Received: 13 January 2025 | Revised: 26 February 2025 | Accepted: 7 March 2025

DOI: 10.1002/dad2.70105

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Rest-activity rhythm characteristics associated with lower cognitive performance and Alzheimer's disease biomarkers in midlife women

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Funding information
National Institutes of Health; National Institute on Aging, Grant/Award Numbers: RF1AG053504, R01AG053504, R21AG074094, 1R36AG088285

Abstract

INTRODUCTION: Disrupted rest-activity rhythms (RARs) have been linked to poorer cognitive function and Alzheimer's disease (AD) biomarkers. Here we extend this work to midlife women, who commonly experience menopause-related sleep and cognitive problems.

METHODS: One hundred ninety-four postmenopausal participants underwent a neuropsychological evaluation, 72 h of wrist actigraphy generating RAR variables, and a blood draw to measure AD biomarkers: phosphorylated tau (p-tau181, p-tau231) and amyloid beta (Aβ40, Aβ42).

RESULTS: Lower interdaily stability (IS) and relative amplitude (RA) and higher interdaily variability (IV) and least active 5 h (L5) were associated with worse processing speed, independent of sleep. Adjustment for sleep significantly attenuated the associations of RA with memory. Lower RA was associated with higher p-tau231 level, independent of sleep. Further adjustment for menopause-related factors modestly accounted for the associations between RAR, cognitive measures, and AD biomarkers.

DISCUSSION: Weaker RAR, particularly RA, was associated with worse cognitive functions, and higher AD biomarkers levels, possibly linking RAR with AD pathology in women.

KEYWORDS
actigraphy, Alzheimer's disease, amyloid beta, cognition, menopause, phosphorylated tau, women

Highlights

- Lower rhythm stability and robustness and higher fragmentation were associated with worse processing speed.
- Lower robustness was associated with higher levels of phosphorylated tau-231.
- Menopause factors did not attenuate the association between rest-activity rhythms and cognitive function.

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1 | BACKGROUND

Sleep and circadian disturbances are risk factors for dementia.[1–3] Evidence from cross-sectional and longitudinal studies shows that disrupted circadian rhythms are associated with prevalent Alzheimer's disease (AD) and mild cognitive impairment (MCI) pathologies, independent of age.[4–10] Compared to cognitively unimpaired adults, those with MCI or AD had higher levels of nighttime activity[10] and lower rhythm strength or robustness,[9,10] characterized by the ratio of daytime to nighttime activity. Suppressed rhythmicity/robustness and greater fragmentation at baseline were also associated with increased risk of MCI or AD and greater cognitive decline, suggesting that changes in rest-activity rhythms (RARs) may predict progression along the AD continuum.[8–14] Furthermore, in preclinical AD and healthy individuals, greater rhythm fragmentation was associated with lower cerebrospinal fluid (CSF) and positron emission tomography (PET) AD biomarkers.[15,16]

RAR disruption is linked to poorer cognitive function in middle-aged and older individuals.[1,9–13,17–19] In population-based studies of middle-aged and older individuals, weaker RARs, marked by lower day-to-day stability and robustness, and greater fragmentation was associated with poorer executive function, processing speed, episodic memory, and verbal fluency.[10,12,17,19] Furthermore, in middle-aged and older individuals, lower rhythm stability was associated with faster verbal memory decline, suggesting that RAR alterations may reflect subtle cognitive changes during aging.[13]

For women, midlife typically coincides with the onset of menopause, occurring on average at 51.4 years of age.[14] During menopause, women show reliable declines in verbal learning and memory, and to a lesser extent processing speed.[20–24] Some studies suggest faster cognitive decline in women than men, particularly in memory,[25] processing speed,[25,26] and global cognition, starting around midlife. Sleep disturbance is also common during menopause,[27] with some data suggesting reduced circadian activity in the postmenopause.[28] Sex differences in RARs show that women typically have less disruption than men, although the effect on cognitive aging remains unclear.[4,5,15,29] Among older women (≥80 years of age), weaker RAR was associated with increased odds of MCI and cognitive decline[11,30,31]; however, the relationship between RARs and cognition among midlife women is unknown. Understanding the factors associated with cognitive health in midlife women is critically important to address sex disparities in cognitive aging and dementia.

The present study aimed to examine the association between RARs, cognitive performance, and blood-based AD biomarkers in midlife women, and explore how menopausal symptoms and hormonal factors contribute to these relationships. We hypothesized that RAR disruption, characterized by higher fragmentation and lower day-to-day stability and robustness would be associated with worse cognitive performance, particularly verbal memory and processing speed, domains known to decline in the menopause transition. Understanding the factors affecting brain and cognitive health in midlife women may help optimize cognitive performance and prevent dementia.

RESEARCH IN CONTEXT

1. **Systematic review**: The author reviewed the literature using traditional methods such as PubMed and Google Scholar and selected peer-reviewed articles addressing the association between rest-activity rhythms (RARs) and cognition and Alzheimer's disease (AD). Most studies included both male and female participants and focused predominantly on older individuals. This study is the first to explore the relationship between RARs and blood-based AD biomarkers in late midlife women, a demographic that may provide new insights into the early identification of AD risk factors.
2. **Interpretation**: Women with weakened RARs had worse processing speed and higher levels of AD biomarkers. RARs may provide future targets for identifying women a greater risk of cognitive decline or AD, before the onset of cognitive symptoms.
3. **Future directions**: Future longitudinal studies focusing on midlife women are needed to further understand the associations of RARs and female brain and cognitive aging.

2 | METHODS

2.1 | Study sample

Participants were enrolled in MsBrain, a cohort study of menopause and brain aging initially conducted in Pittsburgh, Pennsylvania from 2017 to 2020. Recruitment procedures are described elsewhere.[32] Briefly, participants were recruited from the Allegheny County, Pennsylvania community through local advertisements, community fliers, brochures, listservs, and electronic mailing lists, and a subset from MsHeart cohort.[33] MsBrain inclusion criteria included being born female, ages 45–67 years, having a uterus and at least one ovary, and being late perimenopausal or postmenopausal status according to Stage of Reproductive Aging Workshop (STRAW) +10 staging guidelines.[34] Exclusion criteria included a history of stroke or cerebrovascular accident, dementia, seizure disorder, brain tumor, Parkinson's disease, head trauma with loss of consciousness >60 min, hysterectomy and/or bilateral oophorectomy or other procedure ending menses, or active substance use (established via urine toxicology screen and interview); current chemotherapy, pregnancy, intrauterine device, and use of select medications affecting vasomotor symptoms (VMS), including menopausal hormone therapy (oral/transdermal estrogen/progesterone), selective estrogen receptor modulators, aromatase inhibitors, selective serotonin reuptake inhibitors (SSRIs), or serotonin-norepinephrine reuptake inhibitors (SNRIs). To focus on RARs and cognition before impairment, we excluded participants with memory impairment ($N = 38$), defined using a combination of cutoff

scores on the Montreal Cognitive Assessment (MoCA), adjusted for race and education[35] norms, and the California Verbal Learning Test (CVLT; cutoff of 4 on the CVLT delayed recall[36]). Participants were excluded if they met both exclusion criteria on the MoCA and the CVLT.

2.2 | Study protocol

All study procedures were approved by the University of Pittsburgh Human Research Protection Office, and all participants provided written informed consent. After initial screening, eligible individuals completed in-person procedures, including urine toxicology, physical measurements, and questionnaires on health, sleep, mood, and quality of life. Participants were fitted with VMS and rest-wake activity monitoring devices (described in Sections 2.3 and 2.6). Following the monitoring period, participants returned to the laboratory for a fasting blood draw and a 1 h cognitive test battery.

2.3 | Circadian rest-activity pattern assessment

Participants wore an actigraphy watch (Actiwatch-2, Respironics, Inc., Murrysville, Pennsylvania, USA) on their non-dominant wrist for three consecutive days (72 h) and completed a sleep diary. Participants were instructed to press an event marker button on the watch to indicate bedtime and wake time. Actigraphy data were collected in 1 min epochs with a threshold of 40 movements/epochs. Sleep efficiency, defined as the percentage of time spent asleep compared to the total time spent in bed was extracted from Philips Actiware v6.0.0 software. RAR variables were generated from raw actigraphy, which had been reviewed by two independent trained staff members. RARs can be measured using a parametric and a non-parametric approach. The parametric methods assume sinusoidal pattern, whereas the non-parametric approach makes no assumption about the shape of the data. Here, we focused on non-parametric RAR, which has been associated with both cognitive decline and AD biomarkers.[1,9–13,17–19] We implemented the non-parametric approach for RAR analysis using custom R code. All measures were based on the entire time series of minute-to-minute counts. Technical definitions and methods for both measures, which are commonly used, have been published previously.[37] Any 24 h periods with more than three continuous hours of missing data or recordings shorter than 36 continuous hours were excluded from the analyses (n = 11). The RAR variables of interest were interdaily stability (IS), intradaily variability (IV), and relative amplitude (RA). We also looked at the least active 5 h (L5) and most active 10 h (M10) as measures of sleep continuity and maximum activity levels, respectively. IS measures how similar one 24 h activity profile is to the next; higher IS indicates greater (better) stability of the mean 24 h profile across days (Figure 1). IV measures rhythm fragmentation within a 24 h period; higher IV reflects more fragmented (worse) rhythms within days (i.e., napping during the day or high activity levels during nighttime). RA measures the difference between the most and least active periods in a person's 24 h RAR. Higher RA indicates greater (better) robustness or circadian rhythmicity, characterized by lower activity levels at night and higher activity during the day (Figure 1). RA was calculated as the difference between L5 anf M10 divided by their summation ((M10-L5)/(M10+L5)), where L5 represents the mean activity during the five consecutive hours with the lowest activity levels (typically sleep) and M10 represents the 10 consecutive hours with the highest activity level (typically waking hours).

2.4 | Neuropsychological assessment

Participants completed a neuropsychological assessment performed by a trained examiner. Primary outcomes included verbal memory and processing speed. Secondary outcomes included working memory, mental rotation, verbal and semantic fluency, and global cognition.

Verbal learning and memory and semantic clustering were measured using the CVLT.[38] A list of 16 items from four different semantic categories was read to participants, who were asked to recall as many words as possible from that list. Verbal learning was calculated as the sum of words recalled across five learning trials. Participants were then asked to recall words from the list after a short delay and a 20-min delay. Semantic clustering, a mnemonic strategy involving the grouping of words into semantic categories, was calculated as a weighted sum across all learning and recall trials. Processing speed was measured using the Symbol Digit Modalities Test (SDMT).[39] Participants were given a key pairing nine symbols with unique numbers (1–9) and were instructed to match each symbol to its corresponding number as quickly as possible.

Working memory was measured using the Letter Number Sequencing (LNS).[40] Participants were read sequences of numbers and letters and were asked to repeat them either in the same order (LNS Control) or by grouping the letters and numbers (LNS Experimental). Language fluency was measured using letter and semantic fluency, respectively, representing the sum of unique words generated in 1 min that began with a specific letter or belonged to a specific category.[40] Mental rotations, a spatial skill, was tested using the Card Rotation Test (CRT).[41] On each trial, participants were shown a geometric figure followed by eight figures that were either a two-dimensional rotation or mirror image of the target. Participants were instructed to differentiate the two-dimensional rotations from the mirror images. Global cognition was tested using the MoCA, which assesses seven cognitive domains (executive/visuospatial function, naming, attention, language, abstraction, recall, and orientation) generating a score ranging from 0 to 30.[42]

2.5 | Alzheimer's disease biomarkers

Plasma biomarker concentrations of amyloid beta 40 (Aβ40), Aβ42, phosphorylated tau-181 (p-tau181), and p-tau231 were measured using single-molecule array (Simoa) technology on an HD-X instrument (Quanterix, Billerica, Massachusetts, USA). All frozen samples were subjected to a single thawing cycle and measured with the

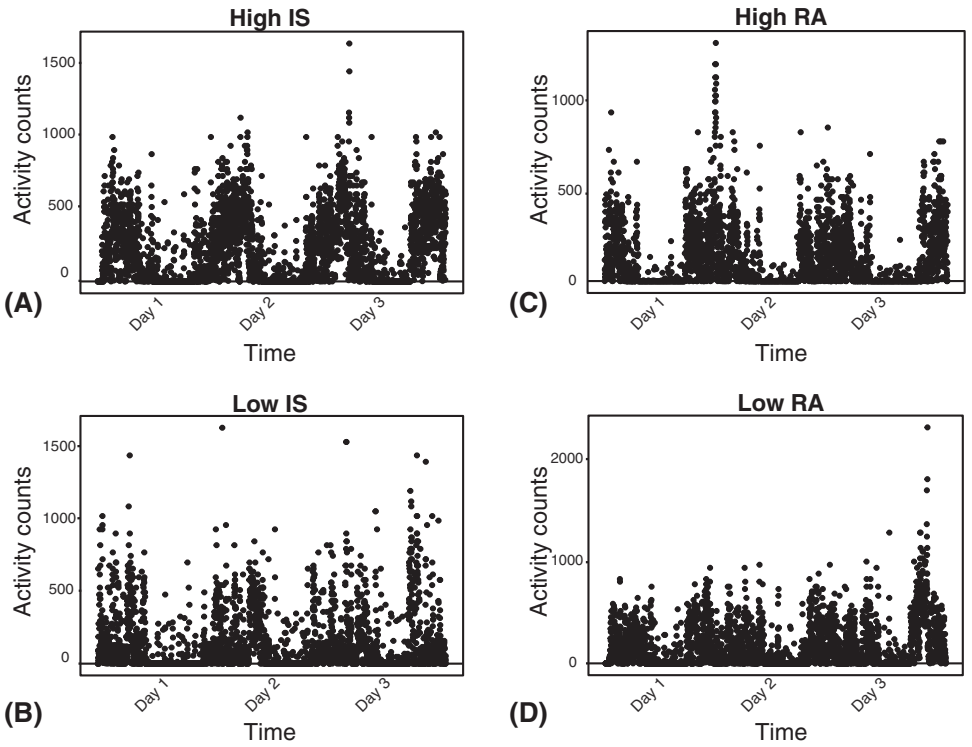

FIGURE 1 Examples of raw actigraphy recordings from the MsBrain study illustrating different measures of rest-activity rhythms. A and B show individuals with high (A) versus low (B) IS, reflecting greater versus lesser consistency and similarity between each 24h period. C and D show individuals with high (C) versus low (D) RA, reflecting greater versus lesser differences between rest and active periods. Abbreviations: IS, interdaily stability; RA, relative amplitude.

Neurology 4-Plex E (number: 103670) commercial assays from Quanterix. Plasma p-tau181 and p-tau231 were measured using validated in-house assays according to published protocols.[43,44] For each assay, two or three quality control samples of varying concentrations were analyzed in duplicate at both the beginning and end of each technical run to ensure reproducibility. The pooled quality control data showed that within- and between-run signal variations were less than 20%, with most variations around 10%. Here we calculated the ratio of Aβ42 to p-tau181.

2.6 | Vasomotor symptom monitoring

Participants were equipped with a VMS monitor (VU-AMS 5fs; Vrije Universiteit Amsterdam, Amsterdam, The Netherlands) to wear for 24 h. This device measures VMS via changes in sternal skin conductance, a validated physiologic measure of VMS.[45] VMSs were identified as a change in skin conductance $\geq$2 $\mu\Omega$ in 30 s. VMS data were downloaded and scored using UFI software (DPS, Morro Bay, California, USA) according to validated methods, with established reliability for this study ($\kappa = 0.89$). Only files with $\geq$70% usable data were included. VMS rates were calculated based on actigraphy-defined wake and sleep times and standardized to a 24 h day (17 h wake, 7 h sleep) to account for variations in monitoring durations.

2.7 | Covariates

Primary covariates included age, education (years), and race (White vs non-White). We ran additional analyses covarying for menopause factors such as time since the last menstrual period (LMP, years), serum estradiol (E2), and follicle-stimulating hormone (FSH). E2 was assessed using liquid chromatography–tandem mass spectrometry (LC-MS/MS) at the University of Pittsburgh's Small Biomarker Core, with inter- and intra-assay coefficients of variation of 5.0 and 8.1%, respectively, and a lower limit of detection of 1.0 pg/mL. FSH was assessed using a commercially available enzyme-linked immunosorbent assay (ELISA) from Cayman Chemical Co. (#500710), with inter- and intra-assay coefficients of variation of 4.5%–8.9% and 1.0%–4.5%, respectively, and an upper limit of detection of 100 mIU/mL. Apolipoprotein E (*APOE*) genotypes (rs429358 and rs7412) were determined using TaqMan genotyping assays,[46] with methods described previously.[32]

2.8 | Statistical analysis

Sample characteristics were reported using descriptive statistics. Normality was assessed visually from the histogram. Sleep efficiency was inverse log-transformed to achieve normality. Three IS observations, four RA observations, two L5 observations, and three M10

observations were removed for being more than 3 SD from the mean. Linear regression models examined the association between RAR variables and cognitive performance, first adjusting for age, education (years), and race (White vs non-White) (Model 1). Next, we performed sensitivity analyses to determine whether sleep efficiency (Model 2), menopause factors (time since LMP, estradiol, and FSH; Model 3) attenuated to the associations between RAR parameters and cognitive functions. Sensitivity analysis also confirmed that *APOE* ε4 presence did not influence the observed associations (not shown). Finally, we included an interaction model to examine whether menopause symptoms moderated the relationship between RAR and cognitive performance. We applied the Benjamini–Hochberg False Discovery Rate (FDR) correction to account for multiple comparisons for secondary (exploratory) outcomes within each model, but not for primary endpoints. Results are presented as standardized betas. All statistical analyses were performed using R (version 4.0.1).

3 | RESULTS

Participants included 194 postmenopausal women who were on average 59.0 ± 4.1 years old and non-Hispanic White (85.6%), had 15.7 ± 2.3 years of education, and were cognitively unimpaired (MoCA score of 27.4 ± 1.9). Demographics are presented in Table 1.

We next considered associations between RAR parameters and cognitive performance. Model 1 results are reported in Table 2. After adjusting for age, race, and education, lower IS was associated with worse processing speed ($B = 0.21$, $p < .01$) such that a 1-unit decrease in IS was associated with a 0.21 SD decrease in processing speed. Similarly, lower RA and higher IV and L5 were associated with worse processing speed (Figure 2). Lower RA and higher L5 were also associated with worse short delay recall ($B = 0.16$, $p = .04$; $B = -0.18$, $p = .02$, respectively), long delay recall ($B = 0.14$, $p = .05$; $B = -0.17$, $p = .02$, respectively), and semantic clustering ($B = 0.16$, $p = .04$; $B = -0.18$, $p = .02$, respectively). Lower RA was also associated with worse mental rotation performance ($B = 0.18$, $p = .02$, $q = 0.09$) and higher p-tau231 levels ($B = -0.22$, $p < .01$, $q = 0.08$; Figure 3); however, these associations were only trending toward significance after adjusting for multiple comparisons. Associations between RAR and cognitive performance was not mediated by any of the menopause factors (data not shown).

Next, we performed a sensitivity analysis on cognitive domains that were significantly associated with RAR, to control for sleep disturbance as measured by sleep efficiency. Because L5 is a measure of sleep disturbance, the model was not further adjusted for sleep efficiency. Model 2 results are reported in Table 3. Adjusting for sleep disturbance modestly attenuated the associations between processing speed and IS, RA, and IV. In contrast, associations of RA and short and long delay recall ($B = 0.11$, $p = .24$; $B = 0.05$, $p = .54$, respectively) and semantic clustering ($B = 0.05$, $p = .55$) were significantly attenuated by sleep disturbance. The association between RA and mental rotation was only modestly attenuated by sleep disturbance, with the coefficient (B) decreasing by 0.02 SD (11.8%). Sleep disturbance mod-

TABLE 1 Sample characteristics.

Characteristic ($N = 194$)	Mean ± SD; N (%)
Demographics	
Age, years	59.0 ± 4.1
Education, years	15.7 ± 2.3
Race, *N* (%)	
White	166 (85.6%)
Black/African American	24 (12.4%)
Asian or Pacific Islander	2 (1.0%)
Mixed race	2 (1.0%)
Body mass index (BMI)	28.6 ± 6.1
Time since LMP (years)	9.0 ± 4.9
Estradiol (pg/mL)	4.6 ± 4.4
FSH (mIU/mL)	68 ± 41
Objectively assessed VMS	6.5 ± 6.4
Center for Epidemiologic Studies Depression	7.8 ± 7.7
Pittsburgh Sleep Quality Index	5.9 ± 3.0
Cognition	
Montreal Cognitive Assessment	27.4 ± 1.9
CVLT—Learning	53.7 ± 8.3
CVLT—Short Delay Recall	11.6 ± 2.7
CVLT—Long Delay Recall	12.4 ± 2.6
CVLT—Semantic Clustering	0.1 ± 0.9
LNS—Experimental	15.5 ± 2.7
LNS—Control	18.0 ± 3.2
Symbol Digit Modalities Test (SDMT)	53.2 ± 7.9
Verbal Fluency (VF)	44.3 ± 10.5
Semantic Fluency (SF)	23.4 ± 5.0
Card Rotation Test (CRT)	77.3 ± 29.4
Alzheimer's disease biomarkers	
p-tau181	2.2 ± 1.7
p-tau231	2.1 ± 2.3
Aβ42/Aβ40	0.08 ± 0.02
Aβ42/p-tau181	0.33 ± 0.25
Actigraphy	
Interdaily stability (IS)	0.3 ± 0.1
Intradaily variability (IV)	1.7 ± 0.2
Relative amplitude (RA)	0.9 ± 0.1
Least active 5 h	13.0 ± 12.7
Most active 10 h	233.5 ± 81.5
Sleep Efficiency (%)	86.5 ± 7.0

Abbreviations: Aβ, amyloid beta; CVLT, California Verbal Learning Test; FSH, follicle-stimulating hormone; LMP, Last Mentrual Period; LNS, Letter Number Sequencing; p-tau, phosphorylated tau; VMS, vasomotor symptoms.

TABLE 2 Associations between rest-activity rhythms, cognitive functions, and Alzheimer's disease biomarkers, adjusted for age, education, and race.

	IS			IV			RA			L5			M10		
Primary outcome	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***
Verbal Learning	0.049	−0.10, 0.19	0.51	−0.028	−0.17, 0.11	0.69	0.11	−0.04, 0.27	0.14	−0.14	−0.29, 0.01	**0.07** *	0.05	−0.09, 0.19	0.49
Short-Delay recall	−0.081	−0.22, 0.06	0.26	0.026	−0.11, 0.16	0.71	0.16	0.01, 0.31	**0.04**	−0.18	−0.33, -0.04	**0.01**	−0.05	−0.19, 0.09	0.46
Long-Delay recall	−0.007	−0.15, 0.13	0.93	−0.028	−0.16, 0.11	0.68	0.14	0.00, 0.29	**0.05**	−0.17	−0.31, -0.02	**0.02**	0.06	−0.07, 0.20	0.37
Semantic clustering	0.016	−0.12, 0.16	0.82	−0.047	−0.18, 0.09	0.50	0.16	0.00, 0.31	**0.04**	−0.17	−0.32, -0.03	**0.02**	0.01	−0.13, 0.14	0.93
Processing speed	0.206	0.07, 0.34	**<0.01**	−0.150	−0.28, -0.02	**0.03**	0.23	0.09, 0.37	**<0.01**	−0.17	−0.31, -0.04	**0.01**	0.13	0.00, 0.26	0.06
Secondary outcome	**B**	**95% CI**	**q value**	**B**	**95% CI**	**q value**	**B**	**95% CI**	**q value**	**B**	**95% CI**	**q value**	**B**	**95% CI**	**q value**
Global cognition	0.00	−0.12, 0.13	0.95	−0.04	−0.16, 0.08	0.59	0.08	−0.05, 0.22	0.43	−0.08	−0.21, 0.05	0.40	0.05	−0.08, 0.17	1.00
Working memory	−0.13	−0.28, 0.01	0.21	0.09	−0.05, 0.22	0.40	−0.03	−0.18, 0.12	0.88	−0.06	−0.20, 0.09	0.62	0.01	−0.13, 0.15	1.00
Working memory	−0.07	−0.21, 0.07	0.55	0.16	0.02, 0.29	0.23	0.05	−0.09, 0.20	0.78	−0.10	−0.24, 0.05	0.36	−0.03	−0.17, 0.11	1.00
Verbal fluency	−0.03	−0.18, 0.12	0.95	−0.06	−0.20, 0.07	0.46	−0.01	−0.17, 0.14	0.89	0.04	−0.11, 0.19	0.64	0.05	−0.09, 0.19	1.00
Semantic fluency	0.01	−0.13, 0.14	0.95	−0.10	−0.23, 0.03	0.40	0.01	−0.13, 0.16	0.89	−0.02	−0.16, 0.12	0.82	0.07	−0.06, 0.20	1.00
Mental rotation	0.07	−0.06, 0.21	0.55	−0.07	−0.20, 0.06	0.44	0.18	0.03, 0.33	**0.09** *	−0.19	−0.33, -0.05	**0.09** *	0.00	−0.14, 0.14	1.00
Ab42/40 ratio	0.01	−0.14, 0.17	0.95	0.00	−0.16, 0.15	0.95	0.04	−0.12, 0.21	0.88	−0.05	−0.21, 0.10	0.64	0.01	−0.13, 0.16	1.00
Ab42/ptau181 ratio	0.17	0.02, 0.33	0.16	0.08	−0.07, 0.23	0.44	0.15	−0.02, 0.31	0.19	−0.13	−0.29, 0.02	0.24	−0.01	−0.16, 0.13	1.00
ptau231 (log)	−0.19	−0.35, -0.03	0.16	−0.11	−0.25, 0.04	0.40	−0.22	−0.38, -0.06	**0.08** *	0.15	−0.01, 0.30	0.24	−0.04	−0.19, 0.11	1.00
ptau181 (log)	−0.10	−0.26, 0.06	0.53	−0.13	−0.28, 0.02	0.40	−0.15	−0.31, 0.02	0.19	0.13	−0.02, 0.29	0.24	0.04	−0.11, 0.18	1.00

Bold values indicate $p < .05$, $^{*}p < .1$.

Abbreviations: Aβ, amyloid beta; IS, interdaily stability; IV, intradaily variablity; L5, least active 5 h; M10, most active 10 h; ptau, phosphorylated tau; RA, relative amplitude.

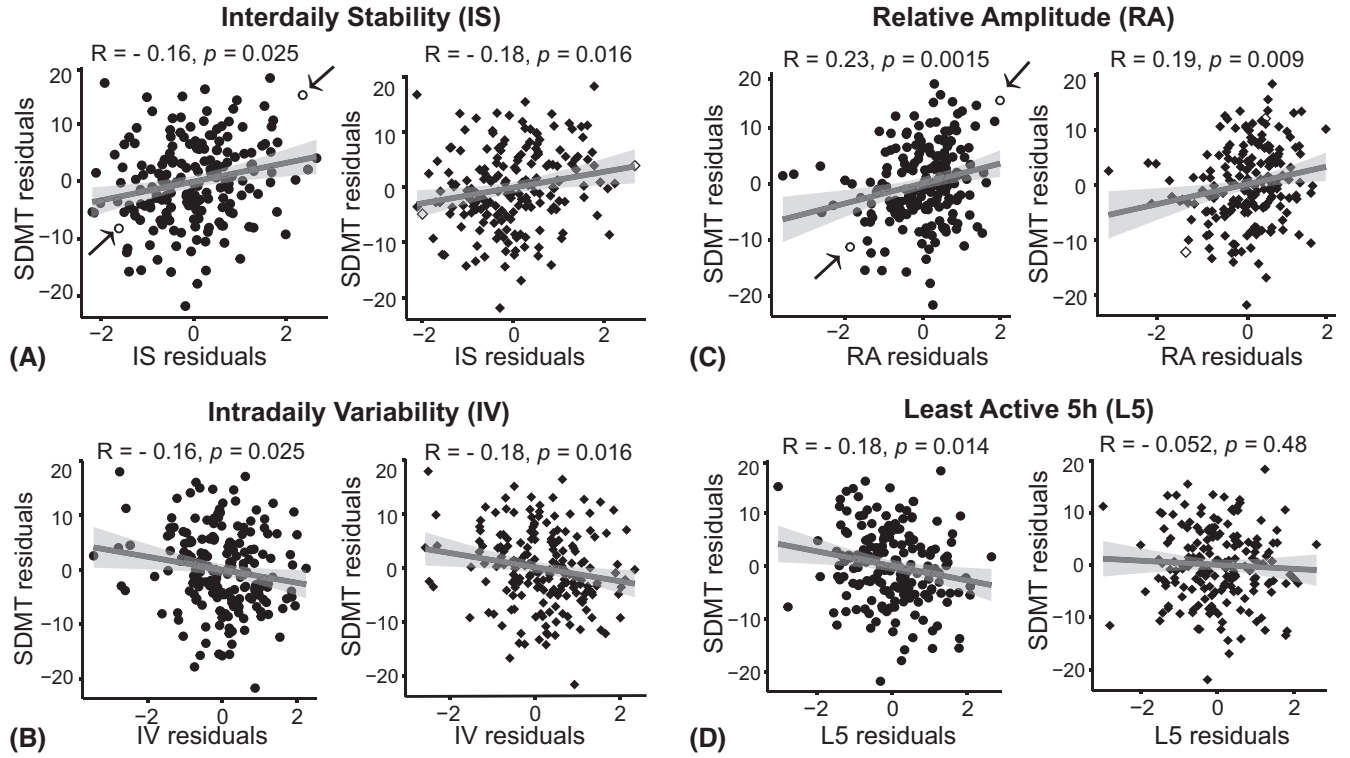

FIGURE 2 Associations between RAR predictors and processing speed. Model 1 (circles): adjusted for age, race, and education. Model 2 (diamonds): adjusted for age, race, education, and sleep efficiency. Empty circles/diamonds represent participants with high or low IS and RA, represented as illustrated in Figure 1. Abbreviations: IS, interdaily stability; IV, intradaily variability; L5, least active 5 h; RA, relative amplitude; RAR, rest-activity rhythm; SDMT, Symbol Digit ModalitiesTest.

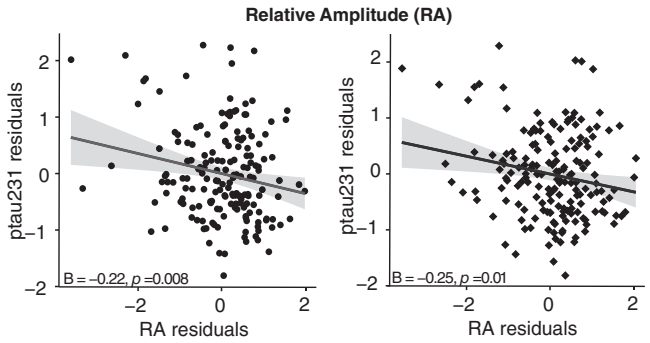

FIGURE 3 Association between RA and p-tau231. Model 1 (circles): adjusted for age, race, and education. Model 3 (diamonds): further adjusted for sleep efficiency, vasomotor symptoms, E2, FSH, and time since last menstrual period. Abbreviations: E2, serum estradiol; FSH, follicle-stimulating hormone; p-tau231, phosphorylated tau-231; RA, relative amplitude.

estly accounted for the association between RA and p-tau231, with an absolute change in *B* of 0.05 SD (22.7%).

In Model 3, menopause factors did not account for the association between RAR and processing speed (Table 3). Similarly, association between RA and p-tau231 levels were unaffected by menopause factors ($B = -0.27$, $p = .03$, $q = 0.13$; Figure 3).

4 | DISCUSSION

This study is the first to examine RAR, cognitive performance, and blood-based AD biomarkers in cognitively unimpaired midlife individuals, considering both sleep and menopause-related factors. Lower rhythm stability (IS) and robustness (RA) and higher fragmentation (IV) and nighttime activity (L5) were associated with worse processing speed, independent of sleep, suggesting the role of RARin this cognitive ability. Lower robustness was associated with worse episodic memory but these associations became non-significant after adjusting for sleep efficiency. Menopause-related factors did not account for the associations between RAR and cognitive performance. Finally, we found that lower robustness was associated with higher p-tau231 levels. Together our results indicate that in cognitively intact postmenopausal women, RAR, particularly robustness, may be indicators of worse cognitive function and increased AD risk.

Several studies have linked RAR characteristics to cognitive performance, but none focused on midlife women under age 65.[9–13,17–19] Our finding that greater fragmentation and lower robustness were associated with slower processing speed[12,17,19] aligns with findings from some of those studies. Some studies found greater fragmentation and lower robustness to also be associated poorer executive functions as measured by Stroop Color Word Test and Trail Making Test, executive functions not assessed here.[10,12,17] We did find those measures to

TABLE 3 Associations between rest-activity rhythms, cognitive functions and Alzheimer's disease biomarkers, adjusted for age, education, race, and sleep efficiency (Model 2), and further adjusted for last menstrual period (LMP), vasomotor symptoms (VMSs), follicle-stimulating hormone (FSH), and estradiol (E2) (Model 3).

Model 2 adjusted for age, education, race, and sleep efficiency.									
	IS			**IV**			**RA**		
Primary outcome	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***
Short delay recall	−0.12	−0.26, 0.02	0.10	0.02	−0.12, 0.15	0.81	0.11	−0.07, 0.30	0.24
Long delay recall	−0.06	−0.20, 0.09	0.44	−0.04	−0.17, 0.09	0.55	0.05	−0.12, 0.23	0.54
Semantic clustering	−0.03	−0.17, 0.11	0.66	−0.06	−0.19, 0.08	0.38	0.06	−0.13, 0.24	0.55
Processing speed	0.18	0.04, 0.31	**0.01**	−0.16	−0.29, -0.03	**0.02**	0.21	0.04, 0.38	**0.02**
Secondary outcome	**B**	**95% CI**	**q value**	**B**	**95% CI**	**q value**	**B**	**95% CI**	**q value**
Mental rotation	0.05	−0.09, 0.19	0.74	−0.08	−0.21, 0.05	0.40	0.15	−0.03, 0.34	0.25
p-tau231 (log)	−0.19	−0.35, -0.03	0.11	−0.10	−0.25, 0.05	0.40	−0.27	−0.46, -0.07	**0.08** †
Model 3 adjusted for age, education, race, and sleep efficiency, LMP, VMS, FSH, E2									
	IS			**IV**			**RA**		
Primary outcome	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***	**B**	**95% CI**	***p***
Short delay recall	−0.13	−0.27, 0.02	0.09	0.06	−0.08, 0.20	0.41	−0.02	−0.10, 0.28	0.81
Long delay recall	−0.05	−0.19, 0.09	0.48	0.00	−0.14, 0.14	0.98	−0.02	−0.14, 0.22	0.80
Semantic clustering	−0.03	−0.17, 0.11	0.69	−0.03	−0.17, 0.11	0.70	0.04	−0.13, 0.25	0.65
Processing speed	0.20	0.06, 0.34	**<0.01**	−0.18	−0.32, -0.04	**0.01**	0.29	0.06, 0.42	**<0.01**
Secondary outcome	**B**	**95% CI**	**q value**	**B**	**95% CI**	**q value**	**B**	**95% CI**	**q value**
Mental rotation	0.06	−0.09, 0.20	0.60	−0.07	−0.21, 0.08	0.45	0.17	−0.02, 0.36	0.26
p-tau231 (log)	−0.15	−0.31, 0.01	0.28	−0.12	−0.28, 0.04	0.45	−0.25	−0.46, -0.05	0.13

Bold values indicate $p < .05$; *$p < .1$.
Abbreviations: Aβ, amyloid beta; IS, interdaily stability; IV, intradaily variability; L5, least active 5 h; M10, most active 10 h; RA, relative amplitude.

be associated with semantic clustering, an executive cognitive strategy that organizes words into categories to facilitate encoding and recall. Prior work also found greater rhythm strength and nighttime activity to be associated with higher composite scores of executive functions and episodic memory including measures of both verbal and non-verbal memory.[10,13,17] We found an association of lower robustness with worse episodic memory that was no longer significant after adjustment for sleep. Although some discrepancies may be attributed to the different cognitive tasks used, these results are largely consistent with the present findings.

The focus on late midlife women raises the question about whether the associations observed here may be due in part to ovarian aging and menopause factors. Menopause-related factors did not account for the associations between IS and processing speed. RAR associations with executive functions and fluency, but not memory or processing speed, were seen in older women, suggesting that the patterns of association between RAR and different cognitive abilities may differ over the lifecourse.[11] Generally, however, our findings suggest that RAR's impact on cognitive function begins earlier, at a point where interventions may be effective in maintaining cognitive functions with age.[11] Future studies on light exposure, exercise timing, and sleep hygiene may be helpful, as light therapy has shown promise in improving cognitive performance in older adults.

Individuals with more fragmented, less stable, and robust rhythms have greater risks of developing AD or MCI[5,7,9] and faster cognitive decline over time.[4,5,9,13] Two studies examined RAR in relation to CSF and PET AD biomarkers in late midlife and older adults. Greater rhythm fragmentation was linked to lower CSF p-tau181/Aβ42[15,16] ratios and higher Aβ PET burden, suggesting that RAR disruption may precede Aβ deposition. Although associations between robustness and p-tau181/Aβ42 did not survive multiple comparisons, we did find that lower robustness was associated with p-tau231 levels, a sensitive marker of early AD pathology. These findings suggest that weaker RAR may indicate early disease progression.

Because circadian rhythms and sleep are closely linked, adjusting for sleep efficiency clarifies whether RAR relates to cognition independently of sleep. The association of RAR with memory and mental rotation but not with processing speed, became non-significant after accounting for sleep efficiency. Similarly, two prior studies found that the associations between RAR and episodic memory were accounted for by sleep features.[11,12] The present findings show that independent

of sleep, RAR measures associate selectively with processing speed in women in late midlife.

The relationship between cognitive performance and RAR is likely bidirectional. Circadian disruption may affect sleep-regulating brain areas, thereby interfering with memory processes. This may explain why episodic memory was not linked to RAR after adjusting for sleep. For instance, longitudinal rhythm fragmentation, observed years before death, was linked to locus coeruleus neurodegeneration, suggesting that RAR disruption precedes sleep-wake issues.[14] In midlife women without memory impairment, disrupted RAR likely drives cognitive decline before AD onset. These findings highlight RAR disruption as a potential target for preventing cognitive decline, especially psychomotor slowing, as women age.

This study has several strengths. First, our large sample of cognitively unimpaired midlife women reveals the link between RAR and cognitive aging before impairment. Subtle midlife cognitive changes have been linked to increased dementia risk, highlighting potential targets for prevention.[47] Second, we used a comprehensive neuropsychological battery to identify cognitive domains associated with circadian RAR, and newly identified mental rotations as a cognitive domain that may be sensitive to RAR. Finally, our study allowed us to control for a wide variety of menopause-related factors that are often overlooked in studies including middle-aged women. The present work also has limitations. First, the cross-sectional design does not allow for conclusions about temporal or causal associations between RAR and cognitive performance. Ongoing longitudinal studies focusing on midlife women are underway to further understand associations of RAR and female cognitive aging. Second, actigraphy data were collected for only 72 h. Although clinical practice guidelines suggest a minimum of 72 h to 14 days of recording, some studies suggest a minimum of 7 days for RAR analysis. Related ongoing work with a 7 day recording period is underway. Third, we did not include standard measures of executive function such as behavioral inhibition or cognitive flexibility, which have been shown to associate with RAR in other studies.[10,12,17] Finally, our sample consisted primarily of White participants, with limited representation from other ethnicities and races. Overall, this study provides strong initial evidence of the associations between RAR and cognition in midlife women, emphasizing the need for further investigation with longitudinal data, extended actigraphy recordings, and more diverse samples to fully elucidate these relationships.

This study expands on circadian rhythms, cognitive function, and AD pathology by showing significant associations between RAR, cognitive performance, and AD biomarkers in midlife women. Better rhythm stability and robustness was linked to better processing speed, independent of sleep disturbance, whereas associations with memory were explained by sleep. Lower rhythm robustness was also linked to higher levels of AD biomarkers. Menopause symptoms did not account for these associations, and more research is needed to explore the role of menopause and RAR as a modifiable risk factor for cognitive decline.

ACKNOWLEDGMENTS

This research was supported by the National Institutes of Health (NIH), the National Institute on Aging (grant numbers: RF1AG053504 and R01AG053504 to R.C.T and P.M.M), R21AG074094, and 1R36AG088285 (Alexandra Paget-Blanc).

All study procedures were reviewed and approved by the University of Pittsburgh Human Research Protection Office. All participants provided written, informed consent.

CONFLICT OF INTEREST STATEMENT

R.C.T. serves on the advisory board of and receives consulting fees from Astellas, Bayer, and Hello Therapeutics. She is a past consultant to Happify Health. P.M.M. serves on the advisory board of Astellas, Bayer, Estrigenix, and rē•spin; receives consulting fees from Astellas, Bayer, and Pfizer; and has equity in Estrigenix, rē•spin, and Midi-Health. A.P., S.F.S. and Y.C. have no financial or personal conflicts of interest to disclose. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

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

How to cite this article: Paget-Blanc A, Thurston RC, Smagula SF, Chang Y, Maki PM. Rest-activity rhythm characteristics associated with lower cognitive performance and Alzheimer's disease biomarkers in midlife women. *Alzheimer's Dement*. 2025;17:e70105. https://doi.org/10.1002/dad2.70105