

Apathy May Herald Cognitive Decline and Dementia in Parkinson's Disease

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Abstract: Apathy is usually defined as a lack of motivation. It may occur as part of another disorder (notably depression and dementia) or as an isolated syndrome. In Parkinson's disease (PD), apathy is common and several studies have reported an association between this condition and more severe cognitive symptoms, such as executive dysfunction. However, this association has not been thoroughly investigated. The aim of this study (in nondepressed, nondemented PD patients) was to examine whether or not cognitive decline and/or dementia occurred more frequently in apathetic subjects than in nonapathetic subjects. Forty consecutive PD patients participated in the study (20 with apathy and 20 without). None of the subjects were either demented or depressed at the time of study entry. The patients' cognitive functions were extensively assessed twice: at study entry and

after an 18-month follow-up period. At study entry, the apathetic PD patients had significantly lower global cognitive status and executive function scores than the nonapathetic subjects. After a median period of 18 months, the rate of conversion to dementia was found to be significantly higher in the apathetic group than in the nonapathetic group (8 of 20 and 1 of 20, respectively). Even in nondemented patients, the decrease over time in cognitive performance (mainly executive function but also memory impairment) was significantly greater in apathetic subjects than in nonapathetic subjects. These findings suggest that in nondemented, nondepressed PD patients, apathy may be a predictive factor for dementia and cognitive decline over time. © 2009 Movement Disorder Society

Key words: dementia; cognition; apathy; basal ganglia

INTRODUCTION

Apathy is a common condition in Parkinson's disease (PD).^{1–5} Several studies have reported an association between apathy and more severe cognitive symptoms, especially executive dysfunction.^{2,6} Pluck & Brown³ reported that highly apathetic, nondemented PD patients performed worse than their less apathetic counterparts—especially in tasks evaluating executive functions. Czernecki et al.⁶ reported significant correlations between the severity of apathy and performance in a set of executive function tests. In previous work,

we showed that low cognitive status was the main factor that contributed to the development and then worsening of apathy.⁵ However, the evidence in favor of an association between apathy and cognitive dysfunction in PD comes mainly from cross-sectional or correlation studies and thus is not strong enough to enable apathy to be considered as a predictive factor for cognitive impairment.

An association between apathy and cognitive impairment has also been reported in other neurodegenerative, dementia-associated disorders. In Alzheimer's disease (AD), apathy has been reported in 55% of the patients⁷ and is associated with more pronounced global cognition deficits and lower functional autonomy.⁸ Interestingly, in a follow-up study of patients with mild cognitive impairment, Robert et al.⁹ showed that the rate of conversion to AD was significantly higher in apathetic patients (AP) than in non-AP (NAP), especially when lack of interest was the main apathy symptom.¹⁰

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TABLE 1. Demographic and clinical characteristics of the participant groups at study entry

	Apathetic PD patients	Nonapathetic PD patients
N (M/F)	20 (16/4)	20 (11/9)
Mean (SD) age, yr	63 (9.25)	60.38 (8.37)
Mean (SD) years in education, yr	11.1 (2.95)	11.05 (2.48)
Mean (SD) disease duration, yr	9.75 (6.89)	6.4 (5.1)
Median Hoehn & Yahr score (min-max)	2.5 (1-4)	2 (1-4)
Mean (SD) score at UPDRS-III*	21.87 (7.67)	17.3 (6.36)
Mean (SD) levodopa equivalent dose (mg/d)	835.42 (653.92)	790.17 (447.32)
Mean (SD) MADRS score*	8.8 (3.97)	5.35 (3.63)
Mean(SD) LARS score*	-12.65 (5.09)	-26.8 (2.99)

*Indicates a significant inter-group difference, $P < 0.05$.

To the best of our knowledge, the question of whether apathy represents a predictive factor for dementia in PD patients has never been investigated. The goal of the present follow-up study in nondepressed, nondemented PD patients was to establish whether or not cognitive decline and/or dementia occurred more frequently in apathetic subjects than in nonapathetic subjects.

METHODS

Participants

Forty patients with probable PD participated in the study. They were recruited prospectively at the Movement Disorders department at Lille University Hospital. PD was defined according to the international criteria.¹¹ None of the patients was suffering from neurologic diseases other than PD. None was suffering from depression or dementia as defined by the DSM-IV criteria. The guidelines published by Marsh et al.¹² were used to diagnose depression and reduce the overlap with apathy. The guidelines published by Emre et al.¹³ were used to improve the diagnosis of PD-associated dementia.

Patients were included in the apathetic group if they met the criteria published by Starkstein et al.¹⁴ and had a score on the Lille Apathy Rating Scale (LARS)¹⁵ of over 17. Twenty patients met these criteria. All diagnoses were made by a senior staff member. The main demographic and clinical characteristics of the two groups on study inclusion are shown in Table 1.

All patients were treated and assessed after receiving their usual anti-parkinsonian medication (see the mean levodopa equivalent dosages in Tables 1 and 2). At the time of assessment, nine patients were on psychoactive drugs: four in the apathetic group (three on anxiolytics and one taking an antidepressant) and five in the nonapathetic group (all on anxiolytics). All participants gave their informed consent to participation in the study.

ASSESSMENTS

Cognitive Function

An extensive neuropsychologic assessment was made to encompass the cognitive domains that are sensitive to dysfunction in PD. *Overall cognitive status* was assessed in terms of the score on the Mattis Dementia Rating Scale (DRS¹⁶).

Memory was assessed using (1) the forward and backward digit span and (2) the French version of the Grober and Buschke 16-item free/cued word learning and recall test.¹⁷ Performance was assessed in terms of the number of words (out of 16) immediately recalled at learning, the total number of words (out of 48) correctly recalled after the three free recall trials, and the total number of words (out of 48) correctly recalled after the three free and cued recall trials. Attention and executive functions were assessed using:

- An oral version of the Symbol Digit Modalities test.¹⁸ Subjects were instructed to associate symbols with digits according to a key code. Performance was evaluated in terms of the number of correct responses given in 90 seconds.
- A 50-item version of the Stroop word color test (to assess response inhibition). The procedure has been described fully elsewhere.¹⁹ Performance was evaluated in terms of the time needed to complete the test's two phases (naming the color of dots and color names, respectively) and the number of errors in the interference phase (Phase 2).

TABLE 2. Clinical characteristics of the participant groups after the 18-month follow-up period

	Apathetic PD patients	Nonapathetic PD patients
UPDRS-III score	20.13 (7.57)	15.7 (6.89)
Levodopa equivalent dose (mg/d)	896.89 (581.25)	900.23 (408.31)
MADRS score	10 (6.25)	4.25 (3.4)
LARS score	-11.65 (6.94)	-28.3 (3.94)

All values represent mean (SD).

- A letter and number sequencing task, corresponding to an oral version of the Trail Making Test (to assess set shifting).¹⁹ Performance was evaluated in terms of the time needed to complete the test's two phases (baseline and alternation, respectively) and the number of errors in the alternation phase.
- A word generation task performed over 60 seconds and in three conditions (to assess action initiation and working memory updating), i.e. phonemic (letter P), semantic (animals) and alternating (letter T and V, alternatively) conditions.

Behavior

Depressive symptoms and apathy were rated using the Montgomery and Asberg Depression Rating Scale (MADRS)²⁰ and the LARS,¹⁵ respectively.

Motor Symptoms

The severity of PD was assessed using the Hoehn and Yahr score.²¹ Motor disability was rated using the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III).²² All the participants were assessed twice: at study entry and at least 12 months later (range: 11–24 months; median: 18 months).

DATA ANALYSIS

Repeated measures analyses of variance (ANOVA) with "time" (at entry and after follow-up) as within factor and "group" (with and without apathy) as between factor were expected. Nevertheless, these analyses require (i) homogeneity of the variances, (ii) homogeneity of multiple dependent variable covariances across the design's cells and (iii) sphericity of the data. Because these assumptions rarely hold, we decided to use a multivariate analysis of variance (MANOVA). Our main hypothesis (involving a greater regression of cognitive function over time in the apathetic group) would thus be supported by a significant "group" (G) \times "time" (T) interaction. When MANOVAs were not applicable or in the event of assumption violation, a Greenhouse-Geisser correction was applied to the univariate models. When justified, post-hoc comparisons and contrast analyses were carried out with a specific mean square error criterion. T-tests or nonparametric Mann-Whitney tests were performed, depending on the data distribution and the homogeneity of the variances.

The chi-squared frequency test was used to compare the two patient groups in terms of the frequency of de-

mentia after the follow-up period. The significance threshold was set to $P < 0.05$ in all statistical tests. All analyses were carried out using *Statistica 8.0 software*.

RESULTS

Clinical and Demographical Characteristics

At study entry, the two groups differed in terms of motor disability ($t(27)=2.52$, $P = 0.018$) and the level of apathy (Mann-Whitney U = 5.39, $P < 0.001$), which were both significantly higher in the AP group (Table 1). The MADRS score at study entry was significantly higher ($t(38) = 2.87$, $P = 0.007$) in the AP group than in the NAP group. However, none of the subjects met the criteria for depression. All these parameters remained stable over time (Table 2).

In view of the clinical differences between the two groups at study entry, we first carried out a multiple regression analysis to ascertain the influence of potential predictors (e.g. the MADRS, UPDRS-III and LARS scores at study entry) on the patients' cognitive status (as evidenced by the Mattis DRS score at follow-up). As none of these predictors (other than the LARS score) correlated significantly with cognitive status (MADRS: $F_{(1,34)} = 0.04$, $P = 0.84$; UPDRS-III: $F_{(1,34)} = 1.64$, $P = 0.21$; LARS: $F_{(1,34)} = 4.60$, $P = 0.039$), these scores were not considered as covariates in the subsequent analyses.

Cognition

Table 3 shows the mean (SD) performance at the cognitive assessment test battery for AP and NAP groups at study entry and 18 months later and summarizes the main results of the statistical analysis.

The ANOVA applied to the Mattis DRS score revealed a significant "group" effect ($F_{(1,38)} = 13.488$, $P < 0.001$) and a significant G \times T interaction ($F_{(1,38)} = 8.16$, $P < 0.007$). This was due to a decline over time in the AP group's overall performance ($F_{(1,38)} = 11.45$, $P < 0.001$).

The MANOVA applied to the digit span test revealed no significant effect. Analysis of performance in the Grober and Buschke 16-item free/cued word learning and recall test revealed the lack of a significant "group" effect or G \times T interaction for immediate recall. The expected G \times T interaction was significant for the total number of words correctly recalled after the three free recall trials ($F_{(1,38)} = 9.94$, $P < 0.003$) and the three free and cued recall trials ($F_{(1,38)} = 12.20$, $P < 0.001$). This interaction showed a stable

TABLE 3. Mean (SD) performance in the cognitive assessment test battery by apathetic PD patients and nonapathetic PD patients at study entry and then at 18 months later

	Entry			Follow-up			Group	Time	G x T
	Apathetic PD patients	Nonapathetic PD patients	Nonapathetic PD patients	Apathetic PD patients	Nonapathetic PD patients	Between groups at entry			
Global efficiency									
Mattis dementia rating scale (out of 144)	134.2 (4.2)	137.5 (4.81)	138.15 (4.81)	130.85 (6.24)	138.15 (4.81)	$P < 0.03$ $\eta^2 = 0.12$	$P < 0.01$ $\eta^2 = 0.31$	$P < 0.001$ $\eta^2 = 0.26$	NS $P < 0.007$ $\eta^2 = 0.17$
Memory									
Forward digit span	4.9 (0.79)	5.15 (1.35)	5.15 (1.38)	5 (1.12)	5.15 (1.38)	NS	NS	NS	NS
Backward digit span	3.15 (0.87)	3.6 (1.27)	4.05 (1.43)	3.45 (0.89)	4.05 (1.43)	NS	NS	NS	NS
Grober & Buschke 16-item recall test	14.3 (1.62)	15.46 (0.88)	15.1 (1.41)	14.85 (1.04)	15.1 (1.41)	$P < 0.03$ $\eta^2 = 0.11$	NS	NS	NS
Immediate recall (out of 16)	25 (5.74)	29.55 (5.62)	29.3 (5.42)	21.0 (6.24)	29.3 (5.42)	$P < 0.001$ $\eta^2 = 0.14$	$P < 0.001$ $\eta^2 = 0.35$	$P < 0.001$ $\eta^2 = 0.27$	$P < 0.001$ $\eta^2 = 0.25$
Total free recall (out of 48)	45.65 (2.28)	46.13 (2.11)	46.39 (1.99)	43.6 (3.96)	46.39 (1.99)	NS	NS	NS	$P < 0.01$ $\eta^2 = 0.14$
Total free + cued recall (out of 48)									
Attention and executive function									
Symbol Digit Modalities test (number of correct responses)	28.65 (10.23)	41.55 (9.59)	40.60 (10.29)	24.35 (11.13)	40.60 (10.29)	$P < 0.001$ $\eta^2 = 0.31$	$P < 0.001$ $\eta^2 = 0.38$	$P < 0.001$ $\eta^2 = 0.36$	$P < 0.001$ $\eta^2 = 0.24$
Stroop word/color test									
Time to complete Phase 1 (s)	46 (9.31)	37.85 (10.71)	38.7 (10.04)	52.8 (13.26)	38.7 (10.04)	$P < 0.01$ $\eta^2 = 0.15$	$P < 0.001$ $\eta^2 = 0.27$	$P < 0.001$ $\eta^2 = 0.25$	$P < 0.01$ $\eta^2 = 0.15$
Time to complete Phase 2 (sec)	85.86 (17.55)	67.65 (17.28)	64.95 (14.89)	106.85 (32.74)	64.95 (14.89)	NS	$P < 0.001$ $\eta^2 = 0.24$	$P < 0.01$ $\eta^2 = 0.16$	$P < 0.001$ $\eta^2 = 0.27$
Errors in Phase 2	3.8 (3.05)	2.35 (2.41)	2.4 (1.82)	6.4 (5.93)	2.4 (1.82)	NS	$P < 0.001$ $\eta^2 = 0.18$	$P < 0.01$ $\eta^2 = 0.16$	$P < 0.04$ $\eta^2 = 0.11$
Letter/number sequencing									
Time to complete phase A (s)	9.72 (3.51)	8.37 (2.24)	8.52 (2.14)	11.97 (5.1)	8.52 (2.14)	NS	$P < 0.008$ $\eta^2 = 0.17$	$P < 0.02$ $\eta^2 = 0.12$	$P < 0.05$ $\eta^2 = 0.10$
Time to complete phase B (s)	39.05 (17.33)	33.5 (13.99)	34.65 (13.88)	59 (37.58)	34.65 (13.88)	NS	$P < 0.01$ $\eta^2 = 0.16$	$P < 0.003$ $\eta^2 = 0.21$	$P < 0.007$ $\eta^2 = 0.18$
Errors	0.4 (0.59)	0.4 (0.75)	0.2 (0.52)	1.05 (1.05)	0.2 (0.52)	NS	$P < 0.002$ $\eta^2 = 0.22$	$P < 0.03$ $\eta^2 = 0.11$	$P < 0.001$ $\eta^2 = 0.18$
Word generation task (60 sec)									
Letter "p"	10.65 (4.6)	13.2 (4.25)	13.65 (3.1)	8.35 (3.91)	13.65 (3.1)	NS	$P < 0.001$ $\eta^2 = 0.37$	$P < 0.001$ $\eta^2 = 0.24$	$P < 0.02$ $\eta^2 = 0.12$
Animals category	15.3 (3.73)	18.9 (5.27)	18.2 (4.69)	11.55 (4.38)	18.2 (4.69)	$P < 0.02$ $\eta^2 = 0.14$	$P < 0.001$ $\eta^2 = 0.36$	$P < 0.001$ $\eta^2 = 0.27$	$P < 0.001$ $\eta^2 = 0.36$
Alternating "T"/"V"	6.85 (2.89)	10.6 (3.17)	9.7 (3.6)	5.4 (3.87)	9.7 (3.6)	$P < 0.001$ $\eta^2 = 0.29$	$P < 0.001$ $\eta^2 = 0.26$	$P < 0.001$ $\eta^2 = 0.33$	NS $\eta^2 = 0.11$

The "between groups" columns indicate the statistical significance of the differences between the AP and NAP groups at entry and follow-up. The right-hand-most columns show the statistical significance of the main effects of the "group" and "time" factors and the "group" x "time" interaction (G x T). The η^2 statistic was used to estimate the size effect when a difference was statistically significant.

performance over the follow-up period for the NAP group ($F_{(1,38)} < 1$, ns) and a score reduction in the AP group ($F_{(1,38)} = 11.19$, $P < 0.002$).

At study entry, the number of symbols correctly coded in the Symbol Digit Modalities Test was lower in the AP than in the NAP group ($F_{(1,38)} = 16.92$, $P < 0.001$). There was a significant G x T interaction ($F_{(1,38)} = 4.9$, $P = 0.03$). At study entry, the AP group was significantly slower than the NAP group ($F_{(1,38)} = 11.04$, $P = 0.002$) in naming the color of the dots in the Stroop word color test, although both groups were similarly sensitive to interference ($F_{(1,38)} = 2.83$, $P = 0.10$). At follow-up, the AP group showed significantly worse performance under both test conditions, whereas the performance of the NAP group did not change ($F_{(1,38)} = 12.66$, $P < 0.001$). Analysis of the test errors showed the same pattern of results, with a significant G x T interaction ($F_{(1,38)} = 4.58$, $P = 0.04$).

At study entry, there was no significant inter-group difference in the various scores in the letter and number sequencing task test ($F_{(1,38)} = 1.57$, $P = 0.218$). However, after follow-up, the AP group's scores were much lower in both the baseline and alternation phases ($F_{(1,38)} = 9.22$, $P = 0.004$), with a significant increase in the error rate ($F_{(1,38)} = 10.5$, $P = 0.002$).

At study entry, the AP group produced fewer words in word generation tasks than the NAP group did ($F_{(1,38)} = 22.56$, $P < 0.001$). Overall, the G x T interaction was significant ($F_{(1,38)} = 7.95$, $P = 0.008$), with a decrease in performance at follow-up in the AP group. Specific contrast analyses revealed that this interaction was only significant for the phonemic and semantic conditions. Statistical analysis in the alternating condition revealed only significant main effects of "group" (performance was lower for the AP group than for the NAP group: $F_{(1,38)} = 18.43$, $P < 0.001$) and "time" (both groups showed a significant worsening of their performance over time: $F_{(1,38)} = 4.94$, $P = 0.03$).

Occurrence of Dementia

At follow-up, eight of the 20 APs and one of the 20 NAPs met the criteria for dementia ($\chi^2 = 7.025$, $P = 0.008$).

DISCUSSION

Our results for nondemented, nondepressed PD patients showed that after a median 18-month follow-up period, the occurrence of dementia was higher in AP than in NAPs. Overall, at study entry, the APs

(even though nondemented) had lower cognitive function scores than NAPs. This was mainly due to lower global efficiency and poorer performance in certain tests of processing speed and executive functions. Moreover, over a mean time period of 18 months, the decline in cognitive function was significantly higher in APs and was not seen in nonapathetic PD patients. These results confirm thus our hypothesis whereby apathy in nondemented, nondepressed PD patients may represent a predictive factor for dementia and cognitive decline over time.

Our comparison of both groups at study entry confirmed previous reports of lower performance levels in tasks assessing executive function in APs^{3,6}. However, this executive impairment was quite moderate, as it only concerned some tasks. By including tasks assessing the main dimensions of executive function, we showed that the executive impairment mainly concerned response inhibition (loss of resistance to interference in the Stroop word color test) and action initiation (loss of self-activation strategies for retrieval from declarative memory in the word generation tasks and in the 16-item free/cued word learning and recall test). According to the model proposed by Levy and Dubois,²³ this specifically corresponds to manifestations of a form of apathy called "cognitive inertia" and suggests a dysfunction of the associative basocortical circuit interconnecting the dorsal areas of the basal ganglia (namely the dorsal portion of the head of the caudate nucleus) and the lateral prefrontal cortex. This circuit is generally considered to be involved in cognitive dysfunction in PD patients.²⁴ Our results suggest that this circuit is more impaired in apathetic PD patients. However, the role of a general slow-down in information processing must also be considered, because the APs performed slowly overall. This suggests a less specific, more general type of cognitive impairment in apathetic PD patients.

After the median 18-month follow-up period, dementia was diagnosed in eight PD patients in the apathetic group and in only one patient in the nonapathetic group. This type of result may be related to Robert et al. findings^{9,10} in mild cognitive impairment (MCI). They showed that conversion to dementia was twice as high in apathetic MCI patients. In PD, the concept of MCI is still subject to debate²⁵⁻²⁷ and thus no consensus criteria have been adopted. At study entry, our APs were more cognitively impaired (particularly in executive function) than the non-APs. However, in the absence of a healthy control group, it was difficult to determine whether or not our patients met the PD-MCI criteria proposed by Caviness et al.²⁶ Nevertheless, our

results indicate that apathy may be a contributory factor in MCI and/or dementia in PD.

In this study, the patients in the two groups were receiving similar, optimal anti-parkinsonian treatments at both assessment times and thus a role for dopamine depletion in the development of apathy appears difficult to justify. However, as underlined by one of the reviewers of this article, optimal dosages of these medications are determined by a clinical motor assessment; as dopaminergic treatments affect motor and nonmotor subregions in the basal ganglia to different extents,²⁸ we cannot rule out a nonoptimal dosage for nonmotor symptoms. In PD, there is also evidence for a dramatic loss of cholinergic neurons in the basal forebrain nuclei - the main source of cholinergic projections to the cortex.²⁹ This loss of cholinergic neurons is considered to be the biologic basis of cognitive decline and certain neuropsychiatric symptoms (namely apathy) in AD and related dementias.^{30,31} Although further studies are needed to demonstrate the involvement of cholinergic depletion in some forms of apathy in PD, our data show more frequent dementia and more severe cognitive decline in apathetic PD patients than in nonapathetic PD patients, suggesting the possible involvement of a cholinergic mechanism in apathy.

One of the strengths of this study is that APs with concomitant depression were not included. This circumvents the frequent problem of the overlap between apathy and depression which could otherwise have explained our results, since depression in PD increases the risk of cognitive decline.^{32,33} Moreover, after an 18-month follow-up, no change in the severity of the depressive symptoms was observed, thus excluding the role of this factor in the appearance of cognitive decline. However, this specific feature constitutes also a limitation, since apathetic, nondepressed individuals appear to represent a small subgroup of PD patients.³⁴

We are aware of a number of other study limitations. First, there was a (nonsignificant) trend towards longer disease duration in the apathetic group. As the incidence of dementia in PD increases with age and disease duration,³⁵ this factor may have contributed to the higher occurrence of dementia in the apathetic group. However, when considering the disease duration distribution, it appeared that four patients had a disease duration over the 75th percentile (i.e. more than 15 years). Of these, only one developed dementia. Moreover, disease duration and cognitive status were only weakly correlated ($r = -0.45$, ns). It is thus unlikely that longer disease duration can explain the higher observed occurrence of dementia in apathetic PD patients. Secondly, due to the low number of patients,

it was impossible to compare the profiles of the demented and nondemented APs after follow-up. High patient numbers would have allowed the potential identification of risk factors for dementia in apathetic PD patients and so this aspect needs to be addressed in the future. Thirdly, as discussed above and even though none of our APs was demented, the latter were more cognitively impaired at study entry than the non-APs. Consequently, we cannot rule out the possibility that conversion to dementia was associated with cognitive impairment, rather than apathy. Further studies with patients who are strictly matched for cognitive status will be required to disentangle these aspects.

In conclusion, this study is the first to show (by extensively assessing cognitive function at two, well-separated time points) that apathy is a predictive factor for dementia in PD. Given that dementia contributes significantly to morbidity and mortality in PD³⁶, our finding underlines the need to detect apathy with valid instruments as early as possible and to keep a close eye on the cognitive status of PD patients in whom apathy is not associated with depression or nonoptimal anti-parkinsonian treatment.

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