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Alzheimer's disease diagnosis, biomarkers, and clinical heterogeneity

Pacific Northwest Neuropsychological Society meeting
January 11, 2021

Thomas J. Grabowski MD

Director, Memory and Brain Wellness Center
Director, Alzheimer Disease Research Center
University of Washington

ADRC
Alzheimer's Disease Research Center

UW Medicine
NEUROSCIENCES INSTITUTE
MEMORY & BRAIN WELLNESS CENTER

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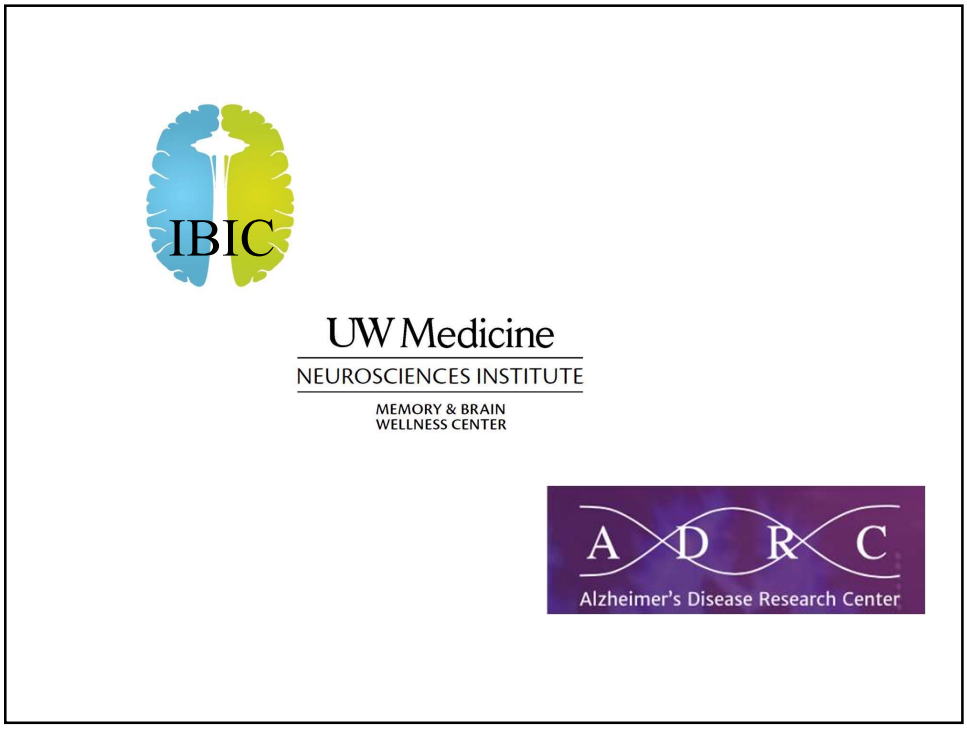

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Outline

- Alzheimer's disease diagnosis update
- Biomarkers of AD
- Cognitive and anatomic heterogeneity in AD
- Memory and Brain Wellness Center/ADRC

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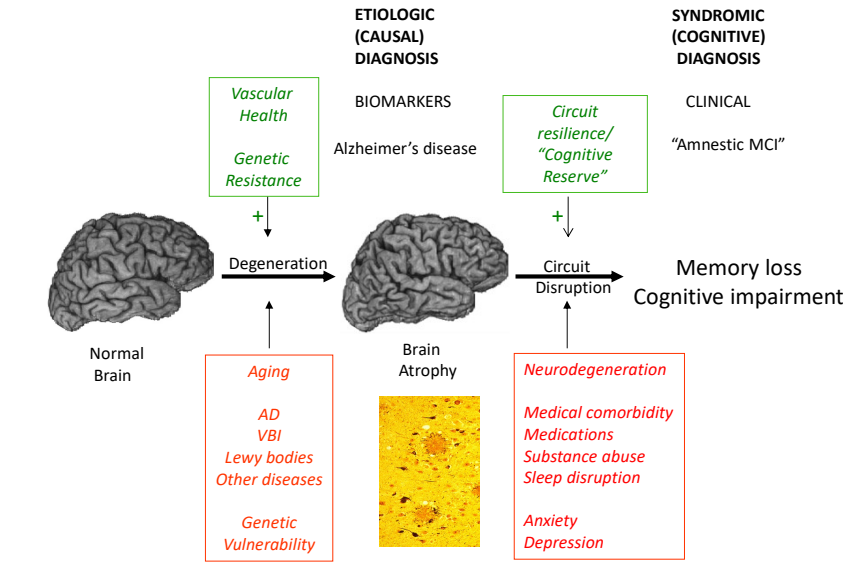

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Keeping diagnosis straight

Cognitive diagnosis vs. Causal diagnosis

- Dementia does not always mean Alzheimer's disease
  - "Comorbidity" is common – vascular, Lewy body, etc.
  - Amnestic dementia has a differential diagnosis
- "Alzheimer's" does not always mean dementia
  - MCI and preclinical states
  - "MCI due to Alzheimer's disease" is not self-contradictory

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Confusing AD and dementia

- Statistics you hear on prevalence of AD (5.8M Americans) correspond to AD *dementia.*
- CPT codes for AD from ICD-9 and ICD-10 mean AD *dementia.*
- Thus there is professional in addition to public conflation of AD and dementia

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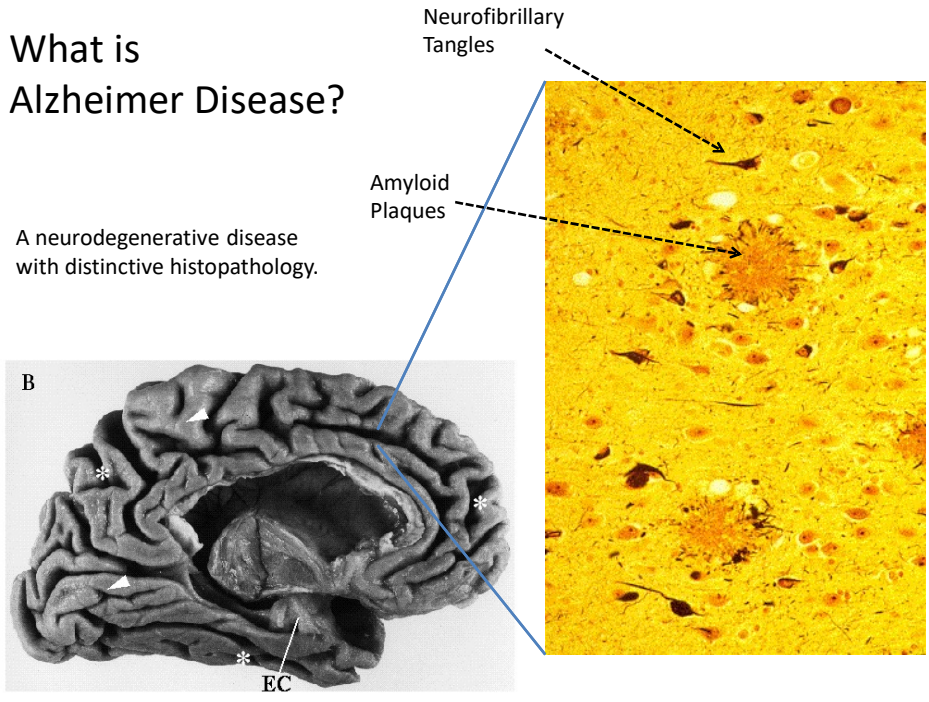
What is Alzheimer Disease?

A neurodegenerative disease with distinctive histopathology.



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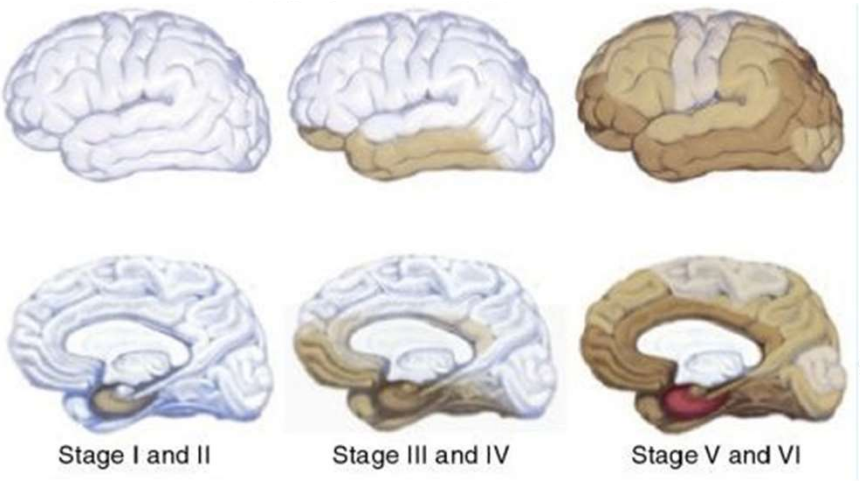
Six stages of AD tau tangles (Braak staging)



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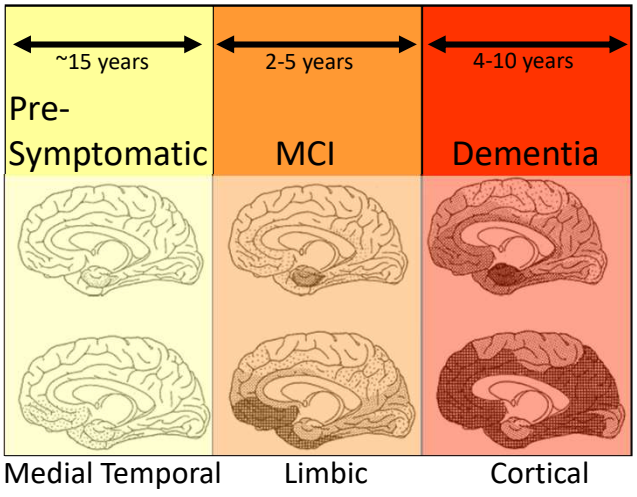

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Tau/NFTs

- 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

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"Typical" Alzheimer's disease

- Early and salient amnesia
- Prodromal aMCI
- Normal neurological examination

Dementia of Alzheimer type

Primary amnestic dementia

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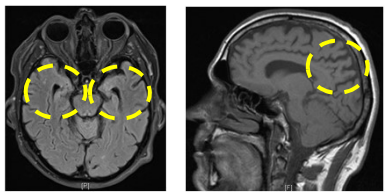
Alzheimer disease dementia

NIA-AA criteria (McKhann et al 2011)

- Dementia
- Insidious onset
- Clear-cut history of worsening
- Initial & most prominent domain impaired:
  - Learning & recall of recent information ***



EARLY ATROPHY OF MEDIAL TEMPORAL AND MEDIAL PARIETAL LOBES

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Accuracy of clinical diagnosis of AD

- *In the best hands*, 85% (neurological, neuropsychological, and imaging assessments)
- Why isn't it better?
  - There are other etiologies of amnestic dementia
    - Primary age-related tau-opathy (PART)
    - Limbic-predominant age-related TDP43 encephalopathy (LATE)
  - Multimorbidity
  - Atypical (not primarily amnestic) presentations

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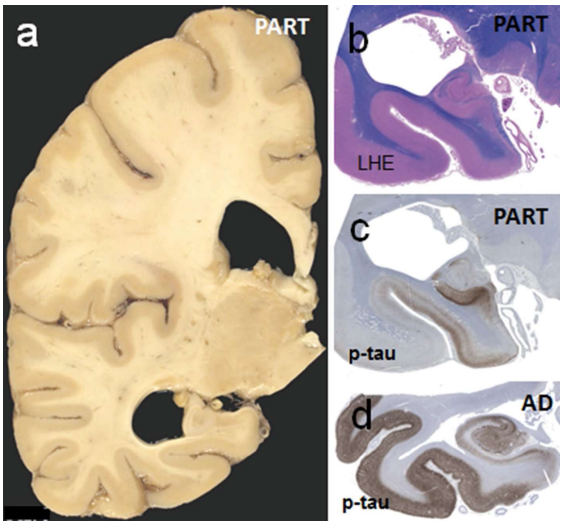
Primary Age-related tauopathy (PART)



Crary

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ADRC autopsies (n=434)

	Amyloid plaque density	Braak stage				
		0	I	II	III	IV
Number of subjects						
PART, definite	None	11	22	25	15	15
PART, possible	Low	4	16	27	16	31
–	Mod	2	11	15	32	50
–	High	3	7	10	39	83
Age at death (average)						
PART, definite	None	81.3	82.4	88.5	88.4*	92.0*,**
PART, possible	Low	88.4	80.4	84.7	89.7*	87.6*
–	Mod	89.0	80.2	87.4*	84.9	86.5
–	High	77.0	84.9	86.7	85.3	84.6
Final MMSE scores						
PART, definite	None	28.0	28.4	26.5	25.1***	24.3***
PART, possible	Low	28.5	25.8	24.4	24.6	21.9*
–	Mod	26.5	26.8	27.3	23.2*	19.8*
–	High	25.5*	24.5	27.9*	21.2*	18.8*,**
APOE ε4 positive (%)						
PART, definite	None	9.1	13.6	0.0	20.0	13.3
PART, possible	Low	25.0	12.5	14.8	37.5	35.5*
–	Mod	0.0	36.4	13.3	34.4*	50.0*
–	High	66.7*	28.6	50.0*	33.3*	56.6*,**

15 (3%) 182 (40%)

Crary et al 2014

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Primary Age-Related Tauopathy

Crary et al , 2014

- NFTs respecting Braak stages, in absence of amyloid pathology
- Ubiquitious, mostly Braak I-II
- Rarely reaching Braak V-VI regions
- Associated with aMCI, mild amnestic dementia
- NO association with APOE e4

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Limbic-predominant **A**ge-related **T**DP-43 dis**E**ase (LATE)

- A “fourth proteinopathy”
- TDP-43 proteinopathy
- Degenerative hippocampal sclerosis
- Another etiology of amyloid-negative amnestic MCI and amnestic dementia

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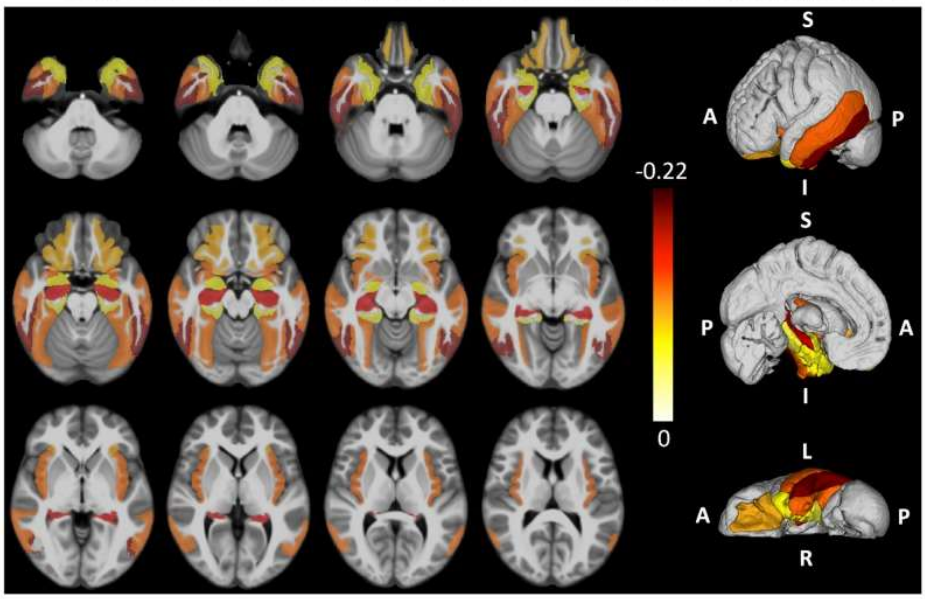

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LATE

- Present in >20% (up to 50%) of individuals > 80 years in large community-based autopsy series.
- Associated with substantial disease-specific cognitive impairment, usually an amnestic dementia syndrome.
- Distinct from FTD-TDP43 …
- Overall prevalence of LATE is on the same order of magnitude as Alzheimer's disease neuropathological changes
- AD and LATE are often comorbid, but which pathology is more severe varies greatly between individuals.

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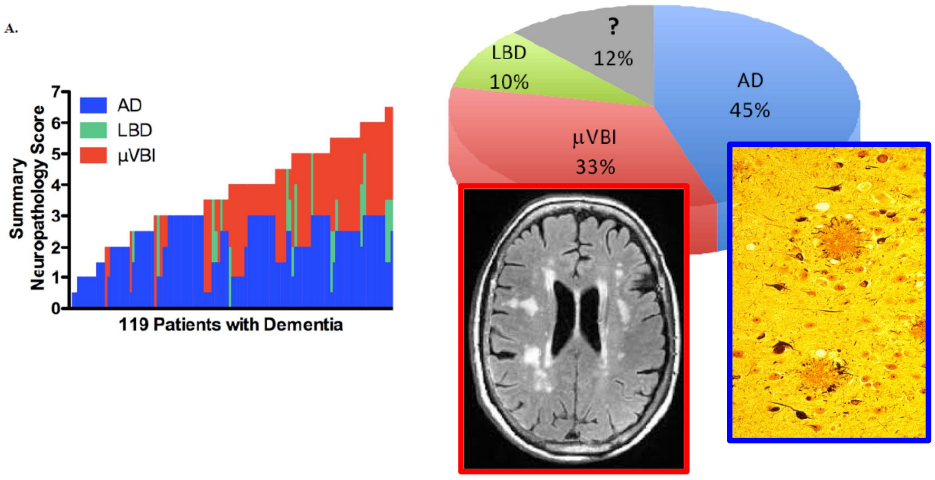
ADRD comorbidity is the rule



Sonnen et al Arch Neurol 201

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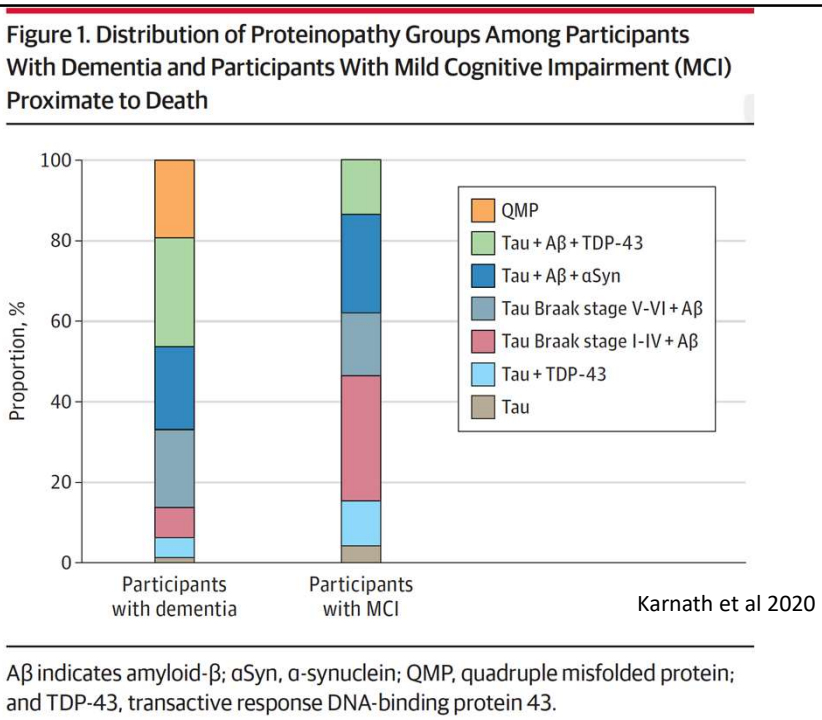

Karnath et al 2020

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NIA-AA Mild Cognitive Impairment

Albert et al 2011

Cognitive concern for a change in cognition reported by patient, informant or clinician
Objective evidence of Impairment in one or more cognitive domains, typically including memory
Preservation of independence in functional abilities
Not demented

Amnestic MCI
Multidomain amnestic MCI
Nonamnestic MCI

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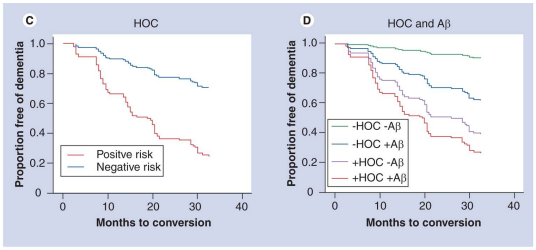
Conversion of aMCI to dementia

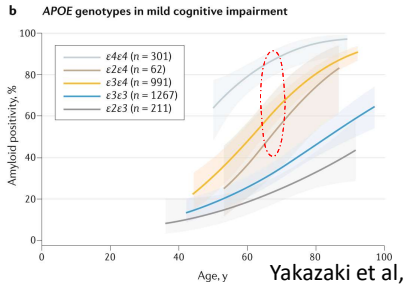
Risk factors:

- multidomain impairment
- low hippocampal volume/occupancy
- APOE genotype (e4)
- Positive amyloid test(s)

10%/yr, asymptote at 70%
50% risk of AD dementia
20% nonAD dementia

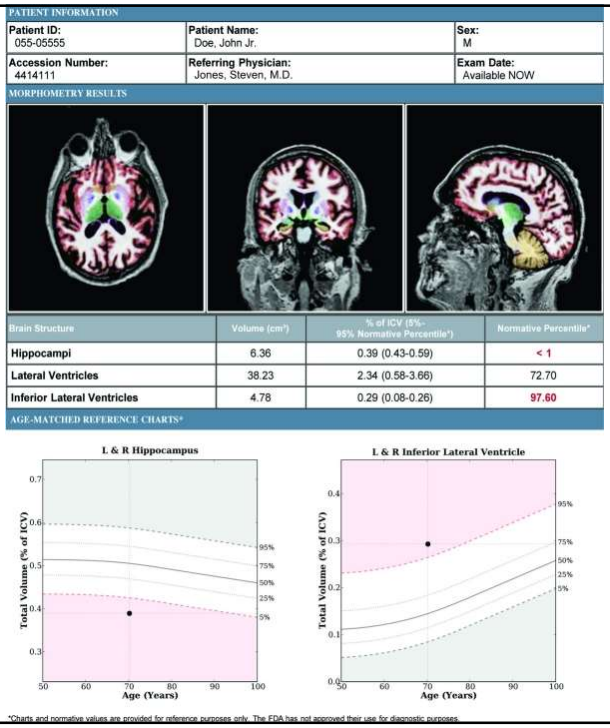


Mcevoy and Brewer



Yakazaki et al,

24



PATIENT INFORMATION

Patient ID: 055-05555	Patient Name: Doe, John Jr.	Sex: M
Accession Number: 4414111	Referring Physician: Jones, Steven, M.D.	Exam Date: Available NOW

MORPHOMETRY RESULTS

Brain Structure	Volume (cm³)	% of ICV (5%-95% Normative Percentile*)	Normative Percentile*
Hippocampi	6.36	0.39 (0.43-0.59)	< 1
Lateral Ventricles	38.23	2.34 (0.58-3.66)	72.70
Inferior Lateral Ventricles	4.78	0.29 (0.08-0.26)	97.60

AGE-MATCHED REFERENCE CHARTS*

*Charts and normative values are provided for reference purposes only. The FDA has not approved their use for diagnostic purposes.

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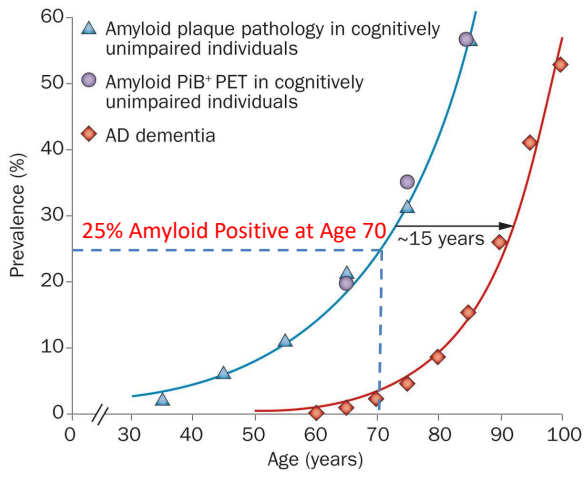

Langbaum, J. B. *et al.* (2013) Ushering in the study and treatment of preclinical Alzheimer disease *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2013.107

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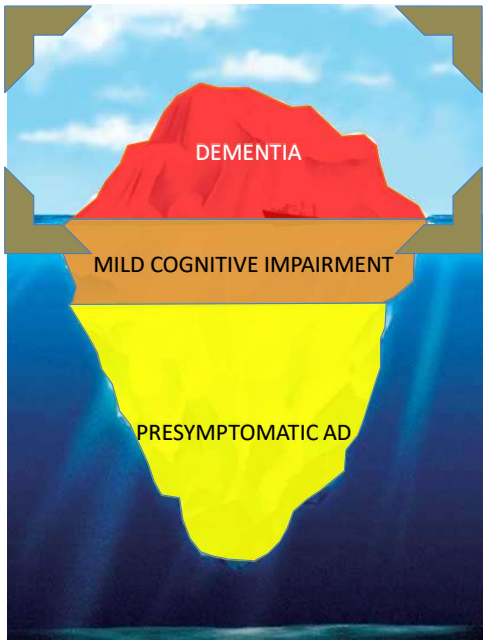

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Preclinical AD is common

Many patients who have Alzheimer's disease in the sense of microscopic changes in the brain do not yet have, or may never progress to, dementia

For every patient with dementia due to Alzheimer's disease, there are two with preclinical AD.

About 25% of 70 yr olds have preclinical AD change.

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Variable susceptibility

- <u>(Biological) Resistance</u>: little pathology develops despite high risk (e.g. no Alzheimer's disease despite very advanced age or APOE4 homozygosity)
- <u>(Functional) Resilience</u>: Mild or no cognitive impairment despite pathologic load ("cognitive reserve")

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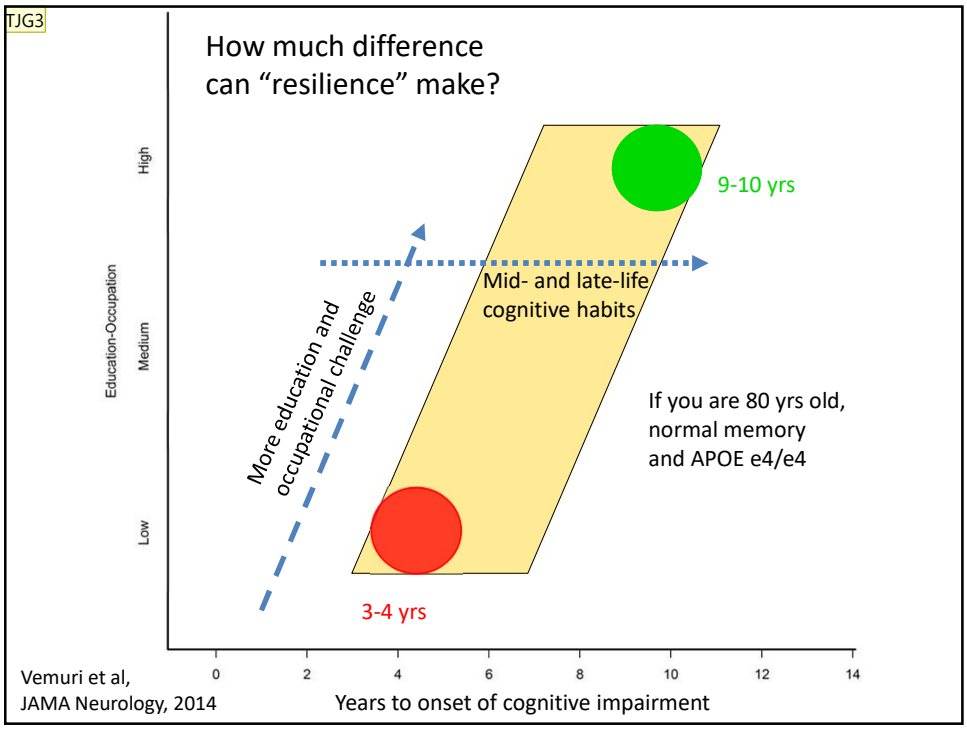

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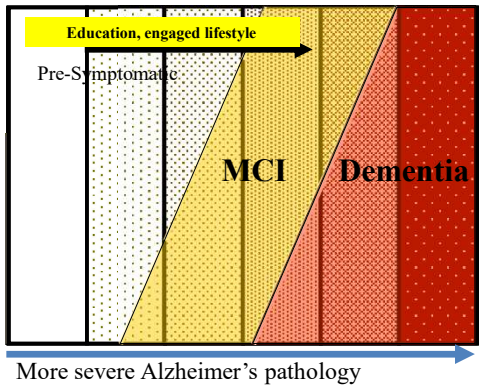
Slide 30

TJG3 Thomas J. Grabowski, 1/11/2021

LEANING IN

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

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Role of Neuropsychology

- In mild cases:
  - Detecting and quantifying mild impairments
  - Profiling impairment and sparing over domains
  - Particularly helpful in assessing executive impairments
  - Establishing baseline; tracking change
- Diagnostic stratification
  - Subjective impairment
  - Nonamnestic MCI
  - aMCI
  - Multidomain MCI
  - Mild dementia
- Areas of retained strength, rehabilitation approaches

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Outline

- Alzheimer's disease diagnosis update
- Biomarkers of AD
- Cognitive and anatomic heterogeneity in AD
- Memory and Brain Wellness Center/ADRC

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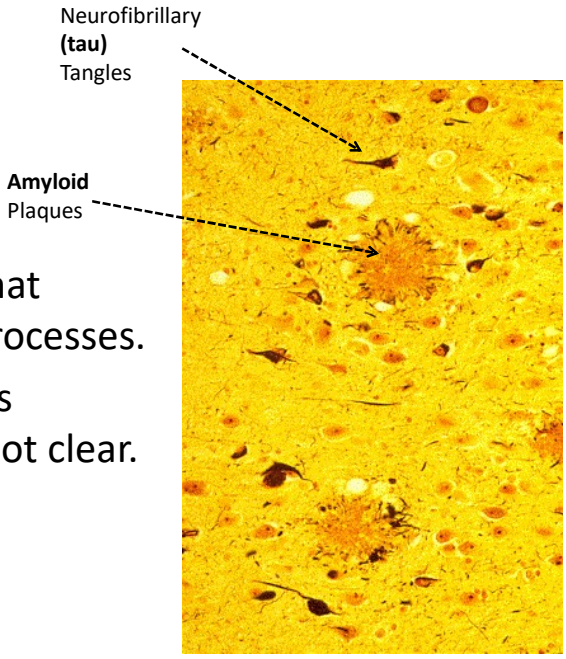
Alzheimer Disease
and
Its markers



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

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Biomarkers

Measurable characteristics that signify disease processes

Imaging tests – MRI, PET

Spinal fluid protein levels

Blood protein levels

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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

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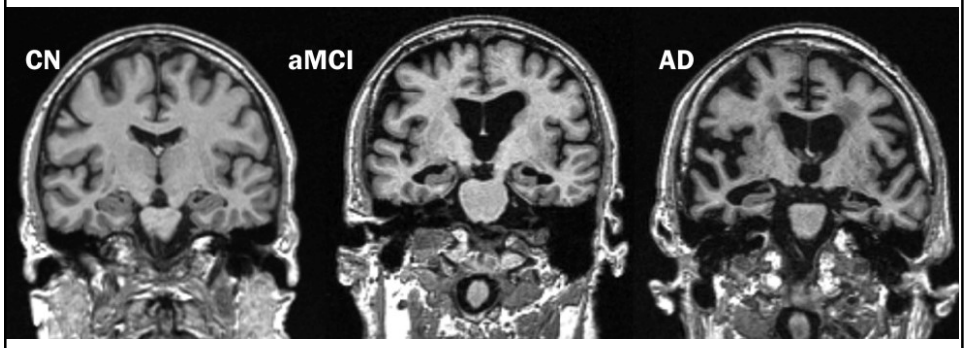
Hippocampal atrophy



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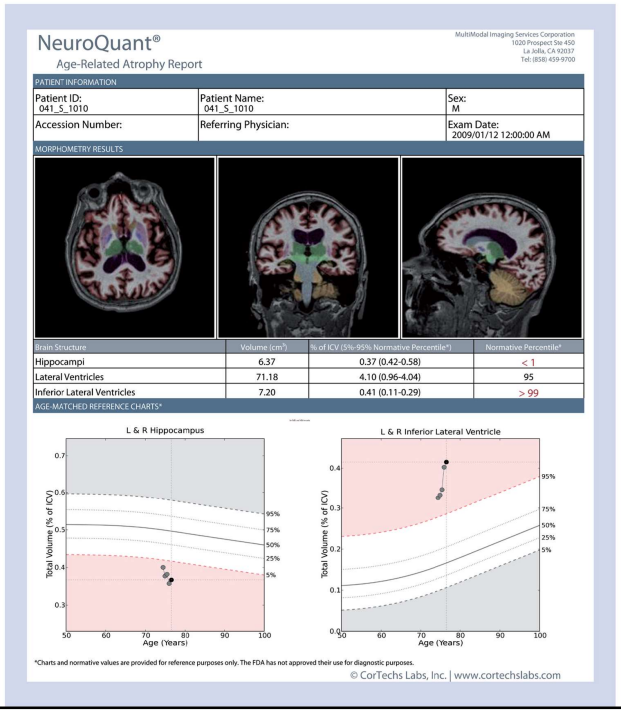

NeuroQuant®
Age-Related Atrophy Report

MultiModal Imaging Services Corporation
1020 Prospect Ste 450
La Jolla, CA 92037
Tel: (858) 459-9700

PATIENT INFORMATION

Patient ID:	Patient Name:	Sex:
041_S_1010	041_S_1010	M
Accession Number:	Referring Physician:	Exam Date:
		2009/01/12 12:00:00 AM

MORPHOMETRY RESULTS

Brain Structure	Volume (cm^3)	% of ICV (5%-95% Normative Percentile*)	Normative Percentile*
Hippocampi	6.37	0.37 (0.42-0.58)	< 1
Lateral Ventricles	71.18	4.10 (0.96-4.04)	95
Inferior Lateral Ventricles	7.20	0.41 (0.11-0.29)	> 99

AGE-MATCHED REFERENCE CHARTS*

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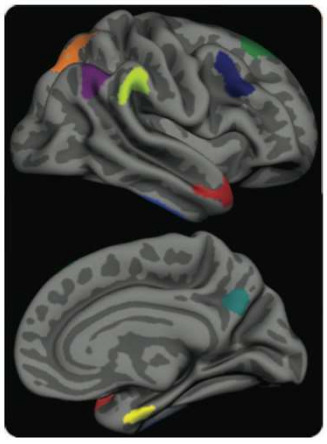
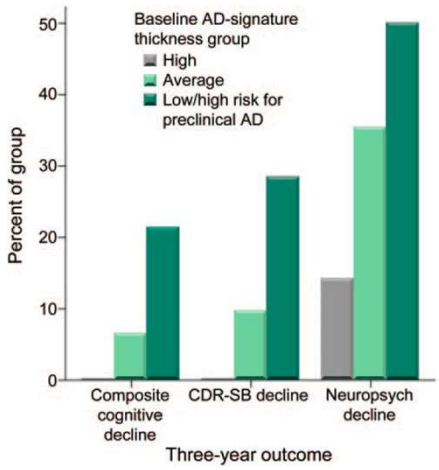
Prediction of Cognitive decline
"AD Signature" regions





Dickerson, et al ADNI 2012

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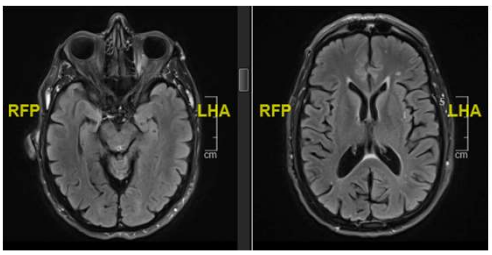
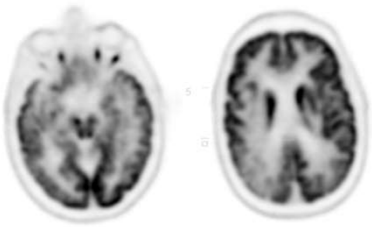


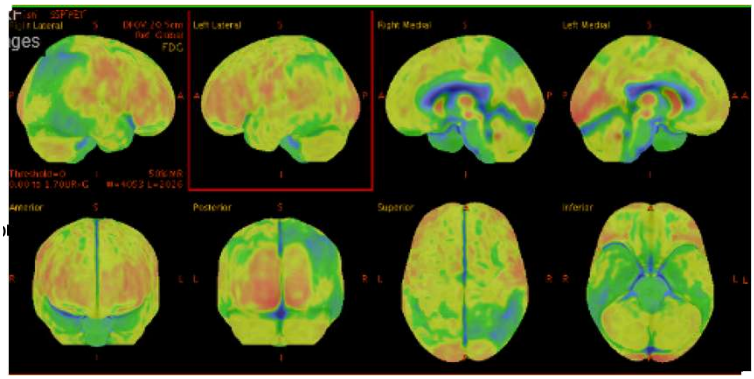


FDG PET

Hippocampal sparing

Rightward asymmetric

Posterior predominant



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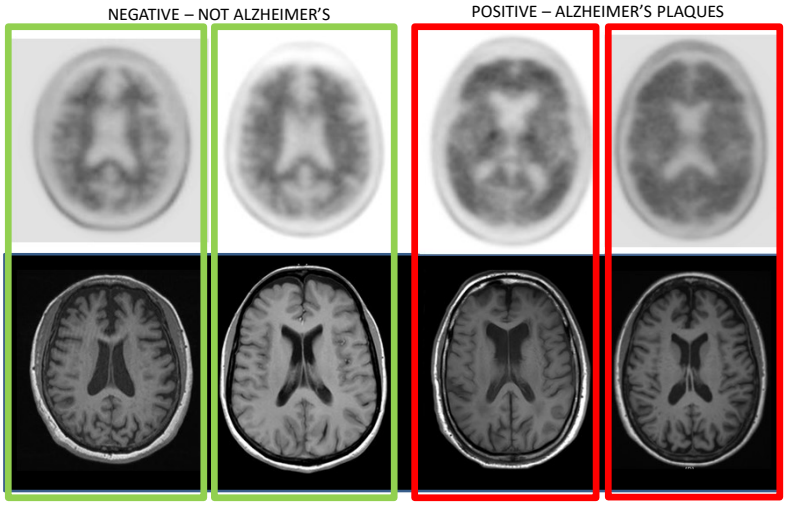
Amyloid PET scans

NEGATIVE – NOT ALZHEIMER'S

POSITIVE – ALZHEIMER'S PLAQUES



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Appropriate use criteria for amyloid PET Johnson et al 2013

- Persistent or progressive unexplained MCI
- Possible AD dementia:
  - Atypical course
  - Comorbidity
- Atypically young-onset dementia

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Not appropriate

- Typical AD
- To determine dementia severity
- Solely for positive family history or APOE e4
- Cognitive complaints not supported on exam
- In lieu of genotyping for mutation carriers
- Asymptomatic individuals
- Non-medical uses

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iDEAS
Imaging Dementia—Evidence For Amyloid Scanning

- **AIM 1:** Determine if amyloid PET associated with a ≥30% change in composite patient management endpoint between the pre-PET and post-PET visit, separately in MCI and dementia.
  - Total sample size 11,050; 80% power within MCI and dementia subgroups.
  - Patient management changed in 60.2% of MCI and 63.5% of dementia patients
  - Most common change was in use of AD medications (Increased in Aβ PET+, decreased in Aβ PET-).
  - Diagnosis changed in 35.6% of patients
  - Increase in diagnostic confidence.
  - Decreased utilization of alternative diagnostics.
- **AIM 2:** Determine if amyloid PET is associated with a ≥10% reduction in 12-months CMS claims-derived hospital admissions and emergency department (ED) visits in study patients vs. controls.
  - Results pending.

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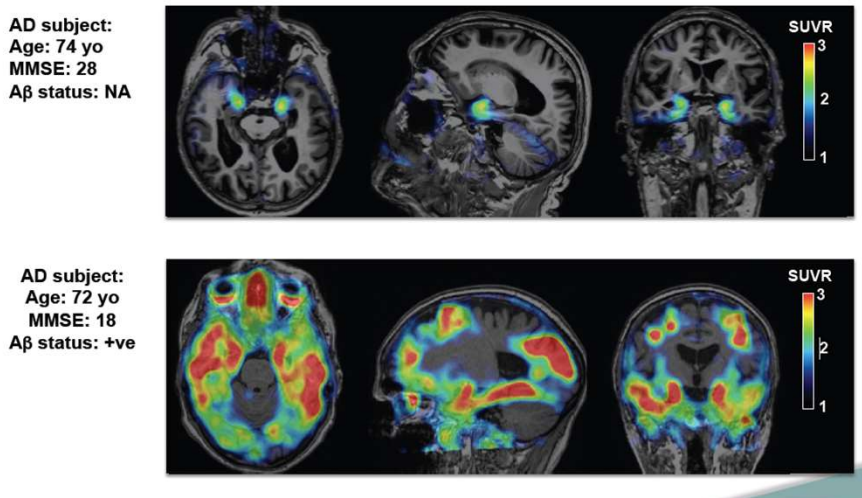
Tau PET with [^{18}F]MK6240



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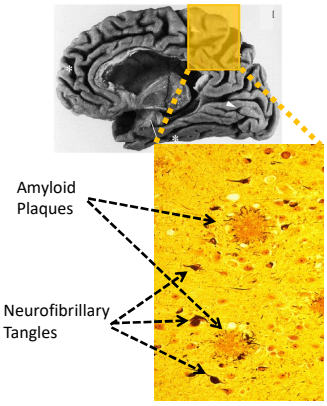
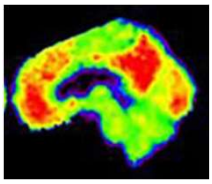
MOLECULAR IMAGING OF ALZHEIMER'S DISEASE

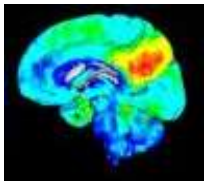




AMYLOID PET SCAN

Detects amyloid plaques
Stereotypical distribution
Leads symptoms by 15 years
Doesn't change over time

Use: to certify diagnosis
Spinal fluid is an alternative.



TAU PET SCAN

Detects tau tangles
Variable distribution
Correlates well with symptoms
Tracks advancing disease

Use: to delineate disease impact
To track treatment

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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]

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

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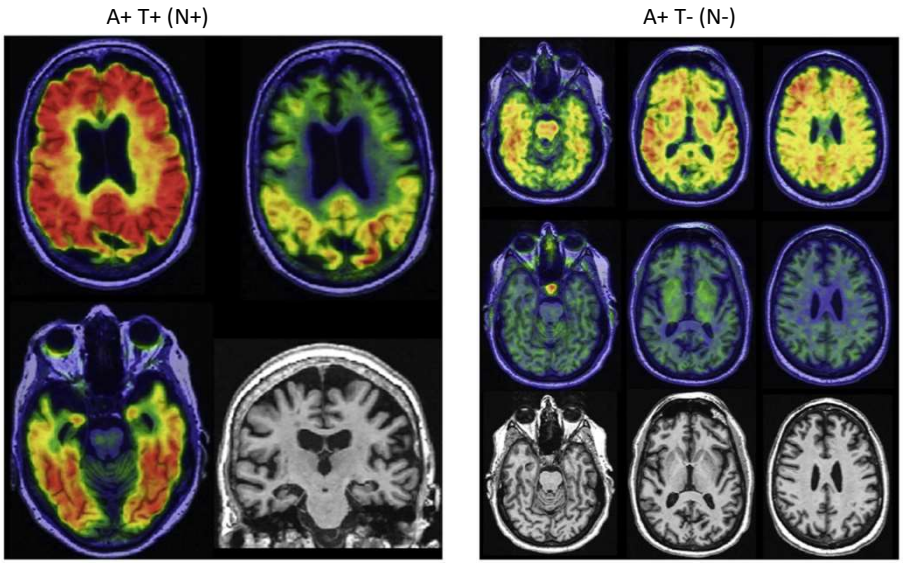

Jack et al , 2018

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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

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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

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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?

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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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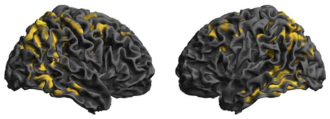
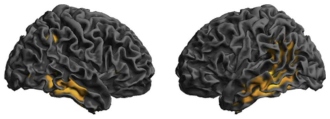
Demonstration of “cognitive reserve” with tau imaging

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

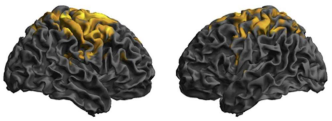
Higher Educated AD vs Control

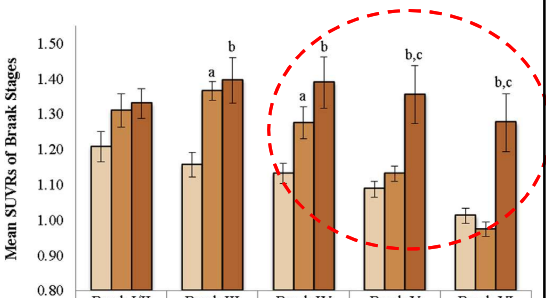


Lower Educated AD vs Control



Higher (17) vs Lower (12) 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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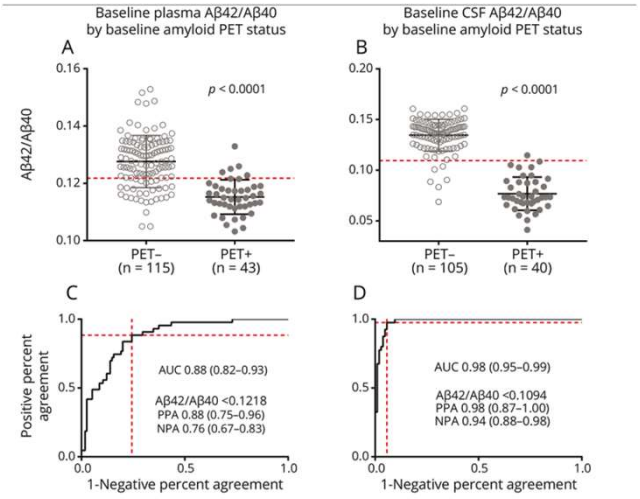
Plasma amyloid biomarkers

Schindler et al 2019



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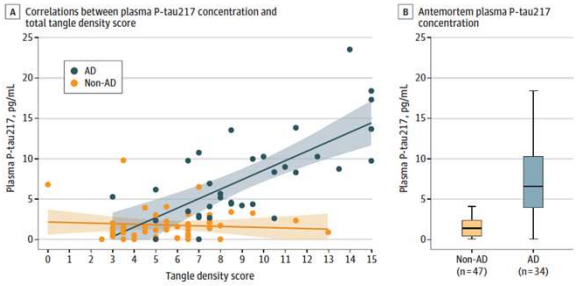
JAMA | Original Investigation

Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders

Sebastian Palmqvist, MD, PhD; Shorena Janelidze, PhD; Yakeel T. Quiroz, PhD; Henrik Zetterberg, MD, PhD; Francisco Lopera, MD; Erik Stomrud, MD, PhD; Yi Su, PhD; Yinghua Chen, MSc; Geidy E. Serrano, PhD; Antoine Leuzy, PhD; Niklas Mattsson-Carlgren, MD, PhD; Olof Strandberg, PhD; Ruben Smith, MD, PhD; Andres Villegas, MD; Diego Sepulveda-Falla, MD; Xiyun Chai, MD; Nicholas K. Proctor, BS; Thomas G. Beach, MD, PhD; Kaj Blennow, MD, PhD; Jeffrey L. Dage, PhD; Eric M. Reiman, MD; Oskar Hansson, MD, PhD

Figure 1. Plasma P-tau217 Concentrations in the Neuropathology Cohort (Cohort 1)



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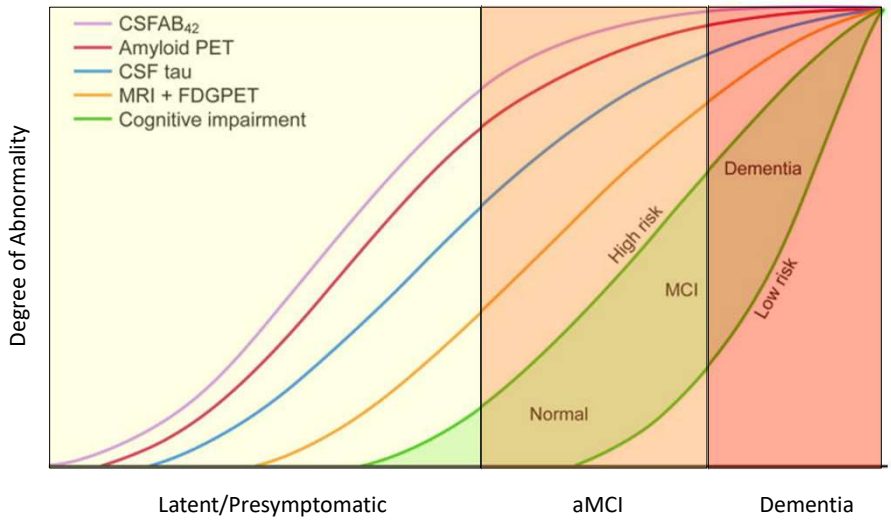
Canonical Sequence of AD Biomarkers



Jack et al, 2013

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Outline

- Alzheimer's disease diagnosis update
- Biomarkers of AD
- Cognitive and anatomic heterogeneity in AD
- Memory and Brain Wellness Center/ADRC

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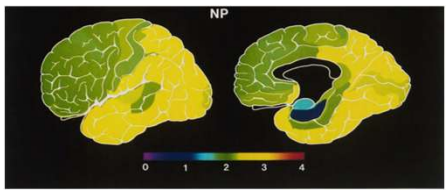
Anatomic and cognitive variability in AD

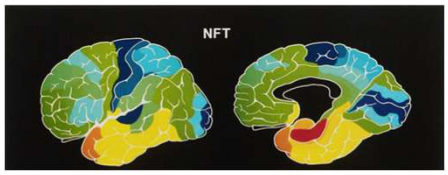
- Across individuals: Variation in quantitative relationship among risk, degeneration, and symptoms
  - *Biological resistance*
  - *Physiological resilience*
- Within an AD brain: pathologic hallmarks distribute differently

61

61

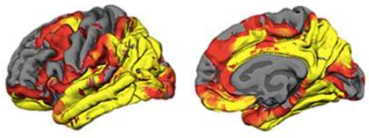


A



T

Arnold et al 1991



N

Canonical profile of AD neurodegeneration

62

Anatomic and cognitive variability in AD

- Across individuals: Variation in quantitative relationship among risk, degeneration, and symptoms
  - *Biological resistance*
  - *Physiological resilience*
- Within an AD brain: pathologic hallmarks distribute differently
- Across individuals: Variation in cortical sectors that degenerate early, and that are spared
  - *Topographic variants have variant cognitive phenotypes*

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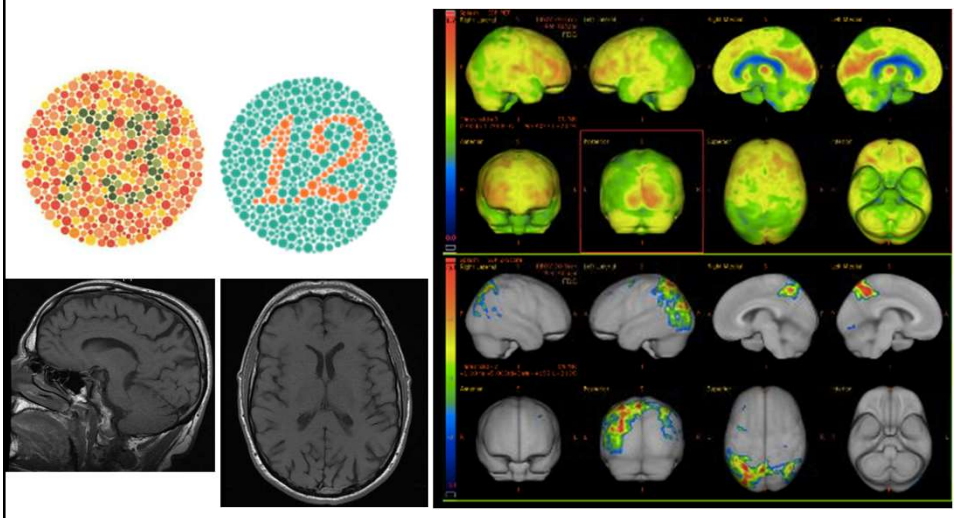
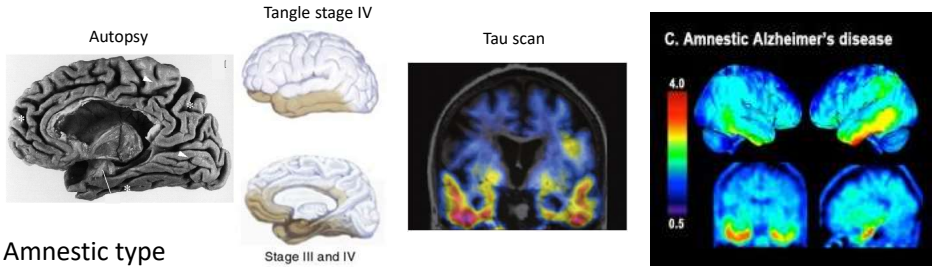
POSTERIOR CORTICAL ATROPHY



FDG PET

64



Amnestic type

65

Variant (non-amnestic) cognitive presentations of AD

- Posterior cortical atrophy ("visual variant AD")
  - Visuospatial processing
- Logopenic primary progressive aphasia
  - Language
- Executive-predominant AD
  - Comportment and behavior

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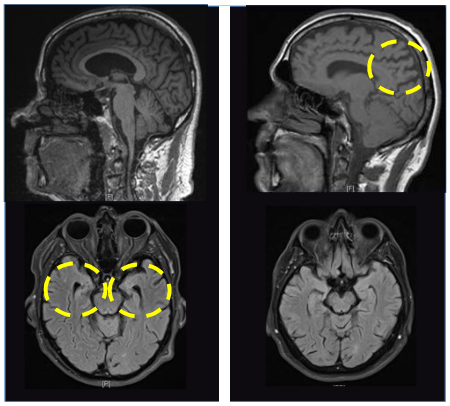
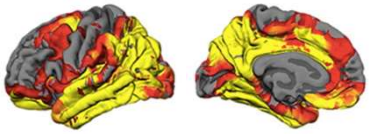
Topographic subtypes of Amnestic AD

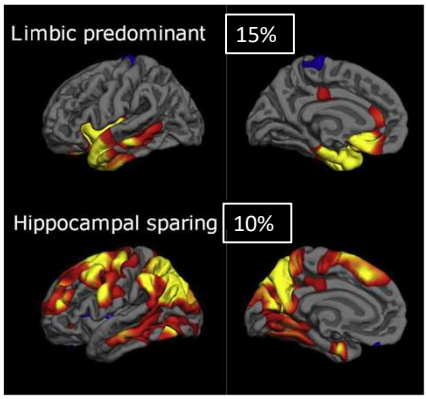


Amnestic with hippocampal atrophy

Amnestic with medial parietal atrophy



Central tendency of AD degeneration

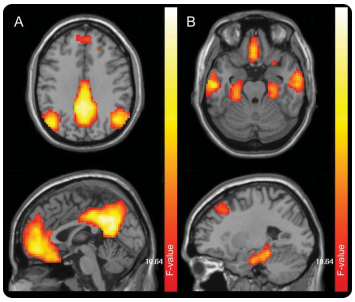


Murray et al, 2011

67

A systems explanation for amnesia:

- Medial temporal lobe & default network act as a system
- Encoding is an externally engaged state – default network is normally deactivated
- Retrieval is an internally engaged state – default network activity is required
- Dysfunction in both/ either MTL and DMN contributes to amnesia in AD



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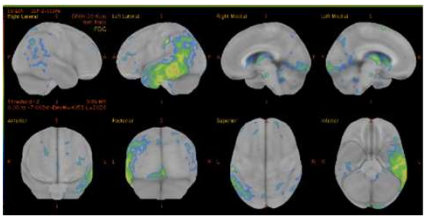
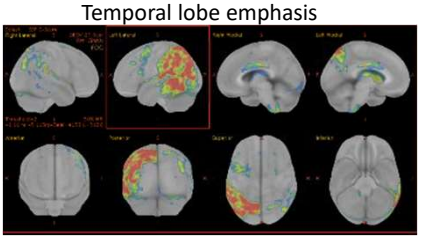
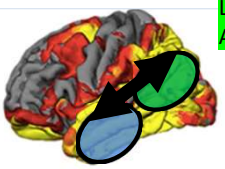
Variable patterns of cortical degeneration in AD



left lateralized
Temporal lobe emphasis

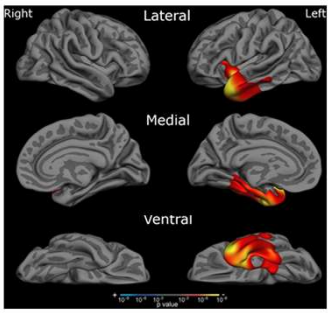


left lateralized
Parietal lobe emphasis



Logopenic Aphasia

Anomia



Domoto-Reilly et al
NeuroImage 2012

69

Variant presentation is common in sporadic late onset disease

- Among 869 incident dementia cases in the ACT study (mean age 82)

Almost half of incident cases

  - 14% had disproportionate visuospatial impairments
  - 9% had disproportionate language impairments
  - 8% has disproportionate executive impairment

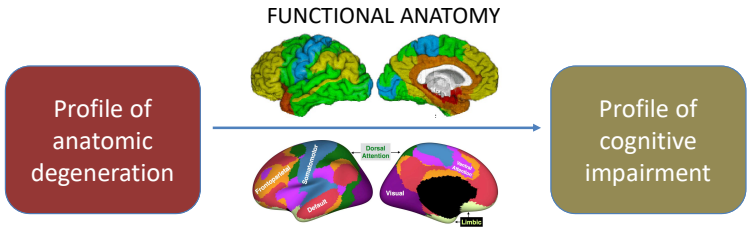
  and

  - 18% had disproportionately severe memory impairments

Crane et al, Alz & Dem, 2017

70

There is a strong relationship between anatomic variability and cognitive variability, reminiscent of general lesion-deficit relationships in neurology



RESILIENCE

COMPENSATIONS

The anatomic profile is probably a closer reflection of the underlying biological disease process

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Case History (1)

56 yo RH F teacher with 16 yrs formal education

Presents 2016 with word-finding trouble, a couple episodes momentary spatial disorientation

MoCA 29/30

Normal neurological examination

Neuropsychology: “mild suppressions in aspects of attention and concentration, no clear domains of impairment, not overly concerning for degenerative disease.”

Dx: Subjective cognitive impairment

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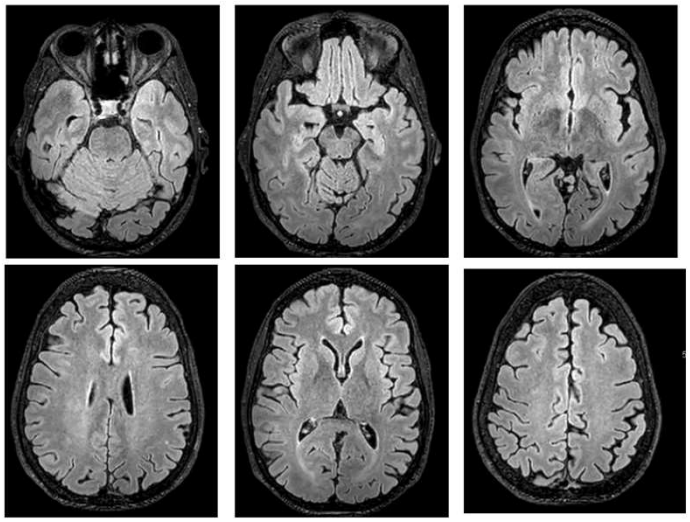
- 2019 : MoCA 25/30
- MRI ordered by PCP: “normal”



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Case History (2)

- 2020 : word finding worse, problems reading, spelling, counting; trouble with clocks, anxious.
- MoCA 23/30, 20/30
- Neuropsychology: declines in processing speed, language (naming, fluency), visuoconstruction, and learning and memory abilities
- Neurologic re-eval: landmark naming 4/20 (problems with Mt Rainier, Space Needle), problems reading Ishihara plates, animal fluency 5 (from 17);l normal neurological examination

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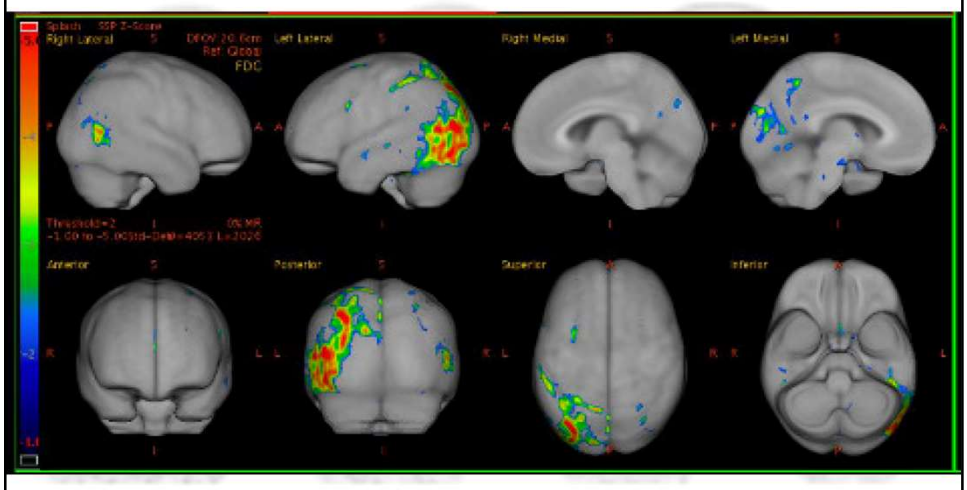

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CSF Biomarkers

p-Tau/Abeta42: 0.045 ratio (HIGH)
Abeta42: 1076 pg/mL
Total-Tau: 437 pg/mL (HIGH)
Phospho-Tau(181P): 47.9 pg/mL (HIGH)

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Summary

- Progressive language and visuospatial syndrome not conforming to LPPA, PCA, SD
- Early onset Alzheimer's disease
- Imaging assessment was key to diagnosis
- Confirmed with a biomarker test.

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Summary

Anatomic & cognitive heterogeneity in AD

- AD degeneration is principled, not diffuse, and captured by Braak staging
- But the profile varies significantly around the central tendency
- The clinical phenomena are rich and varied
- Damage-deficit relationships assist localization

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Outline

- Alzheimer's disease diagnosis update
- Biomarkers of AD
- Cognitive and anatomic heterogeneity in AD
- Memory and Brain Wellness Center/ADRC

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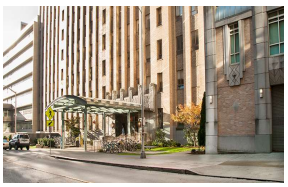
UW MEMORY AND BRAIN WELLNESS CENTER
AT HARBORVIEW

- *Multidisciplinary*
- *Accessible*
  - *Physician or self-referral (20%)*
  - *Harborview Medical Center*
  - *5-10% non-English speaking*
- *1000 new patients annually*
  - *25% UWNC*
  - *25% remainder UW Medicine*
  - *25% Local community referral*
  - *25% Outside Seattle area*



Memory and Brain Wellness Center at Harborview

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MBWC

- Multidisciplinary diagnosis
  - Imaging, biomarkers, neuropsychology, neurogenetics
- Individualized care planning
  - Strengths-based approaches
- Cognitive rehabilitation for MCI, mild dementia (ADAPT program)
- Patient, family and community education
- The Memory Hub
- Systematic opportunities for research

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UNIVERSITY of WASHINGTON

ADRC

Alzheimer's Disease Research Center

UW ADRC
P30 AG066509

BIOLOGICAL HETEROGENEITY
OF ADRD
2020-2025

The mechanistic and biological underpinnings of AD as well as the factors countering degeneration and dementia


Dr. Eric Larson


Dr. Thomas Grabowski


Dr. Astrid Suchy-Dicey


Dr. Kimiko Domoto-Reilly


Dr. Annika Noreen


Dr. C. Dirk Keene


Dr. Ali Shojaie


Meghan Jernigan


Dr. Suman Jayadev


Dr. Caitlin Latimer

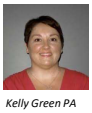

Dr. Jeffrey Iliff


Dr. Dedra Buchwald


Dr. Paul Crane


Dr. Jessica Young


Dr. Ellen Wijsman


Kelly Green PA


Dr. Ed Lein


Dr. Christine Mac Donald


Dr. Tom Bird


Dr. Brian Kraemer


Dr. Lonnie Nelson

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Research Themes

1. Biological heterogeneity of AD
   - Genetic factors
   - Disease mechanisms
   - Biological resistance/Cognitive resilience
   - Anatomical/Cognitive Variability
2. Novel biomarkers / CSF, imaging / in early AD
3. Strengths-based reframing of AD
4. Frontotemporal lobar degeneration
5. ADRD in American Indians

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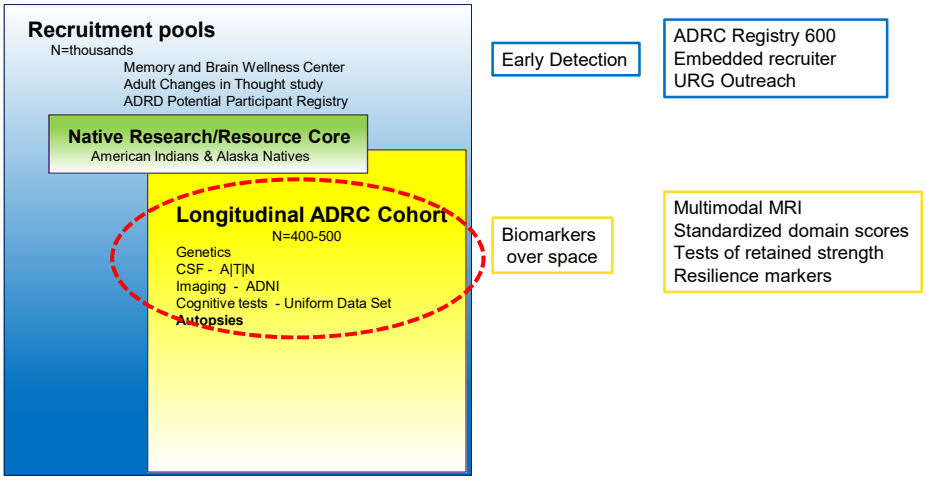
ADRC resource organization



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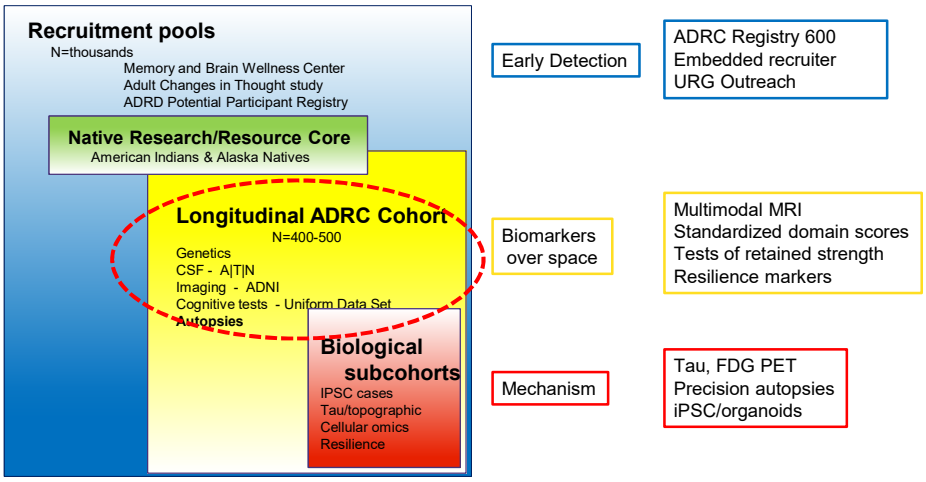
ADRC resource organization



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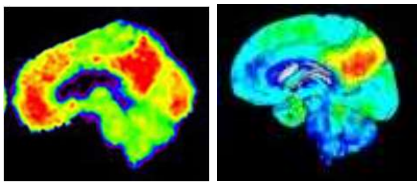
AT(N) biomarkers

Jack et al , 2018

A : **AMYLOID** Aggregated Aβ
- Low CSF Aβ42, or Aβ42/Aβ40
- Amyloid PET

T : **TAU** Aggregated tau (NFTs)
- High CSF phosphorylated tau
- Tau PET

(N): **NEURODEGENERATION**
- Atrophy detected by MRI
- Low metabolism by FDG PET
- High total tau in CSF



AMYLOID PET SCAN	**TAU PET SCAN**
Detects amyloid plaques	Detects tau tangles
Stereotypical distribution	Variable distribution
Leads symptoms	Correlates with symptoms
Little change over time	Tracks advancing disease
To certify diagnosis	To delineate disease impact

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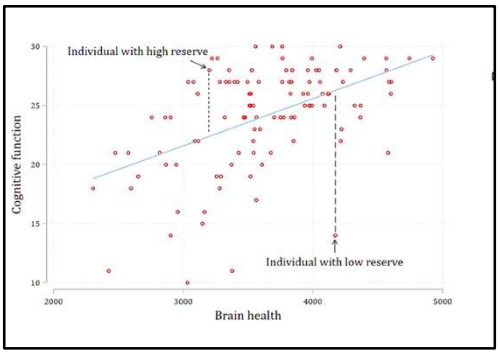
Cognitive resilience: better cognitive performance than expected for a given amount of brain atrophy

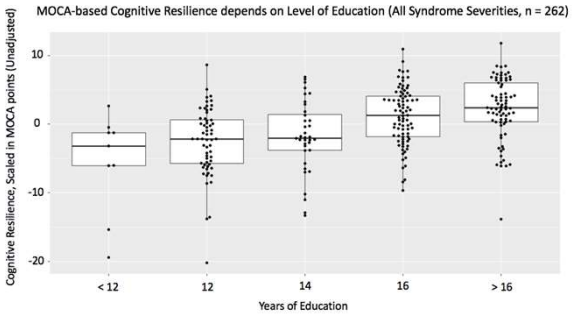


Residual methods
for measuring cognitive resilience

Memory and Brain Wellness Clinic Data

Plot residual against years of Education.

Reslience has a relationship to level of education



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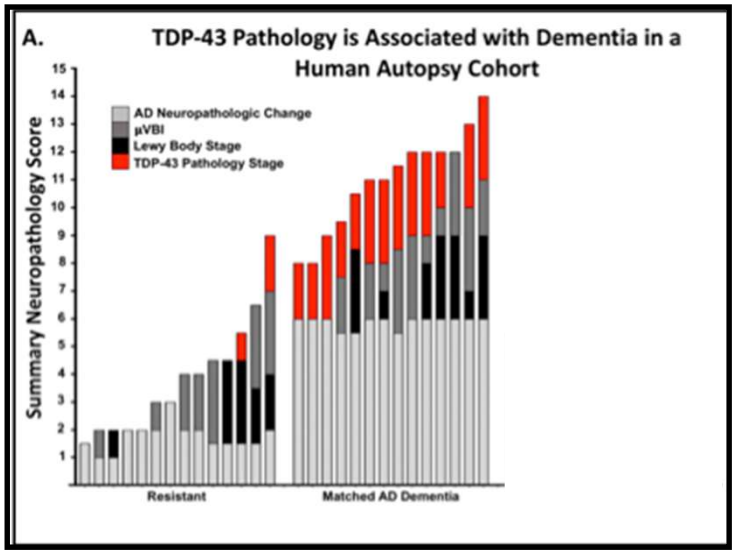
Resistance and Resilience



Caitlin Latimer MD PhD
Acta Neuropath Comm 2019

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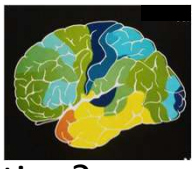
Unexplained anatomic variability

- Why is there varying balance of medial temporal to cortical involvement?
- Why disproportionate involvement of the temporal neocortex?
- What explains asymmetric degeneration?
- Why do some patients (eg PCA) have an extremely atypical phenotype?



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Hypothesis

- AD causes neural degeneration through multiple biological mechanisms, each associated with an anatomic pattern of effect.
- Corollary: The topographic pattern of AD neurodegeneration can be analyzed to stratify patient groups

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Hypothesis: The topographic expression of Alzheimer's disease is related to disease and resilience mechanisms

Three levels of empirical inquiry:

- *In silico* – Analysis of open datasets e.g. AMP-AD, ADNI
  - Genetic discovery
  - Hypothesis generation on open datasets
  - Atlases of brain organization aiding interpretation
- *In vivo* – Study of human subjects with variants of MCI/mild dementia
  - Ascertainment with neuropsychology, tau imaging and other biomarkers
  - Using iPSCs to build *in vitro* models
- *Post mortem* – spatially-extended "-omics"
  - Supported by ex-vivo imaging and brain sampling

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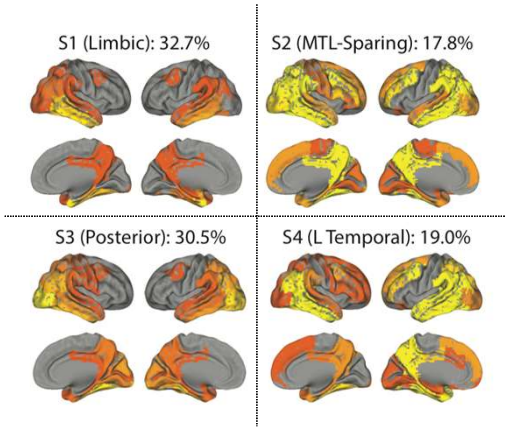
The tau image as phenotype



N=1143 Vogel et al, OHBM 2020 #0309

One component of a multidisciplinary phenotype

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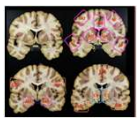
Dramatic advances in neuropathology

- Precision neuropathology
  - RNA-preserving tissue preparation
  - Quantitative protein burdens
  - Topographic sampling
- Post-mortem MRI
- Stem cells from meninges




Dirk Keene
Caitlin Latimer

U19 AG060909 Allen Institute for Brain Science
A platform for cell type-level transcriptomic, epigenomic and spatial interrogation of Alzheimer's disease

- BRAIN initiative cell census technology in AD
- Single cell genomics, spatial transcriptomics


Ed Lein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Summing up

- Diagnosis of AD is increasingly biological, assisted by fluid and imaging biomarkers.
- Preclinical disease, comorbidity, and resilience are key concepts.
- ATN biomarker framework enables approaches to preclinical disease and resistance/resilience.
- Recognizing and analyzing clinical heterogeneity will be increasingly important to diagnosis and treatment.

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UW ALZHEIMER'S DISEASE RESEARCH CENTER

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What can you do to help advance our work

- **Volunteer with community programs or The Memory Hub:**
  Contact Mari Becker, Program Manager of Community Education & Impact
  206.744.2017, mbecker1@uw.edu
- **Participate in a research study:**
  Contact Jessica McDougall, ADRC Lead Research Coordinator
  206.744.0588, uwadrc@uw.ed
- **Help us grow and enhance our ideas:**
  Contact Tom Grabowski, Director MBWC, tgrabow@uw.edu
- **Provide financial support:**
  Help us do something special: The Memory Hub!
  Contact Courtney Stringer, Director for Philanthropy
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