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Identification of circadian-sensitive brain structure and its role in cognitive impairment and dementia

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ABSTRACT

Background Circadian disruption has been suggested to induce cognitive impairment and dementia. It remains unknown which brain structures are involved in the pathology.

Objective To investigate which specific brain structure alterations are associated with dementia and cognitive impairment induced by circadian disruption.

Methods Circadian disruption was represented by two accelerometer-derived circadian variables, composite phase deviations (CPD) and relative amplitude (RA), separately reflecting circadian disruption in timing and amplitude. The outcomes include brain structures (139 imaging-derived phenotypes), cognitive test performances (seven cognitive tests) and dementia (all-cause dementia, Alzheimer's disease, vascular dementia (AD/VD) and non-AD/VD dementia). Association analysis was used to explore the relationships between circadian disruption and brain structure alterations, cognitive test performances and dementia. Mediation analysis was conducted to investigate which brain structure alterations mediated the cognitive impairment and dementia caused by circadian disruption.

Findings A total of 88 461 participants (57% female, 62.0±7.8-year old) were included. CPD and RA correlated with substantially different brain structures. All CPD-related brain structures were located in the cerebrum, whereas most RA-related brain structures were located in the cerebellum. Furthermore, only the CPD-related brain structures, including the hippocampus and thalamus, exhibited significant mediation effects accounting for up to 8.6% of the risk for dementia and 13.5% of the risk for cognitive impairment.

Conclusions Circadian disruption is associated with brain structural alterations involving dementia and cognitive impairments.

Clinical implications These results provide a novel insight into the mechanism underlying circadian disruption-induced neurological disorder and may propose potential preventive strategy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Circadian disruption has been suggested as a risk factor for cognitive impairment and dementia. So far, the mechanisms underlying cognitive impairment and dementia in circadian disruption are poorly understood.

WHAT THIS STUDY ADDS

⇒ Circadian disruption was associated with widespread brain structural alterations in cerebrum and cerebellum.

⇒ Brain alterations in hippocampus, thalamus and total grey matter volume mediated development of non-Alzheimer's disease/vascular dementia dementia. The same brain alterations mediated circadian disruption-related impairment in cognitive tests.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Identification of the sensitive brain structures may stimulate subsequent mechanism exploration and preventive strategies such as early occupational health alert.

BACKGROUND

Diurnal rhythms, regulated by the circadian clock, play a critical role in the human body.[1] In modern society, the disruption of diurnal rhythms as a result of shift work, jet lag or other lifestyle factors has become a public health concern[2] and may contribute to major health outcomes, including brain disorders.[3] Circadian disruption is associated with an increased risk of cognitive impairment and dementia. Circadian rhythm alterations affect the pathology of neurodegenerative diseases.[3] However, the mechanisms through which circadian disruption induces cognitive impairment and dementia require further investigation.

Brain structure serves as an important basis for the normal physiological functions of the brain and the occurrence of brain diseases. Recent studies suggest that circadian disruption may be related to changes in brain regions. Mice exposed to circadian disruption exhibited an increased fraction of immature spines in the hippocampus.[4] Another study suggested that circadian disruption is associated with hypometabolism in AD-signature brain regions, including the angular gyri.[5] These studies imply that circadian disruption may lead to alterations in brain structure associated with cognitive impairment or dementia. MRI, which obtains multidimensional information from in vivo imaging, provides key insights into how human brains are shaped by environmental factors and change with ageing and disease. However, several issues have not been addressed in previous research: (1) no previous study has systematically examined the relationship between circadian disruption and

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MRI imaging of different regions through human brain and (2) whether structural brain alterations mediate cognitive impairment and dementia caused by circadian disruption remains unknown.

OBJECTIVE

The aim of this study, based on a large-scale cohort (UK Biobank), was to investigate (1) the relationship between circadian disruption and brain structural imaging-derived phenotypes (IDPs), cognitive performance and dementia; (2) the mediating role of IDPs and cognitive performance in the relationship between circadian disruption and dementia; (3) the mediating role of IDPs in the relationship between circadian disruption and cognitive impairment. Furthermore, as chronotype (personal morning/evening preference) is a well-known indicator of individual variation in circadian rhythms, stratified analyses by chronotype were performed in order to engage in fine-grained analysis of relationship between circadian disruption and IDPs, cognitive performance and dementia.

METHODS

Participants

The UK Biobank is a population-based cohort, recruiting over 500 000 volunteers from 22 study centres across England, Scotland, and Wales between 2006 and 2010.[6] The UK Biobank study received ethical approval from the North West Multi-Center Research Ethics Committee, and all participants provided written informed consent. Out of over half a million participants in the UK Biobank, 103 666 accepted the invitation to wear a wrist-worn AX3 triaxial accelerometer (Axivity, Newcastle upon Tyne, UK) for 7 days between 2013 and 2015. Detailed inclusion and exclusion criteria are attached in Online supplemental materials. Ultimately, the exclusion criteria resulted in a study sample of 88 461 participants. Online supplemental figure 1 illustrates the general exclusion process and methodology.

Accelerometer data and circadian disruption

GGIR (https://github.com/wadpac/GGIR/wiki/Publication-list) V.2.8.2 was used to process raw accelerometer data in CWA format.[7] To estimate circadian disruption, composite phase deviations (CPD) and relative amplitude (RA) were used. CPD measures behavioural circadian disruption in timing,[8] with higher values reflecting more irregular patterns. RA, derived from physical activity intensity data, is a common non-parametric measure of circadian rhythm amplitude ranging from 0 to 1. A higher RA value indicates a larger difference in activity levels during the most and least active periods of the day; that is, a lower value indicates disrupted circadian rhythms.[9]

MRI acquisition and data processing

Since 2014, MRI data have been collected using a Siemens Skyra 3T scanner with a standard 32-channel healing coil. Details of the imaging protocol are available for free at http://www.fmrib.ox.ac.uk/ukbiobank/protocol/V4_23092014.pdf. Structural data were generated using a UK Biobank image-processing pipeline based on T1-weighted/T2-weighted scans and are available to researchers as distinct IDPs.[10] In this study, IDPs, including total brain volume, whole-brain grey matter volume (GMV), whole-brain white matter volume, white-matter hyperintensities, ventricular cerebrospinal fluid volume, 139 regional IDPs (online supplemental table 1) parcellated from the Harvard–Oxford cortical and subcortical atlases, and the Diedrichsen cerebellar atlas were used for analyses. All volumetric IDPs were normalised to head size by multiplying the raw IDP value by the head size scaling factor, which was estimated by transforming native space into standard space with FSL SIENAX software, as the previous publication suggested.[10] Regional topological metrics estimated by resting-state functional MRI, including nodal efficiency and nodal degree (online supplemental table 1), were derived through a graph theoretical network analysis toolbox (GRETNA, available at http://www.nitrc.org/projects/gretna/). Additional details regarding the image processing procedures and specific measurements obtained from T1-weighted, T2-weighted and resting-state functional MRI can be found in online supplemental materials.

Cognitive tests

Between 2006 and 2010 (baseline) and from 2014 onwards (imaging visit), seven cognitive tests were performed using validated unsupervised methods via a touchscreen.[11] These tests were selected to reflect multidomain cognitive function and were moderately-to-highly correlated with well-validated standard cognitive tests.[11] The cognitive tests included a multidomain test of processing speed, attention and working memory (digit symbol substitution test); a test of executive function/processing speed (reaction time, trail making test A, trail making test B); and memory (numeric memory, pairs matching round 1 and pairs matching round 2). The test scores were mapped to (0,1) using the equation $t_{normalizied} = (t - t_{min}) / (t_{max} - t_{min})$ where $t_{\min}$ is the minimum of the test and t_{max} is the maximum of the test.

Dementia

All dementia recordings were sourced from electronic health records using algorithms provided by the UK Biobank, which included International Classification of Diseases-9 and International Classification of Diseases-10 codes (online supplemental materials). The records were analysed in the following forms: all-cause dementia, Alzheimer's disease (AD), vascular dementia (VD), and non-AD/VD dementia (other types). Notably, follow-up incident dementia was only recorded if the earliest date of dementia code documentation was after the participant had finished wearing the accelerometer. At the time of this study, hospital admission data were available until 31 October 2022, 31 August 2022 and 31 May 2022, for England, Scotland and Wales, respectively, and mortality data were available until 30 November 2022. Dementia-related analyses were censored at the date of death, first disease incident or latest update of hospital admission data, whichever occurred first.

Statistical analysis

Multivariable linear regression models were used to investigate the association between circadian disruption and IDPs as well as cognitive impairment. Cognitive test data collected from 2014 onwards (imaging visit), which was close to the time of accelerometer data collection, were mainly used. However, to maximise the utilisation of the data, four cognitive test outcomes (reaction time, pairs matching round 1, pairs matching round 2 and numeric memory) from 2006 to 2010 (baseline) with a larger sample size were used when screening the tests in the initial association analyses. The Cox proportional hazards model was used to examine the association between circadian disruption and incident dementia (excluding participants with dementia before wearing the accelerometer). The participants were divided based on quartiles of circadian disruption (CPD/RA). Those in the lowest quartile of CPD or the highest quartile of RA were

assigned to the reference group. Several covariates were adjusted in the above models based on the results of previous studies of the association between circadian disruption and cognitive impairment/dementia,[12] including age, sex, body mass index, Townsend deprivation index, ethnicity, employment status, education level, smoking status and drinking status (details on how covariates were collected in online supplemental materials).

Analysis of variance (all IDPs, reaction time, trail making A, trail making B, numeric memory, digit symbol substitution) or the Kruskal-Wallis test (pairs matching round 1, pairs matching round 2) was performed to compare the differences in IDPs and cognitive tests between individuals with dementia (including all-cause dementia and subtypes of dementia) and controls. Mediation analyses were also performed to determine whether IDPs (and cognitive tests) mediated the relationship between circadian disruption and dementia.[13] Mediation analyses were also used to examine the IDPs that mediated the relationship between circadian disruption and cognitive tests. For the IDPs that were significant in the mediation analyses, the multivariable linear regression model was used to preliminarily explore the relationships between circadian disruption and their regional topological metrics. Additionally, the Kruskal-Wallis test was performed to compare the differences in regional topological metrics between individuals with dementia (including all-cause dementia and subtypes of dementia) and controls. Furthermore, for sensitivity analysis, participants who developed dementia within 1 year of the beginning of accelerometry data collection were excluded from the Cox and mediation analyses, and more extreme groupings based on CPD and RA were considered, specifically the lowest 10% of CPD versus the highest 10% of CPD or the highest 10% of RA versus the lowest 10% of RA. Additionally, stratified analyses were performed in all of the above models based on chronotype (definitions in online supplemental materials), which is a possible effect modifier.[14]

Bonferroni correction was used for multiple comparisons (details in the online supplemental materials). All p values were reported as two-sided tests with significance defined as corrected $p<0.05$. Statistical analyses were performed using R software (V.4.2.1, https://www.r-project.org) and Python Software (V.3.8.10, https://www.python.org/). All mediation analyses were performed using the 'Mediation' package (V.4.5.0) or code sourced from https://github.com/oyaxbell/covid_diabetesmx.[15]

FINDINGS

Population characteristics

Of the 103 666 UK Biobank participants who accepted the invitation to wear the accelerometer, 88 461 passed the quality control (online supplemental figure 1). The characteristics of the excluded and included participants were generally comparable, with slight differences in employment status. The mean age of the included participants was 62.0±7.8 years, approximately 57% were women and 97% were white. Detailed demographic information for the eligible and excluded participants is presented in table 1.

Relationship between circadian disruption and brain structures

The association between CPD and RA and IDPs was analysed. This segment of the research was conducted with 16 431 participants. In the adjusted model, there were five Bonferroni-corrected significant associations between IDPs and CPD, and 26 IDPs were significantly associated with RA (online supplemental table 2, figure 1A,B). However, none of the IDPs demonstrated simultaneous associations with CPD and RA (online supplemental table 2, figure 1B). Figure 1A separately labelled the five strongest IDPs associated with CPD or RA. The top five CPD-related IDPs were the whole-brain GMV, volume of the thalamus, hippocampus, caudate and total brain. In terms of RA, 25 of the 26 associated IDPs were located in the cerebellum (figure 1B). All significant associations between CPD and IDPs were inverse, whereas all significant associations between RA and IDPs revealed a positive pattern (online supplemental table 2), figure 1A). As illustrated in figure 1C, compared with the lowest quartile, the highest quartile of CPD was associated with 1.11% (95% CI 0.64% to 1.59%) lower hippocampal volume and a 1.03% (95% CI 0.67% to 1.39%) lower thalamic volume, whereas the lowest quartile of RA, compared with the highest quartile, was associated with up to a 3.21% (95% CI 2.43% to 4.00%) lower level of IDPs in the cerebellum.

Relationship between circadian disruption and cognitive test performance

Associations between cognitive function and CPD and RA were analysed after adjusting for covariates. This part of the study was based on 88 213 participants. Higher CPD was significantly associated with lower performance in six cognitive tasks (table 2), including reaction time ($P_{Bonferroni}=9.16\times10^{-8}$), pairs matching round 1 ($P_{Bonferroni}=8.69\times10^{-7}$), symbol digit substitution ($P_{Bonferroni}=3.41\times10^{-6}$), pairs matching round 2 ($P_{Bonferroni}=1.09\times10^{-3}$), trail making B ($P_{Bonferroni}=1.96\times10^{-3}$) and trail making A ($P_{Bonferroni}=2.96\times10^{-2}$). Lower RA was significantly associated with lower performance in one cognitive task (reaction time ($P_{Bonferroni}=1.89\times10^{-14}$)) after Bonferroni correction (table 2). All significant association results suggest that circadian disruption may lead to decreased cognitive performance.

Relationship between circadian disruption and dementia

The association between circadian disruption and dementia was analysed using the Cox proportional hazards model. This part of the study was based on 88 384 participants. During a median follow-up period of 7.9 years, 714 dementia cases occurred (303 with AD, 130 with VD and 474 with non-AD/VD dementia). As shown in online supplemental figure 2, after adjusting for covariates, the highest quartile of CPD was associated with a 1.37-fold higher risk of all-cause dementia (95% CI 1.18 to 1.58, $p=2.00\times10^{-5}$), and the lowest quartile of RA was associated with a 1.78-fold higher risk of all-cause dementia (95% CI 1.50 to 2.09, $p=8.83\times10^{-12}$). For the outcomes of dementia subtypes, the highest quartile of CPD was also found to be significantly associated with VD (adjusted HR: 1.47, 95% CI 1.04 to 2.08, p=0.030) and non-AD/VD dementia (adjusted HR: 1.57, 95% CI 1.31 to 1.88, $p=6.22\times10^{-7}$) and suggestively associated with AD (adjusted HR: 1.23, 95% CI 0.99 to 1.54, p=0.065). Similarly, RA was significantly associated with AD, VD and non-AD/VD dementia (online supplemental figure 2).

The incident dementia cases diagnosed after wearing the accelerometer and control participants were compared using 31 IDPs and six cognitive tasks that showed significant associations with circadian disruption. The results showed significant differences in 19 IDPs and five cognitive tasks after Bonferroni correction (online supplemental tables 3 and 4).

The mediating role of IDPs in the relationship between circadian disruption and dementia

A mediation analysis was conducted to investigate whether the effect of circadian disruption on dementia was partially

Table 1 Characteristics of included, excluded and overall participants

Characteristics	Included	Excluded	Overall
Sample size (%)	88 461 (85.33)	15 205 (14.67)	103 666 (100.00)
Age at wearing accelerometer (years, mean±SD.d.)	61.97±7.83	60.61±8.01	61.77±7.87
Female (%)	50 050 (56.58)	8220 (54.06)	58 270 (56.21)
White (%)	85 501 (96.65)	14 483 (95.25)	99 984 (96.45)
Social deprivation index (mean±SD.d.)	−1.74±2.81	−1.56±2.93	−1.71±2.83
College degree or more (%)	38 213 (43.20)	6725 (44.23)	44 938 (43.35)
Employed (%)	54 184 (61.25)	10 185 (66.98)	64 369 (62.09)
Current smoker (%)	5991 (6.77)	1284 (8.44)	7275 (7.02)
Daily alcohol drinker (%)	65 325 (73.85)	11 360 (74.71)	76 685 (73.97)
BMI (kg/m^2; mean±SD.d.)	26.69±4.51	27.03±4.75	26.74±4.55
Cognitive tests			
Reaction time (mean±SD.d.)	0.2493±0.0545	0.2467±0.0542	0.2489±0.0545
Pairs matching round 1 (mean±SD.d.)	0.0049±0.0116	0.0052±0.0119	0.0050±0.0117
Pairs matching round 2 (mean±SD.d.)	0.0266±0.0210	0.0265±0.0212	0.0266±0.0210
Numeric memory (mean±SD.d.)	0.6028±0.1132	0.6008±0.1204	0.6025±0.1143
Trail making test A (mean±SD.d.)	0.0913±0.0362	0.0909±0.0344	0.0913±0.0359
Trail making test B (mean±SD.d.)	0.0956±0.0466	0.0961±0.0490	0.0957±0.0470
Symbol digit substitution (mean±SD.d.)	0.5103±0.1423	0.5186±0.1419	0.5115±0.1422
Global MRI measures			
Total grey matter volume (mm^3, mean±SD.d.)	613 620.25±55 6300.41	618 878.24±56 4830.85	614 325.20±55 7740.37
Total brain volume (mm^3, mean±SD.d.)	1 158 355.84±110 862.89	1 168 458.36±112 259.71	1 159 710.30±111 104.52
White matter hyperintensity volume (mm^3, mean±SD.d.)	5104.52±6693.69	4894.51±6859.41	5076.39±6716.50
Dementia			
All-cause dementia(n)	714	–	–
AD(n)	303	–	–
VD(n)	130	–	–
Other types of dementia(n)	474	–	–
RA (mean±SD.d.)	0.85±0.07	–	–
CPD (mean±SD.d.)	1.31±0.90	–	–

The cognitive test outcomes of reaction time, pairs matching round 1, pairs matching round two and numeric memory at the baseline and trail making test A, trail making test B and symbol digit substitution image visit were used. The test scores were mapped to (0,1) using the equation $t_{\text{normalized}} = \frac{t - t_{\min}}{t_{\max} - t_{\min}}$ where t_{min} is the minimum and t_{max} is the maximum. All-cause dementia, AD, VD, other types of dementia showed the number of follow-up incident dementia cases after accelerometry wearing.
AD, Alzheimer's disease; BMI, body mass index; CPD, composite phase deviation; RA, relative amplitude; VD, vascular dementia.

mediated by IDPs. The research in this section involves 16 428 participants. 19 IDPs that showed significant results in the above analyses were examined as mediators. For three of the 19 IDPs, the whole-brain GMV and the volume of the hippocampus and thalamus significantly mediated the effect of CPD on non-AD/VD dementia. Thalamus volume accounted for the highest proportion (about 9%) of the total effect. Hippocampus volume and whole-brain GMV accounted for approximately 8.2% and 6.1% of the total effect, respectively (table 3).

Mediation of IDPs in the relationship between circadian disruption and cognitive function

Since only CPD-associated IDPs were found to mediate the relationship between circadian disruption and dementia, we further analysed whether IDPs mediated the association between CPD and cognitive function. The research in this section involves 15 531 participants.

All indirect effects of mediation analyses achieved a threshold of $p<0.05$ before Bonferroni correction. Even after Bonferroni correction, thalamic volume still significantly mediated the effect of CPD on the reaction time test. Marginally significant mediations of the effects of thalamus, hippocampus volume and whole-brain GMV were also observed in the effect of CDP on the reaction time and pairs matching round 1 (online supplemental table 5). Among these statistically significant results, 13.5% of CPD's total effect on reaction time performance was mediated through having a lower thalamic volume (the indirect effect).

Furthermore, we used cognitive test results as mediators to investigate the relationship between circadian disruption and dementia. As shown in online supplemental table 6, across the five cognitive tasks, reaction time significantly mediated the effect of CPD on non-AD/VD dementia, accounting for 1.2% of the total effect.

Sensitivity analysis

For sensitivity analysis, participants diagnosed with dementia within one year of wearing the accelerometer were excluded, or more extreme groupings were applied based on CPD and RA, namely the lowest 10% of CPD versus the highest 10% of CPD or the highest 10% of RA versus the lowest 10% of RA. The association between circadian disruption and dementia, as well as the mediation effects of IDPs and cognitive tasks, was re-examined in the remaining participants. The sensitivity analysis yielded results similar to those mentioned above (online supplemental tables 10–15).

Stratified analysis

Participants were classified into three subgroups: morning, evening and intermediate chronotypes. Stratified analysis was

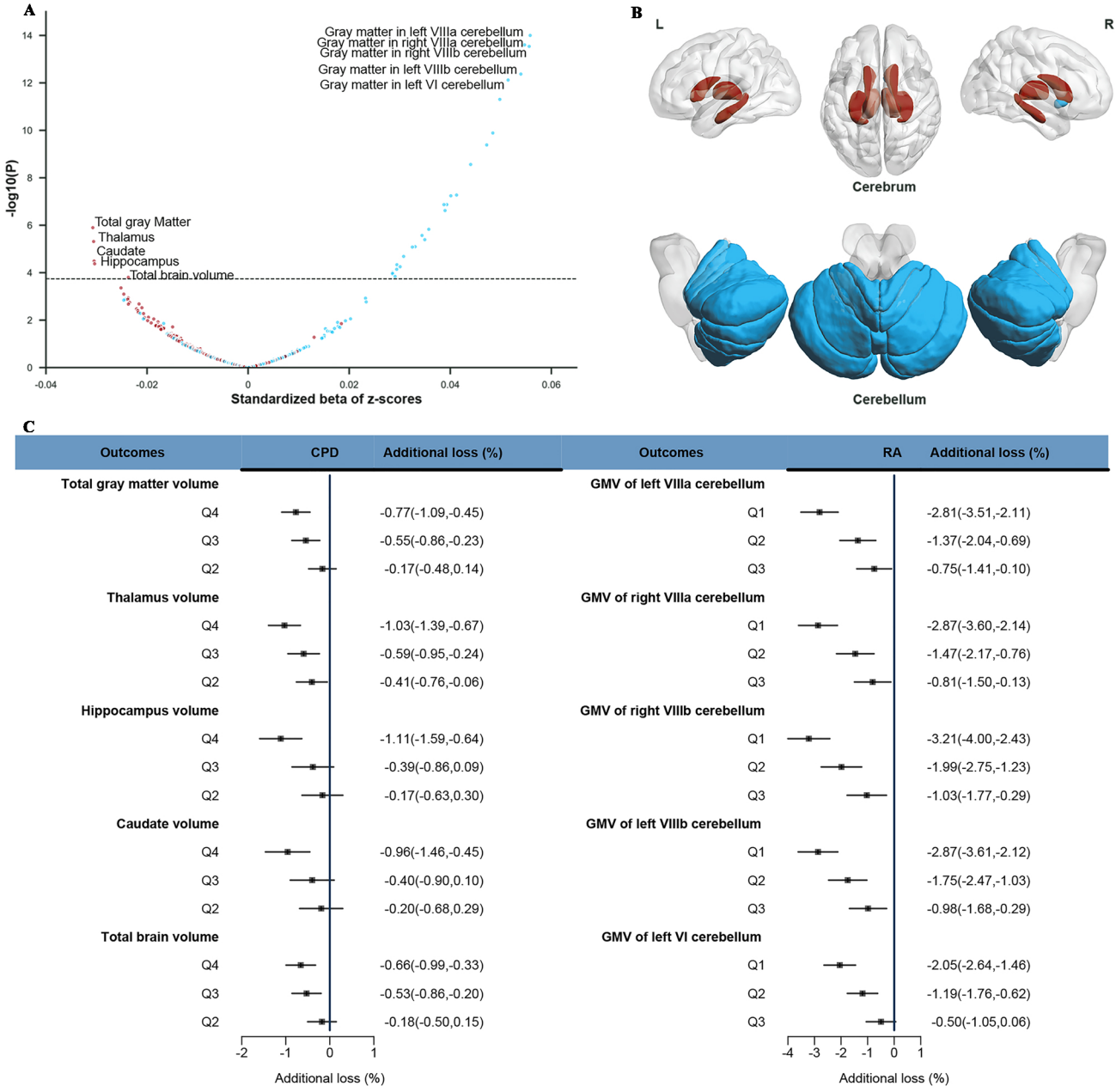

Figure 1 Association of CPD and RA with IDPs. (A) Standardised regression coefficients representing associations between CPD (or RA) and IDPs are presented. P values were adjusted using the Bonferroni correction for multiple comparisons. The results were adjusted for age, sex, body mass index, Townsend deprivation index, ethnicity, employment status, education level, smoking status and drinking status. IDPs were normalised to head size. The results for CPD and RA were separately indicated by red and blue colours, respectively. The Bonferroni-corrected significance threshold was marked with a black dashed line. (B) The location of regional IDPs associated with CPD or RA in the cerebrum and cerebellum is presented. The IDPs associated with CPD and RA were separately marked with red and blue colours. (C) The top five IDPs with largest volume decrease, associated with CPD or RA. CPD, composite phase deviations; IDPs, imaging-derived phenotypes; RA, relative amplitude.

performed to evaluate the association between circadian disruption and brain structure, cognitive tasks and dementia based on chronotypes. No significant interactions were observed in the stratified analyses (online supplemental tables 16–18).

DISCUSSION

Previous studies have suggested that circadian disruption negatively affects cognitive function in humans.[3] Brain structures could serve as early biomarkers of cognitive impairment and dementia, but few studies have investigated the relationship between circadian disruption and brain structure. The aim of this study was to test the hypothesis that certain IDPs mediate the relationship between circadian disruption and cognitive impairment and dementia. Here, we found five and 26 IDPs associated with CPD and RA, respectively, after Bonferroni correction (online supplemental table 2). Among them, three IDPs, encompassing the whole-brain GMV and the volume of the hippocampus and thalamus, mediated CPD-related dementia. In particular, the risk of non-AD/VD dementia could be attributed to IDPs and cognitive tasks for up to 8.6% of the total effect (the thalamus).

Table 2 Association of circadian disruption with cognitive test performance

Circadian index	Cognitive tests	Regression coefficients	P value (Bonferroni corrected)
CPD	Reaction time	0.00107 (0.00071, 0.00144)	9.16×10^{-8}*
CPD	Pairs matching round 1	0.00022 (0.00014, 0.0003)	8.69×10^{-7}*
CPD	Symbol digit substitution	−0.00617 (−0.00851, −0.00383)	3.41×10^{-6}*
CPD	Pairs matching round 2	0.00029 (0.00015, 0.00044)	1.09×10^{-3}*
CPD	Trail making B	0.00158 (0.00077, 0.00239)	1.96×10^{-3}*
CPD	Trail making A	0.00099 (0.00036, 0.00162)	2.96×10^{-2}*
CPD	Numeric memory	−0.00318 (−0.00557, −0.0008)	1.23×10^{-1}
RA	Reaction time	−0.01969 (−0.02451, −0.01486)	1.89×10^{-14}*
RA	Trail making A	−0.00927 (−0.01766, −0.00088)	4.26×10^{-1}
RA	Symbol digit substitution	0.02882 (−0.00238, 0.06002)	9.83×10^{-1}
RA	Pairs matching round 1	0.00059 (−0.00049, 0.00167)	>0.99
RA	Trail making B	−0.00505 (−0.01586, 0.00576)	>0.99
RA	Numeric memory	0.00459 (−0.02607, 0.03524)	>0.99
RA	Pairs matching round 2	−0.00014 (−0.00208, 0.0018)	>0.99

Results of multivariable linear regression were reported as regression coefficients. P values underwent Bonferroni correction for multiple comparisons. The analysis was adjusted for age, sex, body mass index (BMI), Townsend deprivation index, ethnicity, employment status, education level, smoking status, drinking status. To permit comparison of effect size across outcomes, the outcome measures were mapped to (0,1) using the equation $t_{normalizied} = \left(t - t_{min}\right) / \left(t_{max} - t_{min}\right)$ where t_{min} is the minimum and t_{max} is the maximum before analysis.
*The Bonferroni correction adjusted P value<0.05.
CPD, composite phase deviations; RA, relative amplitude.

To the best of our knowledge, this is the first study to demonstrate that the relative difference of hippocampal, thalamic and whole-brain GMV may play a role in non-AD/VD dementia and cognitive impairment caused by circadian disruption. Nevertheless, our results may still be reasonable. In a generally healthy community-based population, adults only experienced 0.18% (middle age) to 0.3% (older age) decrease of their hippocampal volume per year.[16] The 1.11% decrease of hippocampal volume associated with CPD in our study suggested that circadian disruption was associated with a 3.7–6.2 year increase in ageing of the hippocampus. Similar volume decrease was also observed in thalamic and whole-brain GMV, indicating a significantly adverse effect of circadian disruption on brain structure. Additionally, there has been some evidence indicating their roles in cognitive impairment and dementia. In humans, the hippocampus makes critical contributions to learning, memory and cognition.[16] The thalamus, as a part of the limbic system, performs various cognitive functions.[17] Moreover, atrophy of the hippocampus and thalamus has been linked to the emergence of dementia in disorders other than AD and VD, such as Parkinson's disease dementia.[18] Our results indicated that whole-brain GMV mediates the relationship between circadian disruption and dementia/cognitive impairment. Whole brain GMV loss has been recognised as a common characteristic of neurodegenerative disorders. The reduction of GMV in multiple brain regions has also been found to be associated with the development of dementia in older people.[19] In short, the three important IDP atrophies we found were included and comprehended with MRI characterisation of brain structures related to mild cognitive impairment and dementia, and these results supported our findings. Interestingly, we found that CPD was associated with increased nodal degree and nodal efficiency in the left thalamus and left hippocampus (online supplemental tables 7–9). This might suggest a compensatory mechanism of functional connectivity at an early stage of cognitive impairment induced by circadian disruption before dementia developed. This phenomenon is consistent with previous studies, which showed that subjective cognitive decline, a stage of mild neuronal injury with clinically normal cognitive performance, exhibits higher nodal topological properties, including nodal strength, nodal global efficiency and nodal local efficiency.[20] Collectively, our results suggest that hippocampus, thalamus and whole-brain grey matter are involved in mediating the association between circadian disruption and the risk of cognitive impairment and dementia.

Currently, there is no established normal reference value either for CPD or RA. According to the previously published studies, it is a common practice to categorise CPD and RA into quartiles, so as to investigate dose–response relationship and avoid biased estimates. We also performed a sensitivity analysis with more extreme groupings, where the participants with the lowest 10% CPD (or RA) were compared with those with the highest 10% of CPD (or RA). The results of sensitivity analysis were consistent with main analysis. Even with a substantial reduction in the sample size, most of the positive results in the main association analysis remained significant, suggesting that the relationship of CPD and RA with the phenotypes was robust.

There are several possible mechanisms underlying the structural brain changes caused by circadian disruption: (1) the circadian clock participates in various physiological processes in human brain such as memory consolidation and adult neurogenesis.[3] Animal experiments implied that 67% of the total synaptic mRNA in the mouse forebrain (including the hippocampus and thalamus) showed circadian oscillations.[21] Long-term circadian disruption may in turn alter gene expression, cellular metabolism and redox homeostasis in neurons[22] and cause neuronal damage. For example, circadian disruption was reported to induce neuronal mitochondrial dysfunction[23] and a metabolic-related loss of dendritic length and neuron complexity.[24] (2) Circadian disruption has been found to affect waste clearance in the brain,[25] potentially leading to neuroinflammation.[26] Notably, Another animal study also found that circadian disruption induced cognitive dysfunction through neuroinflammation, characterised by microglial activation, and impaired hippocampal neurogenesis.[27] (3) Circadian disruption was also related to depressed levels of

Table 3 Mediation of IDPs in the relationship between circadian disruption and dementia

Circadian index	IDPs	Incident illness	Total effect (HR (95% CI))	$P_{Total\ effect}$	Direct effect (HR (95% CI))	$P_{Direct\ effect}$	Indirect effect (HR (95% CI))	$P_{Indirect\ effect}$ (Bonferroni corrected)	Proportion mediated%
CPD	Caudate volume	All-cause dementia	1.18 (0.94, 1.47)	1.44×10^{-1}	1.17 (0.94, 1.46)	1.65×10^{-1}	1.01 (1.00, 1.02)	>0.99	–
CPD	Caudate volume	Other types of dementia	1.39 (1.06, 1.83)	1.67×10^{-2}	1.38 (1.05, 1.81)	1.98×10^{-2}	1.01 (1.00, 1.02)	>0.99	–
CPD	Caudate volume	AD	1.27 (0.91, 1.77)	1.58×10^{-1}	1.26 (0.90, 1.76)	1.70×10^{-1}	1.01 (1.00, 1.02)	>0.99	–
CPD	Caudate volume	VD	0.99 (0.60, 1.62)	9.57×10^{-1}	0.98 (0.60, 1.62)	9.50×10^{-1}	1.00 (0.99, 1.02)	>0.99	–
CPD	Hippocampus volume	All-cause dementia	1.20 (0.96, 1.50)	1.09×10^{-1}	1.17 (0.93, 1.46)	1.74×10^{-1}	1.03 (1.02, 1.04)	<0.0001	–
CPD	Hippocampus volume	AD	1.31 (0.94, 1.84)	1.13×10^{-1}	1.27 (0.91, 1.78)	1.67×10^{-1}	1.04 (1.02, 1.05)	<0.0001	–
CPD	Hippocampus volume	Other types of dementia	1.41 (1.07, 1.85)	1.39×10^{-2}	1.37 (1.04, 1.80)	2.39×10^{-2}	1.03 (1.02, 1.04)	<0.0001	8.177
CPD	Hippocampus volume	VD	1.00 (0.61, 1.64)	9.93×10^{-1}	0.98 (0.60, 1.61)	9.36×10^{-1}	1.02 (1.00, 1.04)	>0.99	–
CPD	Thalamus volume	All-cause dementia	1.19 (0.95, 1.48)	1.28×10^{-1}	1.16 (0.93, 1.44)	1.94×10^{-1}	1.03 (1.01, 1.04)	3.04×10^{-4}	–
CPD	Thalamus volume	Other types of dementia	1.40 (1.07, 1.84)	1.41×10^{-2}	1.36 (1.04, 1.79)	2.50×10^{-2}	1.03 (1.02, 1.04)	3.04×10^{-4}	8.562
CPD	Thalamus volume	AD	1.28 (0.92, 1.79)	1.44×10^{-1}	1.25 (0.90, 1.75)	1.84×10^{-1}	1.02 (1.01, 1.04)	4.62×10^{-1}	–
CPD	Thalamus volume	VD	0.99 (0.60, 1.62)	9.63×10^{-1}	0.98 (0.60, 1.62)	9.47×10^{-1}	1.01 (0.98, 1.03)	>0.99	–
CPD	Total brain volume	All-cause dementia	1.19 (0.95, 1.49)	1.26×10^{-1}	1.18 (0.94, 1.47)	1.56×10^{-1}	1.01 (1.00, 1.02)	2.09×10^{-1}	–
CPD	Total brain volume	Other types of dementia	1.41 (1.07, 1.85)	1.39×10^{-2}	1.39 (1.06, 1.83)	1.82×10^{-2}	1.01 (1.00, 1.02)	4.72×10^{-1}	–
CPD	Total brain volume	AD	1.29 (0.93, 1.81)	1.31×10^{-1}	1.27 (0.91, 1.78)	1.58×10^{-1}	1.02 (1.00, 1.03)	6.32×10^{-1}	–
CPD	Total brain volume	VD	0.99 (0.60, 1.62)	9.61×10^{-1}	0.99 (0.60, 1.62)	9.56×10^{-1}	1.00 (0.98, 1.02)	>0.99	–
CPD	Total grey matter volume	All-cause dementia	1.18 (0.95, 1.48)	1.38×10^{-1}	1.16 (0.93, 1.45)	1.92×10^{-1}	1.02 (1.01, 1.03)	2.13×10^{-3}	–
CPD	Total grey matter volume	Other types of dementia	1.40 (1.07, 1.84)	1.55×10^{-2}	1.37 (1.04, 1.81)	2.31×10^{-2}	1.02 (1.01, 1.03)	2.17×10^{-2}	6.050
CPD	Total grey matter volume	AD	1.28 (0.92, 1.80)	1.46×10^{-1}	1.25 (0.89, 1.75)	1.93×10^{-1}	1.03 (1.01, 1.04)	2.40×10^{-2}	–
CPD	Total grey matter volume	VD	0.99 (0.60, 1.62)	9.56×10^{-1}	0.98 (0.60, 1.61)	9.36×10^{-1}	1.01 (0.98, 1.03)	>0.99	–
RA	GMV of left cerebellum crus I	AD	0.35 (0.00, 91.25)	7.11×10^{-1}	0.44 (0.00, 116.60)	7.73×10^{-1}	0.79 (0.66, 0.95)	>0.99	–
RA	GMV of left cerebellum crus I	All-cause dementia	0.18 (0.01, 5.39)	3.27×10^{-1}	0.20 (0.01, 5.96)	3.55×10^{-1}	0.91 (0.80, 1.03)	>0.99	–
RA	GMV of left cerebellum crus I	Other types of dementia	0.09 (0.00, 3.74)	2.05×10^{-1}	0.10 (0.00, 4.11)	2.23×10^{-1}	0.91 (0.79, 1.05)	>0.99	–
RA	GMV of left cerebellum crus I	VD	0.73 (0.00, 6168.51)	9.45×10^{-1}	0.83 (0.00, 7145.98)	9.68×10^{-1}	0.87 (0.66, 1.15)	>0.99	–
RA	GMV of left cerebellum crus II	AD	0.31 (0.00, 81.83)	6.81×10^{-1}	0.39 (0.00, 104.82)	7.44×10^{-1}	0.78 (0.66, 0.93)	3.47×10^{-1}	–

Continued

Table 3 Continued

Circadian index	IDPs	Incident illness	Total effect (HR (95% CI))	$P_{Total\ effect}$	Direct effect (HR (95% CI))	$P_{Direct\ effect}$	Indirect effect (HR (95% CI))	$P_{Indirect\ effect}$ (Bonferroni corrected)	Proportion mediated%
RA	GMV of left cerebellum crus II	All-cause dementia	0.18 (0.01, 5.21)	3.20×10^{-1}	0.19 (0.01, 5.54)	3.37×10^{-1}	0.94 (0.84, 1.06)	>0.99	–
RA	GMV of left cerebellum crus II	VD	0.58 (0.00, 4290.45)	9.03×10^{-1}	0.52 (0.00, 3897.80)	8.84×10^{-1}	1.11 (0.86, 1.44)	>0.99	–
RA	GMV of left cerebellum crus II	Other types of dementia	0.09 (0.00, 3.69)	2.05×10^{-1}	0.09 (0.00, 3.77)	2.09×10^{-1}	0.98 (0.86, 1.12)	>0.99	–
RA	GMV of left V cerebellum	AD	0.28 (0.00, 69.18)	6.49×10^{-1}	0.33 (0.00, 84.19)	6.98×10^{-1}	0.83 (0.62, 1.11)	>0.99	–
RA	GMV of left V cerebellum	All-cause dementia	0.18 (0.01, 5.16)	3.17×10^{-1}	0.19 (0.01, 5.55)	3.37×10^{-1}	0.93 (0.77, 1.13)	>0.99	–
RA	GMV of left V cerebellum	VD	0.64 (0.00, 4723.60)	9.22×10^{-1}	0.59 (0.00, 4354.47)	9.06×10^{-1}	1.10 (0.73, 1.65)	>0.99	–
RA	GMV of left V cerebellum	Other types of dementia	0.09 (0.00, 3.68)	2.05×10^{-1}	0.09 (0.00, 3.73)	2.07×10^{-1}	0.99 (0.79, 1.24)	>0.99	–
RA	GMV of left VI cerebellum	AD	0.30 (0.00, 72.75)	6.65×10^{-1}	0.38 (0.00, 94.25)	7.30×10^{-1}	0.78 (0.57, 1.07)	>0.99	–
RA	GMV of left VI cerebellum	VD	0.56 (0.00, 4270.90)	8.99×10^{-1}	0.47 (0.00, 3644.28)	8.67×10^{-1}	1.21 (0.78, 1.88)	>0.99	–
RA	GMV of left VI cerebellum	Other types of dementia	0.09 (0.00, 3.70)	2.07×10^{-1}	0.09 (0.00, 3.50)	1.96×10^{-1}	1.06 (0.84, 1.35)	>0.99	–
RA	GMV of left VI cerebellum	All-cause dementia	0.18 (0.01, 5.17)	3.20×10^{-1}	0.18 (0.01, 5.11)	3.16×10^{-1}	1.02 (0.83, 1.24)	>0.99	–
RA	GMV of left VIIb cerebellum	AD	0.27 (0.00, 67.67)	6.42×10^{-1}	0.38 (0.00, 96.38)	7.33×10^{-1}	0.71 (0.55, 0.90)	3.71×10^{-1}	–
RA	GMV of left VIIb cerebellum	All-cause dementia	0.18 (0.01, 5.10)	3.13×10^{-1}	0.19 (0.01, 5.66)	3.43×10^{-1}	0.90 (0.76, 1.06)	>0.99	–
RA	GMV of left VIIb cerebellum	Other types of dementia	0.09 (0.00, 3.66)	2.03×10^{-1}	0.09 (0.00, 3.83)	2.12×10^{-1}	0.96 (0.78, 1.17)	>0.99	–
RA	GMV of left VIIb cerebellum	VD	0.64 (0.00, 4878.56)	9.22×10^{-1}	0.64 (0.00, 4946.84)	9.21×10^{-1}	1.00 (0.68, 1.47)	>0.99	–
RA	GMV of left VIIIa cerebellum	AD	0.27 (0.00, 67.71)	6.44×10^{-1}	0.40 (0.00, 102.20)	7.49×10^{-1}	0.67 (0.48, 0.92)	>0.99	–
RA	GMV of left VIIIa cerebellum	All-cause dementia	0.18 (0.01, 5.19)	3.19×10^{-1}	0.19 (0.01, 5.65)	3.42×10^{-1}	0.92 (0.74, 1.15)	>0.99	–
RA	GMV of left VIIIa cerebellum	VD	0.68 (0.00, 5272.65)	9.31×10^{-1}	0.75 (0.00, 6022.34)	9.49×10^{-1}	0.90 (0.55, 1.48)	>0.99	–
RA	GMV of left VIIIa cerebellum	Other types of dementia	0.09 (0.00, 3.69)	2.06×10^{-1}	0.09 (0.00, 3.61)	2.01×10^{-1}	1.03 (0.79, 1.33)	>0.99	–
RA	GMV of right cerebellum crus I	AD	0.31 (0.00, 81.81)	6.82×10^{-1}	0.41 (0.00, 108.21)	7.54×10^{-1}	0.76 (0.63, 0.92)	4.34×10^{-1}	–
RA	GMV of right cerebellum crus I	All-cause dementia	0.18 (0.01, 5.30)	3.23×10^{-1}	0.20 (0.01, 5.81)	3.49×10^{-1}	0.91 (0.80, 1.04)	>0.99	–
RA	GMV of right cerebellum crus I	Other types of dementia	0.09 (0.00, 3.75)	2.06×10^{-1}	0.10 (0.00, 4.10)	2.24×10^{-1}	0.92 (0.78, 1.07)	>0.99	–

Continued

Table 3 Continued

Circadian index	IDPs	Incident illness	Total effect (HR (95% CI))	$P_{Total\ effect}$	Direct effect (HR (95% CI))	$P_{Direct\ effect}$	Indirect effect (HR (95% CI))	$P_{Indirect\ effect}$ (Bonferroni corrected)	Proportion mediated%
RA	GMV of right cerebellum crus I	VD	0.64 (0.00, 4895.38)	9.22×10^{-1}	0.64 (0.00, 4964.15)	9.22×10^{-1}	1.00 (0.75, 1.33)	>0.99	–
RA	GMV of right cerebellum crus II	AD	0.32 (0.00, 82.68)	6.86×10^{-1}	0.40 (0.00, 105.08)	7.48×10^{-1}	0.79 (0.67, 0.93)	3.51×10^{-1}	–
RA	GMV of right cerebellum crus II	All-cause dementia	0.18 (0.01, 5.35)	3.27×10^{-1}	0.20 (0.01, 5.86)	3.52×10^{-1}	0.92 (0.82, 1.02)	>0.99	–
RA	GMV of right cerebellum crus II	Other types of dementia	0.09 (0.00, 3.74)	2.07×10^{-1}	0.10 (0.00, 3.98)	2.19×10^{-1}	0.94 (0.82, 1.08)	>0.99	–
RA	GMV of right cerebellum crus II	VD	0.57 (0.00, 4259.53)	9.02×10^{-1}	0.54 (0.00, 4094.90)	8.93×10^{-1}	1.06 (0.83, 1.36)	>0.99	–
RA	GMV of right I-IV cerebellum	All-cause dementia	0.18 (0.01, 5.23)	3.21×10^{-1}	0.19 (0.01, 5.62)	3.41×10^{-1}	0.94 (0.80, 1.09)	>0.99	–
RA	GMV of right I-IV cerebellum	AD	0.28 (0.00, 68.65)	6.53×10^{-1}	0.31 (0.00, 75.78)	6.78×10^{-1}	0.91 (0.72, 1.15)	>0.99	–
RA	GMV of right I-IV cerebellum	Other types of dementia	0.09 (0.00, 3.72)	2.06×10^{-1}	0.09 (0.00, 3.88)	2.14×10^{-1}	0.96 (0.80, 1.16)	>0.99	–
RA	GMV of right I-IV cerebellum	VD	0.65 (0.00, 4820.38)	9.25×10^{-1}	0.61 (0.00, 4549.65)	9.14×10^{-1}	1.06 (0.76, 1.49)	>0.99	–
RA	GMV of right ventral striatum	All-cause dementia	0.17 (0.01, 5.13)	3.11×10^{-1}	0.19 (0.01, 5.77)	3.45×10^{-1}	0.89 (0.79, 1.00)	>0.99	–
RA	GMV of right ventral striatum	Other types of dementia	0.08 (0.00, 3.62)	1.99×10^{-1}	0.09 (0.00, 4.01)	2.18×10^{-1}	0.90 (0.79, 1.04)	>0.99	–
RA	GMV of right ventral striatum	AD	0.27 (0.00, 69.19)	6.43×10^{-1}	0.30 (0.00, 77.41)	6.72×10^{-1}	0.89 (0.75, 1.07)	>0.99	–
RA	GMV of right ventral striatum	VD	0.64 (0.00, 4838.82)	9.21×10^{-1}	0.63 (0.00, 4872.14)	9.20×10^{-1}	1.00 (0.78, 1.30)	>0.99	–
RA	GMV of right VI cerebellum	AD	0.27 (0.00, 67.11)	6.44×10^{-1}	0.33 (0.00, 82.18)	6.95×10^{-1}	0.82 (0.61, 1.10)	>0.99	–
RA	GMV of right VI cerebellum	Other types of dementia	0.10 (0.00, 3.85)	2.16×10^{-1}	0.09 (0.00, 3.47)	1.96×10^{-1}	1.11 (0.88, 1.39)	>0.99	–
RA	GMV of right VI cerebellum	VD	0.59 (0.00, 4383.33)	9.08×10^{-1}	0.51 (0.00, 3865.46)	8.83×10^{-1}	1.16 (0.76, 1.78)	>0.99	–
RA	GMV of right VI cerebellum	All-cause dementia	0.18 (0.01, 5.21)	3.22×10^{-1}	0.18 (0.01, 5.08)	3.15×10^{-1}	1.03 (0.85, 1.24)	>0.99	–
RA	GMV of right VIIb cerebellum	AD	0.29 (0.00, 76.80)	6.62×10^{-1}	0.39 (0.00, 106.29)	7.45×10^{-1}	0.73 (0.58, 0.90)	2.79×10^{-1}	–
RA	GMV of right VIIb cerebellum	All-cause dementia	0.18 (0.01, 5.24)	3.18×10^{-1}	0.20 (0.01, 6.02)	3.57×10^{-1}	0.87 (0.75, 1.01)	>0.99	–
RA	GMV of right VIIb cerebellum	Other types of dementia	0.09 (0.00, 3.66)	2.02×10^{-1}	0.10 (0.00, 4.05)	2.21×10^{-1}	0.91 (0.76, 1.08)	>0.99	–
RA	GMV of right VIIb cerebellum	VD	0.65 (0.00, 5007.00)	9.24×10^{-1}	0.66 (0.00, 5174.24)	9.26×10^{-1}	0.99 (0.70, 1.39)	>0.99	–

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Table 3 Continued

Circadian index	IDPs	Incident illness	Total effect (HR (95% CI))	$P_{Total\ effect}$	Direct effect (HR (95% CI))	$P_{Direct\ effect}$	Indirect effect (HR (95% CI))	$P_{Indirect\ effect}$ (Bonferroni corrected)	Proportion mediated%
RA	GMV of right VIIIa cerebellum	AD	0.25 (0.00, 68.75)	6.33×10^{-1}	0.39 (0.00, 106.67)	7.45×10^{-1}	0.65 (0.47, 0.89)	5.94×10^{-1}	–
RA	GMV of right VIIIa cerebellum	All-cause dementia	0.17 (0.01, 5.14)	3.14×10^{-1}	0.20 (0.01, 5.82)	3.48×10^{-1}	0.89 (0.72, 1.10)	>0.99	–
RA	GMV of right VIIIa cerebellum	Other types of dementia	0.09 (0.00, 3.63)	2.01×10^{-1}	0.09 (0.00, 3.90)	2.14×10^{-1}	0.93 (0.72, 1.20)	>0.99	–
RA	GMV of right VIIIa cerebellum	VD	0.58 (0.00, 4223.67)	9.05×10^{-1}	0.51 (0.00, 3853.20)	8.83×10^{-1}	1.14 (0.70, 1.84)	>0.99	–
RA	GMV of VIIIa cerebellum vermis	AD	0.29 (0.00, 74.15)	6.63×10^{-1}	0.34 (0.00, 87.67)	7.05×10^{-1}	0.85 (0.69, 1.05)	>0.99	–
RA	GMV of VIIIa cerebellum vermis	All-cause dementia	0.18 (0.01, 5.29)	3.24×10^{-1}	0.19 (0.01, 5.56)	3.38×10^{-1}	0.95 (0.83, 1.09)	>0.99	–
RA	GMV of VIIIa cerebellum vermis	Other types of dementia	0.09 (0.00, 3.71)	2.06×10^{-1}	0.09 (0.00, 3.81)	2.11×10^{-1}	0.98 (0.83, 1.15)	>0.99	–
RA	GMV of VIIIa cerebellum vermis	VD	0.63 (0.00, 4858.77)	9.20×10^{-1}	0.63 (0.00, 4910.72)	9.19×10^{-1}	1.01 (0.74, 1.37)	>0.99	–

Mediation analysis only used those identified IDPs that were found significant results in both of the association analyses and difference analyses as the mediator factors. The direct effects, indirect effects, and total effects of CPD and RA on dementia for each structural brain.
AD, Alzheimer's disease; CPD, composite phase deviation; GMV, grey matter volume; IDPs, imaging-derived phenotype; RA, relative amplitude; VD, vascular dementia.

melatonin in cerebrospinal fluid.[28] The cerebrospinal fluid melatonin rhythm plays an important role in the clearance of toxic and pathological molecules from the brain, via the glymphatic system.[28] A multi-omics study found that melatonin can reduce neuron damage by attenuating lipid dyshomeostasis.[29] More research may be necessary to fully explain how circadian disruption induces structural brain changes.

Although we found that both CPD and RA were associated with dementia and cognitive impairment in this study, they affected different brain structures. Only some CPD-related brain structures mediate dementia, providing cues for their differential effects. Indeed, a previous study supports the hypothesis that different dimensions of circadian rhythm may have independent effects on the cognitive system.[30] These results may be important for future studies investigating the potential mechanisms.

Our results highlight the significance of maintaining healthy circadian rhythms in preventing cognitive impairment and dementia. This knowledge can inform educational campaigns and public health initiatives that encourage healthy sleep habits and lifestyle choices. For individuals with specific circadian disruption such as shift workers, the volume of key brain regions such as the hippocampus and thalamus can serve as a potential marker for occupational health screenings, enabling early prediction and treatment of cognitive impairment and dementia.

The present study had some major limitations. First, there was a temporal overlap between the recording of MRI data (2014+) and accelerometric measurements (2013–2015). It is difficult to distinguish between MRI and accelerometric measurements in terms of time sequence. Our study only presents evidence of cross-sectional associations,[12] which precludes the establishment of causal relationships. Prospective studies are needed to further validate the results. Second, although reliability and validity of unsupervised cognitive tests administered by the UK Biobank have been demonstrated,[11] the unsupervised nature of these measures can lead to a lack of control over certain factors that influence cognitive assessment results, such as education level. This may introduce additional uncertainty to the estimation of cognitive tests. Third, the mechanisms underlying cognitive performance and dementia are complex with a number of potential regulators. While we controlled for several covariates, such as age, sex and education level, there could be unmeasured residual confounding factors (eg, genetic predisposition, lifestyle factors or social–economic status). Future studies should take as many confounders as possible into consideration, so as to better clarify the effects of circadian disruption on brain structure and cognition. Fourth, it is worth mentioning that the association between RA and the elevated risk of dementia might be influenced by the level of physical activity during the daytime, which serves as a protective factor against dementia. Previous research revealed that lower RA was still associated with white matter microstructural alterations even when self-reported exercise was adjusted, but the effect size may be modified when exercise levels varied.[9] Further confirmation from more high-quality animal and human studies is warranted. Fifth, we used structural brain measures without considering brain area interactions or functional organisation. This may have overlooked the adverse effects of circadian disruptions on cognition and mental health. Further studies are warranted to confirm these findings of the present study.

In conclusion, the present study suggests that circadian disruption is associated with brain structural alterations, including the hippocampus and thalamus, involving dementia and cognitive impairment. Since circadian disruption is a behaviour-related factor that may be exogenously modifiable, our research findings may have implications for the prevention and treatment of cognitive impairment and dementia.

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REFERENCES

1 Crnko S, Du Pré BC, Sluijter JPG, *et al*. Circadian rhythms and the molecular clock in cardiovascular biology and disease. *Nat Rev Cardiol* 2019;16:437–47.
2 Roenneberg T. The human sleep project. *Nature New Biol* 2013;498:427–8.
3 Canever JB, Queiroz LY, Soares ES, *et al*. Circadian rhythm alterations affecting the pathology of neurodegenerative diseases. *J Neurochem* 2024;168:1475–89.
4 Fang K, Liu D, Pathak SS, *et al*. Disruption of Circadian Rhythms by Ambient Light during Neurodevelopment Leads to Autistic-like Molecular and Behavioral Alterations in Adult Mice. *Cells* 2021;10:3314.
5 Jeon SY, Byun MS, Yi D, *et al*. Circadian rest-activity rhythm and longitudinal brain changes underlying late-life cognitive decline. *Psychiatry Clin Neurosci* 2023;77:205–12.
6 Trehearne A. Genetics, lifestyle and environment. UK Biobank is an open access resource following the lives of 500,000 participants to improve the health of future generations. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2016;59:361–7.
7 Rowlands AV, Yates T, Davies M, *et al*. Raw Accelerometer Data Analysis with GGIR R-package: Does Accelerometer Brand Matter? *Med Sci Sports Exerc* 2016;48:1935–41.
8 Fischer D, Vetter C, Roenneberg T. A novel method to visualise and quantify circadian misalignment. *Sci Rep* 2016;6:38601.
9 Palmer JR, Duffy SL, Meares S, *et al*. Rest–activity functioning is related to white matter microarchitecture and modifiable risk factors in older adults at-risk for dementia. *Sleep* 2021;44:zsab007.

10 Alfaro-Almagro F, Jenkinson M, Bangerter NK, *et al*. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage* 2018;166:400–24.
11 Fawns-Ritchie C, Deary IJ. Reliability and validity of the UK Biobank cognitive tests. *PLoS One* 2020;15:e0231627.
12 Lyall LM, Wyse CA, Graham N, *et al*. Association of disrupted circadian rhythmicity with mood disorders, subjective wellbeing, and cognitive function: a cross-sectional study of 91 105 participants from the UK Biobank. *Lancet Psychiatry* 2018;5:507–14.
13 Cho SH, Huang YT. Mediation analysis with causally ordered mediators using Cox proportional hazards model. *Stat Med* 2019;38:1566–81.
14 Montaruli A, Castelli L, Mulè A, *et al*. Biological Rhythm and Chronotype: New Perspectives in Health. *Biomolecules* 2021;11:487.
15 Bello-Chavolla OY, Bahena-López JP, Antonio-Villa NE, *et al*. Predicting Mortality Due to SARS-CoV-2: A Mechanistic Score Relating Obesity and Diabetes to COVID-19 Outcomes in Mexico. *J Clin Endocrinol Metab* 2020;105:dgaa346:2752–61:.
16 Fraser MA, Walsh EI, Shaw ME, *et al*. Longitudinal trajectories of hippocampal volume in middle to older age community dwelling individuals. *Neurobiol Aging* 2021;97:97–105.
17 Roy DS, Zhang Y, Halassa MM, *et al*. Thalamic subnetworks as units of function. *Nat Neurosci* 2022;25:140–53.
18 Goldman JG, Stebbins GT, Bernard B, *et al*. Entorhinal cortex atrophy differentiates Parkinson's disease patients with and without dementia. *Mov Disord* 2012;27:727–34.
19 Nakazawa T, Ohara T, Hirabayashi N, *et al*. Multiple-region grey matter atrophy as a predictor for the development of dementia in a community: the Hisayama Study. *J Neurol Neurosurg Psychiatry* 2022;93:263–71.
20 Chen H, Sheng X, Luo C, *et al*. The compensatory phenomenon of the functional connectome related to pathological biomarkers in individuals with subjective cognitive decline. *Transl Neurodegener* 2020;9:21.
21 Noya SB, Colameo D, Brüning F, *et al*. The forebrain synaptic transcriptome is organized by clocks but its proteome is driven by sleep. *Science* 2019;366:eaav2642.
22 Fagiani F, Di Marino D, Romagnoli A, *et al*. Molecular regulations of circadian rhythm and implications for physiology and diseases. *Signal Transduct Target Ther* 2022;7:41.
23 Kenche H, Singh M, Smith J, *et al*. Neuronal mitochondrial dysfunction in a cellular model of circadian rhythm disruption is rescued by donepezil. *Biochem Biophys Res Commun* 2021;567:56–62.
24 Karatsoreos IN, Bhagat S, Bloss EB, *et al*. Disruption of circadian clocks has ramifications for metabolism, brain, and behavior. *Proc Natl Acad Sci U S A* 2011;108:1657–62.
25 Albrecht U, Ripperger JA. Circadian Clocks and Sleep: Impact of Rhythmic Metabolism and Waste Clearance on the Brain. *Trends Neurosci* 2018;41:677–88.
26 Uchida K. Waste Clearance in the Brain and Neuroinflammation: A Novel Perspective on Biomarker and Drug Target Discovery in Alzheimer's Disease. *Cells* 2022;11:919.
27 Meng D, Yang M, Zhang H, *et al*. Microglia activation mediates circadian rhythm disruption-induced cognitive impairment in mice. *J Neuroimmunol* 2023;379:578102.
28 Reiter RJ, Sharma R, Cucielo MS, *et al*. Brain washing and neural health: role of age, sleep, and the cerebrospinal fluid melatonin rhythm. *Cell Mol Life Sci* 2023;80:88.
29 Jiang X, Xu Z, Yao D, *et al*. An integrated multi-omics approach revealed the regulation of melatonin on age-dependent mitochondrial function impair and lipid dyshomeostasis in mice hippocampus. *Pharmacol Res* 2022;179:106210.
30 Najjar RP, Wolf L, Taillard J, *et al*. Chronic artificial blue-enriched white light is an effective countermeasure to delayed circadian phase and neurobehavioral decrements. *PLoS One* 2014;9:e102827.