

Apathy in Parkinson's disease: differences between caregiver's report and self-evaluation

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Summary

Apathy is a state of diminished goal-directed speech, motor activity and emotions. The prevalence of apathy in Parkinson's disease (PD) ranges from 16 to 62%. Several studies have investigated the relationships between apathy and other dimensions of PD, but little is known about possible discrepancies between self-evaluation (SE) and caregiver reporting (CR) of this symptom.

The aim of this study is twofold: 1) to investigate the differences in apathy evaluations according to the point of view from which apathy is reported (SE vs CR); 2) to identify the possible relationships between each of the two evaluations (SE and CR) and cognitive and affective dimensions of PD.

Forty-eight patients with PD were assessed using the Apathy Evaluation Scale (AES) in its SE and CR versions (AES-SE and AES-CR); cognitive, affective and behavioral symptoms were also assessed.

AES-SE scores were significantly higher than AES-CR ones. Neither AES version correlated with depression, whereas both correlated with motor impairment, disease stage and behavioral symptoms. Mini-Mental State Examination and Frontal Assessment Battery scores showed significant negative correlations only with AES-SE scores.

Our findings suggest that the point of view from which apathy is seen can lead to significant discrepancies, even when using the same tool. This should be taken into account in order to obtain correct assessment of this disabling and distressing symptom.

KEY WORDS: apathy, Apathy Evaluation Scale, caregivers, informant report, Parkinson's disease.

Introduction

In recent years a great deal of attention has been devoted to the study and assessment of non-motor symptoms of Parkinson's disease (PD). Apathy is one of the most common of these, occurring from the early stages of disease, often in association with decreased quality of life (Barone et al., 2009; Starkstein et al., 2009).

Apathy is a state of diminished goal-directed speech, motor activity and emotions. According to a recent meta-analysis report, apathy affects 16 to 62% of patients with PD, with an average prevalence of 40%, depending on the sample population, diagnostic criteria and evaluation tools. The Authors showed that apathy is associated with higher age, lower mean Mini-Mental State Evaluation (MMSE) score, increased risk of comorbid depression, higher Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale score, and more severe disability (den Brok et al., 2015).

The diagnosis of apathy is challenging since many of its features overlap with symptoms commonly associated with PD, e.g., bradyphrenia, fatigue, etc. Apathy has been related to mesolimbic dopaminergic denervation (Tremblay et al., 2015; Pagonabarraga et al., 2015) and frequently associated with more severe frontal dysfunctions and a high risk of developing dementia (Dirnberger and Jahanshahi, 2013; Santangelo et al., 2014). In addition, the precise pathophysiological mechanisms underlying apathy in PD are still unclear, although it probably arises from the involvement of different brain regions and neural pathways, each separate from those involved in other symptoms of the disease (Robert et al., 2012; Skidmore et al., 2013). Accordingly, some researchers have claimed that apathy should be regarded as a heterogeneous syndrome rather than a single symptom. Levy and Dubois (2006) and Levy (2012) proposed an emerging triad of neurobiological apathy subtypes, namely, auto-activation apathy, which manifests as a lack of activity or initiation of thought or action; emotional-affective apathy, which involves processing of emotional information and is observable as emotional blunting or indifference, and cognitive apathy (or cognitive inertia), observable as an inability to expand on plans, and organize or manage goals associated with plans (Radakovic et al., 2018).

In this setting, most of the scales assessing apathy, including the one adopted in the present study, reflect this multidimensional approach (Marin et al., 1991; Starkstein et al., 1992; Santangelo et al., 2014). They are interview-based tools that consider the caregiver's report (CR) and/or patient's self-evaluation (SE) of apathy.

Several studies have investigated the relationships between apathy and other dimensions of PD, but little attention has been devoted to the topic of possible discrepancies between CR and SE of apathy.

McKinlay et al. (2008) show a low agreement (45%) between CR and SE of apathy in patients with PD, SE scores being significantly higher than those from CR. Conversely, Schiehser et al. (2013) report almost comparable frequency of current apathy when comparing patients' (58.8%) and caregivers' reports (54.9%), but a significant discrepancy when considering the reported frequency of pre-diagnosis patient apathy (31.4% according to patients and 15.7% according to caregivers). Finally, a recent study (Radakovic et al., 2018) has shown, in PD patients a slightly higher overall prevalence of self-rated apathy (38%) versus informant /carer rating of the symptom (33%). Interestingly, in this comparison, only executive apathy was higher in PD patients' as compared with informants' ratings.

The aim of this study is twofold: 1) to investigate possible differences in apathy evaluation according to the point of view from which apathy is reported (CR vs SE); 2) to identify possible relationships between each of the two evaluations (CR and SE) and cognitive and affective dimensions of PD.

Materials and methods

Subjects

Forty-eight patients (31 men and 17 women) with PD were consecutively enrolled at the Neurology Unit of the "S. Giuseppe Moscati" Hospital in Avellino. PD was diagnosed according to the United Kingdom Parkinson's Disease Brain Bank criteria (Douglas et al., 1999). Patients' mean age and duration of education were respectively 72.21 (SD=9.01) and 7.33 years (SD=3.69). The mean disease duration was 6.02 years (SD=3.58). The patients had a mean Hoehn & Yahr scale (H-Y) score of 2.42 (SD=0.79) and a mean Unified Parkinson's Disease Rating Scale motor subscale (UPDRS III) score of 23.54 (SD=8.75).

Procedures

All patients underwent cognitive and behavioral assessment one hour after the last intake of their usual dopaminergic treatment. All underwent a brief neuropsychological evaluation including a scale of global cognitive status (Mini-Mental State Examination, MMSE) (Folstein et al., 1975) and a test to screen "frontal" functions (Frontal Assessment Battery, FAB) (Dubois et al., 2000; Iavarone et al., 2004). Assessment of affective and behavioral symptoms was carried out using a scale for depression (Hamilton Depression Rating Scale, HDRS) (Hamilton, 1960) and one for neuropsychiatric symptoms (Neuropsychiatric Inventory for Psychopathology, NPI-P) (Cummings et al., 1994). Apathy was evaluated using the Apathy Evaluation Scale (AES) (Starkstein et al., 1992; Santangelo et al., 2014) in both its SE and CR versions. The AES consists of 18 items; the score for each item ranges, on a Likert scale, from 1 to 4 points. The total AES score thus ranges from 18 to 72, with higher scores corresponding to more severe symptoms. The AES includes three subscores describing different dimensions of apathy, namely cognitive, behavioral and emotional apathy. The AES (SE version) has been recently validated in an Italian

study, which showed good psychometric properties of the questionnaire in detecting apathy in untreated *de novo* patients with PD (Santangelo et al., 2014); in that study, an AES-SE cut-off score of 37 showed 90% sensitivity and 90% specificity in distinguishing apathetic from non-apathetic patients.

All the patients gave their informed consent to the study, which was carried out in accordance with the Declaration of Helsinki and approved by the local ethics committee. The 48 caregivers were relatives of the patients (in most cases the spouse). None of them suffered from overt cognitive impairment or significant psychiatric disorders.

Statistics

Descriptive statistics were used to summarize the data. Differences between AES-SE and AES-CR (total score and subscores) were analyzed by a paired t-test, with the significance level set at $p=0.0167$ after correction for the number of comparisons. The chi-square test was used to compare the number of SE versus CR apathetic patients. The correlations between total AES scores (SE and CR) and measures of cognitive functioning (MMSE and FAB), motor impairment and clinical staging (UPDRS III and H-Y), and depressive and neuropsychiatric symptoms (HDRS and NPI-P) were described using a partial correlation matrix. Given the number of correlations, the significance level was set at $p=0.008$.

Results

Table I reports the mean values and standard deviation (SD) recorded on the MMSE, FAB, HDRS and NPI-P, and both versions of the AES (SE and CR). On the AES-SE, 44/48 (91.7%) patients scored >37 which classified them as apathetic; applying the same cut-off, 34/48 patients (70.8%) were found to be apathetic on the AES-CR, with a level of agreement of 50%. The difference between the number of SE and CR apathetic patients was significant (chi-square=6.84; $p<0.01$). The mean total AES-SE score was significantly higher than the mean total AES-CR score ($t=2.167$; $p=0.01$). With regard to AES subscores, a significant difference was observed on emotional apathy (mean SE=6.06; SD=1.55; mean CR=5.21; SD=1.96; $t=2.675$; $p=0.01$). No difference approached significance when comparing SE versus CR cognitive and behavioral apathy subscores. The SE and CR total scores were correlated ($r=0.483$; $p=0.0004$).

Table I - Descriptive statistics: total score mean and standard deviation (SD) of each assessment tool.

	Mean	SD
MMSE	22.83	4.71
FAB	10.24	2.86
HDRS	17.56	7.55
NPI-P	27.04	22.46
AES - SE	49.85	10.37
AES - CR	45.14	13.09

Abbreviations: MMSE=Mini-Mental State Examination; FAB=Frontal Assessment Battery; HDRS=Hamilton Depression Rating Scale; NPI-P=Neuropsychiatric Inventory for Psychopathology; AES=Apathy Evaluation Scale (SE: self-evaluation version; CR: caregiver report version).

Table II - Partial correlation matrix.

	MMSE	FAB	UPDRS III	H-Y	NPI-P	HDRS
AES-SE	-0.528 p<0.0001	-0.391 p=0.005	0.426 p=0.002	0.412 p=0.003	0.414 p=0.003	0.142 NS
AES-CR	-0.346 NS	-0.233 NS	0.455 p=0.001	0.374 p=0.008	0.536 p<0.0001	0.165 NS

Abbreviations: AES=Apathy Evaluation Scale (SE: self-evaluation version; CR: caregiver report version); MMSE= Mini-Mental State Examination; FAB=Frontal Assessment Battery; UPDRS III=Unified Parkinson's Disease Rating Scale motor subscale; H-Y=Hoehn & Yahr Scale; NPI-P=Neuropsychiatric Inventory for Psychopathology; HDRS=Hamilton Depression Rating Scale; NS=not significant

Table II reports correlations between AES-SE and AES-CR scores and cognitive, clinical, neurobehavioral and depression measures. Neither of the two AES versions correlated with depression, while scores on both AES versions were significantly correlated with motor impairment (UPDRS III), disease stage (H-Y) and neurobehavioral (NPI-P) symptoms. Interestingly, significant inverse correlations were observed between MMSE and FAB scores and AES-SE scores (i.e., lower MMSE and FAB scores, higher AES scores), whereas no correlation was found between cognitive measures and AES-CR scores.

Discussion

The first finding of the present study is that apathy may be highly frequent in PD, if it is evaluated using sensitive and specific tools. In our sample, apathy was found to affect the majority of the patients, as shown both by self-ratings and informant ratings. The percentage of apathetic subjects was higher than that reported in the literature (den Brok et al., 2015), and the AES-SE scores were higher than those reported in the study by Santangelo et al. (2014) in *de novo* untreated Italian PD patients. Several factors may account for these differences; in particular, our subjects showed a longer disease duration, older age, more advanced disease stage and greater motor impairment, and scored lower on cognitive tests.

Most of these factors have been shown to be associated with the frequency of apathy in PD (den Brok et al., 2015). This insight is further supported by our finding of significant correlations between AES scores (both SE and CR) and those recorded on the UPDRS III and H-Y scales, and, at least in the SE version, also with the MMSE and FAB scores. On the other hand, our data confirm the robust psychometric properties of the AES, at least in the SE version, in assessing apathy in PD, and support the need to include evaluation of apathy, by means of validated tools, as part of diagnostic and follow-up procedures (Santangelo et al., 2014).

The relationship between depression and apathy in PD remains unclear, as the data from the literature is not univocal. The present study shows that apathy, regardless of the point of view from which it is evaluated, is not correlated with depression; indeed, although the association with depression is frequent, about 43% of patients with apathy do not suffer from depression, confirming that apathy in PD also commonly occurs as a separate symptom (den Brok et al., 2015). This may be taken as

an indication of the different pathophysiological mechanisms and neuroanatomical pathways underlying the two disorders (Robert et al., 2012; Skidmore et al., 2013; Pagonabarraga et al., 2015). Furthermore, we would emphasize the conceptual difference between depression and apathy: the former is an "intrinsic" disorder of mood, whereas the latter should be regarded (at least in some of its dimensions) as an impairment of affective processing regardless, at least in part, of the valence that affects may assume.

The main finding of the present study is the discrepancy between SE and CR of apathy. A similar result (45% level of agreement between self and caregiver reports) was obtained in the study by McKinlay et al. (2008). Those Authors ruled out the role of the mental status of caregivers and of depression and stress in caregivers. We agree with this position, also given the absence of overt cognitive and psychiatric disorders among the caregivers of our patients. Furthermore, we excluded a possible role of anosognosia for apathy, since this would have led to a reverse discrepancy (Schiehser et al., 2013). Different results, at least in part, have been shown by Schiehser et al. (2013) who report higher levels of self-rated apathy only before diagnosis. Among the several factors taken into account, caregiver burden and depressive symptomatology were significantly associated with discrepancies. Furthermore, the Authors noticed an association between higher levels of current patient levodopa and larger pre-diagnosis apathy discrepancies. Our data cannot be compared directly with those of Schiehser et al. (2013) since we did not assess pre-diagnosis apathy. However, we agree that their findings should prompt clinicians to pay attention to apathy symptoms also in patients suspected of having PD, given the possible implications for the treatment of the ongoing disease.

A slight discrepancy between self-rating and informant rating was recently reported in a study by Radakovic et al. (2018) (38 vs 33% respectively) in PD patients evaluated by means of the Dimensional Apathy Scale: only executive apathy was found to be significantly higher according to PD patients' as compared with informants' ratings. Conversely, in our sample the emotional dimension of apathy showed a significant difference. In this case too, the different characteristics of the populations and of the assessment tools preclude a direct comparison with our sample. Despite these differences, we would emphasize the relevance of cognitive dimensions of apathy and their relationships with general cognitive and "frontal" functions (Dirnberger and Jahansahi, 2013; Santangelo et al., 2014). From this perspective,

attention should be focused mainly on the self-evaluation of apathy. This is supported, in our sample, by the evidence that correlations between apathy and measures of mental status and of executive functions are significant only when apathy is self-rated.

The possible factors underlying the discrepancies between SE and CR of apathy could hypothetically be due to overestimation of the symptom by patients or, conversely, its underestimation by caregivers. Some findings of the present study may help to disentangle this difficult issue. Overestimation by patients can probably be excluded. The main possible confounding variables, i.e., anosognosia and lack of insight, and concomitant depression, have been shown to act in the opposite way (i.e., AES scores higher in patients than in informants) or to be unrelated to apathy (i.e., no correlation between AES-SE and HDRS scores). On the other hand, caregivers confusing depressive with apathetic symptoms could also be a source of discrepancy. This is probably not the case of our population, since no relationship was observed between depression and CR of apathy.

Another source of discrepancy could be a general failure of caregivers to correctly recognize neuropsychiatric symptoms in their relative, however this, in general, can be excluded, given the significant correlation between AES-CR and NPI-P scores (of note, both informant-based). Conversely, we cannot exclude that this correlation is determined mainly by the heterogeneity of the NPI-P, which assesses both "positive" and "negative" neurobehavioral symptoms. On the basis of this consideration, we hypothesize that underestimation by caregivers could be somehow specific for apathy, and for less "striking" neuropsychiatric symptoms in general.

On the basis of our results, we believe that the main cause of discrepancy between patient and informant ratings of apathy could be a reduced perception of apathetic symptoms by caregivers. As claimed by McKinlay et al. (2008), the caregiver's report may be influenced by a sense of loyalty towards the patient and therefore result in a tendency to underestimate these symptoms. Moreover, caregivers probably tend to maintain a stable representation of the patient, in which the affective relationship and the family role prevent them from perceiving the emotional changes in the patient. This interpretation is supported by the specific differences between SE and CR of apathy, which mainly involve the emotional dimension of the symptom. Another interpretation highlights the role of coping strategies adopted by caregivers. Brandtstadter and Renner (1990) proposed that as individuals face the challenges of aging, they change their life expectations (update their goals) in an effort to preserve a sense of control. In the case of individuals who help to care for a patient, updating of goals may include an acceptance that PD may result in a number of behavioral changes (McKinlay et al., 2008).

Finally, discrepancies could be linked to the role of the informant in caring for the patient and, in so doing, in providing external cues to foster initiative in the patient. This role could make it more difficult for some informants/careers to observe and rate certain aspects of apathy (Radakovic et al., 2018).

In conclusion, the present study suggests that the point of view from which apathy is seen can lead to significant discrepancies in the rating of the symptom, even when using the same tool. This should be taken into account

in order to obtain correct assessment of this disabling and distressing symptom. The interpretation of these discrepancies could be examined, as in other neurodegenerative diseases, from the perspective of the complex representation of the familial relationships between patients and their caregivers (Iavarone et al., 2014).

References

- Barone P, Antonini A, Colosimo C, et al (2009). The PRI-AMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov Disord* 24:1641-1649.
- Brandtstadter J, Renner G (1990). Tenacious goal pursuit and flexible goal adjustment: explication and age-related analysis of assimilative and accommodative strategies of coping. *Psychol Aging* 5: 58-67.
- Cummings JL, Mega M, Gray K, et al (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 44:2308-2314.
- den Brok MG, van Dalen JW, van Gool WA, et al (2015). Apathy in Parkinson's disease: a systematic review and meta-analysis. *Mov Disord* 30:759-769.
- Dirnberger G, Jahanshahi M (2013). Executive dysfunction in Parkinson's disease: a review. *J Neuropsychol* 7:193-224.
- Douglas J G, Eugene O, Sid G (1999). Diagnostic criteria for Parkinson disease. *Arch Neurol* 56:33-39.
- Dubois B, Slachevsky A, Litvan I, et al (2000). The FAB: a Frontal Assessment Battery at bedside. *Neurology* 55:1621-1626.
- Folstein MF, Folstein SE, McHugh PR (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189-198.
- Hamilton M (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23:56-62.
- Iavarone A, Ronga B, Pellegrino L, et al (2004). The Frontal Assessment Battery (FAB): normative data from an Italian sample and performances of patients with Alzheimer's disease and frontotemporal dementia. *Funct Neurol* 19:191-195.
- Iavarone A, Ziello AR, Pastore F, et al (2014). Caregiver burden and coping strategies in caregivers of patients with Alzheimer's disease. *Neuropsychiatr Dis Treat* 10:1407-1413.
- Levy R, Dubois B (2006). Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. *Cereb Cortex* 16:916-928.
- Levy R (2012). Apathy: a pathology of goal-directed behaviour. A new concept of the clinic and pathophysiology of apathy. *Rev Neurol (Paris)* 168:585-597.
- Marin RS, Biedrzycki RC, Firinciogullari S (1991). Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res* 38:143-162.
- McKinlay A, Grace RC, Dalrymple-Alford JC, et al (2008). Neuropsychiatric problems in Parkinson's disease: comparisons between self and caregiver report. *Aging & Mental Health* 12:647-653.
- Pagonabarraga J, Kulisevsky J, Strafella AP, et al (2015). Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. *Lancet Neurol* 14:518-531.

- Radakovic R, Davenport R, Starr JM, Abrahams S (2018). Apathy dimensions in Parkinson's disease. *Int J Geriatr Psychiatry* 33:151-158.
- Robert G, Le Jeune F, Lozachmeur C, et al (2012). Apathy in patients with Parkinson disease without dementia or depression: a PET study. *Neurology* 79: 1155-1160.
- Santangelo G, Barone P, Cuoco S, et al (2014). Apathy in untreated, de novo patients with Parkinson's disease: validation of the Apathy Evaluation Scale. *J Neurol* 261:2319-2328.
- Schiehser DM, Liu L, Lessig SL, et al (2013). Predictors of discrepancies in Parkinson's disease patient and caregiver ratings of apathy, disinhibition, and executive dysfunction before and after diagnosis. *J Int Neuropsychol Soc* 19:295-304.
- Skidmore FM, Yang M, Baxter L, et al (2013). Apathy, depression, and motor symptoms have distinct and separable resting activity patterns in idiopathic Parkinson disease. *Neuroimage* 81:484-495.
- Starkstein SE, Mayberg HS, Preziosi TJ, et al (1992). Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 4:134-913.
- Starkstein SE, Merello M, Jorge R, et al (2009). The syndromal validity and nosological position of apathy in Parkinson's disease. *Mov Disord* 24:1211-1216.
- Tremblay L, Worbe Y, Thobois S, et al (2015). Selective dysfunction of basal ganglia subterritories: from movement to behavioral disorders. *Mov Disord* 30: 1155-1170.