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

Grant Roberts[1], Leonardo Rivera-Rivera[2], Kevin Johnson[1,3], Sterling Johnson[2], Douglas Dean III[1,4], Andrew Alexander[1,5], Oliver Wieben[1,3], and Laura Eisenmenger[3]

University of Wisconsin – Madison: Dept. of
[1]Medical Physics, [2]Medicine, [3]Radiology, [4]Pediatrics, [5]Psychiatry

Abstract #0267

Declaration of Financial Interests or Relationships

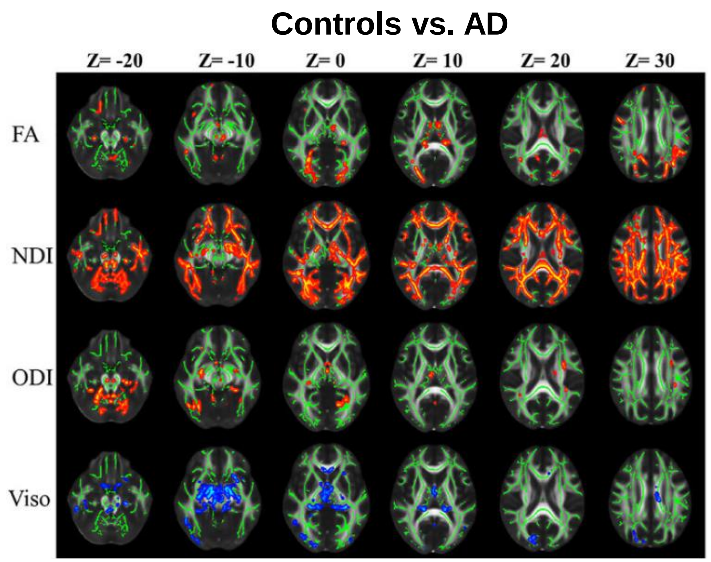
Speaker Name: Grant S. Roberts

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

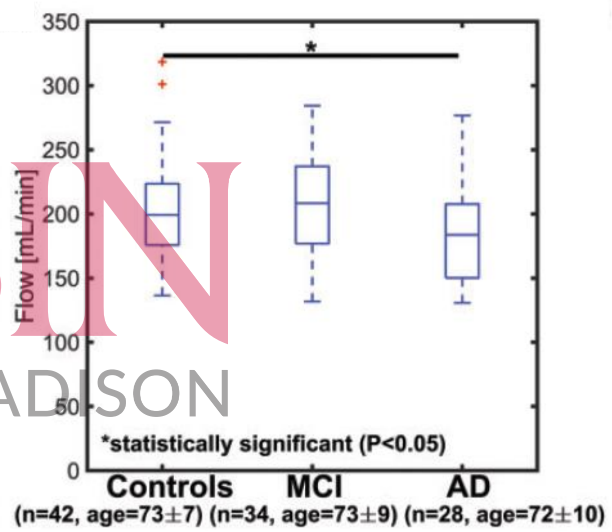
Company Name: GE Healthcare
Type of Relationship: Research Support

Background

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



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



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

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)

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

1. Compare WM axon density between AD/CN groups
2. Correlate WM axon density with vascular measures
a. Carotid pulse wave velocity (stiffness)
b. Carotid pulsatility index (resistance)
c. Total cerebral blood flow

4D Flow

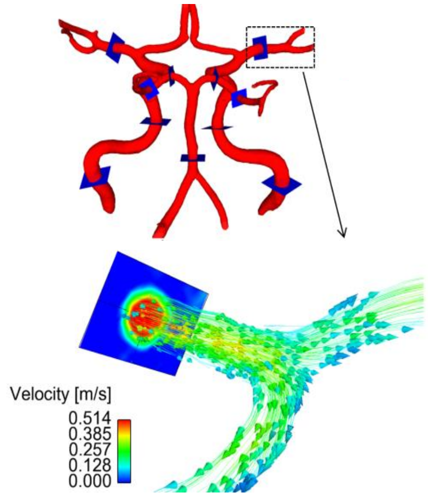
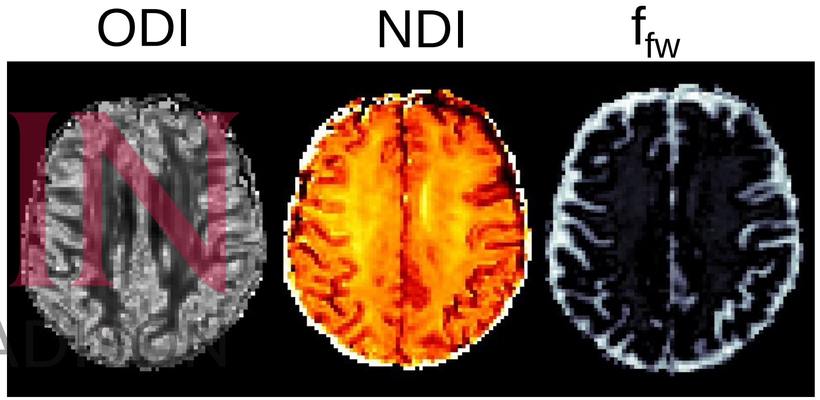


Image: Rivera-Rivera LA, et al (2016). *JCBFM* 36(10).

NODDI



Methods

Patient Demographics

- 20 Alzheimer's disease subjects
  - Characterized as "dementia due to probable AD[1,2]"
- 41 Cognitively normal subjects

	CN (N=41)	AD (N = 20)	p-value
Age (years)	74 ± 7	73 ± 9	0.96[a]
Female (n, %)	23, 56.1	13, 65.0	0.58[b]
Parental history of dementia (n, %)	1, 2.44	7, 35.0	**0.001[b]**
APOE ε4 carrier (n, %)*	1, 2.44	6, 30.0	**2.51e-04[b]**
SBP (mmHg)	132 ± 22	131 ± 19	0.78[a]
DBP (mmHg)	78 ± 9	75 ± 6	0.23[a]
HR (bpm)	62 ± 9	60 ± 11	0.55[a]

CN = cognitively normal; AD = Alzheimer's disease; APOE = apolipoprotein E; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate

[a]Two sample t-test

[b]Fisher's exact test

Bold indicates statistical significance (p<0.05)

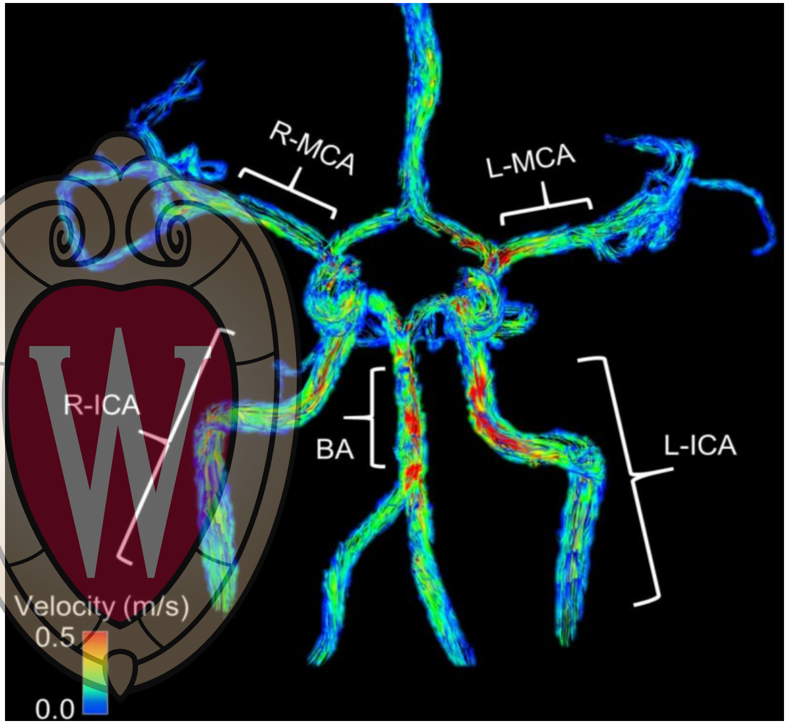
[1]McKhann GM, et al (2011). *Alzheimers Dement* 7(3)
[2]Jack CR, et al (2018). *Alzheimers Dement* 14(4)

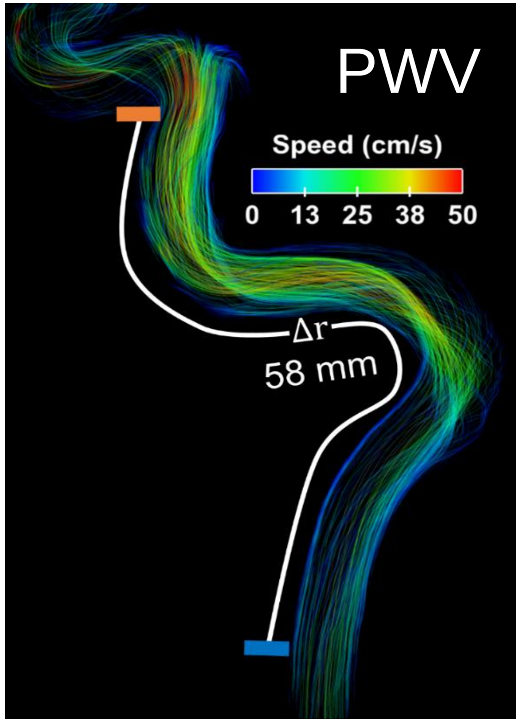
Methods

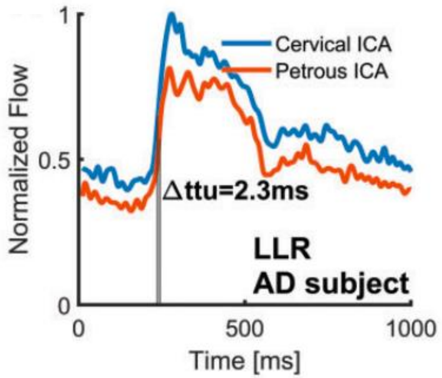
4D Flow Measurements

- 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[1]

MR Parameter	Value
Scanner	3.0T GE Discovery MR750
Coil	32 Channel Head
Sequence	PCVIPR[2,3]
Encoding Scheme	5-point balanced
Projections	11,000
TR	7.4 ms
TE	2.7 ms
V_{enc}	75 cm/s
Resolution	0.7 mm isotropic
Cardiac frames	100





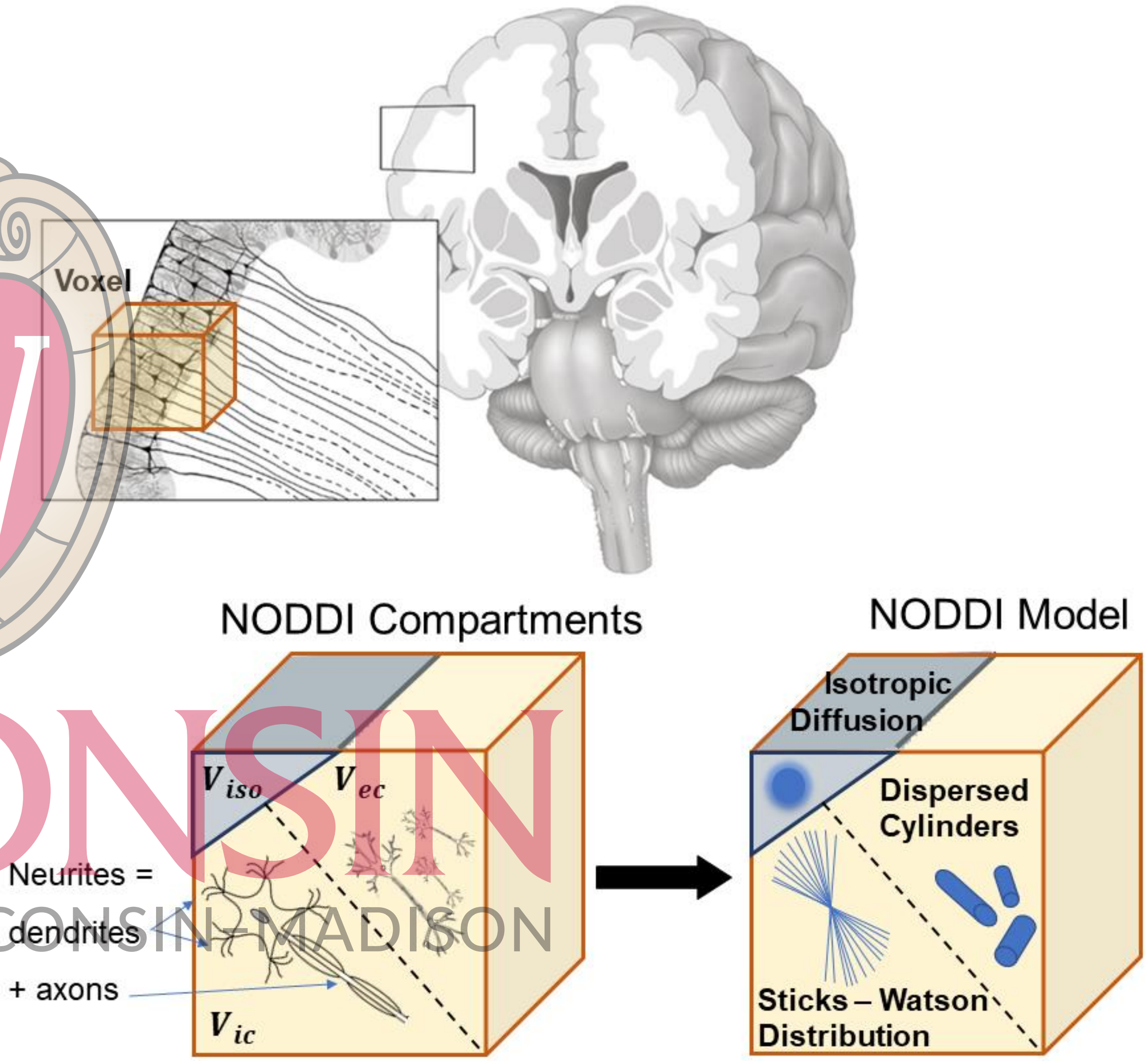


[1]Rivera-Rivera LA, et al (2021). *JCBFM* 41(2).
[2]Gu T, et al (2005). *AJNR* 26(4).
[3]Johnson KM, et al (2008). *MRM* 60(6).

NODDI – Neurite Orientation Dispersion and Density Imaging

- Fit DTI signal into 3 compartment model

1. Intracellular space (V_{ic})
   - Highly-restricted diffusion
   - Axons and dendrites
   - Modelled as dispersed sticks
2. Extracellular space (V_{ec})
   - Hindered diffusion
   - Space between neurites
   - Modelled as dispersed cylinders
3. Cerebrospinal fluid (V_{iso})
   - Free diffusion
   - Modelled as isotropic Gaussian

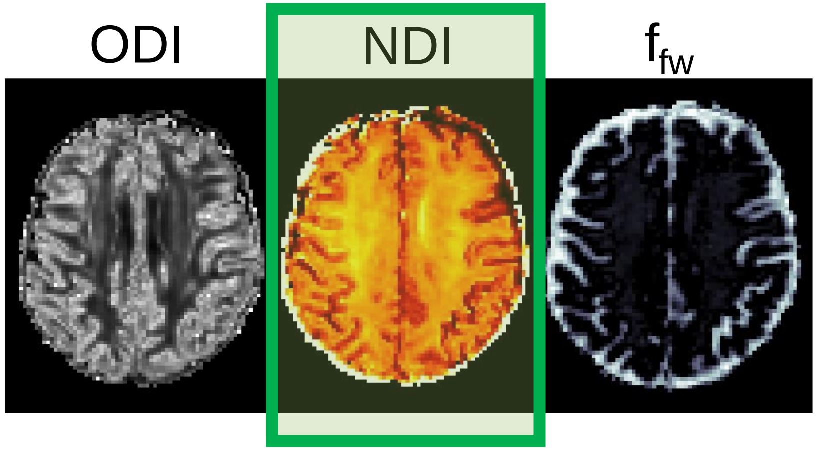


Methods

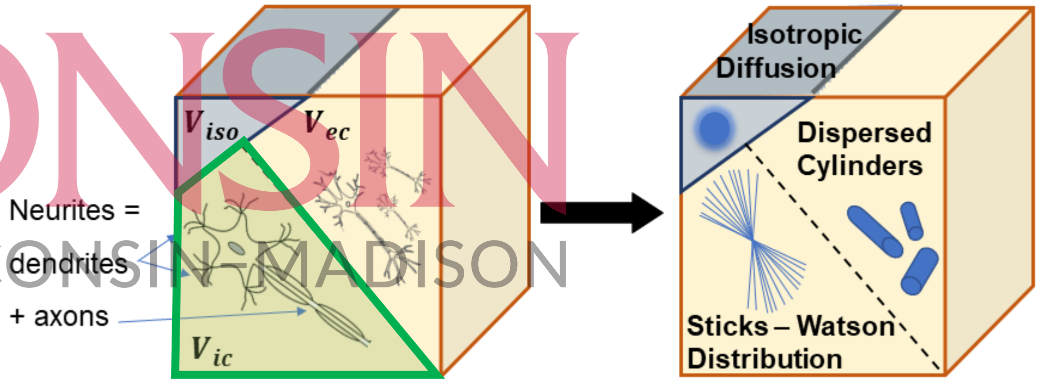
NODDI – Neurite Orientation Dispersion and Density Imaging[1]

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

NODDI



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



[1]Zhang H, et al (2012). *Neuroimage* 61(4).

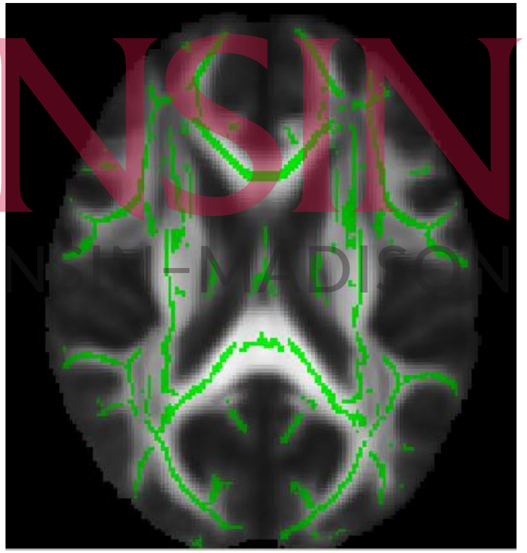
Methods

Diffusion Tensor Data

- FSL/MRtrix
  - Denoise: *dwidenoise*
  - Remove Gibb’s Artifact: *mrdegibbs*
  - Brain extraction: *BET*
  - Eddy current correction: *eddy*
  - Subject motion analysis: *eddy_quad/eddy_squad*
  - DTI Parameter Estimation: *dtifit*

- NODDI Matlab Toolbox
  - NDI maps

- FSL
  - Tract-based Spatial Statistics: *tbss*
  - Statistical Analysis: *Glm (randomise)*

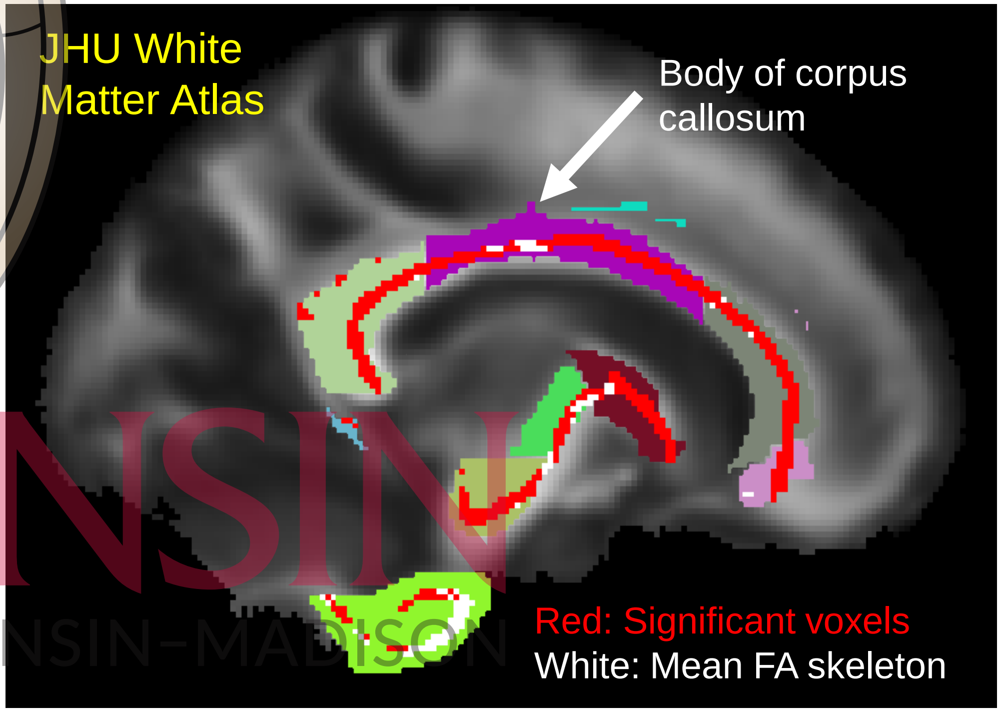


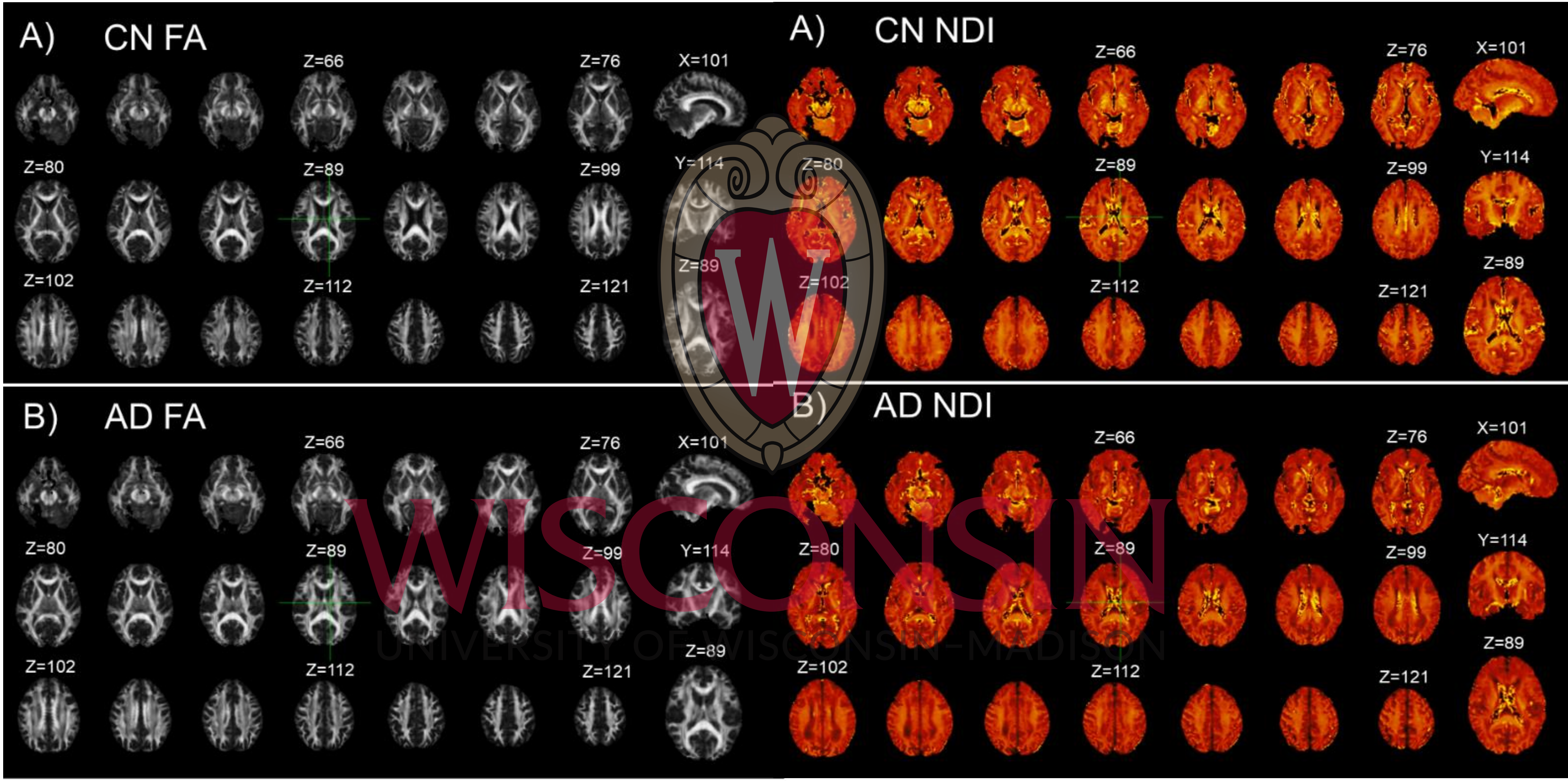
Methods

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




A) CN FA
Z=66
Z=76
X=101
Z=80
Z=89
Z=99
Y=114
Z=102
Z=112
Z=121
Z=89
B) AD FA
Z=66
Z=76
X=101
Z=80
Z=89
Z=99
Y=114
Z=102
Z=112
Z=121
Z=89
A) CN NDI
Z=66
Z=76
X=101
Z=80
Z=89
Z=99
Y=114
Z=102
Z=112
Z=121
Z=89
B) AD NDI
Z=66
Z=76
X=101
Z=80
Z=89
Z=99
Y=114
Z=102
Z=112
Z=121
Z=89

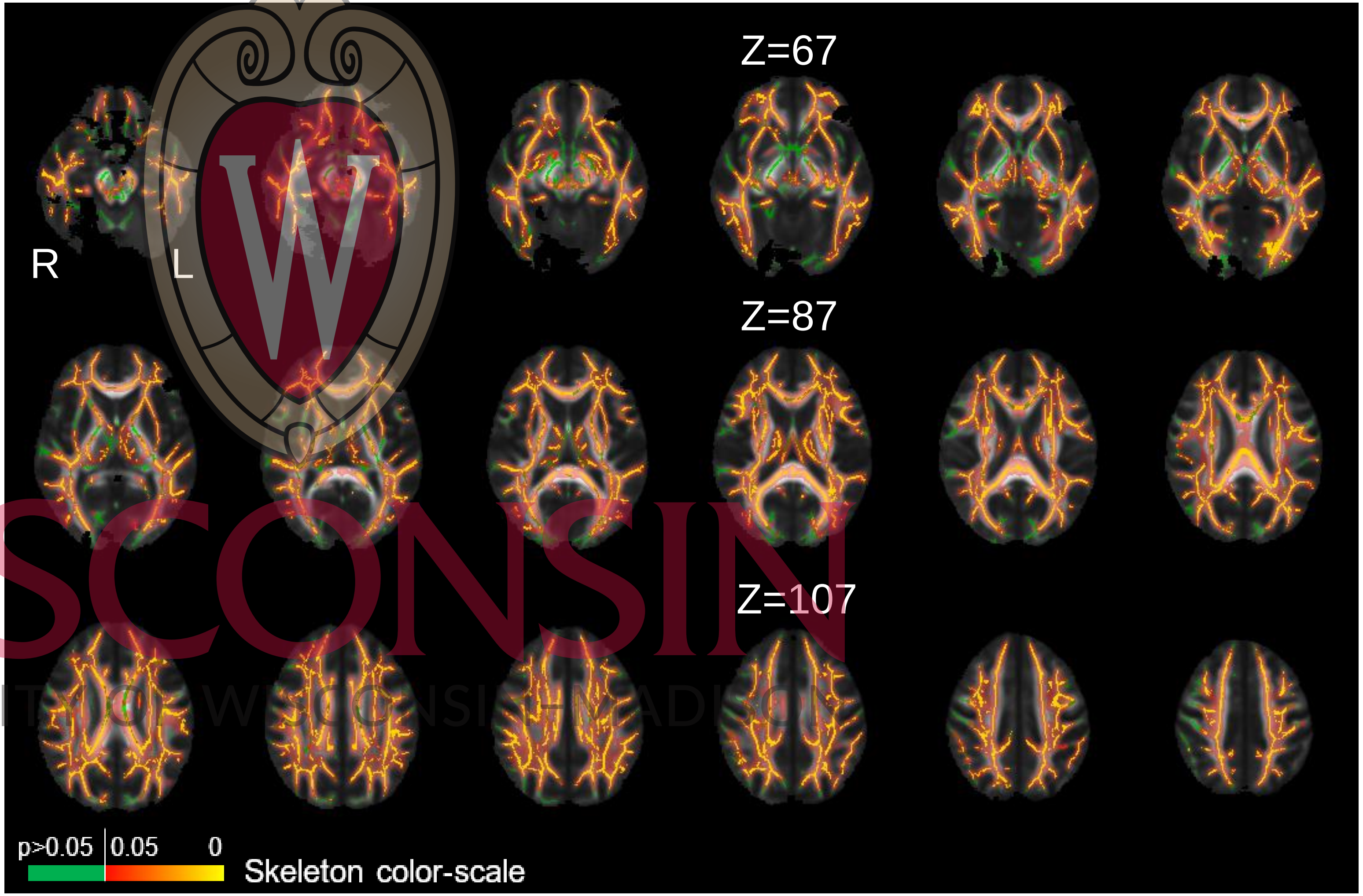
Results

TBSS Hypothesis Tests

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

Similar results observed by Slattery et al[1] and Fu et al[2]

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*
Splenium of Corpus Callosum (5)	0.635 ± 0.031	0.597 ± 0.032	**5.2e-05****
Anterior corona radiata R (23)	0.473 ± 0.056	0.438 ± 0.054	0.0138*
Anterior corona radiata L (24)	0.474 ± 0.053	0.429 ± 0.054	**0.0019****
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*
Posterior thalamic radiation R (29)	0.515 ± 0.041	0.474 ± 0.041	**3.9e-04****
Posterior thalamic radiation L (30)	0.487 ± 0.048	0.438 ± 0.047	**3.3e-04****
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*
External capsule L (34)	0.509 ± 0.026	0.483 ± 0.028	**2.9e-04****
Cingulate gyrus R (35)	0.536 ± 0.023	0.510 ± 0.022	**7.8e-05****
Cingulate gyrus L (36)	0.542 ± 0.024	0.510 ± 0.023	**8.4e-06****
Cingulum (hippocampus) R (37)	0.496 ± 0.029	0.463 ± 0.036	**2.8e-04****
Cingulum (hippocampus) L (38)	0.494 ± 0.022	0.469 ± 0.025	**3.5e-04****
Superior longitudinal fasciculus R (41)	0.592 ± 0.034	0.557 ± 0.056	0.0069*
Superior longitudinal fasciculus L (42)	0.594 ± 0.038	0.552 ± 0.053	**7.8e-04****
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*
Uncinate fasciculus R (45)	0.485 ± 0.026	0.454 ± 0.032	**2.9e-05****
Uncinate fasciculus L (46)	0.484 ± 0.027	0.451 ± 0.022	**1.6e-05****

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

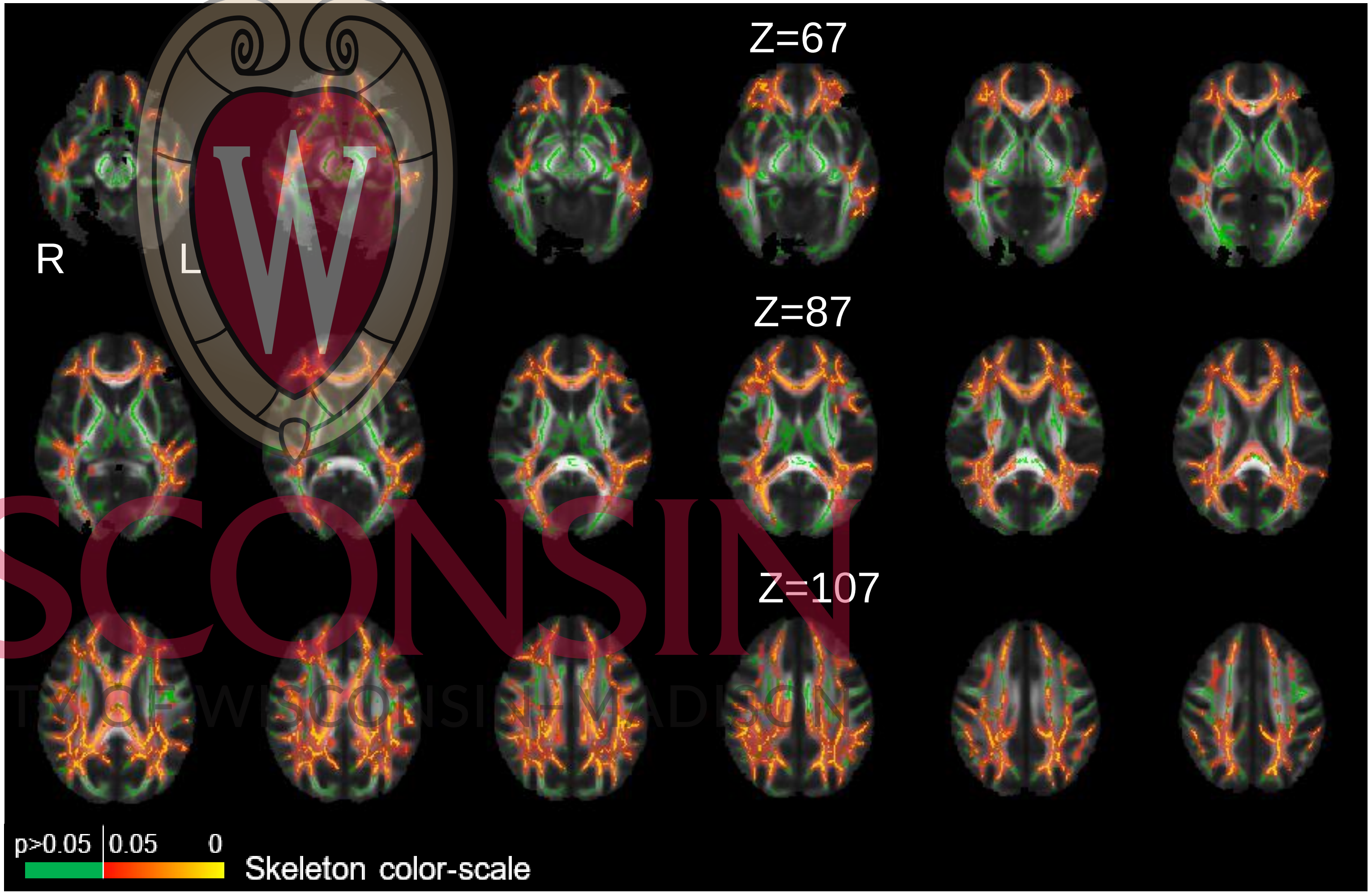
No significant findings!

Results

TBSS Hypothesis Tests

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

CN $\beta_{tCBF} > 0$



Results

ROI Analysis

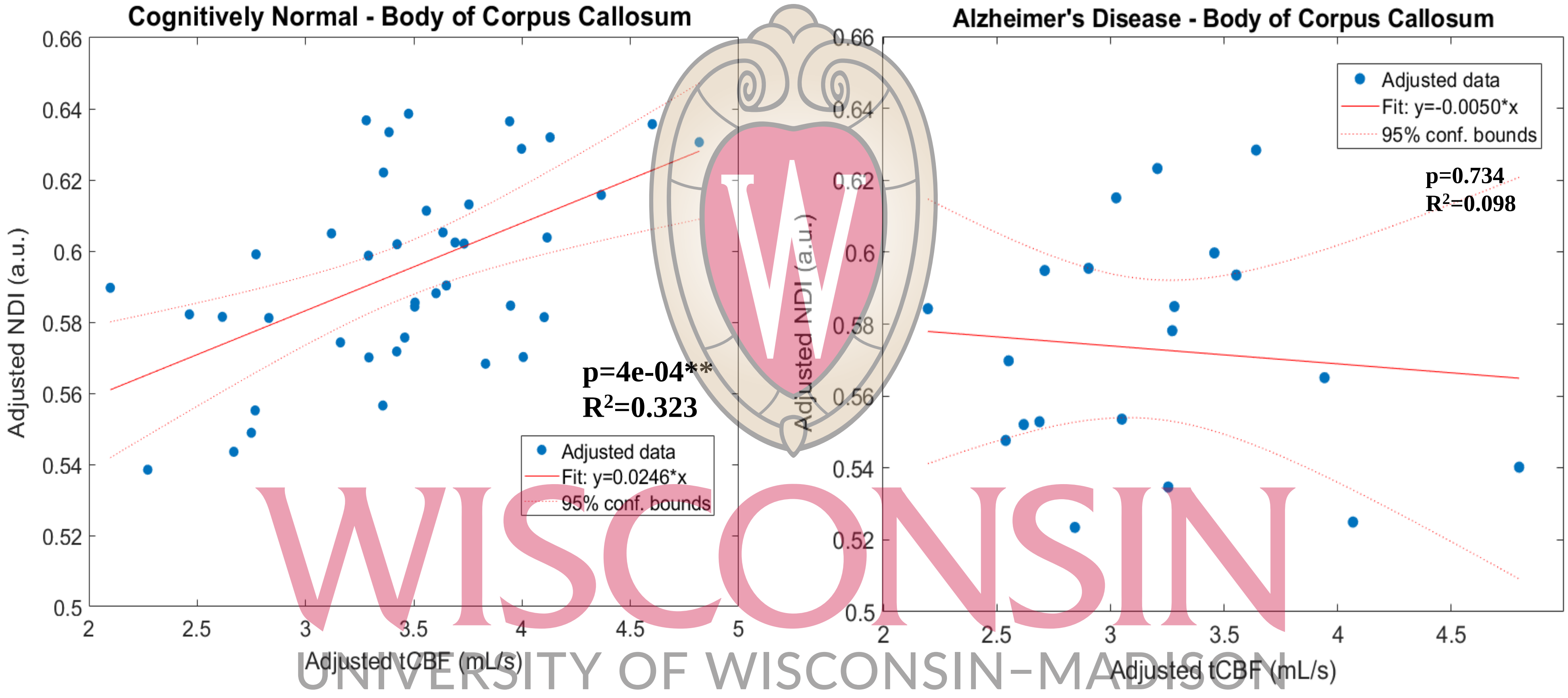
CN $\beta_{tCBF} > 0$

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

	$CN\ \beta_{tCBF} > 0$		
White Matter Regions Identified from TBSS (ICBM-DTI-81 Atlas Label #)	β_{tCBF}	R^2	p-value
Genu of corpus callosum (3)	0.025	0.129	0.019*
Body of corpus callosum (4)	0.025	0.247	**4e-04****
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
Superior long. fasciculus R (41)	0.028	0.349	**0.001****
Superior long. fasciculus L (42)	0.023	0.221	0.012*

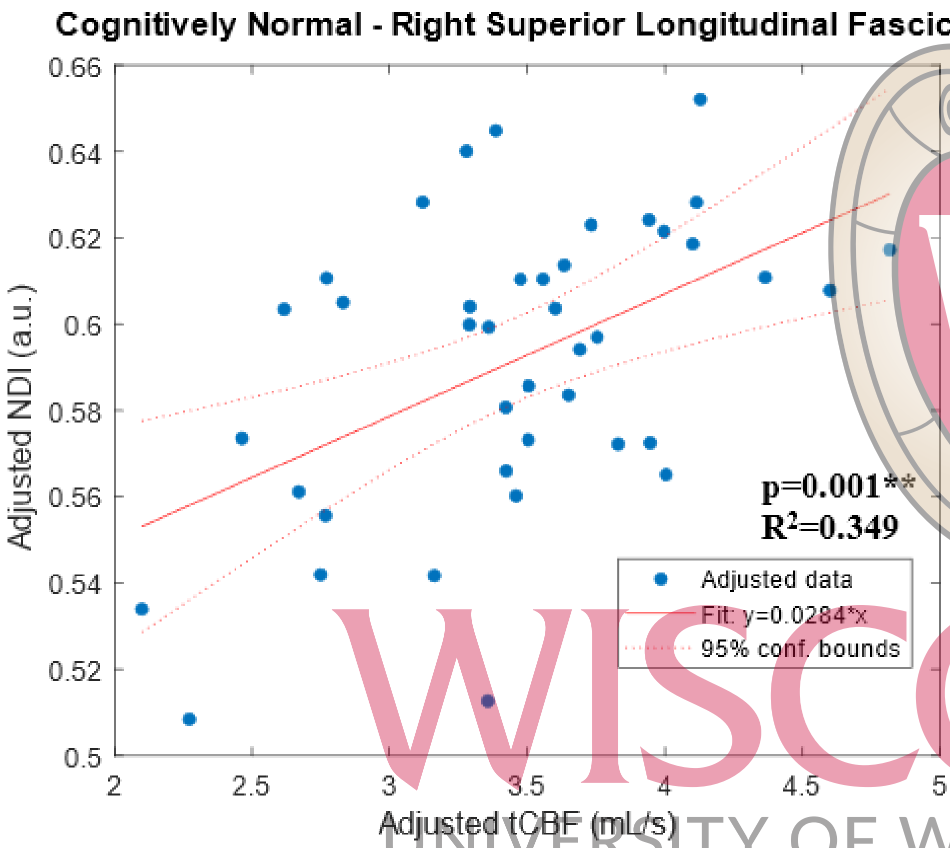
Abbreviations: tCBF = total cerebral blood flow; NDI=neurite density index; CN=cognitively normal; AD=Alzheimer's disease; TBSS=tract-based spatial statistics
β: regression coefficient; R^2: adjusted coefficient of determination
*p-values <0.05; **p-value<0.004 (Bonferroni correction for 13 ROIs).

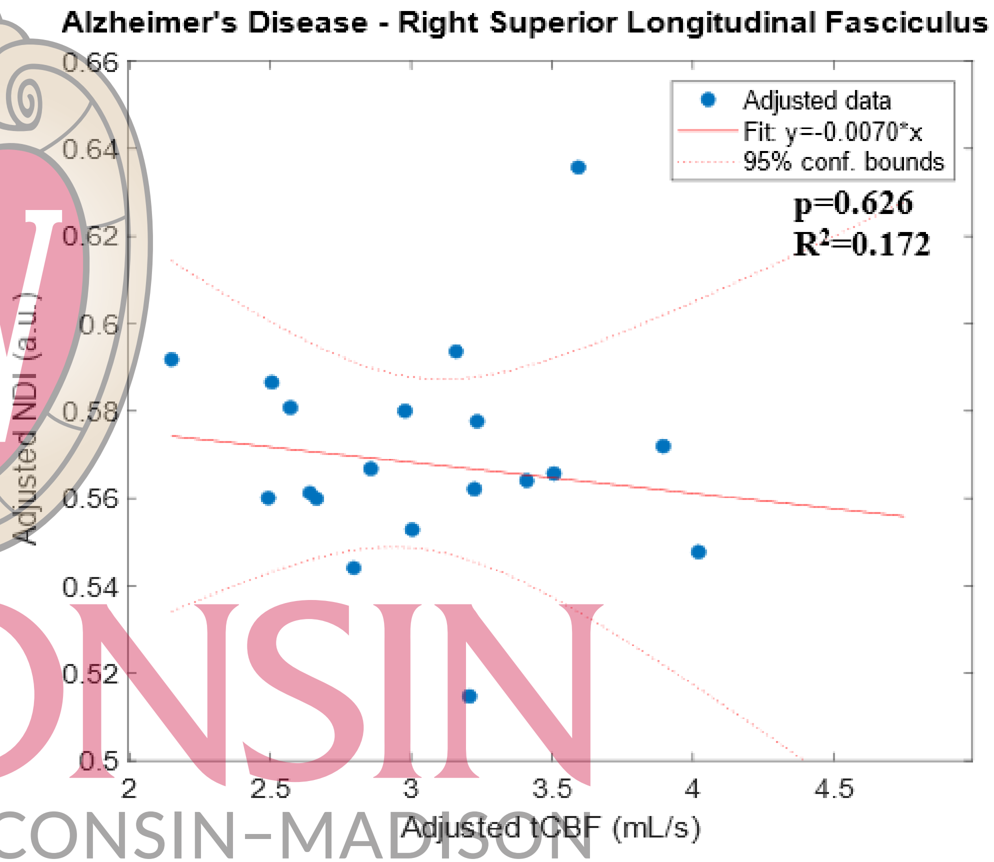
Results

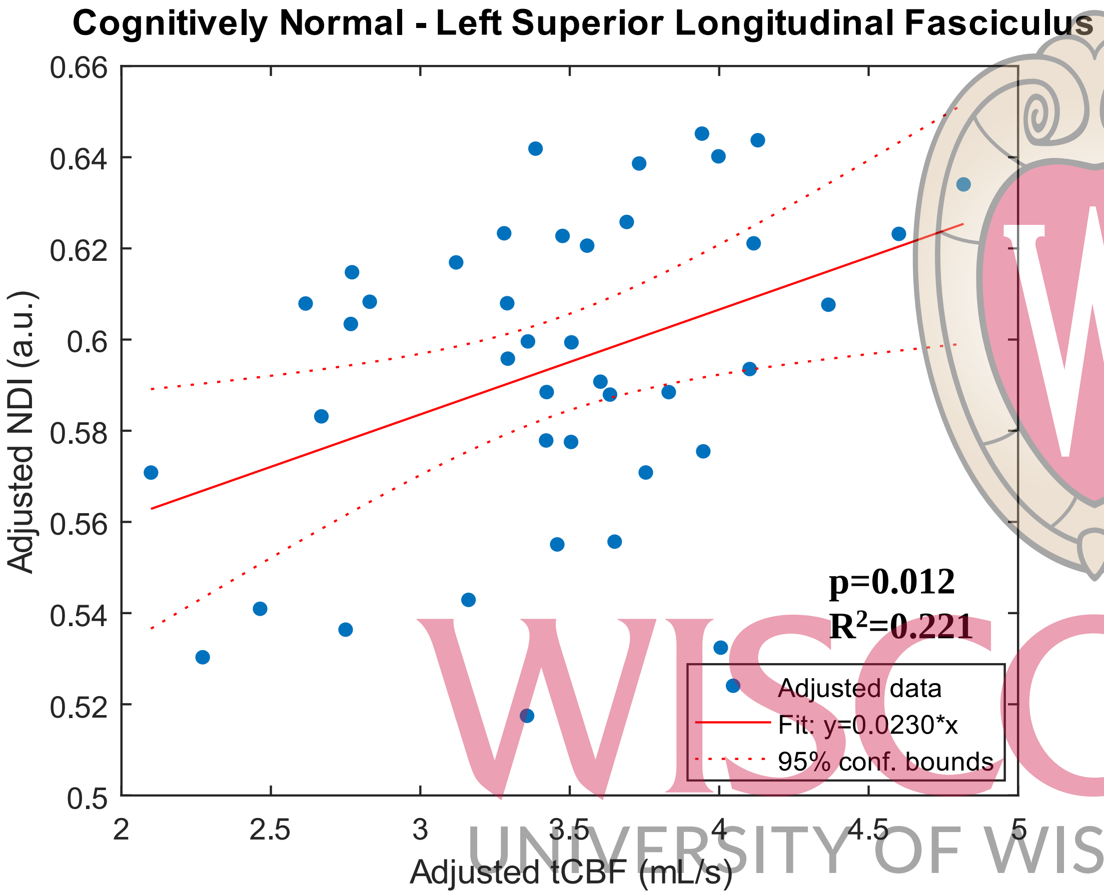


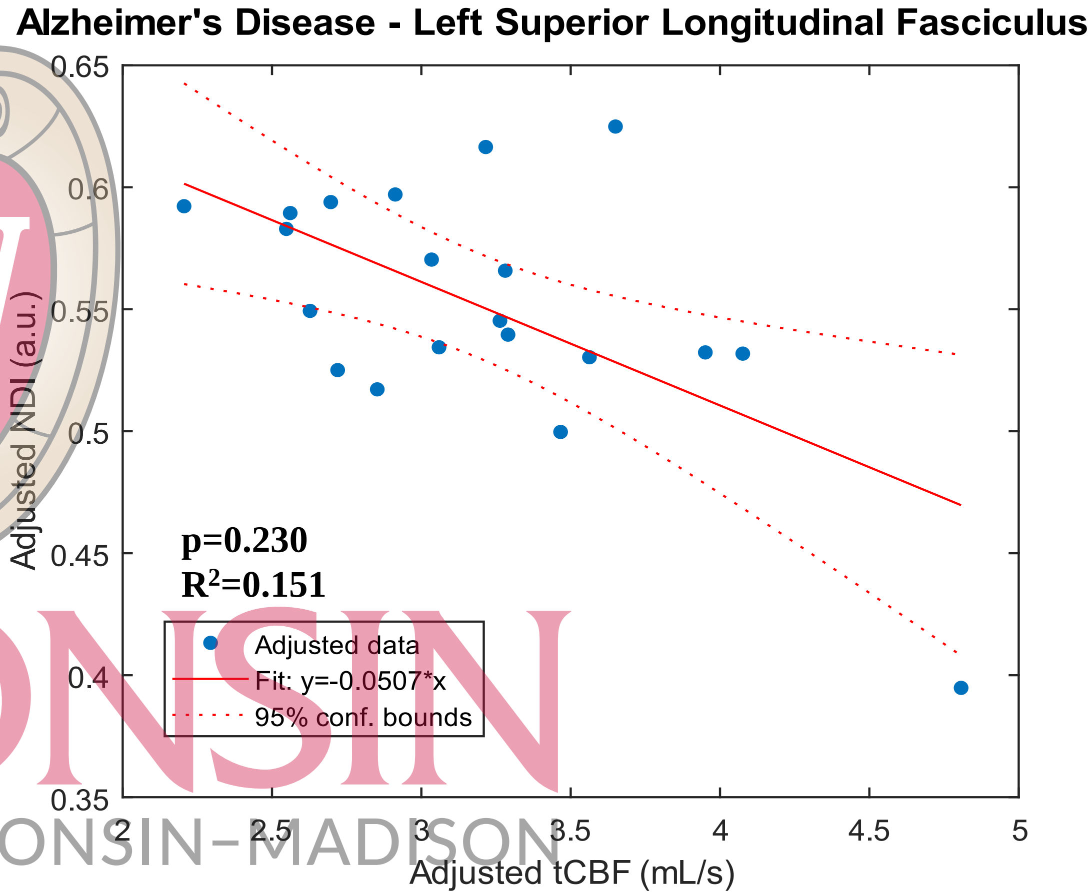
Cognitively Normal - Body of Corpus Callosum
Adjusted NDI (a.u.)
Adjusted tCBF (mL/s)
p=4e-04**
R²=0.323
Adjusted data
Fit: y=0.0246*x
95% conf. bounds
Alzheimer's Disease - Body of Corpus Callosum
Adjusted NDI (a.u.)
Adjusted tCBF (mL/s)
Adjusted data
Fit: y=-0.0050*x
95% conf. bounds
p=0.734
R²=0.098
WISCONSIN
UNIVERSITY OF WISCONSIN–MADISON

Results


Cognitively Normal - Right Superior Longitudinal Fasciculus
Adjusted NDI (a.u.)
Adjusted tCBF (mL/s)
p=0.001**
R^2=0.349
Adjusted data
Fit: y=0.0284*x
95% conf. bounds


Alzheimer's Disease - Right Superior Longitudinal Fasciculus
Adjusted NDI (a.u.)
Adjusted tCBF (mL/s)
Adjusted data
Fit: y=-0.0070*x
95% conf. bounds
p=0.626
R^2=0.172


Cognitively Normal - Left Superior Longitudinal Fasciculus
Adjusted NDI (a.u.)
Adjusted tCBF (mL/s)
p=0.012
R²=0.221
Adjusted data
Fit: y=0.0230*x
95% conf. bounds


Alzheimer's Disease - Left Superior Longitudinal Fasciculus
Adjusted NDI (a.u.)
Adjusted tCBF (mL/s)
p=0.230
R²=0.151
Adjusted data
Fit: y=-0.0507*x
95% conf. bounds

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[1,2]
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 <u>only in control group</u>

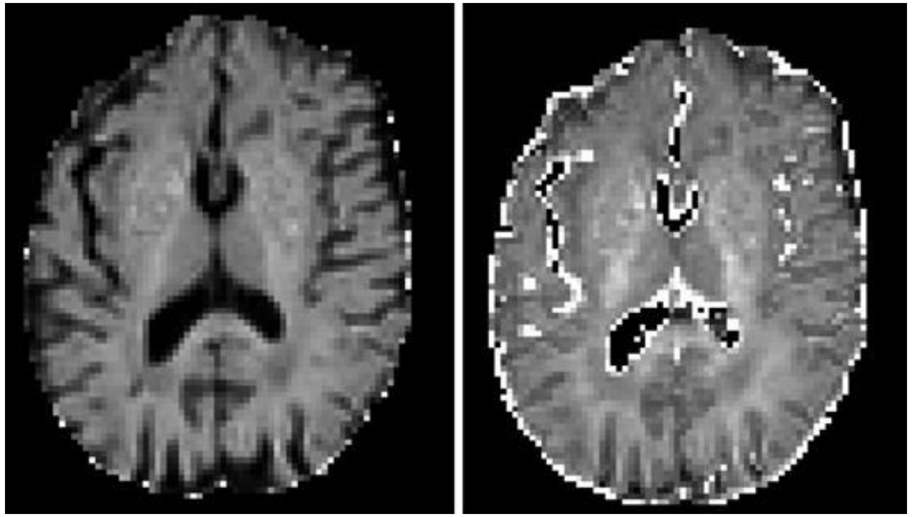
Recent Work

Categorize patients using PET

- Total of 113 subjects from ADRC and WRAP
  - 60 subjects reconstructed so far
    - Using Dmipy for NODDI reconstruction
      - MUCH FASTER!
    - Scanned with 69-volume multi-shell sequence

  - Waiting on 53 remaining subjects
    - Scanned with 91-93 paired HYDI sequence
  - Consider data harmonization techniques

Dmipy | UCL Toolbox



~1 hour | 8 hours

Acknowledgements

- Wieben Lab
- Eisenmenger Lab
- ADRC Vascular Team
- Waisman Brain Imaging Team
- GE Healthcare

Funding: F31AG071183; KL2TR002374; UL1TR002373; AARFD-20-678095; P50AG033514; RO1AG021155