Mathilde Reyt ORCID iD: 0000-0001-5501-5216

Daytime rest: Association with 24-h rest-activity cycles, circadian timing and cognition in older adults

Running title: Daytime rest, circadian timing and cognitive ageing

Mathilde Reyt[1,2], Michele Deantoni[1], Marion Baillet[1], Alexia Lesoinne[1], Sophie Laloux[1], Eric Lambot[1], Justine Demeuse[3], Chiara Calaprice[3], Caroline LeGoff[3], Fabienne Collette[1,2], Gilles Vandewalle[1], Pierre Maquet[1,4], Vincenzo Muto[1], Grégory Hammad[1*], and Christina Schmidt[1,2*]

[1]Sleep & Chronobiology Group, GIGA-CRC-In Vivo Imaging Research Unit, University of Liège, Liège, Belgium

[2]Psychology and Neuroscience of Cognition Research Unit (PsyNCog), Faculty of Psychology and Educational Sciences, University of Liège, Liège, Belgium

[3]Department of Clinical Chemistry, University Hospital of Liège, University of Liège, Liège, Belgium

[4]Department of Neurology, University Hospital of Liège, University of Liège, Liège, Belgium

* Equally contributed

Corresponding author: Christina Schmidt, Sleep & Chronobiology Group, GIGA-CRC-In Vivo Imaging Research Unit, University of Liège, Allée du 6 Août, B30, 4000 Liège, Belgium, Telephone: +32 4 366 23 04

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jpi.12820.

ABSTRACT

Growing epidemiological evidence points towards an association between fragmented 24-h rest-activity cycles and cognition in the aged. Alterations in the circadian timing system might at least partially account for these observations. Here, we tested whether daytime rest is associated with changes in concomitant 24-h rest probability profiles, circadian timing and neurobehavioural outcomes in healthy older adults. Sixty-three individuals (59 – 82 years) underwent field actigraphy monitoring, in-lab dim light melatonin onset (DLMOn) assessment and an extensive cognitive test battery. Actimetry recordings were used to measure daytime rest (DTR) frequency, duration and timing and to extract 24-h rest probability profiles. As expected, increasing DTR frequency was associated with higher rest probabilities during the day, but also with lower rest probabilities during the night, suggesting more fragmented night-time rest. Higher DTR frequency was also associated with lower episodic memory performance. Moreover, later DTR timing went along with an advanced circadian phase as well as with an altered phase angle of entrainment between the rest-activity cycle and circadian phase. Our results suggest that different daytime rest characteristics, as reflective indices of wake fragmentation, are not only underlined by functional consequences on cognition, but also by circadian alteration in the aged.

Keywords: actigraphy, melatonin, circadian rhythm, cognition, ageing, rest

INTRODUCTION

The internal circadian clock provides temporal organisation to the sleep-wake cycle through adaptive arousal mechanisms.[1–3] Alignment between the circadian clock and the rest-activity cycle is fundamental to many physiological and neurobehavioural processes.[4] Accordingly, misalignment affects state stability[3,5] and is associated with

deterioration in vigilance, cognitive performance and its cerebral correlates, particularly when sleep propensity is high.[6–8]

More fragmented 24-h rest-activity cycles in ageing have been associated with worse cognitive performance[9–11] and with an increased incidence of Alzheimer's disease.[12–14] Concomitantly, recent epidemiological reports promote actimetry-derived daytime rest as a health risk factor in the aged,[15,16] including for cognitive fitness.[17,18] In the same vein, frequent and long-duration actimetry-derived daytime rest has been associated with Alzheimer's disease progression and prognosis.[18]

Considering its strong implication in sleep timing, differences in circadian physiology might at least partially contribute to the increased incidence of DTR and associated changes in neurobehavioural outcomes during ageing. The circadian process is notably impacted by age through changes in clock gene expression, an advanced phase, a reduced amplitude of melatonin secretion[19,20] and a putative alteration in circadian sleep-wake propensity drives.[21,22] Concomitantly, an overall age-related reduction in the maximal capacity for sleep has been reported[23] and it was suggested that ageing affects the ability to maintain sleep and wake states over extended periods of time, resulting in more fragmented rest-activity cycles.[24] Within this perspective, the increasing intrusion of consolidated rest bouts into the active wake period in the aged might be underlined by altered circadian regulation and associated functional consequences on cognition.

In the current cross-sectional study, we applied a chronobiological approach to investigate whether DTR characteristics, such as frequency, duration and timing, explain inter-individual variability in 24-h rest-activity organisation, circadian timing and cognition in the aged.

METHODS

Participants

Sixty-three healthy retired older volunteers, screened for medical conditions, were recruited. Eighty-one percent of the sample subjectively reported to regularly nap (see supplemental information for detailed inclusion criteria). Actigraphy monitoring revealed no daytime rest period over the recording for three participants. These subjects were excluded from the main analysis due to the unfeasibility to extract DTR timing; one of our primary outcomes (but see supplemental material for a confirmatory analysis including these participants on a reduced statistical model, not including DTR timing). Three subjects were further excluded due to a poor fit quality of melatonin data due to contamination during sampling or technical issues during extraction. Demographic characteristics of the final sample of 57 participants (24 females, aged 68.86±5.54 years [mean ± standard deviation (SD)], range 59-82) are summarised in Table S1.

Study procedure

After study enrolment, participants underwent a night of polysomnography at the laboratory, during which the sleep apnea/hypopnea index (AHI) was determined. Then, at least 8 days of actigraphy were recorded to extract DTR characteristics and 24-h rest probability profiles while maintaining daily routines and self-selected sleep schedules at home (see Figure 1A for the study timeline and Figure 1B for an example of actigraphy recording). In a next step, participants were requested to follow a pre-defined and individually-adapted sleep-wake schedule centred around an 8-h night-time sleep opportunity during 7 days. Compliance with the regimen was verified at admission. Participants were further instructed to abstain from alcohol and energetic drinks during this week to prevent withdrawal effects. After the week of fixed

actimetry, participants classically arrived at the laboratory 6 hours after scheduled wake-up time and completed a cognitive test battery probing episodic memory, attention and executive functions performance (Figure 1A). Thereafter, participants underwent a 40-h multiple nap protocol (Figure 1A, supplemental information) under controlled constant-routine conditions according to light input (<5 lux, see supplemental information for details about light specifications, Table S2), ambient temperature (~19 °C), body posture (semi-recumbent during wake periods, except for scheduled bathroom visits) and isocaloric food intake, without access to external time cues. Salivary melatonin was collected at regular intervals (~1.25 hours) throughout the 40-h protocol. The protocol was preceded and followed by an 8-h baseline and recovery night, respectively. The study was approved by the local Ethics Committee of the University Hospital and of the Faculty of Psychology, Logopedics and Educational Sciences at the University of Liège (Belgium) and performed in accordance with the Declaration of Helsinki. Participants gave written informed consent and received a financial compensation.

Circadian phase assessment: Melatonin

Saliva samples were obtained by passive drooling. Salivary melatonin levels were analysed via a liquid chromatography coupled to a tandem mass spectrometer (see supplemental information). Secretion profiles were determined with a skewed baseline cosine function.[25] Circadian phase was assessed by extracting the timing of the dim light melatonin onset (DLMOn) and dim light melatonin offset (DLMOff). The latter were defined as the point in time at which melatonin levels reached 25% of the fitted peak-to-baseline amplitude of individual data (Figure 1C). To assess phase relationships between rest-activity cycles and circadian phase, the interval between

DLMOn time and actigraphy-derived activity offset time were further computed (phase angle of entrainment[26]). Circadian outcomes are reported in

Table 1.

Daytime rest characteristics and 24-h rest probability profiles: Actigraphy

Participants wore an actigraph (Motionwatch 8, CamNtech, UK) at the non-dominant wrist and completed a sleep diary for at least 8 consecutive days, with a maximum duration of 15 days (13.58±1.81 days). Locomotor activity data and light levels were aggregated into 30-sec epochs and processed by the open-source software pyActigraphy (v1.0).[27] Periods of actigraph removal were visually identified according to sleep diaries and excluded from the analysis. The automatic scoring of the Munich Actimetry Sleep Detection Algorithm (MASDA)[28] was used to detect consolidated rest periods. The latter was set to classify consecutive epochs of at least 15 minutes with activity counts below 15% of the 24-h centered moving average as rest periods. We assessed the performance of the algorithm against visual scoring of an independent sub-sample of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort with comparable demographical characteristics (N= 336, age range=59–82 y.o., Caucasian, retired, 189 women).[29] Agreement between the MASDA and visual scoring is reported in the supplemental information.

For the generation of 24-h rest probability profiles, classification scores from MASDA were first averaged over 24-h apart time points for each time of day, then resampled by averaging the probabilities over each 10 minutes period and smoothed by a Gaussian-filter rolling average (Gaussian window: size=120 min and standard deviation=20 min). Profiles were normalized for the total rest probability over 24 hours to emphasize their temporal distribution (Figure 1C). For statistical comparisons, rest profiles were further aligned to the individual's DLMOn (Figure 2).

Daytime rest periods were determined with a duration comprised between 15 minutes and 4 hours during the biological day (see Figure 1B for illustration of consolidated rest bout detection). The biological day was defined as the time window between the group averaged DLMOff +2h (DLMOff: 7.95±1.13 h) and DLMOn -2h (DLMOn: 21.44±1.23 h), respectively. This time window was chosen to exclude potential confounding effects of transition periods during the early morning and late evening hours.

Three characteristics were extracted from actigraphy-derived rest bouts: (1) daily frequency, calculated as the mean number of DTR bouts per day, (2) duration, defined as the overall mean duration of DTR bouts and (3) timing, defined as the median delay between DTR bouts start time and DLMOn. Furthermore, correlation analyses between automatically-detected rest periods by the MASDA and subjectively-reported nap characteristics were performed.

Activity onset- and offset times were automatically detected in each daily profile as the times at which the ratio between activities over the previous 15 minutes and the following 15 minutes are the highest and the lowest, respectively. The latter were visually verified by indications provided in sleep diaries (see supplemental information). Actigraphy-derived daily activity levels were estimated from the mean activity count over 24-h periods not classified as rest while night-time rest was expressed as the mean duration of automatically detected rest periods during the night, i.e. between activity offset and onset times. Finally, night-time rest fragmentation was estimated using transition probabilities from rest to activity (kRA index).[30] Actigraphy-derived variables are summarised in Table 1.

Finally light levels were measured at the non-dominant wrist and two parameters[31] were extracted: (1) mean light timing above the threshold of 500 lux ($MLiT^{500}$),

representing average timing of light exposure being greater than 500 lux and (2) time above threshold (TAT), defined as the number of epochs above a threshold of 100 lux (TAT^{100}) multiplied by the epoch length.

Neuropsychological assessment

A test battery, composed of a series of validated cognitive tasks (see supplemental information), was administered to assess episodic memory, executive functions and attention performance. A composite Z-score was computed by cognitive domain. Cognitive scores are summarised in

Table 1.

Statistical analyses

The associative value of DTR characteristics (frequency, duration, timing; independent variables), was investigated for 24-hour rest probability profiles, circadian markers and cognitive performance (dependent variables), respectively.

For 24-h rest probability profiles, linear regressions were computed using one-dimensional statistical non-parametric mapping (S(n)PM),[32] as implemented in the SPM1D Python package.[33] The latter applies random field theory to make statistical inferences about regional effects for continuous measurements, such as the rest probability over 24-h. For each DTR characteristic, a statistical map, SPM{t}, is created by calculating t-statistics for each 10-min interval of the 24-hour rest probability profile. The association between a DTR characteristic and the rest probability at a given time was deemed significant if the SPM{t} crosses the critical threshold (t*). This threshold is determined by permutations tests (iterations=10000), as the 95th percentile of the total of maximal t values, obtained for each permuted statistical map. Permutation tests were also used to determine the cluster-level p-

values ($p_{cluster}$) associated with the detected suprathreshold clusters. Significance was based on a p-value< 0.05.

To assess the association between DTR characteristics and circadian rhythm outcomes (circadian phase and phase angle as dependent variables), univariate linear multiple regression models were applied. Average daily activity level, night-time rest duration, lights parameters ($MLiT^{500}$ and TAT^{100}) and AHI were added as covariates. A Bonferroni correction was applied to correct for multiple comparisons (p_{corr}< 0.025).

Finally, a multivariate multiple regression model (Type III) was performed to explore whether DTR characteristics are associated with cognitive performance. Univariate multiple regressions were also computed to assess the relationship between DTR and specific cognitive domains. Regressions were controlled for age, gender, educational level, body mass index, daily activity level, night-time rest duration, AHI, circadian phase and phase angle. Statistical significance for multiple comparisons were corrected by applying a Bonferroni correction (p_{corr}< 0.016).

Except for the S(n)PM analysis, all statistics were performed in R3.6.3[34] using packages including stats[34] and QuantPsyc.[35] Multivariate analysis required the packages tidyverse,[36] Mvoutlier[37] and Mvnormtest.[38] Distribution normality was assessed by the Shapiro-Wilk test. Multicollinearity of each univariate model was assessed by calculating variance inflation factors and applying a maximum threshold of 5.

RESULTS

Daytime rest characteristics: automatic detection vs. subjective nap reports

Automatically-detected rest bouts by the MASDA were significantly associated with naps reported in the sleep diary with respect to frequency (Kendall's rank correlation: τ=0.29, p< 0.01), duration (Kendall's rank correlation: τ=0.32, p< 0.01) and timing

(Pearson's correlation: R=0.83, p< 0.0001). As depicted in Bland-Altman plots (Figure S1), the MASDA algorithm detected 0.24 times more rest periods than subjectively-reported naps (Figure S1A). The mean duration for detected rest bouts was on average 3.43 minutes longer than naps reported in the sleep diary (Figure S1B). Timing of detected rest bouts was on average 15.12 minutes later compared to reported naps (Figure S1C).

Daytime rest characteristics and 24-h rest probability profiles

As depicted in Figure 2, DTR duration, frequency and timing predicted rest probabilities at specific time windows over the 24-h profile.

Higher **DTR duration** was associated with increased rest probabilities during a very circumscribed daytime period (6.50–6.33 hours before DLMOn, $p_{cluster}$< 0.05, green line,

Figure 2).

Higher **DTR frequency** was significantly related to increased rest probabilities during daytime (between 4.50–6.50 hours ($p_{cluster}$< 0.001) and 8.00–9.17 hours ($p_{cluster}$< 0.01) before DLMOn, red line, Figure 2). Interestingly, increasing DTR frequency was further associated with reduced rest probabilities during the second part of the night-time period (between 5.17–7.83 hours after DLMOn; $p_{cluster}$< 0.001). Similarly, DTR frequency was positively associated with rest-to-activity transition probabilities (kRA index) during night-time (Kendall's rank correlation; τ=0.20, p< 0.05, see Figure S2).

Later DTR was significantly related to decreased rest probabilities in the late evening hours, close to DLMOn (1.00 hour before DLMOn to 2.17 hours after DLMOn, $p_{cluster}$< 0.001) as well as increased rest probabilities during a time window in the early morning hours, encompassing DLMOff (8.00–11.33 hours after DLMOn, $p_{cluster}$< 0.01, blue line, Figure 2).

Daytime rest characteristics and circadian timing

Daytime rest frequency and duration were not significantly associated with circadian outcomes (Table S3). However, taking into account average daily activity level, night-time rest duration, light parameters and AHI, DTR timing was related to circadian phase, such that later DTR was linked to an earlier DLMOn (β=-0.69, t=-6.67, $p< 0.001$, Figure 3) and a longer phase angle of circadian entrainment (interval between DLMOn and actigraphy-derived activity offset times, β=0.63, t=5.83, $p< 0.001$, Figure 3; see Table S3 and Figure S3 for similar results using DLMOff).

In addition, lower night-time rest duration, introduced as a covariate into the statistical model, was associated with a longer phase angle of entrainment (β=-0.31, t=-2.72, $p< 0.01$ for interval between DLMOn and activity offset times, Table S3).

Daytime rest characteristics and cognition

A multivariate multiple regression model including attentional, executive and episodic memory performance revealed that DTR frequency tended to predict cognitive performance ($F_{3,42}$=2.72, p=0.06, Table S4). Univariate analyses by cognitive domain showed that episodic memory performance was negatively associated with DTR frequency (β=-0.40, t=-2.64, $p_{corr}< 0.016$, Figure 4, Table S4), while no significant associations were observed for executive functions and attention performance ($p_{corr}> 0.016$; see Table S4).

DISCUSSION

Our data provide first evidence that DTR in the aged is linked to an overall altered 24-h rest-activity organisation. In addition, later DTR went along with an altered circadian phase and phase angle of entrainment and overall night-time rest duration. Finally, our results support earlier findings on the detrimental effects of DTR frequency on neurobehavioural performance in older individuals.[18]

The temporal distribution of rest-activity alternation changes over lifespan and appears to be disrupted with increasing age.[10,30] The intrusion of consolidated rest bouts during daytime may reflect a relative inability to maintain continuous activity levels during the active wake period, underlined by altered circadian regulation. Under entrained conditions, the circadian wakefulness drive is maximum 2–3 hours before habitual bedtime.[39] This time window of maximal circadian wake promotion has been characterized as the wake-maintenance zone (WMZ).[40] The use of a circadian phase marker, such as DLMOn, has been suggested as a requirement for the identification of the circadian WMZ.[41] By adjusting our data to DLMOn, we observed that later DTR is associated with decreased rest probabilities during a time window that encompasses the WMZ. Resting at strategic time windows might thus, in some contexts, be employed to reboost or maintain period of sustained activity at the end of the "ordinary" waking day. Similarly, later DTR was associated with increased probabilities to rest in the early morning hours. Within this perspective, the contribution of DTR to polysomnography-derived night-time sleep structure in the context of age-related changes in sleep-wake regulation should be further assessed. It is important to mention here, that concomitantly to changes in rest probabilities at circadian-strategic time windows, later DTR was further associated with advanced circadian phase assessed by DLMOn, and a longer phase angle of circadian entrainment, thereby indicating misalignment. These data may point to strategic rest placement to refrain from early awakenings and/or sleep times induced by advanced circadian phase; thereby being the cause or the consequence of an altered phase angle of entrainment. Furthermore, entrainment is a necessary and important adjustment of circadian phase to the environment, including light exposure.[42] Delayed sleep timing with respect to circadian phase has been shown less recuperative[43,44] and associated

with shorter night-time rest duration,[45] as observed in the present study through a significant negative association between the phase angle of entrainment and the night-time rest duration in older adults.

Our results also revealed that frequent daytime rests are not only associated with increased probability to rest in the afternoon hours, but also with increased night-time rest fragmentation in the second part of the night, which might be the most vulnerable time window to keep a consolidated state of sleep in the context of altered sleep promotion.[19] These results are a call for intervention studies to determine a potential cause-and-effect relationship between daytime rest chronicity and night-time sleep fragmentation; with direct clinical implications for insomnia treatment in the elderly.

Previous studies observed that rest-activity fragmentation can affect cognitive performance during ageing.[9,11,12] Using actimetry-derived DTR characteristics, we observed that increased DTR frequency was associated with worse episodic memory performance, which is particularly prone to be affected by the ageing process.[46] While this is the first report assessing the association between actimetry-derived DTR frequency and episodic memory performance in the aged, a previous report revealed a negative association between questionnaire-derived nap frequency and self-rated memory, even after adjusting for daytime sleepiness in the aged.[47] Moreover, an experimental study showed that a 90-min afternoon nap benefits episodic memory retention in young adults but not in older adults.[48] Finally, fractal regulation in temporal activity fluctuation has been shown to be altered with ageing[49] and its degradation has been associated with cognitive impairment[50], dementia[49,51] and a higher prevalence of Alzheimer's disease.[52] Considering the involvement of the suprachiasmatic nucleus, central circadian pacemaker, in the generation of fractal patterns of locomotor activity,[53] further studies should determine whether the

disorganisation of the global 24-h rest-activity cycle observed with DTR characteristics is associated with fractal regulation, considered as a temporal rhythm integration index.

Study limitations & perspectives

The primary outcome of the current study was actimetry-derived daytime rest with the underlying assumption that the intrusion of consolidated resting behavior into the active daytime period reflects circadian alteration and is associated with functional consequences on cognition in older adults. Actimetry-derived daytime rest detection does not reflect absolute daytime sleep[54] as such. While in our sample, mainly composed of self-reported nappers, actimetry-derived DTR characteristics correlated with napping as derived from sleep diaries, actimetry does not necessarily reflect a measure of an individual's sleep state as such. This might be particularly true when assessing rest during the active daytime period, characterized by varying levels of activity, including sedentary wakefulness. Hence, an exciting research avenue would consist in assessing the content of these daytime rest periods in terms of wakefulness and sleep, as the latter could be the mediator of the observations made in our study. In the same vein, the association between DTR characteristics and night-time sleep architecture would be interesting to be assessed using polysomnography. Within this context, it appears important to monitor sleep pathological events, such as sleep apnea, the incidence of which increases with increasing age.[55] Indeed, even if we excluded participants with major sleep disorders, varying degrees of sleep apnea had an impact daytime rest frequency. We therefore included participants' sleep apnea index in statistical models assessing the association between DTR characteristics, circadian outcomes and episodic memory.

Finally, our experiment was conducted from August 2018 to December 2020, thus including seasonal transitions. Seasonal components and associated modulation in light exposure throughout the year have been observed to affect the sleep-wake cycle and circadian rhythmicity.[56] To take into account differences in light exposure between participants, two light parameters were added in models assessing the association between DTR characteristics and circadian outcomes and the association between DTR timing and cirdian phase and phase angle remained significant. However, light levels measured at the wrist reflects only approximate measure of retinal light exposure and does generally not allow to discriminate between artificial light and natural light.[57]

Conclusion

Altogether, our findings suggest that the intrusion of consolidated rest-bouts into the active wake period goes along with both altered organisation of the 24-h rest-activity cycle and its phase relationship with circadian phase, but also with altered episodic memory performance.

As such, DTR might be a useful and biologically underlined marker of early cognitive impairment in the elderly.[17] Interestingly, it was recently observed that older adults tended to rest longer and more frequently and that increased rest frequency and duration was predictive for worse cognition a year later. Also a bi-directional link between actimetry-derived daytime rest and Alzheimer's disease progression and prognosis has been reported.[18]

Better understanding the mechanisms associated with the increased intrusion of rest or sleep into the active wake period is of relevance, particularly when considering that the latter are increasingly used as a potential health indicators in the aged population. Studies objectively assessing daytime rest remain scarce, and even more those

distinguishing between duration, frequency and timing.[58] Interventional and longitudinal designs might bring evidence into the causal link between increased wake fragmentation, circadian integrity and cognitive ageing. For example, reducing nap frequency and thereby consolidating night-time sleep might be beneficial for neurobehavioural outcomes and circadian alignment. Likewise, recommendations about nap timing and duration may help to keep consolidated sleep-wake cycles, despite alterations in underlying regulation processes. Finally, our findings highlight the usefulness of digital, but also circadian markers, in understanding the association between age-related changes in the 24-h rest-activity organisation and neurobehavioural outcomes.

ACKNOWLEDGEMENTS

This work was supported by the European Research Council (ERC, ERCStG-COGNAP) under the European Union's Horizon 2020 research and innovation programme (Grant agreement No. 757763). This work was also supported by the Fonds de la Recherche Scientifique - FNRS under Grant nr T.0220.20. CS, FC and GV are research associates and MD is a FRIA grantee of the Fonds de la Recherche Scientifique - FNRS, Belgium.

AUTHOR CONTRIBUTIONS

CS, MR, MD, FC and VM designed the study. MR, MD, AL, MB, SL, EL, VM and CS collected data. JD, CC and CL analysed melatonin samples. MR, VM, CS and GH developed methods, analysed and interpreted the data. All authors prepared, revised and contributed to the submitted version of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Daytime rest: Association with 24-h rest-activity cycles, circadian timing and cognition in older adults at 10.5281/zenodo.5876746.

REFERENCES

1. Borbély AA. A two process model of sleep regulation. *Hum Neurobiol*. 1982;1(3):195-204.

2. Daan S, Beersma DGM, Borbély AA. Timing of human sleep: recovery process gated by a circadian pacemaker. *Am J Physiol*. 1984;246(2 Pt 2):R161-R178.

3. Edgar D, Dement W, Fuller C. Effect of SCN lesions on sleep in squirrel monkeys: evidence for opponent processes in sleep-wake regulation. *J Neurosci*. 1993;13(3):1065-1079.

4. Roenneberg T, Merrow M. The Circadian Clock and Human Health. *Curr Biol*. 2016;26(10):R432-R443.

5. DelRosso LM, Hoque R, James S, Gonzalez-Toledo E, Chesson AL. Sleep-Wake Pattern Following Gunshot Suprachiasmatic Damage. *J Clin Sleep Med*. 2014;10(04):443-445.

6. Dijk DJ, Duffy JF, Czeisler CA. Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *J Sleep Res*. 1992;1(2):112-117.

7. Wyatt JK, Cecco AR-D, Czeisler CA, Dijk D-J. Circadian temperature and melatonin rhythms, sleep, and neurobehavioral function in humans living on a

20-h day. *Am J Physiol Integr Comp Physiol*. 1999;277(4):R1152-R1163.

8. Muto V, Jaspar M, Meyer C, et al. Local modulation of human brain responses by circadian rhythmicity and sleep debt. *Science*. 2016;353(6300):687-690.

9. Oosterman JM, Van Someren EJW, Vogels RLC, Van Harten B, Scherder EJA. Fragmentation of the rest-activity rhythm correlates with age-related cognitive deficits. *J Sleep Res*. 2009;18(1):129-135.

10. Lim ASP, Yu L, Costa MD, et al. Increased fragmentation of rest-activity patterns is associated with a characteristic pattern of cognitive impairment in older individuals. *Sleep*. 2012;35(5):633-640.

11. Luik AI, Zuurbier LA, Hofman A, Van Someren EJW, Ikram MA, Tiemeier H. Associations of the 24-h activity rhythm and sleep with cognition: a population-based study of middle-aged and elderly persons. *Sleep Med*. 2015;16(7):850-855.

12. Lim ASP, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons. *Sleep*. 2013;36(7):1027-1032.

13. Weissová K, Bartoš A, Sládek M, Nováková M, Sumová A. Moderate changes in the circadian system of Alzheimer's disease patients detected in their home environment. *PLoS One*. 2016;11(1):1-19.

14. Musiek ES, Bhimasani M, Zangrilli MA, Morris JC, Holtzman DM, Ju Y-ES. Circadian Rest-Activity Pattern Changes in Aging and Preclinical Alzheimer Disease. *JAMA Neurol*. 2018;75(5):582-590.

15. Leng Y, Stone K, Ancoli-Israel S, Covinsky K, Yaffe K. Who Take Naps? Self-Reported and Objectively Measured Napping in Very Old Women. *Journals Gerontol Ser A*. 2018;73(3):374-379.

16. Leng Y, Goldman SM, Cawthon PM, Stone KL, Ancoli-Israel S, Yaffe K. Excessive daytime sleepiness, objective napping and 11-year risk of Parkinson's disease in older men. *Int J Epidemiol*. 2018;47(5):1679-1686.

17. Leng Y, Redline S, Stone KL, Ancoli-Israel S, Yaffe K. Objective napping, cognitive decline, and risk of cognitive impairment in older men. *Alzheimer's Dement*. 2019;15(8):1039-1047.

18. Li P, Gao L, Yu L, et al. Daytime napping and Alzheimer's dementia: A potential bidirectional relationship. *Alzheimer's Dement*. 2022.

19. Duffy JF, Zitting K-M, Chinoy ED. Aging and Circadian Rhythms. *Sleep Med Clin*. 2015;10(4):423-434.

20. Skeldon AC, Derks G, Dijk D-J. Modelling changes in sleep timing and duration across the lifespan: Changes in circadian rhythmicity or sleep homeostasis? *Sleep Med Rev*. 2016;28:96-107.

21. Dijk DJ, Duffy JF, Czeisler CA. Contribution of circadian physiology and sleep homeostasis to age-related changes in human sleep. *Chronobiol Int*. 2000;17(3):285-311.

22. Munch M, Knoblauch V, Blatter K, et al. Age-related attenuation of the evening circadian arousal signal in humans. *Neurobiol Aging*. 2005;26(9):1307-1319.

23. Klerman EB, Dijk DJ. Age-related reduction in the maximal capacity for sleep--implications for insomnia. *Curr Biol*. 2008;18(15):1118-1123.

24. Carskadon MA, Brown ED, Dement WC. Sleep fragmentation in the elderly: Relationship to daytime sleep tendency. *Neurobiol Aging*. 1982;3(4):321-327.

25. Van Someren EJW, Nagtegaal E. Improving melatonin circadian phase estimates. *Sleep Med*. 2007;8(6):590-601.

26. Duffy JF, Wright Jr. KP. Entrainment of the human circadian system by light. *J Biol Rhythm*. 2005;20(4):326-338.

27. Hammad G, Reyt M, Beliy N, et al. pyActigraphy: Open-source python package for actigraphy data visualization and analysis. *PLOS Comput Biol*. 2021;17(10):e1009514.

28. Roenneberg T, Keller LK, Fischer D, Matera JL, Vetter C, Winnebeck EC. Chapter Twelve - Human Activity and Rest In Situ. In: Sehgal A, ed., Methods in Enzymology. Academic Press; 2015:257–283.

29. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: Objectives and design. *Am J Epidemiol*. 2002;156(9):871-881.

30. Lim ASP, Yu L, Costa MD, et al. Quantification of the Fragmentation of Rest-Activity Patterns in Elderly Individuals Using a State Transition Analysis. *Sleep*. 2011;34(11):1569-1581.

31. Reid KJ, Santostasi G, Baron KG, Wilson J, Kang J, Zee PC. Timing and intensity of light correlate with body weight in adults. *PLoS One*. 2014;9(4).

32. Pataky TC, Vanrenterghem J, Robinson MA. Zero- vs. one-dimensional, parametric vs. non-parametric, and confidence interval vs. hypothesis testing procedures in one-dimensional biomechanical trajectory analysis. *J Biomech*. 2015;48(7):1277-1285.

33. Pataky TC. One-dimensional statistical parametric mapping in Python. *Comput Methods Biomech Biomed Engin*. 2012;15(3):295-301.

34. R Core Team. R: A language and environment for statistical computing. 2020. R Foundation for Statistical Computing, Vienna, Austria. https://www.r-project.org/

35. Fletcher TD. QuantPsyc: Quantitative Psychology Tools. 2012. R package version 1.5. https://cran.r-project.org/package=QuantPsy/

36. Wickham H, Averick M, Bryan J, et al. Welcome to the Tidyverse. *J Open Source Softw*. 2019;4(43):1686.

37. Filzmoser P, Gschwandtner M. mvoutlier: Multivariate Outlier Detection Based on Robust Methods. 2021. R package version 2.1.1. https://cran.r-project.org/package=mvoutlier/

38. Slawomir J. mvnormtest: Normality test for multivariate variables. 2012. R package version 0.1-9. https://cran.r-project.org/package=mvnormtest

39. Reichert CF, Maire M, Gabel V, et al. Cognitive brain responses during circadian wake-promotion: evidence for sleep-pressure-dependent hypothalamic activations. *Sci Rep*. 2017;7(1):5620.

40. Dijk DJ, Czeisler CA. Paradoxical timing of the circadian rhythm of sleep

propensity serves to consolidate sleep and wakefulness in humans. *Neurosci Lett*. 1994;166(1):63-68.

41. Shekleton JA, Rajaratnam SMW, Gooley JJ, Van Reen E, Czeisler CA, Lockley SW. Improved Neurobehavioral Performance during the Wake Maintenance Zone. *J Clin Sleep Med*. 2013;09(04):353-362.

42. Golombek DA, Rosenstein RE. Physiology of Circadian Entrainment. *Physiol Rev*. 2010;90(3):1063-1102.

43. Watanabe T, Kajimura N, Kato M, et al. Sleep and Circadian Rhythm Disturbances in Patients with Delayed Sleep Phase Syndrome. *Sleep*. 2003;26(6):657-661.

44. Campbell SS, Murphy PJ. Delayed Sleep Phase Disorder In Temporal Isolation. *Sleep*. 2007;30(9):1225-1228.

45. Taillard J, Sagaspe P, Philip P, Bioulac S. Sleep timing, chronotype and social jetlag: Impact on cognitive abilities and psychiatric disorders. *Biochem Pharmacol*. 2021;191:114438.

46. Nyberg L. Functional brain imaging of episodic memory decline in ageing. *J Intern Med*. 2017;281(1):65-74.

47. Owusu JT, Wennberg AMV, Holingue CB, Tzuang M, Abeson KD, Spira AP. Napping characteristics and cognitive performance in older adults. *Int J Geriatr Psychiatry*. 2019;34(1):87-96.

48. Scullin MK, Fairley J, Decker MJ, Bliwise DL. Effects of an Afternoon Nap on Episodic Memory in Young and Older Adults. *Sleep*. 2017;40(5):zsx035.

49. Hu K, Van Someren EJW, Shea SA, Scheer FAJL. Reduction of scale invariance of activity fluctuations with aging and Alzheimer's disease: Involvement of the circadian pacemaker. *Proc Natl Acad Sci U S A*. 2009;106(8):2490-2494.

50. Li P, Yu L, Yang J, et al. Interaction between the progression of Alzheimer's disease and fractal degradation. *Neurobiol Aging*. 2019;83:21-30.

51. Hu K, Riemersma-Van Der Lek RF, Patxot M, et al. Progression of Dementia Assessed by Temporal Correlations of Physical Activity: Results from a 3.5-Year, Longitudinal Randomized Controlled Trial. *Sci Rep*. 2016;6:1-10.

52. Li P, Yu L, Lim ASP, et al. Fractal regulation and incident Alzheimer's disease in elderly individuals. *Alzheimer's Dement*. 2018;14(9):1114-1125.

53. Hu K, Meijer JH, Shea SA, et al. Fractal Patterns of Neural Activity Exist within the Suprachiasmatic Nucleus and Require Extrinsic Network Interactions. *PLoS One*. 2012;7(11).

54. Lockley SW, Skene DJ, Arendt J. Comparison between subjective and actigraphic measurement of sleep and sleep rhythms. *J Sleep Res*. 1999;8(3):175-183.

55. Moraes W, Piovezan R, Poyares D, Bittencourt LR, Santos-Silva R, Tufik S. Effects of aging on sleep structure throughout adulthood: A population-based study. *Sleep Med*. 2014;15(4):401-409.

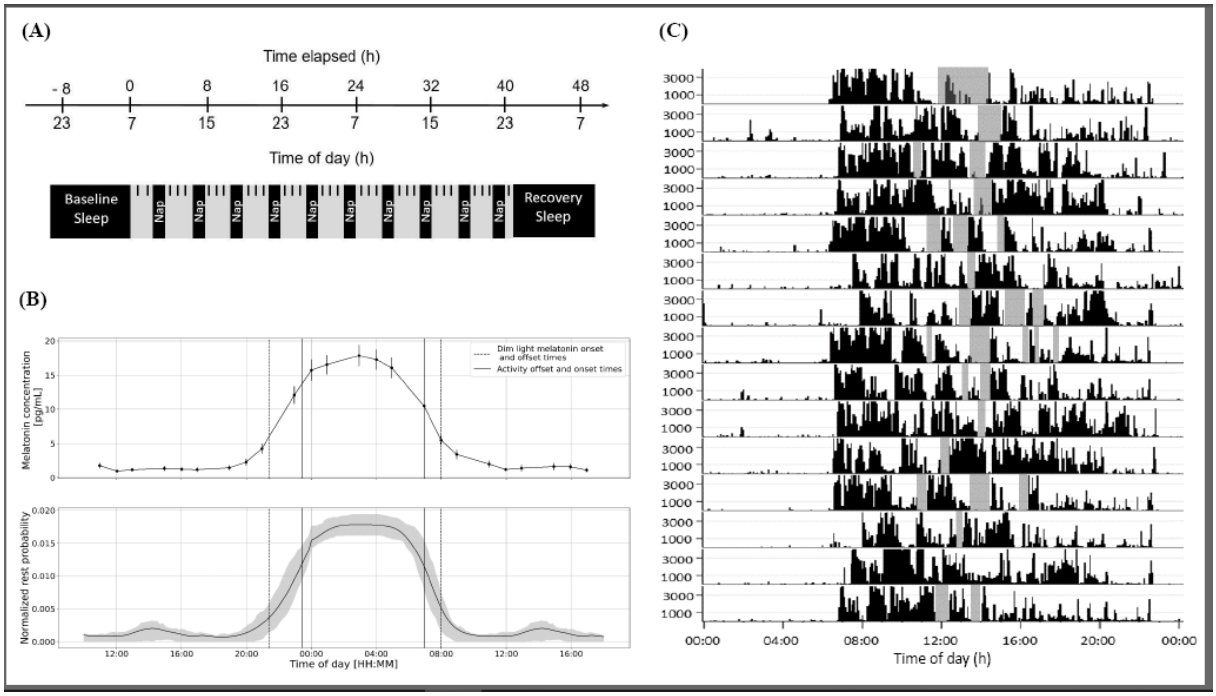
56. Stothard ER, McHill AW, Depner CM, et al. Circadian Entrainment to the Natural Light-Dark Cycle across Seasons and the Weekend. *Curr Biol*.

2017;27(4):508-513.

57. Falck RS, Crockett RA, Davis JC, Khan KM, Liu-Ambrose T. Shining the Light on the MotionWatch8 Light Sensor for Sleep and Aging Research: What Can We Measure and What Are We Missing? *J Alzheimer's Dis Reports*. 2021;5(1):55-63.

58. Zhang Z, Xiao X, Ma W, Li J. Napping in Older Adults: a Review of Current Literature. *Curr Sleep Med Reports*. 2020;6(3):129-135.

FIGURE LEGENDS



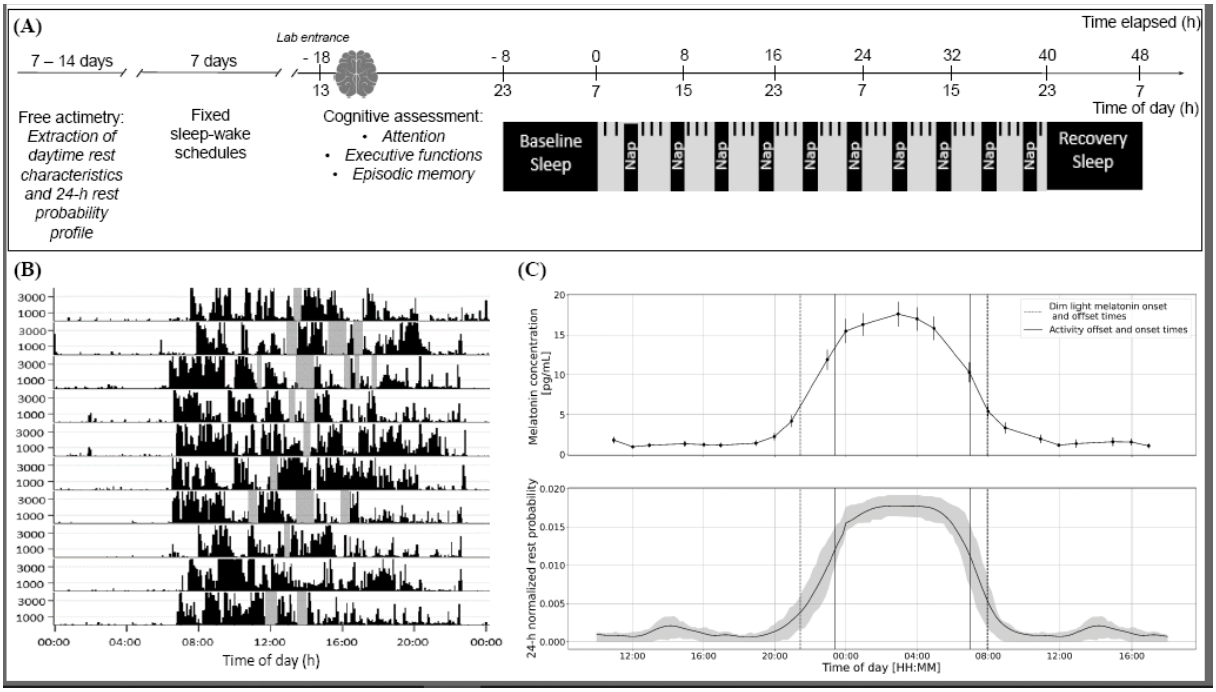
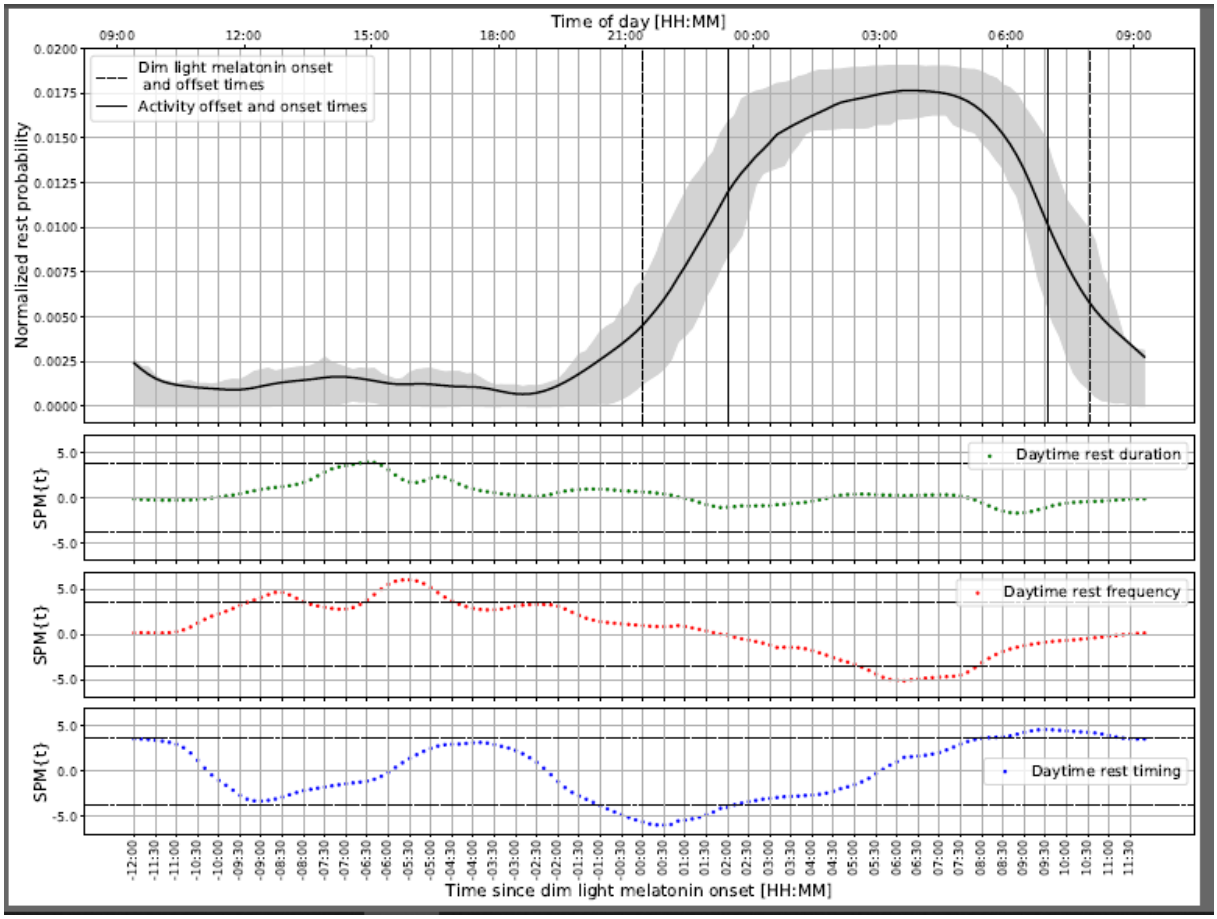


Figure 1. (A) Schematic illustration of the study timeline including daytime rest characterisation and rest-activity cycle estimation in the field as well as cognitive and circadian phase assessment. Circadian phase was extracted through a 40-h constant routine. The latter comprised 10 short sleep-wake cycles, each compassing 160 minutes of wakefulness (grey) alternating with 80 minutes of sleep opportunities (black). The protocol was preceded and followed by 8-h of sleep (black). Light levels (< 5 lux during wakefulness and 0 lux during sleep), temperature (~19°C), caloric intake (standardised meals every 4 h) and body posture (semi-recumbent position during scheduled wakefulness and recumbent during naps) were controlled to minimize potential masking effects on the circadian timing system. Salivary melatonin (black short lines) was collected through the 40 hours, with an average sampling rate of 80 minutes starting 50 minutes after wake up. (B) 24-h actogram for 10 days from a representative participant displaying in grey rest periods detected by the Munich Actimetry Sleep Detection Algorithm (MASDA). (C) Melatonin time course (upper panel) during the circadian phase assessment and rest probability profile

(lower panel) extracted from actigraphy recordings (N = 57). Dotted lines represent dim light melatonin onset and offset times. Continuous lines correspond to activity offset and onset times. First and third quartiles of rest probability are modelled by the grey area.



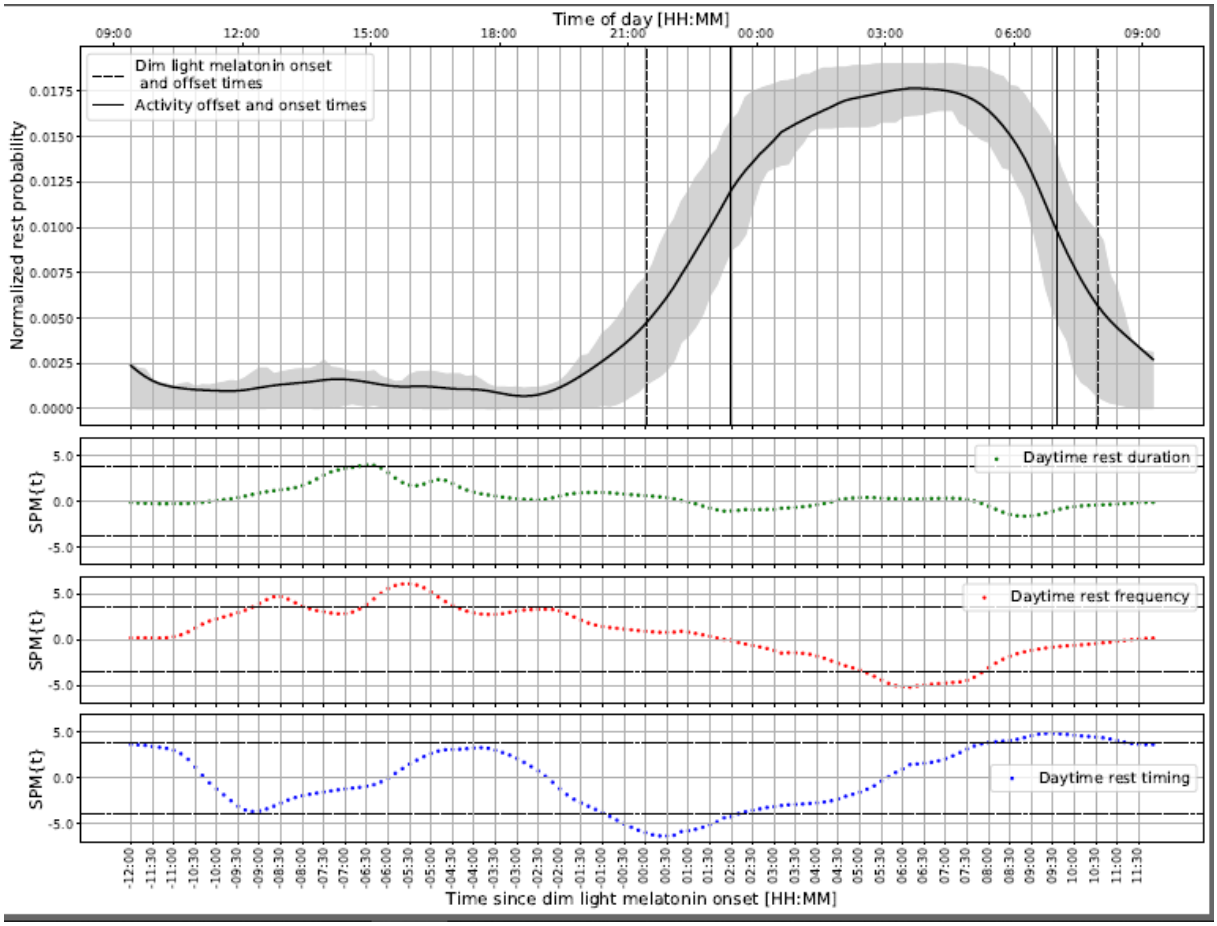
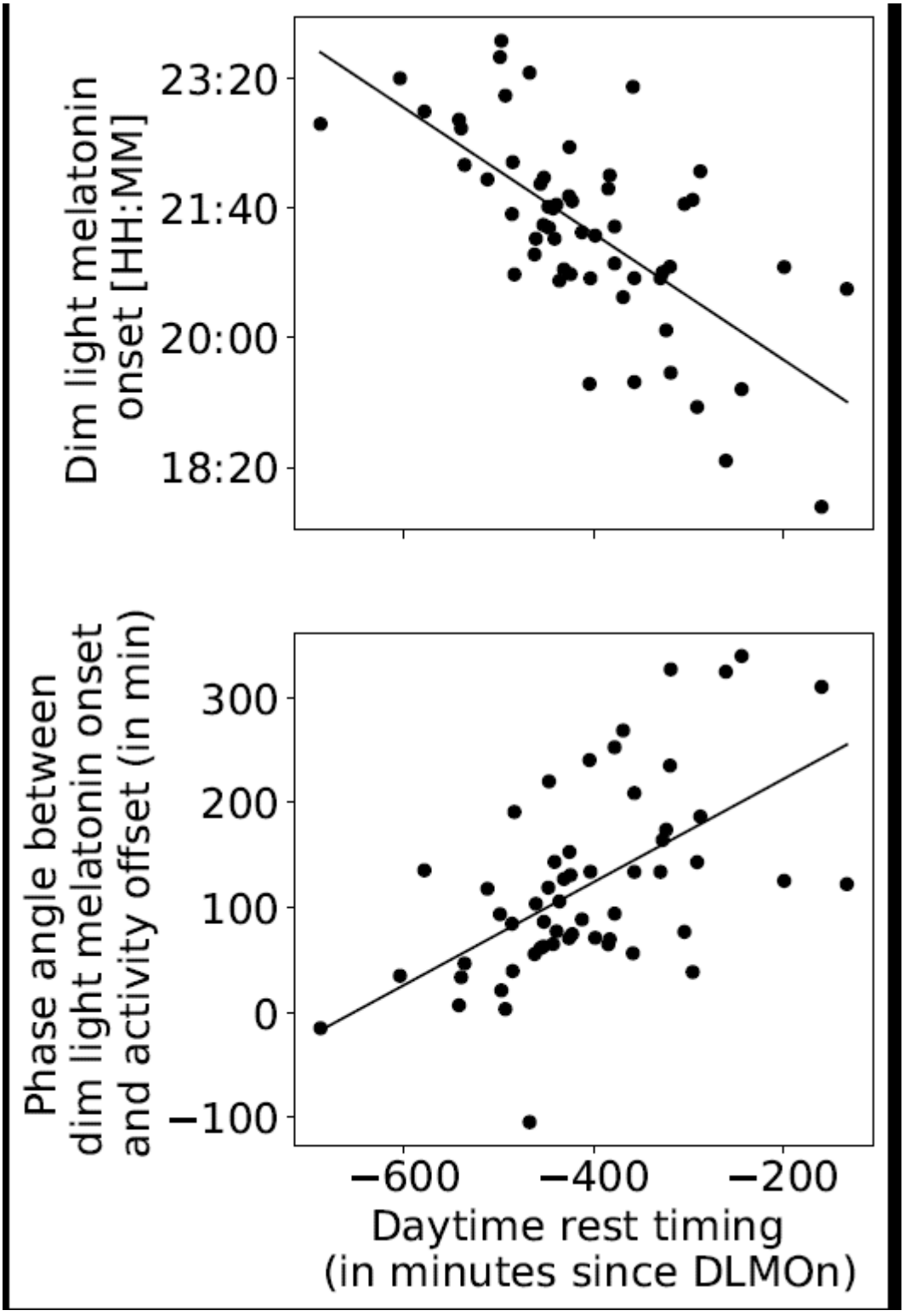


Figure 2. Rest probability profile and its associations with daytime rest characteristics. The upper panel displays the 24-h rest probability profile aligned on the individual's dim light melatonin onset (N = 57; DLMOn: 21.44 ± 1.27 h). First and third quartiles of rest probability are modelled by the grey area. Corresponding time of day is plotted in the upper X-axis. Vertical dotted black lines correspond to dim light melatonin onset and offset times. Vertical continuous black lines represent activity offset and onset times. Linear regressions were performed to assess whether each daytime rest characteristic was associated with rest probability at specific time windows over the 24-h profile. Curves in green, red and blue correspond to these statistical values, named SPM{t}, respectively for daytime rest duration, daytime rest frequency and daytime rest timing. A cluster is significant if SPM{t} crossed a critical threshold t* and represented by horizontal dotted lines in the lower panel.



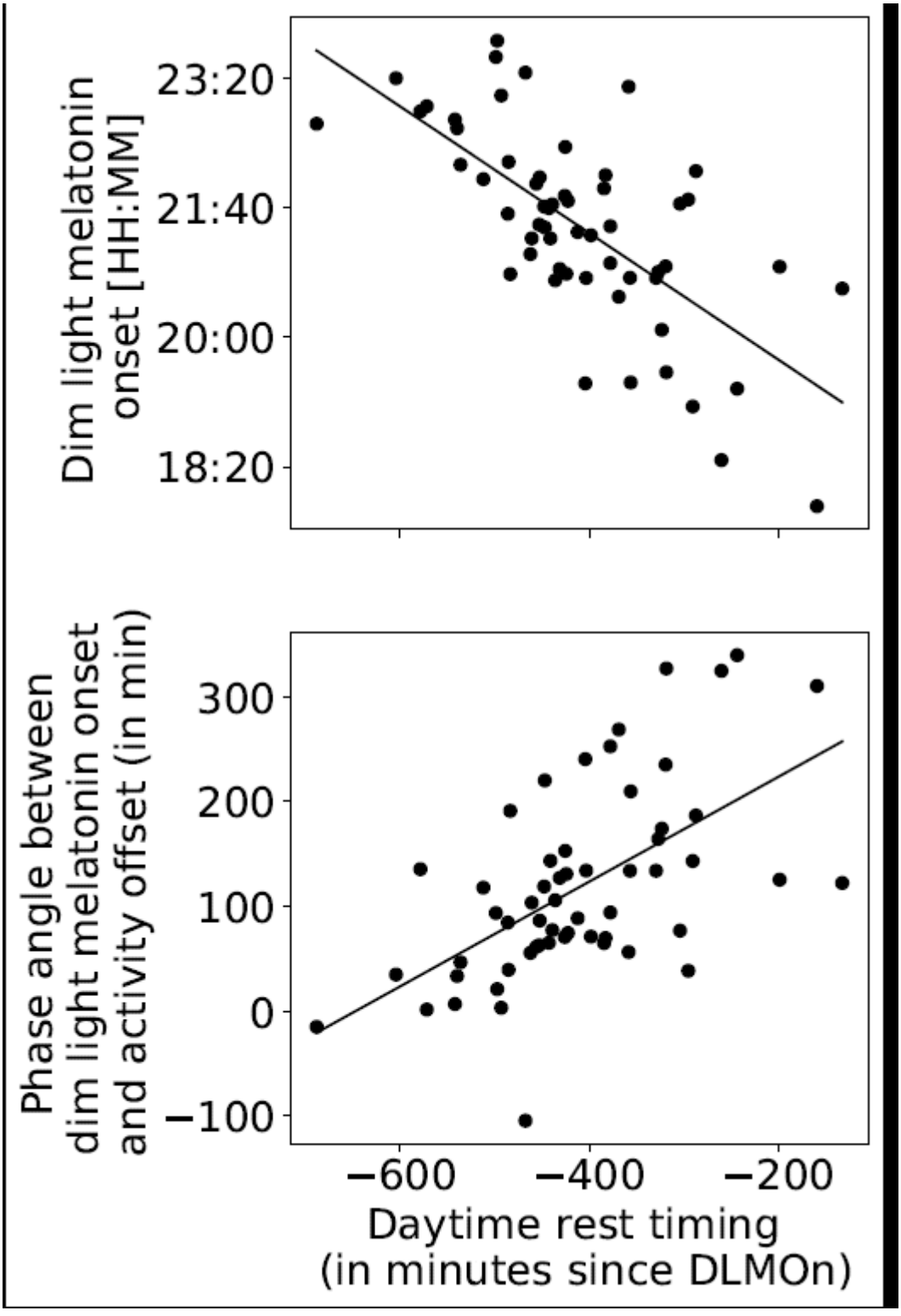


Figure 3. Scatter plots of the associations between daytime rest timing and dim light melatonin onset (DLMOn) as circadian phase marker (upper panel), and phase angle of entrainment (distance between dim light melatonin onset and actigraphy-derived

activity offset times; lower panel) (N = 57). Regressions were used for visual display only, and not as a substitute for the linear regression model (see Table S3).

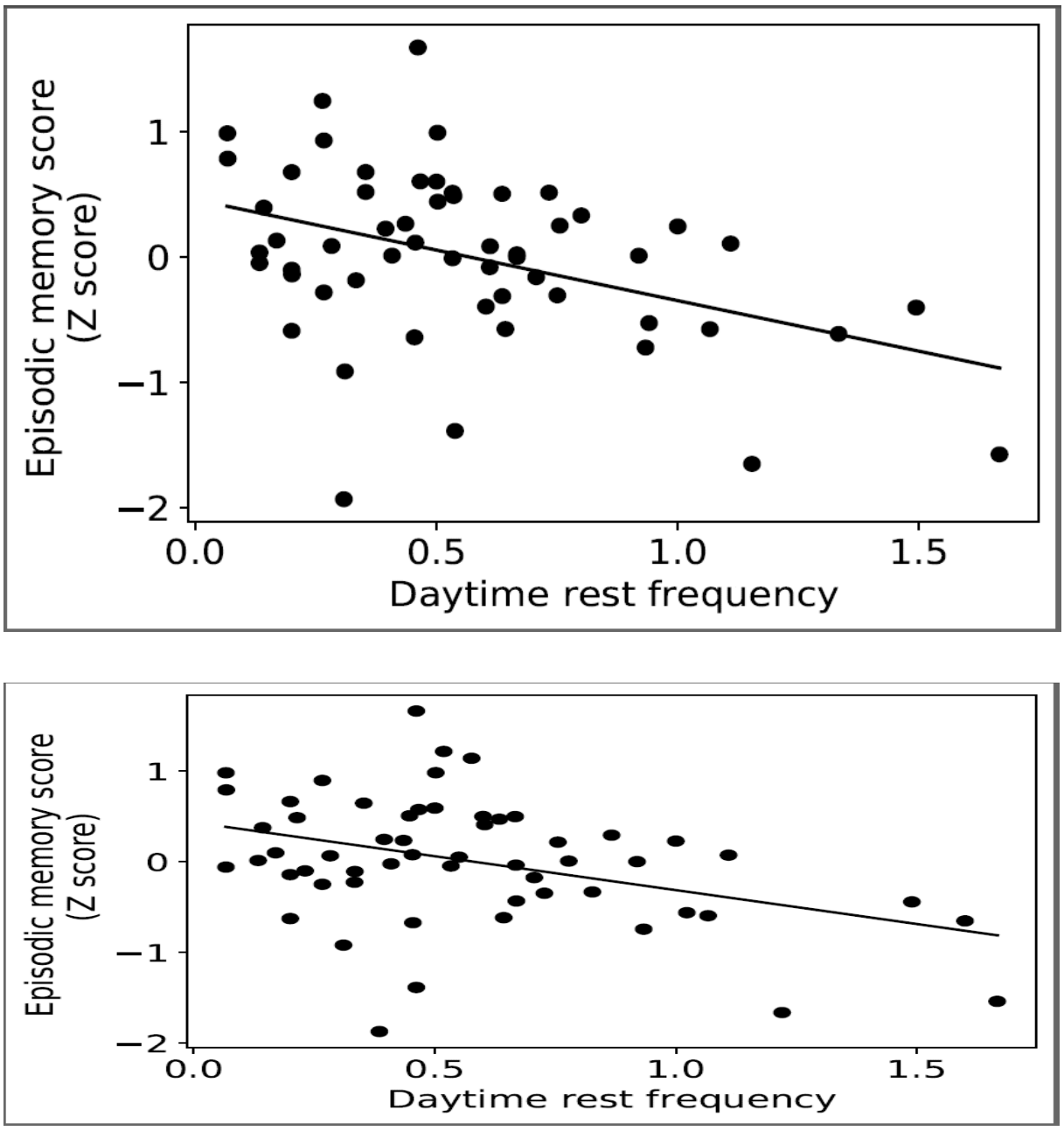


Figure 4. Scatter plot of the association between episodic memory performance and daytime rest frequency (N = 57). Regression was used for visual display only, and not as a substitute for the linear regression model (see Table S4).

Table 1. Descriptive statistics of circadian parameters, actigraphy-derived daytime rest characteristics and others variables, and cognitive performance (N = 57).

	Mean	**SD**[a]	**Min**	**Max**
Circadian outcomes				
DLMO onset (DLMOn), *hours*	21.44	1.27	17.83	23.81
DLMO offset (DLMOff), *hours*	7.95	1.13	5.63	11.72
Distance between DLMOn and activity offset, *minutes*	118.23	90.93	-104.28	339.60
Distance between DLMOff and activity onset, *minutes*	-57.84	59.89	-241.50	64.18
Daytime rest and others actigraphy-derived variables				
Duration, *minutes*	45.59	19.50	16.83	130.00
Frequency	0.56	0.35	0.07	1.67
Timing, *minutes*	-410.95	106.17	-688.30	-132.62
Daily activity level	252.85	91.11	137.56	624.68
Night-time rest duration, *hours*	7.51	0.99	5.17	10.10
Activity onset time, *hours*	6.98	0.86	5.08	8.58
Activity offset time, *hours*	23.40	0.93	21.50	25.25
Rest-activity transition probability	0.05	0.02	0.02	0.12
Cognitive characteristics				

Attentional performance[b], *z-score*	0.01	0.62	-1.60	1.16
Executive functions[c], *z-score*	0.00	0.56	-1.02	1.42
Episodic memory performance[d], *z-score*	0.01	0.70	-1.88	1.66

Note: [a] SD: Standard Deviation; [b] Missing value: 1; [c] Missing value: 3; [d] Missing value: 2.