Rethinking approaches to CSF and Imaging Biomarkers

Dr. Brian A Gordon, PhD

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Department of Radiology

Washington University in St. Louis
SCHOOL OF MEDICINE

What we say and what we mean

- “Levels of beta-amyloid do not predict cognition”
  - This is clearly wrong
  - Literature indicates Aβ predicts longitudinal risk

- “Markers of neurodegeneration better predict cognition”

- “Levels of neurodegeneration are better predictors of concurrent or short-term cognitive impairment, although levels of beta-amyloid are effective long-term predictors”

- Why do we get this wrong?

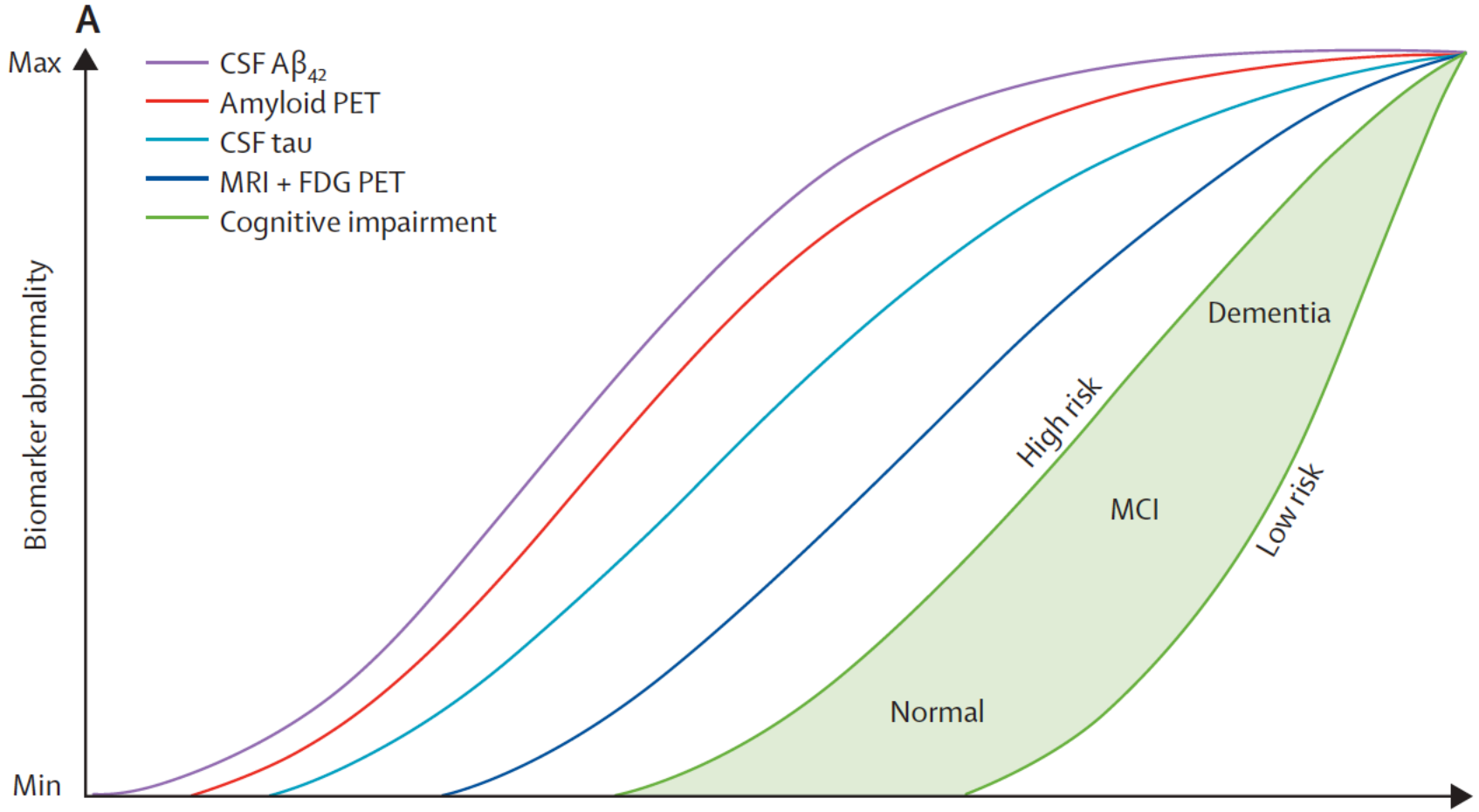
Staging Alzheimer Disease

- Greater call to incorporate biomarkers
  - NIA-AA Working Groups (Jack et al., 2011) and IWG-2 Criteria (Dubois et al., 2014)
- Two Classes of Biomarkers
  - Beta-Amyloid
    - Low CSF $A\beta_{42}$ and High PET Amyloid
  - Neurodegeneration
    - High CSF t-tau or p-tau_{181}, FDG hypometabolism, atrophy on MRI, and now elevations in PET tau
- Amyloid, tau, neurodegeneration/injury "A/T/N"
  - A: CSF $A\beta_{42}$ and PET amyloid
  - T: CSF p-tau_{181} PET tau
  - N: t-tau, hypometabolism, and atrophy
  - Describes pathology rather than disease labels
  - Independent of any one diagnostic scheme

Staging Alzheimer Disease

- We equate biomarkers into the same class
- Should the data we collect actually be related?
- Some potential assumptions:
  - Tests measure the same pathology
  - All markers are sensitive to AD
  - Biomarkers are selectively sensitive to AD
  - *There is a linear relationship with biomarkers*
  - *Measures change at the same point in the disease*
  - *Biomarker values reflects similar measurement properties*
- Validity of assumptions vary with:
  - Disease progression
  - Different pairings of biomarkers
  - Longitudinal vs. Cross-sectional data
  - Group vs. individual level relationships

Temporal Model of Alzheimer Pathology

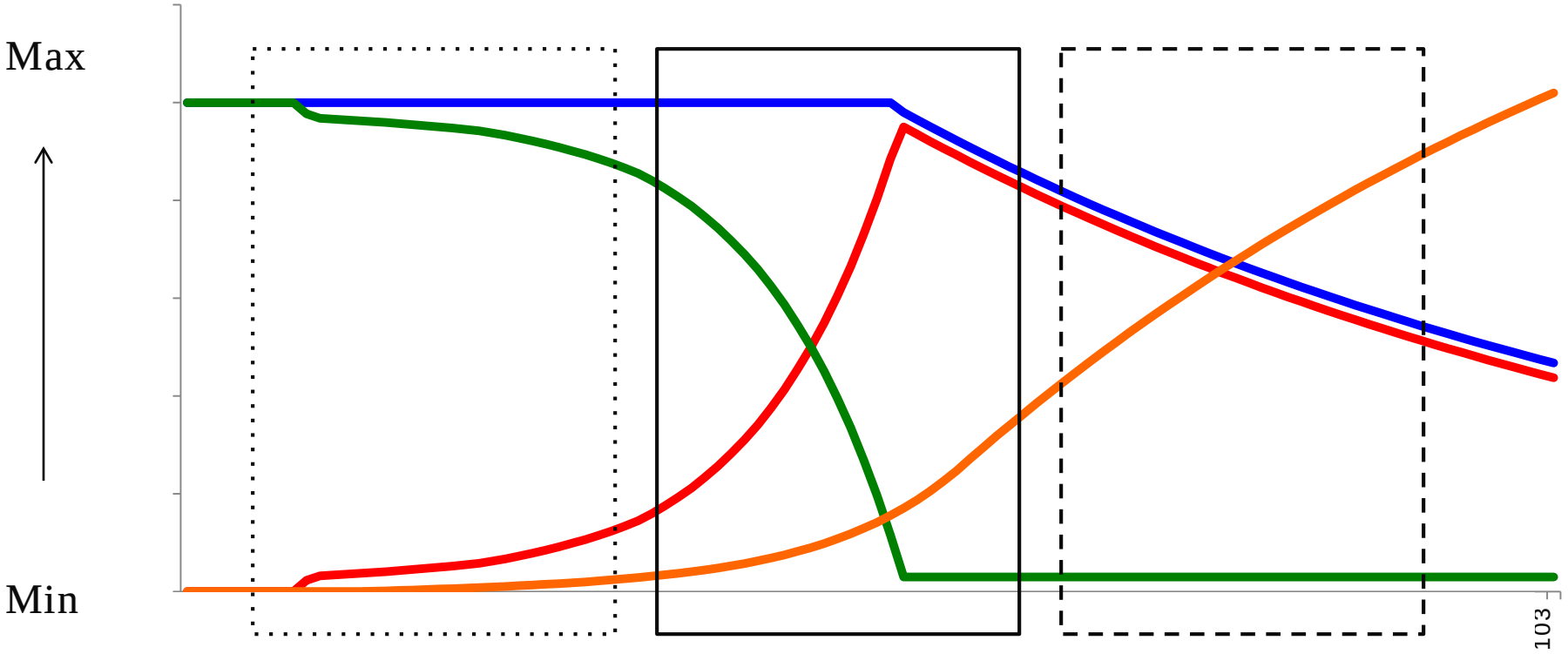


From (Jack et al., 2013)

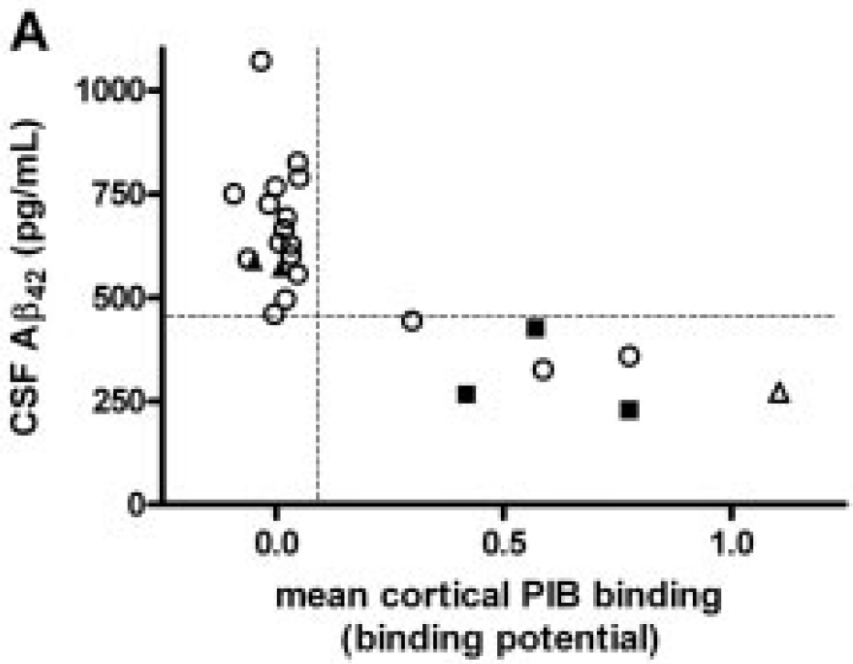
Consider Beta-Amyloid

- CSF $A\beta_{42}$ represents a snapshot of:
  - Amount of available Aβ (production and clearance)
    - Aβ is modulated by neuronal activity (Cirrito et al., 2005)
    - Could be altered over the course of the disease
  - $A\beta_{42}$ accumulation into plaques
    - Rate likely accelerates over time
    - May plateau and CSF measure may reach a floor
  - Represents *active* processes
- Longitudinal CSF $A\beta_{42}$ represents
  - Change in availability/deposition $A\beta_{42}$
  - An *active* change
- Cross-sectional PET represents
  - *Cumulative* measure of all prior plaque formation
- Longitudinal PET
  - Change in plaque deposition
  - An *active* change

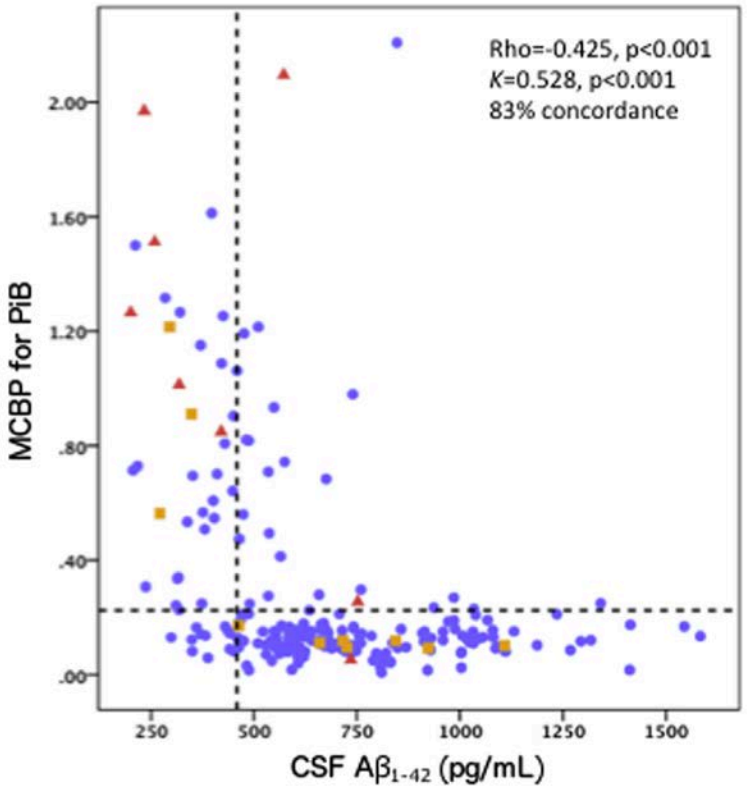
Evolution of Amyloid Pathology



Relationship Between CSF and PET Amyloid

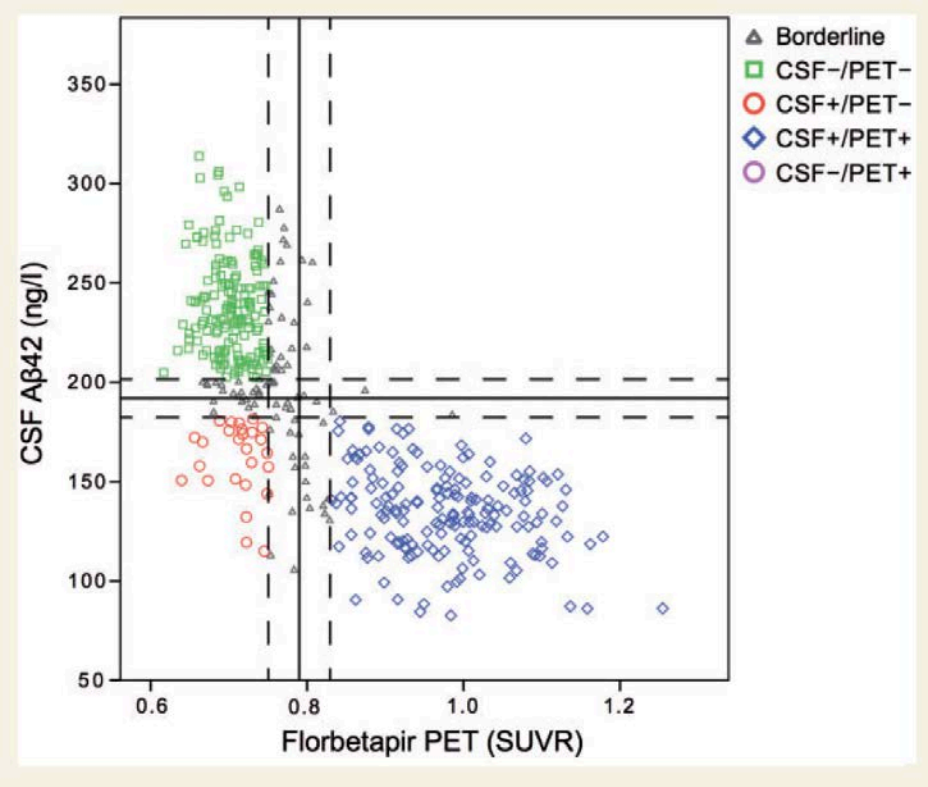


Fagan et al. 2006

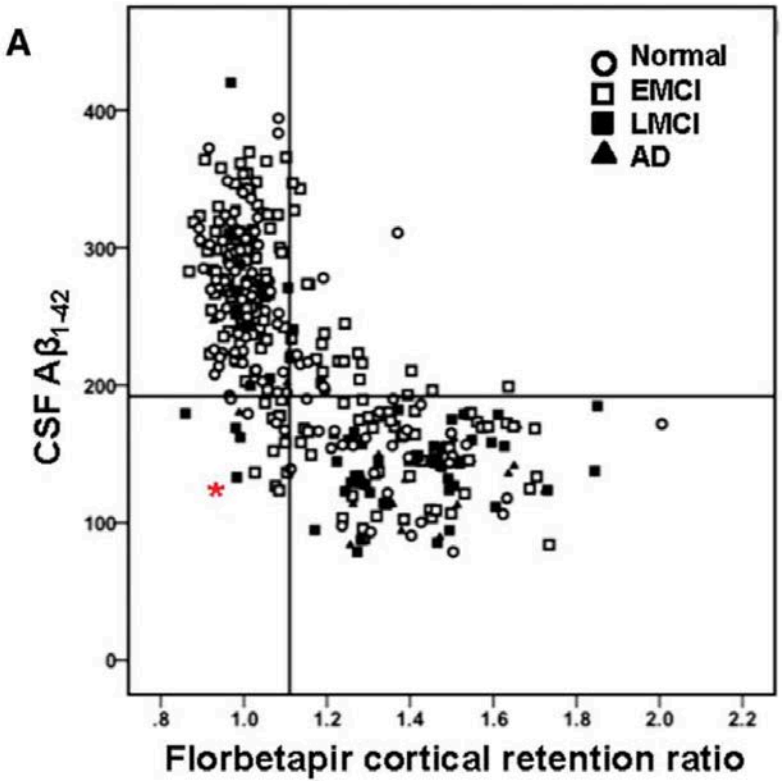


Vos et al. 2016

Relationship Between CSF and PET Amyloid

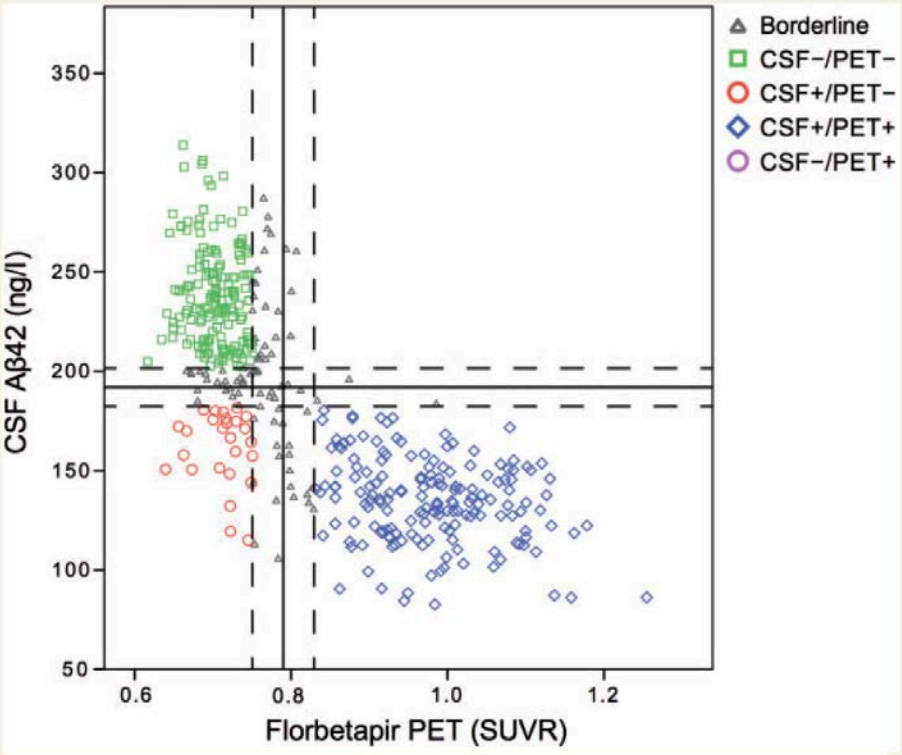


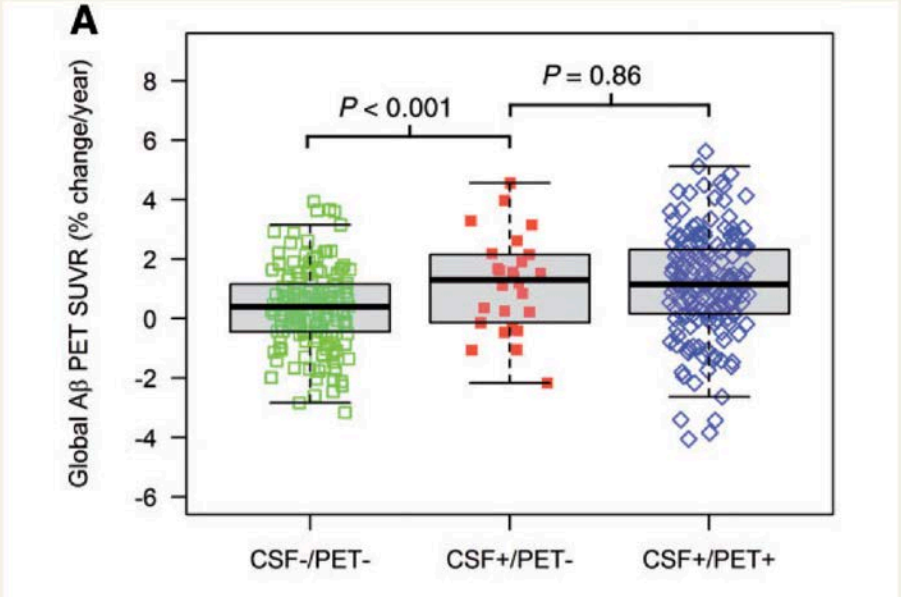
Palmqvist et al., 2016



Landau et al., 2013

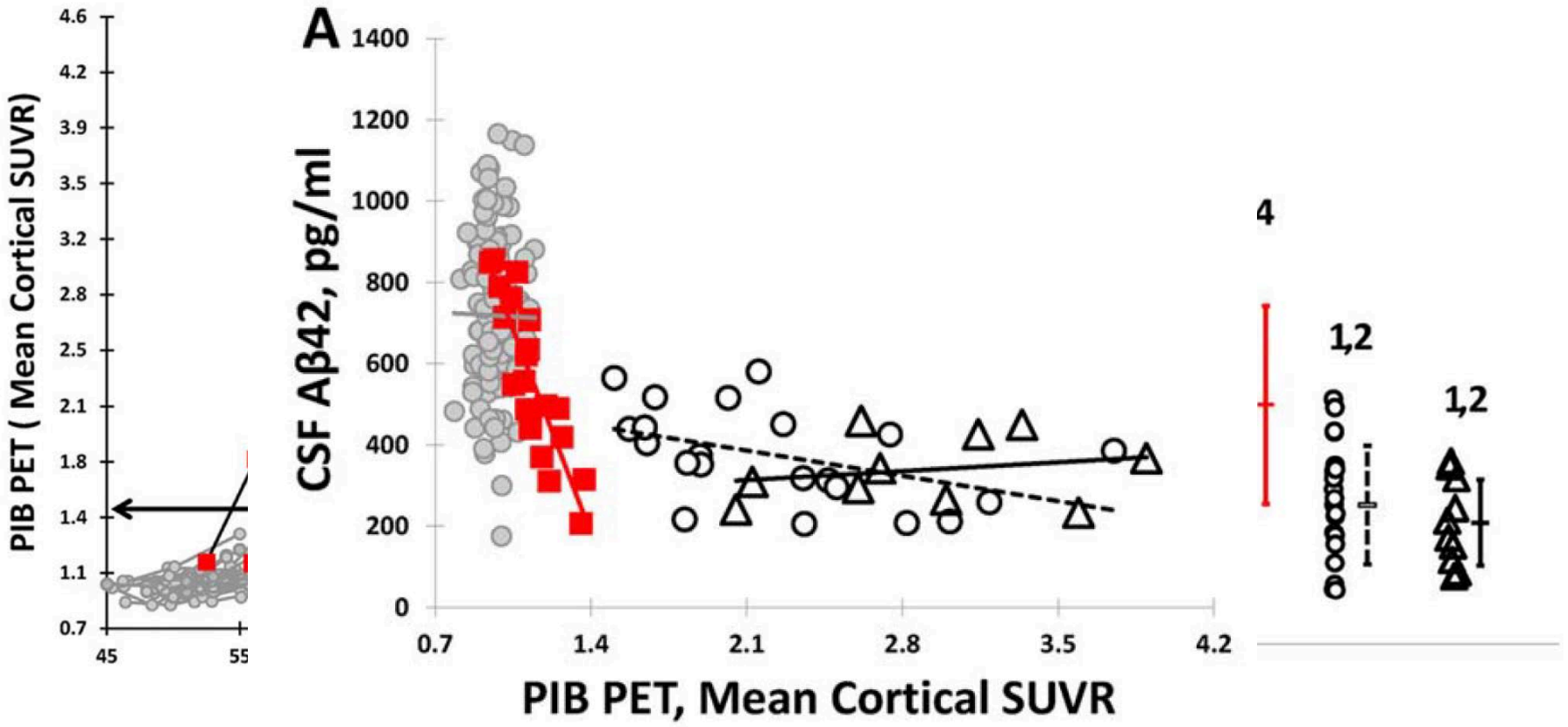
CSF $A\beta_{42}$ Changes Before PET Amyloid





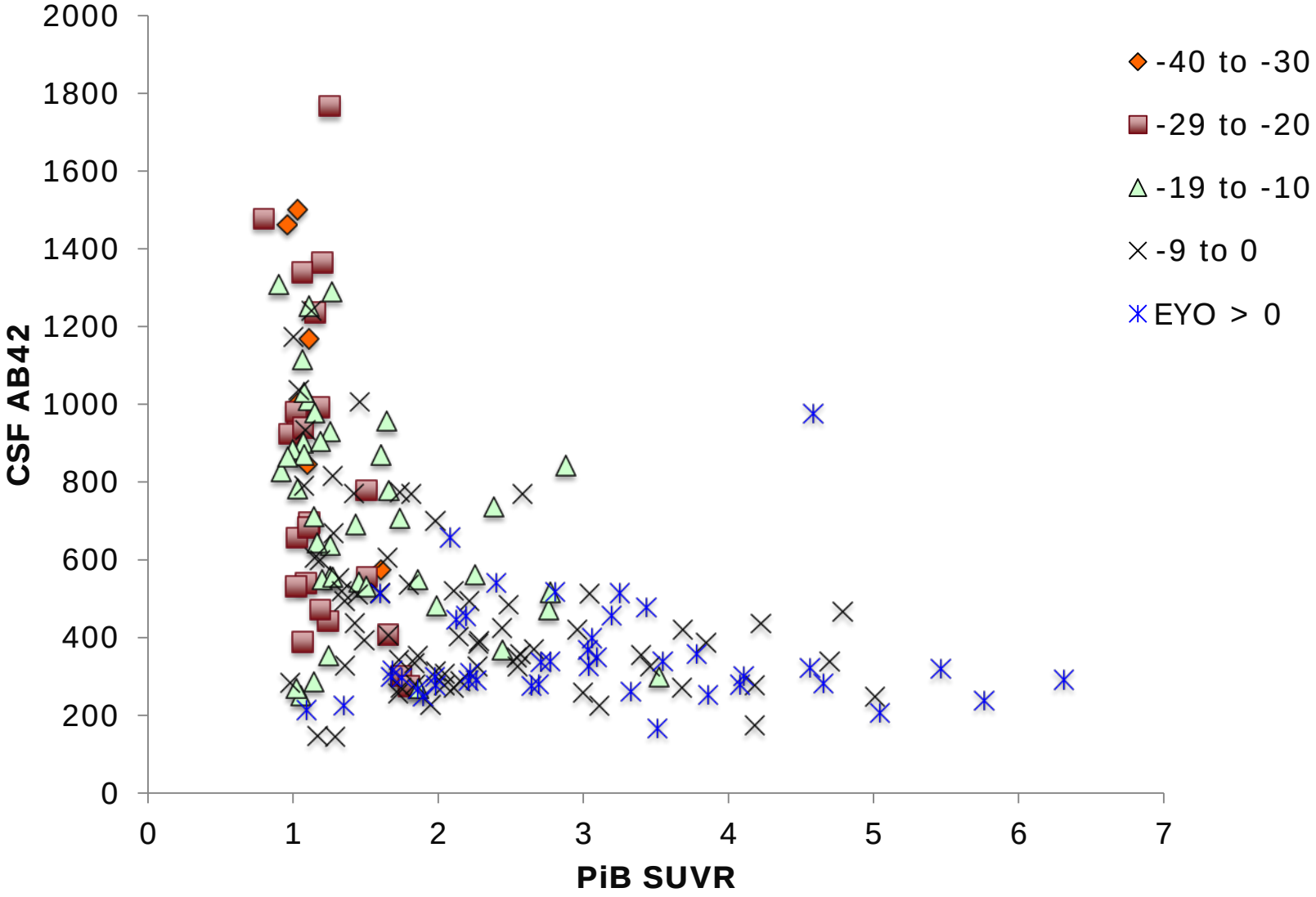
Palmqvist et al., 2016

CSF $A\beta_{42}$ Changes Before PET Amyloid

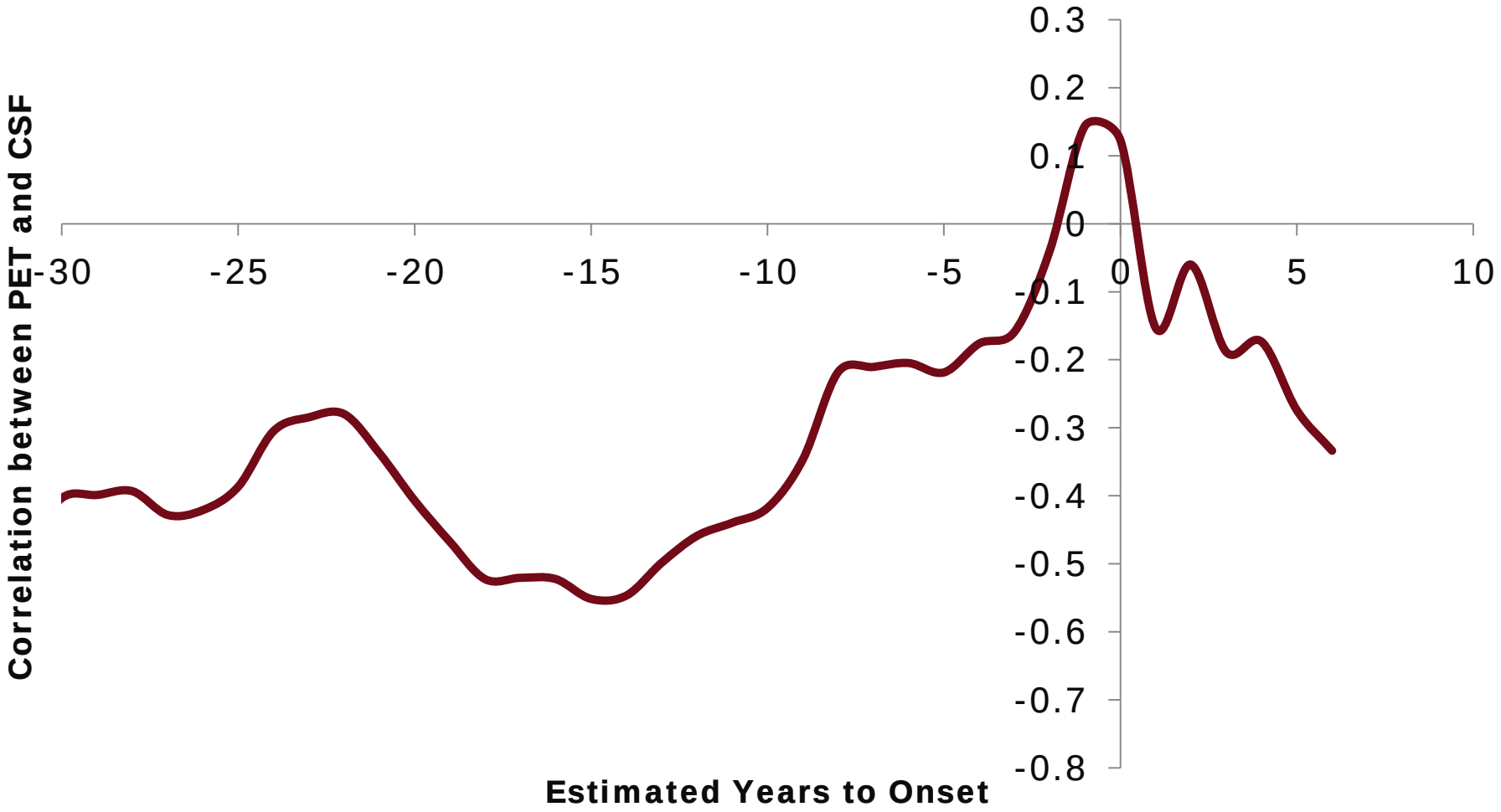


Vlassenko et al., 2016

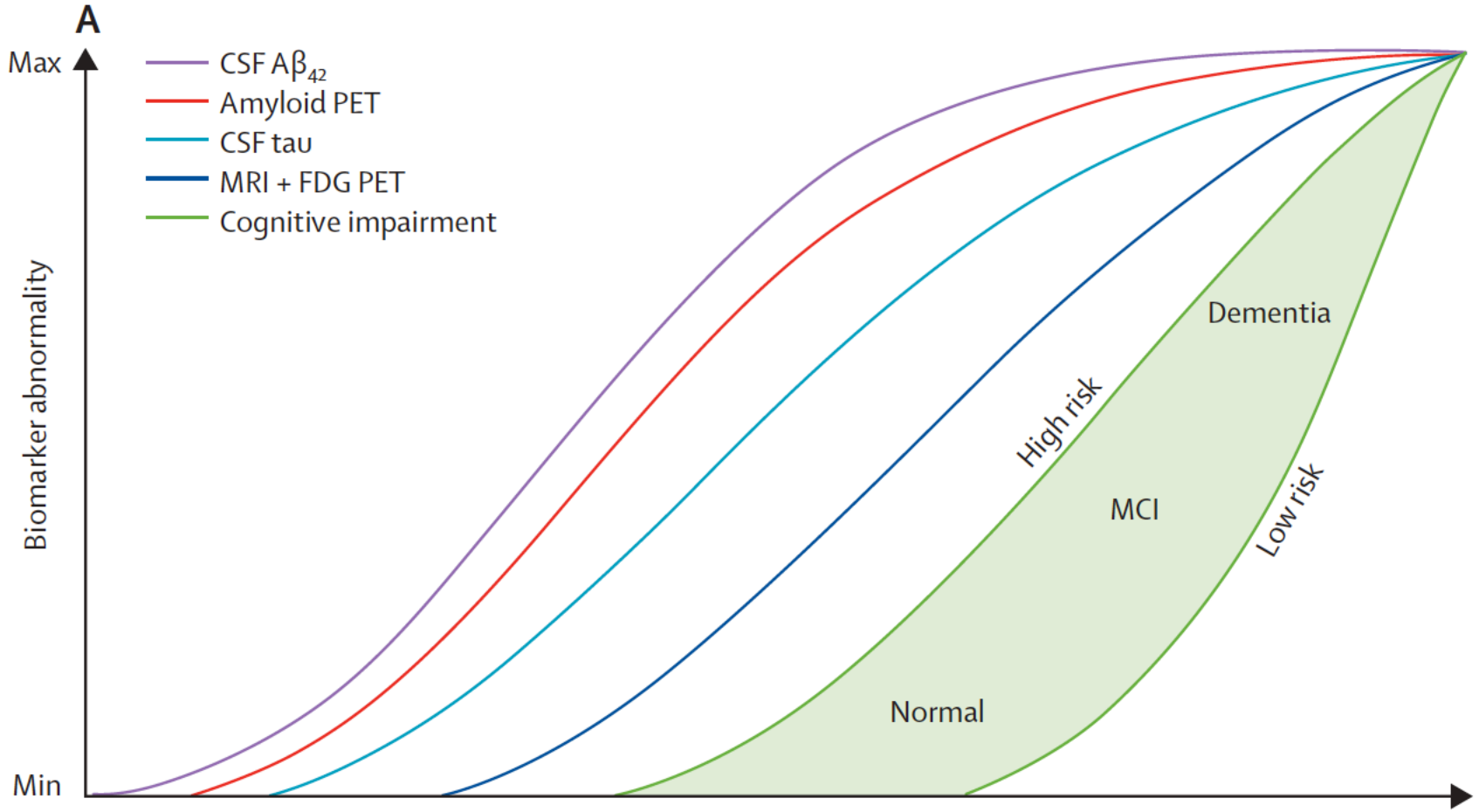
CSF and PET Relationship in ADAD



CSF and PiB Relationship in ADAD



Temporal Model of Neurodegeneration



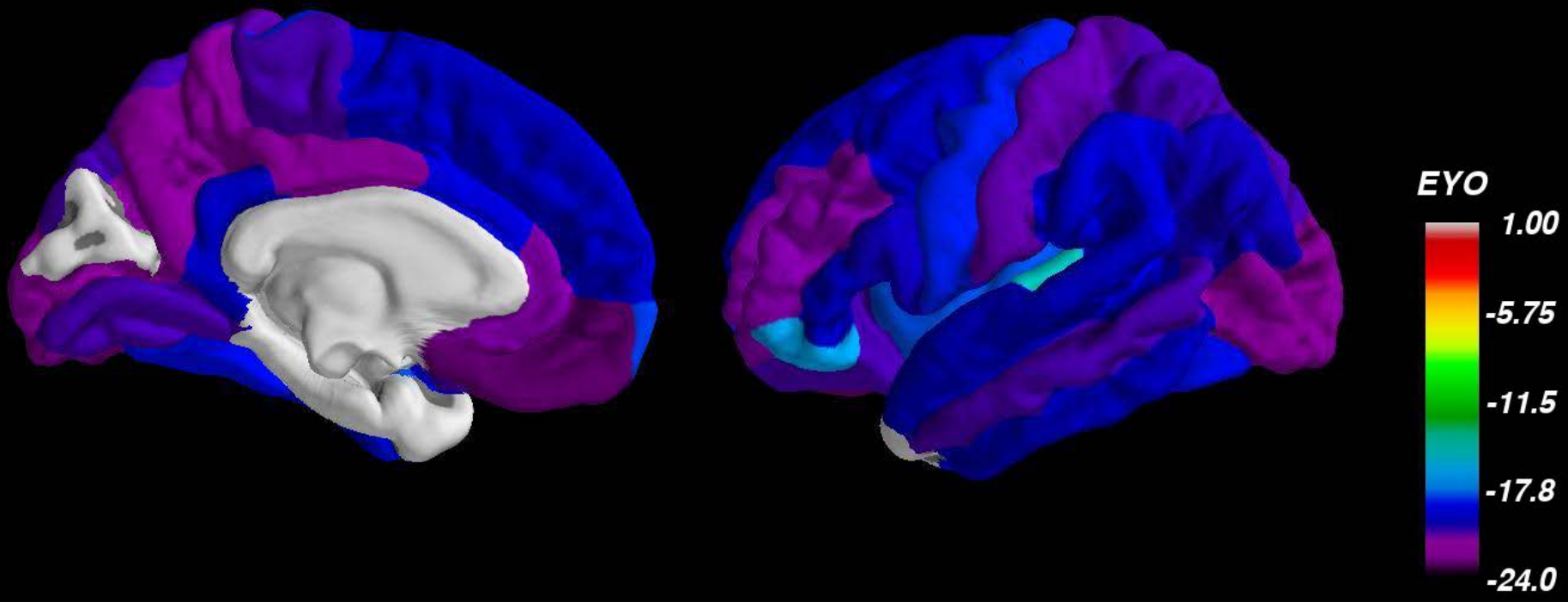
From (Jack et al., 2013)

Longitudinal Change in Imaging Biomarkers

- Using Linear Mixed Effects Models
- When do rates of change differ in carriers and non-carriers?
  - 134 Non-Carriers, 139 Asymptomatic Carriers, 85 symptomatic carriers
  - Any Data: 358 with MRI, 338 with FDG, 332 with PiB
  - Longitudinal: 218 with MRI, 179 with PiB, 192 with FDG

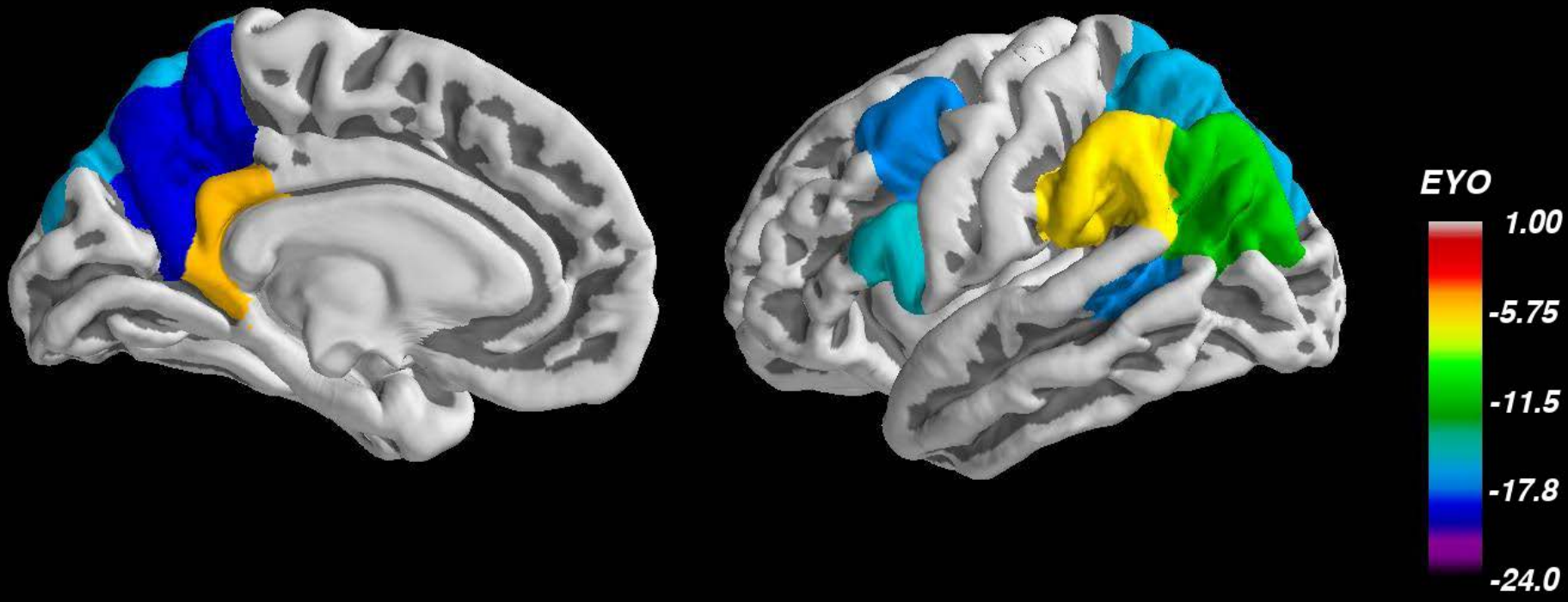
	T=1	T=2	T=3	T=4	T=5	T=6	N=
PIB	153	130	29	14	5	1	332
FDG	146	137	33	16	5	1	338
MRI	140	151	41	15	9	2	358

Earliest Detectable Change in Longitudinal PiB



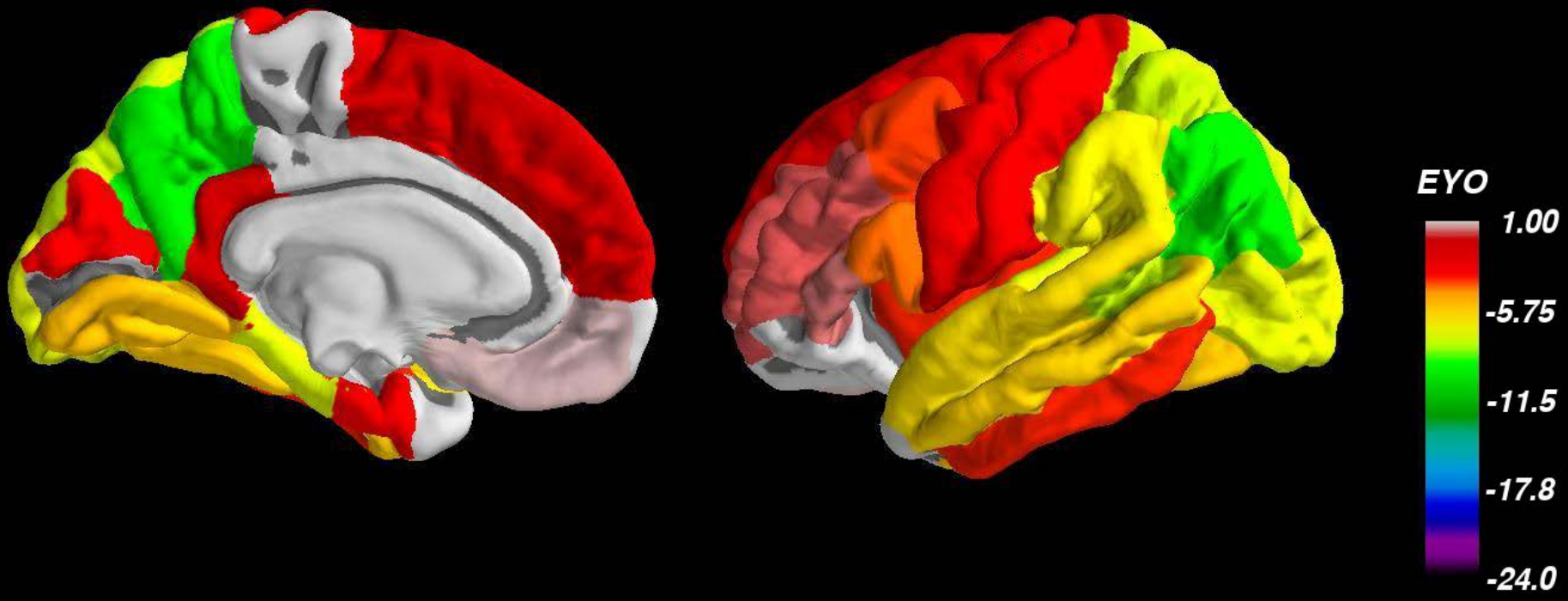
Gordon et al., in prep

Earliest Detectable Change in Longitudinal FDG



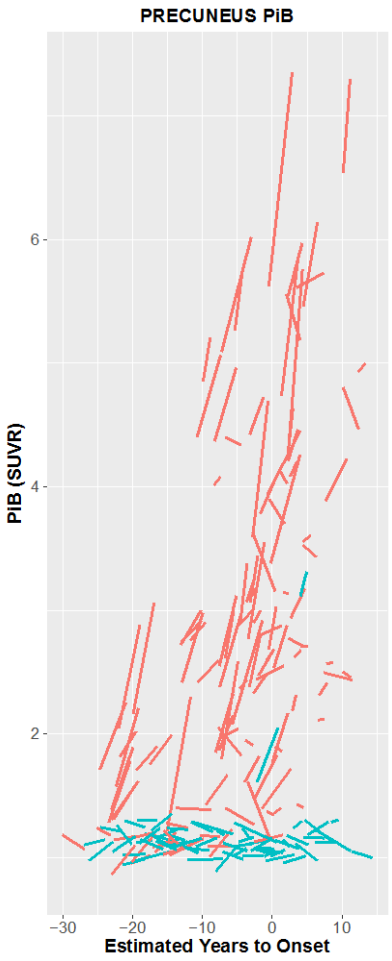
Gordon et al., in prep

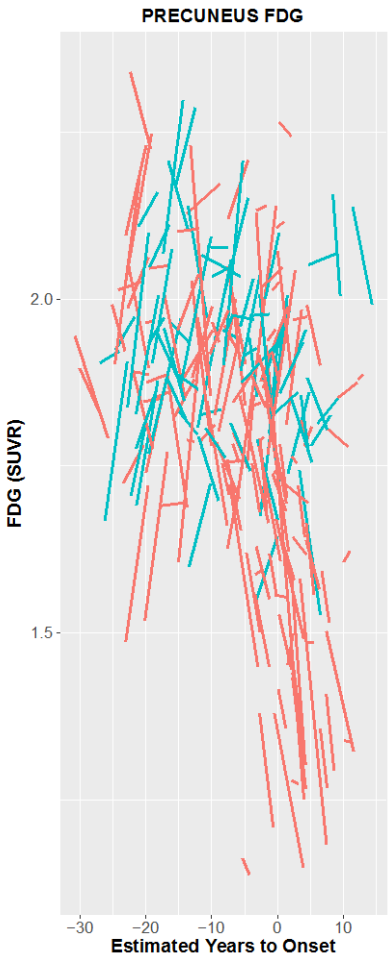
Earliest Detectable Change in Longitudinal Thickness

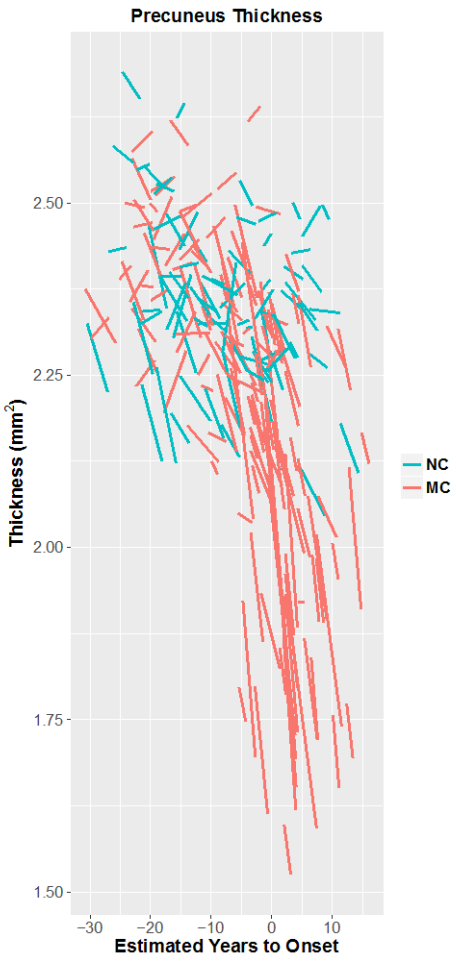


Gordon et al., in prep

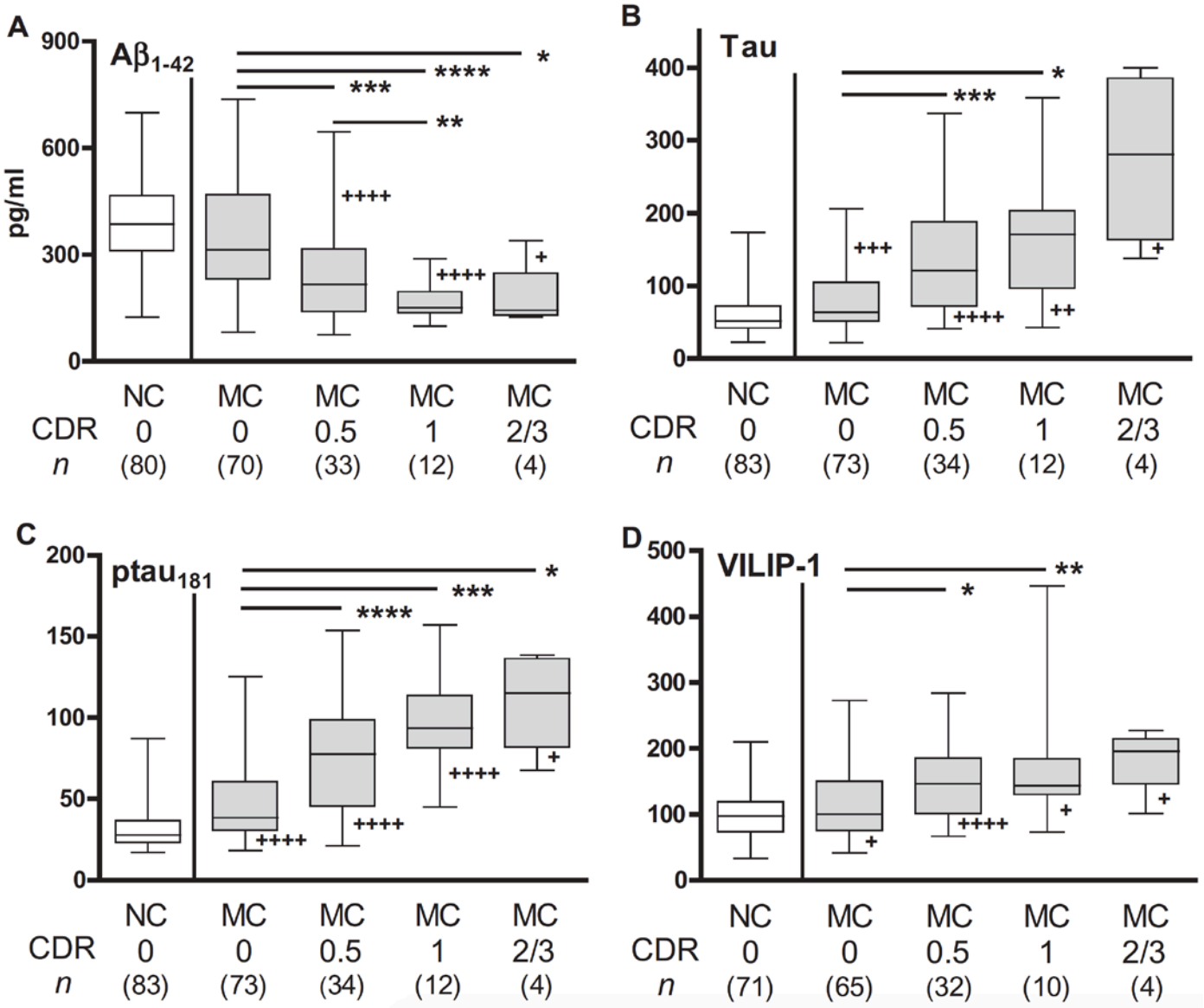
Neuroimaging Trajectories: ADAD





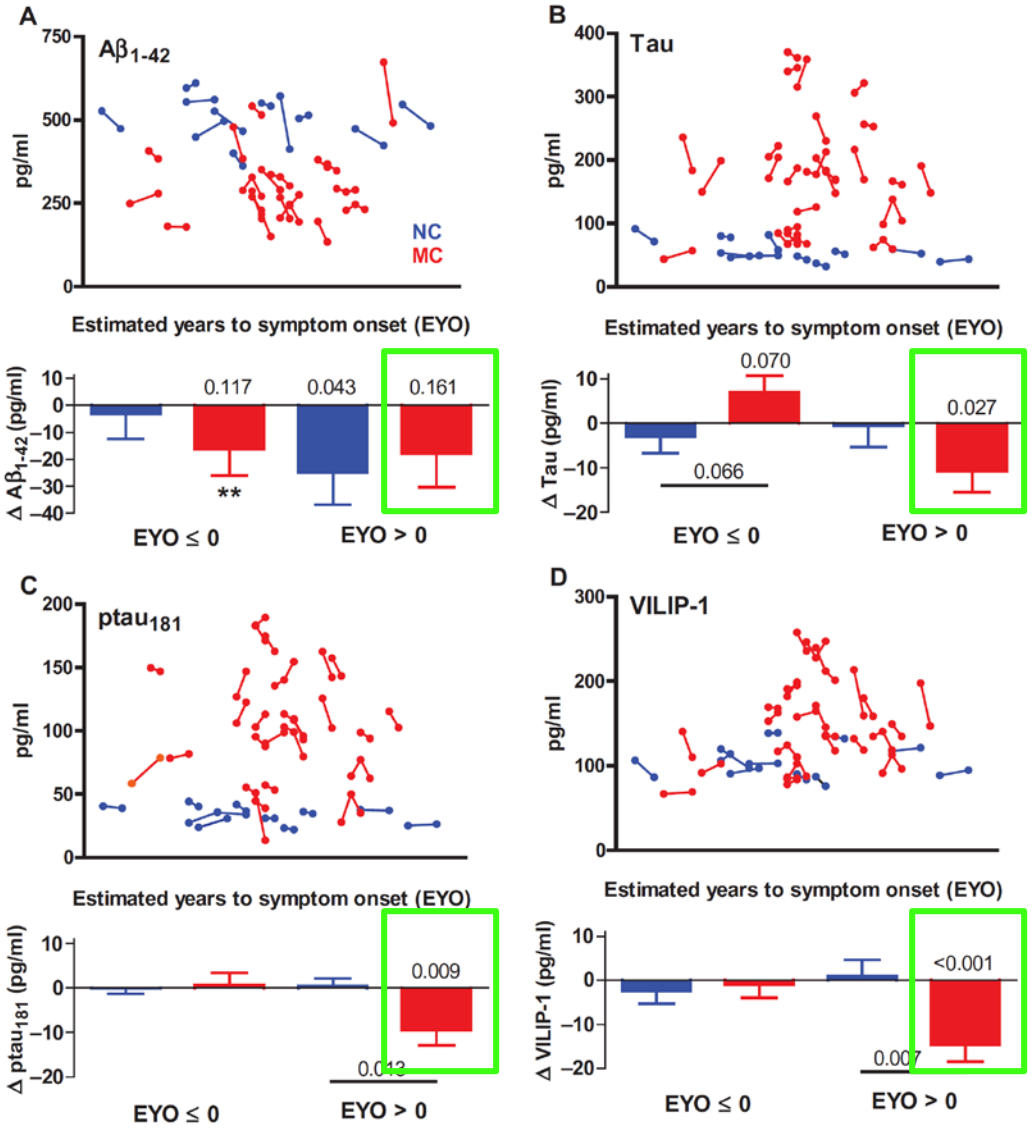


CSF Cross-Sectional Differences: ADAD



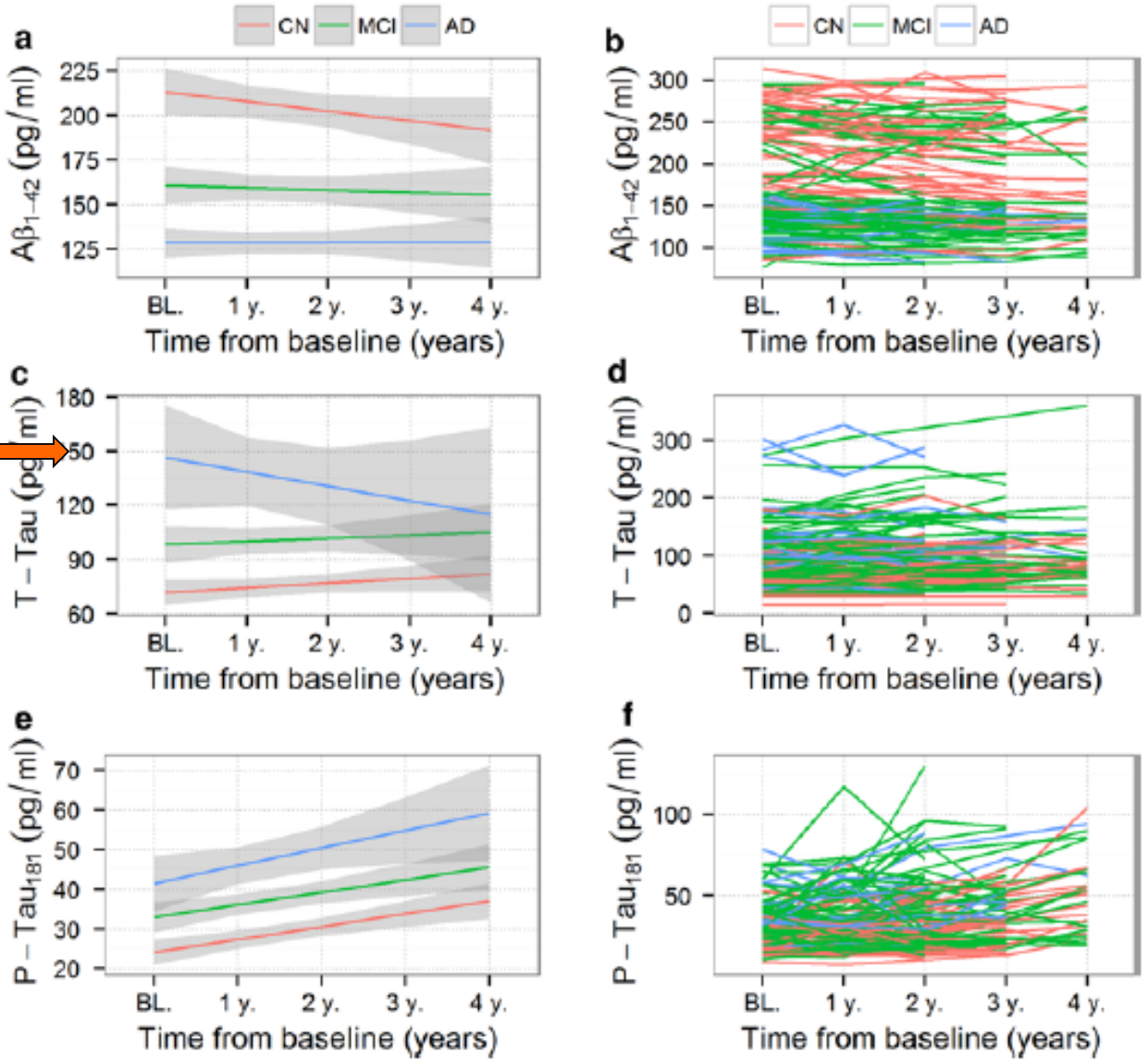
Fagan et al., 2014

CSF Trajectories: ADAD



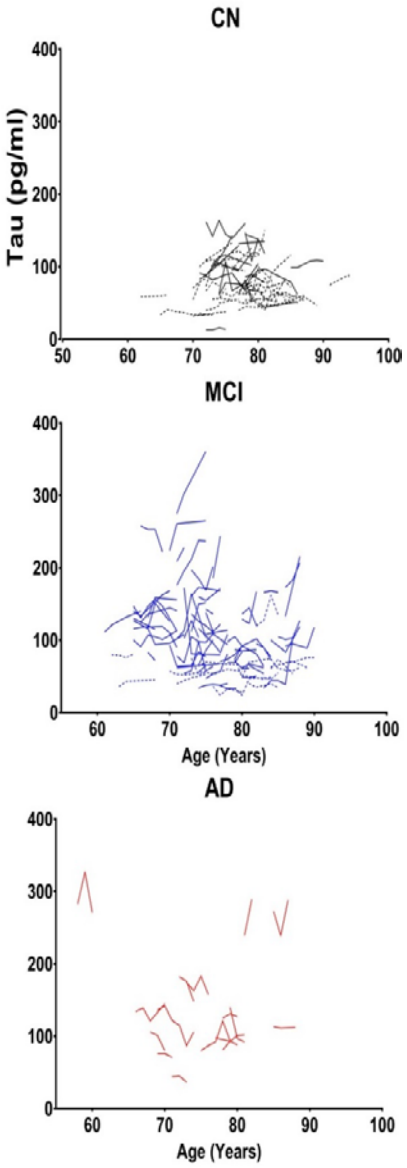
Fagan et al., 2014

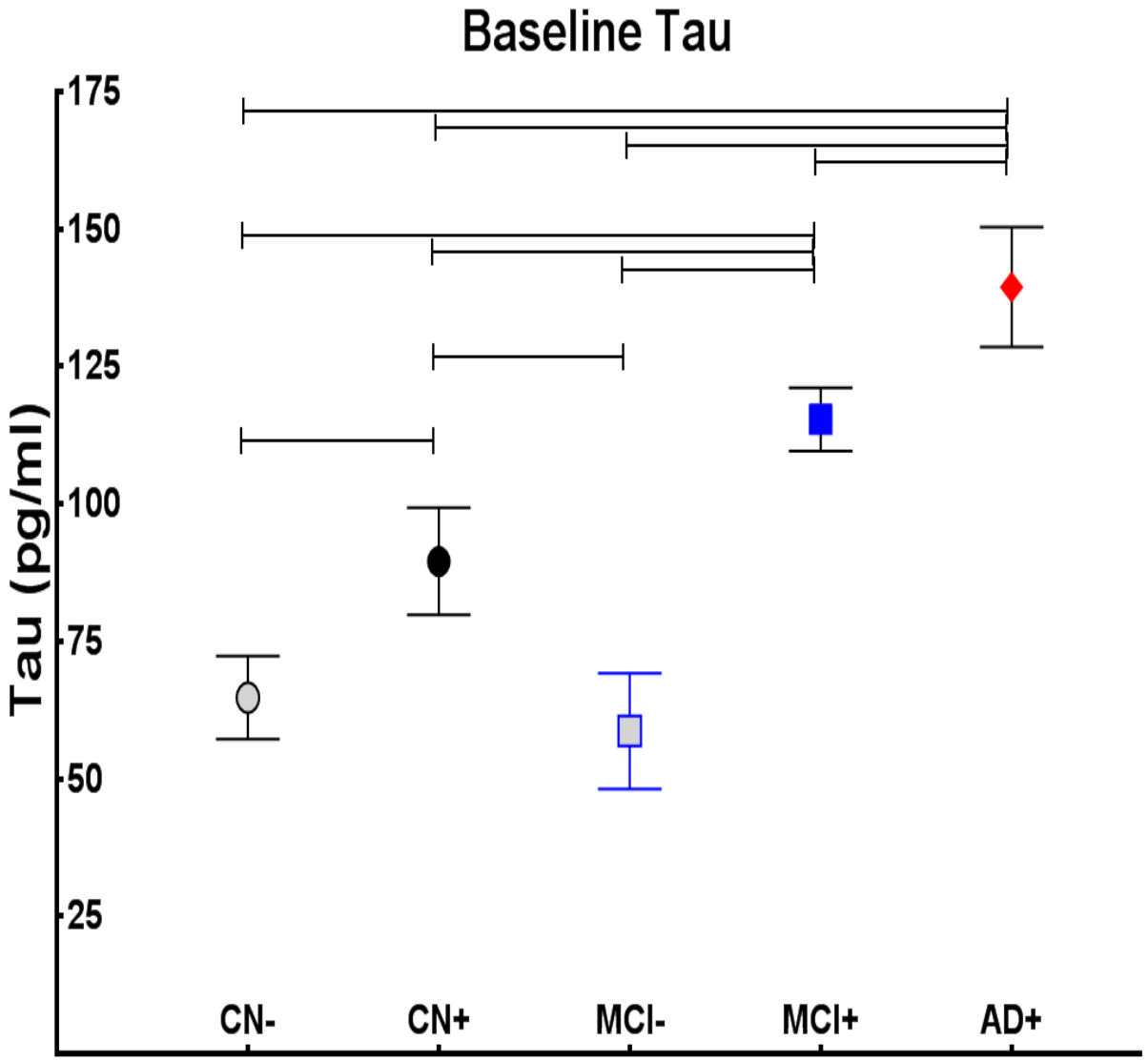
CSF Trajectories: Sporadic AD



(Toledo et al., 2013, Acta Neuropathol)

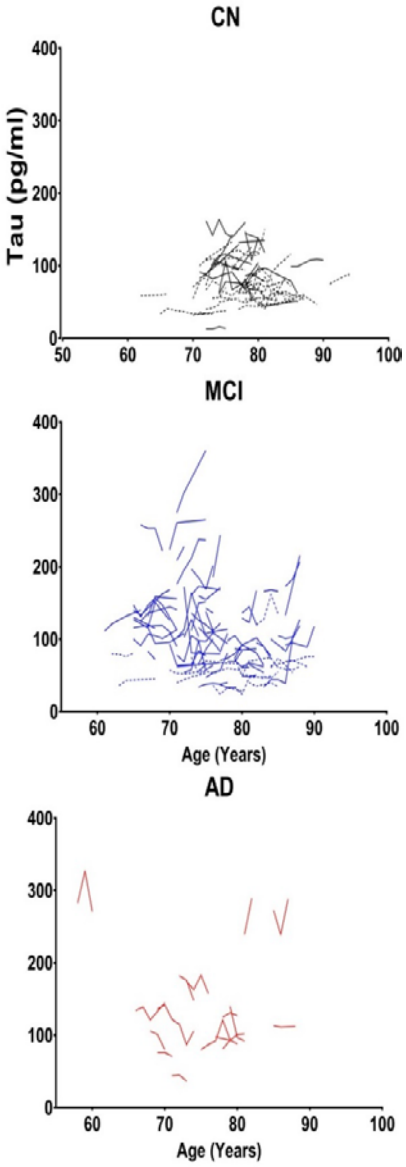
CSF Trajectories: Sporadic AD

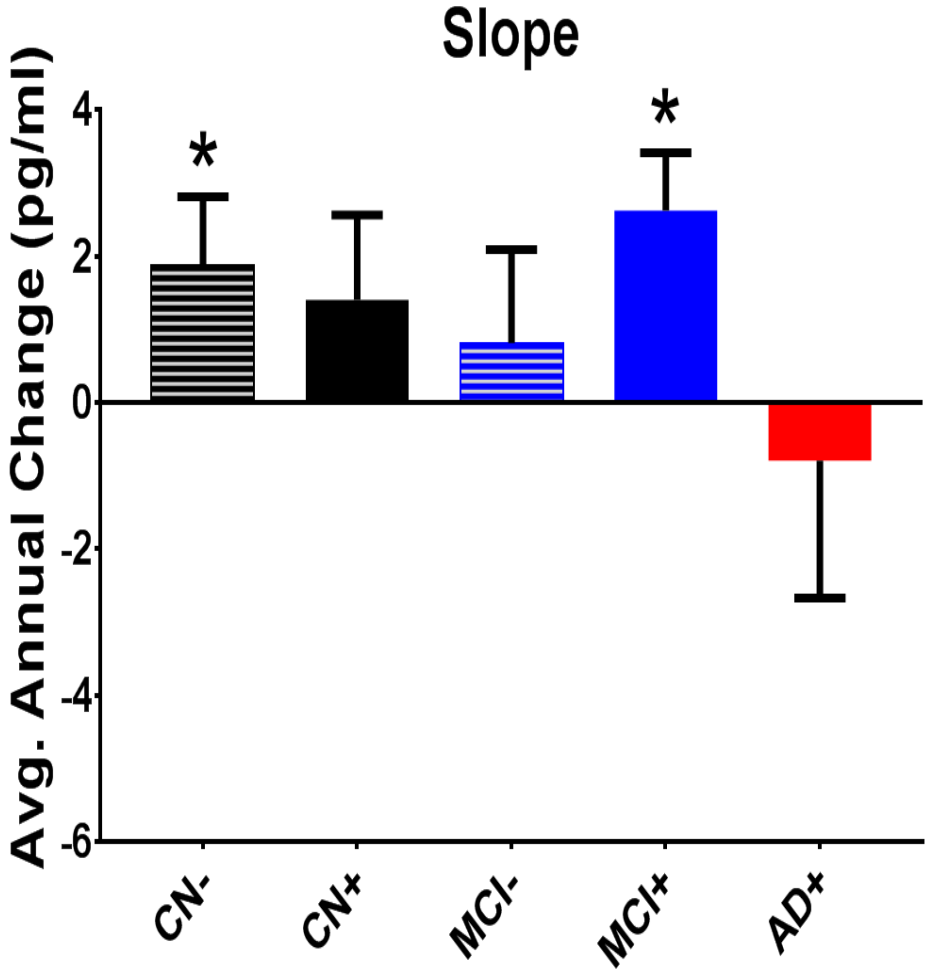




Sutphen et al., in prep

CSF Trajectories: Sporadic AD

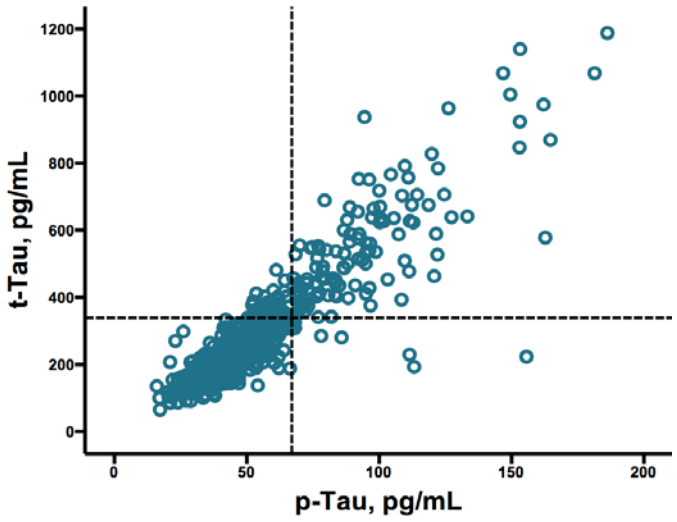




Sutphen et al., in prep

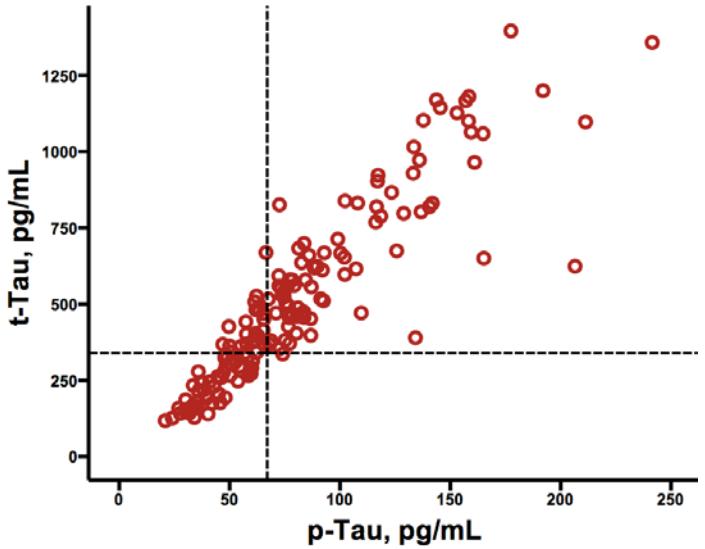
Relationship between CSF t-Tau and p-Tau

Cognitively Normal



Spearman's rho= .894 p< .001

Cognitively Abnormal

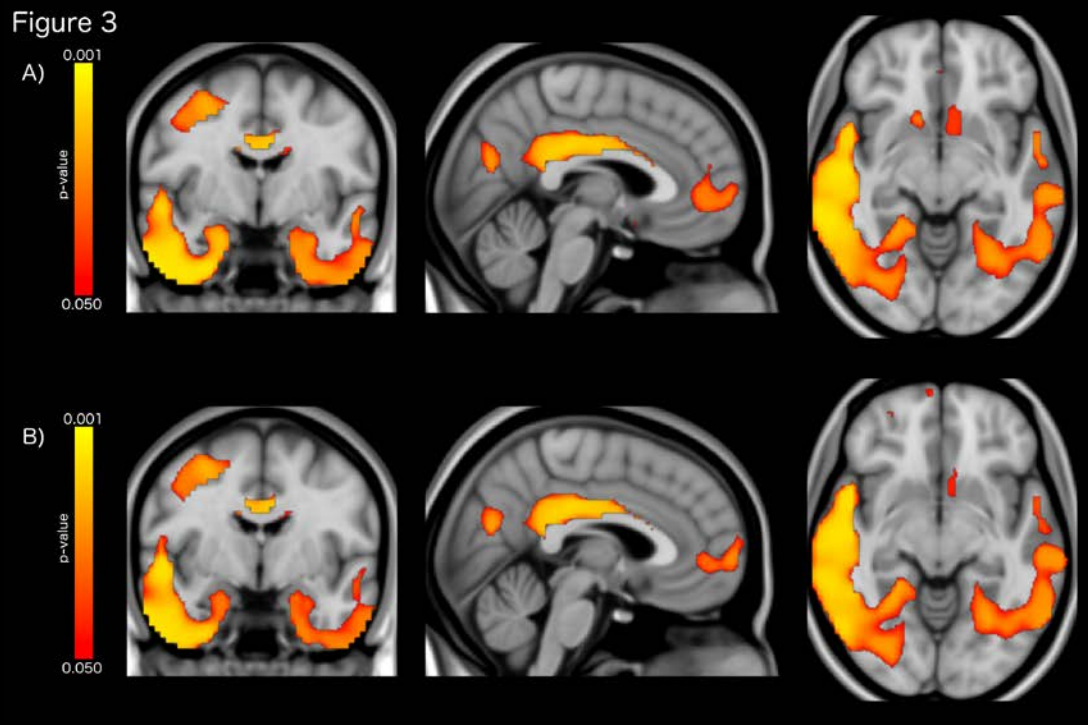


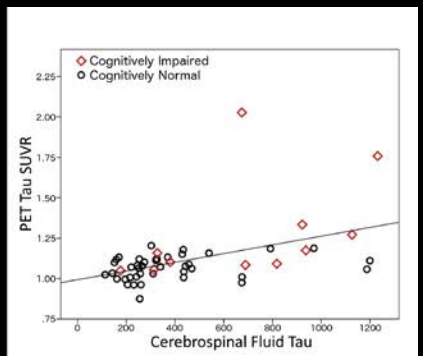
Spearman's rho= .929 p< .001

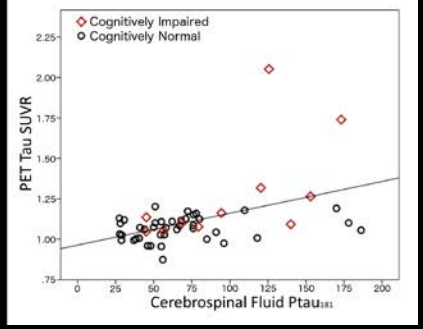
Figures courtesy of Stephanie Schultz and Anne Fagan

Relationship between CSF Biomarkers and PET Tau

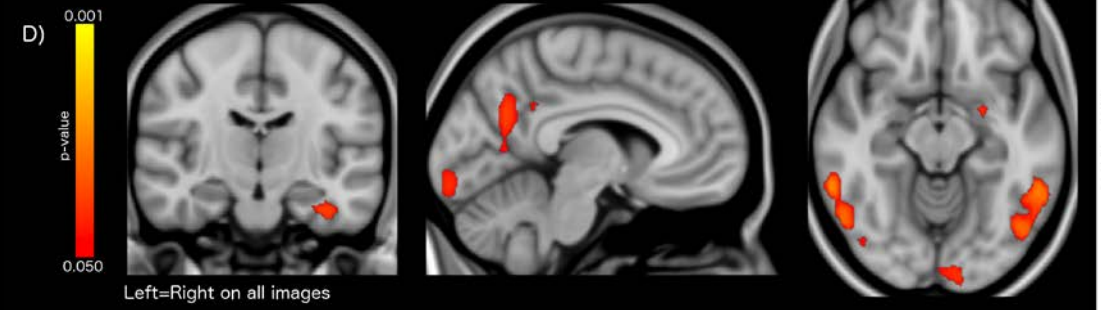
Entire Cohort

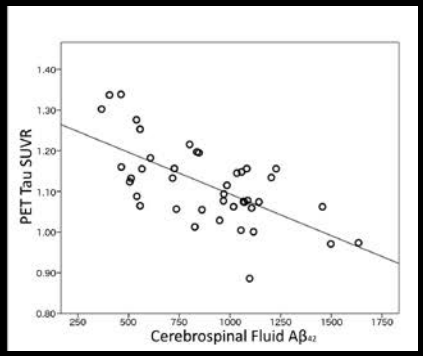






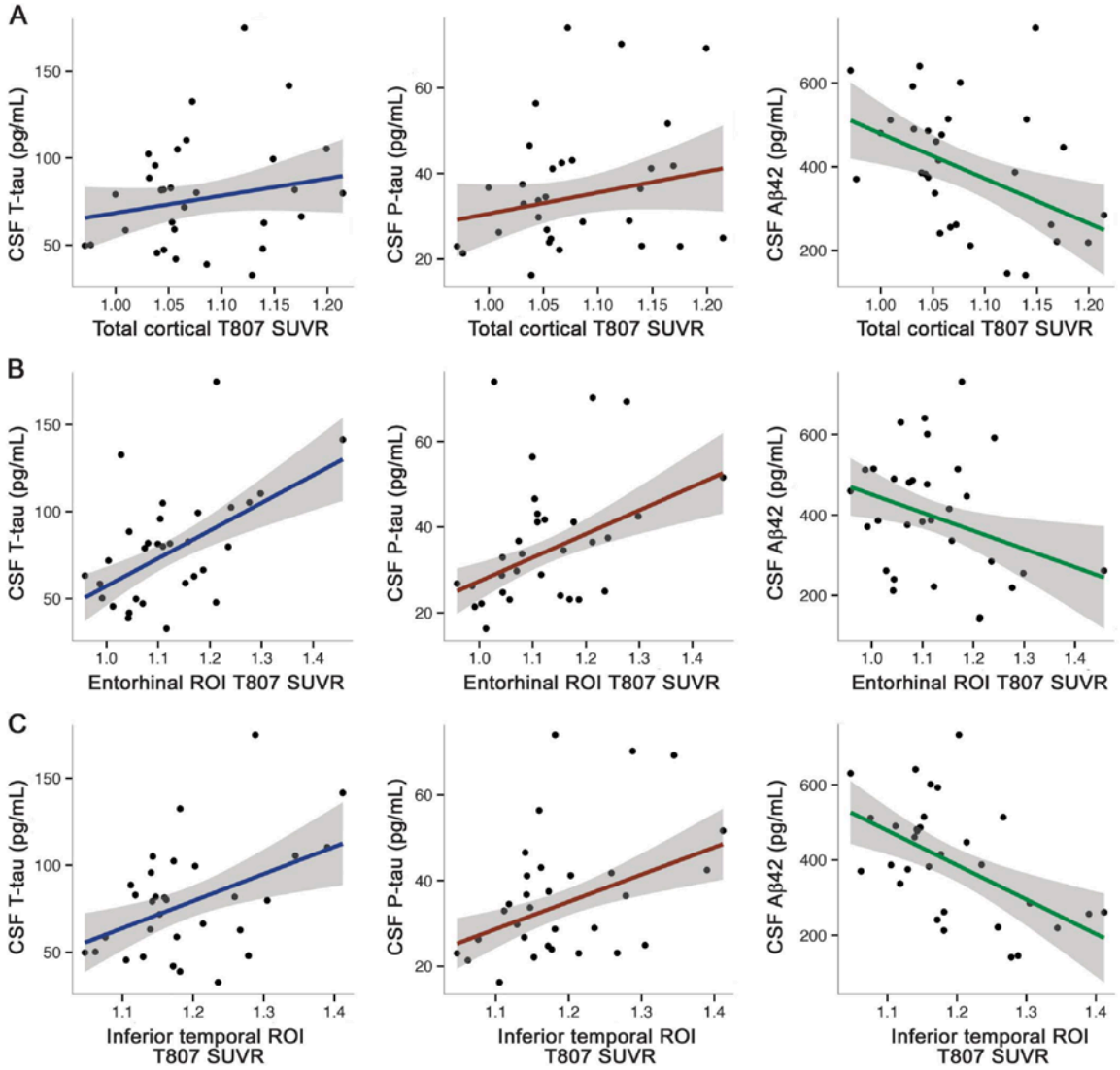
Cognitively Normal Individuals





Gordon et al., 2016 Brain

Relationship between CSF and PET Tau



Chhatwal et al., 2016

Other Neurodegenerative Markers

- Congruent Relationships
  - Wang et al., 2015 – CSF p/tau and cortical thickness
  - Souza et al., 2012 – CSF p/tau and hippocampal volume
  - Henneman et al. 2009 – CSF ptau hippocampal volume
  - Lowe et al. 2013, Hippocampal volume and FDG
  - Henneman et al., 2009 – ptau and hippocampal atrophy
  - Ossenkoppele et al. 2015 – PET tau and FDG
- Mixed or Incongruent Relationships
  - Alexopoulos et al., 2014 – FDG, hippocampal volume, and ptau
  - Vos et al., 2016 – CSF p/tau and hippocampal volume
  - Gordon et al., 2016 CSF p/tau and hippocampal volume
  - Jack et al. 2015 – Hippocampal volume, FDG, and signature thickness
  - Toledo et al., 2014 Hippocampal volume, FDG, CSF tau
  - Jagust et al., 2009 – p/tau and FDG
  - Wirth et al., 2013, FDG, hippocampal volume, and cortical thickness

Overview

- Amyloid Biomarkers
  - Consistently related, but it is nonlinear
- Neurodegenerative Biomarkers
  - Preliminary agreement between PET/CSF tauopathy measures
  - Mixed agreement among others
- The nature of biomarkers
  - Neuroimaging markers represent *cumulative* pathology
  - CSF represent *active* process
  - Move towards longitudinal change
- Pathology is temporally evolving
  - Group differences do not equate to individual differences
  - Cross-biomarker relationships vary over the disease
  - Begin to examine lagged relationships
  - Divergent CSF and Imaging trajectories later in the disease
  - Strong implications for clinical trials

Acknowledgements

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- Courtney Sutphen
- Stephanie Schultz
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- Tyler Blazey
- Dr. Yi Su
- Dr. John Morris
- Dr. Randall Bateman
- DIAN Network
- Knight ADRC

Mallinckrodt Institute of Radiology

NIL NEUROIMAGING LABS

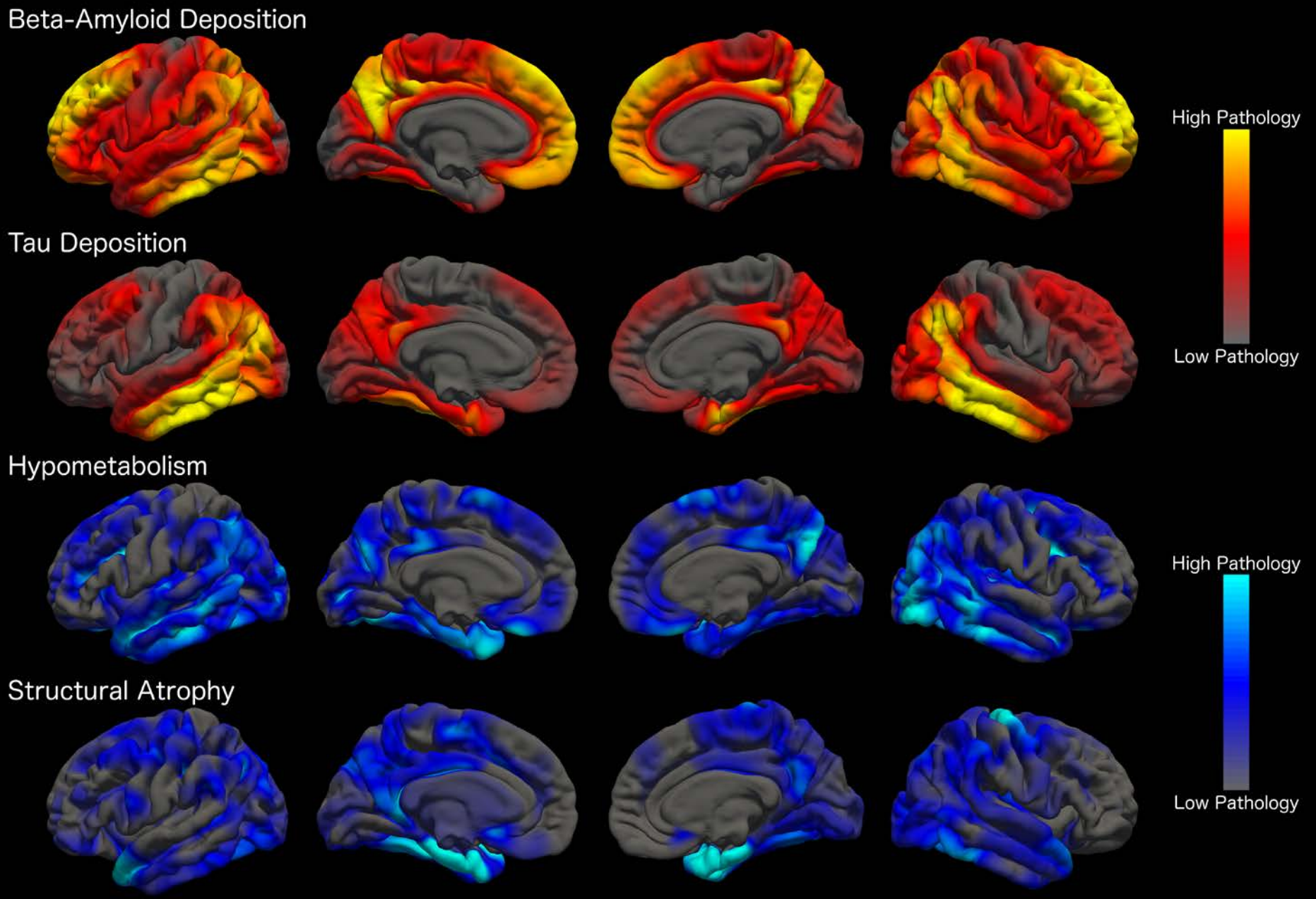
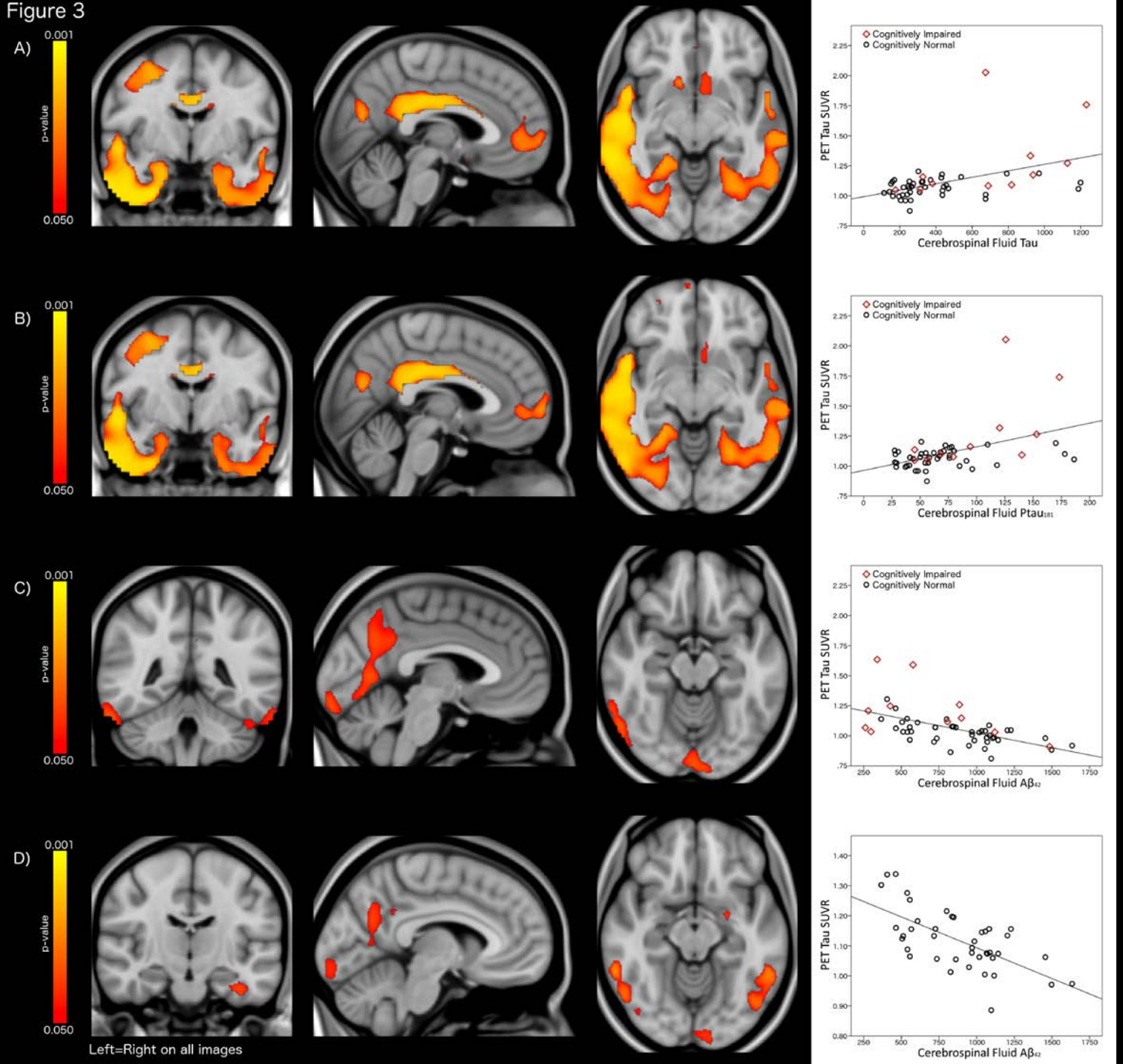

Beta-Amyloid Deposition
Tau Deposition
Hypometabolism
Structural Atrophy
High Pathology
Low Pathology
High Pathology
Low Pathology

Figure 3


A)
B)
C)
D)
0.001
p-value
0.050
Left=Right on all images
Cognitively Impaired
Cognitively Normal
PET Tau SUVR
Cerebrospinal Fluid Tau
Cerebrospinal Fluid Ptau181
Cerebrospinal Fluid Aβ42
Cerebrospinal Fluid Aβ42

Regional Mixed Effects Model

- A linear mixed effects model use to fit longitudinal imaging data in 34 different brain regions simultaneously (Verbeke et al., 2012)
  - using Stan (http://mc-stan.org/)
  - Averaged L and R ROIs
  - Run separately for each modality (MRI, PET, FDG)
- Effects included the following variables and interactions:
  - Mutation Status
  - Baseline Estimated Years to Onset (EYO)
    - Used mutation specific EYO when possible
  - Quadratic Spline for EYO (EYO^{spline})
    - Spline is a piecewise polynomial
    - Similar results if using EYO^2
  - Time from baseline
  - Mutation *EYO and Mutation * (EYO^{spline})
  - EYO * Time and (EYO^{spline}) * Time
  - Mutation*Time
  - **Mutation*EYO*Time and Mutation*(EYO^{spline})*Time**
- The model also included a random intercept and slope term for each subject

Regional Mixed Effects Model

$$Y_{ij} = X_{ij}\beta + Z_{ij}b_i + \varepsilon$$

Where:

- i = Subject
- j = Time point
- K = Number of regional responses
- P = Number of fixed effects
- Q = Number of random effects
- Y_{ij} = Vector for K responses for subject i at time j
- X_{ij} = Vector of P fixed effects variables for subject i at time j
- β = P by K matrix of fixed effects coefficients
- Z_{ij} = Vector of Q random effects variables for subject i at time j
- b_i = Q by K matrix of random effects variables for subject i
  - $b \sim N(o,\Sigma)$ where Σ is a $Q*K$ by $Q*K$ covariance matrix
- ε = Vector of k independent and identically distributed random errors