

Fatigue in Parkinson's disease is not related to excessive sleepiness or quality of sleep

Eva Havlikova^{a,*}, Jitse P. van Dijk^{b,c}, Jaroslav Rosenberger^b, Iveta Nagyova^b, Berrie Middel^c,
Tatiana Dubayova^a, Zuzana Gdovinova^a, Johan W. Groothoff^c

^a *Safarik University Kosice, Faculty of Medicine, Department of Neurology, Kosice, Slovakia*

^b *Safarik University Kosice, Faculty of Science, Institute of Social Sciences and Kosice Institute for Society and Health, Kosice, Slovakia*

^c *Department of Social Medicine, University Medical Center Groningen, University of Groningen, The Netherlands*

Received 25 September 2007; received in revised form 1 February 2008; accepted 15 February 2008

Available online 26 March 2008

Abstract

Objectives: Many patients with Parkinson's disease (PD) suffer from non-motor symptoms like sleep disturbances, excessive daytime sleepiness and fatigue. The aim of our research was to explore whether fatigue is related to sleepiness and sleep problems, depression and functional status, controlled for age, gender and disease duration.

Methods: The sample consisted of 78 PD patients from Eastern Slovakia (52% males, mean age 68.8 ± 8.7 , mean disease duration 7.2 ± 6.8). The Multidimensional Fatigue Inventory (5 dimensions), the Epworth Sleepiness Scale, the Pittsburgh Sleep Quality Index, Hospital Anxiety and Depression Scale and the Unified Parkinson's Disease Rating Scale were used. Demographic data were obtained in a structured interview. Multiple linear regression was used to analyse the data.

Results: Sleepiness did not show significant association with fatigue in any of the fatigue domains; neither did quality of sleep. Depression was significantly associated with all domains of fatigue, the strongest being the relationship with general fatigue ($\beta .42$), reduced motivation ($\beta .39$), mental fatigue ($\beta .35$) ($p < .001$), and physical fatigue ($\beta .31$) ($p < .01$), while the relationship with reduced activity was less strong ($\beta .22$) ($p < .05$). Worse functional status was significantly related to reduced activity ($\beta .50$), general fatigue ($\beta .35$), physical fatigue ($\beta .35$), and mental fatigue ($\beta .35$) ($p < .001$).

Conclusion: Fatigue is not related to daytime sleepiness or night-time sleep dysfunction. Fatigue is more strongly influenced by the presence of depression and worse functional status.

© 2008 Elsevier B.V. All rights reserved.

Keywords: Parkinson's disease; Fatigue; Sleepiness; Quality of sleep

1. Introduction

Fatigue is a common symptom in the general population as well as in people with chronic disorders. Approximately 10% of visits to primary care providers is for assessment of fatigue [1–5]. In Parkinson's disease (PD) patients the prevalence of fatigue ranges from 33% to 58% [6]. One third of PD patients consider fatigue their single most disabling symptom [1,5].

Fatigue is a complex phenomenon involving a number of psychosocial and behavioural processes. The concept of fatigue, as a multidimensional phenomenon in Parkinson's disease patients, was postulated by Lou et al. [7]. It is characterized by difficulty in initiating and sustaining mental and physical tasks in the absence of motor or physical impairment [1,7,8]. The study by Lou et al. demonstrated that the severity of physical fatigue does not correlate with

* Corresponding author. Department of Neurology, Medical Faculty, University of PJ Safarik, Trieda SNP 1, 040 01 Kosice, Slovakia. Tel.: +421 911 128314; fax: +421 55 7898546.

E-mail addresses: eva.havlikova@upjs.sk, e_havlikova@yahoo.com (E. Havlikova).

that of mental fatigue, suggesting that the two are to a certain extent independent [7].

It may be difficult to separate fatigue and sleepiness from each other. These two terms are often used interchangeably, or under the general rubric of being ‘tired’, despite the distinct diagnostic or therapeutic implications that each of them has [9], leading to suboptimal interventions or management strategies in response to patients’ complaints.

Sleepiness is a ubiquitous phenomenon, experienced not only as a symptom in a number of medical, psychiatric and primary sleep disorders, but also as a normal physiological state by most individuals over any given 24 h period [9]. Sleepiness can be considered abnormal when it occurs at inappropriate times, or does not occur when desired. Excessive daytime sleepiness (EDS) was reported in approximately 15% of PD patients, with an 8-year prevalence of 54% [10]. Its manifestation may be either rapid – ‘sleep attacks’, or slow – patients may feel sleepy and slowly drift off to sleep [11]. If unrecognized and untreated, sleepiness can result in poor attention and memory and even to accidents. The study by Gjerstad et al. showed that EDS was related to higher age, male gender and use of dopamine agonists [10]. Recent studies performed in chronic neurological diseases and primary sleep disorders have shown that the level of fatigue does not correlate with the levels of daytime sleepiness, suggesting that fatigue and EDS are not causally related to each other [12,13].

As many as 98% of patients with PD may suffer at some time from nocturnal symptoms that can disturb their sleep [11]. These symptoms may be grouped into four broad categories; insomnia, motor, urinary and neuropsychiatry problems. PD patients show reduced total sleep time and sleep efficiency, and an increased number of sleep arousals and fragmentations of sleep [11]. About 40% of PD patients take sedatives, significantly more than are taken by elderly people without PD. Sleep disturbance correlates with disease severity, and depression is another factor strongly related with sleep problems [14].

To our knowledge, the relationship between fatigue and sleep problems has not been studied in a group of PD patients, and little is known even about patients with other chronic diseases. The study by Kaynak was performed with multiple sclerosis (MS) patients [15]; 27 MS patients reporting fatigue were compared with 10 MS patients without fatigue and with 13 participants in the control group. Fatigued patients were found to have worse sleepiness and worse quality of their sleep, thus the conclusion was that fatigue could be partially explained by poor subjective sleep quality.

Fatigue in PD still remains an imperfectly understood problem, and it seems to have been recognized as serious only recently. While more is known about its prevalence and impact on patients’ lives, little progress has been made so far in understanding its aetiology and pathogenesis. Biological [16], clinical and psychosocial variables may all play a role [17,18].

A study by Shulman reported fatigue as being associated with anxiety and activities of daily life, but not with gender, age or depression, or with motor dysfunction [17]. A study by Abe et al. also did not find any correlation of fatigue with motor dysfunction [16]. In a longitudinal study by Alves et al., fatigue was related to disease severity, depression, and excessive daytime somnolence (EDS) [18,19].

The aim of our research was to explore whether fatigue is related to sleepiness and sleep problems, depression and functional status, controlled for age, gender and disease duration.

2. Methods

2.1. Patients

This cross-sectional study evaluated fatigue in a study population of 78 patients with Parkinson’s disease. The patients were recruited from the hospitals and outpatients departments in the East Slovakian region between February 2004 and November 2005. All patients were diagnosed according to the United Kingdom Parkinson’s Disease Society Brain Clinical Criteria [20] and their mental abilities were assessed with the Mini-Mental State Examination (MMSE) [21]. Exclusion criteria were defined as follows: 1. MMSE lower than 24; 2. disease duration longer than 15 years; 3. presence of co-morbidity associated with the fatigue variable.

The study was approved by the local Ethics Committee. Informed consent was obtained from each patient.

2.2. Data collection

Data were collected by means of a mailed questionnaire comprising questions on socio-demographic background, medical history and current medication, as well as self-report questionnaires including the Multidimensional Fatigue Inventory (MFI), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI) and Hospital Anxiety and Depression Scale (HADS). After three weeks all patients were interviewed on relevant issues that were not part of the questionnaire. After this structured interview, a neurologist assessed each patient’s disease severity with Unified Parkinson’s Disease Rating Scale (UPDRS) Version 3.0 [22], including Hoehn & Yahr staging [23] and the Schwab and England disability scale [24]. Patients who were not able to fill in the questionnaires by themselves because of motor impairment of their hands answered the questions during an oral interview.

2.3. Measures

Fatigue was assessed with the Multidimensional Fatigue Inventory (MFI). The MFI is a 20-item self-report instrument designed and validated by Smets et al. [25]. It measures five fatigue domains: general fatigue, physical fatigue, mental

fatigue, reduced motivation, and reduced activity. There are four items in each domain. The score on each item ranges from 1 (no fatigue) to 5 (very fatigued), so the score in each dimension ranges from 4 (no fatigue) to 20 (highest possible fatigue). This instrument is frequently used for patients with neurological diseases [7]. The instrument was found to have good internal consistency with a Cronbach's alpha coefficient of .89 in our sample. Cronbach's alpha results for the subscales were as follows: general fatigue .84, physical fatigue .79, reduced activity .80, reduced motivation .71, mental fatigue .82.

For the evaluation of daytime somnolence the Epworth Sleepiness Scale (ESS) [26] was used. ESS relies on measuring dozing behaviour in eight different situations. The questionnaire asks the respondent to rate the likelihood of falling asleep on a scale from 0 to 3, where 0 indicates no chance and 3 represents the greatest chance of dozing. The total ESS score is the sum of all the responses and ranges from 0 to 24, with higher scores reflecting greater sleep propensity. Consistent with the reports of a number of previous investigations, a score of 10 as the cut-off point was used for normal, while scores above this imply pathological sleepiness [27]. Hagell and Broman demonstrated good psychometric properties of the ESS in PD patients, giving the evidence basis for using it in PD [28]. The instrument was found to have good internal consistency with a Cronbach's alpha coefficient of .84 in our sample.

The Pittsburgh Sleep Quality Index (PSQI) [29] was used to assess night-time sleeping problems. PSQI assesses global sleep quality and disturbances in sleep patterns during the previous month in seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep

Table 2

Description of the study variables in the sample ($n=78$)

Variable	n, %, Mean \pm SD
1. HADS-D	6.61 \pm 3.9
≥ 11	11 (14.3%)
2. ESS	7.74 \pm 4.9
> 10	20 (25.6%)
3. PSQI	10.8 \pm 5.6
≥ 5	65 (83.3%)
4. MFI	
General fatigue	13.8 \pm 4.0
Physical fatigue	13.7 \pm 3.3
Reduced activity	12.5 \pm 3.8
Reduced motivation	10.7 \pm 3.8
Mental fatigue	11.8 \pm 3.5

HADS—Anxiety and Depression Scale. ESS—Epworth Sleepiness Scale. PSQI—Pittsburgh Sleep.

Quality Index. MFI—Multidimensional Fatigue Inventory.

disturbances, use of sleep medication and daytime dysfunction. Scoring of answers ranges from 0 (no difficulty) to 3 (severe difficulty). After recoding, each component has possible scores of 0–3, where 3 indicates the negative extreme. The global PSQI score is the sum of all the component scores (range 0–21); a score of 5 or more indicating a poor sleeper. Although not validated for PD, this instrument is widely used in PD studies [30–32]. The instrument was found to have good internal consistency with a Cronbach's alpha coefficient of .81 in our sample.

Depression was assessed using the Hospital Anxiety and Depression Scale (HADS). This self-administered scale simultaneously evaluates anxiety (HADS-A) and depression (HADS-D). It was designed to identify mood disorders in non-psychiatric outpatients attending hospital consulting rooms. It consists of 14 items (7 for the assessment of anxiety and 7 for the assessment of depression) scoring from 0 (no problem) to 3 (extreme problem). The cut-off values as proposed by the HADS developers [33] were applied in order to determine the proportion of patients considered as unimpaired (not depressed, scoring ≤ 7 on each subscale), possibly impaired (8–10 on each subscale), or probably impaired (≥ 11 on each subscale). In the present study Cronbach's alpha was 0.79 for the depression domain.

The Unified Parkinson's Disease Rating Scale is a four-subscale combined scale—mental state, activities of daily living, motor examination, and complications. Two further instruments are attached to the UPDRS, namely: (1) a modified Hoehn & Yahr Staging, an ordinal scale that is applied to gauge the course of disease over time; and (2) the Schwab & England Scale, a measure of functional independence providing scores that, though expressed as percentages, form an ordinal scale. Scores are obtained by interview and examination. It is currently used as a standard reference scale in clinical practice and research [22–24].

Basic socio-demographic data (age, gender) and disease duration were obtained from the structured interview.

Table 1

Demographic and clinical description of the sample ($n=78$)

Variable	n, %, Mean \pm SD
1. Gender	
Male ($n=41$)	52.6%
Female ($n=37$)	47.4%
2. Age	68.8 \pm 8.7
3. Disease duration	7.2 \pm 6.8
4. UPDRS	35.9 \pm 20.3
5. H&Y	2.0 \pm 1.1
≤ 2.0	55 (71.4%)
> 2.0	23 (28.6%)
6. S&E	70.4 \pm 21.2
$\leq 70\%$	33 (42.3%)
$> 70\%$	45 (57.7%)
7. Antiparkinsonian drugs used	
l-dopa	8 (10.3%)
Dopamine agonists	21 (26.8%)
l-dopa+COMT inhibitors	12 (15.4%)
l-dopa+Dopamine agonists	6 (7.7%)
l-dopa+COMT inhibitor+dopamine agonists	6 (7.7%)
Other	25 (32.1%)

UPDRS—Unified Parkinson's Disease Rating Scale. S&E—Schwab & England Scale. H&Y—Hoehn & Yahr Staging.

Table 3

Linear regression model: associations of functional status, depression and sleepiness with each of the five domains of MFI (controlled for age, disease duration and gender)

Step	Variables	General fatigue		Physical fatigue		Reduced activity		Reduced motivation		Mental fatigue	
		beta	ΔR^2	beta	ΔR^2	beta	ΔR^2	beta	ΔR^2	beta	ΔR^2
1	Age	-.10		.02		-.04		.16		-.03	
	Gender	.02		.14		.01		.02		-.03	
	Disease duration	-.03	.05	-.10	.07	.03	.07	-.07	.10	.04	.07
2	UPDRS	.35***	.19	.35***	.18	.50***	.29	.21	.09	.35***	.17
3	Depression	.43***	.16	.31**	.09	.22*	.04	.39***	.13	.35***	.10
4	ESS	.10	.01	.16	.02	.12	.01	.13	.01	.05	.01
	Adjusted R^2	.36***		.31***		.37**		.28*		.29**	

UPDRS—Unified Parkinson's Disease Rating Scale, ESS—Epworth Sleepiness Scale; ΔR^2 —change in explained variance after adding the variable.

* $-p \leq .05$, ** $-p \leq .01$, *** $-p \leq .001$.

2.4. Statistical analysis

The relationships linking age and gender with disease duration, functional status, depression and sleepiness or sleep quality were analyzed with multiple linear regression analysis, using all separate fatigue domains as dependent variables. Statistical analyses were performed using the statistical software program SPSS 12.0 for Windows.

3. Results

Out of 203 patients with PD meeting the inclusion criteria, 14 did not wish to participate in the study; and 91 did not respond to the invitation. Total response rate was 38.4%. Out of those who agreed to participate, 7 patients were eliminated because of the exclusion criteria, 13 patients were not included because of missing data (these patients agreed to participate in the study, filled in the questionnaire, but refused to come for the oral interview), and 78 remained for analysis. Non-responders did not differ significantly from the analyzed group in age (mean difference 1.6 years, $SE = 1.22$; $t = 1.315$; 95%CI -0.798 – 4.003) or gender (difference between proportions .095, $SE = .066$, 95% CI -0.0343 – 0.224) (difference of proportions test) [34].

Having completed the questionnaire, the 78 patients were interviewed, and then subsequently examined by the neurologist (41 men, 52.6%). The mean age of the patients was 68.8 ± 8.7 years. Mean age at disease onset was 59.5 ± 11.1 years. Mean disease duration was 7.2 ± 6.8 years. Details of the clinical profile and the study variables of the patients are shown in Tables 1 and 2.

The Spearman's correlation of ESS and PDQI showed no significant relations (Spearman's coefficient .048).

As sleepiness may be one of the major symptoms reflecting sleep disturbances, two models of multiple linear regression analysis were performed to explore the relative contributions of functional status, depression and sleepiness (Table 3), or subjective quality of sleep (Table 4), in each MFI domain, controlled for age, gender and disease duration.

The Unified Parkinson's Disease Rating Scale had significant effects on all domains of fatigue except reduced motivation in both models. Depression had a significant effect on all fatigue domains in both models, the strongest being on reduced motivation in both models (beta .50 in the sleepiness model, and .48 in the quality of sleep model).

Sleepiness did not contribute significantly to fatigue in any of the fatigue domains (betas ranged from .05 to .16). When all variables were added into the model, the R^2 change

Table 4

Linear regression model: associations of functional status, depression and sleep quality with each of the five domains of MFI (controlled for age, disease duration and gender)

Step	Variables	General fatigue		Physical fatigue		Reduced activity		Reduced motivation		Mental fatigue	
		beta	ΔR^2	beta	ΔR^2	beta	ΔR^2	beta	ΔR^2	beta	ΔR^2
1	Age	-.09		.05		-.03		.17		-.02	
	Gender	.01		.12		-.01		.01		-.06	
	Disease duration	-.02	.05	-.08	.07	.04	.07	-.05	.10	.05	.07
2	UPDRS	.33**	.19	.32**	.18	.48***	.29	.20	.10	.31**	.17
3	Depression	.42***	.16	.31**	.09	.21*	.05	.40***	.13	.32**	.10
4	PSQI	.12	.01	.17	.02	.16	.02	.09	.01	.20	.04
	Adjusted R^2	.36***		.31***		.38*		.28*		.32*	

UPDRS—Unified Parkinson's Disease Rating Scale, PSQI—Pittsburgh Sleep Quality Index, ΔR^2 —change in explained variance after adding the variable.

* $-p \leq .05$, ** $-p \leq .01$, *** $-p \leq .001$.

for sleepiness ranged from .01 in general fatigue, reduced activity and mental fatigue to .02 in physical fatigue and reduced motivation in the model.

Similar results were found in the quality of sleep model. **Quality of sleep was not a significant variable contributing to fatigue in any of the fatigue domains** (betas ranged from .10 to .20), its R^2 change scores ranging from .01 in general fatigue and reduced motivation, .02 in mental fatigue and reduced activity to .04 in mental fatigue.

None of the variables which the analysis was controlled for, whether age or gender or disease duration, proved to be significant for any of the five fatigue outcomes in either of the models.

The proposed model for sleepiness explained 36% of the variance in general fatigue, 31% of the variance in physical fatigue, 37% in reduced activity, 28% in reduced motivation and 29% in mental fatigue. The proposed model for quality of sleep explained 36% of the variance in general fatigue, 31% of the variance in physical fatigue, 38% in reduced activity, 28% in reduced motivation and 32% in mental fatigue.

4. Discussion

The aim of our study was to evaluate whether fatigue is related to sleepiness and nocturnal sleep problems, depression and functional status, controlled for age, gender and disease duration. **Neither sleepiness during the day, nor nocturnal sleep problems (quality of sleep) contributed to fatigue in any of the five fatigue domains.** Depression contributed significantly to all five fatigue domains, and functional status to four domains.

Looking closer at fatigue, sleepiness and sleep disturbances, clear associations are difficult to define as overlaps among them exist. Many patients reporting fatigue have daytime sleepiness or night-time sleep complaints [15], and many sleep-disordered patients have psychological complaints [13]. The terms are also often used interchangeably, grouped together by patients under the complaint of being ‘tired’. On closer examination, however, it can be seen that sleepiness, sleep disturbances and fatigue are distinct, but interrelated symptoms.

ESS has been described in 8–50% of PD patients [17], and in our sample it was observed in 25.6% of the patients. When put into the linear regression model, sleepiness did not have a significant relationship with fatigue in any of the five fatigue domains. This contrasts with the study by Alves et al. [19], who found in a sample of 233 PD patients that fatigue was associated with excessive daytime sleepiness, although when the patients with excessive daytime sleepiness were excluded, the prevalence of fatigue was still high, indicating the possibility that fatigue may result from sleepiness, but not necessarily so. The relative independence of fatigue and sleepiness was also reported for the multiple sclerosis patients in the study by Kaynak et al. [15], although these two populations are difficult to compare as MS and PD affect different age groups.

Sleep problems are well-known and well-described non-motor symptoms in PD. They may result from uncontrolled motor complications, medication side-effects, or as a result of degeneration of the neuro-anatomical substrate responsible for the sleep–wake cycle [11]. As many as 60% of PD patients suffer from sleep disturbances, and up to 98% may suffer at some time from nocturnal symptoms that can disturb their sleep [11]. In our sample, 83.3% of patients reported poor sleep. When analyzing quality of sleep in the proposed fatigue models, poor sleep quality did not have a significant relationship to fatigue in any of the five fatigue domains. Only Karlsen et al., studying a sample of 233 PD patients, evaluated the association of fatigue and sleep problems, which they measured in terms of the use of sedatives; they found that the incidence of fatigue correlated with the use of sleeping pills [35].

4.1. Mood disorders

Depression is common among PD patients [17]. In our study it was reported by 14.3% of patients. Depression proved to be an important contributor to fatigue in all the fatigue domains; the greater the depression, the greater the fatigue. These results contrast with those of Shulman et al. [17], who in their sample of 99 PD patients did not find fatigue correlating with depression, using the Fatigue Severity Scale and the Beck Depression Inventory. Similar results to Shulman were published by Abe in a sample of 26 PD patients [16], using the Fatigue Severity Scale and Zung’s self-assessed depression scale. Looking at the multidimensional construct of fatigue, Lou et al. with a sample of 39 PD patients found that depression was associated with the mental dimension of fatigue, but not with the physical dimensions [7]. The relationship between fatigue and depression is still controversial as there may be an overlap between them; fatigue is among the diagnostic criteria for depression.

4.2. Functional status

We found that functional status had a significant influence on fatigue for the domains of general fatigue, physical fatigue and mental fatigue, the strongest being with the domain of reduced activity. These findings do not correspond with previous results. In their study of 233 PD patients, Karlsen et al. [35] found that disease severity did not have significant associations with fatigue, measured with the Nottingham health profile questionnaire, in its dimension ‘lack of energy’; and Lou et al. [7] also found no significant correlations of disease severity measured with Hoehn & Yahr with any of the dimensions in the MFI.

4.3. Limitations

Our sample consisted mostly of patients who were able to come for the interview, so we assume that the non-

responders were patients with worse functional status compared to those in our sample. Nonetheless, our study suggests that even in this selected population of PD patients, fatigue is already a serious problem.

As fatigue was shown to be a complex construct, with the physical and mental components independent from each other [7], the Multidimensional Fatigue Inventory was selected for measuring fatigue. This instrument as a generic measure also gives the possibility of comparisons with other diseases, in contrast to the disease-specific Parkinson's Fatigue Scale [36], or the Fatigue Severity Scale, which measures fatigue per se [37].

4.4. Implications

In our study we discovered that all the fatigue domains, mental as well as physical, are strongly related to depression and worse functional status, but are independent from subjective sleep disorders or sleepiness. As symptoms of fatigue and sleep dysfunction overlap, further research should be performed, cross-sectional as well as longitudinal, to better understand these associations. The explanation of this issue is important as it may influence the future clinical management of PD patients. We also stress the importance of identifying possible treatable disorders leading to fatigue. Recognition and proper treatment of depression, and proper management of the disease symptoms, may lead to improvement in both the mental and the physical dimensions of fatigue.

5. Conclusions

Fatigue is not related to daytime sleepiness or night-time sleep dysfunction. Fatigue is more strongly influenced by the presence of depression and worse functional status.

Acknowledgements

This work was supported by the Slovak Research and Development Agency under Contract No. APVV-20-038305.

References

- [1] Friedman JH, Brown RG, Comella C, Garber CE, Krupp LB, Lou JS, et al. Working Group on Fatigue in Parkinson's Disease. Fatigue in Parkinson's disease: a review. *Mov Disord* 2007;22:297–308.
- [2] French MA. The clinical significance of tiredness. *Can Med Assoc J* 1960;82:665–71.
- [3] Buchwald D, Sullivan JL, Komaroff AL. Frequency of 'chronic active Epstein-Barr virus infection' in a general medical practice. *JAMA* 1987;257:2303–7.
- [4] Norrelund N, Hollnagel H. Fatigue among 40-year-olds. *Ugeskr Laeger* 1979;141:1425–9.
- [5] Kroenke K, Wood DR, Mangelsdorff AD, Meier NJ, Powell JB. Chronic fatigue in primary care. Prevalence, patient characteristics, and outcome. *JAMA* 1988;260:929–34.
- [6] van Hilten JJ, Hoogland G, van der Velde EA, Middelkoop HA, Kerkhof GA, Roos RA. Diurnal effects of motor activity and fatigue in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1993;56:874–7.
- [7] Lou JS, Keams G, Oken B, Sexton G, Nutt J. Exacerbated physical fatigue and mental fatigue in Parkinson's disease. *Mov Disord* 2001;16:190–6.
- [8] Chaudhuri A, Behan PO. Fatigue and basal ganglia. *J Neurol Sci* 2000;179:34–42.
- [9] Shen J, Barbera J, Shapiro CM. Distinguishing sleepiness and fatigue: focus on definition and measurement. *Sleep Med Rev* 2006;10:63–76.
- [10] Gjerstad MD, Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. Excessive daytime sleepiness in Parkinson disease: is it the drugs or the disease? *Neurology* 2006;67:853–8.
- [11] Dhawan V, Healy DG, Pal S, Chaudhuri KR. Sleep-related problems of Parkinson's disease. *Age Ageing* 2006;35:220–8.
- [12] Merkelbach S, Schulz H, Fatigue Collaborative Study Group. What have fatigue and sleepiness in common? *J Sleep Res* 2006;15:105–6.
- [13] Hossain JL, Ahmad P, Reinish LW, Kayumov L, Hossain NK, Shapiro CM. Subjective fatigue and subjective sleepiness: two independent consequences of sleep disorders? *J Sleep Res* 2005;14:245–53.
- [14] Adler CH, Thorpy MJ. Sleep issues in Parkinson's disease. *Neurology* 2005;64:S12–21.
- [15] Kaynak H, Altıntaş A, Kaynak D, Uyanik O, Saip S, Ağaoğlu J, et al. Fatigue and sleep disturbance in multiple sclerosis. *Eur J Neurol* 2006;13:1333–9.
- [16] Abe K, Takanashi M, Yanagihara T. Fatigue in patients with Parkinson's disease. *Behav Neurol* 2000;12:103–6.
- [17] Shulman LM, Taback RL, Bean J, Weiner WJ. Comorbidity of the nonmotor symptoms of Parkinson's disease. *Mov Disord* 2001;16:507–10.
- [18] Havlikova E, Rosenberger J, Nagyova I, Middel B, Dubayova T, Gdovinova Z, et al. Clinical and psychosocial factors associated with fatigue in patients with Parkinson's disease. In press. *Parkinsonism Relat Disord* 2007, doi:10.1016/j.parkreldis.2007.07.017.
- [19] Alves G, Wentzel-Larsen T, Larsen JP. Is fatigue an independent and persistent symptom in patients with Parkinson disease? *Neurology* 2004;63:1908–11.
- [20] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–4.
- [21] 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.
- [22] Fahn S, Elton RL. Members of the UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne DB, Lieberman A, editors. *Recent developments in Parkinson's disease*, vol. 2. Florham Park, NJ: MacMillan Healthcare Information; 1987. p. 153–63.
- [23] Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967;17:427–42.
- [24] Schwab RS, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson IMI, editors. *Third symposium on surgery in Parkinson's disease*. Livingstone: Edinburg; 1969. p. 152–7.
- [25] Smets EMA, Grassen B, Bonke B, De Haes JCJM. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995;39:315–25.
- [26] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540–5.
- [27] Bailes S, Libman E, Baltzan M, Amsel R, Schondorf R, Fichten CS. Brief and distinct empirical sleepiness and fatigue scales. *J Psychosom Res* 2006;60:605–13.
- [28] Hagell P, Broman JE. Measurement properties and hierarchical item structure of the Epworth Sleepiness Scale in Parkinson's disease. *J Sleep Res* 2007;16:102–9.
- [29] Buysse DJ, Reynolds 3rd CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
- [30] Ferreira JJ, Desboeuf K, Galitzky M, Thalamos C, Brefel-Courbon C, Fabre N, et al. Sleep disruption, daytime somnolence and 'sleep attacks' in Parkinson's disease: a clinical survey in PD patients and age-matched healthy volunteers. *Eur J Neurol* 2006;13:209–14.

- [31] Pal PK, Thennarasu K, Fleming J, Schulzer M, Brown T, Calne SM. Nocturnal sleep disturbances and daytime dysfunction in patients with Parkinson's disease and in their caregivers. *Parkinsonism Relat Disord* 2004;10:157–68.
- [32] Boddy F, Rowan EN, Lett D, O'Brien JT, McKeith IG, Burn DJ. Subjectively reported sleep quality and excessive daytime somnolence in Parkinson's disease with and without dementia, dementia with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry* 2007;22:529–35.
- [33] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta psychiatr Scand* 1983;67:361–70.
- [34] Newcombe RG, Altman DG. Proportions and their differences. In: Altman DG, Machin D, Bryant TN, Gardner MJ, editors. *Statistics with confidence*. Bristol: British Medical Journal; 2005. p. 45–56.
- [35] Karlsen K, Larsen JP, Tandberg E, Jørgensen K. Fatigue in patients with Parkinson's disease. *Mov Disord* 1999;14:237–41.
- [36] Brown RG, Dittner A, Findley L, Wessely SC. The Parkinson fatigue scale. *Parkinsonism Relat Disord* 2007;11:49–55.
- [37] Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46:1121–3.