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Original Article

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Rest-activity rhythm fragmentation and synchronization are linked with reduced cortical thickness in older adults "at risk" for dementia

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Abstract

Study Objectives: While alterations in rest-activity rhythms are common in older adults "at risk" for dementia, it is unclear how rest-activity rhythms relate to underlying brain integrity.

Methods: Older adults aged ≥50 years (n = 143, mean age = 67) with subjective and/or objective cognitive impairment underwent magnetic resonance imaging scanning and 14 days of actigraphy. The following nonparametric measures were computed: intra-daily variability (IV), inter-daily stability (IS), relative amplitude (RA), and average activity during the least active 5-h period (L5). A vertex-wise analysis correcting for age, sex, and clinical variables examined the association between nonparametric actigraphy measures and cortical thickness.

Results: When controlling for age, sex, and body mass index (BMI), lower IV was associated with greater cortical thickness in the right cuneus (cluster-wise p-values [CWP] < 0.001), left middle frontal gyrus (CWP < 0.001), and lateral orbital frontal cortex (CWP = 0.004). When controlling for age, sex, medical burden (CIRS-G), BMI, and antidepressant use, lower IS was associated with lower cortical thickness in the left (CWP = 0.002) and right superior frontal gyrus (CWP < 0.001), left superior temporal gyrus (CWP = 0.043), and left post-central gyrus (CWP = 0.033). There were no significant associations between RA or L5 and cortical thickness.

Conclusions: In older adults "at risk" for dementia, variability and stability of rest-activity rhythms were associated with reduced cortical thickness in frontal, temporal, parietal, and occipital regions. Further studies could focus on determining the prognostic utility of such markers longitudinally.

Key words: cortical thickness; actigraphy; aging; rest-activity; mild cognitive impairment

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Graphical Abstract

Rest-activity rhythm fragmentation and synchronisation are linked with reduced cortical thickness in older adults "at risk" for dementia.

Study population

143 older adults 'at risk' for dementia.

44 with SCI
99 with MCI

Actigraphy

14 days of actigraphy data.

Non-parametric actigraphy measures:

- Intra-daily variability (IV)
- Inter-daily stability (IS)
- Relative amplitude (RA)
- Average activity during the least active 5-hour period (L5)

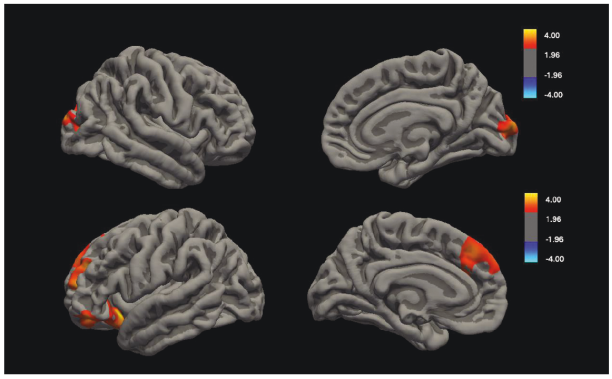
MRI scan

3T GE Discovery MR750 scanner.

T1-weighted BRAVO Spoiled Gradient-Recalled sequence.

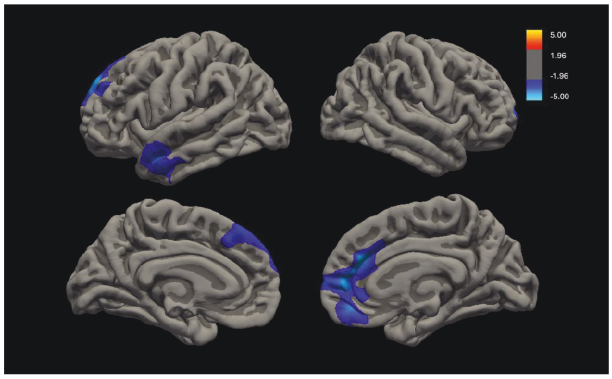
Cortical thickness was derived from FreeSurfer.

Cortical thickness differences between IV tertiles



When controlling for age, sex, and body mass index (BMI), lower IV was associated with greater cortical thickness in the right cuneus (CWP< 0.001), left middle frontal gyrus (CWP< 0.001) and lateral orbital frontal cortex (CWP= 0.004).

Cortical thickness differences between IS tertiles



When controlling for age, sex, medical burden (CIRS-G), BMI and antidepressant use, lower IS was associated with lower cortical thickness in the left (CWP= 0.002) and right superior frontal gyrus (CWP< 0.001), left superior temporal gyrus (CWP= 0.043) and left post-central gyrus (CWP= 0.033).

Conclusion

In older adults "at risk" for dementia, variability and stability of rest-activity rhythms were associated with reduced cortical thickness in frontal, temporal, parietal and occipital regions. Further studies could focus on determining the prognostic utility of such markers longitudinally.

Statement of Significance

This study is among the first to demonstrate associations between rest-activity rhythm variability and stability with cortical thickness in key brain regions associated with aging and dementia. The findings provide novel insights into how rest-activity rhythm markers may reflect underlying brain integrity in older adults "at risk" for dementia. Moreover, these results suggest the potential utility of actigraphy in memory clinic settings, where markers like intra-daily variability and inter-daily stability may help identify underlying brain changes and predict disease progression. As many patients in memory clinics report poor sleep quality, actigraphy offers a cost-effective and ecologically valid tool for detecting rest-activity rhythm disturbances. Longitudinal studies are warranted to further evaluate the prognostic value of these markers and to explore whether interventions targeting rest-activity rhythms may mitigate brain atrophy and cognitive decline.

It is well established that aging is associated with changes in sleep and circadian systems. Sleep changes include greater time spent in light sleep, increased nocturnal awakenings, less time spent in deep sleep, as well as increases in sleep-disordered breathing [1, 2]. Circadian alterations may include earlier onset and offset, decreased melatonin, and more variable and fragmented rest-activity rhythms [3]. In neurodegenerative diseases, including Alzheimer's disease (AD), such changes are particularly pronounced [4], even in the earlier "at risk" stage of subjective cognitive concerns [5] and in mild cognitive impairment (MCI) [6, 7], where there is a high risk of conversion to dementia within 5 years [8, 9].

While circadian rhythms are best captured via direct outputs of the suprachiasmatic nucleus [10], rhythmicity can be inferred by the examination of actigraphy-derived rest-activity metrics [11, 12]. Aside from being more feasible than laboratory studies of melatonin, actigraphic assessment offers ecological validity as it is usually worn in an individual's habitual environment over longer time periods of (typically) 7–14 days.

Some studies examining rest-activity rhythms have used cosinor analysis, with commonly assessed metrics including mean activity levels (mesor), timing of the peak of the activity rhythm (acrophase), and amplitude of the rhythm [13]. These showed that reduced amplitude is linked to cognitive decline and conversion to MCI/dementia longitudinally [14, 15]. However, cosinor modeling may not be well suited for such approaches as it may not adhere to the sinusoidal curve [16] and nonparametric models may be more appropriate [17]. These produce a number of measures that characterize the 24-h rest-activity rhythm including: intra-daily variability (IV) as a marker of fragmentation of the rest-activity rhythm; inter-daily stability (IS) as a marker of synchronization to the 24-h light-dark cycle; relative amplitude (RA) of the rhythm as measured by difference in mean activity during the least active 5-h period and most active 10-h period; and average activity during the least active 5-h period (L5) [2].

Nonparametric measures of the rest-activity rhythm appear to be related to a number of dementia risk factors [18], depression [19], as well as being linked to cognitive impairment [20]. Interestingly, in a sample of 189 community-dwelling older adults, higher rest-activity rhythm fragmentation, as defined by IV, was shown to be associated with both increased positron emission tomography (PET) defined β-amyloid positivity and increased cerebrospinal fluid phosphorylated-tau to β-amyloid ratio [21]. In a recent large prospective study, lower RA and higher IV were predictive of an increased risk of developing AD over a 15 year follow-up period [22]. Moreover, a faster transition to AD from MCI was predicted by lower RA and IS, and higher IV [22].

Although such findings suggest that key rest-activity rhythms may be an early marker of underlying disease pathology and risk of future decline, our understanding of how rest-activity rhythms relate to brain integrity is in its infancy. A retrospective analysis of 138 older people showed that higher IV was related to visual ratings of medial temporal lobe atrophy [23]. In 141 cognitively unimpaired older people, IV was associated with reduced gray matter volume of bilateral inferior-lateral frontal cortices [24]. In a sample of 108 older adults "at risk" for dementia, lower IS, later onset of L5 and greater activity of L5 were linked to a greater likelihood of higher white matter lesions (WMLs) in the anterior thalamic radiation [25], the superior longitudinal fasciculus and whole-brain respectively [25] and body mass index (BMI) and medical burden may be important moderators of these interrelationships [26]. However, the association between cortical thickness and rest-activity rhythms in older adults "at risk" of cognitive decline remains unexplored.

In this study, we aimed to examine if rest-activity rhythms are associated with cortical thickness in a clinical sample of older adults "at risk" for dementia who were experiencing either subjective cognitive impairment (SCI) or MCI. Based on previous evidence we explored the nonparametric measures of IV, IS, RA, and L5.

Materials and Methods

Participants

Participants were recruited through the Healthy Brain Ageing Clinic (Brain and Mind Centre, University of Sydney), a specialist research memory clinic that receives referrals for older adults (aged 50 years or older) who are seeking assessment for new onset cognitive and/or mood concerns. As described previously [27], exclusion criteria were: primary language other than English, significant neurological disorder (e.g., Parkinson's disease, epilepsy), previous stroke or head injury with loss of consciousness exceeding 30 min, history of significant psychiatric illness other than major depression (e.g., schizophrenia, bipolar disorder); current or past substance misuse or abuse. For the current study, additional exclusion criteria included Mini-Mental State Examination (MMSE) score less than 24 [28] or a diagnosis of dementia. All participants provided written informed consent before participation in the study and all research activities were approved by the University of Sydney Human Research Ethics Committee.

Clinical assessment

All participants underwent a semi-structured interview with a medical specialist, neuropsychologist, and research psychologist. The medical specialist recorded a detailed medical and sleep history, medication use, BMI, alcohol intake, and a rating of medical burden using the Cumulative Illness Rating Scale-Geriatric Version [CIRS-G] [29]. As described previously [27] all participants were assessed by a Clinical neuropsychologist, of which premorbid intellect (WTAR) and global cognition scores (MMSE) are reported here for descriptive purposes. Participants also completed self-report questionnaires to assess current depressive symptoms (Geriatric Depression Scale-15 item [GDS-15]) [30], current subjective sleep quality (Pittsburgh Sleep Quality Index; PSQI) [31], and total physical activity (modified Active Australia Survey [AAS]) [32]. Physical activity was calculated by adding the total minutes spent in walking and moderate activities with double the time spent in vigorous activities [32]. To prevent inaccuracies from over-reporting, all activity data exceeding 1680 min were curtailed to 1680 min [32].

Following clinical assessment, a consensus meeting was held with the medical specialist and two neuropsychologists to derive MCI classifications according to established clinical criteria of at least 1.5 SD decline (relative to premorbid estimates) in one or more cognitive domains with largely intact daily functioning [33]. Participants who did not demonstrate objective cognitive impairments were classified as meeting criteria for SCI (i.e., given that all participants sought referral to the clinic for concerns regarding their cognition).

Actigraphy

As per published protocols [12], participants were instructed to wear a wrist actiwatch for 14 days on their nondominant arm (Actiwatch Spectrum, Minimitter-Respironics, OR) and

to complete a daily sleep diary. All participants underwent at least 7 days of actigraphy recording within 3 months of clinical assessment. After the recording period, actigraphy data was downloaded and used to estimate the rest interval period and wake time across the entire recording period. Actiware 5.0 software was used to generate actigrams of rest-wake intervals, in conjunction with manual scoring incorporating the sleep diary and actigraphy-recorded light information. The wake threshold value was set at a medium sensitivity of 40 counts per epoch, with 30 s epochs.

Imputation.

As described previously [26], missing activity data (median = 2.16%, range ≤ 1.0%–9.42%) were imputed using the *mice* R package, version 3.9.0 [34]. White light exposure (in lux) and accelerometer counts (30 s epochs) were included in the imputation model with the random forest method. Observed versus imputed datasets were examined to evaluate the effectiveness of imputation for all participants.

Nonparametric actigraphy analysis.

Nonparametric actigraphy measures of IV, IS, RA, and L5 were derived from the actigraphy data with the *nparACT* R package; version 0.8 [35] (Table 1). Higher IV is indicative of greater rhythm fragmentation within 24-h periods. IS determines the similarity of daily activity patterns to the average daily activity pattern. RA is derived from the difference in mean activity during the least active 5-h period (L5) and most active 10-h period. For details on the distribution of nonparametric actigraphy measures, refer to Supplementary Figure 1. The distribution of each nonparametric actigraphy variable of interest was then divided into low, mid, and high portions based on the derived tertile cutoff (see Supplementary Table 1 and Supplementary Figure 2). Tertiles provide a clear structure for evaluating individuals based on potentially clinically meaningful cutoffs, thereby offering a practical approach to identifying patterns and assessing risk in a clinical context [36–38].

For descriptive purposes and to control for any potential confounder in the analysis, total sleep time in minutes (i.e., total rest interval—wake after sleep onset), sleep efficiency as a percentage (i.e., total sleep time/time in bed), time of sleep onset (24-h clock time), and time of sleep offset (24-h clock time) were also calculated.

Magnetic resonance imaging acquisition

Magnetic resonance imaging (MRI) was undertaken using a 3T GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI) at the Brain and Mind Centre, the University of Sydney. T1-weighted structural images were acquired with an 8-channel phased array head coil and T1-weighted BRAVO Spoiled Gradient-Recalled (SPGR) sequence (phase acceleration factor = 2) with 196 sagittal slices and repetition time = 7.2 ms, echo time = 2.8 ms, flip angle = 12°, acquisition matrix = 256 × 256 with 0.9 mm isotropic voxels.

Cortical thickness

For this study, we used a data-driven vertex-wise neuroimaging approach. Cortical thickness for each participant was derived from the FreeSurfer *recon-all* T1-weighted analysis pipeline (version 6.0; http://surfer.nmr.mgh.harvard.edu/), as described previously [39]. The resulting cortical parcellations were visually inspected for errors and outliers. 10 mm FWHM smoothing

Table 1. Demographic, clinical, and nonparametric actigraphy descriptive statistics for the entire group

Measure	N	Mean (SD)
Sex, female, *n* (%)	143	92 (64.34)
Age, y	143	67.41 (7.96)
MMSE, /30	143	29.00 [28.00, 30.00]
GDS-15	131	3.00 [1.00, 4.50]
Body mass index	137	26.40 [23.04, 30.90]
CIRS-G total	133	4.00 [2.00, 6.00]
Alcohol, drinks per week	116	2.00 [0.00, 7.00]
Antidepressant use (%)[†]	143	34 (23.78)
Total physical activity time (min)	132	630.67 [240.00, 956.25]
PSQI total	135	6.00 [4.00, 9.00]
Total sleep time (min)	137	435.21 [398.29, 475.46]
Sleep onset (min)	120	35.47 [25.25, 46.69]
Sleep offset (min)	120	34.55 [17.78, 45.47]
Sleep efficiency, /100	134	0.91 [0.89, 0.94]
Intra-daily variability (IV)	143	0.79 (0.20)
Inter-daily stability (IS)	143	0.53 (0.12)
Relative amplitude (RA)	143	0.90 [0.84, 0.93]
Average activity = least active 5-h period (L5)	143	7.05 [4.33, 11.46]

Mean (SD); Median [IQR]; All missing data were excluded using pairwise deletion. Abbreviations: MMSE = mini-mental state examination; GDS-15 = geriatric depression scale-15 item; CIRS-G = cumulative illness rating scale-geriatric version; PSQI = Pittsburgh Sleep Quality Index.
[†]SSRI = 17, SNRI = 15, and TCA = 2.

Table 2. Correlations between clinical and sleep variables and nonparametric actigraphy measures

	Intra-daily variability (IV)	Inter-daily stability (IS)	Relative amplitude (RA)	Least active 5-h period (L5)
Age	0.09	0.05	−0.10	0.00
MMSE, /30	−0.02	−0.07	0.15	−0.13
GDS-15	0.01	−0.11	−0.20	0.15
Body mass index	0.23*	−0.16	−0.22*	0.09
CIRS-G total	0.24*	−0.20	−0.27**	0.16
Total physical activity time (min)	−0.31	0.02	0.16	−0.10
Total sleep time (min)	−0.12	0.2	0.38**	−0.46**
Sleep onset (min)	0.05	0.03	0.17	−0.19
Sleep offset (min)	−0.15	0.03	0.09	−0.11
Sleep efficiency, /100	−0.2	0.2	0.53**	−0.52**

Pearson correlations, p-values are corrected for family-wise error rate using Bonferroni's method for each variable separately. Abbreviations: MMSE = mini-mental state examination; GDS-15 = geriatric depression scale-15 item; CIRS-G = cumulative illness rating scale-geriatric version.
*$p < .05$;
**$p < .01$.

was applied prior to statistical analysis with significant clusters defined at a level of $p < .05$ via Monte Carlo simulation with 5000 permutations. Cortical locations of significant effects are reported according to the Desikan–Killiany cortical parcellation atlas [40].

Statistical analysis

General linear models were used to assess vertex-wise differences in cortical thickness between tertile groups. Comparisons were conducted between any pair of tertile groups for a given actigraphy variable. Age and sex were included as covariates in all models. In order to control for potential confounds, relevant clinical (e.g., depression, BMI), sleep (e.g., total sleep time), and lifestyle (e.g., physical activity, alcohol) were modeled as covariates when either (a) correlated with the dependent variable or (b) they differed between the tertile groups. Multiple comparison corrected cluster-wise p-values (CWP) are reported, as well as the maximum difference in millimeters (mm) between the tertiles for each significant cluster (not corrected for covariates). The difference between each tertile adjusted for covariates (maximum gamma value) is also reported for significant clusters. Gamma values represent the contrast effect size, indicating the magnitude and direction of differences between groups. Positive values indicate increased cortical thickness and negative values indicate a decrease after controlling for covariates. Z-scores are provided in the figures to indicate the statistical significance of these differences, with higher z-scores representing more significant findings. Although this study was not specifically designed to examine sex differences across tertiles, we conducted an additional analysis to evaluate the interaction between tertiles and sex, adjusting for age.

All other statistical analyses were completed using R (R Core Team, 2021 [41]). Mean and standard deviation (SD) or median and interquartile range (IQR) are reported for descriptive purposes. Actigraphy measures were curtailed to ±3SD. For correlation analyses and subsequent post-hoc tests, p-values were adjusted using the Bonferroni correction method. The remaining statistical tests are reported in the captions of the corresponding tables. Missing data were excluded using pairwise deletion, and all analyses were two-tailed with the alpha-level set to 0.05.

Results

An initial 156 participants were recruited for the study. Of these, 13 were excluded due to actigraphy data not being appropriate for nonparametric analysis (7), poor MRI scan quality (4), abnormal anatomical findings (1), or actigraphy recording occurring greater than 3 months from MRI (1). A total of 143 participants were included in the study, all of whom had at least 7 days of actigraphy recording (mean days = 13.65; median = 14; range = 7–24) and nonparametric actigraphy measures (mean age = 67 years, SD = 8.0). The mean time between the MRI scan and the actigraphy data collection was 0.46 months (SD = 0.56, range = 0–3 months) or 13.74 days (SD = 17.57, range = 0–101 days). Furthermore, 90% ($n = 129$) of participants had their MRI scan and actigraphy data within the same month. Sample characteristics and summary actigraphy measures are presented in Table 1. Of the 143 participants included, 99 were classified as meeting clinical criteria for MCI. While those with MCI were significantly older than those without MCI (Supplementary Table 2), they did not differ from those with SCI on any other clinical, demographic, or actigraphy variables. Hence, both groups were combined for subsequent analyses.

Correlations between clinical and actigraphy measures

Table 2 shows correlations between nonparametric actigraphy measures and clinical and sleep variables. IV and RA were associated with the medical burden (CIRS-G) and BMI, but not with age, MMSE or GDS-15. RA and L5 were correlated with total sleep time and sleep efficiency. No other significant correlations were found. Correlations among actigraphy metrics are presented in Supplementary Table 3 for descriptive purposes.

Clinical differences between nonparametric actigraphy tertile groups

Table 3 shows clinical and demographic data for the low, mid, and high groups for the following nonparametric actigraphy measures:

- IV: BMI was higher in the high IV group compared to the low IV group ($p = .027$, Bonferroni corrected).
- IS: BMI was higher in the low IS tertile group compared to the high IS tertile group ($p = .026$, Bonferroni corrected).

Table 3. Differences in clinical and sleep variables among nonparametric actigraphy tertile groups

(3a)				
Intra-daily variability (IV)				
	Low	**Mid**	**High**	**P-value**
n	54	44	45	
IV value	0.59 (0.07)	0.78 (0.04)	1.02 (0.13)	
Age[†]	66.69 (7.65)	68.16 (8.22)	67.56 (8.16)	.656
Sex, female (%)[‡]	36 (66.67)	28 (63.64)	28 (62.22)	.894
MCI (%)[‡]	35 (64.81)	32 (72.73)	32 (71.11)	.663
GDS-15	2.00 [1.00, 4.00]	3.00 [1.00, 5.00]	3.00 [1.00, 5.00]	.430
PSQI total	6.00 [3.50, 9.00]	7.50 [3.75, 10.00]	6.00 [4.00, 9.00]	.657
MMSE, /30	29.00 [28.00, 30.00]	30.00 [29.00, 30.00]	29.00 [28.00, 30.00]	.410
CIRS-G total	3.00 [2.00, 6.00]	4.00 [2.00, 6.25]	5.50 [2.75, 7.25]	.110
Alcohol, drinks per week	2.25 [0.00, 6.25]	3.00 [0.75, 14.00]	2.00 [0.00, 4.00]	.145
Body mass index[*,c]	26.10 [22.45, 28.53]	26.40 [23.35, 29.08]	28.16 [24.59, 34.36]	.024
Antidepressant (%)[‡]	10 (18.52)	10 (22.73)	14 (31.11)	.335
Total physical activity time (min)	736.63 [240.00, 1061.25]	624.03 [305.00, 810.00]	592.08 [255.00, 825.00]	.743
Total sleep time (min)	459.27 [420.21, 503.84]	422.38 [382.50, 464.36]	430.46 [394.52, 473.47]	.096
Sleep onset (min)	33.47 [15.20, 19.45]	34.18 [16.51, 25.47]	36.61 [13.97, 20.88]	.744
Sleep offset (min)	34.14 [17.23, 27.67]	33.79 [17.18, 26.98]	28.18 [16.65, 28.53]	.254
Sleep efficiency, /100	91.65 [90.00, 94.00]	89.75 [88.00, 93.00]	88.92 [89.00, 94.00]	.345
(3b)				
Inter-daily stability (IS)				
	Low	**Mid**	**High**	**P-value**
n	48	52	43	
IS value	0.40 (0.009)	0.55 (0.02)	0.65 (0.04)	
Age[†]	66.40 (7.90)	67.23 (8.76)	68.77 (6.92)	.360
Sex, female (%)[‡]	28 (58.33)	34 (65.38)	30 (69.77)	.514
MCI (%)[‡]	29 (60.42)	39 (75.00)	31 (72.09)	.256
GDS-15	3.00 [1.00, 5.00]	2.00 [1.00, 6.00]	2.00 [1.00, 3.00]	.397
PSQI total	5.00 [3.00, 9.00]	6.00 [4.75, 9.00]	7.00 [3.75, 9.00]	.173
MMSE, /30	29.00 [29.00, 30.00]	29.50 [28.00, 30.00]	29.00 [28.00, 30.00]	.973
CIRS-G total[***]	5.00 [3.00, 7.25]	3.00 [2.00, 6.00]	4.00 [2.00, 6.00]	.052
Alcohol, drinks per week	2.25 [0.00, 7.38]	2.00 [0.25, 6.00]	3.00 [0.00, 7.00]	.957
Body mass index[*,c]	28.41 [24.91, 33.70]	25.48 [22.63, 31.75]	26.00 [22.65, 28.10]	.018
Antidepressant (%)[*,‡,§]	14 (29.17)	16 (30.77)	4 (9.30)	.028
Total physical activity time (min)	648.87 [180.00, 945.00]	640.98 [270.00, 835.00]	675.54 [255.00, 1065.00]	.659
Total sleep time (min)	434.52 [398.50, 475.46]	433.22 [390.49, 476.83]	448.22 [415.46, 499.46]	.206
Sleep onset (min)	34.98 [25.10, 50.30]	35.56 [28.03, 48.16]	29.24 [26.17, 43.34]	.821
Sleep offset (min)	29.24 [8.12, 45.31]	33.38 [21.24, 48.16]	32.96 [20.33, 42.23]	.745
Sleep efficiency, /100	89.06 [89.00, 94.00]	90.23 [88.00, 94.00]	91.05 [89.00, 94.00]	.878
(3c)				
Relative amplitude (RA)				
	Low	**Mid**	**High**	**P-value**
n	53	44	46	
RA value	0.76 (0.11)	0.90 (0.02)	0.94 (0.01)	
Age[†]	68.19 (8.59)	66.11 (8.34)	67.76 (6.74)	.417
Sex, female (%)[‡]	29 (54.72)	29 (65.91)	34 (73.91)	.134

Table 3. Continued

(3c)				
Relative amplitude (RA)				
	Low	**Mid**	**High**	**P-value**
MCI (%)[‡]	39 (73.58)	27 (61.36)	33 (71.74)	.389
GDS-15	3.00 [1.00, 6.50]	2.00 [1.00, 4.00]	2.00 [1.00, 4.00]	.466
PSQI total	7.00 [4.00, 10.00]	5.50 [3.00, 9.00]	6.00 [4.00, 8.00]	.247
MMSE, /30	29.00 [28.00, 30.00]	29.00 [28.75, 30.00]	29.00 [29.00, 30.00]	.401
CIRS-G total	4.50 [3.00, 7.00]	3.50 [2.00, 6.00]	3.00 [2.00, 6.00]	.173
Alcohol, drinks per week	1.00 [0.00, 5.75]	4.00 [0.50, 10.00]	2.00 [0.00, 4.00]	.190
Body mass index	28.10 [24.50, 33.32]	25.91 [23.03, 29.58]	26.45 [22.20, 29.91]	.217
Antidepressant (%)[*,‡,c]	19 (35.85)	10 (22.73)	5 (10.87)	.014
Total physical activity time (min)	554.16 [207.00, 815.00]	648.00 [267.50, 855.00]	751.34 [285.00, 1227.50]	.103
Total sleep time (min)[**,c]	418.03 [374.71, 477.47]	437.65 [399.54, 475.36]	458.21 [424.82, 494.89]	<.001
Sleep onset (min)	32.73 [23.30, 49.15]	35.33 [27.12, 47.65]	36.10 [28.82, 46.54]	.458
Sleep offset (min)	26.40 [9.29, 42.35]	34.61 [21.38, 48.57]	35.27 [25.34, 45.38]	.060
Sleep efficiency, /100[**,b,c]	86.86 [85.50, 93.00]	89.80 [88.00, 92.25]	93.44 [92.00, 95.00]	<.001
(3d)				
Least active 5-h period (L5)				
	Low	**Mid**	**High**	**P-value**
n	49	51	43	
L5 value	3.57 (1.00)	7.59 (1.51)	16.80 (6.36)	
Age[†]	66.84 (8.15)	67.80 (7.01)	67.60 (8.88)	.819
Sex, female (%)[‡]	29 (59.18)	36 (70.59)	27 (62.79)	.477
MCI (%)[‡]	34 (69.39)	36 (70.59)	29 (67.44)	.947
GDS-15	3.00 [1.00, 7.00]	2.00 [1.00, 4.00]	2.00 [1.00, 4.00]	.434
PSQI total	5.50 [4.00, 9.00]	6.00 [4.00, 8.00]	7.00 [3.00, 10.00]	.648
MMSE, /30	29.00 [28.00, 30.00]	29.00 [29.00, 30.00]	29.00 [28.00, 30.00]	.498
CIRS-G total	4.00 [2.25, 7.00]	3.00 [2.00, 6.00]	4.00 [2.00, 6.00]	.536
Alcohol, drinks per week	1.50 [0.00, 7.50]	2.00 [0.00, 4.00]	3.00 [0.00, 7.75]	.796
Body mass index	26.40 [24.35, 33.06]	26.50 [22.60, 30.70]	26.40 [23.85, 30.30]	.677
Antidepressant (%)[**,‡,a]	18 (36.73)	5 (9.80)	11 (25.58)	.006
Total physical activity time (min)	708.72 [260.00, 1215.00]	604.46 [190.00, 999.00]	642.31 [296.25, 911.00]	.545
Total sleep time (min)[**,c]	458.00 [425.57, 493.00]	445.15 [398.50, 485.36]	397.23 [371.53, 439.84]	<.001
Sleep onset (min)	35.84 [29.17, 47.54]	36.71 [27.06, 49.20]	29.94 [16.19, 41.07]	.095
Sleep offset (min)[*,§]	36.57 [26.31, 45.49]	30.77 [12.13, 48.46]	26.50 [10.67, 42.33]	.048
Sleep efficiency, /100 [**,a,c]	93.33 [92.00, 95.00]	90.13 [89.00, 92.00]	85.04 [82.75, 93.00]	<.001

Mean (SD); Median [IQR]; Kruskal–Wallis test unless otherwise noted. Abbreviations: MMSE = mini-mental state examination; GDS-15 = geriatric depression scale-15 item; CIRS-G = cumulative illness rating scale-geriatric version; PSQI = Pittsburgh Sleep Quality Index.
[†]One-way ANOVA.
[‡]Chi-square test.
[*]p < .05; [**]p < .01; [***]p = .052.
[§]The effect did not withstand Bonferroni multiple comparison correction; Post-hoc tests were Dunn's test for body mass index and the chi-square test for antidepressant, using a significance level of .05 (p-values were Bonferroni corrected):
[a] = significant difference between low and mid,
[b] = significant difference between mid and high, and
[c] = significant difference between low and high. Post-hoc tests were only applied when the overall test was significant.

Lower antidepressant use was observed in the high IS tertile group compared to the other groups (p = .028), although this effect did not withstand Bonferroni correction. A trend was noted for CIRS-G (p = .052).

- RA: a higher proportion of antidepressant use was observed in the low compared to the high RA tertile group (p = .024, Bonferroni corrected). Total sleep time was longer in the high RA tertile group compared to the low RA tertile group (p < .001, Bonferroni corrected). Sleep efficiency was higher in the high RA group compared to the low (p < .001, Bonferroni corrected) and mid (p < .001, Bonferroni corrected) RA tertile groups.

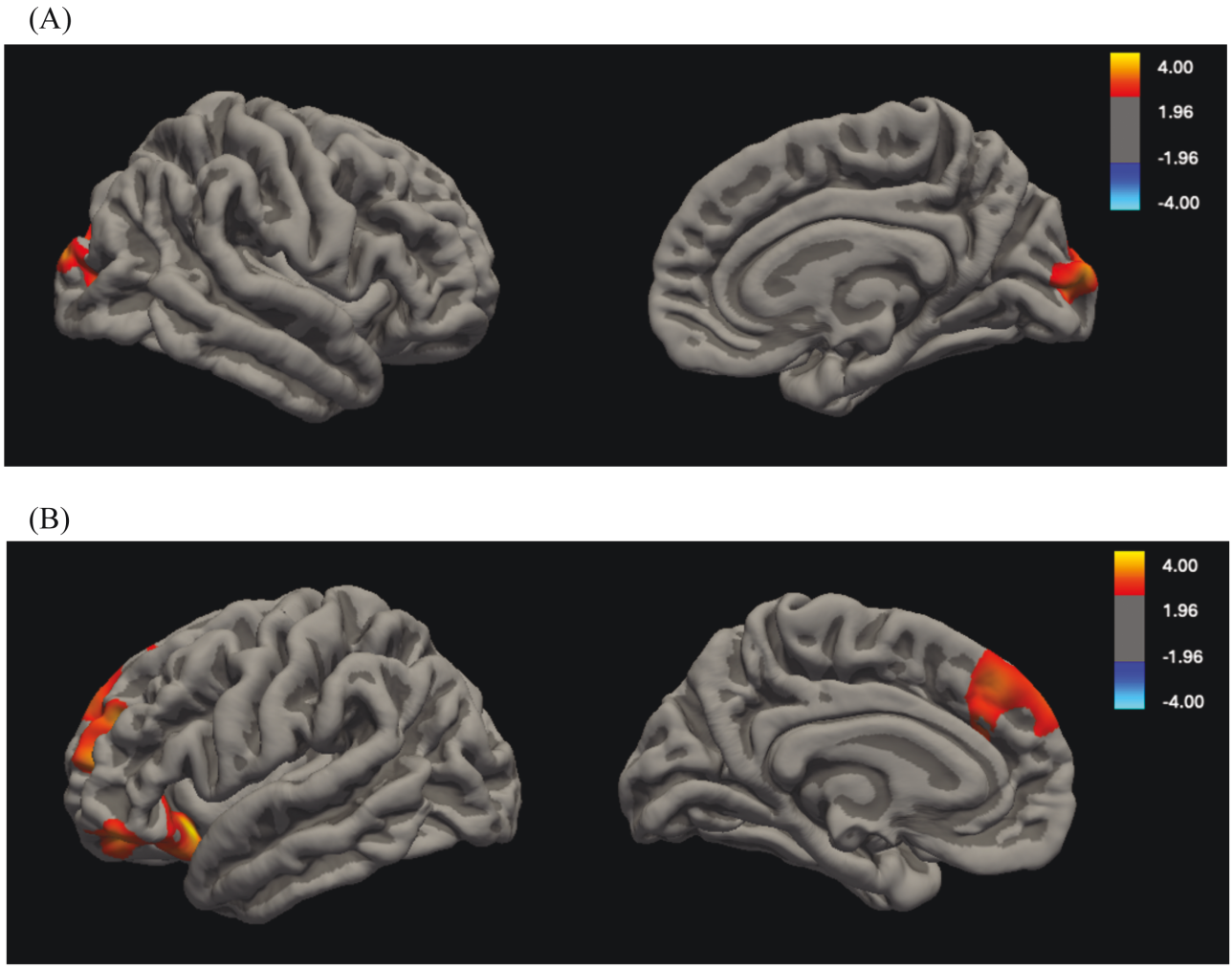


Figure 1. Cortical thickness differences between IV tertiles. The figure shows the results of the general linear model analysis used to assess vertex-wise differences in cortical thickness between IV tertile groups after controlling for age, sex, and BMI. Note: (A) Low IV with greater cortical thickness than high IV in right cuneus (CWP < 0.001) and (B) mid IV with greater cortical thickness than high IV in left middle frontal gyrus (CWP < 0.001) and lateral orbitofrontal (CWP = 0.004). This figure shows significant clusters after cluster-wise p-value correction. Colors show z-score values. The z-scores in the fully adjusted model were calculated using the "Z Monte Carlo" simulation method.

- L5: antidepressant use was higher in the low compared to the mid tertile group ($p = .009$, Bonferroni corrected). Total sleep time was longer in the low ($p < .001$, Bonferroni corrected) and mid ($p < .001$, Bonferroni corrected) L5 tertile groups compared to the high L5 tertile group. Sleep efficiency was higher in the low L5 tertile group compared to the mid ($p < .001$, Bonferroni corrected) and, high ($p < .001$, Bonferroni corrected) L5 tertile groups. Furthermore, sleep offset was higher in the low L5 tertile group compared to the high L5 tertile group ($p = .024$), though this effect did not withstand Bonferroni correction.

Nonparametric actigraphy and cortical thickness

- IV: when controlling for age, sex, and BMI, the low IV group (greater rhythm fragmentation) had greater cortical thickness than the high IV group in the right cuneus (CWP < 0.001, max gamma = 1.9, and max difference = 0.19 mm). Furthermore, the mid IV group had greater cortical thickness than the high IV group in the left middle frontal gyrus (rostral middle frontal; CWP < 0.001, max gamma = 2.1, and max difference = 0.14 mm) and lateral orbital frontal cortex (CWP = 0.004, max gamma = 2.5, and max difference = 0.25 mm) (Figure 1).
- IS: when controlling for age, sex, CIRS-G, BMI, and antidepressant use, both the low and mid IS groups (i.e., those having poorer synchronization to the 24-h light-dark cycle) had lower cortical thickness than the high IS group in the left and right superior frontal gyri, extending into the anterior cingulate and medial orbitofrontal cortices (low IS vs. high IS: left CWP = 0.002, max gamma = –2.4, max difference = 0.12 mm; right CWP < 0.001, max gamma = –2.9, max difference = 0.15 mm; mid vs. high: left CWP = 0.009, max gamma = –2.2, max difference = 0.12 mm; right CWP = 0.02, max gamma = –2.4, and max difference = 0.14 mm). In addition, the low IS group had lower cortical thickness in the left superior temporal gyrus (CWP = 0.043, max gamma = –2.7, and max difference = 0.06 mm) and the mid IS group showed lower cortical thickness in the left post-central gyrus (CWP = 0.033, max gamma = –3.4, max difference = 0.10 mm) (Figure 2).
- RA: when controlling for age, sex, total sleep time, sleep efficiency, and antidepressant use, no significant group differences in cortical thickness were found between any

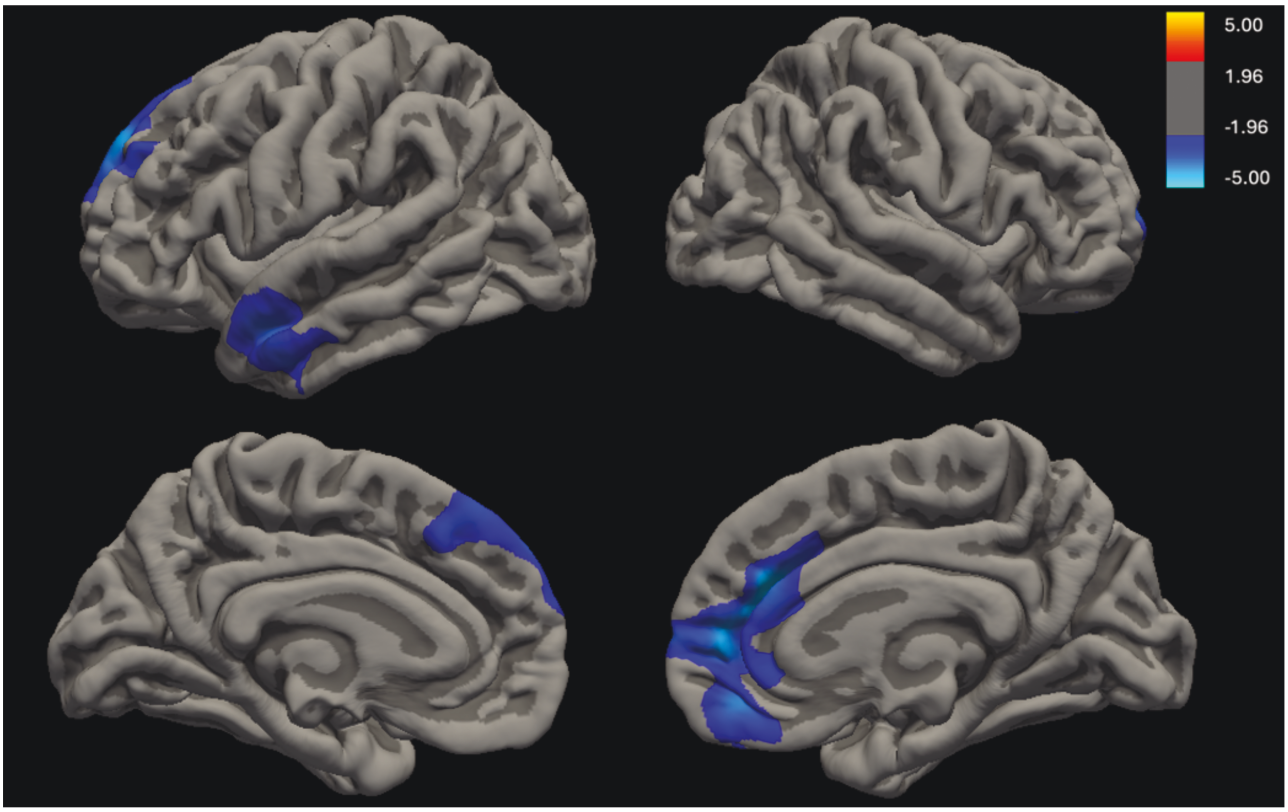


Figure 2. Cortical thickness differences between IS tertiles. The figure shows the results of the general linear model analysis used to assess vertex-wise differences in cortical thickness between IS tertile groups after controlling for age, sex, CIRS-G, antidepressant use, and BMI. Note: Low IS with lower cortical thickness than high IS in left and right superior frontal gyrus, extending into the anterior cingulate and medial orbitofrontal cortices (left CWP = 0.002, right CWP < 0.001) and left superior temporal gyrus (CWP = 0.043). This figure shows significant clusters after cluster-wise p-value correction. Colors show z-score values. The z-scores in the fully adjusted model were calculated using the "Z Monte Carlo" simulation method.

of the RA tertile groups in left or right hemispheres (all CWP > 0.05).

- L5: when controlling for age, sex, total sleep time, sleep efficiency, sleep offset, and antidepressant use, no significant group differences in cortical thickness were found between any of the L5 tertile groups in left or right hemispheres (all CWP > 0.05).

Interaction between nonparametric actigraphy tertiles groups and sex

The analysis revealed no significant interaction effect between sex and nonparametric actigraphy tertiles group on cortical thickness within the models.

Discussion

This is the first known study to investigate the association between cortical thickness and rest-activity rhythms in older adults "at risk" for cognitive decline. We found that 24-h rest-activity rhythm disruption is associated with reduced cortical thickness in older people "at risk" for dementia. Specifically, using a data-driven neuroimaging approach, we found that after controlling for age, sex, and other potential confounds, greater rhythm fragmentation (IV) and poorer synchronization to the 24-h light-dark cycle (IS) were associated with lower cortical thickness in frontal, temporal, parietal, and occipital cortices, indicating extensive cortical involvement across these key rhythms. However, our data did not support an association between cortical thickness and the RA (i.e., difference in mean activity during the least active 5-h period and most active 10-h period, RA) and nocturnal disturbance (during the least active nocturnal period, L5) in this "at risk" sample.

Rhythm fragmentation (IV) has been the most widely investigated marker of sleep-wake dysfunction in older adults. To date though, most of this work has examined relationships in cognitively unimpaired older adults and/or community samples. In some prior work with healthy older adults, increased IV has been linked to both gray and white matter structural alterations, including gray matter volume reductions in the medial prefrontal cortex, thalamus and medial temporal lobe, as well as the presence of white matter hyperintensities, cerebral microbleeds and amyloid markers of AD [21, 23, 24, 42, 43]. It is interesting to note that in healthy older people, gray matter atrophy in frontal regions has also been implicated in alterations to overnight sleep micro-architecture, such as reduced slow-wave activity [43, 44]. Our actigraphy findings in a memory clinic, and predominantly MCI sample, corroborate those observed in healthy elderly individuals. We found that the high IV group had lower cortical thickness in both the middle frontal and lateral orbitofrontal gyri compared to the mid IV group. Although causality cannot be inferred, it is possible that frontal gray matter integrity may mediate or moderate key aspects of sleep-wake rhythms or alternatively may even result from sleep-wake perturbations.

An interesting yet unexpected outcome of our data-driven approach was the association between high IV with lower cortical thickness in the cuneus, a key part of the occipital lobe, but this was evident only when the high IV group was compared to the low IV group. This is somewhat aligned with prior research in healthy older adults, which found that reduced cortical thickness in the occipital gyrus is linked to shorter sleep duration [45] and increased daytime sleepiness [46]. Disparate work suggests that individuals with MCI exhibit structural and functional alterations in the cuneus when compared to healthy controls [47–49]. Interestingly, a longitudinal study examining individuals from families with autosomal dominant Alzheimer's disease revealed that the cuneus showed reductions in cortical thickness ~2.5 years before the onset of symptoms [50]. Therefore, our finding that the high IV group is associated with reduced cortical thickness in the cuneus compared to the low IV group suggests that this area may play a unique role in sleep-wake rhythm disturbances, particularly in individuals at greater risk for AD. However, because we could not stratify our participants based on Alzheimer's disease biomarkers (e.g., APOE4 positive/negative), it remains unclear whether this association is directly related to AD pathology. Further studies incorporating biomarker classification are needed to clarify the relationship between IV, AD risk, and cortical thickness in these specific regions.

In terms of synchronization to the 24-h light-dark cycle, this study showed an association between lower IS, suggesting poorer synchronization, and lower cortical thickness in the temporal, parietal, and frontal cortices. Studies have revealed that with aging, the neurons from the suprachiasmatic nucleus of the hypothalamus, responsible for the circadian clock, send weaker circadian outputs [51] and become less synchronized to each other [52], leading to circadian disorganization. While there are no known studies linking IS to cortical thickness, decreased synchronization to the 24-h zeitgeber has been documented in patients with MCI and dementia [53]. Furthermore, Li et al. [22] found that a faster transition from MCI to dementia was predicted by decreased IS in older adults with MCI, and lower IS has been linked with worse episodic memory and executive dysfunction. The relationship between cognitive decline, lower IS and lower cortical thickness may be explained by the effect of IS on sleep-wake activity. When synchronization with the external world weakens, it is possible to detect a reduction in motor capacity and sleep-wake cycle fragmentation. This has been shown to significantly increase IV and L5 values [2]. This, in turn, could lead to lower cortical thickness due to increased cerebral beta-amyloid deposition [54]. Alternatively, neuronal degeneration may disrupt key brain circuits that support the stability of sleep across days (IS). Longitudinal studies integrating Alzheimer's and other neurodegenerative biomarkers will be required to delineate these inter-relationships.

In this study, we did not find any significant associations between circadian amplitude (i.e., RA) and cortical thickness. This is consistent with one known prior study, which also reported null associations between RA, medial temporal lobe, and amyloid burden in people with MCI [55]. While prior actigraphy studies using cosinor techniques showed that low amplitude was linked to cognitive decline, and progression to MCI and dementia [14, 15, 56], actigraphy studies using nonparametric analysis have found this to be evident only for progression to dementia, but not to MCI [22, 57]. Thus, it is possible that the association between RA and cortical thickness may increase once substantial cognitive decline (i.e., dementia diagnosis) is apparent or that it may be more pertinent longitudinally.

One unexpected finding was the lack of significant associations between greater activity or arousals during the least active period (i.e., L5) and cortical thickness. Previous studies have shown that in people with MCI, both poor sleep quality [58] and nocturnal awakenings [59] are associated with functional disconnection among temporoparietal brain regions, as well as with neuropsychological impairment [12]. Specifically for L5, recent work by Roh et al. [55] revealed that higher L5 was associated with reduced medial temporal gray matter volume and greater memory dysfunction, specifically in amyloid-positive participants. While etiological mechanisms underpinning these links are not yet known, it is possible that the greater nocturnal activity may disrupt slow-wave sleep and potentially reduce glymphatic clearance, which in turn could lead to an increase in cerebral beta-amyloid deposition [54, 60]. As previously mentioned, we were unable to classify our participants by Alzheimer's disease biomarkers (e.g., amyloid-positive vs. negative). Since the effect of L5 on gray matter appears to be closely linked to amyloid pathology, our limited capacity to classify our at-risk sample according to amyloid status may account for the lack of significant findings. Further studies with biomarker stratification are needed to explore these potential associations more accurately.

While this study has focused on cortical gray matter, the association between rest-activity rhythms and white matter integrity is also likely to be important. Evidence has shown that increased rest-activity rhythm fragmentation, particularly the amplitude of the rest-activity rhythm and synchronization to the 24-h light-dark cycle, is associated with discrete WMLs in healthy older adults [3]. In addition, in older adults with MCI, both IS and RA have been linked to white matter microstructural alterations, with these relationships being moderated by clinical factors such as BMI, medical burden, vascular risk, and depressive symptoms [26]. Since we did not find RA to be related to lower cortical thickness, this raises the possibility that RA may be linked to cognitive decline predominantly via white rather than gray matter disruption.

From a clinical perspective, it may be worth considering the utilization of actigraphy within the memory clinic setting. Not only can such markers identify potential sleep disturbances, but can also identify key rest-activity rhythm markers that may be pathophysiologically linked to disease and to prognosis, such as IV and IS. Given that the majority of patients attending memory clinics report poor sleep quality [61], greater detection and management of sleep-wake rhythm disturbances using cost-effective, efficient and ecologically valid tools may be warranted, particularly if the evidence base builds for the use of both non-pharmacological and pharmacological sleep and circadian treatments [12, 62].

Implications of this study are limited by their cross-sectional nature. Longitudinal studies focused on characterizing the bidirectionality of these relationships are now vital as well as those determining the prognostic utility of rest-activity rhythm changes for clinical and functional outcomes. Notably, we did not include any measures of sleep-disordered breathing, such as the apnea-hyponea index (AHI) or oxygen desaturation. It has been shown previously that indices of obstructive sleep apnea (OSA) severity are associated with cortical thinning [63] and functional brain disconnection [64] in older clinical samples. Furthermore, it should be noted that rest-activity rhythms are surrogate markers of circadian rhythms, and therefore further studies, with gold-standard markers of circadian endpoints (e.g., melatonin secretion) would be required to draw firm conclusions about the relationship between brain integrity with circadian functioning in

this population [65, 66]. In prior work by our team [7] the onset of melatonin secretion occurred earlier in MCI, compared to control participants, which in turn was associated with increased nocturnal wakefulness and delayed latency to REM sleep. Given that our study indicated that there are alterations in IS in older adults "at risk" for dementia, future research should investigate the relationship between melatonin, IS, and brain integrity.

We acknowledge that dividing participants into tertiles may add complexity to interpreting distinct brain patterns across the groups, especially regarding the observed differences between the high IV group when compared to the low and mid IV groups. The mechanisms driving these differences are currently unclear, making it challenging to determine why certain brain regions show variations only at specific IV levels. Therefore, further research is essential to explore the underlying mechanisms that may explain these distinct patterns across tertile groups. Furthermore, while tertiles are widely used in similar studies, their practical value and clinical relevance still require external validation, particularly given the relatively small sample size of the current study. Hence, validation of our findings in an external cohort is needed to strengthen their generalisability. Additionally, while it is unlikely that structural brain markers would change substantially over short-term timeframes, the varied intervals between imaging and actigraphy, although typical for cross-sectional studies, may introduce a degree of variability that could influence the findings. Future studies should consider minimizing these intervals when possible or incorporating the time difference into statistical models to better account for this variability. Lastly, the neuropathological substrates underlying lower cortical thickness in this group remain unknown, highlighting the need for longitudinal studies to better understand these changes and their implications.

Considering that our sample included older adults who were experiencing either SCI or MCI, and that we did not use AD biomarkers to document underlying disease, the ultimate clinical trajectory of the sample is unknown. It is hence possible that a diverse range of underlying diseases underpinned the cognitive phenotype, including Alzheimer's and vascular pathologies as well as synucleinopathies and tauopathies. However, this sample is reflective of real-life clinical practice within which it is possible to identify potential risk factors for dementia. Importantly, regardless of the underlying etiology and heterogeneity of the sample, these findings demonstrate critical links between brain integrity and rest-activity rhythms.

This study overall presents new evidence of associations between rest-activity rhythms and cortical thickness in older adults "at risk" for dementia. While rest-activity rhythm disturbance may contribute to lower cortical thickness, it is equally plausible that neurodegenerative brain changes give rise to rest-activity rhythm fragmentation. Future longitudinal and prospective studies, as well as clinical trials targeting rest-activity rhythms are still required to delineate these interrelationships.

Supplementary material

Supplementary material is available at *SLEEP* online.

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Disclosure Statement

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Data Availability

The data supporting this article is available upon reasonable request to the corresponding author, subject to approval by the relevant ethics committee.

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