alzheimer's association®

Business Consortium

AABC Webinar
Updates in Neuroimaging
12/9/19

Make sure you have a solid internet connection.
Use a headset/earbuds for the best audio experience.

Please ask questions by typing them in on the bottom of the screen at “Q&A”.
Q&A will be 5:50 p.m.

alzheimer's association®

Business Consortium

Michael Ewers, PhD
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Functional Connectomics to Predict Tau Spreading and Cognitive Resilience in Alzheimer's disease

Beau Ances, MD, PhD, MSc
bances@wustl.edu
Neuroimaging Insights from the Dominantly Inherited Alzheimer's Network (DIAN)

Liana Apostolova, MD, MSc, FAAN
lapostol@iu.edu
Improving our understanding of Alzheimer's disease heterogeneity: LEADS neuroimaging component

Functional connectomics to predict tau spreading and cognitive resilience in Alzheimer‘s disease

Michael Ewers

Institute for Stroke and Dementia Research (ISD)

Ludwig Maximilian University, LMU Munich

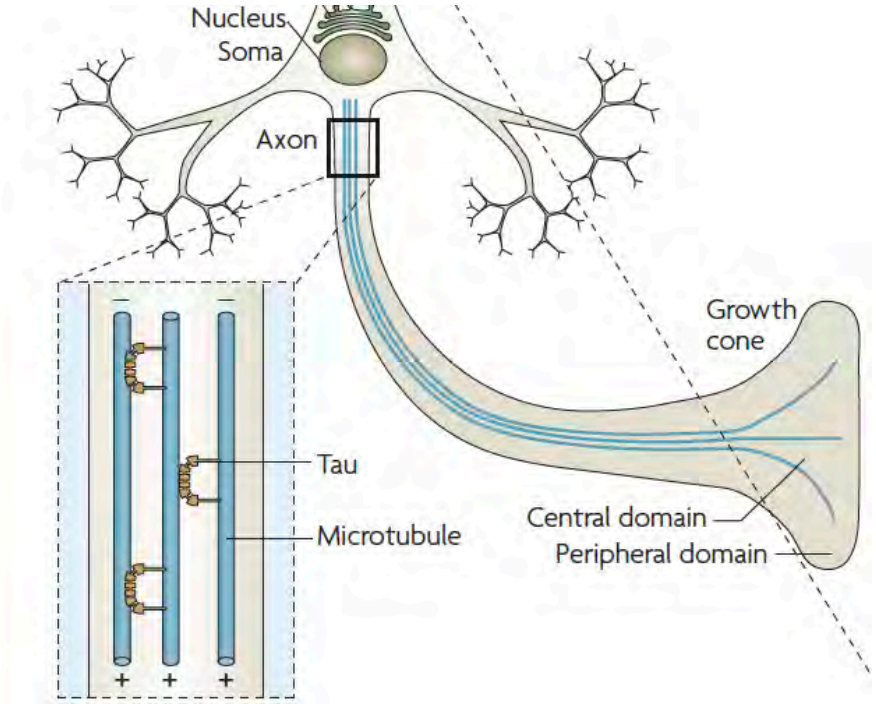
LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

Institute for Stroke and Dementia Research (ISD)

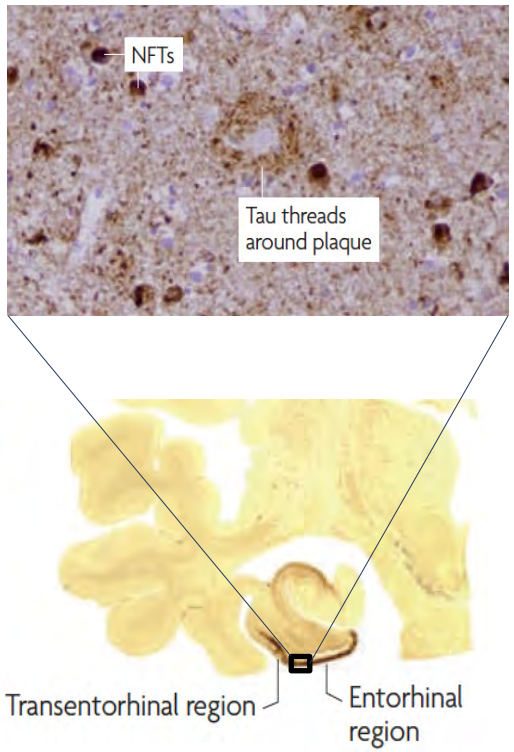
Funded by: Solorz-Żak Research Foundation

Tau pathology in Alzheimer‘s disease

Tau protein stabilizes microtubules



Fibrillar tau

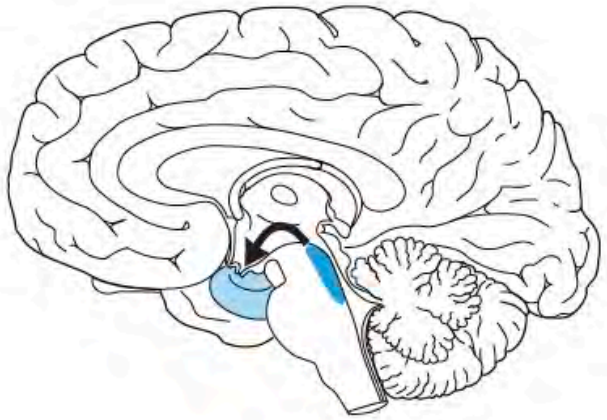


Goedert et al. Frontiers in Neurol 2018; Conde et al. Nat. Rev. Neurosci 2009

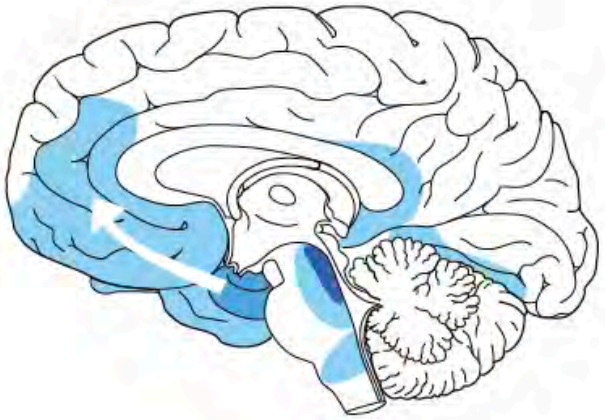
Braak Staging of progressive tau pathology

Pathologic Tau

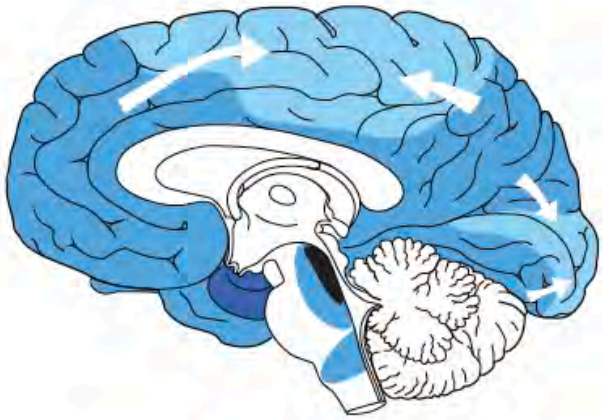
Stage I-III



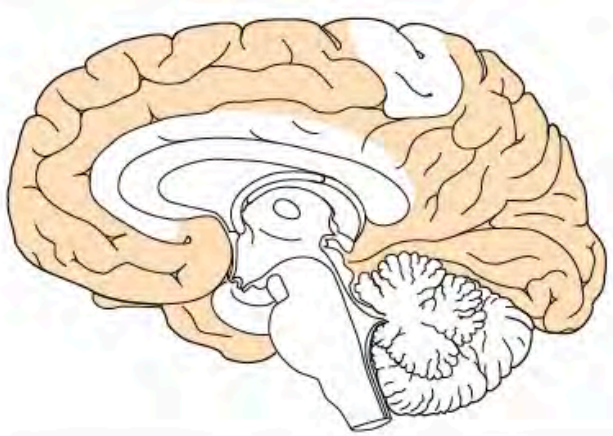
Stage III- IV

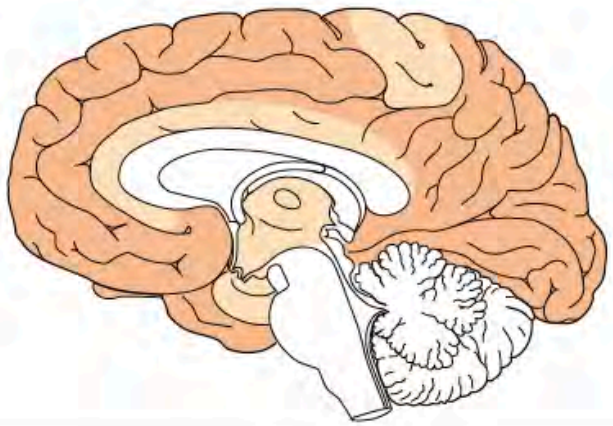


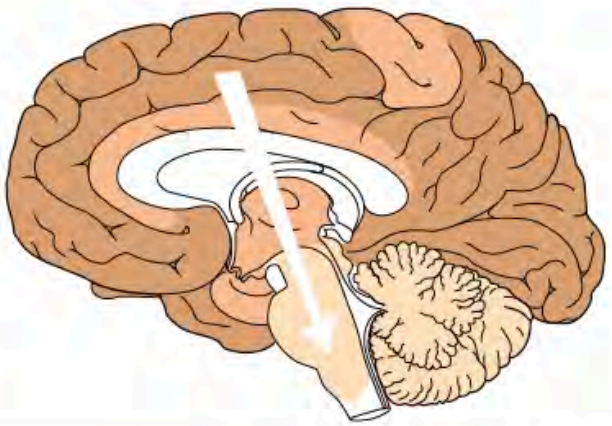
Stage V - VI



Aβ

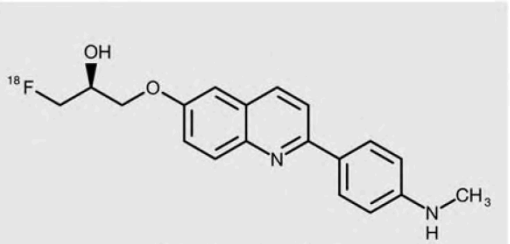






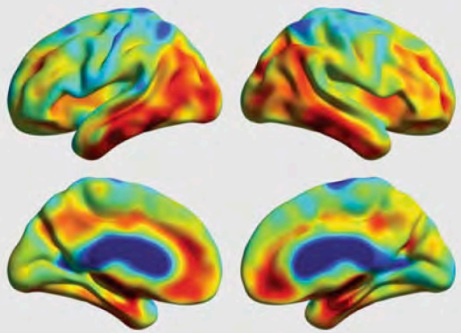
Braak et al. Acta Neuropathol 2006, J N Exp Neurol 2011, Jucker et al. Nature 2013

PET-Tracer of fibrillar Tau

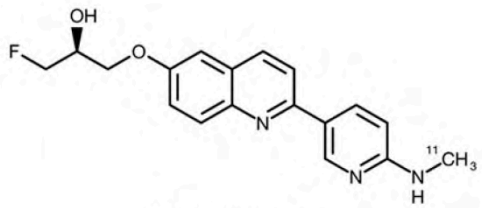


[^{18}F]THK5317

AD dementia, 75 yrs, MMSE 24

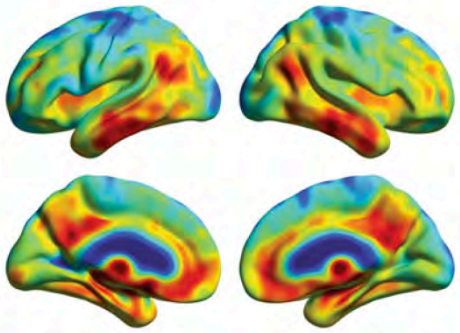


0.5 DVR 1.5

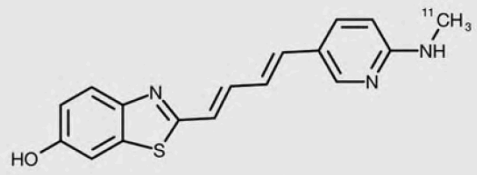


[^{11}C]THK5351

Prodromal AD, 70 yrs, MMSE 30

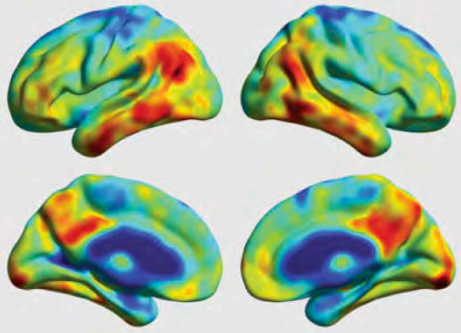


0.5 DVR 2.2

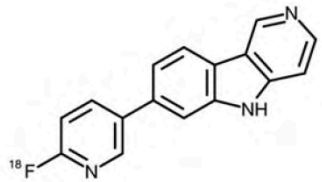


[^{11}C]PBB3

Prodromal AD, 70 yrs, MMSE 30

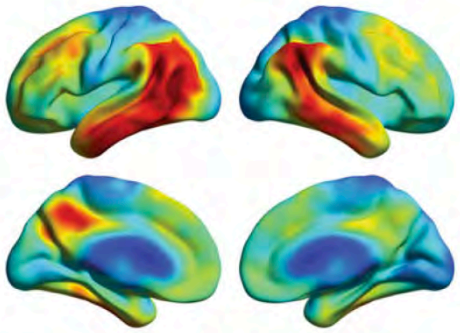


0.6 DVR 1.6



[^{18}F]AV1451
(T807, flortaucipir)

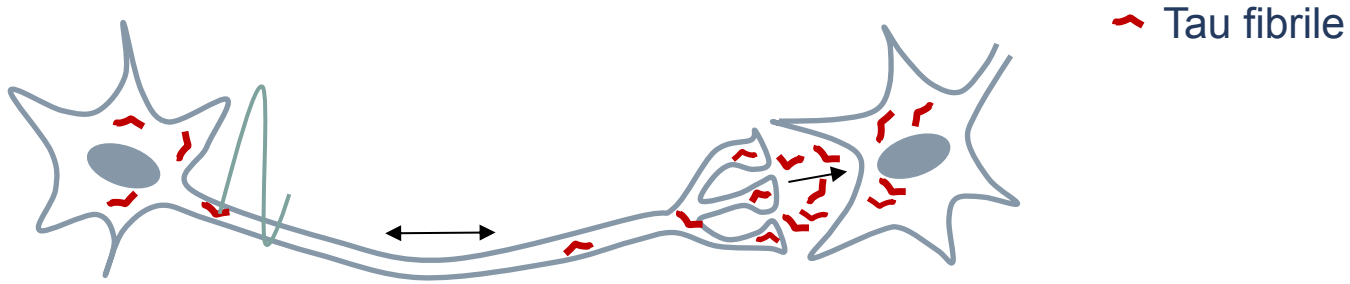
AD dementia, 74 yrs, MMSE 14



0.0 SUVR 3.5

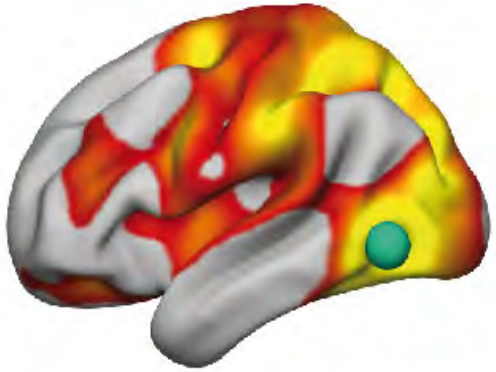
Leuzy et al. Mol. Psych. 2019

Tau spreading | functional connectivity

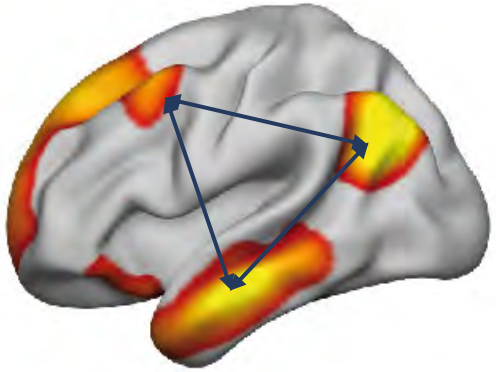


Resting state fMRI detected functional networks

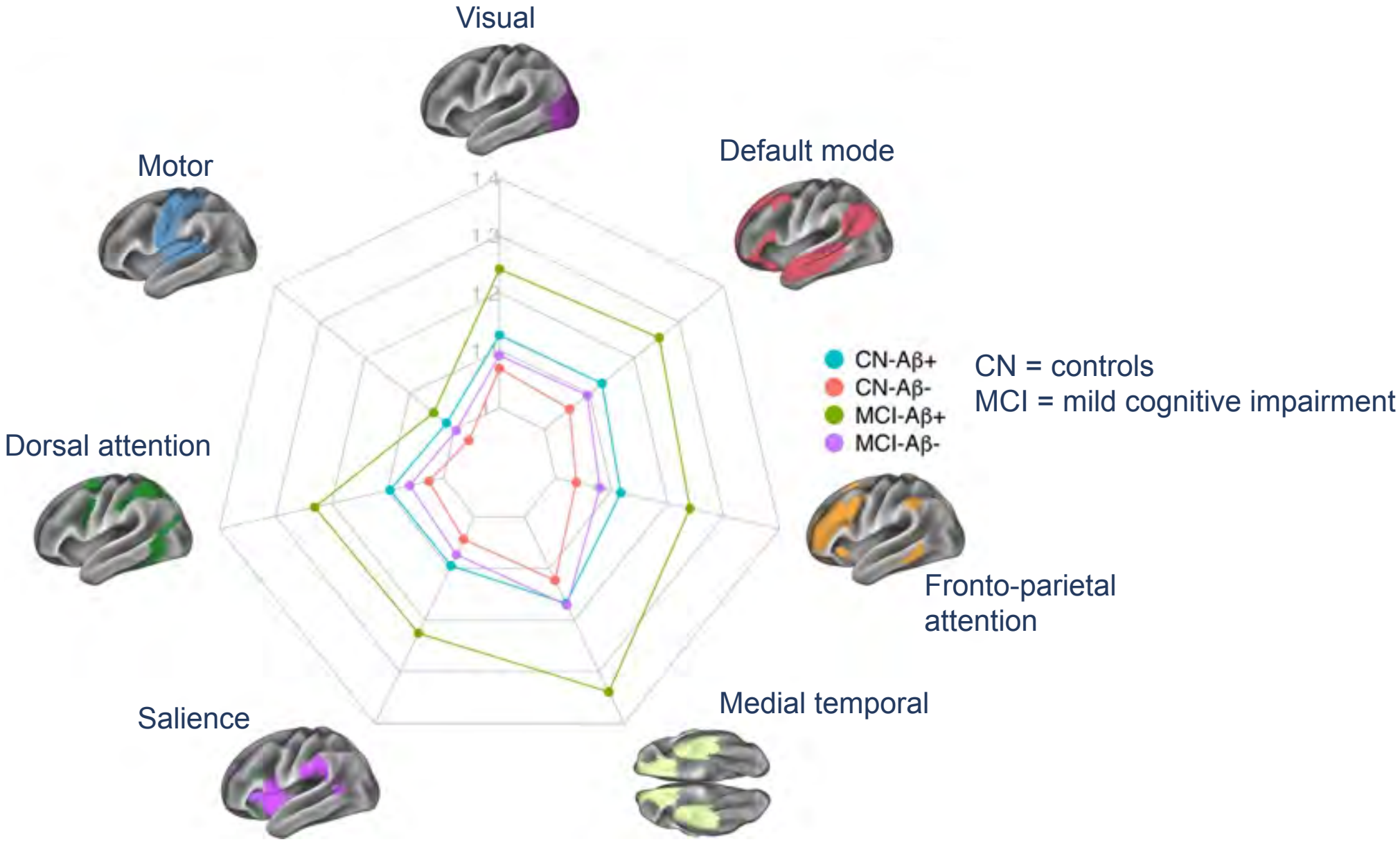
Dorsal attention



Default Mode



Tau PET | Functional Networks

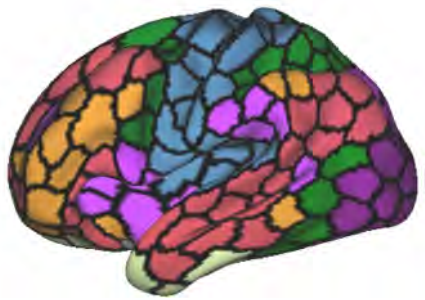


Franzmeier et al. Brain, 2019

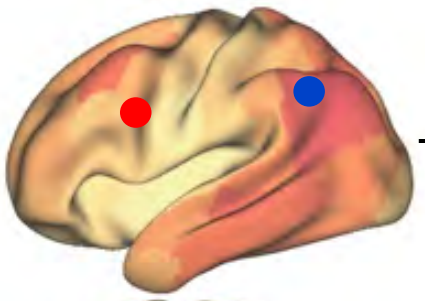
Assessing connectivity

Resting state fMRI – functional connectivity (FC)

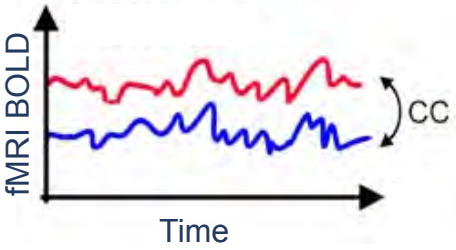
Brain atlas



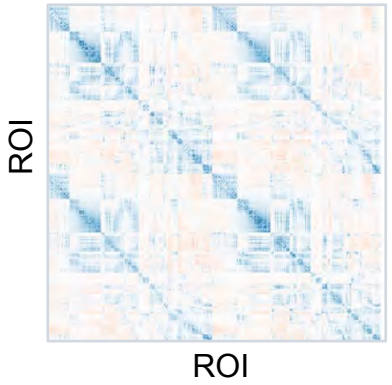
fMRI data



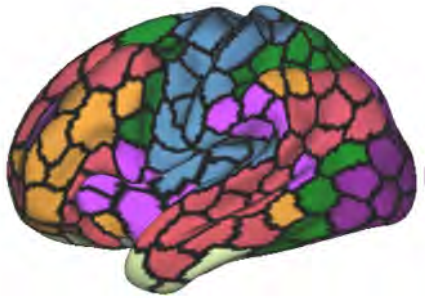
Assess FC between all ROI pairs



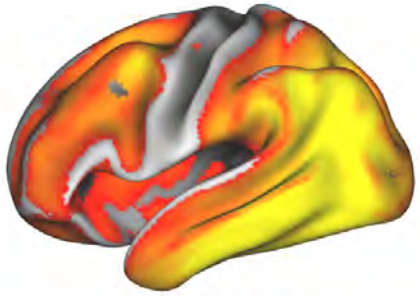
Functional connectivity



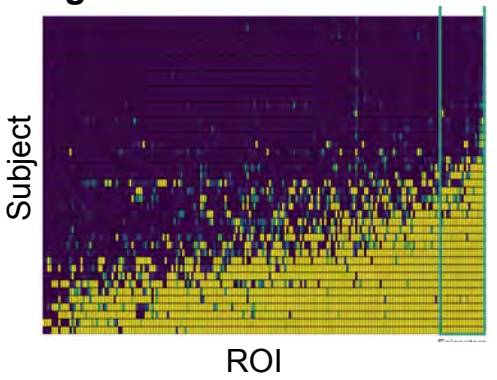
Tau PET covariance



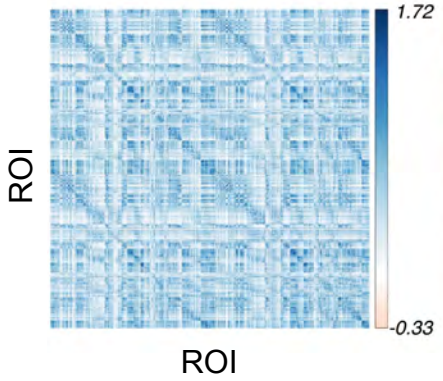
Tau PET



Regional tau values

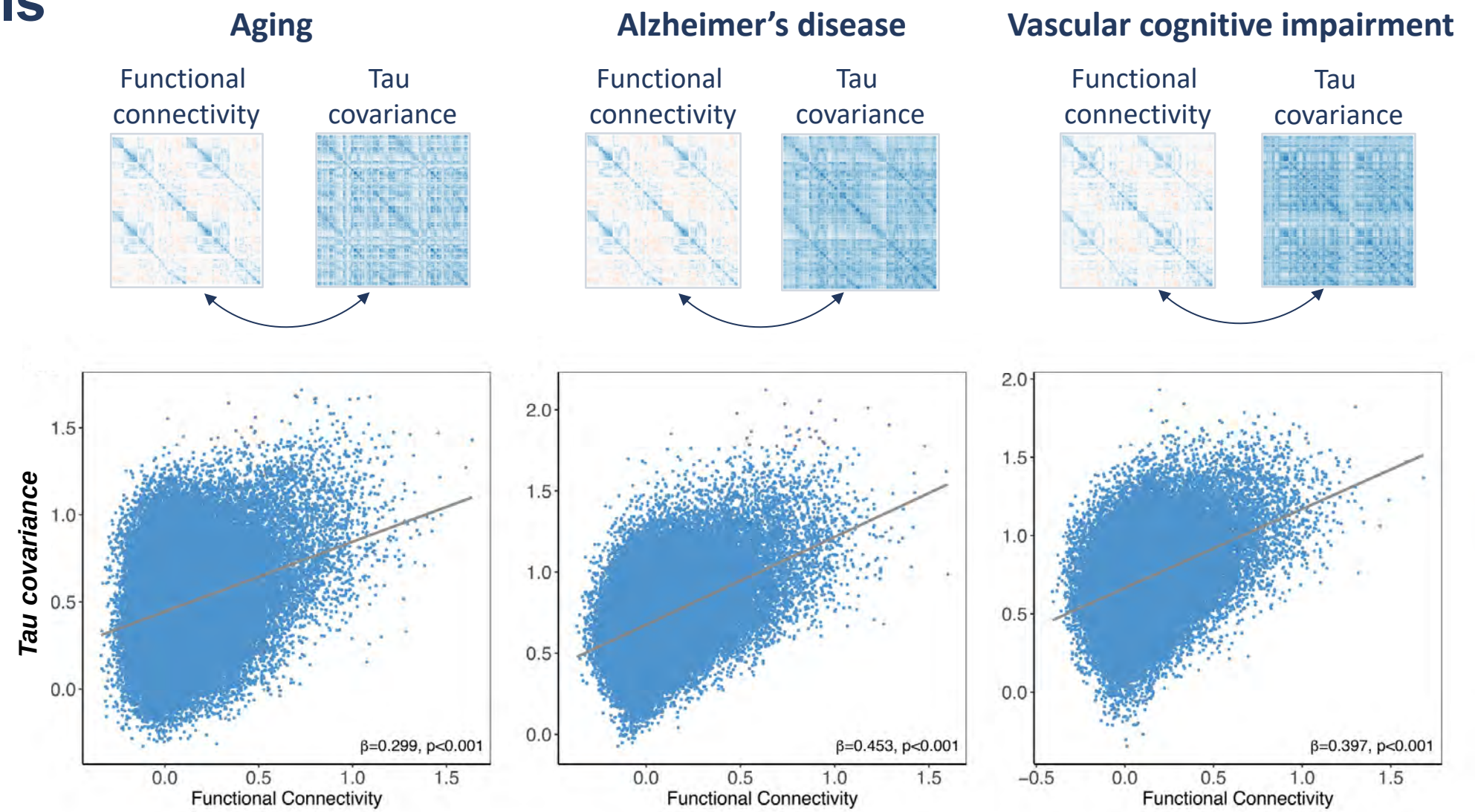


Tau covariance



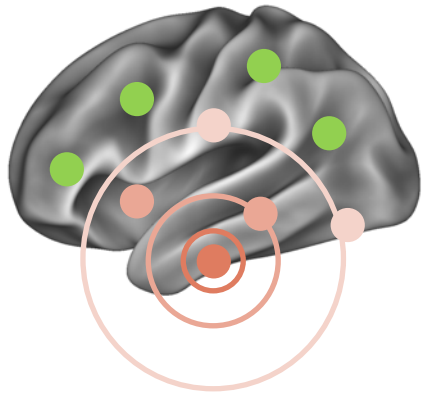
Franzmeier et al. Brain, 2019

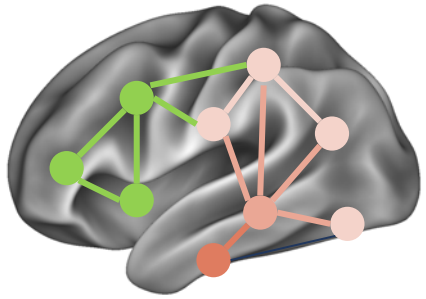
Regions with high functional connectivity show covarying tau levels

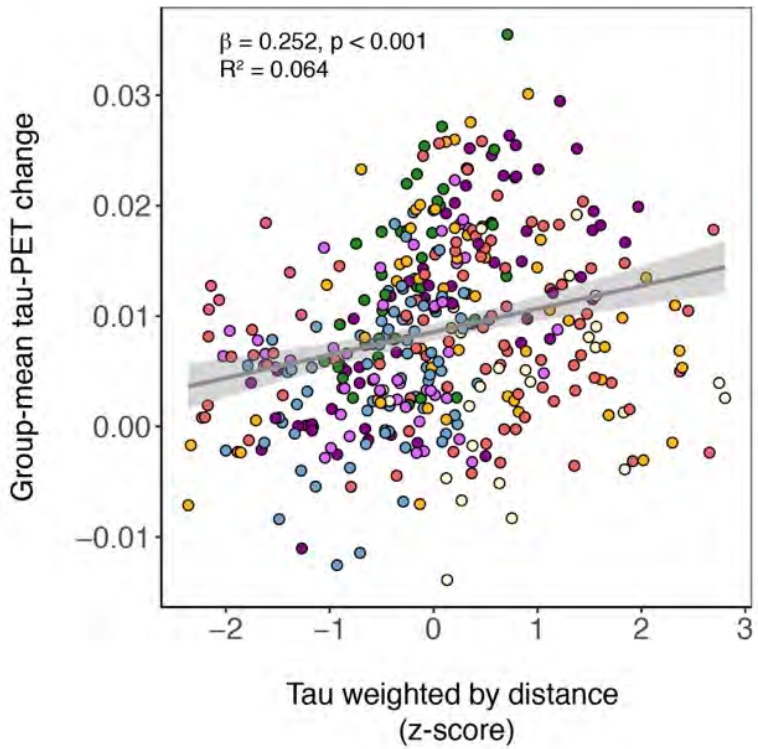


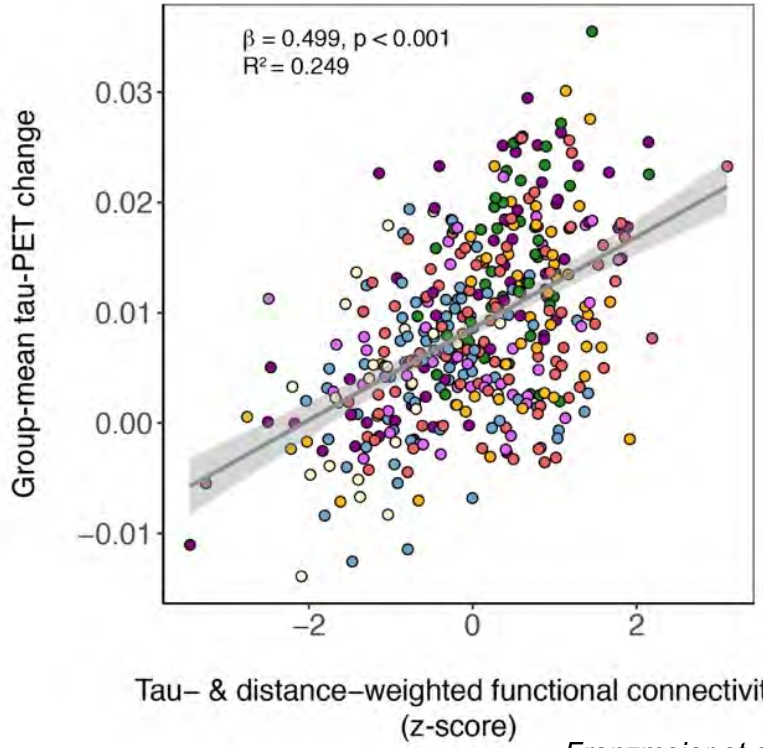
Franzmeier et al., Brain, 2019

Modeling future tau accumulation



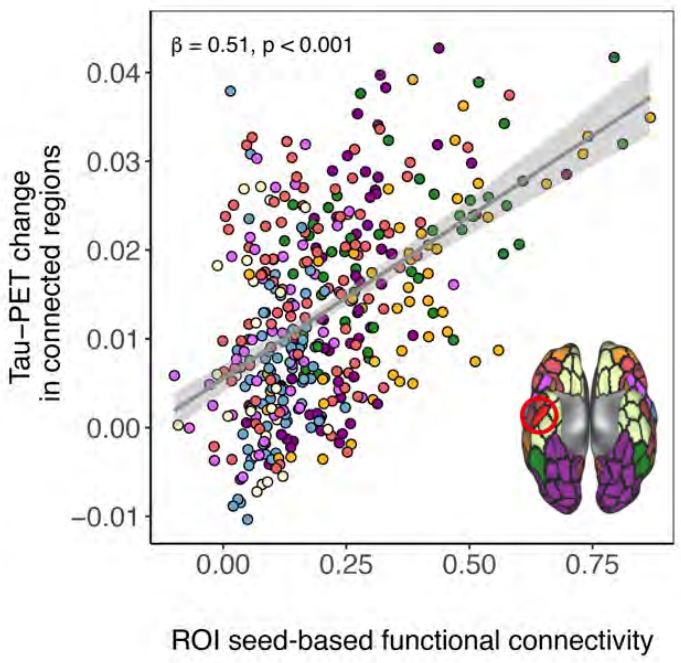


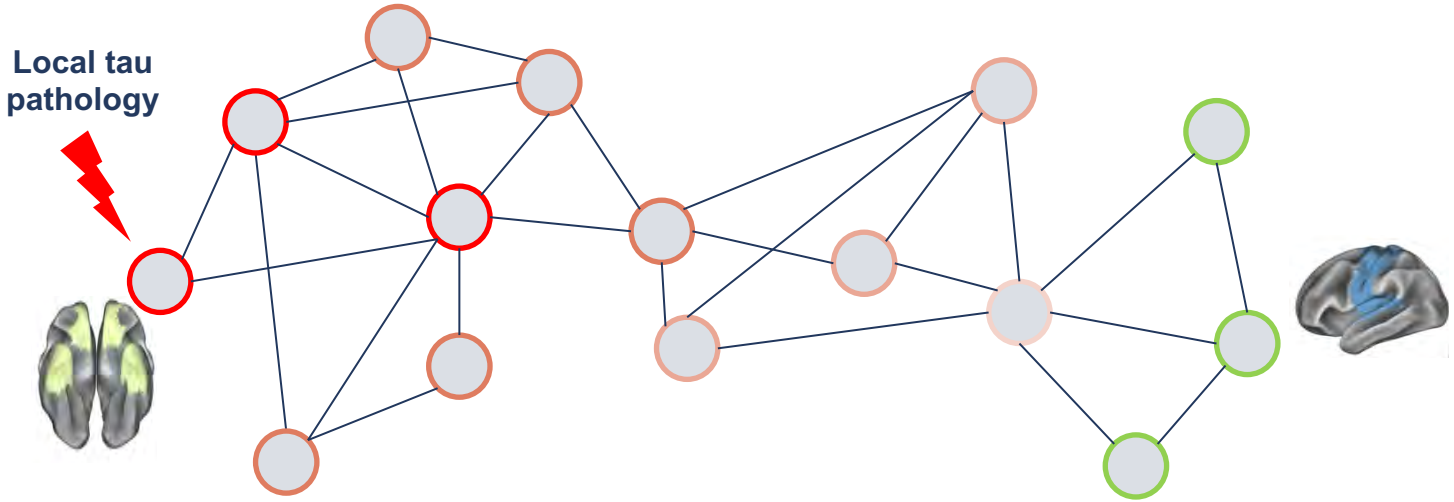




Franzmeier et al. (Nature Communications, in press)

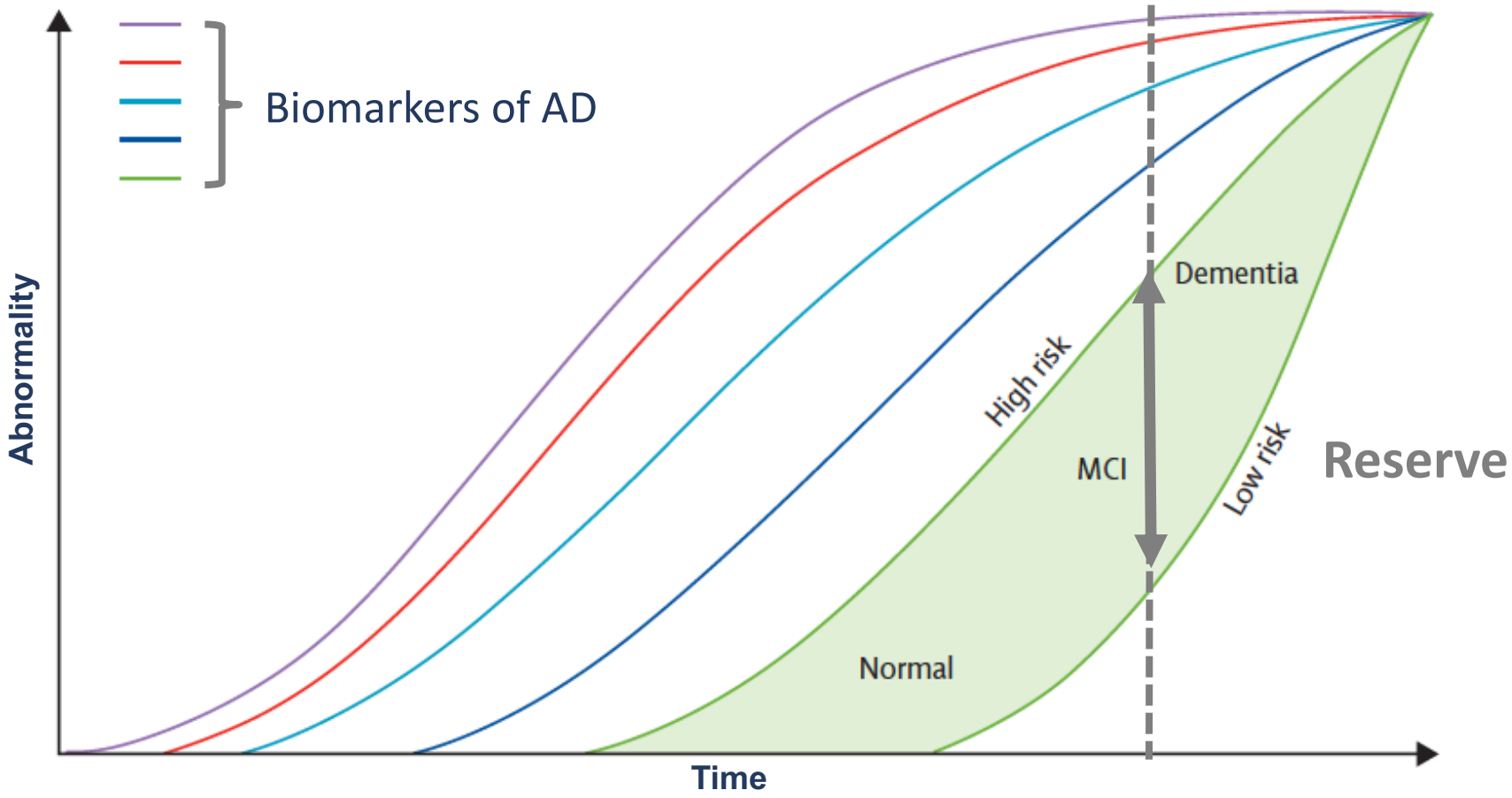
Summary


β = 0.51, p < 0.001
0.04
0.03
0.02
0.01
0.00
−0.01
Tau–PET change
in connected regions
0.00
0.25
0.50
0.75
ROI seed-based functional connectivity


Local tau
pathology

Reserve | cognitive decline

Reserve: Ability to **maintain cognition** relatively well **at a given level of pathology**

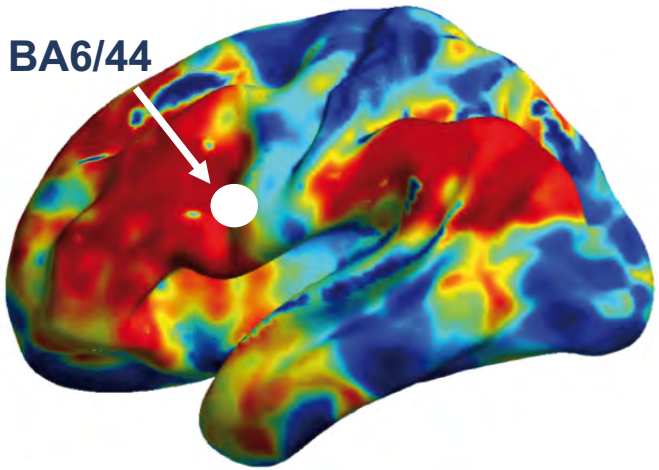


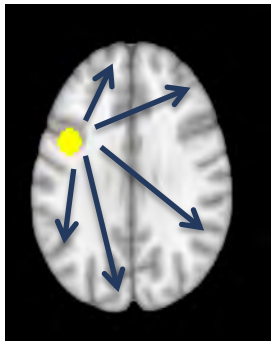
Institute for Stroke and Dementia Research (ISD)

*Adopted from Jack et al. **Lancet Neurol**., 2013*

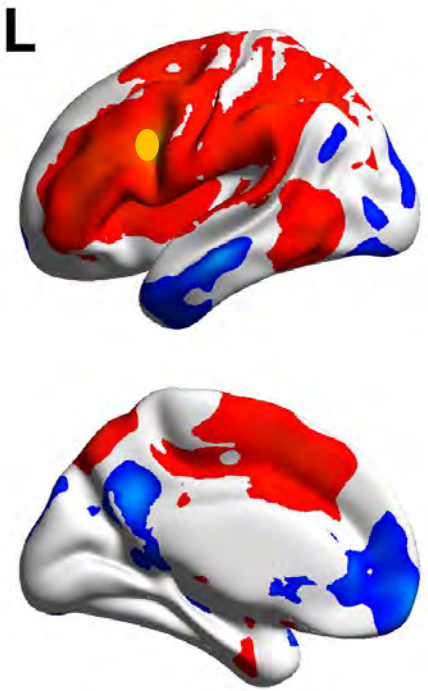
Hub connectivity in the left lateral frontal cortex as a putative substrate of reserve

Distribution of brain hubs





Left frontal cortex (LFC) hub connectivity



- **Associated with higher IQ in young subjects**

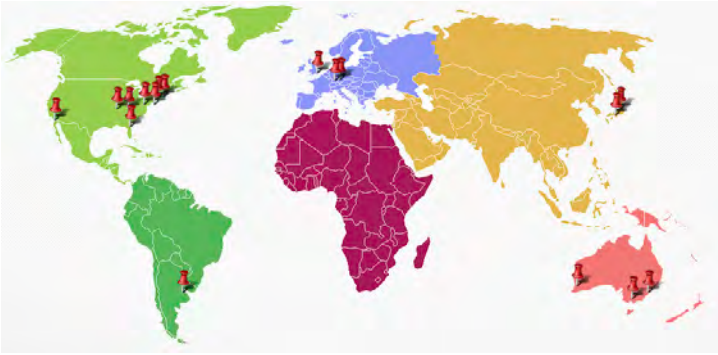
Cole et al., Neuroimage 2013

LFC connectivity in sporadic and genetically caused AD

Genetically caused AD from DIAN (N = 129)

DIAN	Mutation (n=74)	Controls (n=55)	p-value
Age	37.49 (10.05)	37.84 (10.31)	0.848
Gender (f/m)	42/32	34/21	0.563
MMSE	27.04 (5.1)	29.45 (1.02)	< 0.001

DIAN
Dominantly Inherited Alzheimer Network



Sporadic late-onset AD from DELCODE (N = 75)

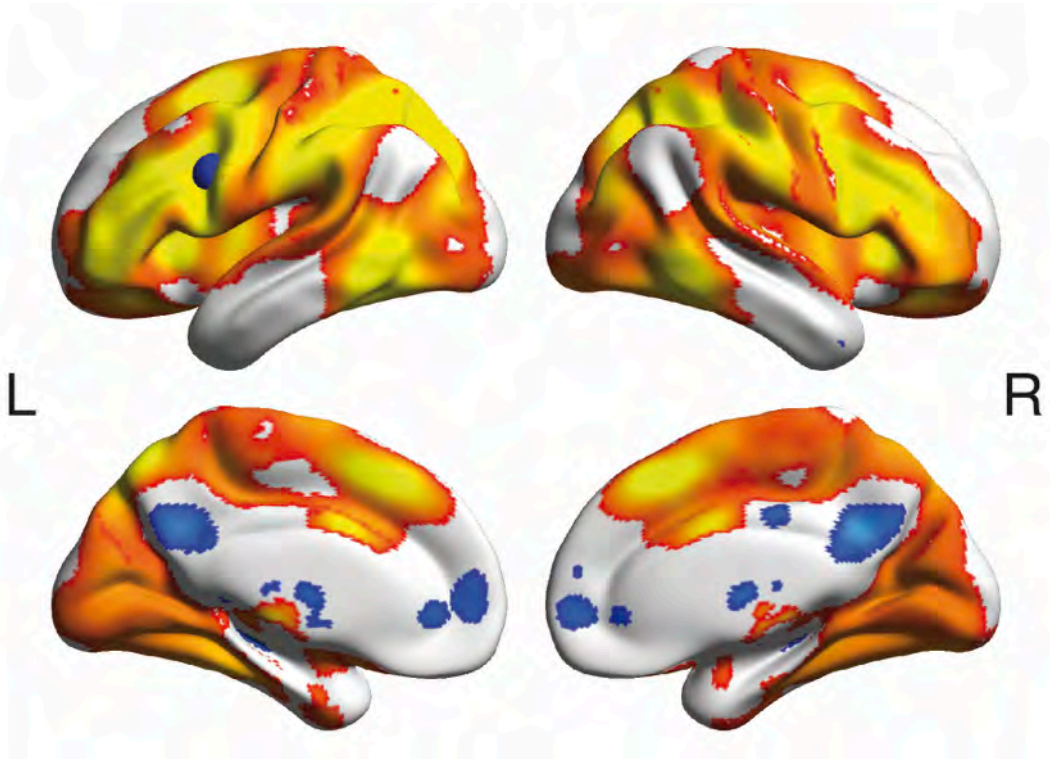
DELCODE	CN (n=25)	SCD (n=23)	MCI (n=14)	AD dementia (n=13)	p-value
Age	57.76 (5.23)	72.26 (4.16)	74.64 (5.34)	71.31 (6.18)	< 0.001
Gender (f/m)	16/9	10/13	5/9	9/4	0.164
MMSE	29.20 (0.96)	29.39 (0.78)	27.71 (1.68)	23.85 (2.82)	< 0.001

DZNE
German Center for Neurodegenerative Diseases
within the Helmholtz Association

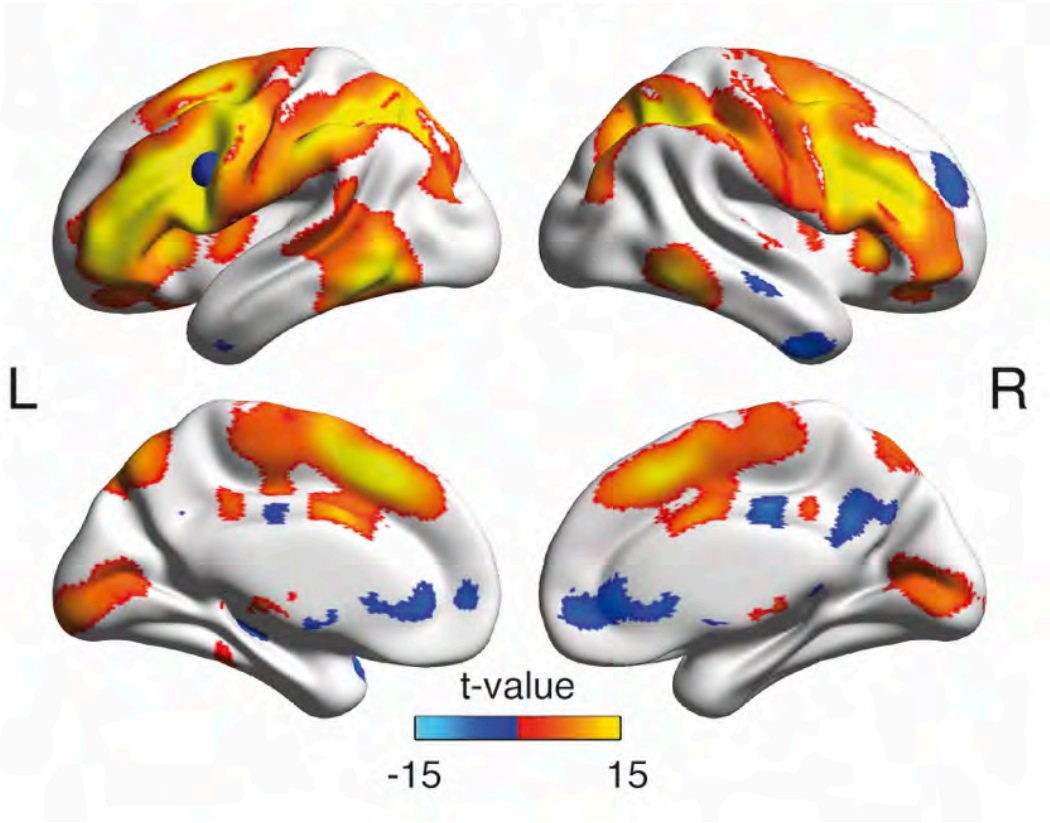
Institute for Stroke and Dementia Research (ISD)

LFC connectivity maps

DIAN

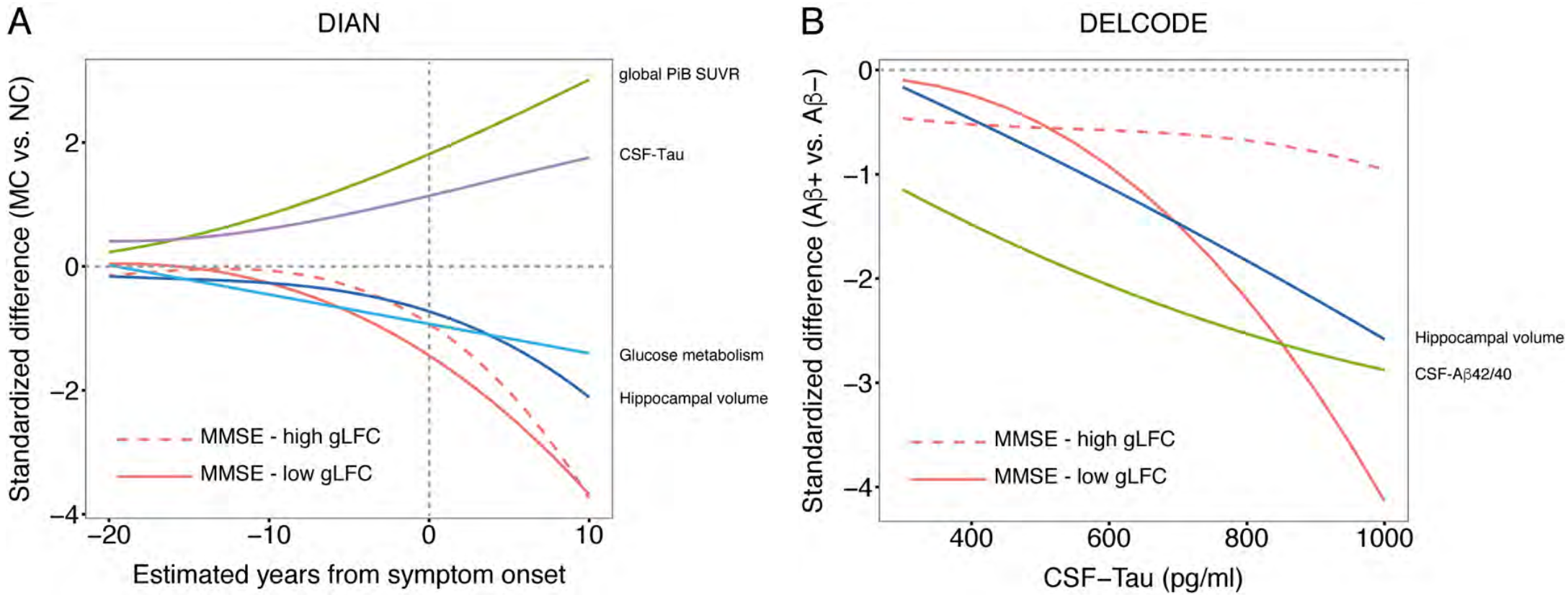


DELCODE



Franzmeier et al., Brain 2018

Modeling the impact of global LFC connectivity on cognition

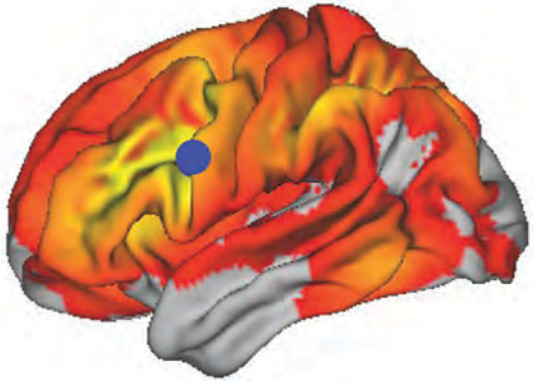


Franzmeier et al., Brain 2018

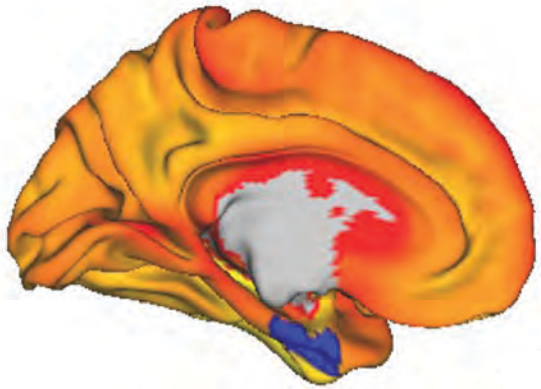
Left frontal hub connectivity modulates effect of tau on memory

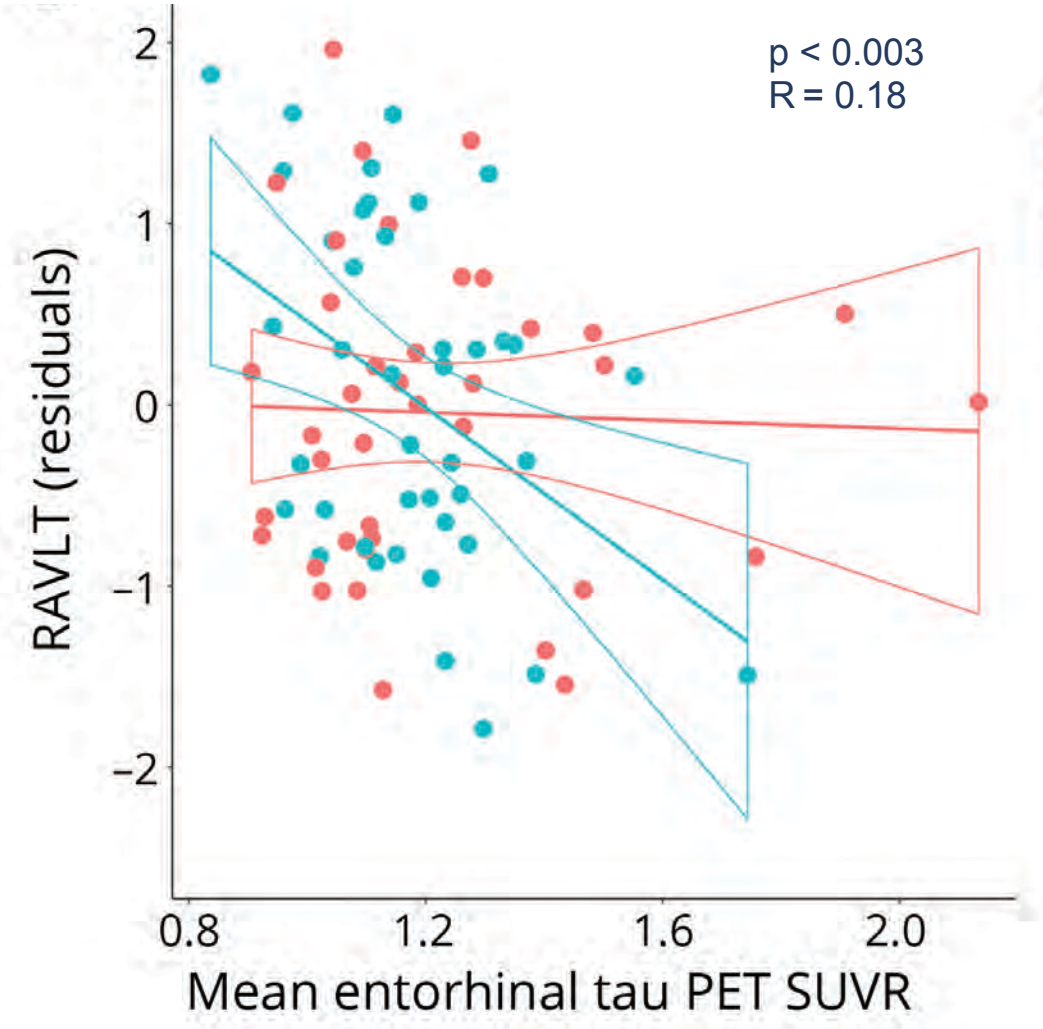
82 controls & 43 MCI

Left frontal hub connectivity



Entorhinal tau PET ROI

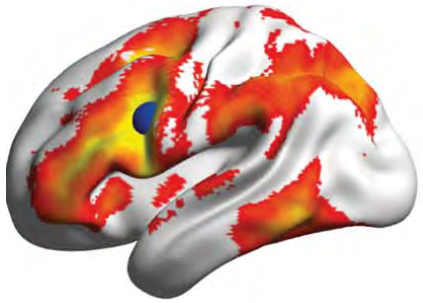




Institute for Stroke and Dementia Research (ISD)

Neitzel et al. ***Neurology*** *2019*

Model of functional brain mechanism underlying reserve



Protective factors (Education)

Franzmeier et al. Brain, 2018
Franzmeier et al. Neurology, 2017
Ewers et al. Neurology, 2013

→ **LFC hub connectivity Control network**

→ **Network efficiency**

Franzmeier et al. Alz Res Therapy, 2018

AD pathology ⊣ → **Cognitive impairment**

Neitzel et al. Neurology, 2019
Franzmeier et al. Brain, 2018
Franzmeier et al. Neurology, 2017

Acknowledgements

EwersLab

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UCSF

Michael Weiner

DZNE/DELCODE

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Emrah Düzel

DIAN

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Kathrin Paumier
Anne Fagan
John Morris

University of Texas, Dallas

Denise Park
Zhuang Song

University of Bordeaux

Bertrand Mazoyer

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Xi-Nian Zuo

Samsung Medical Center, Seoul

Sang Won Seo
Duk Na

McGill University, Montreal

Sylvie Belleville
Sylvia Villeneuve

Technische Universität München

Christian Sorg
Katja Koch

Institute for Stroke and Dementia Research (ISD)

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Neuroimaging Insights from the Dominantly Inherited Alzheimer's Network (DIAN)

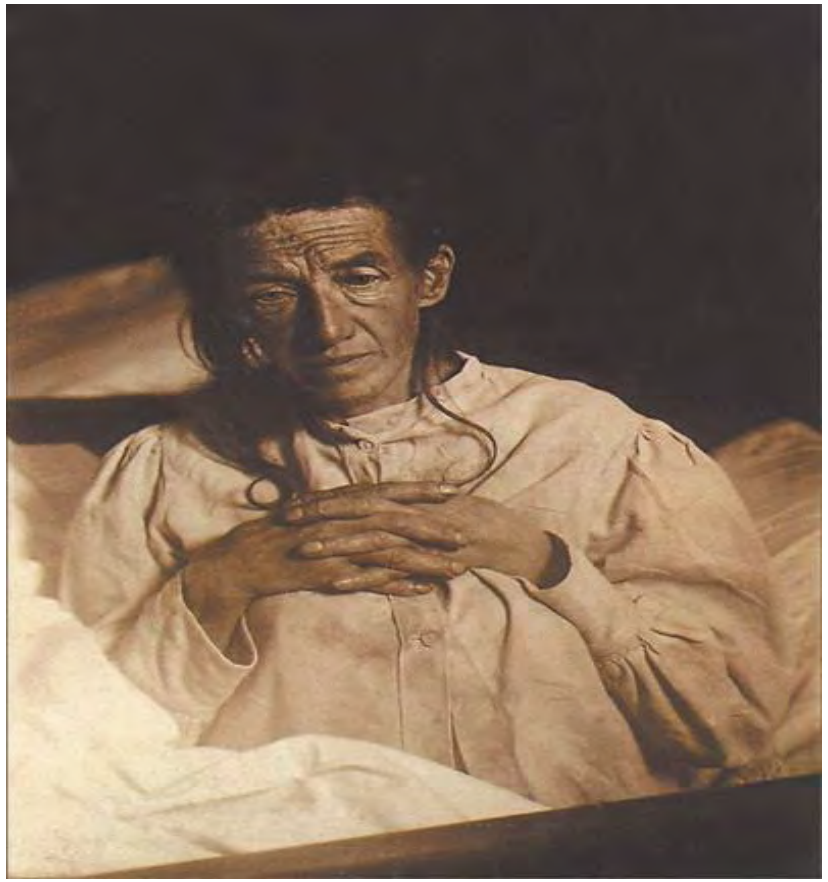
Beau M. Ances MD, PhD, MSc, FANA, FAAN
Daniel J Brennan MD Professor of Neurology
Departments of Neurology, Radiology, and Biomedical Engineering
Washington University in Saint Louis (WUSTL)

AABC Updates in Neuroimaging Webinar
December 9, 2019

Dr. Ances has no financial disclosures

Autosomal Dominant Alzheimer Disease (ADAD)

- A rare form of Alzheimer's disease (AD)
  - Less than 1% of AD cases result from ADAD mutations
- Caused by an inherited gene mutation in one of three genes directly involved in amyloid beta (Aβ) production
  - Amyloid precursor protein (*APP*)
  - Presenilin 1 (*PSEN1*)
  - Presenilin 2 (*PSEN2*)
- 50% chance of passing the gene to a child
- Individuals with ADAD develop symptoms earlier in life
- Mutations cause predictable age of onset and allows for determination of estimated years to onset (EYO)



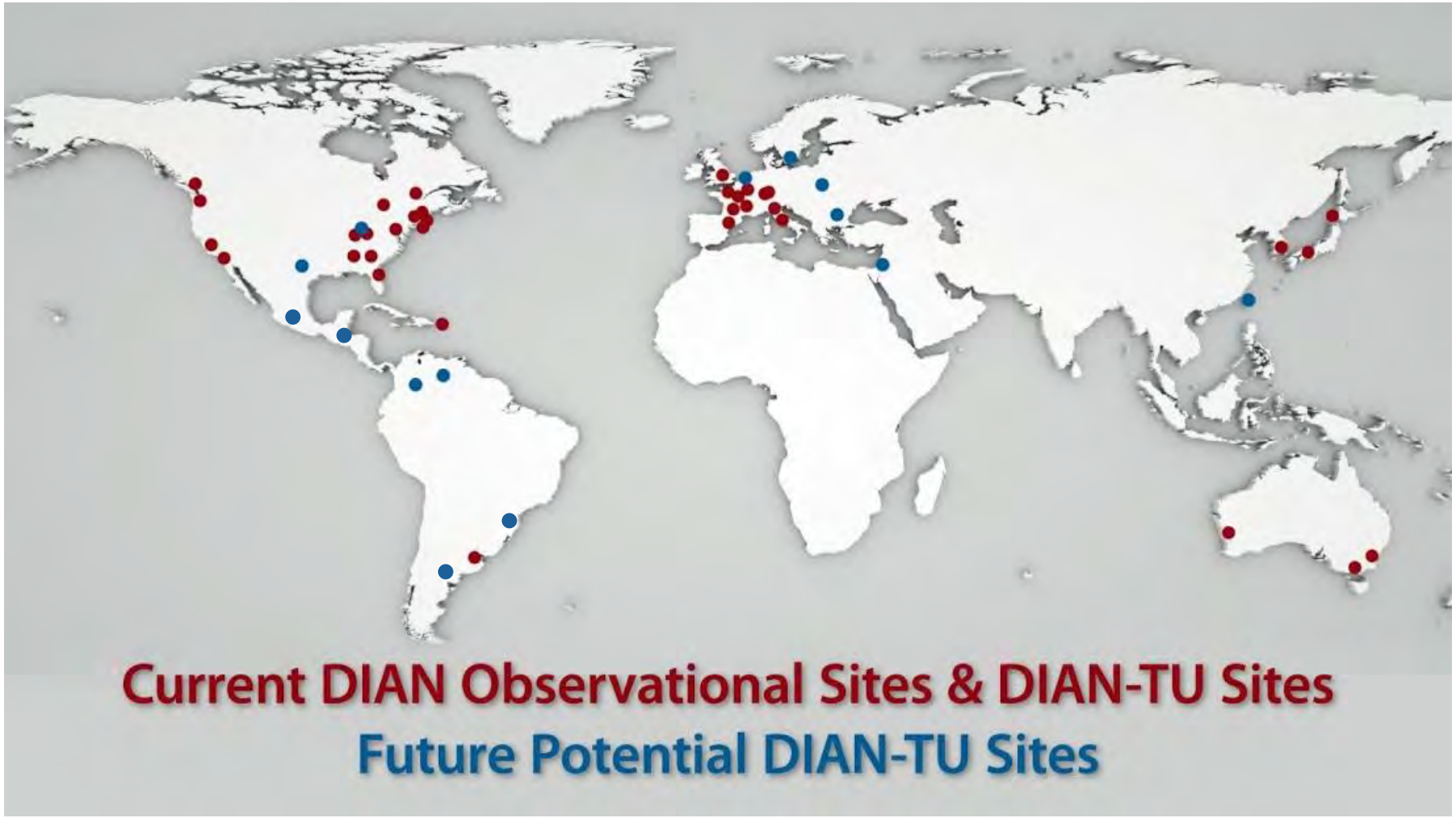
Auguste D., the first AD patient described by Dr. Alois Alzheimer, was later found to have an ADAD mutation in Presenilin 1 (F176L)

Comparison of ADAD and Late Onset Alzheimer's Disease (LOAD)

	ADAD	LOAD
Clinical presentation	Amnestic	Amnestic
Cognitive deterioration	Memory, frontal/executive, generalized cognitive decline	Memory, frontal/executive, generalized cognitive decline
Magnetic resonance imaging (MRI)	Hippocampal atrophy and whole brain atrophy	Hippocampal atrophy and whole brain atrophy
Amyloid positron emission tomography (PET)	Cortex **plus basal ganglia**	Cortex
Flurodeoxyglucose (FDG) PET	Parieto-occipital hypometabolism	Parieto-occipital hypometabolism
Cerebrospinal fluid (CSF) Aβ 42	Decreased by 50%	Decreased by 50%
CSF tau	Increased by 2-fold	Increased by 2-fold

Scientific data supports drug trial for ADAD to potentially translate to LOAD.

DIAN Observational Sites Throughout the World



DIAN observational study has enrolled more than 550 participants.

DIAN Observational Cohort Demographics

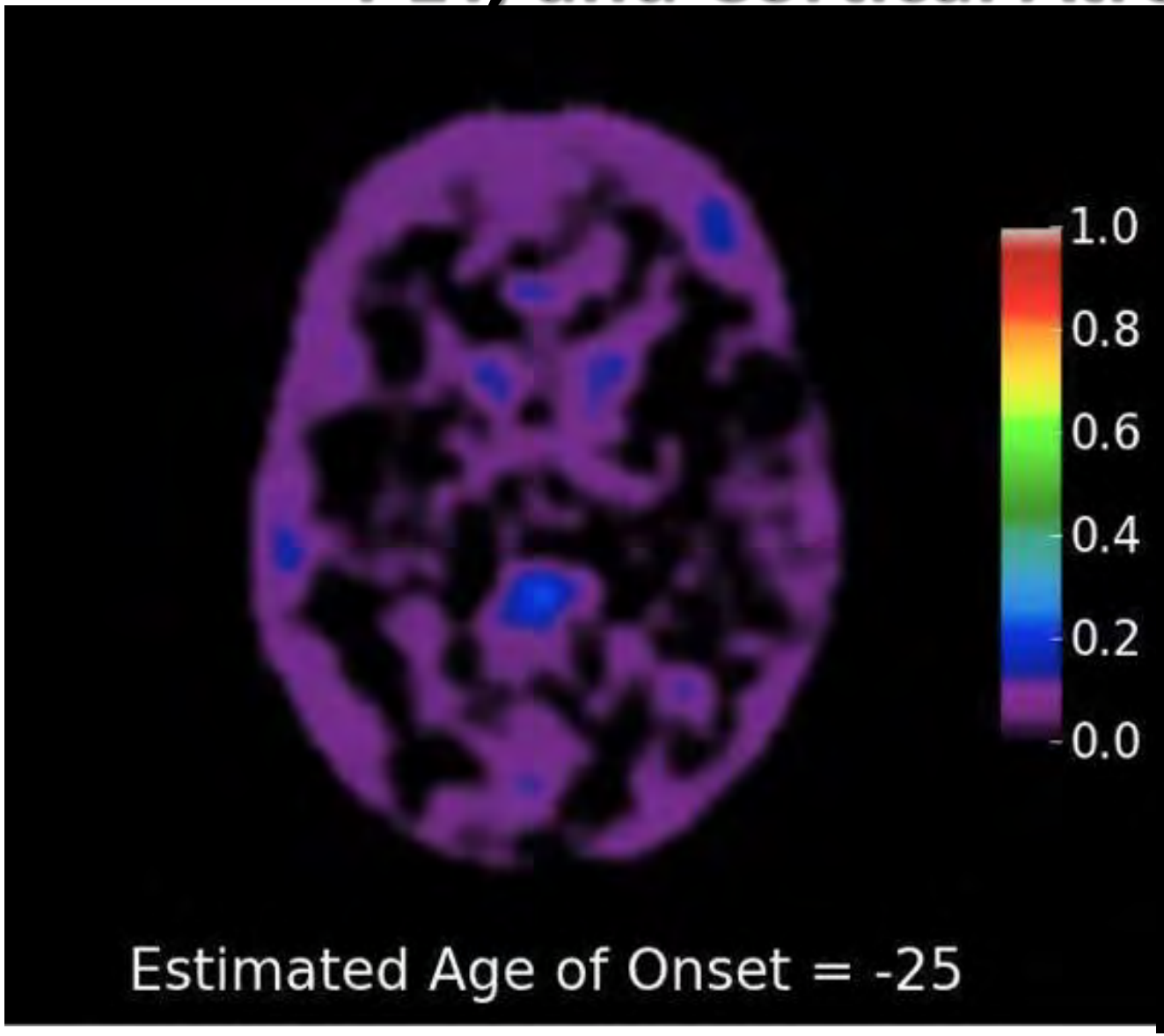
N = 562* *(Target 80% Asymptomatic, 20% Symptomatic) (*Table based on 534 participants. 28 Mutations in Process)*	**Asymptomatic** *415 (73.8%) 391 with confirmed mutation status*		**Symptomatic** *145 (25.8%) 141 with confirmed mutation status*	
	199 (NC) (50.9%)	192 **(MC)** (49.1%)	11 (NC) (7.8%)	130 **(MC)** (92.2%)
Age, Mean (SD)	43.9 (12.1)	40.0 (10.0)	50.1 (11.0)	52.4 (9.5)
Gender (% Female)	118 (59.3%)	107 (55.7%)	6 (54.5%)	74 (56.9%)
Parental Age of Onset, Mean (SD)	47.2 (6.6)	48.5 (7.1)	48.1 (5.9)	45.6 (8.6)
Education, Mean (SD)	15.0 (2.8)	14.9 (2.8)	11.3 (3.8)	13.5 (3.3)
MMSE, Mean (SD)	29.2 (1.2)	29.0 (1.2)	28.2 (1.6)	19.4 (8.4)
ApoE4+ ***1 E4***	60 (30.2%)	56 (29.2%)	3 (27.3%)	32 (24.6%)
2 E4	3 (1.5%)	1 (0.5%)	0 (0%)	7 (5.4%)

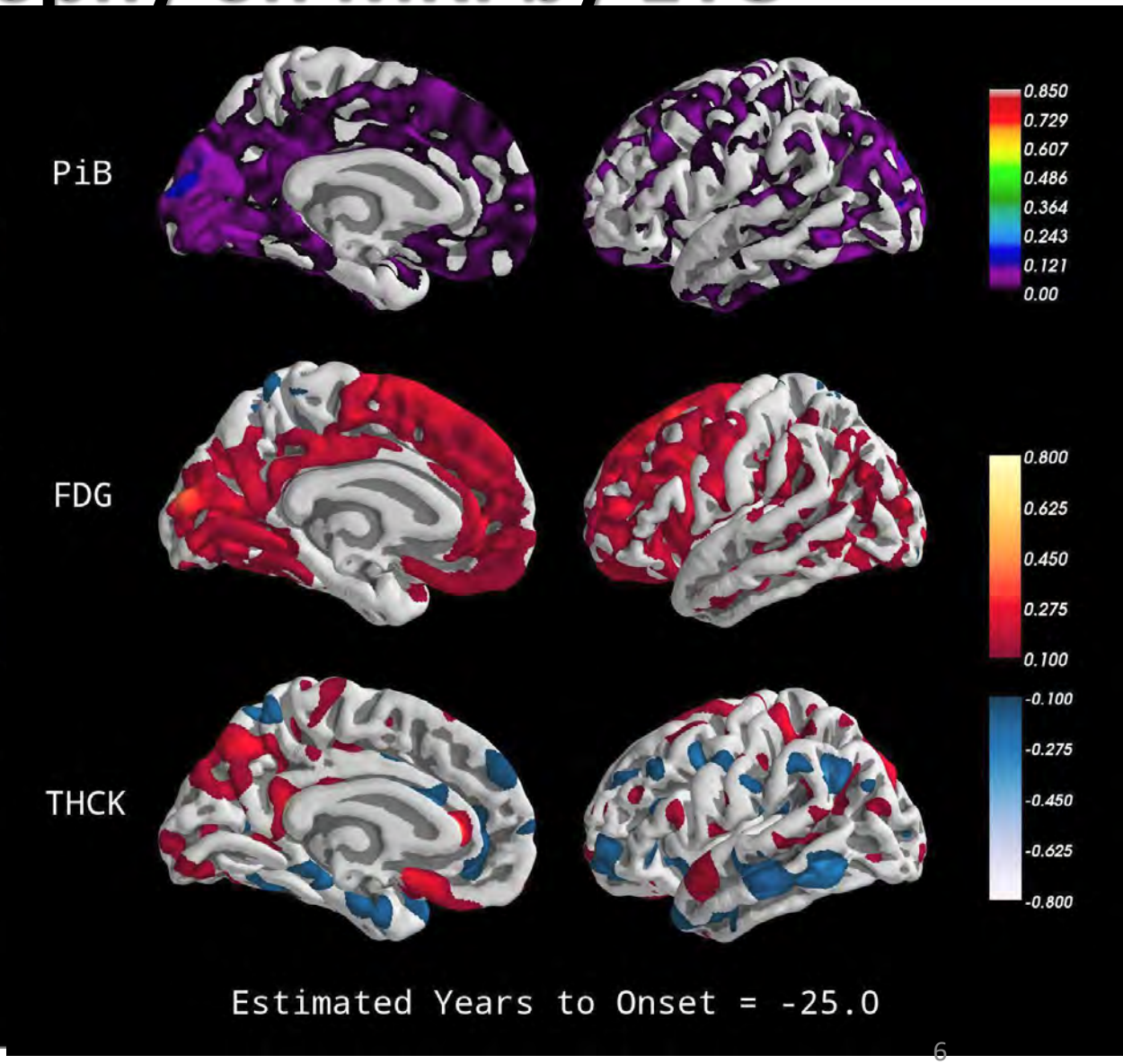
MC = Mutation Carrier; NC = Non-carrier

*Table statistics based on 534 participants with confirmed mutation data available as of 03/01/2019. Of them 323 (60.5%) are mutation carriers (of these, CDR score is missing for 1), 211 (39.5%) are mutation non-carriers (of these, CDR score is missing for 1)

- >560 participants enrolled since 2008
- Biomarker collection rate >80-90%
- More than 52% of participants are 10 years or more prior to EYO

Amyloid PET Deposition, Hypometabolism on FDG PET, and Cortical Atrophy on MRI by EYO

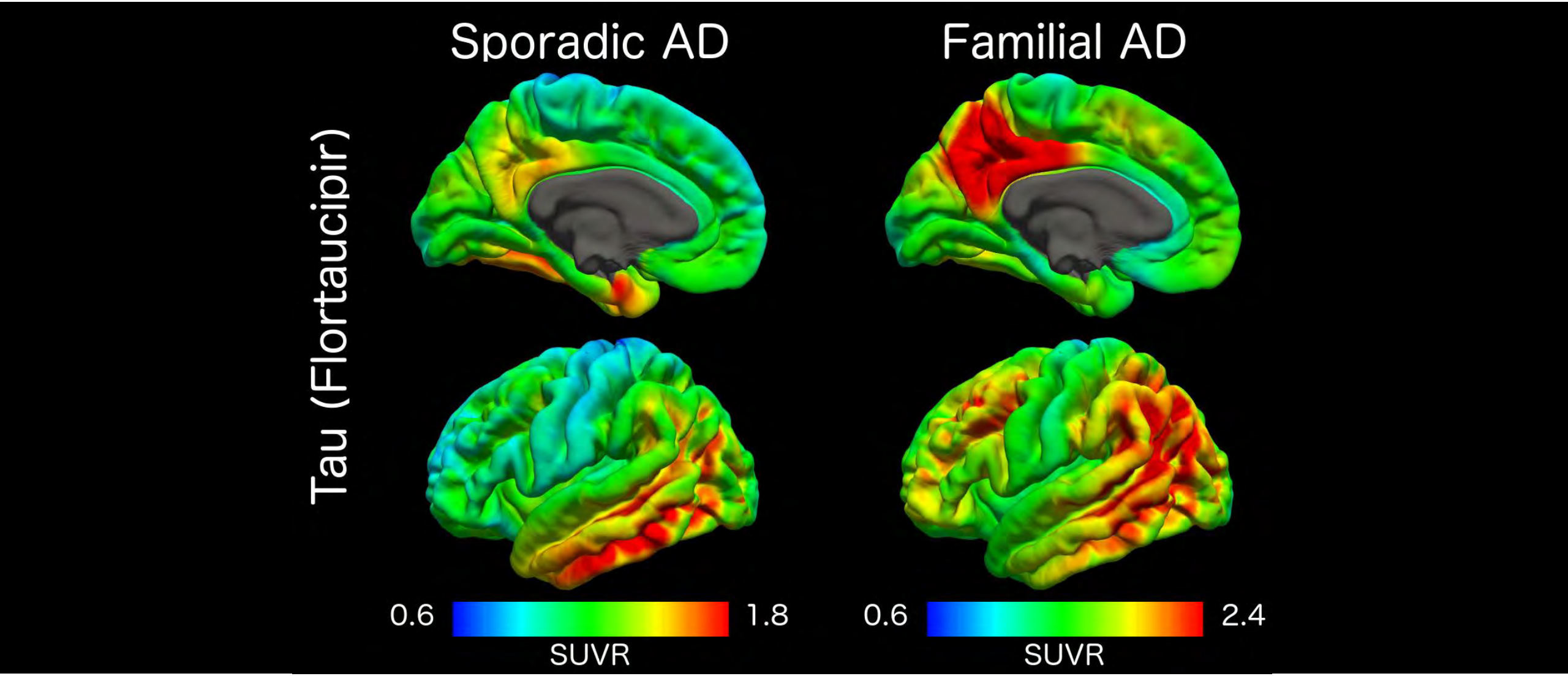




Bateman et. al., *NEJM,* 2012

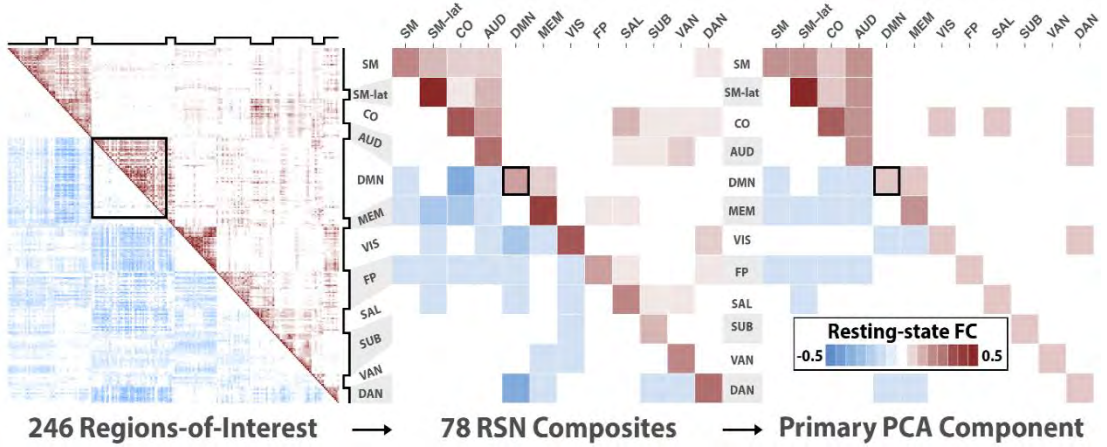
Benzinger et. al., 2015, *PNAS*

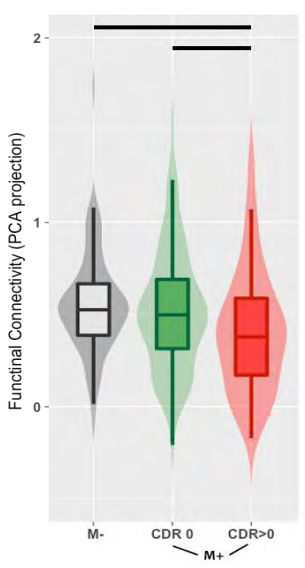
Comparison Between ADAD and LOAD Using Tau PET

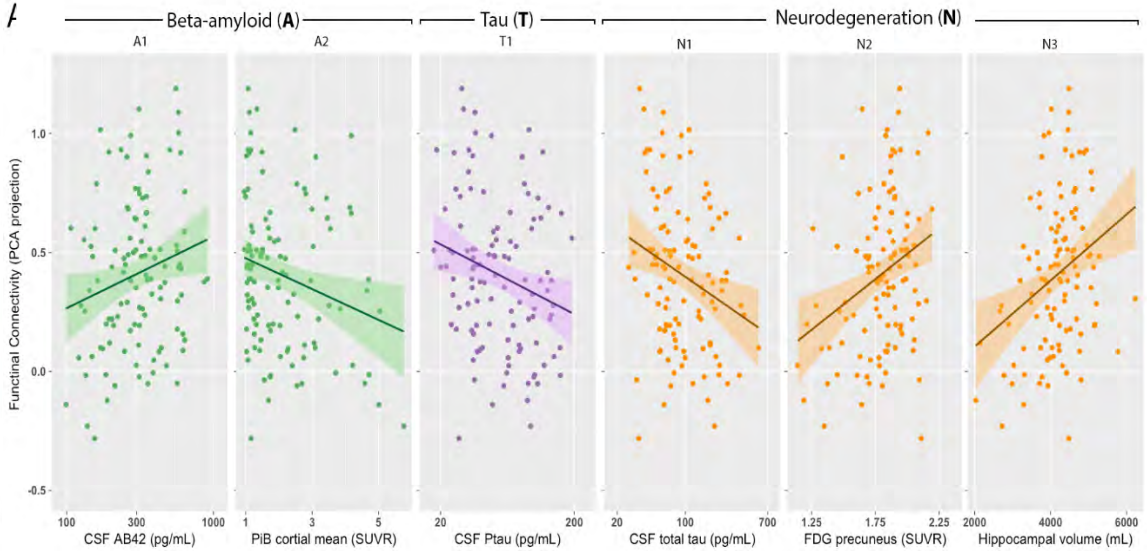


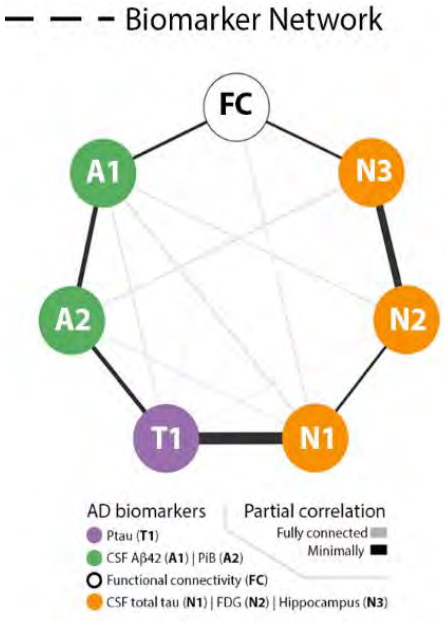
Gordon et. al., 2018 *Brain*

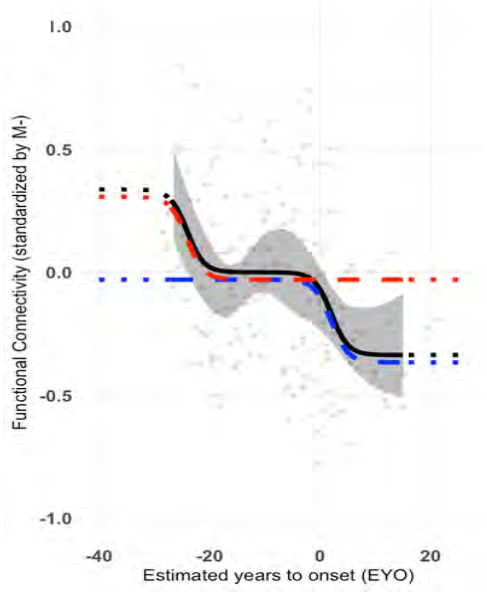
Global Resting State Functional Connectivity (Rs-fc) Signature Relative to Other Biomarkers in ADAD





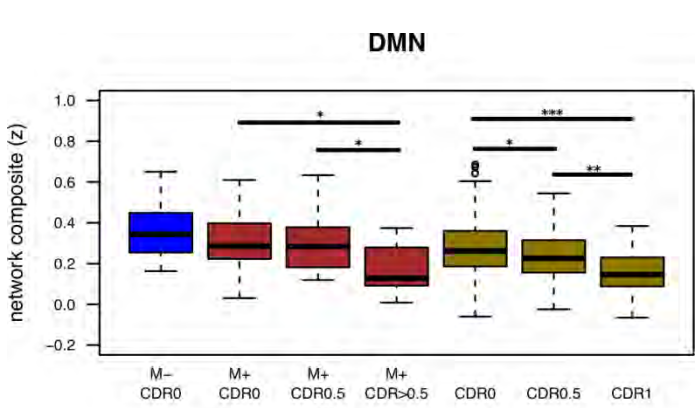


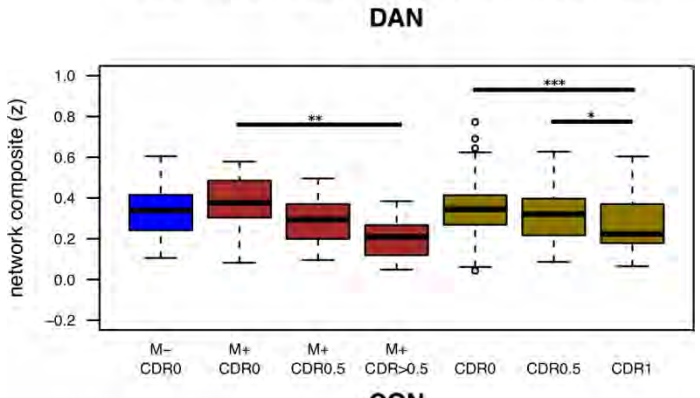


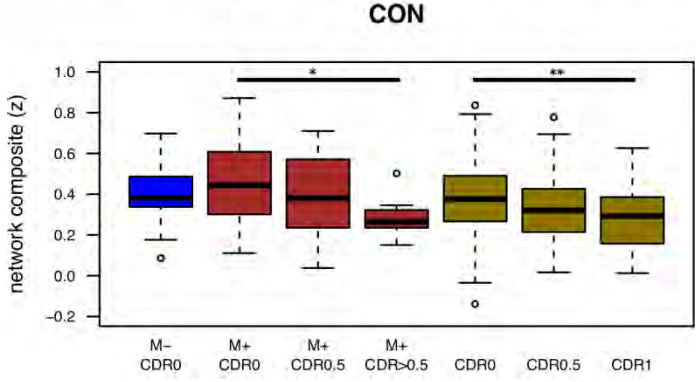


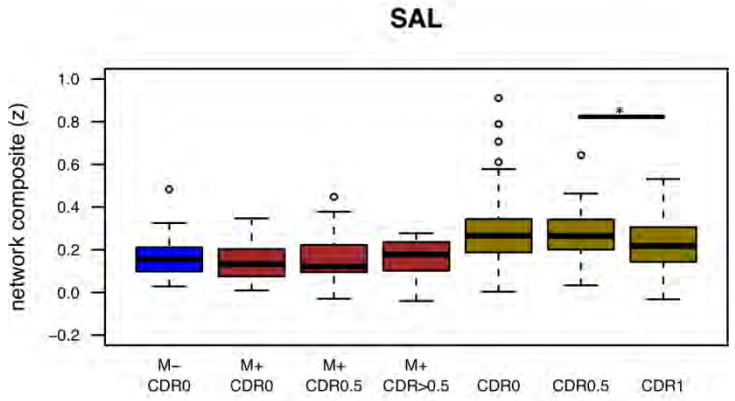
Smith et al., *under review*

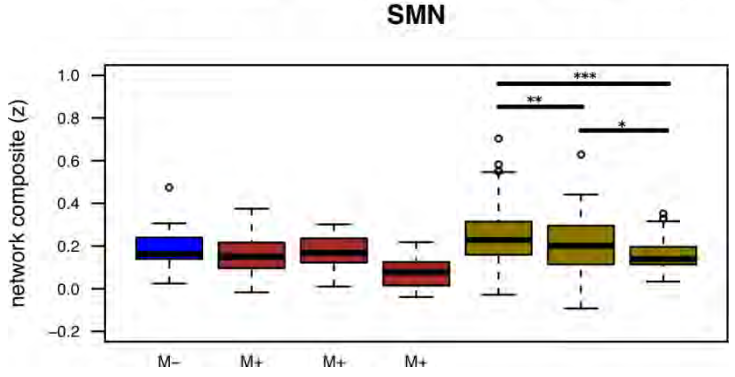
Loss of Intra-Network Rs-fc in ADAD is Similar to LOAD









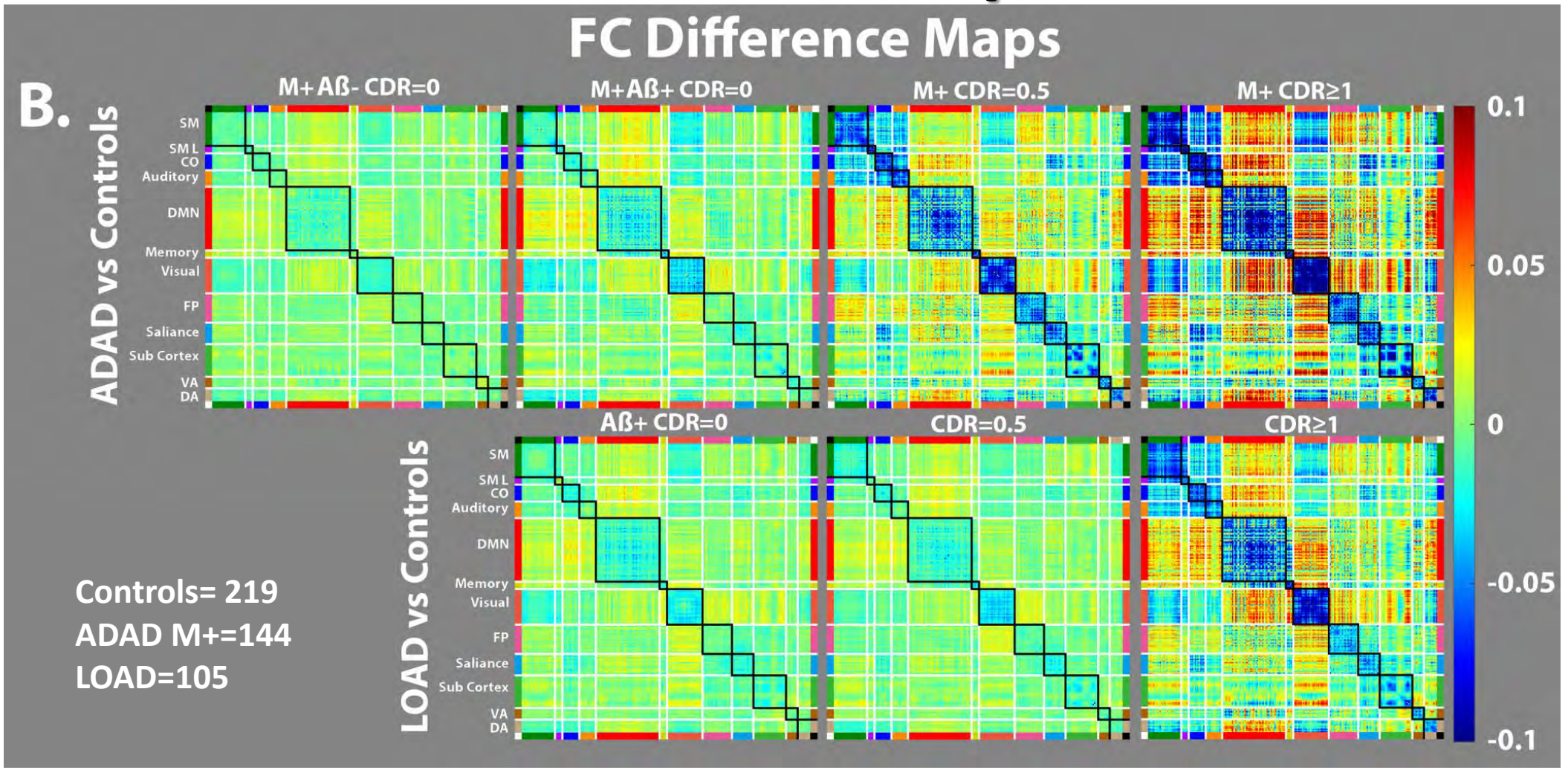


M- CDR 0= 30
M+ CDR 0= 25
M+ CDR 0.5 =12
M+ CDR ≥ 1= 7

sAD CDR 0= 300
sAD CDR 0.5 =62
sAD CDR ≥ 1= 10

Thomas et al., 2014, *JAMA Neurol*

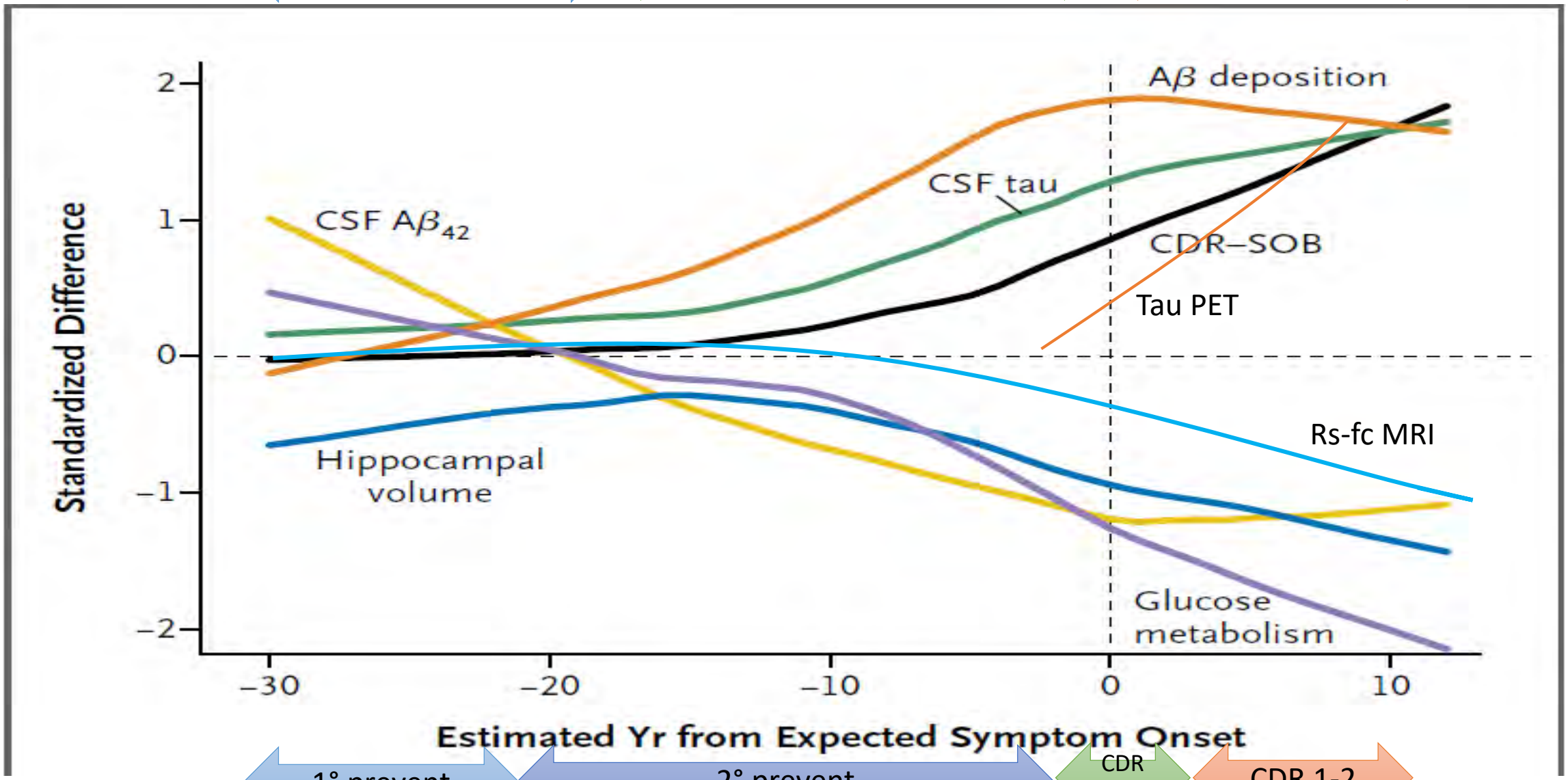
The Spatial Topography of ADAD is Similar But Is Accelerated When Compared to LOAD



Strain et al., *under review*

Stages of ADAD Based on Cross Sectional Data

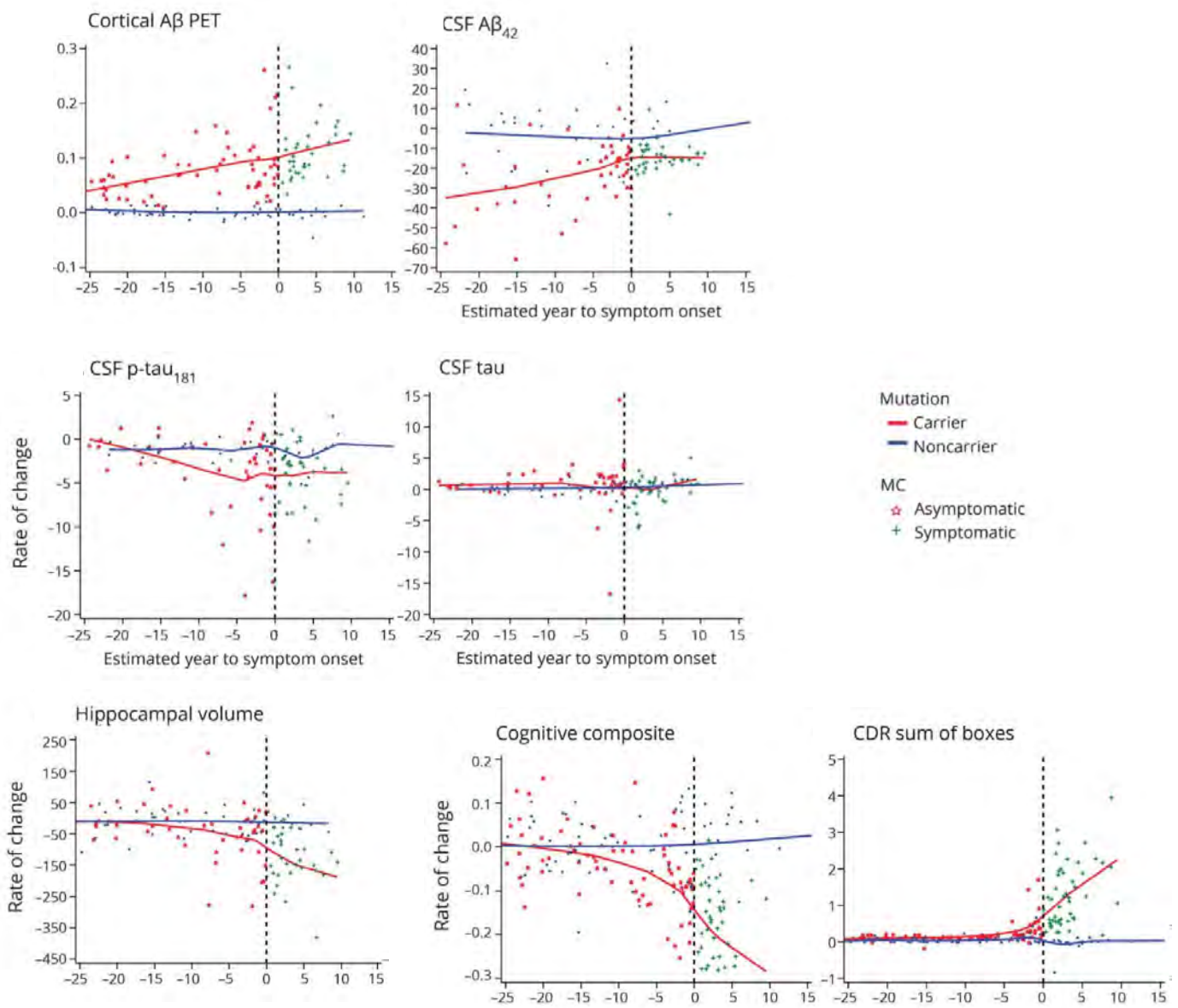
Pre-pathology | Plaques | Tangles



1° prevent | 2° prevent | CDR 0.5 | CDR 1-2

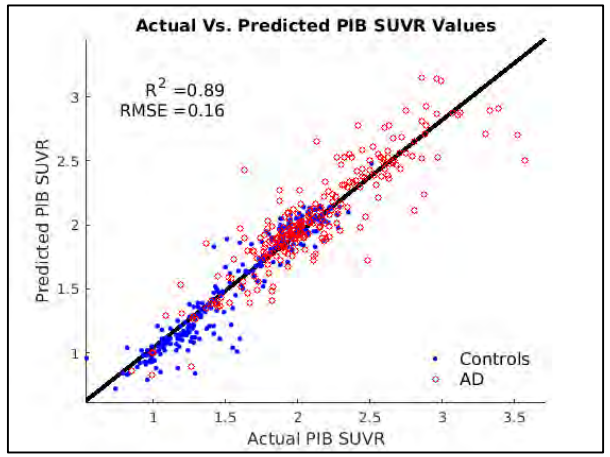
Bateman et. al *NEJM* 2012

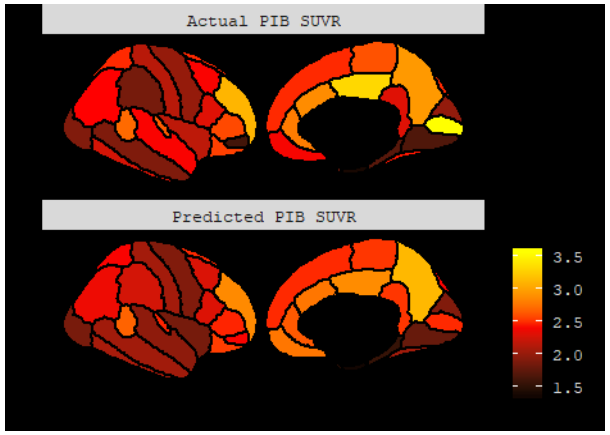
Longitudinal Changes in Biomarkers in ADAD

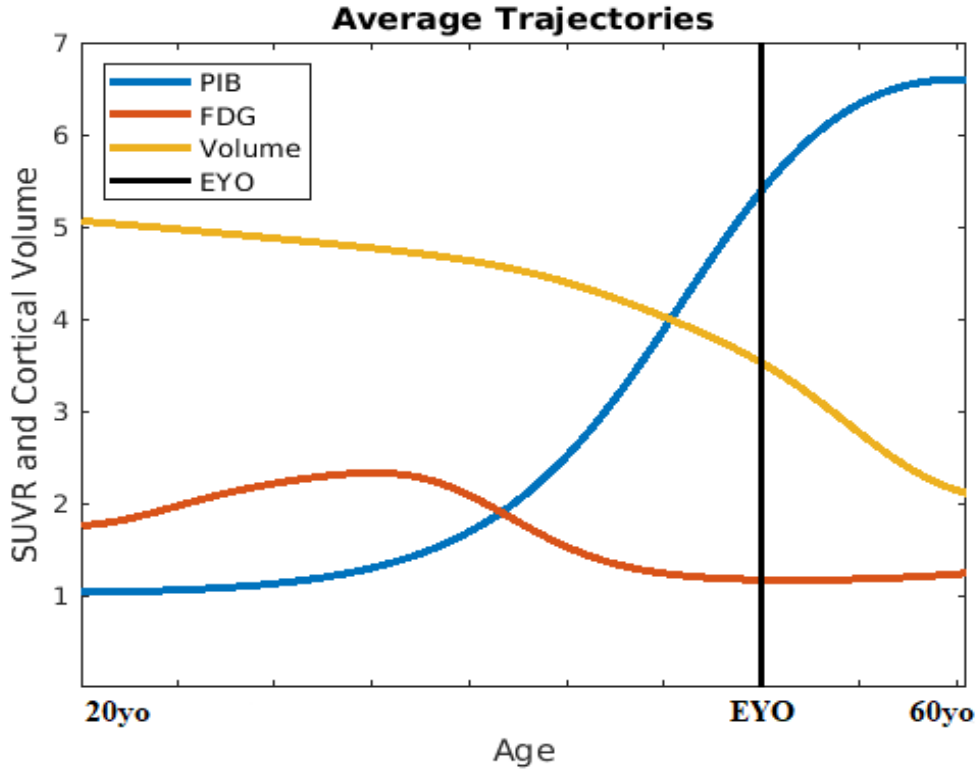


McDade et al., 2018, *Neurology*

Artificial Neural Network Modeling of the Progression of Disease in ADAD Using Longitudinal Biomarkers







Luckett et al., *under review*

DIAN- Trials Unit (TU) Trial Platform Design

- Tests **multiple drugs with diverse mechanisms of action** in parallel
  - **Amyloid-beta -** with monoclonal antibodies and BACE inhibitors
  - **Tau** – anti-bodies, genetic-based therapies, small molecule aggregation inhibitors
  - **Novel targets**
  - **Combination therapy**
- **Pooled placebo** (including DIAN Observational Study Data)
- **Adaptive** in response to new findings
  - Dose adjustment to increase drug effect
  - Addition of novel biomarkers (e.g. tau PET imaging, neurofilament light chain (NfL))
  - Sensitive ADAD-specific cognitive composite endpoint
  - ADAD-specific statistical model

Through public/private support and partnership, the DIAN-TU has launched trials to provide advancement of treatments, scientific understanding and improvements in the approach to Alzheimer's disease drug developments.

Alzheimer's Association

DIAN-TU Pharma Consortium

Current Members

Biogen
Eisai
Eli Lilly & Co./Avid Radiopharmaceuticals
Janssen
Hoffman La-Roche/Genentech
United Neuroscience

National Institute on Aging
National Institutes of Health
U01 AG042791, R01 AG046179, R01/R56 AG053267, R13 AG055232, U01 AG059798

***Financial support has also been provided by anonymous sources.**

GHR Foundation

Cogstate

Bracket

Accelerating Medicines Partnership / Foundation for the National Institutes of Health

DIAN
Dominantly Inherited
Alzheimer Network

Resources

Websites:

- DIAN & DIAN-TU: https://dian.wustl.edu/
- DIAN Expanded Registry: https://dian.wustl.edu/our-research/registry/

Contact Information:

- DIAN EXR email: dianexr@wustl.edu
- DIAN EXR Coordinator: **844-DIAN-EXR (844-342-6397)**
- DIAN Observational Deputy Director **314-747-1940**

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  - Dave Balota PhD

Alumni of ABL

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- Mario Ortega PhD
- Matt Brier MD, PhD
- Laurie Baker PhD
- Patrick Wright PhD
- Anika Guha
- Jaimie Navid

- US Collaborators
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  - Serena Spudich MD- Yale
  - Tricia Burdo PhD- Temple
  - Victor Valcour MD- UCSF
  - Jaroslaw Harezlak PhD- Indiana
  - David Hass PhD- Vanderbilt
  - Turner Overton MD- UAB
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  - Marie Brouillette MD- McGill
  - Dan Stein MD- Capetown, South Africa
  - John Joska MD- Capetown, South Africa
  - Damien Ferguson MD- University of Dublin, Ireland
  - Edwina Wright MD- Monash University, Australia
  - Bruce Brew MD- St. Vincent Hospital, Australia

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- NINR
- Bright Focus
- Riney Family
- Brennan Family

Thank you for your attention

Ances Bioimaging Laboratory (ABL)
at Washington University in St. Louis

http://neuro.wustl.edu/labs/ances_b

Please contact with questions or if interested in collaborations:

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Improving Our Understanding of Alzheimer's Disease Heterogeneity: LEADS neuroimaging component

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Barbara and Peer Baekgaard Professor of Alzheimer's Disease Research
Clinical Core Leader, Indiana Alzheimer's Disease Center
Department of Neurology
Indiana University School of Medicine

Funding Sources

- R56/U01 AG057195
- R01 AG057739
- R01 AG040770
- K02 AG048240
- P30 AG010133

Case 1: FORGETFUL

- 75 yo woman
- Progressive short-term memory loss - repeats herself
- Difficulty recalling names and word searching pauses
- Got lost a couple of times when driving but managed to get to her destination
- Has been forgetting to pay bills and paid one twice
- Buying duplicates
- Quieter in social situations

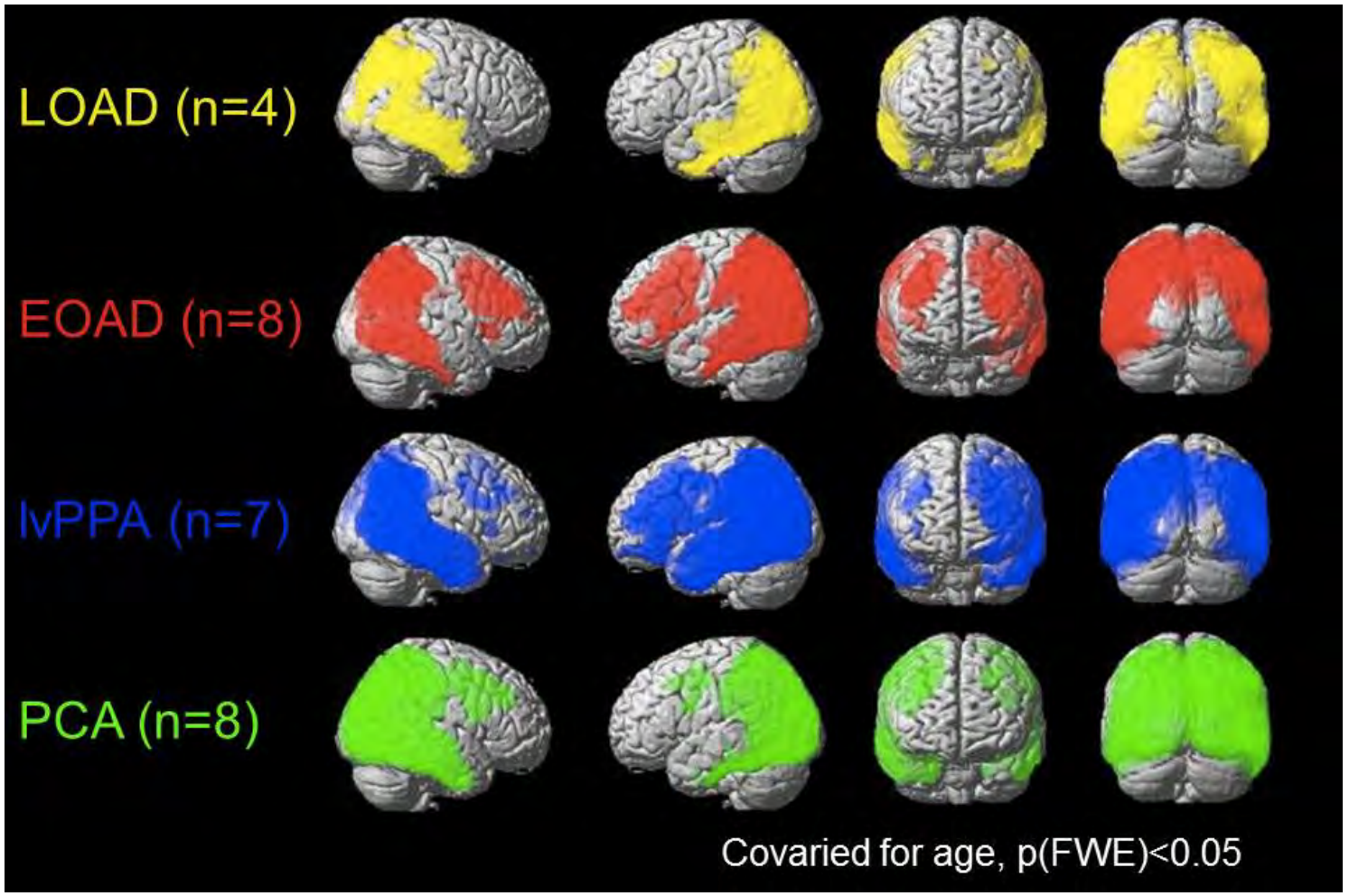
Case 2: "I Can't See"

- 59 yo woman
- **Many** ophthalmologic exams and prescription changes later – no better
- Husband came back from deployment to find notes with directions all over the house
- Trouble driving – veering off
- Difficulty finding items that are right in front of her
- Confuses left and right
- Problems writing and doing math
- Memory intact

Case 3: Tongue Tied

- 76 yo man
- Significant word finding issues
- Circumlocutions
- Empty speech with heavy use of filler words (“it”, “that thing”, “there”)
- Mispronouncing and misusing words
- Tonsils - “the things in my throat”
- Stethoscope - "you stick that in your ears and you plug it up against someone else”
- Difficulty repeating

Atrophy and Tau PET Patterns Correlate with AD Phenotype



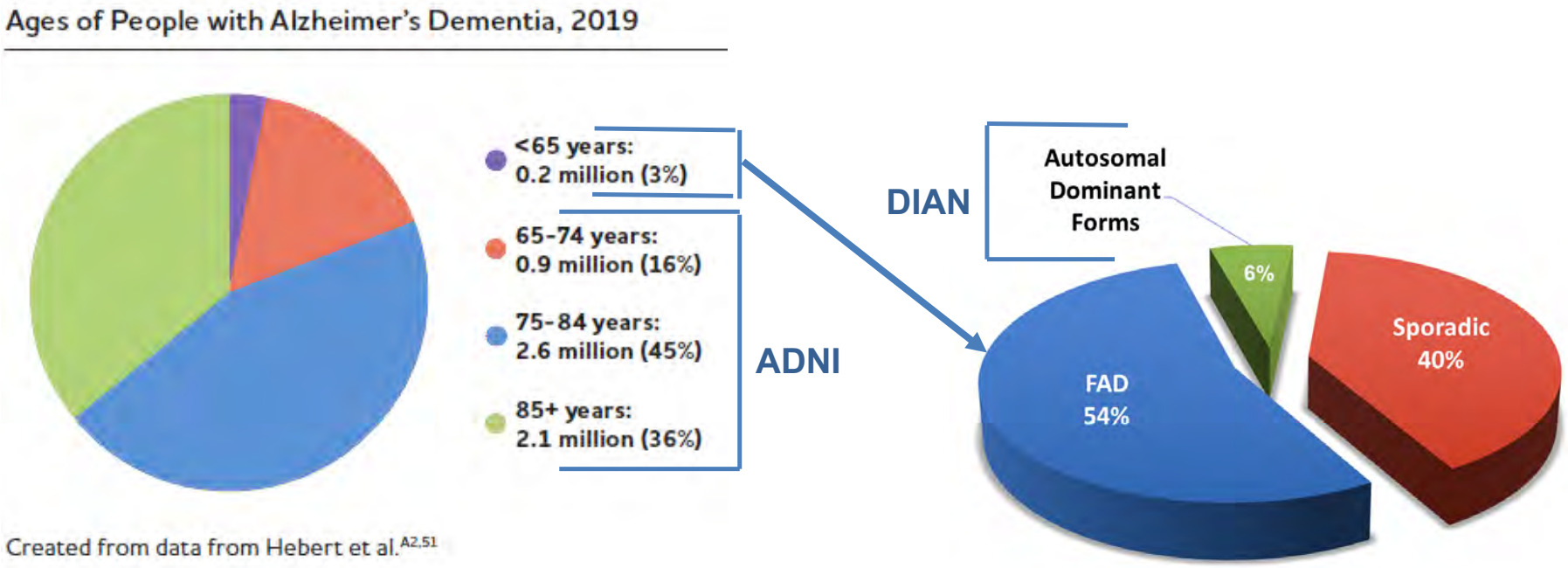
FORGETFUL

TONGUE TIED

I CAN'T SEE

Ossenkoppele et al., Brain 2016

Major AD Initiatives in the US



Demographics and Social Impact

- Approximately 3-5% of the 5.6 million Americans with AD (200,000-300,000)
- The second most common early onset dementia – FTD, affects ~20,000-30,000 Americans Knopman and Roberts, 2011
- Devastating consequences for patients and their families
  - Still in the workforce, not ready to retire, primary bread winners for their families
  - Many are still raising children
  - Not eligible for Medicare
- Much more aggressive disease course

Fujimori 1998, Seltzer 1983, Koss 1996, Filey 1986, Ioring 1985, Jacobs 1994

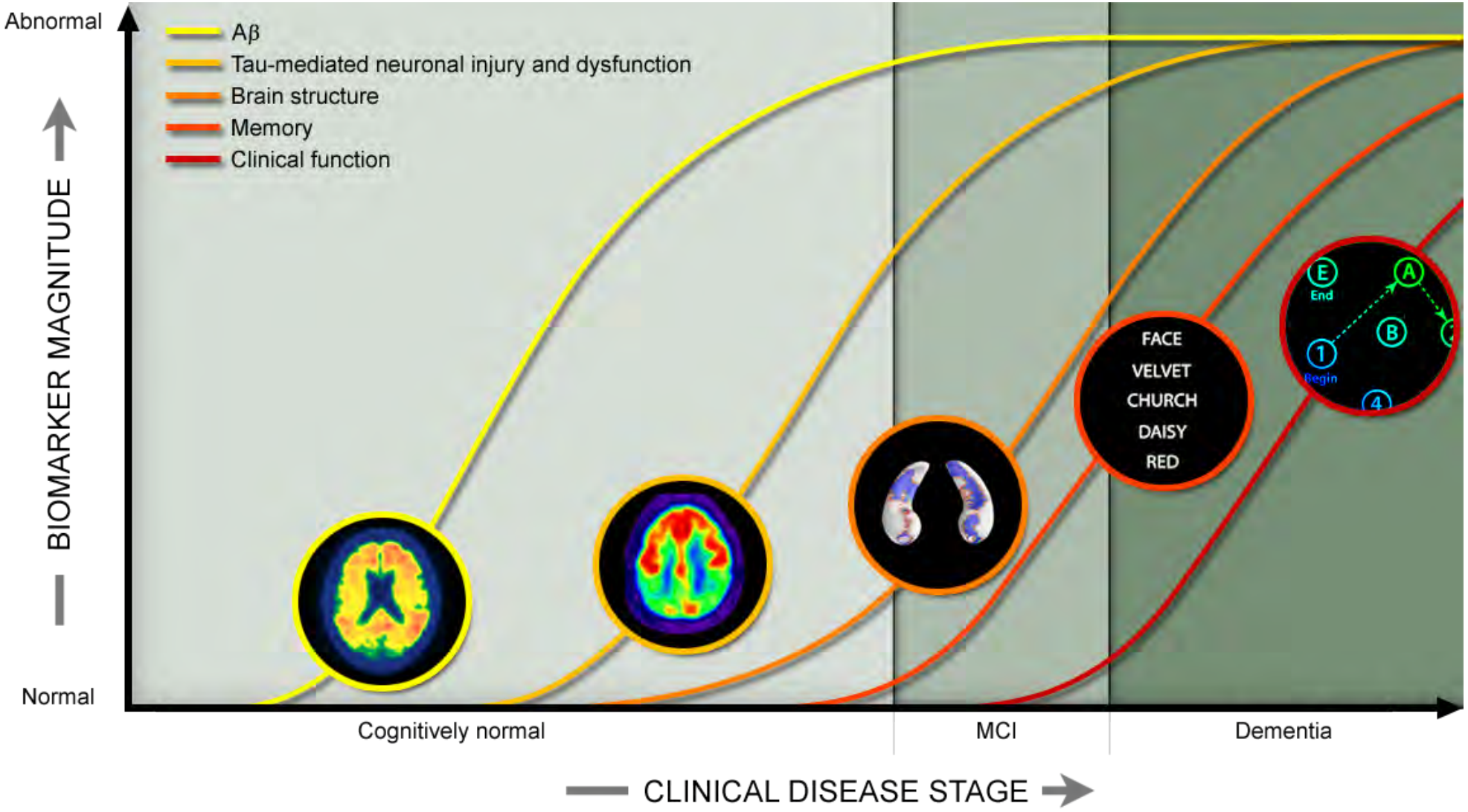
Diagnostic Challenges

- Atypical presentations are very common
  - 33-50% of EOAD present with memory decline as the initial symptom compared to 75-78% of LOAD

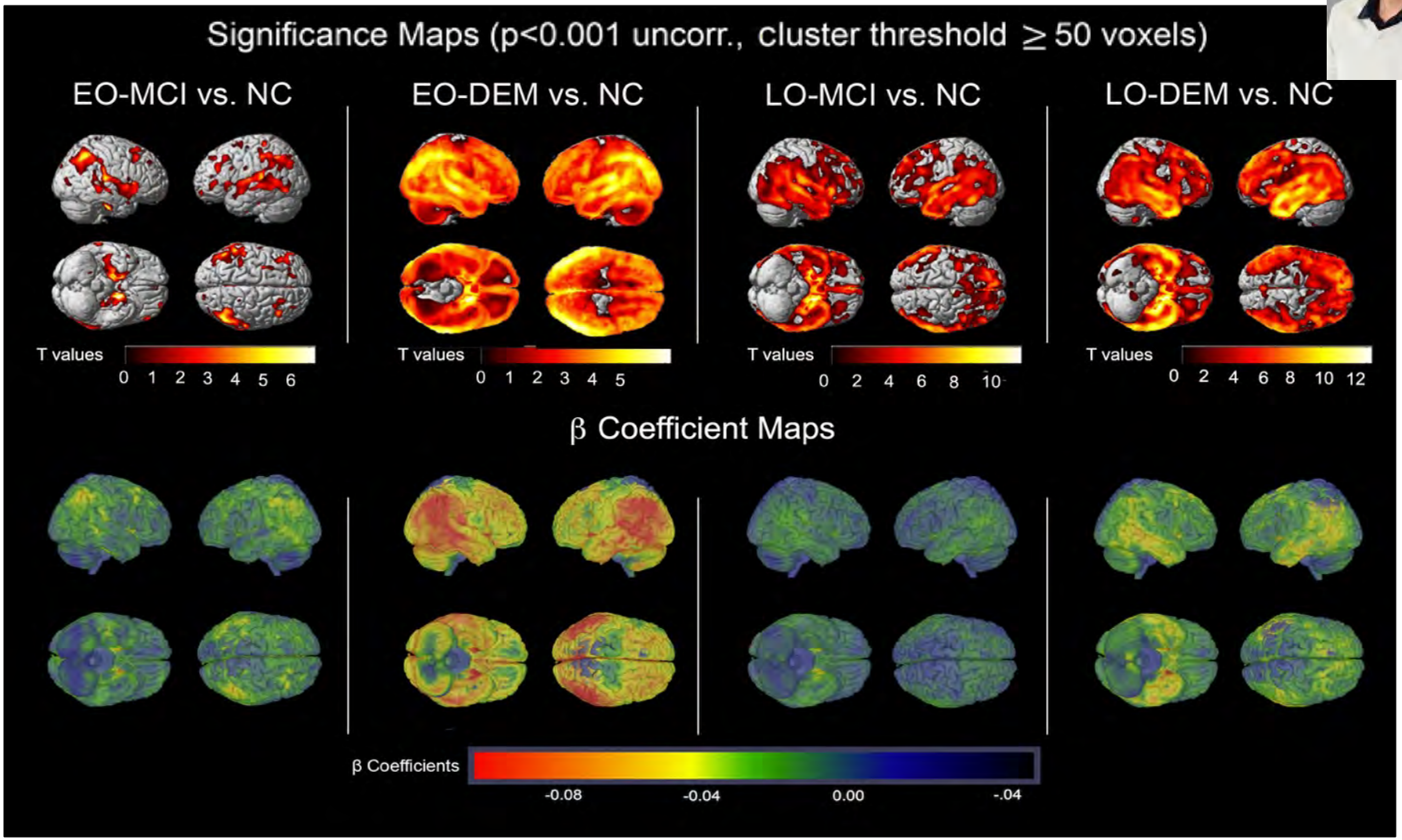
Mendez 2012; Jacobs1994; Koedam 2010

- Atypical variants are commonly misdiagnosed
  - Posterior cortical atrophy – vision problems, psychiatric, malingering
  - Logopenic aphasia – stroke, VaD, FTD
  - Frontal variant – FTD, TBI, psychiatric d/o

Biomarker Cascade in AD



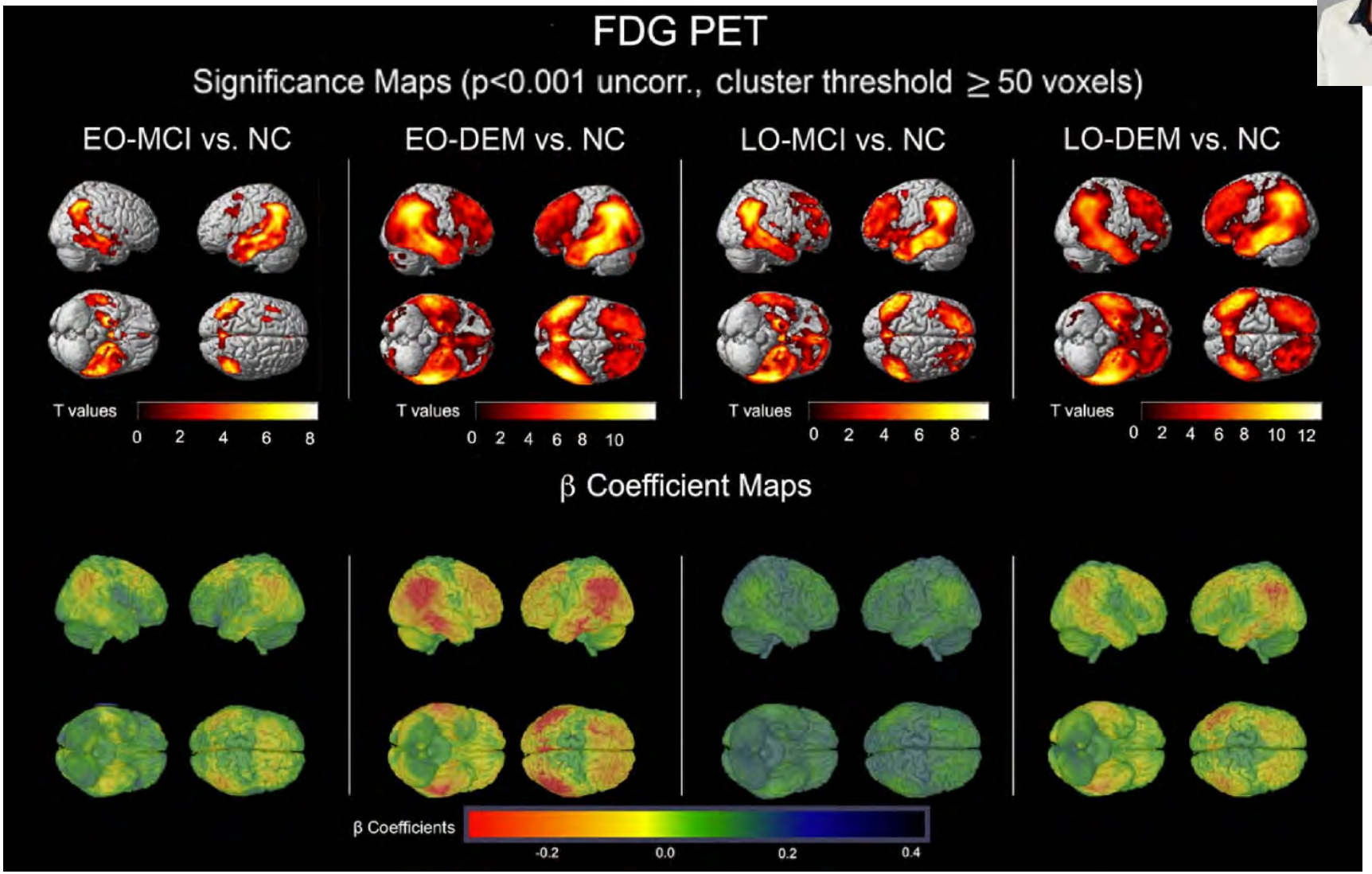
MRI



SCHOOL OF **MEDICINE**

Stage et al, submitted

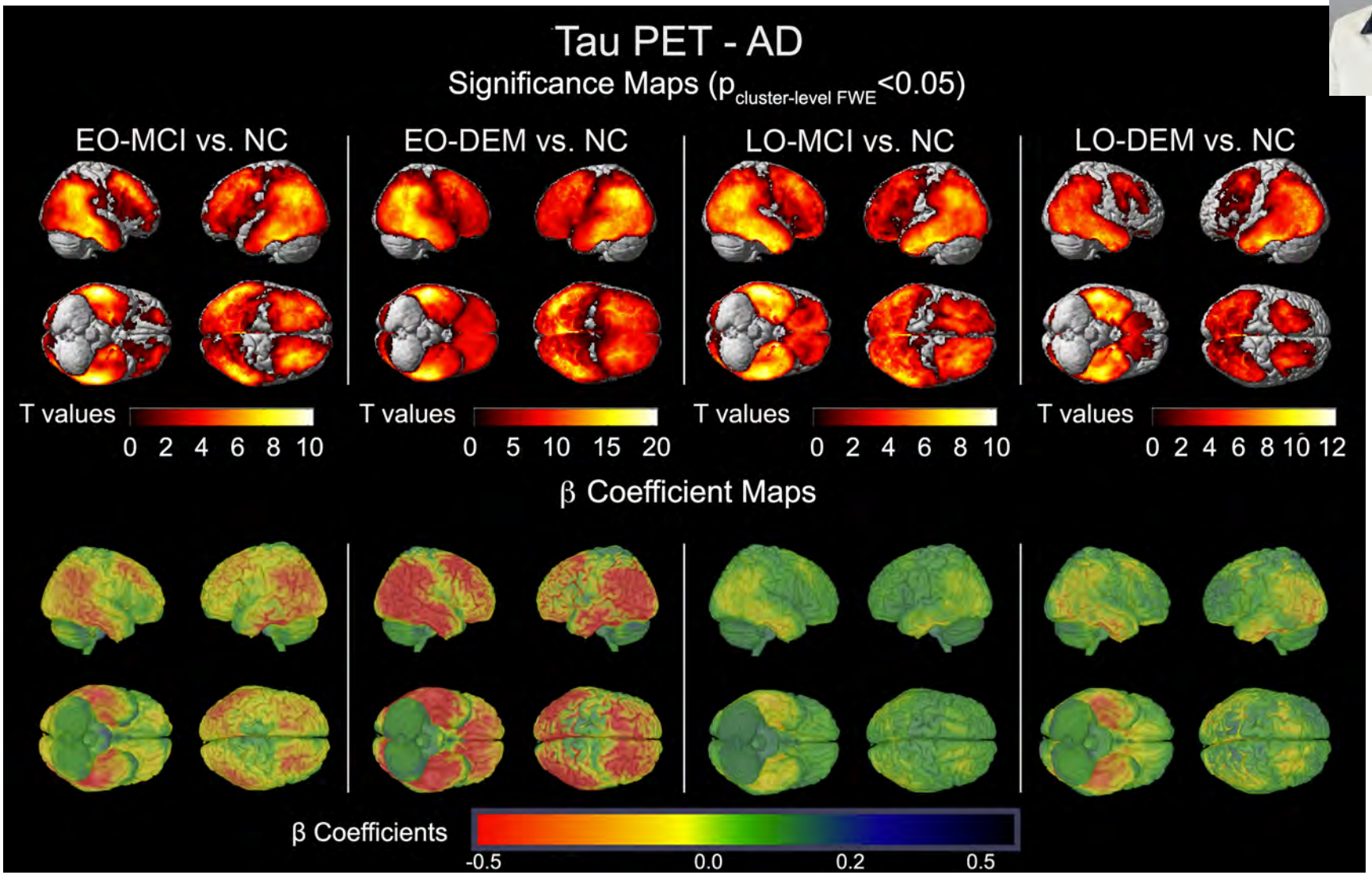
FDG PET



SCHOOL OF **MEDICINE**

Stage et al, submitted

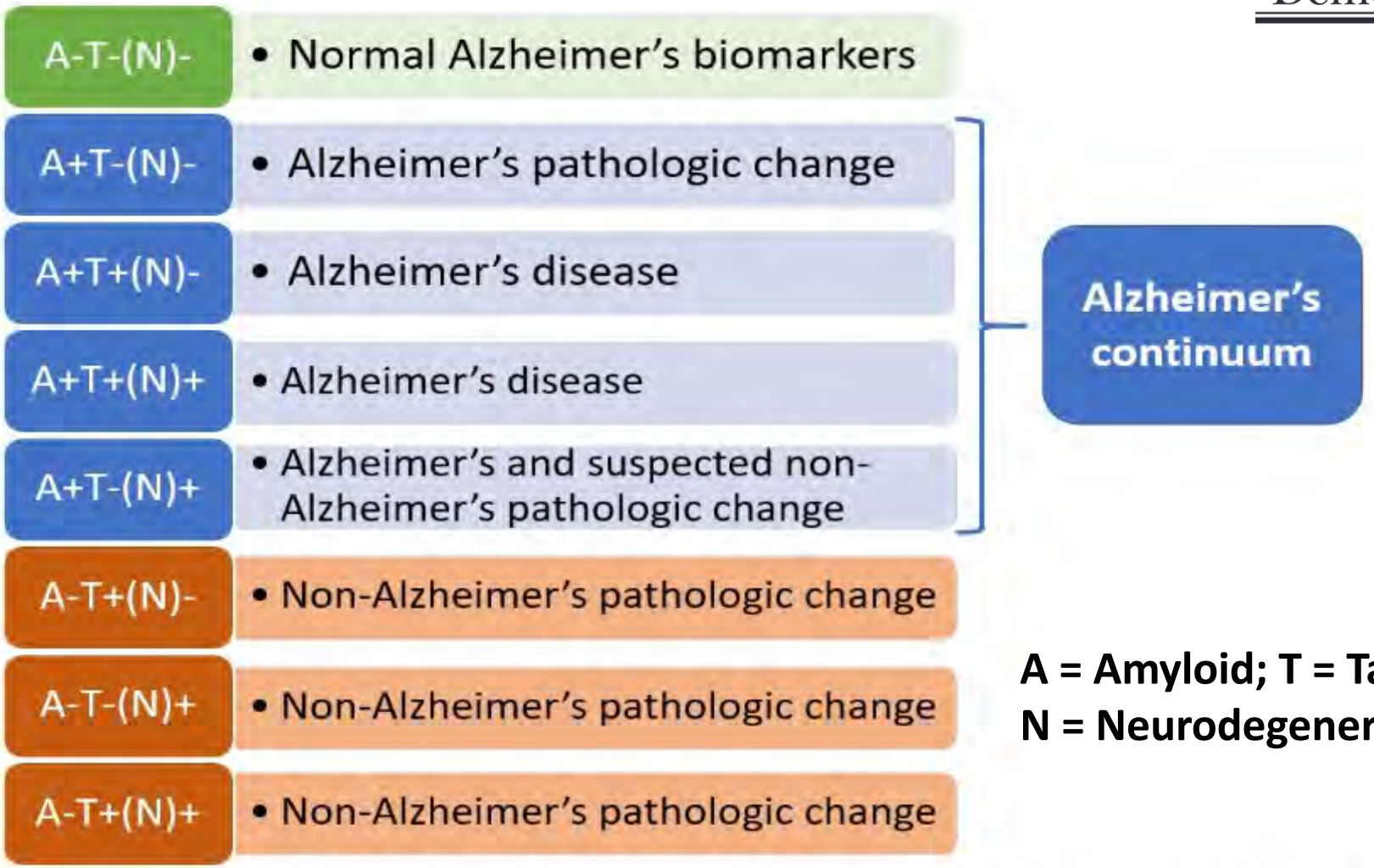
Tau PET



Stage et al, HAI 2019

2018 NIA-AA Research Framework

Alzheimer's & Dementia



A = Amyloid; T = Tau;
N = Neurodegeneration

Adapted from Jack et al., *Alzheimer's & Dementia* (2018) 14(4): 535-562.

LEADS

Longitudinal Early-Onset Alzheimer's Disease Study

R56 / U01 AG057195

PI Team:

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Gil Rabinovici

Brad Dickerson

Maria Carrillo

UCSF Weill Institute for Neurosciences
Memory and Aging Center

MGH 1811

alzheimer's association

NACC

Keck School of Medicine of USC
Alzheimer's Therapeutic Research Institute

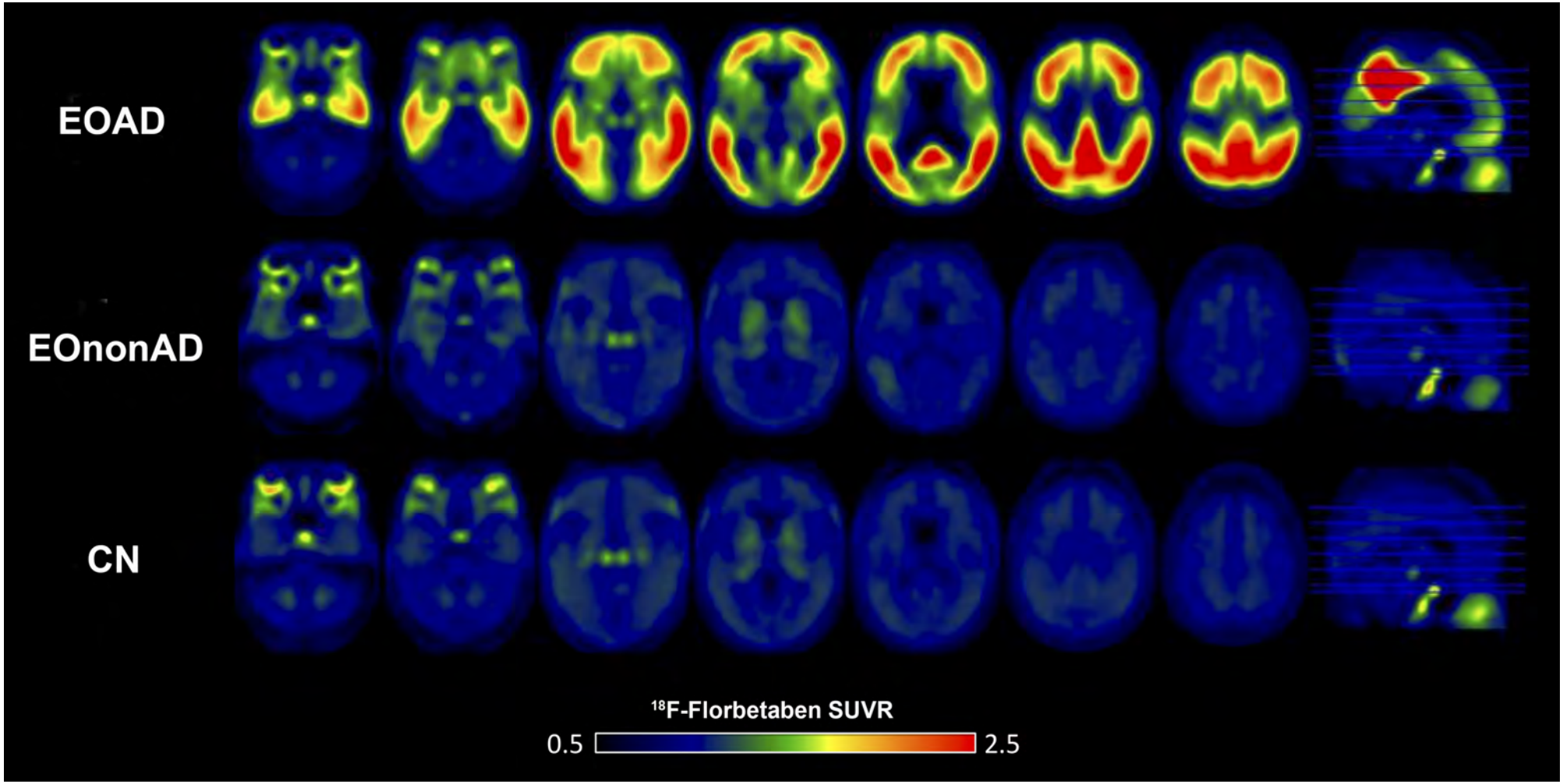
Recruitment

- 20 US academic institutions
- 15 sites across the US
- Recruitment goals:
  - 400 subjects meeting NIA-AA criteria for MCI due to AD or AD dementia ages 40-64 with global CDR≤1
    - Subjects meeting criteria for lvPPA, PCA or frontal variant AD will be allowed
    - Subjects with *APP*, *PSEN1*, *PSEN2* mutation will be excluded
  - 100 cognitively normal subjects ages 40-64
  - NEW: Will also follow amyloid-negative group - N=200

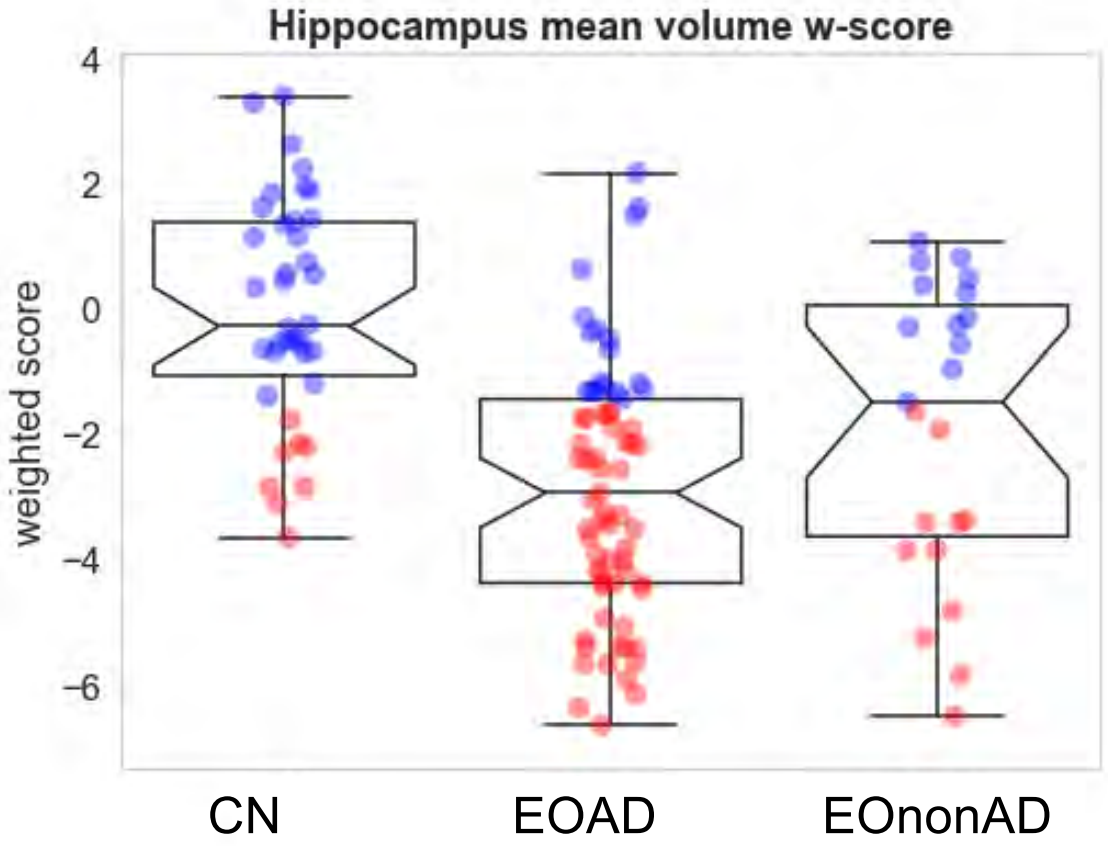
Demographics

	CN	EOAD	EAnonAD	EOADvsCN	EOnonADvsCN	EOAD vs. EOnonAD
N	47	77	23	-	-	-
Age	54.4 (6.0)	58.3(4.0)	58.0 (6.0)	**0.0016**	**0.022**	NS
Sex (M/F)	16/31	32/45	17/6	NS	**0.0039**	**0.013**
Education, yrs.	16.9 (2.4)	15.6(2.6)	15.6(2.5)	**0.048**	**0.043**	NS
MMSE	29.3 (0.8)	21.9(4.9)	26.0(2.5)	**<0.001**	**<0.001**	**<0.001**

Amyloid PET – Mean SUVR

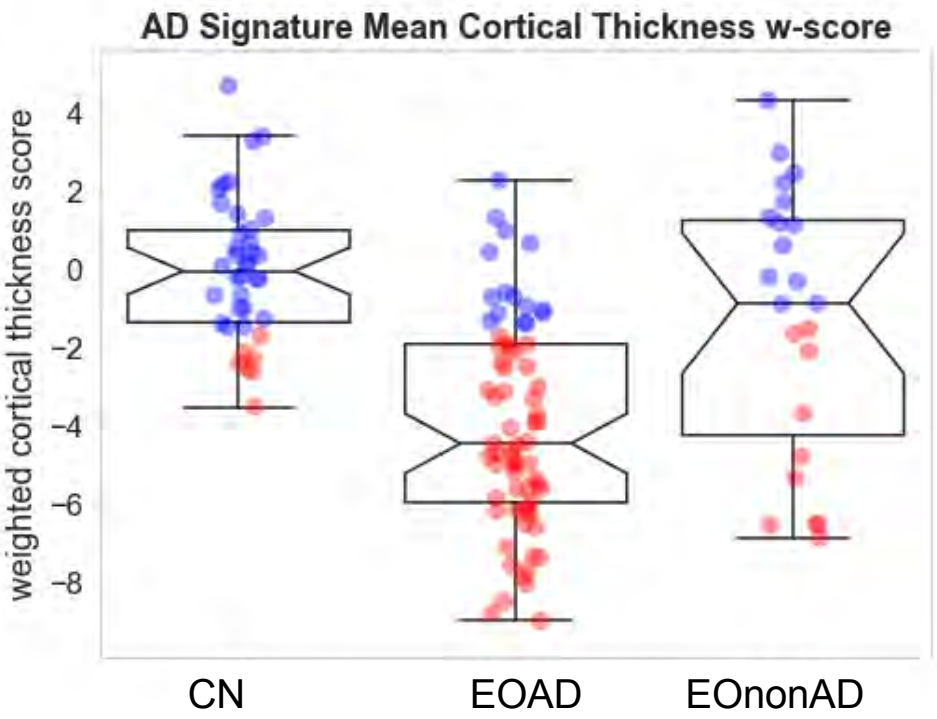


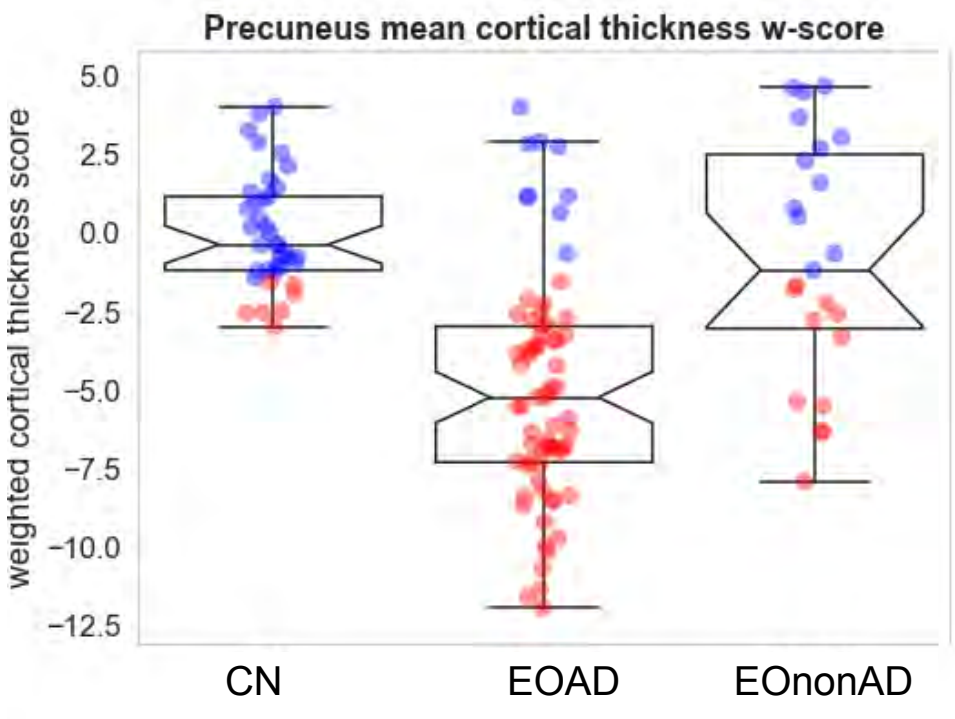
MRI Results - Hippocampus



% of subjects 1.5 SD below control mean: EOAD 74% EOnonAD 48%

MRI Results – Cortical Thickness

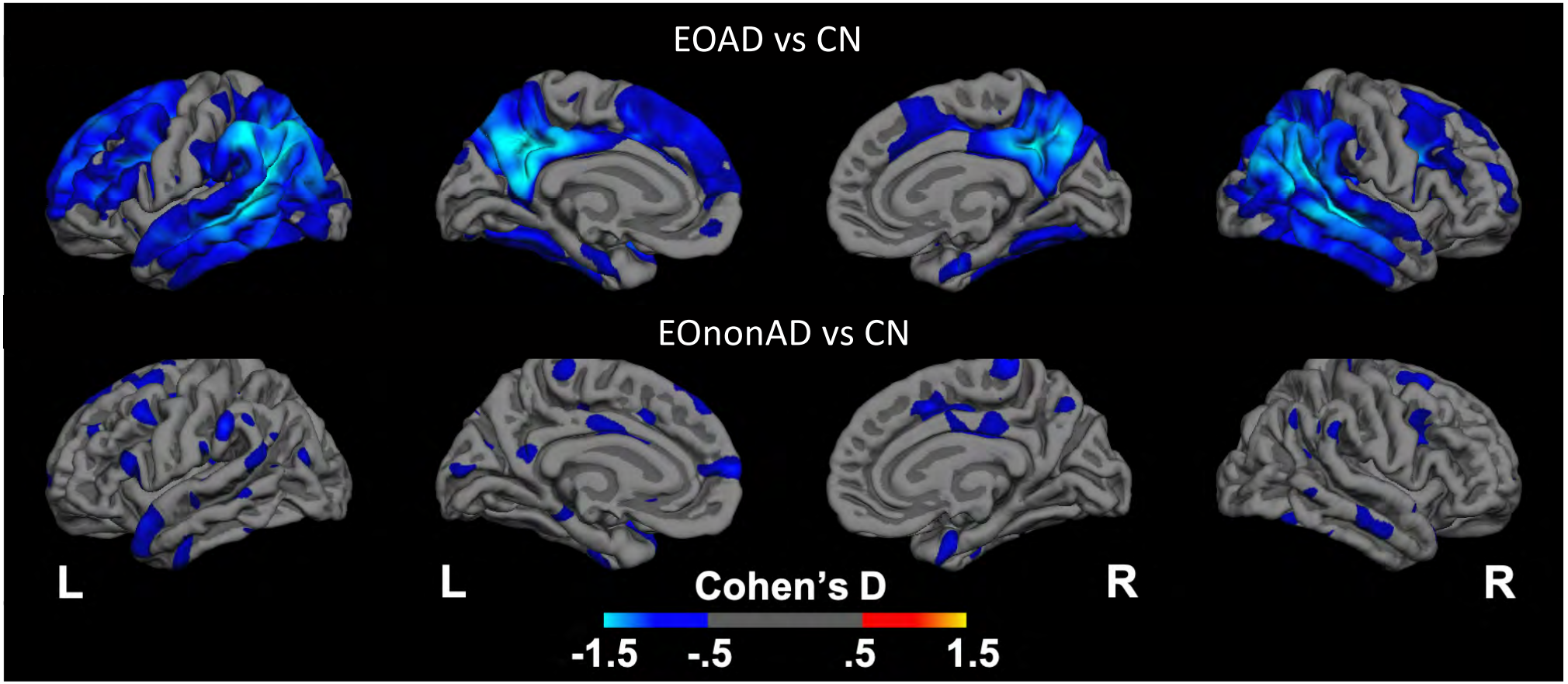




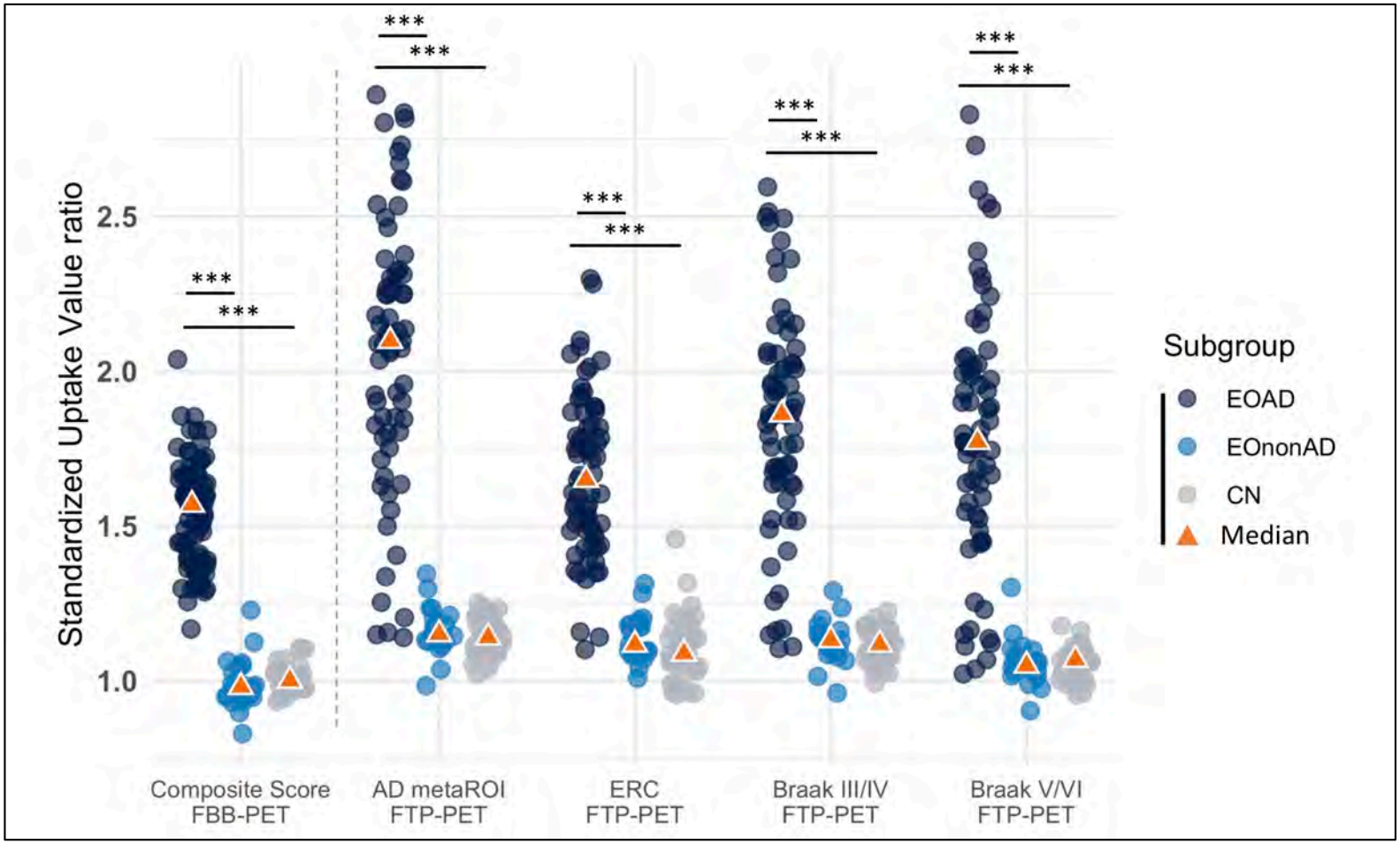
% of subjects 1.5 SD below control mean:

AD signature: EOAD 78% EOnonAD 43%
Precuneus: EOAD 87% EOnonAD 48%

MRI Results - Cortical Thickness

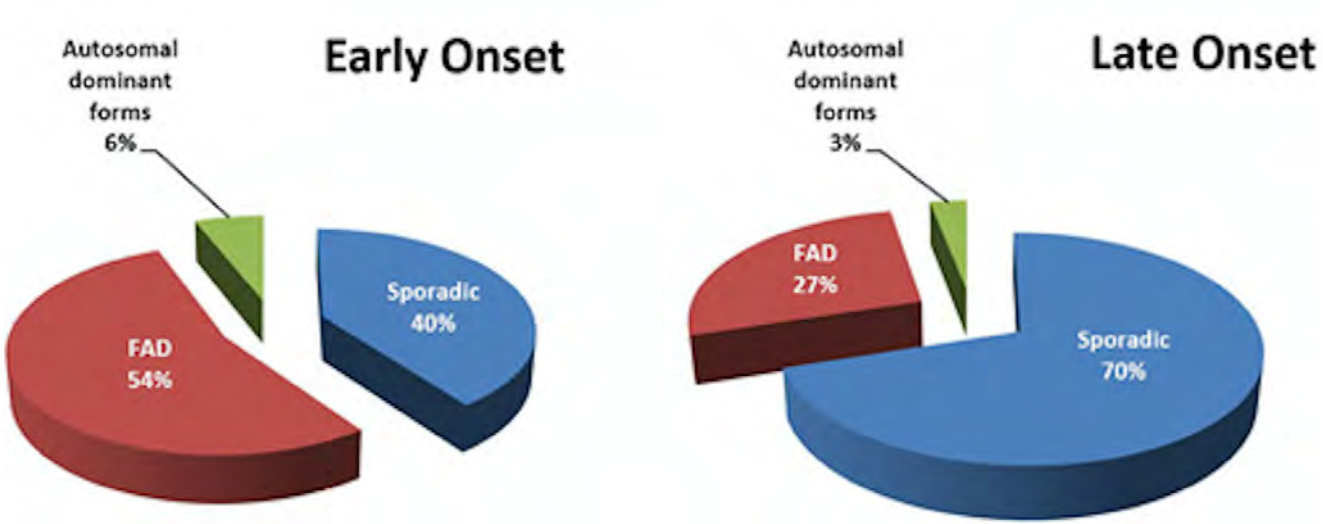


Tau PET Results



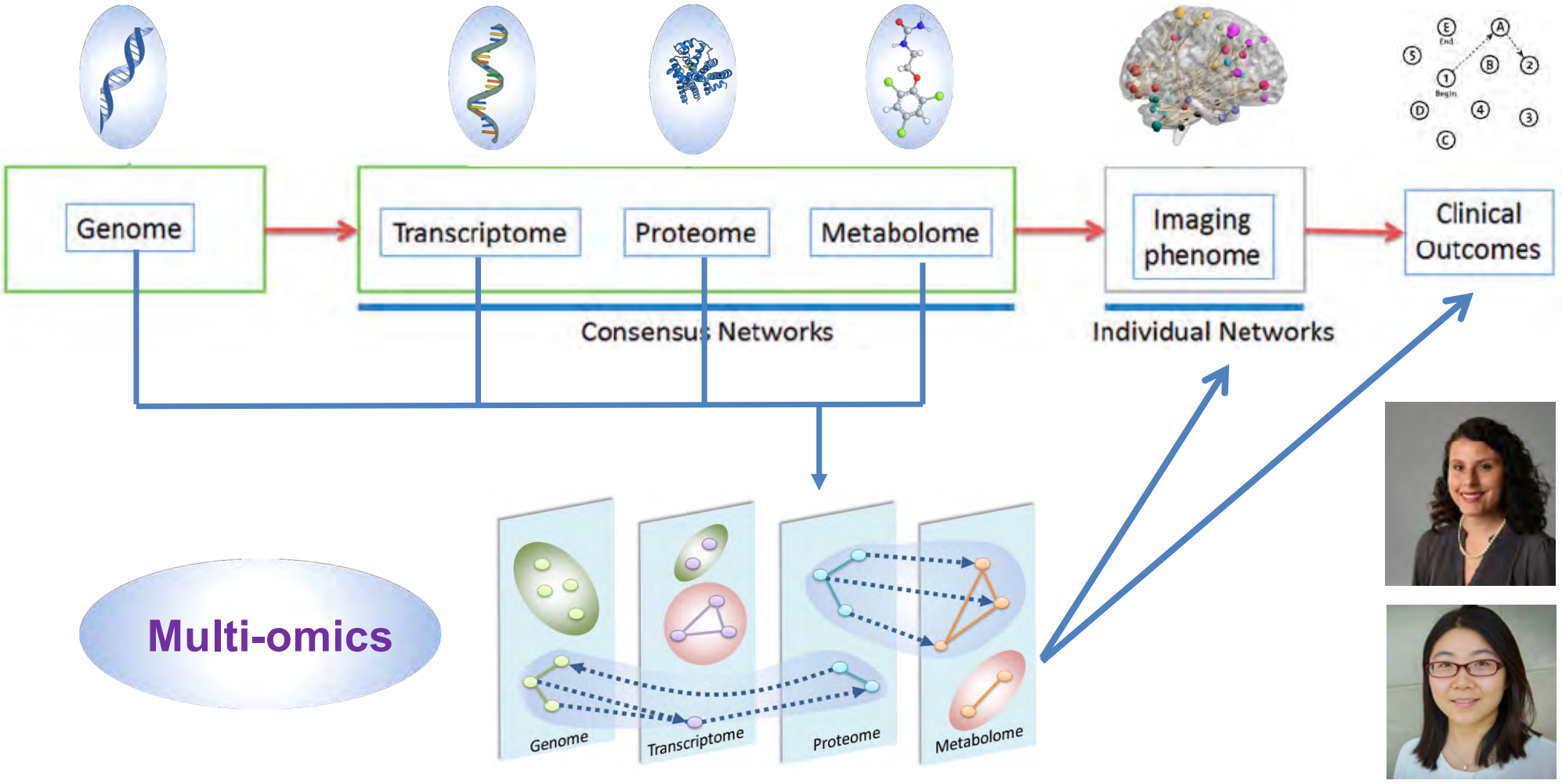
Genetic Heterogeneity in EOAD

- Common misconception: All EOAD cases are autosomal dominant



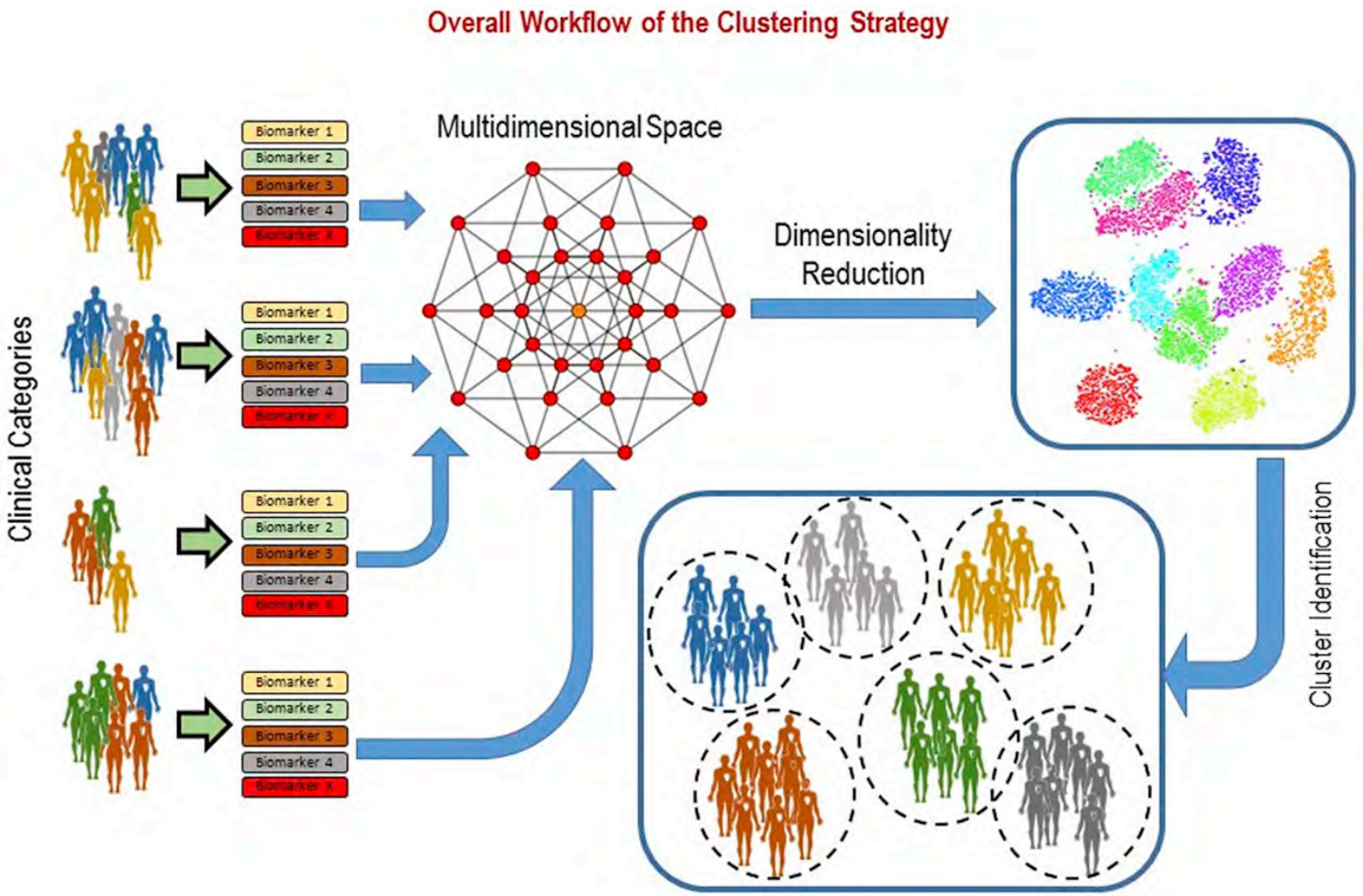
- Greater heritability in EOAD compared to LOAD suggests an enrichment for yet unknown genetic risk factors
  - 92%-100% heritability in EOAD vs. 70%-80% LOAD
  - fewer EOAD compared to LOAD carry *ApoE4*

Towards Precision Medicine



Adapted from Yan et al., Briefings in Bioinformatics, 2018

Towards Precision Medicine



Toshi et al, Neurobiol Aging, 2019

LEADS Study Investigators