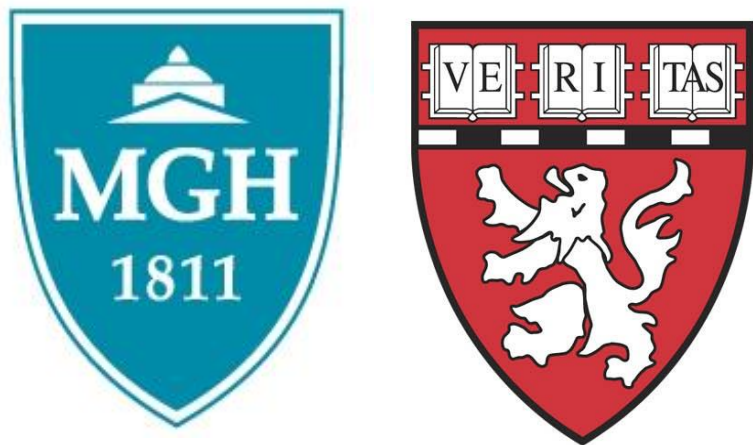
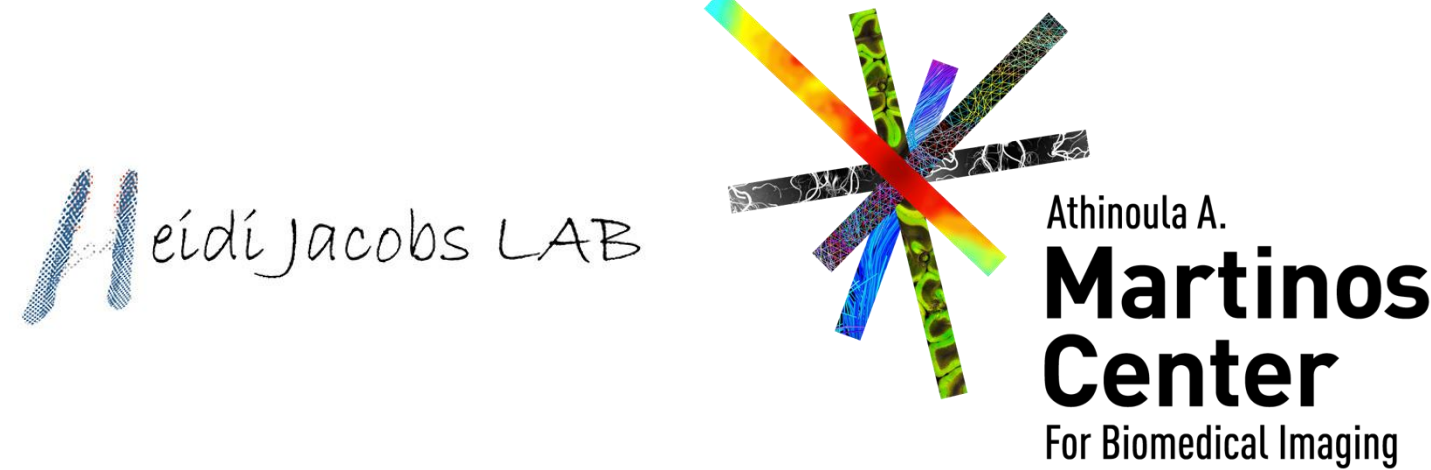




Locus Coeruleus Metabolic Activity is Associated with Age, and Interacts with Amyloid Burden to predict Tau Pathology in Cognitively Unimpaired Older Adults



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Background

The locus coeruleus (LC) is one of the earliest sites of tau pathology in Alzheimer's disease (AD)¹, and is vulnerable to neurodegeneration, with the rostral and middle regions particularly affected ²⁻³. Previous work has shown that higher LC metabolism is protective on tau accumulation and cognitive decline ⁴⁻⁵. As amyloid starts accumulating, individuals become particularly vulnerable to tau progression suggesting that LC metabolism may play a critical role during this early disease stage. Here, we investigate associations between LC FDG-PET signal and tau PET across amyloid stages in preclinical disease. We further explored the selective vulnerability across the rostral-caudal axis of the LC in the preclinical stage.

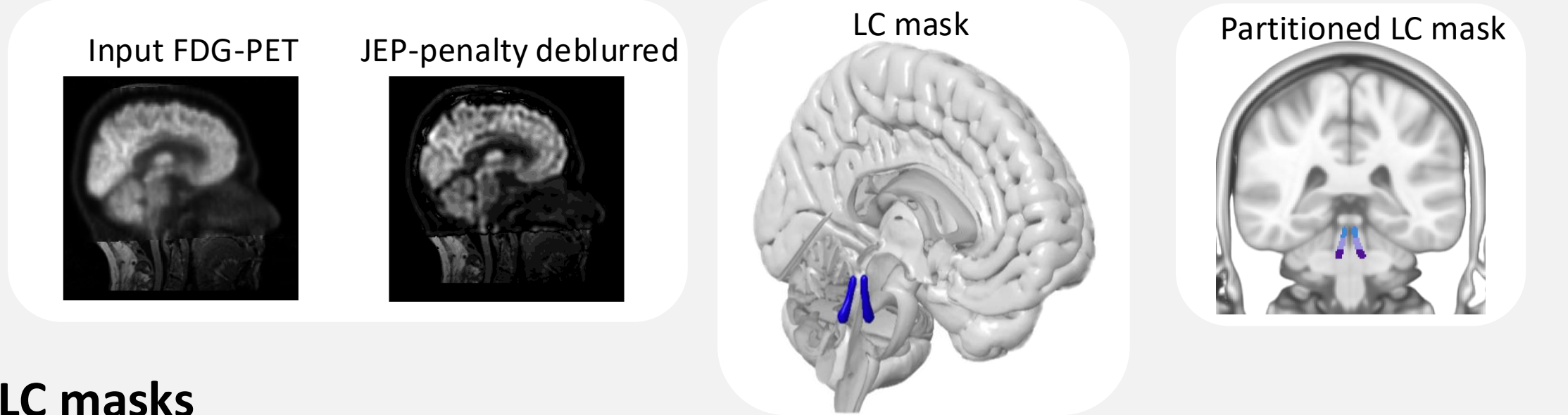
Aim: To examine whether LC FDG-PET signal is associated with tau PET in the context of amyloid burden, and whether this association depends on amyloid stage in cognitively unimpaired older adults.

Methods

Cohort: N= 118 cognitively unimpaired older adults (CDR = 0) from the Harvard Aging Brain Study (HABS) were included.

FDG PET analysis

LC FDG-PET signal was extracted from FDG-PET images aligned to the native space T1 and processed using an MR joint-entropy-prior penalty deblurring algorithm developed for small brainstem regions⁶. Processed FDG-PET images were referenced to cerebellar white matter. The smoothed LC template⁷ was registered to native space T1.



LC masks

A smoothed LC template⁷ was used to extract overall LC signal. The binarized LC mask was partitioned into three equal-length segments along its rostro-caudal extent, based on the bounding voxel coordinates of the mask, to define rostral, middle, and caudal subregions.

AD pathology PET markers

Global beta-amyloid burden was defined using PiB [¹¹C Pittsburgh Compound B] PET (DVR) FLR, and meta-ROI tau burden was defined using FTP [¹⁸F Flortaucipir] PET (SUVR) scans (both PVC-corrected; referenced to cerebellar gray). PiB was transformed to Centiloids (CL). Regional information was extracted with FreeSurfer v8 derived regions.

* meta-ROI: bilateral entorhinal cortices, amygdala, fusiform gyrus, parahippocampal cortex, inferior and middle temporal cortices, weighted by regional volume.

Amyloid groups

Participants were stratified into amyloid-negative (CL < 10), intermediate or evolving (CL 10-30), and established (CL > 30) amyloid groups, reflecting the AMYPAD consortium criteria ⁸.

Statistics

Linear regressions related LC FDG-PET signal to age, meta-ROI FTP burden, and global PiB FLR. Age and sex were used as covariate in models on PiB and FTP.

Characteristics of participants

Table 1. Characteristics of participants. The mean and standard deviation are given for age, education level, LC FDG-PET, MMSE score, PiB FLR, and meta-ROI FTP. All participants had a CDR score of 0.

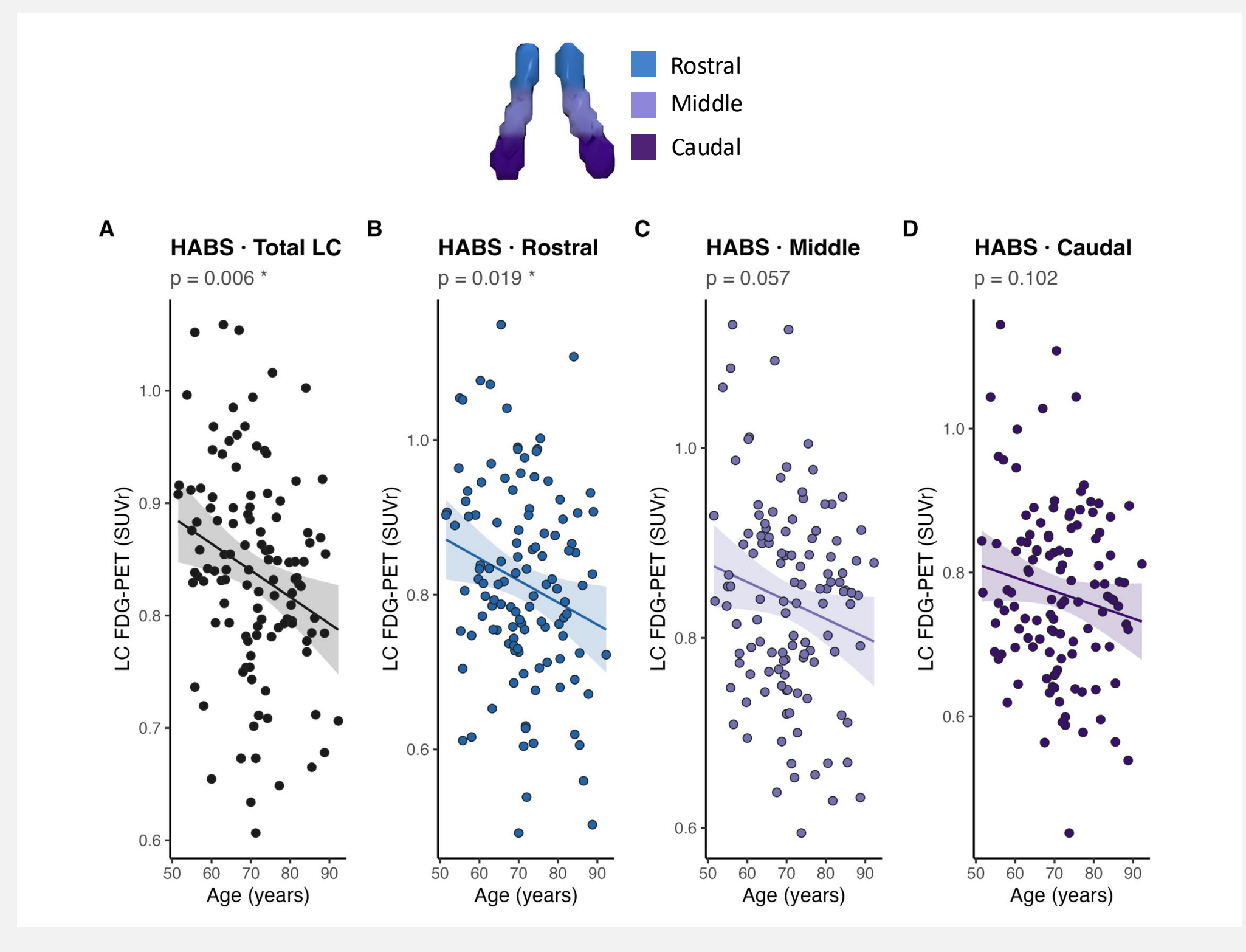
Variable	Overall N = 118 ¹	Amyloid-negative N = 57 ¹	Intermediate N = 39 ¹	Established N = 22 ¹	p-value ²
Age (years)	70.9 (9.7)	67.4 (9.7)	72.7 (8.8)	77.0 (7.4)	<0.001
Sex					0.7
Female	67 (57%)	32 (56%)	24 (62%)	11 (50%)	
Male	51 (43%)	25 (44%)	15 (38%)	11 (50%)	
Education (years)	15.8 (2.9)	16.1 (2.6)	15.6 (3.2)	15.5 (3.0)	0.7
APOEε4 status					<0.001
ε4-	88 (75%)	49 (86%)	30 (77%)	9 (41%)	
ε4+	30 (25%)	8 (14%)	9 (23%)	13 (59%)	
LC FDG-PET (SUVR)	0.84 (0.1)	0.86 (0.1)	0.81 (0.1)	0.84 (0.1)	0.018
MMSE (total)	29.3 (1.0)	29.4 (1.0)	29.2 (1.0)	29.3 (1.0)	0.8
PiB CL (PVC)	21.2 (26.6)	6.8 (2.5)	14.6 (4.1)	70.6 (26.9)	<0.001
Meta-ROI FTP SUVR (PVC)	1.4 (0.2)	1.3 (0.)	1.4 (0.1)	1.5 (0.2)	<0.001

¹Mean (SD); n (%)

²Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Abbreviations: LC = locus coeruleus, CDR = clinical dementia rating scale, FDG = [¹⁸F]Fluorodeoxyglucose, FTP = [¹⁸F]Flortaucipir, SUVR = Standard Uptake Value referenced to cerebellar gray matter, PiB = Pittsburgh Compound B, PET = Positron Emission Tomography, MMSE = Mini-Mental State Examination, CL = centiloid, PVC = partial volume corrected.

LC-age association strongest in rostral LC

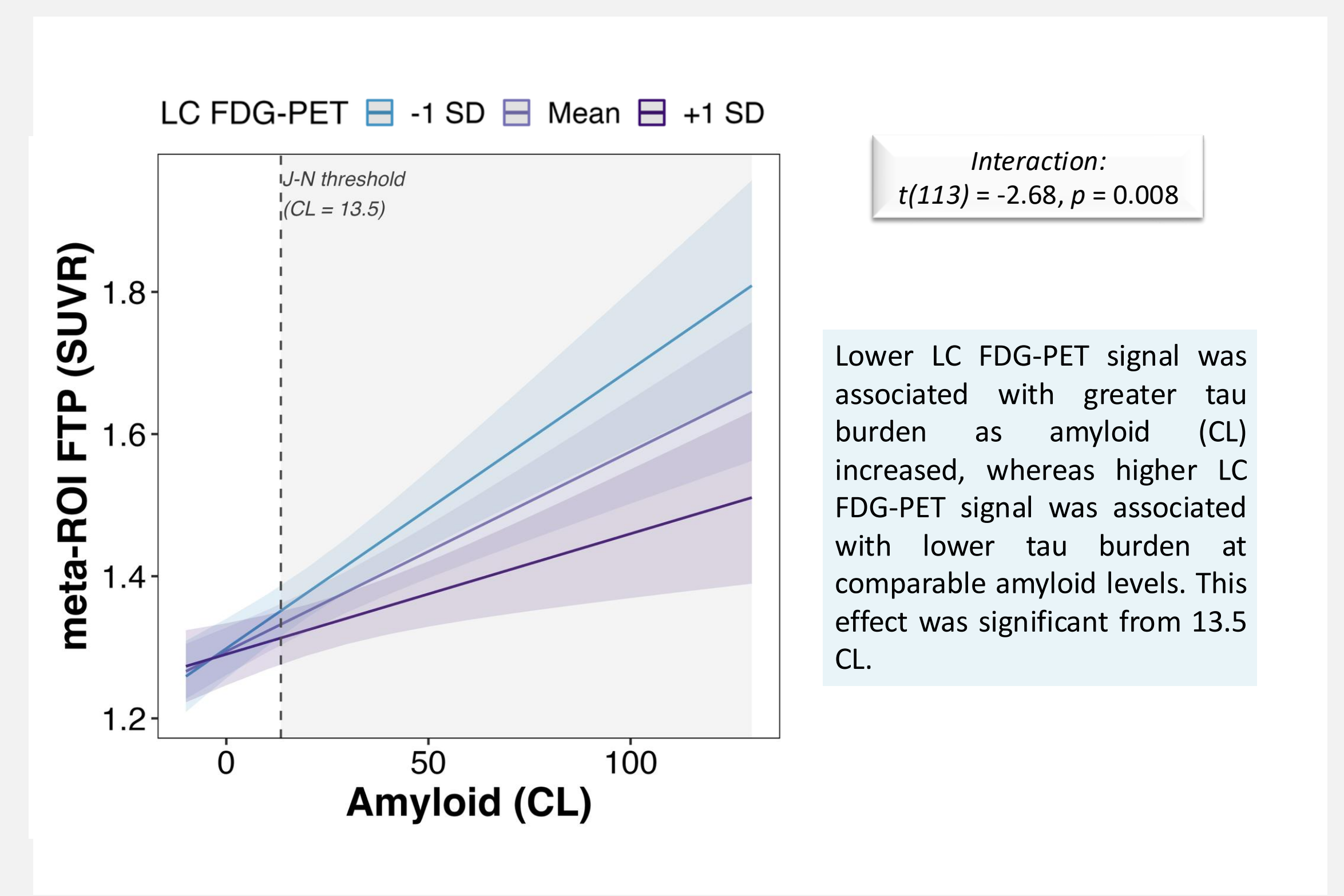


Conclusion & Implications

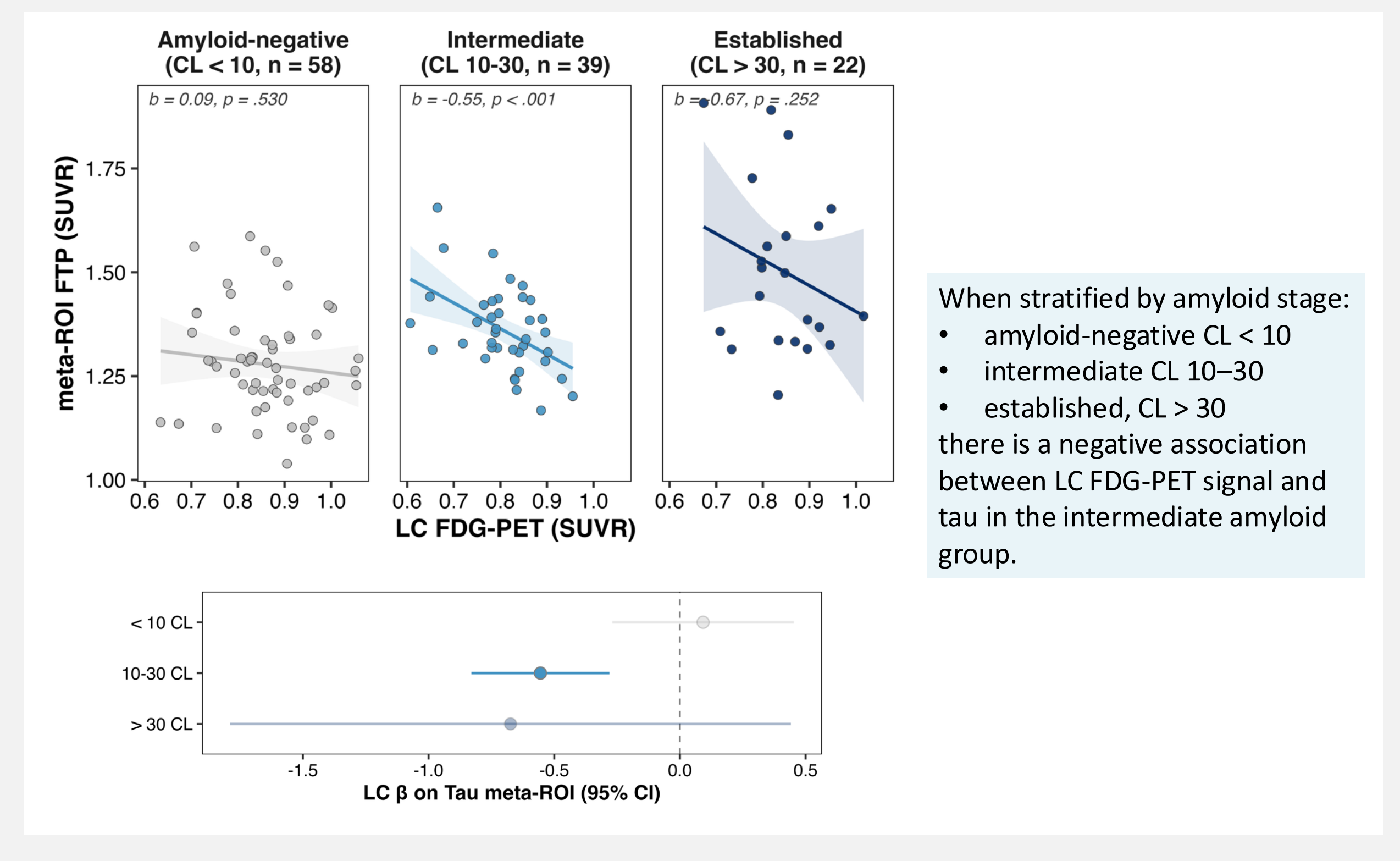
LC metabolism, measured with FDG-PET, is lower in older individuals and is sensitive to early amyloid accumulation, with age-related reductions most prominent in the rostral LC.

Lower LC metabolism may amplify tau pathology even at sub-threshold amyloid levels (>13.5 CL), with this vulnerability most pronounced during the intermediate amyloid stage. This positions the LC as an early vulnerability factor in the Alzheimer's disease cascade.

LC FDG-PET interacts with amyloid to predict tau burden



LC-tau association specific to intermediate amyloid stage



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