

Associations between regional [C-11]UCB-J PET and blood proteomic biomarkers

Kao Lee Yang¹, Alexandra DiFilippo², Max McLachlan³, Darby Peter¹, Yue Ma¹, Ramiro Eduardo Rea Reyes⁴, Rachael Wilson⁴, Bradley Christian³, Sterling Johnson^{1,4,5}, Henrik Zetterberg^{1,4,6,7,8,9}, & Barbara Bendlin^{1,4}



Wisconsin Alzheimer's Disease Research Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

¹Wisconsin Alzheimer's Disease Research Center, University of Wisconsin, Madison, WI USA
²Yale University, New Haven, CT, USA
³Department of Medical Physics, University of Wisconsin, Madison, WI USA
⁴Wisconsin Alzheimer's Institute, University of Wisconsin, Madison, WI USA
⁵Geriatric Research Education and Clinical Center, William S. Middleton Veterans Hospital, Madison, WI, USA

⁶Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden
⁷Department of Neurodegenerative Disease, University College London Institute of Neurology, Queen Square, London, UK
⁸UK Dementia Research Institute at University College London, London, UK
⁹Hong Kong Center for Neurodegenerative Diseases, Hong Kong, China



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BACKGROUND

- Alzheimer's disease (AD) dementia is characterized by widespread synaptic loss^{1,2}.
- [C-11]UCB-J PET provides an *in vivo* quantification of synapse density in AD³. Fluid biomarker analysis provides complementary information about synaptic dysfunction and loss, as well as other processes potentially related to neurodegenerative disease.
- However, little is known about the associations between blood proteins quantified using an ultra-high-sensitivity Nucleic acid Linked Immuno-Sandwich Assay (NULISA) CNS proteomic platform⁴ and synaptic density measured with UCB-J PET.

OBJECTIVES

This preliminary analysis examined the relationship between NULISA-measured CNS proteins and UCB-J PET.

METHODS

- Participants were recruited from the Wisconsin Alzheimer's Disease Research Center and Wisconsin Registry for Alzheimer's Prevention.
- We utilized data from 28 participants with available [C-11]UCB-J PET and plasma NULISA data.
- Synaptic density was quantified from [C-11]UCB-J PET using Logan Graphical Analysis with a cerebellar white matter reference region.
- We identified regions of interest (ROIs) using *FreeSurfer* T1w-MRI parcellation: hippocampus, entorhinal cortex, parahippocampal gyrus, fusiform gyrus, amygdala, and temporal pole.
- Plasma samples were analyzed using the NULISAseq CNS Disease Panel on the Alamar Argo HT platform and sequencing was performed on an Illumina NextSeq1000. A total of 121 proteins were assayed.
- We examined overall associations between synaptic density and plasma protein levels using Pearson correlations. Results that survived FDR correction were considered significant.

FIGURES & TABLES

Table. Correlations between [C-11]UCB-J DVR in regions of interest with plasma proteins of inflammation and neurodegeneration

Region of interest	Protein	Pearson r	p-value	FDR-corrected p-value
Amygdala	ENO2	0.394	0.038	0.045
Amygdala	IL16	0.398	0.036	0.045
Amygdala	VSNL1	-0.469	0.012	0.036
Entorhinal Cortex	CCL3	-0.386	0.043	0.045
Entorhinal Cortex	CHI3L1	-0.573	0.001	0.030
Entorhinal Cortex	ENO2	0.388	0.041	0.045
Entorhinal Cortex	NPTX2	-0.434	0.021	0.045
Entorhinal Cortex	TREM1	-0.483	0.009	0.036
Entorhinal Cortex	VEGFA	-0.386	0.043	0.045
Fusiform gyrus	CXCL1	0.421	0.026	0.045
Hippocampus	CCL22	0.518	0.005	0.033
Hippocampus	IL16	0.404	0.033	0.045
Hippocampus	IL2	0.375	0.049	0.049
Hippocampus	SAA1	0.474	0.011	0.036
Parahippocampal gyrus	CCL22	0.488	0.008	0.036
Parahippocampal gyrus	CXCL1	0.430	0.022	0.045
Parahippocampal gyrus	SAA1	0.408	0.031	0.045
Temporal Pole	IL5	-0.385	0.043	0.045
Temporal Pole	NPTX2	-0.399	0.035	0.045
Temporal Pole	VEGFA	-0.447	0.017	0.045
Temporal Pole	VSNL1	-0.523	0.004	0.033

Abbreviations
ENO2 = Enolase 2;
IL16 = Interleukin 16;
VSNL1 = Visinin-like protein 1;
CCL3 = C-C motif chemokine ligand 3;
CHI3L1 = Chitinase 3-like 1;
NPTX2 = Neuronal pentraxin 2;
TREM1 = Triggering receptor expressed on myeloid cells 1;
VEGFA = Vascular endothelial growth factor A;
CXCL1 = C-X-C motif chemokine ligand 1;
CCL22 = C-C motif chemokine ligand 22;
IL2 = Interleukin 2;
SAA1 = Serum amyloid A1;
IL5 = Interleukin 5.

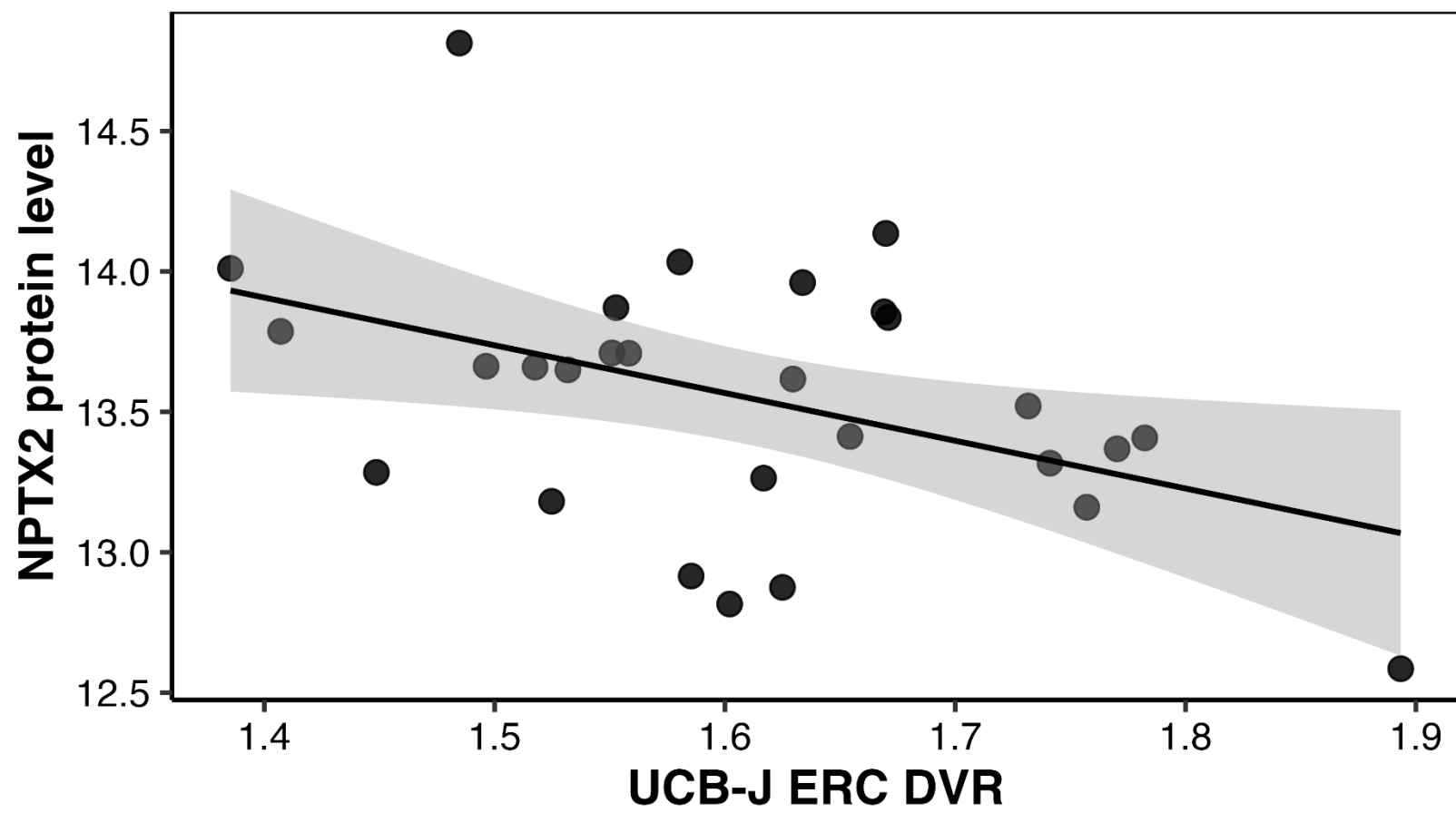


Figure 1. UCB-J ERC DVR and NPTX2 correlation

This figure displays the Pearson correlation between [C-11]UCB-J DVR in the entorhinal cortex (ERC) and NPTX2 levels. Lower UCB-J ERC DVR was associated with higher plasma NPTX2 levels. This correlation was moderate in magnitude and statistically significant after FDR correction ($r = -0.43$, $p = 0.021$, FDR $q = 0.045$).

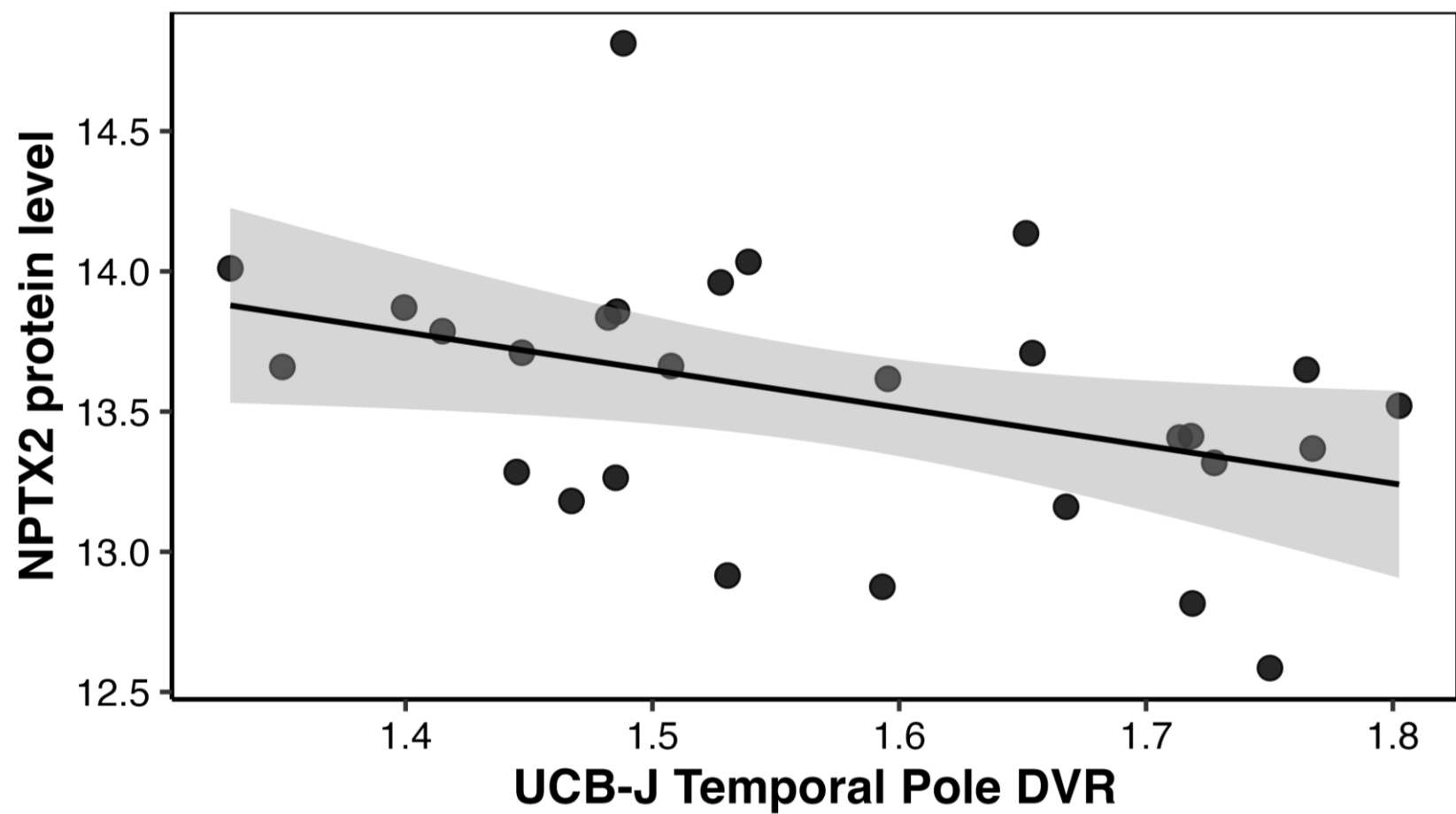


Figure 2: UCB-J Temporal Pole DVR and NPTX2

This figure displays the Pearson correlation between [C-11]UCB-J DVR in the temporal pole and NPTX2 levels. Lower UCB-J temporal pole DVR was associated with higher plasma NPTX2 levels. This relationship was moderate in magnitude and remained significant after FDR correction ($r = -0.39$, $p = 0.035$, FDR $q = 0.045$).

RESULTS

- Participants (N=28) were mostly middle-aged (mean = 72.5 ± 7.1 years), female (n=17, 60.7%), amyloid PET positive (n = 20, 71.4%), and *APOE* $\epsilon 4$ carriers (n=18, 64.3%). The analysis included participants who were cognitively-unimpaired (n = 20, 71.4%), diagnosed with MCI (n = 7, 25%) and one person with dementia, (n = 1, 3.6%). Most participants identified as White (n = 22, 78.6%), 3 identified as Black or African American (10.7%), and 3 as American Indian or Alaska Native (10.7%).
- We observed significant correlations between synaptic density and plasma biomarkers of inflammation and neurodegeneration (Table) across all ROIs.
- Synaptic density in the entorhinal cortex (Figure 1) and temporal pole (Figure 2) were negatively correlated with plasma neuronal pentraxin 2 (NPTX2), a potential biomarker of synaptic loss.

CONCLUSIONS

Our results suggest that PET measures of synaptic density may reflect ongoing processes related to neurodegeneration and inflammation, as evidenced by several relationships between UCB-J and fluid biomarkers on the NULISA panel. Unexpectedly, lower UCB-J DVR in the ERC and temporal pole, regions that are vulnerable to AD-related degeneration, were associated with higher NPTX2 in the plasma. Prior evidence has shown NPTX2 to be decreased in postmortem AD brains⁵. Additional studies are needed to better understand these paradoxical findings. Future studies are also needed to determine the impact of diagnostic status on these relationships, as well as longitudinal trajectories.

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