Amyloid-Beta and Beyond: Clues from Biosignatures

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Disclosures

- Lilly LLC – Speakers bureau
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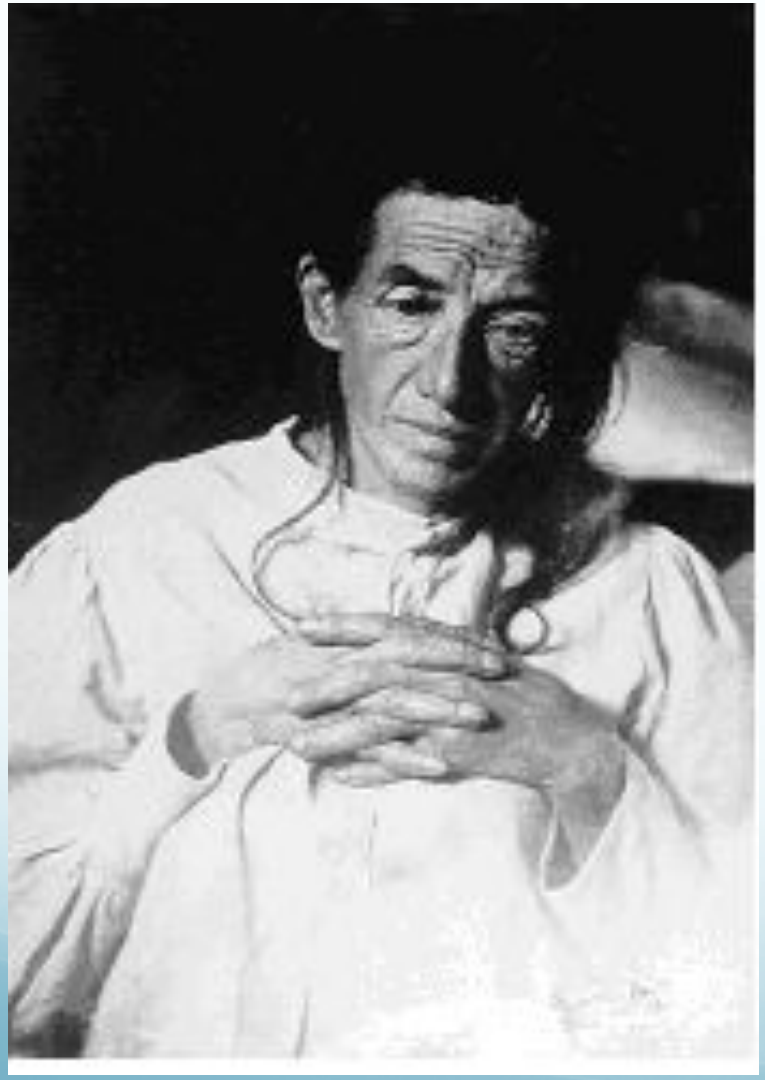
- Grifols – Advisory Board Member

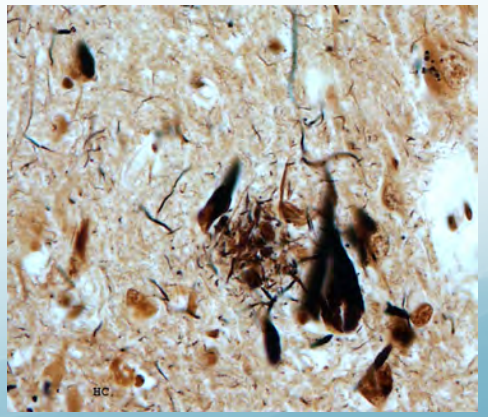
Alois Alzheimer

- Described the first AD case in 1906

The case of Auguste D.



- Rapid memory loss
- Disoriented to time and place
- Delusions
- Postmortem heavy build-up of unusual deposits that will later become known as amyloid plaques and neurofibrillary tangles

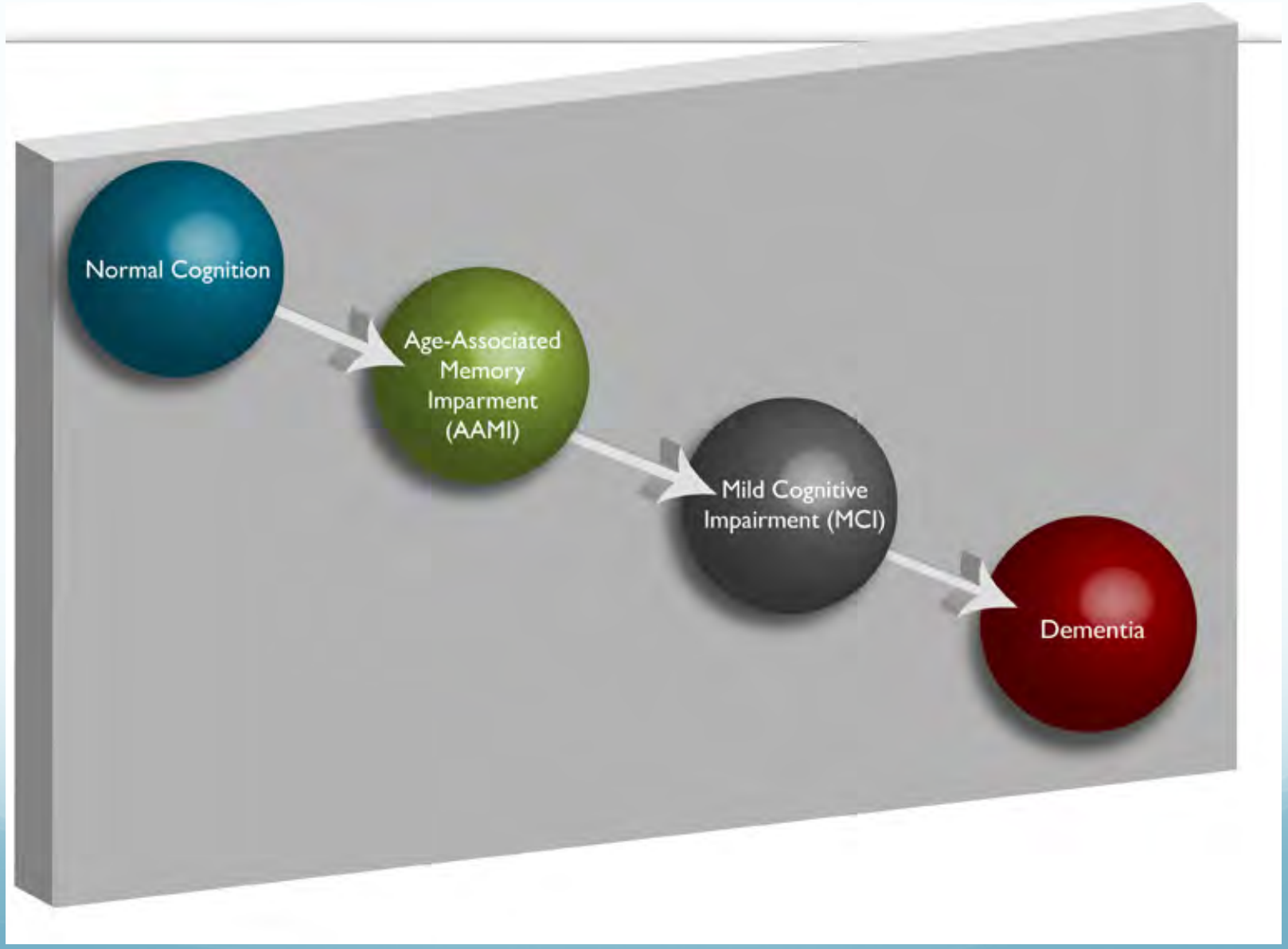


Dementia subtypes

- Primary dementia
  - Alzheimer's disease (AD) 63 %
  - Frontotemporal lobar degeneration 9 %
  - Creutzfeldt – Jacob disease 1 %
  - Hippocampal sclerosis 1 %
- Dementia "plus"
  - Vascular dementia 10 %
  - Dementia with parkinsonism
    - Parkinson disease 2 %
    - Dementia with Lewy bodies 15 %
    - Progressive supranuclear palsy rare
    - Corticobasal degeneration 1 %

Source: Grabowski, et al. Disorders of cognitive function. Continuum. No. 2, Apr 2002

The Aging-Dementia Cascade



DSM-V Dementia Definitions

- Minor Neurocognitive Impairment
  - Cognitive decline 1-2 SD from normal on formal cognitive testing
  - Do not interfere with independence
  - Not due to delirium or other medical or psychiatric disorder
- Major Neurocognitive Impairment
  - Cognitive decline ≥2 SD from normal on formal cognitive testing
  - Interfere with independence
  - Not due to delirium or other medical or psychiatric disorder

NIA-AA Dementia Syndrome

- Objective cognitive or behavioral impairment in **at least 2 of the following**:
  - Memory
  - Reasoning and handling complex tasks
  - Visouspatial abilities
  - Language functions
  - Personality, behavior or comportment
- Decline from previous level of functioning
- Functional impairment

Sperling et al, Alzheimer's and Dementia 2011

NIA-AA Probable Alzheimer's Dementia Criteria

- Meets criteria for dementia
- Insidious onset
- Gradual progression
- Initial symptoms
  - Amnestic
  - Nonamnestic (language, executive)
- No other contributors (VaD, DLB, FTD, other)
- Positive biomarkers increase Dx certainty

NIA-AA Mild Cognitive Impairment

- Concern for cognitive decline by patient, informant or physician
- Objective evidence of cognitive decline in 1 or more domains
- Intact functional abilities
- Not Demented
- Positive AD biomarkers can support MCI due to AD

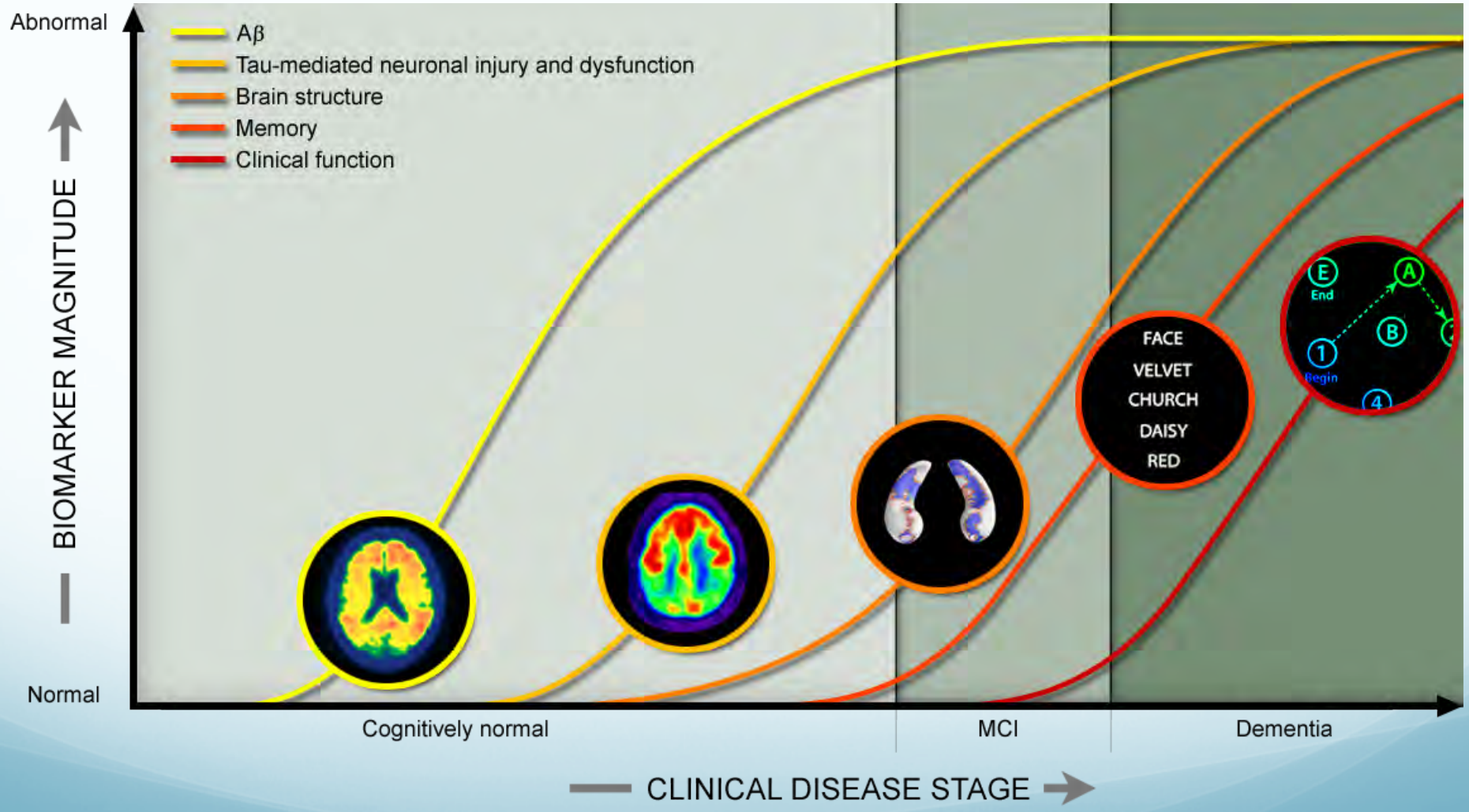
Albert et al, Alzheimer's and Dementia 2011

NIA-AA - Preclinical AD

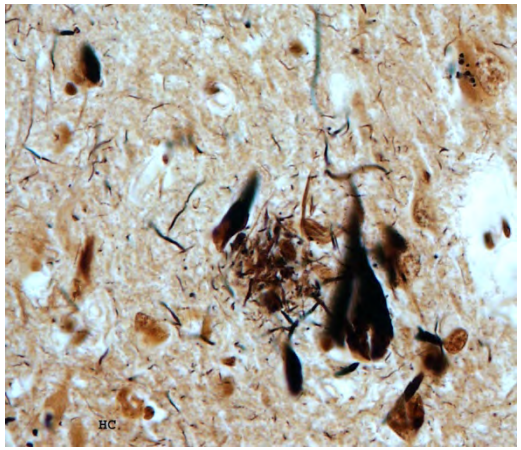
- Stage 1 – asymptomatic amyloidosis
- Stage 2 – asymptomatic amyloidosis and neurodegeneration
- Stage 3 – amyloidosis, neurodegeneration and subtle cognitive impairment

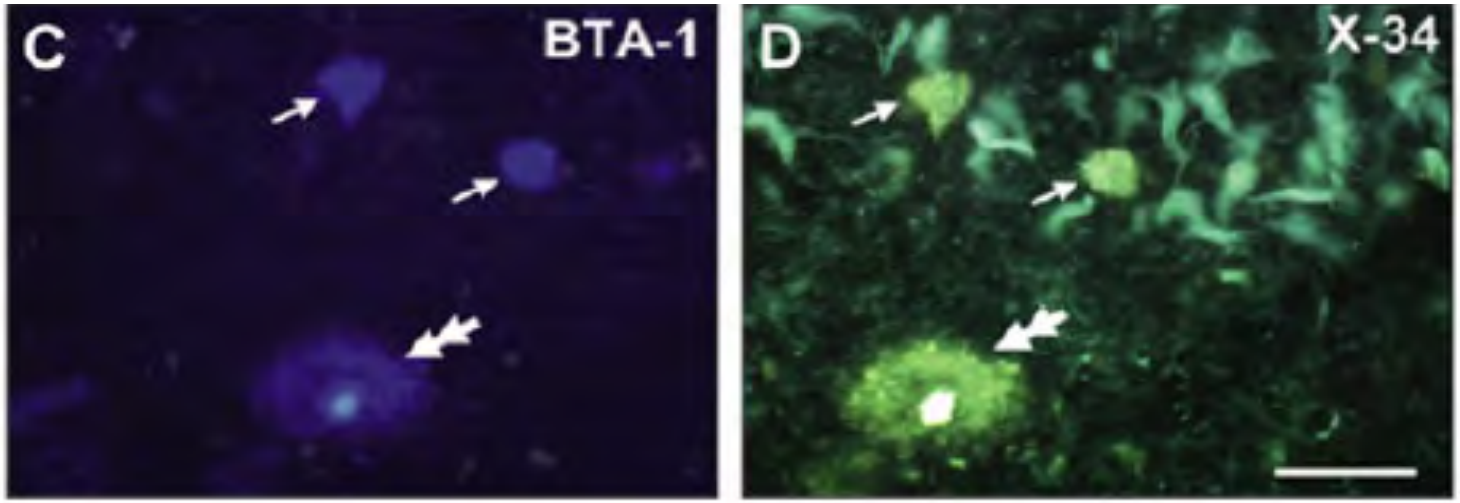
Sperling et al, Alzheimer's and Dementia 2011

The AD Biomarker Cascade



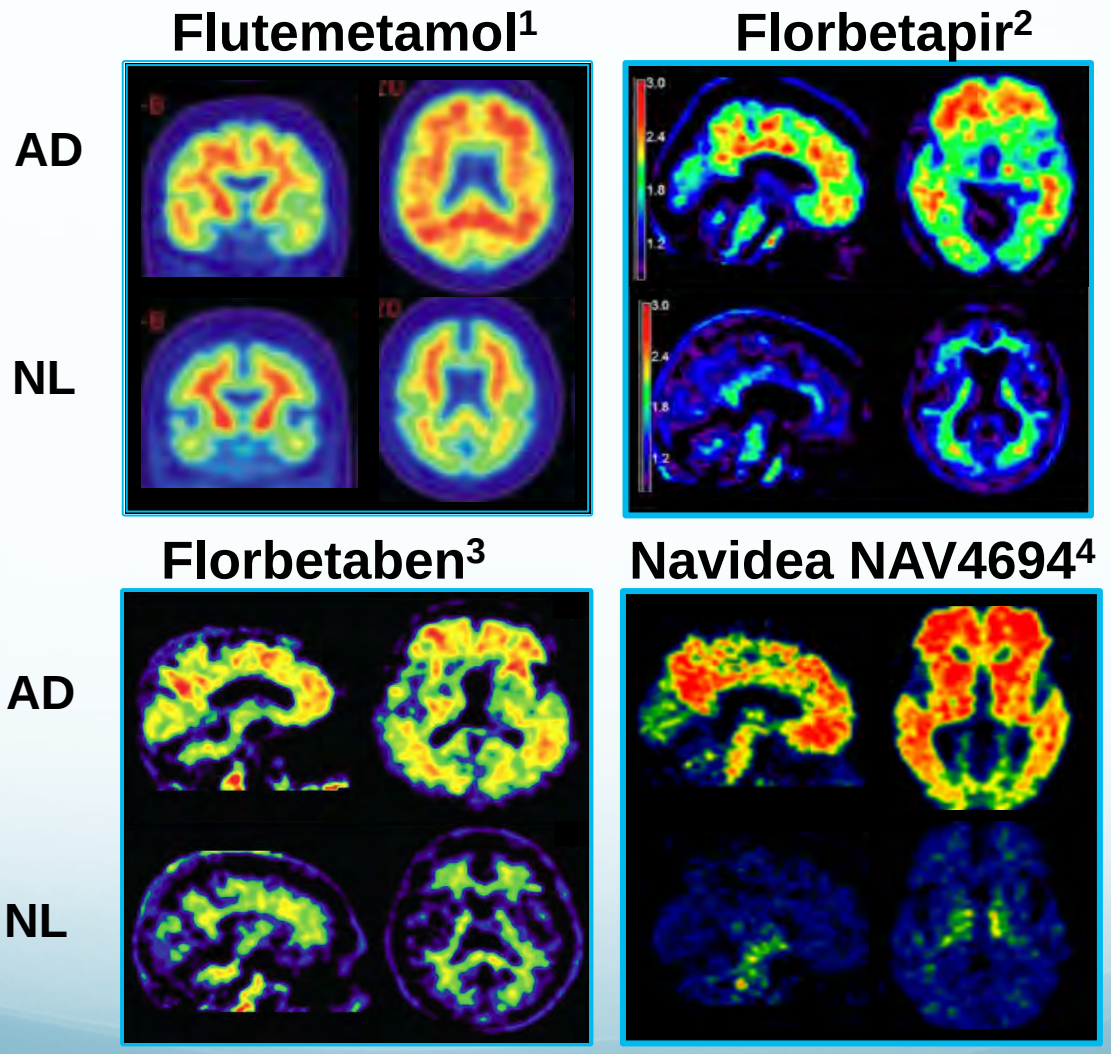
Amyloid Imaging Pathologic Validation



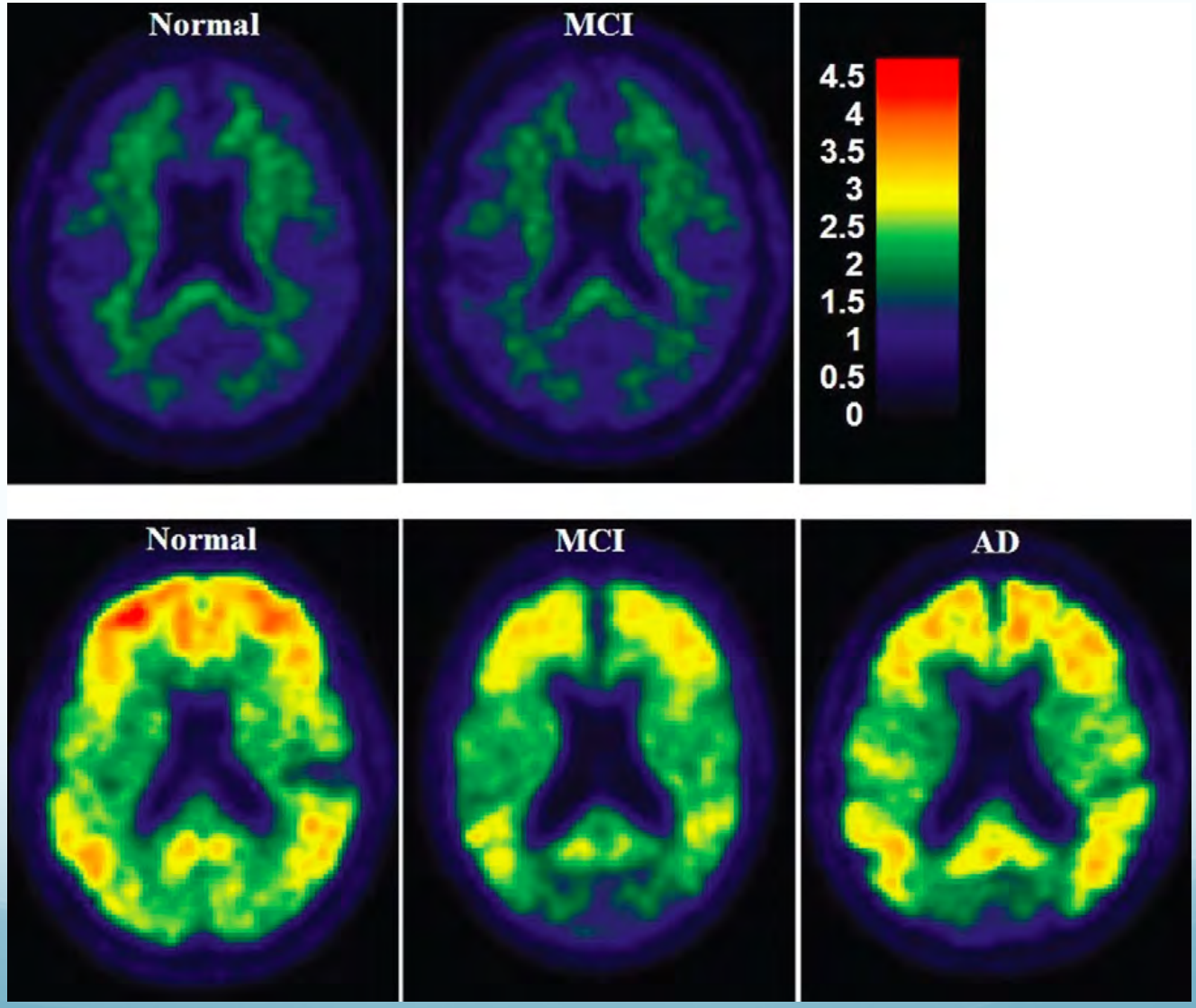


BTA-1 = PIB Ikonomovic et al, 2008

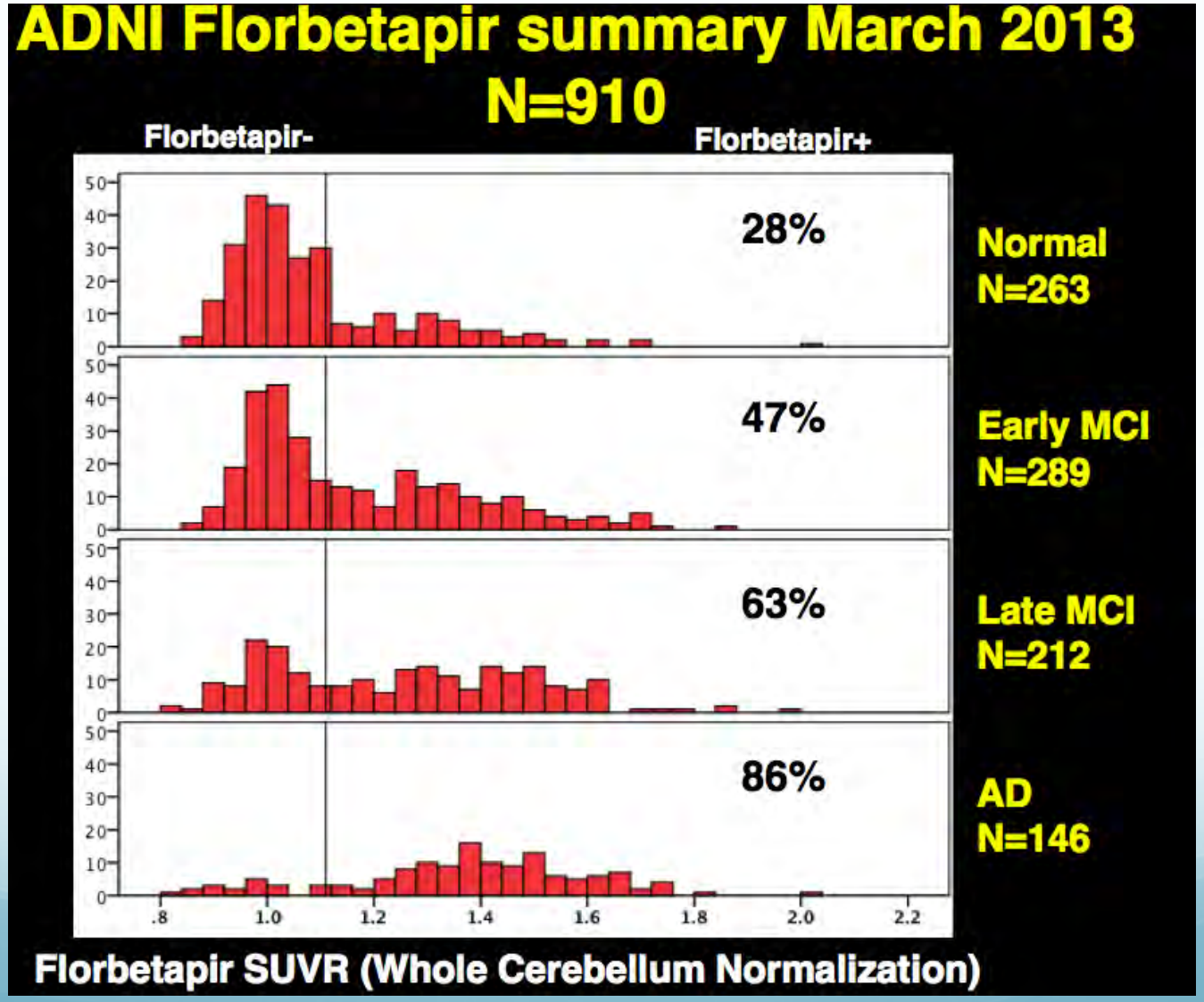
Amyloid PET Ligands



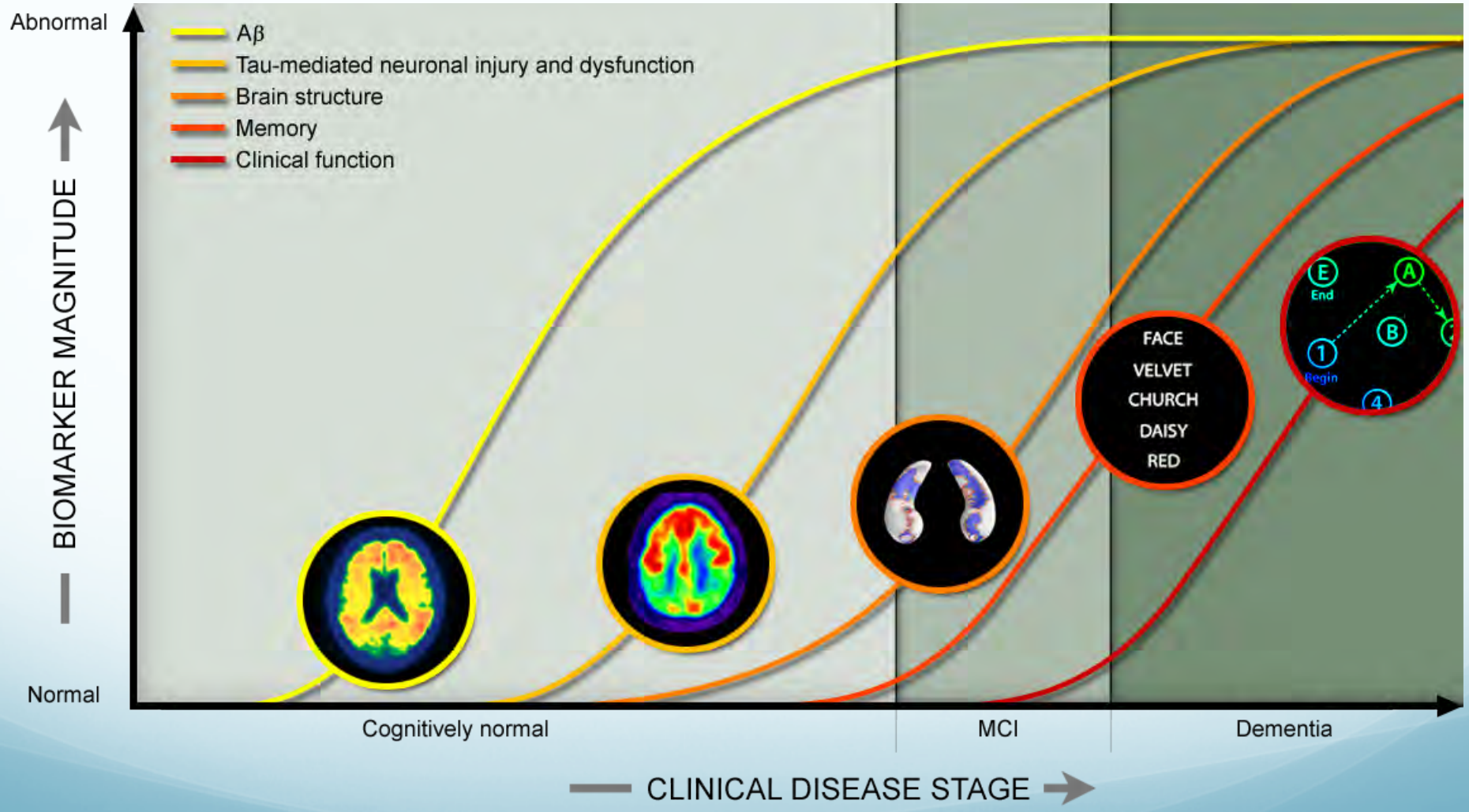
The Amyloid PET Spectrum



Prevalence of brain amyloidosis in ADNI



The AD Biomarker Cascade

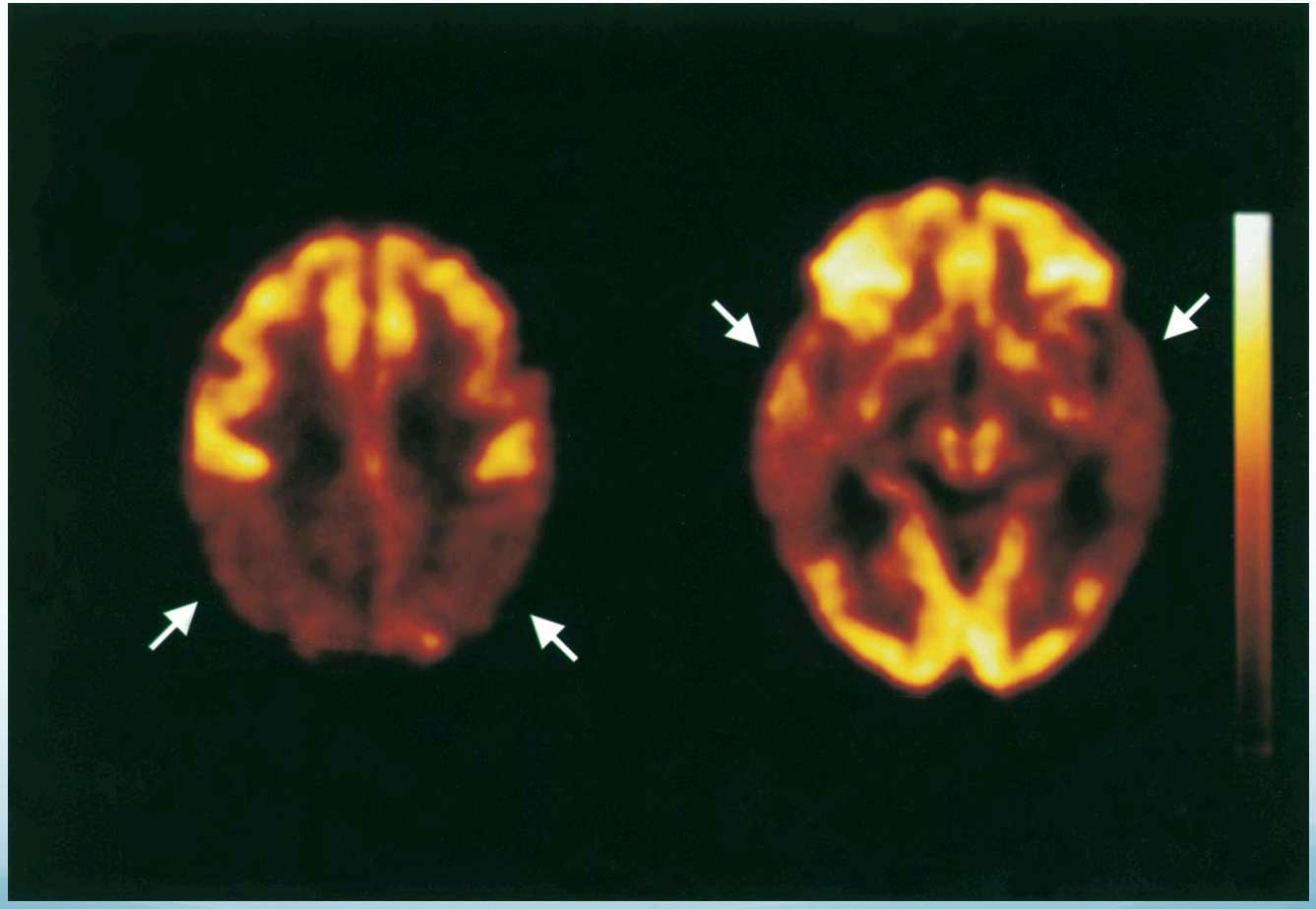


Functional Neuroimaging: FDG-PET

- Classic pattern of hypometabolism in temporoparietal regions and medial parietal lobes bilaterally in AD

- Approved by MediCare in the differential diagnosis between AD and frontotemporal dementia

Positron Emission Tomography in Alzheimer's Disease



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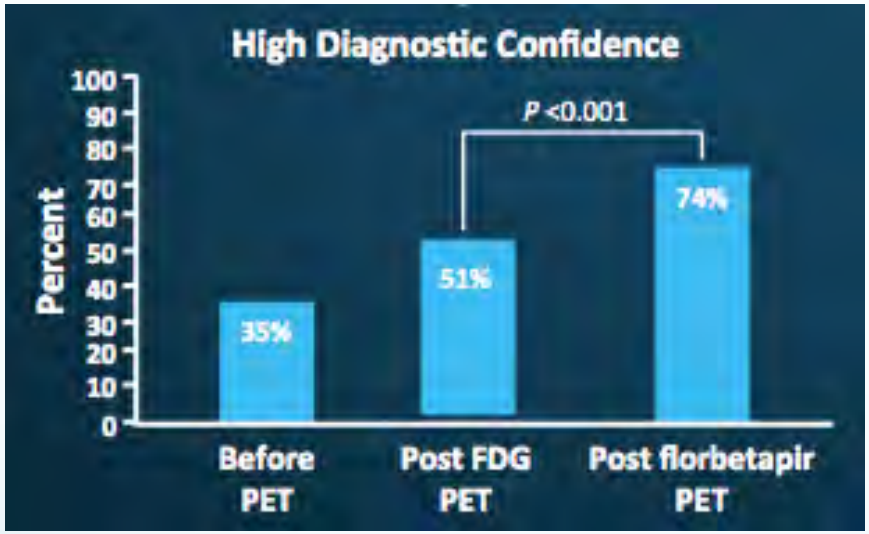
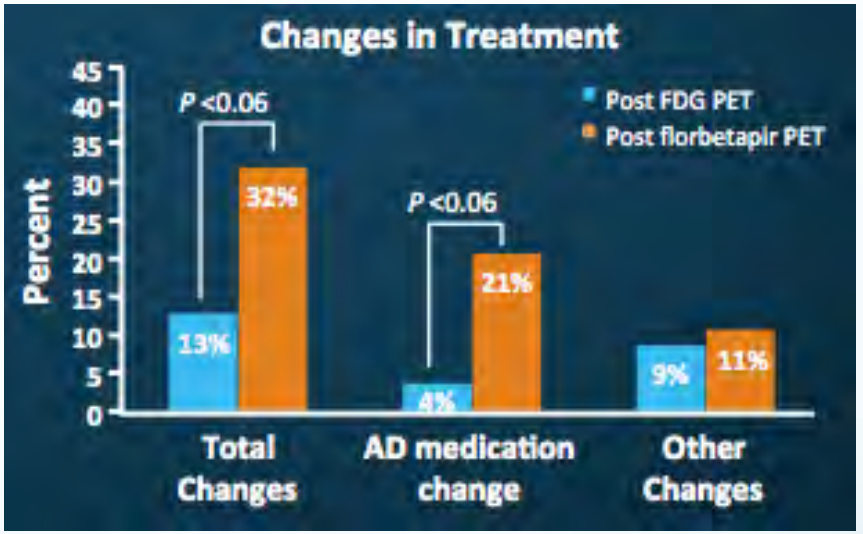
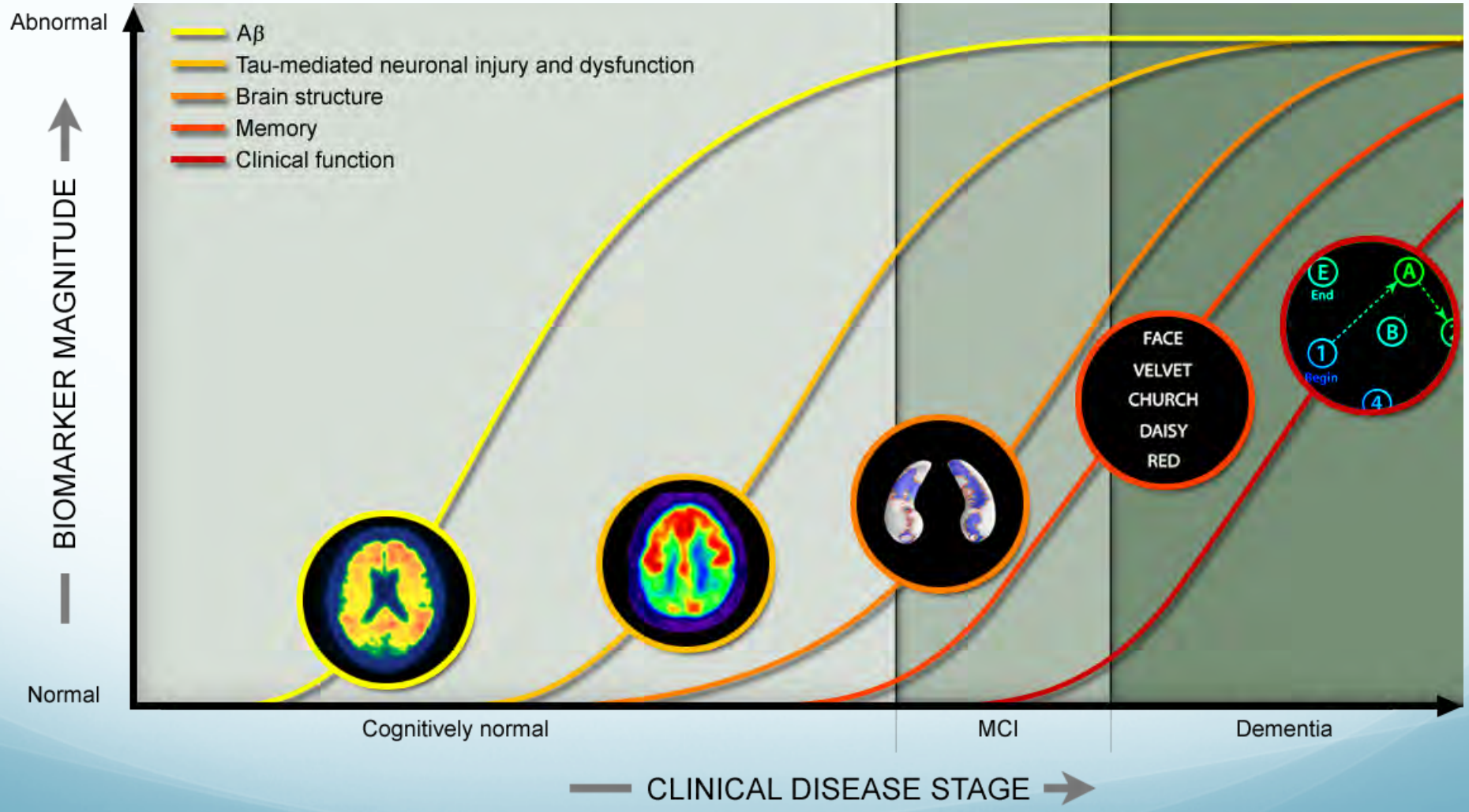


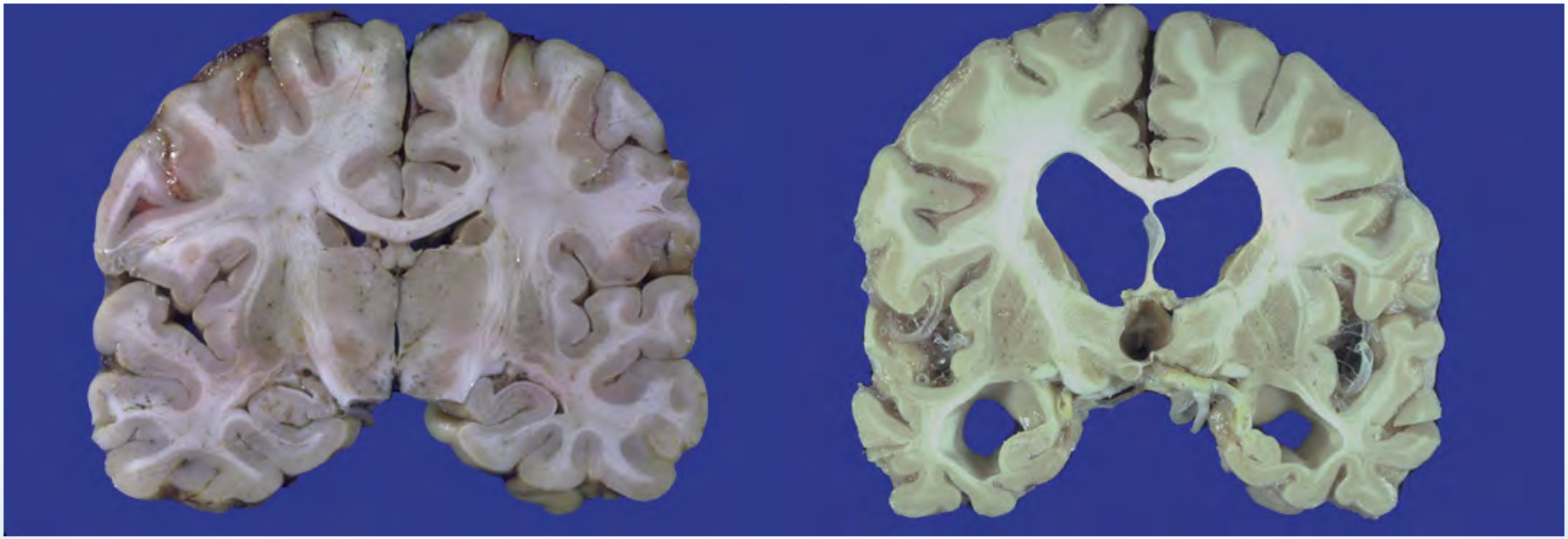


Ghosh PM et al. AAIC, 2014.

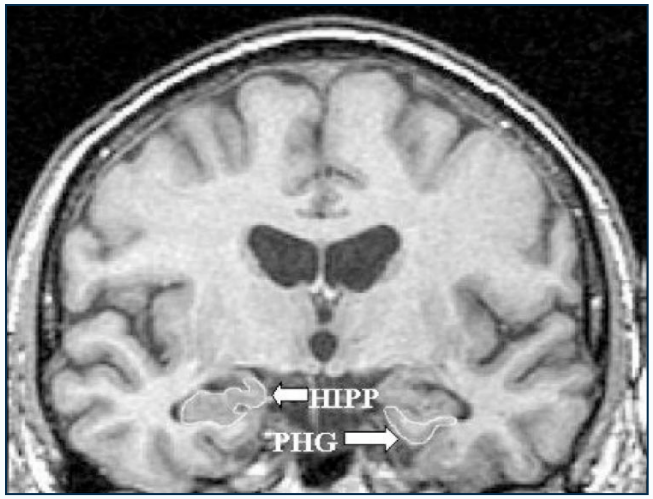
The AD Biomarker Cascade



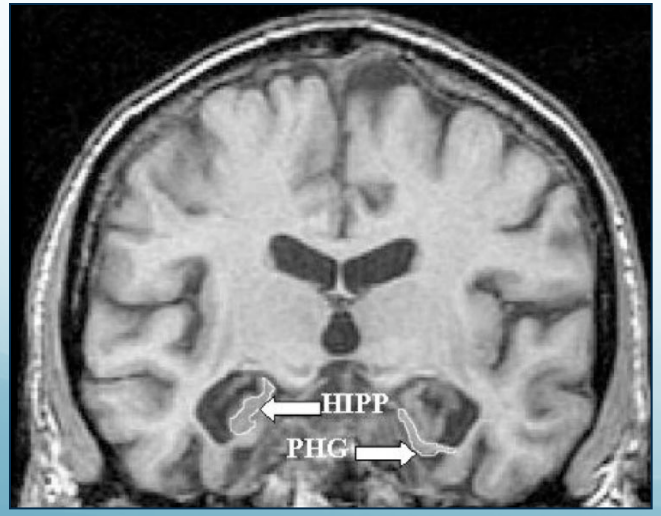
Normal vs. Severe Alzheimer's Brain



MRI in MCI



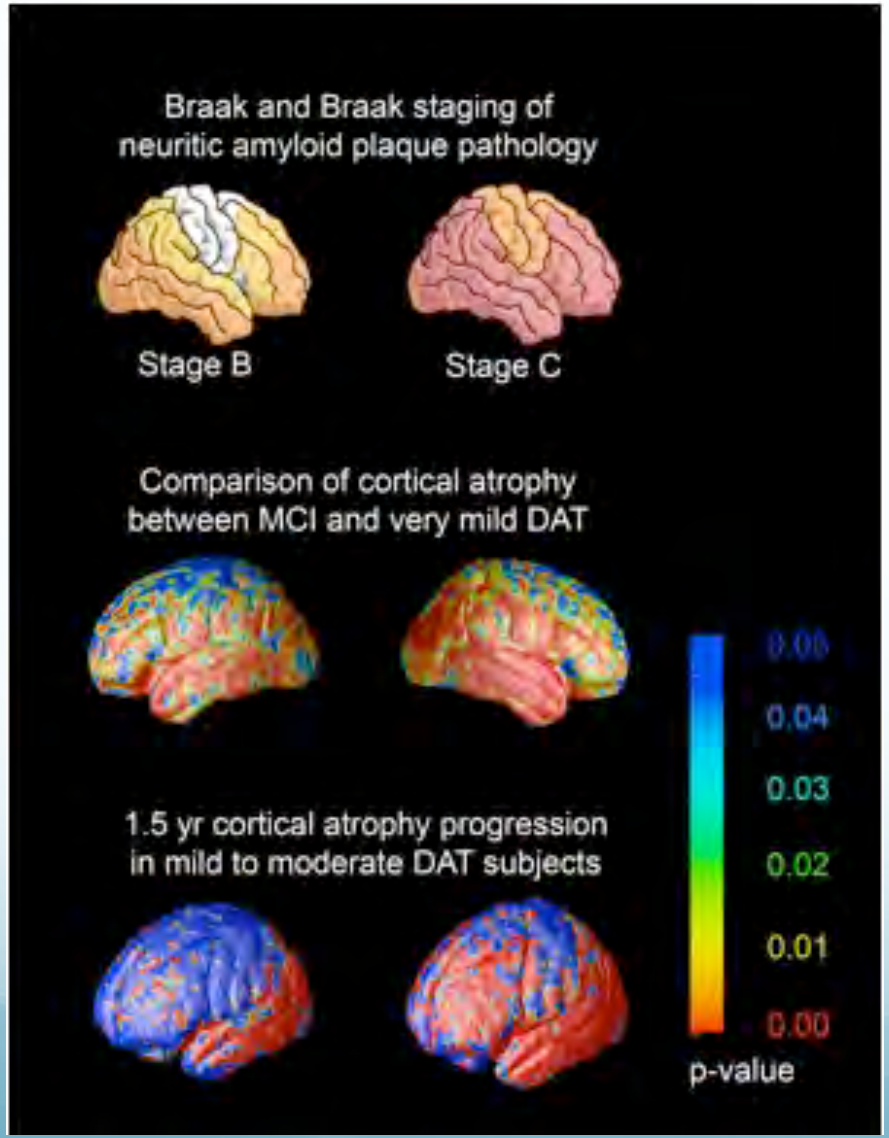
No MTA; less likely to progress to dementia



MTA; likely to progress to dementia

Devanand DP et al. Neurol 2007; 68: 828-836

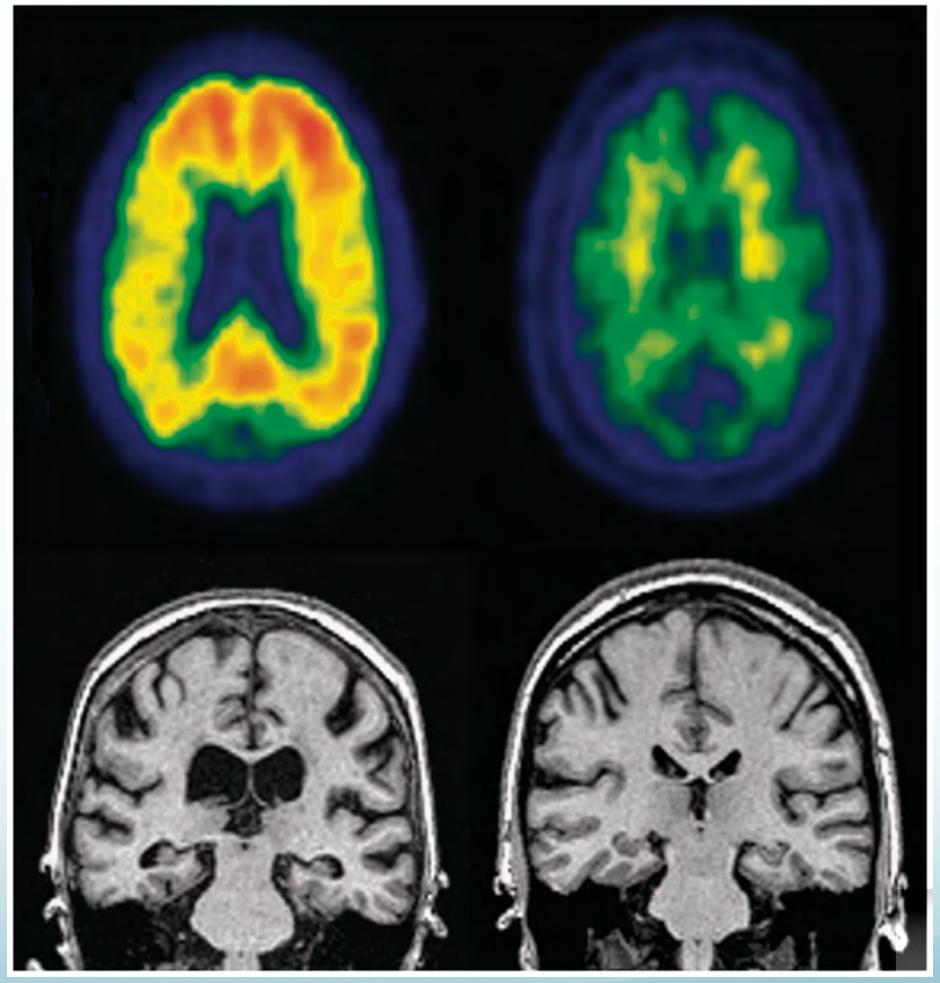
AD progression as seen on 3D Cortical Imaging



Apostolova et al,
Arch Neurol 2007

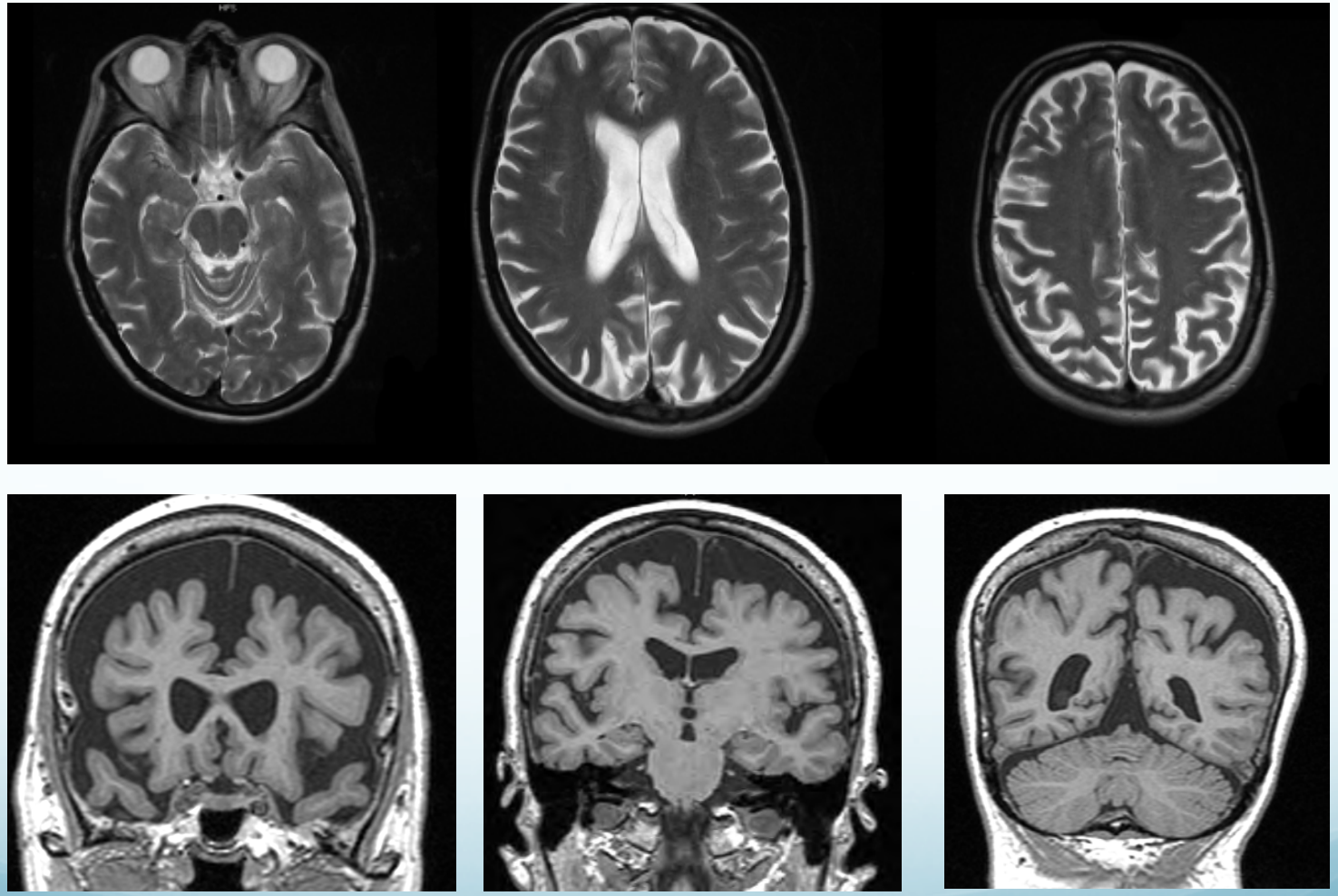
Thompson et al,
Cereb Cortex 2004

Biosignatures can assist accurate diagnosis and prognosis



Jack et al. Brain 2010

AD or not AD?



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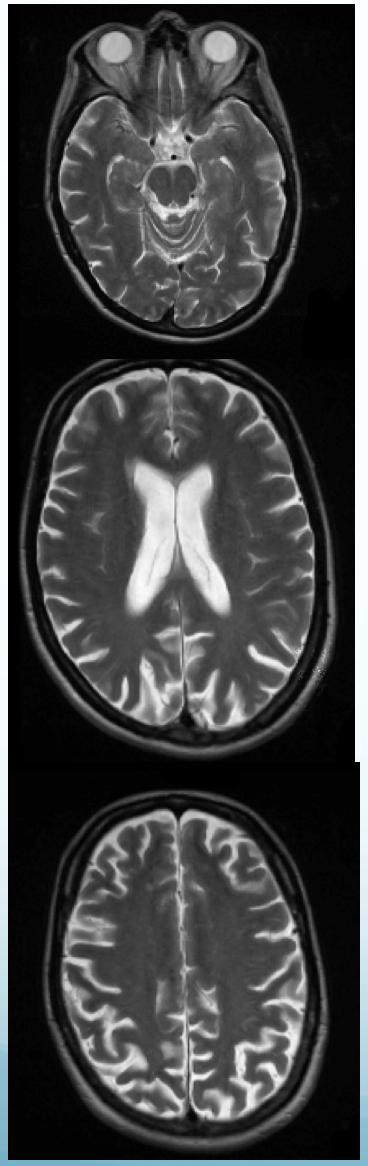

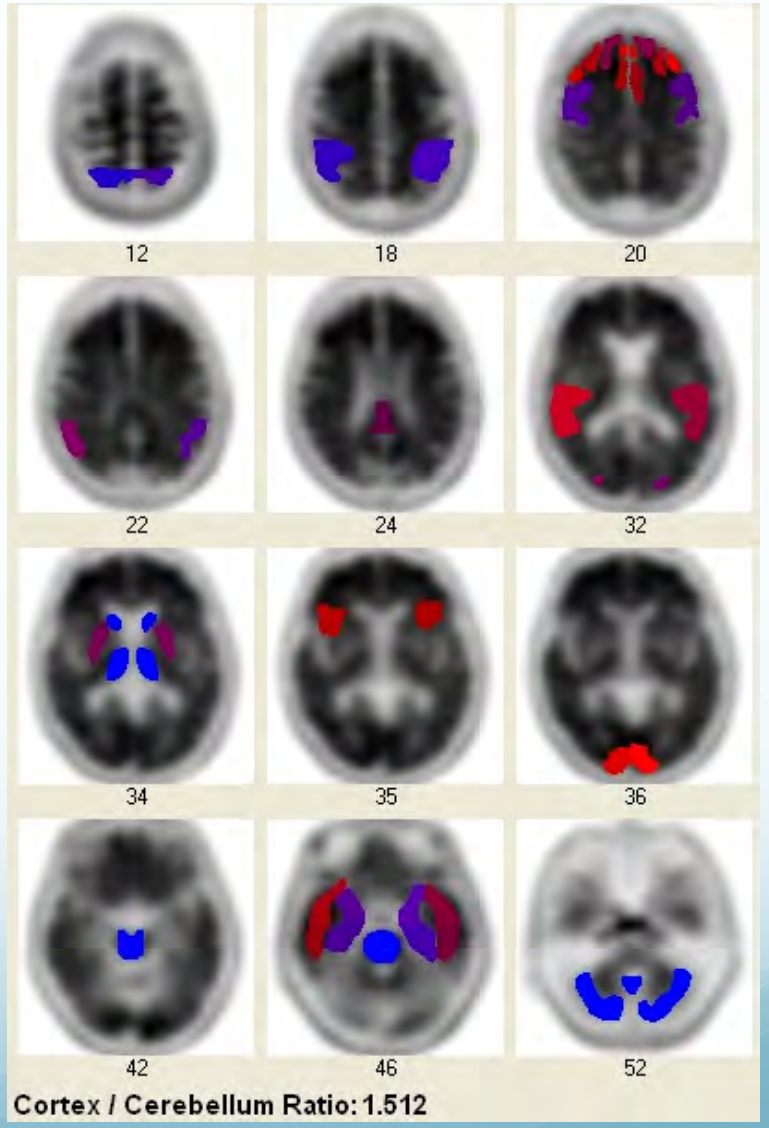

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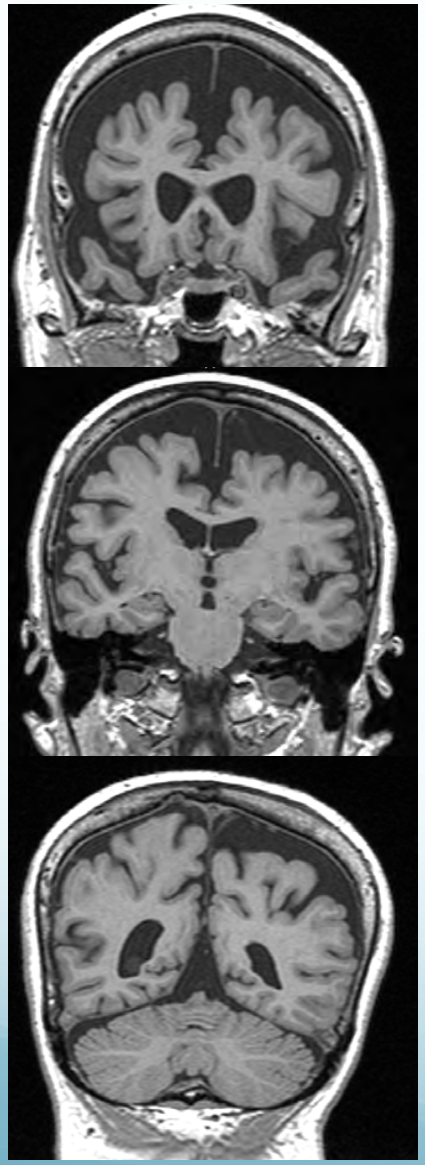
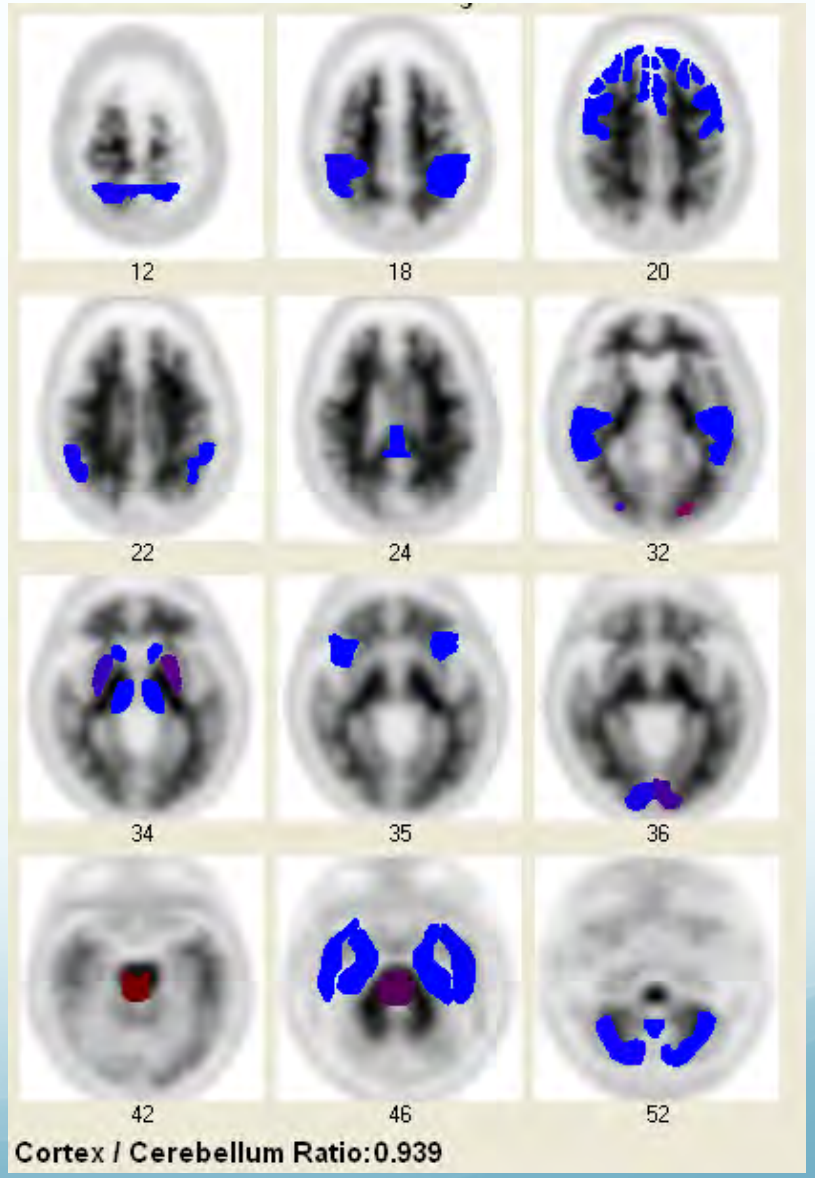
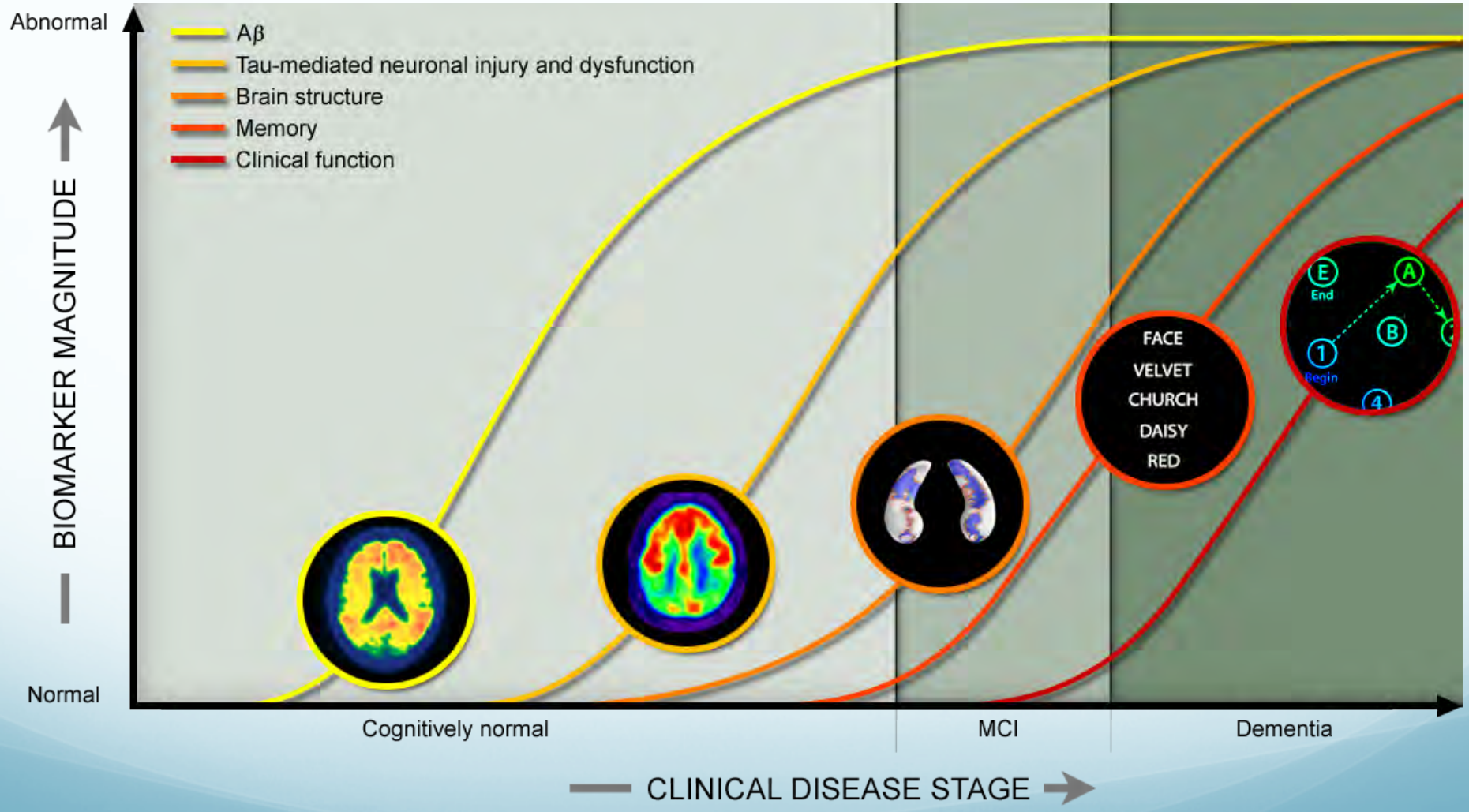
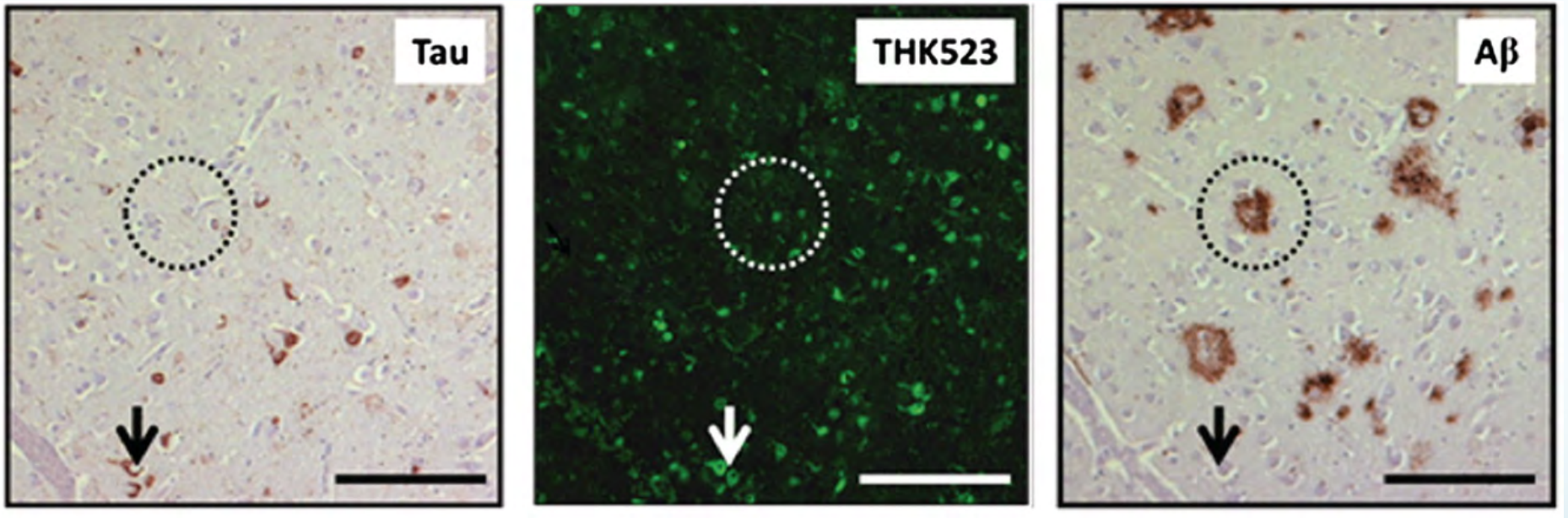




The AD Biomarker Cascade

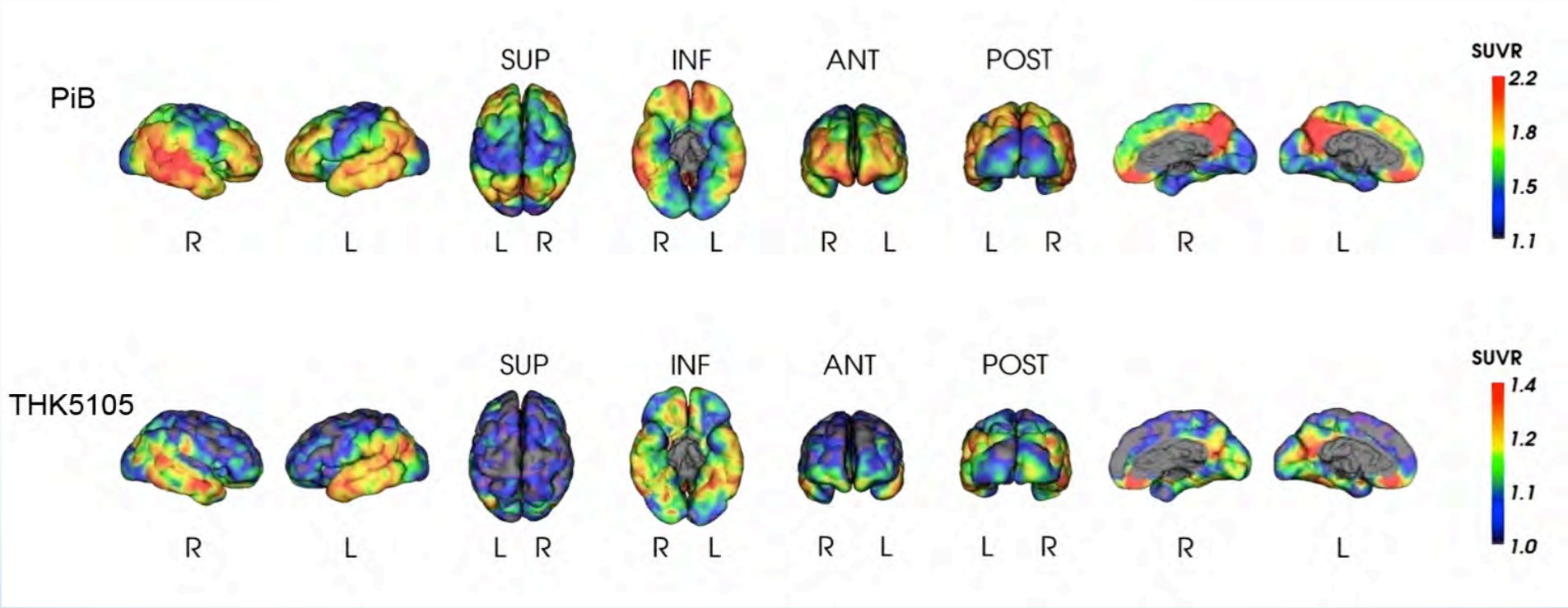


Tau Imaging



Fodero-Tavoletti et al, 2011

Amyloid and Tau PET Patterns

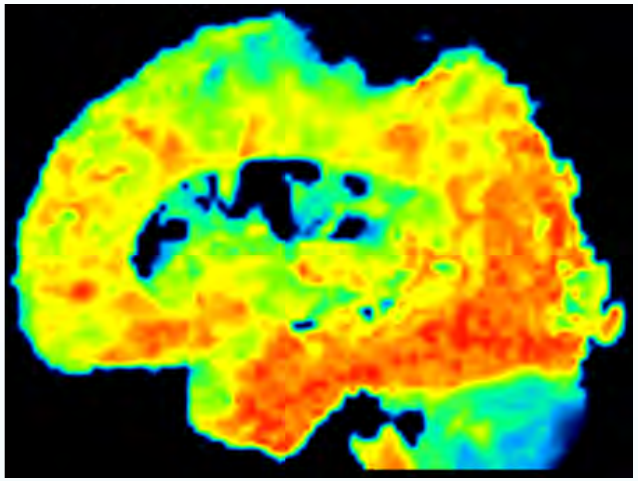


Images generated through CapAIBL® (*milxcloud.csiro.au*)
CSIRO Biomedical Imaging Group

Villemagne, AAIC 2014

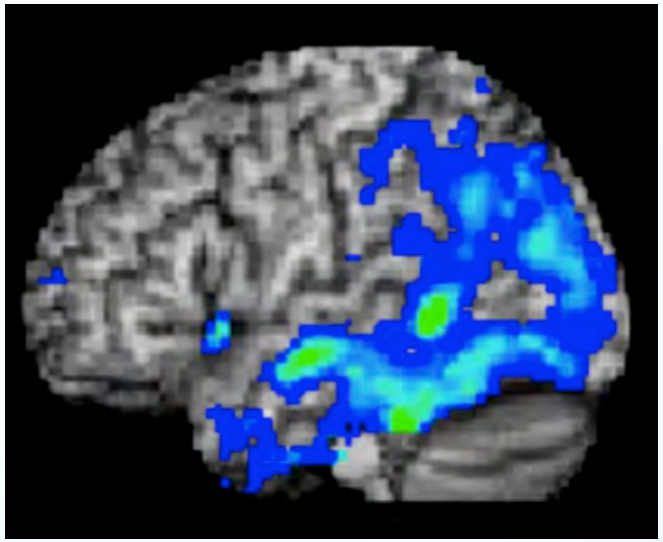
Tau PET and MRI patterns

^{18}F-THK5117

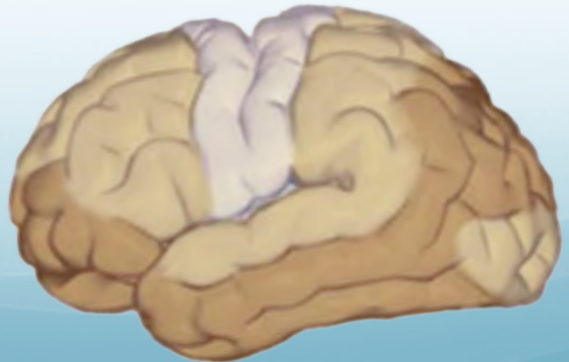


Tau (neurofibrillary tangles)

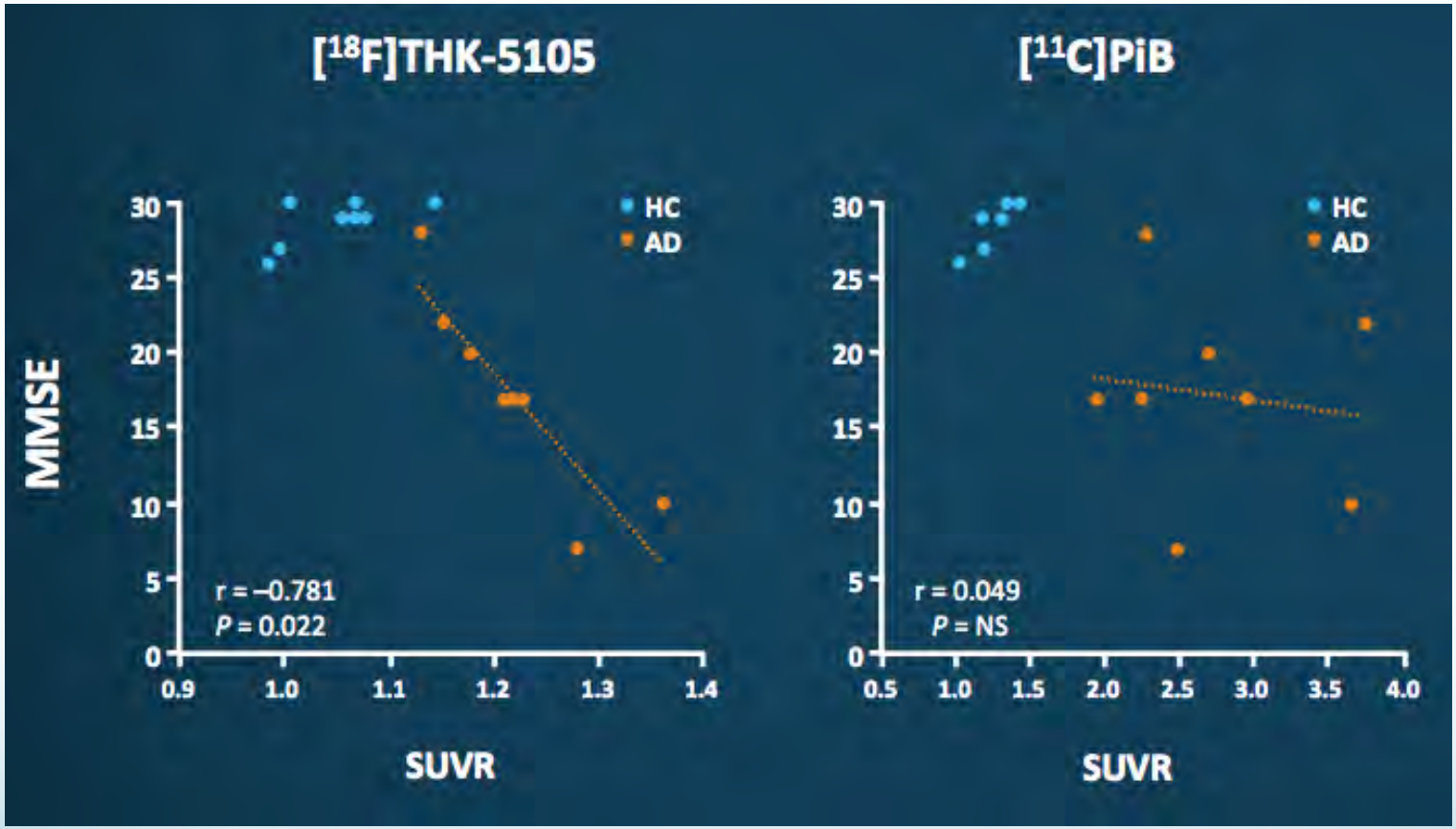
Voxelwise analysis



Cortical grey matter atrophy



Amyloid and Tau PET cognitive correlations



Okamura N et al. *Brain.* 2014;137:1762-1771.

Value of Biomarkers in the Clinic

- Improved diagnostic accuracy
  - Nearly 50% of patients with clinically diagnosed MCI, and 20% of those with dementia are misdiagnosed with AD
- Accurate diagnosis can prevent:
  - Excess diagnostic testing
  - Inappropriate treatments
  - Inappropriate long term planning and use of resources
  - INCREASED COST
- Accurate diagnosis promotes:
  - Education
  - Safety
  - Future planning

Amyloid PET Interpretation

- A negative amyloid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition
- A negative scan reduces the likelihood that a patient's cognitive impairment is due to AD
- A positive amyloid scan indicates moderate to frequent Amyloid neuritic plaques
- Neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition.

Amyloid imaging is appropriate in the following situations:

- A cognitive complaint with objectively confirmed impairment
- Performed only after full standard w/u is completed:
  - Structured clinical evaluation with objective neurocognitive testing
  - Structural brain imaging
  - Relevant laboratory tests
- AD as a possible diagnosis, but uncertain
- Knowledge of Aβ pathology would increase diagnostic certainty and alter management
- Should only be ordered by dementia experts
  - Specialty training, ≥25% dementia care practice
  - Geriatric Psychiatry and Neurology

Johnson KA et al. *Alzheimers Dement*. 2013 Jan;9(1):e-1-16; Johnson KA et al. *J Nucl Med*. 2013; 54:1–3.

Inappropriate Use Amyloid PET Imaging

- For evaluation of individuals without cognitive complaints
- For evaluation of individuals with cognitive complaints but without objective cognitive decline
  - NOTE: preclinical AD may become indication for Amyloid Imaging if preventive treatments are proved to be effective
- In the absence of complete standard work up
- As a stand alone diagnostic for AD dementia
- To assess disease progression

Johnson KA et al. *Alzheimers Dement*. 2013 Jan;9(1):e-1-16; Johnson KA et al. *J Nucl Med*. 2013; 54:1–3.