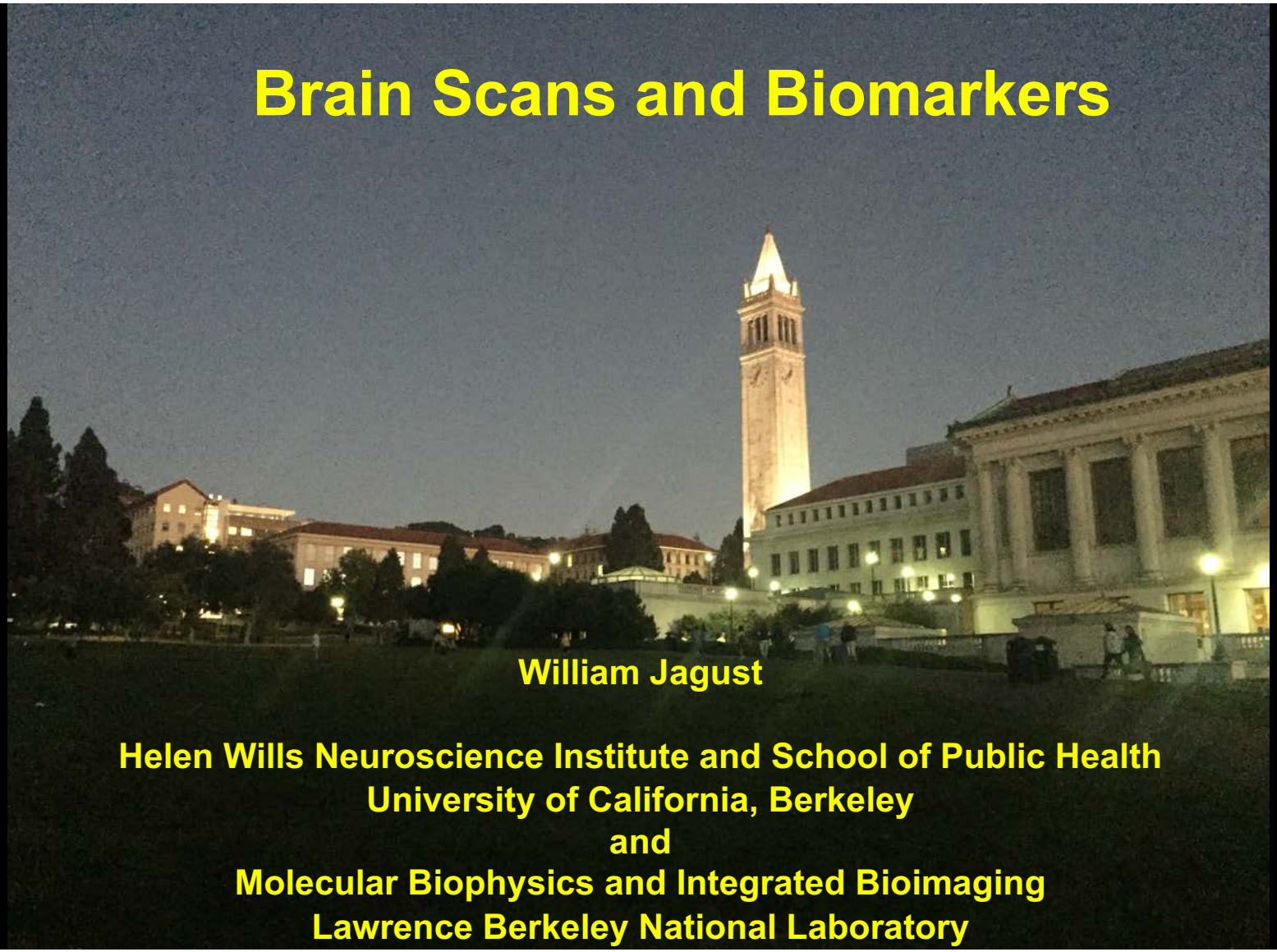
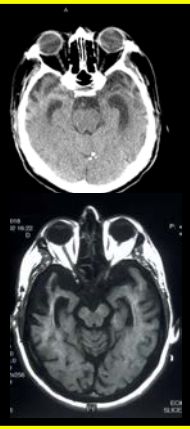
Brain Scans and Biomarkers



William Jagust

Helen Wills Neuroscience Institute and School of Public Health
University of California, Berkeley
and
Molecular Biophysics and Integrated Bioimaging
Lawrence Berkeley National Laboratory

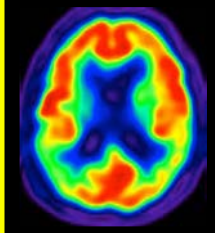


1970's onward

Structural Imaging
(CT⇒MRI)

Atrophy

1980's onward



Functional Imaging

Metabolism
(FDG-PET)

Hypometabolism

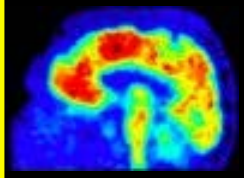
1990's onward

Functional Imaging

fMRI, resting BOLD

Activation
and network changes

2000's onward



Molecular Imaging

(Amyloid/tau PET)

Protein aggregates

Structural, functional, and molecular imaging are all crucial components of research evaluations of dementia patients today

Clinical diagnosis of Alzheimer's disease:
Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD; Donald Price, MD; and Emanuel M. Stadlan, MD

1984: Publication of widely accepted clinical diagnostic criteria for Alzheimer's disease

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

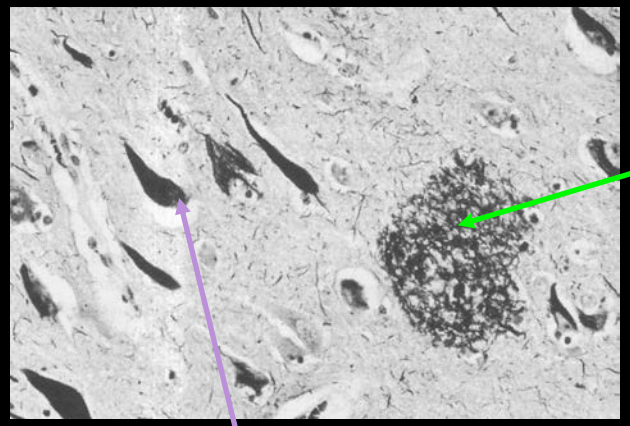
NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

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], Reisa Sperling[s]
Contributors[†]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

2018: Publication of a novel research framework – Alzheimer's disease as a biological disorder

34 years to move from a clinical diagnosis to a biological model of AD

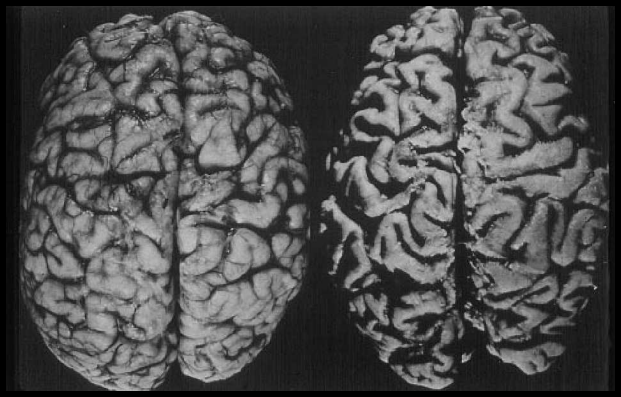
Alzheimer's Disease: Neuropathology



β-amyloid (Aβ)
Plaque pathology

Tau
Neurofibrillary Tangles

Brain atrophy is a sign of neurodegeneration



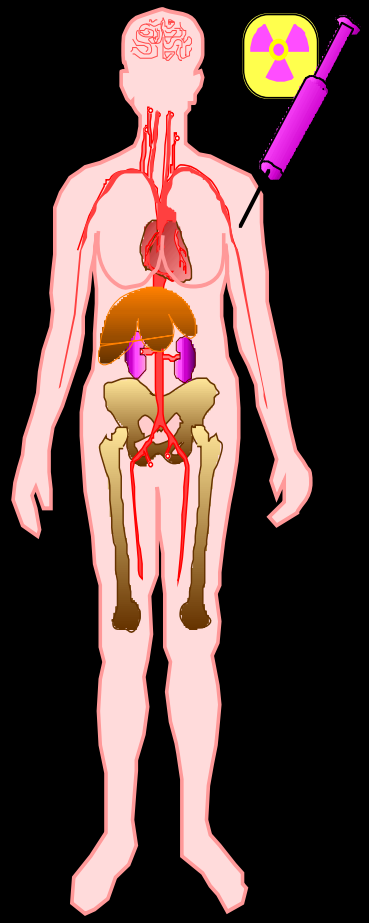
Positron Emission Tomography

Central Radiopharmacy for F18

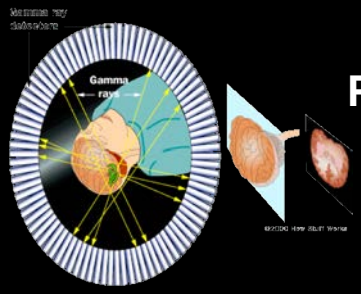
Cyclotron for production of short-lived radionuclides (C11, F18)

Fast Radiochemical synthesis of PET tracers

Injection into participant



PET Scan



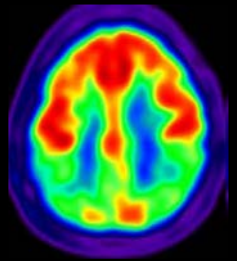


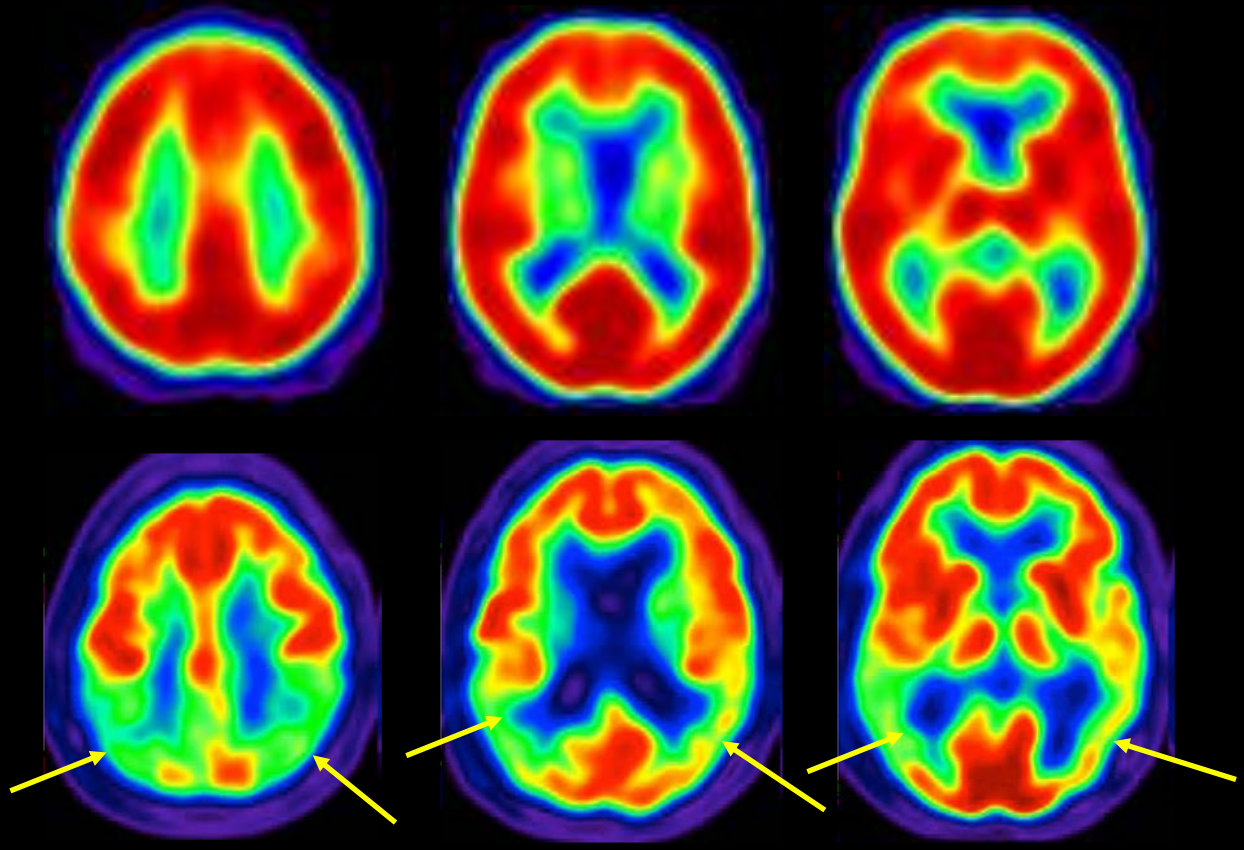
Image reconstruction and data analysis

Fluorodeoxyglucose (FDG) – PET

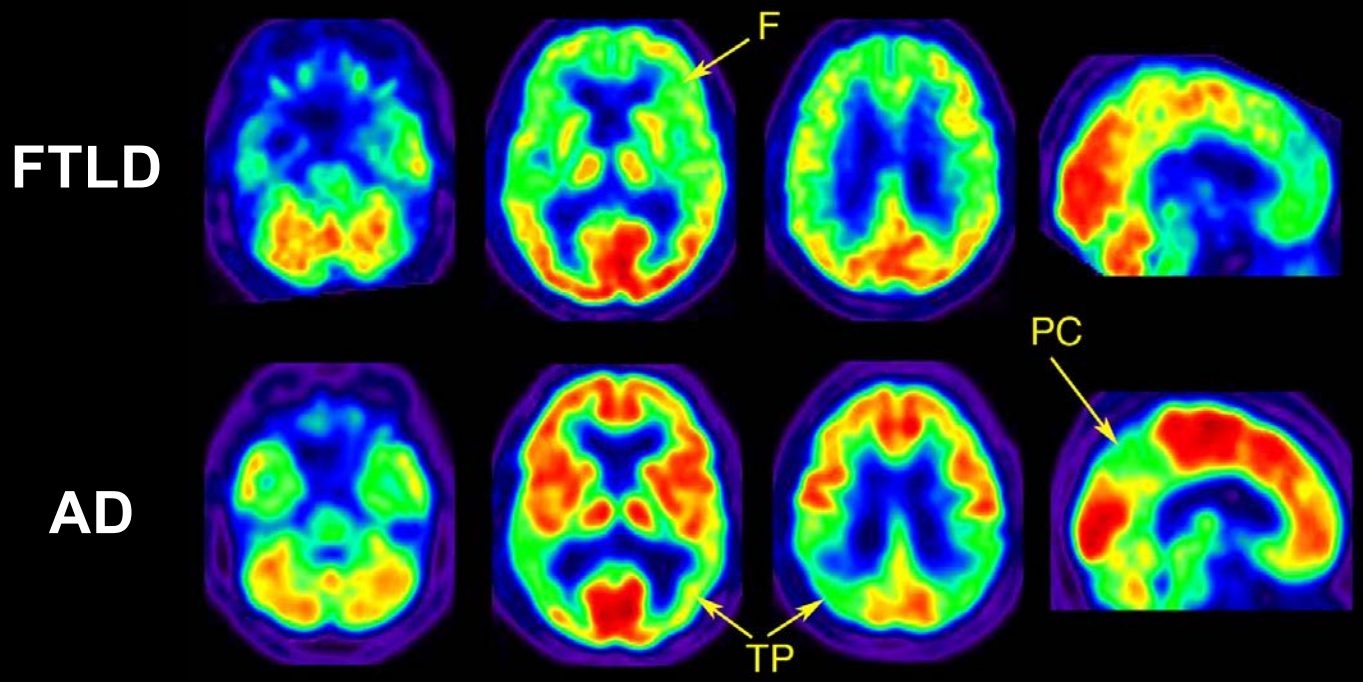
Reduced glucose metabolism in Alzheimer's Disease likely reflects synaptic dysfunction

Normal

Alzheimer's Disease

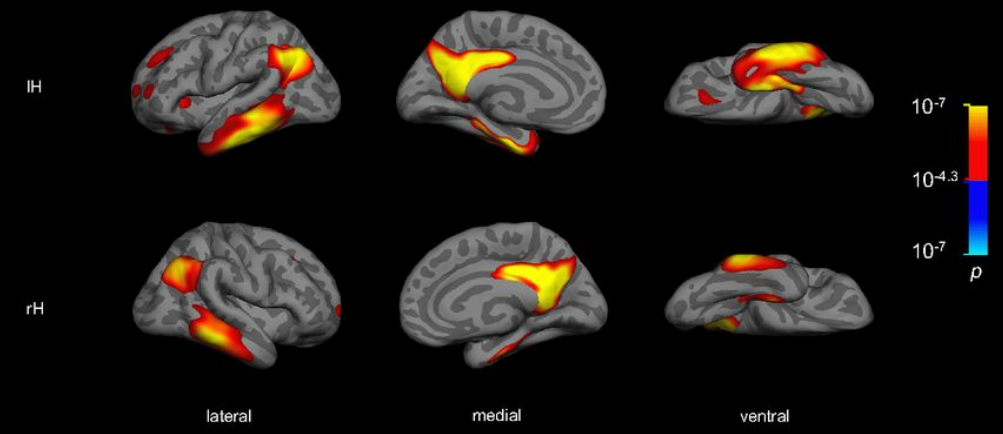


FDG-PET in Alzheimer's and FTLD



F = frontal cortex, TP = Temporoparietal cortex, PC = posterior cingulate/precuneus

Glucose Metabolism Declines in AD



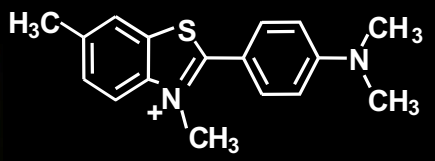
Characteristic brain regions affected in Alzheimer's disease:

Medial parietal lobe, lateral temporal/parietal cortex, medial temporal lobe

Similar regional vulnerability in structure and function

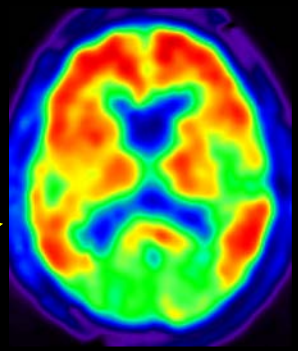
Wirth et al *J Neuroscience* 2013

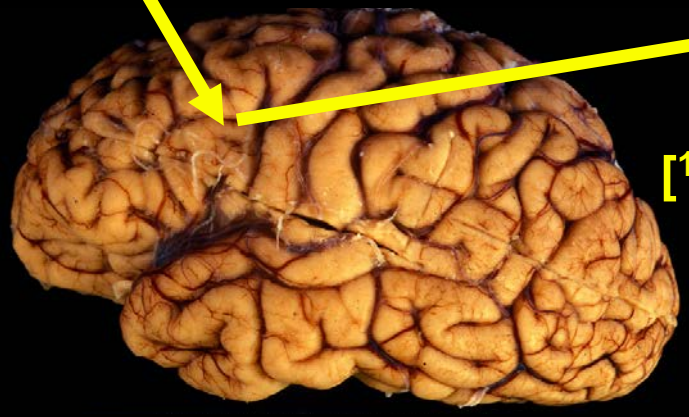
In vivo Amyloid Imaging with Pittsburgh Compound B (PIB)



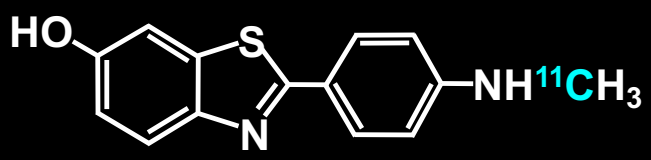
Histology - Thioflavin T

Fibrillar Aβ

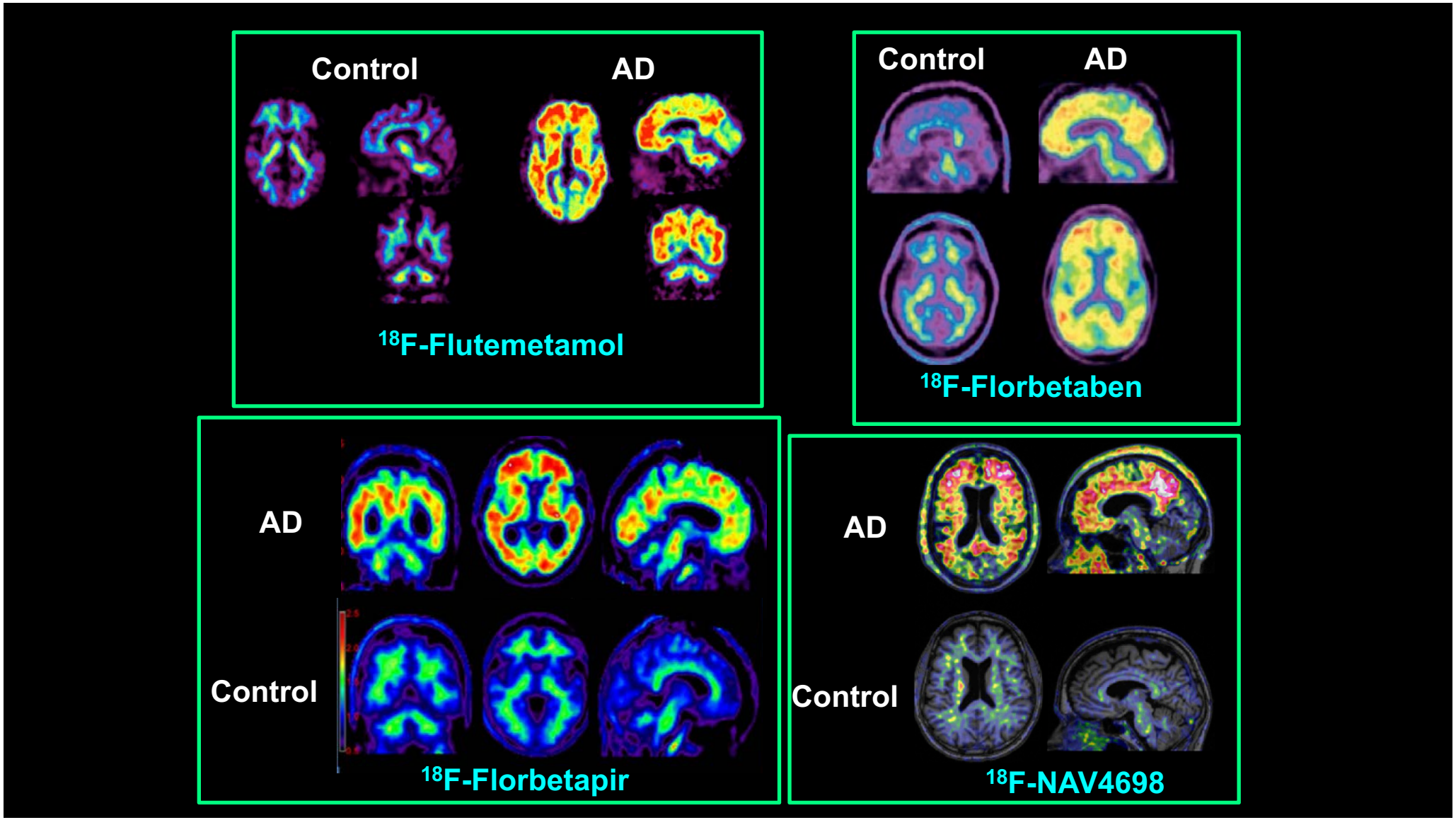




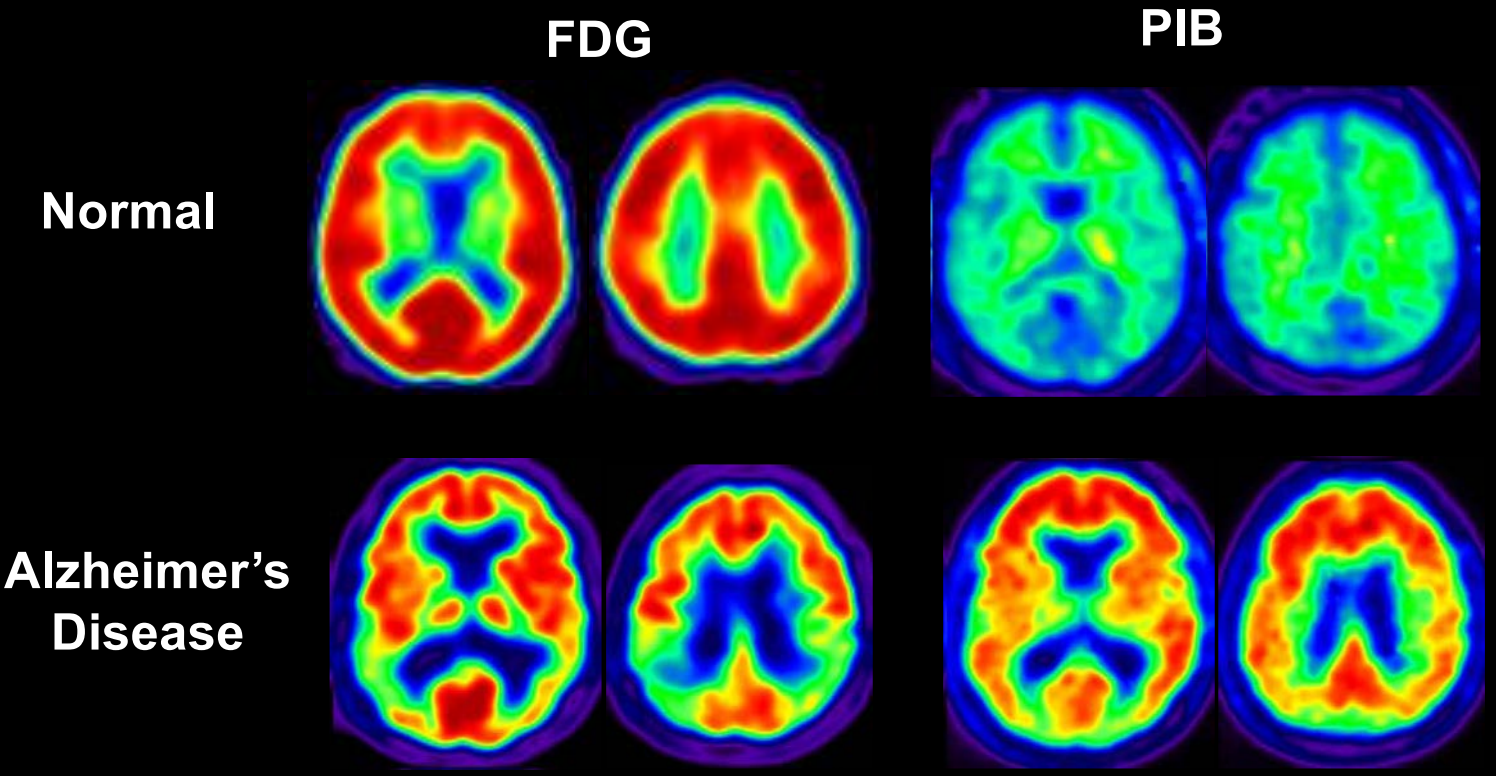
PET Imaging -
[^{11}C]6-OH-BTA-1 (PIB)



Chet Mathis and Bill Klunk, University of Pittsburgh

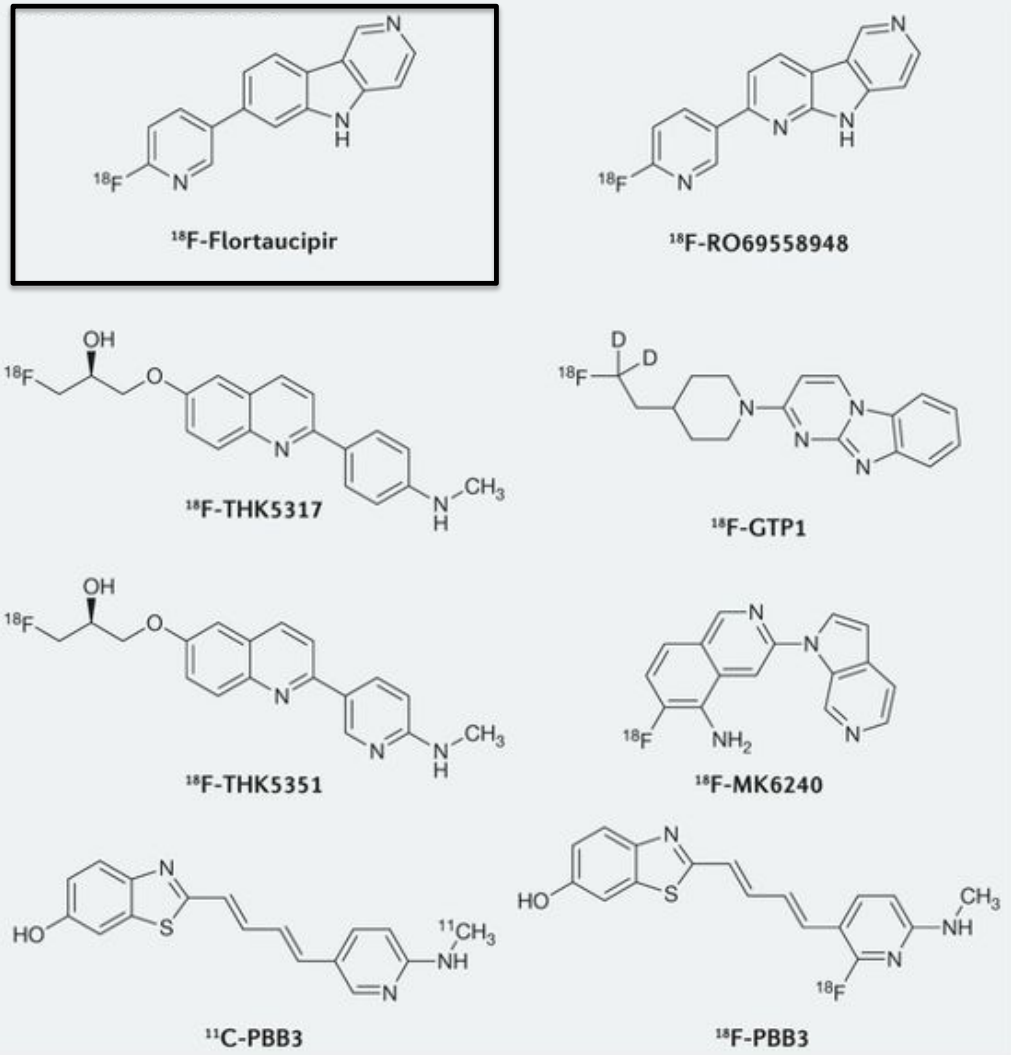

Control
AD
^{18}F-Flutemetamol
Control
AD
^{18}F-Florbetaben
AD
Control
^{18}F-Florbetapir
AD
Control
^{18}F-NAV4698

FDG (glucose metabolism) vs PIB (β-amyloid)
Neurodegeneration vs Molecular Pathology



Molecular Biomarkers vs Neurodegeneration Biomarkers

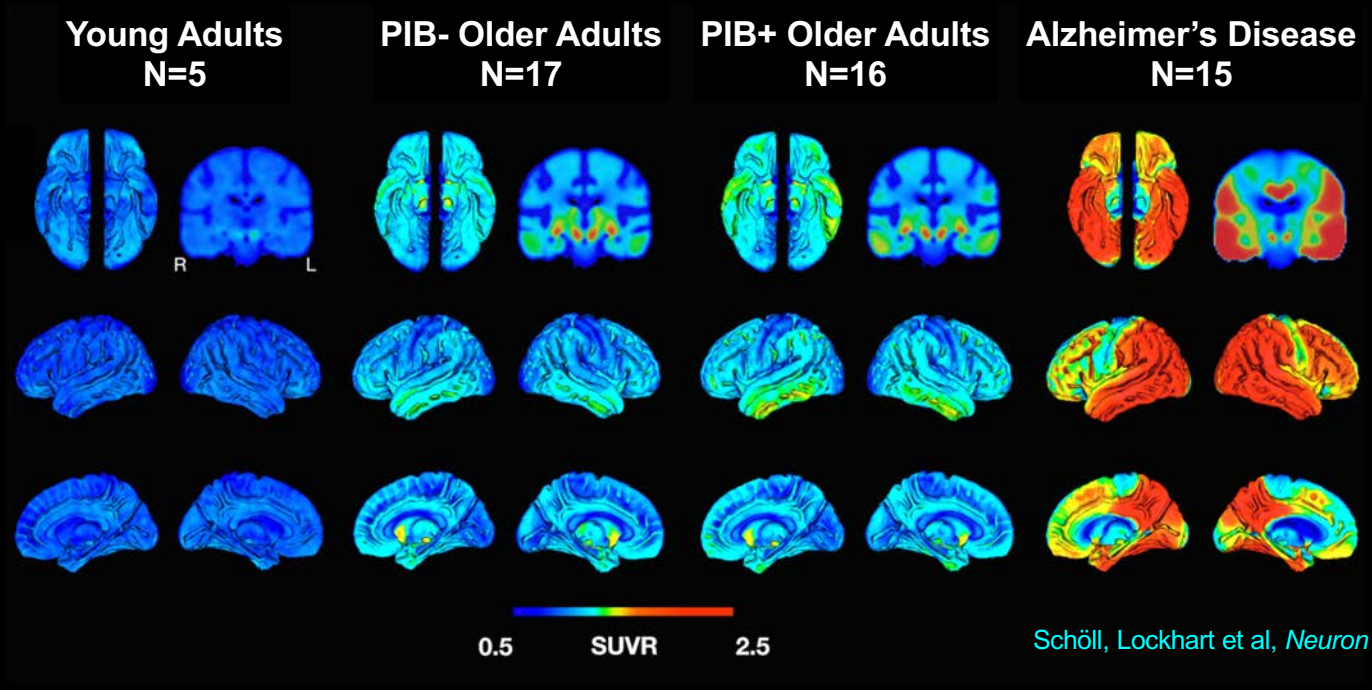
Neurodegeneration	Molecular
Indicative of brain damage	Indicative of pathology
Non-specific (as to cause)	Specific
May be complex to interpret	Relatively straightforward
Correlation with symptoms	May or may not correlate with symptoms
Questionable utility for therapeutic testing	Should be useful for therapeutic testing



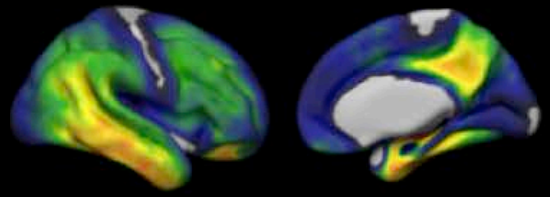
Multiple tau radiopharmaceuticals are now available for PET imaging

Villemagne et al, Nat Rev Neurol 2018

Tau Imaging with Flortaucipir

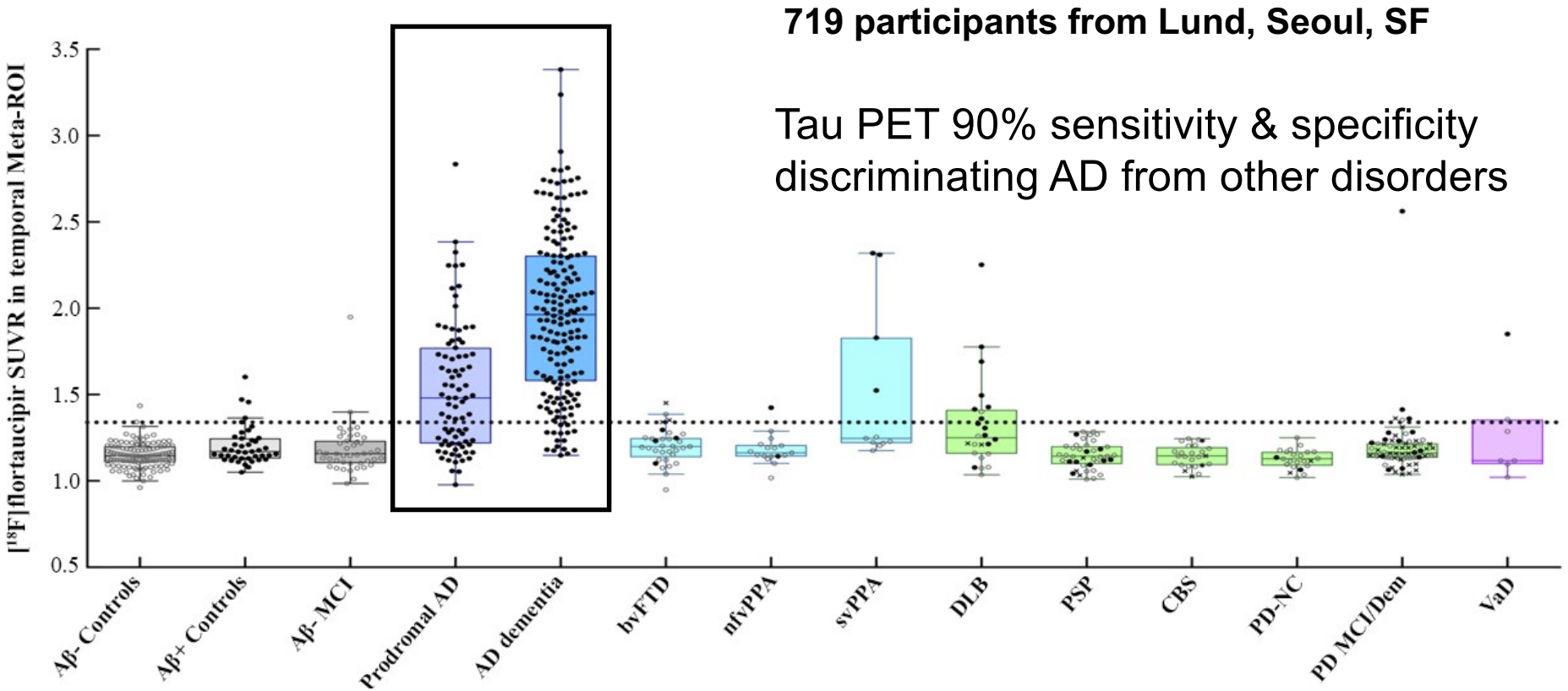


Schöll, Lockhart et al, *Neuron* 2016



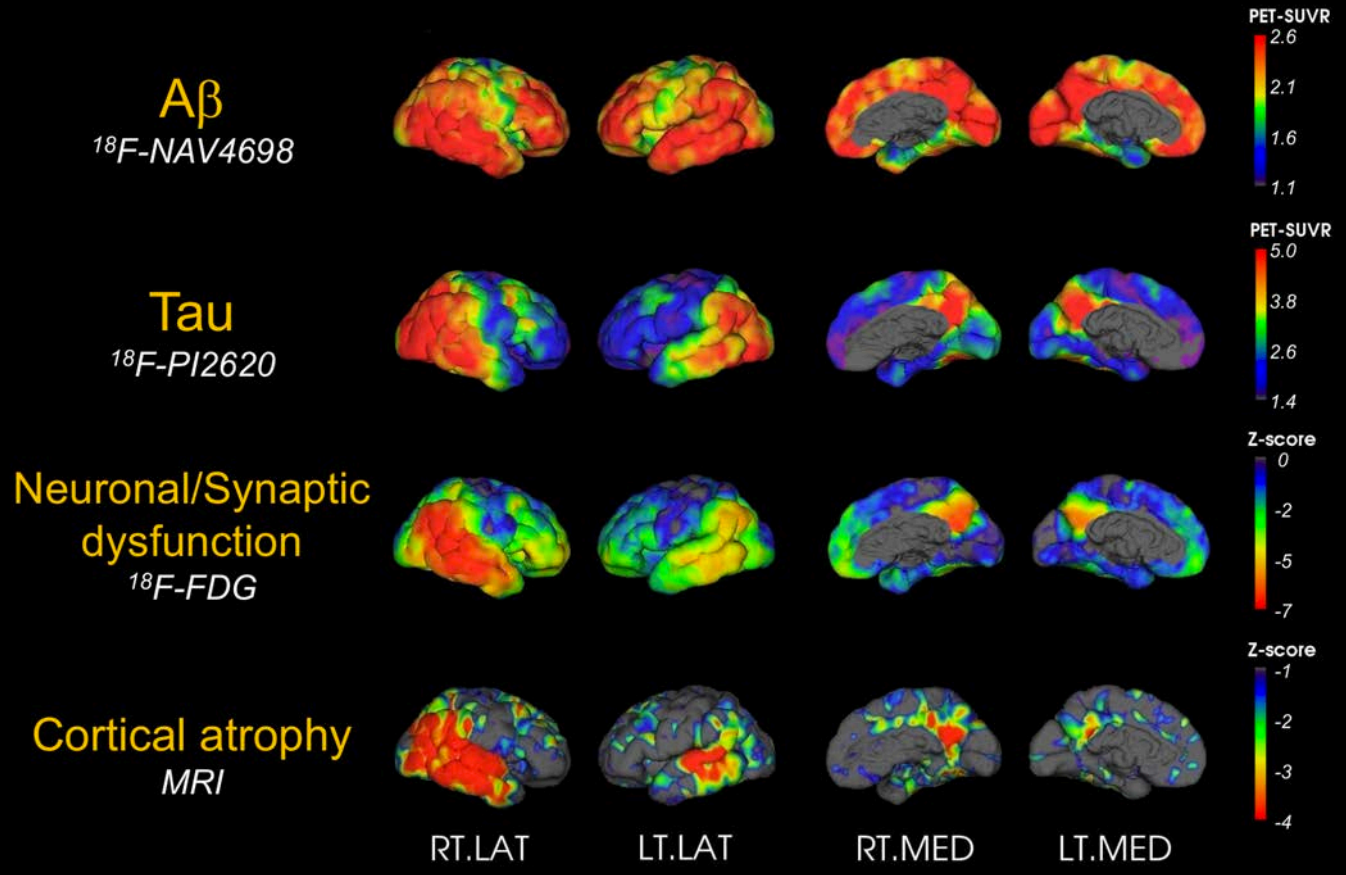
Topography of tau deposition in the AD continuum reflects Braak Pathological staging

Utility of Tau PET in Differential Diagnosis



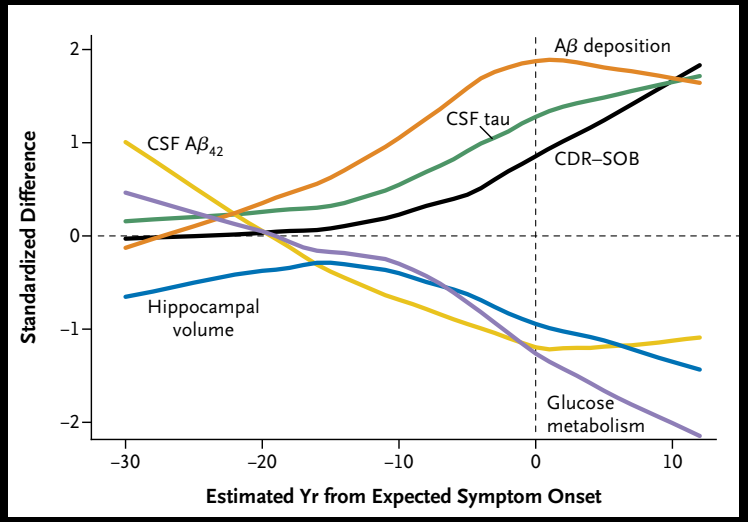
Ossenkoppele et al *JAMA* 2018

Biomarker Patterns: Similarities and Differences



Biomarker Measurement in Autosomal Dominant AD Supports the Amyloid Hypothesis

The Dominantly Inherited Alzheimer's Disease (DIAN) Study



Bateman et al, NEJM 2012

Cross-sectional data on biomarkers from autosomal dominant, symptomatic and asymptomatic family members

Because age-at-onset is preserved across generations, biomarker values in relation to age-at-onset can be calculated

Results show that the earliest biomarker change is elevation of Aβ in brain, about 20 years before expected onset

***The Amyloid Hypothesis*: Amyloid deposition is the initiating event in AD, leading to NFTs-tau, brain degeneration, and dementia**

NIA-AA Research Framework

Alzheimer's disease defined by 3 pathological processes: β-amyloid deposition (A), tau deposition (T), and neurodegeneration (N)

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	

Alzheimer's Continuum:
Amyloid Positivity (A+)

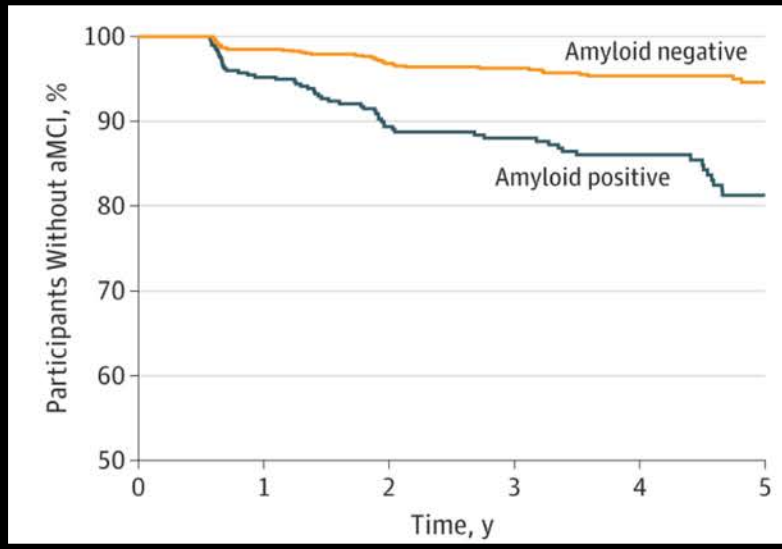
Alzheimer's Disease:
Amyloid and tau positivity (A+T+)

This is currently a framework meant only for research, not clinical care

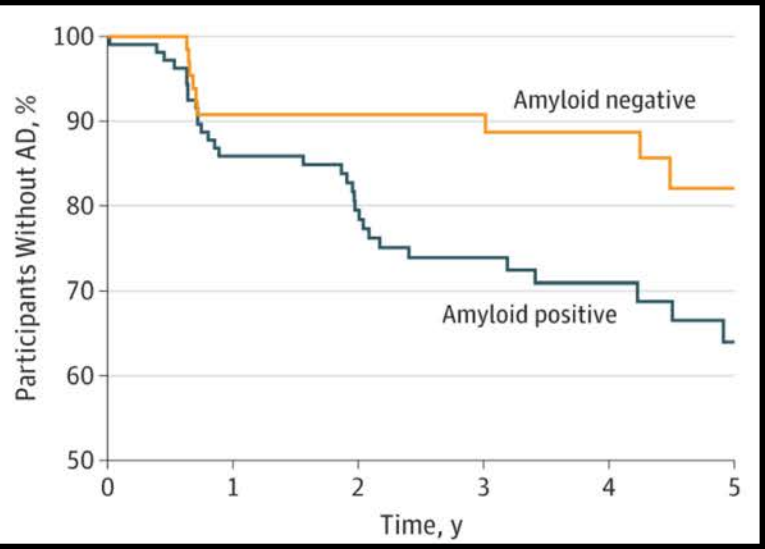
Jack et al *Alz & Dementia* 2018

Amyloid Status Predicts Clinical Conversion

Normal → MCI conversion

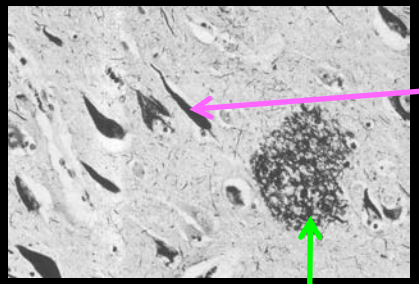


MCI → AD conversion



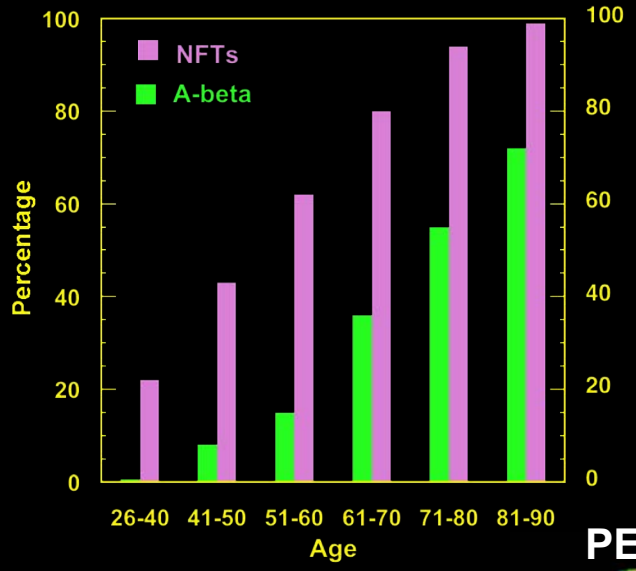
Roberts et al. *JAMA Neurol* 2018

AD Neuropathology in Normal Cognitive Aging

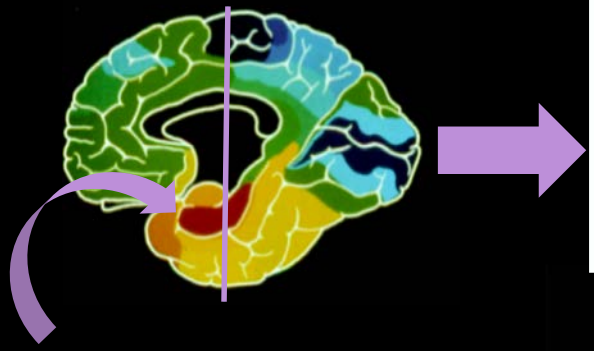


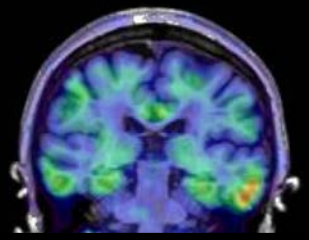
Neurofibrillary Tangles (NFTs) Tau Protein

β-amyloid plaques (Aβ)



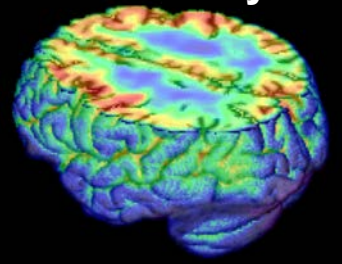
MRI: Neurodegeneration





Tau-NFTs in aging accumulate in the medial temporal lobe (atrophy on MRI, tau with PET)

PET: Tau

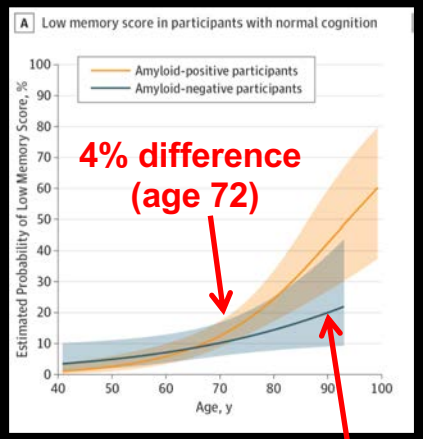


PET: Amyloid

Aβ plaques appear diffusely throughout the brain (visible with PET)

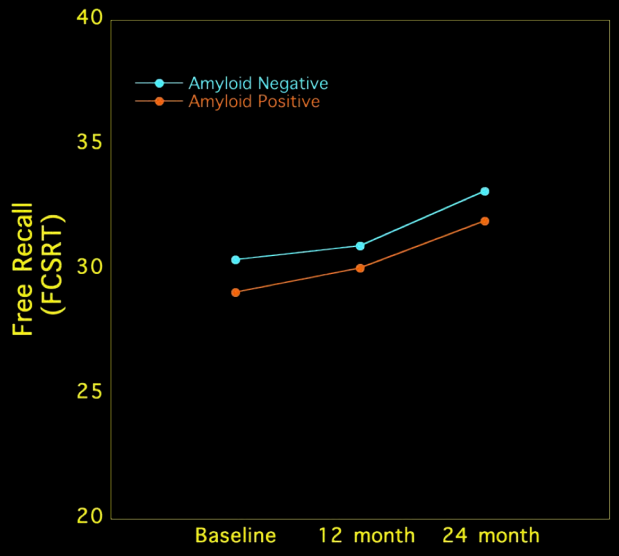
How Well Does Aβ Predict Cognition in Normal Aging?

Cross-sectional meta-analysis



N = 2908

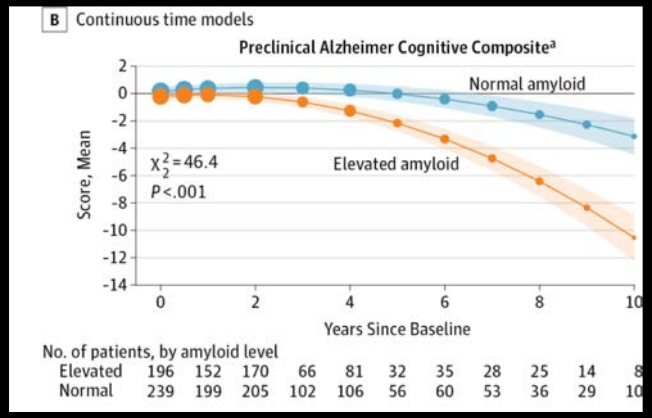
Jansen et al *JAMA Psychaitry,* 2018

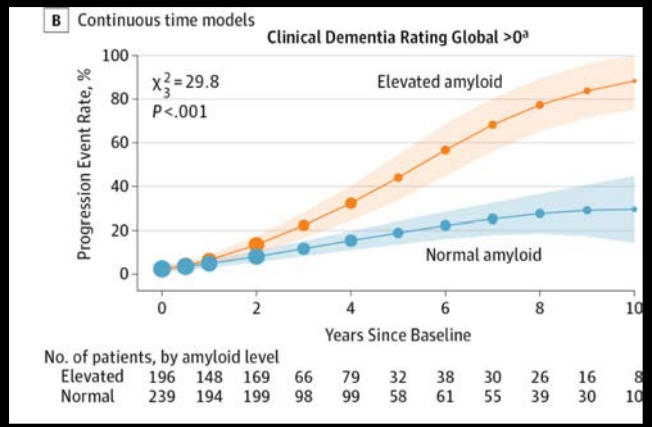


No Aβ effect for: FCSRT, MMSE, Trails, Frontal Assessment Battery

N = 313

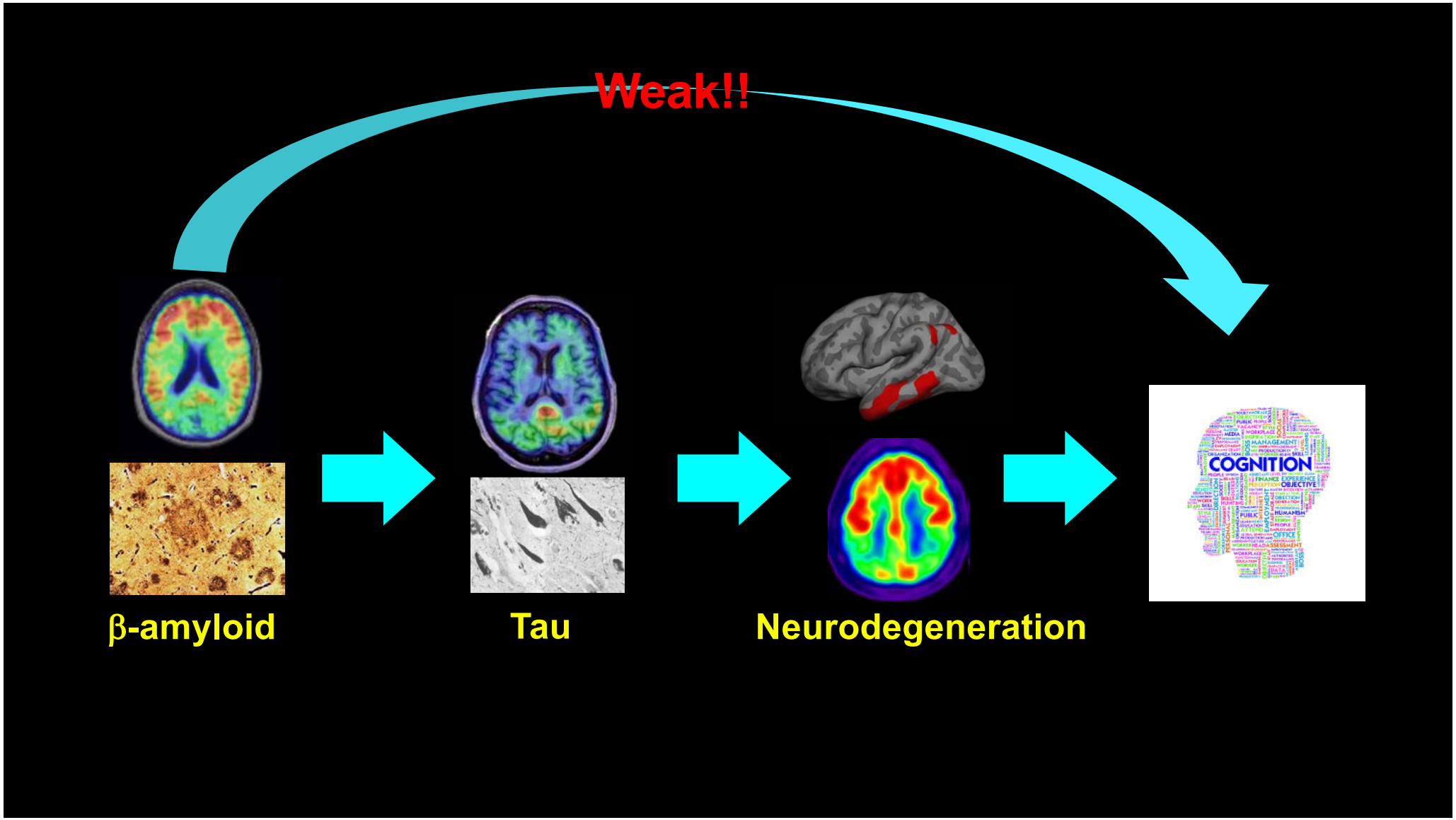
Dubois et al *Lancet Neurology* 2018

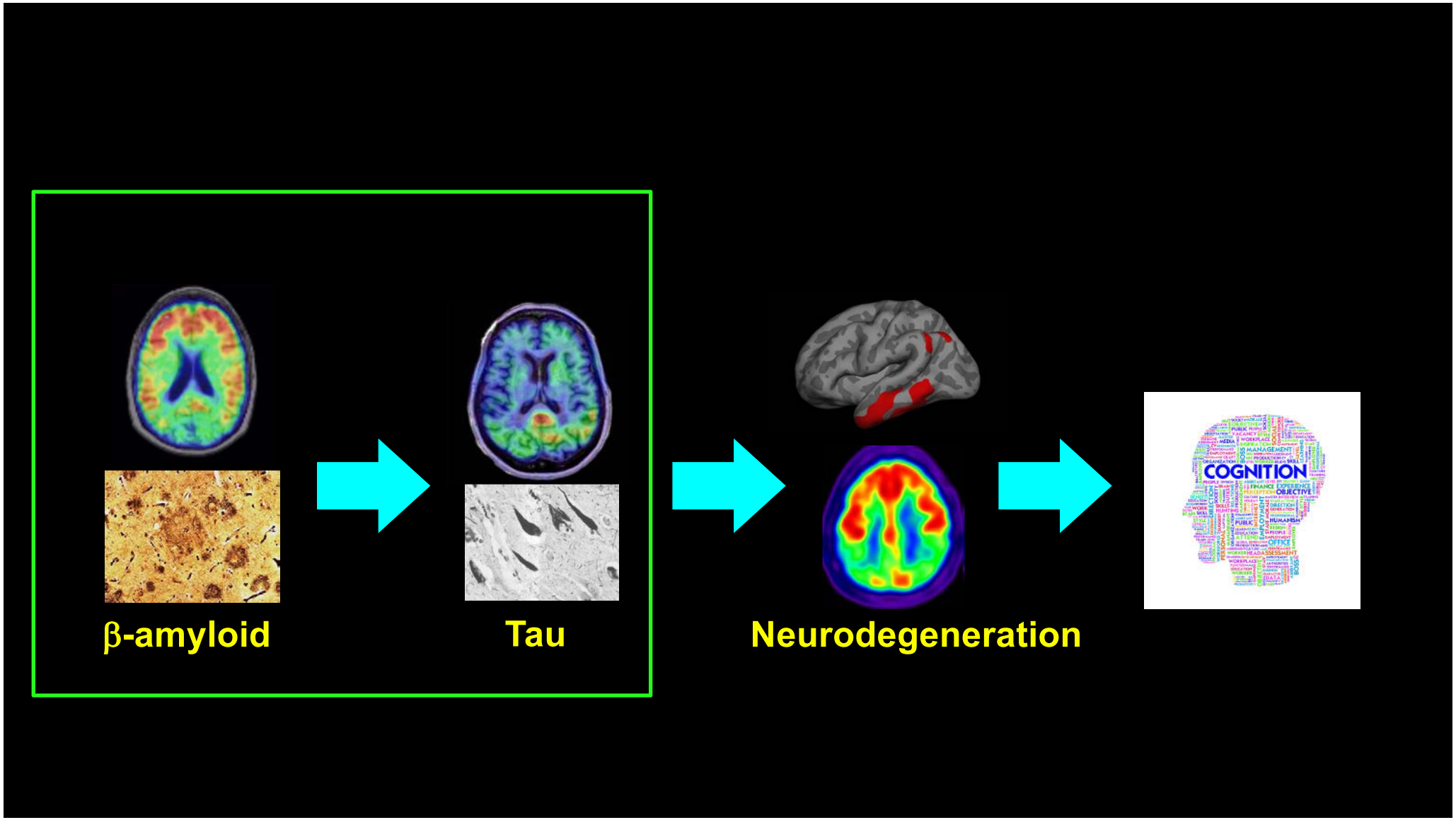




N = 445

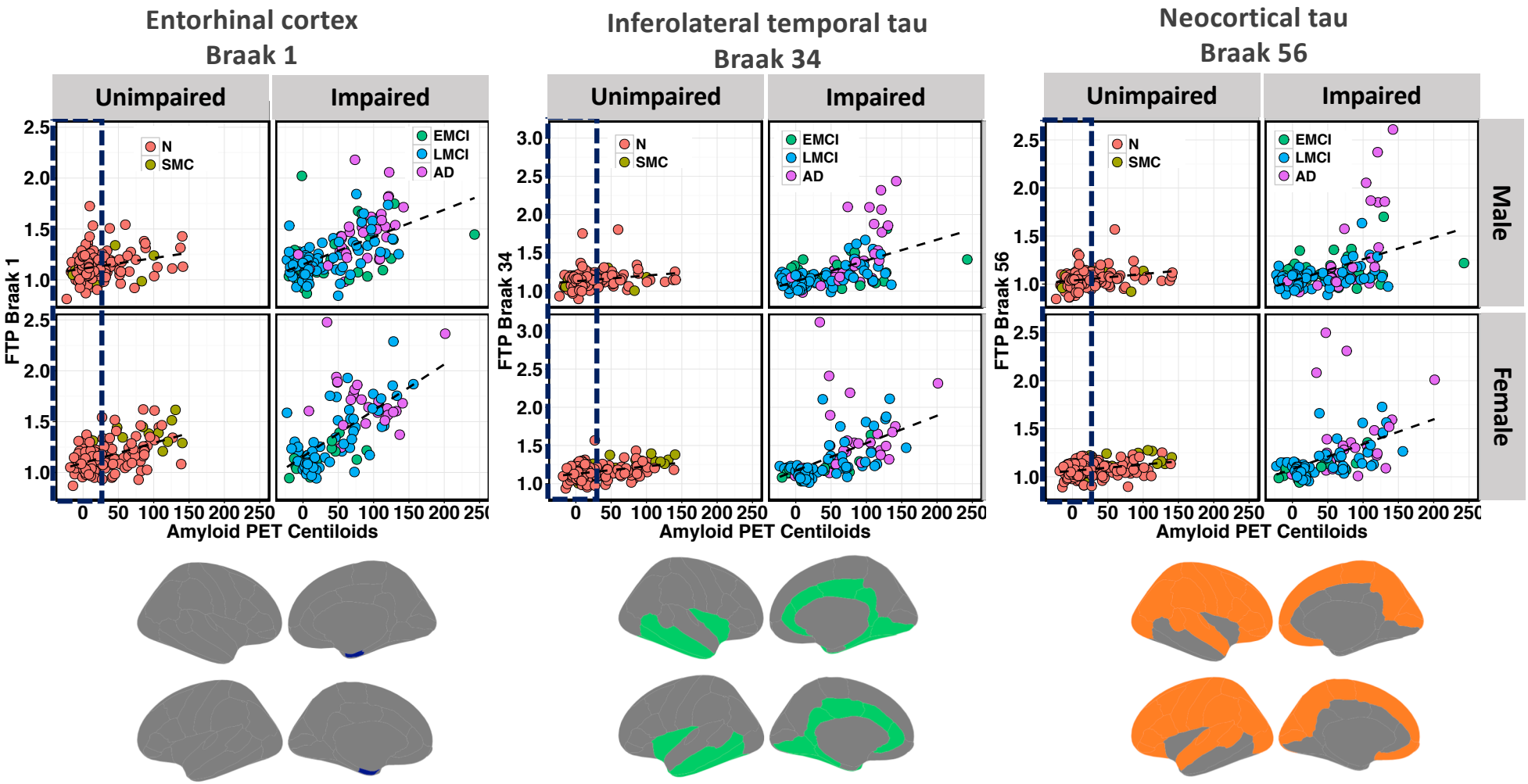
Donohue et al *JAMA* 2017


Weak!!
β-amyloid
Tau
Neurodegeneration
COGNITION

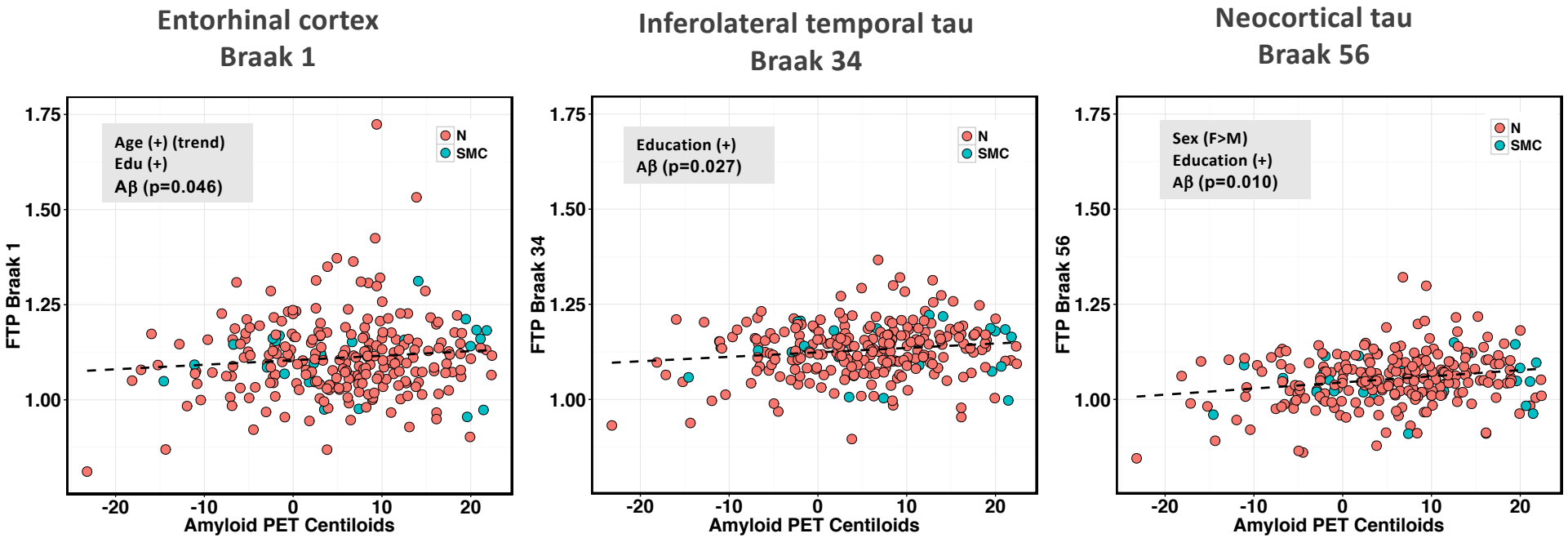

β-amyloid
Tau
Neurodegeneration
COGNITION

Amyloid (FBP/FBB) is Associated with Tau (FTP)

N = 646

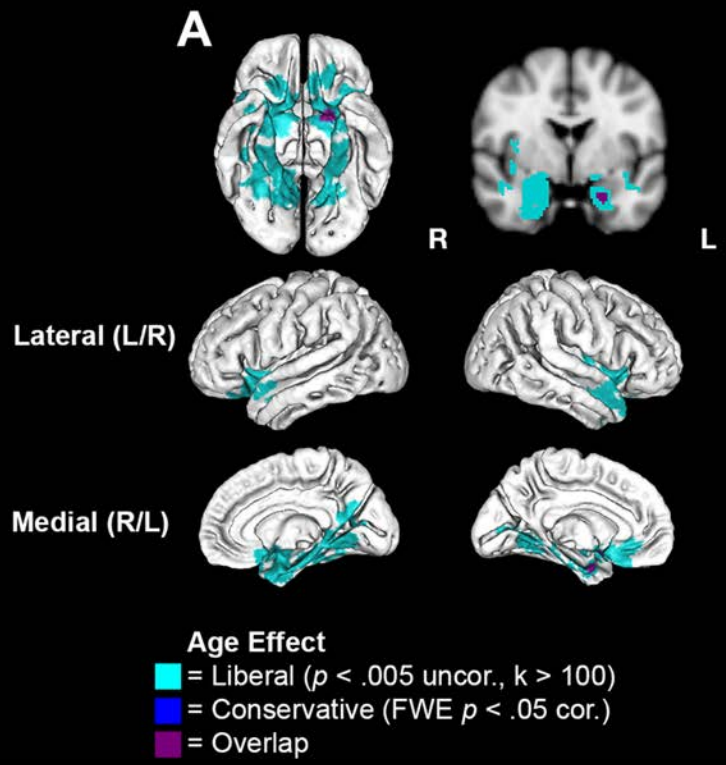


Aβ within the Negative Range Affects FTP Control Subjects

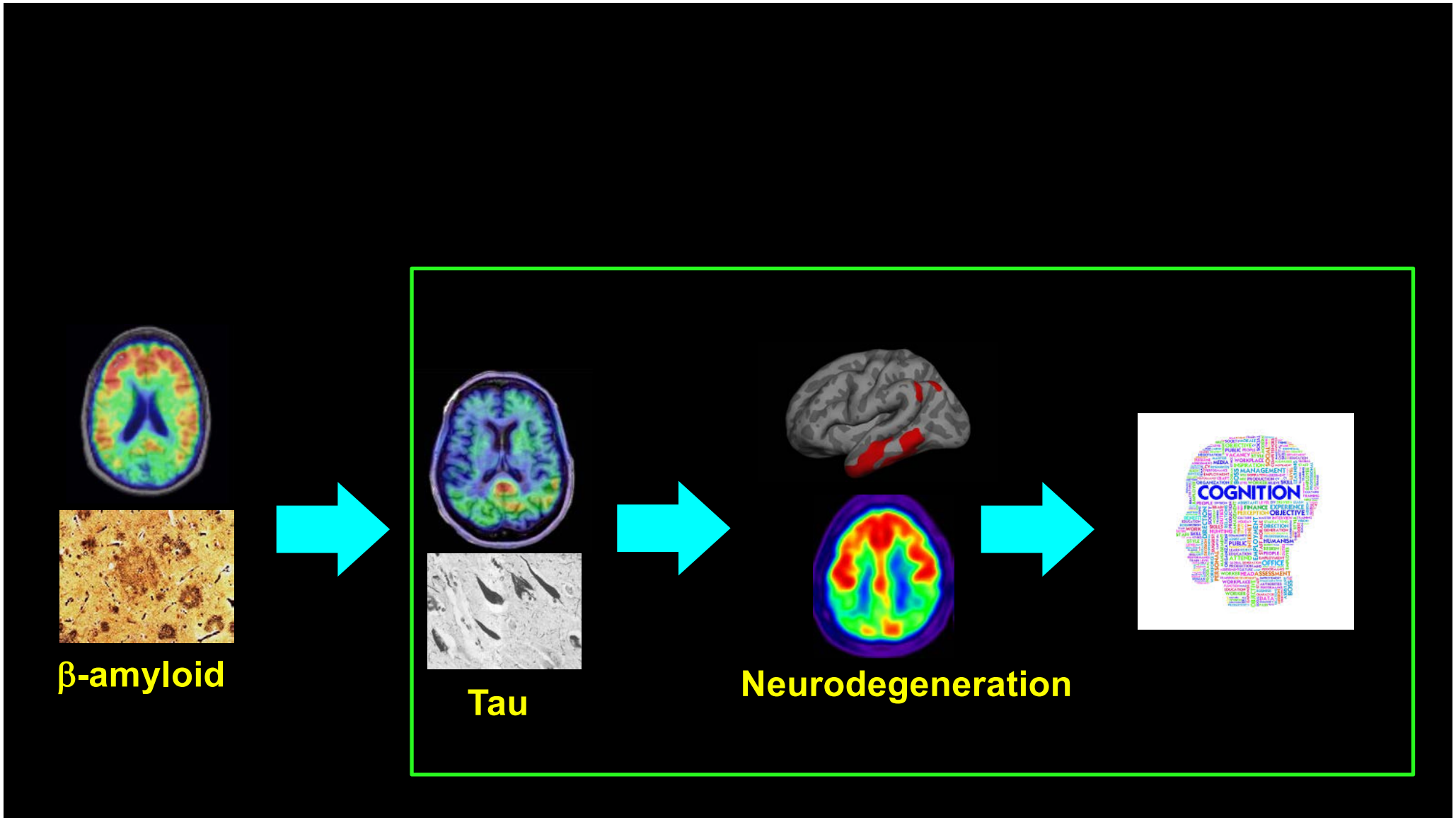


Predictors: Age, Sex, Edu, APOE4, FTP, Aβ (continuous)

Age, Aβ, and tau associations among healthy elderly

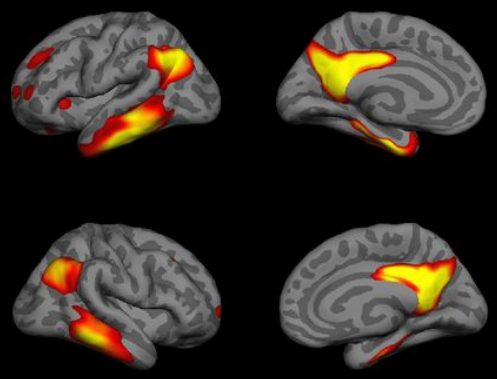


Schöll, Lockhart et al, *Neuron* 2016

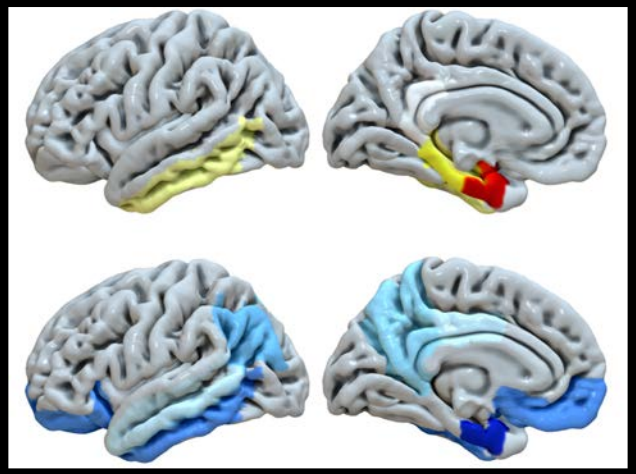

β-amyloid
Tau
Neurodegeneration
COGNITION

Medial Temporal Lobe tau is Associated with Reduced Glucose Metabolism in Amyloid+ Aging

Glucose Metabolism in AD



21 Cognitively normal amyloid positive older people (78 years)



Increases of tau in MTL regions

are associated with

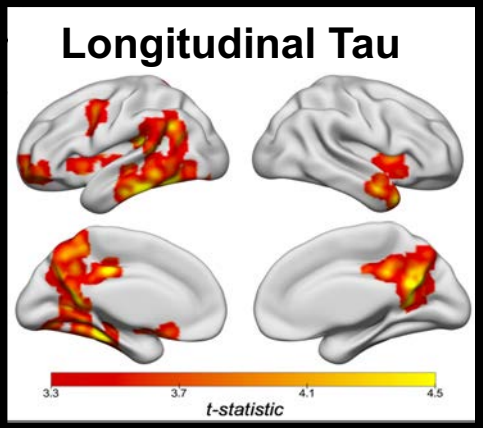
decreases of FDG in temporal, parietal, and orbitofrontal regions

The hypometabolic brain regions reflect downstream neural targets in medial temporal lobe pathways and are also the brain regions affected by Alzheimer's disease

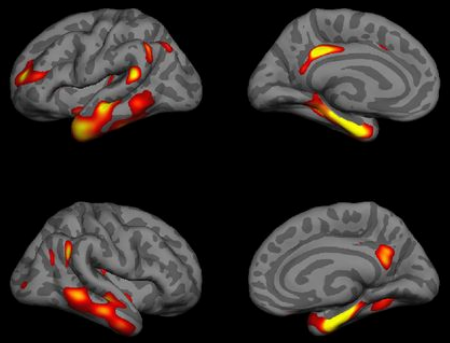
Adams et al, *Cerebral Cortex*, 2018

Tau Accumulates Over Time and Parallels Brain Atrophy in Cognitively Normal Older People

42 Cognitively normal adults followed for ~2 years



Cortical Thinning in AD

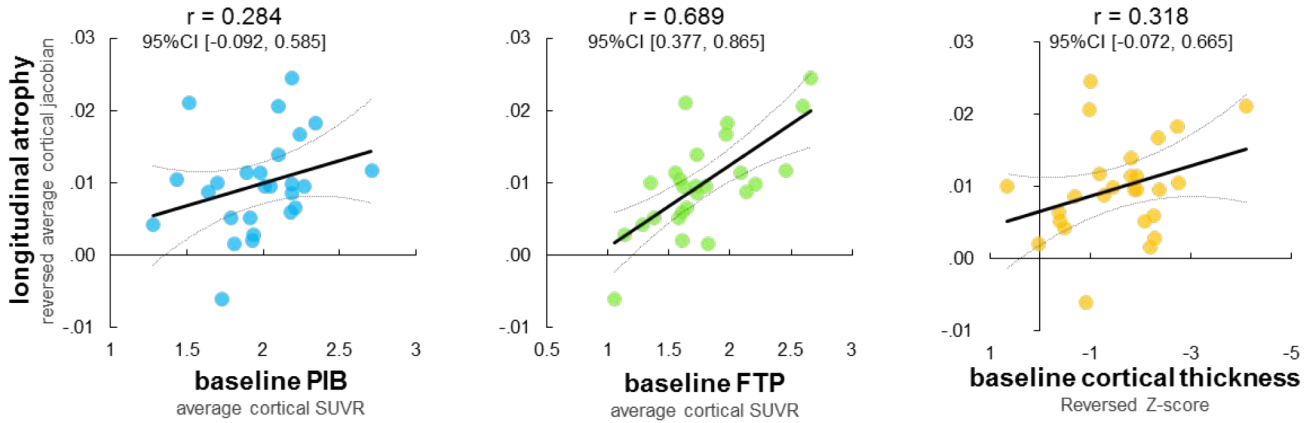


Harrison et al, *Ann Neurol* 2019

Baseline Tau Predicts Longitudinal Atrophy in AD

(N = 26 PIB+ AD)

A. Global associations



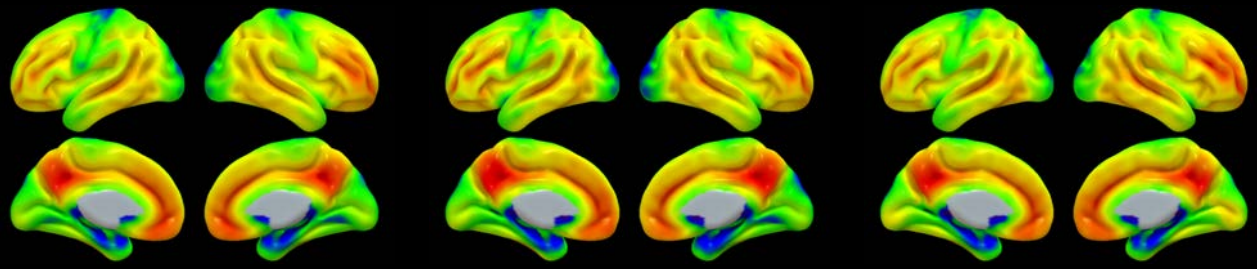
Renaud LaJoie

Tau Correlates with AD Phenotypes

(Aβ does not)

Marginal mean maps | centered for age (~65yo), CDR-SB (~4), and global cortical SUVR

PIB SUVR
2.8
0.8

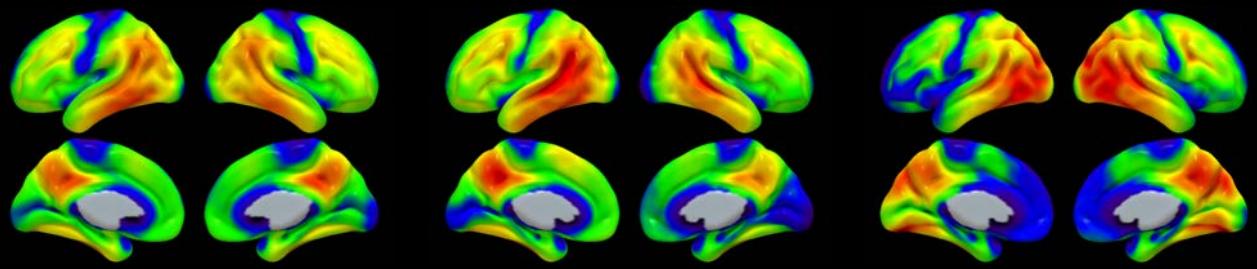


AD (N=60)

lvPPA (N=19)

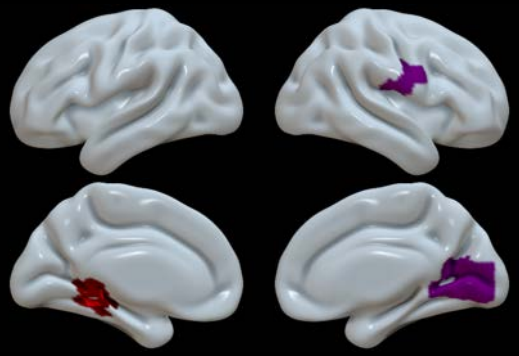
PCA (N=18)

FTP SUVR
2.8
0.8

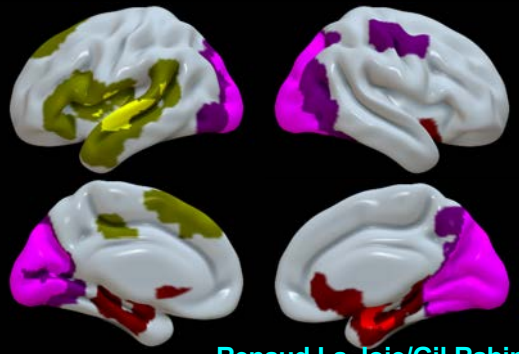


Group comparison

cov: age, CDR-SB + cortical SUVR

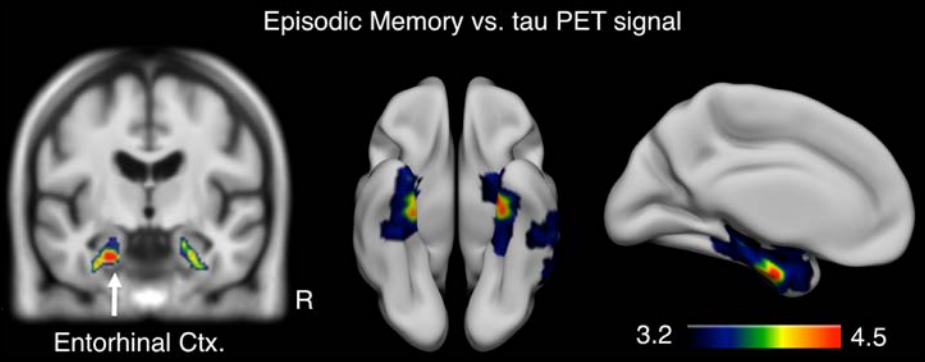


	$p_{unc}<0.001$	$p_{FWE}<0.05$
PCA > others		
lvPPA > others		
AD > others		

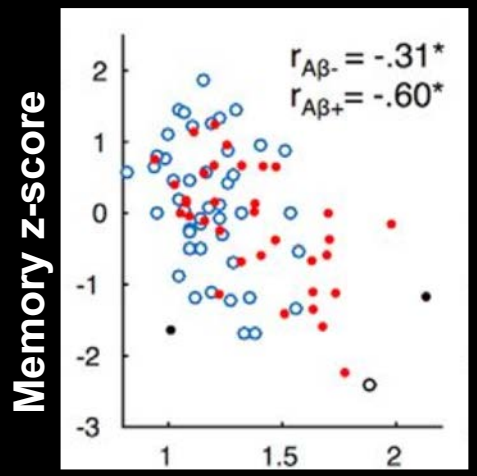


Renaud La Joie/Gil Rabinovici

Tau and Memory in Normal Older People



Cognitively normal individuals with more tau in these brain regions (entorhinal cortex) show worse performance on memory tests

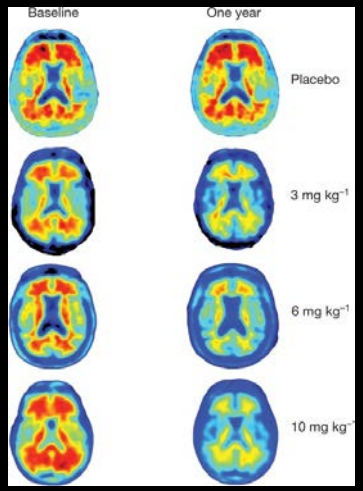


Maass et al J Neuroscience 2018

Clinical Trials:
Biomarkers for subject selection and target engagement

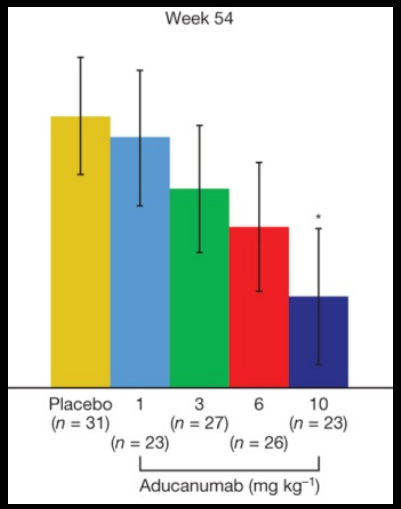
Aducanumab: Mild AD and MCI

Amyloid PET Scans: Reductions in Aβ



Antibodies directed at β-amyloid lowered PET scan measurements after 26 and 54 weeks of treatment – dose effect

Cognitive Testing: Dose-Related Improvement



Clinical benefit by 1-year: less cognitive decline with higher doses

Sevigny et al *Nature* 2016

The Future?

Therapeutic trials of amyloid lowering therapies

- Asymptomatic people with genetic risks
- Asymptomatic individuals with positive amyloid biomarkers

Other targets

- Tau lowering therapies
- Lifestyle interventions (POINTER study)

Biomarkers will play a major role in subject selection and treatment monitoring

Thanks

National Institutes of Health
Tau Consortium