



Lower resting-state phasic locus coeruleus activity is associated with tau accumulation, and cognitive decline in preclinical AD



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1. Background

- The noradrenergic locus coeruleus (LC) is one of the earliest regions accumulating tau pathology in Alzheimer's Disease (AD)¹.
- LC lesioning in AD animal models was linked to cortical NE depletion, astrogliosis, and accumulation of cortical tau and amyloid-beta (A β) pathology².
- Previous animal and human imaging research suggested that novelty-like phasic LC activity protects against tau's downstream effects in cognition^{3,4,5}.

The main objectives of the present study are

- To investigate whether in-vivo resting-state phasic LC activity is associated with the accumulation of cortical tau pathology and cognitive decline in preclinical AD.
- To examine whether astrogliosis exacerbates the impact of reduced LC phasic activity on tau pathology

2. Methods

Cohort 1

- 92 Cognitively healthy individuals from the Harvard Aging Brain Study.

Imaging

BOLD-fMRI

- 3T resting-state BOLD-fMRI (144 whole-brain T2*-EPI volumes).
- Voxel size = 2 mm³ isotropic, TR/TE = 800/37 ms.

Tau-PET

- 18F-Flortaucipir-PET (SUVR, PVC).
- Cross-sectional data: N=92; Longitudinal data: N=71

Cognition

- Longitudinal data up to 8 years (Mean (M) = 2.93, Standard Deviation (SD) = 12.24); 546 observations in total.
- Cognitive composite score (PACC v5)

Cohort 2

- 68 older adults from a lifespan study, Maastricht University, The Netherlands

Imaging

BOLD-fMRI

- 7T resting-state BOLD-fMRI (230 whole-brain T2*-EPI volumes).
- Voxel size = 1.25 mm³ isotropic, TR/TE = 800/37 ms.

Plasma markers

- pTau-231 was measured using in-house Simoa methods.

Detection of phasic LC activity

- Phasic-like LC activity events were defined at BOLD-fMRI signal peaks, maximizing activity integration (spatial entropy) within the entorhinal cortex (EC).
- The proportion of LC activity explained by the detected events was quantified using the R²-coefficient.

Table 1: Demographics and characteristics of participants in study 1

n, No.	92
Age (years)	74.50 [69.25, 81.88]
Sex, No. (%) = Female	56 (60.8)
Education (years)	16.50 [15.50, 18.00]
Neocortical (FLR) PiB (DVR-PVC)	1.21 [1.17, 1.35]
Elevated PiB, No. (%)	25 (27.17)
NP follow-up time (years)	6.2 [5.29, 6.55]
Entorhinal (EC) tau (SUVR-PVC)	1.30 [1.13, 1.55]
Inferior temporal (IT) tau (SUVR-PVC)	1.35 [1.27, 1.46]
LC phasic activity (a.u.)	0.17 [0.15, 0.19]

Table 1. Data are presented as medians [and interquartile ranges] and proportions for dichotomous data.

Abbreviations: Arbitrary units (a.u.), Distribution Volume Ratio (DVR), Frontal, laterotemporal and retrosplenial cortices (FLR), Locus coeruleus (LC), Neuropsychological evaluation (NP), partial volume corrected (PVC), Pittsburgh compound B (PiB), Standard Deviation (S.D.), Standardized uptake value ratio (SUVR).

3.1. Lower LC phasic activity is related to greater cortical tau accumulation

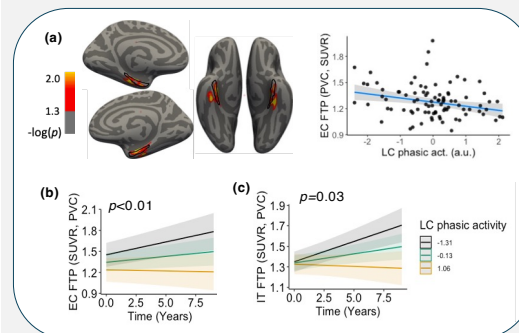


Fig 1. (a) Cortical vertex-wise associations between FTP-PET and LC phasic activity. Lower LC phasic activity was associated with greater bilateral EC tau deposition. (b-c) Lower LC phasic activity was also associated with faster tau accumulation in the EC (b) and inferior temporal cortex (IT) (c).

Abbreviations: entorhinal cortex (EC), inferior-temporal cortex (IT), 18F-Flortaucipir (FTP), natural logarithm (log), locus coeruleus (LC), Partial volume corrected (PVC), Standardized uptake value ratio (SUVR).

Table 2: Demographics and characteristics of participants in study 2

n, No.	68
Age (Years)	60.50 [52, 70]
Sex, No. (%) = Female	34 (50)
Education (Years)	15 [14, 15]
p-tau231 (pg/mL)	7.93 [6.43, 9.49]
GFAP (pg/mL)	133 [111, 179]
APOE, No. (%) = E4+	20 (32.8)

Table 1. Data are presented as medians [and interquartile ranges] and proportions for dichotomous data.

Abbreviations: picograms (pg), milliliter (mL), Apolipoprotein E (APOE), Glial Fibrillary Acidic Protein (GFAP), phosphorylated tau (p-tau)

3.2. Astrocyte reactivity modulates the negative relationship between spontaneous LC phasic activity and plasma tau phosphorylation

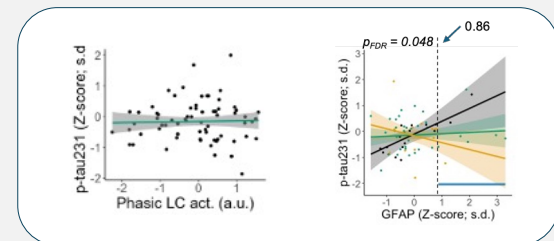


Fig 4. Left panel: No relationship between spontaneous LC phasic activity and o-tau231. Right panel: Lower LC phasic activity was related to elevated p-tau231 levels, particularly at elevated GFAP levels.

Abbreviations: Glial Fibrillary Acidic Protein (GFAP), phosphorylated tau (p-tau), locus coeruleus (LC); arbitrary units (a.u.), standard deviation (s.d.), false discovery rate (FDR).

4. Conclusions

- Our findings show that lower levels of spontaneous phasic LC activity are related to faster accumulation of cortical tau pathology and steeper downstream AD-related cognitive decline.
- The also suggest that astrocyte reactivity may play an important gating role between C-NE system dysfunction and emerging tau pathology
- These results could inform the design of targeted interventions to support optimal LC phasic activity, promoting cognitive resilience.

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