






Assessment & Biomarkers/Imaging Correlates of Dementia

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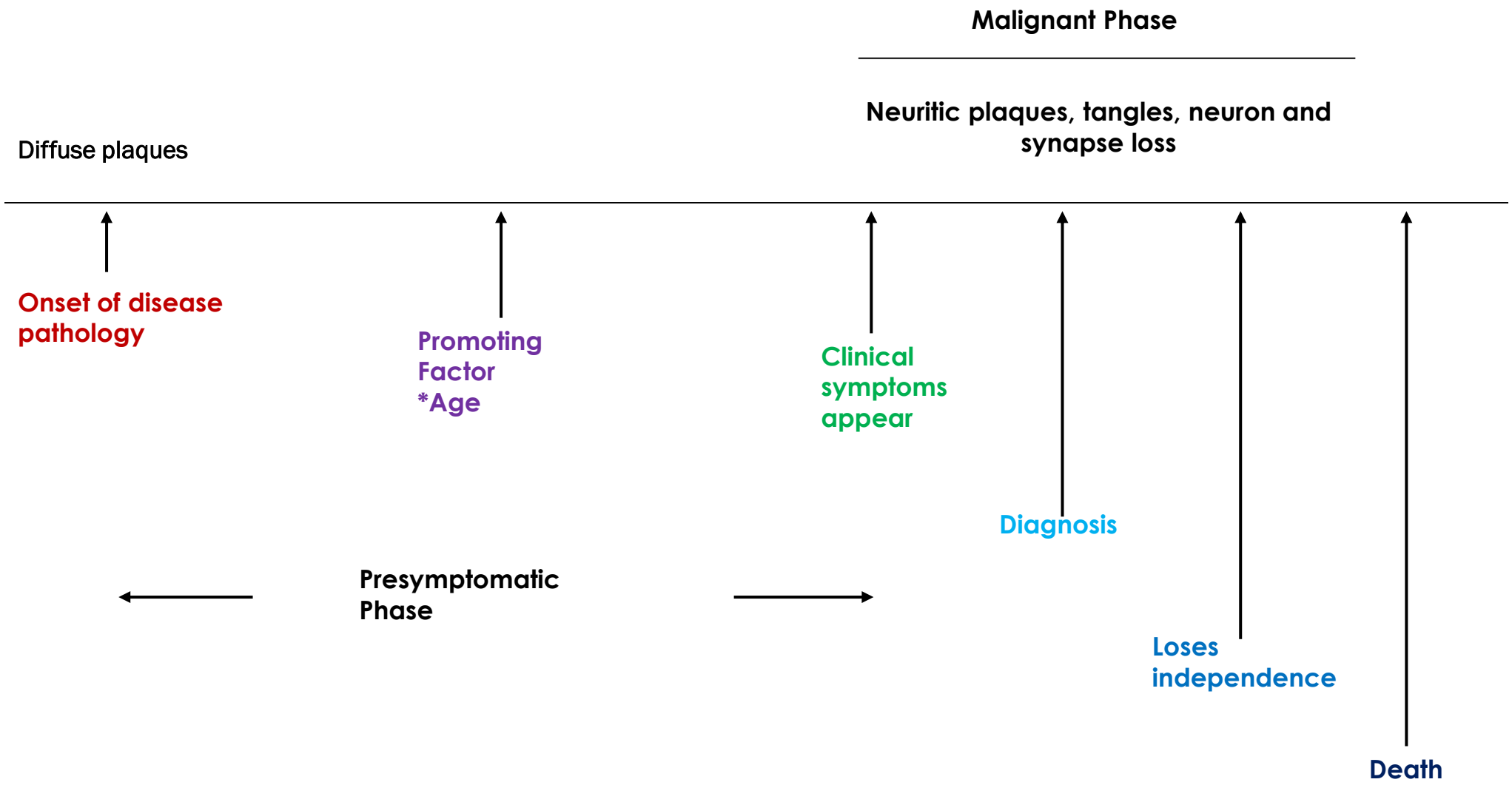
Impact of Alzheimer's Disease: Most Common Cause of Dementia

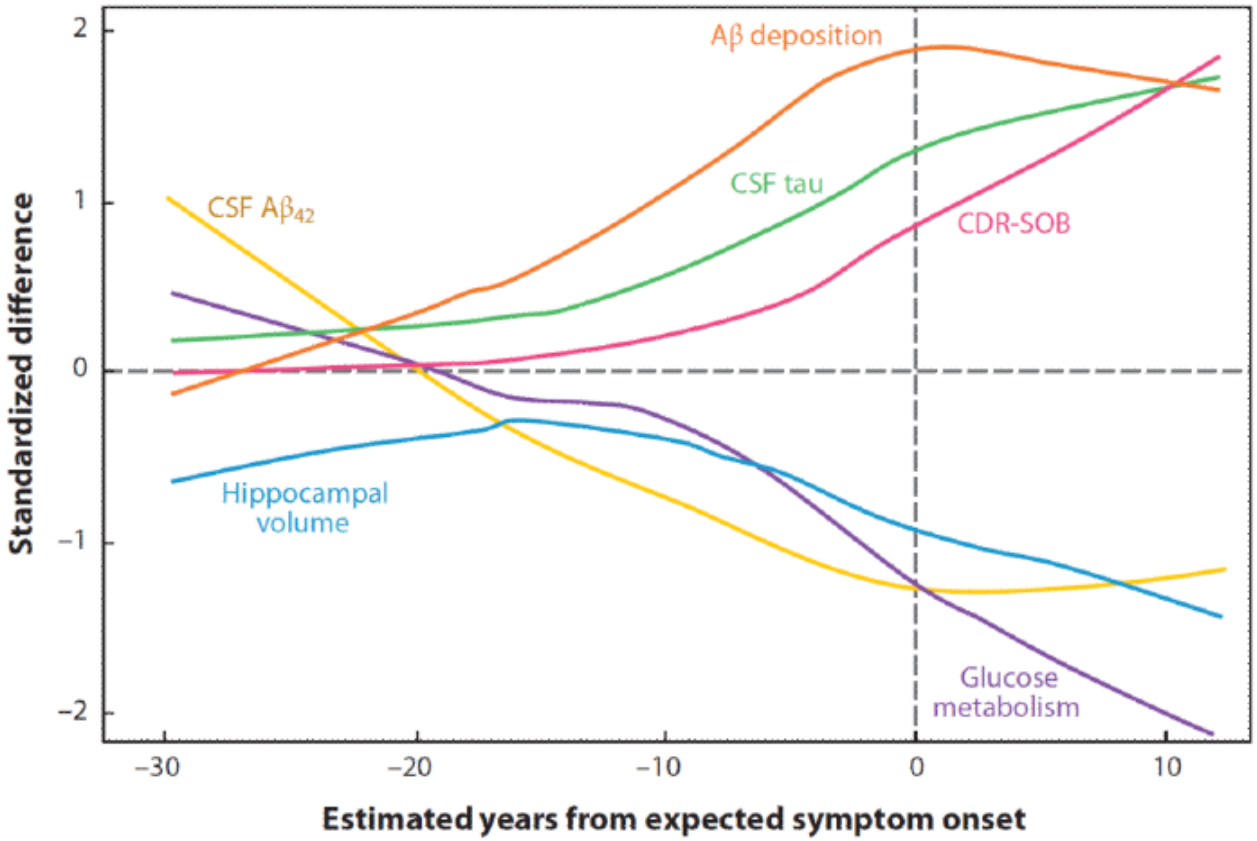
- 5.5 million Americans have AD; 16 million by 2050
- 6th leading cause of death (5th over age of 65)
- Someone is diagnosed with AD every 66 seconds
- Mortality from AD has increased by 89% since 2000
- Over $259 billion in health care costs in 2017
- 1n 2016, 15 million Americans provided care valued at $230 billion

2017 Alzheimer's Association Facts & Figures

Stages of Alzheimer's Disease

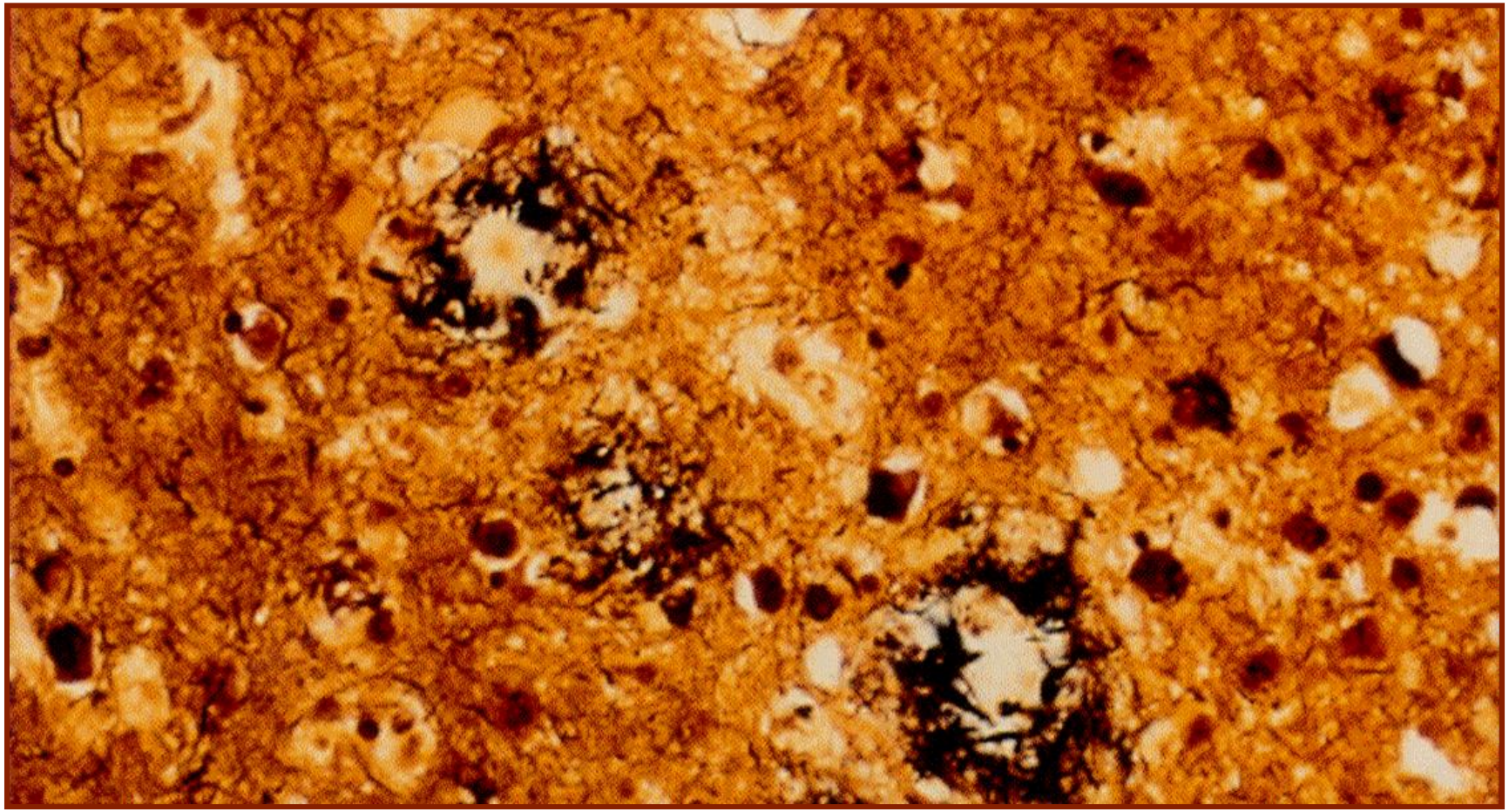


DIAN Study: Estimated Biomarker Changes Relative to Symptom Onset

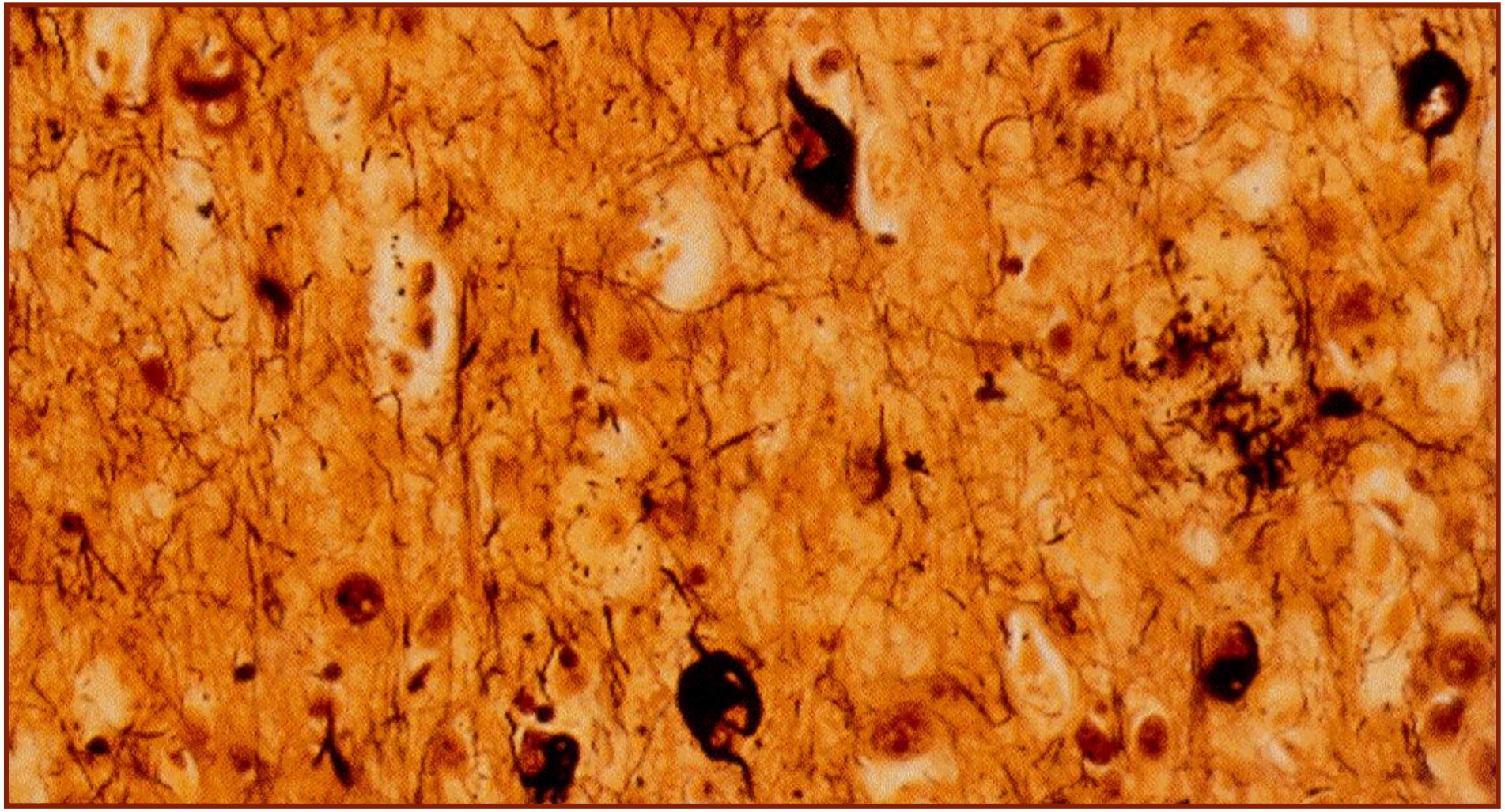


Bateman et al., *New England J Med*; 367; 795-804, 2012

Diagnostic Hallmark of AD: Amyloid Plaque



Diagnostic Hallmark of AD: Neurofibrillary Tangle



NIA/Alzheimer's Association Diagnostic Criteria for Dementia

- Cognitive/behavioral symptoms that:
  - Interfere with functional ability
  - Represent a decline from previous function
  - Are not explained by delirium or major psychiatric disorder
  - Are detected through a combination of history taking & objective cognitive assessment
  - Affect at least 2 cognitive domains (memory, reasoning/judgment, visuospatial skills, language, personality)

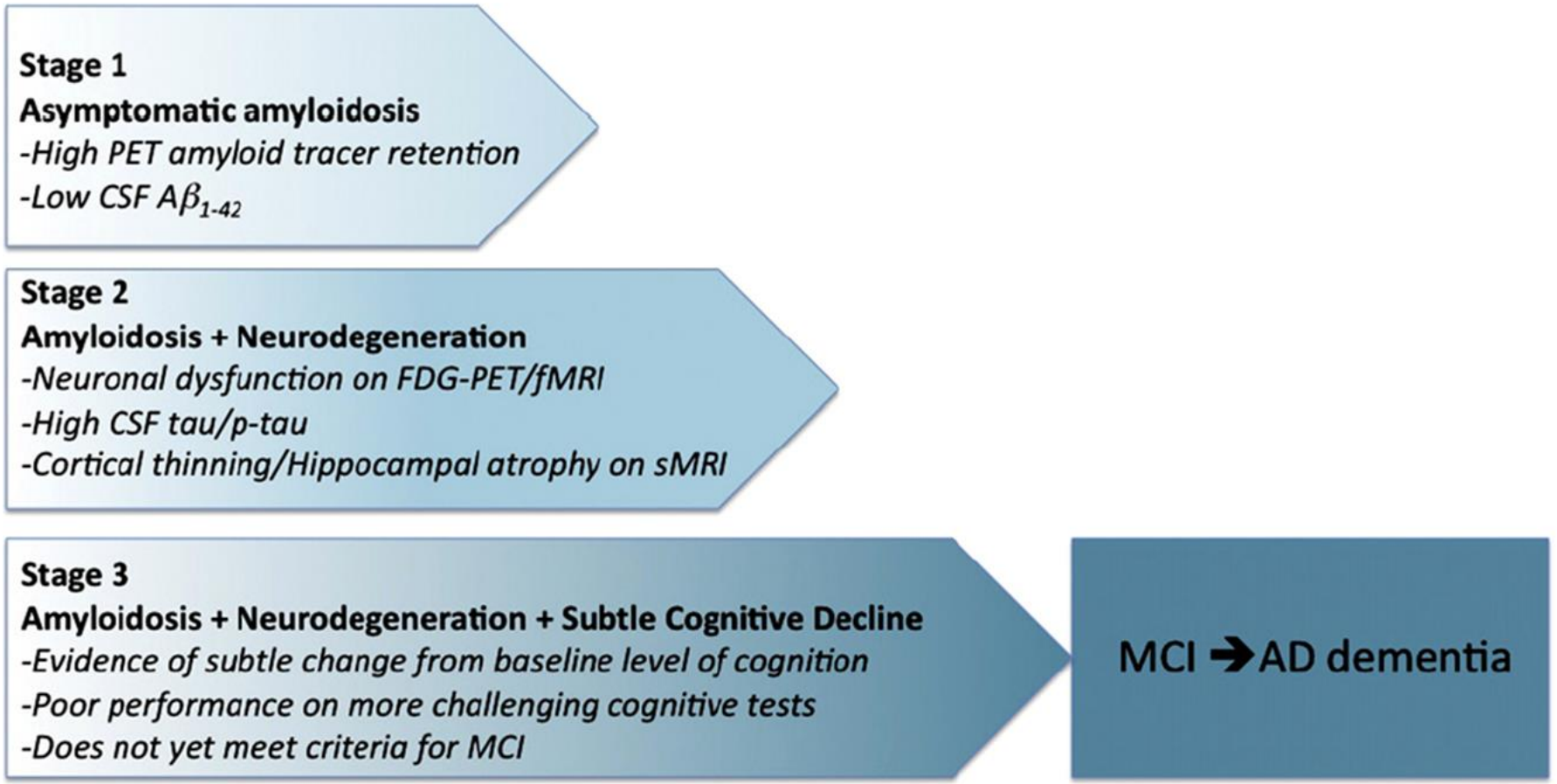
McKhann et al. Alzheimer's & Dementia 2011;7:263-269

NIA/Alzheimer's Association Diagnostic Criteria for Probable AD

- Meets criteria for dementia
- Gradual onset
- Initial & most prominent cognitive deficits:
  - Amnestic (memory)
  - Non-amnestic (language, visuospatial, executive dysfunction)
- *Probable AD with increased certainty:*
  - documented decline
  - genetic mutation
  - Biomarker positivity

McKhann et al. Alzheimer's & Dementia 2011;7:263-269

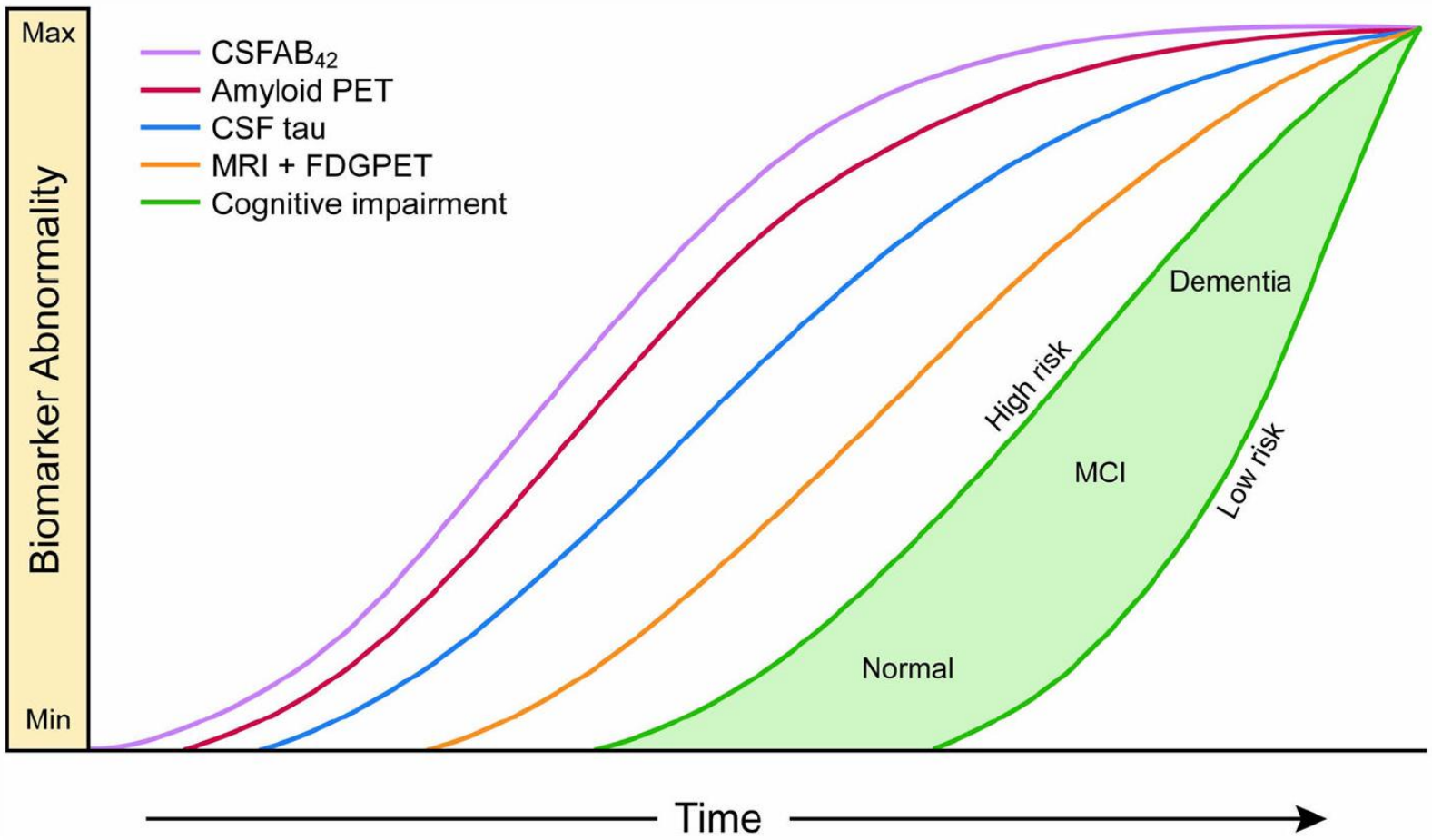
Stages of Alzheimer's Disease



New ATN Classification of Alzheimer's Disease

Biomarker Profile	Syndromal Cognitive Stage: Cognitively unimpaired	MCI	dementia
A-T-N-	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
$A^+T^-N^-$	Preclinical Alzheimer's pathophysiology	Alzheimer's pathophysiology contributing to MCI	Alzheimer's pathophysiology contributing to dementia
$A^+T^-N^+$	Preclinical Alzheimer's pathophysiology	Alzheimer's pathophysiology contributing to MCI	Alzheimer's pathophysiology contributing to dementia
$A^+T^+N^-$	Preclinical Alzheimer's disease	Alzheimer's disease contributing to MCI	Alzheimer's disease contributing to dementia
$A^+T^+N^+$	Preclinical Alzheimer's disease	Alzheimer's disease contributing to MCI	Alzheimer's disease contributing to dementia

Biomarkers of Alzheimer's Disease



Jack et al. Lancet Neurology; 12(2): 207-216, 2013

Neuroimaging Biomarkers of AD

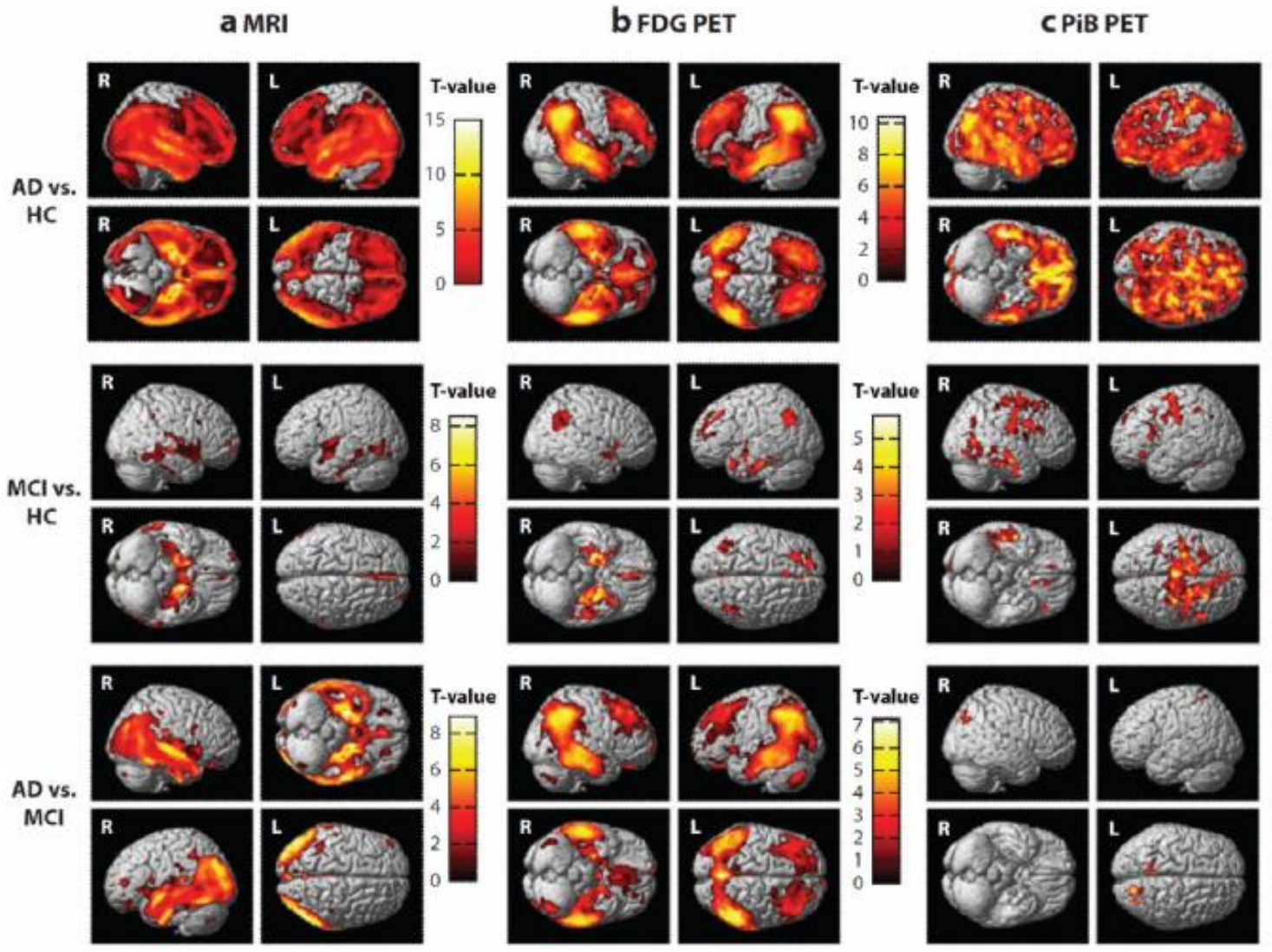
Magnetic Resonance Imaging (MRI)

- Widespread atrophy of medial temporal lobe (MTL), hippocampus, parietal, temporal and frontal lobes
- DTI/DWI reveal white matter and axonal disintegration and atrophy
- Conflicting results on functional MRI, but reduced activation on memory encoding tasks in MTL, post. Cingulate, precuneus, etc.

Positron Emission Tomography (PET) Imaging

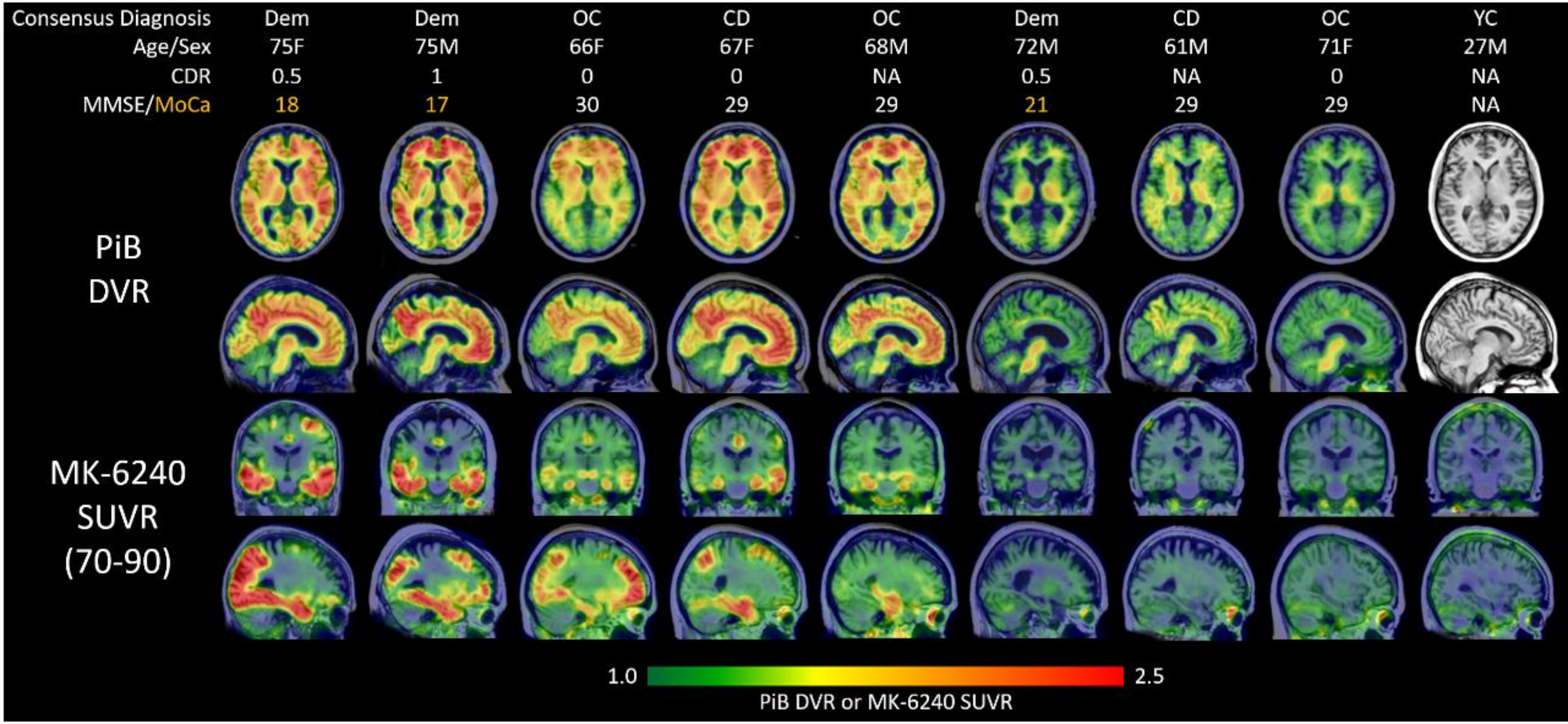
- Amyloid and tau imaging reveals deposition of these proteins in areas known to be afflicted by AD
- FDG PET reveals reduced metabolism in temporoparietal, posterior cingulate, MTL
- Neuroinflammation and receptor imaging

MRI and PET Imaging in Alzheimer's Disease



Risacher et al. *Annual Rev Clin Psychol; 9:621-648, 2013*

Wisconsin ADRC: PET Amyloid and Tau Imaging



CSF Biomarkers of Alzheimer's Disease

AD Pathology-Related Mechanism	CSF Measure
Amyloid Deposition	Aβ40, Aβ42, sAPPα, sAPPβ, Aβ oligomers, BACE1 levels/activity, ratios e.g., Aβ42/p-Tau, Aβ40/Aβ42, N-terminal truncated Aβ42 APLP-1
Neurodegeneration	Total Tau, p-Tau, oligomeric forms of Tau
Neuronal/Axonal Damage and White Matter Integrity	Neurofilament L (NFL),
Synaptic Function/Damage	Neurogranin, SNAP25, Visinin-like-protein 1 (VLP1),
Neuroinflammation	YKL-40, MCP1, Soluble form of TREM2, cytokines, chemokines, com3, S-100

Meta-analysis of CSF Biomarkers of AD

- Olsson et al. analyzed CSF data from 231 studies involving over 15,600 patients with AD, and more than 13,000 healthy controls
- Four CSF biomarkers – total tau, p-tau, neurofilament light chain (NFL) and Aβ-42 emerged as the most robust measures differentiating AD from controls
- Moderate effect sizes were observed for VILIP-1, neuron-specific enolase (NSE), YKL-40 and heart fatty acid-binding protein (HF-ABP)
- AD and controls could not be differentiated on CSF levels of Aβ-38, Aβ-40, sAPP α or β, MCP-1, GFAP and CSF-plasma ratio of albumin

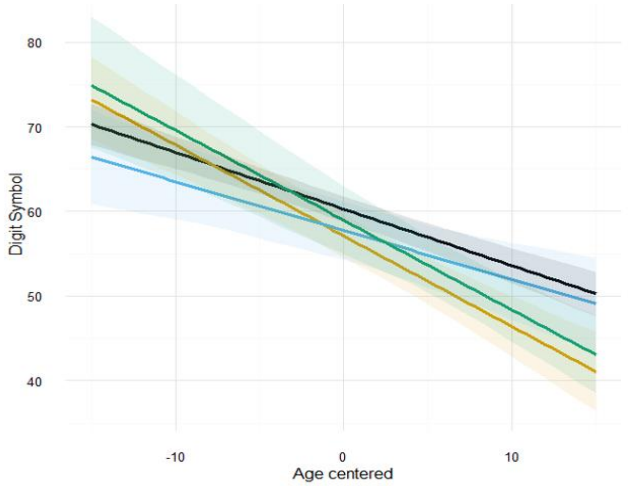
Olsson B, Lancet Neurol. June 15(7), 673-694, 2016

Wisconsin Cohorts on Preclinical AD

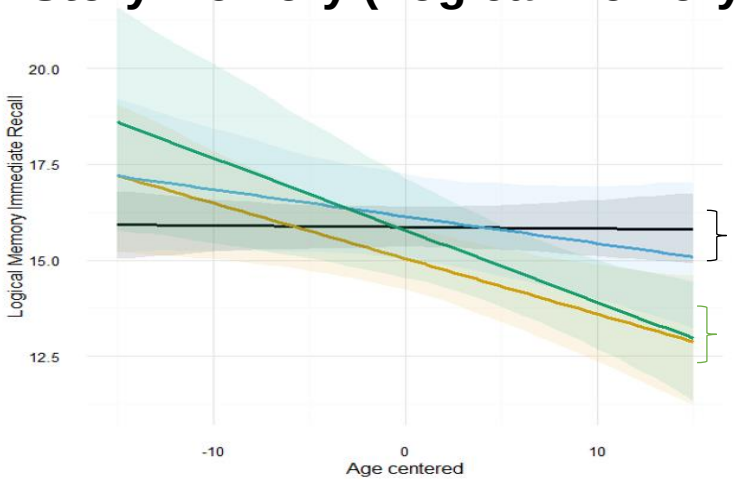
	University of Wisconsin Alzheimer's Disease Program	
	NIH Wisconsin ADRC	
Cohort	**IMPACT**	**WRAP**
Cohort characteristics	Ages 45-65 years at baseline AD parental history positive (PH+, 75%) and negative (PH-, 25%)	Ages 45-65 years at baseline AD parental history positive (PH+, 70%) and negative (PH-, 30%)
Sample size	n=450	n=1560
Year started	2009	2001
Visit frequency	Every other year	Every other year
Cognitive battery	NACC (National Alzheimer's Coordinating Centers) cognitive battery & additional tests	Extensive cognitive battery
Computerized cognitive battery	NIH Toolbox cognitive battery	Cogstate computerized battery
Questionnaires	Medical history, medications, lifestyle factors, sleep, cognitive activities, physical activity	Medical history, medications, lifestyle factors, sleep, cognitive activities, physical activity
Cerebrospinal fluid (CSF) samples	Baseline CSF samples in consented subjects; as of 2015, CSF collected every 2 years	Baseline and follow-up CSF samples in subset
Neuroimaging	Structural MRI, perfusion, 4-D flow, DTI	ADRC MRI, amyloid PET, tau PET

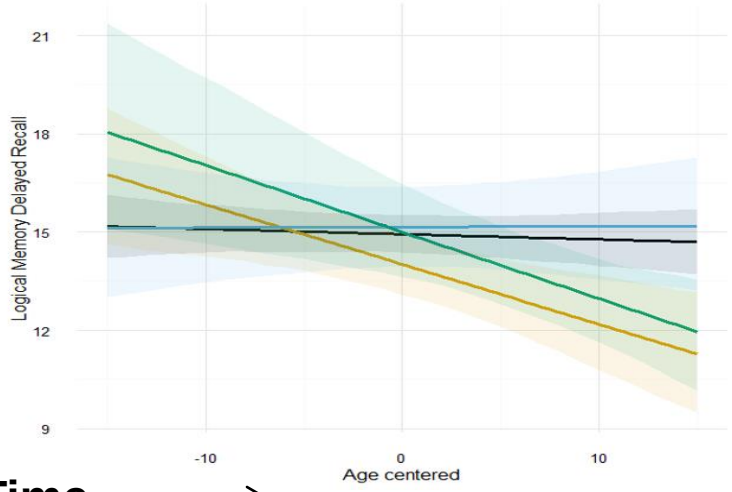
Wisconsin ADRC: CSF Biomarkers and Cognitive Function Trajectories in At Risk Study Participants

Executive Functioning (Digit Symbol)



Story Memory (Logical Memory)





Aβ-/Tau-
Aβ-/Tau+
Aβ+
Aβ+/Tau+

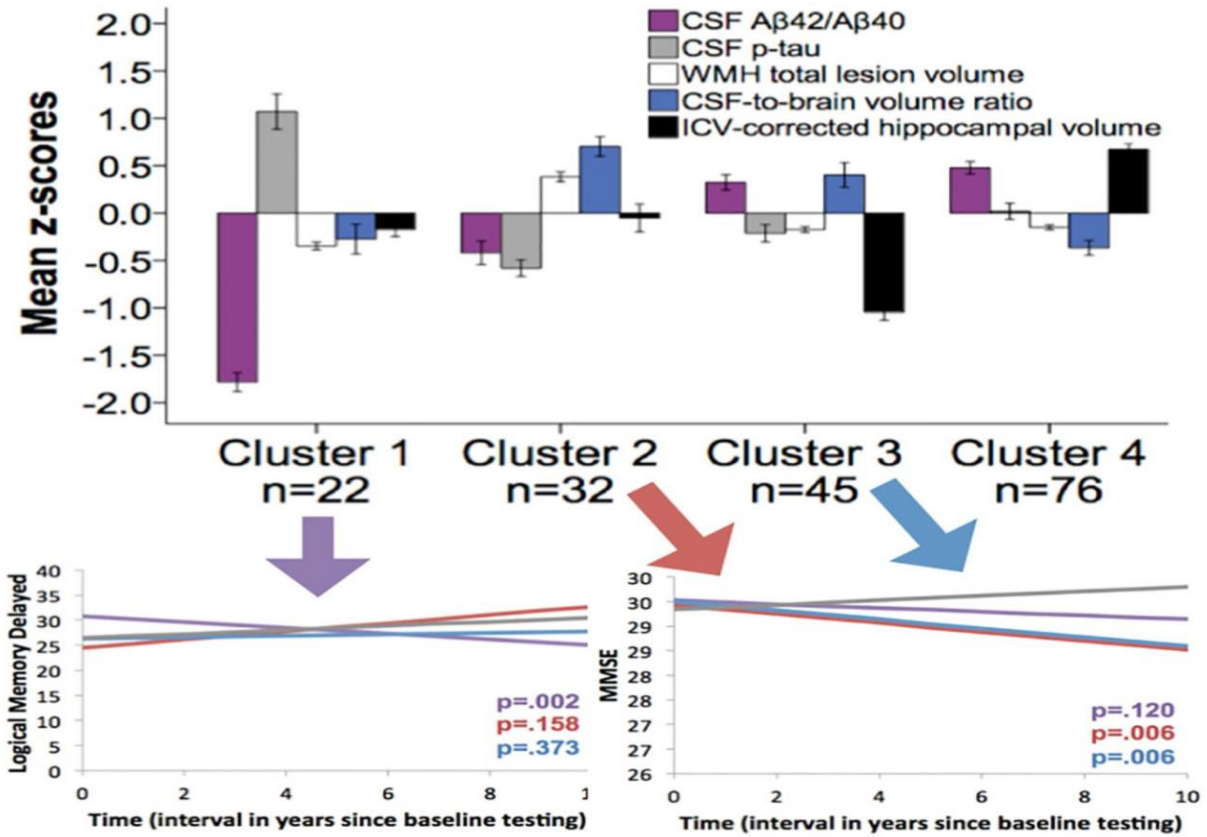
Time ⟶

Fixed Effects:
Biomarker Group
Slope (Age at each visit)
Gender
Education
Practice Effects
Biomarker Group x Age at each visit

Random Effects:
Intercept
Slope

Mixed-effects regression models (R lme4)

Wisconsin ADRC: Clinical Utility of Multimodal Biomarker Data – AD Risk Prediction



Annie M. Racine et al. Brain 2016;139:2261-2274

BRAIN A JOURNAL OF NEUROLOGY

What does resilience to dementia look like?

Hypothesis: lower gliosis, less neural injury, and less synaptic degeneration

Three groups compared:

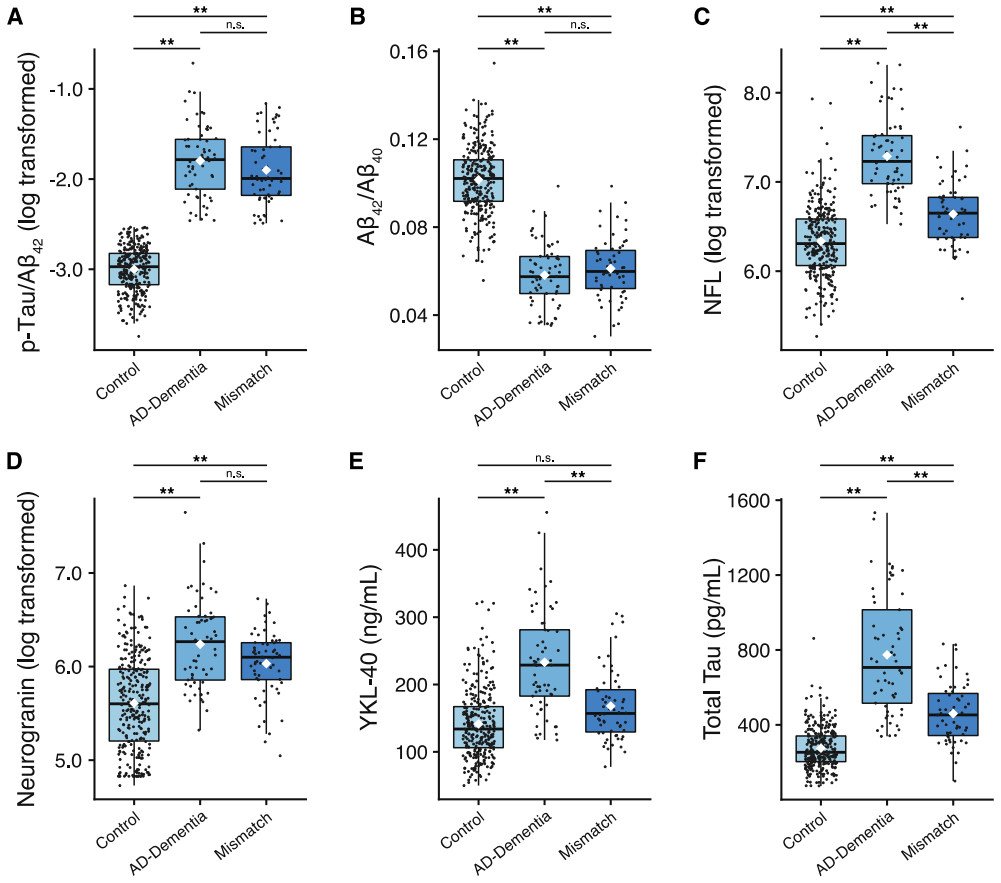
- Dementia-AD (n=40): **YES** dementia, **YES** amyloid/tau
- Controls (n=25): **NO** dementia, **NO** amyloid/tau
- Mismatches (n=14): **NO** dementia, **YES** amyloid/tau

CSF Biomarkers of interest:

- p-Tau/Aβ42: Alzheimer's pathology
- Aβ42/Aβ40: Amyloid pathology
- NFL: Axonal degeneration
- Neurogranin: Synaptic degeneration
- YKL-40: Activated microglia & astrocytes
- Total Tau: Neurodegeneration

Results:

- The "mismatch" group (normal cognition despite AD-level of plaques and tangles) had lower NFL (C), less gliosis (E) and lower total tau (F) than participants with dementia.

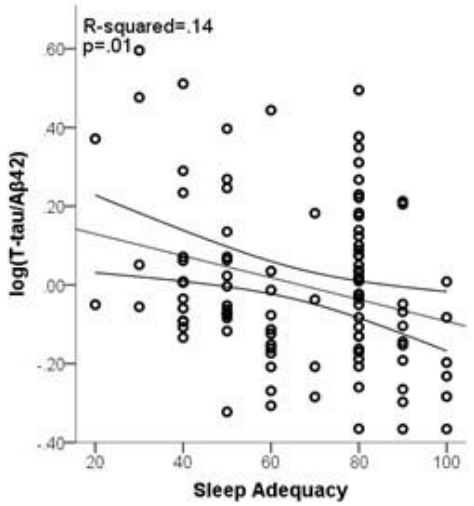


Merluzzi et al., Under Review

Wisconsin ADRC: Healthy Behaviors and CSF and Imaging Markers of AD

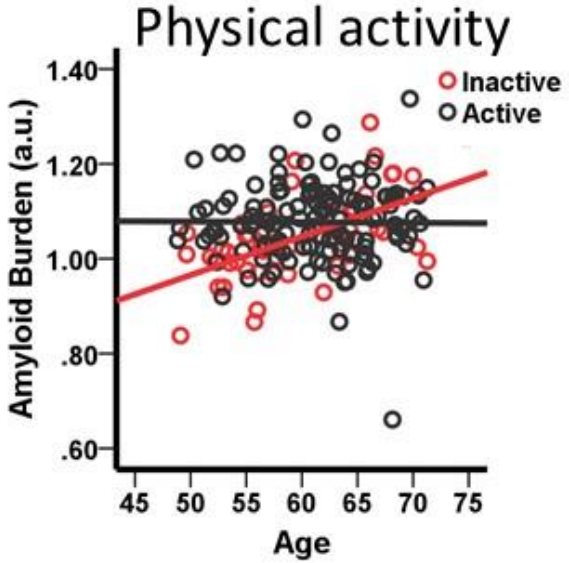
Health Behaviors and AD pathology / risk

Sleep



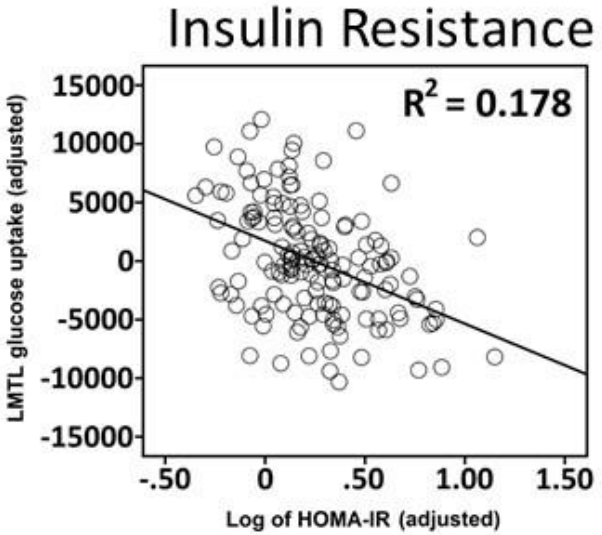
Associations with sleep and AD pathology
Sprecher et al *Neurology* (2017—in press)
Sprecher et al neurobiology of aging (2015)

Physical activity



Okonkwo et al 2014, *Neurology*
Greater phys activity --> lower amyloid burden with age

Insulin Resistance

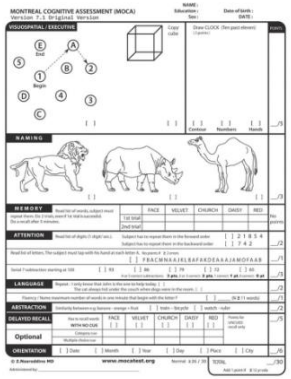


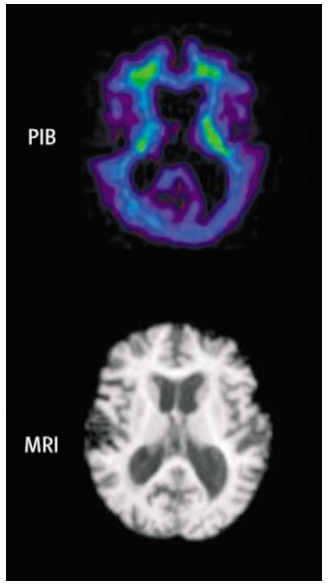
Insulin resistance is associated with FDG
Willette et al 2015 JAMA Neurol

Similar findings seen with amyloid
Willette et al 2013

Multimodal Approach to the Diagnosis of AD

Patient presents to clinic with concern about AD risk

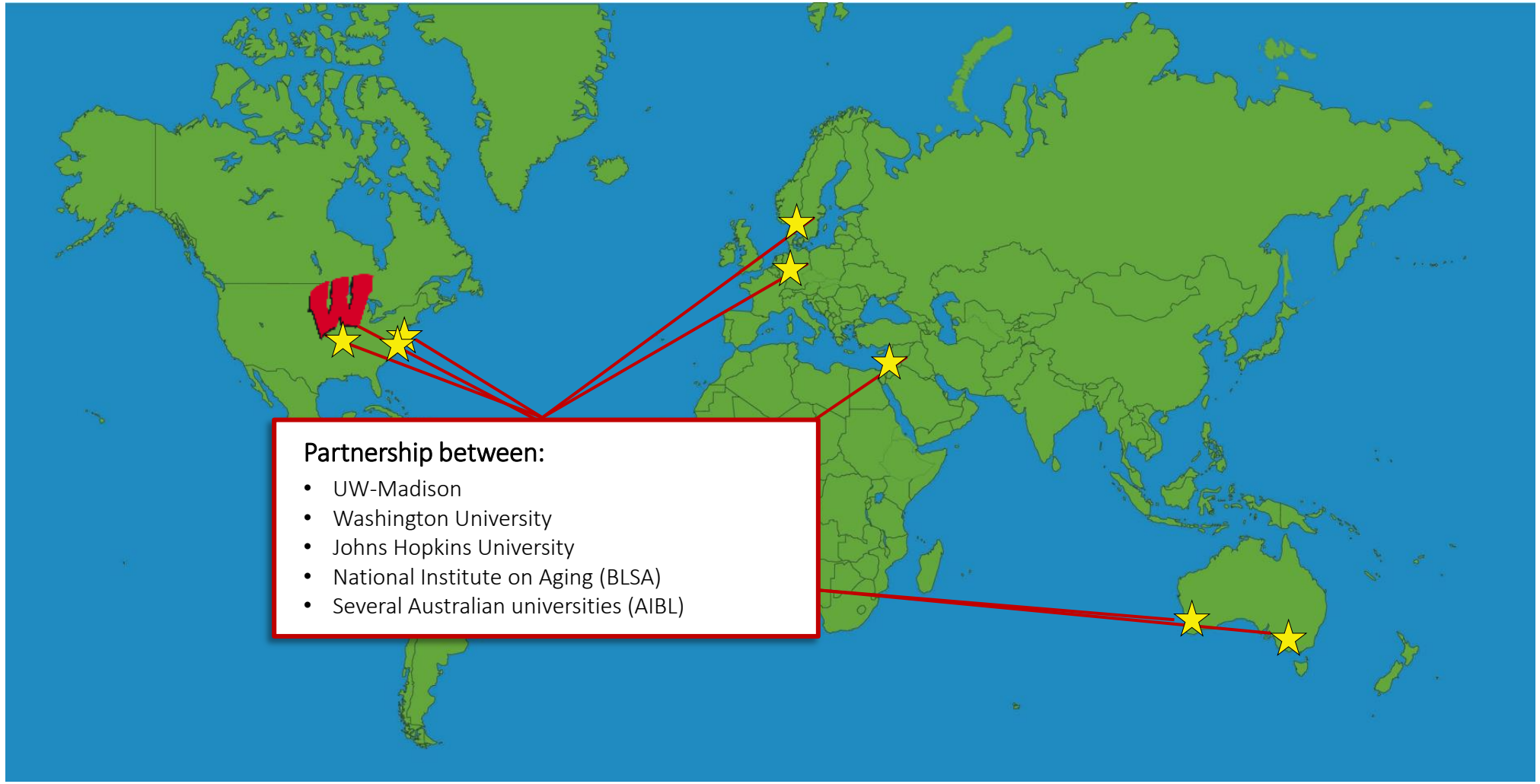




Alzheimer's Risk Profile

- ☐ High risk
- ☐ Moderate risk
- ☐ Low risk
- ☒ Very low risk

Preclinical AD Consortium



Conclusions

- Clinical diagnosis of Alzheimer's disease can now be made reliably with comprehensive medical evaluation and the use of cognitive testing, neuroimaging and CSF assays
- An important caveat in interpretation of CSF biomarker data is variability in sample processing, storage, shipment and analytical techniques between studies and sites
- Better understanding of who is amyloid and tau positive and if they develop clinical symptoms will be key to understanding risk and resilience to AD
- Neuroimaging and CSF biomarkers will become important components of multimodal approaches to predict conversion from preclinical to clinical stages of AD
- Neuroimaging and CSF biomarkers can represent favorable effects of healthy behavior on AD pathology
- The validity and clinical utility of PET amyloid/tau imaging and CSF biomarkers has to evaluated in larger clinical studies before widespread applications for patient care