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Associations of 24-h Rest-activity Rhythm Fragmentation, Cognitive Decline, and Postmortem Locus Coeruleus Hypopigmentation in Alzheimer's Disease

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Abstract

Objective: While studies suggested that locus coeruleus (LC) neurodegeneration contributes to sleep-wake dysregulation in Alzheimer's disease (AD), the association between LC integrity and circadian rest-activity patterns remains unknown. Here, we investigated the relationships between

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Author Contributions

M.V.E, D.A.B., and H.I.L.J. contributed to the conception and design of the present study and/or to the acquisition and analysis of data; all authors contributed to drafting the text.

Potential Conflicts of interest

Nothing to report.

24-h rest-activity rhythms, cognitive trajectories, and autopsy-derived LC integrity in older adults with and without cortical AD neuropathology.

Methods: This retrospective study leveraged multi-modal data from participants of the longitudinal clinical-pathological Rush Memory and Aging Project. Indices of 24-h rest-activity rhythm fragmentation (intradaily variability) and stability (interdaily stability) were extracted from annual actigraphic recordings, and cognitive trajectories were computed from annual cognitive evaluations. At autopsy, LC neurodegeneration was determined by the presence of hypopigmentation, and cortical AD neuropathology was assessed. Contributions of comorbid pathologies (Lewy bodies, cerebrovascular pathology) were evaluated.

Results: Among the 388 cases included in the study sample (age at death=92.1±5.9 years; 273 women), 98(25.3%) displayed LC hypopigmentation, and 251(64.7%) exhibited cortical AD neuropathology. Logistic regression models showed that higher rest-activity rhythm fragmentation, measured up to ~7.1 years before death, was associated with increased risk to display LC neurodegeneration at autopsy (OR=1.46, $CI_{95\%}$:1.16–1.84, p_{BONF}=0.004), particularly in individuals with cortical AD neuropathology (OR=1.56, $CI_{95\%}$:1.15–2.15, p_{BONF}=0.03) and independently of comorbid pathologies. In addition, longitudinal increases in rest-activity rhythm fragmentation partially mediated the association between LC neurodegeneration and cognitive decline (estimate=−0.011, $CI_{95\%}$:−0.023–−0.002, p_{BONF}=0.03).

Interpretation: These findings highlight the LC as a neurobiological correlate of sleep-wake dysregulation in AD, and further underscore the clinical relevance of monitoring rest-activity patterns for improved detection of at-risk individuals.

Introduction

Human aging is characterized by marked alterations in the regulation of sleep and wakefulness,[1] which have been identified as important risk factors for the clinical and neuropathological trajectories of several neurodegenerative diseases, including Alzheimer's disease (AD).[2] AD often involves an exacerbated form of age-related sleep-wake dysregulation and circadian rhythm disturbances that manifests in micro- and macrostructural sleep changes[3] along with a disruption of rest-activity rhythms across the sleep-wake cycle.[4] These modifications in the organization and composition of sleep and wake states were linked to abnormal accumulation or reduced clearance of amyloid-β (Aβ) and tau proteins, hallmarks of AD pathogenesis, as early as in the preclinical stages of the disease.[5–7] Accordingly, in older asymptomatic individuals, worsening of cognitive symptoms and clinical progression of AD were tightly linked to longitudinal deterioration in 24-h rest-activity patterns, as manifested by gradual increases in rest-activity rhythm fragmentation and instability.[8]

Recently, the brainstem locus coeruleus (LC) was put forward as a critical early neural substrate connecting AD-related processes and sleep-wake dysregulation.[9] Postmortem findings indicate that the LC is among the first sites of tau pathology, before any cortical tau deposition,[10] and undergoes substantial neurodegeneration in AD.[11] As part of the intricate subcortical sleep-wake circuitry, the LC is critically involved in the regulation of sleep and wakefulness states through the timely release of norepinephrine to the entire

cortex.[12] Animal studies showed that the activity of LC neurons is under circadian influence through indirect input from the suprachiasmatic nucleus (SCN),[13] the central pacemaker located in the anterior hypothalamus, and that LC lesions induced modifications in the circadian organization of the sleep-wake cycle.[14] In addition, recent *in vivo* studies reported that lower structural integrity of the LC was linked to subjective sleep-wake measures of daytime dysfunction[15] and nighttime fragmentation in older individuals.[16] However, to our knowledge, no studies have investigated the relationships between LC integrity and 24-h rest-activity patterns in humans. Furthermore, while both LC neurodegeneration and rest-activity rhythm disruption have been previously reported as correlates of cognitive decline in separate studies of older cohorts,[8,17,18] the interplay between these two factors on longitudinal cognitive trajectories remains to be investigated within a single framework. Addressing these important gaps constitutes a critical step to establish the LC as a key neurobiological substrate of altered rest-activity rhythms in the context of AD, and to disentangle the respective contribution of LC neurodegeneration and rest-activity rhythm disruption for AD-related cognitive decline. In turn, this will provide new targets to improve the early detection and monitoring of individuals at risk for AD trajectories. Here, we leveraged a large, longitudinal clinical-pathological dataset to elucidate the relationships between *antemortem* actigraphy-derived 24-h rest-activity patterns and neuropathological evaluation of LC neurodegenerative processes in older individuals with and without autopsy-derived cortical AD neuropathology. We further investigated whether the previously identified association between LC neurodegeneration and cognitive decline could be mediated by a deterioration in rest-activity rhythms over time.

Methods

Participants

This dataset included individuals aged ≥ 60 years from the Rush Memory and Aging Project (MAP), an ongoing observational clinical-pathological study that began in 1997.[19] Participants were recruited from retirement communities and subsidized senior housing facilities in Chicago and northeastern Illinois. Inclusion criteria for the MAP study were older age, absence of known dementia at enrollment, and consent to annual clinical/cognitive evaluation and brain donation at death. Eligibility criteria for the present analysis sample included data availability for at least two actigraphic assessments and two cognitive evaluations prior to death, and for *postmortem* LC pigmentation ratings. Participants who received a final clinical consensus diagnosis of dementia with a primary cause other than AD ($n = 6$) were further excluded. According to these criteria, 388 participants were eligible. The MAP study was conducted in accordance with the Declaration of Helsinki and was approved by the Human Subjects Committee of Rush University Medical Center. All participants signed an informed consent, an Anatomical Gift Act, and a repository consent for data sharing.

Actigraphic assessments

Assessments of rest-activity rhythm characteristics were performed annually using actigraphy (Fig. 1A), a non-invasive tool to objectively investigate 24-h rest-activity rhythms in ecological settings and infer clinically relevant metrics about the circadian organization

of the sleep-wake cycle.[20] The Actical device (Philips Respironics, Bend, OR, USA) was worn on the non-dominant wrist to continuously record locomotor activity (1-second sample activity counts summed over 15-second epochs) for up to 10 days during each annual visit. Conventional non-parametric indices of intradaily variability (IV) and interdaily stability (IS) were computed on hourly-resampled actigraphy data as previously described[8,21,22] to assess the fragmentation and day-to-day stability, respectively, of participants' rest-activity rhythm. Typically, IV values are higher in individuals with more frequent daytime sleep periods or nocturnal awakenings, whereas lower IS values reflects poorer synchronization of an individual's rest-activity rhythm with environmental zeitgebers ("time givers"), such as the light-dark cycle.[20,21] IV and IS values were extracted at the actigraphy time point furthest from death (hereafter referred to as 'baseline actigraphy', on average 2.35 ± 2.39 years after enrollment) and across all actigraphy time points over the follow-up to estimate the slope of evolution. The mean number of available actigraphy time points per participant was 4.65 ± 2.40, with a mean time of 7.12 ± 3.33 years between the baseline actigraphy time point and death.

Neuropathological measures

Upon participants' death, brains were extracted and weighed, and the brainstem and cerebellar hemispheres were removed. The mean time interval between death and brain removal was 9.23 ± 8.71 hours. As previously described,[18] one hemisphere and the brainstem were fixed in 4% paraformaldehyde solution for at least three days, and sectioned into 1-cm-thick coronal slabs for neuropathological evaluation.

Locus coeruleus pigmentation

A qualitative rating of the presence of hypopigmentation in the LC ('Yes' *vs.* 'Maybe' *vs.* 'No'), a macroscopic measure of LC neurodegeneration,[18] was provided by a trained neuropathology technician after examination of the pallor of the LC. To increase the reliability and robustness of this qualitative variable, we excluded ambiguous cases (LC pigmentation rating of 'Maybe', $n = 66$) and only considered data from clear-cut cases (LC pigmentation ratings of 'Yes', $n = 98$, or 'No', $n = 290$) in the statistical analyses.

Cortical Alzheimer's disease neuropathology

The presence of cortical AD neuropathology was determined using the dichotomized version of the modified NIA-Reagan diagnosis of AD,[23] which combines information from the Braak staging scheme (neurofibrillary tangles)[24] and modified Consortium to Establish a Registry for AD (CERAD) score (neuritic plaques).[25] The dichotomized version aggregates scores from the four-level version into 'Low likelihood/no AD' *vs.* 'High/intermediate likelihood of AD'. The modified NIA-Reagan diagnosis of AD was made blinded to the final clinical diagnosis.

Additional comorbid pathologies

Lewy body pathology was assessed following examination of paraffin-embedded brain tissue sections (midfrontal, midtemporal, inferior parietal, anterior cingulate, entorhinal cortices, amygdala, and midbrain) immunostained for α-synuclein (Zymed; 1:50).[26]

The presence of Lewy body disease was rated as ‘not present’, ‘nigral-predominant’, ‘limbic-type’, or ‘neocortical-type’,[26] using modified criteria from McKeith et al.[27] As in previous work,[28] we dichotomized the presence of Lewy body pathology as ‘not present’ *vs.* ‘present’ (nigral-predominant, limbic-type, or neocortical type). Additionally, cerebrovascular pathology was investigated by rating the severity of arteriolosclerosis in vessels of the anterior basal ganglia with a semi-quantitative grading system ranging from 0 (none) to 7 (occluded)[29] compressed into a four-level scale (‘none’, ‘mild’, ‘moderate’, or ‘severe’), and by rating the severity of cerebral atherosclerosis in major arteries at the Circle of Willis and their proximal branches with a semi-quantitative scale ranging from 0 (no atherosclerosis) to 6 (severe atherosclerosis) collapsed into a four-level scale (‘none or possible’, ‘mild’, ‘moderate’, or ‘severe’).

Cognitive evaluation and clinical diagnosis

Annual assessments of cognitive function were administered using a battery of 21 neuropsychological tests (Fig. 1A). Based on 19 tests, summary scores were computed for global cognition and across five cognitive domains (episodic memory, working memory, semantic memory, perceptual speed, and visuospatial ability/perceptual orientation) at each visit, as previously described.[30] In addition, clinical diagnosis was determined annually by a neuropsychologist and a clinician, and a final consensus diagnosis was made by a neurologist after death, blinded to *postmortem* data, according to the criteria recommended by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA).[31]

Statistical analyses

Statistical analyses were performed using R (version 4.1.1, www.r-project.org). Logistic regression models assessed the relationship between *antemortem* rest-activity rhythm metrics (predictor) and *postmortem* LC pigmentation ratings (outcome, Fig. 1B). Models were adjusted for age at death, sex, education, *postmortem* interval, and time interval from baseline actigraphy to death. Linear mixed effect (LME) models adjusted for age and sex were used to extract individual slopes of evolution of IV and IS values across all actigraphy time points (median number of longitudinal actigraphic assessments = 4 ± 2.40, range 2 – 12). Similarly, LME models aligned with the baseline actigraphic assessment and adjusted for age, sex, and education, provided individual slopes of evolution of global and domain-specific cognitive performances over all subsequent evaluations until death (median number of cognitive assessments following baseline actigraphy time point = 9 ± 3.69, range = 2 – 21). Random effects included participants’ intercept and slope (time). A mediation analysis was conducted to test the mediating effect of rest-activity rhythm fragmentation on the relationship between LC hypopigmentation and global or domain-specific cognitive decline (Fig. 1C). These mediation models were performed with the *mediation* package in R, and the indirect effect was tested using a quasi-Bayesian Monte Carlo simulation with 5000 iterations. Post-hoc sensitivity analyses were conducted by including additional covariates related to comorbid pathologies in the logistic regression and mediation models to evaluate the potential influence of Lewy body disease and cerebrovascular pathology on the observed associations. Threshold for statistical significance in all analyses was two-tailed $p < 0.05$. Adjustment for multiple comparisons across logistic regression models was performed by

applying the Bonferroni correction (indicated by p_{BONF} values) per actigraphic metric. For the mediation analysis, the Bonferroni correction was applied to the p values associated with the indirect effect estimates across all mediation models (*i.e.,* 6 models in total).

Results

Demographic characteristics, actigraphic variables, and *postmortem* neuropathological features of the study sample are summarized in Supplementary Table S1. Among the 388 participants included in the analysis, mean age at death was 92.07 ± 5.91 years, and 273 (70.36%) were females. Participants included in the present analyses were diagnosed as cognitively unimpaired (CU, n = 299 (77.06%)) or mild cognitive impairment (MCI, n = 89 (22.94%)) at enrollment. At the time of the baseline actigraphic assessment, 279 (71.91%) were CU, 95 (24.48%) were MCI, and 14 (3.61%) were diagnosed with AD dementia. At death, 150 (38.66%) individuals received a final clinical consensus diagnosis of CU, 95 (24.48%) of MCI, and 143 (36.86%) of AD dementia. Sixty-nine (17.78%) individuals were carrier of at least one APOE ε4 allele.

At neuropathological examination, 98 (25.26%) participants displayed hypopigmentation in the LC. Logistic regression models adjusted for age at death, sex, education, and *postmortem* interval showed that the probability to display LC hypopigmentation at autopsy was higher in individuals who received a final clinical consensus diagnosis of AD dementia compared to CU individuals (adjusted odds ratio (AOR) = 2.52, 95% confidence interval ($CI_{95\%}$): 1.44 – 4.49, p = 0.001), and in males compared to females (AOR = 1.83, $CI_{95\%}$: 1.09 – 3.06, p = 0.02). Based on the dichotomous NIA-Reagan diagnostic criteria, 251 (64.7%) cases displayed *postmortem* evidence of cortical AD neuropathology. In addition, individuals who received a final clinical consensus diagnosis of MCI or AD dementia had increased odds to display evidence of cortical AD neuropathology (MCI: AOR = 3.08, $CI_{95\%}$: 1.77 – 5.45, p < 0.001; AD: AOR = 6.87, $CI_{95\%}$: 3.88 – 12.61, p < 0.001) compared to CU individuals.

Consistent with previous findings based on a larger sample of the MAP cohort,[8] rest-activity rhythm fragmentation and instability were greater in individuals who received a final clinical consensus diagnosis of AD dementia compared to CU individuals, both when considering baseline IV and IS values (IV: $t(382) = 3.40$, p = 0.002; IS: $t(382) = -2.58$, p = 0.03) or the slope of changes in IV and IS values (IV: $t(384) = 3.79$, p < 0.001; IS: $t(384) = -3.77$, p < 0.001, Supplementary Fig. S1). In addition, baseline IS values were lower in individuals with autopsy-derived Lewy body disease ($t(371) = -2.36$, p = 0.02), and baseline IV values were higher in the presence of ‘mild’ or ‘moderate’ arteriolosclerosis compared to ‘none or possible’ ($t(381) = 3.04$, p = 0.003, Supplementary Fig. S2).

Rest-activity rhythm fragmentation, but not instability, is associated with postmortem LC hypopigmentation

Using logistic regression models, we first found that each 1-SD increase in rest-activity rhythm fragmentation measured on average 7.12 years before death, as indicated by baseline IV values, was associated with 46% increased probability to display hypopigmentation in the LC at autopsy (AOR = 1.46, 95% confidence interval ($CI_{95\%}$): 1.16–1.84, p_{BONF}

= 0.004; Fig. 2A, Table 1). Similarly, worsening of rest-activity rhythm fragmentation over time, as reflected by a higher slope of changes in IV values across the follow-up, was associated with 44% increased odds of *postmortem* LC hypopigmentation (AOR = 1.44, $CI_{95\%}$: 1.13–1.85, p_{BONF} = 0.02, Table 1). By contrast, none of the IS values were significantly associated with LC pigmentation ratings (all $p_{BONF} > 0.51$; Supplementary Table S2). In a second step, we focused on a subsample of participants with *postmortem* evidence of cortical AD neuropathology based on the dichotomous NIA-Reagan diagnostic criteria ($n = 251$), and found similar associations between higher IV values and presence of LC hypopigmentation at autopsy (baseline IV values: AOR = 1.54, $CI_{95\%}$: 1.17–2.07, p_{BONF} = 0.01; slope of IV values: AOR = 1.56, $CI_{95\%}$: 1.15–2.15, p_{BONF} = 0.03; Fig. 2B, Table 1). Conversely, we did not detect such relationships in individuals with no or low cortical AD neuropathology ($n = 137$, baseline IV values: AOR = 1.18, $CI_{95\%}$ = 0.74 – 1.88, $p = 0.48$; slope of IV values: AOR = 1.12, $CI_{95\%}$ = 0.71 – 1.76, $p = 0.63$). In addition, considering only individuals who both received a final clinical consensus diagnosis of AD-related cognitive impairment (MCI or dementia) and displayed cortical AD neuropathology yielded similar significant associations ($n = 187$, baseline IV: AOR = 1.52, $CI_{95\%}$ = 1.13 – 2.07, $p = 0.006$; slope of IV values: AOR = 1.43, $CI_{95\%}$ = 1.04 – 1.99, $p = 0.03$). Furthermore, sensitivity analyses showed that including the presence of comorbid pathologies (Lewy body disease, cerebrovascular pathology) as additional covariates did not change any of the observed associations (Supplementary Tables S3–S4).

Rest-activity rhythm fragmentation mediates LC-related cognitive decline

Given the previously reported associations between cognitive decline and rest-activity rhythm disruption[8,17] as well as LC neurodegeneration,[18] we performed a mediation analysis to test hypothesis-driven models integrating the relationships between LC integrity, longitudinal rest-activity rhythm fragmentation, and global or domain-specific cognitive decline. First, we replicated previous findings by showing that LC hypopigmentation was associated with faster global cognitive decline (total effect: $t(385) = -3.31$, $p = 0.001$, Fig. 3A), and this association remained after adjusting for cortical AD neuropathological measures (Supplementary Table S5). Second, as highlighted above, LC hypopigmentation was linked to steeper slopes of increase in IV values ($t(385) = 2.89$, $p = 0.004$, Fig. 3B). Third, higher IV slope values were related to steeper global cognitive decline ($t(385) = -4.34$, $p < 0.001$). This association was independent of the effect of LC hypopigmentation when considered jointly in a regression model (IV slope: $t(384) = -3.92$, $p < 0.001$; LC hypopigmentation: $t(384) = -2.77$, $p = 0.006$, Fig. 3C). A commonality analysis using an unadjusted model indicated that IV slope values explained 71.10% of unique variance in global cognitive decline and 17.28% was attributed to LC hypopigmentation, whereas the shared variance explained by both factors was 11.62%. Evaluation of the indirect effect revealed that the relationship between LC hypopigmentation and global cognitive decline was partially mediated by a worsening of rest-activity rhythm fragmentation over time (estimate = −0.010, $CI_{95\%}$: −0.021 – −0.002, p_{BONF} = 0.02, proportion mediated = 0.17; Fig. 3D). Furthermore, slopes of IV values partially mediated the association between LC hypopigmentation and cognitive decline for all domains, although only the mediation effect on episodic memory decline survived the correction for multiple comparisons (estimate = −0.011, $CI_{95\%}$: −0.023 – −0.002, p_{BONF} = 0.03, proportion mediated = 0.18, Supplementary

Fig. S3). Finally, the magnitude of these mediating effects was greater in the subsample of individuals with *postmortem* evidence of cortical AD neuropathology (estimate = −0.014, $CI_{95\%}$: −0.030 – −0.003, p_{BONF} = 0.02, proportion mediated = 0.22). Including comorbid pathologies as additional covariates in all branches of the mediation analysis did not modify the statistical outputs obtained in the whole sample or in the cortical AD neuropathology subsample.

Discussion

Recently, LC neurodegeneration has been proposed to crucially contribute to the behavioral and neuropsychiatric manifestations that emerge as early as in the preclinical stages of AD, such as sleep-wake dysregulation.[15,16,32] In the present clinical-pathological analysis, we found that worse rest-activity rhythm fragmentation, measured on average 7.12 years before death, was associated with increased probability to display LC hypopigmentation at autopsy, and this relationship was driven by individuals with *postmortem* evidence of cortical AD neuropathology. In addition, our mediation analysis indicated that worsening of rest-activity rhythm fragmentation over the follow-up was partially mediating the association between LC hypopigmentation and cognitive decline, with the most robust effect observed for episodic memory. Furthermore, all the highlighted relationships were independent of the effect of comorbid pathologies. Altogether, these findings expand on previous animal and human studies by highlighting novel associations between LC neurodegeneration and early AD-related clinical changes, including fragmentation of 24-h rest-activity rhythms, and they further emphasize the relevance of monitoring rest-activity patterns in older populations to identify individuals at higher risk for AD trajectories.

Our results support that rest-activity rhythm fragmentation may constitute an objective marker associated with increased likelihood of LC neurodegeneration in the context of AD-related processes. The actigraphy-derived IV metric is directly influenced by the presence of daytime rest or nighttime activity and is often considered as a proxy measure of sleep-wake fragmentation, *i.e.* the inability to sustain consolidated periods of wakefulness and/or sleep.[20,33] Animal studies established that the LC plays a major role in sleep-to-wake transitions[12,34] and in the circadian regulation of arousal across the sleep-wake cycle.[13,14] Thus, our findings corroborate these observations and expand on previously identified associations between *in vivo* quantification of LC structural integrity and subjective variables of daytime dysfunction and sleep disturbances,[15,16] by demonstrating a relationship with a broader and objective metric of sleep-wake fragmentation in humans. Furthermore, the association between rest-activity rhythm fragmentation and LC hypopigmentation was particularly expressed in individuals exhibiting AD neuropathological hallmarks. Accordingly, we previously showed that the relationship between LC integrity and self-reported nocturnal awakenings was moderated by plasma total tau levels in older individuals.[16] Although IV values do not discriminate between fragmentation of daytime and nighttime periods, this metric has been linked to subjective reports of naps[6,33] and specifically correlates with a focal actigraphy-derived measure of wakefulness fragmentation in older individuals.[35] Interestingly, chronic daytime napping behavior, which reflects fragmentation of the wakefulness period, was recently highlighted as an important risk factor for AD-related trajectories,[36] although the underlying

neurobiological substrates were not investigated in that study. Our findings therefore support neurobiological frameworks positing that the integrity of the LC may constitute a pivotal interface between sleep-wake fragmentation and AD.[9,37]

Rest-activity rhythm fragmentation was reported to be increased as early as in the preclinical stages of AD.[6] Critically, the time windows considered in our analyses indicate that a single assessment of rest-activity rhythm fragmentation several years before death, at a time when individuals display limited or no cognitive symptoms, may provide valuable information regarding the likelihood of ongoing neurodegenerative processes in the LC. Thus, beside the previously identified clinical relevance of longitudinal recordings of rest-activity rhythms to predict cognitive decline in older individuals,[4,8,36] our results pinpoint rest-activity rhythm fragmentation as an early marker of increased risk of displaying neurodegeneration within a key region associated with the earliest AD-related processes. By contrast, we observed no associations between LC hypopigmentation and IS values. The actigraphy-derived IS metric reflects the ability of the circadian timing system to synchronize the rest-activity rhythm with mainly photic (light-dark cycle) environmental time givers.[20] It is therefore possible that, rather than neurodegeneration only within the LC, the integrity of the connections between the LC and the SCN (e.g., the SCN-dorsomedial hypothalamus-LC pathway)[13] may be more closely associated with day-to-day stability in the circadian organization of rest-activity rhythms.[38]

Importantly, the LC is embedded in a complex subcortical circuitry comprising sleep- and wake-promoting neuronal populations that are also vulnerable early in AD, such as the hypothalamic orexinergic or histaminergic neurons.[11,37,39] While animal studies suggested that the LC may constitute a crucial effector of the inputs from upstream wake-promoting neuronal populations, including the hypothalamic orexinergic neurons,[40] future studies assessing the respective contribution of neurodegeneration among these nuclei to circadian dysregulation of the sleep-wake cycle in AD are therefore warranted to better characterize the role of the LC in this pathway.

Our mediation analyses suggest that part of the previously reported relationship between LC neurodegeneration and cognitive decline involves increasing fragmentation of the rest-activity rhythm over time. In addition, this indirect effect was more robustly observed for episodic memory decline, a hallmark cognitive impairment of the early phases of AD.[41] Interestingly, the LC and its neuromodulatory norepinephrine system play a key role in learning and memory,[42] not only during wakefulness but also through sleep-dependent pathways.[9,12,43] We therefore speculate that LC neurodegeneration may be related to episodic memory decline not only directly through its neuromodulatory effect, but also indirectly by driving fragmentation of wakefulness and sleep which would impede LC-related memory processing. In turn, increased fragmentation of the sleep-wake cycle may precipitate cognitive decline by contributing to the unfolding of AD pathophysiological processes, including the accumulation of tau pathology in LC neurons and their neurodegeneration.[44,45]

Importantly, results from the sensitivity analyses indicated that all the highlighted relationships were independent of the presence of Lewy body disease and arteriolosclerosis/

atherosclerosis. Sleep-wake fragmentation and circadian disturbances have been previously linked to both the presence of Lewy bodies[46,47] and cerebrovascular pathology.[22,48] Similarly, LC neurons are particularly affected by alpha-synuclein pathology[49,50] and recent autopsy studies showed that LC neurodegeneration was associated with cerebrovascular pathology.[28,51] Our sensitivity analyses therefore support some degree of specificity in the observed relationships between rest-activity rhythm fragmentation and LC hypopigmentation, independently of the potential contributing effects of key comorbid pathologies on both of these factors.

This study also has limitations. First, LC neurodegeneration was assessed with a semi-subjective evaluation of LC hypopigmentation during neuropathological examination. Although LC pigmentation ratings were produced following a standardized protocol within a unique laboratory, the use of more unbiased and quantitative measures of LC integrity, such as stereological quantification of total or tau-positive LC neuronal count,[18,39] would constitute a more robust and fine-grained approach to elucidate the relationship between rest-activity rhythms and LC integrity in aging and AD. Even though similar quantitative LC measures have been collected for a small subsample of the MAP cohort,[18] the eligibility criteria related to the present study and the limited overlap in data availability with actigraphic recordings prevented us from using these more detailed LC metrics. Nevertheless, we aimed to increase the reliability of the current qualitative variable by excluding ambiguous cases (LC pigmentation rating of 'Maybe'), thus only considering clear-cut options ('Yes' and 'No' pigmentation ratings) in our analysis. Second, while actigraphic recordings provide useful information about the circadian organization of rest and activity periods in ecological conditions, the use of actigraphy-derived metrics precludes from drawing specific conclusions about sleep-wake phenotypes, which would require polysomnographic assessments. Such polysomnographic recordings would further help identifying individuals with sleep-wake comorbidities (*e.g.* sleep apnea, insomnia) that may contribute to rest-activity rhythm fragmentation and potentially confound the reported associations. In particular, sleep apnea has been linked to increased accumulation and/or reduced clearance of Aβ and tau proteins,[52,53] as well as earlier onset of AD cognitive symptoms.[54] Third, due to unavailability in LC pigmentation ratings and/or actigraphic data for a portion of the MAP cohort, the sample used in the present study only included White individuals. In light of the reported influence of race/ethnicity on AD risk[55] as well as sleep and circadian rhythms,[56] future studies of more diverse populations are warranted to extend the present findings to other racial/ethnic groups. Finally, *antemortem* information about the presence and magnitude of AD pathology was not available in this sample. Given the previously reported link between AD pathophysiological measures and actigraphy-derived 24-h rest-activity patterns[6,57] or LC integrity[18,58] in asymptomatic individuals, collecting *in vivo* data related to ongoing AD pathophysiological processes would allow to evaluate their role in the highlighted associations already in the preclinical stage of the disease. Likewise, given the nature of the study sample, it mainly comprises very old individuals and additional studies in younger populations are therefore still required to examine earlier associations (*e.g.* during midlife) between rest-activity patterns and LC integrity, for example by leveraging MRI-derived investigation of LC structure and function *in vivo*,[59] in the context of initial AD-related processes.

Over the recent years, growing interest emerged regarding the role of the LC in the disruption of wakefulness and sleep typically observed during the course of AD.[9] In line with this framework, this clinical-pathological study showed that *antemortem* rest-activity rhythm fragmentation was associated with increased probability of LC neurodegeneration at autopsy, and mediated LC-related cognitive decline. These findings highlight the LC as a neurobiological correlate of sleep-wake dysregulation in aging and AD, and further emphasize the clinical relevance of monitoring rest-activity patterns in older populations to identify at-risk individuals for the successful implementation of preventive strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

Data and resources related to the Rush Memory and Aging Project are available upon request from the Rush Alzheimer's Disease Center Resource Sharing Hub (www.radc.rush.edu).

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Summary for Social Media If Published:

@DrMVanEgroo, @grinberg_t, @HeidiJacobsLab

While recent studies suggested that neurodegeneration of the brainstem locus coeruleus (LC) is critically involved in sleep-wake dysregulation in Alzheimer's disease (AD), the associations between LC integrity, circadian rest-activity patterns, and cognitive trajectories remain unknown. This study therefore investigated the relationships between *antemortem* 24-h rest-activity rhythms, *postmortem* LC pigmentation, and cognitive decline in older adults with and without autopsy-derived cortical AD neuropathology. Our results demonstrate that fragmentation of the rest-activity rhythm, measured up to ~7.1 years before death, is associated with increased risk to display neurodegeneration in the LC at autopsy, particularly in individuals with cortical AD neuropathology and independently of other comorbid pathologies. In addition, worsening of rest-activity rhythm fragmentation over time partially mediated the relationship between LC neurodegeneration and cognitive decline. These findings highlight the LC as a neurobiological correlate of sleep-wake dysregulation in aging and AD, and further underscore the clinical relevance of monitoring rest-activity patterns for improved detection of individuals at risk for AD trajectories.

Draft tweet:

Van Egroo et al. report that rest-activity rhythm fragmentation is associated with postmortem LC neurodegeneration, and mediates LC-related cognitive decline in Alzheimer's disease

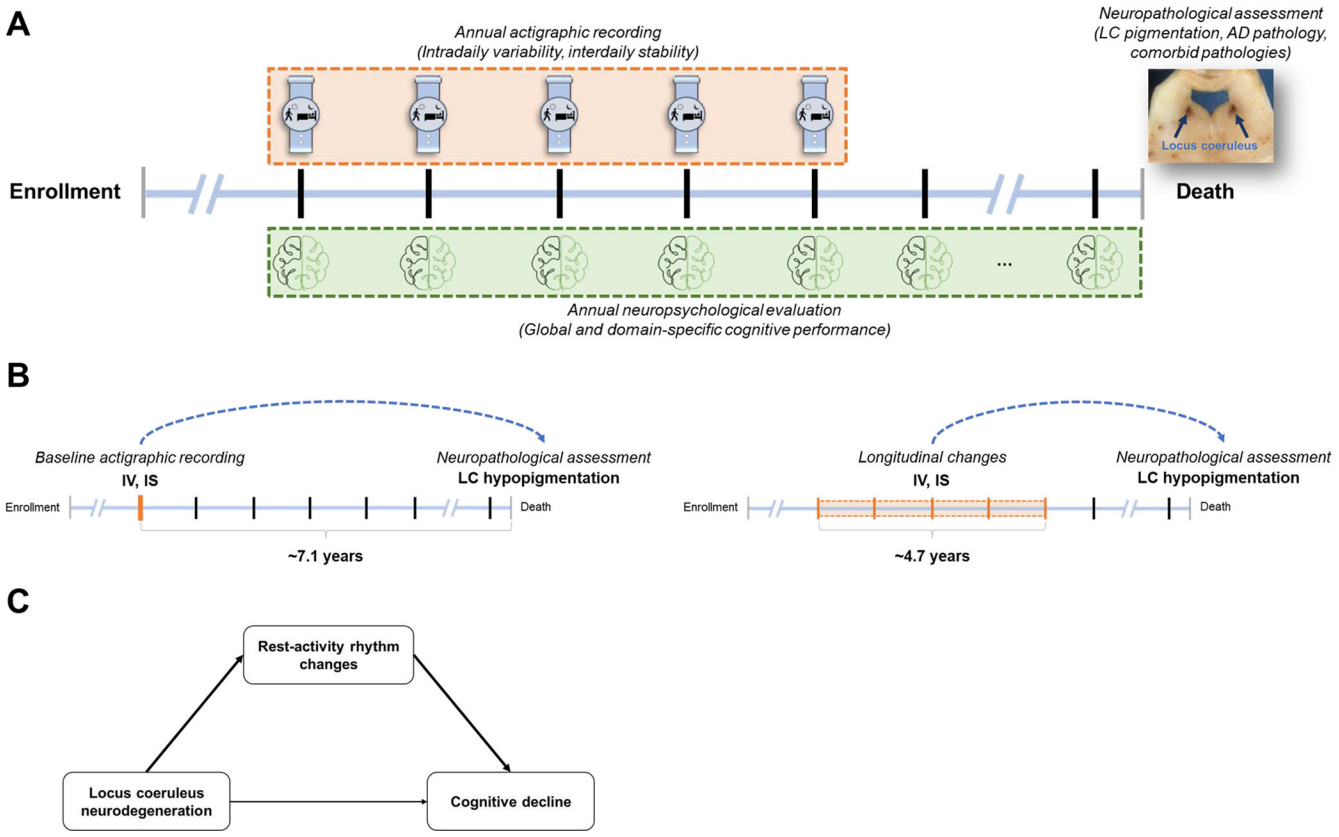

Figure 1. Graphical representation of the study design and statistical analyses.

(A) Illustrative timeline of the measurements of interest for a representative participant. Baseline and longitudinal changes in rest-activity rhythm fragmentation (intradaily variability, IV) and stability (interdaily stability, IS) were derived from annual actigraphic recordings. Slopes of cognitive decline were computed based on annual neuropsychological assessments. At autopsy, locus coeruleus (LC) pigmentation ratings were obtained after neuropathological examination of the brainstem. Cortical Alzheimer's disease (AD) neuropathology was assessed using the modified NIA-Reagan diagnostic criteria, and presence of comorbid pathologies (Lewy bodies, cerebrovascular pathology) was also evaluated. **(B)** Visual representation of the logistic regression models testing whether the presence of *postmortem* LC hypopigmentation is predicted by *antemortem* IV and IS values derived from the baseline actigraphic recording (on average 7.1 years before death, left panel) and over the duration of the follow-up (lasting on average 4.7 years, right panel). **(C)** Visual representation of the hypothesis-driven mediation models integrating the relationships between LC integrity, longitudinal rest-activity rhythm changes, and global or domain-specific cognitive decline. Abbreviations: AD, Alzheimer's disease; IS, interdaily stability; IV, intradaily variability; LC, locus coeruleus.

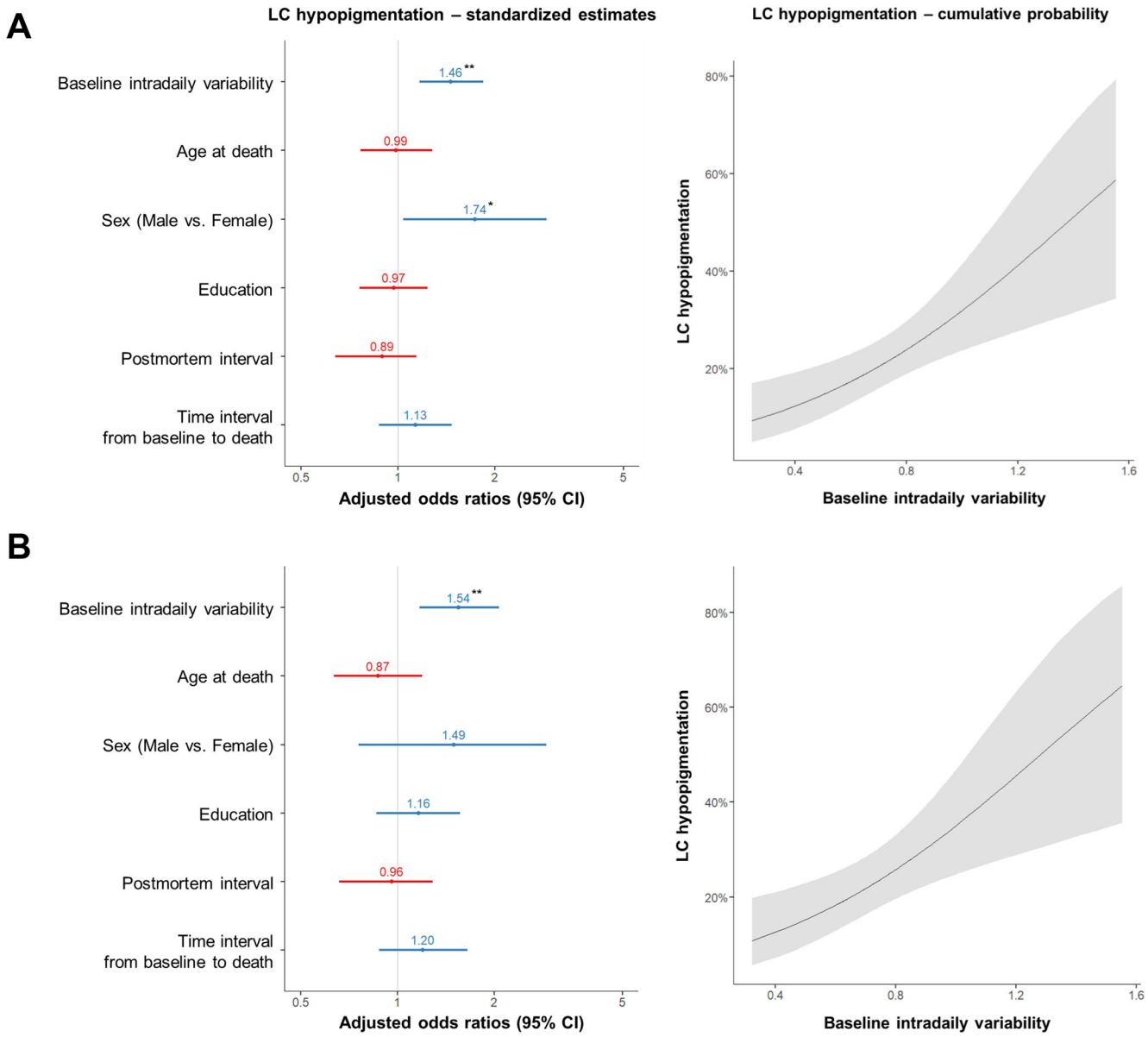

Figure 2. Statistical outputs of the logistic regression analysis.

Forest plot of adjusted odds ratios (left) and cumulative probability plot (right) of the logistic regression models testing the association between actigraphy-derived intradaily variability at baseline and *postmortem* LC hypopigmentation for **(A)** the whole sample (n = 388) and **(B)** in a sub-sample of individuals with *postmortem* evidence of cortical AD neuropathology (n = 251). Horizontal lines and shaded areas represent 95% confidence intervals related to the respective estimates. Abbreviations: CI, confidence interval; LC, locus coeruleus. *$p < 0.05$, **$p < 0.005$

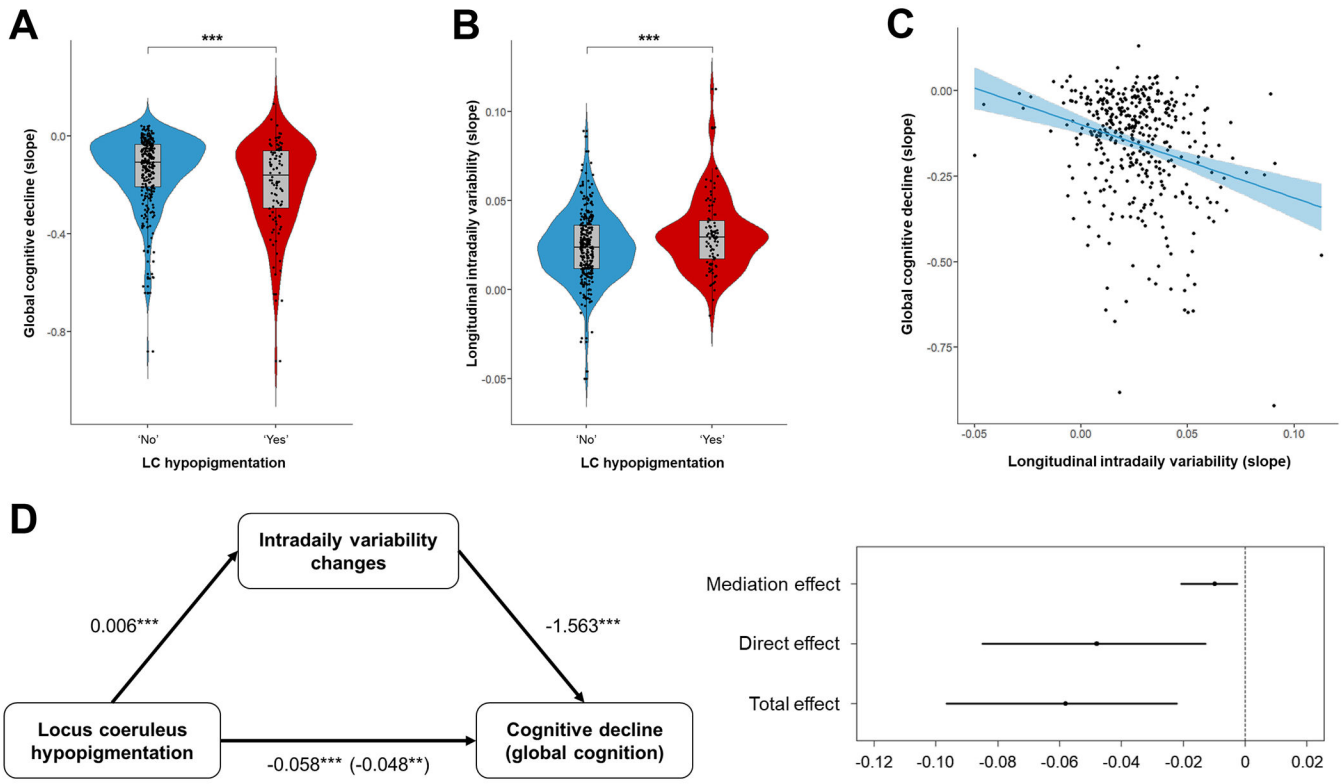

Figure 3. Statistical outputs of the mediation analysis in the whole sample (n = 388).

(A) Violin plots showing that individuals displaying *postmortem* LC hypopigmentation exhibit steeper slopes of global cognitive decline ($t(385) = -3.31$, p = 0.001). **(B)** Violin plots showing that individuals with *postmortem* LC hypopigmentation display higher longitudinal increases in intradaily variability values ($t(385) = 2.89$, $p = 0.004$). **(C)** Scatterplot of the relationship between higher longitudinal increases in intradaily variability values and steeper slopes of global cognitive decline ($t(384) = -3.92$, $p < 0.001$), independently of the effect of LC hypopigmentation. **(D)** Graphical representation of the mediation model testing the likelihood of longitudinal increase in rest-activity rhythm fragmentation (IV slopes) as mediator of the relationship between LC hypopigmentation and global cognitive decline. Numerical values along the arrows represent regression coefficients. Abbreviations: LC, locus coeruleus. *$p < 0.05$, **$p < 0.01$, ***$p < 0.005$

Table 1.

Statistical outputs of the logistic regression models with *antemortem* rest-activity rhythm fragmentation (intradaily variability values over time windows of interest) as predictor and *postmortem* LC hypopigmentation as output, both for the whole analysis sample (n = 388) and in the subsample of individuals with *postmortem* evidence of cortical Alzheimer's disease neuropathology (n = 251).

	Whole sample (n = 388)			
	Baseline actigraphy time point		**Longitudinal slope**	
	Odds ratio ($CI_{95\%}$)	*P* value	Odds ratio ($CI_{95\%}$)	*P* value
Intradaily variability, 1-SD increase	1.46 (1.16–1.84)	0.004 *	1.44 (1.13–1.85)	0.02 *
Age at death, 1-unit increase	1.00 (0.96–1.04)	0.91	1.00 (0.95–1.04)	0.88
Male sex	1.74 (1.04–2.89)	0.03	1.79 (1.07–2.98)	0.02
Education, 1-unit increase	0.99 (0.91–1.08)	0.81	0.99 (0.91–1.08)	0.86
Postmortem interval, 1-unit increase	0.99 (0.95–1.02)	0.42	0.99 (0.95–1.02)	0.44
Time interval from baseline to death, 1-unit increase	1.04 (0.96–1.12)	0.34	1.05 (0.97–1.14)	0.23
	Cortical AD neuropathology subsample[a] (n = 251)			
	Baseline actigraphy time point		**Longitudinal slope**	
	Odds ratio ($CI_{95\%}$)	*P* value	Odds ratio ($CI_{95\%}$)	*P* value
Intradaily variability, 1-SD increase	1.54 (1.17–2.07)	0.01 *	1.56 (1.15–2.15)	0.03 *
Age at death, 1-unit increase	0.97 (0.92–1.03)	0.38	0.97 (0.92–1.03)	0.37
Male sex	1.49 (0.76–2.90)	0.24	1.64 (0.83–3.18)	0.15
Education, 1–unit increase	1.05 (0.95–1.17)	0.32	1.06 (0.95–1.17)	0.29
Postmortem interval, 1-unit increase	1.00 (0.95–1.03)	0.81	0.99 (0.95–1.03)	0.74
Time interval from baseline to death, 1-unit increase	1.06 (0.96–1.17)	0.26	1.08 (0.98–1.20)	0.12

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; LC, locus coeruleus.

[a] based on dichotomous NIA-Reagan Alzheimer's disease pathology criteria.

* Bonferroni-corrected *P* values.

Table 2.

Statistical outputs of the logistic regression models with *antemortem* rest-activity rhythm fragmentation (intradaily variability values over time windows of interest) as predictor and *postmortem* LC hypopigmentation as output, both for the whole analysis sample (n = 388) and in the subsample of individuals with *postmortem* evidence of cortical Alzheimer's disease neuropathology (n = 251).

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