



Hillary D. Protas^{1,3}, Marisa N. Denlinger^{1,2,3}, Valentina Ghisays^{1,2,3}, Alpana Singh^{1,2,3}, Shan Li^{1,3}, Ji Luo^{1,3}, Javad Sohankar^{1,3}, Yinghua Chen^{1,3}, Dhruvan D. Goradia^{1,3}, Michael Malek- Ahmadi^{1,3}, Wendy Lee^{1,3}, Vivek Devadas^{1,3}, Eric M. Reiman^{1,3,4,5}, Nicholas J. Ashton^{1,2,3}, Yi Su^{1,3,5}

¹Banner Alzheimer's Institute & Sun Health Research Institute, Banner Research | ²Fluid Biomarker Program | ³Arizona Alzheimer's Consortium | ⁴Translational Genomics Research Institute | ⁵Arizona State University

INTRODUCTION

Background

- Plasma p-tau217 is a leading blood-based biomarker for Alzheimer's disease (AD), yet its temporal relationship to tau PET remains unclear.
 - Determining whether circulating p-tau217 captures tau pathology *earlier* than PET is central to disease staging, therapeutic targeting, and clinical trial design
- ### Study aims
- We evaluated whether brain-derived p-tau217 (BD-pTau217) associates with and predicts tau PET burden across disease stages.
 - Evaluated whether BD-pTau217 predicted 2-year tau PET taking into effect the baseline tau.
 - Further assess whether BD-pTau217 predicted individual trajectories of tau accumulation.
 - See whether BD-pTau217 statistically mediates the association between amyloid PET and subsequent tau accumulation.
 - Compare whether BD-pTau217 better predicts downstream tau PET than non-specific pTau217 from conventional assays.

METHODS

Study Design

- Predicting longitudinal tau PET changes in ADNI participants from cross-sectional plasma NULISaseq measurements

Participants / Samples

- ADNI participants with plasma NULISaseq CNS panel
- Total sample: N = 1,427-223 AD, 675 MCI, 529 CU
- A longitudinal subset (41 impaired, 53 CU) underwent FTP PET, with the first scan 2.8 ± 2.9 years from plasma baseline and follow-up imaging $\sim 2.0 \pm 0.2$ years later.

Measurements

- Plasma biomarkers: BD-pTau217, pTau217
- Plasma: 3 levels for each plasma biomarker determined by 95% sensitivity and specificity.
- FTP tau PET: metatemporal (MT) tau PET SUVR and entorhinal (BK1) SUVR and strength(str).

Statistical Analysis

- Predictive models evaluated whether plasma predicted 2-year tau PET, adjusting for baseline tau, age, sex, diagnosis, and plasma-to-PET interval.
- Linear mixed effects model to look at whether plasma predicted individual trajectories of tau accumulation
- Parallel mediation analyses with residual covariance estimated to account for overlap between plasma biomarkers.

CONCLUSION / DISCUSSION

Conclusions

- BD-ptau217 correlates strongly with future tau PET.
- BD-pTau217 predicts future tau PET independent of baseline tau PET unlike pTau217.
- BD-pTau217 predicted individual trajectories of tau accumulation.
- Mediation analyses demonstrated that BD-pTau217 significantly mediates the relationship **between amyloid PET and downstream tau PET accumulation** and also that BD-pTau217 shows stronger mediation on tau PET accumulation than pTau217.

Implications

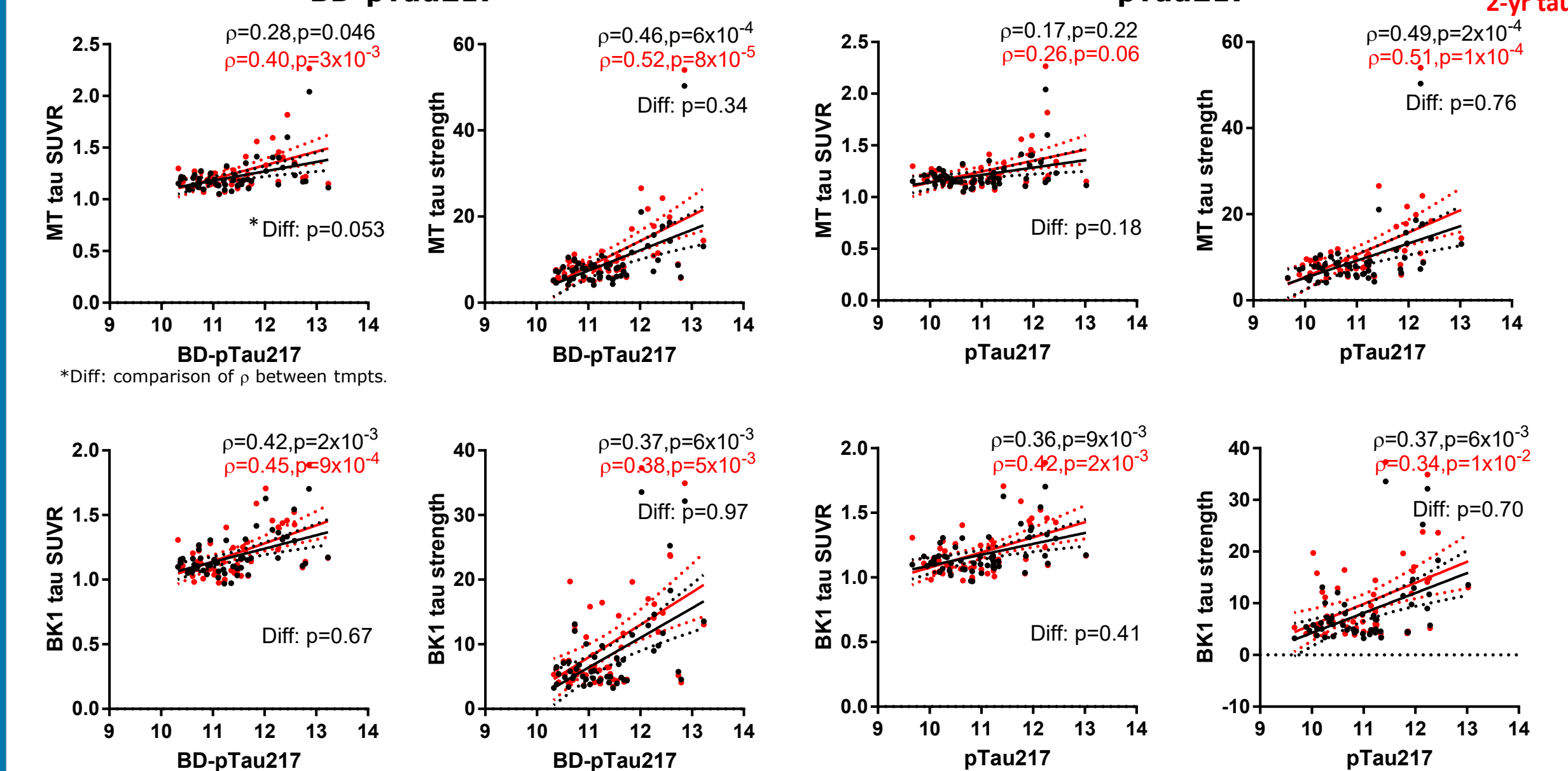
- BD-pTau217's ability to predict future tau PET independent of baseline pathology, combined with evidence supporting a mediating role between amyloid and tau accumulation, positions BD-pTau217 as a **key transitional biomarker in the AD pathological cascade**.
- These findings support BD-pTau217 as an early, biologically meaningful indicator of tau propagation with strong potential for early detection, staging, and therapeutic trial enrichment, possibly better than non-specific pTau217.

Take-home message

- BD-pTau217 shows robust cross-sectional relationships with tau PET and stronger associations with tau PET measured years later, consistent with a **temporally upstream** role relative to PET-detectable tau spread.

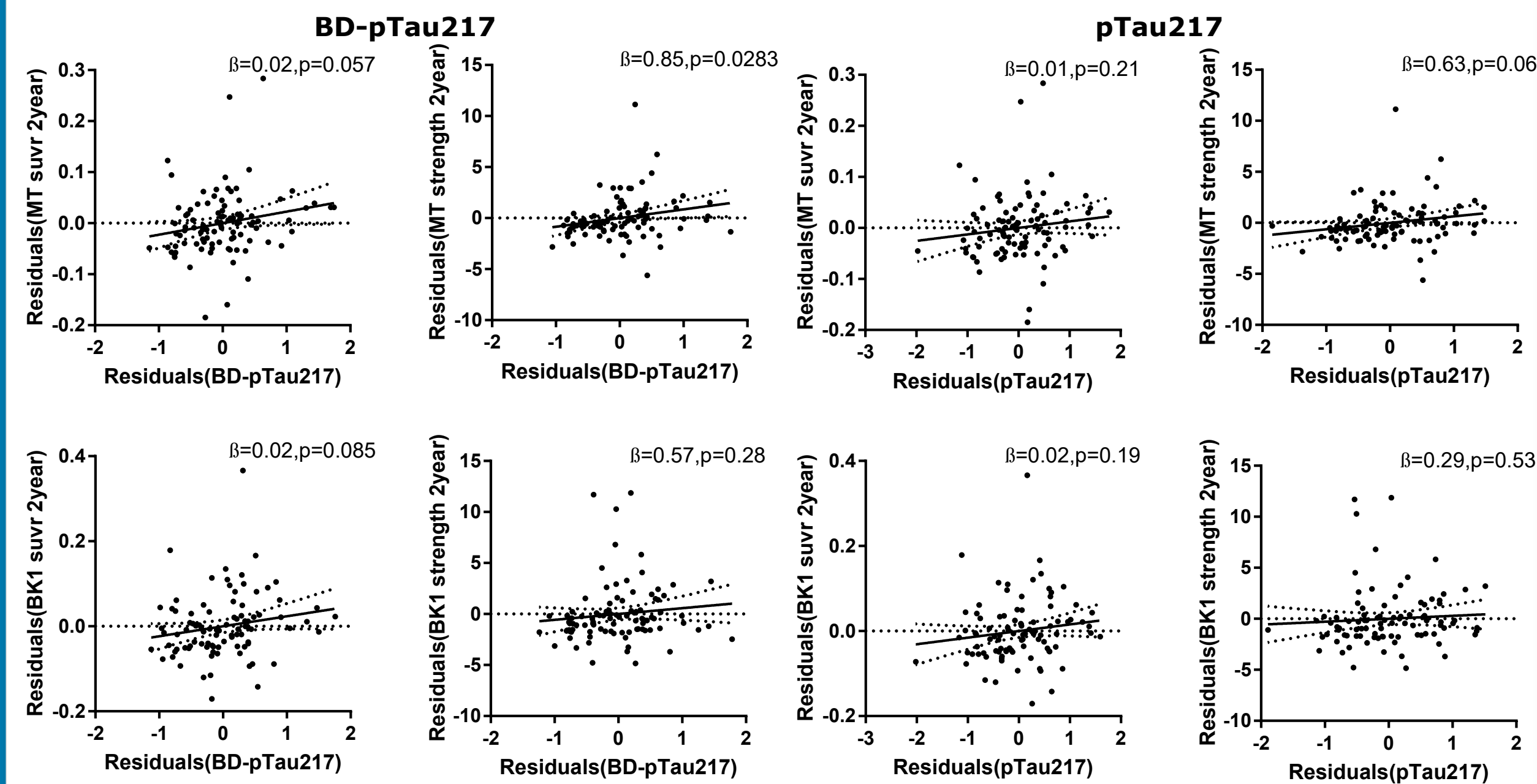
RESULTS

Figure 1. Future tau PET correlated with Plasma BD-pTau217 in CU



- Associations with **future tau PET** were consistently stronger than with baseline tau PET.

Figure 2. BD-pTau217 predicts 2-year tau PET adjusting for baseline tau PET



- BD-pTau217 significantly predicts 2-year MT strength while adjusting for baseline tau PET while pTau217 does not.

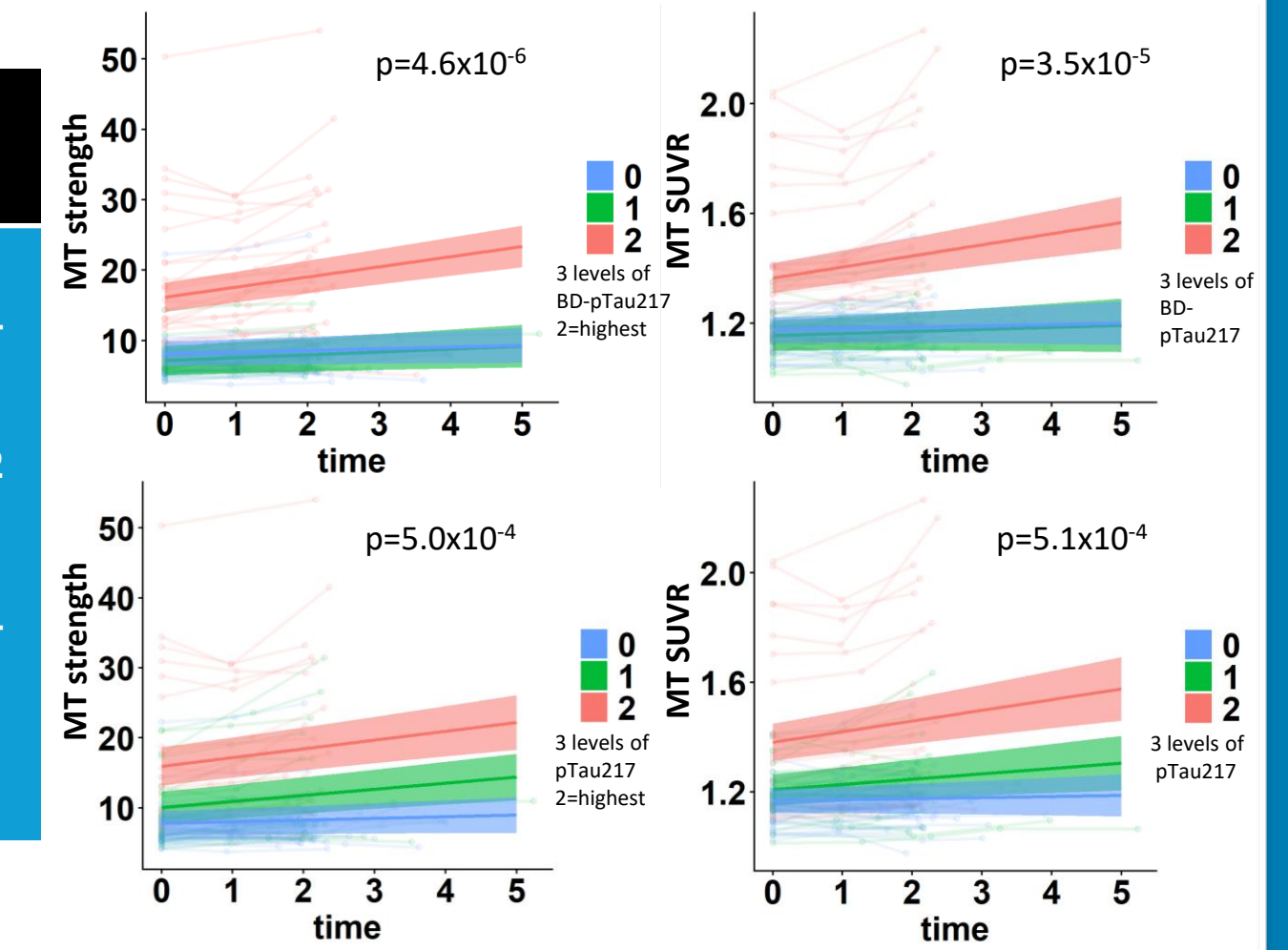
REFERENCES

- Chong JR, Hilal S, Venketasubramanian N, et al. Plasma brain-derived p-Tau217 outperforms other p-Tau species in detecting abnormal brain amyloid in an Asian cohort of older people with cerebrovascular disease burden. *J Prev Alzheimers Dis*. Jun 5 2026;13(7):100615. doi:10.1016/j.tjpad.2026.100615
- Protas, H., Ghisays, V., Goradia, D. D., Bauer, R., 3rd, Devadas, V., Chen, K., Reiman, E. M., & Su, Y. (2023). Individualized network analysis: A novel approach to investigate tau PET using graph theory in the Alzheimer's disease continuum. *Front Neurosci*, 17, 1089134. https://doi.org/10.3389/fnins.2023.1089134
- Jack CR, Jr., Wiste HJ, Weigand SD, et al. Defining imaging biomarker cut points for brain aging and Alzheimer's disease. *Alzheimers Dement*. Mar 2017;13(3):205-216. doi:10.1016/j.jalz.2016.08.005
- Schöll M, Lockhart SN, Schonhaut DR, et al. PET Imaging of Tau Deposition in the Aging Human Brain. *Neuron*. Mar 2 2016;89(5):971-982. doi:10.1016/j.neuron.2016.01.028

Table1/Figure 3. Mixed Effects Model

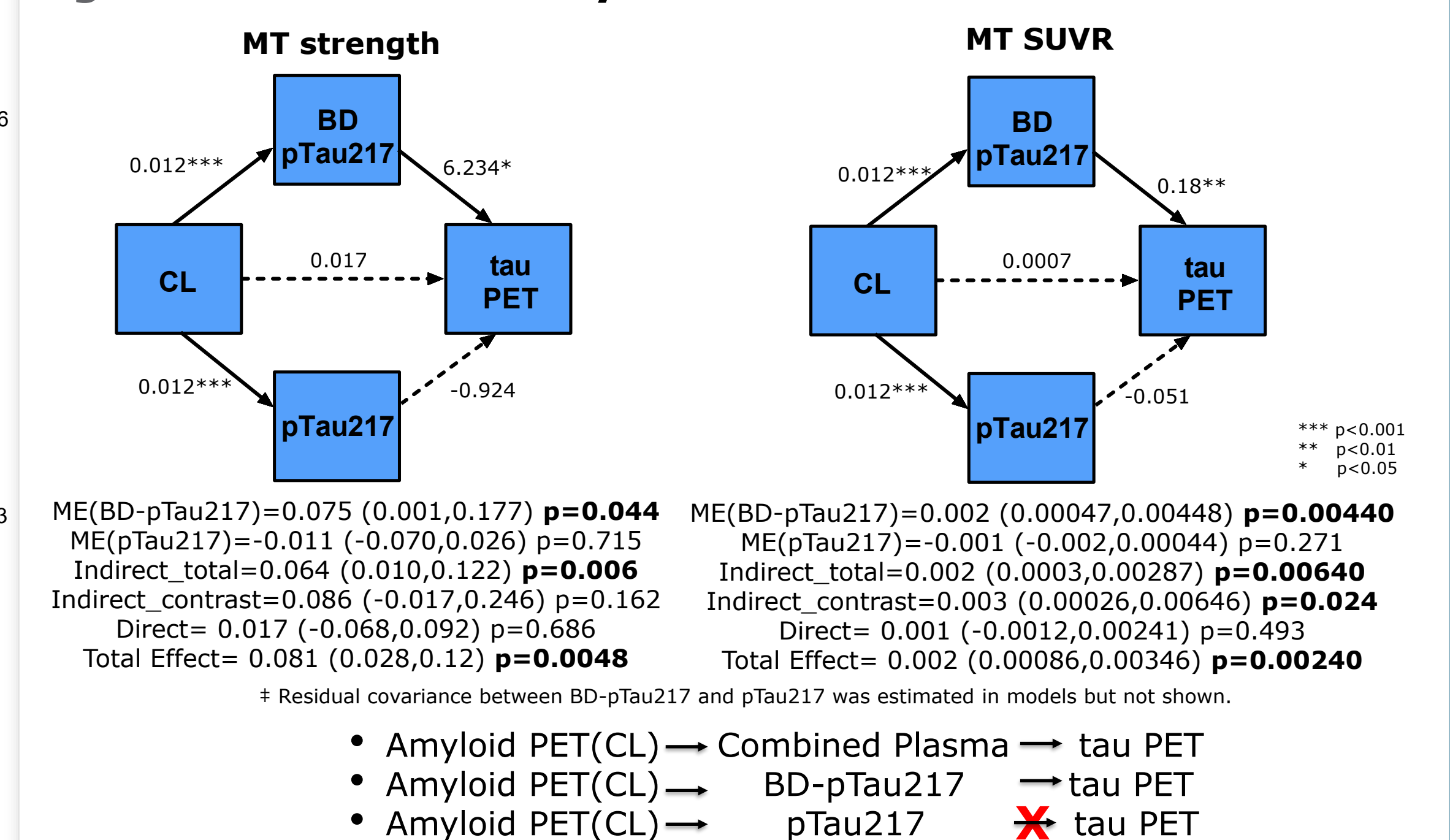
p-value significance of association of plasma with tau PET

	BD-pTau217	pTau217
MT SUVR	1.29x10 ⁻⁵	3.53x10 ⁻⁴
BK1 SUVR	8.00x10 ⁻³	2.43x10 ⁻²
MT strength	1.45x10 ⁻⁴	5.64x10 ⁻⁴
BK1 strength	0.14	0.29



- BD-pTau217 predicted individual paths of tau accumulation, better than pTau217 although not significantly.
- Plasma biomarkers predicted MT SUVR/ strength better than entorhinal (BK1) tau PET.

Figure 4. Mediation analyses†



- BD-pTau217 exhibits significantly stronger mediation of tau accumulation as measured by MT SUVR than pTau217.

ACKNOWLEDGMENTS

R01AG069453, RF1AG073424, P30AG072980, State of Arizona (CTR057001), Arizona Alzheimer's Research Consortium, ADNI (NIA grant U19AG024904)

Email for more info

hillary.protas@bannerhealth.com