Chapter 1

General introduction
Introduction

Parkinson’s disease

In 1817, James Parkinson wrote his essay on the shaking palsy in which he described most of the motor symptoms currently attributed to idiopathic Parkinson’s disease (PD). He characterized the disease as: ‘an involuntary tremulous motion, with lessened muscular power; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured’ [1]. Fifty years later, Jean-Martin Charcot distinguished bradykinesia as a separate cardinal feature of the disease and recognized that patients were not markedly weak and did not necessarily have tremor. In addition, he distinguished the tremorous and the rigid or akinetic form of the disease and suggested the term ‘Parkinson’s disease’, rejecting the earlier proposed description of shaking palsy [2].

PD is the second most common neurodegenerative disorder after Alzheimer’s disease, imposing an increasing social and economic burden [3]. Prevalence rates in Europe range from 1.3% to 1.5% for people above the age of 60 years [4]. Nowadays, PD is defined as a neurological disorder associated with progressive neuronal loss in the substantia nigra and other brain structures and with Lewy body inclusions in some of the remaining nerve cells [5]. To date, clinical diagnosis is still based on the presence of bradykinesia and at least one of the other cardinal motor signs of PD: tremor, rigidity and postural instability [6], together with a substantial and sustained response to dopaminergic treatment and no symptoms suggestive for other disease [7]. Bradykinesia is considered conditional for PD [6]; however, a definite diagnosis of PD can only be obtained by autopsy [7].

A variety of non-motor symptoms, such as olfactory dysfunction, autonomic dysfunction, anxiety, depression, fatigue, and sleep disorders [8], may precede the cardinal motor signs that characterize PD [9]. Both motor and non-motor symptoms contribute to disability and reduced disease-specific health-related quality of life (HRQOL) [10]. Despite a growing number of scientific publications about fatigue in patients with PD, fundamental questions regarding the impact of fatigue on daily life as well as the assessment and the treatment of fatigue remain unanswered.

Fatigue in Parkinson’s disease

Fatigue is a common non-motor symptom in patients with PD: approximately 32% to 50% of patients complain about fatigue [11, 12] and one third of patients considers
fatigue as their most disabling symptom [13]. The perception of fatigue is subjective which makes it difficult to distinguish the lay notion of tiredness from clinically relevant symptoms of fatigue [14]. Although no widely accepted definition exists, fatigue usually refers to the difficulty in initiating or sustaining voluntary activity [14]. Fatigue is often subdivided into physical and mental fatigue [13]. Physical fatigue involves a sense of physical exhaustion and lack of energy to perform physical tasks despite the capacity and motivation to perform the task [15], whereas mental fatigue refers to the cognitive effects experienced during and after prolonged periods of cognitive activities that require sustained concentration [15].

Recently, Kluger and colleagues [16] proposed a unifying taxonomy for fatigue and fatigability in patients with neurologic disorders and distinguished between fatigue being either a primary or secondary manifestation of disease. Different aspects of fatigue are believed to result from a complex interplay between underlying disease, peripheral control systems (i.e. fatigability), central control systems (i.e. subjective perception of fatigue) and environmental factors [14]. Several pathophysiological mechanisms, such as reduced concentrations of cytokines, inflammation, abnormalities of the hypothalamic adrenal axis and disturbances in the basal ganglia [14], have been suggested; however, the exact mechanisms contributing to fatigue in patients with PD are still not well understood [13].

The impact of fatigue on health-related quality of life and physical activity in Parkinson’s disease

Patients with PD are likely to experience reduced HRQOL [10] and are about 30% less physically active compared to age-matched controls [17]. Both motor and non-motor symptoms contribute to HRQOL and the amount of physical activity; unfortunately, the factors that determine HRQOL and physical activity are not fully understood. Previous studies suggested that fatigue has a negative impact on HRQOL [18-20] and physical activity [20, 21], and may affect community walking in patients with PD [22]. However, the real impact of fatigue is unknown and likely distorted by factors such as depression and sleep disturbances. These symptoms commonly overlap with, or exacerbate feelings of subjective fatigue [23] and may also contribute to reduced HRQOL and physical activity.

A few studies have investigated the relationship between, on the one hand, fatigue and on the other hand HRQOL [18-20] and physical activity [21, 24, 25]. Unfortunately, these studies used cross-sectional analyses [18-21, 24, 25], whereas perception of fatigue and real life performance fluctuate in time and are known to be time-dependent.
Therefore, the quasi-causal relationships between fatigue and other factors that contribute to HRQOL and physical activity may be more accurately reflected using longitudinal study designs with intensive repeated measures in time.

Assessment of fatigue in Parkinson’s disease

The assessment of fatigue can be conceptualized as either a subjective feeling or a performance decrement, which is reflected in the two approaches to measuring fatigue (i.e. through self-report questionnaires or direct observation of behavior [26]). A large number of self-report questionnaires are available to evaluate fatigue as either a unidimensional or multidimensional construct. However, these questionnaires may assess different aspects of fatigue, hampering the selection of an appropriate instrument to evaluate fatigue in patients with PD. The Movement Disorders Society Task Force on Rating Scales for Parkinson’s disease recommended the Multidimensional Fatigue Inventory (MFI) and the Fatigue Severity Scale (FSS) for the assessment of fatigue in patients with PD [15]. Unfortunately, these recommendations were largely based on studies in non-PD samples and the methodological quality of underlying studies was not taken into account. This makes it difficult to judge the strength of the evidence supporting these recommendations and it remains unclear whether some of the measurement properties of these self-report questionnaires are appropriate in patients with PD.

Pharmacological and non-pharmacological interventions for fatigue in Parkinson’s disease

Given that mechanisms contributing to fatigue are still not well known and the impact of fatigue on daily life is likely influenced by other factors, effective management of fatigue is difficult. Treatment of fatigue usually involves pharmacological and non-pharmacological interventions. Recently, a systematic review about treatments for non-motor symptoms of PD [27] included three studies that investigated the effect of methylphenidate [28] or modafinil [29, 30] on fatigue. Seppi and colleagues [27] concluded that there was insufficient evidence for the efficacy and safety of methylphenidate and modafinil for the treatment of fatigue in patients with PD. The effects of non-pharmacological interventions for fatigue in PD however, have never been evaluated in a systematic review.

A medication regime targeting motor performance and mood disorders, combined with a rehabilitation program that will focus on exercise capacity, may reduce symptoms of fatigue. However, the effects of these multimodal programs have not yet been investigated in patients with PD.
Framework to investigate the impact of fatigue on health-related quality of life and physical activity

The lack of an appropriate definition and the multidimensional character of fatigue make it difficult to investigate the relationship between fatigue on the one hand and HRQOL and physical activity on the other hand. In the present thesis, we will focus on the subjective perception of fatigue rather than fatigability [16]. We will describe three existing theoretical models to improve our understanding about the relationship between fatigue, HRQOL and physical activity in patients with PD. The International Classification of Functioning, Disability and Health (ICF) model [31] is often used in rehabilitation medicine to understand the relationship between clinical factors and functioning in daily life. The model by Van Houdenhove and colleagues [32] and the model proposed by Chaudhuri and Behan [14] may complement each other in conceptualizing the complex relationship between fatigue and physical activity in patients with PD.

Fatigue, health-related quality of life and physical activity within the framework of the ICF

Figure 1.1 shows the ICF model [31]. This model can be used to evaluate fatigue in terms of body functions and structures, activity, and participation. Although the ICF provides no specific classification for fatigue, the description of fatigue as proposed by Chaudhuri and Behan [14] implies that fatigue can be evaluated as a limitation in activity and participation that is influenced by impairment in body functions and body

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**Figure 1.1** International Classification of Functioning, Disability and Health (ICF) [31].
structures, as well as environmental and personal factors. However, it has been argued that fatigue severity, much like ‘sleep’ and ‘energy and drive functions’, can be classified as impairment in body functions [33, 34]. Both classifications for fatigue are used; in the present thesis however, we will evaluate fatigue in terms of perceived limitations in activity and participation as measured by the MFI [35].

We will use the Parkinson’s Disease Questionnaire-39 (PDQ-39) [36] to assess HRQOL. Different domains of HRQOL classify an individuals’ perception of impairment in body function or limitation in activity and participation.

Physical activity and community walking can be classified within the ICF domains activity and participation. Qualifiers for these classifications make it possible to separate the patient’s capacity to perform physical activity and the performance of physical activity in his or her actual environment [31]. The amount of physical activity can be evaluated by self-report questionnaires. However, these instruments are subjective and susceptible to recall bias or providing desirable answers, which may affect estimations of levels of activity. Therefore, we will use ambulatory accelerometry to more objectively measure the actual amount and type of a patient’s physical activity performed in his or her own living environment. We will use the mobility domain of the Nottingham Extended Activities of daily living Index (NEAI) [37] to evaluate community walking.

**Fatigue and physical activity: conceptual model by Van Houdenhove et al.**

Figure 1.2 presents a conceptual model that distinguishes two aspects that contribute to physical activity (i.e. motor performance) in patients with chronic fatigue syndrome [32]. The first aspect, effort capacity, refers to the capacity to initiate and maintain physical activity. The second aspect, effort tolerance, refers to the capacity of the neurobiological stress system to tolerate the stress of physical activity and to adequately recover from it [32].

Van Houdenhove and colleagues hypothesized that decreased physical activity in patients with chronic fatigue syndrome can primarily be understood in terms of reduced effort tolerance, often in interaction with factors that decrease effort capacity [32].
Fatigue and physical activity: conceptual model by Chaudhuri and Behan

Figure 1.3 presents a conceptual model that illustrates the relationship between fatigue and physical activity in patients with neurological disorders [14]. In the context of the ICF classification, we assume that work output can be interpreted as a performance qualifier that describes a patient’s actual performed physical activity in his or her environment, whereas the set point for applied effort may be classified as a capacity qualifier that describes the ability to execute physical activity. The set point for applied effort is controlled by motivational input and feedback from motor, sensory and cognitive functions that establish the level of perceived exertion [14]. Pathological fatigue could develop because of dissociation between the level of internal input and that of perceived exertion and can be induced by changes in one or more determinants regulating work output [14].

Common motor and non-motor symptoms of PD may contribute to work output through the level of internal input and perceived exertion; however, symptoms may also directly relate to work output. The model proposed by Chaudhuri and Behan emphasizes the pathway through the level of internal input and perceived exertion, and as such, disregards the direct contribution of symptoms to work output that may confound the association between fatigue and physical activity. To date, little is known about these possible confounding factors and how they affect the association between fatigue and physical activity.
Objectives and outline of the present thesis

This thesis presents the results of a prospective study in which we investigate the impact of perceived fatigue on HRQOL and physical activity in patients with PD. We use data collected in the ‘Rescue trial’ (Rehabilitation in Parkinson’s disease: strategies for cueing). This randomized clinical trial (RCT), financed by the European Commission within the 5th framework (FP5), was a collaboration between three European centers: Northumbria University, Newcastle upon Tyne (UK); Katholieke Universiteit Leuven, Leuven (Belgium); and the VU University Medical Center, Amsterdam (The Netherlands). Till so far, it has been the largest RCT that used ambulatory accelerometry to investigate the effects of cueing training on gait and gait-related activity in patients with PD [38].

The overall objectives of this thesis are threefold. First, we aim to investigate the longitudinal association between, on the one hand, fatigue and on the other hand HRQOL and actual performed physical activity in patients with PD. To this end, we will explore the possible confounders that distort the assumed association (Chapter 2 and Chapter 3). Subsequently, we will develop a multivariable logistic regression
model for predicting community walking in patients with PD (Chapter 4). Second, we aim to investigate the measurement properties of self-report questionnaires that can be used to assess fatigue in patients with PD. In Chapter 5 we will critically appraise the measurement properties of questionnaires validated in patients with multiple sclerosis, PD or stroke and investigate the reliability and structural validity of the MFI [35] in patients with PD (Chapter 6). In both studies we use the recently developed COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) taxonomy [39] to summarize the quality of the measurement properties. Third, we aim to investigate the effect of pharmacological and non-pharmacological interventions on fatigue in patients with PD. To this end, we will systematically review the literature to identify RCTs that investigated the effect of pharmacological or non-pharmacological interventions on fatigue in patients with PD (Chapter 7). Finally, in Chapter 8 we will discuss the main findings of the present thesis.

References


