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Relationship between Apathy and Sleep Disturbance in Mild and Moderate Alzheimer's Disease: An Actigraphic Study

Emmanuel Mulin[a,*], Jamie M. Zeitzer[b,c], Leah Friedman[b], Franck Le Duff[d], Jerome Yesavage[b], Philippe H. Robert[a] and Renaud David[a]
[a]*Centre Mémoire de Ressources et de Recherche, CHU, University of Nice Sophia Antipolis, Nice, France*
[b]*Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, USA*
[c]*Psychiatry Service, VA Palo Alto Health Care System, Palo Alto, CA, USA*
[d]*Department of Epidemiology, CHU, University of Nice Sophia Antipolis, Nice, France*

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Abstract. Apathy is the most frequently reported neuropsychiatric symptom across all stages of Alzheimer's disease (AD). Both apathy and sleep disorders are known to have independent negative effects on the quality of life in individuals with AD. The aim of this study was to assess the relationship between apathy and sleep/wake patterns in individuals with AD using ambulatory actigraphy. One hundred and three non-institutionalized individuals with AD wore a wrist actigraph continuously over seven consecutive 24-h periods. Apathy was assessed using the Neuropsychiatric Inventory. Daytime mean motor activity (dMMA) was calculated from daytime wrist actigraphy data. Actigraphic parameters of sleep included total sleep time (TST), wake after sleep onset (WASO), time in bed (TIB), WASO normalized by TIB, sleep latency, and nighttime mean motor activity (nMMA). Among the 103 individuals with AD (aged 76.9 ± 7.2 years; MMSE $= 21.4 \pm 4.3$), those with apathy had significantly lower dMMA, higher WASO (both raw and normalized), and spent more time in bed during the night than those without apathy. Sleep latency, nMMA and TST did not differ significantly between the two subgroups. To our knowledge, this study is the first to identify a relationship between apathy and sleep disturbance in those with mild or moderate AD: apathy was associated with increased TIB during the night and more WASO. These results suggest that AD patients with apathy have less consolidated nocturnal sleep than those without apathy.

Keywords: Actigraphy behavioral disturbances, Alzheimer's disease, apathy, sleep disorders

INTRODUCTION

Apathy and sleep disturbance form part of the clinical picture of Alzheimer's disease (AD) and other dementias. Irrespective of the severity of the disease, the most frequently encountered symptom is apathy [1, 2]. Apathy is present very early in the disease process and is the most common neuropsychiatric symptom observed in individuals with mild cognitive impairment [3–7]. Several studies have also indicated that apathy explains, at least partially, the loss of autonomy in activities of daily living in AD patients [8].

Usually, apathy is assessed through a structured interview, using input from either the caregiver and/or the patient. The most widely used instrument in clinical research on apathy is the Neuropsychiatric Inventory (NPI) apathy item, although other scales such as the Structured Clinical Interview for Apathy [9], the Apathy Evaluation Scale [10], the Apathy Scale, the Apathy Inventory [11], and the Lille Apathy Rating Scale [12] are also used. Specific diagnostic criteria for apathy have been recently proposed [13, 14].

*Correspondence to: Emmanuel Mulin, Centre Mémoire de Ressources et de Recherche, Hôpital Cimiez, 4 Avenue Reine Victoria, 06003 Nice, France. E-mail: mulin.e@chu-nice.fr.

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Sleep disorders are also common in those with AD with an incidence of 12.9 to 18.1% [1–15]. Sleep disturbance in AD is associated with cognitive decline, functional decline [16, 17], more rapid institutionalization, and impairment of their caregiver's sleep quality [18]. Sleep disruption has been found to influence the severity of memory disruption in amnestic mild cognitive impairment [19].

One of the main difficulties in assessing apathy and other neuropsychiatric symptoms is the absence of a reliable objective measure. Ambulatory actigraphy has been widely validated as a method for detecting sleep disturbance [20, 21]. For example, ambulatory actigraphy has demonstrated that sleep disorders in older individuals include nocturnal and diurnal changes, with increased sleep latency, fragmentation of nocturnal sleep, longer sleep times, and increased number of naps during the day [22, 23]. Actigraphy has also been used as an objective method for evaluating agitation [24] and apathy [25, 26] in individuals with dementia, as well as for individuals with depression. The confluence of apathy and sleep disturbance in individuals with AD has yet to be determined.

Some studies have clustered neuropsychiatric symptoms in AD. Aalten and colleagues, using factorial analysis, distinguished four neuropsychiatric subsyndromes among the twelve NPI-domains: hyperactivity, psychosis, affective symptoms, and apathy [27]. In this analysis, sleep disturbance was part of the apathy cluster. Further evidence for a connection between sleep and apathy comes from the physiology of these systems, both of which are organized by the circadian clock and which that may have diminished amplitude in individuals with AD.

The aim of this study is to examine the relationship between apathy and sleep in individuals with AD, with the hypothesis that individuals with apathy will have greater sleep disruption.

MATERIALS AND METHODS

Sample

Participants with a diagnosis of mild or moderate AD were recruited at the Nice Memory Center and at the Stanford/Veterans Affairs-National Institute on Aging Alzheimer's Disease Core Center. To be included, participants were required to meet NINCDS-ADRDA criteria for AD [28], a Mini Mental State Examination (MMSE) [29] higher than 15, be able to wear an actigraph and have a caregiver willing and able to complete a sleep-wake diary. Individuals were excluded if they had a history of head trauma with loss of consciousness, a diagnosis of sleep apnea and/or restless legs syndrome, psychosis or major depressive disorder or if they were undergoing treatment for cancer. In addition, individuals with Unified Parkinson Disease Rating Scale (UPDRS) [30] subscores greater than zero for tremor at rest (item 20), action or postural tremor of hands (item 21), and rigidity (item 22) were not included in this study. With the exception of the apathy and sleep disturbance subscales, individuals with any NPI domain frequency × severity sub-score greater than four were excluded.

All participants were free of dopaminergic antidepressants, antipsychotic medications, and sedative hypnotics. Cholinesterase inhibitors, if present, were at a stable dose for more than six months prior to study participation. Each participant and their family gave informed consent to participate in the study. Authorization of the Nice ethics committee and the Stanford University Institutional Review Board was granted for this study.

Behavioral assessment

Preceding actigraphic recordings, all participants received a behavioral examination. Neuropsychiatric symptoms were assessed using the NPI [31]. The NPI is a structured interview with a caregiver who is familiar with the subject. Apathy was assessed by calculating the NPI subscore (frequency × severity) and defined as a subscore greater than four. A single rater in each center (Nice and Stanford) performed the NPI and MMSE testing.

Actigraphic and sleep parameters assessment

Participants were asked to wear a wrist actigraph continuously over seven consecutive 24-h periods, starting at the clinic visit, and to concomitantly complete a 24-h sleep-wake diary at bedtime and wake time with the assistance of a caregiver living with the participant. The actigraph was worn on the non-dominant wrist and set to record in 60-s epochs, resulting in a total activity count for each minute of the day (Micro-Mini MotionLogger, Ambulatory-Monitoring, Inc., Ardsley, NY). The patient was asked to remove the device during bathing. Actigraphy allows for continuous, unobtrusive data acquisition in the home environment [32] through the use of a piezoelectric accelerometer. Actigraphy, which has been shown to

correlate highly with polysomnography (the gold standard of sleep metrics), is considered to be a valid and objective method for measuring sleep [33].

Both wake period (daytime), defined as the time between final awakening in the morning and time into bed at night, and sleep period (nighttime), defined as the time between time into bed in the evening and final awakening in the morning, were based on in and out bedtimes reported on patients' sleep logs. Daytime and nighttime actigraphic parameters were analyzed with Action4 software (Ambulatory-Monitoring, Inc.). using the validated Cole-Kripke algorithm [34] in zero crossing mode [35]. The following actigraphic parameters were calculated: 1) sleep latency, the difference between the time reported by the diary for getting into bed and the start of the first sleep epoch as determined by actigraphy; 2) total sleep time at night, number of minutes scored as sleep during the nighttime; 3) wake after sleep onset (WASO), the number of minutes of wake during the sleep period; 4) daytime inactivity (e.g., napping), the number of minutes of inactivity during the daytime (there was no minimum duration of inactivity set to qualify a period as inactivity); 5) 24 h-mean motor activity (MMA) = the mean of all 1-min activity count epochs during daytime (dMMA) and nighttime (nMMA); and 6) WASO normalized for the total time in bed after sleep onset to limit the impact of a correlation between the length of TIB and duration of waking periods during the night. We calculated for each group, the mean ratio: WASO divided by the time in bed after sleep onset (= total time in bed minus sleep latency).

Statistical analysis

Population was divided as a function of the independent variable (presence or absence of apathy according to the cut-off >4 for the domain apathy of the NPI). After verifying the normality of distribution, group comparisons were made using a *t*-test (continuous variables) or a Chi-square test (categorical variables). Within-group analyses using the apathy domain score of the NPI with a cut-off of four to distinguish apathetic and non-apathetic individuals were performed using a Bonferroni correction. Significance was assessed for $p < 0.05$. Correlations were determined using the Pearson correlation coefficient or the Spearman Rho to assess the relationship between actigraphic sleep estimates and scores for the domains of apathy and sleep disturbance on the NPI. SPSS 14.0 was used to compute statistics. Data are presented as average ± standard deviation.

RESULTS

One hundred and three individuals with a diagnosis of AD were recruited: 76 from the Nice Memory Center (CMRR) and 27 from the Stanford/Veterans Affairs National Institute on Aging Alzheimer's Disease Core Center. Data for an additional 14 subjects were collected but excluded due to equipment failure, fewer than three days of actigraphy collected, or the sleep diary was incorrectly completed. The participants from Nice and Stanford were statistically indistinguishable for gender, age, MMSE, and apathy NPI domain. As such, the groups were combined for analytic purposes. Demographic and clinical characteristics of the combined samples, including subgroups of individuals with and without apathy, are presented in Table 1. The two subgroups were distinguishable only by their preselected NPI apathy scores and total NPI scores.

Actigraphic data are reported in Table 2. There was no statistically significant difference between those with and without apathy for sleep latency, number of nocturnal awakenings, TST or nMMA. WASO ($p < 0.01$), TIB ($p < 0.05$) and mean duration of daytime inactivity periods ($p < 0.001$) were significantly higher in those with apathy as was the WASO normalized for time in bed ($p = 0.02$). In this subgroup, dMMA ($p < 0.001$) was significantly lower.

As indicated in Table 3, the severity of apathy and sleep disturbance evaluated with the NPI items were weakly, but significantly correlated with both WASO and WASO normalized for time in bed.

Table 1
Descriptive characteristics of the total sample and of the two subgroups, with and without apathy on the NPI

	No apathy $n = 64$	Apathy $n = 39$	Total sample $n = 103$
Age (yrs)	75.9 ± 8.1	78.6 ± 5.0	76.9 ± 7.2
Gender (F/M)	40/24	20/19	60/43
MMSE	21.8 ± 4.1	20.9 ± 4.5	21.4 ± 4.3
NPI total score	7.4 ± 6.6	16.2 ± 7.8**	10.7 ± 8.2
Delusion	0.2 ± 0.7	0.5 ± 1.2	0.3 ± 0.9
Hallucination	0.1 ± 0.3	0.3 ± 0.9	0.1 ± 0.6
Agitation	0.9 ± 2.2	1.1 ± 1.4	1.0 ± 1.9
Depression	1.0 ± 1.8	0.6 ± 1.2	0.8 ± 1.6
Anxiety	1.4 ± 2.2	1.7 ± 2.1	1.5 ± 2.2
Euphoria	0.2 ± 0.8	0.1 ± 0.4	0.1 ± 0.7
Apathy	0.4 ± 0.9	6.7 ± 2.6**	2.8 ± 3.5
Disinhibition	0.3 ± 0.9	0.5 ± 1.2	0.4 ± 1.0
Irritability	1.1 ± 1.9	1.6 ± 2.0	1.3 ± 1.9
Aberrant motor behavior	0.5 ± 1.3	0.8 ± 1.4	0.6 ± 1.4
Sleep disturbances	1.1 ± 2.3	1.8 ± 2.8	1.3 ± 2.5
Appetite disorders	0.4 ± 1.2	0.5 ± 1.1	0.4 ± 1.2

**$p < 0.01$, *t*-test.

Table 2
Comparison of actigraphic parameters between AD subjects with or without apathy

	No apathy $n=64$	Apathy $n=39$	Total sample $n=103$
Nap mean duration (min)	79.5 ± 75.8	163.5 ± 153.2**	109.7 ± 116.4
Daytime MMA (dMMA)	176.9 ± 25.3	155.4 ± 28.4**	168.8 ± 28.4
Sleep latency (min)	15.5 ± 16.0	12.1 ± 13.8	14.2 ± 15.2
Number of nighttime awakenings	9.8 ± 6.0	11.4 ± 5.6	10.4 ± 5.9
Wake after sleep onset (WASO) (min)	59.3 ± 44.7	88.3 ± 51.4**	70.3 ± 49.2
WASO normalized for time in bed	0.11 ± 0.08	0.16 ± 0.09**	0.13 ± 0.09
Total sleep time (TST) (min)	454.4 ± 63.3	464.2 ± 88.0	458.1 ± 73.3
Nighttime MMA (nMMA)	23.9 ± 11.0	27.7 ± 12.8	25.3 ± 11.7
Time in bed (TIB) (min)	521.8 ± 65.1	561.6 ± 85.7*	536.9 ± 75.7

*$p<0.05$, **$p<0.01$, t-test

Table 3
Correlation between severity of apathy and sleep disturbance items on NPI evaluation and actigraphic WASO or WASO normalized for time in bed (Pearson Correlation or Spearman Rho, *$p<0.05$, **$p<0.01$)

	WASO	Normalized WASO
NPI apathy (severity)	0.254**	0.218*
NPI sleep disturbance (severity)	0.207*	0.206*

DISCUSSION

To our knowledge, this study is the first to examine the relationship between sleep/wake parameters measured by actigraphy over seven days and apathy in individuals with mild or moderate AD. Results are in line with our initial hypothesis that during the day, those with apathy had lower mean motor activity while at night they have longer TIB and more WASO. The lower daytime activity levels are similar to those previously observed in individuals with apathy and acquired brain damage [25] and a previous brief examination of activity levels in 15 individuals with AD and apathy [36].

In the present study, the mean TST was equivalent in the two AD subgroups, whether or not apathy was present. However, those individuals with AD and apathy had significantly higher WASO scores than those without apathy, whereas there was no statistical difference in the number of awakenings during the night. When the increase in WASO was normalized to TIB, which was also increased in those with apathy, the amount of WASO per unit TIB was still increased in those with apathy, indicating that the increase in WASO observed in those with apathy is not secondary to increased TIB. Given the similar number of awakenings and the increased WASO, this could be interpreted as increased difficulty in returning to sleep after waking during the night for those with apathy. These data suggest that in those individuals with AD, the ones with apathy better fit the "classic" criteria for defining sleep disturbance in those with AD [37]: less than six hours of nocturnal sleep and/or an increase of WASO and a decrease of TST relative to their premorbid nocturnal sleep pattern, as well as, low levels of daytime activity and desynchronization of their sleep/wake rhythm [18]. The decrease in motor activity during the day, coupled with increased disruption of nocturnal sleep, is consistent with diminished amplitude of circadian processes. As mood is also thought to be under circadian control [38], apathy may be due to the same circadian dysfunction. Neurodegeneration of the suprachiasmatic nucleus, the site of the central circadian pacemaker, in fact has been identified in individuals with AD [39]. Since apathy does not occur in all individuals with AD, the diminished circadian oscillation would have to interact with some other modulatory system, such as ventral tegmental dopamine.

Interestingly, sleep disturbance as evaluated by the NPI domain did not differ between participants with or without apathy. Nevertheless, actigraphic parameters indicate differences between these two subgroups (Fig. 1). A lack of sensitivity of the sleep disturbance domain on the NPI could explain these results. The NPI is scored according to caregivers' interview responses concerning the observations that individuals [31]: 1) have difficulties to fall asleep; 2) get up during the night; 3) wander, pace or get involved in inappropriate activities; 4) awake at night, dress and plan to go out; 5) wake too early; or 6) have other sleep behaviors. This kind of scoring is based on subjective interview and only accounts for behaviors caregivers could see [40]. Bouts of wakefulness after sleep onset occur during the night and do not, necessarily, disturb the sleep of caregivers. Even so, WASO and WASO normalized for time in bed were weakly correlated with the sleep domain of the NPI. This could be explained by the fact that WASO scores assess a specific pattern of sleep (fragmentation) by mechanical device whereas the NPI

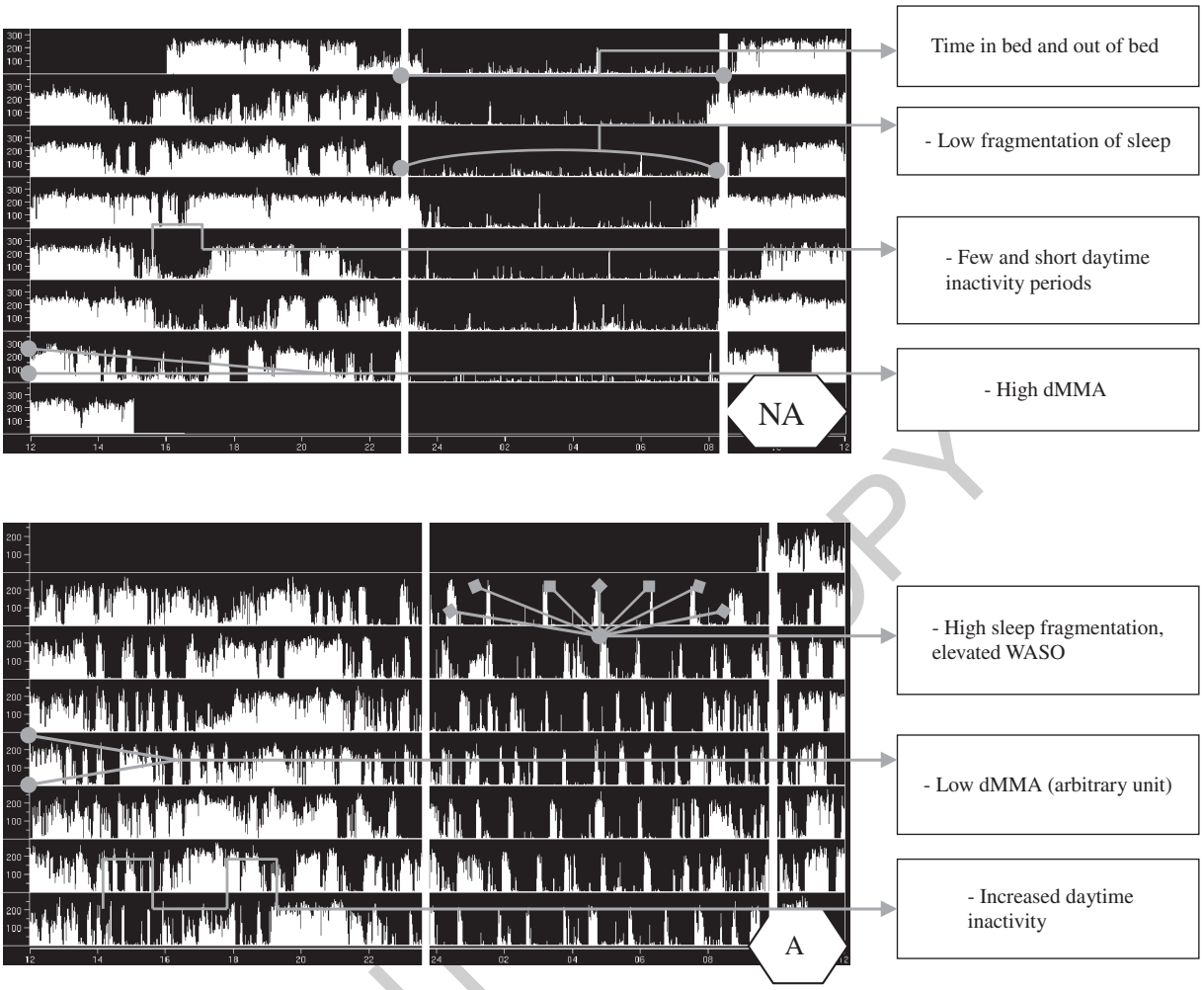

Fig. 1. Example of an actigraphic recording of one individual without apathy (NA) and of one with apathy (A). Individual NA is an 80 year old male, MMSE = 19, NPI total = 4, NPI apathy = 2, and NPI sleep disturbance = 0. He had a dMMA of 181 and an average WASO of 2.2 min per night. Individual A is an 80 year old male, MMSE = 18 and NPI total = 12, but an NPI apathy = 8 and NPI sleep disturbance = 4. He had a dMMA of 123 and an average WASO of 27.4 min per night. Vertical white lines indicate the mean time getting into and out of bed (based on sleep diary), horizontal axis is time of day, and vertical axes are arbitrary actigraph units.

scoring alternatives provide a more general observation by human being of sleep/wake behavior. Additionally, there was great variability in many of the sleep measures among the individuals with apathy, indicating a possible heterogeneity regarding sleep within the apathetic group. These results suggest that the NPI and actigraphy are somewhat orthogonal in their capturing of sleep-related phenomena. We recommend that studies evaluating sleep/wake in AD supplement subjective measures of sleep disruption with objective tools, such as actigraphy.

While actigraphy is a useful method for examining sleep patterns, it does not examine sleep physiology directly. Future use of polysomnography would be of interest for this purpose [41]. Additionally, there was high variance in many of the sleep measures among the individuals with apathy, indicating a possible heterogeneity within the apathetic group, which should be explored with larger group sizes and moderator analyses.

It is now well established that AD patients have more disturbed nighttime sleep. One could hypothesize that apathetic patients with a high WASO have especially disturbed circadian rhythms. This suggests more serious impairment of the biological clock. Clinically, this would imply that these patients may be appropriate candidates for evaluating efficacy of melatonin and light therapies. Recently, Merlino and coworkers found

that among sleep disturbances, only excessive daytime sleepiness was significantly associated with the presence of dementia in the elderly and was present across the different categories of cognitive decline, suggesting that it could be an early marker of neurodegenerative disorders, including AD, in some older adults [42].

In summary this study found that individuals with AD and apathy have lower levels of activity during the day and poorer nocturnal sleep quality than those without apathy. This information may be helpful clinically in determining a therapeutic target. It is important to deliver this information to caregivers in order for them to have greater understanding of the interactions among patients' behavioral symptoms. It may thereby encourage caregivers to keep patients more active during daytime. This, in turn, might limit the inactivity associated with apathy's disruptive impact on sleep and simultaneously treat both apathy and sleep disturbances.

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