# *Cranial Hemodynamics assessed with MRI: An introduction with relevance to AD*

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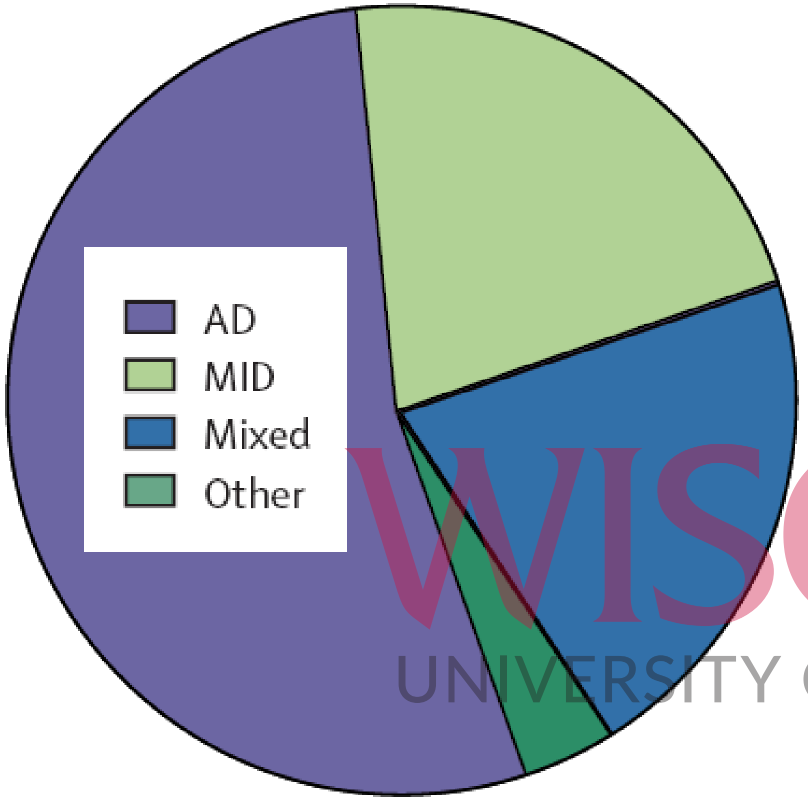
## Overview

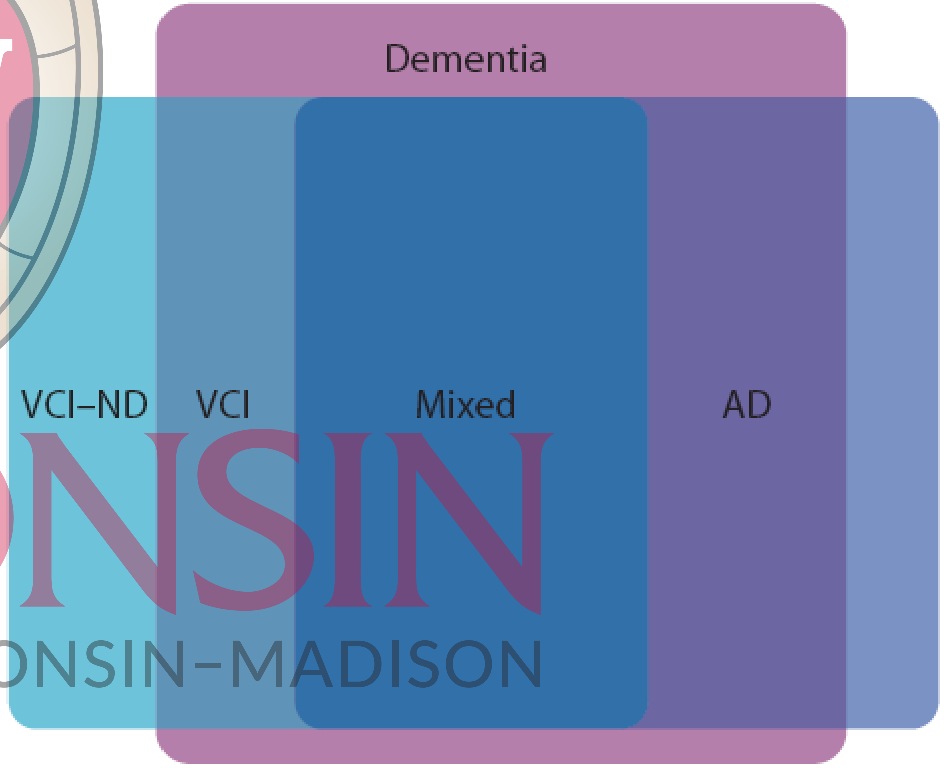
- **Clinical Introduction** to vascular disease and Alzheimer's
  - —Laura Eisenmenger, Assistant Professor, Radiology
- **Perfusion measures** using Arterial Spin Labeling
  - —Kevin Johnson, Assistant Professor, Medical Physics and Radiology
- Study of **vascular-tissue biomechanics**
  - —Leonardo Rivera-Rivera, Postdoctoral Fellow
- **Tissue properties** using Magnetic Resonance Elastography
  - —Grant Roberts, PhD Candidate, Medical Physics

# Contribution of Vascular Disease to Dementia

**Traditional**




**Revised**

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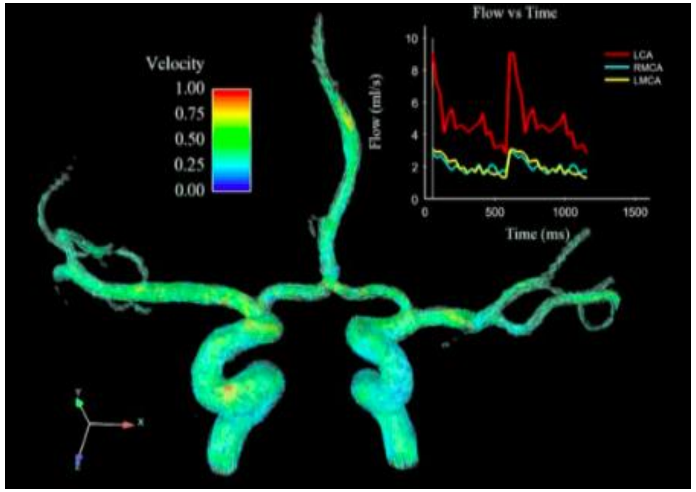
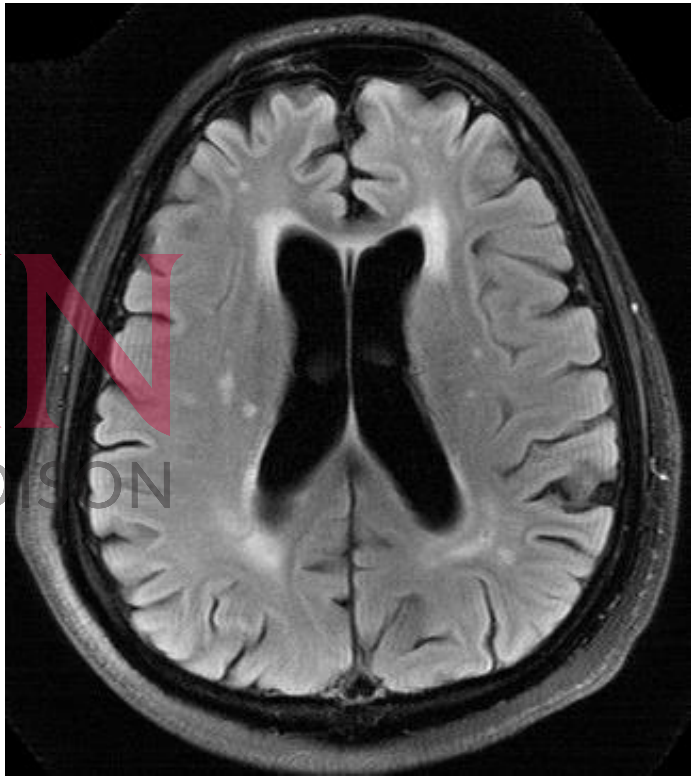
Moorhouse et al. Vascular cognitive impairment: current concepts and clinical developments. *Lancet Neurology*. 2008.

# Alzheimer's Disease and Cerebrovascular Disease (CVD)

- Vascular disease is associated with increased risk of dementia
- Hypotheses suggest CVD is present in prodromal AD and maybe involved in the evolution of AD
- AD – CVD hypotheses need testing:
  - Additive, causative, AND/OR combinatorial effects ?
  - Will CVD biomarkers improve early diagnosis of dementia?
- Challenging to assess with current vascular disease measures



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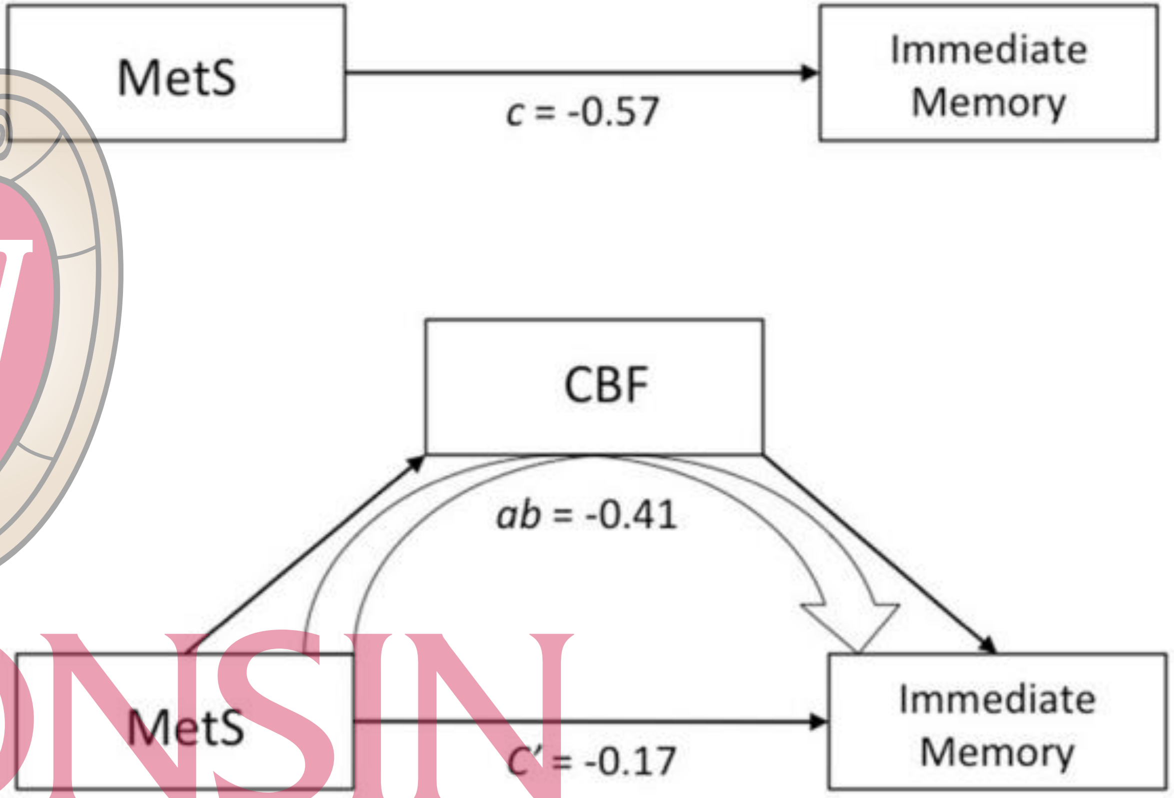
# Vascular Disease Related Risk Factors

Hypertension (in midlife)
High body mass index (in mid- and latelife)
Hyperhomocysteinaemia
Diabetes
Orthostatic hypotension
Weight loss (in late life)
Physical exercise
Smoking
Sleep
Cerebrovascular disease
Atrial fibrillation
Stress

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Yu et al. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *Cognitive neurology.* 2020.

Birdsill et al. Low cerebral blood flow is associated with lower memory function in metabolic syndrome. *Obesity.* 2013.

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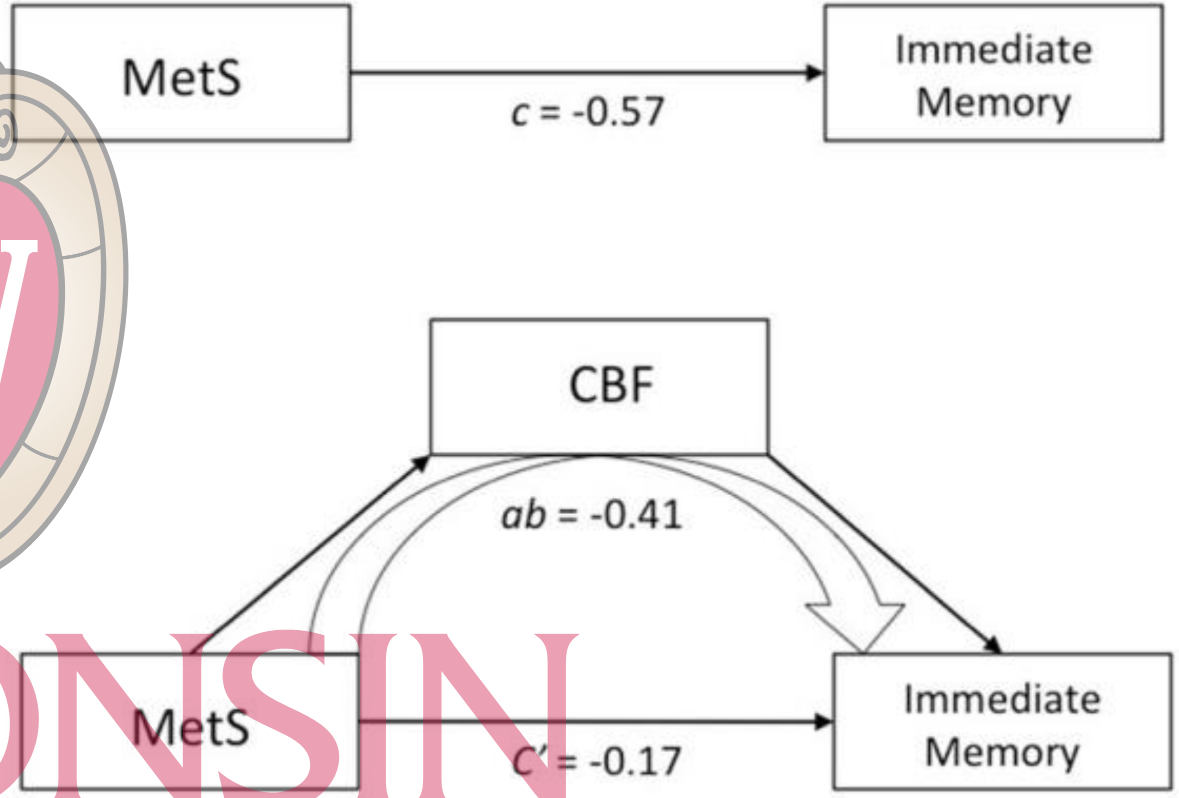


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# Role of Imaging in Dementia

- Identify treatable causes / exclude alternate diagnoses
  - Metabolic
  - Infectious
  - Neoplastic
  - Hydrocephalus
  - Post-traumatic --- etc.

- Refine likely substrate(s) for dementia
  - Degenerative – identify regional patterns

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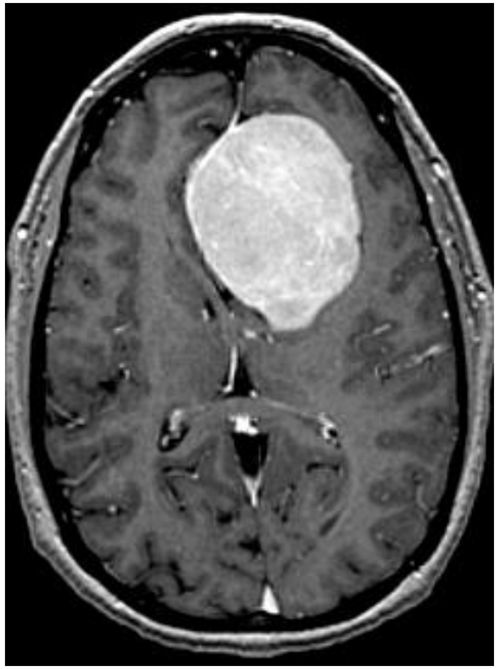
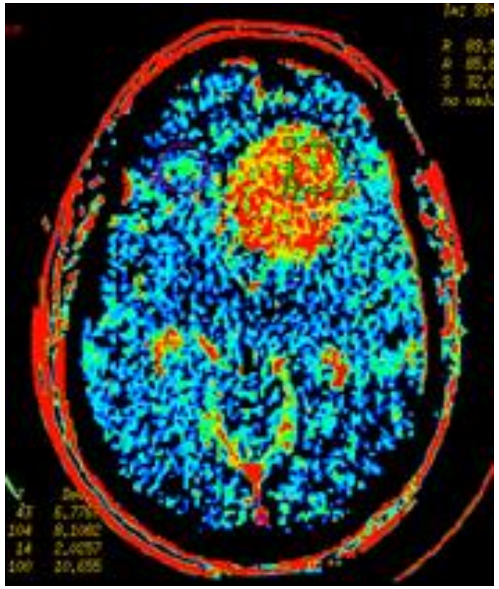
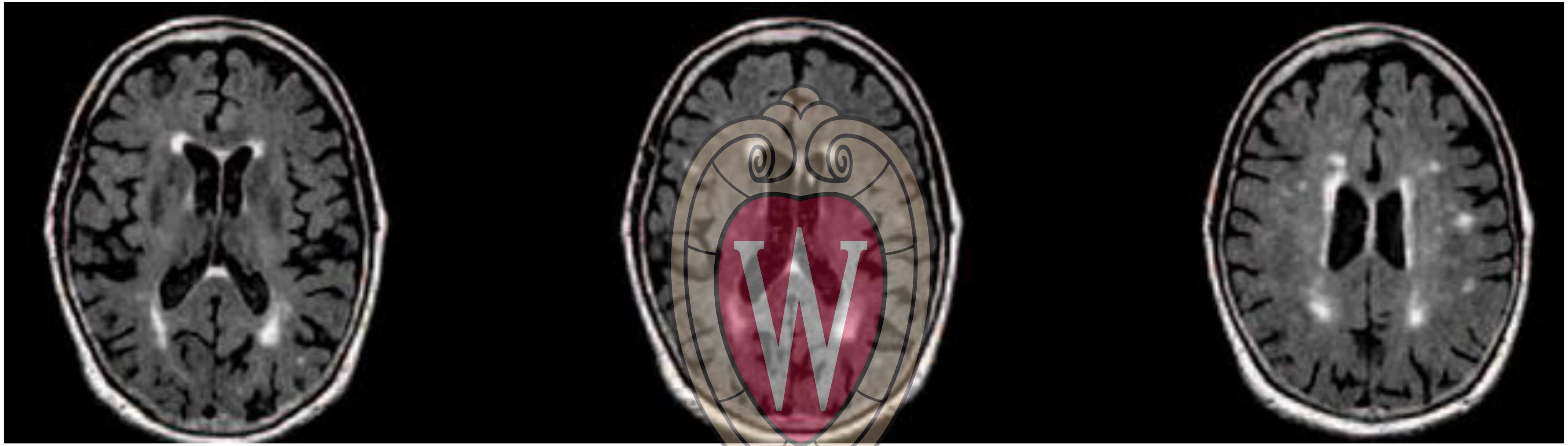




# White Matter Hyperintensities



- Commonly see white matter hyperintensities with age
- Marker of vascular disease?
  - Deep white matter/subcortical: chronic small vessel ischemic
  - Periventricular: relates to a combination of demyelination, ependymitis granularis, and subependymal gliosis, less closely tied with ischemia

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# White Matter Hyperintensities

- Are all WMHs the same?
- Multiple types of pathology are bright on T2
  - Ischemia / gliosis
  - Damage to small blood vessel walls
  - Breaches of the barrier between the cerebrospinal fluid and the brain
  - Loss and deformation of the myelin sheath

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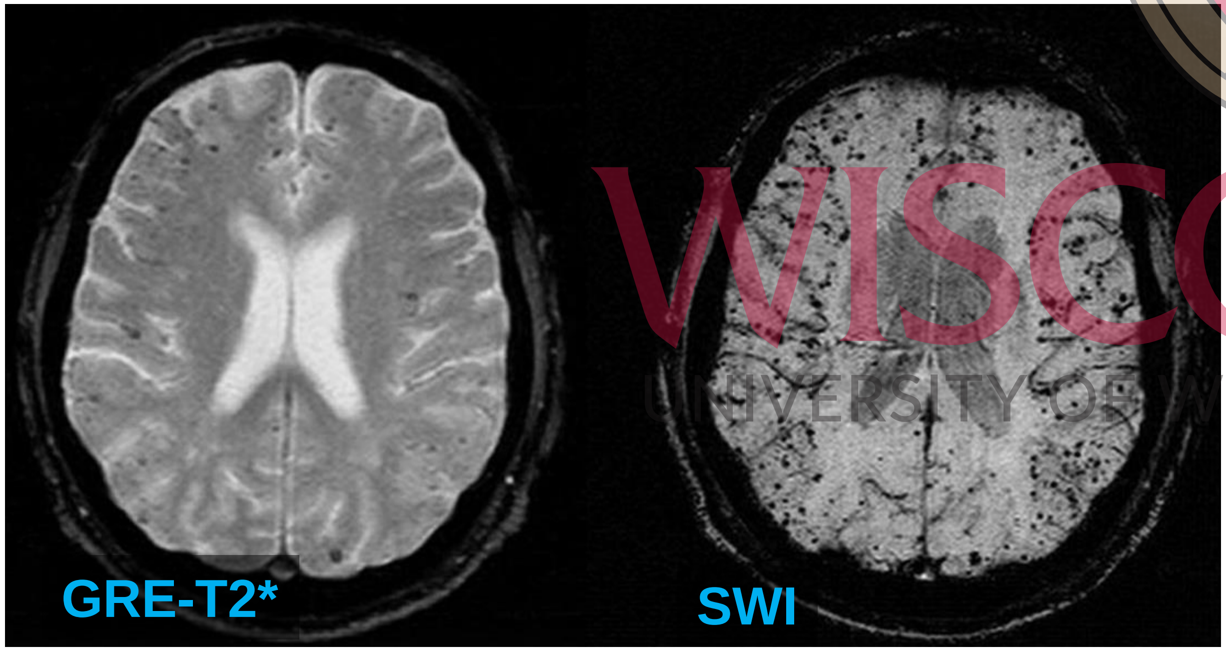
# Microhemorrhages

- *Nonspecific*
- Cerebral amyloid angiopathy continuum
  - CAA incidence of 80-90% in Alzheimer's Disease
- Amyloid β Angiitis

MRI Findings

- Leukoencephalopathy
- Small cortical infarcts
- Lobar/subarachnoid hemorrhage
- Superficial siderosis
- Microbleeds

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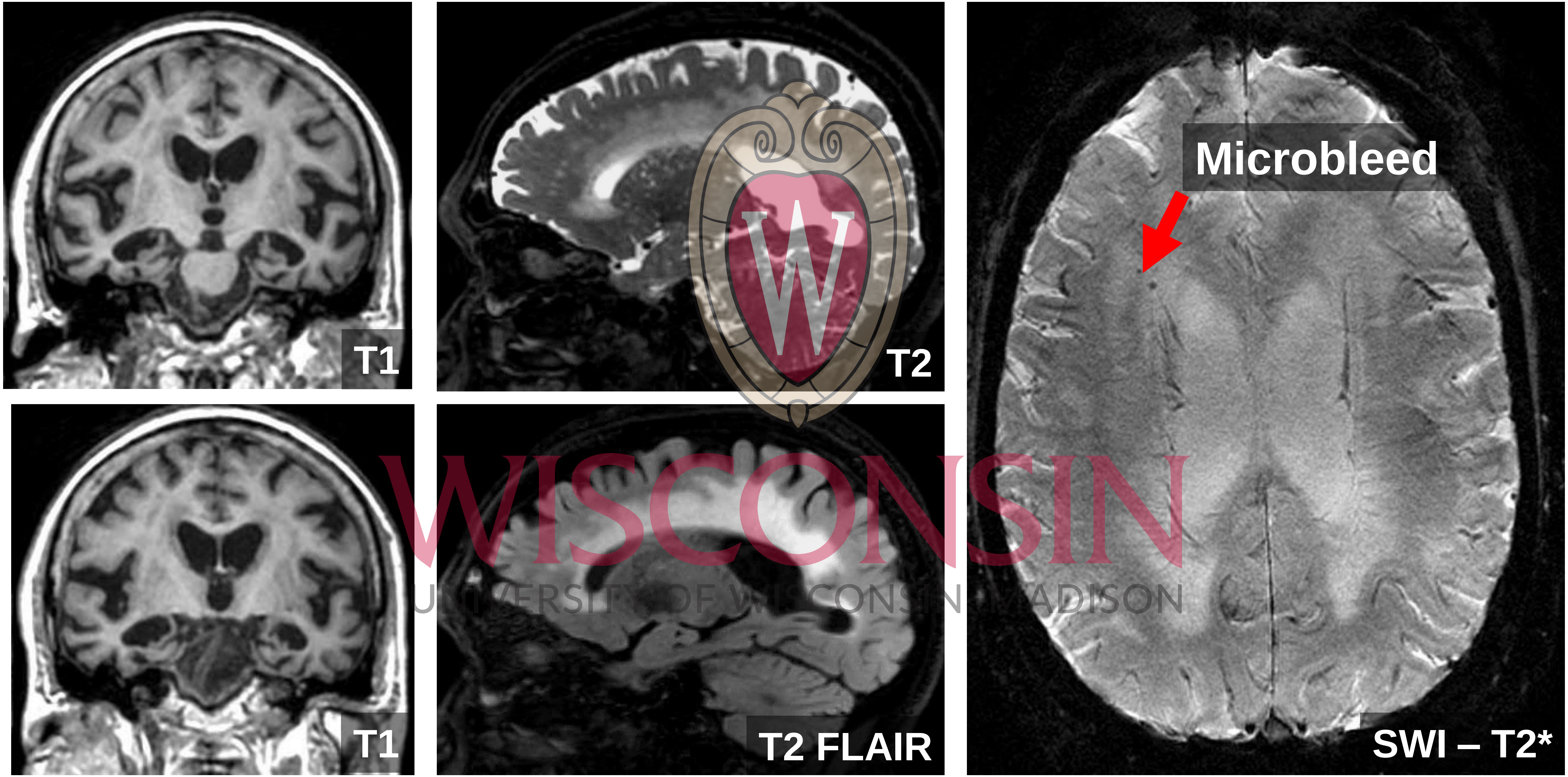
# 85 F Mixed AD + Vascular Dementia

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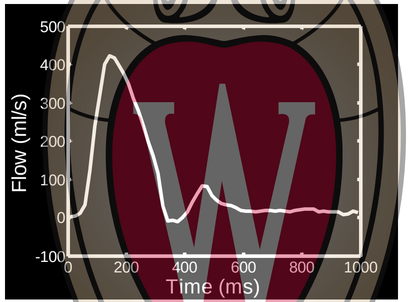
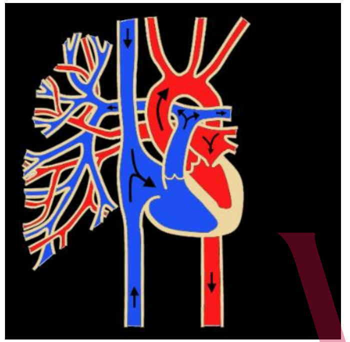
# Vascular System

Arterial Network

*transport + regulation*



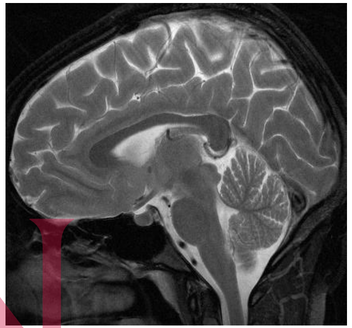

*Systemic risk factors*



*Brain Tissue*

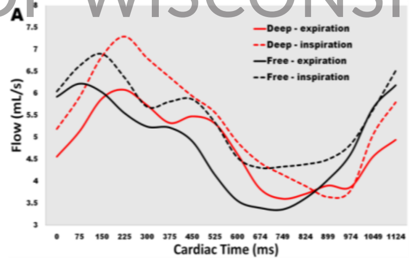
Capillary Bed

*exchange + regulation*



Venous Network

*transport (waste clearance)*

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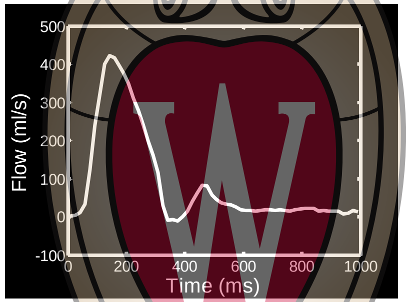


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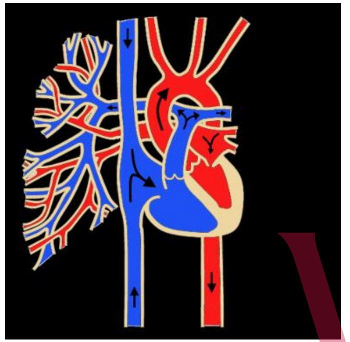

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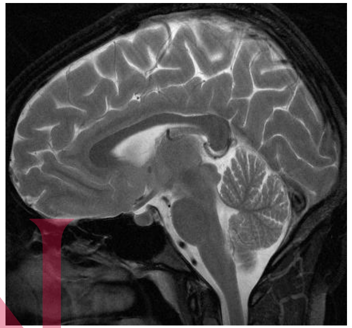

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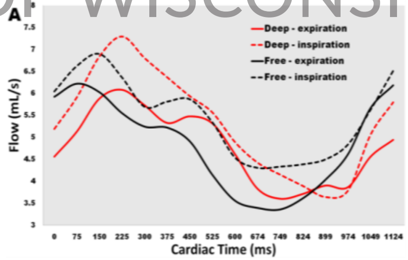


Glymphatic system

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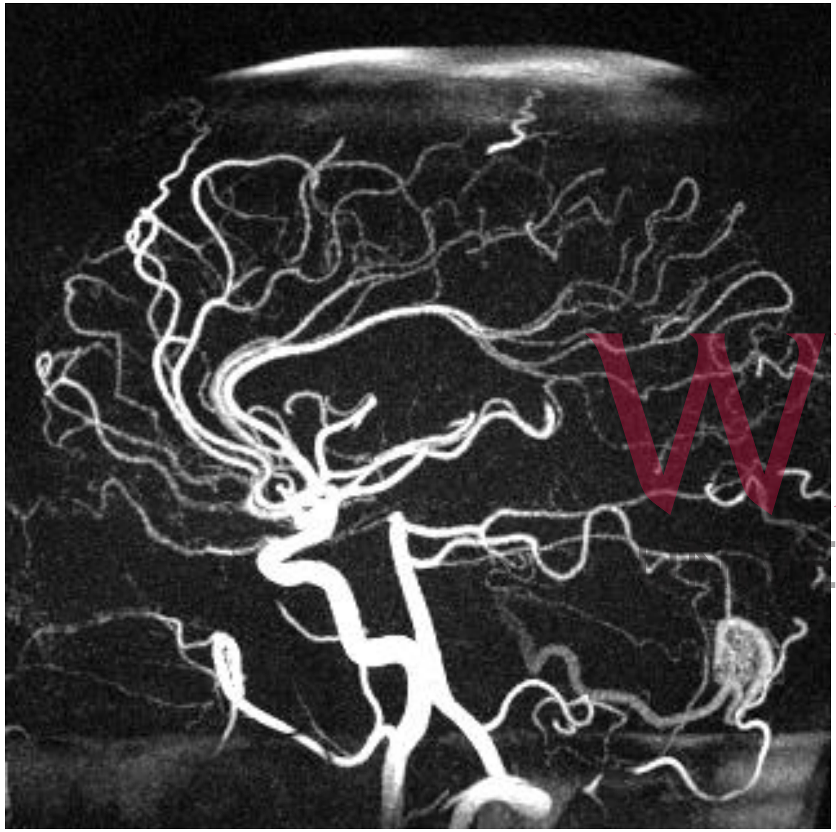
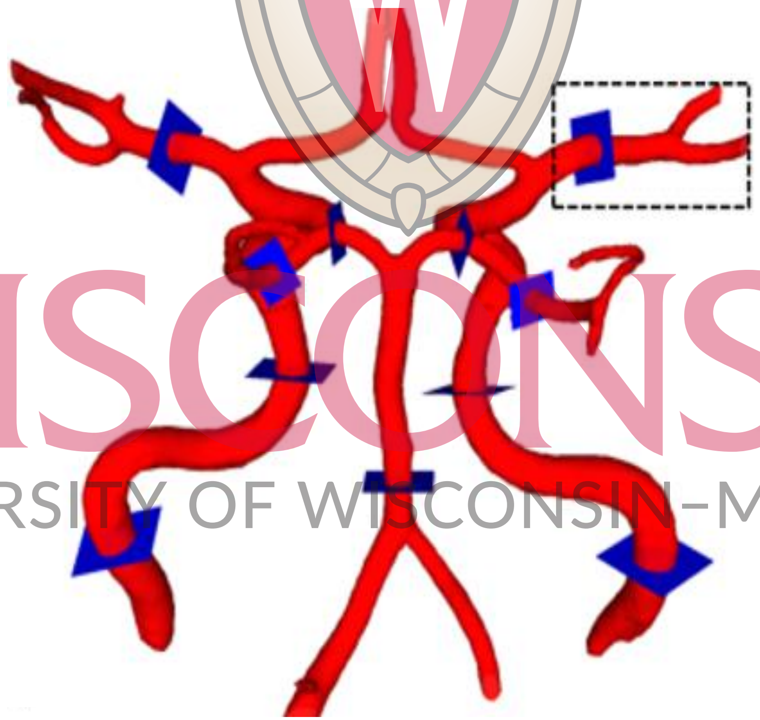
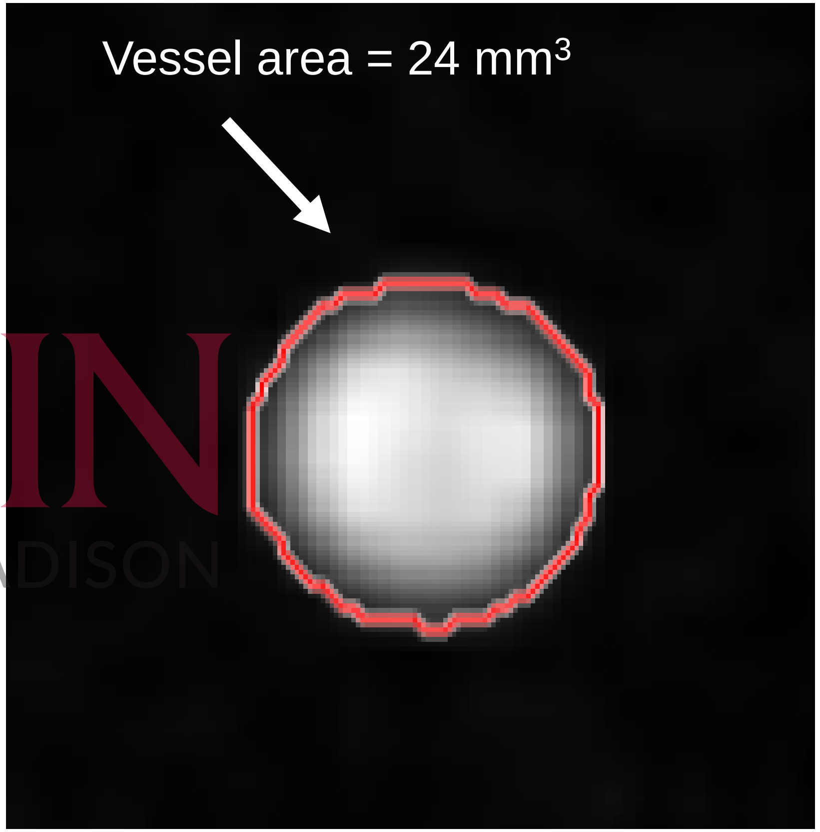
# Vessel morphology

- Vessel Areas
- Vessel lengths

- Presence of plaque
  - Vessel wall enhancement
  - Intraplaque hemorrhage





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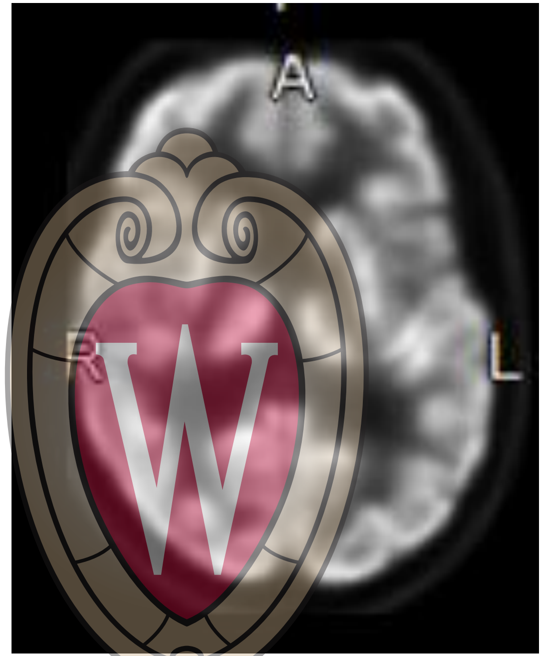
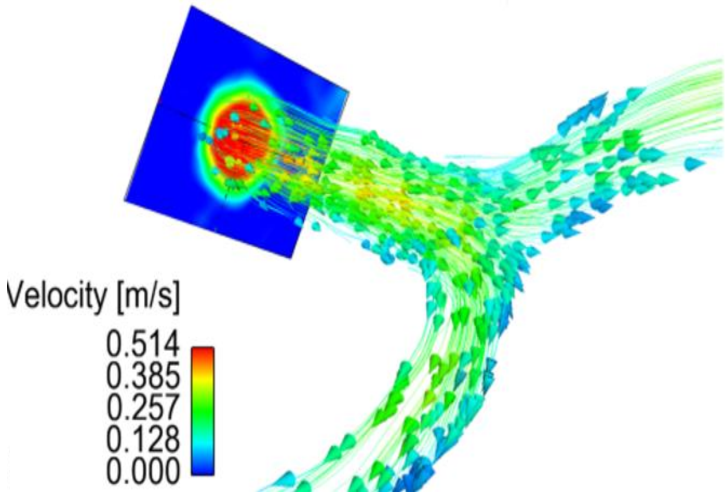
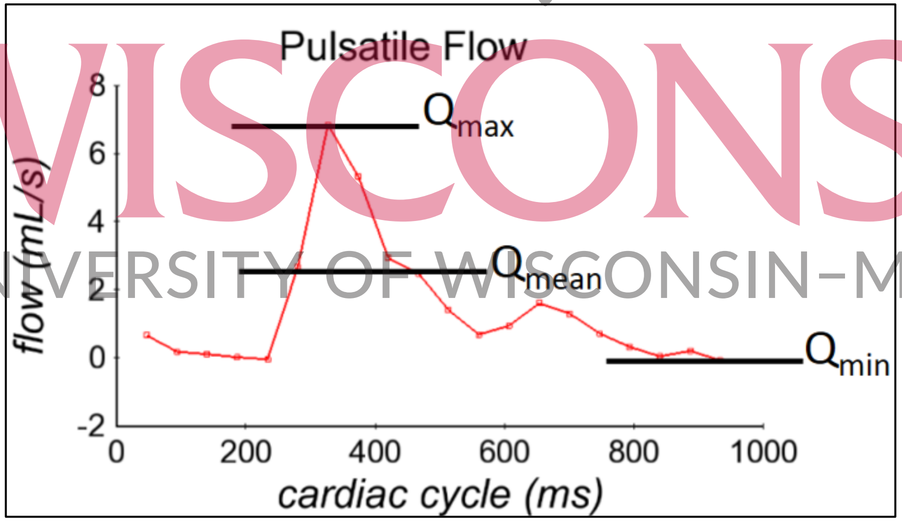
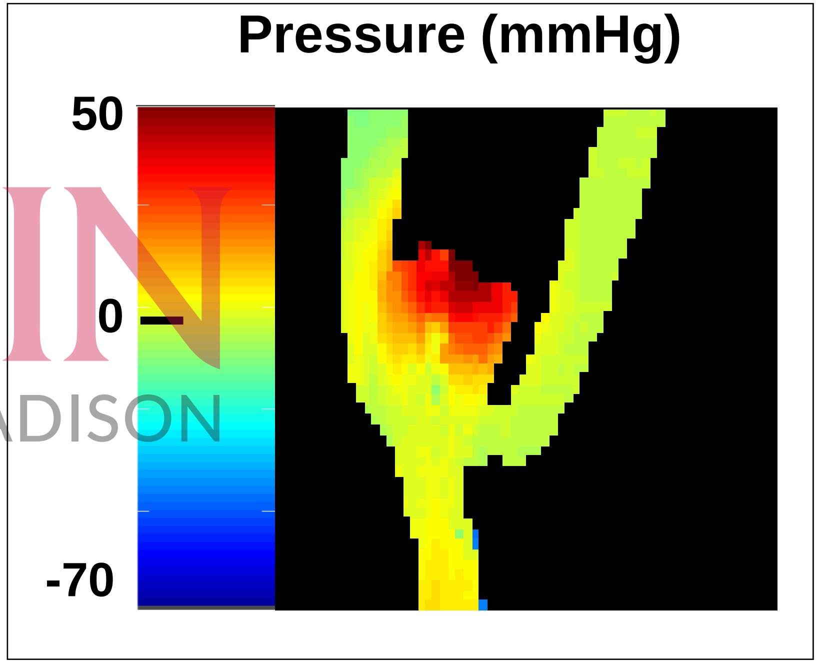
# Functional vascular measures

- Blood flow
  - Average
  - Cardiac cycle
  - Low frequency oscillations
- Blood velocities
- Pulsatility Index
- Resistivity Index
- Pressure maps
- Wall-shear stress
- Kinetic energy

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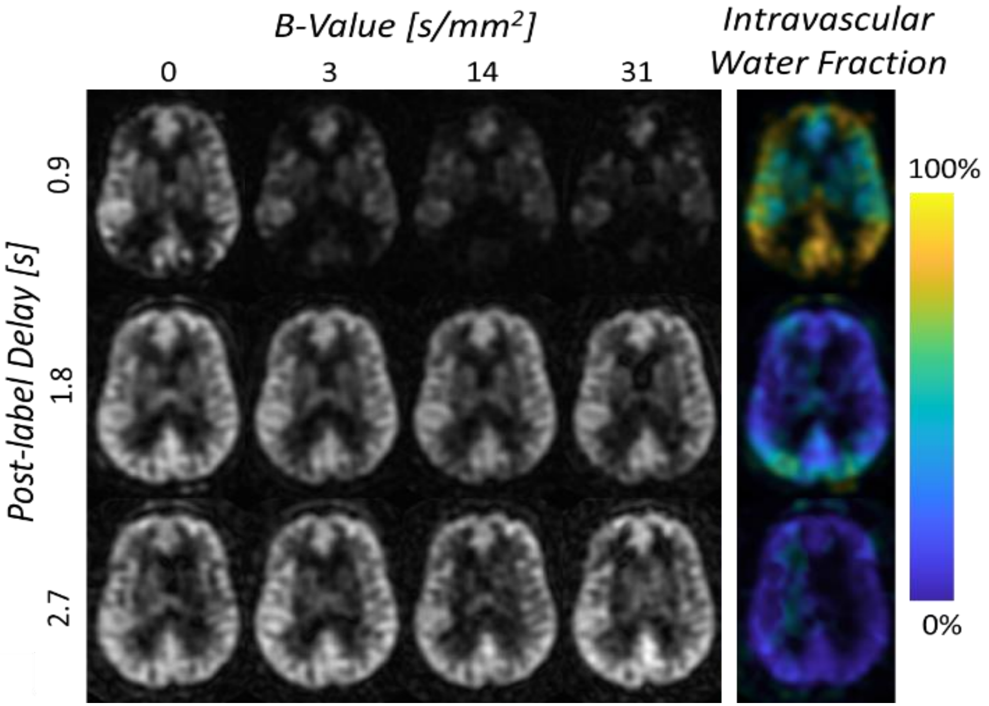
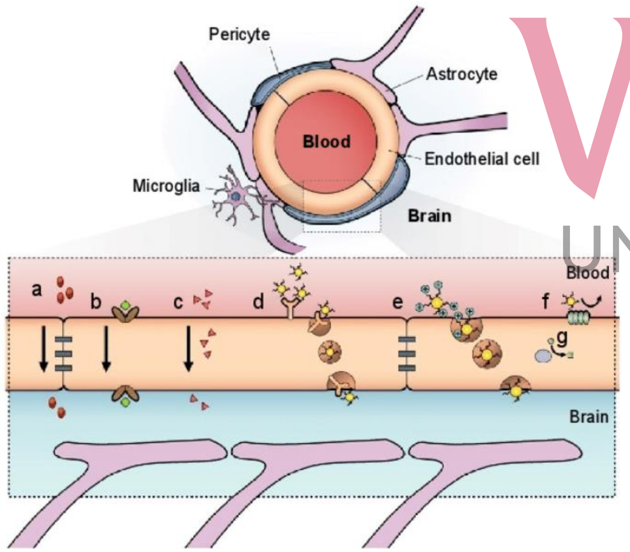
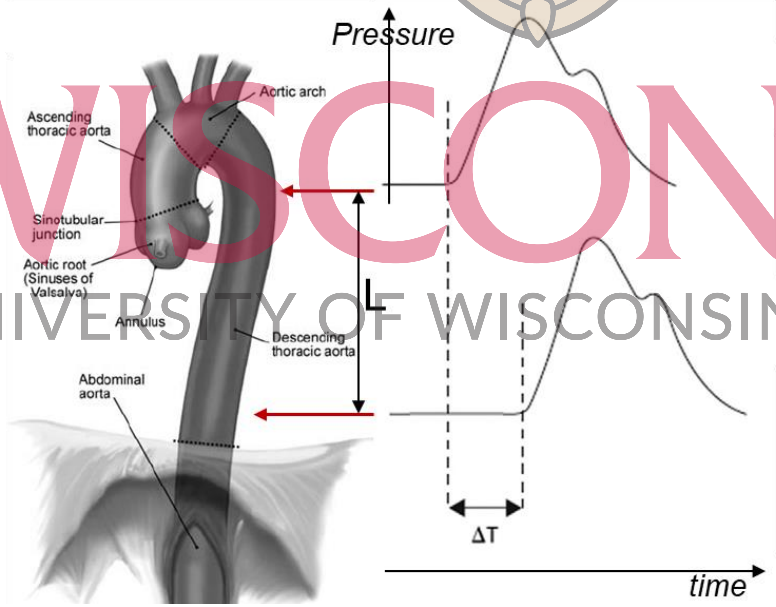
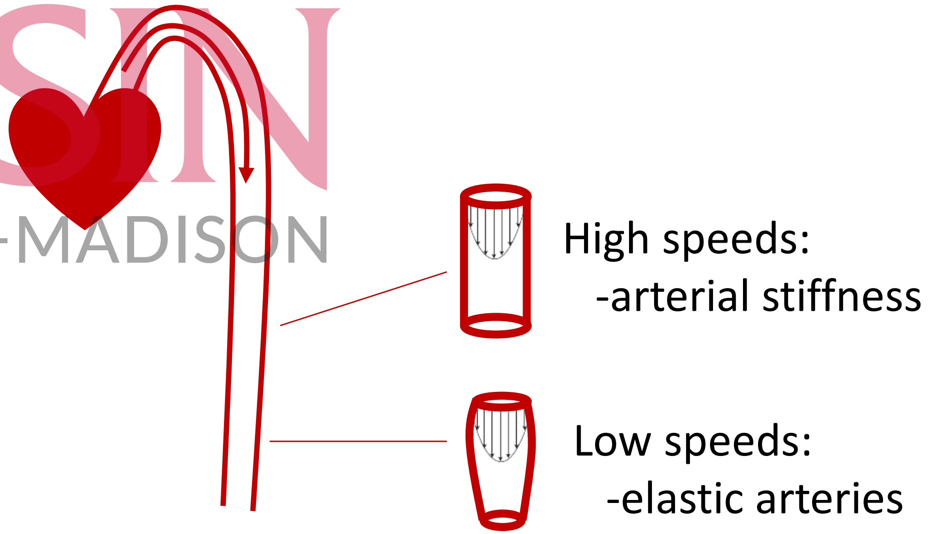
# Vessel wall

- Altered cerebrovascular reactivity/autonomic regulation
  - cerebrovascular reactivity
- Remodeling/Stiffening
  - pulse wave velocity, pulsatility
- Endothelial/blood brain barrier dysfunction
  - diffusion-prepared ASL, dynamic contrast enhancement



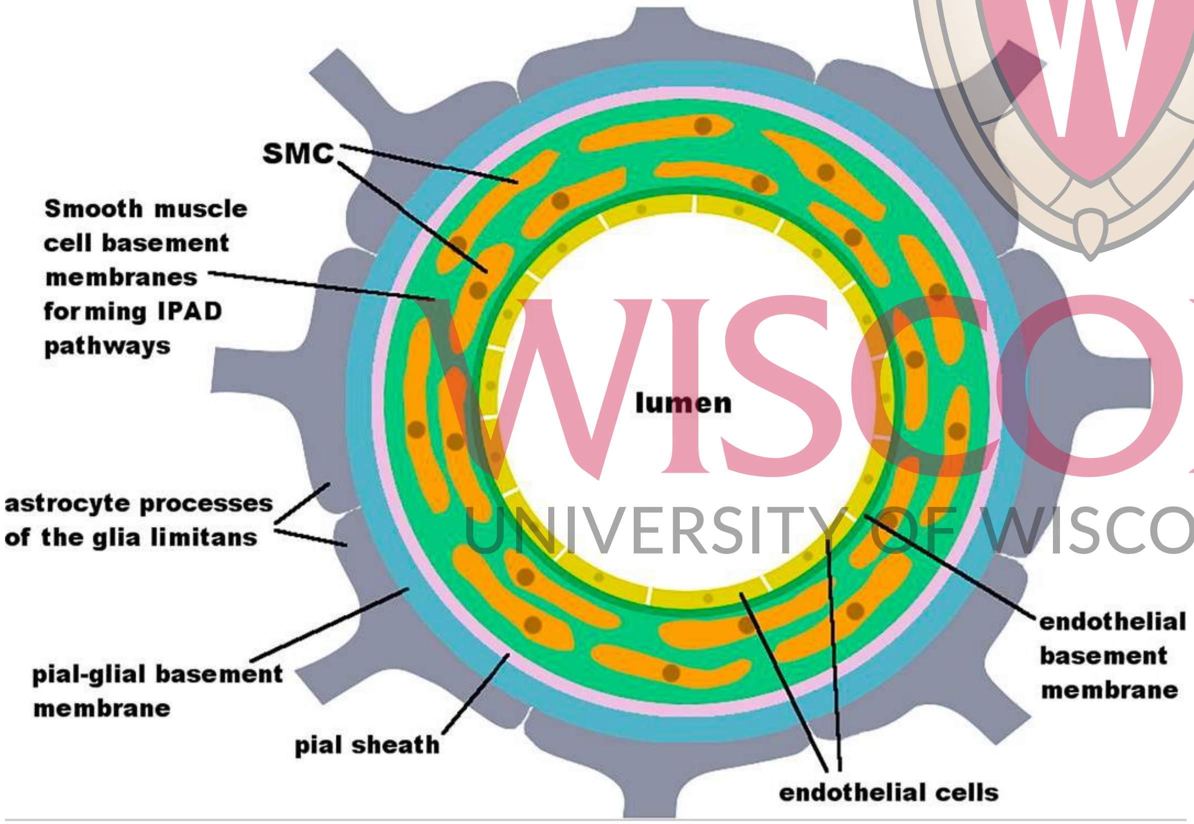



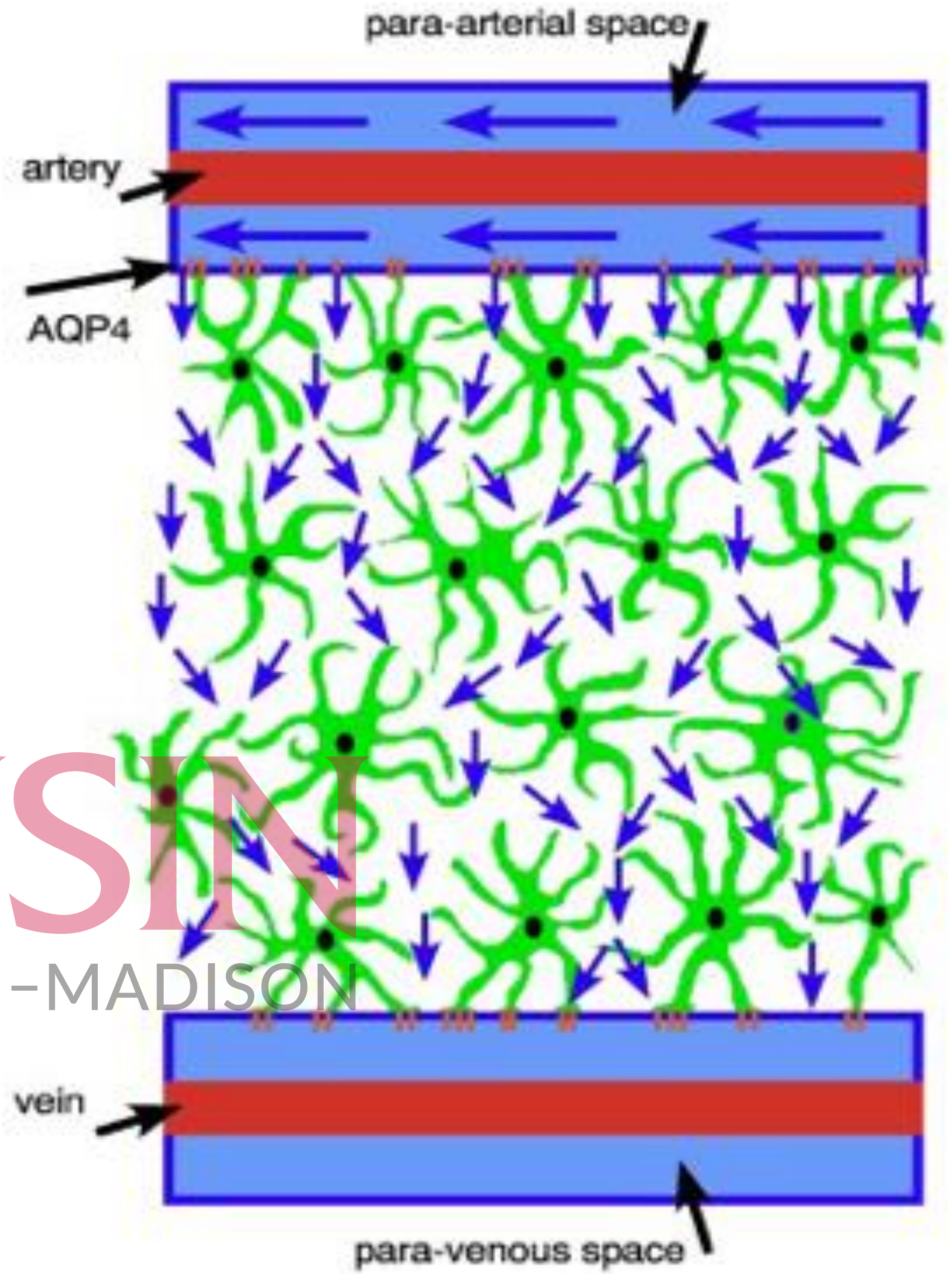



# Metabolite clearance

- Glymphatic system - waste clearance system of the cerebrospinal fluid (CSF) through the perivascular and interstitial spaces
- Intramural periarterial drainage (IPAD) - drainage of interstitial fluid along basement membranes of the smooth muscle cells of cerebral arteries

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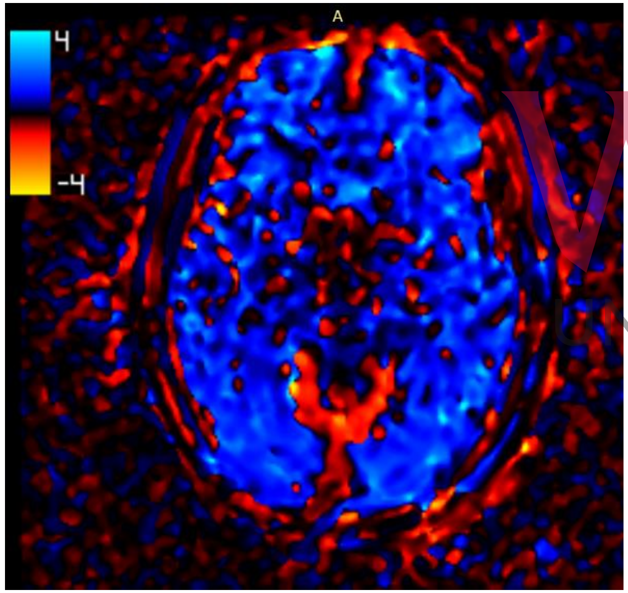
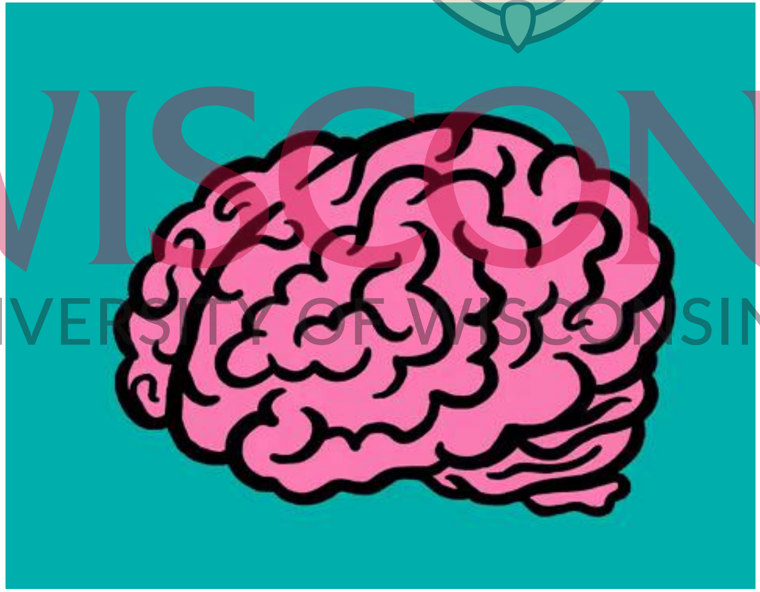
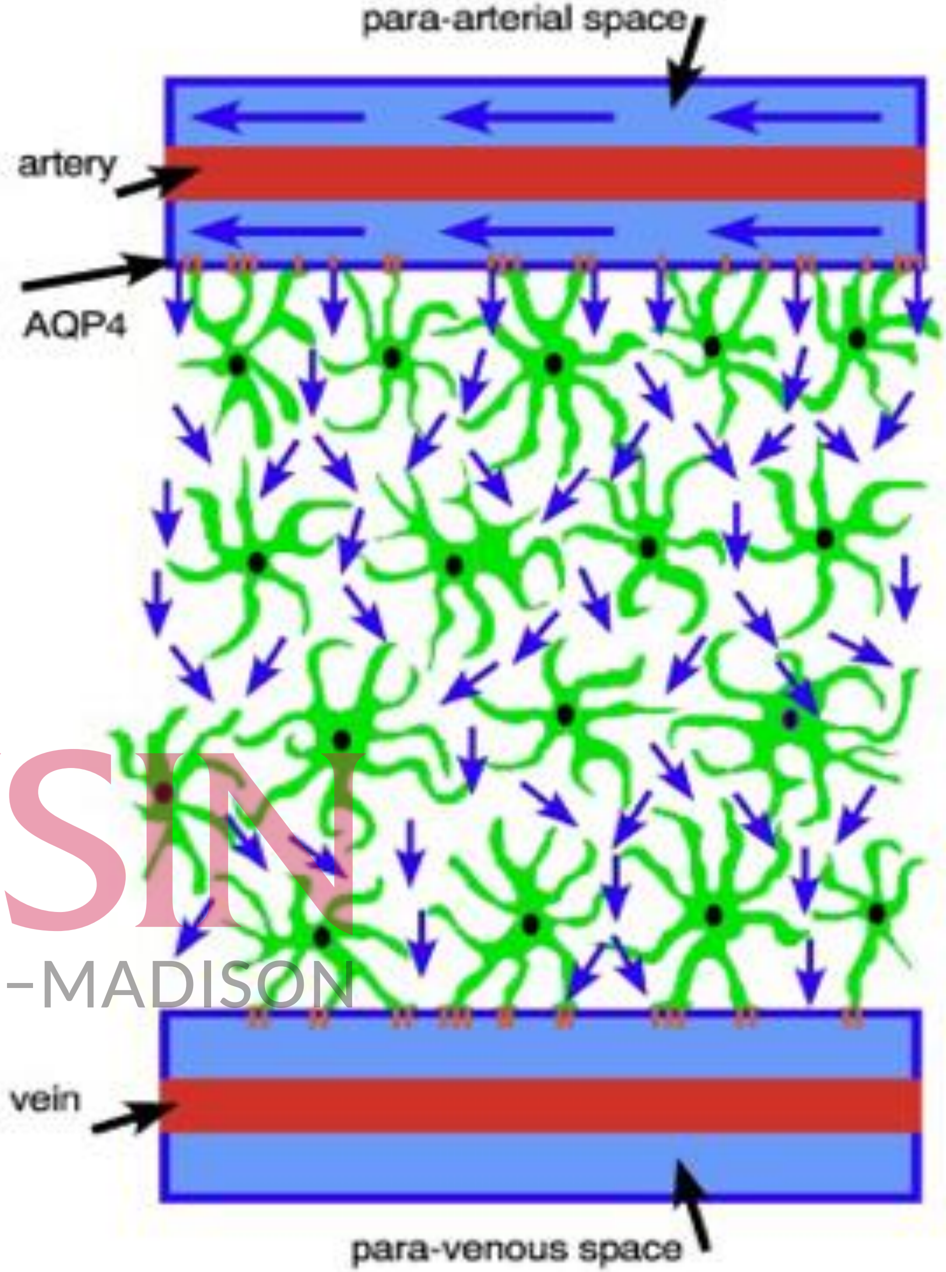
# Glymphatic system

- Interaction of the vascular system with brain tissue is multi-faceted
  - transport and hemodynamics of large vessels
  - direct interactions between the microvasculature and brain tissue
  - drainage from CSF and veins
- Decoupling of this system has been implicated in altered clearance



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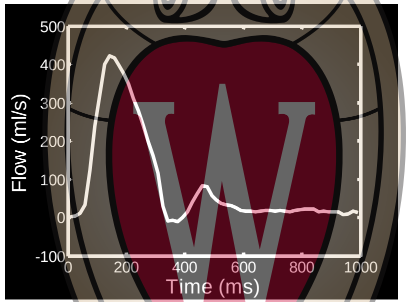
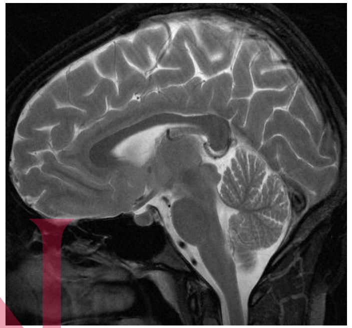
*transport + regulation*




*Brain Tissue*

Capillary Bed
*exchange + regulation*



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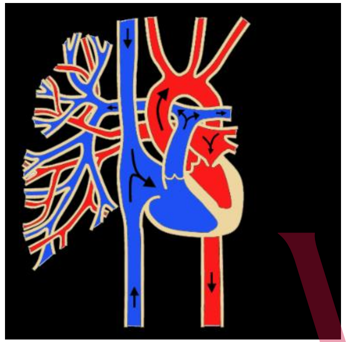
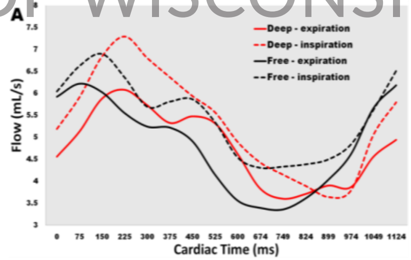


Venous Network
*transport (waste clearance)*

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# Generic Perfusion Methodology

1) **Modify upstream** signal from blood

2) **Measure tissue signal** over a period after

3) **Model** the concentration curve to extract parameters **(Blood flow, mL/min/100 mg tissue)**

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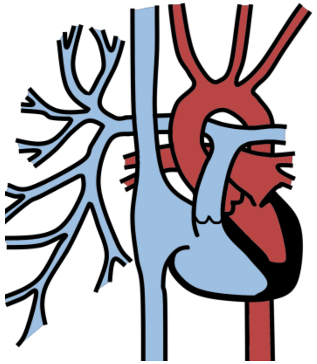
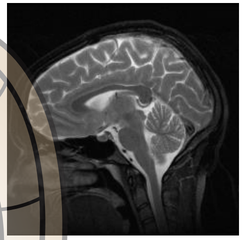
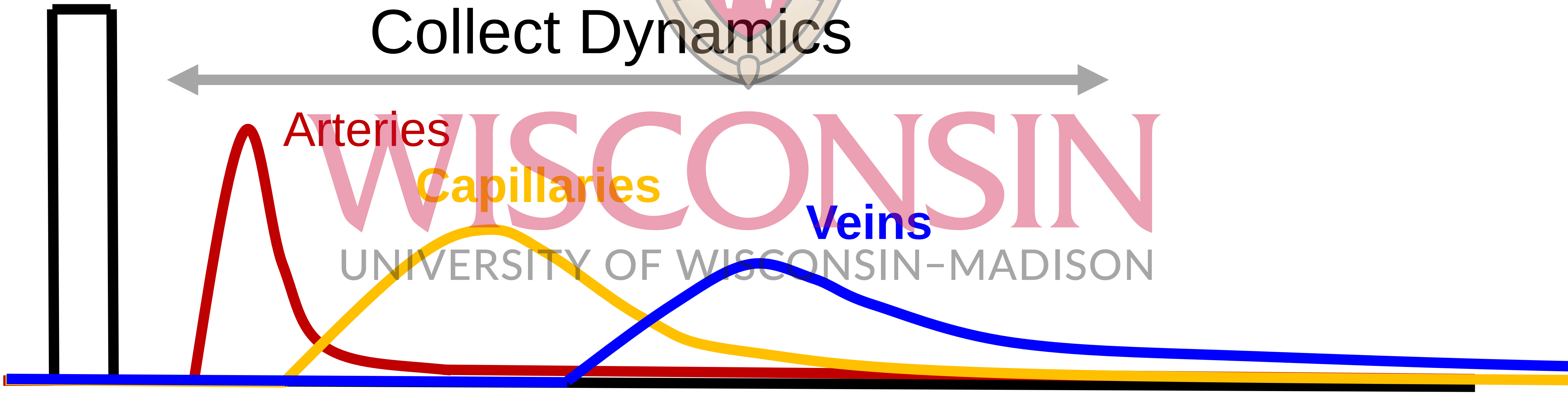
# Agent Kinetics for Perfusion

I.V. Injection → Heart → Arteries → Capillaries → Veins





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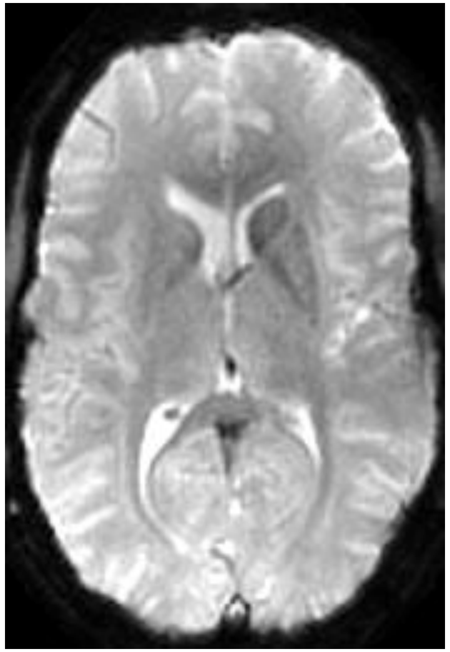
# Perfusion using Injectable Media

Source



$S(t) = M_0 e^{-TE*R2^*(t)}$

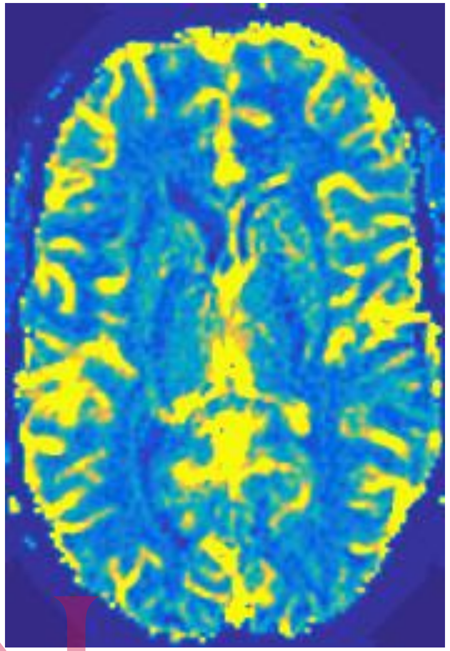
*(T2* Weighted signal)*

*Signal Model*

ΔR2*

*Kinetic Model*

*Blood volume, Blood flow*



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*To measure perfusion we need to observe the distribution of blood into the brain*

# Potential target to track

- **Exogenous Media**
  - —I.V. delivered agent
    - Radioactively labeled water ($^{15}O$ PET, gold standard)
    - Gadolinium based MRI contrast agents
    - Iodine based CT contrast agents
  - —**Advantages:** general robust, high sensitivity
  - —**Disadvantages:** complex setup, disrupt study visit

- **Endogenous Media**
  - —Use MRI techniques to label water in blood (no injection)
  - —**Arterial Spin Labeling (ASL) MRI**

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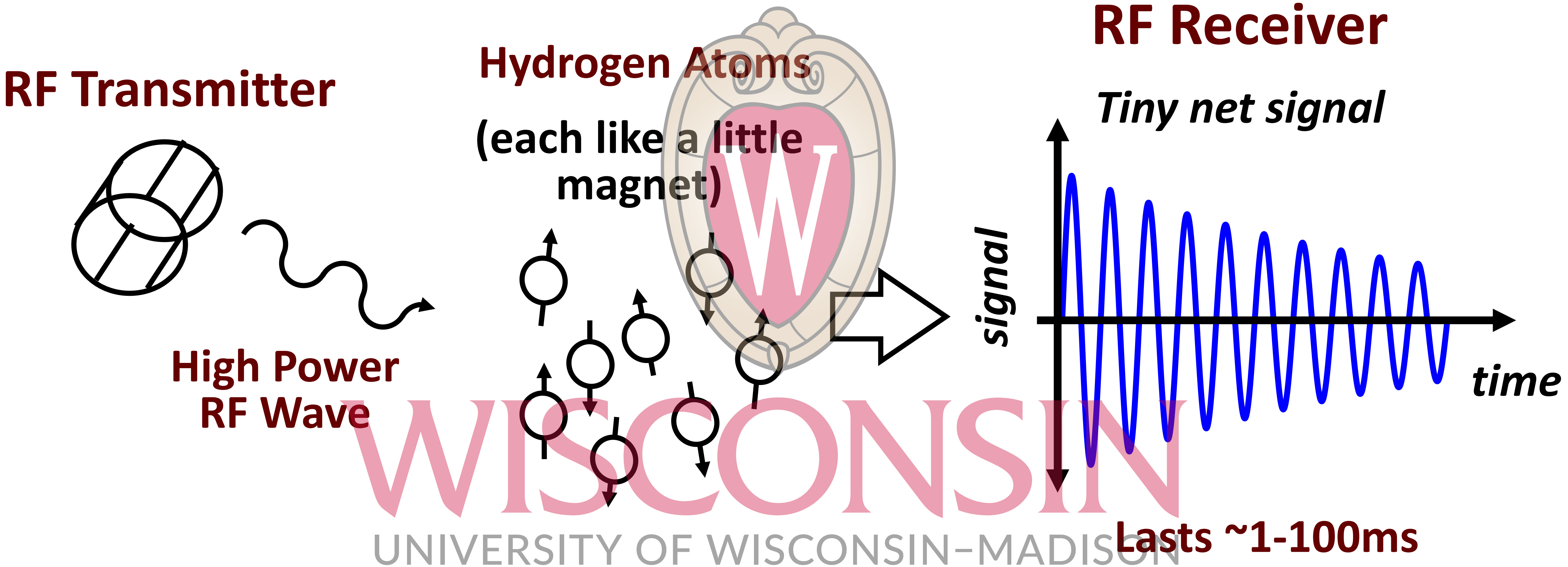
# MRI : Excitation

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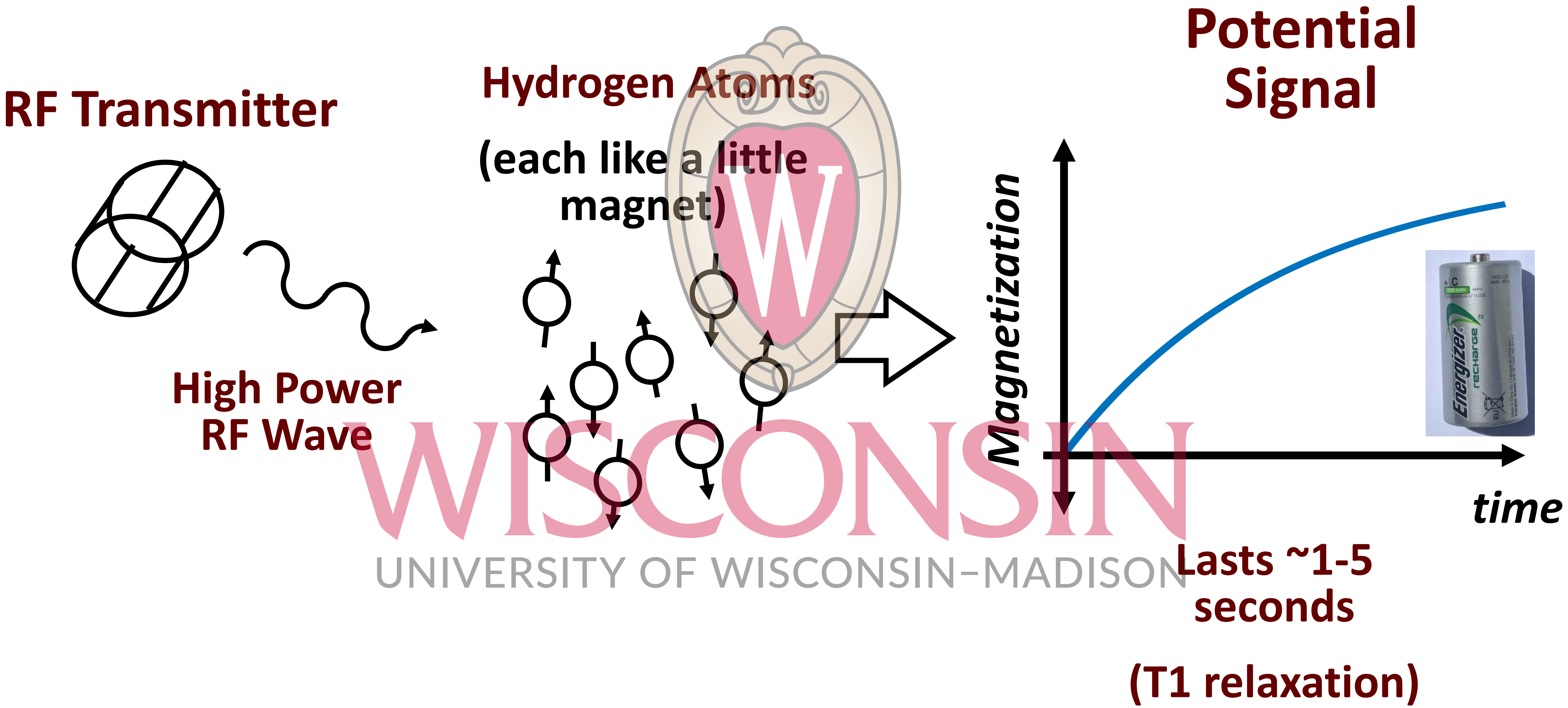
# MRI : Excitation

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# Premise of ASL

**RF Transmitter**

Selectively saturate the signal as it enters the brain

t=0

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# Premise of ASL

**RF Transmitter**

Selectively saturate the signal as it enters the brain

t=0.2s

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# Premise of ASL

t=0.4s

**RF Transmitter**

Selectively saturate the signal as it enters the brain

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t=1.4s

**RF Transmitter**

Selectively saturate the signal as it enters the brain

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# Premise of ASL

**RF Transmitter**

Selectively saturate the signal as it enters the brain

t=1.4s

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# Premise of ASL

t=1.4s

**RF Transmitter Off**

*Post-Label Delay*

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# Premise of ASL

t=1.6s

**RF Transmitter Off**

*Post-Label Delay*

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# Premise of ASL

t=2.2s

**RF Transmitter Off**

*Post-Label Delay*

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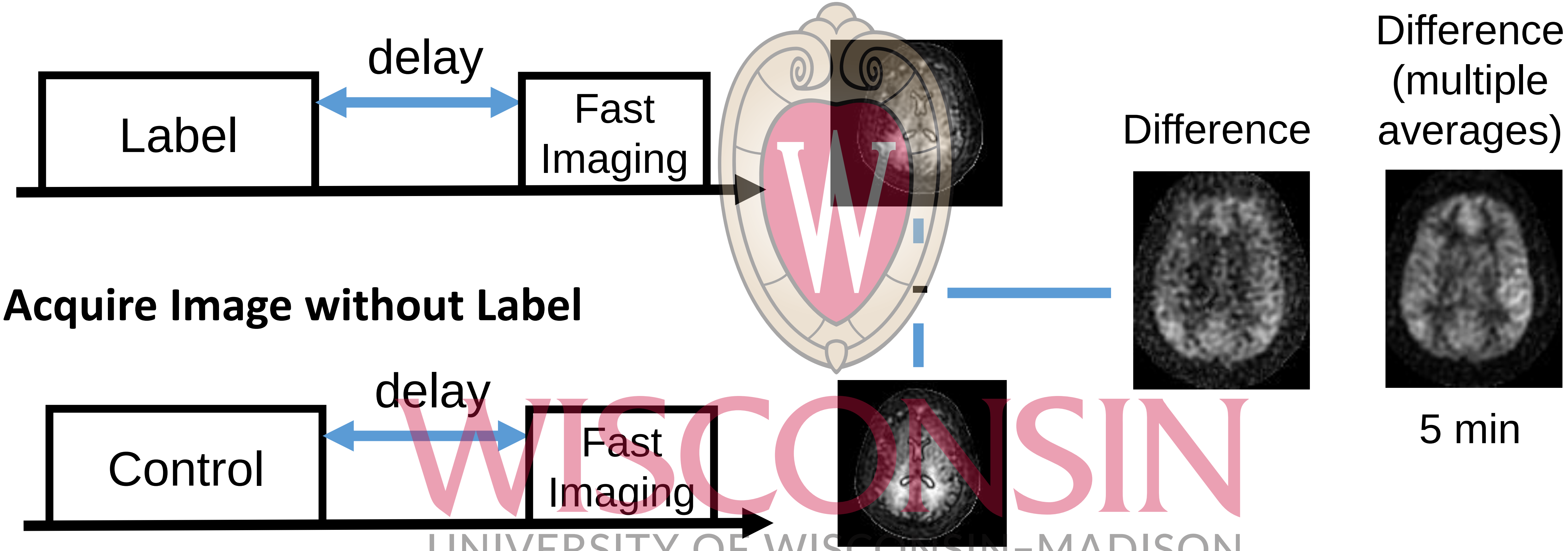
# Background Signal

## Acquire Image with Label

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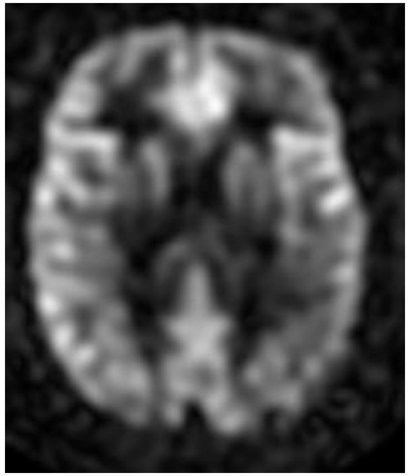
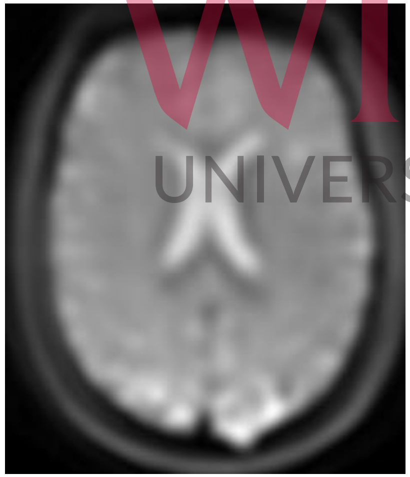
# ASL Cerebral Blood Flow Quantification (Single Delay)

**Difference Image @ One Delay**

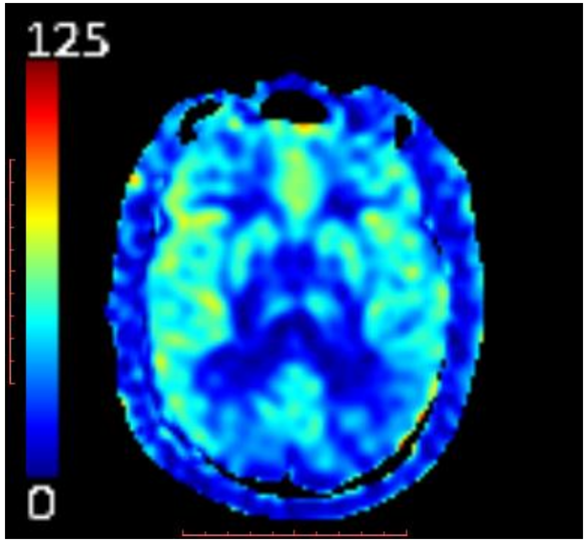


**Proton Density**



*Correct Image Intensity*

Fit to model




**Cerebral Blood Flow (CBF)**

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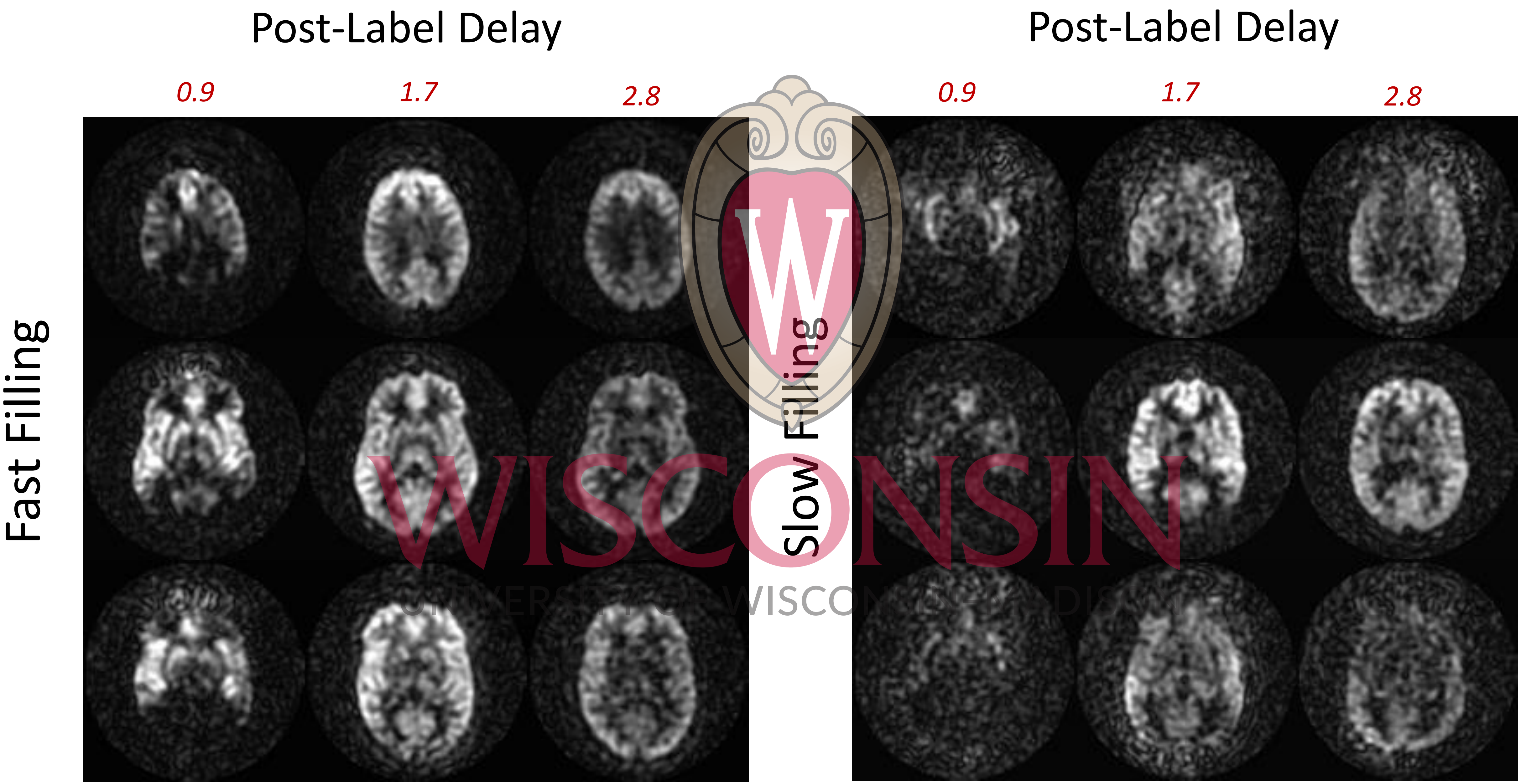
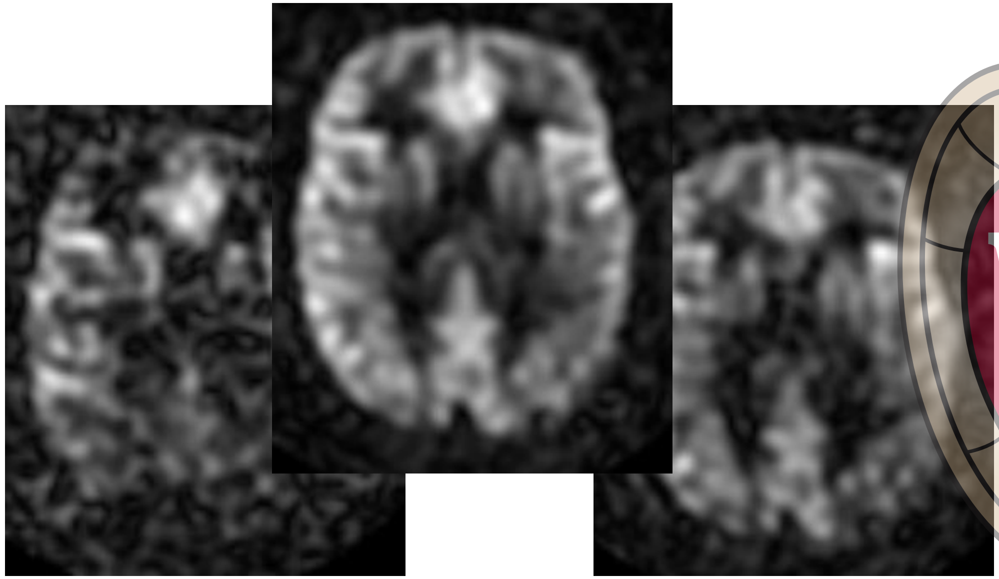
# Multi-Delay ASL

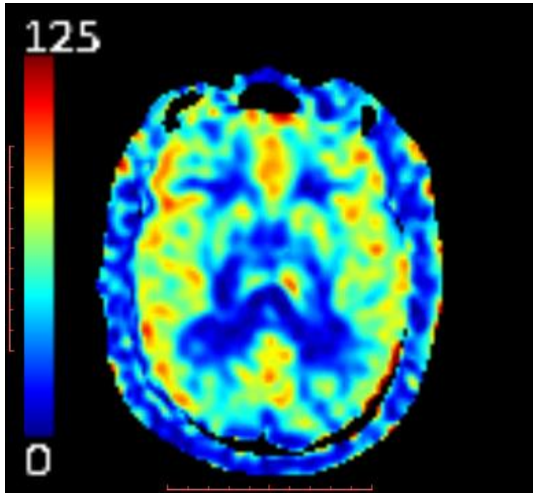


# ASL Cerebral Blood Flow Quantification (Multi-Delay)

## Difference Images @ Multiple Delays

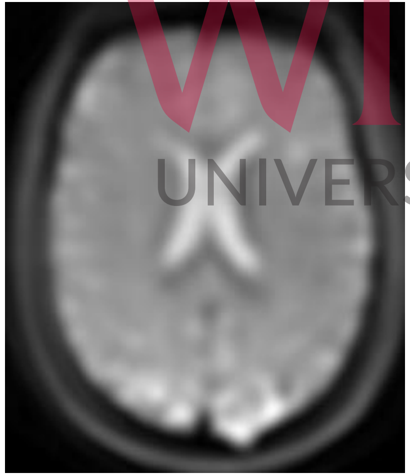


Fit to model




**Cerebral Blood Flow (CBF)**

**Proton Density**



*Correct Image Intensity*

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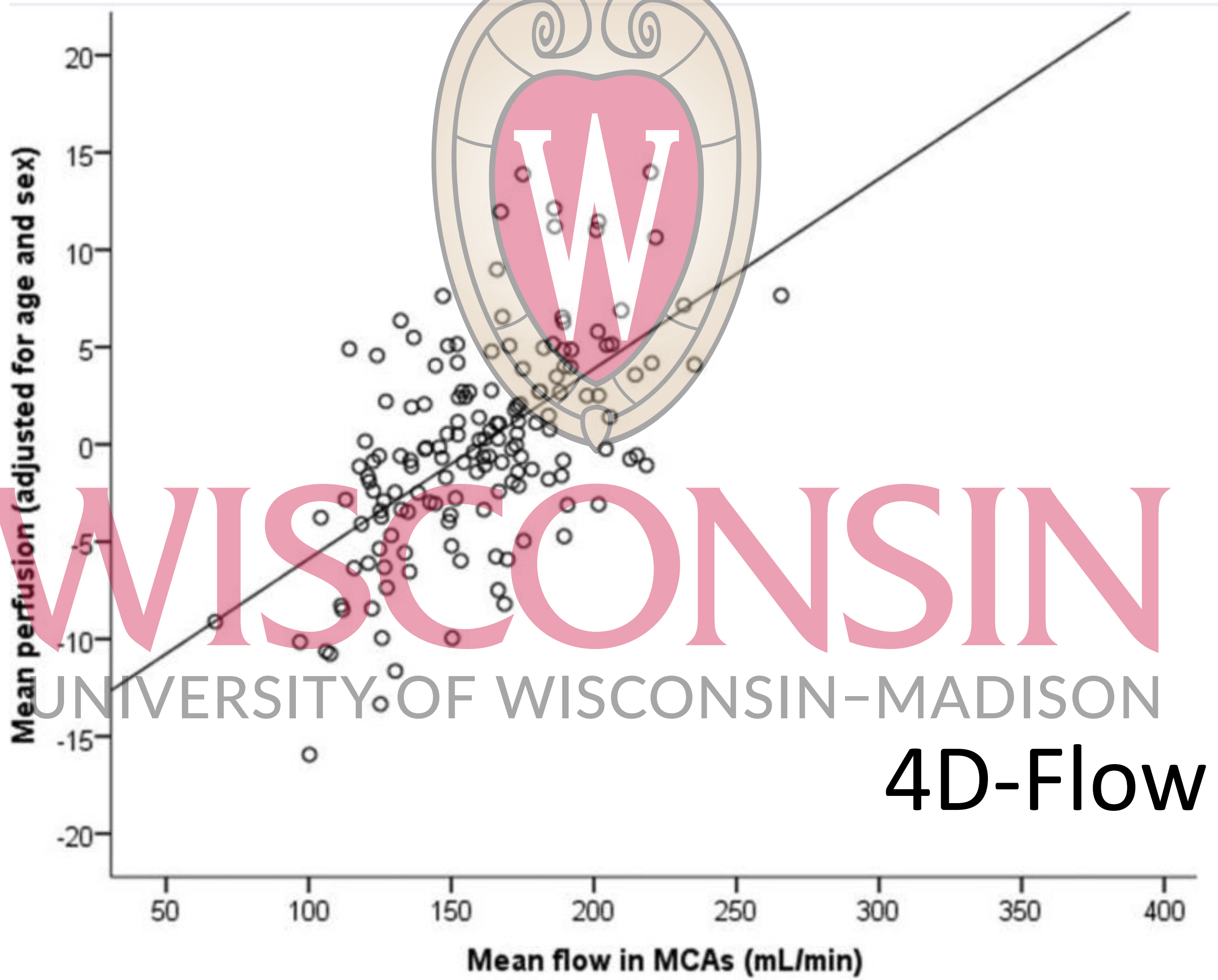
# Results in AD and Aging

- Clark et al. 17' AD
- ASL and 4D-Flow highly associated

ASL



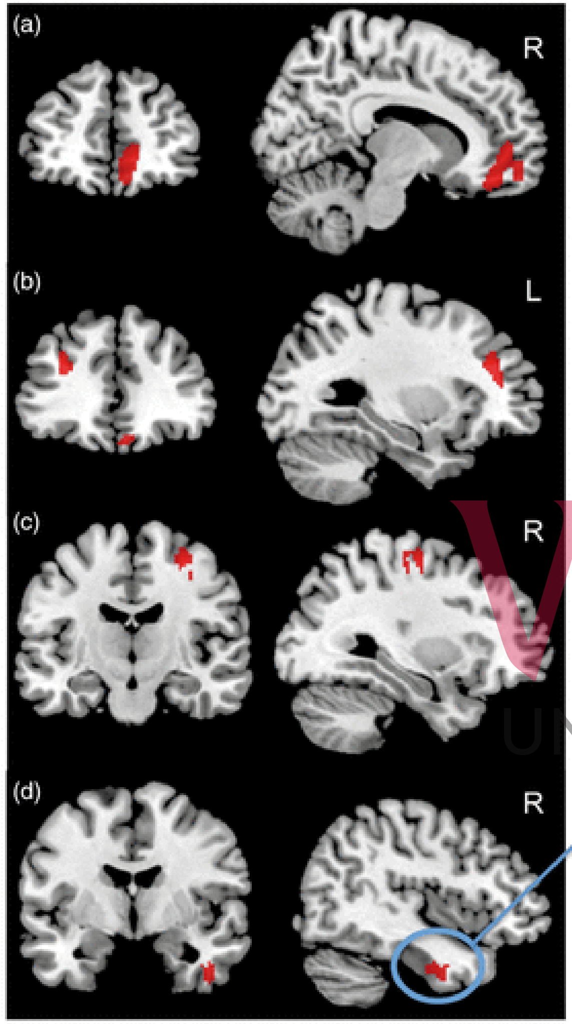

4D-Flow

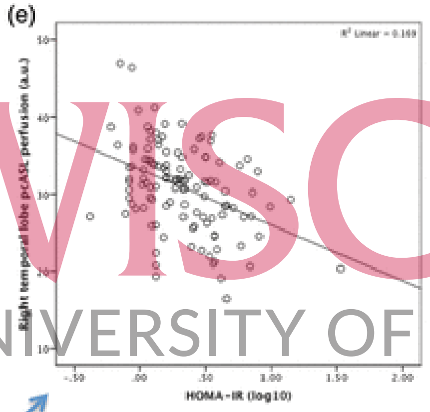
# Results in AD and Aging

- Hoscheidt et. Al. 16’ JCBFM
- Insulin resistance associated with lower CBF

**ASL**

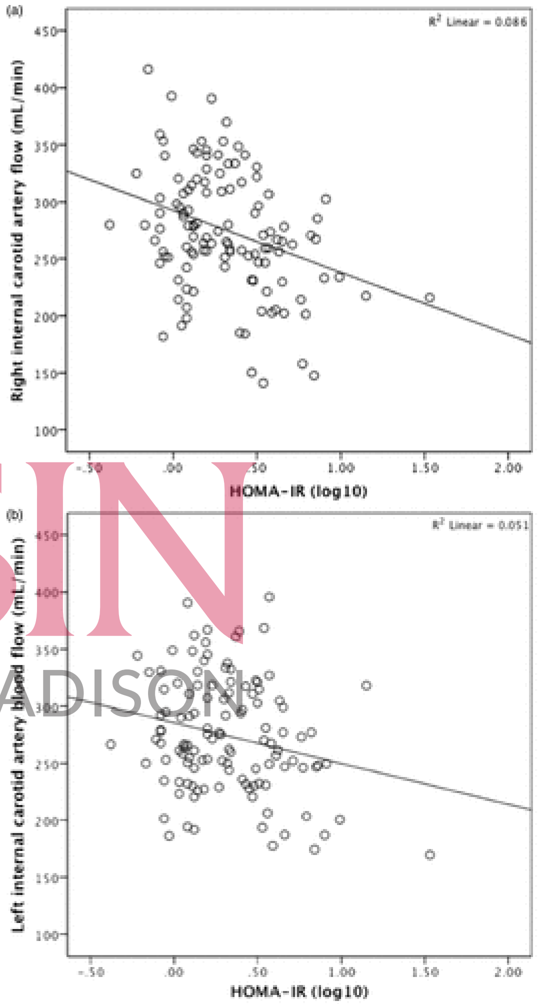
**(regional)**




**4D-Flow**

**(global)**

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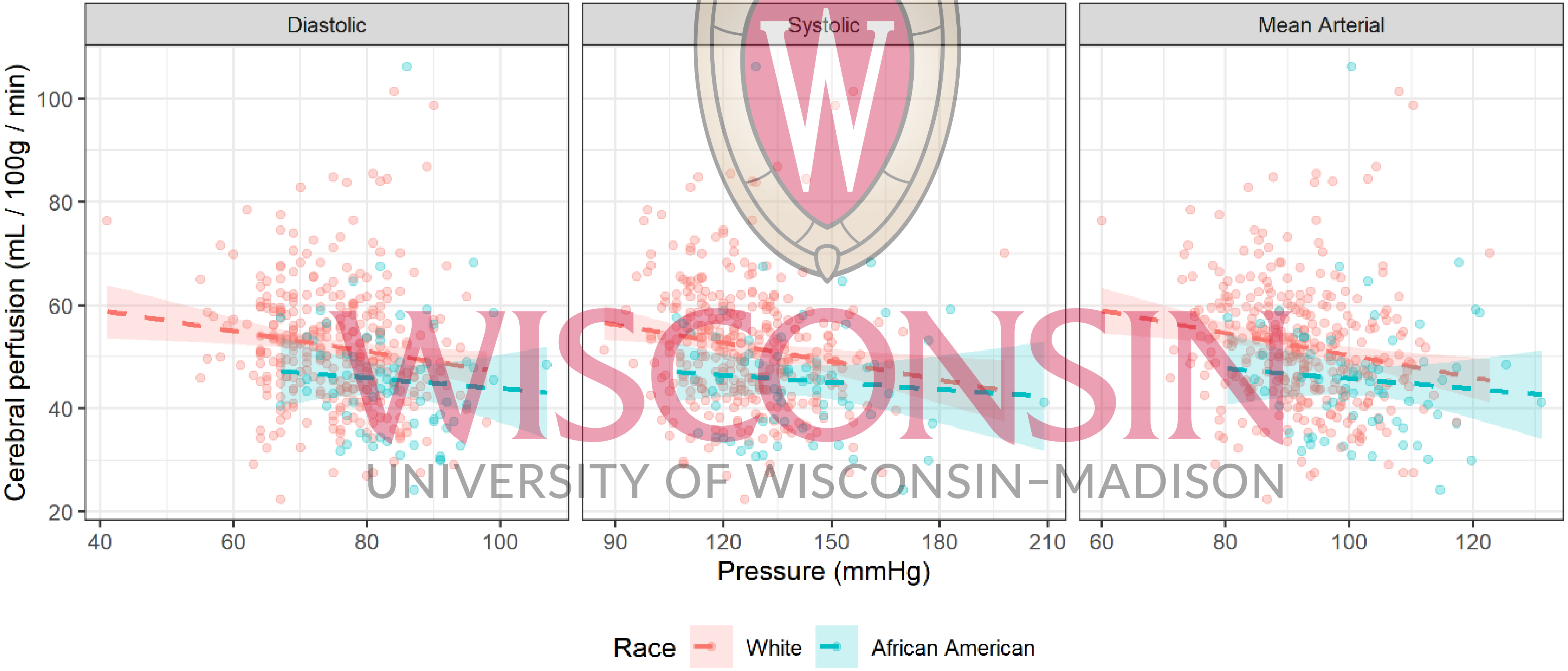
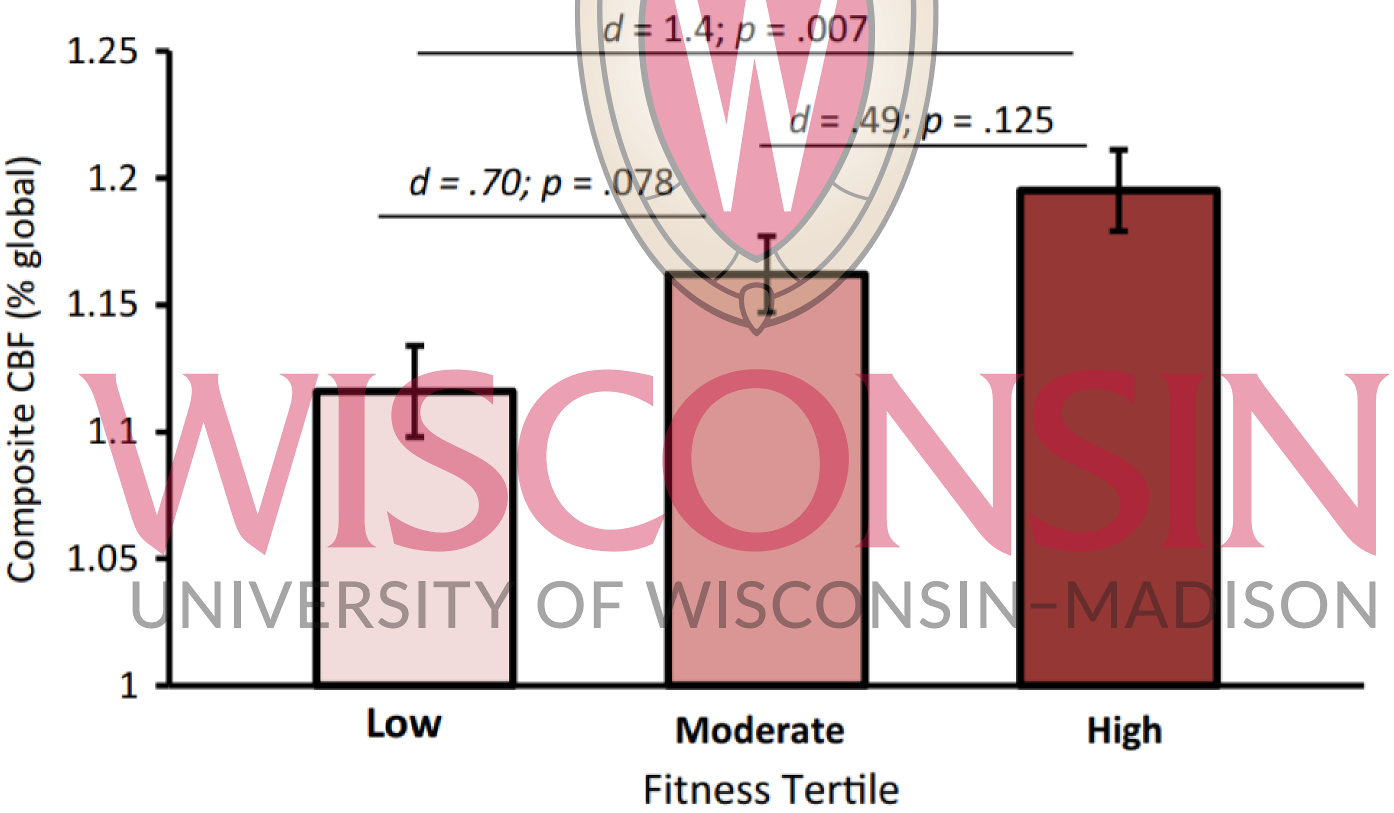
# Results in AD and Aging

- Clark et. Al. 20’ Journal of AD
- Diastolic blood pressure significantly associated with mean perfusion, no associating with race but higher risk in African Americans



# Results in AD and Aging

- Dougherty et. Al. 20’ Brain Imaging and Behavior
- Fitness explains CBF values in female participants

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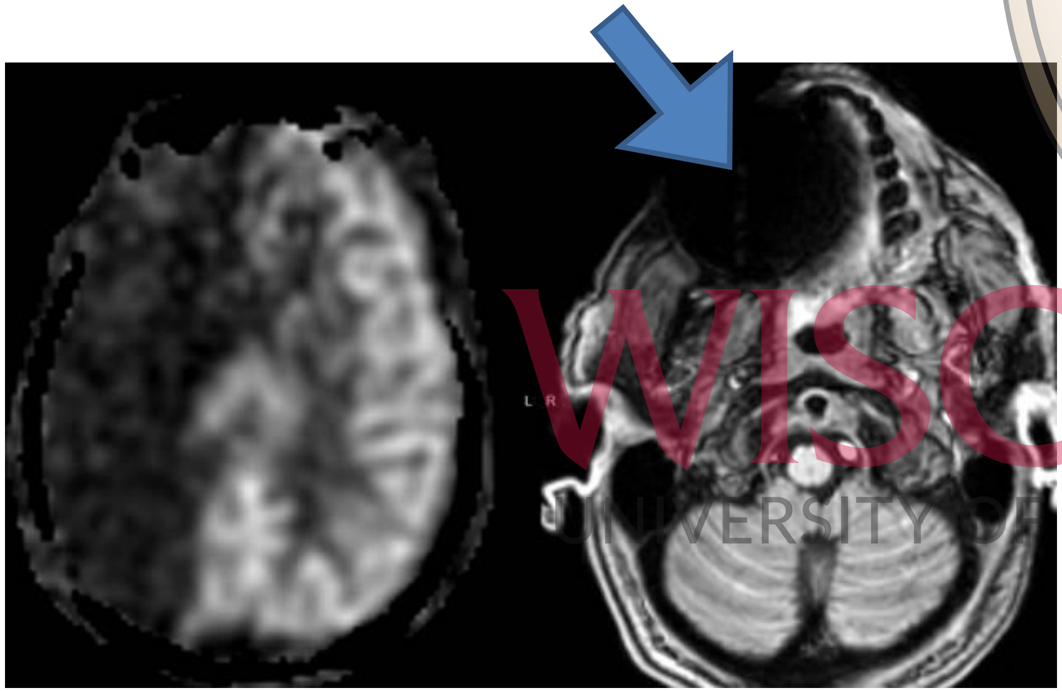
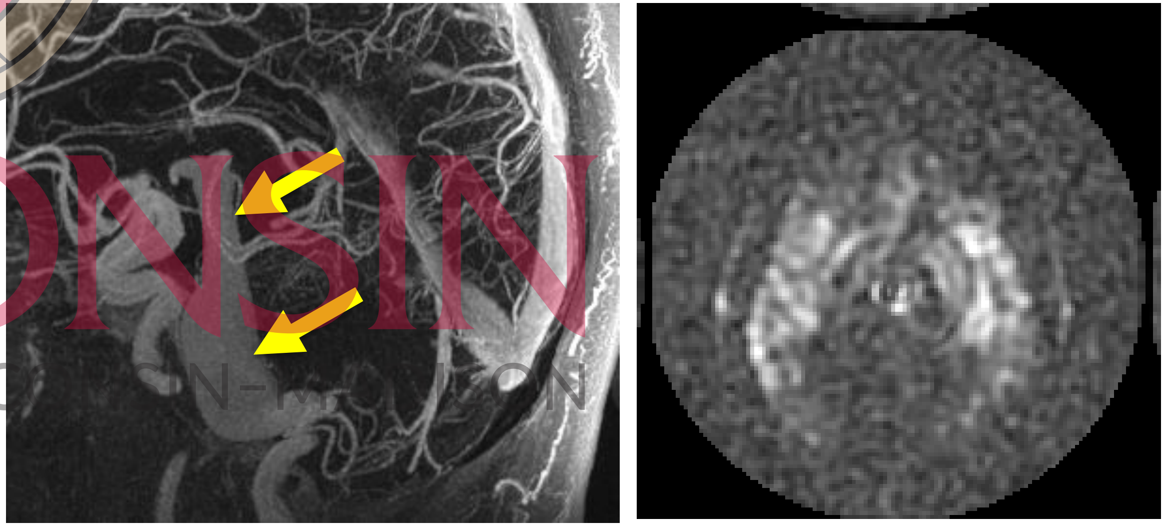
# ASL Challenges

- Tagging can fail
  - Here dental implants led to low perfusion signal on one side of the brain



- Low signal sensitive to artifacts
  - Motion, ghosting, etc
  - Here large aneurysm leads to artifacts



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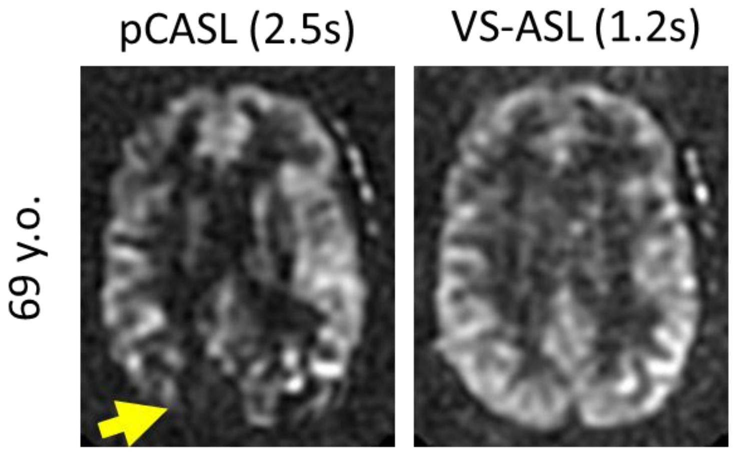
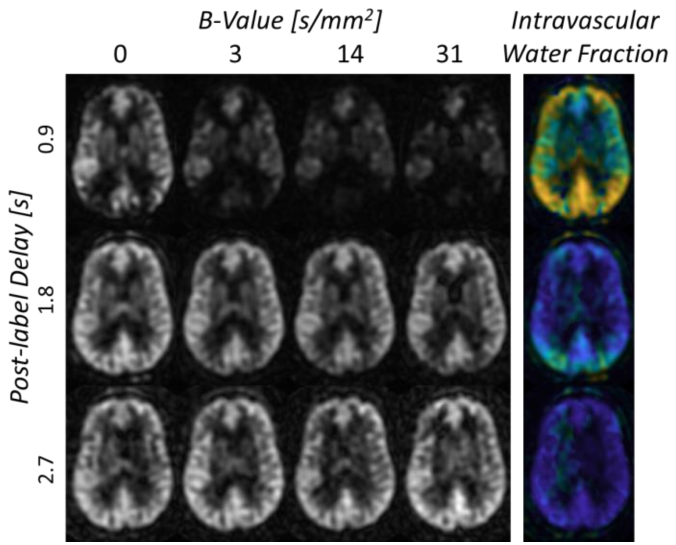
# ASL Methods in Development

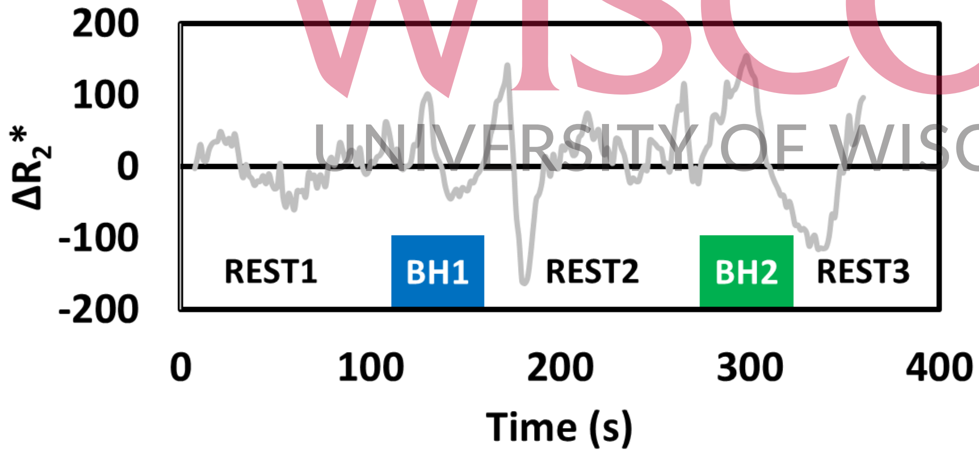
## Delay independent ASL with velocity labeling

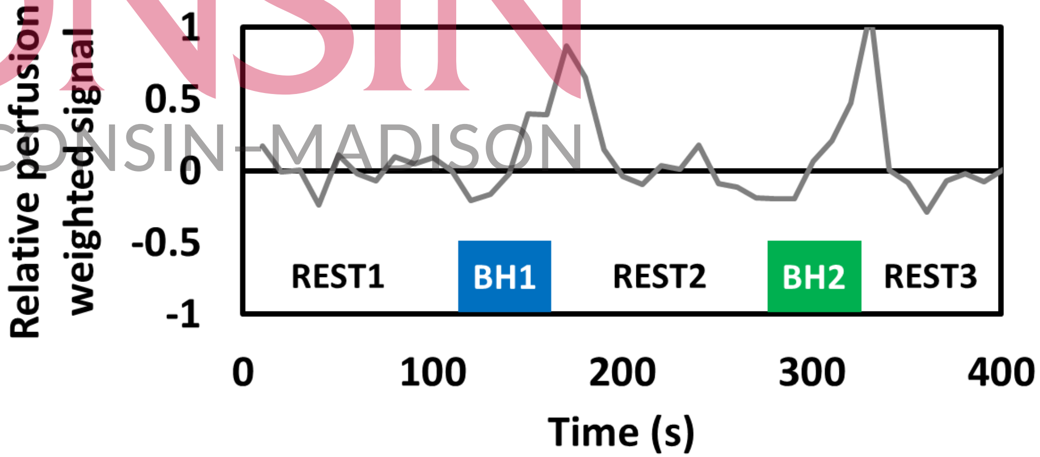



## Diffusion + ASL (permeability)




## Realtime ASL for Functional Challenges

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# Overview

- **Clinical Introduction** to vascular disease and Alzheimer's
  - —Laura Eisenmenger, Assistant Professor, Radiology
- **Perfusion measures** using Arterial Spin Labeling
  - —Kevin Johnson, Assistant Professor, Medical Physics and Radiology
- Study of **vascular-tissue biomechanics**
  - —Leonardo Rivera-Rivera, Postdoctoral Fellow
- **Tissue properties** using Magnetic Resonance Elastography
  - —Grant Roberts, PhD Candidate, Medical Physics

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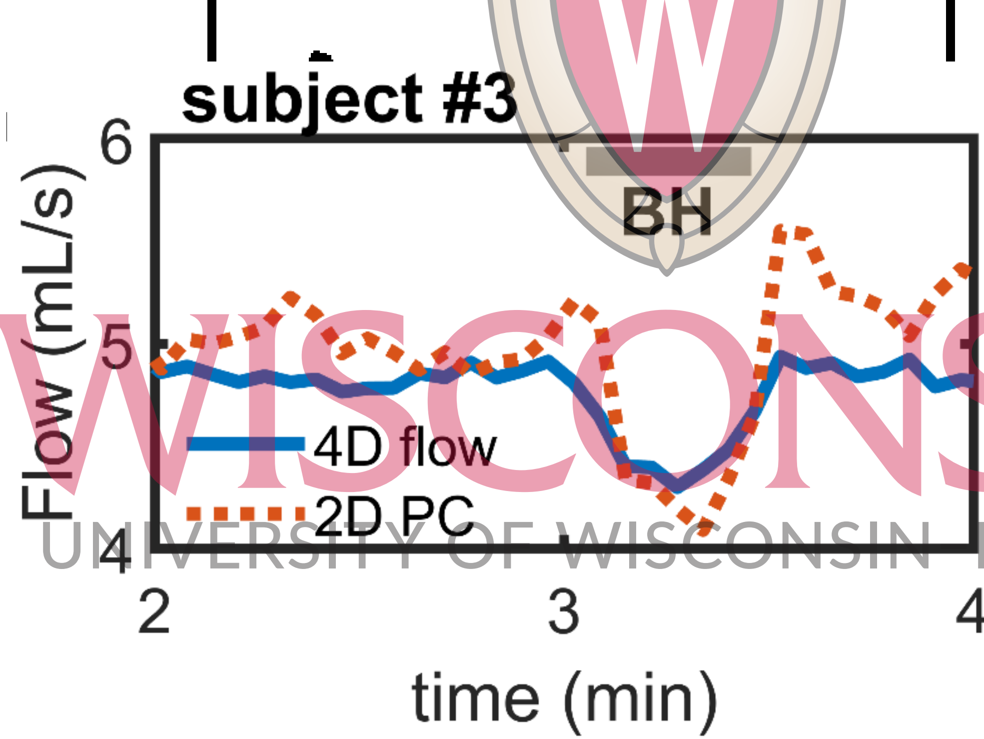
# Cerebrovascular Health Assessment using 4D flow MRI

- … oscillations e.g. 1Hz)
- … instead of to the cardiac cycle
    - Driven by … cardiac
        - Low freque… 0.1Hz) ?





[1] Iliff J.J., et al. Sci Transl Med. 2012 Aug 15;4(147):147ra111. doi: 10.1126/scitranslmed.3003748
[2] Aldea R, et al. Front Aging Neurosci. 2019 Jan 23;11:1. doi: 10.3389/fnagi.2019.00001. eCollection

# Frequency content of a typical functional MR signal

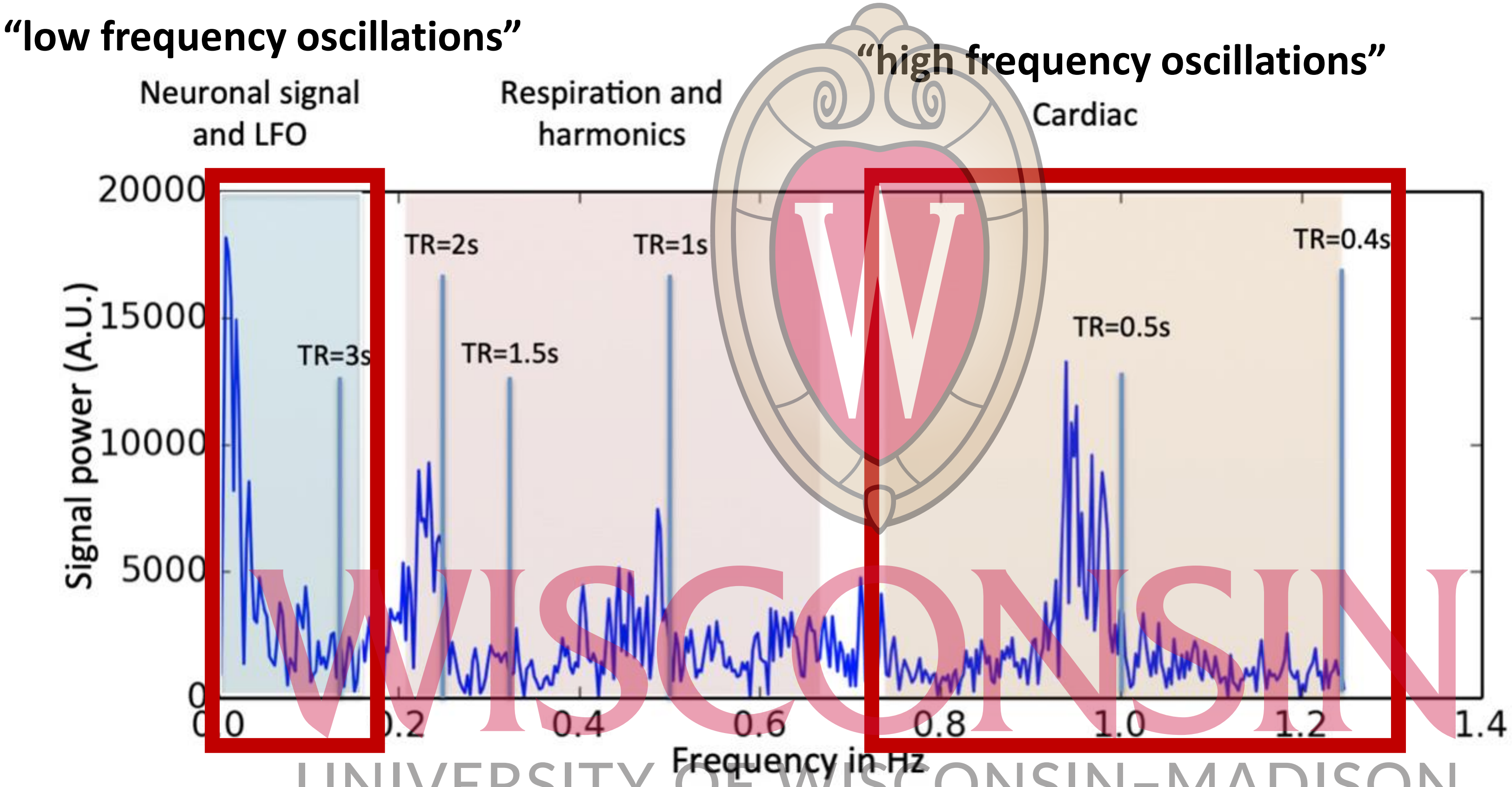



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Figure adapted from Tong Y, et al. Front Neurosci. 2019; 13: 787

# Study population recruited from WADRC

| N total = 112 | **AD** (N = 23) | **Older Controls** (N = 36) | **APOE4+, FH+** (N = 23) | **APOE4-, FH-** (N = 30) |
|---|---|---|---|---|
| Age (years) | 72 ± 10 | 73 ± 7 | 59 ± 3 | 57 ± 5 |
| CHS scores | 3.5 ± 2.3 | 2.7 ± 1.6 | 1.4 ± 0.6 | 1.6 ± 1.0 |

CHS, Cardiovascular Health Study scores use to quantify white matter hyperintensities

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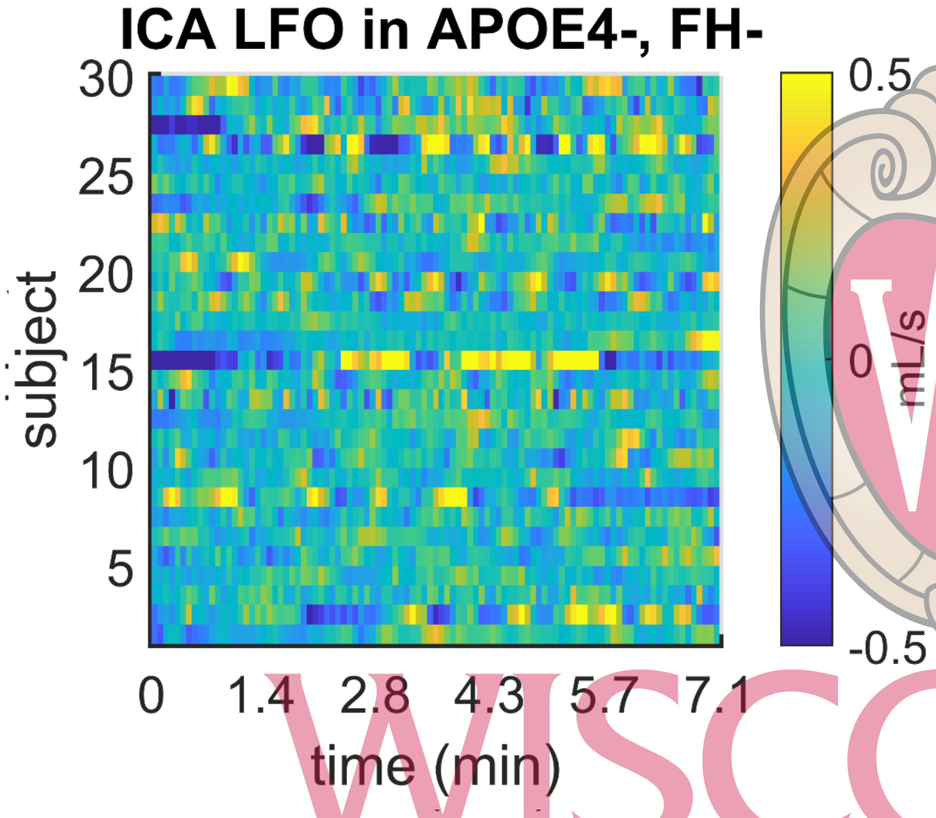
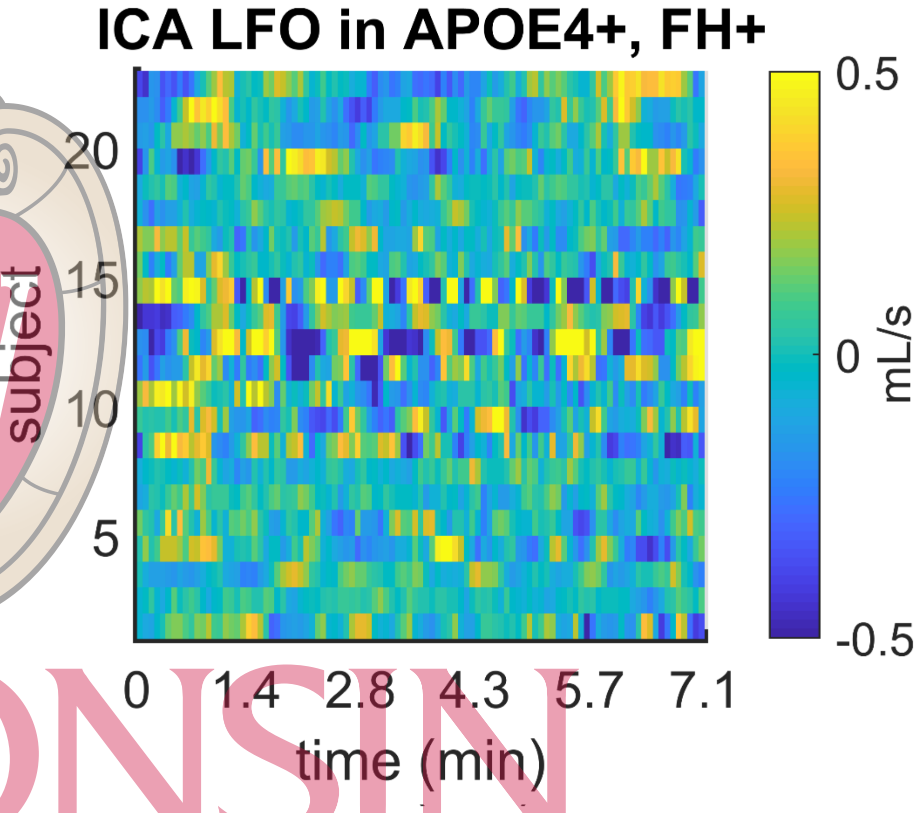
- Measurements:
  - superior sagittal sinus (SSS)
  - internal carotid artery (ICA)

# Demeaned Blood Flow Measures

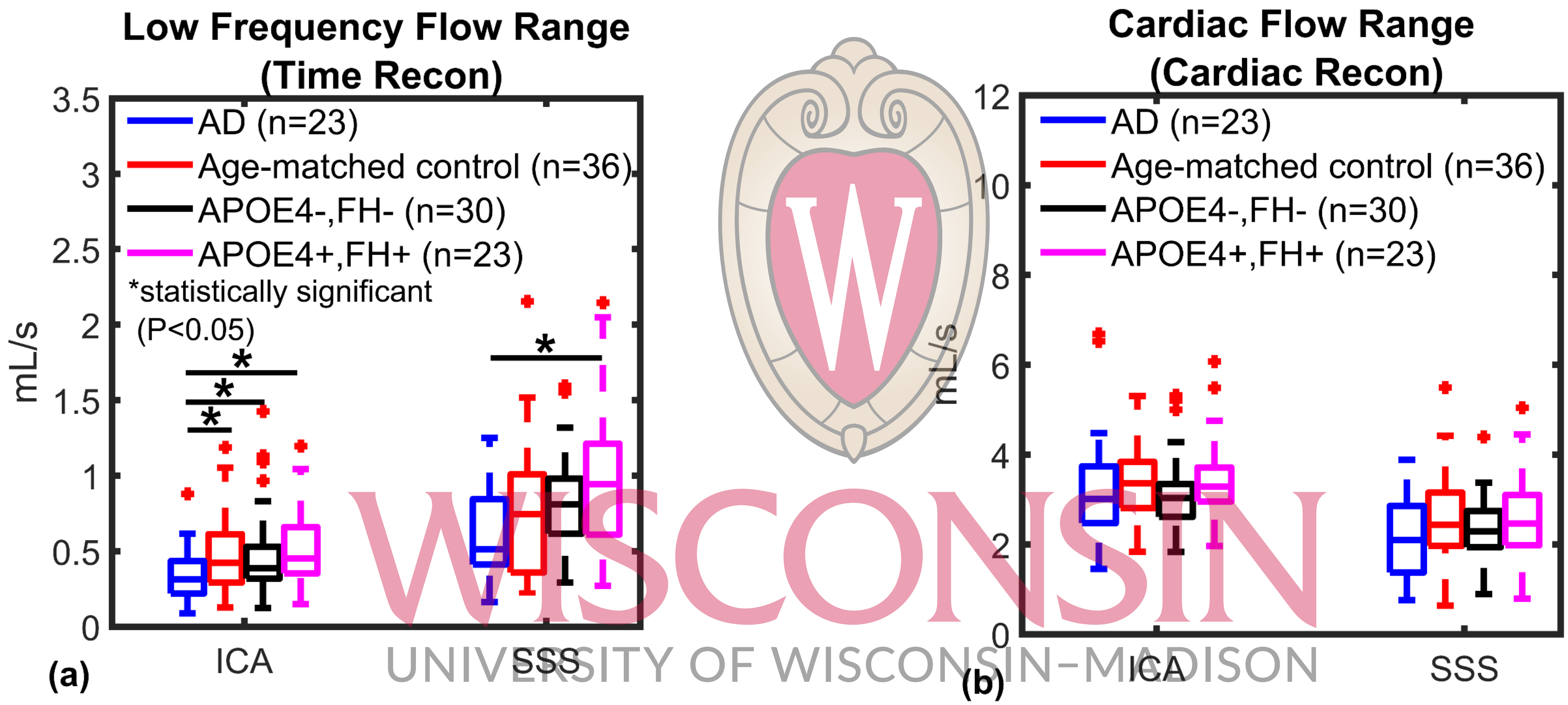



- Higher δf in subjects at higher risk (APOE4+, FH+) than lower risk (APOE4-, FH-)
- Lower δf in AD than age-matched controls

[1] Rivera-Rivera LA et al. NeuroImage: Clinical. *Under revisions.*

# Blood Flow Range: Low  vs High Frequencies (4.3s vs 50ms)

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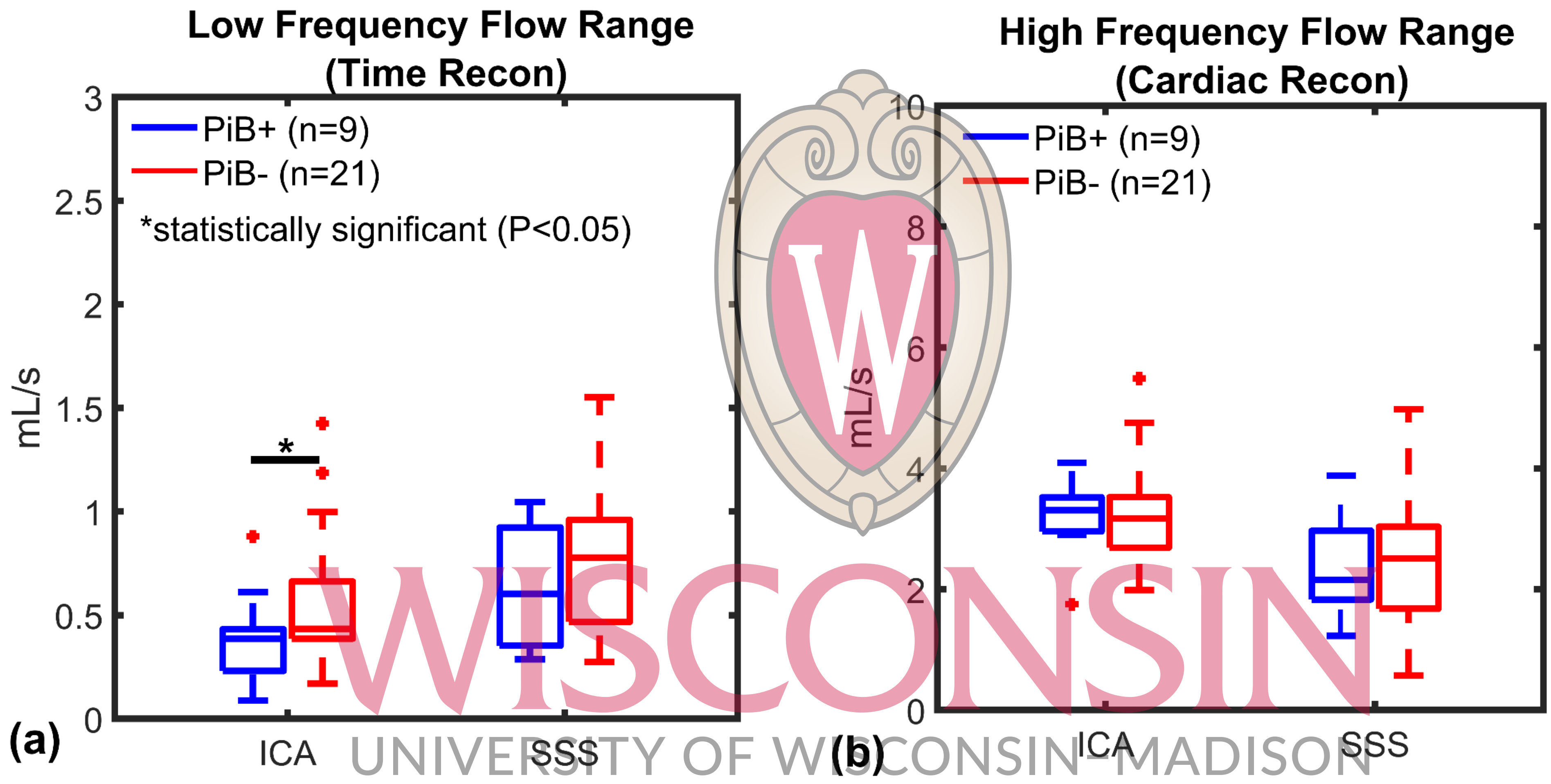
- Decreased low frequency flow range in AD
- Not as strong correlation with cardiac pulsation range (high frequency)

[1] Rivera-Rivera LA et al. NeuroImage: Clinical. *Under revisions.*

# LFOs and Amyloid Pathology

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- Significant decreased in LFOs markers in amyloid positive subjects
- Cardiac pulsations (high frequency) markers were similar between groups

# 4D flow based LFOs

- Is feasible to measure LFOs in the intracranial arteries and veins from 4D flow MRI data
  - Protocol optimization
  - Motion correction

- LFOs typically assess with BOLD fMRI
  - 4D flow advantages
    - Directly from vessels
    - Signal type (PC vs R2*)

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# 4D flow based LFOs

- Results suggest
  - decreased vasomotion in clinical AD
  - compensatory mechanisms in healthy APOE4+, FH+ ?

- 4D flow-based imaging markers vs AD pathology ?
  - Cognitively normal amyloid positive studies

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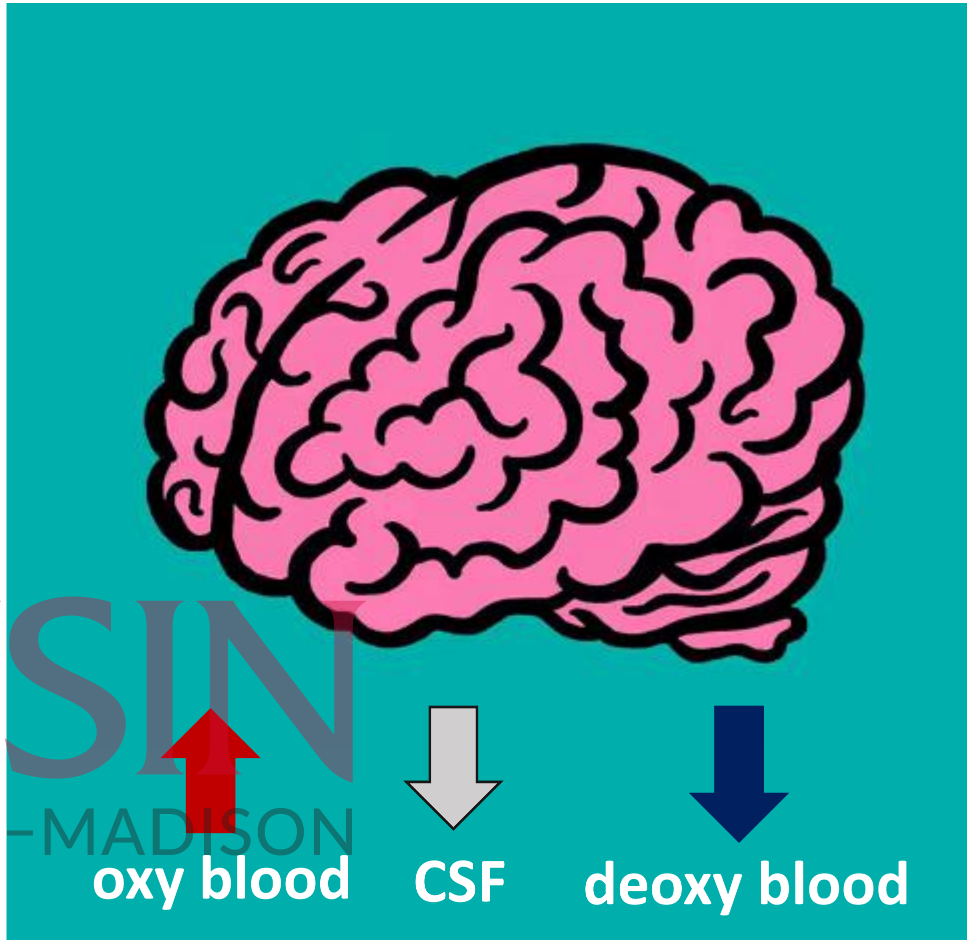
# Tissue-Vascular Interactions

- Cardiac pressure leads to brain tissue pulsations [1]

- **How does dysfunction of brain-vascular interactions impact brain health ?**

- **A problem of multiple compartments!**
    - fast (blood)
    - slow (CSF)
    - tissue response

- **First, how to probe compartments ?**
    - Large arteries and veins, CSF -> 4D flow
    - Capillary pulsations, vessel caliber changes and biomechanical interactions ?

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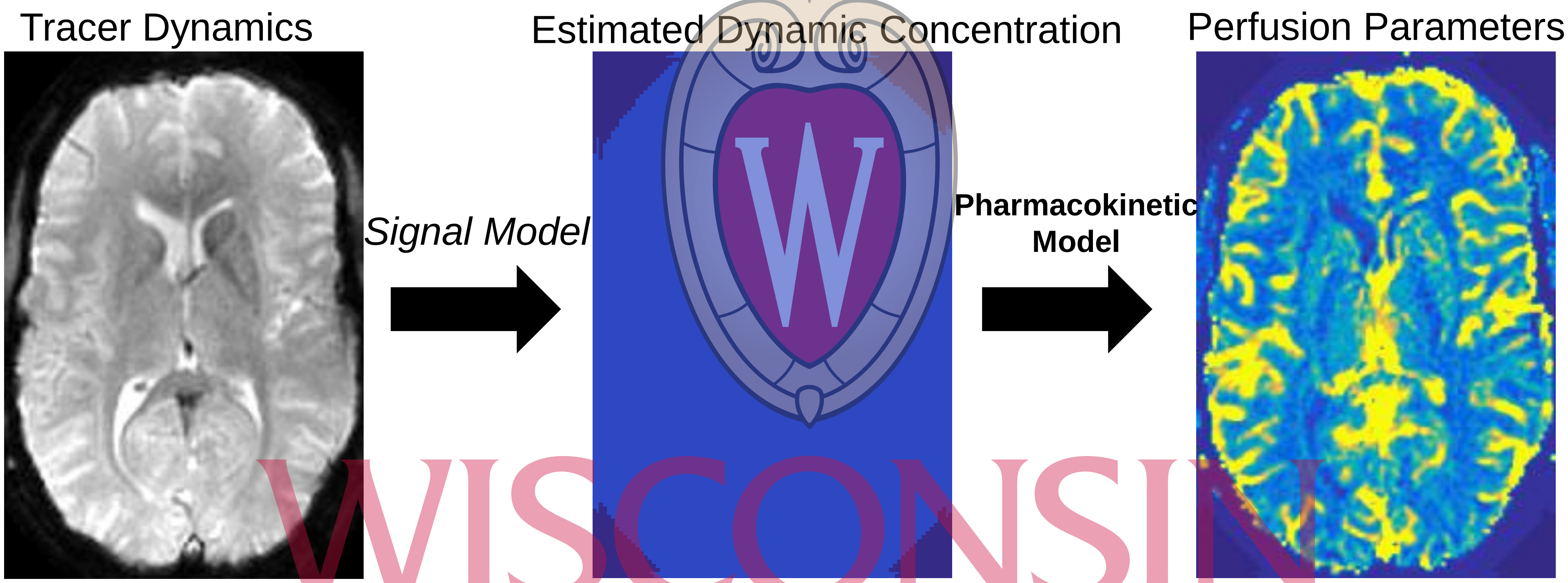
[1] Rivera-Rivera LA et al. Magn Reson Med. 2019 Jun;81(6):3588-3598.

# Capillary Pulsations with Contrast-Enhanced MRI

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**CE-MRI is an alternative when signals are too low for ASL-based detection**

# Ferumoxytol-enhanced MRI

- **Ferumoxytol** for contrast enhanced MRI:
  - iron supplement therapy in CKD patients
  - superparamagnetic
    - strong T1 and T2* shortening effects!
  - concerns over anaphylaxis reaction [1]

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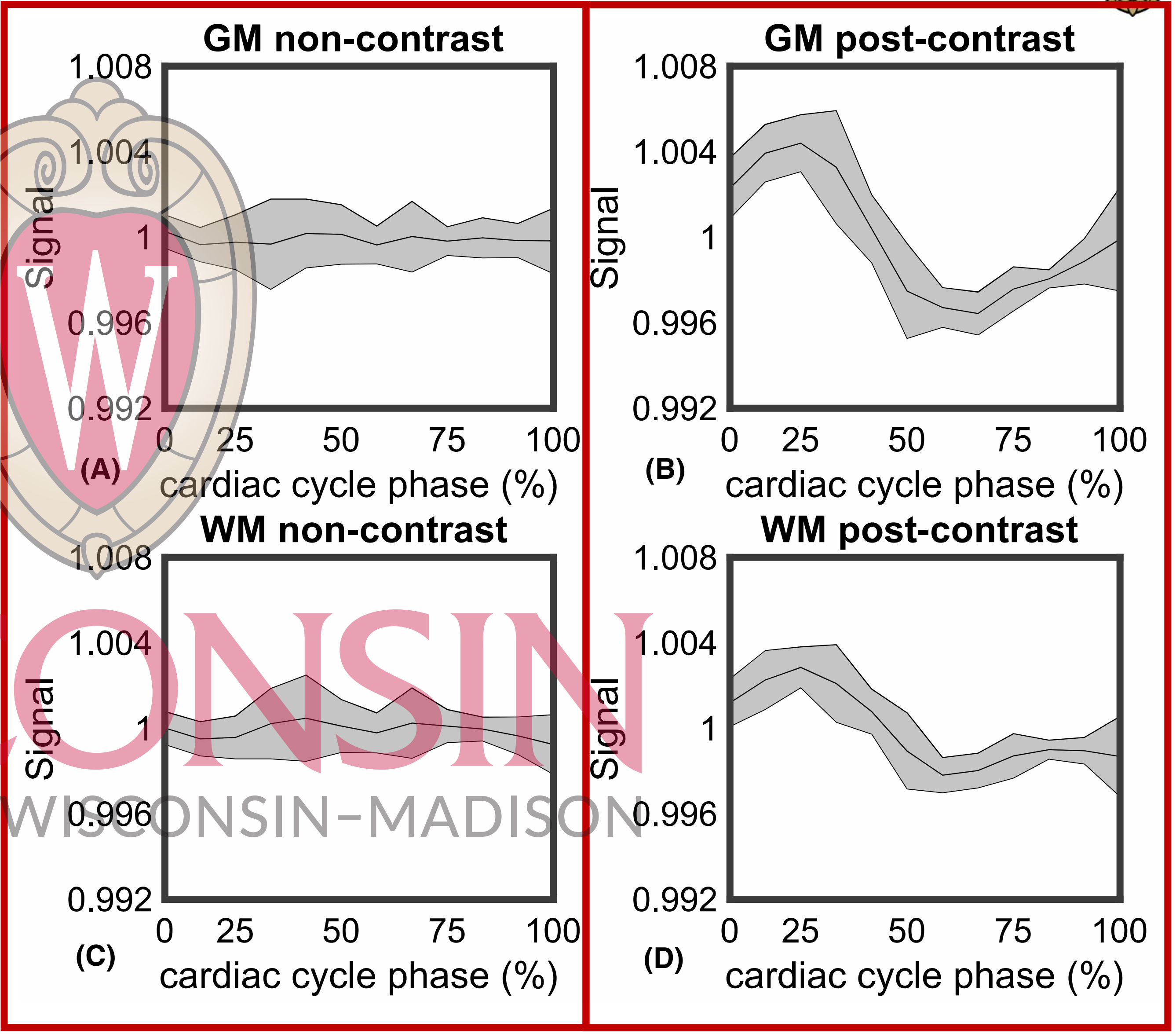
Angiogram derived from Ferumoxytol-enhanced data

[1] Varallyay CG, Toth GB, Fu R, et al. What does the boxed warning tell us? Safe practice of using ferumoxytol as an MRI contrast agent. AJNR Am J Neuroradiol 2017;38:1297–1302.

# Tissue Pulsations from Ferumoxytol-Enhanced T2* MRI

- Post-5mg FE/kg injection pulsatility became observable
- Pre-contrast tissue pulsations were observed

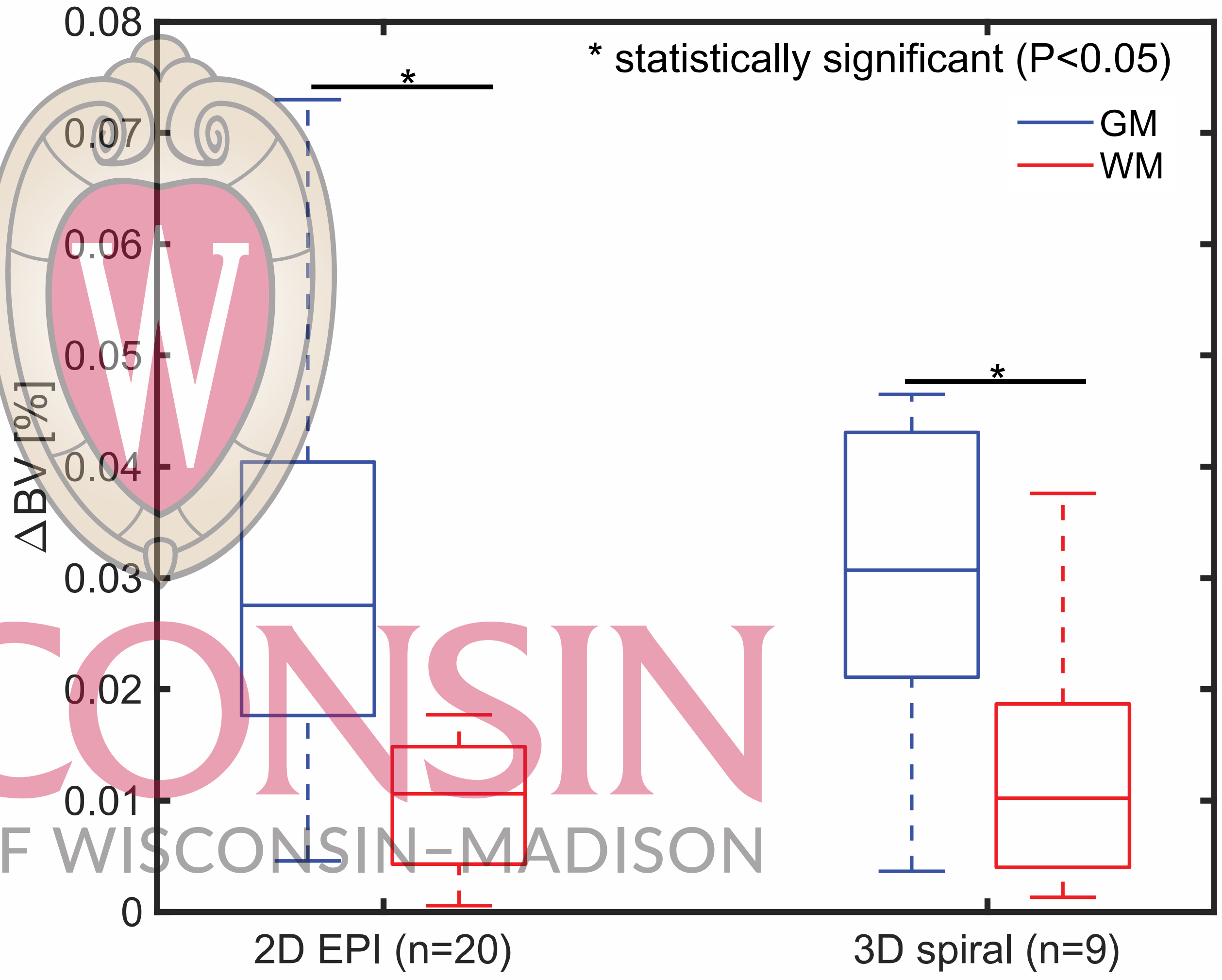




[1] Rivera-Rivera LA, et al. Magn Reson Med. 2018 Jun;79(6):3072-3081.
[2] Rivera-Rivera LA, et al. Magn Reson Med. 2019 Jun;81(6):3588-3598.
[3] Rivera-Rivera LA, et al. NMR Biomed. 2019 Dec;32(12):e4175.

# Blood Volume Changes During Tissue Pulsations

- Significantly higher blood volume changes in GM compared to WM

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[1] Rivera-Rivera LA, et al. Magn Reson Med. 2018 Jun;79(6):3072-3081.
[2] Rivera-Rivera LA, et al. Magn Reson Med. 2019 Jun;81(6):3588-3598.
[3] Rivera-Rivera LA, et al. NMR Biomed. 2019 Dec;32(12):e4175.

# Tissue-Vascular Interactions

- Capillary pulsatility can be assess using Ferumoxytol-enhanced MRI
  - exogenous contrast injection

- What about other tissue-vascular biomechanical interactions ?
  - tissue stiffness decreases with age [1]
  - vessel caliber changes and tissue strain

- Use displacement encoding with stimulated echoes (DENSE) MRI

- Similar principles to 4D flow MRI
  - Instead of encoding velocities, encode displacement to track tissue motion

[1] Takamura T et al. J Magn Reson Imaging. 2019 Aug 1. doi: 10.1002/jmri.26881

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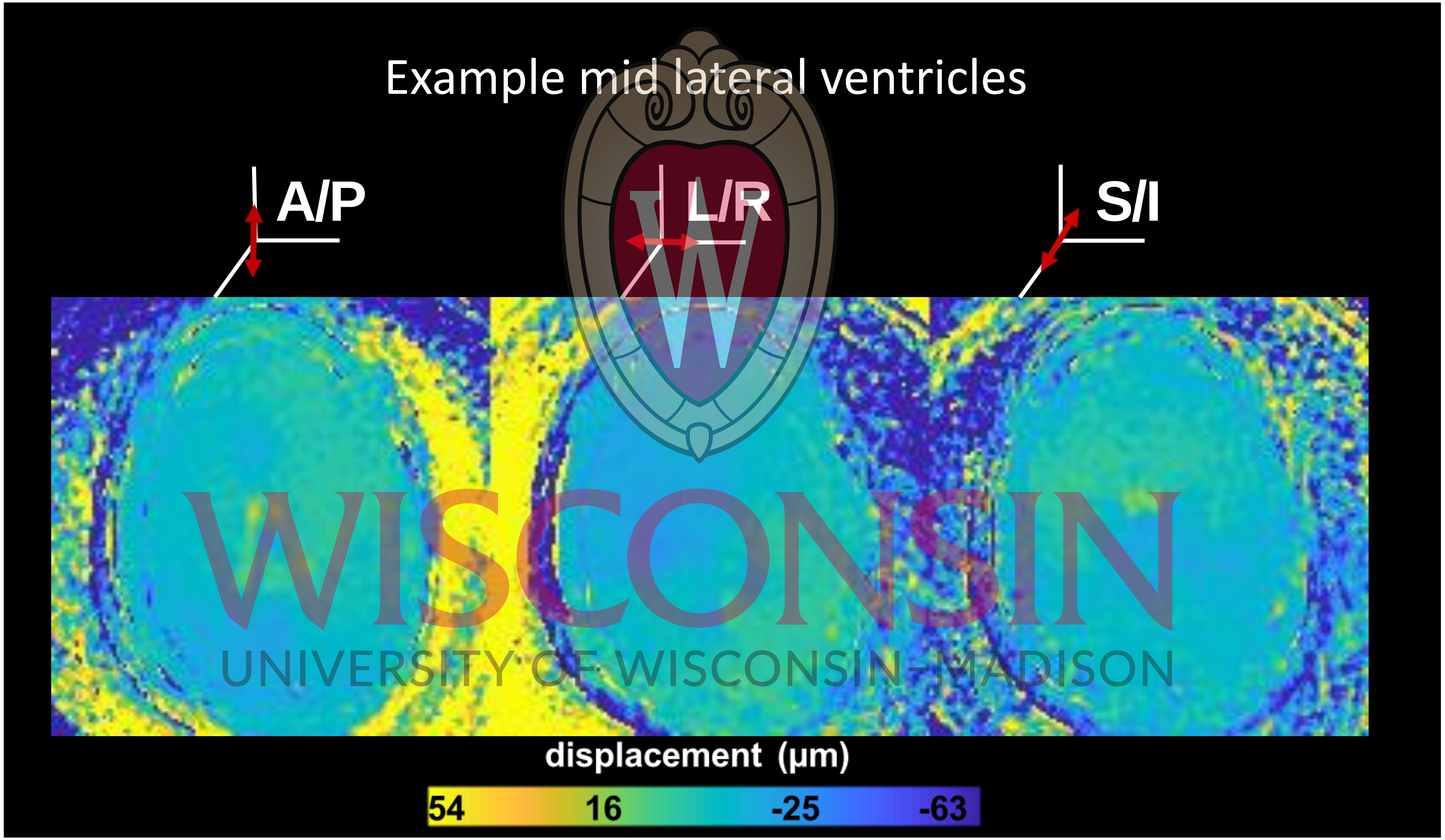
# 2D DENSE

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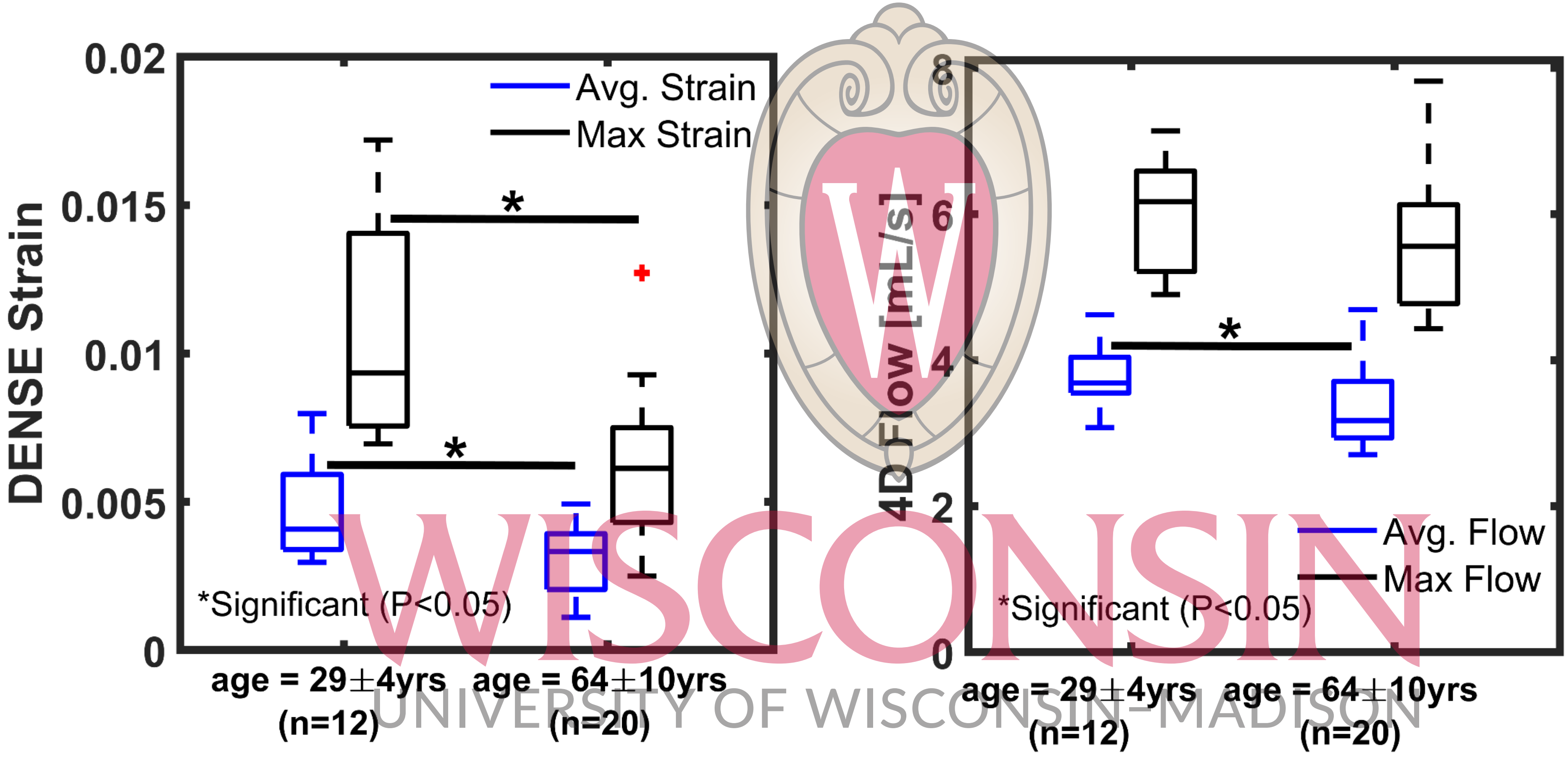
# Tissue Strain and Blood Flow during Aging

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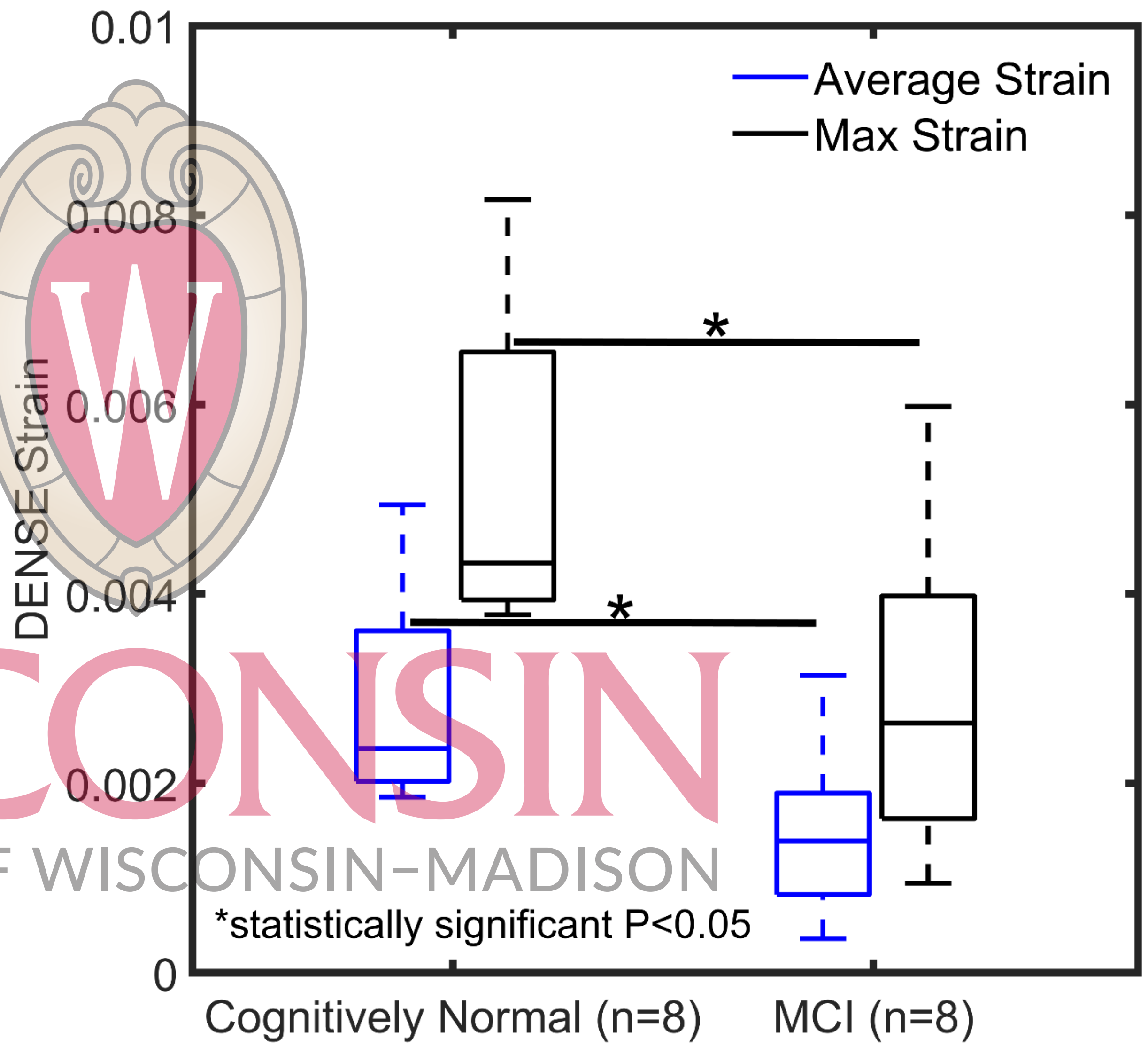
- Brain strain and cerebral blood flow are significantly lower in the older group.

# Preliminary Results in MCI

- Subjects diagnosed with mild cognitive impairment (MCI)
  - n=8, 3f
  - age = 74 ± 6 yrs
- Cognitively Normal
  - n=8, 3f
  - age = 71 ± 7 yrs

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# DENSE MRI

- Aging leads to diminish tissue strain presumably from reduced vasomotion [1,2]

- Preliminary data in MCI suggests reduced micro-vessel caliber changes
  - diminished brain clearance mechanisms ?
  - impaired mechanical stimuli from the vasculature damages tissue structural integrity ?

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[1] Amin-Hanjani Se t al. J Cereb Blood Flow Metab. 2015 Feb; 35(2): 312–318.
[2] Takamura T et al. J Magn Reson Imaging. 2019 Aug 1. doi: 10.1002/jmri.26881

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- **Tissue properties** using Magnetic Resonance Elastography
  —Grant Roberts, PhD Candidate, Medical Physics

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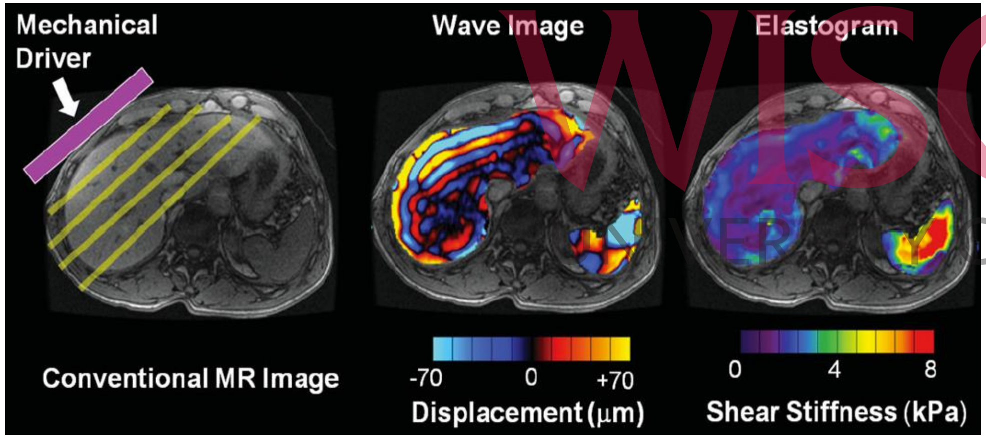
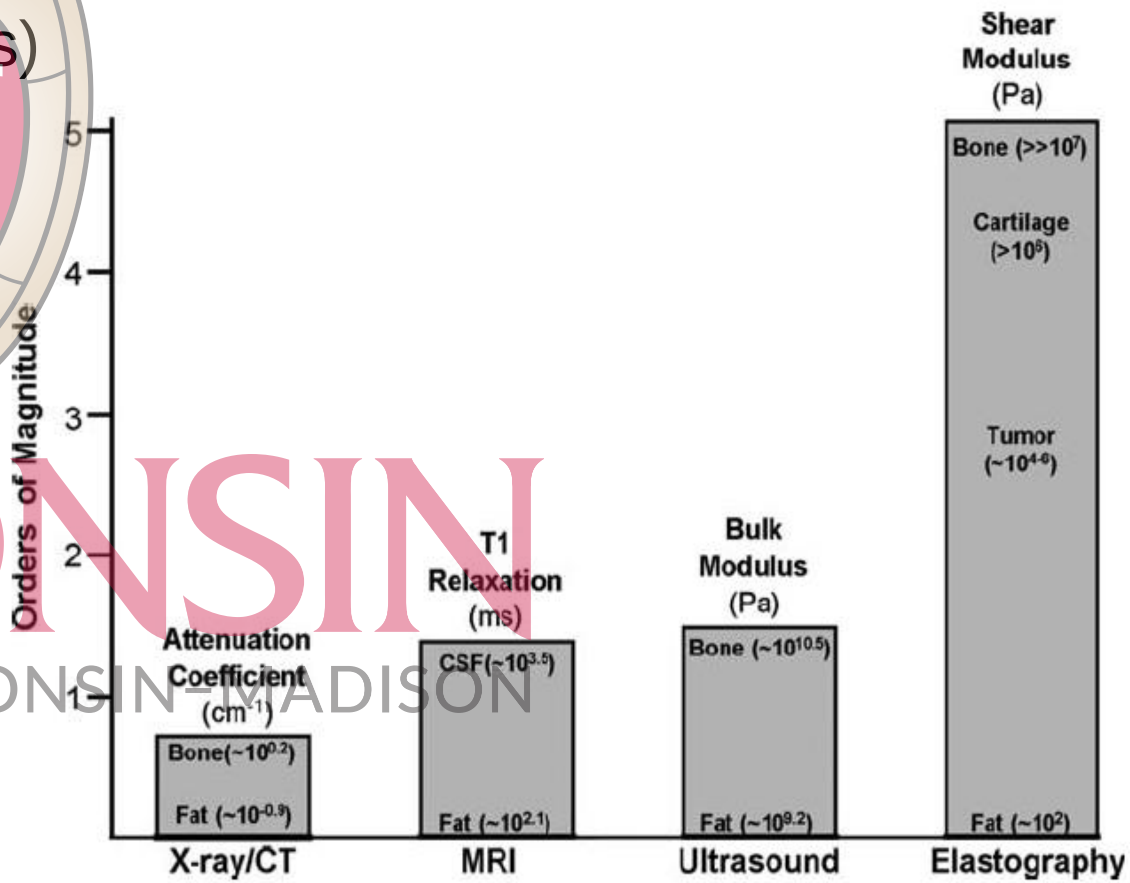
# MR Elastography (MRE)

- MRE allows for **quantitative analysis** of **tissue stiffness**
  - Phase contrast technique (1995)
  - Introduce shear waves into body (vibrations)
- Termed "Virtual palpation"
  - Tissue mechanics change with disease
  - Large dynamic range of tissue stiffness




Venkatesh, et al. *JMRI* (2013)




Mariappan, et al. *Clin Anat* (2010)

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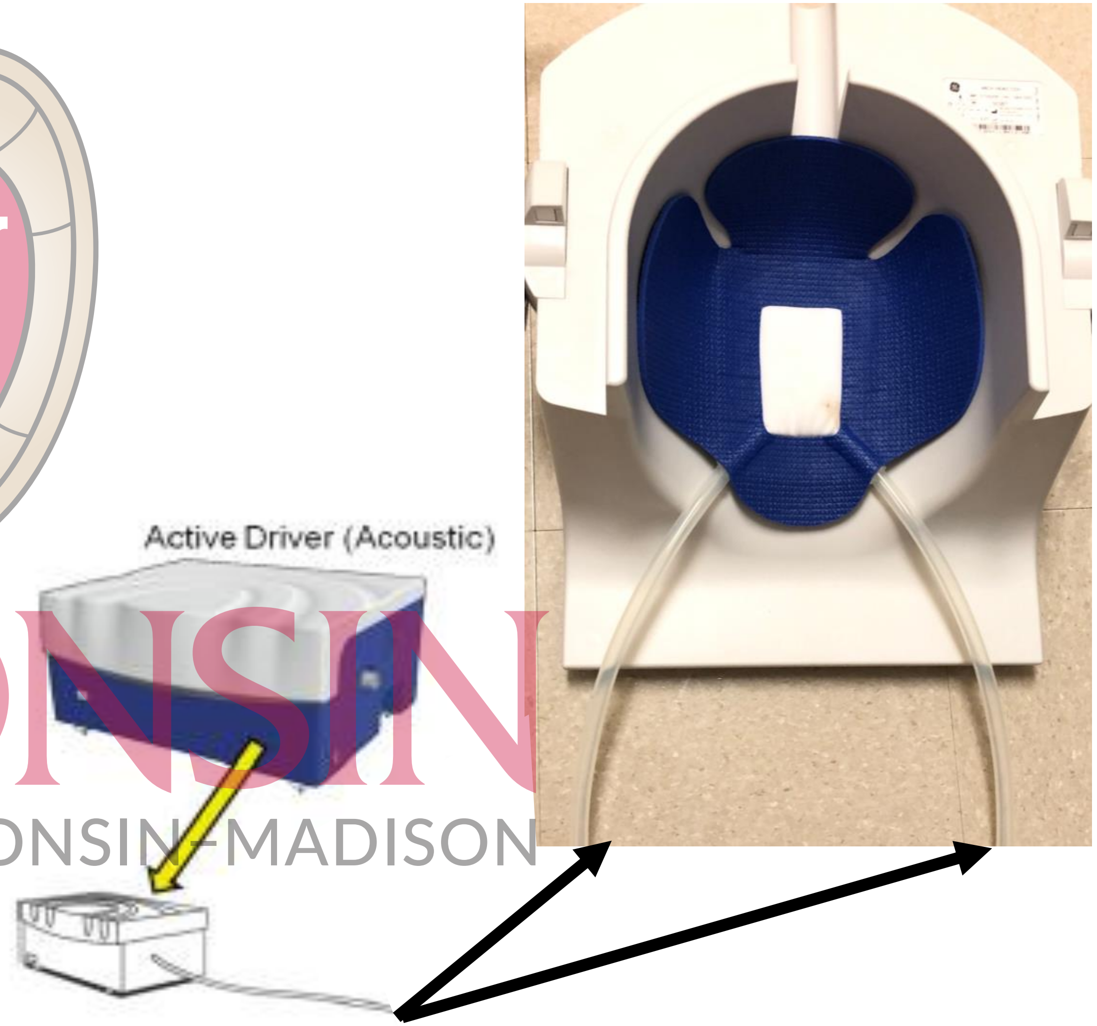
# MRE – External Wave Generation

- Introduce shear waves mechanically
- Shear waves are introduced by driver (20-200Hz)
  - Active driver placed outside of MR room
  - Passive driver placed under patient’s head
- Equipment installed in WIMR MR1
  - One of only a few sites that can perform brain MRE imaging

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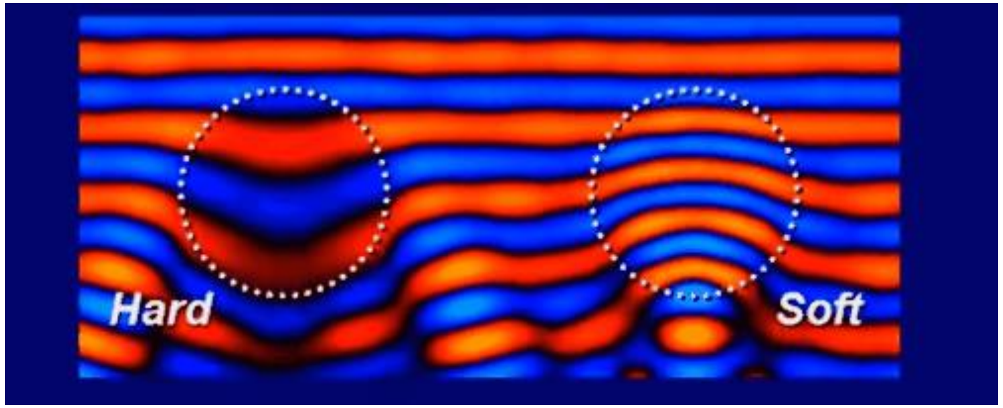
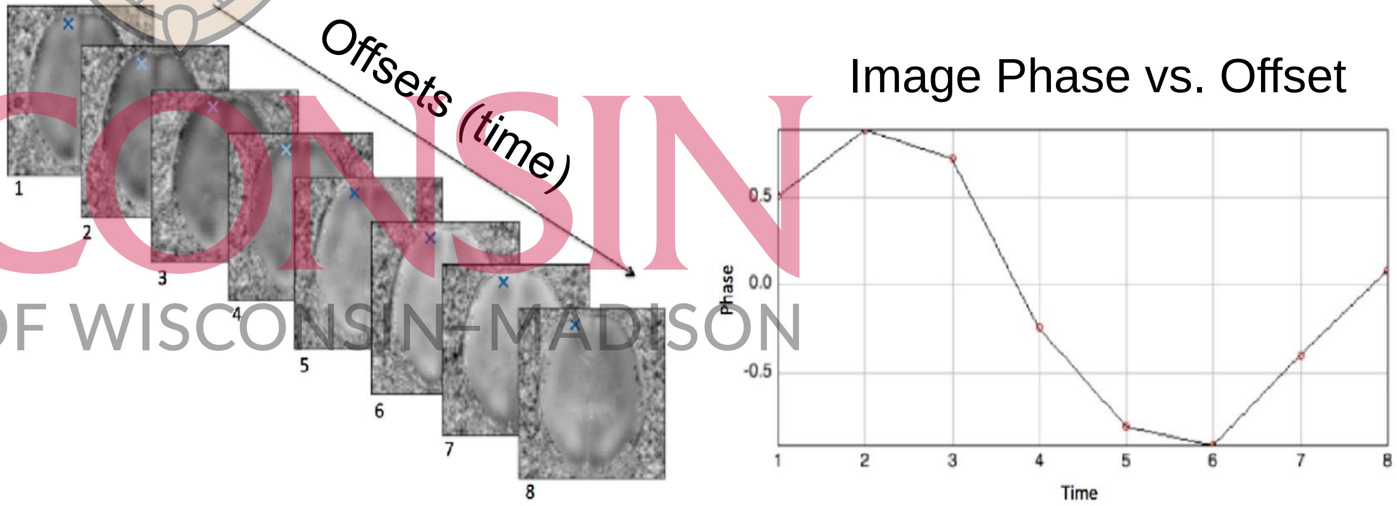
# MRE - Principles

- Wavelength dependent on tissue stiffness
  – Waves propagate rapidly in rigid tissue, slower in softer tissue
- Mechanical properties obtained from *complex shear modulus*
  – Inversion reconstructions
- Different from DENSE
  – MRE → shear stiffness
  – DENSE → tissue strain




From: https://www.youtube.com/watch?v=CcmZi0Ju3Y




Hiscox. *Phys Med Biol* (2016)

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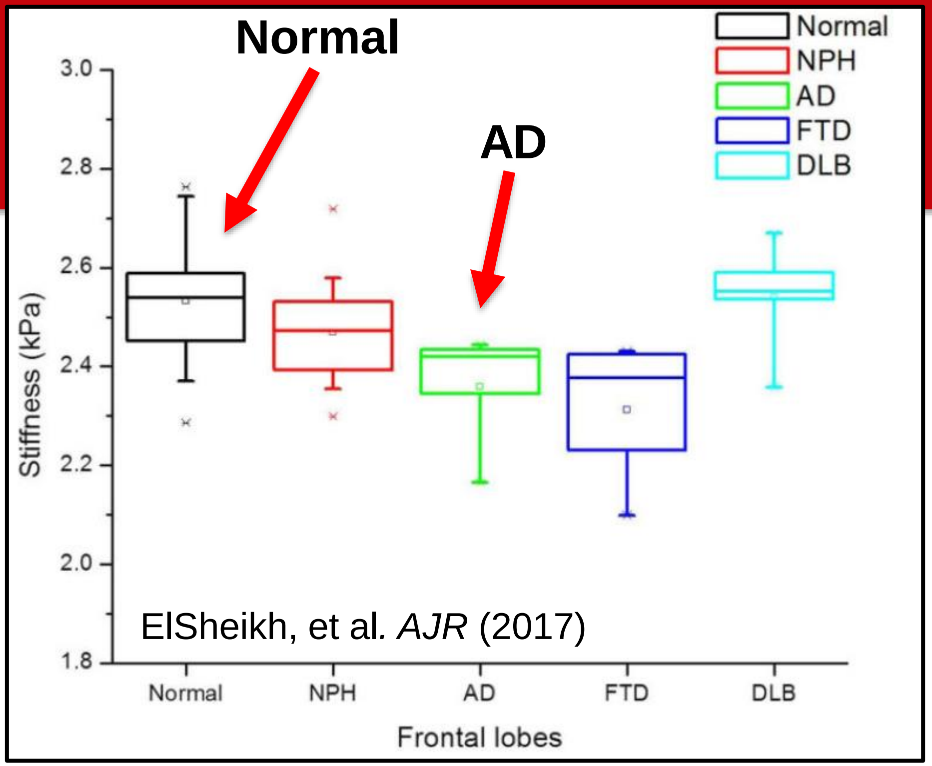
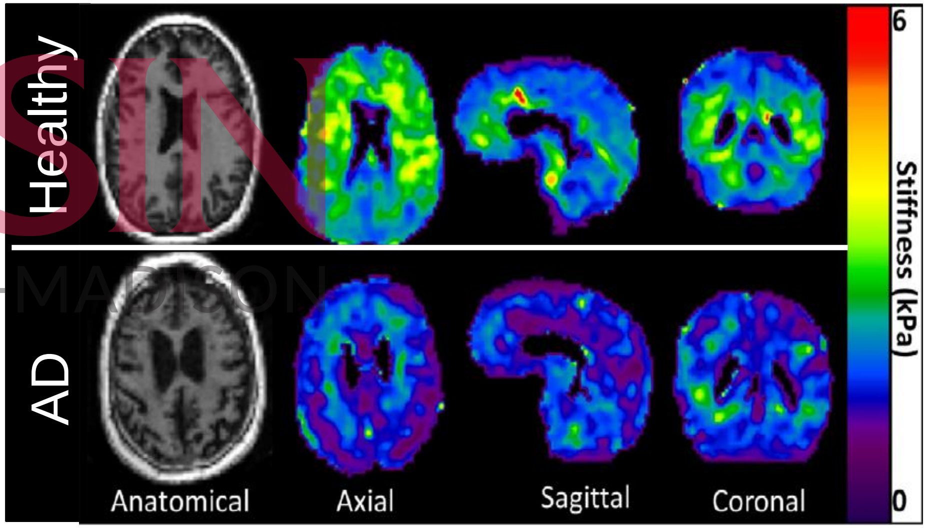
# MRE – Studies in AD

- Brain MRE Studies:
  - In healthy subjects: ~27 publications
  - In AD/dementia subjects: 6 publications
- Studies have evaluated both global and regional brain stiffness changes.
  - Decreased global brain stiffness
  - Decreased stiffnesses in frontal, temporal, and parietal lobes as well as hippocampus
- Hypothesized that decreased stiffness may be caused by cell architecture degradation
- Interplay between stiffness and vascular disease in AD?



ElSheikh, et al. *AJR* (2017)



Arani, et al. *Neuroimage* (2015)

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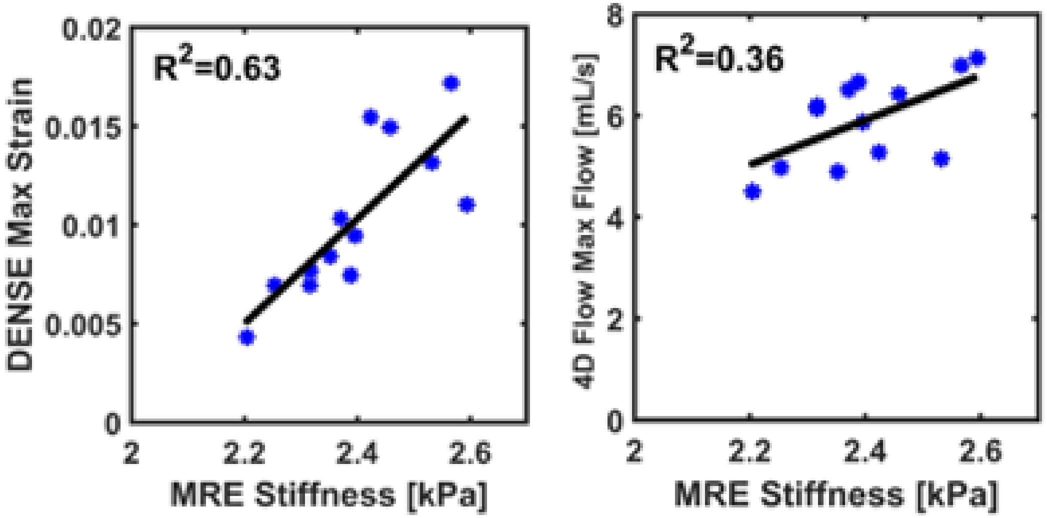
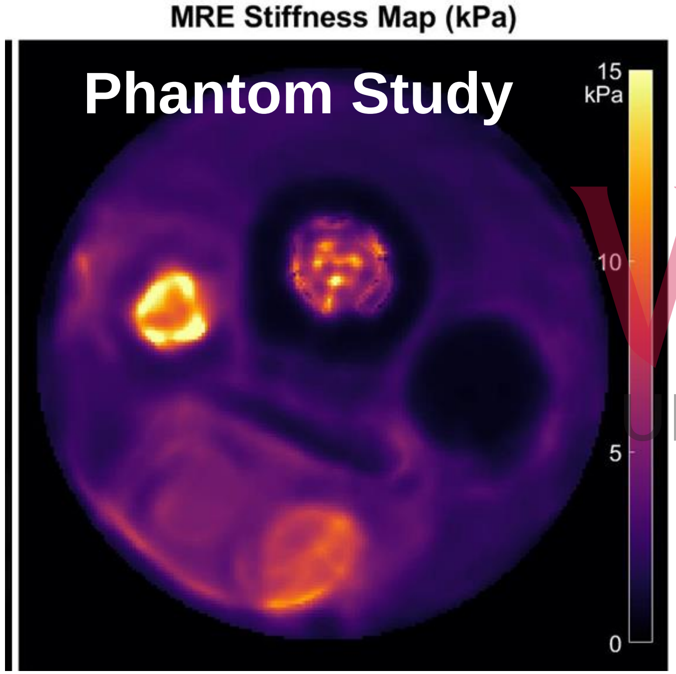
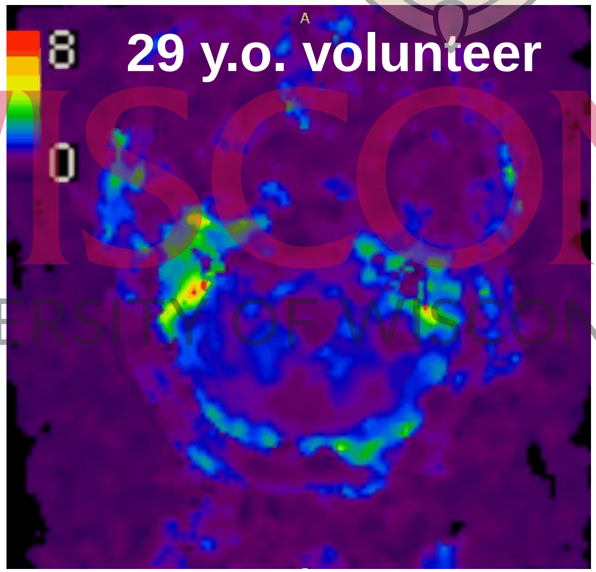
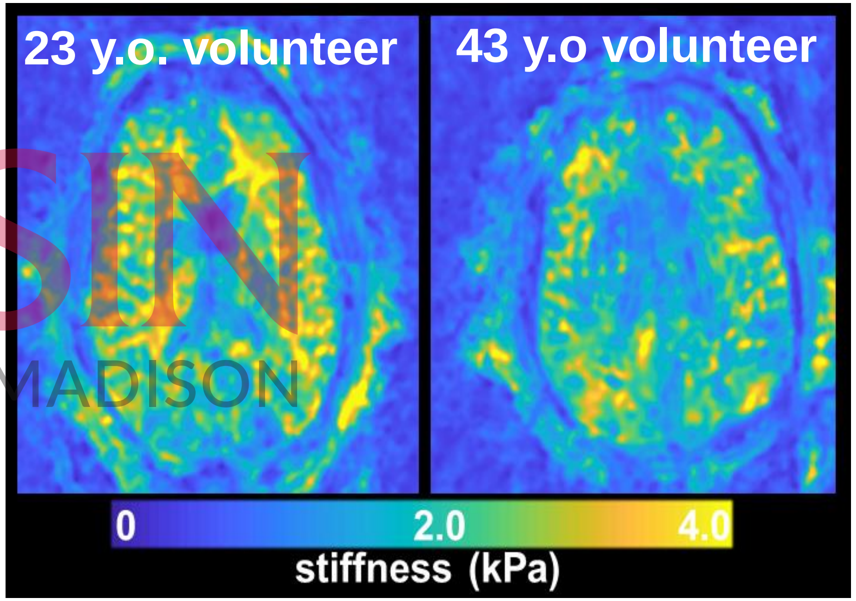
# MRE – Ongoing Work

- Developed a hydrogel phantom
  - Validated stiffness measures
- Scanned 6 younger and 13 older volunteers successfully



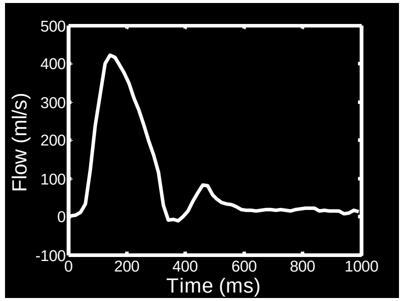

From : Rivera-Rivera LA et al. *ISMRM 2020*

# Vascular System – MRI Biomarkers

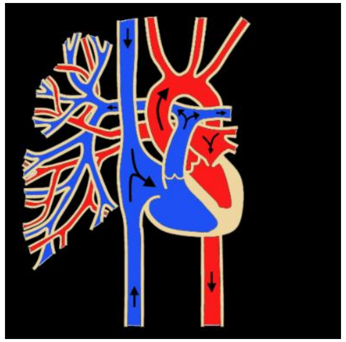
**Macroscopic Blood flow**

Mean flow (4D Flow)
Pulsatility / Resistivity (4D Flow)
Low frequency oscillations (4D Flow)
Vessel Stiffness
Pulse Wave velocity (4D Flow)

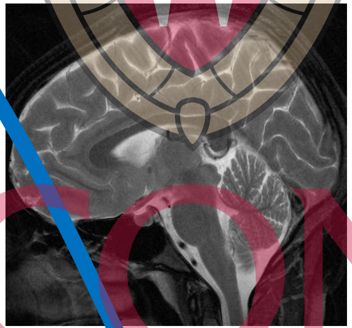
Arterial Network
*transport + regulation*




*Systemic risk factors*



*Brain Tissue*
*Capillary Bed*
*exchange + regulation*



**Microscopic Flow**

CBF - Cerebral Blood Flow (ASL)
global and local
Endothelial/blood brain barrier dysfunction
diffusion-prepared ASL

**Brain Pulsations – Tissue Vascular Interactions**

Vessel caliber changes
Blood volume changes ΔBV (Fe T2*)
Tissue Strain (DENSE)
Tissue Stiffness (MR Elastography)

Venous Network
*transport (waste clearance)*

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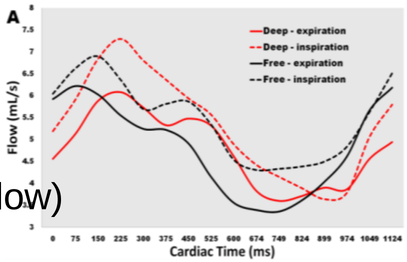
Glymphatic system

**Venous Blood flow**

Mean flow (4D Flow)
Pulsatility / Resistivity (4D Flow)
AV Transit times (4D Flow)



# Vascular Measures with MRI

**Vascular tissue damage**

White Matter Hyperintensities

Microbleeds (T2*)

**Microscopic Flow**

CBF - Cerebral Blood Flow (ASL)

**Brain Tissue Stiffness**

Tissue Stiffness (MR Elastography)

**Brain Pulsations – Tissue Vascular Interactions**

Tissue Strain (DENSE)

Delta Blood Volume (Fe+ MRI)

**Macroscopic Blood flow**

Mean flow (4D Flow)

Pulsatility / Resistivity (4D Flow)

Low frequency oscillations (4D Flow)

**Vessel Wall**

Stiffness / Pulse Velocity (4D Flow)

Permeability (Diffusion ASL)

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# Acknowledgements


<u>The ADRC</u>

Sanjay Asthana
Sterling C. Johnson
Barbara Bendlin
Cynthia Carlsson
Howard A. Rowley
Lindsay R. Clark
Ozioma Okonkwo
Sara E. Berman
Tobey Betthauser
Karly Cody
Caitlin Cleary
Amy A. Hawley
Chuck Illingworth
Paul Cary
Jennifer Oh
Robert Cadman
Bill Bevis and many more!

<u>UW MR Support Staff</u>

Kelli Hellenbrand
Sara John
Marti Garcia
Annelise Van Keulen

<u>Funding:</u>

NIH grants
- P50-AG033514
- R01NS066982
- R01AG021155

Alzheimer's Association fellowship
- AARFD-20-678095


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**Thank You!**