Acta Neurologica Scandinavica

Acta Neurol Scand 2015: 131: 80–87 DOI: 10.1111/ane.12282
© 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd
ACTA NEUROLOGICA SCANDINAVICA

The associations between fatigue, apathy, and depression in Parkinson's disease

Skorvanek M, Gdovinova Z, Rosenberger J, Ghorbani Saeedian R, Nagyova I, Groothoff JW, van Dijk JP. The associations between fatigue, apathy, and depression in Parkinson's disease. Acta Neurol Scand 2015: 131: 80–87.
© 2014 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd.

Objectives – Fatigue and apathy are two of the most common and most disabling non-motor symptoms of Parkinson's disease (PD). They have a high coincidence and can often be confused; moreover, their relationship is not fully understood. The aim of our study was to describe the coincidence of apathy with different fatigue domains in the presence/absence of depression and to separately describe the associations of different aspects of primary and secondary fatigue with apathy and other clinical and disease-related factors. *Materials and methods* – A total of 151 non-demented patients with PD were examined using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Starkstein Apathy Scale, Multidimensional Fatigue Inventory (MFI), Beck Depression Inventory-II, and Epworth Sleepiness Scale. *Results* – The prevalence and severity of fatigue and apathy were significantly higher in depressed PD patients. However, our results show that depression, fatigue, and apathy can be clearly distinguished in PD. Apathy was associated with the MFI's-reduced motivation domain in both depressed and non-depressed patients. However, apathy was associated with mental fatigue aspects only in non-depressed patients, and it was not related to the physical aspects of fatigue in any of the studied groups. *Conclusions* – Although the pathophysiology of fatigue and apathy in PD is clearly multifactorial, in a proportion of PD patients, these symptoms are associated with depression, dopaminergic depletion in the mesocorticolimbic structures, and disruption of the prefrontal cortex-basal ganglia axis. Therefore, in some PD patients, adequate management of depression and optimal dopaminergic medication may improve both fatigue and apathy.

M. Skorvanek[1,2,3], Z. Gdovinova[1,2], J. Rosenberger[3], R. Ghorbani Saeedian[3,4], I. Nagyova[3,4], J. W. Groothoff[5], J. P. van Dijk[3,5]

[1]Department of Neurology, Safarik University, Kosice, Slovak Republic; [2]Department of Neurology, L. Pasteur University Hospital, Kosice, Slovak Republic; [3]Graduate School Kosice Institute for Society and Health, Safarik University, Kosice, Slovak Republic; [4]Department of Social Medicine, Institute of Public Health, Safarik University, Kosice, Slovak Republic; [5]Department of Community and Occupational Health, University Medical Center Groningen, Groningen, The Netherlands

Key words: apathy; depression; excessive daytime somnolence; fatigue; Parkinson's disease

M. Skorvanek, MD, Department of Neurology, Safarik University and L. Pasteur University Hospital, Trieda SNP 1, 04066 Kosice, Slovakia
Tel.: +421949275277
Fax: +421557898546
e-mail: mskorvanek@gmail.com

Accepted for publication June 26, 2014

Introduction

Fatigue and apathy are two of the most common non-motor symptoms of Parkinson's disease (PD), having been previously found, according to the study population and measures used, in up to 77.6% of PD patients for fatigue (1) and up to 72% of PD patients for apathy, respectively (2). Both fatigue and apathy have been described in all stages of PD, including the early and untreated disease (2, 3).

Currently, there is no universally accepted definition of fatigue. Fatigue in PD can be divided into 'peripheral fatigue', which refers to an objectively measurable process in which a muscle loses strength after repeated contractions, and 'central fatigue', which refers to a feeling state, perception, or experience that is not yet objectively measurable (4) and which can be further divided into physical and mental fatigue domains. Most published studies have found a strong association between fatigue and depression, and according to the presence or absence of mood disorder and excessive daytime sleepiness (EDS), a concept of primary and secondary fatigue has been proposed (1). Both of these fatigue groups differed significantly regarding factors associated with different fatigue domains. Functional status or other disease-

related factors have not been associated with primary fatigue (fatigue in the absence of mood disorder and EDS). In the secondary fatigue group (fatigue in the presence of mood disorder or EDS), associations between some fatigue domains and functional status, older age, male gender, and higher anxiety scores have been found (1).

Apathy has been characterized as a lack of motivation manifested by diminished goal-directed cognition and behavior, with decreased emotional involvement (5). Diagnostic criteria for apathy in non-demented PD patients have been recently validated (6). Apathy is also most commonly associated with depression (7), although previous studies have shown that these two symptoms can be clearly distinguished, and depending on the studied population, up to 33.4% of the PD patients were found to have 'pure' apathy in the absence of depression and dementia (2, 7). Apathy may also be associated with cognitive decline and in fact can present a predictive factor for developing dementia (8).

Despite the high coincidence of fatigue and apathy in PD, reports correlating these two non-motor symptoms are very scarce. In a study by Funkiewiez et al. (9), PD patients after deep brain stimulation (DBS) often confused apathy with fatigue; they reported feeling tired and having difficulties in starting any activities. The only study which has directly correlated fatigue with different apathy domains so far showed that fatigue in their PD sample was significantly associated with the Lille Apathy Rating Scale total score, as well as with the intellectual curiosity and action initiation subscores (10). However, no study to date has evaluated the relationship of apathy to different fatigue domains, and in fact, while apathy is most commonly associated with the dopaminergic system (11), primary fatigue was related to serotonergic deficits (12). Moreover, the relationship between apathy and fatigue in PD is most likely influenced by the presence or absence of depression, as both of these symptoms are part of the DSM-IV criteria for diagnosing depression (13, 14). This demonstrates the complexity of the problem, and the relationship between fatigue and apathy in PD is certainly not fully understood.

Therefore, the aim of our study was to describe the coincidence of apathy with different fatigue domains in the presence or absence of depression and to describe the associations of different aspects of primary and secondary fatigue with apathy and other clinical and disease-related factors.

Materials and methods

Patients

Patients were recruited from 25 neurology outpatient clinics in eastern Slovakia between June 2011 and August 2012. All patients were diagnosed according to the UK PD Society Brain Bank Criteria (15), and their mental abilities were assessed with the Mini-Mental State Examination (MMSE) (16). A total of 205 patients initially agreed to participate in the study. Patients with MMSE scores lower than 24 ($N = 18$), forms of parkinsonism other than idiopathic Parkinson's disease ($N = 8$), those who initially agreed to participate and filled in the questionnaire but did not come for the oral interview ($N = 14$), and those whose data were partially missing ($N = 14$) were excluded. A total of 151 non-demented patients (75%) remained for analysis.

Data collection

One week before the interview an invitation letter, a written informed consent form and questions on sociodemographic background, medical history, current medication, and self-report questionnaires (described below) were sent by postal mail to patients diagnosed with PD. During the interview, a trained interviewer assessed the cognitive functioning of patients using the MMSE and reviewed the questionnaires together with the patient to ensure that no values were missing. After this, a single neurologist specialized in movement disorders (M.S.) assessed each patient's disease severity using the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (17), including Hoehn and Yahr staging (18). Patients who were unable to fill in the questionnaires by themselves due to motor impairment answered the questions during the oral interview. The study was approved by the local ethics committee. All patients participated voluntarily and gave written informed consent prior to the interview. The investigation was performed according to the Declaration of Helsinki.

Measures

Sociodemographic data, including age, gender and education, were obtained from the structured interview. Education level was classified as: low (primary school or unfinished high school), middle (finished high school or specialization after high school—not a college or university), or high

(university undergraduate or postgraduate or higher academic degree achieved).

Disease and medication-related data – Information on disease duration, antiparkinsonian medication, and other treatment was obtained during the interview. The levodopa equivalent daily dosage (LEDD) was calculated using a previously published formula (19). Motor symptoms were rated in the ON state using the MDS-UPDRS part III (motor examination). The MDS-UPDRS is a four-subscale combined scale (non-motor experiences of daily living, motor experiences of daily living, motor examination and motor complications) (17). This scale was recently translated into Slovak and approved as an official non-English translation of the MDS-UPDRS (20). Scores were obtained by a semi-structured interview and examination. The disease stage was assessed by the Hoehn & Yahr scale (HY), which is applied to gauge the course of the disease over time (18).

Fatigue, apathy, depression, and excessive daytime somnolence – The multidimensional fatigue inventory (MFI) is a 20-item self-report questionnaire (21) that measures five dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. Each subscale contains four items, which are scored on a five-point Likert-scale. Scores range from 4 (absence of fatigue) to 20 (maximum fatigue) for each subscale. Its reliability and structural validity in patients with PD has been recently published (22). We used a uniform cutoff score of $\geq$13 in each MFI domain to define the presence of fatigue (1). Cronbach's alpha for the MFI in this study was 0.89.

The Apathy scale is a self-administered 14-item scale for assessing apathy (23). Each answer is scored from 0 (not at all) to 3 (a lot), with a higher summary score meaning more apathy. A cutoff of $\geq$14 is used to define the presence of apathy. In the present study, Cronbach's alpha was 0.77.

The Beck Depression Inventory-II (BDI-II) is a self-administered 21-item scale for assessing depression (24). Each answer was scored as 0–3. The cutoff values used are 0–13: normal range; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. Higher total scores indicate more severe depressive symptoms. Cronbach's alpha for BDI-II in our study was 0.90

The Epworth Sleepiness Scale (ESS) is a self-administered 8-item questionnaire to assess excessive daytime somnolence (25). The ESS asks the respondent to rate the likelihood of falling asleep on a scale from 0 to 3, while higher scores reflect greater sleep propensity. Consistent with a number of previous investigations, a score of 10 as the cutoff point was used for normal, while scores above this imply pathological sleepiness. In the present study, Cronbach's alpha was 0.84.

Statistical analyses

Statistical analyses were performed using the statistical software program PASW SPSS version 18.0 for Windows (SPSS Inc, Chicago, IL, USA). First, we described the demographic and clinical characteristics of our study groups. Significant differences between group characteristics were analyzed by independent sample t-tests and chi-square tests. Statistical differences regarding the coincidence of fatigue in different domains and apathy in both depressed and non-depressed patients were tested using the Fisher's exact test. Finally, separate multiple linear regression analyses were performed to study the relationship of sociodemographic factors, disease duration, disease severity, depression, EDS, and apathy with different fatigue domains in depressed and non-depressed patients.

Results

The mean age of the total PD sample was 69.7 ± 8.6 years; the mean disease duration was 6.9 ± 4.9 years, and the mean HY stage was 2.4 ± 0.9. A total of 119 patients (78.8% of the sample) were fatigued in at least one MFI domain, and 71 patients (47% of the sample) were found to be apathetic. After dividing the sample, 87 patients remained in the group with depression (the 'secondary' fatigue and apathy group), and 64 remained in the group without depression (the 'primary' fatigue and apathy group). The two groups did not differ significantly in age, gender distribution, disease duration, education level, HY stage, MDS-UPDRS part IV subscore, or treatment. The depressed patients had significantly higher scores in MDS-UPDRS parts I-III and higher apathy, EDS, and fatigue scores as well as a higher prevalence of apathy, EDS, and fatigue in all MFI domains. Baseline characteristics of the study groups can be found in Table 1.

Apathy without the presence of depression was found in 19 patients (13%), both apathy and depression in 52 patients (34%), depression only in 35 patients (23%), and neither apathy nor depression in 45 patients (30%). The prevalence

Table 1 Baseline characteristics of the study population ($N = 151$)

	Depressed patients	Non-depressed patients	Significant difference between depressed and non-depressed patients (P)
Number of patients	87	64	
Gender (male/female)	42/45	38/26	ns
Age	70.4 ± 8.7	68.8 ± 8.6	ns
Disease duration	7.3 ± 5.3	6.4 ± 4.2	ns
Education level			
Low *N* (%)	38 (44%)	26 (41%)	ns
Middle *N* (%)	31 (36%)	26 (41%)	
High *N* (%)	18 (20%)	12 (18%)	
Hoehn and Yahr stage	2.5 ± 0.9	2.2 ± 0.9	ns
H&Y ≤ 2 *N* (%)	41 (47%)	42 (66%)	
H&Y > 2 *N* (%)	46 (53%)	22 (34%)	
MDS-UPDRS part I	15.2 ± 6.0	8.7 ± 4.8	**<0.001**
MDS-UPDRS part II	16.5 ± 8.7	10.1 ± 7.5	**<0.001**
MDS-UPDRS part III	39.4 ± 14.8	31.9 ± 14.3	**<0.01**
MDS-UPDRS part IV	3.7 ± 4.0	2.6 ± 3.7	ns
BDI-II	22.3 ± 8.7	8.2 ± 3.5	**<0.001**
>13pts *N* (%)	87 (100%)	0	
ESS	8.0 ± 4.2	5.6 ± 3.8	**<0.003**
>10pts *N* (%)	24 (28%)	5 (8%)	
Apathy scale	14.7 ± 5.5	11.0 ± 5.0	**<0.001**
≥14pts *N* (%)	52 (60%)	19 (30%)	
MFI general fatigue	15.1 ± 3.0	11.4 ± 3.5	**<0.001**
≥13pts *N* (%)	68 (78%)	22 (34%)	
MFI physical fatigue	14.8 ± 3.4	12.2 ± 3.6	**<0.001**
≥13pts *N* (%)	63 (72%)	30 (47%)	
MFI-reduced activity	13.4 ± 3.5	11.0 ± 4.1	**<0.001**
≥13pts *N* (%)	50 (57%)	19 (30%)	
MFI-reduced motivation	11.0 ± 3.9	8.5 ± 3.1	**<0.001**
≥13pts *N* (%)	27 (31%)	7 (11%)	
MFI mental fatigue	11.8 ± 3.4	8.4 ± 2.9	**<0.001**
≥13pts *N* (%)	33 (38%)	4 (6%)	
LEDD (mg/day)	576 (0-2972)	487 (0-1780)	ns
L-dopa only	22 (25%)	12 (19%)	ns
Dopamine agonist only	19 (22%)	16 (25%)	ns
L-dopa + dopamine agonist	38 (44%)	29 (45%)	ns
No dopaminergic treatment	8 (9%)	7 (11%)	ns
Rasagiline	26 (30%)	23 (36%)	ns
Amantadine	21 (24%)	11 (17%)	ns
Antidepressants	14 (16%)	9 (14%)	ns
Sleep pills	36 (41%)	13 (20%)	**<0.01**

MDS-UDPRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; BDI-II, Beck depression inventory-II; ESS, Epsworth sleepiness scale; MFI, multidimensional fatigue inventory; LEDD, total levodopa equivalent daily dosage; ns, non-significant; bold <0.05.

of fatigue in these groups of patients and statistical differences in the prevalence of each fatigue domain between the apathetic and non-apathetic patients in both depressed and non-depressed groups can be found in Table 2.

Determinants of fatigue in the secondary fatigue group (group with depression) – Older age was strongly associated with higher reduced motivation and mental fatigue scores. Male gender was related to higher reduced activity. Lower education was significantly associated with higher mental fatigue. MDS-UPDRS-III was significantly associated with more fatigue in all domains except reduced motivation and mental fatigue, and apathy was strongly associated with reduced motivation. Depression and EDS were not associated with any MFI domain in this group (see table 3).

Determinants of fatigue in the primary fatigue group (group without depression) – Higher MDS-UPDRS-III scores were associated with general fatigue, and EDS was associated with higher general fatigue and physical fatigue scores. Higher apathy scores were strongly related to reduced motivation, mental fatigue, and reduced activity scores, respectively (see table 3).

Discussion

To the best of our knowledge, this is the first study to separately describe the relationship between primary and secondary fatigue and apathy in depressed and non-depressed PD patients. Depression, apathy, and fatigue are some of the most common non-motor symptoms in PD with a high coincidence and often can be confused in both clinical practice and research settings. As our study shows, all of these symptoms can be clearly distinguished in PD, as patients with pure depression, pure apathy, and pure fatigue can be found.

In secondary fatigue, older age was strongly associated with higher reduced motivation and mental fatigue scores, male gender was related to higher reduced activity, and lower education was significantly associated with higher mental fatigue. These results are in agreement with our previous study, in which the determinants of primary and secondary fatigue were studied separately (1).

The MDS-UPDRS part III (motor examination) was significantly associated with general and physical fatigue and reduced activity domains in the depressed group, but it was related only to general fatigue in non-depressed patients. Previous studies have found conflicting results regarding the correlation of functional status with fatigue (26, 27). Moreover, a previous study with a similar construct found no association of the old UPDRS version part III with any of the primary fatigue domains (1). To our knowledge, this is the first study to directly correlate the MDS-UPDRS with primary and secondary fatigue in PD, and it might point to a potential connection

Table 2 Coincidence of fatigue with apathy and depression (cutoffs: MFI for all domains ≥ 13pts; AS ≥ 14pts; BDI-II > 13pts)

	Depressed ($N = 87$)			Non-depressed ($N = 64$)		
	Apathetic ($n = 52$)	Non-apathetic ($n = 35$)	Statistical difference ($P < 0.05$)	Apathetic ($n = 19$)	Non-apathetic ($n = 45$)	Statistical difference ($P < 0.05$)
MFI—general fatigue ($N = 90$)	43 (83%)	25 (71%)	P = ns	6 (32%)	16 (36%)	P = ns
MFI—physical fatigue ($N = 93$)	36 (69%)	27 (77%)	P = ns	11 (58%)	19 (42%)	P = ns
MFI—reduced activity ($N = 69$)	35 (67%)	15 (43%)	$P < 0.03$	9 (47%)	10 (22%)	P = ns
MFI—reduced motivation ($N = 34$)	23 (44%)	4 (11%)	$P = 0.002$	4 (21%)	3 (7%)	P = ns
MFI—mental fatigue ($N = 37$)	27 (52%)	6 (17%)	$P < 0.001$	3 (16%)	1 (2%)	P = ns

MFI, multidimensional fatigue inventory, BDI, Beck depression inventory-II, AS, apathy scale.

Table 3 Determinants of fatigue in depressed and non-depressed PD patients

	Depressed patients (BDI>13pts)					Non-depressed patients (BDI≤13pts)				
	MFI					MFI				
	GenF	PhyF	RedA	RedM	MentF	GenF	PhyF	RedA	RedM	MentF
Age	0.14	0.12	0.14	**0.29****	**0.32****	−0.17	−0.16	−0.05	0.08	−0.02
Male gender	0.04	0.03	**0.25***	−0.05	0.15	−0.06	−0.22	−0.03	0.11	0.06
Higher education	−0.09	−0.11	−0.14	−0.12	−**0.24***	0.11	−0.02	0.05	−0.16	−0.01
MDS-UPDRS III	**0.32****	**0.29***	**0.27***	0.18	−0.07	**0.26***	0.19	0.23	0.08	−0.01
Disease duration	−0.11	0.07	0.11	−0.06	0.08	−0.08	0.19	0.22	0.10	0.04
BDI	0.18	0.02	0.03	0.04	0.17	0.19	0.15	0.23	0.03	0.26
ESS	0.11	−0.06	0.00	−0.02	0.14	**0.27***	**0.28***	0.03	−0.10	−0.03
Apathy scale	−0.09	0.07	0.13	**0.44*****	0.19	−0.03	0.05	**0.25***	**0.49*****	**0.34****
R square	0.19	0.14	0.22	0.46	0.32	0.22	0.29	0.26	0.30	0.20
Adj. R square	0.11	0.05	0.14	0.41	0.25	0.10	0.19	0.15	0.20	0.09

MFI, Multidimensional Fatigue Inventory; GenF, General Fatigue; PhyF, Physical Fatigue; RedA, Reduced Activity; RedM, Reduced Motivation; MentF, Mental Fatigue; MDS-UDPRS III, Movement Disorder Society-Unified Parkinson's Disease Rating Scale motor examination subscale; ESS, Epsworth Sleepiness Scale; BDI-II, Beck Depression Inventory-II.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; bold <0.05.

of the dopaminergic system with at least some aspects of primary fatigue.

As expected, apathy was most strongly associated with the MFI-reduced motivation domain in both primary and secondary fatigue. Apathy was also associated with the MFI-reduced activity and mental fatigue domains, but only in non-depressed patients. The association of apathy with the mental aspects of primary fatigue in PD is intriguing, as both of these non-motor symptoms have been previously associated with different neurotransmitter systems.

Apathy is a common finding in early untreated PD (2), and in a proportion of patients, it might have a good response to dopaminergic therapy (28, 29), which supports the role of dopamine in the pathophysiology of apathy in non-demented PD patients. In a well-constructed PET study, where 2 weeks after implantation of subthalamic DBS dopaminergic medication was reduced by 82%, 34 of 63 patients became apathetic (11). In this study, patients with apathy showed decreased [11C]-raclopride binding bilaterally in the orbitofrontal cortex, the posterior cingulate cortex, the left dorsolateral prefrontal cortex, the bilateral striatum, the left thalamus, and the right amygdala, suggesting that an increase of D2/D3 dopamine receptors or a reduction of synaptic dopamine levels might be related to subthalamic DBS-induced apathy. These findings suggest that in selected patients with PD displaying no cognitive deterioration, post-operative apathy can be seen as a model of a pure mesolimbic hypodopaminergic syndrome that is unmasked by post-operative drug withdrawal (11).

On the other hand, a previous PET study (12) in PD patients with primary fatigue found reduced serotonin transporter binding in the caudate, putamen, ventral striatum, thalamus, cingulate, and amygdala and concluded that fatigue in PD is associated with reduced serotonergic function of the basal ganglia and limbic structures. This study was, however, conducted only in a small number of participants, and the results were not specifically correlated with physical or mental aspects of fatigue. Therefore, it remains

unclear whether serotonergic dysfunction in these regions is associated with PD-related fatigue as such, or with some of its specific aspects. The mentioned study also found a reduced ^{18}F-dopa uptake in the caudate and insula, which could point to a potential role of the dopaminergic system in at least some aspects of primary fatigue in PD (12). In fact, the role of dopaminergic dysfunction in PD-related primary fatigue might also be supported by some previous reports showing improvement of fatigue after initiation of dopaminergic therapy (3, 28). On the other hand, not all patients with PD or dopaminergic depletion develop apathy or fatigue; therefore, the pathophysiology of these symptoms in PD is clearly multifactorial.

Apathy in PD may be present after direct lesions to both the prefrontal cortex (PFC) and basal ganglia, and it clearly presents a consequence of the disruption of the PFC-basal ganglia axis (30). Recently, de la Fuente-Fernandez (31) proposed a frontostriatal cognitive dysfunction staging divided into three stages, which reflects a sequential process of dopamine depletion occurring in different regions of the striatum (stages I and II) and the frontal cortex (stage III). In this staging system, among other symptoms, mental fatigue is attributed to stage I and apathy to stage IIb, and although the concept of mental fatigue in this staging system is not fully explained in this study, it presents an interesting framework for further hypothesis testing. The potential role of the dopaminergic system as well as of disruption of the PFC-basal ganglia axis in the pathophysiology of both fatigue and apathy in at least some PD patients might also be supported by results of some previous studies with methylphenidate in PD (32). Methylphenidate is a CNS stimulant that blocks the presynaptic dopamine transporter (DaT) and the noradrenaline transporter in the striatum and in the PFC in particular (32). Although the results of these studies are not fully conclusive, especially due to the small sample sizes examined and due to some methodological issues, improvements were reported in both fatigue and apathy after treatment with methylphenidate; therefore, further studies in this field should be encouraged (32). Another very important link between apathy and especially mental fatigue may be suggested via pathology of the mesolimbic dopaminergic pathways. As discussed above, apathy belongs to the concept of hypodopaminergic syndrome, and multiple studies have emphasized the importance of dopaminergic denervation in the mesocorticolimbic structures (11, 33–36). The role of dopaminergic depletion in these symptoms is highlighted also by results of a 12-week prospective, placebo-controlled, randomized, double-blinded trial of a relatively selective D2/D3 dopamine agonist piribedil in treating apathy following subthalamic nucleus deep brain stimulation with subsequent reduction of dopaminergic medication, with results showing a significant reduction of apathy in the piribedil vs placebo arm group (37).

Strengths and limitations

To the best of our knowledge, this is the first study to specifically correlate apathy with different physical and mental aspects of primary and secondary fatigue in PD patients. Independent analyses for depressed and non-depressed patients enabled us to better understand the coincidence and associations between depression, fatigue, and apathy, which are often confused in both research and clinical settings. There are some limitations of our study. The sample consisted of more motivated patients who agreed to participate in the study and who were able to attend the examination. Also, the cross-sectional design of the study does not allow us to further explore the causal pathways between the studied variables. Another limitation of the study is that depression and apathy were assessed through self-report questionnaires only; however, all instruments used have been validated and repeatedly utilized for the purpose of distinguishing apathy from depression in patients with PD (7, 14); moreover, both BDI-II and AS have been recommended for using in PD patients by the Movement Disorder Society (38).

Conclusions and implications for future studies and clinical practice

Depression, apathy, and fatigue are some of the most common non-motor symptoms in PD with a high coincidence and are often confused in both clinical practice and research settings. As shown in our study, all of these symptoms can be clearly distinguished in PD. The pathophysiology of fatigue and apathy is clearly multifactorial; however, in a proportion of patients, these symptoms are associated with the presence of depression, dopaminergic depletion in the mesocorticolimbic structures, and disruption of the PFC-basal ganglia axis. Therefore, in clinical practice, adequate management of depression as well as optimal dopaminergic medication or addition of a dopamine agonist may improve both fatigue and apathy. Further clinical trials with methylphenidate

should be performed to better understand its position in the treatment of fatigue and apathy. In research settings, further clinical, neurophysiological, and imaging studies should be performed especially in primary fatigue and primary apathy to better understand their relationship and underlying pathophysiological mechanisms.

Acknowledgments

The authors thank Martina Krokavcova, Dominika Lazurova, Maria Anna Ficikova and Cecilia Bukatova (all at Safarik University in Kosice, Slovakia) for their technical support. The authors also thank Daniel Klein (Safarik University in Kosice, Slovakia) for statistical advice.

Conflict of interest and Sources of funding statement

The authors declare no potential conflict of interests in regard to this article. This work was supported by the Slovak Research and Development Agency under contract no. APVV-0220-10 (80%). Furthermore, this work was supported by the Agency of the Slovak Ministry of the Education, Science, Research and Sport of the Slovak Republic for the Structural Funds of the EU under project no. ITMS: 26220120058 (20%).

References

1. Skorvanek M, Nagyova I, Rosenberger J et al. Clinical determinants of primary and secondary fatigue in patients with Parkinson's disease. J Neurol 2013;**260**:1554–61.
2. Cubo E, Benito-Leon J, Coronell C et al. Clinical correlates of apathy in patients recently diagnosed with Parkinson's disease: the ANIMO study. Neuroepidemiology 2012;**38**:48–55.
3. Schifitto G, Friedman J, Oakes D et al. Fatigue in levodopa-naïve subjects with Parkinson disease. Neurology 2008;**71**:481–5.
4. Friedman JH, Abrantes A, Sweet LH. Fatigue in Parkinson's disease. Expert Opin Pharmacother 2011;**13**: 1999–2007.
5. Marin RS. Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci 1991;**3**:243–54.
6. Drijgers RL, Dujardin K, Reijnders JS et al. Validation of diagnostic criteria for apathy in Parkinson's disease. Parkinsonism Relat Disord 2010;**16**:656–60.
7. Kirsch-Darrow L, Marsiske M, Okun MS et al. Apathy and depression: separate factors in Parkinson's disease. J Int Neuropsych Soc 2011;**17**:1058–66.
8. Dujardin K, Sockeel P, Delliaux M et al. Apathy may herald cognitive decline and dementia in Parkinson's disease. Mov Disord 2009;**24**:2391–7.
9. Funkiewiez A, Ardouin C, Caputo E et al. Long term effects of bilateral subthalamic stimulation on cognitive function, mood and behavior in Parkinson's disease. J Neurol Neurosurg Psychiatry 2005;**75**:834–9.
10. Saez-Francas N, Hernandez-Vara J, Corominas Rojo M et al. The association of apathy with central fatigue perception in patients with Parkinson's disease. Behav Neurosci 2013;**127**:237–44.
11. Thobois S, Ardouin C, Lhommee E et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinsons's disease: predictors and underlying mesolimbic denervation. Brain 2010;**133**:1111–27.
12. Pavese N, Metta V, Bose SK et al. Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. Brain 2010;**133**:3434–43.
13. Beiske AG, Svensson E. Fatigue in Parkinson's disease: a short update. Acta Neurol Scand 2010;**122**:78–81.
14. Oguru M, Tachibana H, Toda K et al. Apathy and depression in Parkinson's disease. J Geriatr Psychiatry Neurol 2010;**1**:35–41.
15. Hughes AJ, Daniel SE, Kilford L et al. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;**55**:181–4.
16. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;**12**:189–98.
17. Goetz CG, Tilley BC, Shaftman SR et al. Movement disorder society-sponsored revision of the unified parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;**15**: 2129–70.
18. Hoehn MM, Yahr MD. Parkinsonism onset progression and mortality. Neurology 1967;**17**:427–42.
19. Tomlinson CL, Stowe R, Patel S et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;**25**:2649–53.
20. Skorvanek M, Kosutzka Z, Valkovic P, et al. [Validation of Slovak version of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS)]. Cesk Slov Neurol N 2013;**76**:463–8.
21. Smets EMA, Grassen B, Bonke B et al. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;**39**:315–25.
22. Elbers RG, van Wegen EEH, Verhoef J et al. Reliability and structural validity of the Multidimensional Fatigue Inventory (MFI) in patients with idiopathic Parkinson's disease. Parkinsonism Relat Disord 2012; **18**:532–6.
23. Starkstein SE, Mayberg HS, Preziosi T et al. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992;**2**: 134–9.
24. Beck AT, Steer RA, Ball R et al. Comparison of Beck Depression Inventories –IA and –II in psychiatric outpatients. J Pers Assess 1996;**3**:588–97.
25. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;**14**:540–5.
26. Havlikova E, Rosenberger J, Nagyova I et al. Clinical and psychosocial factors associated with fatigue in patients with Parkinson's disease. Parkinsonism Relat Disord 2008;**14**:187–92.
27. Fabbrini G, Latorrre A, Suppa A et al. Fatigue in Parkinson's disease: motor or non-motor symptom? Parkinsonism Relat Disord 2013;**19**:148–52.
28. Chaudhuri KR, Martinez-Martin P, Antonini P et al. Rotigotine and specific non-motor symptoms of Parkinson's disease: Post hoc analysis of RECOVER. Parkinsonism Relat Disord 2013;**19**:660–5.
29. Starkstein SE, Brockman S. Apathy and Parkinson's disease. Curr Treat Options Neurol 2011;**13**:267–73.
30. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex 2006;**16**:916–28.

31. De la Fuente-Fernandez R. Frontostriatal cognitive staging in Parkinson's disease. Parkinsons Dis 2012; **2012**: UNSP 561046, doi: 10.1155/2012/561046.
32. Devos D, Moreau C, Delval A et al. Methylphenidate a treatment for Parkinson's disease? CNS Drugs 2013; **27**:1–14.
33. Martinez-Horta S, Pagonabarraga J, Fernandez de Bobadilla R et al. Apathy in Parkinson's disease: more than just executive dysfunction. J Int Neuropsychol Soc 2013;**19**:571–82.
34. Martinez-Horta S, Riba J, Fernandez de Bobadilla R et al. Apathy in Parkinson's disease: neurophysiological evidence of impaired incentive processing. J Neurosci 2014;**34**:5918–26.
35. Lhommee E, Klinger H, Thobois S et al. Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours. Brain 2012;**135**:1463–77.
36. Krack P, Hariz MI, Baunez C et al. Deep brain stimulation: from neurology to psychiatry? Trends Neurosci 2010;**33**:474–84.
37. Thobois S, Lhommee E, Klinger H et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. Brain 2013;**136**:1568–77.
38. http://www.movementdisorders.org/MDS/Education/Rating-Scales.htm