

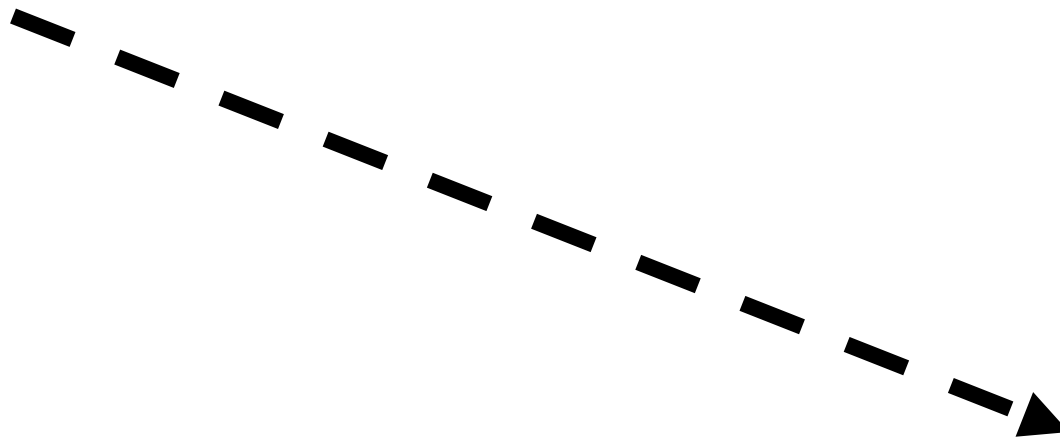
# ApoE, Brain Networks and Behavior: A Cautionary Tale



Michael Greicius, MD

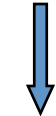
Functional Imaging in Neuropsychiatric Disorders (FIND) Lab  
Department of Neurology and Neurological Sciences  
Stanford University School of Medicine

**SNP**

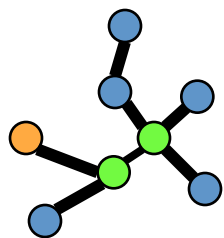


**Phenotype**

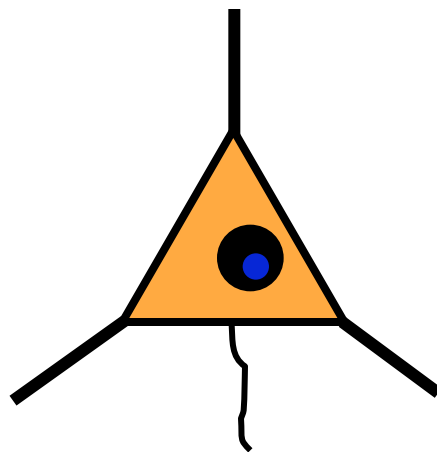
**SNP**



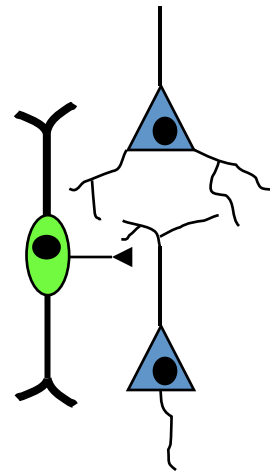
**Gene**



**Protein**

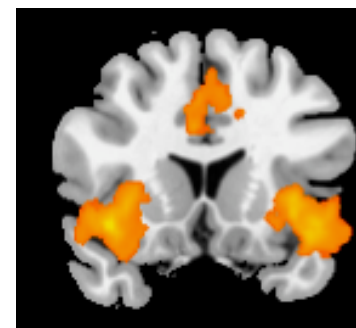


**Neuron**

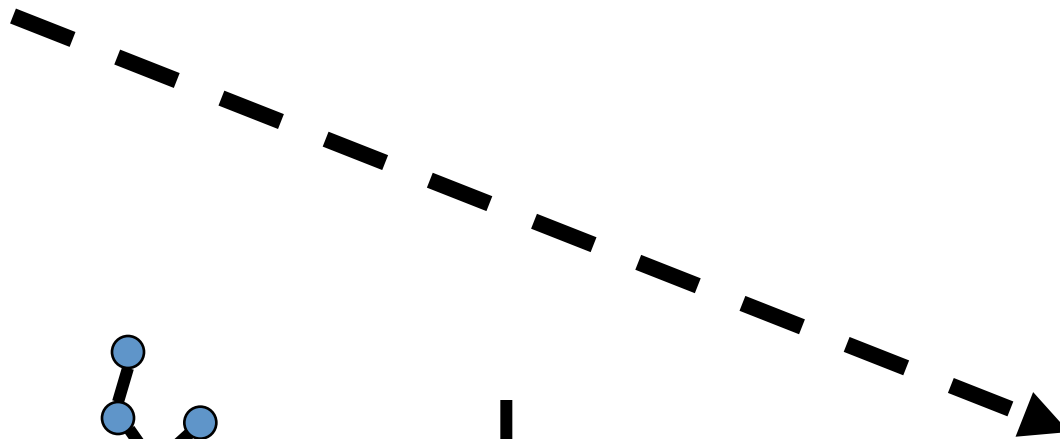


**Microcircuit**

**Phenotype**



**Network**

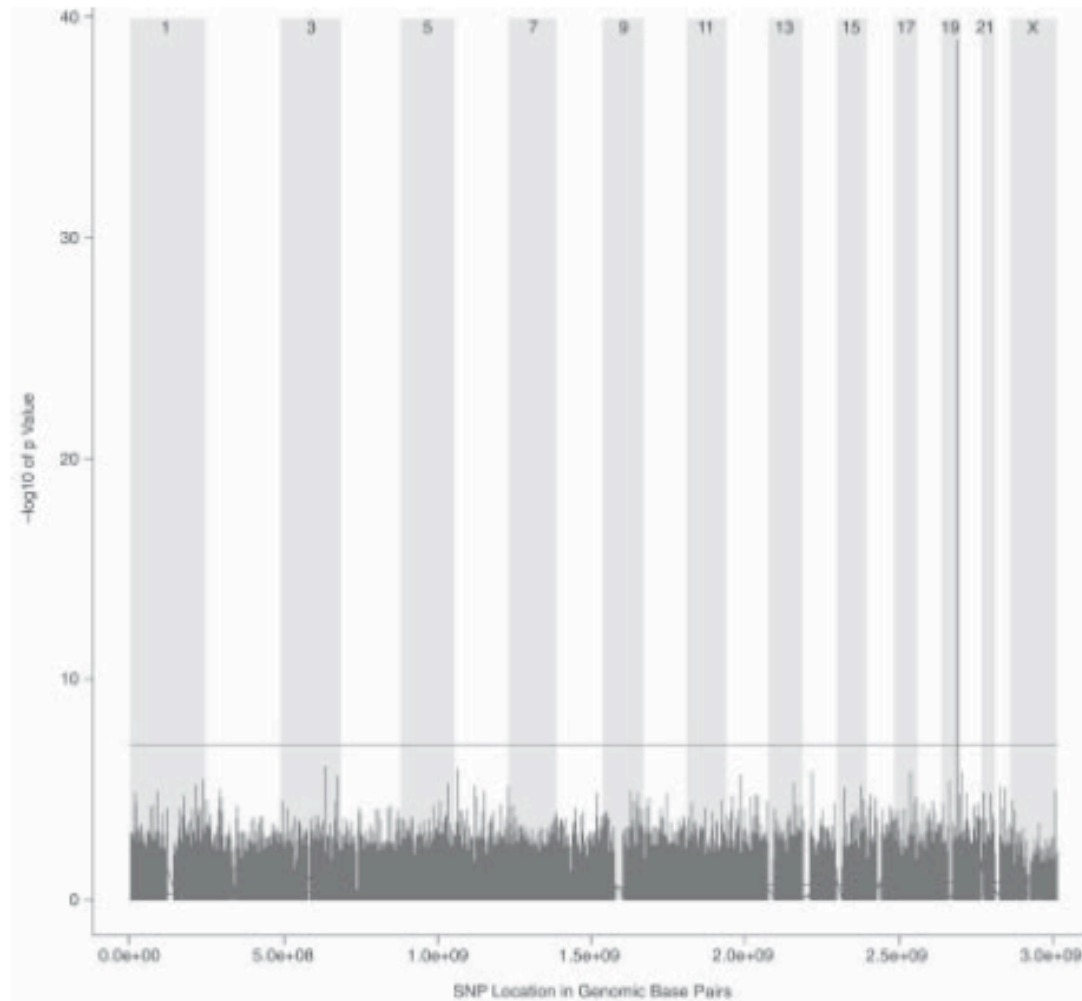


# ApoE and Alzheimer's Disease Risk

- Apolipoprotein E three common allele variants: 2,3,4
- ApoE4 allele is over-represented in AD(0.5) vs. controls (0.16)
  - Strittmatter et al., *PNAS*, 1993, >2400 citations
- Numerous potential mechanistic connections to AD
  - >14,000 PubMed references
- E4 risk is attenuated and E2 protection reversed in certain ethnic groups
- E4 reduces age of onset

# ApoE: In a League of Its Own

Figure 1. Ultra-High-Density SNP Whole-Genome Association Scans Identify *APOE* as the Locus Most Strongly Associated With AD in 1086 Individuals (664 with AD, 422 controls)\*



Coon et al., *J Clin Psychiatry*, 2007

# AAN Recommendations for Work -Up of Dementia

- B12, TSH +/- RPR (if risk factors)  
    remarkably low yield (about 9% partially reversible, 1-3% fully reversible)
- Imaging: routine CT or MRI
- Screen for depression
- Neuropsychological measures incorporated in NINCDS-ADRDA criteria for AD
- **Recommended against** volumetric MRI/PET  
/SPECT/**APOE**/CSF studies

Knopman et al., *Neurology*, 2001.

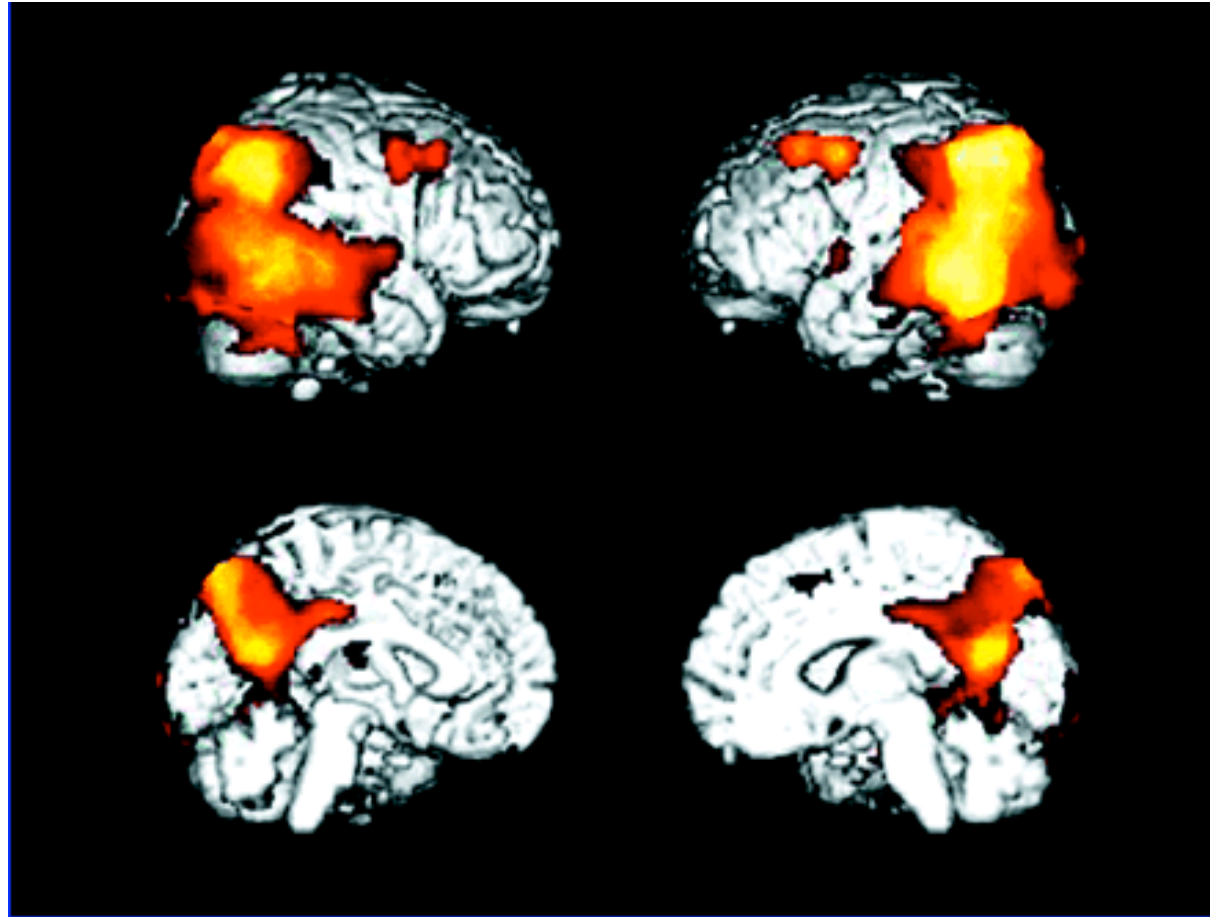
# My Genome, My Self



Jeff Riedel for The New York Times

Pinker, *NY Times Magazine*, January 7 2009

# Hypometabolism in AD

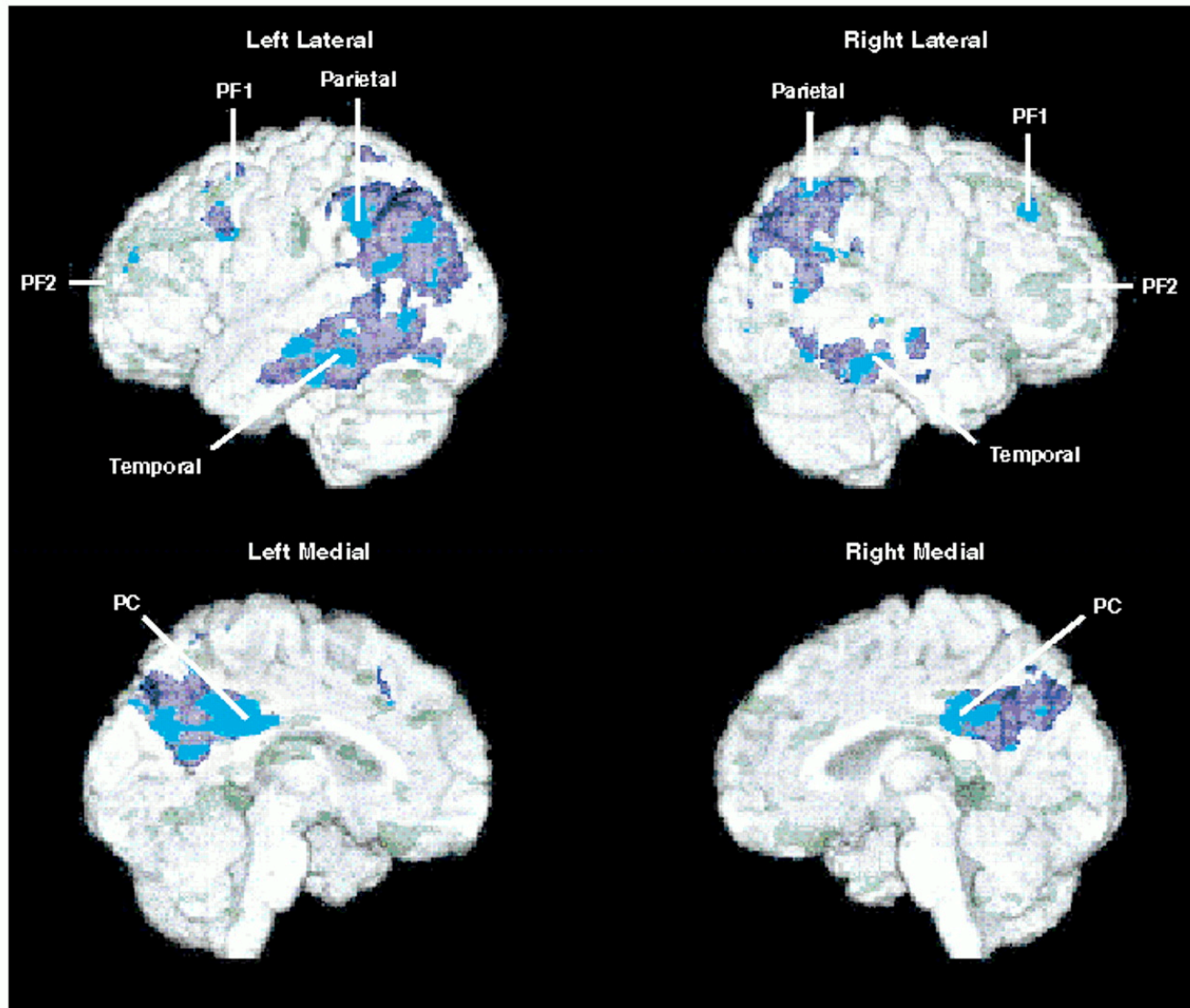


Resting PET 34 healthy subjects versus 14 AD patients.

Alexander et al., *Am J Psychiatry*, 2002 (after Minoshima et al., *J Nucl Med*, 1995)

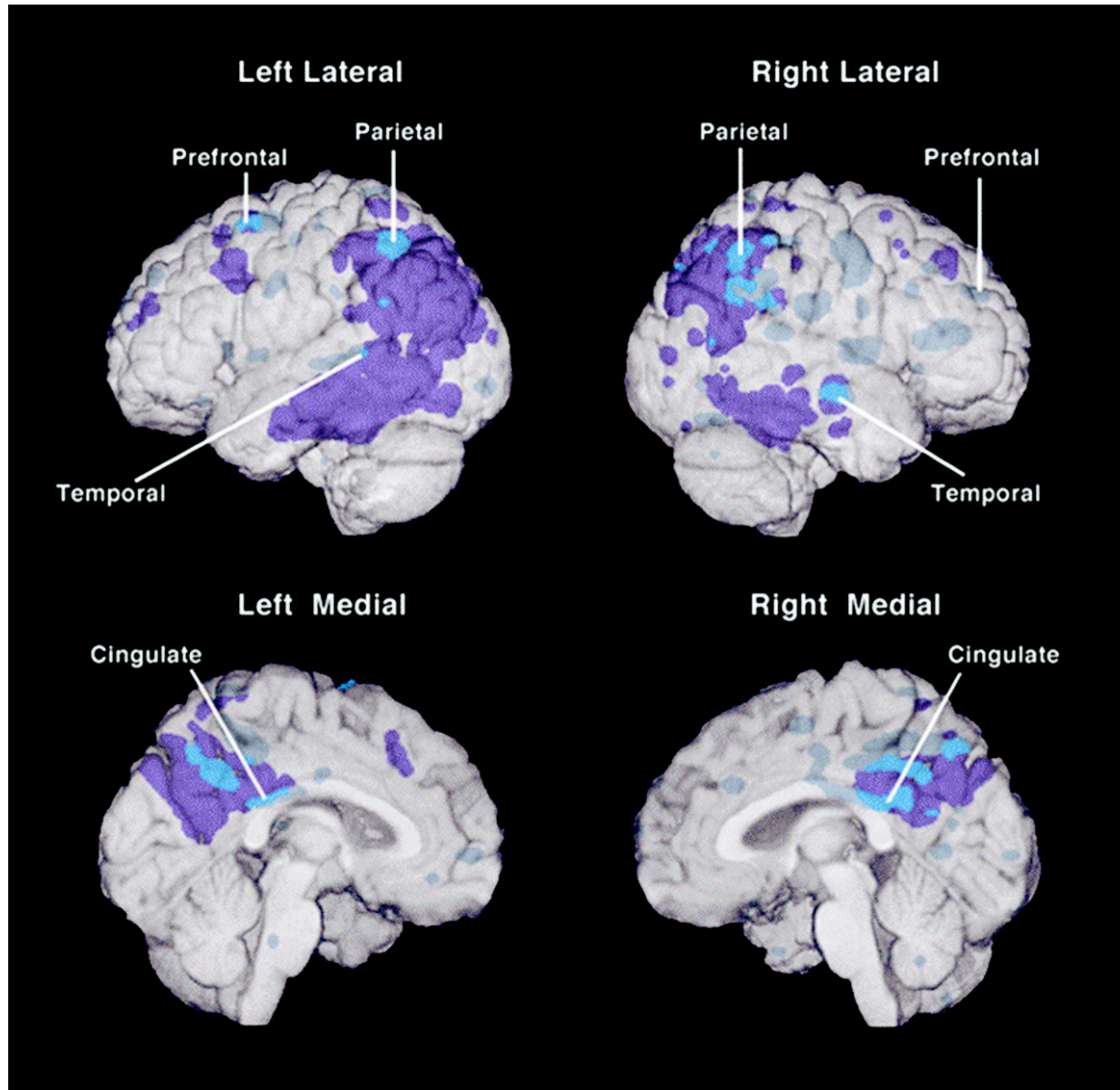


# Reduced Metabolism in Middle-Aged E4 Carriers



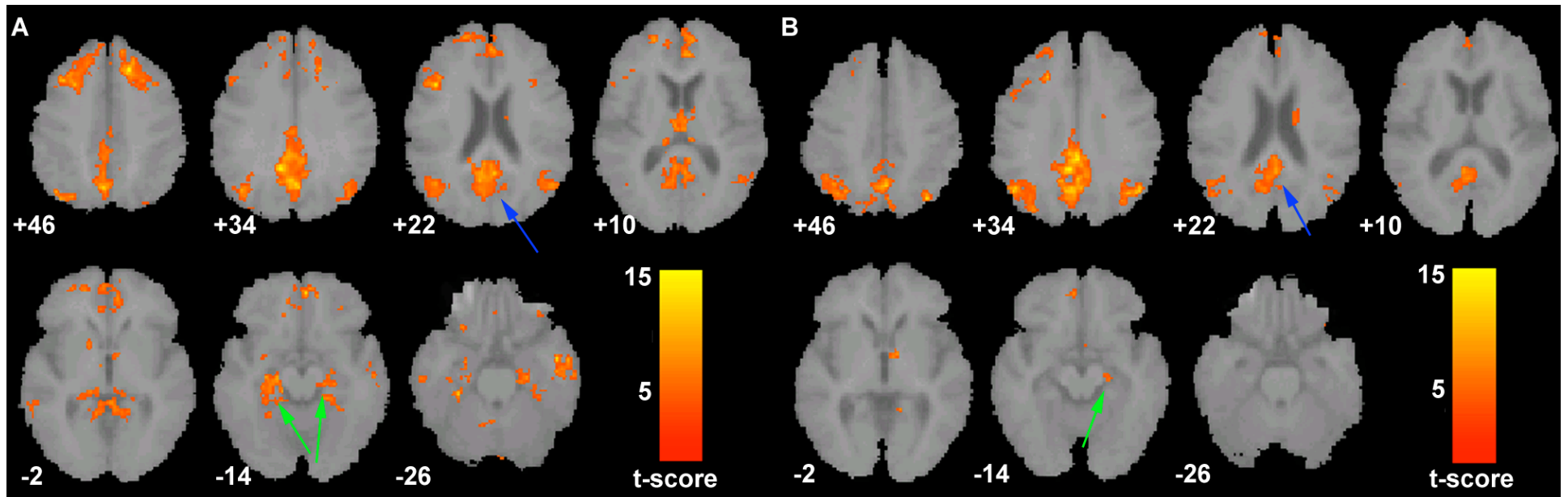
Reiman et al., *NEJM*, 1996

# Reduced Metabolism in Young E4 Carriers



Reiman et al., *Proc Natl Acad Sci*, 2004

# Default-Mode Network in AD

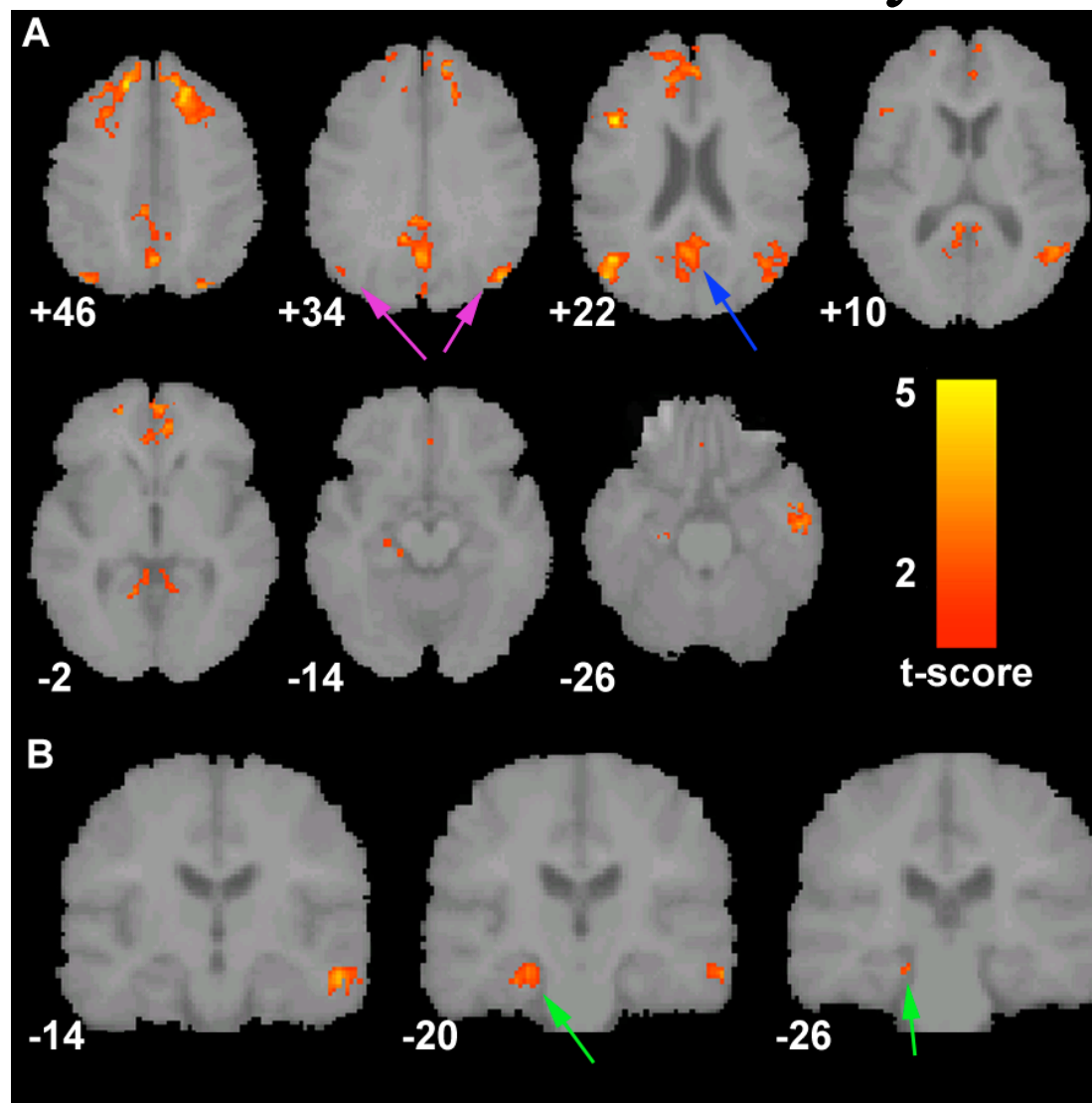


Healthy Aging

AD

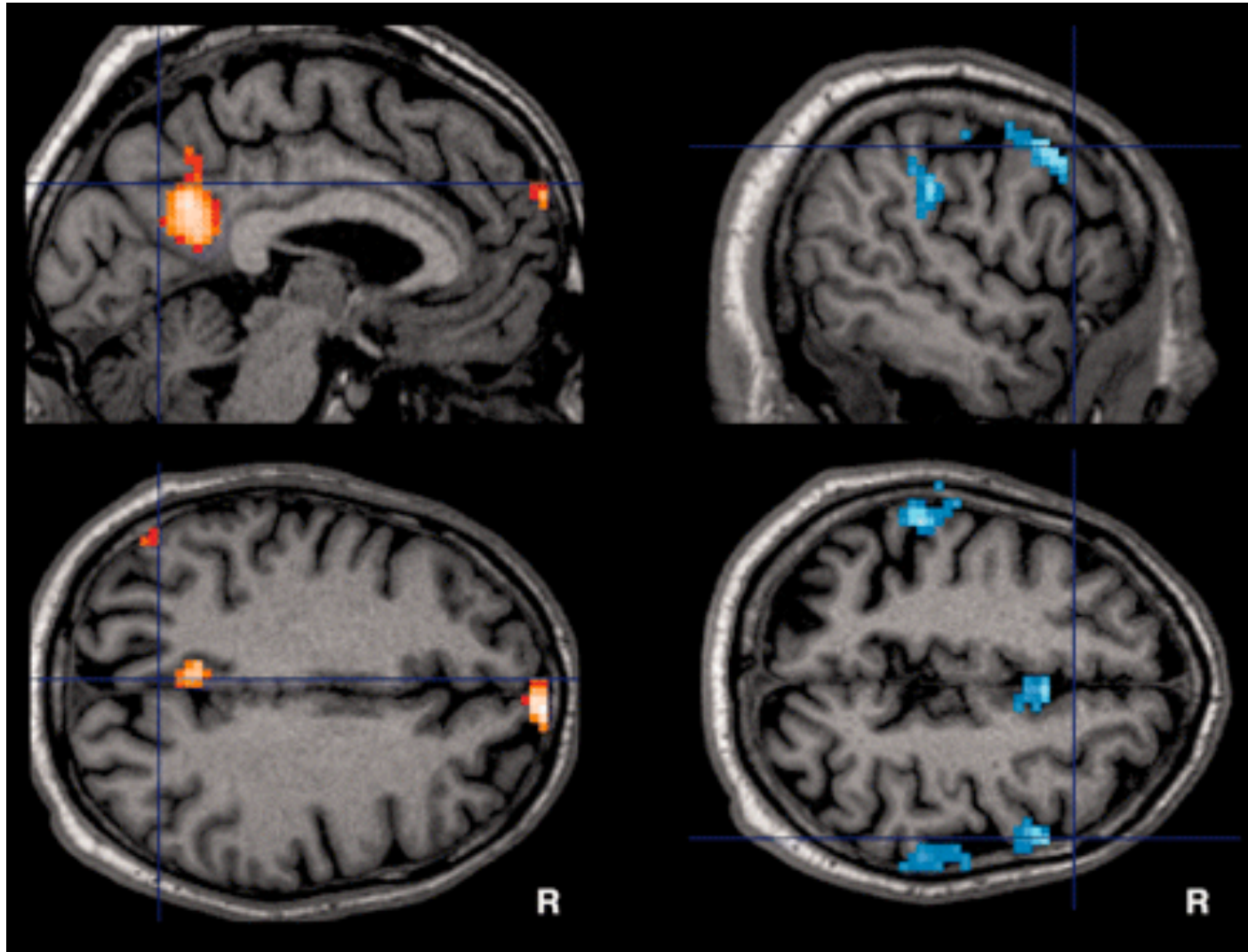
Greicius et al., *PNAS*, 2004

# Reduced DMN Connectivity in AD



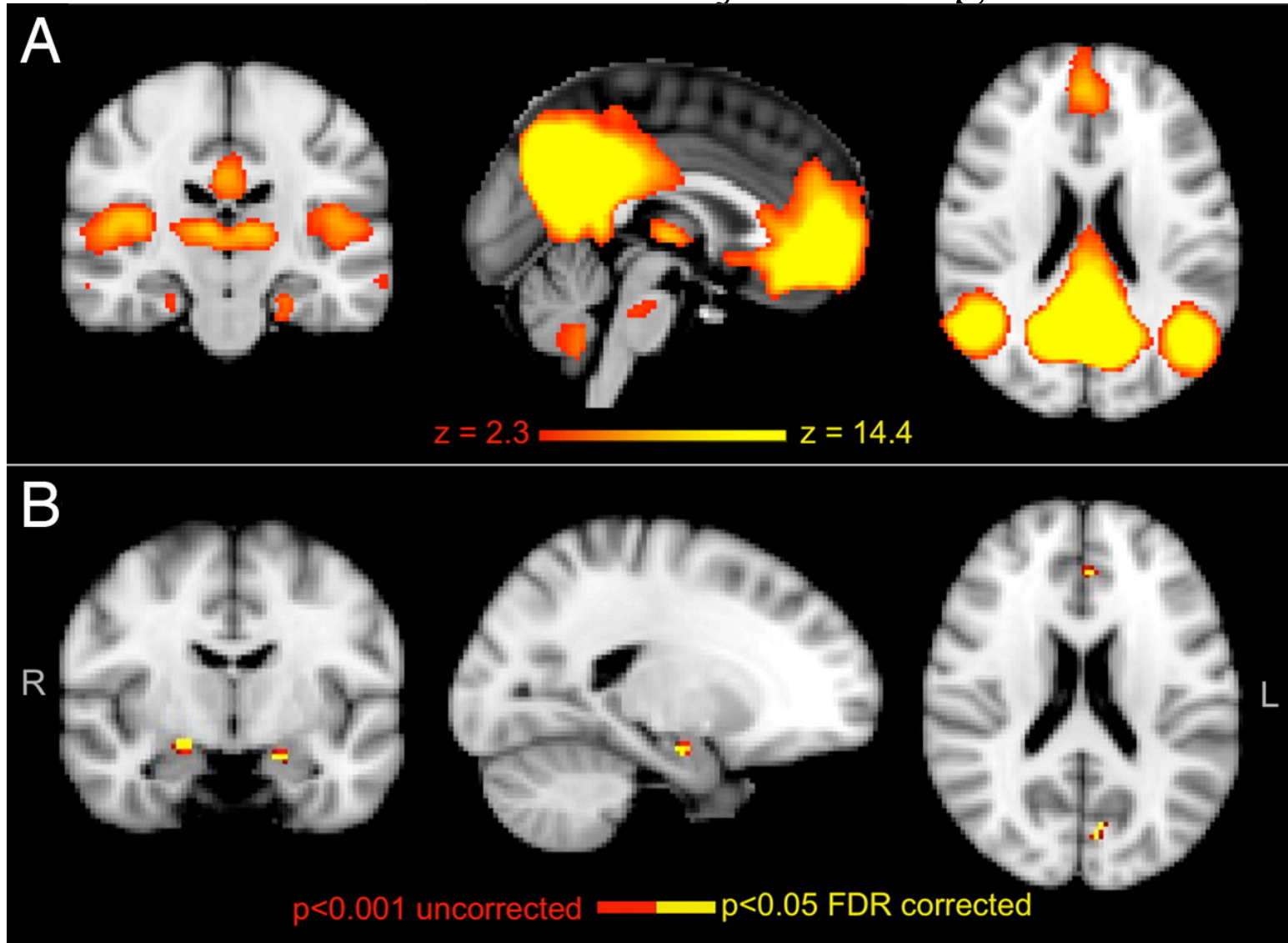
Greicius et al., *PNAS*, 2004

# Reduced DMN Connectivity in MCI



Sorg et al., *PNAS* 2007

# Increased DMN Connectivity in Young E4 Carriers



Filippini et al., *PNAS*, 2009

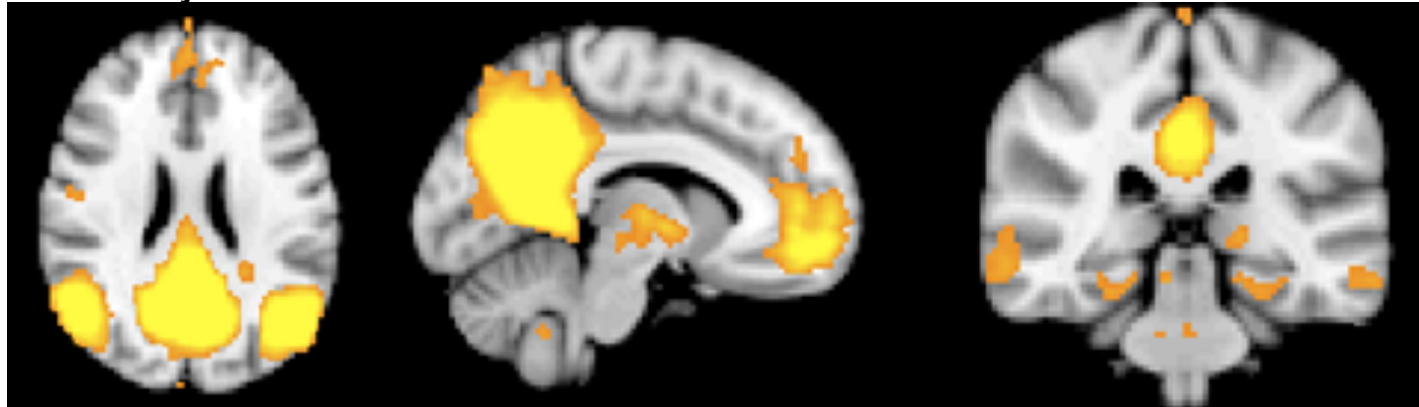
\*Also found increased hippocampal activation in E4 carriers during a memory task

# Effect of ApoE on Default Mode Network Connectivity in Healthy Older Subjects

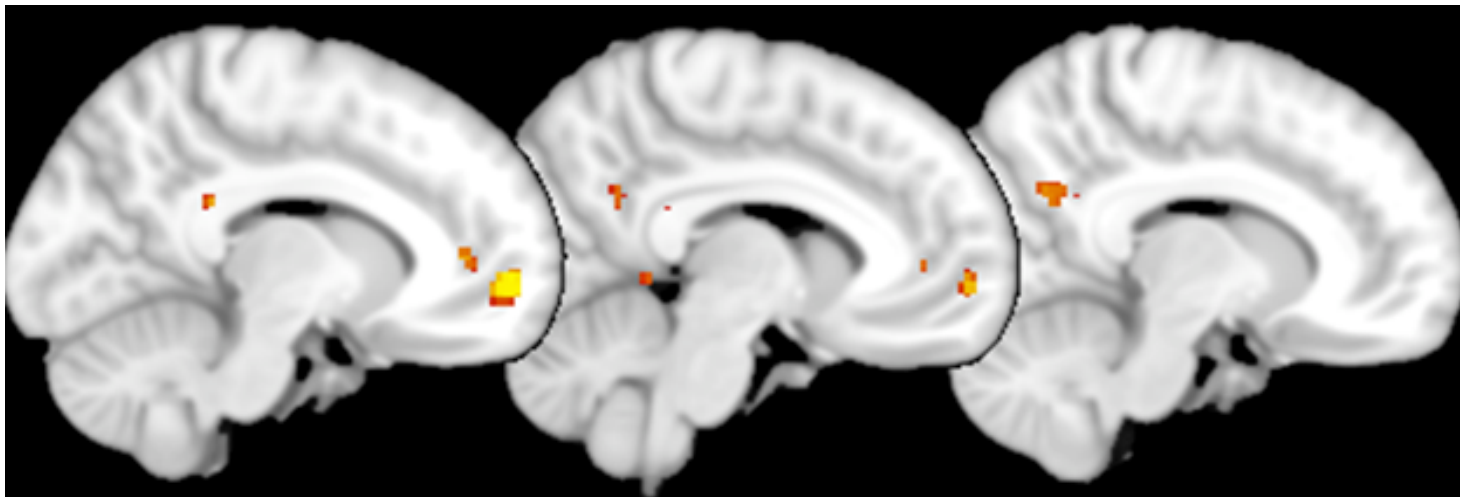
	<i>APOE3</i> (homozygotes)	<i>APOE4</i> (carriers)	<i>P</i>
Age	69.2 (± 6.9)	68.8 (± 8.3)	0.899
Gender (m/f)	7/6	7/6	1
Education (years)	18.1 (± 1.3)	16 (± 2.5)	0.015
CVLT short delay	12.0 (± 2.4)	10.5 (± 3.5)	0.218
CVLT long delay	13.0 (± 2.2)	11.7 (± 3.0)	0.215
Modified Trails, time (s)	25.8 (± 8.8)	24.4 (± 6.9)	0.659
Rey complex figure recall	11.5 (± 1.7)	11.9 (± 2.7)	0.712

# Decreased Connectivity in Older ApoE4 Carriers

All subjects

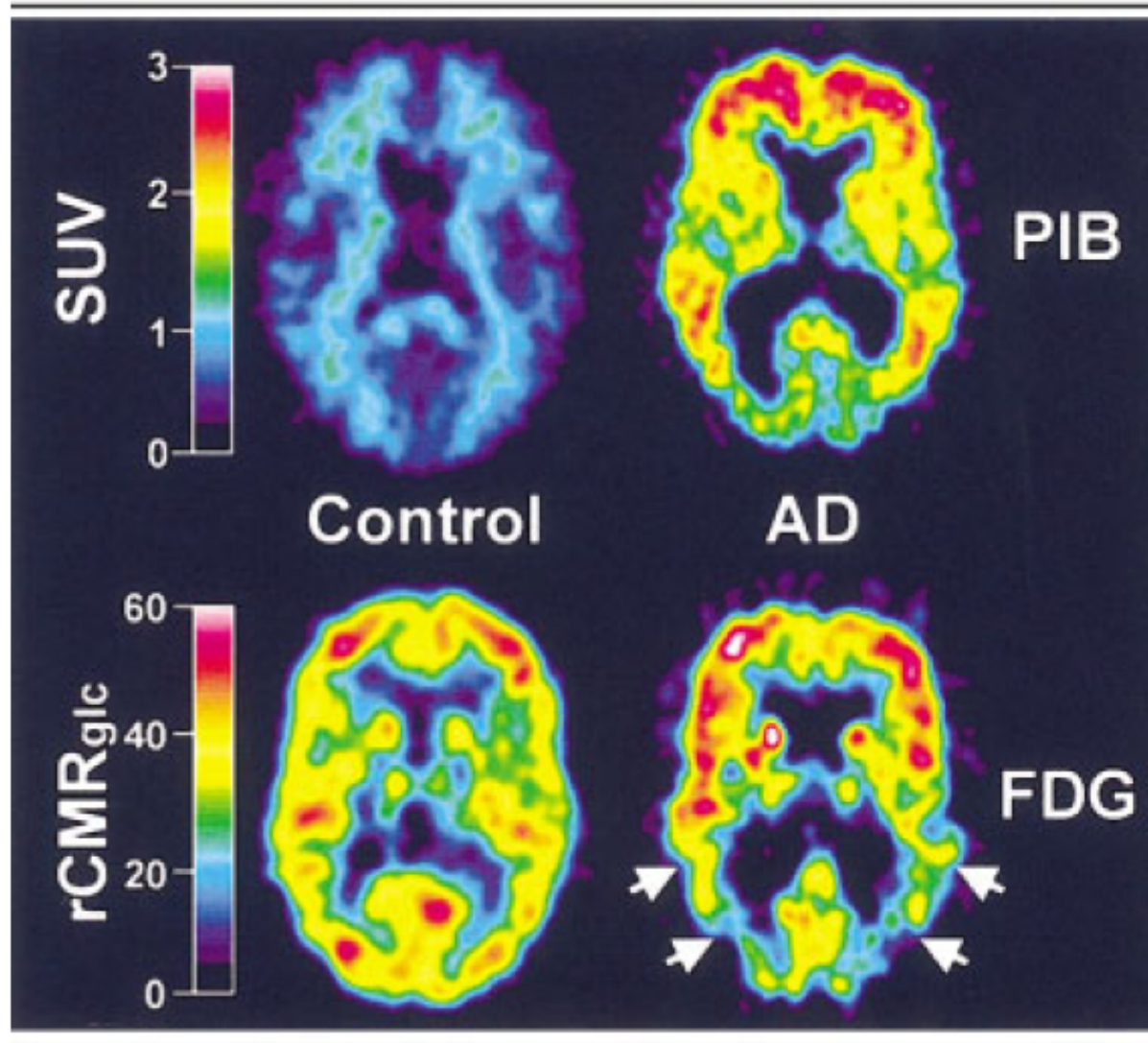


E3>E4



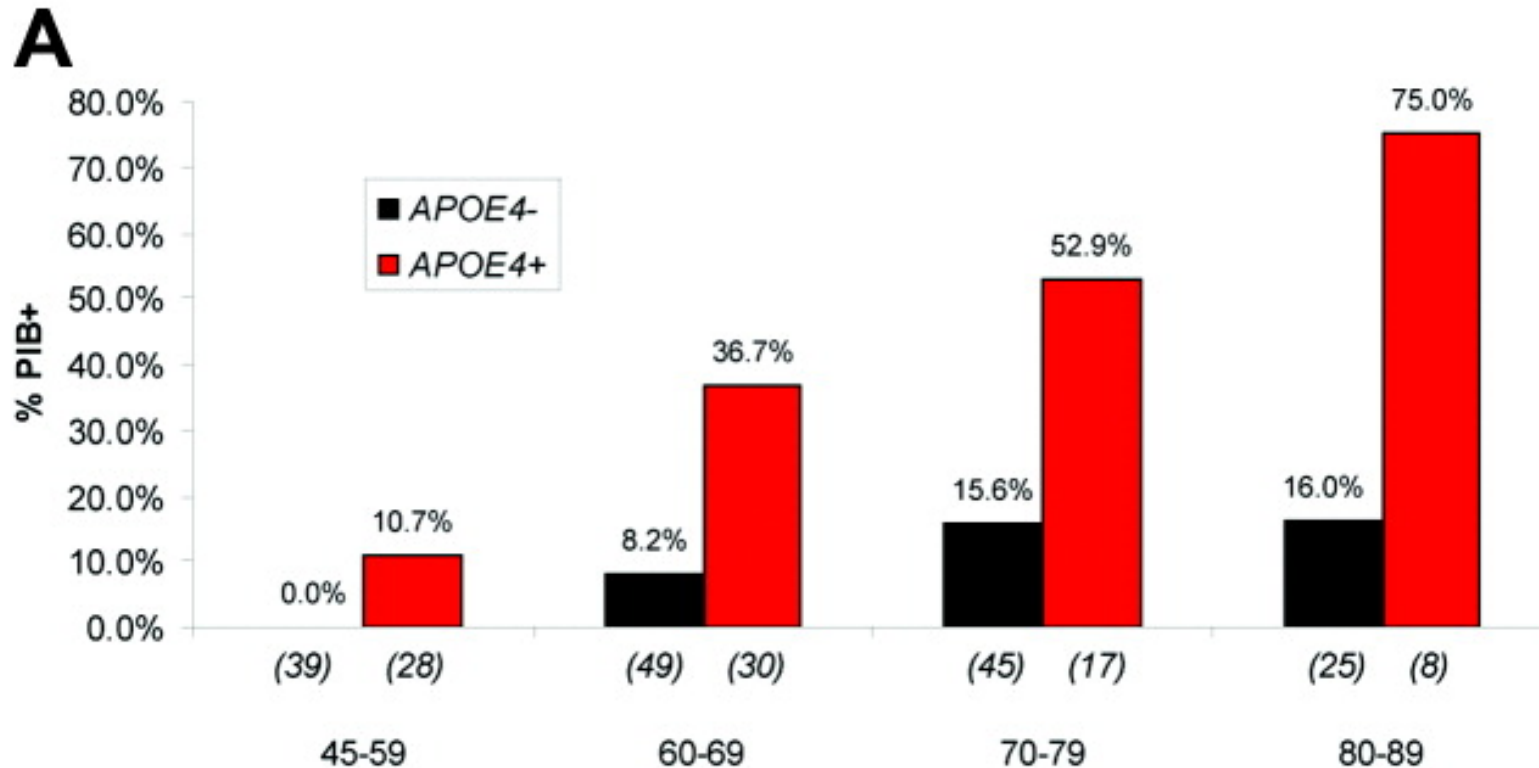


# Imaging Amyloid Plaques with Pittsburgh Compound B (PIB)



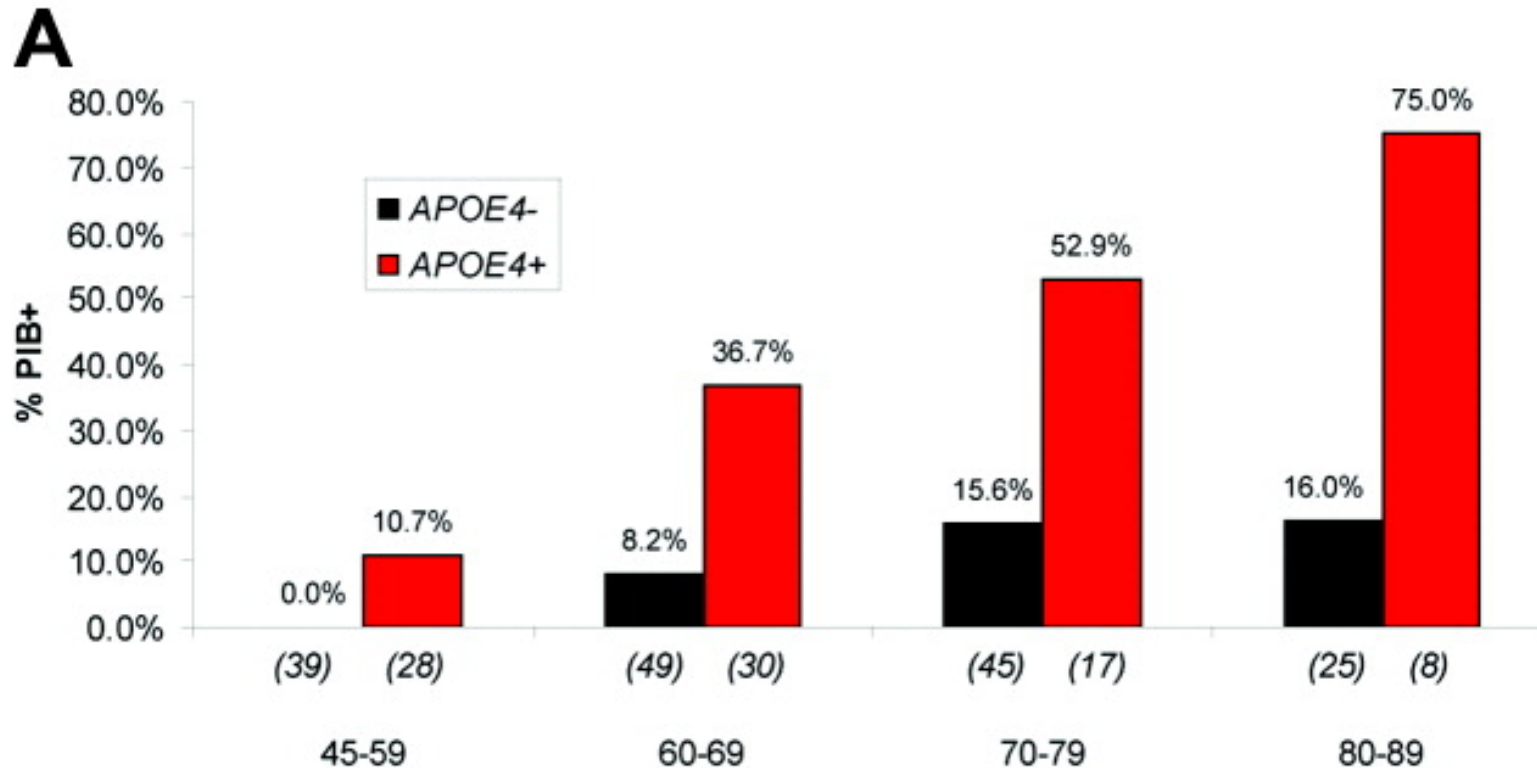
Klunk et al., *Ann Neurol*, 2004

# Increased Amyloid Deposition with E4



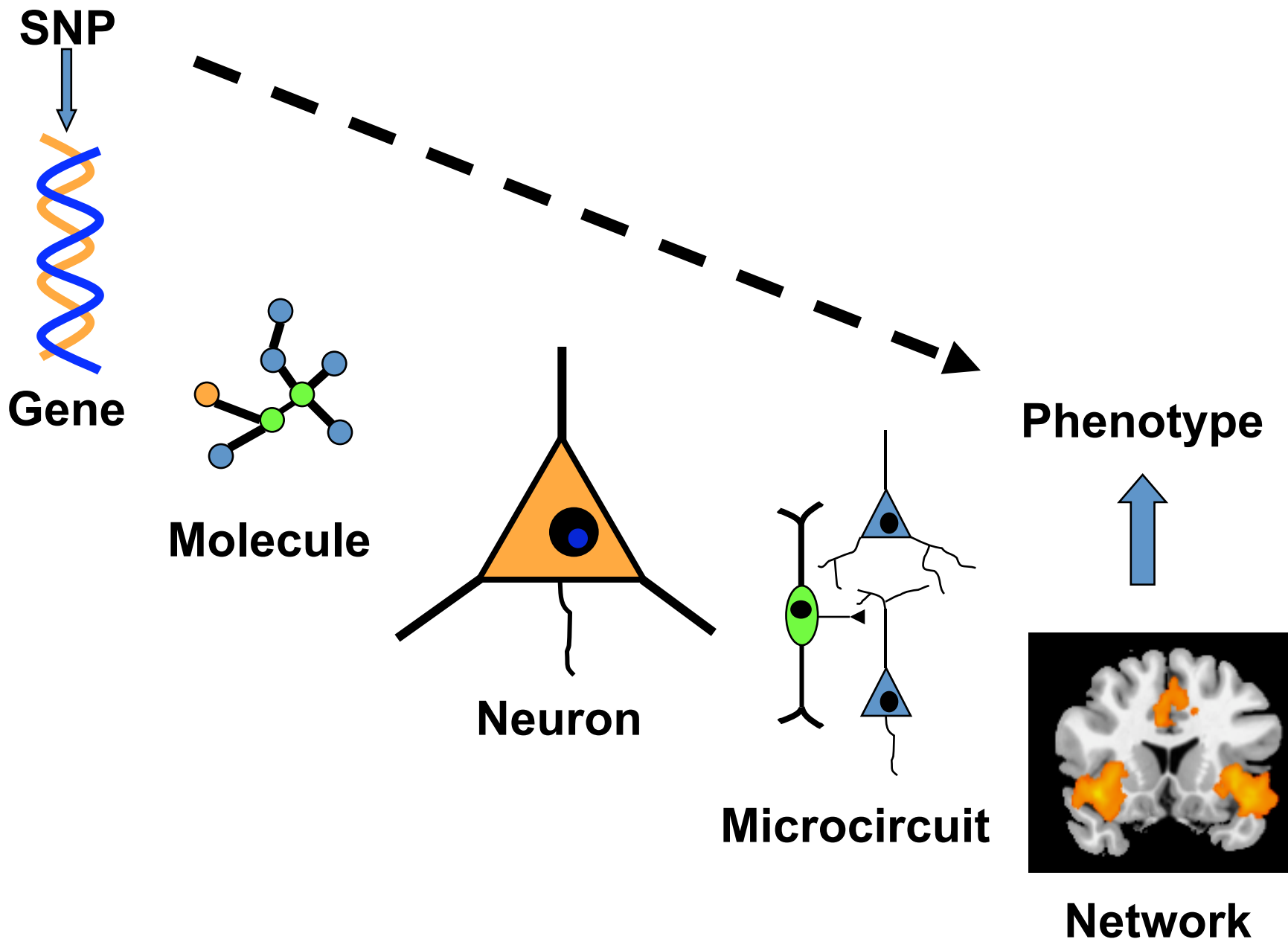
Morris et al., *Ann Neurol*, 2010

# Increased Amyloid Deposition with E4

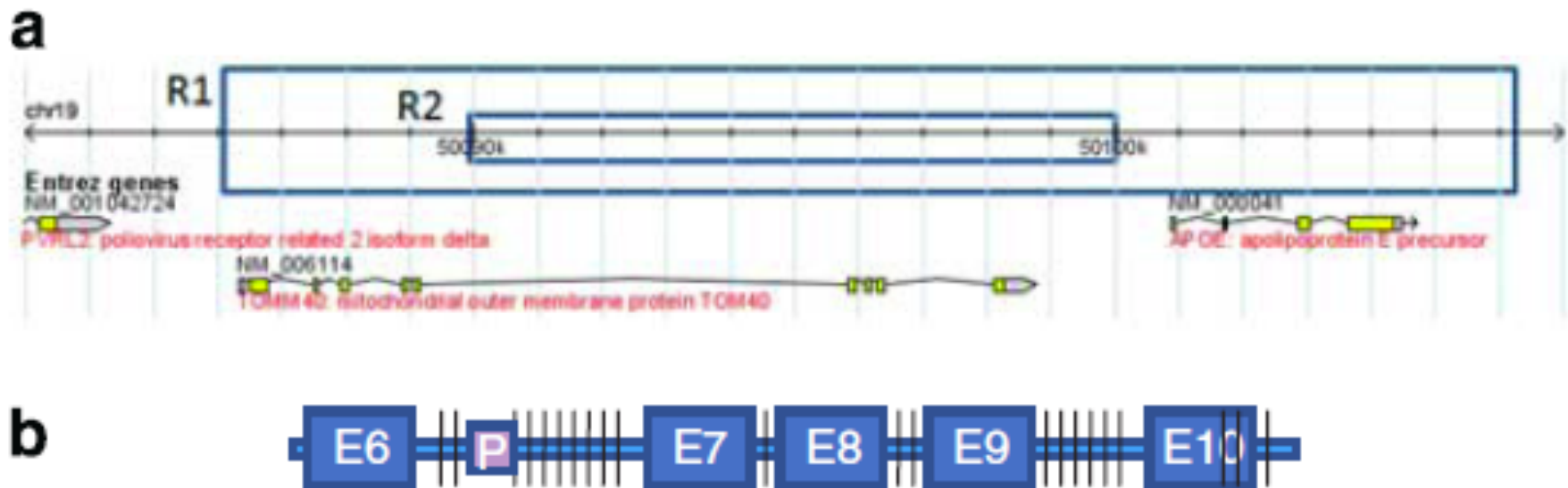


But no effect on tau levels in the spinal fluid

Morris et al., *Ann Neurol*, 2010

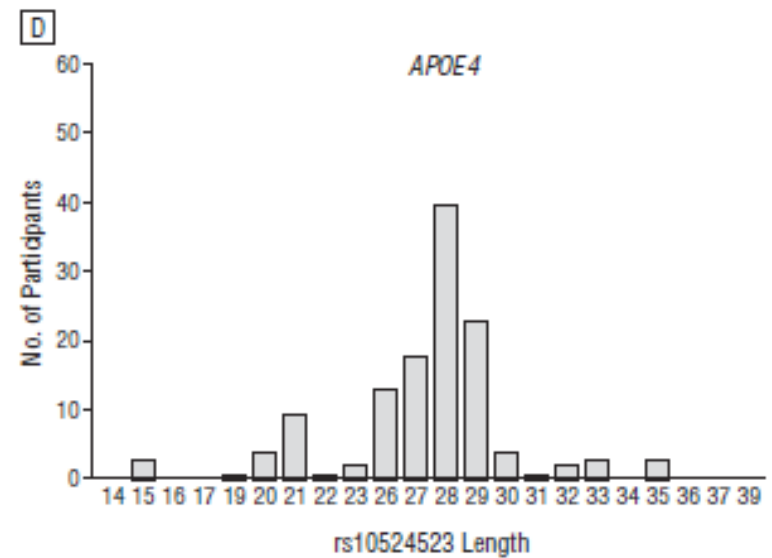
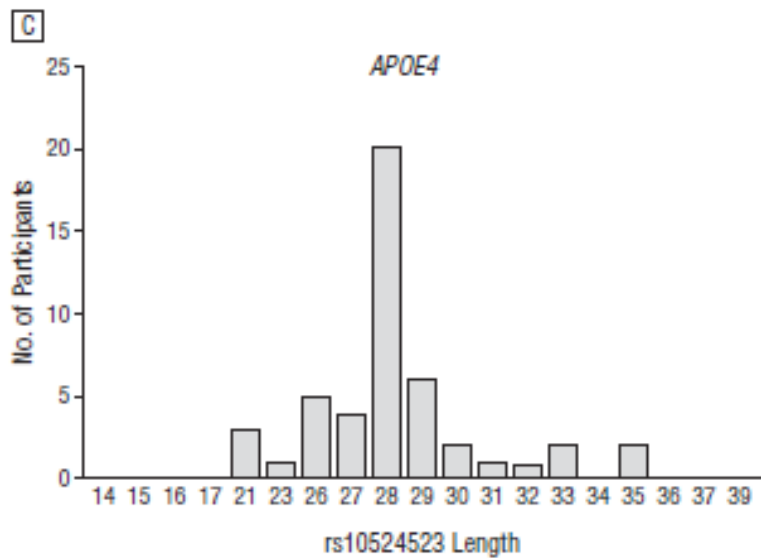
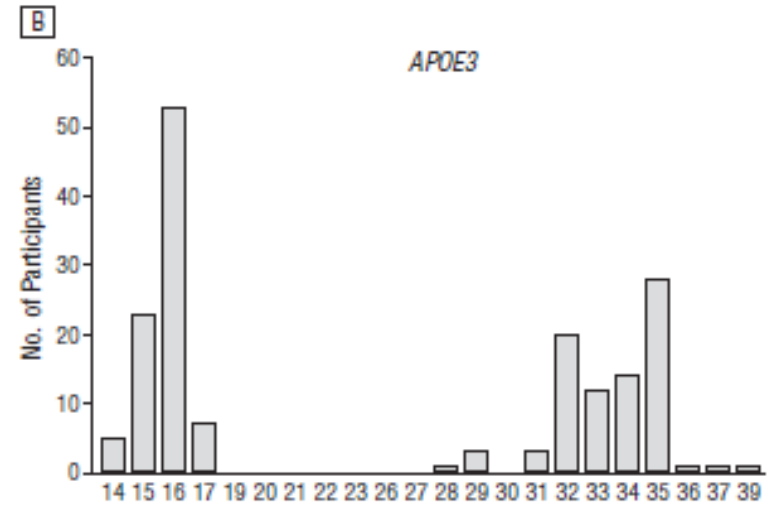
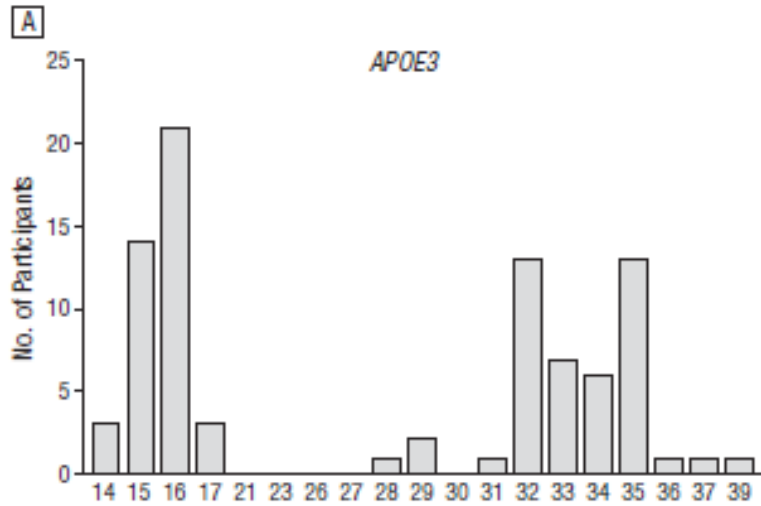


# ApoE or TOMM40: The Perils of Linkage Disequilibrium



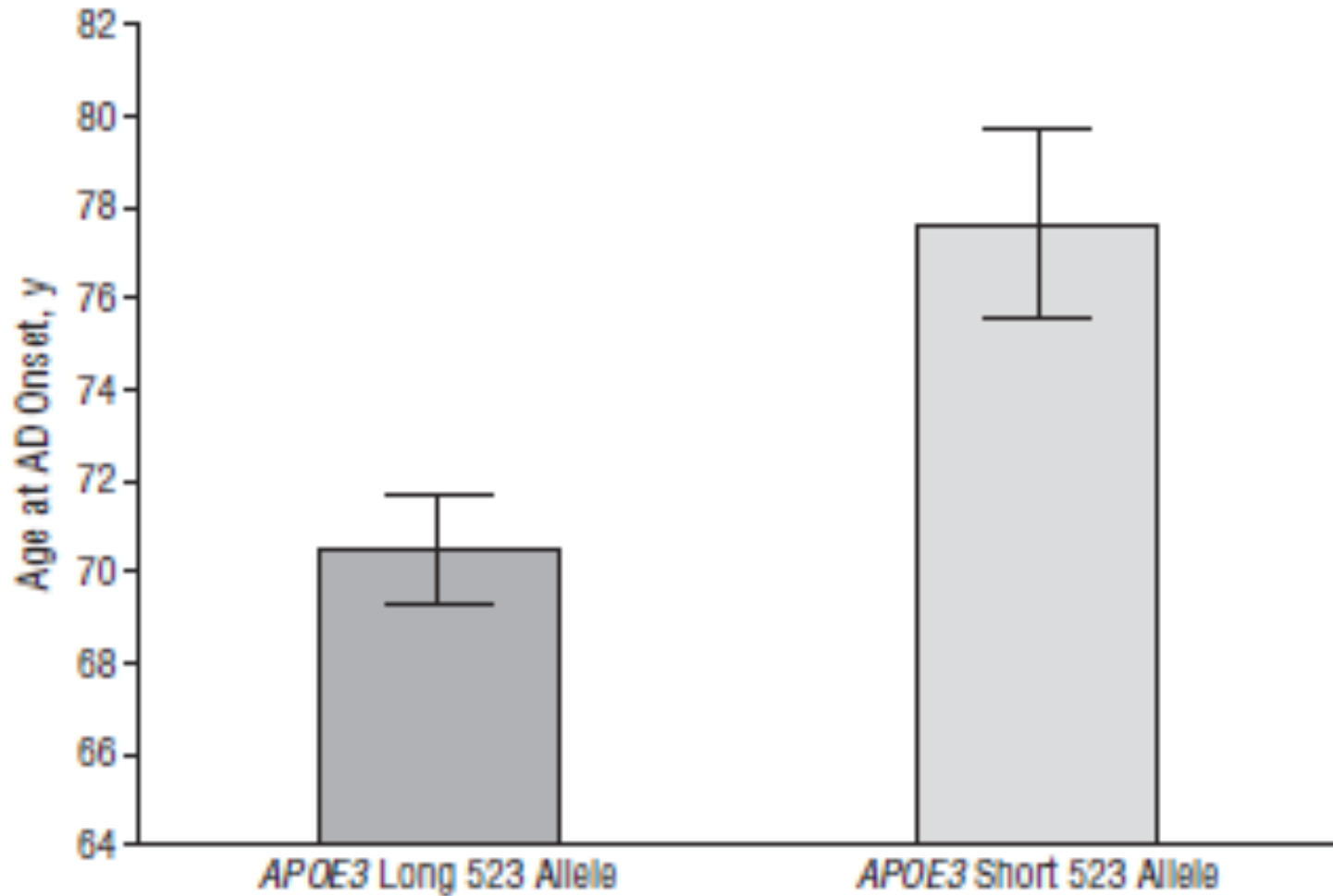
Roses et al., *Pharmacogenomics J*, 2009

# ApoE or TOMM40



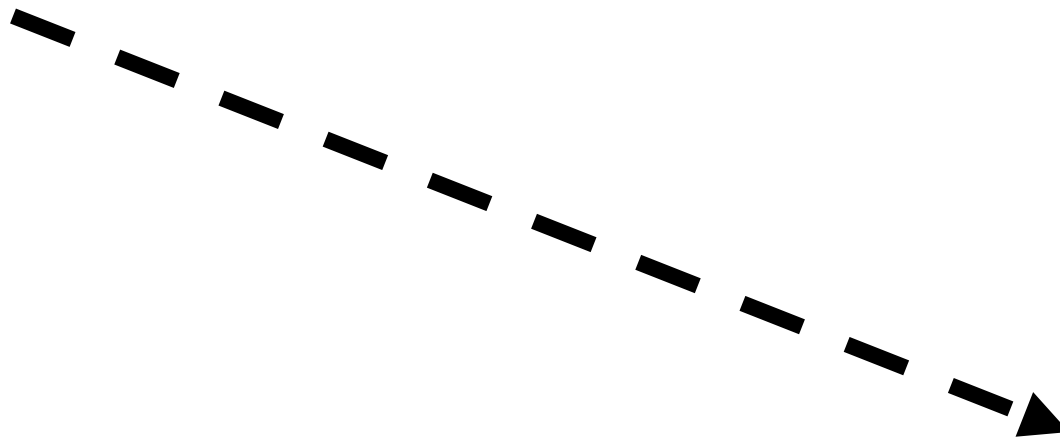
Roses et al., *Arch Neurol*, 2010

# ApoE or TOMM40



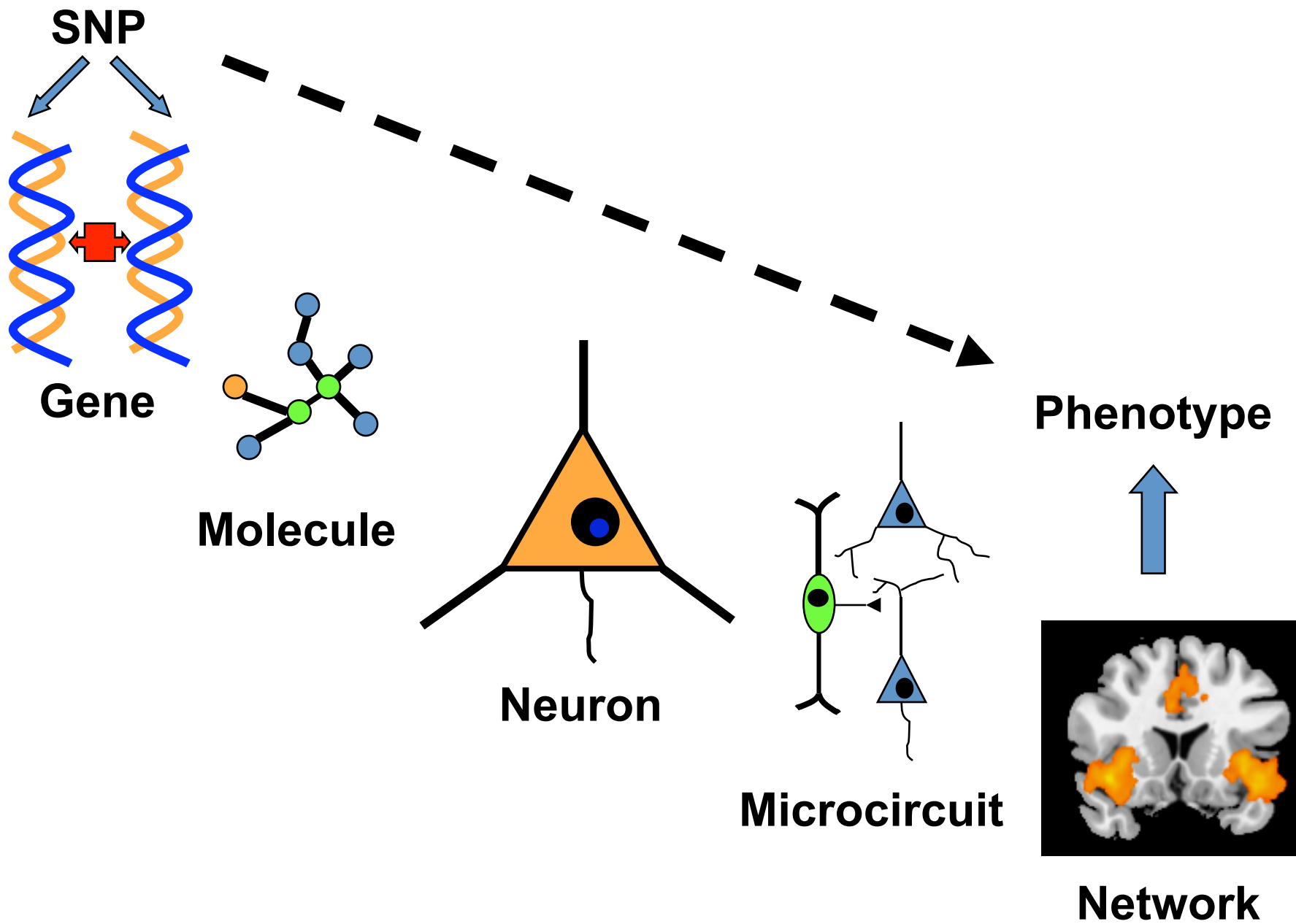
Roses et al., *Arch Neurol*, 2010

**SNP**



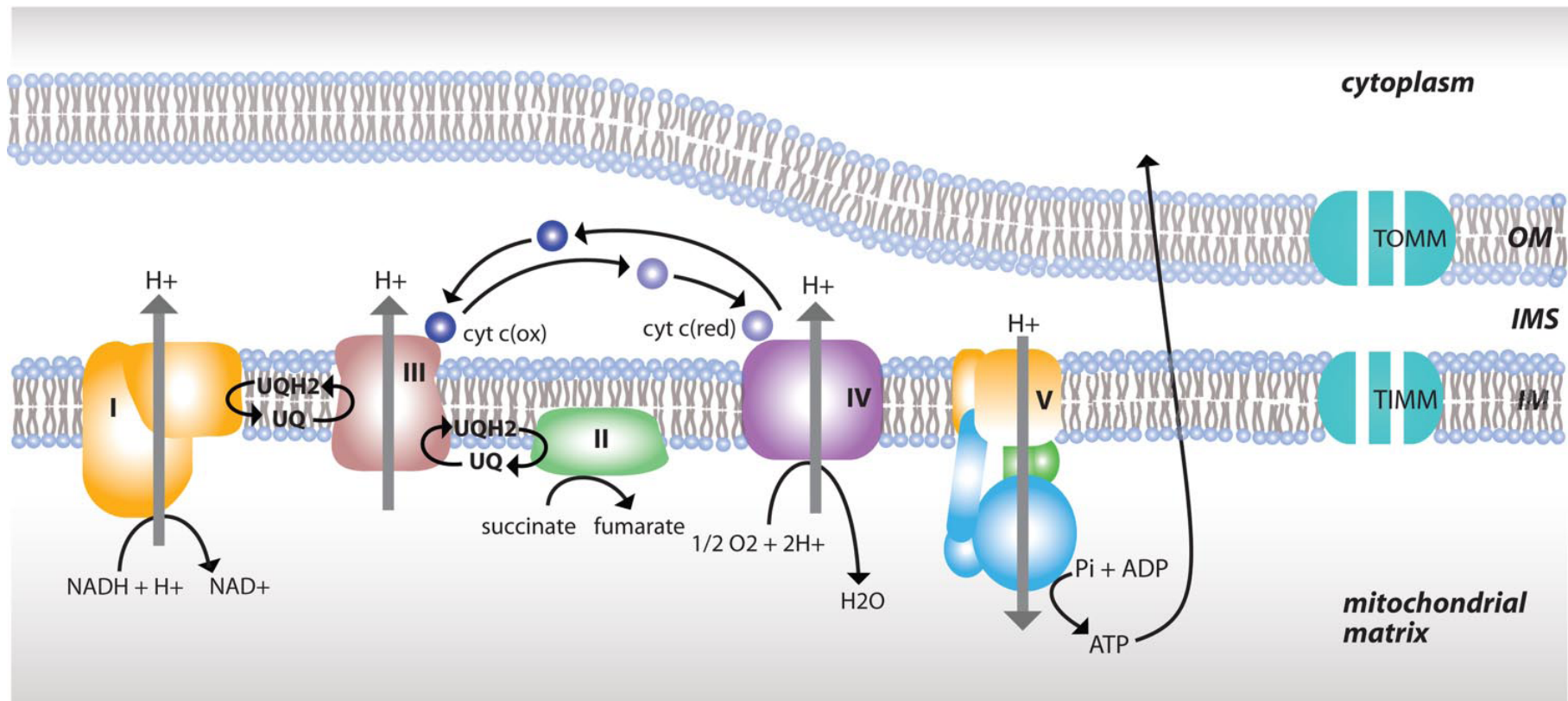
**Phenotype**







# AD Reduces Mitochondrial Gene Expression in Layer III Posterior Cingulate Neurons



Liang et al., *PNAS*, 2008

# Conclusions

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- Need for bridges between SNPs and their genetic/molecular/cellular/network effects
- Humans make the best models for human diseases
- Multimodal approaches: imaging, csf studies, post-mortem gene expression
- Untargeted, personal genotyping is not a clinically sound undertaking at this point



# Collaborators

## Stanford

Vinod Menon

Jeske Damoiseaux

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Will Shirer

## UCSF

Bill Seeley

Bruce Miller

Joel Kramer

Helen Zhou

## Allen Institute for Brain Science

Mallar Chakravarty

Mike Hawrylycz

Ed Lein

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# ApoE4 and Age of Onset of FTD with Progranulin Mutations

Study	Age of Onset E4 Carriers	Age of Onset E4 Non-Carriers	P-value
Gass et al., <i>Hum Mol Genet</i> , 2006	63±7 years; N=10	57±7 years; N=29	0.01
Beck et al., <i>Brain</i> , 2008	62 ± 2 N=3	56 ± 4 N= 13	0.005
Rademakers et al., <i>Lancet Neurol</i> , 2007	55.9 N=12	57 N=14	0.59