

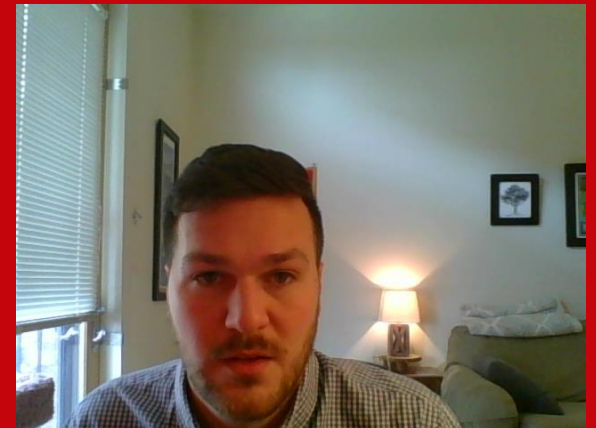


# Assessment of Cerebrovascular Disease and White Matter Neurite Density in Alzheimer's Disease

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**Abstract #0267**

# **Declaration of Financial Interests or Relationships**

Speaker Name: Grant S. Roberts

I have the following financial interest or relationship to disclose with regard to the subject matter of this presentation:

Company Name: GE Healthcare

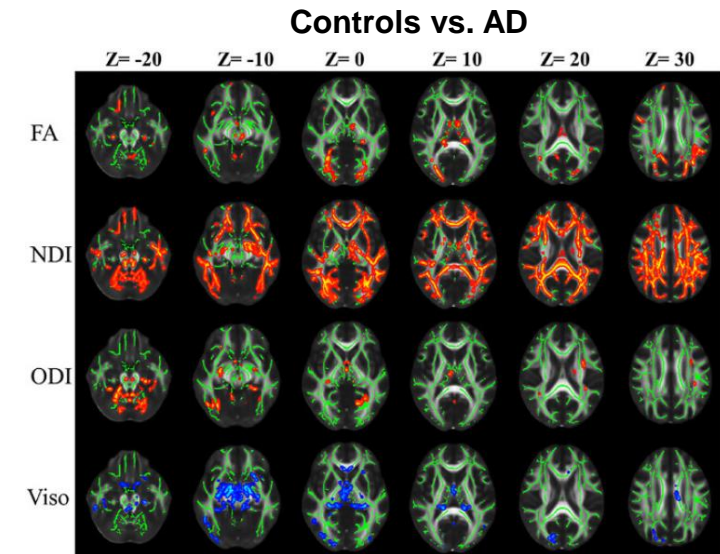
Type of Relationship: Research Support



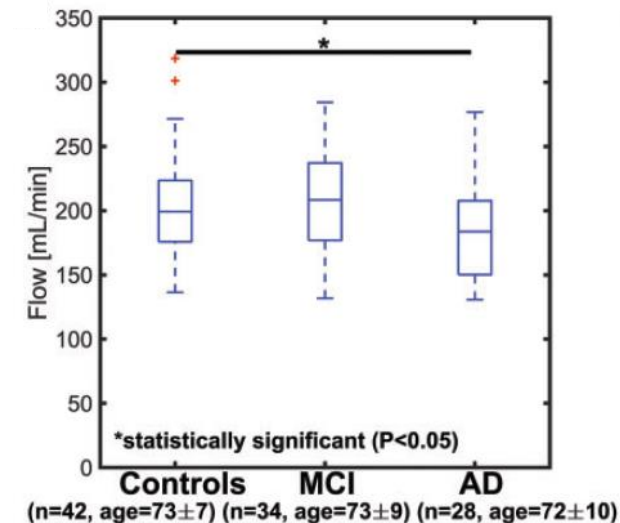
# Background

- Alzheimer's disease (AD)
  - A $\beta$  plaques and neurofibrillary tangles
  - Cortical atrophy
  - Typically thought of as disease of grey matter
- However, white matter (WM) alterations also occur<sup>1-4</sup>
  - Likely vascular-mediated
    - Disrupts brain microcirculation
    - Impaired clearance of waste products
- We have also shown vascular changes present in AD<sup>5-7</sup>

1. Brun A, Englund, E (1986). *Ann Neurol* 19(3)
2. Agosta F, et al (2011). *Radiology* 258(3)
3. Slattery CF, et al (2017). *Neurobiol Aging* 57
4. Fu X, et al (2020). *Clin Neuroradiol* 30(3)
5. Rivera-Rivera LA, et al (2016). *JCBFM* 36(10)
6. Berman SE, et al (2015). *Neuroimaging* 1(4)
7. Rivera-Rivera LA, et al (2021). *JCBFM* 41(2)



Adapted From: Fu X, et al (2020). *Clin Neuroradiol* 30(3)



From: Rivera-Rivera LA, et al (2020). *JCBFM* 41(2)



# Background

- Relationship between macrovascular flow and WM microstructure alterations is still unclear
  - Goal:**
    - Utilize **4D Flow MRI** (cerebrovascular dynamics)
    - Utilize DTI **NODDI** (WM microstructure)
      - 20 AD and 41 cognitively normal (CN) subjects
- Compare WM axon density between AD/CN groups
  - Correlate WM axon density with vascular measures
    - Carotid pulse wave velocity (stiffness)
    - Carotid pulsatility index (resistance)
    - Total cerebral blood flow

## 4D Flow

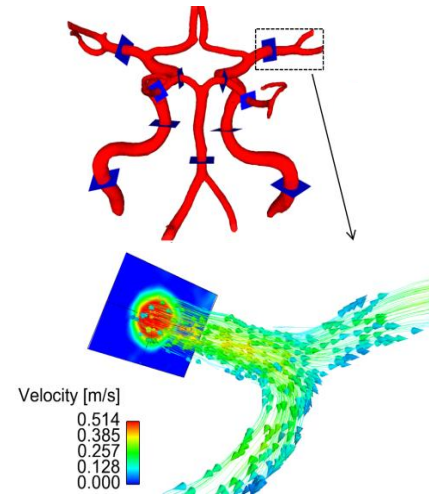
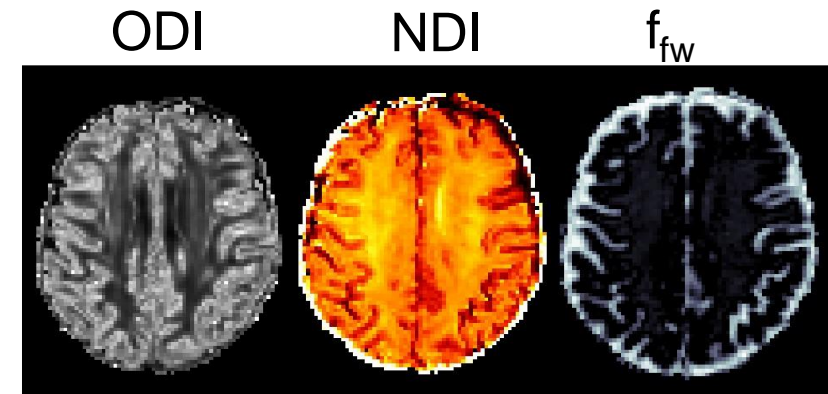


Image: Rivera-Rivera LA, et al (2016). *JCBFM* 36(10).

## NODDI



# Methods

## Patient Demographics

- 20 Alzheimer's disease subjects
  - Characterized as “dementia due to probable AD<sup>1,2</sup>”
- 41 Cognitively normal subjects

	CN (N=41)	AD (N = 20)	p-value
Age (years)	74 ± 7	73 ± 9	0.96 <sup>a</sup>
Female (n, %)	23, 56.1	13, 65.0	0.58 <sup>b</sup>
Parental history of dementia (n, %)	1, 2.44	7, 35.0	<b>0.001<sup>b</sup></b>
APOE ε4 carrier (n, %)*	1, 2.44	6, 30.0	<b>2.51e-04<sup>b</sup></b>
SBP (mmHg)	132 ± 22	131 ± 19	0.78 <sup>a</sup>
DBP (mmHg)	78 ± 9	75 ± 6	0.23 <sup>a</sup>
HR (bpm)	62 ± 9	60 ± 11	0.55 <sup>a</sup>
CN = cognitively normal; AD = Alzheimer's disease; APOE = apolipoprotein E; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate			
<sup>a</sup> Two sample t-test			
<sup>b</sup> Fisher's exact test			
Bold indicates statistical significance (p<0.05)			

<sup>1</sup>McKhann GM, et al (2011). *Alzheimers Dement* 7(3)

<sup>2</sup>Jack CR, et al (2018). *Alzheimers Dement* 14(4)



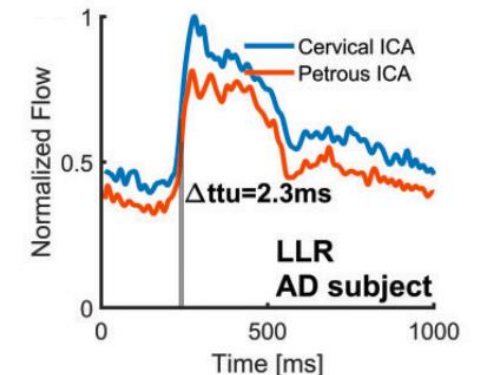
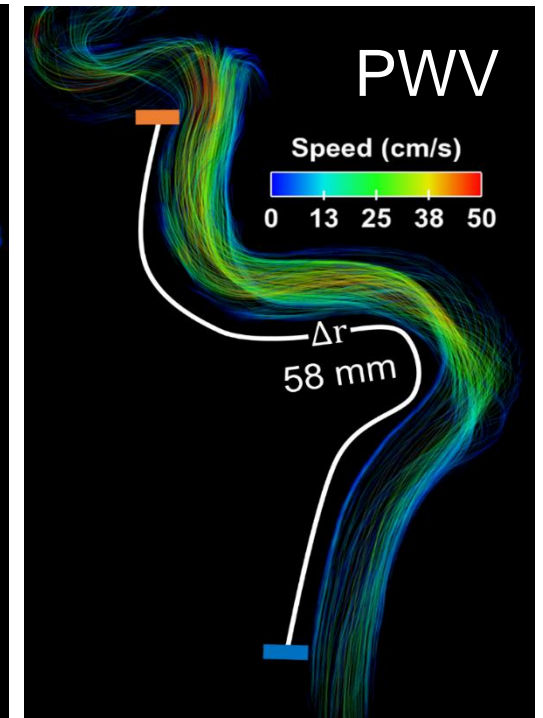
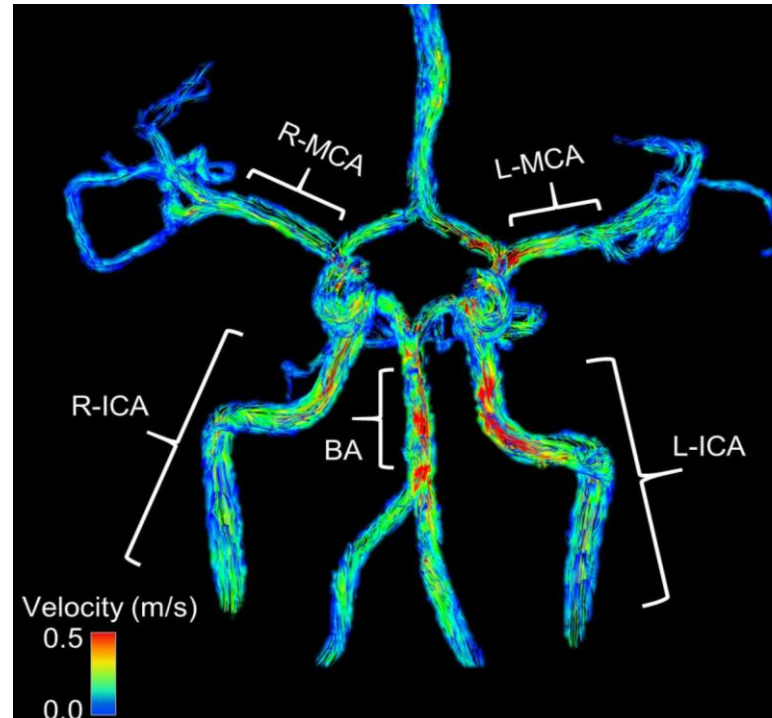


# Methods

## 4D Flow Measurements

- Total cerebral blood flow (tCBF)
  - $tCBF = Flow_{ICA} + Flow_{BA}$
- Pulsatility index (PI)
  - Vascular resistance
- Pulse wave velocity (PWV)
  - Vascular stiffness
  - Local low rank reconstruction<sup>1</sup>

MR Parameter	Value
Scanner	3.0T GE Discovery MR750
Coil	32 Channel Head
Sequence	PCVPR <sup>2,3</sup>
Encoding Scheme	5-point balanced
Projections	11,000
TR	7.4 ms
TE	2.7 ms
V <sub>enc</sub>	75 cm/s
Resolution	0.7 mm isotropic
Cardiac frames	100



<sup>1</sup>Rivera-Rivera LA, et al (2021). *JCBFM* 4(12).

<sup>2</sup>Gu T, et al (2005). *AJNR* 26(4).

<sup>3</sup>Johnson KM, et al (2008). *MRM* 60(6).

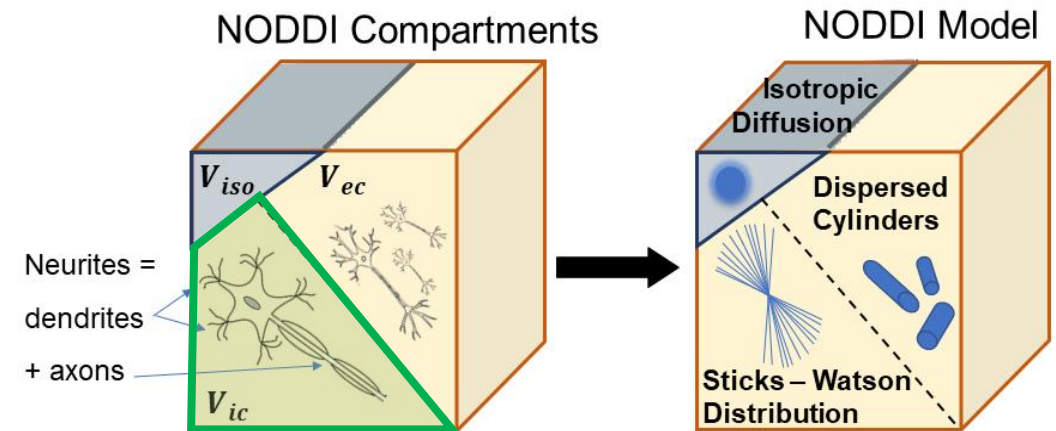
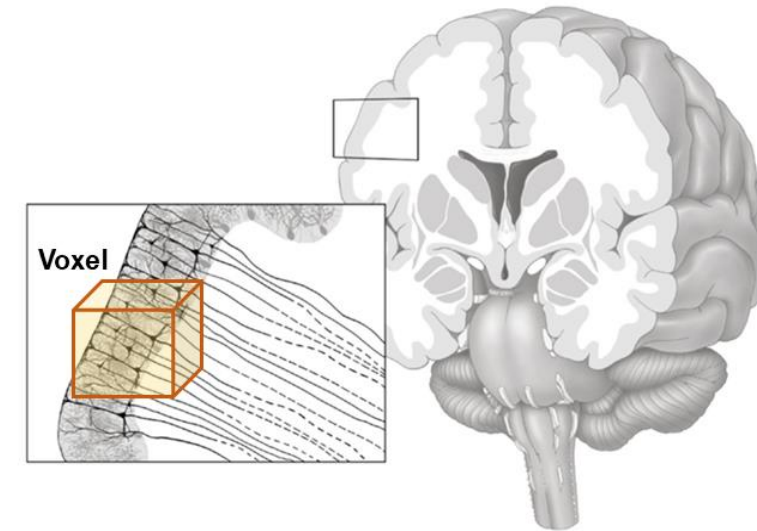


# Methods

## NODDI – Neurite Orientation Dispersion and Density Imaging<sup>1</sup>

- Neurite density index (NDI)
- Orientation dispersion index (ODI)
- Free water fraction ( $f_{fw}$ )

MR Parameter	Value
Scanner	3.0T GE Discovery MR750
Coil	32 Channel Head
Sequence	Spin-echo EPI
Shells	$6 \times b=0 \text{ s/mm}^2$ $9 \times b=500 \text{ s/mm}^2$ $18 \times b=800 \text{ s/mm}^2$ $36 \times b=2000 \text{ s/mm}^2$
Resolution	2 mm isotropic
TR	8575 ms
TE	76.8 ms
Flip angle	8 degrees



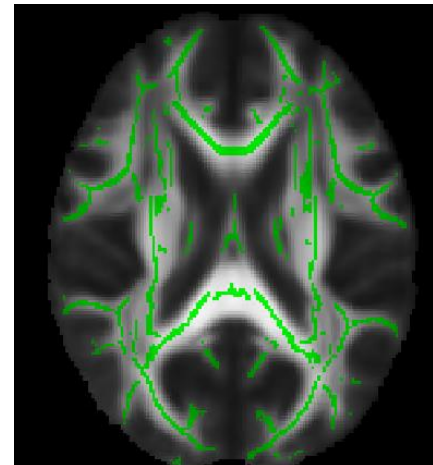
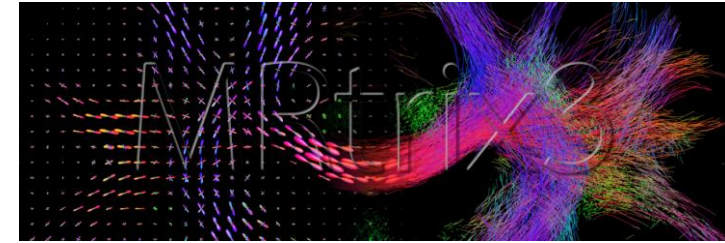
<sup>1</sup>Zhang H, et al (2012). *Neuroimage* 61(4).



# Methods

## Diffusion Tensor Data

- FSL/MRtrix<sup>1,2</sup>
- NODDI Matlab Toolbox<sup>3</sup>
  - NDI maps
- FSL
  - Tract-based Spatial Statistics: *tbss*<sup>4</sup>
  - Statistical Analysis: *Glm (randomise)*<sup>5</sup>



<sup>1</sup>Jenkinson M, et al (2012). *Neuroimage* 62

<sup>2</sup>Tournier JD, et al (2019). *Nueroimage* 14

<sup>3</sup>Zhang H, et al (2012). *Neuroimage* 61(4)

<sup>4</sup>Smith SM, et al (2006). *Neuroimage* 31(4)

<sup>5</sup>Winkler AM, et al (2014). *Neuroimage* 92(100)

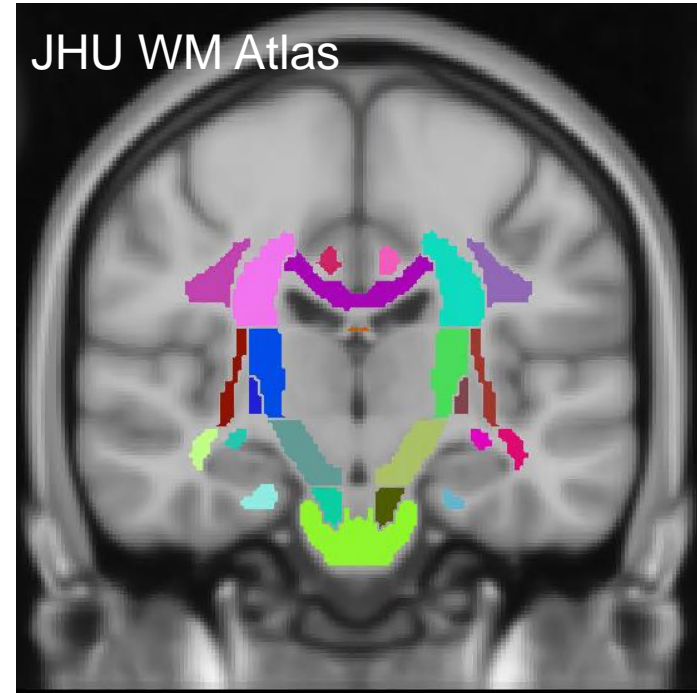




# Methods

## TBSS Hypothesis Tests

- Are there differences in NDI Between AD and CN subjects?
- Are there correlations between PWV/PI/tCBF and NDI for AD and CN subjects?
- *Post hoc* analysis in significant tracts
  - ROIs identified with JHU WM atlas
  - Mean NDI values were extracted for each subject



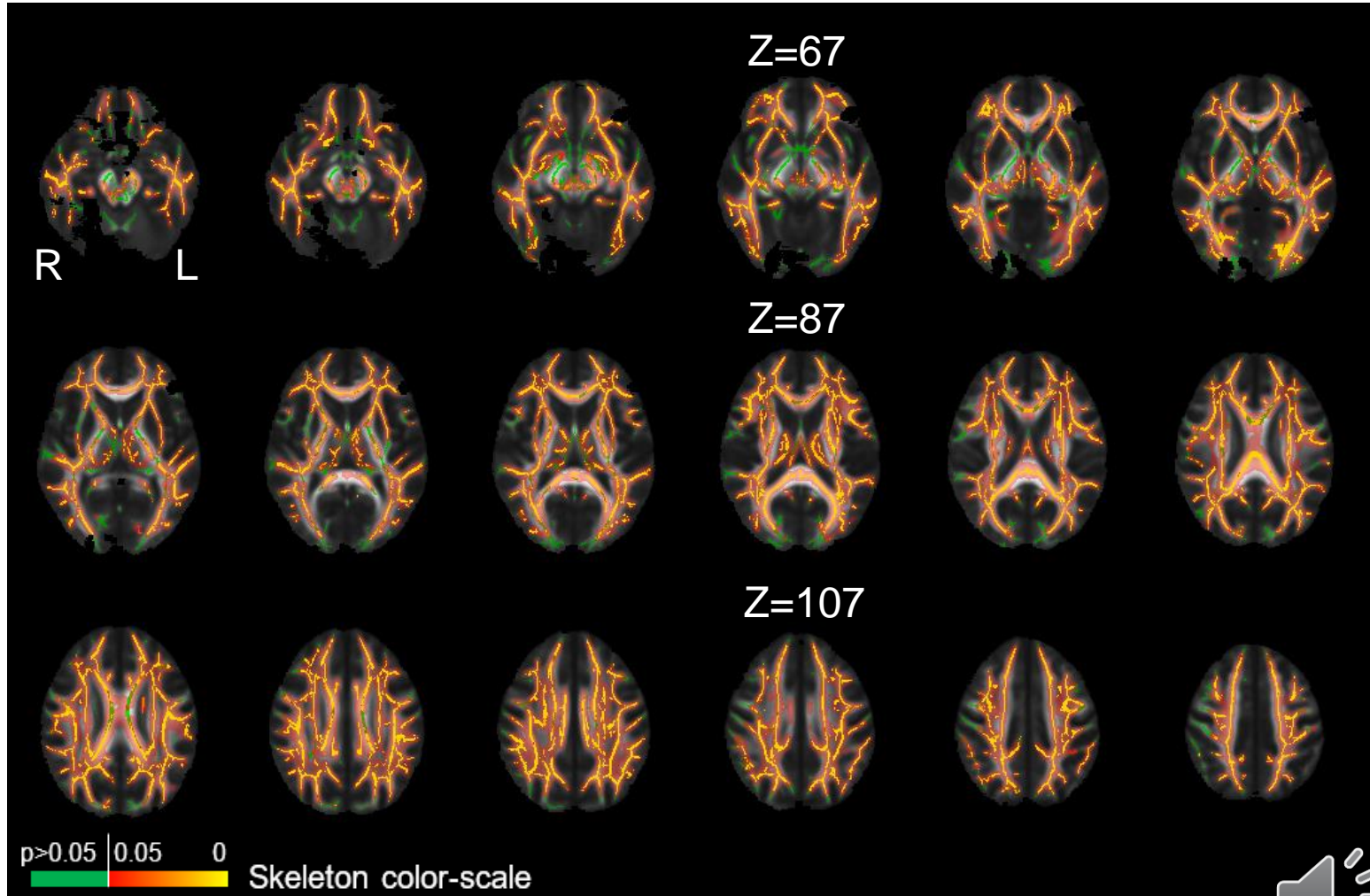
# Results

## TBSS Hypothesis Tests

- Compare NDI Between AD and CN
  - CN NDI > AD NDI?

Similar results observed by  
Slattery et al<sup>1</sup> and Fu et al<sup>2</sup>

CN NDI > AD NDI



1. Slattery CF, et al (2017). *Neurobiol Aging* 57

2. Fu X, et al (2020). *Clin Neuroradiol* 30(3)



# Results

## ROI Analysis

- CN NDI > AD NDI
- WM regions identified on TBSS using JHU WM atlas
- ANCOVA
  - Adjusted for age/sex
  - Corrected for multiple comparisons

White Matter Regions Identified from TBSS (ICBM-DTI-81 Atlas Label #)	CN Mean NDI	AD Mean NDI	p-value
Genu of Corpus Callosum (3)	0.526 ± 0.041	0.507 ± 0.047	0.1329
Body of Corpus Callosum (4)	0.595 ± 0.028	0.573 ± 0.034	0.0137*
<b>Splenium of Corpus Callosum (5)</b>	0.635 ± 0.031	0.597 ± 0.032	<b>5.2e-05**</b>
Anterior corona radiata R (23)	0.473 ± 0.056	0.438 ± 0.054	0.0138*
<b>Anterior corona radiata L (24)</b>	0.474 ± 0.053	0.429 ± 0.054	<b>0.0019**</b>
Superior corona radiata R (25)	0.590 ± 0.046	0.556 ± 0.058	0.0113*
Superior corona radiata L (26)	0.583 ± 0.048	0.541 ± 0.059	0.0024*
Posterior corona radiata R (27)	0.512 ± 0.055	0.473 ± 0.063	0.0153*
Posterior corona radiata L (28)	0.505 ± 0.054	0.467 ± 0.049	0.0104*
<b>Posterior thalamic radiation R (29)</b>	0.515 ± 0.041	0.474 ± 0.041	<b>3.9e-04**</b>
<b>Posterior thalamic radiation L (30)</b>	0.487 ± 0.048	0.438 ± 0.047	<b>3.3e-04**</b>
Sagittal stratum R (31)	0.510 ± 0.030	0.492 ± 0.033	0.0558
Sagittal stratum L (32)	0.487 ± 0.035	0.467 ± 0.038	0.0541
External capsule R (33)	0.506 ± 0.030	0.485 ± 0.028	0.0075*
<b>External capsule L (34)</b>	0.509 ± 0.026	0.483 ± 0.028	<b>2.9e-04**</b>
<b>Cingulate gyrus R (35)</b>	0.536 ± 0.023	0.510 ± 0.022	<b>7.8e-05**</b>
<b>Cingulate gyrus L (36)</b>	0.542 ± 0.024	0.510 ± 0.023	<b>8.4e-06**</b>
<b>Cingulum (hippocampus) R (37)</b>	0.496 ± 0.029	0.463 ± 0.036	<b>2.8e-04**</b>
<b>Cingulum (hippocampus) L (38)</b>	0.494 ± 0.022	0.469 ± 0.025	<b>3.5e-04**</b>
Superior longitudinal fasciculus R (41)	0.592 ± 0.034	0.557 ± 0.056	0.0069*
<b>Superior longitudinal fasciculus L (42)</b>	0.594 ± 0.038	0.552 ± 0.053	<b>7.8e-04**</b>
Superior fronto-occipital fasciculus R (43)	0.557 ± 0.074	0.520 ± 0.061	0.0317*
Superior fronto-occipital fasciculus L (44)	0.542 ± 0.081	0.482 ± 0.070	0.0026*
<b>Uncinate fasciculus R (45)</b>	0.485 ± 0.026	0.454 ± 0.032	<b>2.9e-05**</b>
<b>Uncinate fasciculus L (46)</b>	0.484 ± 0.027	0.451 ± 0.022	<b>1.6e-05**</b>

Abbreviations: NDI=neurite density index; AD=Alzheimer's disease; CN=cognitively normal; TBSS=tract-based spatial statistics; R=right; L=left

\*p-values <0.05; \*\*p-value<0.002 (Bonferroni correction for 25 ROIs).



# Results

## TBSS Hypothesis Tests

- Compare NDI Between AD and CN
  - CN NDI > AD NDI?
- Correlation - PWV and NDI
  - No significant findings
- Correlation - PI and NDI
  - No significant findings

**No significant findings!**

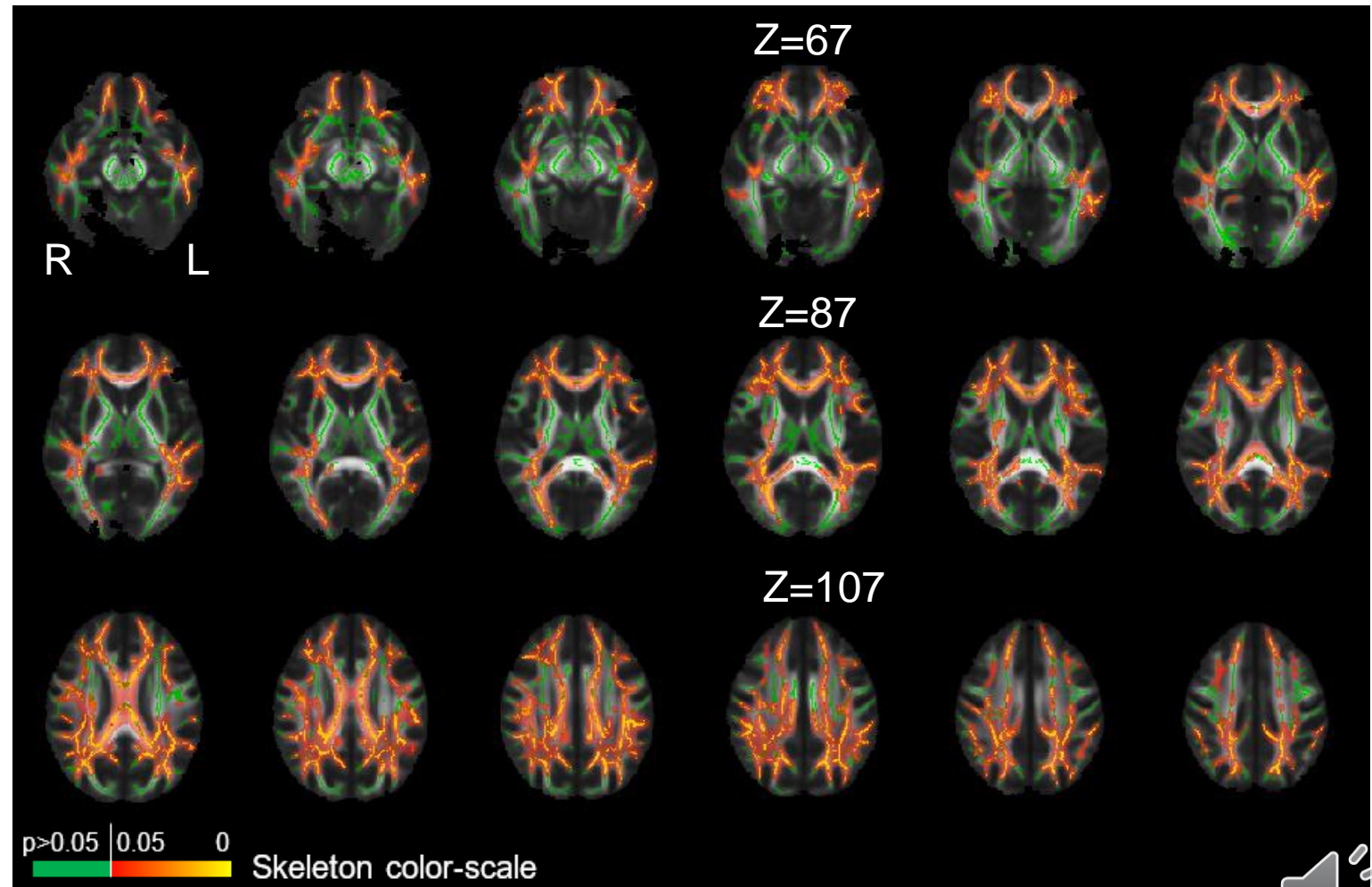


# Results

## TBSS Hypothesis Tests

- Compare NDI Between AD and CN
  - $\text{CN NDI} > \text{AD NDI}$ ?
- Correlation - PWV and NDI
  - No significant findings
- Correlation - PI and NDI
  - No significant findings
- Correlation - tCBF and NDI
  - $\text{CN } \beta_{\text{tCBF}} \neq 0$ ?
  - ~~$\text{AD } \beta_{\text{tCBF}} \neq 0$ ?~~

$\text{CN } \beta_{\text{tCBF}} > 0$





# Results

## ROI Analysis

CN  $\beta_{tCBF} > 0$

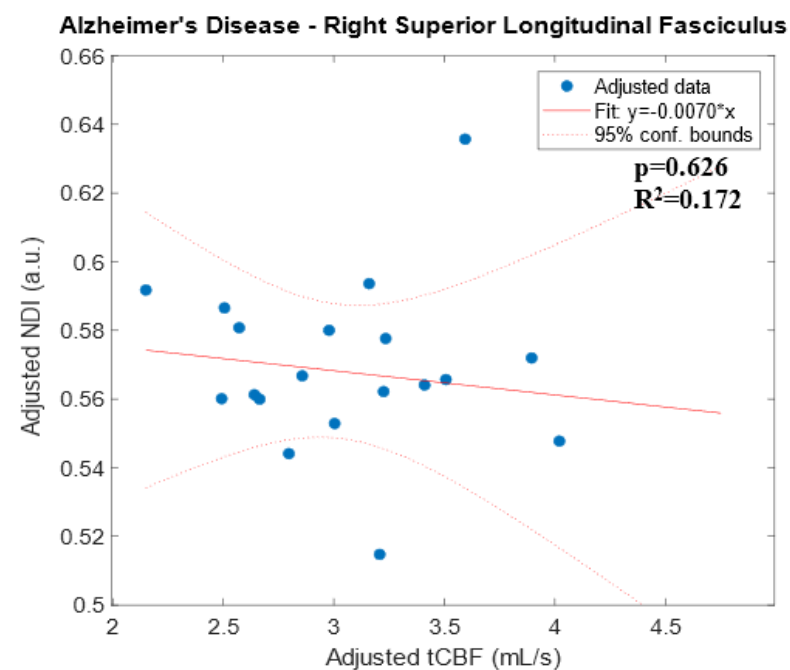
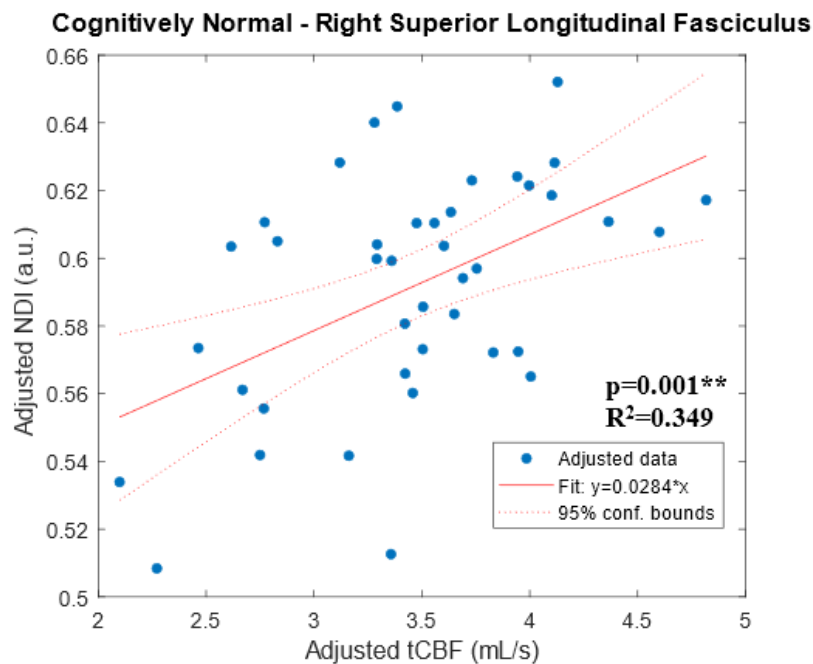
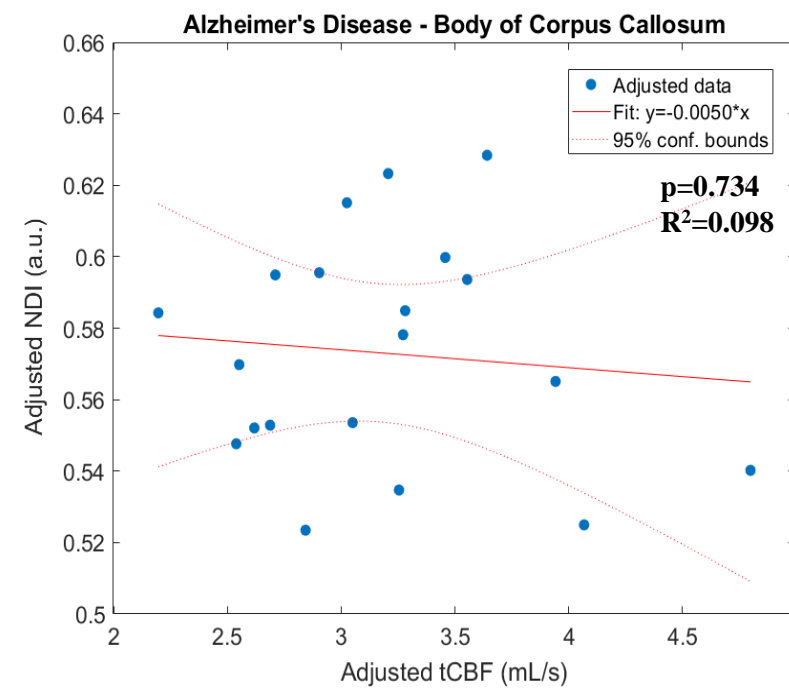
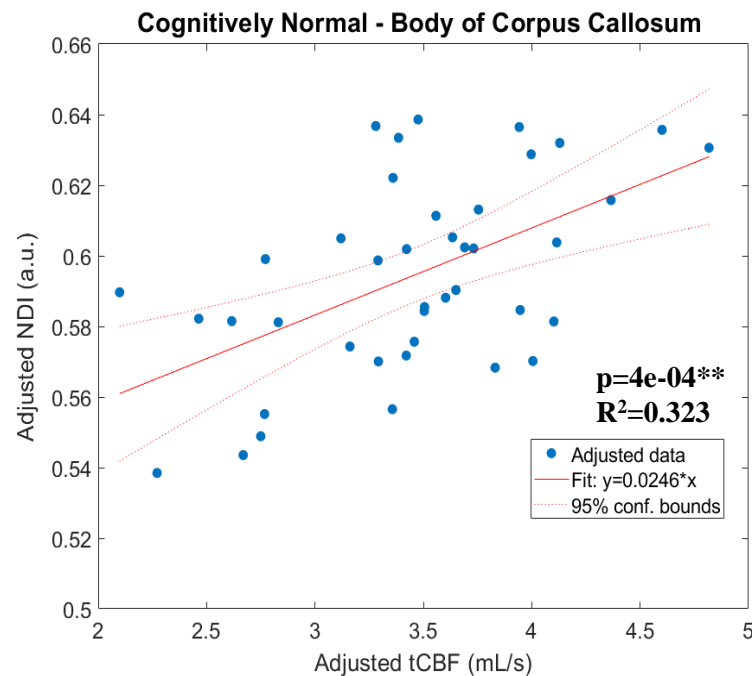
- Multiple Regression
  - Adjusted for age/sex
  - Corrected for multiple comparisons

White Matter Regions Identified from TBSS (ICBM-DTI-81 Atlas Label #)	CN $\beta_{tCBF} > 0$		
	$\beta_{tCBF}$	R <sup>2</sup>	p-value
Genu of corpus callosum (3)	0.025	0.129	0.019*
<b>Body of corpus callosum (4)</b>	0.025	0.247	<b>4e-04**</b>
Splenium of corpus callosum (5)	0.019	0.176	0.013*
Anterior corona radiata R (23)	0.026	0.283	0.045*
Anterior corona radiata L (24)	0.027	0.212	0.034*
Superior corona radiata R (25)	0.019	0.237	0.075
Superior corona radiata L (26)	0.015	0.174	0.203
Posterior corona radiata R (27)	0.036	0.245	0.007*
Posterior corona radiata L (28)	0.035	0.216	0.008*
Posterior thalamic radiation R (29)	0.020	0.206	0.049*
Posterior thalamic radiation L (30)	0.021	0.169	0.078
<b>Superior long. fasciculus R (41)</b>	0.028	0.349	<b>0.001**</b>
Superior long. fasciculus L (42)	0.023	0.221	0.012*

Abbreviations: tCBF = total cerebral blood flow; NDI=neurite density index; CN=cognitively normal; AD=Alzheimer's disease; TBSS=tract-based spatial statistics  
 $\beta$ : regression coefficient; R<sup>2</sup>: adjusted coefficient of determination  
 \*p-values <0.05; \*\*p-value<0.004 (Bonferroni correction for 13 ROIs).



# Results



# Discussion

1. Slattery CF, et al (2017). *Neurobiol Aging* 57
2. Fu X, et al (2020). *Clin Neuroradiol* 30(3)

## Significant Findings

1. White matter density was decreased in AD subjects
  - Variety of WM regions<sup>1,2</sup>
2. Positive correlation between cerebral blood flow and axon density in CN subjects
  - Corpus callosum
  - Superior longitudinal fasciculus
3. No associations between CVD and NDI for AD subjects

## Limitations and Future Work

- Small sample size
- Need longitudinal data with subjects along the AD continuum to look at potential *causative* affects of CVD on WM microstructure

## Conclusion

- WM microstructure alterations, as measured by NDI, were observed in AD group
- Cerebral blood flow was significantly correlated with WM axon density only in control group





# Acknowledgements

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