Age-associated difference in circadian sleep–wake and rest–activity rhythms

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Abstract

Using actigraphic monitoring of wrist activity, we investigated the sleep and rest–activity patterns of 65 young, middle-aged, old and the oldest subjects in their natural environmental conditions. To assess the effects of age and gender on sleep and circadian rhythms in activity, multivariate analyses were performed. Age significantly affected circadian sleep and rest–activity rhythms. In the old and oldest groups, the actigraphic estimates of “actual sleep time” and “sleep efficiency” decreased significantly. The estimates of “sleep latency,” the number of “nighttime awakening,” sleep fragmentation and daytime naps significantly increased in the old and oldest groups. Concerning the circadian patterning of rest and activity, the interdaily stability (IS) was similar in the four age groups, while the old and oldest subjects showed significant increases in intradaily variability (IV) and nighttime activity and a decrease in amplitude (AMP). The present study demonstrated weakened and fragmented circadian sleep and rest–activity rhythms during aging. However, no gender-related difference was found. © 2002 Elsevier Science Inc. All rights reserved.

Keywords: Circadian rhythm; Sleep; Rest–activity; Amplitude; Aging

1. Introduction

Circadian rhythms, i.e., rhythms of approximately 24 h, are present in all physiological and behavioral phenomena, such as rest–activity, sleep–wake, body temperature and hormone levels. Several studies have shown that circadian rhythms altered with age. The deterioration of circadian rhythms in the elderly is thought to contribute to sleep disturbances and reduced daytime function [1–5]. Age-related alterations in sleep include a decrease in slow wave sleep, an increased number and duration of nighttime awakening and shorter sleep duration [6–8]. Whereas the wakefulness during sleep increases, the daytime activity level decreases with age [9–11]. Though it is generally stated that circadian rhythms change with aging, the actual data of previous reports not consistent. Some studies failed to find age-related changes in the sleep and circadian rest–activity rhythm [12,13]. Some recent studies have questioned whether a shortening of the free-running period and a reduction in the amplitudes of circadian rhythms actually exist in normal human aging [14]. The most likely reason for the discrepancy between results is a difference in assessment methods, which include subjective sleep questionnaires, objective assessments in the laboratory or in naturalistic living environments. Questionnaires may not correspond well with objective sleep estimates. Laboratory polysomnography might not reflect sleep patterns at home because of distortions produced by the laboratory procedure [8]. In order to obtain objective recordings under natural environmental conditions, we applied actigraphy, i.e., an ambulatory activity monitoring, which recorded the information of circadian sleep and rest–activity patterns for 5–7 consecutive days.

2. Materials and methods

2.1. Subjects

A total number of 65 healthy volunteers participated in the study. The subjects were divided into four groups: young...
MANOVA shows main effects of age on sleep–wake rhythm \([ F(3, 57) = 5.71, P < .01] \). IS: interdaily stability, IV: intradaily variability, AMP: activity amplitude, L5: activity in the low active 5 h.

* \( P < .01 \) represents significance among four age groups.

** \( P < .001 \) represents significance among four age groups.

(21–34 years), middle-aged (36–44 years), old (61–79 years) and oldest (80–91 years) (Table 1). The young volunteers were students of Anhui Medical University and the middle-aged volunteers were residents in the city of Hefei. The old and oldest subjects were recruited from the Hefei Retired House, P.R. China. Before entering the assessment, all subjects were physically and psychologically screened to exclude the following: major physical illness requiring treatment, psychiatric or neurological disease, cognitive disorders, insomnia, alcohol or drug abuse. All subjects did not meet the criteria for dementia and depression according to DSM-IV. The Anhui Medical University review board approved of this study and all participants gave informed consent. All the subjects were screened for educational level, weight and biological life events. In addition, extreme morning and evening types were excluded through the subjective statement. All the subjects kept a sleep diary and wore an actimeter under natural environmental conditions during the investigation.

2.2. Instrumentation

All the subjects kept a sleep diary and wore an actigraphy (Actiwatch-L+plus, Cambridge Neurotechnology, Cambridge, UK) on the wrist in their natural environmental conditions. The consecutive registration days were 5–7 days from Monday to Sunday (26 subjects for only 5 days, others for 7 days). To minimize the difference of sleep and activity patterns between workday and weekend, we chose the 5 registration days excluding weekend. The Actiwatch was programmed to integrate and store movement-induced accelerations over 1-min interval. Rhythmwatch software allows for actogram and average plotting of activity data and further circadian rhythm and movement analysis. Sleepwatch Analysis 98 software allows for the calculation of sleep parameters derived from activity data collected by actigraphy (Cambridge Neurotechnology). The actigraphy also monitored the light exposure ranging from 0.01 to 100,000 lx. The recordings were edited for periods of actigraphy removal related with bathing. The sleep diary contained quantitative and qualitative aspects of sleep behavior as follows: bed-in and bed-out time, number of nocturnal awakening, subjective sleep quality.

2.3. Analysis

2.3.1. Variables

The 5-day, 1 min sampling actigraphic time series were analyzed in three ways. First, using the Sleep-Analysis 98 software (Cambridge Neurotechnology), which compares favorable to other such packages [15], the activity patterns were scored automatically in order to generate estimates of sleep variables including “actual sleep time,” “sleep efficiency,” “sleep latency,” “nap number” in day time and nocturnal “fragmentation index,” which describes the overall fragmentation of sleep. The sleep variables including “time in bed” and “wake number” at night were derived from sleep diary. The settings for lights-off and lights-on times were estimated with the aid of sleep diary information. The sensitivity of the software was kept at its default “medium” setting for all subjects. The “number of

<table>
<thead>
<tr>
<th>Variables</th>
<th>Young</th>
<th>Middle-aged</th>
<th>Old</th>
<th>Oldest</th>
<th>( F(3, 57) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in bed (min)</td>
<td>454 ± 33</td>
<td>449 ± 31</td>
<td>458 ± 32</td>
<td>460 ± 31</td>
<td>2.11</td>
</tr>
<tr>
<td>Actual sleep time (min)</td>
<td>405 ± 35.6</td>
<td>388 ± 32</td>
<td>376 ± 42</td>
<td>351 ± 38</td>
<td>3.87*</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>7 ± 3</td>
<td>10 ± 4</td>
<td>16 ± 6</td>
<td>20 ± 7</td>
<td>9.15**</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>88.95 ± 9.11</td>
<td>86.15 ± 8.38</td>
<td>81.14 ± 3.49</td>
<td>77.33 ± 4.85</td>
<td>15.81**</td>
</tr>
<tr>
<td>Wake number</td>
<td>0.60 ± 0.42</td>
<td>0.67 ± 0.45</td>
<td>1.47 ± 0.51</td>
<td>1.81 ± 0.63</td>
<td>10.26**</td>
</tr>
<tr>
<td>Napping number</td>
<td>0.73 ± 0.12</td>
<td>0.86 ± 0.15</td>
<td>1.76 ± 0.17</td>
<td>2.12 ± 0.15</td>
<td>11.24**</td>
</tr>
<tr>
<td>Fragment index</td>
<td>26.12 ± 3.01</td>
<td>32.26 ± 3.20</td>
<td>43.32 ± 4.11</td>
<td>46.02 ± 5.24</td>
<td>8.14**</td>
</tr>
</tbody>
</table>

MANOVA shows main effects of age on sleep–wake rhythm \([ F(21, 246) = 5.71, P < .01] \). * \( P < .05 \) represents significance among four groups.

** \( P < .01 \) represents significance among four groups.
daytime naps” was determined from the Nap-Analysis of Sleep-Analysis 98 software. The duration per nap ranged from 15 to 60 min and the sensitivity was kept at “medium” setting for all subjects.

Second, the 1-min data were aggregated in 1-h bins in order to calculate four nonparametric variables describing the circadian organization of the rhythm [16]. These variables are more suitable for the analysis of activity patterns than, e.g., cosine analysis or other frequently used parametric methods [16]. (1) The interdaily stability (IS) quantifies the invariability between the days, i.e., the strength of coupling of the rhythm to supposedly stable environmental Zeitgeber. It is the 24-h value from the chi-square periodogram [17] that normalized for the number of data and can easily be calculated as the ratio between the variance of the average 24-h pattern around the mean and the overall variance. (2) The intradaily variability (IV) gives an indication of the fragmentation of the rhythm, i.e., the frequency and extent of transitions between rest and activity, and is calculated as the ratio of the mean squares of the difference between all successive hours (first derivative) and the mean squares around the grand mean (overall variance). (3) The nocturnal activity was estimated by the variable L5, which is the least active 5-h period (L5) in the average 24-h pattern.

Fig. 1. The actograms of a subject of young, middle-aged, old and oldest group, which were registered by actigraphy for 5 consecutive days (left side). Note that the daytime activity level (0600–2200 h) of the old and oldest subjects is much lower than that of the young and middle-aged subjects, whereas the nighttime activity level (2200–0600 h) is significantly increased in the old and oldest subjects. The right side shows double plots of the average 24-h activity level (solid line) and 1 S.D. (dashed line) of the four subjects (right side).
(4) A nonparametric description of the amplitude (AMP) of the rhythm can be calculated from L5 and the most active 10-h period in the average 24-h pattern [16].

Third, the average light intensity that the wrist was exposed to was calculated as an average over the registration.

2.3.2. Statistical analyses

All the dependent variables were entered into STATISTICA for statistical analyses. To examine main effects and interaction of age and gender on the circadian sleep and rest–activity rhythms, two-way multivariate analyses of variance (MANOVA) were performed. Instead of subjecting many variables to MANOVA analyses, we divided these parameters into two clusters of coherent variables so as to reflect sleep and circadian rhythms, respectively, as mentioned above. In case MANOVA detected a significant effect, it was followed by the LSD post-hoc procedure to assess the specific difference between two age groups. A level of \( P < .05 \) was considered to be significant. In addition, correlation was tested by Pearson product-moment correlation procedure.

3. Results

For the cluster of sleep variables, the two-way MANOVA model yielded an overall significant difference for the factor age \( [F(21,246) = 5.71, P < .01] \). No gender effect \( [F(7,82) = 1.32, P > .05] \) and no significant Age \( \times \) Gender interaction \( [F(21,246) = 0.92, P > .05] \) were found in the group as a whole. As illustrated in Table 2, the sleep parameters are significantly different among four age groups. Post-hoc analysis showed much decreased “actual sleep time,” lower “sleep efficiency,” longer “sleep latency” and increased “wake number” in the old and oldest groups as compared to young and middle-aged groups (“actual sleep time”: \( P < .05 \), the other “sleep” parameters: \( P < .01 \), in each comparison). No significant difference was found between young and middle-aged groups and between old and the oldest groups (\( P > .05 \)). The lowest “actual sleep time,” “sleep efficiency,” the highest “sleep latency” and “wake number” were found in the oldest subjects. Dramatic changes were found in “napping number” in daytime and “fragmentation index” of the sleep in four age groups (Table 2). Post-hoc analysis showed an increased “napping number” and a higher sleep “fragmentation index” in the old and oldest subjects as compared to young and middle-aged subjects (both parameters: \( P < .01 \), in each comparison). Furthermore, Fig. 3a shows a negative correlation of age and “sleep efficiency” using the Pearson product-moment correlation analysis \( (r = -0.69, P < .001) \). The “time in bed” derived from the sleep diary reported an average of 7.5 h of sleep among all age groups without any age-related difference \( (P > .05) \). Overall, MANOVA showed a general weakened and fragmented sleep in the old and oldest subjects.

Two-way MANOVA analysis of the rest–activity rhythm also produced an overall significance among the four age
groups \(F(12,243) = 6.27, P < .01\). But no gender difference \(F(4,85) = 1.09, P > .05\) and no Age × Gender interaction \(F(12,243) = 0.71, P > .05\) were found in activity patterns. As shown in Table 3, dramatic changes were found in the parameters IV, AMP and L5. Post-hoc analysis revealed much increased IV and L5 in the old and oldest subjects as compared to young and middle-aged subjects (IV: \(P < .001\), L5: \(P < .01\), in each comparison). AMP significantly decreased in the old and oldest volunteers as compared to young and middle-aged volunteers (\(P < .001\), in each comparison), moreover, the lowest AMP and highest IV and L5 were expressed in the oldest group. IS was found to be similar in all groups \(F(3,57) = 0.55, P > .05\]. Thus, here was a significantly fragmented and attenuated rest–activity rhythm of the old and oldest subjects, with moreover high levels of nocturnal activity.

Fig. 1 shows the raw actograms of a representative of young, middle-aged, old and oldest subjects and the mean curve of activity for the given subjects (Fig 1). The old and oldest subject showed more activity dips during the daytime, which were possibly related to daytime napping. Fig. 2 gives the overall mean plot of activity per group. In addition, a negative correlation between age and AMP \((r = -.62, P < .001)\) and a positive correlation between age and L5 \((r = .57, P < .001)\) were indeed present (Fig. 3b,c).

Finally, the light exposure was comparable over the four age groups (Table 1).

4. Discussion

4.1. Sleep variables

Our study on 65 volunteers aged from 21 to 91 years demonstrated significantly weakened and fragmented sleep in the healthy old and oldest subjects as compared to young and middle-aged subjects. This result is consistent with some previous investigations [18–20], though inconsistent with the finding of Jean-Louis et al. [13], who reported no significant effect of age on sleep patterns. The equivocal results in previous studies may be related to the limited number of subjects included and the difference in investigation methods. In present study, the “time in bed” averaged about 7 h in all four age groups. The old and oldest subjects showed increased numbers of “nighttime awakening” and “daytime naps.” Consistent with some, but not all previous reports [13,18–20], we found a strong decline in “actual sleep time” and “sleep efficiency,” as well as increased “sleep latency” in the old and oldest volunteers. Most strikingly, the significant increase in sleep “fragment index” indicated an overall fragmented circadian sleep in the old and oldest people. Here, we proposed for the first time that it is a sensitive and reliable parameter to describe the function of the circadian sleep. In the present study, no gender differences in sleep variables were observed, though two previous reports documented longer sleep duration and higher sleep efficiency among women based on the polysomnography and questionnaire [21,22].
4.2. Circadian rest–activity profile

IS, an index of coupling between the sleep and 24-h Zeitgeber, showed the lowest level in the oldest volunteers of present study. However, no significant alteration was found among the four age groups. This is consistent with the previously reported lack of difference in IS between young and elderly [12]. In fact, Monk et al. [23] showed that healthy elderly have a greater regularity in daily life style than the young, possibly developed as a response to age-related changes in the circadian system.

We found that the IV of the old and oldest groups was significantly higher than that of young and middle-aged groups; whereas another group did not find this [12]. The increased IV indicates an increased fragmentation of the rest–activity rhythm and is probably related to the increased daytime napping and nocturnal awakenings in the old and oldest subjects [16,20]. Thus, we demonstrated that the old and oldest people have an increased frequency and extent of transitions between rest and activity. Apparently, IV is more sensitive than IS to age-related changes in the circadian rhythm organization of rest and activity.

Furthermore, significantly decreased AMP and increased L5 were found in the old and oldest subjects, consistent with the reports of Jean-Louis et al. [13]. The reduced amplitude is considered to be one of the most prominent circadian rhythm changes in aging [24]. The decreased daytime activity and the increased nighttime wakefulness in old people are reflected in their decreased AMP and increased L5. However, Lieberman et al. [25] observed an increase in daily activity of elderly. A possible explanation may be the different recording condition. The subjects of present study were recorded in their natural environment, whereas the subjects of the study of Lieberman et al. resided at a clinical center.

Degeneration of the suprachiasmatic nucleus (SCN) in older people likely plays an important role in their poor sleep and weakened circadian rhythm in their rest–activity pattern. The SCN is the major circadian pacemaker of the mammalian brain and coordinates hormonal and behavioral circadian rhythms [26]. The number of vasopressin-expressing neurons in the SCN is decreased in the oldest people (>80 years) [27]. In addition, the attenuation of amplitude of the circadian rhythms in vasopressin and vasoactive intestinal polypeptide expression in the SCN began after 50 years of age [28,29].

It was reported that lifestyle might influence the circadian organization of physiology and behavior [30]. Sleep diary information indicated that in the present study, the regularity of the lifestyle was comparable over the four age groups. The young volunteers were university students and lived in a dormitory, where the light-on and light-off times were strictly controlled by the regulations of the campus. This is different from other cultures where there is no control over students’ bedtimes. The daily work and rest periods of the middle-aged subjects were also regular. The old and oldest subjects similarly lived a regular life as indicated by relatively fixed bedtime, get-up time and exercises. In addition, the average illumination intensity was similar in each group (Table 1). Thus, differences in lifestyle cannot account for our findings of changing circadian rhythms during aging.

Therefore, we suggest the changes of circadian sleep and rest–activity rhythms in old people may mainly result from the degeneration of the structure and function of circadian timing system during aging. In the present study, we emphasized observations of the patterns of sleep and rest–activity cycles under natural yet comparable environmental conditions and established a group of healthy controls that can serve as a reference database for research on sleep and circadian rhythm disorders in patients with Alzheimer’s disease.

5. Conclusion

In present study, sleep and the circadian rhythm of activity measured under natural environmental conditions showed significant age-related alterations. Both sleep and activity rhythms become fragmented and attenuated in old people. The degeneration of the circadian timing system likely contributes to the age-related changes in sleep and the circadian rhythm in activity.

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