Circadian Rest–Activity Rhythm Disturbances in Alzheimer's Disease

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Previous studies showed circadian rhythm disturbances in patients with Alzheimer's disease. Rest–activity rhythm disturbances manifest themselves through a fragmentation of the rhythm, a weak coupling with Zeitgebers, and high levels of activity during the night. The aim of the present study was to investigate which factors contribute to the presence of these disturbances. Therefore, several rest–activity rhythm, constitutional, and environmental variables were assessed in a heterogeneous group of 34 patients with Alzheimer's disease, including presenile and senile patients living at home or in a nursing home, as well as in 11 healthy controls. Circadian rest–activity rhythm disturbances were most prominent in institutionalized patients. Regression analyses showed the involvement of the following variables. First stability of the rest–activity rhythm is associated with high levels of daytime activity and high levels of environmental light resulting from seasonal effects as well as from indoor illumination. Presenile onset contributed to instability of the rhythm. Second, fragmentation of periods of activity and rest is associated with low levels of daytime activity, and is most prominent in moderately severe dementia. Third, night-time activity level is higher during the times of the year when the days are getting shorter and lower when the days are growing longer. These findings indicate that rest–activity rhythm disturbances may improve by increasing environmental light and daytime activity, an assumption for which empirical evidence has recently been published.

Key Words: Circadian rhythms, Alzheimer's disease, sleep, activity, light–dark cycle, suprachiasmatic nucleus, actigraphy

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Introduction

A great number of physiological and behavioral phenomena, including rest–activity, sleep–wakefulness, body tem-

perature, and hormone levels show a marked circadian (i.e. $\pm$ 24-hour) rhythm. It has been suggested that desynchro-

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nization of rhythms is involved in shift work and jet lag (cf. Reinberg and Smolensky 1983), but is of less importance in seasonal affective disorder (Wirtz-Justice et al 1993). Several findings indicate an attenuation of the circadian rhythm amplitude with aging (e.g., in body temperature, hormones, rest–activity, and sleep–wake rhythm). In Alzheimer's disease more prominent changes have been reported (for reviews, see Bliwise 1993; Van Gool and Mirmiran 1986; Van Someren et al 1993).

Animal experiments have shown that the hypothalamic suprachiasmatic nucleus (SCN) is of crucial importance for the generation and synchronization of circadian rhythms. This nucleus is considered to be the biological clock (Moore 1992). Environmental clues ("Zeitgebers"), especially light, synchronize the SCN rhythms to the 24-hour day, a mechanism referred to as "entrainment." The SCN receives information about the environmental light–dark cycle through a direct retinohypothalamic projection and an indirect retina–intergeniculate leaflet–hypothalamic projection (Moore 1992). Other entraining factors, for which the pathways are less well described, include physical activity, feeding times, and social contacts. Efferent SCN pathways include other hypothalamic nuclei, the thalamus, basal forebrain, and periaqueductal grey (Moore 1992), but the mechanisms by which these projections ultimately result in driving different circadian rhythms have only recently become the subject of investigation (Kalsbeek and Buijs 1992). The human SCN is considered to be homologous to that of rodents. This concerns not only the localization, afferents, efferents, and chemical neuroanatomy (Moore 1992) but also its functions, since a lesion in the suprachiasmatic region results in disturbed circadian rhythms (Cohen and Albers 1991; Schwartz et al 1986). Yet the evidence that the SCN is the only or predominant clock in the human brain is still limited at present.

The attenuation of circadian rhythms in elderly people and Alzheimer patients may thus result from changes at several levels: a reduction of environmental Zeitgebers or their appreciation, a loss of functionality of the biological clock, and deficiencies in one or more of the output systems driven by the clock. Several findings suggest that changes at all levels are indeed involved (Mirmiran et al 1992).

First, on the input side, elderly people and, even more so, Alzheimer patients expose themselves to significantly less bright environmental light than younger subjects (Campbell et al 1988). Also, light transmission through the eyeball and sensitivity of the visual system to light decline with age (Birren et al 1948; Boettner and Wolter 1962). In Alzheimer patients degeneration of the optic nerve and retinal ganglion cells has been reported (Blanks et al 1989; Hinton et al 1986; Katz et al 1989; Trick et al 1989). Thus,

entrainment is likely to be hampered by a reduction in perceived environmental light. Considering other Zeitgebers, physical activity and social contacts may also be limited in elderly people.

Second, age-related anatomical changes in the biological clock that are likely to have functional implications have been reported. In postmortem studies a reduced expression of vasopressin was found in the SCN of subjects over the age of 80 years, and an even more pronounced reduction occurred in Alzheimer patients (Swaab et al 1985). Recently, the number of vasoactive intestinal polypeptide expressing neurons was also found to be decreased in Alzheimer patients (Zhou et al 1995).

Although age-related changes at the third level, the output systems, have received little attention in chronobiological research, it is not unlikely that these systems function suboptimally. Since several of the output variables (e.g., physical activity and melatonin) are known to feed back on the biological clock, reduced output levels could in turn attenuate the input to the circadian system.

In elderly people, circadian rhythm disturbances may contribute to sleep and performance problems (Van Someren et al 1993). Restlessness during the night may be such a burden to the partner or primary caregiver that institutionalization is inevitable (Pollak and Perlick 1991; Sanford 1975). Circadian rhythm disturbances may also underlie so-called "sundowning" behavior (i.e., the relative increase in agitation in the late afternoon or early evening frequently reported in demented patients) (Vitiello et al 1992). In the nursing home, sundowning and nighttime restlessness continue to be a burden for the nursing staff. However, although the disturbances may be extreme in some patients, they are not obvious at all in others. From a clinical point of view, knowledge of the major factors involved in the development of the disturbance could guide therapeutic efforts. The objective of the present study was to investigate which factors are related to the severity of rhythm disturbances. To accomplish this, the nighttime activity level as well as the day-to-day variability and fragmentation of the actigraphically obtained rest–activity rhythm were assessed in three groups of Alzheimer patients, including 10 presenile patients (i.e., age of onset before 65 years) living at home, eight senile patients (i.e., age of onset after 65 years) living at home, and 16 institutionalized senile patients. Several factors involved in the generation and entrainment of circadian rhythms were assessed to evaluate their association with the rest–activity rhythm disturbances, including type of dementia (senile/presenile), housing condition (home vs. nursing home), gender, age, severity of the dementia, use of hypnotics or neuroleptics, damage to the eyes limiting the perception of light, environmental light exposure, season, and daytime activity level.

Methods

Subjects

Initially 42 Alzheimer patients were selected, but due to withdrawal of consent, aggressive behavior with the actigraph, removal of the actigraph and failing actigraphs, the number of successful recordings was limited to 34, including apparently agitated as well as sedentary patients. The diagnosis of probable Alzheimer's disease was based on medical history, a clinical evaluation including neurological and psychiatric examination, and laboratory assessments including electroencephalography, computed tomography, and blood examination. All patients met the criteria of "primary degenerative dementia of the Alzheimer type" according to the DSM-III-R (American Psychological Association 1987) and of "probable Alzheimer's disease" according to the NINCDS/ADRDA (McKahn et al 1984). To limit further the probability of including patients with multi-infarct dementia (MID), patients with a Hachinski Ischemic Score (Hachinski et al 1975) higher than 4 were excluded. The sample included 10 presenile patients living at home, eight senile patients living at home, and 16 senile institutionalized patients. Furthermore, a control group of 11 healthy elderly (72 ± 1.2 [SE] years of age) men living at home, of whom only one used (cardiovascular) medication was included. This group was not matched to Alzheimer patients on most variables, and merely served as a reference for rest-activity variables in healthy subjects. All subjects, or their partner or caretaker, were informed about the purpose and protocol of the study and signed an informed consent.

Assessment of Variables Describing Circadian Rest-Activity Rhythm Disturbances

The rest-activity level was measured continuously for 84-168 (on average 155) hours using the actigraphy methodology. The small ($57 \times 46 \times 22$ mm) and lightweight (70 g) wristworn actigraph (a miniaturized version of the actigraph described by Mirmiran et al [1988]) senses movement-induced accelerations, and is so sensitive that even small movements are detected. If a movement is detected a counter is activated and the input is blocked for 16 s. The number of counts per hour, a value between 0 and 225, is stored in an EEPROM memory read out off-line by an EEPROM-reader for further analysis. Alzheimer patients were recorded around the year and control subjects in March and April. From the actigraphy data three variables, described previously by Witting et al (1990), were calculated. The interdaily stability (IS) is the 24-hour value from the chi-square periodogram (Sokolove and Bushell 1978), normalized for the number of data, and gives an indication of the strength of coupling between the

rest-activity rhythm and Zeitgebers. IS is a signal-to-noise measure, calculated as the ratio between the variance of the average 24-hour pattern around the mean and the overall variance.

$$IS = \frac{n \sum_{h=1}^p (\bar{x}_h - \bar{x})^2}{p \sum_{i=1}^n (x_i - \bar{x})^2}$$

where n is the total number of data, p the number of data per day (in this study 24) $\bar{x}_h$ the hourly means, $\bar{x}$ the mean of all data, and x_i the individual data points. The intradaily variability (IV) gives an indication of the fragmentation of the rhythm (i.e., the frequency of transitions between rest and activity) and is calculated as the ratio of the mean squares of the difference between consecutive hours (first derivative) and the mean squares around the grand mean (overall variance). IV is based on hourly values and reflects transitions of relatively long periods of rest and activity, rather than frequent transitions of more and less activity as occurring in most daily pursuits.

$$IV = \frac{n \sum_{i=2}^n (x_i - x_{i-1})^2}{(n-1) \sum_{i=1}^n (x_i - \bar{x})^2}$$

The nighttime activity level (L5) is described by the mean of the 5-hour period with the lowest activity level in the average 24-hour pattern. High L5 values indicate nocturnal restlessness.

Assessment of Variables Describing Patient and Environment

Nominal variables were assessed by interviewing the patients and caregivers and checking the clinical dossier and included type of dementia (senile/presenile), housing condition (home vs. nursing home), gender, use of hypnotics or neuroleptics, damage to the eyes limiting the transmission of light in a significant way (i.e., cataract, glaucoma, loss of an eye, often in combination with macular degeneration). If the medical dossier only reported macular degeneration, this was not considered to be a sufficient condition for assignment to the visually deficient patient group, since macular degeneration appears to be present in most Alzheimer patients (Blanks et al 1989). Continuous variables included age, severity of the dementia, environmental light exposure, season, and daytime activity level. The degree of dementia at the time

Table 1. Overview of Group Characteristics

Group	n	M/F	Age	MMSE	Neuroleptics	Visual Deficit	Minutes Outdoors	Light {log}	M10	IS	IV	L5
Controls	11	11/0*	72 (1.2)*						134 (8)	0.69 (0.04)	0.62 (0.06)	11 (3)
Presenile/home	10	2/8	60 (1.8)*	16.0 (1.2)			1073 (159)*	2.63 (0.11)	136 (11)	0.64 (0.05)	0.79 (0.11)	19 (5)
Senile/home	8	4/4	78 (2.6)*	13.3 (1.9)	1	2	519 (193)*	2.57 (0.24)	131 (9)	0.69 (0.04)	0.79 (0.05)	15 (3)
Senile/institutionalized	16	3/13	86 (1.6)*	4.4 (1.4)*	5	3	43 (16)*	2.40 (0.07)	87 (14)*	0.49 (0.05)*	0.85 (0.10)	16 (2)

Columns indicate, respectively: group (age of onset before (presenile) or after (senile) 65 years of age and living at home or institutionalized); n, number of subjects per group; m/f, proportion of male (m) and female (f) patients; average age and standard error of the mean (s.e.); MMSE, average Mini Mental State Examination and s.e.; number of subjects using hypnotics or neuroleptics; number of patients with a severe visual deficit; minutes outdoors, minutes spent outdoors during one week; light {log}, logarithm of the light intensity (in lux) as measured at the place where the patient was usually seated; M10, average daytime activity level; IS, interdaily stability; IV, intradaily variability; L5, average nighttime activity level. An asterisk (*) indicates that the group differs on this variable from other groups in the multiple comparison using Fisher's PLSD, $p < 0.05$.

of the actigraphic recordings was evaluated using the Mini Mental State Examination (MMSE; Folstein et al 1975). Two procedures were followed to estimate the exposure of Alzheimer patients to environmental light. First, the average indoor light intensity was approximated by a single measurement (BBC Goertz Metrawatt MX 4 lux-meter) of the light intensity at the place where the patient was usually seated. In most cases, the indoor light intensity depended mainly on the electric illumination, and was hardly influenced by day-to-day changes in the outdoor brightness reaching the patient through windows. However, in a few patients, favorably positioned in front of a window, the single measurement may have been somewhat less reliable. Since the light-intensity registrations diverged widely, a log transform was applied to the raw data, in agreement with Okudaira et al (1983) and Witting et al (1993). Second, since the intensity of outdoor light is usually several times higher than that of indoor light, even when it is not sunny, caregivers kept a log of the time spent outdoors during 1 week. No light intensity or hours outdoors data were available in the control group, but given the active lifestyle of this group it is likely that they spent more time outdoors and exposed themselves to more bright light than the Alzheimer patients, as was previously reported by Campbell et al (1988). Since patients were registered throughout the year and time-of-year effects are known to exist in (for example, seasonal affective disorder) (Rosenthal et al 1984) and a neuronal population of the SCN (Hofman and Swaab 1992; Hofman et al 1993), rest-activity assessment might be influenced by the season of registration. Therefore, the time of year of the recording was expressed in two variables included in the regression analyses: the average day length and the rate of change during the week of registration. The rate of change was calculated as the first derivative of the day length, (i.e., the average day length during the week of registration minus the average day length during the previous week). The daytime activity level was derived from the actigraphic output and calculated as the mean of the 10-hour period with the highest activity level (M10) in the average day.

Although M10 is, like IS, IV and L5, derived from the actigraphic output, the variables are not intrinsically dependent on each other. Also, whereas IS, IV, and L5 reflect rhythm disturbances, M10 merely describes the average daytime activity level. An increase in activity level may either improve or worsen IS and IV, depending on whether the increase occurs at random times of the day or in a scheduled way. High M10 values indicate an active lifestyle, which, in Alzheimer patients, may indicate pacing behavior. Low M10 values indicate that the subject leads an inactive life.

Statistical Analyses

Between-group differences (control group and three groups of Alzheimer patients) were tested using analyses of variance (ANOVAs), which in case of significance were followed by multiple comparisons using Fisher's Protected Least Significant Difference (PLSD; Milliken and Johnson 1984). Chi-square tests were applied to nominal data. Furthermore, a backward stepwise regression analysis was performed on the data of Alzheimer patients, to investigate how the three variables describing circadian rhythm disturbances were related to other variables, and to deconfound possibly correlated predictors. Twelve predictors were introduced in each of the three regression analyses: dementia type (senile/presenile), housing condition, gender, use of hypnotics or neuroleptics, visual deficit, age, dementia severity (MMSE), indoor light intensity, minutes outdoors per week, day length, rate of change in day length, and activity level. Critical significance levels of 0.05 were applied in all tests; in the regression analyses the critical F-values were set to 4.14, corresponding roughly to a significance level of 0.05 for any single test (Neter et al 1990).

Results

Subject and Group Characteristics

Table 1 gives an overview of the characteristics of the

groups. The control group and Alzheimer groups all differed significantly from each other in age (group effect: $p < 0.0001$, Fisher's PLSDs < 0.05). Furthermore, the institutionalized patients were more severely demented than the two groups of patients living at home according to the MMSE (group effect: $p < 0.0001$, Fisher's PLSDs < 0.05). Chi-square tests indicated group differences in the proportion of the genders ($p < 0.0001$), which was due to the absence of females in the control group, since no significant differences were found between the patient groups. No significant differences between the Alzheimer groups were found regarding the use of hypnotics or neuroleptics (used by six patients) or the presence of a severe visual deficit (present in five patients).

Light Exposure

The means of the light exposure variables for the Alzheimer patient groups are also summarized in Table 1. All patient groups differed significantly from each other regarding weekly minutes spent outdoors (group effect: $p < 0.0001$, Fisher's PLSDs < 0.05), whereas no significant differences were found between the groups regarding light exposure as measured at the place where the patient was usually seated. The measured light intensities typically varied around 240 lux (median value), although some outliers, favorably positioned in front of a window, were exposed to intensities of over a 1000 lux (maximum 4000 lux), resulting in a mean intensity of 521 lux for the whole sample.

Activity Level

Institutionalized Alzheimer patients were less active than Alzheimer patients living at home and control subjects (M10 group effect: $p < 0.007$, Fisher's PLSDs < 0.05).

Circadian Rest-Activity Rhythm Disturbances

An activity plot was made of each registration. Observation of these plots suggested rhythm disturbances in some, but not all, Alzheimer patients (see Figure 1). Furthermore, none of the plots clearly indicated sundowning behavior, which should be reflected in an increased activity during the late afternoon or evening. Figure 1 shows examples of regular and disturbed rhythms. The means of the rest-activity variables for the control subjects and the three Alzheimer groups are summarized in Table 1 and visualized in Figure 2. The rhythms of the institutionalized Alzheimer patients were less stable than the rhythms of Alzheimer patients living at home and control subjects (IS group effect: $p < 0.02$, Fisher's PLSDs < 0.05). The four groups did not differ significantly on IV and L5.

Backward Stepwise Regression Analysis

The regression analysis showed several variables associated with rhythm disturbances, which are summarized in Table 2. For the interdaily stability, four significant predictors accounted for 70% of the variance. A low interdaily stability was associated with a low daytime activity level, short days, presenile onset, and a poorly illuminated environment. For the intradaily variability two significant predictors accounted for 58% of the variance. A high intradaily variability was associated with a low daytime activity level and a high MMSE score (i.e., less severe dementia). For nighttime activity only one of the predictors reached significance. Nighttime activity level was higher when the shortening of the days was most prominent (in the fall).

Discussion

In summarizing the findings of the present study, circadian rest-activity rhythm disturbances as indicated by a low interdaily stability were found predominantly in institutionalized Alzheimer patients. Although the intradaily variability and nighttime activity tended to be higher in Alzheimer patients than control subjects, the group differences did not reach significance. The daytime activity level of institutionalized patients was significantly lower than that of control subjects and Alzheimer patients living at home.

Backward stepwise regression analyses revealed that interdaily stability and intradaily variability were both strongly associated with a daytime activity. This interrelatedness does not result from an intrinsic mathematical dependence and means that high levels of daytime activity occur in an organized way rather than at random, resulting in a relatively intact organization of the circadian rhythm. Since high levels of daytime activity in Alzheimer patients may result from pacing, this behavioral "disturbance" may actually be related, or even beneficial, to the preservation of the circadian organization. It was reported previously that pacing is associated with a better general health in nursing home residents (Cohen-Mansfield et al 1991).

The regression analyses furthermore indicated, after the effect of activity level is partialled out, the importance of environmental light. A low interdaily stability was associated with low levels of light, as measured both by the day length and the indoor light intensity. The nighttime activity level was lowest during spring and highest during fall.

Furthermore, two constitutional factors appeared to be related to rhythm disturbances. Presenile onset contributed to instability and the severity of the dementia correlated negatively with intradaily variability.

Figure 1. Examples of activity plots in Alzheimer patients. Each bar represents the activity counts in 1 hour. The upper panel (A) shows a rhythm that does not differ significantly from rhythms of control subjects. Panel B shows the rhythm of a patient with a low interdaily stability (IS), panel C a patient with a high intradaily variability (IV), and the lower panel (D) a patient with both low IS and high IV.

Before we can reach a conclusion, several issues concerning the methodology of the present study have to be addressed. Research on demented patients inherently limits freedom of choice in assessed variables. First, there are

more elaborate psychometric instruments for the evaluation of the severity of dementia than the presently used MMSE. However, lengthy testing of patients is not always possible. Still, significant effects were found with the

Figure 2. Individual scores (dots) and mean values (bars) of the control group (C) and Alzheimer patients classified into three groups: presenile living at home (PH), senile living at home (SH), and senile institutionalized (SI). The panels visualize the rest-activity variables Interdaily Stability (IS, upper), Intradaily Variability (IV, middle) and nighttime activity level (L5, lower). Note that all Alzheimer groups tend to deviate (nonsignificantly) from control scores on the variables IV and L5, while deviant scores on IS are found predominantly in senile institutionalized Alzheimer patients (statistically significant).

MMSE in the present study. Second, for the assessment of environmental light a single measurement of the indoor light intensity, combined with a log on the time spent outdoors, cannot be considered as optimal. Actigraphs equipped with a light sensor that continuously measures environmental light are presently available, but they still have the drawback that they do not measure the actual light intensity that reaches the retina, which depends on several aspects of the eye (e.g., diameter of the pupil and light transmission through the eyeball). We also have the experience that continuous assessment in Alzheimer pa-

tients is facilitated by hiding the actigraph under the sleeves, in which case an integrated light sensor is of no use. Still, our single measurement of indoor light intensity was found to be significantly related to interdaily stability. Third, the assessment of the circadian rhythm was limited to the rest-activity rhythm, since it is difficult to measure other circadian output variables (e.g., body temperature, plasma melatonin, or polysomnographical sleep-wake state) in noncomplying subjects such as Alzheimer patients. Prinz et al (1984), for example, reported a failure to register rectal temperature in 22 of 28 Alzheimer patients.

Table 2. Results of Backward Stepwise Regression

IS: $R^2 = 0.70$, $F = 17.10$, $df = 4.29$, $p < 0.0001$			
Predictor	beta	F	p
M10	0.80	53.53	0.0001
Day-length	0.34	7.79	0.01
Senile onset	0.28	4.89	0.04
Light	0.23	4.71	0.04
IV: $R^2 = 0.58$, $F = 21.41$, $df = 2.31$, $p < 0.0001$			
M10	-0.83	42.57	0.0001
MMSE	0.39	9.48	0.004
L5: $R^2 = 0.13$, $F = 4.68$, $df = 1.32$, $p < 0.04$			
Day length change	-0.36	4.68	0.04

Results of the backward stepwise regression analysis to determine predictors for the level of, from top to bottom, IS, IV, and L5. R^2 , Coefficient of multiple determination; F, F-statistic; df, degree of freedom; beta, standardized partial regression coefficient; p, significance.

In previous research (Witting et al 1990) we found that most patients tolerate wearing an actigraph sensitive enough to assess rest-activity rhythm disturbances of clinical importance. Fourth, the control group existed of healthy men, and were not matched for gender or season of measurement with the Alzheimer patients. In a previous study, no gender differences were found in the actigraphically obtained rest-activity data of healthy elderly subjects (Van Hilten et al 1993). Seasonal influences on objectively assessed rest-activity rhythms in healthy elderly people have, nevertheless, to our knowledge, not yet been reported. Thus, the control group data should be interpreted merely as a reference for rhythm variables, and the aim of the present study was to investigate possible factors associated with rest-activity rhythm disturbances within a heterogeneous group of Alzheimer patients.

The findings will now be discussed in some more detail. The most obvious explanation of the finding that rhythm disturbances mainly occur in institutionalized Alzheimer patients is that patients developing rhythm disturbances are the most likely candidates for institutionalization: home care becomes extremely difficult when patients lose their day-night rhythm. Behavioral restlessness has indeed been mentioned as an important cause of institutionalization (Pollak and Perlick 1991; Sanford 1975). Another possibility is that rhythm disturbances follow and result from institutionalization. We are aware of only one follow-up study on the sleep patterns of healthy elderly people moving into a nursing home. Clapin-French (1986) studied the subjective experience of sleep quality and reported earlier bedtimes, more napping, and interrupted sleep following admission. Other polysomnographic (Kerkhof and Wauquier 1993) and actigraphic (Ancoli-Israel et al 1989; Jacobs et al 1989) studies indicated rhythm fragmentation in institutionalized elderly people.

However, these studies were of a comparative design and consequently do not indicate whether the rhythm disturbances followed or induced institutionalization. In conclusion, more follow-up studies have to be performed in order to reveal cause and effect. As a consequence of the finding that rhythm disturbances are found predominantly in institutionalized Alzheimer patients, one should be cautious with the generalization of the finding of SCN deterioration in Alzheimer patients (Swaab et al 1985), since the material was obtained exclusively from formerly institutionalized patients.

The second main finding of the present study is that daytime activity level appears to be of central importance in circadian rest-activity rhythm disturbances. This indicates that high levels of daytime activity occur in an organized way. With a lack of high activity levels, IS and IV indicate that the remaining periods of little and very little or no activity occur in a random way. As stated in the introduction, the activity level functions as an output as well as an input of the circadian timing system. Since physical activity was found to enhance circadian amplitude in mice (Welsh et al 1988) and circadian entrainment in mice (Edgar and Dement 1991), hamsters (Van Reeth et al 1992), and humans (Schmidt et al 1990) (i.e., to be an input factor), it may be hypothesized that rhythm disturbances found in Alzheimer patients partly result from a low level of activity. This contention is supported by immobilization studies in healthy human subjects. Winget et al (1972) and Campbell (1984) found that hypokinesia induced by forced bed rest disturbs sleep and depresses the mean and amplitude of the body temperature rhythm, which moreover tend to become desynchronized with the environment. It is thus tempting to suggest that an increase in daytime activity improves circadian organization (Van Someren et al 1994).

The third main finding is that environmental light is of central importance in the occurrence of rest-activity rhythm disturbances. The rhythm tends to be less stable with poor indoor illumination and shorter days (winter), both indicators of the amount of daily bright light. Nocturnal restlessness is most prominent during fall, when the days shorten at the highest rate. These findings appear to be related to the changes in SCN cell number that parallel changes in day length. In the postmortem human SCN of subjects younger than 50 years, the number of vasopressin- (VP) expressing cells is low during the summer, when days are long, and elevated during fall. This annual rhythm disappears with aging (Hofman and Swaab 1992, 1995). The integration of the present functional findings and the previous anatomical findings suggests that more VP cells are probably activated both when environmental illumination is low and when the days are shortening at a high rate, and that in elderly people the VP cells may have subop-

timal activation. In Alzheimer patients the decreased VP cell population (Swaab et al 1985) may completely fail to live up to these demands, resulting in a prominent appearance of rhythm disturbances in fall and winter. Given the importance of environmental light for the entrainment of circadian rhythms and some positive results of bright light therapy in demented patients (for a review, Van Someren et al 1993), the present study further subscribes to the application of bright light in the management of rhythm disturbances in Alzheimer's disease.

Two constitutional variables were associated with rhythm disturbances. First, the rhythms of presenile patients were the least stable. This finding may again be related to changes in the SCN: presenile Alzheimer patients have less vasoactive intestinal polypeptide- (VIP) expressing neurons than senile patients (Zhou et al 1995). Second, the intradaily variability was found to be negatively correlated with the severity of the dementia. Thus, with increasing severity of the dementia the rest-activity rhythm tends to be less fragmented, although it is still more fragmented than in elderly controls. A somewhat similar finding was reported by Reisberg et al (1989b), who found that the incidence of sleep disturbances shows an inverted U relation with the degree of dementia as assessed with the Global Deterioration Scale (GDS). Our finding of a decline in the severity of rest-activity fragmentation parallels part of Reisberg's inverted U relation as we estimate that, given the strong relation between GDS and MMSE values (Reisberg et al 1989a), 85% of our patients would have been categorized in GDS scales 5, 6, and 7, which formed the descending part of the sleep disturbance incidence inverted U curve.

The contradictory results of previous reports on rest-activity rhythm disturbances in Alzheimer patients appear to support both the inverted U relation between the severity of the dementia and the rhythm disturbance, as described above, and the involvement of institutionalization. Aharon-Peretz et al (1991) performed an actigraphy study on mildly to moderately demented Alzheimer patients living at home and found a relatively normal rest-activity rhythm that did not differ from that of control subjects. Erkinjuntti et al (1987) studied restlessness during sleep in Alzheimer patients and reported that movements are present for 38% of the time in bed in mildly demented patients and for 48% of the time in bed in moderately and severely demented patients, compared to 10% in healthy age-matched control subjects. The housing condition of the patients was not reported on, but institutionalization is likely given the severity of the dementia. Witting et al (1990) studied in-patients, mostly with a GDS of 5, and found clear rhythm disturbances, as would be predicted from Reisberg's inverted U curve in sleep disturbance incidence, which peaked at this severity

score (Reisberg et al 1989b). Allen et al (1987) studied very severely demented institutionalized Alzheimer patients and reported that their activity shows a 24-hour pattern that differs only slightly (in amplitude) from that of control subjects. Furthermore, within this group of very severely demented patients, sleep during daytime was negatively correlated with the severity of dementia. Campbell et al (1986) found no differences in activity rhythm between elderly controls and Alzheimer patients, but did not report on the severity of the dementia or housing condition. One study does not seem to support the inverted U hypothesis: whereas modest rhythm disturbances would be predicted, strong disturbances were reported by Satlin et al (1991) in very severely demented institutionalized Alzheimer patients. However, this group contained no patients with a less severe dementia, whose rest-activity rhythm might, theoretically, be even more disturbed. Thus, in general, rest-activity disturbances appear to be most pronounced in institutionalized patients with a dementia of intermediate severity.

In conclusion, the present study investigated which factors are involved in the disturbances of the circadian timing system in Alzheimer patients, as reflected in one of its outputs: the rest-activity rhythm. On the input side of the circadian timing system, activity level and environmental light appeared to be involved. Of the variables considered to reflect deterioration of the "hardware" of the circadian timing system (eyes, type and severity of the dementia) both type (presenile/senile) and severity (MMSE) of the dementia appeared to be involved. The seasonal effect on the rest-activity rhythm, for the first time described in the present study, may be seen as an effect of either "input" or "hardware," since the light-induced seasonal fluctuation in VP expression in the SCN is absent in the elderly (Hofman and Swaab, 1992, 1995; Hofman et al 1993). Although it must be stressed that the present study had a correlative character, the results suggest that efforts directed towards an increase of the input of the circadian timing system may improve rhythm disturbances. Attempts to enhance the day-night rhythms of Alzheimer patients with bright light have been successful (e.g., Okawa et al 1993; Satlin et al 1992). The association of nighttime arousals with low interdaily stability stresses the importance of undisturbed sleep: nighttime noise levels in nursing homes are quite high (Schnelle et al 1993) and reducing these is likely to be therapeutic. It may be difficult to increase physical activity in Alzheimer patients in order to improve rhythms, and no studies investigating its effect on circadian rhythms have been reported. However, some studies on healthy elderly people report positive effects on either daytime functioning (e.g., Dustmann et al 1990; Shay and Roth 1992) or nighttime sleep (Bevier et al 1992; Edinger et al 1993;

Vitiello et al 1992). These and other nonpharmacological therapies (for a review, see Van Someren et al 1993) deserve serious attention in the management of rhythm disturbances in Alzheimer patients.

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