

# Imaging in “Healthy” Aging & Dementia: A Bigger Sand Box

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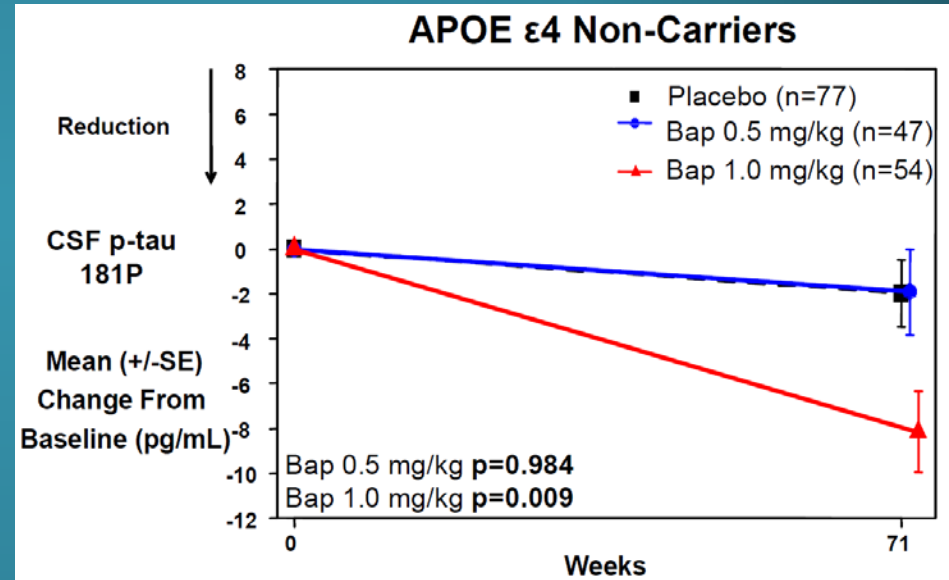
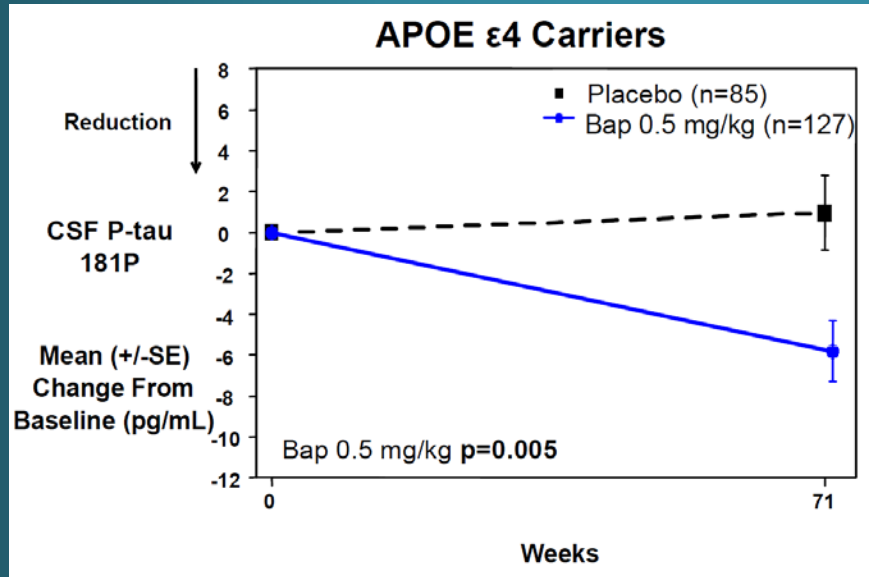
Lisa C. Krishnamurthy, PhD

with Salman Shahid, PhD; Qixiang Lin,

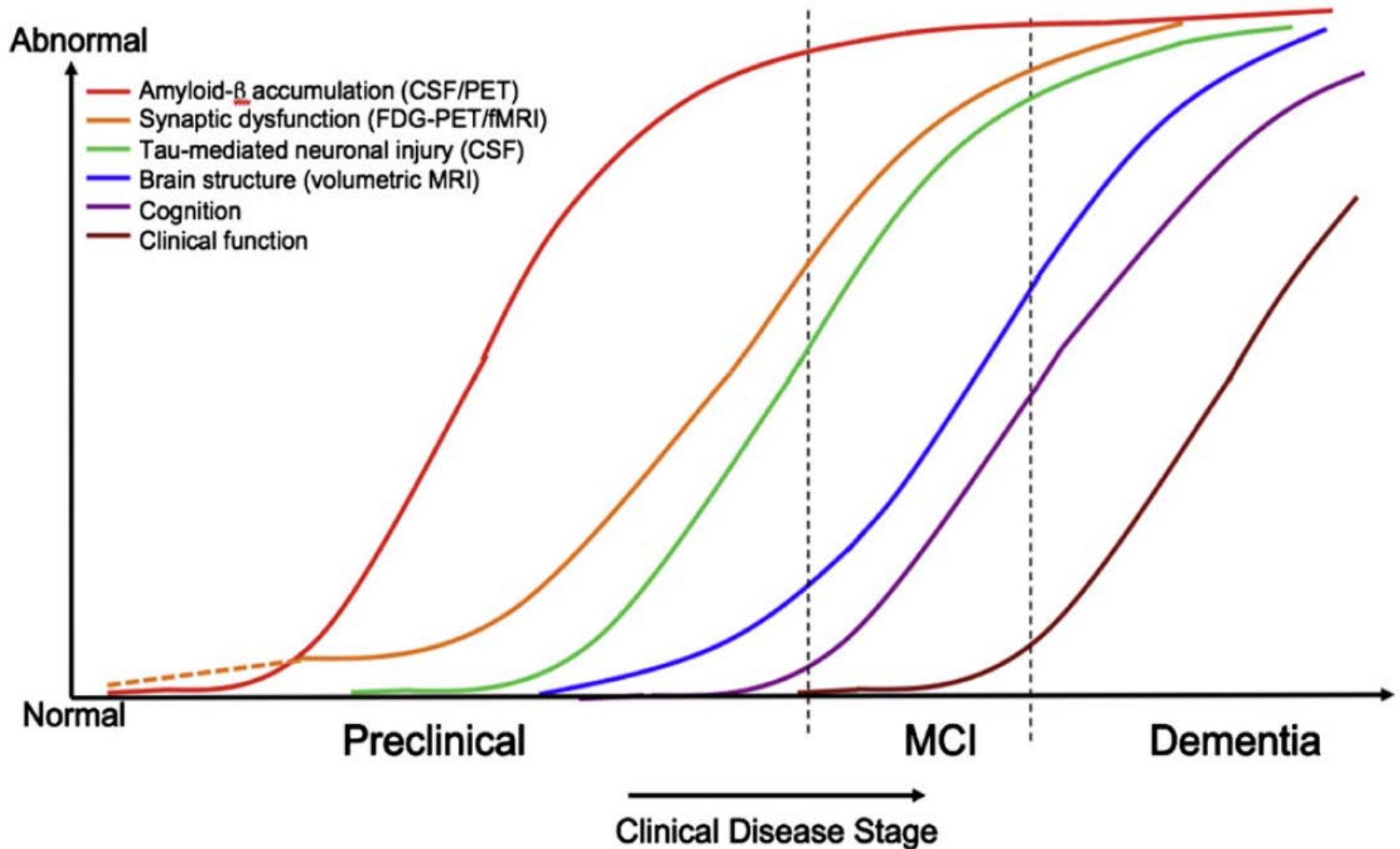
PhD; Antoine Hone-Blanchet, PhD;

Anastasia Bohsali, PhD

# Failed Clinical Trials in Early AD



# Staging of Alzheimer's Disease



# The German National Cohort Study

[https://www.helmholtz.de/en/research\\_infrastructure/national\\_cohort\\_study/](https://www.helmholtz.de/en/research_infrastructure/national_cohort_study/)

- The goal is development of new strategies for risk assessment, early detection and prevention of common widespread diseases, focusing on emergence of important chronic diseases (e.g., neurodegenerative diseases), their sub-clinical pre-stages, and functional changes.
- 200,000 study participants aging between 20 and 69 years old in 18 different study centers, with 30,000 having MRI scans.
- MRI images listed are T1-weighted (1 mm<sup>3</sup>), FLAIR (.9 X .9 X 4 mm), and resting-state BOLD (3.1 mm<sup>3</sup>, TR=2 s)

# The Rhineland Study

<https://www.dzne.de/en/research/research-areas/population-health-sciences/rhineland-study.html/>

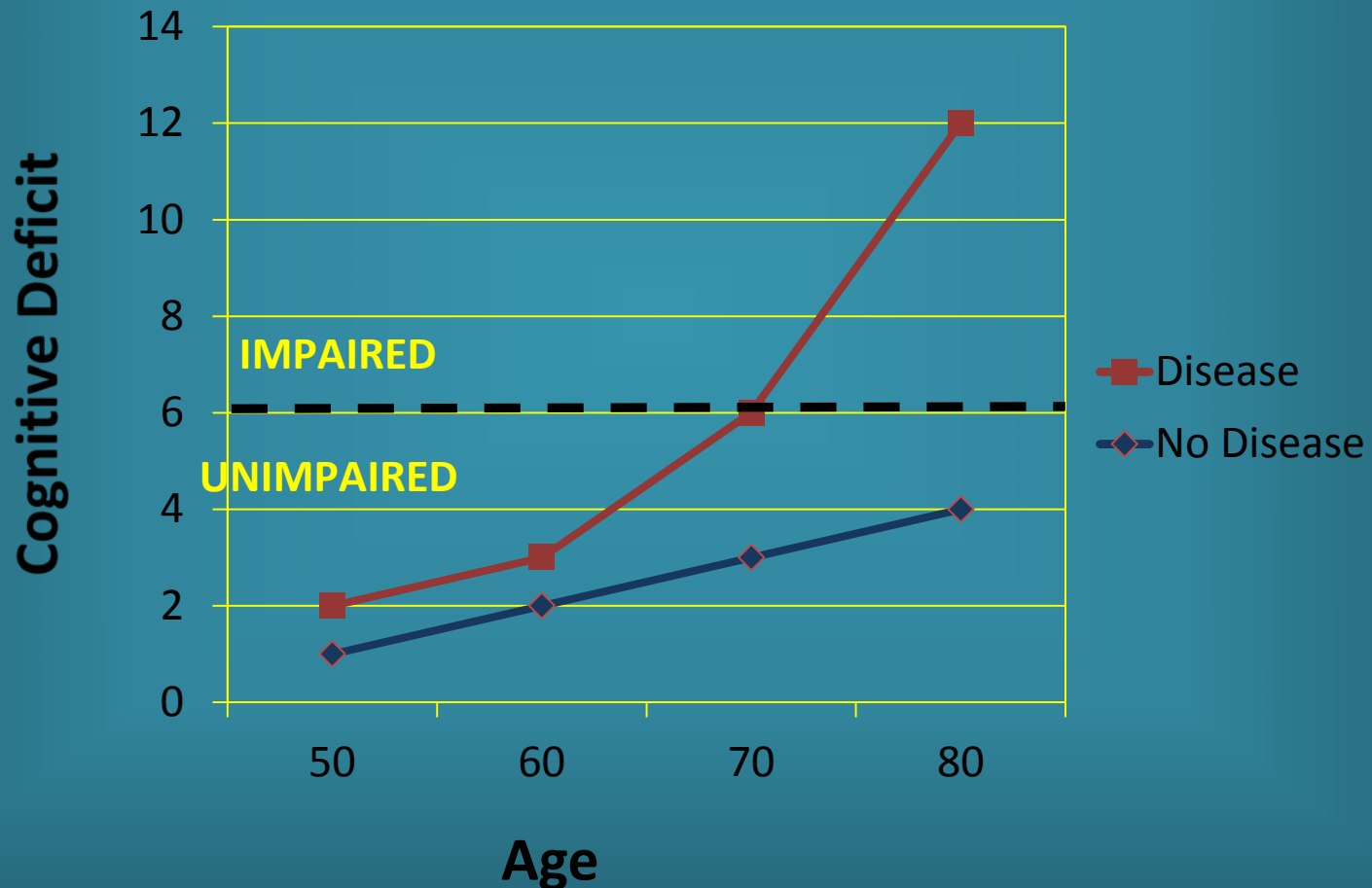
- The goals are identifying modifiable and non-modifiable causes of neurodegenerative or neuropsychiatric diseases, investigating biomarkers to identify individuals at risk of neurodegenerative or neuropsychiatric diseases who would benefit from preventive measures, and understanding the normal and pathological brain structure and function over the adult life course.
- 30,000 participants  $\geq$  30 years old at 7 centers.
- Core protocol includes T1-weighted, T2-weighted, multi-echo T2\*-weighted, functional MRI, and spin-echo EPI diffusion weighted MRI. Additionally, each participant will undergo at least 1 of the following: ASL, body-fat evaluation, metabolic imaging (CSI), quantitative imaging (T1 and T2), magnetization transfer quantification, and zoomed high resolution imaging (<0.5mm) in target ROIs such as the hippocampus or the locus coeruleus, task-related fMRI.

# The UK Biobank Study

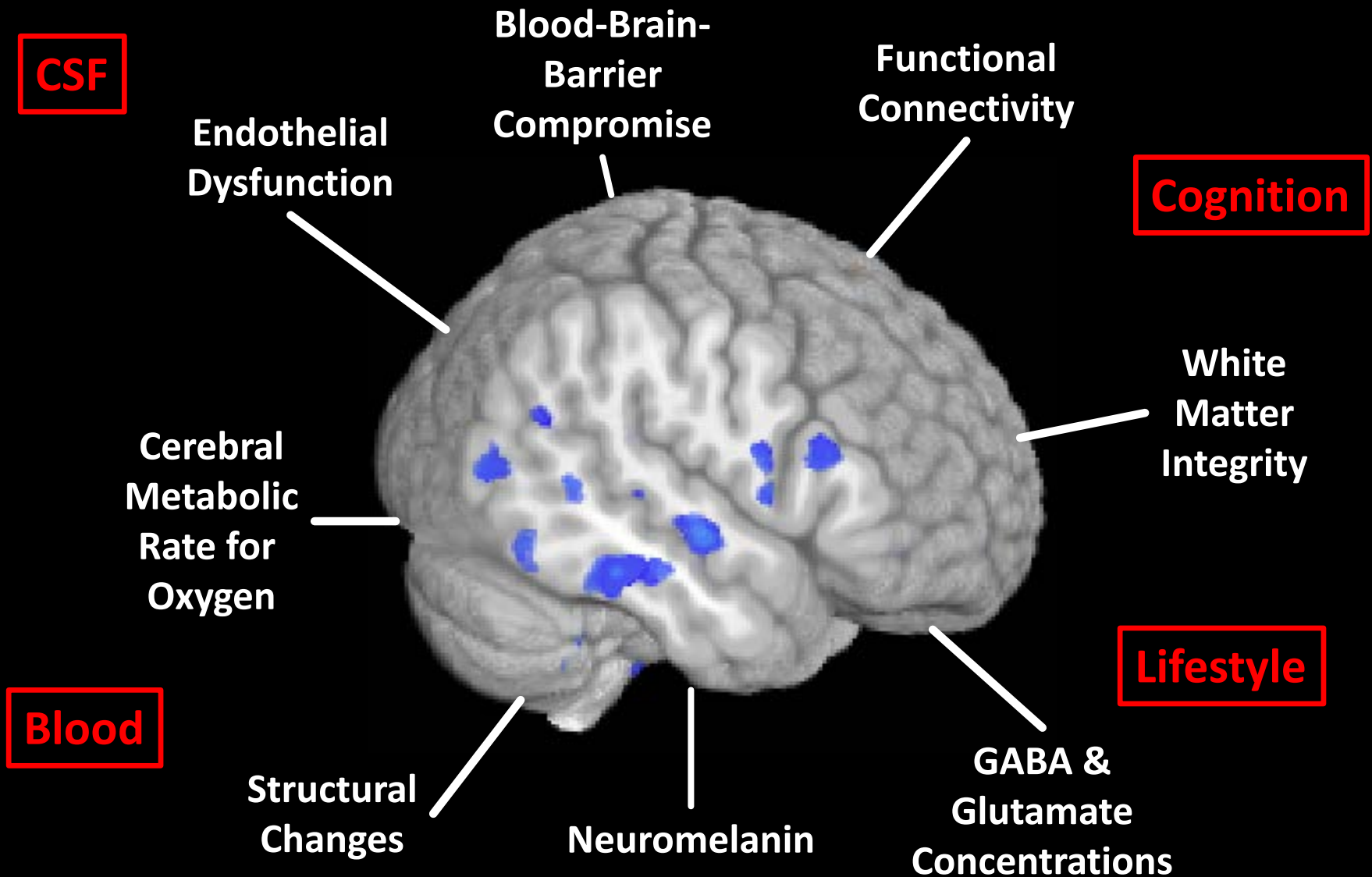
<http://imaging.ukbiobank.ac.uk/>

- Medical imaging has enormous potential for early disease prediction, but is impeded by the difficulty and expense of acquiring datasets prior to symptom onset. UK Biobank aims to address this problem directly by acquiring high quality, consistently acquired imaging data from 100,000 predominantly healthy participants, with health outcomes tracked over coming decades.
- 100,000 participants 40 – 69 years old. Within the imaged cohort, 1800 participants are expected to develop Alzheimer's disease by 2022.
- MRI images listed are T1, T2 FLAIR, susceptibility weighted MRI, Resting fMRI, Task fMRI, and Diffusion MRI.

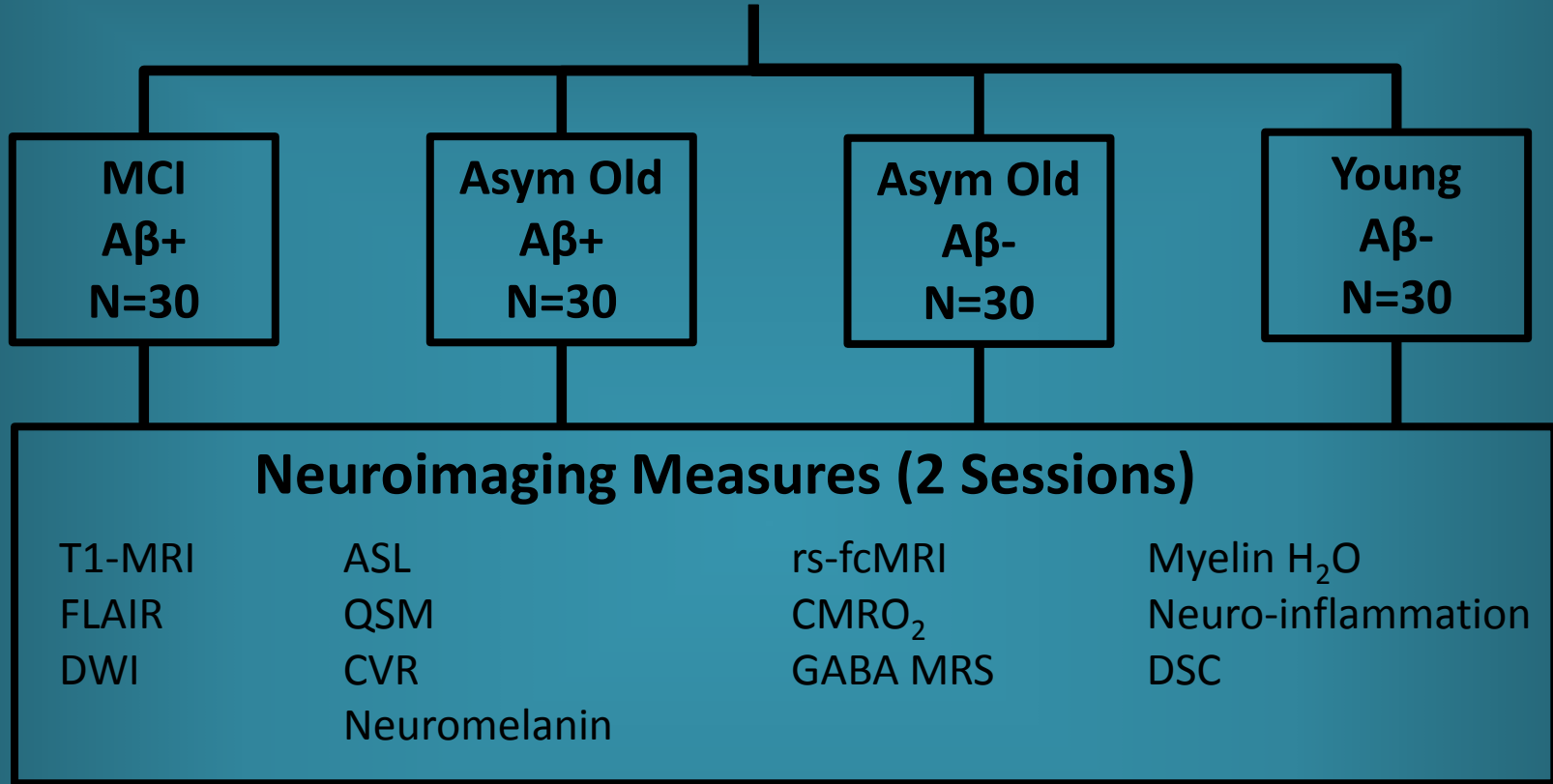
# Age X Disease Interaction (with disease burden held constant)



# Neuroimaging Measures for EHAS



# HAS Neuroimaging Pilot Study (Phase 1)

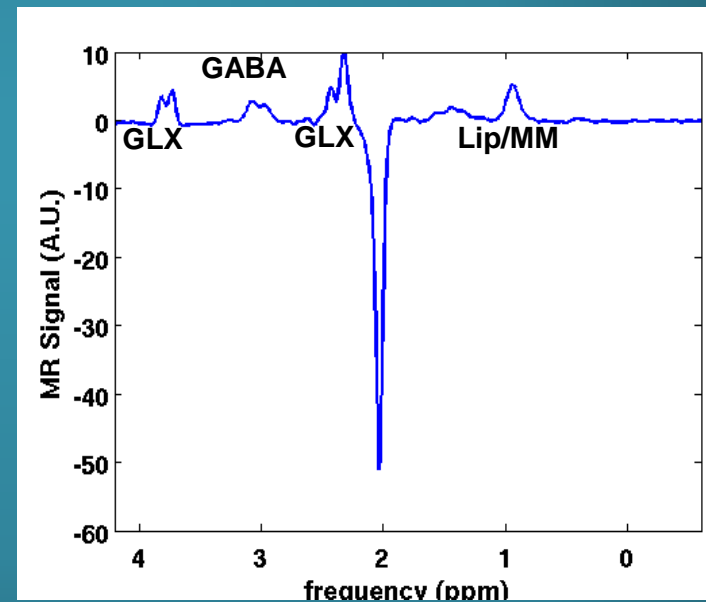
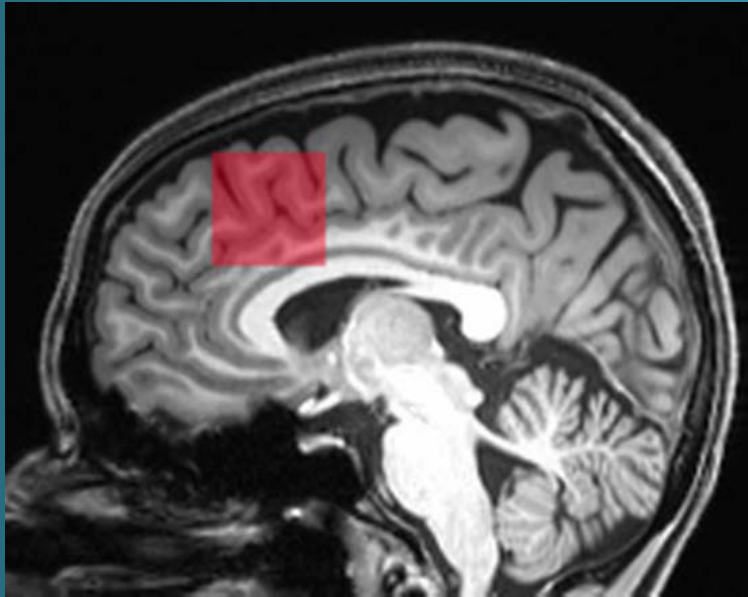


**HAS N=1,000 (Phase 2)**

# Neuroimaging Protocols for Healthy Aging

## 1. GABA MRS

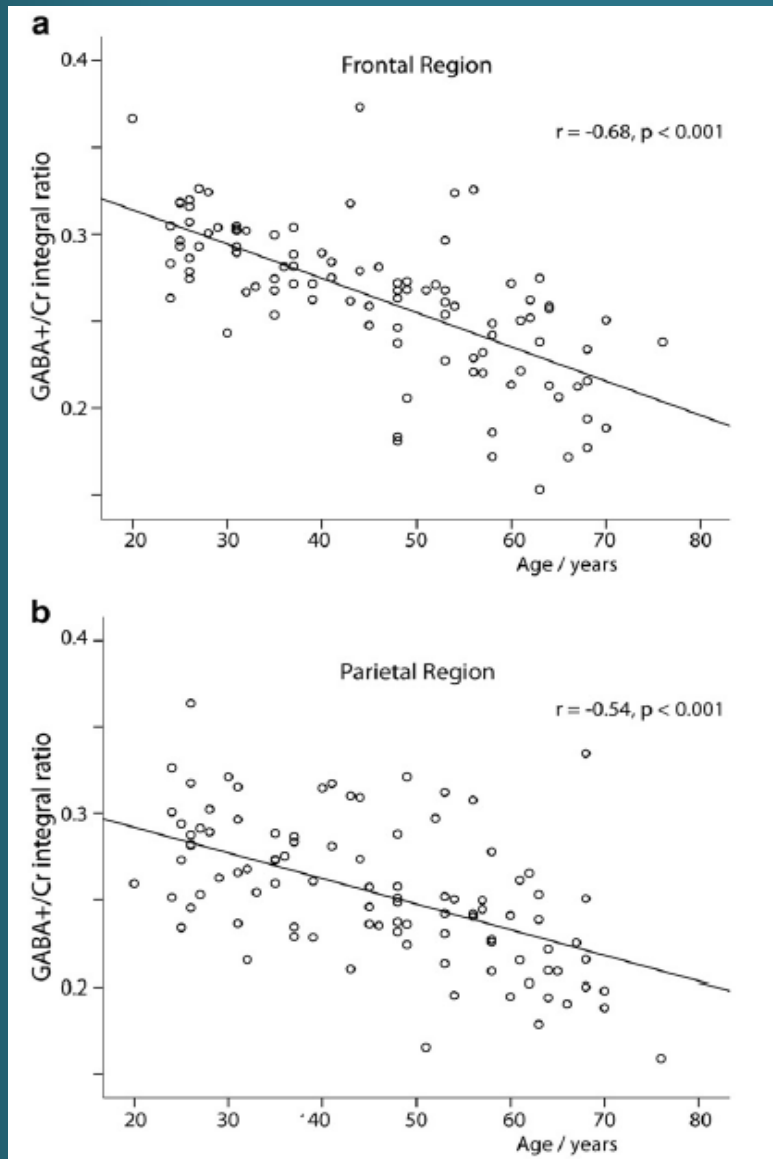
# GABA MRS



Courtesy of Lisa Krishnamurthy

## 1. GABA MRS

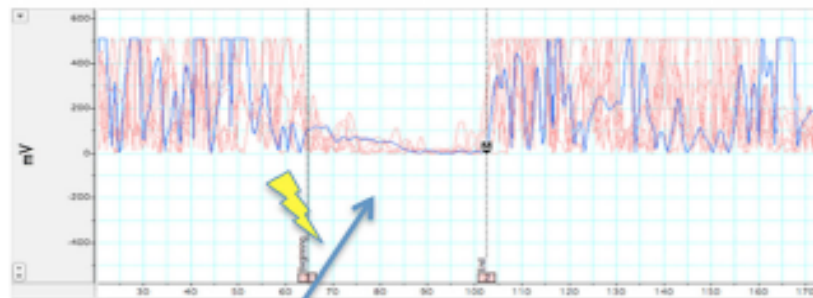
# GABA MRS and Aging



In pre-SMA, GABA concentration (corrected for creatine concentration), accounts for 46% of the variance in aging. Considering that fitness probably also accounts for some of the aging variance, as does a gender X age interaction, this is a very strong GABA signal. It also implies reliability.

## 1. GABA MRS

# Ipsilateral Silent Period (iSP) Is Reduced in Older Adults



**FIGURE 3 |** When left M1 is stimulated by a single TMS pulse during isometric contraction of the left first dorsal interosseous muscle, after a delay >40 ms (~65 ms in the illustration), there is a temporary reduction of EMG activity in that muscle. The length the reduction in EMG activity is averaged across several trials to obtain a stable iSP.

iSP seems to be driven by GABA<sub>B</sub> mechanisms. For example, it is enhanced by baclofen, a GABA<sub>B</sub> agonist, enhances iSP.

McGregor et al. (2011) showed that iSP was reduced in sedentary older (65-80) adults relative to both young (18-37) adults and physically active older adults. Active older adults show reduced iSP relative to young adults.

McGregor et al. (2012, 2013) showed that iSP was reduced in sedentary middle-aged (41-60) adults relative to both young (18-37) adults and physically fit middle-aged adults. There is no difference in iSP length between young and fit middle-aged adults. There was no iSP difference between fit and sedentary young adults.

# 3-Month Aerobic Exercise Program Increases iSP

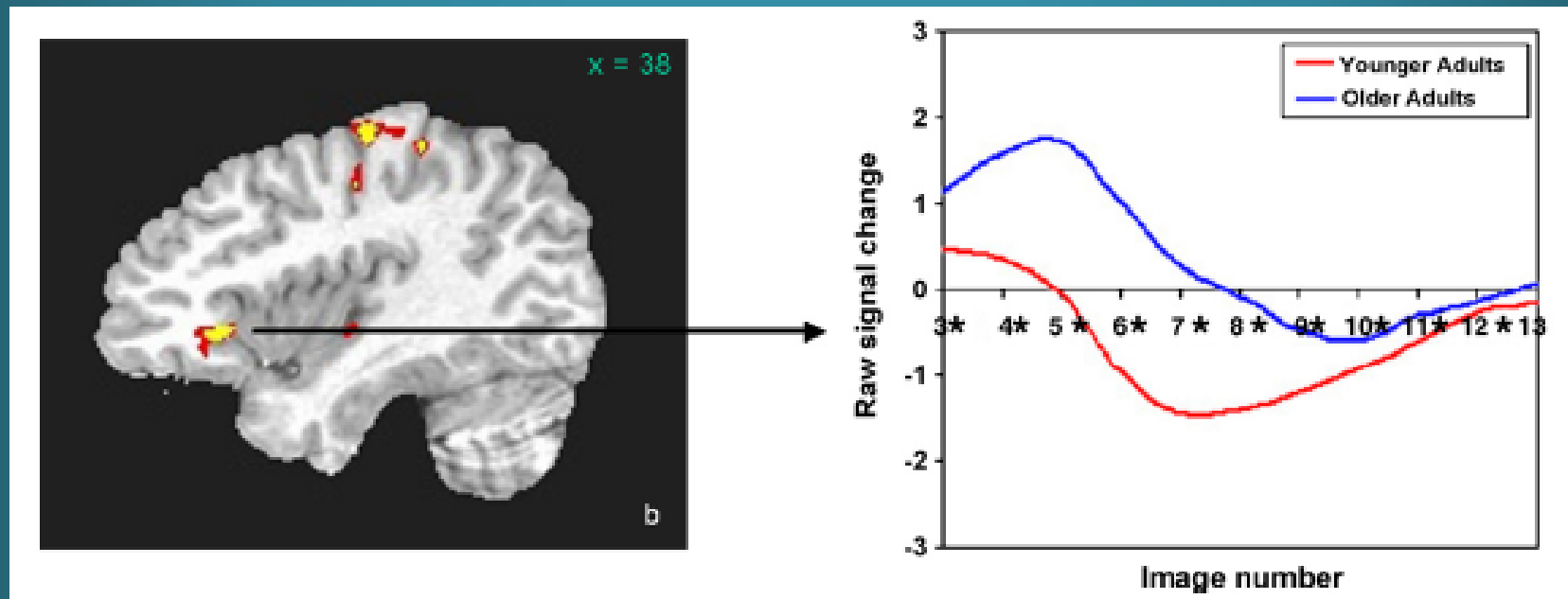
**TABLE 5** | TMS change measures after interventions.

Metric	Spin	Balance	<i>p</i> -value
RMT change	−6.60 (4.1)	−7.18 (5.98)	0.54
<b>iSP change</b>	<b>2.22 (2.96)</b>	<b>−0.41 (2.75)</b>	<b>0.05</b>
pplHI change	−0.01 (0.38)	0.04 (0.11)	0.72

*RMT, Resting motor threshold; iSP, ipsilateral silent period; IHI, paired pulse interhemispheric inhibition. iSP is measured in ms, while IHI is percentage change from baseline pulse to preconditioned pulse. BOLD denotes statistical significance below  $p = 0.05$ .*

## 1. GABA MRS

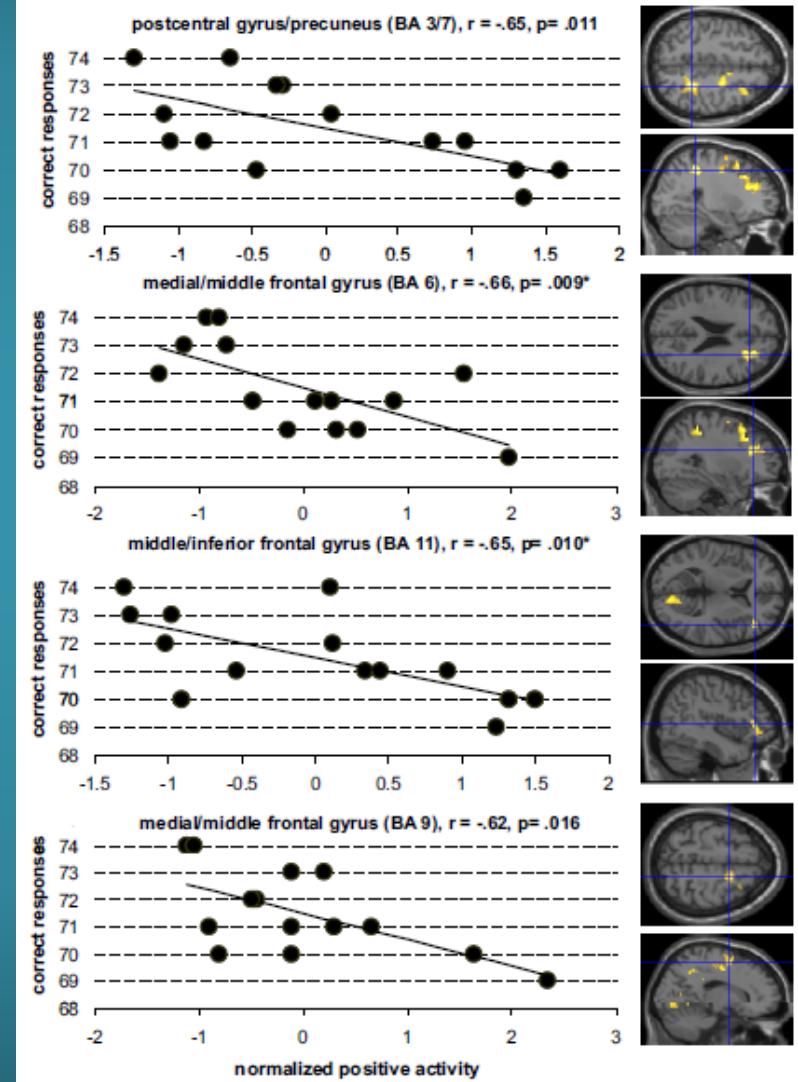
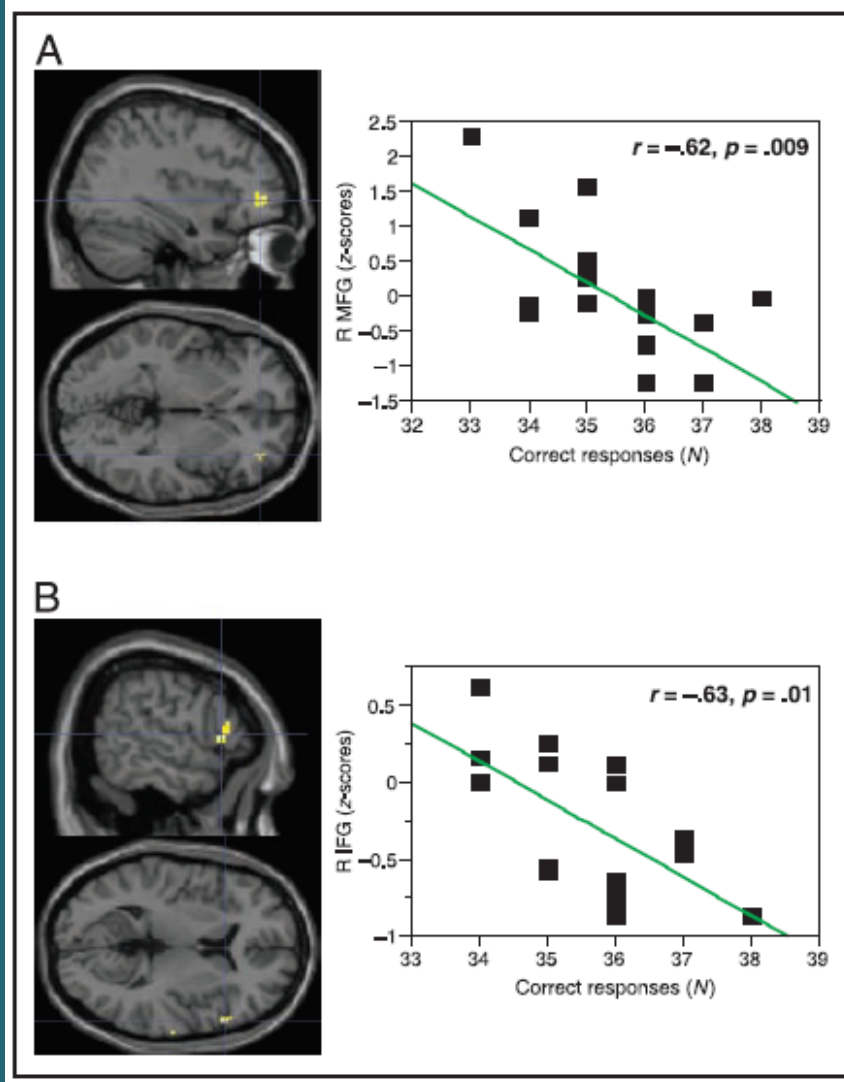
# Negative Activity during Picture Naming in Young Adults Converts to Positive Activity in Old Adults



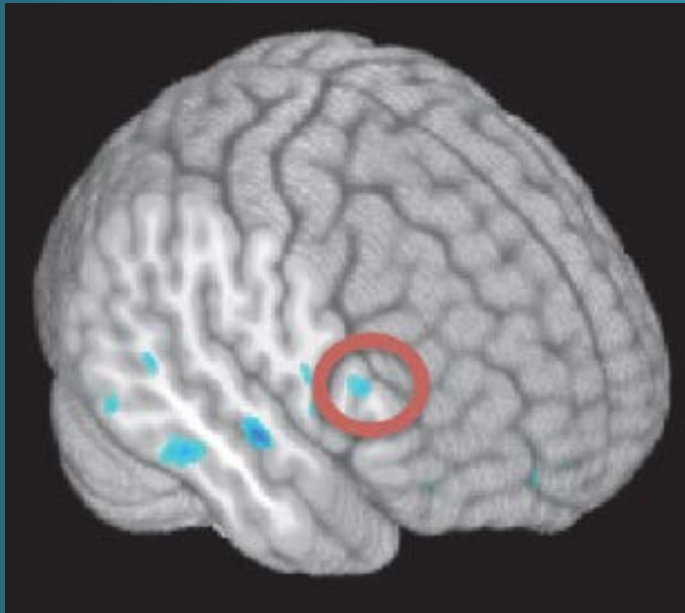
Wierenga et al., *Neurobiology of Aging*, 2008

# 1. GABA MRS

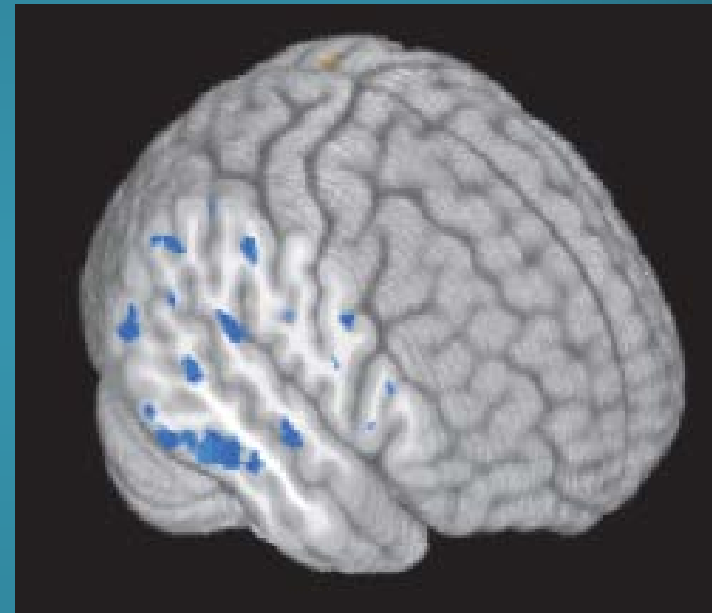
## Increases in BOLD Activity for Older Adults Also Confirmed For Semantic Fluency and Are Negatively Correlated with Accuracy



# Aerobic Exercise decreases BOLD activity during Semantic Fluency



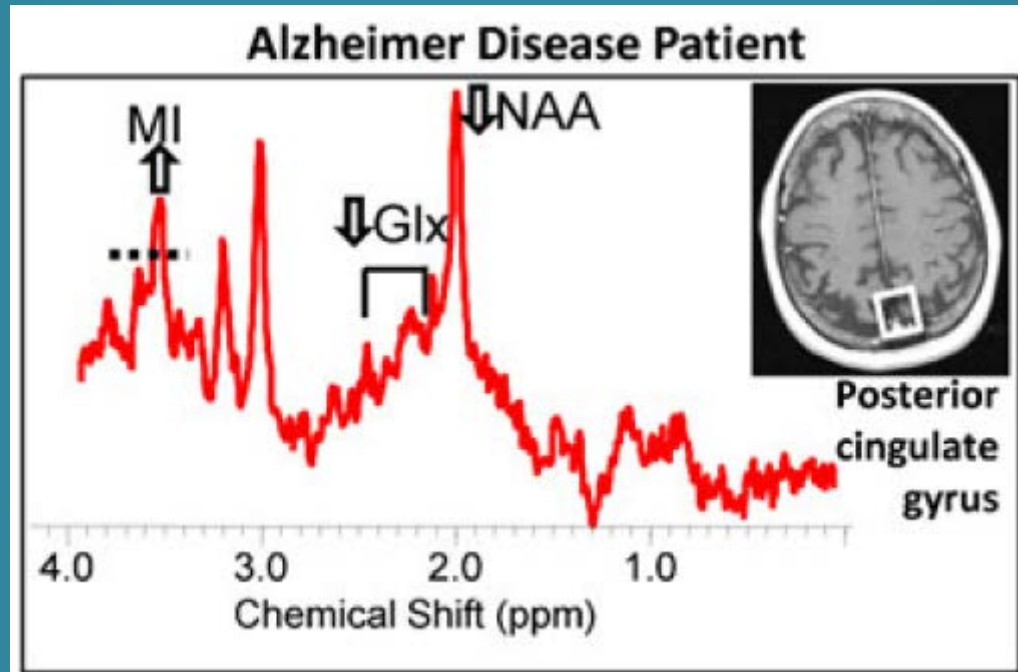
Decrease in BOLD activity during semantic fluency for Aerobic vs Control Intervention



Regression of  $VO_2$  max change on change in BOLD activity change for semantic fluency

## 2. Neuroinflammation with MRS

# Lower glutamate levels in AD may indicate neuroinflammation

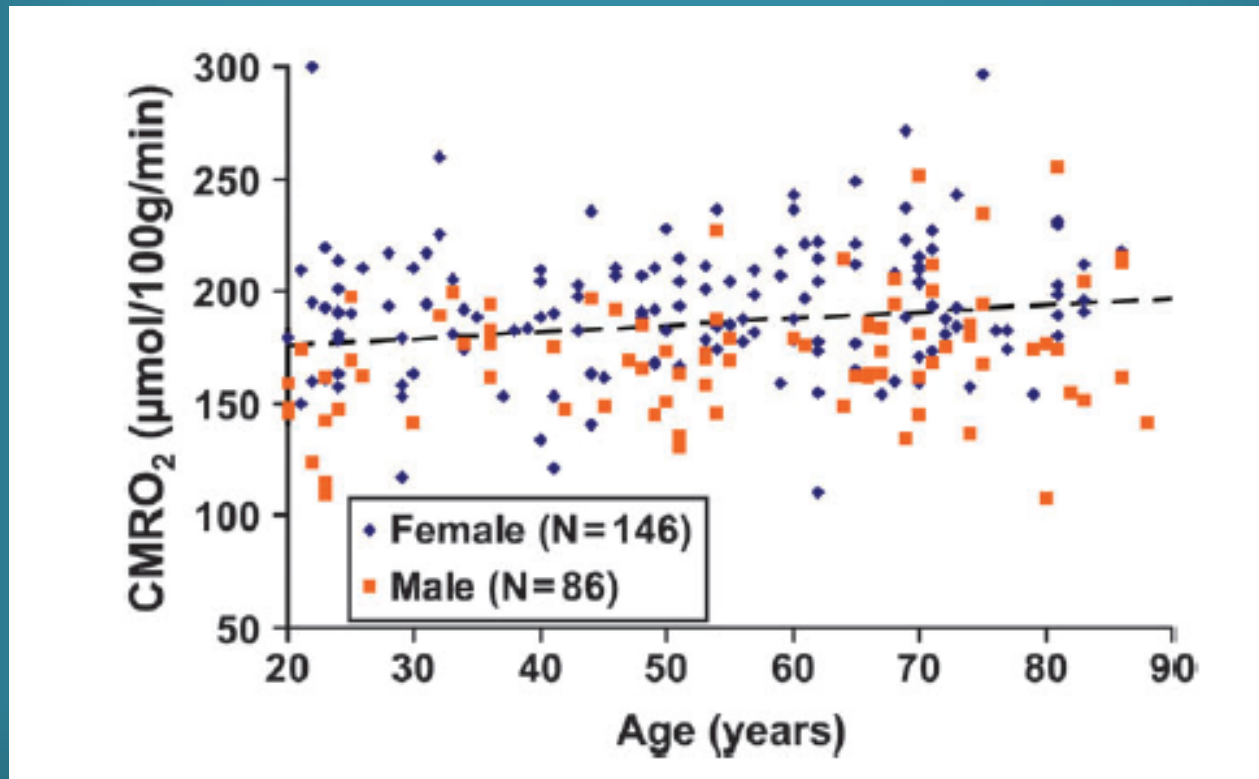


**Table 3** Metabolite abnormalities in selected brain regions evaluated in degenerative brain disorders

Disorder	Myo-inositol, MI/tCr or scyllo-inositol	NAA or NAA/tCr	Creatine or PCr	Choline or Cho/tCr or Cho/NAA	Glutamate, Glu/Cr, Glx or Glx/tCr	GABA
Alzheimer's disease	↑ MI or MI/tCr in Parietal (GM > WM) and temporoparietal region	↓ NAA and NAA/tCr in Parietal GM > WM; ↓ NAA/tCr in hippocampus and anterior temporal lobe (correlated with MMSE, CDR, and clock drawing test)	↓ tCr in PCG and in whole brain GM	no change in PCG or whole brain GM; ↓ Cho/tCr in Hippocampus	↓ Glu/tCr in PCG and hippocampus	not assessed

### 3. Cerebral Metabolic Rate for Oxygen (CMRO<sub>2</sub>)

There is paradoxical increase of CMRO<sub>2</sub> with age (P = 0.0101). Average CMRO<sub>2</sub> of typical 20-year-old subjects is approximately 164.1  $\mu\text{mol}/100\text{g}/\text{min}$ , and it increases with age at rate of 2.6  $\mu\text{mol}/100\text{g}/\text{min}$  per decade.



### 3. Cerebral Metabolic Rate for Oxygen (CMRO<sub>2</sub>)

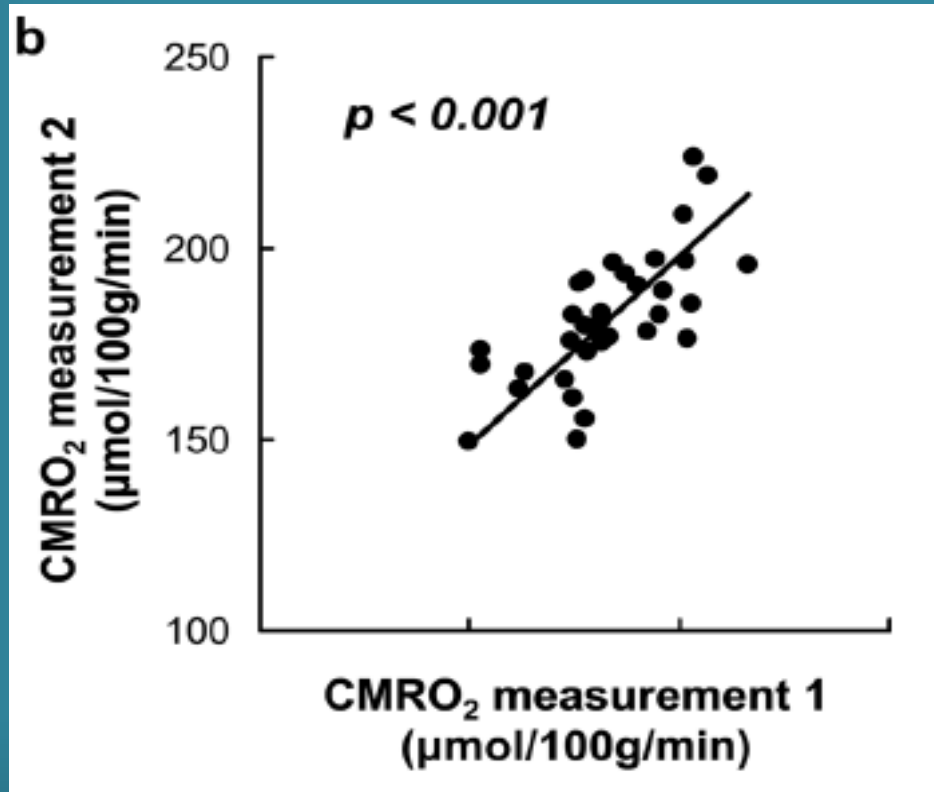
**CMRO<sub>2</sub> is reduced by 11% in aMCI  
compared to normal controls**

<b>aMCI:</b>	<b>113.6 ± 15.7 μmol/100 g/min</b>
<b>normal controls:</b>	<b>127.1 ± 17.1 μmol/100 g/min</b>

### 3. Cerebral Metabolic Rate for Oxygen (CMRO<sub>2</sub>)

Intrasession CoV = 3.84% ± 1.44

Intersession CoV = 6.59% ± 1.56



R = 0.67  
Intrasession

# Medial Temporal Atrophy before Conversion from aMCI to AD

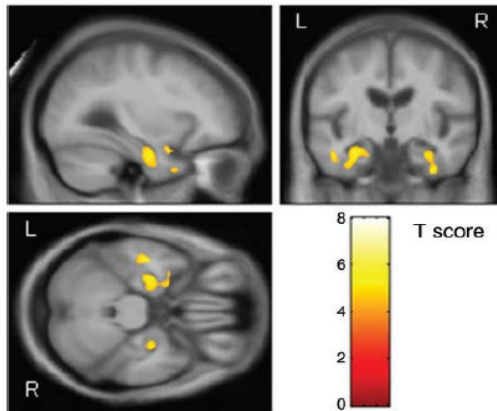


Fig. 2 Patterns of grey matter atrophy in the aMCI progressors ~3 years (18–54 months) before progression to AD. The results are shown on a 3D surface render (top) and overlaid on representative axial, coronal and sagittal slices (bottom). L = left; R = right.

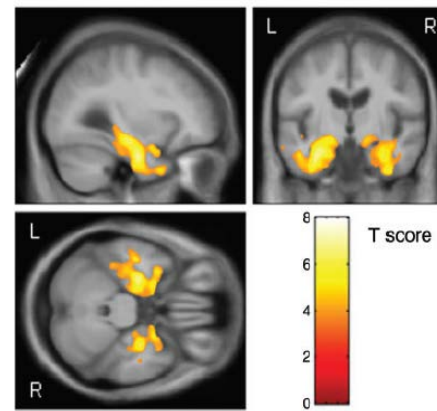


Fig. 3 Patterns of grey matter atrophy in the aMCI progressors ~1 year (9–18 months) before progression to AD. The results are shown on a 3D surface render (top) and overlaid on representative axial, coronal and sagittal slices (bottom). L = left; R = right.

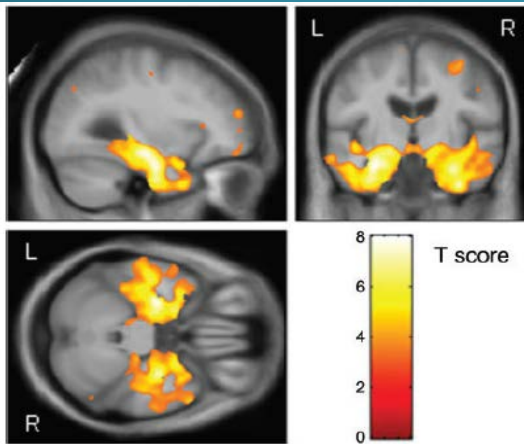
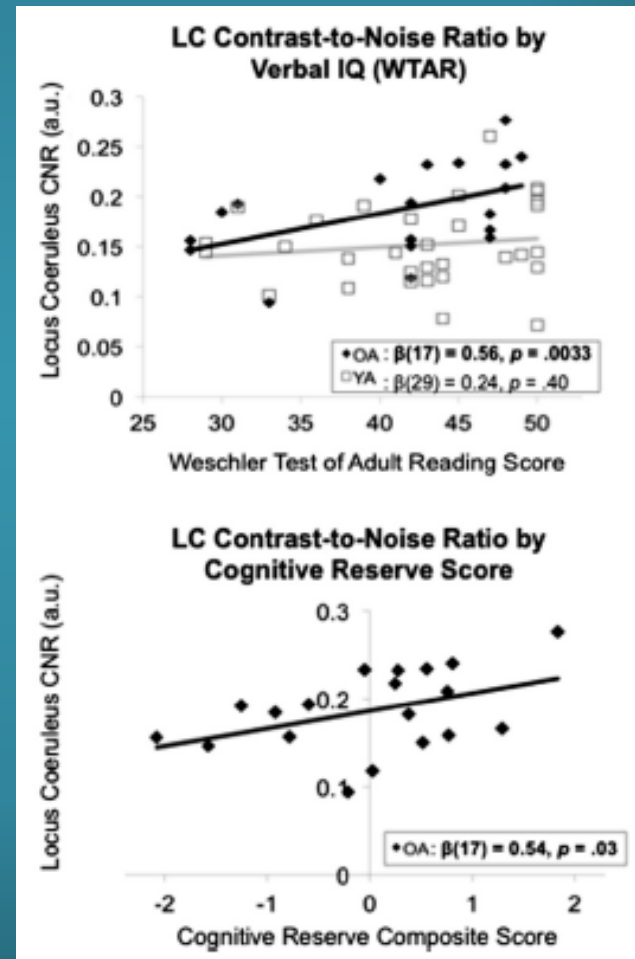
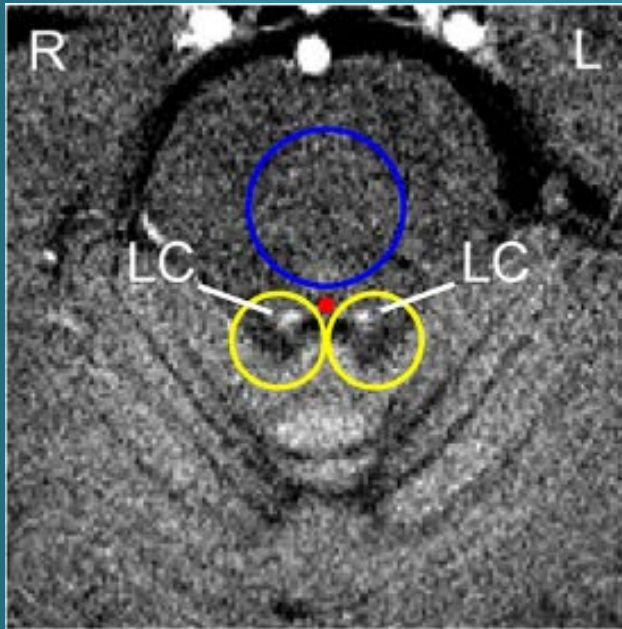


Fig. 4 Patterns of grey matter atrophy in the aMCI progressors at the time of a diagnosis of AD. The results are shown on a 3D surface render (top) and overlaid on representative axial, coronal and sagittal slices (bottom). L = left; R = right.

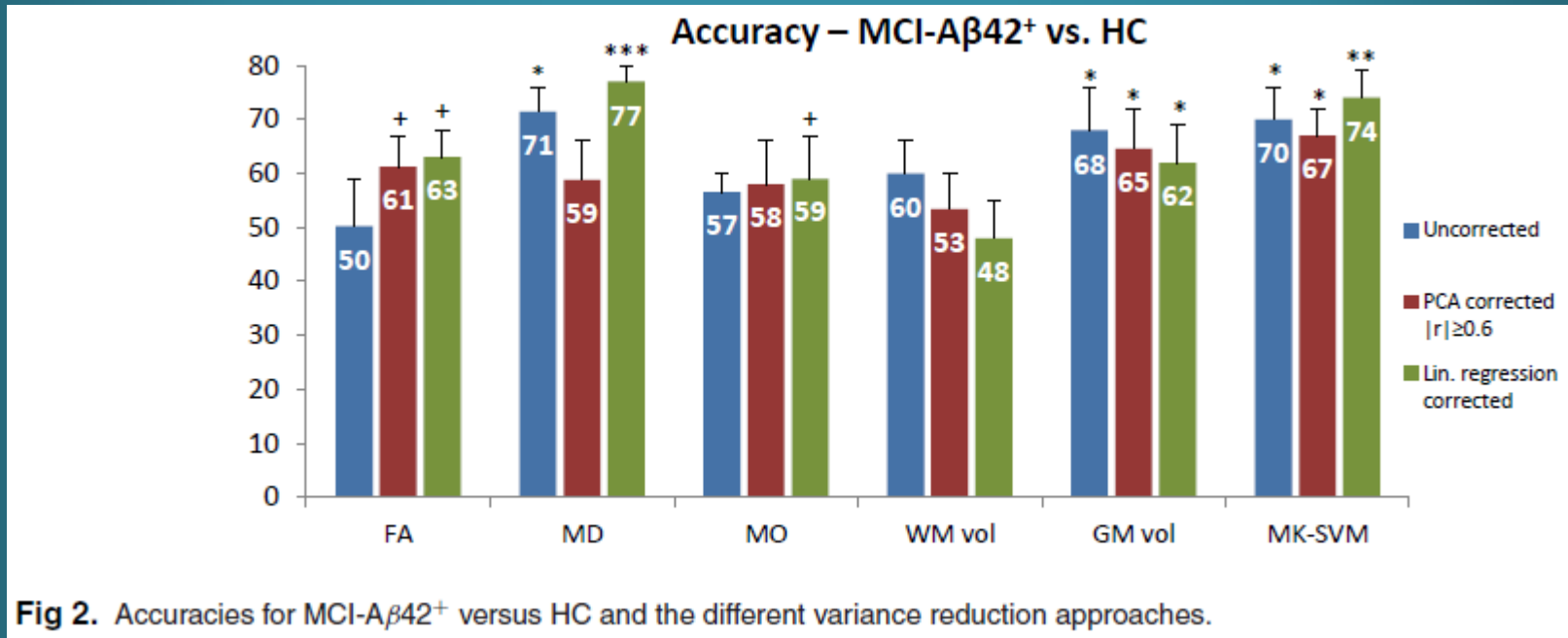
## 5. Neuromelanin Imaging

# Involvement of Locus Coeruleus in Early AD (Ross et al., *Neurobiology of Stress*, 2015)



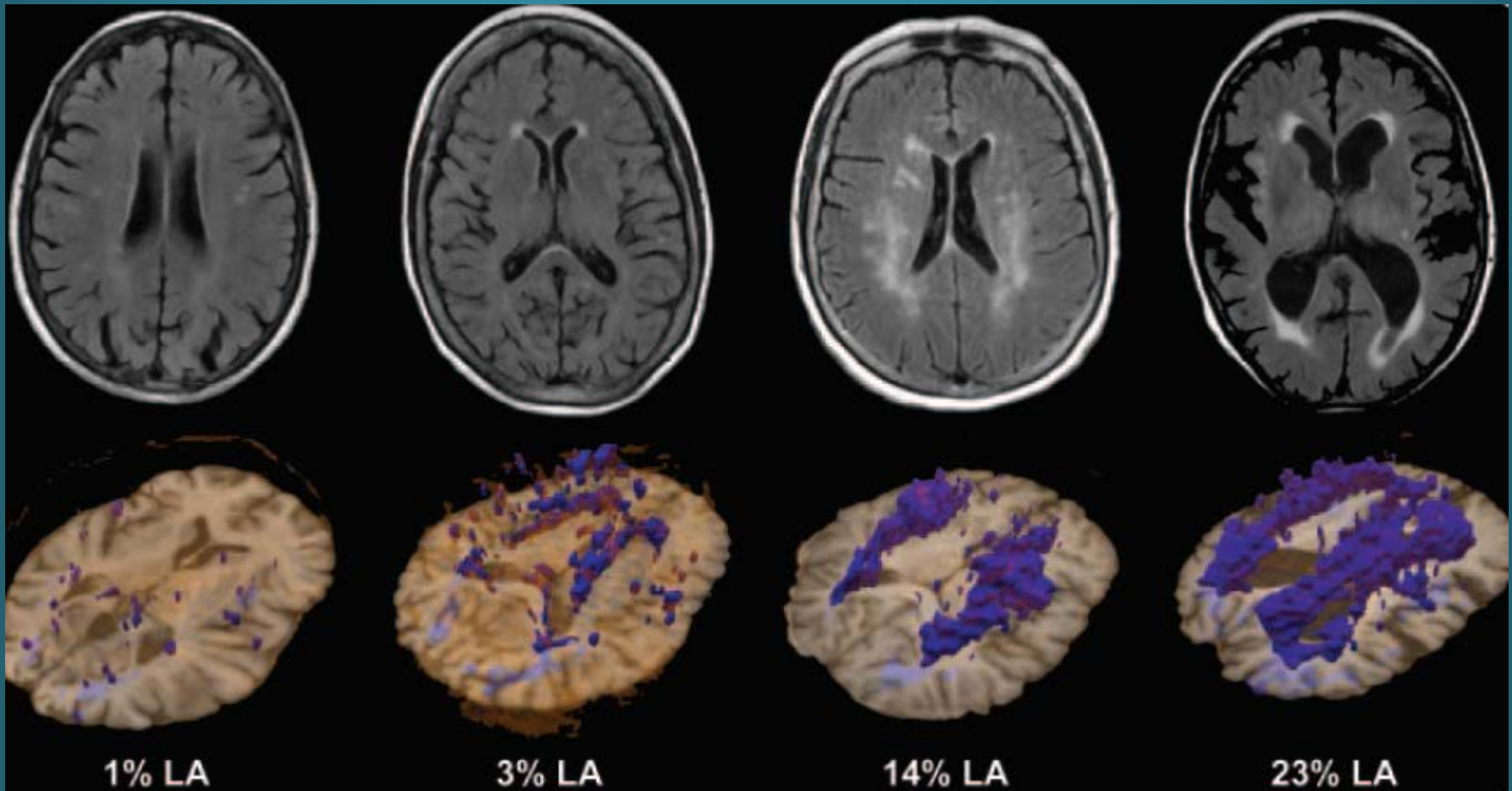
## 6. Diffusion Weighted Imaging (DWI)

Measures derived from DWI have varied in Predicting AD or prodromal AD

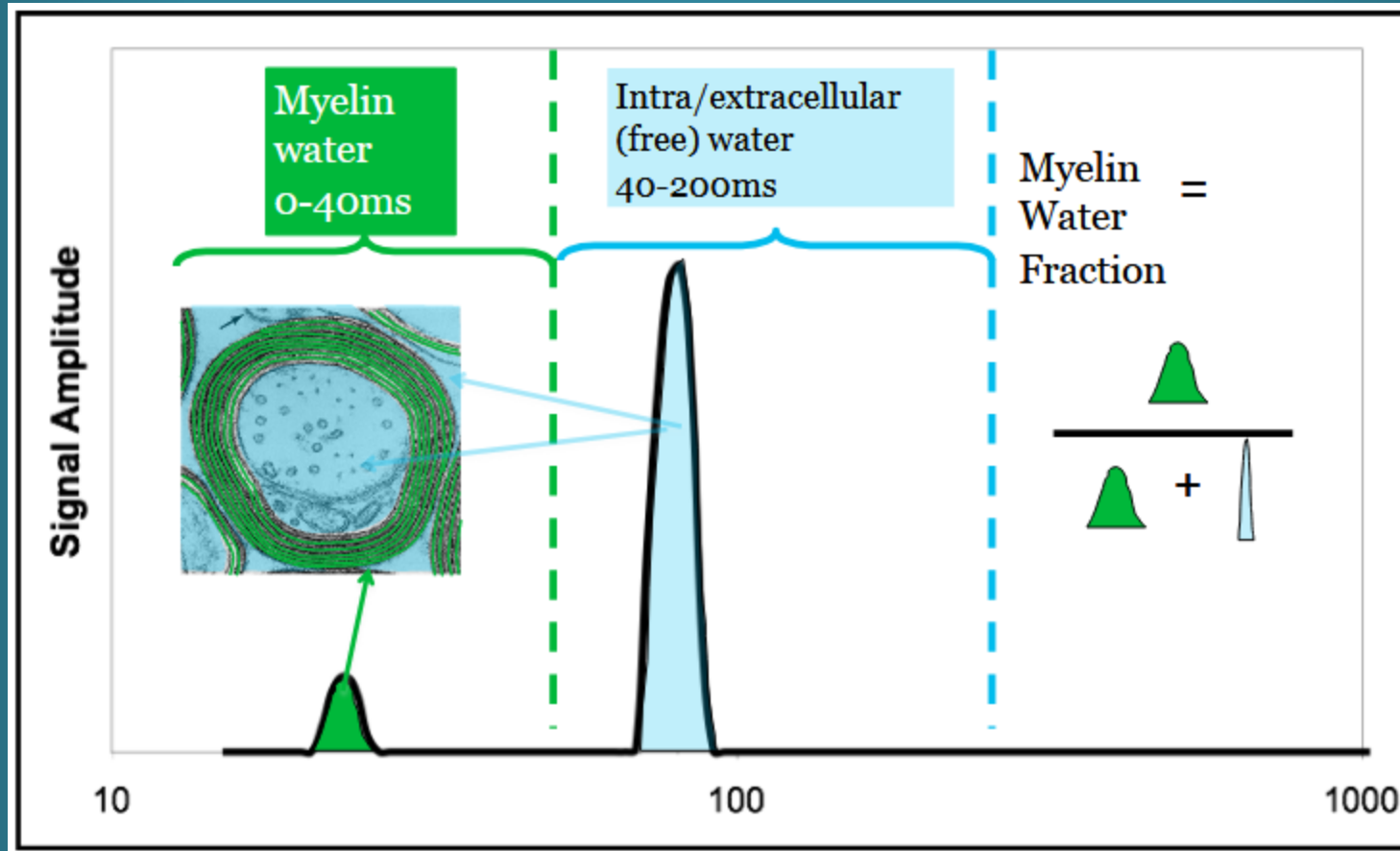


## 7. Fluid Attenuated Inversion Recovery (FLAIR) images

**Leukoaraiosis explains working memory performance  
After 3% involvement and visuoconstructional  
Impairment after 14% involvement**



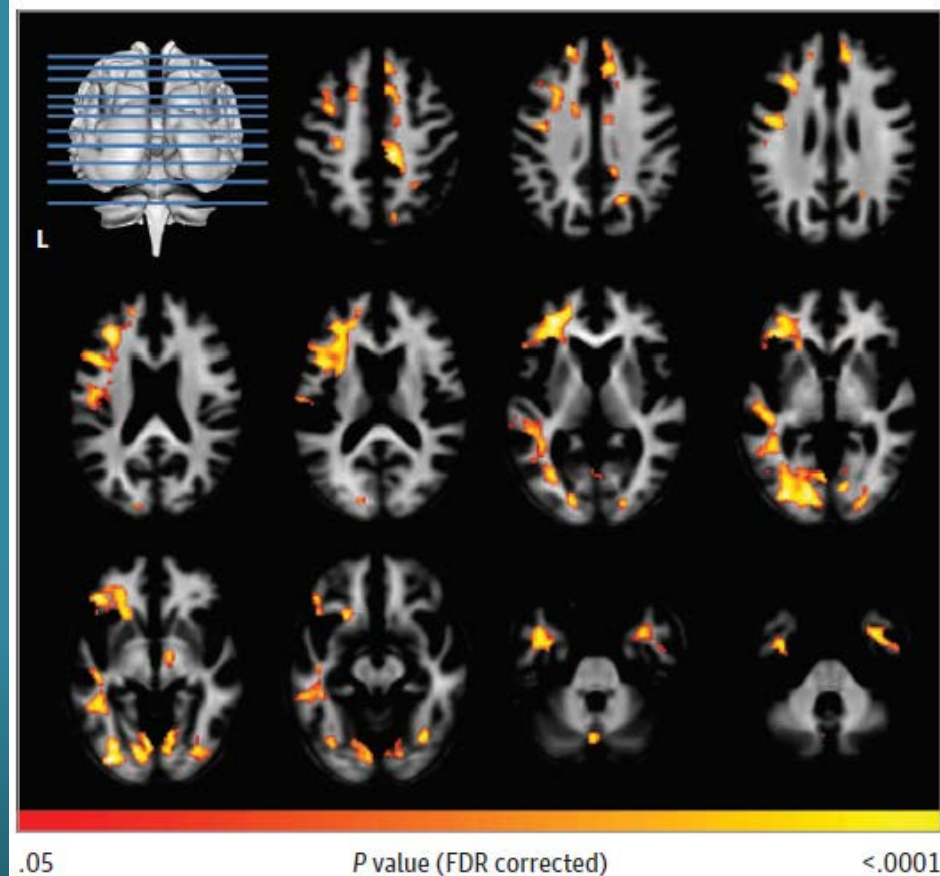
# 8. Myelin Water Fraction (MWF)



## 8. Myelin Water Fraction

High levels of Amyloid Precursor Protein are associated with decline in MWF in cognitively normal older adults

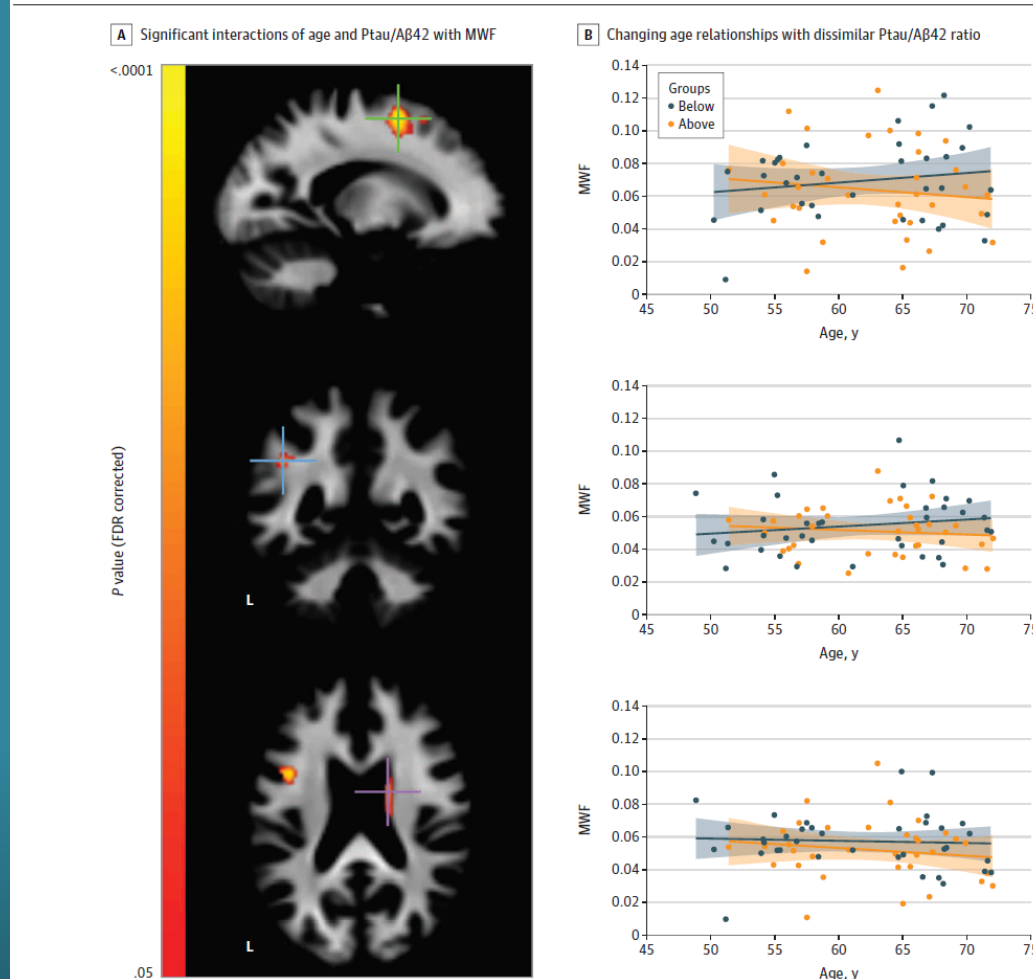
Figure 2. Regional White Matter Myelin Content, as Measured by Myelin Water Fraction (MWF), Associated With Soluble Amyloid Precursor Protein/ $\beta$ -Amyloid 42 (sAPP $\beta$ /A $\beta$ 42)



## 8. Myelin Water Fraction

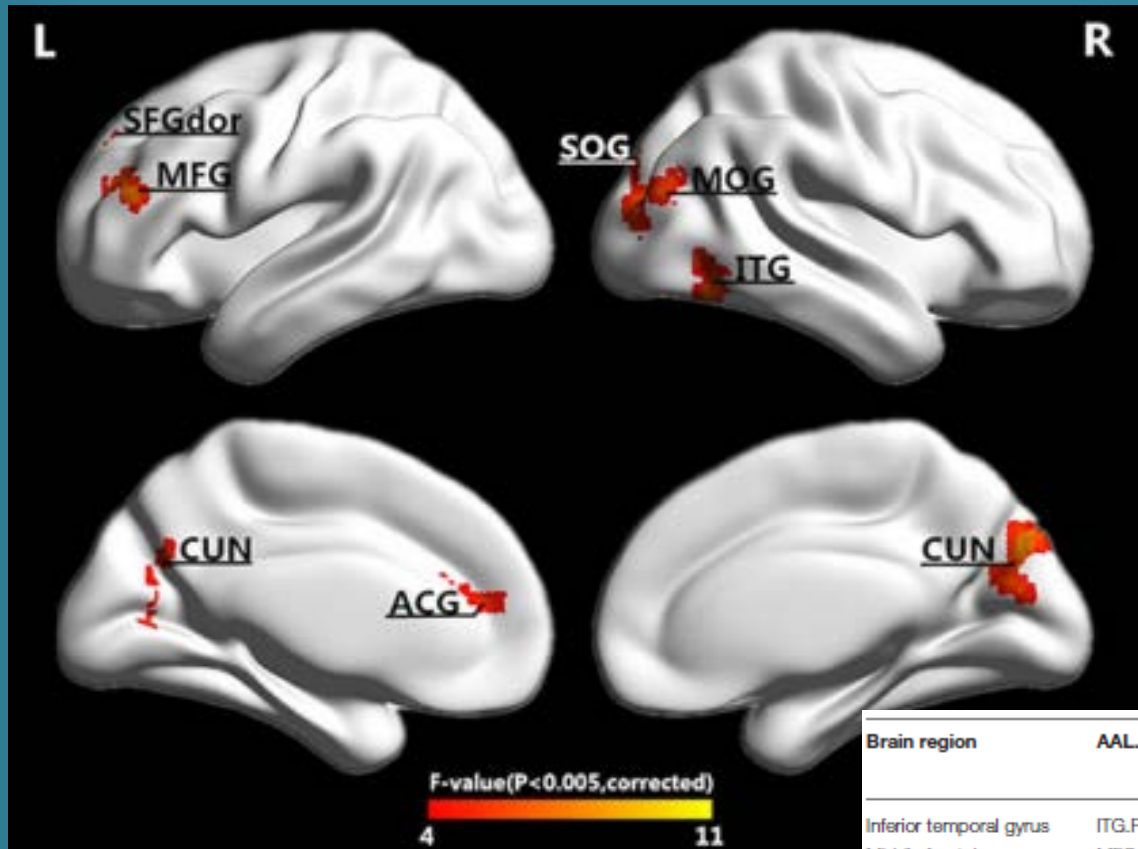
# Higher levels of phosphorylated tau lead to increased decline in MWF with increasing age

Figure 4. Levels of Phosphorylated Tau (Ptau181)/ $\beta$ -Amyloid 42 (A $\beta$ 42) Moderate Age-Related Changes of Myelin Water Fraction (MWF)



## 9. Resting-state fMRI

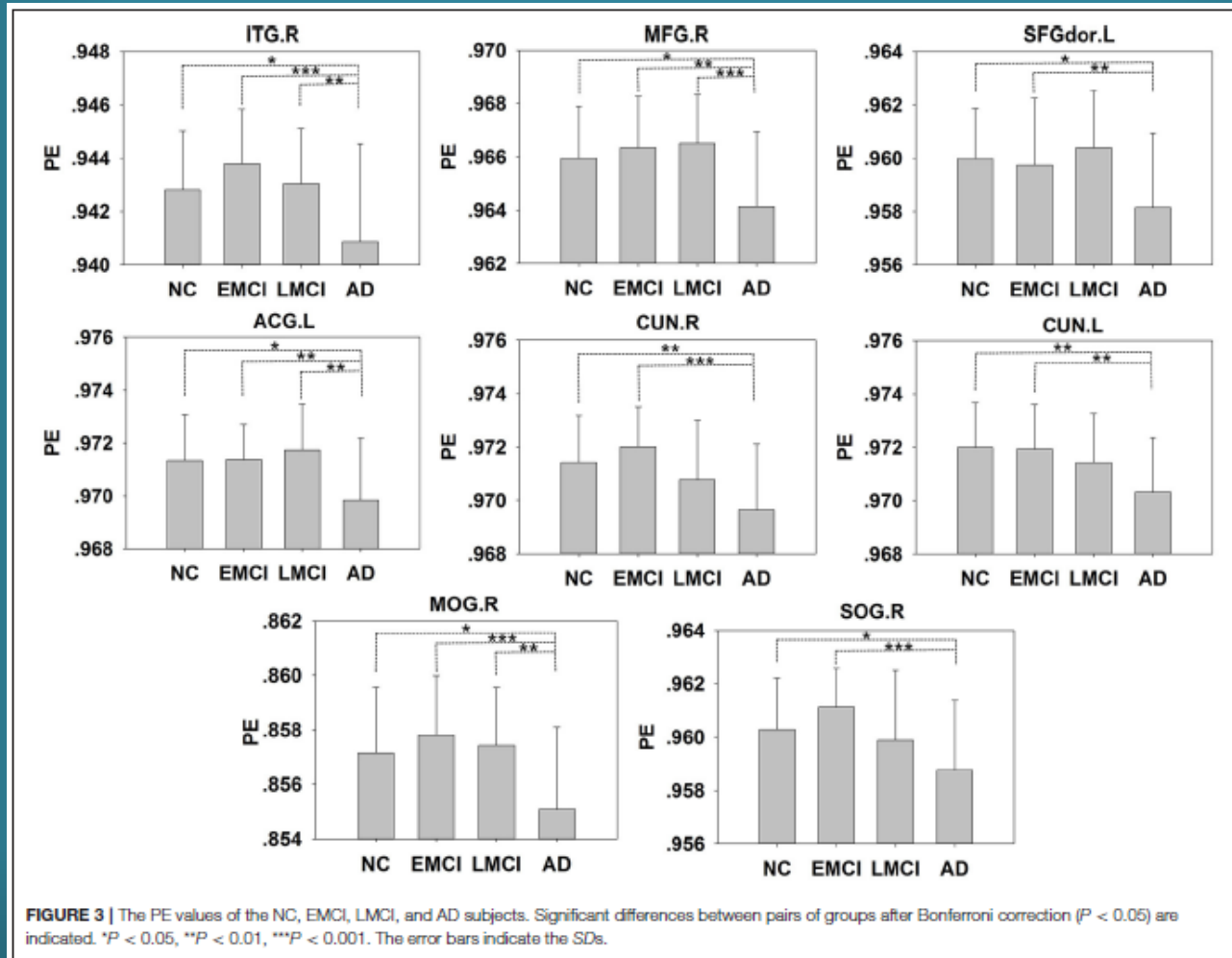
# Significant differences in Permutation Entropy: Control vs Early MCI vs Late MCI vs AD



Brain region	AALAbbr	Peak MNI (X, Y, Z)	Cluster voxels	Voxel F value
Inferior temporal gyrus	ITG.R	(51, 63, 15)	117	8.15
Middle frontal gyrus	MFG.L	(-33, 41, 24)	278	10.82
Superior frontal gyrus	SFGdor.L			
Anterior cingulate gyrus	ACG.L	(-12, 44, 15)	59	8.13
Right cuneus	CUN.R	(12, 78, 30)	126	8.61
Left cuneus	CUN.L			
Middle occipital gyrus	MOG.R	(45, 78, 21)	201	8.42
Superior occipital gyrus	SOG.R			

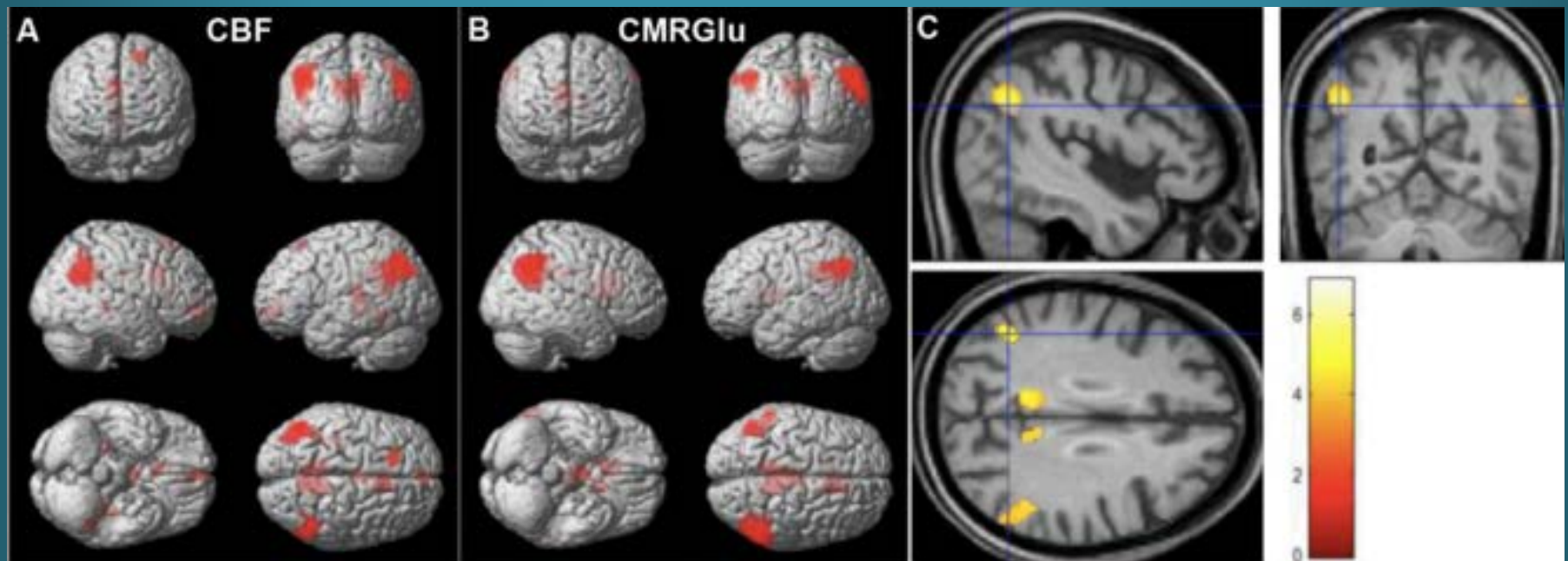
## 9. Resting-state fMRI

# Permutation Entropy distinguishes AD from Controls, Early MCI, and Late MCI



## 10. Arterial Spin Labeling (ASL)

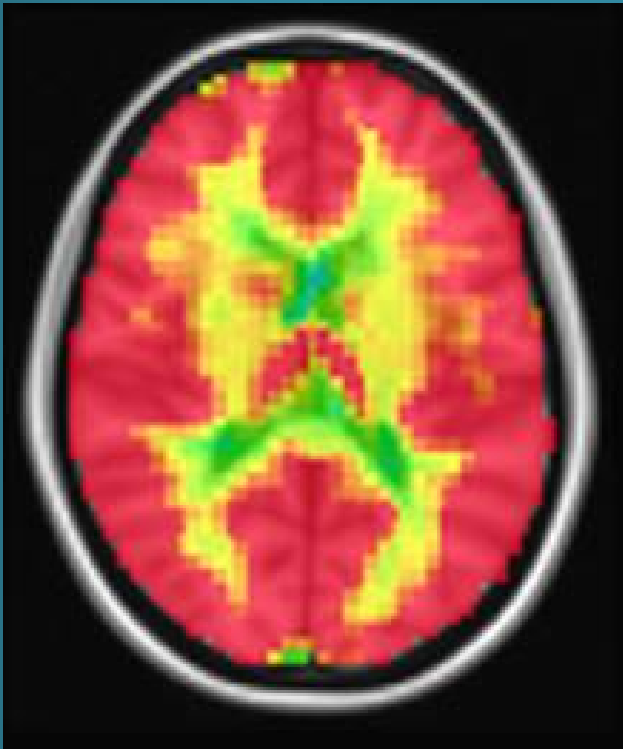
# ASL correlates with FDG PET in AD



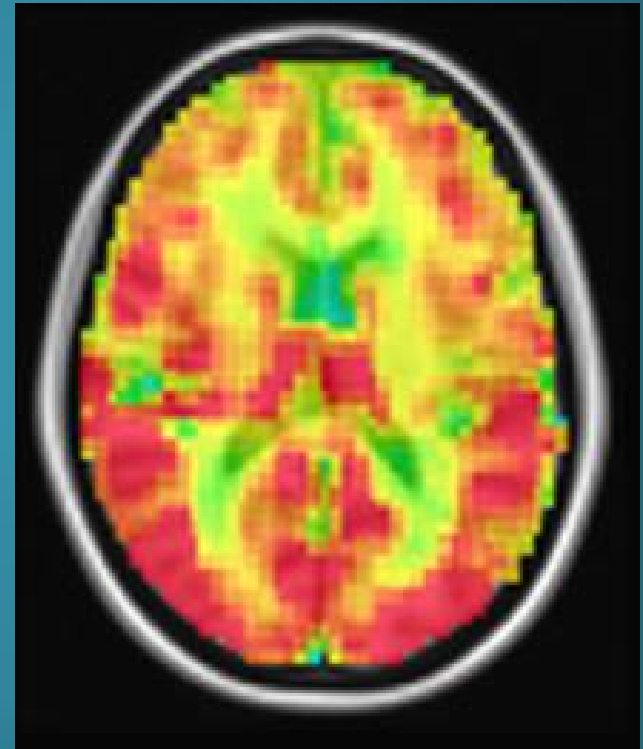
Wolk & Detre, *Current Opinion in Neurology*, 2012

## 10. Arterial Spin Labeling (ASL)

**Older persons show decreased CBF especially in frontal cortex**



Young

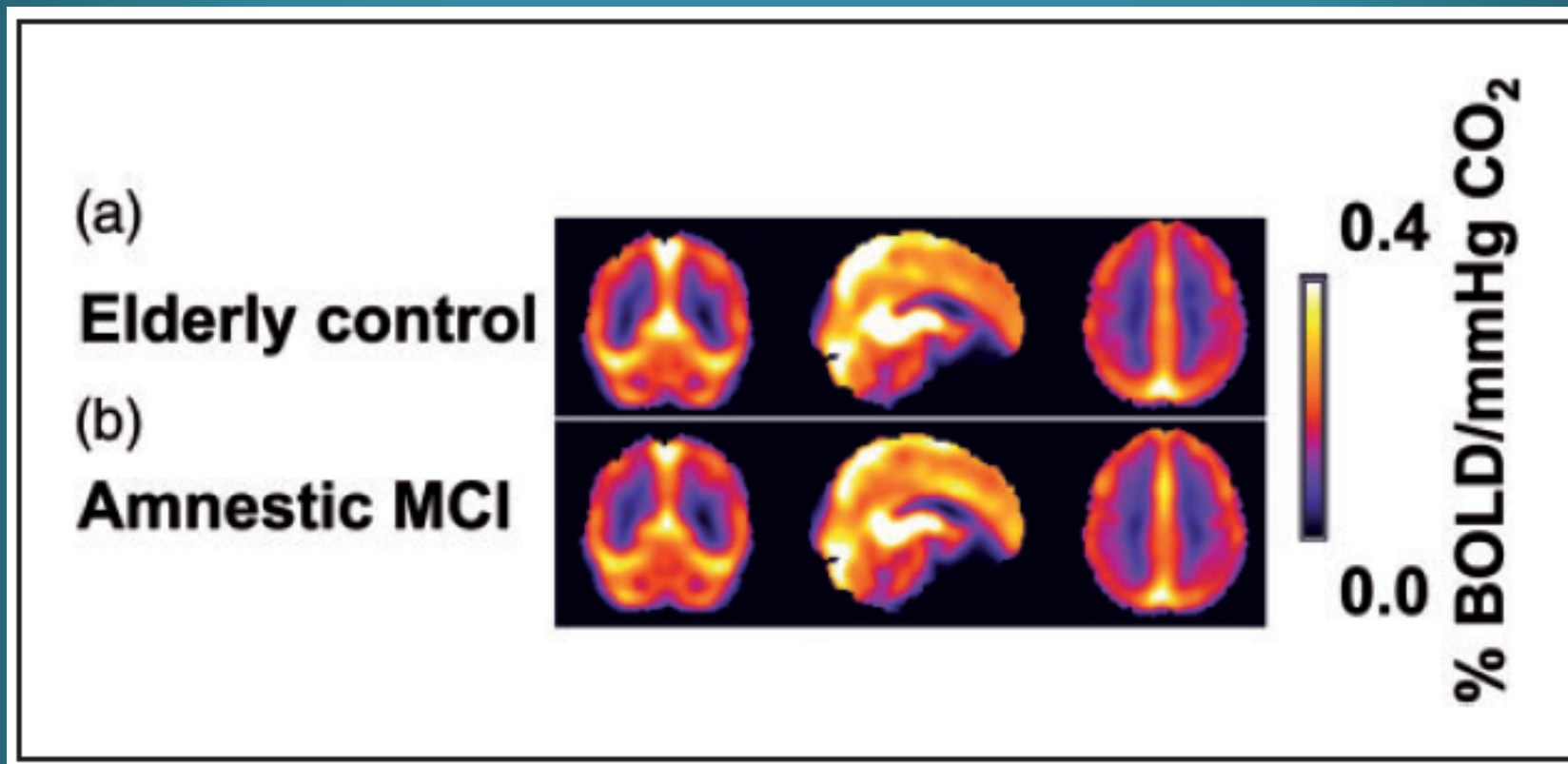


Old

Courtesy of Lisa Krishnamurthy

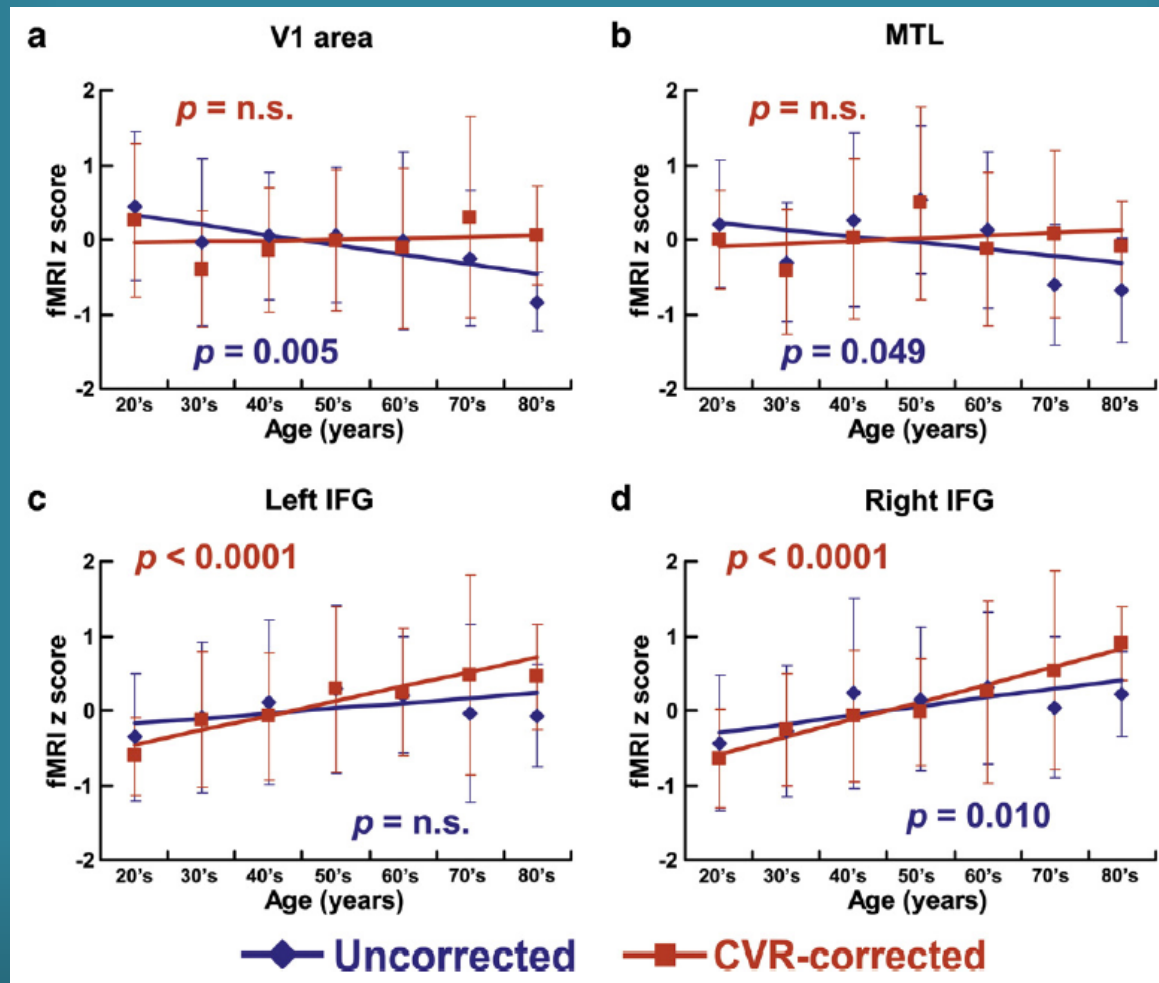
## 11. Cerebrovascular Reactivity (CVR)

One recent study showed no difference in CVR between aMCI and controls



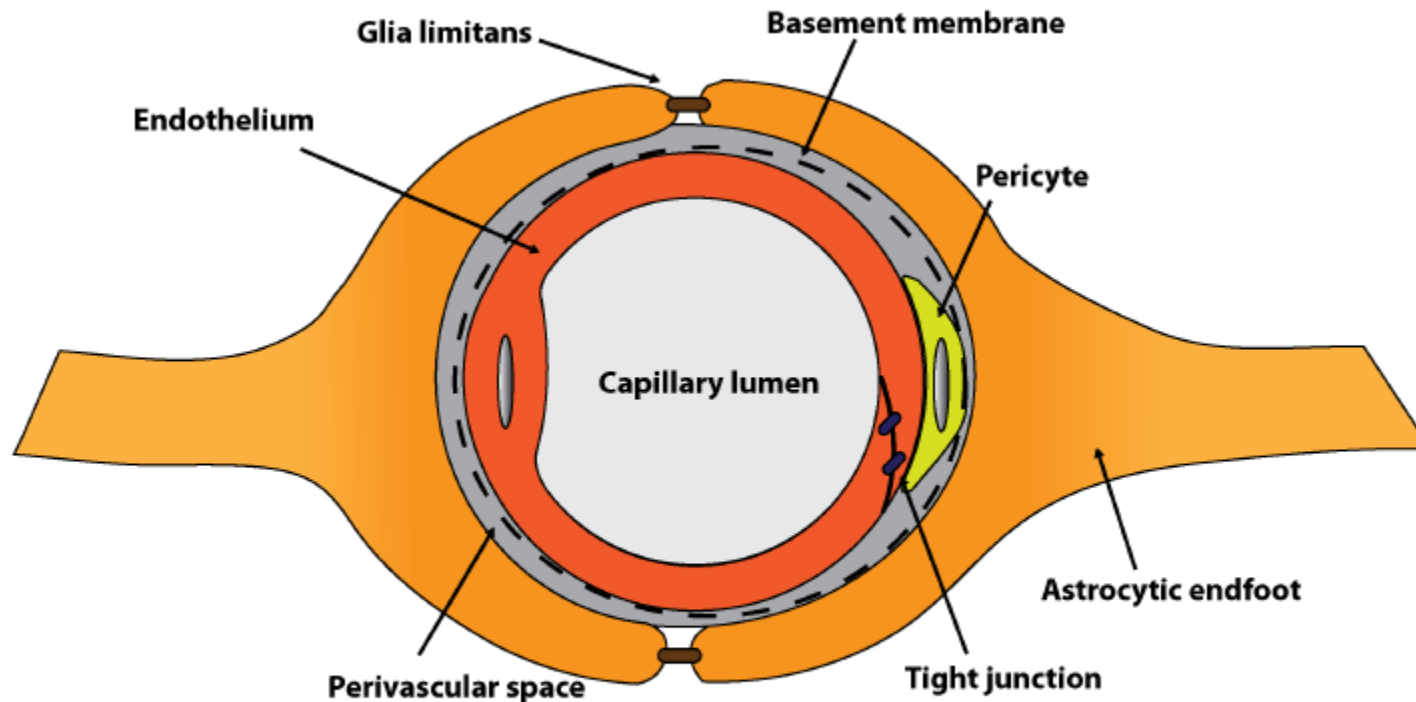
## 11. Cerebrovascular Reactivity (CVR) (CVR)

# Correcting for CVR Differences in Aging Studies



## 12. Dynamic Susceptibility Contrast (DSC)

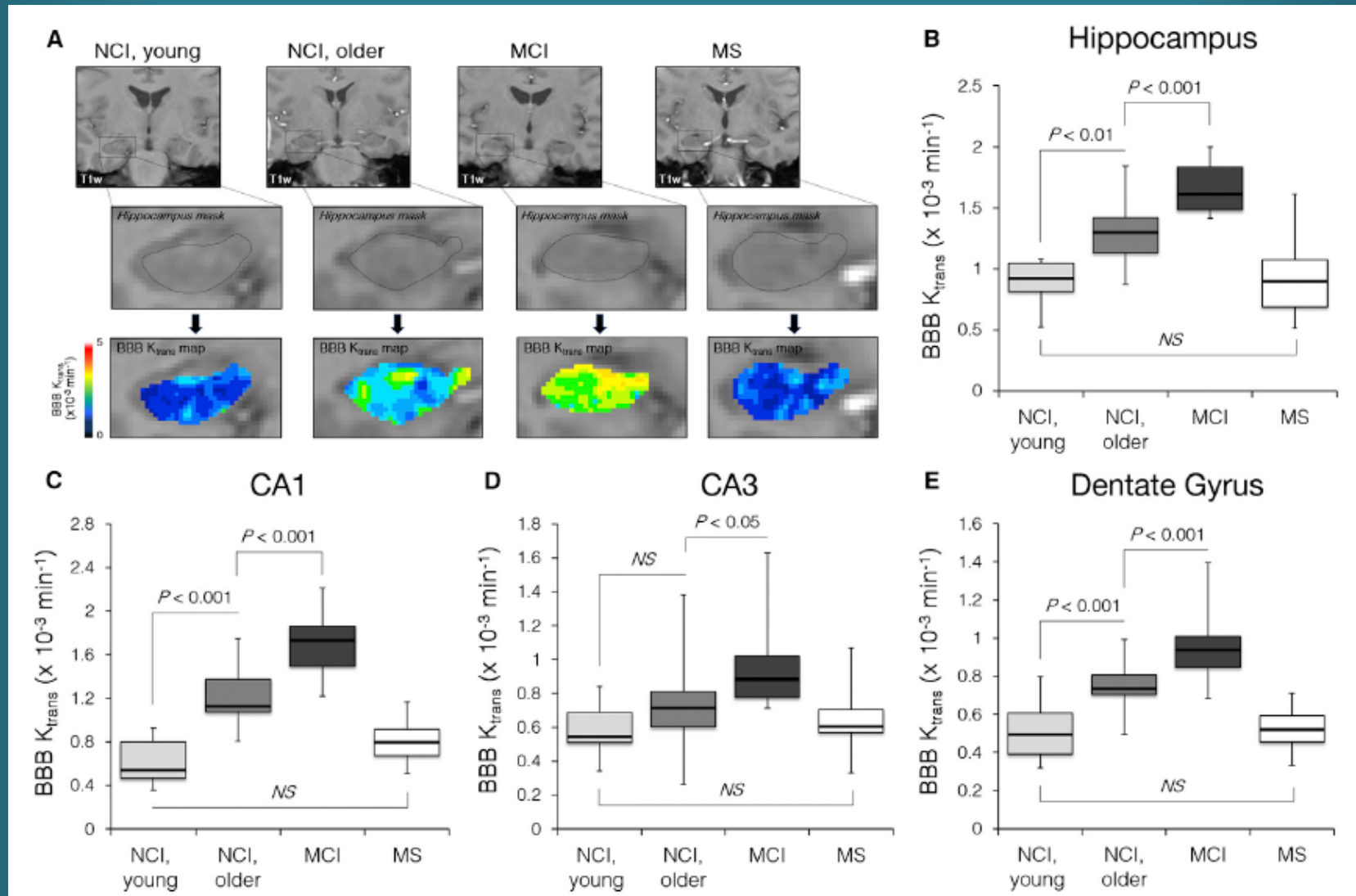
# Blood-Brain Barrier



**Fig 1. Schematic of the NVU.** The NVU comprises the cerebral microvascular endothelium (shown in red), its basement membrane, and associated pericytes (yellow) and astrocytes (orange). The perivascular space exists between the endothelium and astrocytic endfeet. The endothelium provides the structural and functional basis for the blood–brain barrier (BBB), while astrocytes and pericytes control barrier induction and maintenance [7]. Junctional proteins exist between endothelial cells and astrocytes (glia limitans) to help regulate entrance into the CNS parenchyma. *Image credit: Gareth R. John & Benjamin M. Laitman.*

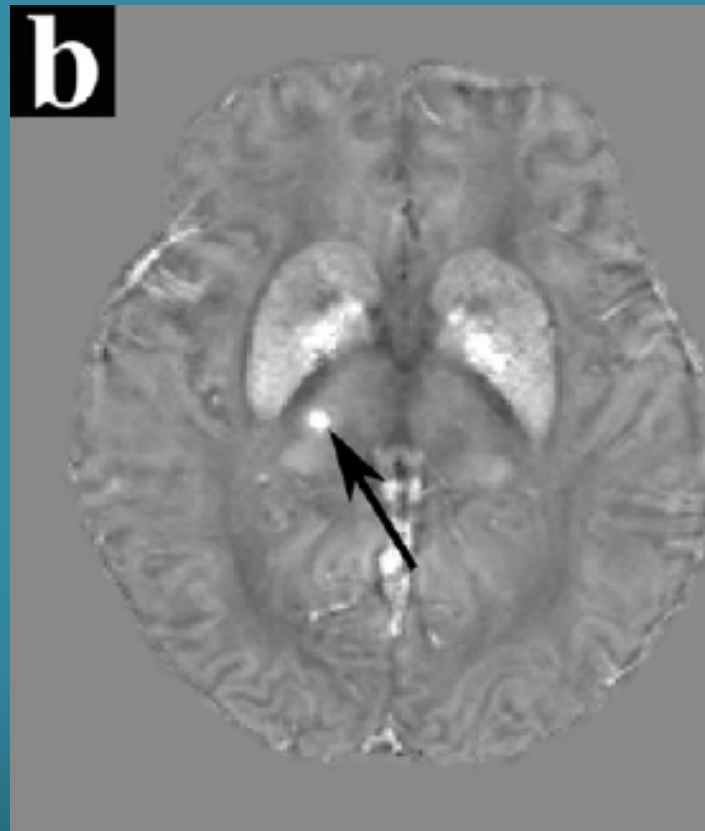
## 12. Dynamic Susceptibility Contrast (DSC)

# Blood-Brain Barrier breakdown occurs early in aging



### 13. Quantitative Susceptibility Mapping (QSM)

QSM can be used to assess microbleeds



Cronin et al., *NeuroImage*, 2017

## 13. Quantitative Susceptibility Mapping

But, QSM also can be used to measure tissue iron concentrations after removing large microbleeds and vessels

