Network-Based Spread in AD: Evidence from Multi-Modal Human Neuroimaging

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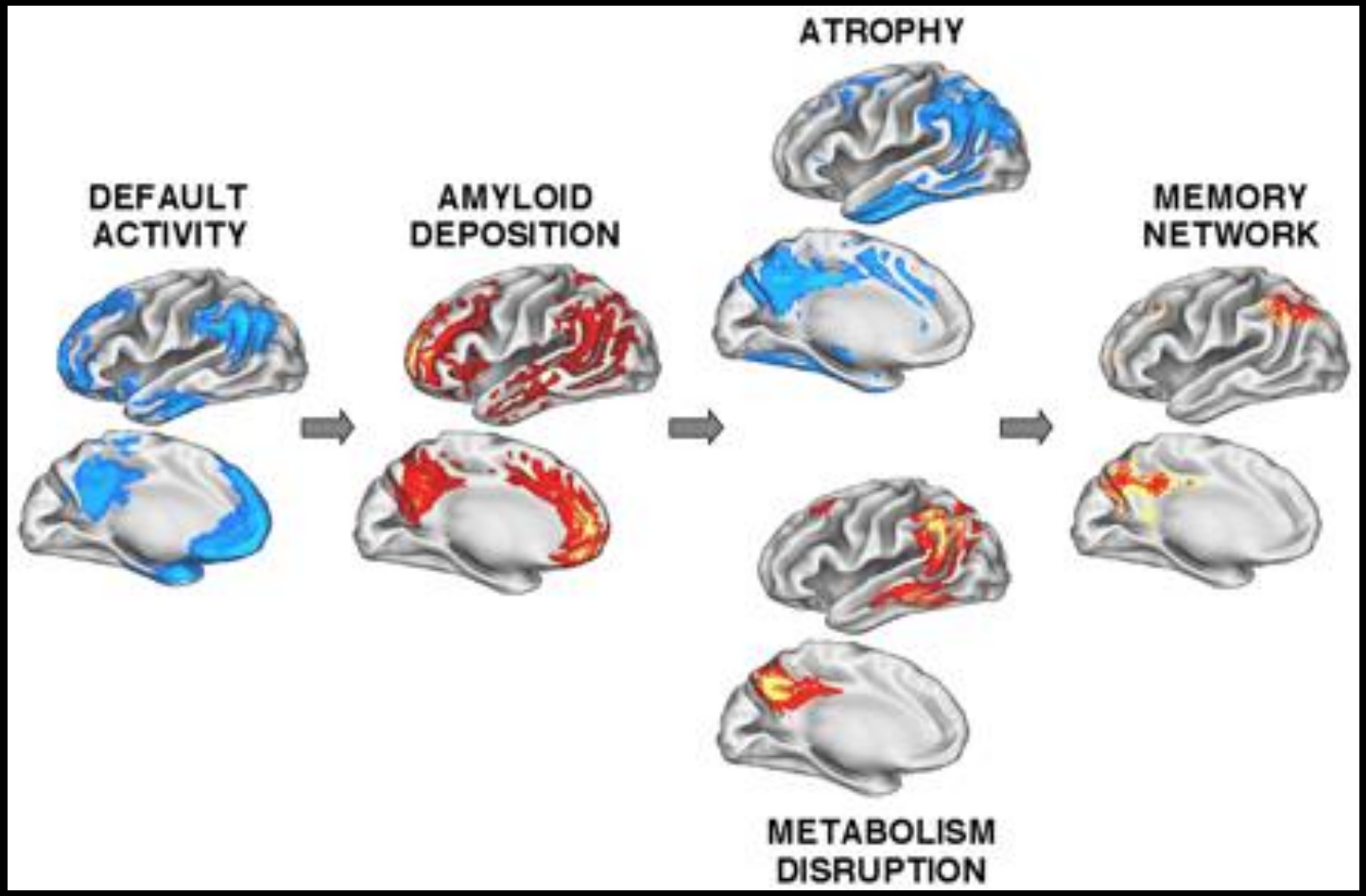
15th Annual Mt. Sinai MCI Symposium

January 14, 2017

Disclosures

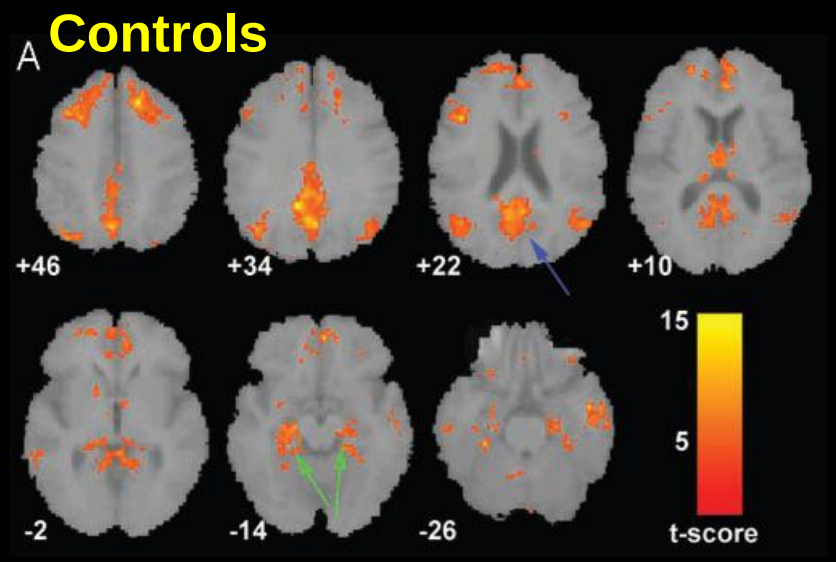
- Research support
  - Avid Radiopharmaceuticals/Eli Lilly, GE Healthcare, Piramal Imaging
- Consulting/honoraria
  - Eisai, Genentech, Lundbeck, Merck, Putnam, Roche
- Presentation includes the amyloid tracer [^{11}C]PIB and tau tracer [^{18}F]AV1451 which are not FDA-approved for clinical use

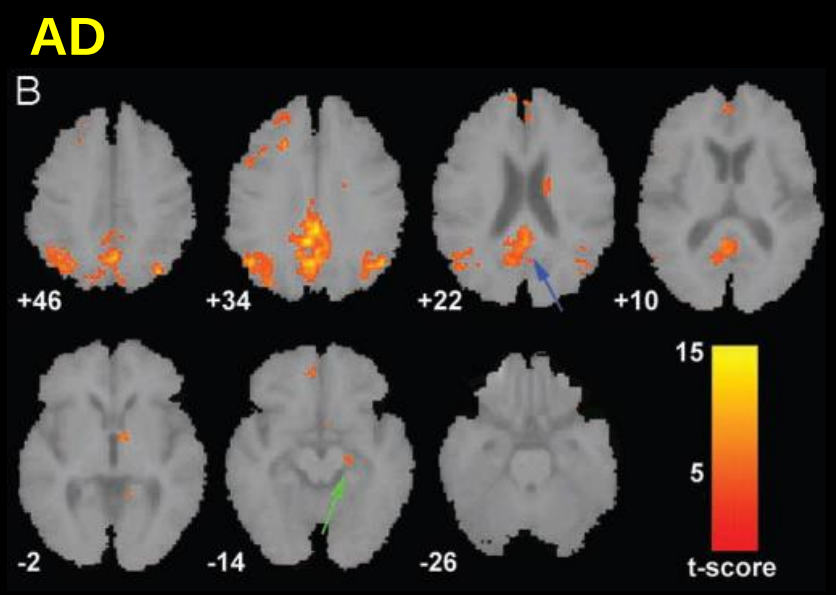
Default Mode Network (DMN) Overlaps with AD

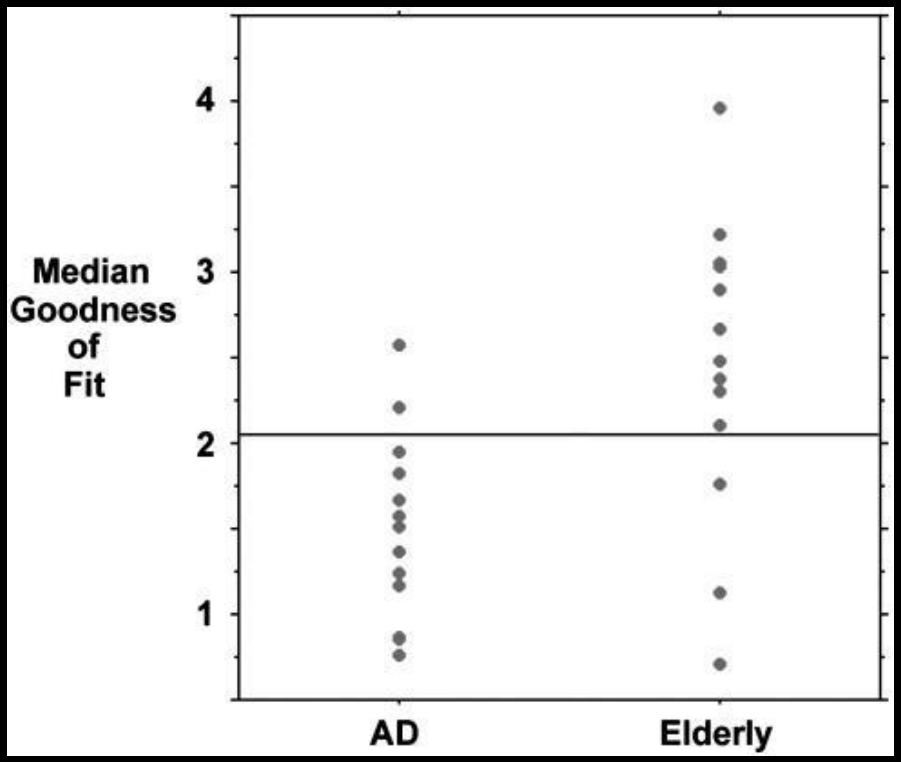


Raichle et al., PNAS 2001
Buckner et al., J Neurosci 2005

DMN Connectivity Distinguishes AD from NC

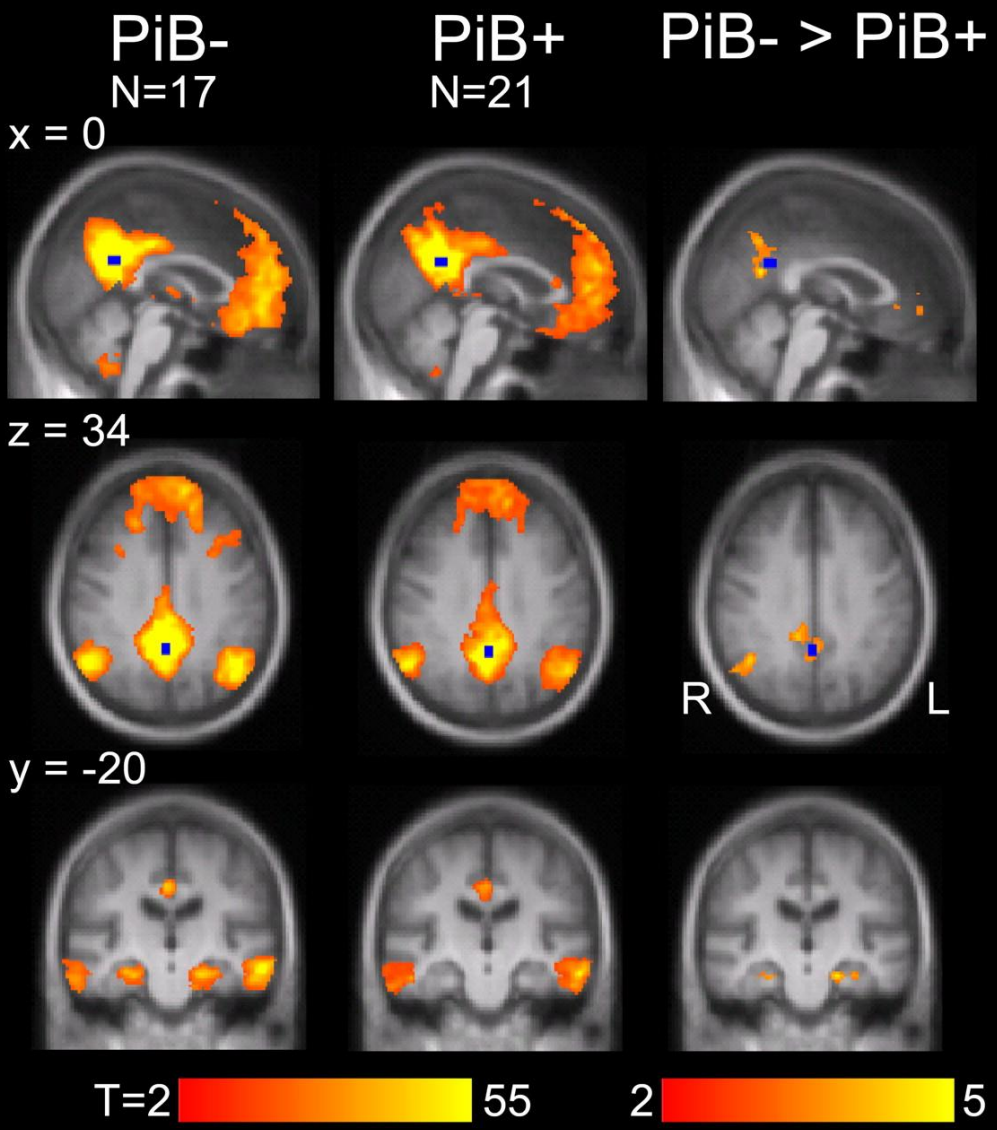






Greicius et al., PNAS 2004

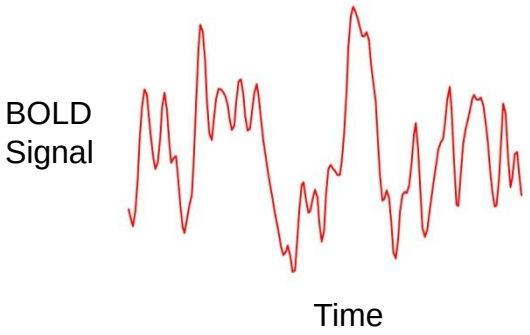
Reduced DMN Connectivity in Aβ+ Controls



Hedden et al., J Neurosci 2009

Functional Connectivity MRI of the "Resting State"

r = 0.80

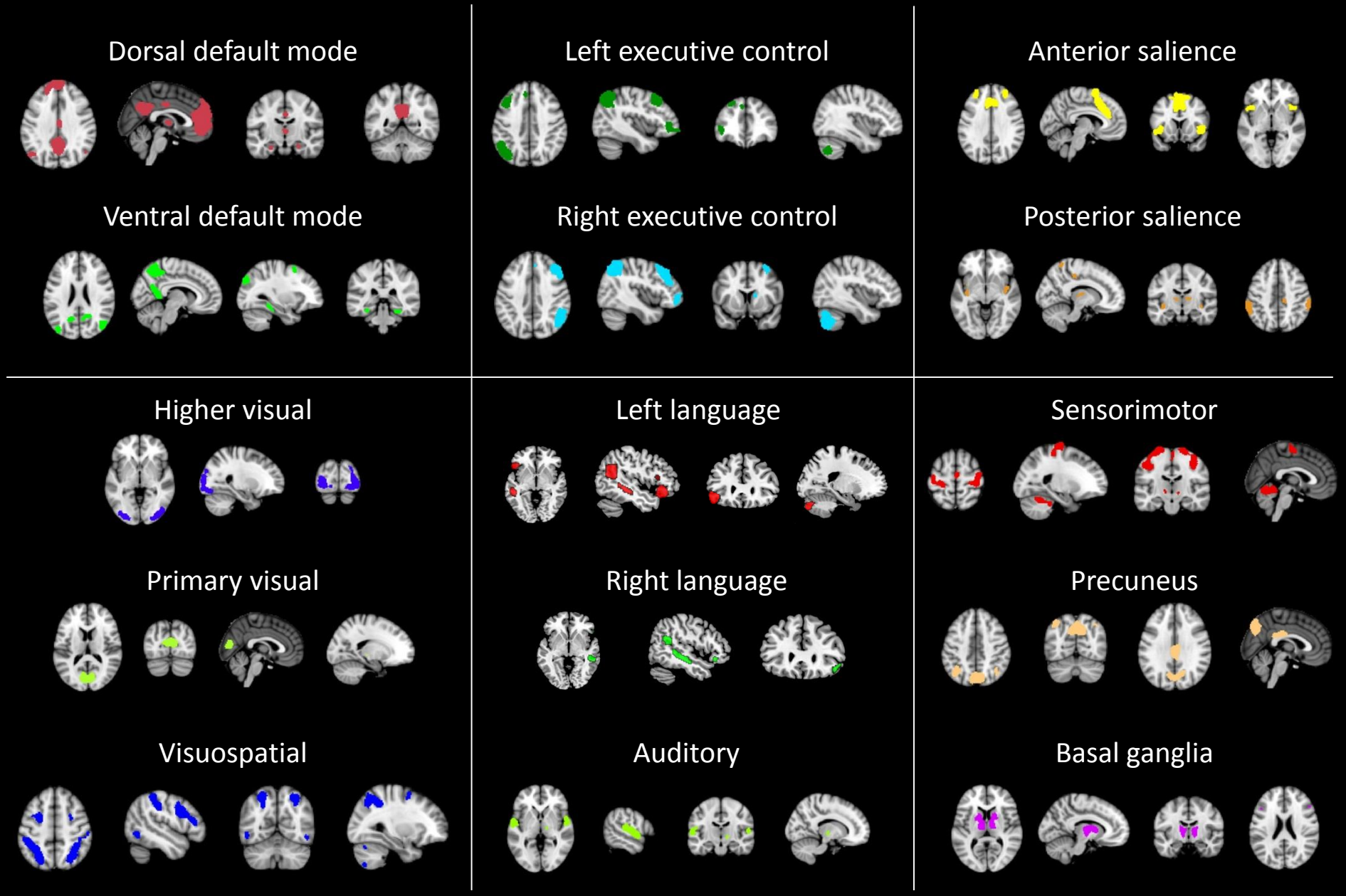


r = 0.59

r = 0.75

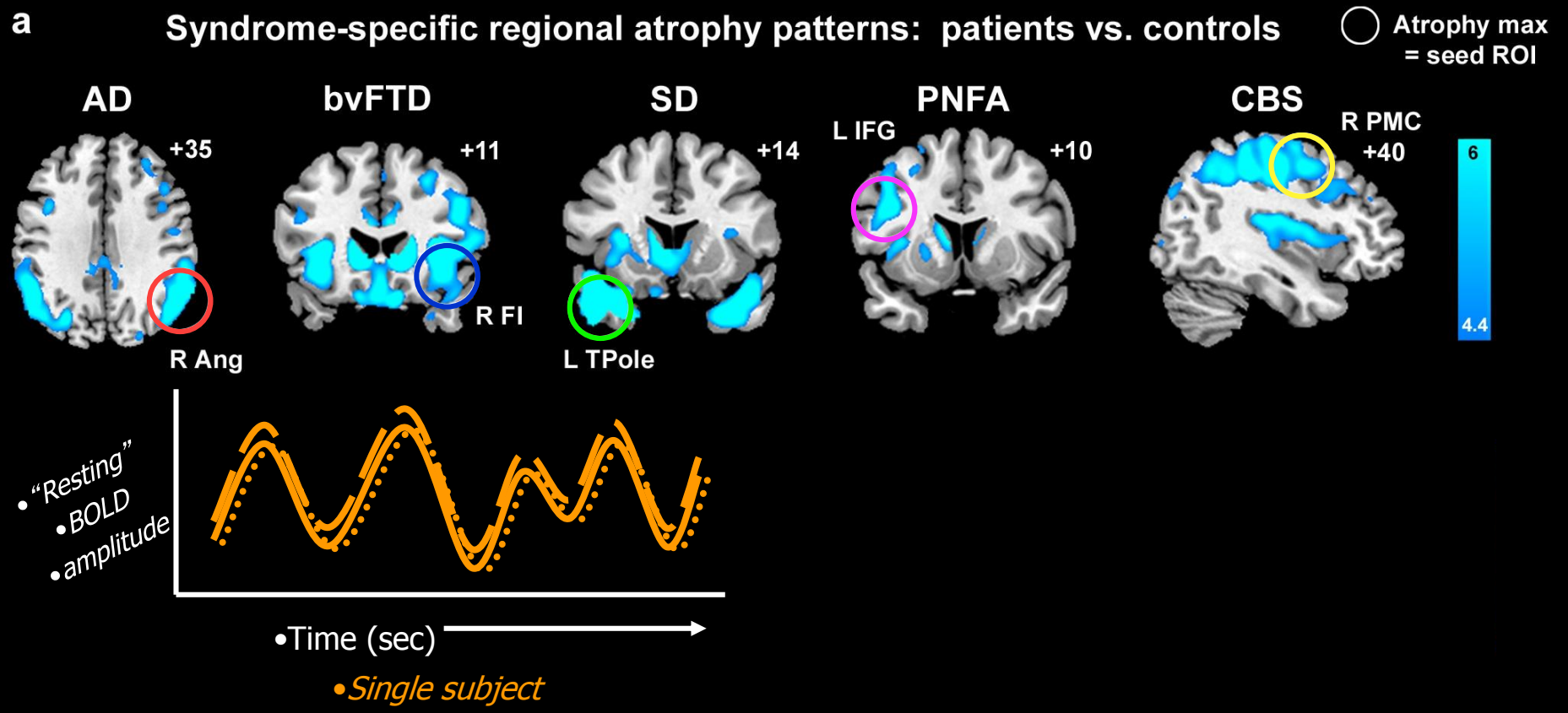
Slide courtesy of Michael Greicius

fcMRI Identifies Functional Networks



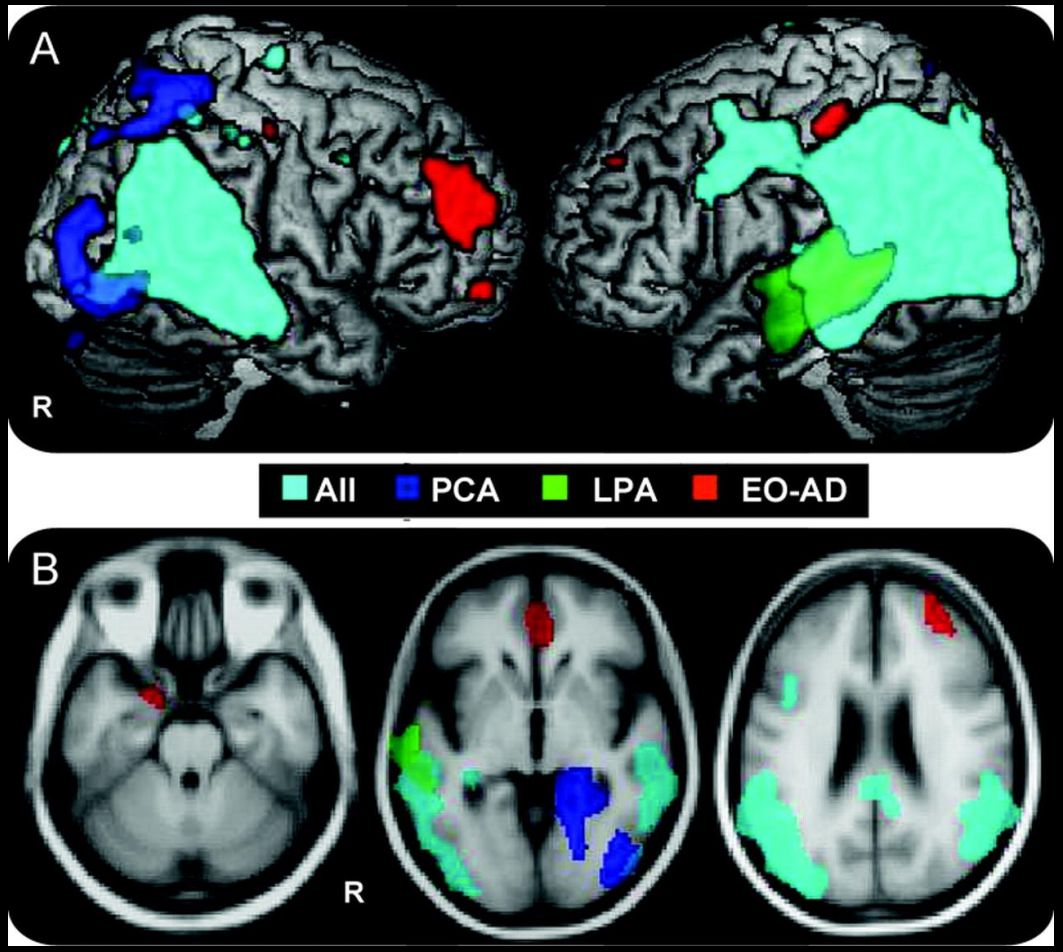
Shirer et al., Cereb Cortex 2012

Neurodegenerative Diseases Target Large Scale Brain Networks



Seeley et al., Neuron 2009

Can Network Involvement Explain Heterogeneity in AD?



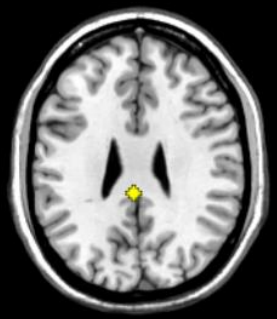
Migliaccio et al., Neurology 2009

Common and Variant-Specific AD Regions

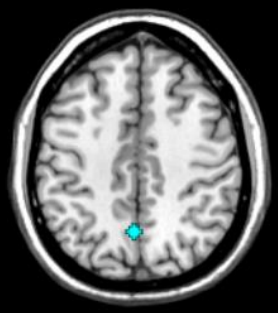
Regions commonly atrophied in AD variants

Left inferior parietal
(MNI -51 -58 10)

Right posterior cingulate cortex (PCC)
(MNI -2 -33 28)

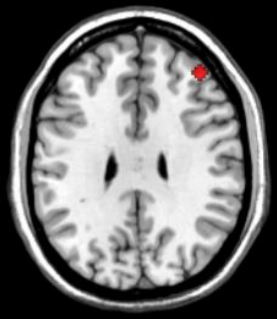


Left precuneus
(MNI -2 -60 44)

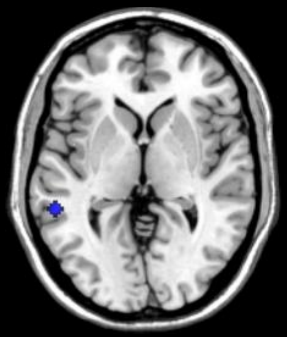


Regions specifically atrophied in AD variants

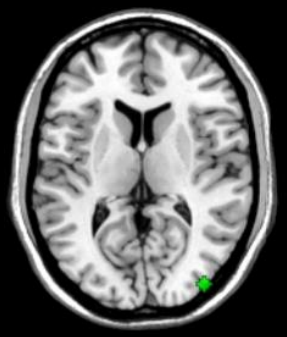
AD-MEM/EXEC
Right middle frontal gyrus
(MNI 40 42 30)



AD-LANG
Left superior temporal sulcus
(MNI -56 -40 1)

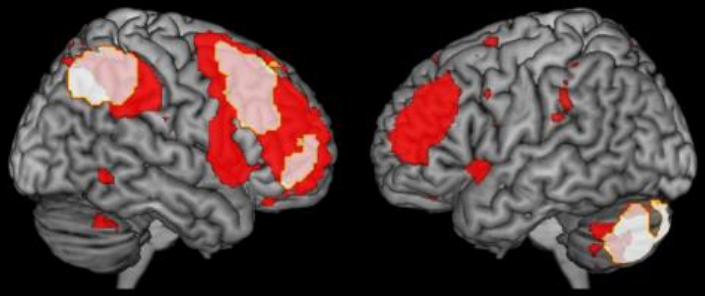


AD-VISUAL
Right middle occipital gyrus
(MNI 39 -88 10)

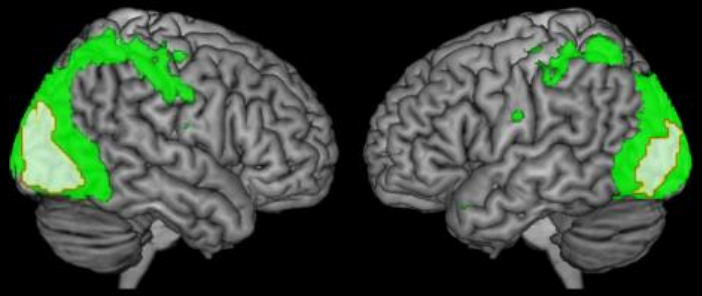


Lehmann et al., PNAS 2013

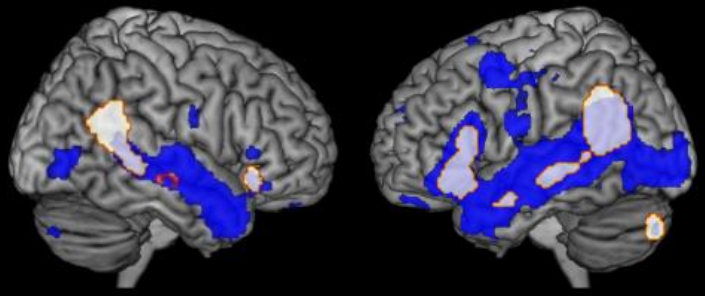
AD Variants Target Distinct Brain Networks and Converge in DMN



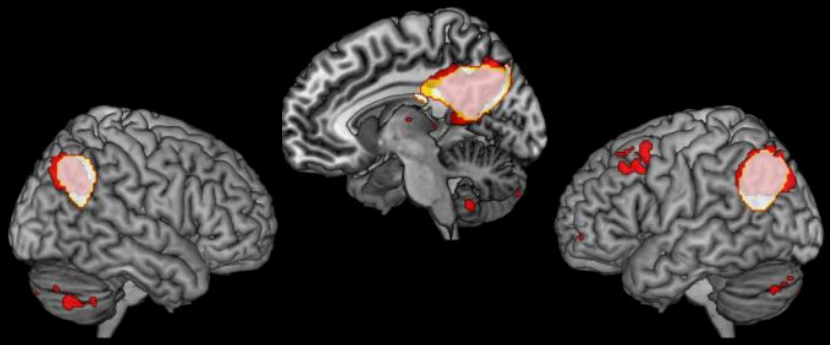
EO-AD (executive)
Executive control network



PCA (visuospatial)
Higher visual network



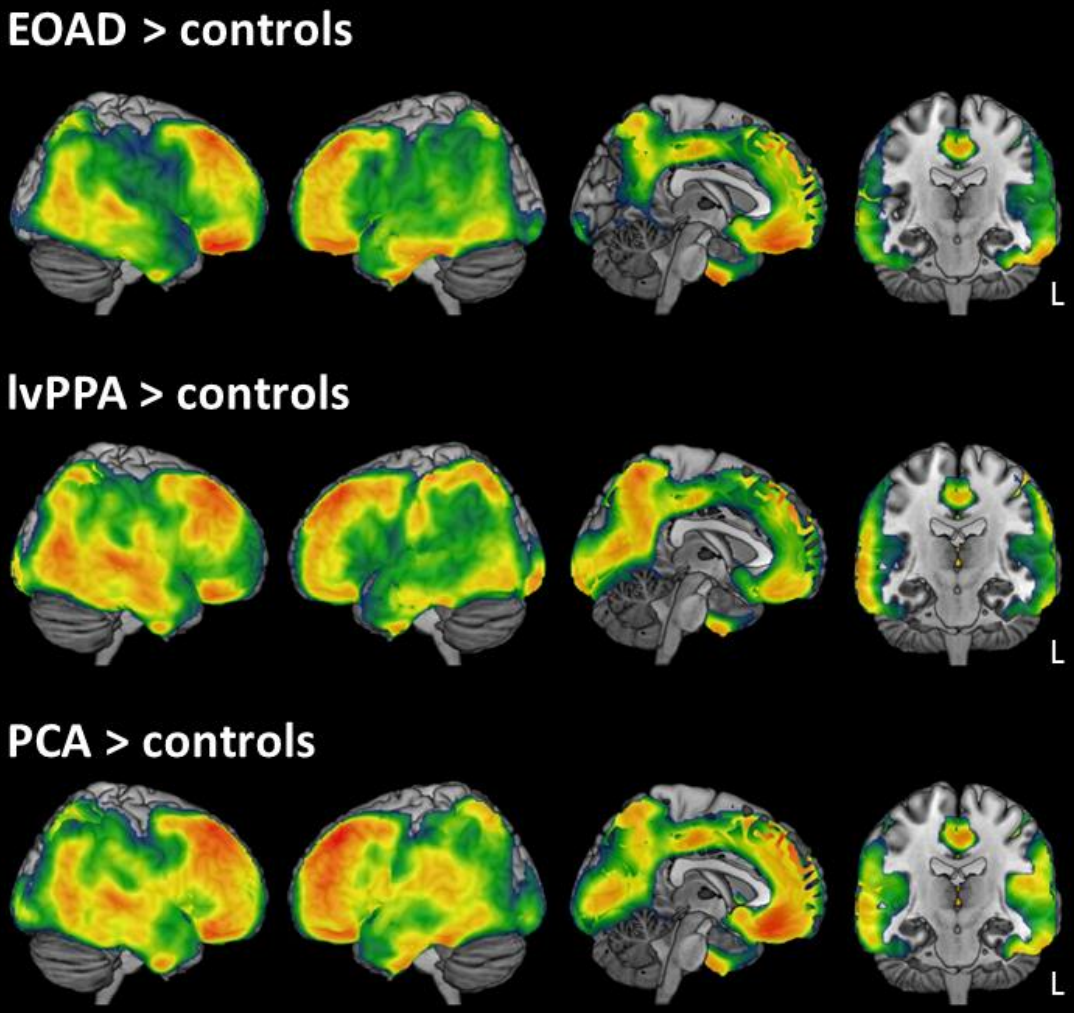
LPA (language)
Language network



All AD Variants
Default mode network

Lehmann et al., PNAS 2013

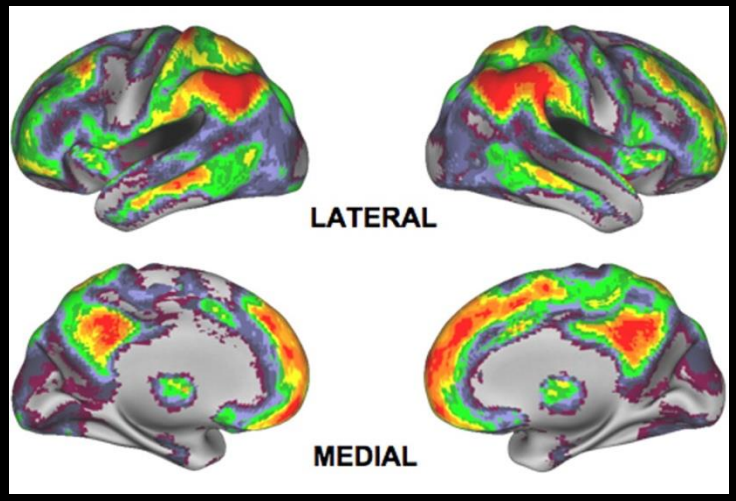
Amyloid Patterns Do Not Explain Heterogeneity



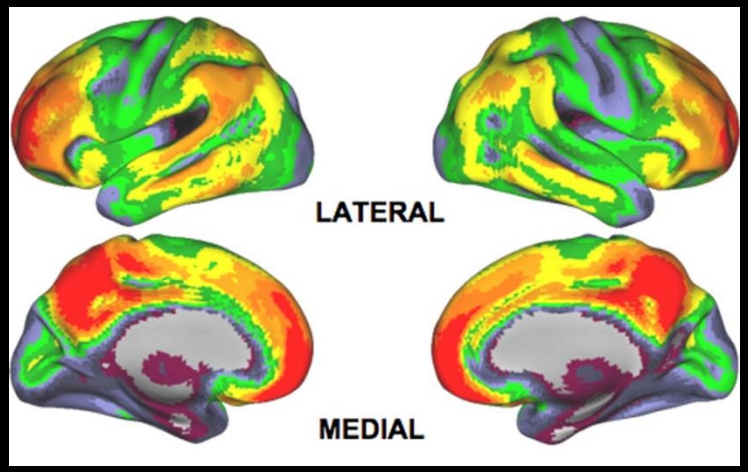
Lehmann et al., Brain 2013

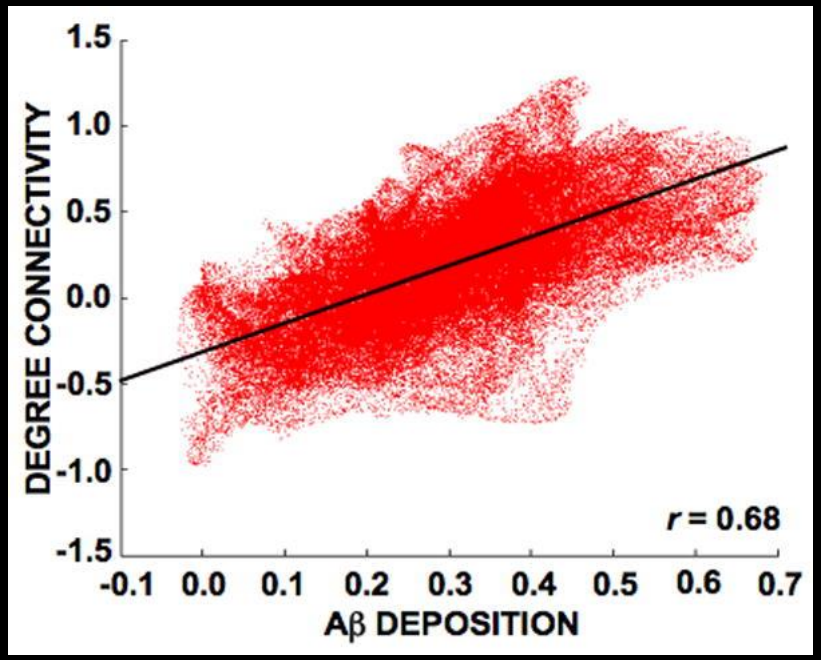
Cortical Hubs Accumulate Aβ

Degree connectivity (Controls)



Aβ deposition (AD)

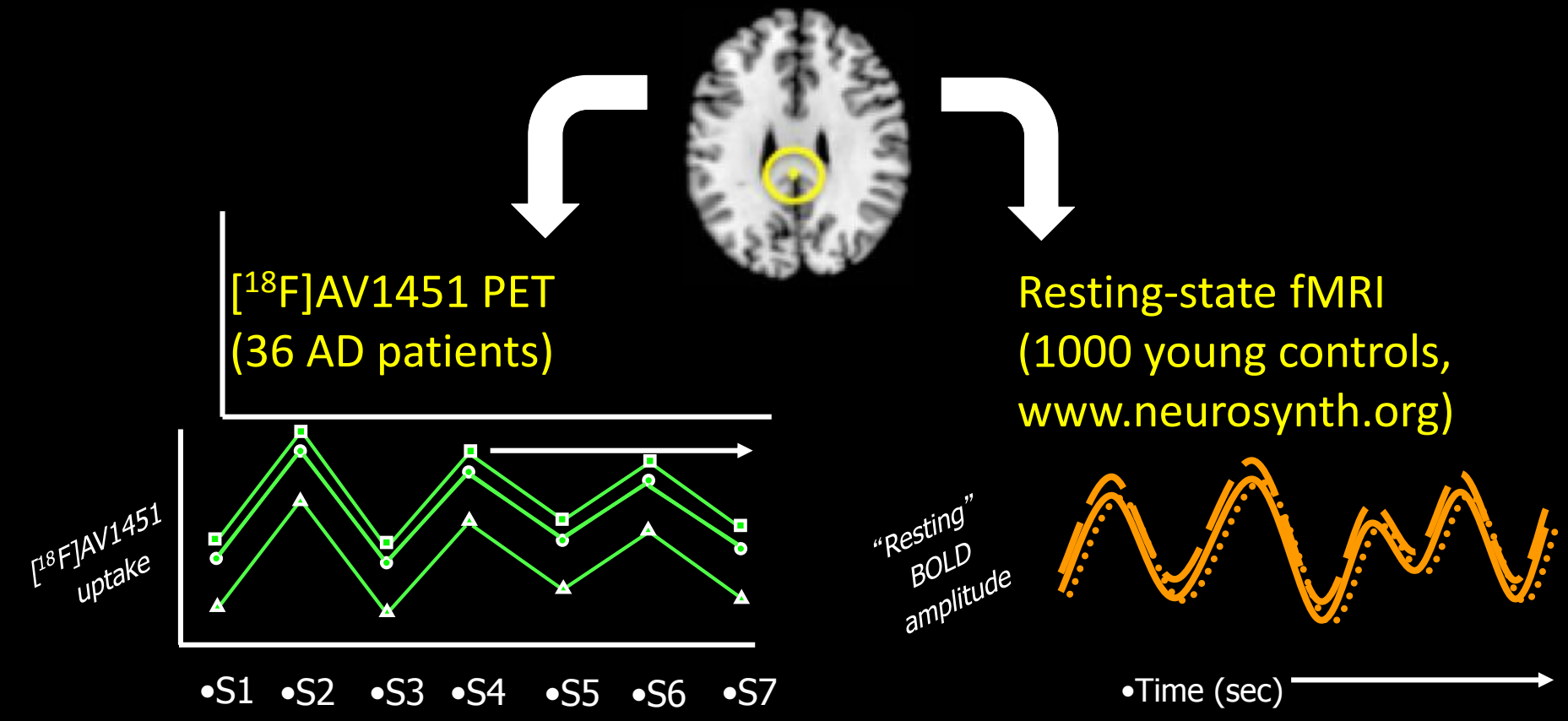




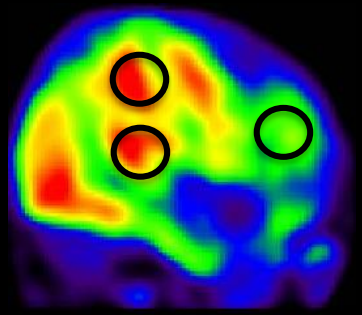
Buckner et al., J Neurosci 2009

Relationships Between Tau Patterns in AD and Normal Brain Connectivity

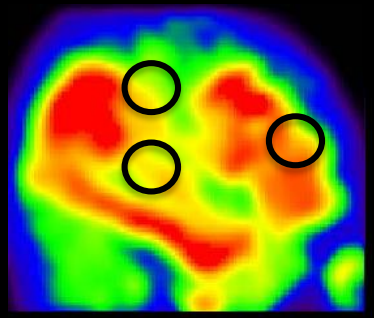
Generated covariance maps from seed regions



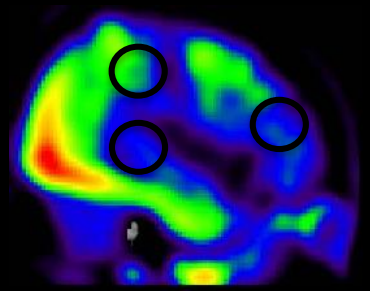
Ossenkoppele et al., in prep



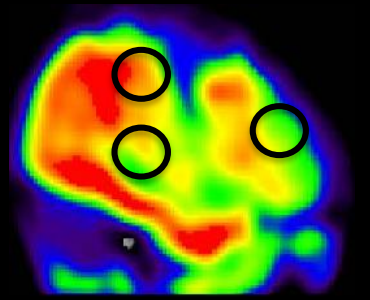
AD01



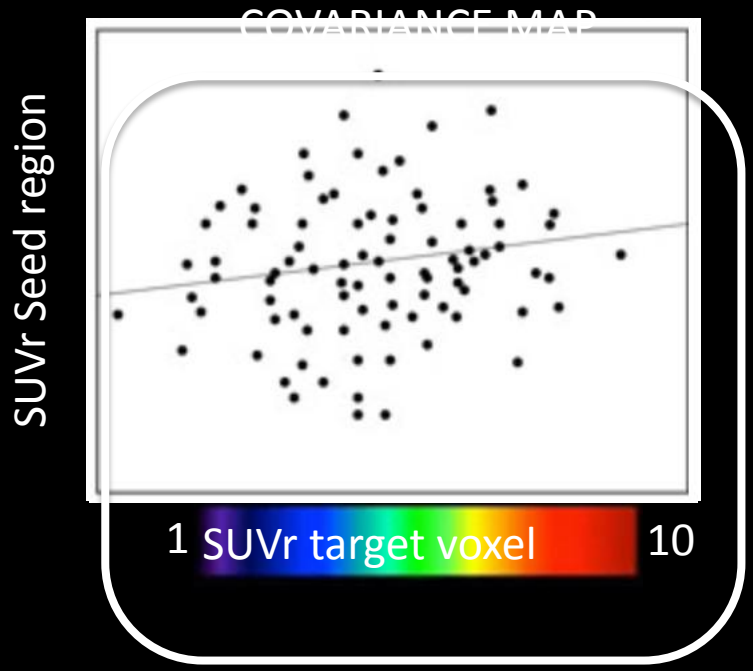
AD02



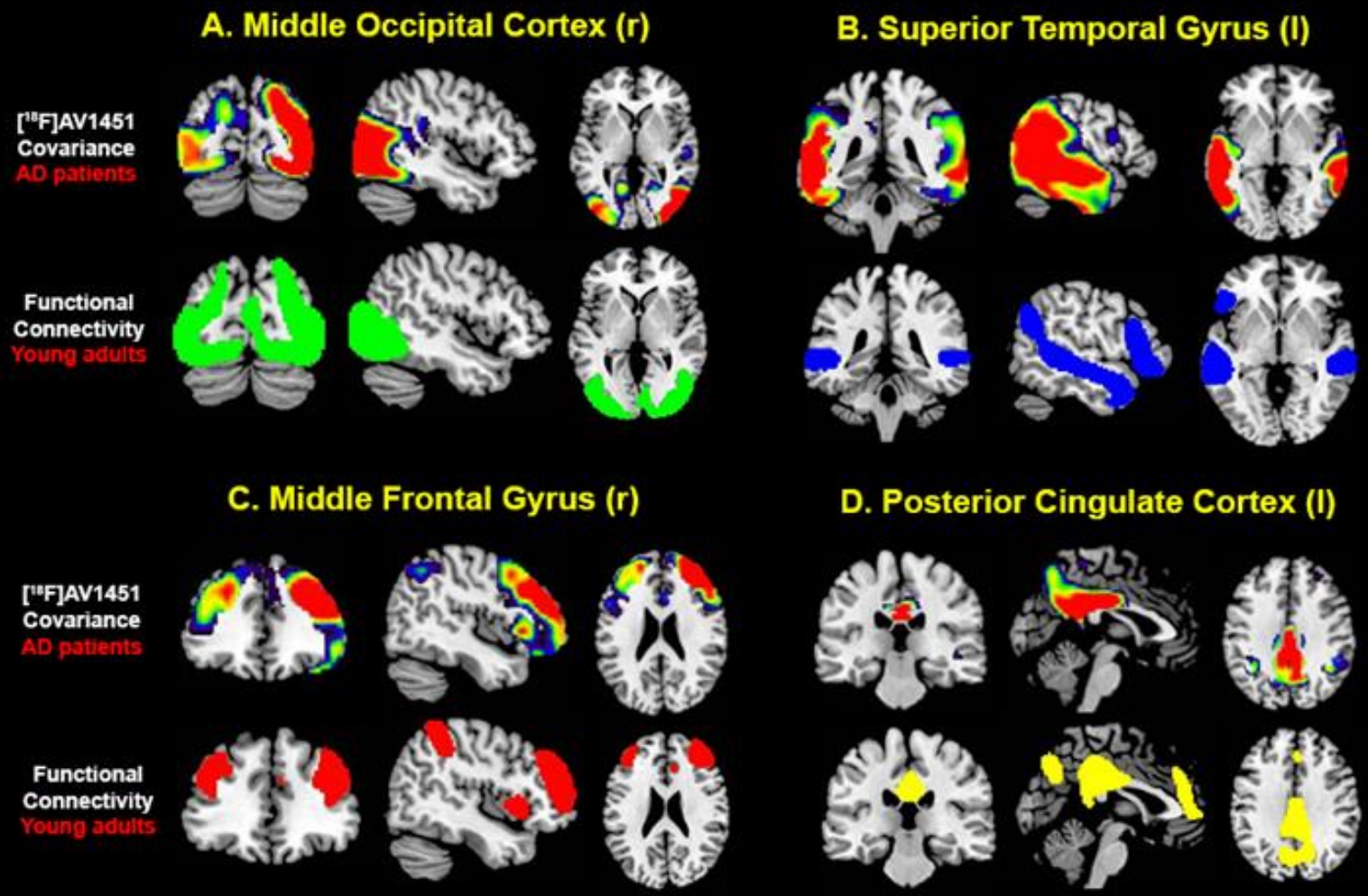
AD….



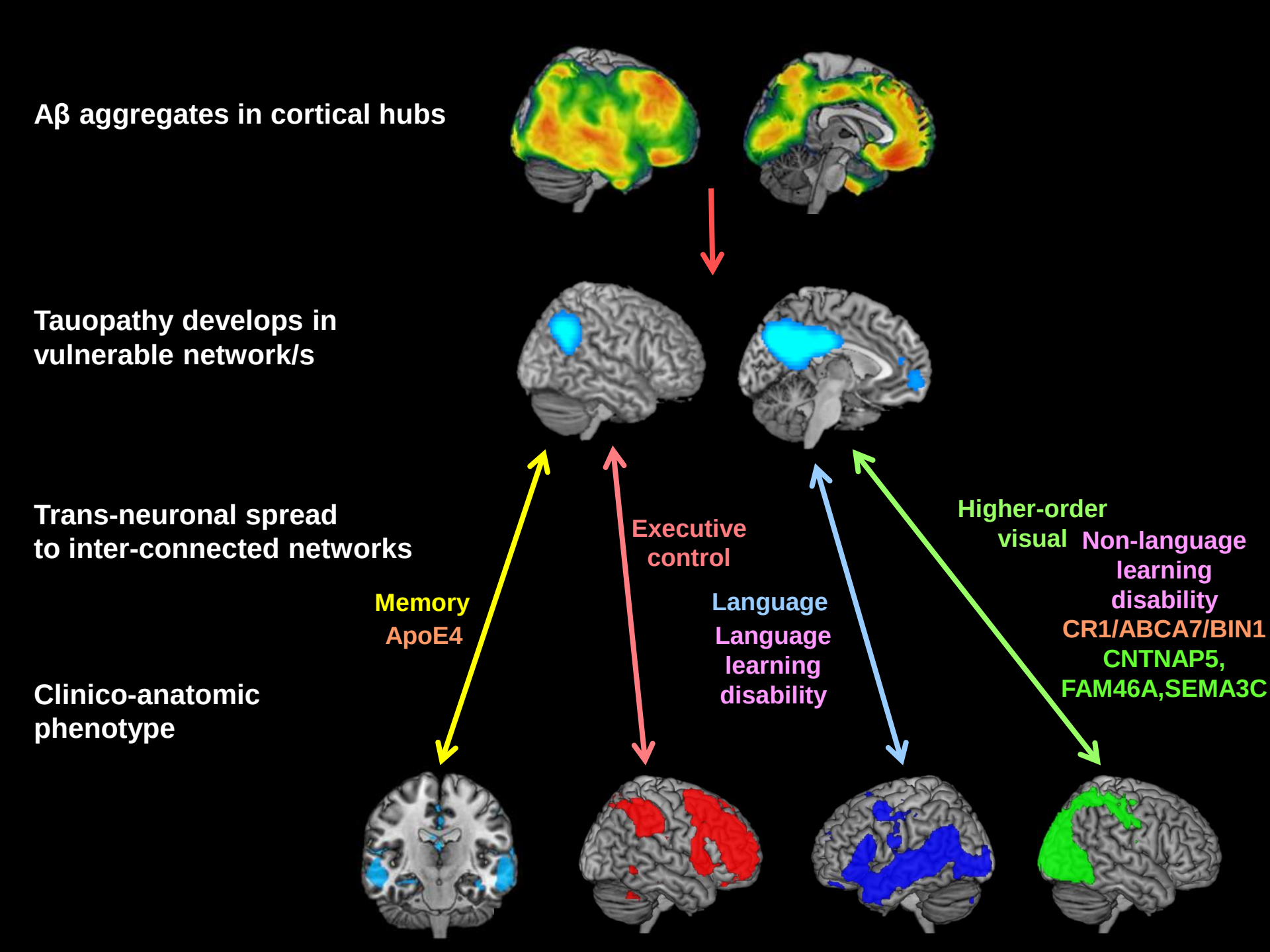
AD36



Tau Covariance Patterns Mirror Functional Networks



Ossenkoppele et al., in prep


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
Non-language learning disability
CR1/ABCA7/BIN1
CNTNAP5, FAM46A,SEMA3C

Take Home Points

- fcMRI supports the concept of “network-based” neurodegeneration in AD
  - Clinical features represent failure of specific networks
  - DMN implicated across AD phenotypes
- Aβ/Tau associated with distinct network features
  - Regions of high connectivity (“hubs”) susceptible to Aβ
  - Tau may spread from epicenters via network connections, driving neurodegeneration
- Multi-modal neuroimaging powerful tool for testing disease models *in vivo*

“Sick Brain” “Healthy Brain”

Naomi Rabinovici, age 5.5, Sept 2013

Acknowledgments

UCSF-MAC

Bruce Miller
Manja Lehmann
Rik Ossenkoppele
Nagehan Ayakta
Alexandre Bejanin
Averill Cantwell
Leonardo Iaccarino
Andreas Lazaris
Mariella Lauriola
Ashley Mensing
Daniel Schonhaut
Gautam Tammewar
Adam Boxer
Lea Grinberg
Marilu Gorno-Tempini
Anna Karydas
Lisa Kritikos
Robin Ketelle
Joel Kramer
Zach Miller
Howie Rosen
Miguel Santos
Salvatore Spina
Bill Seeley

UC Berkeley/LBNL

Bill Jagust
Jim O'Neill
Kris Norton
Suzanne Baker
Mustafa Janabi
Henry Schwimmer
Jake Vogel

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Melissa Murray
Susan Resnick
Chris Rowe
Philip Scheltens
Sang Won Seo
Victor Villemagne

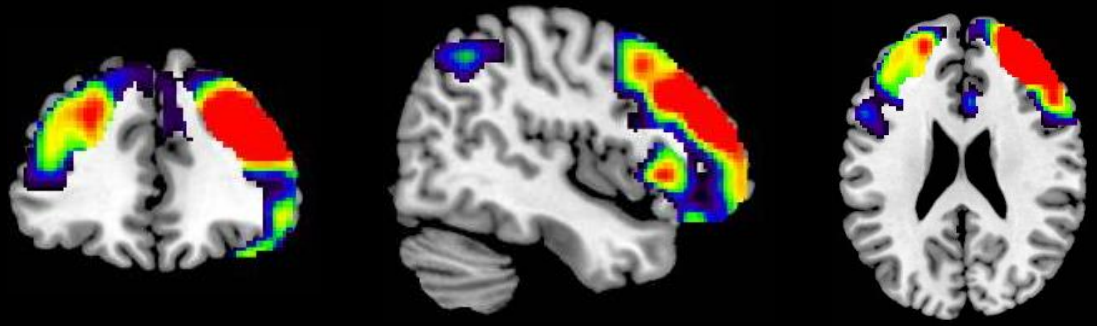
Funding

NIA R01-AG045611, P01-AG1972403, P50-AG023501
NINDS U54NS092089
Alzheimer's Association
Tau Consortium
AFTD
Avid Radiopharmaceuticals
American College of Radiology
Michael J. Fox Foundation
French Foundation

Extra Slides

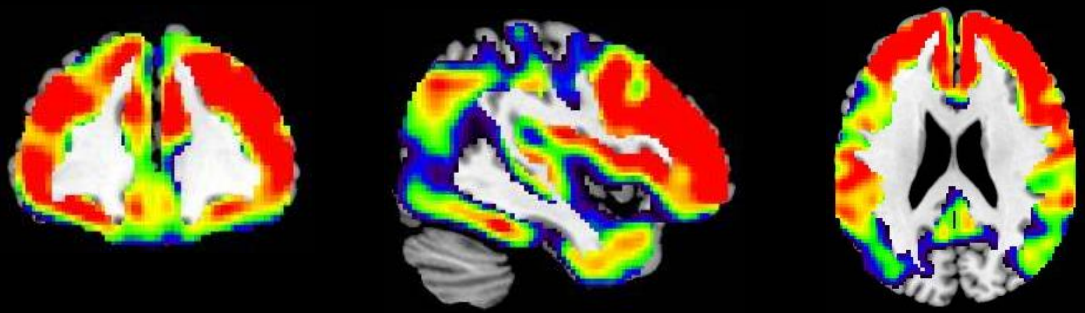
PIB Covaraince Patterns are Non-Specific

AV1451 covariance maps (p<0.05 FWE)



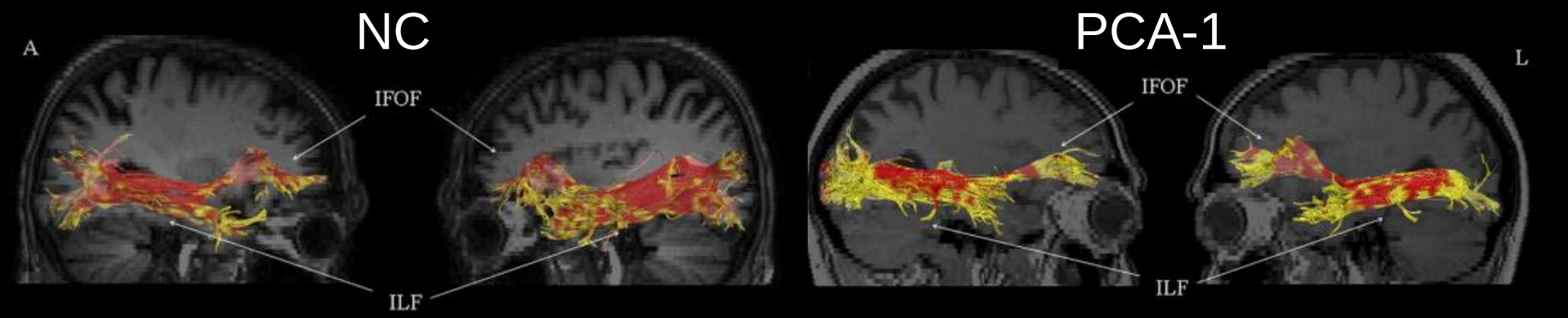
fMRI connectivity maps (p<0.01 FDR)

PIB covariance maps (p<0.05 FWE)

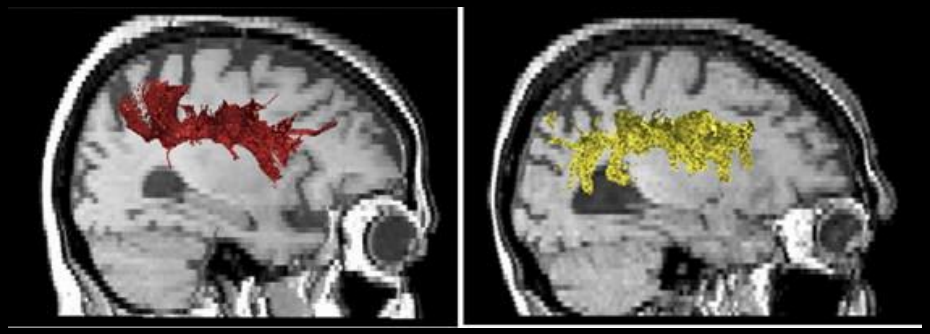


Visual Networks in PCA

Ventral visual stream



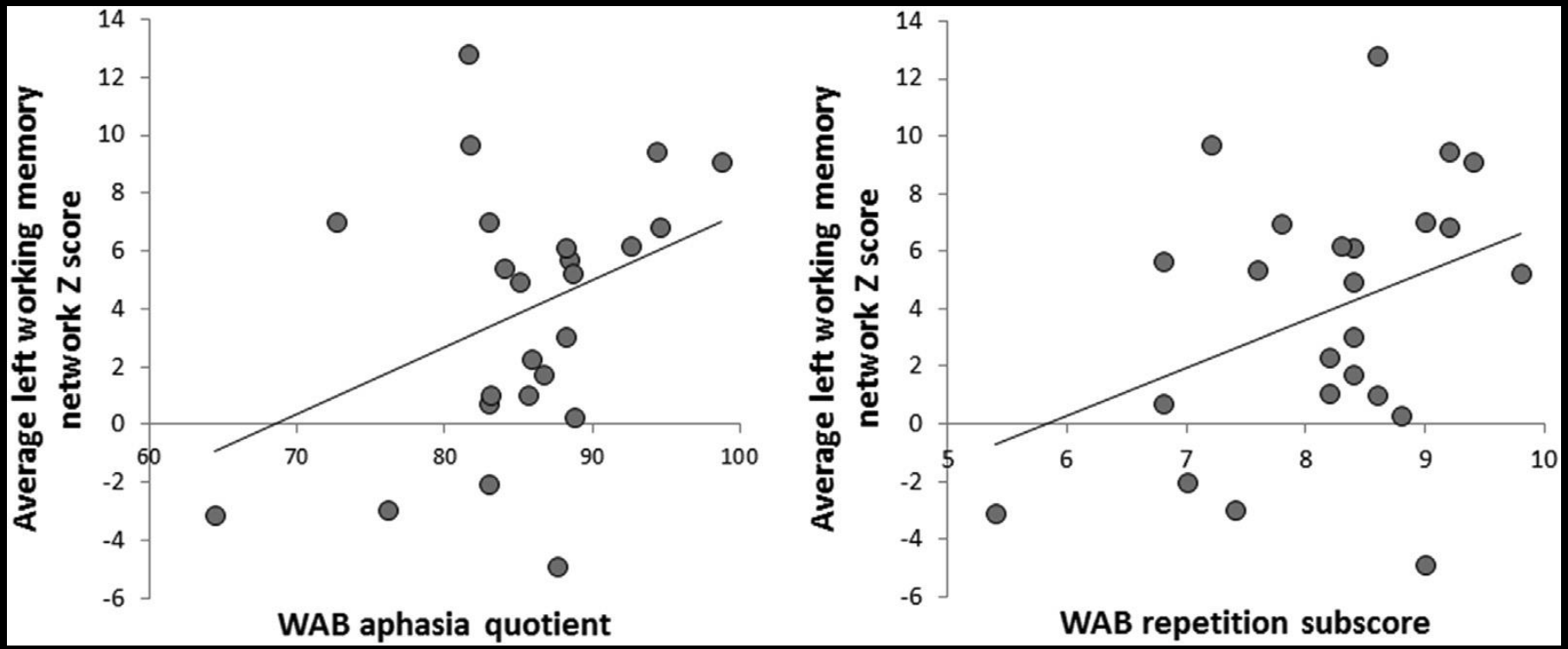
Dorsal visual stream



PCA-6 PCA-2

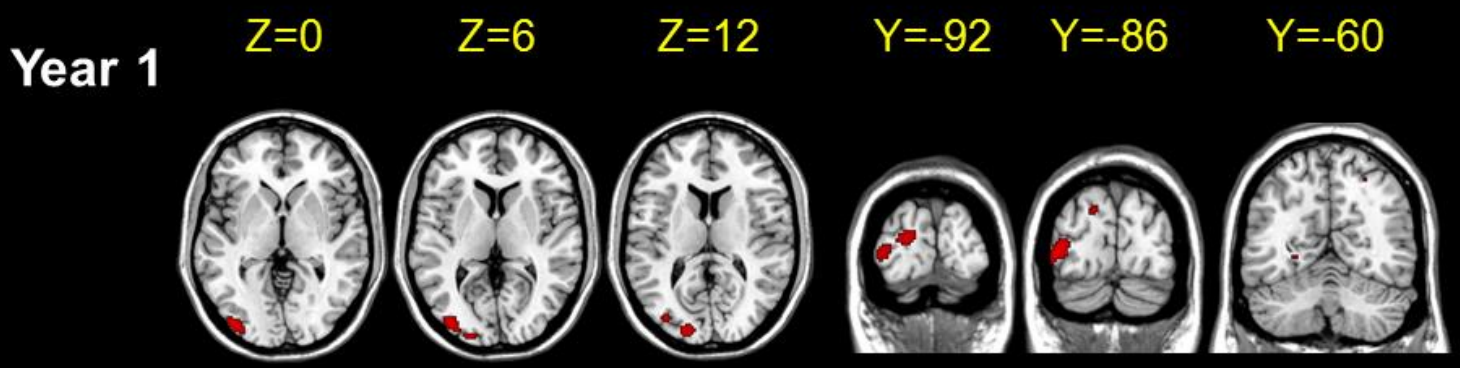
Migliaccio, Agosta et al., Neurobiol Aging 2012

fcMRI versus Cognition in lvPPA



Whitwell et al., Neurobiol Aging 2015

Imaging Prodromal PCA

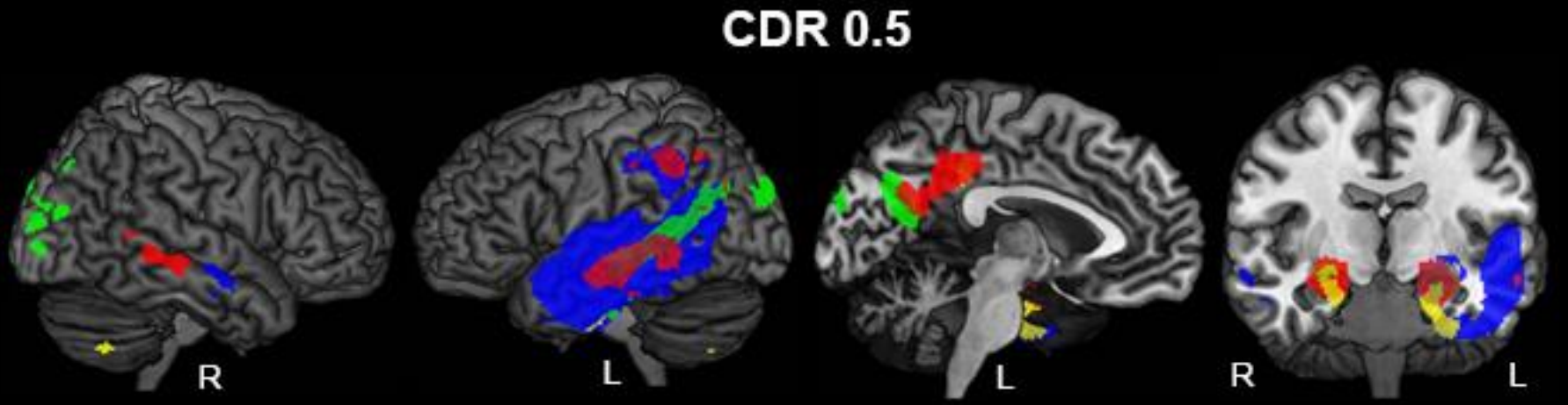


Chan et al., Neurocase 2015

MRI Atrophy (VBM)

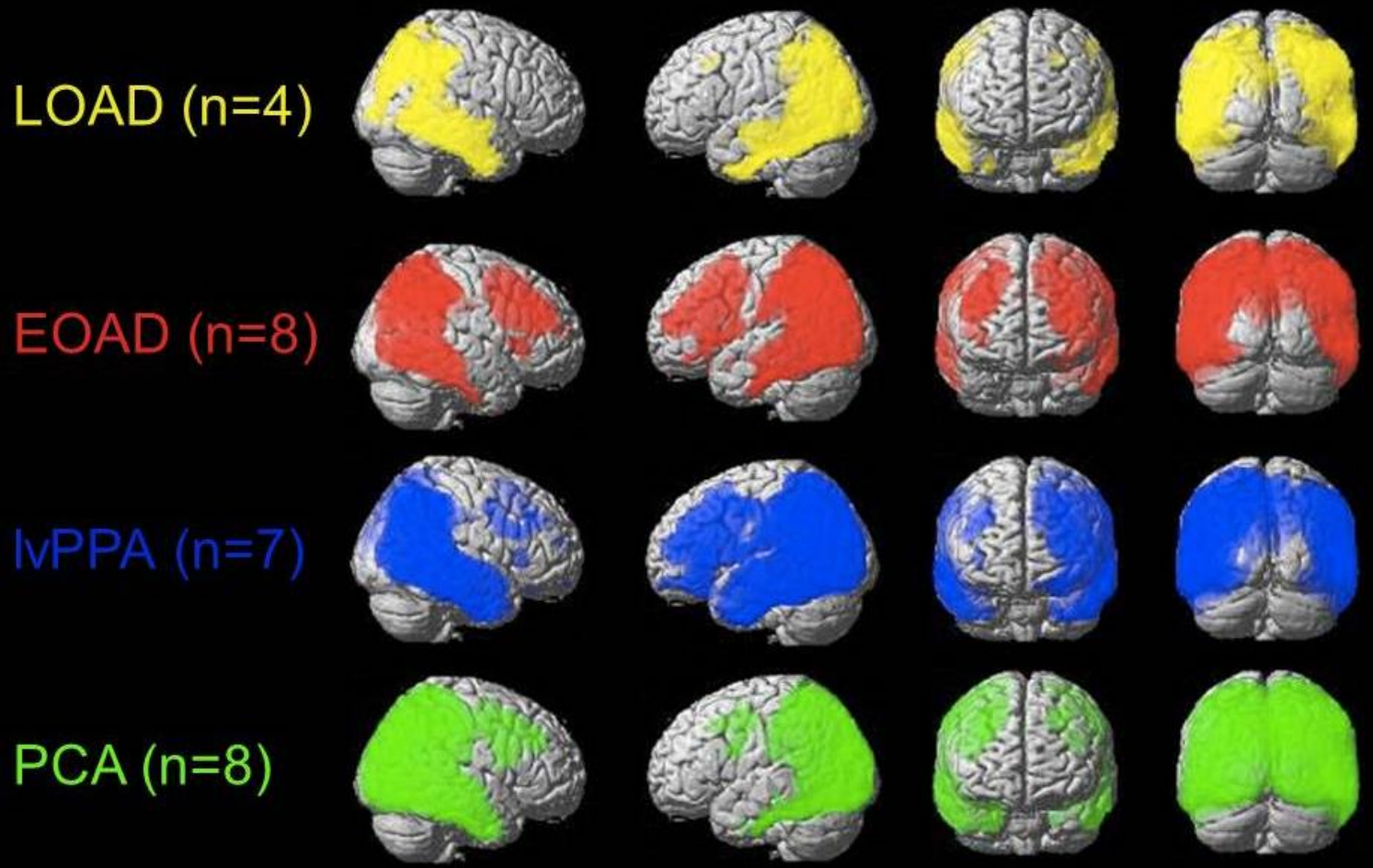
395 AD subjects from UCSF/VUMC

44% CDR 0.5 / 56% CDR 1.0



Ossenkoppele et al., HBM 2015

Tau PET Patterns Correlate with AD Phenotype



Covaried for age, p(FWE)<0.05

Ossenkoppele et al., Brain 2016