



CHRONIC PAIN ASSOCIATIONS WITH PLASMA p-tau217 AND ALZHEIMER'S-SIGNATURE BRAIN STRUCTURE IN OLDER MEN

Tyler R. Bell, PhD;¹ McKenna E. Williams, PhD;¹ Tina Vo, PhD;¹ Rongxiang Tang, PhD;² Robert A. Rissman, PhD;³ Imanuel Lerman, MD;¹ Diane M. Jacobs, PhD;¹ Amy J. Jak, PhD;⁴ Chandra A. Reynolds, PhD;⁵ Matthew S. Panizzon, PhD;¹ Christine Fennema-Notestine, PhD;¹ Anders M. Dale, Ph.D;¹ Jeremy A. Elman, PhD;¹ Carol E. Franz, PhD;¹ William S. Kremen, PhD;¹ for the Vietnam Era Twin Study of Aging.



¹University of California San Diego; ²Texas A&M University ³Alzheimer's Therapeutic Research Institute, University of Southern California, CA, USA ⁴University of Michigan ⁵University of Colorado Boulder

INTRODUCTION

Chronic pain is common in later life and has been linked to faster cognitive decline and higher dementia risk, but that evidence rests on broad cognitive endpoints rather than measures tied to Alzheimer's disease (AD) pathology

Gap: Whether chronic pain relates to AD-specific neurodegeneration in adults who are cognitively unimpaired

Objective: Test whether chronic pain measured from ~age 56 to 68 predicts AD-related brain structure, plasma p-tau217, and their 6-year change, and whether associations depend on age and APOE ε4 dosage

METHODS

Participants

Vietnam Era Twin Study of Aging (VETSA)

n = 871 men, cognitively unimpaired at Wave 3
Chronic pain: Waves 1–3 (mean age 56, 62, 68)
AD measures: Wave 3 (mean age 67.5); Wave 4, 6 years later (mean age 73.2)

Chronic Pain (Waves 1–3)

- Moderate-to-severe pain present at first three waves (~age 56, 62, and 68),
- Reported on the SF-36 (Ware & Sherbourne, 1992)
- Chronic pain in 151 (17.3%)

AD-related Measures (Waves 3 & 4 only)

- Plasma p-tau217:** ALZpath assay, Quanterix Simoa HD-X [Wave 3 n = 745; Wave 4 n = 478]
- AD cortical signature:** Weighted composite of Free Surfer (6.0) measured cortical thickness in 7 AD-vulnerable regions plus hippocampal volume; ADNI-derived weights (Williams et al., 2023). [Wave 3 n = 354; Wave 4 n = 317]
- AD mean diffusivity signature:** Weighted composite of mean diffusivity in the same regions plus hippocampus. [Wave 3 n = 329; Wave 4 n = 281]

Statistical Analyses

Linear mixed models (lmer in R 4.5.3) adjusted for age, opioid use, depressive symptoms (CESD 20), and APOE ε4 dosage. Random intercept for twin pairs.

Moderators: Age and APOE ε4 dosage. The chronic pain × age interaction was probed at ±1 SD (ages 65 and 70).

FDR-corrected (Benjamini-Hochberg)

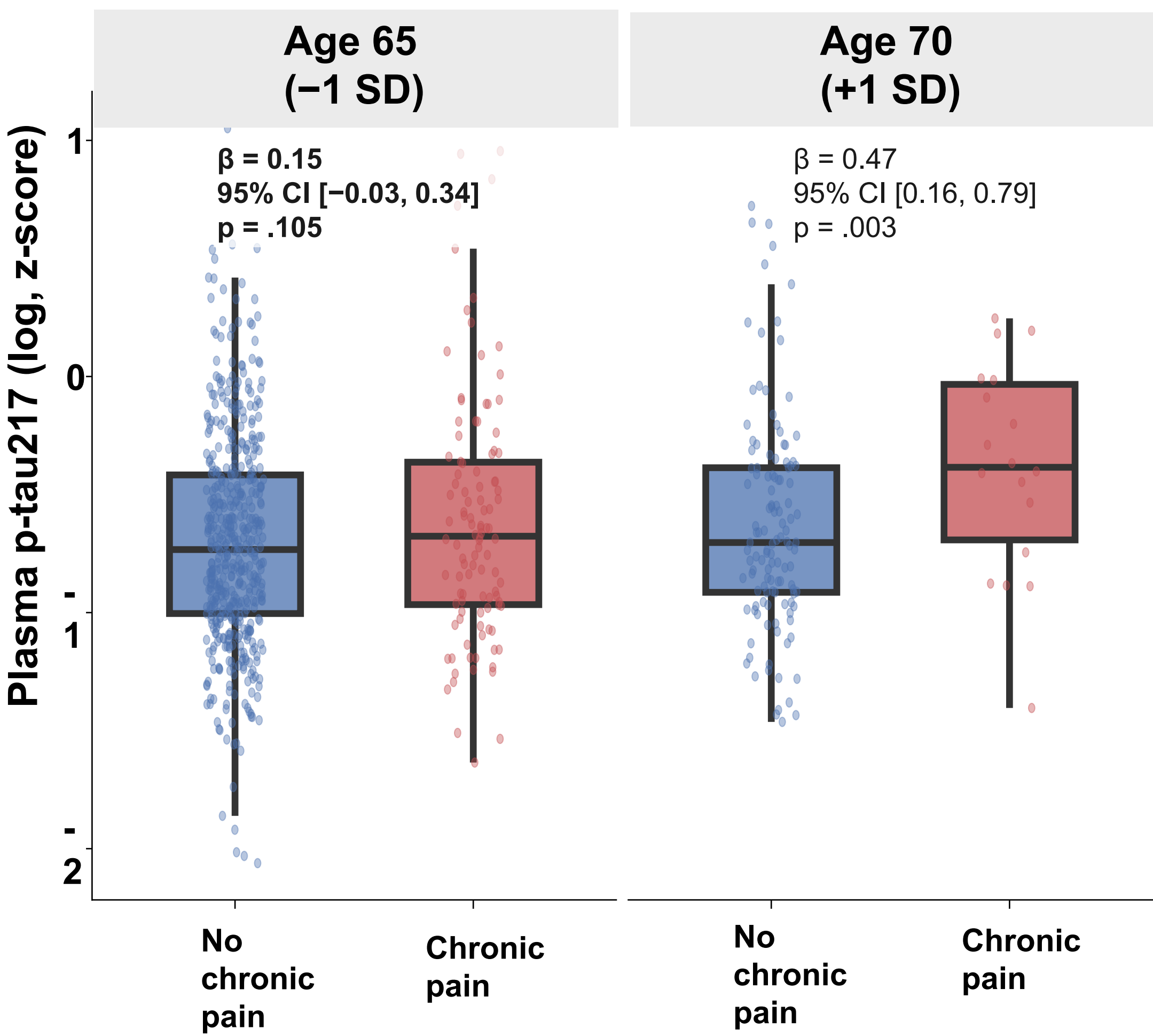
RESULTS

Table 1. Key linear mixed model results.

Outcome	Chronic Pain	Chronic Pain × age	Chronic Pain × time	Chronic Pain × time × age
	β (SE)	β (SE)	β (SE)	β (SE)
p-tau217	.178 (.094)	.086 (.039)*	-.009 (.017)	-.005 (.007)
AD cortical signature	-.297 (.141)	.058 (.057)	-.053 (.021)*	-.024 (.008)*
AD mean diffusivity signature	.193 (.143)	-.048 (.060)	.044 (.024)	.023 (.010)*

Note. β (SE) per AD-related measure. × time = 6-year slope difference; × age terms = how associations are modified by Wave 3 age. Models included lower-order terms, covariates, and a twin-pair random intercept. *p < .05

Figure 1. Chronic pain status and plasma p-tau217.



CONCLUSIONS

- Chronic pain was associated with higher plasma p-tau217 at Wave 3**
- Chronic pain predicted faster degeneration in AD-vulnerable cortical structures**
- Pain-related AD risk strengthened with age, which may reflect pain accelerating AD processes that emerge later in life**
- Mechanisms remain to be established. Neuroinflammation is a likely candidate, given that chronic pain facilitates inflammatory signaling**

Notes:

- Participants with chronic pain were older at Wave 3, had greater depressive symptoms, and more likely to take an opioid (ps < .05)
- APOE ε4 dosage did not moderate any associations (ps > .05)

Figure 2. Chronic pain and 6-year change in AD brain signatures.

