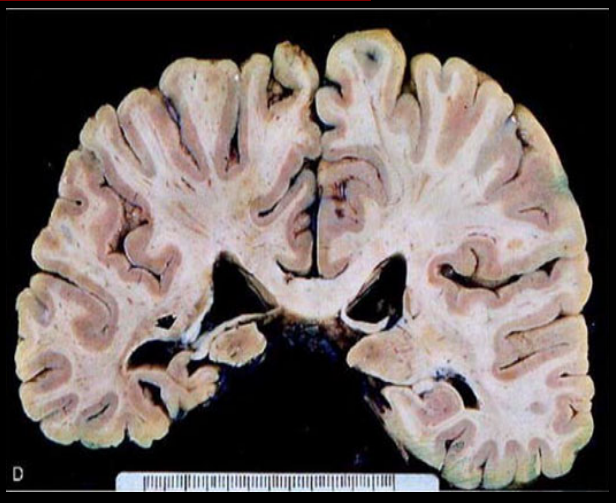
Introduction to Alzheimer's Disease

Aaron Ritter, MD
Lou Ruvo Center for Brain Health
Cognitive Disorders Clinic
Behavioral Neurology and Neuropsychiatry

Alzheimer's as a Disease Continuum

- Historically AD "probable" based on exclusion of other potential etiologies
  - Only confirmed by brain biopsy



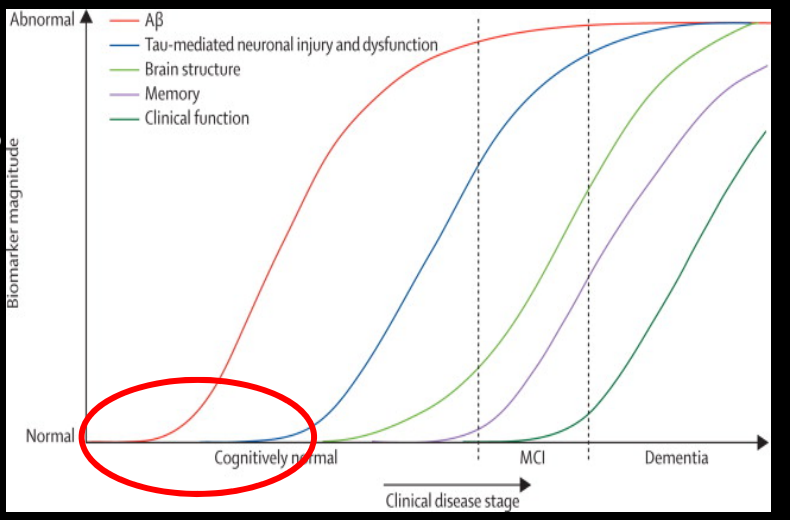
Alzheimer's as a Disease Continum

- Later, AD recognized as a clinical entity with several stages

Stage	Stage Name	Characteristic	Expected Untreated AD Duration (months)	Mental Age (years)	MMSE (score)
1	Normal Aging	No deficits whatsoever	--	Adult	29-30
2	Possible Mild Cognitive Impairment	Subjective functional deficit	--		28-29
3	Mild Cognitive Impairment	Objective functional deficit interferes with a person's most complex tasks	84	12+	24-28
4	Mild Dementia	IADLs become affected, such as bill paying, cooking, cleaning, traveling	24	8-12	19-20
5	Moderate Dementia	Needs help selecting proper attire	18	5-7	15
6a	Moderately Severe Dementia	Needs help putting on clothes	4.8	5	9
6b	Moderately Severe Dementia	Needs help bathing	4.8	4	8
6c	Moderately Severe Dementia	Needs help toileting	4.8	4	5
6d	Moderately Severe Dementia	Urinary incontinence	3.6	3-4	3
6e	Moderately Severe Dementia	Fecal incontinence	9.6	2-3	1
7a	Severe Dementia	Speaks 5-6 words during day	12	1.25	0
7b	Severe Dementia	Speaks only 1 word clearly	18	1	0
7c	Severe Dementia	Can no longer walk	12	1	0
7d	Severe Dementia	Can no longer sit up	12	0.5-0.8	0
7e	Severe Dementia	Can no longer smile	18	0.2-0.4	0
7f	Severe Dementia	Can no longer hold up head	12+	0-0.2	0

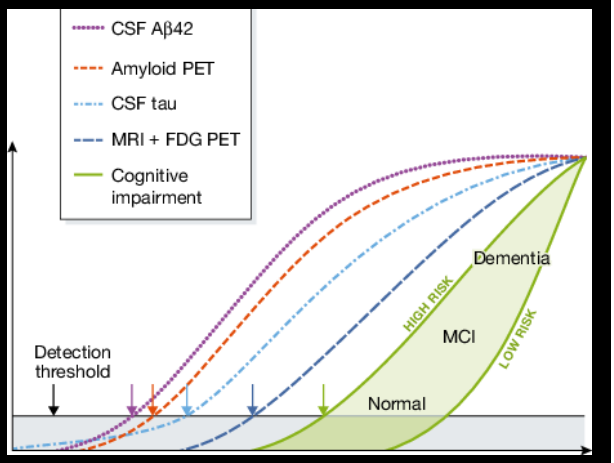
Alzheimer's as a Disease Continuum

- Now, its clear that pathophysiological changes occur many years (at least 15 years) before the onset of disease symptoms



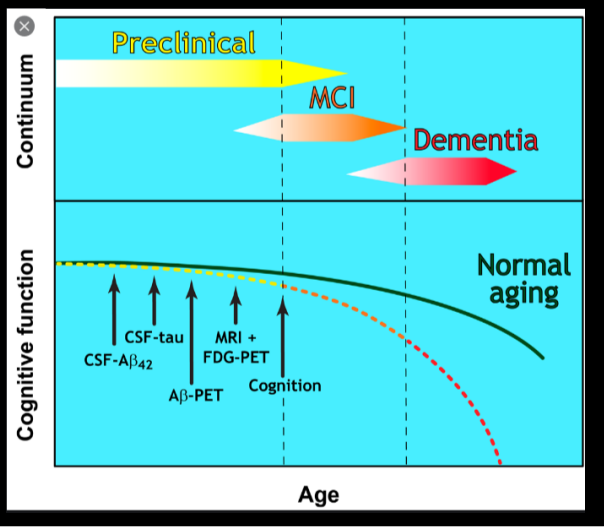
AD as a Continuum

- Viewed along a biological and clinical continuum covering both preclinical and symptomatic stages
- Continuum= seemless sequence in which adjacent elements are not are not perceptibly different from each other although the extremes are distinct



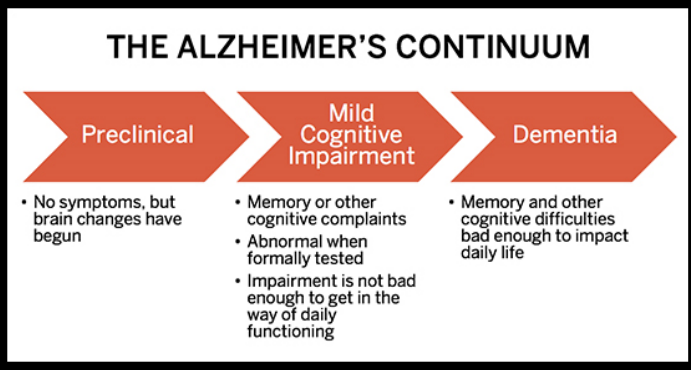
Disease as Continuum

- Continuum=seemless sequence in which adjacent elements are not are not perceptibly different from each other although the extremes are distinct



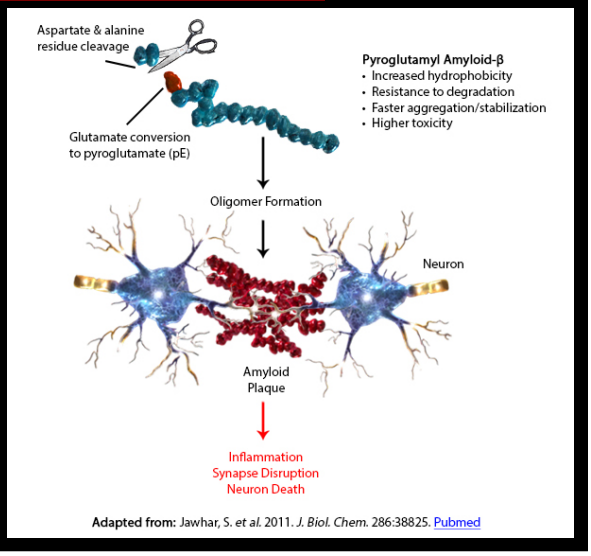
AD Continuum

- Asymptomatic, preclinical period
  - Increasing biomarker evidence of disease
- Symptomatic phase
  - Pathophysiology leads to symptoms of cognitive impairment and then functional impairment



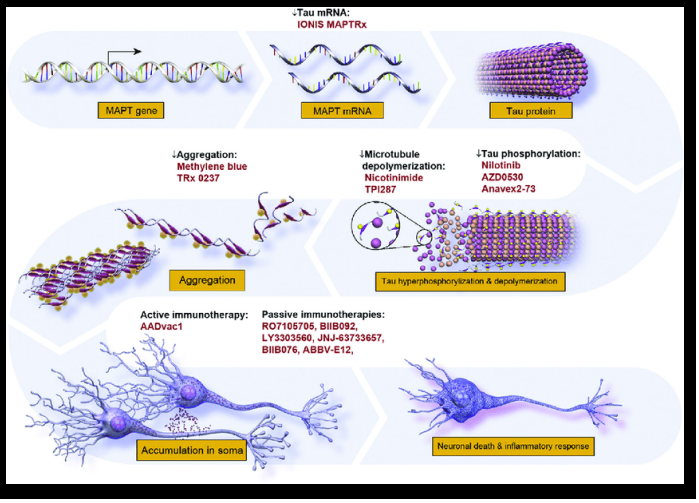
Pathophysiology

- Amyloid is likely still first process
  - Genetic mutations in PS1, PS2, Trisomy 21
- Amyloid alone likely insufficient to cause symptoms



Pathophysiology

- Tau as facilitator of downstream effects of amyloid
- Others: synaptic, mitochondrial, metabolic, inflammatory, neuronal, cytoskeletal, myelin, etc



Three Key Processes

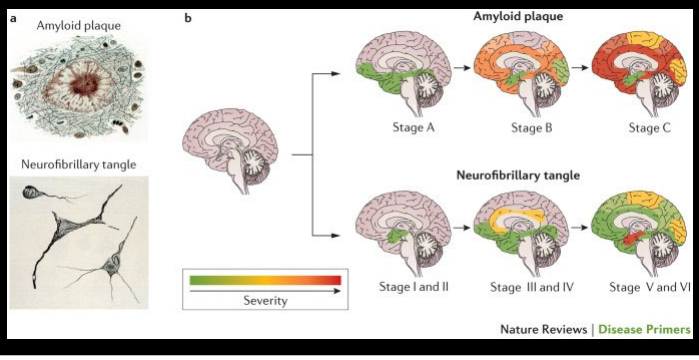
1) Amyloid accumulation into neuritic plaques
2) Formation of neurofibrillary tangles
3) Neurodegeneration-progressive loss of neurons and their processes

Amyloid

Tau

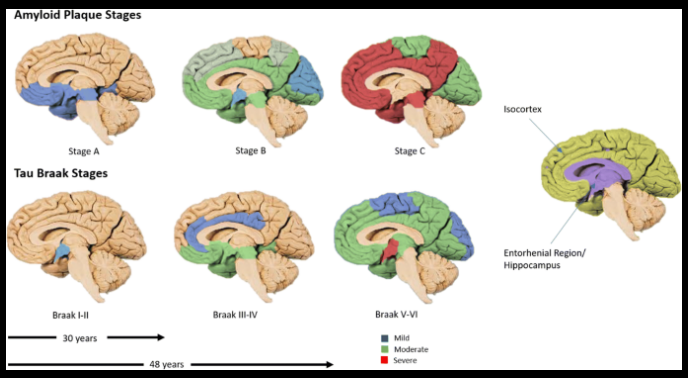
Neurodegeneration

ATN framework



Transition from normal to preclinical AD

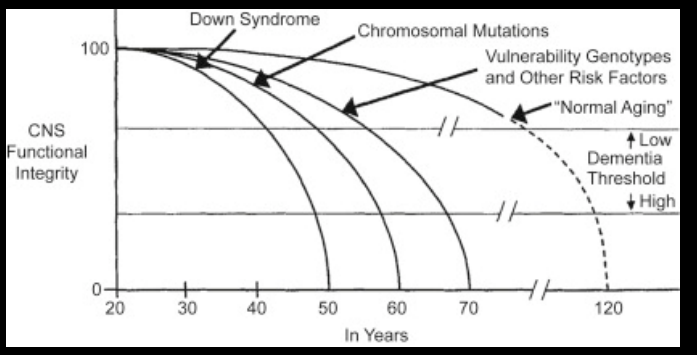
- Not well defined
- Likely Influenced by genetic and environmental factors
  - APOE
  - Cardiovascular, diet, physical exercise, and cognitive engagement



Cognitive Reserve

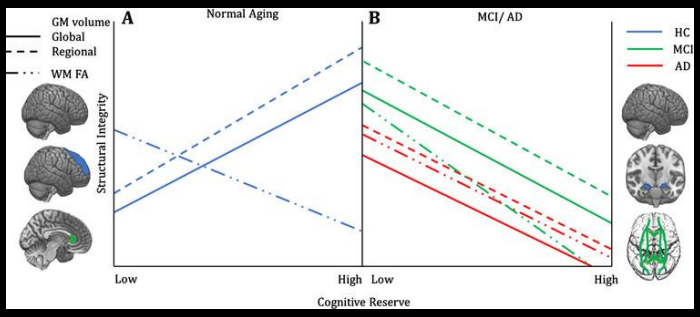
Cognitive reserve=the ability of the brain to engage alternate brain networks of cognitive strategies to cope with effects of encroaching pathology

- Likely influenced by physical activity, cardiovascular factors, cognitive engagement



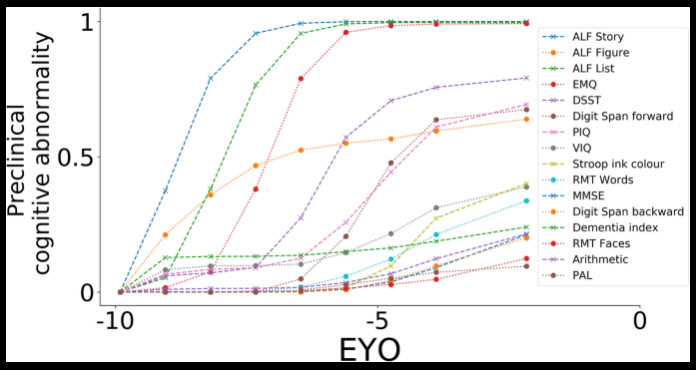
Transition to the Clinical Phase of AD

- Not clear about amount of pathology to cause disease
  - Abeta accumulation plus other changes
- Thought to be at least 15 years
- Cognition and function
  - MCI due to AD/prodromal AD
  - Mild AD
  - Moderate AD
  - Severe AD



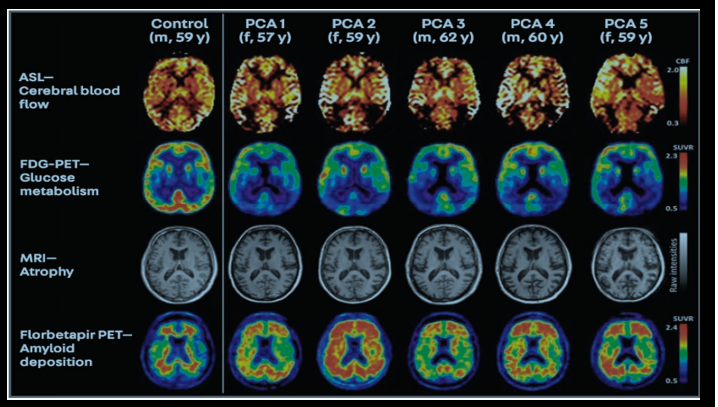
Disease Progression

- Episodic memory/hippocampal type
  - Diminished free and cued recall
- Executive
- Language
- Functional decline
  - Complex ADLs
  - Basic ADLs



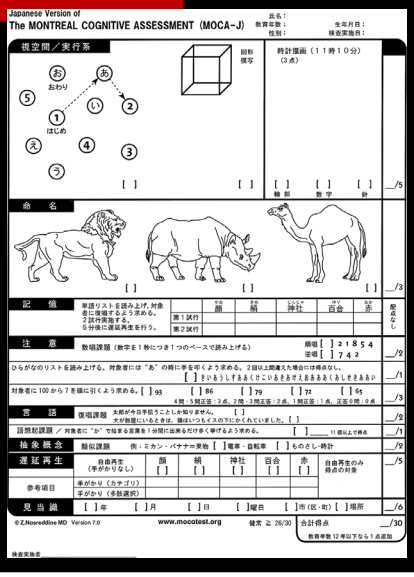
Role of Biomarker Assessment

- Research criteria: Amyloid, Tau, Neurodegeneration (ATN framework)
- No longer just for clinical use
  - Amyloid PET
  - Tau PET
  - CSF
  - FDG PET
  - Volumetric analysis
- Biomarkers are only diagnostic (have limited prognostic capabilities)



Role of Clinical Assessment

- Importance of obtaining history, not only from patient but knowledgeable informant
- Supplemented by assessment of functional and cognitive abilities
- Tests of episodic memory favored over processing speed and attention



Summary

- We now have enough evidence to support AD along a disease continuum
- Biomarker assessment becoming important for symptomatic individuals, but provide limited prognostic information
- Future of AD, personalized approach with early detection as cornerstone