Biomarker Patterns in AD Subtypes: Implications for Pathophysiology and Diagnosis

Gil Rabinovici, M.D.

Associate Professor of Neurology

UCSF Memory & Aging Center

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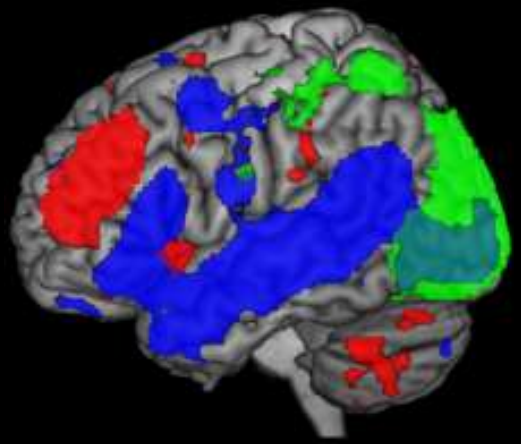
  - American College of Radiology Imaging Network
  - Association for Frontotemporal Lobar Degeneration
  - John Douglas French Foundation
  - Michael J. Fox Foundation
  - Tau Consortium

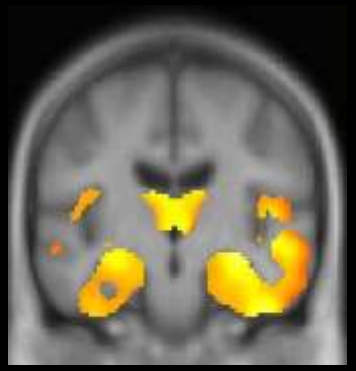
AD Patients seen at UCSF by Predominant Cognitive Phenotype (1998-2012)

AD-"FRONTAL"– 6%
Dysexecutive, Behavioral

AD-LANGUAGE – 18%
Logopenic Primary Progressive Aphasia



AD-VISUAL – 13%
Posterior Cortical Atrophy

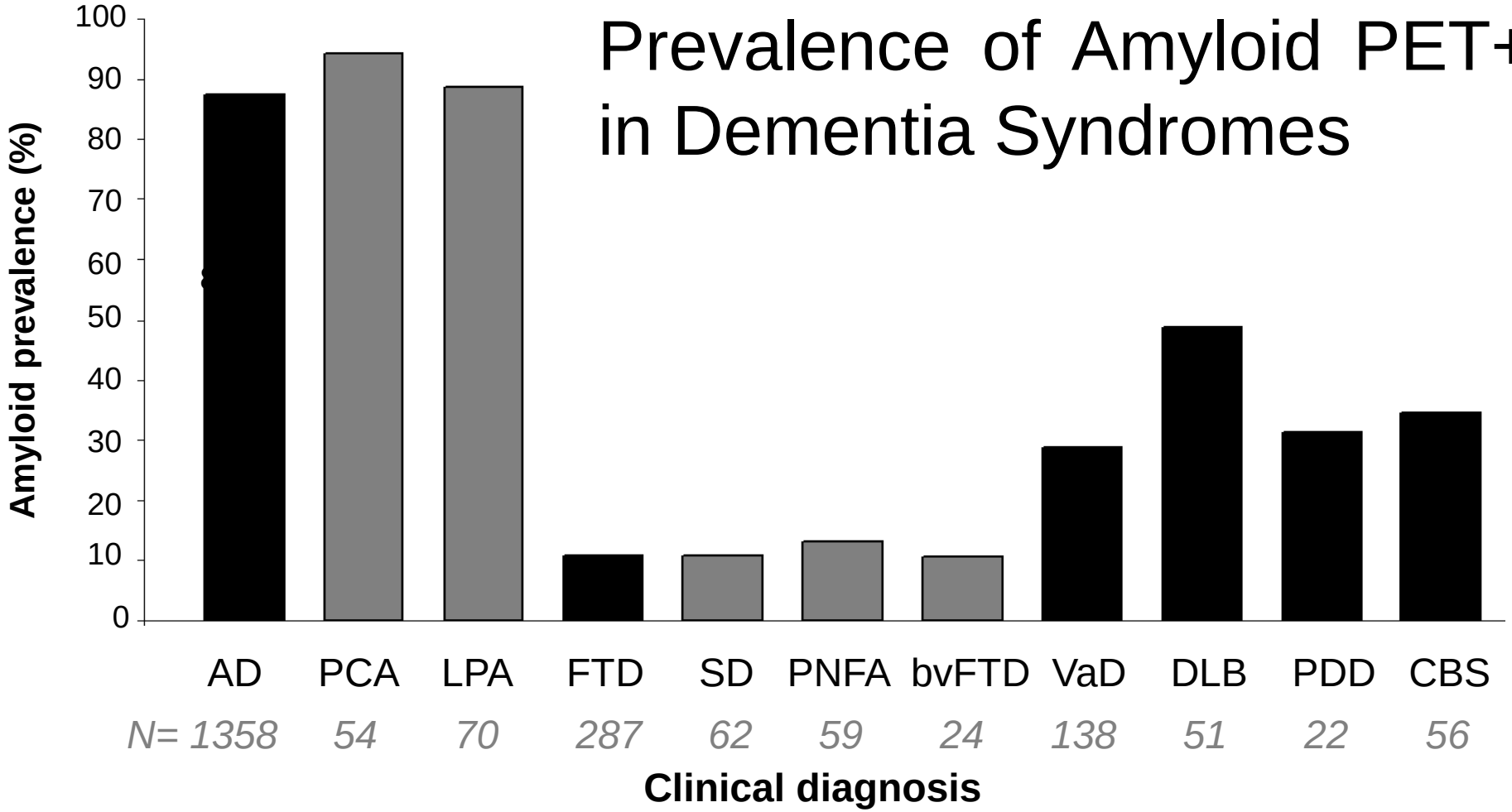


AD-MEMORY – 63%
"Typical" AD

Non-Amnestic Presentations in Current AD Diagnostic Criteria

- Probable AD dementia (NIA-AA)
  - Initial and most prominent deficit can be amnestic (most common) or non-amnestic (language, visuospatial or executive functions)
  - Aβ and neuronal injury markers increase confidence in AD pathophysiology
- Atypical AD (IWG-2)
  - PPA (logopenic-variant), PCA, “frontal-variant”
  - Pathophysiology marker required
    - Positive amyloid PET
    - CSF: low $A\beta_{42}$, high total tau/p-Tau

Prevalence of Amyloid PET+ in Dementia Syndromes



AD=Alzheimer's disease; PCA=Posterior cortical atrophy; LPA=Logopenic aphasia; (bv)FTD= (behavioral variant) Frontotemporal dementia; SD=Semantic dementia; PNFA= Progressive non-fluent aphasia; VaD=Vascular dementia; DLB=Dementia with Lewy bodies; PDD=Parkinson's disease dementia; CBS=Corticobasal syndrome.

Ossenkoppele et al., JAMA 2015

CSF Biomarkers in Typical and Atypical AD

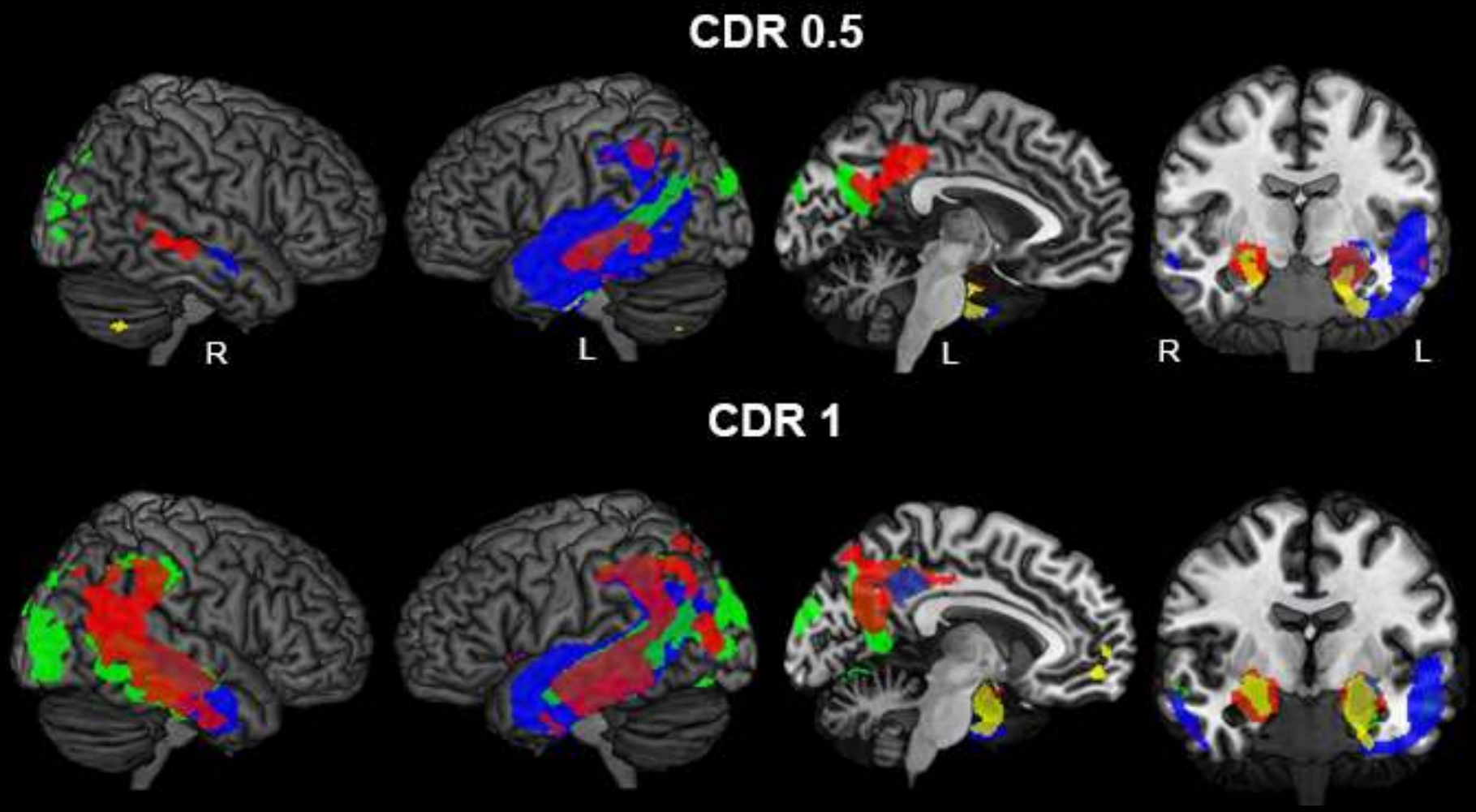
Table 1 Demographics and CSF profiles of individuals fulfilling IWG-2 criteria for typical/atypical Alzheimer's disease

	Asymptomatic controls ($n = 30$)	Typical Alzheimer's disease ($n = 61$)	Atypical Alzheimer's disease ($n = 36$)	Typical vs atypical Alzheimer's disease (p value)
Age at LP [median and interquartile range]	59.8 ± 9.9 [63.5 (50.0–67.0)]	62.5 ± 6.6 [62 (59.0–68.0)]	62.3 ± 7.4 [62.5 (56.5–67.5)]	0.90
Sex (% male)	46.7	26.2	44.4	0.08
MMSE	29.7 ± 0.5**	20.6 ± 6.4	19.1 ± 7.5	0.54
Months to LP	–	43.3 ± 25.2	48.0 ± 28.6	0.42
Estimated rate of decline (MMSE/year)*	–	2.5 (1.3–4.6)	2.8 (1.4–5.3)	0.60
Aβ1-42 (pg/ml)	844.7 ± 246.3**	276.8 ± 100.8	293.3 ± 104.6	0.45
T-Tau (pg/ml)*	235.7 (198.0–386.4)**	694.9 (415.0–892.1)	642.6 (520.4–878.5)	0.63
P-Tau (pg/L)	52.6 ± 18.6**	96.2 ± 44.7	96.0 ± 34.9	0.98
Tau/Aβ1-42 ratio*	0.3 (0.2–0.4)**	2.5 (1.8–3.9)	2.5 (1.7–4.1)	0.92
NFL (ng/L)*	649 (516–850)**	1125 (737–1400)	1235 (1070–1610)	0.03^
YKL-40 (ng/L)	0.127 ± 0.06**	0.169 ± 0.06	0.181 ± 0.07	0.46

Paterson et al., J Neurol 2015
Ossenkoppele et al., Neurobiol Aging 2015

MRI Atrophy (VBM)

395 AD subjects from UCSF/VUMC
44% CDR 0.5 / 56% CDR 1.0



Ossenkoppele et al., HBM 2015

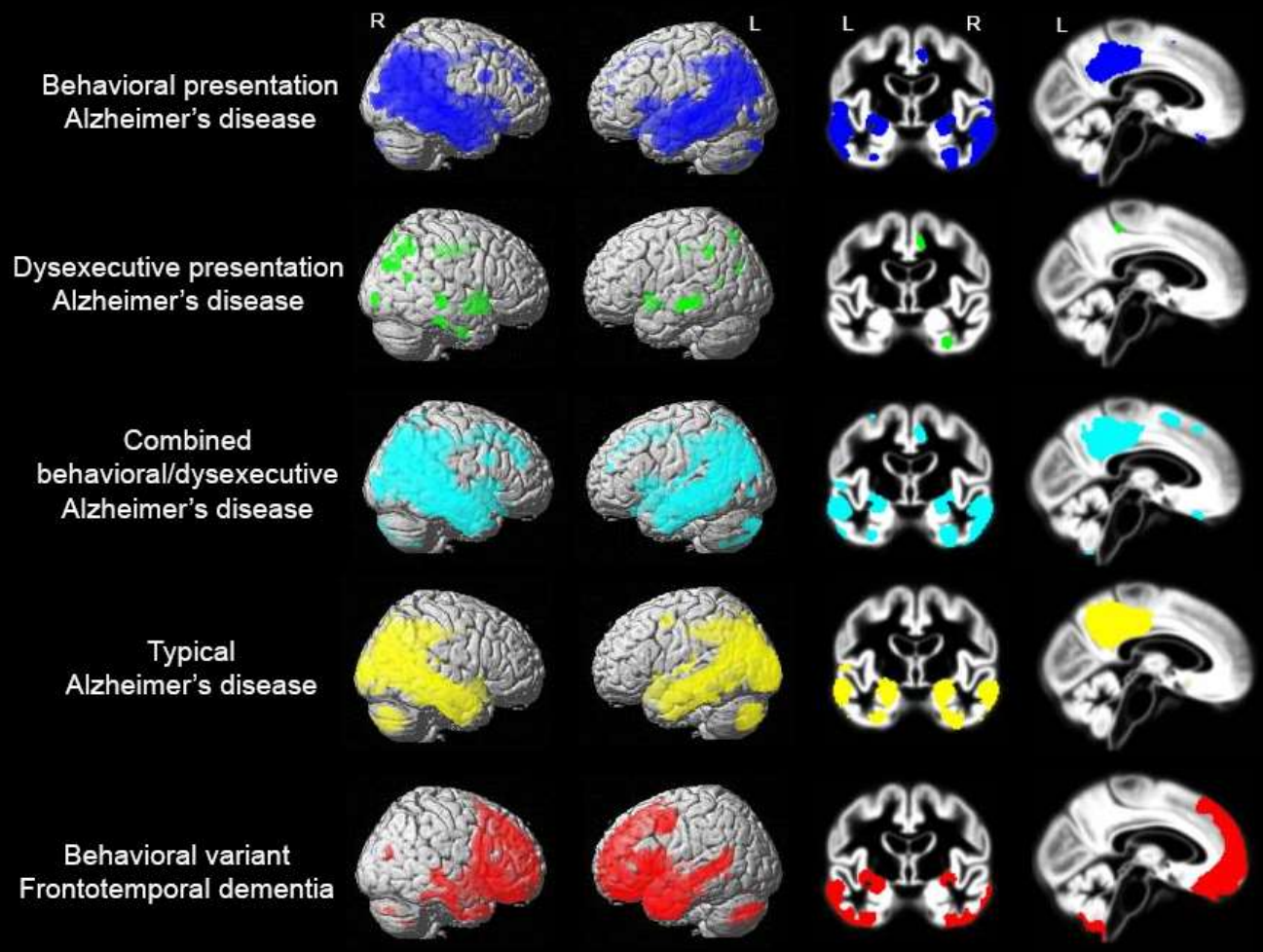
Posterior Cortical Atrophy More Sensitive than Hippocampal Volume in Atypical AD

Sensitivity

	Hippo Vol (adj)	**TempPar Thickness**
LO-AD (ADNI), N=97	90%	86%
EO-AD, N=14	43%	93%
lvPPA, N=18	28%	100%
PCA, N=17	35%	82%
All EO/atypical AD, N=49	35%	92%

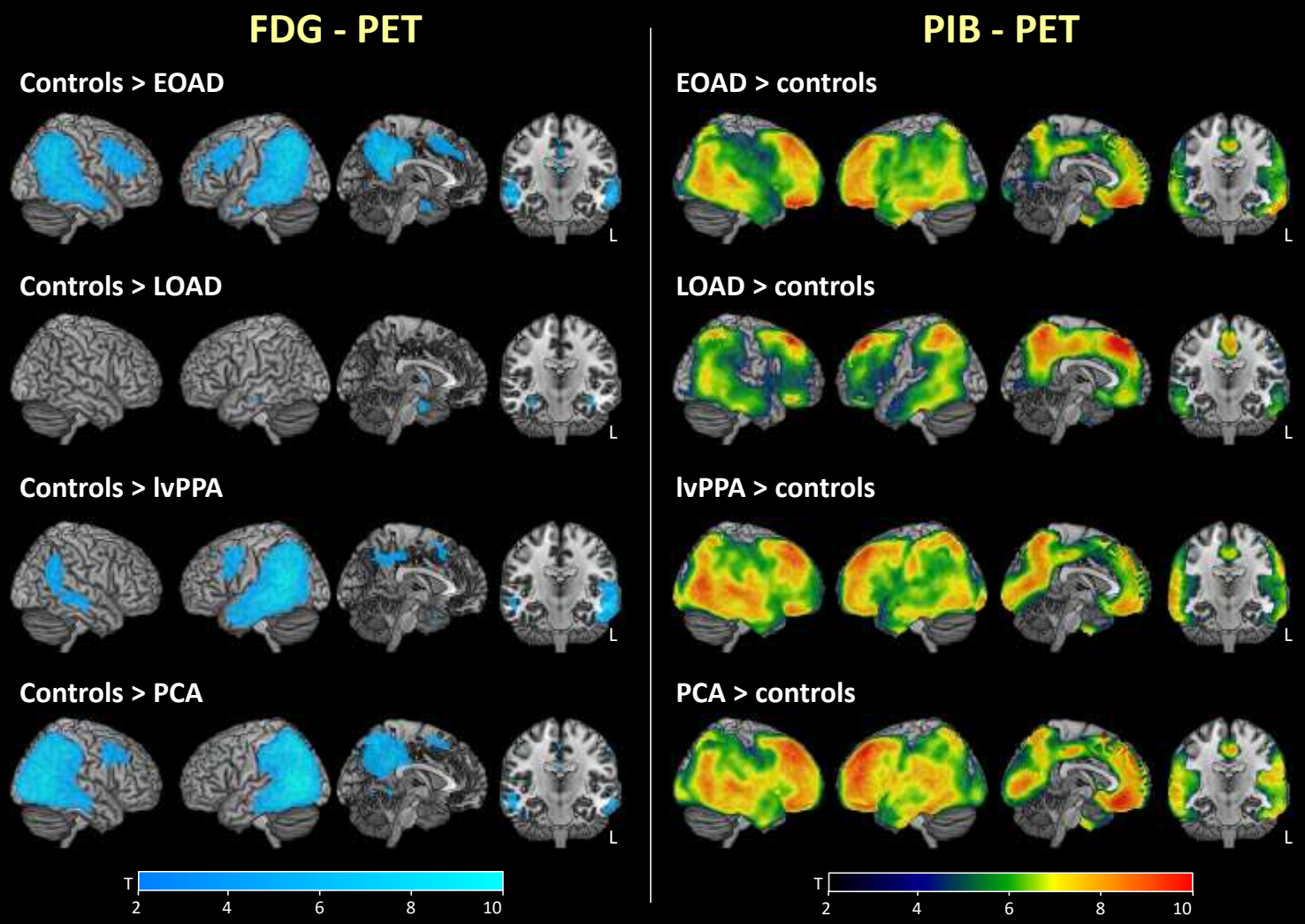
Cohn-Sheehy et al., *in prep*

Posterior Predominant Atrophy in Behavioral/Dysexecutive AD

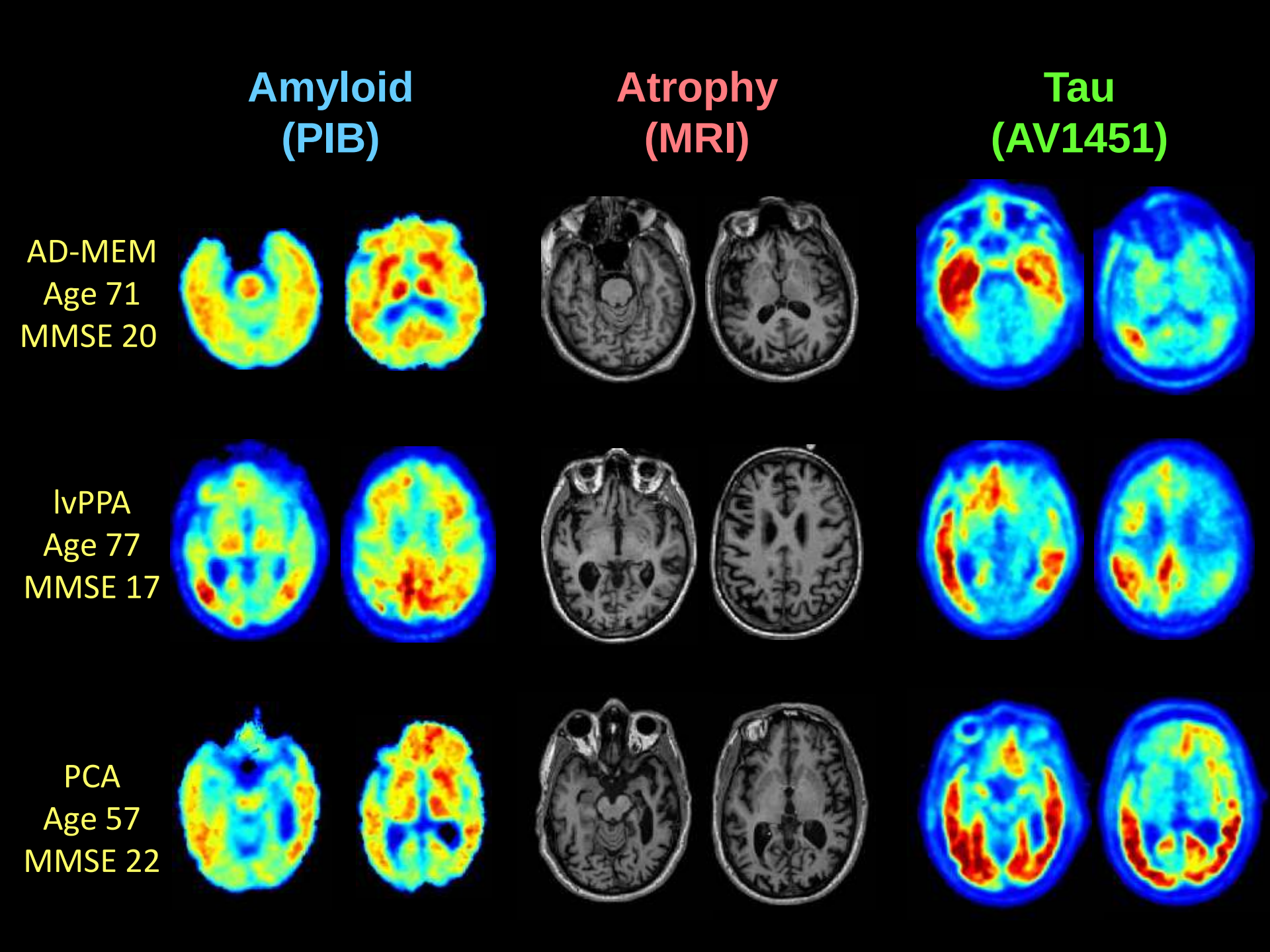


Ossenkoppele et al., Brain 2015

Diverging Amyloid and Hypometabolism Patterns in AD Variants

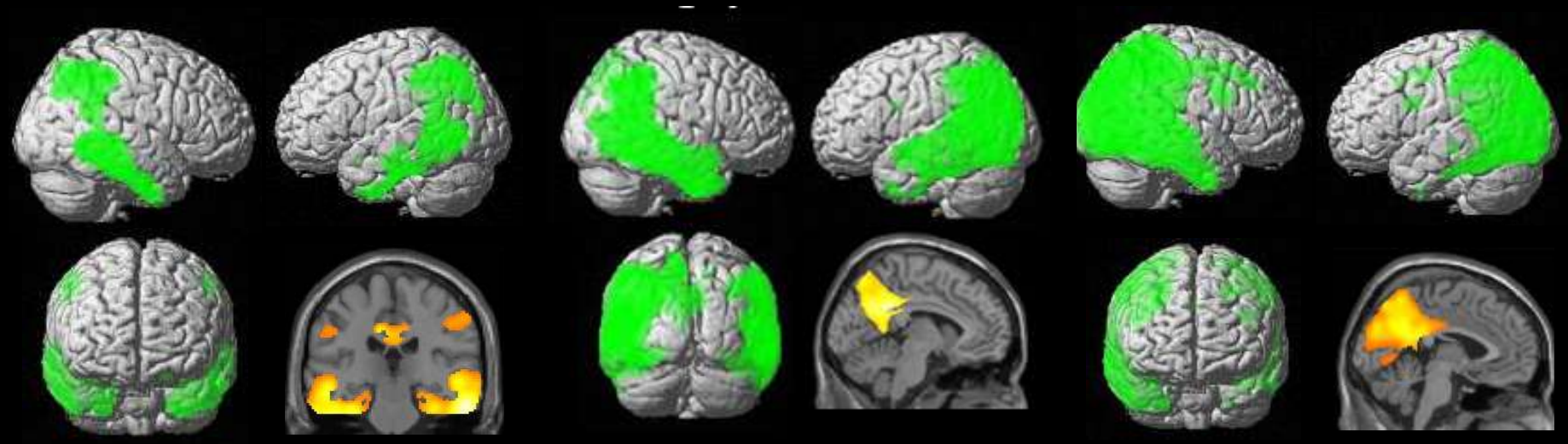


Lehmann et al., Brain 2013


Amyloid
(PIB)
Atrophy
(MRI)
Tau
(AV1451)
AD-MEM
Age 71
MMSE 20
lvPPA
Age 77
MMSE 17
PCA
Age 57
MMSE 22

Tau PET Patterns Correlate with AD Phenotype

AD-MEM > NC **lvPPA > NC** **PCA > NC**

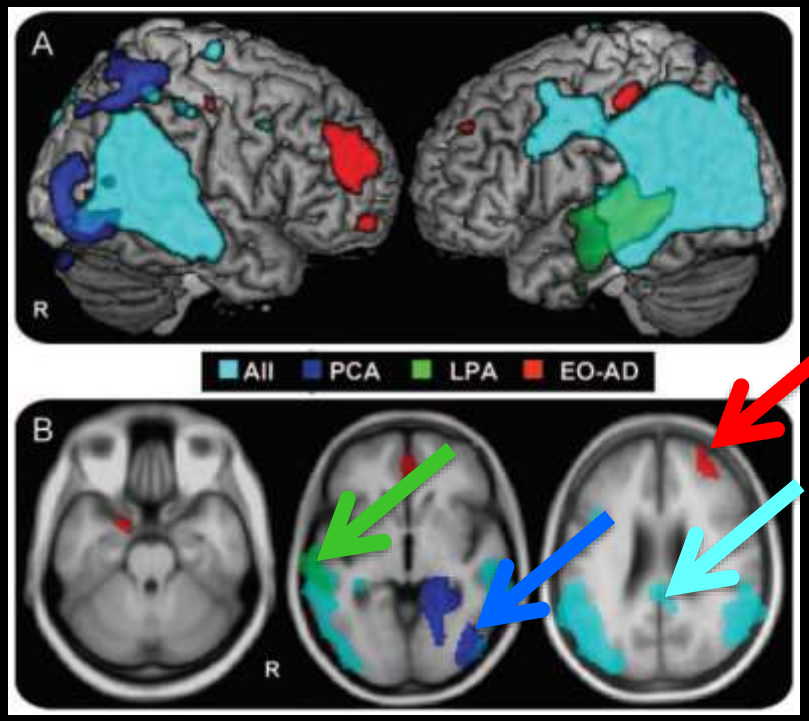


[^{18}F]AV-1451, 80-100 min SUVR, p(FWE)<0.05

Ossenkoppele et al., under review

Defining Vulnerable Networks in AD Variants

Seeds defined based on common and distinct atrophy



Selected peak atrophy voxels:

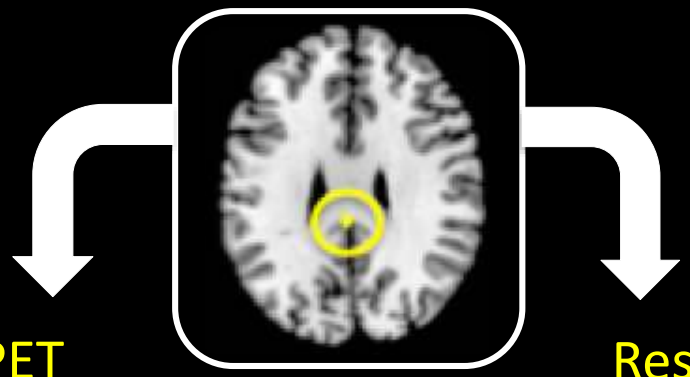
1. Posterior cingulate cortex (all AD variants)
2. R. Middle occipital cortex (PCA)
3. L. Superior temporal gyrus (lvPPA)
4. R. Middle frontal gyrus (EO-AD)

Migliaccio et al., Neurology 2009

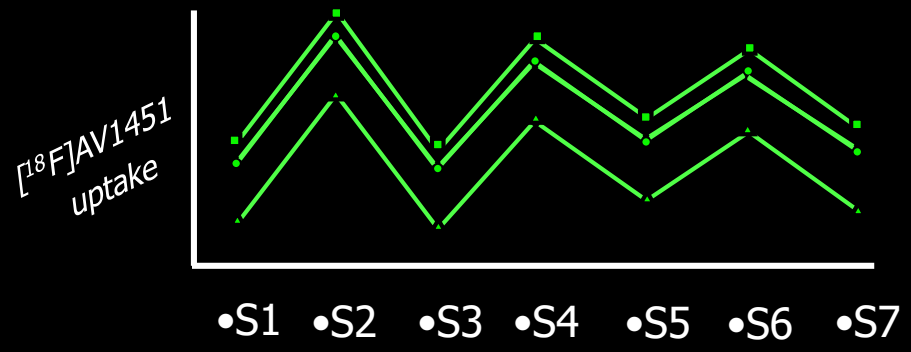
Ossenkoppele et al., HAI 2016

Defining Vulnerable Networks in AD Variants

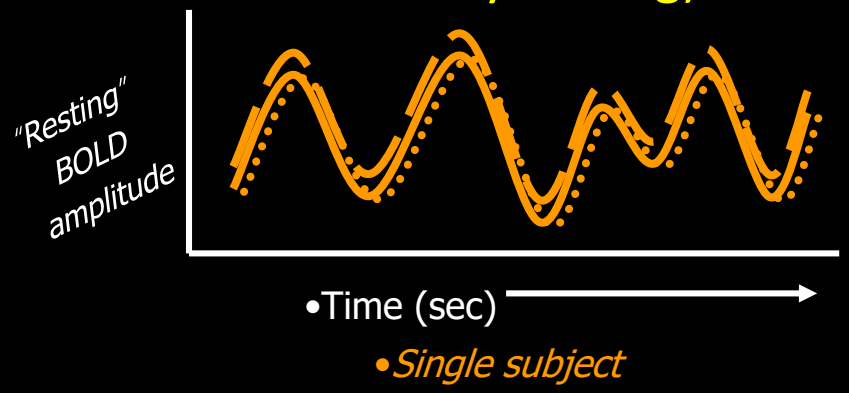
Generated covariance maps from seed regions



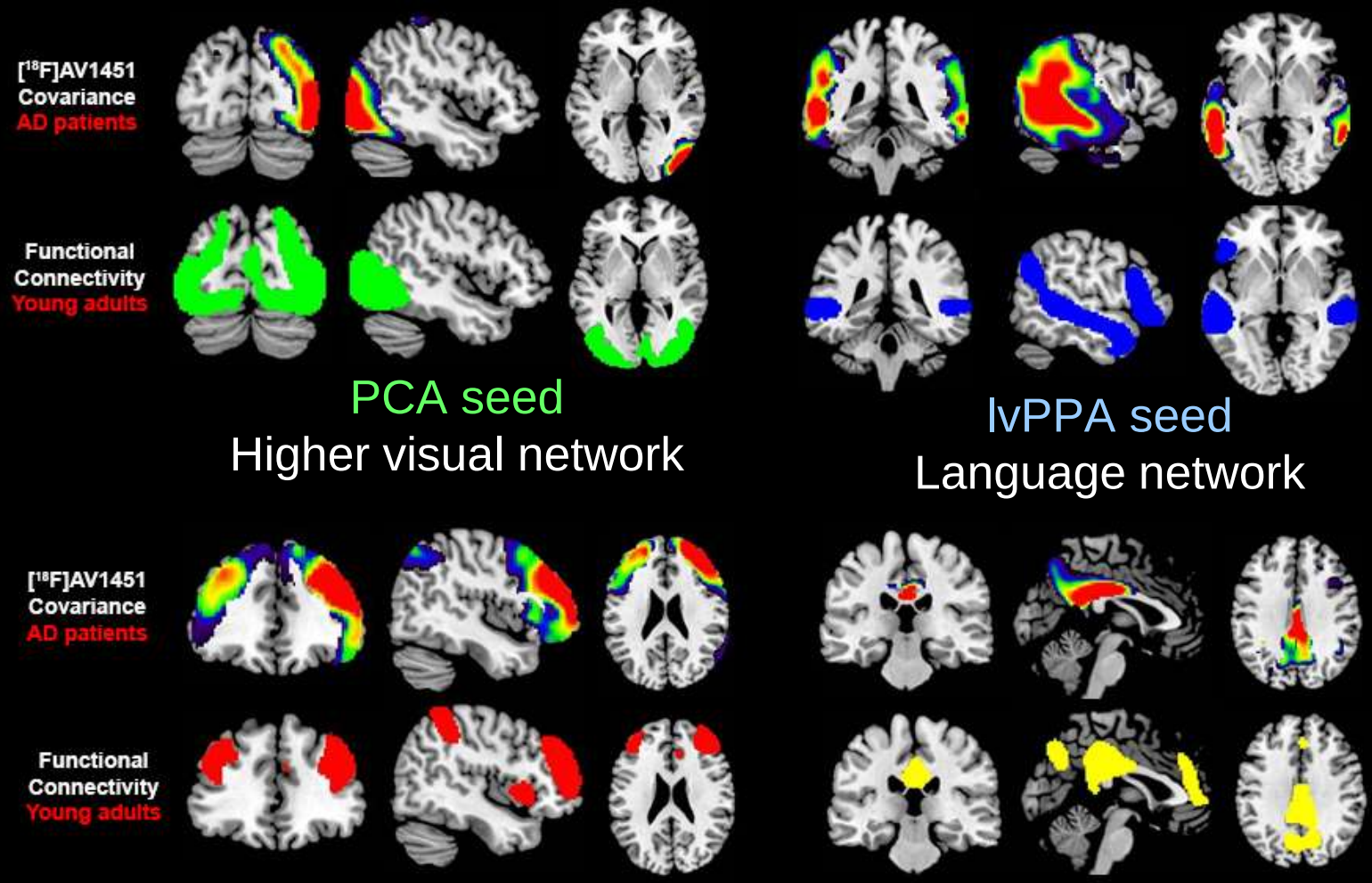
[^{18}F]AV1451 PET
(27 AD patients)

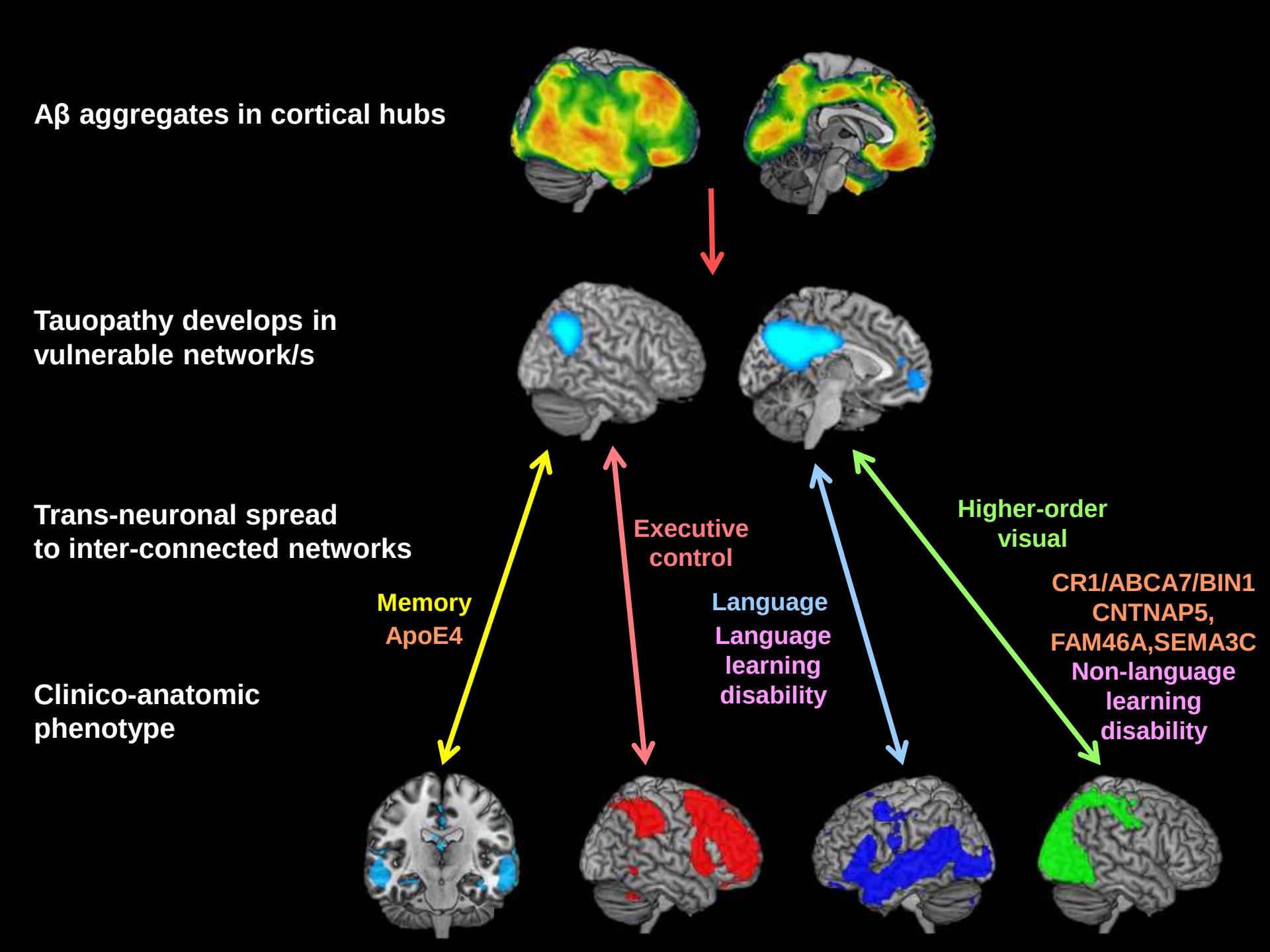


Resting-state fMRI
(1000 young controls,
www.neurosynth.org)



Tau Covariance Patterns Match Functional Networks




Aβ aggregates in cortical hubs
Tauopathy develops in vulnerable network/s
Trans-neuronal spread to inter-connected networks
Clinico-anatomic phenotype
Memory
ApoE4
Executive control
Language
Language learning disability
Higher-order visual
CR1/ABCA7/BIN1
CNTNAP5,
FAM46A,SEMA3C
Non-language learning disability

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AFTD
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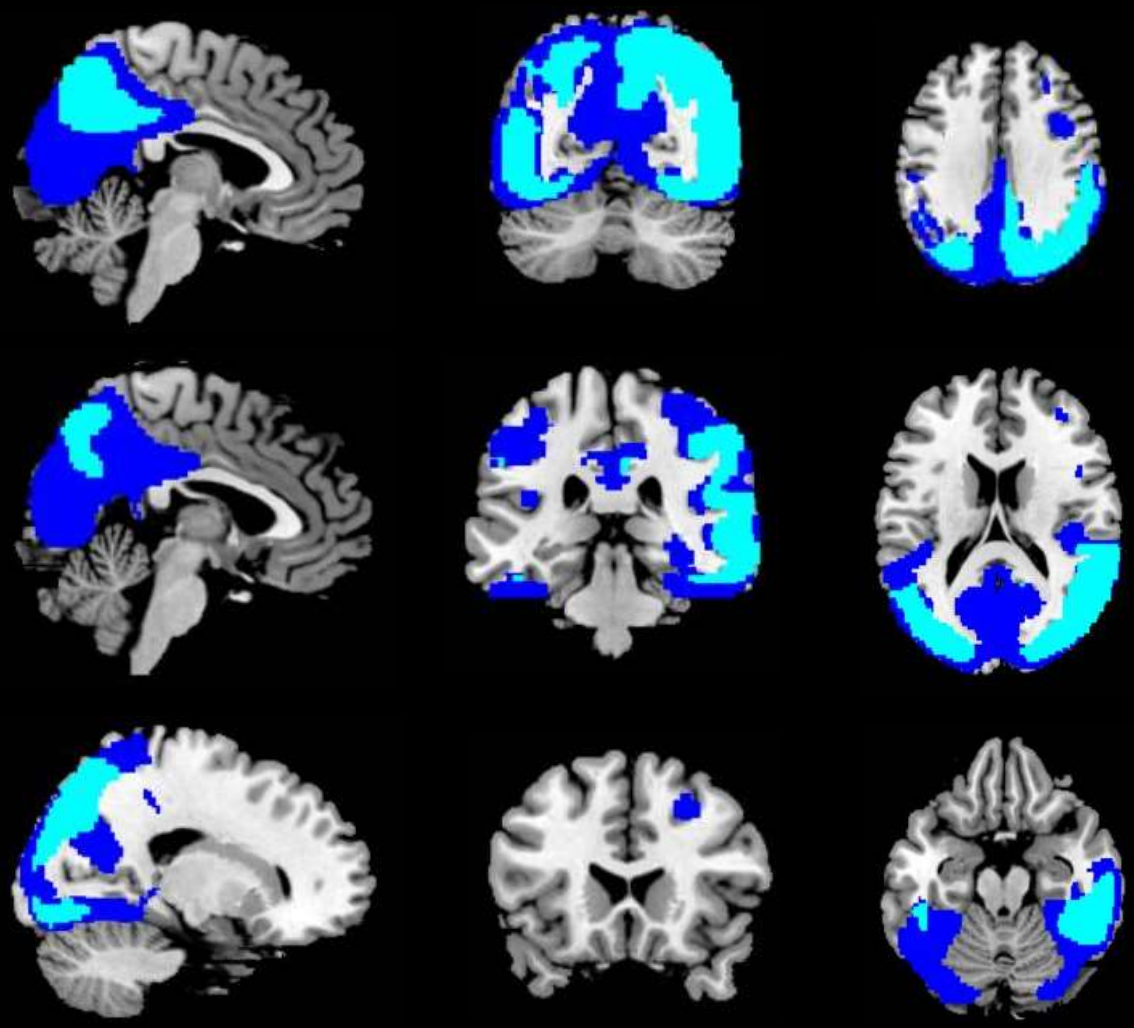
American College of Radiology
Michael J. Fox Foundation

Extra Slides

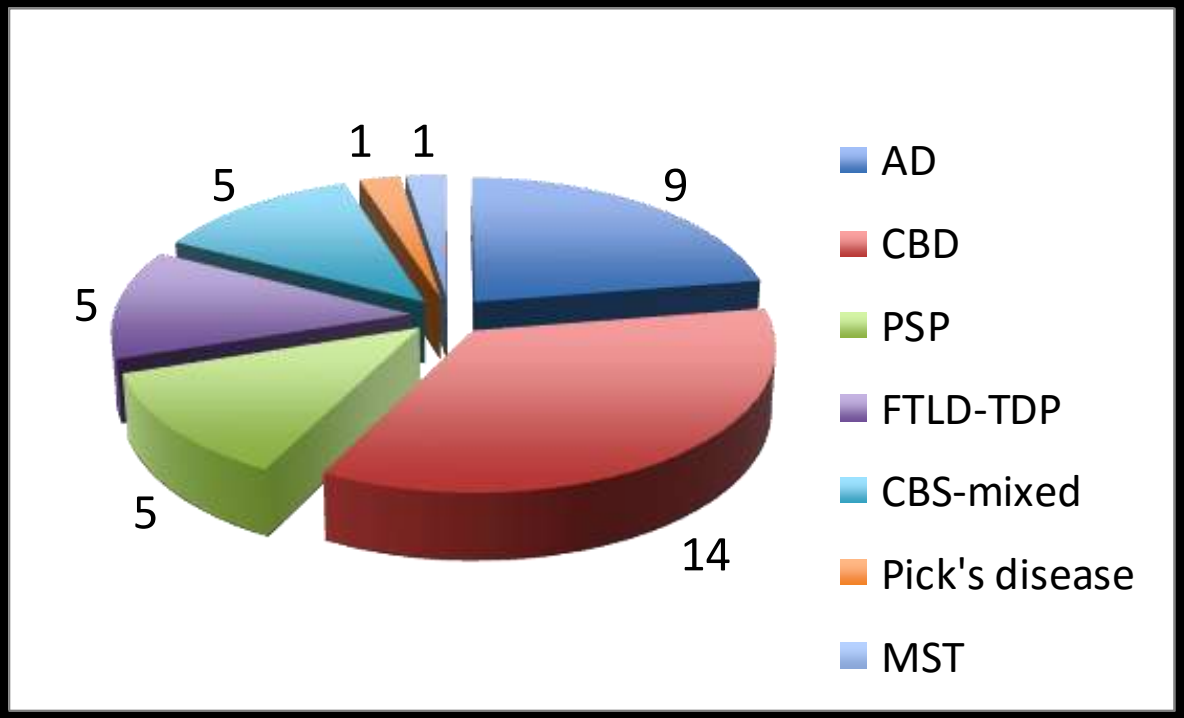
PCA (n=7) vs. NC (n=28)

AV1451 + FDG AV1451 only



Underlying Pathology in CBS

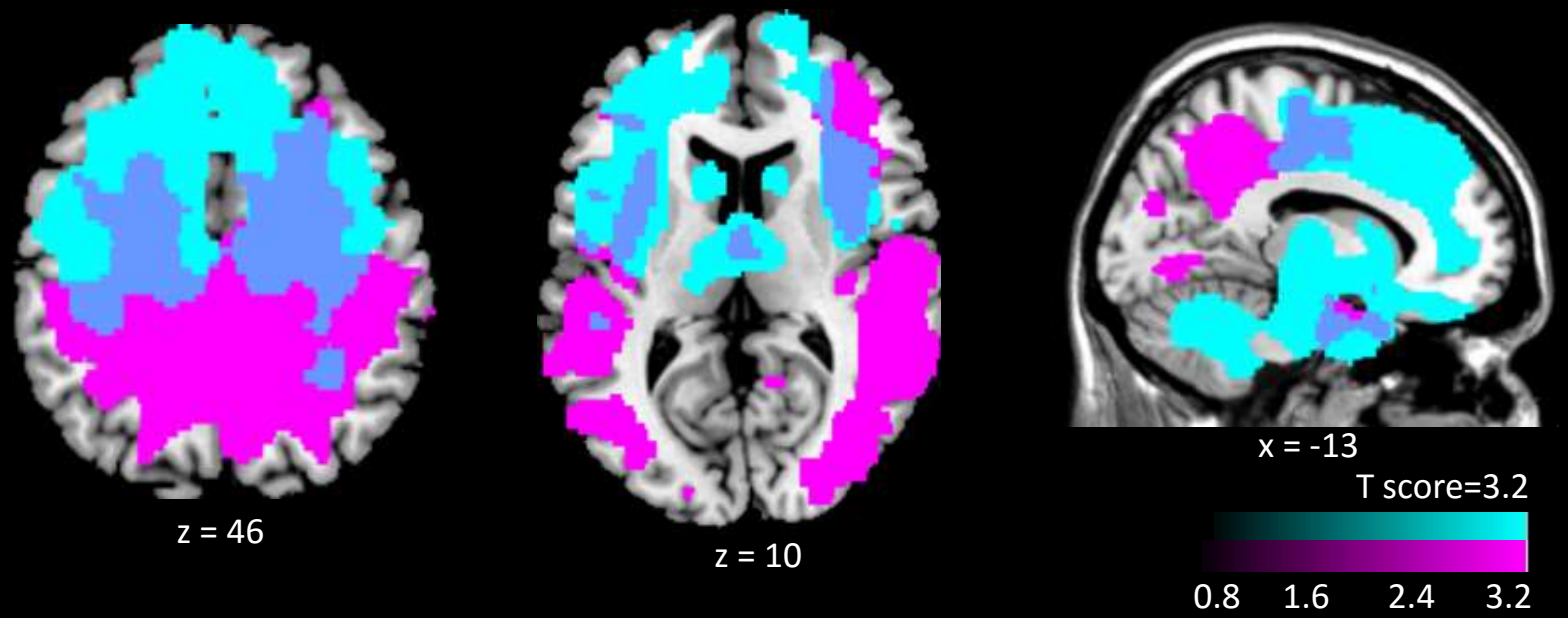
Autopsy diagnosis (N=40)



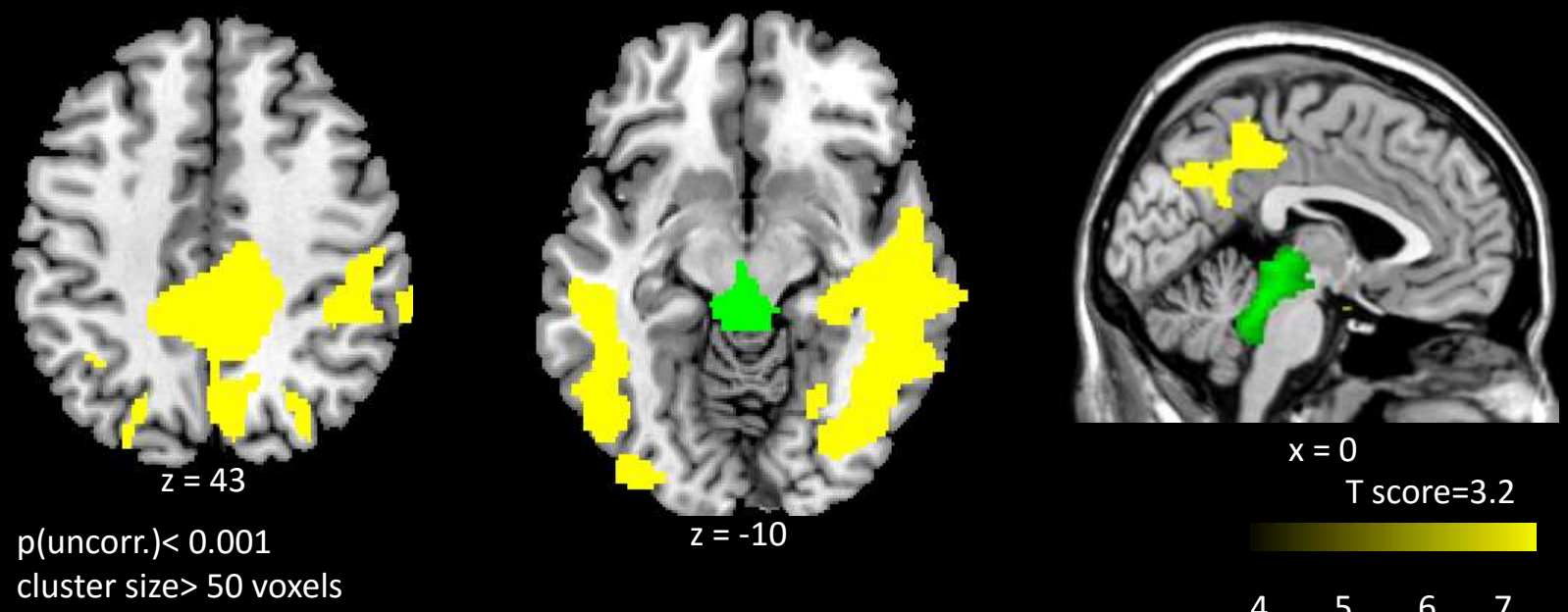
AD – Alzheimer's disease; CBD – corticobasal degeneration; PSP – progressive supranuclear palsy; FTLD-TDP – FTLD with TDP-43 inclusions; MST – multi-system tauopathy

Lee, Rabinovici et al. Ann Neurol 2011

CBS-AD < NC and CBS-FTLD <NC

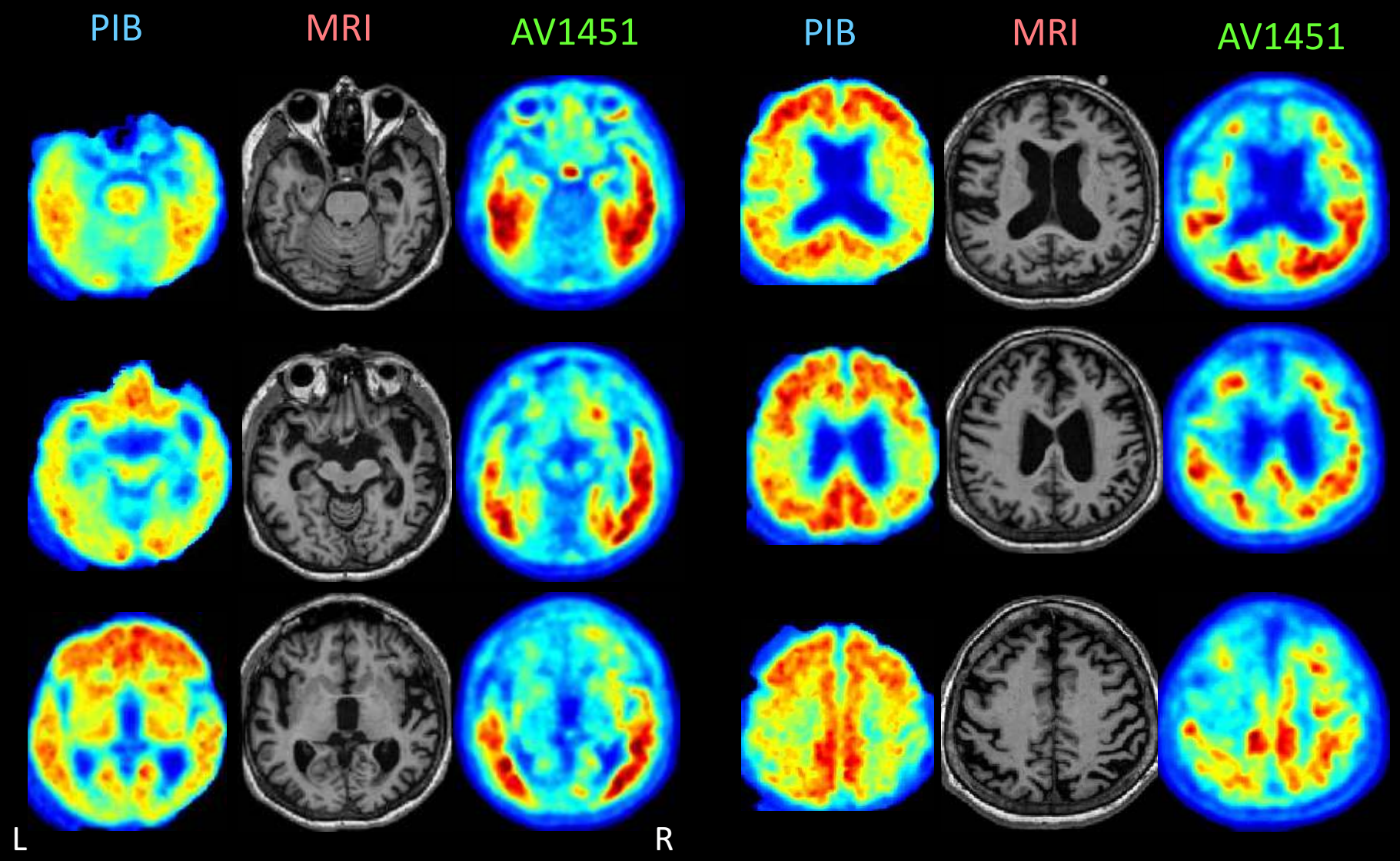


CBS-AD< CBS-FTLD and CBS-FTLD < CBS-AD

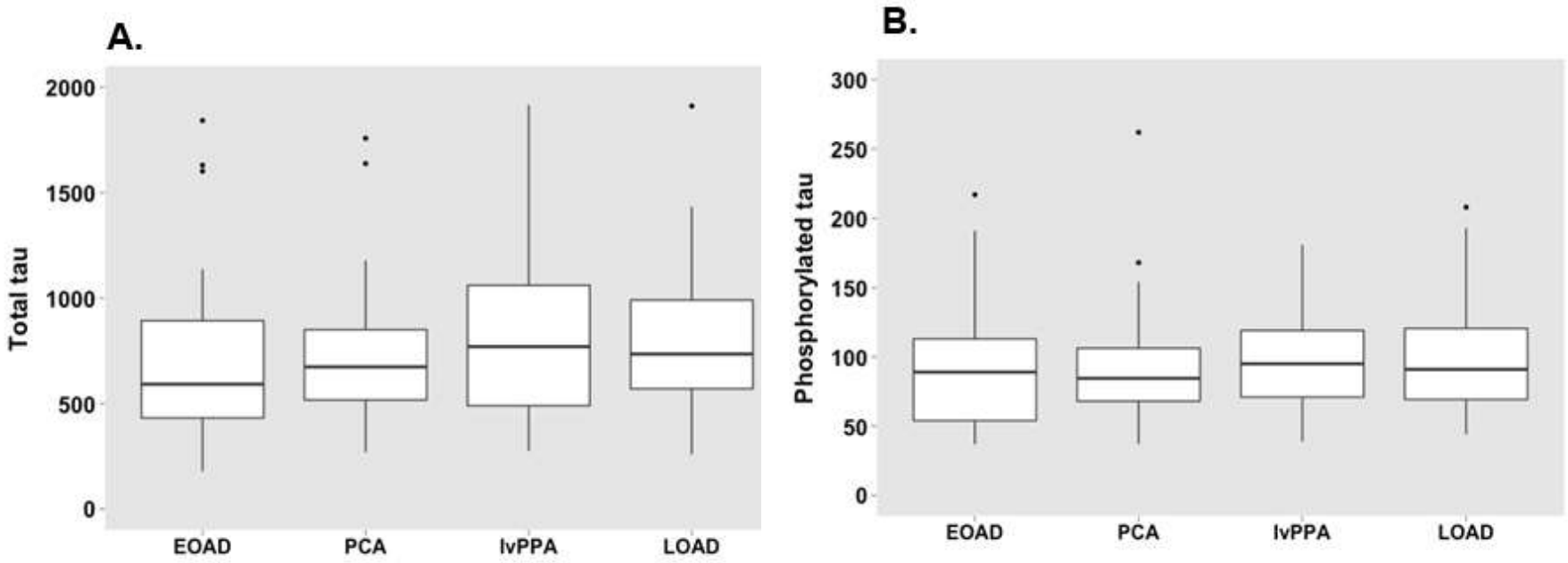


p(uncorr.)< 0.001
cluster size> 50 voxels

60 yo Corticobasal Syndrome due to AD (?)



CSF Tau in AD Variants

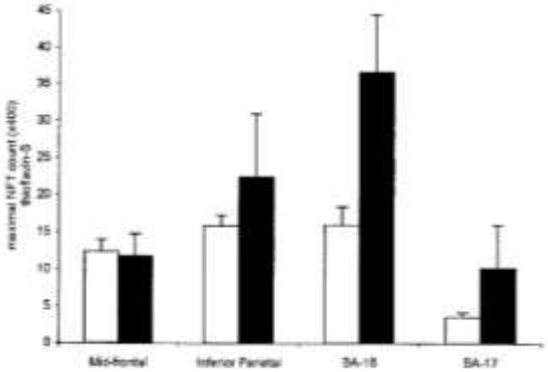


Ossenkoppele et al., Neurobiol Aging 2015

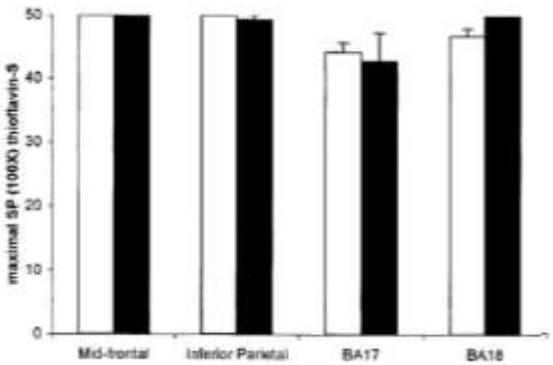
Neuropathology of Non-Amnestic AD

Posterior Cortical Atrophy

NFTs

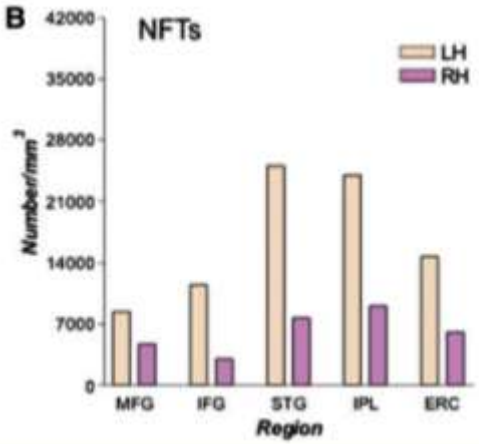


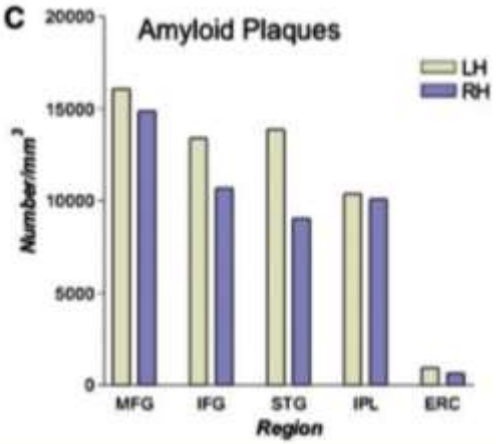
Senile plaques



Tang-Wai et al. Neurology 2004

Primary Progressive Aphasia

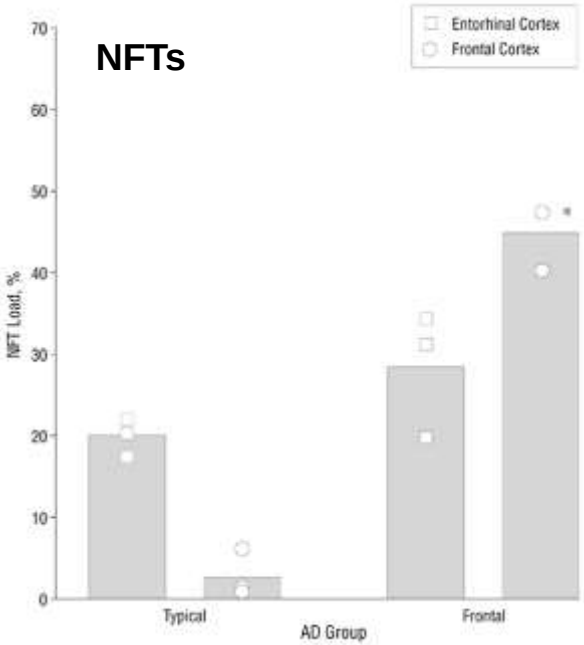




Gefen et al. Brain 2012

Frontal-Variant AD

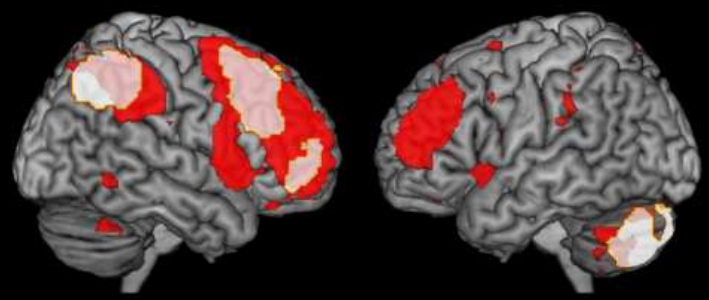
NFTs



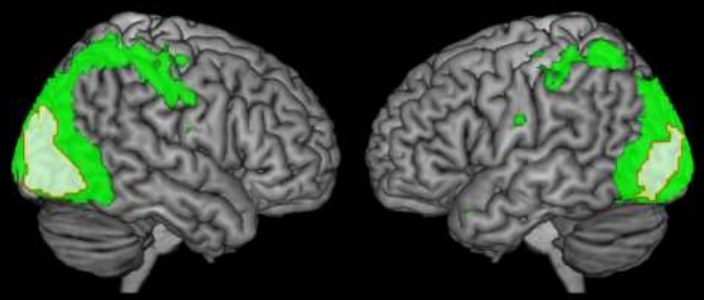
No difference in plaque distribution

Johnson et al. Arch Neurol 1999

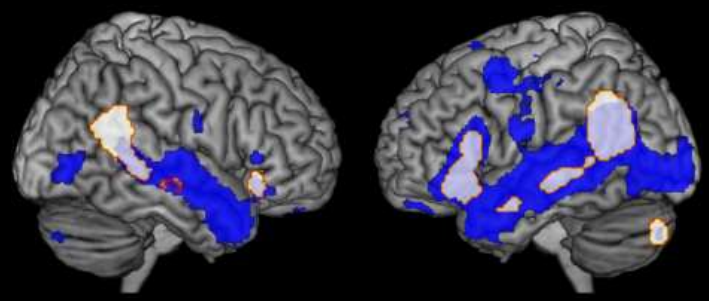
Functional Connectivity: AD Variants Target Specific Networks; Converge in DMN



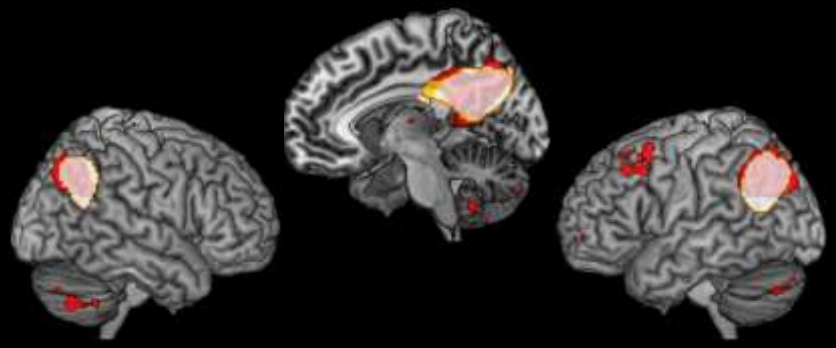
EO-AD seed
Executive control network



PCA seed
Higher visual network



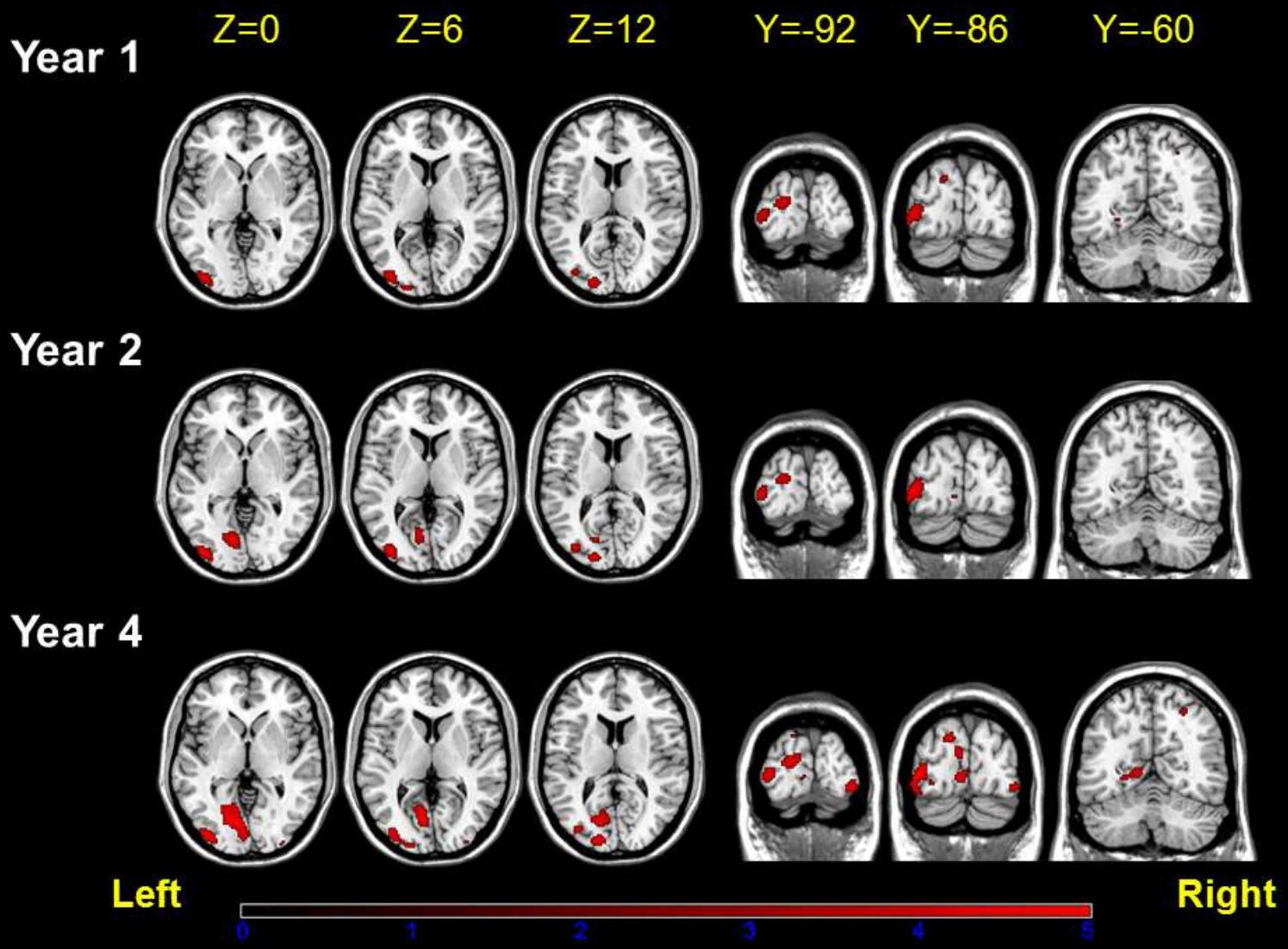
lvPPA seed
Language network



Common (PCC) seed
Posterior DMN

Lehmann et al., PNAS 2013

Imaging Prodromal PCA



Chan et al., Neurocase 2015