Advances in Clinical Diagnosis

ALZHEIMER'S DISEASE 2019

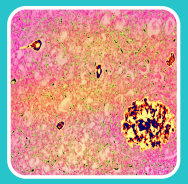
David Sultzer, MD

Institute for Memory Impairments and Neurological Disorders
Department of Psychiatry and Human Behavior

UCI University of California, Irvine

Alzheimer's Disease

Improving Clinical Diagnosis



"Jewels"

- Amyloid Plaques
- Neurofibrillary Tangles
- Lewy Bodies

Tools

- Neuroimaging
- Fluid Biomarkers
- Clinical Assessments

Rules

- Diagnostic Criteria
- Differential Diagnosis

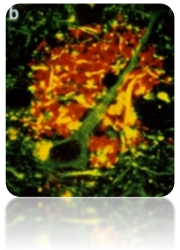
Early Concepts of Dementia

Plato, 350 BC	Cognitive decline is an inevitable consequence of aging due to the weakness of the brain
Cicero, 50 BC	A consequence of weak will. An active mental life could prevent or postpone cognitive decline
Galen, 200 AD	Psychic and cognitive abilities are localized to the brain
Willis, 1650	Developmental disability separate from acquired dementia; specific etiologies for dementia, including head injury, aging, and stroke
19th Century	Psychiatric and neurologic conditions were distinguishable; cortical atrophy recognized; vascular calcification prominent; Kraepelin "dementia praecox"; "general paresis" (neurosyphilis) in $\geq$ 10% ; arteriosclerotic brain atrophy is predominant cause of senile dementia

Causes of dementia Esquirol, 1838
Sequelae of delivery
Head injuries
Menstrual disorders
Severe weather conditions
Progression of age (20%)
Mania
Syphilis and mercury abuse
Dietary excess
Wine abuse
Masturbation
Unhappy love
Political upheavals
Unfulfilled ambitions
Poverty
Domestic problems

Assal 2019

Alzheimer 1906



New histological stains – cortex

51 yo woman with confusion and psychosis

- Presenile dementia
- Prominent plaques and tangles
- vs Senile dementia: arteriosclerosis
- Distinction persisted for 50 years

1960s: Blessed, Tomlinson, Roth

- In older adults (mean age 78), cognition and function during life associated with cortical neuritic plaque density at post-mortem

Clinical Diagnostic Criteria

NINCDS-ADRDA, 1984

Probable AD

- Dementia, objective testing
- Two or more cognitive domains
- Progressive worsening
- No disturbance of consciousness
- Onset between age 40 and 90
- Absence of other CNS or systemic etiology
- Supportive factors
  - Progressive decline in characteristic domains
  - Impaired ADLs and "patterns of behavior"
  - Family history
  - CT: atrophy
  - May be depression, psychosis, emotional outbursts
  - No focal neuro signs, seizures, or gait change early

Possible AD

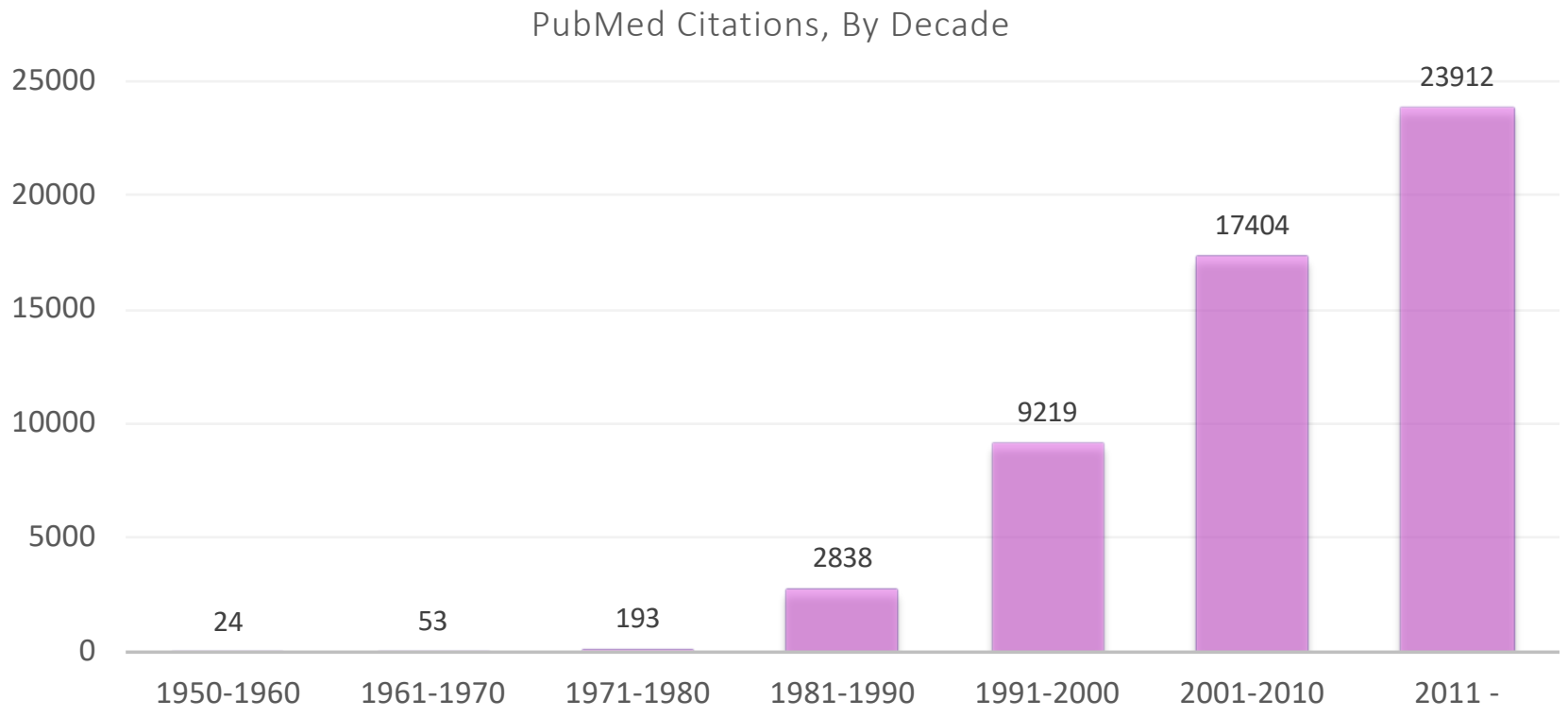
- Variations in the onset, presentation, or clinical course
- Another systemic or CNS disorder that may be driving the dementia
- Single cognitive deficit

Definite AD

- Clinical criteria for Probable AD
- Histopathologic evidence

McKhann 1984

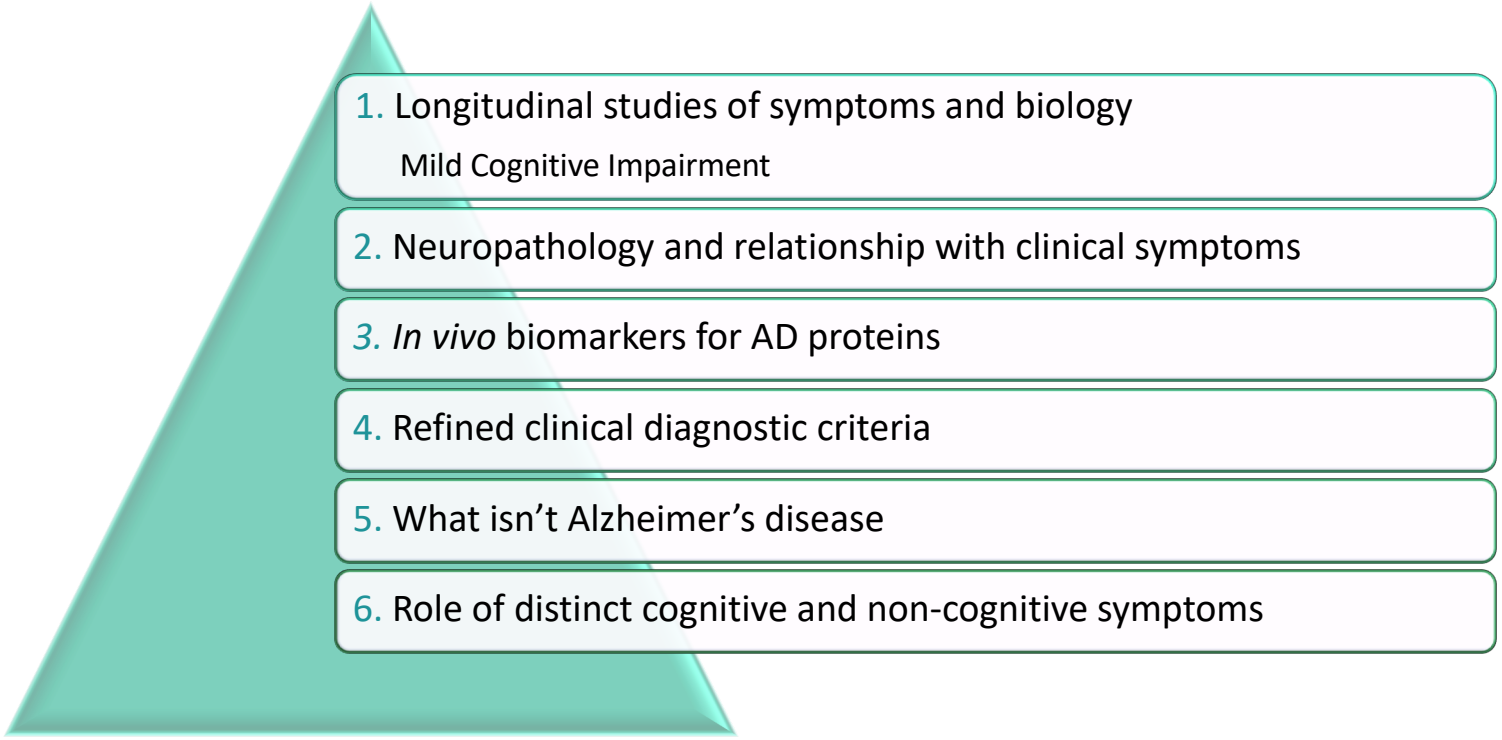
AD Clinical Diagnosis



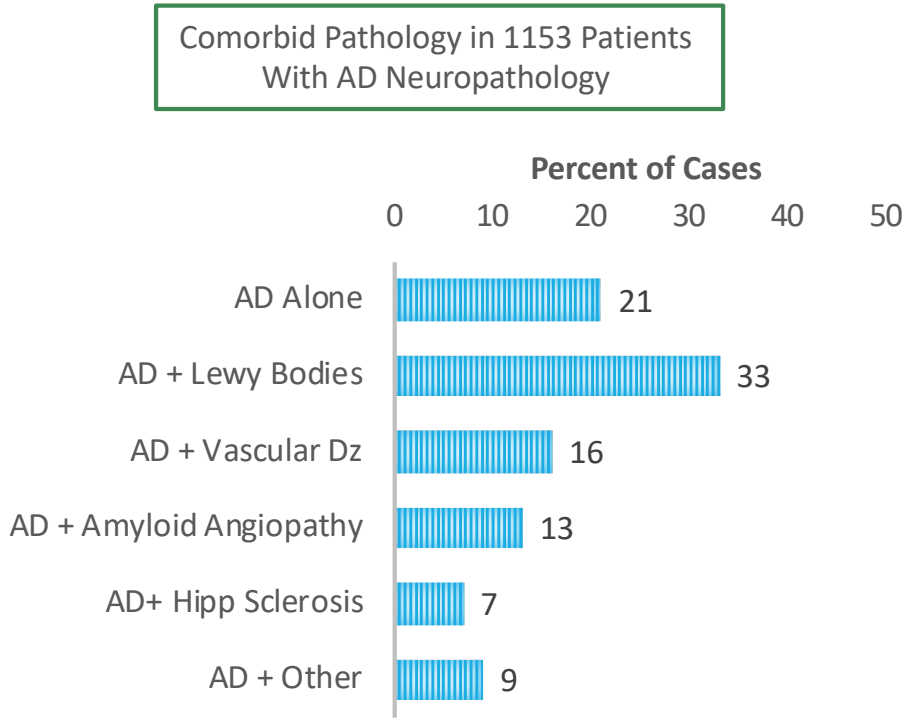
Pub Med; Sept 24, 2019

Key Advances

Improving Clinical Diagnosis



Alzheimer's Pathology Isn't Alone



- Mixed cases are very common in the brain

  43% of cases with AD pathology had at least 3 different pathologies

- Clinicians aren't always seeing AD pathology

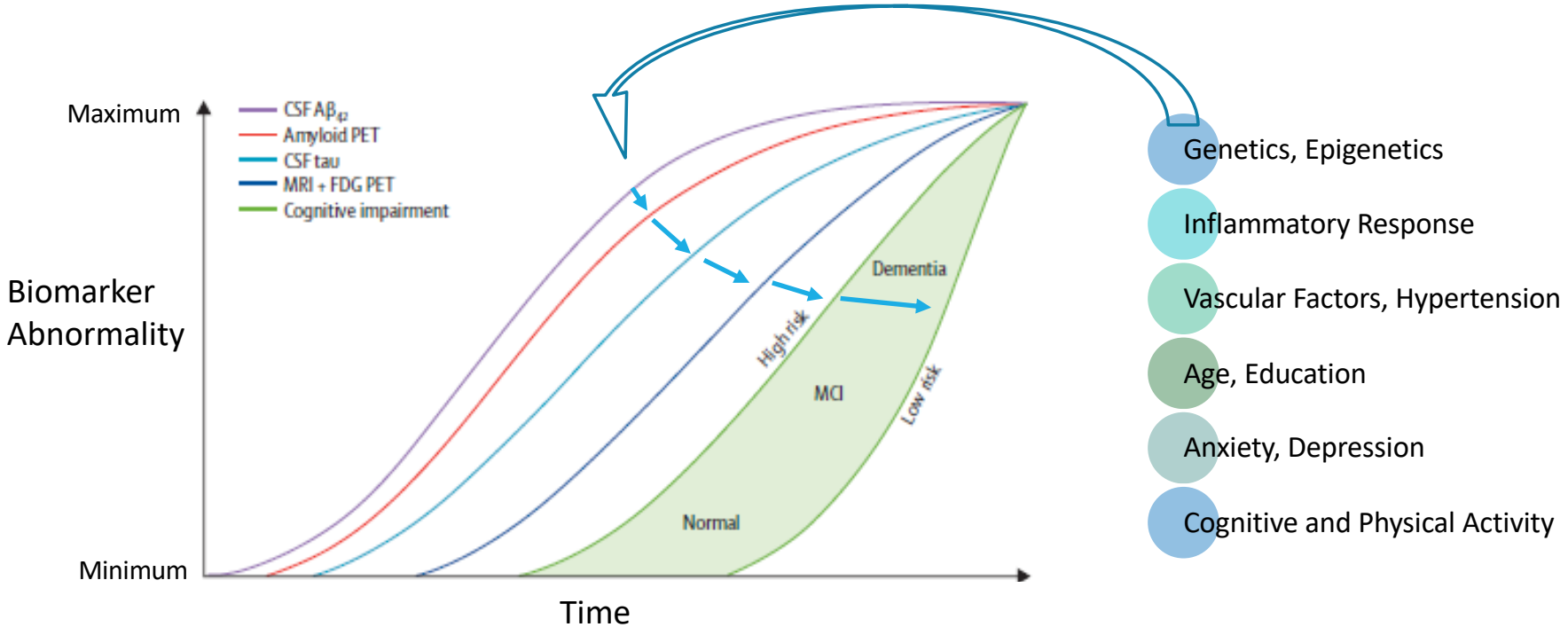
  More than one-third of those with "pure AD" at autopsy were thought to have a non-AD diagnosis during life

- Clinicians often see "AD" when other pathologies are present

  ~ 80% of those with a clinical diagnosis of AD have mixed pathologies (70%) or no AD pathology (~10%)

Mayo Clinic Brain Bank 2007-2016; DeTure 2019

Biomarkers for Alzheimer's Disease

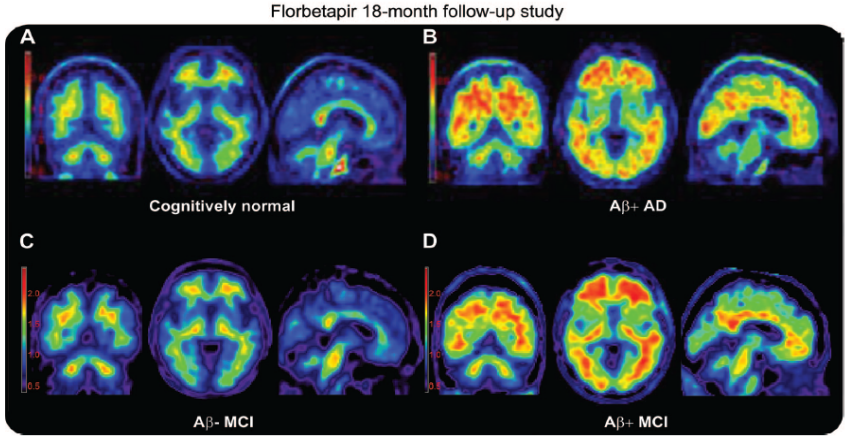


- AD biomarker changes occur at least 15 years before memory is compromised.

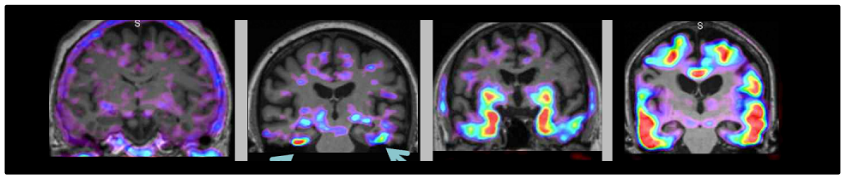
Jack 2013

PET Imaging - Amyloid and Tau

Amyloid



Tau



Healthy Control | Preclinical AD Asymptomatic | Prodromal AD MCI | AD Dementia

➢ Amyloid Imaging – Clinical

- Persistent or progressive unexplained MCI
- Possible AD: atypical course or mixed etiologies
- Early-onset progressive dementia

Assuming:

- Dementia expert involved
- Cognitive deficit present
- Expected to increase dx certainty or change management

An Outcome Study:

N=11,409 with MCI or dementia

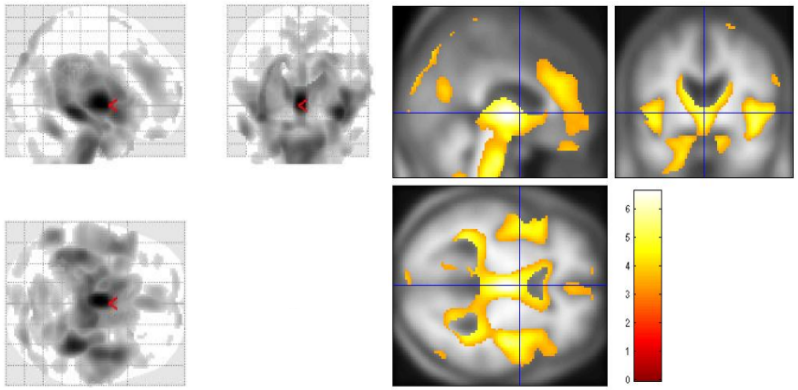
60% with change in med rx or safety/planning

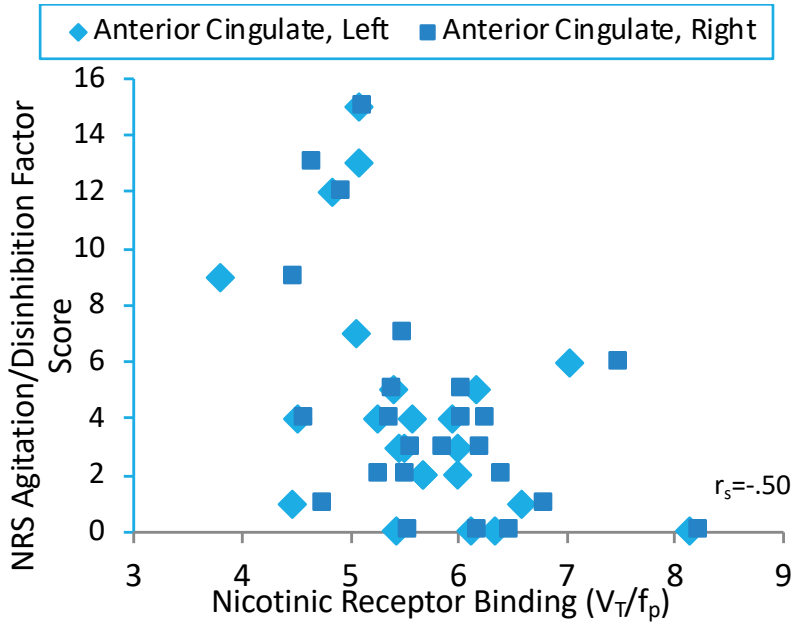
25% with dx change from AD to non-AD

Johnson 2013

Rabinovici 2019

Cholinergic Receptor Binding in AD and MCI





Lower binding in MCI and AD

- Medial thalamus
- Medial temporal cortex (hipp, amyg, parahipp)
- Anterior cingulate
- Insula

➢ In healthy older adults, cholinergic, binding is strongly inversely correlated with age

Sultzer 2017

Richter 2018, *Brain*

➢ Clinical and cortical activation (fMRI) response to AChEI treatment in MCI depends on local acetylcholinesterase enzyme activity (MP4A-PET imaging)

Fluid Biomarkers

Cerebrospinal Fluid

- Low β-amyloid 42 may precede amyloid seen on PET imaging
- Variable lab assays
- Elevated P-tau and tau levels
- Synaptic markers: neurogranin

Blood Plasma

- Small proportion of brain proteins in plasma
- High concentration of usual blood proteins
- β-amyloid 42, tau
- Neurofilament light protein

More Comprehensive Diagnostic Criteria

	AD Biomarker	NIA-AA Criteria 2011	IWG Criteria 2010, 2014
Normal Cognition	-	x	x
	+	Preclinical AD Stage 1: Amyloid + Stage 2: Amyloid + and injury (Tau, FDG-PET, hipp or med parietal atrophy)	Asymptomatic at risk for AD (CSF amyloid + tau, PET amyloid) Presymptomatic AD, if genetic carrier
Subtle Cognitive Decline	+	Preclinical AD, Stage 3	Not distinguished from normal
Mild Cognitive Deficit, Preserved ADLs	-	MCI (one or more domains: memory, executive, language, visuospatial, attention)	MCI
	+	MCI due to AD Hi likelihood: Amyloid + Injury + Intermed likelihood: Amyloid or injury + ; other n/a Uninformative: either +; other -	Prodromal Alzheimer's disease Memory +/- other domain Otherwise: Atypical AD
Significant Cognitive Deficit, With Functional Impairment	-	Probable AD dementia At least two domains: memory, reasoning, visuospatial, language, personality/behavior Possible AD dementia – atypical course or mixed etiology	"Dementia"
	+	Probable or possible AD dementia - With AD pathology	Alzheimer's disease Memory +/- other domain Otherwise: Atypical AD

“Alzheimer’s Disease”

*“When **I** use a word,” Humpty Dumpty said, in rather a scornful tone,*
“it means just what I choose it to mean – neither more nor less.”

Humpty Dumpty, *Through the Looking Glass* (Lewis Carroll 1872)

ATN Research Criteria

Biomarker Profile	Cognitive stage		
	Cognitively Unimpaired	**Mild Cognitive Impairment**	**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 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
$A^- T^-(N)^+$			
$A^- T^+(N)^+$			

Alzheimer's continuum

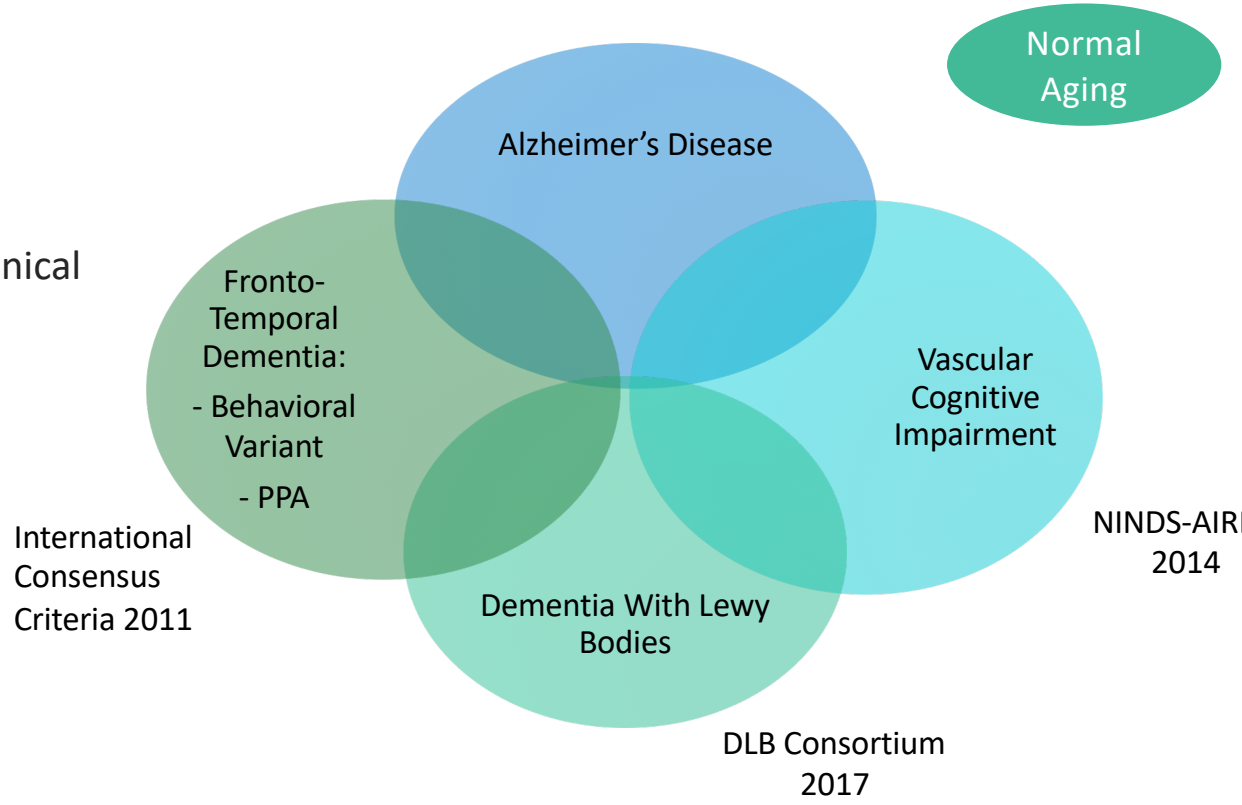
Suspected non-Alzheimer disease pathophysiology (SNAP)

A: CSF or PET imaging amyloid
T: CSF p-tau, tau imaging
N: MRI volume, FDG-PET, CSF total tau

Jack 2018

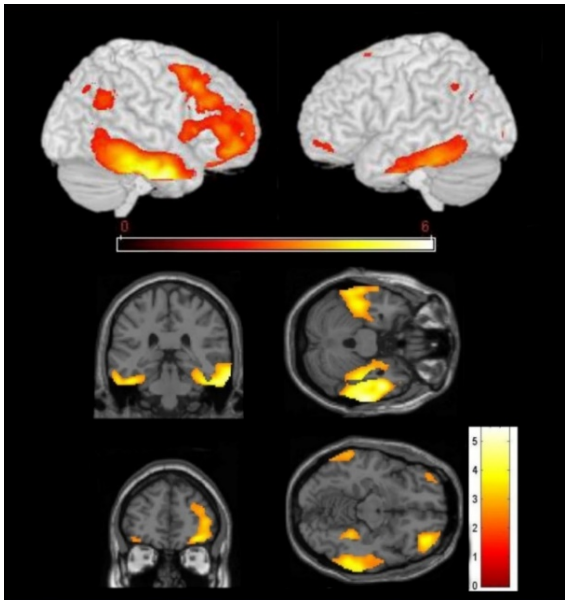
What Isn't Alzheimer's Disease

- More refined clinical phenomenology and clinical diagnostic criteria



Profiles of Cognitive and Noncognitive Symptoms

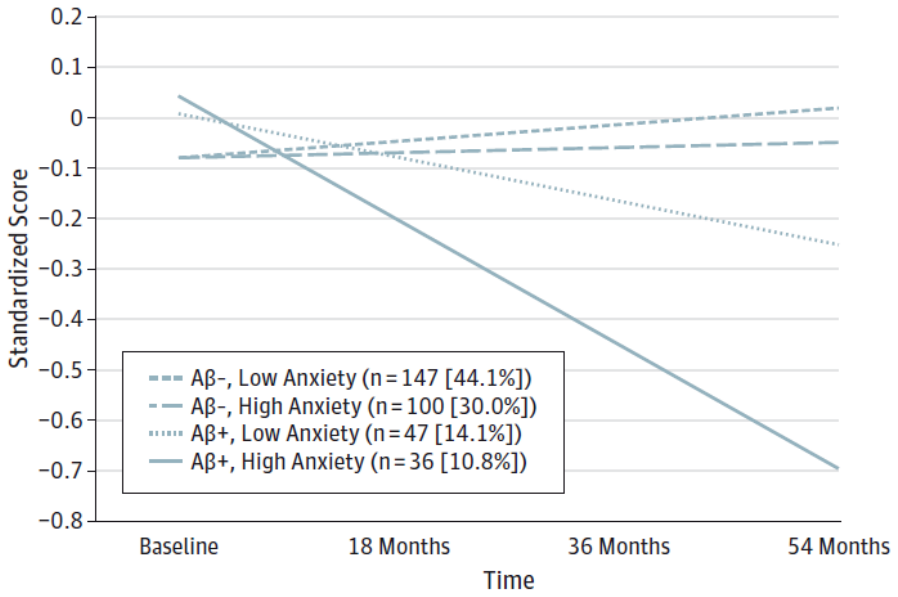
- Amnestic memory deficit
  - vs. retrieval deficit with cue benefits
- Neuropsychiatric symptoms over the course of clinical AD
  - Fundamental expression of the degenerative process
- Depression is a risk factor for AD
- Apathy and anxiety can be early symptoms, before memory impairment
  - Shared biology?



Sultzer 2014

Anxiety Drives Amyloid Toxicity

Figure 1. Slopes of Change in Verbal Memory Composite Score by Amyloid-β (Aβ) and Anxiety Levels



- Prospective cohort, 333 healthy older adults
- Amyloid imaging
- Measures: Anxiety/depression, Neuropsych
- Anxiety moderated the effect of amyloid burden
  - Larger effect in those with clinically meaningful symptoms
- No effect of depression
  - Low scores
- Mechanism?
- Intervention opportunity?

Pietrzak 2015

Mild Behavioral Impairment

- Changes in behavior or personality, age ≥ 50
  - Decreased motivation
  - Affective dysregulation
  - Impulse dyscontrol
  - Social inappropriateness
  - Abnormal perception or thought
- Social or occupational consequences
- Not attributable to a psychiatric disorder
- No dementia; MCI can be concurrent

NPS-PIA
Alzheimer's Association, 2015

Mild Behavioral Impairment Checklist (MBI-C)

Date: _____

Rated by: ☐ Clinician ☐ Informant ☐ Subject

Location: ☐ Clinic ☐ Research

Label

Circle "Yes" **only** if the behavior has been present for at least **6 months** (continuously, or on and off) and is a **change** from her/his longstanding pattern of behavior. Otherwise, circle "No".

Please rate severity: **1 = Mild** (noticeable, but not a significant change); **2 = Moderate** (significant, but not a dramatic change); **3 = Severe** (very marked or prominent, a dramatic change). If more than 1 item in a question, rate the most severe.

	YES	NO	SEVERITY
This domain describes interest, motivation, and drive			
Has the person lost interest in friends, family, or home activities?	Yes	No	1 2 3
Does the person lack curiosity in topics that would usually have attracted her/his interest?	Yes	No	1 2 3
Has the person become less spontaneous and active – for example, is she/he less likely to initiate or maintain conversation?	Yes	No	1 2 3
Has the person lost motivation to act on her/his obligations or interests?	Yes	No	1 2 3
Is the person less affectionate and/or lacking in emotions when compared to her/his usual self?	Yes	No	1 2 3
Does she/he no longer care about anything?	Yes	No	1 2 3
This domain describes mood or anxiety symptoms			
Has the person developed sadness or appear to be in low spirits? Does she/she have episodes of tearfulness?	Yes	No	1 2 3
Has the person become less able to experience pleasure?	Yes	No	1 2 3
Has the person become discouraged about their future or feel that she/he is a failure?	Yes	No	1 2 3
Does the person view herself/himself as a burden to family?	Yes	No	1 2 3
Has the person become more anxious or worried about things that are routine (e.g. events, visits, etc.)?	Yes	No	1 2 3
Does the person feel very tense, having developed an inability to relax, or shakiness, or symptoms of panic?	Yes	No	1 2 3
This domain describes the ability to delay gratification and control behavior, impulses, oral intake and/or changes in reward			
Has the person become agitated, aggressive, irritable, or temperamental?	Yes	No	1 2 3
Has she/he become unreasonably or uncharacteristically argumentative?	Yes	No	1 2 3
Has the person become more impulsive, seeming to act without considering things?	Yes	No	1 2 3
Does the person display sexually disinhibited or intrusive behaviour, such as touching (themselves/others), hugging, groping, etc., in a manner that is out of character or may cause offence?	Yes	No	1 2 3

www.MBItest.org

So How Do These Advances Improve Diagnosis and Benefit Care?

Challenges To Detection and Accurate Diagnosis

- “Progressive cognitive difficulties are normal with age”
- Limited confidence among some primary care providers
- Few specialty memory clinics
- Assessment time and cost
- Therapeutic nihilism
- Denial, stigma, Public Health reports

Clinical Diagnosis - Basics 2019

- Screening in high-risk people and those with cognitive complaints or early symptoms
- Clinical history: specific symptoms, onset, course
- Medication review, substance misuse
- Neuro exam
  - Focal deficit
  - Tremor, rigidity, gait
- Psychiatric symptoms
  - Apathy
  - Depression
  - Anxiety
- Cognitive assessment
  - MMSE+, MOCA+, others
  - Memory/Learning and Executive skills
  - Neuropsychological testing in some cases
- Function and social assessment

- Labs
  - Chem, CBC, LFTs
  - B12, TSH, (Vitamin D)
  - If indicated: syphilis serology, HIV
- Neuroimaging
  - MRI
  - CT, if MRI challenges

➢ Added value – MRI findings

- Hippocampal volume
- Pattern of regional atrophy
- Small-vessel cerebrovascular disease
- Progression of atrophy over time

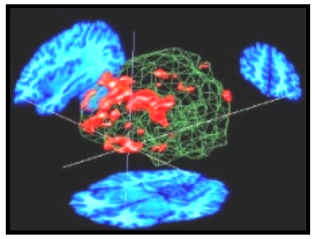
Diagnostic Advances

Specific Circumstances

- FDG-PET
- DAT to exclude DLB
- Amyloid PET
  - If objective impairment, AD is a possible dx, but dx is uncertain after comprehensive assessment
  - Knowledge of amyloid status would change dx or management
  - Persistent unexplained MCI, or early onset of progressive dementia
- CSF biomarkers
  - Early onset or atypical dementia
  - Persistent, progressive, unexplained MCI
  - Consider reliability, ratios, and cutoffs
  - Non-AD: prion, infectious, other rapidly progressive
- Plasma biomarkers
  - Limited clinical value currently
- Genetic testing
  - Presenilin 1, 2, APP - Familial AD
  - GRN, C9orf72 - Familial FTD

Summary and The Future

Improved Clinical Diagnosis



- Longitudinal symptoms and biology; MCI
- Neuropathology heterogeneity
- Biomarkers
- Refined diagnostic criteria
- What isn't Alzheimer's disease
- Neuropsychiatric symptoms

Next Steps -

- Embrace heterogeneity while refining distinct clinical syndromes
- Practical assessment in the community
- Biomarker advances
  - Plasma – e.g., NF-L or synaptic proteins
  - Clinical outcomes
- Early or preclinical diagnosis
  - Individualized risk score
- Optimal candidates for specific interventions