

# A Multimodal MRI Approach to Longitudinal Vascular and Microstructural Change in a Canine Model of Alzheimer's Disease

Claire L. Illeck<sup>1</sup>, Jessica N. Lingard<sup>1</sup>, Julie M. Loritsch<sup>1</sup>, Hamsanandini Radhakrishnan<sup>1,2</sup>, Zoe Treadwell<sup>1</sup>, Margo F. Ubele<sup>3</sup>, Kathy Boaz<sup>3</sup>, Jennifer L. Mefford<sup>3</sup>, Erin D. Jones<sup>3</sup>, Jessica A. Perpich<sup>3</sup>, Katie McCarty<sup>3</sup>, Beverly Meacham<sup>3</sup>, Stasia A. Bembenek Bailey<sup>3</sup>, László G. Puskás<sup>3</sup>, David K. Powell<sup>3</sup>, Christopher M. Norris<sup>3</sup>, Elizabeth Head<sup>1</sup>, Craig E.L. Stark<sup>1</sup>

<sup>1</sup> University of California, Irvine, California. <sup>2</sup> University of Pennsylvania, Philadelphia, Pennsylvania. <sup>3</sup> University of Kentucky, Lexington, Kentucky. <sup>4</sup> Aperus Pharma, Szeged, Hungary

## Introduction

Dogs are a valuable natural model of Alzheimer's disease (AD)

- They exhibit age-related cognitive decline and AD-relevant neuropathology similar to humans
  - Dogs naturally develop  $\beta$ -amyloid pathology, reduced neurogenesis, oxidative damage, and cerebrovascular pathology<sup>1</sup>
- Prior MRI studies have identified cortical atrophy and hippocampal growth associated with behavioral enrichment<sup>2</sup>
- Diffusion-weighted imaging (DWI) provides markers of microstructural integrity
- Arterial spin labeling (ASL) provides a noninvasive measure of cerebral perfusion

### Questions

What microstructural changes occur across time?

What perfusion changes occur across time?

## Methods

### Study Design

- Five-year longitudinal study of 43 beagles (36 female; baseline age  $6.47 \pm 1.10$  years)
  - All dogs received behavioral enrichment
  - Annual MRI, cognitive testing, fluid biomarker collection, and neuropathology assessment



### MRI Metrics

#### Diffusion Weighted Imaging

##### Diffusion Tensor Metrics

|    |                       |
|----|-----------------------|
| AD | Axial Diffusivity     |
| FA | Fractional Anisotropy |
| RD | Radial Diffusivity    |

##### Neurite Orientation Dispersion and Density Imaging Metrics (NODDI)

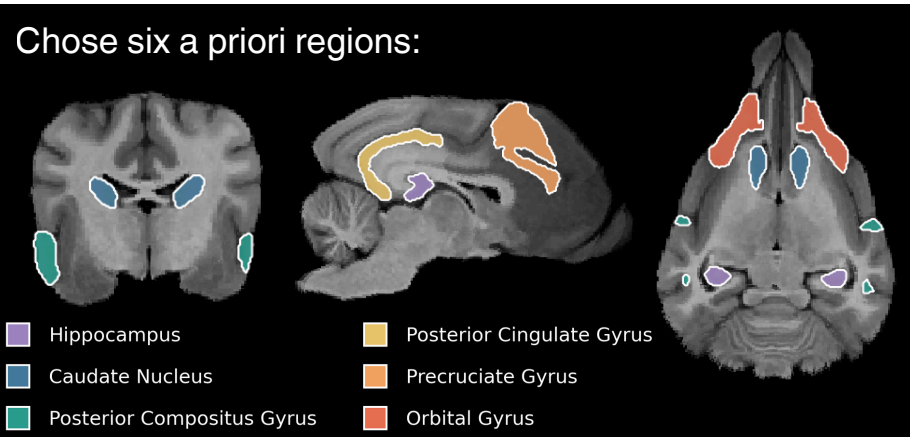
|     |                              |
|-----|------------------------------|
| FWF | Free Water Fraction          |
| NDI | Neurite Density Index        |
| ODI | Orientation Dispersion Index |

#### Arterial Spin Labeling

|     |                                   |
|-----|-----------------------------------|
| CBF | Cerebral Blood Flow (ml/100g/min) |
| ATT | Arterial Transit Time (s)         |

### Statistical Analyses

1. Extracted mean MRI values from 40 Johnson atlas regions
2. Ran linear mixed-effects models in 6 a priori regions



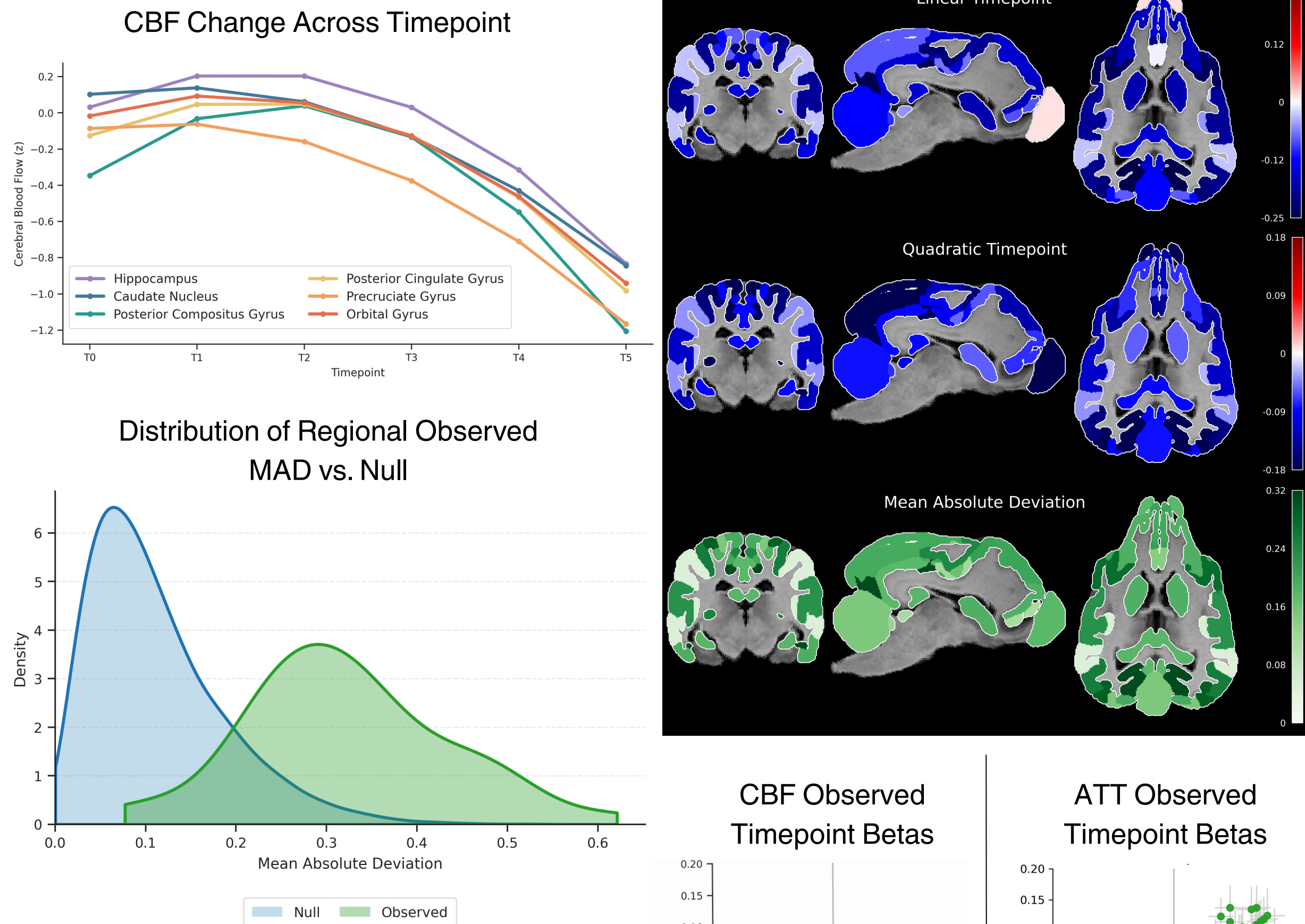
$$MRI\ Metric \sim Baseline\ Age + Timepoint + Timepoint^2 + (1|Dog)$$

3. Generated null distributions with 720 permutations of the linear and quadratic effects across 40 regions
4. Summarized regional betas using mean absolute deviation (MAD) to identify changes agnostic to shape.

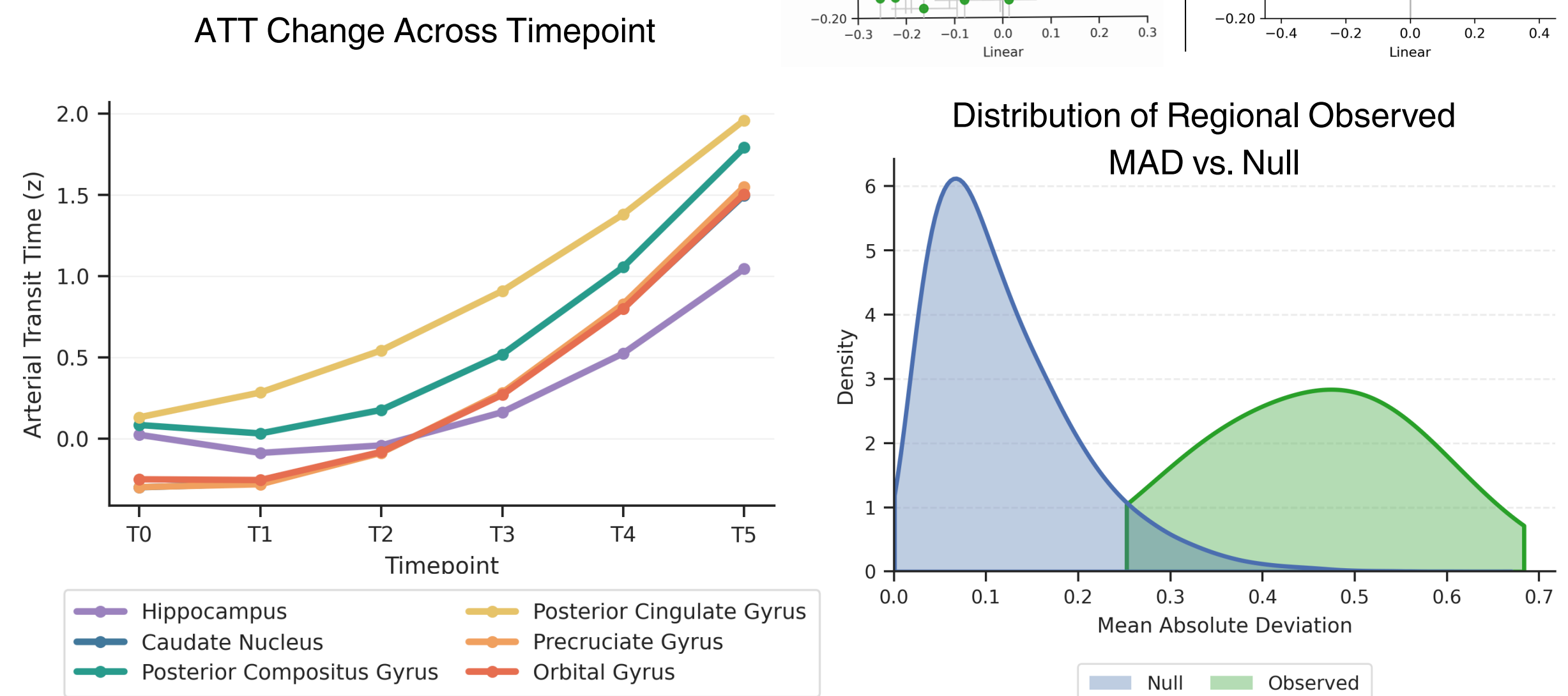
## Results

### Arterial Spin Labeling Metrics Show Whole-Brain Longitudinal Changes

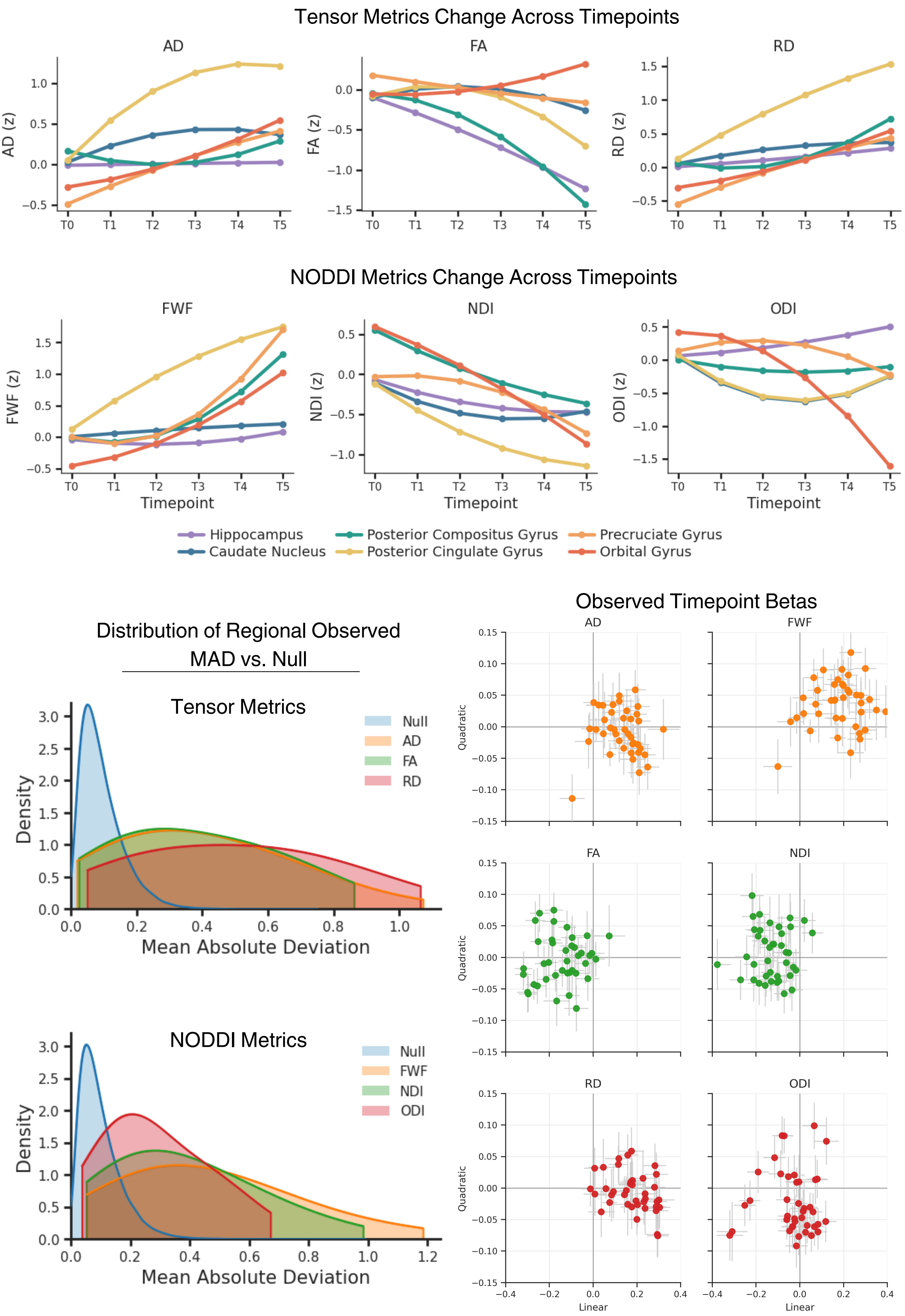
#### Cerebral Blood Flow



#### Arterial Transit Time



### Diffusion Metrics Show Region-Specific Longitudinal Changes



## Discussion

ASL provides a noninvasive measure of cerebral perfusion. Across the whole brain, CBF increased while ATT decreased, a pattern broadly consistent with normal human aging and potentially reflecting age-related changes in vascular function and neurovascular coupling.

Diffusion metrics showed region-dependent change, with overall decreases in NDI and FA and increases in FWF, AD, and RD, consistent with age-related reductions in microstructural organization and tissue integrity observed in human aging.

### Future Directions

- Determine whether these longitudinal imaging changes are associated with cognitive decline and fluid biomarkers, including CSF A $\beta$ 42/40 and NfL.
- Voxelwise analyses to increase spatial sensitivity

## References

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2. Noche, J. L., Radhakrishnan, H., Ubele, M. F., Boaz, K., Mefford, J. L., Jones, E. D., van Rooyen, H. Y., Perpich, J. A., McCarty, K., Meacham, B., Smiley, J., Bailey, S. A. B., Puskás, L. G., Powell, D. K., Sordo, L., Phelan, M. J., Norris, C. M., Head, E., & Stark, C. E. L. (2024). Age-Related Brain Atrophy and the Positive Effects of Behavioral Enrichment in Middle-Aged Beagles. *Journal of Neuroscience*, 44(20).
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