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General introduction

Introduction

Multiple sclerosis (MS) is primarily a chronic inflammatory disorder of the central nervous system (CNS) in which focal lymphocytic infiltration leads to damage of myelin and axons.¹ Demyelination results in slower conduction, or even a conduction block. Axonal loss results in sustained disabilities.² In MS, lesions may occur in all parts of the CNS causing a wide variety of symptoms, including visual problems, altered sensation, muscle weakness, bladder- bowel or sexual problems, brainstem problems, and changes in cognitive function. In addition, patients with MS often experience severe fatigue.³

The incidence of MS is approximately 7 per 100,000 and the prevalence 80–120 per 100,000 in the Northern-American and Western-European countries,⁴ with almost 16,000 people affected in the Netherlands.⁵ MS is the most common neurological disorder affecting young adults, and with disease onset typically between the 20 and 40 years of age. Women are affected approximately two times more often than men.

The exact etiology of the disease is unknown, but most likely MS is caused by a complex interplay between genetic, environmental and autoimmune factors.¹ The clinical course of MS is highly variable and hard to predict.¹ In approximately 85% of the patients, the disease starts with a relapsing-remitting (RR) course that is characterised by episodic acute periods of worsening clearly separated in time. A stable level of disability characterises the interval between the exacerbations. In RR-MS full recovery after an exacerbation is possible, disability evolves because recovery is incomplete. In 80% of the patients with MS the RR course is followed by the secondary progressive phase (SP-MS). This course is characterised by progressive deterioration, with or without exacerbations and remissions. In a relative small proportion, about 10%, of MS patients a continuously disease progression is seen from onset, without relapses, and referred to as primary progressive MS (PP-MS). PP-MS patients experience increasing disability without the presence of relapses.^{1,4,6,7} The most sporadic disease course is the progressive relapsing form of the disease, diagnosed in only 5% of the patients.

The diagnosis MS is made on objective demonstration of dissemination in time (i.e. more than one disease event) and dissemination in space (i.e. involvement of more than one region in the CNS) on clinical grounds alone, or by careful and standardized integration of clinical and MRI findings or detection of oligoclonal bands in cerebrospinal fluid analysis.⁸

Determination of a detailed prognosis of MS at the individual level is difficult, while knowledge on prognostic factors is derived from large group studies. However a recent systematic review has revealed several determinants indicative for long-term bad prognosis with an unfavourable disease course, such as: polysymptomatic onset with initial pyramidal, cerebellar, and sphincter involvement; an initially progressive disease course; higher age at the time of diagnosis; a high number of early relapses; a short inter-relapse interval; and early residual disability.⁹

A curative treatment for MS does not exist yet. Pharmacological treatment is focused on the pathophysiological mechanisms of MS, i.e. reducing the inflammatory response and with that the number of relapses.^{10,11} Besides treatment focussed on the neurodegenerative component of MS, multidisciplinary symptom management is critical in the care of MS patients for improving quality of life and the ability to work.¹⁰

Fatigue in MS

To comprehend the full extent of fatigue in MS, the International Classification of Functioning, Disability and Health (ICF) can be used as a framework.¹² Figure 1.1 shows the domains of the ICF and their mutual relationships. The domains are defined as body functions and structures (impairments), activities (limitations) and participation (restrictions). These three domains are related to health condition, in this context MS, and to two contextual factors, namely environmental and personal. In this context functioning denotes the positive aspects of the interaction between an individual (with a health condition) and that

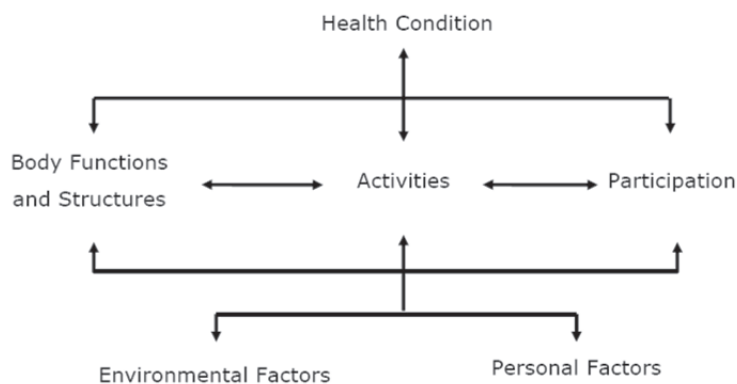


Figure 1.1 The international classification of functioning, disability and health. A schematic representation of the relationships between the domains.

individual's contextual factors (environmental and personal factors), and disability denotes the negative aspects of the interaction between an individual (with a health condition) and that individual's contextual factors (environmental and personal factors). Next to describing health and disability in terms of functioning, the ICF framework can be used to classify outcome measures.¹²

Fatigue is considered to be one of the main causes of impaired daily activities and reduced quality of life in MS, reported by approximately 53%¹³ up to 92%¹⁴ of all MS patients. The poor understanding of the etiology underlying fatigue, the diverse consequences of fatigue, and the lack of adequate methods of measuring the impact of fatigue result in the current challenge of developing, testing, and prescribing effective interventions in patients with MS experiencing disabling fatigue.^{15,16}

Different definitions of fatigue are proposed. A common used definition is the difficulty initiating or sustaining voluntary physical or mental activity.^{3,17-19} According to the ICF, fatigue is defined at the level of body functions and operationalised by code b1308: energy and drive functions, other specified [fatigue].¹²

Several pathophysiological mechanisms, such as dysregulation of the immune system, impaired nerve conduction, and neuro-endocrine and neurotransmitter changes have been suggested to explain fatigue in MS,^{3,20,21} however, the exact mechanisms remain unknown. Despite the poor understanding of the etiology, it is well accepted that fatigue is subjective and multidimensional in nature.²²⁻²³ The multidimensionality is believed to result from complex interactions between the underlying disease process,^{3,25,26} psychological^{22,27} and physical characteristics,²⁶ as well as patients' environmental factors.^{28,29} Based on assumed underlying pathophysiological mechanisms, the construct of fatigue in MS is often classified either into central and peripheral³ or into primary and secondary fatigue.²¹ Chaudhuri³ defined central fatigue as the failure to initiate and/or sustain attentional tasks (mental or cognitive fatigue) and physical activities (physical fatigue), and peripheral fatigue as muscle fatigability due to disorders of muscle and neuromuscular junctions. In the other classification, primary fatigue is considered to be a direct consequence of pathophysiological mechanisms of the MS disease process,^{3,21} while factors secondary to MS, such as pain and muscle spasms, and concomitant conditions such as viral infections, urinary infections, pregnancy, alcohol or substance abuse and depression may also contribute to feelings of fatigue.^{3,17,20,26} The Multiple Sclerosis Council for Clinical Practice Guidelines (MSCCPG)¹⁷ distinguishes chronic persistent fatigue from acute fatigue. Chronic persistent fatigue is

defined as “being present for any amount of time on 50 percent of the days, for more than 6 weeks”, whereas acute fatigue is defined as “new or significant increase in feelings of fatigue in the previous six weeks”. Both chronic and acute fatigue can severely affect daily activities (i.e. activities and participation) and reduce quality of life.

The present thesis is focussed on studying three corner stones in management of fatigue in patients with multiple sclerosis, namely: (1) measurement properties of outcomes to assess fatigue and daily physical activity; (2) the relationship between fatigue and daily physical activity; and (3) multidisciplinary treatment of fatigue.

Fatigue assessment

Fatigue can be assessed by using performance-based or self-report measures. Performance based assessment quantifies a change in performance or sustained mental or physical activity,¹⁸ and is not included in this thesis. Self-report assessment quantifies the perceived level of fatigue or perceived impact of fatigue. Most of the time fatigue in MS is assessed by means of self-report questionnaires.

Fatigue according to the ICF is defined at the level of body functions, however most of the time it is assessed at the level of activity and participation. Assessment of fatigue is challenged by absence of a golden standard. Furthermore, a broadly accepted definition of fatigue is lacking,³ and with that, the determination of its many dimensions.^{3,30}

The multidimensionality of MS related fatigue is illustrated by the different conceptual approaches for measuring fatigue, as each questionnaire is characterized by its own underlying concept. As a result, the different self-report questionnaires may measure different aspects or dimensions of fatigue.³¹ To address the multidimensionality of fatigue some studies use a combination of scales.²⁶ In preparation for our randomized controlled trial on the effect of an individually tailored, multidisciplinary outpatient rehabilitation programme on chronic fatigue in MS presented in **chapter 7**, we have selected three questionnaires for outcome measurement. The selection of the Checklist Individual Strength (CIS20R), the Fatigue Severity Scale (FSS), and the Modified Fatigue Impact Scale (MFIS) was based on evidence and existing guidelines at that time. The CIS20R seems a promising questionnaire for use in fatigue evaluation. It recognises the multidimensional nature of fatigue in MS, but its use in MS research has been limited until now. The FSS is perhaps the most commonly used self-report questionnaire of fatigue severity in patients with MS, and

for reasons of comparability with other studies on fatigue in MS it was incorporated in the outcome set. The MFIS was recommended for assessment of fatigue in patients with MS by the Multiple Sclerosis Council for Clinical guidelines¹⁷ and more recently in a review on self-report assessment of fatigue in MS.³² However, the measurement properties of these three questionnaires have not been assessed in the same sample of patients. Therefore, in **chapter 2** of this thesis the concurrent validity of CIS-20R, FSS and MFIS was studied. Next to concurrent validity, reliability and measurement error were studied in the same group of patients with MS.

The multidimensionality of MS-related fatigue is also illustrated by the large number of self-report fatigue questionnaires used in MS samples.³² Kos and colleagues³² found in 2004 eighteen instruments, either fatigue specific or as part of quality of life instruments, that evaluate fatigue in MS. Guidelines¹⁷ and systematic reviews performed with the aim to help clinicians and researchers in choosing appropriate outcome measures by evaluating measurement properties of fatigue questionnaires, often show the limitation of not using uniform definitions and standards for the assessment of the methodological quality of the included studies. **Chapter 3** of this thesis presents a systematic review of measurement properties of self-report questionnaires used in multiple sclerosis, Parkinson's disease and stroke. A critical appraisal tool, the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN)³³ was used, containing standards for systematically evaluating the methodological quality of studies on the measurement properties of health measurement instruments.

Daily physical activity in MS

Amassing evidence^{34,35} indicates that patients with MS are less physically active than non-diseased people. However, they show quite similar activity levels compared to patients with, for example, chronic fatigue syndrome, chronic obstructive pulmonary disease or cerebral palsy.³⁴

According to the ICF,¹² daily physical activity is defined at the level of activity and participation. Activity concerns the ability to execute a task or action by an individual, and participation as involvement in a life situation. However, while activity and participation are separately defined within the ICF, they are treated as one category. According to the ICF, daily physical activity is operationalised by codes like code d410; changing basic body position, code d415; maintaining a body position, code d430; lifting and carrying objects, code d435; moving objects with lower extremities, code d440; fine hand use, code d445; hand and arm

use code d450; walking, code d455; moving around, code d460; moving around in different locations, code d510; washing oneself, code d530; toileting, code d540; dressing, code d550; eating, code d560; drinking.¹² The inability to perform such a task is classified as an activity limitation. Participation concerns attainment of meaningful goals, such as performing work, visiting a supermarket or attending school or social activities. The inability of involvement in life situations is classified in the ICF as restrictions to participation.¹²

The observed reduction in the daily activity is often held against underlying impairments such as, muscle weakness, spasticity, ataxia and fatigue.^{3,35,36} Next to fatigue, limitations in physical activity are acknowledged as a key problem, with up to 85% of patients reporting walking difficulties.^{37,38} Moreover, walking impairments have major impact on execution of tasks or actions (activities), and involvement in life situations (participation).

Daily physical activity measurement

Key questions are how real world activities of daily living performed in patients own home environment such as lying, sitting, performing transfers and walking are related to perceived fatigue assessed with self-report questionnaires, and which strategies patients use to manage their 24 hour diurnal rhythm. Previously used methods to assess the level of physical activity are: (1) behavioural mapping by clinical observations;³⁹ (2) using self-report questionnaires;^{40,41} (3) using patient diaries;⁴² and (4) applying semistructured interviews.⁴³

However, these instruments measure at discrete moments in time and typically give a subjective indication of activity level. Advances in technology have fostered the development of objective methods allowing more continuous monitoring of daily physical activity using actigraphy⁴⁴ and/or accelerometry⁴⁵ in patients' natural environment. Self-reported activities are only moderately related to objective registration and do not completely match actual activity because of possible recall bias.⁴⁶

Following the ICF,¹² Activity Monitoring (AM) measures can be classified at the body functions and structures (impairments), activities (limitations) or participation (restrictions) domain. Unfortunately, reproducibility of 24 hour AM has not been investigated in patients with MS. Therefore, in **chapter 4** of this thesis, reliability and measurement error of 24-hour monitoring of mobility-related activities in patients with MS was studied.

Studies investigating actual free-living physical activity behaviour of patients with MS are rare. From the literature, there is accumulating evidence that patients with MS have lower

physical activity levels than healthy age- and gender-matched subjects,^{34,35} but little is known about diurnal differences in distribution of these activities. From this perspective, AM allows to measure patients daily activity profiles in association with perceived fatigue. Better insight in these longitudinal associations may give clinicians information about: (1) patients preferred strategies to manage fatigue; and (2) patients ability to handle with the fluctuating energy levels on a day. In addition, the impact of related, sometimes confounding factors such as MS-type, EDSS severity, medication intake, age, and depression on the relationship between AM and fatigue can be investigated. Therefore, in **chapter 5** a study is presented that investigated the amount, type and distribution of daily physical behaviour in patients with MS living in their own community setting. MS patients were compared with age and gender matched healthy controls.

Fatigue and the relationship with daily physical activity

The assumed vicious circle of the impact of fatigue on decline in capacity to perform activities of daily living is poorly understood. Figure 1.2 shows the proposed determinants of motor performance: effort capacity and effort tolerance. In this relationship both factors seem to mutually influence each other.⁴⁷ An impaired balance between, on the one hand, the capacity to produce effort (action) and, on the other hand, the tolerance to cope with increased effort (perception) is believed to worsen over time, acknowledging that increased physical activity may enhance feelings of fatigue, whereas increased feelings of fatigue may limit physical activity.⁴⁷

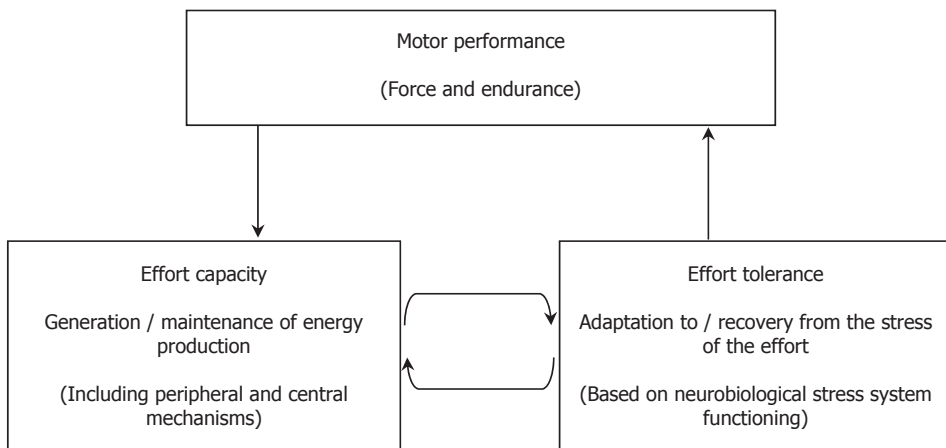


Figure 1.2 Proposed determinants of motor performance: effort capacity and effort tolerance (according to the model of Van Houdenhove et al. 2007).

As a consequence, it has been hypothesized that being less active due to fatigue can lead to a vicious circle in which impaired fitness due to a reduction in physical activity in turn may result in increased feelings of fatigue.⁴⁸ However, these relations are rather speculative and unexplored in people with MS is unclear.

In addition, several studies in patients with MS also found significant associations of fatigue with variables such as age,¹³ physical disability,^{13,49,50} disease sub-type,¹³ anxiety,⁵¹ depression,^{49,50} and health-related quality of life.⁴⁹ Motl and colleagues³⁵ found a small but significant association between fatigue and depression with self-reported physical inactivity ($r=0.42$) even when corrected for disease severity (Expanded Disability Status Scale [EDSS] score) or MS-disease course. In a recent qualitative study, Kayes et al.⁵² reported that fatigue is seen by MS patients as a barrier to taking part in physical activity related to the previously mentioned vicious cycle. However, Vercoulen et al.⁵³ found no significant correlation for patients with MS between physical activity (assessed with an actometer), and perceived fatigue assessed with the Checklist Individual Strength subscale 'Subjective Fatigue' over a period of 12 days. Therefore, a potential found relationship of physical activity with fatigue might be specific to the type of fatigue questionnaire used, as questionnaires typically evaluate different underlying constructs of fatigue.^{31,54} In addition, the method used to measure physical activity by using self-report scales⁴⁶ or activity monitoring^{46,55,56} may also affect found relationships between physical activity and fatigue.

Chapter 6 presents a study that aimed to determine the relationship between the actual amount of physical activity performed over a 24-hour period in MS patients' own community setting, and self-reported perceived fatigue as assessed by three common used self-report questionnaires (i.e. FSS, MFIS and CIS-20R). Additionally, we investigated whether the associations between physical activity and perceived fatigue were confounded by factors such as age, disability status, disease duration, disease sub-type, depression and anxiety, as previous studies have not addressed this.

Fatigue management

The pathophysiological basis of fatigue remains unclear and consequently effective treatment is limited. A number of clinical trials have tested a variety of pharmacological and non-pharmacological interventions for MS-related fatigue. Several drugs such as amantadine, pemoline, modafinil, and aminopyridine have been advocated with respect to their effect on fatigue in MS. The evidence for effects of pharmacological treatment is not established, with

exception of amantadine, which might be of benefit to some MS patients.⁵⁷⁻⁶² Moreover, for most above-mentioned pharmacological agents adverse effects have been reported.^{58,63,64} In addition, several non-pharmacological treatment interventions, such as aerobic training,⁶⁵⁻⁶⁹ cognitive behaviour therapy^{61,70} and energy management strategies^{71,72} aim to reduce the impact of fatigue on patients with MS and are not associated with adverse effects. There is some evidence from RCTs^{61,65,67-72} that these interventions might be beneficial to MS patients. However, rigorous evidence underpinning them is also lacking.

In view of the multidimensional character, it is suggested that fatigue in MS should be managed in a tailored, multidisciplinary way. Acknowledging that there is limited evidence that some MS patients benefit from particular interventions, gaps remain in the current evidence base. Moreover, to date, few randomized clinical trials have evaluated the effects of a combination of these treatment interventions on chronic fatigue in MS as the main focus of intervention, with subjective fatigue as the primary measure of outcome.⁷³

Chapter 7 describes a single-blinded, randomized controlled trial (RCT) in which the effects of a multidisciplinary outpatient rehabilitation programme on chronic fatigue was investigated and compared to monodisciplinary consultation by an MS nurse. For this Treatment of Fatigue (ToF) trial, an individually tailored, multidisciplinary outpatient rehabilitation programme was developed in the MS Center of the VU University medical center (VUmc). In this programme we focussed on treatment of chronic fatigue, acknowledging the recommendation of the MSCCPG¹⁷ that chronic fatigue should be distinguished from acute fatigue, and requires different management approaches. In our trial we used descriptive modifiers postulated by the MSCCPG¹⁷ to differentiate between acute and chronic fatigue.

In the general discussion in **chapter 8**, the main findings, methodological issues, clinical implications, and future directions following from this thesis are provided.

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