Amyloid-related brain dysfunction: Evidence for a presymptomatic stage of AD

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Massachusetts General Hospital
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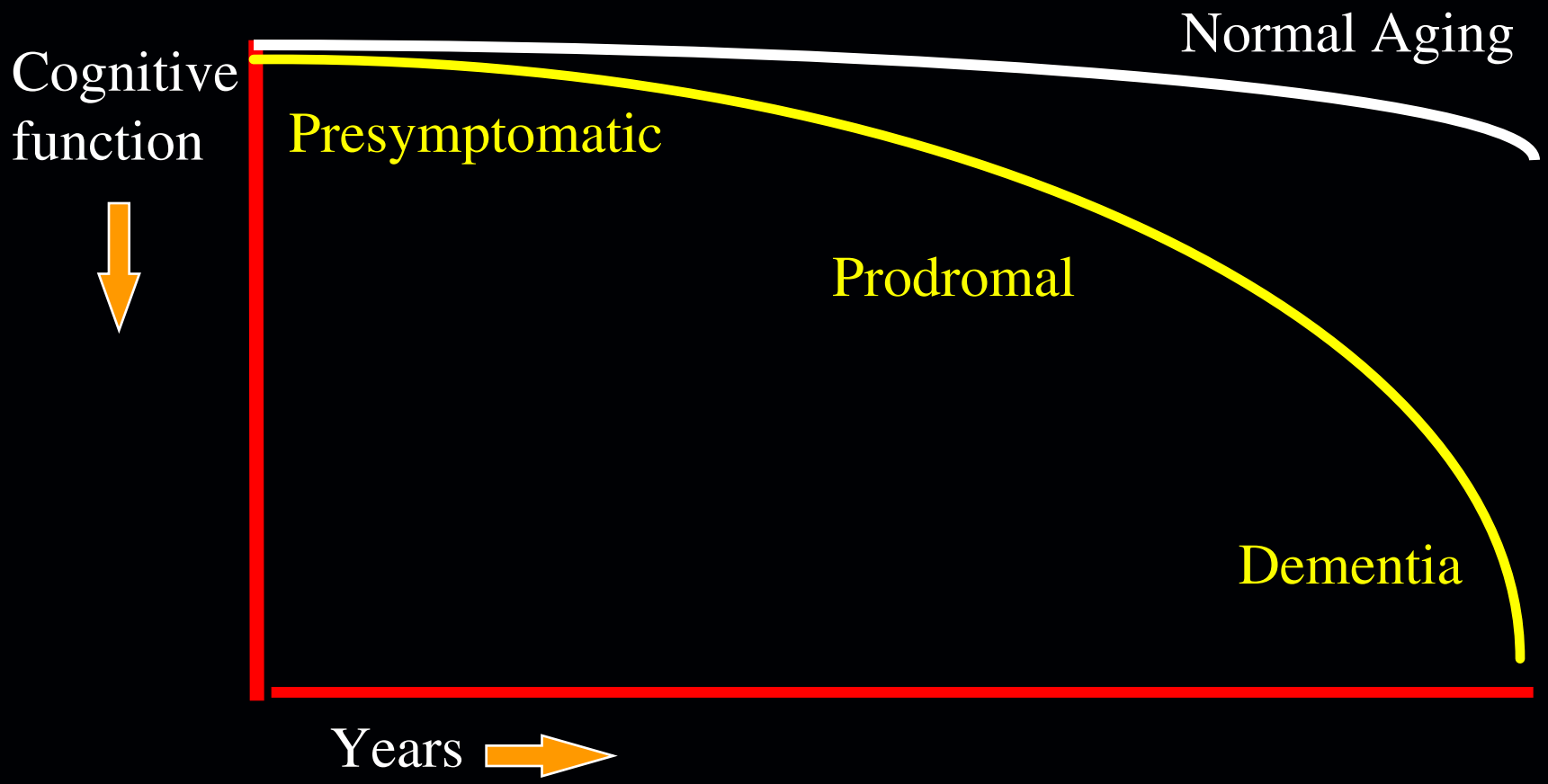
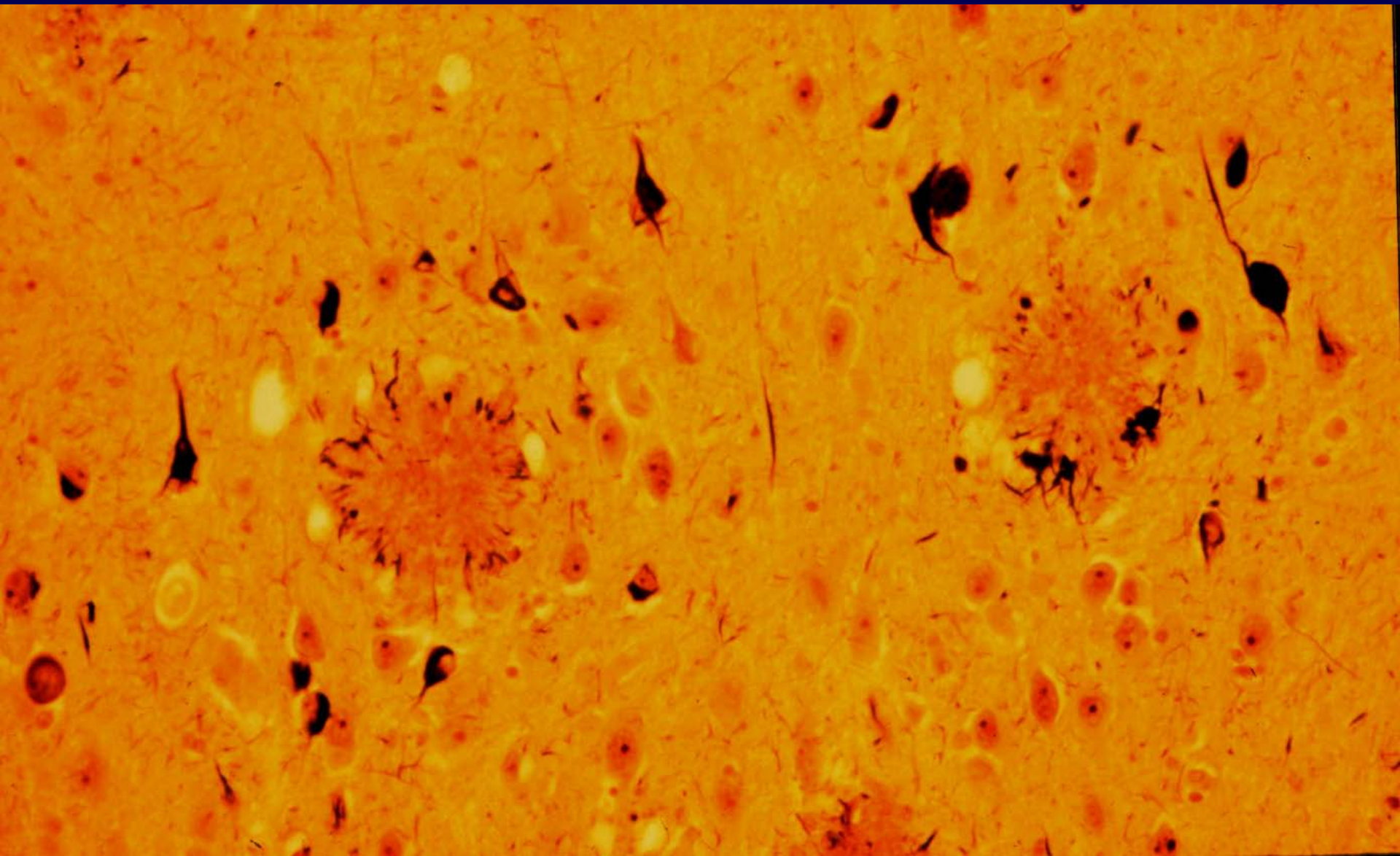
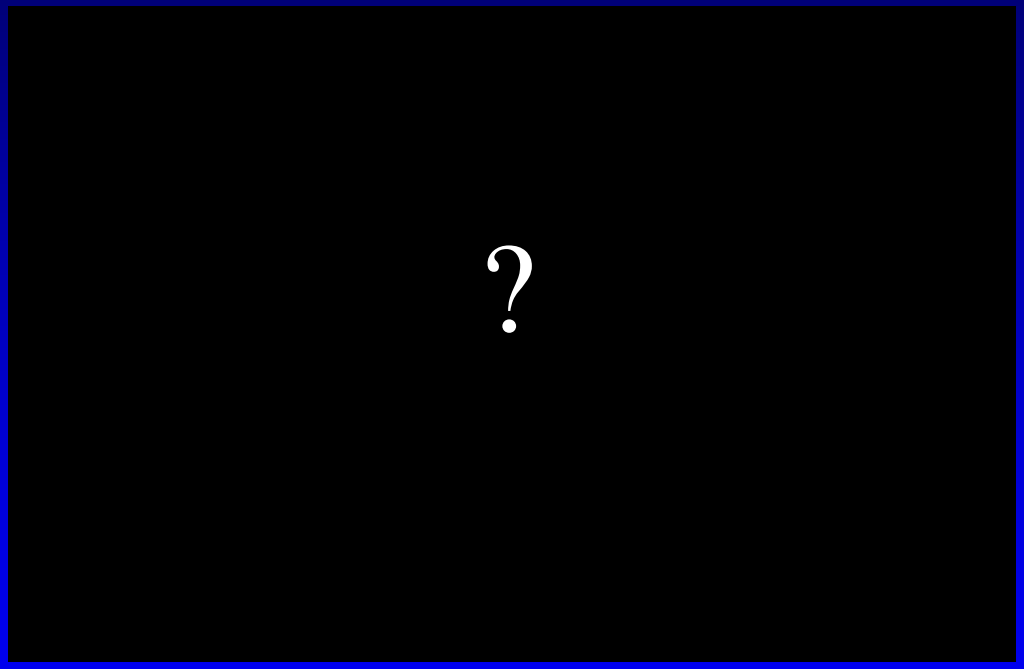
Alzheimer's Disease



Pathology of AD

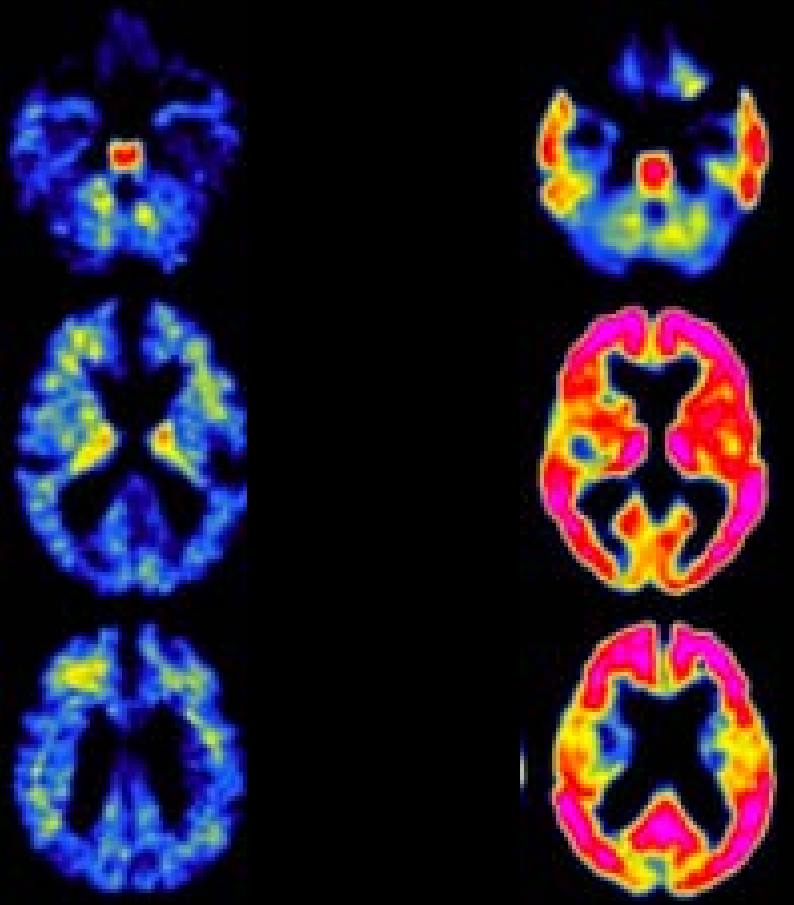


Pathophysiological Process of AD



Cognitive and Behavioral Symptoms of AD

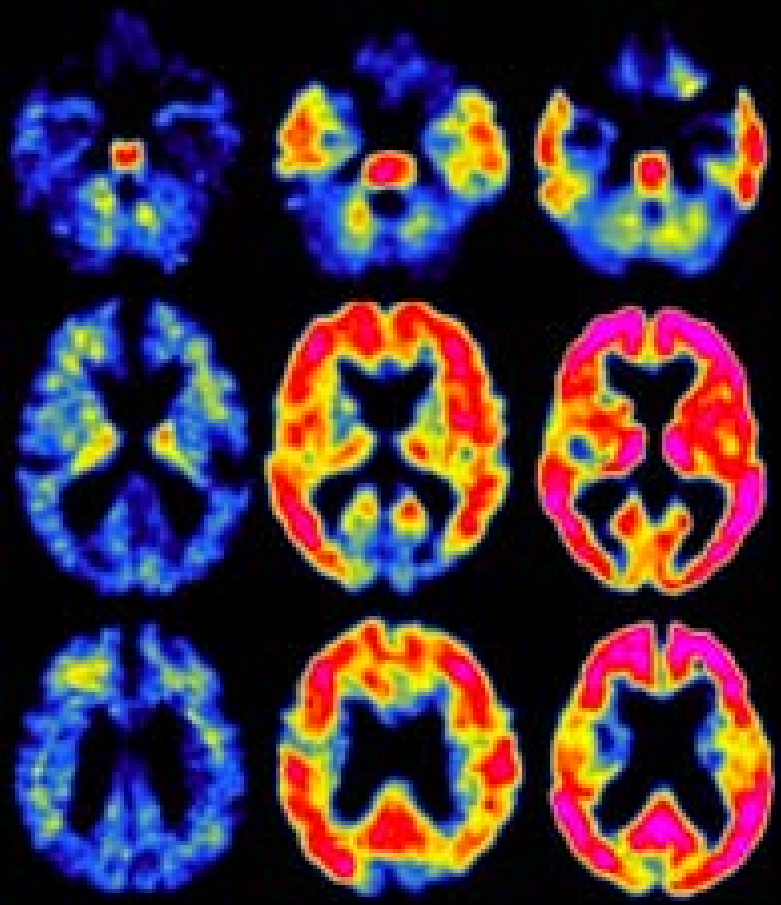
What we know…..



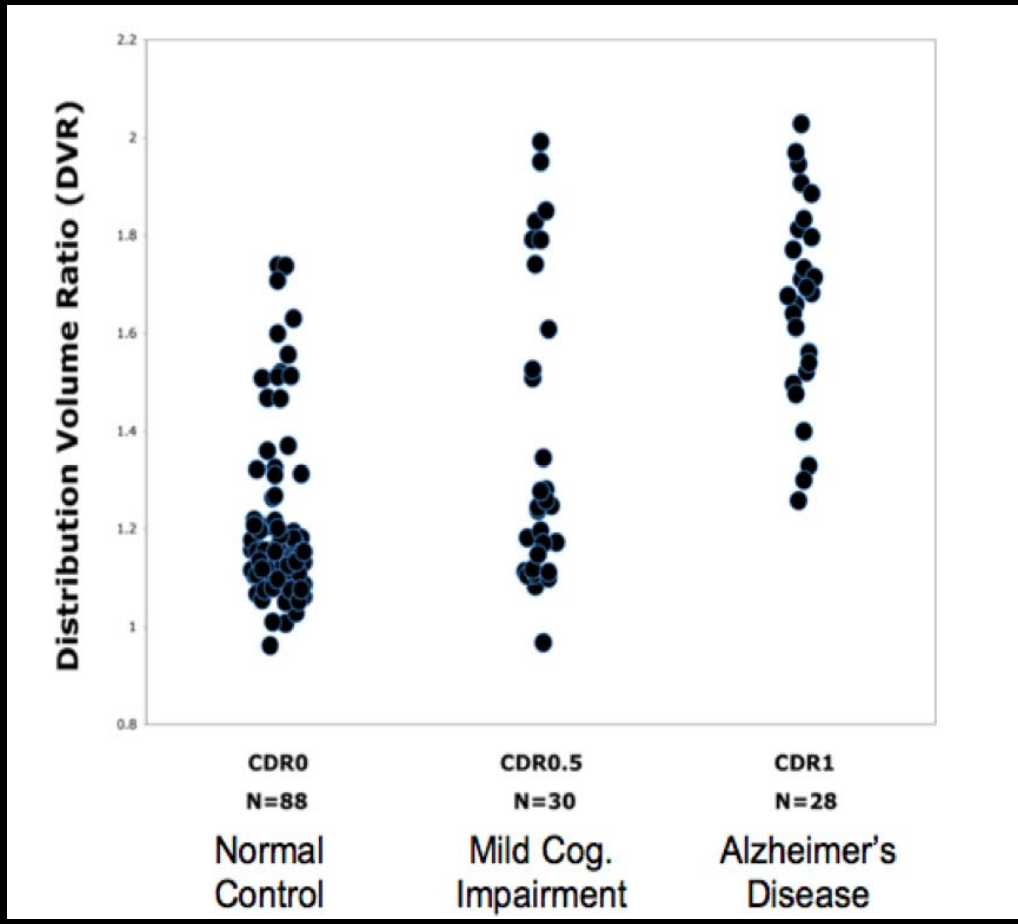
Normal

Mild AD

What we don't yet know…



NC PiB- NC PiB+ AD



Sperling R et al. *NeuroMolecular Med* 2010

Linking pathology to cognitive impairment: Connundrums

- Anatomic distributions of amyloid and tangles do not always map well onto classical brain-behavior relationships
- Amyloid plaque load does not correlate well with dementia severity, tangles somewhat better, synaptic loss correlates best
- Individuals with a “head full of amyloid” are still cognitively normal

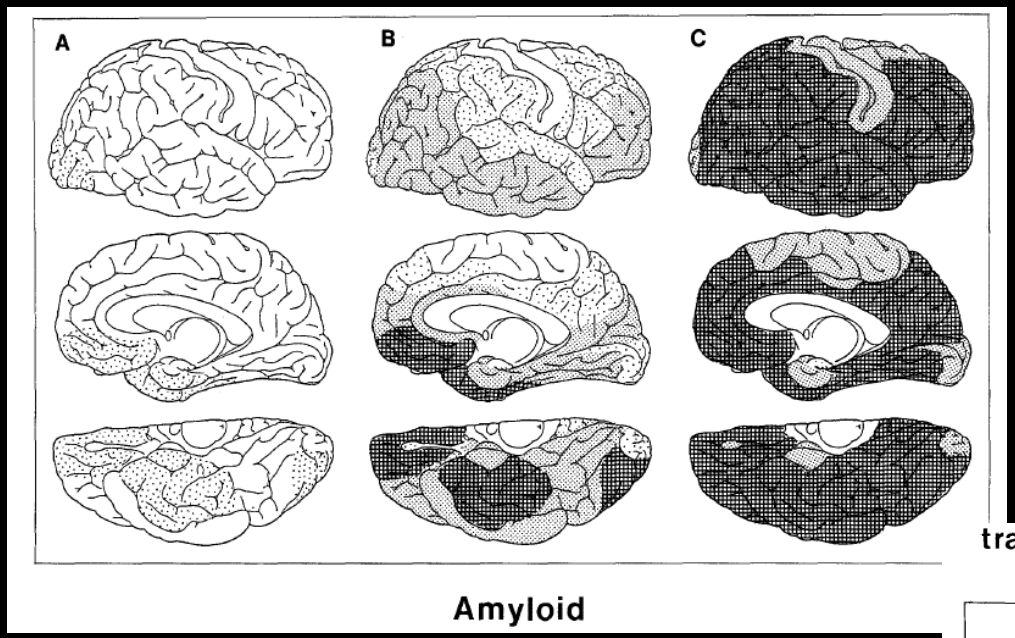
Linking pathology to cognitive impairment: SPACE-TIME CONTINUUM

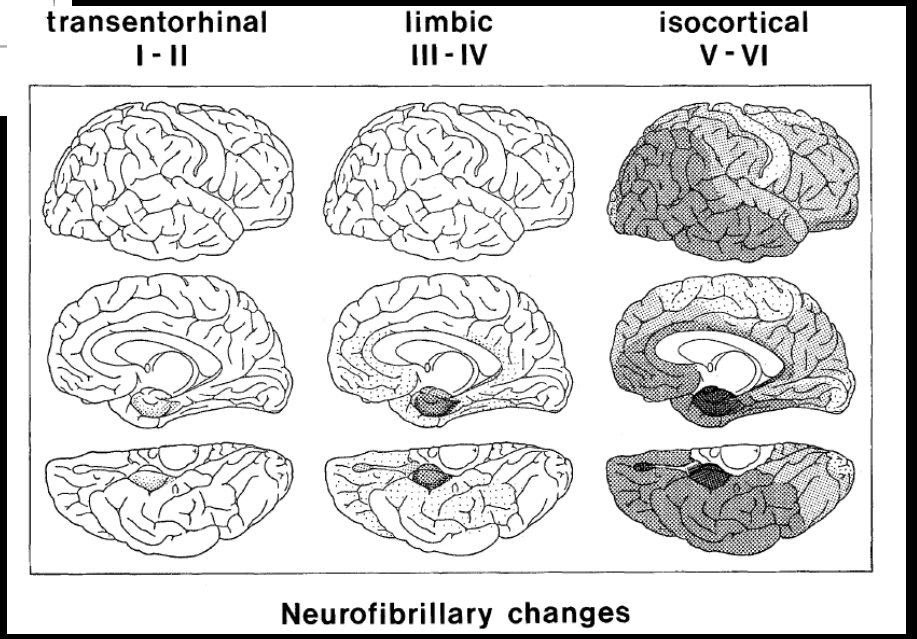
- SPACE: pathology =? domain localization
  - Networks rather than "lightbulbs" or regions
  - Oligomeric forms poorly localized
- TIME: pathology =? stage of impairment
  - Lag between development of pathology and appearance of symptoms
  - Threshold of pathological burden
- CAPACITY: brain and cognitive reserve
  - Capacity to tolerate pathology
  - Compensation

SPACE

Linking anatomic distributions of pathology to brain-behavior systems and networks

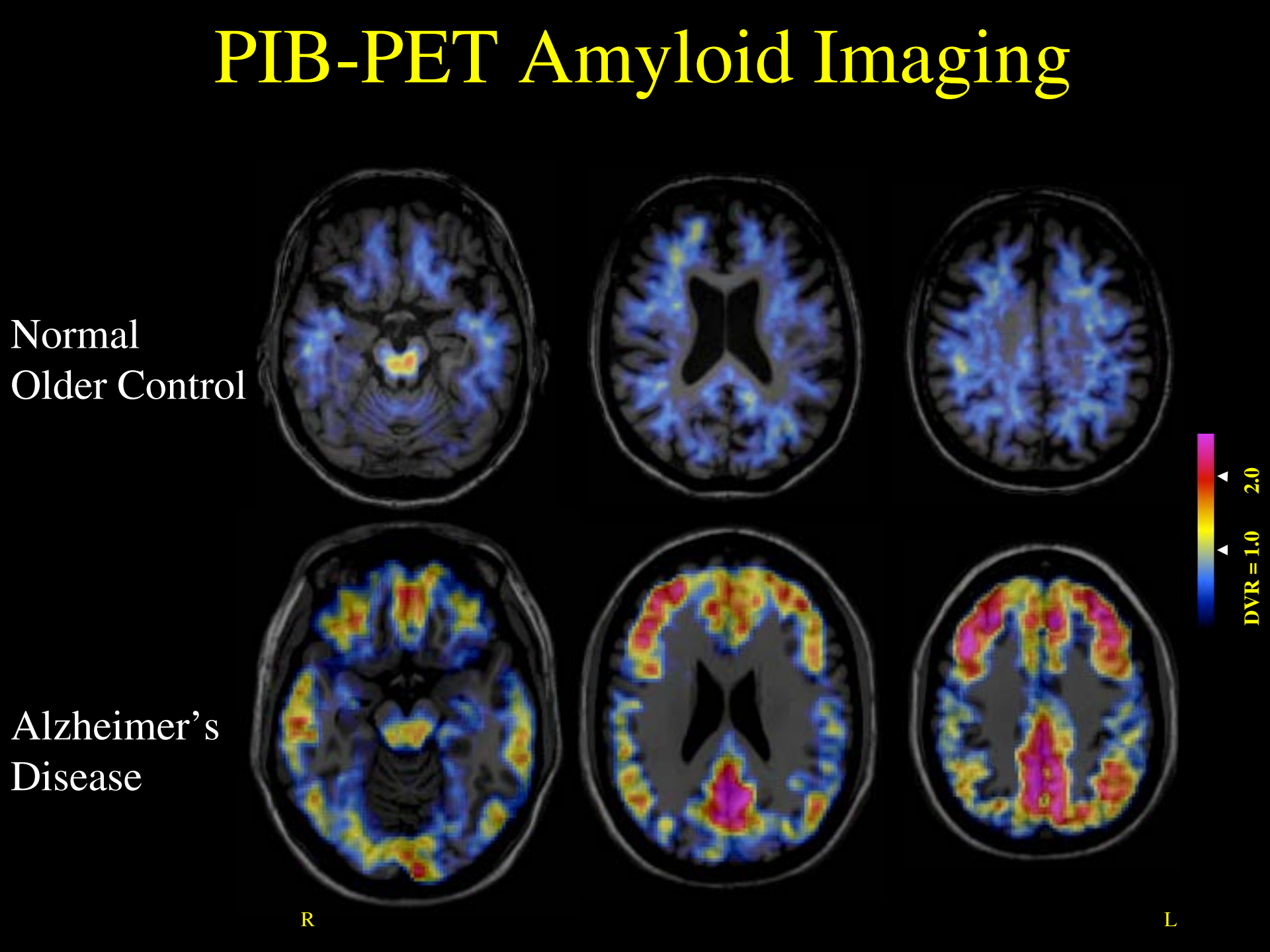
Autopsy Series: Amyloid and Neurofibrillary Tangles





Braak and Braak *Acta Neuropath* 1991

PIB-PET Amyloid Imaging



Hippocampal Atrophy

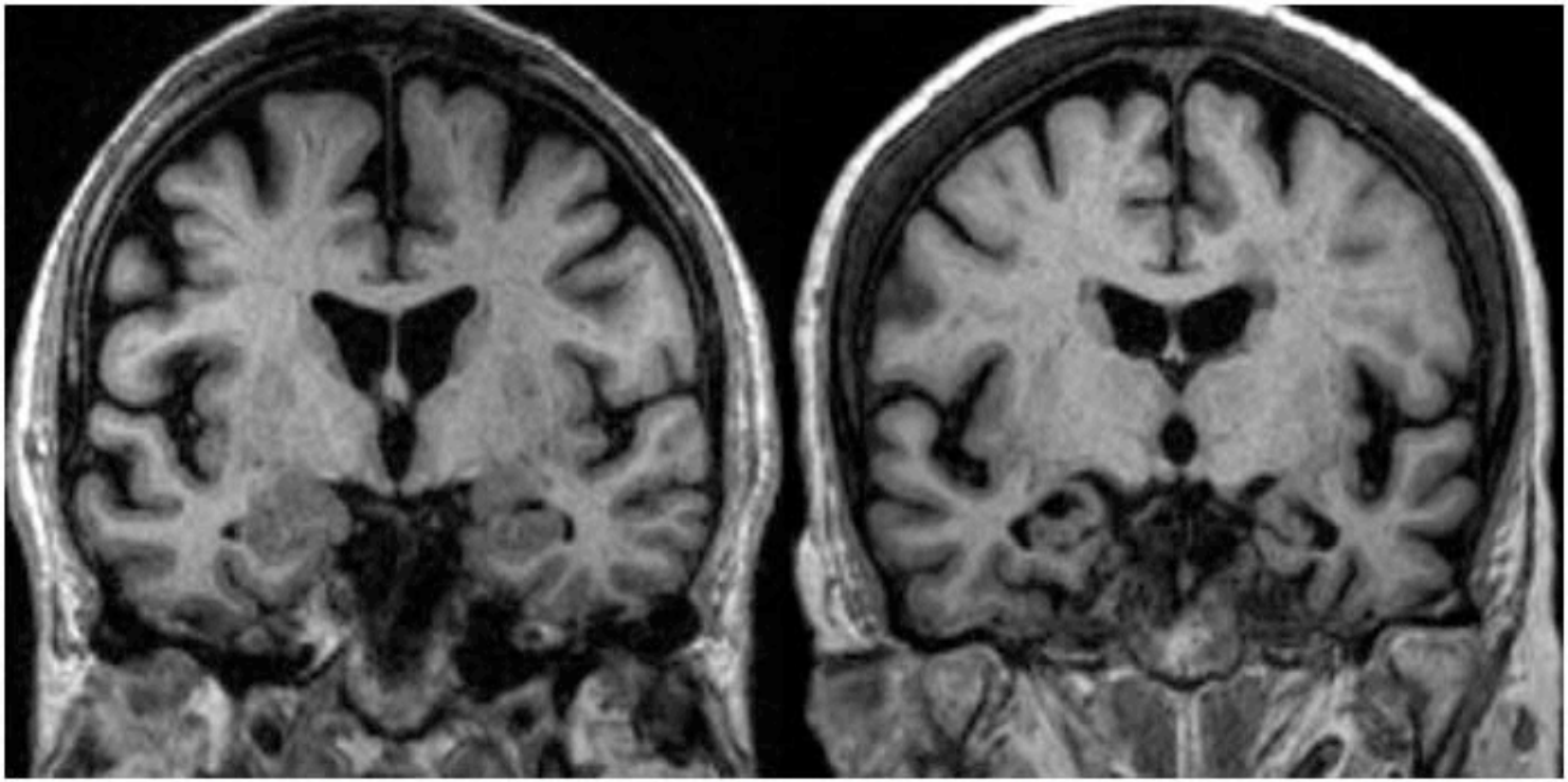
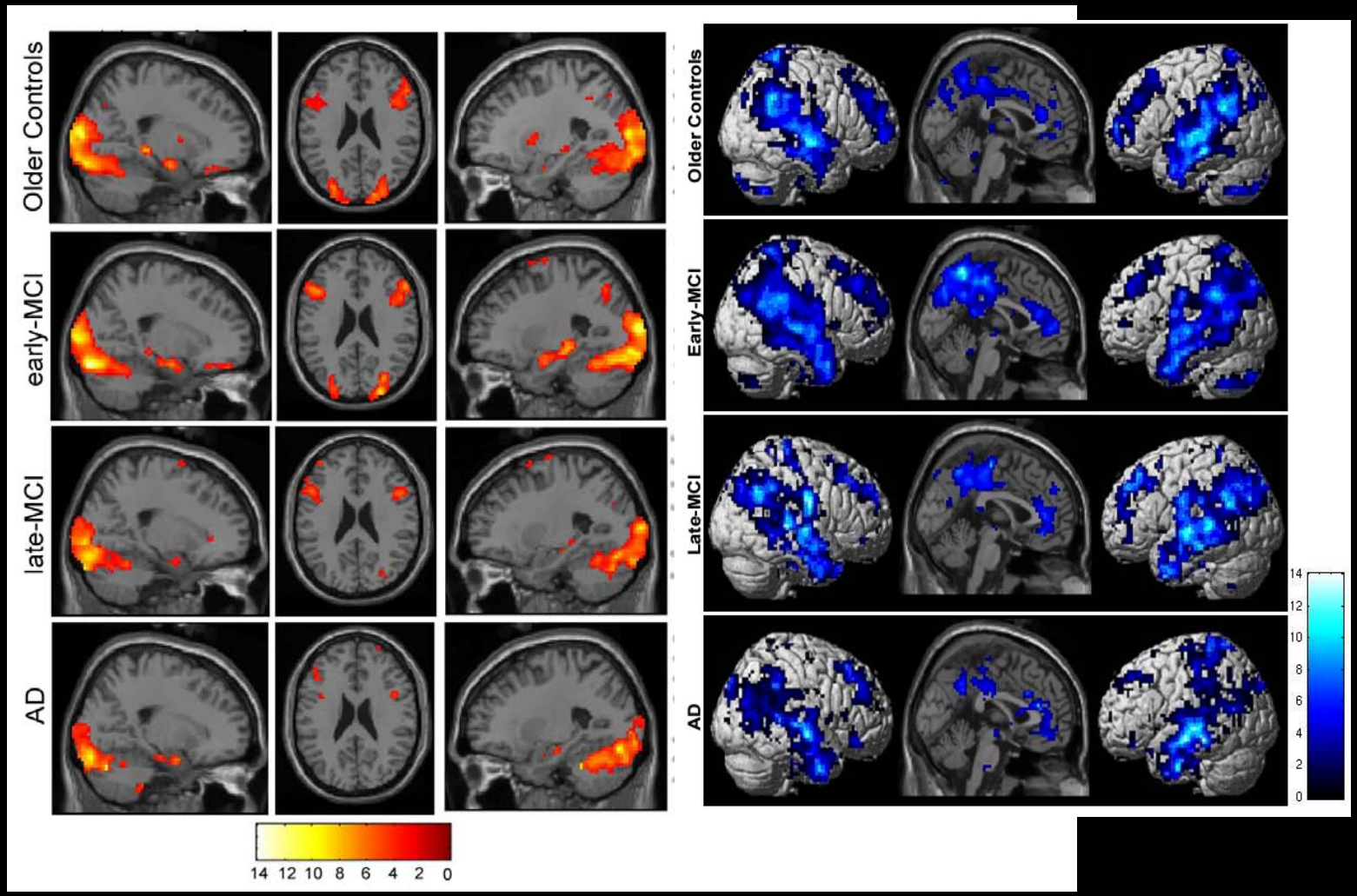


Figure 2. Coronal T1-weighted MRI scans of control (left) and patient with AD (right). Both subjects are 75 years old. The patient with AD shows clear atrophy of the hippocampus.

Scheltens, P. Imaging in AD. Dialogues in Clinical Neuroscience (2009)

Memory Networks in Aging, MCI and AD

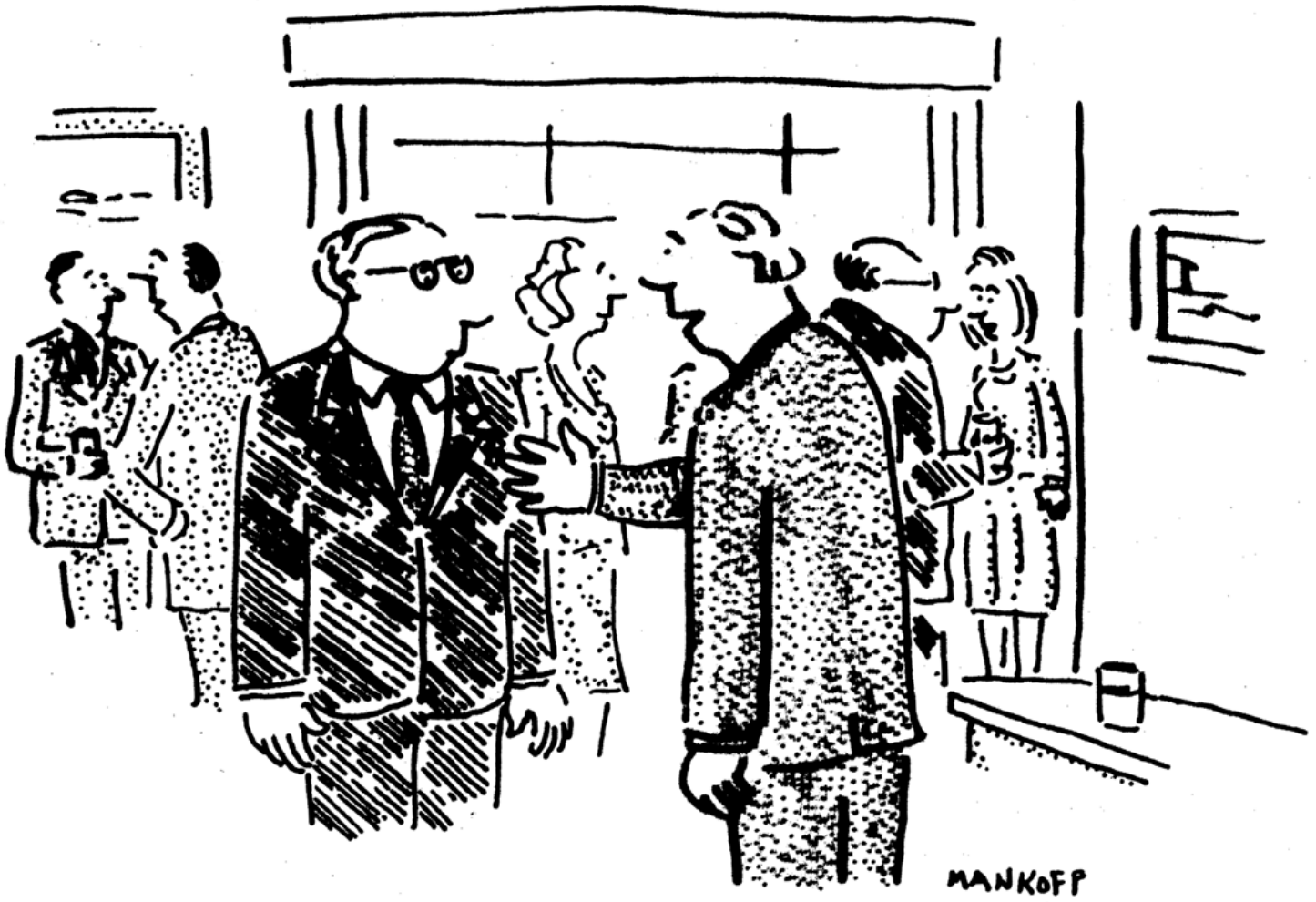


Celone K et al. *J Neuroscience* 2006

Face-Name Association

- Remembering proper names is the most common memory complaint of older individuals.
- Difficult paired associative memory task
  - Faces and names inherently unrelated
  - Requires the formation of a novel association across visual and verbal domains
- Likely requires the coordination of multiple brain regions, in particular the hippocampal formation

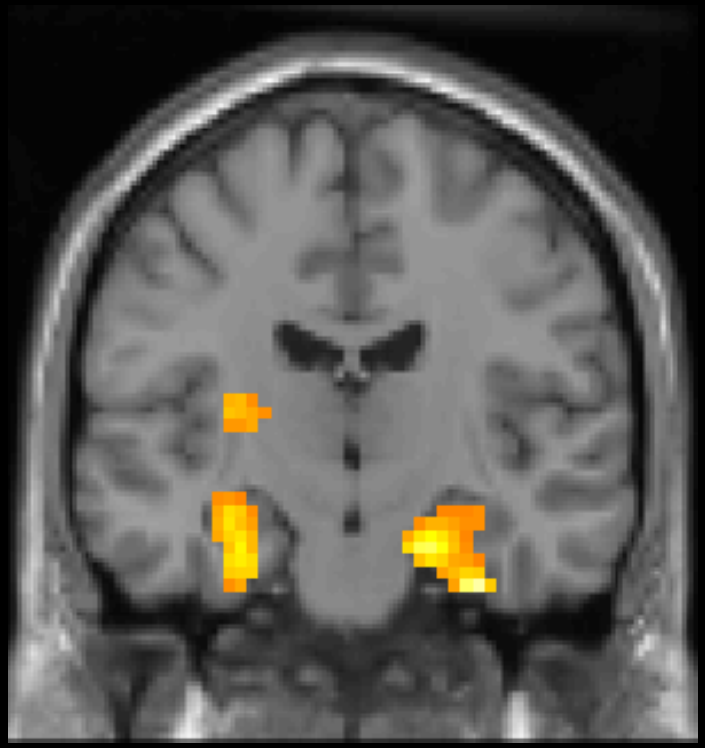
Lenny

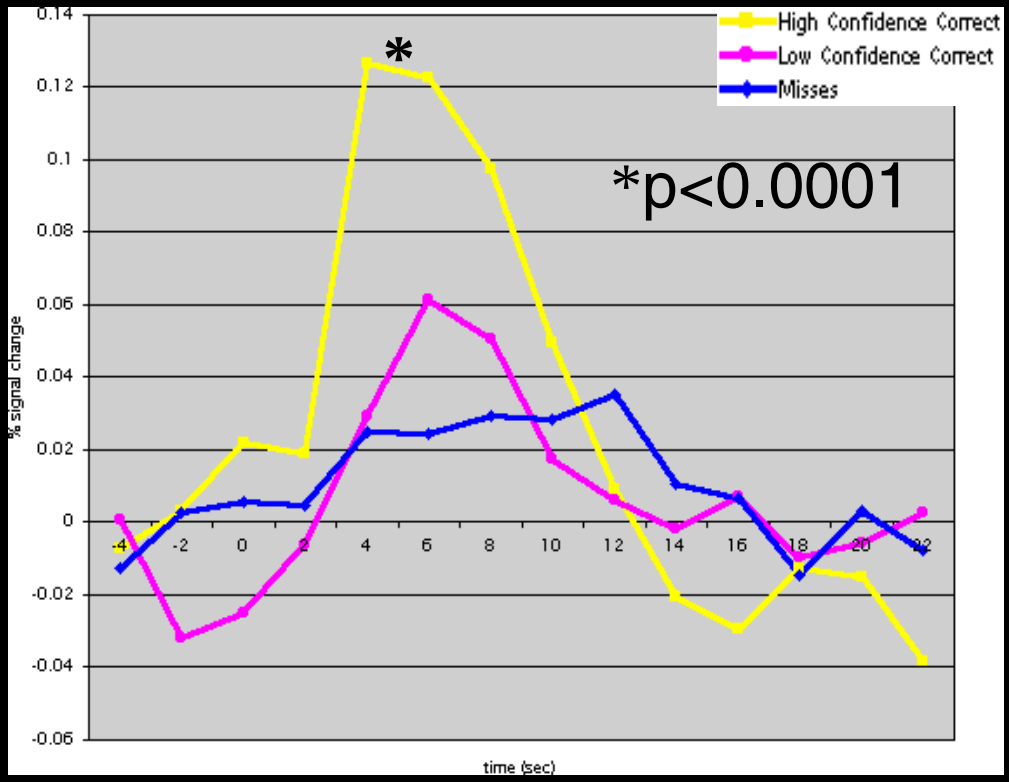


*"Hi. I'm, I'm, I'm . . . **You'll have to** forgive me, I'm terrible **with names.**"*

Event-Related fMRI - Subsequent Memory

"Correctly Remembered vs. Forgotten" Face-Name pairs



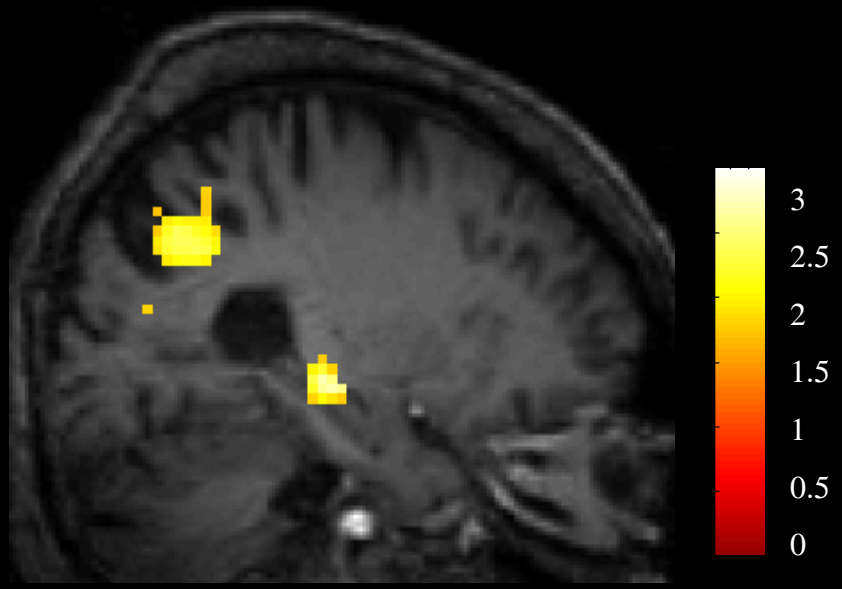


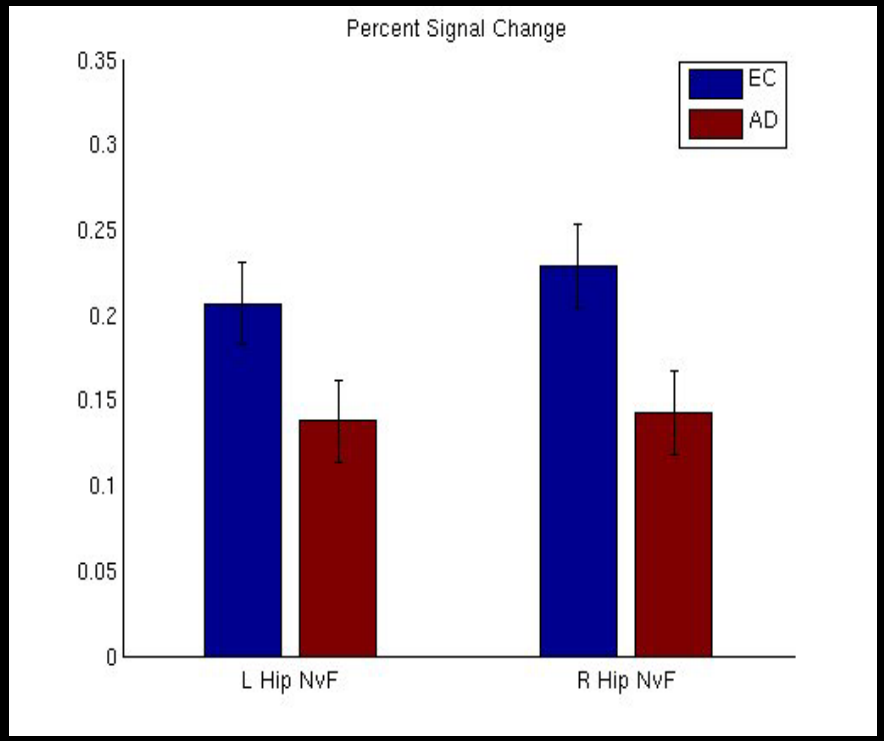
Young Subjects (n=16)

MR Signal: Right Anterior Hippocampus (27, -15, -15)

Sperling et al. *NeuroImage* 2003

Decreased Hippocampal Activation in AD compared to Normal Aging





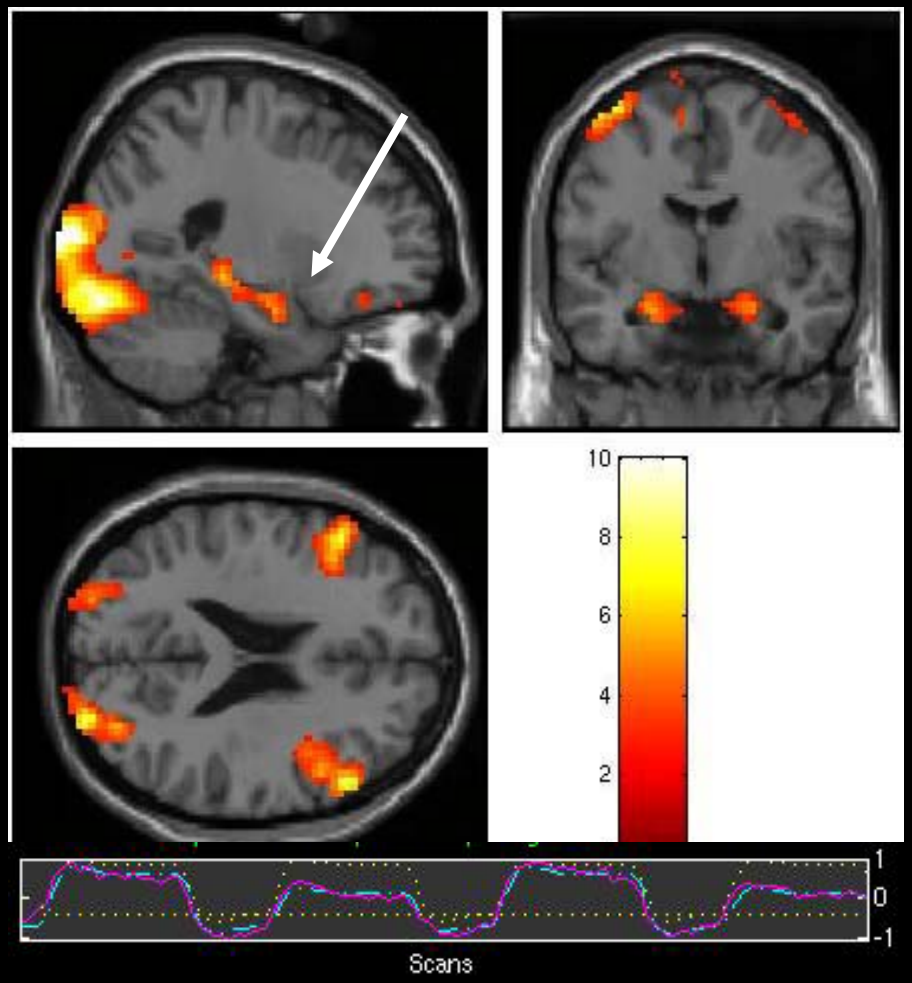
Mild AD patients < Normal Older Controls

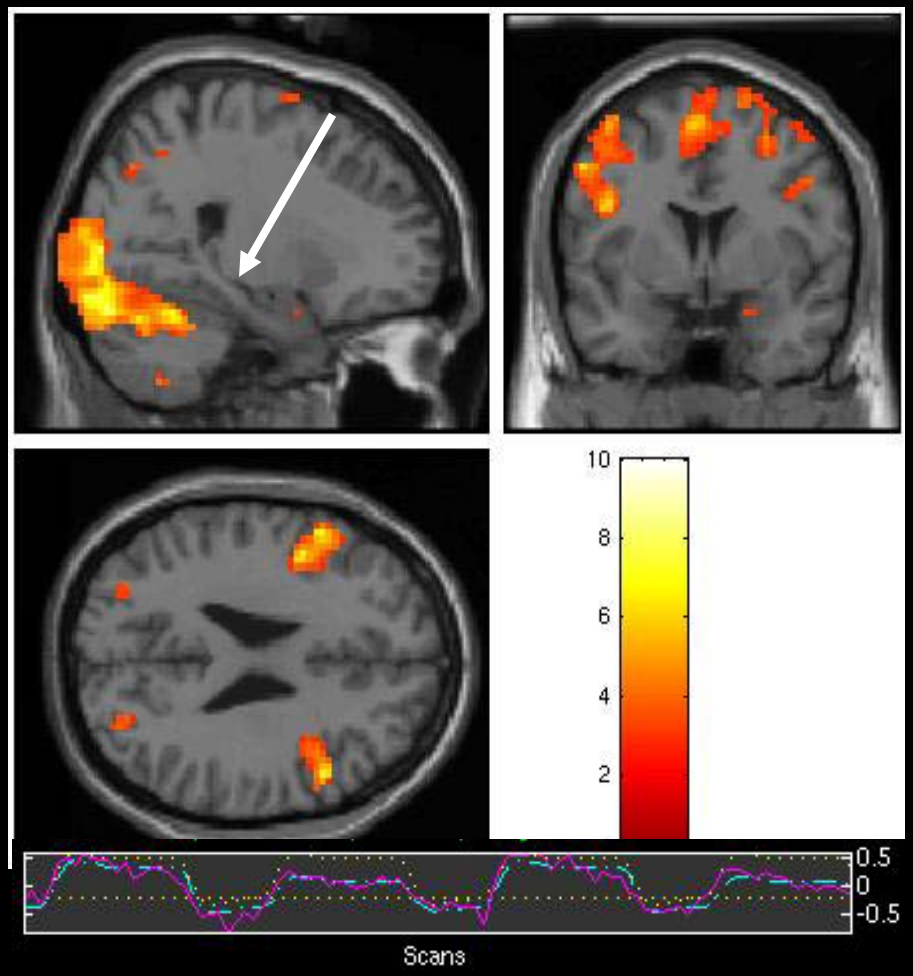
Sperling R et al *JNNP* 2003

Hippocampal function fails during MCI

Early MCI
CDR-SB 0.5-1.5

Late MCI
CDR-SB 2.0-3.5



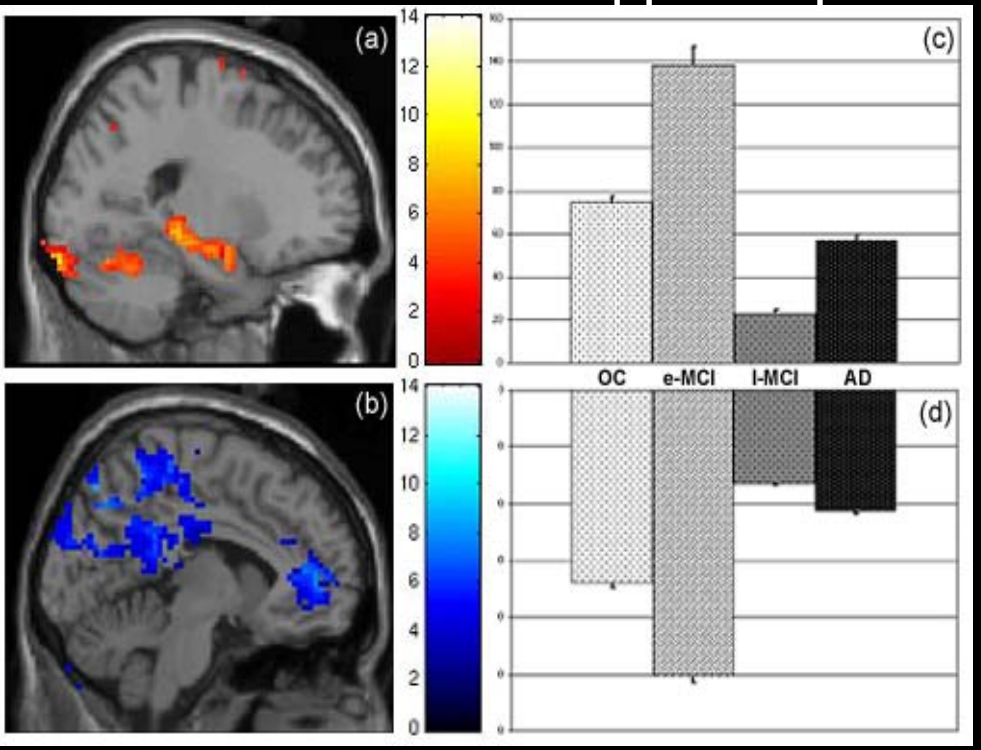


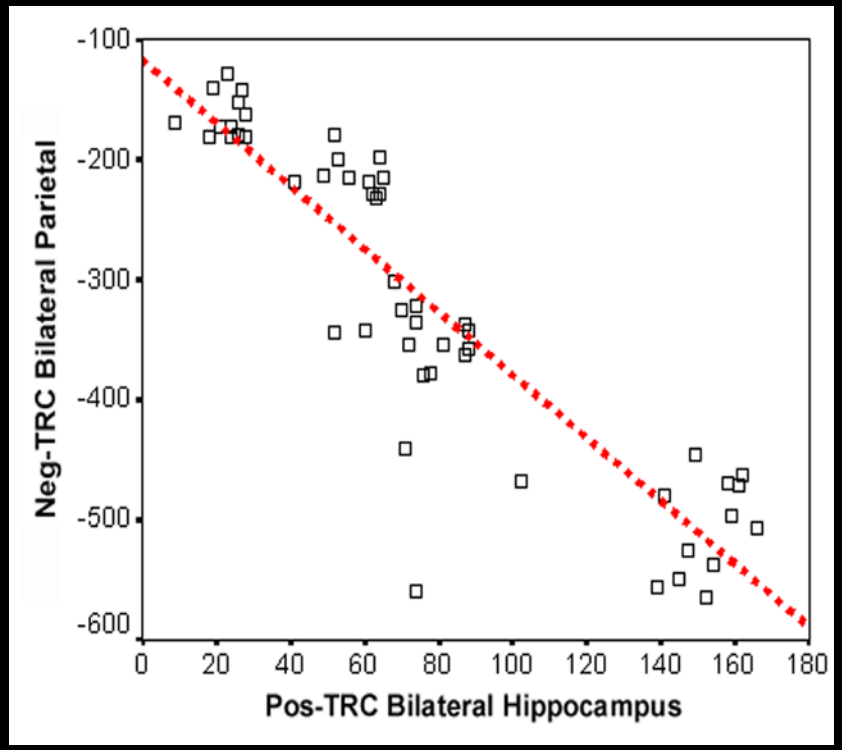
Celone K et al. *J. Neuroscience* 2006

Reciprocal relationship between hippocampal activation and parietal deactivation

Pos-TRC

Hippocampal ROI



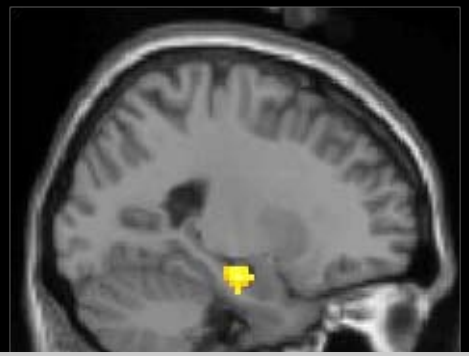


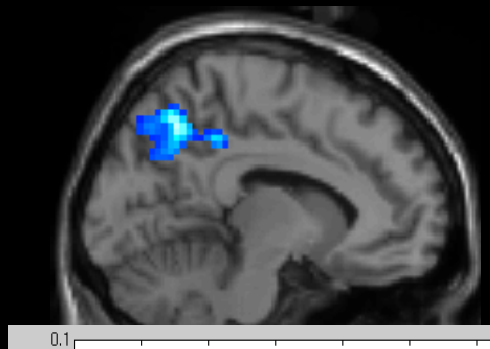
Neg-TRC

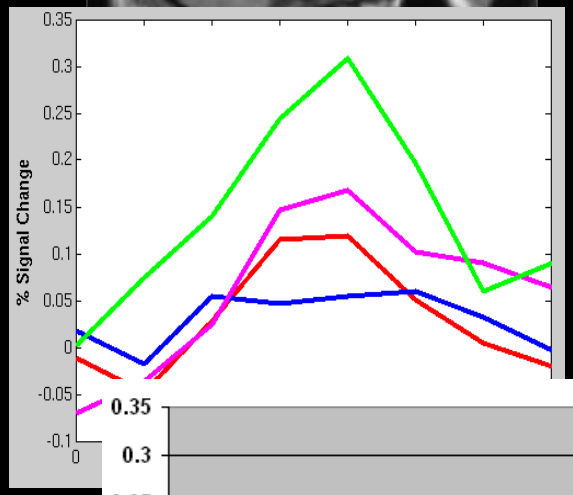
Parietal ROI

Celone K et al. *J Neuroscience* 2006

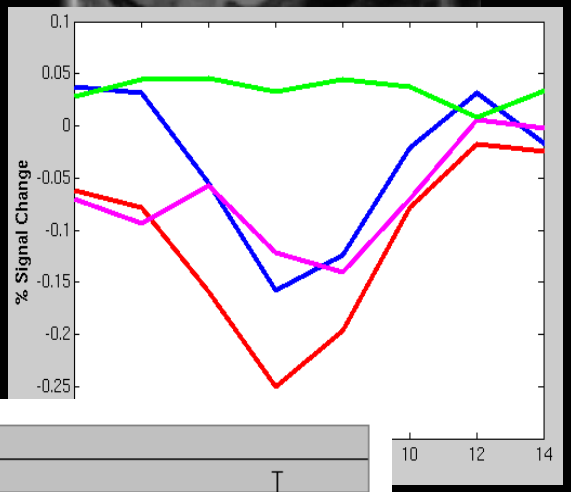
Hippocampal and Precuneus/Post Cingulate fMRI during Successful Memory Formation

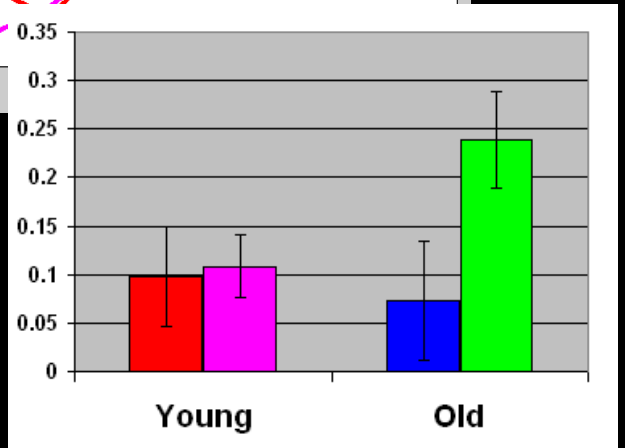




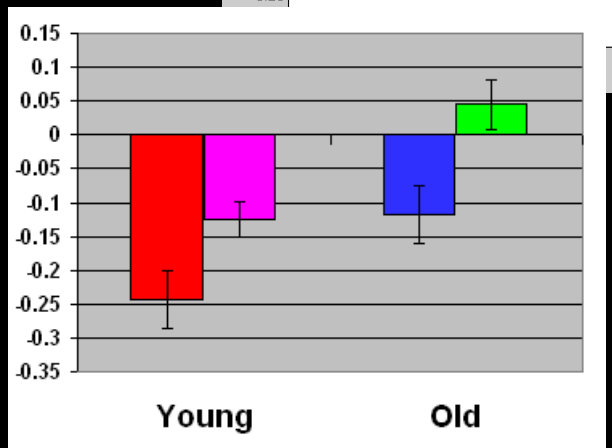


High Performing Young
High Performing Old
Low Performing Young
Low Performing Old

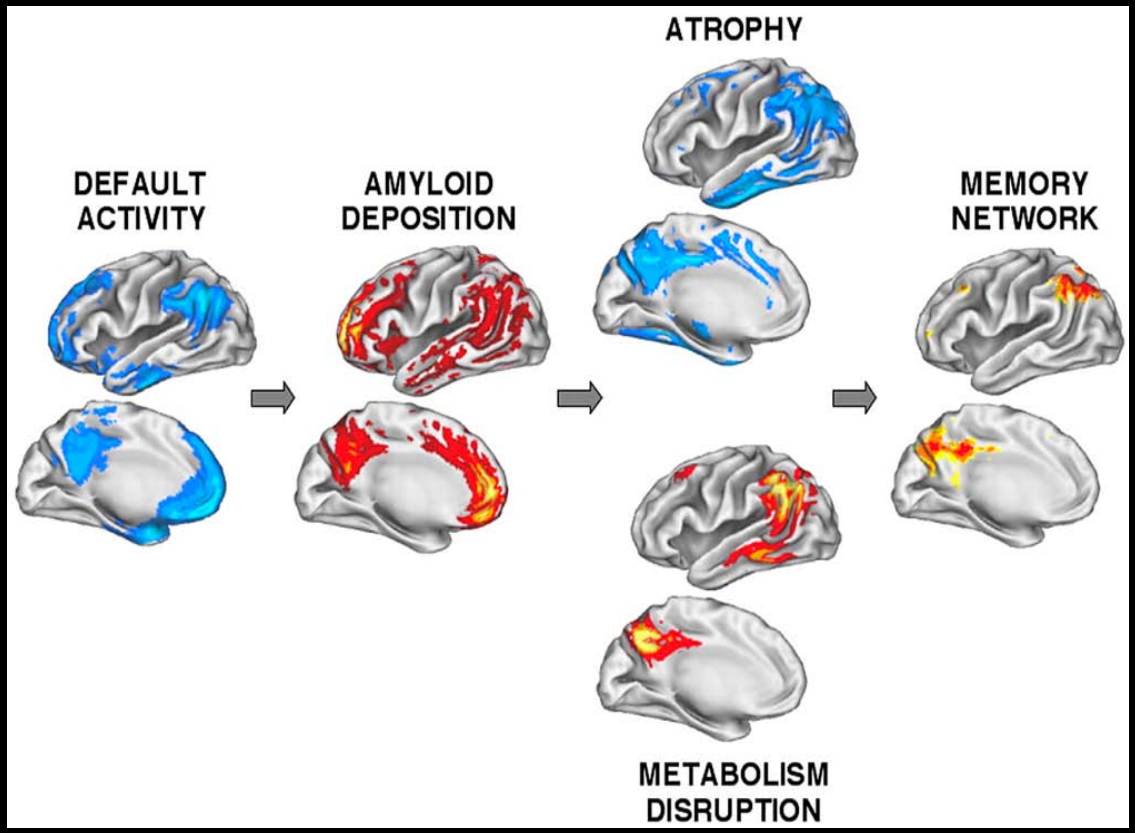




Miller S
PNAS
2008

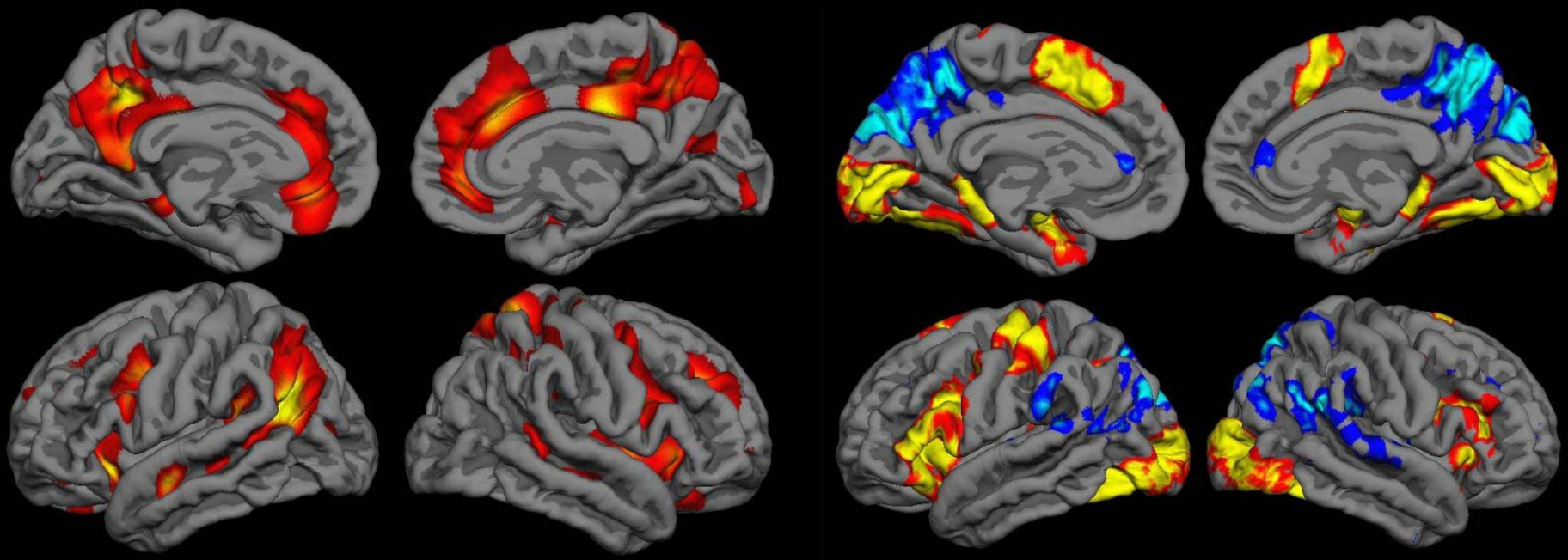


Relationship of amyloid deposition to the "default network" in AD



Buckner R et al. *J Neurosci 2005*

Anatomic overlap of amyloid deposition with default network during memory formation

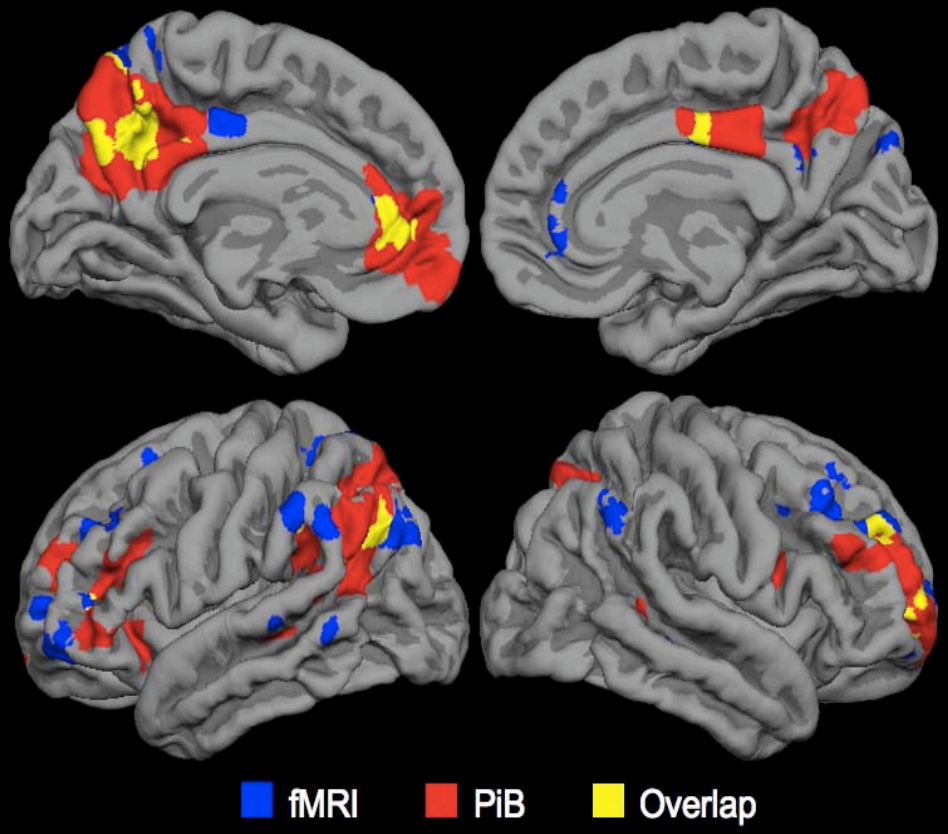


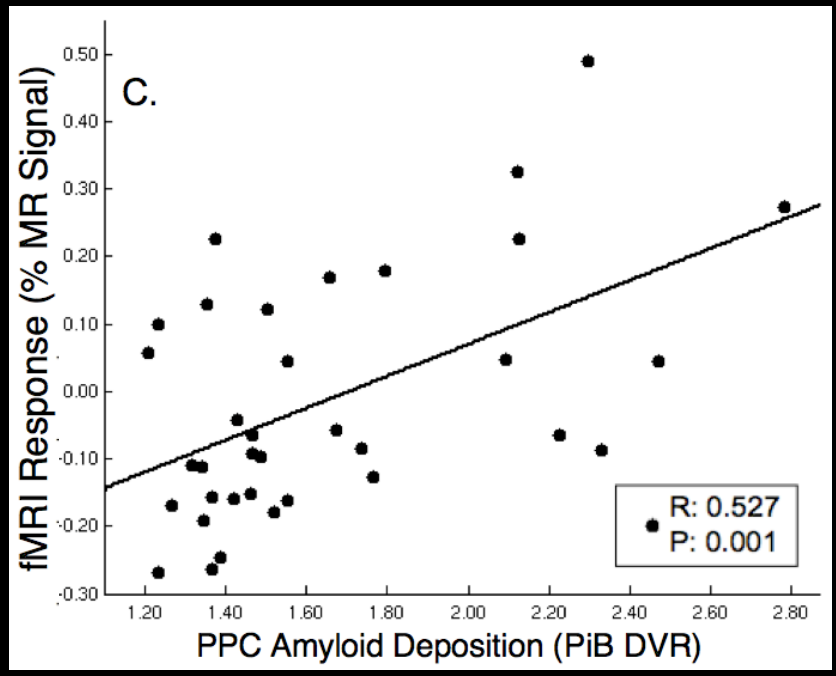
PIB retention

fMRI Activity

Sperling R et al *Neuron* 2009

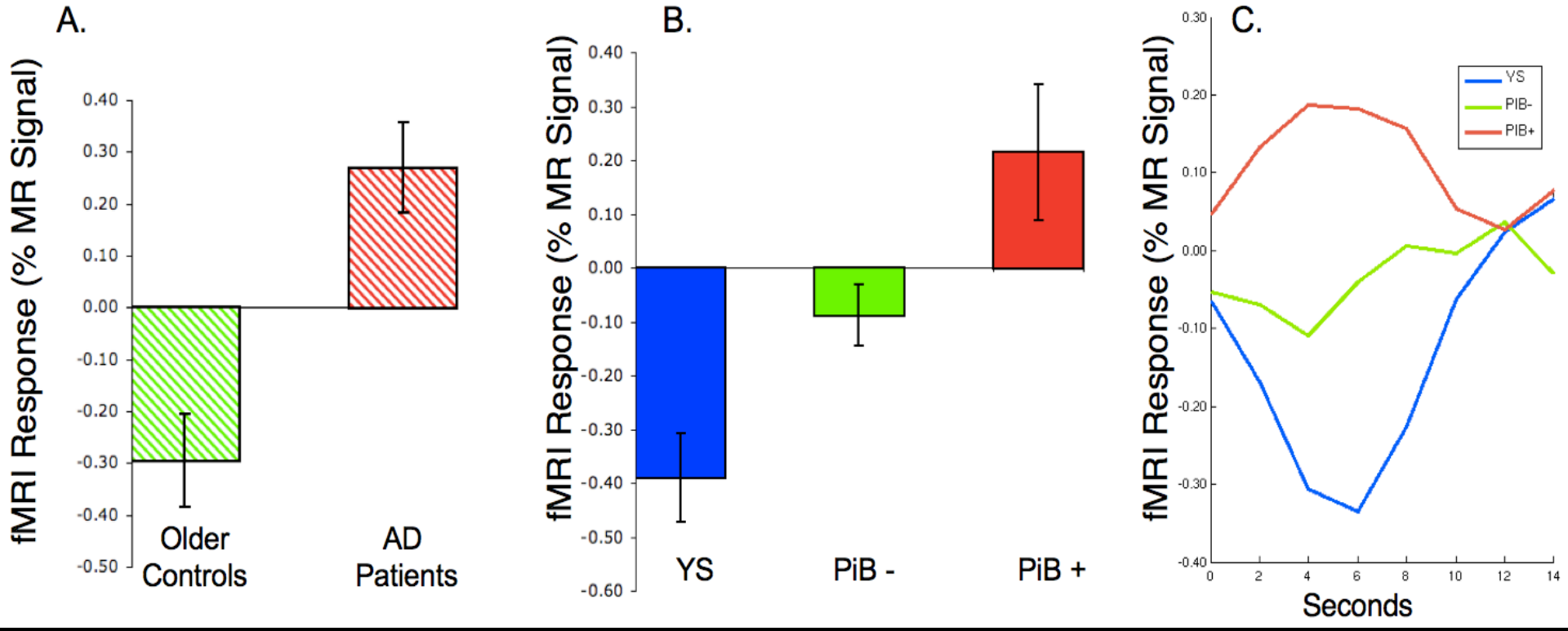
Relationship of amyloid deposition to default network activity





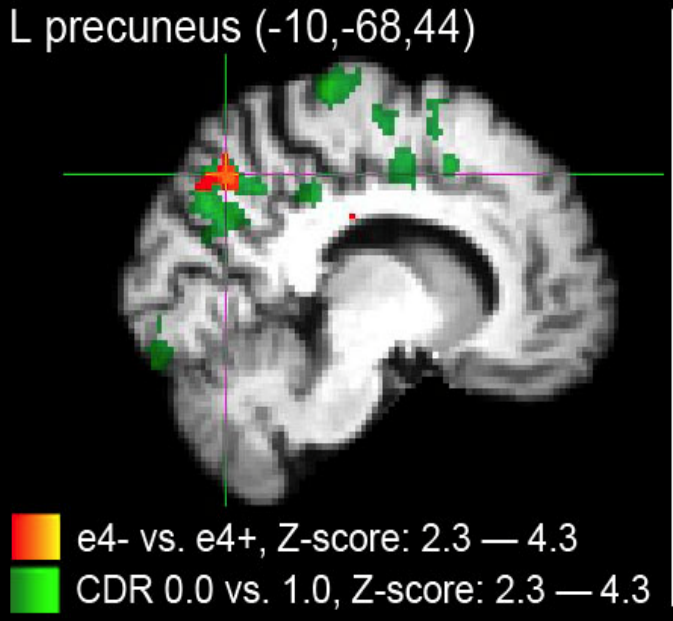
Sperling et al *Neuron 2009*

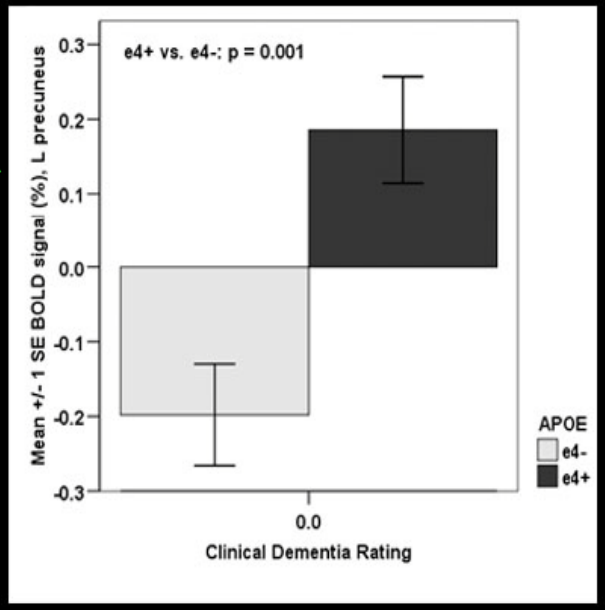
Relationship of amyloid deposition to default network failure

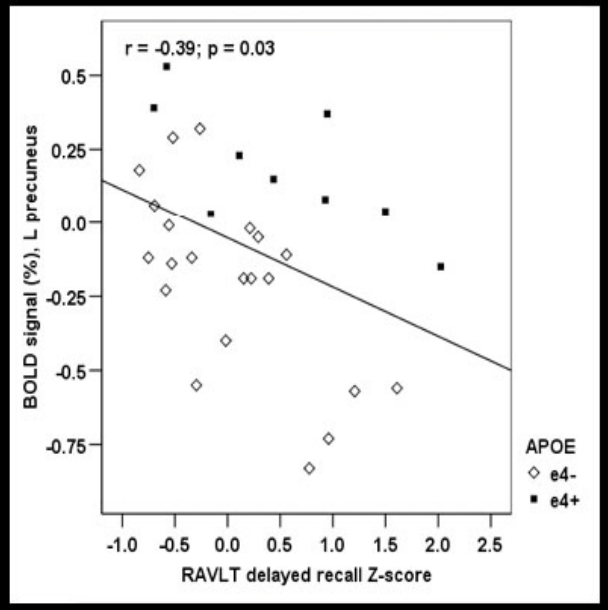


Sperling R et al *Neuron 2009*

Failure of Default Network in Cognitively Normal Older ApoE ε4 carriers





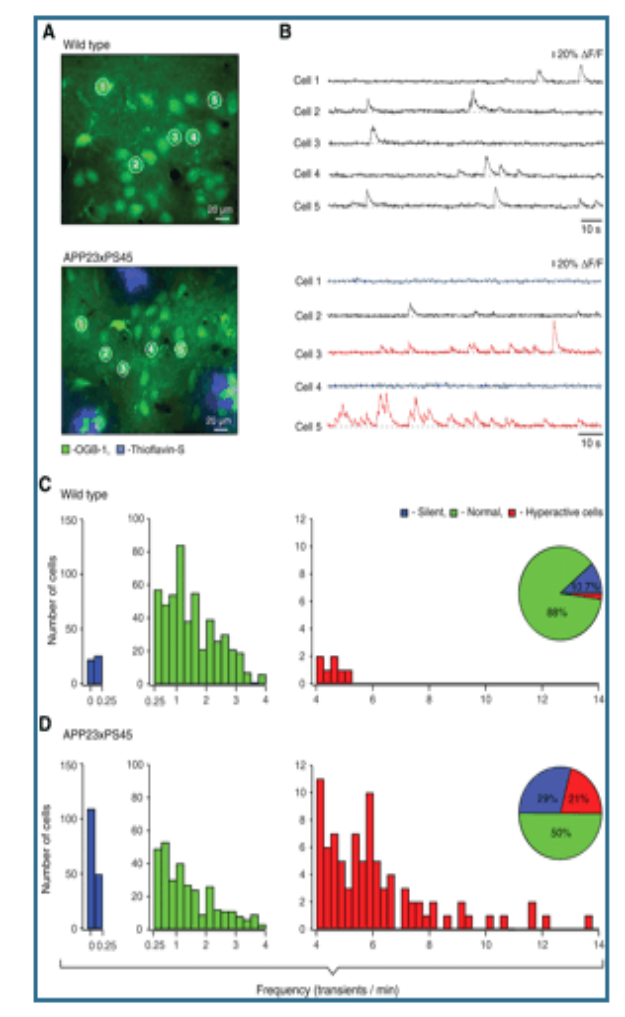


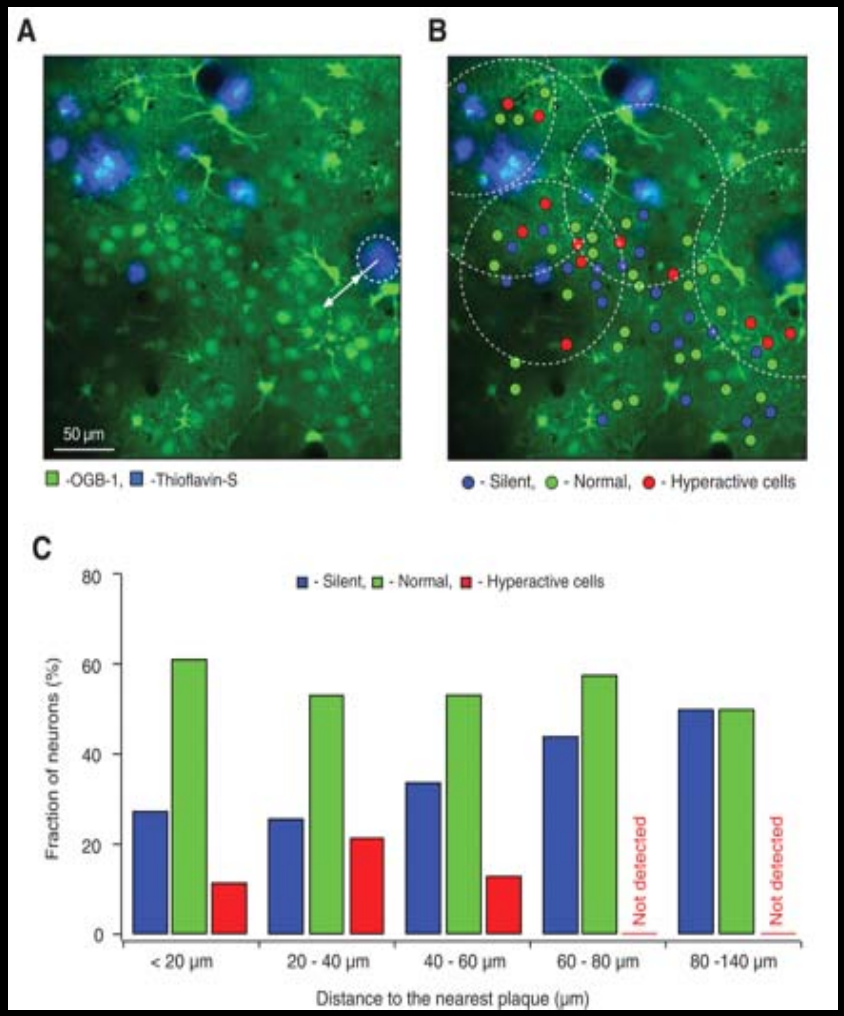
Pihlajamaki M *et al* *ADAD* 2010

Potential mechanisms underlying increased activity

- Cholinergic (ChAT) upregulation in MCI
  - DeKosky *Annals Neurology* 2002
- Aberrant cholinergic or noradrenergic sprouting
  - Hashimoto and Masliah *Neurochem Res* 2003
  - Szot *J Neuroscience* 2006
- De-synchronization of neuronal firing
  - Stern *J Neuroscience* 2004
- Lower baseline metabolism or perfusion
  - Mosconi *Neurology* 2005
- Compensatory neuronal recruitment
  - Sperling *Ann NY Acad Sci* 2007
- Excitotoxicity – harbinger of neural system failure

Hyperactive neurons near amyloid plaques



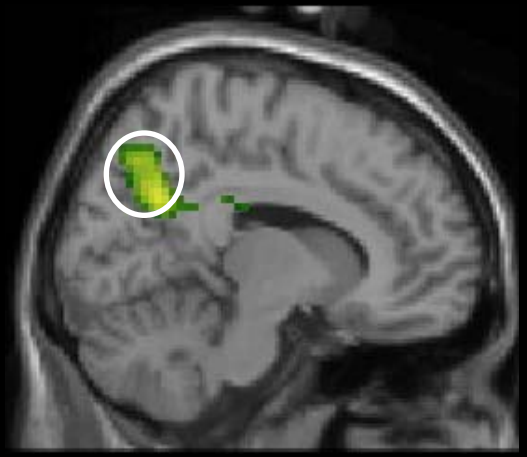


Busche *et al. Science* 2008

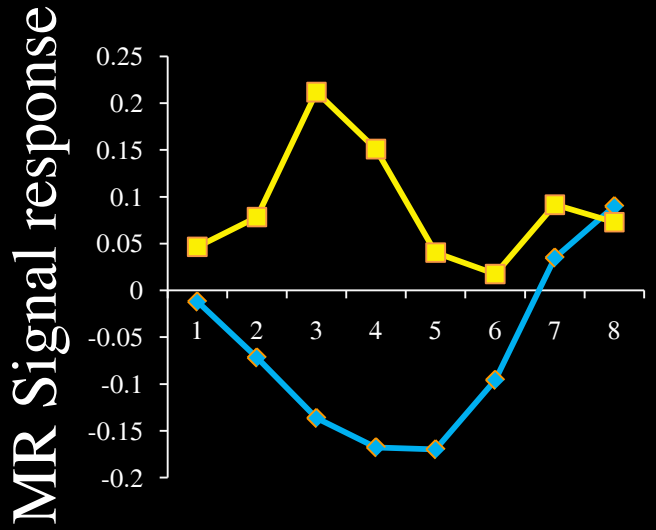
Name ?

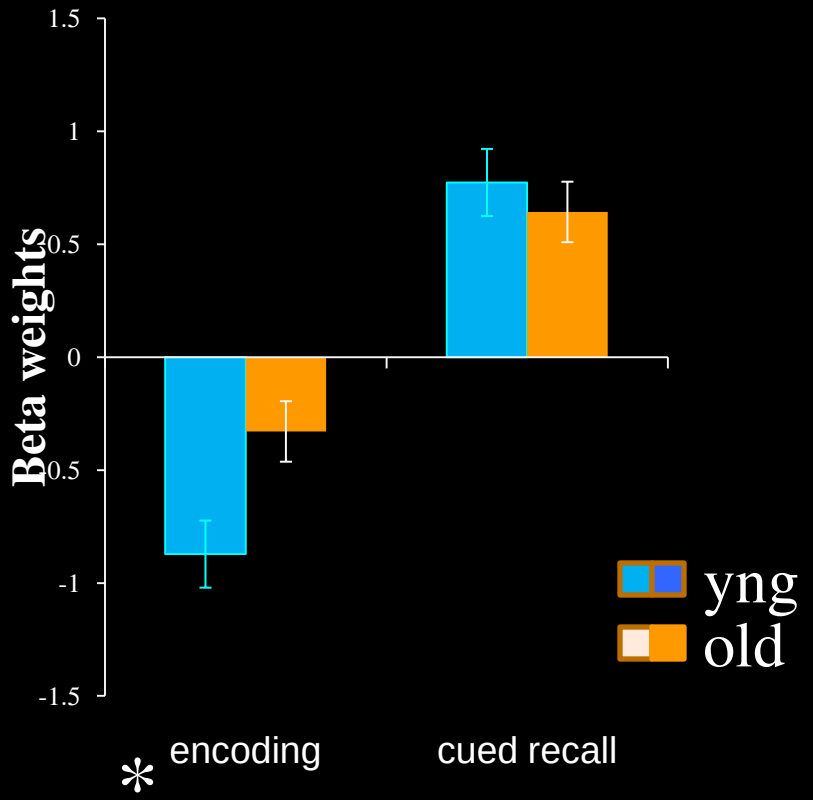
What goes down must come up…

Encoding vs. Retrieval



P<.001,
extent = 5voxels

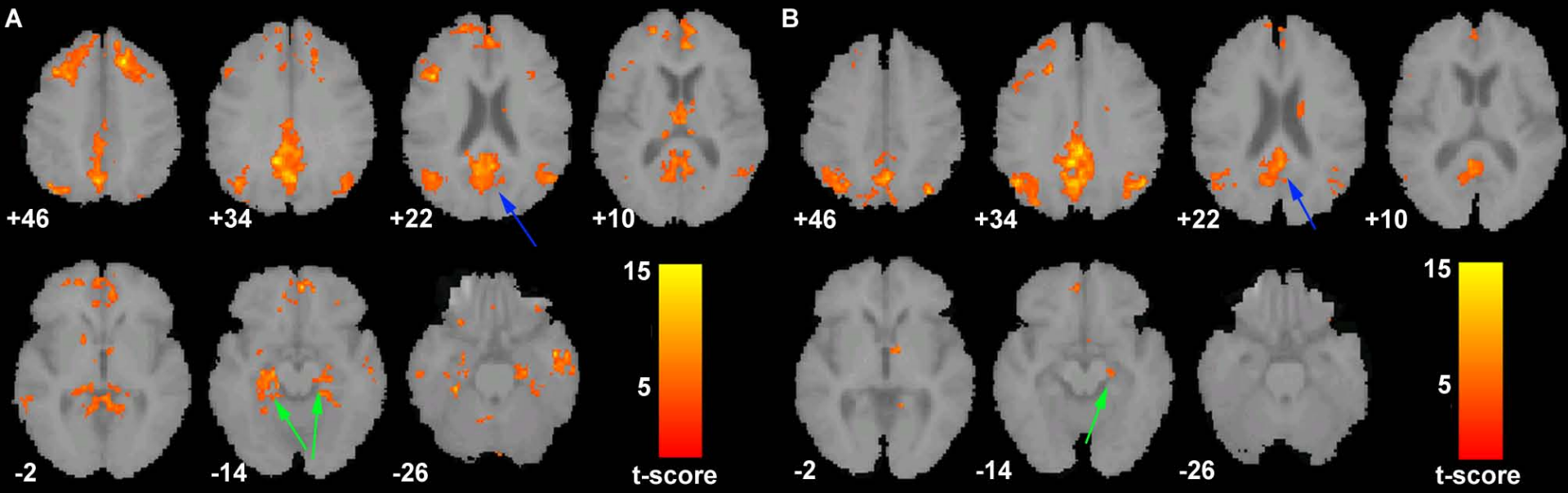




* F(1,38) = 5.19, p=.028

Vannini P *et al Cerebral Cortex* (In Press)

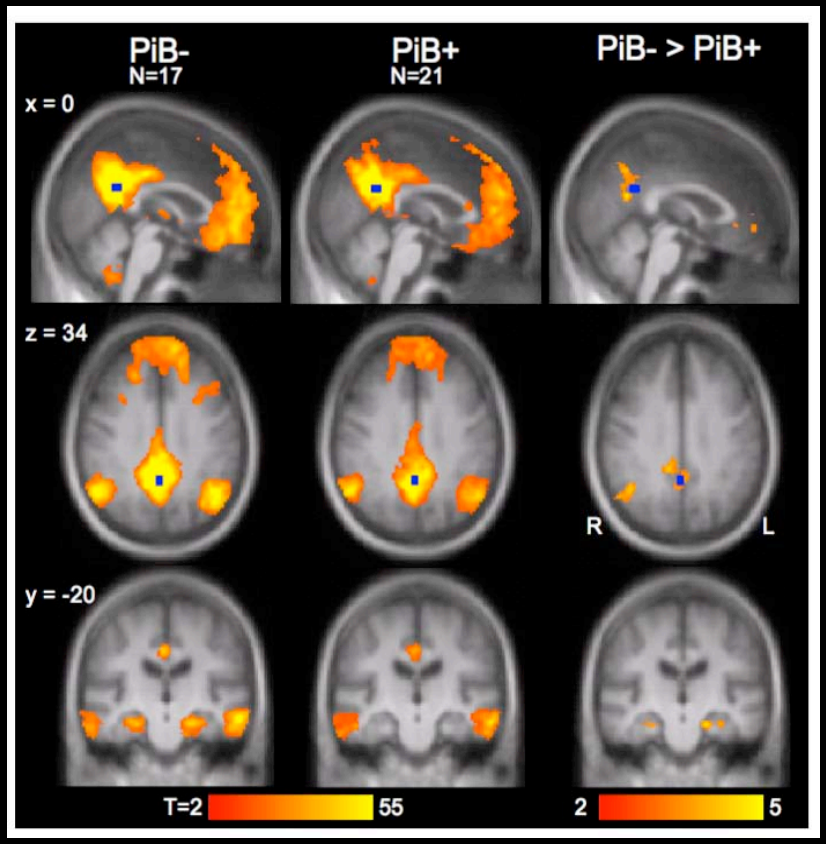
Default-Mode Network in AD

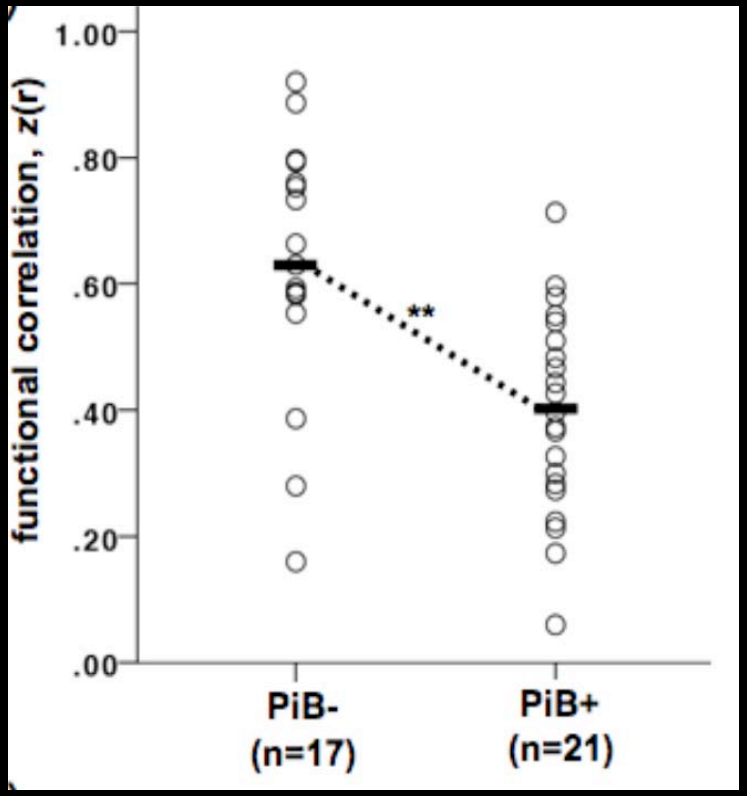


ICA-based detection of default-mode network in healthy aging (A) and AD (B).

Greicius et al., *PNAS*, 2004

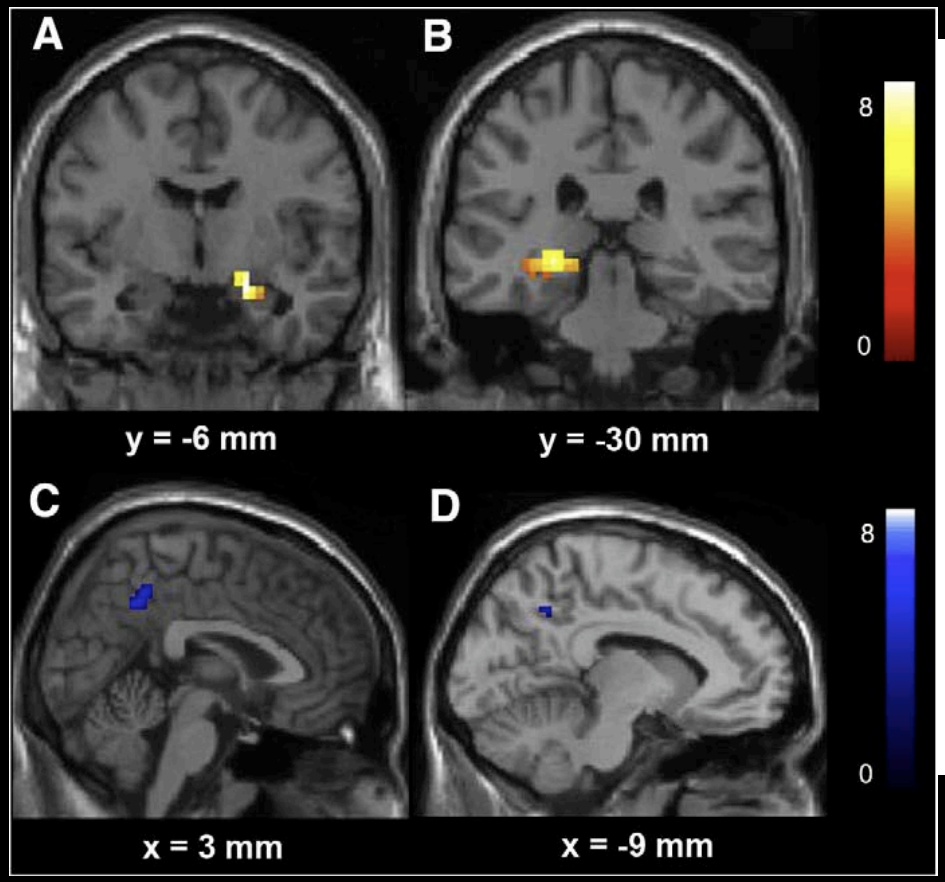
Amyloid-related disruption of intrinsic connectivity among asymptomatic elderly

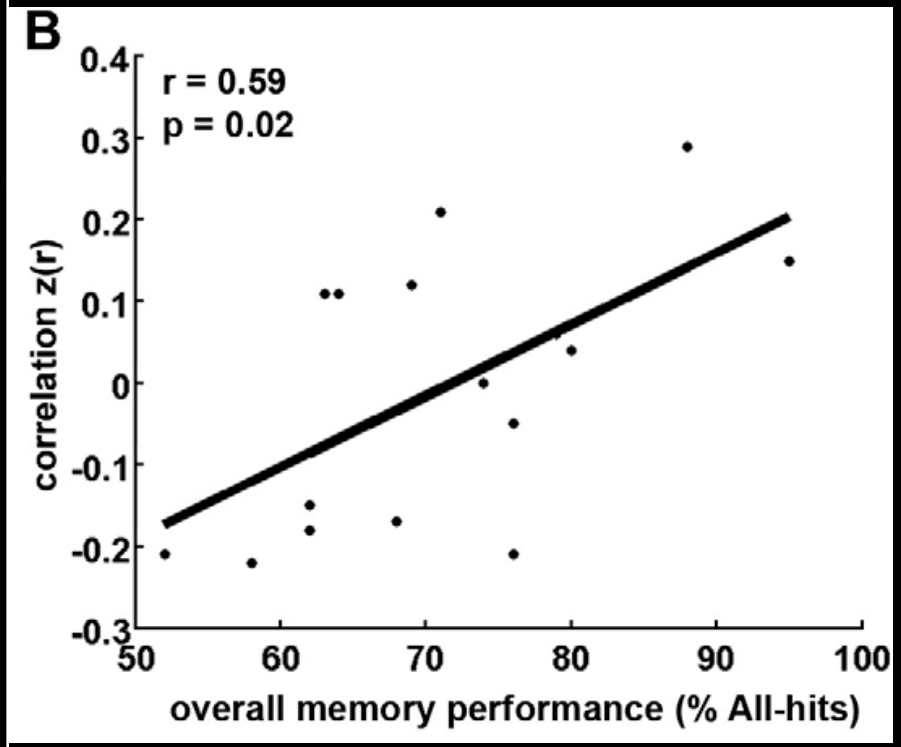




Hedden T et al *J Neuroscience* 2009

Default network connectivity predicts memory performance in older individuals

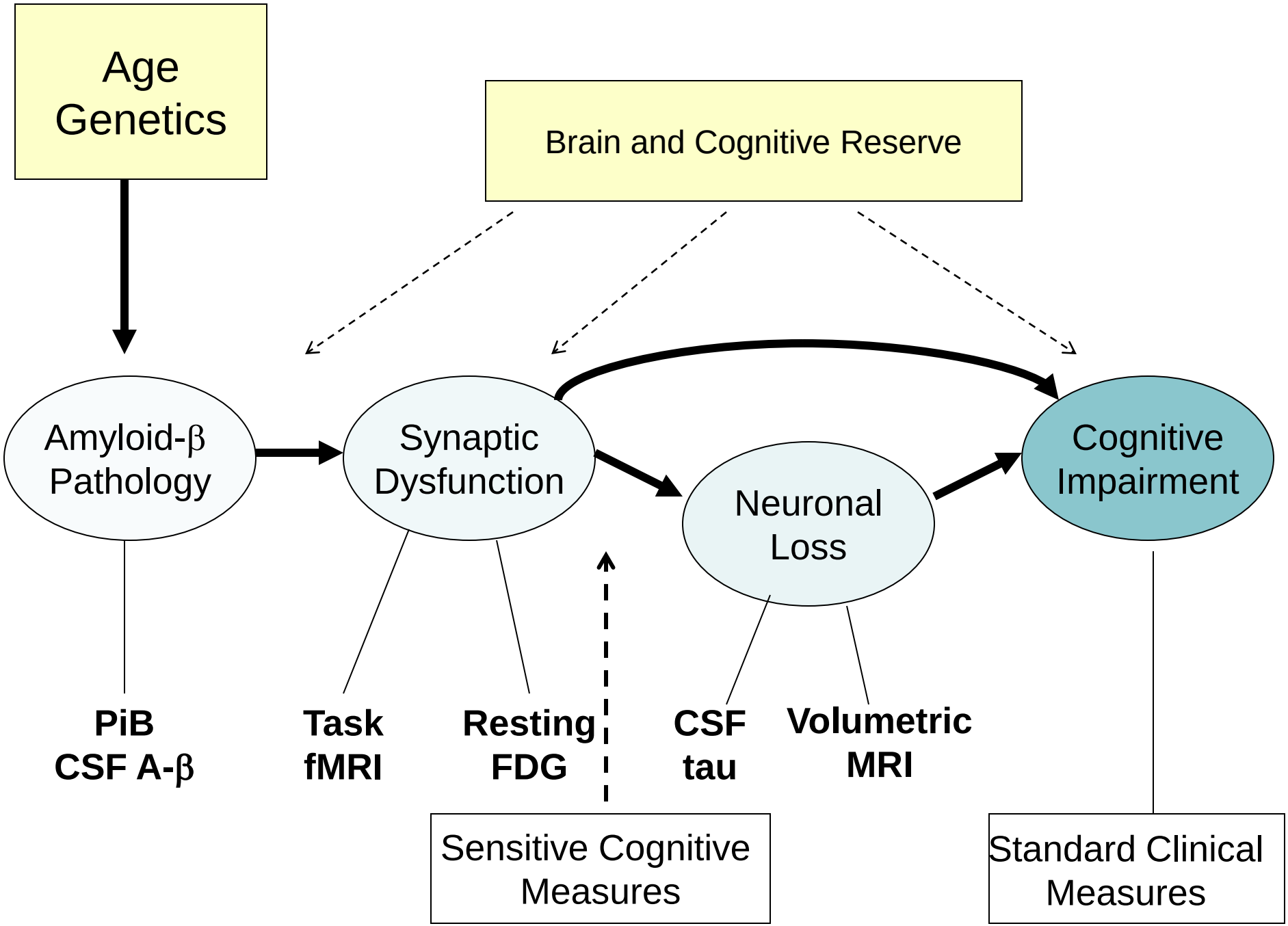




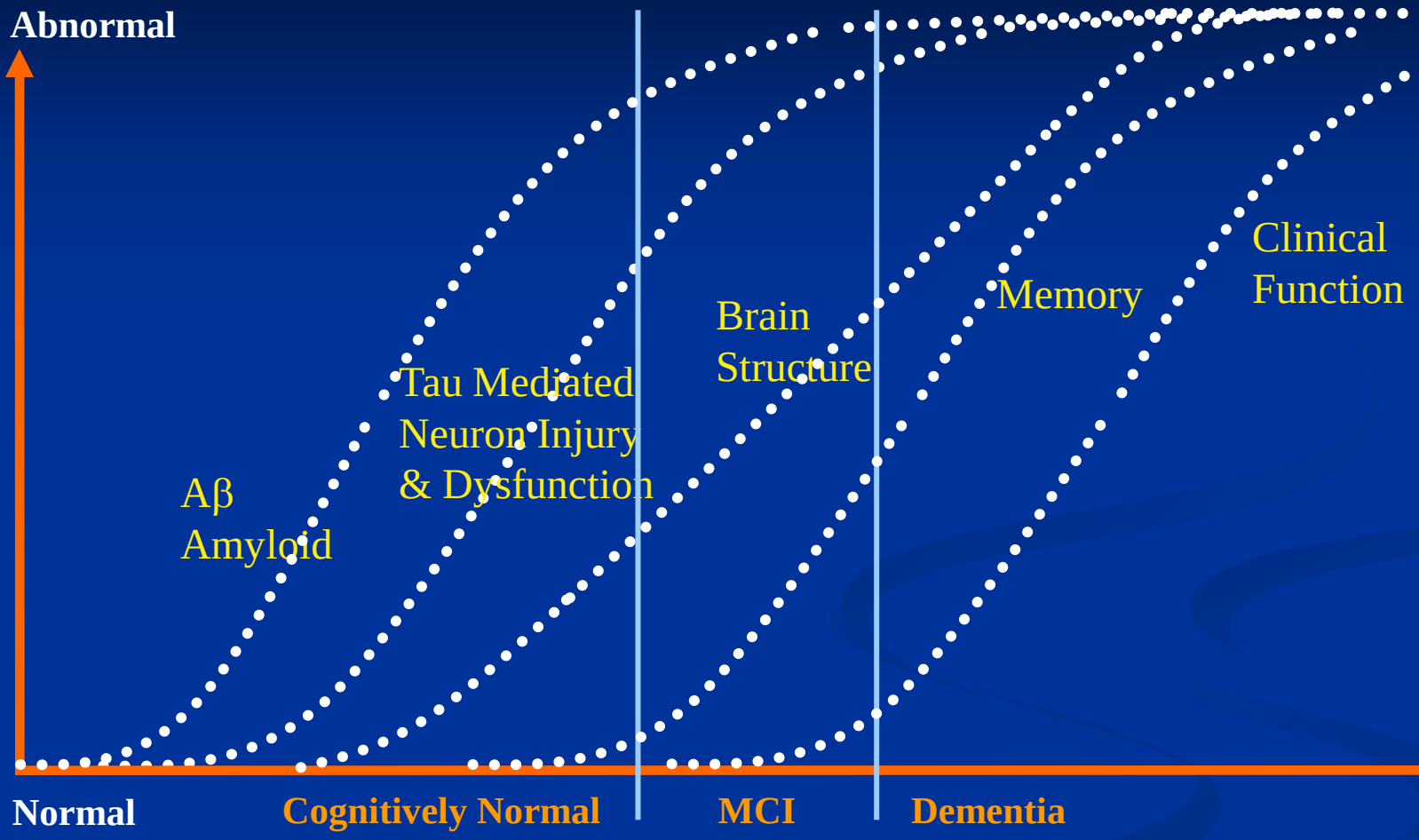
Wang L *NeuroImage (In press)*

TIME

Linking the pathophysiological sequence of Alzheimer's disease to the progression of clinical impairment

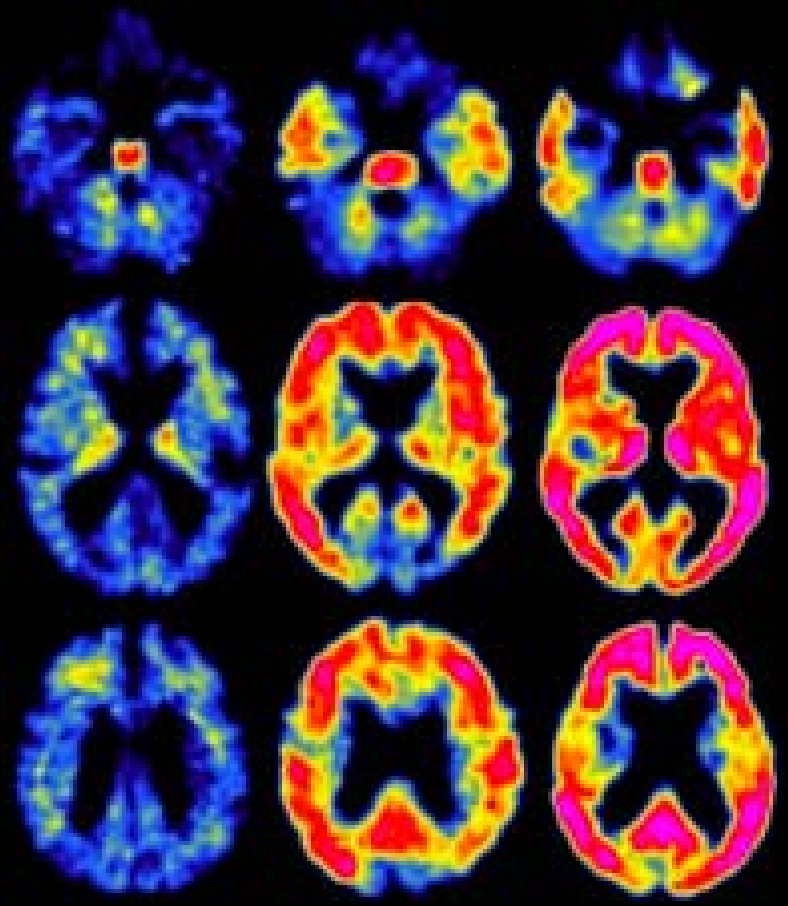

Age
Genetics
Brain and Cognitive Reserve
Amyloid-β
Pathology
Synaptic
Dysfunction
Neuronal
Loss
Cognitive
Impairment
PiB
CSF A-β
Task
fMRI
Resting
FDG
CSF
tau
Volumetric
MRI
Sensitive Cognitive
Measures
Standard Clinical
Measures

Dynamic Model of Biomarkers of the Alzheimer's Pathological Cascade

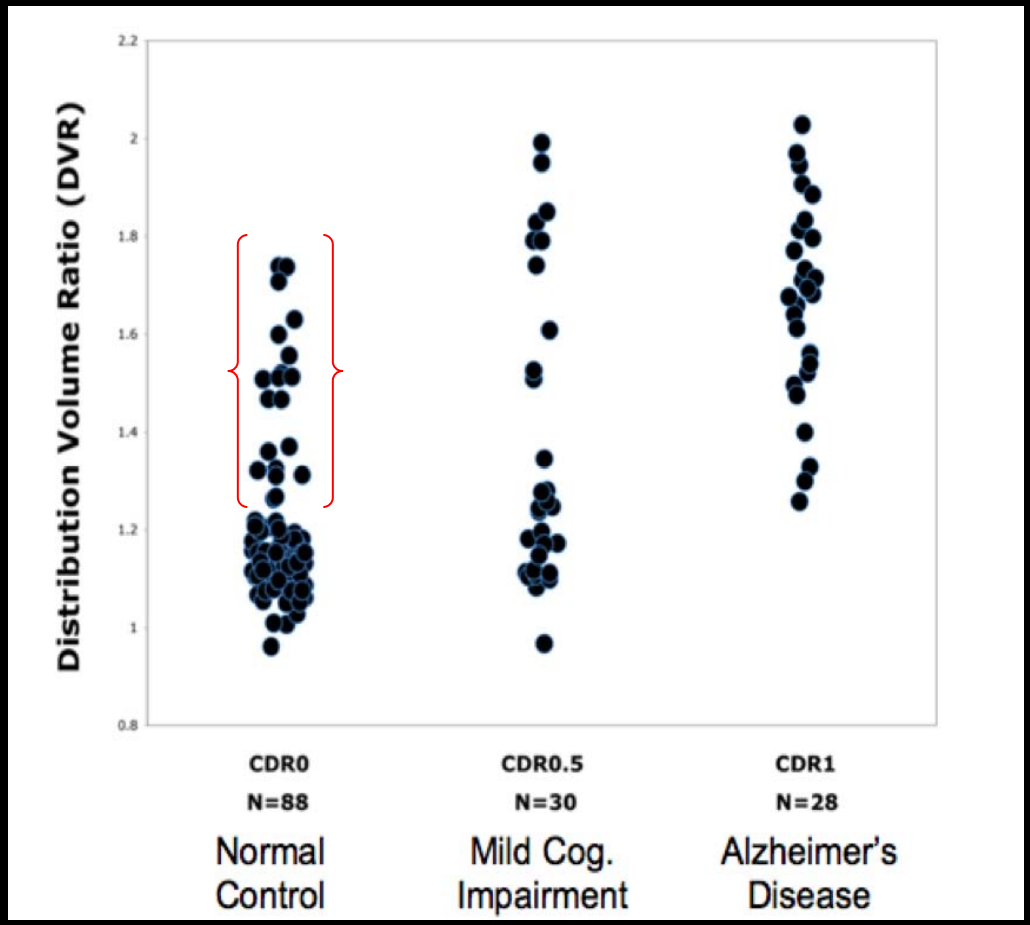


Jack C. *Lancet Neurology* 2010

Heterogeneity of amyloid burden in asymptomatic elderly



NC PiB- NC PiB+ AD



Sperling R et al. *NeuroMolecular Med* 2010

Appearance of Plaques vs. Dementia

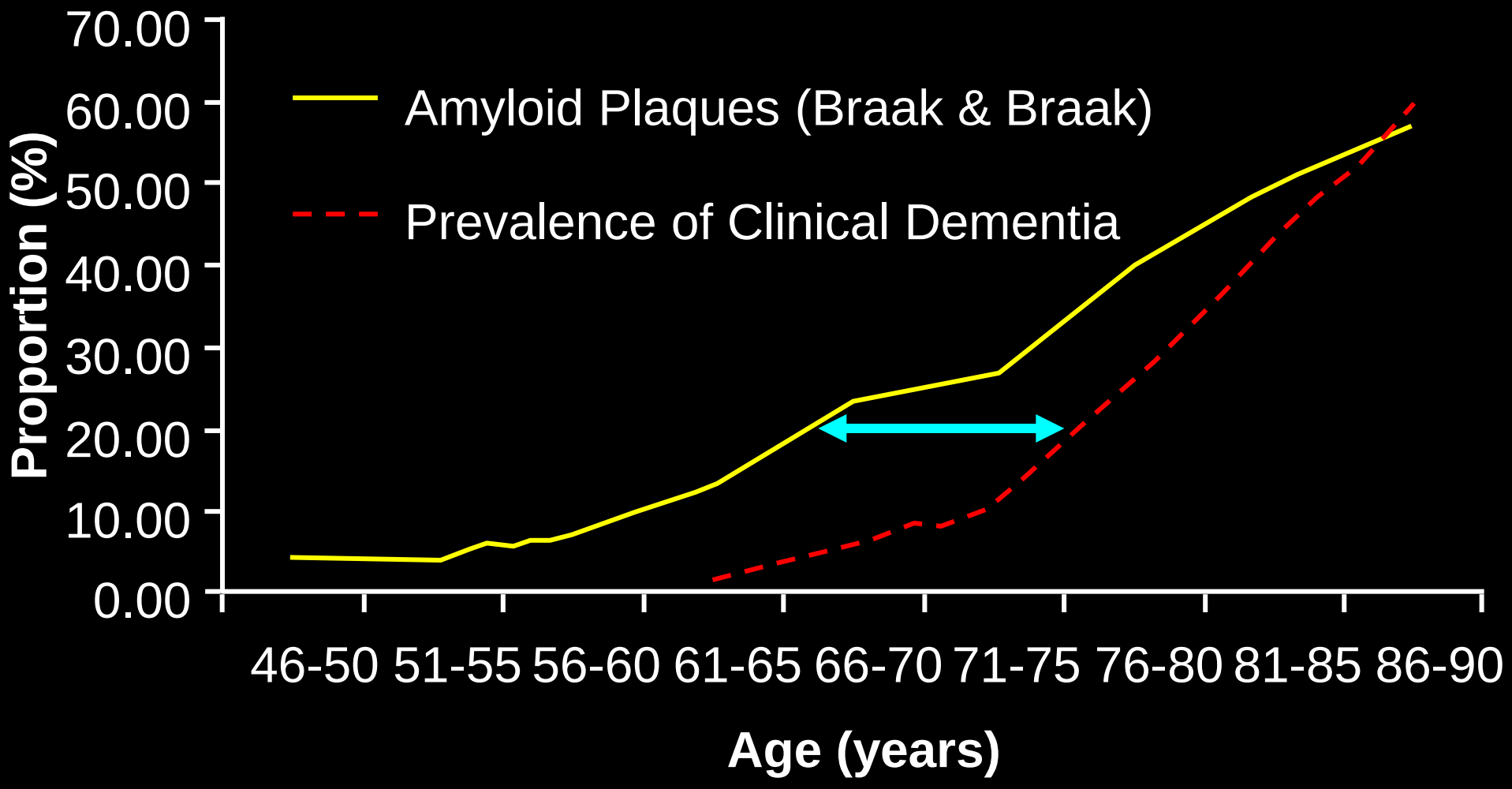
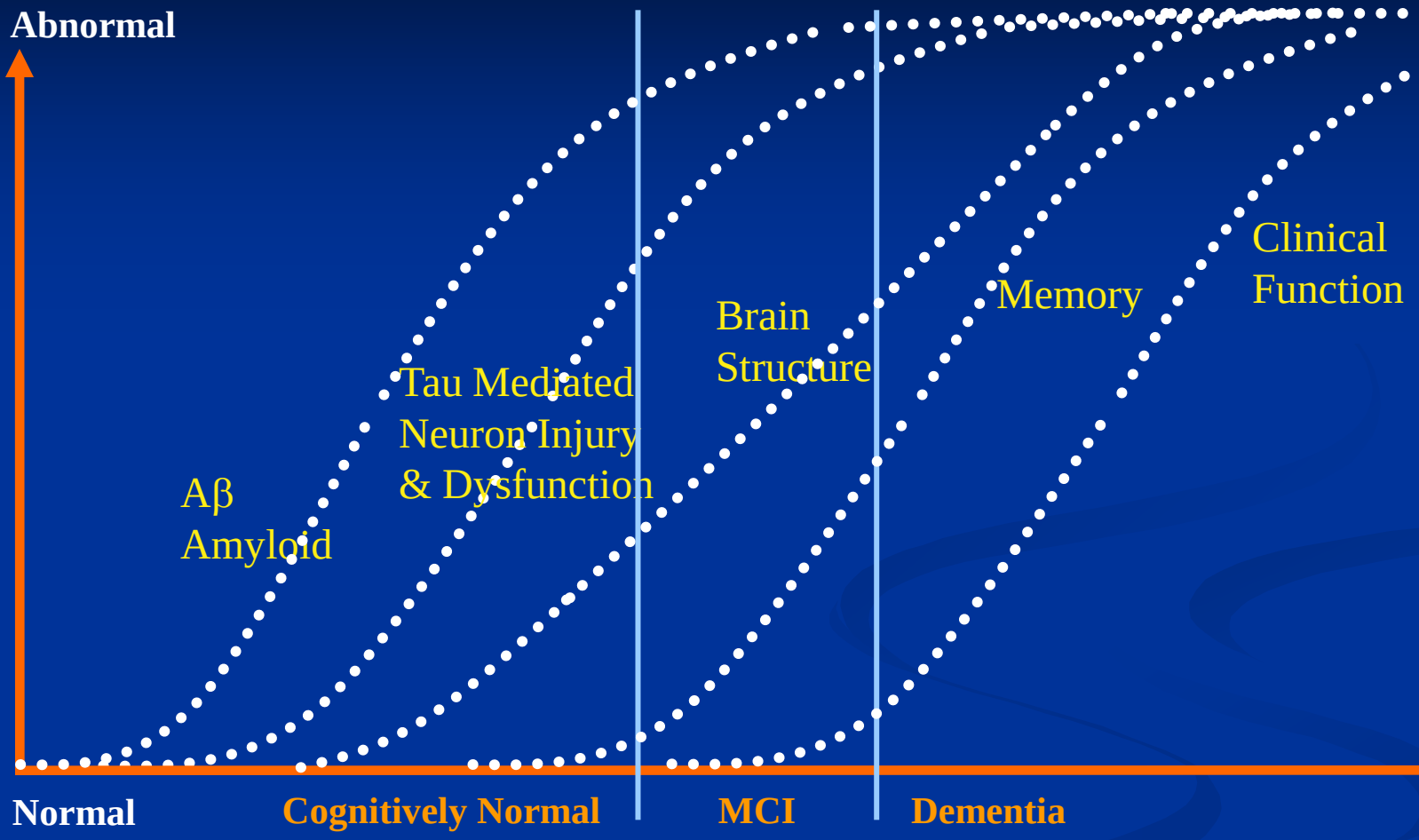


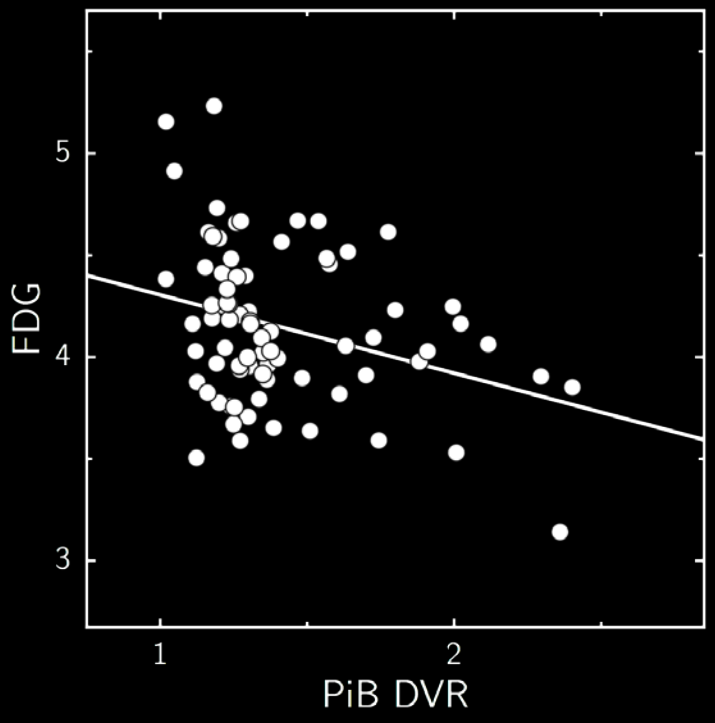
Figure courtesy of Mark Mintun and John Morris, Washington University

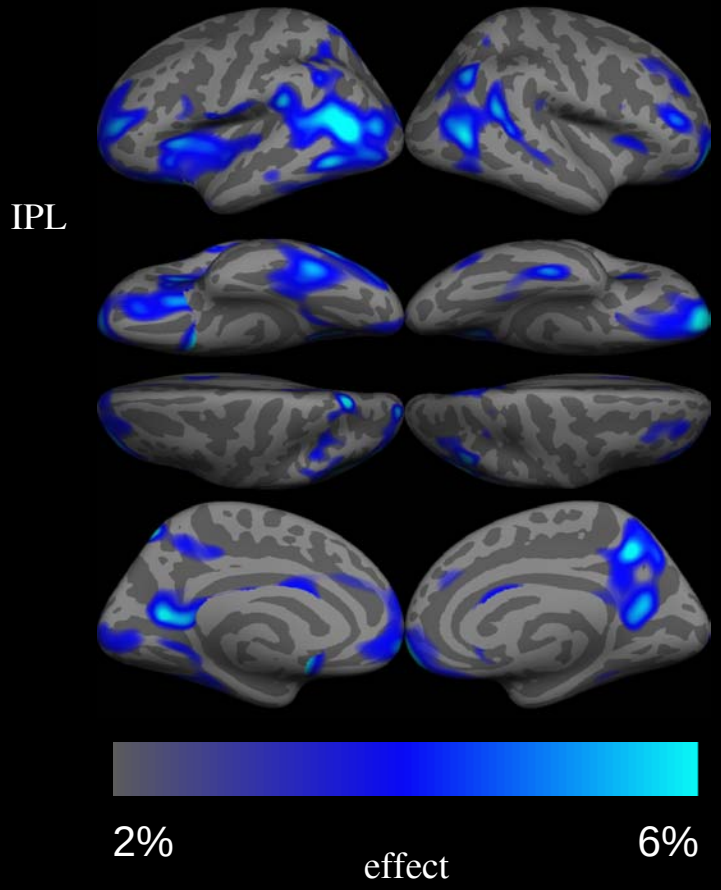
Dynamic Model of Biomarkers of the Alzheimer's Pathological Cascade



Jack C. *Lancet Neurology* 2010

Decreased metabolism with increased amyloid: FDG vs precuneus PiB



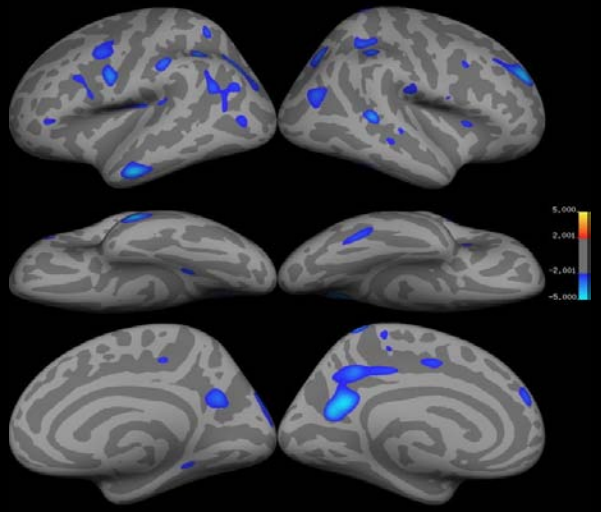


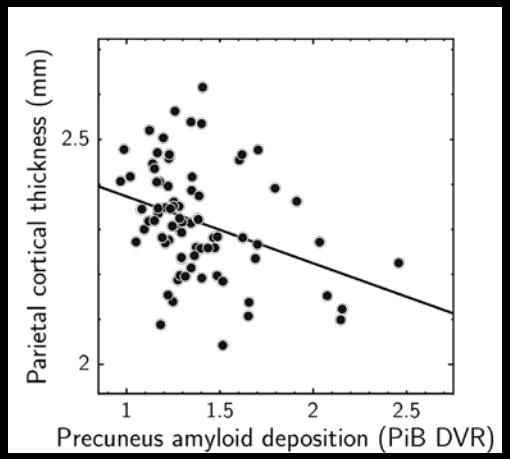
All CN (N=77)

J.A. Becker HAI 2010

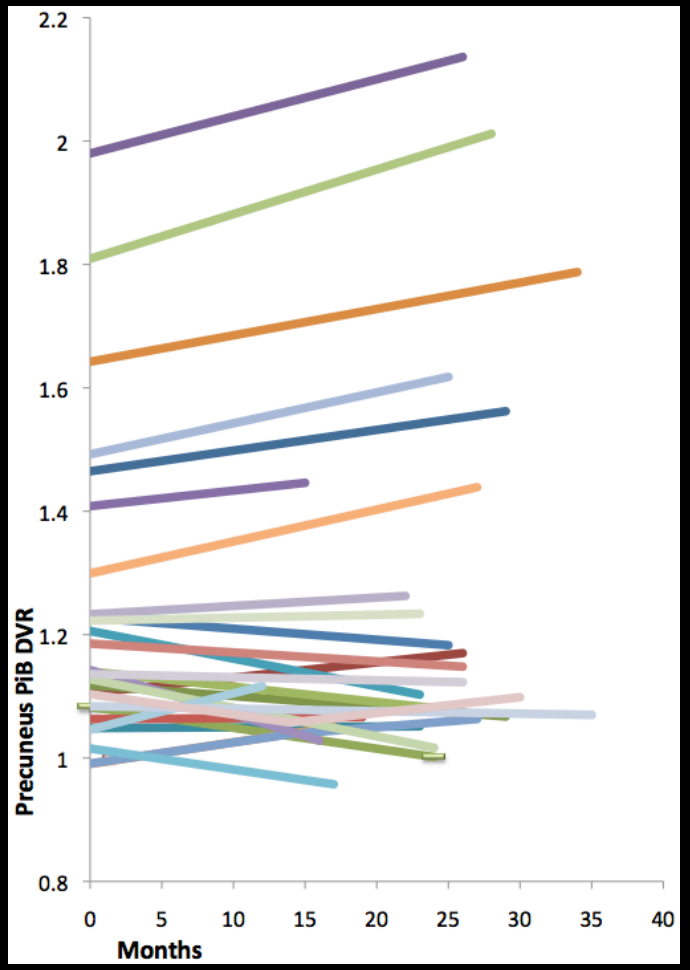
Longitudinal Amyloid Accumulation and AD markers

Baseline PiB vs. Cortical thickness





Longitudinal PiB

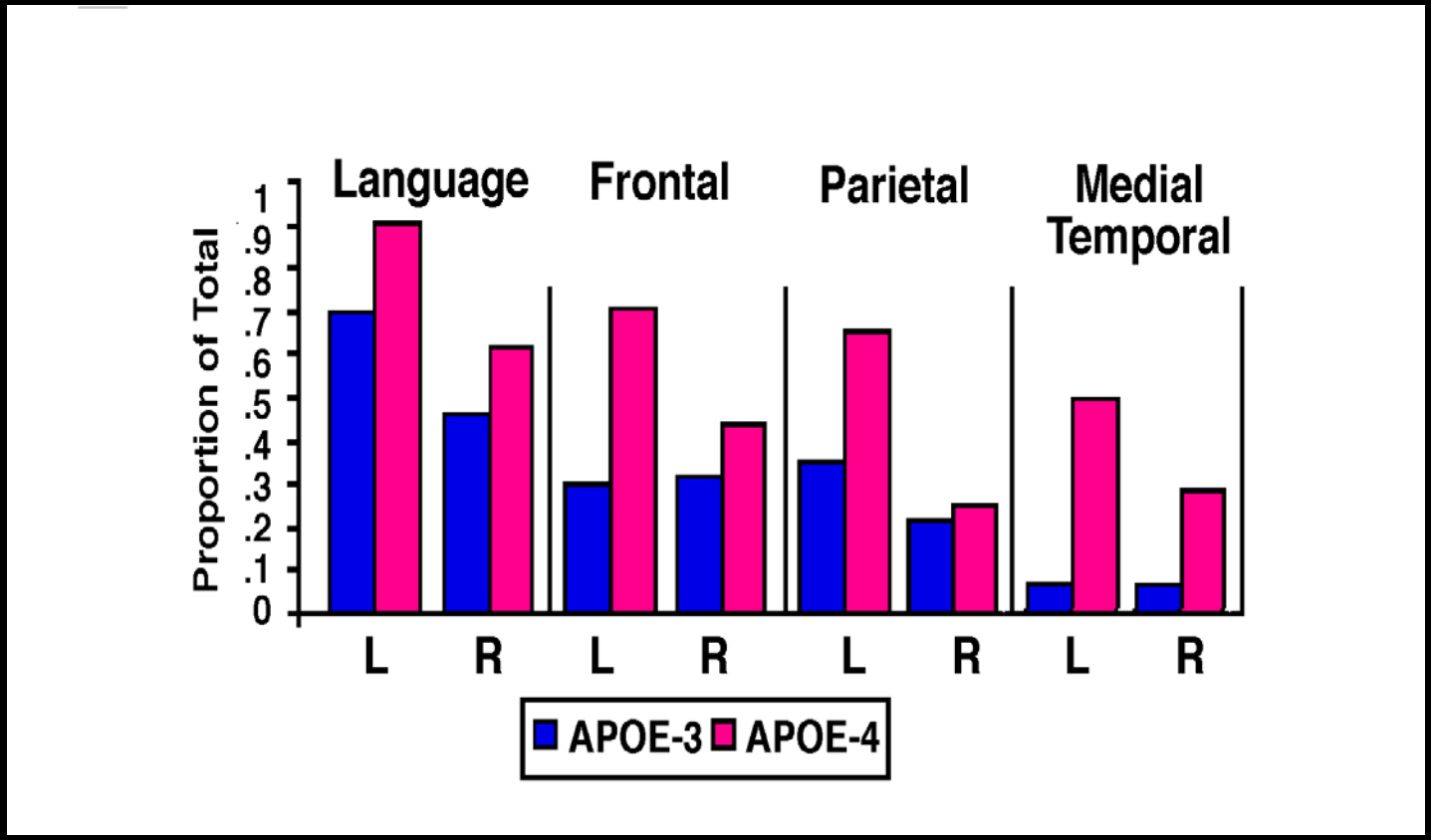


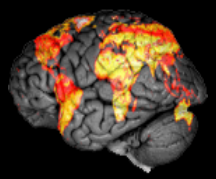
Johnson K (in preparation)

CAPACITY

Brain and Cognitive Reserve Compensation?

Pre-symptomatic genetic at-risk for AD

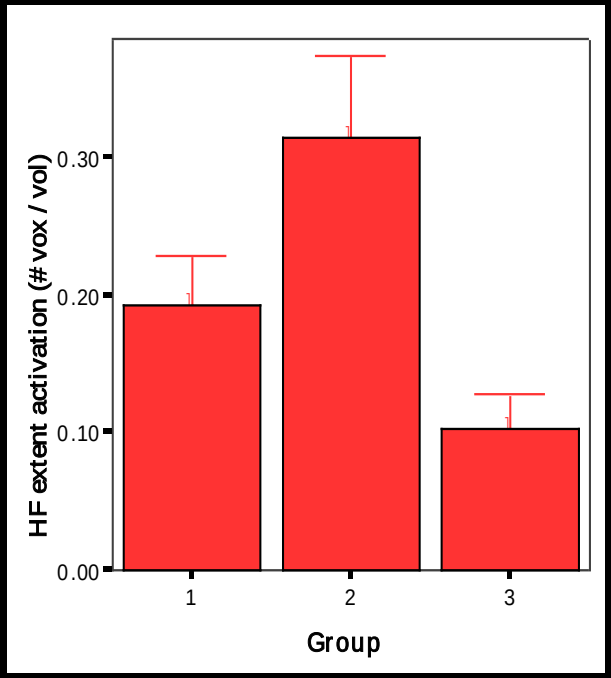




Bookheimer et al., NEJM 2000

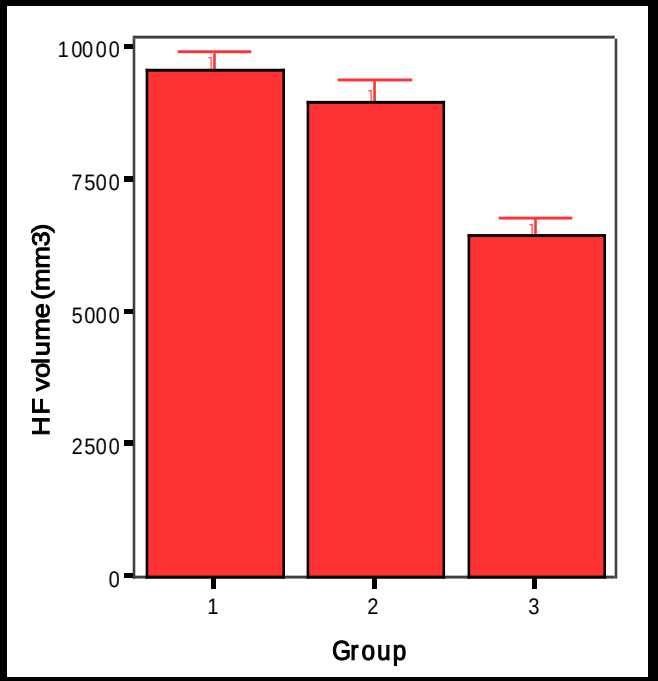
Increased hippocampal fMRI activation in early MCI

Left HF Functional Activation



NC vMCI AD

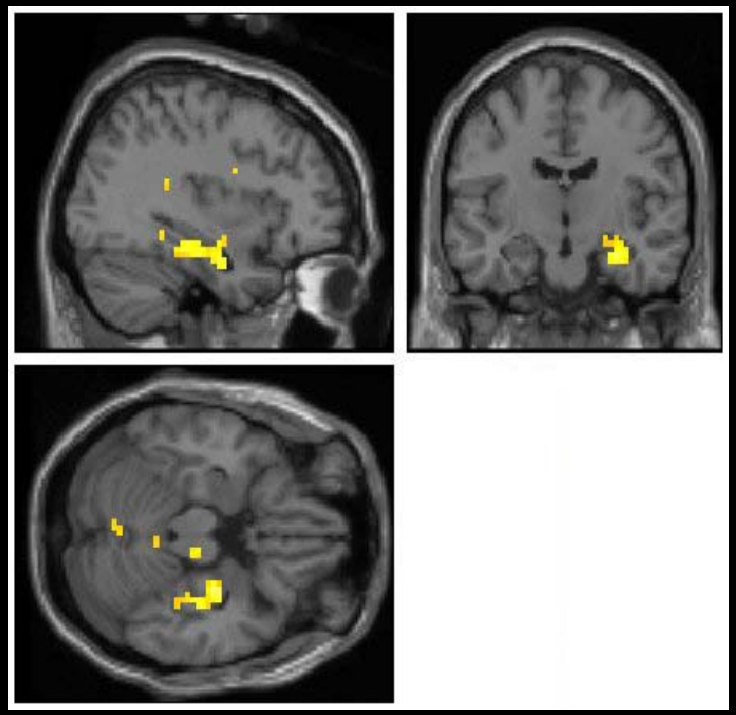
Left HF Volume



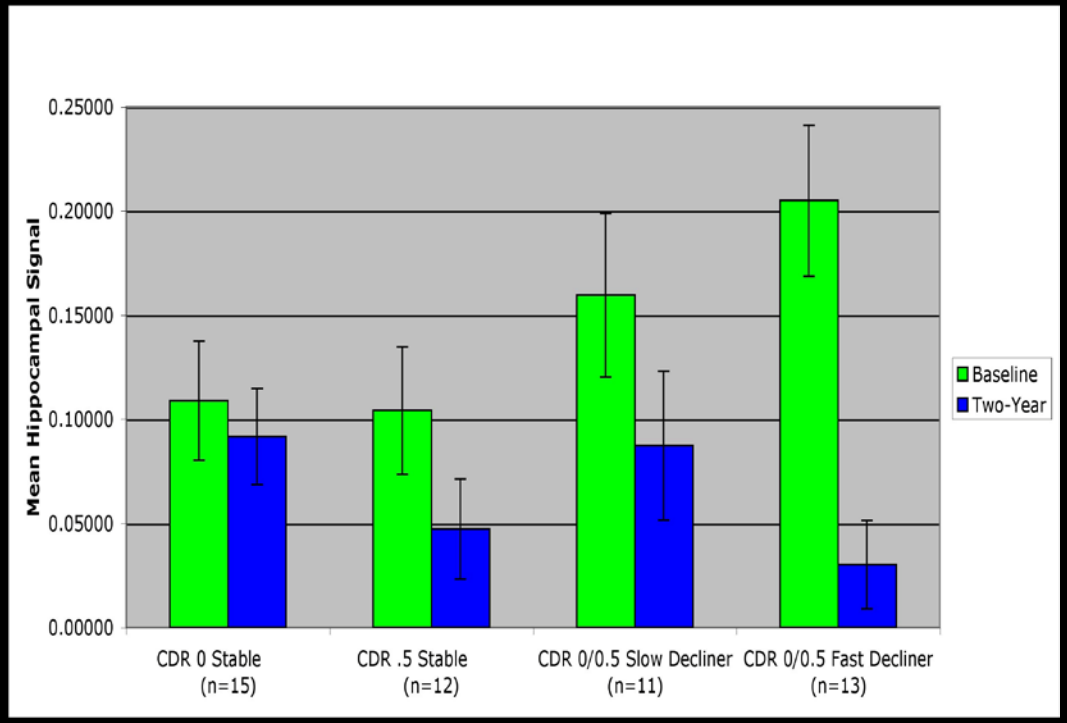
NC vMCI AD

Dickerson et al. *Neurology* 2005

Longitudinal fMRI in MCI: Change in Hippocampal Activation Baseline vs. Two year follow-up



Baseline >Year 2
n = 51; p<0.001



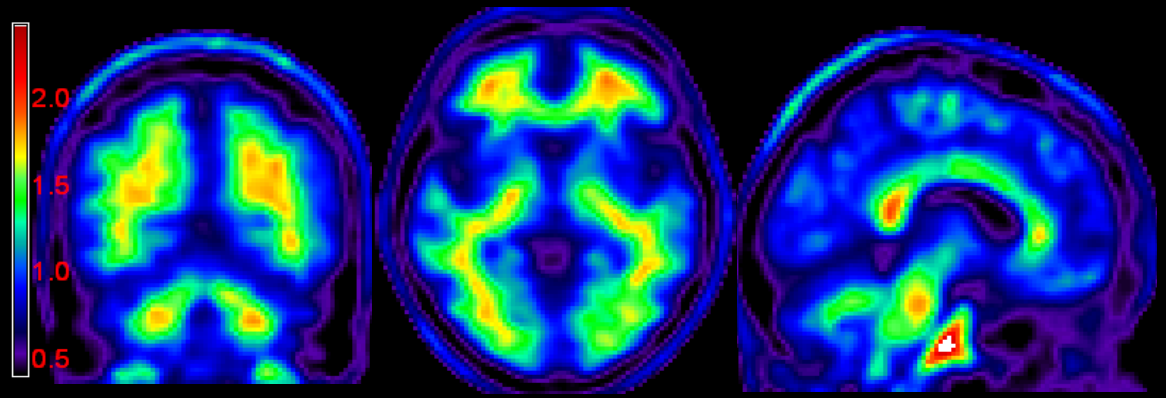
O'Brien J et al *Neurology* (in press)

CAPACITY

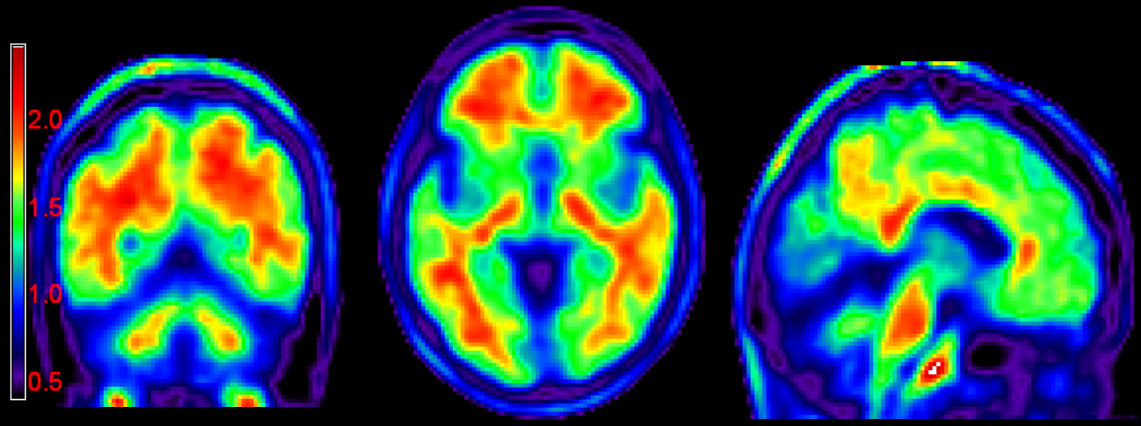
What is “Normal”?

^{18}F-AV-45 Representative Images: Healthy Controls

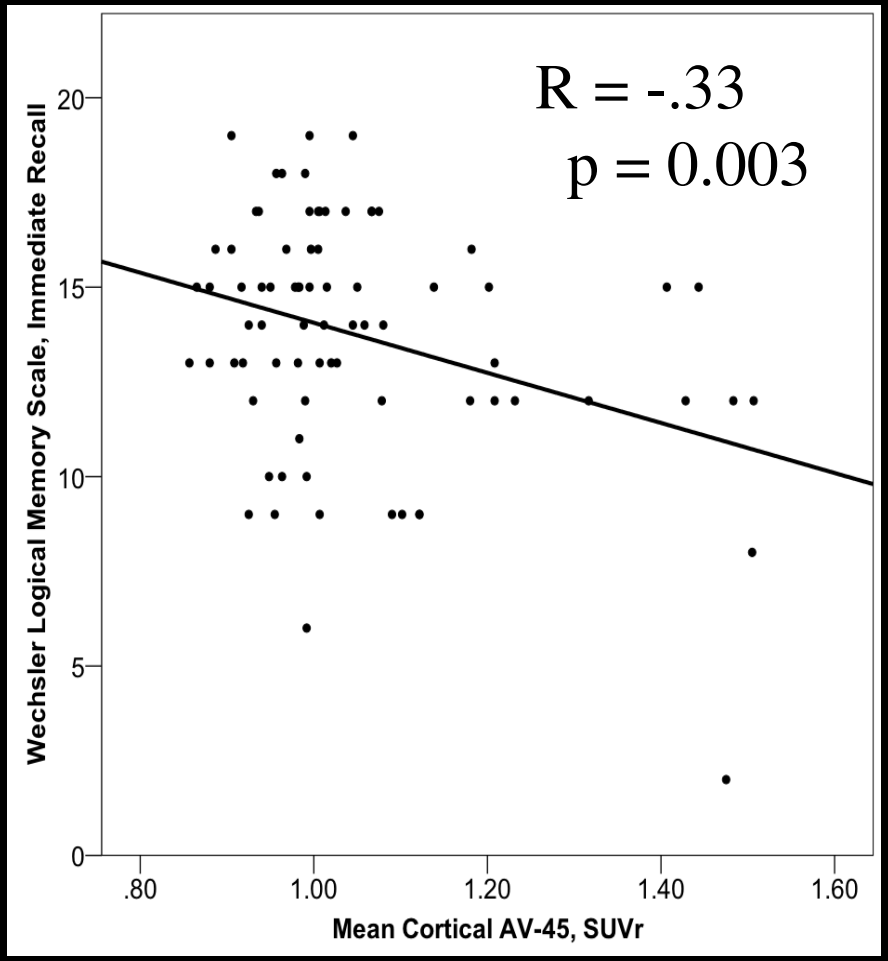
Amyloid Negative HC



Amyloid Positive HC

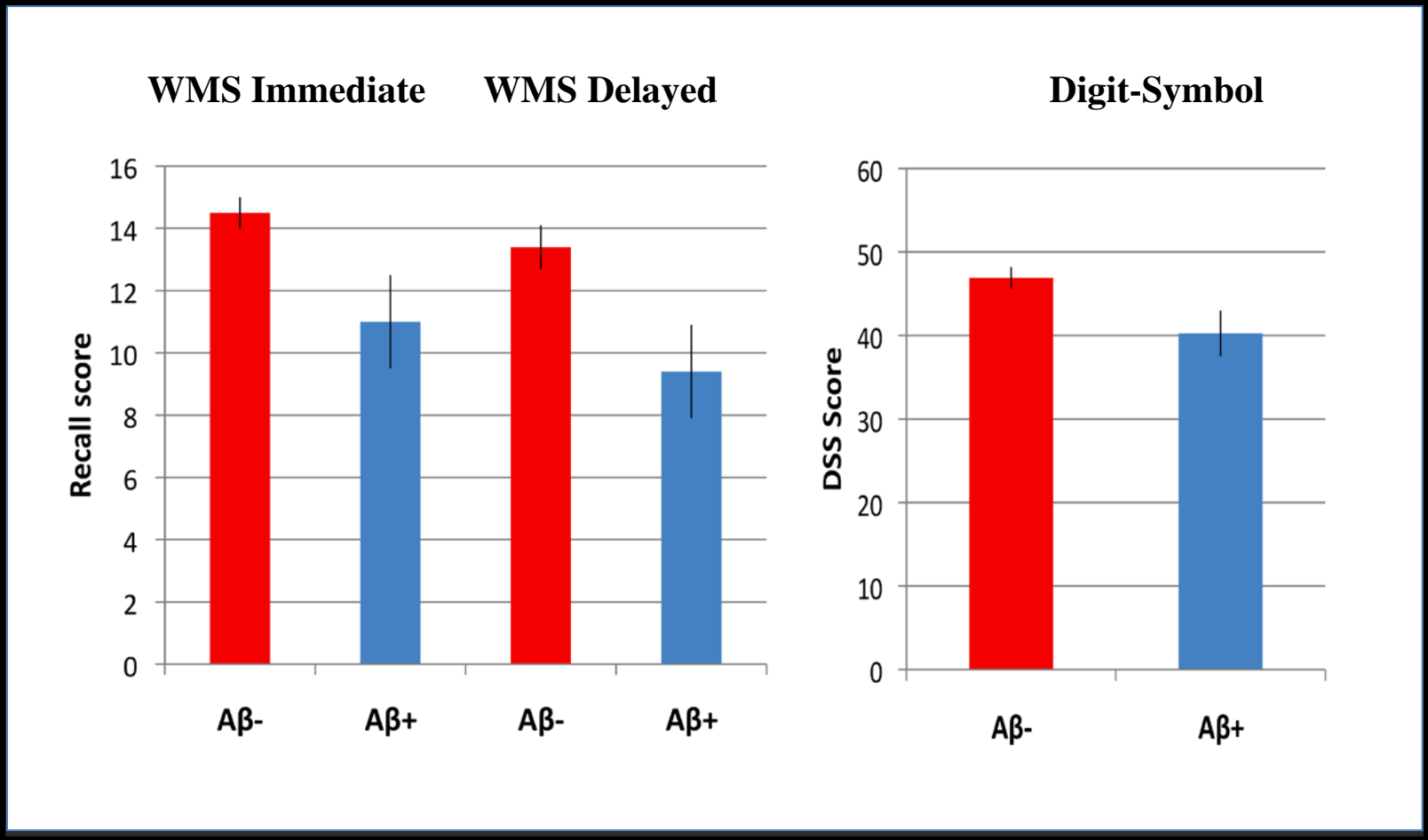


WMS-Immediate Recall



SUVr: partial r = -.334
p = 0.027
Age: partial r = .067
p = .562

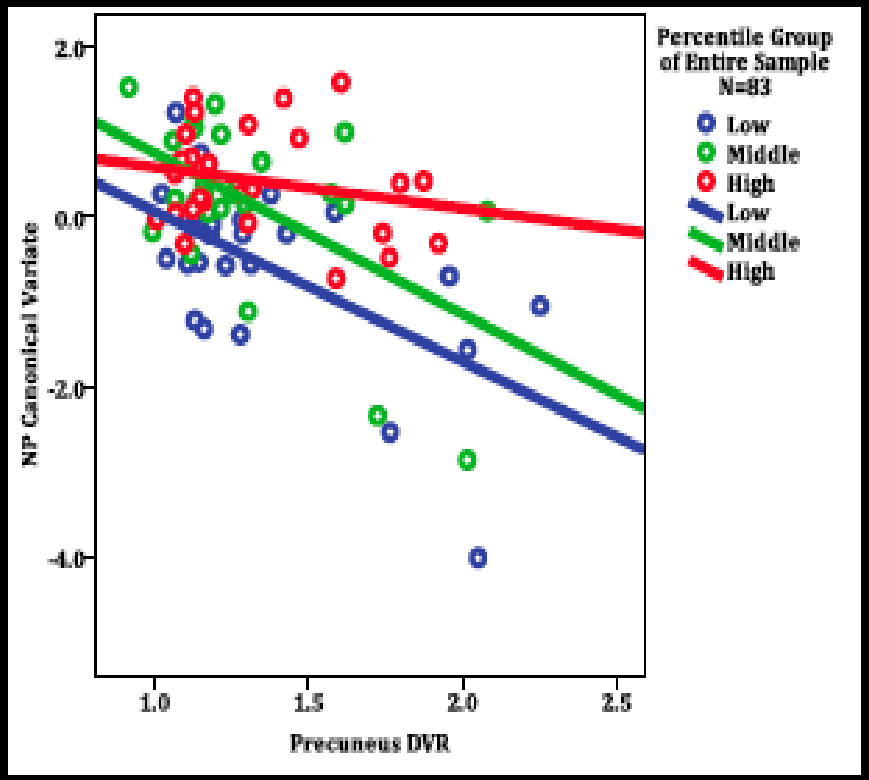
Cognition in Aβ Pos vs. Neg in HC > 70 years old



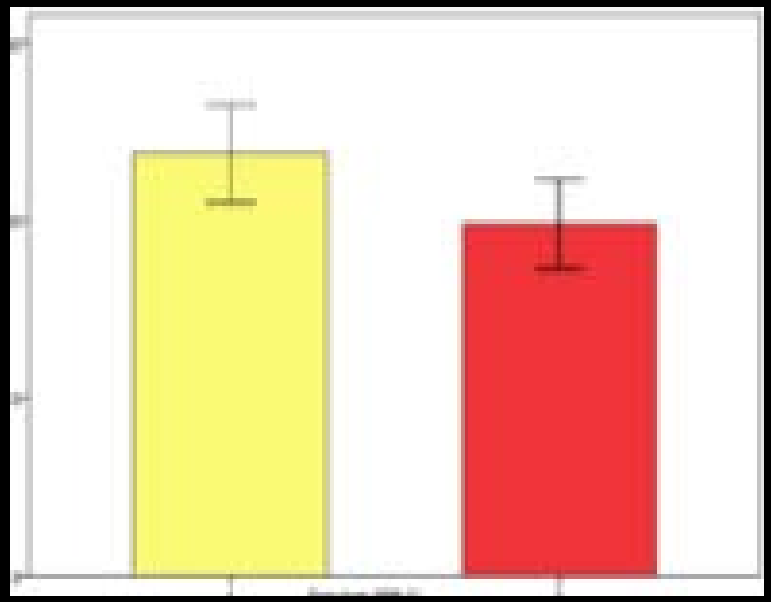
Sperling et al. HAI 2010

Superman in his later years

Cognitive Reserve mediates clinical expression of amyloid burden



Memory Capacity Test*
Delayed Recall



PiB- PiB+

* MCT - Courtesy of Dr. Herman Buschke

Rentz D et al *Annals of Neurology* 2010

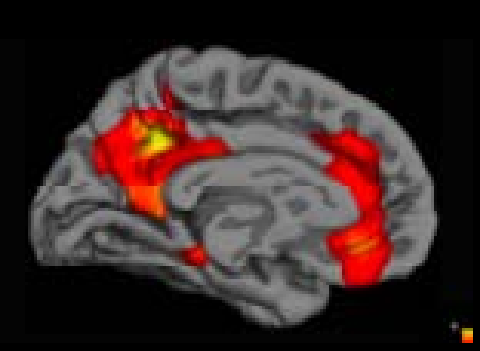
Summary of what we know

- Anatomic overlap of AD pathology and critical nodes of brain networks subserving memory function
  - Amyloid (default network)
  - Neurofibrillary pathology (medial temporal lobe)
- Converging evidence from multiple imaging modalities that there are functional abnormalities in this network prior to symptoms
- Early evidence that amyloid is associated with very subtle memory impairment

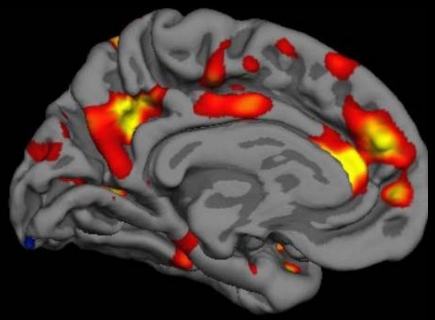
Remaining questions?

- Is there a specific threshold of amyloid burden that will trigger downstream pathological cascade and eventual impairment?
- Is the anatomic location of amyloid pathology critical for predicting decline?
- Is fibrillar amyloid deposition (as assessed by imaging) a reasonable proxy for presence of oliogmeric forms that may be responsible for the synaptic dysfunction?

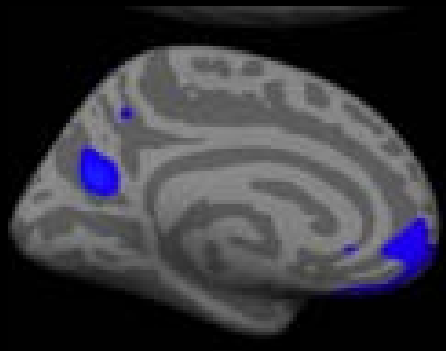
Investigate amyloid-related alterations in neural function and structure at molecular, synaptic, network, and behavioral levels



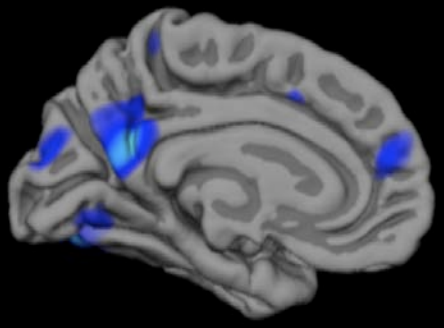
PiB



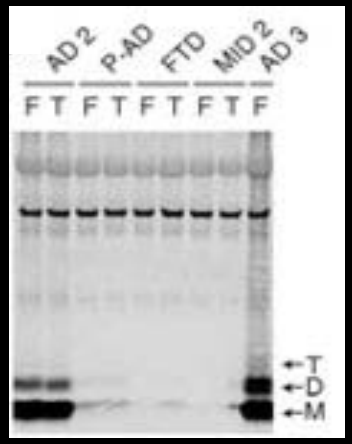
fMRI



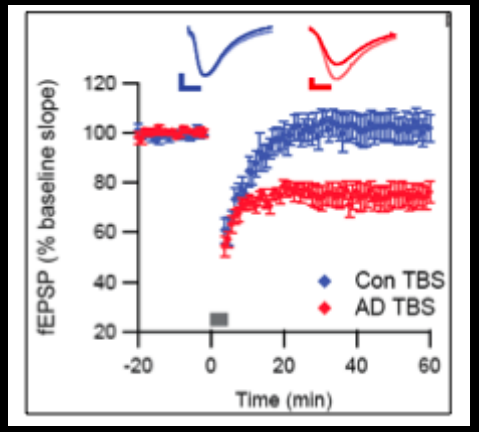
FDG-PET



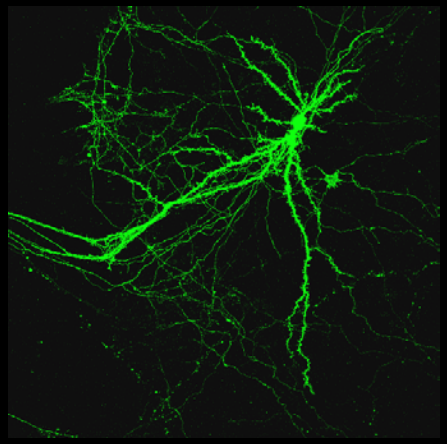
vMRI



Molecular



Electrophysiological



Microscopic

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