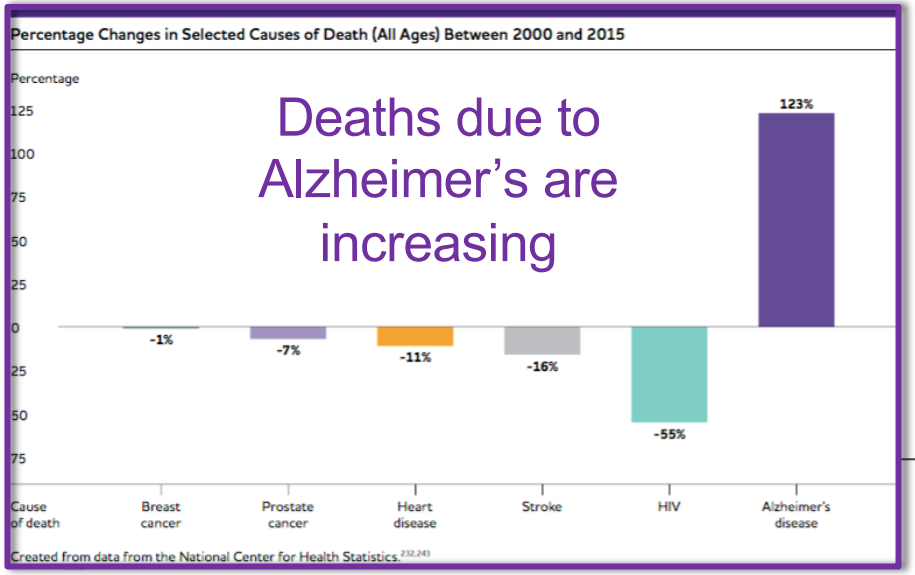
RESEARCH FRAMEWORK FOR ADRD

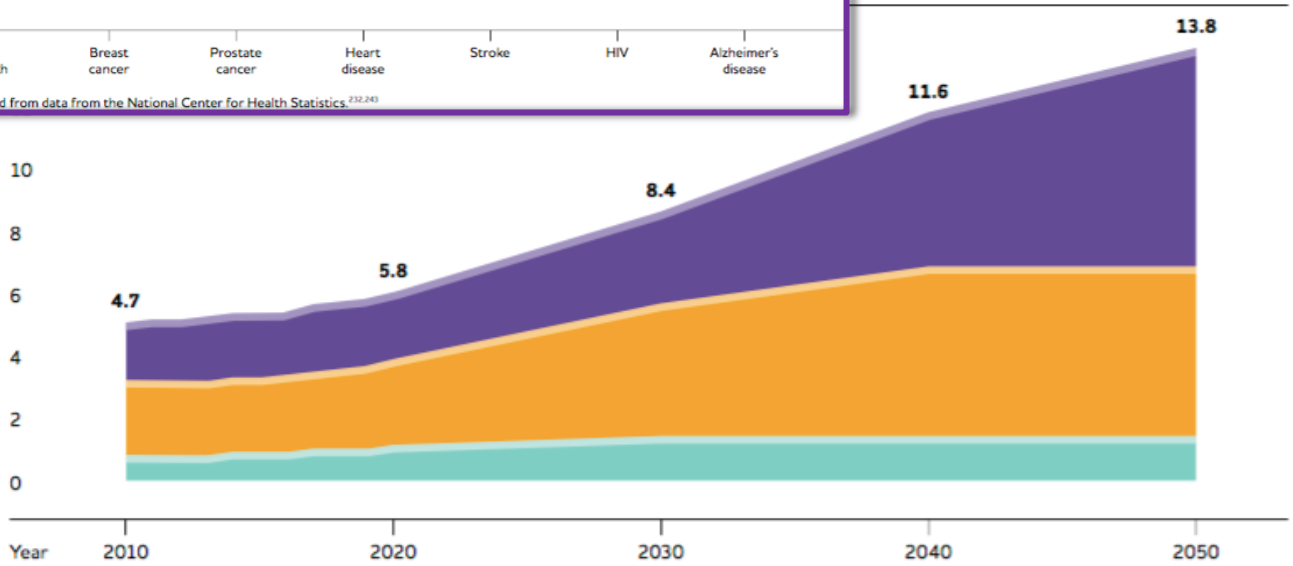
NAD-RCMAR EVENT

Thomas J. Grabowski, MD
UW Radiology and Neurology
Director, UW Memory and Brain Wellness Center
Director, UW Alzheimer's Disease Research Center
April 29, 2019

Alzheimer's Disease: The Biomedical Challenge of our Time



Deaths due to Alzheimer's are increasing



Created from data from Hebert et al.[A11,30]

alzheimer's association

Outline

- Understanding dementia vs AD
- What is “ADRD”?
- Biomarkers of AD
- The research framework for AD diagnosis
- Preclinical AD and resilience to dementia
- Practicalities of research diagnosis
- Considerations for study of Native populations

ADRD: Alzheimer's disease and Related Dementias

Dementia
(DSM5: Major Neurocognitive Disorder)

1. Substantial cognitive decline in one or more domains based on the concerns of the individual, a knowledgeable informant, or the clinician

Complex attention	*Language*
Executive function	*Perceptual-motor function*
Learning and memory	*Social cognition*

2. Decline in neurocognitive performance, typically involving test performance two or more standard deviations below appropriate norms on formal testing or equivalent evaluation

3. The cognitive deficits are sufficient to interfere with independence (requiring more than minimal assistance with IADLs)

Dementia
(DSM5: Minor Neurocognitive Disorder)

1. Modest cognitive decline in one or more domains based on the concerns of the individual, a knowledgeable informant, or the clinician

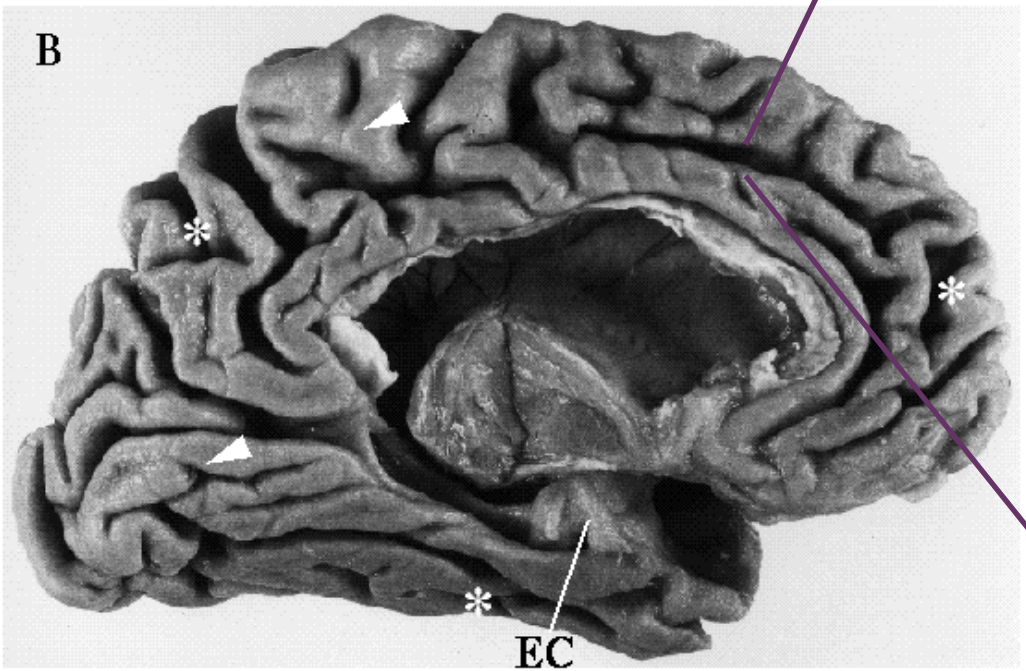
Complex attention	*Language*
Executive function	*Perceptual-motor function*
Learning and memory	*Social cognition*

2. Decline in neurocognitive performance, typically involving test performance one to two standard deviations below appropriate norms on formal testing or equivalent evaluation

3. The cognitive deficits are insufficient to interfere with independence (though greater effort, compensatory strategies, or accommodation may be required)

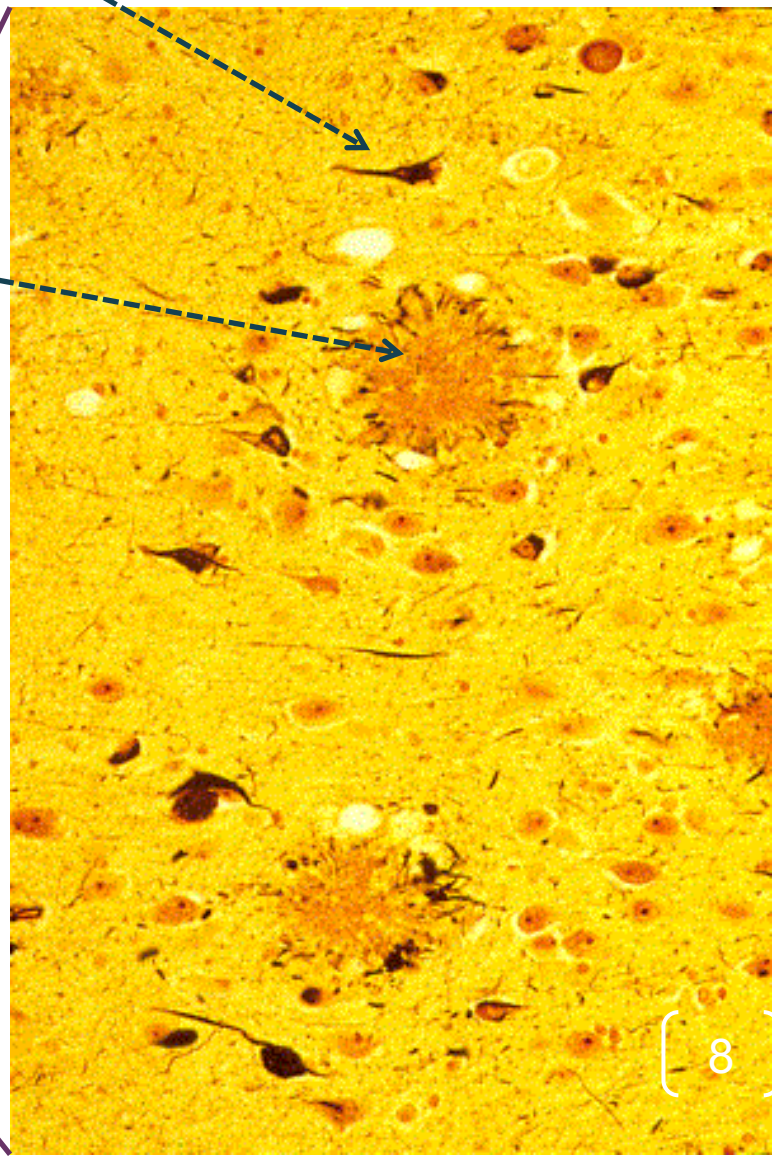
- Dementia/Major neurocognitive disorder and MCI/Minor neurocognitive disorder, are clinical terms describing the state of cognition and everyday function
- There are many potential etiologies, and some of them are not even degenerative

What is Alzheimer Disease?



Neurofibrillary Tangles

Amyloid Plaques



Alzheimer's disease

A degenerative disease of the brain with distinctive histopathology, specifically characterized by tissue loss accompanied by neuritic amyloid plaques and neurofibrillary tangles in the brain

- Alzheimer's disease is a pathological term describing a disease state of the brain
- Dementia is the typical manifestation of AD but there are also milder and preclinical manifestations

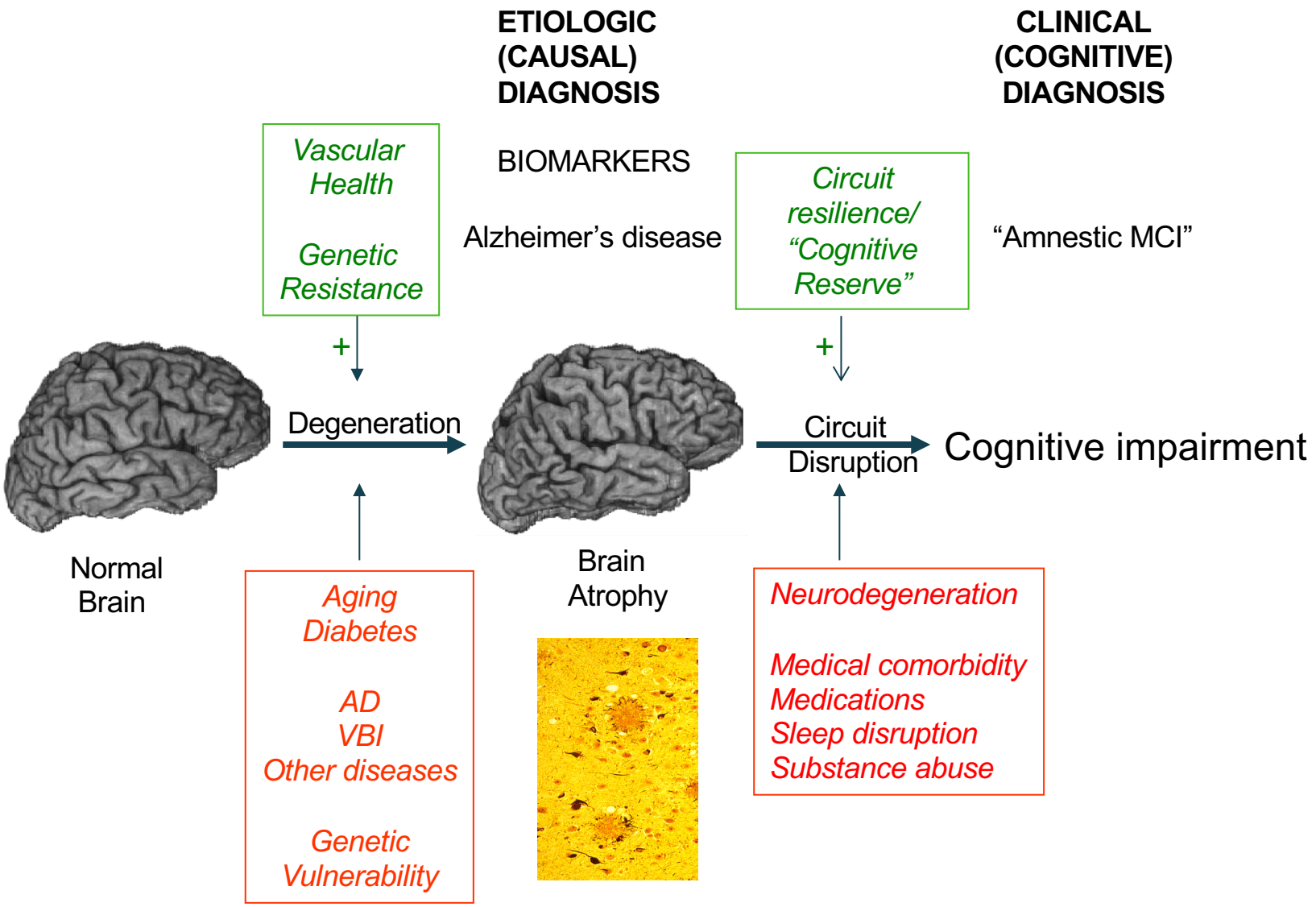
Confusing AD and dementia

- Statistics you hear on prevalence of Alzheimer's Disease (e.g. 5.8M Americans) means AD *dementia.*
- CPT codes from ICD-9 and ICD-10 for Alzheimer's disease mean AD *dementia.*
- There is no easy way to ICD-10 code "amnestic MCI due to Alzheimer's disease."
- So there is both public and professional conflation of AD and dementia

Keeping diagnosis straight

Cognitive diagnosis vs. Causal diagnosis!

- Dementia does not always mean Alzheimer's disease
  - "Comorbidity" is common – vascular, Lewy body, etc.
- "Alzheimer's" does not always mean dementia
  - "MCI due to Alzheimer's disease" is not self-contradictory


ETIOLOGIC (CAUSAL) DIAGNOSIS
CLINICAL (COGNITIVE) DIAGNOSIS
Vascular Health
Genetic Resistance
BIOMARKERS
Alzheimer's disease
Circuit resilience/ "Cognitive Reserve"
"Amnestic MCI"
+
+
Degeneration
Circuit Disruption
Cognitive impairment
Normal Brain
Brain Atrophy
Aging
Diabetes
AD
VBI
Other diseases
Genetic Vulnerability
Neurodegeneration
Medical comorbidity
Medications
Sleep disruption
Substance abuse

What else causes dementia?

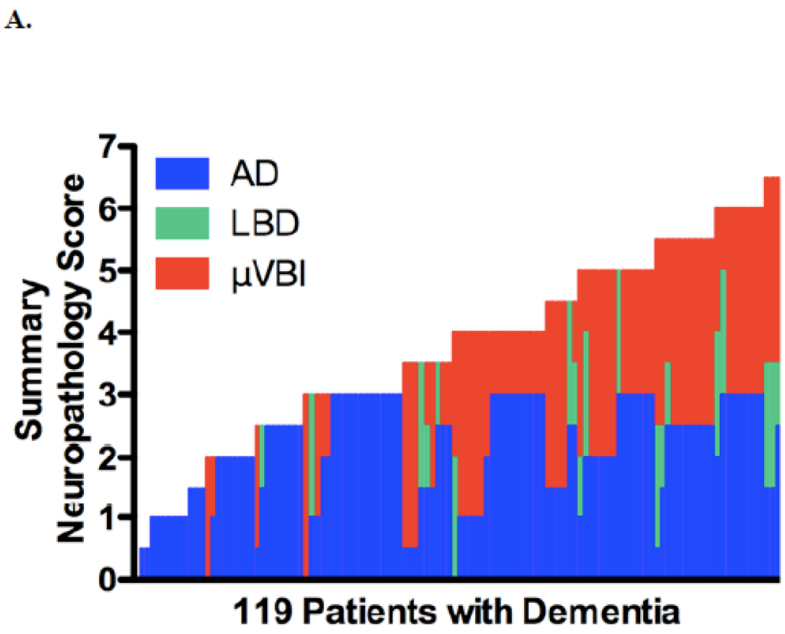
ADRD

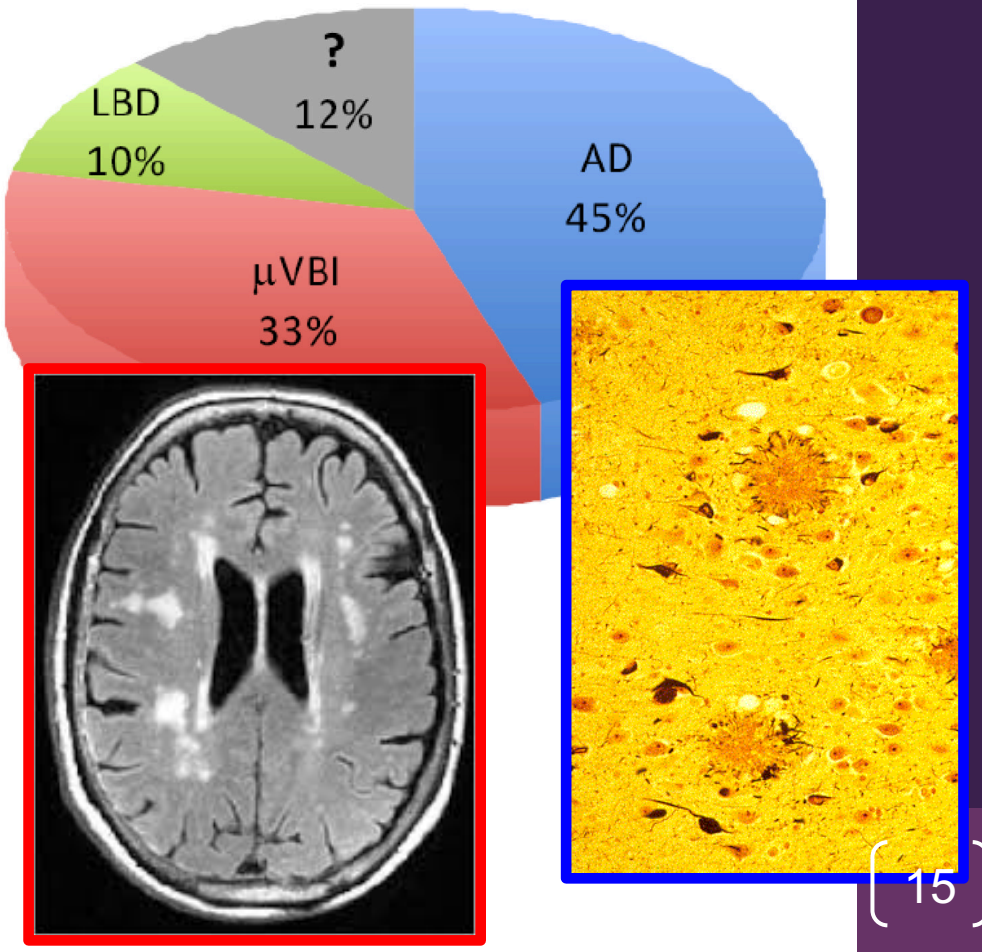
- Vascular brain injury
- Lewy body disease
- Frontotemporal degeneration

So designated officially by NIH

- Depression
- Metabolic disorders
- Structure disruption in the brain – hydrocephalus, tumor, subdural hematoma, etc
- And many more

ADRD comorbidity is the rule





Sonnen et al Arch Neurol 2011

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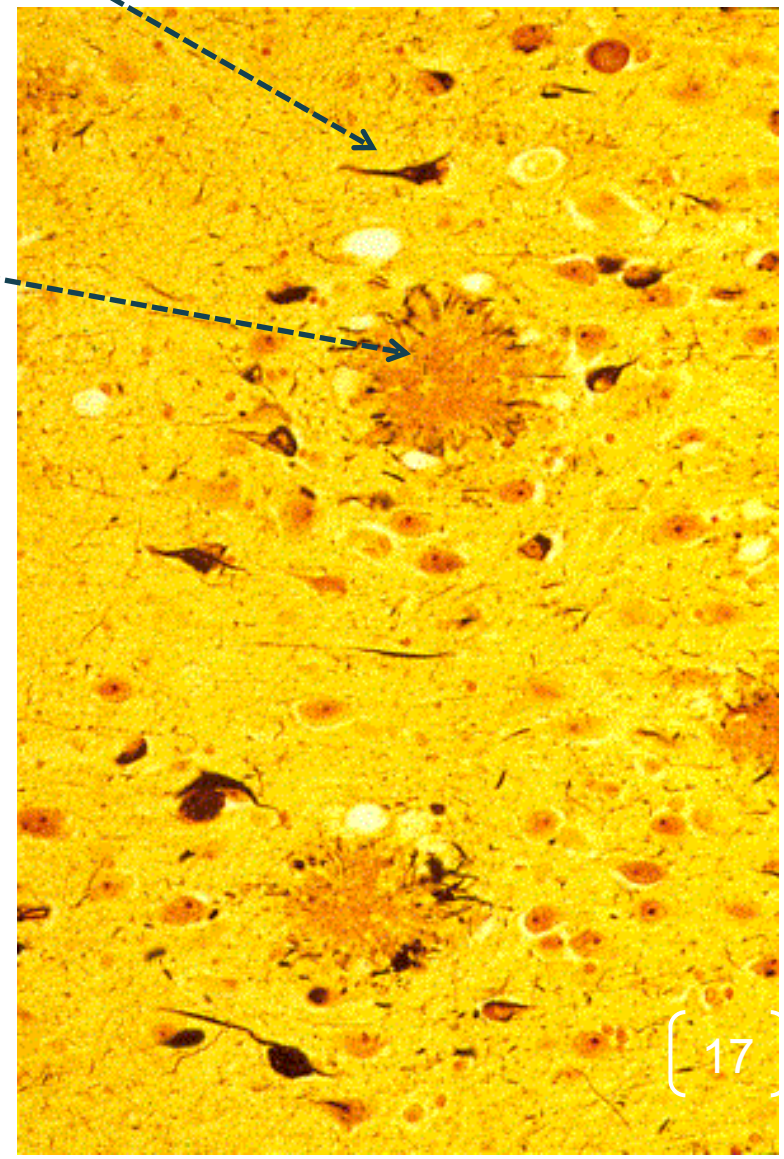
Alzheimer Disease and Its markers

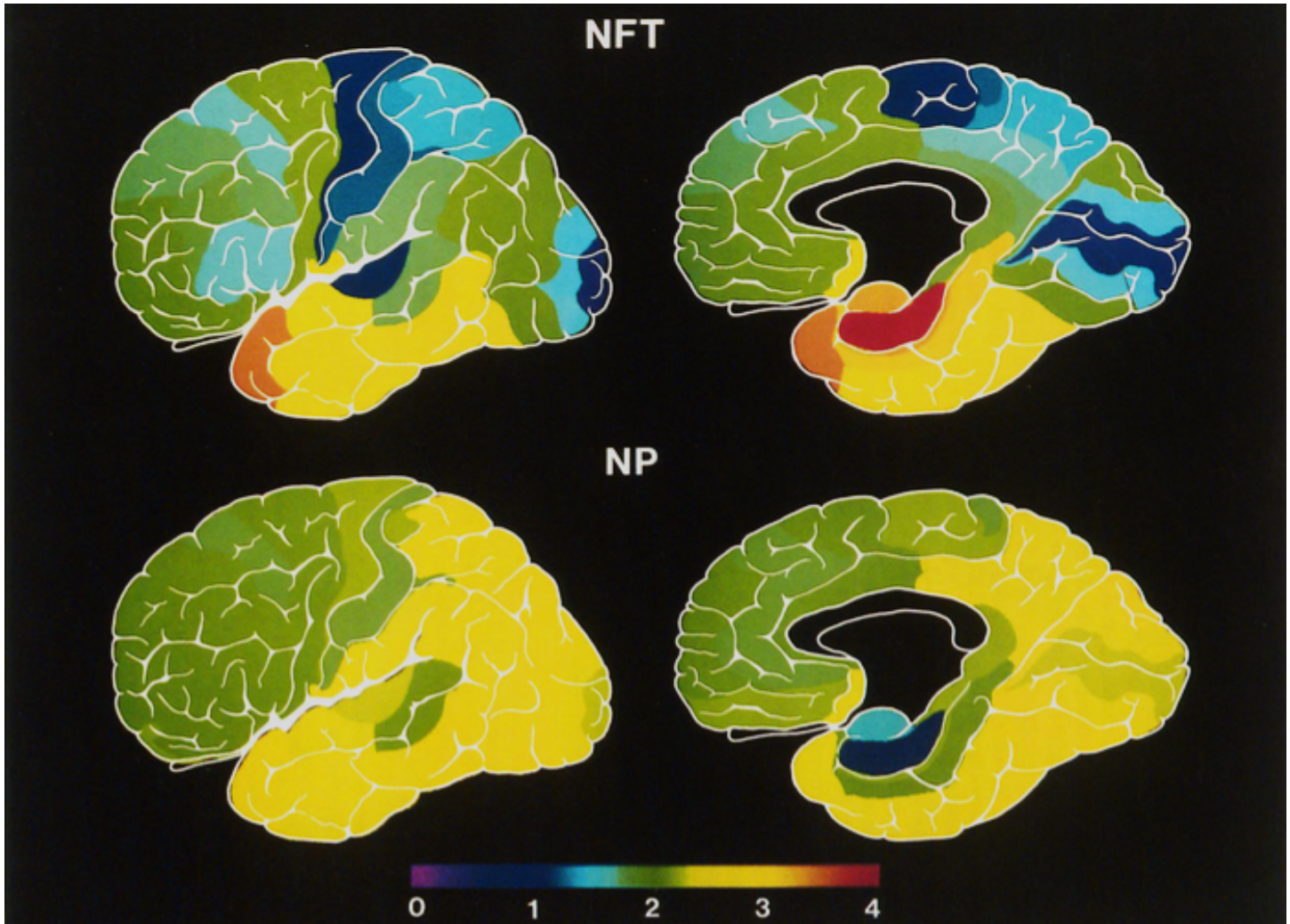
- Characteristics that signify disease processes.
- But the processes themselves are not clear.



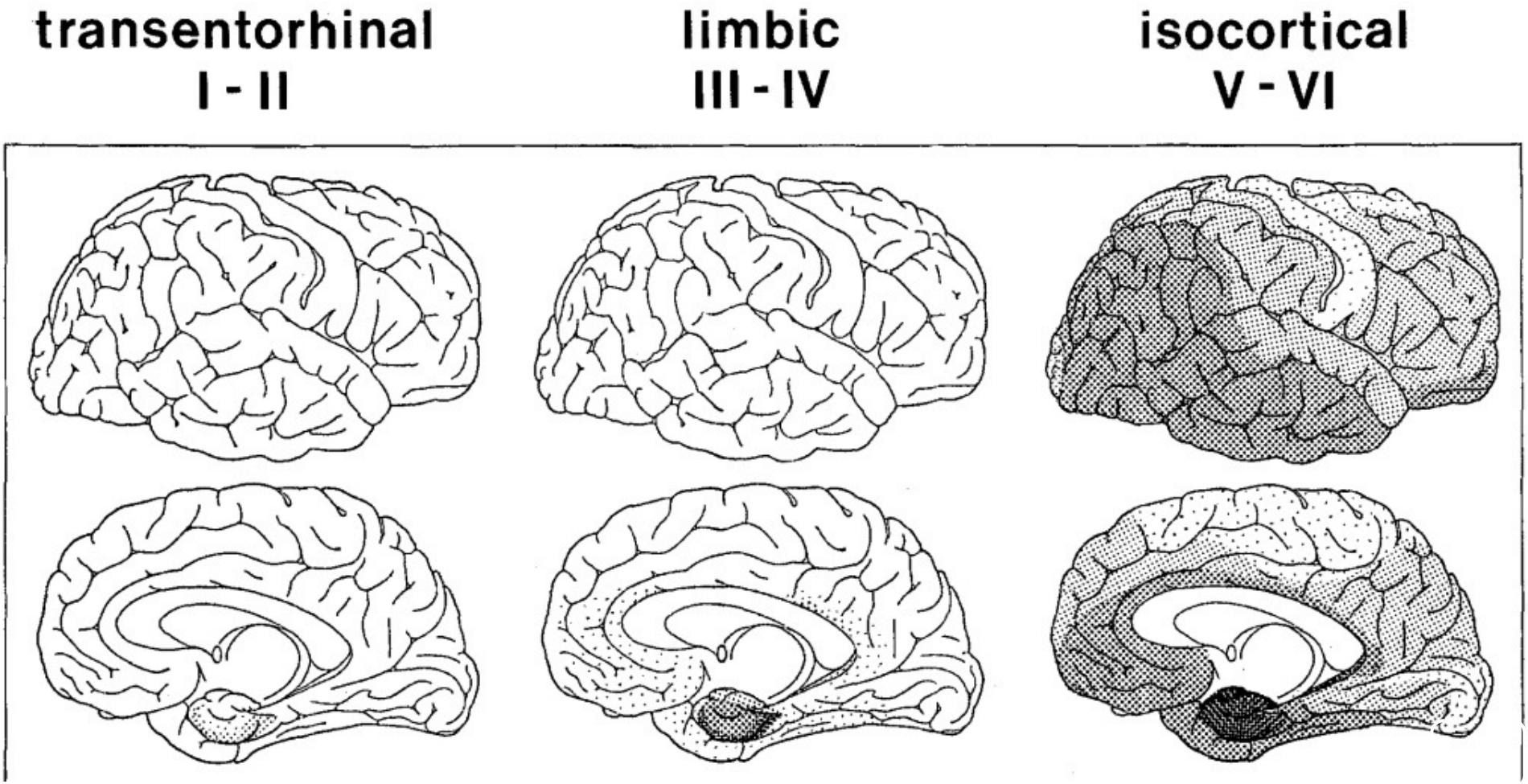
The Topographical and Neuroanatomical Distribution of Neurofibrillary Tangles and Neuritic Plaques in the Cerebral Cortex of Patients with Alzheimer's Disease

Steven E. Arnold,[1] Bradley T. Hyman,[1] Jill Flory,[2] Antonio R. Damasio,[1] and Gary W. Van Hoesen[1,2]

Departments of [1]Neurology and [2]Anatomy, University of Iowa College of Medicine, Iowa City, Iowa 52242



Braak Staging of Alzheimer's disease based on spread of neurofibrillary tangles



Tau/NFTs

- Early deposition in medial temporal lobe transentorhinal/entorhinal region
- Then hippocampus (CA1)

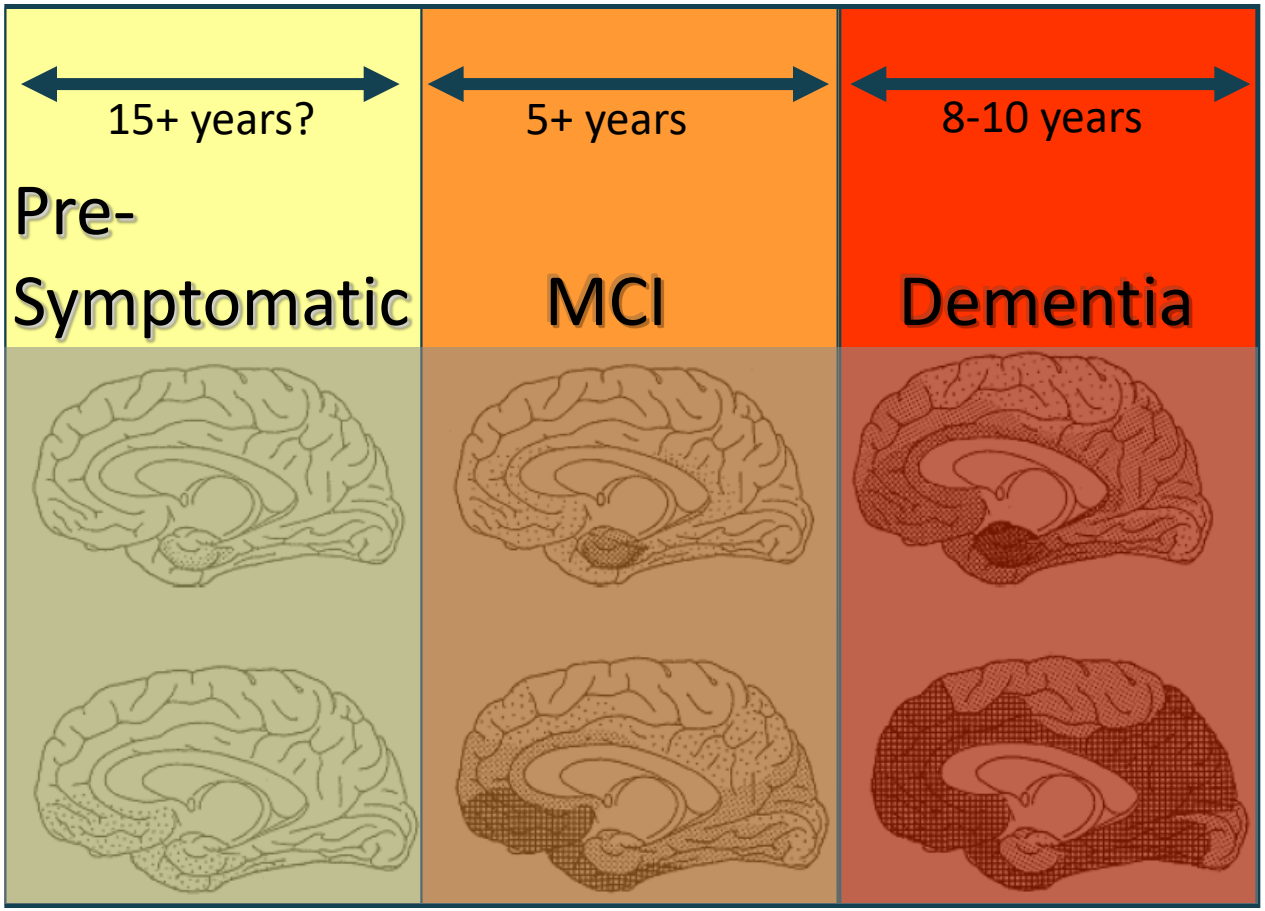
Memory loss

- Then association cortex – especially posterior

Cognitive loss

- Primary cortex last, motor cortex spared

Sensorimotor sparing

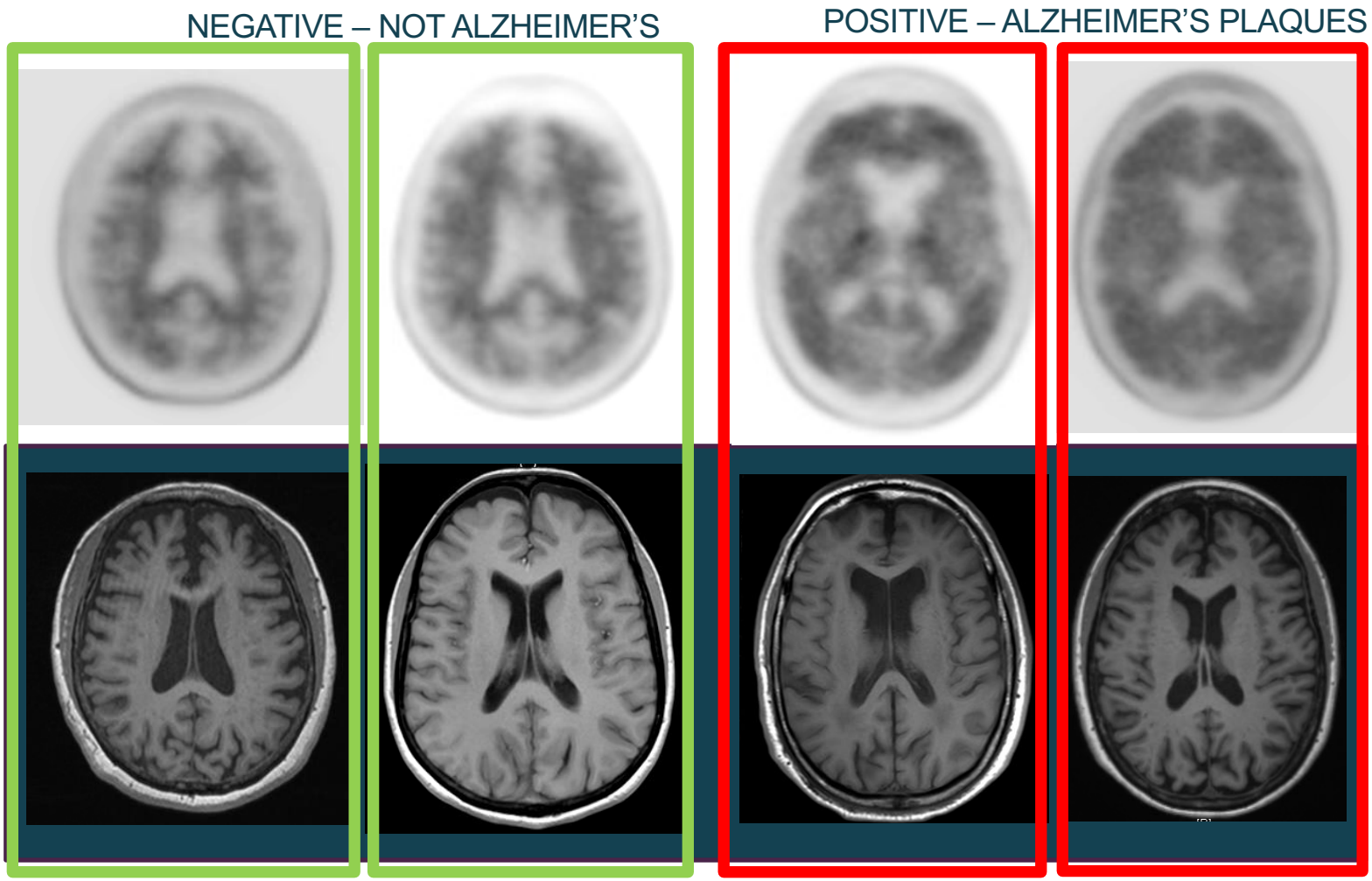

15+ years?
5+ years
8-10 years
Pre-Symptomatic
MCI
Dementia
Medial Temporal
Limbic
Cortical

Biomarkers

Measurable characteristics that signify disease processes

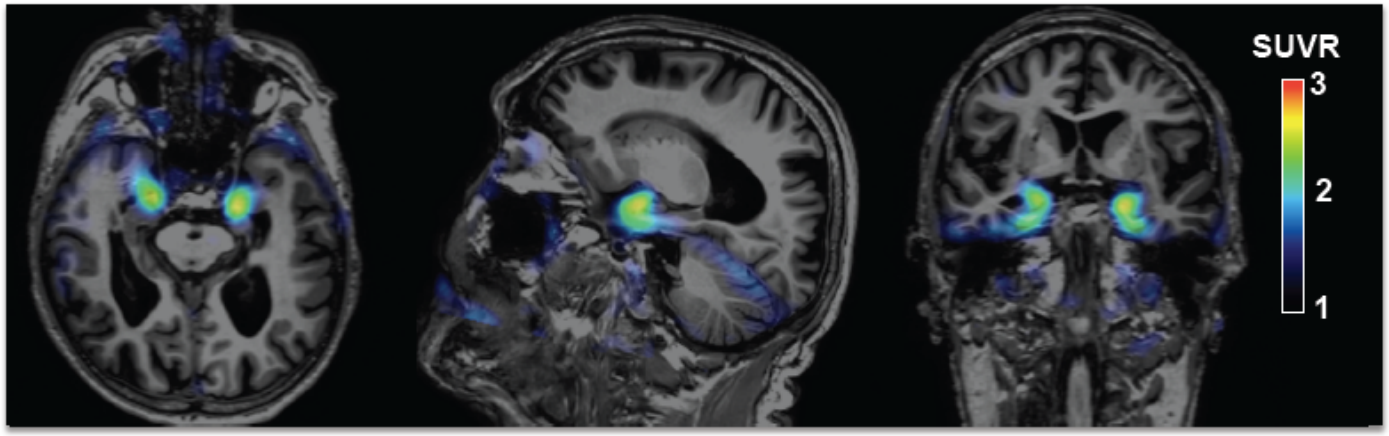
- Imaging tests – MRI, PET
- Spinal fluid protein levels

Amyloid PET scans

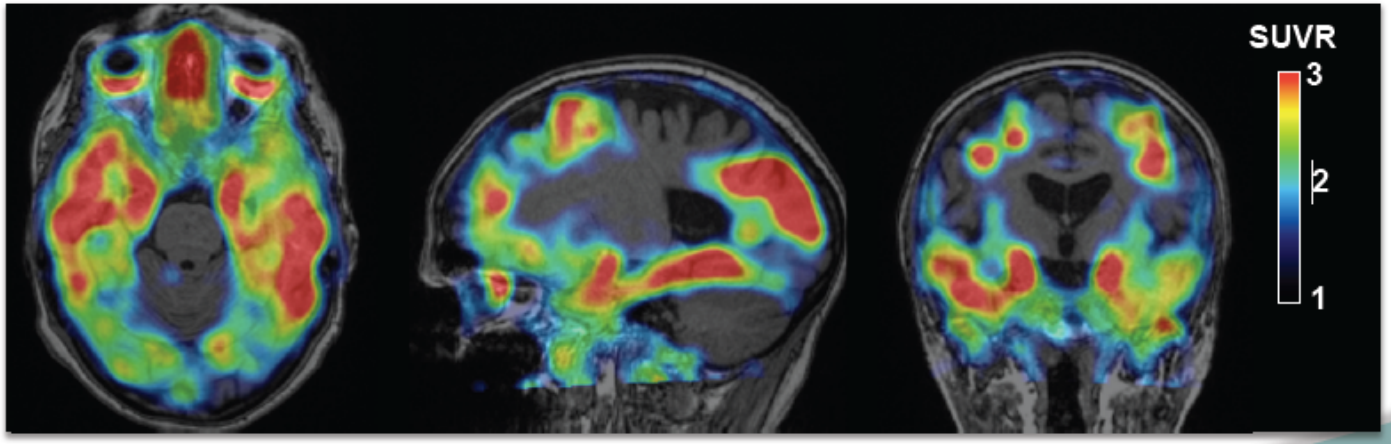


Tau PET with [^{18}F]MK6240

AD subject:
Age: 74 yo
MMSE: 28
Aβ status: NA

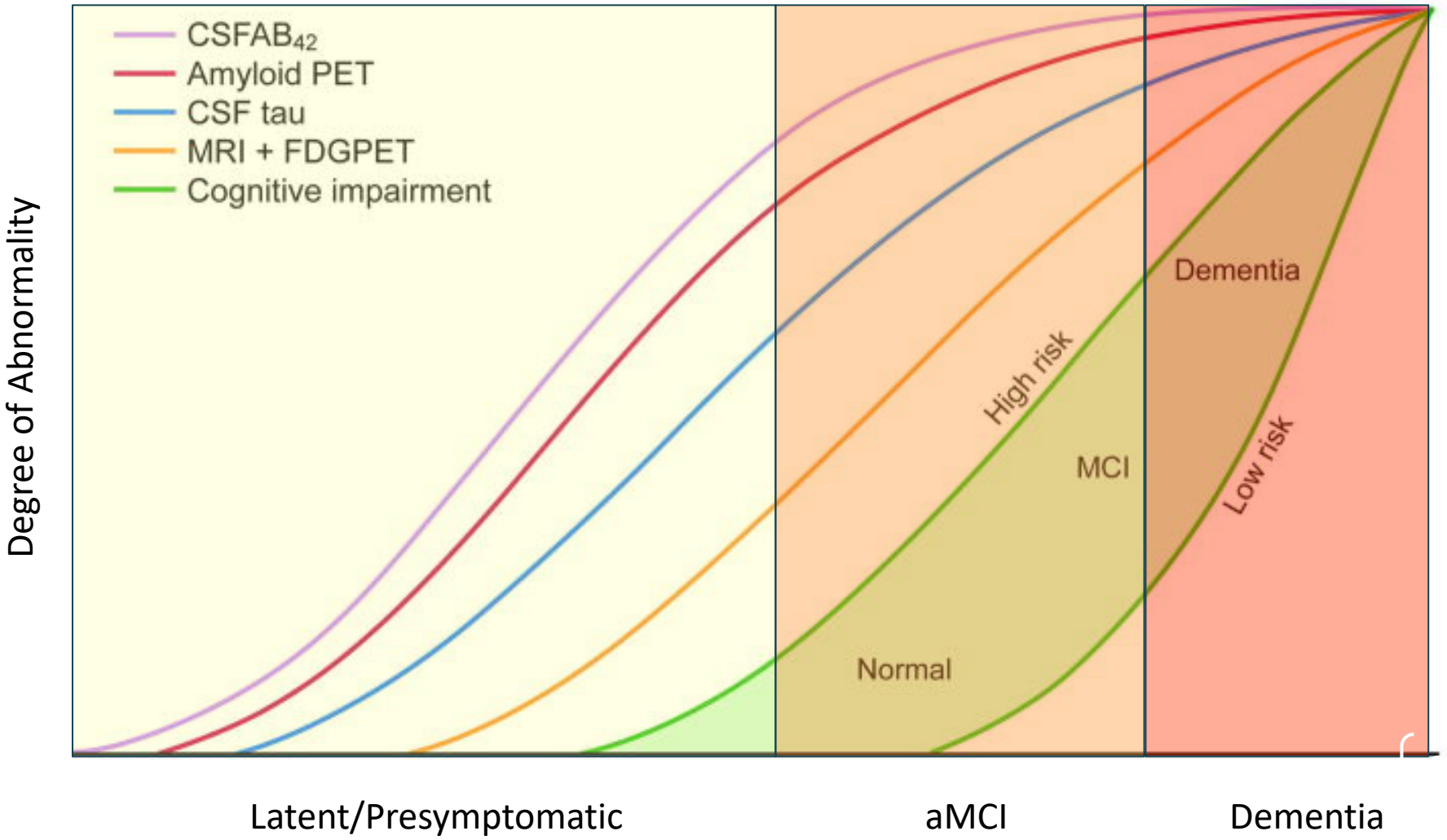


AD subject:
Age: 72 yo
MMSE: 18
Aβ status: +ve



TRANSLATIONAL BIOMARKERS

Canonical Sequence of AD Biomarkers



Jack et al, 2013

Outline

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- Considerations for study of Native populations

Alzheimers Dement. 2018 April ; 14(4): 535–562. doi:10.1016/j.jalz.2018.02.018.

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack Jr.[a,*], **David A. Bennett**[b], **Kaj Blennow**[c], **Maria C. Carrillo**[d], **Billy Dunn**[e], **Samantha Budd Haeberlein**[f], **David M. Holtzman**[g], **William Jagust**[h], **Frank Jessen**[i], **Jason Karlawish**[j], **Enchi Liu**[k], **Jose Luis Molinuevo**[l], **Thomas Montine**[m], **Creighton Phelps**[n], **Katherine P. Rankin**[o], **Christopher C. Rowe**[p], **Philip Scheltens**[q], **Eric Siemers**[r], **Heather M. Snyder**[d], and **Reisa Sperling**[s]

AT(N) biomarkers

A : **AMYLOID** Aggregated Aβ or associated pathologic state

- Low CSF Aβ42, or Aβ42/Aβ40 ratio
- Amyloid PET

T : **TAU** Aggregated tau (NFTs) or associated pathologic state

- High CSF phosphorylated tau
- Tau PET

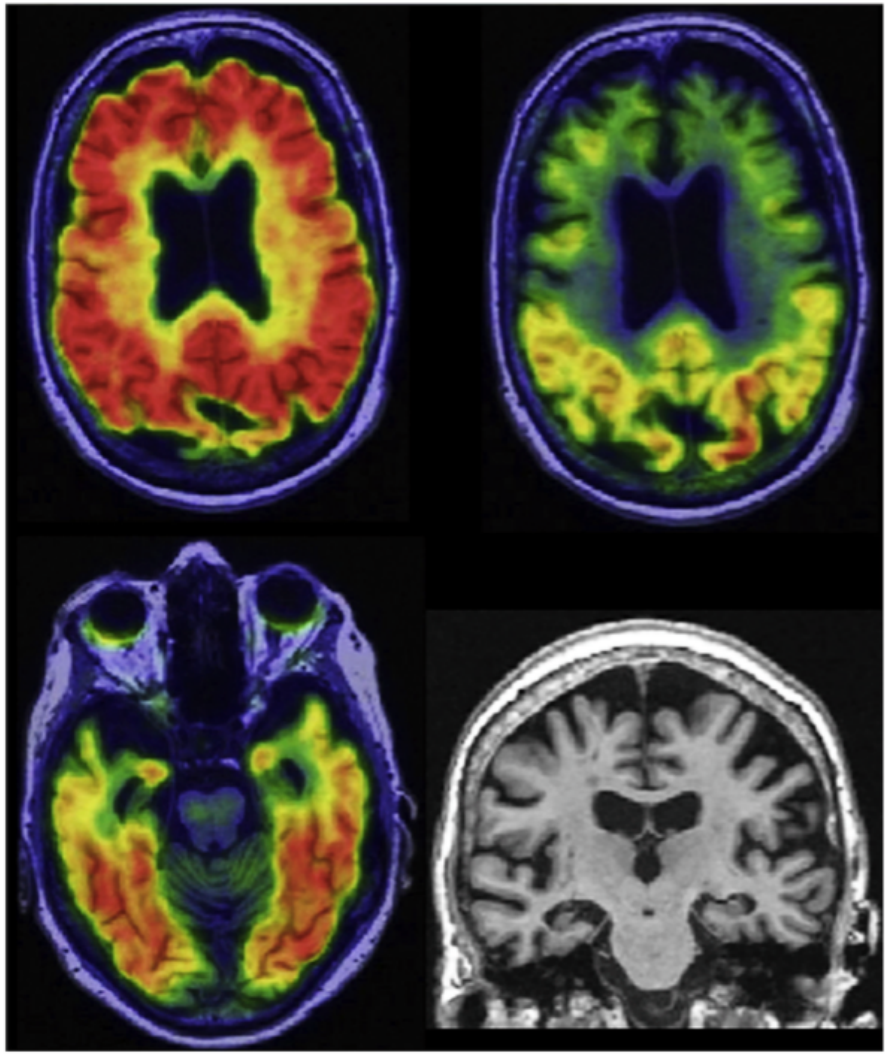
(N): **NEURODEGENERATION** or neuronal injury

- Atrophy detected by MRI
- Low metabolism detected by FDG PET
- High total tau in CSF

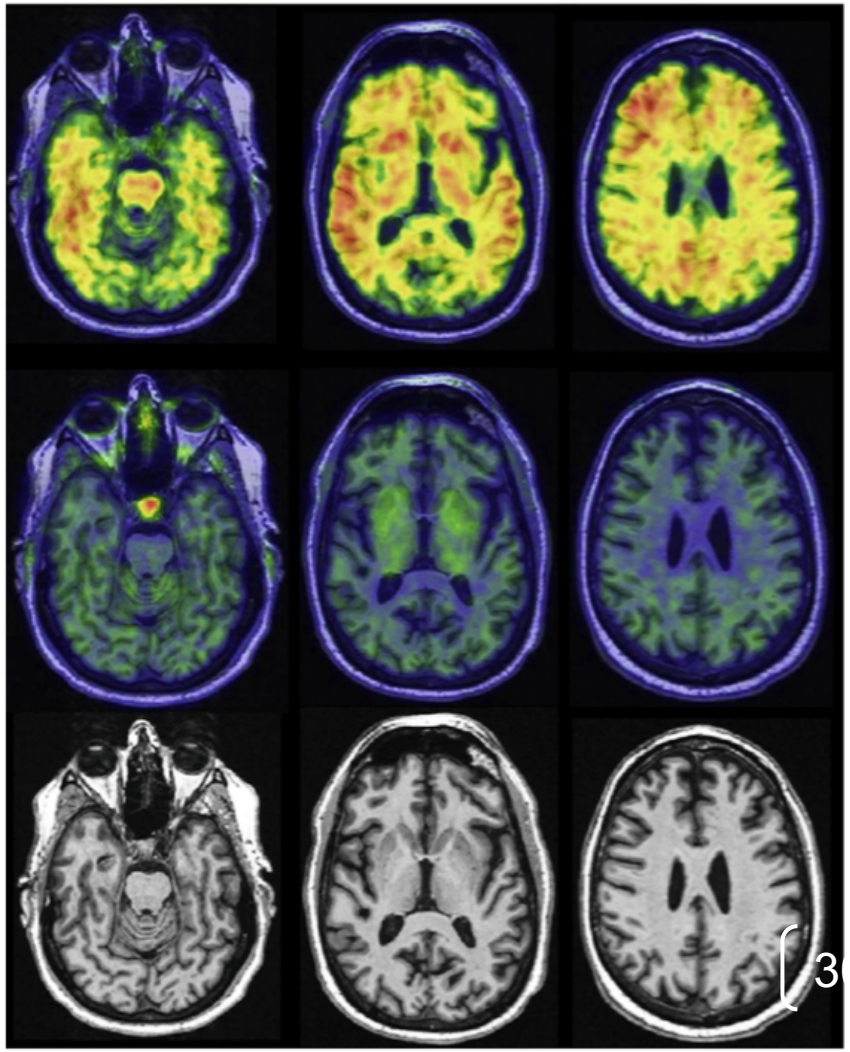
Jack et al , 2018

In the new NIA-AA research framework, everyone can be classified according to whether they are positive or negative for A, T & N

A+ T+ (N+)



A+ T- (N-)



Jack et al , 2018

AT(N) biomarker framework

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N>	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Jack et al , 2018

AT(N) biomarker framework

		Cognitive stage		
		Cognitively Unimpaired	**Mild Cognitive Impairment**	**Dementia**
Biomarker Profile	$A^- T^- (N)^-$	normal AD biomarkers. cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	$A^+ T (N)$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	$A^+ T^+ (N)^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI(Prodromal AD)	Alzheimer's disease with dementia
	$A^+ T^+ (N)^+$			
	$A^+ T (N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
	$A^- T^+ (N)^-$	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia
	$A^- T^- (N)^+$			
	$A^- T^+ (W^+$			

Jack et al , 2018

Pushback

- Issues around semantics of the term “disease”
  - Many with A+T+ at autopsy are not demented
  - Should asymptomatic persons be diagnosed as having Alzheimer *disease*?
- Issues around the stigma attached to the term “Alzheimer’s disease”
  - The framework is not for clinical work, but is it feasible in the information age to keep a distinction?

This is progress

- AT(N) radically respects the difference between syndrome and disease
- AT(N) defines specific biological states, targetable by interventions
- AT(N) offers a principled way to analyze preclinical AD, when there are no symptoms
- AT(N) can also bring resistance and resilience to AD to attention

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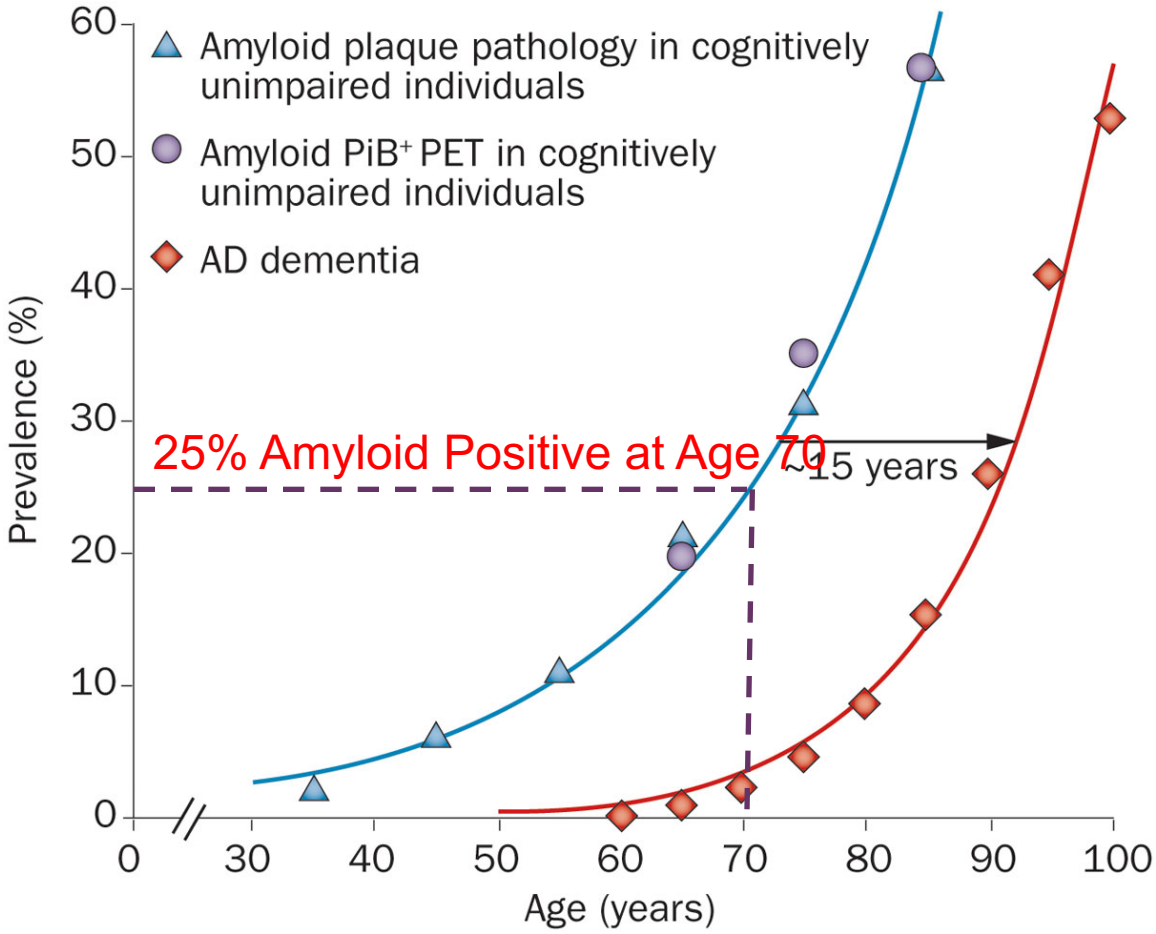


Langbaum, J. B. *et al.* (2013) Ushering in the study and treatment of preclinical Alzheimer disease *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2013.107

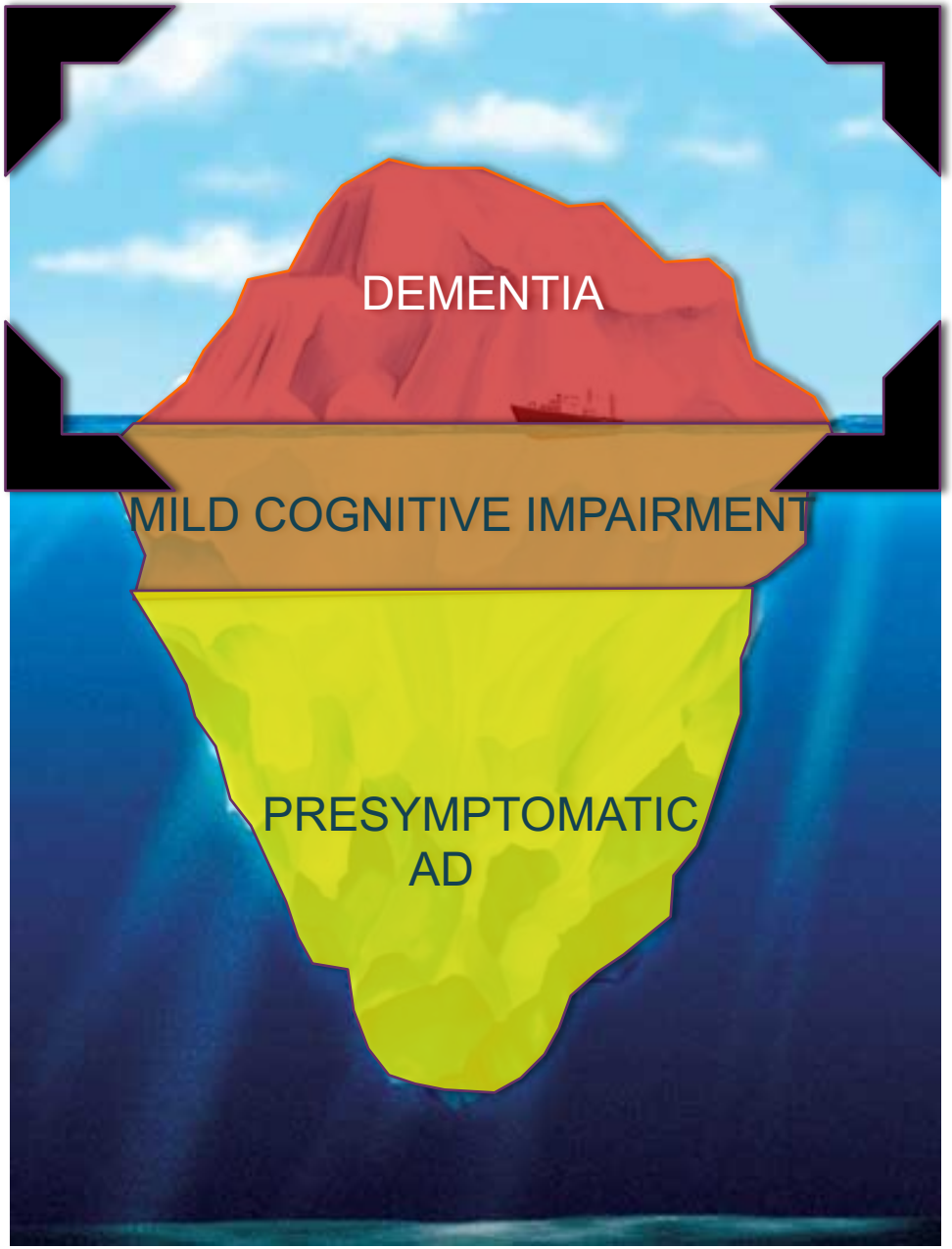
Implication : preclinical AD is common

Biomarkers of AD indicate disease processes are clinically latent years in advance of symptoms.

Amyloid PET scans lead clinical disease by 15 yrs and are already maximally abnormal at the stage of mild cognitive impairment.

Prevalence of preclinical Alzheimer's pathologic change is about 25% at age 70

For every patient with dementia due to Alzheimer's disease, there are probably two more people with preclinical Alzheimer's disease


DEMENTIA
MILD COGNITIVE IMPAIRMENT
PRESYMPTOMATIC
AD

Variable susceptibility

- Resistance: little pathology develops despite high risk (e.g. no Alzheimer's disease despite very advanced age or APOE4 homozygosity)

- Resilience: Mild or no cognitive impairment despite pathologic load ("cognitive reserve")

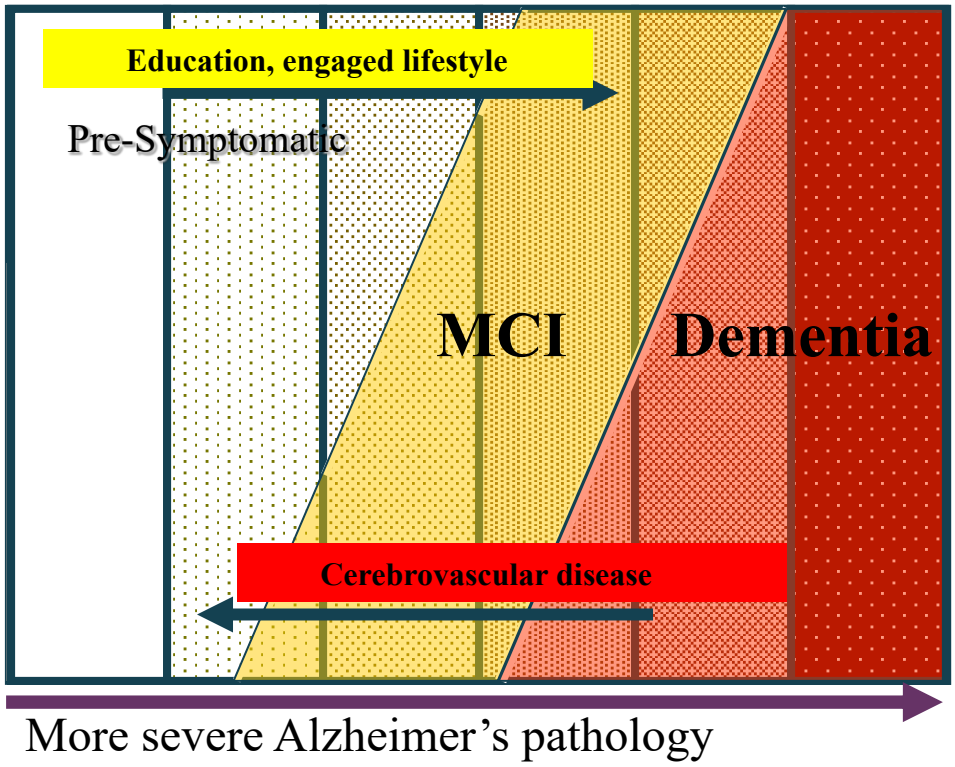
Variable susceptibility

- (Biological) Resistance: little pathology develops despite high risk (e.g. no Alzheimer's disease despite very advanced age or APOE4 homozygosity)

- (Functional) Resilience: Mild or no cognitive impairment despite pathologic load ("cognitive reserve")

LEANING IN TO AD

THE RELATIONSHIP OF ALZHEIMER'S CHANGES TO SYMPTOMS IS MODIFIABLE



The point at which memory will tip can be delayed by years by lifestyle:

Exercising the mind
Social engagement
Physical exercise
Vascular health

These effects are likely to be additive with any effects of medicine in the future treatment of Alzheimer's

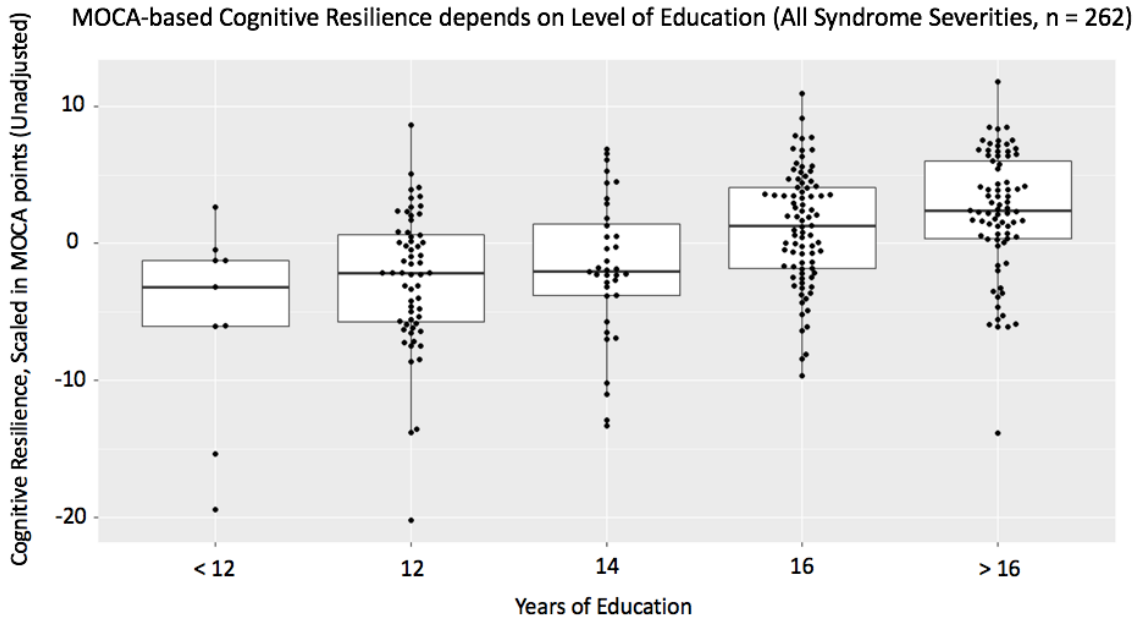
Functional resilience: better cognitive performance than expected for a given amount of brain atrophy

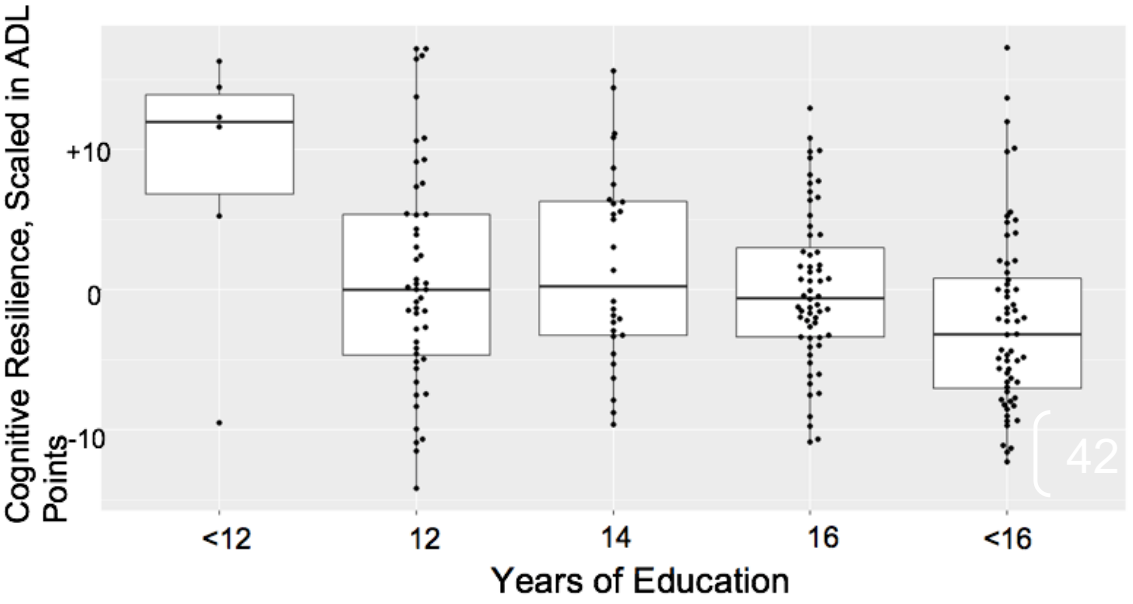
Demonstrated here with Memory and Brain Wellness Clinic Data

Regress brain volume/TICV on MoCA, adjusting for age

Regress brain volume/TICV on IADL score, adjusting for age

Plot residual against years of Education.

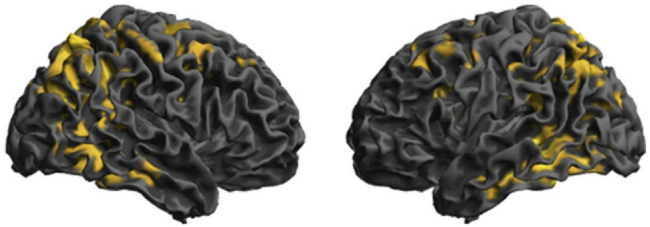




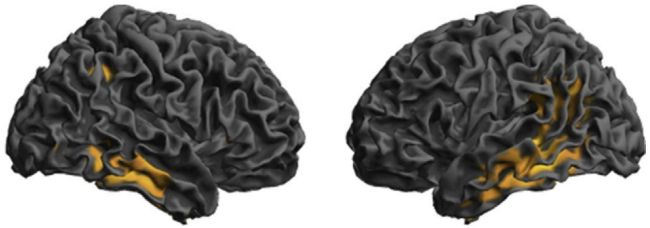
Demonstration of “cognitive reserve” with tau imaging

It takes higher tau burden to cause dementia in those who have more education

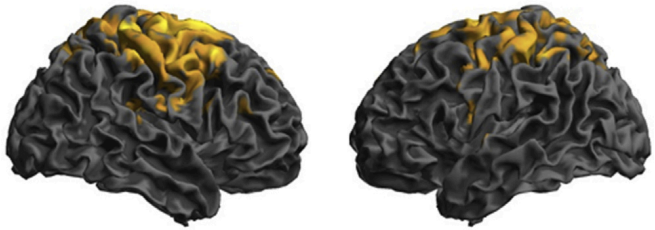
Higher Educated AD vs Control

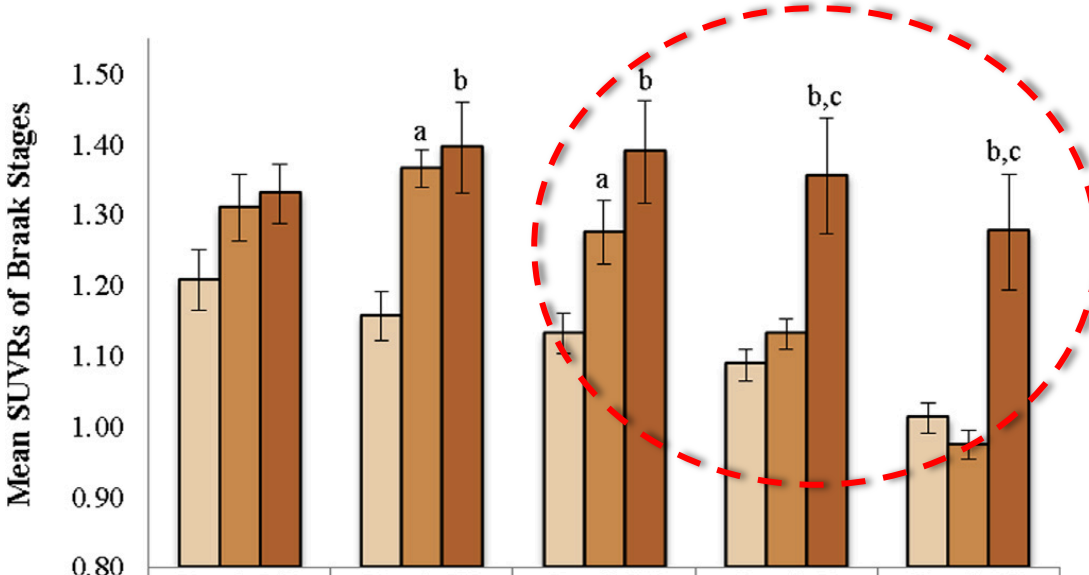


Lower Educated AD vs Control



Higher (17yrs) vs Lower (12yr) Educated AD





	Braak I/II	Braak III	Braak IV	Braak V	Braak VI
Healthy	1.21	1.16	1.13	1.09	1.01
LEAD	1.31	1.37	1.28	1.13	0.97
HEAD	1.33	1.40	1.39	1.36	1.28

Hoenig et al Neurobiology of Aging 2017

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Research diagnosis of dementia

- The difference between MCI (mild NCG) and dementia (major NCG) hinges:
  - Cognitive performance (tested by qualified person)
  - Performance of instrumental ADLs (by informant)
  - Medical situation (judged by a clinician)
- In practice, research diagnosis is done by expert consensus.

Major Neurocognitive Disorder: due to Probable Alzheimer's Disease (DSM-5)

1. Decline in memory or learning, and one other cognitive area, based on history or trials of neuropsychological testing

2. Steady cognitive decline, without periods of stability, and

3. No indicators of other psychological, neurological, or medical problems responsible for cognitive decline.

Consensus diagnosis of AD (without biomarkers)

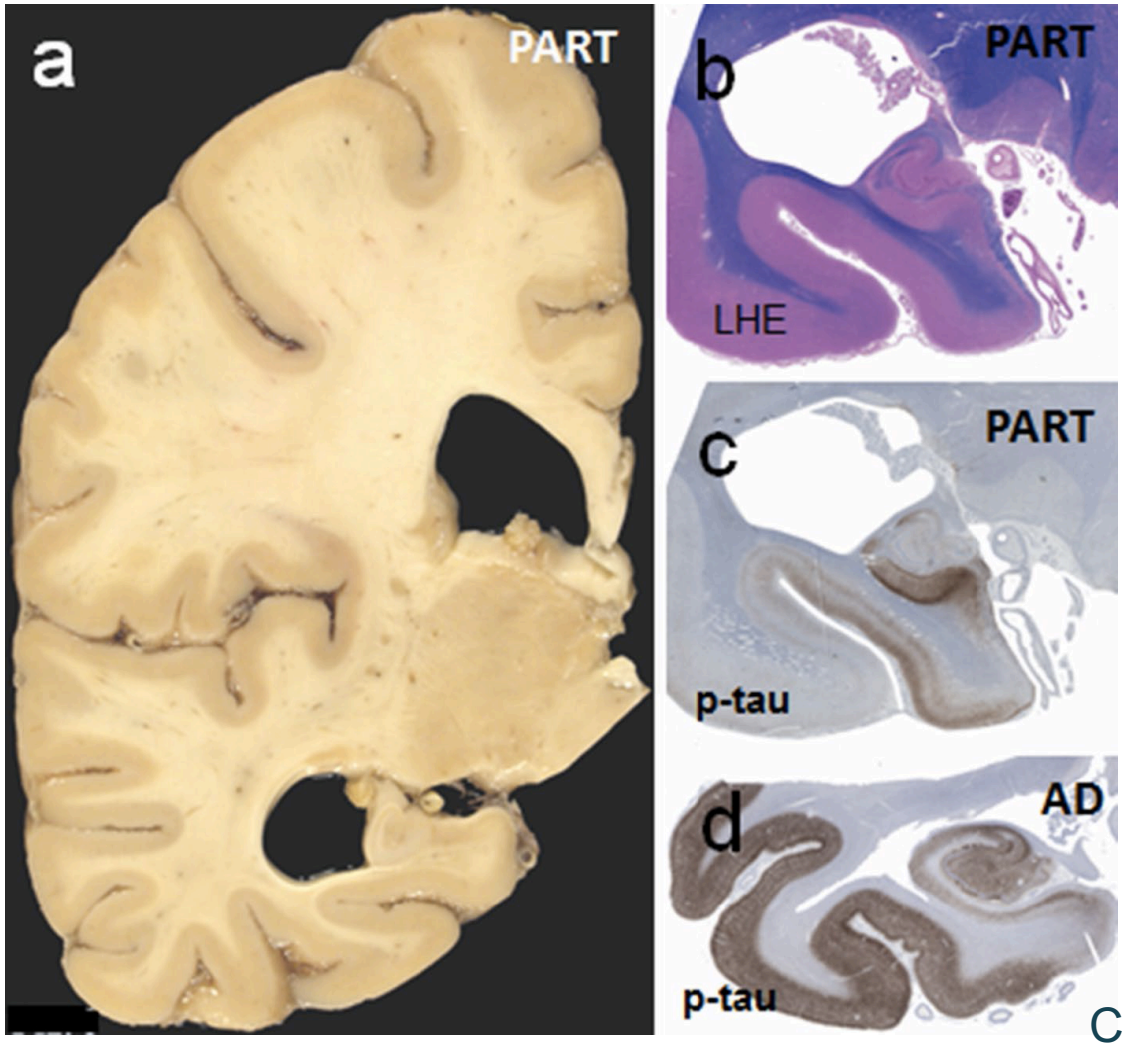
- The common presentation is dementia leading in with memory loss, and with sensorimotor sparing: progressive amnesic dementia ("dementia of Alzheimer type")
- This diagnosis is wrong about 15% of the time, in the best hands
  - Progressive amnestic dementia has a differential diagnosis
  - AD has atypical nonamnestic presentations that can also be misdiagnosed

One AD mimic: **L**imbic-predominant **A**ge-related **T**DP-43 dis**E**ase (LATE)

- Degenerative hippocampal sclerosis
- Associated with TDP-43 proteinopathy, not AD
- A cause of amyloid-negative amnestic MCI and amnestic dementia
- Prevalence 25-50% > 80 yrs old

Nelson et al 2019

Another cause:
Primary Age-related tauopathy (PART)



Crary et al 2014

Another issue: accuracy of clinical "diagnosis" of normal controls

- Prevalence of preclinical Alzheimer's pathologic change is about 20-25% at age 70.
- Variable functional resilience is another source of variability to be aware of, within both normal cognition and cognitively impaired groups.

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Considerations for study of Native populations (1)

- True incidence and prevalence of ADRD in Native populations is not known, but is probably higher than in white Americans (Mayeda et al 2016)
- Essentially no work has been done with amyloid and tau biomarkers in Native populations.
- APOE E4 risk may differ – more work needed
- There are likely to be differences across Native groups.
- High rates of medical comorbidity (e.g. hypertension, diabetes)
- Brain comorbidity is likely to be high, especially VBI

Considerations for study of Native populations (2)

- Protective factors of education, control of hypertension may lag the majority culture
- Norms are not established for cognitive tests in Native populations
- There are probably culture-specific issues in functional assessment

Some final thoughts

- Hewing to the distinction between cognitive and etiologic diagnosis is of key importance.
- There are important limits to clinical diagnosis, both of AD and of non-AD.
- Preclinical AD/ADRD is commonplace and ultimately very important as an intervention window.
- For many other reasons (problems with norms and measures, cultural differences, comorbidity, N) a biomarker-based approach to AD seems particularly needed for this population.
- Study of this population may be hampered by lack of good biomarkers for degree of vascular brain injury.
- Due to variable education and cognitive lifestyle, Native populations might be a good setting to study functional resilience.


QUESTIONS?

Thomas J. Grabowski, MD
UW Radiology and Neurology
Director, Memory and Brain Wellness Center
Director, Alzheimer's Disease Research Center

uwadrc.org

UW Medicine
UW ALZHEIMER'S DISEASE RESEARCH CENTER