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Ambulatory actigraphy correlates with apathy in mild Alzheimer's disease

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Abstract

Aim: Apathy is one of the most common behavioral symptoms in Alzheimer's disease (AD). The aim of our study was to assess the relationship between apathy and locomotor activity in mild Alzheimer's disease (AD).

Methods: Thirty AD subjects and fifteen healthy controls were recruited from the Nice Memory Center. Apathy was assessed with the Apathy Inventory (AI). Patients with a score greater than three on the AI caregiver version are considered in this report as having apathy. Locomotor activity was assessed using a wrist-worn actigraph for 75 minutes, during which a neuropsychological and behavioral examination were performed (60 minutes) followed by 15 minutes of free activity.

Results: AD patients shown lower motor activity than healthy subjects. AD patients with apathy had lower motor activity than AD patients without apathy. Apathy total score correlated negatively with mean motor activity. Most of the total score correlation was accounted for by

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correlations between the apathy dimensions lack of initiative and lack of interest, with mean motor activity.

Conclusion: Ambulatory actigraphy could be a simple technique to assess apathy objectively as part of routine assessment of AD patients.

Keywords

actigraphy, Alzheimer's disease, apathy, locomotor activity

There is wide agreement that motivation, interest, action initiation and emotional reactivity are dimensions of apathy, and that lack of motivation is at the core of the syndrome. The importance of the symptomatology is related to the high frequency of apathy in individuals with Alzheimer's disease (AD) (Mega, Cummings, & Fiorello, 1996) and other dementing disorders, and to its negative impact on caregivers. Apathy is, in fact, the most frequent neuropsychiatric symptom across all stages of AD (Benoit, et al., 1999; Benoit, et al., 2003). Studies using the Neuropsychiatric Inventory (Cummings, 1997) show that apathy is present in up to 70% of individuals with Alzheimer's disease (AD).

One of the main difficulties in assessing apathy and other neuropsychiatric symptoms is the absence of a reliable objective measure. Usually, the assessment is subjective structured interview-based, using input from either the caregiver and/or the patient.

Ambulatory actigraphy, consisting of a piezoelectric accelerometer designed to record arm movement in three dimensions, has been proposed as objective evaluation method in different disorders including sleep/wake disorders (Yesavage, et al., 1998), Attention Deficit/Hyperactivity Disorder (Dane, Schachar, & Tannock, 2000) and Periodic Limb Movement Disorder (Kemlink, Pretl, Sonka, & Nevsimalova, 2007). In neurodegenerative disorders, actigraphy has been used to evaluate agitated behaviors (Mahlberg & Walther, 2007). There are significant correlations between Cohen-Mansfield Agitation Inventory total scores and mean wake actigraphic activity (Nagels, et al., 2006). In psychiatric disorders, psychomotor retardation has been studied using actigraphy, showing increased mean motor activity during wake in depressed patients after four weeks treatment with imipramine (Volkers, et al., 2002).

The aim of the present study was to investigate the relationship between apathy and motor activity in individuals diagnosed with mild Alzheimer's disease. The specific hypotheses were: 1) mean motor activity will be higher in control subjects than in those with mild AD; 2) those with mild AD and apathy will have less motor activity than those with mild AD and no apathy; and 3) the mean motor activity of the AD subjects will remain significantly correlated to apathy even after scores on depression measures are taken into account.

Methods

Subjects and clinical assessment

Thirty subjects with diagnosis of mild AD and 15 healthy controls were recruited at the Nice Memory Center. Each patient and family gave informed consent to participate in the study. Diagnosis of AD was established using the Diagnosis and Statistical Manual of Mental

Disorders (DSM-IV) criteria (American Psychiatric Association, 1994). Patients were excluded 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 (UPDRS) (Fahn, 1987). All patients were free of dopaminergic antidepressant and antipsychotic medication. Cholinesterase inhibitors, if present, were at a stable dose for more than six months prior to study.

General cognitive status was determined in the course of a comprehensive clinical assessment and included the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), Trail Making Test (TMT, parts A and B) (Reitan, 1955), digit spans (WAIS III-R), phonological and semantic verbal Fluency (Cardebat, Doyon, Puel, Goulet, & Joannette, 1990), a naming test (DO 80), and according to the MMSE score the free and cued selective reminding test (FCSRT) (Grober & Buschke, 1987) for the patients with a MMSE score lower than 17 and the Alzheimer's Disease Assessment Scale for Cognition (Rosen, Mohs, & Davis, 1984) for the subjects with a MMSE score higher than or equal to 17.

Neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory (NPI), which is based on a structured interview with a caregiver who is familiar with the patient. Depression was additionally rated with the Montgomery Asberg Depression Rating Scale (MADRS).

Apathy was assessed using the Apathy Inventory (AI), designed to provide a separate assessment of the three dimensions of apathy: emotional blunting, lack of initiative and lack of interest. The patient, caregiver and clinician versions of the AI were each administered as appropriate (P. H. Robert, et al., 2002). The range of scores on the caregiver version is from 3 to 12, with scores greater than three being considered clinically significant (Brocker, Claret, Benoit, & Robert, 2003). Thus, individuals with a score greater than three on the caregiver version are considered in this report as having apathy. The AI clinician version, based on the clinician's (medical doctor, psychologist, member of the care staff) observations during the consultation, was also administered (Leone et al., 2008).

Actigraphy assessment and procedure

Motor activity was assessed over 75 consecutive minutes using a wrist-worn actigraph (Actiwatch-L, MiniMitter) on the non-dominant wrist (see Figure 1). Data were collected

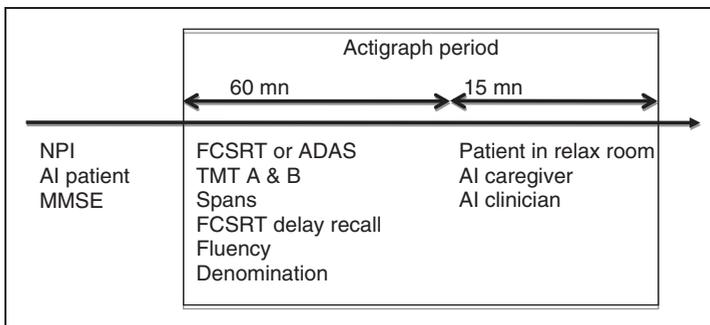


Figure 1. Organization of the subject time with the actigraph

and stored as integrated activity over 15 seconds using arbitrary units. A neuropsychological and behavioral evaluation was performed during the first 60 of the 75 minutes. The last 15 minutes were spent *ad libitum* in the waiting room. Actigraphy data were analyzed to determine the mean motor activity, the total motor activity, and the number of minutes without movement over the entire 75 minutes record (Actiware-Sleep v.3.1, Cambridge Neurotechnology). SPSS 14.0 was used to compute statistics. Group comparisons were made using the Kruskal-Wallis one-way analysis of variance and specified between groups comparisons were made with the Mann-Whitney U-Test. Paired group comparisons were made with the Wilcoxon Signed-Ranks test for matched pairs. Correlations were determined using the Spearman rank correlation coefficient.

Results

Descriptive statistics for the three subject groups (controls, AD with apathy, AD without apathy) are presented in Table 1. Mean age in the healthy control group was significantly lower than in either AD group ($p < 0.05$), but age did not significantly differ between the two AD subgroups ($p = 0.63$). As planned, mean MMSE score was significantly higher in healthy controls than AD patients ($p < 0.01$), but there was no significant difference between the two AD subgroups ($p = 0.058$). All groups were equivalent in term of NPI-scored depression and agitation, two parameters that may confound interpretation of actigraphic measurements.

The three subject groups were significantly different on all actigraphic parameters (mean motor activity, $p < 0.01$; total motor activity, $p < 0.01$; number of minutes without movements, $p < 0.01$; number of minutes with movements, $p < 0.01$).

Table 1. Descriptive statistics for healthy controls and the two groups of AD subjects. Data shown as mean \pm SD

	Controls (N = 15)	AD with apathy (N = 17)	AD without apathy (N = 15)
Sex ratio (M/F)	0.60 \pm 0.51	0.29 \pm 0.47	0.27 \pm 0.46
Age (yrs)	73.13 \pm 6.01	78.65 \pm 7.36	80.20 \pm 4.96
MMSE	30.00 \pm 0.00	22.59 \pm 2.72	20.40 \pm 3.16
MADRS	3.33 \pm 3.08	5.29 \pm 4.48	4.73 \pm 4.93
AI total score (caregiver)	*	0.62 \pm 1.19	13.69 \pm 6.45
AI total score (patient)	0.07 \pm 0.27	0.00 \pm 0.00	6.93 \pm 8.42
AI total score (clinician)	0.08 \pm 0.29	2.40 \pm 1.68	13.13 \pm 4.75
NPI delusion	*	1.56 \pm 3.97	0.57 \pm 2.14
NPI hallucination	*	1.56 \pm 0.67	0.00 \pm 0.00
NPI agitation	*	1.33 \pm 2.06	2.36 \pm 3.13
NPI depression	*	2.78 \pm 4.63	1.79 \pm 2.78
NPI anxiety	*	2.33 \pm 3.26	2.57 \pm 4.38
NPI exaltation	*	0.44 \pm 1.33	0.86 \pm 1.88
NPI disinhibition	*	1.33 \pm 2.83	0.50 \pm 1.02
NPI irritability	*	1.67 \pm 2.35	2.00 \pm 2.94
NPI aberrant motor	*	0.89 \pm 2.67	2.14 \pm 3.30
NPI sleep	*	0.00 \pm 0.00	2.43 \pm 3.06
NPI appetite	*	0.44 \pm 1.33	1.50 \pm 3.28

* NPI and the AI caregiver version were not assessed in the control population.

Controls had greater mean motor activity and less time spent without movement than both of the groups of AD subjects (Table 2). AD subjects without apathy also exhibited significantly greater mean motor activity and less time spent without movement than AD subjects with apathy in all comparison time periods. On average, mean motor activity was higher for the three groups during the 15 minutes *ad libitum* period than during the neuropsychological evaluation, but these differences were not statistically significant (controls, $p=0.075$; AD without apathy, $p=0.394$; AD with apathy, $p=0.074$). Similarly the percent of time spent without movement was lower during the *ad libitum* period, except for the AD patients without apathy. However, this difference was only significant for the control group ($p < 0.05$) (AD without apathy, $p=0.65$; AD with apathy, $p=0.43$).

Mean motor activity was negatively correlated with age ($r=-0.36$; $p < 0.05$), AI patient and caregiver version total scores ($r=-0.35$; $p < 0.05$), AI clinician version total score ($r=-0.56$; $p < 0.01$) and positively correlated with MMSE score ($r=0.51$; $p < 0.01$). There were no significant correlations between mean motor activity and the MADRS ($r=0.03$, $p=0.86$) or NPI agitation domain ($r=0.33$, $p=0.1$).

Using partial correlations, relations between mean motor activity and caregiver AI scores remained significant when controlling for age (-0.61 ; $p < 0.01$), MMSE (-0.64 ; $p < 0.01$), and MADRS total score (-0.6 ; $p < 0.01$). This was the same for the AI clinician scores when controlling for age (-0.43 ; $p < 0.05$), MMSE (-0.54 ; $p < 0.05$), and MADRS total score (-0.52 ; $p < 0.05$).

In examining the three components of the AI, mean motor activity was significantly correlated with the lack of initiative dimension on all three versions of the AI and with the lack of interest dimension on the AI clinician and patient versions (Table 3). Emotional blunting did not correlate with mean motor activity on any of the three AI versions.

Table 2. Actigraphic parameters for the three groups and comparison between AD patients without apathy vs AD patients with apathy (Mann-Whitney U-Test: $p < 0.05^*$, $p < 0.01^{**}$) and AD patients without apathy vs. Controls (Mann-Whitney U-Test; $p < 0.05^\dagger$, $p < 0.01^{\dagger\dagger}$). Data shown as mean \pm SD

	Controls	AD without apathy	AD with apathy
Mean motor activity (full 75 min)	43.93 \pm 22.59	28.88 \pm 18.27	10.30 \pm 10.98**
Mean motor activity (60 min testing)	38.99 \pm 27.83	26.72 \pm 20.90	7.76 \pm 9.20**
Mean motor activity (15 min <i>ad libitum</i>)	67.05 \pm 32.15	33.53 \pm 28.44 ^{††}	12.99 \pm 13.98*
Time without movement (full 75 min)	27.87 \pm 14.23%	40.71 \pm 19.07%	60.11 \pm 19.37%**
Time without movement (60 min testing)	28.41 \pm 16.65%	38.78 \pm 21.89%	63.59 \pm 15.76%**
Time without movement (15 min <i>ad libitum</i>)	18.15 \pm 11.85%	41.55 \pm 20.92% ^{††}	59.95 \pm 23.16%*

Table 3. Correlation between mean motor activity and apathy dimensions for the three versions of the Apathy Inventory (Spearman with $p < 0.05^*$, $p < 0.01^{**}$)

AI dimension	Patient N = 45	Caregiver N = 30	Clinician N = 45
Emotional blunting	-0.12	-0.27	-0.25
Lack of initiative	-0.35*	-0.49**	-0.58**
Lack of interest	-0.31*	-0.35	-0.55**

Discussion

Neuropsychiatric symptoms are now proposed as a major component of the dementia syndrome. There is a growing interest in these symptoms as they can be present from the earliest stages of the disease, constitute a marker of disease progression, are responsible for a large share of the suffering of patients and caregivers, and strongly determine the patient's lifestyle and management. It is therefore important to have good subjective and objective assessment methods of these symptoms.

We found a relationship between motor activity and apathy in individuals with mild AD such that individuals with AD and apathy had less motor activity than individuals with AD but without apathy. The healthy control subjects had greater motor activity than either of the AD groups.

Motor activity was particularly related to the lack of initiative AI dimension within the apathy group either as assessed by caregivers or clinicians. Interestingly lack of initiative was found to be the most frequently occurring feature of apathy in a prospective European multi-centre study (ICTUS) that evaluated 216 AD patients for apathy, using the AI (Robert, & Benoit, 2005). Lack of initiative was also related to a more general diminished goal-directed cognitive activity domain in the ICTUS study.

The AI is designed to permit a separate assessment of the three apathy dimensions: emotional blunting, lack of initiative, and lack of interest. Actigraphy-derived mean motor activity was correlated with the apathy dimensions 'lack of initiative' and 'lack of interest', but not with emotional blunting. This finding is in agreement with Muller's study (Muller, Czymbek, Thone-Otto, & Von Cramon, 2006) that suggests a relationship between motor activity and self-initiated action, which is mainly associated with lack of initiative and interest rather than with emotional blunting.

Since apathy and the dopamine system are related (David, et al., 2008), as are locomotion and the dopamine system (van den Munckhof, Gilbert, Chamberland, Levesque, & Drouin, 2006), it may be that activity levels and apathy are two measurable markers of the dopamine system. A better understanding of the relationship between apathy, locomotion, and dopamine may lead to better measurements of apathy.

Among the limitations of the current study is the fact that only a small number of subjects were evaluated. Further, these evaluations occurred across different times of days and motor activity levels can vary across time of day (Yoon, Kripke, Youngstedt, & Elliott, 2003). Since subjects were randomly scheduled, we do not believe that this limitation increased error to a significant degree, but it will be important to take time of day into account in future studies. A third limitation was that our control group was significantly younger than the other groups and age has been related to motor activity (Volkers, et al., 2002).

A fourth consideration is that even though the difference was not statistically significant, AD subjects with apathy were older and had lower MMSE scores than AD patients without apathy. However, partial correlations controlling for age and MMSE remained statistically significant between mean motor activity and the AI total score. The AD subjects as a group also had moderate agitation and depression, which can respectively enhance (Nagels, et al., 2006) or decrease motor activity (Stanley, Fairweather, & Hindmarch, 1999; Teicher, 1995; Volkens, et al., 2002; Volkens, et al., 2003), but these two parameters did not distinguish the AD subjects with and without apathy.

In summary, the present study showed that AD patients had lower motor activity levels than healthy subjects and AD patients with apathy had lower motor activity levels

than AD patients without apathy. This suggests that actigraphic locomotor activity assessment may be a useful, objective method to evaluate the severity of apathy in AD patients.

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