

# Biomarkers of the Alzheimer's pathological cascade and clinical expression: role of MRI

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# Objectives

- to describe, and provide evidence in support, of a dynamic biomarker based model of AD progression
- To place the role of MRI within this context

# Outline

- Temporal ordering and dynamic nature of AD biomarkers → graphical models
- Role of MRI

# Parallels: Imaging & CSF Biomarkers; 4 classes

## ■ Brain Amyloidosis

- PET - amyloid plaque imaging
- CSF AB 1-42

## ■ Neuronal dysfunction and tau mediated injury

- CSF t-tau and p-tau
- FDG PET
- Functional MRI (activation and resting state)

## ■ Neurodegeneration

- Structural MRI
- MR Spectroscopy
- Diffusion MRI
- Perfusion MRI

## ■ Inflammation - PET

Biomarker Reviews

Hampel, Alzheimer's Dement 2008

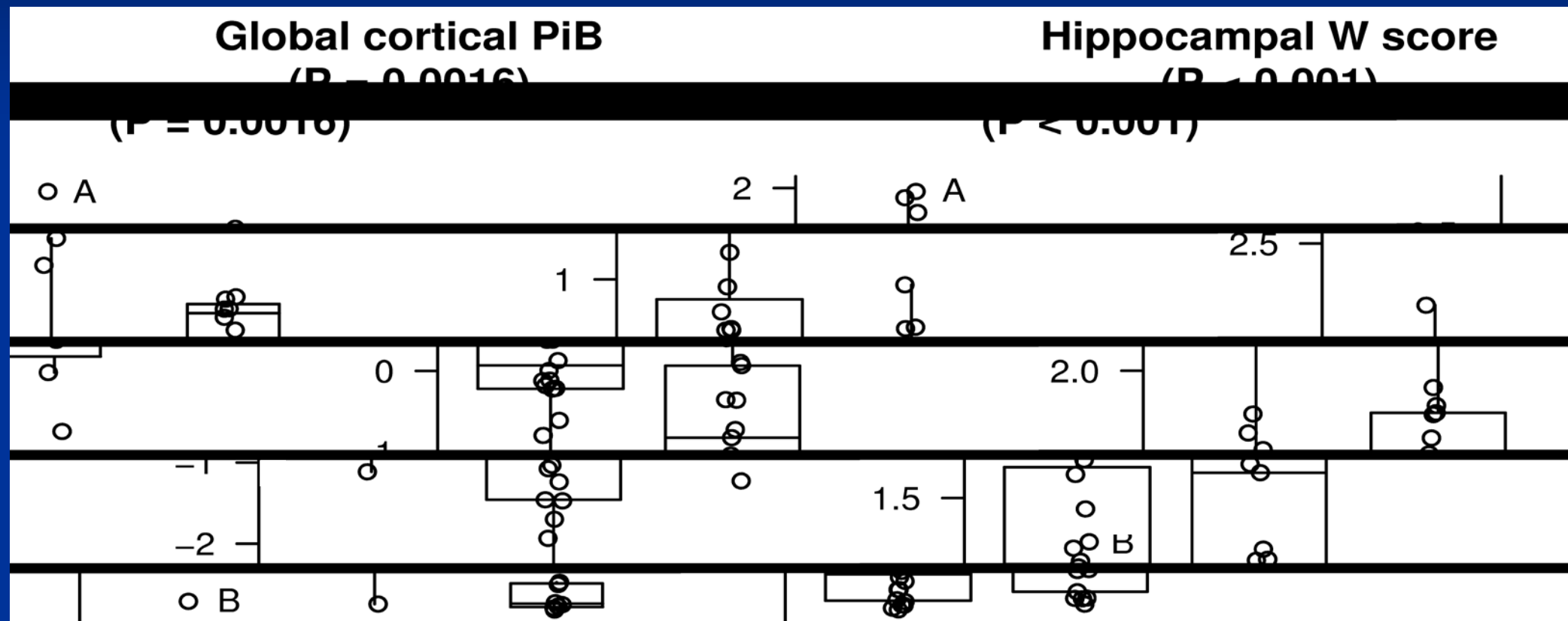
Shaw, Nat Rev Drug Discov 2007

# Model of disease staging based on PIB & MRI

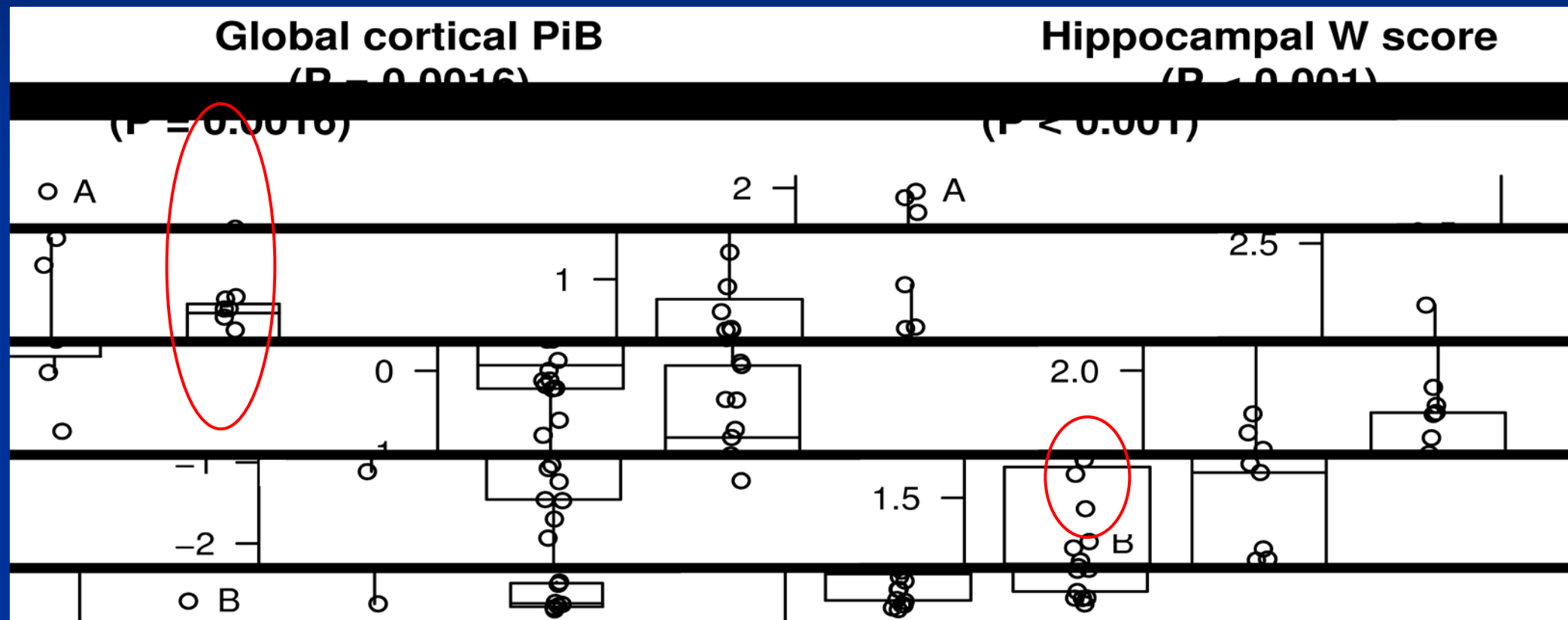
## Publications in 2008 and early 2009

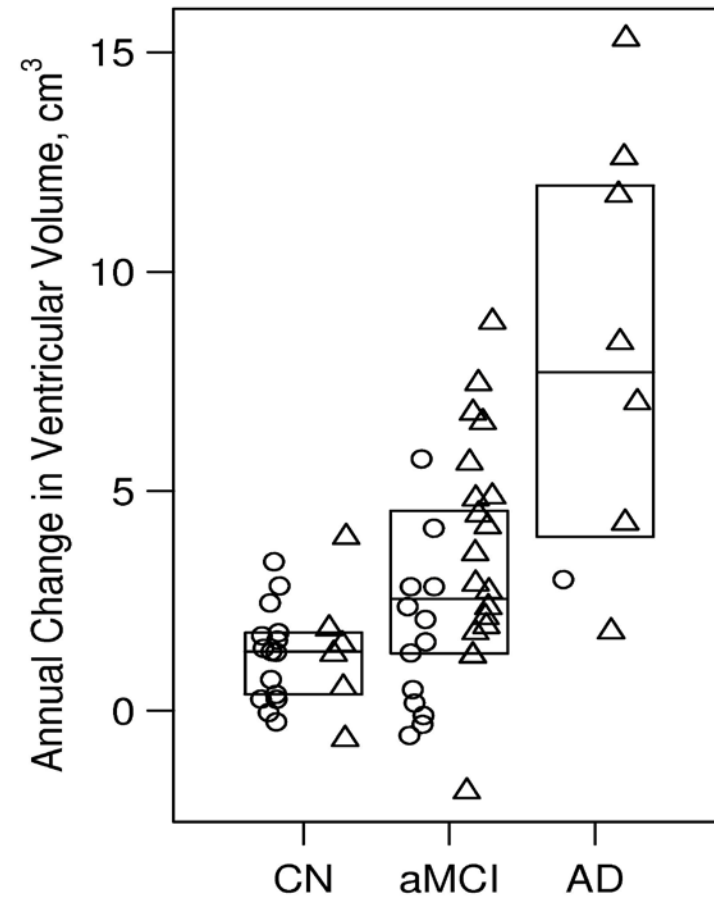
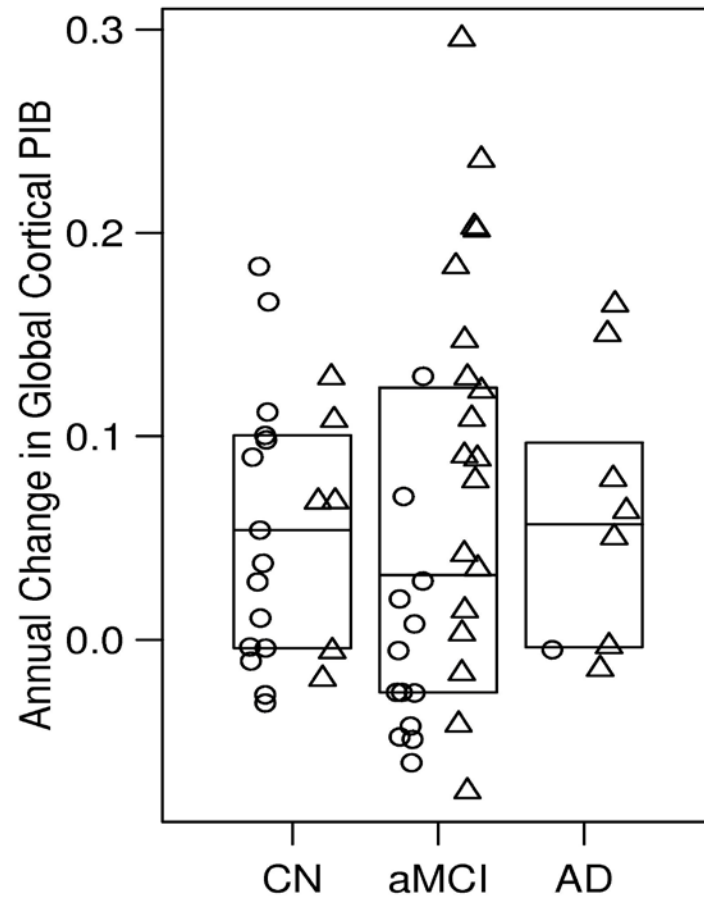
- *11C PIB and Structural MRI Provide Complementary Information in Imaging of AD and Amnestic MCI.* [Brain 2008;131\(Pt 3\):665-680](#)
- *Serial PIB and MRI in normal, MCI, and AD: implications for sequence of pathological events in AD.* [Brain 2009 132\(Pt 5\):1355-65](#)
- **Objective:** understand temporal relationships amyloid, neurodegeneration, cognition
- **11C PIB** → biomarker of amyloid load
- **structural MRI** → biomarker of stage of neurodegeneration
- Mormino et. al. [Brain 2009; 132\(Pt 5\):1310-23](#)

# Cross sectional group-wise comparison global cortical PiB and hippocampal volume



# Cross sectional group-wise comparison global cortical PiB and hippocampal volume





Annual change in global PIB ratio and ventricular volume by clinical diagnosis

Mayo plus ADNI data



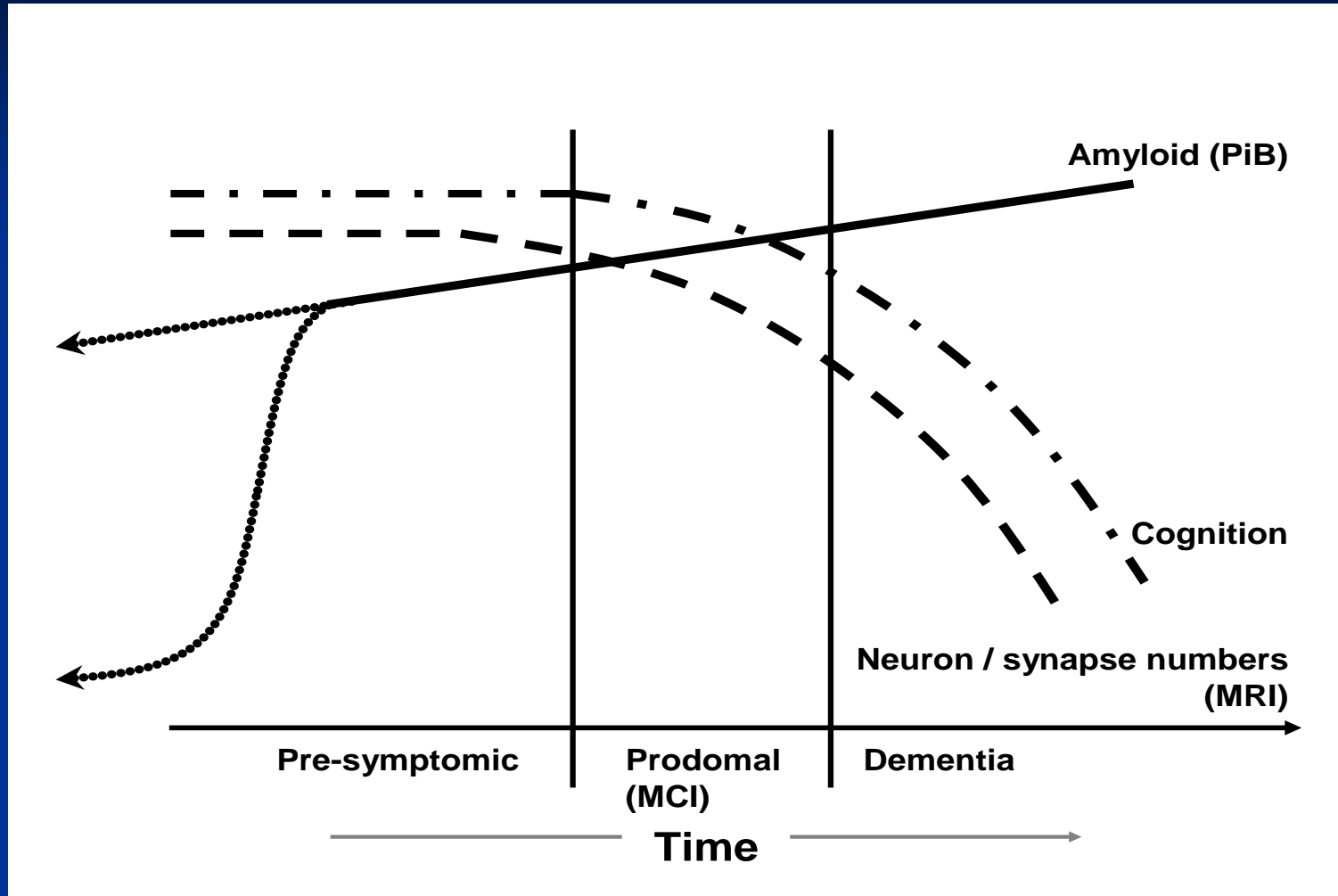
# Summary: Data derived from imaging consistent with model of typical late onset AD with 3 main features

Brain 2008;131(Pt 3):665-680, and Brain 2009 132(Pt 5):1355-65

- significant plaque deposition occurs prior to neuro degeneration and clinical decline
- Dissociation: Change in cognition is closely coupled to rate of neurodegenerative progression, not to rate of amyloid deposition
- Bi-phasic disease process: amyloid dynamic early vs. neurodegeneration dynamic mid to late stage

# Graphical model of the dynamic biomarkers of AD pathological progression

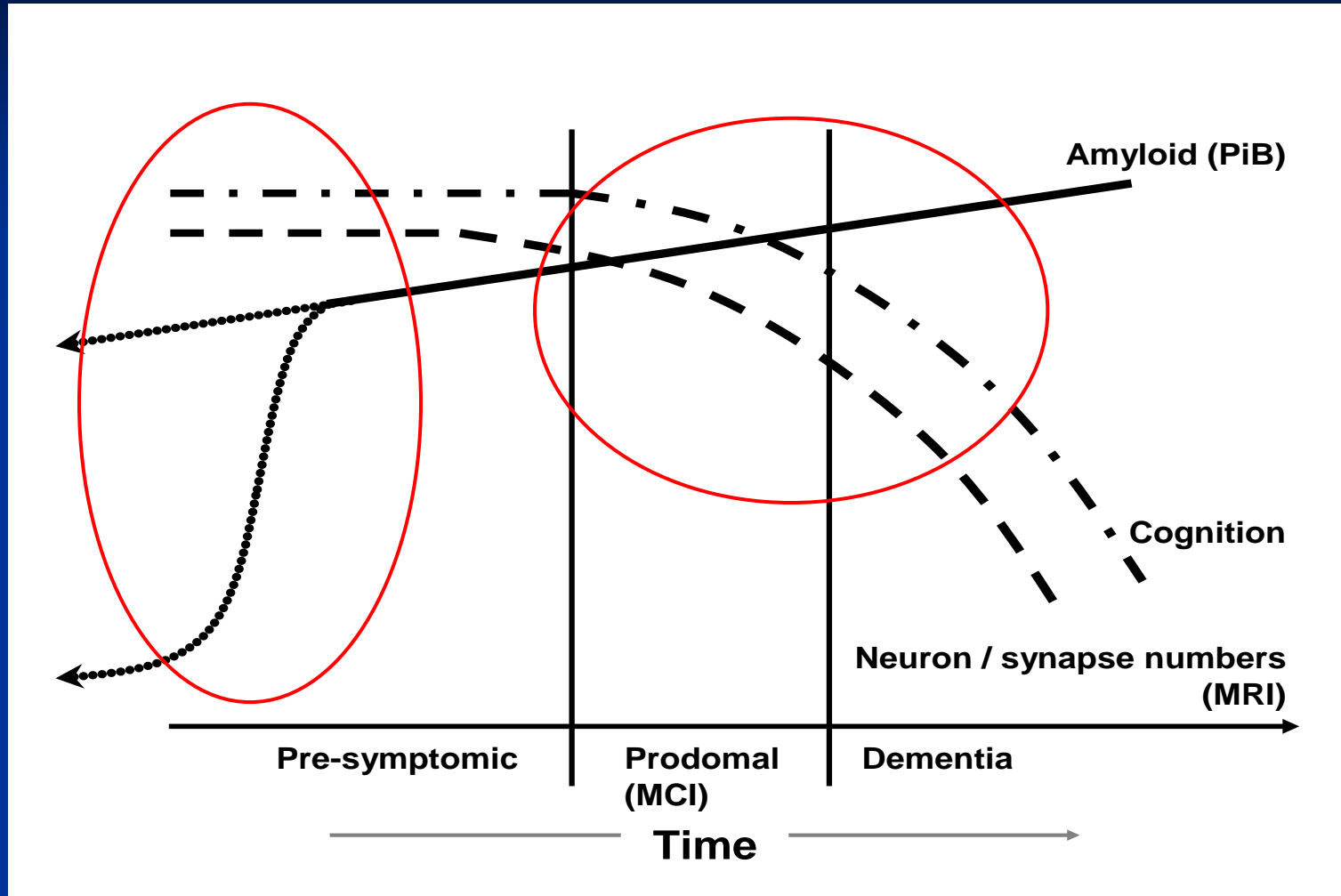
Brain 2009 132 (Pt 5):1355-65



Proposed model relating imaging (pathology) and clinical presentation over an individual's adult lifetime.

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Brain 2009 132 (Pt 5):1355-65



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Biomarker Reviews

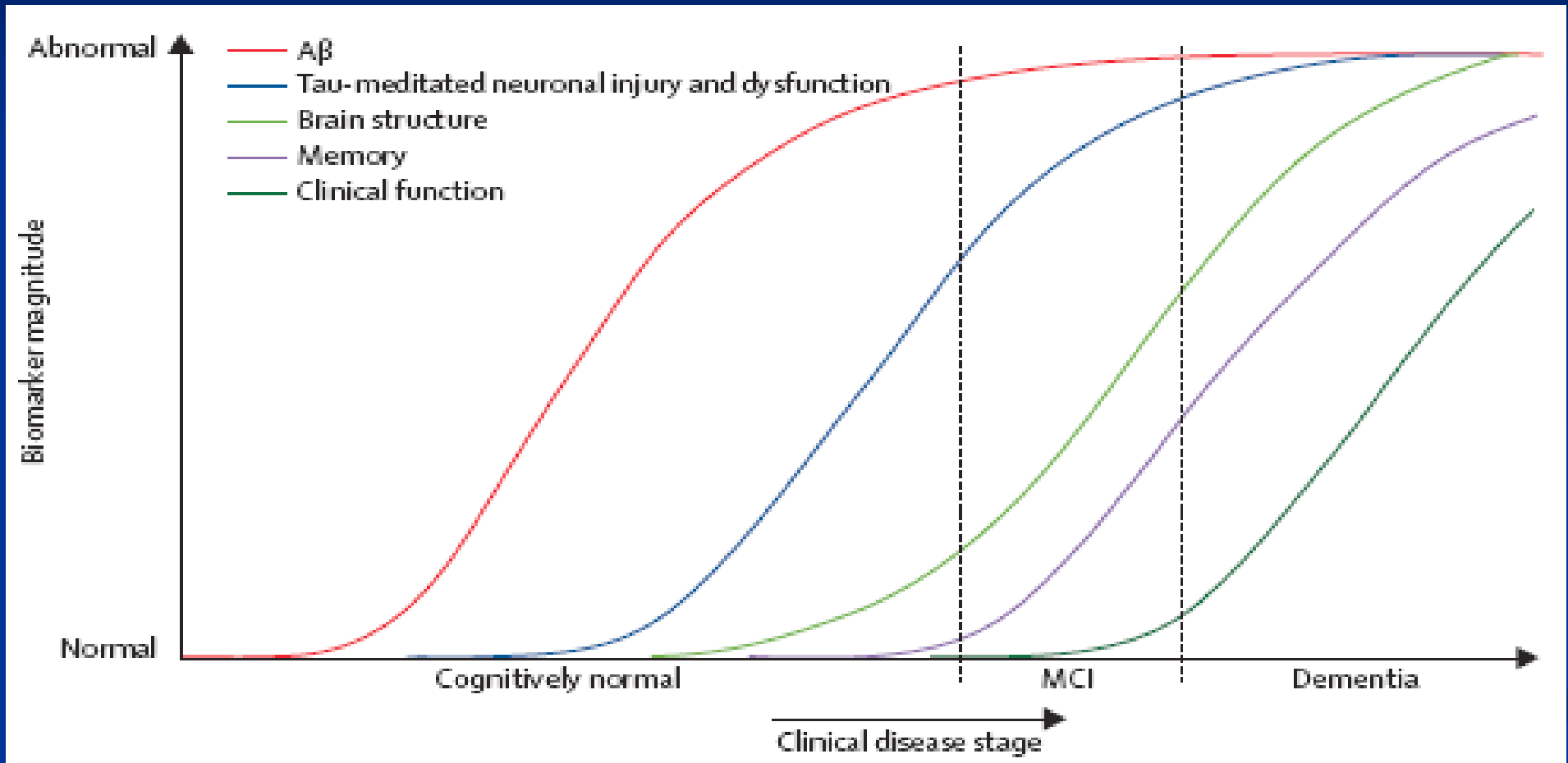
Hampel, Alzheimer's Dement 2008

Shaw, Nat Rev Drug Discov 2007

# Evidence of temporal ordering of biomarkers

- **Amyloid imaging** [Mintun, 2006; Aizenstein, 2008; Klunk 2004; Rowe 2007; Mormino 2009]
- **CSF A $\beta$ 42** [Peskind, 2006; Shaw, 2009; Fagan, 2007; Li, 2007; Fagan 2009; Vemuri 2009]
- **CSF tau** [Bouwman 2007; de Leon 2006; Wahlund 2003; Stefani 2006; Sluimer 2008; Hansson 2006; Sunderland 1999; Blennow 2003; Vemuri 2009]
- **FDG PET** [Minoshima, 1997; Chetelat, 2002; de Leon, 2001; Reiman, 1996; Small 1995]
- **MRI** [Fox 1997; Fox 1999; Kaye, 1997; Killiany 2000; Dickerson 2009]
- **Conclusions**
  - Biomarker abnormalities precede clinical symptoms
  - Amyloid biomarkers become abnormal first
  - Little evidence for ordering of amyloid imaging vs CSF AB42
  - FGD PET changes before MRI [Reiman 1998]
  - Little evidence for ordering of FDG PET vs CSF tau
  - MRI last onset but correlates with clinical Sx longest [Vemuri, 2009]
  - Non-linear functions (over long period) [Chan 2003; Carlson 2008]

# Dynamic Biomarkers of the Alzheimer's Pathological Cascade

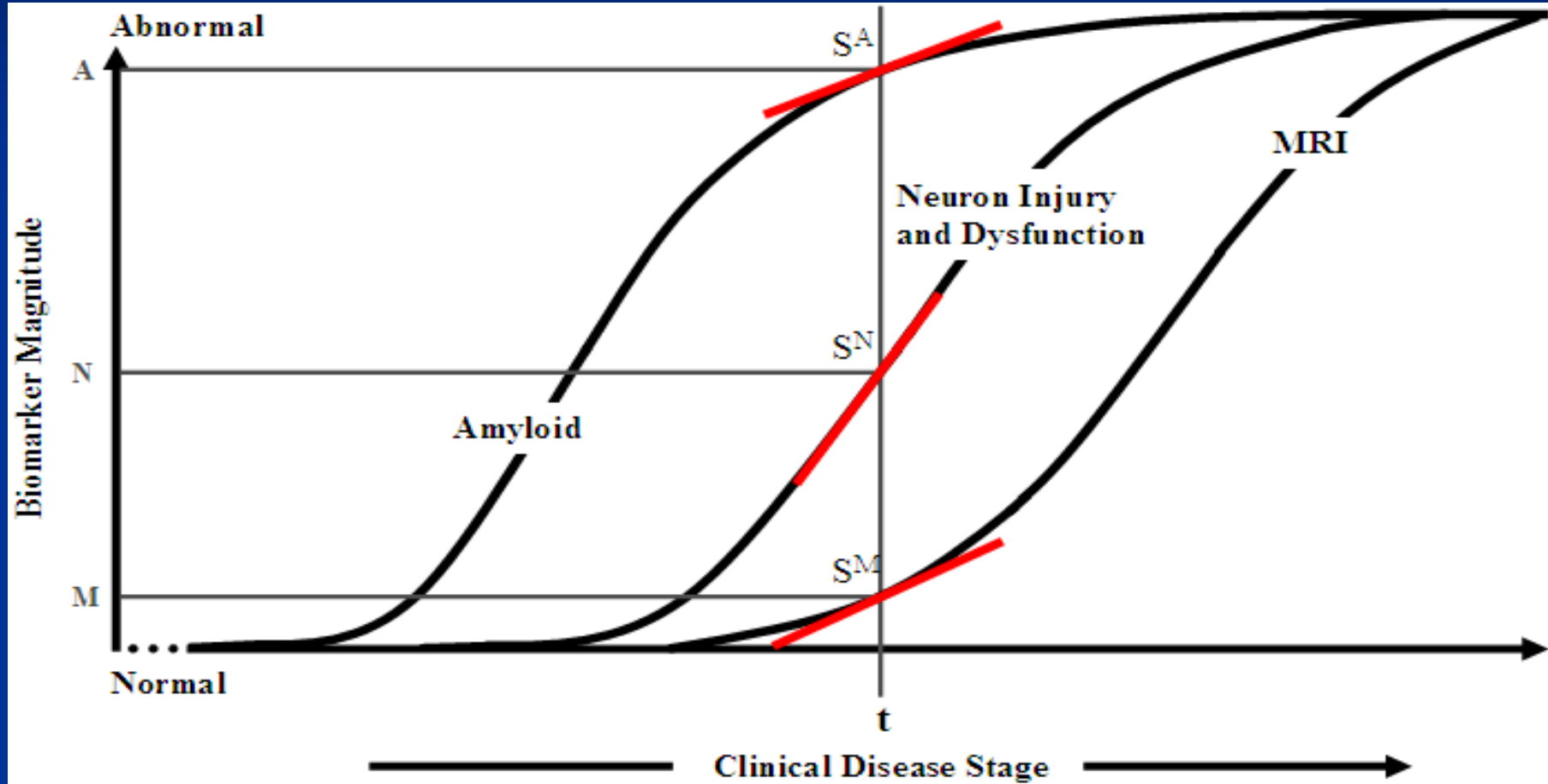


**Lancet Neurol 2010; 9: 119-28**

**Ab Amyloid = CSF Ab42 or amyloid PET imaging; Tau Mediated Neuron Injury and Dysfunction = CSF tau or FDG PET; Brain Structure = structural MRI**

# Sequence = Biomarker Dymanism Changes with Time

## Simultaneously active, not start – stop, start-stop



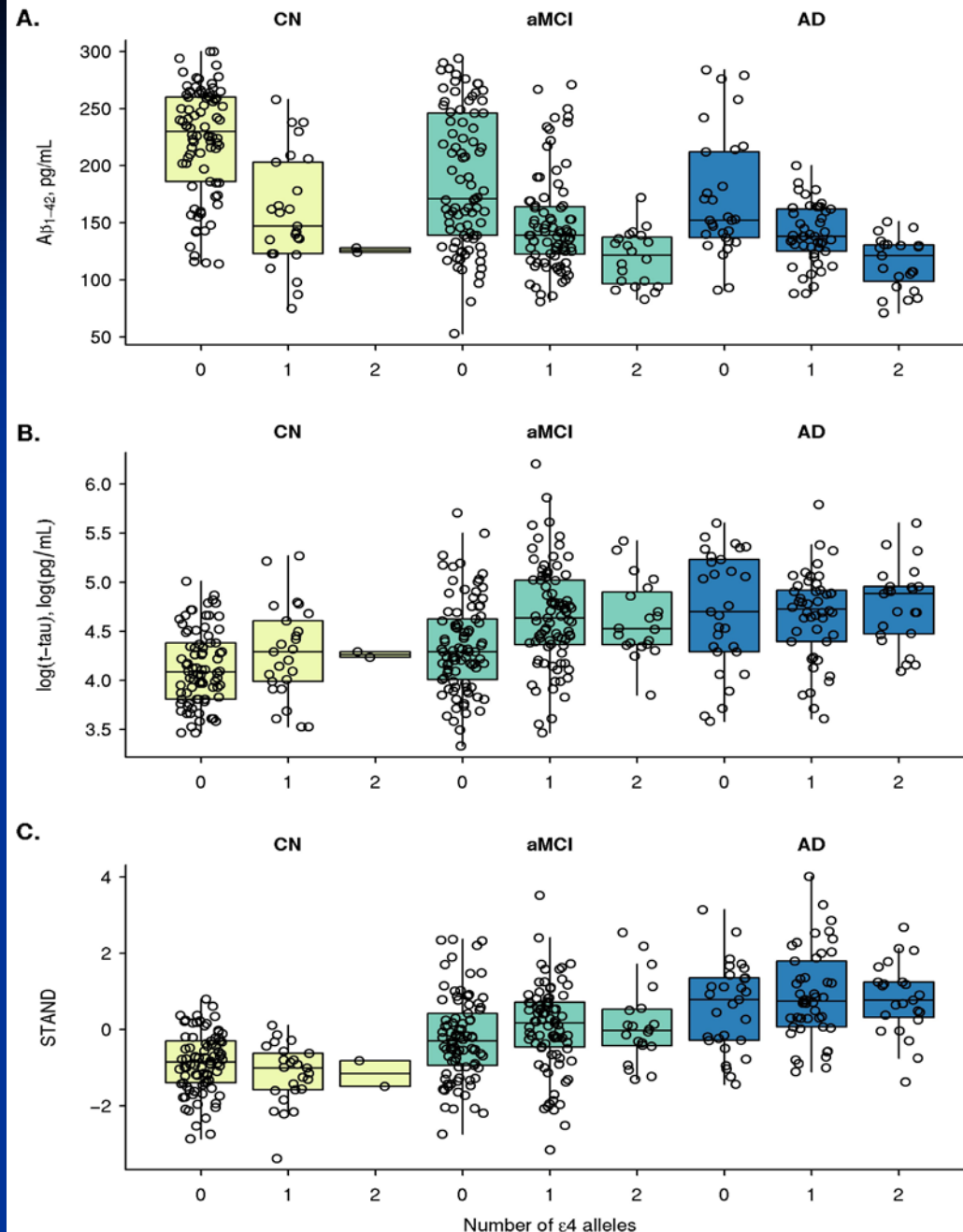
# Outline

- Temporal ordering and dynamic nature of AD biomarkers → graphical model
- **Role of MRI**
  - How is it useful?
  - Provide evidence for useful applications



# How is structural MRI not useful?

- Not an indicator of an AD-specific pathology or molecular pathway – AB amyloid biomarkers
- Not the earliest biomarker of disease – AB amyloid
- Not the earliest biomarker of neuronal pathology/injury – FDG PET or CSF tau



## Effect of APOE 4 on biomarkers

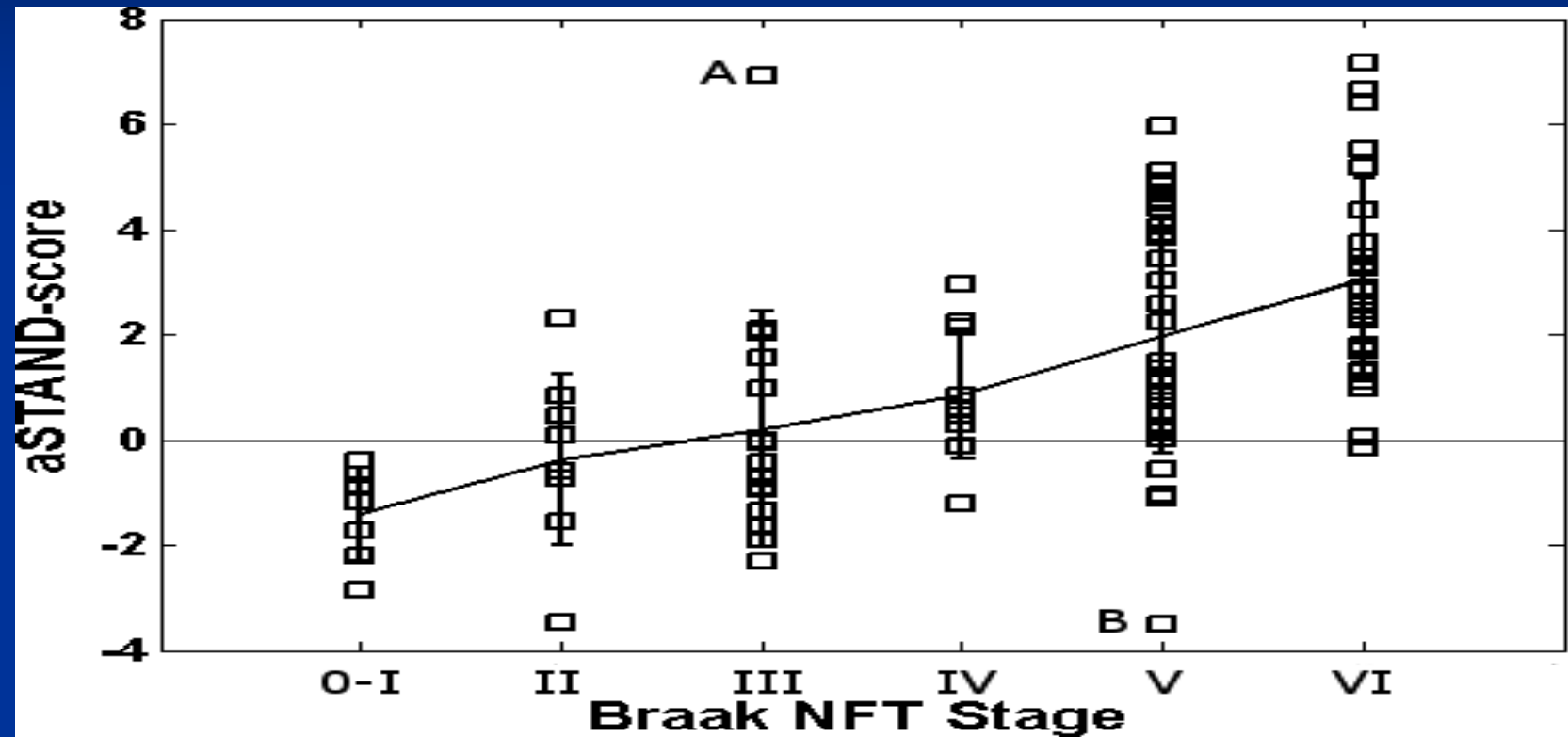
- AB chaperone

Vemuri et al, Annals of Neurology, April 2010

# How is structural MRI useful?

- Measure of downstream pathological event – not necessarily bad
- Measure of pathologic process that is closely linked with cognitive impairment – i.e. neurodegeneration
- Clinical usefulness hinges on MRI being accurate measure of stage of neurodegenerative pathology
  - cross sectional → stage
  - longitudinal → change in stage

# Antemortem MRI based Structural Abnormality Index (STAND)- Scores Correlate with Postmortem Braak Neurofibrillary Tangle Stage



Vemuri, NeuroImage 2008

# Role of MRI – clinical utility

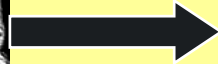
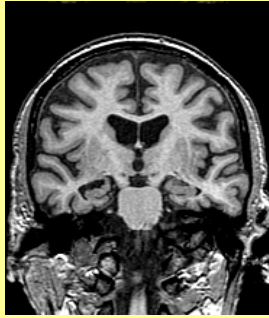
- Biomarker evidence in support of a diagnosis of AD
- Predict future cognitive course = early diagnosis
  - In MCI
  - in pre symptomatic subjects
- Measure disease progression

# Aid in clinical diagnosis

- 2 ways this can be operationalized

# STAND algorithm for Individual Diagnosis

MRI Scan



STAND Algorithm

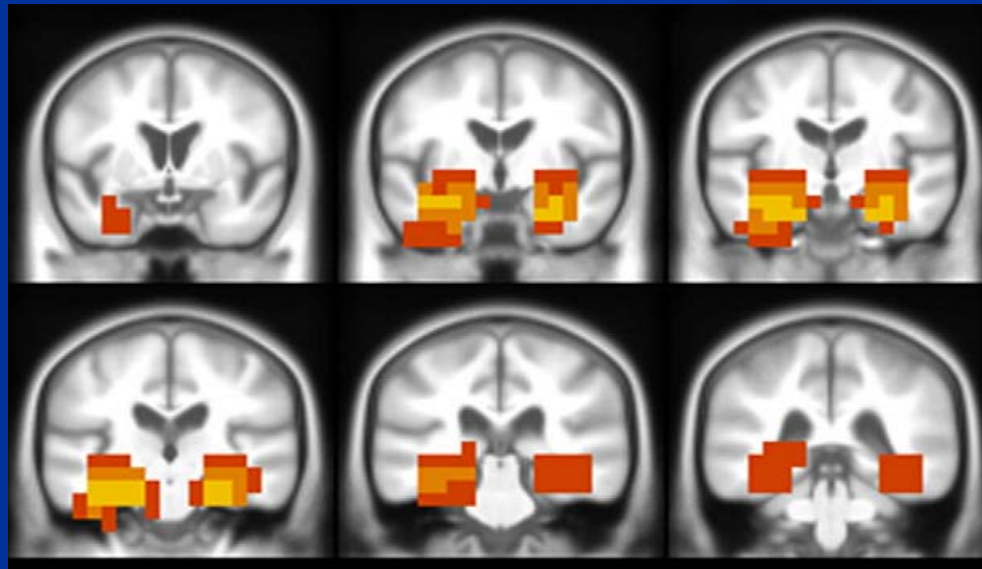


$\geq 0$  ABNORMAL

$< 0$  NORMAL

## Main Component of the STAND-Algorithm

Large library of (AD and CN) MRI scans from which regions differentiating AD from CN are detected and used to score new incoming cases.



**Vemuri et al**  
**NeuroImage 2008;**  
**39: 1186-1197**

# “Automated” AD Diagnosis\*

- Kloppel et al 2008
- Driscoll et al 2009
- Davatzikos et al 2009
- Fennema-Notestine et al 2009
- Vemuri et al 2008



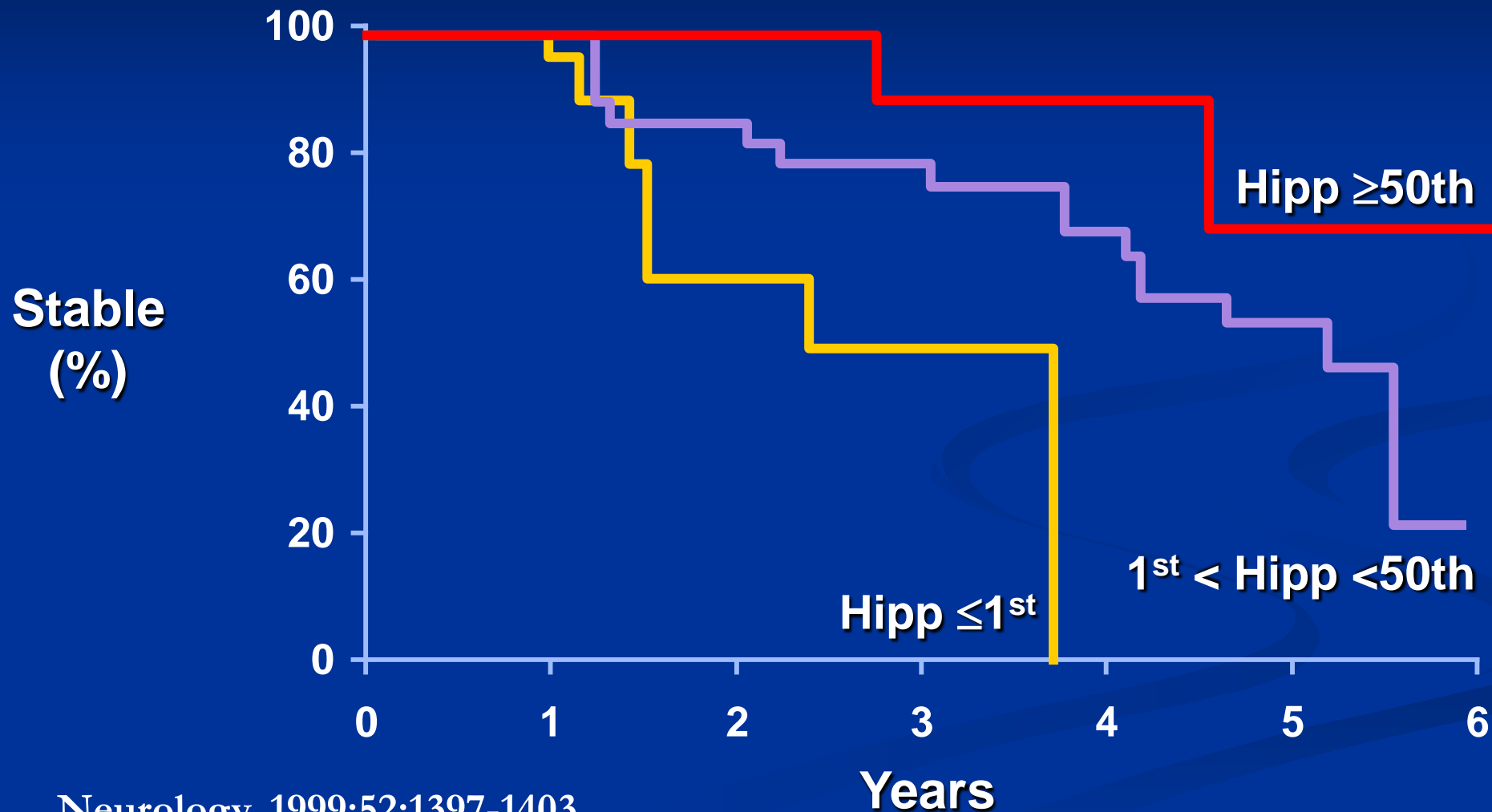
# Prediction

## ■ MCI to AD

- Apostolova, 2006
- Visser, 1999
- Devanand, 2007
- Stoub, 2005
- Convit, 2000
- Killiany, 2000
- Dickerson, 2001
- Risacher, 2009 #6500

## ■ Pre symptomatic subjects

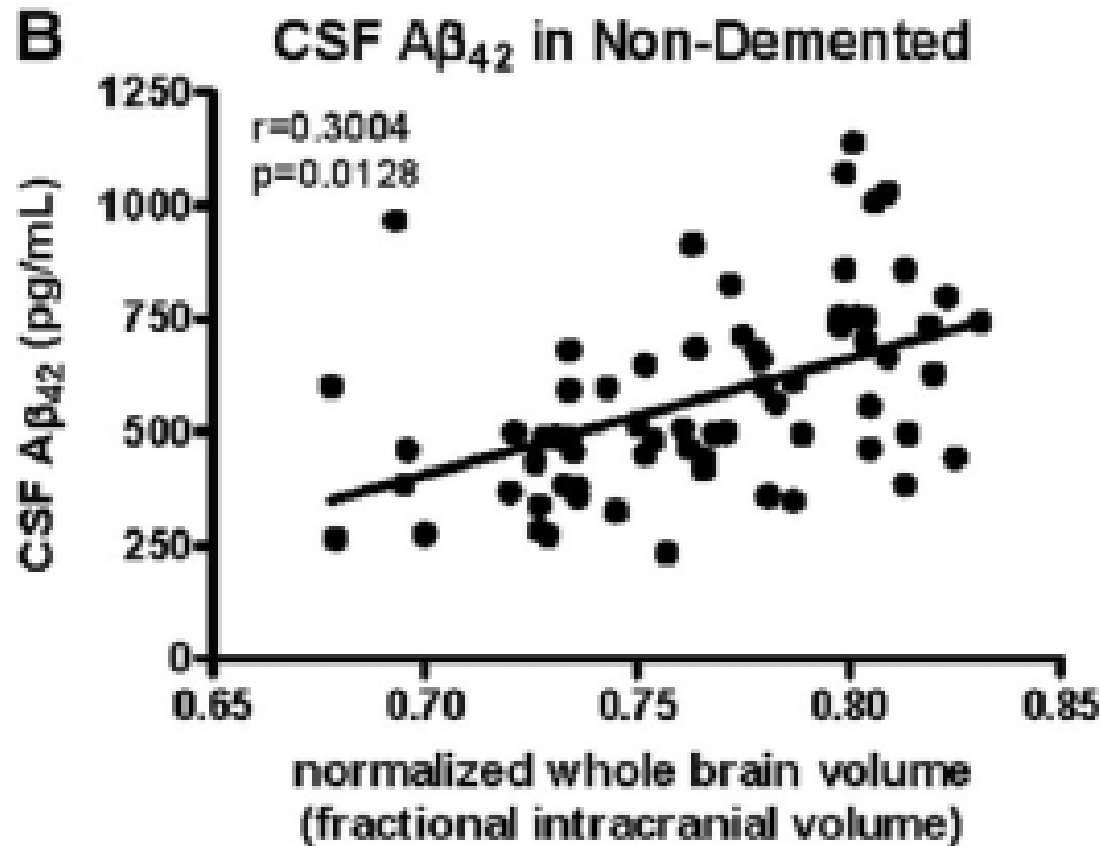
## Baseline adjusted hippocampal volume: relationship to progression from MCI to AD



Neurology, 1999;52:1397-1403

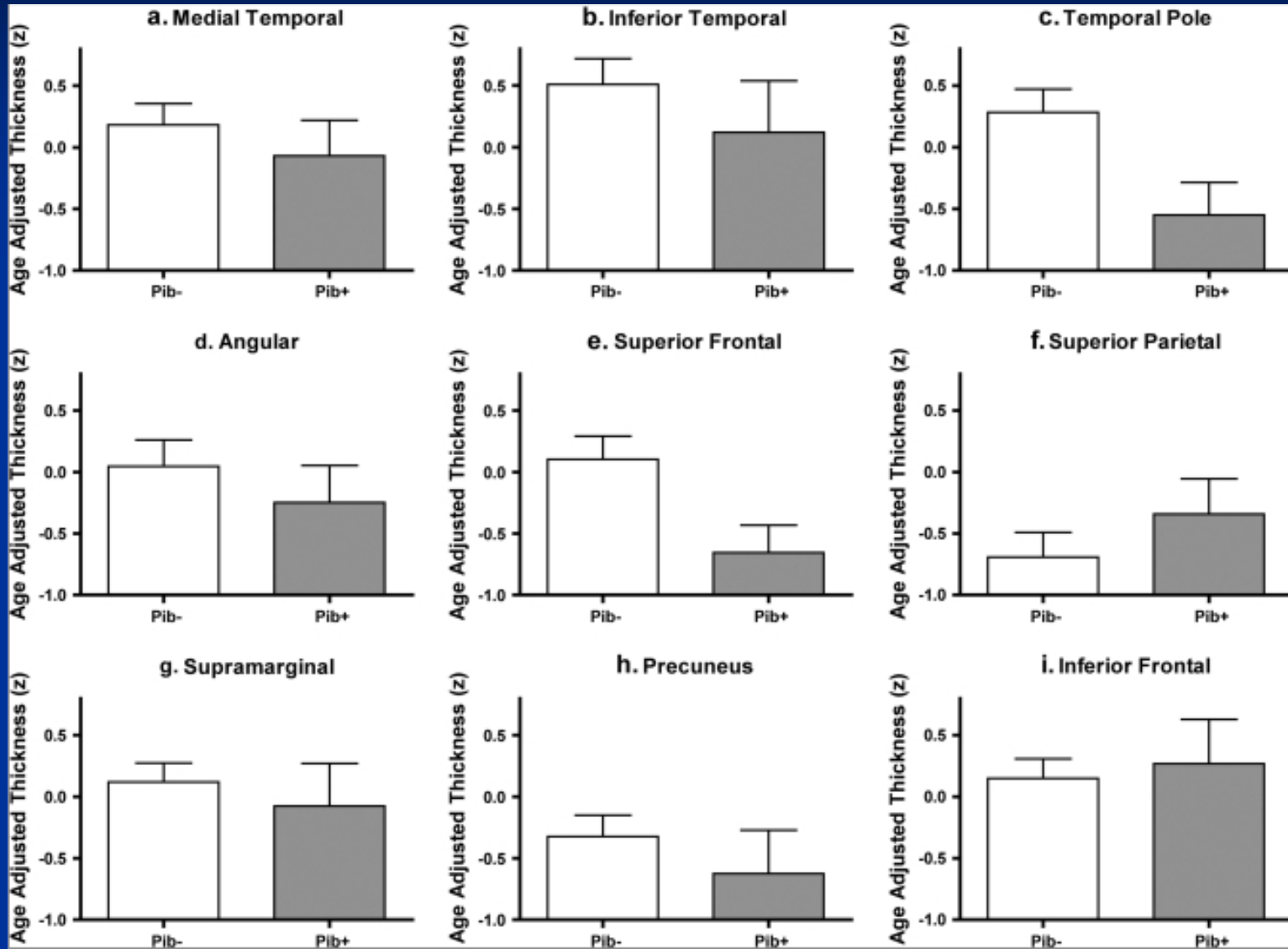
# CSF A $\beta$ and decreased brain volume in cognitively normal elderly (CDR 0)

Fagan et al Annals 2009



# Cortical Thickness in PIB + vs – control elderly

## Dickerson et al Cereb Cortex 2009



# Measure of Disease Progression



# ADNI: sample size per arm to detect a 25% reduction in rate (0 -12 months) of decline in AD

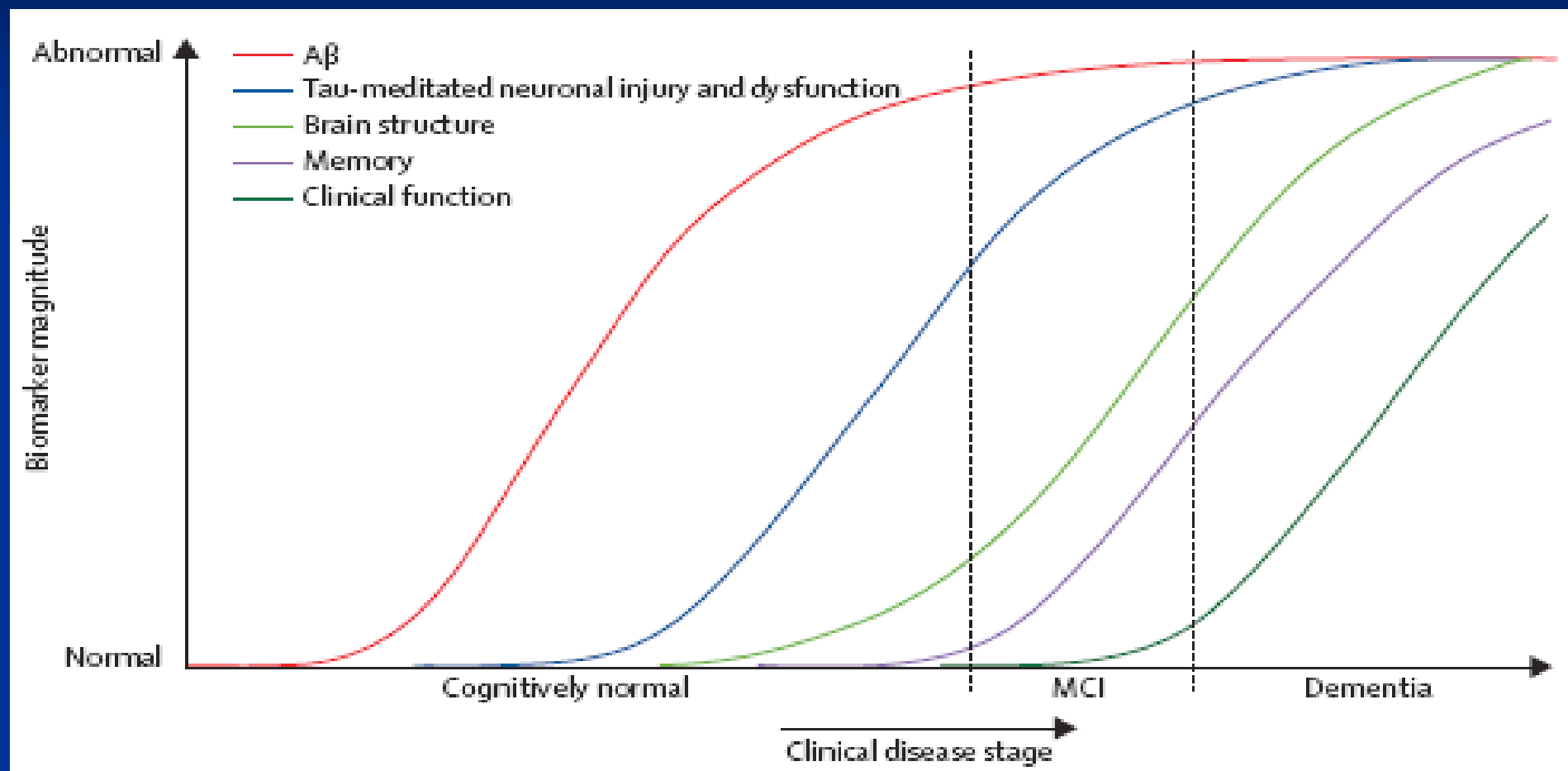
MRI,FDG PET, cognitive tests, in AD, n=30

Lab	Modality	Variable	SS/arm					
	Cog.	MMSE	703					
	Cog.	ADAS-Cog	514					
Foster	PET	Hypometab 2	508					
	Cog.	CDR SOB	495					
Jagust	PET	ROI-avg	396					
Schuff- FS	MRI	Ventricles	95					
Reiman	PET	CV - fROI	91					
Thompson	MRI	CV % change	53					
Fox	MRI	BSI% change	50					

# Summary: Biomarker-based disease staging

- Modeling provides a framework for hypothesis testing that relates temporal changes in AD biomarkers with clinical disease stage and with each other
- Specific details of model will undoubtedly change
- However, certain principles will stand up
  - Biomarkers measure specific aspects of AD path
  - Temporally ordered: amyloid => neuronal path => cognition
  - Temporal ordering: both onset and ceiling
  - Non linear function of time
  - Combination of biomarkers needed for comprehensive staging

# Structural MRI: diagnosis, prediction, measure progression



**Lancet Neurol 2010; 9: 119-28**

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# Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade

Lancet Neurology 2010; 9: 119-28

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