Western Graduate&PostdoctoralStudies

Western University

Scholarship@Western

Electronic Thesis and Dissertation Repository

7-15-2019 9:00 AM

A Study of Multiple Predictors of Cognitive Fatigue in Individuals with Multiple Sclerosis

Leila M. Mackay
The University of Western Ontario

Supervisor
Johnson, Andrew M
The University of Western Ontario

Graduate Program in Health and Rehabilitation Sciences
A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science
© Leila M. Mackay 2019

Follow this and additional works at: https://ir.lib.uwo.ca/etd

Part of the Cognition and Perception Commons

Recommended Citation

Abstract

Persons with Multiple Sclerosis (PwMS) commonly experience cognitive fatigue (CF), defined as a decrease in cognitive performance over a sustained activity and measured objectively or subjectively. In the present research, we evaluated the extent to which depression, anxiety, information processing speed, sleep quality, and disease disability predict subjective and objective CF, in a sample of 55 PwMS (37 females, $M = 44.23$ years of age). Although no statistically significant predictors of objective CF were demonstrated, all variables predicted subjective CF, $R^2_{adj} = .384$ [$F (6, 40) = 5.783$, $p = .0002$]. In particular, depression and information processing speed were found to be significant predictors of subjective CF when controlling for anxiety, sleep quality, and disease disability. Findings are discussed in the context of treating subjective CF through treatment of these affective and cognitive factors (e.g., through psychotherapy).

Keywords: Multiple Sclerosis, Cognitive Fatigue, Depression, Anxiety, Sleep Quality, Disease Severity, Information Processing Speed

Lay Abstract

Multiple Sclerosis (MS) is an autoimmune disorder that causes physical and cognitive impairments. Among them, is cognitive fatigue (CF) which is objectively defined as a decrease in cognitive performance over a sustained cognitive activity. CF can be measured objectively, by measuring performance during a cognitive task, or subjectively, in which persons with MS (PwMS) report the level of CF they experience on average. In the current research, we evaluated the extent to which depression, anxiety, information processing speed, sleep quality, and disease disability predict subjective and objective CF, in a sample of 55 PwMS (37 females, $M = 44.23$ years of age). While there were no significant predictors of objective CF, all variables predicted subjective CF, $R^2_{adj} = .384$ [$F (6, 40) = 5.783$, $p = .0002$]. In particular, depression and information processing speed were found to be significant predictors of subjective CF when anxiety, sleep quality, and disease disability were controlled for. Findings are discussed in the context of treating subjective CF through treatment of these affective and cognitive factors (e.g., through psychotherapy).

Acknowledgements

The current research would not have been possible without the support and guidance of many people. In particular, my supervisor Dr. Andrew Johnson, whose mentorship was invaluable during the past two years of our research. Thank you very much for sharing your wisdom with me, and inspiring me to strive for perfection. I have learned a great deal during our time together. This research is also the product of my fearless advisory committee, Dr. Sarah Morrow and Dr. Sheila Moodie. Thank you very much for generously offering me your expertise, and your time. The research would also not be possible without Heather Rosehart and Jordan Ward. Thank you for answering my endless questions with patience and for graciously welcoming me into your space. It has been an honour and a pleasure to work with all of you.

I would also like to thank Dr. Amy Robinson, my mentor and friend. Thank you for sharing your insight and experiences with me, without you I would be lost. I eagerly await what you do next, as I know it will be amazing. In addition, I would like to thank my research lab for introducing me to new and exciting areas of research, as well as for providing a stimulating environment to grow as a researcher.

I would also like to acknowledge those who participated in the research. You have all been inspirations to me with your enduring positivity and desire to help others. I hope that one day the research we conduct will benefit you as much as I have benefitted from meeting you.

Finally, I would like to thank my family. Your love and encouragement mean the world to me. Thank you for always believing in me and motivating me to never give up. I am eternally grateful to you for all that you continue to do. I love you.

Table of Contents

List of Tables

Chapter 1

1.1 Multiple Sclerosis Overview

Multiple Sclerosis (MS) is an autoimmune disease caused by inflammation within the central nervous system that results in damage to the myelin sheath (demyelination). This is the primary determinant of the clinical symptoms (neurological deficits) of MS. As myelin is affected in different patterns for each individual, clinical symptoms are highly variable, meaning that the presentation of symptoms within the population of Persons with Multiple Sclerosis (PwMS) is highly heterogeneous (van Noort, 1996). Common clinical symptoms include: muscle weakness, spasticity, tremors, bladder dysfunction, speed and vision impairments, vertigo, and ataxia (National Institutes of Health, 2019).

Approximately 85% of PwMS (Multiple Sclerosis International Federation, 2013), will initially present with Relapsing Remitting MS, which is characterized by intervals of clinical symptoms (relapse) and intervals of partial recovery (remit) (van Noort, 1996). As many as 80% of PwMS diagnosed with Relapsing Remitting MS (Chiaravalloti & DeLuca, 2008), will then progress into the Secondary Progressive stage, characterized as a gradual worsening of disability with no interval of recovery. Some PwMS will, however, initially present in the progressive stage, and are considered to have Primary Progressive MS. Individuals with this form of MS will not have any intervals of recovery and will show a gradual increase in disability. The rate at which the disease progresses is variable from individual to individual: it can be slow and gradual, taking decades for the symptoms to increase, or it can be rapid, with disability increasing in a matter of months (van Noort, 1996).

The heterogeneity of MS is such that there is not yet a definitive etiology, but rather evidence of multiple risk factors including genetics, social, and environmental factors (Beck, Metz, Svenson, & Patten, 2005; van Noort, 1996).

1.1.1 Prevalence of MS

With an onset between 20 and 40 years old, MS is the most common neurological disease (Beiske et al., 2008; Chylova et al., 2009). It affects individuals in the midst of their developing careers, families, and relationships (Paty, Noseworthy, & Ebers, 1998). In 2013, the Multiple Sclerosis International Federation updated their 2008 research investigating the incidence and prevalence of MS worldwide. The number of individuals diagnosed with MS worldwide increased to 2.3 million in 2013 from 2.1 million reported in 2008. MS has been shown to affect twice as many women as it does men worldwide, with a ratio of 2.6:1 in the Americas and 3:1 in Asia. The highest prevalence rates of MS are in Europe and Canada (Multiple Sclerosis International Federation, 2013). The most detailed research of prevalence rates of MS in Canada was conducted by Beck et al. (2005). This study investigated the overall prevalence of MS in Canada, as well as the differences between five regions of Canada: British Columbia, the Prairies, Ontario, Québec, and Atlantic Canada. The overall prevalence in 2005 was 240 per 100,000 people. It is likely that this number has increased since the study was conducted, as worldwide prevalence has increased since then, but this research remains relevant as it identified the prevalence rates in the five main regions of Canada. The highest prevalence was in Atlantic Canada, with 350 per 100,000 people, while the lowest prevalence was in Québec with 180 per 100,000 people. Despite these demonstrated regional differences, no environmental risk factors were identified – Atlantic Canada and the Prairies were the two highest prevalence rates and do not share many environmental similarities (Beck et al., 2005).

1.1.2   Symptoms of MS

The most common complaint of PwMS is fatigue, with approximately 95% of PwMS reporting fatigue (Learmonth et al., 2013; Penner et al., 2015). Fatigue is defined as mental or physical exhaustion, and lack of energy that has negative effects on an individual's quality of life. It is sometimes termed the "hidden symptom", as it is a symptom that is not always immediately apparent to family members or caregivers—and also because it is a symptom that an individual will experience subjectively (Golan et al., 2018; Penner et al., 2015).

As listed above, the clinical symptoms of MS range from bladder dysfunction to vision and speech impairment (National Institutes of Health, 2019). Clinical severity or disability due to disease (disease disability) may be quantified in a variety of ways, but the most commonly used measurement tool is the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). The EDSS measures seven areas of concern for PwMS: pyramidal, cerebellar, brainstem, sensory, bowel/bladder, visual, and cerebral. Each aspect of the scale contributes to an overall score of disability that ranges from zero (no disability), to ten (death). Scores from 0 to 4.0 are ambulatory, and are characterized by the ability to walk without assistance (from another person, or an aid), scores 4.5 to 7.0 are characterized as impaired walking, and 7.5 to 9.5, which is described as inability to walk. Some of the scales are more basic, such as bowel/bladder and vision, while others are less intuitive, such as the cerebral scale, which measures difficulties with memory and thinking. The pyramidal scale measures muscle weakness, the cerebellar scale assesses ataxia, loss of balance, coordination, and tremors. The brainstem scale evaluates problems with speech and swallowing, while the sensory scale measures numbness and loss of sensation.

While there are many documented physical symptoms, PwMS also experience cognitive impairment (CI), which can impact their lives even before a confirmed diagnosis of MS (Brissart et al., 2013).

1.1.2.1   Cognitive Impairment in MS

CI affects between 40 to 65% of PwMS (Malivoire, Hare, & Hart, 2018; Morrow, Rosehart, & Pantazopoulos, 2016), and can occur in all stages of MS (Kinsinger, Lattie, & Mohr, 2010; Rogers & Panegyres, 2007). Typically, later stages will experience the most severe impairments (Brissart et al., 2013; Rogers & Panegyres, 2007); however, CI has been diagnosed during the earliest stages of the disease (Brissart et al., 2013; DiGiuseppe, Blair, & Morrow, 2018). CI describes deficiencies in memory (working, episodic, and long-term), verbal fluency, learning, attention, executive function, and most commonly, information processing speed (Blair et al., 2016; Brissart et al., 2013; Kinsinger et al., 2010; Malivoire et al., 2018; Morrow et al., 2016; Rogers & Panegyres, 2007). This suggests that PwMS experiencing CI will have difficulties making decisions, thinking clearly, remembering, and processing information in a timely manner. As such, CI is associated with decreased Quality of Life (QoL), vocational disability, social impairment, and psychopathology, particularly depression and anxiety (Benedict et al., 2005; Kinsinger et al., 2010; Malivoire et al., 2018; Morrow et al., 2016; Rogers & Panegyres, 2007). For individuals that experience CI, it can be very difficult to interact with others and carry on a vocation. Oftentimes, CI will be comorbid with mood disorders, such as depression and anxiety (Gill, Santo, Blair, & Morrow, 2019; Kinsinger et al., 2010; Malivoire et al., 2018), perhaps resulting in further negative effects on QoL, vocation, and socialization (Gill et al., 2019). However, it has been demonstrated that improving psychological symptoms has lessened perceived CI (Kinsinger et al., 2010).

In the literature, CI is measured by performance on cognitive testing (objective) and by self-report questionnaires (perceived or subjective). While results on both measurement methods yield evidence of CI and both were associated with depression, objective measures were not affected by treatment (therapy), while subjective measures were improved. Meaning that PwMS reported less impairment following treatment, but performed the same as pre-treatment (Kinsinger et al., 2010). As such, there are no standardized treatments available for CI in PwMS.

1.1.3 Psychosocial Impact of MS

While mood disorders are not considered to be a part of the natural progression of MS, mood disorders are quite common among PwMS, particularly depression (Beiske et al., 2008) and anxiety (Lester, Stepleman, & Hughes, 2007). Depression and anxiety are more prevalent in the MS population than other neurological disorders (Viner et al., 2014), and are three times more prevalent than in the non-MS population (Beiske et al., 2008; Viner et al., 2014). Depression among PwMS has been suggested to have a lifetime prevalence of approximately 50%, meaning that half of PwMS will experience depression at some point in their lifetime (Feinstein & Feinstein, 2001; Lester et al., 2007). Research has found that point-prevalence for depression is estimated at approximately 30% (Lester et al., 2007) and anxiety point-prevalence may be as high as 41% (Beiske et al., 2008). A study conducted by Hoang, Stenager, and Stenager (2017) measured depression and anxiety, using the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), among PwMS in the post-diagnostic period (characterized as the first six weeks following diagnosis). The study found that the prevalence of depression in this population was 49.2% (Hoang et al., 2017). The prevalence of anxiety in the post-diagnostic period has been suggested to be approximately 34% (Lester et al., 2007).

Research into the relationship between mood disorders and MS has yielded multiple potential predictors for the increase in depression and anxiety in this population.

1.1.3.1   Predictors of Mood Disorders in PwMS

Predictors of mood disorders in PwMS include social isolation, unpredictable disease course, adjustment/coping with illness, and decreased QOL (Beiske et al., 2008; Lester et al., 2007; Rudick & Miller, 2008). Multiple studies have identified a link between unemployment due to illness and depression, and highlight the impact of MS on an individual's social inclusion (Beiske et al., 2008; Rudick & Miller, 2008). Additionally, mood disorders are a significant predictor of QOL among PwMS. QOL is defined as the ability to feel satisfaction from life, despite disease (Benedict et al., 2005). Studies have (not surprisingly) consistently shown a negative correlation between QOL and depression/anxiety (Beiske et al., 2008; Benedict et al., 2005; Lester et al., 2007). QOL measures typically involve the assessment of physical disease disability, fatigue, and CI (Benedict et al., 2005).

Another predictor of depression and anxiety in PwMS is the unpredictable disease course (Lester et al., 2007; Rudick & Miller, 2008). As aforementioned, MS is a variable disease that leaves PwMS wondering if or when the disease will exacerbate, and how severe the relapse will be (Lester et al., 2007). As such, this near constant worry over the variability of the disease is likely to have negative health impacts – not only on mental health variables, such as depression and anxiety, but on the body's reaction to the stress itself. More specific to MS, there is evidence to suggest that stress exacerbates symptoms of the disease (van Noort, 1996). In relation to the unpredictable nature of the illness, it is possible that trying to cope or adjust to the illness is related to mood disorders (Lester et al., 2007; Rudick & Miller, 2008). Research suggests that

this predictor is most closely related to the post-diagnostic prevalence of depression and anxiety as the PwMS are still trying to understand the illness (Lester et al., 2007).

1.1.3.2   Correlates of Mood Disorders in PwMS

To date, many studies have investigated correlates of mood disorders in the MS population. From this research, three main correlates have emerged: fatigue (Beiske et al., 2008; Kinsinger et al., 2010; Lester, Stepleman, & Hughes, 2007), CI (Blair et al., 2016; DiGiuseppe et al., 2018; Gill et al., 2019; Kinsinger et al., 2010; Lester et al., 2007; Malivoire et al., 2018; Morrow et al., 2016; Rogers & Panegyres, 2007), and disease factors such as onset, duration, and disability (Beiske et al., 2008; Lester et al., 2007).

Beiske et al. (2008) found that both age and early onset of the disease were significantly related to depression, and that age, early onset, disease disability, and disease-related pain were significantly related to anxiety. They found that the younger the individual was at diagnosis of illness, the more depressed and anxious they were on the day of testing. Beiske et al. (2008) also found that lower EDSS scores were associated with higher anxiety. On the other hand, higher pain ratings were associated with higher anxiety, a finding that is consistent with earlier work by Kalia and O'Connor (2005).

Another strong correlate of mood disorders in PwMS is CI. As mentioned above, CI impacts many aspects of daily living, and so it is unsurprising that it is related to depression and anxiety among in PwMS. Lester et al. (2007) found that CI accounts for the most variance in depression and anxiety. They proposed that the cognitive symptoms of MS create a sense of helplessness, leading to depression and anxiety.

Beiske et al. (2008) also found that depression is significantly associated with fatigue but were unable to specify a directionality for the prediction – in other words, the fatigue may have

been a result of depression, or the depression, may have been the result of the fatigue. Similarly, the study evidence was equivocal with regards to the mediating effects of fatigue and depression within the symptom model that was presented. Penner et al. (2015) found that pharmaceutical treatment of fatigue reduced the depression experienced by PwMS, thus suggesting that the relationship between depression and MS is mediated by fatigue.

1.2 Fatigue

1.2.1 Physical Fatigue and Cognitive Fatigue

Fatigue is the most debilitating symptom experienced by PwMS and it is also the most common (Bailey, Channon, & Beaumont, 2007; Barak & Achiron, 2006; Paul, Beatty, Schneider, Blanco, & Hames, 1998; Penner et al., 2015; Touzet, 2017). Fatigue experienced by PwMS is reported to be an increased feeling of weakness, independent of activity level and time of day, accompanied by a persistent and unusual feeling of tiredness (Barak & Achiron, 2006). Fatigue can be broken down into two categories: physical or motor fatigue; and cognitive fatigue (CF; Sindermann et al., 2018). Fatigue may also be objectively defined as a decline in performance during a sustained activity. Physical fatigue may be measured by performance of muscle contractions during a sustained activity, while CF is typically measured by evaluating sustained performance on cognitive measures. While physical fatigue is a construct of muscle weakness and decline in physical strength (Schwid et al., 2003), CF is a construct of information processing speed, attention, executive function, and working memory (Bailey et al., 2007). CF is known to negatively impact an individual's everyday life, such as: talking, eating, cooking, shopping, going to work or school, and driving (Touzet, 2017). While physical fatigue has been associated with age, gender, physical dysfunction and disease duration, CF has not been found to be correlated with these dimensions (Walker, Berard, Berrigan, Rees, & Freedman, 2012). Paul

et al. (1998) demonstrated a positive correlation between cognitive and physical fatigue. CF is often further broken down into two subcategories: objective CF and subjective CF (Bryant, Chiaravalloti, & DeLuca, 2004).

1.2.2   Objective Cognitive Fatigue and Subjective Cognitive Fatigue

Objective CF is the measurement of decreased performance on or inability to sustain a cognitive activity at a single point in time (Bryant et al., 2004). Subjective CF, then, is a subjective, or self-reported measurement of CF, in which an individual reports on their own CF over a period of time (Walker et al., 2012). Thus, in addition to differences in the method of measurement, these constructs may differ in terms of their assessment of acute (objective CF) versus chronic (subjective CF) impairment. Over the past few years, researchers have endeavored to investigate the relationship between objective and subjective CF. Research thus far has been quite heterogeneous, utilizing different measurement methods, which makes it difficult to compare the results. Genova et al. (2013) used functional magnetic resonance imaging to visualize the relationship between cognitive performance and perception of fatigue. They found that brain activation matched self-reported levels of cognitive fatigue. Other studies have used questionnaires and cognitive tasks to assess the relationship between objective and subjective CF (e.g., Bailey et al., 2007; Berard, Smith, & Walker, 2019), but only one of these studies demonstrated a statistically significant positive correlation between these variables (Walker et al., 2012). Interestingly, the objective measurement of CF in this study did not result in a statistically significant CF as compared with controls.

Similar results were seen by Golan et al. (2018), in a study exploring the impact of subjective fatigue on cognitive function. These researchers examined the association between cognitive function and subjective CF and found that subjective CF was not related to objective

cognitive function. However, the specific findings of the research demonstrated an association between subjective CF and independent measures of cognitive function. The constructs that were related to subjective CF were: memory, attention, information processing speed, executive function, and motor skills. Many of these constructs (i.e. memory, attention, information processing speed, and executive function) are hallmarks of objective CF, so it is interesting that when a calculation accounts for all cognitive function tasks, the association is diminished. It is, however, important to note that the correlations between these factors and subject CF were weak.

In sum, while the preponderance of evidence within the literature would suggest that there is no significant relationship between perception of CF and cognitive performance, there is still a lot of variability in the tests that are used to conduct this research, suggesting that this question remains undecided.

1.2.3   Measures of Objective CF

Tests for objective CF evaluate cognitive function or performance, such as: endurance, attention, memory and information processing speed (Touzet, 2017). Some of the measures that are commonly used to assess objective CF include:

1) **Digit Ordering Test**. This is a test of verbal working memory, in which seven digits are presented, and must be recalled immediately in ascending numerical order for each trial. This measure has 15 trials, and CF is calculated by comparing the first and last thirds of the test (Schwid et al., 2003).

2) **Boston Naming Test**. The outcome of this measure is the number of correctly identified images out of 60 (Bryant et al., 2004).

3) **Stroop Colour and Word Test**. This task is used to measure attention, and individuals

   completing this test must read colour names that are not printed in the colour of the word

   (Bryant et al., 2004).

4) **Word List Learning**. This task, which presents 14 words to a participant, and asks that

   he/she recall as many words from the list as possible, was created by the researchers for

   the purpose of measuring how well PwMS can learn over a sustained period of time (Paul

   et al., 1998).

5) **The Gordon Distractibility Task**. This test is used to assess vigilance, in which

   individuals must react to number sequences presented in three different positions on the

   computer screen, by pressing a key when the sequence appeared in the center (Paul et al.,

   1998).

6) **The Computerized Test of Information Processing**. A test of reaction time and

   vigilance in which individuals must press a key if words are not in order (Walker et al.,

   2012).

7) **The Paced Auditory Serial Addition Test.** This is the "industry standard" for assessing

   cognitive fatigue (PASAT; Gronwall, 1977; Morrow, Rosehart, & Johnson, 2015; Rao,

   Leo, Bernardin, & Unverzagt, 1991; Schwid et al., 2003; Walker et al., 2012). It has been

   validated for the MS population (Morrow et al., 2015), and when compared to the

   previous measures of objective CF has consistently been found to be more sensitive, and

   more accurate in assessing CF (Bryant et al., 2004; Schwid et al., 2003; Walker et al.,

   2012). The task requires participants call out the sum of the last two single digit numbers

   that are presented on an audio recording at a rate of one every three seconds. Participants

   may make a total of 60 responses on the task, following the completion of a series of

practice questions to ensure understanding of the test. For example, if the first four numbers presented were: 5, 7, 3, and 2, the expected answers are: 12, 10 and 5. One of the reasons the PASAT is such an efficient test for CF is because of the constructs that it measures: information processing speed, working memory, and attention (Morrow et al., 2015). The key to the task is that the individual completing the test must be attentive to ensure they hear all the numbers presented, he/she must process the simple addition of the last two numbers presented, and then keep the last heard number fresh for the next number presented. The idea of the test is that an individual who is experiencing CF will not be able to sustain their performance throughout the task, while an individual not experiencing CF will improve the longer the task is performed. Thus, researchers using this measure typically compute a CF variable by comparing the first and last thirds of the test (Morrow et al., 2015; Walker et al., 2012).

1.2.4 Measures of Subjective CF

Measures of subjective CF are relatively simple when compared to objective CF testing. All the tests for subjective CF are self-report questionnaires, as subjective CF is measuring an individual's perceived CF. **The Fatigue Impact Scale** (FIS) is a validated measure of subjective CF (Fisk et al., 1994; Strober & Arnett, 2005) of subjective CF. The FIS is 36 questions relating to the impact of fatigue on three dimensions of life: physical (10 items), cognitive (10 items), and psychosocial (16 items). The **Modified Fatigue Impact Scale** (MFIS) was created for, and validated within, the MS population (Learmonth et al., 2013). The MFIS is a shorter version of the FIS that includes 10 items on cognitive fatigue, 9 items on physical fatigue, and 2 items on psychosocial fatigue. Each of the subscales are evaluated using a five-point Likert scale ranging from 0-4, 0 being "never", and 4 being "almost always". The MFIS yields a total score (the sum

of all items), and three scale scores calculated as the sum of the items within each subscale. Examples of the questions are: "I have been clumsy and uncoordinated" (physical); "I have been unable to think clearly" (cognitive); "I have been limited in my ability to do things away from home" (psychosocial). The cognitive subscale of the MFIS has been used in the MS literature as the primary assessment of subjective CF (Berard, Smith, & Walker, 2019), and due to the multidimensionality of the test, it has been recommended to utilize the subscales over the total score (Mills, Young, Pallant, & Tennant, 2010). The FIS and MFIS are the two most commonly used subjective CF scales in literature.

While the FIS and MFIS are retrospective subjective CF scales, that assess subjective CF over a four-week (one month) period, some studies testing the subjective/objective CF relationship have created tests that measure subjective CF after every objective measure. Bailey et al. (2007) asked participants to select a number from 0 (not at all) to 8 (extremely, the most tired/fatigued I've ever been) to reflect their perceived fatigue or tiredness. To assess the extent to which subjective fatigue was associated with objective fatigue, they conducted this assessment at the outset of testing, and then again following every objective measure (participants completed a total of four assessments). This testing framework allowed researchers to evaluate the change in subjective fatigue during cognitive tasks. Another study adapted previously created scales to measure subjective fatigue, modifying the scales to estimate current fatigue, rather than a subjective aggregate of fatigue over the preceding month (Paul et al., 1998). These scales used a five-point Likert scale that ask participants to select a number from 1 (not at all) to 5 (a great deal) in their assessment of subjective cognitive (e.g., "do you currently have problems concentrating?") and physical ("are you having any problems with tiredness?") fatigue. Paul et

al. (1998) had participants complete these scales at the start of testing, and then again at the end of testing, to gauge the change in subjective CF after completing the cognitive battery.

1.3   Cognitive Fatigue in PwMS

CF in PwMS has been well documented in the past and is known to have a large impact on an individual's daily life, resulting in a decreased quality of life (Barak & Achiron, 2006). Four main predictors of CF in PwMS have emerged within the literature: information processing speed, sleep quality, disease disability, and depression.

1.3.1   Information Processing Speed

Information processing speed is often assessed in clinical settings, as it is closely related to CI and can help to determine the cognitive ability and CF of an individual (Benedict et al., 2001; Morrow et al., 2015). Previous research has also shown a relationship between information processing speed and mood disorders in PwMS (Bailey et al., 2007; Diamond, Johnson, Kaufman, & Graves, 2008). Despite the fact that information processing speed has been proposed as the underlying cause of CF in PwMS (Bailey et al., 2007), it is important to consider the potential mediation of depressive symptoms, as depression has been demonstrated to be associated with both CF and information processing speed (Golan et al., 2018; Morrison & Stuifbergen, 2016; Sindermann et al., 2018).

Diamond et al. (2008) attempted to quantify the extent to which depression mediated the relationship between information processing speed and CF. First, the study determined that information processing speed, as measured by Visual Threshold Serial Addition Test, and depression, as measured by the Center for Epidemiological Studies of Depression Scale (CES-D), were significantly related. Next, the variability associated with mood and fatigue was removed from the equation, to calculate the unique contribution of information processing speed.

The researchers concluded that mood and fatigue accounted for 66% of the variance in information processing speed, but that mood and fatigue were not impactful on the relationship between information processing speed and effortful processing (as measured by two cognitive performance tasks, separate from CF).

In addition, research conducted by Golan et al. (2018), found a significant negative correlation between subjective CF and information processing speed, meaning that as subjective CF increased information processing speed decreased. After controlling for depression and disease disability, however, the relationship between information processing speed and subjective CF was diminished. This result could be attributed to the method of assessment used for measuring information processing speed. Golan et al. (2018) used a computerized cognitive testing battery that assessed multiple cognitive domains: memory, executive function, visual-spatial processing, verbal function, motor skills, attention, and information processing speed. When investigating information processing speed as a main predictor of CF, an information processing speed specific test should be used in order to better compare the results of each domain.

1.3.2   Sleep Quality

Sleep quality has been identified as an important predictor of both objective (Berard et al., 2019) and subjective CF (Strober & Arnett, 2005), with the primary predictors of sleep quality being sleep disturbances, day-time sleepiness, and sleep latency. Although often associated with depression, research has found that sleep quality remains a unique predictor among PwMS for both objective CF (Berard et al., 2019) and subjective CF (Strober & Arnett, 2005).

Strober and Arnett (2005) completed some of the earliest work in this domain – the literature to this point was largely correlation-based, and thus the goal of this research was to

understand more about CF in PwMS. The study found that sleep quality, depression, and disease disability were all predictive of CF in PwMS, with sleep quality accounting for the most variance. When investigating the interrelatedness of the constructs, it was found that depression and sleep quality were significantly correlated with each other. This significant association was not due to item overlap across the questionnaires, as the researchers created a new Sleep Composite derived from questions pertaining to sleep from the depression questionnaires used. The researchers reviewed depression questionnaires (Beck Depression Inventory, Chicago Multiscale Depression Inventory, and Sickness Impact Profile Sleep and Rest Scale), and removed all items pertaining to sleep. They next composed a new questionnaire with a unique set of eight items. An example of the questions on this Sleep Composite are: "Fitful Sleep" (Chicago Multiscale Depression Inventory); "I sit around half-asleep" (Sickness Impact Profile); and, "Difficulty Sleeping" (Beck Depression Inventory). While the Sleep Composite was useful for the study, and the tests used to compose the composite have been validated, the Sleep Composite as a whole was not a validated measurement of sleep quality.

Berard et al. (2019) sought to update the research by Strober and Arnett (2005) by including a measure for objective CF, the PASAT. The study predicted that the results from Strober and Arnett (2005) would translate to objective CF. For the most part, the hypothesis was borne out: sleep quality was the best predictor, followed by depression. The study also found that depression was the best predictor in sleep quality, suggesting that depression causes decreased sleep quality, which is then predictive of CF. The study also found that sleep was significantly associated with subjective CF, as measured by the MFIS. Unlike the previous research, disease disability was not found to be predictive of CF; this is most likely due to the change from subjective to objective CF.

Another difference between the two studies is the sleep quality measure. Berard et al. (2019), used the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), while Strober and Arnett (2005) used a composite of "sleep items" from validated depression measures. Psychometrically, the PSQI is a better choice of measurement tool, as it has been validated as a whole, unlike the questionnaire created by Strober and Arnett (2005). It measures seven components of sleep: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and day-time dysfunction. Participants are asked to think about the past month when completing the questionnaire. The questionnaire is divided into Likert-scale questions (i.e., "not during the past month", "less than once a week", "once or twice a week", or "three or more times a week"), and open-ended questions pertaining to sleep habits (e.g., How many hours of actual sleep do you get at night?). Scores on each of the seven components range from 0 to 3, with a total score of five or higher being indicative of poor sleep quality. The questionnaire can also be analysed by the individual facets of sleep.

1.3.3 Disease Disability

As mentioned previously, disease disability as measured by the EDSS, is related to information processing speed, depression, and CF (Berard et al., 2019; Golan et al., 2018; Morrison & Stuifbergen, 2016; Strober & Arnett, 2005). Disease disability tends to predict only a small amount of the variance in CF among PwMS (Schwid et al., 2003), with the relationship often found to be mediated by other factors that are related to CF, such as sleep (Berard et al., 2019; Strober & Arnett, 2005), physical fatigue (Golan et al., 2018), and depression (Bailey et al., 2007; Sindermann et al., 2018).

1.3.4 Depression

The construct most consistently associated with CF in PwMS is depression (Berard et al., 2019; Golan et al., 2018; Morrison & Stuifbergen, 2016; Sindermann et al., 2018; Strober & Arnett, 2005). Strober and Arnett (2005) found depression (as measured by the Chicago Multiscale Depression Inventory) to be a unique predictor of CF. Berard et al. (2019) found that depression (as measured by the Patient Health Questionnaire 9) was a unique predictor of CF, as well as a significant predictor for sleep quality.

Morrison and Stuifbergen (2016) found depression (as measured by the CES-D) to be the most significant predictor of subjective CF (as measured by the MFIS) among PwMS. Furthermore, depression has been strongly associated with objective CF among PwMS, with Golan et al. (2018) demonstrating that, although subjective and objective CF were not related, depression (as measured by the Beck Depression Inventory; BDI) was significantly associated with both objective and subjective CF. Golan et al. (2018) aimed to explore variables that impact cognitive function, and determined that depression and not CF affected cognitive performance.

Surprisingly, the research on depression in PwMS remains equivocal, this is possibly due to the variability in the assessments used to evaluate depression, such as the CES-D (Morrison & Stuifbergen, 2016), and the BDI (Golan et al., 2018). This suggests that the next step in research on predictors of CF in PwMS may be to standardize the measures used. The HADS is a measure of depression and anxiety that is commonly used in the MS population, and might be a suitable candidate for widespread adoption – particularly given that it simultaneously measures anxiety, a variable that has been somewhat neglected in previous research on predictors of CF.

1.4   Current Research

The primary objective of the current study was to investigate the predictors of both subjective and objective CF in PwMS, and in accordance with previous research on the predictors of these variables, we chose to include the following predictors: depression, disease disability, sleep quality, and information processing speed. Unlike previous research, a new variable was included: anxiety.

It was hypothesized that depression and anxiety would be the strongest predictors of both objective and subjective CF in PwMS. It was also hypothesized that information processing speed, sleep quality, and disease disability would be significant predictors of both objective and subjective CF. Based on previous research, our secondary aim was to investigate the association between objective and subjective CF. Furthermore, we hypothesized that there would be a strong association between depression, anxiety, and sleep quality; a strong relationship between disease disability, depression, and anxiety; and information processing speed would be strongly related to depression, anxiety, sleep quality, and disease disability.

The PASAT was selected as the method of assessment for objective CF and the MFIS was selected as the assessment of subjective CF. The HADS was selected for the assessment of depression and anxiety, given that it has been validated within populations of PwMS. To ensure comparability with studies that have previously used measures of sleep quality (e.g., Berard et al., 2019), we selected the PSQI for evaluating sleep quality. In the literature, information processing speed has been measured inconsistently, and as information processing speed can be affected by a number of external variables (Diamond et al., 2008), two measurements were used. The first was the Symbol Digit Modalities Test (SDMT) validated for the MS population (Morrow et al., 2010), and conducted verbally to avoid any compounding motor processing

impairments (Rao et al., 1991). The second is the ZVT (Oswald & Roth, 1987; Vernon, 1993), a

trail-making test that requires significantly less motor involvement than other established trail

making tests. Finally, the EDSS was used to assess disease disability for all participants, as this

is the current standard of practice for evaluating disease disability in PwMS.

1.5   References

Bailey, A., Channon, S., & Beaumont, J. G. (2007). The relationship between subjective fatigue and cognitive fatigue in advanced multiple sclerosis. *Multiple Sclerosis*, *13*(1), 73–80. https://doi.org/10.1177/1352458506071162

Barak, Y., & Achiron, A. (2006). Cognitive fatigue in multiple sclerosis: Findings from a two-wave screening project. *Journal of the Neurological Sciences*, *245*(1–2), 73–76. https://doi.org/10.1016/j.jns.2005.09.015

Beck, C. A., Metz, L. M., Svenson, L. W., & Patten, S. B. (2005). Regional variation of multiple sclerosis prevalence in Canada. *Multiple Sclerosis*, *11*(5), 516–519. https://doi.org/10.1191/1352458505ms1192oa

Beiske, A. G., Svensson, E., Sandanger, I., Czujko, B., Pedersen, E. D., Aarseth, J. H., & Myhr, K. M. (2008). Depression and anxiety amongst multiple sclerosis patients. *European Journal of Neurology*, *15*(3), 239–245. https://doi.org/10.1111/j.1468-1331.2007.02041.x

Benedict, R. H. B., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., & Weinstock-Guttman, B. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society*, *12*(04). https://doi.org/10.1017/S1355617706060723

Benedict, R. H. B., Priore, R. L., Miller, C., Munschauer, F., & Jacobs, L. (2001). Personality Disorder in Multiple Sclerosis Correlates With Cognitive Impairment. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *13*(1), 70–76. https://doi.org/10.1176/jnp.13.1.70

Benedict, R. H. B., Wahlig, E., Bakshi, R., Fishman, I., Munschauer, F., Zivadinov, R., & Weinstock-Guttman, B. (2005). Predicting quality of life in multiple sclerosis: accounting

for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *Journal of the Neurological Sciences*, *231*(1–2), 29–34. https://doi.org/10.1016/j.jns.2004.12.009

Berard, J. A., Smith, A. M., & Walker, L. A. S. (2019). Predictive Models of Cognitive Fatigue in Multiple Sclerosis. *Archives of Clinical Neuropsychology*, *34*(1), 31–38. https://doi.org/10.1093/arclin/acy014

Blair, M., Gill, S., Gutmanis, I., Smolewska, K., Warriner, E., & Morrow, S. A. (2016). The mediating role of processing speed in the relationship between depressive symptoms and cognitive function in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *38*(7), 782–794. https://doi.org/10.1080/13803395.2016.1164124

Brissart, H., Morele, E., Baumann, C., Perf, M. Le, Leininger, M., Taillemite, L., … Debouverie, M. (2013). Cognitive impairment among different clinical courses of multiple sclerosis. *Neurological Research*, *35*(8), 867–872. https://doi.org/10.1179/1743132813y.0000000232

Bryant, D., Chiaravalloti, N. D., & DeLuca, J. (2004). Objective Measurement of Cognitive Fatigue in Multiple Sclerosis. *Rehabilitation Psychology*, *49*(2), 114–122. https://doi.org/10.1037/0090-5550.49.2.114

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research*, *28*(2), 193–213.

Carone, D. A., Benedict, R. H. B., Munschauer, F. E. M., Fishman, I., & Weinstock-Guttman, B. (2005). Interpreting patient/informant discrepancies of reported cognitive symptoms in MS. *Journal of the International Neuropsychological Society*, *11*(05). https://doi.org/10.1017/S135561770505068X

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurology*, *7*(12), 1139–1151. https://doi.org/10.1016/S1474-4422(08)70259-X

Chylova, M., van Dijk, J. P., Rosenberger, J., Nagyova, I., Gavelova, M., Gdovinova, Z., & Groothoff, J. W. (2009). P02-211 Depression, anxiety and health status in patients with multiple sclerosis. *European Psychiatry*, *24*, S901. https://doi.org/10.1016/S0924-9338(09)71134-4

Diamond, B. J., Johnson, S., Kaufman, M., & Graves, L. (2008). Relationships between information processing, depression, fatigue and cognition in multiple sclerosis. *Archives of Clinical Neuropsychology*, *23*(2), 189–199. https://doi.org/10.1016/j.acn.2007.10.002

DiGiuseppe, G., Blair, M., & Morrow, S. A. (2018). *Prevalence of cognitive impairment in newly diagnosed relapsing-remitting multiple sclerosis* (pp. 153–157). pp. 153–157.

Feinstein, A., & Feinstein, K. (2001). Depression associated with multiple sclerosis. *Journal of Affective Disorders*, *66*(2–3), 193–198. https://doi.org/10.1016/S0165-0327(00)00298-6

Feuillet, L., Reuter, F., Audoin, B., Malikova, I., Barrau, K., Cherif, A. A., & Pelletier, J. (2007). Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Multiple Sclerosis*, *13*(1), 124–127. https://doi.org/10.1177/1352458506071196

Fisk, J. D., Ritvo, P. G., Ross, L., Haase, D. A., Marrie, T. J., & Schlech, W. F. (1994). Measuring the Functional Impact of Fatigue: Initial Validation of the Fatigue Impact Scale. *Clinical Infectious Diseases*, *18*(Supplement_1), S79–S83. https://doi.org/10.1093/clinids/18.Supplement_1.S79

Freedman, M. S., Selchen, D., Arnold, D. L., Prat, A., Banwell, B., Yeung, M., … Lapierre, Y. (2013). Treatment Optimization in MS: Canadian MS Working Group Updated

Recommendations. *Canadian Journal of Neurological Sciences*, *40*(3), 307–323.
https://doi.org/10.1017/S0317167100014244

Gill, S., Santo, J., Blair, M., & Morrow, S. A. (2019). Depressive Symptoms Are Associated
With More Negative Functional Outcomes Than Anxiety Symptoms in Persons With
Multiple Sclerosis. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *31*(1), 37–
42. https://doi.org/10.1176/appi.neuropsych.18010011

Genova, H. M., Rajagopalan, V., DeLuca, J., Das, A., Binder, A., Arjunan, A., … Wylie, G.
(2013). Examination of Cognitive Fatigue in Multiple Sclerosis using Functional
Magnetic Resonance Imaging and Diffusion Tensor Imaging. *PLoS ONE*, *8*(11), e78811.
https://doi.org/10.1371/journal.pone.0078811

Glanz, B. I., Healy, B. C., Hviid, L. E., Chitnis, T., & Weiner, H. L. (2012). Cognitive
deterioration in patients with early multiple sclerosis: a 5-year study. *Journal of
Neurology, Neurosurgery & Psychiatry*, *83*(1), 38–43.
https://doi.org/10.1136/jnnp.2010.237834

Golan, D., Doniger, G. M., Wissemann, K., Zarif, M., Bumstead, B., Buhse, M., … Gudesblatt,
M. (2018). The impact of subjective cognitive fatigue and depression on cognitive
function in patients with multiple sclerosis. *Multiple Sclerosis*, *24*(2), 196–204.
https://doi.org/10.1177/1352458517695470

Gronwall, D. M. A. (1977). Paced Auditory Serial-Addition Task: A Measure of Recovery from
Concussion. *Perceptual and Motor Skills*, *44*(2), 367–373.
https://doi.org/10.2466/pms.1977.44.2.367

Hoang, H., Stenager, E., & Stenager, E. (2017). The risk of depression and anxiety in the post-
diagnostic period of multiple sclerosis measured by screening instruments and structured

interviews. *European Psychiatry*, *41*, S236.

https://doi.org/10.1016/j.eurpsy.2017.01.2252

Kalia, L. V., & O'Connor, P. W. (2005). Severity of chronic pain and its relationship to quality

of life in multiple sclerosis. *Multiple Sclerosis*, *11*(3), 322–327.

https://doi.org/10.1191/1352458505ms1168oa

Kinsinger, S. W., Lattie, E., & Mohr, D. C. (2010). *Relationship between depression, fatigue,*

subjetive cognitive impairment, and objective neuropsychological functioning in patients

with multiple sclerosis (pp. 573–580). pp. 573–580.

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability

status scale (EDSS). *Neurology*, *33*(11), 1444–1444.

https://doi.org/10.1212/WNL.33.11.1444

Learmonth, Y. C., Dlugonski, D., Pilutti, L. A., Sandroff, B. M., Klaren, R., & Motl, R. W.

(2013). Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue

Impact Scale. *Journal of the Neurological Sciences*, *331*(1–2), 102–107.

https://doi.org/10.1016/j.jns.2013.05.023

Lester, K., Stepleman, L., & Hughes, M. (2007). The Association of Illness Severity, Self-

Reported Cognitive Impairment, and Perceived Illness Management with Depression and

Anxiety in a Multiple Sclerosis Clinic Population. *Journal of Behavioral Medicine*, *30*(2),

177–186. https://doi.org/10.1007/s10865-007-9095-6

Malivoire, B. L., Hare, C. J., & Hart, T. L. (2018). Psychological symptoms and perceived

cognitive impairment in multiple sclerosis: The role of rumination. *Rehabilitation*

Psychology, *63*(2), 286–294. https://doi.org/10.1037/rep0000180

Mills, R. J., Young, C. A., Pallant, J. F., & Tennant, A. (2010). Rasch analysis of the Modified

Fatigue Impact Scale (MFIS) in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, *81*(9), 1049–1051. https://doi.org/10.1136/jnnp.2008.151340

Morrison, J. D., & Stuifbergen, A. K. (2016). Predictors of Fatigue Impact in Persons With Long-Standing Multiple Sclerosis: *Journal of Neuroscience Nursing*, *48*(3), 143–150. https://doi.org/10.1097/JNN.0000000000000208

Morrow, S. A., O'Connor, P. W., Polman, C. H., Goodman, A. D., Kappos, L., Lublin, F. D., … Benedict, R. H. B. (2010). Evaluation of the symbol digit modalities test (SDMT) and MS neuropsychological screening questionnaire (MSNQ) in natalizumab-treated MS patients over 48 weeks. *Multiple Sclerosis*, *16*(11), 1385–1392. https://doi.org/10.1177/1352458510378021

Morrow, S. A., Rosehart, H., & Johnson, A. M. (2015). Diagnosis and quantification of cognitive fatigue in multiple sclerosis. *Cognitive and Behavioral Neurology*, *28*(1), 27–32. https://doi.org/10.1097/WNN.0000000000000050

Morrow, S. A., Rosehart, H., & Pantazopoulos, K. (2016). Anxiety and Depressive Symptoms Are Associated With Worse Performance on Objective Cognitive Tests in MS. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *28*(2), 118–123. https://doi.org/10.1176/appi.neuropsych.15070167

Oswald, W. D., & Roth, E. (1987). *Der Zahlen Verbindungs Test (ZVT). Handanweisung (Manual)*. Gottingen, Germany.: Hogrefe.

Paty, D. W., Noseworthy, J. H., & Ebers, G. C. (1998). Diagnosis of Multiple Sclerosis. In D. W. Paty & G. C. Ebers (Eds.), *Multiple Sclerosis* (pp. 85–91). Philadelphia, PA: F.A. Davis Co.

Paul, R. H., Beatty, W. W., Schneider, R., Blanco, C. R., & Hames, K. A. (1998). Cognitive and

    Physical Fatigue in Multiple Sclerosis: Relations Between Self-Report and Objective

    Performance. *Applied Neuropsychology*, *5*(3), 143–148.

    https://doi.org/10.1207/s15324826an0503_5

Penner, I. K., Sivertsdotter, E. C., Celius, E. G., Fuchs, S., Schreiber, K., Berkö, S., …

    TYNERGY trial investigators. (2015). Improvement in Fatigue during Natalizumab

    Treatment is Linked to Improvement in Depression and Day-Time Sleepiness. *Frontiers*

    in Neurology, *6*(18). https://doi.org/10.3389/fneur.2015.00018

Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple

    sclerosis.: I. Frequency, patterns, and prediction. *Neurology*, *41*(5), 685–691.

    https://doi.org/10.1212/WNL.41.5.685

Rogers, J. M., & Panegyres, P. K. (2007). Cognitive impairment in multiple sclerosis: Evidence-

    based analysis and recommendations. *Journal of Clinical Neuroscience*, *14*(10), 919–927.

    https://doi.org/10.1016/j.jocn.2007.02.006

Rudick, R. A., & Miller, D. M. (2008). Health-Related Quality of Life in Multiple Sclerosis:

    Current Evidence, Measurement and Effects of Disease Severity and Treatment. *CNS*

    Drugs, *22*(10), 827–839. https://doi.org/10.2165/00023210-200822100-00004

Schultheis, M. T., Weisser, V., Ang, J., Elovic, E., Nead, R., Sestito, N., … Millis, S. R. (2010).

    Examining the Relationship Between Cognition and Driving Performance in Multiple

    Sclerosis. *Archives of Physical Medicine and Rehabilitation*, *91*(3), 465–473.

    https://doi.org/10.1016/j.apmr.2009.09.026

Schwid, S. R., Tyler, C. M., Scheid, E. A., Weinstein, A., Goodman, A. D., & McDermott, M. P.

    (2003). Cognitive fatigue during a test requiring sustained attention: a pilot study.

    Multiple Sclerosis, *9*(5), 503–508. https://doi.org/10.1191/1352458503ms946oa

Sindermann, C., Saliger, J., Nielsen, J., Karbe, H., Markett, S., Stavrou, M., & Montag, C.

    (2018). Personality and Primary Emotional Traits: Disentangling Multiple Sclerosis

    Related Fatigue and Depression. *Archives of Clinical Neuropsychology*, *33*(5), 552–561.

    https://doi.org/10.1093/arclin/acx104

Strober, L., & Arnett, P. (2005). An examination of four models predicting fatigue in multiple

    sclerosis. *Archives of Clinical Neuropsychology*, *20*(5), 631–646.

    https://doi.org/10.1016/j.acn.2005.04.002

Touzet, C. (2017). Cognitive fatigue: an impaired cortical inhibitory replenishment. *Brain Injury*,

    31(12), 1625–1631. https://doi.org/10.1080/02699052.2017.1344300

van Noort, J. M. (1996). Multiple sclerosis: an altered immune response or an altered stress

    response? *Journal of Molecular Medicine*, *74*(6), 285–296.

    https://doi.org/10.1007/BF00207506

Vernon, P. A. (1993). Der Zahlen-Verbindungs-Test and other trail-making correlates of general

    intelligence. *Personality and Individual Differences*, *14*(1), 35–40.

    https://doi.org/10.1016/0191-8869(93)90172-Y

Viner, R., Fiest, K. M., Bulloch, A. G. M., Williams, J. V. A., Lavorato, D. H., Berzins, S., …

    Patten, S. B. (2014). Point prevalence and correlates of depression in a national

    community sample with multiple sclerosis. *General Hospital Psychiatry*, *36*(3), 352–354.

    https://doi.org/10.1016/j.genhosppsych.2013.12.011

Walker, L. A. S., Berard, J. A., Berrigan, L. I., Rees, L. M., & Freedman, M. S. (2012). Detecting cognitive fatigue in multiple sclerosis: Method matters. *Journal of the Neurological Sciences*, *316*(1–2), 86–92. https://doi.org/10.1016/j.jns.2012.01.021

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

Chapter 2

2.1   Introduction

Multiple Sclerosis (MS) is a debilitating disease caused by inflammation in the central nervous system resulting in demyelination (Paty, Noseworthy, & Ebers, 1998). In addition to the more well-known physical symptoms of the disease, persons with Multiple Sclerosis (PwMS) suffer from a wide array of cognitive symptoms, including cognitive impairment (Benedict et al., 2005; Rao, Leo, Bernardin, & Unverzagt, 1991), and cognitive fatigue (CF; Berard, Smith, & Walker, 2019; Morrow, Rosehart, & Johnson, 2015; Schwid et al., 2003). CF has been defined as a worsening of cognitive performance over the course of a sustained cognitive activity task (Schwid et al., 2003). It may be objectively measured using the Paced Auditory Serial Addition Test (PASAT), a cognitive test that assesses both processing speed and working memory (Rao et al., 1991). Morrow et al. (2015) presented evidence to suggest that the PASAT is a valid method of measuring CF in PwMS, by comparing the first third of the test to the last third of the test. Alternatively, it is possible to assess *perceived* or *subjective* cognitive fatigue, using self-report questionnaires, such as the cognitive subscale of the Modified Fatigue Impact Scale (MFIS; Fisk et al., 1994)

While objective and subjective CF have been well documented in the MS population (Barak & Achiron, 2006; Bryant, Chiaravalloti, & DeLuca, 2004) there has been much debate over the relationship between objective and subjective CF (Bailey, Channon, & Beaumont, 2007; Berard et al., 2019; Paul, Beatty, Schneider, Blanco, & Hames, 1998; Walker, Berard, Berrigan, Rees, & Freedman, 2012). To date, some researchers have found a significant correlation between objective CF and subjective CF (Walker et al., 2012), while others have not (Bailey et al., 2007; Berard et al., 2019; Paul et al., 1998).

Another complaint often seen in PwMS is depression (Berard et al., 2019; Fricska-Nagy et al., 2016). Although PwMS often experience both depression and cognitive fatigue, the relationship between these symptoms is not well understood, as it is difficult to identify whether there is a direct causal link between the symptoms, or whether the relationship between depression and cognitive fatigue is due to other characteristics of MS. Research by Berard and colleagues (2019) found that although depression was significantly correlated with CF, depression was not a significant predictor of CF, but rather a predictor of sleep quality, which was the strongest predictor of objective CF. Contrarily, Morrison and Stuifbergen (2016) found that depressive symptoms are the strongest direct predictor of CF in PwMS. A key source of variability within the research literature may relate to the measurement tools applied to the assessment of depression. The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) is a validated and often-used measure of depression and anxiety in PwMS (Honarmand & Feinstein, 2009). It is a quick and efficient test for depression – and its ability to also provide insight into patient anxiety makes it ideal for studies of cognitive fatigue, as this has been recommended as an important dimension for further study among PwMS (Berard et al., 2019).

Past research in the non-MS population, has further shown an association between depression and slowed information processing speed (Sheline et al., 2006). McDermott and Ebmeier (2009) conducted a meta-analysis that found significant correlations among measures of depression severity, information processing speed, and memory. It has been demonstrated that individuals within the non-MS population that experience both depression and CF have deficits in executive function, working memory, and information processing speed (Papakostas, 2014). Within the MS population, Diamond, Johnson, Kaufman, and Graves (2008) found that

decreased processing speed was significantly correlated with both depression and fatigue as measured by MFIS. Researchers were, however, unable to determine the direction of the relationship among the three variables.

The current study aimed to investigate the extent to which objective and subjective CF can be predicted by depression, anxiety, sleep quality, disease disability, and information processing speed. To this end, participants were asked to complete: (1) the Paced Auditory Serial Addition Test (PASAT) to assess levels of objective cognitive fatigue; (2) the Symbol Digit Modalities Test (SDMT) and the Zahlen Verbindungs Test (ZVT) to assess information processing speed; (3) the Hospital Anxiety and Depression Scale (HADS) to assess anxiety and depression; (4) the Expanded Disability Status Scale (EDSS) to assess the disability of their MS symptoms; (5) the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality; and (6) the Modified Fatigue Impact Scale (MFIS) to assess overall fatigue and subjective CF. It was hypothesized that the combination of variables would predict both objective and subjective CF, and that there would not be a relationship between objective and subjective CF.

2.2   Methods

2.2.1   Participants

This study recruited 55 PwMS (37 females), aged 20 to 62 ($M = 44.23$, $SD = 11.19$) from an outpatient MS clinic in London, Ontario, Canada, between January and April of 2019. Participants were included in the study if they were over the age of 18, fluent in English, and had a diagnosis of either Relapsing/Remitting, Secondary Progressive or Primary Progressive MS. Participants were excluded from participation if they had been diagnosed with a neurological disorder (other than MS), and if they used daily antipsychotics, narcotics, amphetamine stimulants, cannabis or benzodiazepines (other than at night). Two participants were excluded *(n*

= 53) from the analysis. One participant decided to stop testing due to fatigue level, and another participant was excluded due to cannabis usage on the day of testing.

2.2.2   Measures

Demographics. Demographic information was collected within a demographic interview, at the outset of the study. Any information that a participant was unable to provide was collected (with permission from the participant) from his or her medical chart. Medication and psychological history were collected but used only to ensure that no exclusion criteria were met.

Paced Auditory Serial Addition Test (PASAT). The PASAT is a validated measure of cognitive fatigue in PwMS that measures working memory and processing speed (Morrow et al., 2015). The task requires participants to call out the sum of the last two single digit numbers that are presented on an audio recording at a rate of one every three seconds. Participants may make a total of 60 responses on the task, following the completion of a series of practice questions to ensure understanding of the task. Per the recommendations of Morrow et al. (2015), a "cognitive fatigue score", the PASAT CF, was generated by subtracting the number of correct responses given during the first third of the PASAT, from the number of correct responses given during the last third of the PASAT. In this way, it may be seen that participants with a negative score on this measure are demonstrating a reduced level of function over the course of the test (i.e., their performance on the last third of the test was worse than their performance on the first third of the test), which may be indicative of cognitive fatigue.

Symbol Digit Modalities Test (SDMT). The SDMT is a part of the standard battery of neuropsychological tests for PwMS and is used to assess information processing speed (Morrow et al., 2010). In the current study, the SDMT was conducted orally to avoid any compounding motor processing impairments (Rao et al., 1991). The SDMT is a symbol-digit matching test, in

which the numbers 1-9 are paired with a unique symbol located in a key at the top of the test page. The task gives participants 90 seconds to call out as many correctly matched numbers as possible without missing any. Participants were given ten practice trials, and if the participant responded incorrectly during the practice questions, the researcher corrected the participants, and indicated how to correctly identify the corresponding number. As this test was performed orally, the researcher kept score of correct and incorrect numbers for the participant on a duplicate test page the participant did not see. The number of correctly identified symbols in the allotted time represents an individual's score on the test, with the high score being 110.

Hospital Anxiety and Depression Scale (HADS). The HADS was used to assess participant anxiety and depression (Honarmand & Feinstein, 2009). There are 14 questions total (7 questions for anxiety and 7 questions for depression), with scores for each question ranging from 0-3. For example, "I feel cheerful" measures depression, and the possible responses are: (3) "Not at all", (2) "Not often", (1) "Sometimes", and (0) "Most of the time". Scores on the HADS are interpreted as continuous variables, with a total score of 42, or scale scores ranging from 0-21.

Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-report questionnaire that measures an individual's sleep quality (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI investigates 7 components of sleep: subjective sleep quality, latency, duration, efficiency, disturbances, medications, and daytime dysfunction. Participants are asked to think about the past month when completing the questionnaire. The questionnaire is divided into Likert-scale questions (i.e., "not during the past month", "less than once a week", "once or twice a week", or "three or more times a week"), and open-ended questions pertaining to sleep habits (e.g., "How many hours of actual sleep do you get at night?"). Scores on each of these components range from 0 to 3 with a total score ranging from 0-21.

Der Zahlen Verbindungs Test (ZVT). The ZVT (Oswald & Roth, 1987) was used as a secondary analysis of information processing speed, investigating trail-making abilities. Although the ZVT has not previously been used to assess information processing speed in the MS population, it has a high reliability, and has been shown to be an effective measure of information processing speed (Vernon, 1993). In addition, the ZVT is a fairly simple task that takes only 45 seconds to complete. The ZVT, as used in this study, is administered on a single sheet of paper with circles numbered from 1-90 placed at random (see Appendix A). For this task, participants were asked to connect the numbered circles in ascending numerical order as quickly as possible, beginning with the circle marked "start" (1). The test is scored by the highest number the participant reached, minus the number of errors made. For the purposes of this test, skipped numbers are also considered to be errors.

Modified Fatigue Impact Scale (MFIS). The MFIS is a self-report questionnaire that is widely used as a fatigue scale for the MS population (Learmonth et al., 2013). Fatigue is assessed on three subscales: physical (9 items; e.g., "I have been clumsy and uncoordinated); cognitive (10 items; e.g., "I have been unable to think clearly"); and psychosocial (2 items; e.g., "I have been limited in my ability to do things away from home"). Each of the 21 questions have a five-point Likert scale ranging from 0-4, 0 being "never", and 4 being "almost always". This test yields a total score (the sum of all items), and three scale scores calculated as the sum of the items within each subscale. The cognitive subscale of the MFIS is the measurement of subjective CF in the current study. The cognitive subscale of the MFIS has been used in the MS literature as the primary assessment of subjective CF (Berard, Smith, & Walker, 2019), and due to the multidimensionality of the test, it has been recommended to utilize the subscales over the total score (Mills, Young, Pallant, & Tennant, 2010).

2.2.3   Procedure

All participants completed the test battery in the same order: (1) PASAT; (2) SDMT; (3) HADS; (4) PSQI; (5) ZVT; and (6) MFIS. Participants who had completed any of these tests within the past 6 months were not re-tested, with the previous testing result added to the study data.

2.3   Results

Table 2.1 summarizes the demographic and disease characteristics of the sample of PwMS used in the current study. The sample is primarily Caucasian (87%), with 77% of individuals completing post-secondary education, and 40% of individuals unemployed due to disability.

Pearson correlations suggested statistically significant relationships between a number of variables (see Table 2.2). As expected, age is significantly negatively correlated with both the SDMT ($r = -.48, p < .001$) and the ZVT ($r = -.30, p < .001$). Age is also significantly positively correlated with disease disability ($r = .42, p < .001$). Disease disability is associated with information processing speed, as measured by both the SDMT ($r = -.45, p < .001$) and the ZVT ($r = -.47, p < .001$). Disease disability is also correlated with depression ($r = .34, p = .01$). This suggests that as disease disability increases, individuals are more likely to have a slower information processing speed and are more likely to show symptoms of depression.

Objective CF and subjective CF were not significantly related ($r = -.16$). Of note, the objective CF measure, the PASAT CF, did not demonstrate a statistically significant relationship with any of the collected variables. The scale used to assess subjective CF (the cognitive scale of the MFIS), however, demonstrated a statistically significant relationship with the SDMT ($r = -.29, p = .05$), ZVT ($r = -.32, p = .03$), HADS depression ($r = .61, p < .001$), HADS anxiety ($r = .54, p < .001$), and the total PSQI ($r = .33, p = .02$).

Table 2.1 Descriptive Characteristics of Participants

	Participants (n = 53)
Demographic information	
Age (years)	
Mean ± standard deviation	44.23 ± 11.19
Range	20-62
Sex	
Male	16
Female	37
Ethnicity	
Caucasian	46
African Canadian	2
First Nations	4
Other	1
Marital Status	
Single or Divorced/Separated	22
Married or Cohabitating	31
Education	
≤ High school	12
Post-Secondary	41
Employment	
Working (Full-Time: Part-Time)	22:8
Unemployed due to disability	21
Retired	2
MS Characteristics	
Type	
Relapsing-Remitting	47
Secondary Progressive	5
Primary Progressive	1
Disease Duration	
Mean ± standard deviation	13.25 ± 8.41
Range	1-36
Expanded Disability Status Scale	
Median ± standard deviation	2.0 ± 1.71

Table 2.2 Zero-Order Correlations Among Variables.

Measure	1	2	3	4	5	6	7	8	9
1 Age	—	—	—	—	—	—	—	—	—
2 EDSS	.42**	—	—	—	—	—	—	—	—
3 PASAT CF	.22	.09	—	—	—	—	—	—	—
4 MFIS Cognitive	.07	.21	-.16	—	—	—	—	—	—
5 SDMT	-.48 **	-.45**	-.22	-.29*	—	—	—	—	—
6 ZVT	-.30*	-.47**	-.14	-.32*	.75**	—	—	—	—
7 HADS Depression	.14	.34*	.03	.61**	-.20	-.31*	—	—	—
8 HADS Anxiety	-.16	.11	-.11	.54**	.05	-.08	.69**	—	—
9 PSQI Total	.08	.10	.03	.33*	-.19	-.22	.39**	.39**	—

Note. $*p = .05, **p < .001$.

As there were no statistically significant zero-order correlations with objective CF, we did not carry out a direct entry linear regression that evaluated all of these variables simultaneously. Subjective CF, however, demonstrated statistically significant relationships with all of the experimental variables we measured. Thus, it is important to evaluate the extent to which these variables are predictive of subjective CF when relationships among variables are controlled. Direct entry regression suggests a strong predictive equation when all six variables are used, $R^2_{adj} = .384$ [$F (6, 40) = 5.783, p = .0002$]. A summary of the model coefficients is presented in Table 2.3. This regression suggests that there is a statistically significant unique contribution from both the SDMT and depression. Furthermore, anxiety approached significance as a unique predictor within the model.

As it is possible that the prediction of subjective CF by depression is mediated by information processing speed, further analyses were conducted to calculate the potential mediating effect. Four steps were completed in testing for this mediation effect.

Table 2.3 Subjective CF Regression Analysis

Variable	b	SE	t	p
EDSS	-.563	.747	-.754	.455
ZVT	.023	.101	.227	.821
SDMT	-.249	.123	-2.024	.049*
Depression	.844	.400	2.109	.041*
Anxiety	.611	.320	1.908	.064
Sleep Quality	.145	.291	.486	.629

Note. Subjective CF as measured by the cognitive subscale on the MFIS. Depression as measured by the HADS depression subscale, Anxiety as measured by the HADS anxiety subscale, Sleep Quality as measured by the total score on the PSQI. * statistically significant at p = .05.

First, it is necessary to demonstrate a statistically significant correlation between depression and subjective CF. This is illustrated in Table 2.2, $r = .61$, $t(47) = 5.23$, $p < .001$.

The second step is to demonstrate a statistically significant correlation between depression and information processing speed – and this relationship is also illustrated in Table 2.2. As there are two measures of information processing speed, both scores were considered. The SDMT, a test of sustained attention, does not demonstrate a statistically significant relationship ($r = -.20$). The ZVT, however, a rapid decision-making test, *did* demonstrate a statistically significant relationship with depression, $r = -.31$, $t(49) = 2.32$, $p = .025$. This suggests that individuals who are more depressed are more likely to demonstrate slowed information processing speed.

Third, we need to demonstrate a statistically significant relationship between information processing speed and subjective CF. The ZVT is significantly correlated with subjective CF, $r =$

-.32, t(45) = 2.30, *p* = .026. This relationship suggests that individuals with faster information processing speed are less likely to self-report CF.

The final step is to demonstrate that depression is less predictive of subjective CF when information processing speed is controlled within the regression analysis. To evaluate the effect of the indirect path between depression and subjective CF, Sobel's (1982) indirect test for mediation was used. The analysis suggested that including information processing speed as a mediator changes the path coefficient between depression and subjective CF by .116, which is not statistically significant, z = 1.09. This finding suggests that although both depression and information processing speed are correlated with subjective CF, information processing speed does not completely mediate the relationship between depression and subjective CF.

The PSQI is a multidimensional measure of sleep quality, and so it is worthwhile considering the extent to which each of the individual subscales are predictive of subjective CF. Zero-order correlations among the PSQI subscales, and subjective CF, are presented in Table 2.4. Interestingly, when we regress all seven subscales of the PSQI onto subjective CF, we find a statistically significant predictive relationship, R^2_{adj} = .21 [F (7, 41) = 2.84, *p* = .017]. Additionally, as seen in Table 2.5, only three components of sleep quality were found to be statistically significant at the univariate level: subjective sleep quality (*p* = .014), sleep latency (*p* = .038), and sleep duration (*p* = .028).

Table 2.4 PSQI Component Correlations

Measure	1	2	C1	C2	C3	C4	C5	C6	C7
1 MFIS Cognitive	—	—	—	—	—	—	—	—	—
2 PSQI total	.33*	—	—	—	—	—	—	—	—
C1 Subjective Sleep Quality	.39*	.71**	—	—	—	—	—	—	—
C2 Sleep Latency	.38*	.78**	.50**	—	—	—	—	—	—
C3 Sleep Duration	.09	.65**	.56**	.56**	—	—	—	—	—
C4 Sleep Efficiency	.16	.61**	.29*	.46**	.51**	—	—	—	—
C5 Sleep Disturbances	.18	.48**	.22	.31*	.08	.20	—	—	—
C6 Medication for Sleeping	-.03	.47**	.19	.16	.05	.06	.04	—	—
C7 Daytime Dysfunction	.33*	.56**	.38*	.34*	.03	.06	.52**	.17	—

Note. *p = .05, **p <.001.

Table 2.5 Subjective CF Regression Analysis as Predicted by the PSQI

Variable	b	SE	t	*p*
Subjective Sleep Quality	5.235	2.039	2.567	.014*
Sleep Latency	3.253	1.513	2.150	.038*
Sleep Duration	-4.202	1.852	-2.268	.028*
Sleep Efficiency	.682	1.357	.503	.617
Sleep Disturbances	-.364	2.257	-.161	.873
Medication for Sleeping	-1.007	.914	-1.101	.278
Daytime Dysfunction	1.324	1.953	.678	.502

Note. * statistically significant at *p* = .05.

Sobel's (1982) indirect test for mediation was used to evaluate any mediating effect of depression on the three components of sleep quality. These findings suggest that although sleep quality and depression correlate with subjective CF, depression does not mediate the relationship between sleep quality and subjective CF.

2.4   Discussion

2.4.1   Findings

The current research conducted two regression analyses, one for subjective CF and one for objective CF. Similar to the findings of Bailey et al. (2007) no significant predictors of objective CF were observed within these data. Subjective CF was, however, found to be predicted by depression, anxiety, information processing speed, sleep quality and disease disability. Depression and information processing speed were found to be unique significant predictors of subjective CF in PwMS – and subsequent mediator analyses suggested that these factors had a direct effect on subjective CF. Although not statistically significant, anxiety showed a substantive relationship with subjective CF that might be worthy of future research. Interestingly,

neither sleep quality nor disease disability were found to be uniquely predictive of subjective CF – a result that runs contrary to previously reported findings within the literature (Berard et al., 2019; Strober & Arnett, 2005). This may be reflective of the inclusion of information processing speed and anxiety within the testing battery, as these two variables are not typically included within test batteries that are intended to explore predictors of CF and perhaps reduced the effect of sleep quality and disease disability.

It was also found that only one test of information processing was predictive of subjective CF within the simultaneous regression equation. While both the SDMT and ZVT were correlated with subjective CF, only the SDMT was a statistically significant predictor within the final equation. There are two potential reasons for this finding. First, this could be due to the different mechanisms of information processing the tests are measuring. The ZVT is a trail-making test, looking for immediate decisions and quick action, while the SDMT measures learning, working memory, and attention. The other potential reason for the difference is that the ZVT requires the individual to use a pen to connect the circles while the SDMT was administered orally to avoid any potential motor involvement. As disease disability is significantly related to both the SDMT and ZVT, it follows that the slower the information processing speed, the worse the disease disability. As higher EDSS scores relate to motor impairment, this could explain lower scores on the ZVT as it becomes more difficult to draw.

Interestingly, sleep quality was not found to be significantly predictive of subjective CF when combined with the other variables. However, when evaluating the relationship between subjective CF and the seven individual components of the PSQI, subjective CF was found to be predicted by three components of sleep quality: subjective sleep quality, sleep latency, and sleep duration.

Also, of interest within the results was the demonstrated negative relationship between information processing speed and disease disability. This suggests that scores on the SMDT and ZVT decrease as disease disability increases. Meaning, that increased disability reduces information processing speed. The cerebral measure on the EDSS assesses problems with thinking, memory, and attention, which are some of the constructs involved in information processing speed. Therefore, it is logical that as the score on the EDSS reflects cognitive impairment, disease disability would be strongly correlated with information processing speed. This relationship has been previously demonstrated by Golan et al. (2018).

Disease disability was also significantly positively associated with age, suggesting that older individuals tended to demonstrate greater disease disability. With MS most individuals will begin in the Relapsing Remitting stage and progress into the Secondary Progressive stage. Thus, as the disease course continues the disability will also continue; therefore, it would follow that as PwMS grow older, and their disease duration increases their disease disability would also increase. The correlational analysis also revealed that age was significantly positively associated with information processing speed. In a similar fashion, as the disease progresses, disability increases, and information processing is slowed. It has also been seen in the literature, that aside from MS, older individuals have slower processing speeds, and more difficulty with working memory (Diamond et al., 2000).

The present results also suggest that disease disability is positively correlated with depression, as measured by the HADS. This relationship agrees with previously published research, and is likely to reflect decreased quality of life that is caused by increased disease symptoms (Benedict et al., 2005).

Information processing speed was found to be significantly associated with depression when measured by the ZVT, but not when measured by the SDMT. This is interesting as the SDMT and ZVT are very strongly correlated with one another and show a similar pattern of correlations within the variables measured in this study. The two main differences between the measures are physical capabilities (holding and using a pen) and memory, as both tests require some form of attention and decision making. As working memory and depression are reported to be strongly correlated (Airaksinen, Larsson, Lundberg, & Forsell, 2004; Christopher & MacDonald, 2005), it does not follow that this would be the cause of the not significant relationship between the SDMT and depression. Thus, a possible explanation for the ZVT to be significant and not the SDMT, is the physical impairment of the participants, as mentioned above. Specifically, if a participant were struggling with the use of a pen, this may impact on their ZVT score to a greater extent than a participant who does not have impaired grip strength. The current study did not collect specific impairment information for analysis, in order to test this, further research would need to be conducted. While possible, this explanation does not explain the significant correlation between the SDMT and disease disability. Therefore, the most likely potential explanation for the difference is that the ZVT was consistently given later in the test battery (after both the SDMT and the HADS), and participants may be more fatigued when completing the measure. This would support the greater correlation between subjective CF and the ZVT than the relationship between the SDMT and subjective CF, as literature suggests that subjective CF increases during cognitive activity (Bailey et al., 2007; Paul et al., 1998).

Another interesting, but expected, finding is the interaction between depression, anxiety, and sleep quality. Vitkova et al. (2014) demonstrated that anxiety (as measured by the HADS) is only significantly associated with sleep quality in the early stages of MS (i.e., less than five years

from point of onset). Additionally, anxiety (as measured by the State-Trait Anxiety Inventory), has shown a significant overall association with sleep quality in PwMS (Siengsukon et al., 2018). The strong correlation between depression and sleep quality has been previously demonstrated (Berard et al., 2019; Strober & Arnett, 2005). As the seven components of sleep quality revealed unique relationships with subjective CF, the seven facets were correlated with depression and anxiety. The correlations revealed the same three components correlated with both depression and anxiety: subjective sleep quality, sleep disturbances, and daytime dysfunction.

Finally, subjective CF, as measured by the MFIS cognitive subscale, was correlated with all collected variables. Previous research has found that subjective CF is not significantly associated with age (Walker et al., 2012), disease disability (Berard et al., 2019), or objective CF (Bailey et al., 2007; Berard et al., 2019; Bryant et al., 2004; Golan et al., 2018) – and this lack of relationship was similarly borne out in the present study. It has also been demonstrated in past research that subjective CF is significantly associated with depression (Berard et al., 2019; Strober & Arnett, 2005), information processing speed (Bailey et al., 2007; Golan et al., 2018), and sleep quality (Berard et al., 2019; Strober & Arnett, 2005). Unique to this study is the strong positive correlation with anxiety.

2.4.2   Limitations

The major limitation of the current study is the small sample size. Convenience sampling was used to recruit participants for this study, wherein patients were approached and asked if they would be interested in participating in the current study following their appointments at the clinic. As such, many interested patients may have chosen not to participate due to fatigue following their appointment. Therefore, the fatigue caused by the appointment is suggestive of increased CF which may have resulted in decreased participation. Therefore, it is possible that

patients that were less fatigued by the appointment were more amenable to participate in the study, thus representing a less fatigable sample. Moreover, individuals that are more likely to agree to participate in research following an appointment are less likely to experience the variables that were being tested for. For example, the sample only included six non-Relapsing Remitting PwMS (89% of participants were Relapsing Remitting). Therefore, disease disability is likely lower than it would be if more participants were in the progressive stage of the disease – and this may help to explain why disease disability was not predictive of subjective CF, as has been previously demonstrated (Strober & Arnett, 2005).

Another limitation of the study is the self-report measurements used. It is interesting that the majority of significant findings in the current research were dependent upon the participants' perception of self (mood, fatigue, and sleep quality). It would have been interesting to include objective measurements of sleep quality and mood disorders. In addition to investigating the relationship between CF and objective mood and sleep quality, it would be beneficial to observe the relationship between subjective and objective measures of mood and sleep quality. This could be another direction in which the research could continue.

2.4.3 Future Directions

It is recommended that further research be conducted on objective CF and its potential relationship with information processing speed and anxiety. Also, as recommended in previous research (Beiske et al., 2008; Morrison & Stuifbergen, 2016), non-pharmacological treatment for PwMS experiencing subjective CF should be implemented. As subjective CF is strongly associated with depression, cognitive therapy could be beneficial. There is currently research being conducted in regard to mindfulness for PwMS, and if this proves fruitful, further research into non-pharmacological potential treatment options should be conducted.

2.4.4   Conclusions

In conclusion, depression and information processing speed are both strongly associated with subjective CF in PwMS. As depression, anxiety, and slowed information processing speed are negatively associated with quality of life (Benedict et al., 2005) more research is needed to continue to learn about the individual mechanisms contributing to depression, anxiety, and information processing speed in PwMS. The current study has found evidence to support further research into anxiety and information processing speed, and to determine what is causing anxiety, depression, and the difference between information processing speed measures.

2.5   References

Airaksinen, E., Larsson, M., Lundberg, I., & Forsell, Y. (2004). Cognitive functions in

depressive disorders: evidence from a population-based study. *Psychological Medicine*,

34(1), 83–91. https://doi.org/10.1017/S0033291703008559

Bailey, A., Channon, S., & Beaumont, J. G. (2007). The relationship between subjective fatigue

and cognitive fatigue in advanced multiple sclerosis. *Multiple Sclerosis*, *13*(1), 73–80.

https://doi.org/10.1177/1352458506071162

Barak, Y., & Achiron, A. (2006). Cognitive fatigue in multiple sclerosis: Findings from a two-

wave screening project. *Journal of the Neurological Sciences*, *245*(1–2), 73–76.

https://doi.org/10.1016/j.jns.2005.09.015

Beiske, A. G., Svensson, E., Sandanger, I., Czujko, B., Pedersen, E. D., Aarseth, J. H., & Myhr,

K. M. (2008). Depression and anxiety amongst multiple sclerosis patients. *European

Journal of Neurology*, *15*(3), 239–245. https://doi.org/10.1111/j.1468-1331.2007.02041.x

Benedict, R. H. B., Wahlig, E., Bakshi, R., Fishman, I., Munschauer, F., Zivadinov, R., &

Weinstock-Guttman, B. (2005). Predicting quality of life in multiple sclerosis: accounting

for physical disability, fatigue, cognition, mood disorder, personality, and behavior

change. *Journal of the Neurological Sciences*, *231*(1–2), 29–34.

https://doi.org/10.1016/j.jns.2004.12.009

Berard, J. A., Smith, A. M., & Walker, L. A. S. (2019). Predictive Models of Cognitive Fatigue

in Multiple Sclerosis. *Archives of Clinical Neuropsychology*, *34*(1), 31–38.

https://doi.org/10.1093/arclin/acy014

Bryant, D., Chiaravalloti, N. D., & DeLuca, J. (2004). Objective Measurement of Cognitive

    Fatigue in Multiple Sclerosis. *Rehabilitation Psychology*, *49*(2), 114–122.

    https://doi.org/10.1037/0090-5550.49.2.114

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The

    Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research.

    Psychiatry Research, *28*(2), 193–213.

Christopher, G., & MacDonald, J. (2005). The impact of clinical depression on working memory.

    Cognitive Neuropsychiatry, *10*(5), 379–399. https://doi.org/10.1080/13546800444000128

Diamond, B. J., DeLuca, J., Rosenthal, D., Vlad, R., Davis, K., Lucas, G., … Richards, J. A.

    (2000). Information processing in older versus younger adults: Accuracy versus speed.

    International Journal of Rehabilitation and Health, *5*(1), 55–64.

    https://doi.org/10.1023/A:1012911203468

Diamond, B. J., Johnson, S., Kaufman, M., & Graves, L. (2008). Relationships between

    information processing, depression, fatigue and cognition in multiple sclerosis. *Archives*

    of Clinical Neuropsychology, *23*(2), 189–199. https://doi.org/10.1016/j.acn.2007.10.002

Fisk, J. D., Ritvo, P. G., Ross, L., Haase, D. A., Marrie, T. J., & Schlech, W. F. (1994).

    Measuring the Functional Impact of Fatigue: Initial Validation of the Fatigue Impact

    Scale. *Clinical Infectious Diseases*, *18*(Supplement_1), S79–S83.

    https://doi.org/10.1093/clinids/18.Supplement_1.S79

Fricska-Nagy, Z., Füvesi, J., Rózsa, C., Komoly, S., Jakab, G., Csépány, T., … Bencsik, K.

    (2016). The effects of fatigue, depression and the level of disability on the health-related

    quality of life of glatiramer acetate-treated relapsing-remitting patients with multiple

sclerosis in Hungary. *Multiple Sclerosis and Related Disorders*, *7*, 26–32.

https://doi.org/10.1016/j.msard.2016.02.006

Golan, D., Doniger, G. M., Wissemann, K., Zarif, M., Bumstead, B., Buhse, M., … Gudesblatt,

M. (2018). The impact of subjective cognitive fatigue and depression on cognitive

function in patients with multiple sclerosis. *Multiple Sclerosis*, *24*(2), 196–204.

https://doi.org/10.1177/1352458517695470

Honarmand, K., & Feinstein, A. (2009). Validation of the Hospital Anxiety and Depression

Scale for use with multiple sclerosis patients. *Multiple Sclerosis*, *15*(12), 1518–1524.

https://doi.org/10.1177/1352458509347150

Learmonth, Y. C., Dlugonski, D., Pilutti, L. A., Sandroff, B. M., Klaren, R., & Motl, R. W.

(2013). Psychometric properties of the Fatigue Severity Scale and the Modified Fatigue

Impact Scale. *Journal of the Neurological Sciences*, *331*(1–2), 102–107.

https://doi.org/10.1016/j.jns.2013.05.023

McDermott, L. M., & Ebmeier, K. P. (2009). A meta-analysis of depression severity and

cognitive function. *Journal of Affective Disorders*, *119*(1–3), 1–8.

https://doi.org/10.1016/j.jad.2009.04.022

Mills, R., Young, C., Pallant, J., & Tennant (2010). Rasch analysis of the Modified Fatigue

Impact Scale (MFIS) in mulitple sclerosis. *Journal of Neurology, Nuerosurgery and

Psychiatry, 81(9)*, 1049-1051. doi:10.1136/jnnp.2008.151340

Morrison, J. D., & Stuifbergen, A. K. (2016). Predictors of Fatigue Impact in Persons With

Long-Standing Multiple Sclerosis: *Journal of Neuroscience Nursing*, *48*(3), 143–150.

https://doi.org/10.1097/JNN.0000000000000208

Morrow, S. A., O'Connor, P. W., Polman, C. H., Goodman, A. D., Kappos, L., Lublin, F. D., …
    Benedict, R. H. B. (2010). Evaluation of the symbol digit modalities test (SDMT) and
    MS neuropsychological screening questionnaire (MSNQ) in natalizumab-treated MS
    patients over 48 weeks. *Multiple Sclerosis*, *16*(11), 1385–1392.
    https://doi.org/10.1177/1352458510378021

Morrow, S. A., Rosehart, H., & Johnson, A. M. (2015). Diagnosis and quantification of cognitive
    fatigue in multiple sclerosis. *Cognitive and Behavioral Neurology*, *28*(1), 27–32.
    https://doi.org/10.1097/WNN.0000000000000050

Oswald, W. D., & Roth, E. (1987). *Der Zahlen Verbindungs Test (ZVT). Handanweisung
    (Manual)*. Gottingen, Germany.: Hogrefe.

Papakostas, G. I. (2014). Cognitive Symptoms in Patients With Major Depressive Disorder and
    Their Implications for Clinical Practice. *The Journal of Clinical Psychiatry*, *75*(01), 8–
    14. https://doi.org/10.4088/JCP.13r08710

Paty, D. W., Noseworthy, J. H., & Ebers, G. C. (1998). Diagnosis of Multiple Sclerosis. In D. W.
    Paty & G. C. Ebers (Eds.), *Multiple Sclerosis* (pp. 85–91). Philadelphia, PA: F.A. Davis
    Co.

Paul, R. H., Beatty, W. W., Schneider, R., Blanco, C. R., & Hames, K. A. (1998). Cognitive and
    Physical Fatigue in Multiple Sclerosis: Relations Between Self-Report and Objective
    Performance. *Applied Neuropsychology*, *5*(3), 143–148.
    https://doi.org/10.1207/s15324826an0503_5

Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple
    sclerosis.: I. Frequency, patterns, and prediction. *Neurology*, *41*(5), 685–691.
    https://doi.org/10.1212/WNL.41.5.685

Schwid, S. R., Tyler, C. M., Scheid, E. A., Weinstein, A., Goodman, A. D., & McDermott, M. P. (2003). Cognitive fatigue during a test requiring sustained attention: a pilot study. *Multiple Sclerosis*, *9*(5), 503–508. https://doi.org/10.1191/1352458503ms946oa

Sheline, Y. I., Barch, D. M., Garcia, K., Gersing, K., Pieper, C., Welsh-Bohmer, K., … Doraiswamy, P. M. (2006). Cognitive Function in Late Life Depression: Relationships to Depression Severity, Cerebrovascular Risk Factors and Processing Speed. *Biological Psychiatry*, *60*(1), 58–65. https://doi.org/10.1016/j.biopsych.2005.09.019

Siengsukon, C. F., Aldughmi, M., Kahya, M., Lynch, S., Bruce, J., Glusman, M., … Billinger, S. (2018). Individuals with mild MS with poor sleep quality have impaired visuospatial memory and lower perceived functional abilities. *Disability and Health Journal*, *11*(1), 116–121. https://doi.org/10.1016/j.dhjo.2017.04.011

Sobel, M. E. (1982). Asympotic confidence intervals for indirect effects in structural equation models. In S. Leinhardt (Ed.), *Sociological Methodology* (pp. 290–312). Washington, DC: American Sociological Association.

Strober, L., & Arnett, P. (2005). An examination of four models predicting fatigue in multiple sclerosis. *Archives of Clinical Neuropsychology*, *20*(5), 631–646. https://doi.org/10.1016/j.acn.2005.04.002

Vernon, P. A. (1993). Der Zahlen-Verbindungs-Test and other trail-making correlates of general intelligence. *Personality and Individual Differences*, *14*(1), 35–40. https://doi.org/10.1016/0191-8869(93)90172-Y

Vitkova, M., Gdovinova, Z., Rosenberger, J., Szilasiova, J., Nagyová, I., Mikula, P., … van Dijk, J. P. (2014). Factors associated with poor sleep quality in patients with multiple sclerosis

differ by disease duration. *Disability and Health Journal*, *7*(4), 466–471.

https://doi.org/10.1016/j.dhjo.2014.05.004

Walker, L. A. S., Berard, J. A., Berrigan, L. I., Rees, L. M., & Freedman, M. S. (2012).

Detecting cognitive fatigue in multiple sclerosis: Method matters. *Journal of the*

Neurological Sciences, *316*(1–2), 86–92. https://doi.org/10.1016/j.jns.2012.01.021

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta*

Psychiatrica Scandinavica, *67*(6), 361–370. https://doi.org/10.1111/j.1600-

0447.1983.tb09716.x

Chapter 3

3.1   General Discussion

3.1.1   Relationship Between Subjective and Objective CF

The current study measured subjective cognitive fatigue (CF) using the cognitive subscale of the Modified Fatigue Impact Scale (MFIS), a common test of perceived fatigue used in Persons with Multiple Sclerosis (PwMS), and measured objective CF with the Paced Auditory Serial Addition Test (PASAT), a test of information processing speed, attention, and working memory, commonly used to assess CF in PwMS. As hypothesized, the current research did not find a relationship between subjective and objective CF. In previous research, objective and subjective CF has been significantly associated (Walker, Berard, Berrigan, Rees, & Freedman, 2012), but more commonly not associated with one another (Bailey, Channon, & Beaumont, 2007; Berard, Smith, & Walker, 2019; Golan et al., 2018). The findings of Berard et al. (2019) have been replicated in the current study as the same measurements were utilized (i.e., PASAT and MFIS). The PASAT and MFIS have consistently demonstrated objective and subjective CF in PwMS and therefore are logically the best and most reliable indicators of CF (Berard et al., 2019; Morrow, Rosehart, & Johnson, 2015; Schwid et al., 2003; Walker et al., 2012). Perhaps with different measurements a relationship would be seen between subjective and objective CF; however, this seems unlikely, as other researchers have been unable to find a relationship using varying methods of measurement, including the Fatigue Impact Scale, the *n* -Back test, the Computerized Test of Information Processing, and other measures of cognitive dysfunction (Bailey et al., 2007; Golan et al., 2018; Paul, Beatty, Schneider, Blanco, & Hames, 1998). Finally, given the concordance with earlier research, including studies with substantially larger

sample sizes (e.g., Golan et al., 2018), it is unlikely that the lack of significant relationship is reflective of power issues within the present study.

3.1.2   Predictors of Objective CF

The current study did not find any significant predictors of objective CF. Previous research had found sleep quality and depression to be significant predictors of objective CF (Berard et al., 2019), and it was hypothesized that in addition to sleep quality and depression, anxiety, disease severity, and information processing speed would also be significant predictors of objective CF. The current research used the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality, the Hospital Anxiety and Depression Scale (HADS) to assess both depression and anxiety, the Symbol Digit Modalities Test (SDMT) and the Zahlen Verbindungs Test (ZVT) to assess information processing speed, and the Expanded Disability Status Scale (EDSS) to assess disease disability. The PSQI and EDSS had been previously analyzed in relation to objective CF, and it was found that while both were a part of the best fit model, only the PSQI was a uniquely significant predictor of objective CF in PwMS (Berard et al., 2019). As information processing speed and anxiety had not been previously analyzed as predictors of objective CF, it was of interest to see how these variables interacted, if at all, to predict objective CF. Interestingly, our sample did not yield any significant findings with the PASAT. While there was a difference observed between the first third and last third of the PASAT for some of the sample, there was no significant finding of objective CF. This could be a function of small sample size, or participants having improved performance on the PASAT due to repetitive testing (i.e. practice effect).

3.1.3   Predictors of Subjective CF

The regression analysis for subjective CF found that the combination of variables (depression, anxiety, sleep quality, information processing speed, and disease disability) was significantly predictive of subjective CF in PwMS. When evaluated together in a direct-entry regression model, depression and information processing speed (as measured by the SDMT), uniquely predicted subjective CF. Literature has suggested that depression, sleep quality, and disease disability are significant predictors of subjective CF, accounting for 43% of the variance (Strober & Arnett, 2005). Interestingly, sleep quality and disease disability were not found to be unique significant predictors of subjective CF in the current research. This is most likely due to the inclusion of anxiety and information processing speed, as they had not been previously investigated as predictors of subjective CF. The finding that information processing speed and anxiety predict subjective CF has not been demonstrated in past research.

While research has not previously demonstrated a predictive relationship between information processing speed and subjective CF, an association between the two has been demonstrated in the past (Golan et al., 2018). It may be that an individual with a slower information processing speed may need to engage in additional processing, and may therefore experience a subjectively greater level of CF.

Depression has been previously demonstrated to be a strong independent predictor of subjective CF (Morrison & Stuifbergen, 2016; Strober & Arnett, 2005). Past research has also highlighted the relationship between sleep quality and depression. It has been suggested that poor sleep quality is a symptom of depression (Morrison & Stuifbergen, 2016), although other research has suggested that sleep quality is independent of depression, and a result of physical complaints rather than psychosocial complaints (Strober & Arnett, 2005).

3.1.4   Sleep Quality

While overall sleep quality was not uniquely predictive of subjective CF, further analysis revealed that the combination of the seven components is predictive of subjective CF. In particular three components of sleep quality are unique predictors of subjective CF. As previous work has demonstrated a relationship between subjective CF and sleep quality (Berard et al., 2019; Strober & Arnett, 2005), and the current study found a significant relationship between subjective CF and sleep quality, we were interested in delving into the facets of sleep quality to learn more about the interaction. This was the first study to examine the independent components of sleep quality, and their predictiveness of subjective CF. It was found that subjective sleep quality (what an individual perceives their sleep quality to be), sleep latency (how long it takes an individual to fall asleep at night), and sleep duration (how long an individual is asleep on average each night), predict subjective CF in PwMS. This means that individuals who sleep less, take longer to fall asleep, and perceive poor sleep quality are more likely to experience subjective CF.

As the link between insomnia and depression is well established (e.g., Baron, Corden, Jin, & Mohr, 2011), it follows that sleep quality would not be uniquely predictive of subjective CF when both sleep quality and depression are combined. However, when depression and sleep quality were correlated, the three dimensions of sleep quality associated with depression were: subjective sleep quality, sleep disturbances, and daytime dysfunction. This suggests that there is no significant relationship between depression and sleep latency and duration, key aspects of insomnia. Daytime dysfunction can be considered a result of the sleep disturbances (e.g. too hot, pain, and noises), which are characterized in the PSQI as reasons for sleep interruptions. Due to the relationships observed, it may be that Strober and Arnett (2005) were closest in their

prediction that sleep quality is a symptom of physical (e.g. pain and temperature) rather than psychosocial (e.g. depression and anxiety) complaints. From this perspective, our observation that there is no statistically significant mediation relationship between depression and subjective CF, is unsurprising.

3.1.5   Mediation Analysis

As information processing speed has been linked with depression in the past (Diamond, Johnson, Kaufman, & Graves, 2008; Golan et al., 2018; Mackin et al., 2014; Siengsukon et al., 2018), and both were found to be significantly predictive of subjective CF in the current research, a mediation analysis was conducted to determine whether or not they are unique predictors of subjective CF. It was thought that information processing speed was slowed in PwMS due to the added symptoms of depression, and resulted in an elevated experience of subjective CF. The results of the mediation analysis did not reveal a mediating effect of information processing speed between depression and subjective CF. Thus, suggesting that information processing speed is not a result of depression in PwMS, but an independent predictor of subjective CF. This finding makes sense in the current sample, as only the ZVT was correlated with depression, and the SDMT was the unique predictor of subjective CF, not the ZVT. As information processing speed has not been investigated in this manner previously, further research into the varying methods of measuring information processing speed should be examined.

3.2   Implications

The current research concludes that cognitive facets of MS are more closely related to subjective CF than physical symptoms. Those who experience CF are more likely to have depression, anxiety and a slower information processing speed than those who do not experience

CF. This may suggest that individuals with depression and anxiety may feel more cognitively fatigued than individuals that do not experience depression and anxiety. The overarching finding of the research is that CF is predicted by slowed information processing speed, depression, and anxiety. Therefore, it may be that the best method for alleviating feelings of subjective CF would be improving depression, anxiety, and information processing speed. Within the non-MS population, it has been demonstrated that treating depression can have a positive impact on information processing speed (Mackin et al., 2014). As the relationship between CI (i.e. information processing speed) and mood disorders (i.e. depression and anxiety) has been consistent between the non-MS population (McDermott & Ebmeier, 2009; Papakostas, 2014; Sheline et al., 2006) and the MS population (Diamond et al., 2008; Lester, Stepleman, & Hughes, 2007), it is plausible that treating symptoms of depression among individuals with MS, would be an effective method of improving feelings of cognitive fatigue. Future research would do well to investigate the impact of psychotherapy on depression, anxiety, and information processing speed in PwMS.

3.3   Directions for Future Research

The findings of the current research could have a long-lasting impact on treatment options for PwMS experiencing subjective CF, as they suggest that the treatment of depression may have a direct impact on the experience of cognitive fatigue in this population. The relationship between objective and subjective CF remains concerning, however, and future research should attempt to further elucidate the nature of this relationship. Additionally, the impact of anxiety on the subjective experience of cognitive fatigue is a worthwhile avenue for future study. Although the measurement of anxiety and depression with a single scale (the HADS) is convenient, the confounding impact of method variance on the predictive power of each of these variables

suggests that future studies may wish to include additional measures of anxiety, in an effort to add richness to the measurement model that might be brought to bear in the investigation of CF. Given that objective and subjective CF demonstrate independent models of prediction, it may also be interesting to evaluate self-report measures of information processing speed, and their relationship with the variables measured in the current research. It is possible that depression and anxiety have an even stronger predictive effect on *feelings of cognitive slowness*, as compared to actual cognitive slowing.
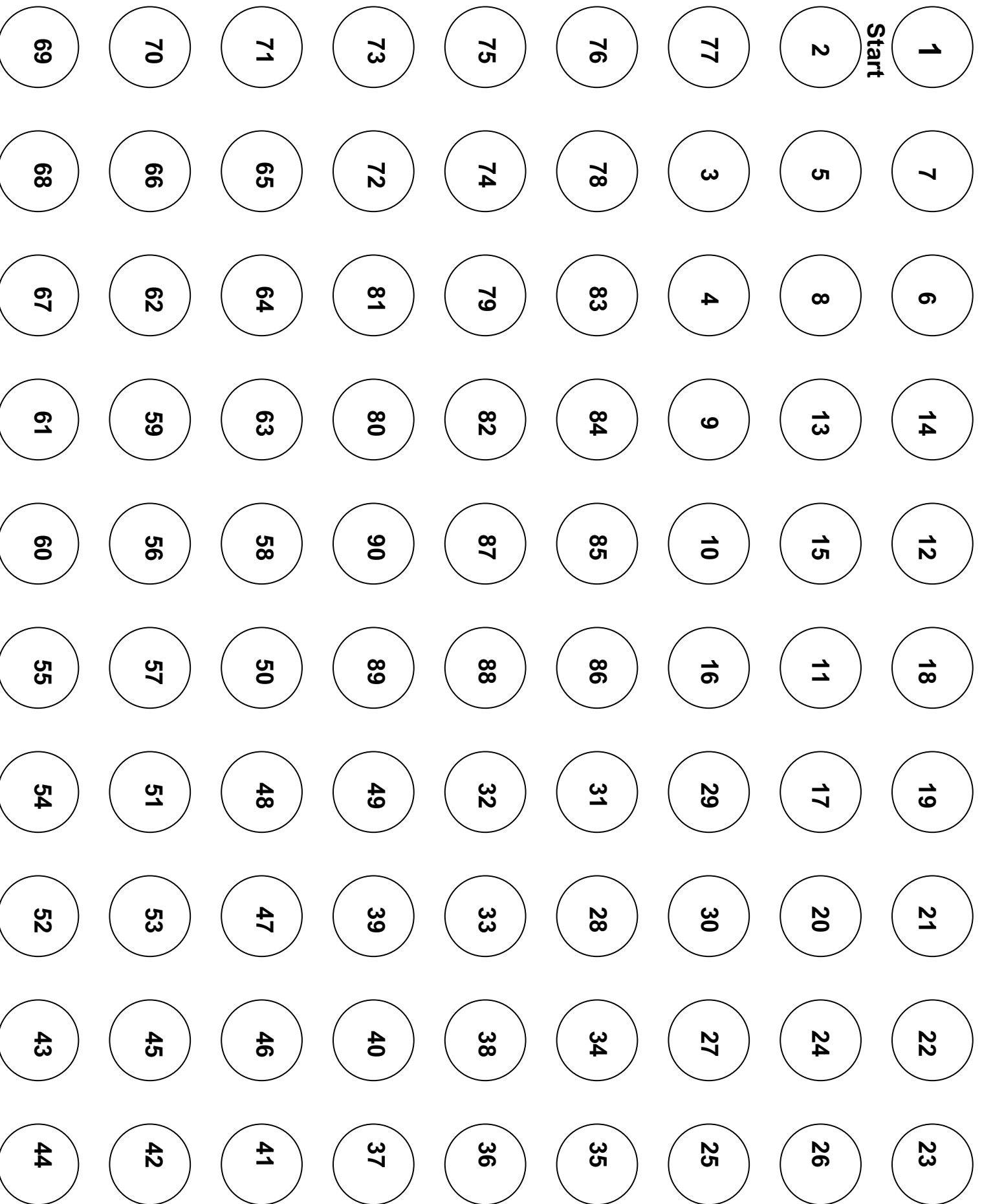
Finally, previous research within our research group has typically included cannabis usage as an exclusion criterion. While this is defensible, from the standpoint that cannabis is known to have an impact on cognition and mood disorders (Wadsworth, Moss, Simpson, & Smith, 2006), and also from the standpoint that cannabis usage was likely to be infrequent before it was legalized in Canada, future research should investigate the impact of cannabis usage in this population. As cannabis usage increases within Canada (and within this population) it will be important to understand how this substance interacts with medical treatments of MS, as well as non-medical treatments (e.g., psychotherapy) – and how these multiple factors impact on cognitive fatigue.

3.4   References

Bailey, A., Channon, S., & Beaumont, J. G. (2007). The relationship between subjective fatigue and cognitive fatigue in advanced multiple sclerosis. *Multiple Sclerosis*, *13*(1), 73–80. https://doi.org/10.1177/1352458506071162

Baron, K. G., Corden, M., Jin, L., & Mohr, D. C. (2011). Impact of psychotherapy on insomnia symptoms in patients with depression and multiple sclerosis. *Journal of Behavioral Medicine*, *34*(2), 92–101. https://doi.org/10.1007/s10865-010-9288-2

Berard, J. A., Smith, A. M., & Walker, L. A. S. (2019). Predictive Models of Cognitive Fatigue in Multiple Sclerosis. *Archives of Clinical Neuropsychology*, *34*(1), 31–38. https://doi.org/10.1093/arclin/acy014

Diamond, B. J., Johnson, S., Kaufman, M., & Graves, L. (2008). Relationships between information processing, depression, fatigue and cognition in multiple sclerosis. *Archives of Clinical Neuropsychology*, *23*(2), 189–199. https://doi.org/10.1016/j.acn.2007.10.002

Golan, D., Doniger, G. M., Wissemann, K., Zarif, M., Bumstead, B., Buhse, M., … Gudesblatt, M. (2018). The impact of subjective cognitive fatigue and depression on cognitive function in patients with multiple sclerosis. *Multiple Sclerosis*, *24*(2), 196–204. https://doi.org/10.1177/1352458517695470

Lester, K., Stepleman, L., & Hughes, M. (2007). The Association of Illness Severity, Self-Reported Cognitive Impairment, and Perceived Illness Management with Depression and Anxiety in a Multiple Sclerosis Clinic Population. *Journal of Behavioral Medicine*, *30*(2), 177–186. https://doi.org/10.1007/s10865-007-9095-6

Mackin, R. S., Nelson, J. C., Delucchi, K., Raue, P., Byers, A., Barnes, D., … Arean, P. A. (2014). Cognitive Outcomes After Psychotherapeutic Interventions for Major Depression

in Older Adults with Executive Dysfunction. *The American Journal of Geriatric Psychiatry*, *22*(12), 1496–1503. https://doi.org/10.1016/j.jagp.2013.11.002

McDermott, L. M., & Ebmeier, K. P. (2009). A meta-analysis of depression severity and cognitive function. *Journal of Affective Disorders*, *119*(1–3), 1–8. https://doi.org/10.1016/j.jad.2009.04.022

Morrison, J. D., & Stuifbergen, A. K. (2016). Predictors of Fatigue Impact in Persons With Long-Standing Multiple Sclerosis: *Journal of Neuroscience Nursing*, *48*(3), 143–150. https://doi.org/10.1097/JNN.0000000000000208

Morrow, S. A., Rosehart, H., & Johnson, A. M. (2015). Diagnosis and quantification of cognitive fatigue in multiple sclerosis. *Cognitive and Behavioral Neurology*, *28*(1), 27–32. https://doi.org/10.1097/WNN.0000000000000050

Papakostas, G. I. (2014). Cognitive Symptoms in Patients With Major Depressive Disorder and Their Implications for Clinical Practice. *The Journal of Clinical Psychiatry*, *75*(01), 8–14. https://doi.org/10.4088/JCP.13r08710

Paul, R. H., Beatty, W. W., Schneider, R., Blanco, C. R., & Hames, K. A. (1998). Cognitive and Physical Fatigue in Multiple Sclerosis: Relations Between Self-Report and Objective Performance. *Applied Neuropsychology*, *5*(3), 143–148. https://doi.org/10.1207/s15324826an0503_5

Schwid, S. R., Tyler, C. M., Scheid, E. A., Weinstein, A., Goodman, A. D., & McDermott, M. P. (2003). Cognitive fatigue during a test requiring sustained attention: a pilot study. *Multiple Sclerosis*, *9*(5), 503–508. https://doi.org/10.1191/1352458503ms946oa

Sheline, Y. I., Barch, D. M., Garcia, K., Gersing, K., Pieper, C., Welsh-Bohmer, K., … Doraiswamy, P. M. (2006). Cognitive Function in Late Life Depression: Relationships to

Depression Severity, Cerebrovascular Risk Factors and Processing Speed. *Biological Psychiatry*, *60*(1), 58–65. https://doi.org/10.1016/j.biopsych.2005.09.019

Siengsukon, C. F., Aldughmi, M., Kahya, M., Lynch, S., Bruce, J., Glusman, M., … Billinger, S. (2018). Individuals with mild MS with poor sleep quality have impaired visuospatial memory and lower perceived functional abilities. *Disability and Health Journal*, *11*(1), 116–121. https://doi.org/10.1016/j.dhjo.2017.04.011

Strober, L., & Arnett, P. (2005). An examination of four models predicting fatigue in multiple sclerosis. *Archives of Clinical Neuropsychology*, *20*(5), 631–646. https://doi.org/10.1016/j.acn.2005.04.002

Wadsworth, E. J. K., Moss, S. C., Simpson, S. A., & Smith, A. P. (2006). Cannabis use, cognitive performance and mood in a sample of workers. *Journal of Psychopharmacology*, *20*(1), 14–23. https://doi.org/10.1177/0269881105056644

Walker, L. A. S., Berard, J. A., Berrigan, L. I., Rees, L. M., & Freedman, M. S. (2012). Detecting cognitive fatigue in multiple sclerosis: Method matters. *Journal of the Neurological Sciences*, *316*(1–2), 86–92. https://doi.org/10.1016/j.jns.2012.01.021

Appendix A

65

Start

1 2 77 76 75 73 71 70 69

7 5 3 78 74 72 65 66 68

6 8 4 83 79 81 64 62 67

14 13 9 84 82 80 63 59 61

12 15 10 85 87 90 58 56 60

18 11 16 86 88 89 50 57 55

19 17 29 31 32 49 48 51 54

21 20 30 28 33 39 47 53 52

22 24 27 34 38 40 46 45 43

23 26 25 35 36 37 41 42 44

Western Research

Date: 11 September 2018

To: Dr. Andrew Johnson

Project ID: 112092

Study Title: An evaluation of the association among cognitive fatigue and depression among individuals with MS

Application Type: HSREB Initial Application

Review Type: Full Board

Full Board Reporting Date: 04/Sep/2018 13:00

Date Approval Issued: 11/Sep/2018 16:08

REB Approval Expiry Date: 11/Sep/2019

_____

Dear Dr. Andrew Johnson

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Demographics	Paper Survey	30/Jul/2018	1
Email Consent Form	Paper Survey	01/Mar/2006	NS5567
HADS	Paper Survey	30/Jul/2018	1
HADS_Scoring	Paper Survey	Received 10Sept2018	
LOI, 2018.09.07	Written Consent/Assent	07/Sep/2018	3
MFIS	Paper Survey	30/Jul/2018	1
MFIS_Manual	Paper Survey	Received 10Sept2018	
PASAT (Form A)	Other Data Collection Instruments	30/Jul/2018	1
PASAT_Manual	Paper Survey	Received 10Sept2018	
SDMT	Paper Survey	30/Jul/2018	1
SDMT_Manual	Paper Survey	Received 10Sept2018	
ZVT	Paper Survey	30/Jul/2018	1
ZVT_Script	Paper Survey	Received 10Sept2018	

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Nicola Geoghegan-Morphet, Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

VITA

Name:	Leila Mackay

Education

BA (Hons)
Honours Specialization in Psychology
Brescia University College
London, Ontario, Canada
2012-2017

MSc
Health Promotion
Health and Rehabilitation Sciences
Western University
2017-2019

Honours and Awards:

Western Graduate Research Scholarship
2017-2018, 2018-2019

Related Work Experience

Research Assistant
The University of Western Ontario
2017-2018, 2019

Teaching Assistant
The University of Western Ontario
Brescia University College
2017-2018, 2018-2019

Publications:

Robinson, A. E., Shelley, J. J., Holmes, J. D., Specht, J. A., Mackay, L. M., & Johnson, A. M.
Partners in education, health, and safety: Development and implementation of concussion
policy in Ontario school boards. *13th World Congress on Brain Injury*, Toronto, Ontario

Tenk, C., & Mackay, L. Degree of food processing influences memory of food images in
females. *Canadian Society for Brain, Behaviour & Cognitive Science,* Waterloo, Ontario