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CHAPTER 3

The rest-activity rhythm and physical activity in early-onset dementia

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Abstract

Background: A substantial part of elderly persons with dementia show rest-activity rhythm disturbances. The rest-activity rhythm is important to study in people with early-onset dementia (EOD) for rest-activity rhythm disturbances are predictive of institutionalization, and caregivers of young patients suffer from high distress.

Objective: The aim of this study was to study 1) whether EOD patients have more rest-activity rhythm disturbances compared with cognitively intact adults; and 2) which factors contribute to a disturbed rhythm.

Methods: We included 61 patients with EOD (mean age: 61.9 (4.9) y, 41 (67%) men) and 67 cognitively intact adults (mean age 61.6 (4.5) y, 28 (41%) men). Rest-activity rhythm was assessed by actigraphy.

Results: EOD patients tended to have higher intradaily variability (0.46 (0.16) and 0.39 (0.10), $p = .03$). EOD patients also lay for a longer time in bed (time in bed: 08:49 (0:51) h and 08:07 (0:47) h, $p < .001$) and needed more time to fall asleep (sleep onset latency: 23 (22) min and 15 (15) minutes, $p = .02$). Disturbances in the rest-activity rhythm were predicted by a low level of physical activity, use of antidepressants and central nervous system neurological medications, and being male.

Conclusion: EOD patients showed more variability in the rest-activity rhythm compared with cognitively intact adults. The main predictor for rest-activity rhythm disturbances was a low level of physical activity.

Introduction

The rest-activity rhythm is one of the 24-hour circadian cycles seen in healthy individuals.¹ The rest-activity rhythm is produced by a complex interaction of both endogenous and exogenous factors.¹ A strong rest-activity rhythm is important because sleep has restorative functions that are vital for maintaining physical and mental wellbeing.² Alterations in the biological clock, the hypothalamic suprachiasmatic nucleus, may cause disruptions in the rest-activity rhythm. These disruptions occur in aging³ and are exaggerated in dementia.⁴ Approximately two third of the patients with dementia show disturbances in the rest-activity rhythm.^{5,6} A fragmentation of the rhythm, as reflected by a heightened intradaily variability (IV) measured by actigraphy,⁷ has been observed in most subtypes of dementia⁴ and may be present already in early stages of the disease.^{8,9} High IV is characterized by multiple short naps during the day in combination with nocturnal restlessness. When the suprachiasmatic nucleus becomes affected by neurodegenerative disease, external signs become more important to preserve a good rhythm.¹⁰ Physical activity is one of these external signs and is strongly related to the rest-activity rhythm.¹¹

Many studies focus on rest-activity rhythm disturbances in persons with late onset dementia (LOD). As patients with early-onset dementia (EOD) often present with a different disease course than patients with LOD,¹² it is not sensible to generalize findings from rest-activity rhythm studies from a LOD to an EOD population. In EOD, the rest-activity rhythm has not been studied extensively. One study examined patients with EOD as a subpopulation (n = 10). Results have shown that an early onset was associated with a lower stability of the rest-activity rhythm over days.¹³ The clinical relevance of further studying the rest-activity rhythm in EOD patients is that, next to the finding that disturbances in the rest-activity rhythm may increase caregiver burden,^{5,14} caregivers of patients with EOD have additional higher distress levels than caregivers of patients with LOD.¹⁵ Because of the young age, a double burden arises for caregivers, considering social roles such as breadwinning

and parenting. Moreover, disturbances in the rest-activity rhythm are among the highest predictors of institutionalization in LOD.^{5,16} Therefore, the aims of the present study were 2-fold: to study 1) whether patients with EOD have more rest-activity rhythm disturbances compared to cognitively intact adults of the same age; and 2) which demographic, clinical, and lifestyle factors contribute most to a disturbed rhythm in EOD.

Methods

DESIGN

The present study made use of a cross-sectional design. The medical ethics review committee of the VU University Medical Center (VUmc) approved the study. We obtained written informed consent of each participant and his/her caregiver.

PARTICIPANTS

We studied 61 patients with EOD and 67 cognitively intact subjects. Patients with EOD were recruited mainly in the VUmc Alzheimer Center in Amsterdam, the Netherlands. The cognitively intact controls were recruited using printed information leaflets. Diagnoses were based on multidisciplinary consensus according to established clinical criteria.¹⁷⁻²¹ Detailed descriptions of the recruitment process are provided elsewhere.²²

Inclusion criteria for EOD patients were the following: 1) diagnosis of EOD (onset of complaints below 66 y); 2) mild to moderate stage of dementia (Mini Mental State Examination (MMSE)²³ score > 15); and 3) the presence of a primary caregiver. *Exclusion criteria* were: 1) wheelchair bound; 2) diagnosis of a neurodegenerative disease that primarily results in motor impairments; 3) diagnosis of serious cardiovascular disease; 4) substance abuse; 5) head injury involving loss of consciousness > 15 minutes in the medical history;

6) severe psychiatric illness; 7) severe visual problems; 8) severe hearing problems; and 9) insufficient mastery of the Dutch language.

Inclusion criteria for cognitively intact participants were: 1) age between 55 and 70 years; and 2) normal cognitive status (MMSE > 25). *Exclusion criteria* were: acute or chronic health problems, and, in addition, exclusion criteria 1, and 4 to 9 as applied in the EOD group.

Demographic, clinical, and lifestyle factors: age, sex, sedative medication, antidepressants, central nervous system (CNS) neurological medications, and the level of physical activity. We only included current medications. For each participant, we added the number of medications in each category. CNS neurological medications included medications for neurological disorders (i.e. antiepileptic drugs, drugs for neurodegenerative disorders, etc) and not for psychiatric disorders of the CNS. Physical activity (steps per day) was measured using a pedometer (OMRON HJ-113, OMRON Healthcare CO. Ltd. Kyoto, Japan). The pedometer was worn for 7 consecutive days. The number of steps was recorded in a diary.

MATERIAL AND PROCEDURE

WRIST-ACTIGRAPHY

The Actiwatch-4 (AW4) activity monitor (Cambridge Neurotechnology, Ltd., Cambridge, Great Britain) was used to measure rest-activity rhythm and sleep variables. The actiwatch detects motor activity by a piezoelectric sensor. It was set to sum the activity counts in 1-minute epochs. The actiwatch was worn on the dominant wrist for seven consecutive days and nights.⁷ Actigraphy has been recommended to explore rest-activity rhythm in patients in dementia.⁴ Participants kept a sleep diary in which they recorded bed and waking times. Assistance was provided by the caregiver when needed. In the actigraphic data, periods larger than 1 hour with missing data (because of bathing or when participants forgot to wear the actiwatch) were removed from analyses.

REST-ACTIVITY RHYTHM ANALYSIS

We analyzed the data using Actiwatch Sleep Analysis Software, 2001, version 1.06, Cambridge Neurotechnology. The following non-parametric variables of the rest-activity rhythm were calculated (for a more detailed description see Van Someren, 1999)²⁴:

- **Intradaily Variability (IV):** The degree of fragmentation of periods of rest and activity. Typically, the rest-activity rhythm of a healthy person includes 1 major rest period (nighttime) and 1 major active period (daytime) every 24-hour cycle. Values range from 0 to 2, with higher values indicating a more fragmented rhythm.
- **Interdaily Stability (IS):** The regularity in the rest-activity rhythm over days. It also gives an indication of the strength of the coupling between the rest-activity rhythm to Zeitgebers. Scores range from 0 to 1, where 0 indicates a total lack of rhythm and 1 indicates a perfectly stable rhythm.
- **Relative Amplitude (RA):** The normalized difference between the most active 10-hour period in the 24-hour cycle (M10) in relation to the uninterrupted least active 5-hour period (L5). Values range from 0 to 1, with higher values indicating a higher amplitude, meaning a larger difference between daytime activity and nighttime rest and therefore a stronger rhythm.

SLEEP ANALYSIS

Sleep variables were calculated using Respirationics software for the actiwatch (Philips, 2008).

- **Time in bed (hours and minutes):** Major rest intervals were automatically derived in Respirationics. Respirationics based these rest intervals on the amount of activity in a period. Patients with dementia are known to be restless during the night.⁴ Owing to this abnormal high nighttime activity, Respirationics might falsely consider the restlessness as a wake period. Therefore, when the start and end times of the automatically derived rest interval deviated more than one hour from start and end time of the rest interval as reported in the sleep diary, we neglected the automatically derived interval and used the rest interval as recorded by the participant.
- **Total sleeping time (hours and minutes):** The amount of actual sleep time.

- **Onset latency (minutes):** The period of time from bedtime to the onset of sleep.
- **Sleep efficiency (percentage):** Actual sleep time expressed as a percentage of time in bed.
- **Wake after sleep onset (WASO: minutes):** The period of time that a person is awake after falling asleep.
- **Wake bouts:** The number of times a person is awake after falling asleep.

STATISTICAL ANALYSIS

For statistical analysis we used SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL).

Values were represented as mean (SD) unless otherwise stated. Sleep and rest-activity rhythm variables were not normally distributed and were transformed using van der Waerden transformation. The van der Waerden transformation converts raw scores into Z-scores corresponding to the estimated cumulative proportion of the distribution equivalent to a particular rank.²⁵ The RA variable was not conform to the normal distribution after van der Waerden transformation. Group differences were considered using independent sample *t*-test, Mann-Whitney *U* test, and χ^2 -tests when appropriate. Effect sizes were calculated in terms of standardized mean differences (Cohen's *d*).²⁶ A Cohen's *d* of 0.2, 0.5 and 0.8 were considered as small, medium and large effect sizes, respectively. Because of multiple comparisons *p*-values were set at .01. *p*-values between .01 and .05 were considered a trend.

Forward multiple linear regression analysis (stepwise) in the entire sample was used to establish which demographic, clinical, and lifestyle factors contributed to a disturbed rest-activity rhythm. IV, IS, and RA were the dependent variables (each in separate analysis). Independent variables were age, sex, sedative medication, antidepressants, CNS neurological medication, mean steps per day, and group, and were entered stepwise (forward). The interaction between group and the significant predictors was assessed

to establish whether the relation was the same for the EOD group and the control group. Probability for entry was set at .05 and removal was set at .10. In case of significant predictors, we repeated the multiple regression analyses in the EOD group exclusively, to study whether the found relationships were the same for patients with AD and patients with other subtypes of EOD. Independent variables were significant predictors from the main analyses and diagnosis, that is, AD versus non-AD.

Results

GROUP DIFFERENCES

An overview of the group differences is given in Table 1 (p. 56). MMSE score was lower in the EOD group, $U = 235.5$, $p < .001$. Males were overrepresented in the EOD group, $\chi^2(1) = 9.22$, $p = .003$. Patients with EOD used more antidepressants, $\chi^2(1) = 10.94$, $p = .001$, and more CNS neurological drugs, $\chi^2(1) = 52.08$, $p < .001$.

REST-ACTIVITY RHYTHM MEASURES

Comparisons showed that IV tended to be higher in EOD patients than in controls, that is, patients with EOD had more fragmentation of the rest-activity rhythm within 24 hours, with a small to medium effect size: $t(113) = 2.19$, $p = .03$, and $d = 0.39$. IS and RA were not different between groups.

MEASURES OF SLEEP

Patients with EOD spent more time in bed and tended to need more time to transition from wakefulness to sleep compared with controls, showing a large (time in bed) and small to medium (onset latency) effect size: $t(128) = 4.69$, $p < .001$, $d = 0.83$; onset latency: $t(128) = 2.43$, $p = .02$, $d = 0.43$. No differences were observed in total sleep time, sleep efficiency, WASO, and the number of wake bouts.

ASSOCIATIONS BETWEEN IV, IS, AND RA AND DEMOGRAPHIC, CLINICAL, AND LIFESTYLE FACTORS

An overview of the regression coefficients (B), standard errors (SE), 95% confidence intervals (95% CI), standardized regression coefficients ($Beta$) and the proportions explained variance, is given in Table 2 (p. 57).

Higher IV, that is, more fragmentation of the rhythm within 24 hours, was associated with a lower mean number of steps per day, the use of antidepressants, and the use of CNS neurologic medication. The best fitting model explained 18.3% of the variance ($F(3,118) = 8.82, p < .001$).

The model that most strongly predicted IS, that is, the stability of the rhythm over days, only included mean steps per day. A lower daily step count was predictive for a less stable rhythm over days, which explained 11.1% of the variance ($F(1,120) = 14.94, p < .001$).

Finally, a lower amplitude of the rhythm, that is, a less strong rhythm, was associated with being male, which accounted for 6.4% of the variance ($F(1,120) = 8.25, p = .005$). There were no interactions present between group and the main predictors, and therefore the associations are the same for the EOD group and the control group.

The multiple regression analyses predicting IV, IS, and RA in the EOD group exclusively showed similar Beta's (IV: mean steps per day $\beta = -.31, p = .02$, antidepressants: $\beta = .24, p = .07$, CNS neurological medication $\beta = .17, p = .20$; IS: mean steps per day $\beta = .30, p = .03$; RA: sex $\beta = .10, p = .43$). The results were the same for patients with early-onset AD and patients with other subtypes of EOD (diagnosis: IV: $\beta = .09, p = .49$; IS: $\beta = -.10, p = .47$; RA: $\beta = -.03, p = .81$).

Discussion

The main findings of this study are that EOD patients tended to have higher IV, spent more time in bed, and tended to have longer onset latency before falling asleep. Furthermore, disturbances in rest-activity rhythm variables

were associated with a low level of physical activity, medication use, and being male.

The higher IV implies a more fragmented rhythm within 24 hours in the EOD group. Although the patients with EOD have higher IV than the controls, IV values are lower when compared to research in the LOD group (present study: $IV = 0.46$, LOD patients: $IV \approx 0.80$).^{13,27} One study determined the rest-activity rhythm of a small subset of patients with EOD ($n = 10$).¹³ In this study, the IV was 0.79, similar to the studies in patients with LOD. The difference with the present study might be explained by dementia severity: the mean MMSE score was lower in that study (16 (1.2)) than in our study (24 (3.6)). This might indicate that IV is already increased in mild to moderate stages of EOD and becomes even more disturbed in more severe stages of EOD. Furthermore, patients with EOD spent on average 8:43 hours per 24 hours in bed, while cognitively intact adults of the same age spent 8:07 hours in bed. These results are similar to previous findings in which older patients with AD were compared to healthy older adults.²⁸⁻³⁰ Also, EOD patients needed more time to fall asleep than cognitively intact adults.³⁰ The clinical relevance of the above mentioned findings is that disturbances in the rest-activity rhythm increase caregiver burden,^{5,14} whereas caregivers of patients with EOD already have high distress levels.¹⁵ We did not observe differences between groups concerning the IS, RA, the time being awake after sleep onset, the sleep efficiency, and the total sleep time, which is in contrast to studies on LOD.^{13,30,31} The differences between those studies and the present study might be because of the age and/or dementia severity of the participants. It is known that age is negatively correlated with the rest-activity rhythm.³

We have shown that IV and IS are predicted by the level of physical activity. Patients with lower levels of physical activity have higher IV, that is, a more fragmented rhythm within 24 hours, and lower IS, that is, a less stable rhythm over days. This holds for both EOD patients and cognitively intact adults of middle age. This finding is consistent with previous findings that have shown that healthy middle-aged and older adults and patients with LOD, who

have higher levels of daytime physical activity, have more stable and less fragmented rest-activity rhythms.^{13,31,32} This finding is of particular importance for these young patients, because they are more capable of performing physical activity than elders, and hence can adopt more easily an active lifestyle, which might be beneficial for the rest-activity rhythm. A high level of physical activity is associated with other health benefits such as lower body mass index,³³ better mood,³⁴ and less cardiovascular risk factors.³⁵ Higher levels of physical activity are also related to better cognitive functioning.³⁶ Moreover, when walking is performed outside and accompanied by others, it may also increase light exposure and social activity; factors that are associated with a better rest-activity rhythm.²⁴ IV was also explained by the use of antidepressants and CNS neurological medication. It is known that antidepressants have a negative effect on the rest-activity rhythm.³⁷ Finally, RA was explained by sex. Being male was associated with a lower amplitude of the rest-activity rhythm, and hence a less strong rhythm. This is in correspondence to a previous finding in healthy persons of middle age.³⁸

This is the first study that compared the rest-activity rhythm of patients with EOD to that of cognitively intact adults of the same age. A strength of this study is that variables concerning the rest-activity rhythm and physical activity were measured using objective methods. Limitations are that we did not consider factors that may have also affected the rest-activity rhythm such as the amount of light exposure (day length, indoor light exposure) or seasonal influence.³⁹ However, both patients with EOD and controls were included during the entire year, and therefore patients and controls were included in all seasons, decreasing the effect of seasonal influence when studying the differences in the rest-activity rhythm between the groups. In addition, with respect to the association between the rest-activity rhythm and physical activity, we cannot ignore the possibility of reverse causality. To determine what the direction of causality is, intervention studies are needed.

In conclusion, we found a tendency of increased IV in patients with EOD, and a relation between the rest-activity rhythm and physical activity. Within

the scope of these findings, it seems appropriate to advise patients to perform ambulatory activities to stimulate an active lifestyle.

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Table 1. Characteristics of patients with EOD and cognitively intact adults of the same age

	EOD (n = 61)		Controls (n = 67)		<i>p</i> ^a
	<i>Median</i>	<i>Range</i>	<i>Median</i>	<i>Range</i>	
Age	62.5	50-71	63.0	54-69	.82
MMSE	25	16-30	30	26-30	<.001
	<i>Frq</i>	<i>%</i>	<i>Frq</i>	<i>%</i>	<i>p</i> ^b
Gender (Male)	41	67.2	28	40.6	.003
Educational level					
Low	4	6.6	2	2.9	.456
Medium	25	41.0	34	49.3	
High	32	52.5	33	47.8	
Diagnosis					
AD	46	75.4			
VaD	5	8.2			
DLB	7	11.5			
FTD	2	3.3			
Dem nao	1	1.6			
Medication					
Antidepressants	9	14.8	0	0	.001
Sedatives	2	3.3	0	0	.13
CNS neurologic	34	55.7	0	0	<.001
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>p</i> ^c
Rest-activity rhythm					
IV	0.46	0.16	0.39	0.10	.03
IS	0.79	0.10	0.81	0.10	.23
RA	0.68	0.15	0.72	0.12	.12 ^a
Sleep					
Time in bed (h:min)	8:49	0:51	8:07	0:47	<.001
Total sleep time (h:min)	6:13	1:22	5:57	1:12	.23
Onset latency (h:min)	0:23	0:22	0:15	0:15	.02
Sleep efficiency (%)	71.9	15.1	74.1	11.6	.42
WASO (h:min)	1:48	1:15	1:33	0:52	.44
Wake bouts (number)	25.5	8.6	24:8	6.2	.86

Notes:

^a Mann-Whitney *U* test

^b χ^2 -test

^c Independent sample *t*-test

Abbreviations: AD = Alzheimer's disease; Dem nao = dementia not otherwise specified; DLB = lewy-body dementia; EOD = early-onset dementia; FTD = fronto temporal dementia; IS = interdaily stability; higher values reflect more stable rhythm; IV = intradaily variability; higher values reflect more; MMSE = mini-mental state examination; RA = relative amplitude; higher values reflect greater amplitude and a stronger rhythm; VaD = vascular dementia;; fragmented rhythm; WASO = wake after sleep onset.

Table 2. Associations between IV, IS, and RA and demographic, clinical, and lifestyle factors in EOD and cognitively intact adults

	IV (n = 122)			IS (n = 122)			RA (n = 122)		
	B (SE)	95% CI	Beta	B (SE)	95% CI	Beta	B (SE)	95% CI	Beta
Age	ns	ns	ns	ns	ns	ns	ns	ns	ns
Gender	ns	ns	ns	ns	ns	ns	.46 (.16)**	0.15 - 0.77	.25
Sedative medication	ns	ns	ns	ns	ns	ns	ns	ns	ns
Antidepressants	0.74 (.30)*	0.15 -1.33	.21	ns	ns	ns	ns	ns	ns
CNS neurologic medication	0.40 (.19)*	0.04 - 0.76	.18	ns	ns	ns	ns	ns	ns
Meansteps per day	-0.02 (.00)***	-0.02 - -0.01	-.30	0.02 (.00)***	0.01 - 0.02	.33	ns	ns	ns
Group	ns	ns	ns	ns	ns	ns	ns	ns	ns
R ²	.18***			.11***					.06**

Notes:

Associations were assessed using multiple linear regression analysis (stepwise).

R²: of the model that best predicted the dependent variable.

****p* < .001; ***p* < .01; **p* < .05; ns = Beta not significant, excluded from the model

Abbreviations: IV = Intradaily Variability; IS = Interdaily Stability; RA = Relative Amplitude.