

# Associations of plasma p-tau181 with hippocampal subfield integrity and cognition in older adults

Adea Rich<sup>1</sup>, Hwamee Oh<sup>1,2</sup>

<sup>1</sup>Brown University, RI, <sup>2</sup>Department of Psychiatry and Human Behavior

## Overview

Plasma biomarkers for Alzheimer's disease (AD) may offer broader clinical utility. We evaluate the diagnostic capabilities of plasma p-tau181 by examining its association with AD pathology and cognition.

## Background

- Plasma biomarkers show promise as non-invasive, cost-effective, and accessible diagnostic markers of AD
- Plasma p-tau181 is an increasingly established diagnostic marker for AD, but its relationship to AD pathology and cognition remains unclear
- A hallmark of AD is episodic memory impairment, underscored by atrophy in the hippocampal (HC) formation, which comprises subfields differentially affected by various disorders
- We examine the relationship between p-tau181, HC subfield integrity, and cognition to better understand the diagnostic capabilities of plasma biomarkers

## Methods

**Sample:** 213 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database with:

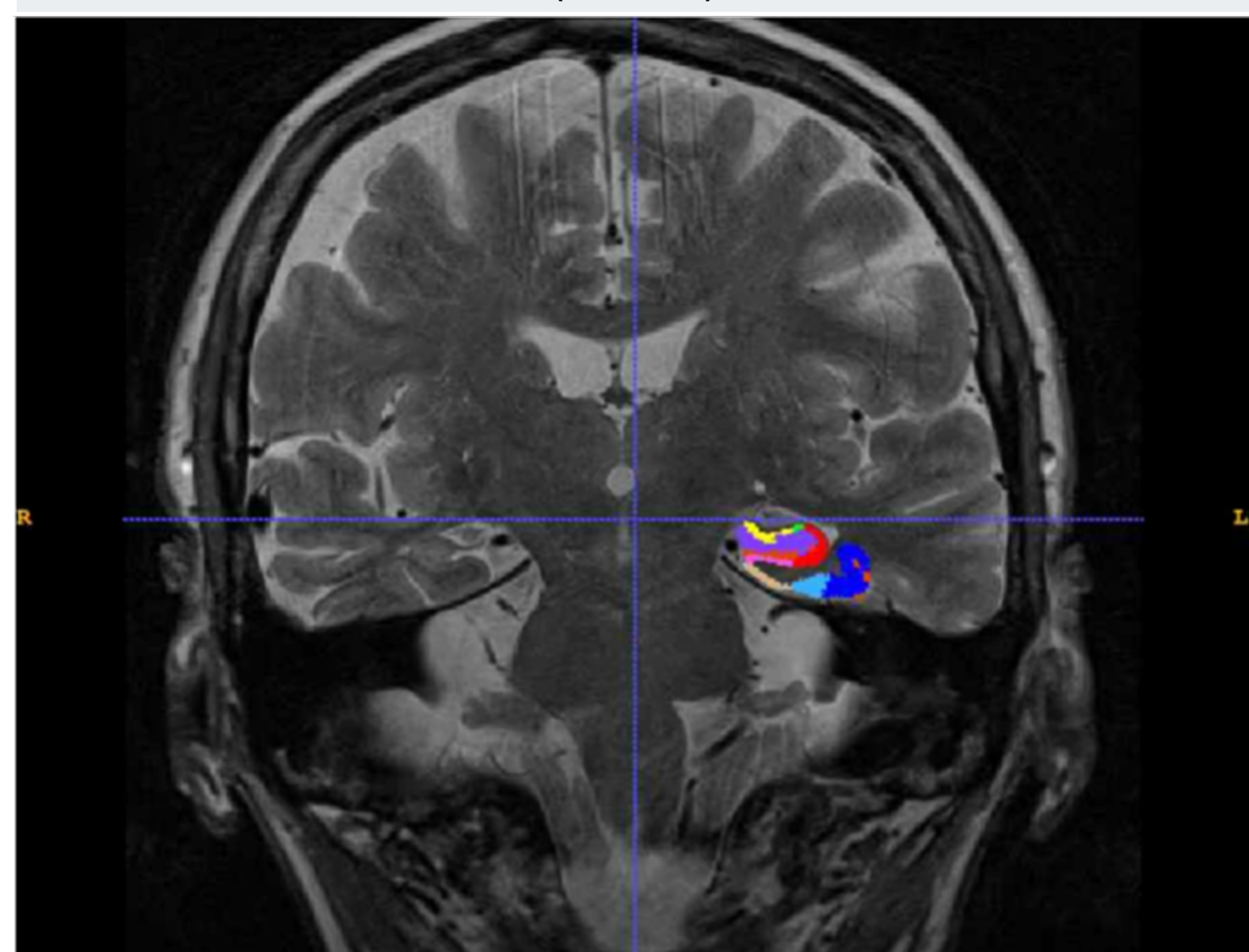
- ✓ Measurements of plasma p-tau181 (pg/mL)
- ✓ High resolution T2-weighted MRI scans
- ✓ Memory and executive functioning composite scores

**Table 1: Demographic and clinical characteristics of subjects**

	CN (N=57)	MCI (N=109)	AD (N=47)
Female	26 (46 %)	46 (42 %)	26 (55 %)
Age	74(7.4)	73(7.8)	74(8.5)
Education	17(2.6)	17(2.7)	16(2.4)
MMSE	29(1.3)	28(2.2)	21(4.5)
ADNI-MEM	1.2(0.69)	0.53(0.84)	-1.1(0.70)
ADNI-EF	0.98(0.85)	0.48(0.95)	-0.99(1.1)
P-tau 181	15(8.8)	17(11)	28(17)

Mean (SD); n (%). CN, Cognitively normal; MCI, Mild cognitive impairment; MMSE, Mini Mental State Examination; ADNI-MEM, Memory composite score; ADNI-EF, Executive Functioning composite score

**MRI Processing:** HC subfield volume was obtained using the Automated Segmentation of Hippocampal Subfields (ASHS) Software



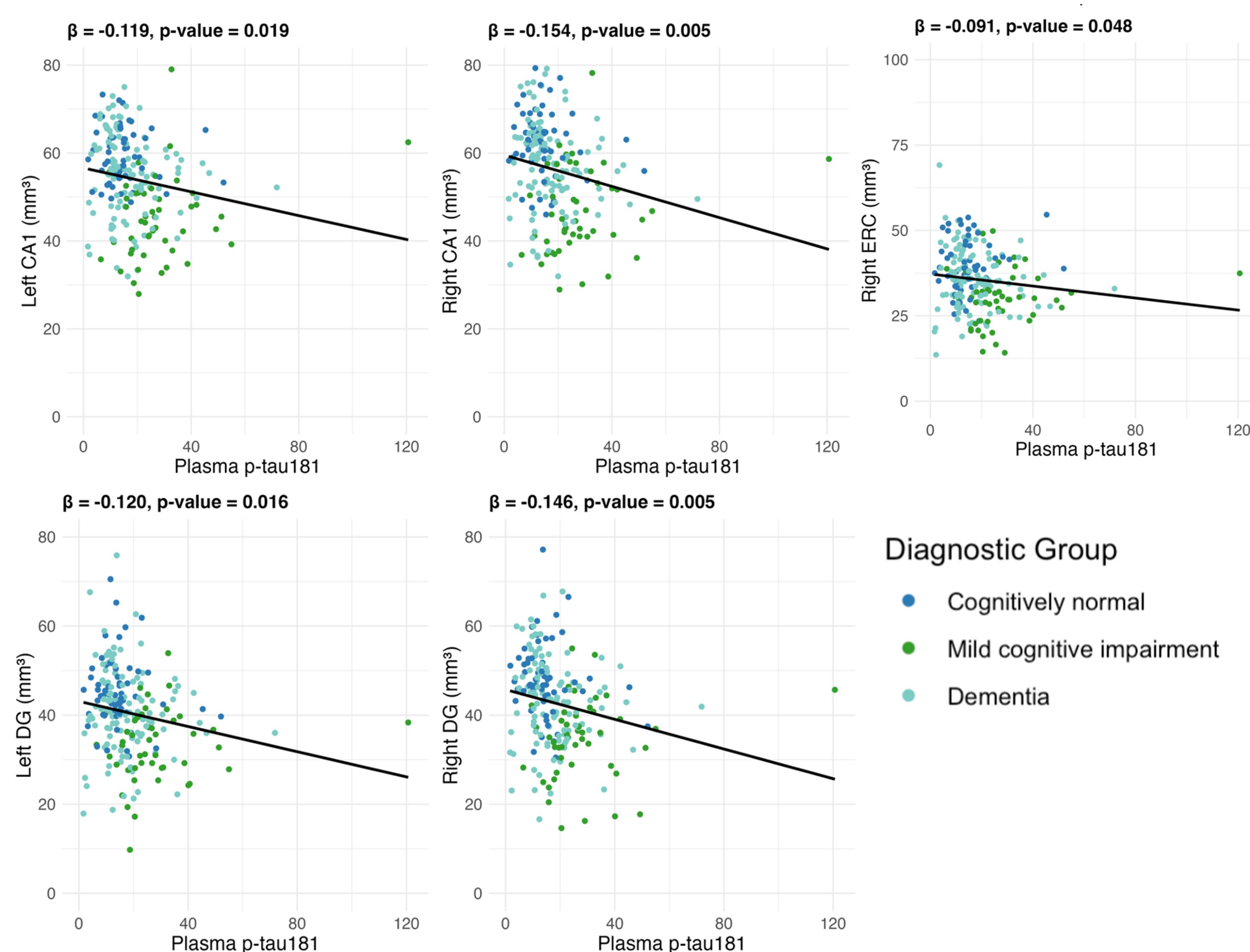
**Regions of Interest:** dentate gyrus (DG), cornu ammonis 1-3 (CA1-3), entorhinal cortex (ERC), subiculum (SUB)

### Statistical Analysis:

- ✓ Multiple linear regression assessed the relationship between plasma p-tau181 and HC subfield volume
- ✓ Bootstrapped mediation analysis examined HC subfield integrity as a mediator of the relationship between p-tau181 and cognition

## Results

**Figure 1: Association between plasma p-tau181 concentration and HC subfield volume across diagnostic groups, adjusted for age and sex**



**Table 2: Association between plasma p-tau181 and cognition mediated by HC subfield integrity, adjusted for age, sex, and years of education**

### a) Memory Composite Score

HC Subfield Volume (mm <sup>3</sup> )	a Action Path	b Theory Path	*ab Indirect Effect	c' Direct Effect
Left CA1	-0.12 [-0.22, -0.02]	0.06 [0.04, 0.07]	-0.08 [-0.15, -0.02]	-0.02 [-0.03, -0.01]
Right CA1	-0.16 [-0.26, -0.05]	0.05 [0.04, 0.06]	-0.09 [-0.15, -0.04]	-0.02 [-0.03, -0.01]
Left DG	-0.12 [-0.22, -0.02]	0.05 [0.04, 0.06]	-0.07 [-0.12, -0.03]	-0.02 [-0.03, -0.01]
Right DG	-0.15 [-0.25, -0.04]	0.05 [0.03, 0.06]	-0.08 [-0.14, -0.04]	-0.02 [-0.03, -0.01]
Right ERC	-0.10 [-0.19, -0.01]	0.04 [0.03, 0.06]	-0.05 [-0.09, -0.01]	-0.03 [-0.04, -0.01]

\*Completely standardized coefficient (LLCI, ULCI)

### b) Executive Functioning Score

HC Subfield Volume (mm <sup>3</sup> )	a Action Path	b Theory Path	*ab Indirect Effect	c' Direct Effect
Left CA1	-0.12 [-0.22, -0.02]	0.04 [0.03, 0.06]	-0.06 [-0.11, -0.02]	-0.03 [-0.04, -0.02]
Right CA1	-0.16 [-0.26, -0.05]	0.03 [0.02, 0.05]	-0.06 [-0.12, -0.02]	-0.03 [-0.04, -0.02]
Left DG	-0.12 [-0.22, -0.03]	0.04 [0.02, 0.05]	-0.05 [-0.09, -0.02]	-0.03 [-0.04, -0.02]
Right DG	-0.15 [-0.25, -0.04]	0.03 [0.02, 0.05]	-0.05 [-0.01, -0.02]	-0.03 [-0.04, -0.02]
Right ERC	-0.01 [-0.19, -0.01]	0.03 [0.01, 0.05]	-0.03 [-0.07, -0.01]	-0.03 [-0.04, -0.02]

\*Completely standardized coefficient (LLCI, ULCI)

## Conclusion

- Across diagnostic groups, higher plasma p-tau181 levels were associated with lower HC subfield volume in the CA1, DG, and right ERC, suggesting that plasma p-tau181 may indicate underlying neurodegenerative changes in the brain
- Higher plasma p-tau181 levels associated with decreased cognition were partially mediated by decreased volume in the CA1, DG, and right ERC
- We found consistent associations of plasma p-tau181 with subfields vulnerable to atrophy in AD (CA1, ERC) and normal aging (DG)
- Despite being a well-established biomarker for distinguishing between AD and healthy individuals, plasma p-tau181 may also have the potential to predict age-related cognitive decline, regardless of a dementia diagnosis

## References



## Acknowledgments

Thanks to Zachary Kunicki, Jenna Bluijus, and Courtney Burton for their assistance and insights.