THE RELATIONSHIP BETWEEN SELF-REPORTED FATIGUE, FATIGABILITY, AND SLEEP QUALITY IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

By

Mayis Aldughmi

B.S. Jordan University of Science and Technology, Physical Therapy, 2011

Submitted to the graduate degree program in Rehabilitation Science and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

_____

Chairperson Catherine F. Siengsukon, PT, PhD

_____

Patricia M. Kluding, PT, PhD

_____

Jessie M. Huisinga, PhD

_____

Jeff Radel, PhD

_____

Jared Bruce, PhD

Date Defended: July 12th, 2016

The Dissertation Committee for Mayis Aldughmi

certifies that this is the approved version of the following dissertation:

THE RELATIONSHIP BETWEEN SELF-REPORTED FATIGUE, FATIGABILITY, AND SLEEP QUALITY IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

_____

Chairperson Catherine F. Siengsukon, PT, PhD

Date approved: July 19th, 2016

Abstract

The average lifetime cost of care for people with Multiple Sclerosis (PwMS) in the United States is approximately $2.2 million per person affected, and up to 80% of PwMS are unemployed within 10 years of disease onset. MS-related fatigue is a debilitating symptom experienced by around 90% of PwMS, it can significantly affect an individual's functional quality of life by interfering with activities of daily living (ADLs), causing reduced work performance, and contributing to loss of employment. MS-related fatigue is an umbrella term that encompasses the individual's perceptions of fatigue (*perceived fatigue*) and measurable deterioration in performance (*fatigability*). Perceived fatigue and fatigability interfere with the individual's efficient performance of physical and cognitive tasks and both should be considered during the assessment and management of MS-related fatigue. What further makes MS-related fatigue complex is that not only the disease process itself can cause fatigue, but also other prevalent comorbidities likely contribute to fatigue in MS such as depression and sleep disturbances. Therefore, the approach undertaken in the current body of research was under the notion that a multidisciplinary approach would seem best to optimally assess fatigue in PwMS.

Perceived fatigue in PwMS is measured using self-reported scales which are used extensively in the MS-related fatigue field of research. However, there have been recent concerns regarding the psychometric properties of commonly used perceived fatigue scales in PwMS. This is an issue as interpreting the findings of those previous studies is now somewhat difficult. The current study utilized a more psychometrically sound perceived fatigue scale that has been validated for use in PwMS, called the *Neurological Fatigue Index (NFI-MS).* What makes the NFI-MS a unique measure of perceived fatigue in PwMS is that to our knowledge, it

is the only perceived fatigue scale that includes two sleep components acknowledging the importance of considering sleep quality during the assessment of fatigue.

Chapter 2 attempted to explore the relationship between the NFI-MS and measures of physical and cognitive fatigability. Previous evidence showed conflicting results regarding the relationship between perceived fatigue and fatigability, as some showed associations while others did not. Fatigability is distinguished from perceived fatigue by the concept of change, i.e., a measurable difference in the performance of a task over a period of time. We initially hypothesized that there are certain items on the NFI-MS that objectify the performance ability of the individual and therefore can be associated with fatigability. A total of 52 ambulatory participants took part in this cross-sectional design study. Physical fatigability was measured using percent change in meters walked on the *Six Minute Walk Test* and percent change in force exerted on a repetitive maximal *hand grip test*. Cognitive fatigability was measured by *Response Speed Variability* on the *Continuous Performance Test*. The fatigability measures utilized in this study have been previously utilized before and where further modified in both administration and scoring in the current study to better capture fatigability in our study sample. Perceived physical and cognitive fatigue were measured using the NFI-MS. Current perceptions of fatigue were examined immediately before and after performing the fatigability measures using a 1-item *Visual Analogue Fatigue Scale*.

The results of Chapter 2 showed that cognitive fatigability was significantly associated with the NFI-MS physical domain and NFI-MS cognitive domain. However, physical fatigability was not associated with the NFI-MS. All participants demonstrated significantly higher perceptions of current fatigue after performing the physical and cognitive fatigability measures. The findings suggest that the NFI-MS appears to capture the cognitive aspect of MS-related

fatigue (meaning it captures both perceived cognitive fatigue and cognitive fatigability), but not the physical aspect (only captures perceived physical fatigue not physical fatigability), and the fatigability measures utilized were fatiguing to the participants which is a clinically important finding. We can conclude that both perceptions of fatigue and fatigability should be measured collectively for a comprehensive assessment of fatigue in PwMS.

Next, because an extensive body of evidence demonstrated a strong relationship between perceived fatigue and self-reported sleep quality, but conflicting results regarding the association between perceived fatigue and objective sleep quality; we aimed in Chapter 3 to explore the relationship between the NFI-MS and self-reported and objective sleep quality measures which have never been explored before. All participants filled out the *Pittsburgh Sleep Quality Index* to asses sleep quality, and the *Epworth Sleepiness Scale* to assess daytime sleepiness. To objectively quantify sleep quality, the participants wore an *actigraph* device on their dominant wrist for one week after the assessment day. The results indicated that higher perceived fatigue is significantly associated with poorer self-reported sleep quality and excessive daytime sleepiness, but not with objective sleep quality.

Our findings from Chapter 3 support previous research that showed higher perceived fatigue measured using other scales is associated with poorer self-reported sleep quality and daytime sleepiness. Regarding the lack of association between perceived fatigue and objective sleep quality, we argued that perhaps there is a limitation of actigraphy to accurately assess sleep in this sample, as evidence showed that the actigraph may overestimate sleep efficiency and total sleep time. Furthermore, actigraphy findings might be limited by wear time. Perhaps PwMS need to wear the actigraph for more than one week to accurately assess their sleep quality. A previous study that found significant associations between actigraphy and fatigue had the participants

wear the actigraph for two weeks. Based on our findings we encourage a wider use of the NFI-MS in clinical and research settings to assess and manage the role sleep quality has on perceived fatigue in the MS population.

The relationship between sleep quality and fatigability has never been explored before. Due to the involvement of central nervous system dysfunction mechanisms of both MS-related fatigue and sleep disturbances, and due to the evidence that shows a relationship between perceived fatigue and poor sleep quality, we hypothesized that there would be an association between higher physical and cognitive fatigability and poor sleep quality in our study sample. The results of Chapter 4 showed that several components of the Pittsburgh Sleep Quality Index and several actigraph parameters were significantly associated with physical fatigability and cognitive fatigability. We provide the first body of evidence showing the relationship between poor sleep quality and fatigability in PwMS. Fatigability is an important construct of MS-related fatigue that is a common debilitating symptom in the MS population, and more emphasis should be put on considering the role of sleep quality on exacerbating MS-related fatigue.

In summary, the work presented in this dissertation expands on the body of evidence showing the relationship between perceived fatigue, fatigability, and sleep quality in PwMS. Our experiments and findings are novel and significant through the use of the NFI-MS as a measure of perceived fatigue and through the assessment of the association between sleep quality and fatigability in PwMS. For a comprehensive and multidimensional assessment of MS-related fatigue, the measures used in this study can be easily administered in clinical and research settings. In addition, more emphasis should be put on considering the role of sleep quality on exacerbating MS-related fatigue in those with the mild-disease forms of MS. Around 70% of PwMS report some sort of a sleep disturbance, and up to 50% have a diagnosable sleep disorder.

Poor sleep quality in PwMS has been associated with a reduction in several quality of life indices, including physical function, psychological well-being, self-care, work ability, and interpersonal relationships. Clinicians and therapists may need to consider sleep assessment and treatment as part of the MS-related fatigue management plan.

Acknowledgements

Great many people have contributed to the production of this dissertation. I owe my gratitude to all those people who have made this dissertation possible and because of whom my graduate experience has been one that I will cherish forever.

I would like to express my sincere gratitude to my advisor Dr. Catherine Siengsukon for the continuous support of my PhD study and related research, for her patience, motivation, and immense knowledge. Her guidance helped me in all the time of research and writing of this dissertation. I could not have imagined having a better advisor and mentor for my PhD study.

Besides my advisor, I would like to thank the rest of my dissertation committee members: Dr. Patricia Kluding, Dr. Jessie Huisinga, Dr. Jeff Radel, and Dr. Jared Bruce for their insightful comments and encouragement, but also their constructive criticisms at different stages of my research that helped me focus my ideas and incented me to widen my research from various perspectives.

I would like to thank the PTRS department staff, faculty, and fellow PhD students past and present who where a great source of encouragement, hope, and support. It was a pleasure to know and work with each one of you. I would like to acknowledge Dr. Irina Smirnova whom I cannot thank enough for her support and guidance she has given to me and to the other students in our PhD program.

Many friends have helped me stay sane through these difficult years and were my family here in Kansas. Their support and care helped me overcome setbacks and stay focused on my graduate study. I greatly value their friendship and I deeply appreciate their belief in me.

None of this would have been possible without the love, support, and patience of my family. My immediate family to whom this dissertation is dedicated to, has been a constant source of love, support and strength all these years. **Dad**, **Mom**, **Rami**, and **Rasha** I love you all from the bottom of my heart and I dedicate this entire work for you. Without your constant support and encouragement despite the thousands of miles that kept us apart for years, I would have never accomplished what I am today. I would like to also express my heart-felt gratitude to my extended family that has aided and encouraged me throughout this endeavor.

Finally, I would like to thank my soon to be husband **Alaa**. You came into my life unexpectedly when I was still in the beginning of my PhD journey, and it was the best thing that happened to me. I believe that God sent you to me to encourage me, support me, laugh with me, cry with me, and most importantly push me towards reaching my goal. Thank you Alaa for being patient all these years, thank you for making the distance shorter, thank you for just being in my life. I love you and I cannot wait to spend the rest of my life with you.

The Prophet Muhammad (peace be upon him) said:
"*One who treads a path in search of knowledge has his path to Paradise made easy by God*"

Table of contents

Chapter 1.

Introduction

1.1. Specific aims and purpose of study

People with multiple sclerosis (PwMS) often experience a variety of symptoms. Fatigue is the most common symptom in multiple sclerosis (MS) experienced by 75% to 92% of PwMS and is difficult to treat.[1-3] Fatigue is considered one of the most debilitating symptoms of MS and can significantly affect an individual's quality of life, interfering with activities of daily living (ADLs), causing reduced work performance and contributing to loss of employment.[4-7] While the disease process itself can cause fatigue, other prevalent comorbidities likely contribute to fatigue in MS, including depression,[8-11] sleep disorders,[9,12-14] and cognitive impairments. Thus, MS-related fatigue is a multidimensional phenomenon.[9,15-17] Multiple self-reported scales are used to assess perceived fatigue in PwMS, but those scales are limited in their ability to adequately capture the multidimensional nature of fatigue.

Another important dimension of fatigue is fatigability,[18,19] which is defined as the magnitude of change in the performance of a physical or a cognitive task over a period of time.[18,19] Fatigability interferes with the individual's everyday life, as it diminishes the individual's ability to efficiently perform tasks that requires prolonged or effortful activity such as walking or engaging in a conversation.[19,20] Perceived fatigue and fatigability are different constructs, but they are related and both lie under the umbrella term of MS-related fatigue.[18,19] Hence, it is important to delineate the association between the two constructs.[19]

Sleep quality is further an important factor to consider in the assessment of MS-related fatigue. Sleep disturbances are common in PwMS[21,22] and are associated with an increase in the perception of fatigue by this population. [14,23] Improved sleep quality recently has been shown to be a relieving factor, and poor sleep quality as an aggravating factor of self-reported MS-related

fatigue.[24] However, no studies as yet give evidence if and how sleep quality contributes to fatigability.

The Neurological Fatigue Index (NFI-MS) was developed in 2010 based on a multidimensional definition of MS-related fatigue developed by Mills and Young in 2008,[24] specifically for use in PwMS.[25] Also, the NFI-MS is the only known self-reported MS-related fatigue scale that has a sleep component. Hence, the NFI-MS may provide a more efficient measure of MS-related fatigue. However, the relationship between self-reported fatigue as measured using the NFI-MS, fatigability, and objective measures of sleep quality has not been studied. Another unknown to be delineated is the concordance if any between the NFI-MS and other commonly used MS-related fatigue scales.

The **main purpose** of this study is to assess the relationship between perceived fatigue (also referred to as self-reported fatigue) using the NFI-MS, physical and cognitive fatigability, and sleep quality in PwMS. A **secondary purpose** of this study is to determine the level of agreement between the NFI-MS and other commonly used MS-related fatigue scales. Establishing and clarifying the relationship between the above factors as proposed in this study would serve as a basis to guide clinicians and researchers in their assessment and treatment of MS-related fatigue. The ultimate goal is better treatment for MS-related fatigue and a better quality of life for PwMS.

Specific Aim 1: to determine the relationship between self-reported fatigue, physical and cognitive fatigability, and sleep in PwMS We hypothesize that physical fatigability (measured using the Six Minute Walk Test (6MWT) and grip strength percent change) will make a significant contribution in explaining the variability of perceived fatigue as reported on the NFI-MS. We also hypothesize that cognitive fatigability (measured by the Continuous Performance

Test (CPT) response speed variability score) will make a significant contribution in explaining the variability on perceived fatigue as reported on the NFI-MS. We hypothesize that the sleep quality (measured by actigraphy and the Pittsburgh Sleep Quality Index) will make a significant contribution in explaining the variability on perceived fatigue as reported on the NFI-MS.

Specific Aim 2: To determine the level of agreement between the NFI-MS and other commonly used fatigue scales. We hypothesize that the NFI- MS will have sufficient agreement with the Modified Fatigue Impact Scale (MFIS) and Visual Analogue Fatigue Scale (VAFS) using Bland–Altman graphical analysis.

1.2. Overview of MS

Multiple sclerosis (MS) is a neurodegenerative disease characterized by the destruction of myelin in the axons of the brain and spinal cord.[26] Most common symptoms of MS include fatigue, progressive cognitive impairments, physical decline, and sleep disturbances.[11,27,28] MS affects 1/1000 individuals in the United States.[29] The average lifetime cost of care for PwMS in the united states is approximately $2.2 million per person affected, and the national annual cost is estimated to be over $6.8 billion.[30] Furthermore, 50-80% of PwMS are unemployed within 10 years of disease onset.[31] MS is a particularly devastating disease due to the early onset of symptoms, affecting the quality of life of these individuals.

1.3. Overview of MS-related fatigue

Reported by 75% to 90% of PwMS,[1-3] fatigue is the most common symptom experienced by PwMS. Around 40% of PwMS describe fatigue as their worst symptom.[32,33] Fatigue has been

shown to be related to a poorer quality of life, unemployment, and reduced ADLs in the MS population.[4,6,7,34]

MS-related fatigue (defined in section 1.4.) is an umbrella term that includes both perceived (self-reported) fatigue and fatigability.[19] Fatigability is the magnitude of change in the performance of a physical or a cognitive task over a period of time[19] (Discussed in sections 1.5 and 1.6). Perception of fatigue and fatigability are interrelated, and together negatively affects the individual's quality of life.[20] Evidence suggests that other prevalent factors associated with MS including sleep disturbances,[12] cognitive impairments,[15] and depression[8] also contribute to fatigue in PwMS.

The etiology of MS-related fatigue is poorly understood and is classified as primary or secondary depending on the cause.[19,35,36] Primary fatigue is caused by the disease itself through axonal loss and demyelination throughout the CNS.[38] Secondary fatigue is caused by factors or symptoms that accompany MS, such as sleep disturbances[12], depression[8], environmental factors[37], and medication use[38] (Figure

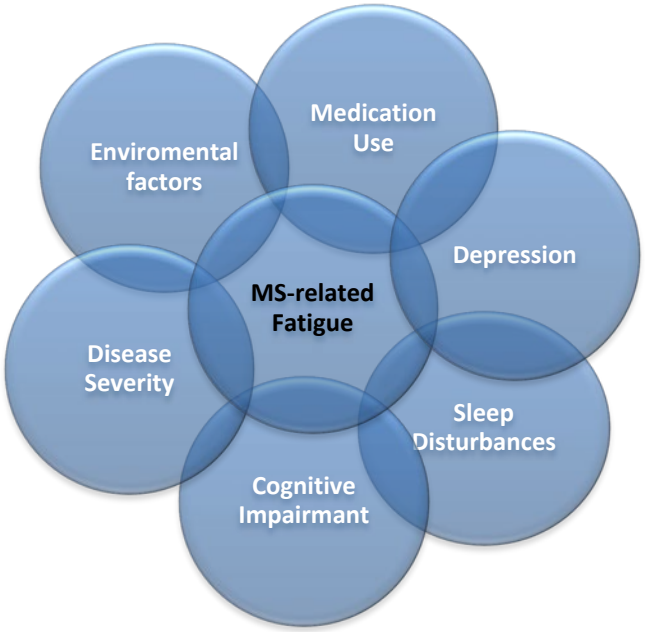


Figure 1. A diagram showing the interaction of contributing factors to MS-related fatigue

Due to the complex and multifactorial nature of fatigue, a multidisciplinary approach would seem best to optimally manage fatigue in PwMS.[39-42] A combination of pharmacological and/or non-pharmacological treatments are recommended in the fatigue management plan.[12,39,41] Medications such as Amantadine, Pemoline, and Modafinil are often used in an attempt to lessen fatigue and its effects in PwMS.[39,41] Several studies have employed non-pharmacological interventions to manage MS-related fatigue. Such interventions include education such as to avoid extreme weather conditions like heat and humidity, addressing lifestyle factors like diet and exercise, learning strategies for energy conservation, and adapting to work and household environments.[39,43-45] However, a recent review by Khan et al.[39] showed that the effects of both pharmacological and non-pharmacological treatments of fatigue in the MS population vary considerably, and that the best treatment option for MS-related fatigue is often difficult to determine.

1.4. Development of a definition of MS-related fatigue

While studies acknowledge the complexity, and multifactorial nature of MS-related fatigue, its clear definition has been lacking. Some of the current definitions for fatigue include the following: "*overwhelming sense of tiredness, lack of energy or feelings of exhaustion*";[46] *"difficulty initiating or sustaining voluntary effort"*;[47] *"feelings of physical tiredness and lack of energy distinct from sadness or weakness"*.[32] These definitions are incomplete and use simplified and unclear terms to describe the complex symptom of fatigue. Some of these definitions encompass the perceived nature of fatigue but neglect fatigability, such as *"overwhelming sense of tiredness, lack of energy or feelings of exhaustion"*. Another definition: "*difficulty initiating or sustaining voluntary effort",* includes only the fatigability component. None of the definitions listed mention anything pertaining to sleep quality. A complex symptom like fatigue requires a clear and comprehensive definition. Due to the multifactorial nature of fatigue in MS, an accurate definition of fatigue is one that would include the different factors that contribute to fatigue such as sleep quality and the individual's perception of fatigue as well as fatigability.

In an attempt to develop a clearer medical definition of fatigue, Mills et al. (2008)[24] conducted a two phase study. The first phase was a qualitative phase. Forty individuals with MS underwent a semi-structured interview and were asked to simply explain the term "fatigue". Themes were created out of these interviews, specific themes such as motor features, cognitive features, and sleep patterns. The motor features theme seeks to describe the physical component of MS-related fatigue, but the researches refer it to it as motor. For example, the participants, in general described fatigue as heaviness in their limbs that caused difficulty to sustain tasks like walking, worsening of coordination throughout the day, and, sometimes, speech difficulties. The participants described the cognitive theme as having difficulties concentrating on simple tasks

that became worse throughout the day, making mistakes when they were tired, and difficulty sustaining attention. Sleepiness and disrupted nocturnal sleep emerged as aggravating factors of perceived fatigue, while daytime sleep was seen as a relieving factor. The latter finding is important, as sleep has been found to be associated with MS-related fatigue in other studies (Refer to section 1.8.).

The second phase of the study by Mills et al was a quantitative phase in which the researchers developed a self-report symptom inventory consisting of 46 questions from the emergent themes created in the first phase. The inventory was sent to over 1200 individual with MS. After analyzing the inventories, the researchers developed the following definition of MS-related fatigue: *"a reversible, motor and cognitive impairment with reduced motivation and desire to rest, either appearing spontaneously or brought on by mental or physical activity, humidity, acute infection and food ingestion. It is relieved by daytime sleep or rest without sleep. It can occur at any time but is usually worse in the afternoon. In MS, fatigue can be daily, has usually been present for years and has greater severity than any premorbid fatigue"*. This definition provides a more comprehensive description of MS-related fatigue, focusing not only on perceived fatigue, but also on how disrupted sleep is an aggravating factor. The definition also includes fatigability as indicated by *"brought on by mental or physical activity"*.

In the development of the above definition, sleep emerged as an important factor associated with perceived fatigue as reported by the MS participants, both as an aggravating factor (disturbed nocturnal sleep) and as a relieving factor (sleep or rest during the day).[24] No other commonly used definition of MS-related fatigue includes a sleep component. Furthermore, the motor and cognitive features of the definition of MS-related fatigue by Mills et al. take into account both perceived physical and cognitive fatigue as well as physical and cognitive fatigability. This

explains why the self-reported NFI-MS was chosen as a primary measure of perceived fatigue in this study, because it was developed based on Mills et al. definition[24]. Furthermore, we believed that physical fatigability and cognitive fatigability measures might be well associated with the NFI-MS based on how the two constructs were considered during the development of the definition, as well as in the NFI-MS (the development of the NFI-MS is discussed in section 1.9.)

1.5. Perceived fatigue and fatigability

In healthy people, fatigue usually comes after prolonged activity, is a predictable symptom, and is resolved by rest.[19] However, MS-related fatigue is usually chronic, causes disability that interferes with activities of daily living, and is unpredictable.[19] MS-related fatigue negatively affects the individual's quality of life, interferes with physical and cognitive tasks, can occur every day, can be exacerbated by environmental factors, as is related to sleep quality.[4-7]

Kluger et al[19] recently introduced a unified terminology and taxonomy of fatigue.[18,19] Their approach distinguishes between fatigue as experienced and described by the individual with MS and fatigue as objectively quantified. The former is termed perceived fatigue; the latter is called fatigability.[19]

Perceived fatigue (or self-report fatigue) is reported by the individual as a lack of motivation and tiredness in performing physical and cognitive tasks and that interferes with activities of daily living.[18,48] Perceived fatigue is measured in many clinical fatigue studies using self-reported scales.[19,49,50] The self-reported fatigue scales can vary widely in how they measure perceived fatigue:[19] They can measure perceived fatigue in different domains (physical and cognitive), momentary vs. chronic perceptions of fatigue, and the severity and impact of fatigue

on function and daily life activities.[19,49,50] Most studies rely on the assessment of fatigue using self-report.[49-51] It is true that the perception of the individual is important to consider, and this is why a self-report scale in needed. However, one of the issues that arise in assessing fatigue is that most of the self-report scales do not capture the multidimensional nature of MS-related fatigue. In addition, assessing the perceptions of fatigue together with objective measures might be more sufficient to capture the multidimensionality of fatigue.[19,24]

Fatigability is the measure of change in the performance of physical or cognitive tasks over a period of time.[18,19] Fatigability objectively quantifies how much fatigue impacts the performance of several daily activities over time physically and cognitively.[19,20,52] Physical fatigability and cognitive fatigability are the two measurable domains of fatigability.[18,20,52] Physical fatigability is the measured change in the continuous performance of a prolonged physical task, such as repetitive or sustained movements and walking speed over a period of time. Cognitive fatigability is the change in the continuous performance of a prolonged cognitive task, such as ability to sustain the same efficient level of attention over time. Fatigability is distinguished from perceived fatigue by the concept of change, i.e., a measurable difference in the performance of a task over a period of time.[53] Fatigability objectifies the individual's perception of fatigue levels as a deterioration in performing activities, whether physical or cognitive.[19,20] Therefore, fatigability and perceived fatigue can be related but different constructs.

Development of the concept and classifications of fatigability is ongoing.[52] The definition and domain specification for fatigability that are used in this proposed study were introduced recently by Kluger et al. and other researchers.[18-20,52,53] Fatigability studies in PwMS have mostly looked at changes in hand grip strength across repetitive movements, change in walking speed across time, and changes in sustained attention over time.[54-60] Some studies have failed to

associate perceived fatigue and fatigability,[16,61,62] while others did show an association.[54-57] We believe that previous studies failed to establish a relationship because fatigue and fatigability are poorly understood and because the self-reported fatigue scales might not accurately capture the perception of fatigue in relation to change in performing physical or cognitive activities.

One of the main purposes of this study is to delineate the relationship between perceived fatigue, as measured using the self-reported NFI-MS, and fatigability as measured using change in performance on physical and cognitive tests. The physical and cognitive tests used in this study were modified in both administration and scoring to detect fatigability. This study explores the percent change scores in two physical tests, the six minute walk test (6MWT) and the grip strength dynamometer test. A change score was calculated between the number of meters walked by the participant during the last and the first minute on the 6MWT. A change score was also calculated between the last and the first trial of maximal force exerted in (Kg) on the grip strength dynamometer test. These methods to measure physical fatigability have been used in prior studies and are associated with self-reported physical fatigue in PwMS.[55,63] Change in response speed variability (RSV) over time is the main outcome criterion of cognitive fatigability in this study, using the computerized Continuous Performance Test (CPT), which measures sustained attention.[64] Change in RSV has been utilized in a previous study and was found to be associated with perceived cognitive fatigue by PwMS.[56]

1.6. Central and peripheral components of MS-related fatigue

MS-related fatigue has central and peripheral physiologic components.[18,19,47,65] Physiologically, central fatigue (refer to Figure 2) results from a reduced central drive from the motor cortex, axonal nerve impulse blockage in demyelinated neurons, loss of feedback centrally from the

muscle spindle afferents, disruption of non-motor pathways in the basal ganglia and the striato-thalamo-cortical fibers, and poor coordination between the firing of central nervous system (CNS) motor units.[18,47] Peripheral fatigue is the decline in excitation or the complete failure to excite muscles due to delayed conduction within the muscle itself, often due to changes in muscle tissue and deficits in the function of the neuromuscular junction.[18,47,66] Several studies have proposed that both perceived fatigue and fatigability in PwMS are central in nature due to physiological alterations in the CNS from the disease process,[9,19,47,67-69] although peripheral components may also contribute.[18,66,67] For this study, we are only considering central fatigue as it appears to be the largest contributor to MS-related fatigue (discussed as a potential limitation of study in chapter 5 section 5.3.4).

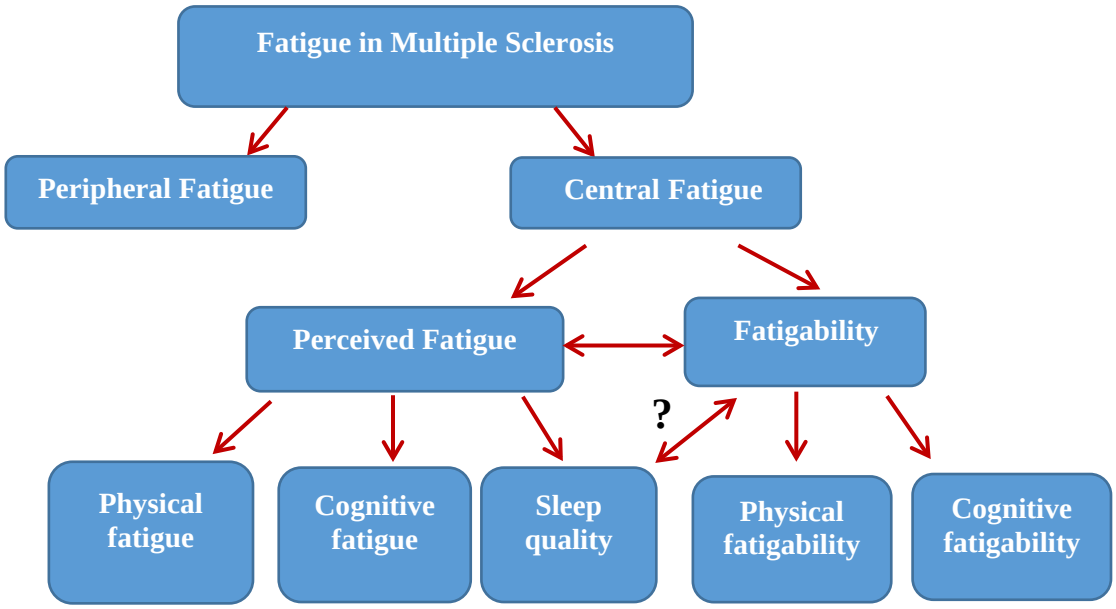


Figure 2. A diagram showing the components of MS-related fatigue

Neuroimaging studies[70-73] have showed an association between perceived fatigue measures and dysfunction in several brain regions in PwMS. A study by Filippi et al.[72] found a significant association between perceived fatigue and less cerebral activation in regions related to motor planning and cognition. A recent study by Wilting et al.[73] showed that in persons with early stage (< 10 years since diagnosis), relapsing-remitting MS, perceived cognitive fatigue is associated with microstructural changes, including altered molecular motion and cellular alignment within the fiber tracts, in several brain regions, but mainly in the thalamus. Perceived fatigue in PwMS has also been found to be associated with lesions in the areas and pathways associated with the limbic system and the basal ganglia.[47]

To our knowledge, no studies have yet been published that associate the fatigability measures utilized in the current study and specific brain regions or nerve fiber tracts in PwMS. However, a recent functional neuroimaging study showed that PwMS demonstrated a decline in the activation of cortical motor and non-motor regions during a sustained motor task compared to healthy controls, suggesting the involvement of central factors with physical fatigability.[74] In addition, neuroimaging studies found higher RSV is associated with dysfunction of the fronto-cortical networks and decreased white matter brain volume in other populations.[75] Nerve stimulation and transcranial magnetic stimulation (TMS) studies in healthy people have shown an association between physical fatigability and alterations in the excitability of the motor cortex and spinal cord.[76,77] Factors resulting in secondary fatigue, such as depression, have been shown to be associated with white matter brain lesions and dysfunctions in the temporal, frontal, and parietal areas, as well as in the limbic system.[78,79]

1.7. Physical and cognitive fatigability

Fatigability was described and defined in section 1.5. In this section details of the two fatigability constructs are discussed: physical and cognitive fatigability.

Physical fatigability is the reduced ability to complete sustained physical tasks, even in the absence of profound motor weakness.[47,80] Physiologically, physical fatigability is due to a dysfunction in the CNS that leads to a decline in muscle activity.[18,48,80,81] At the central level (in spinal cord), physical fatigability results from diminished coordination of spinal motor neurons, resulting in an increased feedback from muscle afferents, type 3 and 4 and loss of feedback from type 1 muscle spindles.[81] Details on how physical fatigability is measured and how the current study advanced those measures is discussed previously in section 1.5.

Cognitive fatigability is the reduced ability to efficiently sustain cognitive tasks, even when no profound cognitive dysfunction is present.[47] It is described as the inability to sustain concentration and attention during demanding cognitive tasks like following conversations or calculating numbers, resulting in diminished mental flexibility and decreased planning ability.[47,54,56,82] While there is no specific objective measure of cognitive fatigability, various cognitive tests have been proposed to detect cognitive fatigability, either by a different method of scoring or by repeated administration of tests.[54,56,83,84]

A proposed method for detecting cognitive fatigability is testing for a change in response speed variability (RSV) over time on the Continuous Performance Test (CPT). Previous research has shown that high RSV or high reaction time variability (RTV), are associated with self-reports of cognitive fatigue in PwMS[56] and in other like populations such as people with chronic fatigue syndrome.[85] Research suggests that persons with high RSV exert less alertness and attention on a cognitive task than people with normal responses.[56] Functional neuroimaging studies have shown

that response variability is associated with central factors such as disruptions in the thalamo-cortical circuits and a decrease in white matter.[75,86,87]

It is important to note that cognitive fatigue and cognitive fatigability are not that same as cognitive impairments.[88] Perceived cognitive fatigue and cognitive fatigability can occur in the absence of a cognitive impairment. [68,69] An individual with MS can achieve a high performance on a cognitive task but at the same time report high cognitive fatigue and fatigability. Evidence suggests that in PwMS, cognitive fatigue and fatigability can result from physiologic compensation processes in the brain to achieve high performance in cognitive tests. As a result of those compensation processes PwMS tend to experience higher fatigue to achieve the same level of performance compared to their healthy counterparts[73,89] The latter is supported by the finding that perceived cognitive fatigue is itself associated with pathways in the brain that mediate cognitive functions, specifically the striatal-thalamic-frontal network.[90-92] On the other hand, cognitive fatigability can become worse in the presence of a cognitive impairment.[88,93] More cognitively-impaired participants may develop cognitive fatigue more quickly or have higher cognitive fatigability, as they may require more time and effort to complete the tests.[94]

When assessing for cognitive fatigue and cognitive fatigability, one must consider the cognitive state of each participant. Severe cognitive impairments may interfere with the testing of cognitive fatigability and could be a confounding factor rendering results inconclusive. For the purposes of this study, those with severe cognitive impairments were excluded from participating.

1.8. Contribution of sleep to MS-related fatigue

Sleep problems in individuals with MS are very common. Approximately 50% of patients with MS have a diagnosable sleep disorder, and up to 67% report some sort of sleep disturbance.[21,22,95-98] Sleep disturbances and sleep disorders in PwMS have been overlooked by clinicians and researchers for years, and it is believed that a high percentage of PwMS have an unknown and underdiagnosed sleep disorder.[99-101] An article published by Attarian et al. in 2009[99] emphasized the importance of sleep quality in PwMS. The amount of published research on sleep in the MS population since that article was published has been doubled that done in the previous two decades.[102]

Sleep disturbances in PwMS are classified as either primary (caused by the disease itself), or secondary (caused by disease-accompanied factors such as pain, medication, anxiety, depression, and bladder problems).[36,102-104] Common sleep disorders diagnosed in PwMS, include insomnia, central or obstructive sleep apnea (OSA), restless leg syndrome (RLS), rapid eye movement (REM) behavior disorder, and narcolepsy.[21,105-107] Poor sleep quality has been associated with a reduction in several quality of life indices, including physical function, psychological well-being, self-care, work ability, and interpersonal relationships.[11] Evidence shows that poor sleep quality is an independent predictor of reduced quality of life in PwMS.[99,103]

Sleep quality is often measured subjectively using self-reported scales. The Pittsburgh Sleep Quality Index (PSQI) is most commonly used.[108] The PSQI provides a global self-reported sleep quality measure of the individual's sleeping habits over one month. The PSQI also provides separate scores for seven different sleep components: use of sleep medication, sleep duration, habitual sleep efficiency, day-time dysfunction, sleep latency, sleep disturbances, and sleep quality. A global score of more than 5 on the PSQI reflects poor sleep quality across all age groups.[108] Another construct of sleep quality that is important to consider is daytime sleepiness.

A common self-reported scale used to measure daytime sleepiness is the Epworth Sleepiness Scale (ESS). [109] In the ESS the participants rate how likely they would doze off in eight different scenarios of daily activities. The eight ESS items use a 4-point Likert scale in which a higher score indicates higher daytime sleepiness. Both the PSQI and the ESS were used in this study as measures of self-reported sleep quality.

To better characterize the individual's sleeping habits, objective measures of sleep quality are needed.[110] The "gold standard" objective measure of sleep quality is polysomnography (PSG).[111] PSG provides a detailed overlook of the individual's sleep quality and sleep stages, and is often used to diagnose sleep disorders such as OSA.[112] Actigraphy[113] is another objective measure used extensively in sleep research. Actigraphy uses a watch-like device, an accelerometer worn on the wrist to record the participant's sleep/wake cycle and circadian rhythms over a specified time frame. The actigraph has advantages over the PSG in that it costs less, portable, and records data in the subject's natural sleep environment over multiple nights in a row. In the current study the actigraph was used to measure sleep quality over seven consecutive nights.

Evidence demonstrates that sleep disturbances are associated with an increase in perceived fatigue in the MS population.[13,14,102,105,114-116] Those studies suggest that the presence of sleep disturbances causes excessive activation of the CNS which, in turn, exacerbates MS-related fatigue. The excessive activation of the CNS may result from recurrent sleep arousals, and central mechanisms such as lesions on the suprachiasmatic nucleus in the hypothalamus that regulates circadian rhythms.[115,116] In addition, MS-related fatigue is mediated by an increase in the activity of pro-inflammatory cytokines in the cerebrospinal fluid,[117-119] an increase in the activity of similar pro-inflammatory cytokines are also associated with sleep disturbances.[118,120]

Thus, MS-related fatigue is associated with an increased incidence of sleep disturbances in PwMS. A recent study by Veauthier et al.[121] demonstrated that individuals with MS who were treated for sleep disorders had significantly lower perceived fatigue than those who did not receive treatment for their sleep disorders. In the current study, persons with diagnosed but untreated sleep disorders are not included in this study, since the presence of an untreated sleep disorder would be a confounding factor. A limitation of the current study is the inclusion of participants with undiagnosed sleep disorders (discussed as a potential limitation of study in chapter 5 section 5.3.3).

Several studies have investigated the association between sleep quality and perceived fatigue in PwMS using either self-reported sleep quality measures like the PSQI and ESS[13,102,105,114-116,122,123] or objective measures like actigraphy.[105,124-126] Using actigraphy, Attarian et al.[105] demonstrated that fatigued PwMS have more disturbed sleep wake cycles than those who are not fatigued. Furthermore, several studies[13,14,127,128] showed a significant relationship between perceived fatigue and the presence of a sleep disorder, like narcolepsy, OSA, RLS, and REM sleep behavior disorders. These studies have also found that perceived fatigue is associated with an increased number of nocturnal arousals and decreased sleep efficiency.[13,14,127,128] Strober et al.[102] recently developed a model to predict fatigue in PwMS using variables that include sleep disturbances, disease duration, and depression. Sleep disturbance was the most significant predictor of fatigue in PwMS, accounting for 25% of the variance followed by depression. In summary, sleep disturbances clearly impact fatigue in people with MS.

Most of the previously mentioned studies[13,14,23,119] that showed a relationship between sleep disturbances and perceived fatigue used the Modified Fatigue Impact Scale (MFIS) as the measure of perceived fatigue. This research highlights the importance in assessing sleep in

conjunction with fatigue either by a self-report measure or by admission to a sleep lab or use of Actigraphy to objectively assess sleep. Therefore, we believe that establishing a relationship between objective and self-reported sleep quality and perceived fatigue using the self-reported NFI-MS would provide support the NFI-MS is a more efficient way to explore the effects of sleep quality on perceived fatigue. As to our knowledge, the NFI-MS is the only validated scale that measures how sleep impacts fatigue in PwMS.

1.9. Other contributing factors to MS-related fatigue

The following section discuss the secondary factors that contribute to MS-related fatigue. Those factors are important to consider in both the assessment and management of MS-related fatigue.

1.9.1. Depression

Depression is very common in PwMS, affecting almost half of the MS population. [129,130] Several studies have found an association between depression and fatigue and have shown that depression must be controlled for when assessing MS-related fatigue. [9-11] As fatigue can also be a symptom of depression,[131] both may clinically overlap, especially in PwMS.[10] Therefore, To the use of a depression scale that lacks fatigue-related questions has been recently recommended when attempting to measure depression in PwMS.[9] The use of a depression scale with fatigue-related questions may show a significant, but inaccurate correlation between depression and MS-related fatigue, skewing study results and their interpretation.[9] In this study, depression is controlled for as a covariate in the analysis. Depression was measured in this study by asking participants to complete the Beck Depression Inventory-Fast screen (BDI), [132] which lacks fatigue-related questions.

1.9.2. Other Factors: Disease severity, subtype, pain, anxiety

Other factors may contribute to MS-related fatigue. Disease severity has been studied extensively in the MS-related fatigue research. However, results conflict regarding the association between disease severity and MS-related fatigue. Some studies have found a relationship between fatigue and disease severity as measured by the Expanded Disability Status Scale (EDSS),[133-138] but other studies have not.[78,139-141] Disease severity may be a possible confounding factor and is used as a covariate in the analysis in this study.

MS subtype may contribute to MS-related fatigue. Fatigue has been associated with more severe forms of progressive MS.[137,142] Pain has also been found to exacerbate fatigue in the MS population.[133,139] Medication use is suggested as another contributing factor to MS-related fatigue.[3,116,138,143,144] Poly-pharmacy, side effects of medications, like pain killers, and immunosuppressive therapies, particularly interferon- β use, increase fatigue in the MS population. Cognitive impairment is also suggested as a contributing factor.[9,90-92] In addition, psychological factors, such as stress and anxiety, serve to increase fatigue in individuals with MS.[145-147] In this study we gathered information regarding disease severity, MS type, medication us, and anxiety. Those with severe forms of MS, who cannot ambulate independently with or without an assistive device, were not included in this study.

1.10. Commonly used perceived fatigue scales in MS

Several self-report scales are used in research and clinical settings to assess perceived fatigue.[49,50] The most commonly used fatigue scales are the Modified Fatigue Impact Scale (MFIS),[148] the Fatigue Severity Scale (FSS),[149] and the Visual Analogue Fatigue Scale (VAFS).[150] Despite the fact that the Multiple Sclerosis Council for Clinical Practice Guidelines

advocated further psychometric evaluation of the MFIS to establish its validity,[151] researchers continue to use the scale despite its lacking a proper psychometric evaluation.[152] The MFIS[148] consists of twenty-one items divided into three components: physical, cognitive, and psychosocial. A higher score indicates a greater level of fatigue. The FSS[149] consists of nine questions; and again, a higher score denotes more fatigue. Although the MFIS and FSS are commonly used scales, they have some disadvantages as well, as revealed by the Rasch model analysis. The VAFS[150] is a single item scale; the individual marks a number that best rates his/her current perceived fatigue. The VAFS is considered very simple and easy to use, and, unlike the aforementioned scales, the VAFS measures current fatigue, i.e., how much the person is fatigued at the moment.

The Rasch model analysis[153,154] is a statistical analysis that uses a psychometric approach to develop and refine patient reported outcomes. The concept behind the Rasch model is that a participant's response to items on a scale eventually produce linear measurements. In other words, the Rasch analysis is uni-dimensional; it measures both the participant's ability to answer an item and the difficulty of that item under the same construct. For example, on an accurate fatigue scale, a person who's highly fatigued would be able to distinguish and affirm items expressing high levels of fatigue.[154,155]

The FSS does not fit the Rasch model.[156] Certain items on the FSS interact, and their removal improves its psychometric properties and accuracy. In addition, evidence reveals how the FSS is not sensitive enough to capture the multidimensional nature of MS-related fatigue in studies using the scale as a main outcome measure.[157,158]

The MFIS also does not fit the Rasch model.[159] The different components of the scale, i.e., items on the cognitive subscale and items on the physical subscale interact and affect the scale's

accuracy and the interpretation of its results. Specific items from the physical and cognitive components of the MFIS should be removed for the scale to fit the Rasch model. Also, the psychosocial component should be totally eliminated because it interacts with the physical component. Rasch analysis of the MFIS renders the total score of the MFIS invalid and thus compromises the findings of previous studies that used the scale's total score. In addition, Larson et al. in 2013[152] argue that future studies are needed to solve several other issues affecting the MFIS. For example, the MFIS fails to distinguish adequately between the different constructs of sleepiness/alertness and fatigue affecting the interpretation of results obtained by use of the MFIS.[152]

The MFIS has been used to examine the associations between physical fatigability and perceived physical fatigue.[55,57] Results vary between studies. When the change in walking speed is used as a measure of physical fatigability, an association between perceived physical fatigue as indicated on the MFIS and physical fatigability is established.[55] But when change in grip strength is the criterion used to assess physical fatigability, researchers find no association between physical fatigability and perceived physical fatigue.[57] Studies using the MFIS to measure cognitive fatigability also show conflicting results. [15,54,83,160] As there are no established objective measures of cognitive fatigue, previous studies attempted to use cognitive tests to quantify cognitive fatigability, mostly tests of information processing speed and attention have been used.[15,54,83,160] However, we believe that its either because the MFIS does not accurately capture cognitive fatigability or perhaps the cognitive tests used in those studies are not specific in measuring cognitive fatigability, most of the attempts to associate perceived cognitive fatigue via the MFIS and cognitive fatigability were not successful.[15,54,83,160]

1.11. Development of the NFI-MS

This section provides an overview of the development of the NFI-MS highlighting the reasons for choosing the NFI-MS to assess perceived fatigue over commonly used scales for the current study.

Mills et al.[24] have developed a definition for MS-related fatigue (Section 1.4.). The same researchers have expanded their work following guidelines from the Food and Drug Administration (FDA)[161] for developing outcome measures and the standards of the Rasch model analysis[154] for developing patient reported outcomes. The FDA created specific guidelines[161] for researchers in clinical trials that aim to develop new patient reported outcomes. Those guidelines include identifying both the specific domains to be measured and the population of interest, generation of adequate domains, and clearly stating the method of data collection.

The Neurological Fatigue Index (NFI-MS)[25] was developed in 2010 following the second quantitative phase of the effort by Mills et al. to define MS-related fatigue (Section 1.4.). After the collection of the 46 questions from the MS individuals, a draft scale was developed by a multidisciplinary team of neurologists specialized in the treatment of MS, MS-specialized nurses, physical therapists, occupational therapists, rheumatologists, and a specialist in sleep medicine. To identify wording issues, the draft scale was sent to fifteen PwMS for their feedback. Revisions were made based on the feedback, and the revised draft scale was mailed to 1223 PwMS to complete. Questions on demographics, disease information, and other fatigue scales (FSS, MFIS, VAFS) were also sent for completion to facilitate comparative analysis.

The NFI-MS has been validated for use in PwMS using external construct validity and has been shown to have good test-retest reliability (more than 0.7 for all the scales) and a relatively small minimal clinically important difference (MCID).[162] Less than 10% of scale range for all

components. These findings show that the NFI-MS scores accord with the participant's perception of fatigue. The correlation analysis of each component with the other commonly used scales, the MFIS,FSS, and VAS evidences moderate to strong correlation, ranging from r= 0.4 to r= 0.7. Furthermore, the NFI-MS meets the standards of a fundamental outcome measure since the scale follows the Rasch model analysis, Thus, the NFI-MS is more suitable for parametric statistical tests than scales that do not fit the Rasch model[25], such as the MFIS[159] and the FSS.[156]

In addition, the NFI-MS has certain items that seem to reflect both physical and cognitive fatigability: *"The longer I do something the more difficult it becomes"*; *"My coordination gets worse as the day goes on"; "Mental effort really takes it out of me"*. Statements such as these demonstrate a deterioration of performance on effortful physical and cognitive activities over time. The NFI-MS is the only perceived fatigue measurement tool that has a separate two sleep-related component. The sleep components of the NFI-MS measure the effect of sleep on fatigue in two different aspects: relief of fatigue by diurnal sleep or rest, and exacerbation of fatigue due to abnormal nocturnal sleep and sleepiness. The NFI-MS is based on Mills et al.'s definition of MS-related fatigue[24] (Section 1.4), and so outline the different aspects of sleep quality and their relation to perceived fatigue.

In summary, the self-reported NFI-MS seems to capture the multidimensional aspects of perceived fatigue and also, as well as possible, fatigability by assessing physical, cognitive, and sleep-related contributions to perceived fatigue.

1.12. Significance of this research

Fatigue is the most common symptom in multiple sclerosis, experienced by up to 90% of MS patients, and is often difficult to treat.[33,36,163] MS-related Fatigue negatively affects the quality of life of these individuals and has a profound economic impact as it is associated with a

reduced work load and high unemployment rates.[5,7] Evidence shows that MS-related fatigue can lead to people with MS quitting their jobs and becoming home-bound which negatively impacts interpersonal relationships and income.[164-167] Social interaction is also compromised due to fatigue leading to psychological distress, stress, and anxiety.[6] Both perceived fatigue, fatigability, and disrupted sleep quality interfere with the performance of ADL such as simple house-hold activities, cause deterioration in the performance of effortful physical and cognitive tasks, and lead to the loss of function and the worsening of other symptoms.[4,19,20,168]

Although a wide variety of self-reported scales of perceived MS-related fatigue are in use,[169] no consensus exists on the best clinically relevant, reliable, and responsive outcome measurement tool.[36,170,171] In addition, no clearly established measure of fatigability exists, perhaps due to the poor understanding of how fatigability results and whether perceptions of fatigue are related to it or not. The latter explains why recent research acknowledges that establishing an association between fatigability and perceived fatigue has been difficult.[19] Whether perceived fatigue and fatigability are associated or not, considering both during the assessment and management of MS-related fatigue is crucial. In recent clinical research, a unified multidimensional approach to measure fatigue is recommended, so it seems that a better approach to measure MS-related fatigue includes both perceived fatigue and fatigability.[19,20]

Considering sleep quality as part of the comprehensive assessment of MS-related fatigue also makes this study significant. Sleep disturbances affects almost 50% of PwMS,[21,22,95] and there is extensive evidence that disturbed sleep is highly associated with increased perceived fatigue in the MS population.[13,14,71-74] In addition, to our knowledge no previous study attempted to explore the relationship between sleep quality and fatigability. Recently there has been

recommendations encouraging the need to assess both sleep and fatigue in the MS population for more accurate sleep quality assessment and more affective fatigue management in PwMS.[13,14,23]

To date, no study has collectively assessed physical fatigability, cognitive fatigability, and sleep quality objectively, and then attempted to explore the associations between these factors with perceived fatigue in the MS population.[54,99,172] In the latter studies, perceived fatigue was measured using other scales like the FSS and the MFIS. The researchers who developed the NFI-MS, Mills et al., have explored the relationship between perceived fatigue using the NFI-MS and other clinical features of MS.[122] The researchers correlated the NFI-MS with subjective measures of depression, anxiety, motor function, and sleep quality. However, no fatigability measures of any component were used in the study. Also, sleep quality was quantified by self-estimation of the participants only; they estimated the duration of both nocturnal and diurnal sleep. A self-report measure, such as a well-known standard self-reported scale, was not used, nor were objective measures of sleep. Our study seeks to remedy the limitations of the above studies and to further elucidate the relationship between sleep quality and MS-related fatigue.

A more comprehensive assessment of MS-related fatigue will improve the ability of clinicians to determine the impact of interventions directed toward treating that fatigue. In addition, a better understanding of which specific factors significantly contribute to an individual's fatigue would allow clinicians to more narrowly target treatments to those specific factors. Showing in this study that reduced sleep quality and the other factors of physical and cognitive fatigability are highly associated with perceived MS-related fatigue encourage the development and use of interventions to improve sleep quality, thereby reducing MS-related fatigue. Physical and cognitive training paradigms that increase both physical and cognitive stamina may be developed lessening MS-related fatigue. For example, studies that have assessed

the impact of exercise on fatigue have had mixed results. However more accurate outcome measures of fatigue may clarify the relationship.[156-159,173]

Fatigability and sleep quality can be easily assessed in research and clinical settings using the modified measures employed in this study. Establishing and clarifying a relationship between perceived fatigue, fatigability, and sleep quality will foster the understanding of MS-related fatigue and will guide both researchers and clinicians to better and more accurately assess, measure, and eventually target treatments of MS-related fatigue.

In summary, this study is significant because to our knowledge there has been no previous attempt to establish a multidimensional approach in measuring MS-related fatigue, using measures of perceived fatigue as measured using the NFI-MS, objective measurements of fatigability, and sleep quality. Establishing a comprehensive assessment of MS-related fatigue and understanding what factors contribute to this complex symptom, will eventually guide clinicians toward more effective treatments of MS-related fatigue. This would dramatically impact the quality of life of PwMS and would reduce the overall cost of a lifetime of care for these individuals.

Chapter 2.

The relationship between fatigability and perceived fatigue measured using the Neurological Fatigue Index in people with MS

Submitted to *International Journal of MS care*-July 8th-2016

Co-authors: Jared Bruce, PhD, Catherine Siengsukon, PT, PhD

2.1. Abstract

Background: Perceived fatigue and fatigability are components of MS-related fatigue. Understanding the relationship between these two constructs could lead to more effective interventions to manage MS-related fatigue. However, the relationship between physical and cognitive perceptions of fatigue measured using the Neurological Fatigue Index (NFI-MS), which is a psychometrically accurate measure of perceived fatigue in people with multiple sclerosis (PwMS), and physical and cognitive fatigability in PwMS is unknown. **Objective:** To explore the relationship between the NFI-MS and physical and cognitive fatigability in PwMS. **Methods:** Fifty-two participants **(**mean age: 46.8 ± 10.1) completed the study. Physical fatigability was measured using percent change in meters walked on the 6MWT and percent change in force exerted on a repetitive maximal hand grip test. Cognitive fatigability was measured by Response Speed Variability (RSV) on the Continuous Performance Test (CPT). Perceived physical and cognitive fatigue were measured using the NFI-MS. Current perceptions of fatigue were examined immediately before and after performing the fatigability measures using a 1-item Visual Analogue Fatigue Scale (VAFS). **Results:** Cognitive fatigability was significantly associated with the NFI-MS physical domain ($r = .326$, $p = .020$), and NFI-MS cognitive domain ($r = .276$, $p = .05$). However, physical fatigability was not associated with the NFI-MS. Participants demonstrated significantly higher perceptions of current fatigue after performing the fatigability measures ($p \leq .001$). **Conclusions:** The NFI-MS and the fatigability measures utilized in this study are easy to administer. We encourage a wider use of those measures in clinical and research settings for a comprehensive assessment of MS-related fatigue.

2.2. Introduction

Fatigue is the most debilitating symptom of Multiple Sclerosis (MS).[1] It interferes with daily function, affects work load, and hampers interpersonal relationships, often leading to reduced quality of life.[7] MS-related fatigue is multidimensional consisting of different components such as perceived physical and cognitive fatigue and fatigability,[146] and results from disruptions in cortico-subcortical brain regions[174] as well as due to other comorbidities, such as depression[10] and cognitive impairments.[9]

A recent study by Kluger et al.[19] introduced a unified taxonomy to guide the assessment and management of fatigue in neurologic populations. The taxonomy distinguished between fatigue that is perceived by the individual, referred to as "perceived fatigue," and fatigue that can be objectively quantified by the researcher or clinician, referred to as "fatigability." Perceived fatigue in people with MS (PwMS) is defined as a lack of motivation and/or sense of tiredness that makes it difficult to efficiently perform daily physical and cognitive tasks.[18,48] Perceived fatigue can be measured using a variety of self-report scales.[19,49,50] These self-report measures differ widely in how they gauge perception of fatigue and measure perceived fatigue under different constructs, such as physical or cognitive, or as momentary vs. chronic.[19,49,50] Researchers frequently use the Modified Fatigue Impact Scale (MFIS)[151] to assess MS-related perceived fatigue.[148] However, a recommendation from the Multiple Sclerosis Council for Clinical Practice Guidelines suggests that the MFIS needs further psychometric evaluation.[152] The MFIS does not fit into the Rasch model analysis,[159] which uses a psychometric approach to develop and refine patient-reported outcomes, and renders the score of the MFIS invalid. This might partially explain the conflicting results in prior studies that attempted to explore the relationship between perceived fatigue assessed using MFIS and fatigability in PwMS.[55,60]

Fatigability is defined as a measure of change in the performance of a physical or a cognitive task over time[18,19] and can be objectively quantified by the clinician or researcher. There is no established measures of fatigability, and research is ongoing in terms of the measurement and classifications of fatigability.[52] Previous studies have attempted to measure fatigability in PwMS in two ways: *physically,* through changes in walking speed or repetitive maximal upper and lower limb contractions over time, and *cognitively,* through changes in cognition over a period of time.[54-60,175] Perception of fatigue can be related to fatigability if items in the self-report measure objectify the individual's perception of fatigue levels as a deterioration in performing physical or cognitive activities.[19,20] Nevertheless, fatigability is generally distinguished from perceived fatigue by the concept of change (a measurable difference in the performance of a task over a period of time)[53] and how it is measured (quantified by clinician/researcher vs. reported by patient).

Mills et al. developed the Neurological Fatigue Index (NFI-MS) to assess perceived fatigue in PwMS.[25] The NFI-MS fits the Rasch model analysis, was developed following guidelines from the Food and Drug Administration (FDA)[161], and has good external validity compared to commonly used scales in MS (MFIS and the Fatigue Severity Scale (FSS)). This makes the NFI-MS more psychometrically sound than commonly used fatigue scales in measuring perceptions of fatigue in PwMS.

The relationship between perceived fatigue assessed using the NFI-MS and physical and cognitive fatigability is unknown in PwMS. Therefore, the main aim of this study was to explore the relationship between perceived fatigue, as measured using the NFI-MS, and physical and cognitive fatigability in PwMS. Both perceived fatigue and fatigability interfere with the performance of household activities, can lead to deterioration in the performance of physical and

cognitive tasks, and can worsen other symptoms, such as depression, sleepiness, and attention related problems.[4,19,20,168] Understanding the relationship between fatigability and perceived fatigue could lead to more effective interventions to address these constructs and may encourage a wider use of these measures in clinical and research settings.

2.3. Methods

This study was performed in accordance with the University of Kansas Medical Center's (KUMC) Institutional Review Board. The inclusion criteria include: (1) 18-60 years of age, (2) relapsing remitting or secondary progressive[176], (3) able to ambulate with or without an assistive device, and (4) score > 24 on the Mini Mental Status Exam (MMSE)[177]. The exclusion criteria include: (1) history of alcohol/drug abuse or nervous system disorder other than MS, (2) severe physical, neurological, or sensory impairments that would interfere significantly with testing, (3) developmental history of learning disability or attention-deficit/hyperactivity disorder, (4) relapse and/or corticosteroid use within four weeks of assessment, (5) known untreated sleep disorder (such as sleep apnea) (6) uncorrected vision loss that would interfere significantly with testing, (7) acute ischemic cardiovascular event or coronary artery bypass surgery less than 3 months ago, and (8) uncontrolled blood pressure with medication (BP > 190/110mmHg). PwMS were recruited to participant in this study at the MS clinic located at KUMC and through personal referral from participants and physicians. Informed consent was obtained from all participants.

Fifty-two participants completed the study procedures. Medical history, medication usage, and demographic characteristics were obtained from the participants. Prior to testing, participants were asked to refrain from taking medications other than what they typically take and consuming caffeine beyond their typical daily consumption. Participants were instructed to

refrain from exercise for 24 hours prior to testing. On the day of the assessment, participants first completed a battery of self-reported questionnaires and then the fatigability measures which were randomized in order.

Perceived fatigue was measured using the NFI-MS.[25] The NFI-MS[25] is a validated scale for use with PwMS that assesses perceptions of fatigue during the past two weeks. It consists of 23 questions, each on a Likert scale from 0-3, with higher score indicating more fatigue. The NFI-MS measures perceived fatigue under three domains: physical, cognitive, and sleep quality. It also consists of a summary scale that includes both the physical and cognitive domains. For the purposes of this study, only the physical domain, cognitive domain, and summary score were used in data analysis. A validated ordinal to interval transformation of the raw scores of the NFI-MS that was developed by Mills et al. was used.[25]

Physical fatigability was measured using the Six-Minute Walk Test (6MWT) and a grip strength test. The 6MWT is a frequently used measure of physical performance and endurance.[178] It has been previously modified in administration and scoring to assess physical fatigability in PwMS.[55,60,172,179] The version used in this study was utilized by Goldman et al.[55] Specifically, instructions regarding permitted rest and encouragement phrases were eliminated and instructions regarding speed were emphasized. The administration was further modified for the current study by eliminating reminders every minute of how much time was remaining, and the participants were not informed that they would be walking for six minutes. Participants were instructed to walk as fast and as safe as they could back and forth along a 15-meter path marked with tape in a hallway. A cone marked the turn-around at each end. The tape was marked with a red marker every one meter to ease calculating the distance walked. Participants were allowed to use their assistive device if they used one for community ambulation. During the test, the

administrator marked on the tape using a sticky tab where the participant was located at the end of every minute. Physical fatigability was calculated as a percent change in the distance walked between the first and the sixth minute.

The second measure to assess physical fatigability was a grip strength test. Grip strength is a frequently used method to measure hand grip strength[180] and has been previously used to assess physical fatigability in PwMS by measuring change in grip force in kilograms (kg) through repetitive maximal hand grip over time.[57,63,181] A JAMAR hydraulic hand-held dynamometer[182] was used in this study; the handle was first adjusted according to the participant's grip size.[183] The participant was then instructed to sit upright, shoulder adducted to neutral, elbow flexed at 90 degrees, forearm and wrist in neutral position.[184] Each participant was instructed to squeeze the hand-held dynamometer with maximum strength when the examiner said, "Squeeze now," and continued to squeeze the handle maximally until the examiner said, "Stop." Participants performed 15 trials of maximal hand grip contractions, holding each contraction for five seconds, with a five-second rest in between each repetition. The participants were not informed of the number of trials or the length of each trial. A metronome heard only by the examiner using a headset was used to maintain the 5 second intervals. The maximal force exerted for each trial was recorded. Physical fatigability was calculated by measuring the percent change between the first and last trial. The test was first administered using the dominant hand and then repeated using the non-dominant hand. Due to the recent evidence that demonstrate no significant difference in grip fatigability between dominant and non-dominant hands in PwMS,[57] data is only reported on the dominant hand in the current study.

Cognitive fatigability was measured using the Continuous Performance Test (CPT) (Conners CPT 3™)[64] which is a well-known computerized measure of sustained attention.

Participants were seated in front of a computer screen and instructed to press the space bar when any letter of the alphabet except the letter X appeared on the monitor. To assess fatigability, the test was modified by eliminating instructions that emphasize the participants to respond as fast as they can and participants were not informed how long the test lasted. The test takes 14 minutes to complete with no rest provided. Cognitive fatigability was measured using the Response Speed Variability (RSV) score, which was previously found to be effective in detecting cognitive fatigability in PwMS.[56] The RSV measures the consistency of how fast the participant responds throughout the test. The mean RSV T-scores of the participants was used as the main outcome variable.

Perception of current fatigue was assessed immediately preceding and following each fatigability measure using the 1 item-VAFS[150]. The participants were instructed to place a mark (X sign) on a 100 mm line indicating their current level of fatigue from “not at all fatigued” to “extremely fatigued.” The outcome measure was the value of the length in mm along the line where the participants placed the mark.

Due to their associations with MS-related fatigue, depression, quality of life, functional status, and disease severity were also assessed using the Beck Depression Inventory (BDI-fast screen)[185], the Multiple Sclerosis Quality of Life-54 Instrument (MSQOL),[186] the Functional Status Questionnaire (FSQ),[187] and the Patient Determined Disease Steps (PDDS) scale.[188]

Data was analyzed using SPSS version 23 (IBM SPSS Statistics 23, ©IBM). Descriptive statistics were calculated for the demographics. Assumptions of normality were tested using the Shapiro-Wilk test and Normal Q-Q plots. When assumptions of normality were met, Pearson product correlations were utilized to examine the associations between perceived fatigue,

fatigability measures, and demographics. If the assumptions of normality were not met, Spearman product correlations were utilized. Wilcoxon Signed-Rank tests were used to examine the differences between the first minute and last minute on the 6MWT, between first trial and last trial on the grip strength test, and to examine differences in current fatigue measured using the 1-item VAFS from before to after each of the fatigability measures. Stepwise multivariate linear regression was utilized to examine which factors significantly predicts perceived fatigue in PwMS using the summary score of the NFI-MS as the dependent variable. Alpha level was set at 0.05.

2.4. Results

A total of 52 participants with a mean age of 46.8 years old (± 10.1 SD) were included in the analysis. Refer to Table 1 for demographic information and clinical characteristics. Forty-four females and eight males participated, 47 with relapsing-remitting MS and five with secondary-progressive MS. Participants presented mostly with mild disease (PDDS 1.8 ± 1.6), minimal to mild depression (BDI 3.7 ± 3.1), and no severe global cognitive impairments (MMSE 28.7 ± 1.6).

2.4.1. Change in performance on fatigability measures and current fatigue

Total meters walked on the 6MWT in the last minute (average 66.3 m ± 20.4) compared to the first minute (average 74.6 m ± 18.2) decreased by 12.7%. The total force in kg exerted in the last trial in the grip strength test (average 16.1 kg ± 6.2) compared to the first trial (average 24.9 kg ± 8.4) decreased by 35.9%. Figure 1 illustrates performance at every minute on the 6MWT and during each trial on the grip test of the dominant hand. Meters walked in the sixth minute were significantly lower than those walked in the first minute in the 6MWT ($Z = -6.130$, $p = \leq .001$). The force exerted at trial 15 was significantly lower than the force exerted in the first trial

in the grip strength test of the dominant hand (Z= -6.303, p= ≤ .001). Current perceived fatigue was significantly higher following performance of each fatigability measures compared to current perceived fatigue measured before performing the measures (Grip strength test: Z= -5.691, p= ≤ .001, 6MWT: Z= -5.906, p= ≤ .001, CPT: Z= -6.150, p= ≤ .001; Figure 2).

2.4.2. NFI-MS and fatigability

The percent change score of the 6MWT was not significantly associated with the NFI-MS physical domain (r=-.119, p= .409), cognitive domain (r=.072, p=.620) or summary score (r= -.092, p=.523). The grip strength test change scores for the dominant hand were not significantly associated with the NFI-MS physical domain (r= .063, p= .661), cognitive domain (r= .082, p= .566), or summary score (r= .066, p= .646). In contrast, cognitive fatigability was significantly associated with the NFI-MS physical domain (r= .326, p= .020; Figure 3-A), NFI-MS cognitive domain (r = .276, p=.05-B), summary score (and r= .336, p= .016; Figure 3-C). The bivariate correlations analyses between the NFI-MS and the fatigability measures are shown in Table 2.

2.4.3 NFI-MS and clinical characteristics

Depression was significantly associated with the NFI-MS domains (physical: r=.426, p= .002, cognitive: r=.458, p= .001) and summary score (r=.470, p= ≤ .001). Disease severity was also significantly associated with the NFI-MS domains (physical: r=.571, p= ≤ .001, cognitive: r=.442, p= .001) and the summary score (r=.546, p= ≤ .001). Further correlation analysis indicated that the NFI-MS domains were significantly and strongly associated with subjective functional status as measured using the FSQ (physical domain r= -.541, p= ≤ .001; cognitive domain r= -.516, p= ≤ .001; summary score r= -.575, p= ≤ .001). Mental quality of life as measured using the MSQOL was significantly and negatively associated with the NFI-MS domains (physical r= -.452, p= .001; cognitive r= -.530, p= ≤ .001; summary score r= -.488, p= ≤

.001). Physical quality of life as measured using the MSQOL was also significantly and negatively associated with the NFI-MS domains (physical r= -.700, p= ≤ .001; cognitive r= -.624, p= ≤ .001; summary score r= -.677, p= ≤ .001). Age and disease duration were not significantly associated with either the physical or cognitive domain or the summary score of the NFI-MS. Table 3 displays the bivariate correlations analysis between the NFI-MS scales and the clinical characteristics.

2.4.4. NFI-MS regression analysis

Variables that were significantly associated with the NFI-MS summary score (PDDS, FSQ, BDI, physical and mental MSQOL, and RSV) were included in the regression model. The analysis retained only physical quality of life as a significant predictor of perceived fatigue, explaining 45.8% of the variance in the NFI-MS summary scale (R^2= .458, p= ≤ .001). Due to the confounding effect of depression on fatigue, in which fatigue can be a symptom of depression or vice versa[10]; the regression analysis was repeated including the BDI score as a covariate. After controlling for depression, the physical quality of life remained a significant predictor explaining 34.3% of the variance in the NFI-MS summary scale (β = -.586, R^2= .343, p= ≤ .001).

2.5. Discussion

This is the first study to explore the relationship between perceived fatigue assessed using the NFI-MS and physical and cognitive fatigability in PwMS. The findings of this study indicate that higher cognitive fatigability is associated with higher perceptions of physical and cognitive perceived fatigue and overall perceived fatigue. Interestingly, physical fatigability was not associated with perceived physical fatigue, perceived cognitive fatigue, or overall perceived

fatigue. Another important finding is the strong significant association between physical quality of life and overall perceived fatigue in the study sample even after controlling for depression.

Cognitive fatigability was significantly associated with perceived physical fatigue, perceived cognitive fatigue, and overall perceived fatigue. Only one previous study[56] also used the RSV as a measure of cognitive fatigability, and they too found an association between cognitive fatigability and perceived cognitive fatigue measured using the Fatigue Impact Scale (FIS). Surprisingly, cognitive fatigability was associated with perceived physical fatigue in the current study. Perhaps the nature of the CPT (in which participants sat continuously for 14 minutes without rest and used their finger to tap on the space bar continuously) contributed to the association with perceived physical fatigue. Furthermore, functional neuroimaging studies found that response variability was associated with central factors such as disruptions in the thalamo-cortical circuits and decreased white matter volume,[75,86,87] which might explain the involvement of physical perceptions of fatigue.

Interestingly, physical fatigability was not associated with perceived physical fatigue, perceived cognitive fatigue, or overall perceived fatigue. This lack of association is supported by prior studies that also failed to find an association between these constructs,[57,60] but other studies have found an association between perceived physical fatigue and physical fatigability.[55,58] The conflicting results may be due to different scoring and administration methods to calculate physical fatigability.[55,60] Similar to the results of the current study, Leone et al.[60] found no association between physical fatigability (measured using 6MWT percent change scores) and perceived fatigue (measured using the MFIS). However, Goldman et al.[55] found that higher perceived physical fatigue (measured using the MFIS) was associated with lower meters walked on the 6MWT. Although the latter study recorded meters walked every minute, their main

outcome measure used in the analysis was total meters walked, not percent change as the current study and Leone et al. utilized.[60] Severijns et al.[57] found that perceived fatigue (measured using the MFIS) was not associated with grip fatigability in PwMS, which is consistent with the current study findings. However, a recent study by Wolkorte et al.[58] found that perceived physical fatigue measured by the MFIS was weakly associated with index finger muscle fatigability measured using a force transducer. Due to the variability in methods to assess physical fatigability and perceived fatigue in PwMS, future studies should establish a valid measure of physical fatigability in PwMS and expand the use of the NFI-MS as a measure of perceived fatigue in research and clinical settings.

MS-related fatigue is an umbrella term that encompasses both perceived fatigue and fatigability. Therefore, based on the findings of the current study, it appears that the NFI-MS captures the cognitive aspect of MS-related fatigue (meaning it captures both perceived cognitive fatigue and cognitive fatigability), but not the physical aspect (only captures perceived physical fatigue not physical fatigability). Larger scale studies are needed to verify these conclusions. One possible explanation is that perhaps the items on the NFI-MS physical domain are not worded in a manner that objectifies the individual's performance physical fatigability, hence the lack of association. However, items on the NFI-MS cognitive domain such as *"My coordination gets worse as the day goes on"* and *"Mental effort really takes it out of me"* are worded in a manner that captures both perceptions of cognitive fatigue and cognitive fatigability. In addition, the confounding effect of peripheral fatigue might be another reason for the lack of association with perceived physical fatigue,[18,67] which is the decline or complete failure to excite muscles often due to changes in muscle tissue or deficits in the function of the neuromuscular junction.[18,47] Although several studies have proposed that both perceived fatigue and fatigability in PwMS are

due to disease caused physiological alterations in the central nervous system,[9,19,47,67] peripheral components may also contribute.[18,67] Therefore, perhaps in order to capture the physical aspect of MS-related fatigue, both perceived physical fatigue measures and physical fatigability measures are needed collectively to capture the peripheral and central components of physical MS-related fatigue. Future studies with adequate sample size are needed to confirm these conclusions.

Interestingly, most of the variability of perceived fatigue was explained by lower physical quality of life in this study sample even after controlling for the confounding effect of depression. This is an important finding that affirms the serious effects perceived fatigue has on the physical quality of life in PwMS. Only one previous study explored the relationship between perceived fatigue assessed using NFI-MS and MS-related clinical characteristics.[122] The lack of association between perceived fatigue and age and disease duration is similar to those of Mills et al.,[122] who observed no associations between perceived fatigue and age or disease duration, but found strong association with disease severity. Mills et al found higher perceived fatigue was associated with a higher physical and psychological impact of MS measured using the Multiple Sclerosis Impact Scale (MSIS-29)[122], which is somewhat similar to our finding in which reduced physical quality of life is associated with higher perceived fatigue in PwMS. Our study findings differ from Mills et al. in we found that depression was strongly associated with perceived fatigue, in contrast to the weak association found in their study. However, several previous studies found significant associations between depression and perceived fatigue in PwMS.[9-11] This might be due to the clinical overlap between depression and fatigue[10] as fatigue can be a symptom of depression and vice versa.

The finding that current perceptions of fatigue increased significantly after performing the fatigability tests in a sample of individuals with mild disease severity is relevant for daily life. The fatigability measures used in this study resemble activities of daily living, and the finding that the those tasks where fatiguing the participants reflects how an individual with MS might be struggling functionally on a daily basis. The 6MWT is a walking task that resembles daily activities such as community ambulation. A strong, sustained grip is often needed to carry groceries or shopping bags. Sustained attention (CPT) is necessary for individuals to effectively perform continuous and repetitive activities, such as following clinician or therapist instructions. Being fatigued may affect the performance of these tasks and limit the individual's functional abilities. Therapists and clinicians may need to consider structuring their interventions to limit increasing MS-related fatigue. For example, Karpatkin et al.[179] suggested that PwMS might exhibit less perceived fatigue if they walk intermittently instead of continuously. This study showed that PwMS who walked intermittently for six minutes (walked every two minutes and rested another two minutes), had less perceived fatigue and walked more distances compared to those who continuously walked for six minutes.

There are some limitations to the current study. First the cross-sectional design of the study makes it difficult to interpret the associations into a cause-effect relationship. In addition, our study findings are not generalizable to individuals with MS with moderate to severe disease severity, as the study sample on average had mild disease severity. Participants were permitted to take their usual medications the day of testing, which might have affected their performance on the tests. Furthermore, results should be interpreted with caution as due to the exploratory nature of the study, correction for multiple comparisons have not been made.

2.6. Conclusions

In summary, perceived fatigue is associated with cognitive fatigability but not with physical fatigability in PwMS, and decreased physical quality of life is a large contributor to perceived fatigue in PwMS with mild disease severity. Due to the exploratory nature of the current study, larger scale future studies are needed to verify these findings and to explore the association between perceived fatigue and fatigability in those with more severe disability due to MS.

2.7. Tables

Table 1. Demographics and clinical characteristics of the participants.

Gender	Age	MS Type	Disease Duration	PDDS	MMSE	BDI	FSQ	Physical MSQOL	Mental MSQOL
44 Females 8 Males	46.8 (10.1)	47 RR 5 SP	12.5 (7.6)	1.8 (1.6)	28.7 (1.6)	3.7 (3.1)	79.7 (13.9)	60.3 (18.6)	67.6 (20.3)

Data is reported as mean (standard deviation). RR: Relapsing Remitting MS, SP: Secondary Progressive MS, PDDS: Patient Determined Disease Steps, MMSE: Mini Mental Status Exam, BDI: Beck Depression Inventory, FSQ: Functional Status Questionnaire, MSQOL: Multiple Sclerosis Quality Of Life.

Table 2. Bivariate correlations between the NFI-MS and the fatigability measures.

Variable	NFI-MS Physical	NFI-MS Cognitive	NFI-MS Summary
Grip % change (Dominant)	.063 (.661)	.082 (.566)	.066 (.646)
6MWT % change	-.119 (.409)	.072 (.620)	-.092 (.523)
CPT RSV	.326* (.020)	.276* (.050)	.336* (.016)

Data is reported as correlation co-efficient r (p-value). * Correlation is statistically significant at an alpha level ≤ 0.05. NFI-MS: Neurological Fatigue Index, 6MWT: Six Minute Walk Test, CPT: Continuous Performance Test, RSV: Response Speed Variability.

Table 3. Bivariate correlations between the NFI-MS and the clinical characteristics.

Variable	NFI-MS Physical	NFI-MS Cognitive	NFI-MS Summary
Age	.075 (.598)	-.004 (.978)	.032 (.821)
Disease Duration (years)	-.095 (.501)	-.121 (.393)	-.099 (.487)
PDDS	.571* (≤ .001)	.442* (.001)	.546* (≤ .001)
BDI	.426* (.002)	.458* (.001)	.470* (≤ .001)
FSQ	-.541* (≤ .001)	-.516* (≤ .001)	-.575* (≤ .001)
MSQOL-Mental	-.452* (.001)	-.530* (≤ .001)	-.488* (≤ .001)
MSQOL-Physical	-.700* (≤ .001)	-.624* (≤ .001)	-.677* (≤ .001)

Data is reported as correlation co-efficient r (p-value). *Correlation is statistically significant at an alpha level ≤ 0.05. NFI-MS: Neurological Fatigue Index, PDDS: Patient Determined Disease Steps, BDI: Beck Depression Inventory, FSQ: Functional Status Questionnaire, MSQOL: Multiple Sclerosis Quality Of Life.

2.8. Figure Legends

Figure 1. Physical fatigability for both the 6MWT and grip strength tests. (A) Meters walked every minute for a total of six minutes on the 6MWT. (B) Force exerted every trial for a total of 15 trials on the grip strength test. 6MWT: Six Minute Walk Test.

Figure 2. The difference in current perceived fatigue (VAFS) pre and post performing the fatigability measures. ***Difference is significant at an alpha level ≤ 0.001. 6MWT: Six Minute Walk Test, CPT: Continuous Performance Test.

Figure 3. Scatter plots of cognitive fatigability (RSV) and the (A) physical, (B) cognitive, and (C) summary scores of the NFI-MS. NFI-MS: Neurological Fatigue Index, RSV: Response Speed Variability.

2.9. Figures

Figure 1.A.

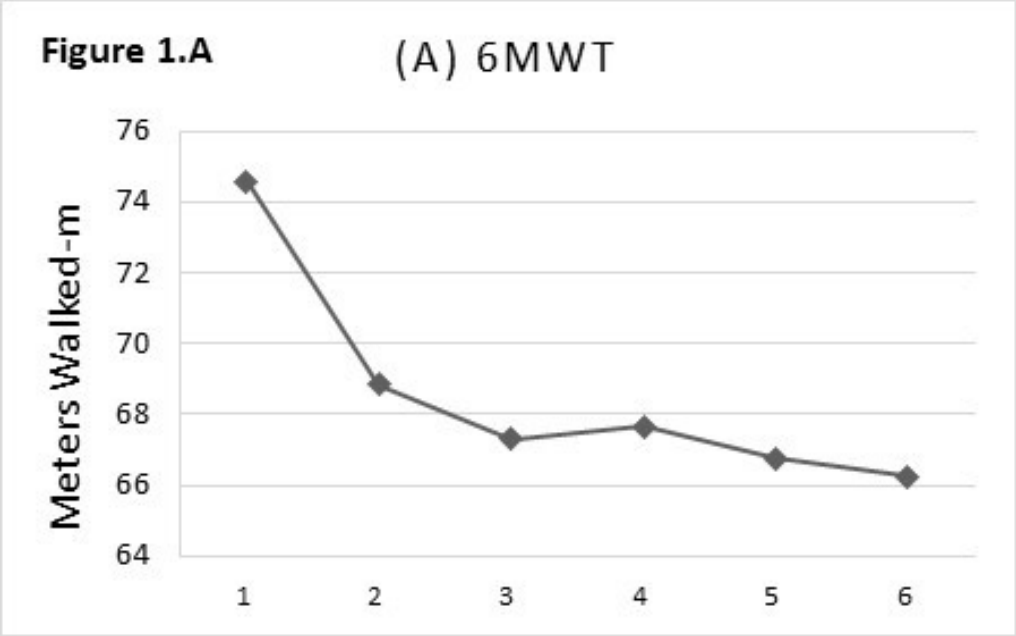


Figure 1.B.

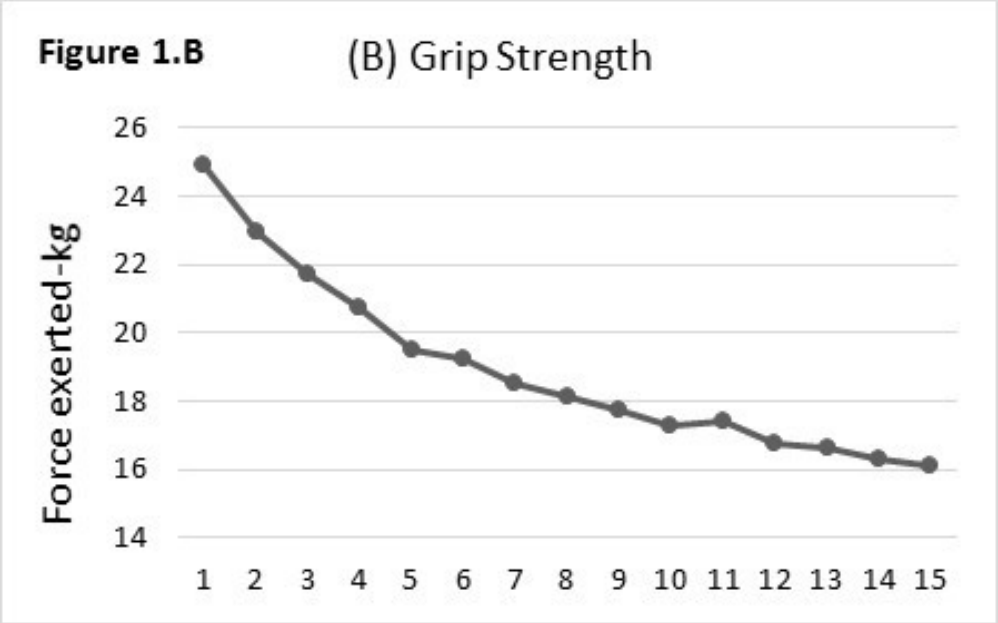


Figure 2.

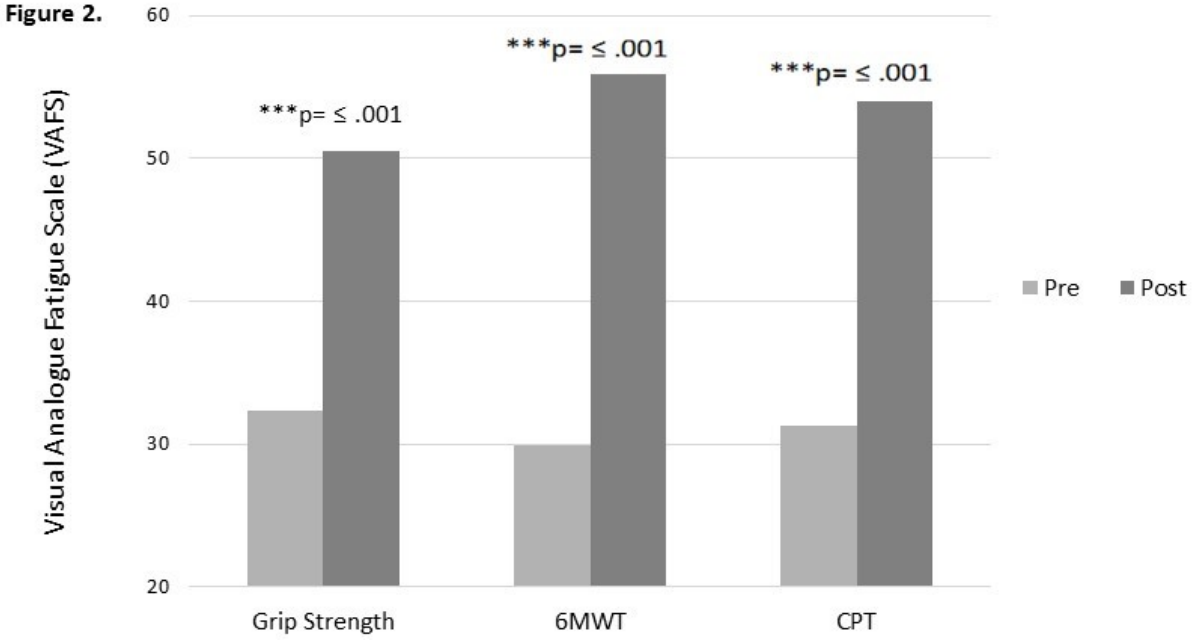


Figure 3.A.

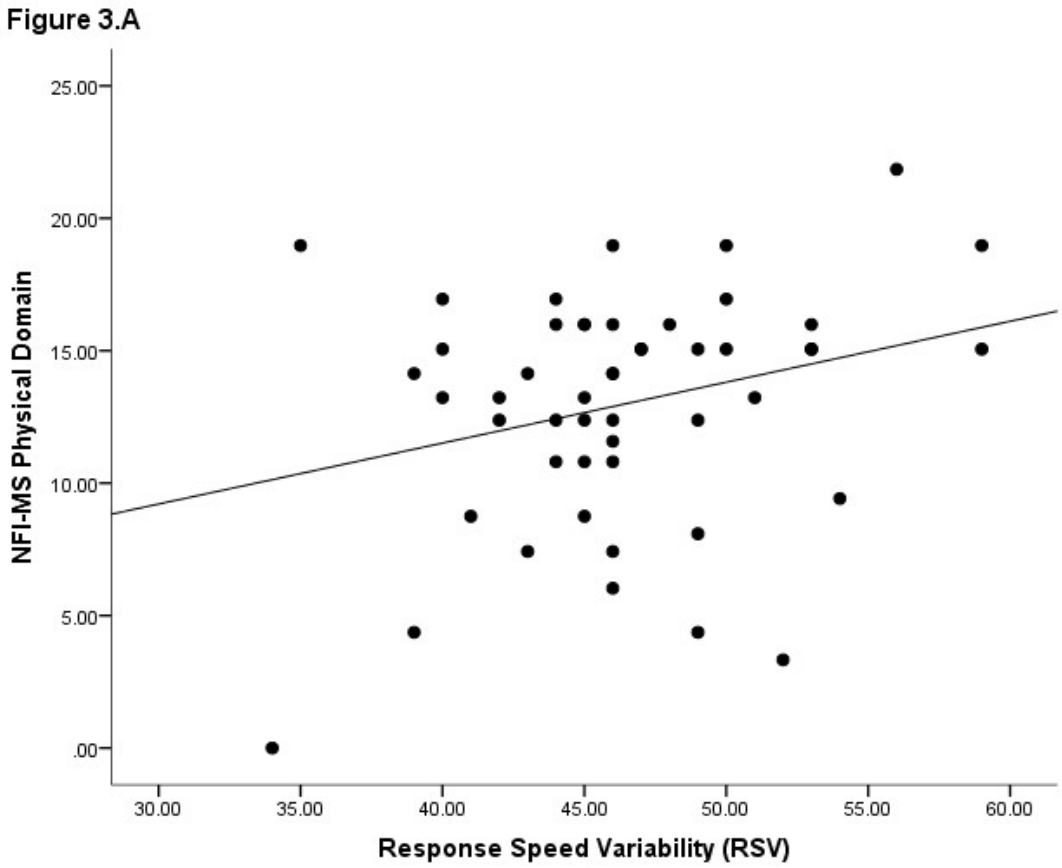


Figure 3.A
25.00
20.00
15.00
10.00
5.00
.00
NFI-MS Physical Domain
30.00
35.00
40.00
45.00
50.00
55.00
60.00
Response Speed Variability (RSV)

Figure 3.B.

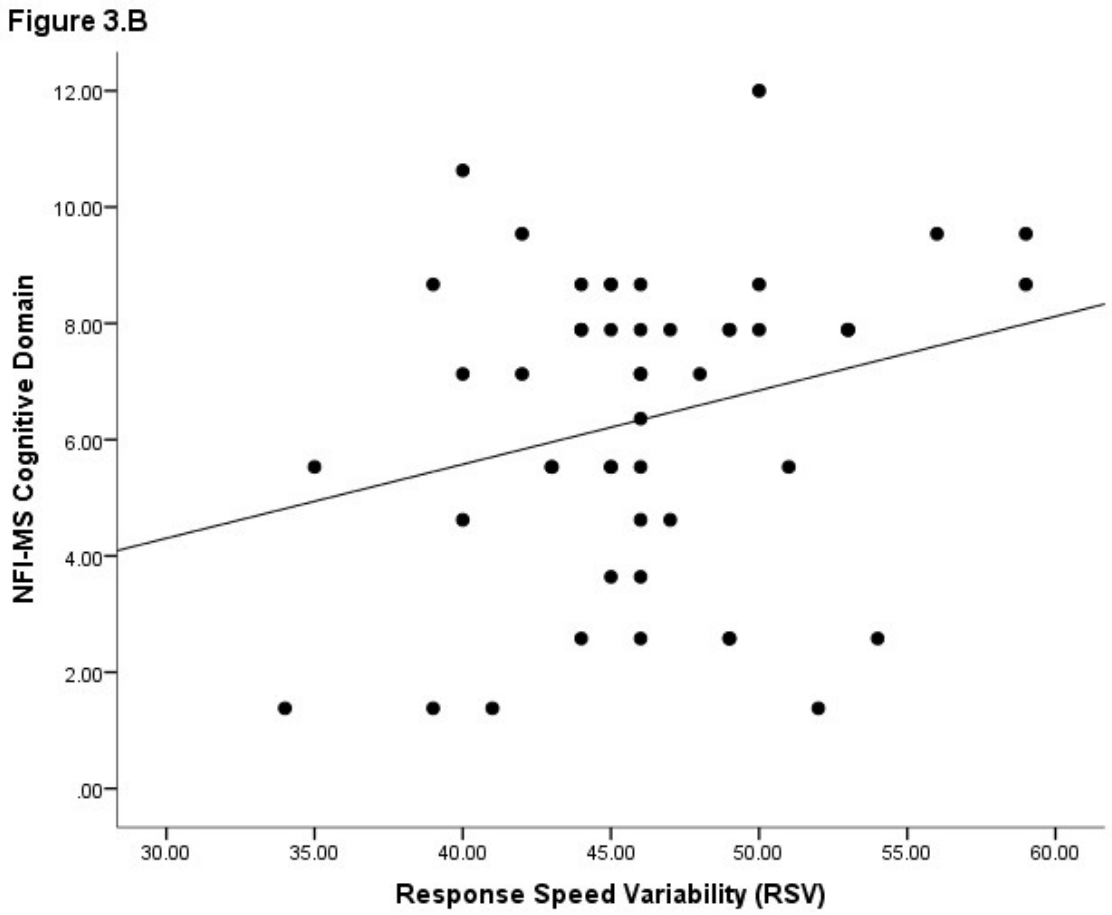


Figure 3.B
12.00
10.00
8.00
6.00
4.00
2.00
.00
NFI-MS Cognitive Domain
30.00
35.00
40.00
45.00
50.00
55.00
60.00
Response Speed Variability (RSV)

Figure 3.C.

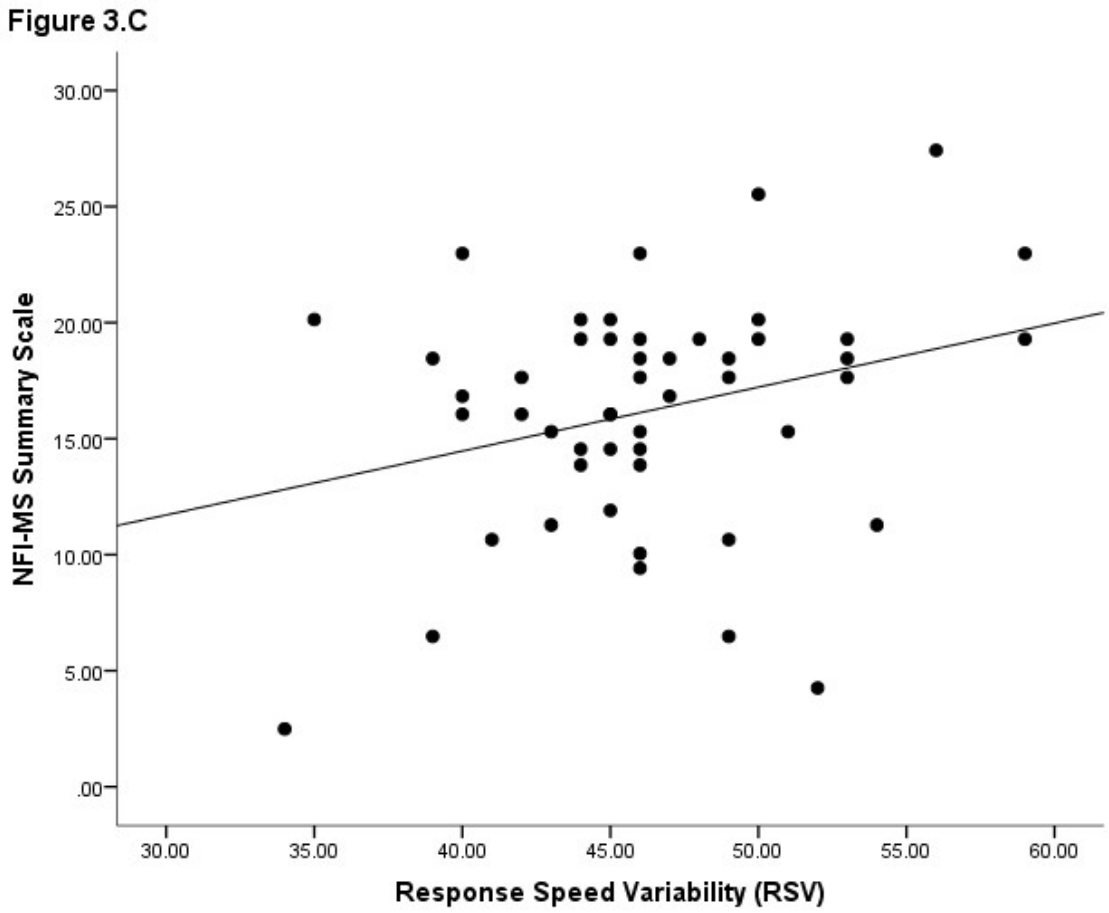


Figure 3.C
NFI-MS Summary Scale
30.00
25.00
20.00
15.00
10.00
5.00
.00
30.00
35.00
40.00
45.00
50.00
55.00
60.00
Response Speed Variability (RSV)

Chapter 3.

The relationship between sleep quality and perceived fatigue measured using the Neurological Fatigue Index in people with MS

Submitted to *Journal of Neurological Research* –May 18th-2016

Co-authors: Catherine Siengsukon, PT, PhD

3.1. Abstract

Objectives: The Neurological Fatigue Index (NFI-MS) is the only known perceived fatigue scale to include questions that consider the contribution of sleep quality to symptoms of fatigue in people with multiple sclerosis (PwMS). However, the relationship between the NFI-MS and sleep quality measures is unknown. This study aimed to explore the relationship between the NFI-MS and self-reported and objective sleep quality. Understanding the relationship between the NFI-MS and sleep quality measures could encourage a wider use of the NFI-MS in research and clinical settings. **Methods:** Fifty-one participants took part in this cross-sectional study (mean age: 47 ± 10.1 years old). Participants completed the NFI-MS to assess perceived fatigue, the Pittsburgh Sleep Quality Index (PSQI) to asses sleep quality, and the Epworth Sleepiness Scale (ESS) to assess daytime sleepiness. The participants wore an actigraph device one week on the dominant wrist to objectively quantify sleep quality. **Results:** Higher perceived fatigue is significantly associated with poorer self-reported sleep quality and excessive daytime sleepiness, but not with objective sleeps quality. **Discussion:** The NFI-MS can be administered in clinical and research settings to assess the impact of sleep on perceived fatigue in the MS population.

3.2. Introduction

Multiple sclerosis (MS) is a progressive neurological disease characterized by the destruction of the myelin sheath that covers and protects the axons of the brain and spinal cord.[26] The most common symptoms of MS include fatigue, cognitive impairments, physical decline, and sleep disturbances.[11,27,28] MS affects 1/1000 individuals in the United States,[29] and the average national annual cost of care for people with MS (PwMS) is estimated to be over $6.8 billion.[30] Furthermore, 50-80% of PwMS are unemployed within 10 years of disease onset. MS is a particularly devastating disease due to the early onset of symptoms, affecting the quality of life of these individuals.[31]

MS-related fatigue affects up to 90% of PwMS and is often described as being the most severe symptom.[1,33] Fatigue has been shown to be a major cause of unemployment and reduced function in the MS population.[4,6,7,34] Self-report scales are widely used in research and clinical settings to assess the individual's perception of fatigue, often referred to as "perceived fatigue."[49,50] Evidence suggests that perceived fatigue in the MS population is multifactorial, meaning that other prevalent factors associated with MS, including sleep disturbances,[12] cognitive impairments,[15] and depression,[8] contribute to perceived fatigue in PwMS. Due to this complexity, a comprehensive approach that takes into account the other associated factors in MS is recommended for both the assessment and management of perceived fatigue in the MS population.[13]

Sleep problems in individuals with MS are very common. Approximately 50% of patients with MS have a diagnosable sleep disorder, and up to 67% report a sleep disturbance.[96-98] Evidence shows that poor sleep quality is an independent predictor of reduced quality of life[99,103] and has been associated with a reduction in several quality of life indices, including physical

function, psychological well-being, work ability, and interpersonal relationships.[11] Sleep quality can be measured subjectively using self-report scales[108] or objectively using polysomnography (PSG)[111] or actigraphy.[113]

Sleep disturbances have been shown to be associated with an increase in perceived fatigue in PwMS.[13,14,102,105,107,114,116,189] Evidence suggests that the presence of a sleep disorder or poor sleep quality contributes to excessive activation of the central nervous system (CNS) which, in turn, exacerbates MS-related fatigue.[116] Most studies have used the Modified Fatigue Impact Scale (MFIS) or the Fatigue Severity Scale (FSS) to assess perceived fatigue. However, the psychometric properties of the MFIS[152,159] and FSS[156] have recently been questioned, making interpretation of results difficult. Studies using self-reported sleep quality (the Pittsburgh Sleep Quality Index (PSQI) and/or the Epworth Sleepiness Scale (ESS)) have found a significant association between sleep quality and perceived fatigue in PwMS.[102,107,114] Unfortunately, only limited studies that have examined the association between perceived fatigue and sleep quality utilizing objective measures (PSG[14,190,191] or actigraphy[105,125,189]), and those studies have conflicting results, with some finding an association between fatigue and sleep quality[26,105] while others failed to find an association.[36,125,189,191] Although an association between poor sleep quality and perceived fatigue has been widely reported, those studies differ in terms of the fatigue scales used, means of measuring sleep quality (self-report vs. objective), exclusion or inclusion of those with sleep disorders, and differences in the study sample's disease severity (mild vs. severe), which can contribute to the conflicting results.

The Neurological Fatigue Index (NFI-MS)[25] was developed using the outcome measure development guidelines from the Food and Drug Administration (FDA)[161] based on a detailed medical definition of fatigue in PwMS.[24] Unlike the MFIS[159] and FSS,[156] the NFI-MS fits into a

Rasch model analysis[155] that uses a psychometric approach to accurately represent responses and produce linear measurements. Furthermore, to our knowledge, the NFI-MS is the only validated fatigue scale that, along with physical and cognitive components, includes two separate sleep components, acknowledging the importance of sleep quality during the assessment of perceived fatigue in the MS population. The sleep components in the NFI-MS are "relief by diurnal sleep or rest" in which a higher score indicates fatigue is relieved by sleep or rest during the day, and "abnormal nocturnal sleep and sleepiness" in which a higher score indicates fatigue is attributed to fragmented sleep or reduced sleep quality during the night and daytime sleepiness.

Only one prior study by Mills et al.[122] has examined the relationship between the NFI-MS summary score and self-reported sleep quality and daytime sleepiness in PwMS.[122] Perceived fatigue was higher in those that reported sleeping more during the day, fragmented nocturnal sleep, and higher daytime sleepiness. Therefore, the primary aim of this study is to expand the work of Mills et al. Specifically, it will explore the relationship between the NFI-MS and the gold-standard self-report sleep quality measure (the PSQI) and explore the relationship between the NFI-MS and objective sleep quality using actigraphy.

3.3. Methods

A cross-sectional study design was used and performed in accordance with the University of Kansas Medical Center's (KUMC) Institutional Review Board. Participants were recruited from the MS clinic at KUMC and through personal referral from participants and area physicians. Eligibility for the study required participants to be (1) 18-60 years of age, (2) have relapsing-remitting or secondary-progressive MS, (3) able to ambulate with or without an assistive device, and (4) score > 24 on the Mini Mental Status Exam (MMSE)[177]. The exclusion criteria includes the following: (1) history of alcohol/drug abuse or nervous system disorder other than MS, (2)

severe physical, neurological, or sensory impairments that would interfere significantly with testing, (3) developmental history of learning disability or attention-deficit/hyperactivity disorder, (4) relapse and/or corticosteroid use within four weeks of assessment, (5) untreated sleep disorder (such as sleep apnea), and (6) uncorrected vision loss that would interfere significantly with testing.

Written informed consent was received from all study participants. Information regarding medical history, demographics, and medication use were collected. All study participants were instructed to refrain from consuming alcohol or caffeine beyond their normal daily consumption and refrain from taking medications other than the ones they usually take for the day of assessment. After completing a battery of questionnaires, each participant was given an actigraph device to objectively assess sleep quality. The participants were instructed to wear the actigraph on their dominant wrist for a week and return the actigraph using a postage-paid envelope.

3.3.1. Perceived fatigue measure

Perceived fatigue during the past two weeks was assessed using the Neurological Fatigue Index (NFI-MS).[25] The NFI-MS consists of 23 questions, each on a Likert scale from 0-3 with higher score indicating more fatigue. The NFI-MS consists of four components: physical, cognitive, relief by diurnal sleep or rest, and abnormal nocturnal sleep/sleepiness. A higher score in the “relief by diurnal sleep or rest” component indicates fatigue is relieved by sleep or rest during the day. A higher score in the “abnormal nocturnal sleep/sleepiness” component indicates fatigue is attributed to fragmented sleep or reduced sleep quality during the night and daytime sleepiness. A summary score is calculated by adding together the physical and cognitive components except one question from the physical component is not included.

3.3.2. Sleep measures

Self-reported sleep was measured using the Pittsburgh Sleep Quality Index (PSQI).[108] The PSQI is a validated and well-known measure of sleep quality in which the participant reports their sleeping habits over the past month. It consists of 19 self-rated questions; each is rated on a scale of 0-3 with 0 indicating no sleep difficulty and 3 indicating severe sleep difficulties. The PSQI global score ranges from 0–21, with a score of > 5 indicating poor sleep quality.[192] Seven component scores (sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction) were also calculated.

Daytime sleepiness was measured using the Epworth Sleepiness Scale (ESS).[109] The participant rates how likely they would doze off in eight different scenarios of daily activities. The eight ESS items use a 4-point Likert scale in which a higher score indicates higher daytime sleepiness.

Actigraphy was utilized to objectively quantify sleep quality.[113] An actigraph is a portable device that records movement over extended periods of time and has been used in the study of sleep and circadian rhythms in PwMS.[105,125] Each participant was instructed to wear an actigraph device (Model wGT3X-BT®, ActiGraph corp. Pensacola, FL) on the dominant wrist for seven consecutive days. The participants were instructed to temporarily remove the watch during exposure to water (i.e. showering or swimming). The parameters of interest from the actigraph include: sleep efficiency (SE), total sleep time (TST), total time in bed (TTB), wake after sleep onset (WASO), and number of awakenings.

3.3.3. Other measures

Participants completed the following assessments due to the possible association with fatigue and sleep quality in PwMS: the Patient Determined Disease Steps (PDDS)[188] to assess disease severity, the Beck Depression Inventory (BDI)[132] to assess depression, and the State Trait Anxiety Inventory (STAI)[193] to measure both current anxiety using the state subscale (STAI-S) and general anxiety using the trait subscale (STAI-T).

3.3.4. Data Analysis

Wear time validation for the actigraph data was confirmed first using the following criteria: wear time of at least four valid days out of the seven days with a valid day defined as having a wear time of at least 600 minutes during a 24-hour period (12 am to 11:59 pm).[194] ActiLife software (version 6.11.8) was utilized to analyze the sleep data using Cole-Kripke algorithm, which has been validated for use in adult populations between 35 and 65 years of age.[195] The Cole-kripke method uses a seven-minute window to determine if each epoch is sleep or awake using the following algorithm: (.001 * (106 * Epochx-4 + 54 *Epochx-3 + 58 * Epochx-2 + 76 * Epochx-1 + 230 * Epochx+ 74 * Epochx+1+ 67 * Epochx+2). Any missing epochs are considered zero and if the result of the algorithm is < 1, then the current epoch is considered as sleep. All data was entered into SPSS version 23 (IBM SPSS Statistics 23, ©IBM) for analysis. Assumptions of normality were first tested using the Shapiro-Wilk test and Normal Q-Q plots. Descriptive statistics were calculated for the demographics and all other variables. An established ordinal to interval scores of the NFI-MS are available to use for parametric testing.[25] Therefore, Pearson's product correlations were utilized to explore the association between perceived fatigue and sleep quality. When the assumptions of normality were not met and for

ordinal data, Spearman's product correlations were utilized to explore the associations between the outcome measures of interest. Alpha level was set at 0.05.

3.4. Results

Fifty-one participants (mean age of 47 years ± 10.1; 43 females) participated in the study. Forty-six participants had relapsing-remitting MS and five had secondary-progressive MS. The overall disease status of the sample was mild (PDDS: 1.8 ± 1.6), with minimal to mild depression (BDI: 3.7 ± 3.1), minimal general anxiety (STAI-T: 40.4 ± 10), and no severe global cognitive impairments (MMSE: 28.7 ± 1.6). The study sample had on average poor self-reported sleep quality (PSQI: 8.1± 3.8 and ESS: 8.7 ± 4.5). Refer to Table 1 for descriptive statistics.

3.4.1. Association between NFI-MS and self-reported sleep quality

The NFI-MS physical component, abnormal nocturnal sleep/sleepiness component, and summary score were significantly associated with the PSQI global score (r= .427, p= .002; r= .566, p= ≤ .001; r= .388, p= .005, respectively; Table 2; Figure 1). The NFI-MS cognitive component and relief by diurnal sleep component were not associated with the PSQI global score (r= .231, p= .102 and r= .116, p= .419, respectively).

Analysis of the components of the PSQI revealed that the daytime dysfunction component was significantly associated with all the NFI-MS components (Table 2), indicating that higher daytime dysfunction is associated with higher perceived fatigue on all aspects of the NFI-MS (summary: r= .571, p= ≤ .001, physical: r= .545, p= ≤ .001, cognitive: .486, p= ≤ .001, relief by diurnal sleep: r= .316, p= ≤ .001, abnormal nocturnal sleep/sleepiness: r= .432, p= ≤ .001). The abnormal nocturnal sleep/sleepiness component of the NFI-MS was significantly associated with four of the PSQI components (sleep duration r= .414, p= .003; sleep disturbances r= .420, p= .004; daytime dysfunction r= .432, p= ≤ .001), indicating that higher perceived fatigue that is

attributed to abnormal nocturnal sleep/sleepiness is associated with lower sleep duration, higher sleep disturbances, and higher daytime dysfunction. The NFI-MS relief by diurnal sleep component was significantly associated with the PSQI daytime dysfunction component (Table 2), indicating that higher fatigue that is relieved by diurnal sleep or rest is associated with higher daytime dysfunction.

All the NFI-MS components were significantly associated with higher daytime sleepiness as measured using the ESS (summary: r= .341, p= .014, physical: r= .344, p= .013, cognitive: .296, p= .035, relief by diurnal sleep: r= .313, p= .025, abnormal nocturnal sleep and sleepiness: r= .377, p= .006; Table 2), indicating higher perceived fatigue on all aspects of the NFI-MS is associated with higher daytime sleepiness.

3.4.2. Association between NFI-MS and objectively assessed sleep

The study sample had an average SE of 89.5% ± 4.7, average TST 439.1 minutes ± 86, average TIB 489.3 minutes ± 85.4), a WASO of 48.2 minutes ± 21, and an average number of awakenings of 12.3 times ± 4.7; Table 3). None of the NFI-MS component scores were significantly associated with any of the actigraph sleep parameters (Table 4).

3.5. Discussion

This is the first study to examine the association between perceptions of fatigue using the NFI-MS and self-report and objective measures of sleep quality in PwMS. The findings of the current study indicate that poor self-report sleep quality is associated with increases in perceptions of fatigue in PwMS. However, objective sleep quality measured using actigraphy is not associated with perceived fatigue in this study sample.

The findings of this study support the results by Mills et al., which is the only other study that evaluated the relationship between the NFI-MS and sleep quality.[122] Mills et al. measured sleep quality through self-estimating the hours of diurnal and nocturnal sleep and whether nocturnal sleep was fragmented throughout the night. Their findings showed that those who slept more during the day and had fragmented nocturnal sleep reported higher fatigue on the NFI-MS summary score. Similar to the current study, Mills et al. found a significant association between the NFI-MS summary score and the ESS score. Results from the current study demonstrate that self-report sleep quality but not objectively measured sleep quality is associated with self-perceived fatigue in PwMS.

It is difficult to compare our findings with other previous studies due to the variety of perceived fatigue measures used, but several studies had similar findings regarding the association between perceived fatigue and self-reported sleep quality measures.[102,107,114] Strober et al.[102] found significant associations between perceived fatigue measured using the MFIS and poor sleep quality measured using the PSQI. Similarly, Cameron et al.[114] found significant associations between perceived fatigue measured using the MFIS and FSS and poor sleep quality measured using the PSQI. Stanton et al.[107] found that excessive daytime sleepiness measured using the ESS was significantly associated with perceived fatigue measured using the FSS. Although these studies had similar findings to our results, what makes the current study significant and different is the use of the NFI-MS as a measure of perceived fatigue. Mills et al., who developed the NFI-MS, recommended researchers to reevaluate using the total scores of the MFIS and FSS.[156,159] Those scores are considered invalid based on the Rasch analysis and thus would affect the interpretation of the findings of previous studies. The NFI-MS is a more

psychometrically sound scale of perceived fatigue compared to the commonly used ones and therefore interpreting the results would be more accurate.

An important finding is the lack of association between perceived fatigue and the actigraph parameters. Previous studies that explored the relationship between actigraphy and perceived fatigue in PwMS had conflicting results, but comparing the current study findings with previous research is difficult due to different measures of perceived fatigue used.[105,125,189] Perhaps the lack of association in the current study between perceived fatigue and the actigraph parameters is due to a limitation of actigraphy to accurately assess sleep in this sample. Evidence showed that the actigraph may overestimate sleep efficiency and total sleep time[15,54] which may impact the interpretation of results.[113,196] Furthermore, actigraphy findings might be limited by wear time. Perhaps PwMS need to wear the actigraph for more than one week to accurately assess their sleep quality. Attarian et al.[105] who found significant associations between actigraphy and fatigue had the participants wear the actigraph for two weeks. Future studies are needed to verify these findings and explore if a longer wear time might more accurately assess sleep quality in PwMS.

Due to the novel purpose of this study, statistical correction was not used despite the number of correlation analyses conducted. Furthermore, because the sample had mostly mild disease severity, the findings are not generalizable to those with more severe disease forms of MS. In addition, it is possible that there might be participants in the current study sample with an undiagnosed sleep disorder. It is acknowledged in the literature that a high percentage of PwMS are underdiagnosed with sleep disorders and therefore more emphasis should be put on this matter.[100] Future studies may need to consider assessing the relationship between the NFI-MS and sleep quality in those with severe forms of MS and in those assessed for the presence of sleep disorders. We expect that the results of the current study would differ as evidence

demonstrates higher perceived fatigue in those with more disease severity and in those with sleep disorders such as insomnia and obstructive sleep apnea.[23,135] Furthermore, the participants were allowed to continue the use of their normal medications on the day of the assessment, so taking sleep or fatigue-related medication may affect their responses to the questionnaires.

The findings of the current study have important clinical implications. Sleep quality should be considered during both the assessment and management of fatigue in PwMS. The use of the NFI-MS can be easily utilized in research and clinical settings to assess the crucial role of poor sleep quality in relation to perceived fatigue in PwMS. The current study results emphasize the need for health care providers to consider address sleep disturbances as part of the perceived fatigue treatment plan in PwMS.

3.6. Conclusions

The current study findings demonstrate that higher perceived fatigue is significantly associated with poorer self-reported sleep quality and excessive daytime sleepiness, but not with objectively assessed sleep quality. The NFI-MS is an efficient method to assess and manage the role sleep quality has on perceived fatigue in the MS population. Future studies are needed to verify these findings.

3.7. Tables

Table 1. Descriptive statistics of the participants.

Gender	*Age*	*MS Type*	*Disease Duration*	*PDDS*	*MMSE*	*BDI*	*STAI-S*	*STAI-T*	*PSQI*	*ESS*
43 Females	47	46 RR	12.6	1.8	28.7	3.7	31.9	40.4	8.1	8.7
8 Males	(10.1)	5 SP	(7.6)	(1.6)	(1.6)	(3.1)	(8.8)	(10)	(3.8)	(4.5)

Data is reported as mean (standard deviation). RR: Relapsing Remitting MS, SP: Secondary Progressive MS, PDDS: Patient Determined Disease Steps, MMSE: Mini Mental Status Exam, BDI: Beck Depression Inventory, STAI: State Trait Anxiety Inventory (S: State, T: Trait)

Table 2. Bivariate correlations between the NFI-MS and the self-reported sleep quality and daytime sleepiness measures.

	NFI-MS				
PSQI	*Summary*	*Physical*	*Cognitive*	*relief by diurnal sleep or rest*	*abnormal nocturnal sleep/sleepiness*
Global	.388* (.005)	.427* (.002)	.231 (.102)	.116 (.419)	.566* (≤ .001)
Sleep quality	.249 (.078)	.250 (.077)	.207 (.146)	.060 (.677)	.619* (≤ .001)
Sleep latency	.244 (.084)	.246 (.082)	.115 (.424)	.190 (.182)	.251 (.075)
Sleep duration	.214 (.131)	.266 (.060)	.094 (.512)	-.010 (.946)	.414* (.003)
Sleep efficiency	.161 (.258)	.180 (.206)	.056 (.699)	.050 (.728)	.197 (.166)
Sleep disturbances	.147 (.304)	.211 (.137)	-.020 (.889)	.002 (.988)	.420* (.002)
Sleep medication	.085 (.551)	.119 (.406)	.107 (.454)	.013 (.927)	.208 (.144)
Daytime dysfunction	.571* (≤ .001)	.545* (≤ .001)	.486* (≤ .001)	.316* (≤ .001)	.432* (≤ .001)
ESS	.341* (.014)	.344* (.013)	.296* (.035)	.313* (.025)	.377* (.006)

Data is reported as correlation co-efficient r (p-value). * Correlation is statistically significant at an alpha level < 0.05. NFI-MS: Neurological Fatigue Index, PSQI: Pittsburgh Sleep Quality Index, ESS: Epworth Sleepiness Scale.

Table 3. Descriptive statistics of the Actigraph parameters.

SE (percentage)	*TST (min)*	*WASO (min)*	*TTB (min)*	*Number of Awakenings*
89.5 (4.7)	439.1 (86)	48.2 (21)	489.3 (85.4)	12.3 (4.7)

Data is reported as mean (standard deviation). SE: Sleep Efficiency, TST: Total Sleep Time, WASO: Wake After Sleep Onset, TTB: Total Time in Bed.

Table 4. Bivariate correlations between the NFI-MS and the Actigraph parameters.

	NFI-MS				
Actigraph	*Summary*	*Physical*	*Cognitive*	*Relief by diurnal sleep or rest*	*Abnormal nocturnal sleep/sleepiness*
SE	-.258 (.068)	-.260 (.065)	-.197 (.166)	-.205 (.150)	-.116 (.417)
Latency	.265 (.061)	.275 (.053)	.110 (.441)	.182 (.202)	.160 (.262)
TST	-.101 (.481)	-.136 (.341)	-.064 (.658)	.062 (.664)	-.018 (.900)
WASO	.216 (.128)	.202 (.155)	.179 (.209)	.211 (.136)	.075 (.602)
TTB	-.043 (.766)	-.082 (.569)	-.018 (.902)	.118 (.408)	.004 (.980)
Number of Awakenings	.139 (.332)	.091 (.527)	.216 (.128)	.142 (.321)	-.012 (.933)

Data is reported as correlation co-efficient r (p-value). * Correlation is statistically significant at an alpha level < 0.05. NFI-MS: Neurological Fatigue Index, SE: Sleep Efficiency, TST: Total Sleep Time, WASO: Wake After Sleep Onset, TTB: Total Time in Bed.

3.8. Figure Legend

Figure 1. Scatter plot between the PSQI global score and the NFI-MS physical component (A) the abnormal nocturnal sleep/sleepiness component (B) and the summary score (C). PSQI: Pittsburgh Sleep Quality Index, NFI-MS: Neurological Fatigue Index.

3.9. Figures

Figure 1.A.

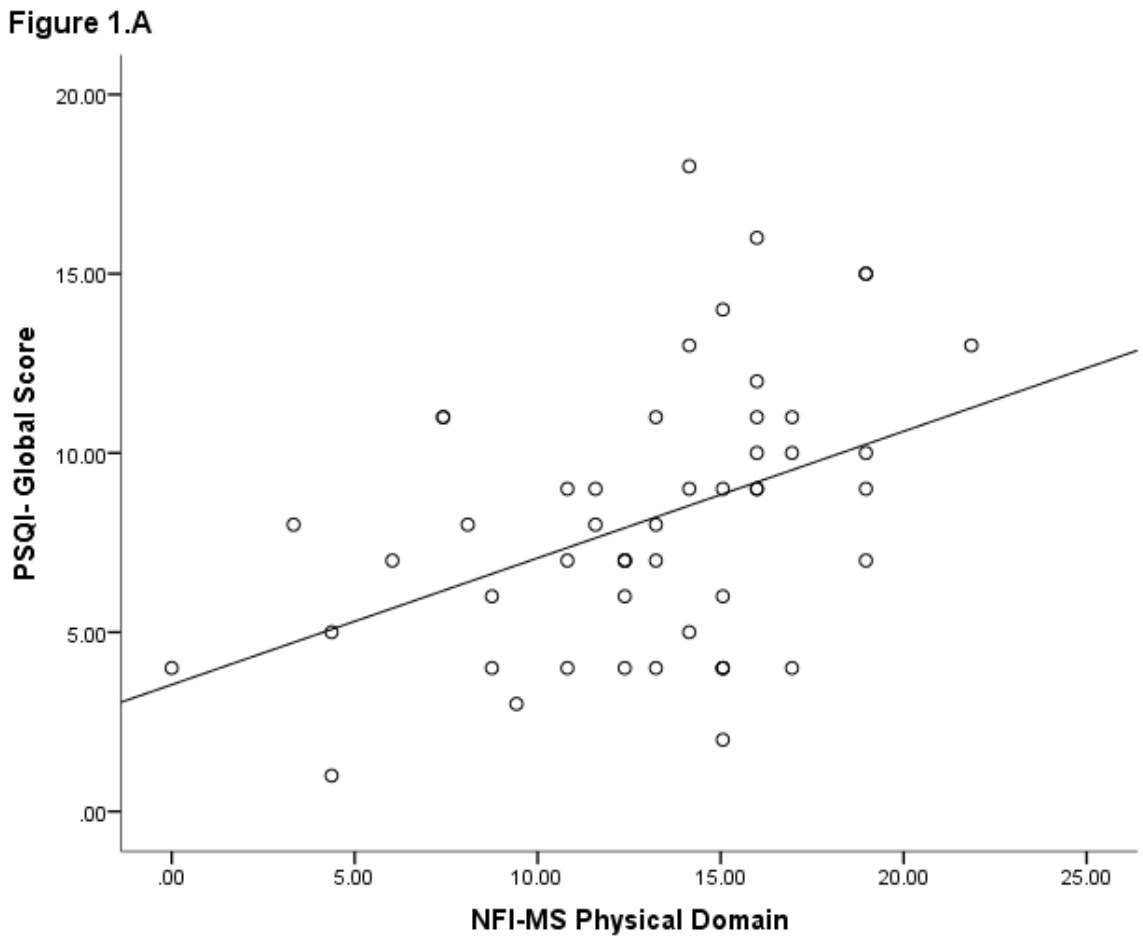


Figure 1.B.

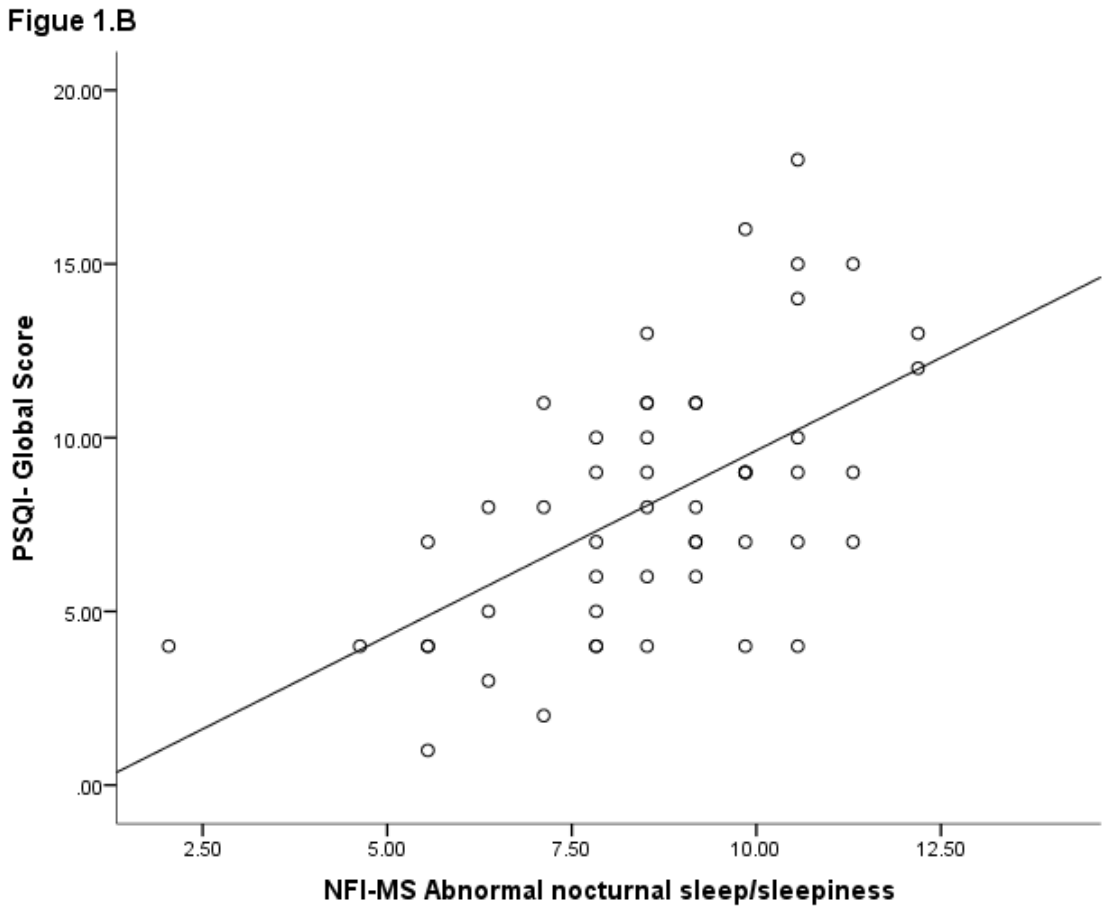

Figue 1.B
20.00
15.00
10.00
5.00
.00
PSQI- Global Score
2.50
5.00
7.50
10.00
12.50
NFI-MS Abnormal nocturnal sleep/sleepiness

Figure 1.C.

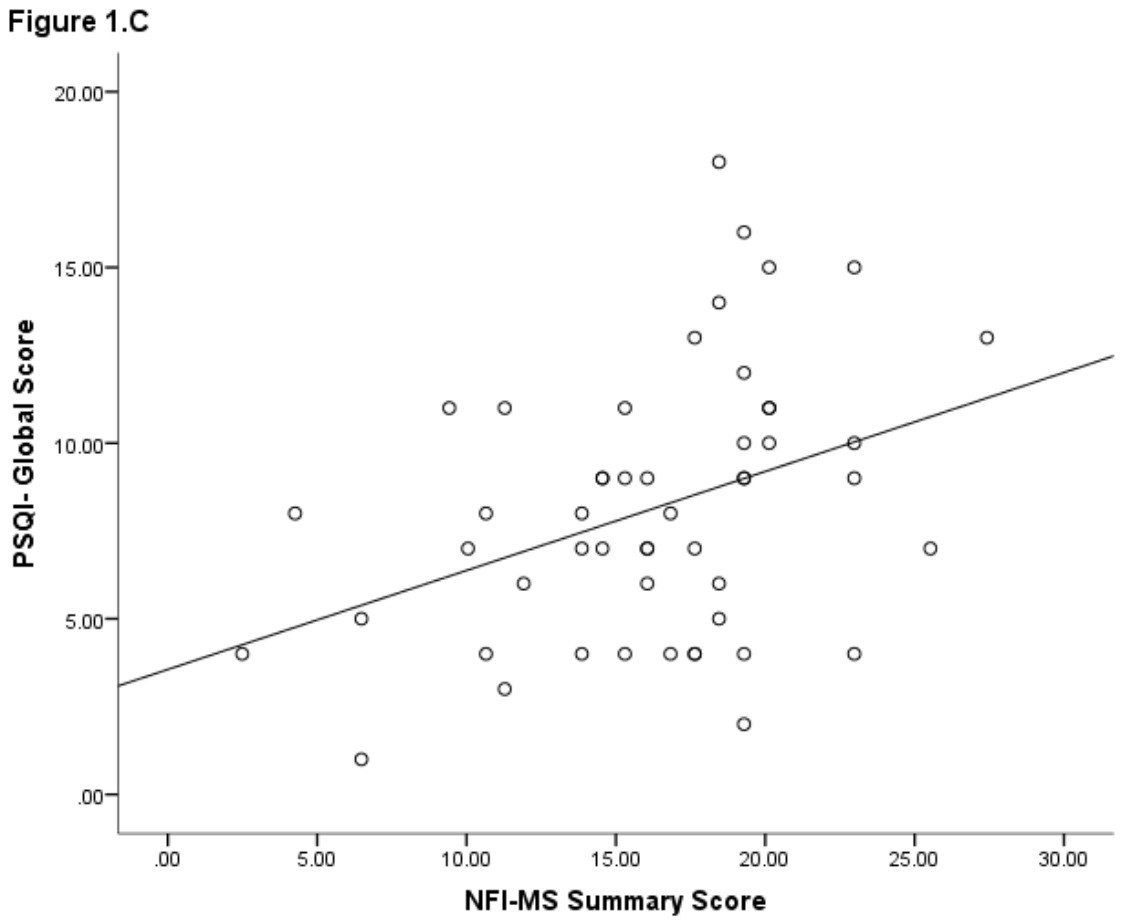


Figure 1.C
PSQI- Global Score
20.00
15.00
10.00
5.00
.00
.00
5.00
10.00
15.00
20.00
25.00
30.00
NFI-MS Summary Score

Chapter 4.

The relationship between fatigability and sleep quality in people with MS

Submitted to *Multiple Sclerosis Journal-Experimental, Translational and Clinical (MSJ-ETC)*

July 18th-2016

Co-authors: Jessie Huisinga, PhD, Sharon Lynch, MD, Catherine Siengsukon, PT, PhD

4.1. Abstract

Background: Perceived fatigue and fatigability are constructs of multiple sclerosis (MS) related fatigue. Sleep disturbances leads to poor sleep quality which has been found to be associated with perceived fatigue in people with MS (PwMS). However, the relationship between fatigability and sleep quality is unknown. **Objective:** To explore the relationship between physical and cognitive fatigability with self-reported and objective measures of sleep quality in PwMS. **Methods:** Fifty-one ambulatory PwMS participated in the study. Physical fatigability was measured by percent-change in meters walked on the Six-Minute Walk Test (6MWT) and in force exerted on a repeated maximal hand grip test. Cognitive fatigability was measured using response speed variability on the continuous performance test. Self-report sleep quality was measured using the Pittsburgh Sleep Quality Index, and objective sleep quality was measured using 1 week of actigraphy. **Results:** Components of the Pittsburgh Sleep Quality Index and several actigraph parameters were significantly associated with physical fatigability and cognitive fatigability. **Conclusion:** Poor sleep quality is related to fatigability in MS. Clinicians and researchers need to consider the role poor sleep quality has on physical and cognitive fatigability in PwMS and may consider interventions targeted to improve sleep quality.

4.2. Introduction

Multiple sclerosis (MS) related fatigue is one of the most debilitating symptoms affecting people with MS (PwMS).[1] It interferes with daily function and is a major cause of unemployment.[7] MS related fatigue is an umbrella term consisting of two different constructs: perceived fatigue and fatigability.[19] Perceived fatigue is reported by the individual as tiredness in performing physical and cognitive tasks that interfere with daily function.[18] Fatigability can be objectively quantified by a clinician or researcher and is the measure of change in the performance of physical or cognitive tasks over a period of time.[19] Physical fatigability is the reduced ability to complete sustained physical tasks such as walking constantly for several minutes.[19] Cognitive fatigability[19] is described as the inability to sustain concentration and attention during demanding cognitive tasks such as following conversations.

Approximately 60% of PwMS report experiencing sleep disturbance that eventually results in overall poor sleep quality.[98] Evidence suggests that sleep disturbances might exacerbate MS-related fatigue through excessive activation of the central nervous system (CNS).[115] The excessive activation of the CNS may result from recurrent sleep arousals, central mechanisms such as lesions on the suprachiasmatic nucleus in the hypothalamus that regulates circadian rhythms, and elevated certain inflammatory cytokines in the cerebrospinal fluid that are associated with both sleep disturbances and increased MS-related fatigue.[115] Poor sleep quality has been associated with a reduction in several quality of life indices including physical function, psychological well-being, and work ability.[11] Furthermore, reduced sleep quality is associated with increased perceived fatigue in PwMS.[13,102,105,114] However, it is unknown if poor sleep quality is associated with fatigability in PwMS. Understanding the relationship between fatigability and sleep quality will emphasize the need to consider sleep quality as an important

clinical characteristic during the management of MS-related fatigue, specially that sleep disturbances are often overlooked by clinicians in PwMS.[101] Fatigue is one of the most frequently reported symptoms of MS, so if poor sleep quality is found to be associated with fatigability in PwMS, then management of sleep disturbances could lead to improvements in fatigability and associated improvement in daily function for PwMS. Therefore, the purpose of this study was to investigate the relationship between fatigability and self-report and objectively assessed sleep quality in PwMS.

Due to the involvement of the aforementioned central mechanisms in sleep disturbances and MS-related fatigue as well as the previous evidence that shows an association between poor sleep quality and perceived fatigue in PwMS, we hypothesized that poor sleep quality would be associated with physical and cognitive fatigability in PwMS.

4.3. Materials and Methods

4.3.1. Participants

Participants were recruited from the MS clinic at the University of Kansas Medical Centre (KUMC) and through personal referral from consented participants. The inclusion criteria were (1) 18-60 years of age, (2) relapsing-remitting or secondary-progressive MS,[176] (3) ability to ambulate with/without an assistive device, and (4) a score > 24 on the Mini Mental Status Exam (MMSE).[177] Participants were excluded if they had (1) a history of alcohol/drug abuse or nervous system disorder other than MS, (2) severe physical, neurological, or sensory impairments that would interfere significantly with testing, (3) developmental history of learning disability or attention-deficit/hyperactivity disorder, (4) relapse and/or corticosteroid use within four weeks of assessment, (5) known untreated sleep disorder (such as sleep apnea), (6) uncorrected vision loss that would interfere significantly with testing, (7) acute ischemic cardiovascular event or

coronary artery bypass surgery less than 3 months ago, and (8) uncontrolled blood pressure with medication (BP > 190/110mmHg). The study protocol was approved by the KUMC institutional review board.

4.3.2. Procedure

Participants were instructed to refrain from exercise for at least 24 hours prior to testing day, consuming caffeine beyond typical daily consumption, and taking medications other than the ones they typically use. Participants first underwent a battery of questionnaires to assess their mood and sleep quality then performed the fatigability measures in random order. After the assessment, each participant was given an actigraph device and instructed to wear it for a week. Medical history and demographic characteristics were obtained from all the participants.

4.3.3. Sleep measures

The Pittsburgh Sleep Quality Index (PSQI)[108] was utilized to measure self-report sleep quality over the past month. The PSQI is comprised of seven different components scores as well as a single global score ranging from 0–21 with a higher score indicating worse sleep quality.

An actigraph was used to objectively quantify sleep quality. Actigraphy is a cost effective method to measure sleep/wake cycles and has been used in PwMS.[113] Each participant was given an actigraph device (Model wGT3X-BT®, ActiGraph corp. Pensacola, FL) with a stamped envelope to return it via USPS. Instructions were to wear the actigraph on their dominant wrist for seven consecutive days and remove it only during showering or swimming. The parameters of interest from the actigraph include: sleep efficiency, total sleep time, total time in bed, wake after sleep onset, and number of awakenings.

4.3.4. Fatigability measures

Detailed information about the method of administration and scoring of the fatigability measures is described elsewhere.[197] In short, physical fatigability was measured using change in performance on the Six-Minute Walk Test (6MWT) and hand held dynamometer grip strength test. The 6MWT has been previously modified in administration and scoring to assess physical fatigability in PwMS.[55] In addition, time-remaining prompts were eliminated and participants were not informed of the test length. Physical fatigability was calculated as a percent change in the distance walked between the first and sixth minute.

The second measure to assess physical fatigability was change in performance on a grip strength test previously used in PwMS.[57] Participants performed 15 trials of maximal hand grip contractions using a JAMAR hydraulic hand-held dynamometer,[57] holding each contraction for five seconds, with a five-second rest between repetitions. The examiner informed the participants when to squeeze the handle by saying “Squeeze now” and then continue squeeze maximally until the examiner said “Stop”. A metronome heard only by the examiner using a headset was used to maintain the five-second intervals. Physical fatigability was calculated by measuring the percent change in kilograms (kg) between the first and last trial. The test was first administered using the dominant hand and then repeated using the non-dominant hand.

The Continuous Performance Test (Connors 3™)[64] was utilized to assess cognitive fatigability using the Response Speed Variability (RSV) score. RSV was previously found to be effective in detecting cognitive fatigability in PwMS.[56] The mean RSV T-score, the primary outcome measure of the RSV of the participant was used as the main outcome variable.

4.3.5. Other measures

To demonstrate that the fatigability tests were fatiguing the participants, current perceptions of fatigue were assessed immediately preceding and following each measure using the 1 item visual analog fatigue scale.[150] The participants placed a mark (X sign) on a 100 mm line between "not at all fatigued" to "extremely fatigued" to indicate their current level of fatigue. The outcome measure was the value of the length in mm along the line the participants placed the mark at. Participants also completed the Beck Depression Inventory-Fast Screen[132] to assess depression and the Patient Determined Disease Steps[188] which measures disease status in PwMS.

4.3.6. Actigraph data analysis

ActiLife software (version 6.11.8) was used to perform wear time validation and to analyze the sleep data using the Cole-Kripke algorithm which has been validated for use in adult populations.[195] To be included in the data analysis, participants had to have at least four valid days of wear time (a valid day was defined as at least 10 hours of wear time per day which is equivalent to 600 minutes).[194]

4.3.7. Statistical analysis

Data were entered into SPSS version 23 (IBM SPSS Statistics 23, ©IBM) for statistical analysis. Descriptive statistics were calculated for the demographics and all other variables and assumptions of normality were tested using the Shapiro-Wilk test. If assumptions of normality were met for continuous variables, Pearson's product correlations were utilized to explore the association between the fatigability measures and sleep quality measures. Spearman's product correlations were utilized when the assumptions of normality were not met and in variables of ordinal level. Differences in pre- and post-testing acute perceptions of fatigue measured using the

1-item visual analogue fatigue scale were analyzed using Wilcoxon Signed-Rank tests. Alpha level was set at 0.05.

4.4. Results

Fifty-one individuals participated in this study with a mean age of 47 years old ± 10.1, mild disease severity 1.8 ± 1.6, and minimal to mild depression 3.7 ± 3.1 (Table 1). Actigraph details are listed in Table 2.

4.4.1. Fatigability and current perceived fatigue

Results of the fatigability measures and the VAFS is described elsewhere.[197] Briefly, there was a decrease in meters walked on the 6MWT by 12.7% ($p < .001$), the force exerted in the grip strength test decreased by 35.9% on the dominant hand ($p < .001$) and 33.2% on the non-dominant hand ($p < .001$), and current perceived fatigue was significantly higher following performance of each fatigability measure ($p < .001$ on all tests).

4.4.2. Association between physical fatigability and self-reported sleep quality

There were no significant associations between the PSQI global score and any of the physical fatigability measures (Table 3). There was a significant association between the sleep duration component of the PSQI and grip test percent change in the dominant hand (rho= -.397, p= .004) and non-dominant hand (rho= -.366, p= .008). There was also a significant association between the sleep quality component (a single self-rating question of the overall sleep quality) and the grip test percent change of the non-dominant hand (rho= -.284, p= .043). The 6MWT percent change score was not significantly associated with any of the PSQI components (Table 3).

4.4.3. Association between cognitive fatigability and self-reported sleep quality

There was no significant association between the PSQI global score and the cognitive fatigability measure (Table 3). The RSV score was significantly associated with the daytime dysfunction component of the PSQI (rho= .303, p= .030). There was no significant association between cognitive fatigability and the remaining PSQI components (Table 3).

4.4.4. Association between physical fatigability and actigraphy sleep quality

The 6MWT percent change score was significantly associated with the average awakenings time (rho=-.393, p= .004). The grip test percent change score of the non-dominant hand showed a significant association with sleep efficiency (r= .364, p= .009) and total sleep time (r=.357, p= .010). The grip test percent change score of the non-dominant hand was also significantly associated with wake after sleep onset (r=-.311, p= .026). The remaining actigraph parameters were not significantly associated with the fatigability measures (Table 4).

4.4.5. Association between cognitive fatigability and actigraphy sleep quality

The RSV score was significantly associated with sleep efficiency (r=-.342, p= .015). The variability score was also significantly associated with wake after sleep onset (r=.294, p=.039). Cognitive fatigability was not associated with the remaining actigraph parameters (Table 4).

4.5. Discussion

This is the first study that explored the relationship between physical and cognitive fatigability and sleep quality in PwMS. The findings demonstrate that less reported time spent sleeping is associated with higher physical fatigability and higher cognitive fatigability is associated with higher daytime dysfunction. The findings using actigraphy indicate that higher physical fatigability is associated with a longer duration of awakenings during the night, higher physical fatigability is associated with lower sleep efficiency, lower total sleep time, and longer

wake time after the initiation of sleep. Higher cognitive fatigability is associated with lower sleep efficiency and longer wake time after the initiation of sleep. These findings agree with our hypothesis that poor sleep quality would be associated with physical and cognitive fatigability in PwMS.

The fatigability measures utilized in this study resemble everyday life activities (walking, hand motion, sustained attention, etc.) and these activities are fatiguing the participants based on the significant deterioration in performance and the significant increase in acute perceptions of fatigue. In line with our findings, Goldman et al[55] showed deterioration in walking performance during the 6MWT in PwMS compared to healthy controls. Functional neuroimaging evidence demonstrates an association between decreased activation of motor and non-motor cortico-subcortico pathways in the brain during the execution of a motor task in PwMS.[74] The motor tasks represented in the present study are the 6MWT and hand grip test which both showed deterioration in performance for PwMS and are interpreted as physical fatigability. The correlation between physical fatigability and poor sleep quality based on actigraph measures may be explained through central mechanisms that involve decreased activation of non-motor pathways that are involved in regulating sleep quality like the hypothalamus, and through elevated inflammatory cytokines in the CNS that are associated with increased MS-related fatigue and sleep disturbances in PwMS. Poor sleep quality seems to exacerbate physical fatigability in PwMS and therefore should be considered as part of the management plan of MS-related fatigue.

The RSV measure has previously shown to be higher in PwMS compared to healthy controls,[56] and neuroimaging studies found higher RSV is associated with dysfunction of the fronto-cortical networks and decreased white matter brain volume.[75] It is possible that

dysfunction of the fronto-cortical networks might be partially explained by the imbalance of certain inflammatory cytokines that are associated with sleep disturbances in PwMS. Furthermore, the decreased white matter volume may cause dysfunction in regions that regulates sleep quality, specially that evidence demonstrates a strong association between white matter volume and sleep disorders such as sleep apnea in the general population.[198] Future studies are needed to verify these conclusions.

In the present study, actigraph sleep parameters were significantly correlated with grip physical fatigability differently based on hand dominance. Severijns et al.[57] used a similar hand grip test protocol to measure fatigability in PwMS and showed that despite a deterioration in performance during the test of both hands, there was no significant difference in physical fatigability based on hand dominance or affected side in PwMS. The authors argued that the involvement of central factors rather than peripheral muscle weakness influenced the findings.[57] A recent functional neuroimaging study showed that PwMS demonstrated a decline in the activation of cortical motor and non-motor regions during a sustained motor task compared to healthy controls, suggesting the involvement of central factors with fatigability.[74] Therefore, it is likely that the significant association between the actigraph and physical fatigability of the non-dominant hand but not with the dominant hand in the current study is not due to hand dominance. Instead, it is possible that failure of the motor central regions to excite hand muscles was further exacerbated during the grip test on the non-dominant hand as it always followed the dominant side test. Further studies are needed to verify these conclusions and perhaps explore if a resting period between the two tests might change the findings.

The current study found that actigraph sleep parameters showed more relationships with physical fatigability measures than self-report sleep parameters. One possible explanation is the

previously reported lack of agreement between self-report sleep quality on the PSQI and objective sleep measures using actigraphy[199]: 1) PwMS have been shown to underestimate their sleep quality on the PSQI[200], 2) the length and time period of reporting the two sleep quality measurements is different; one month for the PSQI reported before the assessment vs. 1-week for actigraphy measured after the assessment. Furthermore, actigraphy has also been shown to overestimate sleep efficiency and total sleep time.[196] Future studies are necessary to explore if having the actigraph measurement overlap with the PSQI reports would yield more agreement between the sleep quality measures.

The current study has some limitations. First, generalizability is limited as the sample had mild disease severity and mostly relapsing-remitting MS. However, our findings are clinically important as they demonstrated the association between poor sleep quality and fatigability in a sample of individuals with mild disease impairments. Another limitation is the participants were instructed to continue taking their usual medications on the day of the assessment. This might affect the results by improving or inhibiting performance and responses on the tests depending on the medication, but our results clearly show there are still detriments in performance as well as poor sleep quality even with the usage of fatigue or sleep related medications. In addition, keeping the participants on their usual medication provide clinically relevant information as it reflects their normal daily habits.

Around 50% of PwMS have a diagnosable sleep disorder, but a much higher percentage of sleep disorders remain undiagnosed.[100] Although individuals with an known untreated sleep disorder were excluded from participating in the current study, it is possible that there were participants with an undiagnosed sleep disorder which may have influenced our findings. There is evidence suggesting a significant association between obstructive sleep apnea and higher

perceived fatigue in PwMS,[116] and based on the findings of the current study we expect the presence of sleep disorders would affect the performance of physical and cognitive tasks. Future studies should consider actively screening for sleep disorders and then explore the relationship between sleep disorders and fatigability in PwMS. In addition, future studies may explore if treatment of sleep disorders or sleep disturbances improve fatigability, as evidence suggests that treating sleep disorders significantly decreases perceived fatigue in PwMS.[121] In sum, clinicians should consider sleep assessment and management as part of their treatment and rehabilitation plan.

Fatigability is an important construct of MS-related fatigue that is a common debilitating symptom in the MS population. What makes the current study findings significant is that poor sleep quality (self-reported and actigraphy) is related to decreased task performance in both physical and cognitive aspects, which is likely clinically meaningful. As fatigability is related to the ability to efficiently perform tasks that require effortful activity such as walking or engaging in a conversation,[19] poor sleep quality may further aggravate fatigability and may worsen the performance of everyday life tasks. Therefore, sleep quality should be considered as an important clinical characteristic during the assessment and management of MS-related fatigue. More emphasis should be put on considering the role of sleep quality on exacerbating fatigue and exploring the effect of treating sleep disorders on fatigability in PwMS. Future studies might also need to explore the effect of non-pharmacological treatments of poor sleep quality such as sleep hygiene education on improving fatigability in PwMS.

4.6. Tables

Table 1. Demographic and clinical characteristics of the study sample.

Gender	Age	MS Type	Disease Duration	Patient Determined Disease Steps	Mini Mental Status Exam	Beck Depression Inventory
43 F/ 8 M	47 (10.1)	46 RR 5 SP	12.6 (7.6)	1.8 (1.6)	28.7 (1.6)	3.7 (3.1)

Data is reported as mean (standard deviation). RR: Relapsing Remitting MS, SP: Secondary Progressive MS

Table 2. Descriptive statistics of the self-reported (PSQI global score) and objective (actigraph) sleep measures.

PSQI (global score)	Total Time In Bed (min)	Total Sleep Time (min)	Sleep Efficiency (percentage)	Wake After Sleep Onset (min)	Number of Awakenings	Average Awakening time (min)
8.1 (3.8)	489.3 (85.4)	439.1 (86)	89.5 (4.7)	48.2 (21)	12.3 (4.7)	4.1 (1.6)

Data is reported as mean (standard deviation). PSQI: Pittsburgh Sleep Quality Index.

Table 3. Bivariate correlation analysis between the fatigability measures and the PSQI components.

	Fatigability Measures			
PSQI	6MWT %change	Grip test % change Dominant	Grip test % change Non-Dominant	RSV
Global	-.040 (.781)	-.216 (.128)	-.125 (.382)	.045 (.755)
Sleep quality	.100 (.487)	-.212 (.136)	**-.284* (.043)**	.064 (.656)
Sleep latency	-.175 (.221)	-.120 (.401)	-.034 (.812)	-.068 (.635)
Sleep duration	.074 (.604)	**-.366* (.004)**	**-.366* (.008)**	.112 (.434)
Sleep efficiency	.036 (.801)	-.265 (.061)	-.106 (.459)	-.070 (.624)
Sleep disturbances	.027 (.852)	.029 (.841)	-.133 (.353)	-.031 (.832)
Sleep medication	-.046 (.748)	.082 (.568)	.082 (.569)	-.049 (.733)
Daytime dysfunction	-.015 (.917)	-.103 (.472)	-.034 (.811)	**.303* (.030)**

Data is reported as correlation co-efficient r (p-value). * Statistically significant, $p < 0.05$. PSQI: Pittsburgh Sleep Quality Index, 6MWT: Six Minute Walk Test, RSV: Response Speed Variability.

Table 4. Bivariate correlation analysis between the fatigability measures and the actigraph sleep parameters.

	Fatigability Measures			
Actigraph	6MWT %change	Grip test % change Dominant	Grip test % change Non-Dominant	RSV
Sleep Efficiency	.080 (.574)	.128 (.371)	**.364* (.009)**	**-.342* (.015)**
Total Sleep Time	-.220 (.122)	.242 (.088)	**.357* (.010)**	-.028 (.849)
Wake After Sleep Onset	-.137 (.337)	-.128 (.371)	**-.311* (.026)**	**.294* (.039)**
Total Time In Bed	-.249 (.079)	.259 (.067)	.254 (.073)	.048 (.740)
Number of Awakenings	.181 (.204)	-.050 (.725)	-.066 (.645)	.163 (.257)
Average Awakening time	**-.393* (.004)**	-.044 (.760)	-.240 (.090)	.142 (.326)

Data is reported as correlation co-efficient r (p-value). * Statistically significant, $p < 0.05$.

6MWT: Six Minute Walk Test, CPT: Continuous Performance Test.

Chapter 5.

Agreement between the NFI-MS and the MFIS

5.1. Introduction

One of the widely used measures of perceived fatigue in the MS population is the Modified Fatigue Impact Scale (MFIS).[201] The MFIS was created as a modified version of the Fatigue Impact Scale (FIS),[148] it specifically measures perceptions of fatigue in people with MS (PwMS) on three aspects reported in the past four weeks: physical, cognitive, and psychosocial. The MFIS was recommended for use by the Multiple Sclerosis Council for Clinical Practice Guidelines.[170]

The recently validated Neurological Fatigue Index (NFI-MS) by Mills et al.[25] measures perceived fatigue reported in the past two weeks in PwMS. The NFI-MS generates four different components: physical, cognitive, and two sleep related components. The NFI-MS was developed following the standards from the FDA and following a proper psychometric model analysis for developing patient reported outcomes.[25]

The NFI-MS is not commonly used in clinical practice or research, and it is unknown if the NFI-MS physical and cognitive domains agree with the physical and cognitive domains of the MFIS. During the validation process of the NFI-MS, the physical and cognitive domains of the scale were moderately to strongly correlated with the physical and cognitive domains of the MFIS (r=.72 and r=.69 respectively).[25] However, a high correlation does not necessary imply that the two measures agree.[202] Therefore, the purpose of Chapter 5 was to explore the agreement level between the physical domains of the NFI-MS and MFIS and the agreement level between the cognitive domains of the NFI-MS and the MFIS in PwMS. If both measures showed sufficient agreement, the NFI-MS can be used interchangeably with the MFIS to measure physical and cognitive perceptions of fatigue in PwMS.

5.2. Methods

5.2.1. Procedure

The current study utilized a cross sectional study design. All the study procedures and details are described elsewhere (Chapter 2, Chapter 3, and Chapter 4). On the day of the assessment, all the participants completed the NFI-MS first and then the MFIS.

5.2.2. Measures

The Neurological Fatigue Index (NFI-MS): Consists of 23 item, each on a Likert scale from 0-3, with higher score indicating more perceived fatigue. The NFI-MS measures perceived fatigue under three domains: physical, cognitive, and sleep quality. For the purposes of this chapter, only the physical domain and cognitive domain were used in data analysis. The physical domain of the NFI-MS consists of eight items with a score ranging from 0-24. The cognitive domain of the NFI-MS consists of four items ranging from 0-12.

The Modified Fatigue Impact Scale (MFIS): consists of 21 items, each on a Likert scale from 0-4, with higher score indication more perceived fatigue. The MFIS generates three components: physical, cognitive, and psychosocial. For the purposes of this chapter, only the physical domain and cognitive domain were used in data analysis. The physical domain of the MFIS consists of nine items with a score ranging from 0-36. The cognitive domain of the MFIS consists of ten items ranging from 0-40.

5.2.3. Data Analysis

Data was analyzed using SPSS version 23 (IBM SPSS Statistics 23, ©IBM). Descriptive statistics were calculated for the demographics. Bland-Altman analysis was utilized to explore the level of agreement between first the physical domains of the NFI-MS and the MFIS, then

between the cognitive domains of the NFI-MS and the MFIS.[202,203] A one sample t-test was first used to explore if there is a significant variation from zero between the two measures, in which the difference in the scores was the test variable. Bland-Altman plots were constructed to visually explore the anomalies and trends across the data points. On each plot, the mean difference horizontal line was plotted, and the upper and lower 95% confidence limit lines were plotted using the formulae ((standard deviation of the difference * 1.96) ± mean of the difference). To explore if there is a significant proportional bias across the data points, linear regression was utilized were the mean difference was set as the dependent variable and the mean of the two measures was set as the independent variable. Alpha level was set at ≤ 0.05.

5.3. Results

A total of 52 participants with a mean age of 46.8 years old (± 10.1 SD) were included in the analysis. Forty-four females and eight males participated, 47 with relapsing-remitting MS and five with secondary-progressive MS. Participants presented mostly with mild disease (PDDS 1.8 ± 1.6), and an average disease duration of 12.5 ± 7.6.

5.3.1. Agreement between the physical domains

The mean difference value of the two measures was -5.13, the upper confidence limit was 3.28, and the lower confidence limit was -13.55. The initial analysis showed that there was a significant difference between zero and the mean difference of the two scales ($p \leq .001$). This means the two scales are significantly different from each other and they cannot show a useful level of agreement. This finding is further supported by the regression analysis that showed a significant proportional bias between the two measures ($p \leq .001$). Refer to Figure 1 for the Bland-Altman plot.

5.3.2. Agreement between the cognitive domains

The mean difference value of the two measures was -12.17, the upper confidence limit was -0.23, and the lower confidence limit was -24.06. The initial analysis showed that there was a significant difference between zero and the mean difference of the two scales ($p \leq .001$). This means the two scales are significantly different from each other and they cannot show a useful level of agreement. This finding is further supported by the regression analysis that showed a significant proportional bias between the two measures ($p \leq .001$). Refer to Figure 2 for the Bland-Altman plot.

5.4. Discussion and Conclusions

The findings demonstrate that the physical and cognitive domains of the NFI-MS and the MFIS significantly differ from each other in how they measure perceptions of physical and cognitive fatigue in a sample of mild disease MS. Also, the physical and cognitive domains of the two measures do not show useful level of agreement measured using the Bland-Altman analysis.

Based on the findings of Chapter 5, one can conclude that the NFI-MS cannot be used interchangeably or replace the use of the MFIS to measure perceived physical and cognitive fatigue in PwMS. Based on the mean difference values and the values of the data points across the Bland-Altman plots, it seems that the MFIS overestimates perceptions of fatigue compared to the NFI-MS. The lack of agreement between the two measures can be explained by several reasons. First, recent evidence shows some concerns regarding the psychometric properties of the MFIS.[152,159] According to Mills et al.[159] specific items from the physical and cognitive components of the MFIS should be removed for the scale to fit the Rasch model. The Rasch model analysis is a recommended psychometric approach to develop and refine patient reported

outcomes.[155] In addition, different components of the MFIS scale, i.e., items on the cognitive subscale and items on the physical subscale interact and affect the scale's accuracy and the interpretation of its results. On the other hand, the NFI-MS physical and cognitive domains fits in to the Rasch model analysis and no further evaluation of their items is needed.[25] Therefore, the lack of agreement might be explained by the presence of those items in the scale that Mills et al recommended its removal for a more accurate assessment of fatigue. Future studies should explore the agreement between the two measures after the removal of the recommended items from the MFIS.

Furthermore, we believe that part of the lack of agreement between the cognitive domains of the two measures might be due to the large number of cognitive items on the MFIS compared to the low number of items on the NFI-MS (10 items compared to four items respectively). In addition, the difference in the scoring value between the two measures might affect the results. The MFIS will always generate a higher score that the NFI-MS especially for those that report higher levels of fatigue. This because the Likert scale range on the MFIS is 0-4 compared to 0-3 on the NFI-MS.

In summary, the NFI-MS cannot replace the use of the MFIS to measure perceptions of physical and cognitive fatigue in PwMS with mild disease forms. Future studies are needed to verify these conclusions and explore if evaluating the psychometric properties of the MFIS would enhance its agreement with the NFI-MS

5.5. Figure legends

Figure 1. Bland-Altman plot between the physical domains of the NFI-MS and MFIS. NFI-MS: Neurological Fatigue Index, MFIS: Modified Fatigue Impact Scale.

Figure 2. Bland-Altman plot between the physical domains of the NFI-MS and MFIS. NFI-MS: Neurological Fatigue Index, MFIS: Modified Fatigue Impact Scale.

5.6. Figures

Figure 1.

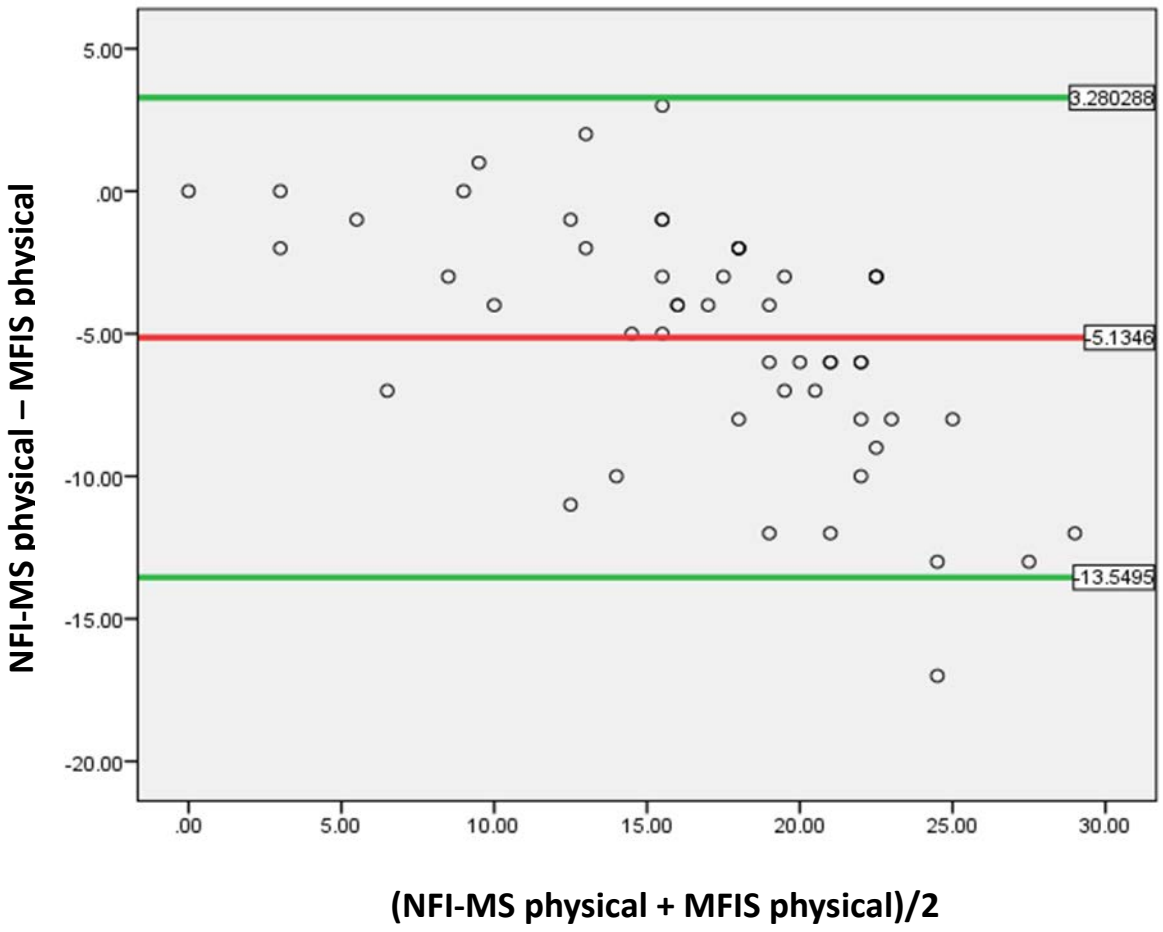
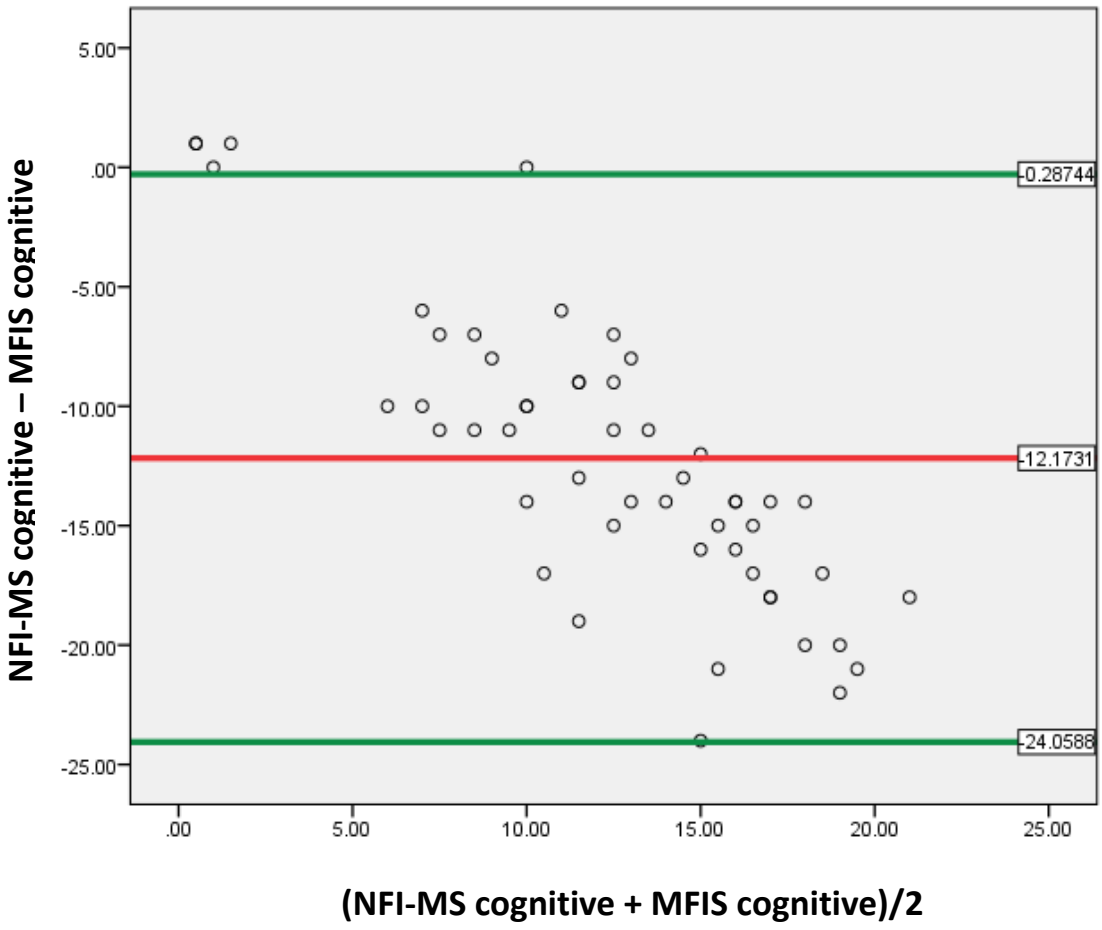


Figure 2.


5.00
.00
-5.00
-10.00
-15.00
-20.00
-25.00
-0.28744
-12.1731
-24.0588
.00
5.00
10.00
15.00
20.00
25.00
NFI-MS cognitive – MFIS cognitive
(NFI-MS cognitive + MFIS cognitive)/2

Chapter 6.

Discussion and Conclusions

6.1. Summary of findings

The research and body of work presented in the current study aimed to understand the relationship between perceptions of fatigue, fatigability, and sleep quality in people with MS (PwMS). MS-related fatigue is a complex multidimensional symptom that significantly degrades the functional life of PwMS.[4-7] Sleep disturbances are common in the MS population and are more likely to increase MS-related fatigue. [14,21-23] Perceived fatigue is a construct of fatigability that was studied extensively in previous research.[19,49,50] However, there have been recent concerns regarding the psychometric properties of the most commonly used scales of perceived fatigue in PwMS.[156,159] Our study utilized a more psychometrically sound scale of perceived fatigue called the Neurological Fatigue Index (NFI-MS) that is validated for use in PwMS.[25]

One of the primary goals of this research was to explore the relationship between perceived fatigue using the NFI-MS and physical and cognitive fatigability. Our findings demonstrated that perceived physical fatigue is not associated with physical fatigability, while physical and cognitive perceived fatigue were associated with cognitive fatigability (Chapter 2). We also explored the relationship between the NFI-MS and sleep quality that is measured using self-reported scales and objectively using 1-week actigraphy. Our results showed that perceived fatigue is associated with only self-reported sleep quality but not with any of the actigraph parameters (Chapter 3). Finally, we explored the relationship between fatigability and sleep quality which to our knowledge has never been explored before. Our findings showed that physical and cognitive fatigability are both associated with several self-reported and objective sleep quality parameters (Chapter 4). This chapter summarizes the findings presented in this body of work and discusses important clinical implications, limitations of our research, and future directions for which studies should be based.

6.1.1. Chapter 2. The relationship between fatigability and perceived fatigue measured using the Neurological Fatigue Index in people with MS

Previous studies that explored the relationship between perceived fatigue and fatigability had conflicting results.[55,58] None of those previous studies measured perceived fatigue using the NFI-MS. Instead, those studies used the most common perceived fatigue scales that are recently being questionable in terms of their psychometric properties. The main purpose of Chapter 2 was to explore the relationship between the NFI-MS and measures of physical and cognitive fatigability in PwMS. We utilized in the current study physical and cognitive measures that had been previously modified and used to capture physical and cognitive fatigability in PwMS.[55,57,63,181] We further modified these tests to better capture fatigability in our sample. Physical fatigability was measured through percent change in meters walked on the six Minute Walk Test (6MWT), percent change in the force exerted on a repetitive grip strength test, and Response Speed Variability (RSV) measured using the Continuous Performance Test (CPT). We further determined whether the fatigability measures were fatiguing the participants by measuring their current perceptions of fatigue right before and after performing each fatigability measure. We initially hypothesized that due to proper psychometric evaluation and validation of the NFI-MS together with items within the scale that reflect fatigability, there will be significant associations between the NFI-MS and physical and cognitive fatigability. However, our results demonstrated an association between the NFI-MS and cognitive fatigability, not with physical fatigability.

Although it is believed that the etiology behind both perceived fatigue and fatigability is due to dysfunction of the motor and cognitive cortical and subcortical networks centrally,[9,19,47,67] peripheral factors might also be involved with physical fatigability.[18,67] This may explain the lack

of association between perceived fatigue and physical fatigability in our sample. Furthermore, we believe that the physical component of the NFI-MS may lack items that objectify performance fatigability and that might have affected the results. On the other hand, perceived fatigue and physical fatigability might simply be independent constructs, and in order to measure MS-related fatigue, measures of perceived fatigue and fatigability should be utilized collectively in both research and clinical settings. The fatigability measures further demonstrated that they are fatiguing the participants in our study, which was presented by both a significant detriment in performance and a significant increase in current perceived fatigue post testing. Future studies are needed to verify these conclusions.

6.1.2. Chapter 3. The relationship between sleep quality and perceived fatigue measured using the Neurological Fatigue Index in people with MS

The relationship between perceived fatigue and sleep quality has been studied extensively before, especially in the last several years, as more attention is being drawn towards the effect of sleep disturbances and sleep disorders on several life indices in the MS population.[19,28-34] What makes the current body of work significant and different is the utilization of the NFI-MS as a measure of perceived fatigue. The NFI-MS was developed following the standards of a proper psychometric model analysis for developing patient reported outcomes.[25] Furthermore, to our knowledge the NFI-MS is the only validated perceived fatigue scale that has two sleep components acknowledging the importance of considering sleep quality as a factor when one wants to assess perceived fatigue in PwMS. Chapter 3 focused on exploring the relationship between the NFI-MS and sleep quality in PwMS. We utilized self-reported and objective measures of sleep in the current study. Specifically, we used the gold standard self-reported sleep

quality scale, the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). We used one week of actigraphy to objectively quantify sleep quality in our study sample.

Our findings demonstrated that perceived fatigue was associated with poorer self-reported sleep quality but not with any of the actigraph parameters. We argue that perhaps the underestimation of the self-reports[200] vs the overestimation of the objective measure[113,196] affected the results. Furthermore, there was no overlap between the time we gave the actigraph to the participants and the time they reported their sleep quality, which might have affected the findings. In addition, a longer actigraph wear time of two weeks might be needed to detect poor sleep quality in our study sample. Attarian et al.[105] who found associations between perceived fatigue and actigraph parameters in PwMS, had a longer actigraph wear time of two weeks. However, our results support previous research in that higher perceived fatigue is associated with poorer sleep quality in PwMS. Specifically, higher perceived fatigue that is attributed to abnormal nocturnal is associated with poorer self-reported sleep quality in our study sample. The NFI-MS can be easily administered and scored in clinical and research settings to measure the effect sleep quality has on perceived fatigue in PwMS.

6.1.3. Chapter 4. The relationship between fatigability and sleep quality in people with MS

It is believed that fatigability in PwMS may result from a dysfunction in motor and cognitive networks in several cortical regions in the brain and the spinal cord in PwMS.[19,204] Furthermore, it is thought that sleep disturbances result from excessive activation of the central nervous system, hence its association with perceived fatigue.[116] However, the relationship between sleep quality and fatigability have never been studied before. Therefore, the main aim of Chapter 4 was to explore the relationship between physical and cognitive fatigability with sleep quality in

PwMS. Due to the involvement of central factors of both fatigability and sleep quality, we hypothesized that both will be associated.

We utilized the same fatigability measures used in chapter 2, and the same sleep quality measures from chapter 3. Our results showed that poorer self-reported sleep quality was associated with higher physical fatigability on both the 6MWT and grip test, and was also associated with higher cognitive fatigability. Several parameters from the actigraph were associated with higher grip physical fatigability (only non-dominant hand) and with higher cognitive fatigability. Our findings support the theory behind the involvement of central factors for both fatigability and sleep quality and will provide the framework and basis for future research in this field.

6.1.4. Chapter 5. Agreement between the NFI-MS and the MFIS

The Modified Fatigue Impact Scale (MFIS) is a widely used measure of perceived fatigue in the MS population. It is also recommended for use by the Multiple Sclerosis Council for Clinical Practice Guidelines. The Neurological Fatigue Index (NFI-MS) have been recently validated for use as a measure for perceived fatigue in PwMS but is still not commonly used. Although the physical and cognitive domains of the two measures highly correlate with each other, the agreement between the two measures has never been explored before. The purpose of Chapter 5 was to explore the agreement level between the physical domains of the MFIS and the NFI-MS, and the agreement level between the cognitive domains of the two measures.

The Bland-Altman analysis revealed significant differences between both the physical and cognitive domains of the two measures, as well as significant proportional bias across the data points of the physical and cognitive domains. Our findings demonstrate that the MFIS and the NFI-MS cannot show a useful level of agreement in measuring physical and cognitive

perceptions of fatigue in our study sample. We argue, that perhaps the psychometric concerns regarding the MFIS and the difference in the number of items and scoring scales between the two measures may have contributed to the lack of agreement. Future studies are needed to verify these conclusions.

6.2 Clinical Implications

The findings of the current body of work have several interesting clinical implications. First, the NFI-MS is a validated, easy to administer, and easy to score scale that can be used more widely in clinical settings to measure perceptions of fatigue in different domains in PwMS. In addition, the physical measures utilized in this study to capture physical fatigability are already commonly used in clinical settings and can be easily modified by the clinician or therapist to capture physical fatigability. The CPT can be easily purchased and used as a measure of cognitive fatigability. The measures utilized in the current study can be used before and after treatment and rehabilitation interventions as outcome measures to explore the effect of different treatments on MS-related fatigue in PwMS.

Despite our study participants being functionally independent individuals with active life styles, this sample had a significant detriment in physical and cognitive performance and high perceptions of fatigue that negatively affected their physical and mental quality of lives. This finding clearly shows the negative effect MS-related fatigue has on the functional quality of life of PwMS regardless of their functional independency and mild disease status. This was supported by the important finding in Chapter 2 in which higher perceived fatigue was significantly associated with a decreased physical quality of life. Those findings are clinically important, and clinicians and therapists may need to emphasize management and treatment options of MS-related fatigue in those with even less severe forms of MS. Despite those

individuals having independent, active lives, their fatigue can affect other important life indices: such as their interpersonal relationships, their sleep quality, and their mood and psychological well-being. Based on the findings of this study, we assume that perceived fatigue and fatigability would have a larger impact on those with severe forms with MS. Therefore, health care providers should also emphasize treatment and management options of MS-related fatigue in severe forms of MS to enhance the quality of life of those individuals.

Our findings demonstrated the significant effect poor sleep quality has on MS-related fatigue. The results from Chapter 3 supports previous research that showed how self-reported poor sleep quality is associated with perceived fatigue in PwMS. Sleep disturbances are common in the MS population and have been shown to be associated with mood disturbances, reduced work load, and physical function in PwMS. We encourage a wider use of the NFI-MS especially because it is the only known scale to include sleep components that measure the effect of sleep quality on perceived fatigue in the MS population. Chapter 4 findings are novel in terms of the association between poor sleep quality and higher physical and cognitive fatigability. The fatigability measures utilized in this study resemble everyday life activities, and the finding that poor sleep quality may be a detriment to the performance of those tasks is clinically vital.

Clinical settings should emphasize the need to assess sleep quality in PwMS and perhaps consider focusing part of their treatment plan to manage sleep disturbances that may contribute to the management of MS-related fatigue. It is important to note here that although we excluded those with untreated sleep disorders, it is possible that there were participants with an undiagnosed sleep disorder. The assessment of sleep disorders in the MS population is often overlooked by clinicians,[100,101] and we encourage clinical settings to consider assessing for sleep disorders by referring their patients to sleep specialists. There is evidence that showed treating

sleep disorders decreased perceived fatigue in the MS population.[121] Based on the findings of the current study, sleep quality seems to be an important clinical characteristic that is necessary to consider during the assessment and management of MS-related fatigue.

6.3. Limitations

The authors of this research acknowledge that although they attempted to avoid and minimize limitations where possible, some limitations are unavoidable with clinical research. Specific limitations are discussed in detail in individual chapters, but in this section we outline several broad limitations of the discussed chapters.

6.3.1. Cross-sectional study design

As with all cross-sectional study designs, we cannot interpret our findings into a cause-effect relationship. And gathering information at a single time point would prevent us from knowing if our findings would differ over time or in response to any external stimulus. Despite our attempt to schedule the participants on a similar time for the assessments, this was difficult to accomplish due to personal preference or due to work conflicts that made the time of the assessments variable across the participants. We tried to minimize the effect of those factors by instructing our participants to refrain from exercise 24 hours before the assessment day, and alcohol and caffeine consumption beyond usual intake at least 24 hours before assessment day. Furthermore, the temperature and humidity in the testing area were kept constant almost all the time (measured using a temperature/humidity sensor), and if any of the participants felt over-heated a fan was available to cool the participants. We believe for the purposes of our study, a cross-sectional study design was adequate to explore the associations between the outcome measures of interest.

6.3.2. Medication usage

Prior to assessment, none of the participants were instructed to refrain from taking their usual fatigue and/or sleep related medications. In fact, we instructed the participants to continue using their usual medications and only avoid taking medications other than their typical ones. This might have affected their performance and response on the study measures. In addition, we attempted initially to collect current medication usage from all participants during the screening procedure. However, it was difficult to collect all the medication lists from all the participants as some forgot to bring the list on the day of the assessment and cannot remember all the medications they take, and due to difficulty contacting them after the assessments to gather this information. Therefore, there was not enough information regarding the sample's medication usage to use for post-hoc analysis. However, we tried to explore their sleep quality and MS-related fatigue without drastic changes to their usual medication usage. We believed it would be more difficult to interpret the findings if we asked the participants to stop their usual medications, because they will get back to their daily habits after the assessments and it will be hard to generalize our findings. Furthermore, the study has an important part of assessment which is the one week of actigraphy after the testing day. If the participants stopped their usual medications on the day of the study assessment, it will make more sense to ask them to stop their medications through the one week of actigraphy measure to accurately interpret the results. However, the authors believe that this is un-ethical to do and might have health consequences on the participants that would interfere significantly with the findings of the study.

6.3.3. Study sample clinical characteristics

The findings of the current research are not generalizable to individuals with MS with moderate to severe disease severity, as the study sample on average had mild disease severity

with mostly relapsing-remitting MS. The authors believe that some of the measures utilized in the study, specifically the physical and cognitive measures, would be difficult for those with more severe forms of MS to perform. Out of the 52 participants in the study, only five had secondary-progressive MS in which all were independent in mobility even with the use of an assistive device. Therefore, the findings of the study are well representable for only those PwMS who are functionally independent.

In addition, pain has been found to exacerbate fatigue in the MS population.[133,139] However, we did not collect or measure pain related information, which might have influenced the participants' responses on our outcome measures. Another factor that may have influenced our findings is the possible presence of an undiagnosed sleep disorder. We tried to control for this factor by excluding those with known untreated sleep disorders, but with the current study procedures utilized we cannot control for those with an underdiagnoses of a sleep disorder. It is acknowledged in the literature that a high percentage of PwMS are undiagnosed with sleep disorders,[100] which is an issue that needs serious attention from clinicians.

6.3.4. Involvement of peripheral physical factors

Performance on the physical fatigability measures utilized in the current study may have been influenced by peripheral factors.[18,66,67] It will be difficult to conclude that our findings are purely the result of the dysfunction of the central motor networks. But it is believed that central factors appear to be the largest contributor to MS-related fatigue rather than peripheral ones.[19,68,69,204] The involvement of peripheral factors might also be the reason why other studies that utilized similar physical fatigability measures did not find any association with perceived physical fatigue.[57,60] However, the authors of the current research acknowledge that perceptions of fatigue and fatigability are two independent constructs of MS-related fatigue, and the lack of

association does not necessary mean a negative result. We believe that both constructs should be considered collectively for a more accurate comprehensive assessment of MS-related fatigue.

6.3.5. Lack of correction for multiple comparisons

Correction for multiple comparisons have not been made in the current study. However, the authors consider the current research exploratory due to the novel use of the NFI-MS as a measure of perceived fatigue to investigate its relationship with sleep quality and fatigability in PwMS. Furthermore, a larger sample size may reveal further significant results, but the required sample size was calculated during the study development, and enrollment was successfully achieved. Therefore, the authors are confident in the number of participants enrolled for every study chapter.

6.4. Future directions

Important implications for future studies can be derived from the experiments and findings conducted by this current body of work. The following section discusses the future directions that are relevant to the MS-related fatigue field of research.

6.4.1. Investigating the effect of exercise interventions on perceived fatigue and fatigability in PwMS

Different exercise interventions have been utilized before to explore their effect on perceived fatigue in PwMS.[157,158,173,205] However, those studies had conflicting results: some found benefits of exercise on perceived fatigue, while others found no difference. To date, there is no consensus on what is the optimal type of exercise (aerobic, resistive, or combined) and intensity of exercise (moderate or vigorous) that decreases perceived fatigue in PwMS. Furthermore, none of those previous studies have utilized the NFI-MS before, and to our knowledge no previous study has explored the effect of exercise on fatigability in PwMS.

Therefore, it would be interesting to explore the effect of different modes of exercise on perceived fatigue and fatigability in PwMS. If found beneficial, exercise can be used as a non-pharmacological treatment of MS-related fatigue and therefore lessen the side effects and the financial burden of the fatigue-related medications in PwMS. We recommend future studies to collectively use the NFI-MS and the fatigability measures used in the current study as outcome measures pre and post the exercise interventions.

6.4.2. Assessing the relationship between sleep quality measured using Polysomnography and fatigability in PwMS

Polysomnography (PSG) is the gold standard objective measure of sleep quality.[111] The use of PSG can yield different sleep quality information compared to actigraphy (such as time spent in the different sleep stages), and can be used as a diagnostic tool for several sleep disorders. Few studies have explored the relationship between perceived fatigue and PSG.[14,190,191] Those studies showed an association between higher perceived fatigue and sleep disorders and alterations in the sleep stages compared to healthy controls. None of the previously mentioned studies have used the NFI-MS as a measure of perceived fatigue. Perhaps future PSG studies might demonstrate different interesting findings with the use of the NFI-MS instead of the commonly used scales.

Evidence demonstrates that the treatment of sleep disorders decreases perceived fatigue in PwMS.[14,121] However, the relationship between sleep disorders and sleep quality measured using PSG and fatigability is unknown in PwMS. It is acknowledged in the literature that a high percentage of PwMS may have an undiagnosed sleep disorder.[100] Future studies and even clinical and research settings should emphasize the need to assess for sleep disorders in the MS population. Based on the findings of Chapter 4, we assume that the presence of an untreated

sleep disorder would further increase fatigability. Future studies should perhaps investigate the effect of treating sleep disorders on fatigability in PwMS. Furthermore, poor sleep quality can occur even in the absence of a sleep disorder. Therefore, future studies can investigate the effect of non-pharmacological sleep-related treatment options, such as sleep hygiene educational programs that can indirectly affect fatigability through the improvement of sleep quality.

6.4.3. Neural correlates with the NFI-MS and fatigability in PwMS

Several neuroimaging studies[70-73,206] have showed an association between perceived fatigue and several brain regions and microstructures in PwMS. However, none of those studies used the NFI-MS as a measure of perceived fatigue. Future neuroimaging studies might consider using the NFI-MS and explore its relationship with central regions. Perhaps because the NFI-MS is a more psychometrically sound scale than other scales, as different findings might be yielded.

Nerve stimulation and transcranial magnetic stimulation (TMS) studies in healthy people have shown an association between physical fatigability and alterations in the excitability of the motor cortex and spinal cord.[76,77] In addition, cortical alterations and dysfunction of the cognitive and motor planning networks that are associated with perceived fatigue in PwMS support the theory behind the involvement of central factors with fatigability.[19] A combined assessment with magnetic resonance imaging (MRI) and transcranial magnetic stimulation (TMS) showed that perceived fatigue is associated with motor regions in the brain that are responsible for movement preparation, suggesting the possible involvement of physical fatigability in PwMS.[204] The research on fatigability is still ongoing and we encourage future imaging studies to collectively measure MS-related fatigue using the NFI-MS and the fatigability measures utilized in the current research. For example, Diffusion Tensor Imaging (DTI)[207] technique that is used to extensively characterize changes in white matter fiber tracts (such as demyelination), can be used

to explore the relationship between those microstructural changes and the NFI-MS and fatigability in PwMS. Exploring structural neural correlates with the NFI-MS and the fatigability would further support the central theory behind MS-related fatigue and lessens the ambiguity of this complex symptom. In addition, understanding the relationship between MS-related fatigue and the central nervous system can potentially guide clinical studies to develop more effective medications to manage MS-related fatigue.

6.5. Conclusions

In conclusion, the work presented in this dissertation expands on the body of evidence showing the relationship between perceived fatigue, fatigability, and sleep quality in PwMS. Our experiments and findings are novel and significant through the use of the NFI-MS as a measure of perceived fatigue and through the assessment of the association between sleep quality and fatigability in PwMS. The findings of this work demonstrate that perceived fatigue is associated with cognitive fatigability but not with physical fatigability in PwMS, and that decreased physical quality of life is a large contributor to perceived fatigue in PwMS with mild disease severity. Furthermore, higher perceived fatigue is significantly associated with poorer self-reported sleep quality and excessive daytime sleepiness, but not with objectively assessed sleep quality. The presented work also provides the first evidence that poor sleep quality may contribute to fatigability in PwMS. More emphasis should be put on considering the role of sleep quality on exacerbating MS-related fatigue in those with the mild-disease forms of MS. Clinicians and therapists may need to consider sleep assessment and treatment as part of the MS-related fatigue management plan. Future studies can investigate the effect of different exercise interventions or sleep hygiene educational programs on MS-related fatigue using the outcome measures utilized in this work.

References

1. Berger JR, Pocoski J, Preblick R, Boklage S. Fatigue heralding multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* Feb 25 2013.
2. Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil.* Mar 1984;65(3):135-138.
3. Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. *Sleep.* Aug 2010;33(8):1061-1067.
4. Goksel Karatepe A, Kaya T, Gunaydn R, Demirhan A, Ce P, Gedizlioglu M. Quality of life in patients with multiple sclerosis: the impact of depression, fatigue, and disability. *Int J Rehabil Res.* Dec 2011;34(4):290-298.
5. Smith MM, Arnett PA. Factors related to employment status changes in individuals with multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* Oct 2005;11(5):602-609.
6. Blaney BE, Lowe-Strong A. The impact of fatigue on communication in multiple sclerosis. The insider's perspective. *Disabil Rehabil.* 2009;31(3):170-180.
7. Glanz BI, Degano IR, Rintell DJ, Chitnis T, Weiner HL, Healy BC. Work productivity in relapsing multiple sclerosis: associations with disability, depression, fatigue, anxiety, cognition, and health-related quality of life. *Value Health.* Dec 2012;15(8):1029-1035.
8. Siegert RJ, Abernethy DA. Depression in multiple sclerosis: a review. *J Neurol Neurosurg Psychiatry.* Apr 2005;76(4):469-475.
9. Bol Y, Duits AA, Hupperts RM, Vlaeyen JW, Verhey FR. The psychology of fatigue in patients with multiple sclerosis: a review. *J Psychosom Res.* Jan 2009;66(1):3-11.

10. Kinsinger SW, Lattie E, Mohr DC. Relationship between depression, fatigue, subjective cognitive impairment, and objective neuropsychological functioning in patients with multiple sclerosis. *Neuropsychology.* 2010;24(5):573.

11. Lobentanz IS, Asenbaum S, Vass K, et al. Factors influencing quality of life in multiple sclerosis patients: disability, depressive mood, fatigue and sleep quality. *Acta Neurol Scand.* Jul 2004;110(1):6-13.

12. Bamer AM, Johnson KL, Amtmann DA, Kraft GH. Beyond fatigue: Assessing variables associated with sleep problems and use of sleep medications in multiple sclerosis. *Clin Epidemiol.* May 1 2010;2010(2):99-106.

13. Veauthier C, Paul F. Fatigue in multiple sclerosis: which patient should be referred to a sleep specialist? *Multiple sclerosis (Houndmills, Basingstoke, England).* Feb 2012;18(2):248-249.

14. Veauthier C, Radbruch H, Gaede G, et al. Fatigue in multiple sclerosis is closely related to sleep disorders: a polysomnographic cross-sectional study. *Multiple sclerosis (Houndmills, Basingstoke, England).* May 2011;17(5):613-622.

15. Diamond BJ, Johnson SK, Kaufman M, Graves L. Relationships between information processing, depression, fatigue and cognition in multiple sclerosis. *Arch Clin Neuropsychol.* Mar 2008;23(2):189-199.

16. Krupp LB, Elkins LE. Fatigue and declines in cognitive functioning in multiple sclerosis. *Neurology.* 2000;55(7):934-939.

17. Weinges-Evers N, Brandt AU, Bock M, et al. Correlation of self-assessed fatigue and alertness in multiple sclerosis. *Multiple Sclerosis.* 2010;16(9):1134-1140.

18. Finsterer J, Mahjoub SZ. Fatigue in Healthy and Diseased Individuals. *Am J Hosp Palliat Care.* Jul 26 2013.

19. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy. *Neurology.* Jan 22 2013;80(4):409-416.

20. Murphy S, Niemiec SS. Aging, Fatigue, and Fatigability: Implications for Occupational and Physical Therapists. *Current Geriatrics Reports.* 2014;3(3):135-141.

21. Bamer AM, Johnson KL, Amtmann D, Kraft GH. Prevalence of sleep problems in individuals with multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* Sep 2008;14(8):1127-1130.

22. Fleming WE, Pollak CP. Sleep disorders in multiple sclerosis. *Semin Neurol.* Mar 2005;25(1):64-68.

23. Veauthier C, Paul F. Sleep disorders in multiple sclerosis and their relationship to fatigue. *Sleep medicine.* Jan 2014;15(1):5-14.

24. Mills RJ, Young CA. A medical definition of fatigue in multiple sclerosis. *Qjm.* Jan 2008;101(1):49-60.

25. Mills RJ, Young CA, Pallant JF, Tennant A. Development of a patient reported outcome scale for fatigue in multiple sclerosis: The Neurological Fatigue Index (NFI-MS). *Health Qual Life Outcomes.* 2010;8:22.

26. Compston A, Coles A. Multiple sclerosis. *Lancet.* Oct 25 2008;372(9648):1502-1517.

27. Janardhan V, Bakshi R. Quality of life in patients with multiple sclerosis: the impact of fatigue and depression. *J Neurol Sci.* Dec 15 2002;205(1):51-58.

28. Motl RW, McAuley E, Snook EM, Gliottoni RC. Physical activity and quality of life in multiple sclerosis: intermediary roles of disability, fatigue, mood, pain, self-efficacy and social support. *Psychol Health Med.* Jan 2009;14(1):111-124.

29. Pryse-Phillips W, Costello F. *The epidemiology of multiple sclerosis.* New York: Marcel Dekker, Inc.; 2001.

30. Whetten-Goldstein K, Sloan F, Goldstein L, Kulas E. A comprehensive assessment of the cost of multiple sclerosis in the United States. *Multiple sclerosis* 1998;4(5):419-425.

31. Grant I, McDonald WI, Trimble MR, Smith E, Reed R. Deficient learning and memory in early and middle phases of multiple sclerosis. *Journal of neurology, neurosurgery, and psychiatry.* Mar 1984;47(3):250-255.

32. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. *Archives of neurology.* Apr 1988;45(4):435-437.

33. Charvet L, Serafin D, Krupp LB. Fatigue in multiple sclerosis. *Fatigue: Biomedicine, Health & Behavior.* 2013(ahead-of-print):1-11.

34. Ongagna J, Passadori A, Pinelli J, Isner-Horobeti M, Zaenker C, De Seze J. [Difficulties experienced at work by patients with multiple sclerosis]. *Revue neurologique.* 2015.

35. DeLuca J. 19 Fatigue: Its Definition, Its Study, and Its Future. *Fatigue as a window to the brain.* 2005:319.

36. Kos D, Kerckhofs E, Nagels G, D'Hooghe M B, Ilsbroukx S. Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabil Neural Repair.* Jan-Feb 2008;22(1):91-100.

37. Johnson SL. The concept of fatigue in multiple sclerosis. *Journal of neuroscience Nursing.* 2008;40(2):72-77.

38. Huijbregts SC, Kalkers NF, de Sonneville LM, de Groot V, Polman CH. Cognitive impairment and decline in different MS subtypes. *J Neurol Sci.* Jun 15 2006;245(1-2):187-194.

39. Khan F, Amatya B, Galea M. Management of fatigue in persons with multiple sclerosis. *Front Neurol.* 2014;5:177.

40. Gallo P, Van Wijmeersch B. Overview of the management of relapsing-remitting multiple sclerosis and practical recommendations. *Eur J Neurol.* Oct 2015;22 Suppl 2:14-21.

41. Branas P, Jordan R, Fry-Smith A, Burls A, Hyde C. Treatments for fatigue in multiple sclerosis: a rapid and systematic review. *Health Technol Assess.* 2000;4(27):1-61.

42. Kraft GH. Rehabilitation principles for patients with multiple sclerosis. *J Spinal Cord Med.* Apr 1998;21(2):117-120.

43. Thomas S, Thomas PW, Kersten P, et al. A pragmatic parallel arm multi-centre randomised controlled trial to assess the effectiveness and cost-effectiveness of a group-based fatigue management programme (FACETS) for people with multiple sclerosis. *J Neurol Neurosurg Psychiatry.* Oct 2013;84(10):1092-1099.

44. Simpson R, Booth J, Lawrence M, Byrne S, Mair F, Mercer S. Mindfulness based interventions in multiple sclerosis--a systematic review. *BMC Neurol.* 2014;14:15.

45. Asano M, Finlayson ML. Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. *Mult Scler Int.* 2014;2014:798285.

46. Leocani L, Colombo B, Comi G. Physiopathology of fatigue in multiple sclerosis. *Neurological Sciences.* 2008;29(2):241-243.

47. Chaudhuri A, Behan PO. Fatigue in neurological disorders. *Lancet.* Mar 20 2004;363(9413):978-988.

48. Landmark-Hoyvik H, Reinertsen KV, Loge JH, et al. The genetics and epigenetics of fatigue. *Pm r.* May 2010;2(5):456-465.

49. Mota DD, Pimenta CA. Self-report instruments for fatigue assessment: a systematic review. *Research and Theory for Nursing Practice.* 2006;20(1):49-78.

50. Flachenecker P, Kümpfel T, Kallmann B, et al. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Multiple Sclerosis.* 2002;8(6):523-526.

51. Elbers RG, Rietberg MB, van Wegen EE, et al. Self-report fatigue questionnaires in multiple sclerosis, Parkinson's disease and stroke: a systematic review of measurement properties. *Qual Life Res.* Aug 2012;21(6):925-944.

52. Eldadah BA. Fatigue and fatigability in older adults. *Pm r.* May 2010;2(5):406-413.

53. Schnelle JF, Buchowski MS, Ikizler TA, Durkin DW, Beuscher L, Simmons SF. Evaluation of two fatigability severity measures in elderly adults. *J Am Geriatr Soc.* Aug 2012;60(8):1527-1533.

54. Walker LA, Berard JA, Berrigan LI, Rees LM, Freedman MS. Detecting cognitive fatigue in multiple sclerosis: method matters. *J Neurol Sci.* May 15 2012;316(1-2):86-92.

55. Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. *Multiple sclerosis (Houndmills, Basingstoke, England).* Apr 2008;14(3):383-390.

56. Bruce JM, Bruce AS, Arnett PA. Response variability is associated with self-reported cognitive fatigue in multiple sclerosis. *Neuropsychology.* Jan 2010;24(1):77-83.

57. Severijns D, Lamers I, Kerkhofs L, Feys P. Hand grip fatigability in persons with multiple sclerosis according to hand dominance and disease progression. *J Rehabil Med.* Sep 30 2014.

58. Wolkorte R, Heersema DJ, Zijdewind I. Muscle Fatigability During a Sustained Index Finger Abduction and Depression Scores Are Associated With Perceived Fatigue in Patients With Relapsing-Remitting Multiple Sclerosis. *Neurorehabil Neural Repair.* Sep 2015;29(8):796-802.

59. Wolkorte R, Heersema DJ, Zijdewind I. Reduced Voluntary Activation During Brief and Sustained Contractions of a Hand Muscle in Secondary-Progressive Multiple Sclerosis Patients. *Neurorehabilitation and neural repair.* 2015:1545968315593809.

60. Leone C, Severijns D, Dolezalova V, et al. Prevalence of Walking-Related Motor Fatigue in Persons With Multiple Sclerosis: Decline in Walking Distance Induced by the 6-Minute Walk Test. *Neurorehabil Neural Repair.* Jul 27 2015.

61. Lou JS, Kearns G, Benice T, Oken B, Sexton G, Nutt J. Levodopa improves physical fatigue in Parkinson's disease: a double-blind, placebo-controlled, crossover study. *Mov Disord.* Oct 2003;18(10):1108-1114.

62. Bailey A, Channon S, Beaumont JG. The relationship between subjective fatigue and cognitive fatigue in advanced multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* Jan 2007;13(1):73-80.

63. Lamers I, Timmermans AA, Kerkhofs L, Severijns D, Van Wijmeersch B, Feys P. Self-reported use of the upper limbs related to clinical tests in persons with multiple sclerosis. *Disabil Rehabil.* 2013;35(23):2016-2020.

64. Conners CK. Conners 3rd edition (Conners 3). *North Tonawanda, NJ: Multi-Health System.* 2008.

65. Chaudhuri A, Behan PO. Fatigue and basal ganglia. *J Neurol Sci.* Oct 1 2000;179(S 1-2):34-42.

66. Garner DJ, Widrick JJ. Cross-bridge mechanisms of muscle weakness in multiple sclerosis. *Muscle & nerve.* Apr 2003;27(4):456-464.

67. Latash M, Kalugina E, Nicholas J, Orpett C, Stefoski D, Davis F. Myogenic and central neurogenic factors in fatigue in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* Feb 1996;1(4):236-241.

68. Kindred JH, Ketelhut NB, Rudroff T. Glucose uptake heterogeneity of the leg muscles is similar between patients with multiple sclerosis and healthy controls during walking. *Clinical biomechanics (Bristol, Avon).* Feb 2015;30(2):159-165.

69. Kindred JH, Koo PJ, Rudroff T. Glucose uptake of the spinal cord in patients with multiple sclerosis detected by (1)(8)F-fluorodeoxyglucose PET/CT after walking. *Spinal cord.* Nov 2014;52 Suppl 3:S11-13.

70. Roelcke U, Kappos L, Lechner-Scott J, et al. Reduced glucose metabolism in the frontal cortex and basal ganglia of multiple sclerosis patients with fatigue: a 18F-fluorodeoxyglucose positron emission tomography study. *Neurology.* Jun 1997;48(6):1566-1571.

71. Bester M, Lazar M, Petracca M, et al. Tract-specific white matter correlates of fatigue and cognitive impairment in benign multiple sclerosis. *J Neurol Sci.* Jul 15 2013;330(1-2):61-66.

72. Filippi M, Rocca MA, Colombo B, et al. Functional magnetic resonance imaging correlates of fatigue in multiple sclerosis. *NeuroImage.* Mar 2002;15(3):559-567.

73. Wilting J, Rolfsnes HO, Zimmermann H, et al. Structural correlates for fatigue in early relapsing remitting multiple sclerosis. *European radiology.* 2015:1-9.

74. Steens A, Heersema DJ, Maurits NM, Renken RJ, Zijdewind I. Mechanisms underlying muscle fatigue differ between multiple sclerosis patients and controls: a combined electrophysiological and neuroimaging study. *NeuroImage.* Feb 15 2012;59(4):3110-3118.

75. Walhovd KB, Fjell AM. White matter volume predicts reaction time instability. *Neuropsychologia.* Jun 11 2007;45(10):2277-2284.

76. McNeil CJ, Giesebrecht S, Gandevia SC, Taylor JL. Behaviour of the motoneurone pool in a fatiguing submaximal contraction. *The Journal of physiology.* 2011;589(14):3533-3544.

77. Hoffman B, Oya T, Carroll T, Cresswell A. Increases in corticospinal responsiveness during a sustained submaximal plantar flexion. *J Physiol.* 2011;589(14):3533-3544.

78. Bakshi R, Shaikh ZA, Miletich RS, et al. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Multiple sclerosis (Houndmills, Basingstoke, England).* Jun 2000;6(3):181-185.

79. Greim B, Benecke R, Zettl UK. Qualitative and quantitative assessment of fatigue in multiple sclerosis (MS). *J Neurol.* May 2007;254 Suppl 2:Ii58-64.

80. Dobkin BH. Fatigue versus activity-dependent fatigability in patients with central or peripheral motor impairments. *Neurorehabil Neural Repair.* Mar-Apr 2008;22(2):105-110.

81. Davis MP, Walsh D. Mechanisms of fatigue. *J Support Oncol.* Jul-Aug 2010;8(4):164-174.

82. Tartaglia MC, Narayanan S, Arnold DL. Mental fatigue alters the pattern and increases the volume of cerebral activation required for a motor task in multiple sclerosis patients with fatigue. *Eur J Neurol.* Apr 2008;15(4):413-419.

83. Holtzer R, Foley F, D'Orio V, Spat J, Shuman M, Wang C. Learning and cognitive fatigue trajectories in multiple sclerosis defined using a burst measurement design. *Multiple sclerosis (Houndmills, Basingstoke, England).* Oct 2013;19(11):1518-1525.

84. Schwid SR, Tyler CM, Scheid EA, Weinstein A, Goodman AD, McDermott MP. Cognitive fatigue during a test requiring sustained attention: a pilot study. *Multiple Sclerosis.* 2003;9(5):503-508.

85. Fuentes K, Hunter MA, Strauss E, Hultsch DF. Intraindividual variability in cognitive performance in persons with chronic fatigue syndrome. *Clin Neuropsychol.* May 2001;15(2):210-227.

86. Bellgrove MA, Hester R, Garavan H. The functional neuroanatomical correlates of response variability: evidence from a response inhibition task. *Neuropsychologia.* 2004;42(14):1910-1916.

87. Stuss DT, Murphy KJ, Binns MA, Alexander MP. Staying on the job: the frontal lobes control individual performance variability. *Brain.* Nov 2003;126(Pt 11):2363-2380.

88. DeLuca J. 3 Fatigue, Cognition, and Mental Effort. *Fatigue as a window to the brain.* 2005;37.

89. Calabrese P, Penner IK. Cognitive dysfunctions in multiple sclerosis--a "multiple disconnection syndrome"? *J Neurol.* May 2007;254 Suppl 2:Ii18-21.

90. Calabrese M, Rinaldi F, Grossi P, et al. Basal ganglia and frontal/parietal cortical atrophy is associated with fatigue in relapsing-remitting multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* Oct 2010;16(10):1220-1228.

91. Pardini M, Bonzano L, Mancardi GL, Roccatagliata L. Frontal networks play a role in fatigue perception in multiple sclerosis. *Behavioral neuroscience.* Jun 2010;124(3):329-336.

92. Tellez N, Alonso J, Rio J, et al. The basal ganglia: a substrate for fatigue in multiple sclerosis. *Neuroradiology.* Jan 2008;50(1):17-23.

93. Parmenter BA, Denney DR, Lynch SG. The cognitive performance of patients with multiple sclerosis during periods of high and low fatigue. *Multiple Sclerosis.* 2003;9(2):111-118.

94. Schwid SR, Covington M, Segal BM, Goodman AD. Fatigue in multiple sclerosis: current understanding and future directions. *J Rehabil Res Dev.* Mar-Apr 2002;39(2):211-224.

95. Tachibana N, Howard RS, Hirsch NP, Miller DH, Moseley IF, Fish D. Sleep problems in multiple sclerosis. *Eur Neurol.* 1994;34(6):320-323.

96. Kallweit U, Baumann CR, Harzheim M, et al. Fatigue and sleep-disordered breathing in multiple sclerosis: a clinically relevant association? *Mult Scler Int.* 2013;2013:286581.

97. Dias RA, Hardin KA, Rose H, Agius MA, Apperson ML, Brass SD. Sleepiness, fatigue, and risk of obstructive sleep apnea using the STOP-BANG questionnaire in multiple sclerosis: a pilot study. *Sleep Breath.* Dec 2012;16(4):1255-1265.

98. Boe Lunde HM, Aae TF, Indrevag W, et al. Poor sleep in patients with multiple sclerosis. *PLoS One.* 2012;7(11):e49996.

99. Attarian H. Importance of sleep in the quality of life of multiple sclerosis patients: a long under-recognized issue. *Sleep medicine.* Jan 2009;10(1):7-8.

100. Brass SD, Li CS, Auerbach S. The underdiagnosis of sleep disorders in patients with multiple sclerosis. *J Clin Sleep Med.* 2014;10(9):1025-1031.

101. Braley TJ, Segal BM, Chervin RD. Underrecognition of sleep disorders in patients with multiple sclerosis. *J Clin Sleep Med.* Jan 15 2015;11(1):81.

102. Strober LB. Fatigue in multiple sclerosis: a look at the role of poor sleep. *Front Neurol.* 2015;6:21.

103. Merlino G, Fratticci L, Lenchig C, et al. Prevalence of ‘poor sleep’among patients with multiple sclerosis: an independent predictor of mental and physical status. *Sleep medicine.* 2009;10(1):26-34.

104. Brass SD, Duquette P, Proulx-Therrien J, Auerbach S. Sleep disorders in patients with multiple sclerosis. *Sleep medicine reviews.* 2010;14(2):121-129.

105. Attarian HP, Brown KM, Duntley SP, Carter JD, Cross AH. The relationship of sleep disturbances and fatigue in multiple sclerosis. *Archives of neurology.* Apr 2004;61(4):525-528.

106. Merlino G, Fratticci L, Lenchig C, et al. Prevalence of 'poor sleep' among patients with multiple sclerosis: an independent predictor of mental and physical status. *Sleep medicine.* Jan 2009;10(1):26-34.

107. Stanton BR, Barnes F, Silber E. Sleep and fatigue in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* Aug 2006;12(4):481-486.

108. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* May 1989;28(2):193-213.

109. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep.* Dec 1991;14(6):540-545.

110. Krystal AD, Edinger JD. Measuring sleep quality. *Sleep medicine.* 2008;9:S10-S17.

111. Rechtschaffen A KA. *A manual of standardized terminology, techniques, and scoring system for sleep stage scoring of human subjects.* U.S.Department of Health, Education and Welfare: Bethesda, MD; 1968.

112. Force AOSAT, Medicine AAoS. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine.* 2009;5(3):263.

113. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak C. The role of actigraphy in the study of sleep and circadian rhythms. American Academy of Sleep Medicine Review Paper. *Sleep.* 2003;26(3):342-392.

114. Cameron MH, Peterson V, Boudreau EA, et al. Fatigue is associated with poor sleep in people with multiple sclerosis and cognitive impairment. *Mult Scler Int.* 2014;2014:872732.

115. Caminero A, Bartolome M. Sleep disturbances in multiple sclerosis. *J Neurol Sci.* Oct 15 2011;309(1-2):86-91.

116. Kaminska M, Kimoff RJ, Schwartzman K, Trojan DA. Sleep disorders and fatigue in multiple sclerosis: evidence for association and interaction. *J Neurol Sci.* Mar 15 2011;302(1-2):7-13.

117. Heesen C, Nawrath L, Reich C, Bauer N, Schulz KH, Gold SM. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? *J Neurol Neurosurg Psychiatry.* Jan 2006;77(1):34-39.

118. Flachenecker P, Bihler I, Weber F, Gottschalk M, Toyka KV, Rieckmann P. Cytokine mRNA expression in patients with multiple sclerosis and fatigue. *Multiple sclerosis (Houndmills, Basingstoke, England).* Apr 2004;10(2):165-169.

119. Heesen C, Koehler G, Gross R, Tessmer W, Schulz KH, Gold SM. Altered cytokine responses to cognitive stress in multiple sclerosis patients with fatigue. *Multiple sclerosis (Houndmills, Basingstoke, England).* Feb 2005;11(1):51-57.

120. Suarez EC. Self-reported symptoms of sleep disturbance and inflammation, coagulation, insulin resistance and psychosocial distress: evidence for gender disparity. *Brain Behav Immun.* Aug 2008;22(6):960-968.

121. Veauthier C, Gaede G, Radbruch H, Gottschalk S, Wernecke K-D, Paul F. Treatment of sleep disorders may improve fatigue in multiple sclerosis. *Clinical neurology and neurosurgery.* 2013;115(9):1826-1830.

122. Mills RJ, Young CA. The relationship between fatigue and other clinical features of multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* May 2011;17(5):604-612.

123. Strober LB, Arnett PA. An examination of four models predicting fatigue in multiple sclerosis. *Arch Clin Neuropsychol.* Jul 2005;20(5):631-646.

124. Melamud L, Golan D, Luboshitzky R, Lavi I, Miller A. Melatonin dysregulation, sleep disturbances and fatigue in multiple sclerosis. *Journal of the neurological sciences.* 2012;314(1):37-40.

125. Mendozzi L, Tronci F, Garegnani M, Pugnetti L. Sleep disturbance and fatigue in mild relapsing remitting multiple sclerosis patients on chronic immunomodulant therapy: an actigraphic study. *Multiple sclerosis (Houndmills, Basingstoke, England).* Feb 2010;16(2):238-247.

126. Attarian H, Applebee G, Applebee A, et al. Effect of eszopiclone on sleep disturbances and daytime fatigue in multiple sclerosis patients. *International journal of MS care.* 2011;13(2):84-90.

127. Moreira N, Damasceno R, Medeiros C, et al. Restless leg syndrome, sleep quality and fatigue in multiple sclerosis patients. *Brazilian Journal of Medical and Biological Research.* 2008;41(10):932-937.

128. Chen JH, Liu XQ, Sun HY, Huang Y. Sleep disorders in multiple sclerosis in China: clinical, polysomnography study, and review of the literature. *J Clin Neurophysiol.* Aug 2014;31(4):375-381.

129. Feinstein A. Multiple sclerosis and depression. *Multiple Sclerosis Journal.* 2011;17(11):1276-1281.

130. Giordano A, Granella F, Lugaresi A, et al. Anxiety and depression in multiple sclerosis patients around diagnosis. *Journal of the neurological sciences.* 2011;307(1):86-91.

131. Maes M, Mihaylova I, Kubera M, Ringel K. Activation of cell-mediated immunity in depression: association with inflammation, melancholia, clinical staging and the fatigue and somatic symptom cluster of depression. *Progress in neuro-psychopharmacology and biological psychiatry.* 2012;36(1):169-175.

132. Benedict RH, Fishman I, McClellan MM, Bakshi R, Weinstock-Guttman B. Validity of the Beck Depression Inventory-Fast Screen in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* Aug 2003;9(4):393-396.

133. Patrick E, Christodoulou C, Krupp LB. Longitudinal correlates of fatigue in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* Feb 2009;15(2):258-261.

134. Pittion-Vouyovitch S, Debouverie M, Guillemin F, Vandenberghe N, Anxionnat R, Vespignani H. Fatigue in multiple sclerosis is related to disability, depression and quality of life. *J Neurol Sci.* Apr 15 2006;243(1-2):39-45.

135. Kale N, Agaoglu J, Tanik O. Neuropsychiatric manifestations in multiple sclerosis: correlation of fatigue and depression with disease progression. *Neurological research.* Mar 2010;32(2):221-223.

136. Bol Y, Duits AA, Vertommen-Mertens CE, et al. The contribution of disease severity, depression and negative affectivity to fatigue in multiple sclerosis: a comparison with ulcerative colitis. *J Psychosom Res.* Jul 2010;69(1):43-49.

137. Kroencke DC, Lynch SG, Denney DR. Fatigue in multiple sclerosis: relationship to depression, disability, and disease pattern. *Multiple sclerosis (Houndmills, Basingstoke, England).* Apr 2000;6(2):131-136.

138. Iriarte J, Subira ML, Castro P. Modalities of fatigue in multiple sclerosis: correlation with clinical and biological factors. *Multiple sclerosis (Houndmills, Basingstoke, England).* Apr 2000;6(2):124-130.

139. Trojan DA, Arnold D, Collet JP, et al. Fatigue in multiple sclerosis: association with disease-related, behavioural and psychosocial factors. *Multiple sclerosis (Houndmills, Basingstoke, England).* Sep 2007;13(8):985-995.

140. Koch M, Mostert J, Heerings M, Uyttenboogaart M, De Keyser J. Fatigue, depression and disability accumulation in multiple sclerosis: a cross-sectional study. *Eur J Neurol.* Mar 2009;16(3):348-352.

141. van der Werf SP, Jongen PJ, Lycklama a Nijeholt GJ, Barkhof F, Hommes OR, Bleijenberg G. Fatigue in multiple sclerosis: interrelations between fatigue complaints, cerebral MRI abnormalities and neurological disability. *J Neurol Sci.* Oct 8 1998;160(2):164-170.

142. Lerdal A, Celius EG, Krupp L, Dahl AA. A prospective study of patterns of fatigue in multiple sclerosis. *Eur J Neurol.* Dec 2007;14(12):1338-1343.

143. Hadjimichael O, Vollmer T, Oleen-Burkey M. Fatigue characteristics in multiple sclerosis: the North American Research Committee on Multiple Sclerosis (NARCOMS) survey. *Health Qual Life Outcomes.* 2008;6:100.

144. Thelen JM, Lynch SG, Bruce AS, Hancock LM, Bruce JM. Polypharmacy in multiple sclerosis: relationship with fatigue, perceived cognition, and objective cognitive performance. *J Psychosom Res.* May 2014;76(5):400-404.

145. Wood B, van der Mei IA, Ponsonby AL, et al. Prevalence and concurrence of anxiety, depression and fatigue over time in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* Feb 2013;19(2):217-224.

146. Krupp LB, Serafin DJ, Christodoulou C. Multiple sclerosis-associated fatigue. 2010.

147. Bruce JM, Lynch SG. Personality traits in multiple sclerosis: association with mood and anxiety disorders. *Journal of psychosomatic research.* 2011;70(5):479-485.

148. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis.* Jan 1994;18 Suppl 1:S79-83.

149. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of neurology.* Oct 1989;46(10):1121-1123.

150. Lee KA, Hicks G, Nino-Murcia G. Validity and reliability of a scale to assess fatigue. *Psychiatry Res.* Mar 1991;36(3):291-298.

151. Fischer JS, LaRocca NG, Miller DM, Ritvo PG, Andrews H, Paty D. Recent developments in the assessment of quality of life in multiple sclerosis (MS). *Multiple sclerosis (Houndmills, Basingstoke, England).* Aug 1999;5(4):251-259.

152. Larson RD. Psychometric properties of the modified fatigue impact scale. *International journal of MS care.* 2013;15(1):15-20.

153. Conrad KJ, Wright BD, McKnight P, McFall M, Fontana A, Rosenheck R. Comparing traditional and Rasch analyses of the Mississippi PTSD Scale: revealing limitations of reverse-scored items. *J Appl Meas.* 2004;5(1):15-30.

154. Rasch G. *Probabilistic models for some intelligence and attainment tests.* ERIC; 1993.

155. Wright BD, Linacre JM. Observations are always ordinal; measurements, however, must be interval. *Arch Phys Med Rehabil.* Nov 1989;70(12):857-860.

156. Mills R, Young C, Nicholas R, Pallant J, Tennant A. Rasch analysis of the Fatigue Severity Scale in multiple sclerosis. *Multiple sclerosis (Houndmills, Basingstoke, England).* Jan 2009;15(1):81-87.

157. Dalgas U, Stenager E, Ingemann-Hansen T. Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training. *Multiple sclerosis (Houndmills, Basingstoke, England).* Jan 2008;14(1):35-53.

158. Oken BS, Kishiyama S, Zajdel D, et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. *Neurology.* Jun 8 2004;62(11):2058-2064.

159. Mills RJ, Young CA, Pallant JF, Tennant A. Rasch analysis of the Modified Fatigue Impact Scale (MFIS) in multiple sclerosis. *J Neurol Neurosurg Psychiatry.* Sep 2010;81(9):1049-1051.

160. Bryant D, Chiaravalloti ND, DeLuca J. Objective Measurement of Cognitive Fatigue in Multiple Sclerosis. *Rehabilitation Psychology.* 2004;49(2):114.

161. Administration UFaD. *Draft guidance for industry on patient-reported outcome measures: use in medical product development to support labeling claims (Docket 2006D-0044).* 2006.

162. Mills RJ, Calabresi M, Tennant A, Young CA. Perceived changes and minimum clinically important difference of the Neurological Fatigue Index for multiple sclerosis (NFI-MS). *Multiple sclerosis (Houndmills, Basingstoke, England).* Apr 2013;19(4):502-505.

163. Shah A. Fatigue in multiple sclerosis. *Physical Medicine and Rehabilitation Clinics of North America.* 2009;20(2):363-372.

164. Mollaoglu M, Ustun E. Fatigue in multiple sclerosis patients. *J Clin Nurs.* May 2009;18(9):1231-1238.

165. Simmons RD, Tribe KL, McDonald EA. Living with multiple sclerosis: longitudinal changes in employment and the importance of symptom management. *Journal of neurology.* 2010;257(6):926-936.

166. Flensner G, Ek AC, Landtblom AM, Söderhamn O. Fatigue in relation to perceived health: people with multiple sclerosis compared with people in the general population. *Scandinavian journal of caring sciences.* 2008;22(3):391-400.

167. Motl RW, Snook EM, Schapiro RT. Symptoms and physical activity behavior in individuals with multiple sclerosis. *Research in nursing & health.* 2008;31(5):466-475.

168. Jason LA, Evans M, Brown M, Porter N. What is fatigue? Pathological and nonpathological fatigue. *PM R.* May 2010;2(5):327-331.

169. Bol Y, Duits A, Verhey F, et al. Subjective and objective assessment of mental fatigue in patients with multiple sclerosis. *Understanding fatigue in multiple sclerosis.* 2010:51.

170. Rietberg MB, Van Wegen EE, Kwakkel G. Measuring fatigue in patients with multiple sclerosis: reproducibility, responsiveness and concurrent validity of three Dutch self-report questionnaires. *Disabil Rehabil.* 2010;32(22):1870-1876.

171. Chipchase SY, Lincoln NB, Radford KA. Measuring fatigue in people with multiple sclerosis. *Disabil Rehabil.* Jul 22 2003;25(14):778-784.

172. Wetzel JL, Fry DK, Pfalzer LA. Six-minute walk test for persons with mild or moderate disability from multiple sclerosis: performance and explanatory factors. *Physiother Can.* Spring 2011;63(2):166-180.

173. Giesser BS. Exercise in the management of persons with multiple sclerosis. *Therapeutic advances in neurological disorders.* May 2015;8(3):123-130.

174. Bisecco A, Caiazzo G, d'Ambrosio A, et al. Fatigue in multiple sclerosis: The contribution of occult white matter damage. *Multiple sclerosis (Houndmills, Basingstoke, England).* Feb 4 2016.

175. Thickbroom GW, Sacco P, Faulkner DL, Kermode AG, Mastaglia FL. Enhanced corticomotor excitability with dynamic fatiguing exercise of the lower limb in multiple sclerosis. *Journal of neurology.* 2008;255(7):1001-1005.

176. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol.* Jul 2001;50(1):121-127.

177. Pangman VC, Sloan J, Guse L. An examination of psychometric properties of the mini-mental state examination and the standardized mini-mental state examination: implications for clinical practice. *Appl Nurs Res.* Nov 2000;13(4):209-213.

178. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest.* Jan 2001;119(1):256-270.

179. Karpatkin H, Cohen ET, Rzetelny A, et al. Effects of Intermittent Versus Continuous Walking on Distance Walked and Fatigue in Persons With Multiple Sclerosis: A Randomized Crossover Trial. *Journal of neurologic physical therapy : JNPT.* Jul 2015;39(3):172-178.

180. Bohannon RW. Dynamometer measurements of hand-grip strength predict multiple outcomes. *Percept Mot Skills.* Oct 2001;93(2):323-328.

181. Paul RH, Beatty WW, Schneider R, Blanco CR, Hames KA. Cognitive and physical fatigue in multiple sclerosis: relations between self-report and objective performance. *Appl Neuropsychol.* 1998;5(3):143-148.

182. Schapmire D, James JS, Townsend R, Stewart T, Delheimer S, Focht D. Simultaneous bilateral testing: validation of a new protocol to detect insincere effort during grip and pinch strength testing. *Journal of Hand Therapy.* 2002;15(3):242-250.

183. Fess EE. A method for checking Jamar dynamometer calibration. *Journal of Hand Therapy.* 1987;1(1):28-32.

184. Mathiowetz V, Rennells C, Donahoe L. Effect of elbow position on grip and key pinch strength. *The Journal of hand surgery.* 1985;10(5):694-697.

185. Steer RA, Cavalieri TA, Leonard DM, Beck AT. Use of the Beck Depression Inventory for Primary Care to screen for major depression disorders. *Gen Hosp Psychiatry.* Mar-Apr 1999;21(2):106-111.

186. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. *Qual Life Res.* Jun 1995;4(3):187-206.

187. Jette AM, Cleary PD. Functional disability assessment. *Phys Ther.* Dec 1987;67(12):1854-1859.

188. Learmonth YC, Motl RW, Sandroff BM, Pula JH, Cadavid D. Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. *BMC Neurol.* 2013;13:37.

189. Taphoorn M, Van Someren E, Snoek F, et al. Fatigue, sleep disturbances and circadian rhythm in multiple sclerosis. *Journal of neurology.* 1993;240(7):446-448.

190. Kaynak H, Altintas A, Kaynak D, et al. Fatigue and sleep disturbance in multiple sclerosis. *Eur J Neurol.* Dec 2006;13(12):1333-1339.

191. Vetrugno R, Stecchi S, Scandellari C, et al. Sleep--wake and body core temperature rhythms in multiple sclerosis with fatigue. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology.* Jan 2007;118(1):228-234.

192. Grandner MA, Kripke DF, YOON IY, Youngstedt SD. Criterion validity of the Pittsburgh Sleep Quality Index: Investigation in a non-clinical sample. *Sleep and Biological Rhythms.* 2006;4(2):129-136.

193. Julian LJ. Measures of anxiety: State-Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), and Hospital Anxiety and Depression Scale-Anxiety (HADS-A). *Arthritis Care Res (Hoboken).* Nov 2011;63 Suppl 11:S467-472.

194. Tudor-Locke C, Camhi SM, Troiano RP. A catalog of rules, variables, and definitions applied to accelerometer data in the National Health and Nutrition Examination Survey, 2003-2006. *Preventing chronic disease.* 2012;9:E113.

195. Cole RJ, Kripke DF, Gruen W, Mullaney DJ, Gillin JC. Automatic sleep/wake identification from wrist activity. *Sleep.* Oct 1992;15(5):461-469.

196. Chesson Jr M, Coleman M, Lee-Chiong M, Pancer D. Practice parameters for the use of actigraphy in the assessment of sleep and sleep disorders: an update for 2007. *Sleep.* 2007;30(4):519.

197. Mayis Al-dughmi JB, Catherine F. Siengsukon. The relationship between fatigability and perceived fatigue measured using the Neurological Fatigue Index in people with MS. *submitted to journal of Neurorehabilitation & Neural Repair.* 2016.

198. Kim H, Yun C-H, Thomas RJ, et al. Obstructive sleep apnea as a risk factor for cerebral white matter change in a middle-aged and older general population. *Sleep.* 2013;36(5):709.

199. Van Den Berg JF, Van Rooij FJ, Vos H, et al. Disagreement between subjective and actigraphic measures of sleep duration in a population-based study of elderly persons*. *Journal of sleep research.* 2008;17(3):295-302.

200. McCrae CS, Rowe MA, Tierney CG, Dautovich ND, DeFinis AL, McNamara JP. Sleep complaints, subjective and objective sleep patterns, health, psychological adjustment, and daytime functioning in community-dwelling older adults. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences.* 2005;60(4):P182-P189.

201. Tellez N, Rio J, Tintore M, Nos C, Galan I, Montalban X. Does the Modified Fatigue Impact Scale offer a more comprehensive assessment of fatigue in MS? *Multiple sclerosis (Houndmills, Basingstoke, England).* Apr 2005;11(2):198-202.

202. Bland JM, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. *The lancet.* 1986;327(8476):307-310.

203. Giavarina D. Understanding Bland Altman analysis. *Biochemia medica.* 2015;25(2):141-151.

204. Morgante F, Dattola V, Crupi D, et al. Is central fatigue in multiple sclerosis a disorder of movement preparation? *J Neurol.* Feb 2011;258(2):263-272.

205. Andreasen A, Stenager E, Dalgas U. The effect of exercise therapy on fatigue in multiple sclerosis. *Multiple Sclerosis Journal.* 2011;17(9):1041-1054.

206. Pellicano C, Gallo A, Li X, et al. Relationship of cortical atrophy to fatigue in patients with multiple sclerosis. *Archives of neurology.* Apr 2010;67(4):447-453.

207. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics.* Jul 2007;4(3):316-329.