Apathy, fatigue and quality of life in patients with Parkinson's disease

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Chapter 1

Introduction

The focus of this thesis is on non-motor symptoms (NMS) of Parkinson's disease (PD), especially on fatigue, apathy and depression and how they are related to each other. This thesis will also focus on tools for comprehensive assessment of NMS in PD, namely the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the relationship of NMS to Quality of Life (QoL). In this introductory chapter a description of PD is given with a focus on NMS in PD and their assessment followed by a more detailed description of fatigue and apathy in PD. Research questions are then formulated and the chapter ends with an outline of the thesis.

1.1 Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. Historically it has been considered mostly as a disorder associated with dopamine depletion in the basal ganglia and with motor symptoms such as bradykinesia, rigidity and resting tremor (1). However, recent research points to a much more complex pathology involving multiple neuromediator systems and a number of other motor and non-motor symptoms with a major impact on daily activities and the QoL of PD patients. Some of the most common and most disabling symptoms according to multiple studies are in particular neuropsychiatric symptoms, including mood disorders, fatigue and apathy (2-4). The etiology of these symptoms is clearly multifactorial and certainly not fully understood; moreover, their therapy is often not very effective. Therefore, addressing the issue of NMS in PD is one of the most important challenges for future PD research.

1.2 Epidemiology of Parkinson's disease

The prevalence of PD in developed countries is estimated to be between 100 and 300 per 100,000 (5). In the population over 65 years of age the prevalence of PD in a review based on 12 US and European studies was estimated at 950 per 100,000 (6). The prevalence can even increase in the population over 85 years old, where it may reach 3-5% (7). The incidence of PD in studies conducted in Europe were between 9 and 22 per 100,000 (5), with a median of 14 per 100,000 (6). However, in studies restricted to the population aged 65 years or older, the median incidence rate was

160 per 100,000 (6). The occurrence of PD is clearly linked to increasing age. The disease typically starts in the fifth and sixth decade, although approximately 5-10% of all cases may manifest before the age of 40 (young-onset PD), or even before the age of 21 (juvenile parkinsonism). Most studies conducted in Western populations report a higher incidence of PD in men compared with women; however, in most Asian studies this ratio was nearly equal (7). Regarding race, in a California-based study the incidence of PD was highest among Hispanics followed by non-Hispanic Caucasians, Asians and Blacks (8). The number of PD patients in the Slovak Republic is estimated to be 12,000-15,000 (9).

1.3 Pathology and etiology of Parkinson's disease

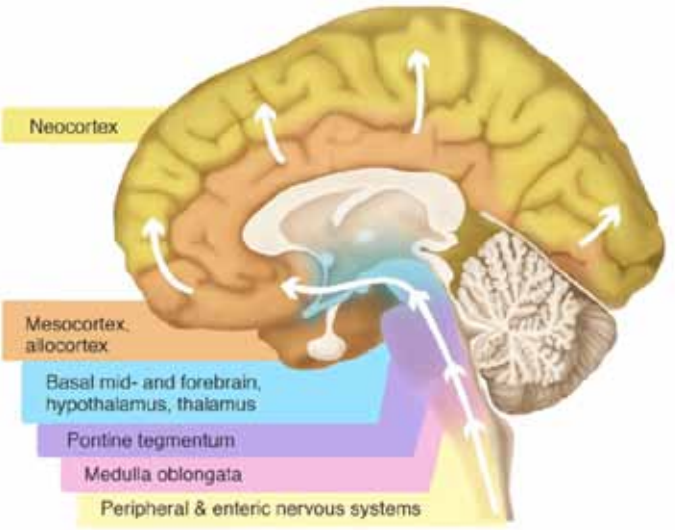
From a neuropathological point of view, PD is no longer considered a pure 'motor' disorder characterized by extrapyramidal symptoms, but a progressive multi-system or rather multi-organ disease with different neurological and non-motor symptoms. It is characterized morphologically not only by degeneration of the dopaminergic nigrostriatal system, which is responsible for the core motor symptoms, but by the multifocal involvement of the central, peripheral and autonomic nervous systems and other organs associated with the widespread occurrence of Lewy bodies and dystrophic Lewy neurites, which result from a deposition of abnormal a-synuclein (10). In fact, multiple other neurotransmitter systems are affected in PD, including e.g. the serotonergic (nuclei raphe), noradrenergic (locus coeruleus), acetylcholinergic (cortex), GABAergic (substantia nigra) and other systems. Braak et al. (11) proposed a model of PD progression divided into 6 stages based on the spreading of the Lewy pathology in the brain. In this model stages 1 and 2 refer to brainstem involvement (pre-motor PD), stage 3 and 4 refer to the mesencephalic and mesocortex affection (early motor phase) and stage 5 and 6 refer to neocortex affection (late stage PD) (see Figure 1.1).

The etiology of PD has not been fully elucidated, although it is clearly multifactorial, including genetic as well as environmental factors (12). Highly penetrant mutations in several genes (e.g. SNCA, LRRK2, VPS35, Parkin, PINK1 and DJ-1) are rare causes of monogenic PD; other mutation variants with incomplete penetrance in the LRRK2 and GBA genes are strong risk factors for PD; and lastly, common variants of small effect size, modulating the risk for PD, have been identified by genome-wide association studies in more than 20 chromosomal loci (13). However, all of these mutations explain only a minority of all PD cases, and most of them are still considered as sporadic.

In PD several mechanisms are considered to underlie the pathological process itself – especially mitochondrial dysfunction, oxidative stress and pathological aggregation of a-synuclein and its prion-like spreading

throughout the peripheral and central nervous system (1,10). Several studies have described a cell-to-cell prion-like transmission of α-synuclein fibrils and aggregates (14-16). However, the impact of Lewy pathology on neurodegeneration still remains unclear – whether it is detrimental and interferes with normal cell function or is a manifestation of a (failed?) cytoprotective response to confine and eliminate cytotoxic proteins (10). How and where the a-synuclein and mitochondrial pathways interact is also not fully understood, although some in vivo studies have demonstrated that a-synuclein oligomers may directly bind to mitochondrial membranes leading to mitochondrial fragmentation and cell death (17,18).

Figure 1.1 Staging of Lewy pathology according to the Braak model
(adapted from Visanji et al. 2013)



1.4 Diagnosis and differential diagnosis of Parkinson's disease

The clinical picture of PD includes motor symptoms as well as a number of non-motor symptoms. Despite growing knowledge about the pathophysiology, genetics, imaging and non-motor symptomatology of pre-motor PD, the diagnosis of PD itself is still mostly based on the typical history of the disease and the presence of cardinal motor features, based on the UK PD Brain Bank criteria (20). The diagnosis of PD is based on 3 logical steps – first, the diagnosis of parkinsonism as such is made; second, exclusion criteria are evaluated; and third, prospective criteria which support the diagnosis of PD are considered (20).

Idiopathic PD represents approximately 80% of all causes of parkinsonism, the remaining 20% of cases present other neurodegenerative and secondary symptomatic causes. The misdiagnosis rate of PD in physicians not specialized in Movement Disorders can be as high as 40%, and this rate is still up to 10% even in specialized centers in the first years of the disease, when atypical symptoms may not have manifested yet (21).

1.5 Classification and prevalence of non-motor symptoms of Parkinson's disease

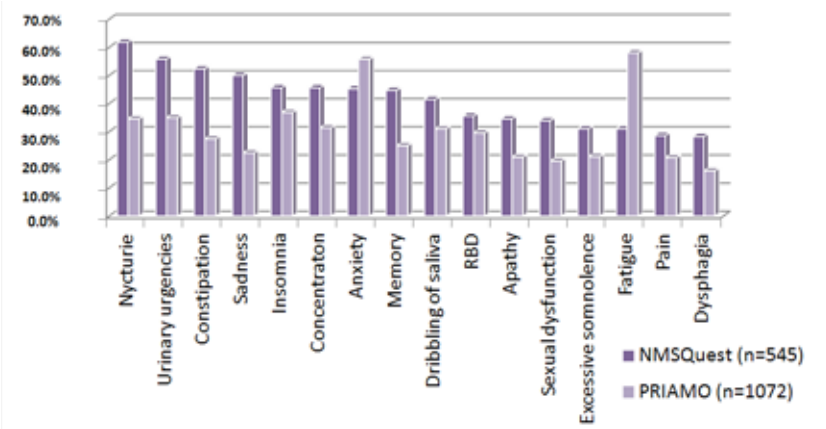
Non-motor symptoms (NMS) of PD are the most under-recognized and under-researched areas of the PD clinical symptomatology when taken as a whole. Despite reports of the presence of NMS even as early as in the first descriptions of PD patients by James Parkinson in 1817 (22,23), the subsequent PD-related research focused very little attention on this area, and most endpoints in clinical trials in the following decades were focused on motor symptoms only. There is a broad spectrum of NMS in PD (see Table 1.1) (23). Although NMS are especially problematic late in the disease course, the symptoms are common across all stages of the disease and it has become increasingly recognized that a number of non-motor features can precede the motor symptoms of PD, sometimes even by many years. Typical pre-motor NMS in PD include hyposmia, constipation, REM-sleep behaviour disorder (RBD) and depression, but other symptoms can occur as well (24).

Several NMS in PD have a relatively poor response to dopaminergic therapy and thus the pathophysiology involving the serotonergic, noradrenergic and other neurotransmitter systems (25). The occurrence of NMS before the motor symptoms in PD is in line with the Braak theory, where peripheral and enteric nervous system and lower brainstem nuclei, including the anterior olfactory nucleus and dorsal motor nucleus of vagus nerve, precede the pathology of the substantia nigra and other structures involved in the major motor features of PD, although this view must not be applied to all patients (11,19,23). The overall burden of NMS increases with disease duration and severity (26). Thus far, only a few complex prevalence studies have been conducted on a wide range of NMS in PD (see Figure 1.2). The most common NMS identified in these studies include fatigue, mood disorders – anxiety and depression – urinary problems, constipation and sleep problems (2,3).

Table 1.1 Classification of non-motor symptoms of PD (23)

Neuropsychiatric symptoms	Sleep disorders and dysfunctions
Depression Anxiety Apathy Hallucinations, delusions, illusions Delirium (may be drug-induced) Cognitive impairment (Dementia, MCI) Dopamine dysregulation syndrome (usually related to levodopa) Impulse control disorders (related to dopaminergic drugs) Panic attacks (could be "off" related)	REM sleep behaviour disorder (possible premotor) Excessive daytime somnolence, narcolepsy type "sleep attack" Restless legs syndrome, periodic leg movements Insomnia Sleep disordered breathing Non-REM parasomnias (confusional wandering)
Fatigue	Sensory symptoms
Central fatigue (maybe related to dysautonomia) Peripheral fatigue	Pain Hyposmia, Functional anosmia Visual disturbance - blurred vision, diplopia, impaired contrast-sensitivity
Autonomic dysfunction	Gastrointestinal symptoms
Bladder urgency, frequency, nocturia Sexual dysfunction (may be drug-induced) Sweating abnormalities (hyperhidrosis) Orthostatic hypotension	Dribbling of saliva Dysphagia Ageusia Nausea, Vomiting Reflux Constipation, Fecal incontinence
Dopaminergic drug-induced behavioural NMS	Dopaminergic drug-induced "other" NMS
Hallucinations, psychosis, delusions Dopamine dysregulation syndrome (usually linked to levodopa intake) Impulse control disorders (e.g. compulsive gambling, hypersexuality, binge eating)	Ankle swelling Dyspnoea (maybe linked to ergot dopamine agonist related cardiac/respiratory failure) Skin reactions Subcutaneous nodules (apomorphine) Erythematous rash (rotigotine patch)
Non-motor fluctuations	Other symptoms
Dysautonomic Cognitive/Psychiatric Sensory/Pain Visual blurring	Weight loss Weight gain (could be related to impulse control disorders)

Figure 1.2 Frequency of the most common NMS of PD in the international multicenter NMSQuest study conducted in 545 PD patients (2) and in the multicenter Italian PRIAMO study conducted in 1072 PD patients (3)



1.6 Comprehensive tools for assessment of NMS in Parkinson's disease

Assessment of the prevalence and severity of the whole spectrum of NMS in PD by symptom-specific scales is practically not possible. This, however, can be performed by some of the comprehensive tools for their assessment, especially the MDS-UPDRS, NMSQuest and NMSS.

The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is a four-subscale combined scale (non-motor experiences of daily living, motor experiences of daily living, motor examination and motor complications) (27). The MDS-UPDRS part I – "Non-motor experiences of daily living" consists of 13 items. Six of these items are evaluated in the form of a semistructured interview – namely Cognitive impairment, Hallucinations and psychosis, Depressed mood, Anxious mood, Apathy and Features of dopamine dysregulation syndrome. Seven items are evaluated in the form of a patient self-report questionnaire – namely Sleep problems, Daytime sleepiness, Pain and other sensations, Urinary problems, Constipation problems, Light-headedness on standing and Fatigue (27). Each item is scored on a scale from 0 to 4, with 0 meaning no affection and 4 meaning the worst frequency and severity of the particular symptom.

The NMS questionnaire (NMSQuest) is a 30-item self-completed questionnaire featuring responses such as 'yes', 'no', and 'don't know' to each item (26). The 30 items were derived from consultations based on the experiences of members of the PD non-motor group as well as the published literature, patient group responses, the experience of the nurse

specialists and the results of a U.K. Parkinson's Disease Society survey of patients and caregivers (conducted among 1,000 members of the society) and a hospital-based survey conducted by Gulati et al. (28).

The Non-motor Symptoms Scale contains 30 non-motor items based on the NMSQuest (29). However, in contrast to the NMSQuest, the NMSS is rated by health professionals and obtained through an interview. The score for each item is based on a multiple of severity (from 0 to 3) and frequency scores (from 1 to 4). The scale can therefore capture symptoms that are severe but relatively infrequent (e.g., hallucinations) and those that may be less severe but persistent (e.g., constipation, fatigue, or mood disturbances). This method increases the weight of symptoms that are persistent and severe simultaneously (29).

1.7 Non-motor symptoms and Health-Related Quality of Life in Parkinson's disease

Non-motor symptoms have been repeatedly associated with worse Health-Related Quality of Life (HRQoL) in the early as well as late stages of PD (3,4,29). The total burden of NMS is likely to be more important than motor symptoms of PD in determining HRQoL across all stages of PD (Martinez-Martin 2014) and also may have a major implication on the cost of care for PD (30). In a study published by the NMSS Validation Group (31) the most important determinants of worse quality of life were sleep disorders, fatigue, mood disorders and apathy. Gallagher et al. (32) commonly found that autonomic dysfunction, mood disorders, fatigue, sleep problems, excessive daytime somnolence, psychosis and pain have a bigger impact on quality of life than motor status evaluated using the Unified Parkinson's Disease Rating Scale part III.

1.8 Fatigue in Parkinson's disease

Fatigue is one of the most common NMS associated with PD, with a prevalence of up to 79% among PD patients (33). Fatigue was found to be the most frequent of all NMS assessed in 1072 consecutive patients examined in the PRIAMO study (3). Fatigue also has a significant impact on quality of life (34). In a study which examined treatment expectations of PD patients, fatigue was found to be the third most relevant problem (35). The first articles highlighting the importance of fatigue in PD were published in 1993 (36,37); however, fatigue has received more attention only in the last decade.

There is currently no universally accepted definition of fatigue. PD patients complaining about fatigue describe it as being different from the fatigue they experienced before developing PD (38). 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, a perception or experience that is yet not objectively measurable (39). Central fatigue can be further divided into physical and mental fatigue.

While more is known about the epidemiology and importance of fatigue in PD, little is known about its etiology, pathogenesis and possible management. One reason is the probable heterogeneity of biological, clinical and psychosocial factors leading to the presence of fatigue. In previous studies disease severity, as measured by the Unified Parkinson's Disease Rating Scale, was associated with fatigue only in some studies (34,40), while others found no such association (41,42). A significant association between disease duration and fatigue has not yet been proven. Indeed, fatigue is present in all PD stages and was previously found in one-third of newly diagnosed, untreated, non-demented and non-depressed PD patients (43). Most previously published articles found a strong link between fatigue and the presence of mood disorders, especially depression (34,44), and excessive daytime sleepiness (EDS) (45). Here is some overlap, since fatigue is one of the DSM-IV diagnostic criteria for depression and anxiety, making interpretation of fatigue in the presence of such problems a major challenge.

Fatigue may also be sometimes misdiagnosed as apathy. In a study by Funkiewiez et al. (46) PD patients after subthalamic nucleus deep brain stimulation (STN DBS) often confused apathy with fatigue: they reported feeling tired and having difficulties in starting any activities. The only study which has thus far directly correlated fatigue with different apathy domains 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 sub-scores (47).

1.9 Apathy in Parkinson's disease

Apathy is a common NMS of many neuropsychiatric disorders, such as PD, Alzheimer's disease and stroke (48-50). Apathy has been characterized as a lack of motivation manifested by diminished goal-directed cognition and behaviour, with decreased emotional involvement (51). Diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders have been recently published (52) and are summarized in Table 1.2. The reported prevalence of apathy in PD varies from 17% to 72% depending on the diagnostic tools used and patient samples examined (50,53). Apathy is present in all stages of PD, including in early and untreated disease, and a possible role of dopamine depletion has been suggested (54,55).

Table 1.2 Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders (adapted from Robert et al. 2009)

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

Thus far depression has been identified as one of the factors most commonly associated with apathy in PD, and a few studies have addressed the issue of whether apathy is an independent syndrome or is mostly a co-morbid condition of depression (56-58). In fact, depending on the studied population, up to 33% of patients were found to have 'pure' apathy in the absence of depression and dementia (53), and it has been repeatedly reported that apathy and depression in PD can be clearly distinguished and can present discrete constructs (57,58). Apathy has also been associated with worse cognitive performance, such as executive dysfunction (59,60). A longitudinal study of cognitive status in initially

non-demented and non-depressed apathetic versus non-apathetic PD patients found a significantly higher rate of conversion to dementia later on in the apathetic group (59). Their findings, as well as those of others (61), suggest that apathy may be a predictive factor for developing dementia and cognitive decline. In the general population, the prevalence of cognitive dysfunction and dementia, which are significant predictors of higher morbidity and mortality (20), increases with age (62). Apathy in otherwise healthy community-dwelling individuals was also shown to increase with increasing age, especially at 65 years of age and over (49). Apathy is significantly associated with older age in PD as well (53,63). Therefore, determining the prevalence of 'pure' apathy as a potential predictive factor for dementia in the elderly PD population is important.

Apathy has repeatedly been associated with worse HRQoL (63-65). In a study of recently diagnosed PD patients, apathetic patients were 2.5-times more likely to have lower HRQoL compared with non-apathetic PD patients after adjusting for sociodemographic factors and disease variables (65). Apathy has been also previously associated with a worse PDQ39 total score and the PDQ39 cognition and stigma subdomains (63). Moreover, in a recent study Leroi et al. (66) found a significantly greater caregiver burden in the carers of PD patients with apathy compared with careers of patients without apathy.

1.10 Primary aim of the study and research questions

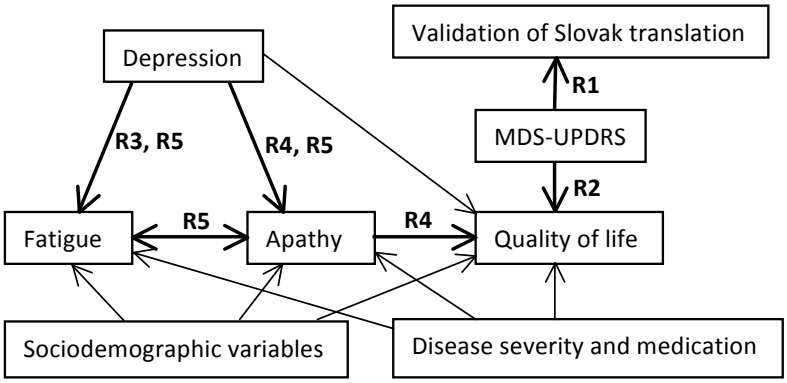
The aim of the first part of this thesis is to validate the Slovak translation of the MDS-UPDRS as a newly developed comprehensive measure for PD, which can be potentially used as a comprehensive tool for assessment of the NMS in PD. The study will also explore the relationship between the MDS-UPDRS and QoL, with a focus on non-motor issues, including fatigue, apathy and depression, in the context of other motor and non-motor PD symptoms.

The aim of the second part of this thesis is to explore the relationship between fatigue, apathy and depression in PD and to explore the relationship of different NMS to QoL in PD. Fatigue, apathy and depression have a high coincidence and can be often confused in both clinical as well as research settings. These three conditions are considered either as combined symptomatic domains or as potentially separable clinical entities. To our knowledge, there have been some studies which tried to separate the constructs of apathy and depression, but no studies aiming to specifically separate fatigue and depression and also not to differentiate between fatigue domains and apathy. Both apathy and fatigue can be part of the clinical symptomatology of depression, and therefore this study will focus on the clinical characteristics of fatigue in the presence or absence of depression, as these probably present different

concepts. Next, the study will evaluate the coincidence and relationship between apathy and depression, and finally it will explore the coincidence and relationship between fatigue and apathy separately in depressed and non-depressed patients.

The basic model of the study is summarized in Figure 1.3. The five research questions listed below are formulated based on the previous model.

Figure 1.3 Model of the relationships examined in the thesis



Research question 1 will explore the validity of the Slovak translation of the MDS-UPDRS, which was designed to be the reference measure for future PD research and a potential tool for assessing NMS in PD.

Research question 2 will explore the relationship between the MDS-UPDRS and QoL and will focus especially on the relationship between MDS-UPDRS non-motor items and QoL.

Research question 3 will explore the relationship between sociodemographic and clinical variables and PD-related fatigue. This relationship will be studied separately for fatigue in the absence of depression and excessive daytime sleepiness – 'primary fatigue' – and for fatigue in the presence of depression or excessive daytime sleepiness – 'secondary fatigue'.

Research question 4 will explore the coincidence of apathy and depression and the clinical determinants of PD-related apathy specifically in the elderly non-demented population of PD patients and their relationships to QoL.

Research question 5 will explore the coincidence of the different domains of primary and secondary fatigue and apathy in the presence or absence of depression and will explore the associations between fatigue, apathy and depression controlled for other sociodemographic and disease-related variables.

1.11 The structure of the thesis

This thesis is divided into two parts and consists of 8 chapters: An Introduction (Chapter 1) and Data source, measures and statistical analyses (Chapter 2), Part I – Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and its relationship to Quality of Life (Chapters 3 and 4), Part II – Determinants of Fatigue and Apathy in PD (Chapters 5-7), and finally a Discussion of the study findings (Chapter 8).

Chapter 1 *'Introduction'* provides information about PD with a focus on its NMS and their relationship to Quality of Life; this chapter also provides information about the holistic tools used to assess the NMS of PD.

Chapter 2 *'Data source, measures and statistical analyses'* provides information about the sample, data source, measures and statistical analyses used in Chapters 3-7.

Chapter 3 *'Validation of the Slovak version of the Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS)'* is a newly developed comprehensive tool to assess PD, which covers a wider range of non-motor PD manifestations than the original UPDRS scale and therefore can be used as a holistic tool for the assessment of NMS in PD. This chapter was part of the Movement Disorder Society program for translation and validation of non-English versions of the MDS-UPDRS. The aim of this study was to validate and confirm the factor structure of the Slovak translation of the MDS-UPDRS compared with the original English version of the scale.

Chapter 4 *'Importance of the non-motor items of the MDS-UPDRS for Quality of Life in patients with Parkinson's disease'* explores the relationship between the MDS-UPDRS and QoL with a focus on the relationship between individual non-motor items of the scale and QoL; the aim of this chapter was to determine the most important NMS regarding QoL when using the MDS-UPDRS, which was designed to be the major reference measure in future PD research.

Chapter 5 *'Clinical determinants of primary and secondary fatigue in patients with Parkinson's disease'* focuses on the role of depression and excessive daytime sleepiness in PD-related fatigue. We expect that fatigue in the absence of these symptoms ('primary fatigue') or in the presence of these symptoms ('secondary fatigue') present different concepts and are associated with different socio-demographic as well as clinical determinants, and therefore future studies investigating PD-related fatigue should be conducted separately in primary and secondary fatigue groups.

Chapter 6 *'Apathy in elderly nondemented patients with Parkinson's disease: Clinical determinants and relationship to quality of life'* explores the clinical determinants of apathy and its relationship to QoL specifically

in an elderly population of PD patients and furthermore compares the results with previously published reports from the general PD population.

Chapter 7 *'The associations between fatigue, apathy and depression in Parkinson's disease'* explores the relationship between fatigue, apathy and depression, which have a high coincidence and can be often confused in PD. The chapter aims to disentangle the implications that apathy and depression may have on the development of fatigue in Parkinson's disease.

Chapter 8 *'Discussion'* presents the condensed outcomes of this study, discusses them in the framework of existing knowledge, argues their strengths and weaknesses, goes into their implications for practice and offers new possibilities for further research.

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