

# Exploring Brain Networks in Neurodegenerative Disease



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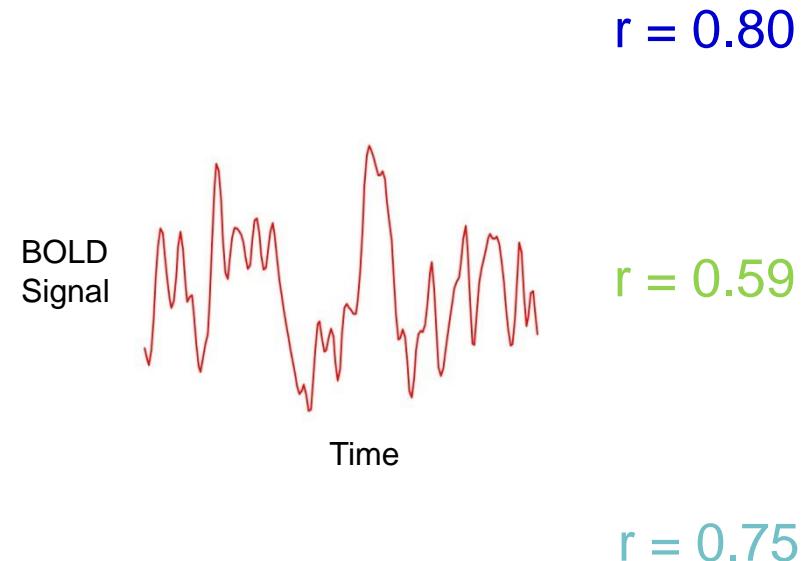
# Disclosure

SBGneuro: co-founder/shareholder  
(resting-state fMRI analysis for clinical trials)

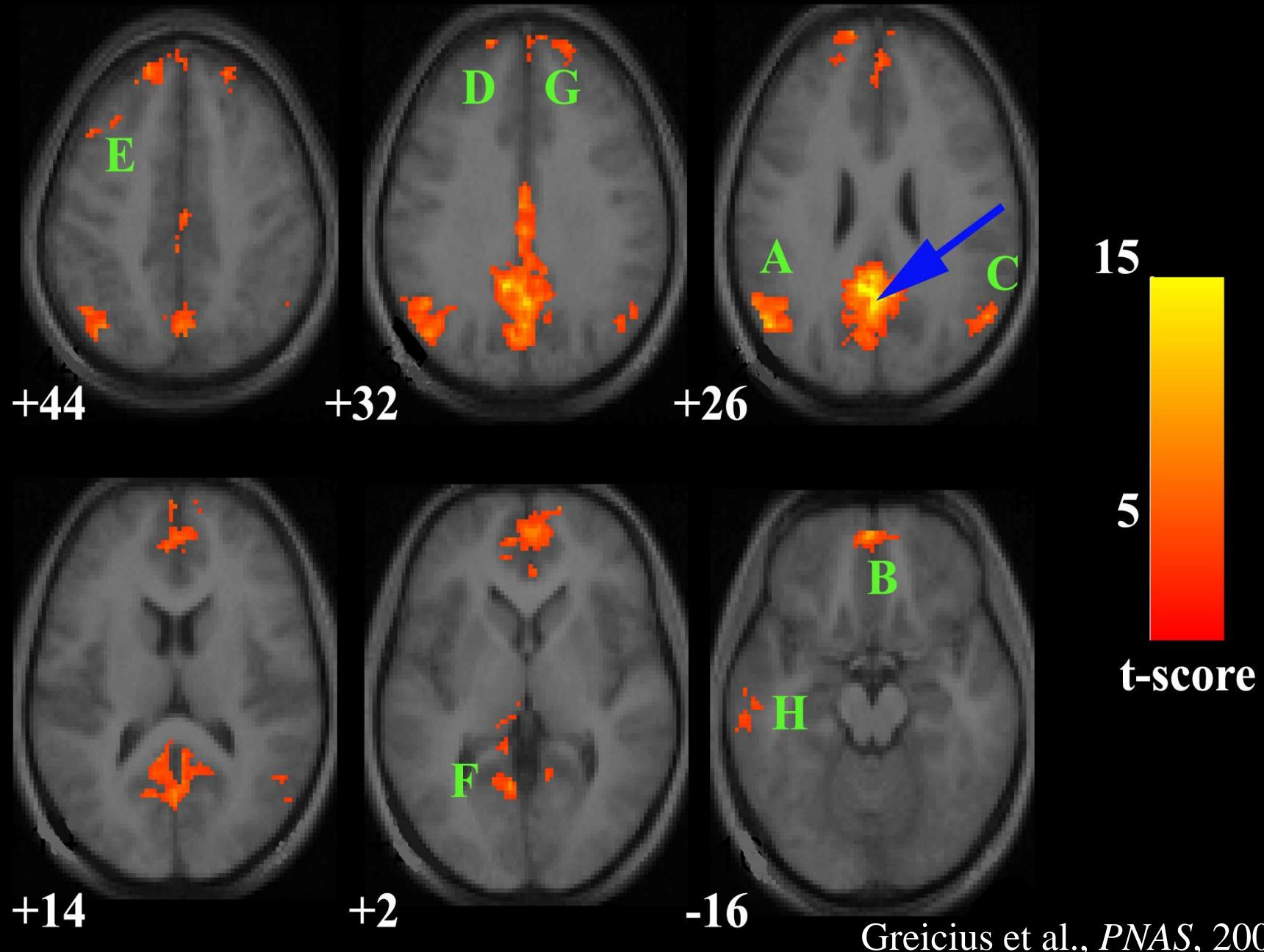
# Overview

- Network imaging with resting-state fMRI
- The default-mode network and Alzheimer's disease
- The salience network and frontotemporal dementia
- Future directions

# Functional Connectivity with Resting-State fMRI

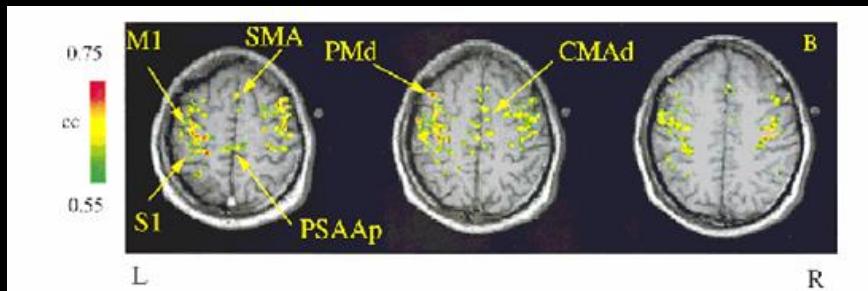


# Resting-State Default-Mode Network

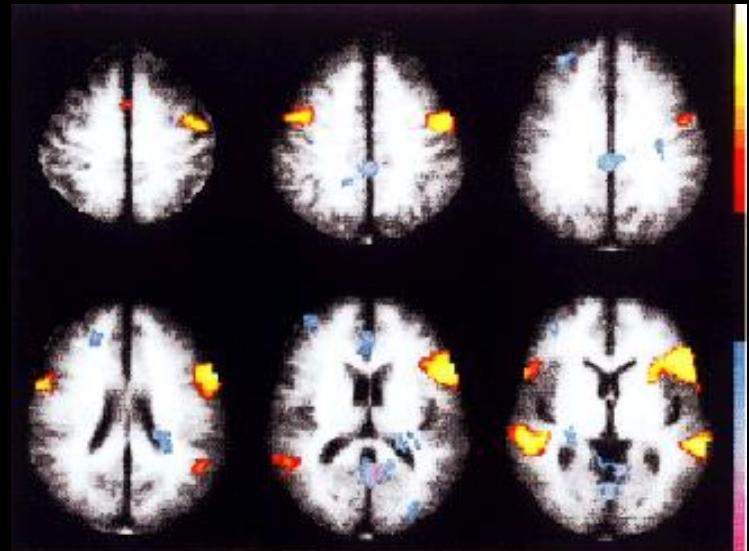


Greicius et al., *PNAS*, 2003

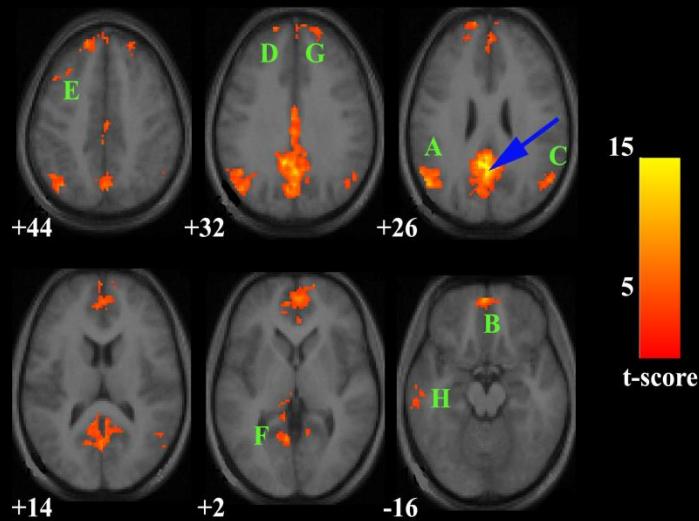
# Multiple Networks Detected with Multiple Seeds



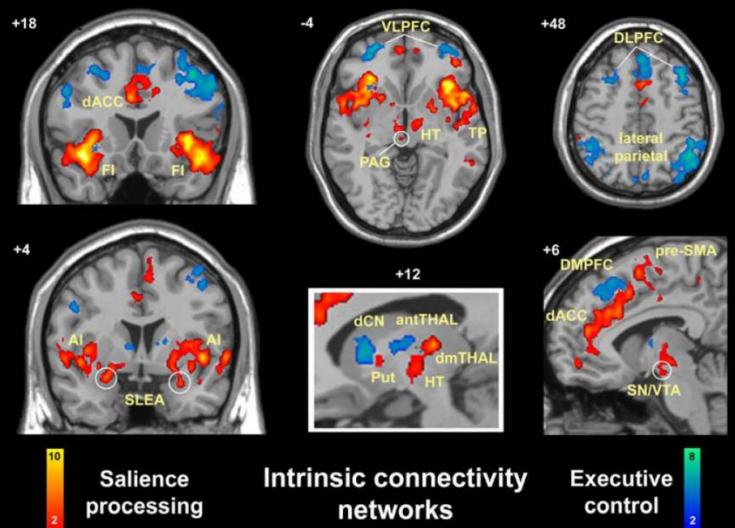
Motor: Xiong et al., 1999



Language: Hampson et al., 2002

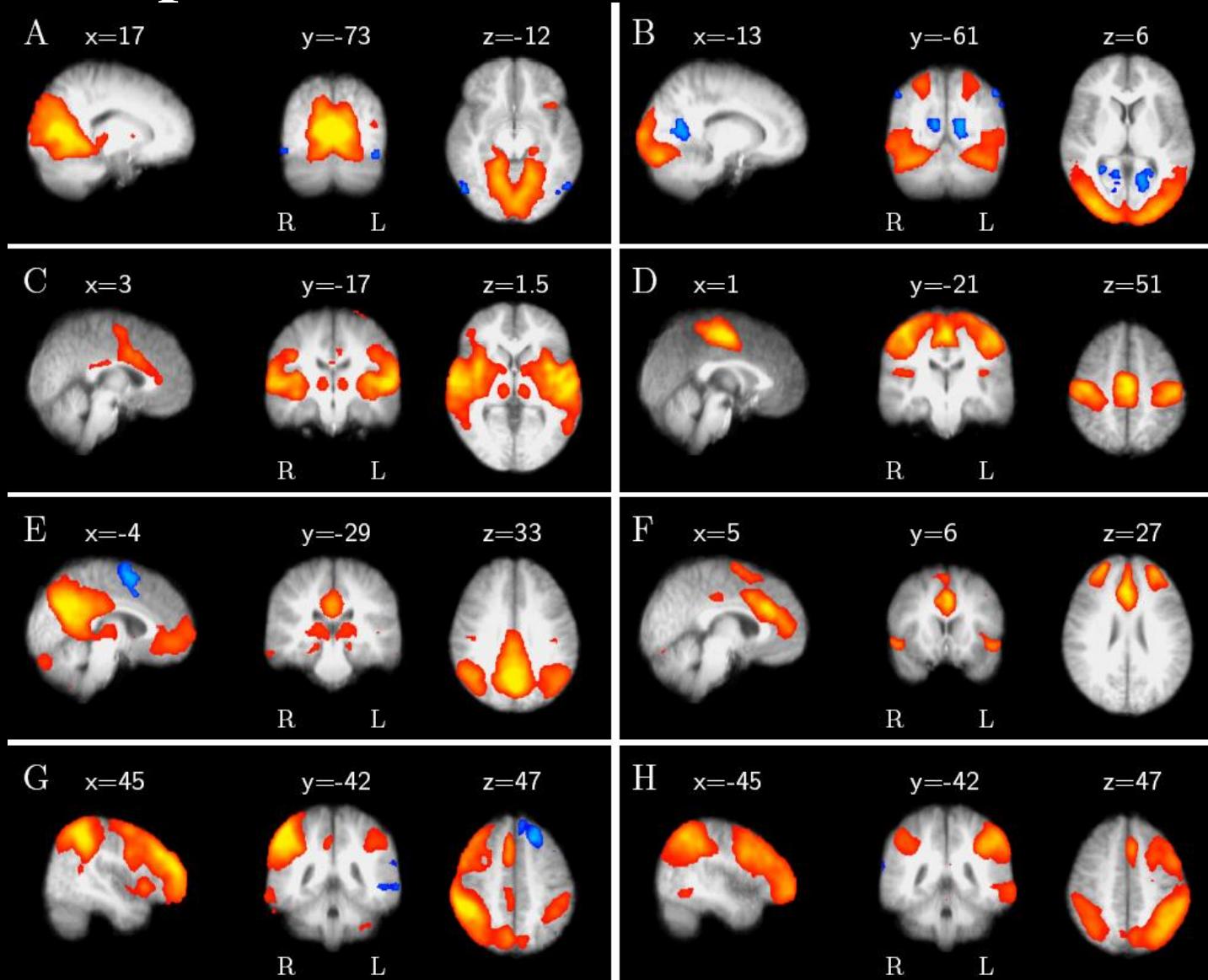


Default Mode: Greicius et al., 2003



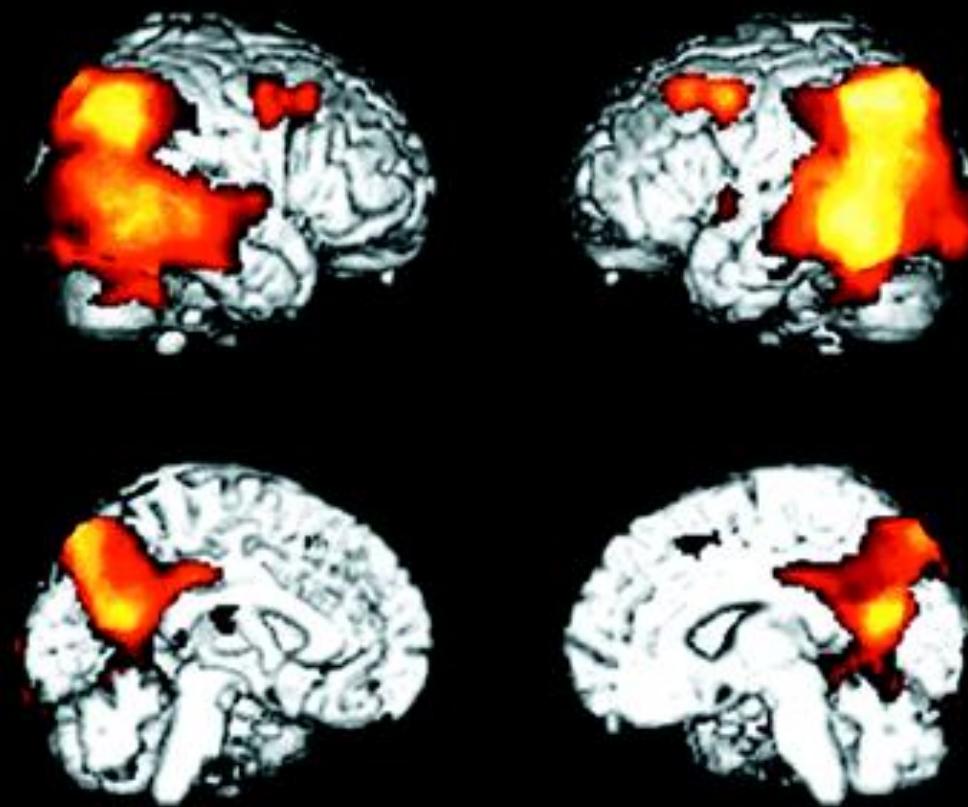
Executive control and Salience: Seeley et al., 2007

# Multiple Networks Detected with ICA



Beckmann et al., *Philos Trans R Soc Lond*, 2005

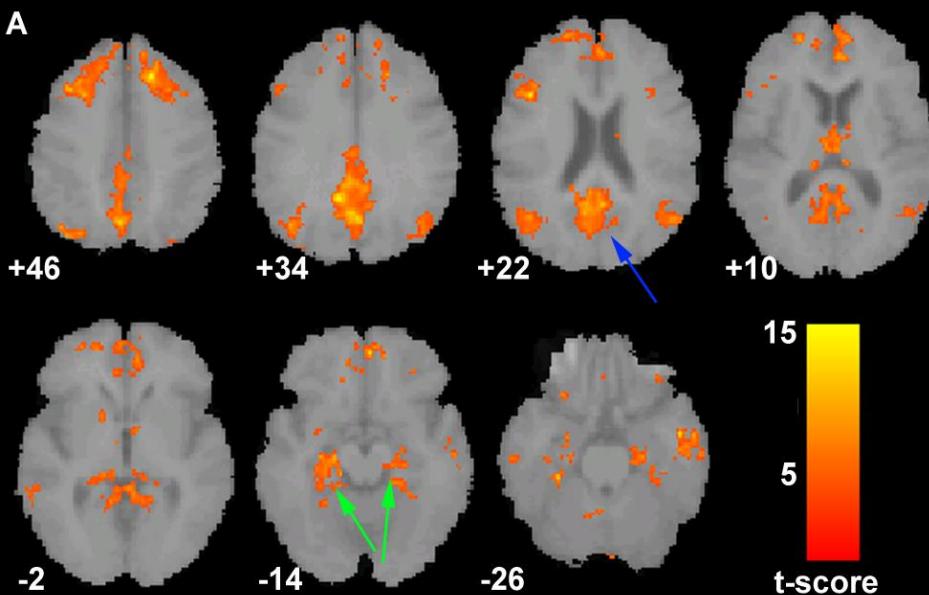
# Hypometabolism in AD



Resting PET 34 healthy subjects versus 14 AD patients.

Alexander et al., *Am J Psychiatry*, 2002.

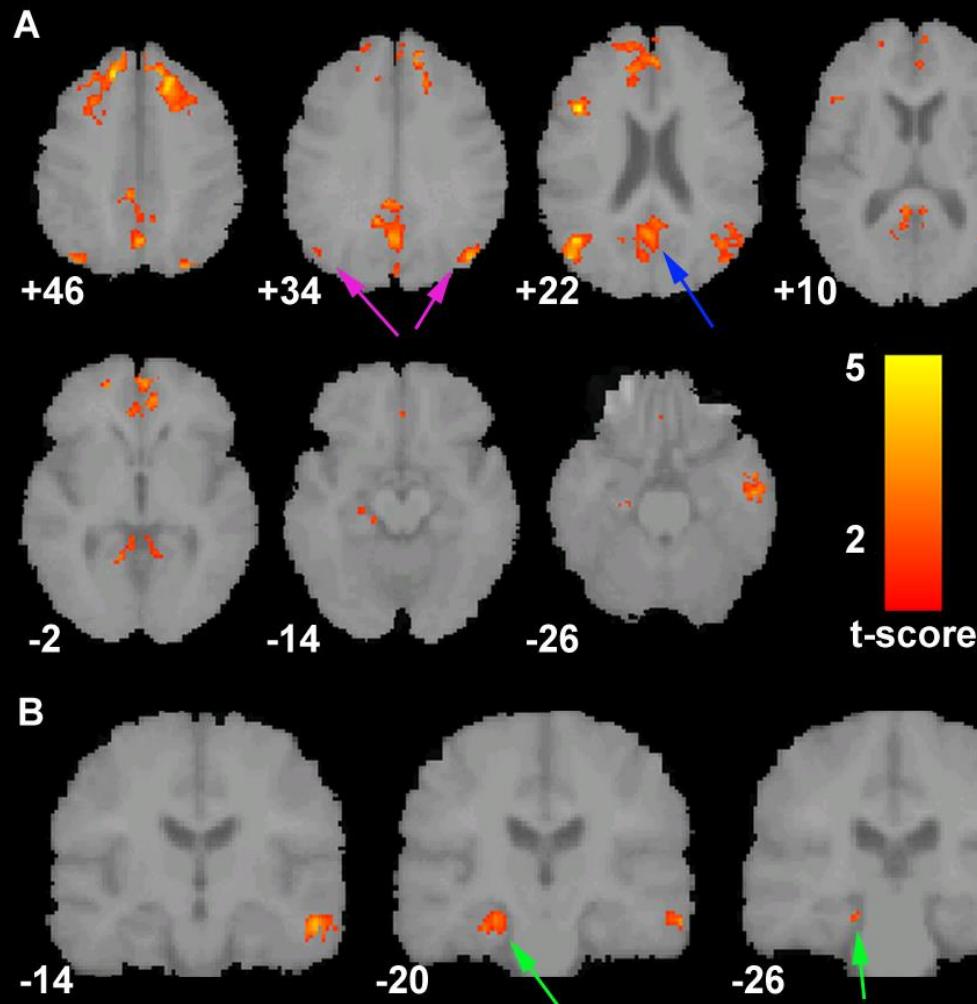
# Default-Mode Network in AD



Healthy Aging

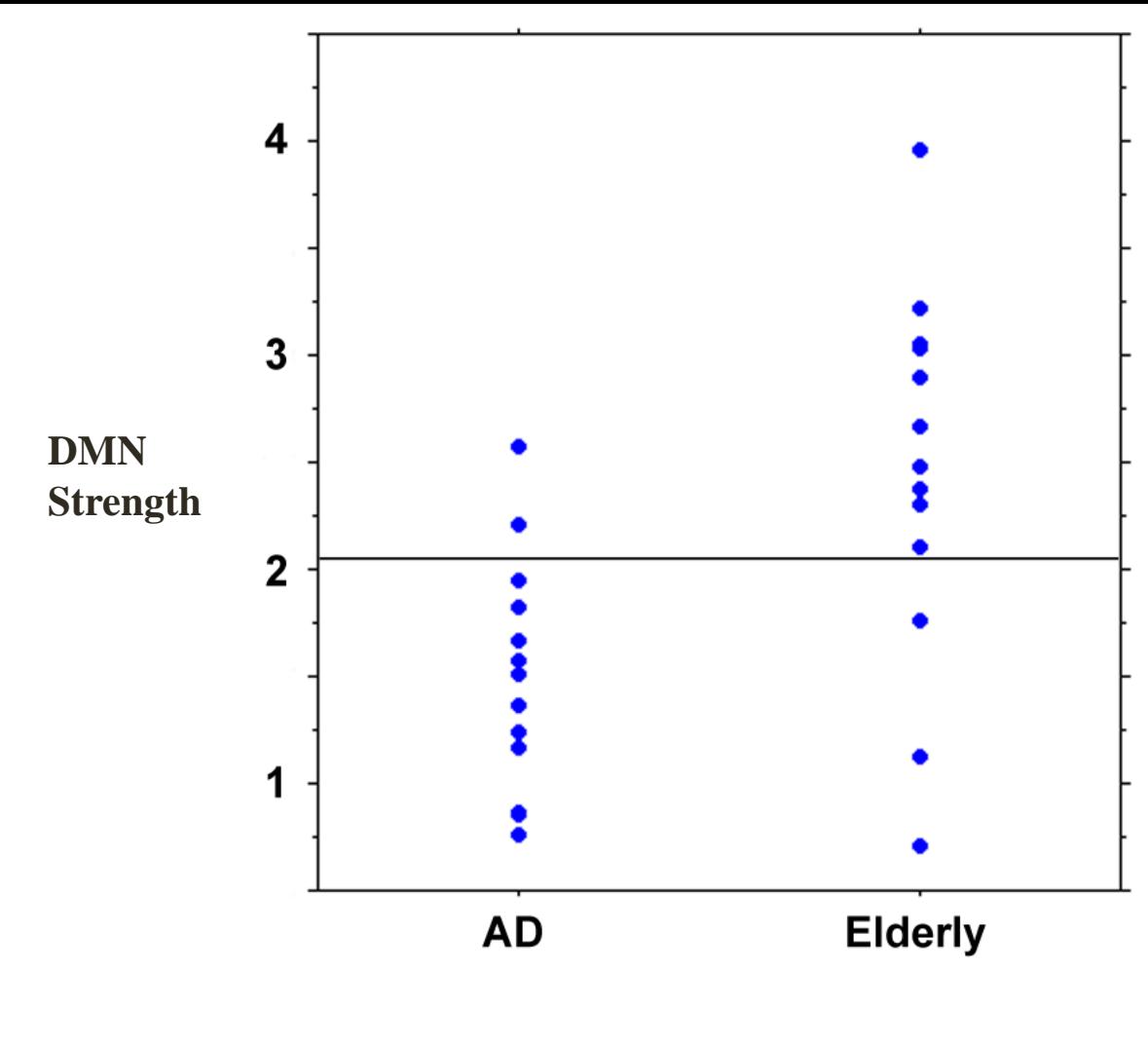
Greicius et al., *PNAS*, 2004

# Default-mode in healthy aging versus AD

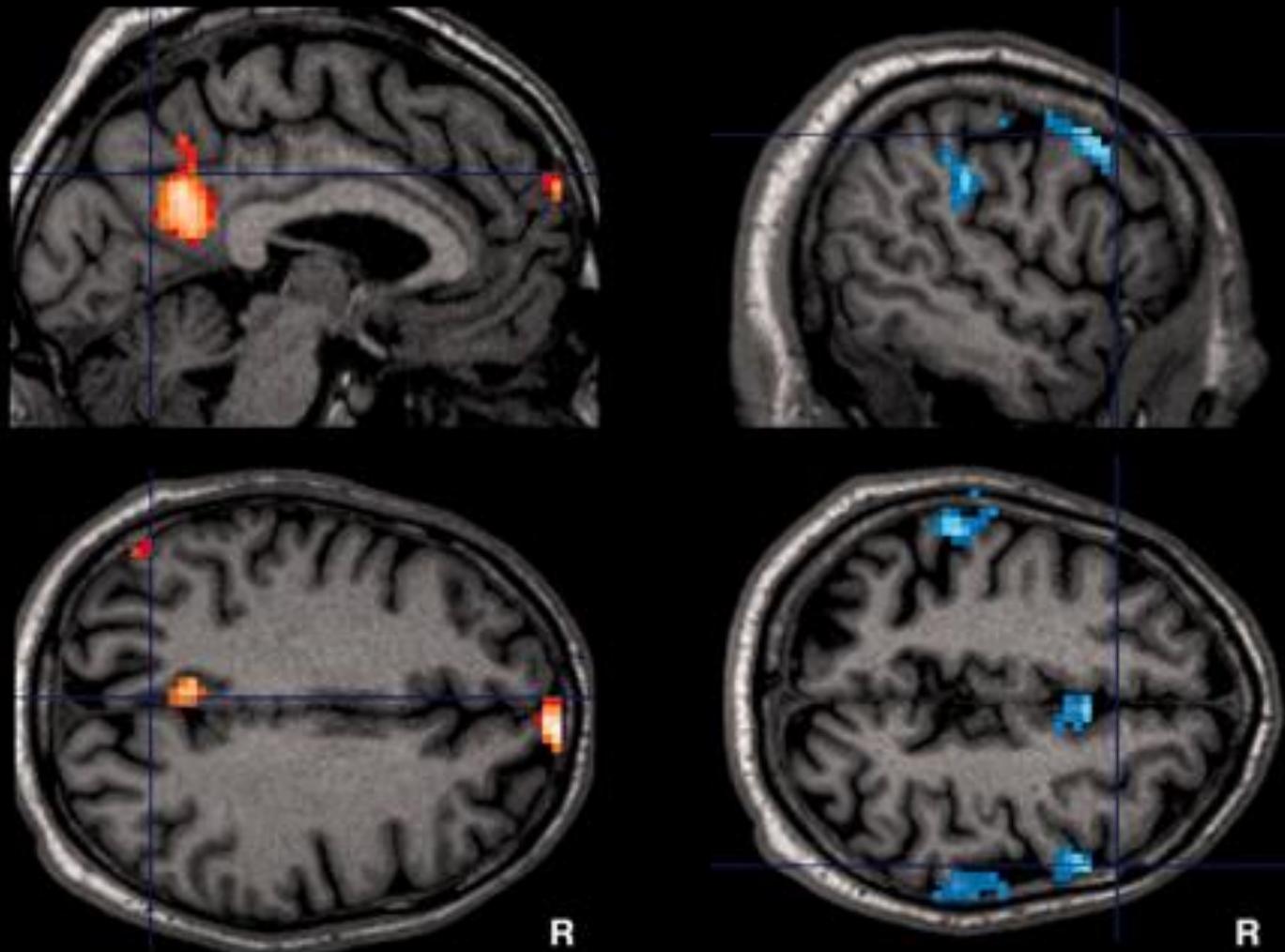


# Single-Subject DMN Measure

85% sensitivity  
77% specificity

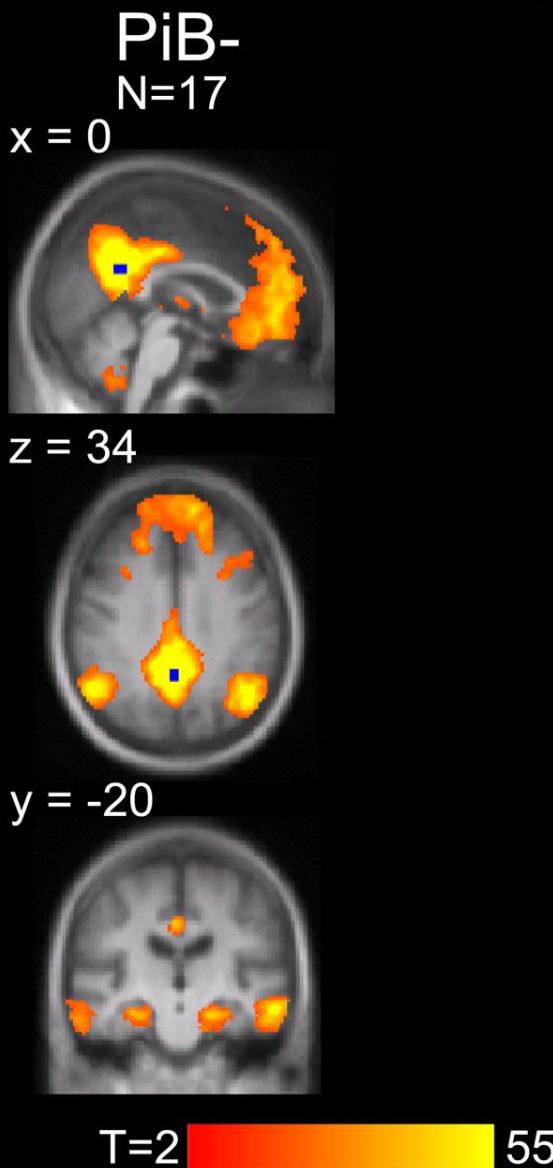


# Reduced DMN Connectivity in MCI



Sorg et al., PNAS 2007

# Reduced DMN Connectivity in PIB+ Controls

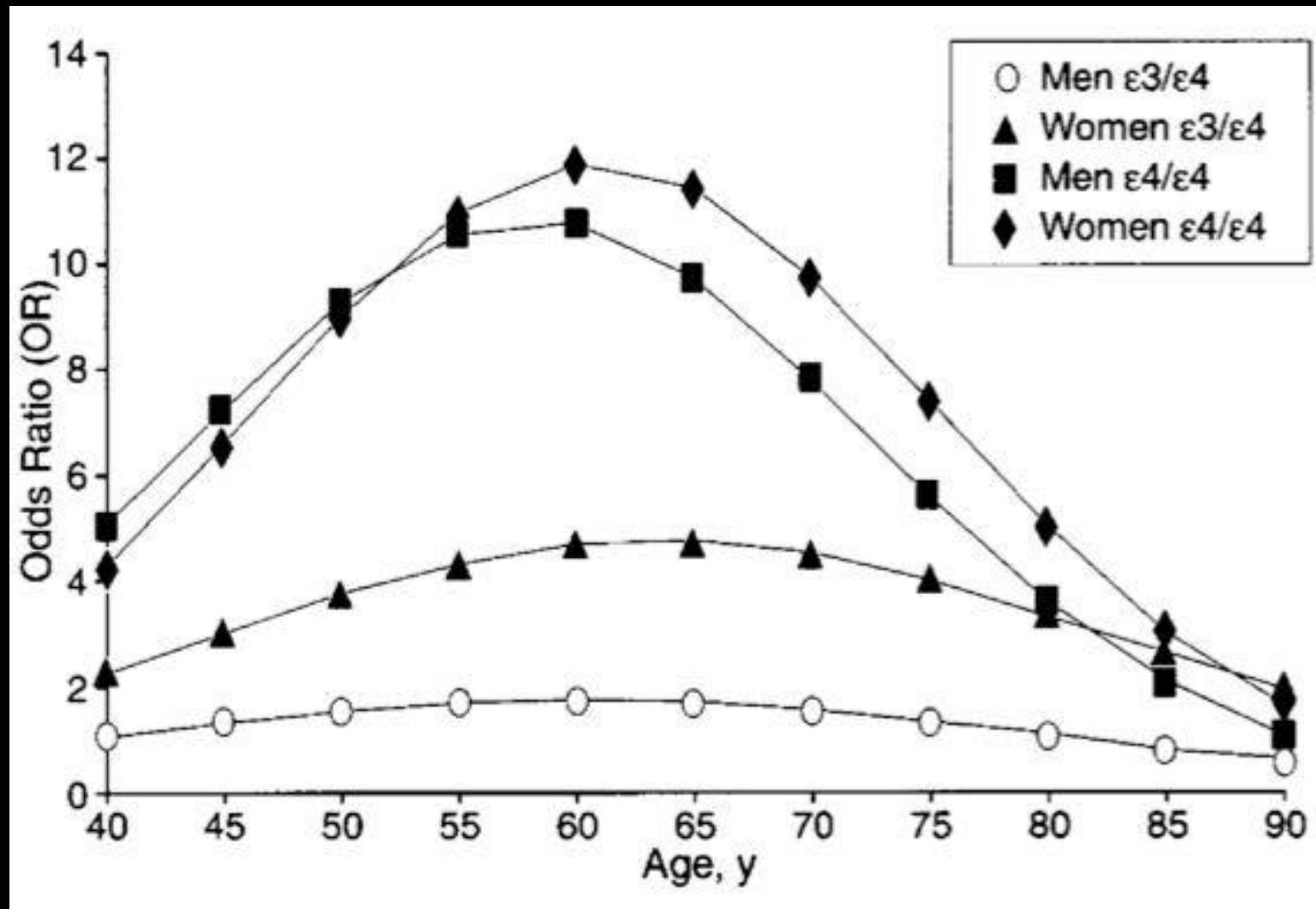


Hedden et al., *J Neurosci*, 2009 (also Sheline et al., *Biol Psych* 2010)

# APOE and Connectivity in Older Controls

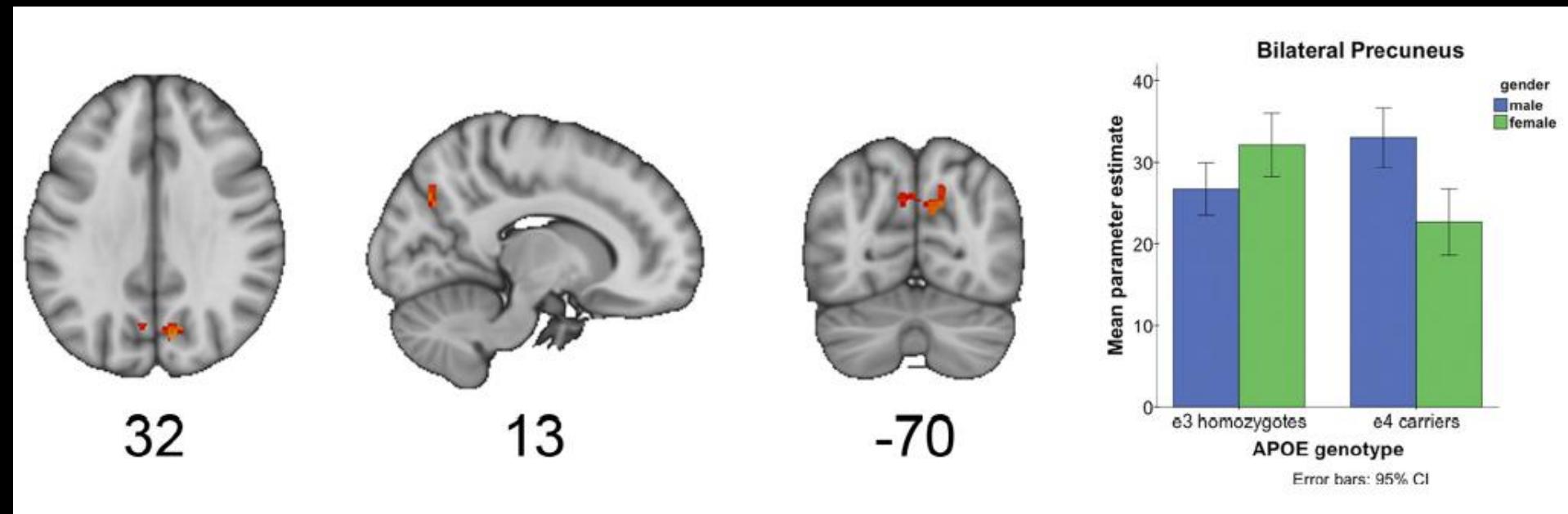
- Sheline et al., 2010
  - E4 carriers show increases and decreases in DMN
- Machulda et al., 2011
  - E4 carriers show decreases in DMN
- Westlye et al., 2011
  - E4 carriers show increases in DMN
- Trachtenberg et al., 2011
  - E4 carriers show no differences in DMN (but some differences in two separate MTL networks)

# APOE x Gender Interaction on AD Risk



Farrer et al, *JAMA*, 1997

# ApoE x Gender Interaction

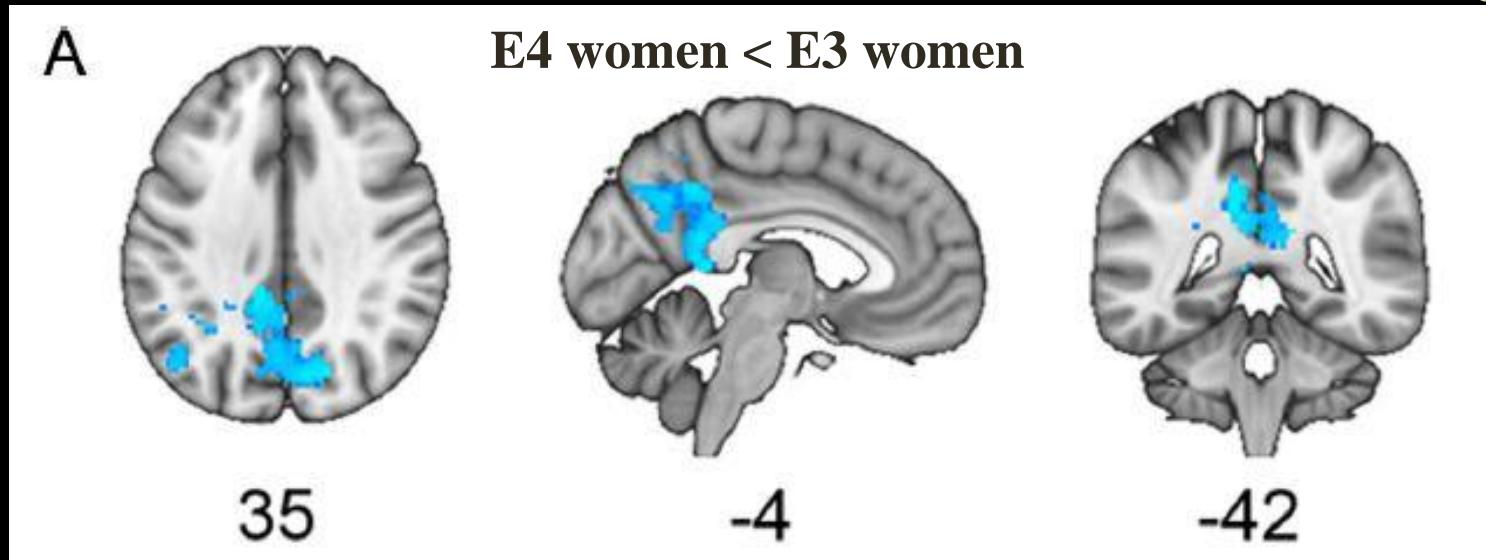


N = 131 healthy older controls

Damoiseaux et al., *J Neurosci*, 2012

# APOE, Gender, and Connectivity

Women  
E4 < E3

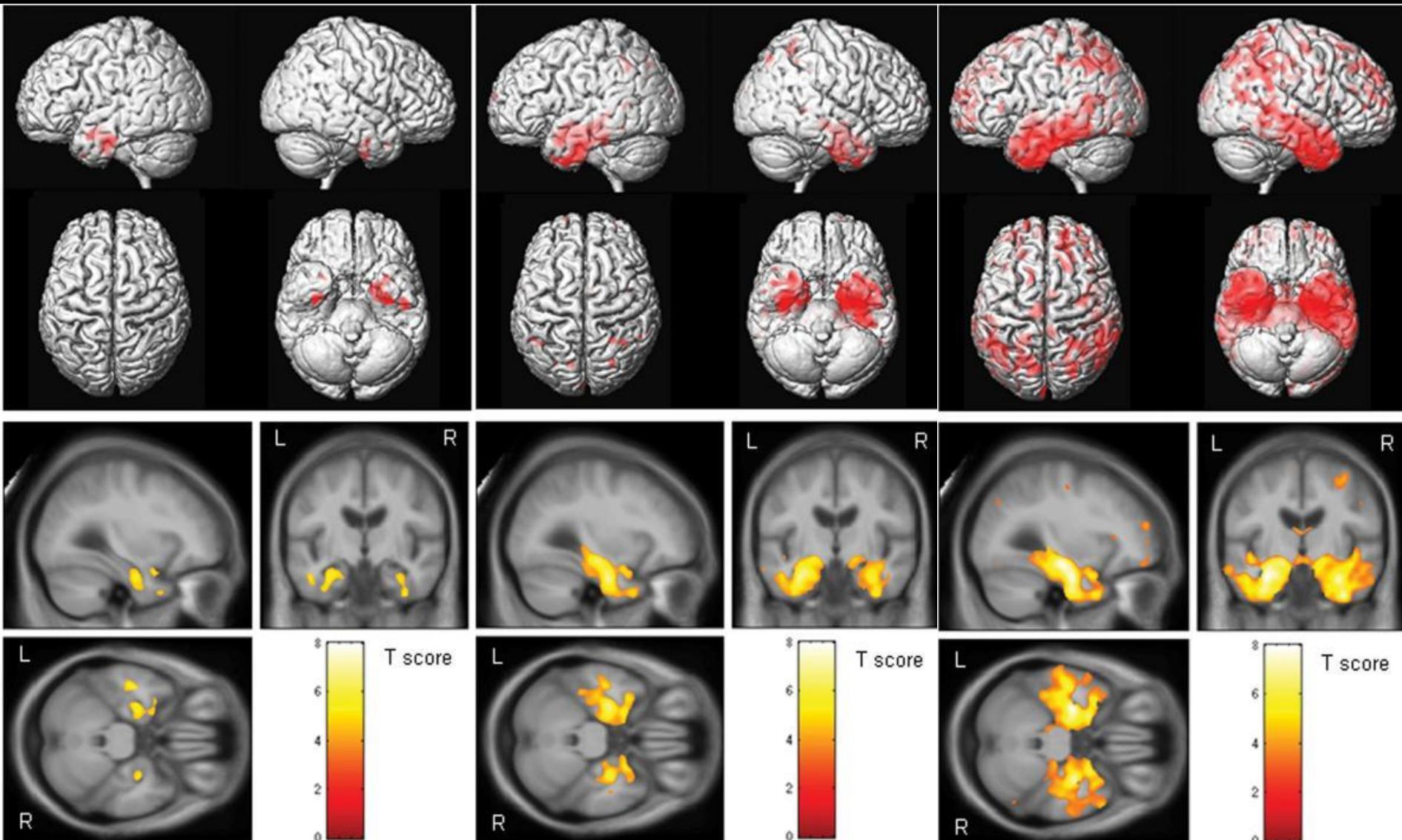


# MCI Marching Along the Network

3 years pre-conversion

1 year pre-conversion

Conversion to AD

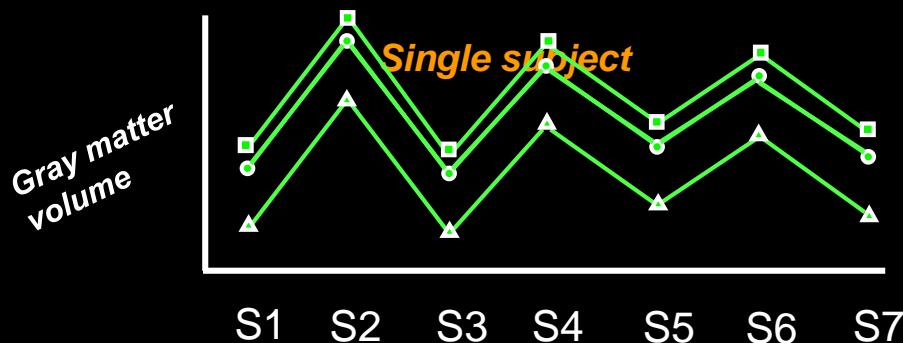
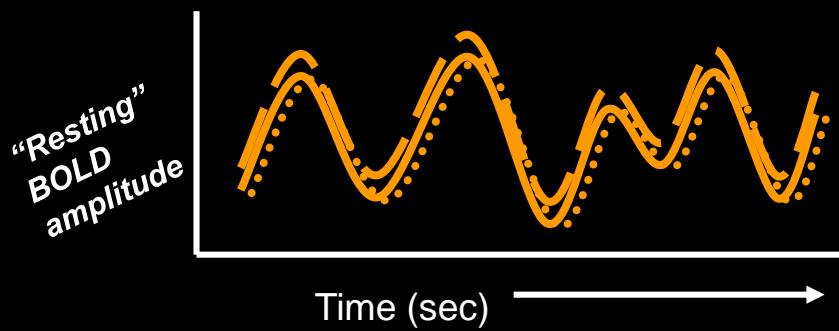
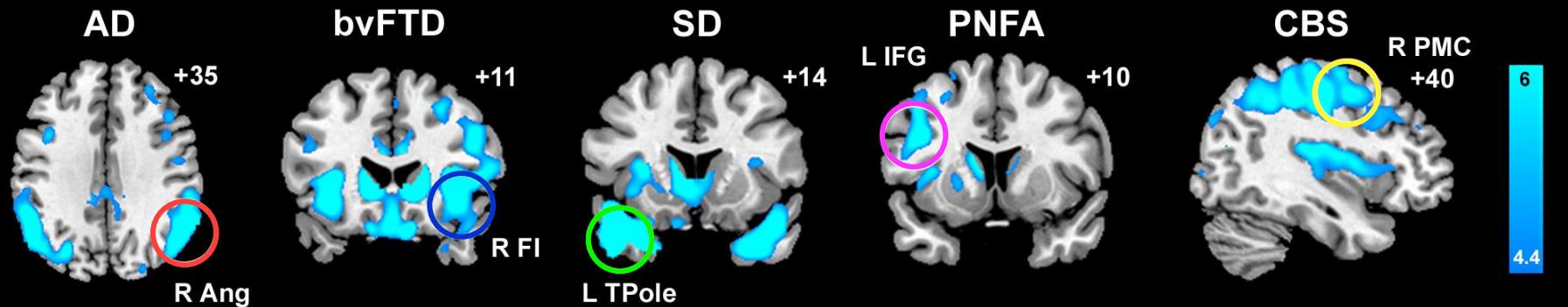


# Network-Based Neurodegeneration Fire Together, Wire Together, Expire Together

a

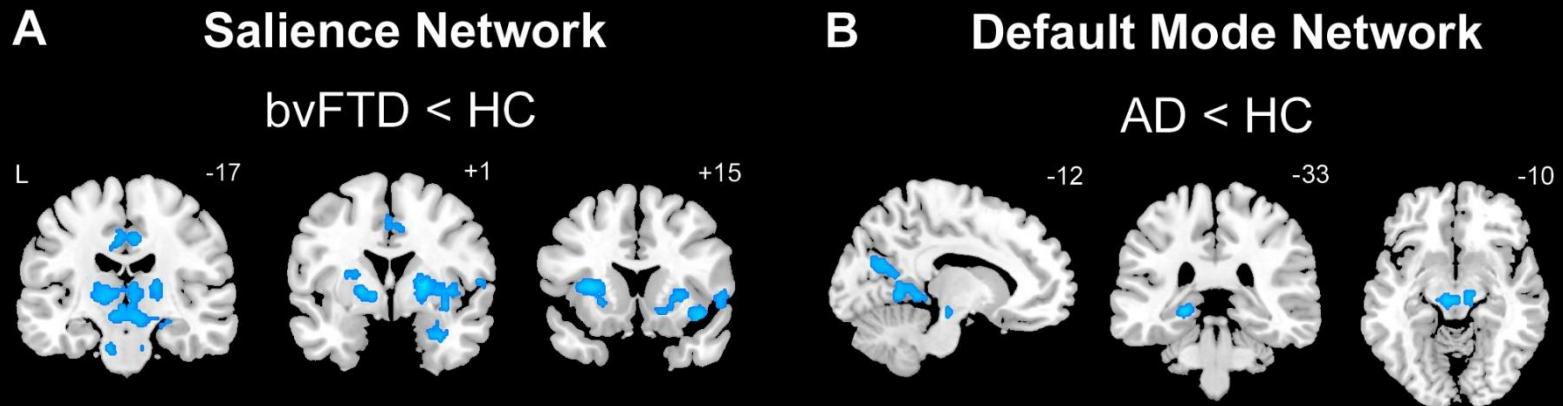
## Syndrome-specific regional atrophy patterns: patients vs. controls

○ Atrophy max = seed ROI



Seeley et al., *Neuron*, 2009

# bvFTD vs AD = Salience vs DMN



# bvFTD vs AD = Salience vs DMN



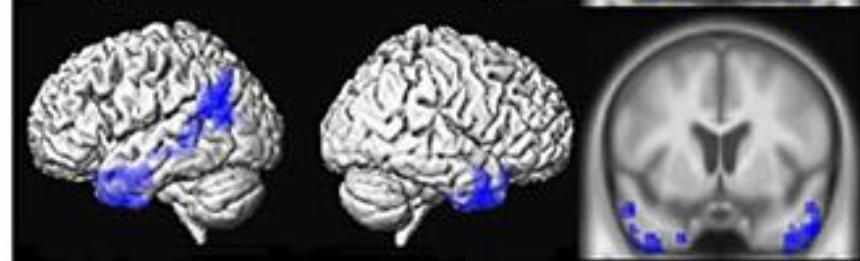
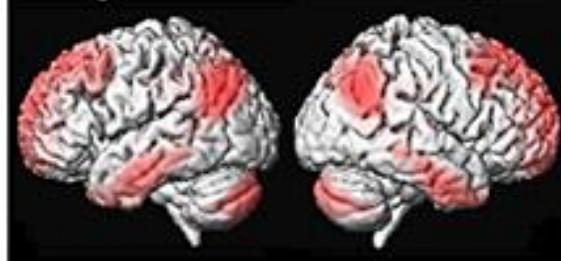
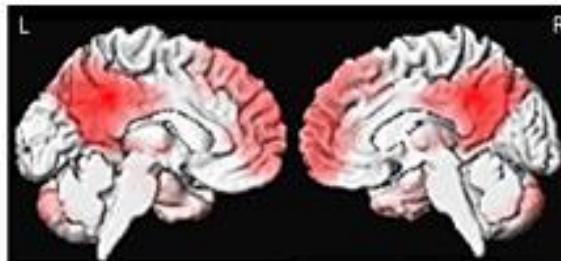
Zhou et al., *Brain*, 2010

# DMN and Salience in E4 Carriers

PCC seed 2, -45, 34

In-phase connectivity in CN APOE ε4 noncarriers

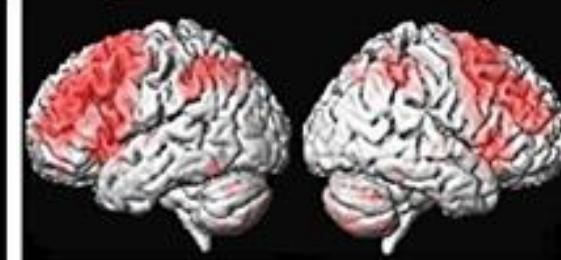
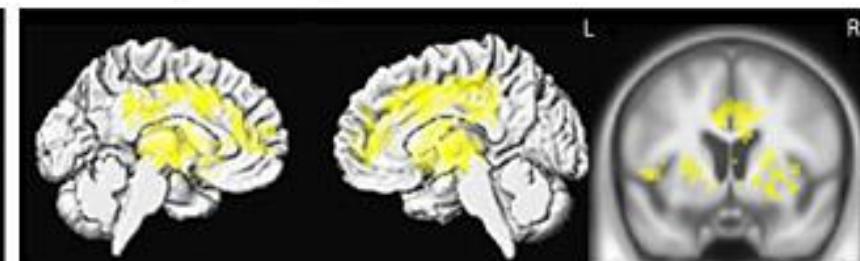
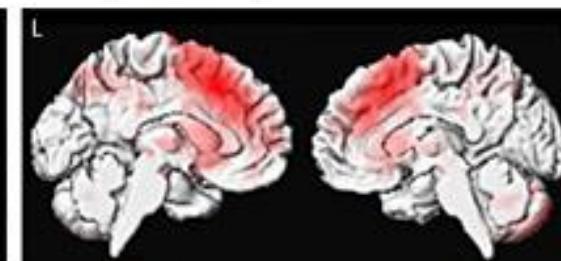
In-phase connectivity reductions in APOE ε4 carriers vs noncarriers



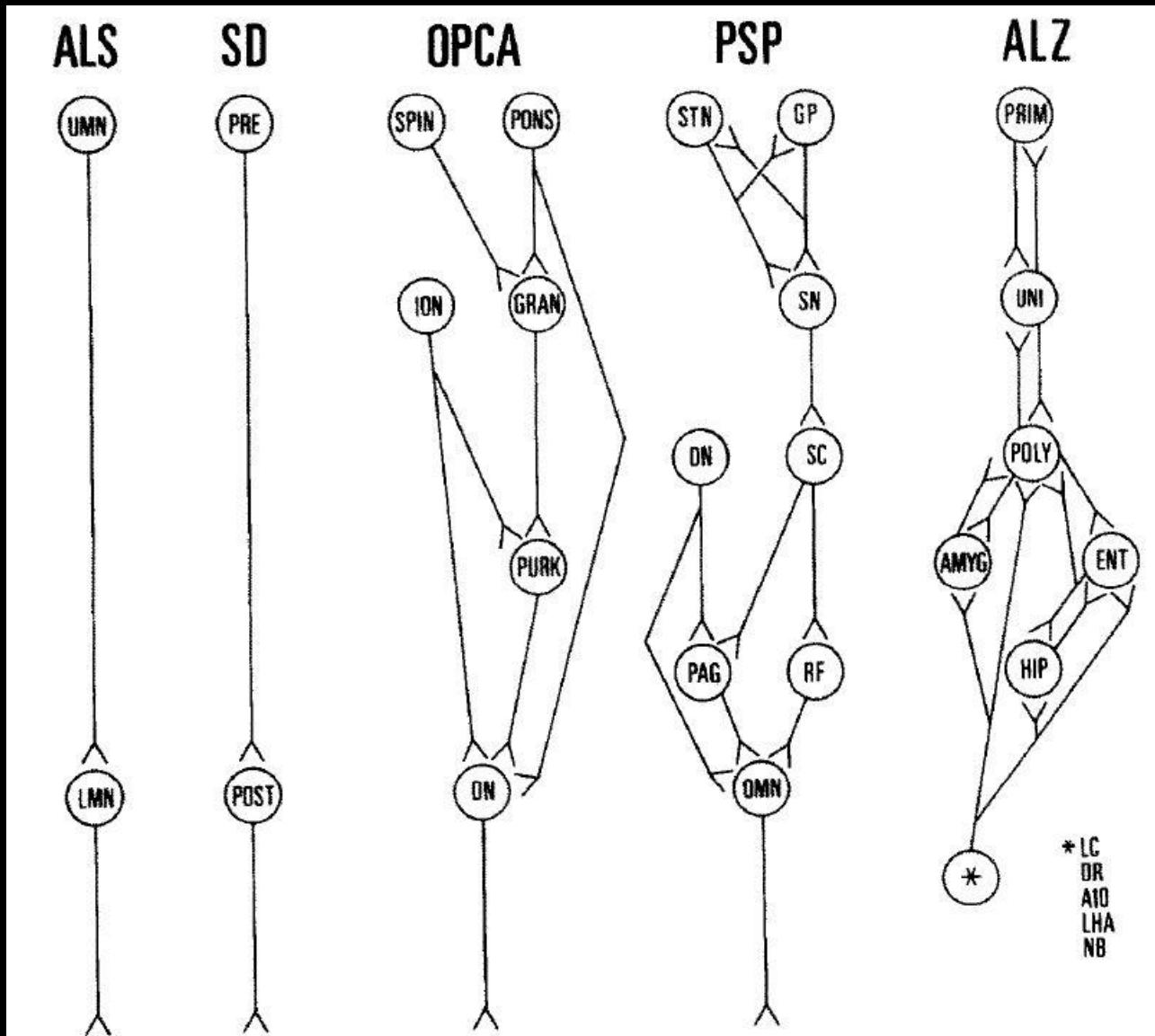
ACC seed -3, 18, 42

In-phase connectivity in CN APOE ε4 noncarriers

In-phase connectivity increases in APOE ε4 carriers vs noncarriers



# What's New Is Old



Saper et al., *Neuroscience*, 1987

# Conclusions

- The brain is segregated into a host of distinct functional networks, detectable with resting-state fMRI
- Specific neurodegenerative disorders appear to target specific networks
- Internetwork interactions deserve attention
- Future studies:
  - genetics
  - plasticity
  - pharmacology

# Acknowledgments

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