

Decreased Daytime Motor Activity Associated With Apathy in Alzheimer Disease: An Actigraphic Study

Renaud David, M.D., Emmanuel Mulin, M.D., Leah Friedman, Ph.D., Franck Le Duff, M.D., Ph.D., Edyta Cygankiewicz, M.D., Olivier Deschaux, Ph.D., Rene Garcia, Ph.D., Jerome A. Yesavage, M.D., Philippe H. Robert, M.D., Ph.D., Jamie M. Zeitzer, Ph.D

Objective: Across all stages of Alzheimer disease (AD), apathy is the most common neuropsychiatric symptom. Studies using the Neuropsychiatric Inventory (NPI) have found that apathy is present in up to 70% of individuals with Alzheimer disease. One of the main difficulties in assessing apathy and other neuropsychiatric symptoms is the absence of reliable, objective measures. Motor activity assessment using ambulatory actigraphy could provide an indirect, objective evaluation of apathy. The aim of our study was to assess the relationship between apathy and daytime motor activity in AD, using ambulatory actigraphy. **Methods:** One hundred seven AD outpatients wore a wrist actigraph (Motionlogger) during seven consecutive 24-hour periods to evaluate motor activity. Participants were divided into two subgroups according to their apathy subscores on the NPI: individuals with apathy (NPI-aphathy subscores >4) and those without. Daytime mean motor activity scores were compared between the two subgroups. **Results:** Individuals with AD who had symptoms of apathy ($n = 43$; age = 79 ± 4.7 years; Mini-Mental State Exam = 20.9 ± 4.8) had significantly lower daytime mean motor activity than AD patients without apathy ($n = 64$; age = 76.3 ± 7.7 ; Mini-Mental State Exam = 21.5 ± 4.7), while nighttime mean motor activity did not significantly differ between the two subgroups. **Conclusions:** Ambulatory actigraphy could be added to currently used questionnaires as a simple, objective technique for assessing apathy in the routine assessment of AD patients. (Am J Geriatr Psychiatry 2011; 00:1–9)

Key Words: Actigraphy, Alzheimer disease, apathy, behavioural disorders

Received August 5, 2010; revised February 28, 2011; accepted June 6, 2011. Centre Mémoire de Ressources de Recherche, Nice University Hospital, Nice, France (RD, EM, EC, OD, PHR); Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA (LF, JAY, JMZ); Psychiatry Service, VA Palo Alto Health Care System, Palo Alto, CA (LF, JAY, JMZ); Laboratoire de Neurobiologie et Psychotraumatologie, University of Nice Sophia-Antipolis, France (OD, RG); Public Health Department, Nice University Hospital, Nice, France (FLD). Send correspondence and reprint requests to Dr. Renaud David, Centre Mémoire de Ressources et de Recherche, CHU Université de Nice Sophia-Antipolis, Hôpital Cimiez, 4 Avenue Reine Victoria, 06002 Nice, France. e-mail: david.r@chu-nice.fr

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Neuropsychiatric symptoms are frequently associated with cognitive deficits during the progression of Alzheimer disease (AD) and other dementia. Among them, apathy is one of the most common neuropsychiatric symptoms across all stages of AD.^{1,2} Studies using the Neuropsychiatric Inventory (NPI)⁴ show that apathy is present in up to 70% of individuals with AD. In these patients, presence of apathy is associated with earlier institutionalization, and faster functional⁵ and cognitive decline.⁶ In addition, presence of apathy is also associated with higher risk of conversion from mild cognitive impairment to AD.⁷

Apathy assessment is usually based on a structured interview, using input from either the caregiver and/or the patient. The NPI apathy item is the most widely used measure for assessing apathy in clinical research. Recently, diagnostic criteria for apathy have been proposed.⁸ A forthcoming version of the NPI, specifically designed for clinicians (NPI-C), will incorporate symptoms proposed by these diagnostic criteria for the apathy item.^{9,10} It has also been proposed that, in addition to current tools, new technologies such as actigraphy could provide an objective assessment of apathy.

Ambulatory actigraphy, consisting of a piezoelectric accelerometer designed to record arm movement in three dimensions, has been proposed as a method for objectively evaluating different disorders including sleep-wake disorders,^{11,12} Attention-deficit/hyperactivity disorder,¹³ and periodic limb movement disorder.¹⁴ Actigraphy has been used to evaluate agitated behavior in neurodegenerative disorders. Significant correlations have been observed between Cohen-Mansfield Agitation Inventory total scores and mean wake time according to actigraphic measurement.¹⁵ Actigraphy has also been used to study psychomotor retardation in psychiatric disorders: depressed patients after 4 weeks of treatment with imipramine were found to have increased mean motor activity during wake.¹⁶ More recent studies have shown that actigraphic locomotor activity assessment may be a useful, objective method to evaluate the severity of apathy in AD patients¹⁷⁻¹⁹ and in patients with acquired brain damage.²⁰

The aim of the present study is to evaluate the relationship between apathy severity and 7 days of

actigraphic-assessed levels of daytime motor activity among AD outpatients.

MATERIAL AND METHOD

Sample

One hundred seven individuals with an AD diagnosis were recruited in two centers: 80 participants at the Centre Hospitalier Universitaire de Nice Memory Center and 27 participants at the Stanford/Veterans Affairs National Institute on Aging Alzheimer's Disease Core Center. An AD diagnosis was determined using the NINCDS-ADRDA criteria.²¹ Patients were not included if they had a history of head trauma with loss of consciousness, psychotic or major depressive disorder, or aberrant motor activity (tremor, rigidity, parkinsonism) as defined by the Unified Parkinson Disease Rating Scale;²² had sleep-disordered breathing²³ and/or high fatigue levels;²⁴ body mass index >30 kg/m²; were undergoing treatment for cancer; or if they had any end-stage disease. All patients were free of dopaminergic antidepressant and antipsychotic medications. Cholinesterase inhibitors, if present, were required to be at a stable dose for more than 6 months prior to study participation. Although restrictive and likely not representative of the "average" individual with AD and apathy, these exclusion criteria would allow us to examine the relatively independent effects of apathy on motor activity in those with AD. Each subject and family gave informed consent to participate in the study. Authorization from the Comité de Protection des Personnes Sud-Méditerranée II and the Stanford University institutional review board was granted for this study.

Neuropsychological Assessment

Participants were administered a cognitive and behavioral examination prior to completing the actigraphic assessment. Neuropsychiatric symptoms were assessed using the NPI.⁴ The NPI is administered in a structured interview with a caregiver who is familiar with the subject. The subject's level of depression was additionally rated with the

Montgomery-Åsberg Depression Rating Scale.²⁵ Apathy was assessed using the NPI subscore (frequency \times severity) for apathy. Participants were considered apathetic if their NPI subscore was greater than four. Participants whose NPI subscores were greater than four for other neuropsychiatric symptoms such as agitation, depression, or aberrant motor disturbance that could interact with motor activity were also excluded. Neuropsychological assessment and actigraphic analyses were performed by two independent raters.

In the French sample, apathy was additionally assessed using the Apathy Inventory (AI),²⁶ designed to evaluate three dimensions of apathy: emotional blunting, lack of initiative, and lack of interest. In agreement with a previous study, participants with an AI total score greater than three were considered apathetic.¹⁷

Actigraphic Assessment

Participants were asked to wear a wrist actigraph continuously over seven consecutive 24-hour periods, starting at the clinic visit, and their caregivers were asked to complete a 24-hour sleep-wake diary recording the participant's bed and wake times each day. The actigraph was worn on the nondominant wrist and was set to record in 60-second epochs, resulting in a total activity count for each minute of the day (MicroMini, MotionLogger, Ambulatory-Monitoring Ardsley, NY). Participants were excluded if they were not able to wear the actigraph and/or they and their caregivers were unable to complete the diary.

Wake period (daytime period) was defined as the time between final awakening in the morning and sleep onset in the evening, and the *sleep period* (nighttime period) was defined as the time between sleep onset in the evening and final awakening in the morning. The following actigraphic parameters were measured: 1) Mean motor activity (MMA) was calculated as the mean of all 1-minute activity counts epochs during daytime (dMMA) and nighttime (nMMA) and 2) daytime napping (i.e., number of minutes of napping) was calculated as the average number of minutes of inactivity (minimal movement detected by the actigraphy) between the final wakeup time in the morning and the subsequent bedtime. There was no minimum duration of inactivity set to

qualify a period as a nap. All intervals determined by the scoring algorithm as sleeping during the out-of-bed period were considered to represent napping.

Daytime and nighttime actigraphic parameters were analyzed with Action4 software (Ambulatory-Monitoring). Wake and sleep periods were measured using a validated algorithm (Cole-Kripke algorithm in Zero Crossing Mode).

Statistical Analysis

After verifying the normality of distribution, group comparisons were made using a *t* test or a χ^2 test (for sex ratio comparison). Within-group analysis was performed using a *post hoc* analysis of variance. Correlations were determined using the Pearson rank correlation coefficient. In addition, a receiver operating characteristic analysis was performed to determine how much dMMA delineates apathy from non-apathy. SPSS 14.0 (SPSS Inc., Chicago, IL) was used to compute statistics. Data are presented as average \pm standard deviation.

RESULTS

A total of 11 subjects were excluded because they had NPI subscores greater than four (except for the NPI apathy subscore), five other subjects were excluded because of technical problems with their actigraph, and five more subjects were excluded because the number of recorded actigraphic 24-hour periods was less than three. Characteristics of the 107 AD participants (including participants both with and without apathy) and their actigraphic data are presented in Table 1. Participants in the French sample were aged 77.5 ± 6.7 years and their mean Mini-Mental State Exam (MMSE) score was 21.4 ± 4.6 . Participants in the U.S. sample were aged 76.2 ± 6.6 years and had a mean MMSE score of 21.37 ± 6.94 . No significant differences were found between the two samples for age, sex ratio, and neuropsychological and actigraphic parameters. The percentage of participants with apathy was 37.5% ($n = 30$) in the French sample and 44% ($n = 12$) in the U.S. sample (the overall percentage of apathetic participants was 39%), a difference that was also not statistically significant. Mean NPI subscores for agitation, irritability, depression, anxiety, and motor aberrant behavior,

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TABLE 1. Characteristics of AD Participants With and Without Apathy, and Comparison Between the Two Subgroups (Apathy Versus no Apathy). Categorical Testing Done With χ^2 Test and Continuous Variable Testing Done With t Test

Sex (female/male)	All Patients (n = 107)		No Apathy (n = 64)		Apathy (n = 43)		Comparison Apathy Versus No Apathy			
	58/49		41/24		17/25		χ^2 5.25	<i>df</i> 1	<i>p</i> 0.022	Cohen's <i>d</i>
	Mean	SD	Mean	SD	Mean	SD	<i>t</i>	<i>df</i>	<i>p</i>	
Age (yrs)	77.2	6.69	76.2	7.45	78.8	4.71	-2.19	105	<0.05	0.04
MMSE	21.4	5.31	21.5	4.71	20.9	4.82	1.30	105	0.165	0.13
Number of nights wearing the actigraph	6.8	0.58	6.8	0.65	6.81	0.46	0.68	105	0.913	0
NPI apathy	2.9	3.7	0.45	1.1	7	2.8	-16.8	105	<0.01	3.08
NPI depression	1	1.6	1.24	1.8	0.67	1.2	1.63	105	0.108	0.37
NPI agitation	0.81	1.6	0.69	1.6	1	1.7	-0.78	105	0.438	0.19
NPI sleep	1.6	2.5	1.27	2.1	2.2	3.1	-1.43	105	0.159	0.35
NPI anxiety	1.5	2.3	1.5	2.3	1.5	2.5	-0.13	105	0.9	0
NPI irritability	0.86	1.5	0.78	1.5	1	1.6	-0.60	105	0.55	0.14
NPI aberrant motor behavior	0.53	1.4	0.42	1.2	0.7	1.8	-0.84	105	0.405	0.18
MADRS	3.7	3.9	3.95	4.7	3.1	2.5	0.49	105	0.629	0.23
Nighttime MMA (nMMA)	25.82	11.79	25.76	10.88	25.93	13.38	-0.06	105	0.949	0.01
Daytime MMA (dMMA)	168.1	30.05	178.8	25.53	151.4	29.19	5.11	105	<0.01	1
Number of naps per day	7.99	6.6	6.2	5.6	10.7	7.3	-3.6	105	<0.01	0.69
Duration of napping per day (min)	91.99	88.1	71.6	67.2	123.6	106.4	-2.83	105	<0.01	0.58
Percent of daytime interval spent napping	11.01	12.4	9.04	12.3	14.2	11.9	-2.13	105	<0.05	0.43
Variance of daily nap duration	69.7	76.5	84.6	80.9	48.01	65.6	2.55	105	<0.05	0.50

MADRS: Montgomery-Åsberg Depression Rating Scale.

which may be potential confounding factors for actigraphic locomotor activity, were at low levels (NPI subscores <2, except for NPI-apathy subscore). The two AD subgroups (apathy versus no apathy) did not significantly differ by MMSE score and were equivalent in terms of NPI subscores for depression, agitation, and aberrant motor behavior (Table 1). Participants in the apathy subgroup were slightly, but significantly older (78.8 ± 4.7 versus 76.2 ± 7.45 , Table 1).

Although our *a priori* hypothesis was to examine mean MMA, we also explored other mathematical transformations of the data. MMA was significantly correlated with and not significantly different from MMA without 0-activity counts, median of locomotor activity, area under the curve of locomotor activity ($p < 0.01$, Pearson $r > 0.85$, $df = 106$). Given the similarity in the terms, we decided to use the mean MMA score to evaluate locomotor activity. We compared nMMA within (day number effect) and be-

tween (with or without apathy) subgroups (Figure 2), and found no statistically significant differences within each subgroup (one-way ANOVA, $p > 0.05$, all $F < 2.5$, $df = 1$, 105) or between the two subgroups ($p > 0.05$, all $t > -1.5$, $df = 105$). However, both the dMMA and the mean duration of napping were significantly lower in the subgroup with apathy (Table 1). dMMA significantly correlated with the NPI subscore for apathy (Pearson $r = -0.439$, $p < 0.01$, $df = 106$) and with the mean duration of napping (Pearson $r = -0.65$, $p < 0.01$, $df = 106$). In addition, we found a significant correlation between dMMA and the NPI subscore for sleep (Pearson $r = -0.34$, $p < 0.01$, $df = 106$). To determine how much dMMA distinguishes apathy from non apathy, a receiver operating characteristic analysis was performed. Using a balanced approach for sensitivity (81%) and specificity (71%), an optimum measure was obtained using a cutoff of mean dMMA equal to 161.2 (arbitrary actigraph unit) (Figure 3).

FIGURE 1. Actigraphic Data From a Subject With AD and Without Apathy (Top) (NPI-Apathy = 0) and Another Subject With AD and With Apathy (Bottom) (NPI-Apathy = 12/12; AI = 30/36). The y-Axis Is in Arbitrary Actigraph Units and the x-Axis Indicates Times of Day. Each Tick Represents the Total Activity Within a 60-Second Bin

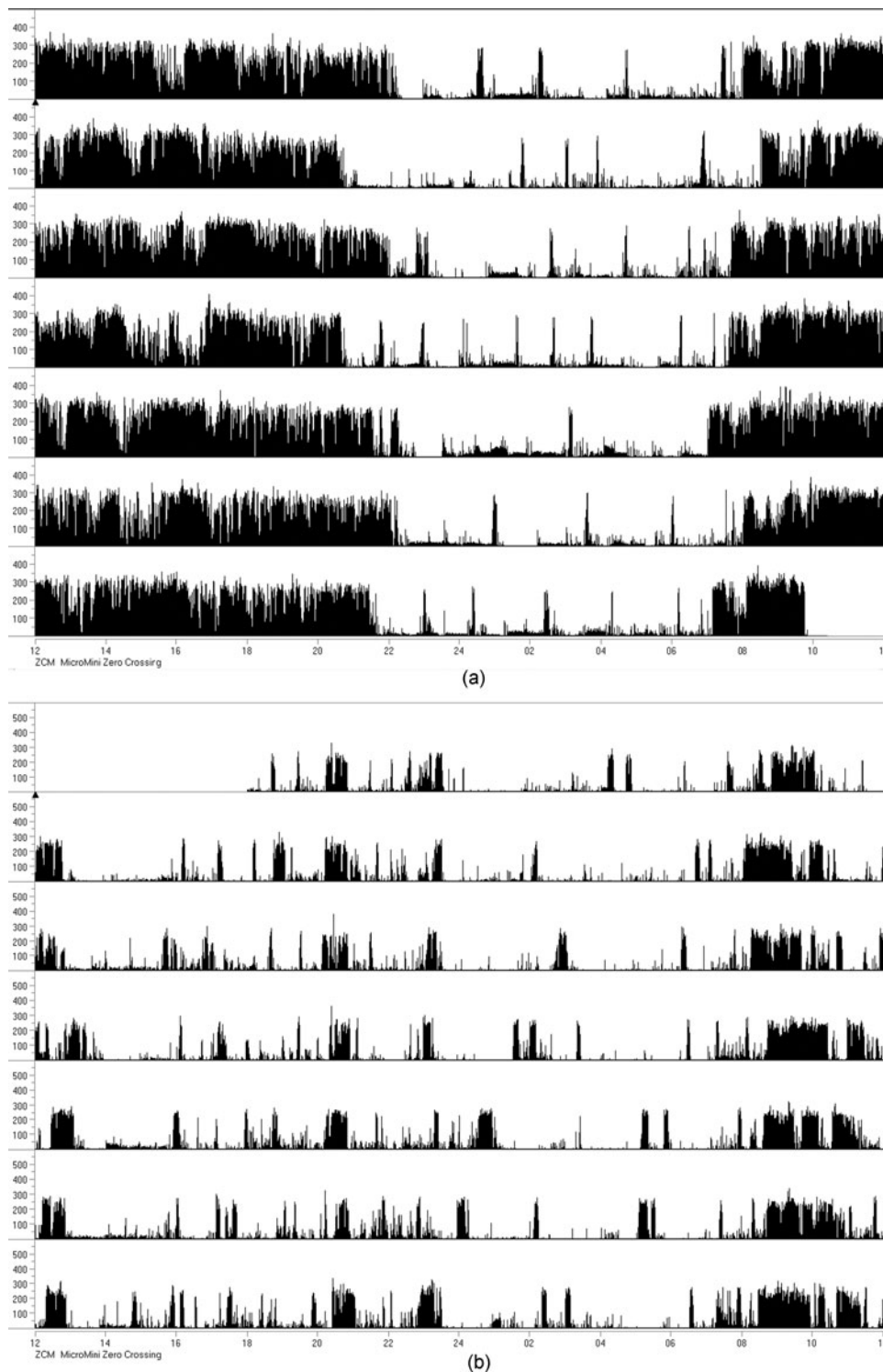
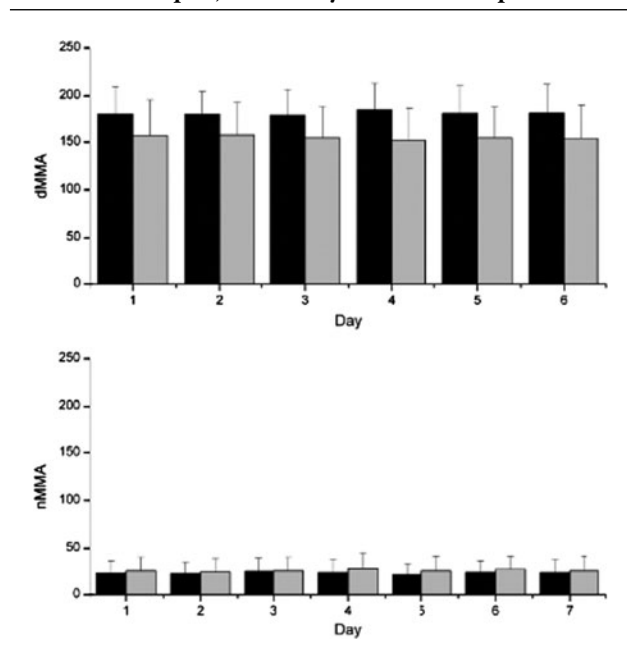


FIGURE 2. Average Daytime Mean Motor Activity (dMMA, Upper Panel) and Nighttime Mean Motor Activity (nMMA, Lower Panel) Over 7 Days for the two subgroups: Presence (Gray Bars) or Absence (Black Bars) of Apathy. Data Were Averaged Across Subjects, From Both U.S. and French Samples, Within Days for Each Group

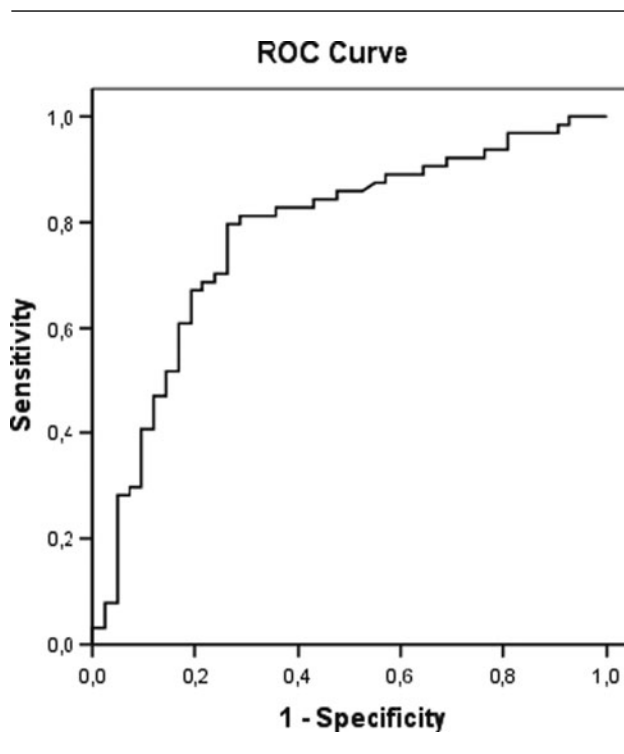


In the French sample, for which data from the AI are available, dMMA correlated negatively with the three dimensions of apathy: emotional blunting, lack of initiative, and lack of interest (Table 3). Using partial correlations controlling for age, MMSE and Montgomery-Åsberg Depression Rating Scale total score, correlations between dMMA and the three apathy dimensions remained statistically significant.

DISCUSSION

In the present study, individuals with AD and apathy had significantly lower mean motor activity during the daytime than those without apathy. This result is in agreement with previous studies^{17,20} and suggests that apathy measurement using actigraphic measurement of daytime mean motor activity is a simple and objective method of discriminating apathy. In our study, apathy was also correlated with the number and duration of naps, as suggested in Muller's study, such that those with apathy had higher mean duration of daytime napping. How-

FIGURE 3. Receiver Operating Characteristic Analysis With a Varying Threshold of dMMA Compared With Separation of Those With and Without Apathy Based on NPI Subscores



ever, the definition of daytime napping differs among studies: some studies (as did ours) have no minimum duration of inactivity set to qualify a period as a nap,²⁷ while others require at least 5 minutes of inactivity with sleep diary confirmation in older subjects²⁴ or 10 minutes in older dementia patients.²⁸ Actigraphy is, in fact, quite poor at discriminating daytime napping (i.e., immobility on a background of movement) from quiet wakefulness.²⁹ As such, although there is good evidence that daytime inactivity can be considered a marker of apathy, there is insufficient evidence to conclude that apathy is associated with increased daytime napping. Daytime napping increases with aging.³⁰ A reduction in daytime napping has been associated with an improvement in mood and functional status in institutionalized demented patients. Daytime sleepiness was also found to be associated with greater impairment in functional status in AD patients.³¹ Recently, Merlino and colleagues³² showed that excessive daytime sleepiness was the only sleep disturbance significantly associated with the presence of demen-

TABLE 2. Characteristics of AD Participants With and Without Apathy in the French Sample (n = 80), and Comparison Between the Two Subgroups (Apathy Versus No Apathy). Categorical Testing Done With χ^2 Test and Continuous Variable Testing Done With *t* Test

Sex (female/male)	No Apathy (n = 50)		Apathy (n = 30)		Comparison Apathy Versus No Apathy			
	31/19		11/19		χ^2 4.825	<i>df</i> 1	<i>p</i> <0.05	Cohen's <i>d</i>
	Mean	SD	Mean	SD	<i>T</i>	<i>df</i>	<i>p</i>	
Age (yrs)	76.4	7.73	78.9	4.59	-1.60	78	0.12	0.39
MMSE	21.5	4.74	20.9	4.74	0.80	78	0.43	0.13
Number of nights wearing actigraph	6.9	0.61	6.9	0.31	-0.36	78	0.72	0
NPI apathy	0.59	1.2	7.3	2.9	-11.8	78	<0.01	3.02
AI total score	2	4.71	18.5	11.3	-7.04	78	<0.01	1.91
AI emotional blunting	0.05	0.31	2.3	3.3	-3.17	78	<0.01	0.96
AI lack of initiative	0.98	2.4	6.7	3.9	-6.43	78	<0.01	1.77
AI lack of interest	0.75	1.7	5.8	4.1	-5.59	78	<0.01	1.61
Nighttime MMA (nMMA)	25.81	10.92	25.93	13.38	-0.06	78	0.95	0.01
Daytime MMA (dMMA)	186.2	19.33	141.2	24.41	9.01	78	<0.01	2.04
Number of naps per day	5.3	4.2	13	7.6	-4.76	78	<0.01	1.17
Duration of napping per day (min)	66.7	68.9	144	112	-3.40	78	<0.01	0.83
Percent of daytime interval spent napping	8.60	13.5	16.3	12.3	-2.60	78	<0.05	0.60
Variance of nap duration across days	92.9	77.6	37.3	24.7	4.57	78	<0.01	0.97

TABLE 3. Correlation Between AI Apathy Total Score and NPI and AI Apathy Subscores and Actigraphic Parameters in the French Sample (Pearson Correlation Coefficient, *p* Values)

	dMMA		nMMA		Mean Number of Naps Per Day		Mean Duration of Napping Per Day (min)	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
NPI apathy	-0.72	<0.01	-0.004	0.971	0.588	<0.01	0.452	<0.01
AI total score	-0.57	<0.01	-0.047	0.699	0.522	<0.01	0.526	<0.01
AI emotional blunting	-0.55	<0.01	-0.13	0.291	0.55	<0.01	0.546	<0.01
AI lack of initiative	-0.52	<0.01	0.02	0.872	0.492	<0.01	0.509	<0.01
AI lack of interest	-0.55	<0.01	-0.12	0.344	0.478	<0.01	0.516	<0.01

tia in older individuals. This association increased progressively with the severity of different categories of cognitive decline, suggesting that it could be an early marker of neurodegenerative disorders, including AD, in some older adults.³² In our study, neither the presence of apathy nor a decrease in daytime MMA was associated with a change in nighttime MMA, indicating that reduced daytime activity likely does not lead to an increase in nighttime motor activity.

In our previous study,¹⁷ we found negative correlations between mean motor activity and only two dimensions of the Apathy Inventory, lack of initiative and lack of interest. This result led us to hypothesize that actigraphic measurement of motor activity could be an indirect evaluation of goal-oriented motor behaviors. In the present study, however, all three dimensions of apathy, including the emo-

tional dimension, negatively correlated with levels of daytime locomotor activity. In our earlier study, motor activity was monitored by actigraphy over a 75-minute period during a standardized neuropsychological evaluation at the memory clinic. Apathy assessment over seven 24-hour days, such as occurs in the present study, appears to be easier to administer and a more accurate assessment method for several reasons. First, equipping ambulatory individuals for 7 days and analyzing their data 7 days later rather than calibrating a precise 75-minute neuropsychological evaluation at the memory clinic was less restrictive of researchers' time and effort. Second, actigraphic data obtained over 7 days at the subject's home probably reflects a more naturalistic spectrum of activity levels than actigraphic data gathered during a 75-minute face-to-face interview in the clinic. In other words, the use of 7 days of ambulatory, in-home

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collection of motor activity is probably a more ecologically valid assessment and more congruent with the diagnostic criteria for apathy.^{8,33} In these criteria, *apathy* is defined as a disorder of motivation that persists over time.

There are some limitations to the present study. First, all recruited patients had low NPI subscores for behavioral disturbances known to potentially interact with actigraphic analysis. Although apathy is present in the early stages of AD and is its most common behavioral symptom, patients often exhibit several different behavioral and psychological symptoms in dementia. Thus, ambulatory actigraphy might be less useful in cases where apathy is associated with agitation, depression, or tremor. Ambulatory actigraphy has found increased motor activity in cases with comorbid agitation¹⁵ and aberrant motor disorder (tremor,³⁴ rigidity, dyskinesia), and decreased motor activity in cases of depression.³⁵ However, more recently, no significant correlations were found between Unified Parkinson's Disease Rating Scale tremor scores and activity levels.³⁵ Further studies that did not exclude patients with potentially confounding behaviors and symptoms would be useful to evaluate the utility of ambulatory actigraphy for the routine assessment of apathy.

A final remark concerns the phenomenology of apathy. Apathy includes cognitive, behavioral, and emotional symptoms,^{36,37} and it can be argued that actigraphy only captures behavior and not emotion.

This is similar to using classical assessment in that it does not cover enough of the aspects of apathy. Descriptive results concerning the use of diagnostic criteria in clinical practice³² have indicated that goal-directed cognitive activities and goal-directed behaviors are the most frequently noted dimensions in those with apathy and these, of course, could not be detected by actigraphy. This indicates that a composite of measures are needed to tap the various cognitive, behavioral, and emotional aspects of apathy.

There is growing interest in neuropsychiatric symptoms in the study of AD since they can be present from the earliest stages and may constitute markers of disease progression. These symptoms are responsible for a large share of the suffering of patients and caregivers, and strongly determine the patient's lifestyle and their management. It is therefore important to have both good subjective and objective methods to assess these symptoms. Our data indicate that reduced daytime MMA could be a good marker for apathy in those with AD, which could help as both a diagnostic tool and in the surveillance of pharmaceutical treatments and the development of new drugs.

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