NETWORK-BASED TAU DEPOSITION PATTERNS ARE RELATED TO FUNCTIONAL NETWORK FAILURE LARGELY VIA BETA-AMYLOID

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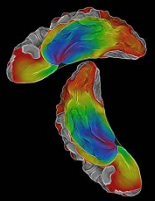
MAYO CLINIC



DISCLOSURES

- None

AD PATHOPHYSIOLOGY

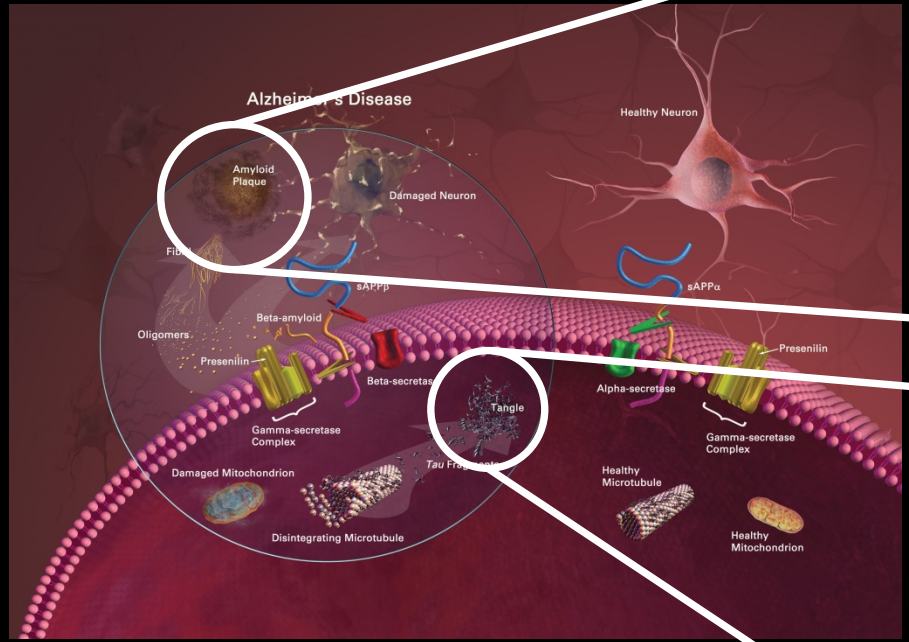
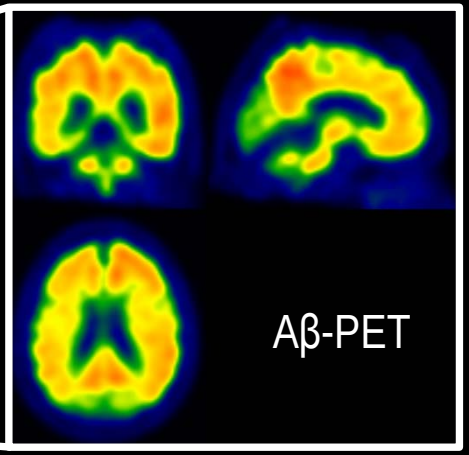
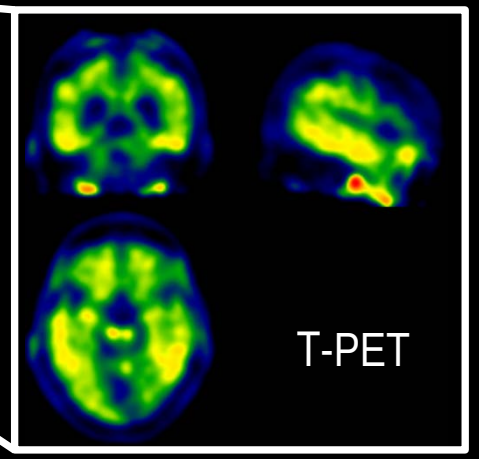


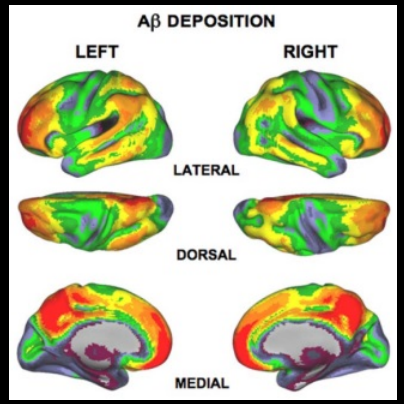
Image courtesy of the National Institute on Aging/National Institutes of Health

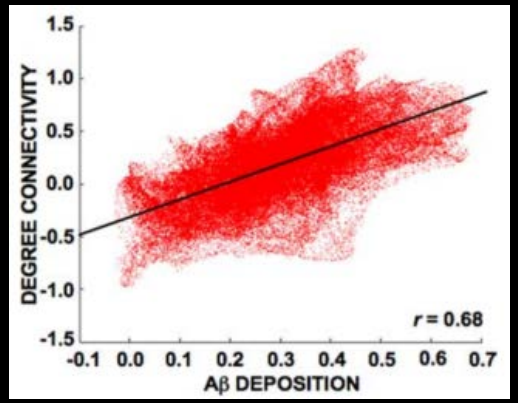




AD PATHOPHYSIOLOGY: NETWORK BASED SPATIAL CONSTRAINTS

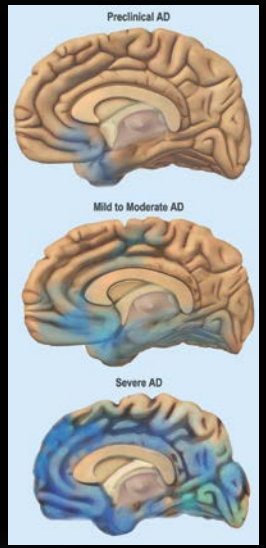
Aβ



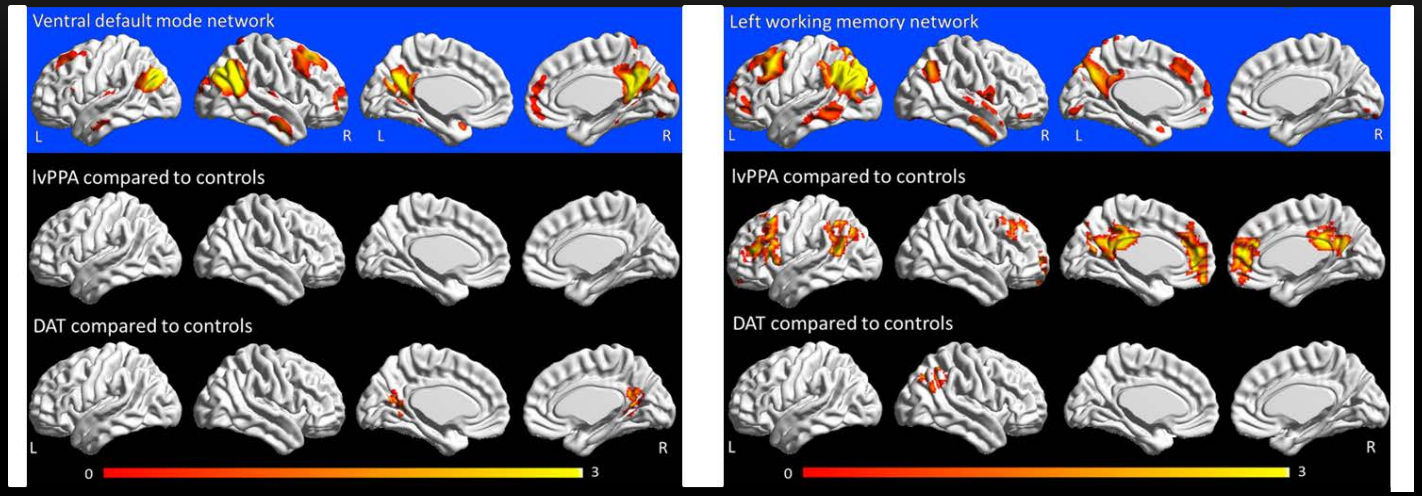


Buchner et. al., 2009

Tau

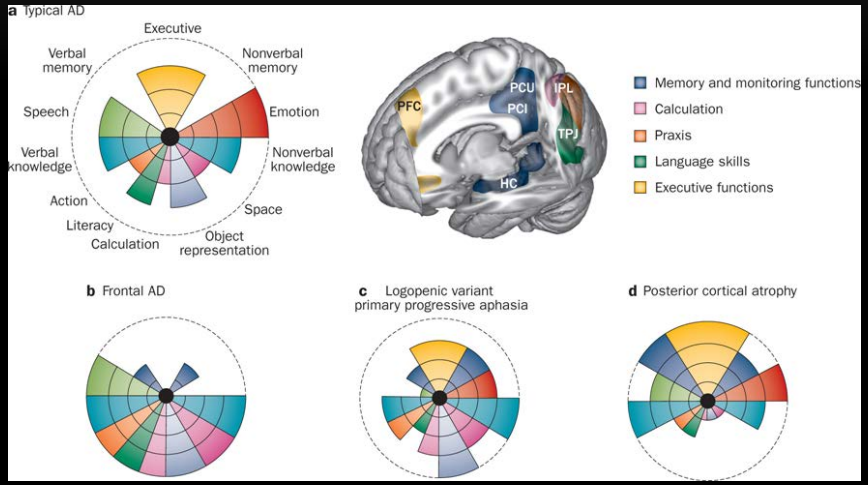


VARIABLE PHENOTYPES, NETWORKS AND VARIABLE TAU (?)



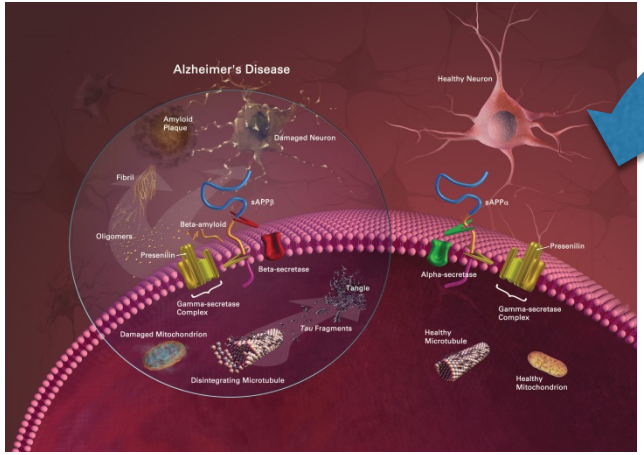
Whitwell, J.L., Jones, D.T., Duffy, J.R., Strand, E.A., Machulda, M.M., Przybelski, S.A., Vemuri, P., Gregg, B.E., Gunter, J.L., Senjem, M.L., et al. (2015). Working memory and language network dysfunction in logopenic aphasia: a task-free fMRI comparison to Alzheimer's dementia. Neurobiol Aging 36, 1245-1252

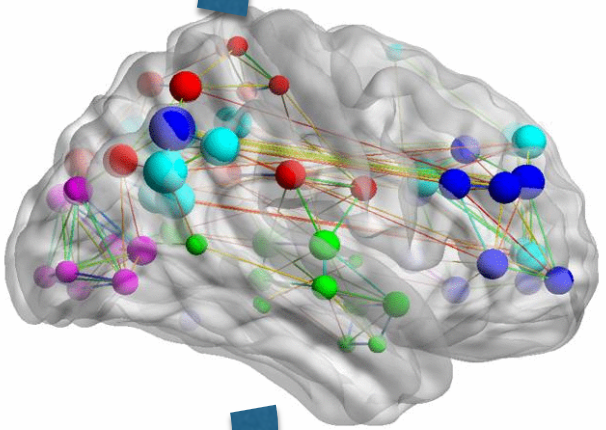
VARIABLE PHENOTYPES, NETWORKS AND VARIABLE TAU (?)

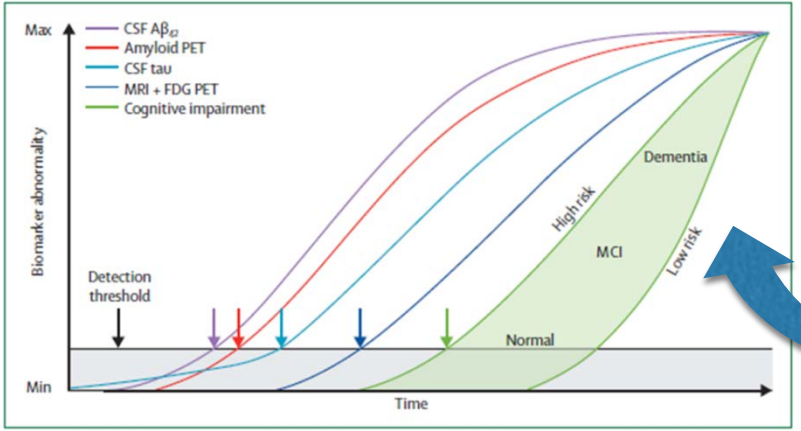


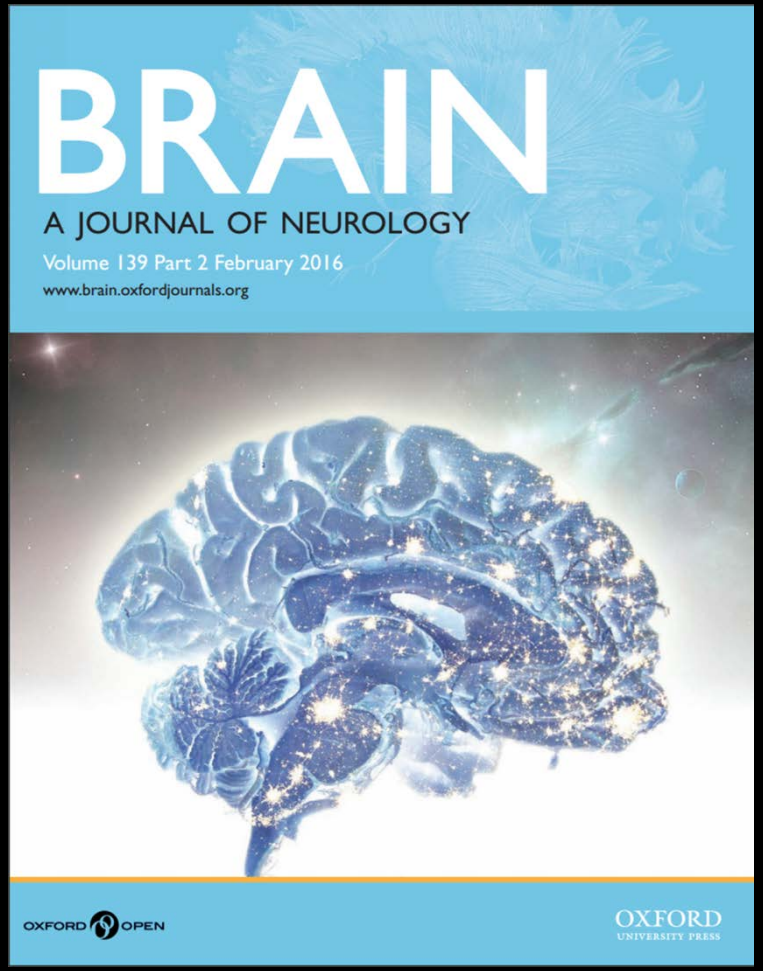
Warren, J. D. *et al.* (2012) The paradox of syndromic diversity in Alzheimer disease *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2012.135

- Alladi, S., et. al. (2007). Focal cortical presentations of Alzheimer's disease. Brain *130*, 2636-2645.
- Mesulam, M.M., et. al. (2014). Asymmetry and heterogeneity of Alzheimer's and frontotemporal pathology in primary progressive aphasia. Brain *137*, 1176-1192.
- Murray, M.E.,et.al. (2011). Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. Lancet Neurology *10*, 785-796.
- Ossenkoppele, R., Schonhaut, D.R., Scholl, M., Lockhart, S.N., Ayakta, N., Baker, S.L., O'Neil, J.P., Janabi, M., Lazaris, A., Cantwell, A., et al. (2016). Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 139,1551-1567

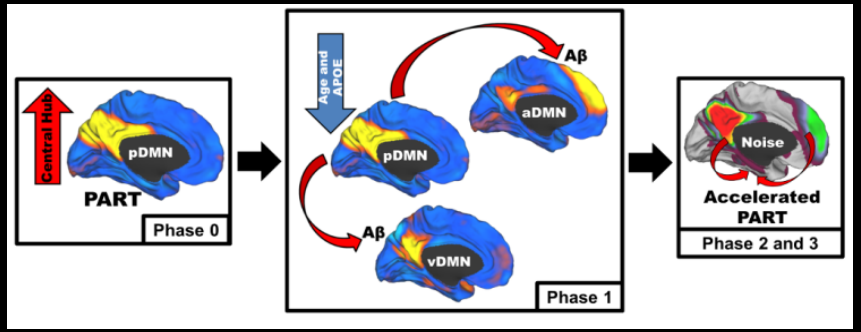

Alzheimer's Disease
Healthy Neuron
Amyloid Plaque
Damaged Neuron
Fibril
sAPPβ
sAPPα
Oligomers
Beta-amyloid
Presenilin
Beta-secretase
Alpha-secretase
Presenilin
Tangle
Gamma-secretase Complex
Gamma-secretase Complex
Damaged Mitochondrion
Tau Fragments
Healthy Microtubule
Disintegrating Microtubule
Healthy Mitochondrion




Max
Min
CSF Aβ42
Amyloid PET
CSF tau
MRI + FDG PET
Cognitive impairment
Biomarker abnormality
Detection threshold
Dementia
High risk
MCI
Low risk
Normal
Time



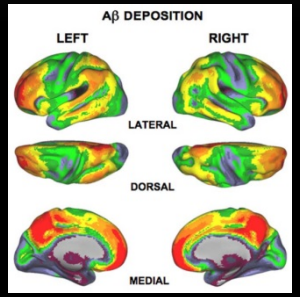
Cascading Network Failure



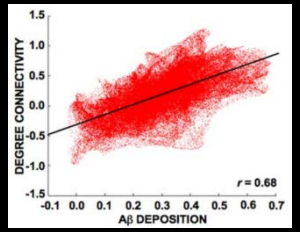
Jones et. al., 2016

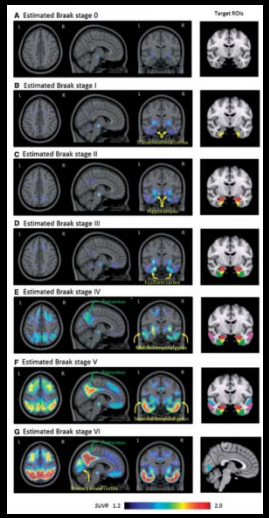
BACKGROUND SUMMARY

- AD Pathophysiology is Spatial Constrained within Large-Scale Brain Networks
  - Beta-amyloid and Tau have unique spatial and temporal profiles

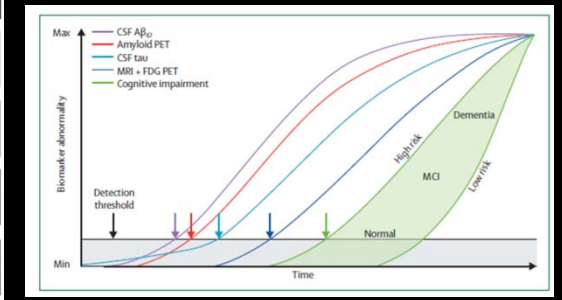


Buchner et. al., 2009



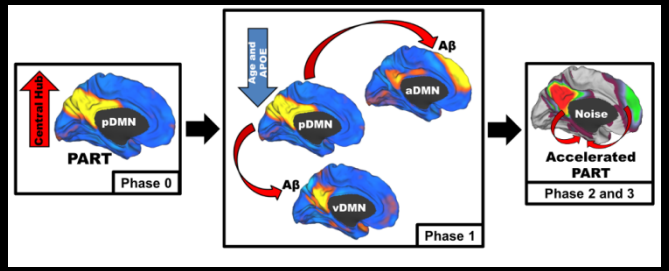


Schwarz et. al., 2016
Cho et al., 2016



Jack et. al., 2013

Cascading Network Failure

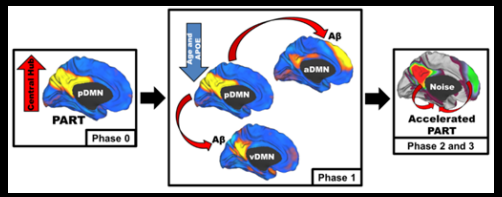


Jones et. al., 2016

OBJECTIVES

1. Determine the spatial pattern(s) of tau deposition across the AD-spectrum
    - One network or several
    - Do these patterns recapitulate Braak NFT staging
2. How do these patterns relate to measures of functional network failure across the AD-spectrum
    - Is this consistent with the cascading network failure model of AD

Cascading Network Failure



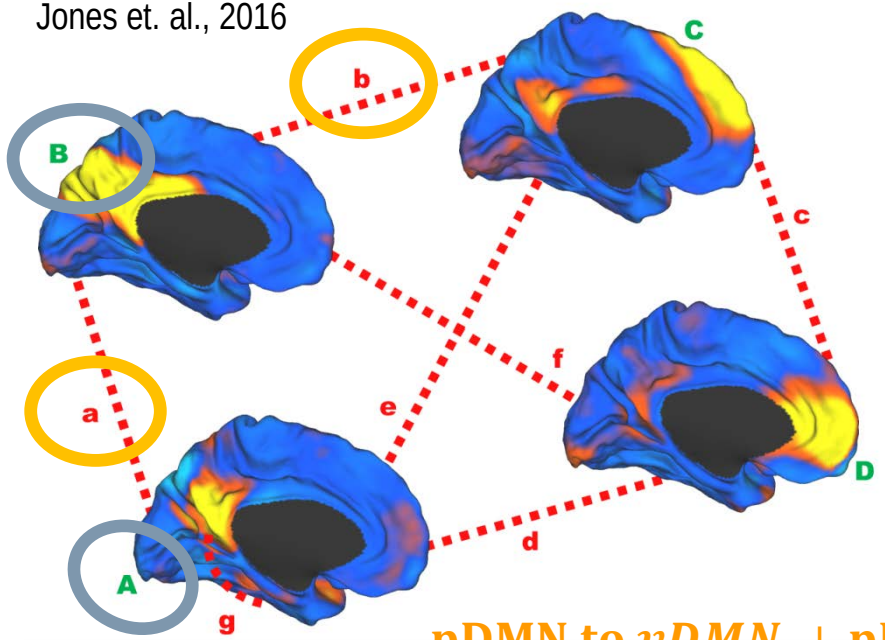
$$Tau \sim A\beta + NFQ + age + \varepsilon$$

METHODS

- Tau-PET (AV-1451), Aβ-PET (PiB), and task free fMRI (TF-fMRI) were obtained in a cohort of subjects across the AD spectrum (n = 218).
- All subjects that were clinically impaired (n = 41) had PiB SUVR > 1.5.
- Tau-PET scans were intensity normalized to the cerebellar gray matter, spatially normalized to standard space, and smoothed. ***Independent component analyses*** was then performed, with biologically relevant components being identified via a strong amyloid effect for the tau components (Bonferroni corrected $p < 0.01$).
- Tau-PET component scores were included in a mediation analyses with PiB-PET and a marker of functional network failure we term the network failure quotient (NFQ).

NETWORK FAILURE QUOTIENT (NFQ)

Jones et. al., 2016



Network Element[a]	Cohen's d	*P* value[b]	*P* value[c]
vDMN (A)	***0.69***	***0.008***	***0.030***
pDMN (B)	***0.80***	***0.002***	0.246
adDMN (C)	-0.04	0.866	0.543
avDMN (D)	***0.57***	***0.034***	0.210
pDMN and vDMN (a)	***-0.60***	***0.003***	***0.049***
pDMN and adDMN (b)	***-0.47***	***0.015***	***0.027***
adDMN and avDMN (c)	0.08	0.589	0.899
avDMN and vDMN (d)	0.24	0.336	0.669
vDMN and adDMN (e)	-0.01	0.808	0.739
pDMN and avDMN (f)	0.05	0.878	0.984
vDMN and MTL (g)	***0.54***	***0.024***	***0.046***

P values less than 0.05 are in bold and italicized text.
[a] Upper case (A-D) and lower case (a-g) letters correspond to labels in Figure S5.
[b] Controlling for motion, age, and gender
[c] Controlling for motion, age, gender, and *APOE ε4*

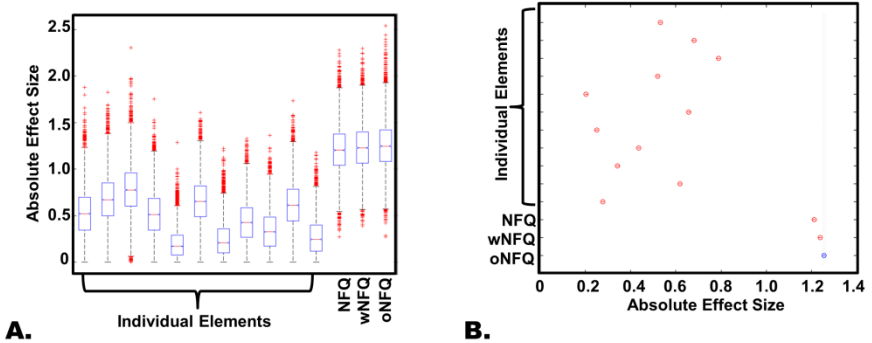
$$NFQ = \frac{\text{pDMN to } vDMN + \text{pDMN to } adDMN}{pDMN + vDMN}$$

Cohen's d = 1.2

Hippocampal Volume Cohen's d = 1.6

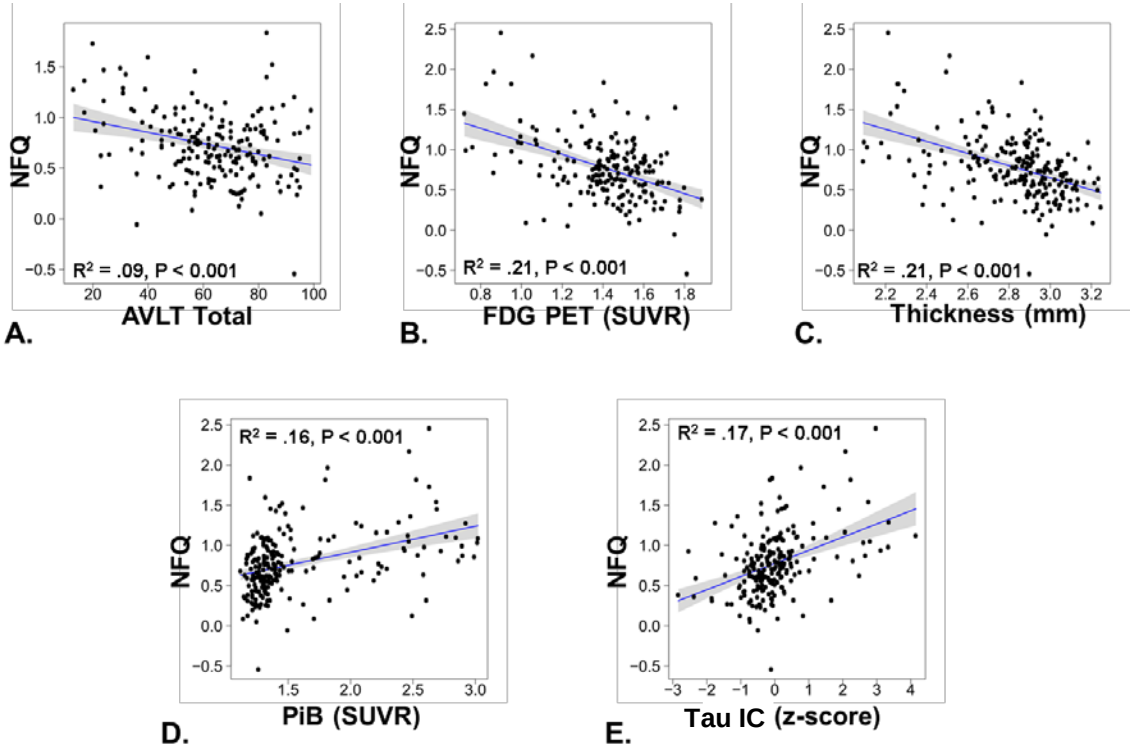
NETWORK FAILURE QUOTIENT (NFQ)

ADNI
Discovery Cohort



Daniela Wiepert et. al. (under review)

NETWORK FAILURE QUOTIENT (NFQ)

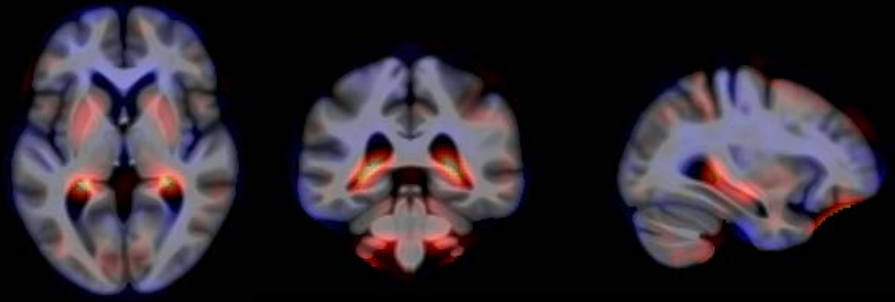


SUBJECTS

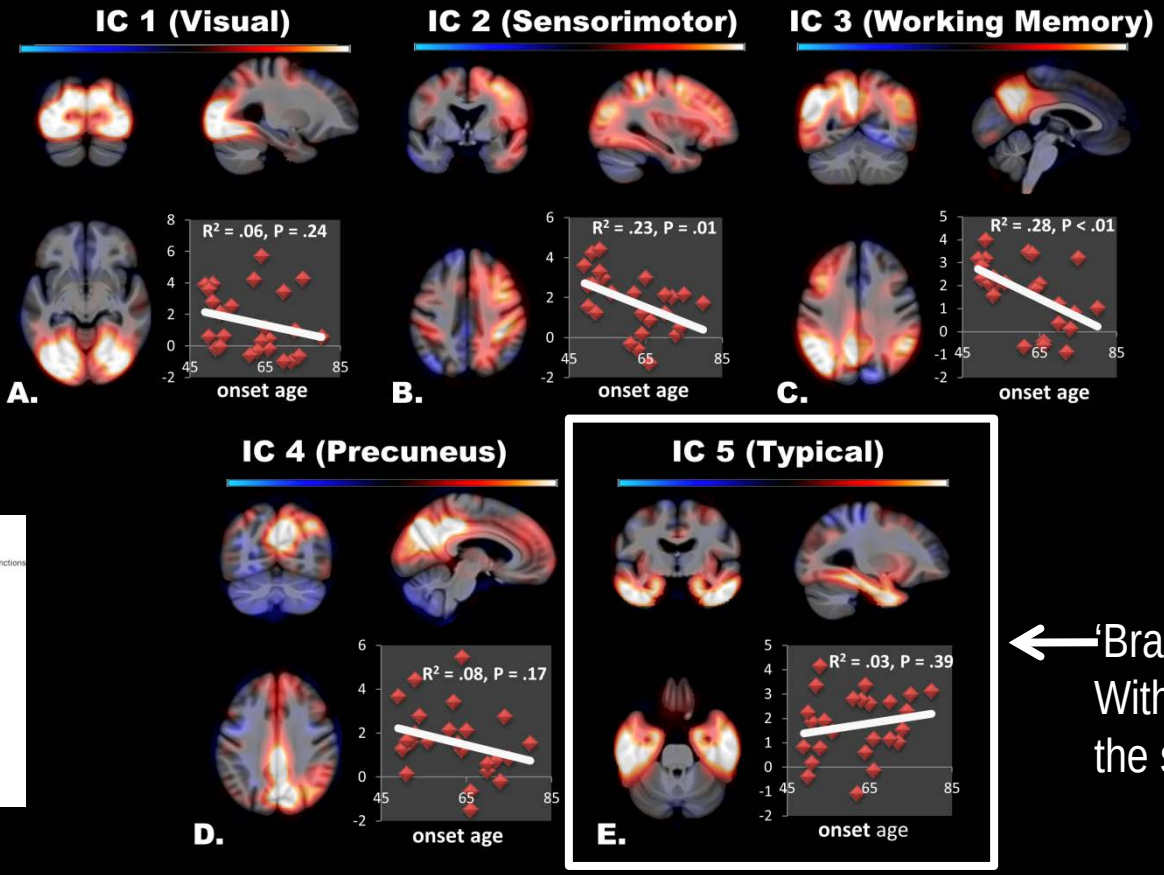
Characteristic	All	CN	Impaired
	(n=218)	(n=177)	(n=41)
Age, years			
Median (IQR)	68 (59,74)	67 (58,73)	68(63,75)
Min, Max	31,90	31,90	55,83
Male gender, no. (%)	126 (58%)	102 (58%)	24 (59%)
Education, years			
Median (IQR)	16 (13,18)	16 (14,17)	16 (13,18)
Min, Max	12,20	12,20	12,20
MMSE			
Median (IQR)	29 (28,29)	29 (28,29)	22 (17,26)
Min, Max	6,30	23,30	6,30
PIB PET, SUVR			
Median (IQR)	1.35 (1.27,1.69)	1.32 (1.26,1.40)	2.47 (2.15,2.69)
Min, Max	1.12,3.02	1.12,2.73	1.51,3.02
>1.4, no. (%)	89 (41%)	48 (27%)	41 (100%)
>1.5, no. (%)	66 (30%)	25 (14%)	41 (100%)

RESULTS: TAU INDEPENDENT COMPONENT ANALYSIS

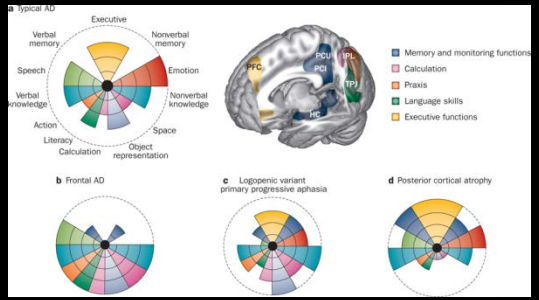
- Information theoretic criteria determined dimensionality: 33
- 5 component showed a strong amyloid effect (Bonferroni corrected $P < 0.001$)
- The remainder were artifacts and off-target binding:



RESULTS: TAU INDEPENDENT COMPONENT ANALYSIS

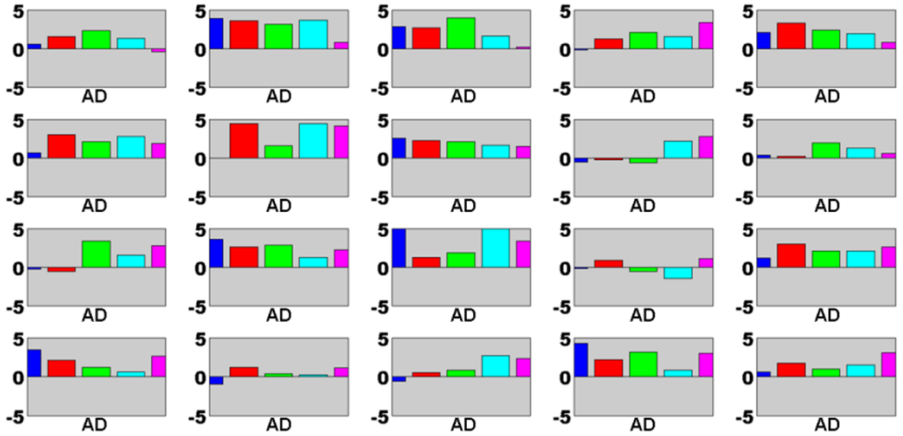


Warren, J. D. *et al.* (2012) The paradox of syndromic diversity in Alzheimer disease *Nat. Rev. Neurol.*



‘Braak-like’
With all stages in the same IC

RESULTS: TAU INDEPENDENT COMPONENT ANALYSIS



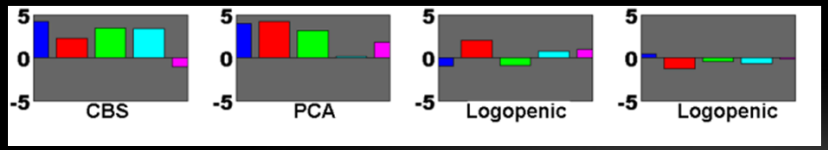
IC-1 Visual

IC-2 Visual-Motor

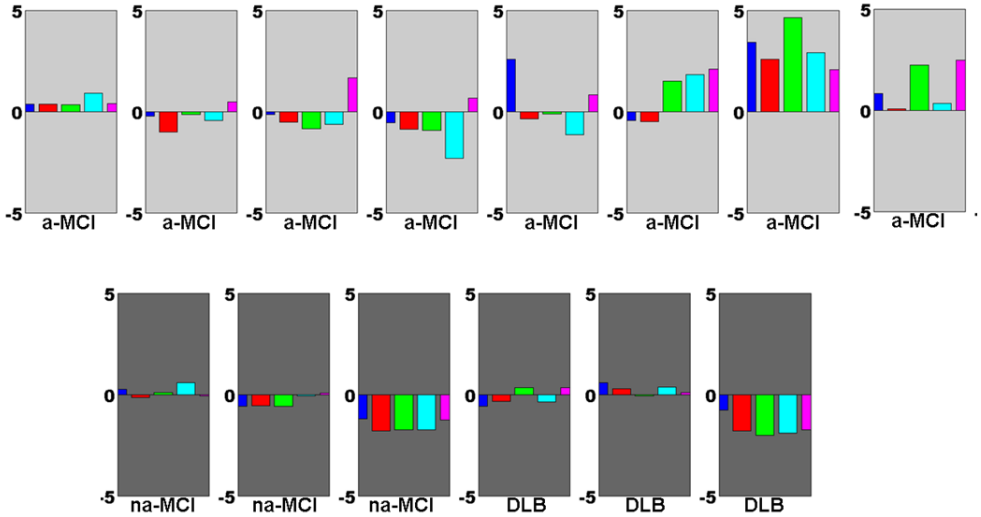
IC-3 Working Memory

IC-4 Precuneus

IC-5 Typical ‘Braak-like’ Tau Pattern



RESULTS: TAU INDEPENDENT COMPONENT ANALYSIS



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IC-2 Visual-Motor

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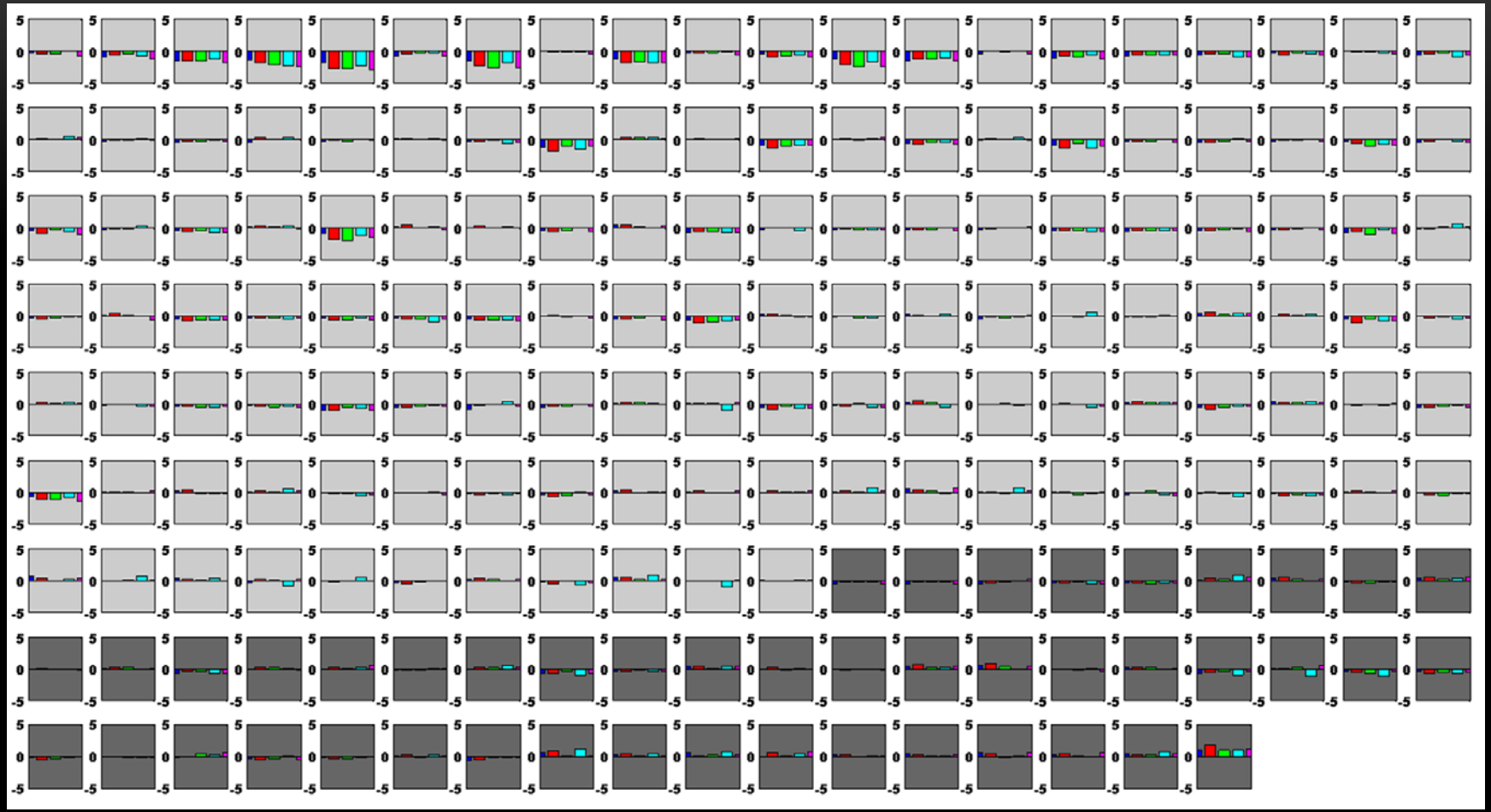
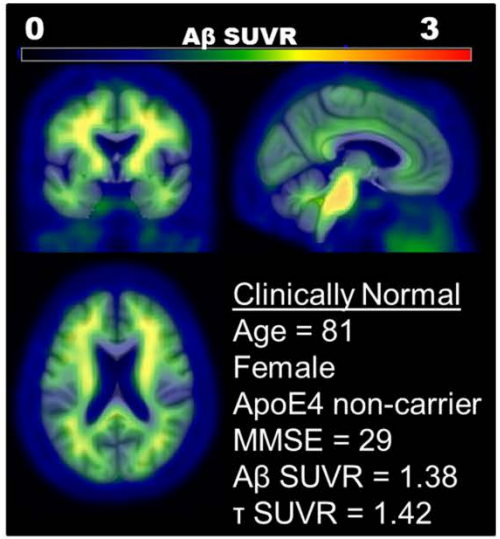
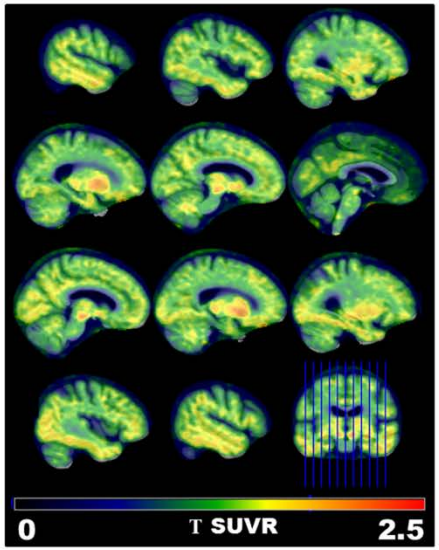
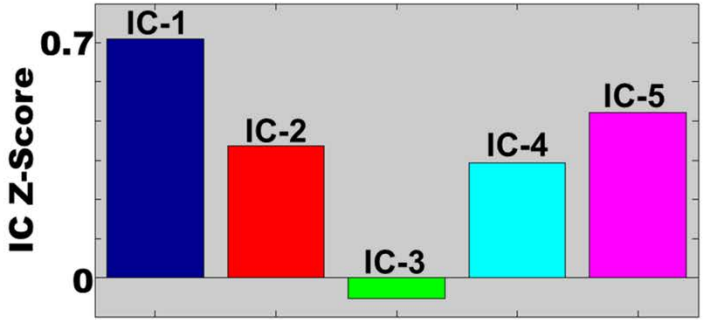

5
0
-5


0
Aβ SUVR
3
Clinically Normal
Age = 81
Female
ApoE4 non-carrier
MMSE = 29
Aβ SUVR = 1.38
τ SUVR = 1.42

A.

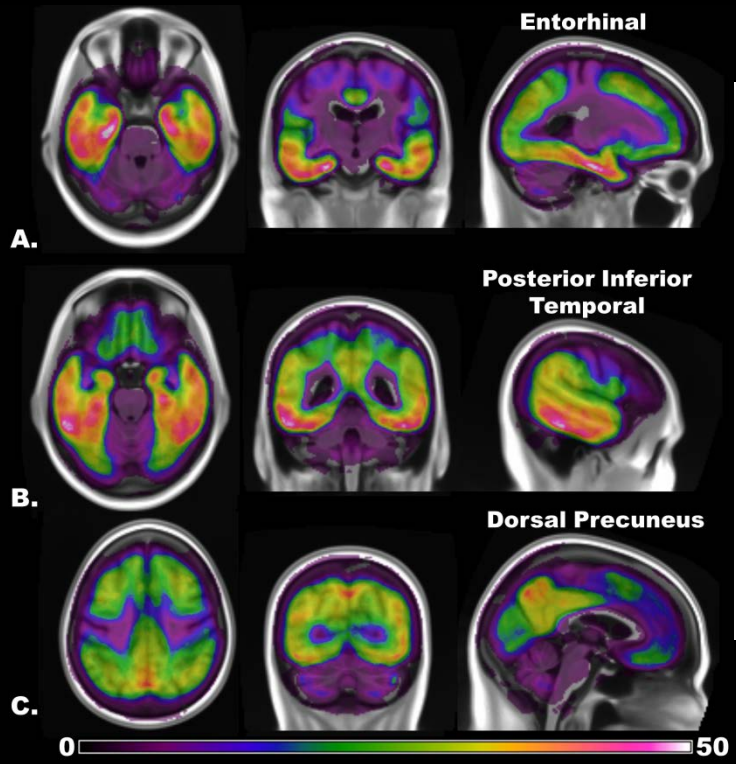

0
T SUVR
2.5

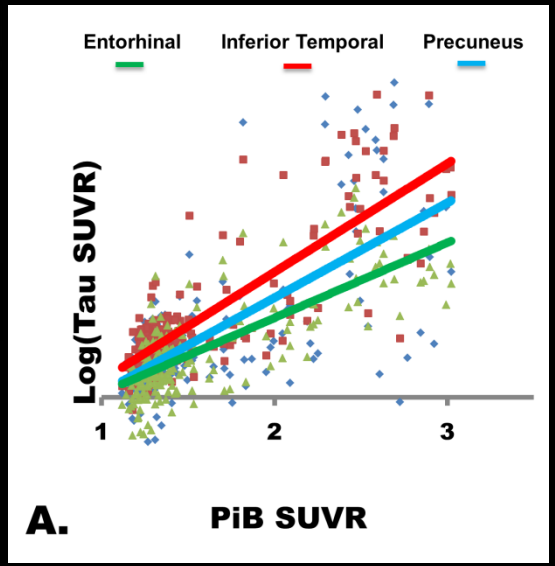
B.

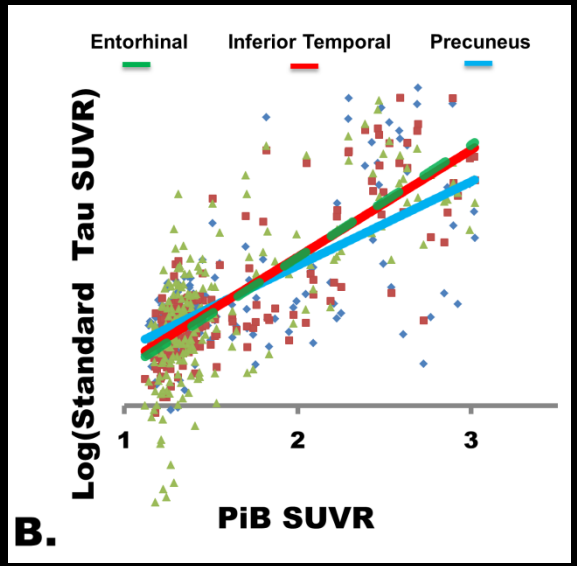

IC Z-Score
0.7
0
IC-1
IC-2
IC-3
IC-4
IC-5

C.

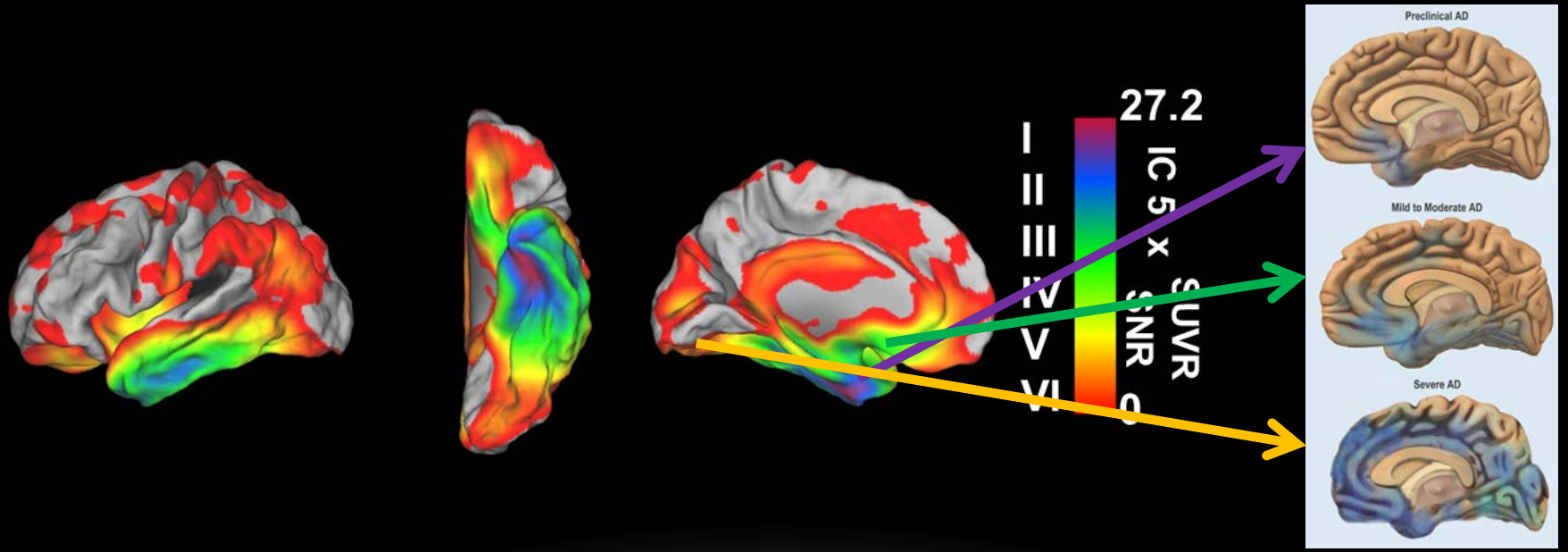
RESULTS: FREQUENCY COUNT OF ELEVATED TAU SIGNAL

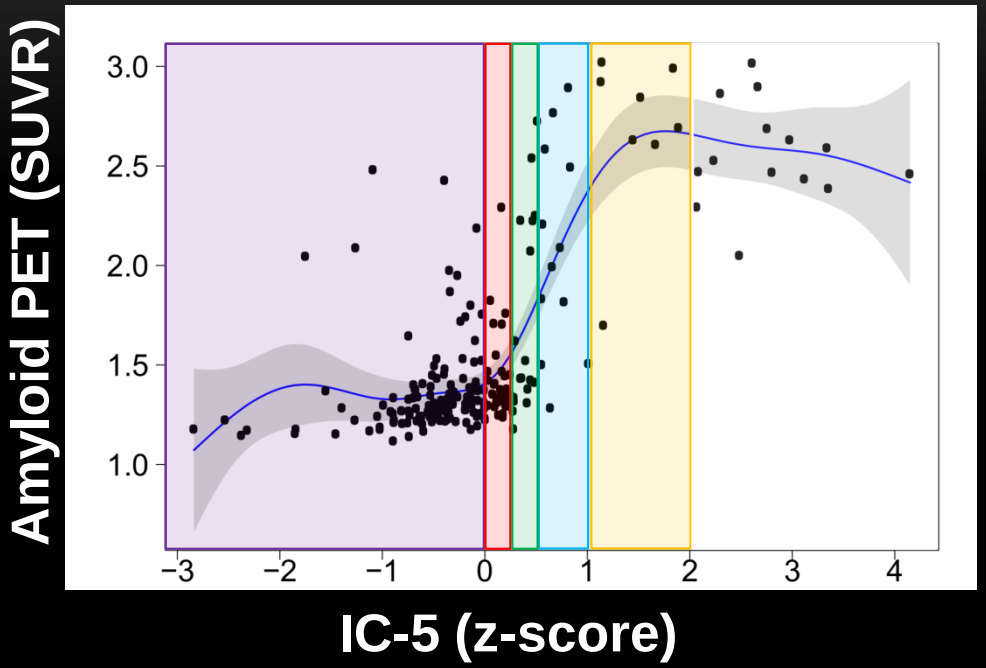


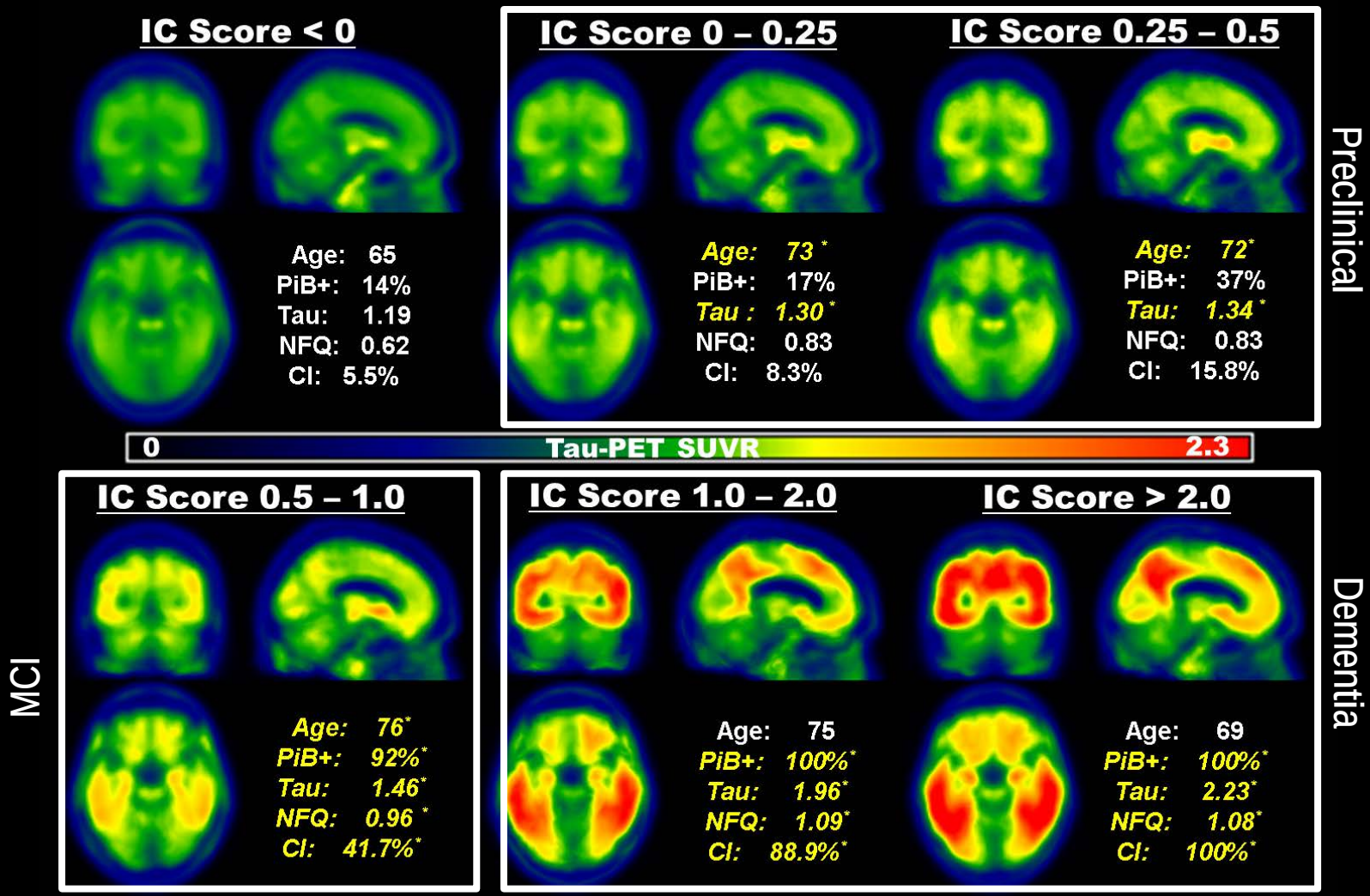




TYPICAL ‘BRAAK-LIKE’ TAU-PET PATTERN (IC-5)

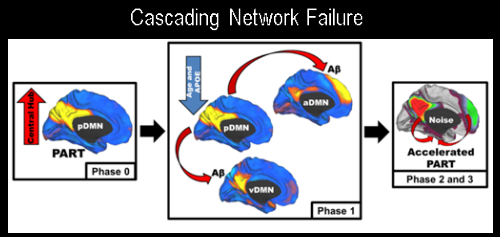



Amyloid PET (SUVR)
3.0
2.5
2.0
1.5
1.0
−3
−2
−1
0
1
2
3
4
IC-5 (z-score)

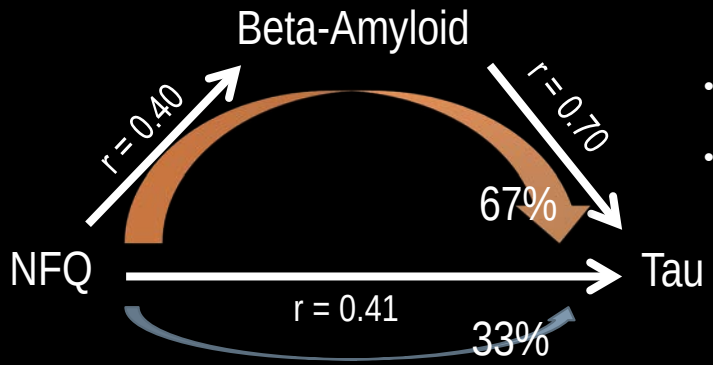

IC Score < 0
Age: 65
PiB+: 14%
Tau: 1.19
NFQ: 0.62
CI: 5.5%
IC Score 0 – 0.25
Age: 73 *
PiB+: 17%
Tau : 1.30 *
NFQ: 0.83
CI: 8.3%
IC Score 0.25 – 0.5
Age: 72*
PiB+: 37%
Tau: 1.34 *
NFQ: 0.83
CI: 15.8%
Preclinical
0
Tau-PET SUVR
2.3
MCI
IC Score 0.5 – 1.0
Age: 76*
PiB+: 92%*
Tau: 1.46*
NFQ: 0.96 *
CI: 41.7%*
IC Score 1.0 – 2.0
Age: 75
PiB+: 100%*
Tau: 1.96*
NFQ: 1.09*
CI: 88.9%*
IC Score > 2.0
Age: 69
PiB+: 100%*
Tau: 2.23*
NFQ: 1.08*
CI: 100%*
Dementia

OBJECTIVES

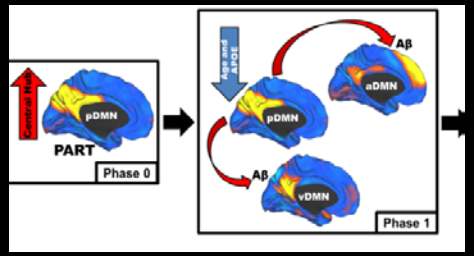
1. Determine the spatial pattern(s) of tau deposition across the AD-spectrum
   - One network or *several*
   - Do these patterns recapitulate Braak NFT staging: *1 of 5*
2. How do these patterns relate to measures of functional network failure
   - Is this consistent with the cascading network failure model of AD

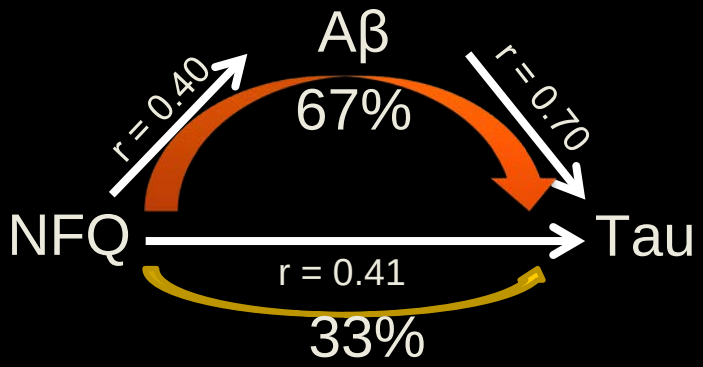


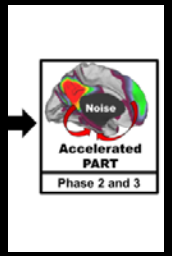
Tau ~ Aβ + NFQ + age + ε



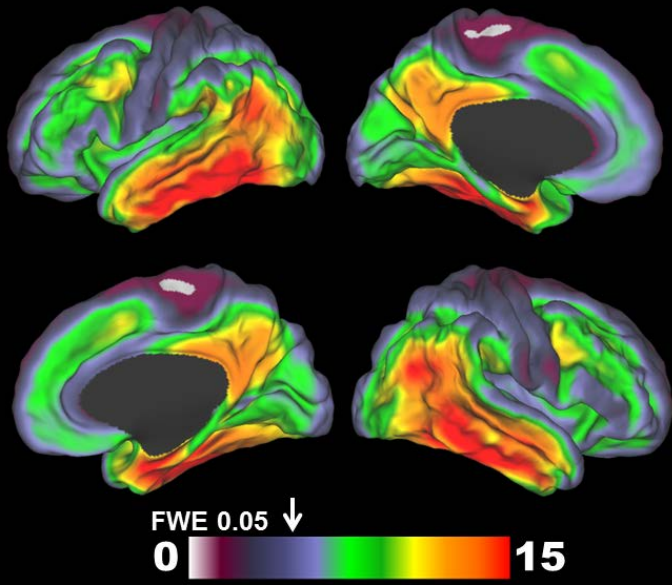
- Amyloid mediation effect = 0.52, 95% CI (0.30, 0.79)
- Total effect = 0.78 (95% CI [0.45, 1.11])
  - 67% being mediated by amyloid

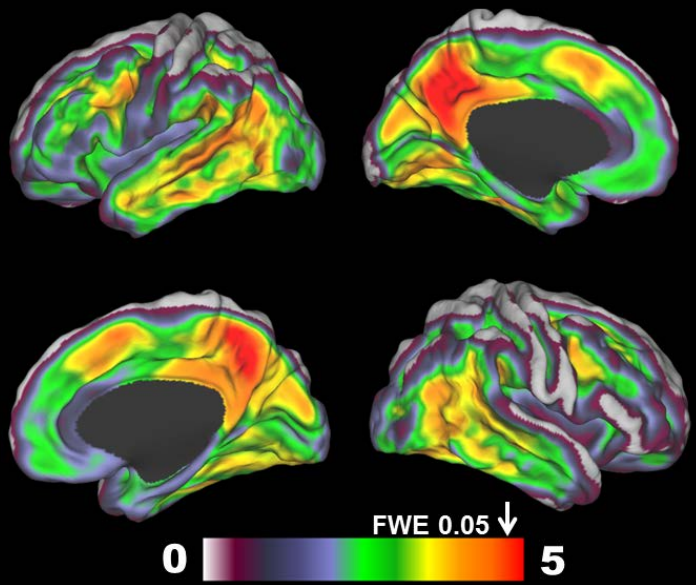






$$Tau_{voxel} \sim \beta_1 A\beta + \beta_2 NFQ + \beta_3 Age + \varepsilon$$





CONCLUSIONS

- *AD-related tau deposition occurs within several distinct functional brain networks*
  - *Atypical tau deposition patterns are associated with age of disease onset*
  - *Elevated Tau-PET signal emerges network-wide rather than focally and sequentially, but longitudinal studies are needed to validate this*

- *Beta-amyloid largely mediates the relationship between networks and tau deposition*

TAKE HOME

- *This study implicates large-scale brain networks in the pathophysiology of tau deposition and supports incorporating large-scale network physiology into disease models linking tau and amyloid.*

- *This study also suggests that quantifying the degree to which certain tau – deposition patterns are present may be an attractive alternative to Braak-like staging of sequential progression through a predetermined/expected pattern of tau deposition.*

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