DOI: 10.1002/alz.091468

BIOMARKERS

POSTER PRESENTATION

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

BIOMARKERS (NON-NEUROIMAGING)

Plasma pTau217, gender, and synaptic density

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Abstract

Background: Synaptic loss is a key feature of Alzheimer's disease (AD) dementia. In the entorhinal cortex (ERC) and hippocampus, phosphorylated tau (pTau) colocalizes with synaptosomes, and its presence may play a role in AD-related synaptic loss. However, the relationship between pTau and synaptic density is not well understood. Plasma pTau represents secreted tau pathology and among the available epitopes, pTau217 has emerged as an accurate biomarker of AD pathology. Here, we tested the relationship between secreted pTau217 and synaptic density.

Method: Participants were recruited from the Wisconsin Alzheimer's Disease Research Center and the Wisconsin Registry for Alzheimer's Prevention (N=38; Table 1). All participants underwent blood sampling for measurement of plasma pTau217 and [C-11]UCB-J PET to assess synaptic density in regions of interest (ROIs: hippocampus, ERC, and fusiform gyrus) known to show early AD tau accumulation. Synaptic density

was quantified using [C-11]UCB-J DVR (LGA, whole cerebellar reference region) and ROIs were identified following FreeSurfer T1w-MRI parcellation. Plasma pTau217 was determined using the ALZpath pTau217 Simoa assay on the Quanterix HD-X platform. We utilized multiple regression analysis to examine the extent to which plasma pTau217 and gender predict synaptic density in ROIs controlling for age. All models were fitted in R and considered significant at Bonferroni-corrected (.05/3) $p<.017$. During analysis we discovered one outlier; a cognitively-unimpaired participant with pTau217 concentration >2.5 standard deviations above the mean and high UCB-J DVR in all ROIs. Results with and without the outlier were considered.

Result: Plasma pTau217 ($b=-.07$, $p=0.01$) and gender ($b=-.05$, $p=0.008$) predicted UCB-J DVR in the hippocampus, but not other ROIs (Table 2). The effect size of plasma pTau217 and gender, as measured by Cohen's f^2, was 0.23 and 0.34, respectively, indicating medium to large effects. Welch's t-test showed a significant gender difference in hippocampal UCB-J DVR (Figure).

Conclusion: Our results indicate that higher levels of plasma pTau217 associated with lower synaptic density in the hippocampus. However, given the individual with high pTau217 and synaptic density, it is possible other processes unaccounted for in this analysis are impacting this relationship. Further examinations could give insight into early processes that confer neuronal injury in the AD pathological cascade.

Table 1. Sample characteristics.

Characteristic	N = 38
Female, *n (%)*	24 (63.2%)
Education, *years*	16.34 ± 2.07
Race, *n*	
White	32
Black or African American	5
American Indian or Alaska Native	1
Age at synaptic PET scan, *years*	70.96 ± 6.35
Years between synaptic PET and blood draw	1.62 ± 2.21
Amyloid PET positive, *n (%)*	16 (42.1%)
Cognitive Status, *n*	
Unimpaired	28
MCI	9
Dementia	1
Plasma pTau 217 levels, *pg/mL*	0.59 ± 0.39
[C-11]UCB-J DVR in ROIs	
Hippocampus	0.97 ± 0.06
Entorhinal Cortex	1.02 ± 0.11
Fusiform Gyrus	1.22 ± 0.08

Values are provided as mean±standard deviation unless noted otherwise.

Plasma pTau217 was obtained using the ALZpath pTau217 assay on the Quanterix HD-X platform. One participant's pTau217 level was 1.67 which is greater than 2.5 times the standard deviation above the mean (0.59). Amyloid positivity was determined through [C-11]PiB PET scans with DVR ≥ 1.19 across 8 bilateral regions that have previously been shown to harbor amyloid plaques: medial orbital frontal, anterior cingulate, posterior cingulate, precuneus, angular, supramarginal, superior temporal and middle temporal gyri (Sprecher et al, 2015). Years between blood draw and synaptic PET scan was calculated by taking the absolute value difference in participant age at the time of each procedure. Abbreviations: PET = positron emission tomography; MCI = mild cognitive impairment; pTau217 = tau phosphorylated at amino acid residue 217; DVR = distribution volume ratio; ROIs = regions of interest.

Table 2. Multiple regression results.

	Predictors		
Synaptic density ([C-11]UCB-J DVR)	pTau217	Age	Gender
Hippocampus	-0.07 (-0.12, -0.02)*	-0.002 (-0.004, 0.001)	-0.05 (-0.08 -0.01)*
Entorhinal Cortex	-0.002 (-0.12, 0.11)	-0.004 (-0.01, 0.003)	-0.03 (-0.10, 0.05)
Fusiform Gyrus	-0.03 (-0.12, 0.05)	-0.001 (-0.006, 0.003)	-0.05 (-0.11, 0.001)

Values are shown as: beta coefficients (95% confidence intervals).
*Indicates a p-value < .017.

This table shows regression coefficients and 95% confidence intervals for models with synaptic density in the hippocampus, entorhinal cortex, and fusiform gyrus as outcomes and plasma pTau217, age, and gender (males/females) as predictors. All models were fitted in R and considered significant at Bonferroni-adjusted p<.017 with and without the individual with high plasma pTau217 concentration. Adjusted R^2 values indicated that models without the outlier provided a better overall fit for predicting UCB-J DVR in the hippocampus (with outlier $R^2 = 0.19$; without outlier $R^2 = 0.40$) and fusiform gyrus (with outlier $R^2 = 0.04$; without outlier $R^2 = 0.09$). Models predicting UCB-J DVR in the entorhinal cortex provided poor overall fit with ($R^2 = 0.0001$) or without the outlier ($R^2 = -0.007$), indicating that other processes may be impacting entorhinal UCB-J uptake. Results presented herein represent data from 37 participants, excluding the outlier, and indicate that plasma pTau217 and gender were significant predictors of synaptic density in the hippocampus but not the entorhinal cortex or fusiform gyrus.
Abbreviations: DVR = distribution volume ratio.

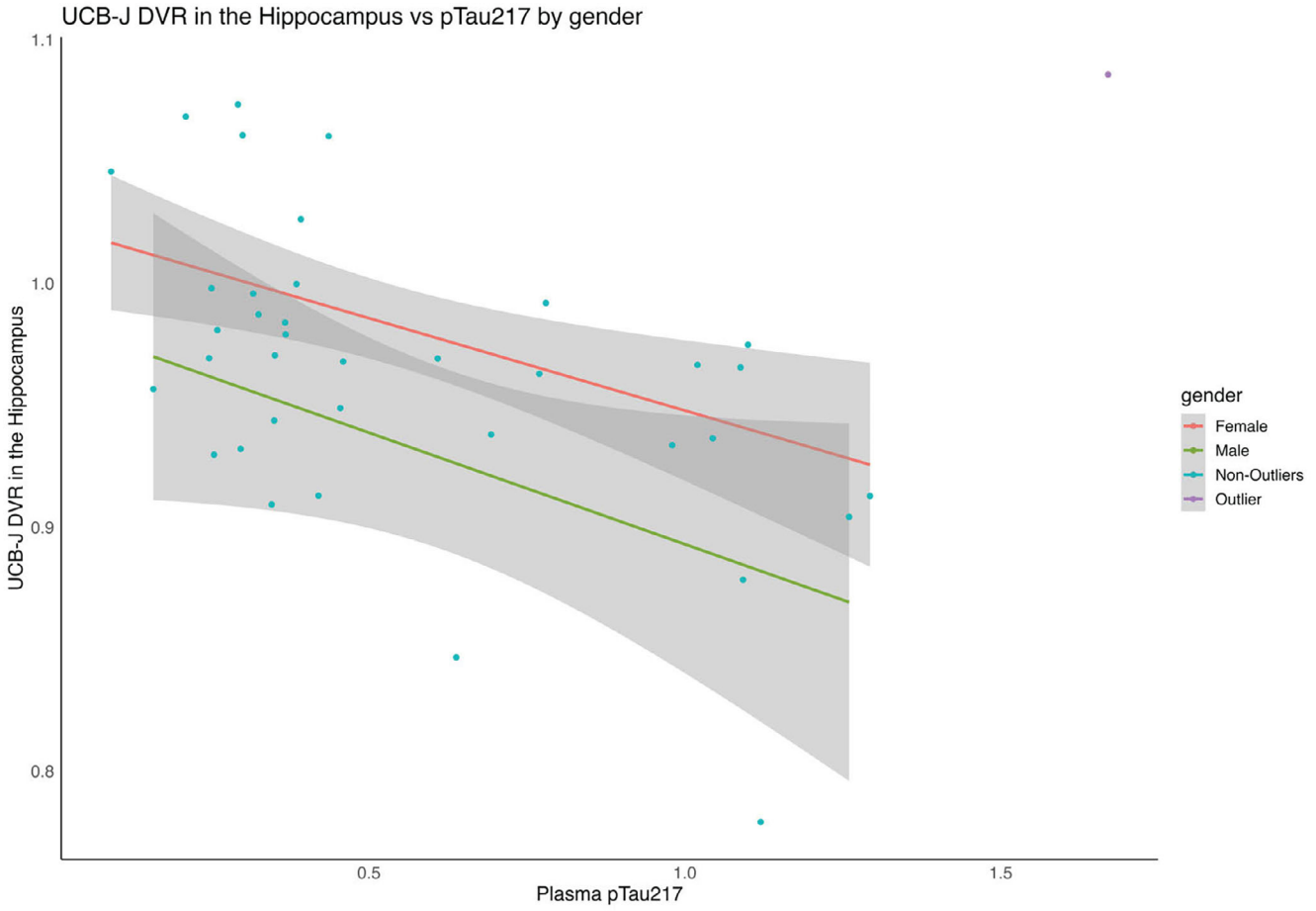

Figure. Synaptic density in the hippocampus differs by gender
This figure displays the relationship between [C-11]UCB-J DVR in the hippocampus (y-axis) with plasma pTau217 (y-axis) by gender in the comparison performed without the outlier. While this comparison was performed with and without the outlier, Welch's t-test showed a significant difference in hippocampal UCB-J DVR between males and females without the outlier, t=2.6(18), p=0.02, though this difference was absent with the outlier included (t=1.9(18), p=0.07). The outlier is plotted here as the purple point in the upper right-hand corner. This individual was cognitively-unimpaired, amyloid positive, has a tau ([F-18]MK-6240) PET SUVR of 1.55, and the highest pTau217 concentration of 1.67 in this sample. It is important to note here that more men (6 MCI, 1 AD) than women (3 MCI) were cognitively impaired, therefore, cognitive status could have driven this relationship. Future investigations will tease apart these relationships. Abbreviations: DVR = distribution volume ratio; pTau217 = tau phosphorylated at amino acid residue 217; SUVR = standardized uptake value ratio.