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RESEARCH ARTICLE

Locus coeruleus integrity and neuropsychiatric symptoms in a cohort of early- and late-onset Alzheimer's disease

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Abstract

INTRODUCTION: Early-onset Alzheimer's disease (EOAD) shows a higher burden of neuropsychiatric symptoms than late-onset Alzheimer's disease (LOAD). We aim to determine the differences in the severity of neuropsychiatric symptoms and locus coeruleus (LC) integrity between EOAD and LOAD accounting for disease stage.

METHODS: One hundred four subjects with AD diagnosis and 32 healthy controls were included. Participants underwent magnetic resonance imaging (MRI) to measure LC integrity, measures of noradrenaline levels in cerebrospinal fluid (CSF) and Neuropsychiatric Inventory (NPI). We analyzed LC-noradrenaline measurements and clinical and Alzheimer's disease (AD) biomarker associations.

RESULTS: EOAD showed higher NPI scores, lower LC integrity, and similar levels of CSF noradrenaline compared to LOAD. Notably, EOAD exhibited lower LC integrity independently of disease stage. LC integrity negatively correlated with neuropsychiatric symptoms. Noradrenaline levels were increased in AD correlating with AD biomarkers.

Lea T. Grinberg and Raquel Sánchez-Valle contributed equally to this work.

DISCUSSION: Decreased LC integrity negatively contributes to neuropsychiatric symptoms. The higher LC degeneration in EOAD compared to LOAD could explain the more severe neuropsychiatric symptoms in EOAD.

KEYWORDS
Alzheimer's disease, early-onset Alzheimer's disease, locus coeruleus, neuromodulatory subcortical systems, neuropsychiatric symptoms, selective vulnerability

Highlights

- LC degeneration is greater in early-onset AD (EOAD) compared to late-onset AD.
- Tau-derived LC degeneration drives a higher severity of neuropsychiatric symptoms.
- EOAD harbors a more profound selective vulnerability of the LC system.
- LC degeneration is associated with an increase of cerebrospinal fluid noradrenaline levels in AD.

1 | BACKGROUND

Anxiety, depression, and sleep disturbances are prevalent symptoms in individuals with Alzheimer's disease (AD), even during the earliest pathological stages.[1] These symptoms significantly affect the quality of life for both patients and their families.[2,3] However, the biological mechanisms underlying these neuropsychiatric symptoms in AD are poorly understood, hindering the development of targeted and effective treatment approaches.[4,5]

This knowledge gap is particularly significant in the case of sporadic early-onset AD (EOAD, non-familial, age at onset < 65 years), where individuals experience severe neuropsychiatric symptoms throughout the progression of the disease, which often do not respond well to antidepressant or anxiolytic medications.[5,6] Although psychosocial factors resulting from the diagnosis of dementia in younger individuals can contribute to these neuropsychiatric symptoms, emerging evidence suggests early AD-related tau degeneration of the neuromodulatory subcortical systems, such as the noradrenergic system, may also play a role.[7–9]

The locus coeruleus (LC) is a pair of nuclei with a column shape in the lateral part of the pontine tegmentum. It is the primary source of noradrenaline in the brain. The LC plays a crucial role in modulating vigilance and mood and refining higher cognitive functions through its distant connections with subcortical and cortical brain areas.[10,11] As a component of the isodendritic core, a complex network of subcortical nuclei displaying high vulnerability to AD, the LC is particularly susceptible to AD.[12–15] In fact, the LC develops AD-type tau pathological changes before the entorhinal cortex does, making the LC one of the first areas affected by AD.[12] We and others showed in *post mortem* brain tissue that the LC undergoes more significant degeneration in EOAD than in late-onset AD (LOAD),[16] which may represent the basis for why individuals with EOAD tend to exhibit a higher burden of neuropsychiatric symptoms than those with LOAD.[6]

As a result, there is increasing interest in understanding the clinical implications of LC degeneration due to AD. Advanced magnetic resonance imaging (MRI) methods, such as neuromelanin-sensitive turbo spin echo (NM-TSE), have emerged as sensitive tools for accurately measuring the structural integrity of the LC in living individuals.[17–21] Additionally, noradrenaline or noradrenaline-derived metabolites in cerebrospinal fluid (CSF) can be measured as an indirect assessment of noradrenergic function.[22,23]

These recent methodological advances allow for probing critical questions regarding the relationship between AD pathology, LC integrity, and neuropsychiatric symptoms in living individuals. This includes investigating if the age at onset (EOAD vs LOAD subtypes) affects the extent of LC deterioration, independent of the stage of AD, and how these differences impact the severity of clinical manifestations of neuropsychiatric symptoms.

To test the hypothesis that AD-driven degeneration of the LC contributes to the extent of neuropsychiatric changes observed in AD, starting at the mild symptomatic stages, we leveraged a cohort of individuals with biomarker-confirmed EOAD and LOAD to better understand the role of the noradrenergic system on the neurobiology of neuropsychiatric symptoms across the AD spectrum. We examined structural MRI and metabolite measurements (CSF noradrenaline) as indicators of LC integrity to (1) compare the integrity of the LC–noradrenergic system across progressive stages of clinical decline and its relationship with AD biomarkers, (2) determine the differences in the severity of neuropsychiatric symptoms and degeneration of the LC–noradrenergic system between EOAD and LOAD, and (3) evaluate the relationship between the degeneration of the LC–noradrenergic system and the severity of neuropsychiatric symptoms taking into account disease stage, age of onset (EOAD vs LOAD) and neuropsychiatric treatments.

2 | METHODS

2.1 | Study population

2.1.1 | Participants with AD diagnosis

The Hospital Clínic de Barcelona Institutional Review Board approved the study, and all participants gave their written, informed consent (HCB/2021/0668). All participants were recruited at the AD and Other Cognitive Disorders Unit, Hospital Clínic de Barcelona (Barcelona, Spain), and met the criteria of biomarker-based AD diagnosis in agreement with the National Institute on Aging and Alzheimer's Association (NIA-AA) diagnostic criteria.[24,25] The diagnostic protocol included a comprehensive neurological and neuropsychological evaluation, structural neuroimaging (computed tomography [CT] or MRI scan), and a lumbar puncture. In cases where the lumbar puncture was contraindicated, amyloid-positron emission tomography (PET) was performed instead.

Participants were classified into two groups (Figure 1):

1. EOAD group (age at onset [AAO] $\leq$ 65 years, $n = 34$): all patients had a typical AD CSF biomarker profile ($n = 32$) or positive amyloid-PET ($n = 2$) and fulfilled the NIA-AA criteria for mild cognitive impairment (MCI) due to AD or mild-moderate AD dementia.[24,25] Subjects with known pathogenic mutations were excluded.
2. LOAD group (AAO $\geq$ 65 years, $n = 70$): patients with a typical AD CSF profile ($n = 68$) or positive amyloid-PET ($n = 2$) fulfilling NIA-AA criteria for MCI due to AD or mild-moderate AD Dementia.[24,25]

2.1.2 | Healthy control participants

Healthy control participants were included for comparative purposes (Figure 1). All control participants performed within the normal range on a comprehensive neuropsychological battery evaluating memory, language, visuospatial, executive functions with Mini-Mental State Examination (MMSE) score $\geq$ 27, and a normal MRI scan without structural lesions (eg, stroke, tumors).

1. MRI control group ($n = 14$): A group of controls underwent neuromelanin-sensitive MRI to determine LC integrity. All of them presented normal cognition and normal levels of plasma pTau181.
2. Noradrenaline control group ($n = 18$): CSF samples of 18 controls were retrospectively included to measure CSF noradrenaline levels. All of them had normal cognition and MRI scans and normal levels of CSF AD biomarkers.

2.2 | Assessment of neuropsychiatric symptoms

Patient informants were assessed by the Neuropsychiatric Inventory (NPI) for the patients they cared for.[26] NPI included 12 behavioral domains (delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, motor disturbance, nighttime behaviors, and appetite). NPI total scores (NPI Total) reflected the sum of 12 domain scores. NPI caregiver distress was rated for each positive neuropsychiatric symptom domain on a scale of 0 to 5 points. A subsample of participants completed the Hamilton Anxiety (HAM-A) scale and Geriatric Depression Scale (GDS).[27,28]

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed and cited relevant articles. *Post mortem* studies previously analyzed the degree of locus coeruleus (LC) neuronal loss in early- and late-onset AD; however, evidence in living individuals confirming these findings in vivo is lacking. Moreover, very little is known about how these differences impact the clinical expression of neuropsychiatric symptoms.
2. **Interpretation**: Our study provides compelling evidence that neurodegeneration of the LC system differs between early- and late-onset AD, driving higher neuropsychiatric symptoms in the former. Our study corroborates the hypothesis of more profound selective vulnerability of the LC system in early-onset presentations.
3. **Future directions**: Studies investigating the neurobiological basis of neuropsychiatric symptoms within the AD spectrum may provide insight for deciphering the selective vulnerability of the neuromodulatory subcortical system and facilitate novel treatment avenues.

2.3 | Neuropsychiatric treatment

The prescription of neuropsychiatric treatments (present/absent) was collected considering the prescription of at least one of the following categories: selective serotonin reuptake inhibitor (SSRI), serotonin antagonist and reuptake inhibitor (SARI; trazodone), noradrenergic and specific serotonergic antidepressants (NaSSA; mirtazapine) benzodiazepines, and atypical antipsychotic (quetiapine).

2.4 | MRI analyses

2.4.1 | MRI acquisition

All participants were scanned with the same 3T Siemens PRISMA-FIT System using a 20-channel head coil at the Magnetic Resonance Imaging Core Facility, IDIBAPS, located at the Hospital Clínic de Barcelona. The MRI protocol included the acquisition of the following sequences:

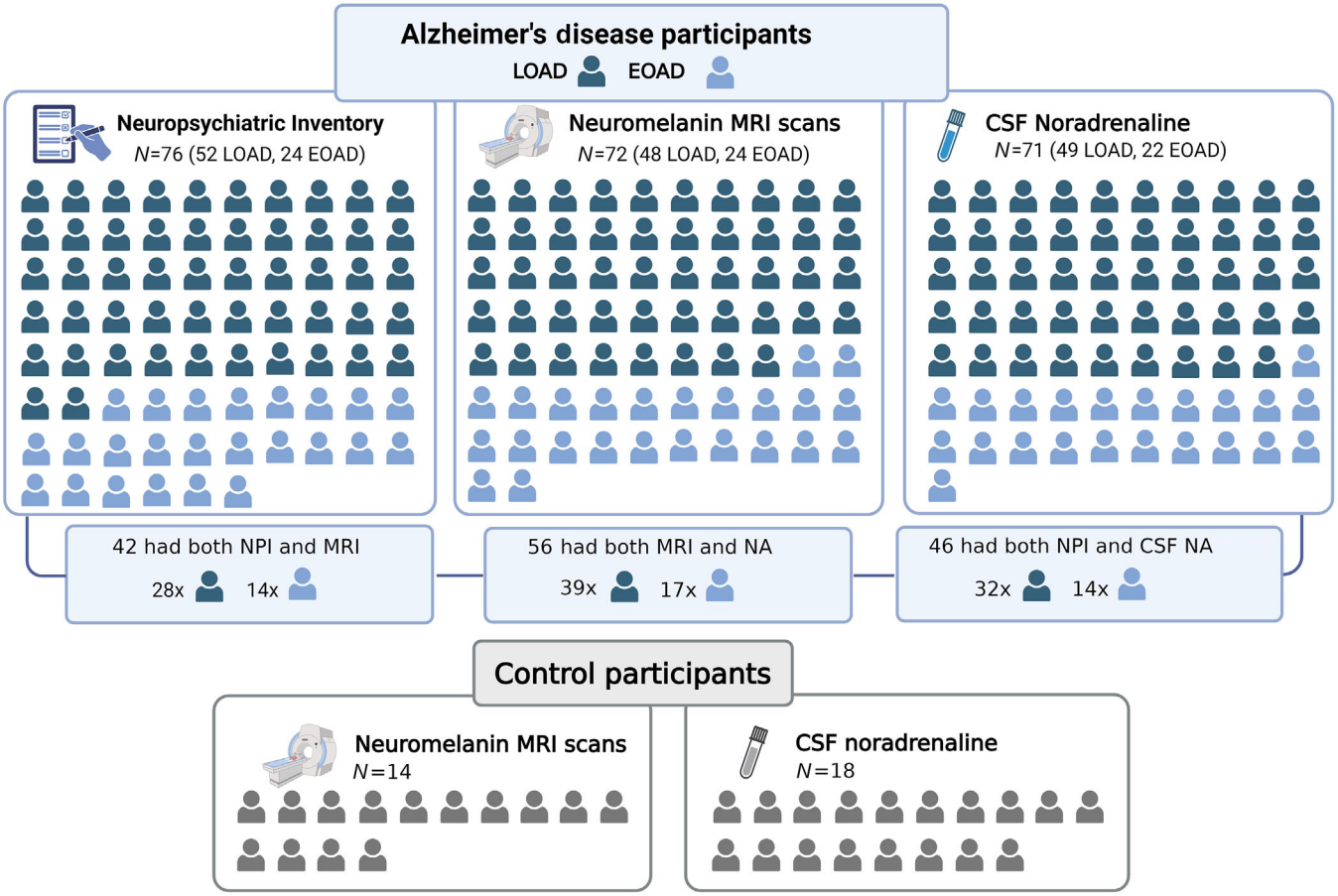

FIGURE 1 Scheme of study sample and tests performed. EOAD, early-onset Alzheimer's disease; LOAD, late-onset Alzheimer's disease. Created by Biorender.com.

1. Three-dimensional (3D) T1-weighted magnetization prepared gradient-echo (MPRAGE) sequence (Repetition time (TR) = 2300 ms, Echo Time (TE) = 2.98 ms, Inversion Time (TI) = 900 ms, flip angle = 9°, bandwidth = 240 Hz/pixel, acquisition matrix = 256 × 256 × 240, isometric voxel size = 1 mm^3).
2. Neuromelanin-sensitive high-resolution, T1-weighted TSE sequence: Aligned perpendicularly to the plane of the respective participant's brainstem (acquisition time = 10.33 min) with the following parameters: TR = 600 ms, TE = 11 ms, flip angle = 120°, bandwidth = 180 Hz/pixel, acquisition matrix = 320 × 320 × 16, voxel size = 0.5 × 0.5 × 1.8 mm^3, number of averages 7. TSE consists of 16 slices without a gap, covering the pons.

2.4.2 | Post-processing

The acquired images were processed to estimate LC integrity and volume: LC characterization was based on the LC map provided by Keren et al. (2009) and the integrity measurement described by Dahl et al. (2019).[17,29] Three areas of interest were identified in the Montreal Neurological Institute (MNI) template, including right and left LC as defined by the 2-standard-deviation LC (2SD-LC) map and a dorsal pontine reference region. Elastic registration between the MNI template and each participant's T1-weighted image was performed to identify these three areas in each subject image. Then the regions identified in the T1-weighted image were translated to the TSE volumes. Since LC is characterized by a high neuromelanin content and, consequently, by brighter voxels in TSE images, the voxels belonging to the 2SD-LC map with an intensity higher than the 75th percentile of the reference area were labeled as LC. The volume of the right and left LC identified in this way was computed. In addition, the integrity of LC was quantified based on the methodology described by Dahl et al. (2019),[17] that is, the ratio between maximum intensity in the 2SD-LC region and the reference area intensity averaged along the longitudinal axis. See Figure 2 for an overview of the MRI processing. Further methodological details including examples of MNI152 T1 registration can be found in Figure S1. Quantitative accuracy assessment following quality assessment recommendations was performed (Figure S2).[30]

2.5 | CSF analyses

1. AD biomarkers: Lumbar punctures to collect CSF samples were all performed during the morning. Levels of CSF amyloid beta ($A\beta_{42}$), total tau (T-tau), and phosphorylated tau (P-tau) were measured using Lumipulse G ELISAs following the manufacturer's instructions

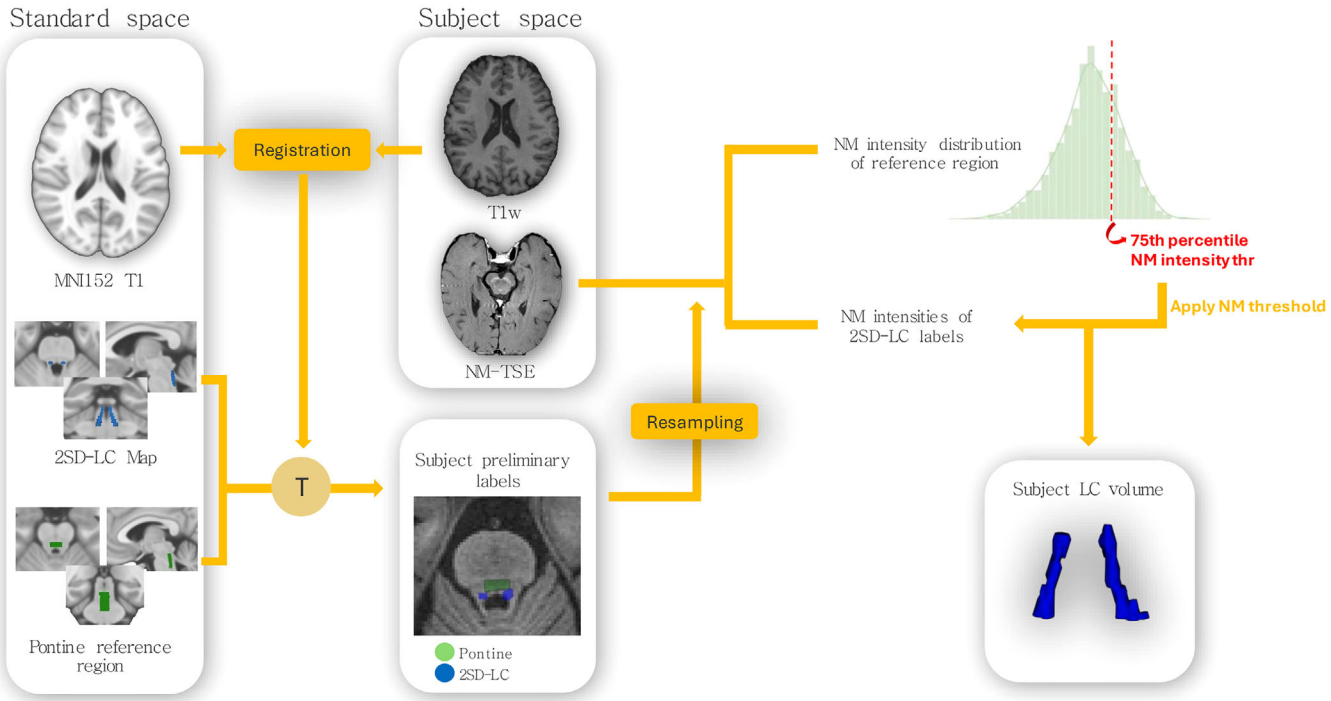

FIGURE 2 Summary of neuromelanin-sensitive (MRI processing. First, the T1-weighted volume from each participant is registered to the MNI template, creating a transformation (T). This transformation is then applied to align the 2-standard-deviation LC map (2SD-LC) and the pons reference region with the T1-weighted volume, yielding preliminary labels for these regions. These region masks are resliced to fit the NM-TSE acquisition. For each subject, the 75th percentile of intensity in the pons reference area is calculated, and only the voxels in the 2SD-LC mask with NM intensities exceeding this threshold are labeled as LC. The volume of the final LC mask is then computed individually for each subject. LC, locus coeruleus; MRI, magnetic resonance imaging; NM-TSE, neuromelanin-sensitive turbo spin echo.

(Fujirebio, Ghent, Belgium). Cut-off values of abnormality for each CSF biomarker were defined according to internal controls: $A\beta_{42} \leq$ 600 pg/mL, T-tau > 385 pg/mL, and P-tau > 65 pg/mL.

2. CSF noradrenaline: We measured the free noradrenaline concentration by using high-performance liquid chromatography with electrochemical detection (Chromsystems). The noradrenaline in a plasma-HPLC kit (Chromsystems) after analytes were extracted from the CSF matrix by adsorption on alumina.

2.6 | Plasma biomarkers

1. p-Tau 181 (P-Tau): Blood samples were obtained from all participants at the first visit, centrifuged to obtain plasma, aliquoted, and stored at −80°C. Plasma biomarker concentrations were measured with the Neurology p-Tau 181 Advantage V2.1 #104111, following the manufacturer's protocol (Quanterix, USA). Cutoff values of abnormality exceeded 16.5 pg/mL.

2.7 | Study sample

In this cross-sectional study, EOAD and LOAD participants completed the NPI[23] ($n = 76$), HAM-A,[27] and GDS scales[28] ($n = 55$) and underwent MRI scans including neuromelanin-sensitive sequence to measure LC integrity ($n = 72$), and CSF noradrenaline levels were measured ($n = 71$). For comparative purposes, a subgroup of control participants underwent the neuromelanin-sensitive MRI scan ($n = 14$). Finally, we used retrospectively collected CSF samples from healthy control participants to measure noradrenaline levels ($n = 18$). Further details on the included participants can be found in Figure 1.

2.8 | Statistical analyses

Differences in demographics, clinical, and CSF data between EOAD and LOAD groups were analyzed by χ^2 test for categorical data and t test for quantitative data. A Kolmogorov–Smirnov test was used to confirm a normal distribution. Additional logarithmic transformations of NPI, GDS, and HAMA values were performed. Multiple group comparisons (controls, MCI-AD, mild AD, moderate AD) of LC integrity and CSF noradrenaline were performed by non-parametric χ^2 test and post hoc Dunn's test due to the small sample size of control groups. Linear regression models were used to analyze the effect of EOAD versus LOAD on LC integrity and noradrenaline. In addition, we analyzed the effect of LC integrity and noradrenaline on the severity of neuropsychiatric symptoms (NPI Total and NPI domain scores). All regression models were controlled for disease stage (CDR global

score). All regression models involving NPI were adjusted by neuropsychiatric treatments (yes/no). Regression models including CSF noradrenaline were adjusted by NaSSa treatment (yes/no). Pairwise correlations between CSF AD biomarkers (Aβ42, P-tau, and T-tau) were performed. Statistical analyses were conducted using Stata/IC 14.2 (College Station, Texas, USA) and R studio version 4.2.1. For all analyses, statistical significance was set at $p < .05$.

3 | RESULTS

3.1 | Demographic and clinical data

Demographic and clinical data for EOAD and LOAD groups are provided in Table 1. Age and AAO were significantly different between EOAD and LOAD, as expected. Conversely, no differences were found between groups in terms of sex, global cognition (MMSE), or functional AD stage (CDR, Clinical Dementia Rating global score). Regarding pharmacological treatments, no differences in the prescription of anticholinesterase inhibitors were found. Levels of Aβ42, P-tau, and T-tau in CSF showed no differences between AD groups.

3.2 | LC integrity and noradrenaline levels across AD clinical continuum

3.2.1 | LC integrity

LC integrity mean (SD) values were 0.123 ± 0.022 in controls, 0.115 ± 0.024 in MCI, 0.103 ± 0.023 in mild dementia, and 0.085 ± 0.014 in moderate dementia stages. Statistically significant comparisons were found in mild and moderate dementia compared to controls ($p = .007$ and $p = .03$, respectively) and in mild and moderate dementia compared to MCI ($p = .03$ and $p = .01$, respectively). No statistical differences were found between controls and MCI (Figure 3A).

3.2.2 | CSF noradrenaline

CSF noradrenaline levels were higher in MCI (135.4 ± 70 vs 79.2 ± 52, $p = .001$) and mild dementia (139.3 ± 70 vs 79 ± 52, $p < .001$) compared to controls (Figure 2B). No statistical differences were found between moderate dementia (104 ± 54) and any of the other groups.

3.3 | Correlation of LC–noradrenaline system and CSF AD biomarkers

We found no correlation between LC integrity and AD biomarkers ($A\beta_{42}$ $r = -0.06$, $p = .96$; T-tau $r = -0.15$, $p = .23$; P-tau $r = -0.15$, $p = .22$). Conversely, CSF noradrenaline showed a weak negative correlation with Aβ42 ($r = -0.24$, $p = .02$) and a positive weak correlation with CSF T-tau ($r = 0.22$, $p = .04$) and a trend toward a positive correlation with P-tau ($r = 0.18$, $p = .08$) (Figure 4).

3.4 | Severity of neuropsychiatric symptoms in EOAD and LOAD

Differences in NPI scores between diagnostic groups are shown in Table 2. Mean comparisons showed that NPI total scores were higher in EOAD compared to LOAD. Regarding NPI-specific domains, EOAD showed higher scores in apathy and appetite changes ($p < .05$) and a trend toward higher depression ($p = .06$). In addition, the severity of depression and anxiety measured by GDS and HAM-A showed higher scores in EOAD than LOAD ($p < .05$). Prescription of neuropsychiatric treatments was more prevalent in EOAD ($p < .05$), mostly due to mirtazapine and SSRI. Group comparisons using these log-transformed values are provided in the supplementary material. The results replicated the finding of an increased NPI Total score in EOAD compared to LOAD (Table S1).

3.5 | LC measures and CSF noradrenaline in EOAD and LOAD

MRI examination unveiled a lower LC integrity in EOAD compared to LOAD ($p = .01$) (Figure 5A). Linear regression models showed that EOAD diagnosis contributed to lower LC integrity ($\beta = -0.27$, $p = .02$) independently of AD stage (CDR) (Figure 5B, Table 3). These results were replicated with LC volumes (Table 3, Figure S3). Additionally, we compared the mean intensity of the reference region (pons) and hippocampal volumes (cubic millimeters) between EOAD and LOAD groups showing similar intensity values of the pons (524.78 ± 49.56 and 502.97 ± 43.76 $p > .1$, respectively) and greater hippocampal volumes in EOAD than LOAD (2960.5 ± 495.4 vs 2593.2 ± 354.3 mm^3, $p < .01$, respectively), confirming that the observed differences in LC integrity are specific. [Correction added on September 4, 2024, after first online publication: In the preceding sentence, 'greater hippocampal volumes in EOAD than EOAD' has been modified to 'greater hippocampal volumes in EOAD than LOAD'] In the case of the CSF noradrenaline levels, we found no differences between EOAD and LOAD groups and regression models controlled by AD stage, and NaSSA treatments showed no effect (Table 3, Figure S3B,S3C). However, linear regression models controlled by AD stage, NaSSA treatments, and EOAD versus LOAD diagnosis showed a negative correlation between LC integrity and CSF noradrenaline levels ($\beta = -0.30$, $p < .05$) (Table 3).

3.6 | Effect of LC–noradrenaline system on severity of neuropsychiatric symptoms

Linear regression models controlling for AD stage, EOAD versus LOAD diagnosis and neuropsychiatric treatments showed an independent

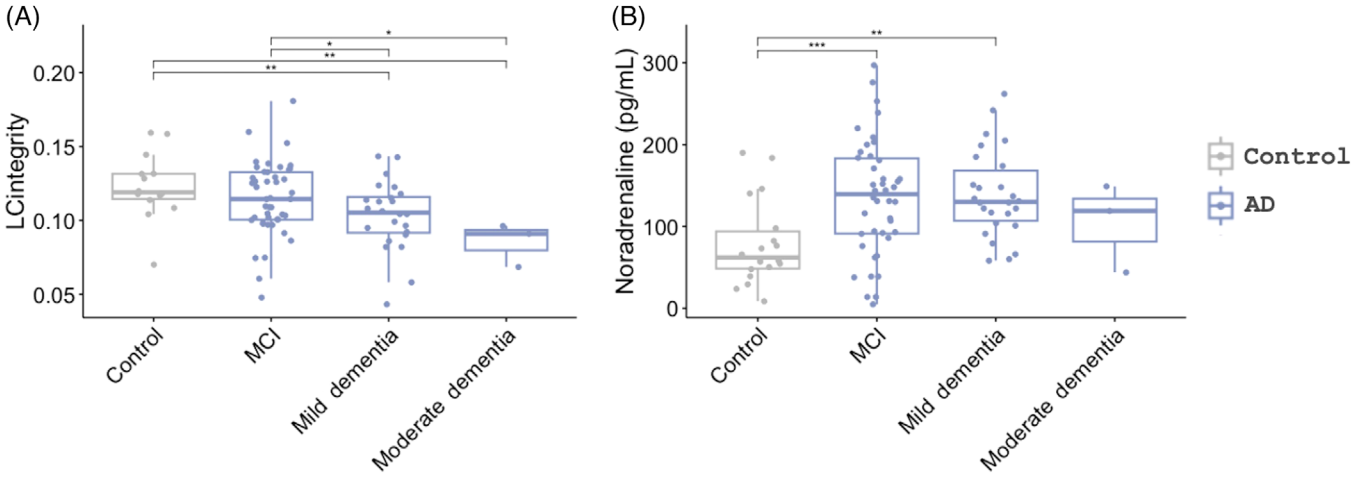

FIGURE 3 LC integrity and CSF noradrenaline levels in controls and AD participants. Figure 2 shows (A) LC integrity and (B) CSF noradrenaline levels across controls and AD stages. Figure 1A includes 14 controls, 45 MCI, 24 mild dementia, and 3 moderate dementia. Figure 2B includes 18 controls, 42 MCI, 26 mild dementia, and 3 moderate dementia. The control group showed preserved LC integrity with lower CSF noradrenaline levels, while AD groups had lower LC integrity and higher CSF noradrenaline. AD, Alzheimer's disease; CSF, cerebrospinal fluid; LC, locus coeruleus; MCI, mild cognitive impairment.

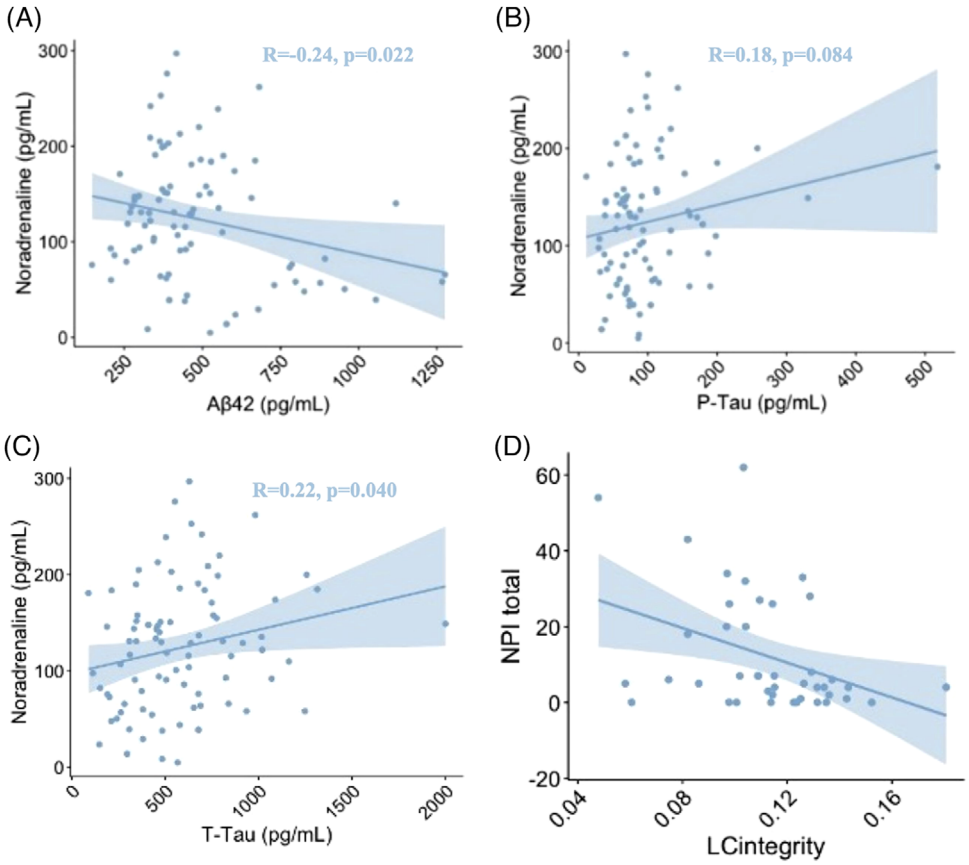

FIGURE 4 Correlation of LC-noradrenaline system with neuropsychiatric symptoms and CSF AD biomarkers. Figure 4A–C shows the correlation of CSF noradrenaline levels with Aβ42 ($r = -0.24$, $p = .04$), T-tau ($r = 0.22$, $p < .04$), and P-Tau ($r = 0.18$, $p = .08$). Figure 4D shows a negative correlation between LC integrity ($\beta = -0.44$, $p < .01$) and the severity of neuropsychiatric symptoms measures (NPI) within the AD cohort. AD, Alzheimer's disease; CSF, cerebrospinal fluid; LC, locus coeruleus NPI, Neuropsychiatric Inventory.

TABLE 1 Demographics and sample characteristics.

(a) Alzheimer's disease participants					
	Total AD (*n* = 104)	**EOAD (*n* = 34)**	**LOAD (*n* = 70)**	**EOAD versus LOAD *Cohen's d***	**EOAD versus LOAD *Sig.***
Age	69.8 ± 5.7	63.3 ± 4.5	72.9 ± 3.0	−2.72	***p* = 0.000**
Age at onset	66.8 ± 5.9	59.9 ± 3.6	70.3 ± 3.3	−3.02	***p* = 0.000**
Sex (women, %)	59.6	56	61	0.11	*p* = 0.589
MMSE	22.9 ± 4.5	22.4 ± 4.5	23.3 ± 4.5	−0.18	*p* = 0.202
CDR total	0.74 ± 0.37	0.75 ± 0.45	0.73 ± 0.33	0.06	*p* = 0.201
Mild cognitive impairment (CDR 0.5, %)	62	67	60		
Mild dementia (CDR 1, %)	33	24	37		
Moderate dementia (CDR 2, %)	5	9	3		
Amnestic phenotype (%)	80	74	83	0.28	*p* = 0.247
Anticholinesterase inhibitors	97%	97%	97%	0.21	*p* = 0.320
CSF biomarkers					
Aβ42 (pg/mL)	390.6 ± 117.7	372.9 ± 114.9	399.2 ± 118.9	−0.22	*p* = 0.155
p-Tau (pg/mL)	102.6 ± 70.7	109.5 ± 94.5	99.3 ± 55.3	−0.17	*p* = 0.259
t-Tau (pg/mL)	631.6 ± 318.1	594.8 ± 345.2	649.3 ± 305.4	0.14	*p* = 0.218
(b) Control participants					
		MRI controls (*n* = 14)			**CSF noradrenaline controls (*n* = 18)**
Age		62.4 ± 9.3			60.5 ± 7.3
Sex (women, %)		63%			100%
CDR total		0 ± 0			0 ± 0
MMSE		29 ± 1			28.5 ± 1.5
Plasma biomarkers					
p-Tau 181 (mg/dL)		9.9 ± 1.9			N/A
CSF biomarkers					
Aβ42 (pg/mL)		N/A			799.3 ± 265.3
p-Tau (pg/mL)		N/A			66.5 ± 31.4
t-Tau (pg/mL)		N/A			335.6 ± 207.8

Note: Data are presented as means ± SD. Significant *p* values marked in bold letters.
Abbreviations: CDR, Clinical Dementia Rating scale; CSF, cerebrospinal fluid; EOAD, early-onset Alzheimer's disease; LOAD, late-onset Alzheimer's disease; MMSE, Mini-Mental State Examination; MRI, magnetic resonance Imaging.

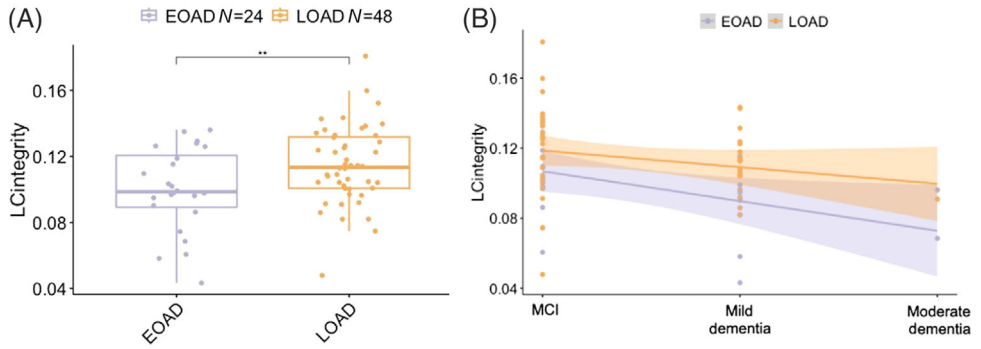

FIGURE 5 LC integrity, measured by MRI in EOAD versus LOAD. Figure 2A shows EOAD versus LOAD group comparisons of LC integrity, and Figure 2B shows LC integrity in EOAD and LOAD over AD stages. AD, Alzheimer's disease; EOAD, early-onset Alzheimer's disease; LC, locus coeruleus; LOAD, late-onset Alzheimer's disease; MRI, magnetic resonance imaging.

TABLE 2 Severity of neuropsychiatric symptoms and treatments.

	EOAD ($n = 24$)	LOAD ($n = 52$)	EOAD versus LOAD *Cohen's d*	EOAD versus LOAD *Sig.*
NPI total	13.3 ± 18.9	9.9 ± 13.7	0.49	**$p = 0.028$**
Delusions	0.0 ± 0.0	0.3 ± 0.9	0.33	$p = 0.096$
Hallucinations	0.0 ± 0.0	0.1 ± 0.3	−0.24	$p = 0.168$
Agitation	1.6 ± 3.4	0.9 ± 0.3	0.26	$p = 0.141$
Depression	2.3 ± .0.7	1.2 ± 2.4	0.38	$p = 0.062$
Anxiety	1.4 ± 3.4	0.8 ± 2.7	0.22	$p = 0.189$
Elation	0.3 ± 1.0	0.2 ± 0.8	0.13	$p = 0.296$
Apathy	3.3 ± 3.9	1.8 ± 3.2	0.44	**$p = 0.039$**
Disinhibition	0.8 ± 2.7	0.5 ± 1.4	0.15	$p = 0.269$
Irritability	2.0 ± 3.2	1.1 ± 2.6	0.30	$p = 0.112$
Motor disturbances	0.8 ± 2.6	0.5 ± 1.9	0.13	$p = 0.304$
Night events	2.0 ± 4.0	1.5 ± 2.3	0.20	$p = 0.220$
Appetite	2.4 ± 4.0	1.0 ± 2.6	0.45	**$p = 0.036$**
NPI caregiver distress	6.8 ± 8.2	4.1 ± 6.4	0.37	$p = 0.069$
Neuropsychiatric treatment (%)	58	35	0.38	**$p = 0.031$**
SSRI (%)	38	21	0.24	$p = 0.074$
SARI (trazodone) (%)	0	0	0.07	$p = 0.293$
NaSSA (mirtazapine) (%)	13	0	0.49	**$p = 0.004$**
Benzodiazepines (%)	20	22	−0.05	$p = 0.472$
Atypical antipsychotic (%)	0	1	0.01	$p = 0.381$
	EOAD ($n = 014$)	**LOAD ($n = 041$)**		**EOAD versus LOAD *Sig.***
HAM-A	16.2 ± 12.0	9.8 ± 9.6	0.63	**$p = 0.02$**
GDS	5.6 ± 3.7	3.7 ± 3.2	0.58	**$p = 0.03$**

Note: Data are presented as means ± SD.

Abbreviations: EOAD, early-onset Alzheimer's disease; GDS, Geriatric Depression Scale; HAM-A, Hamilton Anxiety Rating scale; LOAD, late-onset Alzheimer's disease; NaSSA, noradrenergic, specific serotonergic antidepressants; NPI, Neuropsychiatric Inventory; SARI, Serotonin Antagonist and Reuptake Inhibitors (trazodone); SSRI, Selective Serotonin Reuptake Inhibitors.

negative effect of LC integrity, measured by MRI, on NPI Total score ($\beta = -0.44$, $p < .01$) (Figure 4D, Table 3) and several NPI domains: hallucinations ($\beta = -0.45$, $p < .01$), agitation ($\beta = -0.45$, $p < .01$), depression ($\beta = -0.32$, $p < .01$), elation ($\beta = -0.44$, $p < .05$), apathy ($\beta = -0.41$, $p < .05$), and motor disturbances ($\beta = -0.43$, $p < .01$) (Table 3). Models analyzing the effects of CSF noradrenaline on NPI Total scores or subitem scores showed no statistically significant results. See further details in Table 3. Additional regression models controlled by sex yielded similar results (Table S2). Regression models using these log-transformed values are provided in Table S3. They replicated a significant negative effect of LC integrity in NPI Total and several subscores: hallucinations, agitation, depression, elation, apathy, and motor disturbances.

4 | DISCUSSION

This cross-sectional study demonstrated in a well-characterized in vivo cohort that the LC degenerated more in EOAD than in LOAD individuals. Also, this study supports the notion that increases in noradrenaline levels in MCI and mild dementia stages of AD are paradoxical, which might represent either a compensatory mechanism or the result of extracellular release due to tau-related neuronal destruction. Finally, it underscores the role of LC degeneration underlying neuropsychiatric symptoms in AD by detecting a correlation between more severe neuropsychiatric symptoms and reduced LC integrity, regardless of cognitive stage or use of neuromodulatory medications.

Worse LC integrity in EOAD versus LOAD detected by MRI aligns well with recent *post mortem* studies showing a more significant neuronal loss in EOAD than in LOAD.[13] Despite the seemingly contradictory fact that patients with EOAD are younger, other evidence shows that EOAD is more severe than LOAD. For instance, EOAD shows significantly more neocortical atrophy, highlighting increased brain susceptibility to EOAD, particularly to tau pathology, the underlying causes of which remain unclear.[31–33] Comparing the molecular basis of LC neurodegeneration in EOAD versus LOAD may provide insight into the factors underlying this vulnerability and possibly shine light on the etiology of these two conditions with similar phenotypical

TABLE 3 Regression coefficients from lineal regression models.

Dependent variable	Explanatory variables	Beta	*t*	*p*-value
LC integrity	EOAD versus LOAD	0.271	2.47	**0.016**
	AD stage	−0.304	−2.77	**0.007**
LC volume	EOAD versus LOAD	0.40	3.67	**0.000**
	AD stage	0.048	0.44	0.659
Noradrenaline	EOAD versus LOAD	0.234	1.80	0.331
	AD stage	−0.056	−0.44	0.796
	NaSSa	0.198	1.52	0.203
Noradrenaline	LC integrity	−0.302	−2.11	**0.040**
	EOAD versus LOAD	0.158	1.13	0.263
	AD stage	−0.177	−1.29	0.205
	NaSSa	0.109	0.79	0.436
NPI total score	LC integrity	−0.436	−2.90	**0.006**
	EOAD versus LOAD	0.053	0.35	0.732
	AD stage	−0.161	−1.04	0.306
	Neuropsychiatric treatments	0.111	0.73	0.468
NPI delusions	LC integrity	−0.165	−1.04	0.306
	EOAD versus LOAD	0.238	1.46	0.153
	AD stage	−0.157	−0.96	0.345
	Neuropsychiatric treatments	−0.105	−0.65	0.188
NPI hallucinations	LC integrity	−0.499	−3.51	**0.001**
	EOAD versus LOAD	0.263	1.81	0.078
	AD stage	0.048	0.33	0.744
	Neuropsychiatric treatments	0.142	0.99	0.327
NPI agitation	LC integrity	−0.448	−3.03	**0.004**
	EOAD versus LOAD	0.162	1.07	0.291
	AD stage	−0.172	−1.13	0.267
	Neuropsychiatric treatments	−0.029	−0.22	0.827
NPI depression	LC integrity	−0.324	−2.11	**0.041**
	EOAD versus LOAD	0.166	−1.06	0.296
	AD stage	0.056	0.36	0.723
	Neuropsychiatric treatments	0.130	0.85	0.403
NPI anxiety	LC integrity	−0.189	−1.20	0.238
	EOAD versus LOAD	0.014	0.09	0.932
	AD stage	−0.143	−0.88	0.386
	Neuropsychiatric treatments	−0.238	−1.49	0.143
NPI elation	LC integrity	−0.444	−2.54	**0.017**
	EOAD versus LOAD	0.226	1.28	0.209
	AD stage	−0.045	−0.25	0.802
	Neuropsychiatric treatments	0.038	0.21	0.833
NPI apathy	LC integrity	−0.409	−2.31	**0.028**
	EOAD versus LOAD	−0.056	−0.31	0.758
	AD stage	−0.083	−0.46	0.650
	Neuropsychiatric treatments	−0.032	−0.18	0.861

(Continues)

TABLE 3 (Continued)

Dependent variable	Explanatory variables	Beta	*t*	*p*-value
NPI disinhibition	LC integrity	0.068	0.42	0.675
	EOAD versus LOAD	0.126	0.77	0.447
	AD stage	−0.259	−1.56	0.126
	Neuropsychiatric treatments	−0.126	−0.78	0.442
NPI irritability	LC integrity	−0.200	−1.25	0.220
	EOAD versus LOAD	−0.118	0.72	0.474
	AD stage	−0.030	−0.18	0.855
	Neuropsychiatric treatments	0.097	0.60	0.550
NPI motor disturbances	LC integrity	−0.442	−3.00	**0.005**
	EOAD versus LOAD	0.223	1.48	0.146
	AD stage	−0.152	−1.00	0.325
	Neuropsychiatric treatments	0.124	0.84	0.409
NPI night events	LC integrity	−0.024	−0.17	0.869
	EOAD versus LOAD	0.053	0.06	0.951
	AD stage	−0.219	−1.60	0.117
	Neuropsychiatric treatments	0.351	1.37	0.180
NPI appetite	LC integrity	−0.276	−1.75	0.087
	EOAD versus LOAD	0.111	1.69	0.495
	AD stage	0.122	−0.75	0.459
	Neuropsychiatric treatments	0.160	1.01	0.320
NPI total score	Noradrenaline	0.152	0.87	0.389
	EOAD versus LOAD	−0.057	−0.32	0.752
	AD stage	0.203	1.19	0.242
	NERI	0.025	0.13	0.896

convergence of plaques and tangle deposits but many clinical or pathological differences, suggesting different etiologies.[34] Conversely, the absence of differences in reference regions, such as the pons, between groups and the observation that hippocampal volumes were greater in EOAD than in LOAD (replicating our prior work[35]) suggest that the observed greater degeneration of the LC in EOAD is specific. This finding likely indicates an increased vulnerability of the LC in the EOAD population.

The tau-related degeneration of the neuromodulatory subcortical systems (including the isodendritic core) gradually progresses decades before AD's cognitive symptoms start. The isodendritic core comprises a variety of nuclei controlling several neurotransmitters, such as the noradrenergic LC, serotoninergic dorsal raphe, or the histaminergic tuberomammillary nucleus. For unknown reasons, processes like tau phosphorylation and neurofibrillary tangles' formation have a notable toxic effect within the isodendritic core, driving local cell death within these nuclei, including the LC, and therefore constituting the early stages of tauopathies such as AD.[11,14,15,36] Our results support this biological disease model, showing that LC integrity progressively decreases from mild to advanced disease stages of AD in opposition to healthy controls. Moreover, prior studies showed decreases by 8.4% in LC volume for each Braak stage due to neuronal loss after the accumulation of neurofibrillary tangles onsite, which reinforces the progressive nature of LC degeneration in AD.[13]

Moreover, although subtle, these subcortical changes are not innocuous. Clinicopathological correlations showed that symptoms of anxiety, depression, or sleep problems appear already from early Braak stages when tau pathology remains confined to the LC (and other isodendritic core nuclei) and thus has not yet reached the medial temporal cortex.[1] In a recent longitudinal study, we demonstrated that, in vivo, the severity of neuropsychiatric symptoms is higher in EOAD than in LOAD, driven by differences in scores of anxiety, depression, and nighttime behaviors.[6,37] Based on the pattern of a worse degree of brain atrophy in EOAD and the role of the neuromodulatory subcortical system in modulating neuropsychiatric symptoms, we hypothesized that different EOAD would show a higher degree of LC (one of the main neuromodulatory subcortical systems (NSS) hubs) degeneration than LOAD.[6,37] With the current study, we first replicated our original findings in an independent cohort. The EOAD group showed higher scores of depression, anxiety, apathy, and motor disturbances than LOAD. Next, we went further by showing that LC integrity measured by MRI is worse in EOAD than in LOAD and that LC integrity correlates with the degree of NPI changes. Our work concurs with previous reports showing that the association between

changes in the noradrenergic system has implications for the expression of memory and behavioral symptoms.[22,38–43] Altogether this body of evidence refutes the hypothesis that neuropsychiatric symptoms in AD are a direct result of psychosocial factors such as the impact of disease diagnosis, a claim that is corroborated by our findings that EOAD patients have higher scores of NPI than LOAD, despite the more frequent use of antidepressant/anxiolytic medications in the former.

However, our findings also emphasize that counteracting LC degeneration involves more than merely replenishing noradrenaline. The relationship between LC degeneration and changes in noradrenaline levels is not linear. For instance, we showed that CSF noradrenaline levels were paradoxically increased in AD individuals compared to controls. Furthermore, although LC integrity is significantly associated with NPI severity, we failed to find any association between CSF noradrenaline levels and NPI severity. Also, despite the significantly worse loss of LC integrity in EOAD than in LOAD, the CSF noradrenaline levels in EOAD remained similar to the LOAD ones. The reasons for this paradoxical increase are still under investigation. Some authors suggest there is a compensatory response of the surviving noradrenergic cells secondary to the LC damage.[22,44–48] In this line, an increase of noradrenaline levels or its derived metabolites, such as 3-methoxy-4-hydroxyphenyl ethylene glycol (MHPG), has been previously described in CSF.[22,23] Prior CSF studies reported that greater MHPG levels are associated with the disease stage, and reductions in norepinephrine-producing neurons increase noradrenaline metabolism.[22,23] Moreover, the experimental blockade of alpha-2 adrenoreceptors, resembling LC damage in AD individuals, increases the response to noradrenaline release while its clearance remains unchanged.[44] However, the noradrenergic response of LC to neuronal damage, its functional effectiveness and whether CSF noradrenaline levels accurately reflect the functional response of the LC remain open questions. Our findings, which contrast EOAD and LOAD by integrating CSF noradrenaline levels with MRI and NPI scores, contribute significant new information to this debate. Considering that the increased severity of neuropsychiatric symptoms in EOAD does not align with CSF noradrenaline levels, we suggest that symptom severity is more closely related to the integrity of pre- or postsynaptic structures, which influences noradrenaline affinity. However, additional research is required to fully understand these critical aspects of AD-related noradrenaline dysfunction.

The main strengths of this study are the extensive characterization of the AD patients included in the cohort, including a biomarker-confirmed diagnosis while accounting for EOAD and LOAD variants and different AD stages. We used both structural (LC integrity-MRI) and functional measures (CSF noradrenaline) to characterize the changes in the LC–noradrenergic system within the same cohort. Furthermore, we included two control groups to compare LC integrity and CSF noradrenaline with negative CSF/plasma AD biomarkers, excluding the potential bias of preclinical participants. Nevertheless, the study has several limitations. The sample size of the control groups is limited, and CSF noradrenaline and LC integrity measures were performed in separate control cohorts. Although relatively large, given that it is an uncommon diagnosis, the sample size of EOAD groups might have led to limited power in certain statistical analyses. The detection of in vivo LC changes has inherent technical limitations. However, the fact that we replicated the analyses with two types of measurement (LC integrity and LC volumes), obtaining similar results, increases the reliability. Finally, additional longitudinal data are needed to confirm how the age of onset influences the severity of neuropsychiatric symptoms through its effect on LC integrity.

In conclusion, decreased LC integrity contributes to higher neuropsychiatric symptoms' severity. A greater degeneration of the LC in EOAD than LOAD could explain the more severe neuropsychiatric symptoms observed in EOAD. Overall, this highlights the noradrenergic system degeneration as a main physiopathological process driving neuropsychiatric symptoms in AD and the need for tailored therapeutic approaches within AD variants. Finally, our findings not only have clear implications for managing neuropsychiatric symptoms in individuals with cognitive decline due to AD but also reiterate, in vivo, the theory suggested by *post mortem* studies[1] that new onset of specific neuropsychiatric symptoms in cognitively normal middle-age and older adults may be linked to LC degeneration. They underscore the need for more in-depth clinic-biomarker *post mortem* studies to elucidate the sequence and nature of changes in the neuromodulatory subcortical systems during AD progression for enabling optimized therapies to treat symptoms effectively.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

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