Circadian and Homeostatic Modulation of Sleep in Older Adults During a 90-Minute Day Study

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Study Objectives: To identify age-associated changes in circadian and homeostatic characteristics of sleep in healthy elderly and young adults using electroencephalogram (EEG) power spectral analysis during a 90-minute sleep-wake schedule.

Design: Controlled clinical experiment.

Setting: University sleep laboratory.

Participants: 16 older (77 ± 5 years) and 19 younger adults (23 ± 3 years).

Interventions: Subjects followed a 90-minute sleep-wake schedule (30 minutes in bed, 60 minutes awake) for 60 hours. Sleep was recorded for each bed-rest episode, and core body temperature was continuously recorded. The EEG power density was determined for non-rapid eye movement sleep in each bed-rest episode. Power density data were analyzed with mixed-effects models to assess rhythmic and linear components.

Results: Younger subjects had greater power in delta, theta, and sigma power bands across the study interval. Significant circadian rhythms were observed in delta, sigma, and beta power bands. Age-related differences in circadian modulation of EEG activity, indicated by significant interaction terms, were present in alpha and beta bands. A significant linear component was present in delta and theta power bands, with no significant age-interaction effect.

Conclusions: Despite overall differences in the level of EEG power, older and younger adults exhibited similar rhythmic and linear patterns in most frequency bands. Age appears to affect circadian rhythmicity in higher EEG frequencies and homeostatic drive in lower EEG frequencies.

Key Words: Age, electroencephalogram, circadian, homeostatic, sleep

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INTRODUCTION

SLEEP IN OLDER ADULTS IS CHARACTERIZED BY AN INCREASE IN NOCTURNAL AWAKENINGS, UNWANTED EARLY MORNING WAKEFULNESS, AND MORE FREQUENT DAYTIME NAPPING.1 These observations are reflected in alterations of sleep macrostructure in older age, including reduced sleep efficiency, reduced stages 3 and 4 sleep, and increased stage 1 sleep.2 It has been estimated that over half of community-living adults aged 65 years and older experience some form of chronic sleep disturbance.34 Disturbed sleep in this population is associated with morbidities, including increased risk of falls, reduced functional status and quality of life, inappropriate use of sedative-hypnotic medications, and nursing home placement.1 Causes of sleep disturbances in older adults include medical illness, medications, stress, environmental influences, and maladaptive behavioral patterns. In addition there is evidence to suggest that changes in the circadian and homeostatic regulation of sleep may also contribute to the sleep disturbances experienced by the elderly.25

Circadian rhythmicity of sleep and wake states has long been recognized.67 Circadian variation in sleep propensity has been quantified with a variety of experimental paradigms, including very short (20- to 180-minute) sleep-wake cycles,89 forced desynchrony with long (28-hour) sleep-wake cycles,10 and with the “disentrainment” protocol of prolonged bed rest in darkness.11 Each of these paradigms confirms maximal sleep propensity near the time of core body temperature (CBT) nadir.

With advancing age, the amplitude of the circadian waking signal may become attenuated, resulting in alterations in the macrostructure of nocturnal sleep, such as earlier sleep hours, shorter nocturnal sleep, decreased sleep efficiency at night as well as increased daytime napping.1213 Advancing age is associated with a circadian phase advance that may explain the unwanted early morning wakefulness often experienced by older adults.1416 although such evidence has not been consistently identified.17

Quantitative electroencephalogram (EEG) studies of sleep also reveal characteristic changes with age. As early as the middle years of life there is evidence of reduced EEG power relative to younger adults during non-rapid eye movement (NREM) sleep in frequencies below 14 Hz, including delta, theta, and sigma activity during a single cycle of nocturnal sleep.18 These findings suggest that changes in the basic microstructure of sleep develop with advancing age and are evident in the middle years. Similar findings of reduced delta, theta, and sigma activity in addition to increased beta activity have been reported by Carrier et al.19 The authors postulate that such results suggest reduced homeostatic pressure and increased cortical activation during sleep with advancing age.

Disclosure Statement
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Limited evidence is available regarding circadian regulation of quantitative EEG in either younger or older adults. Dijk and Czeisler reported circadian variation in rapid eye movement (REM) sleep among young adults, with slight circadian modulation of slow-wave activity (SWA), and a robust circadian regulation of sleep spindle activity. They also reported NREM activity between 0.25 and 11.5 Hz to be primarily dependent on prior sleep time and only slightly affected by circadian regulation.

Wei et al. showed attenuated modulation of sleep spindle frequency and amplitude with advancing age but did not specifically address other frequencies.

Homeostatic modulation of sleep in older adults has been analyzed primarily using sleep-deprivation studies. Several studies have demonstrated a similar response to sleep deprivation in both young and older subjects, with an increase in stage 3 and 4 sleep and SWA during the first recovery night. Although the slow-wave sleep response follows the same pattern in subjects of different ages, older adults have lower absolute amounts of slow-wave sleep throughout the sleep deprivation and recovery process compared to young adults. Overall these studies suggest preserved homeostatic regulation of sleep with advancing age in response to sleep deprivation but with a reduced overall level of homeostatic sleep drive.

The goal of the present study was to evaluate age-related changes in circadian and homeostatic aspects of sleep microstructure using EEG power spectral analysis within the context of an ultradian (90-minute) sleep-wake schedule. Such an experimental paradigm allows for the evaluation of sleep episodes over multiple phases of the circadian cycle and permits indirect examination of homeostatic and circadian sleep regulation in terms of linear and 24-hour rhythmic trends in EEG power.

METHODS

Subjects

Subjects for this study included 16 older adults (7 men, 9 women, mean age 77 ± 5 years) and 19 young adults (10 men, 9 women, mean age 23 ± 3 years) without sleep complaints. Subjects provided informed consent after being provided with detailed information regarding the nature, purpose, and risks of the study and were paid for their participation. The research protocol was approved by the University of Pittsburgh Biomedical Institutional Review Board for Health Sciences and complied with the Declaration of Helsinki.

Subjects had no reported history of sleep, neurologic, psychiatric, or acute/unstable medical disorders. Exclusionary criteria included obesity (body mass index > 27 kg/m²), consumption of more than 3 cups of coffee per day or 5 alcoholic beverages per week, or use of medications with established side effects of insomnia, sleepiness, or alterations of sleep structure (eg, aspirin, benzodiazepines, antihistamines). All subjects underwent complete medical history, physical examination, medical record review, routine laboratory panel, and electrocardiogram (older subjects only). Psychiatric history was evaluated with the Structured Clinical Interview for DSM-IV. Subjects were excluded for any current or serious past psychiatric disorders, including mood disorders (major depression, bipolar disorder), panic disorder, and psychotic disorders. In addition, subjects were required to have a score of < 10 on the Hamilton Rating Scale for Depression and 27 on the Mini-Mental State Examination. Sleep screening involved completion of a sleep history questionnaire, the Pittsburgh Sleep Quality Index, and clinical interview. Subjects subsequently underwent complete screening polysomnography to exclude possible severe unsuspected sleep disorders. Specifically subjects were excluded if they had an apnea-hypopnea index of 15 or more or a periodic limb movement arousal index of 15 or greater. Older subjects were determined to be active and highly functional based upon the modified Cumulative Illness Rating Scale (CIRS) and Karnofsky Index of Functional Impairment.

As expected, older subjects had higher scores compared to young adults on the Pittsburgh Sleep Quality Index (4.7 ± 3.1 vs 1.8 ± 1.4, \( P < .001 \)), the Cumulative Illness Rating Scale (2.9 ± 2.2 vs 0.4 ± 0.6, \( P < .0001 \)) and were more likely to be taking medications. However, compared to samples of “usual” aging, our older adults showed excellent physical and mental functioning. Medications taken by the older subjects included antihypertensives (\( n = 5 \)), nonsteroidal anti-inflammatory drugs (\( n = 2 \)), estrogen (\( n = 4 \)), bisphosphonates (\( n = 1 \)), statins (\( n = 3 \)), prostate pump inhibitors (\( n = 1 \)), levo-thyroxine (\( n = 3 \)), and benign prostatic hypertrophy drugs (\( n = 1 \)). One younger subject was taking a nonsteroidal anti-inflammatory medication.

Study Design

Prior to the laboratory sleep study, subjects maintained a constant sleep-wake schedule at their habitual bed timing for 2 weeks, monitored and verified by sleep diary. Laboratory sleep studies were carried out for 3.5 consecutive days in the Clinical Neuroscience Research Center at the University of Pittsburgh. Day 1 consisted of a baseline laboratory day on the subjects’ habitual sleep-wake schedule. The 90-minute sleep-wake schedule was instituted on the morning of Day 2 and continued for 40 cycles of 30 minutes of time in bed and 60 minutes of wakefulness over the next 2.5 days (60 hours). During the 90-minute schedule, subjects were maintained in temporal isolation with 6 small meals equally spaced over each 24-hour period. During waking portions of the study, subjects underwent tests of psychomotor performance and subjective sleepiness ratings. Wakefulness was ensured through very frequent interaction with staff and through scheduled activities such as performance tasks. Subjects were ambulatory within the approximately 250 square foot apartments but were connected at all times to a 20-foot cable for measuring CBT (see below).

EEG Sleep Studies

Subjects wore polysomnography electrodes for the 60-hour duration of the 90-minute day protocol. Sleep recordings for the screening polysomnogram, baseline sleep night, 30-minute sleep episodes, and recovery sleep used the same EEG methods. The basic recording included 1 central and one occipital EEG channel (C4/C3 and O1/O2 referenced to A1+A2), bilateral electrocorticograms (referred to A1+A2), and bipolar submental electromyogram. On the screening night, respiration during sleep was monitored with oral/nasal thermistors, piezoelectric transducer belts, electrocardiogram, and fingertip oximetry. Grass Model 7P511 or Grass Model 15 amplifiers were used, with high-frequency...
frequency filter settings of 100 Hz for EEG and electrooculograms, and 90 Hz for EMG. Low frequency filters were set at 0.3 Hz for EEG and 10 Hz for EMG. EEG sleep and related physiologic signals were digitized and collected onto personal computers at a rate of 256 Hz. Digitized data were transferred to Hewlett-Packard workstations. Digitized data underwent an initial quality check by a quality assurance specialist and the laboratory manager and were subsequently archived. The raw digitized data were bandlimited to 64 Hz by a low-pass FIR (finite impulse response) filter and then decimated to a sampling rate of 128 Hz. Records were scored on computer screen using standard criteria for 20-second scoring epochs.33 Sleep onset was defined as the first epoch of any sleep stage except stage 1 NREM.

Power Spectral Analysis

Power spectral analysis was used to quantify the frequency content of the NREM sleep EEG from 0.25 to 50 Hz.31 Power spectral analysis of the digitized sleep EEG was performed using software that was developed in house. Spectra were computed for nonoverlapping 4-second epochs of the sleep EEG. After weighting each epoch with a Hamming window, fast Fourier transform was used to obtain the power spectrum. Spectra were time averaged into 1-minute epochs to allow for time alignment with visual scoring data. Epochs containing muscle artifact were identified using the algorithm of Brunner et al.29 Thus, each 1-minute spectrum represents the average of all artifact-free 4-second spectra for that minute. EEG power was accumulated into the following frequency bands: delta (0.25-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), sigma (13-16 Hz), and beta (16-32 Hz). Only the 1-minute spectra for NREM stages 2 to 4 were included in the statistical analysis because homeostatic regulation of sleep and wakefulness have most often been related to NREM sleep and because REM sleep shows very different power spectral characteristics compared to NREM sleep.

CBT Recordings

CBT was used as a circadian phase reference for EEG analyses. CBT data were collected using a flexible thermistor (Yellow Springs Instrument Co., Yellow Spring, OH) inserted 10 cm into the rectum and connected via a 20-foot cable to a personal computer. The thermistor measures CBT by detecting small changes in voltage, and has a resolution of approximately 0.1°C.

Statistical Analysis

Power density data for each bin were analyzed with mixed-effects models using first-order autoregressive error structure and fixed 48-hour, 24-hour, 12-hour, 8-hour, 6-hour, and linear components. Only data from the middle 48 hours of the study were included. This permits analysis of an integral number of 24-hour cycles to avoid bias in mixed-model estimates, particularly in the linear component, and also avoids adaptation effects at the beginning of the protocol and anticipation effects at the end of the protocol. The linear component was interpreted to indicate increasing homeostatic sleep drive, whereas the 24-hour component was interpreted to indicate the effects of circadian variation. Significant 24-hour variation was indicated by F ratios for the sinusoidal component of the 24-hour term. Other rhythmic components, including 48-hour, 12-hour, 8-hour, and 6-hour were included to improve modeling of the data but were not used for hypothesis testing. Analyses first evaluated age by time interactions, then subsequently examined main effects of age.

RESULTS

General Results

Figure 1 displays mean CBT rhythms for the 2 subject groups during the 48 hours of the study. The older adult group showed a robust CBT rhythm and appeared to have a later time of minimum temperature (Tmin) relative to the younger group. The “notched” appearance in the temperature rhythms results from the 90-minute cycles with changes in posture and sleep-wake state.34 Mixed-model analysis indicated no significant age by time interactions, indicating similar temporal trends in both age groups. To further test potential phase differences, we used cosinor analyses to obtain Tmin estimates in each subject. Although the mean Tmin for older subjects (4:46 AM ± 2 hours 10 minutes) was later than that for young subjects (4:02 AM ± 1 hour 39 minutes), this difference was not statistically significant (Wilcoxon exact P value = .29). There was a strongly significant main effect for the 24-hour component (cosine 24 F1,20,103 = 432.62, P < .0001; sine 24-hour F1,20,103 = 101.55, P < .0001), indicating a robust circadian rhythm, but no significant linear trend in CBT.

Figure 2 shows the pattern of sleep duration (stage 2-4 NREM) across the 48-hour interval for 2 groups. Twenty-four-hour rhythms were evident in both groups, with no clear difference in phase position and apparently smaller amplitude in the older adult group. Significant main effects were found for age group (F1,857 = 4.18, P < .05), indicating a lower mean value for sleep duration in older adults, and 24 hour rhythm (cosine 24-hour F1,857 = 84.50, P = .0001, sine 24-hour F1,857 = 16.05, P < .0001), indicating a strong circadian pattern across groups. Mean time spent in stage 2 to 4 NREM sleep was 14.0 ± 1.8 minutes for younger subjects and 12.2 ± 2.3 minutes for older subjects (Wilcoxon exact P value = .01).
Delta Power

A trend for group × time interaction was present in the linear component, suggesting a smaller increase in delta power (0.25-4 Hz) over time in the older group ($P = .067$) (Table 1, Figure 3). A significant main effect for age group was present ($P = .0012$), indicating lower overall delta power in the older group. Likewise a significant linear component was present ($P = .0006$), indicating increasing delta activity over the course of the study across groups. A significant 24-hour ($P < .0004$) component was also present, indicating that delta power showed significant circadian variation.

Theta Power

No significant group × time interactions were present in theta (4-8 Hz) power (Table 1, Figure 3). A significant group difference ($P = .0019$) indicates significantly lower power in the older group compared to the younger group. A significant linear trend was also present ($P < .0014$), indicating increasing theta activity as the study progressed.

Alpha Power

No significant group × time interactions nor main effects of age group were present in alpha (8-12 Hz) power (Table 1, Figure 3). A nonsignificant trend for a linear component was present ($P = .095$), suggesting a larger increase in alpha power over time in the younger group. A significant group × 24-hour component was also present ($P = .0068$), indicating stronger circadian modulation in the younger group. The 24-hour component as a main effect approached but did not reach statistical significance ($P = .06$) across subjects.

Table 1—Mixed-Effects Model Results for Power Spectral Analysis Frequency Bands

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<tr>
<th></th>
<th>Delta</th>
<th>Theta</th>
<th>Frequency Bands</th>
<th>Alpha</th>
<th>Sigma</th>
<th>Beta</th>
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Figure 2—Mean time spent in non-rapid eye movement (NREM) stage 2 or deeper sleep among younger and older subjects over the course of the study.
Sigma Power

No significant group × time interactions were present, although the 24-hour × group interaction showed a trend ($P = .095$) in sigma (12-16 Hz) power (Table 1, Figure 3). A significant group effect was present ($P = .0015$) indicating greater overall sigma activity in the younger group. A significant 24-hour component was also present ($P = .0084$), indicating significant circadian modulation of sigma activity.

Beta Power

The group × 24-hour interaction in beta (16-32.25 Hz) power was significant ($P < .02$), indicating stronger circadian modulation in the young adult group (Table 1, Figure 3). No significant main effect of age group was present. A prominent significant 24-hour component was also present ($P < .0001$), indicating that beta activity shows circadian variation. No linear trend was evident.

DISCUSSION

This study used a 90-minute ultradian sleep-wake paradigm to examine rhythmic and linear trends in NREM sleep EEG power in healthy older and younger adults. Our results showed reduced delta, theta, and sigma power in healthy older subjects compared to young adults. Significant circadian modulation across groups was seen in delta, sigma, and beta frequency power, and linear increases were seen in delta and theta power across the 48 hours of the study. Significant differences among age groups in circadian or homeostatic modulation of quantitative EEG measures during NREM sleep were more limited and differed by frequency range. Specifically, alpha and beta revealed significant 24-hour × age group interactions, suggesting stronger circadian modulation in the young adult group. No significant linear × age group interactions were found. These findings suggest that, despite prominent age-related differences in EEG power across frequencies during NREM sleep, circadian regulation of EEG power appears to be reduced only in high-frequency activity with increasing age.

Similar to the studies of Dijk et al,32 Landolt et al,13 and Carrier et al,14,18,35 our results show an age-related decrease in overall power density in NREM sleep involving delta, theta, and sigma power densities. This age-related reduction of EEG power in lower frequency ranges may reflect neuroanatomic changes associated with brain aging, such as loss of cortical gray and white matter volume, which in turn may be related to decreased neuronal size and decreased dendritic connectivity.36 Similar to Carrier et al,19 we also found a nonsignificant trend toward increased power in the beta range among the older subjects. Beta power is often regarded as an indicator of cortical arousal during NREM sleep37,39 and, as such, may be a marker of the “lighten-
We observed a significant 24-hour rhythm in delta, sigma, and beta frequency bands during NREM sleep, with a trend in the alpha band as well. Previous studies in young adults have documented diurnal and circadian variations in waking EEG power, including variation in theta, alpha, and beta bands. EEG power during NREM sleep also shows circadian variation, as demonstrated by forced desynchrony studies with long day lengths. In particular, young adults in these studies showed low-amplitude circadian variation in delta and theta activity and more prominent circadian variation in sleep spindle (sigma, 12-15 Hz) activity. Maximal values for each of these occurred during the usual “biological night.” By contrast, we found a fairly broad activity. Maximal values for each of these occurred during the prominent circadian variation in sleep spindle (sigma, 12-15 Hz) lengths. In particular, young adults in these studies showed low-demonstrated by forced desynchrony studies with long day power during NREM sleep also shows circadian variation, as explained by forced desynchrony studies with long day periods on entrained schedules, but sleep latency is typically prolonged during this time. On the other hand, sleep spindles (reflected in sigma power) are typically most abundant toward the end of the sleep period and depend, in part, on the duration of prior sleep. The 90-minute day paradigm does not permit long sleep episodes to develop and, thus, could limit our ability to see large variations in either delta or sigma (sleep spindle) activity. Delta power is typically highest in the beginning of the sleep period on entrained schedules, but sleep latency is typically prolonged during this time. On the other hand, sleep spindles (reflected in sigma power) are typically most abundant toward the end of the sleep period and depend, in part, on the duration of prior sleep. The 90-minute day paradigm does not permit long sleep episodes to develop and, thus, could limit our ability to see circadian variation in these frequencies. Linear increases in power were seen in the delta and theta bands, which is a finding consistent with the increase in theta observed during increasing durations of wakefulness and the increase in delta activity during sleep after progressive increases in sleep duration. Homeostatic regulation of sleep appears to influence only low-frequency activity, as we saw no significant linear increase in sigma or beta activity.

We found a trend toward a reduced linear component in delta power in older compared to younger adults. Although this interaction was not statistically significant, it is consistent with the hypothesis of reduced homeostatic sleep drive in older adults. Age-related differences in circadian components were seen in higher frequencies, suggesting reduced overall circadian variation in beta and a different pattern of circadian variability in alpha. Previous work by Wei and colleagues demonstrated reduced circadian variation in sleep spindles (analogous to sigma power in the current study) among older adults in a forced desynchrony study. The short sleep episodes in the 90-minute day paradigm may have led to less stable estimates of EEG power, which may in turn have led to decreased statistical power to detect such age \times time interactions. Indeed, although not reaching a formal significance level, age group \times 24-hour interaction terms for all bands approached statistical significance \( (P = .10 \) to 0.12). Thus, clearer evidence for circadian differences with age may be found with larger sample sizes or with longer sleep episodes.

We did not examine REM sleep in the current analyses. REM sleep shows both circadian and homeostatic regulation distinct from those of NREM sleep and has very different EEG spectral power characteristics. However, future analyses of REM sleep may deepen our understanding of age-related changes in sleep. Other limitations of the current study include the short sleep episodes and the resulting increase in error variance that may limit statistical power. On the other hand, the 90-minute day paradigm permits an evaluation of rhythm and linear trends in EEG data over a much shorter time frame than other study designs, such as forced desynchrony protocols. Because of this, ultradian sleep-wake paradigms may be useful for studying subjects with sleep pathologies such as insomnia, hypersomnia, or phase abnormalities. Our basic finding—that older adults' sleep is primarily characterized by alterations in intensity (reflected in group differences in EEG power) rather than alterations in circadian patterns (reflected in group \times 24-hour interactions)—is consistent with most studies using many other methodologies. Consequently, our results suggest that therapeutic interventions for age-related sleep disturbances should be directed primarily at increasing sleep intensity through homeostatic mechanisms and that circadian sleep interventions should be a secondary focus.

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