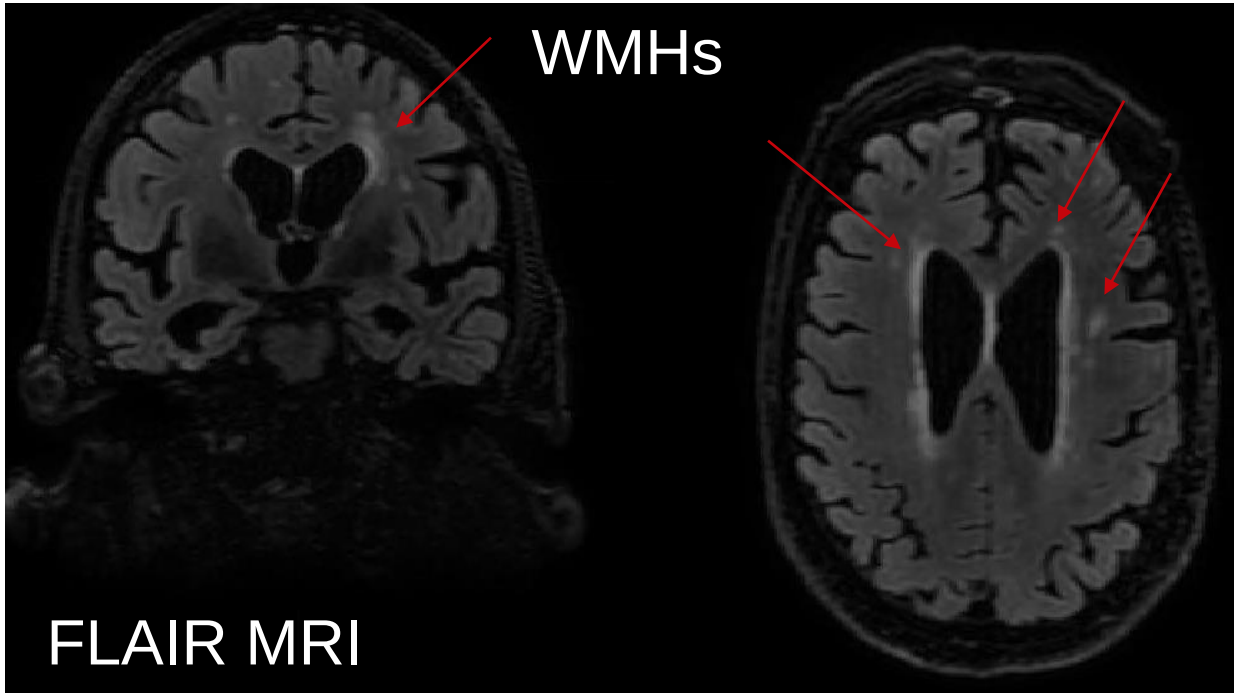
MP 651 – Final Project

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

Grant Roberts

- Alzheimer's disease (AD) is typically thought of as a grey matter (GM) disease
  - Neuronal loss due to amyloid-beta plaque and neurofibrillary tangles
  - Cortical atrophy
- However, white matter (WM) alterations can also occur in AD
  - May precede GM degeneration
  - White matter hyperintensities
- WM alterations are likely caused by cerebrovascular disease (CVD)
  - Disrupts brain microcirculation
  - Impaired clearance of waste products
  - Exact mechanism is not known



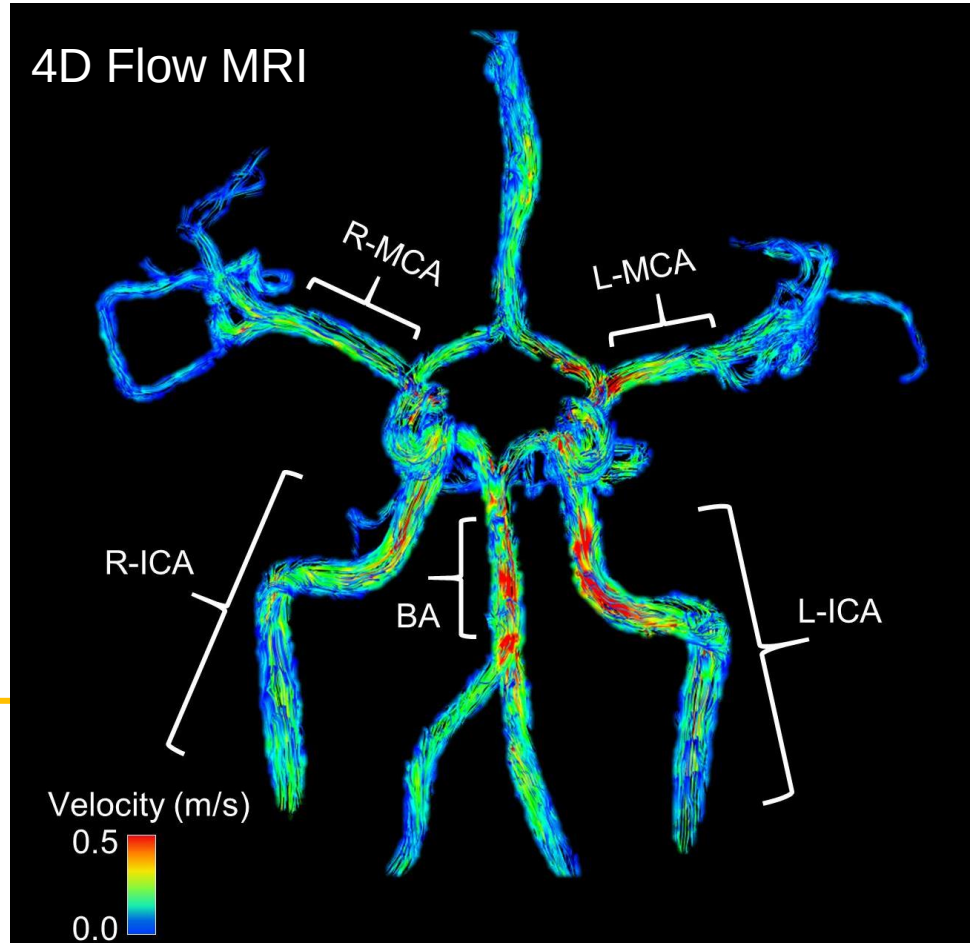
- Studies have also shown CVD exists in AD
- Studies have shown WM microstructure alterations in AD
- No studies have assessed CVD and WM microstructure simultaneously

- Goal:
  - Assess CVD using 4D Flow MRI
  - Assess WM microstructure using DTI NODDI
    - 20 AD and 41 cognitively normal (CN) subjects
  - Perform TBSS and ROI analysis
    - Assess correlations between CVD and WM axonal density.

4D Flow MRI

- Phase contrast MRI
  - Uses phase shift to encode velocity
  - Used to measure blood velocities in vivo
- Every voxel we have a 3D velocity vector
- Quantification of blood flow in any vessel

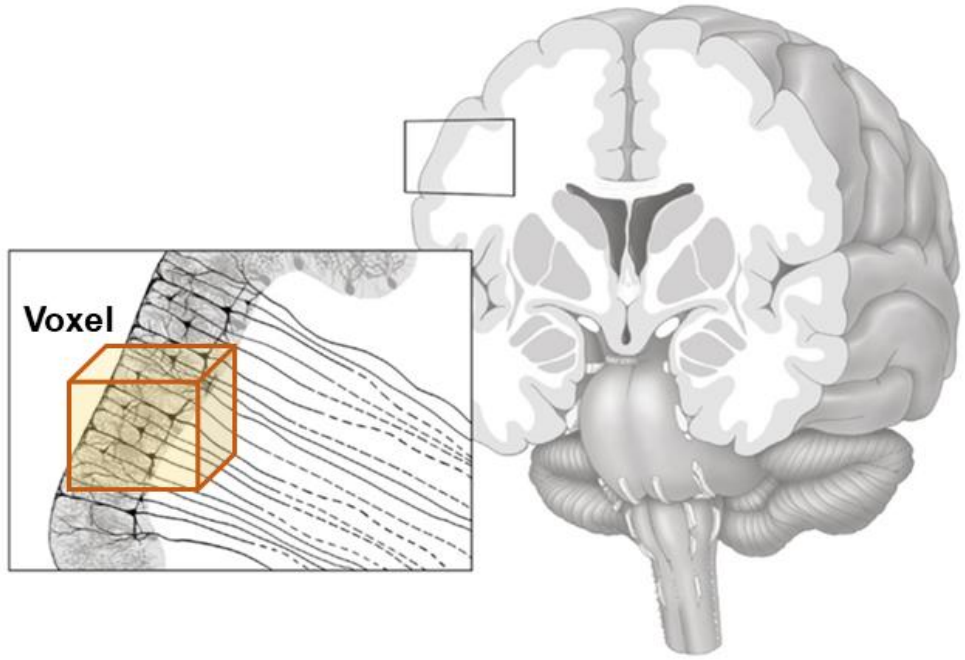
- Obtain measures of global CVD
  - tCBF = Total cerebral blood flow
  - PI = Pulsatility index in ICA
    - Metric for vascular resistance
  - PWV = Pulse wave velocity in ICA
    - Measure of vessel stiffness

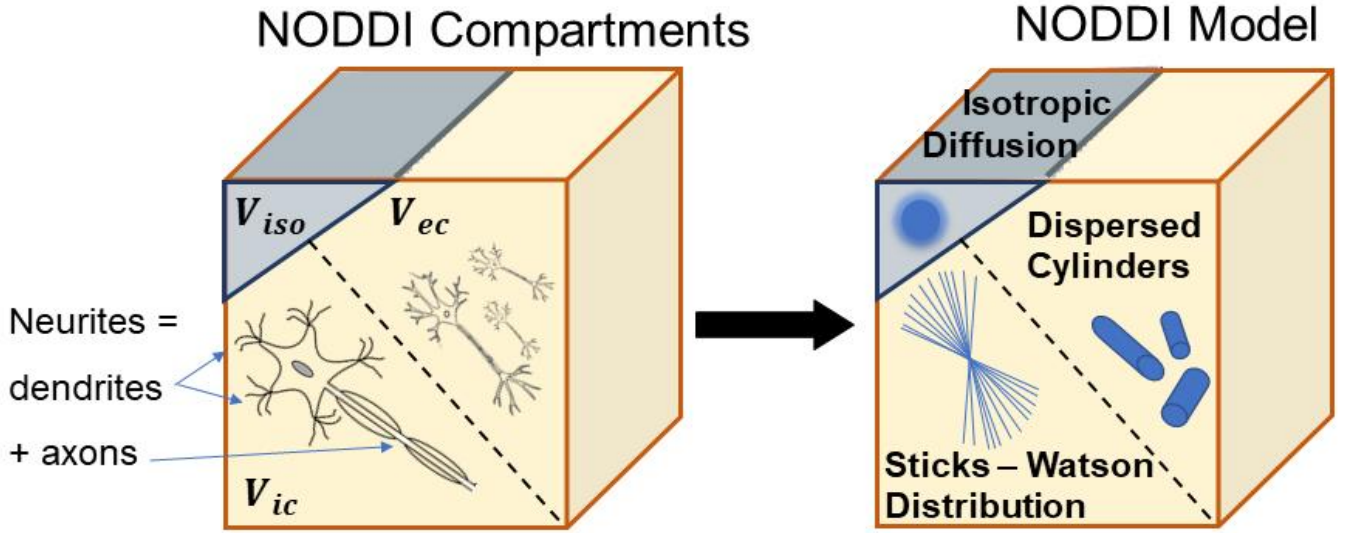


NODDI – Neurite Orientation Dispersion and Density Imaging

- Uses DTI data to fit 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





Top image: Bonilha L, et al (2015). Front. Psychiatry 6:35

NODDI – Neurite Orientation Dispersion and Density Imaging

- Produces 3 common parameters
  - ODI – Orientation Dispersion Index
  - NDI – Neurite Density Index
  - V_{iso} – CSF Volume Fraction

- Obtain measures of WM axonal density
  - NDI (for this study)

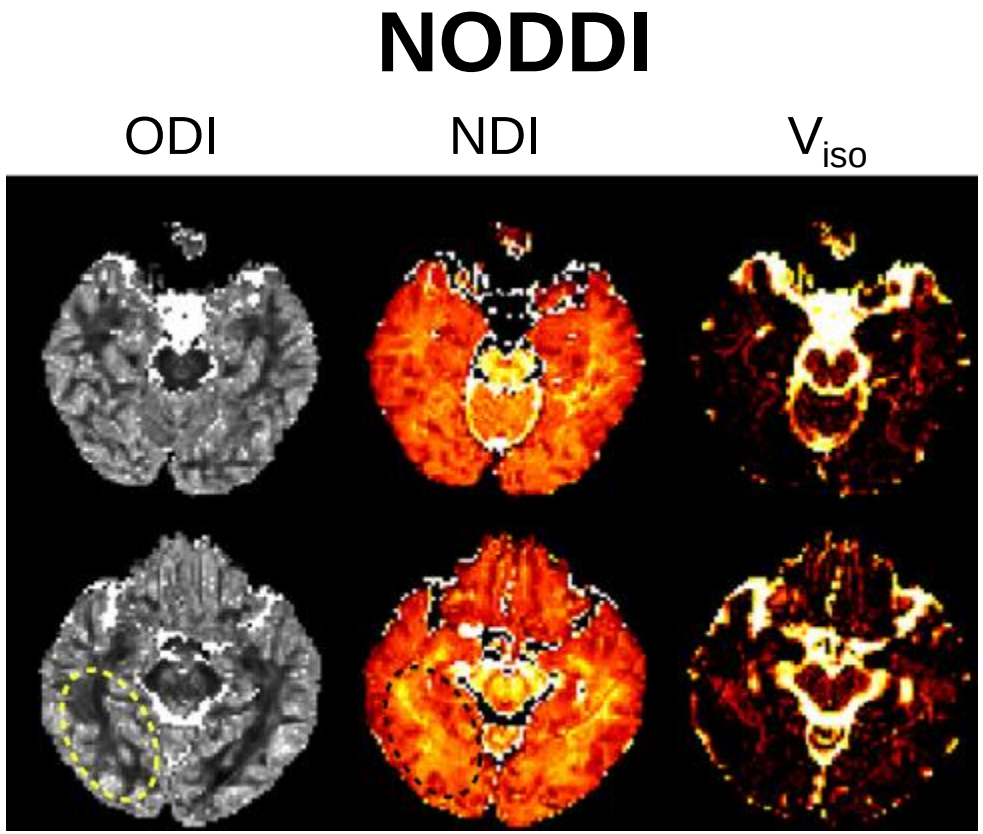
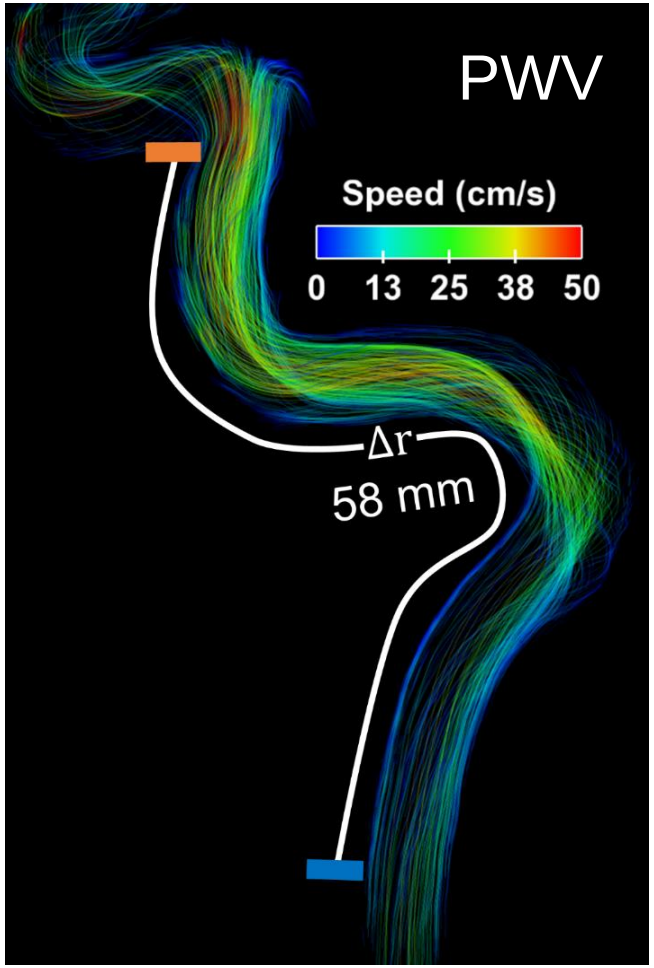
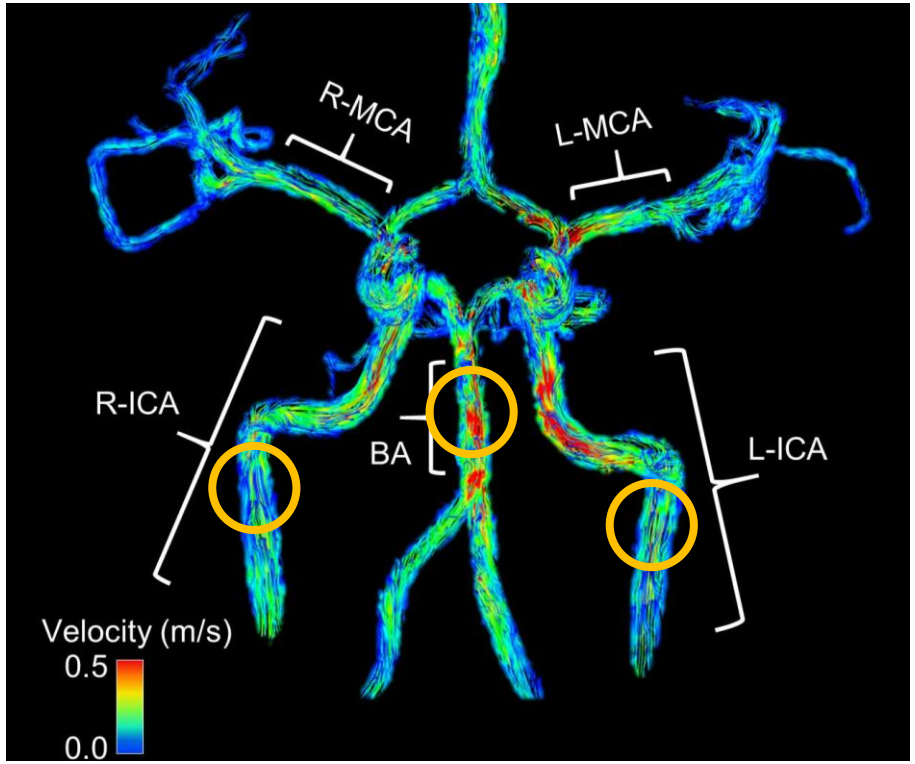


Image: Zhang H, et al (2012). Neuroimage 61(4).

4D Flow Data

- PWV velocity calculated using custom analysis tool
  - Average PWVs between LICA and RICA
- Total cerebral blood flow
  - Sum of flows in LICA, RICA, and Basilar artery
- Pulsatility index
  - Average PIs between LICA and RICA



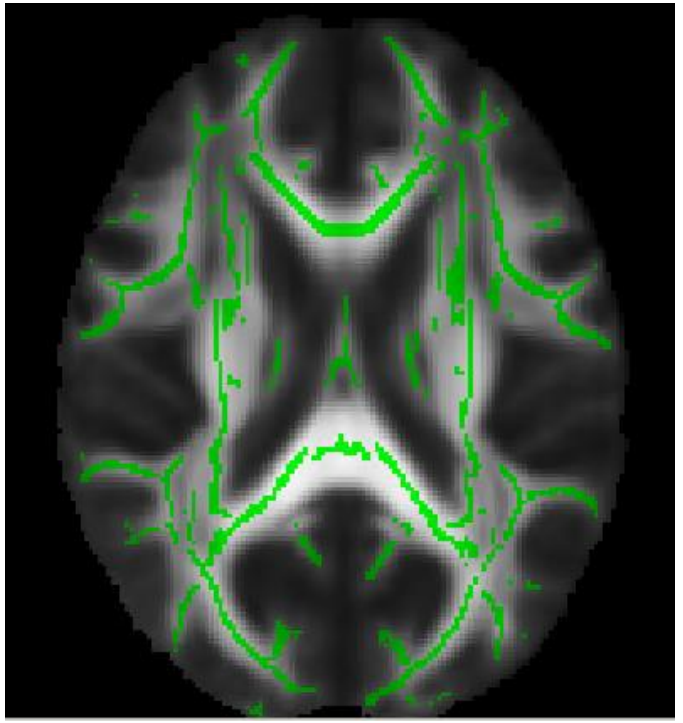


Diffusion Tensor Data

- FSL/Mrtrix
  - *dwidenoise*
  - *mrdegibbs*
  - *BET*
  - *eddy*
  - *eddy_quad*
  - *dtifit*

- MATLAB
  - NODDI Matlab Toolbox (only keep NDI maps)

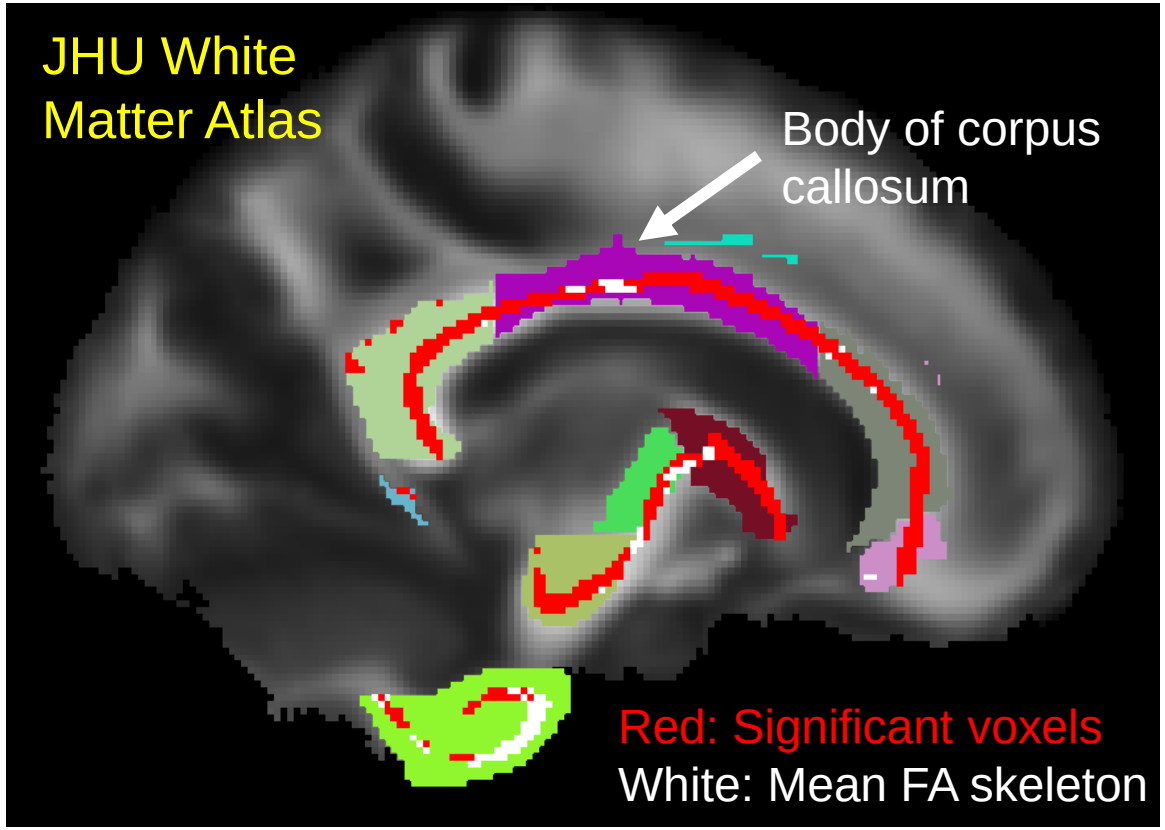
- FSL
  - *tbss*
  - *Glm*

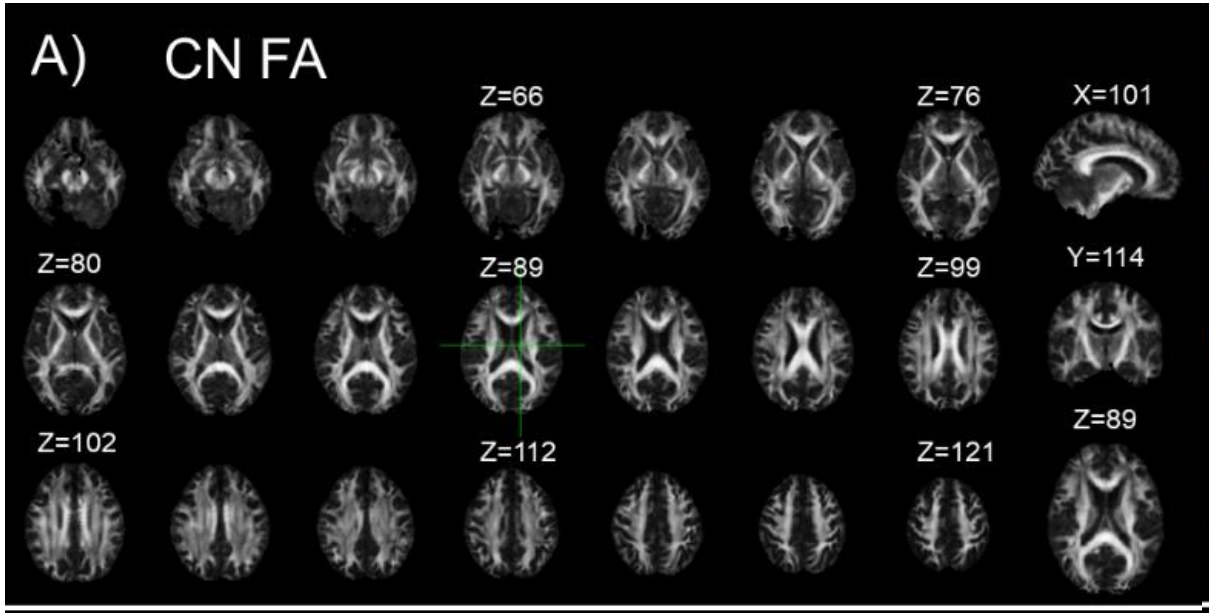


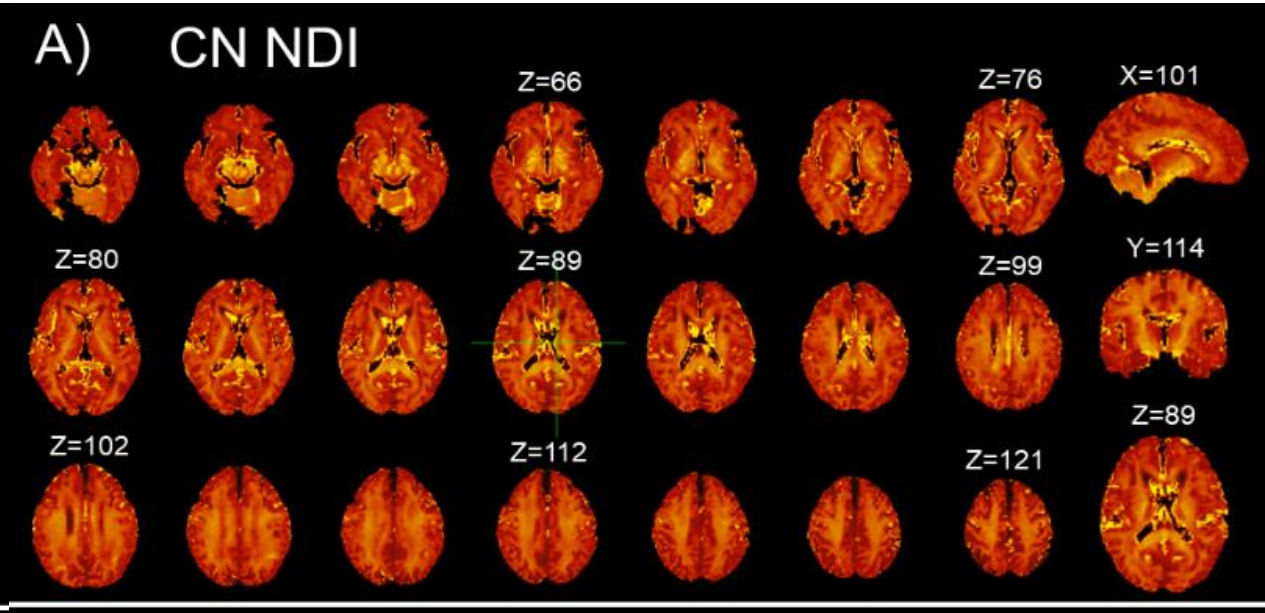
TBSS Hypothesis Tests

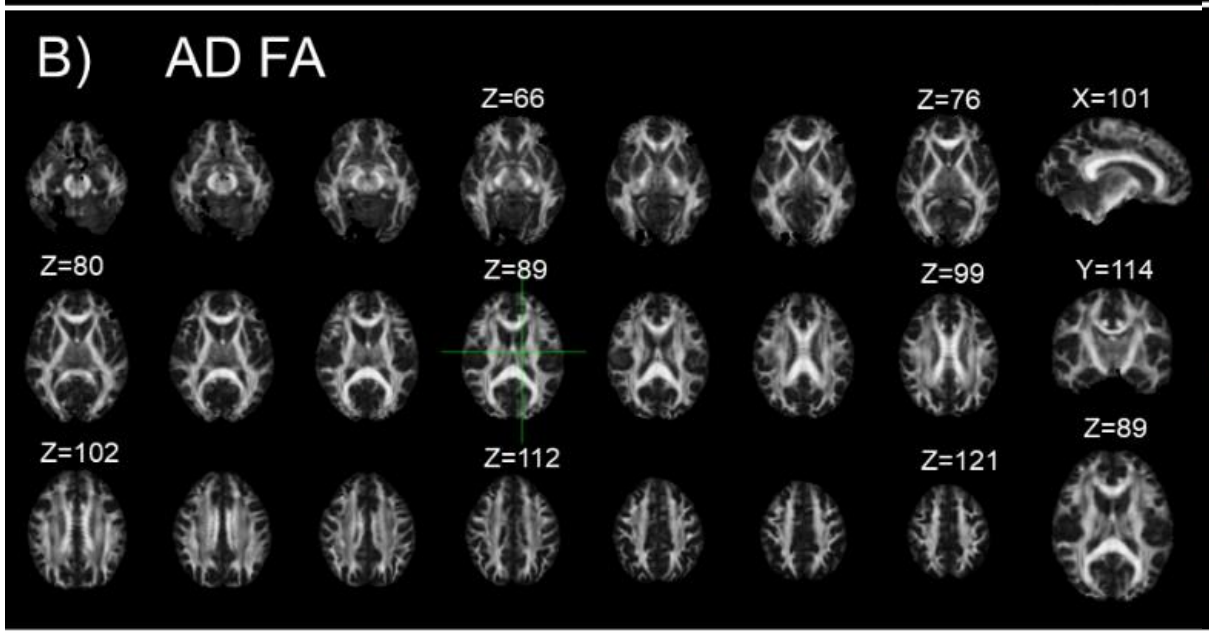
- Are there differences in NDI Between AD and CN subjects?
- Are there correlations between PWV/PI/tCBF and NDI for AD and CN subjects?

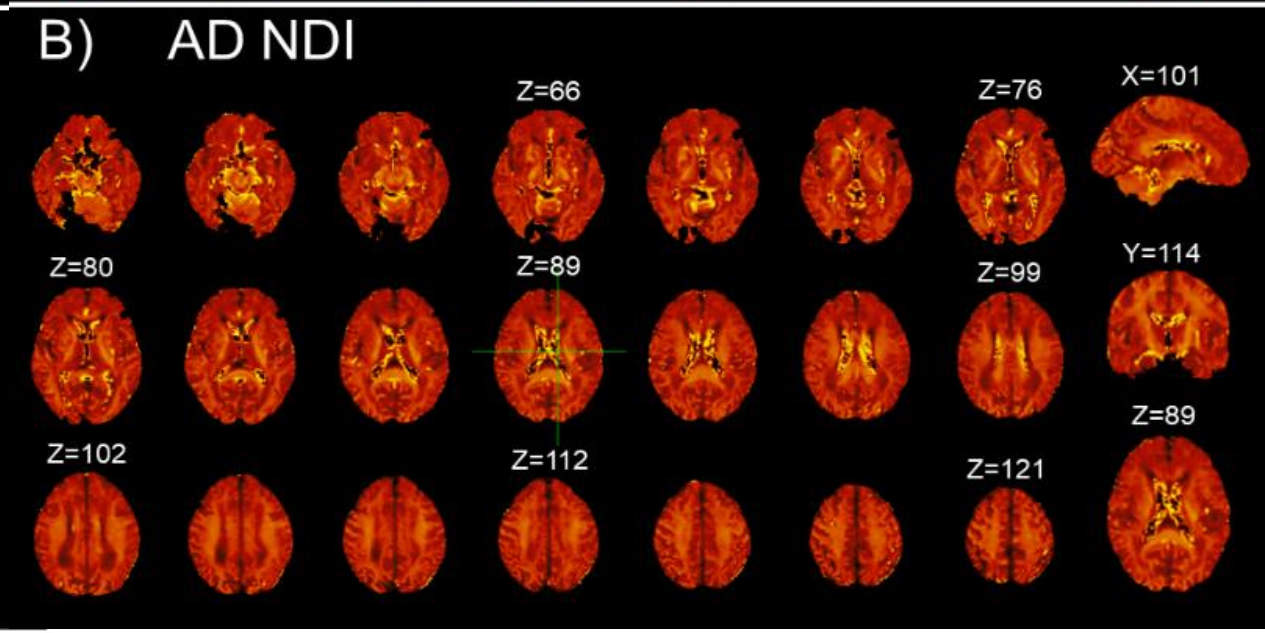
- After performing TBSS, significant regions were identified using the JHU white matter atlas.
- Mean NDI values were extracted from these tracts of interest and statistically compared.




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


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 FA
Z=66
Z=76
X=101
Z=80
Z=89
Z=99
Y=114
Z=102
Z=112
Z=121
Z=89

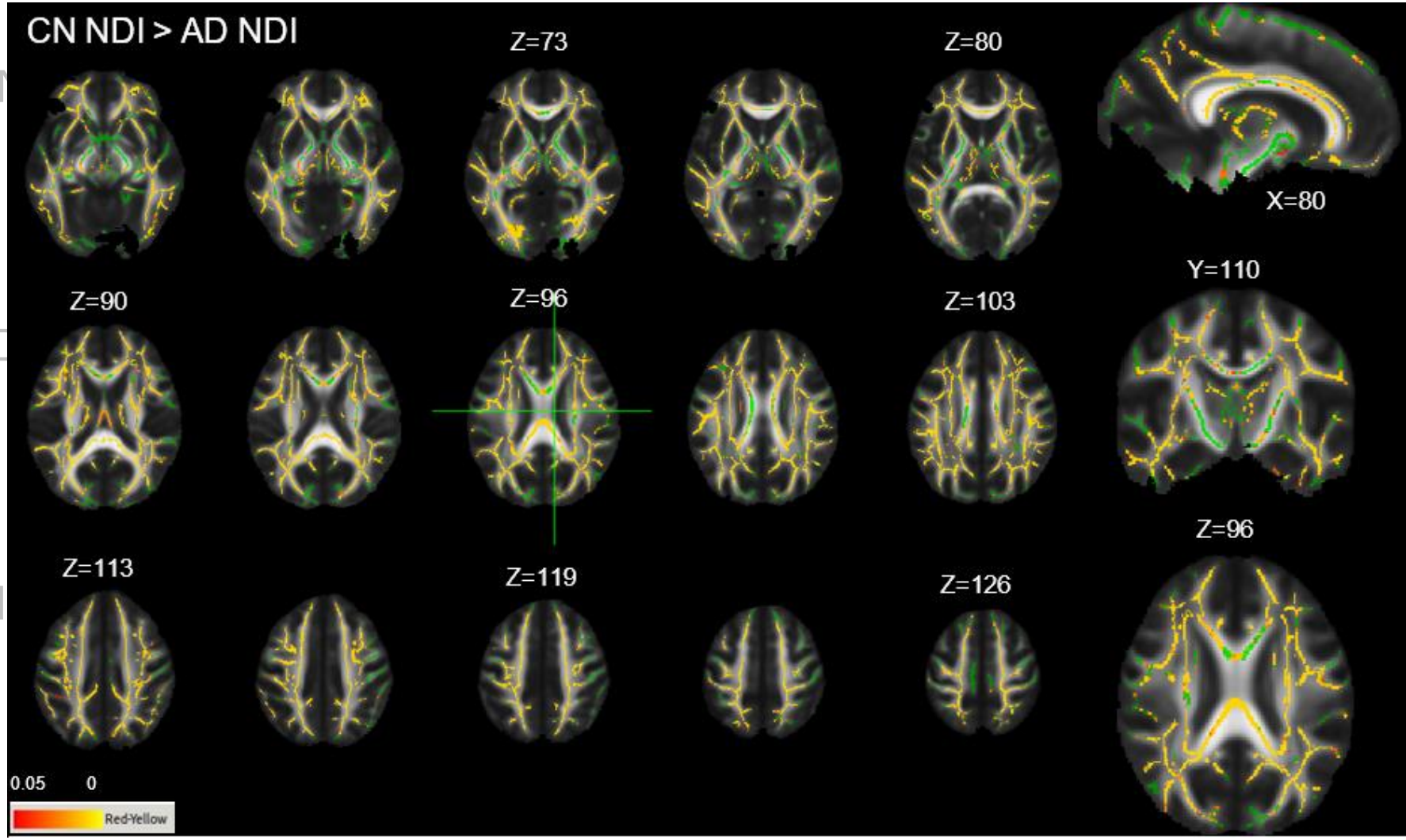

B) AD NDI
Z=66
Z=76
X=101
Z=80
Z=89
Z=99
Y=114
Z=102
Z=112
Z=121
Z=89

TBSS Hypothesis Tests

- Compare NDI Between AD and CN
  1. CN NDI > AD NDI?
  2. AD NDI > CN NDI?
- Correlation - PWV and NDI
  1. CN $\beta_{PI} > 0$?
  2. CN $\beta_{PI} < 0$?
  3. AD $\beta_{PI} > 0$?
  4. AD $\beta_{PI} < 0$?
- Correlations - PI and NDI
  1. CN $\beta_{PI} > 0$?
  2. CN $\beta_{PI} < 0$?
  3. AD $\beta_{PI} > 0$?
  4. AD $\beta_{PI} < 0$?
- Correlations - tCBF and NDI
  1. CN $\beta_{PI} > 0$?
  2. CN $\beta_{PI} < 0$?
  3. AD $\beta_{PI} > 0$?
  4. AD $\beta_{PI} < 0$?

TBSS Hypothesis Tests

- Compare NDI Between AD and CN
  1. CN NDI > AD NDI?
  2. ~~AD NDI > CN NDI?~~
- Correlation - PWV and N
  1. CN $\beta_{PWV} > 0$?
  2. CN $\beta_{PWV} < 0$?
  3. AD $\beta_{PWV} > 0$?
  4. AD $\beta_{PWV} < 0$?
- Correlations - PI and NDI
  1. CN $\beta_{PI} > 0$?
  2. CN $\beta_{PI} < 0$?
  3. AD $\beta_{PI} > 0$?
  4. AD $\beta_{PI} < 0$?
- Correlations - tCBF and
  1. CN $\beta_{tCBF} > 0$?
  2. CN $\beta_{tCBF} < 0$?
  3. AD $\beta_{tCBF} > 0$?
  4. AD $\beta_{tCBF} < 0$?



ROI Analysis

CN NDI > AD NDI?

- WM regions identified on TBSS using JHU WM atlas
- ANCOVA
  - Adjust for age/sex
  - Adjust for multiple comparisons

	CN NDI > AD NDI?			
White Matter Regions Identified from TBSS (JHU Label #)	AD Mean NDI	CN Mean NDI	p-value	Confidence Intervals
Genu of Corpus Callosum (3)†	0.5264	0.5083	0.1329	-0.006, 0.042
Body of Corpus Callosum (4)	0.5946	0.5738	0.0137*	0.004, 0.037
Splenium of Corpus Callosum (5)	0.6358	0.5986	5.2e-05**	0.020, 0.054
Anterior corona radiata R (23)	0.4726	0.4394	0.0138*	0.007, 0.059
Anterior corona radiata L (24)	0.4735	0.4299	0.0019**	0.017, 0.070
Superior corona radiata R (25)	0.5896	0.5573	0.0113*	0.008, 0.057
Superior corona radiata L (26)	0.5825	0.5411	0.0024*	0.015, 0.068
Posterior corona radiata R (27)	0.5120	0.4748	0.0153*	0.007, 0.067
Posterior corona radiata L (28)	0.5048	0.4682	0.0104*	0.009, 0.064
Posterior thalamic radiation R (29)	0.5160	0.4762	3.9e-04**	0.019, 0.061
Posterior thalamic radiation L (30)	0.4872	0.4394	3.3e-04**	0.023, 0.073
Sagittal stratum R (31)†	0.5105	0.4942	0.0558	-0.004, 0.033
Sagittal stratum L (32)†	0.4874	0.4680	0.0541	-0.004, 0.039
External capsule R (33)	0.5061	0.4868	0.0075*	0.005, 0.033
External capsule L (34)	0.5089	0.4840	2.9e-04**	0.012, 0.038
Cingulate gyrus R (35)	0.5363	0.5114	7.8e-05**	0.013, 0.037
Cingulate gyrus L (36)	0.5420	0.5120	8.4e-06**	0.018, 0.042
Cingulum (hippocampus) R (37)	0.4970	0.4647	2.8e-04**	0.016, 0.049
Cingulum (hippocampus) L (38)	0.4945	0.4711	3.5e-04**	0.011, 0.036
Superior longitudinal fasciculus R (41)	0.5920	0.5592	0.0069*	0.009, 0.056
Superior longitudinal fasciculus L (42)	0.5944	0.5534	7.8e-04**	0.018, 0.064
Superior fronto-occipital fasciculus R (43)	0.5553	0.5187	0.0317*	0.003, 0.070
Superior fronto-occipital fasciculus L (44)	0.5397	0.4795	0.0026*	0.022, 0.099
Uncinate fasciculus R (45)	0.4838	0.4528	2.9e-05**	0.017, 0.045
Uncinate fasciculus L (46)	0.4833	0.4514	1.6e-05**	0.018, 0.046

Abbreviations: JHU=Johns Hopkins University; ROI=region of interest; Sig.=significant; R=right; L=left

ªPercentage of significant voxels (obtained from TBSS) along skeletonized tract label (see Figure 2).

†Non-significant ROI analysis. **Bold** indicates statistical significance.

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

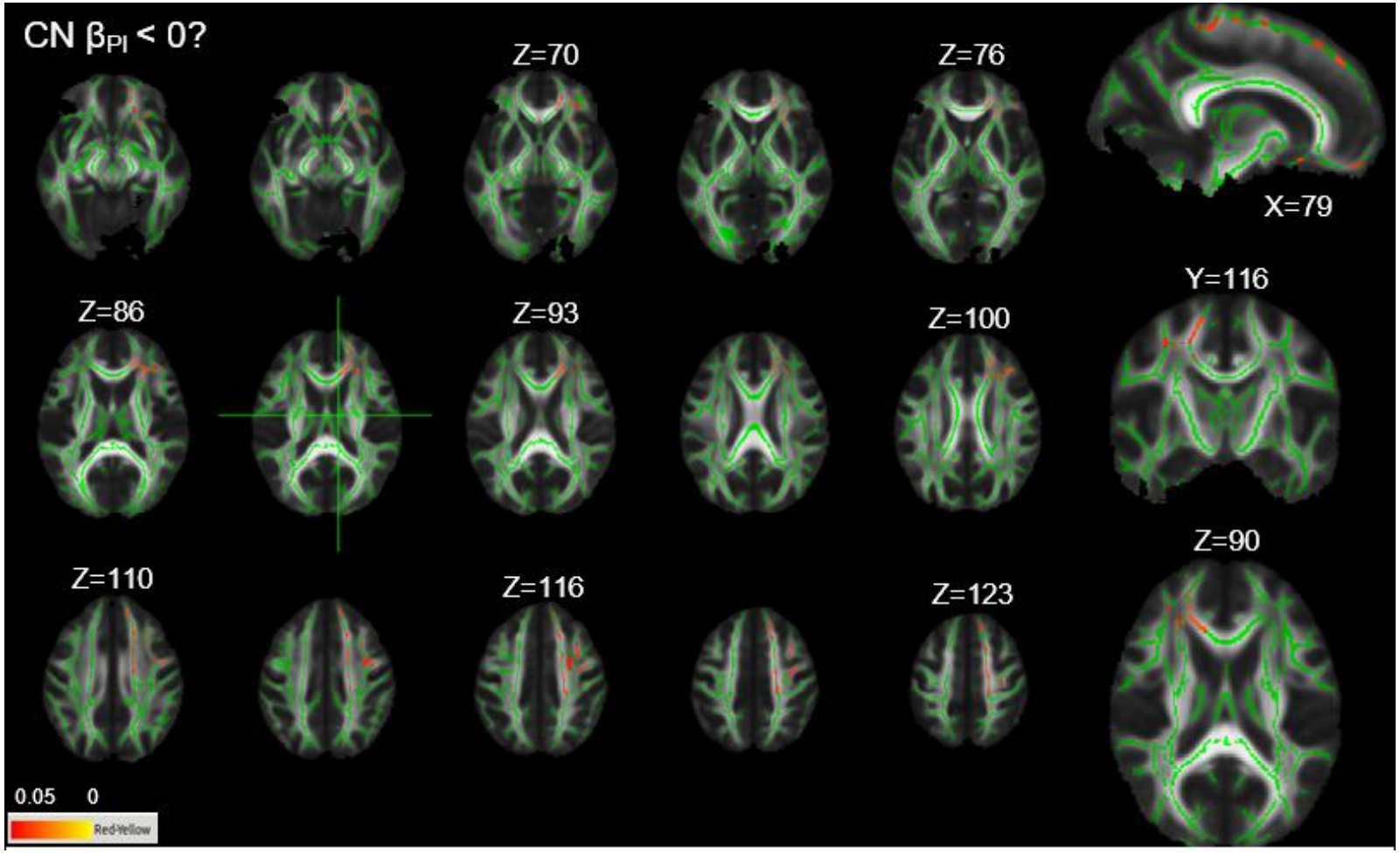
TBSS Hypothesis Tests

- Compare NDI Maps Between AD and CN
  1. CN NDI > AD NDI?
  2. ~~AD NDI > CN NDI?~~
- Correlation - PWV and NDI
  1. ~~CN $\beta_{PWV} > 0$?~~
  2. ~~CN $\beta_{PWV} < 0$?~~
  3. ~~AD $\beta_{PWV} > 0$?~~
  4. ~~AD $\beta_{PWV} < 0$?~~
- Correlation - PI and NDI
  1. CN $\beta_{PI} > 0$?
  2. CN $\beta_{PI} < 0$?
  3. AD $\beta_{PI} > 0$?
  4. AD $\beta_{PI} < 0$?
- Correlation - tCBF and NDI
  1. CN $\beta_{tCBF} > 0$?
  2. CN $\beta_{tCBF} < 0$?
  3. AD $\beta_{tCBF} > 0$?
  4. AD $\beta_{tCBF} < 0$?

No significant findings!

TBSS Hypothesis Tests

- Compare NDI Maps Between AD and CN
  1. CN NDI > AD NDI?
  2. ~~AD NDI > CN NDI?~~
- Correlation - PWV and NDI
  1. ~~CN $\beta_{PWV} > 0$?~~
  2. ~~CN $\beta_{PWV} < 0$?~~
  3. ~~AD $\beta_{PWV} > 0$?~~
  4. ~~AD $\beta_{PWV} < 0$?~~
- Correlation - PI and NDI
  1. ~~CN $\beta_{PI} > 0$?~~
  2. CN $\beta_{PI} < 0$?
  3. ~~AD $\beta_{PI} > 0$?~~
  4. ~~AD $\beta_{PI} < 0$?~~
- Correlation - tCBF and NDI
  1. CN $\beta_{tCBF} > 0$?
  2. CN $\beta_{tCBF} < 0$?
  3. AD $\beta_{tCBF} > 0$?
  4. AD $\beta_{tCBF} < 0$?



ROI Analysis

CN $\beta_{PI} < 0$?

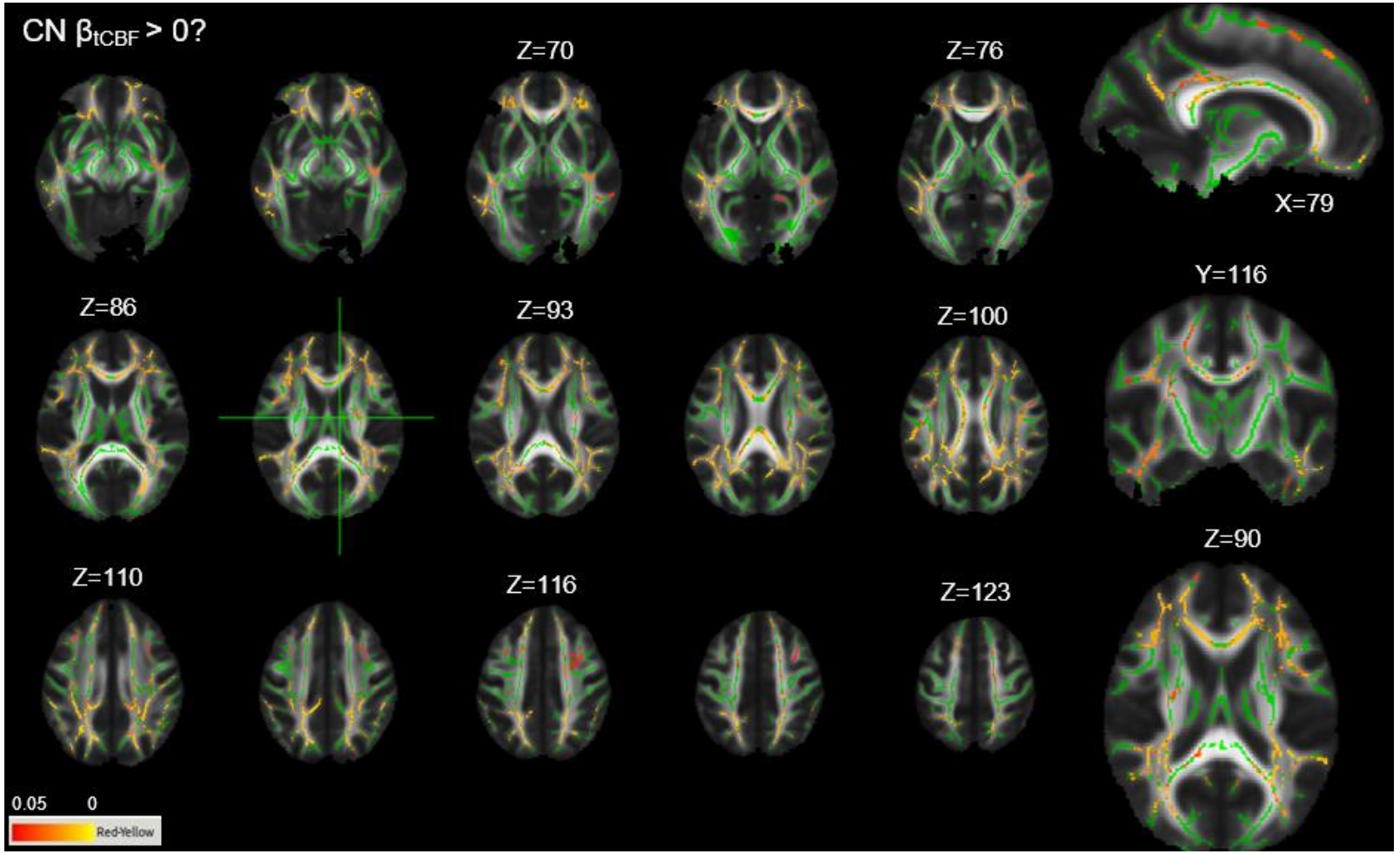
- Multiple Linear Regression
  - Adjust for age/sex
  - Adjust for multiple comparisons

	CN $\beta_{PI} < 0$?		
White Matter Regions Identified from TBSS (JHU Label #)	β_{PI}	R^2	p
Genu of corpus callosum (3)	-0.025	0.041	0.434
Anterior corona radiata R (23)	-0.081	0.292	0.035*
Posterior corona radiata R (27)	-0.051	0.106	0.222

Abbreviations: JHU=Johns Hopkins University; Sig.=significant; R=right; L=left
*p-values <0.05; **p-values > 0.017 (Bonferroni correction for 3 ROIs).

TBSS Hypothesis Tests

- Compare NDI Maps Between AD and CN
  1. CN NDI > AD NDI?
  2. ~~AD NDI > CN NDI?~~
- Correlation - PWV and NDI
  1. ~~CN $\beta_{PWV} > 0$?~~
  2. ~~CN $\beta_{PWV} < 0$?~~
  3. ~~AD $\beta_{PWV} > 0$?~~
  4. ~~AD $\beta_{PWV} < 0$?~~
- Correlation - PI and NDI
  1. ~~CN $\beta_{PI} > 0$?~~
  2. CN $\beta_{PI} < 0$?
  3. ~~AD $\beta_{PI} > 0$?~~
  4. ~~AD $\beta_{PI} < 0$?~~
- Correlation - tCBF and NDI
  1. CN $\beta_{tCBF} > 0$?
  2. ~~CN $\beta_{tCBF} < 0$?~~
  3. ~~AD $\beta_{tCBF} > 0$?~~
  4. ~~AD $\beta_{tCBF} < 0$?~~



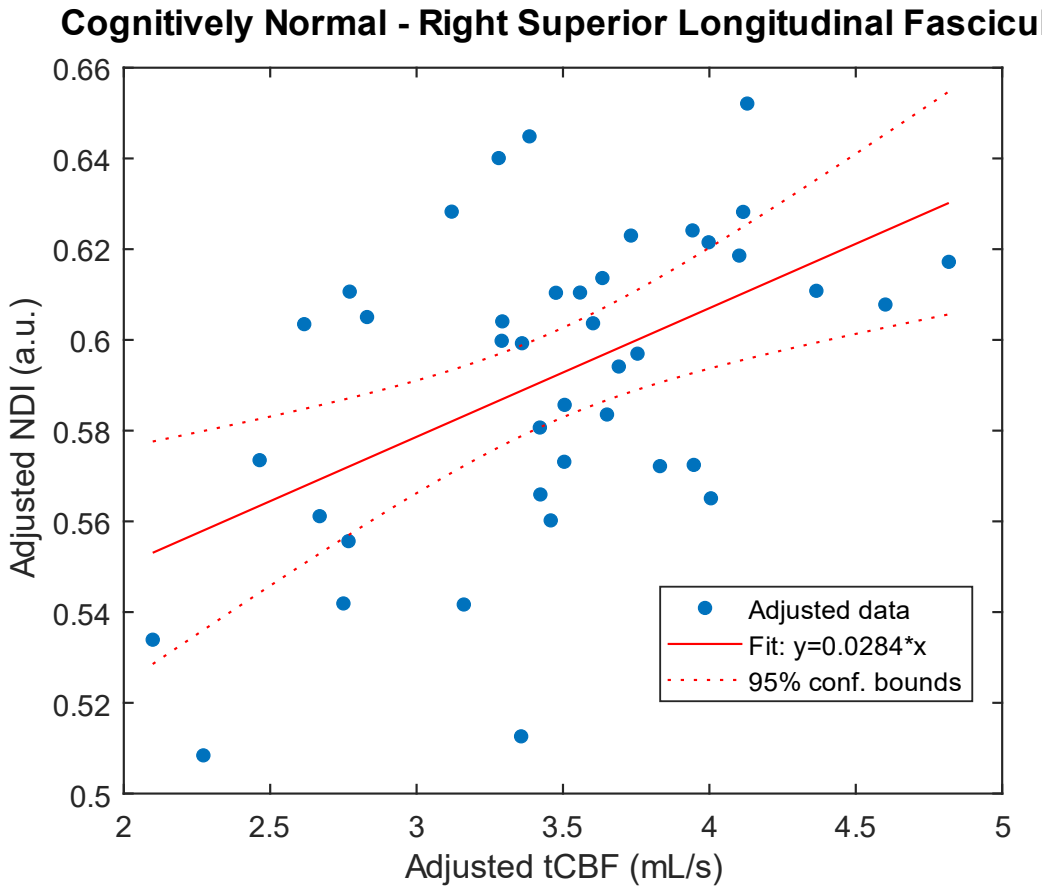
ROI Analysis

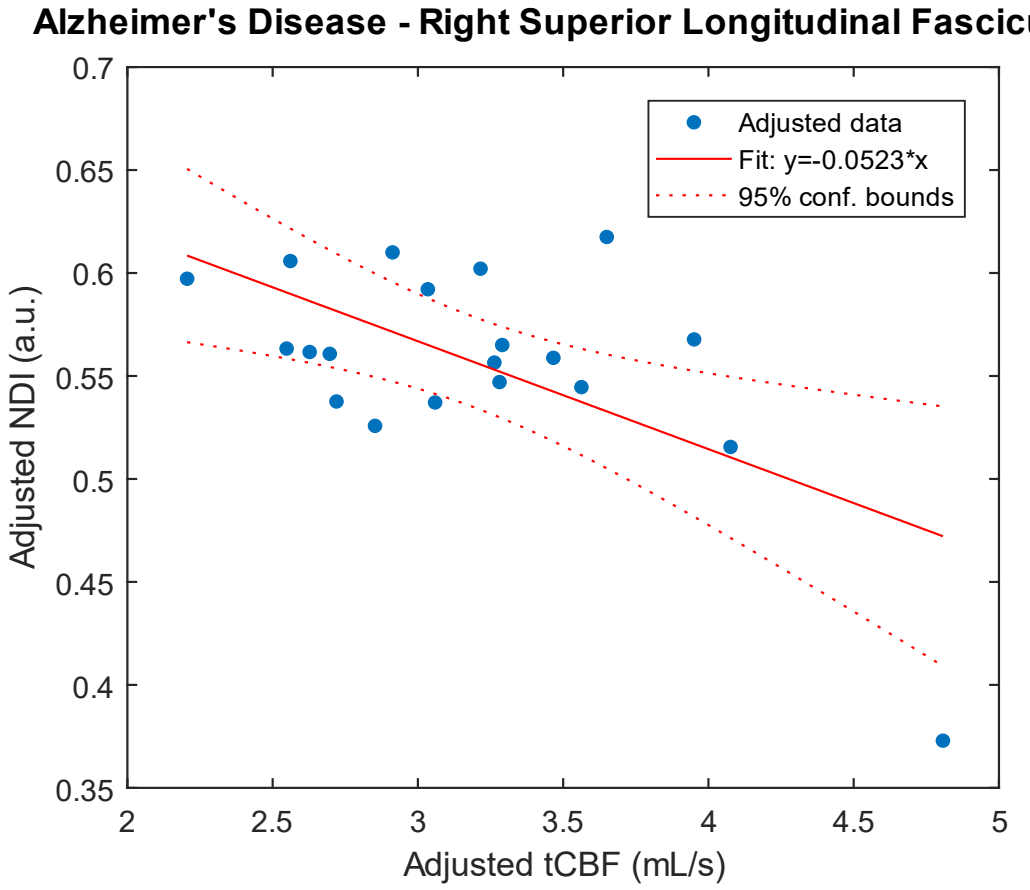
CN $\beta_{tCBF} < 0$?

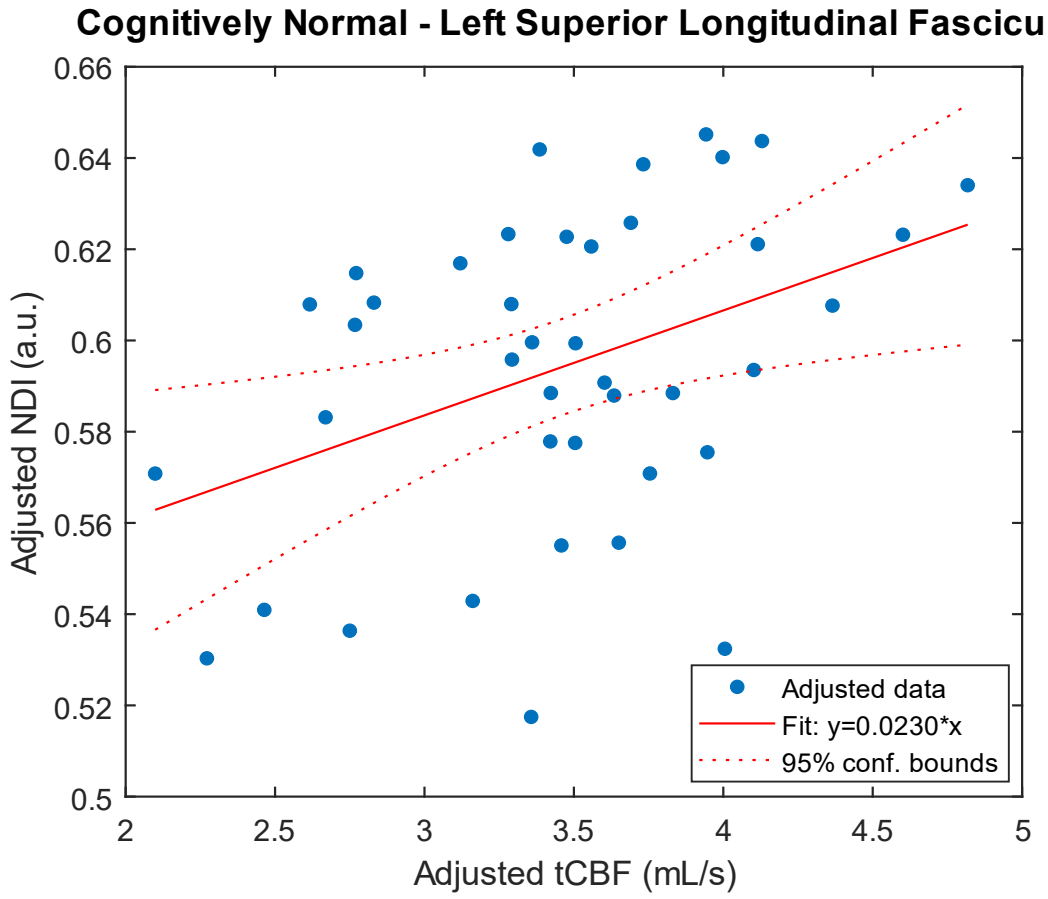
- Multiple Linear Regression
  - Adjust for age/sex
  - Adjust for multiple comparisons

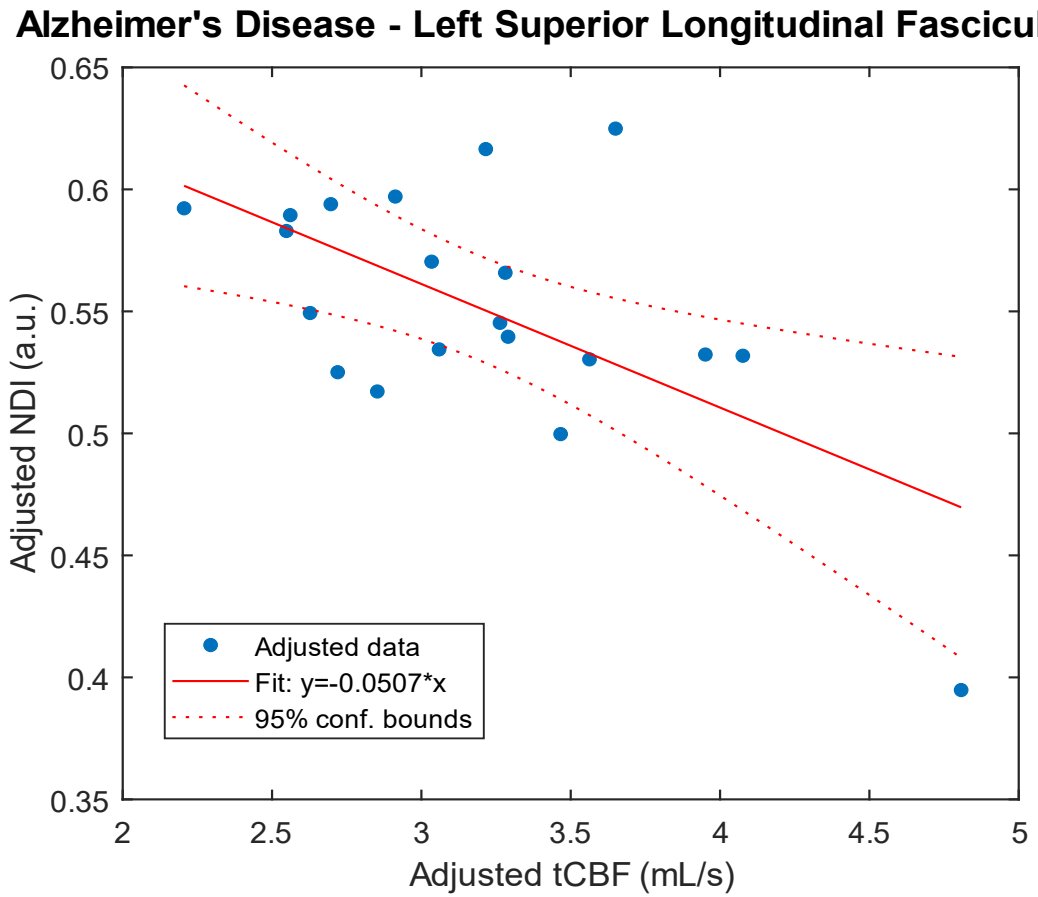
	CN $\beta_{tCBF} > 0$?			*CN β_{tCBF} > AD β_{tCBF}?*
White Matter Regions Identified from TBSS (JHU Label #)	β_{tCBF}	R^2	p-value	p-value
Genu of corpus callosum (3)	0.025	0.129	0.019*	0.760
Body of corpus callosum (4)	0.025	0.247	4e-04*	0.067
Splenium of corpus callosum (5)	0.019	0.176	0.013*	0.248
Anterior corona radiata R (23)	0.026	0.283	0.045*	0.113
Anterior corona radiata L (24)	0.027	0.212	0.034*	0.037*
Superior corona radiata R (25)	0.019	0.237	0.075	0.004*
Superior corona radiata L (26)	0.015	0.174	0.203	0.006*
Posterior corona radiata R (27)	0.036	0.245	0.007*	0.007*
Posterior corona radiata L (28)	0.035	0.216	0.008*	0.006*
Posterior thalamic radiation R (29)	0.020	0.206	0.049*	0.016*
Posterior thalamic radiation L (30)	0.021	0.169	0.078	0.009*
Superior long. fasciculus R (41)	0.028	0.349	0.001**	6e-05**
Superior long. fasciculus L (42)	0.023	0.221	0.012*	5e-04**

Abbreviations: JHU=Johns Hopkins University; Sig.=significant; R=right; L=left
*p-values <0.05; **p-value<0.004 (Bonferroni correction for 13 ROIs).


Cognitively Normal - Right Superior Longitudinal Fasciculus
Adjusted NDI (a.u.)
Adjusted tCBF (mL/s)
Adjusted data
Fit: y=0.0284*x
95% conf. bounds
0.66
0.64
0.62
0.6
0.58
0.56
0.54
0.52
0.5
2
2.5
3
3.5
4
4.5
5


Alzheimer's Disease - Right Superior Longitudinal Fasciculus
Adjusted NDI (a.u.)
Adjusted tCBF (mL/s)
Adjusted data
Fit: y=-0.0523*x
95% conf. bounds
0.7
0.65
0.6
0.55
0.5
0.45
0.4
0.35
2
2.5
3
3.5
4
4.5
5


Cognitively Normal - Left Superior Longitudinal Fasciculus
Adjusted NDI (a.u.)
Adjusted tCBF (mL/s)
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)
Adjusted data
Fit: y=-0.0507*x
95% conf. bounds

Significant Findings

1. Axonal density was greater in CN subjects
    - Variety of WM regions
2. There was a positive correlation between cerebral blood flow and axon density in CN subjects.
    - Superior longitudinal fasciculus
3. There were no associations between CVD and NDI for AD subjects

Limitations

- Did not evaluate ODI or free water maps from NODDI
    - May provide additional WM microstructural information
- Could also perform analysis in mild cognitively compared subjects

Conclusion

- Significant WM alterations, as measured by NDI, were observed between groups
- However, only cerebral flow was significantly correlated with WM axon density.
    - Restricted to CN group

MP 651 – Final Project

Questions?