RESEARCH ARTICLE

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Diagnostic criteria for apathy in clinical practice

E. Mulin[1], E. Leone[1], K. Dujardin[2], M. Delliaux[2], A. Leentjens[3], F. Nobili[4], B. Dessi[4], O. Tible[5], L. Agüera-Ortiz[6], R. S. Osorio[6], J. Yessavage[7,8], D. Dachevsky[9], F. RJ. Verhey[10], A. J. Cruz Jentoft[11], O. Blanc[12], P. M Llorca[12] and P. H. Robert[1]

[1]Centre Mémoire de Ressources et de Recherche, CHU, Université de Nice Sophia, Antipolis, France
[2]Neurology and Movement Disorders, Lille University Medical Center, Lille, France
[3]Department of Psychiatry, Maastricht University Medical Center/Alzheimer Centre Limburg, Maastricht, the Netherlands
[4]Clinical Neurophysiology Unit, Department of Neurosciences, Ophthalmology and Genetics, Azienda Ospedale-Università S. Martino, Genova, Italy
[5]Department of Psychiatry, Université de Nice Sophia, Antipolis, France
[6]Alzheimer Project Research Unit, Cien & Reina Sofia Foundation, Madrid, Spain
[7]Sierra-Pacific Mental Illness Research, Education, and Clinical Center, Palo Alto VA Health Care System, CA, USA
[8]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, CA, USA
[9]Department of Psychiatry; National University Rosario, Argentina
[10]Maastricht University Medical Center/ Alzheimer Centre Limburg, the Netherlands
[11]Servicio de Geriatría, Hospital Universitario Ramón y Cajal, Madrid, Spain
[12]Université d'Auvergne, CHU Clermont-Ferrand, France
Correspondence to: P. H. Robert, E-mail: phil.robert15@orange.fr

Background: Apathy is an important and distressing behavioural symptom in Alzheimer's disease and in various neuropsychiatric disorders. Recently, diagnostic criteria for apathy have been proposed.

Objectives: In groups of patients suffering from different neuropsychiatric diseases, (i) to estimate the prevalence of patients meeting the proposed diagnostic criteria; (ii) to estimate the concurrent validity of the criteria with the neuropsychiatric inventory (NPI) apathy item; (iii) to identify the most frequently met criteria or sub-criteria in each specific neuropsychiatric disease and (iv) to estimate the inter-observer reliability of the diagnostic criteria for apathy.

Methods: This cross-sectional, multicentric, observational study was performed on 306 patients. Each of the participating centres had to check the presence of apathy according to the diagnostic criteria for apathy in consecutive patients belonging to the following diagnoses list: Alzheimer disease (AD), mixed dementia, mild cognitive impairment (MCI), Parkinson's disease (PD), Schizophrenia (DSM-IV) and major depressive episode. In addition to the clinical interview, the assessment included the Mini Mental Score Examination (MMSE) and the NPI. At the end of the visit, clinicians were required to check the diagnostic criteria for apathy.

Results: Using the diagnostic criteria for apathy, the frequency of apathy was of 53% in the whole population, 55% in AD, 70% in mixed dementia, 43% in MCI, 27% in PD, 53% in schizophrenia and 94% in major depressive episode. In AD, mixed dementia, MCI and PD, the NPI apathy score was significantly higher for patient fulfilling the apathy criteria. Goal-directed cognitive activity (criteria B2-Cognition) was the most frequently observed domain followed by goal-directed behaviour (criteria B1—Behaviour) and emotion (criteria B3), respectively. Inter-rater reliability was high for the overall diagnostic (κ coefficient = 0.93; $p = 0.0001$) and for each criteria.

Conclusion: This study is the first one to test the diagnostic criteria for apathy in clinical practice. Results make the diagnostic criteria useful for clinical practice and research. Copyright © 2010 John Wiley & Sons, Ltd.

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Introduction

Apathy is now well recognized as an important behavioural syndrome in Alzheimer's disease (AD) and in several neuropsychiatric disorders (Kulisevsky *et al*., 2008; Geda *et al*., 2008; Ishii *et al*., 2009; Saz *et al*., 2009).

Marin was the first (Marin, 1990, 1991) to present apathy as a disorder of motivation, defined as 'the direction, intensity and persistence of goal-directed behaviour'. Marin structured the clinical expression of apathy around the concept of reduced goal-directed behaviour, cognition and emotional concomitants. Most of the current descriptions acknowledge this point and consider apathy in terms of a lack of goal-directed behaviour, cognition or emotion (Levy and Dubois, 2006).

As indicated by Starkstein and Petracca (2001), apathy is increasingly diagnosed in patients with neurological and psychiatric conditions in spite of the lack of a proper definition and the authors strongly stress the importance of consensus on such criteria in order to facilitate future research in the correlates and impacts of apathy as well as in its treatments (Drijgers *et al*., 2009).

This consensus has been recently organized (task force including members of the Association Française de Psychiatrie Biologique, the European Psychiatric Association, the European Alzheimer's Disease Consortium and experts from Europe, Australia and North America) and a set of diagnostic criteria for apathy (Table 1) has been proposed (Robert *et al*., 2009).

In them, apathy is defined as a disorder of motivation that persists over time and should meet all the following requirements. Firstly, the core feature of apathy, i.e. diminished motivation, must be present for at least 4 weeks; secondly, impairment in at least 2 among the three dimensions of apathy (i.e. reduced goal-directed behaviour, goal-directed cognitive activity and emotions) must also be present; thirdly, there should be identifiable functional impairments attributable to apathy. Finally, exclusion criteria are specified to exclude symptoms and conditions mimicking apathy.

The aim of the present study was to test these diagnostic criteria for apathy in clinical practice in groups of patients suffering from different neuropsychiatric diseases. Specifically, the objectives were: (i) to estimate the prevalence of patients meeting the proposed diagnostic criteria for apathy within some common diagnostic categories; (ii) to estimate the concurrent validity of the criteria with the neuropsychiatric inventory (NPI) apathy item; (iii) to identify the most frequently met criteria or sub-criteria in each specific neuropsychiatric disease and (iv) to estimate the inter-observer reliability of the diagnostic criteria for apathy.

Table 1 Diagnostic criteria for apathy

For a diagnosis of Apathy the patient should fulfil the criteria A, B, C and D.
A—Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his age or culture. These changes in motivation may be reported by the patient himself or by the observations of others.
B—Presence of at least one symptom in at least two of the three following domains for a period of at least four weeks and present most of the time.
Domain B1—Behaviour:
Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following:
Initiation symptom: loss of self-initiated behaviour (for example: starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices)
Responsiveness symptom: loss of environment-stimulated behaviour (for example: responding to conversation, participating in social activities)
Domain B2—Cognition:
Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:
Initiation symptom: loss of spontaneous ideas and curiosity for routine and new events (i.e, challenging tasks, recent news, social opportunities, personal/family and social affairs).
Responsiveness symptom: loss of environment-stimulated ideas and curiosity for routine and new events (i.e, in the person's residence, neighbourhood or community).
Domain B3— Emotion:
Loss of, or diminished, emotion as evidenced by at least one of the following:
Initiation symptom: loss of spontaneous emotion, observed or self-reported (for example, subjective feeling of weak or absent emotions, or observation by others of a blunted affect).
Responsiveness symptom: loss of emotional responsiveness to positive or negative stimuli or events (for example, observer-reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotional-laden news).
C—These symptoms (A - B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.
D—The symptoms (A - B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to diminished level of consciousness or to the direct physiological effects of a substance (e.g. drug of abuse, a medication).

Methods

Population

This cross-sectional, observational study involved 324 patients coming from 11 centres including memory consultation services, and both neurology, geriatric and psychiatric departments (Table 2).

Each centre had to check the presence of apathy according to the diagnostic criteria for apathy in consecutive patients belonging to the following diagnoses list: AD (NINCDS-ADRDA criteria) (Mckhann *et al*., 1984); mixed dementia for patient with both AD and vascular pathology (either DSM-IV), mild cognitive impairment (MCI) (Petersen *et al*., 1999), Parkinson's disease (PD) (UKPDBB criteria, Hughes *et al*., 1992), Schizophrenia (DSM-IV criteria) and major depressive episode (DSM-IV criteria)(American Psychiatric Association, 1994).

Informed consent was obtained from each patient included in the study. Patients were excluded if they presented with pre-morbid mental retardation, or other cerebral disorders, or combination of the previously listed neuropsychiatric disorders, or if no reliable answer can be obtained on the rating scales or questionnaires due the severity of the disease.

Cognitive and behavioural assessment

Subjects were assessed during their regular clinic visit or, in case of patients living in long-term care units, during a routine visit by their clinician. In addition to the clinical interview, the assessment included the Mini Mental Score Examination (MMSE) (Folstein *et al*., 1975) and the NPI (Cummings *et al*., 1994). At the end of the visit, clinicians were required to check the diagnostic criteria for apathy. At the end of the visit, clinicians were required to check the diagnostic criteria for apathy (DCA). For a diagnosis of apathy, the patient should fulfill the criteria A, B, C and D. Criteria A indicates the general definition of apathy. Criteria B describes the three core domains of apathy, i.e. behaviour, cognition and emotion (Table 2). Criteria B is based on the premise that change in motivation can be measured by examining a patient's responsiveness to internal or external stimuli. Therefore, each of the three domains within Criterion B includes two symptoms. The first symptom pertains to self-initiated or 'internal' behaviours, cognitions and emotions (initiation symptom) and the second symptom to the patient's responsiveness to 'external' stimuli (responsiveness symptom).

Statistical analysis

For demographical, clinical and diagnostics of apathy data, group comparisons were performed with the Kruskal–Wallis and χ^2 tests. In order to estimate the concurrent validity of the criteria, the mean NPI apathy score of patients with (DCA+) and without (DCA−) the diagnostic of apathy was compared in each diagnosis group. Cohen's κ statistical measures were used for inter-observer reliability of the diagnostic criteria. Two independent raters (psychiatrists) scored 32 patients and caregiver's interviews.

Results

The demographical and clinical characteristics of the whole population as well as of each diagnostic group are shown in Table 3. The analysis was performed on 306 of the 324 subjects originally included. Eighteen patients were excluded from the analysis because belonging to diagnosis categories not sufficiently represented (Lewy body dementia ($n = 6$): mean age

Table 2 Centres participating in the study, number of patients and diagnostic categories

Centre	$n = 324$	Diagnostic categories of included patients
Nice—A, France	82	AD, MCI, mixed dementia, Parkinson's disease
Nice—B, France	49	Schizophrenia, major depressive episode
Genoa, Italy	49	AD, MCI, mixed dementia
Maastricht A, The Netherlands	10	Parkinson's disease
Maastricht B, The Netherlands	17	AD, MCI
Stanford, USA	24	AD, MCI
Lille, France	30	Parkinson disease
Clermont Ferrand, France	5	Schizophrenia,
Rosario, Argentina	20	Schizophrenia, AD, MCI
Madrid A, Spain	10	AD, mixed dementia, major depressive episode
Madrid B, Spain	28	AD, mixed dementia, major depressive episode

Table 3 Demographics, clinical characteristics and frequency of diagnostic criteria for apathy in the diagnostic groups

	Total population	AD Mean (SD)	Mixed D	MCI	PD	Schiz.	MDE	p [a]
N	306	132	50	30	44	32	18	
Sex ratio M/F	137/169	44/88	23/27	16/14	26/18	22/10	6/12	
Age[a]	71.10 ± 15.99	79.18 ± 6.54	79.10 ± 6.56	74.40* ± 10.19	66.34* ± 9.23	37.88* ± 13.74	60.72* ± 19.21	0.0001
MMSE[a]	21.46 ± 5.88	18.27 ± 4.57	17.48 ± 5.18	25.53* ± 2.73	26.23* ± 3.85	26.88* ± 2.81	27.61* ± 2.4	0.0001
NPI depression[a] ± 3.04	3.02 ± 3.92	2.81 ± 3.67	2.06 ± 2.81	1.62 ± 2.44	2.55			
	4.22 ± 4.18	10.06* ± 2.01	0.0001					
NPI apathy[a] ± 3.88	4.24 ± 4.01	4.09 ± 3.89	4.94 ± 3.89	3.43 ± 3.99	2.32			
	5.16 ± 4.44	7.29* ± 2.85	0.0001					
DCA+ (%)	53	55	70	43	27	53	94	0.0001[b]

M = male; F = female.
AD = Alzheimer's disease, Mixed D = mixed dementia, MCI = mild cognitive impairment, PD = Parkinson disease, Schiz = schizophrenia, MDE = major depressive episode.
DCA+: patients fulfilling the complete diagnostic criteria for apathy.
[a]Kruskall–Wallis H test including the 6 diagnostic groups.
[b]χ^2.
*$p < 0.05$.

(73.3 ± 9.1), mean MMSE (21.5 ± 5.5), frequency of patients fulfilling the diagnostic criteria = 83.3% Fronto temporal dementia ($n = 7$): mean age (77.1 ± 5.7), mean MMSE (13.6 ± 8.0), frequency of patients fulfilling the diagnostic criteria = 85.7%. Unspecified diagnosis ($n = 5$): mean age (49.2 ± 7.2), mean MMSE (27.6 ± 0.9), frequency of patients fulfilling the diagnostic criteria = 0%.). Comparison between included and excluded patients using Student t-test and χ^2 indicated no significant differences for age, MMSE and DCA frequency.

In the included population frequency of the patients fulfilling completely the diagnostic criteria for apathy was significantly different among the diagnostic groups ($\chi^2 = 36\,338$, df = 7, $p < 0.0001$).

The main characteristics of the patients with and without diagnostic criteria for apathy are shown in Table 4. In each diagnostic group, the NPI apathy score was significantly higher for patients fulfilling the apathy criteria except for the MDE group with only one patient in the non-apathy diagnostic group.

When merging all the patients with dementia or a neurodegenerative disease (AD, mixed dementia and PD diagnostic groups), the DCA+ patients ($n = 119$) had a significantly higher ($p < .001$) apathy NPI score (mean 6.7; SD 3.3) than DCA−patients ($n = 105$; mean apathy NPI score = 1.1; SD = 1.9).

Table 5 shows the frequency of the three domains of apathy described in criteria B and Figure 1 shows the frequency for the whole neurodegenerative group. Goal-directed cognitive activity (B2-Cognition) was the most frequently observed domain followed by goal-directed behaviour (B1—Behaviour) and emotion (B3), respectively. In each domain the initiation symptoms were more frequent than the responsiveness symptoms except for the major depressive episode group (B3 responsiveness more frequent than B3 initiation in the DCA+ subgroup).

Inter-rater reliability was high for the overall diagnostic (κ coefficient = 0.93; $p = 0.0001$) and for each criteria; criteria A (κ coefficient = 1; $p = 0.0001$), criteria B1.1 (kappa coefficient = 0.56; $p = 0.002$), criteria B1.2 (κ coefficient = 0.61; $p = 0.0001$), criteria B2.1 (κ coefficient = 0.8; $p = 0.0001$), criteria B2.2 (κ coefficient = 0.63; $p = 0.0001$), criteria B3.1 (κ coefficient = 0.79; $p = 0.0001$), criteria B3.2 (κ coefficient = 0.71; $p = 0.0001$), criteria C (κ coefficient = 0.93; $p = 0.0001$), criteria D (κ coefficient = 0.93; $p = 0.0001$).

Discussion

The first objective of the study was to estimate prevalence of patient meeting the diagnostic criteria for

Table 4 Characteristic of patients with and without diagnostic criteria for apathy

	n =	Sex ratio M/F	Age	MMSE	NPI depression	NPI apathy
AD DCA−	59	16/43	78.9 (6.3)	19.4 (4.5)	1.9 (3)	1.4 (2.2)
AD DCA+	73	27/46	79.4 (6.8)	17.5 (4.5) *	3.8 (4.1)**	6.9 (3.3) **
Mixed D DCA−	15	5/10	79.9 (5)	19.4 (3.9)	1.8 (2.9)	.67 (1.2)
Mixed D DCA−	35	18/17	78.7 (7.2)	16.6 (5.5)	2.2 (2.8)	6.8 (3.1)**
MCI DCA−	17	9/8	75.1 (11.8)	26.5 (2)	1.7 (2.7)	1.3 (1.9)
MCI DCA+	13	8/5	73.5 (8)	24.3 (3.1)	1.4 (1.9)	7.7 (3.6)**
Park D DCA−	32	19/13	65.1 (8.8)	26.6 (3.8)	1.7 (2.8)	.3 (.6)
Park D DCA+	12	7/5	69.6 (9.9)	25.2 (3.9)	4 (3)	5.9 (4.7)**
Schiz DCA−	15	11/4	41 (13.8)	28.3 (2.5)	3 (2.8)	1.3 (1.8)
Schiz DCA+	17	11/6	35 (13.5)	25.6 (2.5)**	5.3 (4.9)	8.5 (3.1)**
MDE DCA−	1	0/1	65	28	9	6
MDE DCA+	17	6/11	60.5 (19.8)	27.6 (2.5)	10.1 (2.1)	7.4 (2.9)
Total population DCA−	139	62/82	70.4 (15)	23.1 (5.4)	1.9 (2.9)	1.2 (1.9)
Total population DCA+	167	76/86	71.7 (16.8)	19.9 (5.9)**	3.9 (4.1)**	7 (3.3)**

M = male; F = female.
AD = Alzheimer disease, Mixed D = mixed dementia, MCI = mild cognitive impairment, Park.D = Parkinson disease, Schiz = schizophrenia, MDE = major depressive episode.
DCA+: Patients fulfilling the complete diagnostic criteria for apathy.
DCA−: Patients not fulfilling the complete diagnostic criteria for apathy.
For each diagnostic group DCA+ *vs.* DCA− Mann–Whitney:
*$p < 0.05$.
**$p < 0.01$.

apathy. Apathy has been described as the most frequent behavioural symptom in AD (Cummings *et al.*, 1996; Robert *et al.*, 2005; Aalten *et al.*, 2007). Reviewing the literature, Van Reekum *et al.* (2005) indicated that its frequency ranges from 55 to 80% in studies using the NPI and from 37 to 86% in studies using specific apathy scales. The present study shows that using the diagnostic criteria for apathy, its frequency in AD (55%) is in the lower part of the range. This is also the case for Parkinson's disease. In the literature, the reported frequencies range from 17 to 70% (Starkstein and Leentjens, 2008). In two recent studies, using the Lille Apathy Rating Scale, Dujardin *et al.* (2007, 2008) observed that respectively 32 and 35% of the PD patients were apathetic with a higher proportion in patients with dementia. In the present study, apathy was diagnosed in 27% of the PD patients. In comparison to assessment scales, the restrictive character of the diagnostic criteria for apathy may be related to the fact that fulfilling diagnostic criteria requires a more in depth comprehensive neuropsychiatric and social evaluation.

However, this is not the case for other diagnostic subgroups than AD. For instance, in MCI the observed rate (43%) is closer to the highest range of the previous

Table 5 Frequency of the three domains of apathy described in criteria B in the different diagnostic groups

	AD *n* = 73	Mixed D *n* = 35	MCI *n* = 13	Park. D *n* = 12	Schiz. *n* = 17	MDE *n* = 17	All patients *n* = 167
B1—Behaviour							
I+ (%)	84	97	85	91.7	82.4	76.5	85.9
R+ (%)	63	57.1	46	50	70.6	41.2	58.3
B2—Cognition							
I+ (%)	89	91.4	85	100	94.1	94.1	90.8
R+ (%)	77	62.9	62	75	82.4	58.8	71.8
B3—Emotion							
I+ (%)	66	40	54	50	94.1	23.5	57.1
R+ (%)	52	17.1	54	41.7	82.4	35.3	44.8

AD = Alzheimer disease, Mixed D = mixed dementia, MCI = mild cognitive impairment, PD = Parkinson disease, Schiz = schizophrenia, MDE = major depressive episode.
DCA+: Patients fulfilling the complete diagnostic criteria for apathy.
DCA−: Patients not fulfilling the complete diagnostic criteria for apathy.
I+: Loss of Initiation.
R+: Loss of Responsiveness.

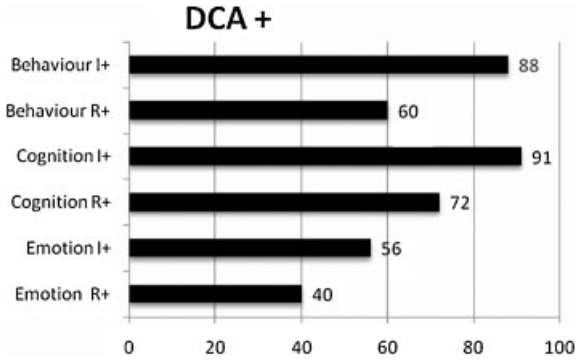

Figure 1 Frequency (%) of the three dimensions of apathy described in criteria B in the overall degenerative group (Alzheimer disease + mixed dementia + Parkinson disease) divided according to the presence (DCA+) of the diagnostic criteria for apathy (I+: Loss of Initiation/ R+: Loss of Responsiveness).

studies, reporting an apathy frequency between 11 and 39% (Geda *et al*., 2004; Hwang *et al*., 2004; Robert *et al*., 2006; Vicini *et al*., 2009). This rate remains questionable because of it heterogeneity, part of them only being probably predemented patients.

More unexpected is the 70% rate observed in mixed dementia, even higher than in the present AD group and than the rate of 33.8% observed in two vascular dementia studies (Aharon-Peretz *et al*., 2000; Lyketsos *et al*., 2002). Mixed dementia is a composite diagnostic category in which both AD-type neurodegeneration and heavy vascular damage contribute to cognitive and behavioural symptoms. This may explain the higher rate of apathy diagnostic in this group. Moreover, the Lykestsos's study was a population-based study and may have produced a lower apathy rate.

Very few data are available concerning schizophrenic patients. The 53% rate is not surprising if we take into account the overlap between apathy and negative symptoms (Brown and Pluck, 2000). For major depressive episode, even if the sample size was small ($n = 18$), the 94% rate confirms the strong overlap between depression and apathy (Levy *et al*., 1998). One of the main reasons of this high rate is probably related to the symptomatic description. Indeed, the DSM-IV as well as the provisional criteria for depression in AD (Olin *et al*., 2002) allows the diagnostic of depressive episode in the absence of depressed mood if three other core symptoms are present and diminished interest is one of these symptoms. However it is important to underline in clinical practice that mood is the core feature of depression.

A last point could help to understand why the percentages of apathy may differ among studies. In the whole population, the DCA+ patients had a significantly lower MMSE score than the DCA− patients (19.9 *vs*. 23.1). In another word, diagnostic for apathy was more frequent in patients with a higher severe cognitive impairment and this difference reached statistical significance in diagnostic subgroup such as AD and in schizophrenia. This is true for apathy and probably for other BPSD and underlines the fact that the severity of the disease must be taken into account to really appreciate the prevalence of apathy in a given disease.

The second objective of the study was to estimate the concurrent validity of the criteria with the NPI apathy item. As there was no independent available gold standard the diagnosis of apathy, concurrent validity was difficult to examine. In the present study, we decided to use the NPI apathy score as a reference because it is the most frequently used in the literature. In addition a cut-off score is available (Verhey *et al*., 2003), a score higher than 3 (range 0–12) being considered as clinically significant. For each diagnostic subgroup of the present study, only patients fulfilling the diagnostic criteria for apathy had a NPI apathy score higher than 3, even when the standard deviation value was taken into account. An interesting aspect of this result is the agreement between the caregiver NPI assessment and the clinician diagnostic choice. However, the NPI was developed for patients with dementia and its use and value in depression, schizophrenia and other diseases is, at least, debatable. In line with this result, the new version of the NPI (De Meideros *et al*., 2009) known as the NPI-C (C for clinician rating methodology) will include in the apathy domain the symptoms described in the criteria.

The third objective of the study was to identify the most frequently met criteria or sub-criteria in each neuropsychiatric disease. Descriptive results indicate that goal-directed cognitive activity (B2-Cognition) is the most frequent in neurodegenerative diseases, closely followed by goal-directed behaviour (B1—Behaviour), especially in the overall dementia group. The importance of the behavioural dimension is probably related to the fact that it is the most externally observable. Using actigraphy, it has been demonstrated that AD patients with apathy have lower motor activity than AD patients without apathy (Mulin *et al*., 2009). This aspect is of interest if we consider that it is possible to develop new and more objective technologies in order to assess apathy and other neuropsychiatric disorders. These two dimensions were always more frequent than the emotion dimension. On the contrary, the latter was the most frequently observed in the schizophrenic patients with apathy diagnostic. This is in line with the daily clinical observation of schizophrenic patients and suggests that relation described between apathy

and negative symptoms must include qualitative differences.

One of the characteristics of the DCA is to allow a separate description of each dimension. The observation of the higher frequency of the initiation symptoms in comparison to the responsiveness symptoms is interesting and needs to be described more precisely because having a potential interest in order to select patient able to respond to non-pharmacological stimulation.

We are aware of the limitation of the study. First of all these results come from a non-random sample and therefore may lead to ascertainment bias. In addition the prevalence estimates coming from a convenience clinical sample are more prone to bias than for a population-based study.

Inter-rater reliability of diagnostic criteria for apathy was high. However, this is one of the limitations of the study because the reliability was only assessed with French raters. This must be verified in other languages. Another important limitation comes from the fact that the study population is rather heterogeneous, with small number of MDE and schizophrenic patients compared to demented patients. Finally the population was also heterogeneous in term of cognitive decline severity and we had no sizable data concerning Lewy body dementia and fronto temporal dementia.

In conclusion, this study is the first one to assess the interest of the diagnostic criteria for apathy in clinical practice. The criteria are applicable across a number of different diseases. Acceptability by clinicians is good. Inter-rater reliability was good as well as the concurrent validity against the NPI, the most widely used measure of apathy. All of the above make the diagnostic criteria useful for clinical practice and research. Further validation in subgroups and according to the level of dementia severity is necessary.

Key Points

- Apathy is defined as a disorder of motivation and there is wide acknowledgement that apathy is an important behavioural syndrome in Alzheimer's disease and in various neuropsychiatric disorders.
- The study shows that diagnostic criteria for apathy are applicable across a number of different diseases.
- Acceptability by patients and clinicians is good. Inter-rater reliability was good as well as the concurrent validity with the neuropsychiatric inventory, the widely used measure of apathy.

Conflict of interest

None declared.

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