18. CIRCADIAN REST-ACTIVITY RHYTHM MONITORING IN AGING AND ALZHEIMER'S DISEASE

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INTRODUCTION

The presence of well pronounced circadian rhythms of sleep-wake, temperature and hormones can be regarded as a basic need for optimal physical and mental functioning (for review see Van Gool and Mirmiran, 1986). The body's immune system, for example, may fail to operate adequately when circadian rhythms are disturbed (Moldofsky et al., 1989), which in turn may result in a reduced life expectancy.

Aging and in particular Alzheimer's disease are often accompanied by moderate to severe disruptions of circadian rhythms and may therefore be more prone to all kinds of diseases. In Alzheimer's disease the disruptions of the circadian rhythms are often of such a severity that they may even contribute to the mental decline (e.g. Fekete et al., 1985).

When studying the complaints of the people supporting elderly patients before they were admitted to the hospital, Sanford (1975) found that sleep distur-
bances and related problems were both most frequently mentioned as one of the main factors causing problems and at the same time among the complaints least well tolerated by the supporters. Since it is often this supporter at home who decides for hospital admission of the elderly dependent on the basis of such problems, disturbances in circadian rhythms may not only have important medical, but also considerable social and economical consequences.

CIRCADIAN RHYTHMS IN ALZHEIMER'S DISEASE

In a recent study, we were able to monitor the circadian rhythm disturbances during aging and in Alzheimer's disease (Witting et al., 1990). Since for studying circadian rhythms it is required to obtain many data per day, a small non-obtrusive portable device was developed that enabled us to study the circadian rhythms of the rest-activity cycle. The weight and size of the device used in the present study were 140 g and 9x4x2 cm. All components were housed inside the device. The principle mechanism of the device is depicted in figure 1. Movements are detected by an acceleration-sensitive component, the induced signal is amplified, and when the signal exceeds a preset level, a counter is raised. To prevent overflowing of the counter the input is then blocked for 16 seconds. Once every hour the contents of the counter is transferred to the EEPROM-memory and the counter is reset to zero. After each recording the contents of the memory can be transferred to a computer for further processing. For more detailed information about the monitor, the reader is referred to Mirmiran et al. (1988).
Figure 1: Block diagram of the main components of the rest-activity monitor. See text for explanation.
In the present study we compared the circadian rest-activity rhythms of 6 young (29-55 years of age) and 13 old (71-85) volunteers, and 12 Alzheimer patients (71-86). The controls were all healthy and recorded in their 'natural environment'. The AD-patients were in-patients residing at the Valerius Kliniek in Amsterdam. All AD-patients met the NINCDS/ADRDA criteria for probable dementia of the Alzheimer type (McKhann et al., 1984). 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. None of the patients suffered from any acute or chronic disorder that may have influenced the recording. Since some of the patients used sedating drugs incidentally, these patients (n=5) were also analysed as a separate group.

Apart from visual comparison of the data we derived some parameters for statistical comparison: the interdaily stability, the intradaily variability, the mean of the five least active hours, and the mean of the ten most active hours (see Witting et al., 1990). The output of the rest-activity recorder is shown in figure 2.

Visual comparison revealed only minor differences between young and old controls. Some old controls showed afternoon naps and/or nocturnal awakenings, but these disturbances were not of such an extent that they would cause statistically significant differences between young and old in the parameters tested. The circadian rhythms in the Alzheimer group varied from normal to practically absent (see figu
re 2, subjects L.E., Z.U., P.E. and W.I.). These alterations were also found in statistical comparisons of the data, since most parameters showed significant changes in the Alzheimer group when compared with old controls: the interdaily stability and the mean of the ten most active hours were reduced, whereas the intradaily variability was increased, all affirming the visually observable circadian disturbances in the Alzheimer group. Furthermore the GDS-score tended to be correlated negatively with the interdaily stability (pearson product moment correlation, \( r = -0.50, p = 0.10 \)), and positively \( (r=0.50 \ p=0.10) \) with the mean of the five least active hours, indicating the relation between mental decline and disturbances in circadian rhythms.

**RELATION BETWEEN MEDICATION AND CIRCADIAN RHYTHMS**

When comparing sedating drugs users with non-users we found that the disturbances were most pronounced in the former group. Although one may be inclined to conclude from this that sedating drugs aggravate the circadian rhythm disturbances, examination of the raw data suggests otherwise. As can be seen from the data of subject W.I. (figure 2), the disturbed circadian rhythm was already present before the drugs were given. This finding does not only suggest that the drugs are rather prescribed to control disturbed circadian rhythms, it also gives an explanation for the negative findings in reported literature so far (Prinz et al., 1984; Campbell et al., 1986, 1988a), since these studies always excluded patients using sedating drugs.
Figure 2: Data from the rest-activity monitor. Between young and old controls no significant differences were observed. Some old controls however showed afternoon naps (indicated with Δ). Circadian rhythms in Alzheimer patients ranged from normal to practically absent (subject W.I.). Alzheimer patients were often less active during the day and more active during the night. Administration of sedating drugs (indicated with △) does not seem to affect the severely disrupted rhythm of subject W.I.
THE BIOLOGICAL BASIS OF DISTURBED CIRCADIAN RHYTHMS

Research is in progress to find the mechanisms underlying circadian rhythm disturbances in elderly and AD. Two major components of the circadian rhythm generating system in this respect are (1) the retino-hypothalamic projections conveying light information into the biological clock and (2) the suprachiasmatic nuclei (SCN) of the hypothalamus (i.e. the biological clock). During aging and especially in Alzheimer's disease alterations have been found in both these components and their related input. First of all, exposure to light, is significantly reduced in aging. Alzheimer patients were even exposed to significantly less light than their age-matched controls (Campbell et al., 1988b). Furthermore, Hinton et al. (1986) found widespread axonal degeneration of the optic nerve in eight out of ten and a reduction of number of retinal ganglion cells and in the thickness of the nerve-fiber layer in the retina in three out of four examined Alzheimer cases. Finally, Swaab et al. (1985) found reductions in cell number and volume of the SCN in aging, which were even more pronounced in Alzheimer's disease (fig. 3).

In spite of these findings, the extent to which the above mentioned factors actually contribute to the circadian rhythm disturbances is still unknown. Further research towards the relations between the different alterations found will therefore be required.
Figure 3: Total cell number of the SCN in different age groups and in Alzheimer's disease. The age of the Alzheimer group was comparable with the '61-80 years of age' group. Total cell number is markedly decreased in the 81-100 years of age group. In addition, total cell number in the Alzheimer group was significantly lower than the most severely affected control group (based upon Swaab et al., 1987).
CONCLUSION

In conclusion, we have shown in the present study that the rest-activity rhythm is often disturbed in Alzheimer patients. The use of rest-activity monitors seems to provide an excellent means of quantifying circadian disturbances and of determining the effectiveness of therapeutical interventions on the disturbed circadian rhythm of Alzheimer patients. Finally, we hypothesized that both the reduction of the amount of light input reaching the biological clock, as well as degeneration of SCN neurons may underlie the disturbances of circadian rhythms found in Alzheimer's disease.
References:


