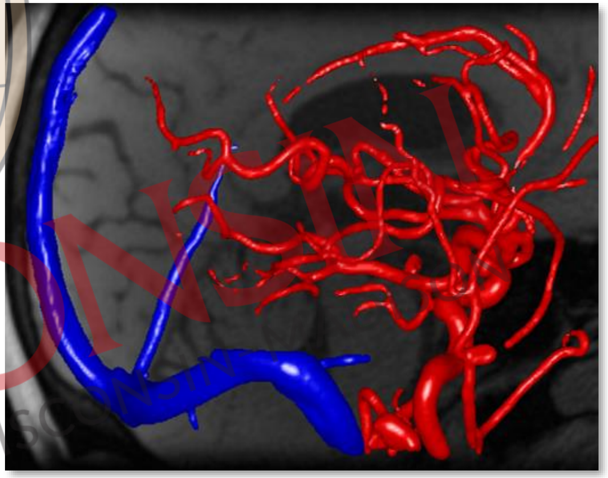
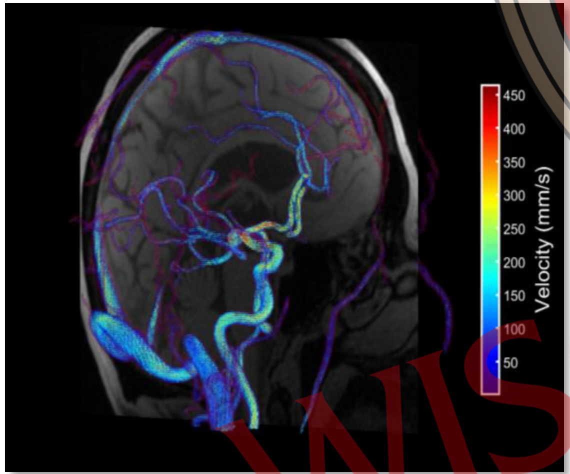
Advancing Functional Assessment for Cerebrovascular 4D Flow MRI



Grant Roberts

Medical Physics Seminar – 01/30/2023

Advisors: Laura Eisenmenger and Oliver Wieben



Outline

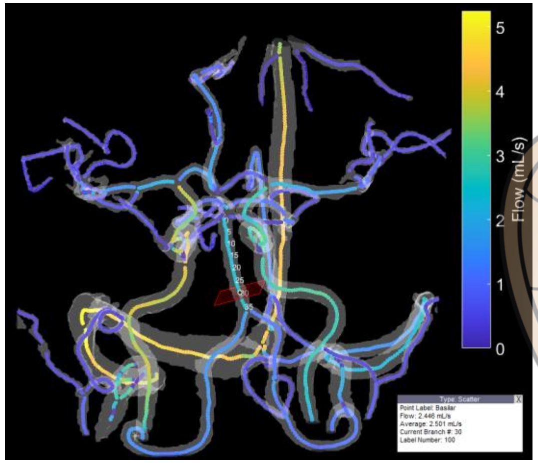
1. Background: 4D Flow MRI

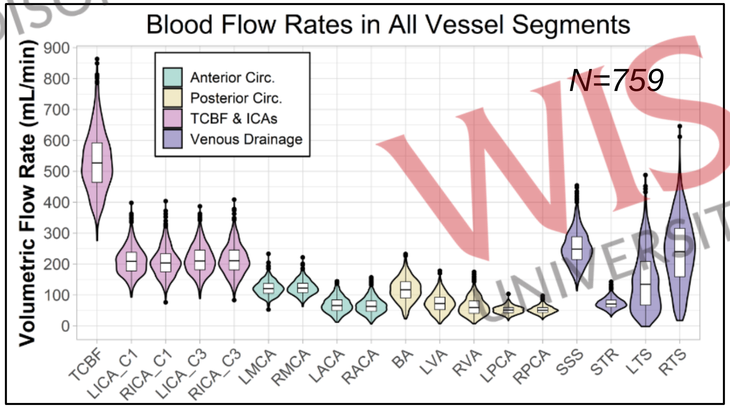
2. Studies

   - Cranial 4D Flow MRI Analysis Tool

   - Defining “Normal” Flow and Pulsatility in Older Adults

3. Summary





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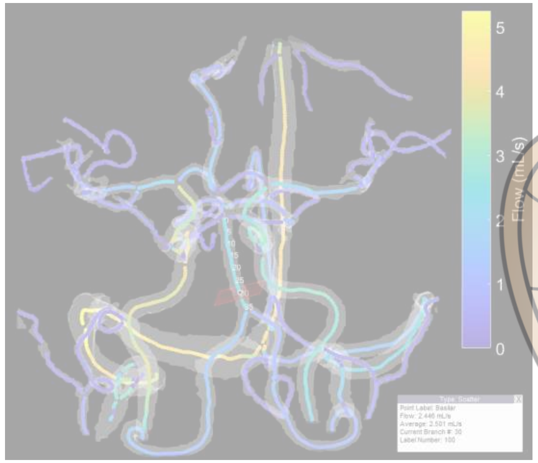
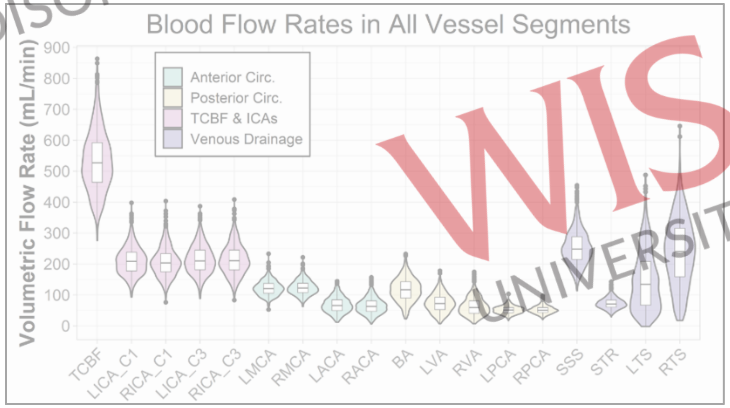
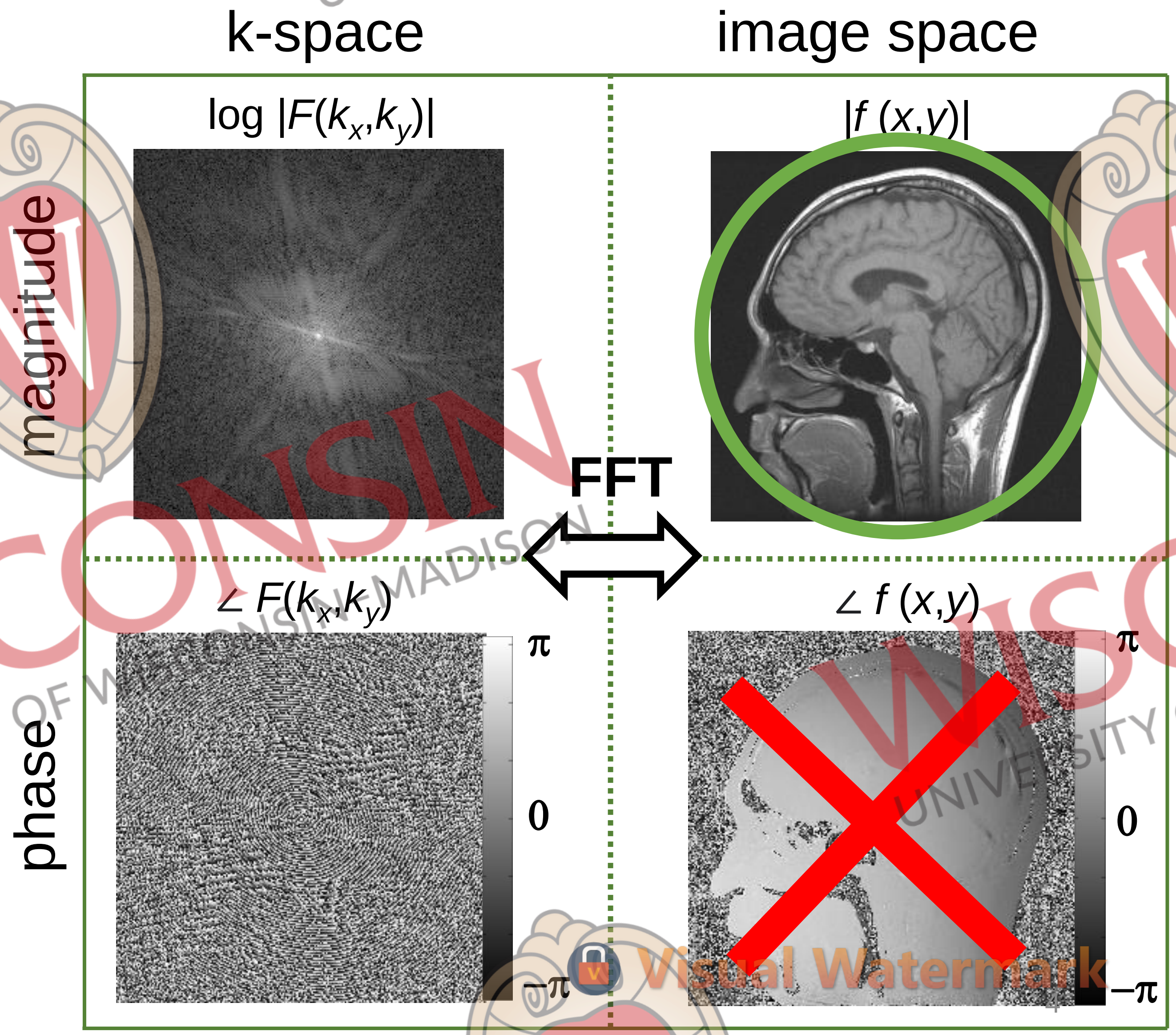




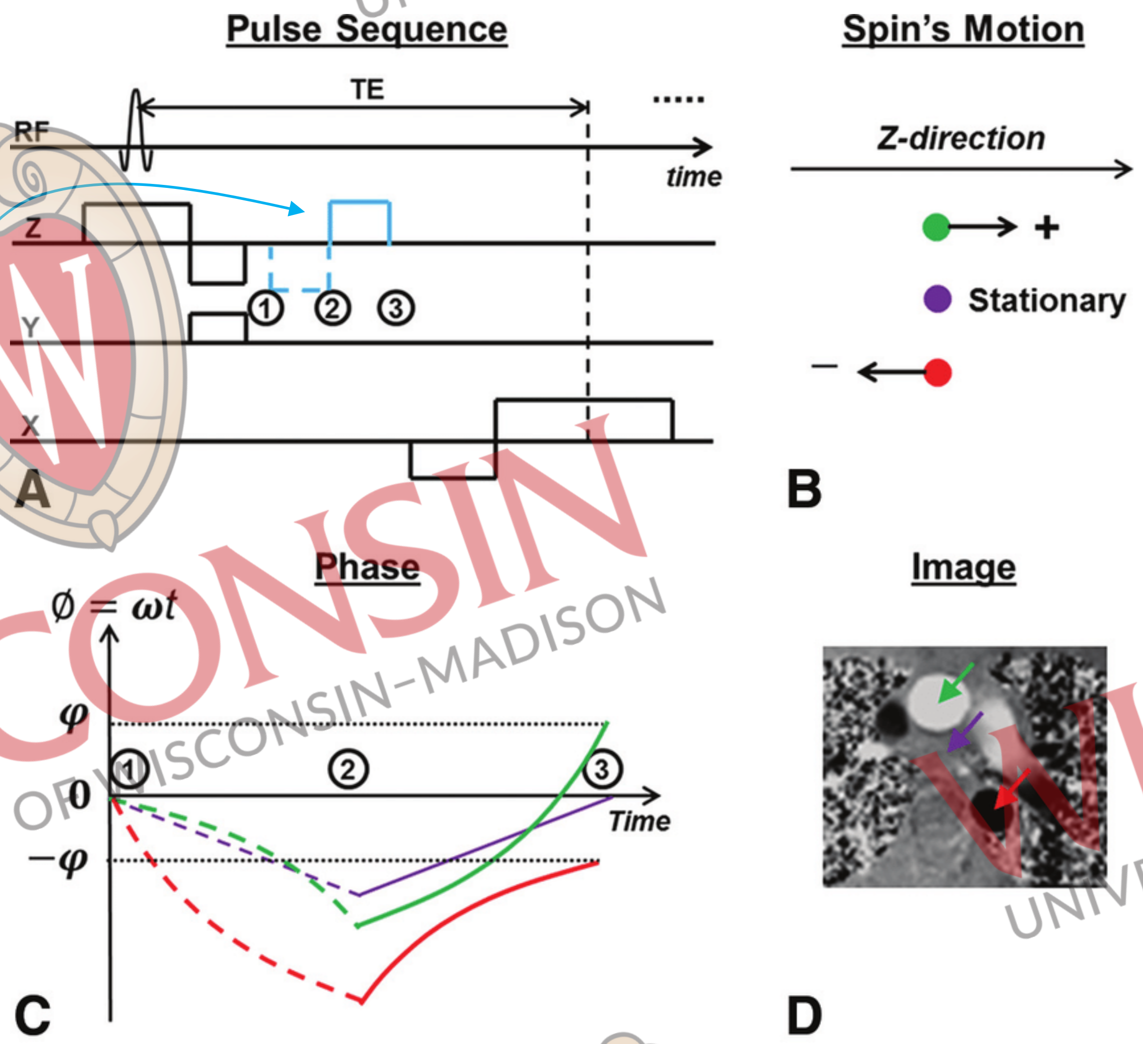
MRI Images Are Complex!

- Acquired data is complex-valued
  - Phase and magnitude
  - Phase maps often discarded



Phase Contrast MRI

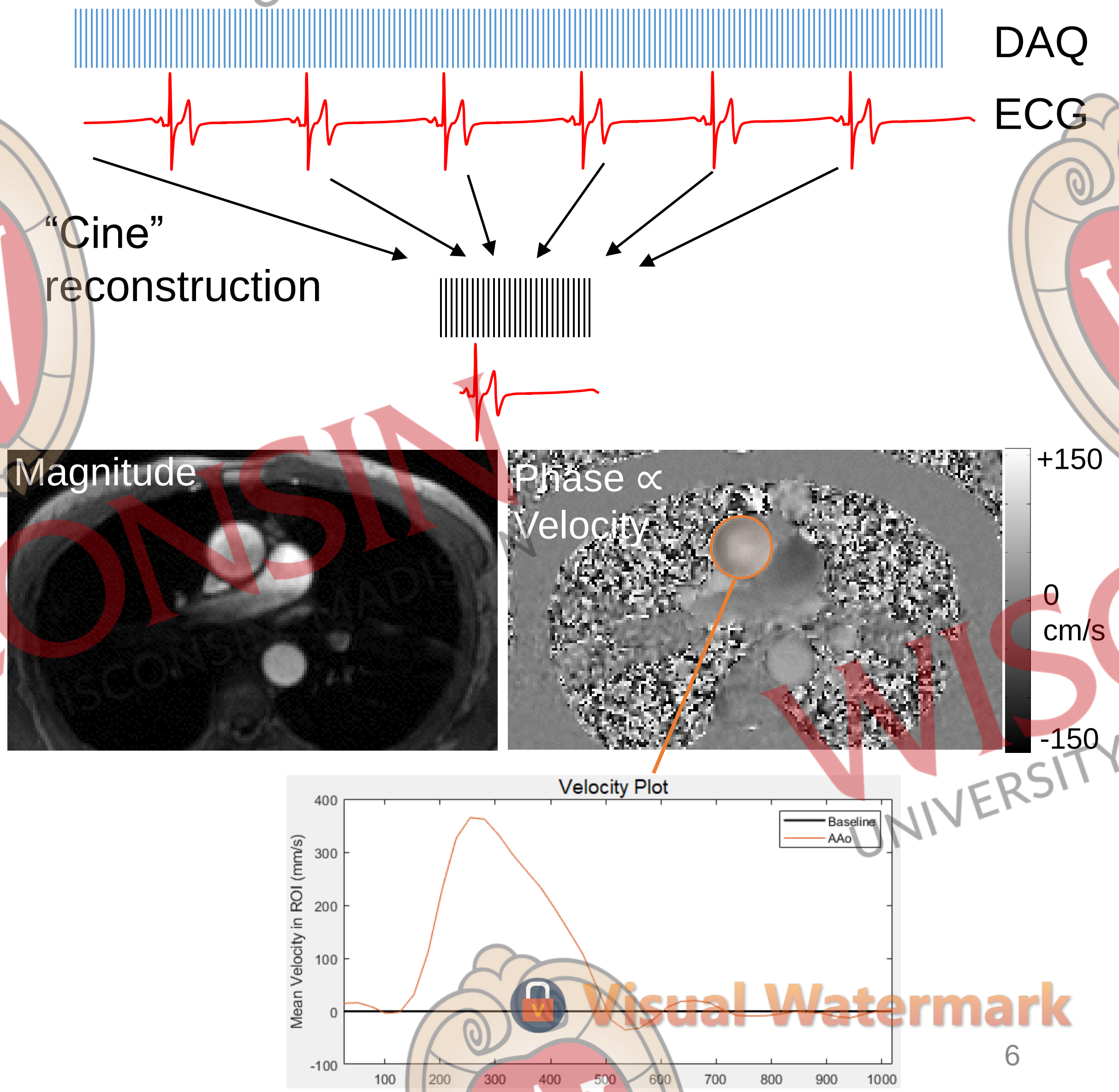
- Acquired data is complex-valued
  - Phase and magnitude
  - Phase maps often discarded
- **Can encode velocity into phase**
  - Bipolar gradients
  - Phase contrast MRI



From: Alves, T, et al (2017). *Neurographics 7*

2D Phase Contrast MRI

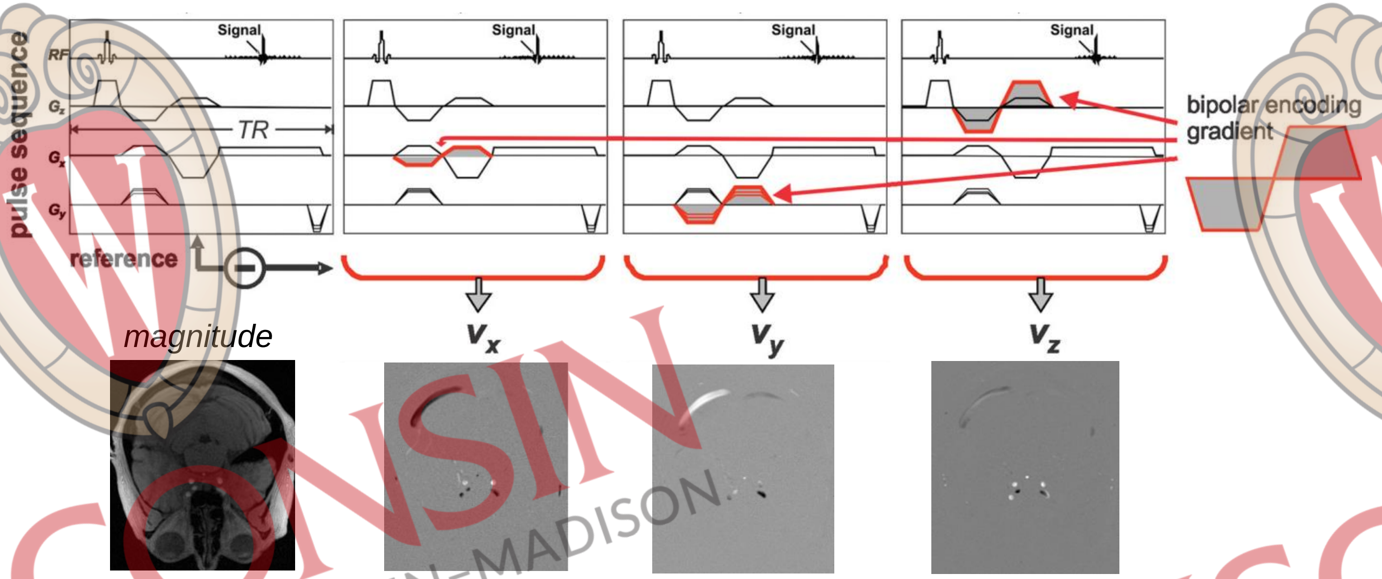
- Acquired data is complex-valued
  - Phase and magnitude
  - Phase maps often discarded
- Can encode velocity into phase
  - Bipolar gradients
  - Phase contrast MRI
- <u>2D Phase Contrast MRI</u>
  - Velocity encoded "through-plane"
  - "Gated" over multiple heartbeats
    - Time-resolved over cardiac cycle

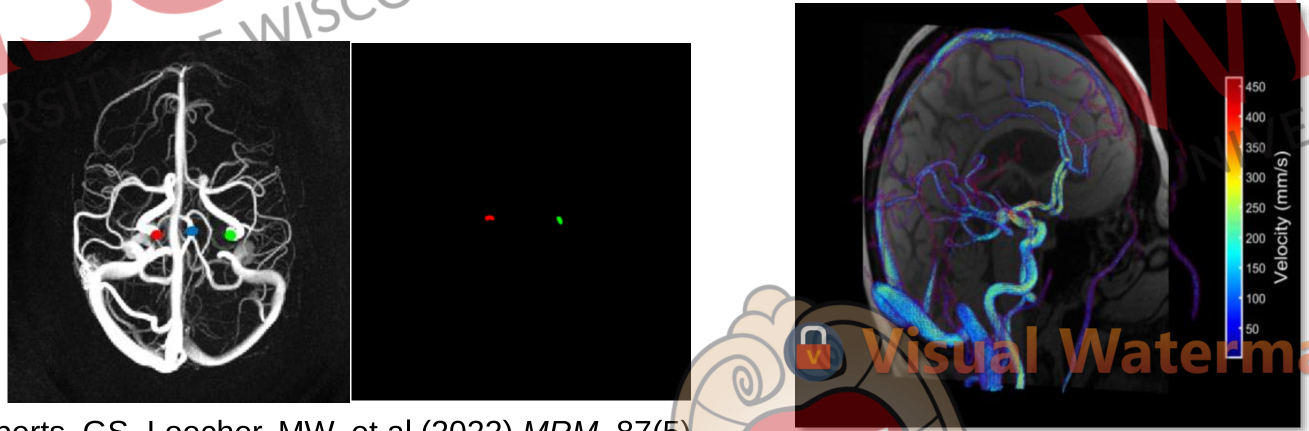


4D Flow MRI

- Acquired data is complex-valued
  - Phase and magnitude
  - Phase maps often discarded
- Can encode velocity into phase
  - Bipolar gradients
  - Phase contrast MRI
- <u>2D Phase Contrast MRI</u>
  - Velocity encoded “through-plane”
  - “Gated” over multiple heartbeats
    - Time-resolved over cardiac cycle
- <u>4D Flow MRI</u>
  - **4D? → 3D Space + 1D Time**
  - 3D velocity fields

Markl M, et al (2012) *JMRI*. 36(5)

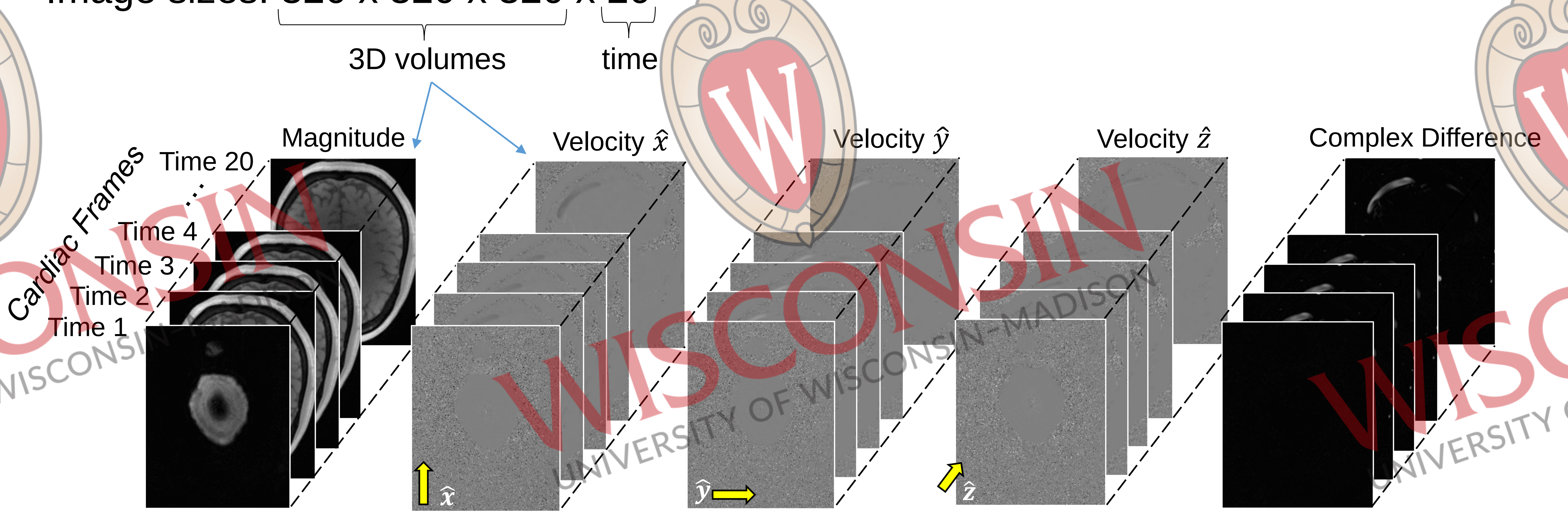




Roberts, GS, Loecher, MW, et al (2022) *MRM*. 87(5)

4D Flow MRI

- We have a lot of data!
- Image sizes: 320 x 320 x 320 x 20



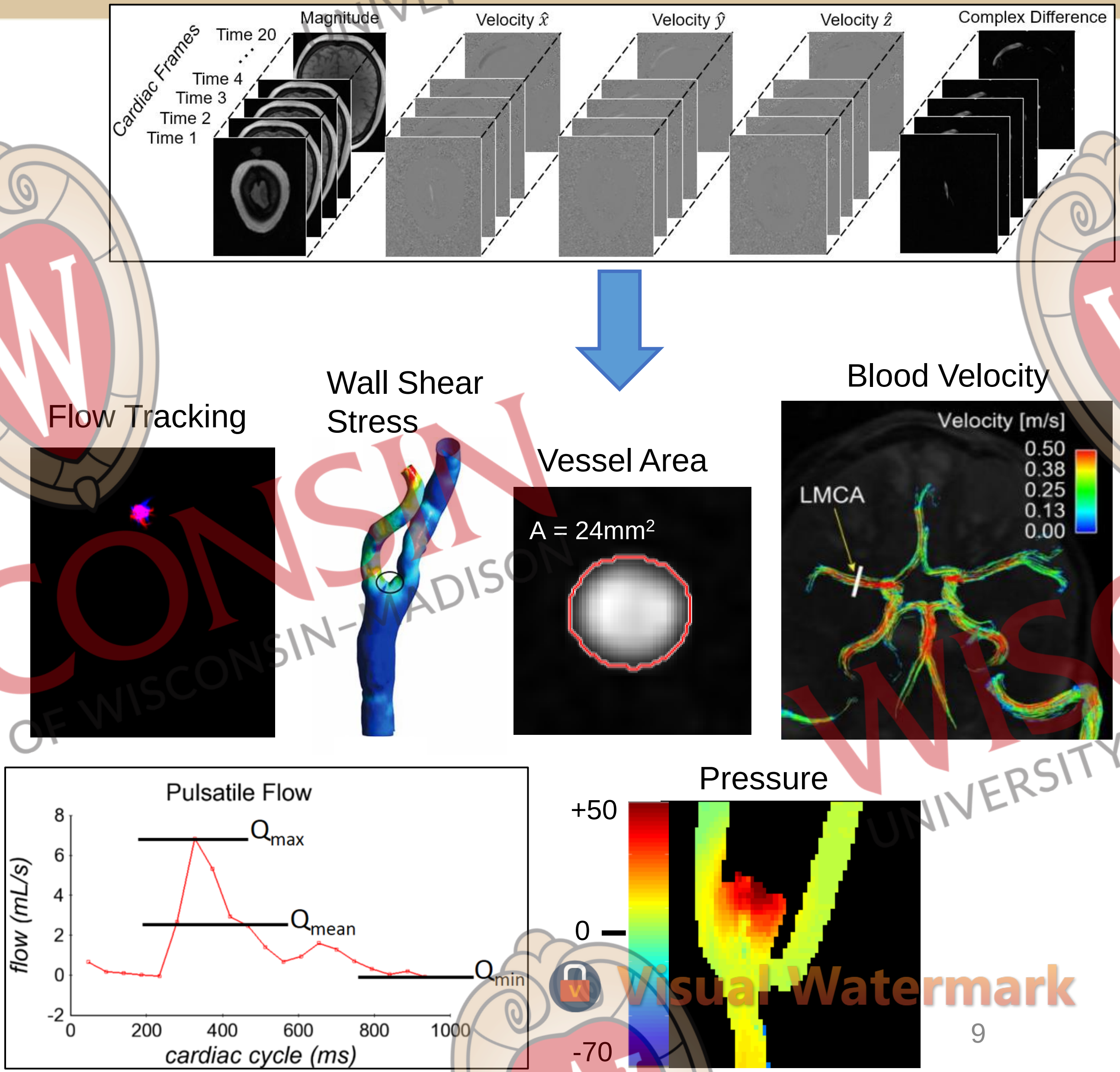
$$CD = M\left|\sin\left(\frac{\|\vec{V}\|/V_{enc}}{2}\right)\right|$$

Post-Processing

1. Boil down large amount of data
2. Extract hemodynamic measures
   - Vessel area
   - Vessel length
   - Flow tracking
   - Blood flow
   - Blood velocity
   - Pulsatility index
   - Resistivity index
   - Pressure maps
   - Wall-shear stress
   - Pulse wave velocity
   - Kinetic energy

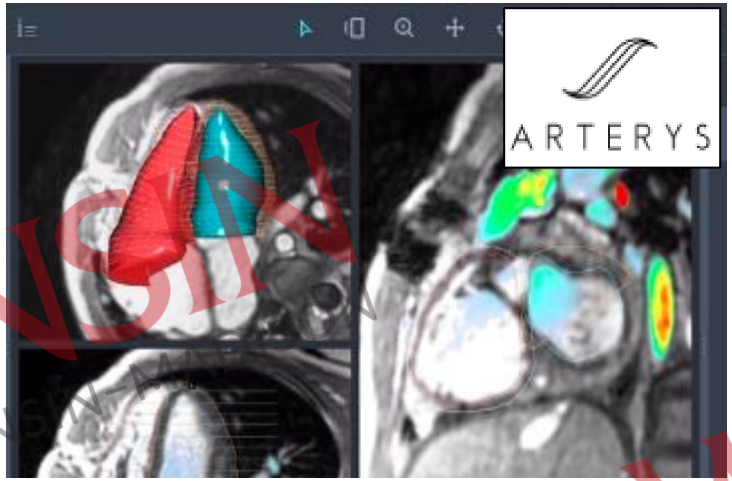
Vessel area, Vessel length, Flow tracking: Structural

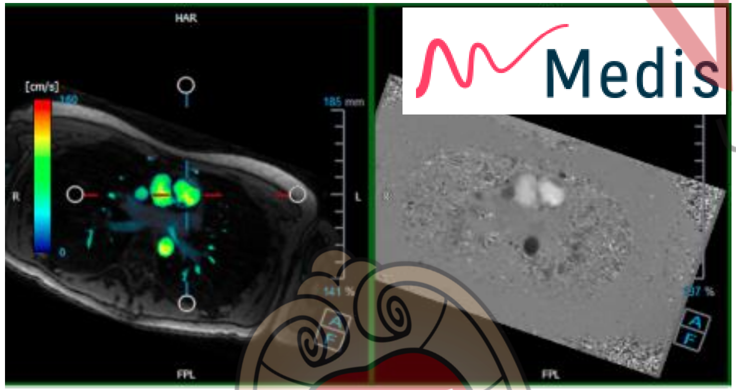
Flow tracking through Kinetic energy: Functional



Commercial Software Tools

- Commercial 4D flow post-processing software exists
  - Applications primarily cardiac
- **No software dedicated to <u>cranial</u> 4D flow**





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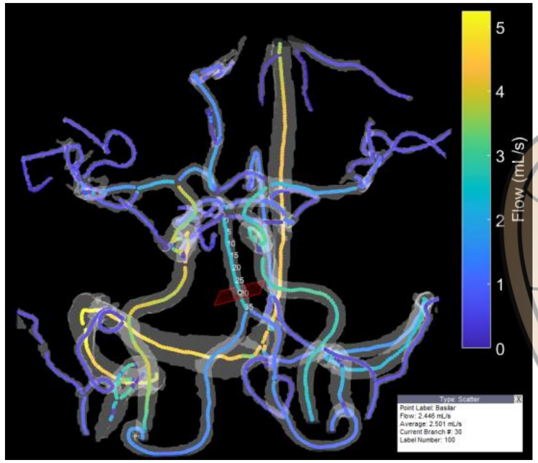
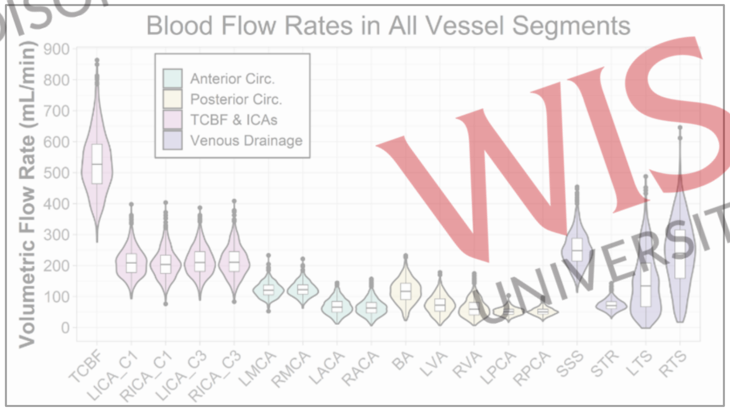


2. Studies:

- **Cranial 4D Flow MRI Analysis Tool**
- Defining “Normal” Flow and Pulsatility in Older Adults



3. Summary

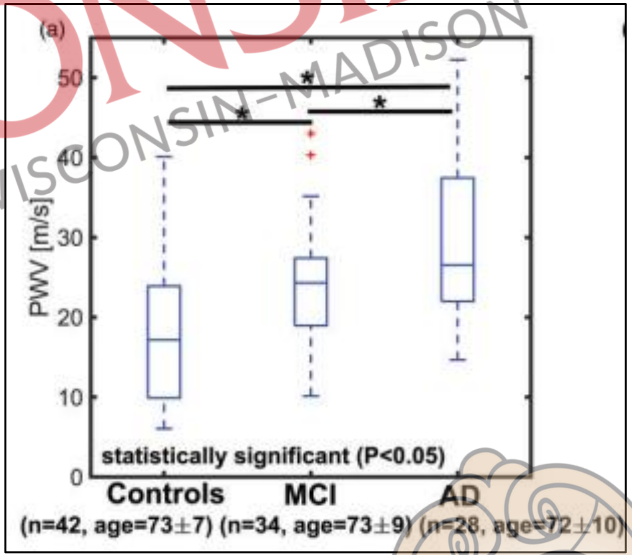
Background

- Motivation
  - Limited software tools for flow analysis in brain
    - Small and tortuous vessels
    - Long post-processing times
  - Vascular alterations in Alzheimer's Disease using 4D Flow MRI


Sara Berman

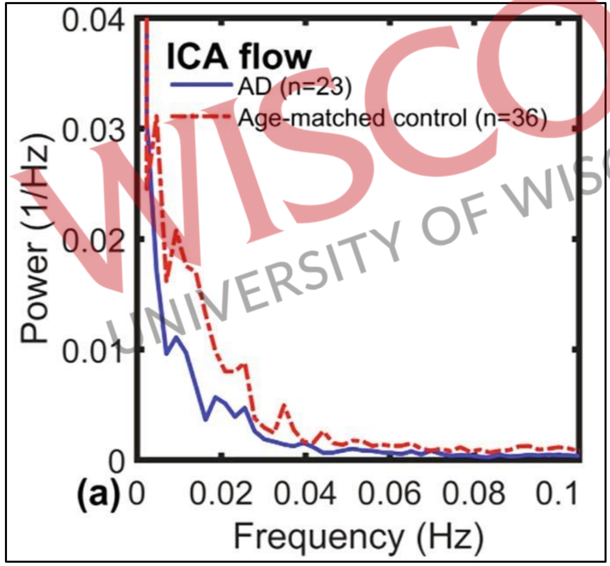

Leonardo Rivera-Rivera

ICA Stiffness



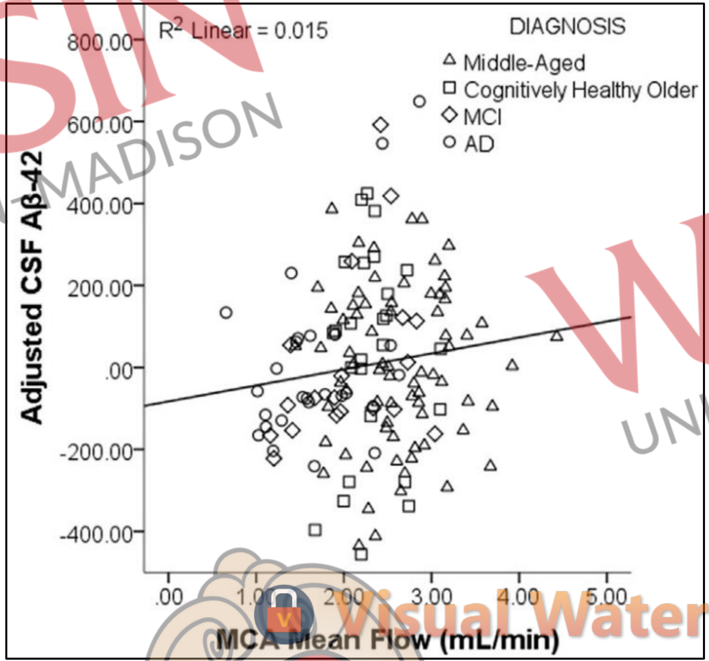
Rivera-Rivera LA, et al (2021). *JCBFM. 41*(2)

Low Frequency Oscillations



Rivera-Rivera LA, et al (2020). *NeuroImage Clin.* 28

Flow vs. Aβ

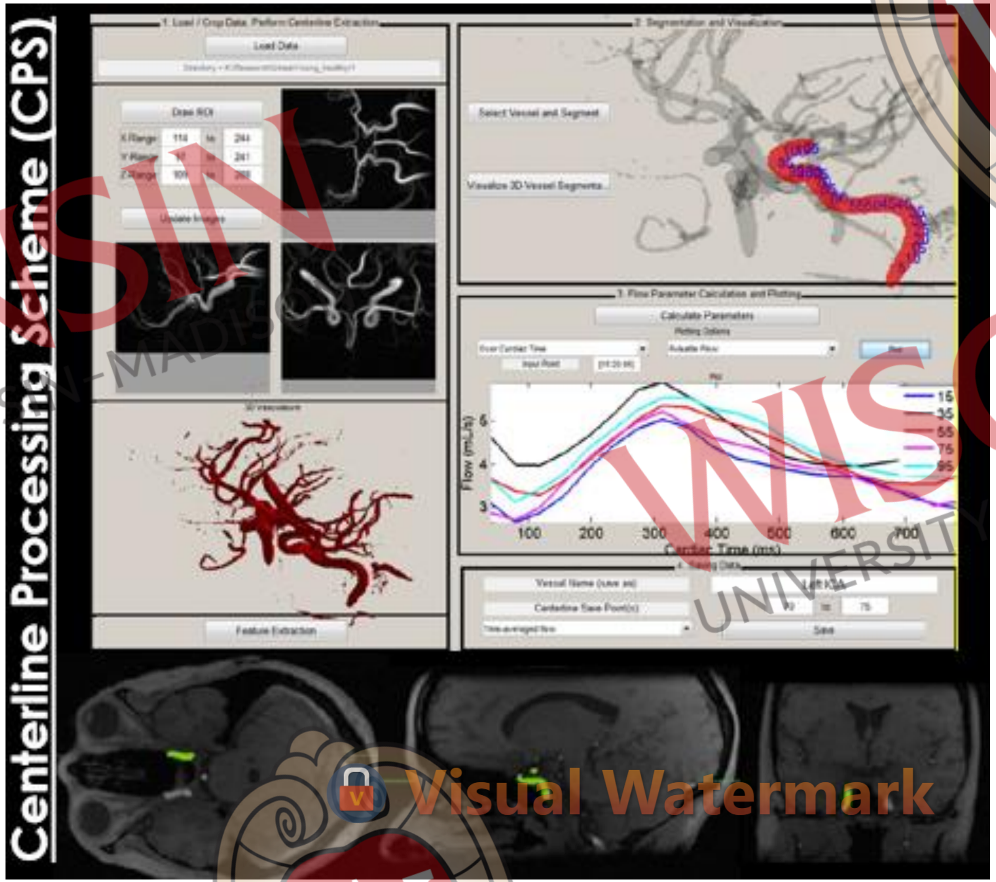


Berman SE, et al (2015). *Alzheimers Dement* 1(4)

Background

- Motivation
  - Limited software tools for flow analysis in brain
    - Small and tortuous vessels
    - Long post-processing times
  - Vascular alterations in Alzheimer's Disease using 4D Flow MRI
- Previous cranial 4D flow analysis tool (CPS)[1]
  - Eric Schrauben + Umea Sweden (2015)
  - Automated segmentation

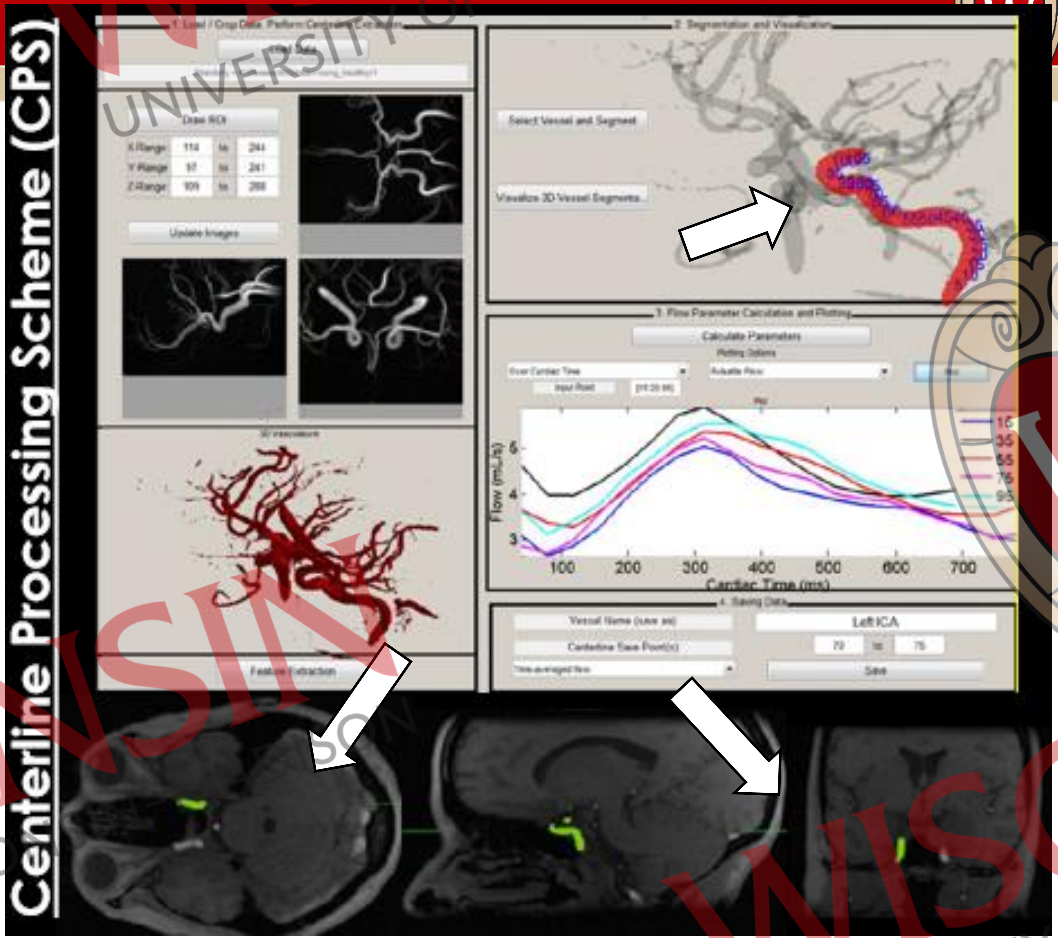
Eric Schrauben

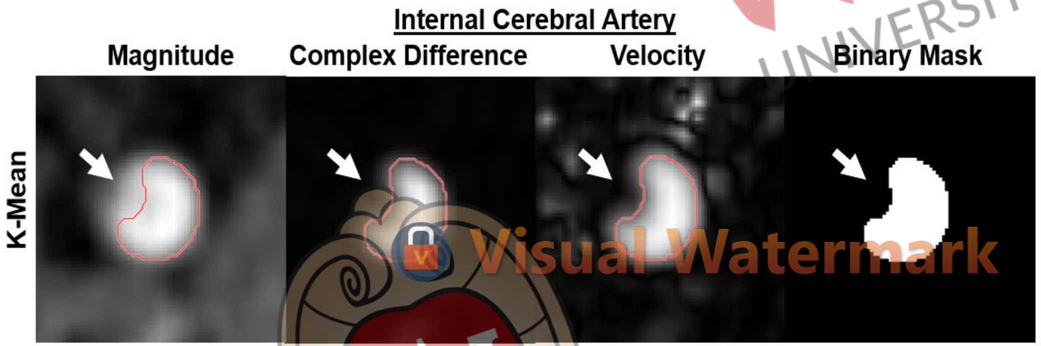


[1]Schrauben E, et al (2015). *JMRI* 42(5)

Background

- Motivation
  - Limited software tools for flow analysis in brain
    - Small and tortuous vessels
    - Long post-processing times
  - Vascular alterations in Alzheimer's Disease using 4D Flow MRI
- Previous cranial 4D flow analysis tool (CPS)[1]
  - Eric Schrauben + Umea Sweden (2015)
  - Automated segmentation
- There were several limitations with this tool
  - Difficult to select vessels of interest
  - Poor angiogram/flow visualizations
  - Lengthy processing times (>15 minutes)
  - K-means segmentation underestimates[2]



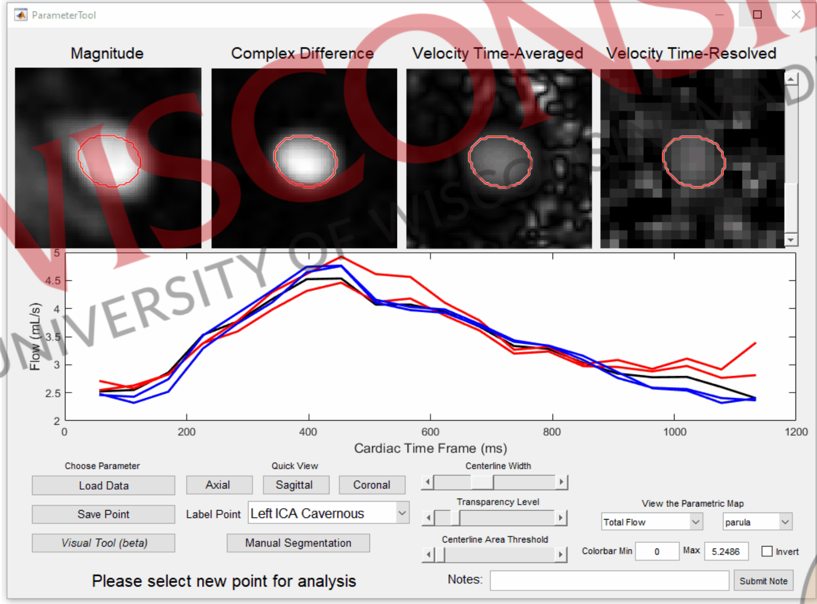


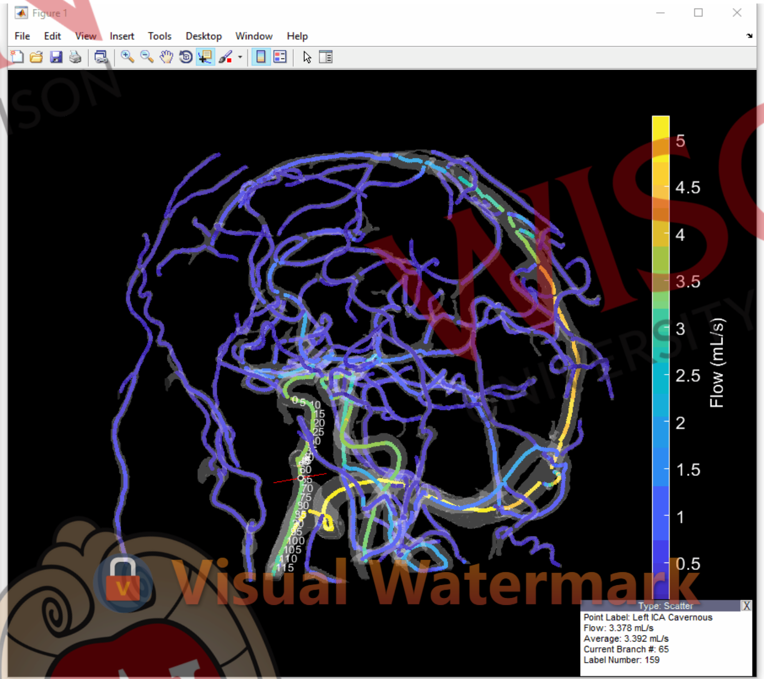
[1]Schrauben E, et al (2015). *JMRI* 42(5)
[2]Dunas, T, et al (2019). *JMRI* 50(2)

Specific Aims

- Develop an improved "quantitative velocity tool"(QVT)[1,2]
  - Interactive (3D) vessel selection
  - Add visualization tools
  - Improve vessel segmentation
    - Develop an automated threshold-based method for segmentation
  - **Reduce processing times** (faster flow quantification)
  - Publicly available: https://github.com/uwmri/QVT
- Validate Tool
  - In vitro (flow phantom)
  - In vivo (healthy volunteers)
  - **Compare CPS and QVT head-to-head**

Carson Hoffman

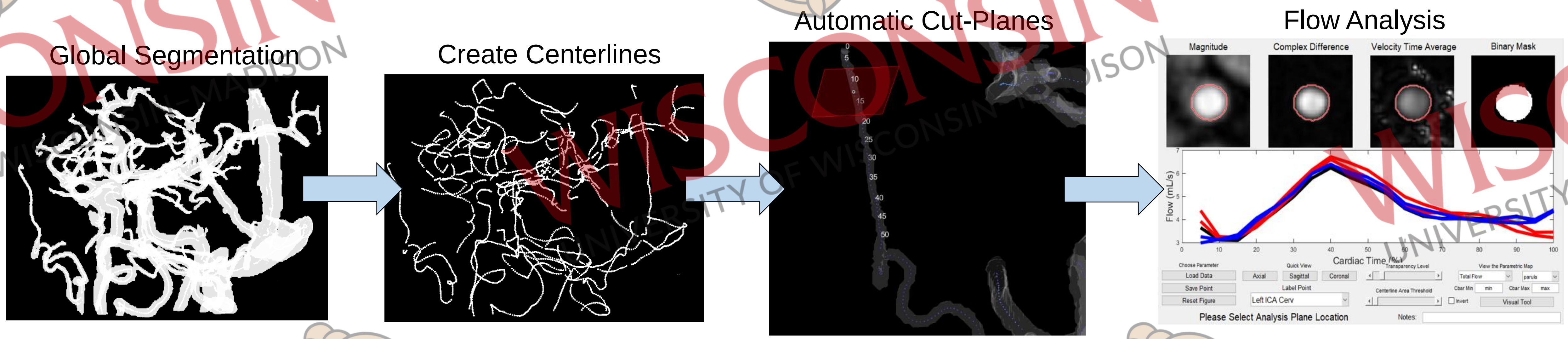




[1]Hoffman CA, et al (2019). *SMRA* p.80
[2]Roberts, et al (2022). *MRM* 97

Customized 4D Flow MRI

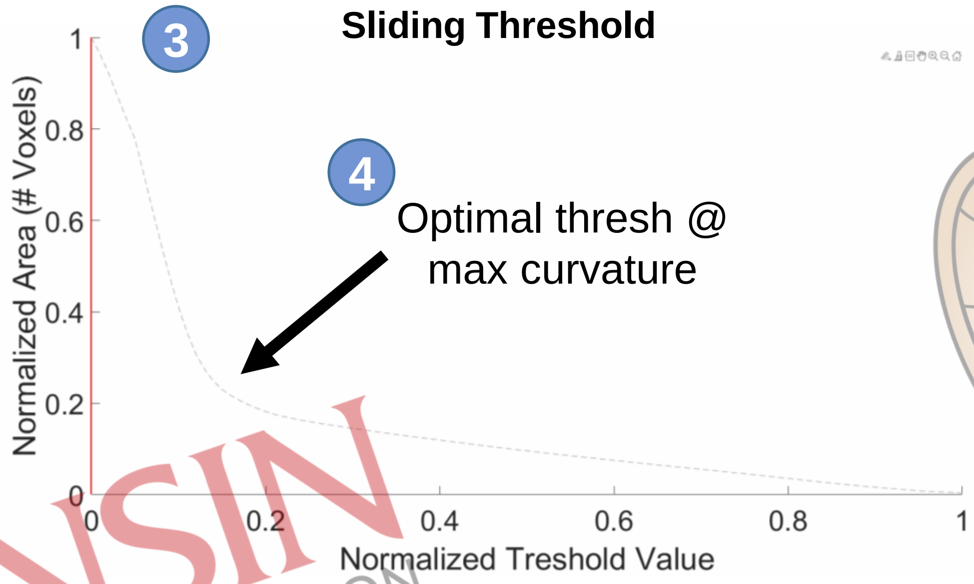
- General outline of automated post-processing steps:
  - Global segmentation
  - Create centerlines (skeletonization)
  - Cut-plane generation
  - In-plane segmentation
  - Calculate hemodynamics

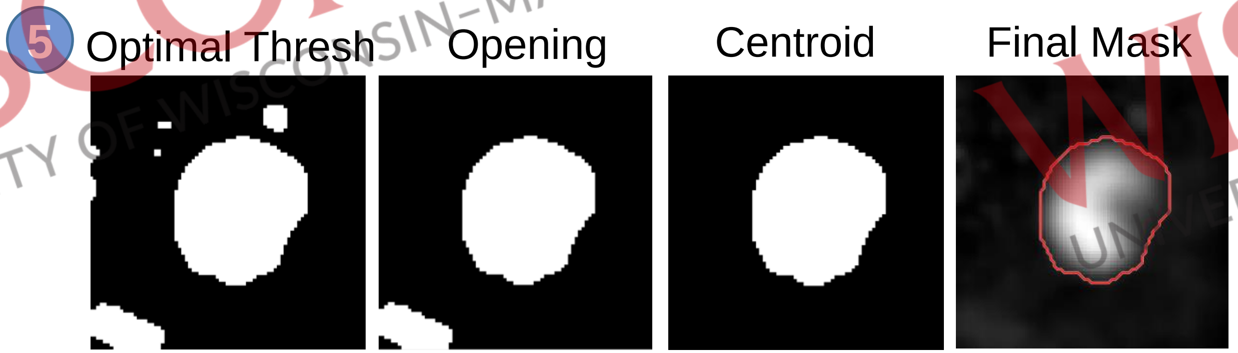


Methods – Sliding Threshold Segmentation

- In-Plane Segmentation
  - “Sliding threshold” method

1. Take initial cut-plane
2. Segment image over large range of threshold values
3. Plot sum of non-zero voxels as a function of threshold value
4. Set threshold as point of max curvature
5. Clean binarized image





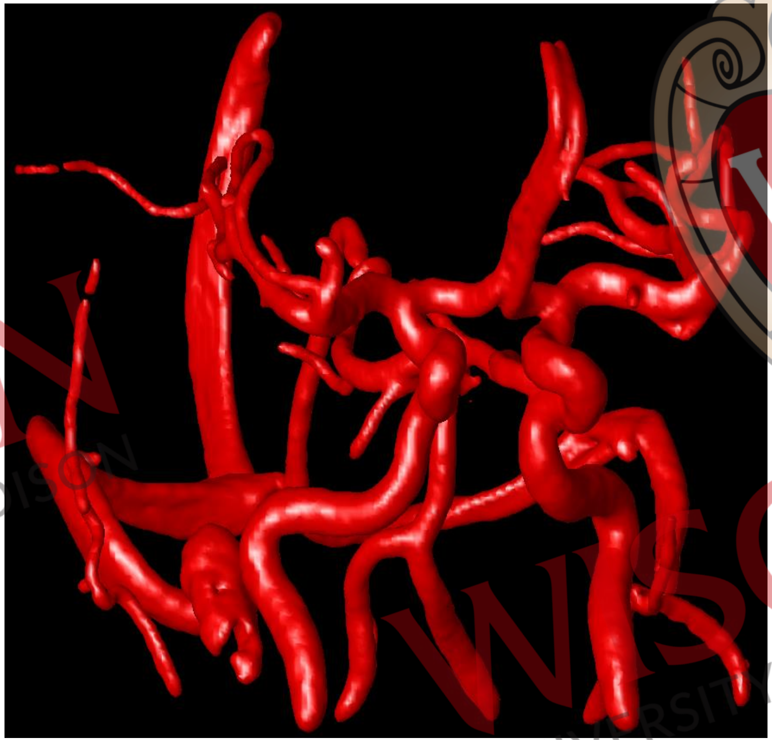
Methods – MRI Parameters

- ADRC Scan Protocol
  - 3T MR750 (GE Healthcare)
  - 4D Flow MRI
    - Radial acquisition (PCVIPR[1,2])
  - FOV: 22x22x22 cm
  - Spatial resolution: 0.68 mm
  - V_{enc} = 80 cm/s
  - Scan Duration: ~7 min
  - 5-point velocity encoding
- Reconstruction
  - Retrospective cardiac gating
  - 20 cardiac phases
  - Temporal radial view sharing

***In Vitro*: Intracranial Flow Phantom**

Scans: 7 pulsatile flow rates (0.8-1.2 L/min)

***In Vivo*: Healthy Controls**



Scans: 10 healthy volunteers

[1]Gu T, et al (2005). *AJNR* 26(4).
[2]Johnson KM, et al (2008). *MRM* 60(6).

Methods – Segmentation Validation

- 4D Flow MRI
  - QVT (new tool)
    - Sliding-threshold segmentation
  - CPS (old tool)
    - K-means segmentation

***In Vitro*: Intracranial Flow Phantom**

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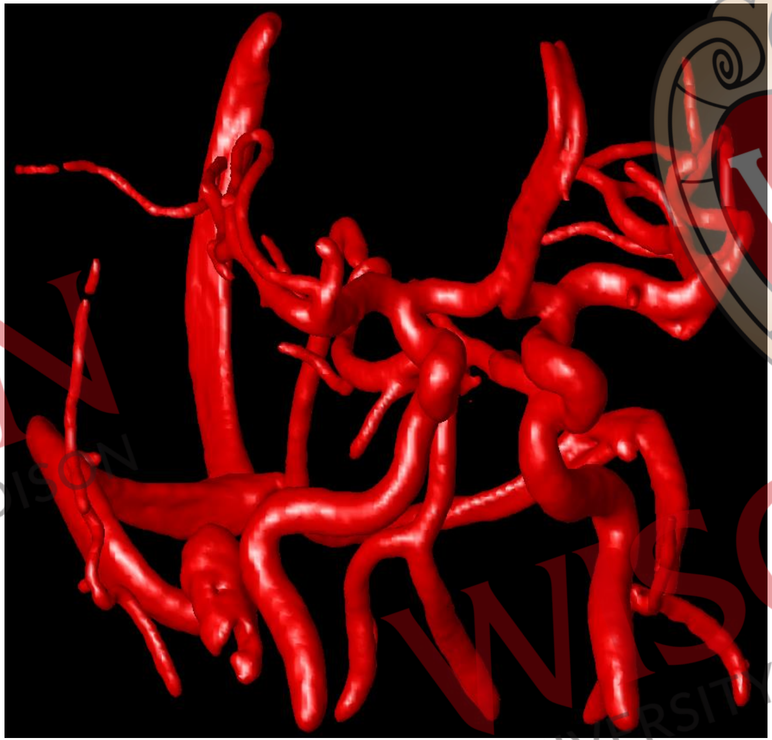


Scans: 10 healthy volunteers

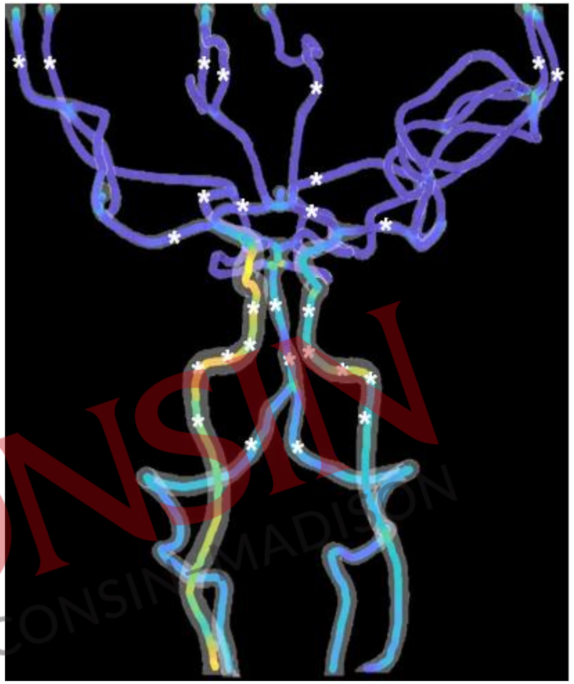
Methods – Segmentation Validation

- 4D Flow MRI
  - QVT (new tool)
    - Threshold segmentation
  - CPS (old tool)
    - K-means segmentation

- *In Vitro*
  - **Reference: Hi-Res CT**
  - Vessel areas
    - 29 locations x 7 flow rates

Cone Beam CT

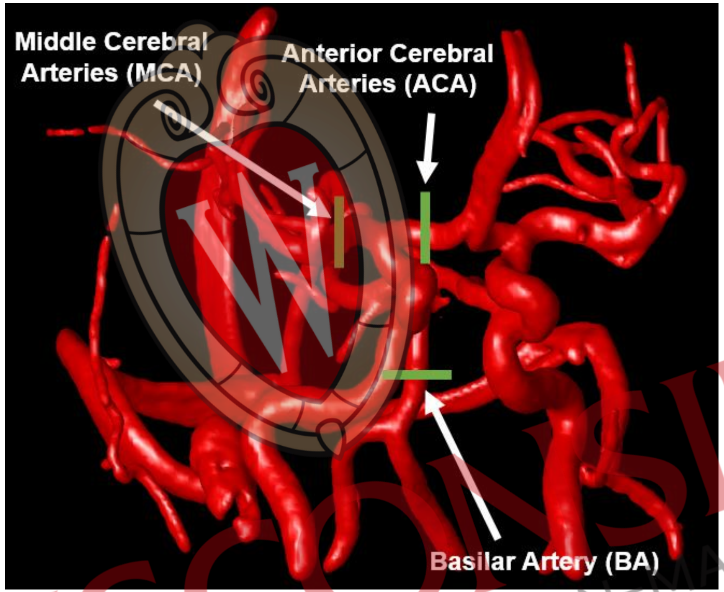
Measurement Locations (*)

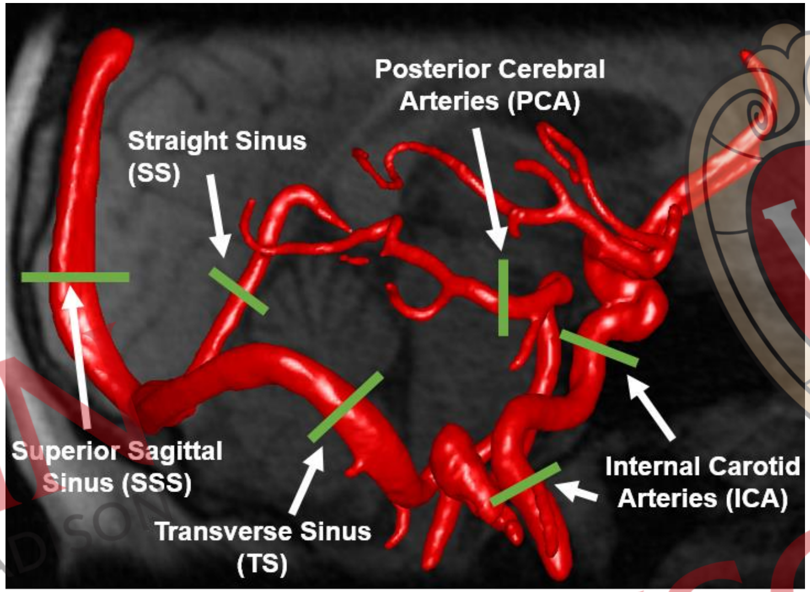


Co-Registered CT-MRI

Methods – Segmentation Validation

- 4D Flow MRI
  - QVT (new tool)
    - Threshold segmentation
  - CPS (old tool)
    - K-means segmentation





- *In Vitro*
  - **Reference: Hi-Res CT**
  - Vessel areas
    - 29 locations x 7 flow rates
- *In Vivo*
  - **Reference: Manual Segmentation**
  - Vessel areas and Dice coefficients
    - 13 locations x 5 neighboring planes x 10 subjects

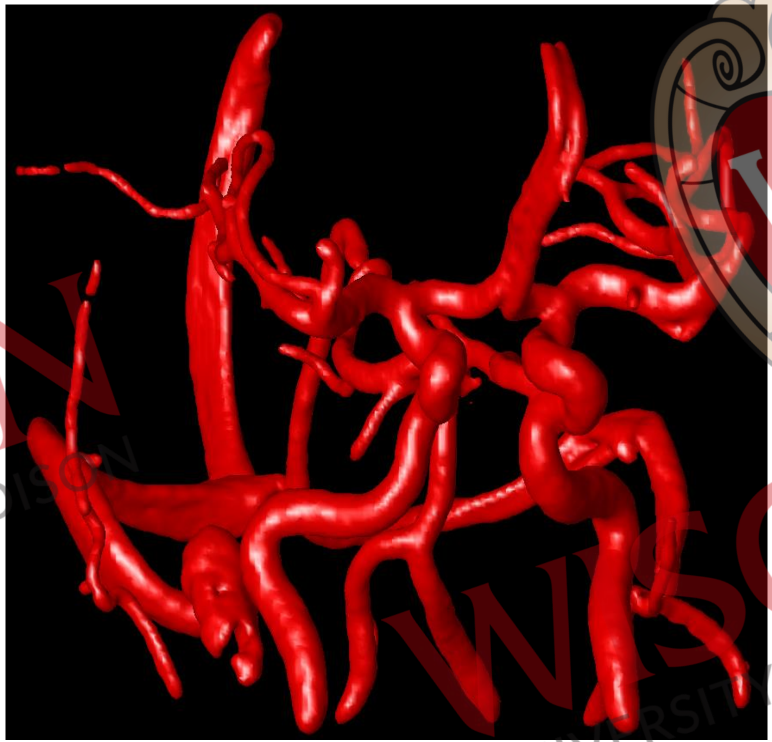
Methods – Flow Validation

- 4D Flow MRI
  - QVT – Flow Rates

***In Vitro*: Intracranial Flow Phantom**

Scans: 7 pulsatile flow rates (0.8-1.2 L/min)

***In Vivo*: Healthy Controls**

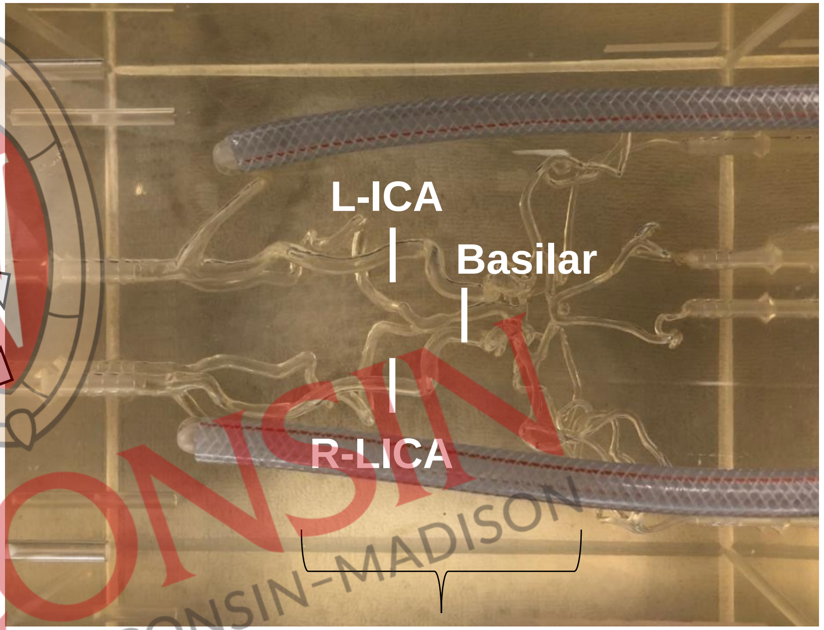


Scans: 10 healthy volunteers

Methods – Flow Validation

- 4D Flow MRI
  - QVT – Flow Rates
- *In Vitro*
  - **Reference: Ultrasound**
  - Inlet/Outlet flow
    - 7 flow rates

Silicon Phantom



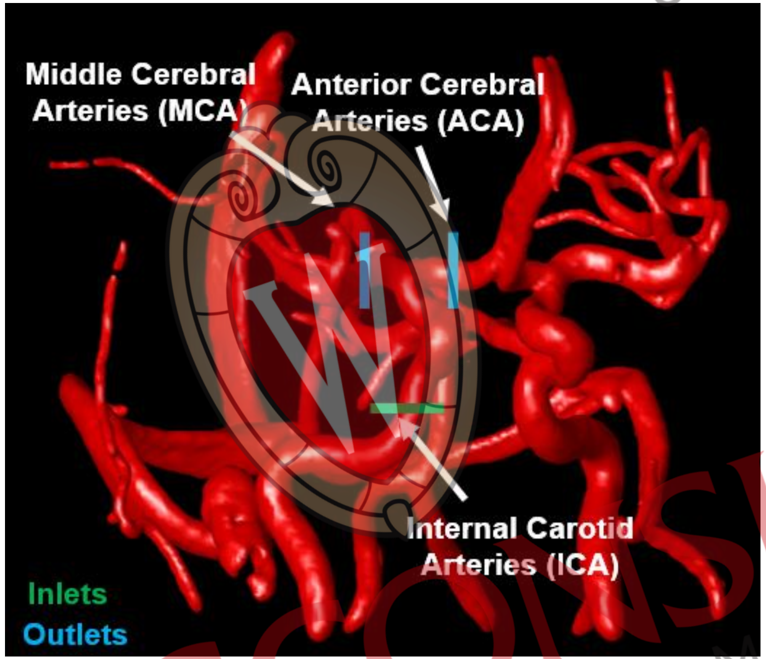
US Flow
Pump Outlet

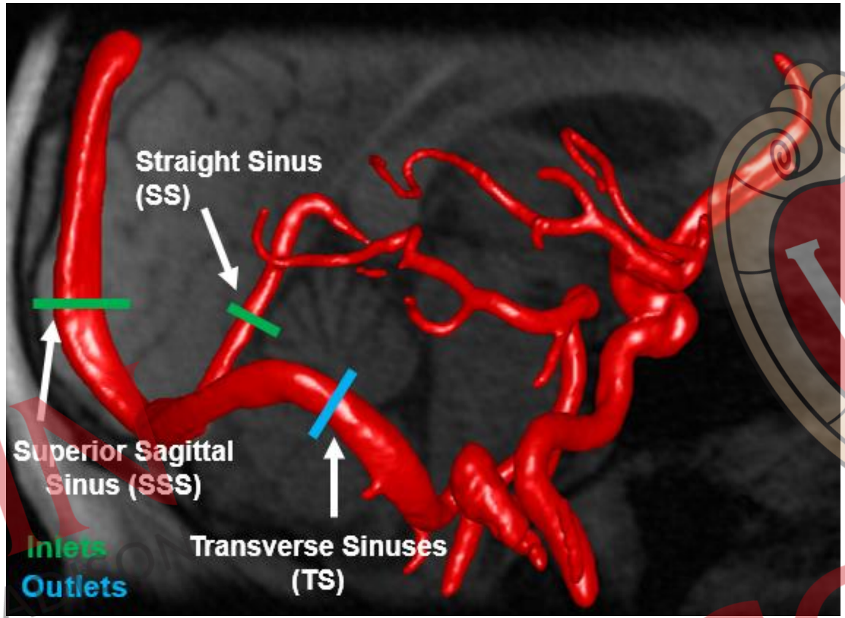
MRI Flow
Phantom Inlet

Methods – Flow Validation

- 4D Flow MRI
  - QVT – Flow Rates

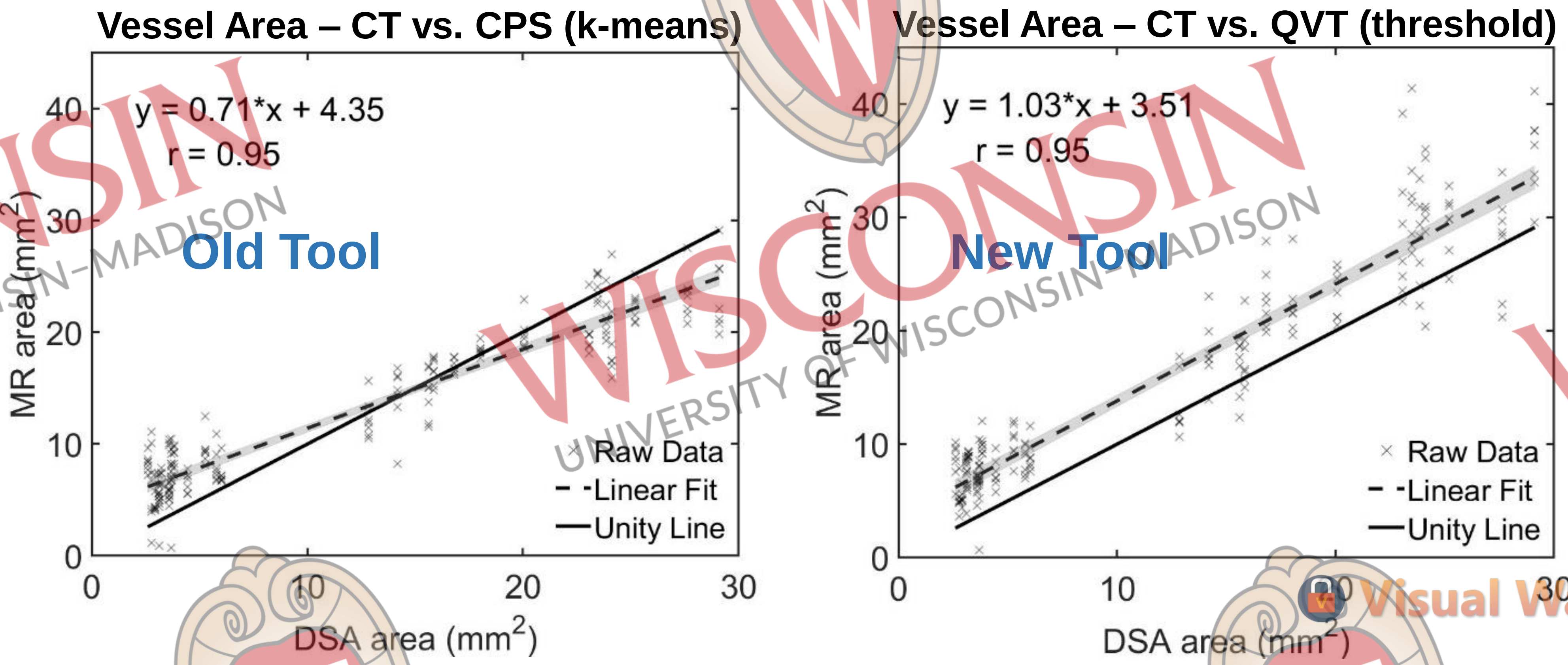
- *In Vitro*
  - **Reference: Ultrasound**
  - Inlet/Outlet flow
    - 7 flow rates
- *In Vivo*
  - **Internal Consistency**
  - Conservation of flow
    - 3 vessel junctions x 10 subjects
      - LICA = LMCA + LACA
      - RICA = RMCA + RACA
      - SSS + SS = LTS + RTS





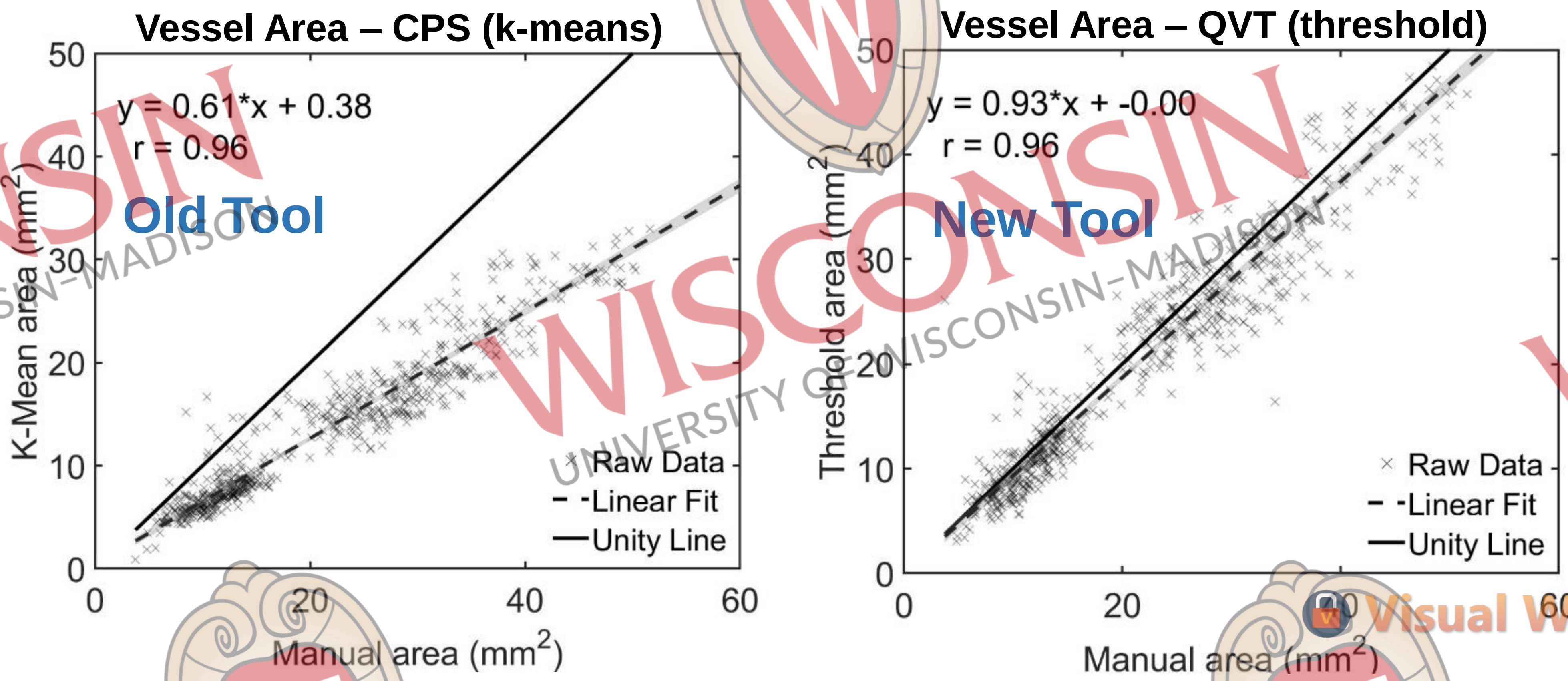
Results – Segmentation In Vitro

- **Reference: Hi-Res CT**
- Vessel areas
  - 29 vessel locations x 7 flow rates



Results – Segmentation In Vivo

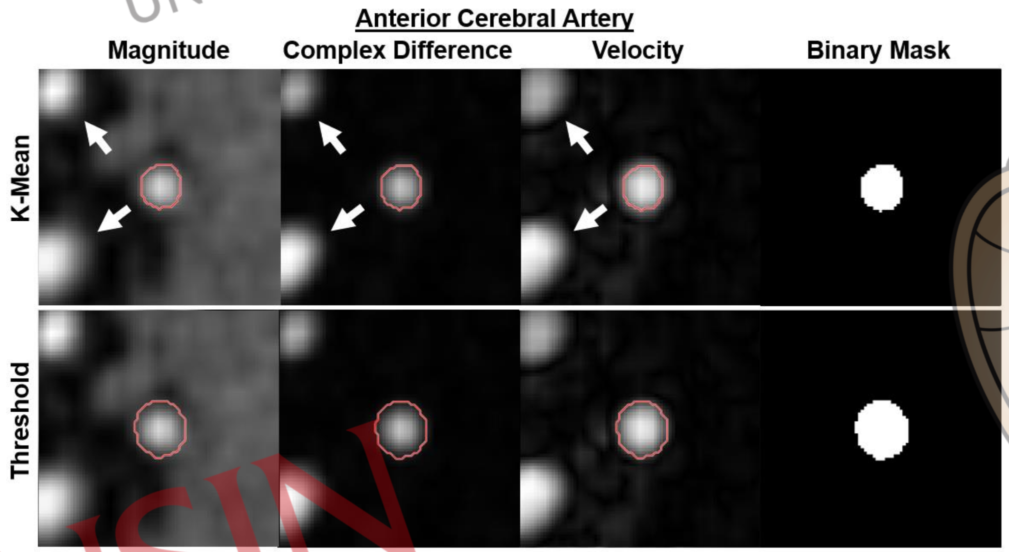
- **Reference: Manual Segmentation**
- Vessel areas
  - 13 locations x 5 neighboring planes x 10 subjects

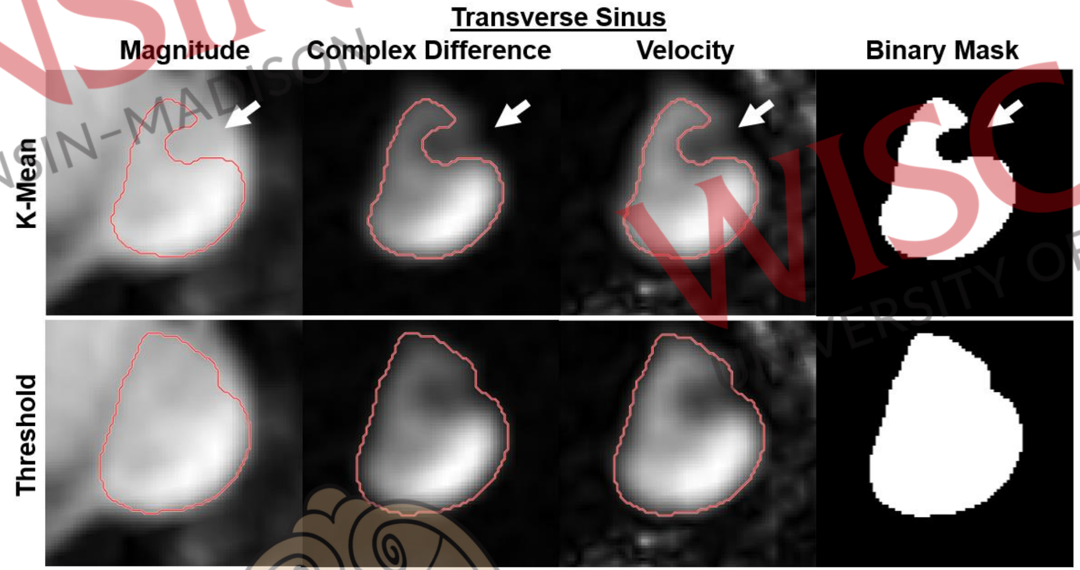


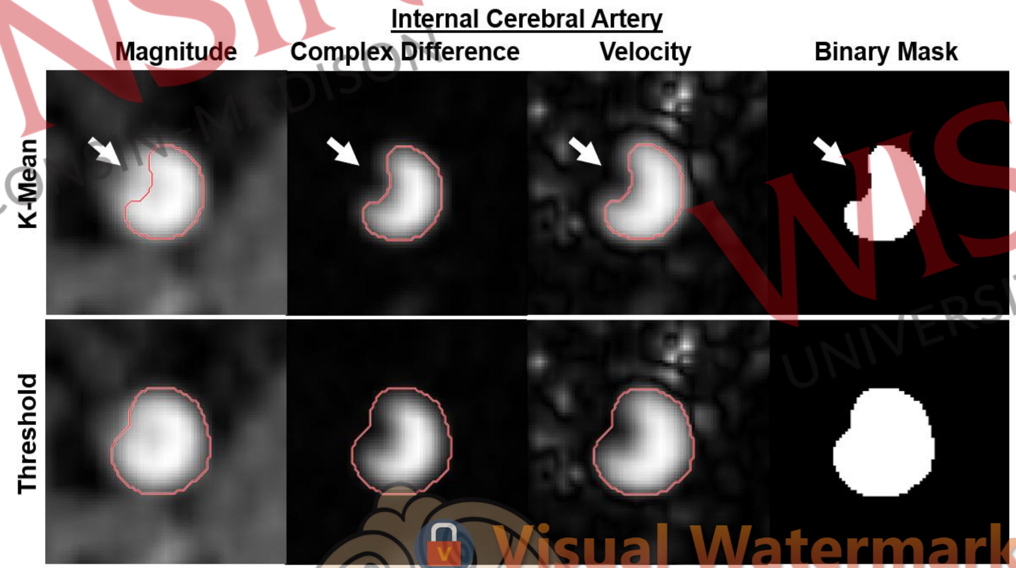
Results – Segmentation In Vivo

- **Reference: Manual Segmentation**
- Dice coefficients
  - 13 locations x 5 neighboring planes x 10 subjects

K-means vs. Manual = **0.77** ± 0.07
Threshold vs. Manual = **0.91** ± 0.06

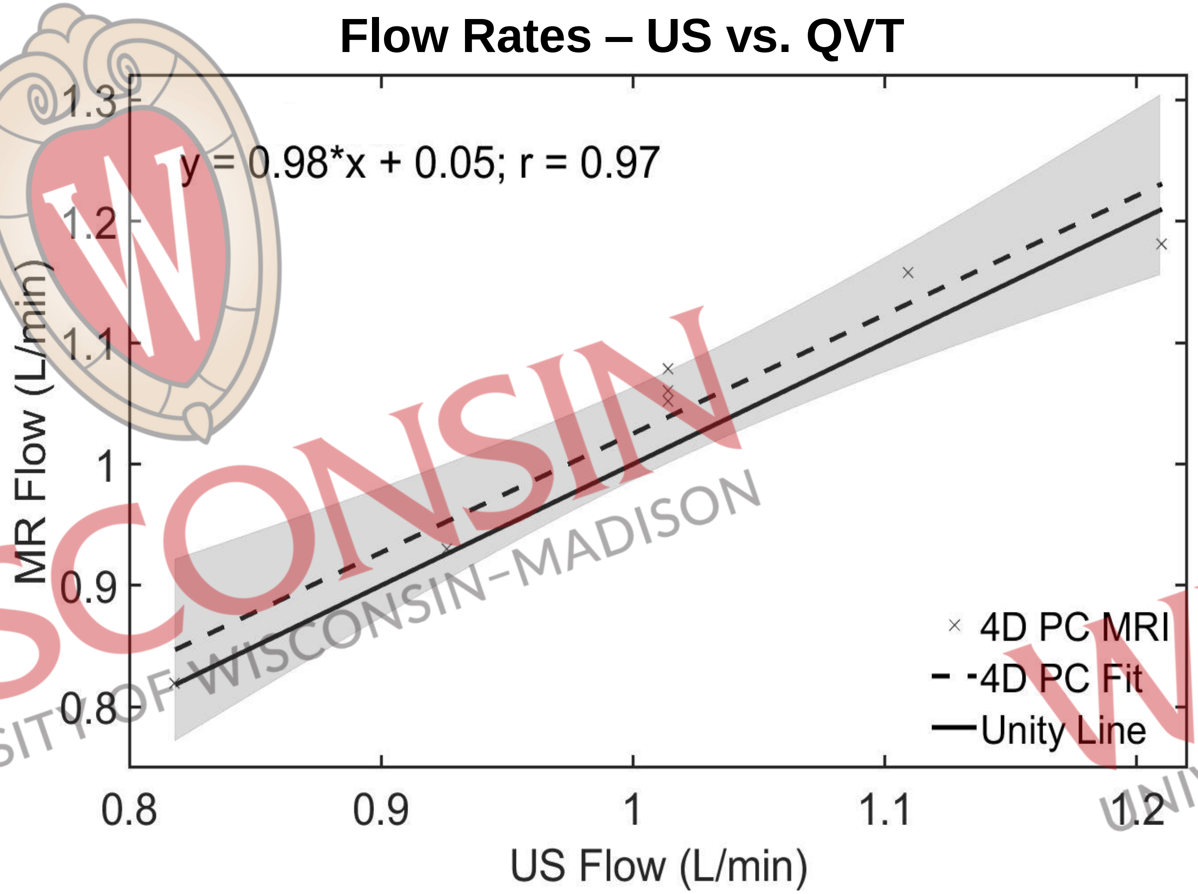






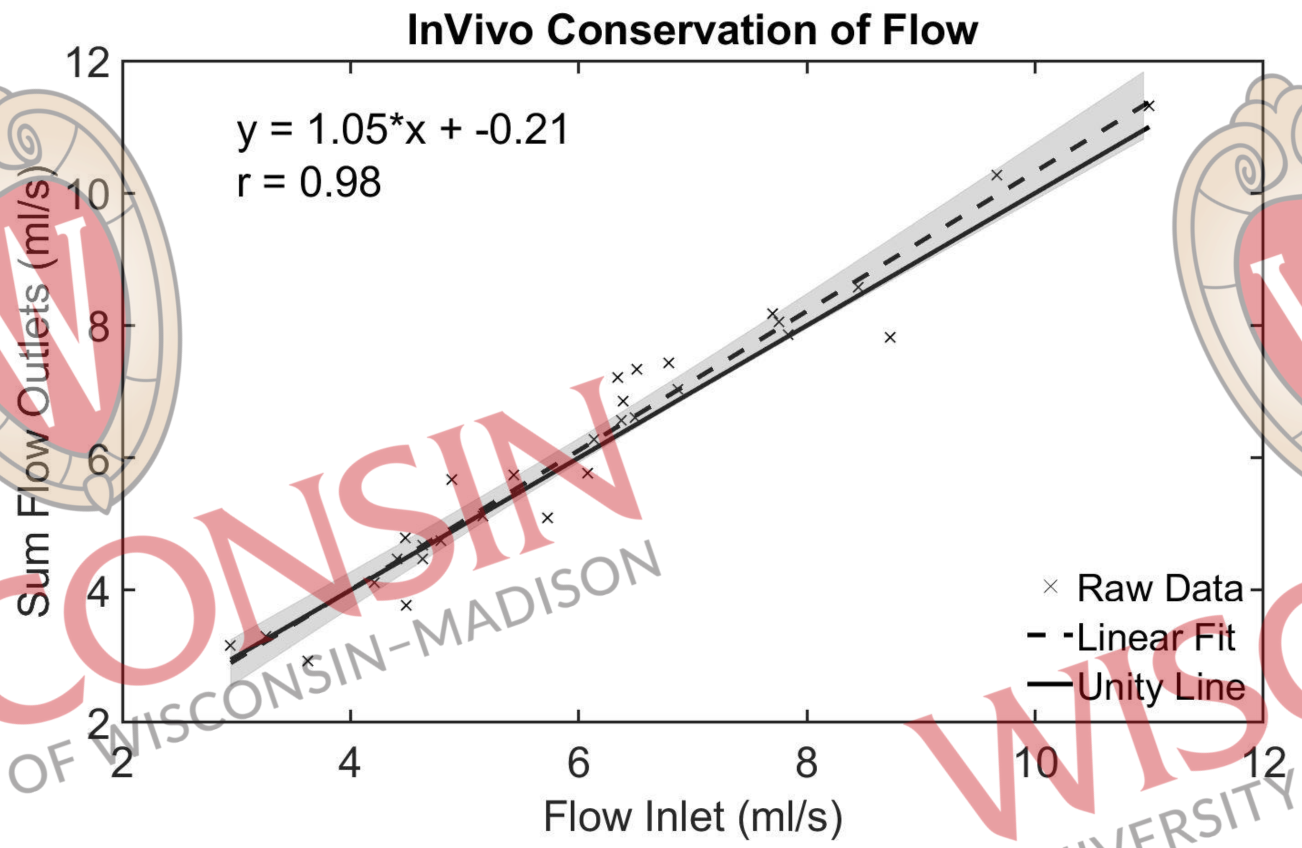
Results – Flow In Vitro

- **Reference: Ultrasound**
- Inlet vs. Outlet Flow
  - 7 flow rates (0.8 – 1.2 mL/min)



Results – Flow In Vivo

- **Reference: Internal Consistency**
  - Conservation of Flow
    - 3 vessel junctions
- Should validate against ground-truth for future studies

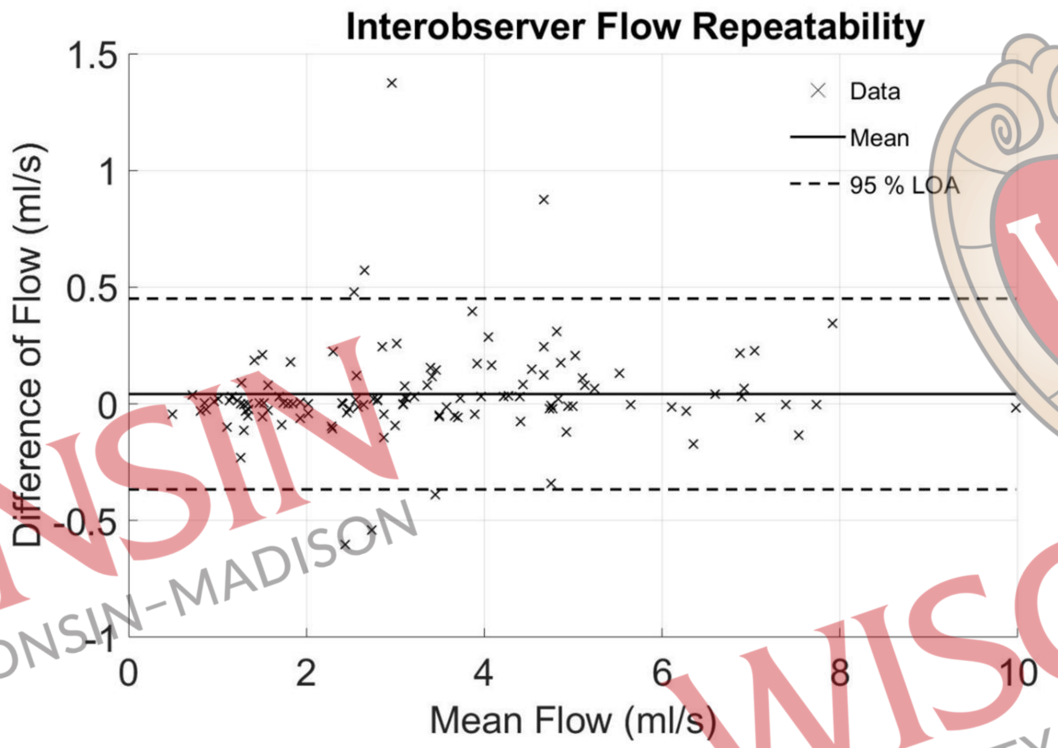


Results – Flow In Vivo

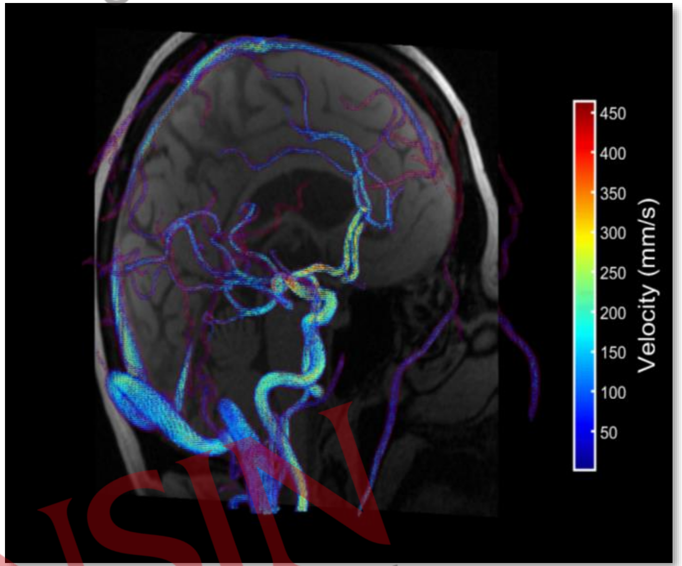
- Flow measures repeatable between observers
- Processing times reduced by >2x

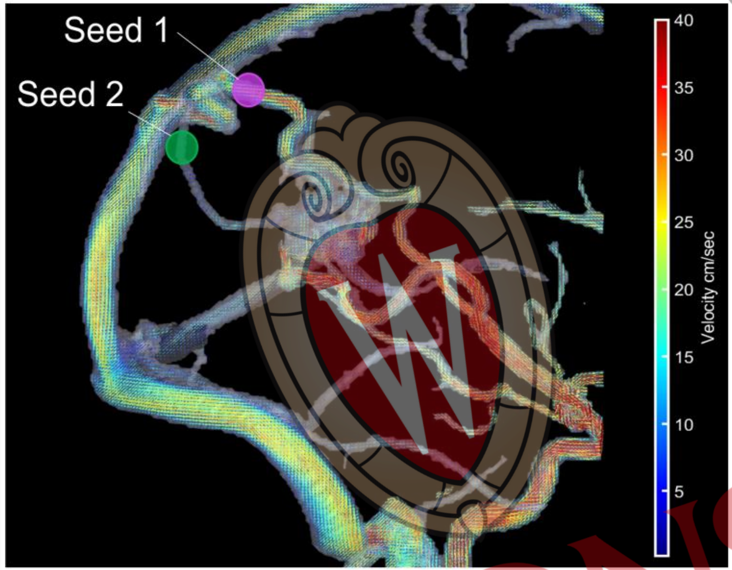
Table 1: Post-Processing Times for CPS and QVT Methods					
Method	Angiogram (min)	Load Data* (min)	Vessel Select (min)	Total Case (min)	Per Plane (min)
CPS	0.8 ± 0.1	1.0 ± 0.2	15.6 ± 3.4	17.5 ± 3.4	1.2 ± 3.2
QVT	0.2 ± 0.02	2.3 ± 0.4	4.7 ± 0.9	7.94 ± 1.0	0.4 ± 1.0

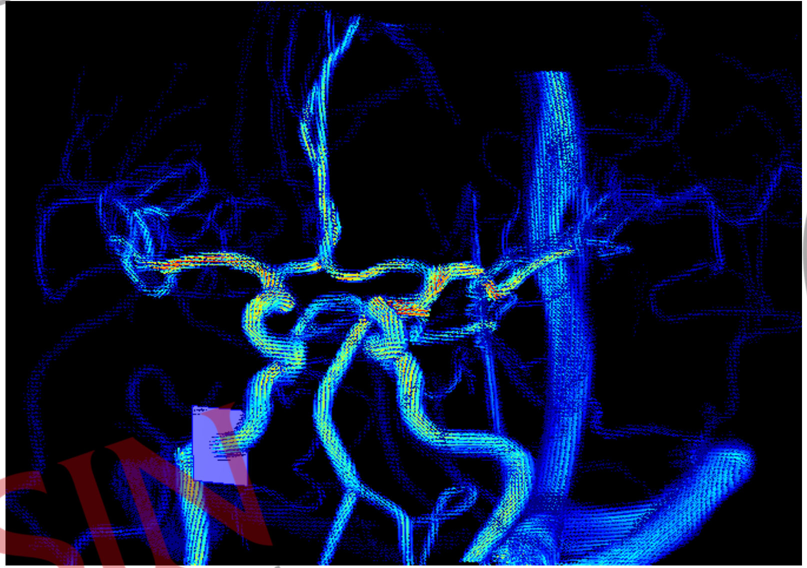
*Data loading for QVT included saving reloadable MATLAB file structures.

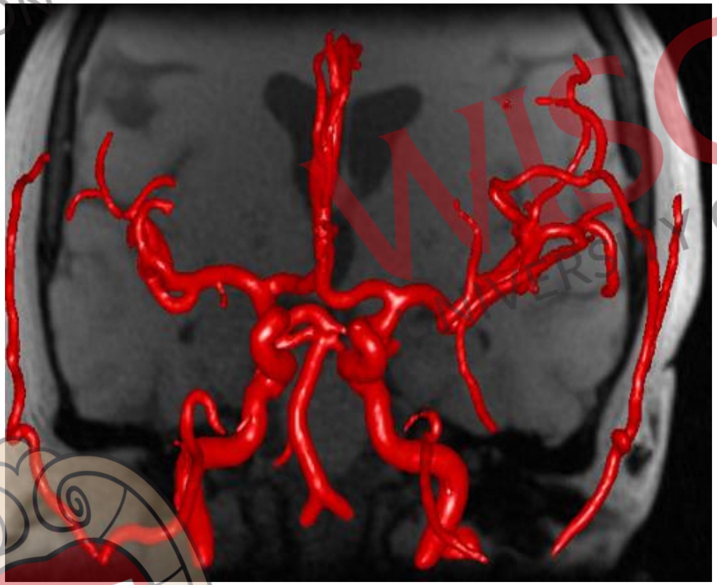


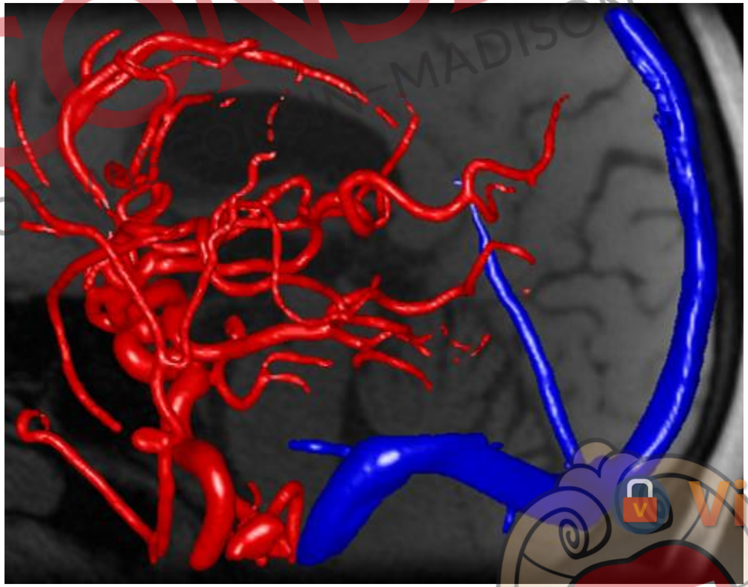
QVT Visualization Features









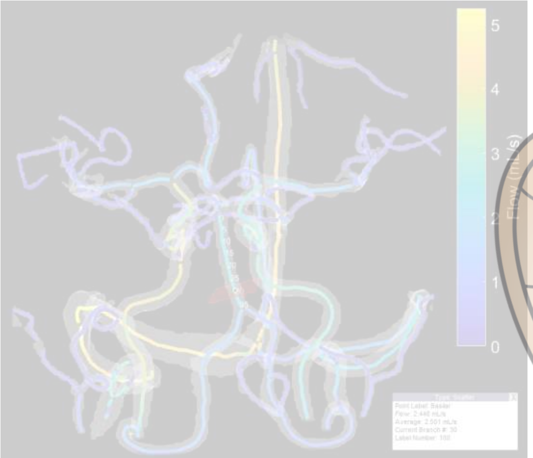


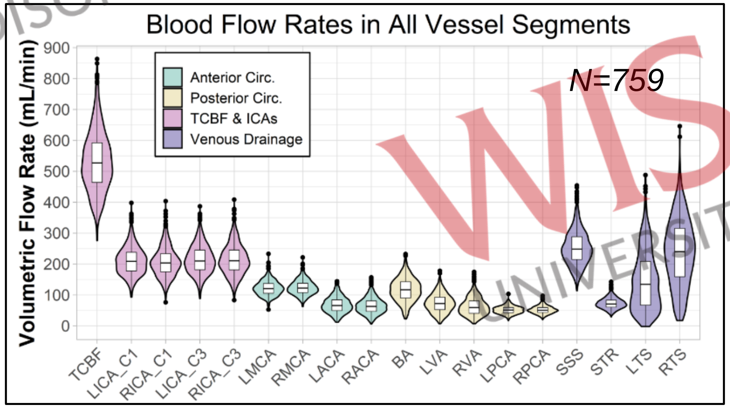
Outline

1. Background: 4D Flow MRI

2. Studies:
    - Cranial 4D Flow MRI Analysis Tool
    - **Defining "Normal" Flow and Pulsatility in Older Adults**

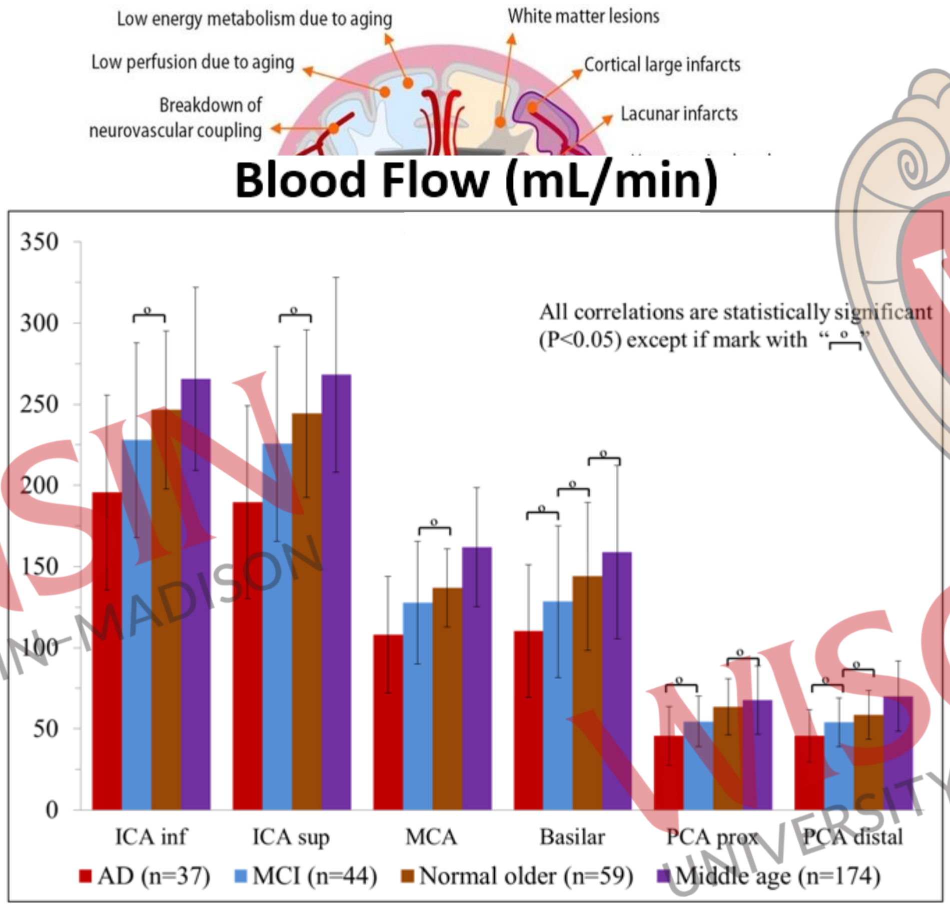
3. Summary





Background – Clinical Motivation

- Adequate cerebral blood flow is important
- As we age, neurovascular changes begin to occur
  - Arterial stiffening[1]
  - Breakdown of neurovascular unit[2]
  - Affect cerebral hemodynamics and cognition
- Relationship with Alzheimer's disease (AD)
  - Macrovascular changes[3-5]
  - Microvascular (perfusion) changes[6]
  - Normative data is still lacking
- <u>Important to establish normal cerebrovascular hemodynamics in older adults</u>



Courtesy: Leonardo Rivera-Rivera, PhD

[1]Mitchell GF, et al (2011). *Brain.* 134(11)
[2]Tarantini S, et al (2017). *Exp Gerontol.* 94
[3]Rivera-Rivera LA, et al (2016). *JCBFM.* 36(10)
[4]Rivera-Rivera LA, et al (2017). *JCBFM.* 37(6)
[5]Rivera-Rivera LA, et al (2020). *NeuroImage Clin.* 28
[6]Clark LR, et al (2017). *Alzheimers Dement.* 7

Specific Aims

- Use QVT to analyze 4D flow MRI data from 759 older adults
  - Obtain reference blood flow rates and flow pulsatility indices in 13 major cerebral arteries and 4 major sinuses
  - Assess the relationship between age and sex on blood flow and pulsatility

Methods – Study Population

- Subjects retrospectively recruited from:
  - Wisconsin Alzheimer's Disease Research Center (ADRC)
  - Wisconsin Registry for Alzheimer's Prevention (WRAP)
  - Between March 2010 – March 2020
- Exclusion criteria:
  - Abnormal cognitive status
  - PiB index > 1.19[1]
  - Image quality and cardiac gating quality
- **759 subjects (mean age 65 years)**
  - Some measures deviate from "normal"
    - Sex (67% females)
    - APOE4 carriers
    - Parental history of dementia

Subject demographics

		Count (n)	Percent (%)	N*
Sex				759
	Female	506	66.7	
	Male	253	33.3	
Race				757
	White	645	85.3	
	Black or African American	82	10.7	
	American Indian	24	3.2	
	Asian	2	0.3	
	Other	4	0.5	
Diabetes		63	9.1	689
Smoker		29	4.2	689
On Anti-hypertensive Meds		240	34.8	689
Parental history of dementia		500	67.6	740
APOE ε4 carrier**		247	35.6	694

	Mean	SD	N*
Age (years)	64.7	7.7	759
Systolic Blood Press. (mmHg)	125.1	16.4	751
Diastolic Blood Press. (mmHg)	76.9	8.3	751
Total Cholesterol (mg/dL)	199.0	39.4	744
Triglycerides (mg/dL)	106.4	56.7	744

*Total number of measured data points over all subjects (759 total).
**APOE ε4 carrier defined as presence of at least one APOE ε4 allele.

[1]Tudorascu DL, et al (2018). *Alzheimers Dement* 10

Methods – Acquisition, Reconstruction, Analysis

- Scan Protocol
  - 3T on 3 different GE scanners
  - Radially-undersampled PCVIPR[1,2]
- Reconstruction
  - 20 cardiac frames
  - Temporal view sharing
  - Parallel imaging with localized sensitivities (PILS)
  - Maxwell term phase correction
  - 3rd order background phase correction
- Analysis
  - Two observers analyzed 759 cases
    - Observer 1 = 302 cases (40%)
    - Observer 2 = 457 cases (60%)
  - Multiple linear regression
  - Linear mixed effects modelling

MRI Scanners and Coils

MRI Coil Type	Discovery MR750 (N=611)	Signa PET/MR (N=8)	Signa Premier (N=140)
48 channel	-	-	140
32 channel	565	-	-
8 channel	46	8	-

MRI Acquisition Parameters

Characteristic	Value
TR (ms)	7.71
TE (ms)	2.63
Flip Angle (degrees)	8
Matrix Size	320
Resolution Size (mm)	0.69
Radial Projections	11000
VENC (cm/s)	80
Encoding Scheme	4-point (58%)
	5-point (42%)
Scan Time (min)	5.6 (58%)
	7.1 (42%)


Anthony Peret

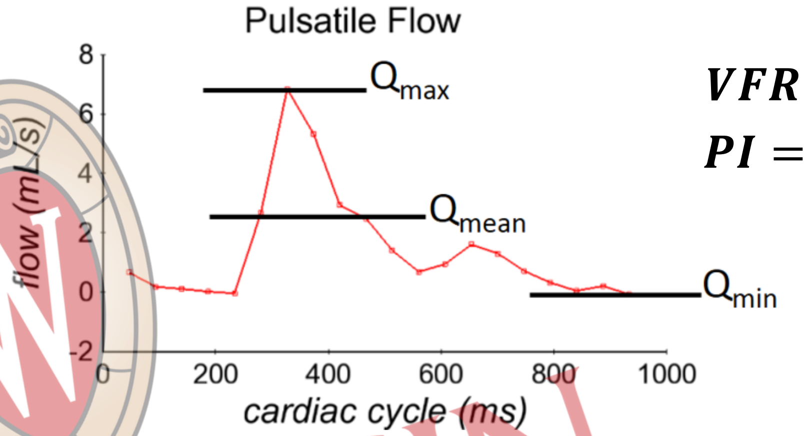

Erin Jonaitis


Rebecca Koscik

[1]Gu T, et al (2005). *AJNR* 26(4).
[2]Johnson KM, et al (2008). *MRM* 60(6).

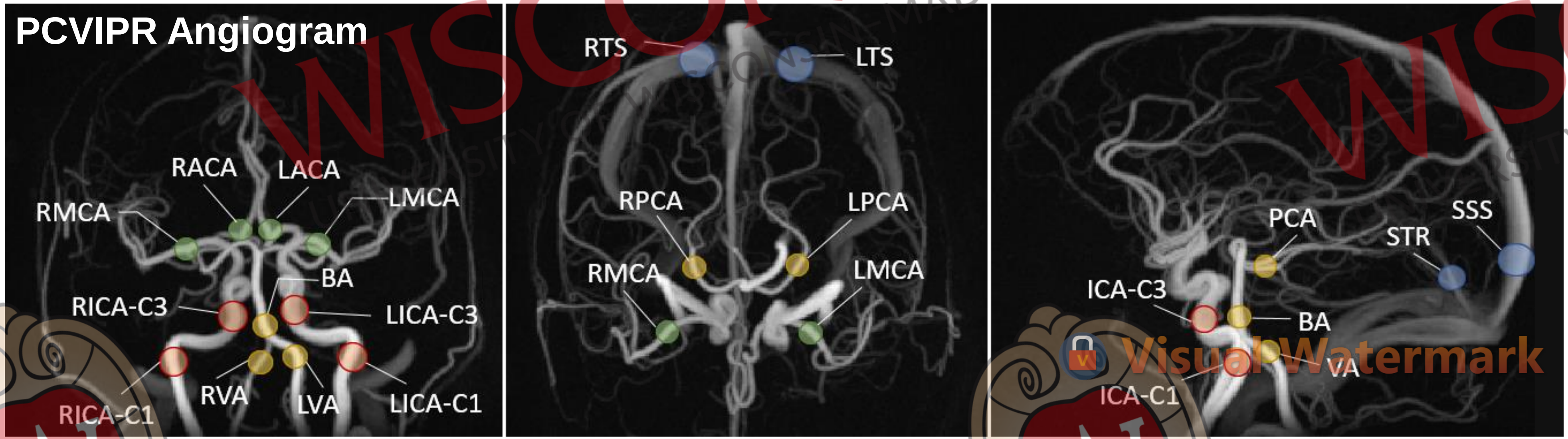
Methods – Post-Processing

- Hemodynamic Measures
  - **Volumetric Flow Rates** (mL/min)
  - **Pulsatility Indices** (a.u.)
  - **Total Cerebral Blood Flow** (mL/min)
    - $TCBF = Q_{ICA} + Q_{BA}$
- Vessel Segment Locations
  - 13 arteries + 4 veins

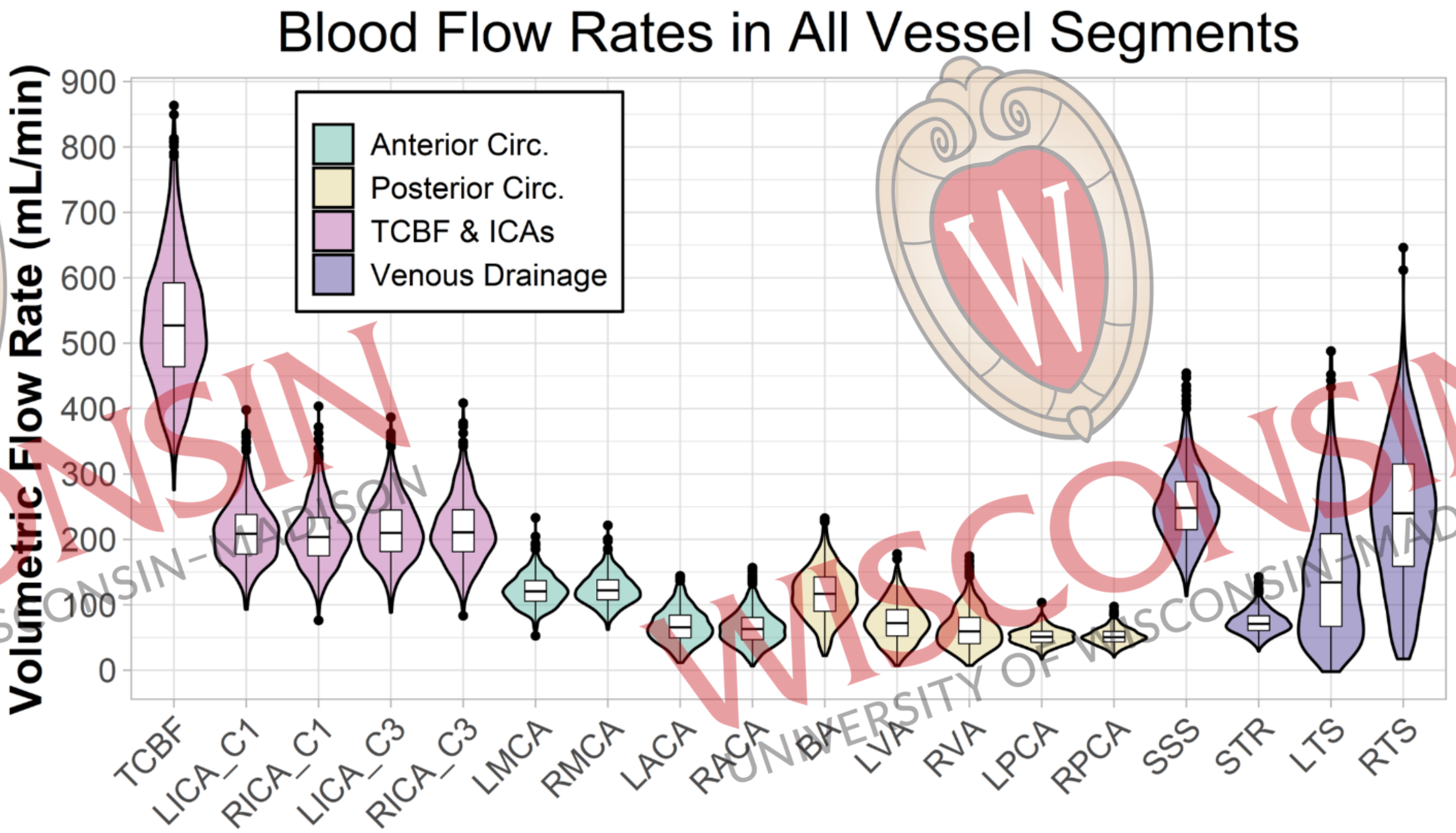


$$VFR = Q_{mean}$$
$$PI = (Q_{max} - Q_{min})/Q_{mean}$$

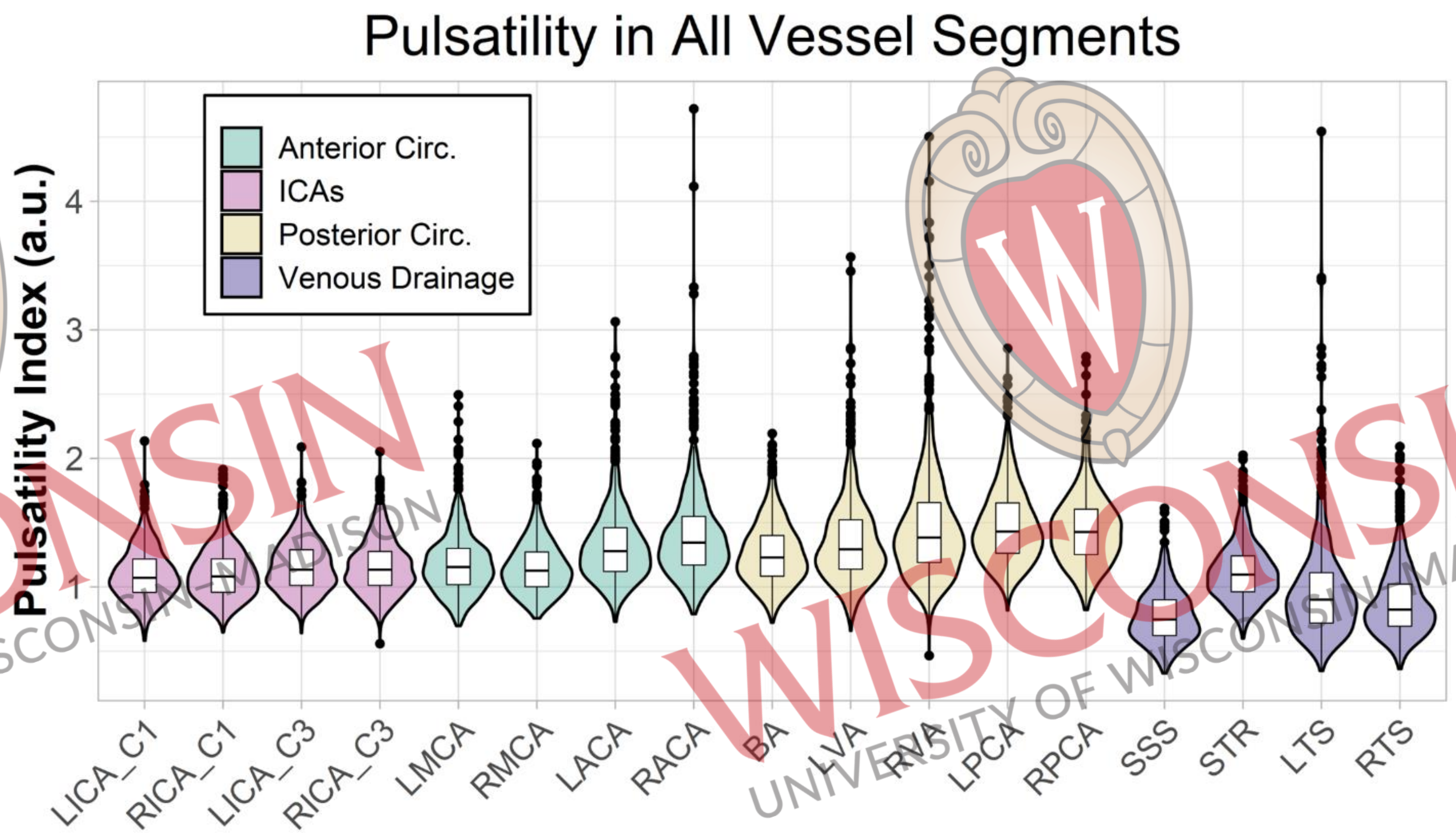
Vessel
Total Cerebral Blood Flow (TCBF)
Cervical ICA (RICA-C1)
Cavernous ICA (RICA-C3)
Middle Cerebral Artery (MCA)
Anterior Cerebral Artery (ACA)
Basilar Artery (BA)
Vertebral Artery (VA)
Posterior Cerebral Artery (PCA)
Superior Sagittal Sinus (SSS)
Straight Sinus (STR)
Transverse Sinus (TS)



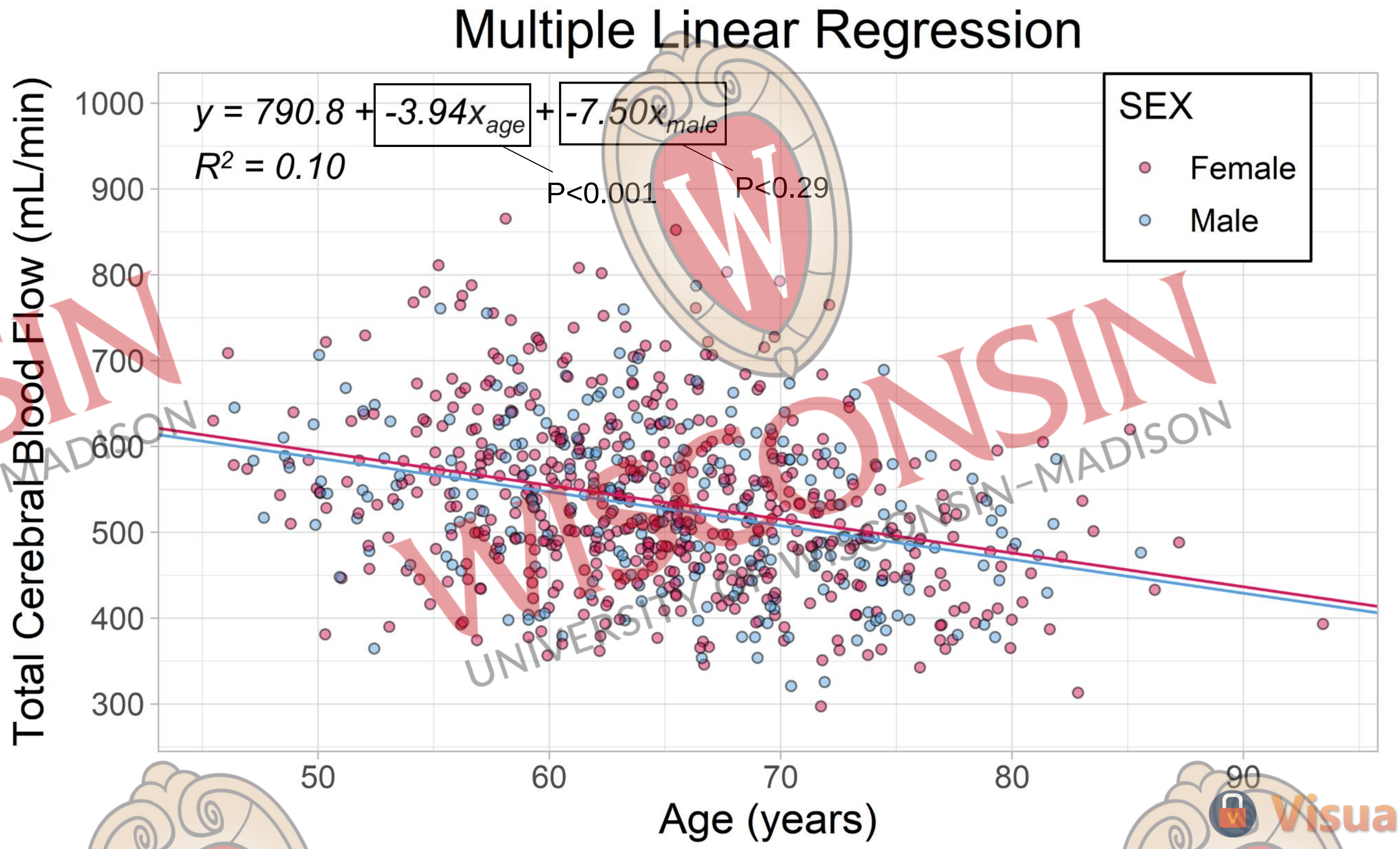
Results – Pulsatility



Results – Pulsatility



Results – Total Flow vs. Age/Sex

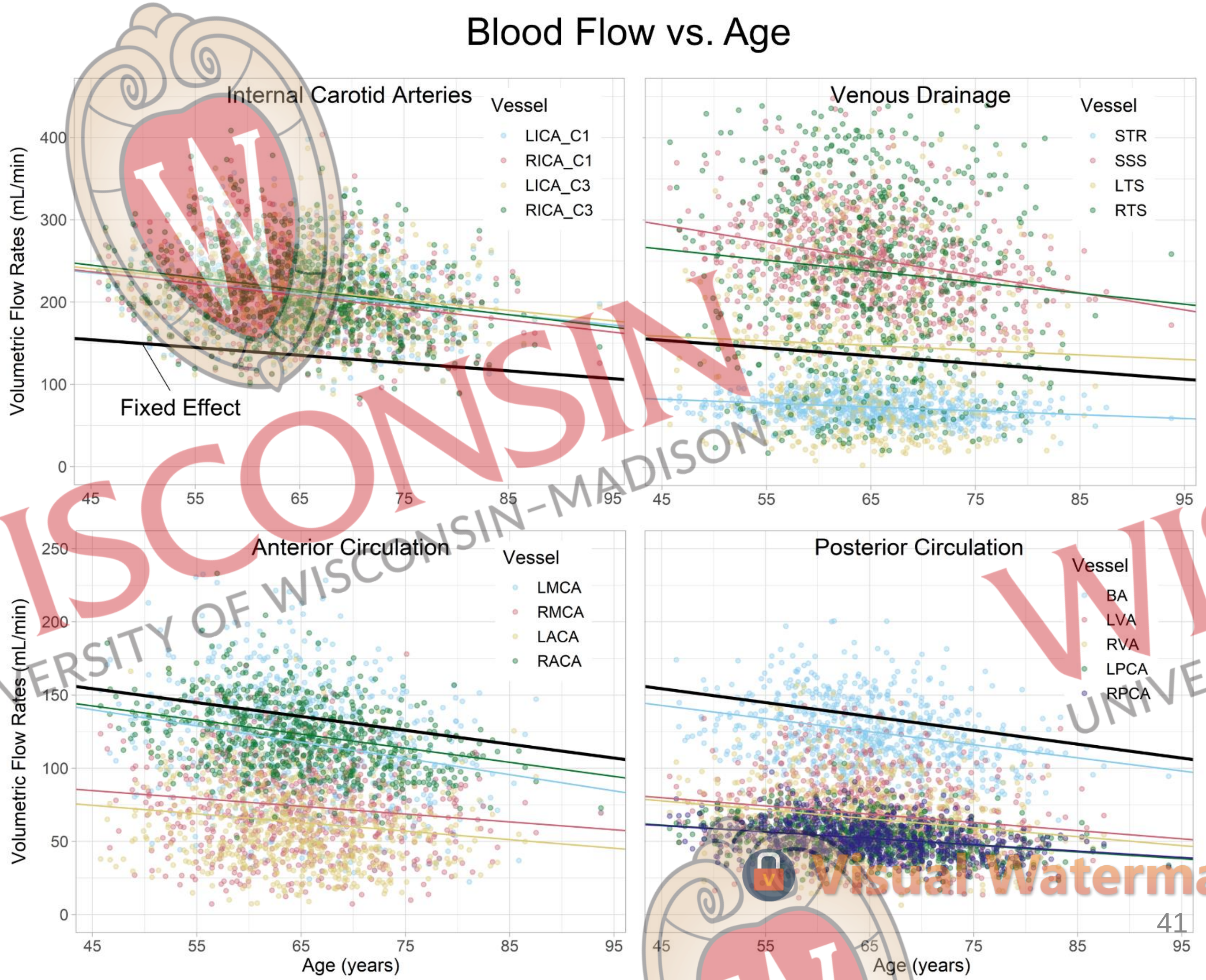


Results – Flow vs. Age/Sex

Mixed Effects Regression: Flow ~ Age + Sex + (1 + Age | Vessel) + (1 | Participant)

	β (coefficients)		
	Intercept	Age	Sex (male)
FIXED EFFECT	**135.4*** **	**-0.95*** **	-1.60
ICA_C1	295.4	-1.33	
ICA_C3	305.4	-1.38	
MCA	188.4	-0.98	
ACA	115.9	-0.72	
BA	198.4	-1.23	
VA	117.6	-0.72	
PCA	88.5	-0.55	
TS	247.0	-0.47	
STR	111.7	-0.58	
SSS	386.0	-2.04	

T-Tests using Satterthwaite's Method
*p<0.05
**p<0.01
***p<0.001

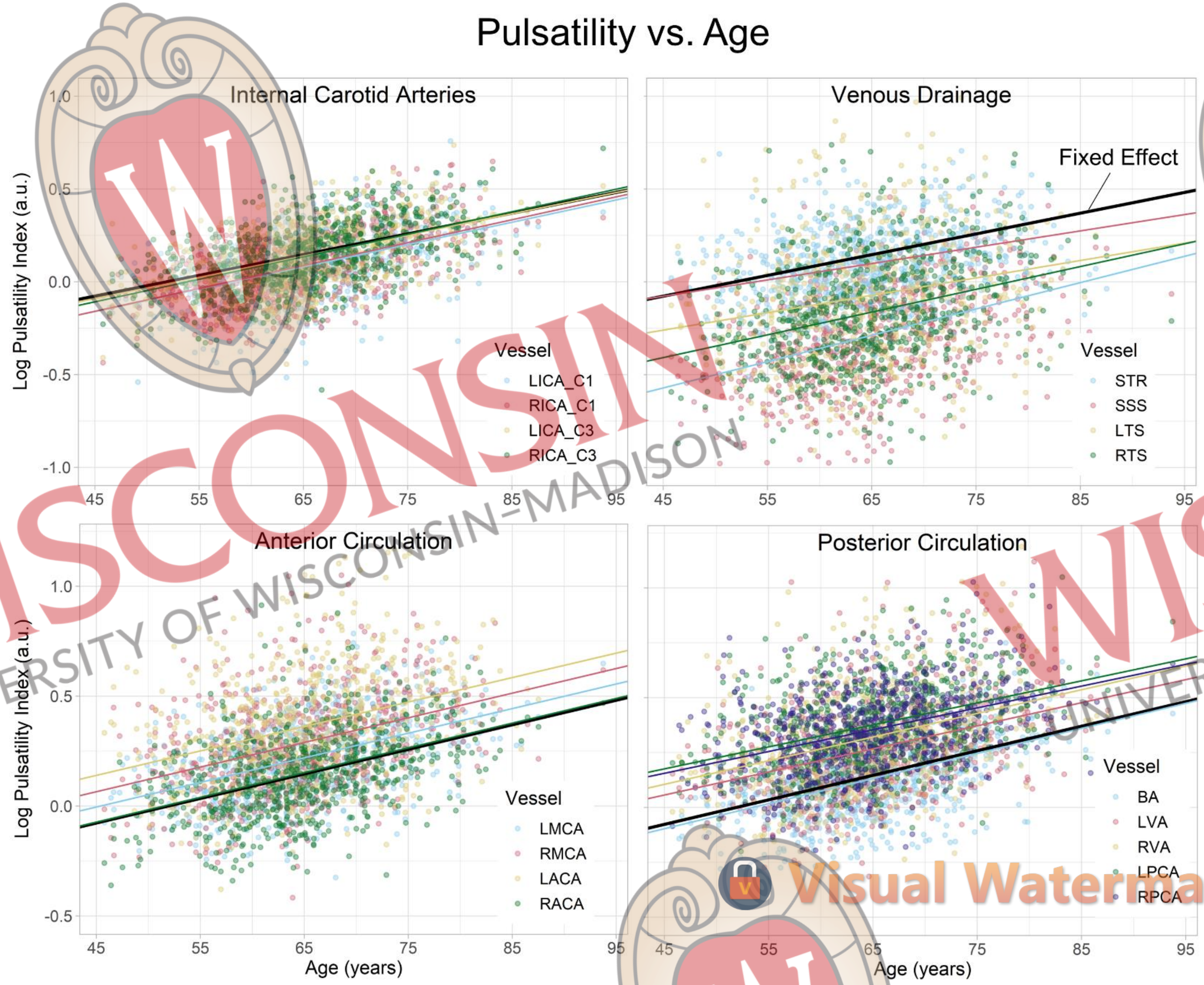


Results – Pulsatility vs. Age/Sex

Mixed Effects Regression: PI ~ Age + Sex + (1 + Age | Vessel) + (1|Participant)

	β (coefficients)		
	Intercept	Age	Sex (male)
FIXED EFFECT	**0.146****	**0.011*****	**-0.018***
ICA_C1	0.174	0.014	-0.012
ICA_C3	0.227	0.014	-0.012
MCA	0.271	0.014	-0.012
ACA	0.333	0.016	-0.012
BA	0.286	0.015	-0.012
VA	0.329	0.017	-0.012
PCA	0.441	0.016	-0.012
TS	0.211	0.011	-0.012
STR	0.405	0.011	-0.012
SSS	0.069	0.011	-0.012

T-tests using Satterthwaite's method
*p<0.05
**p<0.01
***p<0.001



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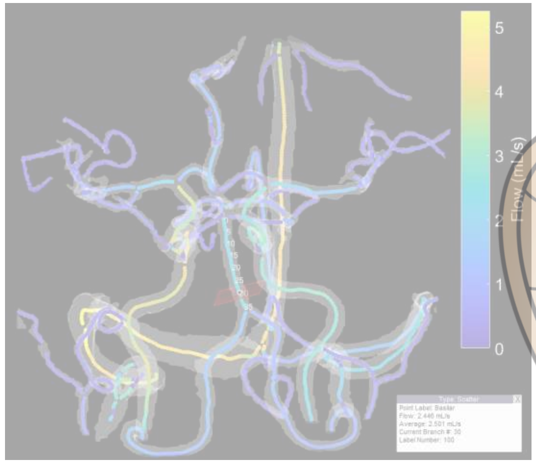
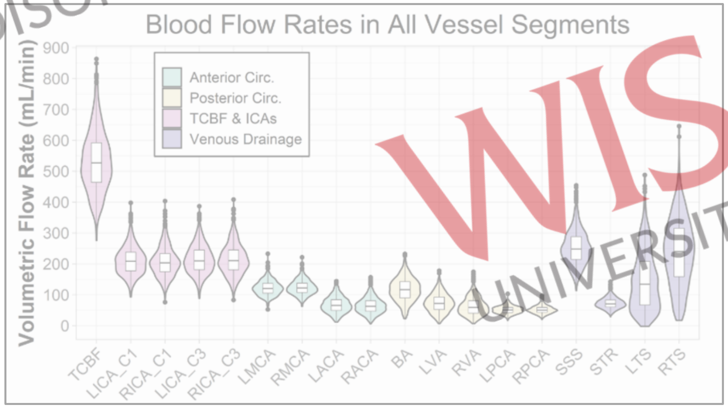
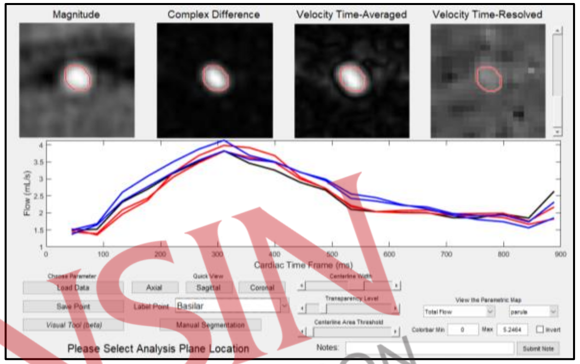


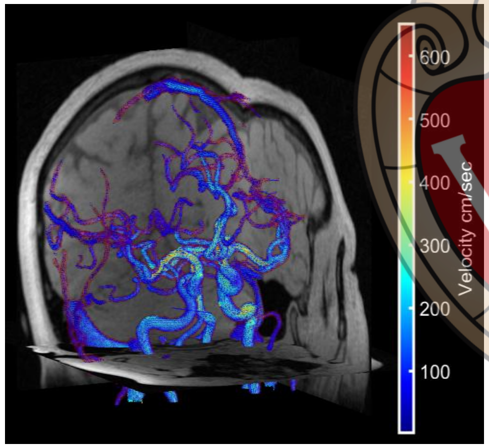


Summary

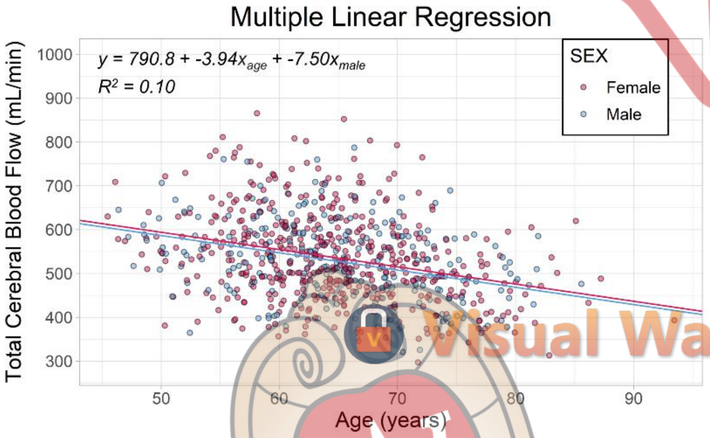
- **4D flow MRI –** powerful method for obtaining 3D velocity fields in vivo
  - Blood velocities, blood flow rates, pulsatility index, etc.

- Developed **cranial 4D flow MRI analysis tool**
  - Interactive 3D vessel selection and visualization
  - Accurate segmentation and flow quantification



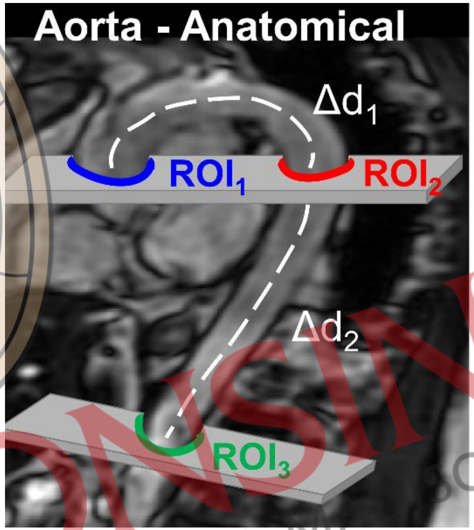


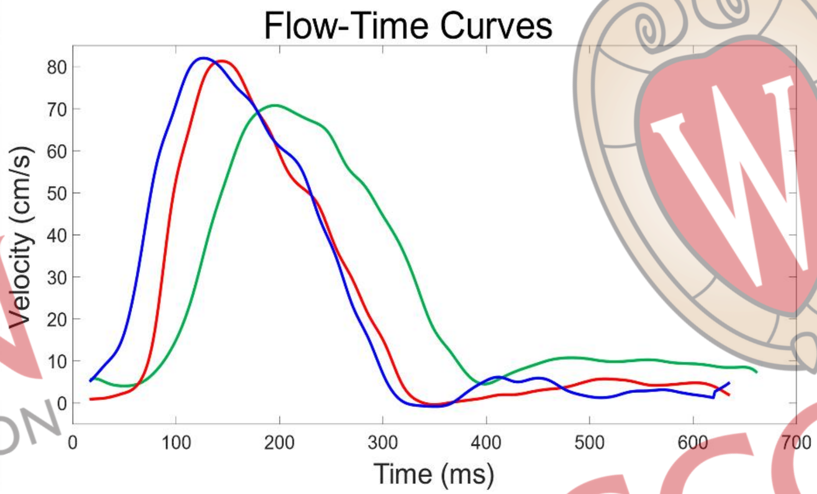
- Established **"normative" intracranial flow/pulsatility** in **759 adults**
  - Strong age dependence on flow and pulsatility
  - One of the largest 4D flow studies to date

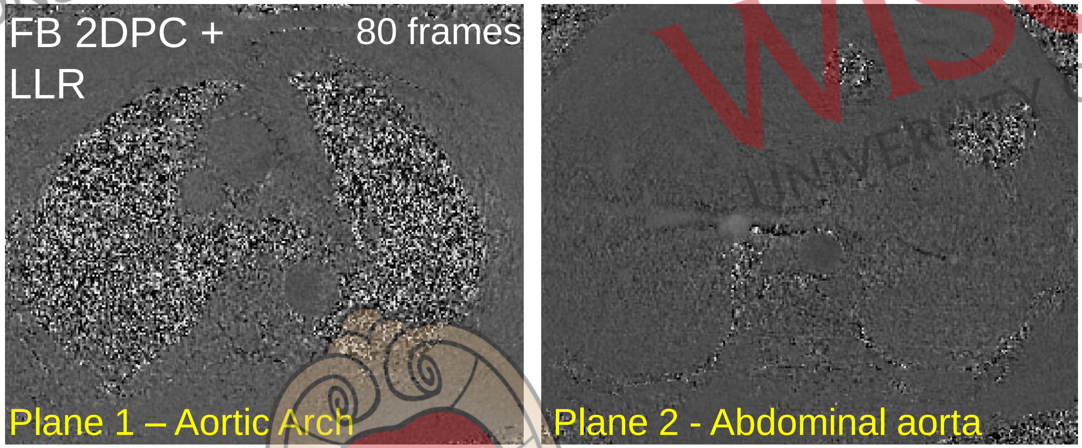


Some Other Projects

Aortic Pulse Wave Velocity with 2DPC MRI








Ozioma Okonkwo


Alyssa Pandos


Bri Breidenbach

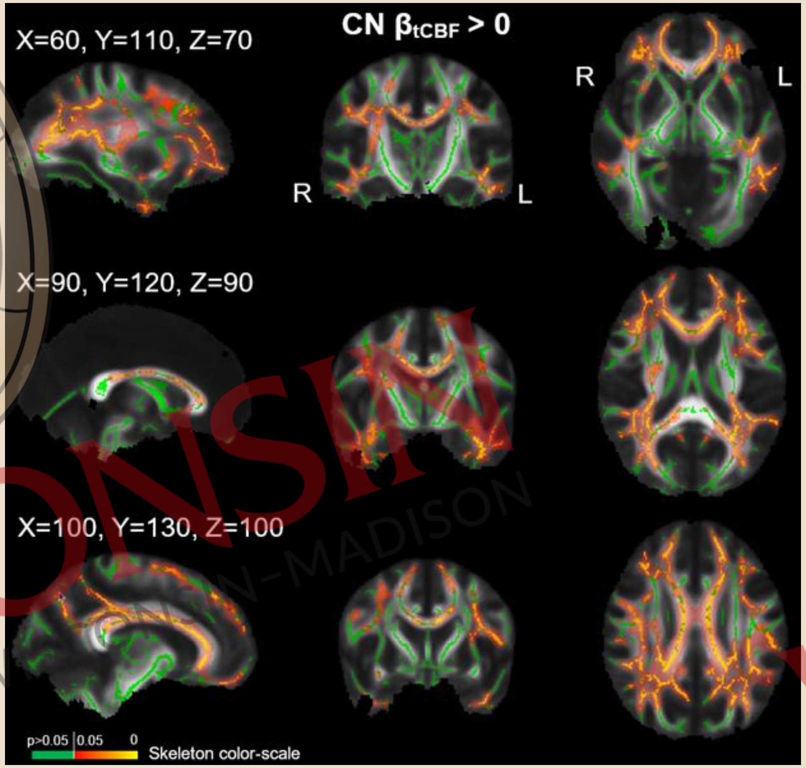
PWV Phantom Validation


Alejandro Roldan


James Rice

Some Other Projects

NODDI DTI vs. 4D Flow MRI




Doug Dean III


Andy Alexander


Jason Moody

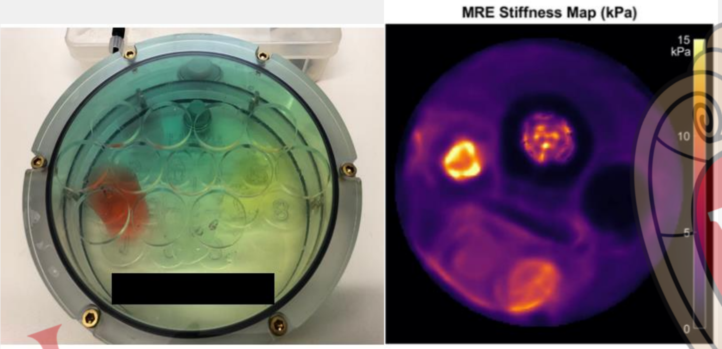

Alma Spahic

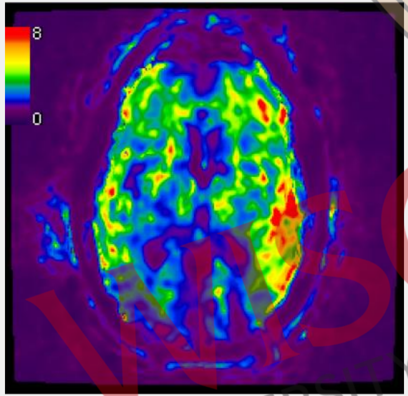
Abdominal 4D Flow MRI


Scott Reeder


Thekla Oechtering

Brain MR Elastography



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Jill Barnes Lab

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Publications relevant to this talk

1. **Roberts, G. S.**, Hoffman, C. A., Rivera-Rivera, L. A., Berman, S. E., Eisenmenger, L. B., & Wieben, O (2023). "Automated Hemodynamic Assessment for Cranial 4D Flow MRI". *Magnetic Resonance Imaging*. 10.1016/j.mri.2022.12.016.
2. **Roberts, G. S.**, Peret, A., Hoffman, C. A., Koscik, R. L., Jonaitis, E. M., Rivera-Rivera, L. A., Cody, K. A., Rowley, H. A., Johnson, S. C., Wieben, O., Johnson, K. M., & Eisenmenger, L. B (2023). "Normative Cerebral Blood Flow and Pulsatility in Cognitively Unimpaired Older Adults using 4D Flow MRI". *Accepted to Radiology*.
3. **Roberts, G. S.**, Loecher, M. W., Spahic, A., Johnson, K. M., Turski, P. A., Eisenmenger, L. B., & Wieben, O. (2022). "Virtual Injections Using 4D Flow MRI with Displacement Corrections and Constrained Probabilistic Streamlines". *Magnetic Resonance in Medicine*. 10.1002/mrm.29134.
4. Eisenmenger, L. B., Peret, A., Famakin, B. M., Spahic, A., **Roberts, G. S.**, Bockholt, H. J., Johnson, K. M., & Paulsen, J. S. (2022). "Vascular Contributions to Alzheimer's Disease". *Translation Research*, 10.1016/j.trsl.2022.12.003.