



Characterizing the relationship between plasma β -synuclein and synaptic density in adults with and without cognitive impairment



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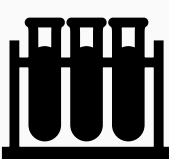
BACKGROUND

Synaptic degeneration is a key link between pathology and cognitive impairment in Alzheimer's disease (AD). β -synuclein has emerged as a candidate blood biomarker for synaptic degeneration in AD, with higher levels associated with amyloid pathology and cognitive impairment. However, the relationship between plasma β -synuclein and synaptic density measured with [¹¹C]UCB-J PET remains unclear.

OBJECTIVE & HYPOTHESIS

In this study, we sought to investigate associations between plasma β -synuclein and synaptic vesicle density as indicated by [¹¹C]UCB-J PET distribution volume ratios (DVR) in participants spanning the Alzheimer's disease continuum, and the extent to which relationships are moderated by clinical diagnosis and amyloid status. We hypothesized that there would be a significant negative association between plasma β -synuclein and UCB-J DVR in regions vulnerable to Alzheimer's disease pathology and synaptic degeneration.

METHODS



Plasma β -synuclein

Plasma β -synuclein was measured by immunoprecipitation mass spectrometry (IP-MS) as previously described.[1]



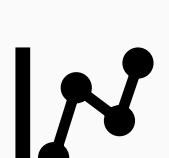
[¹¹C]UCB-J PET

UCB-J PET scans were acquired from 0-70 minutes post-injection, and distribution volume ratio (DVR) images were generated for each scan using Logan graphical analysis, with cerebellar white matter as the reference region and t*=30 minutes.



[¹¹C]PiB PET

Parametric DVR images representing PiB-specific binding were generated using Logan graphical analysis as previously described.[2] A previously established PiB threshold of 21.6 CL [3] was used to determine β -amyloid positivity for each participant.



Statistical Analysis

General linear models (R, version 4.4.2) were used to test associations between plasma β -synuclein and synaptic density. Primary outcomes included whole-brain UCB-J DVR, and UCB-J DVR in regions vulnerable to early development of AD pathology and synaptic degeneration, including the hippocampus, entorhinal cortex, and parahippocampal gyrus. To better understand how relationships between plasma β -synuclein and UCB-J DVR may be modulated by disease stage, secondary analyses tested for moderation of relationships by diagnosis and A β plaque burden as determined by PiB-PET

DEMOGRAPHIC & CLINICAL CHARACTERISTICS

Variable	Overall N = 83	CU A- N = 37	CU A+ N = 20	Impaired A+ N = 26	p-value	Pairwise Comparisons		
						CU A- vs. CU A+	CU A- vs. Impaired A+	CU A+ vs. Impaired A+
Sex					<0.001*	0.077	<0.001	0.13
Female	45 (54%)	28 (76%)	10 (50%)	7 (27%)				
Male	38 (46%)	9 (24%)	10 (50%)	19 (73%)				
Primary Race					0.3*	>0.9	0.2	0.3
Other	10 (12%)	6 (16%)	<5 (<20%)	<5 (<20%)				
White	73 (88%)	31 (84%)	>15 (>80%)	>20 (>80%)				
Age at blood draw, years	72.59 (7.27)	68.48 (5.91)	73.95 (6.75)	77.39 (6.15)	<0.001 [†]	0.003	<0.001	0.11
Difference between blood draw and PET scan, years	0.58 (0.96)	0.64 (1.10)	0.27 (0.69)	0.74 (0.90)	0.5 [‡]	0.3	0.7	0.2
Plasma β -Synuclein, pg/mL	9.63 (4.26)	7.51 (3.16)	9.63 (3.44)	12.66 (4.48)	<0.001 [†]	0.016	<0.001	0.014
Average UCB-J DVR (Cortical)	2.01 (0.18)	2.05 (0.19)	2.04 (0.15)	1.93 (0.15)	0.041 [†]	0.5	0.016	0.084
UCB-J DVR, Hippocampus	1.58 (0.16)	1.65 (0.12)	1.60 (0.12)	1.46 (0.17)	<0.001 [†]	0.2	<0.001	0.001
UCB-J DVR, Parahippocampal Gyrus	1.68 (0.17)	1.75 (0.15)	1.71 (0.10)	1.57 (0.18)	<0.001 [†]	0.2	<0.001	0.003
UCB-J DVR, Entorhinal Cortex	1.59 (0.18)	1.63 (0.16)	1.67 (0.12)	1.46 (0.18)	<0.001 [†]	0.4	<0.001	<0.001

Note: Continuous variables presented as mean (standard deviation) and categorical variables presented as n (%). Primary race was self-reported by participants, and races classified as Other include American Indian or Alaska Native, and Black or African American. P-values represent results of Fisher's exact test for categorical variables and Kruskal-Wallis with Dunn's post-hoc testing for continuous variables.

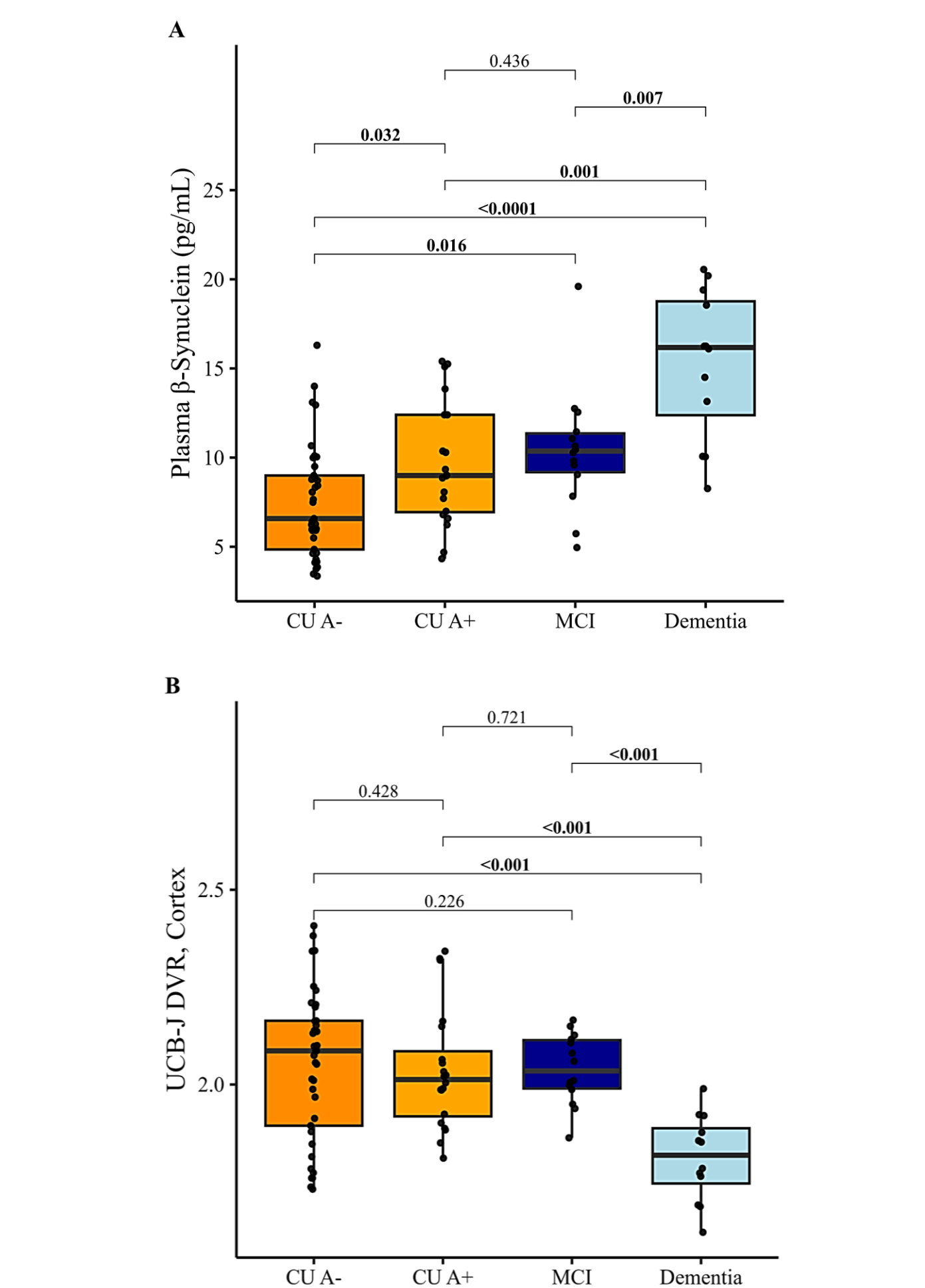
Abbreviations: AD, Alzheimer's disease; CU, cognitively unimpaired; MCI, mild cognitive impairment; A+, β -amyloid positive as determined by PiB-PET; PET, positron emission tomography

*Fisher's exact test

[†]Kruskal-Wallis test

FIGURES & TABLES

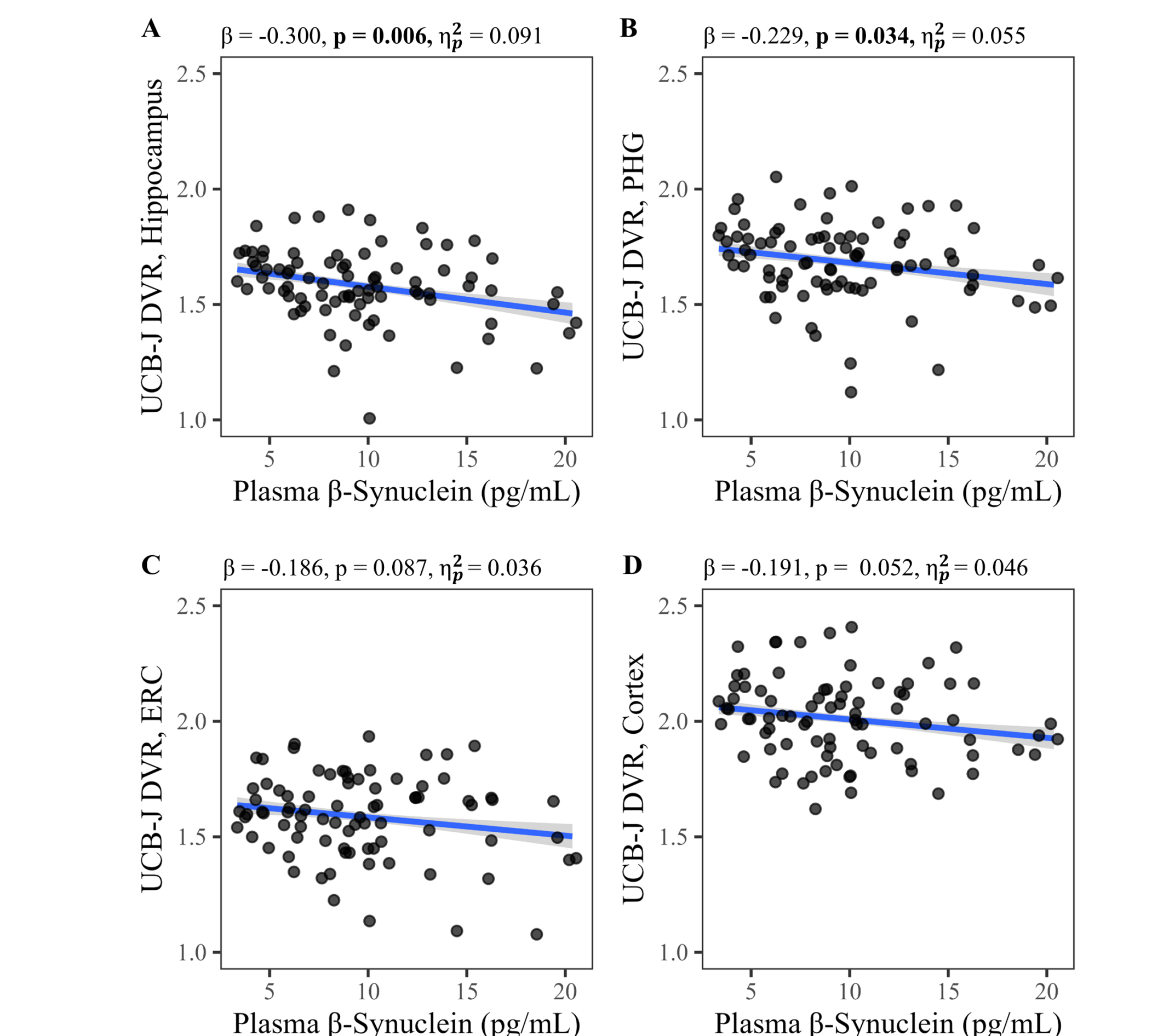
Figure 1. Plasma β -synuclein and UCB-J DVR by diagnosis and amyloid status



Box plots depict plasma β -synuclein concentrations (A) and cortical UCB-J distribution volume ratios (B) by diagnosis and amyloid status. P-values represent results of linear regression with robust standard errors to test the relationship between diagnosis group and plasma β -synuclein or UCB-J DVR while controlling for sex, age at measurement, and PET scanner type where appropriate.

Abbreviations: AD, Alzheimer's disease; CU, cognitively unimpaired; MCI, mild cognitive impairment; A+, β -amyloid positive as determined by PiB-PET; PET, positron emission tomography

Figure 2. Associations between plasma β -synuclein and UCB-J DVR



Scatter plots depict associations between plasma β -synuclein and volume-weighted UCB-J PET DVR in the hippocampus (A), parahippocampal gyrus (B), entorhinal cortex (C), and cortex (D). Relationships are presented as β (standardized coefficient) and p-values from general linear models while controlling for PET scanner type. Negative associations were statistically significant in hippocampus and parahippocampal gyrus (B-C). Relationships were not significantly moderated by diagnosis or amyloid plaque burden, and relationships did not remain statistically significant after additionally controlling for sex, age at PET scan, and time between blood draw and PET scan.

Abbreviations: CU, cognitively unimpaired; A+, β -amyloid positive as determined by PiB-PET; PET, positron emission tomography; DVR, distribution volume ratio; PHG parahippocampal gyrus; ERC entorhinal cortex

RESULTS

- We observed a significant negative association between plasma β -synuclein and UCB-J DVR in the hippocampus and parahippocampal gyrus while controlling for PET scanner
- Relationships between plasma β -synuclein and UCB-J DVR were not significantly moderated by diagnosis or amyloid status in this cohort, and relationships were no longer statistically significant after additionally controlling for sex, age at PET scan, and time between blood draw and PET scan

CONCLUSIONS

Results from this study support prior work showing a preclinical rise in plasma β -synuclein and positive correlation with amyloid pathology. Moreover, the significant correlation between β -synuclein and regional synaptic density is a novel finding, further supporting β -synuclein as a promising blood biomarker of synaptic degeneration. Longitudinal studies will shed more light on the complementary nature of fluid and imaging biomarkers in understanding temporal dynamics of synaptic degeneration in AD.

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