, et al. *Neurology*. 2013;81(16):1409-1416.

Risk and Protection

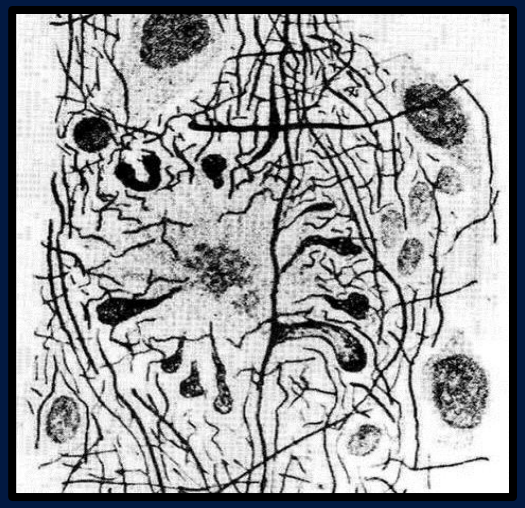
Known or Suspected Non-genetic AD Risk Factors	Potential Protective Factors Against AD

• Diabetes Mellitus[1,3]
• Hypertension[1,2,3]
• Obesity[1,2,3]
• Depression[1]
• Physical Inactivity[1,2]
• Smoking[1,2]
• Low Education[1,2]
• Homocyestine[2]
• History of Head Trauma[3]
• Hypercholesterolemia[3]
	• Physical Activity[2,3]
	• Caffeine Consumption[2]
	• Dietary Antioxidants[2,3]
	  • Vitamin C
	  • Vitamin E
	• Vitamin B(B_6 and B_{12})[2]
	• Folate[2]
	• n-3 Fatty Acid Intake[2]
	• Speaking ≥2 Languages[4]
	• Mediterranean Diet[5]
	• Treatment of Sleep Apnea[6]

1. Barnes DE and Yaffe K. *Lancet*. 2011;10:819-28.
2. Beydon MA, et al. *BMC Public Health.* 2014;14:643-676.
3. Barnard ND, et al. *Neurobiol Aging.* 2014 Sep;35 Suppl 2:S74-8.
4. Freedman M, et al. *Behav Neurol.* 2014;2014:808137.
5. Mosconi L, et al. *J Prev Alzheimers Dis.* 2014;1(1):23-32.
6. Troussiere AC, et al. *J Neurol Neurosurg Psychiatry.* 2014. [Epub ahead of print].

Autopsy Brain Examination

- Grossly atrophic
- Microscopic exam
  - Neuronal loss
  - Neuritic plaques
  - Neurofibrillary tangles



Pictures from: Bick K, ed. *The Early Story of Alzheimer's Disease*. Newark, DE: Raven Press; 1987:page 13.
Maurer K, et al. Auguste D and Alzheimer's disease. *Lancet*. 1997; 349:1546-1549.

The Amyloid Hypothesis of AD

- Amyloid beta protein deposition is considered pivotal in the Alzheimer's disease process
  - Triggers the progression of disease and neuronal damage
- Data suggest that amyloid beta deposits 1 to 2 decades prior to development of symptoms

Cummings JL, et al. *JAMA*. 2002;287(18):2335-2338.

AD Pathology: Two Important Factors

1. Full-blown but subclinical AD pathology appears in the brains of a third of older adults who do not (yet) have cognitive symptoms
   - Seen pathologically and with PET amyloid imaging[1]
2. Mixed pathologies are extremely common in aging
   - Examples: AD + infarcts; AD + Lewy bodies
   - Other pathologies commonly coexist with AD
   - The other pathology may tip these people over the threshold toward expressing dementia from their AD pathology

Johnson KA, et al. *Cold Spring Harb Perspect Med.* 2012; 2(4): a006213.

Treatable Mimics of Early Alzheimer's Disease

1. Medications, especially sedating medication

Drug Class	Examples
Sleep aids	Diphenhydramine, zolpidem
Antispasmotics for bladder control	Oxybutynin
Antidepressants	Trazodone, paroxetine
Antipsychotics	Haloperidol
Anxiolytics	Alprazolam
Analgesics	Codeine

2. Depression
3. Sleep apnea
4. Normal-pressure hydrocephalus

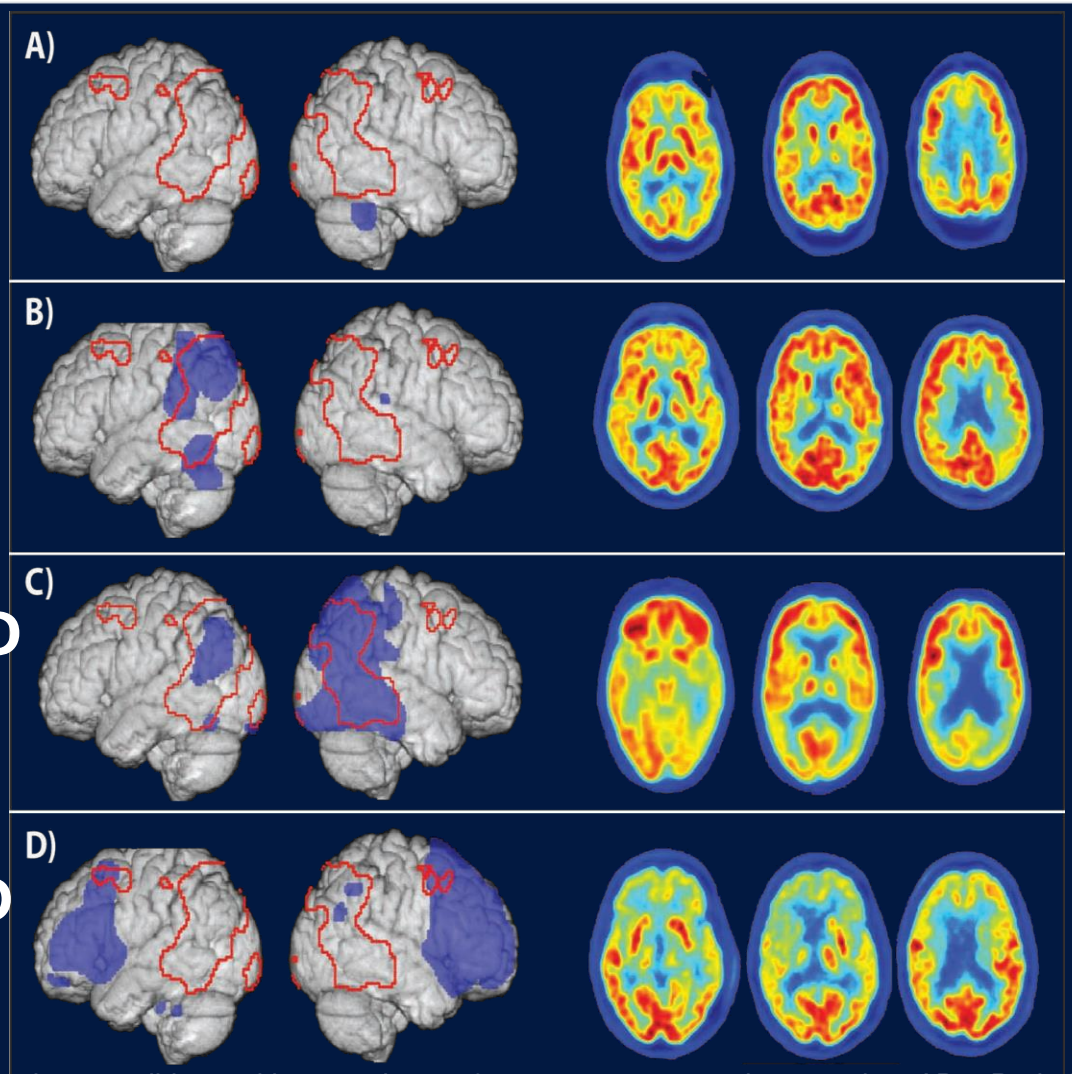
Schott JM, et al. *Pract Neurol.* 2012;12:358-366.

Biomarkers Used for AD Pathology Assessment in the Clinic

1. Structural
   - Magnetic resonance imaging (MRI)
   - X-ray CT
2. Functional
   - Fluorodeoxyglucose positron emission tomography (FDG PET)
   - Functional MRI (fMRI)
3. Molecular and biochemical
   - CSF
   - Amyloid PET
   - Tau PET
   - PET markers of microglial activation

Schindler SE, et al. *Mo Med.* 2013;110(5):401-405.

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

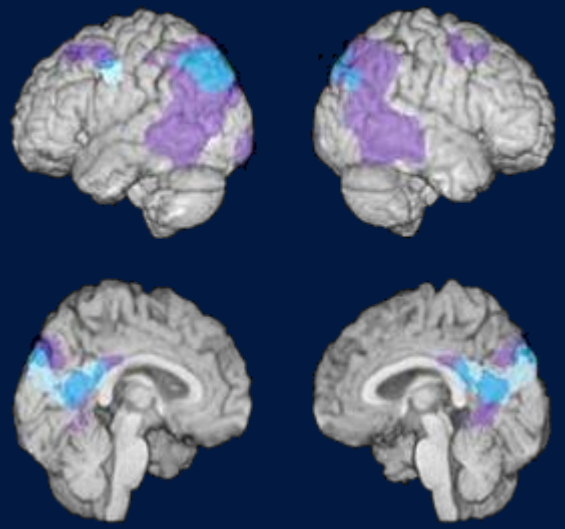


NL

MCI

pAD

fTD



AD dementia

Cognitively normal APOE4 carriers

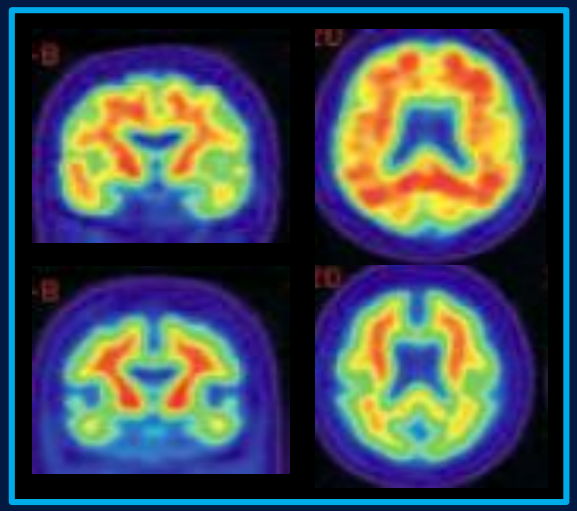
NL: Normal; MCI: Mild Cognitive Impairment fTD = Frontotemporal Dementia; pAD = Probable Alzheimer’s Disease.

[F-18] Amyloid Imaging Tracers

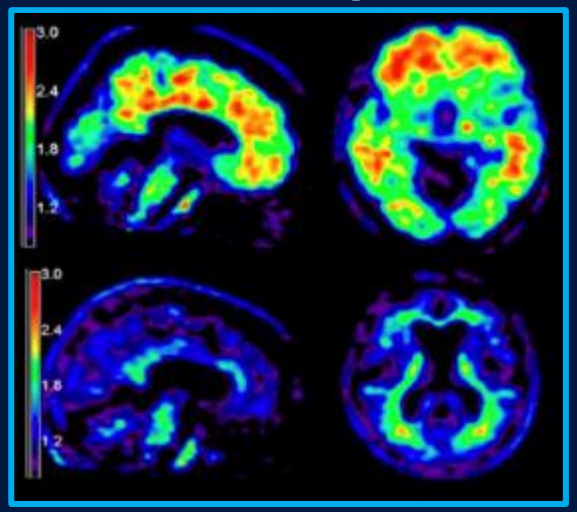
Flutemetamol[1]

AD

NL



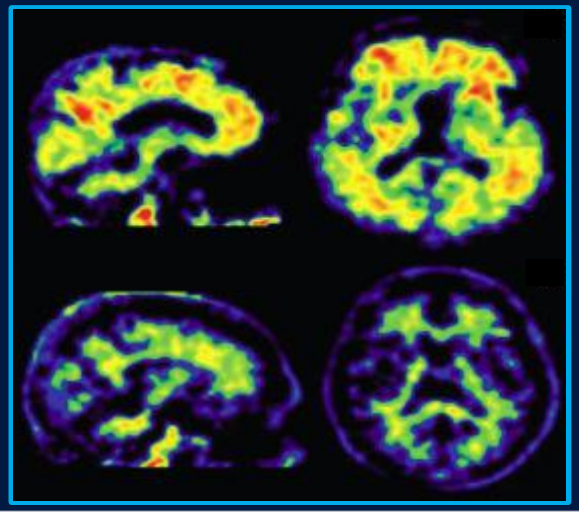
Florbetapir[2]



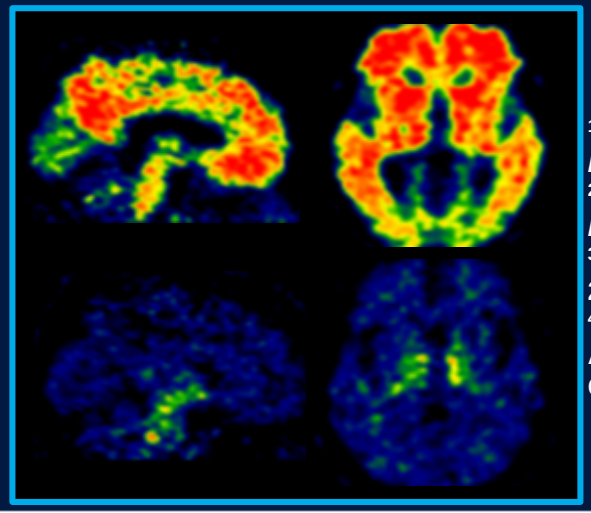
Florbetaben[3]

AD

NL



Navidea NAV4694[4]



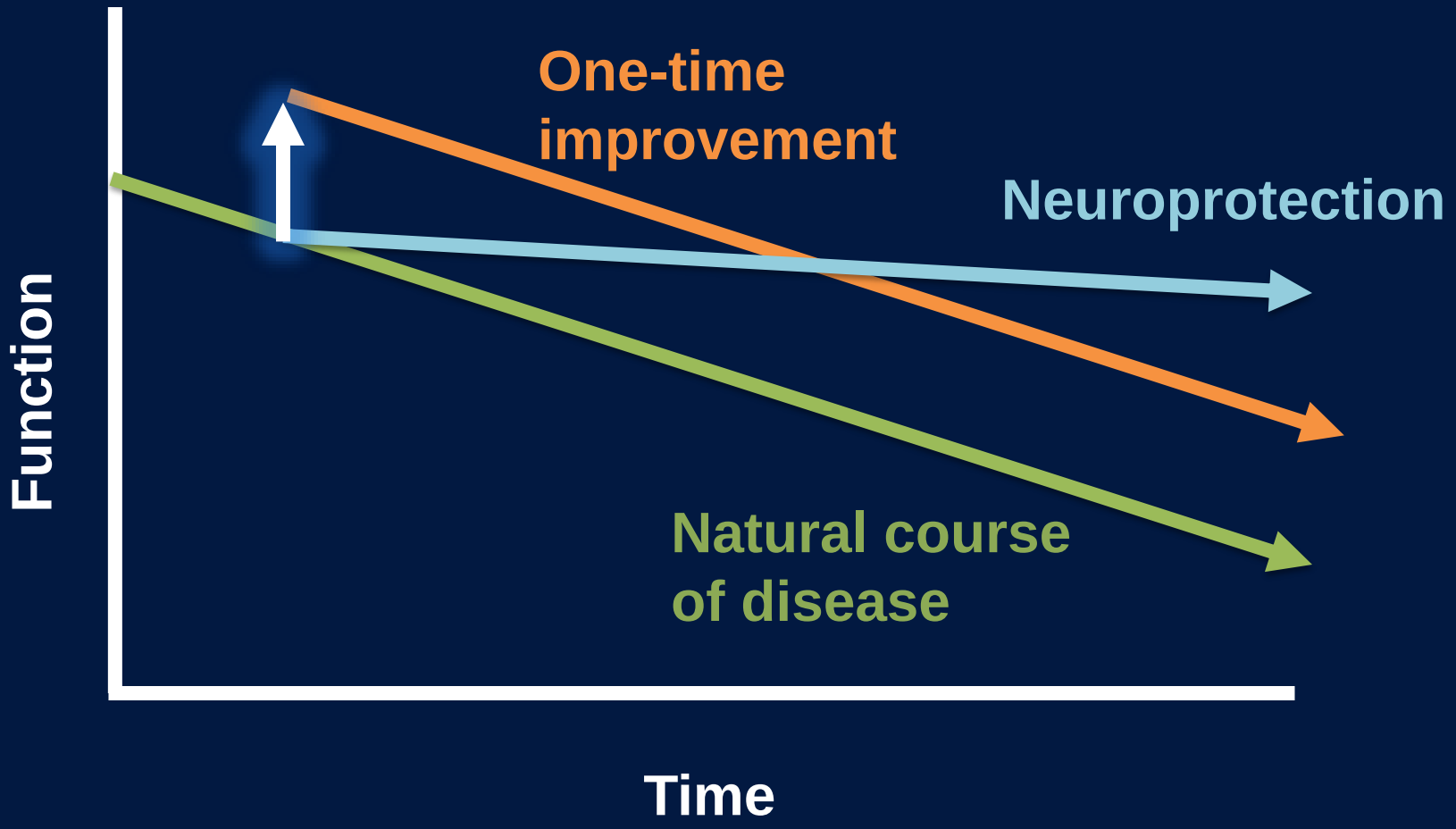
[1]Vandenberghe R, et al. *Ann Neurol*. 2010;68:319-329.
[2]Barthel H, et al. *Lancet Neurol*. 2011;10:424-435.
[3]Wong DF, et al. *J Nuc Med*. 2010;51:913-920.
[4]Chen K, et al. Presented at: AAIC. Vancouver, British Columbia. July 2012.

Diagnosing AD: PET Tau Imaging?

- In vivo markers for abnormally phosphorylated tau protein
  - Tangles correlate best with cognitive impairment
  - Amyloid may be present for years in the absence of impairment
- Combining both amyloid and tau imaging may help with early diagnosis and intervention

Okamura N, et al. *Curr Neurol Neurosci Rep*. 2014;14(11):500.

Neuroprotection vs One-time Improvement



We are still looking for our first neuroprotective agent for AD!

Cholinesterase Inhibitors (CIs)

- Decreased cholinergic innervation from NBM to widespread areas of cortex
- Acetylcholinesterase inhibitors prolong effect of acetylcholine
- At therapeutic doses CIs decrease acetylcholinesterase activity
  - 90% in red blood cells
  - 20% to 40% in central nervous system
- Degree of inhibition limited by side effects
  - Metrifonate
    - Powerful irreversible cholinesterase inhibitor
    - More effective for cognition than other agents
    - Some patients had a myasthenia gravis-like syndrome

Slattum PW, et al. Alzheimer's disease. In: DiPiro JT, et al. eds. *Pharmacotherapy: A Pathophysiologic Approach, 9e.* New York, NY: McGraw-Hill; 2014: chapter 38.
López-Arrieta JM, et al. *Cochrane Database Syst Rev.* 2006;(2):CD003155.
NBM: Nucleus Basalis of Meynert

Using CIs

- Titration schedules
  - Donepezil 5 mg daily for 1 month, then 10 mg
    - Donepezil 23 mg: minimal cognitive benefit, increased side effects relative to 5 mg and 10 mg doses
  - Rivastigmine 1.5 mg BID and titrate up to 4.5-6 mg BID over 1 month
  - Galantamine 4 mg BID for 2-4 weeks, titrate up to 8-12 mg BID
- Adverse events
  - Nausea, diarrhea, nightmares, sleep disturbance
- Rivastigmine patch
  - GI side effects occur less frequently than with oral rivastigmine

Donepezil. Facts and Comparisons eAnswers [database online]. St. Louis, MO: Clinical Drug Information, LLC; 2014.
Rivastigmine. Facts and Comparisons eAnswers [database online]. St. Louis, MO: Clinical Drug Information, LLC; 2014.
Galantamine. Facts and Comparisons eAnswers [database online]. St. Louis, MO: Clinical Drug Information, LLC; 2014.

CIs in Severe (Advanced) Dementia

- Pooled analysis of 3 RCTs (6 months) of donepezil in severe AD (n=736)
- 4-point improvement in Severe Impairment Battery (SIB)
- ADL function improved and neuropsychiatric symptoms decreased in patients with cognitive improvement
- Suggests mild efficacy in advanced dementia
- Need to weigh benefits against risks

Winblad B, et al. *Curr Med Res Opinion.* 2009;25:1577-2587.
ADL: Activities of daily living. RCT: Randomized controlled trials.

Clinical Trials: Anti-inflammatory Drugs in AD

Number of Case-control Studies Analyzed	AD Risk Factor Assessed	Overall Odds Ratio (OR) of AD Development	*P* - Value
7	Arthritis	0.556	<0.0001
4	Steroids	0.656	0.049
3	NSAIDs	0.496	0.0002

Further analyses combined NSAID and steroid use in a single category, yielding an OR of 0.556 (*P*<0.0001)

McGeer PL, et al. *Neurology*. 1996;47(2):425-32.

In Summary

- The dream of all is to delay or prevent AD
- With a combination of genetics and biomarkers we are able to identify people at risk
- Secondary prevention is now underway and our dream may be realized