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Ultradian sleep cycles: Frequency, duration, and associations with individual and environmental factors—A retrospective study

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ABSTRACT

Objective: Sleep varies between individuals in response to sleep-wake history and various environmental factors, including light and noise. Here we report on the intranight variation of the ultradian nonrapid eye movement-rapid eye movement (NREM-REM) sleep cycle in 369 participants who have contributed to different laboratory studies from 1994 to 2020 at the Centre for Chronobiology, Basel, Switzerland.

Results: We observed a large interindividual variability in sleep cycle duration, including NREM and REM sleep episodes in healthy participants who were given an 8-hour sleep opportunity at habitual bedtime in controlled laboratory settings. The median sleep cycle duration was 96 minutes out of 6064 polysomnographically-recorded cycles. The number and duration of cycles were not normally distributed, and the distribution became narrower for NREM sleep and wider for REM sleep later in the night. The first cycle was consistently shorter than subsequent cycles, and moderate presleep light or nocturnal noise exposure had no significant effects on ultradian sleep cycle duration. Age and sex significantly affected NREM and REM sleep duration, with older individuals having longer NREM and shorter REM sleep particularly in the end of the night, and females having longer NREM sleep episodes. High sleep pressure (ie, sleep deprivation) and low sleep pressure (ie, multiple naps) altered ultradian sleep cycles, with high sleep pressure leading to longer NREM sleep in the first cycle, and low sleep pressure leading to longer REM sleep episodes. Positive correlations were observed between N2 and NREM duration, and between N1 and REM duration. Weak intrasleep REM sleep homeostasis was also evident in our data set.

Conclusions: We conclude that ultradian sleep cycles are endogenous biological rhythms modulated by age, sex, and sleep homeostasis, but not directly responsive to (moderate levels of) environmental cues in healthy good sleepers.

Introduction

Daan and Aschoff defined ultradian rhythms as endogenously generated oscillations with periods shorter than circadian rhythms (less than 24 hours), ranging from 20 minutes to 6 hours,[1] and not directly related to environmental cycles. There has been relatively little research on ultradian rhythms compared to circadian rhythms. This is surprising as ultradian rhythms were described more than 100 years ago by famous biologists such as Claude Bernard, Walter Cannon, and Charles Darwin, reviewed in Goh et al and Lloyd and Stupfel.[2,3] To quantify ultradian rhythms and distinguish them from background noise as accurately as possible, ultradian rhythms require recordings of sufficient duration (> 6 hours). Fluctuations in their recordings may be overlooked as random noise by many researchers in biological fields.

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Probably the best-known ultradian rhythm in humans occurs during sleep. The discovery of regularly occurring periods of eye motility during sleep by Eugene Aserinsky, a PhD student of Nathaniel Kleitman in Chicago, 70 years ago, in 1953,[4] marked the beginning of an intensive investigation on human rapid eye movement (REM) sleep and its functional significance, which is very topical, especially in insomnia research.[5] Although REM sleep is the focus of these investigations, the changes between nonrapid eye movement (NREM) and REM sleep throughout the night have attracted less interest in the sleep community. For sleep clinicians, the ultradian sleep cycle does not appear to be clinically relevant and is not mentioned in the Manual for the Scoring of Sleep and Associated Events of the American Academy of Sleep Medicine (AASM).[6] In contrast to polysomnographic parameters in healthy adults,[7] there are no normative data on ultradian sleep cycles. Until now, a single publication by Feinberg and Floyd in 1979[8] has been the basis for the rules used to determine ultradian NREM-REM sleep cycles. Lacking empirical biological evidence, Feinberg and Floyd's definitions are rather arbitrary, but still useful for basic human sleep research.

The following mechanisms have been proposed for the generation of ultradian sleep rhythms (1) An autonomous pacemaker (intrinsic period close to 90 minutes[9]) that drives ultradian cycles, (2) Key populations of REM-on and REM-off neurons in the brainstem and hypothalamus that promote or suppress REM sleep, as formulated in the reciprocal interaction oscillator of Massaquoi and McCarley,[10] (3) A homeostatic process (ie, hourglass mechanism) that drives NREM-REM sleep cycles,[11,12] (4) A long-term process that homeostatically regulates REM sleep propensity and a short-term process that generates the REM-NREM sleep cycle,[13] (5) A slightly modified version of 3 and 4, the so-called asymmetric hypothesis for the NREM-REM sleep cycle, in which REM sleep episodes only determine the duration of a proportional post-REM refractory period during which REM sleep is "forbidden,"[14] and (5) an arousal state feedback to circadian and homeostatic drives that generates ultradian sleep cycles.[15]

The most detailed description of human ultradian sleep cycles comes from the work of Le Bon and co-workers.[16] They showed normal distributions of the number of human sleep cycles per night and their mean duration, and that both measures were strongly related to REM sleep, while the amount of electroencephalographic slow-wave activity was negatively correlated with the number of sleep cycles.[17] Furthermore, Le Bon and Linkowski[18] did not support hypotheses 3-4 (all tested in rodents) due to the lack of strong correlations between REM sleep and subsequent NREM sleep episode durations in humans. This is in contrast to Barbato and Wehr,[19] who also found support for these hypotheses in humans.

Here, we aimed to test hypotheses 3-4 in a larger data set by further investigating the distribution patterns of NREM and REM sleep episode durations and their relation to specific sleep stages. This study was based on a retrospective analysis of polysomnographic data from healthy, well-sleeping individuals who participated in strictly controlled laboratory studies at the Centre for Chronobiology, University of Basel, Switzerland, between 1994 and 2020. In our studies, we focused on different age groups and included both females and males (we used this terminology to refer to biological sex defined at birth). We also manipulated sleep pressure levels and different environmental stimuli, such as light and noise. Therefore, we also investigated whether these factors contribute to the observed variance in ultradian sleep cycles. We defined the duration of the NREM-REM sleep cycles according to Feinberg and Floyd[8] using a self-programmed algorithm.

We set out to answer the following questions.

1. What is the distribution pattern of interindividual ultradian sleep cycles throughout the night?
2. Do individual factors, such as age and sex, modulate ultradian sleep cycles?
3. Do environmental factors such as night-time traffic noise and presleep light exposure modulate ultradian sleep cycles?
4. Do sleep pressure levels (high vs. low) modulate ultradian sleep cycles?
5. Do specific sleep stages predict the duration of ultradian sleep cycles?
6. Is there an intrasleep homeostatic regulation of ultradian sleep cycles (ie, REM sleep refractory period) in human sleep?

Methods

Study participants

All polysomnograms (PSGs) were recorded in healthy study participants who were asked to sleep for 8 hours at their usual bedtime in windowless bedrooms. All study participants reported good to very good sleep quality, which was verified by a test night in the laboratory using PSG. They were also required to maintain a regular sleep-wake cycle before coming to our laboratory. This was checked using wrist-activity monitor recordings, and their health status was assessed by a study physician. In total, our analysis included 369 study participants from younger adults (19-35 years) and older adults (55-80 years), of whom 2/3 were males and 1/3 females. All participants were good sleepers, took no medication, were nonsmokers, and were asked to abstain from alcohol and caffeine before the start of the study. For a detailed description of the inclusion and exclusion criteria and demographics, please refer to the respective trials included in our analyses.[20-41] All studies were conducted at the Centre for Chronobiology, Basel, Switzerland, between 1994 and 2000. The experimental protocols, screening questionnaires, and informed consent forms were approved by the Ethics Committee of Northwest/Central Switzerland and conformed to the Declaration of Helsinki. All participants gave written informed consent. PSGs from all but one study were manually scored by experts at the Centre for Chronobiology. In one study,[41] sleep stages were assessed by an automatic scoring algorithm (ASEEGA, version 4.4.23, PHYSIP, Paris, France), which has been shown to reach good agreement with manual sleep scoring.[42] Sleep stages were scored either according to Rechtschaffen and Kales[43] or according to AASM,[6] with deep or slow-wave sleep always divided into stages 3 and 4.

PSG recordings

All PSGs were recorded using the TEMEC Vitaport 3 system (TEMEC Instruments B.V., Kerkrade, The Netherlands) except for one study[37,41] which used V-Amp digital sleep recorders (Brain Products GmbH, Germany). The sampling rate was 256 Hz (storage rate 128 Hz, 1024 Hz for electrocardiogram [ECG] signals), except for one study (500 Hz).[37] The electroencephalogram (EEG) was recorded at up to 12 different scalp sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz, O2) according to the 10- to 20-electrode system referenced to the averaged mastoids. The electrooculogram (EOG) was recorded from two electrodes placed on the outer canthi of each eye, one above and one below the horizontal plane. The submental electromyogram (EMG) was recorded bipolar. The electrocardiogram (ECG) was recorded from two electrodes placed at the center of the sternum and the left costal arch. Signals were filtered during recording (EEG, EOG, and ECG between 0.159 and 30 Hz; EMG between 1 and 70 Hz).

Definition of sleep cycles

Ultradian sleep cycles were defined as alternating NREM and REM sleep episodes according to the standard criteria of Feinberg and Floyd.[8] Exceptions to these rules and more detailed information can be found in the publication by Rudzik et al.[33] A self-programmed algorithm, written in Delphi (Delphi Embarcadero Technologies,

Austin, TX), read the manually and automatically scored sleep stages and divided the night into sleep cycles according to Feinberg and Floyd,[8] stopping when a rule was violated and asking to manually apply the criteria defined by Rudzik et al[33] to make a meaningful classification of the cycles.

Statistics

Distribution patterns of the number of sleep cycles, the duration of sleep cycles as well as the duration of NREM and REM sleep episodes were calculated using PROC Univariate in the SAS statistical package (version 9.1; SAS Institute, Cary, NC), which includes 3 tests for normality distribution (ie, Kolmogorov-Smirnov, Cramer-von Mises, Anderson-Darling).

For a subset of studies aimed at investigating the influence of individual, environmental, and sleep pressure factors (ie, modulators) on sleep ultradian cycles, the effects of these modulators were tested using generalized linear mixed-model analysis of variance for repeated measures (PROC GLIMMIX, statistical package SAS [version 9.1; SAS Institute, Cary, NC]) separately for the main factors "modulator" (ie, age, sex, noise, light, sleep pressure) and the "sleep cycle number" as a repeated/within-subject factor (ie, cycle 1-4). For the modulator analysis, we restricted the number of sleep cycles to 4, as most other cycles were incomplete. The factors "study participant," "sleep cycle" and "night" were defined as random. As different participants contributed with different numbers of nights, we also included the factor night in the model if possible. The default estimation technique for PROC GLIMMIX, pseudo-likelihood when the data are non-normal, was used. When the interaction modulator × sleep cycle reached significance, post hoc pairwise comparisons were calculated using the Tukey-Kramer test corrected for multiple comparisons. To test whether the duration of the preceding REM episode impacts on subsequent NREM duration, we used Spearman correlations with partial correlations adjusted for participant ID. We considered $p < .05$ to be significant. Effect sizes were estimated according to Albers and Lakens.[44]

Results

Slow and rapid sleep ultradian cycling

Fig. 1 (left panel) illustrates the distribution of the total number of sleep cycles completed during the 8-hour nocturnal sleep episodes. Most nights contained either 3 or 4 complete sleep cycles, while 3.1 % of the nights included 2 and 0.9% 6 cycles showing a non-normal left-skewed distribution. The distribution of sleep cycle duration was not normal showing a right-skewed distribution (Fig. 1, right panel). The median sleep cycle duration was 96 minutes (mean = 99.5 minutes) with an intercycle coefficient of variation (CV) of 29.3% (6064 sleep cycles), an internight CV of 18.5% (1567 nights), and an interindividual CV of 12.7% (369 individuals). The interindividual differences in median NREM and REM episode duration were substantial, ranging from 50 to 106 minutes for NREM and 11-41 minutes for REM episode duration (Supplementary Fig. 1). In order to calculate the within-subject stability, we calculated the CV for each participant over the individual nights, classified according to the maximum number of nights recorded per participant, as the number of nights may influence the within-subject CV. However, rather constant CV values for sleep cycle duration, NREM and REM episode durations independent of the number of nights contributed were found, with more than twice the intrapersonal CV for REM than for NREM sleep episodes on average and higher intra- than inter-individual CVs (12.7 vs. 26.9%, Supplementary Table 2).

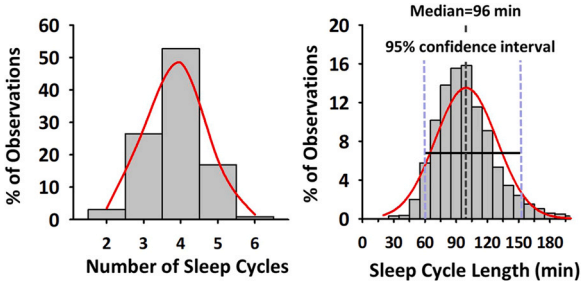

Fig. 1. Left panel: Histogram of the distribution of the total number of sleep cycles during an 8-hour nightly sleep opportunity in gray (6064 sleep cycles from 1054 nights of 369 participants). Most nights contained either 3 or 4 complete cycles. The red curve shows the curve for a normal distribution. Participants with < 3 sleep cycles had long sleep latencies, while those with > 5 sleep cycles had many intermittent rapid eye movement sleep episodes. Right panel: histogram of the nights included with an average duration of overall sleep cycles in gray. The median and the 95% intervals are delineated with a black and blue vertical lines respectively. The red curve shows the curve for a normal distribution. Both the number and duration of sleep cycles deviated significantly from a normal distribution in all 3 tests of normality (Kolmogorov-Smirnov, Cramer-von Mises, Anderson-Darling, see Supplementary Table 1).

Distribution of NREM and REM sleep episode lengths across the night

Next, NREM and REM distribution patterns were calculated for each sleep cycle (1-4) separately (Fig. 2, top panel). All NREM and REM sleep episodes 1-4 showed a non-normal distribution over the night. The distribution of NREM sleep episodes became narrower and that of REM sleep episodes became wider as the night progressed (Fig. 2, bottom panel). The first sleep cycle was shorter than subsequent cycles.[2-4] The reason for this was that the first REM episode was shorter than the others. Also, the first NREM episode started with the first occurrence of N2, whereas the others started with the first occurrence of N1, which "methodically" shortened NREM episode 1. A generalized linear mixed model (GLMM) testing whether sleep cycle duration, NREM and REM sleep episodes changed significantly across the night (ie, four first sleep cycles) revealed significance for the factor sleep cycle for all three measures (Supplementary Table 3). Post-hoc pairwise comparisons (Tukey-Kramer's adjusted for multiple comparisons) across the night revealed significances for sleep cycle duration for cycle 1 vs. cycle 2, and cycle 3 vs. cycle 4. REM sleep episode duration increased significantly and progressively across sleep cycles during the night, while NREM sleep episodes only increased significantly from cycle 1-2, and 3-4, while cycle 1 vs. 4 was not significant.

Individual factors, age and sex, modulating ultradian sleep cycling

To test for individual factors, we grouped the study nights according to age and sex and ran statistical models testing the main effects of age or sex, cycle, and their interaction (Table 1). Older adults had significantly longer NREM sleep episodes than younger adults at the expense of shorter REM sleep episodes (Fig. 3, top panel). The significant interaction age × cycle for the duration of REM sleep episodes (Table 1) indicated a less pronounced increase in REM sleep episode duration across the night in older adults. The significant main effects sex and its interaction with sleep cycle indicated that females had longer NREM sleep episodes than males, which became particularly apparent during sleep cycle 2 (Fig. 3, bottom panel). No sex differences were found for REM sleep duration.

Environmental factors, noise and light, modulating ultradian sleep cycling

To test for environmental factors, noise and light, we selected a study investigating the effects of nighttime traffic noise on sleep and a study investigating the effects of 40 hours of long-term exposure to moderate light (250 lx) on subsequent sleep (for details see[26,33,38,39]). We compared noise-free nights with nights with different nighttime traffic noise scenarios played during the scheduled 8-hour sleep episode. The moderate light at 250 lux was contrasted with a dim light (8 lux) of the

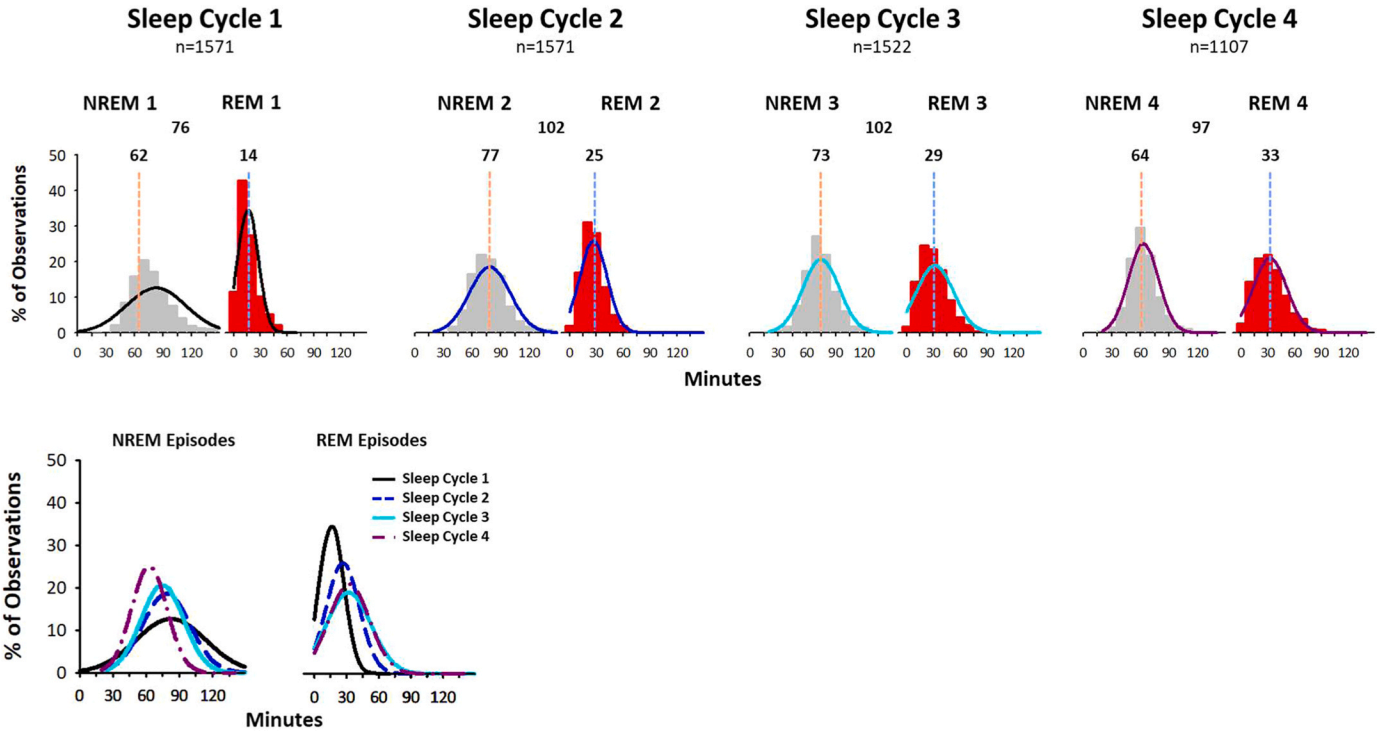

Fig. 2. Top panel: Histogram of the distribution of NREM and REM episode duration per sleep cycle during an 8-hour nightly sleep opportunity in gray (NREM sleep) and red (REM sleep). The number of sleep episodes, the median cycle length and the median NREM and REM episode duration per sleep cycle are indicated. The numbers presented directly above the dashed vertical lines are the median NREM and REM sleep cycle durations (in minutes), and the number presented above that is the overall median NREM-REM cycle duration (in minutes). The multicolored curves shows the curve for a normal distribution per episode and sleep cycle. Bottom panel: Overlay of the normality distribution curves per NREM and REM sleep episodes in sleep cycles 1-4.

same duration. No significant effects of noise or light on NREM or REM sleep episode duration were found in models testing the main effects of noise or light, cycle, and their interaction (Fig. 4 and Table 1).

Sleep state factors, high vs. low sleep pressure, modulating ultradian sleep cycling

We selected studies in which sleep homeostasis was challenged by either prolonging wakefulness to 40 hours or reducing sleep pressure levels in a multiple nap protocol for 40 hours to test the influence of the difference in sleep pressure levels (high vs. low).[24,40,41,45] High sleep pressure levels (40 hours of prior wakefulness) led to an increase in the duration of NREM sleep episodes during the first sleep cycle (Fig. 5 left panel and Table 1) as indicated by a significant interaction sleep pressure × sleep cycle. On the other hand, low levels of sleep pressure (2.5 hours of prior wakefulness after the last nap during the 40-hour multiple nap protocol) led to an increase in the duration of REM sleep episodes during the night (Fig. 5, right panel, significant main effect for "sleep pressure" see Table 1 for details).

Sleep stages modulating ultradian sleep cycles

We tested whether selective sleep stages were associated with sleep cycle duration. NREM sleep duration was highest with N2 - the more N2, the longer the NREM sleep duration, whereas REM sleep duration had the highest correlation coefficient with N1 (Fig. 6).

REM sleep refraction

We correlated the duration of REM sleep episodes with the subsequent duration of the NREM episode (ie, the duration of the inter-REM interval) to test whether REM sleep episodes determine the duration of a proportional post-REM refractory period. Fig. 7 shows significant correlations for sleep cycles 1, 2, and 4 (for statistics see figure legend of Fig. 7). The same analysis correlating the duration of REM sleep episodes with the subsequent duration of REM sleep episodes did not reveal any significant associations (Supplementary Fig. 2).

Discussion

In healthy participants given 8 hours of sleep at their usual bedtime under controlled laboratory conditions, we found large inter- and intra-individual differences in the duration of sleep cycles throughout the night. The median sleep cycle duration was 96 minutes in 6064 PSG-scored sleep cycles. The distribution of the number and duration of sleep cycles was not normal within the first four sleep cycles, becoming narrower for NREM and wider for REM sleep episodes throughout the night. The duration of the first REM sleep episode was consistently shorter than in the subsequent cycles. We have no evidence that moderate presleep light or nocturnal traffic noise exposure altered the duration of ultradian sleep cycles. Individual factors such as age and sex significantly modulated the duration of NREM and REM sleep episodes throughout the night. Older age was associated with longer NREM sleep episodes at the expense of shorter REM sleep episodes, with a slower increase during the night. Females had significantly longer NREM sleep episode durations than males, while we found no sex difference in REM sleep episode duration. Challenging sleep homeostasis, either by total sleep deprivation (40 hours prior wakefulness) or by a multiple nap protocol (2.5 hours wakefulness before nighttime sleep), altered ultradian sleep cycles such that high sleep pressure led to significantly longer NREM sleep episodes in the first cycle, whereas low sleep pressure led to longer REM sleep episodes, particularly in the first 3 sleep cycles. Finally, we found the strongest positive correlations between N2 and the duration of

Table 1
The influence of individual and environmental modulators (effects of age, sex, noise, light, high and low sleep pressure) on the duration of NREM and REM sleep episode duration

	Num DF	Den DF	F-statistic	*p*	ηp²	Effect size
Age effect:						
NREM episodes						
Age	1	1998	8.32	.004	0.004	Small
Sleep cycle	3	1998	100.72	< .0001		
Age × Sleep cycle	3	1998	2.38	.0682		
Night	5	1998	2.55	.0263		
Age × Night	5	1998	1.29	.2644		
Night × Sleep cycle	15	1998	1.5	.098		
Age × Night × Sleep cycle	15	1998	0.6	.8734		
REM episodes						
Age	1	1998	2.95	.0861		
Sleep cycle	3	1998	67.5	< .0001		
Age × Sleep cycle	3	1998	10.87	< .0001	0.016	Medium
Night	5	1998	5.25	< .0001		
Age × Night	5	1998	1.98	.0786		
Night × Sleep cycle	15	1998	1.72	.0411		
Age × Night × Sleep cycle	15	1998	1.25	.2253		
Sex effect:						
NREM episodes						
Sex	1	1997	13.21	.0003	0.007	Small
Sleep cycle	3	1997	110.31	< .0001		
Sex × Sleep cycle	3	1997	3.2	.0225	0.005	Small
Night	5	1997	2.87	.0137		
Sex × Night	5	1997	0.28	.9249		
Night × Sleep cycle	15	1997	1.62	.0605		
Sex × Night × Sleep cycle	15	1997	1.14	.3135		
REM episodes						
Sex	1	1997	0.55	.457		
Sleep cycle	3	1997	88.37	< .0001		
Sex × Sleep cycle	3	1997	1.09	.3539		
Night	5	1997	5.53	< .0001		
Sex × Night	5	1997	0.54	.7498		
Night × Sleep cycle	15	1997	2.27	.0036		
Sex × Night × Sleep cycle	15	1997	0.85	.6251		
Noise effect:						
NREM episodes						
Noise	1	959	1.04	.3088		
Sleep cycle	3	959	22.09	< .0001		
Noise × Sleep cycle	3	959	0.57	.6375		
Night	5	959	0.56	.7275		
Night × Sleep cycle	15	959	2.04	.011		
REM episodes						
Noise	1	959	2.21	.1375		
Sleep cycle	3	959	46.26	< .0001		
Noise × Sleep cycle	3	959	2.49	.0591		
Night	5	959	1.66	.1406		
Night × Sleep cycle	15	959	1.71	.0436		
Light effect:						
NREM episodes						
Light	1	299	0.17	.6829		
Sleep cycle	3	299	17.33	< .0001		
Light × Sleep cycle	3	299	0.66	.5765		
REM episodes						
Light	1	299	0.48	.4911		
Sleep cycle	3	299	15.42	< .0001		
Light × Sleep cycle	3	299	0.22	.8791		
Sleep pressure effect:						
NREM episodes						
Sleep pressure	1	705	0.01	.9229		
Sleep cycle	3	705	23.09	< .0001		
Sleep pressure × Sleep cycle	3	705	5.17	.0015	0.022	Medium
REM episodes						
Sleep pressure	1	705	4.81	.0287	0.007	Small
Sleep cycle	3	705	19.48	< .0001		
Sleep pressure × Sleep cycle	3	705	1.2	.3098		

Summary of the tested modulators (age, sex, noise, light, high, and low sleep pressure) on the duration of NREM and REM sleep episodes with a generalized linear mixed model (GLMM). Fixed effects: modulator, sleep cycle and their interaction, and night in studies with multiple nights contributed by an individual. Included are the degrees of freedom of the numerator and denominator, F values and partial eta square as an index of effect size. The interpretation of the effect size is given for significant fixed effects and their interaction. See the Methods section for more details on the GLMM.

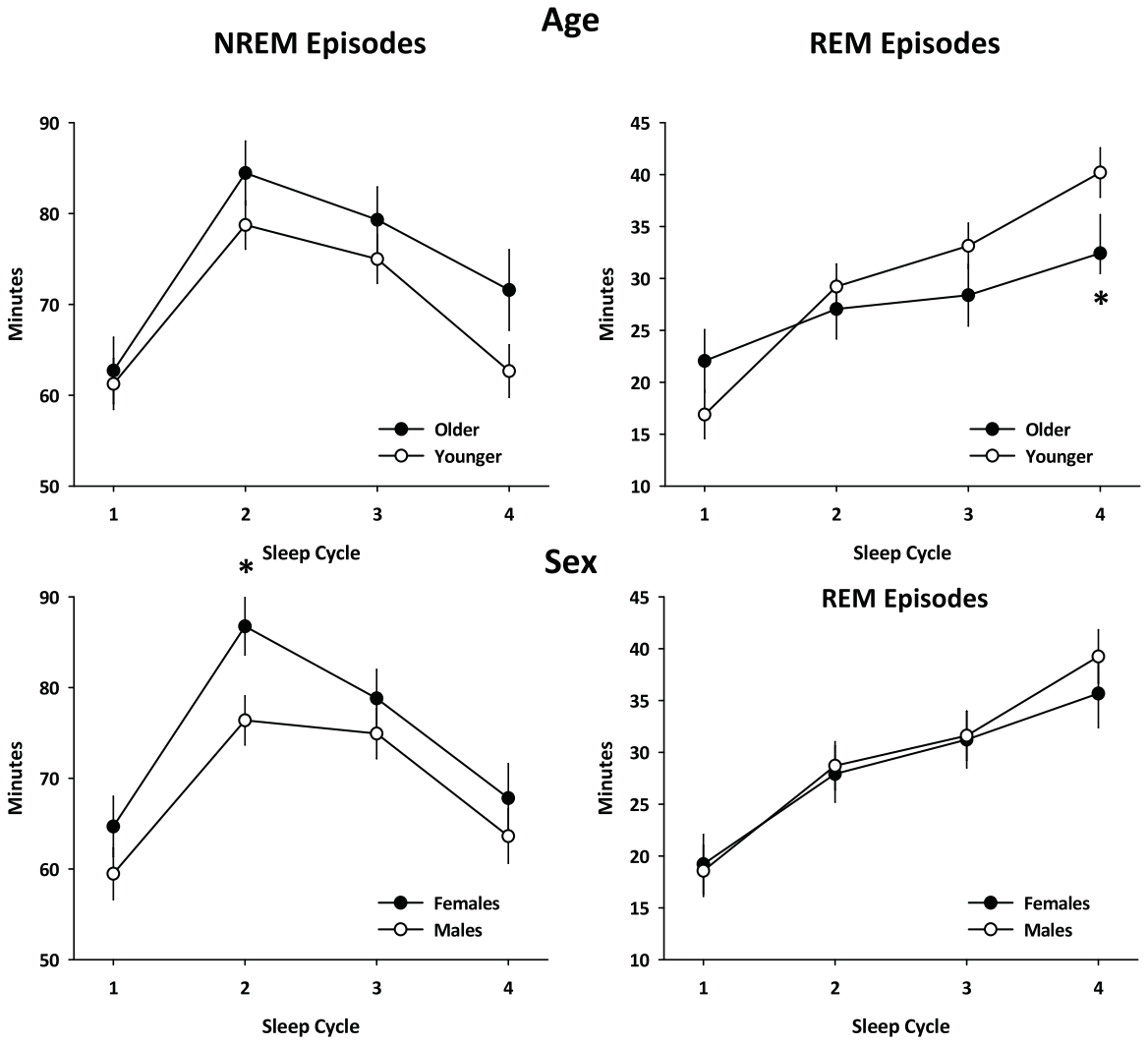

Fig. 3. Influence of age (upper panel) and sex (lower panel) on the duration of nonrapid eye movement (NREM) and rapid eye movement (REM) sleep episodes in minutes over four sleep cycles. Values represent estimated means ± 95% confidence intervals based on generalized linear mixed model (GLMM). A significant main effect of both "age" and "sex" was found for the duration of NREM sleep episodes, with older people and females having longer durations than young people and males. In addition, significant modulator × sleep cycle effects were found for "age" for REM sleep episode duration and for "sex" for NREM sleep episode duration (see Table 1 for details). Asterisks indicate significant post-hoc comparisons after correction for multiple testing (Tukey-Kramer, $p < .05$, only when GLMM indicated a significant modulator × sleep cycle effect).

NREM sleep episodes and N1 and the duration of REM sleep episodes, as well as evidence for intrasleep REM sleep homeostasis in humans.

Distribution patterns

The observed number of sleep cycles, the median duration and the 95% interval range of 60-150 minutes correspond to values reported in previous studies.[46-49] Contrary to Le Bon et al,[16] we could not confirm their reported normal distribution for the number and duration of sleep cycles. In contrast, we observed skewed distributions for all of our measured parameters (ie, number and duration) for NREM and REM sleep episodes. This discrepancy could be due to slightly different definitions of sleep cycles and duration of sleep opportunities. In our case, the latter was limited to 8 hours, whereas in Le Bon et al,[16] the sleep duration ranged from 4.3 to 10.8 hours. We also often subdivided NREM sleep episodes longer than 2 hours when interrupted by wakefulness with N1. The shorter duration of the first REM sleep compared to the subsequent episodes is in line with previous studies.[18,50] One interpretation of this shortening is that homeostatic sleep pressure at the beginning of nocturnal sleep attenuates REM sleep and favors NREM sleep for sleep pressure dissipation. However, a circadian influence cannot be ruled out, with the circadian pacemaker promoting REM sleep toward the end of the night rather than at the beginning.[51]

Individual modulators (age and sex)

We did not expect to observe an age-related increase in the duration of NREM sleep episodes. This is because slow-wave sleep decreases in older adults, which could potentially lead to a shortening of NREM sleep episodes. On the other hand, the significant interaction between age and sleep cycle for the duration of REM sleep episodes, together with a general decrease in REM sleep in the older adults compared to the young adults, may reflect a reduced homeostatic accumulation or a reduced circadian modulation of REM sleep.[45,50] Alternatively, age is associated with more intrasleep wakefulness and N1, often occurring at the end of a REM episode. This may have led to a decrease in the duration of REM sleep episodes, favoring a prolongation of NREM sleep episodes. To our knowledge, there have been no consistent reports of age-related changes in ultradian sleep cycles, other than the observation that younger adults have more cycles than older adults.[16]

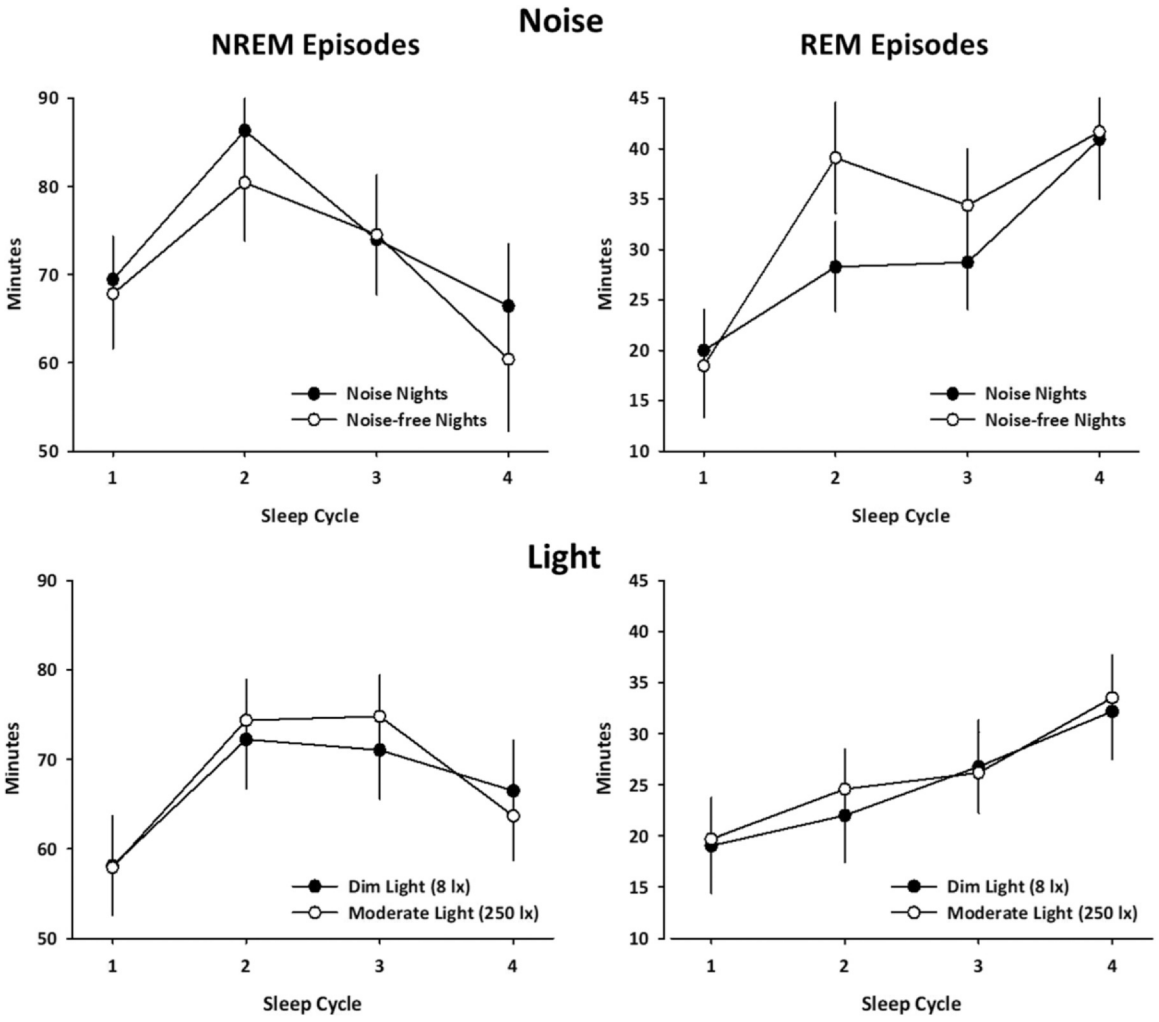

Fig. 4. Influence of noise (upper panel) and light (lower panel) on the duration of NREM and REM sleep episodes in minutes over four sleep cycles. Values represent estimated means ± 95% confidence intervals based on generalized linear mixed model (GLMM). The GLMM yielded no significant effects of the modulators "noise" and "light" or their interaction with "sleep cycle" (see Table 1 for details).

Sex differences were rather small and concerned only the duration of NREM sleep episodes, which were longer in females than in males in the first sleep cycle. Females have higher EEG amplitudes than males, especially during slow-wave sleep.[52] An effect that may have manifested itself at the beginning of the night, when EEG amplitudes during NREM sleep are high due to accumulated sleep pressure during the waking day. However, it needs to be assessed whether the observed prolongation of NREM sleep episodes in females compared to males is trait or state-dependent (ie, whether females are more susceptible to changes in homeostatic sleep pressure than males). With respect to age, there were no reports of sex-related changes in ultradian sleep cycles, other than the observation that males had slightly more cycles than females.[16]

Environment modulators (light and noise)

We found no evidence that exposure to moderate light before sleep or exposure to night-time traffic noise altered the duration of either NREM or REM sleep cycles. This is surprising because both of these environmental factors have been shown in epidemiological studies to affect human sleep.[53,54] However, it is worth noting that only small changes in sleep were reported in the specific studies included in our analysis.[26,33,38] This means that both the light levels and the noise scenarios used were of a rather moderate nature and probably not invasive enough to significantly affect the sleep quality of a good sleeper.

High- vs. low-sleep pressure

We have evidence that different levels of sleep pressure affect the duration of both NREM and REM sleep episodes at the beginning of the night, when the effects of sleep pressure are most obvious. An increase in sleep pressure leads to longer NREM sleep episodes during the first cycle, while a decrease in sleep pressure leads to longer REM sleep episodes. This suggests that the increase in REM sleep throughout the night is under sleep homeostatic control, as previously shown by Dijk et al in forced desynchrony protocols.[51] It also shows that a low sleep pressure state disinhibits REM sleep in the course of the night.

Sleep stages modulating ultradian sleep cycling

Markers of deep sleep, such as EEG delta activity, have been reported to correlate with the number of sleep cycles.[17] We, therefore, wanted to test whether specific sleep stages were associated with the duration of NREM and REM sleep episodes and expected slow-wave sleep to show a high positive correlation with the duration of NREM sleep episodes and negative correlations with the duration of

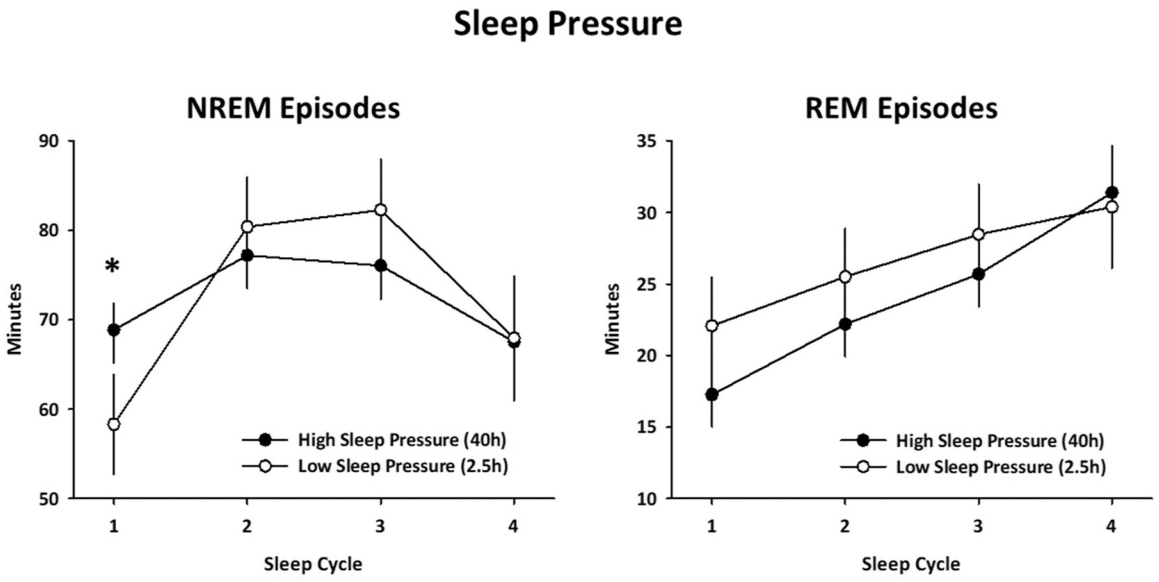

Fig. 5. Influence of high and low sleep pressure on the duration of nonrapid eye movement (NREM) and rapid eye movement (REM) sleep episodes in minutes over four sleep cycles. Values represent estimated means ± 95% confidence intervals based on generalized linear mixed model (GLMM). The low sleep pressure condition was achieved with a nap protocol, while the high sleep pressure condition was achieved with 40 hours of sleep deprivation. A significant main effect "sleep pressure" was found for the duration of REM sleep episodes, with higher values in low than in high sleep pressure conditions. For NREM sleep episode duration, a significant "sleep pressure" × "sleep cycle" effect was found (see Table 1 for details), with a longer duration under high than low sleep pressure conditions in the first sleep cycle. The asterisk indicate significant post-hoc comparisons after correction for multiple testing (Tukey-Kramer, $p < .05$, only when GLMM indicated a significant modulator × sleep cycle effect).

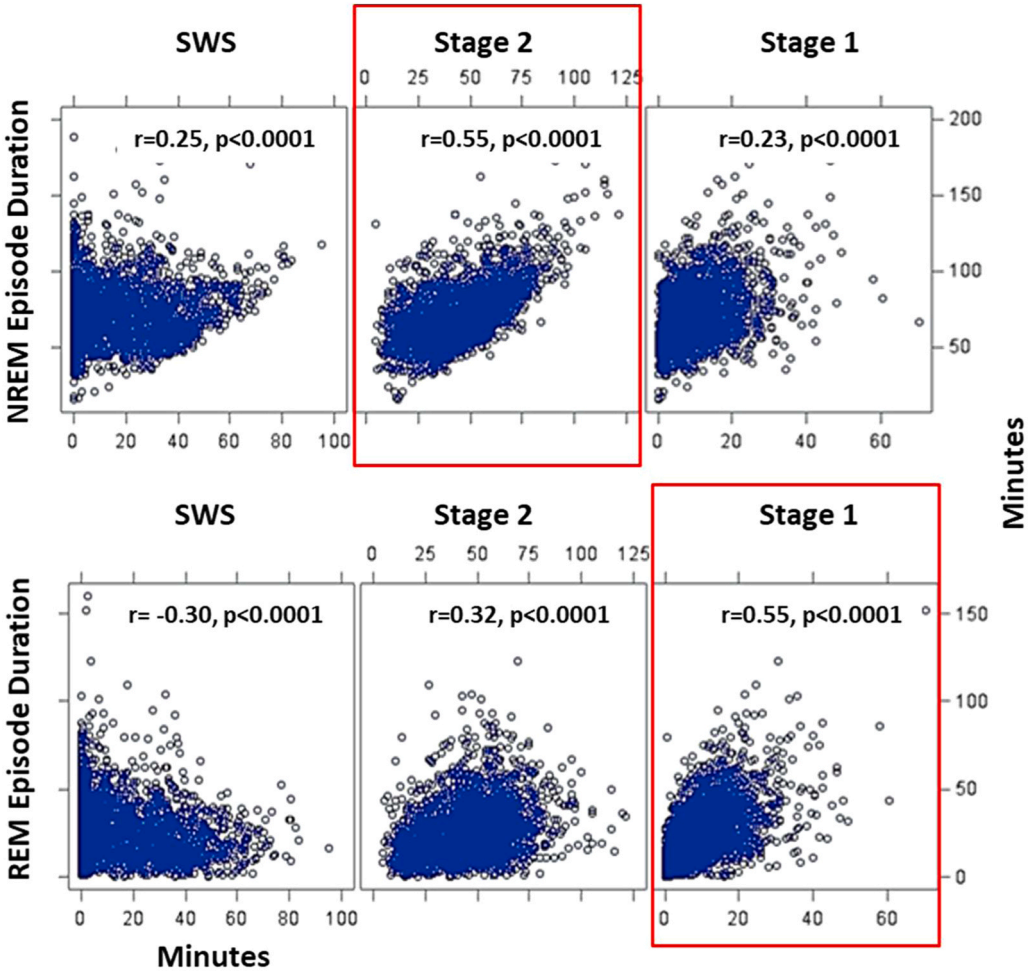

Fig. 6. Spearman correlations between different sleep stages and the duration of nonrapid eye movement (top panel) and rapid eye movement sleep episodes (bottom panel). Spearman partial coefficient r and p values, n = 6047. The red boxes mark correlations with the highest r-values.

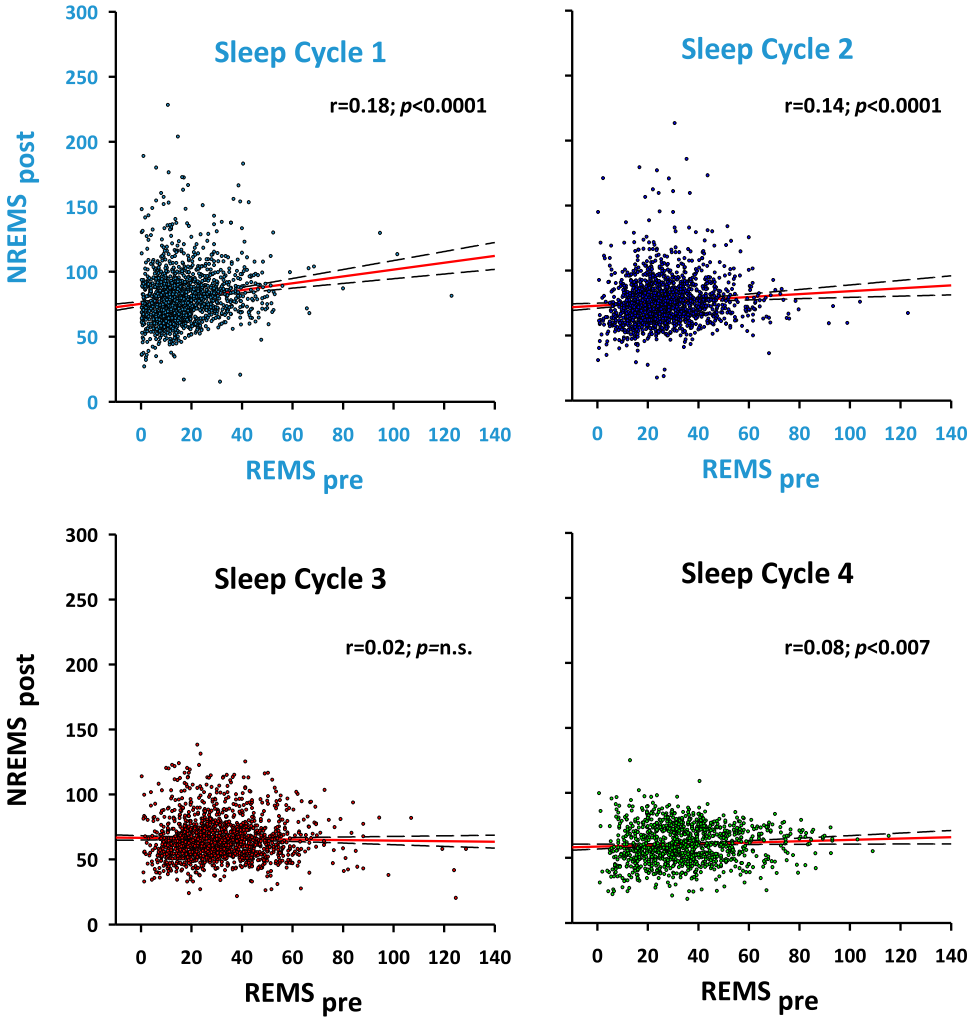

Fig. 7. Spearman correlations between the duration of rapid eye movement (REM) sleep episodes ($REMS_{pre}$) and the duration of subsequent nonrapid eye movement (NREM) sleep episodes ($NREMS_{post}$) per sleep cycle. Regression lines in red with 95% confidence interval stippled lines. Spearman partial correlation coefficient r and *p* values per sleep cycle, N = 1554 in sleep cycle 1; n = 1571 in sleep cycle 2, n = 1522 in sleep cycle 3, and n = 1107 in sleep cycle 4.

REM sleep episodes. However, it was N2 sleep (variance explained: 31%), not slow wave sleep (variance explained 0.06%) that showed the strongest positive correlations with the duration of NREM sleep episodes. We could confirm a negative correlation for slow-wave sleep and the duration of REM sleep episodes. However, the strongest association for REM sleep duration was the amount of N1 sleep, suggesting that less consolidated sleep favors REM sleep, or that EEG similarities of N1 sleep and REM state led to these associations.

Association of REM and NREM sleep episode durations within the night

There is considerable evidence in the animal literature for a short-term homeostatic balance between REM and NREM sleep episodes.[11-13,55] In particular, a REM refractory period has been defined such that the duration of a given REM sleep episode determines the duration of subsequent NREM sleep episodes (ie, the intra-REM interval length). In other words, the longer the REM episode, the longer the subsequent NREM episode, resulting in a significant positive correlation between the two. We could also confirm such an association in our data set. However, the correlation was rather weak in terms of variance explained (0.03% in sleep cycle 1, Fig. 7), but significant with so many data points entering the correlation. Despite the many data points, the REM duration of the first cycle did not correlate with the REM duration of the second cycle and so on, suggesting that the above associations were specific to the intra-REM sleep interval, supporting a REM refractory period also in humans, corroborating the findings of Barbato and Wehr.[19] As the frequency of REM and NREM sleep episodes varies between species, with a strong correlation between cycle duration and brain weight,[56] it may be that smaller animals with many more transitions than humans show a more pronounced REM refractory period.

Future directions

A better understanding of the mechanisms underlying the regulation of the human ultradian sleep cycle would include the following key directions:

1. Finding potential ultradian activity periods during the waking day (as described in mice[57]) and associating them with ultradian sleep cycles (as described in preterm neonates[58]).
   In humans, a potential tool to explore ultradian periods of activity across different states of vigilance (including daytime) would be the assessment of locomotor activity and its reported scale invariance (fractality) over a wide range of time scales from minutes to hours.[59]

Blum et al[57] suggested the existence of a "dopaminergic ultradian oscillator" (DUO) in mice. Located in the dorsal striatum, the DUO is coupled to the circadian oscillator to regulate daily patterns of motor activity. Moreover, Suprachiasmatic nuclei (SCN) neural activity shows modulation not only by circadian phase but also by NREM-REM sleep states.[60] It will be interesting to relate the DUO and sleep state-specific SCN activations to the recent discovery of the importance of transient dopamine signaling in the basolateral amygdala in gating REM sleep by disinhibiting amygdala neurons that send innervations to REM regulatory regions.[61]

2. Finding associations between circadian arousal markers[45] and ultradian sleep cycles to better explain the combined action of circadian and sleep-homeostatic influence on ultradian sleep cycles.
   The master circadian pacemaker has been proposed as a key node for scale-invariant activity fluctuations over multiple time scales from minutes to 24 hours that appear to be independent of schedule and environmental influences.[59] However, while the SCN has emerged as a major control node for fractal dynamics at longer time scales (> 4 hours), the identification of other nodes responsible for shorter time scales (< 4 hours) remains unclear. Thus, the interplay of circadian as well as sleep-wake homeostatic drives on arousal systems containing potential ultradian oscillators may shed more light on how ultradian rhythms are intertwined during waking and sleeping.
3. Promoting studies of ultradian sleep cycling in psychiatric disorders and central hypersomnolence (eg, narcoleptics).

Narcolepsy is characterized by daytime sleep episodes with early REM sleep onset and cataplexy, a sudden loss of muscle tone similar to the muscle atonia observed during REM sleep.[62] These symptoms suggest a loss of REM sleep inhibition in narcolepsy. It is not clear whether excessive daytime sleepiness or REM sleep pressure may be partly explained by an altered ultradian drive. In addition, it would be important to investigate the effect of drugs (ie, alpha-2 receptor or orexin agonists) on ultradian rhythms in people with narcolepsy and mental disorders.

Dr. Czeisler's contributions

Prof. Czeisler is and has been a role model in many aspects of being a scientist: his originality, his persistence in asking critical questions, his clarity in formulating complex issues, the beauty of presenting data in figures at a time when there were no fancy plotting programs, his wit, which also comes out in his brilliant lectures, and his mentorship during the time I was fortunate to be a postdoc in his group at Harvard under the supervision of Prof. Derk-Jan Dijk.

Public health relevance

Unraveling the physiology underlying the regulation of the ultradian sleep-wake cycle not only contributes to our understanding of sleep, and in particular healthy sleep. It also offers new opportunities to develop countermeasures to combat sleep problems and disorders in patients. Such new targets may selectively increase or decrease ultradian sleep cycles.

Author contributions

CC had the idea to perform this retrospective analysis, defined the aims and objectives of the study, and was responsible for the formal analyses. CFR, MM, VG, OS, SLC, CS were project leaders of the studies included in the re-analysis and performed the experiments, data collection, and manual sleep scoring. CC wrote the original draft of the manuscript. CFR, MM, VG, OS, SLC, CS critically reviewed the manuscript. All authors approved the final version of the manuscript.

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Declaration of conflicts of interest

CC, CR, MM, VG, OS, SLC, and CS declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.sleh.2023.09.002.

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