Predictive Testing of Alzheimer's Disease

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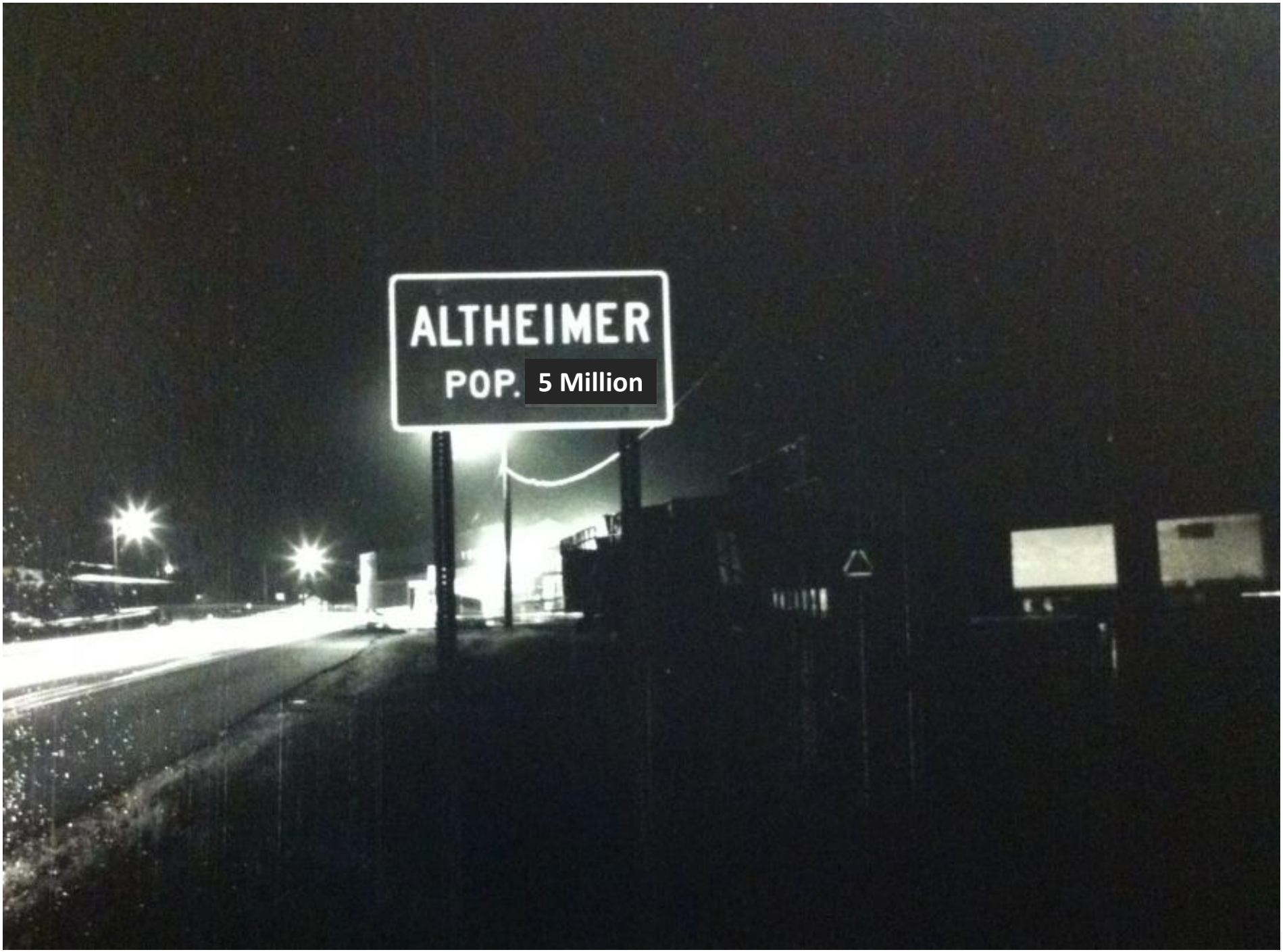
Overview

- Epidemiology and current diagnosis of AD
- Early Symptomatic Detection
  - Prodromal AD (Mild Cognitive Impairment)
- Pre-symptomatic Detection
  - Preclinical AD
- Neuroethical considerations
  - Biomarker testing at different stages of disease
  - Preclinical AD

Core Contextual Points

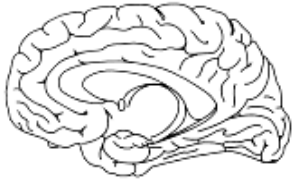
- Highly prevalent disease
- Major public health issue
- Tremendous fear of diagnosis
- Incredible development of diagnostic tools
- Treatment is very limited
- Scarce resources

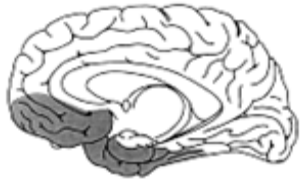

ALTHEIMER
POP. 5 Million

Clinical and Pathological Course of AD

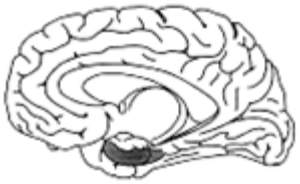
Clinical State	**Normal**	**Pre-Clinical AD**	**MCI**	**AD**
Cognitive State	**No Symptoms**	**No Symptoms?**	**Mild Symptoms**	**Mild-Severe Symptoms**
Pathologic State	**No Disease**	**Early Changes**	**Mild Mod Changes**	**Mod-Severe Changes**

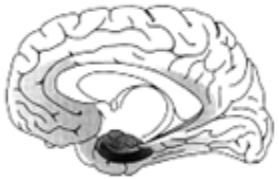
Plaques ⇨

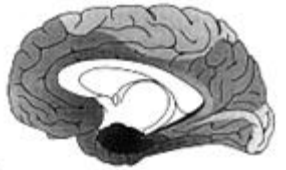




Tangles ⇨

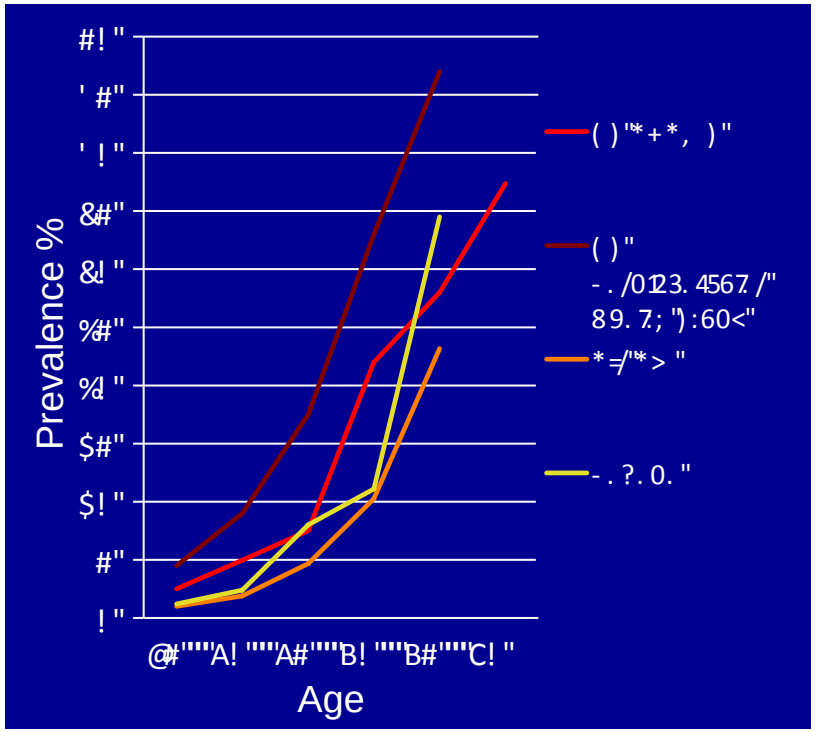


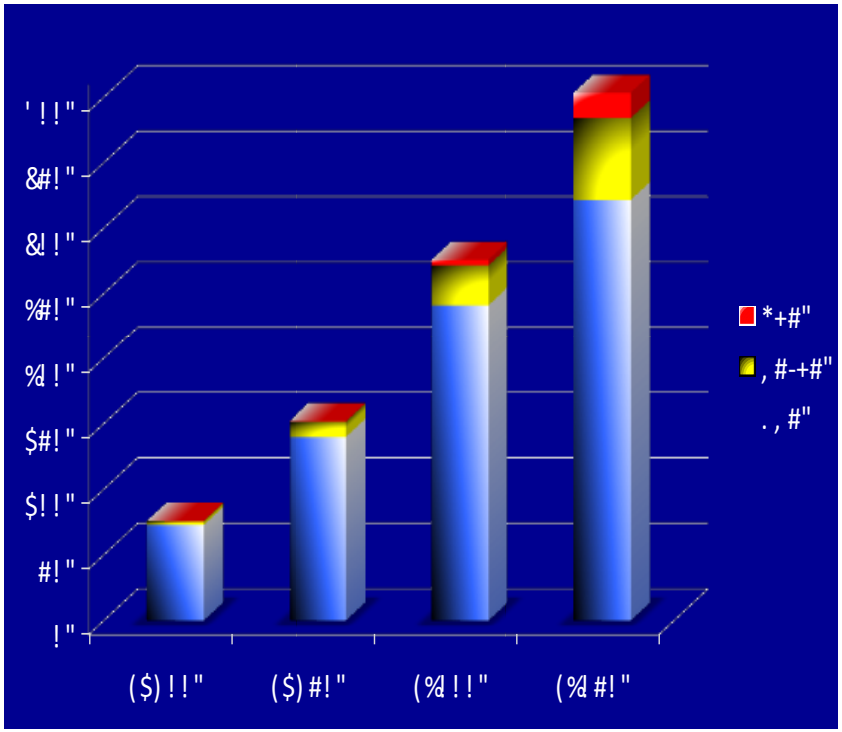




Scope of Problem

Prevalence of Dementia essentially doubles every 5 years after the age of 65.

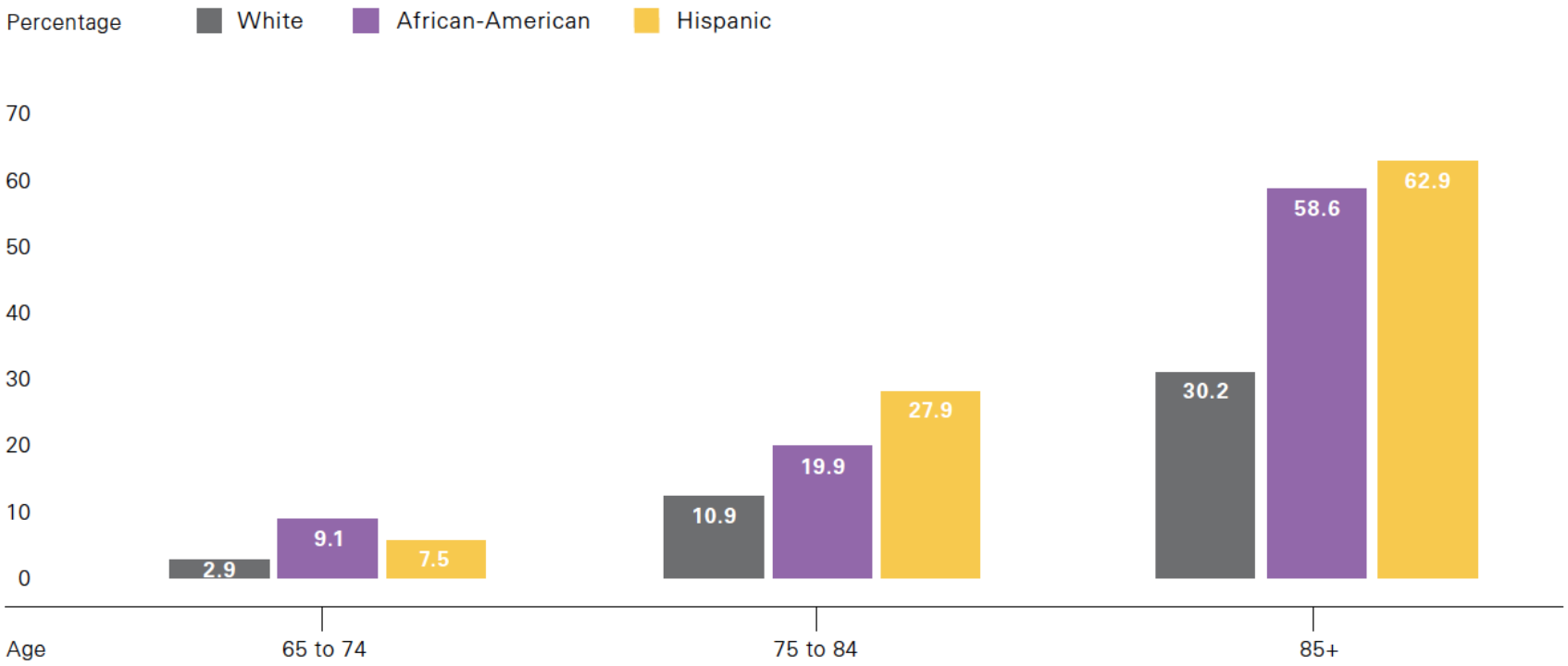




Source, Alzheimer's Association 2010

Prevalence by Age and Race/Ethnicity

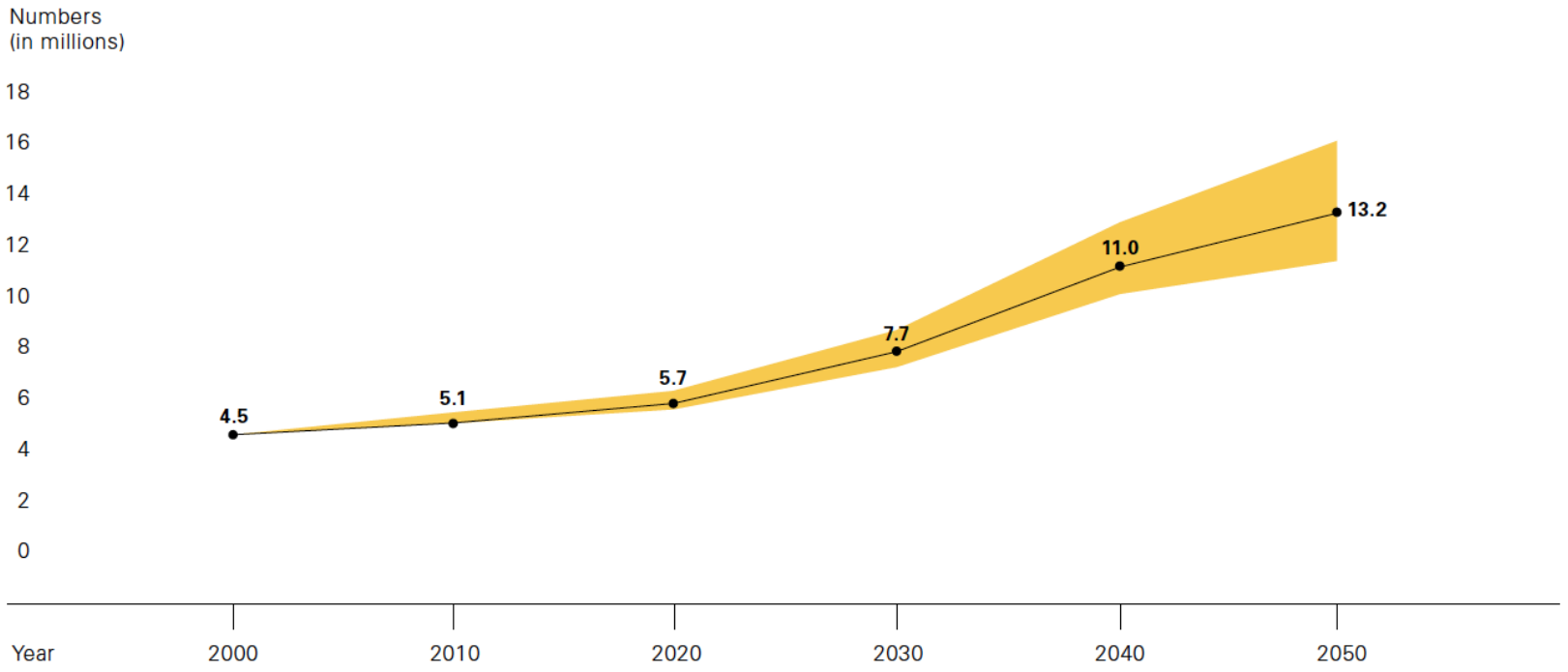
figure **1:** **Proportion of People Age 65 and Older with Alzheimer's Disease and Other Dementias, by Race/Ethnicity, Washington Heights-Inwood Columbia Aging Project, 2006**



Alzheimer's Association, 2012

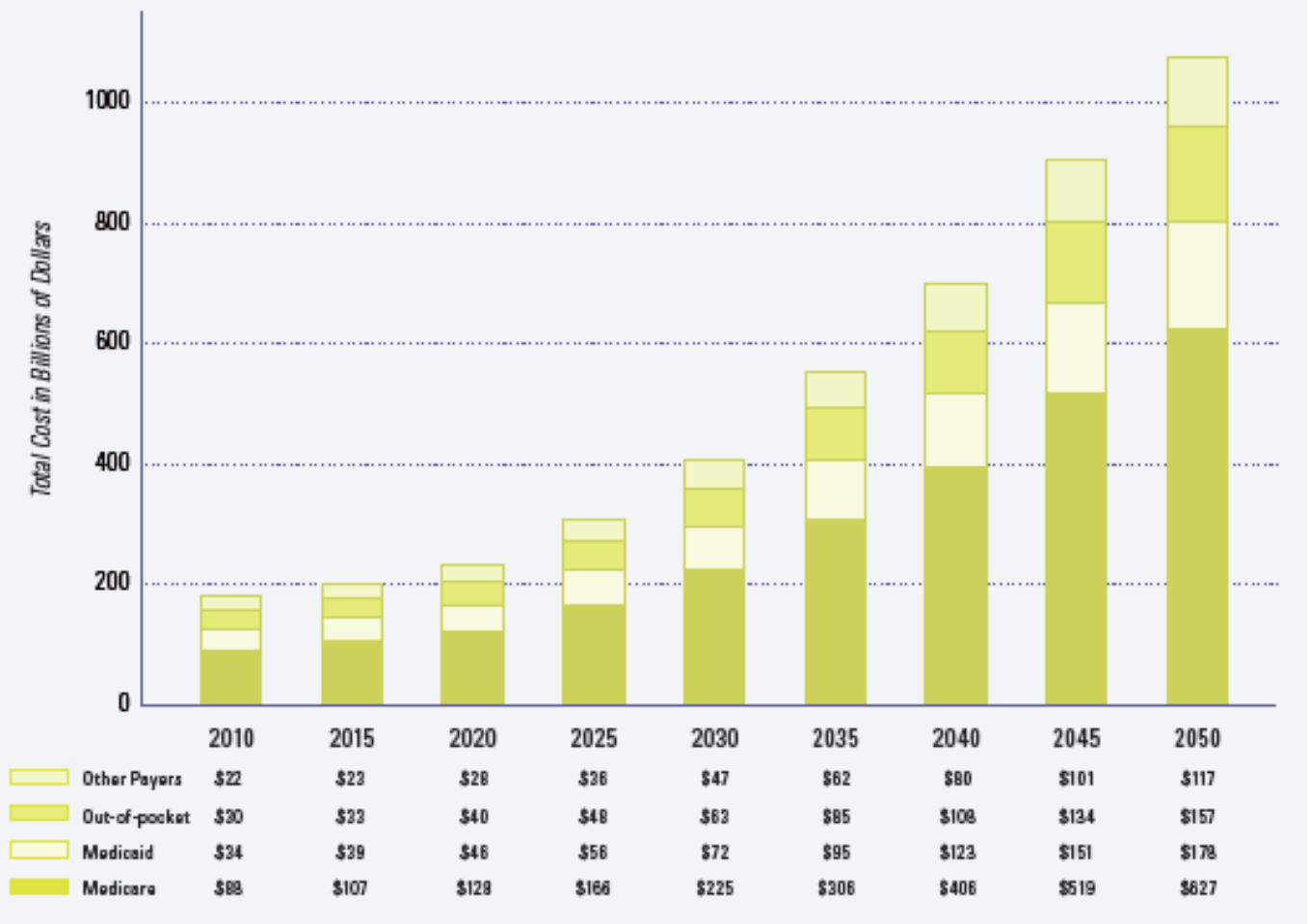
Number of People with Alzheimer's Disease

figure **4:** **Projected Numbers of People Age 65 and Over in the U.S. Population with Alzheimer's Disease Using the U.S. Census Bureau Estimates of Population Growth***



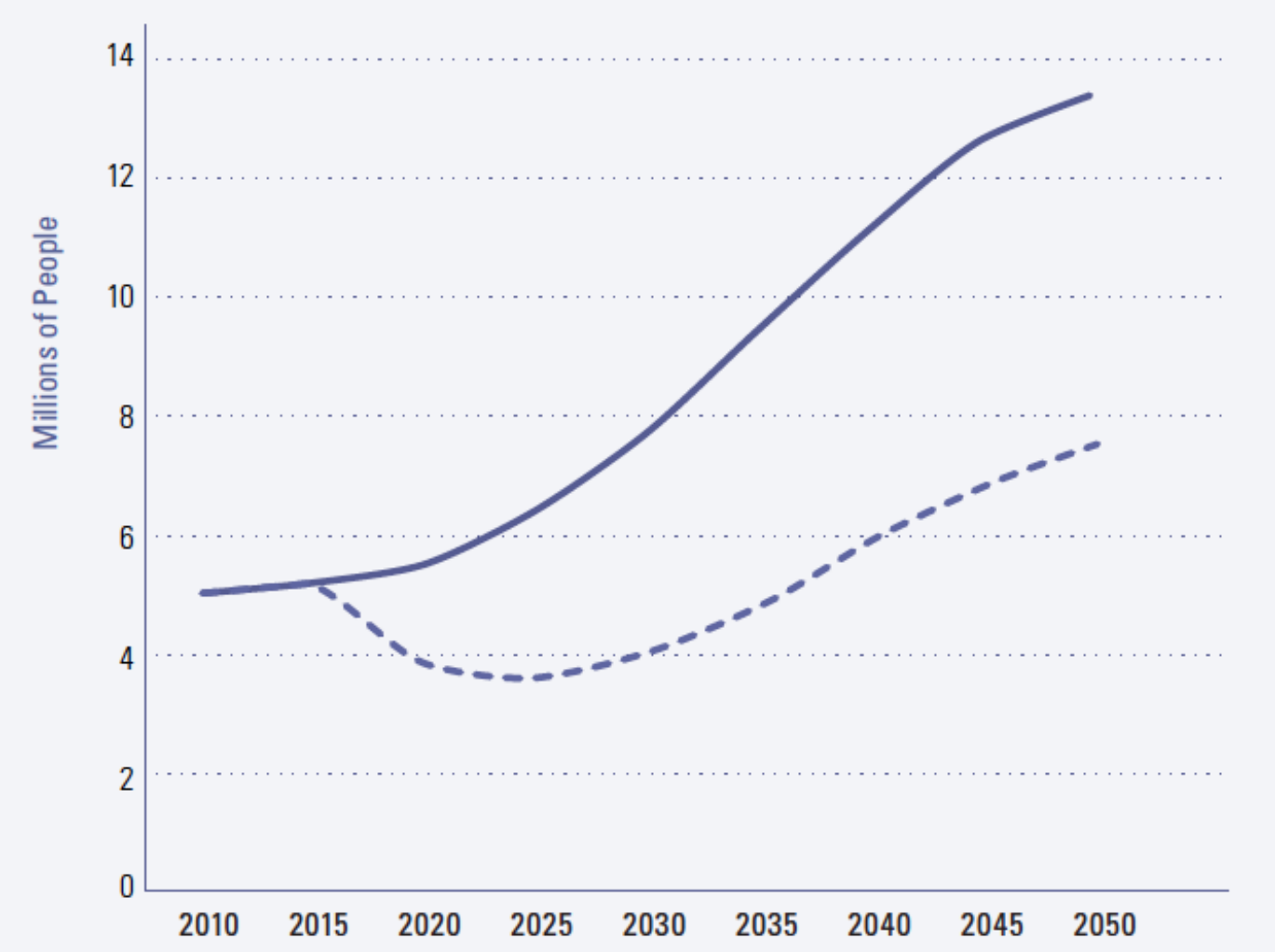
Alzheimer's Association, 2012

Cost of Care Prediction



Alzheimer's Association, 2010

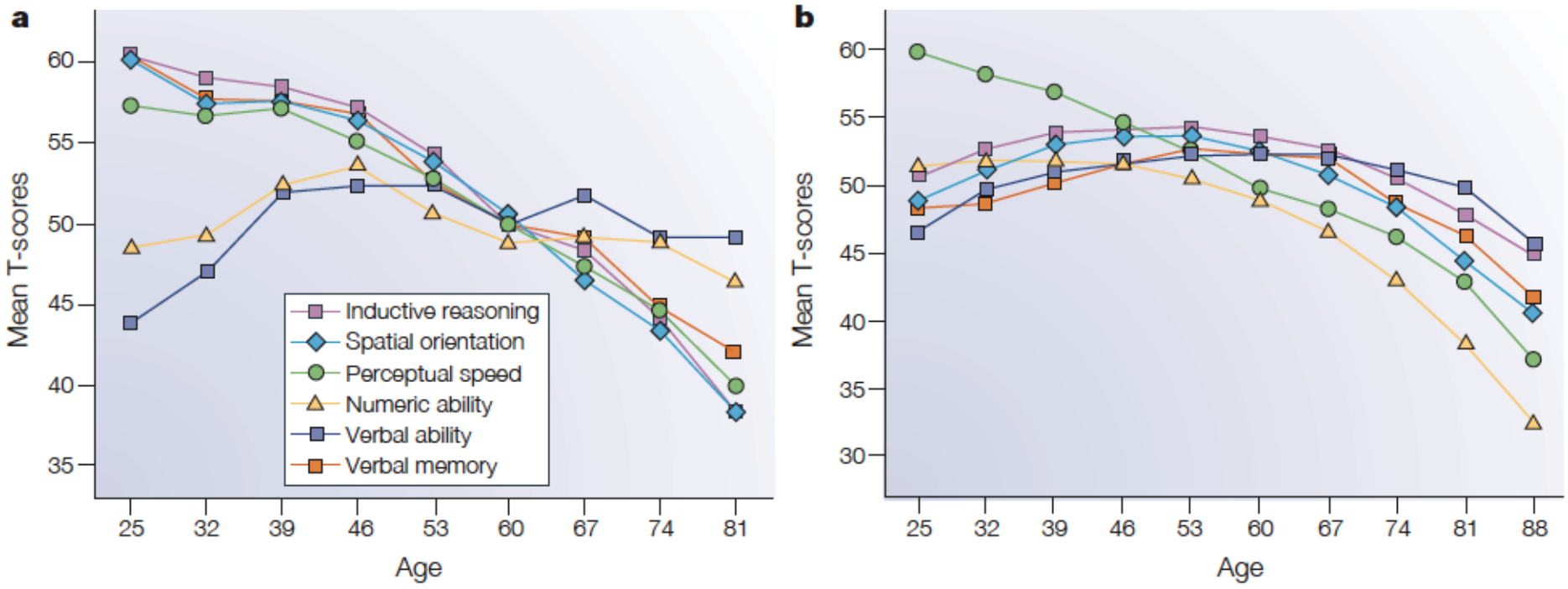
5-year Delay in Onset



Alzheimer's Association, 2010

Aging Versus AD

Age-Associated Cognitive Decline



Hedden and Gabrieli, 2004

What is Dementia?

- Formal Criteria (DSM IV)
- The development of multiple cognitive deficits manifested by both:
  - Memory Impairment
  - At least one of the following cognitive disturbances:
    - Language
    - Skilled motor activities (praxis)
    - Objects and people knowledge (semantic)
    - Judgment, abstractions, planning (executive function)
  - Decline from a previous level and significantly impairs social or occupational functioning.
  - Not transient (delirium)
- However, memory impairment is not prominent in all dementias

Most Common Dementias in Late Life

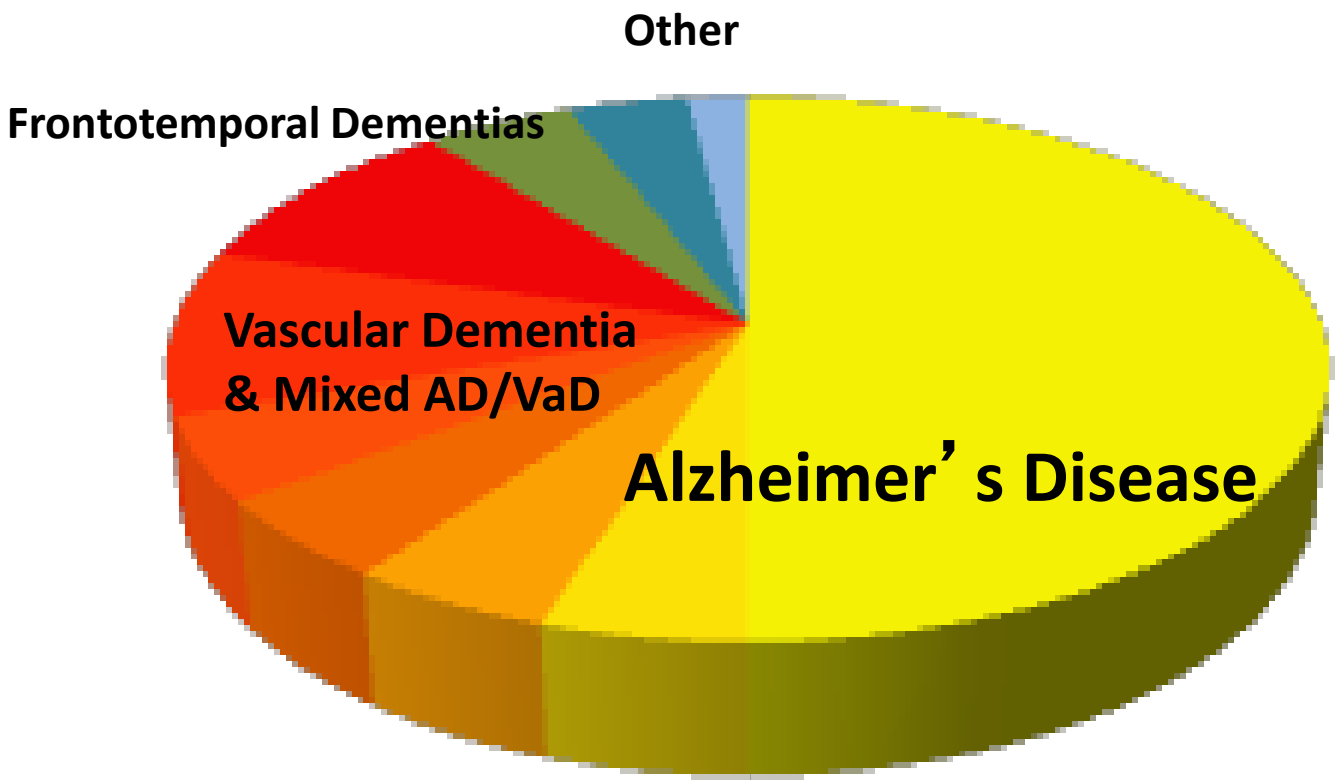
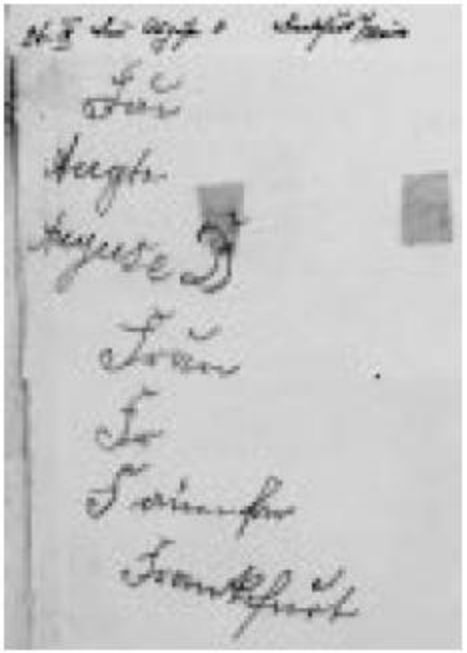
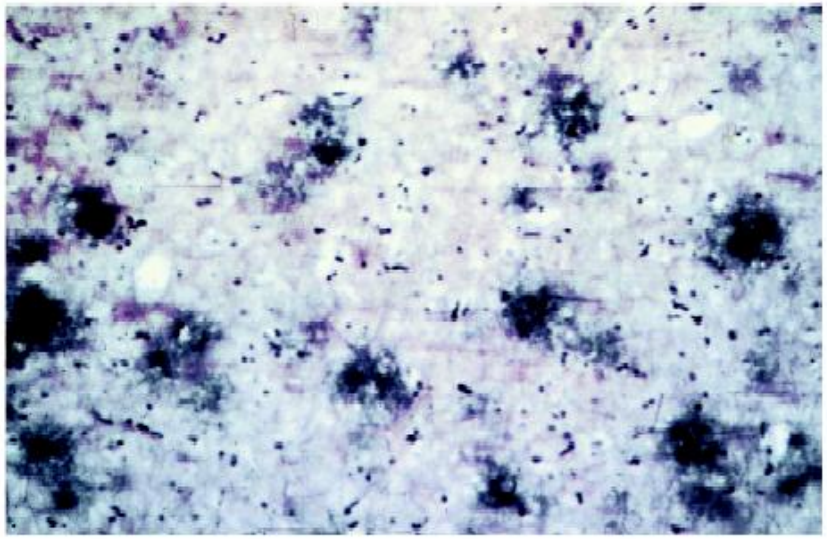
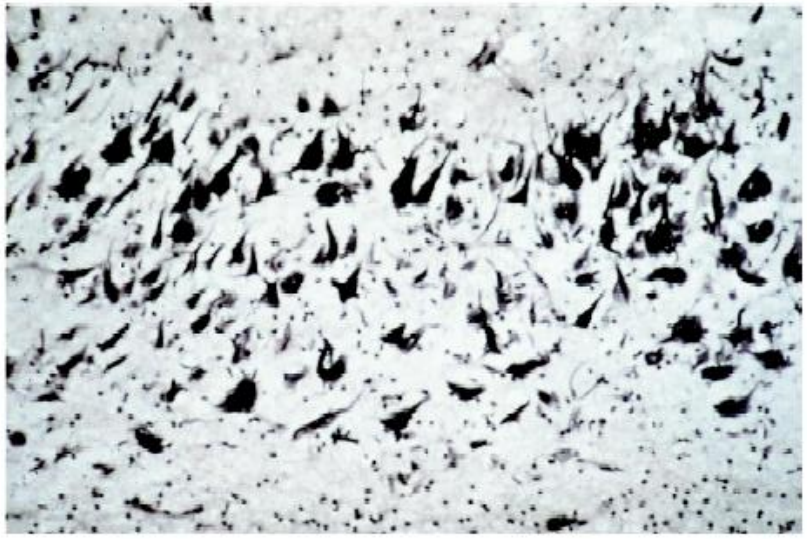


Figure 3: **Auguste D**
Photograph dated November, 1902.

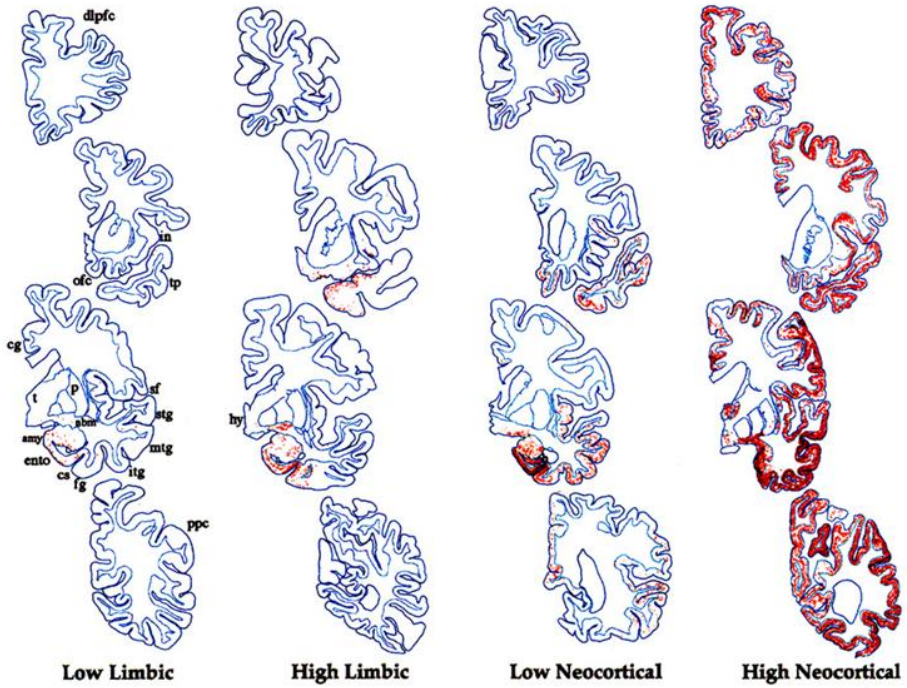


- Amyloid Plaques
  - Extracellular accumulation of Aβ (fragment of the amyloid precursor protein)
  - Abnormal processing of APP critical to pathophysiology of Alzheimer's disease



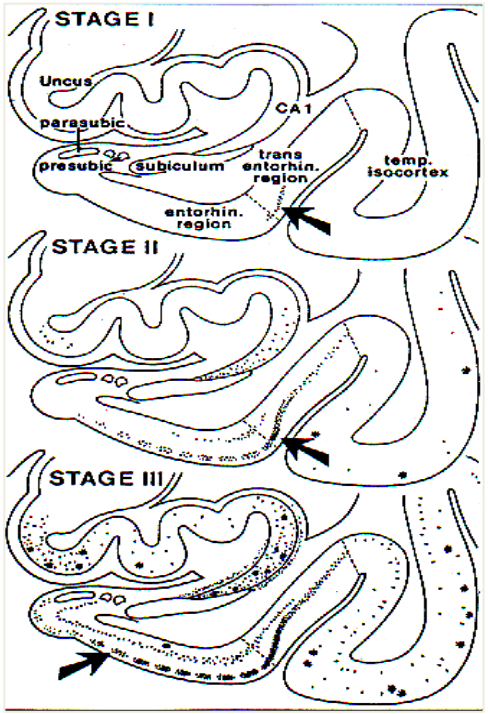


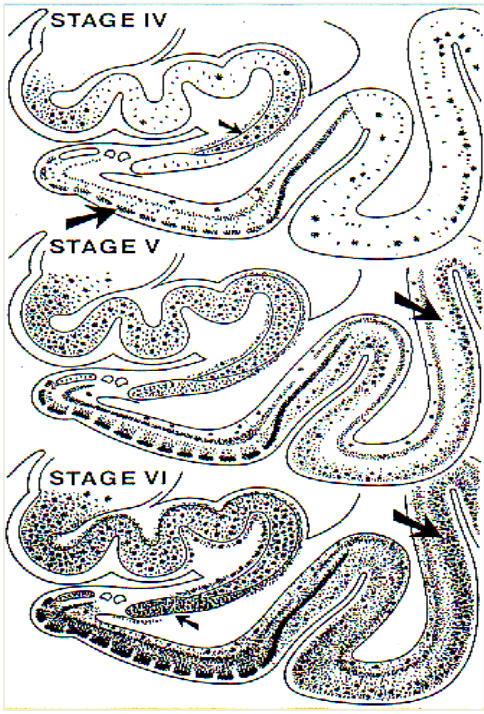
- Neurofibrillary Tangles
  - Intracellular, paired helical structures composed of hyperphosphorylated tau.
  - Correlate well with disease severity and neuronal death.



Why is memory loss an early feature of AD

Mesulam, 1990; Braak and Braak, 1991





NINCDS-ADRDA Criteria (McKhann Criteria, 1985)

- Probable AD
  - Presence of dementia
  - Insidious onset and and progressive worsening of memory and other areas of cognition
  - At least two domains of involvement (memory plus…)
    - Language, visuospatial, praxis, executive
  - Absence of other disease that could result in dementia syndrome

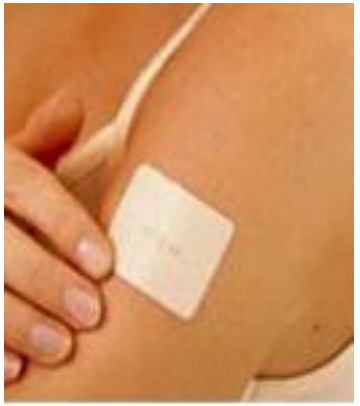
NINCDS-ADRDA Criteria

- Definite AD
  - Histopathological evidence of AD on autopsy or biopsy in context of clinical probable AD
- Sensitivity: ~ 80% (65-96%)
- Specificity: ~ 70% (23-88%)
  - Dubois et al., *Lancet*, 2007

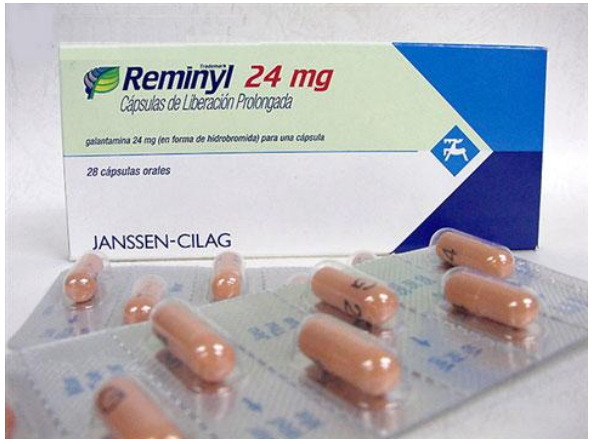
Currently Approved Medicines for the Treatment of Alzheimer's Disease

Aricept / Donepezil

Exelon (Rivastigmine)



Reminyl (Galantamine)



Namenda (Memantine)

Disease-Modifying Clinical Research Trials Now and on the Horizon for Treatment and Prevention of Alzheimer's Disease

Oral Pharmacotherapy

<u>Anti-Amyloid</u>

g- and b- Secretase Inhibitors

<u>Anti-Tau</u>

Methylthioninium

<u>Others</u>

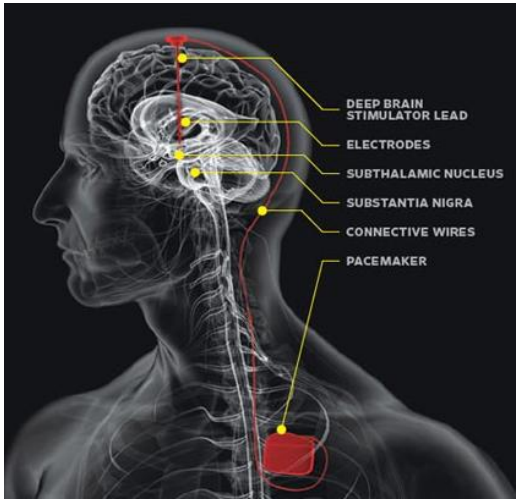
<u>Resveratrol, etc...</u>

Parenteral, Infusion & Other Immunotherapies

Bapineuzumab
Solenuzumab
Gammagard
Epothilones

Neurosurgical

CERE-110 NGF Gene Therapy
Deep Brain Stimulation

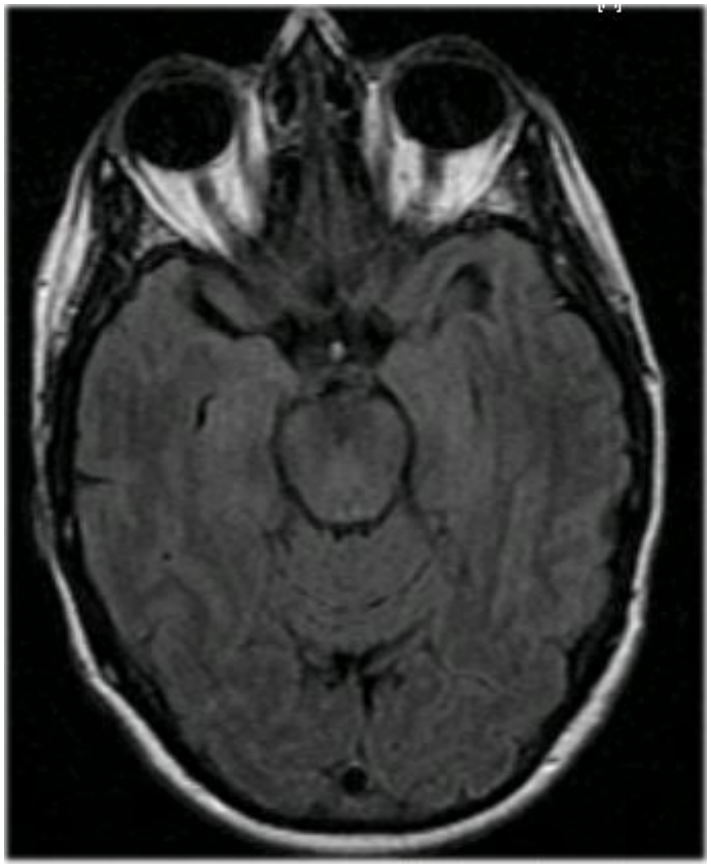


Additional Tests May Enhance Accuracy of Diagnosis – "Biomarkers of AD"

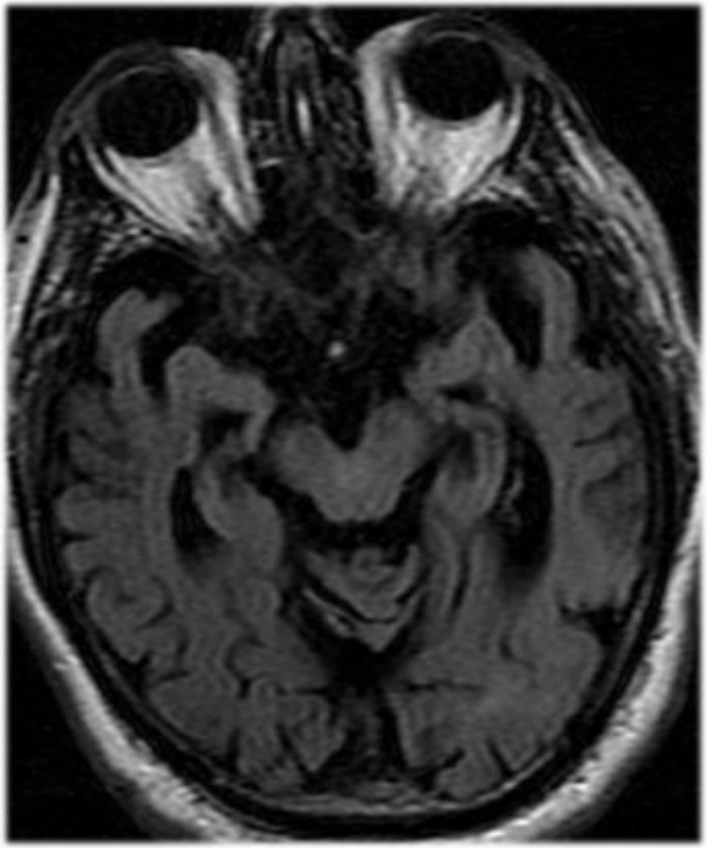
- Markers of Brain Degeneration
  - Look for evidence of brain changes in pattern consistent with AD
  - MRI, Glucose PET scans
- Markers of Brain Pathology
  - Look for molecular evidence of AD
  - Cerebrospinal Fluid (CSF), "Amyloid Imaging"

Qualitative Assessment of Brain Atrophy

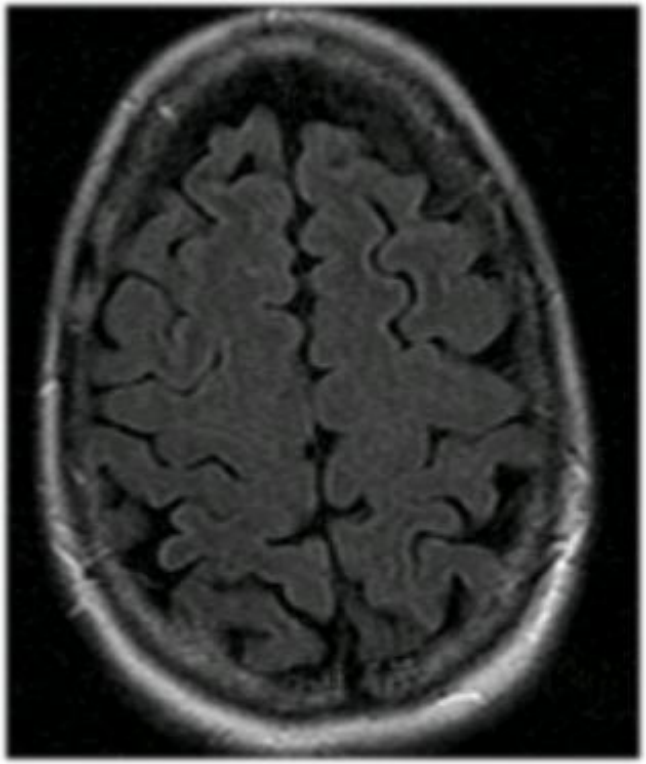
Healthy Older Adult



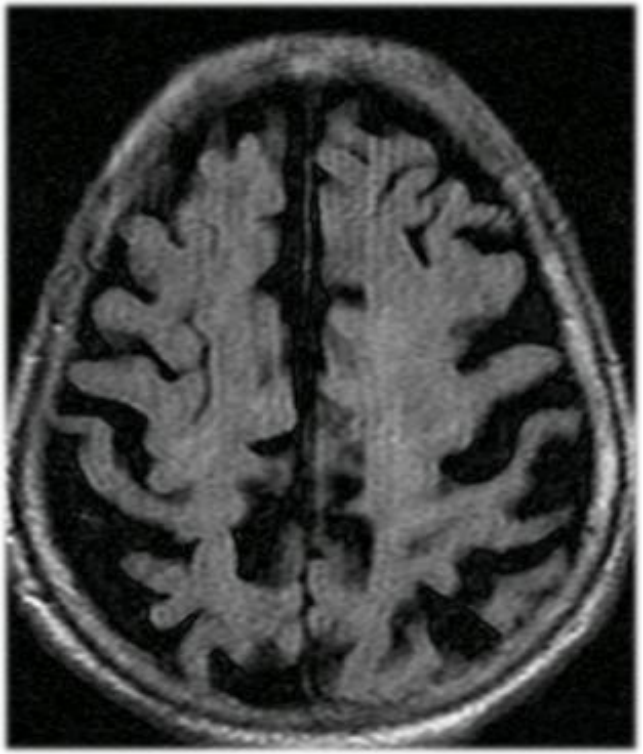
Alzheimer's Disease



Healthy Older Adult



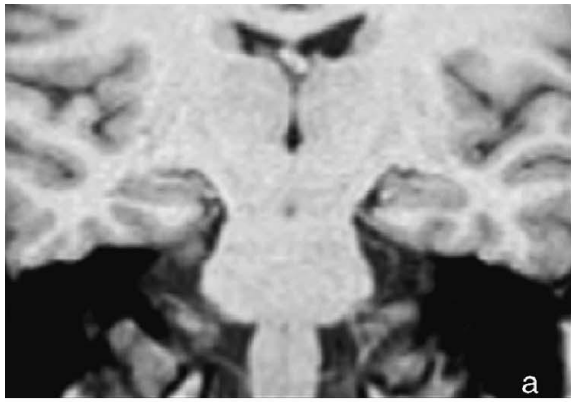
Alzheimer’s Disease



Semi-Quantitative Visual Rating

Scheltens Visual Rating of Hippocampal Atrophy

0 - 0



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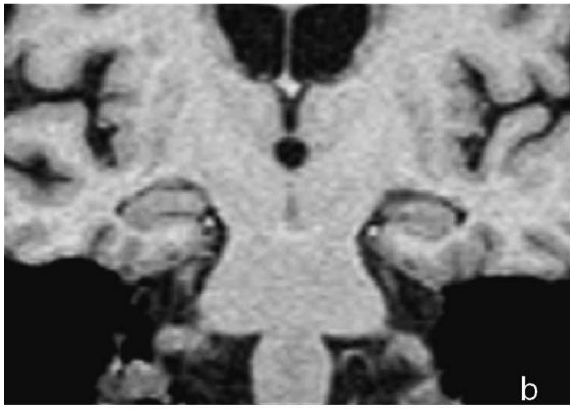

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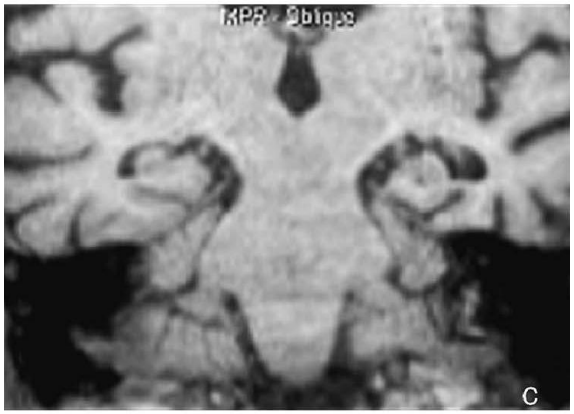

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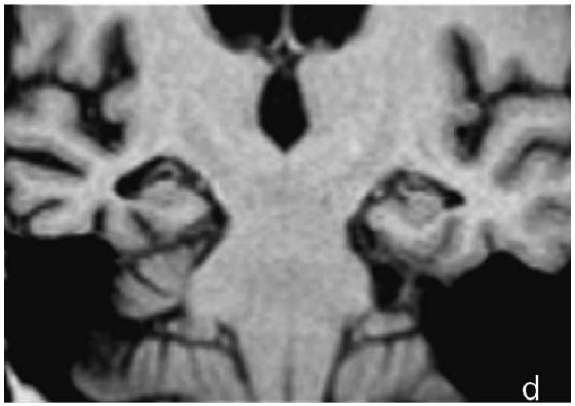

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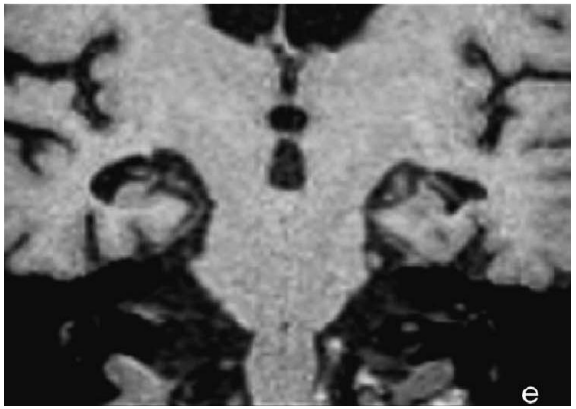
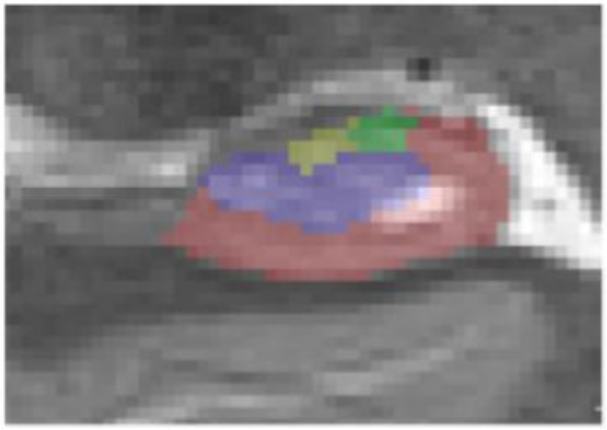
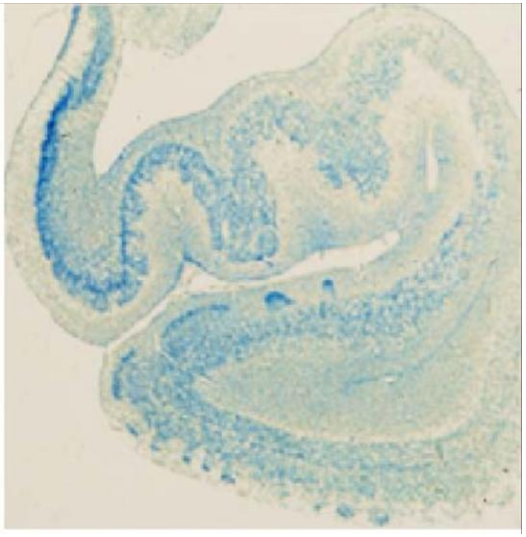


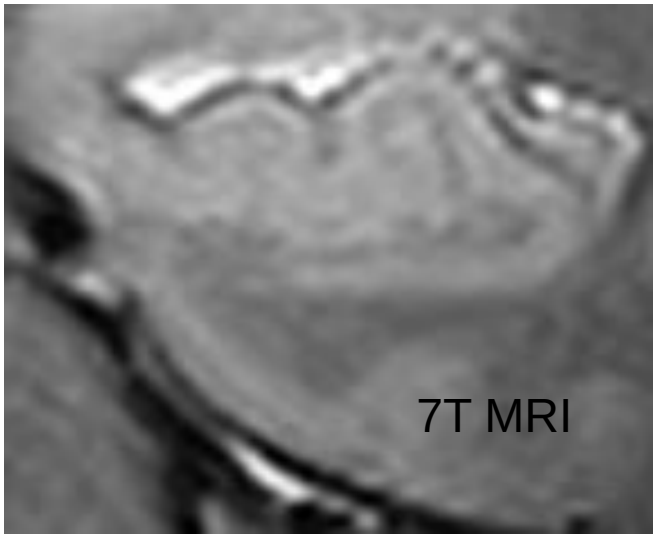
Bastos Leite et al.' 05, based on Scheltens et al.' 92

Quantitative Measures of Hippocampus

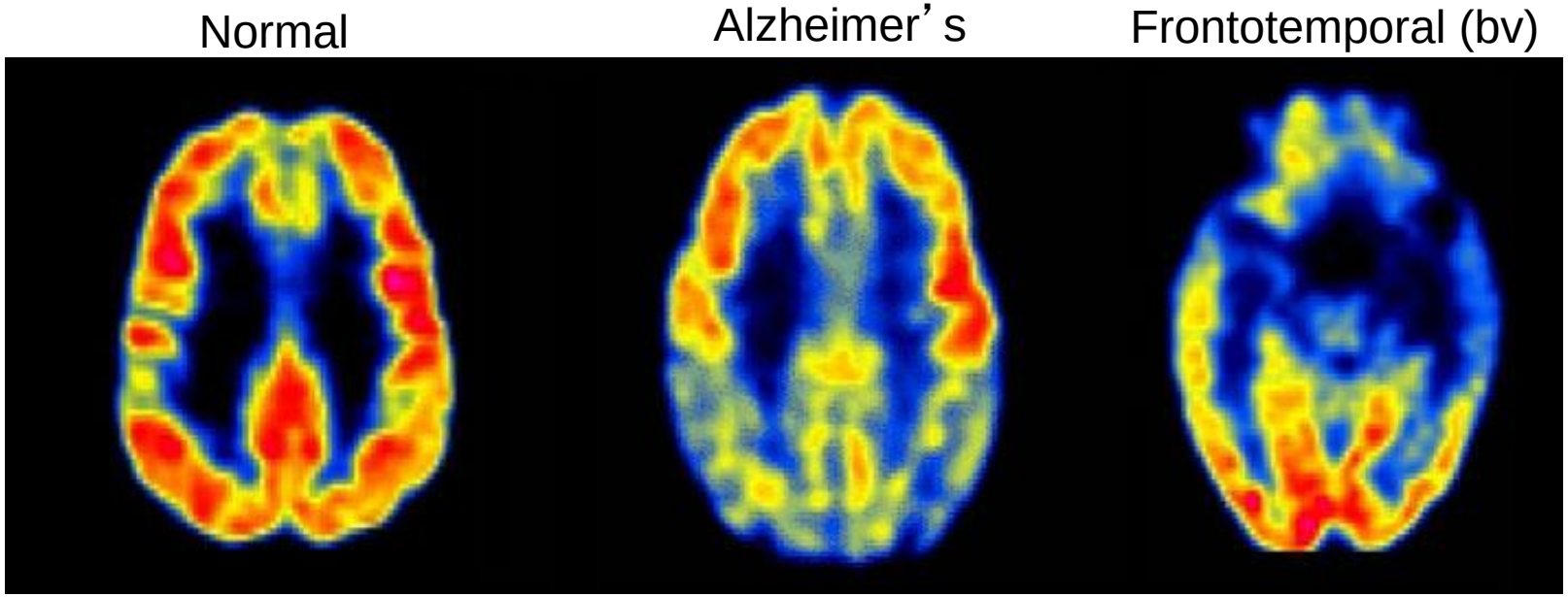


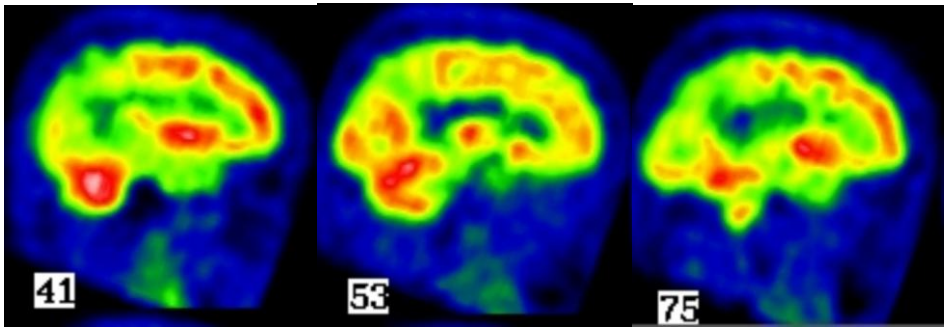
Pluta et al., *JAD*, 2012





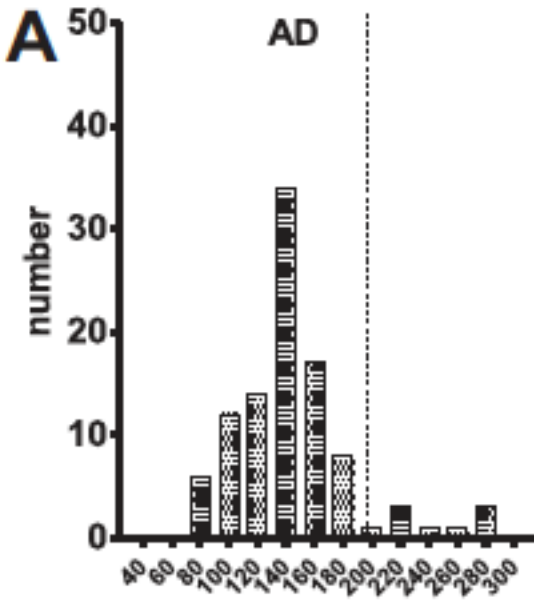
FDG (glucose) Positron Emission Tomography (measures brain activity)





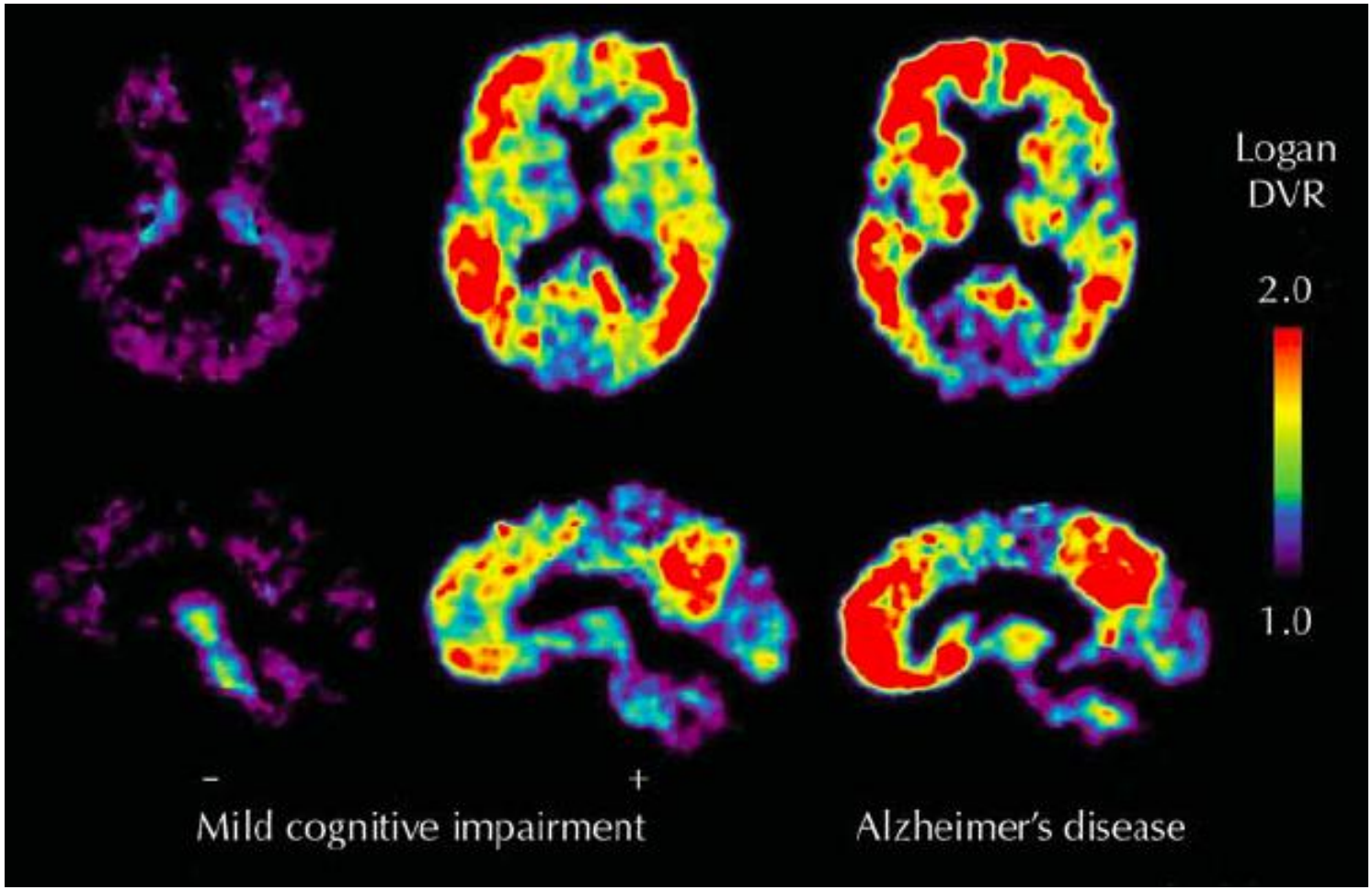
Cerebrospinal Fluid Aβ and tau

- Lumber Puncture to obtain CSF
- Aβ – linked to amyloid plaques
  - Low is abnormal
- Total tau, phospho-tau – linked to neurofibrillary tangles
  - High is abnormal



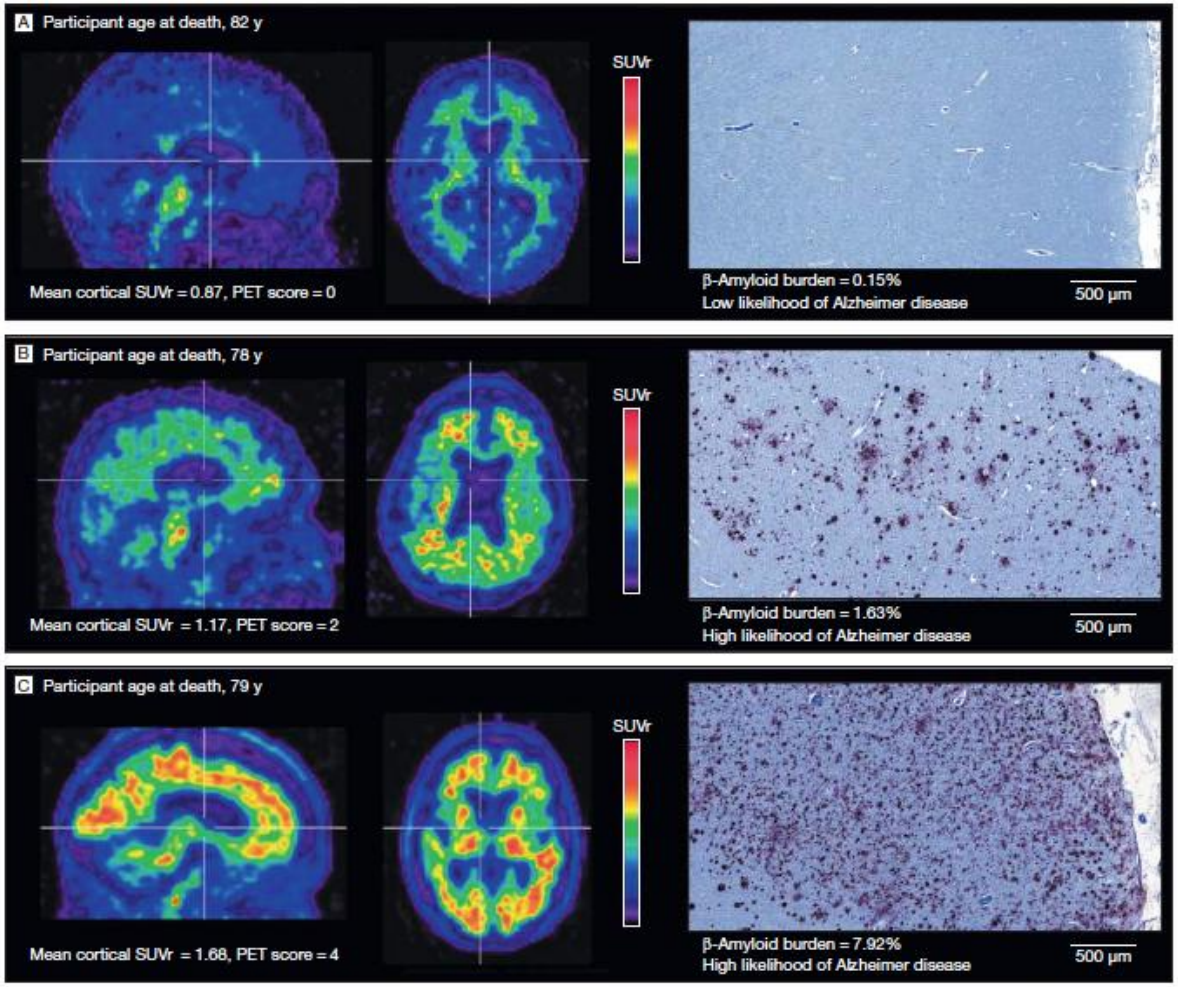
Shaw et al., *Annals of Neurology*, 2009

Amyloid Imaging



Wolk and Klunk, 2009

[^{18}F]Florbetapir (Amyvid)



Clark et al., *JAMA*, 2011

New AD Criteria Incorporates Biomarkers

Table 1
AD dementia criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (CSF tau, FDG-PET, structural MRI)
Probable AD dementia			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With three levels of evidence of AD pathophysiological process	Intermediate	Unavailable or indeterminate	Positive
	Intermediate	Positive	Unavailable or indeterminate
	High	Positive	Positive
Possible AD dementia (atypical clinical presentation)			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With evidence of AD pathophysiological process	High but does not rule out second etiology	Positive	Positive
Dementia-unlikely due to AD	Lowest	Negative	Negative

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, ^{18}fluorodeoxyglucose; MRI, magnetic resonance imaging.

McKhann et al., *Alz & Dementia*, 2011

How much testing should be done?

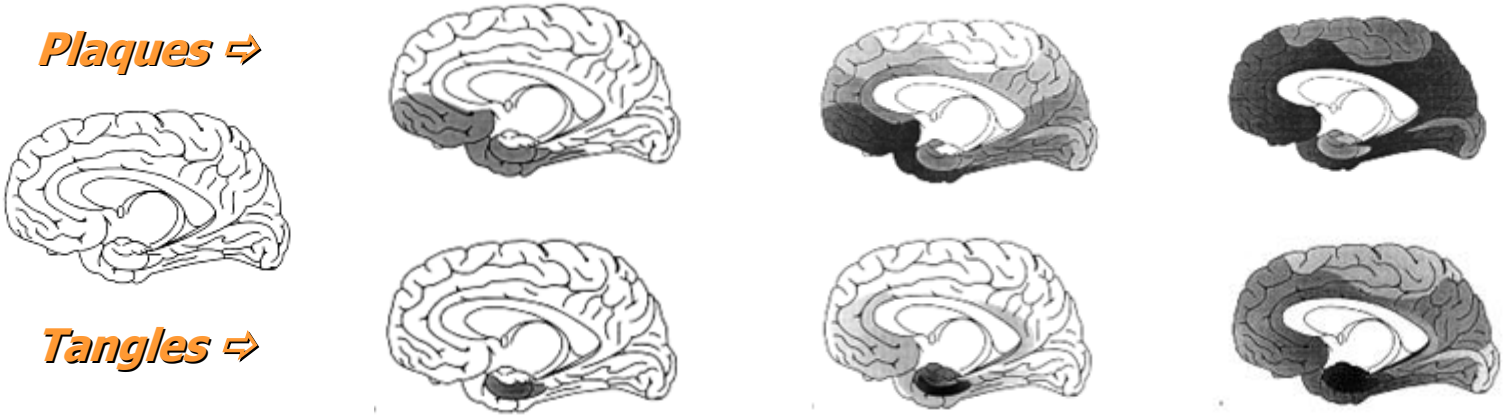
- Treatments for AD is limited
- When wrong, almost always a non-treatable condition
- The only FDA approved biomarker, amyloid imaging, is relatively expensive
- How much do we value getting the correct diagnosis?
  - Are there circumstances in which it would be more valuable
- Who should order these studies?

Clinical and Pathological Course of AD

Clinical State	Normal	Pre-Clinical AD	MCI	AD
Cognitive State	No Symptoms	No Symptoms	Mild Symptoms	Mild-Severe Symptoms
Pathologic State	No Disease	Early Changes	Mild Mod Changes	Mod-Severe Changes

Plaques ⇨

Tangles ⇨



“Petersen Criteria” for MCI (now referred to as amnestic-MCI)

- Memory complaint (preferably corroborated by informant)
- Episodic Memory impairment for age and education
- Largely intact general cognitive function
- Essentially preserved activities of daily living
- Do not meet criteria for dementia

Amnestic MCI

- Enriched in patients with AD pathology
  - Specialty Clinics
    - 10 to 15% "Conversion" to clinical AD per year
      - 1-3% in cognitively normal adults
    - 50-80% over 5 years
  - Community Studies (PAQUID, MoVIES)
    - Lower conversion rate (4 to 8%/year)
    - Reversion to normal (10 to 40% over 2 years)

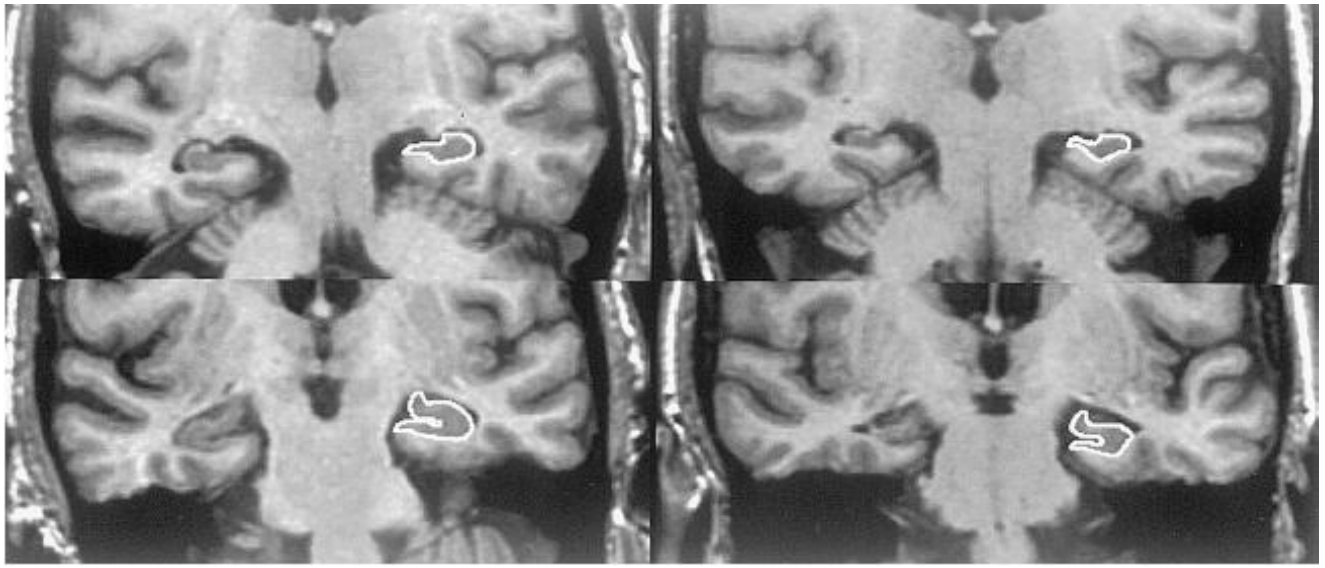
Mild Cognitive Impairment

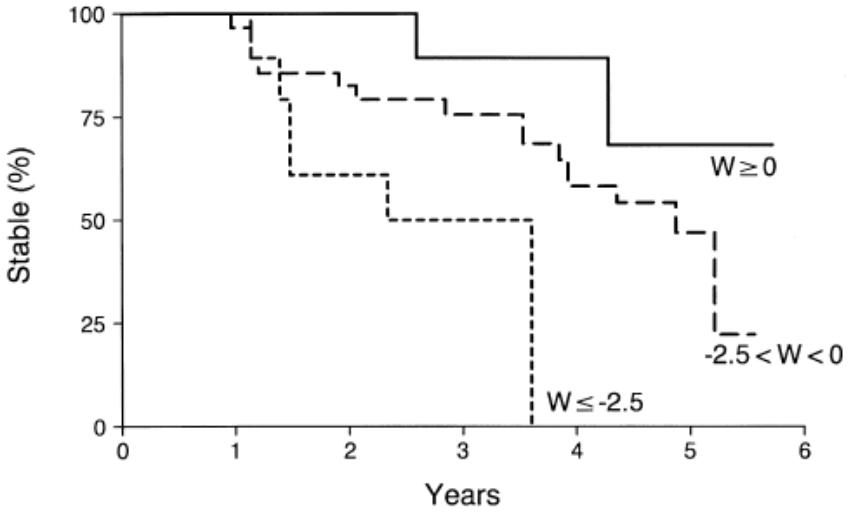
- Heterogeneous Population
  - AD
  - Other neurodegenerative disorders
  - Age-Associated memory loss
    - At border of diagnosis of MCI
  - CVD
  - Hippocampal sclerosis
  - Depression
  - Medications

Can we predict who will develop clinical AD?

- AD biomarkers enhance prediction
- Lots of biomarker data on the imaging, CSF, psychometric characteristics of AD
- The more you look like AD, the more likely you will convert to AD!

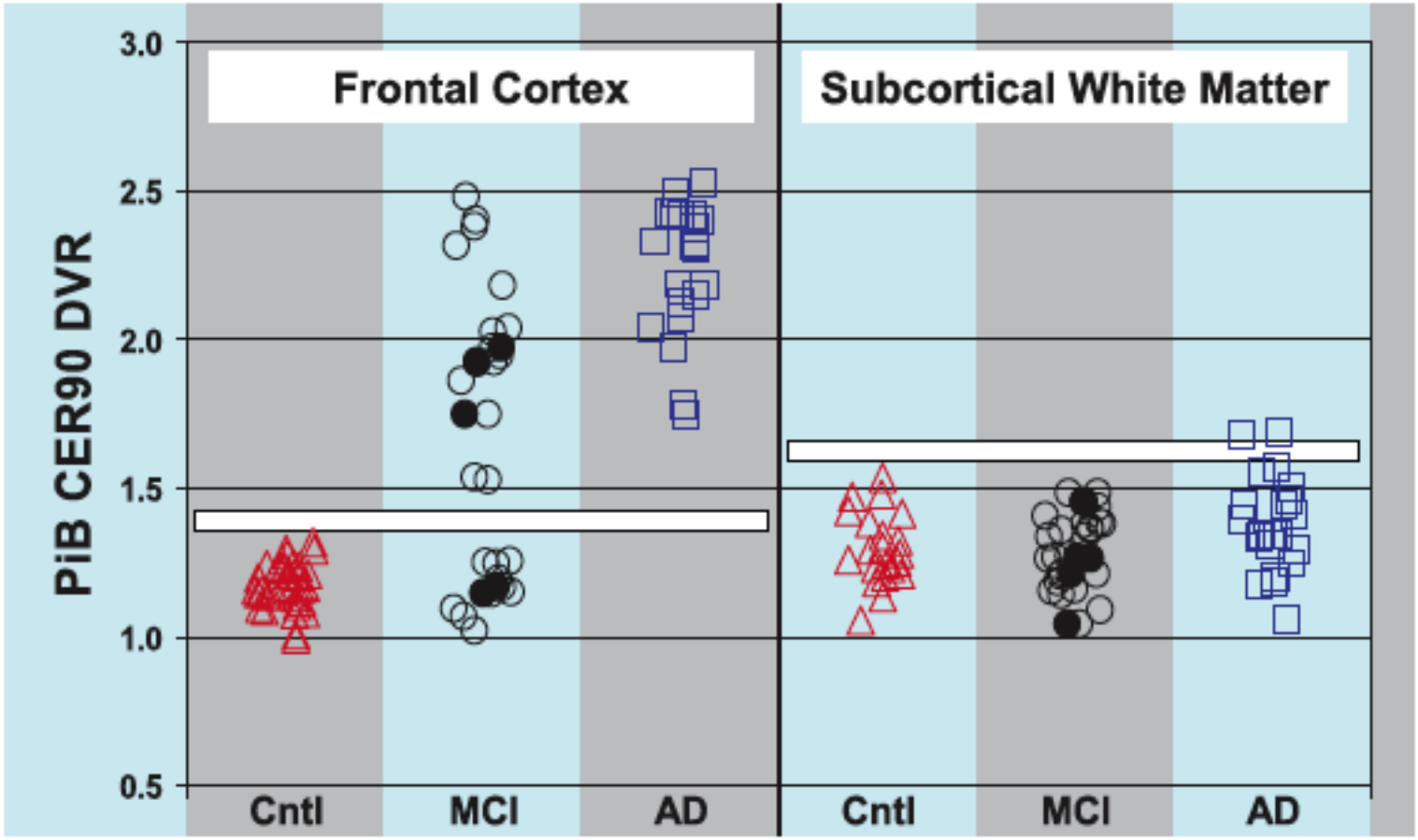
Hippocampal Volume



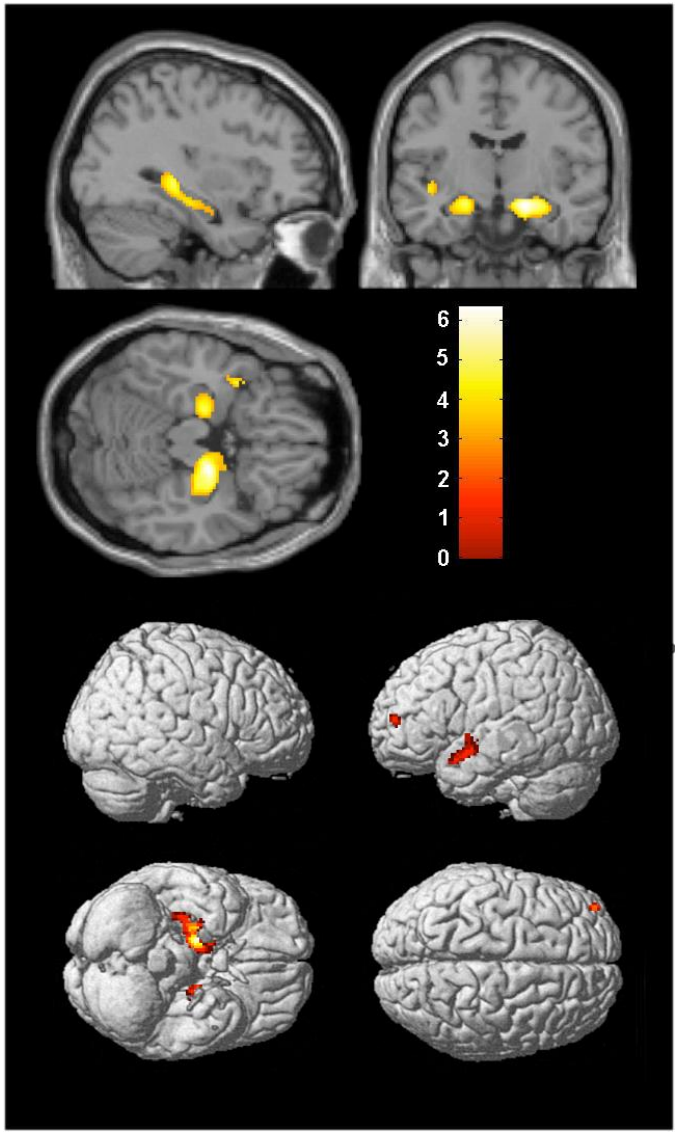


Jack et al., 1999

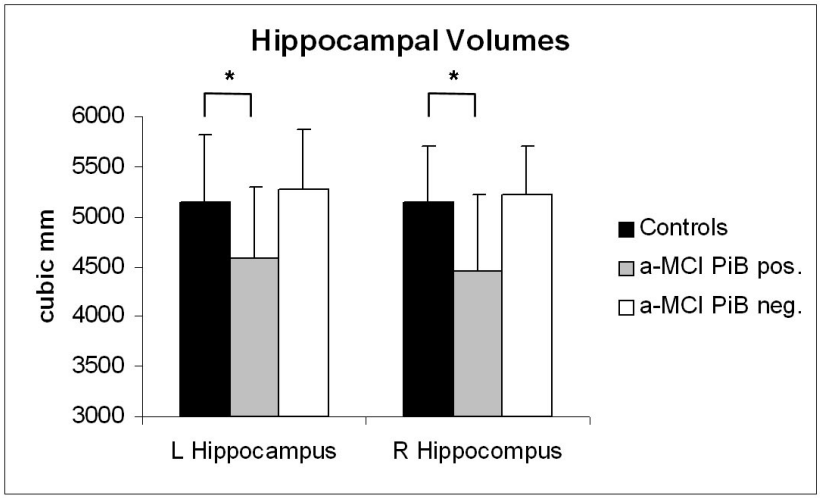
Amyloid Imaging



Wolk et al., *Annals of Neurology*, 2009

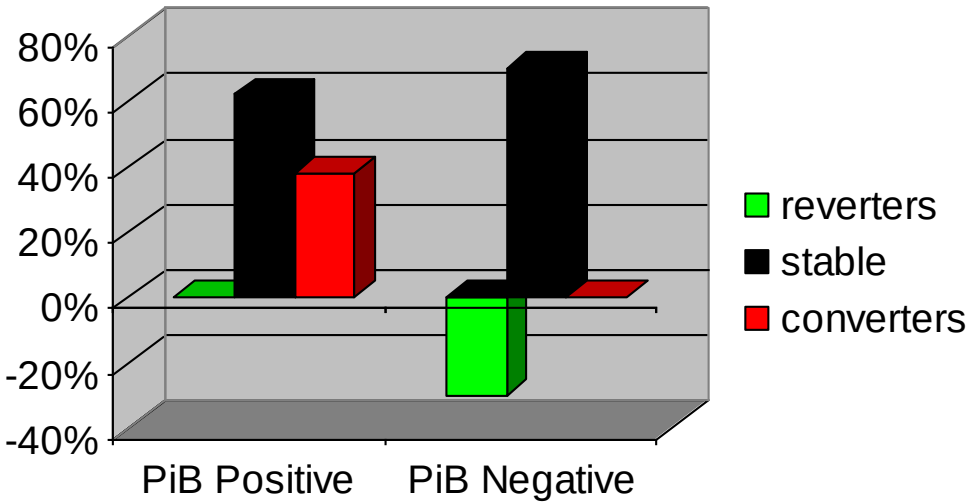


- PiB+ a-MCI vs. Controls
  - Atrophy includes bilateral medial temporal lobes
- PiB- a-MCI vs. Controls
  - No difference
- PiB+ vs. PiB- a-MCI
  - Greater atrophy in PiB+ patients in masked regions



Amyloid Imaging

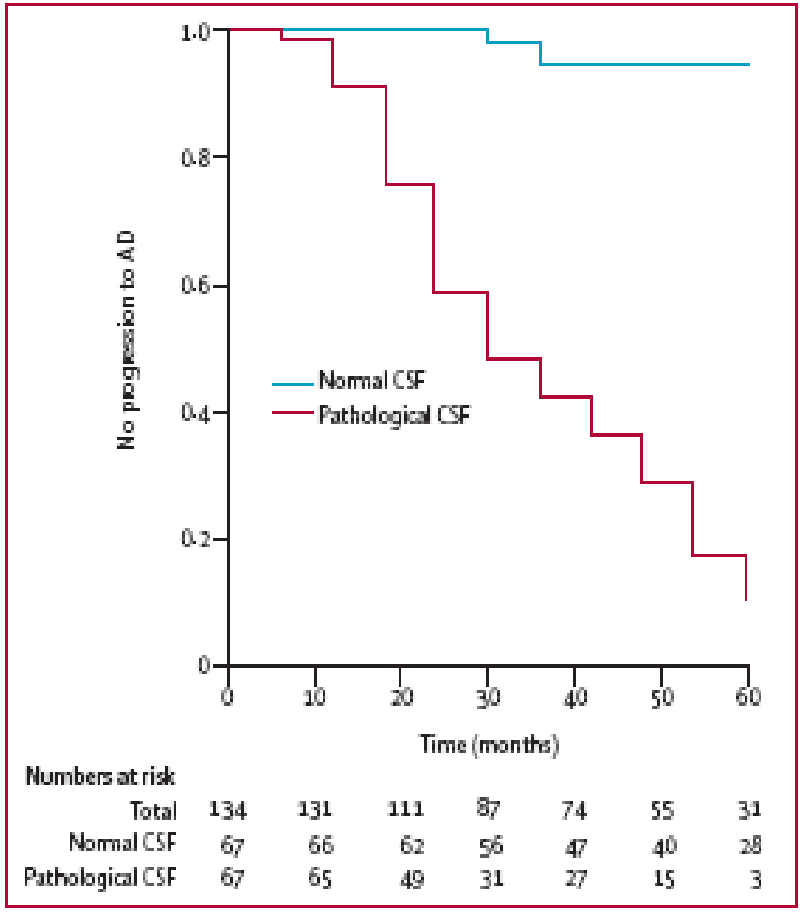
- 23/26 patients have had follow-up ADRC evaluations and consensus discussion
  - Mean f/u: 24.0 months (6-57 months)
  - 13 PiB positive (Mean: 23.6 months)
  - 10 PiB negative (Mean: 24.5 months)



Wolk et al., *Annals of Neurology*, 2009

Association between CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment: a follow-up study

Oskar Hansson, Henrik Zetterberg, Peder Buchhave, Elisabet Londos, Kaj Blennow, Lennart Minthon



- Combination of CSF Total-tau (↑) and Aβ42 (↓):
- Sensitivity of 95% and a specificity of 83% for detection of incipient AD in patients with MCI
- Relative risk of progression to AD = 17.7 ($p<0.0001$)

Hansson et al., *Lancet Neurol*, 2006

NIA-AA MCI Criteria

Diagnostic Category	Biomarker Driven Probability of AD Etiology	Presence of Cerebral Amyloidosis (PET, CSF)	Evidence of Neuronal Injury (tau, FDG, sMRI)
MCI-core clinical criteria	Uninformative	Conflicting/indeterminite/untested	Conflicting/indeterminite/untested
MCI due to AD – Intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD – High likelihood	Highest	Positive	Positive
MCI – unlikely due to AD	Lowest	Negative	Negative

Albert et al., *Alzheimer's & Dementia*, 2011

How should we use biomarkers in MCI?

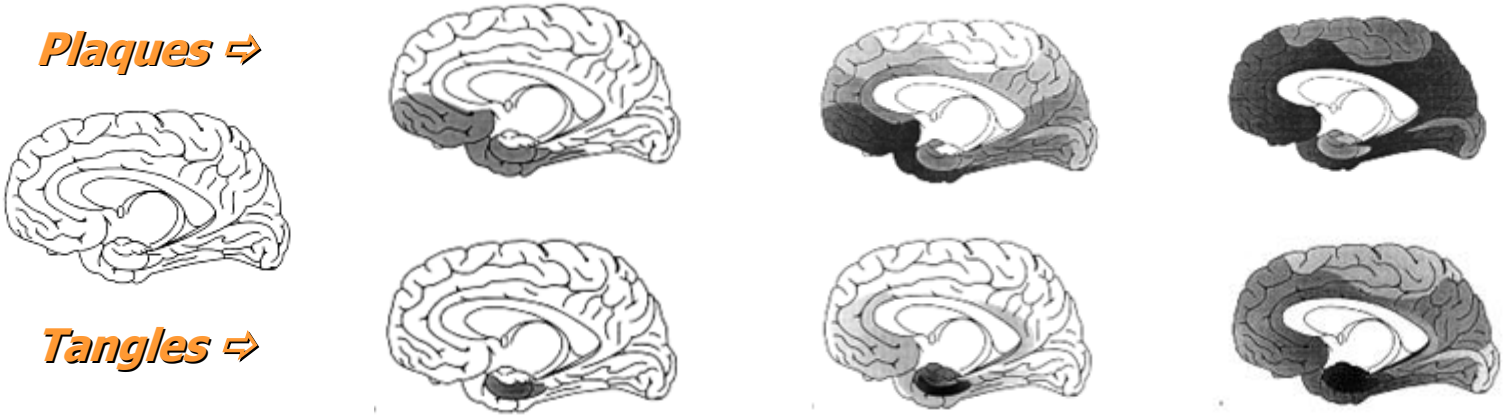
- Prognostic value (although numbers are still very fuzzy)
- Possibly, but unlikely to alter management
- Many patients want to know what is causing their memory issues – value in knowing
- Issues of disclosure
- Potential for discrimination

Clinical and Pathological Course of AD

Clinical State	Normal	Pre-Clinical AD	MCI	AD
Cognitive State	No Symptoms	No Symptoms	Mild Symptoms	Mild-Severe Symptoms
Pathologic State	No Disease	Early Changes	Mild Mod Changes	Mod-Severe Changes

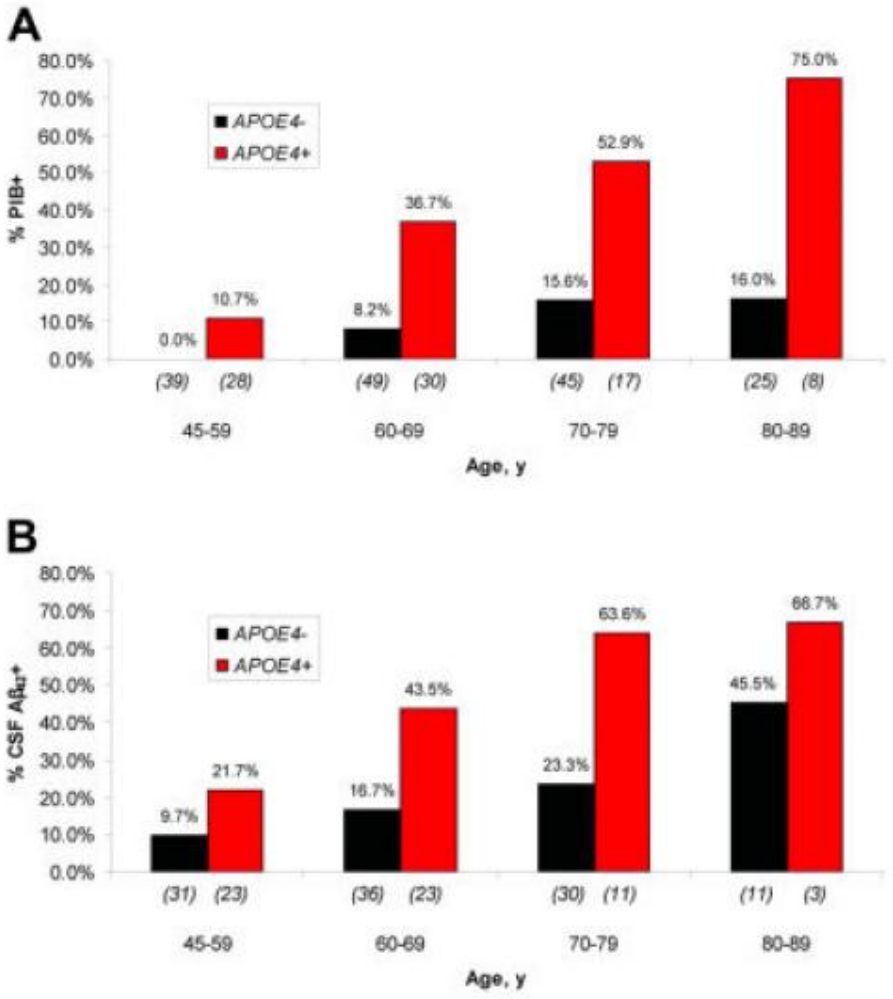
Plaques ⇨

Tangles ⇨



Preclinical Alzheimer's Disease

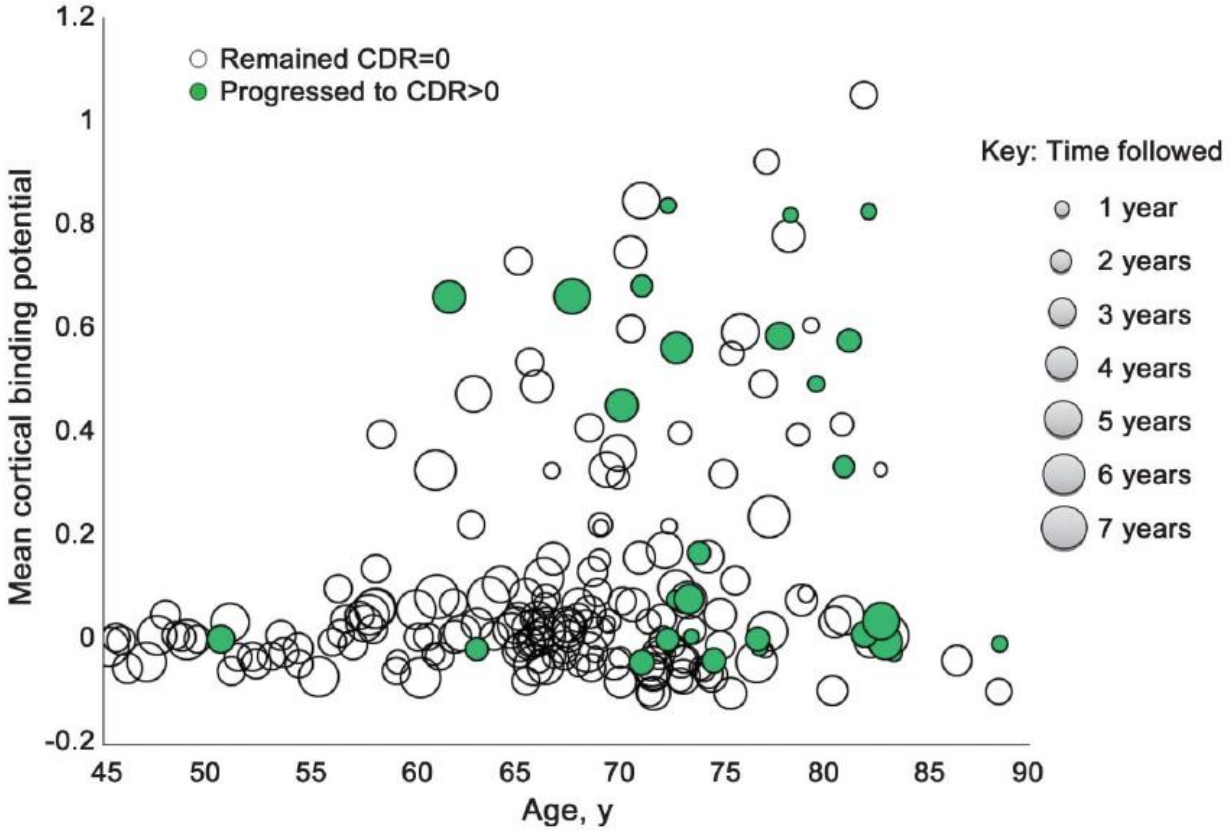
- 25-30% of CN adults with AD molecular biomarker profile
- Consistent with autopsy data



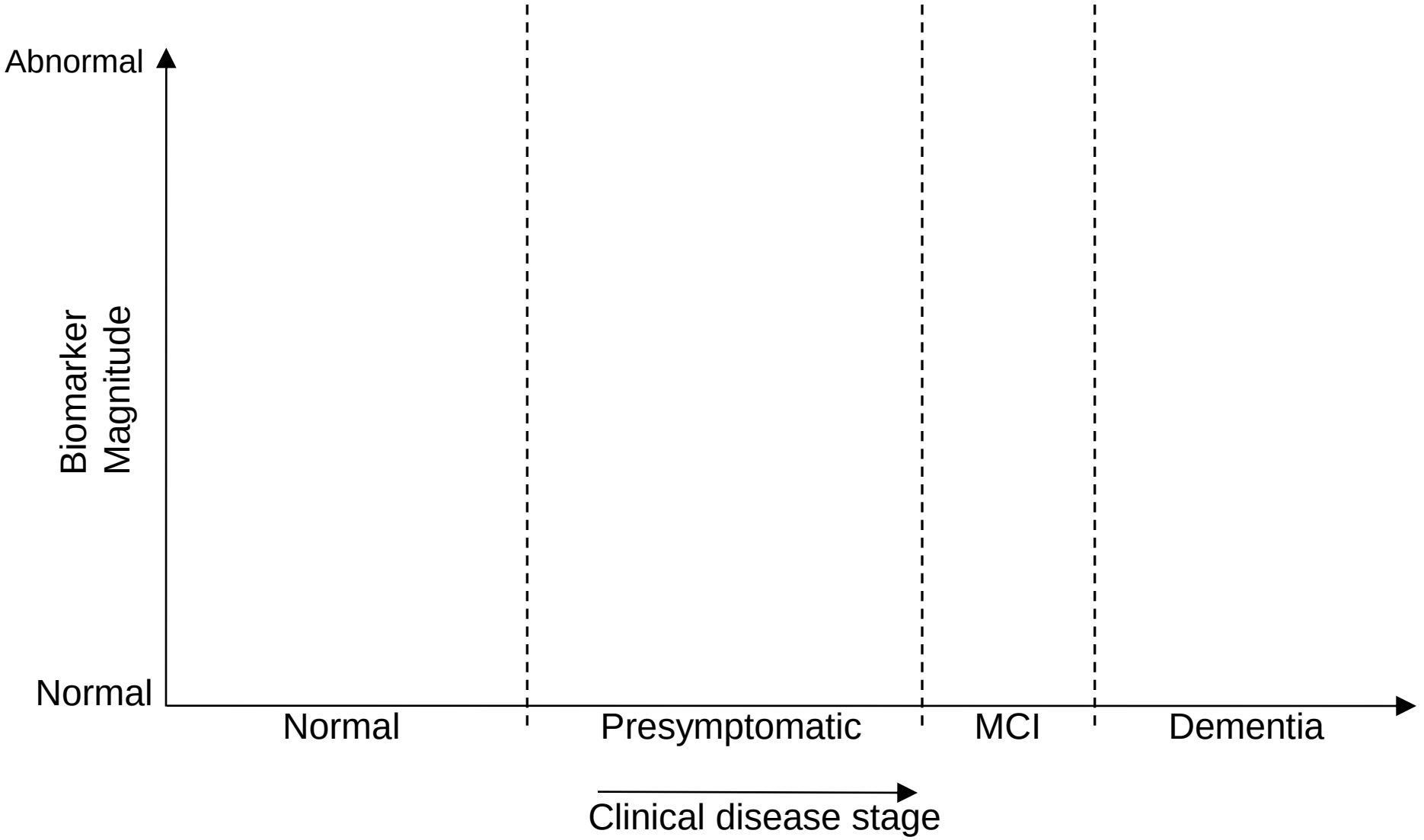
Morris et al., *Annals of Neurology*, 2010

Amyloid Imaging and Cognitive Decline in CN Adults

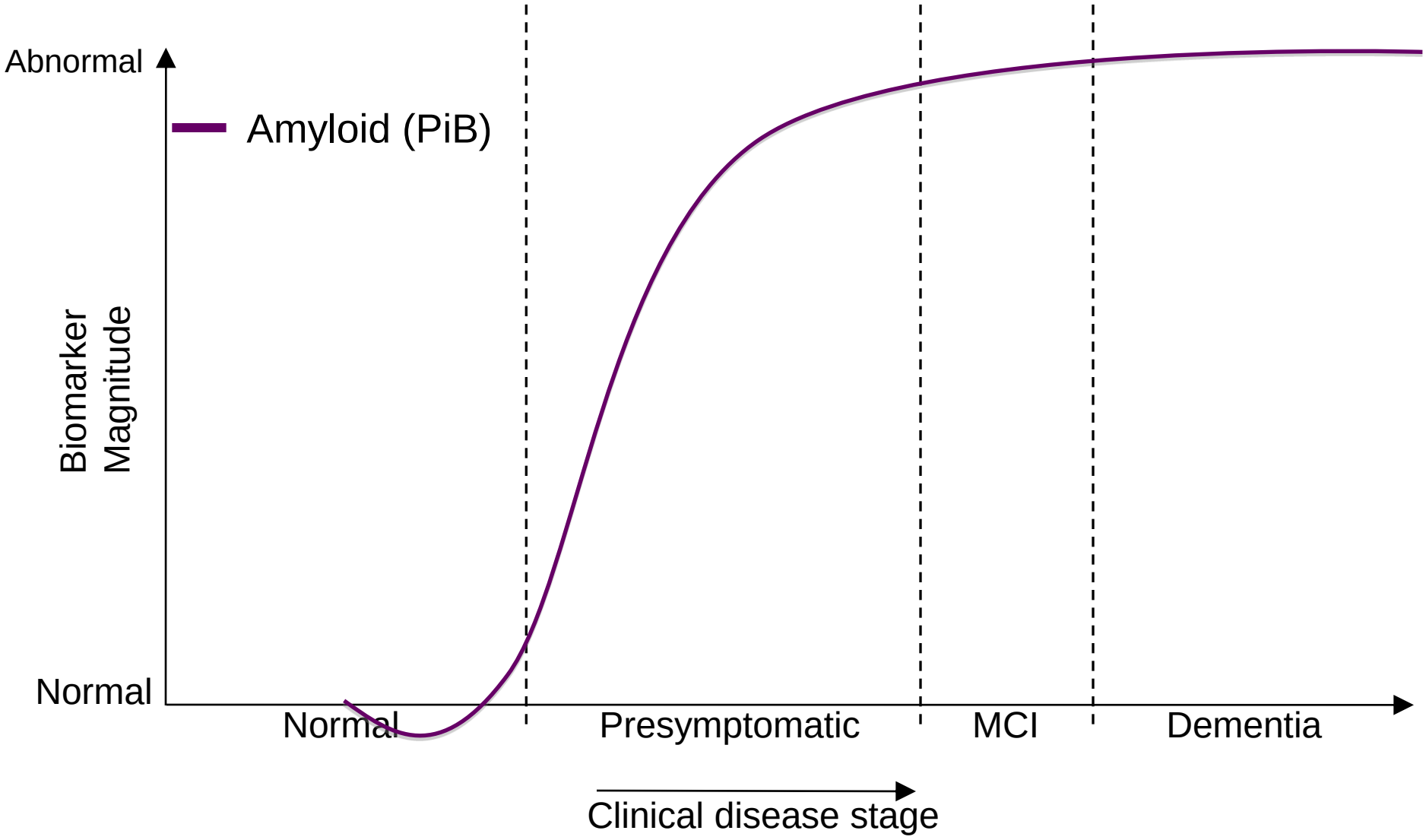
Figure 3 Bubble plot of progression to CDR (Clinical Dementia Rating) >0 as a function of mean cortical binding potential, age, and time



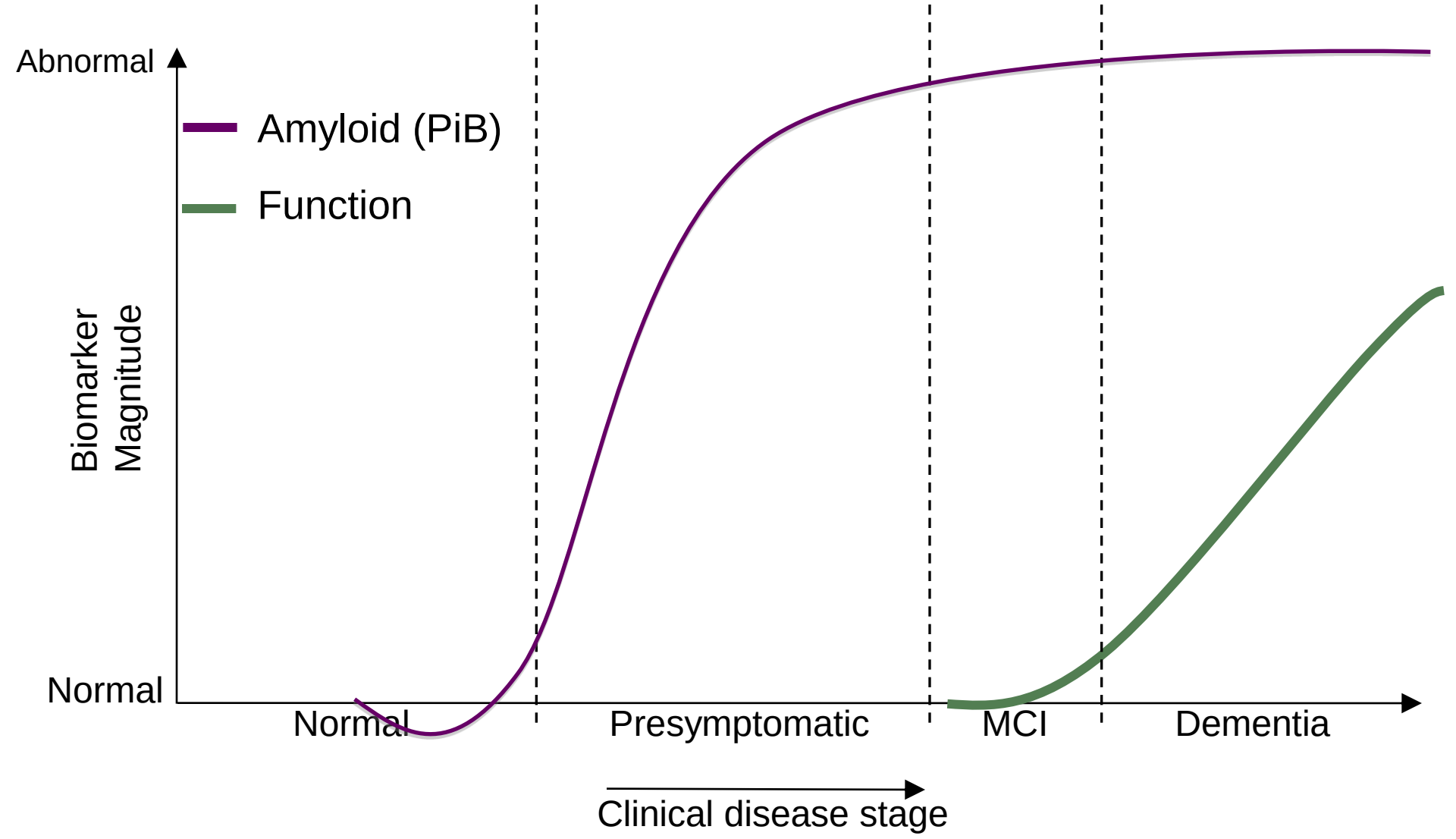
Roe et al., *Neurology*, 2013



Modified from Jack et al., 2010



Modified from Jack et al., 2010



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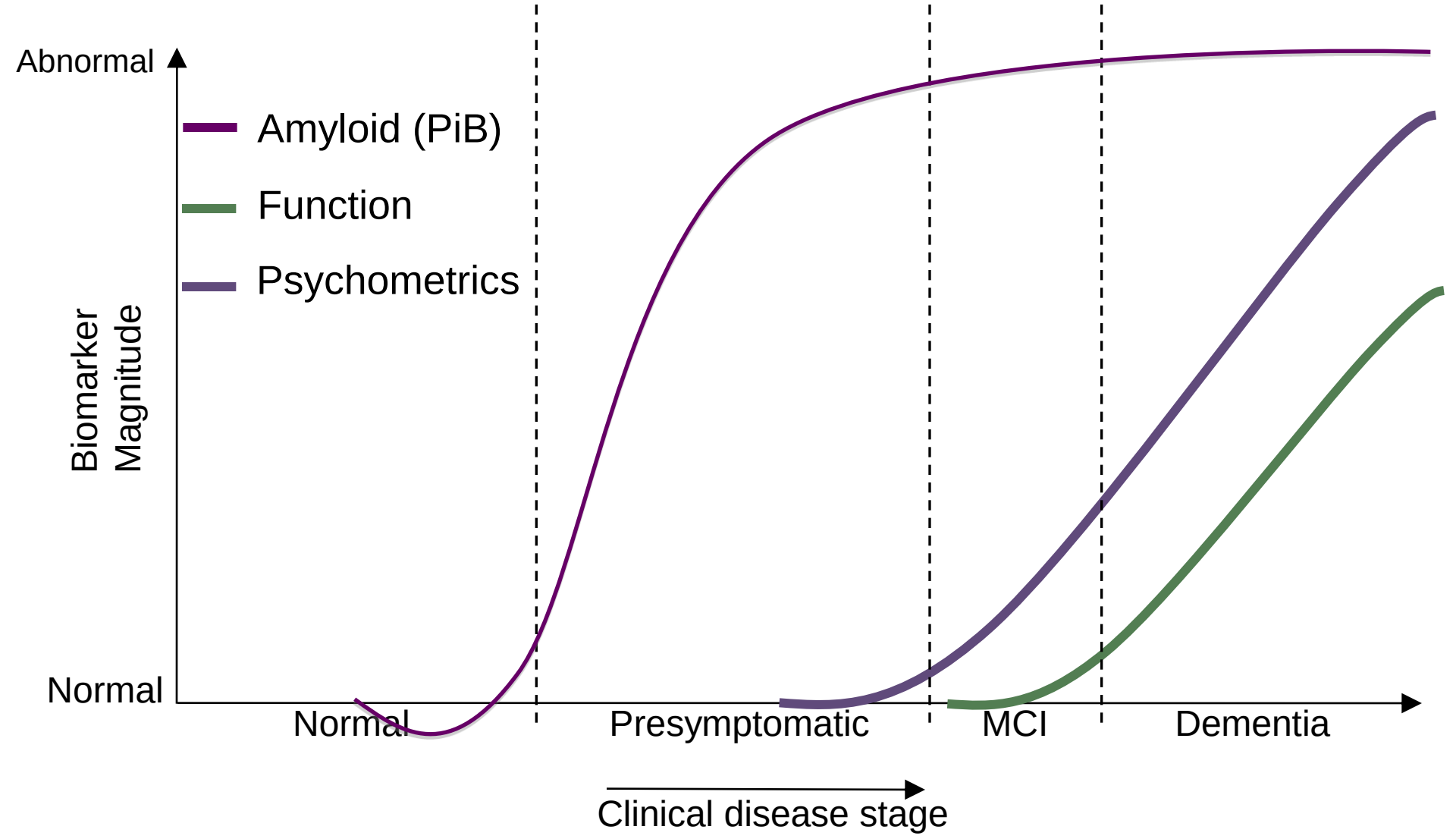
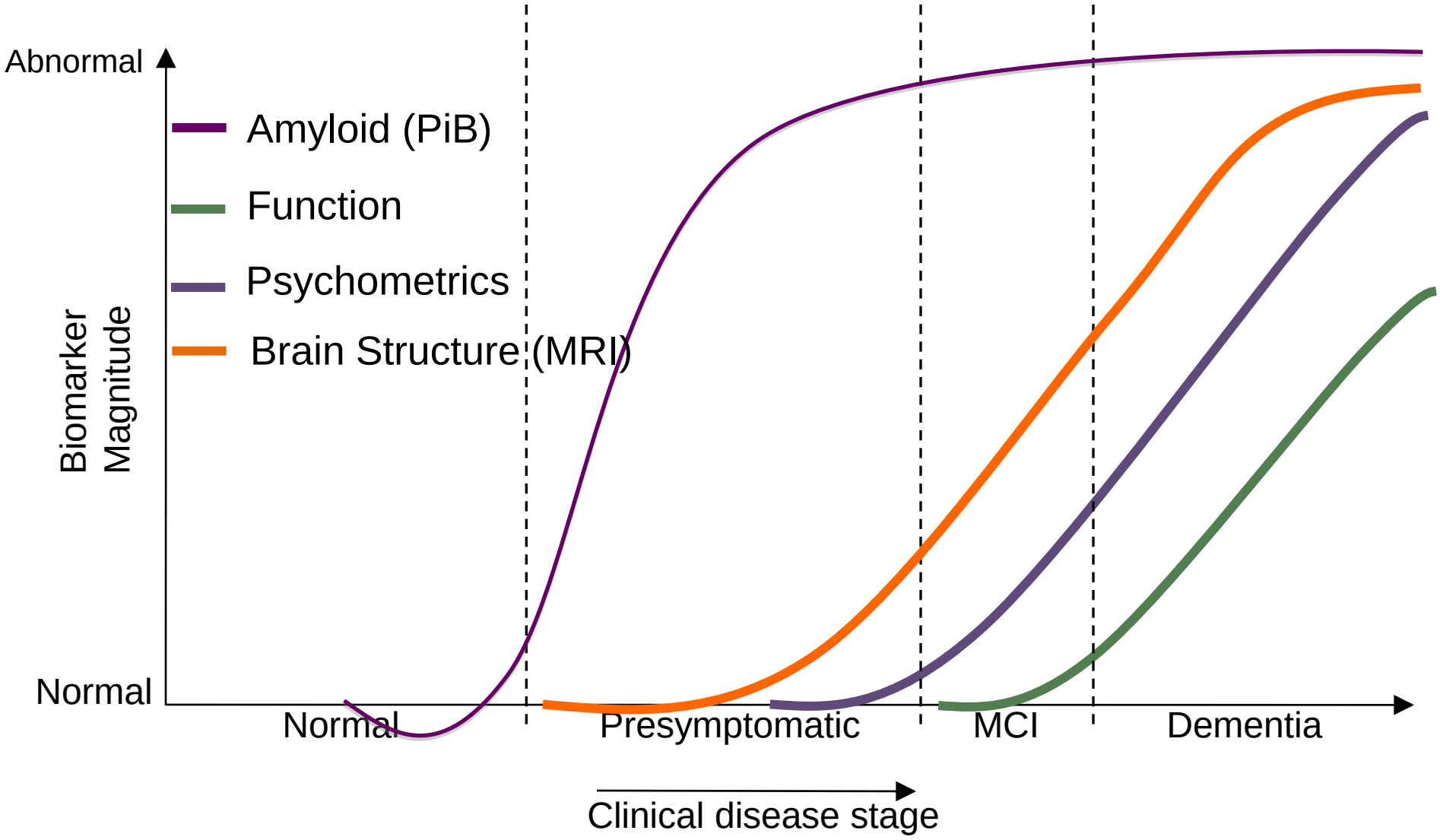
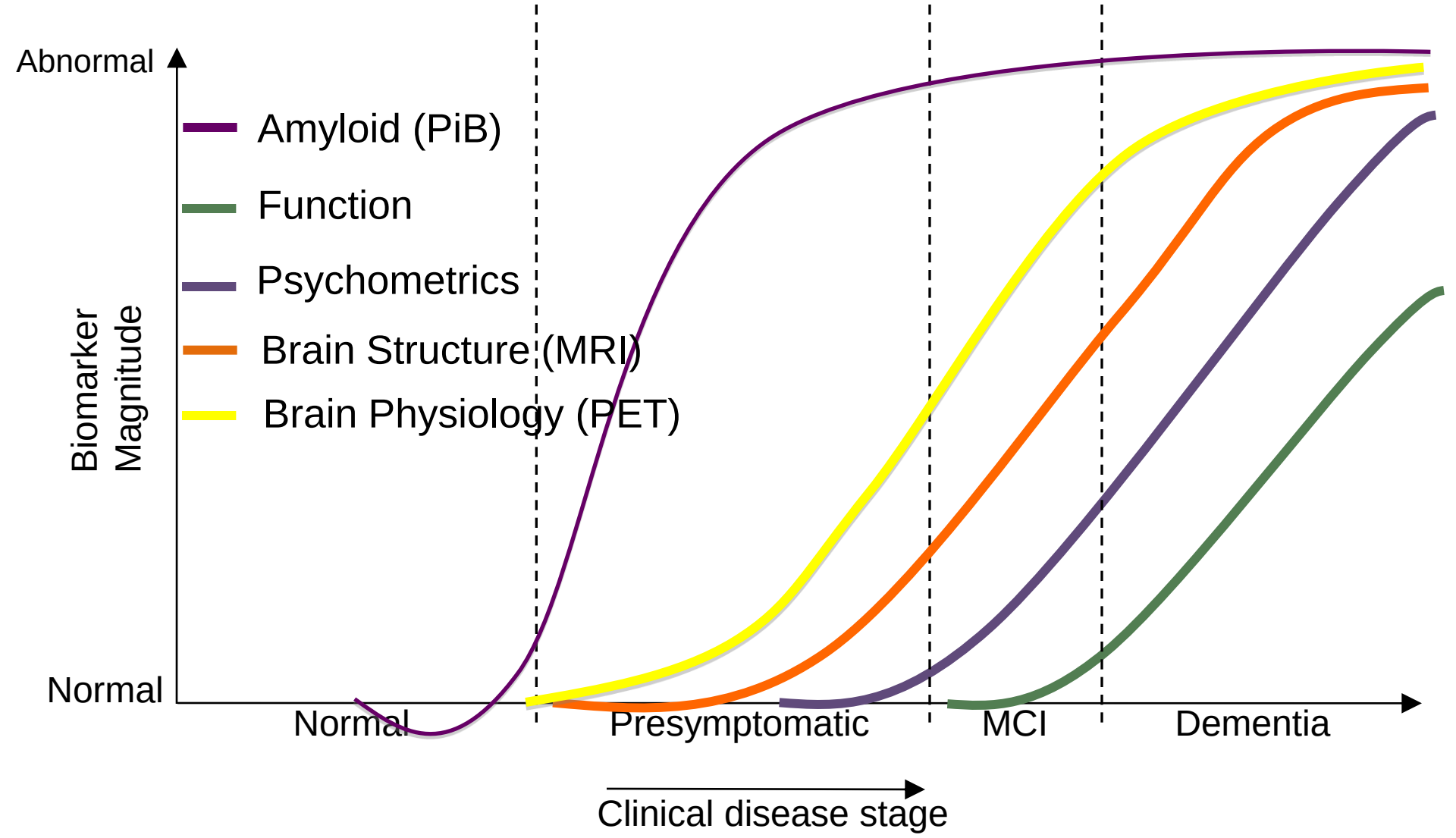


Modified from Jack et al., 2010



Modified from Jack et al., 2010



Modified from Jack et al., 2010

NIA-AA Preclinical AD Criteria

- Research criteria!!
- Stage 1 – presence of amyloid (CSF or PET)
- Stage 2 – amyloid + evidence of neurodegeneration
- Stage 3 – amyloid + neurodegeneration + subtle cognitive change

Implications of Preclinical AD

- Shift in boundary between normal aging and Alzheimer's Disease
  - Some "age-related" changes likely due to AD pathophysiology
- AD is uncoupled from clinical symptoms
  - Change in concept of disease?
  - Disease defined by risk and predictors
    - Or perhaps the critical issue is the risk that "the disease" will produce symptoms

Who should be tested?

- General consensus is that preclinical diagnosis should not be brought into clinical practice
  - However, many want it
- Will be disclosed in several “preclinical AD” treatment trials (secondary prevention)
  - Anti-Amyloid Treatment in Asymptomatic AD
  - Autosomal dominant trials
    - Columbian PSEN1 trial

How to Communicate Diagnosis

- Risk associated with dx
  - Anxiety/depression
- What are the benefits
  - Some want to know and others don't
  - What actions can be taken if evidence of high risk?
- What is appropriate counseling?

ApoE as a Model of Disclosure of Risk

ORIGINAL ARTICLE

Disclosure of *APOE* Genotype for Risk of Alzheimer's Disease

Robert C. Green, M.D., M.P.H., J. Scott Roberts, Ph.D.,
L. Adrienne Cupples, Ph.D., Norman R. Relkin, M.D., Ph.D.,
Peter J. Whitehouse, M.D., Ph.D., Tamsen Brown, M.S.,
Susan LaRusse Eckert, M.S., Melissa Butson, Sc.M., A. Dessa Sadovnick, Ph.D.,
Kimberly A. Quaid, Ph.D., Clara Chen, M.H.S., Robert Cook-Deegan, M.D.,
and Lindsay A. Farrer, Ph.D., for the REVEAL Study Group*

ApoE as a Model of Disclosure of Risk

- Exclusions based on anxiety and depression scales
- Information provided in written and oral format with genetic counselor
- Monitored mood and anxiety after
- Emergency contact
- Assess to mental health
- Similarities and differences to ApoE testing
  - Both assess risk, but is there something different about knowing the pathology is really there

Gaps in Knowledge of What Biomarkers Tell Us

- Specifics are still unknown
  - Absolute risk in any individual
    - Studies are small and populations not always representative
    - Temporal prediction poor
    - Standardization poor
  - Should we be using measures when much of the data just isn't in yet

Legal Ramifications

- Given uncoupling of cognitive capacity and diagnosis, need for privacy and confidentiality laws
  - Insurance risks
  - Discrimination in workplace and elsewhere
- Policy for assessment of capacity in financial and other matters
  - Certain professions that require more rigorous testing?

Development of Health Policy

- What kind of evidence is needed for determining who will receive preclinical testing
- Political impact of a disease of millions
- Who should develop guidelines