Fluctuations of Perceived Stress and Fatigue Impact in Patients with Relapsing Remitting Multiple Sclerosis and the Moderating Role of Coping Mechanisms: A Diary Study

by

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Abstract

Fatigue is one of the most common and time enduring symptom in patients with relapsing-remitting multiple sclerosis and has a profound impact on their quality of life and well-being. Previous research has shown a relation between objective stress (stressful life events) and disease exacerbation manifested by various symptoms, including fatigue. The subjective component of stress and its temporal fluctuations were not studied in relation to fatigue in these patients. The present study explored the hypothesis that weekly fluctuations of perceived stress influence the weekly fluctuations of fatigue impact in patients with relapsing-remitting multiple sclerosis. In addition, the researcher explored whether the relation between perceived stress and fatigue impact may be moderated by factors such as disease duration and coping mechanisms. Seventy-eight patients with relapsing-remitting multiple sclerosis offered weekly self-report data on perceived stress and fatigue impact over the course of a year. Hierarchical linear models were used to test the study hypotheses. Results revealed that perceived stress has an influence on the same week, as well as following week, fatigue impact. Further, only the relation between perceived stress and following week fatigue impact was found to be moderated by the disease duration and coping mechanisms. The findings suggest that perceived stress is a contributing
factor to fatigue in individuals with multiple sclerosis. Clinical implications and directions for future research are discussed.
Table of Contents

Chapter 1. Introduction 2
  1.1. Multiple Sclerosis: Overview 4
    1.1.1. Epidemiology 4
    1.1.2. Etiology and Pathogenesis 5
    1.1.3. Clinical features and diagnosis 6
    1.1.4. Disease course 7
    1.1.5. Fatigue in multiple sclerosis 8
  1.2. Theoretical and conceptual framework 10
    1.2.1. Stressors, perceived stress and disease 10
    1.2.2. Transactional model of stress and coping 12
    1.2.3. Motivational theory of life-span development (life-span theory of control) 14
  1.3. Review of empirical research in multiple sclerosis 19
    1.3.1. Stress and disease 19
    1.3.2. Coping in multiple sclerosis 21
    1.3.3. Predictors of fatigue impact 24
      1.3.3.1. Age and gender 24
      1.3.3.2. Disease duration 26
      1.3.3.3. Cognitive function 27
      1.3.3.4. Depressive symptoms 28
  1.4. Present study 30
1.4.1. Rationale

1.4.2. Specific aims

1.4.3. Hypotheses

1.4.3.1. Main effect of perceived stress on fatigue impact

1.4.3.2. Moderating effect of disease duration on the relation between stress and fatigue

1.4.3.3. Moderating effect of coping strategies by disease duration on the relation between perceived stress and fatigue impact

Chapter 2. Method

2.1. Participants

2.2. Procedures

2.3. Measures

2.3.1. Modified Fatigue Impact Scale

2.3.2. Perceived Stress Scale

2.3.3. Disease duration

2.3.4. Symbol Digit Modalities Test

2.3.5. Center for Epidemiologic Studies Depression Scale Revised

2.3.6. Brief COPE Inventory

2.4. Analytic plan
2.4.1. Descriptive analyses 45
2.4.2. Preliminary analyses 46
2.4.3. Central analyses 46

Chapter 3. Results 52
3.1. Preliminary analyses and descriptive statistics 52
3.1.1. Examination of diary data 52
3.1.2. Analysis of missingness 55
3.2. Preliminary exploration of the diary data 55
3.3. Exploration of the directionality of the relation between perceived stress and fatigue impact 56
3.3.1. Models for predicting fatigue impact 57
3.3.2. Models for predicting perceived stress 58
3.4. Full model: Predictors of fatigue impact. Model 1 59
3.5. Full model: Predictors of fatigue impact. Model 2 66

Chapter 4. Discussion 76
4.1. Study findings 76
4.1.1. Perceived stress – fatigue impact relation 76
4.1.2. Disease duration 78
4.1.3. Disease duration and coping mechanisms 79
4.1.4. Depressive symptoms and fatigue impact 81
4.2. Limitations 81
4.3. Future research directions 84
4.4. Implications for health care professionals

References
List of Tables

Table 3.1 Correlations among aggregated weekly measures and time-invariant measures 54

Table 3.2 Model 1. Unstandardized coefficients and tests of significance for predictors of fatigue impact 61

Table 3.3 Model 2. Unstandardized coefficients and tests of significance for predictors of fatigue impact 65

Table 3.4 Moderator effects for the relation between perceived stress in the previous week (predictor) and fatigue impact. Unstandardized coefficients and significance tests for simple slopes for the 2 way and 3 way interactions 75
List of Figures

Figure 1.1 Disease course in multiple sclerosis (MS) 8
Figure 1.2 Hypothetical life-span trajectories for primary control potential and primary and secondary control strivings 18
Figure 2.1 Study participants 37
Figure 3.1 Number of missing diaries by study participant 52
Figure 3.2 Model 1. MS duration as moderator of the relation between previous-week perceived stress and fatigue impact 63
Figure 3.3 Model 1. Problem-focused coping as moderator of the relation between previous-week perceived stress and fatigue impact for individuals with shorter disease duration 64
Figure 3.4 Model 1. Problem-focused coping as moderator of the relation between previous-week perceived stress and fatigue impact for individuals with longer disease duration 66
Figure 3.5 Model 2. MS duration as moderator of the relation between previous-week perceived stress and fatigue impact 69
Figure 3.6 Model 2. Problem-focused coping as moderator of the relation between previous-week perceived stress and
fatigue impact for individuals with shorter disease duration

Figure 3.7 Model 2. Problem-focused coping as moderator of the relation between previous-week perceived stress and fatigue impact for individuals with longer disease duration

Figure 3.8 Model 2. Avoidant coping as moderator of the relation between previous-week perceived stress and fatigue impact for individuals with shorter disease duration

Figure 3.9 Model 2. Avoidant coping as moderator of the relation between previous-week perceived stress and fatigue impact for individuals with longer disease duration
Foreword

The present study was part of a larger pilot project conducted by Paul Duberstein, PhD (PI), Raluca Topciu, MA, MD (Co-PI), Andrew Goodman, MD (Co-PI), and Jamison Hirsch, PhD.: “The impact of psychosocial factors on health and well-being in a multiple sclerosis population.”

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Fluctuations of perceived stress and fatigue impact in patients with relapsing remitting multiple sclerosis and the moderating role of coping mechanisms: A diary study

Chapter 1. Introduction

Multiple sclerosis (MS) is a chronic, progressive disorder of the central nervous system. The onset of the disorder can be as early as 20 years of age, challenging young adults with various combinations of symptoms such as fatigue, motor, visual, or cognitive impairments that can be burdensome and disabling. Multiple sclerosis is a disorder with an unpredictable course, which brings uncertainty to an individual’s life and future. Disease-related physical and social limitations create everyday challenges. Uncertainty about the future and everyday challenges often creates stress for afflicted individuals. A specific type of stress that is related to experiencing life events - such as interpersonal conflict and disruption in routines - has been shown to precede worsening of multiple sclerosis symptoms in individuals with a relapsing-remitting course (Mohr, Hart, Julian, Cox, & Pelletier, 2004). However, the subjective dimension of the life event (perceived stress) had been shown to play a more important role in predicting health and disease outcomes than the actual event (Cohen, Kessler, & Gordon, 1995). So far, no research has examined the role of perceived stress in the worsening of multiple sclerosis symptoms.
This study has two major aims: First, it is aimed at extending previous findings on life events and symptom exacerbation by examining the relation between perceived stress and fatigue, the most frequent and disabling symptom of multiple sclerosis. Second, this study examines the moderator role of coping mechanisms on the relation between perceived stress and fatigue from a motivational theory of life-span development perspective (Heckhausen & Schulz, 1995; Heckhausen, Wrosch, & Schulz, 2010). These relations are studied in individuals with relapsing remitting multiple sclerosis. Implications of this approach are discussed. Given how disabling fatigue can be to those with MS, identifying moderators of the relation between perceived stress and fatigue is important in developing clinical interventions aimed at uncoupling this relation. The present study investigates these questions using a year long longitudinal design, with weekly diaries assessing perceived stress and fatigue impact.

The remainder of the introduction is organized as follows: First, features of multiple sclerosis including epidemiology, etiology and pathogenesis, clinical features, diagnosis, and disease course are presented. Second, the theoretical and conceptual framework that guided this research study is reviewed. Third, research studies focused on (1) stress and disease in multiple sclerosis, (2) coping strategies in individual with multiple sclerosis, (3) predictors of fatigue impact in multiple sclerosis are reviewed. Finally, the present study and its hypotheses are discussed.
1.1. Multiple Sclerosis: Overview

1.1.1. Epidemiology. Multiple sclerosis is a chronic disease of the central nervous system that affects between 250,000 and 350,000 individuals in the United States (Beatty & Paul, 2000). The estimated prevalence is close to 177 per 100,000 people in the United States (Compston & Confavreux, 2006). The prevalence in Europe ranges from 10 per 100,000 people in the southern countries to 200 per 100,000 in the northern countries (Compston & Confavreux, 2006). Prevalence among women is higher than among men, with 1.4 to 3.1 times more women affected than men (Sadiq, 2005). There is a higher prevalence among Caucasians compared to other racial groups (Sadiq, 2005).

Multiple sclerosis is one of the most common neurological disorders in young adults. The distribution of age at onset peaks between 20 and 30 years of age, with a range between 10 and 60 years of age (Sadiq, 2005). Multiple sclerosis is one of the most disabling disorders in the United States. It is ranked fourth among chronic conditions for the risk of disability causing major activity limitation; 63.3% of people diagnosed with multiple sclerosis meet criteria for disability status. Multiple sclerosis is ranked first for the risk of disability causing need for help in basic life activities; 40.7% of people diagnosed with multiple sclerosis need help in activities of daily living (LaPlante, 1991).
1.1.2. Etiology and Pathogenesis. While progress has been made in identifying etiological factors in multiple sclerosis, the cause of the disease is still not known. The etiology of multiple sclerosis is considered to be related to the interaction between a genetic susceptibility and precipitating environmental factors. The genetic predisposition is suggested by twin studies finding 25%-30% concordance rate for the disease in identical twins, compared to only 2% concordance rate in fraternal twins (Beatty & Paul, 2000; Sadiq, 2005). Among environmental factors found to trigger the onset of the disease are viral infections, including Epstein-Barr virus and human herpes virus 6, which are believed to persist in latent form after an initial infection. Later on, periods of viral reactivation cause clinical relapses. Other environmental factors include physical injury, pregnancy, and emotional distress (Ascherio & Munger, 2007; Compston & Coles, 2002; Compston & Confavreux, 2006; Mei-Tai, Meyerovitz, & Engel, 1970; Sibley, 1997).

The pathogenesis of the disorder is autoimmune. Abnormal immune activity results in the destruction of the myelin sheath around the axons of the neurons in the central nervous system. The triggers for the initiation and signals for the termination of the increased immune activity are not known. The destruction of the myelin sheath results in delayed or blocked nervous impulses. The disturbance in nervous conductivity, in turn, can result in a great array of clinical symptoms.
1.1.3. **Clinical features and diagnosis.** Clinical manifestations and course of multiple sclerosis vary greatly from one patient to another, in part because the disease can affect any part of the central nervous system. The clinical picture includes motor symptoms (e.g., muscle weakness, spasticity, abnormal reflexes), sensory symptoms (e.g., pain, impairment of temperature or touch), autonomic symptoms (e.g., bladder, bowel, or sexual dysfunction), visual impairment, cognitive impairment (e.g., problems with processing speed, attention and concentration), and fatigue (Mohr & Cox, 2001). Although the symptom presentation is heterogeneous from individual to individual, fatigue is the most common symptom in individuals with multiple sclerosis.

The diagnosis of multiple sclerosis is mainly based on clinical symptoms identified by clinical examination and not on laboratory tests. A positive diagnosis of multiple sclerosis requires the presence of two attacks (defined as periods of symptom exacerbation), involving different parts of the central nervous system (i.e., any combination of symptoms described above could be present, such as, visual impairment followed by another attack consisting mainly in spasticity). The attacks should last at least 24 hours and they should be separated by a period of at least one month (Haussleiter, Brune, & Juckel, 2009). The clinical diagnosis is generally supported by magnetic resonance imaging showing active or old lesions in the central nervous system.
1.1.4. Disease course. The disease course in multiple sclerosis is unpredictable. Patients with multiple sclerosis have been categorized by subtypes of disease course based on the patterns of symptom exacerbation and remission (see Figure 1.1). The two main initial courses of the disorder are relapsing-remitting (85% prevalence) and primary progressive (15% prevalence; Sadiq, 2005). The relapsing-remitting course is characterized by recurrent periods of clinical symptoms exacerbations followed by total or partial remissions. The frequency of recurrence varies greatly from one individual to another. The primary progressive course is characterized by gradual and steady progression of symptoms and functional decline. Although the majority of patients in the relapsing remitting group continue on the same course throughout their life, in about 30% of patients (which corresponds to 25.5% of all patients with multiple sclerosis) the disease changes to secondary progressive course where there is a slow progression of clinical symptoms, with no or little remission. The disease course can change at any time from relapsing remitting to progressive.
1.1.5. *Fatigue in multiple sclerosis.* Fatigue is the most common symptom of multiple sclerosis, with 92% of patients characterizing it as the most troubling problem among all symptoms of the disorder (Branas, Jordan, Fry-Smith, Burls, & Hyde, 2000). Fatigue is one of the two major reasons for unemployment among patients with multiple sclerosis, along with physical disability (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). Fatigue has been defined by the Multiple Sclerosis Council of Clinical Practice Guidelines (1998) as “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities.” Research in multiple sclerosis has described fatigue as extreme tiredness and the need to rest (Freal, Craft, & Coryell, 1984), or as physical
tiredness and lack of energy, distinct from sadness or weakness (Krupp, Alvarez, LaRocca, & Scheinberg, 1988). Qualitative research has provided a phenomenological view of fatigue characterizing individuals with multiple sclerosis. Patients' experience of fatigue includes a lowered sense of self-worth, and feelings of shame, sorrow, and anger related to their experience of fatigue (Flenser, Ek, & Soderhamn, 2003). Longitudinal studies of patients with multiple sclerosis found that fatigue persists over time (Johansson, Ytterberg, Hillert, Holmqvist, & von Kock, 2008; Tellez, Rio, Tintore, Nos, Galan, et al., 2006). Fatigue can have a profound impact on daily activities, employment, ability to lead a fulfilling social life, and general well-being. Increased fatigue is related to increased functional disability (limited performance in daily activities, work and leisure activities) and decreased quality of life (Amato et al., 2001; Aronson, 1997; Krupp, Alvarez, LaRocca, & Scheinberg, 1988; Schwartz, Coulthard-Morris, & Zeng, 1996).

Most research on the etiology of fatigue in multiple sclerosis has focused primarily on biological factors. In a recent review of the literature on the biological mechanisms of fatigue in multiple sclerosis, Kos, Kerckhofs, Nagels, D'Hooghe, and Ilsbroukx (2008) found inconsistent and contradictory results. At present there is no consensus on the biological causes of fatigue in multiple sclerosis.
1.2. Theoretical and conceptual framework

Over the past several decades, numerous theories addressing the relation between stress and disease have emerged, as well as numerous theories of coping with stress. This section presents the theoretical framework guiding the present study that examines the relation between stress and disease symptoms (i.e., perceived stress and fatigue), as well as the moderating role of coping style on the stress-fatigue relation.

1.2.1. Stressors, perceived stress and disease. There are wide variations in the definition of stress; however most definitions refer to a process in which “environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease” (Cohen, Kessler, & Gordon, 1995, p. 3). An important body of research showed that stress, acute or chronic, influences an individual’s vulnerability to disease and could also influence the course of an existent disorder (Lazarus, 1983; Lazarus & Laurnier, 1978; Selye, 1974). A range of endocrine, inflammatory, cardiovascular and neoplastic disorders have been identified as having their course influenced by perceived stress (Chrousos & Gold, 1992; Cohen, & Herbert, 1996; Cohen, Tyrrell, & Smith, 1993). Cohen, Kessler and Gordon (1995) distinguish three broad traditions of conceptualizing the role of stress in disease risk, onset, and progression (disease course): biological, environmental (objective), and psychological (subjective) traditions.
The biological stress perspective focuses on the physiological response (i.e., activation of the hypothalamic-pituitary-adrenocortical – HPA - axis) to physical and psychological demands on the organism. Repeated or prolonged activation of these systems, especially within critical periods of early development (Cicchetti & Toth, 2009) have been shown to be a significant risk factor for the development of physical and/or psychiatric disorders (Cohen, Kessler, & Gordon, 1995; Selye, 1974). Moreover, prolonged activation of the HPA axis have been shown to influence the course of immune-mediated disorders (Cohen, & Herbert, 1996). The environmental stress tradition focuses on the assessment of environmental events that are related to adaptive demands on the organism; in this tradition the stressful life events are considered “stressful” from an objective normative perspective, without taking into consideration the individual’s appraisal (subjective stress). An example of such research is Brown and Harris’s work (1989) on stressful life events. Finally, and of foremost interest for the present study, is the psychological (subjective or perceived) stress perspective. In this perspective the focus of research is on the individual’s perception and evaluation of external events as threatening or harmful. One of the most widely researched models reflecting this theoretical perspective, is the transactional model of stress and coping developed by Lazarus and Folkman (1984). This model is discussed in detail next.
1.2.2. Transactional model of stress and coping. One of the most influential models of stress and coping was proposed by Lazarus and Folkman (1984). This model considers stress to be a transaction between the individual and the environment. This has been the most widely used model in the stress coping research in chronic illness (Maes, Leventhal, & deRidder, 1996). This model suggests that both environmental stimuli and the individual's reactions to them should be considered in understanding stress processes. According to this model, the process of stress is triggered when the individuals' appraisal of their resources for coping with stress are exceeded by the appraised external demands (i.e., environmental stimuli). According to this transactional model, the process of stress is triggered when an environmental stimulus is appraised as potentially harmful to the individual. The individual response to a threat is not static, but involves continuous interactions and adjustments, referred to as transactions with the environment.

In the first step, primary appraisal, the individual establishes the meaning of the event; an external event may be appraised as irrelevant, benign, or harmful. In the second step, secondary appraisal, the individual assesses his/her capacity for coping with the event. Stress is likely to occur when an event is appraised as harmful and the individual's capacity to cope with the event is appraised as lower than what would be needed for a successful resolution. This process is continuous, the individual constantly
taking into consideration new information regarding the stimuli (cognitive reappraisal). Within the transactional model, coping is thought of as a constant change in “cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person” (Lazarus & Folkman, 1984, p.141). Coping responses may involve actions aimed at changing the external circumstances, termed problem-focused coping, or cognitive processes aimed at relieving the emotional stress response, called emotion-focused coping (e.g., denial of danger; Lazarus, 1975). This model suggests that the appraisal processes (of both the event and coping resources) are of primary importance when studying the relation between stressful life events and health and disease.

When applied to the research of chronic illness, Lazarus and Folkman’s model has certain limitations. Some of the most important ones are the lack of differentiation between acute and chronic stress, and not taking into account the larger context (e.g., other factors characterizing the situation or the stressor) of the transaction with the environment. Other researchers have tried to address some of these limitations with the inclusion of criteria such as controllability, understood as the inherent opportunities for control within a situation (Perrez & Reicherts, 1992), and time line or duration of the stressor (acute, chronic, cyclic; Leventhal, 1970; Leventhal & Nerenz, 1983). Furthermore, the transactional model lacks a developmental perspective,
which is necessary when studying processes that are time-variant and span over the course of years and different developmental stages, as are chronic illnesses. The coping process with stress related to a chronic illness can be different at different developmental stages. Individuals with multiple sclerosis, depending on age or developmental stage, could perceive disability (as well as experience stress related to disability) differently. For example, an individual whose disability is hindering his capacity to work in his 30s may perceive higher levels of stress, or may need to employ different coping strategies as compared to the stress and coping related to the same type of disability in later years of life.

A relatively recent motivational model of life-time development (Heckhausen & Schulz, 1995; Heckhausen, Wrosch, & Schulz, 2010) addresses this and other important limitations of the transactional model as applied to time-variant stressors.

1.2.3. Motivational theory of life-span development (life-span theory of control). Most existing theories of coping lack or have a limited developmental framework (Carver & Scheier, 1981; Lazarus & Folkman, 1984; Maes, Leventhal, & DeRidder, 1996). When exploring coping strategies in relation to chronic illness, which can span different developmental stages in one’s life, the concept of time becomes important and the standard stress and coping models (e.g., transactional model) do not have thorough explanatory value. In a chronic illness with a relapsing remitting or degenerative course such as
multiple sclerosis, the researcher must explore the relation between stress and disease symptoms, as well as the role of coping, within a developmental framework. Such a framework needs to take into account the challenges posed by the disease, as well as the individual’s resources of coping at any given moment in the course of the illness. The motivational theory of life-span development, also called the life-span theory of control, developed by Heckhausen and her colleagues (Heckhausen & Schulz, 1995; Heckhausen, Wrosch, & Schulz, 2010) offers a developmental framework for looking at coping process over the lifetime. Their theory has motivation and control as primary concepts and the underlying assumption that individuals interact with the environment by producing behavior-event contingencies by which they exert control over their environment (Heckhausen & Schulz, 1995). These behavior-event contingencies are meant to produce changes in the external world to fit the individuals’ needs. The individual’s control over the environment is particularly important around pivotal events in one’s life. From the life-span theory perspective, such events are those that increase, decrease, or threaten existing levels of control (Heckhausen & Schulz, 1995). Within this perspective, the changes brought by the diagnosis of a chronic illness and by disability are pivotal events in an individual’s life, events that threaten or diminish opportunities for control.

The theory was built on Rothbaum’s (Rothbaum, Weisz, & Snyder, 1982) distinction between primary and secondary control. Within the life-span
theory of control framework, the main distinction between primary and secondary control is given by their aim. Primary control is aimed at achieving effects in the external environment, while secondary control is aimed at producing changes within the individual. A second distinction between primary and secondary control in Heckhausen and colleagues’ theory is given by the type of processes involved: primary control consists mostly of actions engaging the external world, while secondary control consists mostly of cognitions. Primary control is more agentic/instrumental, meant to shape the environment to fit the individuals’ needs at different points in their development. Secondary control is mostly meant to facilitate primary control by minimizing losses, maintaining and expanding its influence.

Additionally, the motivational theory of life-span development posits that secondary control is meant to optimize the primary control by disengagement and self-protective strategies when the opportunities for primary control are diminished. These strategies, categorized as compensatory secondary control (Heckhausen & Schulz, 1995), benefit the individual by preventing the investment of energy toward unattainable goals and by re-channeling efforts toward achievable goals. They are aimed at reducing the motivational and emotional impact of loss of primary control (e.g., diminished self-esteem, hopelessness), by strategies such as reducing the importance of a goal.
Further, the motivational theory of life-span development proposes hypothetical trajectories for the capacity for primary control, along with trajectories for primary and secondary control strivings (see Figure 1.2). Individuals strive to maximize primary control, as the capacity for primary control increases in the first part of life, plateaus, and then decreases in the second part of life. As the capacity for primary control decreases, the striving for secondary control increases throughout life. According to Heckhausen and colleagues (2010), individuals increasingly resort to secondary control strategies to minimize the effect of losses in primary control. Maintaining a fluid balance between the two types of control (balance adapted to the opportunity for primary control at any given age) is considered an adaptive capacity of the individual and meant to optimize development.
Figure 1.2. Hypothetical life-span trajectories for primary control potential and primary and secondary control strivings

Note: From Developmental Regulation in Adulthood: Age-Normative and Sociostructural Constraints as Adaptive Challenges, by J. Heckhausen, 1999, Figure 3.1., p. 72. Copyright 1999. Cambridge University Press. Reprinted with permission of the author and publisher.

A similar model could be applied to chronic illness with a degenerative course, where the increasing disabling symptoms decrease gradually the capacity for primary control. As the capacity for control decreases, the use of secondary control aimed at mitigating the effects of loss increases. This increase is believed to have adaptive value. Indeed, a recent 9-year longitudinal study examined control strivings in older adults with serious health problems and their relation with health, well-being and survival (Hall, Chipperfield, Heckhausen, & Perry, 2010). The researchers found that for
individuals with acute conditions, goal engagement (primary control) predicted greater survival, while goal disengagement (one form of secondary control) predicted poorer health. Noteworthy is that for individuals with chronic conditions, goal engagement predicted poorer physical health, while goal disengagement predicted better health.

When faced with a chronic illness at an earlier age, the individual’s adjustments to these new challenges become of primary importance and take precedence over any developmental, age-related phase the individual might be in. This domain specific trajectory can be overlaid on the general age-related trajectory of control, where in the foreground are the more salient, illness-related challenges and in the background are the age-related challenges.

1.3. Review of empirical research on stress, fatigue, and coping in multiple sclerosis

1.3.1. Stress and disease. One of the first clinicians to describe the pathological process and the course of multiple sclerosis was Jean-Martin Charcot. He maintained that among the etiological factors of multiple sclerosis were emotional distress, grief, vexation, and adverse changes in social circumstances (Charcot, 1877). In another notable paper on psychosocial aspects of multiple sclerosis, Langworthy (1948) suggested that individuals with multiple sclerosis were characterized by attributes of a hysterical personality, such as emotional immaturity and immature defense.
mechanisms, which predisposed them to developing multiple sclerosis. However, this ‘predisposing personality structure’ hypothesis was not supported by later research (Pratt, 1951). Similarly, the role of stress in disease exacerbation was not confirmed by early case-control studies (Antonovsky et al., 1968; Pratt, 1951). These early studies had several methodological limitations such as retrospective report, inadequate control groups, and lack of standardized measures.

A meta-analysis (Mohr, Hart, Julian, Cox & Pelletier, 2004) found a significant increase in risk of disease exacerbation following a stressful life event. Mohr and colleagues included 14 studies that had either a case-control or a longitudinal prospective design and used standardized diagnostic criteria for multiple sclerosis with a relapsing course and standardized methods of measuring stressful life events. Of the 14 studies, 13 supported the role of stressful life events in exacerbation of disease, with a medium effect size.

Findings from more recent studies add to the evidence for a relation between stressful life events and disease exacerbation. Mitsonis and colleagues (Mitsonis et al., 2005) found in a prospective study that increased number in reported life events is related to higher risk of relapse in a female population with multiple sclerosis. Another prospective study found a relation between acute events, but not chronic difficulties and risk of relapse in individuals with multiple sclerosis (Brown et al., 2006).
Case-control retrospective studies included in the Mohr and colleagues' meta-analysis (Mohr, Hart, Julian, Cox & Pelletier, 2004) found not only a relation between stressful life events and exacerbations, but also between stressful life events and disease onset (Grant et al., 1989; Warren, Greenhill & Warren, 1982). Approximately 80% of patients with multiple sclerosis reported experiencing stressful life events in the year prior to the onset of the disorder compared to 35% to 50% of patients with other neurological disorders, rheumatoid arthritis, or healthy controls (Grant et al., 1989; Warren et al., 1982).

These findings suggest a connection between stress, defined as stressful life events, and disease activity, in terms of either the onset or exacerbation of symptoms.

1.3.2. Coping in multiple sclerosis. The majority of research on stress and coping in individuals with multiple sclerosis has been based on Lazarus and Folkman’s transactional model (Lazarus & Folkman, 1984; Folkman & Lazarus, 1988). This model identifies two main ways of coping that are defined by the target of the coping efforts: problem-focused coping (i.e., actions aimed at changing or removing the stress stimuli) and emotion-focused coping (i.e., cognitions aimed at reducing the emotional impact of the external stimuli, such as acceptance or denial). Problem-focused coping in the transactional model is similar to primary control in the motivational theory of life-span in that both are aimed at changing the environment; however,
while in the transactional theory, problem-focused coping consists of actions (behaviors), primary control can consist of cognitions as well as actions. Similarly, there is overlap between the concept of emotion-focused coping in the transactional model and secondary control in the motivational theory of life-span development as they are both aimed at changes within self; however, secondary control is not limited to cognition, but may also consists of actions (Heckhausen, Wrosch, & Schulz, 2010).

Folkman and Lazarus found that problem-focused coping tends to be related to greater well-being, whereas emotion-focused coping is either unrelated or related to diminished well-being in healthy individuals (Folkman & Lazarus, 1988; Lazarus & Folkman, 1984). These relations appear to be slightly different in individuals with multiple sclerosis. Several studies found that patients with multiple sclerosis who had a higher level of adaptation to having multiple sclerosis were more likely to use problem-focused coping strategies (Aikens, Fischer, Namey, & Rudick, 1997; O’Brien, 1993; Pakenham, Stewart & Rogers, 1997). Other studies found no relation between problem-focused coping and adaptation (Beatty et al., 1998; Hickey and Greene, 1989). First, such different results may be explained by a failure to consider different aspects of the disease, which may require patients to employ different coping strategies. For example, Mohr and colleagues (Mohr, Goodkin, Gatto, & Van DerWende, 1997) found that in patients with high levels of physical impairment, problem solving was related to lower levels of
psychological distress. In contrast, among patients with less physical impairment, problem-solving coping was unrelated to distress. Second, these different results may be explained by a failure to consider a developmental time-line including age and disease duration. The use of secondary control processes (cognitive strategies oriented at changing the self) in balance with the primary control processes (behavioral and cognitive strategies oriented at changing the environment), and the developmental phase of the individual (age) or of the disorder (disease duration) may explain these differences.

Compared to the volume of research on problem-focused coping in individuals with multiple sclerosis, there has been little research on emotion-focused coping. Extant studies have found that passive, avoidant, emotion-focused coping strategies (such as wishful thinking, self-blame, avoidance) are related to poorer adjustment and lower levels of quality of life in individuals with multiple sclerosis (Aikens, Fischer, Namey, & Rudick, 1997; Buelow, 1991; Pakenham, 1999). Again, these few studies did not include a developmental perspective. The paucity of research on emotion-focused strategies in multiple sclerosis may be due to perceptions of its low effectiveness in the healthy population, in which emotion-focused coping strategies are often related to poor outcomes. However, in a chronic, progressive disease, in which the individual may have fewer options to affect the symptoms, emotion-focused strategies may play an important role in
individuals’ overall coping (Hall, Chipperfield, Heckhausen, & Perry, 2010; Heckhausen & Schulz, 1995; Heckhausen, Wrosch, & Schulz, 2010).

1.3.3. Predictors of fatigue impact
Research on individuals with multiple sclerosis investigated several factors that may contribute to fatigue impact. Integrated models for explaining fatigue in multiple sclerosis, including both physiological and psychological factors, have been proposed (Rosenberg & Shafor, 2005; Strober & Arnett, 2005; van Kessel & Moss-Morris, 2006). Strober and Arnett found that disease severity, depressive symptoms, and insomnia had independent contributions in explaining fatigue impact in multiple sclerosis, accounting for a total of 43% of the variance in fatigue impact. In summarizing the research on psychological factors related to fatigue impact in multiple sclerosis, Bol, Duits, Hupperts, Vlaeyen and Verhey (2009) found that mood, anxiety, cognitive function, personality, and cognitive-behavioral factors contribute to fatigue impact in multiple sclerosis. The most frequently researched factors and their influence on fatigue impact are now discussed.

1.3.3.1. Age and gender. There is ample evidence that in the general population fatigue is associated with aging (see Yu, Lee, & Man, 2010 for a recent review). Epidemiological studies suggest that between 27-50% of community older adults endorse mild to moderate fatigue (Hellstrom, Persson & Hallberg, 2004; Wijeratne, Hickie, & Brodaty, 2007). This increased prevalence of fatigue with age in the general population leads to questions
regarding a similar relation in patients with multiple sclerosis. Most research on fatigue in multiple sclerosis, however, has found no significant relation between age and the prevalence of fatigue (measured as fatigue impact; Putzki, Katsarava, Vago, Diener & Limmroth, 2008; Schwartz, Coulthard-Morris, & Zeng, 1996; Trojan et al., 2007). As most patients with multiple sclerosis endorse fatigue, with a lifetime prevalence as high as 80%, (Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Krupp, Alvarez, LaRocca, & Scheinberg, 1988), the effects of age on fatigue found in the general population seem to be superseded by this high prevalence of fatigue in patients with multiple sclerosis. In addition, fatigue impact in multiple sclerosis was found in most research studies to be unrelated to age (Putzki, Katsarava, Vago, Diener & Limmroth, 2008; Schwartz, Coulthard-Morris, & Zeng, 1996; Trojan et al., 2007). One cross-sectional study found a positive relation between age and fatigue impact in patients with primary progressive multiple sclerosis, but no relation between age and fatigue impact in patients with relapsing remitting or secondary progressive multiple sclerosis (Lerdal, Celius, & Moum, 2003). In a longitudinal study, age was not a predictor of increase in fatigue impact over the course of two years (Johansson, Ytterberg, Hillert, Holmqvist, & Koch, 2008).

Another factor that could be associated with fatigue impact is gender. While in the general population women tend to endorse fatigue more than men (Loge, Ekeberg, & Kaasa, 1998; Pawlikowska et al. 1994), most
research in patients with multiple sclerosis has found no relation between
gender and fatigue impact (Lerdal, Celius, & Moum, 2003; Putzki, Katsarava,
Vago, Diener & Limmroth, 2008; Schwartz, Coulthard-Morris, & Zeng, 1996;
Trojan et al., 2007). No gender differences in an increase in fatigue impact
have been found in longitudinal research (Johansson, Ytterberg, Hillert,
Holmqvist, & Koch, 2008). Thus, the reviewed research suggests that the
prevalence of fatigue and fatigue impact in multiple sclerosis are not
meaningfully related to age or gender.

1.3.3.2. Disease duration. Of particular interest for a developmental
perspective on the adjustment to chronic disorders is the relation between
disease duration and fatigue impact. Most cross-sectional and longitudinal
studies have found no relation between disease duration and fatigue impact
in multiple sclerosis (Flachnercker et al., 2002; Johansson, Ytterberg, Hillert,
Holmqvist, & von Kock, 2008; Putzki, Katsarava, Vago, Diener & Limmroth,
2008; Trojan et al., 2007). One study found greater fatigue impact in
individuals with longer disease duration (Schwartz, Coulthard-Morris, & Zeng,
1996). The reviewed research suggests that fatigue impact is not
meaningfully related to disease duration.

Previous studies explored the existence of a direct relation between
disease duration and fatigue impact. However, the duration of the disease
can be considered an overall proxy for internal adaptive processes (e.g.,
coping mechanisms) as well as external mitigating factors (e.g., social
support) in meeting a new phenomenological reality. Two studies have found that longer disease duration was associated to better adjustment (Fisk, Pontfract, Ritvo, Archibald, & Murry, 1994; Pakenham, Stewart & Rogers, 1997), while other studies found disease duration to be unrelated to adjustment to multiple sclerosis (Maybury & Brewin, 1984; Rudick, Miller, Clough, Gragg, & Farmer, 1992).

The current study does not aim to explore the relation between disease duration and adjustment. However, prior findings warrant consideration that disease duration (through its possible relation to adjustment) might moderate the impact of perceived stress on overall quality of life and disease characteristics such as fatigue.

1.3.3.3. Cognitive function. Cognitive impairment is a common symptom of multiple sclerosis, present in up to 50% of patients (Benedict et al., 2006; Bobholz & Rao, 2003). Most common are impairments of processing speed, sustained attention, cognitive flexibility, and memory retrieval (Zakzanis, 2000). Most research focused on fatigue impact and self-report of perceived cognitive function in patients with multiple sclerosis has found a positive relation between the two (Krupp, Alvarez, LaRocca, & Scheinberg 1988; Middleton, Denney, Lynch, & Parmenter, 2006; Smets, Garssen, Bonke, & Haes, 1995; Vercoulen et al., 1996). Research focused on fatigue impact and cognitive function, measured as performance on cognitive ability tests, has found contradictory results in patients with multiple sclerosis.
Several cross-sectional and longitudinal studies have found a positive relation between fatigue impact and cognitive impairment (Diamond, Johnson, Kaufman, & Graves, 2008; Schwid et al., 2003), whereas others found no relation between the two (Bailey, Channon, & Beaumont, 2007; Krupp & Elkins, 2000; Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009; Parmenter, Denney, & Lynch, 2003). These results may differ due to small sample sizes and thus the possibility of atypical samples, to the use of a short screening battery for neuropsychological functioning that require minimal cognitive effort, or to other methodological problems, such as failing to control for depressive symptoms (Morrow, Weinstock-Guttman, Munschauer, Hojnacki, & Benedict, 2009). In summary, the research on the relation between fatigue impact and cognitive function is inconclusive and warrants further investigation.

1.3.3.4. Depressive symptoms. Individuals with multiple sclerosis are at a higher risk of developing major depression as compared to the general population. The lifetime prevalence of major depression in individuals with multiple sclerosis has been estimated at approximately 50% (Patten & Metz, 1997; Sadovnick et al., 1996), as compared to approximately 16% in the general population (Kessler et al., 2003). The etiology of depression in patients with multiple sclerosis is multifactorial, including biological (disease related) and psychosocial causes. Research suggests that patients with multiple sclerosis are at an increased risk for depression after the onset of
multiple sclerosis (Joffe et al. 1987; Sadovnick et al., 1996). There is evidence of an association between degree of demyelination and depressive symptoms (Bakshi et al., 2000; Zorzon et al., 2001). There is also evidence of an association between depressive symptoms and immunopathological processes characteristic of multiple sclerosis: an increase in immunological activity specific to multiple sclerosis (higher level of T4+ helper cells, lower level of CD8+, and higher level of white blood cells in cerebrospinal fluid) is associated with greater severity of depressive symptoms (Fassbender et al., 1998; Foley et al., 1992). In addition, depressive symptoms can develop in patients with multiple sclerosis as a response to having a chronic disorder with a highly unpredictable course and uncertain prognosis (Dalton & Heinrichs, 2005).

Several cross-sectional studies have found a significant relation between fatigue impact and depressive symptoms (Chwastiak et al., 2005; Schwartz, Coulthard-Morris, & Zeng, 1996). Longitudinal studies have found depressive symptoms severity to predict fatigue impact for up to two years (Johansson, Ytterberg, Hillert, Holmqvist, & Koch, 2008; Patrick, Christodoulou, & Krupp, 2009; Schreus, de Ridder, & Bensing, 2002).

An important methodological issue in the research of fatigue impact and depression in multiple sclerosis is the possibility of shared method variance. The shared items among self-report measures of fatigue impact and depression may account for some of the positive relation between fatigue
impact and depression. Studies of the validity of depression instruments in multiple sclerosis recommended excluding the fatigue items from the depression instruments (Benedict et al., 2003; Mohr et al., 1997). Research using this approach has continued to find a relation between fatigue impact and depression, independent of shared method variance (Chwastiak et al., 2005).

Research on factors influencing fatigue impact suggest that stress has a meaningful role in predicting worsening of disease symptoms (including fatigue), though much of this research has focused on stress related to life events rather than the more subjectively relevant perceived stress. In addition research suggest limited prediction of fatigue impact from common demographic and disease relevant variables (e.g., disease duration). However, depressive symptoms and degree of cognitive impairment appear to represent important predictors of fatigue.

1.4. Present study

1.4.1. Rationale. The reviewed literature indicates a relation between stressful life events and disease activity in patients with a relapsing course of multiple sclerosis. These studies varied in the way their authors conceptualized stress. Most of them used standardized checklists of actual stressful life events the individual experienced, and only a few of them included follow up questions regarding the perceived intensity of those events (Sibley, 1997; Warren, Warren & Cockerill, 1991). However, in the now well-
established transactional model, stress is more comprehensively conceptualized as involving two parts: the environmental, objective trigger and the appraisal (perceptual component) of the event. Research showed that the perceptual component of stress (perceived stress) plays an important role in the course of different disorders (Chrousos & Gold, 1992; Cohen, & Herbert, 1996; Cohen, Tyrrell, & Smith, 1993). Further, the motivational theory of life-span development offers a time-variant framework for looking at the stress-disease relation and at its moderators; in a chronic disorder such as multiple sclerosis that can span over years and developmental periods in one’s life, a time-variant framework for looking at adaptation process (i.e., coping) is essential.

The present study aims to expand previous research by studying the role of perceived stress on fatigue impact in multiple sclerosis over time. This form of stress is defined as the negative cognitive and emotional states elicited when an individual perceives that the external demands exceed his or her ability to cope or adapt (Lazarus & Folkman, 1984).

As the most frequent symptom of multiple sclerosis, fatigue is an important factor in defining quality of life and extent of disability for people diagnosed with the disorder. Increased fatigue could be present at any time during the course of the disorder, not simply as part of the clinical picture of a relapse. Given the implications of fatigue for day-to-day quality of life for people with multiple sclerosis, it is important to study factors that may be
related to fatigue impact and its temporal fluctuations. The present study focuses on the influence of perceived stress on fatigue impact, and on the factors that may moderate this relation, such as disease duration and coping strategies.

This exploration is important because it remains unclear whether there are individual differences that may leave patients with multiple sclerosis more or less vulnerable to the effects of stress over time. The existence of moderating factors is suggested by the inconsistent effects of stress on disease activity across individuals with multiple sclerosis, as well as the generally small to moderate effect sizes found in these studies (Mohr et al, 2000; Mohr, Hart, Julian, Cox & Pelletier, 2004). Moderators of this relation were studied from a developmental perspective. Specifically, the moderating role of disease duration and primary and secondary control - operationally defined in terms of specific coping mechanisms - were explored.

The present study focuses only on the relapsing remitting course of MS, since this course is shown to be influenced by stress in the form of stressful life events (Mohr, Hart, Julian, Cox & Pelletier, 2004). A longitudinal design is used to examine the relation between perceived stress and fatigue impact, as well as the role of primary and secondary control and disease duration. Levels of perceived stress and fatigue impact are measured each week over a period of 50 weeks.
This study adds to the literature in several ways. First, this is the first study taking a phenomenological approach to the study of perceived stress in multiple sclerosis using a prospective diary approach. Second, this diary study involving 50 weekly assessment points allows for the statistical modeling of not only weekly covariations of perceived stress and fatigue impact, but temporal relations between them and baseline determinants of these covariations (namely, depressive symptoms, degree of cognitive impairment, and disease duration).

Third, the present study represents a first exploration of the factors that may influence the perceived stress-fatigue impact relation from a developmental perspective by examining the moderating role of disease duration and coping mechanisms.

1.4.2. Specific aims. This study had two major aims. The first was to examine the relation between perceived stress and fatigue impact among individuals with multiple sclerosis. Specifically, this study examined whether weekly fluctuations of fatigue impact (the most frequent symptom of multiple sclerosis) are associated with weekly fluctuations of perceived stress (measured in the same week as fatigue impact, as well as in previous weeks), independent of intensity of depressive symptoms, degree of cognitive impairment, and disease duration.

The second aim of the study was to examine whether coping mechanisms and disease duration moderate the relation between perceived
stress and fatigue impact. In accordance with the aims of the study, the following series of hypotheses were formulated:

1.4.3. Hypotheses

1.4.3.1. Main effect of perceived stress on fatigue impact: When controlling for baseline severity of depressive symptoms, cognitive impairment, and duration of disease, weekly fluctuations of perceived stress predict weekly fluctuations of fatigue impact (significant positive predictor). On weeks when individuals report higher levels of perceived stress as compared to their average, or across-time, level of perceived stress, they would also report higher levels of fatigue impact as compared to their average level of fatigue impact. To clarify the direction of influence between perceived stress and fatigue impact, several models were examined. First, time t fatigue impact was regressed on time t (same week) perceived stress and time t-1 week and time t-2 week time-lagged stress predictors. It was expected that time t perceived stress and at least one of the lagged stress variables would predict fatigue impact. Second, to further determine the directional nature of the perceived stress-fatigue impact relation, the opposite prediction model was tested. That is, perceived stress was regressed on time t (same week) fatigue impact and t – 1 and t – 2 week lags as predictors. In accord with this hypothesis, only same week fatigue impact was expected to correlate with perceived stress, and one and two week lagged fatigue impact were expected not to be significant predictors.
1.4.3.2. Moderating effect of disease duration on the relation between stress and fatigue impact: When controlling for baseline severity of depressive symptoms, cognitive impairment, and duration of disease, stress-related fatigue impact is greater for individuals with a shorter disease duration and smaller for individuals with a longer disease duration.

1.4.3.3. Moderating effect of coping strategies by disease duration on the relation between perceived stress and fatigue impact: It was hypothesized that the increase in stress-related fatigue impact is smaller for individuals with a shorter disease duration using more problem-focused coping; and is greater for individuals with a longer disease duration using more problem-focused coping. Further, the reverse relation was predicted for avoidant coping. The increase in stress-related fatigue impact is greater for individuals with a shorter disease duration using more avoidant coping; the increase in stress-related fatigue impact is smaller for individuals with a longer disease duration using more avoidant coping.
Chapter 2 Method

2.1. Participants

Participants were 78 patients with a diagnosis of relapsing-remitting multiple sclerosis. Participants were recruited for a year-long study on stress and quality of life in people with multiple sclerosis. A brochure was mailed to all the individuals (approximately 1,300 individuals) residing in Monroe County, New York State who were in the database of the local chapter of the Multiple Sclerosis National Society. The local chapter of the Multiple Sclerosis National Society maintains records of most people diagnosed with multiple sclerosis (all disease courses) at local clinics. The brochure gave a brief description of a study on “stress, coping, and quality of life in persons with multiple sclerosis” and also provided a phone number for individuals interested in participating in the study.

Inclusion criteria for the study were age over 18, fluency in English, and a definite diagnosis of multiple sclerosis relapsing-remitting course. Patient with either primary or secondary progressive course were not included in the study. The protocol allowed participants whose MS diagnosis changed to primary or secondary progressive during the course of the study to complete the study. However, their data would not be included in the analyses. None of the participants had a change in MS diagnosis during their participation in the study. Some participants were excluded from the study
during the baseline assessment, and some were excluded from the final analysis, for having more than 18% of the weekly diary data missing (Figure 2.1).

The final sample included 65 participants, including 54 women and 11 men. Their mean age was 51.32 years (SD=9.55), with a range from 30 to 75. The majority of participants were Caucasian (n=63; 96.9%), with 1 African American (1.5%) and 1 multiracial (1.5%) persons. Their mean educational
level in number of years of completed formal education was 15.49 (SD=2.78). The mean duration of MS in years since diagnosis was 11.14 (SD=6.94; range=1 to 31). Twenty-three participants (35.4%) were employed full- or part-time, 9 (13.8%) were unemployed, 8 (12.3%) were retired, and 25 (38.5%) were receiving disability benefits. Forty-two participants (64.6%) were married, 12 (18.5%) were divorced or legally separated, 6 (9.2%) were single, never married, and 5 (7.7%) were widowed.

2.2 Procedures

For the purpose of the present study, only part of the data collected in a larger study was used. The procedures of the larger study are briefly discussed before the specifics for the present study are detailed. The study had three main assessment times (Time 1, 6-month follow-up, and 12-month follow-up), and a weekly diary component. The Time 1 assessment was conducted over two meetings, each lasting between two and three hours. The 6-month follow up was done by mail and the 12-month follow up was done in one meeting lasting between two and three hours.

*Time 1 assessment.* After the initial phone screening, participants were invited to meet with the researcher at Strong Memorial Hospital. In a few cases, when traveling was problematic for the participant, the interview took place in his or her home. After providing written informed consent the participants were interviewed by the researcher, provided a blood sample for immunological analysis and completed questionnaires. The baseline interview
consistent of a comprehensive demographic assessment, The Structured Clinical Interview for Axis I DSM-IV – Non-patient Version, Axis I disorders (First, Spitzer, Gibbon & Williams, 1996), and a medical history based on patient report. Participants also completed a cognitive test (Symbol Digit Modalities Test; Smith, 1986, 1982) and questionnaires assessing coping style, personality, depressive symptoms over the prior two weeks, lifetime history of traumatic life events, and quality of life during the prior month.

Six-month follow-up. Six months after the first interview, participants were mailed a package of questionnaires assessing depressive symptoms over the prior two weeks, and quality of life over the prior month. The participants filled out the questionnaires at home and sent them back by mail.

Twelve-month follow-up. Twelve months after the Time 1 assessment, the participants were invited to meet with the researcher for the final assessment. They completed an interview, provided blood samples and filled out questionnaires. The interview consisted of a follow-up demographic assessment, the SCID (First et al., 1996), and a follow-up medical history. The participants completed the Symbol Digit Modalities Test (Smith, 1986, 1982) and completed questionnaires assessing personality, depressive symptoms over the prior two weeks, traumatic life events over the past year and quality of life.

Diary assessment. At the end of the Time 1 interview, participants were given 50 diary forms and 50 stamped preaddressed envelopes.
Participants were instructed to fill out a diary each Friday and return it by mail the next day. They were told that the diaries would contribute to the understanding of their general as well as disease related weekly experiences. Each diary was dated with the day it should be completed in an attempt to increase compliance. However, participants were instructed to fill out the date on which they completed the diary, in case they were unable to fill it out on Friday. Diaries received with a postal stamp indicating a date later than seven days after the date printed on the diary were discarded. When a participant missed two consecutive diaries or sent them late, the researcher contacted him/her by phone to remind him/her to fill out the diaries.

Participants were paid $40 after completing the Time 1 assessment, $20 after completing the 6-month follow-up, and $20 after completing the 12-month follow-up. They were not paid for completing the diaries.

2.3. Measures

Weekly measures

2.3.1. Modified Fatigue Impact Scale (MFIS short form; Fisk et al., 1994). This self-report instrument is an indirect measure of perceived fatigue through the effects of fatigue in terms of physical and cognitive functioning in multiple sclerosis patients, namely fatigue impact. The scale is part of a comprehensive assessment of quality of life in patients with multiple sclerosis: the Multiple Sclerosis Quality of Life Inventory (Ritvo et al., 1997). The short form of the scale includes 5 items (e.g., “Because of my fatigue during the
past week I have been less alert," “Because of my fatigue during the past week I have had trouble maintaining physical effort for long periods,”
“Because of my fatigue during the past week I have had trouble concentrating”). The items are rated on a 5-point Likert-type scale, from 0 (almost never) to 4 (always). The total score of MFIS is the sum of the 5 items and can range from 0 to 20. Higher scores indicate a greater impact of fatigue on a patient’s activities (i.e., no items are reverse scored). The scale has good internal consistency with a Cronbach’s alpha of .80 for the short version as well as good discriminant capacity of fatigue impact effects in patients with multiple sclerosis from those experienced by patients with other disorders such as chronic fatigue and hypertension (Fisk et al., 1994).

2.3.2. Perceived Stress Scale (PSS; Cohen & Williamson, 1988). The present study used the 10-item version of the Perceived Stress Scale. The PSS assesses the degree to which respondents appraise their lives as stressful, and the events in their lives as unpredictable and uncontrollable. The items are general in nature and free of specific content to either type of events or a particular population (e.g., “in the last week, how often have you felt that you were unable to control the important things in your life?”). The items are scored on a 5-point Likert-type scale, from 0 (never) to 4 (very often). The total score is obtained by reversing the scores for the four positively stated items and then summing across all 10 items; the total score ranges from 0 to 40 and it indicates the severity of perceived stress (high
scores indicate more severe perceived stress). The PSS has good internal consistency in community samples and college student populations (Cronbach’s alpha = .84 - .86; Cohen et al., 1983), as well as in psychiatric populations (Cronbach’s alpha = .80; Hewitt, Flett, & Mosher, 1992). Test-retest reliability is .85 in college samples after 2 days, and .55 in a community sample after 6 weeks (Cohen, Kamarck & Mermelstein, 1983). To this author’s knowledge there are no published studies (with the exception of two doctoral dissertations) that used PSS with individuals with multiple sclerosis; however, PSS has been used in other with other neurodegenerative disorders such as Alzheimer’s disease (Wahbeh, Kishiyama, Zajdel, & Oken, 2008.)

Baseline level measures

2.3.3. Disease duration. Disease duration was recorded in number of years since a formal diagnosis of multiple sclerosis was given, based on patient report.

2.3.4. Symbol Digit Modalities Test (SDMT; Smith, 1986, 1982). The SDMT is a measure of information processing speed and working memory. The SDMT presents a series of nine symbols, each paired with a single digit in a key at the top of an 8 ½ x 11 inch sheet. The rest of the page presents symbols organized in rows and the participant is asked to identify and say outloud the digit that corresponds to each of the symbols. The participant is given 90 seconds to complete the test. The researcher chose the oral administration version of the test because this version is independent of the
degree of motor impairment or lack of coordination of eyes with the arm and hand. The test is scored by summing the number of correct answers. The SDMT test was ranked highly as a measure of processing speed and working memory in multiple sclerosis population by a panel of multiple sclerosis experts (Benedict et al., 2002) and was found to be highly sensitive to cognitive impairment in multiple sclerosis (Benedict et al., 2006). SDMT scores were normed in a MS population with T score higher than 35 indicating intact performance, and T score less or equal to 35 indicating impaired performance (T=50, SD=10; Parmenter, Testa, Schretlen, Weinstock-Guttman, & Benedict, 2010).

2.3.5. Center for Epidemiologic Studies Depression Scale - Revised (CESD-R; Eaton, Smith, Ybarra, Muntaner, & Tien, 2004). CESD-R is a self-report instrument assessing the frequency of depressive symptoms over the prior two weeks. The scale includes 20 items that survey depressive symptoms reflecting the DSM-IV criteria for a major depressive episode. The items cover depressed mood (e.g., “I could not shake off the blues”), anhedonia (e.g., “Nothing made me happy”), somatic symptoms (e.g., “My appetite was poor,” “My sleep was restless,” “I felt fidgety”), fatigue (e.g., “I could not get going”), feelings of worthlessness or guilt (e.g., “I felt like a bad person”), problems concentrating (e.g., “I could not focus on the important things”), and suicidal ideation (“I wish I were dead”). There is a five-choice response with anchor points describing the duration of the symptoms: “Rarely
or none of the time (less than one day)” is coded 0, “Some or a little of the
time (1-2 days)” is coded 1, “Occasionally or a moderate amount of time (3-4
days)” is coded 2, “Most or all of the time (5-7 days)” and “Nearly every day
for two weeks” are both coded 3. The possible range of scores is 0 to 60, with
higher scores indicating the presence of more symptomatology. A cutoff score
for clinical depression (a score above which there is a high likelihood that the
respondent experience an episode of major depression) was not established
for the revised version of the scale; however, for the initial version (Center for
Epidemiologic Studies Depression Scale [CESD]), different cut-off scores
function of age have been established (Lyness et al., 1997). The CESD-R has
good internal consistency, with Cronbach’s alpha of .92 (Eaton et al., 2004) in
a community sample. To this author’s knowledge, the CESD-R has not been
used in a multiple sclerosis population; however, the initial scale (CESD) was
validated in a multiple sclerosis population (Verdier-Taillefer, Gourlet, Fuhrer
& Alperovitch, 2001) and had a good predictive value in detecting depression
in patients with multiple sclerosis (Pandya, Metz & Pattern, 2005).

2.3.6. Brief COPE Inventory. (Carver, 1997) The brief COPE inventory
is a self-report questionnaire assessing ways people cope with general
stressful situations. The instructions for this study have been modified, to
assess the way in which people cope with multiple sclerosis related stress.
The phrase “Indicate how you usually do when you experience a stressful
event” had been replaced with “Indicate how you usually do when you
experience a stressful event related to your MS.” The brief COPE is a 28-item questionnaire grouped into 14 distinct subscales (e.g., self-destruction, active coping, denial, venting, humor). For the present study, I used only four of the subscales and aggregated them into two higher order scales: problem solving coping and avoidant coping. The problem-focused coping scale was formed by aggregating the following four items: “I’ve been concentrating my efforts on doing something about the situation I am in,” “I’ve been taking action to try to make the situation better,” “I’ve been trying to come up with a strategy about what to do,” and “I’ve been thinking hard about what steps to take.” This scale has good internal reliability with a Cronbach’s alpha of .78 in the present sample. The avoidant coping scale was formed by aggregating these following four items: “I’ve been saying to myself ‘this isn’t real’,” “I’ve been giving up trying to deal with it,” “I’ve been refusing to believe that it had happened,” and “I’ve been giving up the attempt to cope.” Cronbach’s alpha for this scale is .76 in the present sample, indicating acceptable internal reliability. The items are scored on a 4-point scale from 1 (I haven’t been doing this at all) to 4 (I’ve been doing this a lot). High scores indicate higher use of the respective coping strategy.

2.4. Analytic plan

2.4.1. Descriptive analyses. Means and standard deviations of study variables (fatigue impact, perceived stress, age, education, disease duration,
cognitive function, depressive symptoms, problem-focused coping, and avoidant coping) were calculated.

2.4.2 Preliminary analyses. The number of missing (including late diaries) were calculated for each participant. To ensure accuracy of the data, participants with more than 28% missing diaries were excluded from the main analyses.

Further, this researcher examined whether there were significant differences between the participants analyzed in the study and the excluded participants on any of the variables of interest. A multiple logistic regression analysis was employed. The predicted variable had two values: participants included in the study were coded as 0 and the excluded participants were coded as 1. Predictors were gender (male=0, female=1), age, education, MS duration, cognitive function, depressive symptoms and two coping styles, problem-focused and avoidant. All predictors were entered in one block.

The time-variant data (fatigue impact and perceived stress) were tested for the presence of linear trends over the course of 50 weeks.

2.4.3 Central analyses. The hypotheses of this study were tested using a multilevel modeling approach, specifically Hierarchical Linear Modeling (HLM; Raudenbush & Byrk, 2002). The hierarchical nature of the data, with repeated measurements nested within person, requires an approach that takes into account both within person variance of the repeated measures (level 1 analyses) and between-person variance of the trait measures (level 2
analyses; Kenny, Kashy, & Bolger, 1998). In HLM a person is treated as a random effect, rather than fixed, allowing generalization of the findings to the population. One advantage of this modeling technique over regression models is that it allows for within-person slopes to differ significantly from one person to another (Reis, Sheldon, Gable, Roscoe, & Ryan, 2000). Another important advantage of modeling data in HLM is that it can handle missing data at level 1 (the time-variant data) by calculating maximum likelihood estimates of the P-variate distribution of the complete data given incomplete data (Raudenbush & Bryk, 2002).

The person-level predictors in these analyses were depressive symptoms, disease duration, cognitive function, problem-focused coping, and avoidant coping; these predictors are time invariant. As recommended by Raudenbush and Bryk (2002), the person-level variables were centered on the group means.

The week-level predictor was perceived stress assessed the same week as the predicted variable (fatigue impact). There are two main choices for centering the week level predictors: on the individual means or on the grand mean. Centering data on individual means allows the researcher to look at the relation between perceived stress and fatigue impact, while controlling for the influence of individual characteristics or personal traits (e.g., an individual’s propensity to endorse high levels of fatigue as well as high levels of stress). Centering data on the grand mean could confound Level 1
(i.e., perceived stress and fatigue impact) effects with Level 2 (e.g., individual characteristics) effects. However, this type of centering has the benefit of maximizing the between-person variance to be explained, hence maximizing the possibility of finding Level 2 predictors (Schumacker & Bembry, 1995). Specifically, in the present design, centering on the grand mean maximizes the possibilities of finding moderators of the perceived stress – fatigue impact relationship. All Level 1 analyses were tested twice: first with data centered on individual means, and second with data centered on grand means. The results were similar, suggesting the Level 1 effects were robust in both cases and the significant effects found with the grand mean centered data were not due to Level 2 influences. Further, the grand mean centered data are used for Level 2 analyses in order to maximize the possibility of finding significant moderators of the level 1 relations. Therefore, grand mean centered data analyses are reported. Hypothesis 1 was tested by the following equations.

To test the directionality of the relation between perceived stress and fatigue impact, a series of models was tested; all were weekly level effects. In the first series, fatigue impact was the dependent variable and perceived stress was the predictor. The first model included only same week stress as predictor.

\[
\text{FATIGUE}_{ij} = \beta_j + \beta_1 \text{STRESS}_{ij} + e_{ij}
\]

(\text{level 1})

where \( \beta_j \) is the intercept, signifying the person’s level of fatigue impact on an average week and \( \beta_1 \) is the maximum likelihood of the estimate of the
population slope estimating weekly fatigue impact from the weekly levels of perceived stress. STRESS\(_{ij}\) is the level of perceived stress measured each week (i) for each of the participants (j); e\(_{ij}\) is the error term.

The second model included same week stress and stress at t-1 (previous week) as predictors:

\[
\text{FATIGUE}_{ij} = \beta_1 + \beta_2 \text{STRESS}_{ij} + \beta_3 \text{STRESS}_{LAG1}_{ij} + e_{ij}
\]

If both predictors were significant, then a third model included same week stress, stress at t-1 (previous week), and stress at t-2 (two weeks prior) as predictors:

\[
\text{FATIGUE}_{ij} = \beta_1 + \beta_2 \text{STRESS}_{ij} + \beta_3 \text{STRESS}_{LAG1}_{ij} + \beta_4 \text{STRESS}_{LAG2}_{ij} + e_{ij}
\]

In the second series, perceived stress was the dependent variable and fatigue impact was the predictor. The first model included only same week fatigue impact as predictor.

\[
\text{STRESS}_{ij} = \beta_1 + \beta_2 \text{FATIGUE}_{ij} + e_{ij}
\]

(\text{level 1})

Where \(\beta_1\) is the intercept, signifying the person’s level of stress on an average week and \(\beta_2\) is the maximum likelihood of the estimate of the population slope estimating weekly perceived stress from the weekly levels of fatigue impact. \(\text{FATIGUE}_{ij}\) is the level of fatigue impact measured each week (i) for each of the participants (j); e\(_{ij}\) is the error term.

The second model included same week fatigue impact and fatigue impact at t-1 (previous week) as predictors:

\[
\text{STRESS}_{ij} = \beta_1 + \beta_2 \text{FATIGUE}_{ij} + \beta_3 \text{FATIGUE}_{LAG1}_{ij} + e_{ij}
\]
If both predictors were significant, then a third model included same week fatigue impact, fatigue impact at t-1 (previous week), and fatigue impact at t-2 (two weeks prior) as predictors:

$$\text{STRESS}_{ij} = \beta_j + \beta_1 \text{FATIGUE}_{ij} + \beta_2 \text{FATIGUE\_LAG1}_{ij} + \beta_3 \text{FATIGUE\_LAG2}_{ij} + e_{ij}$$

Level 2 predictors were explored for the level 1 model that was expected to be significant ($\text{FATIGUE}_{ij} = \beta_j + \beta_1 \text{STRESS}_{ij} + e_{ij}$). Person-level effects were estimated by:

$$\beta_j = G_{00} + G_{01} \text{MS\_DURATION} + G_{02} \text{COG\_FUNCTION} + G_{03} \text{DEPRESSION} + G_{04} \text{PROBLEM} + G_{04} \text{AVOIDANT} + u_{0j} \quad \text{(level 2)}$$

where $G_{00}$ is the week level intercept for an average person, and $G_{01}$ to $G_{07}$ are the maximum likelihood estimates of the population slopes estimating average levels of fatigue impact across all weeks from disease duration, cognitive function, depressive symptoms, problem-focused coping and avoidant coping; $u_{0j}$ is the error term. While the depressive symptoms were measured three times during the study, only the baseline measurement is included in this equation given that the three measurements are highly correlated and not significantly different from each other and that the baseline measurement can reflect the depressive levels throughout the period of the study.

$$\beta_{ij} = G_{10} + G_{11} \text{MS\_DURATION} + G_{12} \text{DURATION\_PROBLEM} + G_{12} \text{DURATION\_AVOIDANT} + u_{1j} \quad \text{(level 2)}$$
where $G_{10}$ is the week level intercept for an average person, and $G_{11}$ and $G_{12}$ are the maximum likelihood estimate of the population slopes estimating average levels of perceived stress across all weeks from problem-focused coping by disease duration, and from avoidant coping by disease duration; $u_{1j}$ is the error term.
Chapter 3 Results

3.1. Preliminary analyses and descriptive statistics

3.1.1. Examination of diary data. The 74 participants included in the diary part of the study provided 3,268 diaries out of a possible 3,700 (88.33%), indicating good compliance with the study requirements. An inspection of the frequency of missing diaries by study participant (Figure 3.1), revealed a drop after 14 diaries (28%). Sixty-five participants were missing 14 or less diaries. As the remaining 9 were missing between 11 and 41 diaries (equal to or higher than 42%), they were dropped from the analysis.

Figure 3.1. Number of missing diaries by study participant
Of the 65 retained participants, 21 completed all 50 diaries, 17 completed 49 diaries, 6 completed 48 diaries, and 21 completed between 36 and 47 diaries. The 65 retained participants provided 3,058 diaries out of a possible total of 3,250 (94.09%).

In order to calculate descriptive statistics, perceived stress and fatigue impact (time-variant data) were aggregated across the 50 weeks. Table 3.1 presents descriptive statistics and correlations for all study variables for the retained participants.
Table 3.1: Correlations among aggregated weekly measures and time-invariant measures

<table>
<thead>
<tr>
<th></th>
<th>M</th>
<th>SD</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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<td><strong>Weekly measures</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1. Fatigue impact</td>
<td>8.22</td>
<td>5.32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Perceived stress</td>
<td>15.28</td>
<td>8.11</td>
<td>.59**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Perceived stress lag 1 week</td>
<td>15.29</td>
<td>8.08</td>
<td>.54**</td>
<td>.81**</td>
<td></td>
<td></td>
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<td><strong>Time-invariant measures</strong></td>
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<td></td>
<td></td>
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<td></td>
</tr>
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<td>4. Age</td>
<td>51.32</td>
<td>9.55</td>
<td>.13</td>
<td>.01</td>
<td>.01</td>
<td></td>
<td></td>
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</tr>
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<td>5. Gender</td>
<td>.83</td>
<td>.38</td>
<td>.24</td>
<td>.24</td>
<td>.24</td>
<td>.12</td>
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<td>6. Education</td>
<td>15.49</td>
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<td>-.27*</td>
<td>-.16</td>
<td>-.16</td>
<td>-.01</td>
<td>-.01</td>
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<td></td>
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<td>7. MS duration</td>
<td>11.14</td>
<td>6.94</td>
<td>-.05</td>
<td>-.17</td>
<td>-.17</td>
<td>.28**</td>
<td>.06</td>
<td>.06</td>
<td></td>
<td></td>
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<td></td>
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<td>8. Cognitive function</td>
<td>50.43</td>
<td>10.29</td>
<td>-.30*</td>
<td>-.20</td>
<td>-.20</td>
<td>-.39**</td>
<td>.11</td>
<td>.27*</td>
<td>-.14</td>
<td></td>
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<td>9. Depressive symptoms</td>
<td>12.80</td>
<td>10.05</td>
<td>.60**</td>
<td>.56**</td>
<td>.56**</td>
<td>.01</td>
<td>.32**</td>
<td>-.24*</td>
<td>-.10</td>
<td>-.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Problem-focused coping</td>
<td>2.94</td>
<td>.71</td>
<td>.04</td>
<td>-.15</td>
<td>-.15</td>
<td>.05</td>
<td>.01</td>
<td>.13</td>
<td>.04</td>
<td>.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Avoidant coping</td>
<td>1.24</td>
<td>.40</td>
<td>.38**</td>
<td>.40**</td>
<td>.40**</td>
<td>-.11</td>
<td>.27*</td>
<td>-.32*</td>
<td>.07</td>
<td>-.21</td>
<td>.54**</td>
<td>-.09</td>
</tr>
</tbody>
</table>

*p < .05; **p < .01.

Note 1: Correlations among weekly measures are calculated for non-aggregated data (n range: 2896 to 3004) consisting of sets of up to 50 observation from each individual; these correlations are not statistically meaningful. Correlations calculated for each individual range between: r=-.04 to r=.83 for perceived stress and fatigue impact; r=-.14 to r=.75 for perceived stress lag 1 and fatigue impact; and r=-.14 to r=.69 for perceived stress and perceived stress lag 1.

Note 2: Gender was coded: male=0, female=1. Education and MS duration were measured as continuous variables in number of years.

Note 3: Cognitive function was measured using the Symbol Digit Modalities Test (SDMT); standard scores (T=50, SD=10) normed in an MS population are presented to facilitate interpretation: cognitive function is classified as intact (T > 35) or impaired (T < or = 35) (Parmenter, Testa, Schretlen, Weinstock-Guttman, & Benedict, 2010). Raw scores were used in the analyses.

Note 4: Depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale Revised (CESDR; Radloff, 1977); the two fatigue items were not included in the CESDR summed score (full score M=14.97, SD=11.61).
3.1.2. Analysis of missingness. A multiple logistic regression analysis was employed to examine whether the 9 participants excluded from the main analyses were significantly different from the retained participants on any of the variables of interest. The predicted variable had two values: participants included in the study (n=65) were coded as 0 and the excluded participants (n=9) were coded as 1. Predictors were gender (male=0, female=1), age, education, MS duration, cognitive function, depressive symptoms, problem-focused coping and avoidant coping. All predictors were entered in one block. The overall regression analysis was not significant, with $\chi^2(8, n=74)=10.23, p = .25$. The results of the multiple logistic regression analysis suggested that the excluded participants did not differ significantly from the analyzed participants on any of the variables of interest.

3.2. Preliminary exploration of the diary data

The weekly diary data, which consists of up to 50 time-ordered observations clustered within individual, present non-independence of observations (West & Hepworth, 1991). Non-independence can lead to potentially inaccurate results and conclusions. One form of non-independence that could be present in weekly data is a linear trend. A linear trend may be present if there was a linear relation between the estimated parameters and the order of the weeks participants recorded their data. This trend can be modeled by including a predictor representing the week number of each observation.
To test the existence of a linear trend, two conditional level 1 models were constructed and presented below for both fatigue impact and perceived stress as predicted variables, and week number as the predictor variable.

\[
\text{FATIGUE}_{ij} = \beta_0 + \beta_1 \text{WEEK}_{ij} + e_{ij} \\
\text{STRESS}_{ij} = \beta_0 + \beta_1 \text{WEEK}_{ij} + e_{ij}
\]

Results suggested that there was no linear trend for either fatigue impact ($\beta_1 = -.0005$, $t = -.35$, $p = .73$), or perceived stress ($\beta_1 = -.0002$, $t = -1.14$, $p = .25$).

3.3. Exploration of the directionality of the relation between perceived stress and fatigue impact

As perceived stress and fatigue impact can have a reciprocal influence on each other, a series of models were constructed to explore whether a directionality of this relation could be determined. Time lagged variables were created for both perceived stress and fatigue impact. These variables are defined below:

\[
\text{STRESS} = \text{current week observation} \\
\text{STRESS\_LAG1} = \text{data observed one week prior to ‘STRESS’ observation} \\
\text{STRESS\_LAG2} = \text{data observed two weeks prior to ‘STRESS’ observation} \\
\text{FATIGUE} = \text{data observed on the same week as ‘STRESS’} \\
\text{FATIGUE\_LAG1} = \text{data observed one week prior to ‘FATIGUE’ observation} \\
\text{FATIGUE\_LAG2} = \text{data observed two weeks prior to ‘FATIGUE’ observation}
\]
All models used group-centered data, which explored the fluctuations of perceived stress and fatigue impact around their respective group means. First, the researcher fit successive level 1 models for FATIGUE as predicted variable. These models are presented below.

3.3.1. Models for predicting fatigue impact. The first model had only STRESS as predictor:

\[ \text{FATIGUE}_{ij} = \beta_0 + \beta_1 \text{STRESS}_{ij} + e_{ij} \]

Results suggested that perceived stress recorded at the same time as fatigue impact was a significant predictor of fatigue impact ($\beta_1 = .24$, $t=5.64$, $p<.001$). Further, the researcher explored whether the influence of perceived stress on fatigue impact can last as long as one week.

The second model had STRESS and STRESS_LAG1 as predictors. Forty-nine weekly observations were used, because there was no week 1 observation of FATIGUE for STRESS_LAG1.

\[ \text{FATIGUE}_{ij} = \beta_0 + \beta_1 \text{STRESS}_{ij} + \beta_2 \text{STRESS}_\text{LAG1}_{ij} + e_{ij} \]

Results indicate that both perceived stress recorded at the same time as fatigue impact ($\beta_1 = .23$, $t=5.32$, $p<.001$), and perceived stress recorded in the previous week ($\beta_2 = .05$, $t=3.85$, $p<.001$) were significant predictors of fatigue impact. Results showed that the influence of perceived stress on fatigue impact could last as long as one week. Further, the researcher explored whether the influence of perceived stress on fatigue impact can last as long as two weeks.
The third model had STRESS, STRESS_LAG1, and STRESS_LAG2 as predictors. Forty-eight weekly observations were used, because there were no week 1 and week 2 observations of FATIGUE for STRESS_LAG1, and STRESS_LAG2.

\[
FATIGUE_{ij} = \beta_0 + \beta_1 STRESS_{ij} + \beta_2 STRESS\_LAG1_{ij} + \beta_3 STRESS\_LAG2_{ij} + e_{ij}
\]

Results indicated that, as in the previous model, both perceived stress recorded at the same time as fatigue impact ($\beta_1 = .22$, $t=5.28$, $p<.001$), and perceived stress recorded a week prior ($\beta_2 = .03$, $t=2.65$, $p<.005$) were significant predictors of fatigue impact. However, the perceived stress recorded two weeks prior was not a significant predictor of fatigue impact ($\beta_3 = .02$, $t=1.09$, $p=.28$). Results suggested that the influence of perceived stress on fatigue impact lasts as long as one week, but not as long as two weeks.

3.3.2. Models for predicting perceived stress. The first model had only FATIGUE as predictor.

\[
STRESS_{ij} = \beta_0 + \beta_1 FATIGUE_{ij} + e_{ij}
\]

Results suggested that fatigue impact recorded at the same time as perceived stress was a significant predictor of perceived stress ($\beta_1 = .69$, $t=3.69$, $p<.001$). Further, the researcher explored whether the influence of fatigue impact on perceived stress can last as long as one week.
The second model had FATIGUE and FATIGUE_LAG1 as predictors. Forty-nine weekly observations were used, because there was no week 1 observation of STRESS for FATIGUE_LAG1.

\[ \text{STRESS}_{ij} = \beta_0 + \beta_1 \text{FATIGUE}_{ij} + \beta_2 \text{FATIGUE}_{LAG1ij} + e_{ij} \]

Results showed that fatigue impact recorded at the same time as perceived stress was a significant predictor of perceived stress \((\beta_1 = .67, \ t=4.31, \ p<.001)\). However, the fatigue impact recorded in the prior week was not a significant predictor of perceived stress \((\beta_2 = .08, \ t=.86, \ p=.39)\). The results suggest that the relation of fatigue impact to perceived stress does not last as long as a week.

The two models fitted for perceived stress and fatigue impact, as predicted, and predictor variables, measured at the same time, indicated a significant shared variance between the two. However, only perceived stress had a significant influence on fatigue impact measured one week after. This finding suggests that the directionality of this relation is from perceived stress to fatigue impact. Perceived stress predicts fatigue impact during the same week, as well as during the week to come.


From the previous series of models, the most comprehensive level 1 model with significant predictors was chosen to further explore whether the hypothesized relation of perceived stress to fatigue impact was independent of potential confounds such as disease duration, cognitive function and
depressive symptoms. In addition, possible moderators of the relation between perceived stress and fatigue impact were tested, namely disease duration, problem-focused coping, and avoidant coping. The potential confounding factors MS duration, cognitive function, and depressive symptoms (excluding fatigue items), as well as the 2 coping style moderators were entered as level 2 predictors.

\[
\text{FATIGUE}_{ij} = \beta_j + \beta_1 \text{STRESS}_{ij} + \beta_2 \text{STRESS}_L\text{AG}_{1ij} + e_{ij} \quad \text{(level 1)}
\]

\[
\beta_j = G_{00} + G_{01} \text{MS}_\text{DURATION} + G_{02} \text{COG}_\text{FUNCTION} + G_{03} \text{DEPRESSION} + u_{0j} \quad \text{(level 2)}
\]

\[
\beta_1 = G_{10} + G_{11} \text{MS}_\text{DURATION} + G_{12} \text{DURATION}^*\text{PROBLEM} +
G_{13} \text{DURATION}^*\text{AVOIDANT} + u_{1j} \quad \text{(level 2)}
\]

\[
\beta_2 = G_{20} + G_{21} \text{MS}_\text{DURATION} + G_{22} \text{DURATION}^*\text{PROBLEM} +
G_{23} \text{DURATION}^*\text{AVOIDANT} + u_{1j} \quad \text{(level 2)}
\]

The intercept (\(\beta_j\)) effect was modeled as a random effect at level 2 to allow individuals to have different estimates of fatigue impact, depending on several characteristics such as disease duration, depressive symptoms, cognitive function and coping style. The slope (\(\beta_1\) and \(\beta_2\)) effects, which in this case indicated the magnitude of the effect of perceived stress, were modeled as random effects, allowing individuals’ perceived stress to have a variable relation to fatigue impact. Results from this model are presented in Table 3.2.
Table 3.2. Model 1. Unstandardized coefficients and tests of significance for predictors of fatigue impact

<table>
<thead>
<tr>
<th>Predictor</th>
<th>B</th>
<th>Coeff.</th>
<th>SE</th>
<th>T-Ratio</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS duration</td>
<td>G01</td>
<td>-.007</td>
<td>.068</td>
<td>-.11</td>
<td>61</td>
<td>.916</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>G02</td>
<td>-.086</td>
<td>.046</td>
<td>-1.86</td>
<td>61</td>
<td>.068</td>
</tr>
<tr>
<td><strong>Depressive symptoms</strong></td>
<td>G03</td>
<td>.268</td>
<td>.046</td>
<td>-5.85</td>
<td>61</td>
<td>.000</td>
</tr>
<tr>
<td><strong>Stress</strong></td>
<td>G10</td>
<td>.201</td>
<td>.018</td>
<td>11.21</td>
<td>2887</td>
<td>.000</td>
</tr>
<tr>
<td>Stress x MS duration</td>
<td>G11</td>
<td>-.007</td>
<td>.009</td>
<td>-.84</td>
<td>2887</td>
<td>.402</td>
</tr>
<tr>
<td>Stress x MS duration x problem focused coping</td>
<td>G12</td>
<td>.001</td>
<td>.002</td>
<td>.24</td>
<td>2887</td>
<td>.808</td>
</tr>
<tr>
<td>Stress x MS duration x avoidant coping</td>
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<td>.003</td>
<td>.003</td>
<td>.96</td>
<td>2887</td>
<td>.336</td>
</tr>
<tr>
<td><strong>Stress_lag1</strong></td>
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<td>.010</td>
<td>3.34</td>
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<td>.008</td>
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<td>.001</td>
<td>2.12</td>
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<td>.034</td>
</tr>
<tr>
<td>Stress_lag1 x MS duration x avoidant coping</td>
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<td>.001</td>
<td>.002</td>
<td>0.71</td>
<td>2887</td>
<td>.479</td>
</tr>
</tbody>
</table>

Significant main effect predictors of fatigue impact were same-week perceived stress, previous-week perceived stress, and baseline depressive symptoms. There were no significant moderators of the same-week perceived stress relation to fatigue. The relation of previous-week perceived stress to fatigue impact was moderated by disease duration and by the interaction between problem-focused coping and disease duration.

**Model 1 main effects.** As predicted, higher levels of perceived stress in the same, as well as the preceding week predicted greater fatigue impact.
The magnitude of previous-week perceived stress relation to fatigue impact was lower than the magnitude of same-week perceived stress relation to fatigue impact (see Table 3.2). Also, higher levels of baseline depressive symptoms predicted higher levels of fatigue impact.

**Model 1 moderation effects. Disease duration.** In order to further explore the moderation relations the researcher examined the region of significance for the simple slopes using a computational program developed by Preacher and colleagues (Preacher, Curran, & Bauer, 2006). Disease duration significantly moderated the relation between perceived stress in the previous week and fatigue impact within two ranges of values: in the lower bound (between 1 and 12.10 years) and in the upper bound (between 20.53 and 31 years). The simple slope for the lower bound of disease duration was significant at .05 level (B=.020, t=1.96, p < .05). The simple slope for the upper bound of disease duration was significant at .05 level as well, but with a different direction (B=-.086, t=-1.96, p < .05; Figure 3.2; Table 3.4).

Among those afflicted with MS for a shorter period of time, the greater the stress in the previous week, the greater the fatigue impact in the current week. In contrast, among those with a longer duration of disease, the greater the perceived stress in the previous week, the less the fatigue impact in the current week. However, the moderator effect of disease duration on the perceived stress-fatigue impact relation should be interpreted with caution, as it was further specified by the interaction with problem-focused coping style.
Figure 3.2. Model 1. MS duration as moderator of the relation between previous-week perceived stress and fatigue impact.

Model 1 moderation effects. Disease duration by problem solving coping. In order to understand the three-way moderation relation between previous-week stress, disease duration, and problem solving coping, the researcher examined whether the simple slopes of the interaction terms were significantly different from 0 (Preacher, Curran, & Bauer, 2006). Among those who had been diagnosed more recently (1 to 12 years disease duration), a higher use of problem-focused coping (more than 1 standard deviation above the mean of problem-focused coping use in the present sample) was related
to an increased magnitude of the effect of previous-week perceived stress on fatigue impact (B=.021, t=2.15, p<.05). For the same group of individuals, the effect of a lower use of problem-focused coping on the relation between previous-week stress and fatigue impact approached significance (B=.017, t=1.60, p=.11; Figure 3.3; Table 3.4).

Figure 3.3. Model 1. Problem-focused coping as moderator of the relation between previous-week perceived stress and fatigue impact for individuals with shorter disease duration

For individuals with longer disease duration (over 20 years), for whom the previous week stress was negatively associated with current week fatigue...
impact - the use of problem-focused coping further explicates this relation. Among those who had multiple sclerosis for a longer period of time a higher use of problem-focused coping was related to a smaller decrease in magnitude of the previous-week perceived stress-fatigue impact relation (B=-.074, t=-1.98, p<.05), as compared with a lower use of problem-focused coping that was related to a higher decrease in the magnitude of the previous-week perceived stress-fatigue impact relation (B=-.117, t=-2.28, p<.05; Figure 3.4; Table 3.4).
Figure 3.4. Model 1. Problem-focused coping as moderator of the relation between previous-week perceived stress and fatigue impact for individuals with longer disease duration

3.5. Full model: Predictors of fatigue impact. Model 2 (fewer predictors). The initial model found no significant moderators for the relation of same-week perceived stress on fatigue impact. Thus, a second model was constructed with the slope ($\beta_1$) effect for same-week perceived stress treated as fixed effect, as follows:

$$\text{FATIGUE}_{ij} = \beta_j + \beta_1 \text{STRESS}_{ij} + \beta_2 \text{STRESS\_LAG1}_{ij} + e_{ij}$$  \hspace{1cm} (level 1)
\[
\beta_j = G_{00} + G_{01} \text{MS\_DURATION} + G_{02} \text{COG\_FUNCTION} + G_{03} \text{DEPRESSION} + u_{0j} \tag{level 2}
\]

\[
\beta_1 = G_{10} + u_{1j} \tag{level 2}
\]

\[
\beta_2 = G_{20} + G_{21} \text{MS\_DURATION} + G_{22} \text{DUR}\_\text{PROBLEM} + G_{23} \text{DUR}\_\text{AVOIDANT} + u_{1j} \tag{level 2}
\]

The results of this model are presented in Table 3.3.

<table>
<thead>
<tr>
<th></th>
<th>G</th>
<th>Coeff.</th>
<th>SE</th>
<th>T-Ratio</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS duration</td>
<td>G01</td>
<td>-.007</td>
<td>.068</td>
<td>-.11</td>
<td>61</td>
<td>.916</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>G02</td>
<td>-.086</td>
<td>.046</td>
<td>-1.86</td>
<td>61</td>
<td>.068</td>
</tr>
<tr>
<td><strong>Depressive symptoms</strong></td>
<td>G03</td>
<td>.268</td>
<td>.046</td>
<td>-5.85</td>
<td>61</td>
<td>.000</td>
</tr>
<tr>
<td>Stress</td>
<td>G10</td>
<td>.200</td>
<td>.018</td>
<td>11.21</td>
<td>2887</td>
<td>.000</td>
</tr>
<tr>
<td>Stress_lag1</td>
<td>G20</td>
<td>.033</td>
<td>.010</td>
<td>3.42</td>
<td>2887</td>
<td>.001</td>
</tr>
<tr>
<td>Stress_lag1 x MS duration</td>
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<td>-.015</td>
<td>.005</td>
<td>-3.32</td>
<td>2887</td>
<td>.001</td>
</tr>
<tr>
<td>Stress_lag1 x MS duration x problem focused coping</td>
<td>G22</td>
<td>.002</td>
<td>.001</td>
<td>1.97</td>
<td>2887</td>
<td>.049</td>
</tr>
<tr>
<td>Stress_lag1 x MS duration x avoidant coping</td>
<td>G23</td>
<td>.003</td>
<td>.001</td>
<td>2.01</td>
<td>2887</td>
<td>.045</td>
</tr>
</tbody>
</table>

In this second model, significant main effect predictors of fatigue impact were same-week perceived stress, previous-week perceived stress, and baseline depressive symptoms. The relation of previous-week perceived stress to fatigue impact was moderated by disease duration and by the
interactions between problem-focused coping and disease duration, and between avoidant coping and disease duration.

*Model 2 main effects.* As in Model 1, higher levels of perceived stress in the same week, and the preceding week predicted higher levels of fatigue impact. The magnitude of the previous-week perceived stress relation to fatigue impact was lower than the magnitude of the same-week perceived stress relation to fatigue impact (see Table 3.3). Also, higher levels of baseline depressive symptoms predicted higher levels of fatigue impact.

*Model 2 moderation effects. Disease duration.* In order to understand the moderation relations, the researcher examined the region of significance for the simple slopes (Preacher, Curran, & Bauer, 2006). Similarly to Model 1, disease duration significantly moderated the relation between previous-week perceived stress and fatigue impact within two ranges of values: in the lower bound (between 1 and 12.04 years) and in the upper bound (between 16.44 and 31 years). The simple slope for the lower bound of disease duration was significant (B=.019, t=1.96, p < .05). Similar to model 1, the simple slope for the upper bound of disease duration was significant as well, but in a different direction (B=-.049, t=-1.96, p < .05; see Figure 3.5; Table 3.4).

Among those diagnosed more recently, the greater the stress in the previous week, the greater the fatigue impact in the current week. In contrast, among those with longer disease duration, the greater the perceived stress in the previous week, the lesser the fatigue impact during current week.
However, the moderator effect of disease duration on the perceived stress-fatigue impact relation should be interpreted with caution, as it was further specified by the 3-way interaction with problem-focused coping style and avoidant coping style.

Figure 3.5. Model 2. MS duration as moderator of the relation between previous-week perceived stress and fatigue impact

*Model 2 moderation effects. Disease duration by problem solving coping.* The moderation effect of disease duration by problem-focused coping on the relation between previous-week perceived stress and fatigue impact had a similar pattern to the one found in Model 1. As with the previous model,
in order to understand the three-way moderation relations, the researcher examined whether the simple slopes of the interaction terms are significantly different from 0 (Preacher et al., 2006). Among those who had been diagnosed more recently (1 to 12 years disease duration), a higher use of problem-focused coping (more than 1 standard deviation above the mean of problem-focused coping use in the present sample) was related to an increased magnitude of the effect of previous week perceived stress on fatigue impact ($B=0.021$, $t=2.23$, $p<0.05$). For the same group of individuals, a lower use of problem-focused coping approached significance ($B=0.017$, $t=1.69$, $p=0.09$; see Figure 3.6; Table 3.4).
Figure 3.6. Model 2. Problem-focused coping as moderator of the relation between previous-week perceived stress and fatigue impact for individuals with shorter disease duration

A lower use of problem-focused coping among those who had multiple sclerosis for a longer period of time (over 16 years) was related to a decrease in magnitude of the previous-week perceived stress-fatigue impact relation (B=-.060, t=-2.02, p<.05). Within the same group of individuals, the effect of a higher use of problem-focused coping among those who lived with MS for a longer time (more than 16 years) approached significance (B=-.037, t=-1.82, p=.07; see Figure 3.7; Table 3.4).
Figure 3.7. Model 2. Problem-focused coping as moderator of the relation between previous-week perceived stress and fatigue impact for individuals with longer disease duration

Model 2 moderation effects. Disease duration by avoidant coping.

Among those who have been diagnosed more recently (1 to 12 years disease duration), a higher use of avoidant coping strategies (more than one standard deviation above the mean of avoidant coping use in the present sample) was related to a greater magnitude of the effect of previous-week stress on fatigue impact ($B=0.021$, $t=2.12$, $p<0.05$). A lower use of avoidant coping among individuals who were diagnosed more recently had an effect approaching
significance on the relation between previous-week perceived stress and fatigue impact ($B=.018$, $t=1.80$, $p=.07$; see Figure 3.8; Table 3.4).

Figure 3.8. Model 2. Avoidant coping as moderator of the relation between previous-week perceived stress and fatigue impact for individuals with shorter disease duration.

Among those who had multiple sclerosis for a longer period of time (more than 16 years), a lower use of avoidant coping strategies was related to an increase in magnitude of the effect of previous-week perceived stress on the fatigue impact ($B=-.057$, $t=-2.14$, $p<.05$). A higher use of avoidant coping among those who lived with multiple sclerosis for a longer time had a similar
effect on the relation between previous-week perceived stress and fatigue impact, but only approaching significance ($B=-.040, t=-1.70, p=.09$; Figure 3.9; Table 3.4).

Figure 3.9. Model 2. Avoidant coping as moderator of the relation between previous-week perceived stress and fatigue impact for individuals with longer disease duration

A summary of all moderation effects is presented in Table 3.4.
Table 3.4. Moderator effects for the relation between perceived stress in the previous-week (predictor) and fatigue impact. Unstandardized coefficients and significance tests for simple slopes for the 2 way and 3 way interactions.

<table>
<thead>
<tr>
<th>Model</th>
<th>Region of moderator 1</th>
<th>Simple slope for moderator 2</th>
<th>Coeff.</th>
<th>SE</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 2-way</td>
<td>Shorter disease duration</td>
<td>--</td>
<td>.020</td>
<td>.010</td>
<td>1.96</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>Longer disease duration</td>
<td>--</td>
<td>-.086</td>
<td>.044</td>
<td>-1.96</td>
<td>.05</td>
</tr>
<tr>
<td>Model 1 3-way</td>
<td>Shorter disease duration</td>
<td>Lower PFC</td>
<td>.017</td>
<td>.011</td>
<td>1.60</td>
<td>.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Higher PFC</td>
<td>.021</td>
<td>.010</td>
<td>2.15</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>Shorter disease duration</td>
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<td>.051</td>
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<td>.02</td>
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<tr>
<td></td>
<td></td>
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<td>.037</td>
<td>-1.98</td>
<td>.04</td>
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<tr>
<td></td>
<td>Longer disease duration</td>
<td>Lower PFC</td>
<td>-.060</td>
<td>.030</td>
<td>-2.02</td>
<td>.04</td>
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<tr>
<td></td>
<td></td>
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<td>Model 2 2-way</td>
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<td></td>
<td>Longer disease duration</td>
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<td></td>
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<td>.010</td>
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<td></td>
<td>Shorter disease duration</td>
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<td></td>
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<td>Higher PFC</td>
<td>-.037</td>
<td>.020</td>
<td>-1.82</td>
<td>.07</td>
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<td></td>
<td>Shorter disease duration</td>
<td>Lower AC</td>
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<td>.010</td>
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<td>.07</td>
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<td></td>
<td>Higher AC</td>
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<td>.010</td>
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<td>.023</td>
<td>-1.70</td>
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</tr>
</tbody>
</table>

Note: PFC=problem-focused coping and AC=avoidant coping
Chapter 4 Discussion

At the outset of the current study, the prominence of multiple sclerosis as a major public health concern was highlighted and detailed. It was the intent of this study to advance the knowledge base regarding this debilitating chronic disorder. This study was successful in generating findings that explicate critical features of the relation between perceived stress and fatigue impact. It presents novel information in that it is the first study to use a year long weekly diary design to explore and yield findings regarding the relation between perceived stress and fatigue impact in individuals with relapsing remitting multiple sclerosis. Furthermore, it is the first study to explore the moderating role of coping on the perceived stress-fatigue impact relation from a developmental perspective, specifically from the motivational theory of life-span development perspective. Findings demonstrate that perceived stress is an important predictor of fatigue impact. The disease duration, as well as the differential role of coping strategies are shown to moderate this relation.

4.1. Study findings

4.1.1. Perceived stress – fatigue impact relation. As hypothesized, perceived stress was found to be a significant predictor of fatigue impact. Both same week, and previous week perceived stress had a positive relation with fatigue impact. Individuals who experienced higher levels of perceived stress as compared to their average levels of stress, also experienced higher
levels of fatigue impact as compared to their average levels of fatigue impact. In addition, higher levels of perceived stress experienced in the prior week, predicted higher levels of fatigue impact in the current week. Previous week perceived stress had an impact of a lesser magnitude than the same week perceived stress on fatigue. In other words, the level of stress an individual experiences during the current week, is related to the level of fatigue the individual experiences during the current week, as well as the week to come. The reverse relation, prediction of perceived stress from fatigue impact, was not significant except from measurements drawn from the same week. While this is just a correlational relation and cannot address causality issues, it does establish a temporal relation between stress and fatigue. Perceived stress is related to later fatigue impact, while fatigue impact is not related to later perceived stress. The present findings are important in clarifying the direction of the perceived stress-fatigue impact relation in individuals with multiple sclerosis.

Furthermore, the study adds to the literature on life events and relapses in multiple sclerosis. A meta-analysis conducted by Mohr, Hart, Julian, Cox, and Pelletier (2004) concluded that stressful life events are related to relapses in multiple sclerosis. The present study brings evidence that not only objective events are related to exacerbations of symptoms, but the personal perception of stress is associated with increase in specific symptom intensity, such as fatigue.
The life events considered in the studies included in Mohr and colleagues’ review (2004) are generally considered to be associated with high levels of distress; similarly the relapses are characterized by a constellation of MS symptoms usually of intensity large enough to create disability. The present study reveals that this relation between perceived stress and disease symptoms – fatigue impact in this case – exists also at lower levels of intensity. This finding is of great importance for generating specific therapeutic techniques targeting stress.

4.1.2. Disease duration. The hypothesis regarding the moderating role of disease duration on the perceived stress – fatigue impact relation was partially confirmed. No significant moderation by disease duration was found for the relation between concurrently measured perceived stress and fatigue impact. Perhaps disease duration was not found to be a significant moderator because there was no time elapsing between the endorsement of perceived stress and the endorsement of fatigue impact. Disease duration can be considered as a proxy for adaptive processes that may come into the individuals’ coping repertoire as the disease progresses. In order for such adaptive processes to mitigate the effect of perceived stress on fatigue impact, there must be a window of time, from the experience of stress to that of fatigue, in which they can act. Since both perceived stress and fatigue impact were measured at the same time, and there was no time window for adaptive processes to mitigate the effects of stress, these factors could not
have a significant effect on the relation between perceived stress and fatigue impact.

However, disease duration was found to be a significant moderator of the relation between perceived stress measured in the prior week and current week fatigue impact. For individuals who had MS for a shorter period of their life (for up to 12 years), the magnitude of the perceived stress – fatigue impact relation is higher than for individuals who lived with MS for a longer period of time (more than 16 years). This can be accounted for by the learning and adaptation process underwent by people living longer with the disease. Further, this effect was specified by the use of coping strategies.

4.1.3. Disease duration and coping mechanisms. The hypotheses regarding the effect of coping mechanisms on the moderating role of disease duration on the perceived stress – fatigue impact relation were partially confirmed. Problem-focused coping and avoidant coping were found to influence the effect disease duration has on the perceived stress – fatigue impact relation.

As hypothesized, for individuals with shorter disease duration (between 1 and 12 years), the use of avoidant coping was detrimental: perceived stress in the prior week predicted higher elevations in fatigue impact during the current week. Contrary to the hypotheses, for the same individuals, higher use of problem-focused coping was found to be detrimental as well: perceived
stress in the prior week predicted higher elevations in fatigue impact during the current week.

For individuals with longer disease duration (more than 16 years), as hypothesized, lower use of problem solving strategies is beneficial: perceived stress in the prior week predicted lower elevations in fatigue impact during the current week. Contrary to the hypotheses, for the same individuals, lower use of avoidant coping strategies was beneficial as well: perceived stress in the prior week predicted lower elevations in fatigue impact during the current week.

Some of these findings are consistent with the motivational theory of life-span development (Heckhausen & Schulz, 1995; Heckhausen, Wrosch, & Schulz, 2010). Some of the results regarding coping strategies provide support for the benefits of balancing engagement and avoidance of events, and adjusting the use of these coping strategies function of developmental level (disease duration in the case of a chronic illness).

Notably, the two coping mechanism are not correlated ($r = .09$). Most subjects in this study were middle-aged. According to the theory of life-span development (Heckhausen & Schulz, 1995; Heckhausen, Wrosch, & Schulz, 2010), during this period of life primary control capacity increases slightly, reaches a peak and then decreases slightly (in an inverse U shape). At the same time, the use of secondary control strategies (represented here by
avoidant coping) increase very slightly. This may explain why the results regarding the moderator effects of coping mechanisms are inconclusive.

4.1.4. **Depressive symptoms and fatigue impact.** A significant positive relation was found between baseline depressive symptoms and fatigue impact over the year. The baseline measurement of depressive symptoms was used as an indicator of the level of depressive symptoms throughout the year, as the measurements of depressive symptoms at baseline, at six month and 1 year are highly correlated and there are no significant differences among them (i.e., individual levels of depressive symptoms did not change significantly during the year that subjects participated in the study).

Individuals who endorsed higher baseline levels of depressive symptoms had more fatigue impact over the course of the year. This finding is consistent with the research on depression in multiple sclerosis. Studies have found depressive symptoms severity to predict fatigue severity for up to two years (Johansson, Ytterberg, Hillert, Holmqvist, & Koch, 2008; Patrick, Christodoulou, & Krupp, 2009; Schreus, de Ridder, & Bensing, 2002).

4.2. **Limitations**

The sample size of this study may represent a limitation to the generalizability of the study. The relatively high number of data points (50) ensured a high probability of finding the significant relations in the within-person part of design. However, for the between-person part of the design, a larger sample size could reveal other significant relations.
The composition of the sample poses several possible limitations for generalization of the results. The sample was composed mostly of women. While it was representative of the multiple sclerosis population, it did not allow for examination of possible gender differences in the role of coping on the perceived stress-fatigue impact relation. Due to low representation of men in this sample, the findings should be generalized with caution to men. Also, the study sample included only individuals with relapsing-remitting multiple sclerosis. While, for a first exploratory study, the homogeneity of the sample was a methodological gain, these results may not be generalizable to other types of multiple sclerosis (i.e.: primary or secondary progressive multiple sclerosis). In addition, the sampling strategy used in the present study allowed for a self-selection bias; participants volunteered for a time demanding study focused on their chronic disorder and the stress they experience. They may be different from the general population in their motivation to help others, their openness to talk about the disorder, their interest in talking about the stress in their lives, and their commitment to a one year long study. All these attributes may be associated with personal characteristics or levels of distress that may be different as compared to the general multiple sclerosis population. Participants in the study may experience higher levels of stress or more chronic stress (resulting in their interest and commitment to participate in a research study about stress) than other individuals with multiple sclerosis. This would mean that the relations
found in this study are present at a restricted range of experiencing stress, and it is unclear whether they would hold true at lower or less chronic levels of perceived stress.

In addition to the above detailed sample related limitations, there are several design related potential limitations that warrant discussion. Most fundamentally, the results of this study are correlational in nature, and do not answer questions of causality. While the significant effect of perceived stress on levels of fatigue impact is demonstrated by temporal analyses, it is not clear whether there is a latent factor (not measured in this study), which can affect both perceived stress and fatigue impact. All measures in the study are self-report and are vulnerable to reporting biases (i.e. social desirability, recall bias, etc.). Self-report measures are also vulnerable to the individual's interpretation or way of understanding the concepts or experiences probed by the questionnaires. In the case of perceived stress and fatigue impact, the relation found between the two may be partly influenced by the cognitive or experiential style of the respondent.

A year long weekly diary study is also vulnerable to observer-expectancy effect (Heisenberg effect). Even though the weekly diaries were filled out at home and were sent via mail, it is not implausible that participants might have perceived the experimenter as an “unseen” observer/audience of their distress and fatigue impact. Thus, over time, their perceptions, as well as
the reporting, of perceived stress and fatigue impact could have been
influenced by the observer-expectancy effect.

In this study, perceived stress and fatigue impact are measured as
state variables, while coping style is measured as a trait variable, at the
beginning of the study. Individuals may employ different coping strategies at
different levels of perceived stress or may change the type of coping style
over the course of a year. This design does not allow the researcher to
examine situation specific coping strategies.

4.3. Future research directions

Future studies are needed to address the limitations of the present
study and to further explore and expand the research questions addressed
here. Several ways of addressing the limitations presented here are
proposed. A larger sample of men within future studies will allow exploring
possible gender differences in perceived stress-fatigue impact relation and its
moderators. Inclusion of all disease courses will be beneficial in examining
possible differences by disease course in the perceived stress-fatigue impact
relation and its moderators. Inclusion of a wider age range of subjects with a
larger disease duration range will allow for a more accurate testing of the
motivational theory of life span-development.

A follow-up study with a similar longitudinal design in which coping
style is assessed as a time-variant measure - thus being able to look at the
fluid balance between the two coping strategies - could prove to be the next
logical step following the present study. Moreover it is important to explore types of stressors (i.e.: loss, conflict, disagreement, etc.) along with perceived stress. Such a design, would allow the researcher to explore situation specific coping style and any possible changes in coping style over time, or related to the level of perceived stress.

While the present study establishes a relation between perceived stress and fatigue impact, the possible pathways of this relation remain unknown. This research can be expanded by studies with complex design, including both psychological and physiological measures (e.g., immunological markers of fatigue), to start exploring some of the pathways for this relation.

3.4. Implications for health care professionals

Findings of this study will add to the extant body of stress-disease and coping literature in multiple sclerosis. It is hoped that this study will help the health psychology clinician by providing a more comprehensive understanding of the stress (distress) phenomena and adaptive ways of coping in individuals with multiple sclerosis. Specifically, it is important for clinicians to assess the client’s perception of stress (distress), rather than focus on objective life events. It is hoped that addressing both distress and depressive symptoms in multiple sclerosis clients will help impact their level of fatigue, which is one of the most debilitating symptoms of this chronic illness, and further will improve their quality of life.
It is also important for the clinician to consider coping processes from a life-span perspective. This study showed that a developmental framework needs to be employed in understanding coping processes in a chronic illness such as multiple sclerosis. The clinician should be mindful of the length of disease duration - particularly differentiating relatively newly diagnosed patients and patients who lived with MS for a longer time - and that differential use of coping style may be adaptive for different stages in the course of the illness. While, as a general rule, clinicians make efforts to help the client move away from avoidance to acceptance and problem solving, it is important to understand the functional value of avoidance and disengagement in some situations where the degree of disability does not allow for a satisfying level of control over the environment (primary control, active or problem-focused coping).

It is hoped that this line of research will continue, in order to further our understanding of processes that may alleviate some of the psychological and even physical symptoms of this chronic disorder and inform the development of specific treatment modalities, with the ultimate goal of improving the quality of life for individuals with multiple sclerosis.
References


