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FEATURED ARTICLE

MRI-assessed locus coeruleus integrity is heritable and associated with multiple cognitive domains, mild cognitive impairment, and daytime dysfunction

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Abstract

Introduction: The locus coeruleus (LC) undergoes extensive neurodegeneration in early Alzheimer's disease (AD). The LC is implicated in regulating the sleep-wake cycle, modulating cognitive function, and AD progression.

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Methods: Participants were 481 men (ages 62 to 71.7) from the Vietnam Era Twin Study of Aging. LC structural integrity was indexed by neuromelanin-sensitive magnetic resonance imaging (MRI) contrast-to-noise ratio (LC_{CNR}). We examined LC_{CNR} , cognition, amnesic mild cognitive impairment (aMCI), and daytime dysfunction.

Results: Heritability of LC_{CNR} was .48. Participants with aMCI showed greater daytime dysfunction. Lower LC_{CNR} was associated with poorer episodic memory, general verbal fluency, semantic fluency, and processing speed, as well as increased odds of aMCI and greater daytime dysfunction.

Discussion: Reduced LC integrity is associated with widespread differences across cognitive domains, daytime sleep-related dysfunction, and risk for aMCI. These findings in late-middle-aged adults highlight the potential of MRI-based measures of LC integrity in early identification of AD risk.

KEYWORDS

Alzheimer's disease, heritability, locus coeruleus, mild cognitive impairment, neuromelanin magnetic resonance imaging, sleep-wake disturbance

1 | INTRODUCTION

Imaging of the locus coeruleus (LC) has received increased interest in recent years,¹ particularly in the context of Alzheimer's disease (AD). The LC is highly affected during the course of AD and experiences extensive neuronal loss.² Abnormal tau has been found in the LC early in life, leading some to suggest it is one of the first sites of AD pathology.³ The LC is the primary source of norepinephrine (NE) for the brain, so LC dysfunction may result in NE depletion. Disruptions to the LC-NE system may increase amyloid beta ($A\beta$) deposition⁴ and potentiate the inflammatory response to $A\beta$.⁵ NE also has neuroprotective effects; NE reductions leave neurons generally more susceptible to deleterious age- and disease-related processes.⁶ Thus, the LC-NE system is both affected by and a contributor to AD pathophysiology.

Sleep-wake disturbance is common in AD, and may manifest in preclinical AD or mild cognitive impairment (MCI).⁷ Poor sleep quality has also been associated with $A\beta$ deposition.⁸ Poor sleep appears to be both a consequence of, and contributor to, the development of AD pathology.⁹ The LC is highly involved in regulating arousal, vigilance, and the sleep-wake cycle,¹⁰ and recent evidence suggests that daytime sleep-related dysfunction—which is common in AD¹¹—may also be a direct consequence of extensive degeneration of wake-promoting neurons in the LC.¹² Therefore, sleep-wake-cycle disruption and AD pathology may form a bidirectional relationship. The LC represents one potential point of convergence linking early AD with sleep-wake disturbance, and daytime dysfunction in particular.

The LC is also proposed to play a key role in optimizing and maintaining memory,^{6,13-15} but its widespread projections and evidence of its involvement in modulating higher-order cognitive processes¹⁶ suggest that it may impact multiple cognitive domains.

In vivo assessment of LC integrity has been uncommon because it is not visible on conventional T1- or T2-weighted structural scans. However, several magnetic resonance imaging (MRI) protocols make it possible to image the LC.¹ These sequences boost the signal of neuromelanin, a byproduct of NE oxidation, which is concentrated to a higher degree in the LC compared to surrounding regions.⁶ The contrast of signal within the LC relative to a reference region is thought to reflect LC cell density and structural integrity. In a combined MRI and histological study, regions of high signal intensity from MRI colocalized with regions of high concentrations of neuromelanin and with number of NE neurons, providing validation for this method.¹⁷ LC signal contrast has been found to be lower (ie, less structural integrity) among several patient groups compared to controls,¹⁸ but findings specific to MCI and AD are mixed.^{19,20}

Given the very early deposition of tau in the LC, clarifying the relationship of MRI-assessed LC structural integrity with cognitive and behavioral outcomes related to the LC-NE system may facilitate improved early identification of AD risk. Here, we examined whether reduced LC structural integrity is associated with poorer cognitive performance across multiple domains, increased risk of amnesic MCI (aMCI), and increased daytime dysfunction. In addition, we calculated heritability of LC signal contrast.

2 | METHODS

2.1 | Participants

Participants were from wave 3 of the Vietnam Era Twin Study of Aging (VETSA).²¹ VETSA participants comprise a national, community-dwelling sample of male-male twins who are similar to American men in their age range with respect to health and lifestyle characteristics.²¹

Highlights

- The locus coeruleus (LC) undergoes degeneration in early Alzheimer's disease (AD).
- Neuromelanin-sensitive magnetic resonance imaging can assess LC structural integrity.
- LC integrity was associated with performance in multiple cognitive domains.
- Lower LC integrity was associated with mild cognitive impairment and daytime sleep-related dysfunction.
- The LC represents a convergence point for multiple disrupted processes in early AD.

All served in the military sometime between 1965 and 1975, but nearly 80% reported no combat exposure. Additionally, prevalence of traumatic brain injury (TBI) in the full VETSA sample (31.4%) is similar to a Colorado community sample (42.5%)²² and only 1.2% of TBI in the included sample was combat related.

LC imaging data were acquired for 487 of 525 participants who met standard MRI inclusion criteria. Data from six participants were excluded due to poor quality. Of the remaining 481, 480 had cognitive data, and 391 had complete sleep-related data and covariates. The sample comprised 113 monozygotic (MZ) pairs, 67 dizygotic (DZ) pairs, and 121 unpaired twins. Sample characteristics are shown in Table 1.

All participants provided informed consent and the study was approved by the Institutional Review Board at the University of California, San Diego.

2.2 | MRI acquisition and processing

Images were acquired on GE 3T Discovery 750x scanners (GE Healthcare, Waukesha, Wisconsin, USA) with an eight-channel phased array head coil (scanner 1: N = 336, scanner 2: N = 145). The LC was imaged with an axial fast spin-echo T1-weighted image (TR = 600 ms; TE = 14 ms; flip angle = 90°; matrix = 512 × 320; FOV = 220 mm; pixel size 0.42 × 0.68 mm; 10 slices; slice thickness = 2.5 mm; interslice gap = 1 mm).

Each image was manually marked by two of four experienced raters using a modified version of the method described in Clewett et al.²³ Signal intensities were derived from manually marked regions of interest (ROIs) on three axially oriented slices corresponding to rostral, middle, and caudal LC (Figure 1). The middle slice was selected by taking the slice 7 mm below the inferior edge of the inferior colliculus. A 3 mm² voxel cross was placed over left and right LC, with the middle of the ROI centered on the LC voxel with the highest intensity. To control overall signal intensity variability across slices, a 10 mm² reference ROI was placed in the pontine tegmentum (PT). This ROI was placed six voxels ventral to the middle voxel of LC ROIs, and lateral placement was equidistant between the two LC ROIs. The

RESEARCH IN CONTEXT

1. **Systematic review:** We searched PubMed for literature on imaging of the locus coeruleus (LC), sleep-wake disturbance, and mild cognitive impairment (MCI). Prior studies suggest that the LC is affected in early Alzheimer's disease (AD) and that its structural integrity should be associated with these other factors. Relevant references are appropriately cited.
2. **Interpretation:** Magnetic resonance imaging (MRI)-assessed neuromelanin contrast of the LC is heritable and is a valid biological index of its structural integrity. Findings are consistent with the hypothesis that LC damage/dysfunction may partially contribute to risk for amnesic MCI, and poorer cognitive performance and disruptions to the sleep-wake cycle apparent in early AD.
3. **Future directions:** Findings highlight the potential for MRI measures of the LC to assist in early identification of risk for AD. Further work is needed to clarify mechanisms that link reduced LC structural integrity with poorer cognitive and behavioral outcomes such as AD pathology and inflammation.

same rules were used to mark LC and PT ROIs on the slices directly rostral and caudal to the middle slice. Mean signal was then extracted from each ROI. Signal in the left LC was significantly higher than the right ($t_{(480)} = -19.63$, $P < .001$). However, left and right LC values were highly correlated ($r = 0.989$, $P < .001$) and were thus averaged for each slice. LC contrast-to-noise ratio (LC_{CNR}) values were calculated for each slice as $LC_{CNR} = (LC_{intensity} - PT_{intensity}) / PT_{intensity}$. Higher LC_{CNR} values are thought to reflect better LC structural integrity.¹⁷ Extant literature suggests that the rostral and middle portions of the LC are more prone to age- and AD-related degeneration than more caudal, cerebellar-projecting portions.^{1,24} Therefore, the LC_{CNR} values from the two rostral-most marked slices were averaged and used as the final LC_{CNR} for each individual. Values were z-transformed such that coefficients correspond to standardized beta estimates. A training set of 20 images was marked by all four raters. There was a high degree of reliability in LC_{CNR} values (intraclass correlation [ICC] = 0.87, $F_{(19,57)} = 8.6$, $P < .001$).

2.3 | Cognitive domain factor scores

Factor loadings used to calculate composite scores were derived from structural equation models of multiple tests belonging to each cognitive domain. Models have been previously described for episodic memory,²⁵ executive function,²⁶ working memory,²⁶ general verbal fluency,²⁷ semantic fluency,²⁷ and processing speed.²⁸ Individual test scores were corrected for practice effects associated with

TABLE 1 Sample characteristics

	Full sample	Cognitively normal	Amnesic MCI	Non-amnesic MCI
n	481	373	36	22
Age	67.52 (2.60)	67.53 (2.59)	67.09 (2.69)	68.38 (2.23)
Education (years)	13.98 (2.07)	14.10 (2.12)	13.69 (2.11)	13.18 (1.68)*
LC _{CNR} (rostral/middle)	0.11 (0.03)	0.11 (0.03)	0.10 (0.02)*	0.12 (0.03)
Left LC signal (rostral/middle)	762.55 (104.77)	761.25 (102.59)	756.20 (106.07)	784.45 (80.09)
Right LC signal (rostral/middle)	777.02 (108.59)	776.11 (107.19)	767.91 (107.36)	798.00 (83.15)
PT signal (rostral/middle)	691.67 (93.33)	690.10 (91.28)	691.78 (93.01)	709.88 (76.94)
Daytime dysfunction component score	0.56 (0.60)	0.50 (0.58)	0.78 (0.72)*	0.45 (0.60)
Depressive symptoms	5.94 (6.53)	5.57 (6.40)	6.98 (7.57)	6.05 (5.05)
Sleep apnea	93 (19.4%)	67 (18.1%)	9 (25.0%)	5 (22.7%)
APOE ε4 carrier	99 (20.6%)	80 (21.4%)	7 (19.4%)	5 (22.7%)

Notes: Descriptive statistics of the full sample with neuromelanin contrast MRI scans of the locus coeruleus, and subsets of individuals with a diagnosis of cognitively normal, amnesic MCI, and non-amnesic MCI. Signal and contrast-to-noise from rostral and middle sections was used in the primary analyses. Depressive symptoms are determined using the CES-D, excluding the rating for "My sleep was restless." Values presented are mean (SD) for continuous variables and n (%) for categorical variables. Asterisks indicate significant differences in comparison to the cognitively normal group as determined by t-tests or chi-square tests.

Abbreviations: APOE, apolipoprotein E; CES-D, Center for Epidemiological Studies Depression scale; LC, locus coeruleus; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PT, pontine tegmentum; SD, standard deviation.

repeated test assessments as described previously.²⁹ Individual tests are described in the supporting information.

2.4 | MCI classification

We defined MCI according to the Jak-Bondi approach.³⁰ All tests used for classification were also practice-effect corrected.²⁹ Neuropsychological measures were adjusted for young adult general cognitive ability (GCA) so that MCI would reflect change from prior level of function rather than longstanding cognitive performance. Young adult GCA was assessed with the Armed Forces Qualification Test (AFQT),³¹ taken at a mean age of 20. The AFQT is a measure of GCA that correlates highly with Wechsler intelligence quotient (IQ; $r = .84$).³² Impairment was defined as having 2+ measures within a domain >1.5 standard deviations (SDs) below age- and education-adjusted normative means. Individuals with an impaired memory domain were specified as aMCI ($n = 36$). Those with impairments in domains other than memory were classified as non-amnesic MCI (naMCI; $n = 22$). There were 375 cognitively normal (CN) individuals. Analyses of MCI status primarily focused on comparing CN to aMCI, which is thought to more likely reflect a prodromal stage of AD.

2.5 | Daytime dysfunction

We used the daytime dysfunction component of the Pittsburgh Sleep Quality Index (PSQI)³³ because of the severe loss of wake-promoting neurons in the LC.¹² The daytime dysfunction component is based on two questions: "During the past month, how often have you taken medicine (prescribed or 'over the counter') to help you sleep?" and

"During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?" Component scores range from 0 to 3, with greater values reflecting more dysfunction. Only one individual had a rating of 3, so values of 3 were collapsed with 2.

2.6 | Statistical analysis

2.6.1 | Genetically informative twin models

To determine the relative influence of genetic and environmental factors on LC_{CNR}, we fit univariate biometrical (ACE) models. The variance of a phenotype is decomposed into additive genetic (A) influences, common or shared environmental (C) influences (ie, environmental factors that make members of a twin pair similar to one another), and non-shared environmental (E) influences (ie, environmental factors that make members of a twin pair different from one another, including measurement error).³⁴ The proportion of the overall variance attributable to additive genetic influences is the heritability (a^2). Prior to fitting the ACE model, age and MRI scanner were regressed out of the LC_{CNR}. Analysis was performed using the maximum-likelihood based structural equation modeling software OpenMx v2.17.2³⁵ in R v3.6.3. See supporting information for additional details.

2.6.2 | Phenotypic analyses

All phenotypic models include family ID as a random effect to account for non-independence of twin pairs. All analyses controlled for age. Analyses of MCI status and daytime dysfunction included number of

depressive symptoms as a covariate based on the Center for Epidemiologic Studies Depression Scale (excluding "My sleep was restless").³⁶ In analyses including daytime dysfunction, we additionally controlled for sleep apnea. There was no association between LC_{CNR} and scanner, education, or apolipoprotein E (APOE) ε4 status, so they were not included as covariates. Analyses were conducted in R v3.6.3.

The relationship between the LC and cognitive domains was tested with linear mixed-effects models with each of the six cognitive factors as the dependent variable and LC_{CNR} as the predictor. We corrected for multiple comparisons using Benjamini-Hochberg false discovery rate (FDR)-adjustment.³⁷ When effects of LC_{CNR} were significant, models were re-run including an interaction with MCI group to determine whether results were driven by individuals with MCI.

Three models were run testing relationships among LC integrity, diagnosis (aMCI vs CN), and daytime dysfunction: (1) mixed effects ordinal logistic regression with daytime dysfunction as the dependent variable and MCI status as independent variable, (2) mixed effects logistic regression with MCI status as the dependent variable and LC_{CNR} as the independent variable, (3) mixed effects ordinal regression with daytime dysfunction as the dependent variable and LC_{CNR} as independent variable. This third model was re-fit including an interaction between LC_{CNR} and aMCI status to test if effects were similar between groups.

Models were re-run comparing CN and naMCI as supplemental analyses examining the extent to which effects were specific to the amnestic subtype. An additional supplemental analysis included both LC_{CNR} and daytime dysfunction as predictors with MCI status as the dependent variable. Daytime dysfunction was treated as an ordinal variable with orthogonal polynomial contrasts (linear and quadratic).

We additionally ran models using LC_{CNR} derived from caudal LC as well as signal from the PT reference region to investigate regional specificity of effects. Finally, we tested an interaction between LC_{CNR} and young adult GCA on aMCI status to determine whether there was a protective effect of cognitive reserve.

3 | RESULTS

3.1 | LC_{CNR} heritability

LC_{CNR} correlations among twin pairs were 0.60 and 0.41 for MZ and DZ twins, respectively ($P_s < .001$). The LC_{CNR} was significantly heritable: $a^2 = 0.48$ (95% confidence interval [CI]: 0.08 to 0.70). The estimate of common environmental influences was small and non-significant ($c^2 = 0.13$; 95% CI: 0.0 to 0.49), and the estimate of unique environmental influences was significant ($e^2 = 0.38$; 95% CI: 0.29 to 0.51).

3.2 | Relationship of LC_{CNR}, cognition, and aMCI

Age and LC_{CNR} were not correlated in rostral/middle ($r = -0.05$, $P = .25$) or caudal ($r = -0.02$, $P = .68$) sections. There were significant

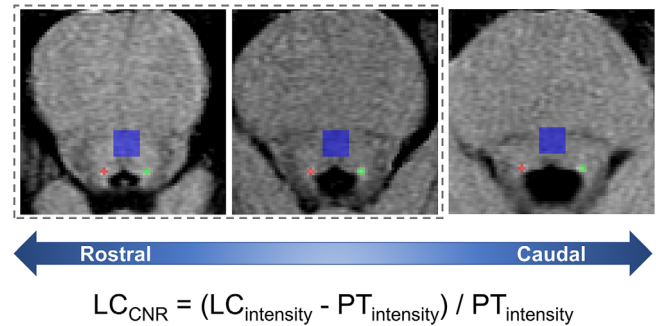


FIGURE 1 Summary of manual marking method. The middle slice is chosen 7 mm below the inferior colliculus. Left (green) and right (red) locus coeruleus (LC) are marked with a 3 mm² cross and the signal is averaged. A 10 mm² square is placed over a reference region in the pontine tegmentum (PT). The same marking rules are used to mark one slice rostral and one slice caudal and a contrast-to-noise ratio (LC_{CNR}) is calculated for each slice. Based on evidence that age- and disease-related effects primarily affect the rostral and middle LC, the LC_{CNR} from only these two slices is averaged and used in the primary analyses. Supplemental analyses substituted LC_{CNR} from the caudal LC or signal from the PT reference regions of interest to examine the regional specificity of effects

TABLE 2 Associations between rostral/middle locus coeruleus and cognitive domains

Cognitive domain	β	SE	<i>P</i> -value
Executive Function	0.071	0.046	.124
Working Memory	0.065	0.045	.145
General Verbal Fluency	0.110	0.046	.018
Semantic Fluency	0.134	0.047	.004
Memory	0.135	0.046	.003
Processing Speed	0.109	0.046	.018

Notes: Standardized coefficient estimates, standard errors, and *P*-values from linear mixed effects regression models testing the effect of rostral/middle locus coeruleus contrast-to-noise (LC_{CNR}) on cognitive domain factor scores. All models additionally adjusted for age and scanner. LC_{CNR} was significantly associated with all domains tested except for Executive Function and Working Memory. Raw *P*-values are bolded to indicate effects that survived FDR-correction for multiple comparisons.

Abbreviations: FDR, false discovery rate; SE, standard error.

associations between rostral/middle LC_{CNR} and four of the six cognitive factors after FDR-correction: General Fluency, Semantic Fluency, Episodic Memory, and Processing Speed (Table 2). Greater LC integrity was associated with better cognitive performance. In additional models examining the interaction with diagnostic group, the association of LC_{CNR} with General Fluency and Semantic Fluency was similar across all groups whereas effects on Episodic Memory and Processing Speed were primarily driven by individuals with MCI (Table S2 in supporting information). Caudal LC_{CNR} was significantly related to only Semantic Fluency and Episodic Memory (Table S3 in supporting information), indicating a gradient of effects. The PT reference region was significantly associated with Executive Function (Table S4 in supporting information).

TABLE 3 Associations among rostral/middle LC_{CNR}, amnesic MCI, and daytime dysfunction

Predictor	Odds ratio	SE	P-value
A. Association of rostral/middle LC integrity with amnesic MCI outcome			
LC _{CNR}	0.59	0.25	.034
Age	0.78	0.24	.296
Depressive symptoms	0.93	0.12	.559
Scanner	0.91	0.51	.853
B. Association of amnesic MCI with daytime dysfunction outcome			
aMCI status	2.94	0.42	.01
Age	0.90	0.12	.383
Depressive symptoms	1.69	0.09	<.001
Sleep apnea	4.11	0.32	<.001
C. Association of rostral/middle LC integrity with daytime dysfunction outcome			
LC _{CNR}	0.72	0.12	.008
Age	0.88	0.12	.3
Depressive symptoms	1.67	0.08	<.001
Sleep apnea	4.30	0.32	<.001
Scanner	1.11	0.27	.695
D. Association of LC rostral/middle integrity and daytime dysfunction with amnesic MCI outcome			
LC _{CNR}	0.61	0.24	.045
Daytime dysfunction (linear)	5.28	0.66	.011
Daytime dysfunction (quadratic)	1.64	0.41	.223
Age	0.79	0.23	.306
Depressive symptoms	0.82	0.13	.147
Sleep apnea	1.12	0.59	.850
Scanner	0.86	0.50	.764

Notes: Odds ratios, standard errors, and *P*-values from mixed effects regression models. Associations with amnesic MCI as the dependent variable were tested with logistic regressions, and associations with daytime dysfunction as the dependent variable were tested with ordinal regressions. Sleep item was removed from the depressive symptoms measure. Abbreviations: LC, locus coeruleus; MCI, mild cognitive impairment; SE, standard error.

Greater LC integrity was associated with lower odds of an aMCI diagnosis (odds ratio [OR] = 0.59; 95% CI: 0.36 to 0.96; *P* = .034) (Table 3A). Supplemental analysis showed that rostral/middle LC_{CNR} was not associated with naMCI compared to CN (OR = 1.09; 95% CI: 0.60 to 1.97; *P* = .787). Similar to the cognitive results, naMCI cases most often demonstrated impairments in executive function and working memory, which were not associated with LC_{CNR}. Neither caudal LC_{CNR} nor the PT were associated with aMCI status (Tables S5A and S6A in supporting information). There was a small yet significant interaction between rostral/caudal LC_{CNR} and young adult GCA (*r* = 0.11, *P* = .018). However, the relationship between LC_{CNR} and aMCI did not differ across levels of young adult GCA.

3.3 | Relationship of daytime dysfunction with LC_{CNR} and aMCI

Individuals with aMCI reported significantly greater daytime dysfunction (OR = 2.94; 95% CI: 1.29 to 6.7; *P* = .010; Table 3B). Age was not significantly related to daytime dysfunction, but more depressive symptoms (OR = 1.69; 95% CI: 1.43 to 2.00; *P* < .001) and sleep apnea (OR = 4.11; 95% CI: 2.18 to 7.74; *P* < .001) were. In contrast, individuals with naMCI were not more likely to report greater daytime dysfunction (OR = 0.54; 95% CI: 0.17 to 1.10; *P* = .292).

Higher rostral/middle LC_{CNR} was associated with lower levels of daytime dysfunction (OR = 0.72; 95% CI: 0.57 to 0.92; *P* = .008; Table 3C). Similar to the previous model, more depressive symptoms (OR = 1.67; 95% CI: 1.42 to 1.97; *P* < .001) and sleep apnea (OR = 4.30; 95% CI: 2.29 to 8.09; *P* < .001) were associated with higher levels of daytime dysfunction. A model including the LC_{CNR} × aMCI interaction indicated that the effect was similar across groups (Table S7 in supporting information). Including an LC_{CNR} × APOE ε4 status interaction did not alter results. Regarding regional specificity, higher caudal LC_{CNR} was also associated with less daytime dysfunction (OR = 0.70; 95% CI: 0.54 to 0.89; *P* = .004), but there was no effect of PT signal (Tables S5B and S6B). LC_{CNR} was not associated with other components of the PSQI.

When daytime dysfunction and rostral/middle LC_{CNR} were both included in a model predicting aMCI status, both remained significant (Table 3D). Greater daytime dysfunction was associated with increased odds of an aMCI diagnosis (linear contrast OR = 5.28; 95% CI: 1.45 to 19.19; *P* = .011) and higher rostral/middle LC_{CNR} was associated with decreased odds of aMCI (OR = 0.61; 95% CI: 0.38 to 0.99; *P* = .045).

4 | DISCUSSION

We found that the LC_{CNR} was heritable and higher LC_{CNR} was associated with better performance across multiple cognitive domains. Furthermore, lower LC_{CNR} was associated with more daytime dysfunction and increased odds of aMCI. Although Aβ and tau are the primary pathologies of AD, a number of interacting factors likely contribute. Our results, combined with those from previous studies, suggest LC dysfunction may influence multiple processes involved in AD pathogenesis. Figure 2 depicts a theoretical overview of how early tau in the LC may cause LC–NE system dysfunction, which exacerbates feedback loops between inter-related factors. The relationships found in the current study may be direct or indirect.

Some,^{20,38} but not all,¹⁹ studies have found differences in LC_{CNR} between CN individuals and those with MCI or AD. We found evidence of lower LC_{CNR} in the aMCI group in a larger sample of CN and aMCI than the previous studies. This is consistent with histological findings of LC neuronal loss in MCI and AD.² As found previously,¹ signal in the left LC was higher than the right. It remains unclear whether this has a biological basis or is driven by acquisition properties. Analyses of caudal LC and PT also suggest a degree of regional specificity. Consistent with previous findings, associations were strongest in rostral/middle LC.^{1,24}

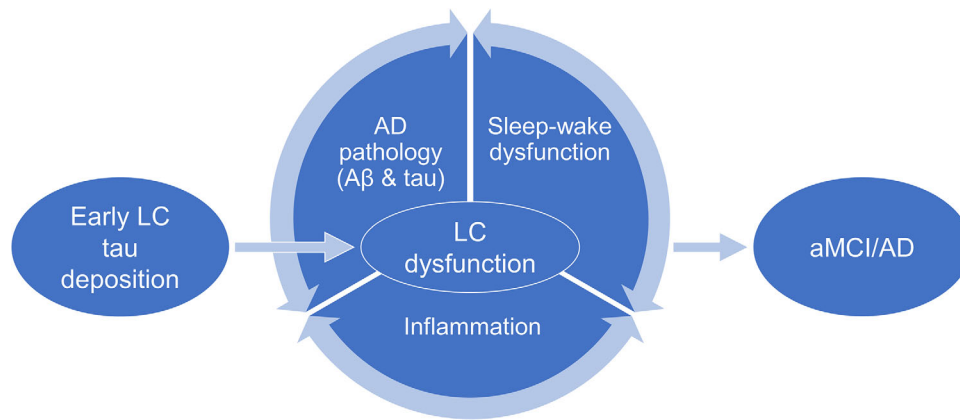


FIGURE 2 Overview describing contributions of locus coeruleus (LC) dysfunction on multiple processes in the development of amnesic mild cognitive impairment (aMCI). The diagram presents an overview based on the results of this study and findings from the literature. Early deposition of abnormal tau in the LC leads to disrupted function and eventual degeneration, as well as reduced release of norepinephrine (NE). Dysfunction of the LC-NE system has deleterious effects on multiple processes and exacerbates the harmful feedback loops between these processes. This model does not propose that damage to the LC is the initiating event in Alzheimer's disease (AD) pathogenesis, but highlights how the LC may have widespread impact on AD progression. Arrows represent associations between factors (direct or indirect), and indicate that evidence from the literature suggests bidirectional relationships between these factors. A β , amyloid beta

Average age was about 8 years younger than aforementioned studies, highlighting the potential of LC integrity as an early biomarker of risk for AD. Although age effects in LC_{CNR} have been reported,³⁹ particularly in the rostral LC, we did not find an effect of age on LC_{CNR}. However, our sample has a narrow age range of <10 years, which may not be optimal for detecting subtle age effects.

Greater daytime dysfunction among the aMCI group is consistent with previous reports of poor sleep and/or daytime sleepiness associated with MCI or AD,^{40,41} to which degeneration of wake-promoting neurons in the LC may directly contribute in AD. Although abnormal tau appearing in the LC quite early in life³ might suggest causality, the relationship between sleep-related impairments and AD pathology appears to be bidirectional.⁷ Longitudinal data will be needed to determine whether LC damage initiates this process.

There are multiple mechanisms through which disruptions to the sleep-wake cycle may increase risk for AD. Inflammation has been proposed as a key driver of AD,⁴² and may serve as a link. Disrupted sleep can increase inflammation,⁴³ and inflammation can promote A β pathology.⁴⁴ In a direct test, inflammation mediated the relationship between disrupted sleep-wake cycle and A β accumulation.⁴⁵ AD pathology is a key inflammatory stimulant,⁴⁶ and heightened inflammation can disrupt sleep processes.⁴⁷ If such deleterious feedback loops could be interrupted, it might slow progression of AD.⁴⁸

Disruption to the sleep-wake cycle has been shown to result in increased degeneration of LC neurons.⁴⁹ LC dysfunction can cause increased inflammation due to reduced levels of NE, which has anti-inflammatory properties.⁴⁶ Noradrenergic depletion can also result in increased A β accumulation,⁴ and LC signal contrast has been shown to correlate with A β in cerebrospinal fluid.³⁸ Moreover, LC-NE system dysfunction can induce a feedback loop in which the inflammatory response to A β is potentiated, and the heightened inflammatory state promotes further A β accumulation.^{5,50} The relationship between the LC and inflammation is bidirectional, with increased inflammation also

causing degeneration of LC neurons.⁵¹ MRI measures of LC integrity will facilitate continued research clarifying the relationships of factors shown in Figure 2.

Associations have been observed between MRI measures of the LC and episodic memory. However, the LC has widespread projections to brain regions that contribute to multiple cognitive processes¹⁶ and may therefore impact performance in multiple domains.⁵² Here, we found that reduced LC integrity was related to episodic memory, but also general verbal fluency, semantic fluency, and processing speed. Episodic memory and verbal fluency are typically prominently impaired early in AD. Moreover, processing speed begins to show age-related decline relatively early in adulthood⁵³ and we previously showed that semantic fluency and episodic memory during middle age predict 6-year conversion to aMCI.⁵⁴ Given that the LC begins to show reduced structural integrity starting in late middle age^{39,52} and is one of the earliest regions affected by AD,³ these results suggest that impaired functioning of the LC may at least partially contribute to age- and disease-related cognitive decline across multiple domains. Interestingly, LC structural integrity was not associated with executive function or working memory. This is consistent with the lack of association with naMCI, which is most often due to executive function impairment in our sample.

Genetic influences accounting for 48% of variance in LC_{CNR} is similar to estimates for regional cortical thickness and somewhat lower than volumetric subcortical measures,⁵⁵ although these measures are not directly comparable because LC_{CNR} is not a morphological measure, but rather an index of cell density derived from signal contrast. Given that LC_{CNR} is genetically mediated, it represents a worthwhile target for research to elucidate specific genes or pathways contributing to variance in LC structural integrity.

There are several limitations to the study. Generalizability may be limited due to the all-male, primarily White sample. For example, sex differences in cognition and behavioral domains have been proposed

to arise in part from sex differences in the LC–NE system.⁵⁶ However, strengths of the VETSA sample include an education level typical of the general population and participants that are younger than many typical studies of AD. Direct physiological measures of sleep and daytime functioning would clarify which aspects of the sleep–wake cycle are most associated with LC structural integrity. We also did not examine measures of inflammation or AD pathology, which may provide insight into potential mechanistic factors driving these relationships. Furthermore, we are unable to determine causal mediation effects without longitudinal data.

The LC–NE system projects throughout the brain and its dysfunction may impact multiple processes involved in AD pathogenesis. Associations with multiple cognitive factors highlight the potentially widespread impact of reduced LC integrity on cognition. These results lend further validation to the use of neuromelanin contrast MRI as a valid biological index. The observed associations in late-middle-aged adults are consistent with findings that tau may disrupt the LC–NE system early on, and highlights the potential utility of MRI-based measures of LC integrity in early identification of AD risk.

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CONFLICTS OF INTEREST

L.K. McEvoy has stock options in CorTechs Laboratories, Inc. A.M. Dale is a founder of and holds equity in CorTechs Laboratories, Inc, and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human Longevity, Inc and receives funding through research agreements with General Electric Healthcare and Medtronic, Inc. The terms of these arrangements have been reviewed and approved by University of California, San Diego in accordance with its conflict of interest policies. The other authors report no conflicts.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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