

Alterations in the Circadian Rest-Activity Rhythm in Aging and Alzheimer's Disease

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The suprachiasmatic nucleus, considered to be the endogenous circadian clock in the mammalian brain, shows morphological changes with aging, which become even more pronounced in Alzheimer's disease (AD). In order to assess possible functional implications of these alterations, circadian rest-activity rhythms of 6 young and 13 old volunteers and of 12 AD patients were studied with a recently developed ambulatory rest-activity monitor (RA24). Young and old volunteers showed no differences in their rest-activity rhythm in any of the variables studied. Comparison of old controls versus AD patients revealed that (1) rest-activity rhythm was markedly disturbed in many of the AD patients and tended to be correlated with the severity of the dementia; (2) disturbances were most pronounced in subjects using sedating drugs; (3) disturbances in the latter group did not result from medication as no differences were found in the rest-activity patterns before and after administration of sedating drugs; (4) negative findings reported in the literature concerning circadian disturbances in AD may well have resulted from selection criteria that excluded the group of patients with the most severely affected rest-activity rhythm; and (5) rest-activity monitors offer a practical and fruitful approach for the study of circadian rhythms in humans.

Introduction

Circadian rhythms are regarded as crucial for optimal functioning of the individual. Alterations in these rhythms during aging have been the subject of many studies (for review see Van Gool and Mirmiran 1986). Experimental disturbance of circadian rhythms resulted in cognitive impairment in both rats (Fekete et al. 1985) and humans (Downey and Bonnet 1987), underlining the relationship that exists between performance in cognitive tasks and circadian rhythms. This suggests that, apart from being a consequence of aging, disrupted circadian rhythms in aged and demented subjects may also contribute to their mental decline (Jolles 1986). Moreover, nocturnal restlessness, a manifestation of disturbed circadian rhythmicity, is an important criterion for hospital admission of geriatric patients (Sanford 1975).

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Although much effort has been put into characterizing the circadian changes during aging, little is known about their underlying causes. In the search for a neuroanatomical basis for circadian abnormalities, it was observed that the suprachiasmatic nucleus (SCN), which is considered to be the central circadian clock in the mammalian brain, shows significant alterations during normal aging and in Alzheimer's disease (AD) (Swaab et al. 1985; Roozendaal et al. 1987; Chee et al. 1988). To what extent these morphological changes actually contribute to the reported alterations in circadian rhythms remains to be investigated.

In recent years progress has been made in therapeutic strategies (in particular, light-therapy) towards treating depression associated with circadian disturbances (Lewy et al. 1987). It is possible that such strategies may affect the disturbed rhythms in AD patients in a similar way. Although the practical possibilities for studying circadian rhythms in human subjects, and especially in AD patients, have been rather limited to date, the recent development of a small ambulatory rest-activity monitor (Mirmiran et al. 1988) has enabled us to study the alterations in the circadian rest-activity rhythm with aging and in AD in detail.

Material and Methods

Subjects

Three groups of subjects were recorded: 6 young controls, 13 old controls, and 12 Alzheimer's disease (AD) patients. The young controls, aged 29-55 (4 men and 2 women), were all employed at the Netherlands Institute for Brain Research. The old controls, aged 71-85 (2 men and 11 women), consisted of friends and relatives of the young group. The controls were all recorded in their "natural environment." None of the controls had used sedative drugs or suffered from any acute or chronic disorder in the course of the study.

The AD patients, aged 71-86 (2 men and 10 women), were all inpatients residing at the Valerius Kliniek in Amsterdam. All patients met the NINCDS/ADRDA criteria for probable dementia of the Alzheimer's type (McKahn et al. 1984). To exclude reversible dementia, all patients were subjected to extensive physical examination, blood and urine screening, electroencephalogram, and computed tomography scan. DSM-III criteria were used to exclude delirium and depression. Hamilton scores ranged from 4 to 17. The Global Deterioration Scale (GDS) for age-associated cognitive decline and for Alzheimer's disease (Reisberg et al. 1982) was used to rate the severity of the disease: 2 patients were classified as stage 4 (moderate cognitive decline), 9 as stage 5 (moderately severe decline), and 1 as stage 6 (severe cognitive decline). None of the patients suffered from any acute or chronic disorder that may have influenced the recording during the course of the study. Two AD patients used alimemazine (Nedeltran) daily, and 2 others had used temazepam (Normison) once during a recording. One patient had used haloperidol (Haldol) 20 hr before recording. Because the use of sedative drugs may influence rest-activity rhythm, sedative users ($n = 5$) and nonusers ($n = 7$) have also been analyzed as separate groups.

The Rest-Activity Monitor

The rest-activity rhythms were recorded continuously for 90-168 hr. Lower arm movements were detected by an acceleration detector in the rest-activity monitor (weight: 140 g, size: $9 \times 4 \times 2$ cm). The sensitivity was set to such a level that practically all

voluntary arm movements were detected. When the induced voltage exceeded the preset level, a counter was raised, and the input was blocked for 16 sec. Consequently, the maximum number of counts per hr was 225 (= 3600/16). Every hr the contents of the counter were stored into the monitor's memory. After each recording period the contents of the memory were transferred to a computer for further processing.

Statistics

The following variables were computed: interdaily stability (IS), intradaily variability (IV), total activity of the 10 most active (M10) and 5 least active hr (L5).

The IS was derived by normalizing (for the number of data) the 24-hr value from the chi-square periodogram (Sokolove and Bushel 1978):

$$IS = \frac{N \sum_{h=1}^p (\bar{X}_h - \bar{X})^2}{p \sum_{i=1}^N (X_i - \bar{X})^2} \quad (1)$$

where N is the total number of data; p is the number of data per day (in this study 24); \bar{X} is the mean of all data; \bar{X}_h are the hourly means; X_i represent the individual data points. As Moore-Ede et al. (1982) pointed out, alterations in IS may indicate a loose coupling between the rest-activity rhythm and its supposedly stable "Zeitgebers," as IS decreases with higher day-to-day variation (i.e., a looser coupling) of the activity patterns.

The IV was calculated by taking the ratio of the mean squared first derivative of the data and the population variance of the data:

$$IV = \frac{N \sum_{i=2}^N (X_i - X_{i-1})^2}{(N-1) \sum_{i=1}^N (\bar{X} - X_i)^2} \quad (2)$$

where IV was included to detect fragmentation of the rest-activity rhythms, and high IV may be an indicative of daytime napping and/or nighttime arousals.

The M10 and the L5 were computed by averaging the 10 highest and 5 lowest hourly means, respectively. M10 represents activity during the most active period of the day; this measure may be influenced by daytime napping. L5 represents movement-activity during sleep plus nighttime arousals. The "amplitude" of the rest-activity rhythm was not calculated, e.g., by subtracting L5 from M10, as this would alter the M10 values only marginally (less than 10%), which was found to have little or no influence on the analyses. Therefore, M10 may be regarded as an adequate approximation of amplitude.

In order to assess the relationship between mental decline and circadian disturbances, GDS ratings were all scored by one observer (I.H.K.), who was not aware of the results from the activity analyses. Young versus old controls, and old controls versus AD patients were compared using the F -test and the t -test for unequal variances (two-tailed). Correlations were calculated using the Pearson product moment correlation test; $p < 0.05$ was considered to be significant. For reasons of readability, the p values of t -tests and

Table 1. Correlation Matrix of 31 Subjects

	IV	M10	L5
IS	-0.63 <0.001	0.58 <0.001	-0.53 0.002
IV		-0.73 <0.001	0.24 0.20
M10			0.12 0.53

Upper value in each quadrant is Pearson's r , lower value is corresponding p value. The results indicate that the disturbances manifest themselves in many variables at the same time.

Pearson product moment correlations were omitted from the text as much as possible; they can be found in Figure 2 and Table 1, respectively.

Results

Visual Inspection of Raw Data

Raw data plots are shown in Figure 1. No overall difference in activity patterns was observed between young and old controls. The activity patterns of some old controls showed afternoon "dips" (e.g., subject A.N.), which may have been the result of napping. In general, the activity level in AD appeared to be lower and the activity patterns were often more fragmented compared with the controls. In AD, the circadian rest-activity rhythms ranged from almost absent (subject W.I.) to normal (subject P.E.). Administration of sedating drugs did not influence the rest-activity rhythms substantially, as the activity patterns before and after time of medication did not differ.

Pearson Product Moment Correlation

Negative correlations were found between IS and IV, IS and L5, and between IV and M10 for all subjects. A positive correlation was found between IS and M10 (Table 1). Analyzing AD patients separately gave similar results. These findings indicate that disturbances in the circadian rest-activity rhythm manifest themselves in many variables at the same time. Despite the small variation in GDS scores of the AD patients, the GDS score tended to be correlated negatively with IS ($r = -0.50$, $p = 0.10$), and positively with L5 ($r = 0.50$, $p = 0.10$).

Comparing Groups

No significant differences were found between young and old control subjects for any of the variables tested. L5 tended to be higher in old subjects with respect to both the mean and variance ($p = 0.11$; Figure 2D).

Interdaily Stability

IS of AD patients tended to be lower compared with old controls (Figure 2A). This difference is due mainly to the sedative users, as no difference was found between old controls and nonusers. Both AD patients as a whole and the subgroup of sedative users

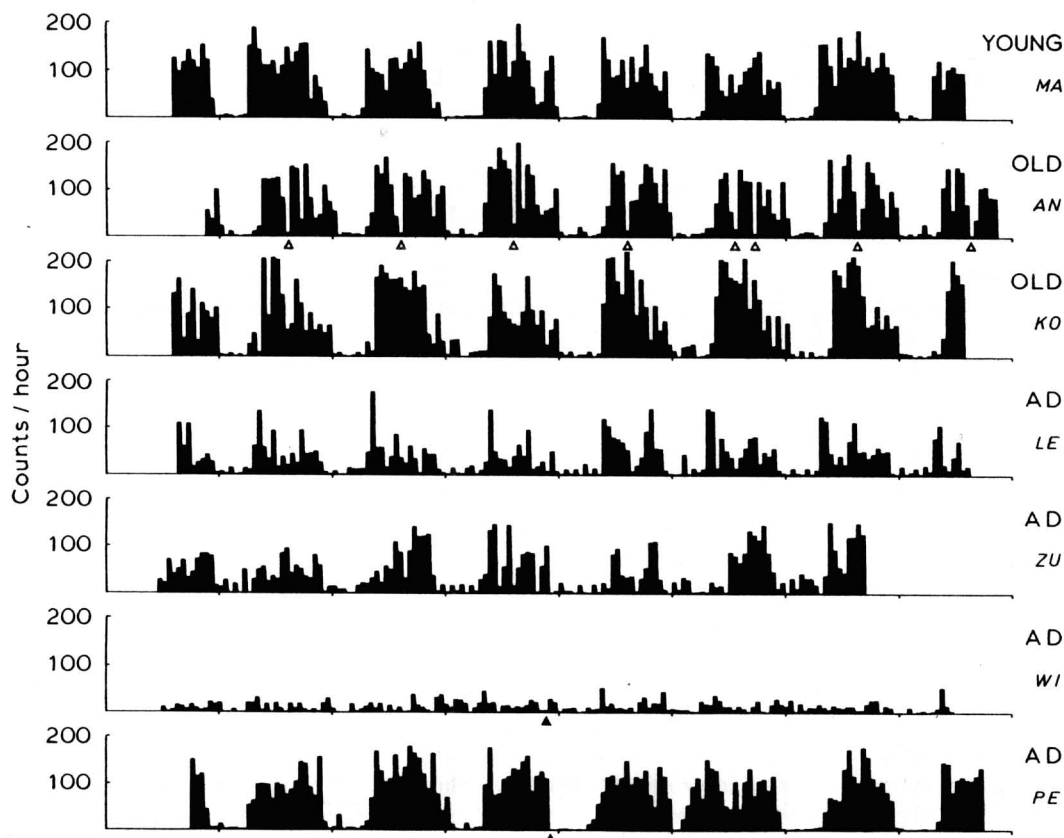


Figure 1. Actograms of 1 young (M.A.) and 2 old (A.N., K.O.) controls, and 4 Alzheimer patients (L.E., Z.U., W.I., P.E.). Some old controls and AD patients show activity dips (Δ) (e.g., A.N.) during the day which are possibly related to daytime naps. Generally, the activity pattern of AD patients is more irregular and the activity level is lower. In some patients, the circadian rest-activity rhythm is almost absent (e.g., subject W.I.). Administration of a sedating drug (\blacktriangle) has no apparent influence on the already disrupted rest-activity pattern.

showed a high variance as compared with old controls ($p = 0.01$, $p = 0.02$, respectively).

Intradaily Variability

AD patients showed a higher IV than did old controls. The IV of sedative users did not differ from old controls, whereas that of nonusers did (Figure 2B). The latter finding may be due to the high variance within the sedative users' group, which differed significantly from old controls ($p = 0.04$) and nonusers ($p = 0.003$).

Most Active 10 Hours

AD patients as a whole and drug users were less active than old controls (Figure 2C). Nonusers showed a trend in the same direction when compared with old controls. Sedative

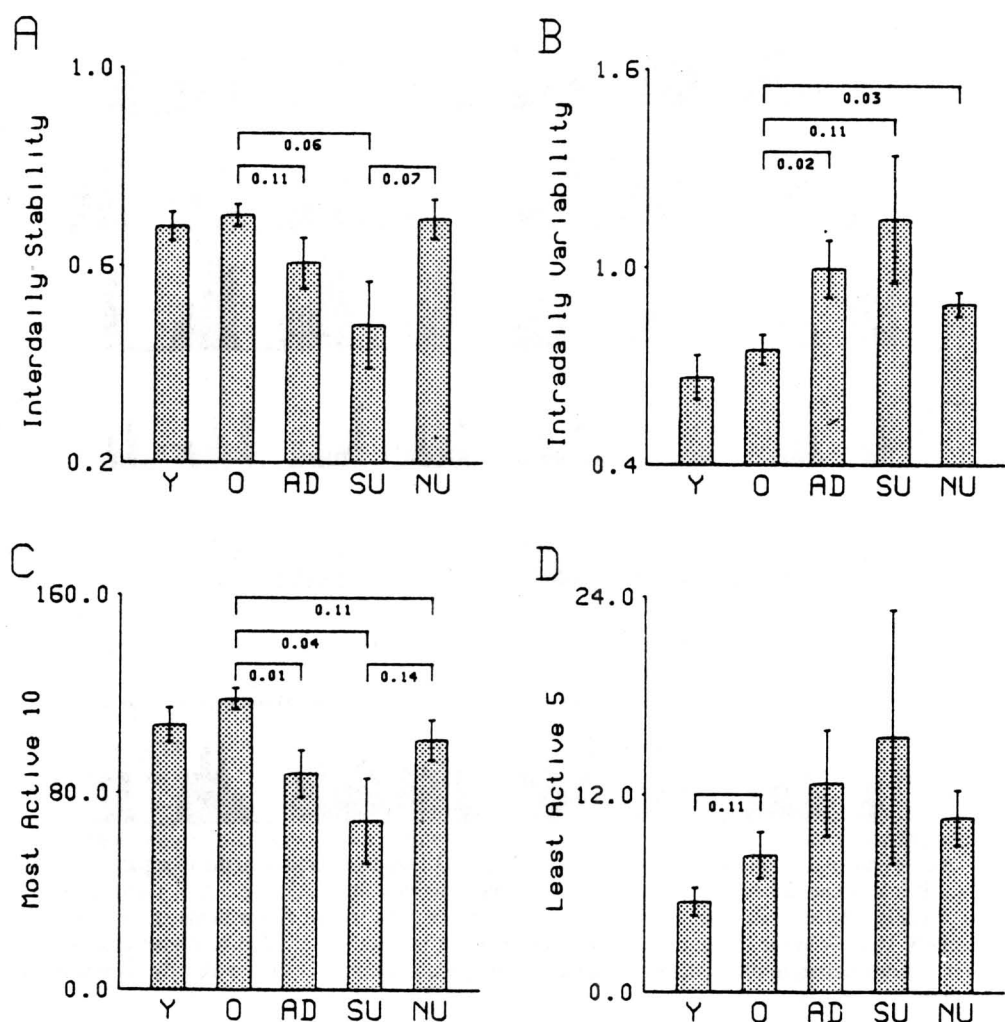


Figure 2. Mean interdaily stability, intradaily variability, most active 10 hr, and least active 5 hr of the different groups. p values of t -test below 0.20 are indicated. No differences are observed between young (Y) and old (O) controls. Although p values may differ, all variables suggest the same negative effect of AD, which is most pronounced in the subgroup of sedative users (SU) as compared with nonusers (NU).

users tended to be less active than nonusers. Compared with old controls, variance was higher in AD patients ($p = 0.004$) and sedative users ($p = 0.02$), but not in nonusers.

Least Active 5 Hours

Mean values did not differ between the old controls and Alzheimer groups (Figure 2D). Variance was lower in old controls than in the AD patients and in the subgroup of sedative users ($p = 0.009$, $p = 0.007$, respectively). As the variance of sedative users was higher than that of nonusers ($p = 0.006$), the differences between AD patients and old controls seem to come mainly from the drug-using group.

Discussion

RA24 Rest-Activity Monitor

Both the recorded subjects and the researchers felt comfortable with the rest-activity monitor. Although some of the control subjects noted frequent awareness of the monitor's presence, none of the recorded subjects considered carrying the monitor a burden. From the researchers' viewpoint, very little effort was required to obtain and analyze the data. Based on these observations and the results given above, it is concluded that the RA24 rest-activity monitor is a convenient, nonobtrusive, and successful method for recording circadian rhythms.

Variables Tested

There is no ideal and indisputable method for analyzing circadian rhythms. However, methods often used by others, like hour-by-hour comparison and cosine fitting have been avoided deliberately. Hour-by-hour comparison was not performed, as 24 measurements per day (thus multiple comparisons) and the likely dependence between successive hours would make it impossible to interpret the results meaningfully. Furthermore, it would probably lead to a futile discussion about when demented people are more or less active compared with controls: It is known, for example, that hospital routines generally hasten arousal and bedtime compared with hours generally maintained at home. Still, this is no sign of disturbed rhythmicity. With respect to cosine fitting, for analyzing rhythms that have no cosine shape, this method is inappropriate. When we analyzed our data with this method, the proportion of variability accounted for (Monk and Fort 1983) was generally poor, and significantly lower in AD than in old controls (mean % \pm SD: 31.3 ± 16.3 versus 48.9 ± 7.8 , $p = 0.004$); therefore, it would be difficult to give a meaningful interpretation of the results. As with hour-by-hour comparison, this would only be complicated by enforced social factors. Although the variables chosen for this study are certainly not free of disturbing influences, for the purpose of this study, i.e., describing the alterations in the circadian aspects of rest-activity behavior, they were found to be the most suitable.

Effect of Aging

Circadian rest-activity rhythms in the elderly have been examined previously. Renfrew et al. (1987) found a decrease in diurnal movement-activity with age. On the other hand, Lieberman et al. (1987) found increased daytime activity in aged people. In our study, no differences between young and old were observed. As there was no indication of a gender difference in our study, this lack of age effects could not be attributed to the mismatch in the male/female distribution between young and old controls. Apart from the limited numbers of subjects recorded in the above-mentioned studies, a possible explanation for at least one of the discrepancies may be the difference in recording environment. The subjects of Renfrew et al. and the controls in our study were recorded in their "natural" environment, whereas the subjects of Lieberman et al. resided at a clinical research center.

Results with regard to nightly activity are consistent in all studies. Both above-mentioned studies found an increased nocturnal activity with age; our study revealed a non-significant trend in this direction. As increased nocturnal movement-activity is likely to

coincide with increased awakenings, these findings are compatible with the reports of increased sleep-complaints in the elderly (Miles and Dement 1980).

Effect of Alzheimer's Disease and Medication

Only one previous study examined the changes in the rest-activity rhythm in AD (Campbell et al. 1986). In this study, no differences were found in AD patients when compared with healthy controls, but because cosine fit and hour-by-hour comparison were used for analysis, the variables tested differed from those in the present study. Studies on temperature rhythms in AD showed similar results: No alterations were found in AD, neither with respect to mean nor to amplitude (Campbell et al. 1986, 1988; Prinz et al. 1984).

In our study, AD patients showed a significant disruption of the rest-activity rhythm which tended to correlate with the severity of the disease as measured by the GDS. The difference was most pronounced in the group of patients using sedating drugs. By observing when AD patients were in or out of bed, Edgar et al. (1988) recently reported a reduced "amplitude" of the sleep-wake rhythm of demented patients using psychoactive medication. These authors, therefore, concluded that psychoactive medications affect sleepiness and alertness across the 24-hr day. At first sight, our results appeared to be consistent with this view. We should realize, however, that medication is usually prescribed to control sleep-wake rhythms of those patients whose rhythm is most severely disturbed. Indeed, visual inspection of the raw data showed that drug administration had no obvious additional effect on the rest-activity rhythms, an observation that is consistent with the lack of effectiveness of sedating drugs in AD.

The alterations in the variables tested indicate that circadian rest-activity rhythms in many AD patients may be essentially different from healthy old people. However, as mentioned before, little is known about the underlying causes for these differences. Alterations have been found in various aspects of the circadian system: (1) AD patients are exposed less to bright light than healthy elderly controls (Campbell et al. 1988); (2) widespread axonal degeneration was found in the optic nerves of AD patients (Hinton et al. 1986); (3) the suprachiasmatic nucleus showed significant changes with aging and in AD (Swaab et al. 1985; Roozendaal et al. 1987; Chee et al. 1988); (4) alterations in various sleep variables are consistently found in AD (Reynolds et al. 1983; Prinz et al. 1987); and (5) studies (Reynolds et al. 1985; Erkinjuntti et al. 1987) have demonstrated a higher incidence of sleep apnea in AD compared with age-matched controls.

In conclusion, we have shown that the rest-activity rhythm is disturbed in many AD patients. Furthermore, we suggest that negative findings in previous studies may well be caused by the criteria used to select the patients and the ways in which the data were analyzed. Further studies are required to assess the contribution of the various above-mentioned factors to the alterations found. However, the procedure used in the present study seems to provide an excellent means of determining the effectiveness of therapeutic interventions such as light or medication on the disrupted rest-activity rhythm of Alzheimer patients.

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