MRI Biomarkers form Bench to Bedside and Back!

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Disclosure: Data Monitoring Safety Board Member; Takeda Global Research & Development Center, Inc., Pfizer and Jannsen Alzheimer's Immunotherapy

Biomarker versus Surrogate Marker

- Biomarker: Laboratory measurement that reflects the activity of a disease process
- Surrogate marker: Laboratory measurement that is used in therapeutic trials as a substitute for a clinically meaningful endpoint.

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Katz et al. *NeuroRx* 2004

Ideal Biomarker for Alzheimer's Disease

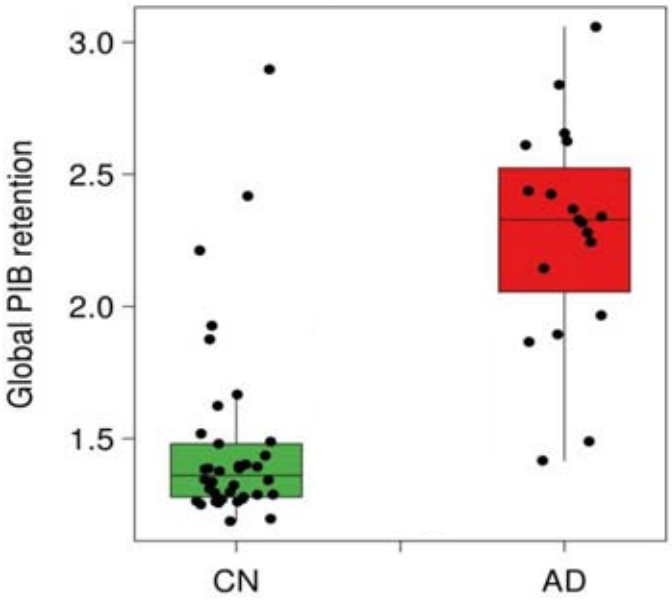
- Accurate: Sensitivity and specificity to the hallmarks of Alzheimer-related pathology
- Precise: Test-retest reproducibility longitudinal tracking of progression
- Surrogate marker in therapeutic trials targeting disease-specific pathology

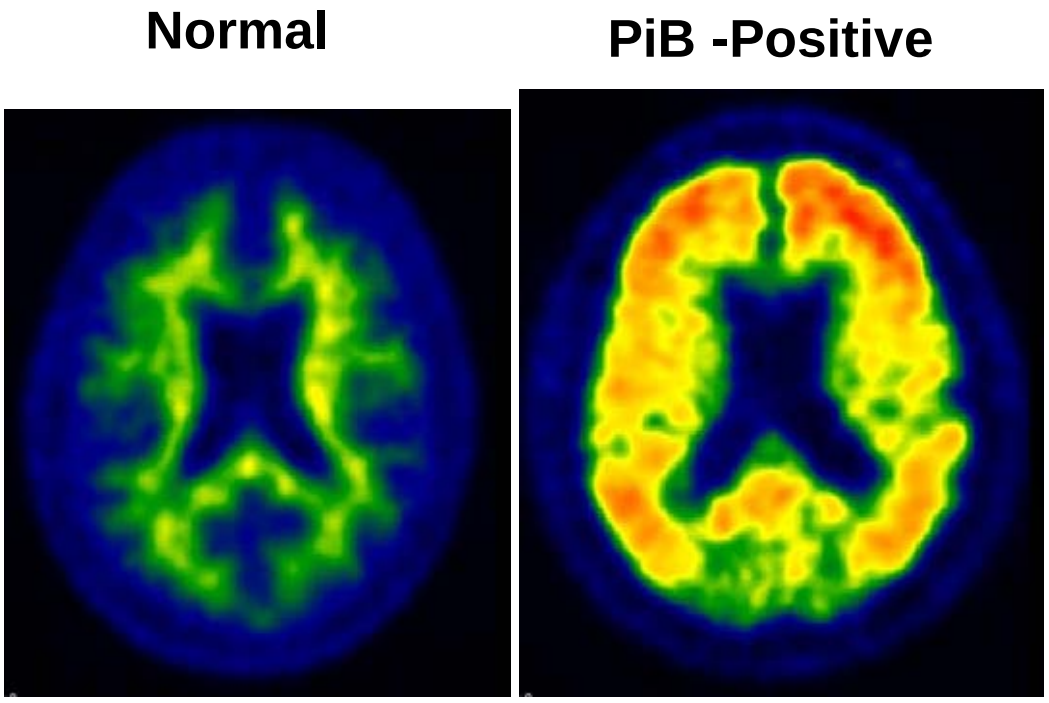
Imaging Biomarkers of AD

- Structural MRI: *macro*structure
- ?Ç Amyloid imaging PET: amyloid load
- FDG-PET: glucose metabolism
- ^{1}H MRS: biochemistry
- DTI: *micro*structure
- ASL-MRI: perfusion
- fMRI: function

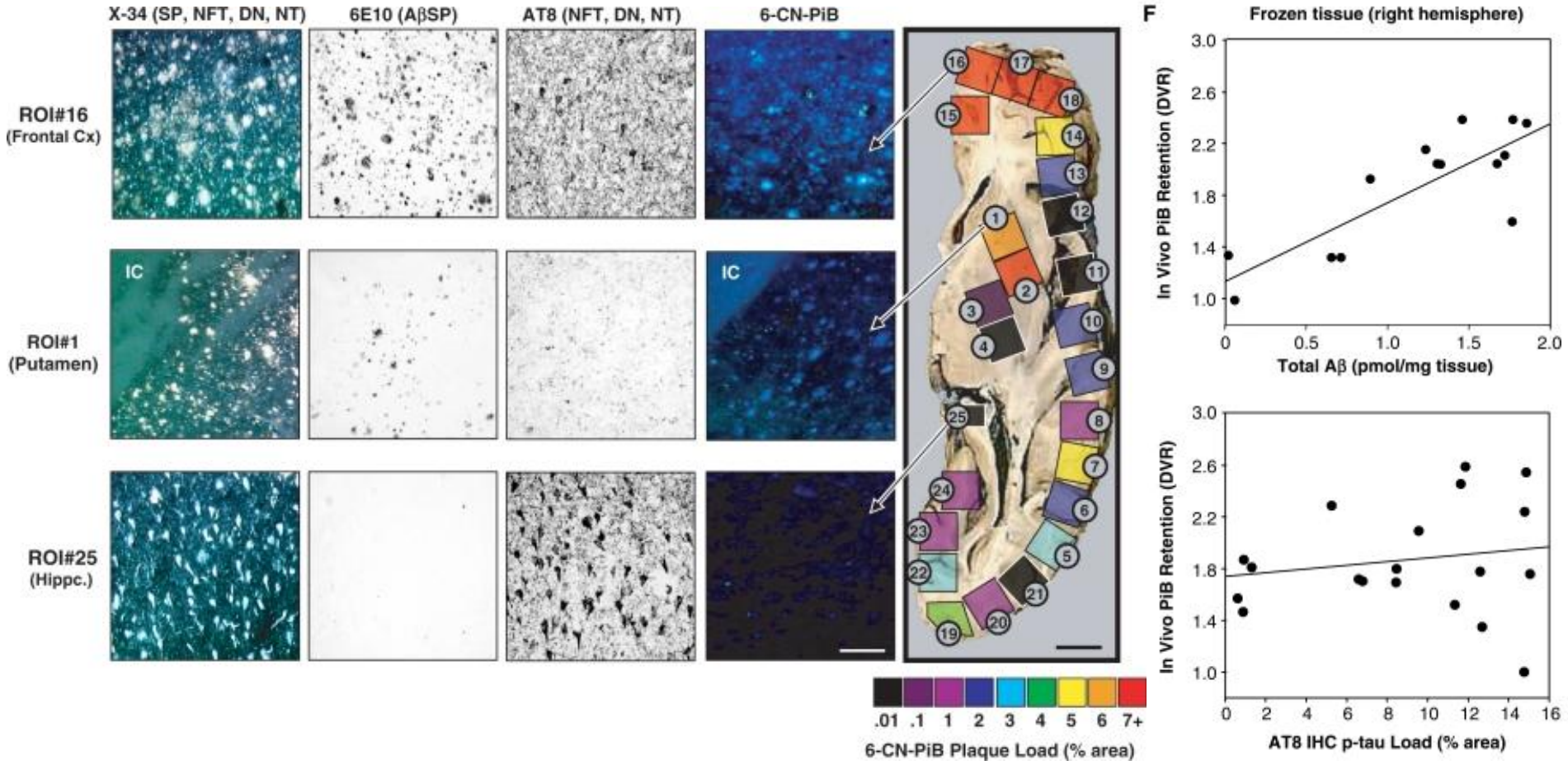
Imaging biomarkers associated with a specific aspect of Alzheimer's disease -related pathology

Case-control studies with autopsy confirmation





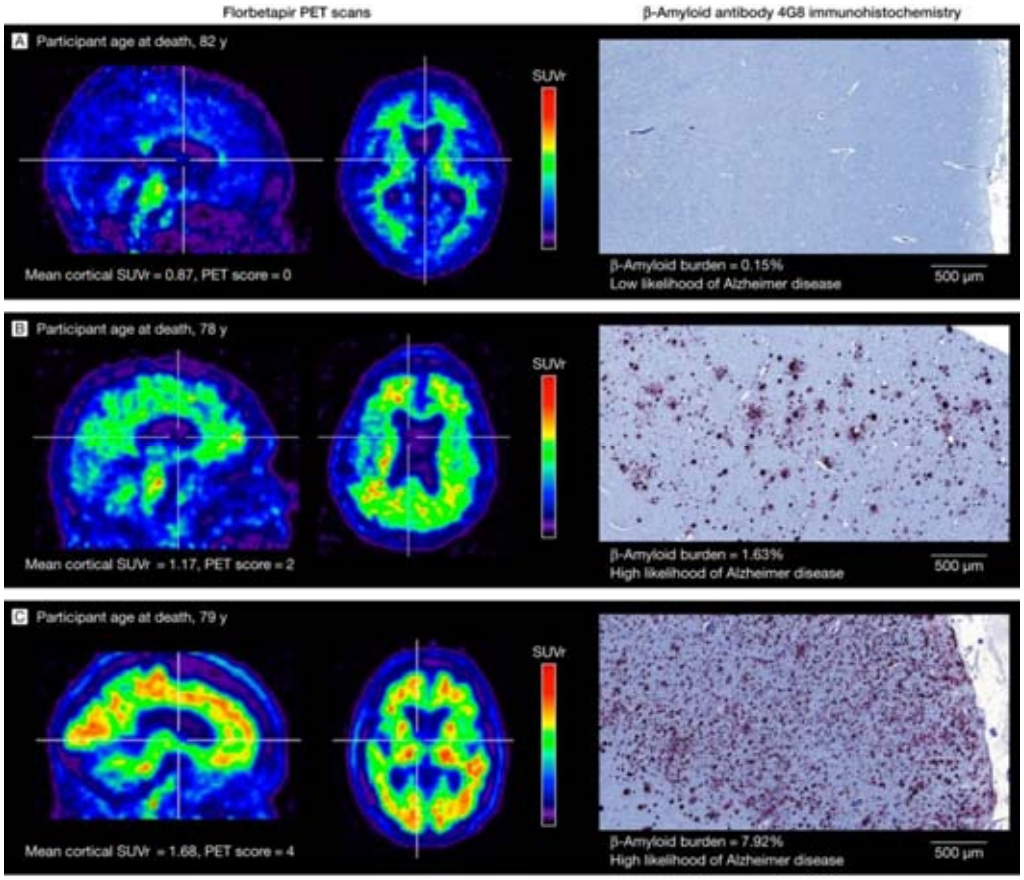
?áAmyloid PET Imaging with 11C-PiB



Ikonomovic et. al. *Brain* 2008

Amyloid PET Imaging with 18F-Ligands

Florbetapir F 18 (18F-AV-45), 18F-flutemetamol (18F-GE067), florbetaben (18F-BAY94-9172), and 18F-FDDNP (Half life: 110 min)



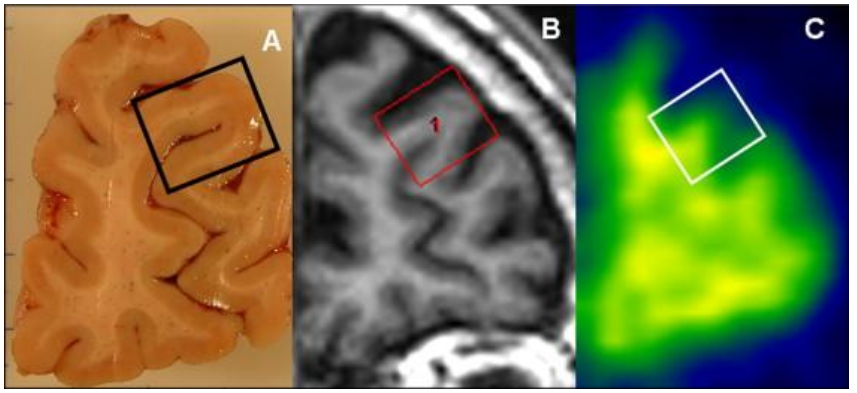
Florbetapir F 18

Sensitivity = 93%
Specificity = 100%

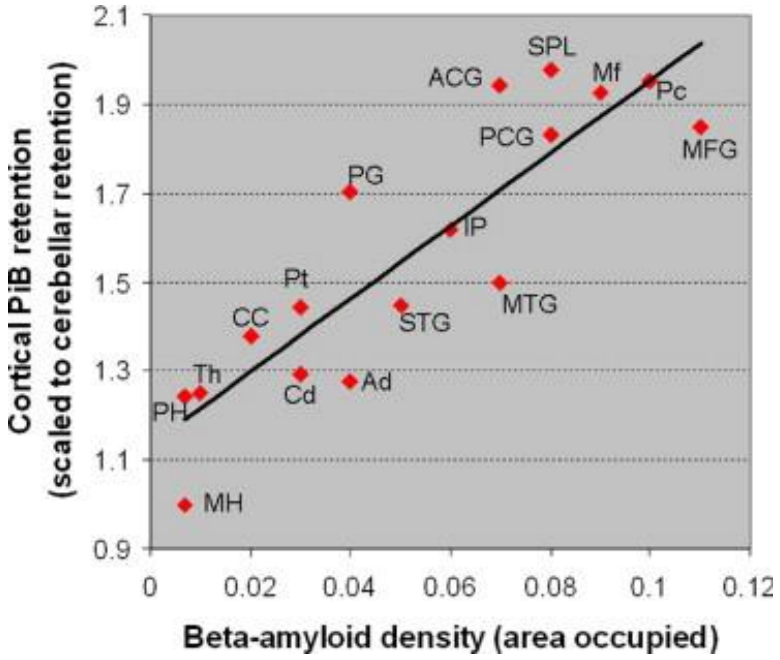
MAYO CLINIC

Clark et. al. *JAMA* 2011

Antemortem Amyloid Imaging with PET and Postmortem Pathologic Correlations in DLB

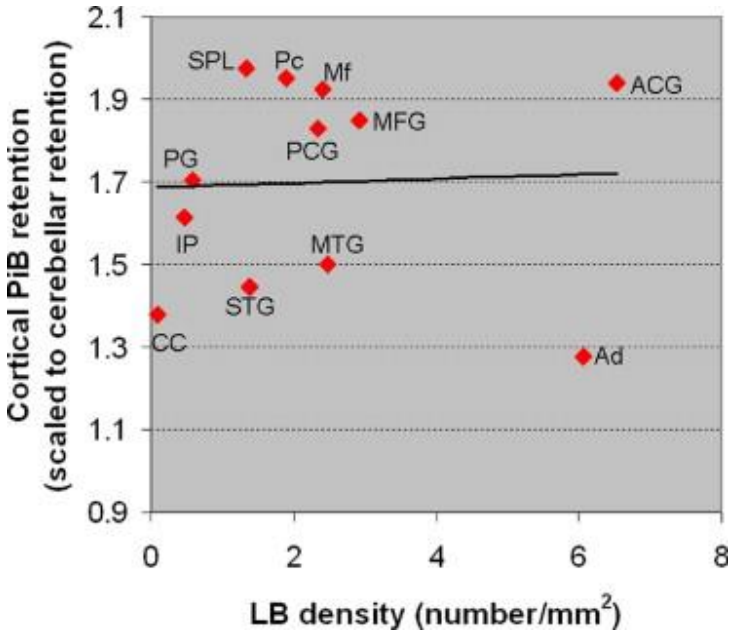


A density



($r = 0.899$; $p < 0.0001$)

Lewy body density



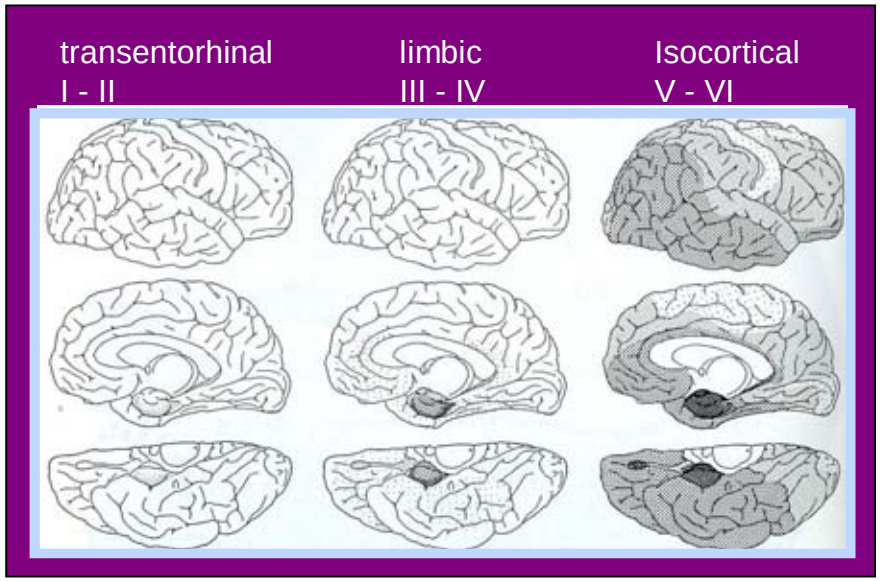
($r = 0.13$; $p = 0.66$)

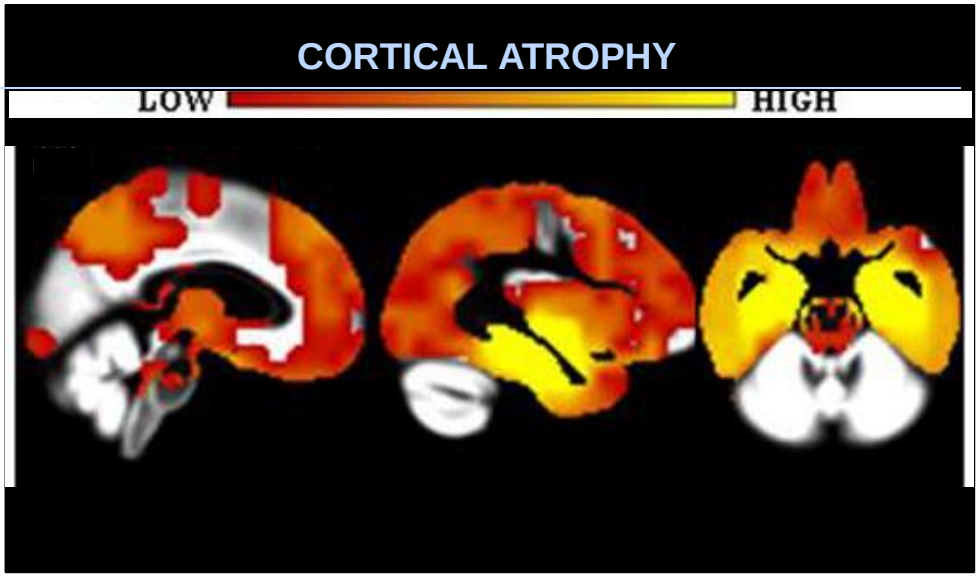
MAYO CLINIC

Kantarci et al. *Neurobiology of Aging 2012b*

Structural MRI:

Neurofibrillary Tangle Pathology is Associated with Atrophy on Volumetric MRI in AD



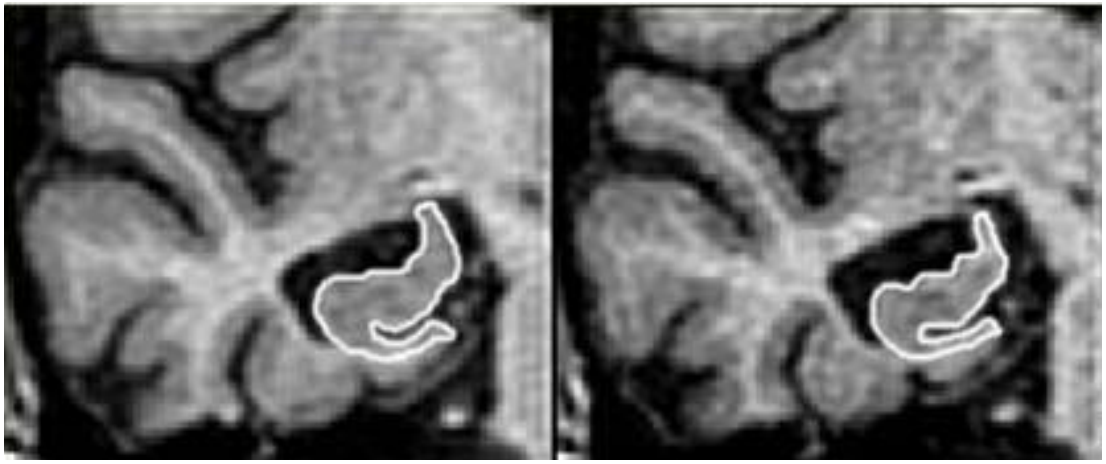


MAYO CLINIC

Braak and Braak *Acta Neuropathol* 1991
Vemuri et al. *Neuroimage* 2008; Whitwell et al. *Neurology* 2008

Structural MRI: Hippocampal Volumes
A Biomarker for structural integrity of hippocampal neurons

Baseline **Follow-up**



<u>Range of Normal – AD pathology:</u>

Hippocampal volumes on MRI correlate with the neurofibrillary tangle pathology and hippocampal neuronal density at autopsy

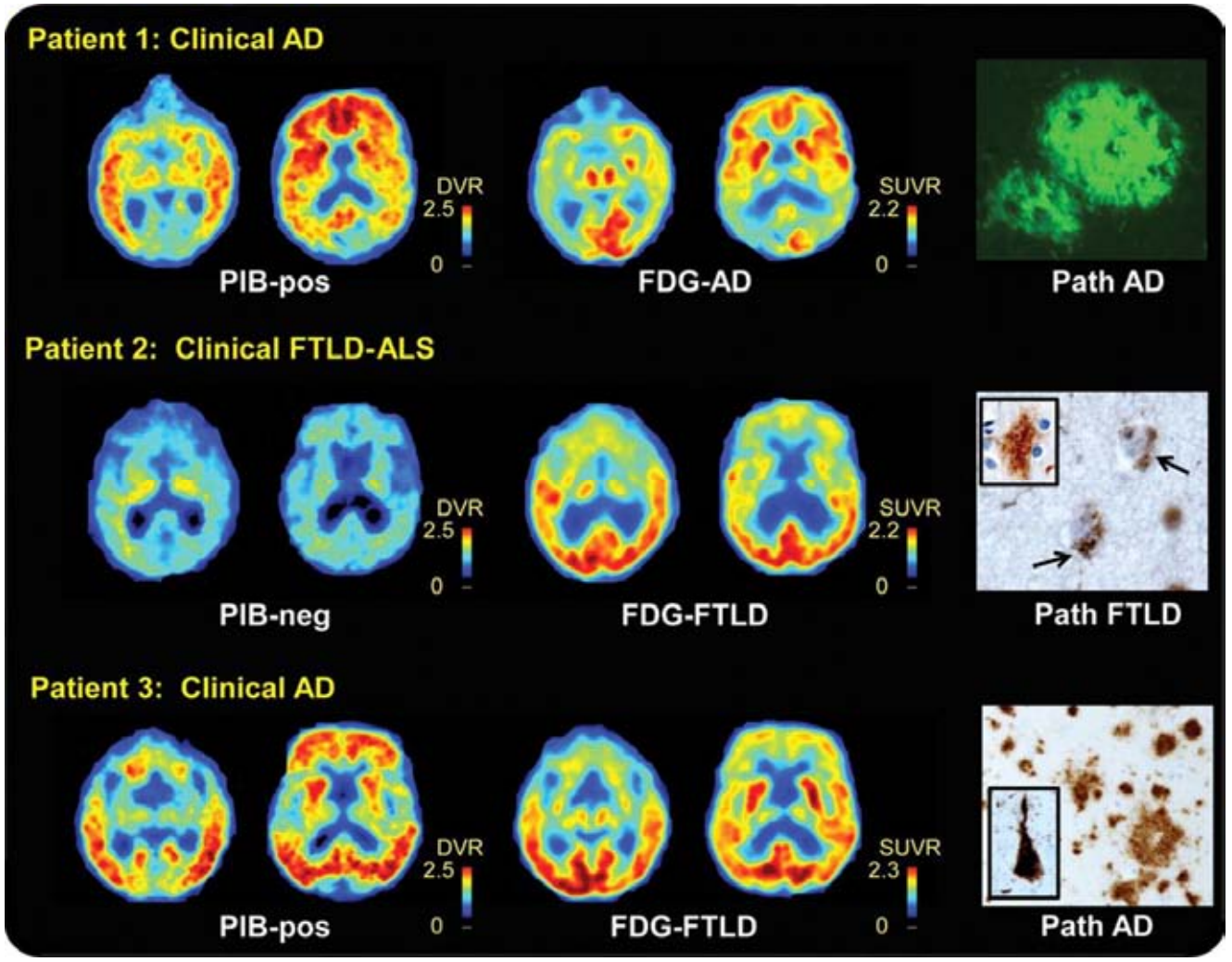
MAYO CLINIC

Jack et al. *Neurology 2002;* Bobinski et al. *J of Neurol Exp Neuropathol 1997*

Imaging biomarkers of Alzheimer's Disease

- Differential diagnosis
- Early diagnosis
- Tracking disease progression
- Treatment planning and assessment of efficacy

Differential diagnosis of AD and FTLD



Sensitivity: 89%
Specificity: 83%

Overall classification accuracy in autopsy-confirmed cases: 97%

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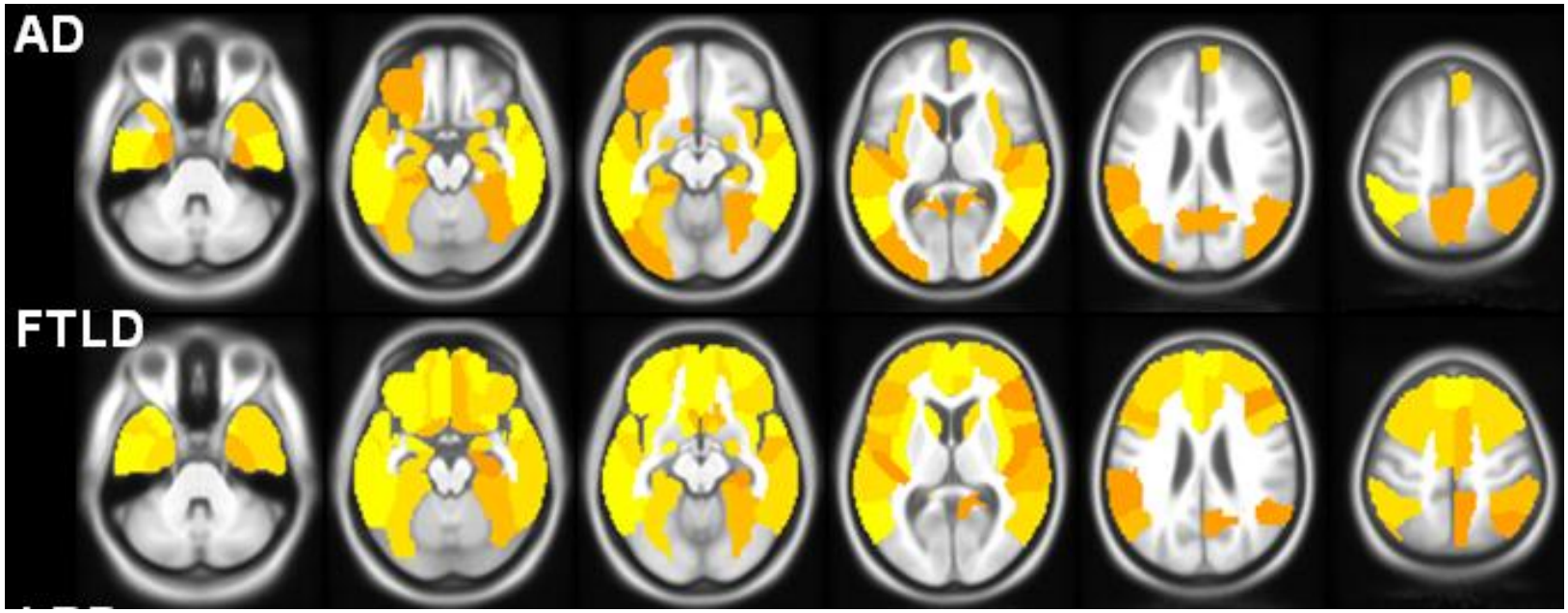
Rabinovici et. al. *Neurology* 2011

Structural MRI differences among autopsy confirmed AD and FTLD

N=37

N=27



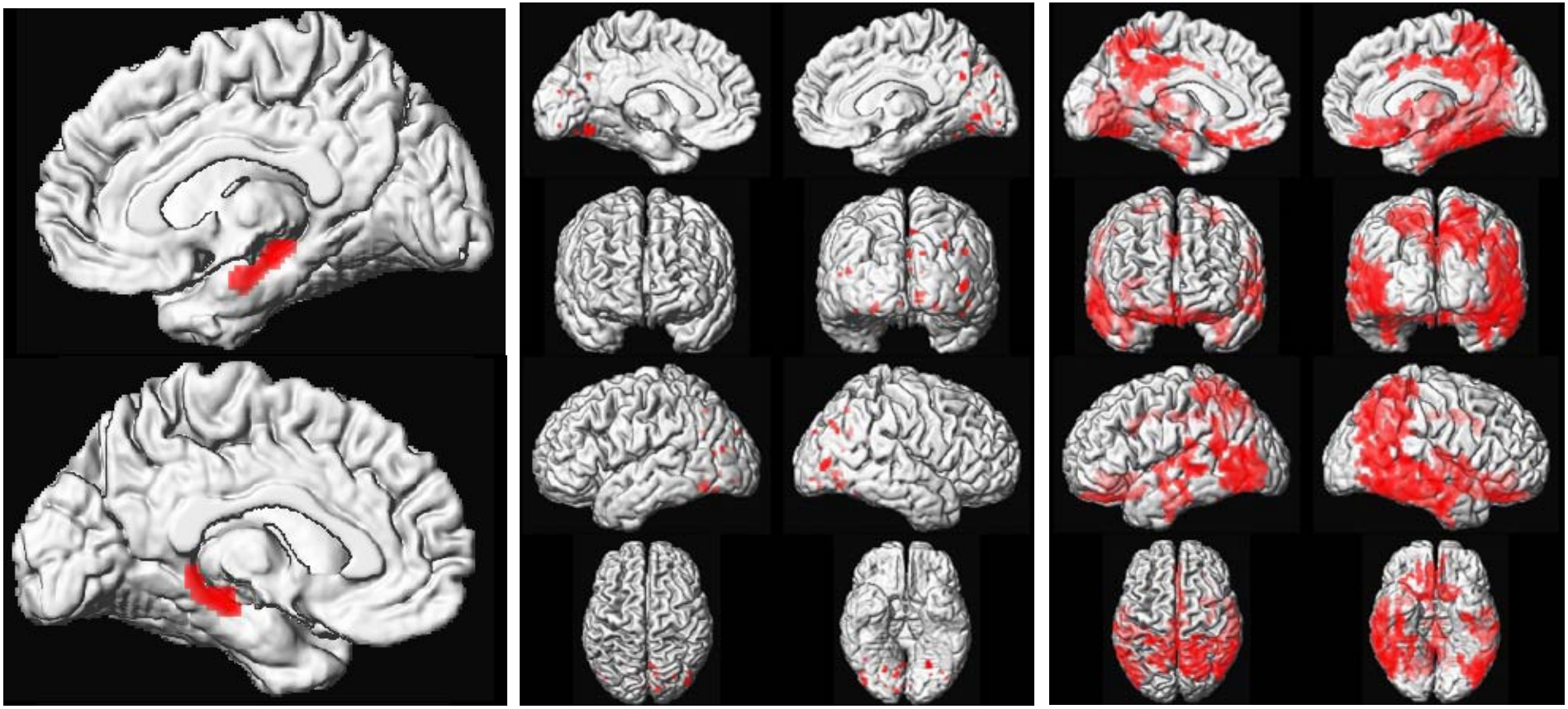
Vemuri et al. *Alzheimer's and Dementia* 2009

Alzheimer's Disease (AD) and Dementia with Lewy Bodies (DLB)

- DLB is the second most common cause of neurodegenerative dementia after Alzheimer's disease (AD).
- Many patients with DLB have a varying degree of AD in addition to Lewy body pathology.
- Imaging markers that predict the contribution of AD and pathology to the dementia syndrome in DLB would have an important role:
  - Treatment decisions
  - Responsiveness to disease-specific treatments

Differential Diagnosis of Alzheimer's Disease and Dementia with Lewy Bodies using Multi-modality Imaging

Atrophy (MRI) Hypometabolism (FDG PET) A? load (^{11}C PiB PET)

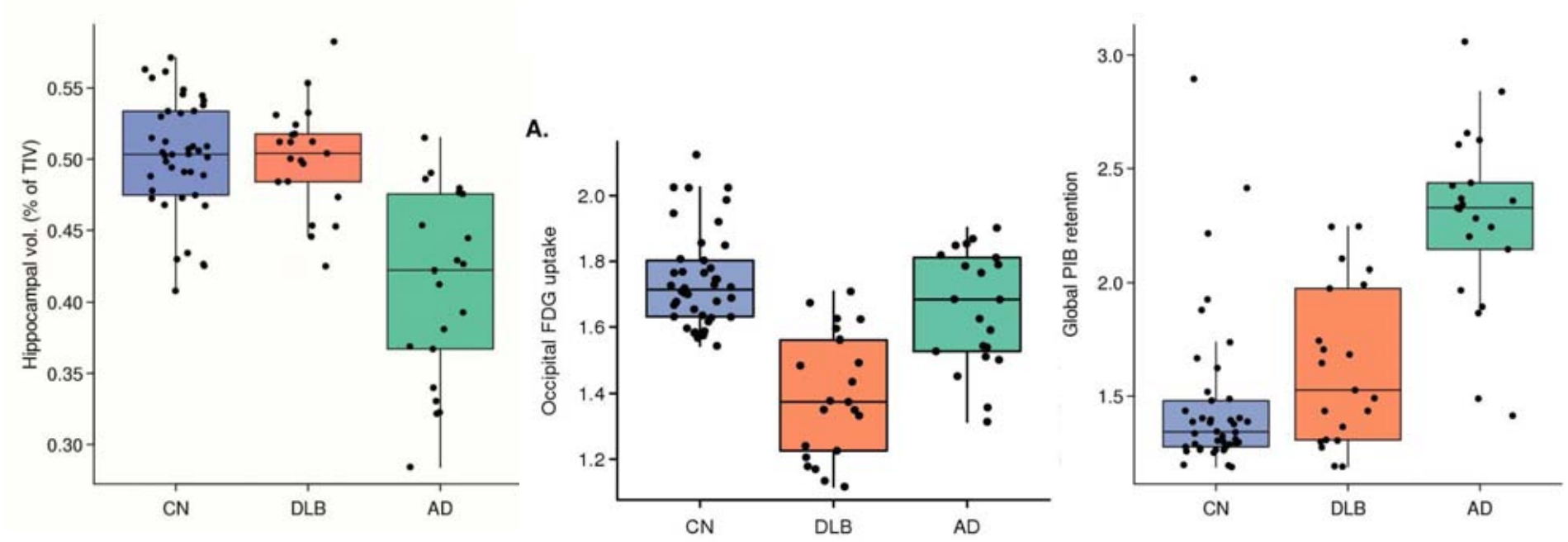


AD > DLB **DLB > AD** **AD > DLB**

Kantarci et al. *Neurobiology of Aging 2012a*

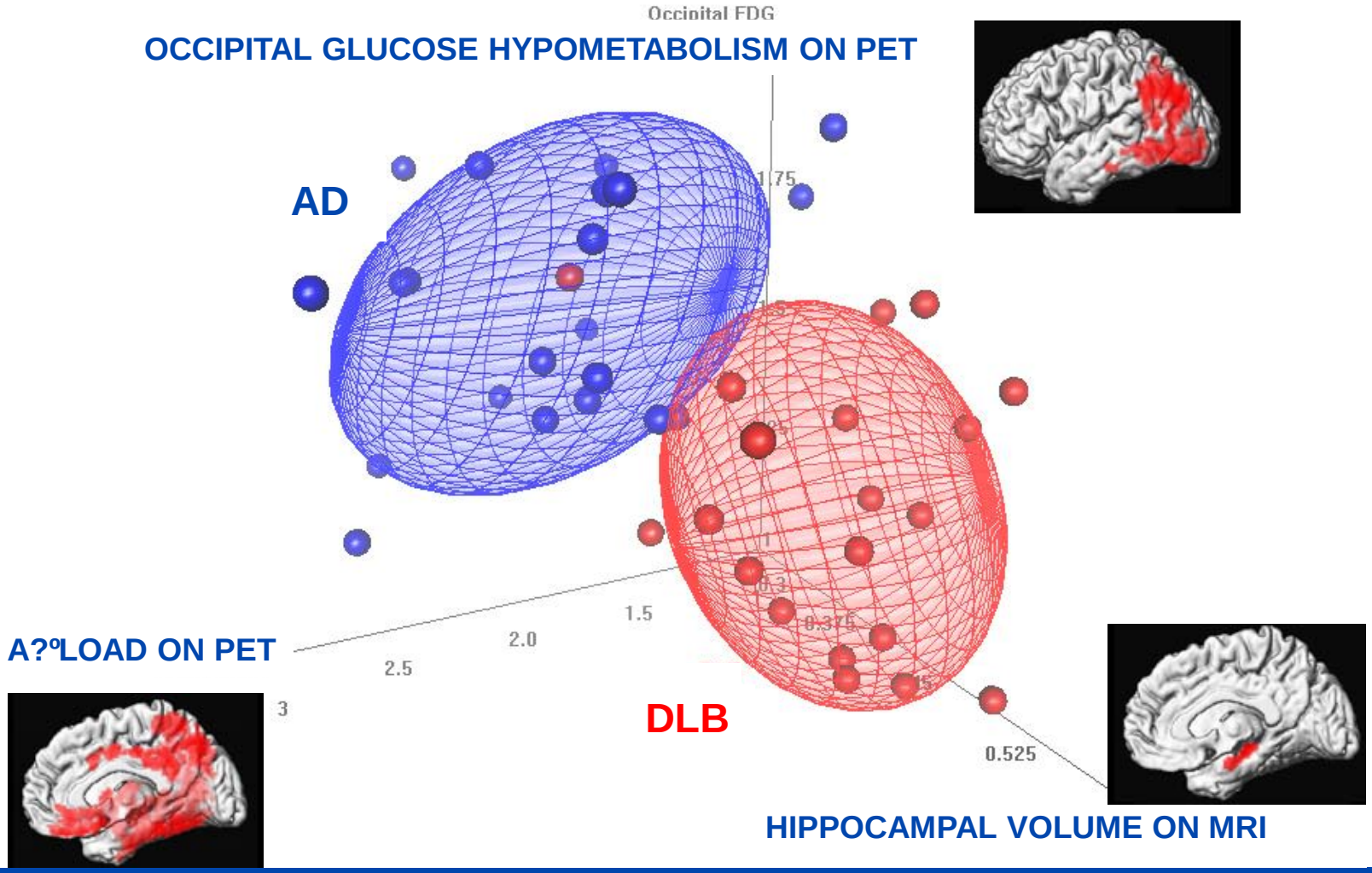
Differential Diagnosis of Alzheimer's Disease and Dementia with Lewy Bodies using Multi-modality Imaging

Atrophy (MRI) **Hypometabolism (FDG PET)** **A?doad (^{11}C PiB PET)**



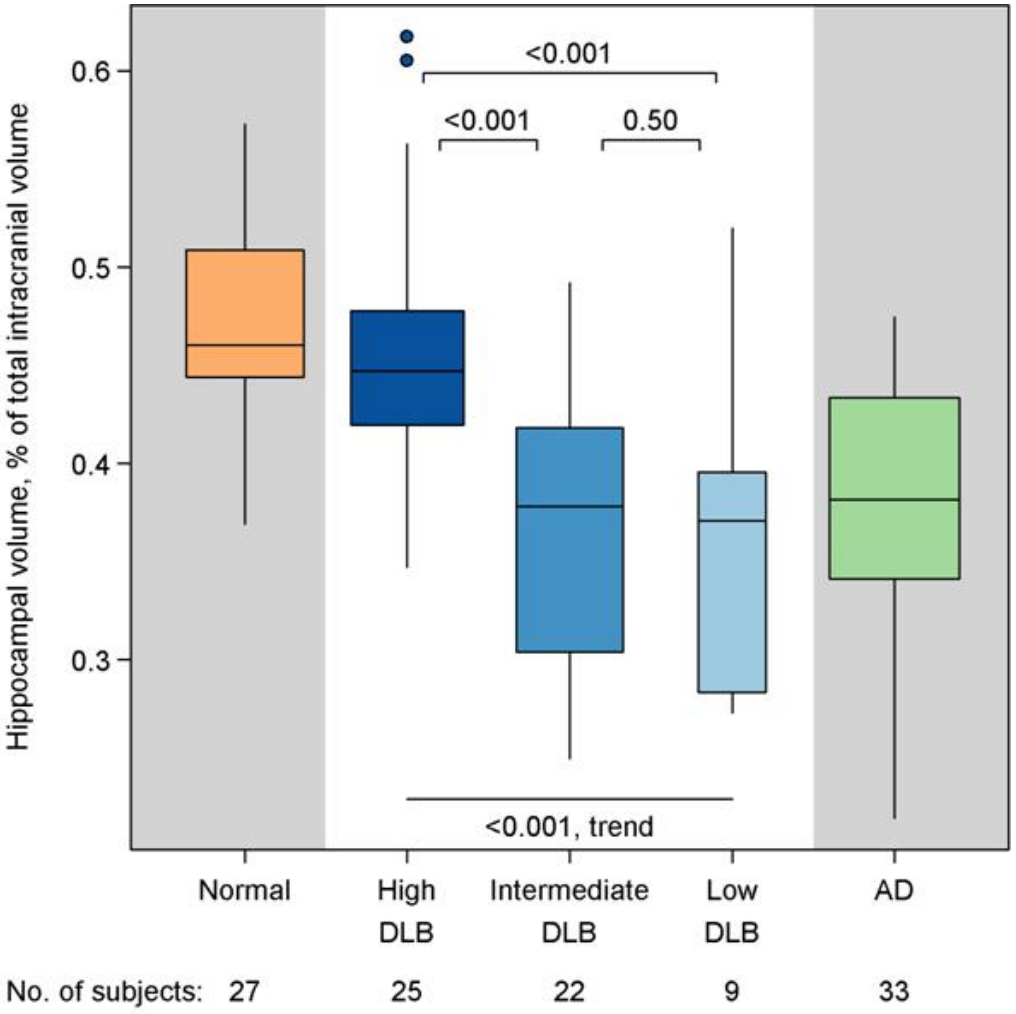
Kantarci et al. *Neurobiology of Aging 2012a*

Multimodality Imaging Markers Distinguishing DLB and AD AUROC=0.98



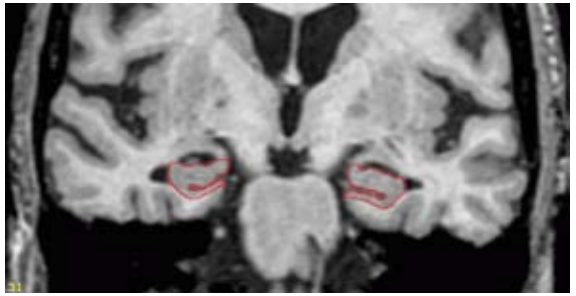
Kantarci et al. *Neurobiology of Aging 2012a*

Hippocampal Volumes and Pathologic Classification of DLB



Smaller hippocampal volumes were associated with a higher Braak NFT stage

(r_p = ?9.63; p<0.001)



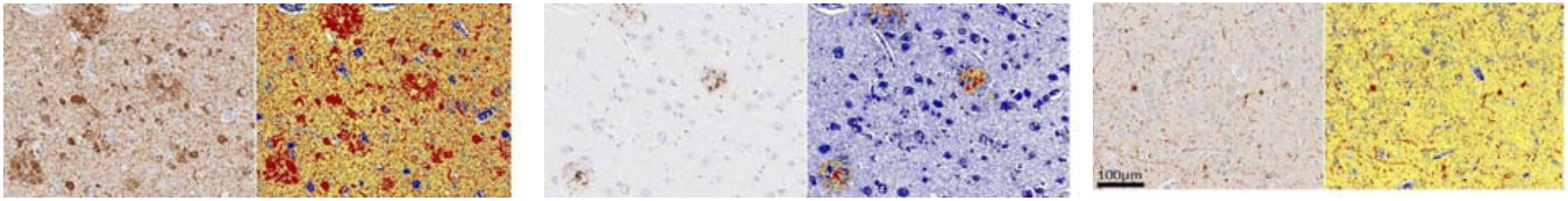
Kantarci et al. *Neurology 2012*

Hippocampal Volumes and protein deposits in AD and DLB (n=72)

Phospho- tau

?aAmyloid

?•Synuclein



percent burden= % area of (red) positivity out of the total stained annotated area

	Rho (95% CI)	Univariate P-value	Multivariate P-value
Phospho-tau burden	-0.34 (-0.53, -0.10)	0.005	0.05
?ÑAmyloid burden	-0.31 (-0.51, -0.08)	0.009	0.13
?=Synuclein burden	-0.15 (-0.038, 0.09)	0.22	

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Murray et al. *Neurology in press*

Imaging biomarkers of Alzheimer's Disease

- Differential diagnosis
- Early diagnosis
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- Treatment planning and assessment of efficacy

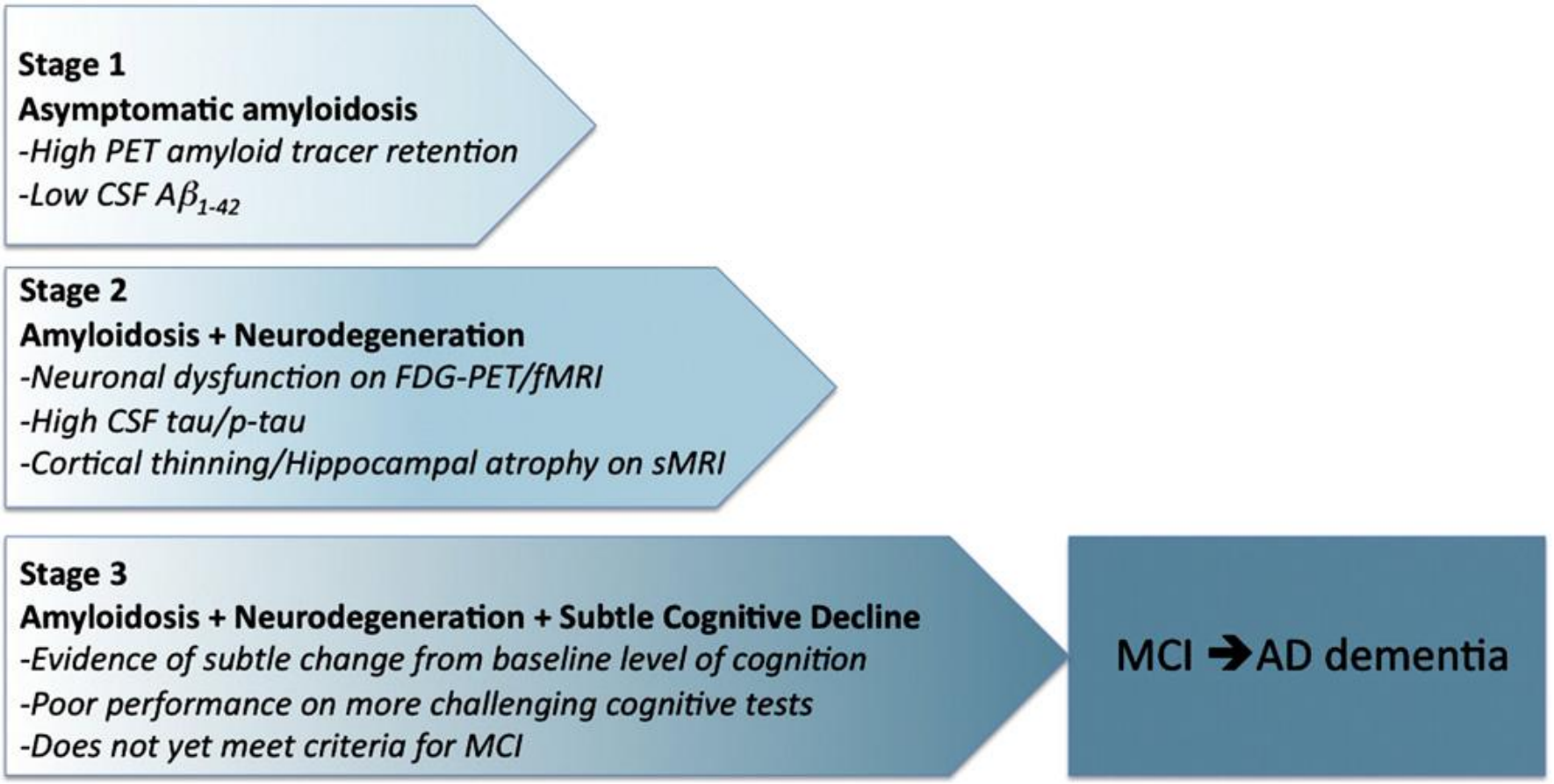
National Institute on Aging and the Alzheimer's Association Workgroup on Diagnostic Guidelines for Alzheimer's Disease

- Preclinical Stages of AD: Biomarker positivity-based staging for research purposes
- Mild Cognitive Impairment: Biomarkers support the likelihood that mild cognitive impairment syndrome is due to the pathophysiological processes of AD
- Alzheimer's Disease: Biomarkers support the likelihood that the pathophysiological processes of AD underlies dementia

Detecting preclinical AD pathology with ?pAmyloid PET: Preclinical AD in the community

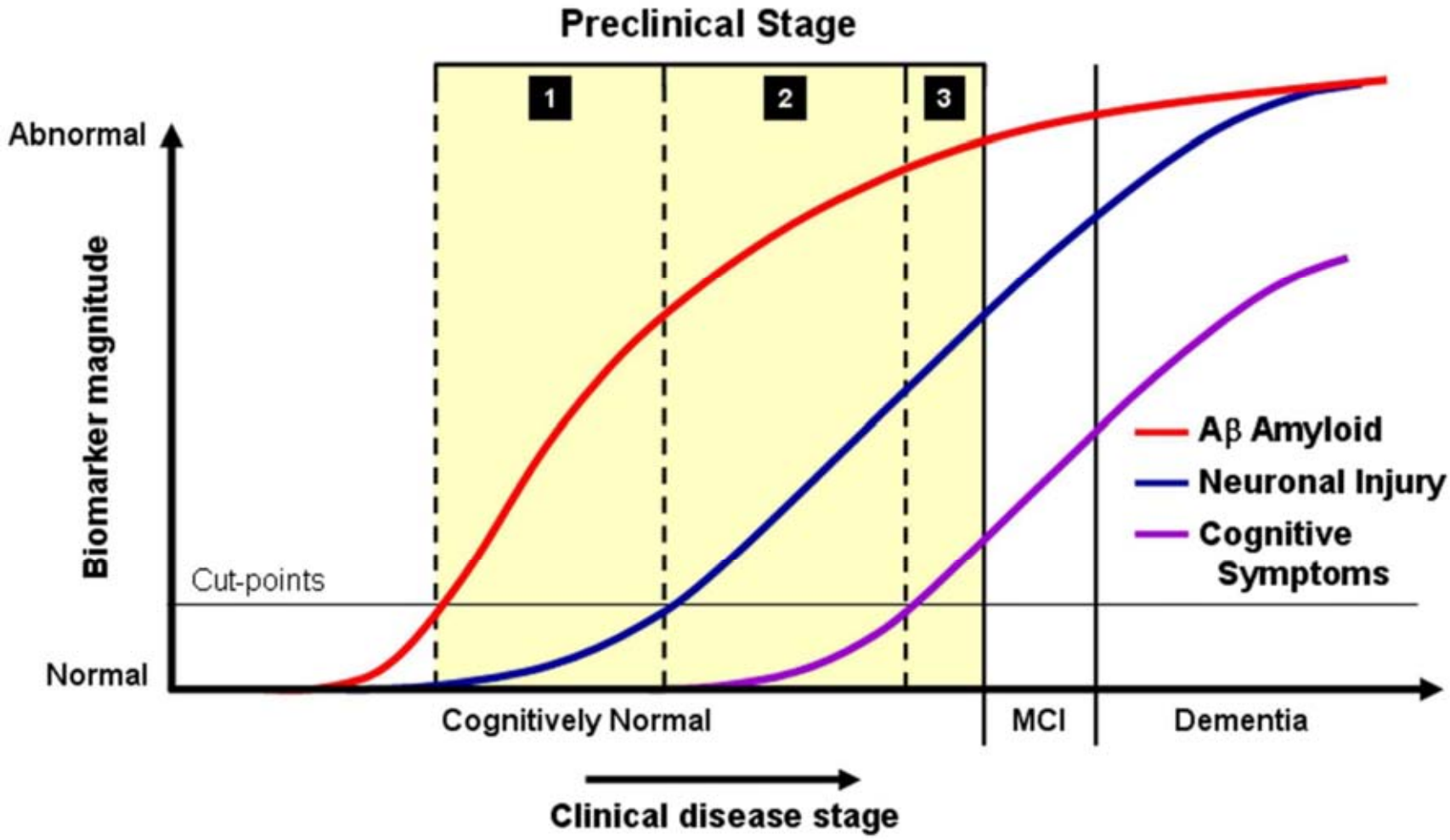
	N	Age	% ?AAmyloid Positive
Aizenstein et al. 2008	43	74	**21%**
Morris et al. 2010	241	75	**26%**
Jagust et al. 2010	19	78	**47%**
Pike et al. 2011	177	72	**33%**
Kantarci et al. 2012	408	79	**34%**

Staging of Preclinical AD
National Institute on Aging and the Alzheimer's Association Workgroup Criteria



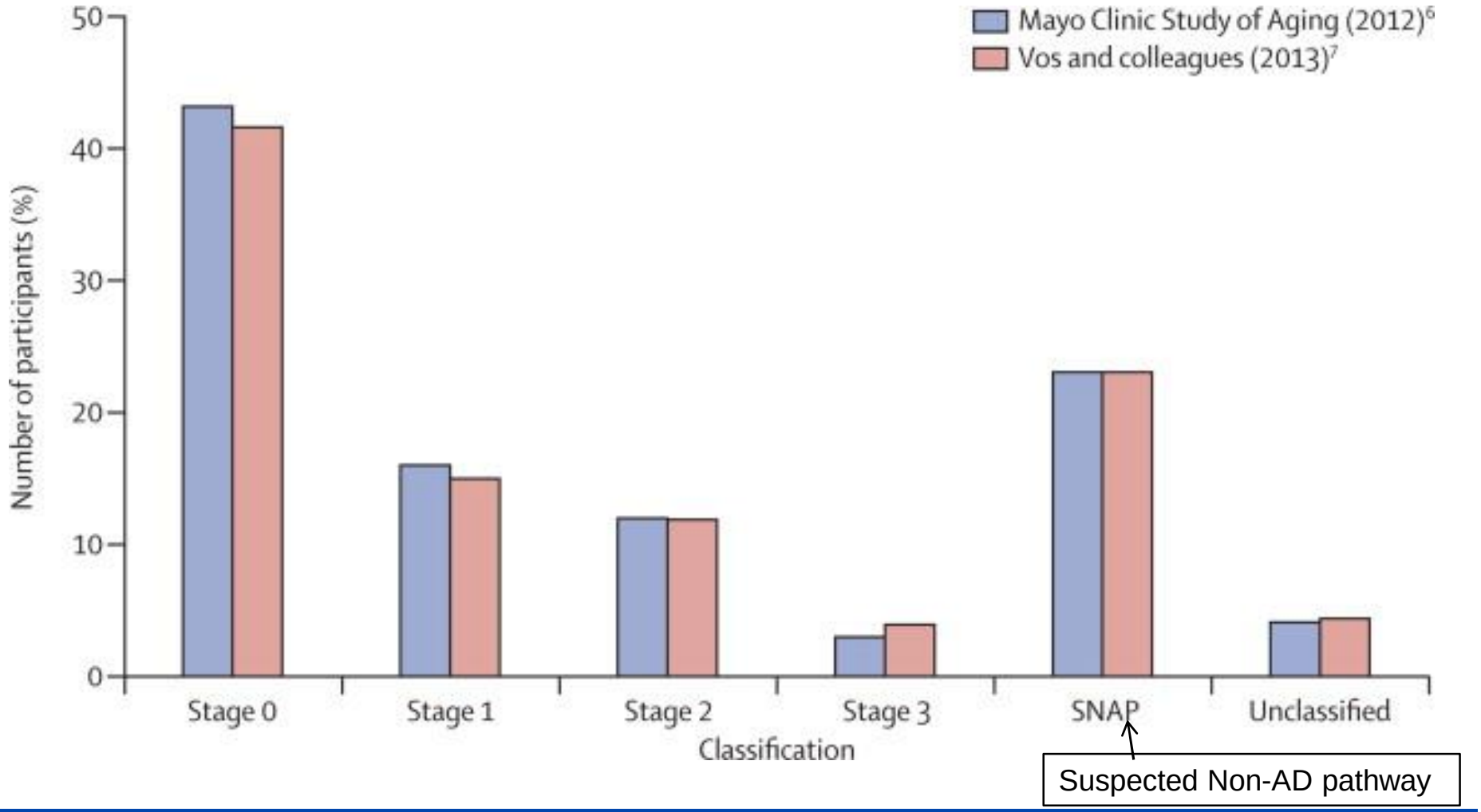
Sperling et. al. Alzheimer's and Dementia 2011

Staging of Preclinical AD



Jack et. al. *Annals of Neurology* 2012

Preclinical AD Staging



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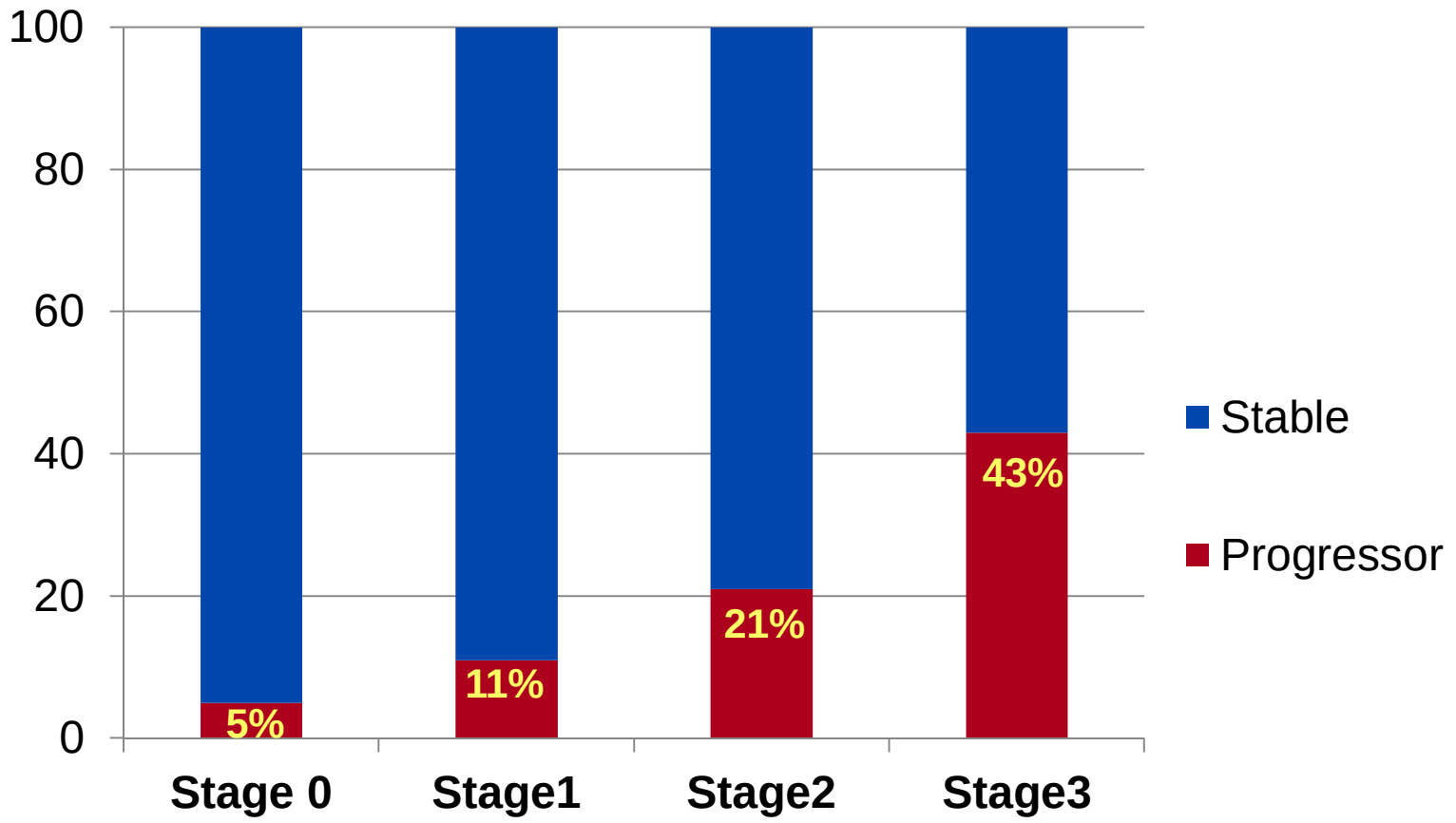
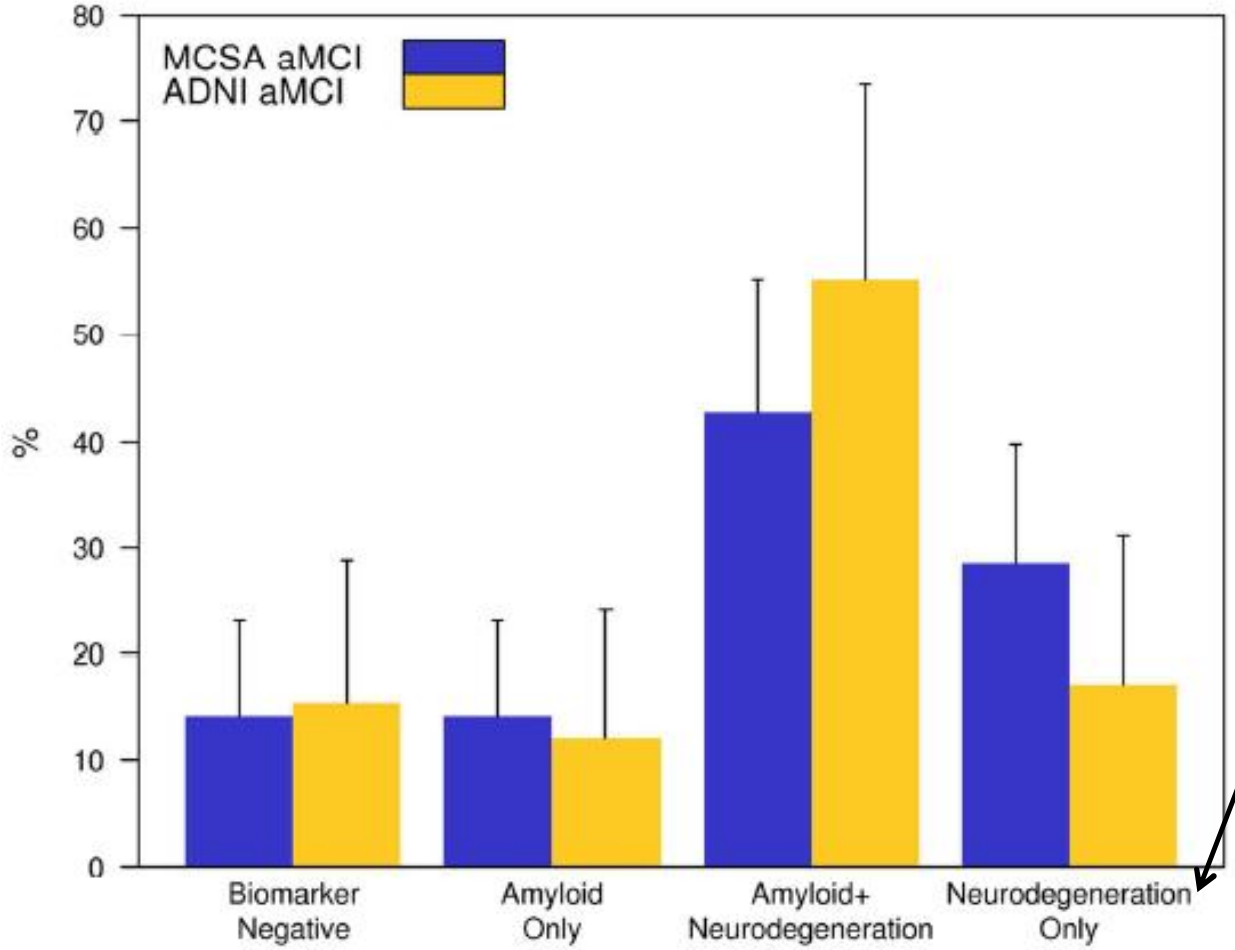
Petersen et. al. *Lancet Neurology* 2013; Vos et al *Lancet Neurology* 2013

Progression from Preclinical AD Stage to MCI within 15 months (n=296)



Knopman et. al. *Neurology* 2012

MCI due to AD in the Community



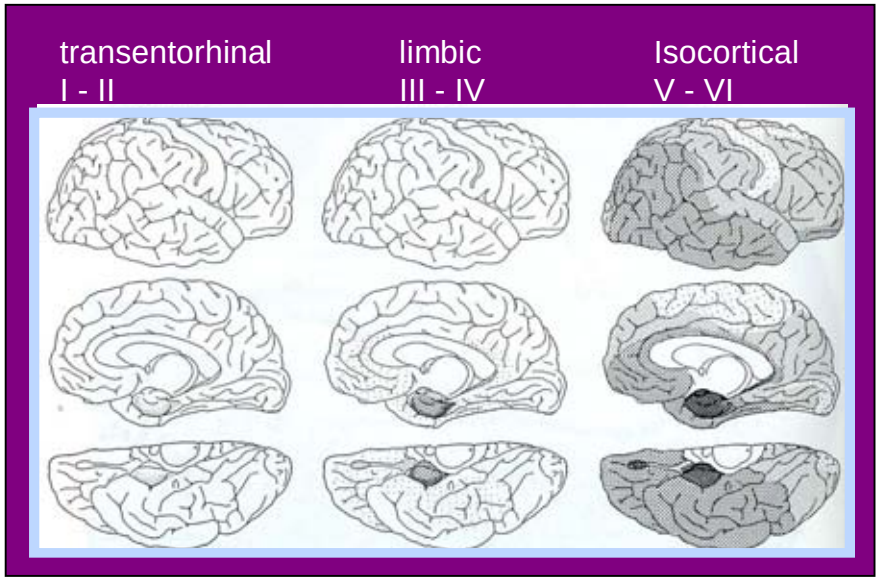
MCI –Suspected non-AD pathway (MCI-sNAP)

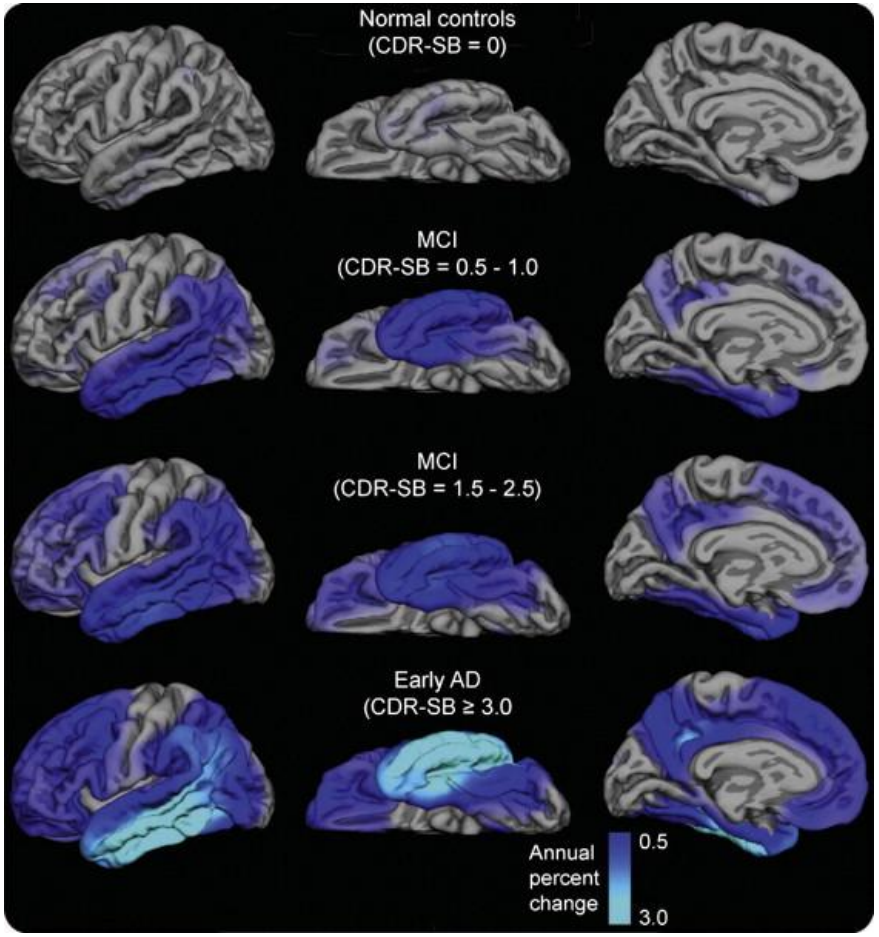
Petersen et al. *Annals of Neurology* 2013

Imaging biomarkers of Alzheimer's Disease

- Differential diagnosis
- Early diagnosis
- Tracking disease progression
- Treatment planning and assessment of efficacy

Tracking Disease progression with Structural MRI





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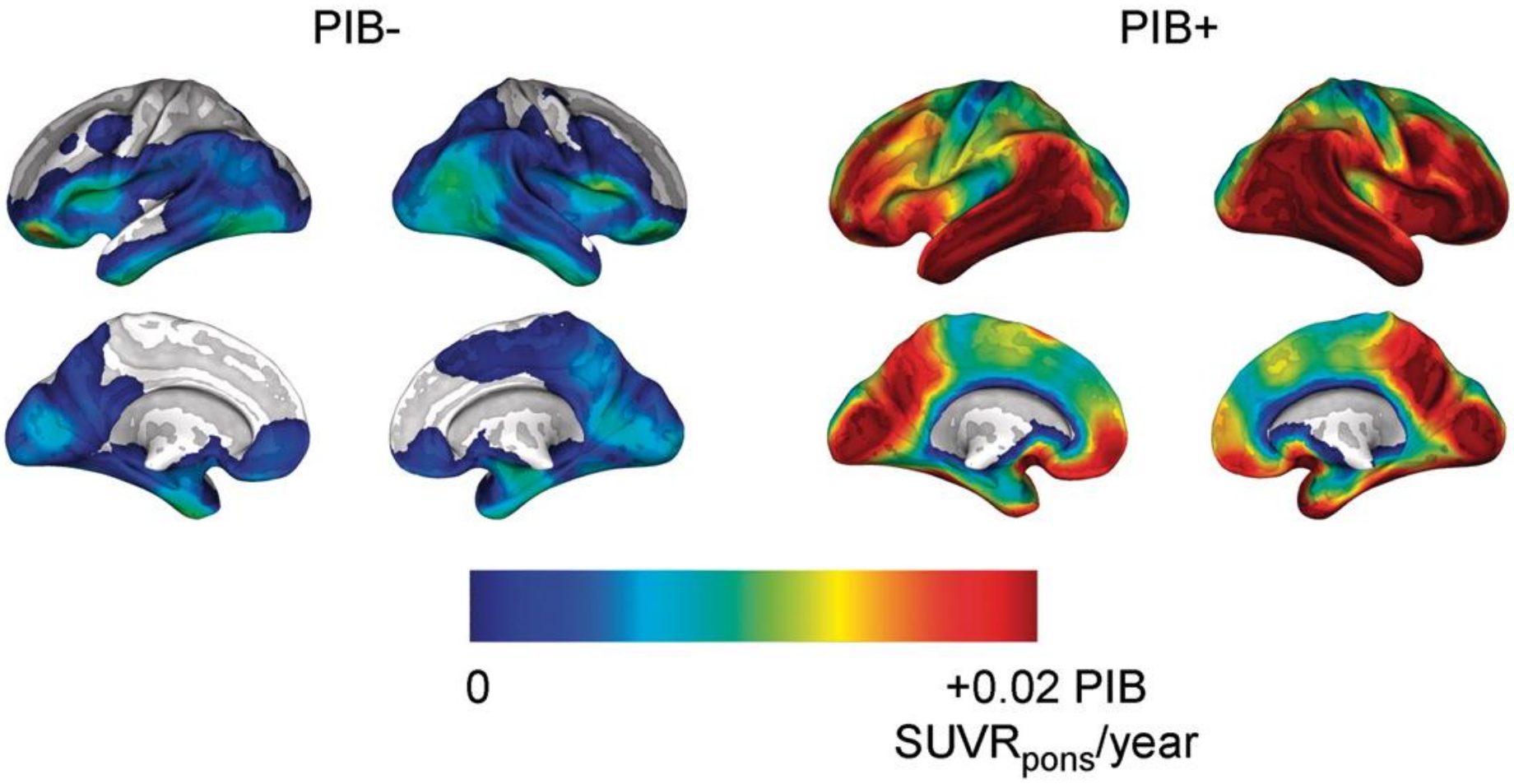
McDonald et al. *Neurology* 2009

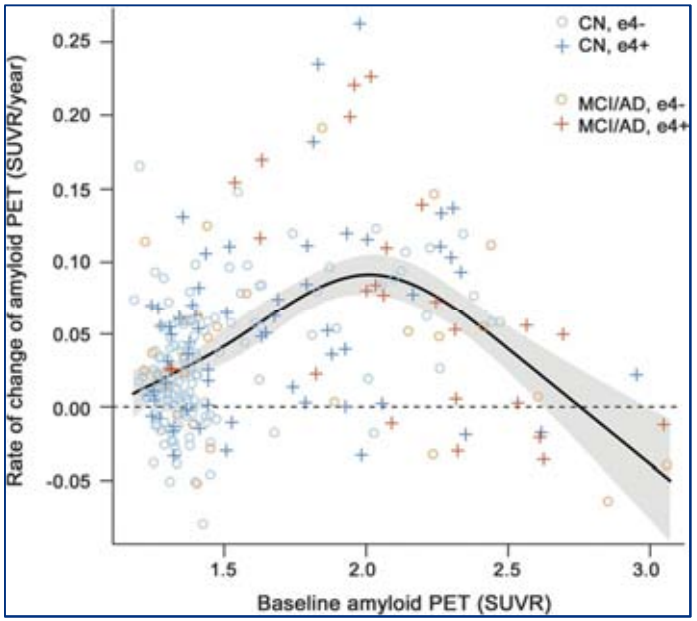
Tracking Disease progression with ??Amyloid PET

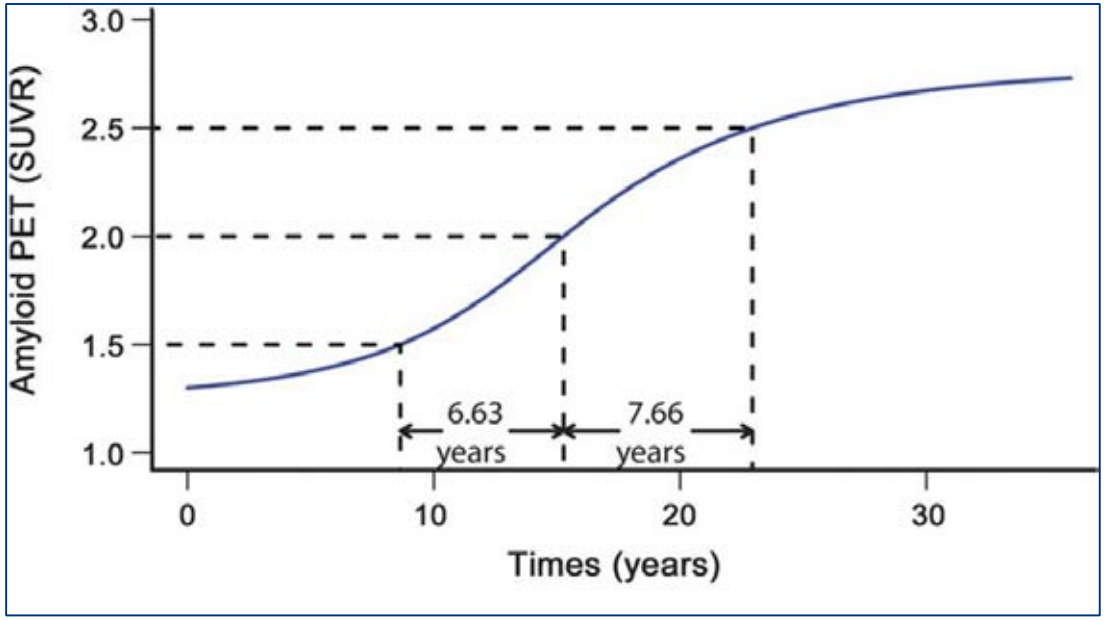


Villain et al. *Brain* 2012

Tracking Disease progression with ?-Amyloid PET

Brain ?´amyloid load approaches a plateau





15-year interval where the slope of the amyloid SUVR vs time curve is greatest and roughly linear represents a large therapeutic window for secondary preventive interventions.

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Jack et al. *Neurology* 2013

Imaging biomarkers of Alzheimer's Disease

- Differential diagnosis
- Early diagnosis
- Tracking disease progression
- Treatment planning and assessment of efficacy

Imaging Biomarkers in Treatment and Prevention of AD

- To determine who has the target pathology
- To determine whether a treatment is modifying the target pathology.

BRAIN
A JOURNAL OF NEUROLOGY

Imaging and acetylcholinesterase inhibitor response in dementia with Lewy bodies

Jonathan Graff-Radford,[1] Bradley F. Boeve,[1] Otto Pedraza,[2] Tanis J. Ferman,[2] Scott Przybelski,[3] Timothy G. Lesnick,[3] Prashanthi Vemuri,[4] Matthew L. Senjem,[4] Glenn E. Smith,[5] David S. Knopman,[1] Val Lowe,[4] Clifford R. Jack Jr,[4] Ronald C. Petersen[1] and Kejal Kantarci[4]

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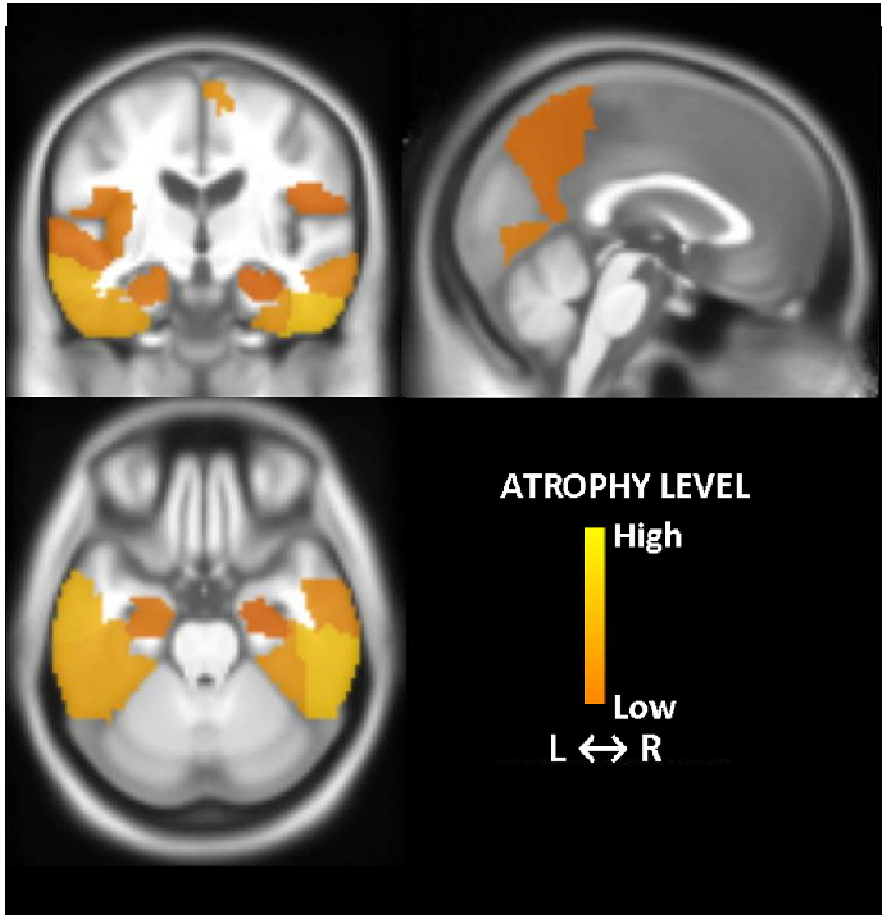
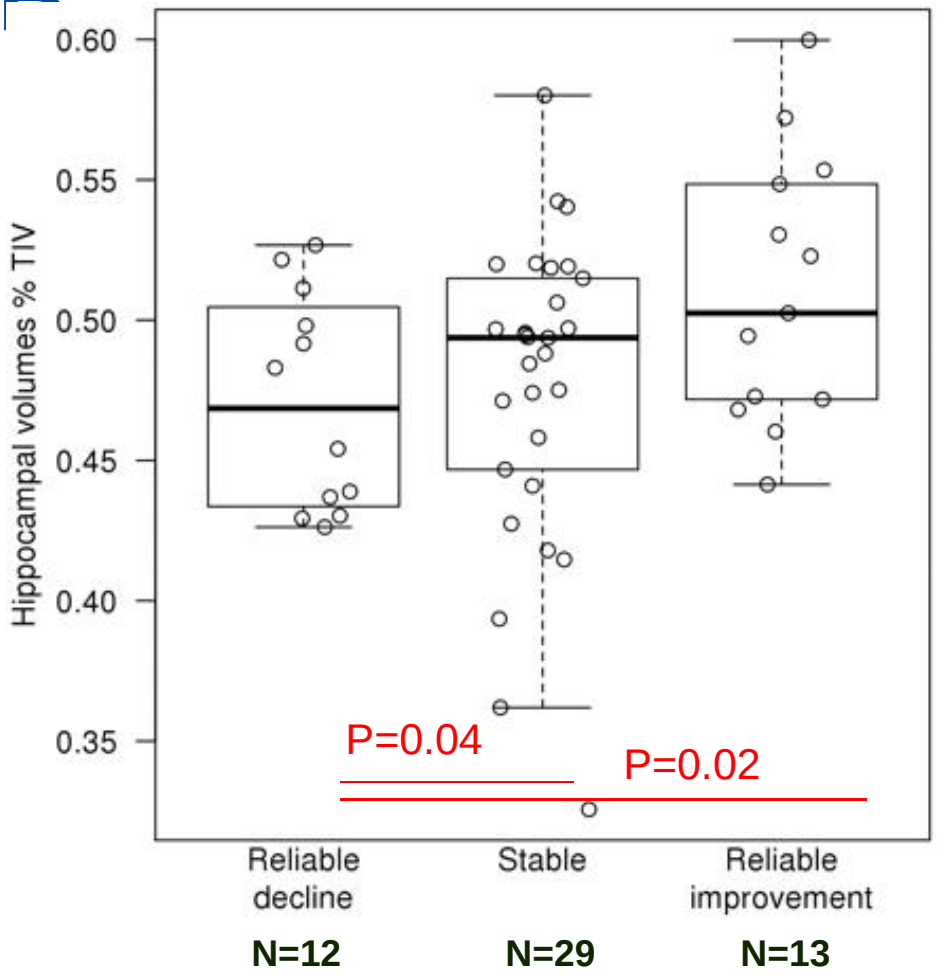
- **Treatment naïve patients with DLB with baseline MRI (n=54)**
- **Normative rates of change on the Mattis dementia Rating Scale (DRS) to determine reliable change**

MAYO CLINIC

Graff-Radford J. et al. *Brain* 2012

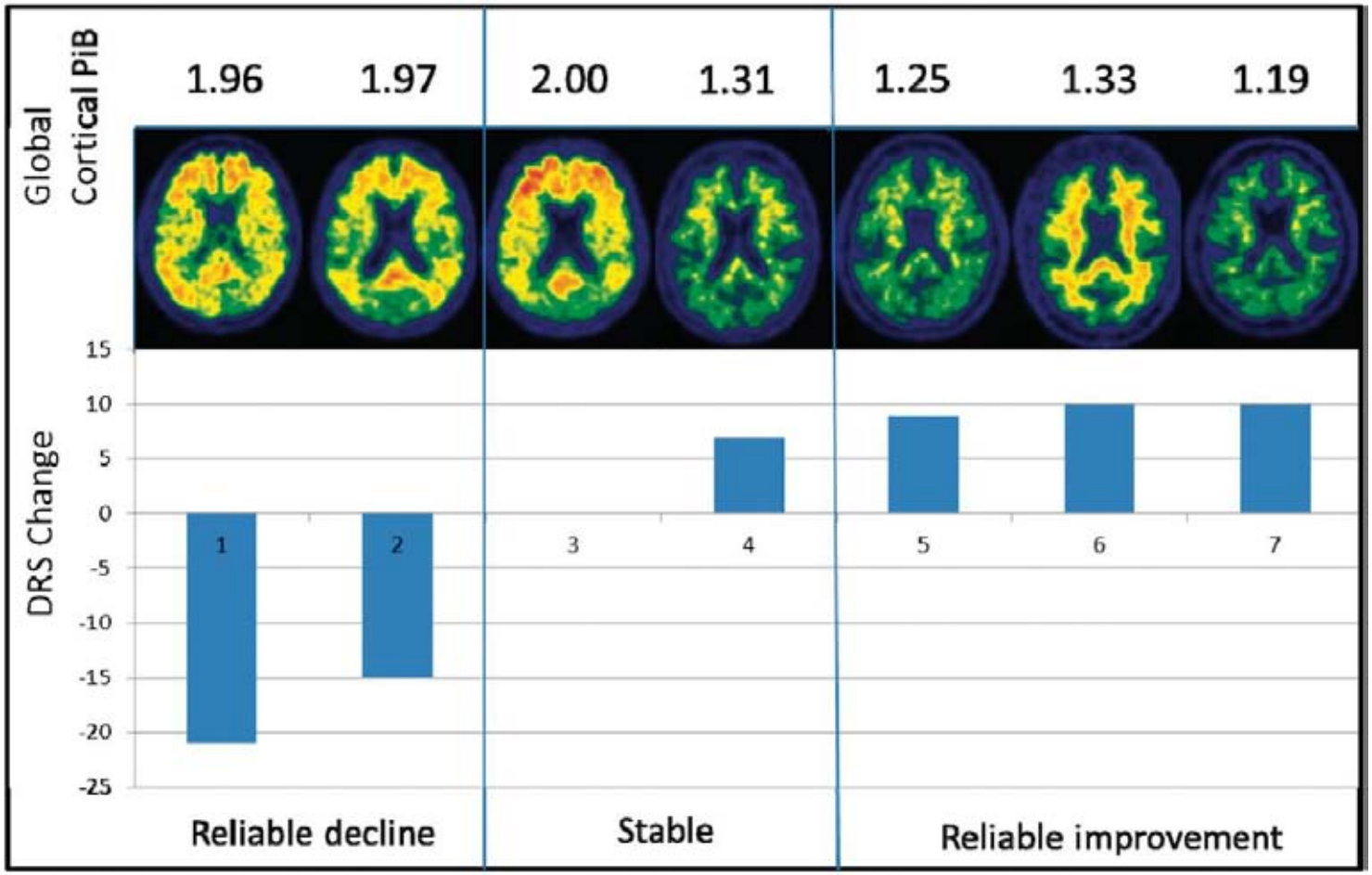
Structural MRI and AChI Response in Treatment Naïve DLB





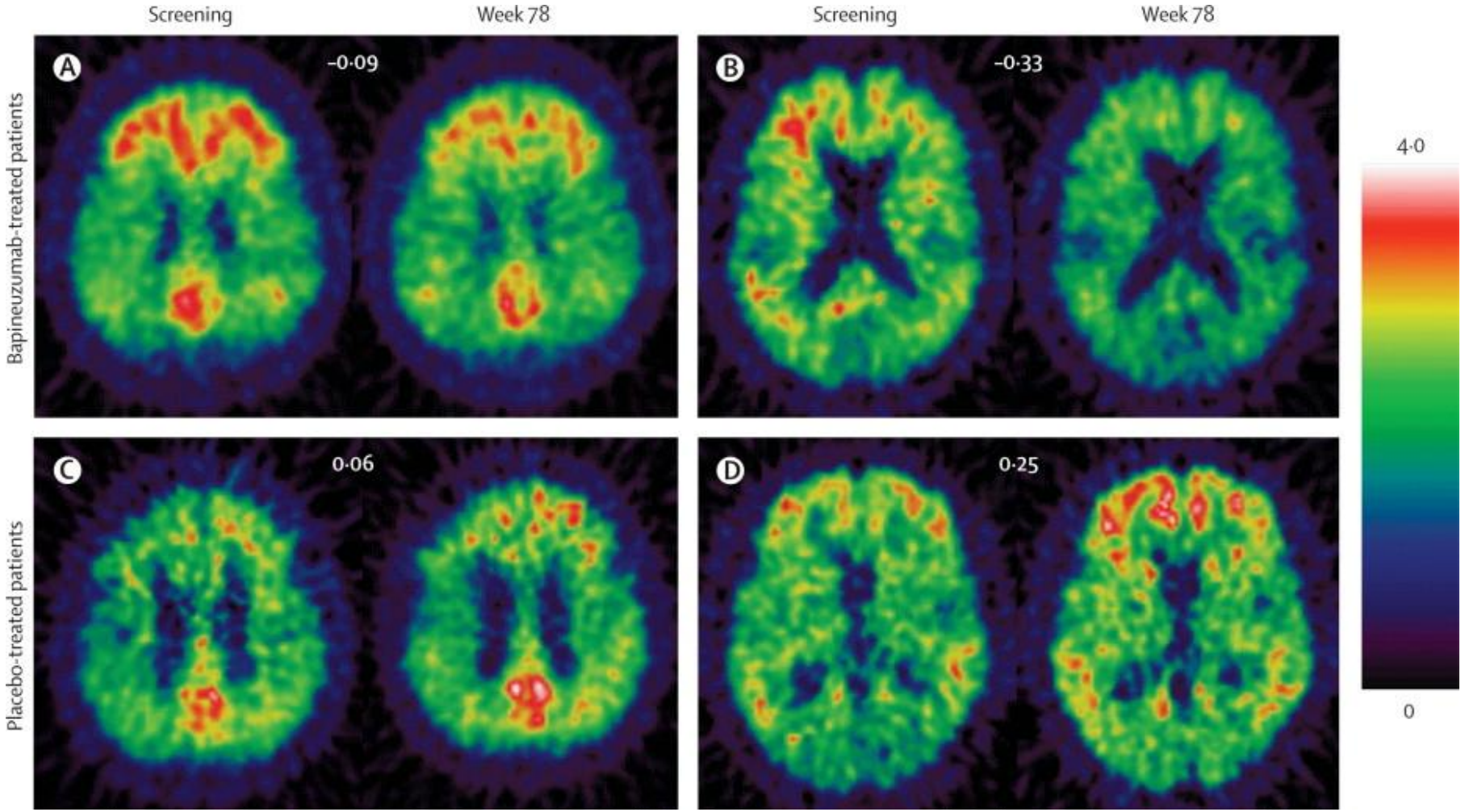
Reliable improvement > Reliable decline

?áAmyloid PET imaging predictors of AChI response in DLB



Graff-Radford J. et al. *Brain* 2012

Bapineuzumab Phase 2 Trial



Rinne et. al. *Lancet Neurology* 2010

Effects of A? Immunization (AN1792) on MRI Measures of Cerebral Volume in AD

- Immunization with synthetic A
- Trial not completed -menningoencephalitis and death
- Modest clinical improvement and clearance of A at autopsy

	N (Placebo/ antibody responder)	Placebo minus antibody responder
Whole Brain Volume	52 / 38	-1.01*
Ventricular Volume	56 / 45	0.61*

* Statistically significant atrophy greater in antibody responder group

MAYO CLINIC

Fox et al. *Neurology* 2005

Effects of A?Vmmunization (AN1792) on MRI Measures of Cerebral Volume in AD

- Amyloid removal ?
- Unrecognized cases of menningoencephalitis ?
- Fluid shifts into CSF spaces ?
- Mobilization of amyloid ?í increased CSF outflow resistance

MAYO CLINIC

Fox et al. *Neurology* 2005

Take Home Messages

- Imaging biomarkers of AD-related pathology are dynamic therefore stage of the disease is important when qualifying
- Standardization for clinical use is incomplete for many imaging biomarkers
- To qualify as a surrogate marker for determining treatment effects:
  - Biomarker effects and clinical effects should have related pathophysiologic mechanisms
  - Potentially leading to parallel clinical and biomarker outcomes

