

Assessing cognitive fatigue in multiple sclerosis: A multidimensional approach

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Abstract

Cognitive fatigue (CF) presents a considerable challenge for individuals with multiple sclerosis (MS) often negatively impacting quality of life. CF can be defined as a decrease in, or inability to sustain, optimal task performance throughout the duration of a continuous cognitive task. The following dissertation presents three original research reports which evaluate CF in MS in three distinct ways using a multidimensional approach. The objective of this dissertation was to comprehensively evaluate and quantify this frequently misunderstood symptom of the disease. The first report examines four theoretical models of CF in MS which evaluate the interrelatedness of disease severity, fatigue, depression, and sleep quality in order to determine their predictive roles with regard to CF. The second report assesses CF longitudinally by examining whether or not the ability to perform optimally on a continuous cognitive task changes as the disease progresses across a three-year time interval. The final report objectively quantifies CF in MS by evaluating changes in global and regional cerebral blood flow during a task of sustained attention using arterial spin labeling perfusion fMRI. Results of all three reports are further discussed in terms of clinical and research implications. CF is a symptom of MS not readily apparent to outside observers but presents a very real burden for people with the disease that negatively impacts their ability to lead active and productive lives. These individuals may be discriminated against because CF has thus far been a largely unverifiable subjective experience. The totality of these three studies allows for a multidimensional quantification of CF. By providing objective support to the self-reports of individuals with MS, not only can they achieve much needed validation, but this can also lead to interventions that may provide further direct benefit to their health-related quality of life.

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List of Acronyms

ACC	Anterior cingulate cortex
ANOVA	Analysis of variance
ASL	Arterial spin labeling
BDI-FS	Beck Depression Inventory - Fast Screen
BICAMS	Brief International Cognitive Assessment for MS
BOLD	Blood oxygen level dependent
BVMT-R	Brief Visuospatial Memory Test - Revised
CBF	Cerebral blood flow
CF	Cognitive fatigue
CFI	Comparative Fit Index
CNS	Central nervous system
D-FIS	Daily Fatigue Impact Scale
EDSS	Expanded Disability Status Scale
EEG	Electroencephalogram
EPI	Echo-planar imaging
ESS	Epworth Sleepiness Scale
FIS	Fatigue Impact Scale
fMRI	Functional magnetic resonance imaging
FSS	Fatigue Severity Scale
GLM	General linear model
IFG	Inferior frontal gyrus
IFI	Incremental Fit Index

IPL	Inferior parietal lobule
IPS	Information processing speed
ISI	Interstimulus interval
MFG	Middle frontal gyrus
mFIS	Modified Fatigue Impact Scale
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
mSDMT	Modified Symbol Digit Modalities Test
MSFC	Multiple Sclerosis Functional Composite
NAART	North American Adult Reading Test
PASAT	Paced Auditory Serial Addition Test
PET	Positron emission tomography
PFC	Prefrontal cortex
PHQ-9	Patient Health Questionnaire - 9
PPMS	Primary-progressive multiple sclerosis
PRMS	Progressive-relapsing multiple sclerosis
PSQI	Pittsburgh Sleep Quality Index
PVT	Psychomotor Vigilance Task
RF	Radiofrequency
RRMS	Relapsing-remitting multiple sclerosis
RT	Reaction time
SDMT	Symbol Digit Modalities Test
SPL	Superior parietal lobule

SPMS	Secondary-progressive multiple sclerosis
VAS	Visual Analogue Scale
WM	Working memory

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CHAPTER 1

Introduction

Multiple sclerosis

Multiple sclerosis (MS) is a chronic, progressive disease of the central nervous system (CNS) characterized by widespread inflammatory lesions in the brain and spinal cord. These lesions, or plaques to which they are sometimes referred, are believed to result from autoimmune processes within the body in which the immune system attacks the myelin sheath surrounding the axons of nerves. The resulting loss of the myelin sheath produces impaired electrical signal conduction between neurons within the CNS. In the past, these MS-related lesions have typically been considered to predominantly affect only the white matter of the CNS. More recent research has shown, however, that grey matter loss and global brain atrophy play an important role in the progression of the disease as well (Kutzelnigg & Lassman, 2005). Recent advances have been made in our understanding of the underlying disease process and although there are multiple contributing factors, it appears to be a combination of genetic susceptibility and environmental factors. Nonetheless, the exact cause of the lesion formation still remains unclear. While lesions are more commonly found in the white matter, particularly in the deep periventricular regions, they may also occur nearly anywhere within the CNS. As such, virtually all functions associated with this particular branch of the nervous system could be affected. Common physical symptoms often presented by those with MS can include: a loss of bladder or bowel control, a loss of function or feeling of the limbs, fatigue, loss of balance, pain, as well as many others. Because of the wide variety of symptoms that can occur with MS, it is likely that no two individuals will

present with the same set of symptoms or disease course thus making it difficult to diagnose and successfully treat the disease.

Diagnosis

In 2000, the International Panel on the Diagnosis of MS was convened with the goal of outlining a new diagnostic criteria for MS to be used by clinicians (i.e. the McDonald criteria) (McDonald et al., 2001). While the Poser criteria had previously been considered the gold standard (Poser et al., 1983), significant advances in MRI technology had been made since the time of its formulation. At the time, MRI was not considered as sufficient evidence for the detection of MS-related lesions as the use of the technology was still in its infancy. Two decades later, however, the technique had evolved and was considered to play a critical role in assessing patients with MS. As such, the McDonald criteria incorporated a larger role for MRI in the detection of lesions and the criteria for diagnosis were revised. In keeping with the Poser criteria, the 2001 McDonald criteria states for a clinically-definite diagnosis of MS there must be objective evidence of dissemination of MS lesions in both time and space. Four years after the initial publication, the McDonald criteria was revised (Polman et al., 2005) in order to more clearly describe what is meant by the dissemination of lesions in time, as well as to clarify the significance of spinal cord lesions. In 2010, the McDonald criteria was further revised in order to simplify the demonstration of lesions in space and time via imaging, and to address criticisms which suggested the 2005 McDonald criteria had low sensitivity and specificity in non-Western Caucasian populations (Polman et al., 2011). The 2010 McDonald criteria states that MRI evidence of dissemination in space includes at least one T2 MRI lesion in at least 2 out of 4 areas of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord). These criteria note that the use of

gadolinium enhancement on MRI is not required for evidence of dissemination in space and that lesions resulting from other neurological disorders are to be excluded from the lesion count. According to the criteria, MRI evidence of dissemination in time includes any new T2 or gadolinium enhancing lesion when compared to a previous scan (irrespective of timing) or the presence of an asymptomatic enhancing lesion or non-enhancing T2 lesion on any one scan. In 2017, the criteria were once again revised in order to broaden the scope with regards to which lesion locations may be used to satisfy the MRI criteria for the dissemination of lesions in space and time. In addition, the presence of CSF-specific oligoclonal bands in those with symptoms of early “probable MS” may now receive a full diagnosis of multiple sclerosis (Thompson et al., 2018).

Prevalence and clinical course

In Canada, the prevalence of MS is amongst the highest in the world (Rosati, 2001) with estimates ranging between 55 and 240 per 100 000 individuals (Beck, Metz, Svenson, & Patten, 2005). Within Canada, the prevalence rate among women is about three times that of men (Orton et al., 2006) and the average age of diagnosis occurs between the ages of 20 and 40 years old (Compston & Coles, 2002).

Among those diagnosed with MS, four possible disease courses have been generally acknowledged in the current MS literature. Approximately 65-70% of those diagnosed with MS present with a relapsing-remitting disease course (Mohr & Cox, 2001). Relapsing-remitting MS (RRMS) typically refers to clearly defined disease relapses with full recovery or residual deficits upon recovery; the periods between disease relapses are characterized by a lack of disease progression. The defining characteristic of this disease course is the acute episodes of neurological deterioration with variable recovery but a stable course between attacks. About 80% of those

previously diagnosed with RRMS will develop a secondary-progressive disease course (Chiaravalloti & DeLuca, 2008). Secondary-progressive MS (SPMS) is viewed as the long-term outcome of patients who initially show a RRMS course and is characterized by a progressive worsening of symptoms with few periods of improvement or remission between attacks. Typically, the switch from RRMS to SPMS is when the baseline between relapses begins to worsen. A third type of disease course, known as progressive-relapsing MS (PRMS), is the least common course of MS; occurring in only approximately 5% of individuals diagnosed with the disease (Tullman, Oshinsky, Lublin, & Cutter, 2004). PRMS is characterized by steady disease progression from symptom onset, with clear, acute relapses, with or without full recovery; the periods between relapses are marked by continuing disease progression. Finally, approximately 20% of those diagnosed with MS will develop a primary-progressive disease course. Primary-progressive MS (PPMS) is characterized by a gradual, nearly continuous worsening of neurological function from first presentation, with some minor fluctuations but no discrete relapses.

Common outcome measures

One of the most commonly used scales to assess disease progression in MS is the Expanded Disability Status Scale (EDSS). This impairment rating scale is frequently used in both clinical and research settings as a method to assess the level of physical disability in MS (Kurtze, 1983). The scale itself consists of eight "functional systems," namely pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral (or mental), and a miscellaneous category termed "other". Each functional system is assigned a score on a scale of 0-5 or 0-6 based on the results of a neurological examination (with the "other" category being given a score of 0 or 1). The results of the

functional system ratings are then collapsed into a total score out of 10 (in possible increments of 0.5) which serves as an individual's overall EDSS score. An EDSS score of 0 signifies a normal neurological examination, whereby the only allowable symptom is one of mood change, with the instruction that this should not impact the overall EDSS score. An EDSS of 10 signifies death. Between these two extremes, the scale evaluates the level of disability with a major emphasis on lower extremity functioning and mobility. EDSS scores, therefore, are heavily weighted towards pyramidal tract and brainstem involvement, with little emphasis on mentation. While the functional system devoted to mentation does consider cognitive impairment, when it comes to the full EDSS score, an individual with profound dementia incapable of independent living will still only score an EDSS of 5.0, which denotes only moderate disability. In addition, mild to moderate cognitive impairment is more likely to be missed during a routine neurological examination (Peyster, Edwards, Poser, & Filskov, 1980), and thus would not be reflected in the rating. Not surprisingly, the scale's focus on ambulation has led to some criticism of its value and utility for examining the behavioural and cognitive aspects of MS as only one item on the scale refers to an individual's cognitive ability (Rudick et al., 1997).

In response to the deficiencies inherent in the EDSS, a task force of MS researchers and clinicians came together to establish the Multiple Sclerosis Functional Composite (MSFC), an outcome measurement scale including three different tasks which better reflect the broad range of disabilities associated with the disease (Cutter et al., 1999). The three tests which make up the MSFC include: a timed 25-foot walk, the nine-hole peg test (average right and left arms), and the Paced Auditory Serial Addition Test (PASAT) - 3 second version. The PASAT provides the only measure of cognitive

functioning in the MSFC. While restrictive in its evaluation of cognition (as the PASAT largely assesses only information processing speed and working memory), its inclusion in the MSFC is an improvement over the EDSS as the PASAT provides an objective measurement of cognition (in comparison to the subjective cognitive evaluation as part of the EDSS). From these three tests, a total score can be calculated by combining the individual z-scores of each of the three tasks into an overall total score. While the MSFC has not entirely replaced the EDSS, studies have shown its utility as a secondary assessment measure of disability in MS (Hobart et al., 2004), and it is being used increasingly as an outcome measure in clinical trials.

Cognitive impairment

Cognitive impairment presents as a significant problem for individuals with MS, affecting up to 70% of those individuals diagnosed (Hoffman, Tittgemeyer, & von Cramon, 2007; Rao, Leo, Bernardin, & Unverzagt, 1991). The impact of cognitive impairment stems from the effects MS has on the brain with the degree of impairment being linked to the total volume of white matter affected by MS-related lesions (Comi et al., 1995), as well as the total amount of overall brain atrophy that has occurred (Summers et al., 2008). Various domains of cognitive functioning can be affected including aspects of attention, information processing speed, visual and verbal memory, as well as many others. Recently, a large body of research has suggested that the primary cognitive deficit that occurs in individuals with MS is an impairment in information processing speed (IPS); such that individuals with MS are unable to process information as quickly as healthy individuals (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004; Denney, Lynch, Parmenter, & Horne, 2004). DeLuca et al. (DeLuca et al., 2004) have formalized this idea and have proposed the Relative Consequence

Model which suggests that the fundamental difficulty in IPS observed in individuals with MS may underlie other areas of cognitive impairment. This presents a problem for current research given that there exist few neuropsychological tests that can easily, reliably, and effectively evaluate these information processing speed deficits without being confounded by other cognitive processes.

Given the number of areas of cognitive functioning potentially affected, it is not surprising that both the type as well as the severity of cognitive dysfunction reported by individuals with MS often significantly varies between individuals. Research has shown that this cognitive dysfunction does not generally correlate well with level of physical impairment (Stenager, Knudsen, & Jensen, 1994) or EDSS score (Kurtze, 1983). While once it was believed that symptoms of cognitive impairment occurred only in those individuals diagnosed with MS who exhibited a high level physical impairment (McKhan, 1982), research has since shown that cognitive dysfunction can be present in those individuals with an EDSS score of less than 3.5, a score which reflects the early stages of the disease when physical disability is not yet so severe as to significantly impact the individual's daily life or ability to work (Ruggieri et al., 2003). Similarly, recent research has shown that individuals who present with clinically isolated syndrome (a term used to describe a first episode of neurologic symptoms as a result of inflammation or demyelination) or radiologically isolated syndrome (described as the incidental discovery of lesions suggestive of MS before symptom expression) can also present with a high frequency of cognitive impairment (Feuillet et al., 2007; Lebrun, Blanc, Brassat, Zephir, & deSeze, 2010). Thus, cognitive impairment presents even in individuals in the pre-clinical/early stages of the disease who have not yet been formally diagnosed with MS.

Cognitive impairment has been documented across all MS subtypes (De Sonneville et al., 2002). Studies have shown, however, that individuals with SPMS demonstrate more severe deficits when compared to RRMS, particularly when it comes to information processing speed (De Sonneville et al., 2002), as well as more severe deficits when compared to PPMS across the domains of language, attention, and visuo-spatial skills (Comi et al., 1995). As such, deficits are generally most severe in progressive forms of the disease, with individuals with SPMS showing the greatest vulnerability. There is debate in the literature, however, regarding the degree of impairment observed in PPMS. The current belief is that the degree of impairment is related to the degree of inflammation (i.e. the more inflammatory attacks, the more likely cognitive impairment will present). As those with PPMS tend to show less inflammation than SPMS, this may explain why those with SPMS are more impaired. Results support the notion that the severity of cognitive impairment coincides with the MRI lesion burden, as those with SPMS typically present with greater brain lesion loads than those with PPMS or RRMS (Thompson et al., 1991).

Fatigue

Fatigue is the most commonly reported complaint associated with MS, occurring in up to 90% of those individuals diagnosed with the disease (Brassington & Marsh, 1998; Minden et al., 2006). Fatigue can be generally defined as a state of reduced capacity for work following a period of mental or physical activity (Schwid, Covington, Segal, & Goodman, 2002) and can result from both primary or secondary mechanisms. Mechanisms of primary fatigue in multiple sclerosis relate directly to disease processes and typically involve impaired immune system function or damage to the CNS resulting in impaired neural conduction. Commonly proposed mechanisms of primary fatigue

include: cytokine activity (Hessen et al., 2006), endocrine/hormonal influences (Cleare, 2003), and axonal loss (Tartaglia et al., 2004). In contrast, secondary fatigue in MS is not caused directly by the disease processes themselves, but rather results from MS symptomatology. Possible secondary causes of fatigue may include: disturbances in sleep, depression, side effects of medication, and pain (Braley & Chervin, 2010). While these secondary mechanisms of fatigue can typically be treated or managed through interventions, primary fatigue persists in MS even when these secondary factors are eliminated.

When compared to healthy controls, individuals with MS report more frequent and more severe levels of fatigue (Paul, Beatty, Schneider, Blanco, & Hames, 1998) and it is often considered to be one of the most debilitating symptoms of the disease. Fatigue can negatively impact an individual's quality of life (Opara, Jaracz, & Broła, 2010), often affecting self-esteem or identity (Aronson, 1997; Janardhan & Bakshi, 2002), and increases the likelihood of unemployment (Edgley, Sullivan, & Dehoux, 1991; Smith & Arnett, 2005). Fatigue is more frequently seen in primary and secondary progressive MS compared to patients with a relapsing-remitting disease course (Leocani, Colombo, & Comi, 2008; Patrick, Christodolou, & Krupp, 2009). In addition, individuals with MS will often indicate their level of fatigue is worse during the second half of the day (Krupp, Serafin, & Christodoulou, 2010; Morris, Cantwell, Vowels, & Dodd, 2002) and is worsened by heat or humid environments (Leavitt, Summowski, Chiaravalloti, & Deluca, 2012). These results coincide with findings that warmer outdoor temperatures have been linked to more frequent clinical exacerbations and higher T2 lesion activity in patients with MS (Y, de Pedre-Cuesta, Söderström, Stawiarz, & Link, 2000).

Despite the disabling impact of fatigue, our understanding of its pathophysiology remains limited. One cause for this limitation may be due to the lack of a clear consensus on how best to appropriately define the construct of fatigue. Many studies fail to adequately define fatigue and among those that do there remains a considerable range in the definitions employed. Past research has used the term “fatigue” to refer to a multitude of concepts including: the subjective experience of physical or mental exhaustion, performance decrements on cognitive tasks, as well as effects of fatigue on muscle and CNS function. Kluger et al. 2013 have suggested that without clear terminology, communication and scientific progress amongst researchers examining fatigue remains restricted. Given the wide range of definitions employed, the authors propose a unified taxonomy to addressing distinct aspects of fatigue by distinguishing between fatigue (i.e. an individual’s subjective sensations) versus fatigability (i.e. objective changes in performance). The authors suggest that the use of this taxonomy can clarify and provide consistency to the assessment and reporting of fatigue in both clinical and research applications (Kluger, Krupp, & Enoka, 2013).

In addition to difficulties with terminology, fatigue also remains a poorly understood symptom of the disease in part due to the fact that the general construct of fatigue can be further broken down into finer grained concepts. While the more apparent type of fatigue can be described as physical fatigue, typically defined as a state of physical exhaustion (Paul et al., 1998), a second type of fatigue, known as *cognitive fatigue*, can impact an individual's cognitive performance on tasks involved in their daily lives. In MS, physical fatigue has been associated with greater levels of physical disability, a progressive disease course, and older age (Colosimo et al., 1995). One aspect of physical fatigue, known as motor fatigue, is reflected by a decline in strength during

sustained muscle contractions (Bigland-Ritchie, Cafarelli, & Vollestad, 1986). In MS, motor fatigue is evaluated experimentally by comparing the maximal strength at the beginning of a muscle contraction with the strength at the end of the contraction.

Typically these contractions are evoked during tests of hand grip, knee extensions, and dominant elbow extensions (Schwid et al., 2002). To date, physical fatigue has been the focus of the majority of research studies in the MS literature which have investigated MS-related fatigue.

Given the subjective nature of fatigue, it is most commonly assessed using self-report questionnaires as these measures are typically quick to administer and reflect subjective perceptions of fatigue. Many of the widely used fatigue scales are not specific to MS, however, and are also used in other diseases such as chronic fatigue syndrome. In addition, some scales attempt to quantify fatigue whereas others assess its impact on daily functioning. While a number of fatigue scales exist, the two most commonly used questionnaires in MS include the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (mFIS) (Amtmann et al., 2012). The FSS is a unidimensional scale with a primarily physical focus (Flachenecker et al., 2002) in which individuals respond to each of the 9 items on a 7-point Likert scale based on their experience with fatigue over the last week. Overall scale scores represent the mean of the individual item scores, with lower scores representing less fatigue. Items on this scale were chosen based on their ability to identify common features of fatigue in patients with MS. All but one of the FSS items focus on aspects of physical fatigue with one item (“My motivation is lower when I am fatigued”) being the sole representation of the cognitive aspects of fatigue. Unlike the FSS, the mFIS is a multidimensional scale with a focus on the physical, cognitive, and psychosocial aspects of fatigue. The mFIS, a 20-item scale, was derived from the larger

40-item Fatigue Impact Scale (FIS) based on items derived from interviews with MS patients concerning how fatigue impacts their daily activities. The mFIS scale includes 9 physical, 10 cognitive, and 2 psychosocial items. Items on this scale are scored from 0 to 4 (0 = Never, 1 = Rarely, 2 = Sometimes, 3 = Often, 4 = Almost always) with lower total scores representing less severe fatigue. Individuals are asked to consider their experience with fatigue during the past month. Both the FSS and mFIS have shown good psychometric properties (i.e. validity, test-retest reliability, etc.) over both short and long follow-up intervals (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989; Learmonth et al., 2013) and show strong correlations with one another (Télez, Rio, Tintoré, Nos, & Galán, 2005). When directly comparing the two scales to one another, Amtmann et al. (2012) suggest that when clinicians and researchers are interested in measuring: i) solely physical fatigue or ii) fatigue in samples whose ratings range from mild to moderate, that either the FSS or mFIS can serve as appropriate self-report measures of fatigue. In this regard, the FSS has the advantage of being shorter in length (though may suffer from less precision). In contrast, the authors suggest that for those who are interested in measuring i) both physical and mental fatigue or ii) fatigue in samples who are expected to have high levels of fatigue, the mFIS is the more appropriate measure given the multidimensional focus and greater overall number of items (Amtmann et al., 2012). One additional consideration when deciding which scale to use for research/clinical applications concerns the differences in the recall periods between the two scales. The FSS utilizes a one week recall period which, while potentially appropriate when evaluating the short-term impact of fatigue, has been shown to be less accurate in measuring mean levels of fatigue when compared to the 1 month recall period used by the mFIS (Broderick et al., 2008).

Cognitive fatigue

While it is important to examine the effects of physical fatigue in MS, recent research is emphasizing the importance of examining cognitive fatigue as well. While currently there is no universally accepted definition of cognitive fatigue (CF), it can be defined as a decrease in, or inability to sustain, task performance throughout the duration of a continuous cognitive task (Bryant, Chiaravalloti, & DeLuca, 2004; Schwid et al., 2002; Walker, Berard, Berrigan, Rees, & Freedman, 2012). In the context of the taxonomy proposed by Kluger et al 2013, this particular definition aligns with their construct of fatigability, more so than fatigue, given the focus on objective change in performance over time (Kluger et al., 2013). This definition may not be the only way to operationalize CF, however, as it likely reflects several underlying deficits (i.e. slowed processing speed, sustained attention deficits, etc.). As such, alternate definitions of cognitive fatigue have included references to aspects of attentional and executive networks as well (ex. declines over time in alerting, orienting, and executive control) (Holtzer, Shuman, Mahoney, Lipton, & Verghese, 2011). Similar to the general construct of fatigue, an issue arises in the literature when attempting to define cognitive fatigue given the inconsistent use of terminology. Past studies have operationally defined objective cognitive declines that occur with sustained cognitive effort over time using not only the term “cognitive fatigue” but also “performance fatigability” and “time-on-task effects” as well. As such, future studies should determine how best to operationally define cognitive fatigue in MS in order to facilitate consistency and reproducibility.

Regardless of specific terminology, cognitive fatigue has not been found to be associated with age, gender, depressive symptoms, overall physical dysfunction, or disease duration, unlike physical fatigue. Similarly, no consistent relationship has been

shown between subjective reports of cognitive fatigue and levels of cognitive performance (Parmenter, Denney, & Lynch, 2003; Paul et al., 1998). Cognitive fatigue occurs in both individuals with MS as well as healthy controls but research has shown that when individuals with MS and healthy controls are asked to perform information processing speed tasks, individuals with MS become cognitively fatigued earlier on, reflected by a breakdown in their task performance occurring earlier in the task when compared with healthy individuals (Bryant et al., 2004; Morrow, Rosehart, & Johnson, 2015; Walker et al., 2012).

Because cognitive fatigue is a frequently misunderstood symptom of the disease, as well as a significant source of frustration for individuals with MS, one of the biggest focuses of previous research has been on determining how we can reliably measure cognitive fatigue in MS. There is currently no universally accepted method of quantification. In most studies, tasks of information processing speed (IPS) and/or working memory (WM) are used to evaluate CF given the sustained attention required in order to perform the task successfully. Past literature has shown that the PASAT, a measure of IPS and WM, can serve as a reliable and sensitive tool to objectively evaluate cognitive fatigue in MS (Morrow et al., 2015; Walker et al., 2012). During this task, individuals are presented with a string of single digit numbers, from 1-9, at set intervals (typically every 3 seconds or 2 seconds) and are instructed to orally add each number to the previous number presented. Sustained cognitive effort must be maintained throughout the task in order to perform successfully. Cognitive fatigue, therefore, can be evaluated using the PASAT by comparing performance at the beginning of the task versus performance at the end of the task. While the PASAT has been commonly used to objectively evaluate cognitive fatigue in MS, other tasks can be used as well. Simple

reaction time tasks often require sustained cognitive effort in order to maintain performance over time. One such task, the Psychomotor Vigilance Task (PVT), has also been used to evaluate cognitive fatigue. The PVT is a simple reaction time test with varying and random inter-stimulus intervals which range from 2 to 10 seconds. Individuals are presented with a millisecond countdown timer and are instructed to react to and stop the counter with a button press as quickly as possible. By comparing reaction times at the start of the PVT to reaction times at the end of the PVT, evidence of cognitive fatigue on this task can be noted even in healthy controls (Lim et al., 2010).

In addition to methodological differences, the evaluation of CF can be broken down into two distinct approaches: 1) examining performance decline over time on a specific task (i.e. within-task CF), and 2) comparing performance on the same task both before and after a prolonged period of cognitive activity (i.e. across-session CF). These differences further illuminate the inconsistency in terminology used in the literature when examining cognitive fatigue. While studies have focused predominantly on within-task CF in MS, little research to date has examined across-session CF. In addition, few studies have examined differences in susceptibility to CF in MS longitudinally, and as such it remains unclear whether or not an individual's level of CF changes over time as the disease progresses.

Sleep disturbances

Subjective complaints of sleep disturbances are reported by 24-50% of individuals diagnosed with MS (Bamer, Johnson, Amtmann, & Kraft, 2008; Caminero & Bartolome, 2011; Kaminska, Kimoff, Schwartzmann, & Trojan, 2011), with MS patients likely experiencing sleep difficulties three times more often than healthy controls (Clark et al., 1992). In addition, women appear to be at a higher risk for sleep disturbances when

compared with men (Bamer et al., 2008). Currently, there are relatively few studies in the MS literature which focus on the relationship between disturbances in sleep quality and MS; however, disturbances in sleep have been linked to other symptoms in MS such as pain, depression, and fatigue (Fleming & Pollak, 2005; Stanton, Barnes, & Silber, 2006). While sleep disturbances have mainly been discussed with regard to fatigue, studies to date on this subject are based on a variety of methods and mostly include small patient groups (Pokryszko-Dragan et al., 2012). Nonetheless, some evidence exists relating sleep disturbances and fatigue in MS. Poorer subjective sleep quality, as measured by the Pittsburgh Sleep Quality Index (PSQI), has been shown to be associated with higher levels of fatigue in MS (Trojan et al., 2007). In addition, a relationship was also found between sleep disturbances and fatigue, independent of depression, using a composite (non-validated) questionnaire to measure sleep quality (Strober & Arnett, 2005). Studies which have assessed daytime sleepiness, as measured by the Epworth Sleepiness Scale (ESS), however, have shown mixed results. In some studies, levels of daytime sleepiness have shown no relationship with levels of self-reported fatigue in MS (Pokryszko-Dragan et al., 2012); suggesting that sleepiness and fatigue are distinct concepts. Others studies, however, have shown some relationship between daytime sleepiness and fatigue in situations that demand self-paced activation (i.e. situations in which external cues contribute to the level of activation such as watching TV or driving a car) (Merkelbach et al., 2011). While it is clear that sleep disturbances are prevalent in MS, and may be associated with significant consequences for patients, no research to date has comprehensively evaluated the relationship between sleep disturbances and cognitive fatigue specifically in MS.

Neuroimaging and cognition

In recent years, both structural and functional neuroimaging have become key elements for the diagnosis and care of individuals with MS. Through the use of structural MRI, measures of cortical atrophy, whole brain atrophy, and lesion loads can be obtained; with these measures correlating with an individual's level of cognitive functioning in MS. Studies have shown that MS patients with greater lesion loads have significantly more cognitive impairment than those with a lesser lesion burden (Arnett et al., 1994; Berg et al., 2000). The width of the third ventricle has also shown a strong association with cognitive performance in MS (Benedict et al., 2004) and can be predictive of an individual's cognitive status (Benedict et al., 2006). Neocortical volume correlates with a wide variety of neuropsychological measures, and can also distinguish between patients with MS who present with cognitive impairment versus those who do not (Benedict et al., 2006).

Compared to structural imaging, the use of functional imaging techniques to study brain function is a relatively newer area of research in the field of MS. Studies using positron emission tomography (PET) and perfusion MRI have shown a reduction in cerebral oxygen use and blood flow in individuals with MS, and that these changes correlate with the degree of cognitive impairment observed (Blinkenberg et al., 2000; Inglese et al., 2008). Functional magnetic resonance imaging (fMRI) allows for non-invasive brain mapping and has provided invaluable information regarding how neural networks underlying cognitive processes are affected by MS. The most extensively studied cognitive domain in MS using fMRI is working memory. Increased activation in the prefrontal cortex (PFC) while performing the PASAT (a working memory task) has been noted in individuals with MS when compared to healthy controls (Chiaravalloti et

al., 2005); results which have been replicated across different working memory tasks (Hillary et al., 2003). These results were interpreted as possible evidence for cerebral reorganization. Working memory (WM) has also been evaluated using the n-back task in which individuals are presented with a sequence of stimuli and must indicate when the current stimulus matches the one they saw n times earlier in the sequence. While performing an n-back task, both individuals with MS and healthy controls tend to activate the same brain regions within the working memory circuitry; the extent of activation, however, has shown mixed results. In most studies, MS patients show significantly greater activation than controls in areas within the WM circuitry (ex. dorsolateral prefrontal cortex) (Sweet, Rao, Primeau, Mayer, & Cohen, 2004). In one study, however, a decrease in activation in these areas was noted for the MS group with greater activation noted in areas beyond the typical WM circuitry (Wishart et al., 2004). This decrease in activation was interpreted as reduced recruitment of these WM areas due to axonal loss, such that there was an inability of the brain to properly utilize these damaged areas. While not as extensively evaluated, the domain of processing speed has also been examined in MS using fMRI (Smith et al., 2012). While performing a modified version of the Symbol Digit Modalities Task (mSDMT), the MS group showed greater activation than healthy controls in the right PFC (Genova, Hillary, Wylie, Rypma, & DeLuca, 2009). In addition, it was found that as performance on the mSDMT task slowed, the level of activation of the PFC increased. While the working memory demands of the mSDMT are minimal (particularly when compared to the PASAT), the increased activation of the PFC mirrors results of more demanding working memory tasks suggesting that perhaps the PFC is recruited in individuals with MS as behavioral

performance decreases regardless of which task is being performed (Caramia, Tinelli, Francia, & Pozzilli, 2010).

Arterial spin labelling (ASL) perfusion fMRI

Recent advances in functional neuroimaging have allowed for more sophisticated analyses to be conducted when evaluating cognitive functioning in those with MS. Of particular interest, arterial spin labelling (ASL) perfusion fMRI has proven to be an invaluable tool when imaging the brain while at work over extended time intervals. ASL is a non-invasive, non-ionizing MRI technique which uses magnetically labeled arterial blood as the endogenous tracer. This technique allows for the quantification of cerebral blood flow changes both across the whole brain (i.e. globally) and at specific regions of interest during the performance of a cognitive task. Over prolonged task durations, ASL has demonstrated excellent reproducibility and superior spatial and temporal resolution compared to traditional neuroimaging techniques (such as BOLD fMRI) (Aguirre, Detre, Zarahn, & Alsop, 2002) making it ideal for studies which utilize cognitive tasks where cognitive performance must be maintained over long periods of time.

Using ASL, studies have shown differences in cerebral blood flow perfusion between those with MS and healthy controls. Abnormalities in grey matter perfusion (ex. hypoperfusion), particularly in thalamic and right frontal regions, have been demonstrated in those with MS compared to controls using ASL (Doche et al., 2017; Ota et al., 2013). In addition, reduced cerebral blood flow in limbic, parietal, and temporal regions has also been documented (Hojjat et al., 2016). Interestingly, not only did cerebral blood flow in the MS group differ from healthy individuals overall, but those with MS who were classified as being cognitively impaired also showed differences in CBF perfusion compared to those within the MS group who were not impaired. These

results suggest that ASL may serve as a useful surrogate measure of disease severity and cognitive functioning in those with MS.

One particular area of study where ASL excels is when evaluating mental or cognitive fatigue. As previously discussed, ASL provides a useful neuroimaging technique when evaluating cerebral blood flow changes over long periods of time. As such, a number of studies have examined changes in CBF perfusion as they relate to fatigability while performing sustained cognitive tasks. Task related changes in cerebral blood flow in the presence of fatigue have been evaluated in those with chronic fatigue syndrome (Staud, Boissoneault, Craggs, Lai, & Robinson, 2018), mild traumatic brain injuries (Möller, Nordin, Bartfai, Julin, & Li, 2017), as well as healthy controls (Lim et al., 2010). While specific results may vary from region to region depending on which population is being studied, overall results suggest that changes in patterns of CBF perfusion over time in the presence of increasing cognitive fatigue can be detected using ASL. To date, no study has yet evaluated cognitive fatigue in MS using the ASL perfusion fMRI technique.

Thesis breakdown

The main objective of this dissertation was to comprehensively evaluate and quantify cognitive fatigue in multiple sclerosis in three distinct ways using a multidimensional approach. The body of this dissertation is, therefore, composed of three original manuscripts. The first research report examines four theoretical models of cognitive fatigue in MS which evaluate the interrelatedness of disease severity, fatigue, depression, and sleep quality in order to determine their predictive roles with regard to cognitive fatigue. Data was collected as a part of a larger neuropsychological battery of tests and was analyzed using path analysis in order to determine which of the theoretical

models best predicted an individual's level of cognitive fatigue. The second research report assesses cognitive fatigue longitudinally by examining whether or not the ability to perform optimally on a continuous cognitive task changes as the disease progresses across a three-year time interval. Data was collected as part of a larger three-year longitudinal study evaluating cognitive changes in those with relapsing remitting MS over time. To date, no study has yet determined how an individual's susceptibility to cognitive fatigue changes over time as the disease progresses. The final research report objectively quantifies cognitive fatigue in MS by evaluating changes in global and regional cerebral blood flow during a task of sustained attention using arterial spin labeling perfusion fMRI. This neuroimaging technique has been shown to be invaluable when attempting to evaluate the neural underpinnings of cognitive fatigue. To date, no study has yet examined cognitive fatigue in MS using ASL. For the purposes of this dissertation, cognitive fatigue was evaluated in each of the three reports from a within-task perspective (i.e. comparing performance from the beginning of a task to the end of the task). While not the only definition, cognitive fatigue was defined in this context as a decrease in, or inability to sustain, optimal task performance throughout a continuous cognitive task. This definition was chosen in order to remain consistent with previous studies that employed similar methodologies when objectively evaluating cognitive fatigue (Morrow et al., 2015; Schwid et al., 2003; Walker et al., 2012). Results from each of the three reports are further discussed in terms of their clinical and research implications.

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CHAPTER 2**Predictive models of cognitive fatigue in multiple sclerosis**

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Abstract

Objective: Cognitive fatigue (CF) can be defined as decreased performance with sustained cognitive effort. The present study examined the interrelatedness of disease severity, fatigue, depression, and sleep quality in order to evaluate their predictive roles of CF in MS. Four theoretical models examining these variables were assessed.

Methods: Fifty-eight individuals with a diagnosis of MS were recruited. CF was measured by examining last third vs. first third performance on the Paced Auditory Serial Addition Test (PASAT). The PASAT and self-report measures of fatigue, depression, and sleep quality were administered. Path analysis was used to evaluate each of the models.

Results: CF was correlated only with depression ($r = .362, p = .006$) and sleep quality ($r = .433, p = .001$). Sleep quality was the greatest significant independent predictor of CF ($\beta = .433, t(55) = 3.53, p < .001$), accounting for 17.3 % of the total variance. The best fitting model showed sleep quality as the largest contributor to CF; however, depression played a smaller predictive role. Furthermore, depression emerged as the strongest predictor of sleep quality and fatigue. Disease severity weakly predicted depression.

Conclusions: Sleep quality is the most significant predictor of CF in MS. As such, sleep quality may be a treatable cause of CF. Sleep quality itself, however, accounted for only 17.3% of the variance in CF suggesting that other variables which were not formally assessed in this sample (ex. anxiety, etc.) may also play a predictive role. Follow-up studies should evaluate how results may differ with a larger sample size

Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system with a wide variety of neurological symptoms typically involving the visual, motor, and autonomic systems. Beyond these primary symptoms, individuals with MS often report secondary symptoms associated with the disease, such as fatigue, depression, and sleep disturbances. These symptoms are often highly prevalent and can negatively impact an individual's quality of life (Amato et al., 2001; Lobentanz et al., 2004). Furthermore, individuals also frequently report a lack of mental energy or mental fatigue, hereafter referred to as cognitive fatigue (CF). While currently there is no universally accepted definition of CF, it can be defined as a decrease in, or inability to sustain, task performance throughout the duration of a sustained attention task (Bryant, Chiaravalloti, & DeLuca, 2004; Schwid, Covington, Segal, & Goodman, 2002). It should be noted that this may not be the only way to operationalize CF as it is likely a reflection of several underlying deficits (i.e. slowed processing speed, sustained attention deficits, etc.). Nonetheless, we chose to remain consistent with past work by defining CF in the context of decreased performance over time. Typically, the assessment of cognitive fatigue relies on self-report measures but these can present with limitations (Cohen et al., 2000; Schwid et al., 2003). An alternative is to assess cognitive fatigue during the performance of a sustained attention task, objectively quantifying CF as a decline in performance from the beginning to the end the task (Krupp & Elkins, 2000; Morrow, Rosehart, & Johnson, 2015; Schwid et al., 2003; Walker, Berard, Berrigan, Rees, & Freedman, 2012). The Paced Auditory Serial Addition Test (PASAT) has been shown to be a sensitive and valid measure to objectively quantify cognitive fatigue in MS (Morrow et al., 2015; Walker et al., 2012). As research has only just recently begun focusing on

evaluating CF in MS, there is a need for a more comprehensive understanding of how other secondary symptoms of the disease (ex. depression, sleep quality, etc.) interact with CF.

Currently, there is a lack of theoretical groundwork that evaluates the relationships between these secondary symptoms and whether or not they can predict an individual's susceptibility to cognitive fatigue. While the study of cognitive fatigue is becoming more predominant in the MS literature, no research to date has examined the interrelatedness of an objective measure of CF and other secondary symptoms of the disease or has established a theoretical model explaining these contributing factors. The goal of the present study, therefore, was to examine the inter-relatedness of fatigue, depression, sleep disturbances, and cognitive fatigue in MS. In addition, the impact of physical disease severity was also examined. The current study attempted to replicate and expand upon the methodology employed by Strober & Arnett (2005). Whereas they evaluated predictors of the construct of 'fatigue' in general (i.e. a construct based on self-report), the current study will evaluate which combination of variables best predict objectively measured cognitive fatigue.

Past research has examined the association between self-reported fatigue and depression, however; results have been mixed. A significant association between fatigue and depression has been reported in some studies (Bakshi et al., 2000; Fisk, Pontefract, Ritvo, Archibald, & Murray, 1994; Ford, Trigwell, & Johnson, 1998), but not in others (Iriarte, Carreno, & de Castro, 1996; Vercoulen et al., 1996). In addition, sleep disturbances have been found to be significantly related to depression (Clark et al., 1992) as well as fatigue (Attarian, Brown, Duntley, Carter, & Cross, 2004). Though there is some evidence that self-reported fatigue, depression, and sleep disturbances may be

related in MS, Strober & Arnett (2005) noted that the existing literature lacks any research which examines these three factors and their combined or interactive effects. At the time of their writing, research had only yet evaluated associations between two variables at a time, thus any higher-level interactions between the variables were not being considered. In their own study, they examined four models designed to predict fatigue that included these three variables concurrently. Their four competing models were formulated based upon the presence of certain relationships among these constructs in MS samples and from findings in other studies that attempted to predict fatigue in similar disorders (ex. systemic lupus erythematosus) (Huysen et al., 1998).

The present study attempted to build upon the work of Strober & Arnett (2005) by incorporating the concept of cognitive fatigue into the statistical model. Whereas the focus of their work was on self-reported fatigue as the outcome variable, in the current study cognitive fatigue was the outcome variable of interest, and thus self-reported fatigue was considered as a possible predictor. One limitation of their study, which was addressed in the current work, concerns their measure of sleep disturbance. In their study a composite measure of sleep disturbances was derived from various measures as opposed to one comprehensive, and psychometrically-sound, measure. In the current study, a previously validated measure of sleep disturbance (Pittsburgh Sleep Quality Index) was used in order to facilitate replicability in the future. The current study was exploratory in nature given the current lack of theoretical background in cognitive fatigue research to date. As such, there are several possible causal pathways involving the predictor variables. Four models were proposed based on suspected relationships between the variables and were tested with a focus on cognitive fatigue as the outcome variable.

Methods

Participants

A total of fifty-eight (58) individuals with a confirmed diagnosis of clinically definite MS based on 2010 McDonald criteria (Polman et al., 2011) were recruited through the MS Clinic at the Ottawa Hospital. Those with probable MS or those with symptoms suggestive of MS without a clinically definite diagnosis were excluded. All individuals were fluent in English and presented with no other neurological, medical, or psychiatric condition which may have impaired cognition (besides MS and depression). Individuals with prior head trauma, learning disabilities, history of seizures or unexplained syncope, or who are currently using drugs (either legal or illegal) that may have an effect on cognitive function were excluded. In addition, those individuals who were currently experiencing an MS exacerbation were considered ineligible.

Procedures

The study was approved by the Ottawa Hospital Research Ethics Board. After undergoing informed consent procedures, participants completed a demographic interview. Individuals completed the PASAT as part of a comprehensive neuropsychological battery evaluating cognitive domains such as information processing speed, executive functions, and working memory, among others. In addition, self-report measures of depression, fatigue, and sleep disturbances were completed. The battery was fixed and as such the PASAT was administered at the same time for all participants.

Measures

Measures are presented in Appendix 1.

Cognitive Fatigue

Paced Auditory Serial Addition Test (PASAT) – The PASAT is a measure of information processing speed and working memory in which participants are instructed to listen to a time-spaced series of single digit numbers (from 1-9) and add each number to the previous number presented. The individual must provide his/her response orally prior to the presentation of the next digit for the response to be considered correct. The speed at which the participant must process information during this task can be manipulated by presenting the series of digits at different rates, i.e. with varying inter-stimulus intervals (ISI). Cognitive fatigue can be evaluated using the PASAT by comparing performance on the 1st half of the task to performance on the 2nd half of the task. The PASAT has been shown to be a sensitive and valid measure to objectively quantify cognitive fatigue in MS (Morrow et al., 2015; Walker et al., 2012).

Fatigue

Modified Fatigue Impact Scale (mFIS) - The mFIS is a self-report measure of fatigue whereby individuals rate the extent to which fatigue has been a problem for them within the past month, including the day of testing (Learmonth et al., 2013; Téllez, Rio, Tintoré, Nos, & Galán, 2005). The mFIS consists of 21-items and is composed of three subscales that describe how fatigue impacts upon cognitive (10 items), physical (9 items), and psychosocial functioning (2 items). Each of these items is given a score from 0 (no problem) to 4 (extreme problem) with resulting mFIS total scores ranging from a minimum of 0 to a maximum of 84, with higher scores indicating more severe levels of fatigue. The mFIS has been validated and has shown good psychometric properties in an MS patient population (Learmonth et al., 2013).

Depression

Patient Health Questionnaire - 9 (PHQ-9) - The PHQ-9 is a 10-item self-report questionnaire of depression. Individuals are asked to indicate how often over the last two-week interval they have been bothered by each of the first 9-items (ex. Poor appetite or overeating; Feeling down, depressed, or hopeless). Each item is scored on a scale of 0 to 3, with 0 being "not at all" and 3 being "nearly every day". From these nine items, a total score is calculated. Scores of 5, 10, 15, and 20 represent cut-off points for "mild", "moderate", "moderately severe", and "severe" depression, respectively (Kroenke, Spitzer, Williams, & Lowe, 2010). The tenth item is a follow-up item that assigns weight to the degree to which any depressive problems noted have affected the patient's level of functioning (Patten et al., 2015).

Sleep Quality

Pittsburgh Sleep Quality Index (PSQI) - The PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over a one-month time interval. Nineteen individual items generate seven "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global total score.

Disease Severity

Expanded Disability Status Scale (EDSS) – The EDSS is a method of quantifying disability in MS and monitoring change in an individual's level of disability over time. This score is largely reflective of an individual's *physical* level of disability. Scores range from 0 (no disability) to 10 (death) in 0.5-unit increments, with higher values representing higher levels of disability.

Analyses

The relationship between each of the independent variables was established first by examining Pearson correlation coefficients. Next, multiple regression analyses were conducted to examine the collective role that these variables played in predicting cognitive fatigue. A hierarchical regression entering the variables in the order of the magnitude of their zero-order correlations with cognitive fatigue was performed to determine whether each predictor accounted for significant independent variance in cognitive fatigue. Finally, path analysis was employed to test each of the various models. To examine each model, fit indices were chosen which take into consideration the relatively small sample size. In particular, the chi-square to degrees of freedom ratio (CMIN/df) was chosen over the chi-square. A ratio less than 2 suggested that the model was acceptable (Ullman, 1996). Additionally, the Comparative Fit Index (CFI) and the Incremental Fit Index (IFI), which address the issues of parsimony and sample size while taking the degrees of freedom into account, were used. Both these indices range from 0 to 1.0, with a value greater than .90 representing good fit (Byrne, 2001). Finally, in order to compare the models directly to one another, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) fit indices were examined. Models with lower AIC and BIC values are preferred.

Results

All statistical analyses were conducted using SPSS Version 23 in conjunction with SPSS AMOS 23.

Demographics and Test Descriptives

Demographic data for the sample as well as descriptive data for each of the variables assessed are presented in Table 1.

Correlations

Pearson correlation coefficients showed that depression was significantly correlated with both fatigue ($r = .749, p = <.0005$) and sleep quality ($r = .694, p = <.0005$). Sleep quality and fatigue were also correlated ($r = .476, p = <.0005$). With regards to cognitive fatigue, CF was related to depression ($r = .362, p = .006$) and sleep quality ($r = .433, p = .001$), but not to self-reported fatigue or disease severity.

Regression

Hierarchical regression entering the variables in the order of the magnitude of their zero-order correlations with cognitive fatigue showed that sleep quality was the greatest and only significant independent predictor of CF ($\beta = .433, t(55) = 3.53, p <.001$), accounting for 17.3% of the total variance.

Path Analyses

The four models tested are outlined in Figure 1. Their corresponding fit indices can be found in Table 2.

Model 1 theorised that sleep disturbances were caused by both disease severity and depression independently and that sleep disturbances in turn caused both self-reported fatigue and cognitive fatigue. It was thought that those who experienced greater physical disease severity (i.e. tremors, restlessness, etc.) and higher levels of depression would report lower sleep quality during the night. In turn, this lower quality of sleep would result in increased cognitive fatigue and greater levels of self-reported general fatigue. This model was a poor fit to the data. Model 2 differed from Model 1 in

that it suggested that depression was caused exclusively by disease severity (i.e. those with greater physical MS symptomatology would have higher levels of depression) and that, similar to Model 1, depression, in turn, impacted sleep quality and subsequent fatigue and cognitive fatigue. This model was also a poor fit to the data. Model 3 was similar to Model 2 though instead suggested that self-reported fatigue was a result of depression (rather than sleep quality). This model theorized that depression had a greater impact on self-reported fatigue than did sleep quality (consistent with the correlations noted) and thus those with higher levels of depression would report more fatigue. This model had an acceptable level of fit, though was not the best model fit for the data. Model 4 was the best fitting of the competing models. This model builds upon Model 3 and suggests that cognitive fatigue is a result of not only sleep disturbances, but that depression also plays a role as well, both in terms of how it relates to sleep disturbance and how it relates to CF more directly. The inclusion of depression as a direct predictor of cognitive fatigue was theorised by the assumption that those with higher levels of depression would be less motivated to perform the task (i.e. our measure of cognitive fatigue) and thus would show more evidence of cognitive fatigue as reflected by poorer task performance.

Discussion

The goal of the present study was to examine the interrelatedness of disease severity, fatigue, depression, sleep disturbances and cognitive fatigue in an MS sample. Four competing models were developed and evaluated to examine how these secondary symptoms might predict cognitive fatigue in MS. The relationships between the individual constructs within the models were developed based on previous evidence in

the literature along with our own theoretical suppositions of how these variables might interact.

Regression analyses revealed that sleep quality was the only significant predictor of CF and as such this relationship was designated in each of the models tested. Consistent with the literature, sleep quality and measures of self-reported fatigue were correlated in the current sample. It seems intuitive that those who would report more disturbances in their sleep would report higher levels of subjective fatigue. This relationship was evaluated in both Model 1 and Model 2. In addition, depression was correlated with sleep quality in the current sample and as such both Models 1 and 2 proposed that depression impacted sleep quality which further impacted cognitive fatigue. These models, however, both showed poor levels of fit. The association between sleep quality and self-reported fatigue was only moderate (factor loading of .47) and as such this association was not as strong in the current sample as was anticipated. This suggests that other factors may impact an individuals' level of reported fatigue besides sleep quality (i.e. depression). The relationship between depression and sleep quality showed a high association (factor loading of .70) consistent with their correlation in the current sample and as such this relationship was maintained in Model 3 and Model 4.

As with Model 1 and Model 2, Model 3 indicated that depression impacted sleep quality and subsequently cognitive fatigue while having no unique contribution to predicting cognitive fatigue directly. This model assumed no unique contribution of depression consistent with the regression analysis. In addition, this model evaluated whether depression had a significant role on an individual's level of self-reported fatigue (previously attributed to sleep quality in Model 1 and Model 2). The association between

these variables was high (factor loading of .74). This model showed an acceptable level of fit, though was not the best fitting model that was tested.

The best fitting model was Model 4 which suggested that sleep quality and depression both played a role in predicting cognitive fatigue despite depression showing no significant unique contribution to CF in the regression analysis. Nonetheless, this relationship was included in the model given the significant correlation observed between these variables ($r = .362, p = .006$). The lack of significance and small factor loading (.12) in the model however suggests that the role that depression plays in directly impacting an individual's level of CF is small. Given the small sample in the current study, future studies should evaluate whether this predictive relationship between depression and cognitive fatigue is maintained, improved, or lost when evaluating larger samples. This model maintains the high associations observed between depression and sleep quality as well as between depression and self-reported fatigue; consistent with the correlations noted within our sample.

The role of disease severity, in particular *physical* disease severity, and how it relates to and interacts with the other variables in each model remains unclear. In this sample, disease severity did not correlate with any of the other variables and as such it is difficult to determine if and where in the models disease severity may have had an impactful role. This indeterminate relationship is evident in the path analysis of our models as factor loadings were small when we suggested it may impact sleep quality (Model 1; factor loading .01) or depression (Models 2-4; factor loading .14) in this sample. The lack of correlation between disease severity and cognitive fatigue (and subsequent non-inclusion in the regression analyses) suggests that disease severity does not play a direct role impacting cognitive fatigue and so its most appropriate place in the

model remains ambiguous. While Strober & Arnett (2005), found that disease severity was an independent predictor of self-reported fatigue (Strober & Arnett, 2005), we did not test this relationship directly as the outcome variable of interest in our case was cognitive fatigue; thus we tested the impact of disease severity on both sleep quality and depression given those were the two variables most correlated with CF. Lastly, whether or not cognitive impairment relates to and/or predicts an individual's level of CF remains unclear. While this relationship was not formally being evaluated *a priori*, *post hoc* analyses were conducted to determine whether cognitive impairment may have played a significant role in the current sample. Despite the fact that 57.9% of individuals were classified as cognitively impaired on one or more cognitive tests (i.e. ≤ 1.5 SD below the mean), adding cognitive impairment to the path analyses made no significant unique contribution to the models. These results are specific to the current sample, however, and may differ with larger sample sizes.

There were limitations to the current study. Given the small sample size, the findings from the various models may be specific to only the current study and could be quite different in larger samples. While fit indices were chosen which attempted to account for the small sample size, future studies should evaluate whether these findings can be replicated in larger samples as the results may differ. In addition, most of the variables assessed were done so as self-reported measures. In particular, only a self-report measure of sleep disturbance was used. Given that sleep quality was the largest predictor of an individual's level of CF, an objective measurement of sleep quality would have been ideal (ex. EEG) as one would expect that those with poorer objective measures of sleep (as evidenced by slower sleep onset or less time spent in slow wave/REM sleep as detected by EEG, for example) would show higher levels of CF.

Unfortunately, this was not assessed in the current study and should be considered as a future direction for research. A third limitation of the present study concerns the subjective nature of fatigue itself. Past research has shown that self-reported measures of fatigue consistently show no correlation with objective measures given its debated etiology (primary vs. secondary symptom of the disease) and overall subjective nature. The current study did not directly explore this relationship as, consistent with past research, the two were uncorrelated in this study's sample. Rather, all of the models tested proposed that fatigue was a result of either depression or sleep quality. As such, the direct relationship between subjective fatigue and objective cognitive fatigue remains unclear. This lack of a seemingly intuitive relationship (i.e. those with higher levels of self-reported fatigue would be expected to show objectively more performance decline (i.e. CF) continues to remain elusive. Future studies should address this relationship more directly in other MS samples and the impact other secondary symptoms might have on this relationship.

Despite the limitations noted, this study has important implications. To the best of our knowledge, this was the first study to examine and develop a theoretical framework for how secondary MS symptoms may predict an individual's objective level of CF. While the models proposed do not represent the entire breadth of possible relationships between the variables evaluated (nor do they represent all possible symptoms which may contribute to CF), given the good model fit for Model 4 we propose that this model represents a valuable starting point for future studies attempting to examine how disease symptomatology may impact CF. Variables which were not directly evaluated in the current study (anxiety, etc.) may also play a role in predicting an individual's level of CF and as such, future research should consider

including these to examine their possible predictive roles. As stated, the major limitation of the current study is its relatively small sample size; thus, whether findings remain consistent with larger sample sizes remains an important issue for future research. Secondly, these findings have important implications for treatment and symptom management. Results suggest that sleep disturbances seem to have the greatest impact on an individual's level of CF and as such improvements in an individual's overall sleep quality may also improve an individual's experience with CF. Future research should consider exploring how levels of objective CF differ between those with higher sleep quality (ex. those with little difficulty falling/staying asleep, those who are getting an appropriate amount of sleep each night, etc.) from those with poorer sleep quality. The hope is that sleep quality may prove to be a treatable cause of cognitive fatigue in MS which may, in turn, improve an individual's overall quality of life.

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Table 1 – Sample demographics and descriptive test data

	Frequency/Mean (SD)
Age	45.44 (9.93)
Education	15.43 (2.68)
MS Subtype	RRMS = 44 (77.2%) SPMS = 9 (15.8%) PPMS = 4 (7.0%)
Sex	Males = 16 (28.1%) Females = 41 (71.9%)
EDSS	2.66 (1.87)
mFIS	29.92 (19.13)
PHQ-9	5.21 (5.45)
PSQI	6.76 (4.88)
PASAT – Change from 1 st third to last third	-1.89 (3.19)

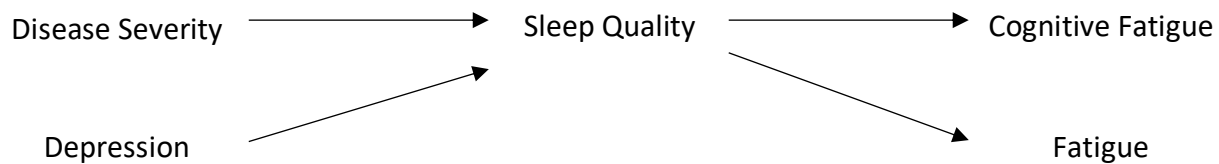
Table 2 – Fit indices of the four competing models

Model	CMIN/d.f.	CFI	IFI	AIC	BIC	Model Fit
Model 1	5.54	.661	.695	61.23	64.59	Poor fit
Model 2	5.36	.675	.707	60.17	63.54	Poor fit
Model 3	.234	1.00	1.00	30.89	34.48	Acceptable fit
Model 4	.176	1.00	1.00	29.40	32.76	Best fit

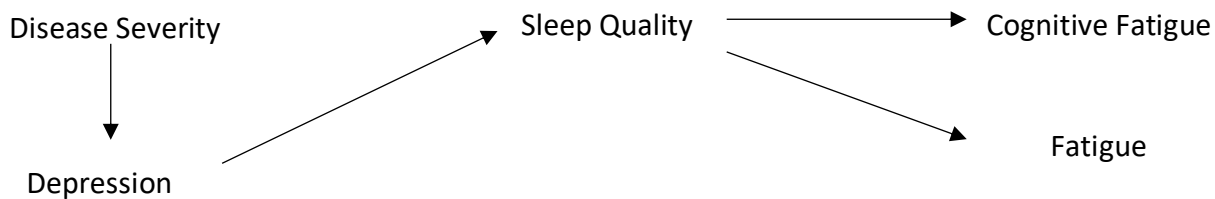
Note: CMIN/d.f.: chi-square to degrees of freedom ratio; CFI: Comparative Fit Index; IFI: Incremental Fit Index; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion

Figure 1 – Four models predicting cognitive fatigue

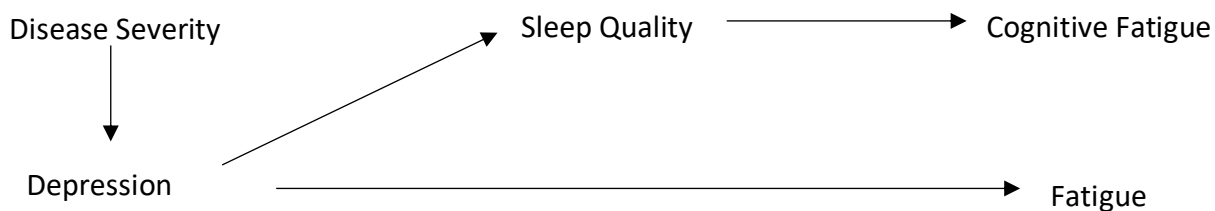
Model 1



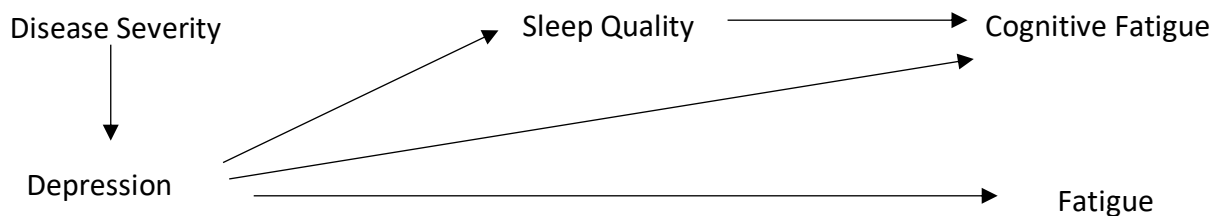
Model 2



Model 3



Model 4



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Appendix

Paced Auditory Serial Addition Test (PASAT)

PASAT - Form A

Name _____ Date _____

PRACTICE	9+1	3	5	2	6	4	9	7	1	4
	10__	4__	8__	7__	8__	10__	13__	16__	8__	5__

RATE #1 (3")	1+4	8	1	5	1	3	7	2	6	9
	5__	12__	9__	6__	6__	4__	10__	9__	8__	15__
	4	7	3	5	3	6	8	2	5	1
	13__	11__	10__	8__	8__	9__	14__	10__	7__	6__
	5	4	6	3	8	1	7	4	9	3
	6__	9__	10__	9__	11__	9__	8__	11__	13__	12__
	7	2	6	9	5	2	4	8	3	1
10__	9__	8__	15__	14__	7__	6__	12__	11__	4__	
8	5	7	1	8	2	4	9	7	9	
9__	13__	12__	8__	9__	10__	6__	13__	16__	16__	
3	1	5	7	4	8	1	3	8	2	
12__	4__	6__	12__	11__	12__	9__	4__	11__	10__	

Total Correct (raw) = _____ Percent Correct = _____

PRACTICE	3+8	2	7	9	1	8	5	2	6	4
	11__	10__	9__	16__	10__	9__	13__	7__	8__	10__

RATE #2 (2")	4+3	7	2	5	1	8	6	9	1	7
	7__	10__	9__	7__	6__	9__	14__	15__	10__	8__
	9	4	6	3	5	8	1	6	2	7
	16__	13__	10__	9__	8__	13__	9__	7__	8__	9__
	5	9	4	5	2	6	4	8	3	5
	12__	14__	13__	9__	7__	8__	10__	12__	11__	8__
	9	7	4	2	8	5	2	1	6	4
14__	16__	11__	6__	10__	13__	7__	3__	7__	10__	
7	3	5	9	6	4	5	3	9	4	
11__	10__	8__	14__	15__	10__	9__	8__	12__	13__	
1	8	3	1	6	8	5	4	2	6	
5__	9__	11__	4__	7__	14__	13__	9__	6__	8__	

Total Correct (raw) = _____ Percent Correct = _____

Modified Fatigue Impact Scale (mFIS)

Modified Fatigue Impact Scale (MFIS)

Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. But people who have medical conditions like MS experience stronger feelings of fatigue more often and with greater impact than others.

Following is a list of statements that describe the effects of fatigue. Please read each statement carefully, the circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. (If you need help in marking your responses, tell the interviewer the number of the best response.) Please answer every question. If you are not sure which answer to select choose the one answer that comes closest to describing you. Ask the interviewer to explain any words or phrases that you do not understand.

Because of my fatigue during the past 4 weeks

	Never	Rarely	Sometimes	Often	Almost Always
1. I have been less alert.	0	1	2	3	4
2. I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3. I have been unable to think clearly.	0	1	2	3	4
4. I have been clumsy and uncoordinated.	0	1	2	3	4
5. I have been forgetful.	0	1	2	3	4
6. I have had to pace myself in my physical activities.	0	1	2	3	4
7. I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
8. I have been less motivated to participate in social activities.	0	1	2	3	4
9. I have been limited in my ability to do things away from home.	0	1	2	3	4
10. I have trouble maintaining physical effort for long periods.	0	1	2	3	4
11. I have had difficulty making decisions.	0	1	2	3	4
12. I have been less motivated to do anything that requires thinking	0	1	2	3	4
13. My muscles have felt weak	0	1	2	3	4
14. I have been physically uncomfortable.	0	1	2	3	4
15. I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16. I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4
17. I have been less able to complete tasks that require physical effort.	0	1	2	3	4

	Never	Rarely	Sometimes	Often	Almost Always
18. My thinking has been slowed down.	0	1	2	3	4
19. I have had trouble concentrating.	0	1	2	3	4
20. I have limited my physical activities.	0	1	2	3	4
21. I have needed to rest more often or for longer periods.	0	1	2	3	4

Instructions for Scoring the MFIS

Items on the MFIS can be aggregated into three subscales (physical, cognitive, and psychosocial), as well as into a total MFIS score. All items are scaled so that higher scores indicate a greater impact of fatigue on a person's activities.

Physical Subscale

This scale can range from 0 to 36. It is computed by adding raw scores on the following items: 4+6+7+10+13+14+17+20+21. _____

Cognitive Subscale

This scale can range from 0 to 40. It is computed by adding raw scores on the following items: 1+2+3+5+11+12+15+16+18+19. _____

Psychosocial Subscale

This scale can range from 0 to 8. It is computed by adding raw scores on the following items: 8+9. _____

Total MFIS Score

The total MFIS score can range from 0 to 84. It is computed by adding scores on the physical, cognitive, and psychosocial subscales. _____

Pittsburgh Sleep Quality Index (PSQI)

Name: _____

Date: _____

Pittsburgh Sleep Quality Index (PSQI)

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. **Please answer all questions.**

1. During the past month, what time have you usually gone to bed at night? _____
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night? _____
3. During the past month, what time have you usually gotten up in the morning? _____
4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.) _____

5. During the <u>past month</u> , how often have you had trouble sleeping because you...	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe:				
6. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
	No problem at all	Only a very slight problem	Somewhat of a problem	A very big problem
8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?				
	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?				

	No bed partner or room mate	Partner/room mate in other room	Partner in same room but not same bed	Partner in same bed
10. Do you have a bed partner or room mate?				
	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
If you have a room mate or bed partner, ask him/her how often in the past month you have had:				
a. Loud snoring				
b. Long pauses between breaths while asleep				
c. Legs twitching or jerking while you sleep				
d. Episodes of disorientation or confusion during sleep				
e. Other restlessness while you sleep, please describe:				

Patient Health Questionnaire – 9 (PHQ-9)

**PATIENT HEALTH QUESTIONNAIRE-9
(PHQ-9)**

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?
(Use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + + +
=Total Score:

If you checked off **any** problems, how **difficult** have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Expanded Disability Status Scale (EDSS)

Kurtzke Expanded Disability Status Scale (EDSS)

- 0.0 - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).
- 1.0 - No disability, minimal signs in one FS* (i.e., grade 1).
- 1.5 - No disability, minimal signs in more than one FS* (more than 1 FS grade 1).
- 2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
- 2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).
- 3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
- 3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).
- 4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters.
- 4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters.
- 5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0).
- 5.5 - Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0).
- 6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

- 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).
- 7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone).
- 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).
- 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).
- 8.5 - Essentially restricted to bed much of day; has some effective use of arm(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).
- 9.0 - Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).
- 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, almost all grade 4+).
- 10.0 - Death due to MS.

*Excludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in Functional Systems scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

Sources: Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983 Nov;33(11):1444-52.

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CHAPTER 3

A longitudinal evaluation of cognitive fatigue on a task of sustained attention in early relapsing-remitting multiple sclerosis

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Minor revisions made as part of thesis evaluation

Abstract

Background: Cognitive fatigue can be objectively measured on tasks of sustained attention and can be defined as decreased performance as a result of sustained cognitive effort. Individuals with MS early in their disease are vulnerable to cognitive fatigue, though this has yet to be evaluated longitudinally. Presently, the goal was to evaluate cognitive fatigue over a 3-year interval in those with early-phase relapsing-remitting MS (RRMS). The sensitivity of the Paced Auditory Serial Addition Task (PASAT) at detecting cognitive fatigue was evaluated, as was the impact of scoring methodology.

Methods: 32 MS and 32 healthy controls completed the 3" and 2" PASAT as a measure of sustained attention at baseline and 3-year follow-up.

Results: Performance on the PASAT remained stable across time, with improvement noted on the 2" likely due to practice and the small sample size. Cognitive fatigue was noted at both times, though sensitivity varied based on scoring methodology. No evidence of worsening cognitive fatigue was noted over time. The MS group performed worse only when cognitive fatigue was the outcome variable.

Conclusions: While individuals with MS continue to be vulnerable to cognitive fatigue at follow-up, severity does not seem to increase with time. Additionally, cognitive fatigue may be a more sensitive marker of cognitive impairment than overall task performance in those with early-phase RRMS. This has important implications given that clinically only task performance is typically assessed.

Introduction

Fatigue is a significant problem in multiple sclerosis (MS), occurring in up to 90% of those diagnosed (Brassington & Marsh, 1998; Kinkel, 2000; Minden et al., 2006). Compared to healthy controls (HC), individuals with MS report more frequent and more severe levels of fatigue (Paul, Beatty, Schneider, Blanco, & Hames, 1998). Fatigue is often considered to be one of the most debilitating symptoms of the disease and can greatly impact quality of life (Opara, Jaracz, & Broła, 2010). Despite the large body of literature examining MS-related fatigue, the concept of fatigue remains poorly understood, likely due to its multifaceted nature and limitations with regard to measurement. In the past, research has focused predominantly on the study of physical fatigue; however, cognitive fatigue can often be equally as debilitating.

Typically, assessment of cognitive fatigue relies on self-report measures but these can present with limitations. Individuals are asked to rate their fatigue without adequate definition, and thus subjective measures of cognitive fatigue are inherently flawed and can be subject to recall bias (Cohen et al., 2000; Schwid et al., 2003). An alternative is to assess cognitive fatigue during the performance of a sustained attention task, objectively quantifying cognitive fatigue as a decline in performance from the beginning to the end of the task (Krupp & Elkins, 2000; Morrow, Rosehart, & Johnson, 2015; Schwid et al., 2003; Walker, Berard, Berrigan, Rees, & Freedman, 2012). While currently there is no universally accepted definition for objective cognitive fatigue, it can be defined as a decrease in, or inability to sustain, task performance throughout the duration of a sustained attention task (Bryant, Chiaravalloti, & DeLuca, 2004; Schwid, Covington, Segal, & Goodman, 2002). During these tasks, individuals with MS show more susceptibility to the effects of cognitive fatigue when compared to HC (Bryant et al.,

2004). Individuals susceptible to cognitive fatigue are less able to maintain the required cognitive effort necessary to continuously meet task demands over time. This is often reflected by a breakdown in task performance as the task progresses. Despite its limitations (Tombaugh, 2006), the Paced Auditory Serial Addition Test (PASAT) has been shown to serve as a sensitive and valid measure of cognitive fatigue in MS (Morrow et al., 2015; Walker, Berard, et al., 2012).

The PASAT is generally acknowledged in the literature to be one of the most sensitive measures of IPS and working memory deficits in MS (Fisk & Archibald, 2001; Tombaugh, 2006). Given its demonstrated sensitivity, the PASAT is used in studies investigating cognitive fatigue in MS where sustained attention must be maintained over time. Cognitive fatigue is objectively assessed by comparing early performance on the task with later performance. Cognitive fatigue has been measured using the PASAT by comparing performance on either the first half versus the second half (Walker, Berard, et al., 2012) or on the first third versus the last third (Morrow et al., 2015). Individuals with MS are expected to perform worse as the task progresses as they have a particularly difficult time processing information quickly enough. This problem increases in frequency as the task progresses resulting in performance declines (DeLuca, Johnson, & Natelson, 1993; Forn, Belenguer, Pacet-Ibars, & Ávila, 2008).

The sensitivity of the PASAT at detecting cognitive fatigue differs depending on the scoring methodology (Walker, Berard, et al., 2012). Traditionally, PASAT performance is scored by the number of correct responses. Individuals may, however, adopt a “chunking method” strategy such that the first two numbers are added, the next number is skipped, the following two numbers are added, and so forth (Fisk & Archibald, 2001; Snyder, Aniskiewicz, & Snyder, 1993). This strategy reduces the

difficulty of the task by decreasing the need to perform multiple cognitive processes simultaneously. While scores within normal limits may be achieved, their performance no longer reflects the ability to cope with the challenging working memory demands nor does it reflect an accurate representation of their ability to perform the task as intended.

The number of correct dyad responses better reflects an individual's ability to successfully meet task demands (Fisk & Archibald, 2001; Snyder, Cappelleri, Archibald, & Fisk, 2001). In this case, a correct score is only assigned when one correct response immediately precedes another. As such, the number of correct responses and the number of correct dyads both provide a measure of *performance accuracy*. One may further calculate a percent dyad score; an indication of the *proportion of time* an individual is performing the task as intended. While not a measure of performance accuracy per se, higher percent dyad scores reflect a greater ability to produce correct responses in accordance with task demands (Fisk & Archibald, 2001). The percent dyad scoring method thus provides a reflection of an individual's *performance strategy*.

Previous work by our group (Walker, Berard, et al., 2012) examined task performance in individuals with early phase relapsing-remitting MS and HC on the PASAT in order to determine if task performance is influenced by cognitive fatigue. Furthermore, we evaluated whether PASAT scoring method influenced its sensitivity. When comparing performance on the first half of the task versus the second half, cognitive fatigue was apparent in the MS sample compared to controls only on the 3" PASAT, and only with the percent dyad scoring method. This is consistent with prior work which found that the percent dyad method (i.e. *performance strategy*) is more sensitive to cognitive fatigue than *performance level* alone (Bryant et al., 2004). In addition, when performance was compared between the last third and the first third of

the PASAT, an average of 2 to 3 fewer correct responses was noted for the MS group suggesting that cognitive fatigue may be reliably detected using thirds on the PASAT as well. These results provided preliminary evidence that cognitive fatigue can be detected using the PASAT in individuals with MS; however, results varied based on the methodology used. Further expansion upon this preliminary work involves determining whether the susceptibility of the MS group to cognitive fatigue changes over time. The primary goal of the current study, therefore, is to evaluate cognitive fatigue longitudinally.

The longitudinal evaluation of cognitive fatigue represents a novel area of research. Given that cognitive dysfunction has been shown to be progressive across longitudinal follow-up (Amato, Ponziani, Siracusa, & Sorbi, 2001; Kujala, Portin, & Ruutiainen, 1997), it is important to determine whether an individual's susceptibility to cognitive fatigue also changes over time. The PASAT was chosen as the tool to measure cognitive fatigue in the current study given its demonstrated sensitivity at detecting IPS deficits in MS, as well as its continued use as a measure of sustained attention. The duration of the test-retest interval (3-years) was selected as longitudinal studies have suggested that a minimum test-retest interval of 2 to 3 years was necessary in order to detect cognitive changes (Bernardin, Rao, & Luchetta, 1993; Kujala et al., 1997). PASAT performance was evaluated by comparing the first and last thirds of the task, thus allowing for the examination and comparison of performance at the extremes of the task which may provide a more precise reflection of early task performance versus performance later on (Morrow et al., 2015).

The primary objective was to examine task performance following a three-year interval in a sample of individuals with RRMS and healthy controls on the PASAT to

determine if task performance is influenced by cognitive fatigue, and whether or not this influence changed over time. Furthermore, we examined whether PASAT scoring method influenced its sensitivity. It was hypothesized that: 1) individuals with MS would perform worse on the PASAT at 3-year follow-up when compared to their performance at baseline. It was expected that the performance of the HC group would remain consistent over time. Similarly, given the presumed progression of cognitive decline over time, it was expected that 2) individuals with MS would perform worse overall than HC on the PASAT at follow-up. In terms of cognitive fatigue, it was hypothesized that 3) both groups would display evidence of cognitive fatigue at baseline and follow-up, however the degree of cognitive fatigue would be greater in the MS group. Similarly, on the basis of disease progression, it was expected that 4) the degree of cognitive fatigue in the MS group at follow-up would be greater than the degree noted at baseline.

Methods

Participants

At baseline, thirty-two individuals with a confirmed diagnosis of relapsing-remitting MS (McDonald et al., 2001) were recruited from the MS Clinic of the Ottawa Hospital to complete a comprehensive battery of neuropsychological tests. All had a mild level of physical disability (EDSS = 1.83(1.18)) and a disease duration of less than 10 years ($M = 4.35(3.09)$). Individuals who were experiencing an exacerbation at the time of baseline recruitment or who had had less than 28 days between the onset of improvement of all signs and symptoms attributable to an MS exacerbation were excluded. Thirty-two age, education, and IQ-matched healthy controls were recruited by word of mouth from the community, as well as newspaper and website advertisements.

All participants were fluent in English and were between the ages of 18 and 65. All were free from previous neurological, medical, or psychiatric illnesses (besides MS and depression) that may have impaired cognition. Individuals who had been exposed to the PASAT within the last 6 months were excluded at follow-up (or were given their follow-up assessment 6 months post-exposure).

Procedure and measures

The study was approved by the Ottawa Hospital Research Ethics Board. After informed consent was obtained, participants completed a demographic questionnaire. At baseline, the North American Adult Reading Test (NAART) was administered as an estimate of premorbid intellectual ability, with participants required to achieve an estimated IQ score of at least 90 in order to be considered eligible. In order to evaluate cognitive fatigue, the 3-second (3") and 2-second (2") PASAT were administered in the context of a larger neuropsychological battery of testing.

Statistical analysis

PASAT performance was compared between ISIs as well as between the first and last thirds of each trial for both groups. In addition, performance at baseline was compared to performance at 3-year follow-up. Responses were recorded, and the following scores were tallied: *total number of correct responses*, *total dyad score*, and *percent dyad score*. Percent dyad scores were calculated using the following formula: $(\text{Dyad score} / \text{Total correct score}) \times 100$. This formula represents a simplified, more user-friendly version of the percent dyad formula employed in past research (Bryant et al., 2004; Fisk & Archibald, 2001) while still maintaining identical calculation results. In

order to examine the degree of change in cognitive fatigue over time, a change score was calculated by subtracting performance on the first third of the PASAT from the last third at both baseline and follow-up for all participants. Once calculated, the change at follow-up was subtracted from the change at baseline in order to obtain an overall score reflective of cognitive fatigue change over time. Each analysis was performed three times for each of the two ISIs (3" and 2"); once for each of the three scoring methods: *total correct score*, *total dyad score*, and *percent dyad score*.

Data Analysis Plan

Hypothesis 1 & 2. A repeated measure analysis of variance (ANOVA) was performed to address whether the MS and HC groups performed differently on the PASAT at 3-year follow-up compared to their respective performances at baseline.

Hypothesis 3. In order to evaluate cognitive fatigue, a 2 x 2 (ISI x Third) repeated measures ANOVA was performed to determine whether individuals performed differently on the last third of the PASAT when compared to the 1st third and to examine whether this difference varied between groups or between ISIs. This analysis was repeated at both baseline and follow-up.

Hypothesis 4. In order to evaluate whether the degree of cognitive fatigue differed between the MS and HC groups and whether the degree changed over time, a 2 x 2 (Group x Time) repeated measures ANOVA was performed using the cognitive fatigue change scores.

Results

The computerized statistical package SPSS – Version 23 was used for all data analyses. A significance level of $\alpha \leq .05$ was used throughout.

Demographics

The HC and MS groups were matched on age, education, and IQ scores. One-way ANOVAs showed no significant differences between the two groups on any of these variables (Table 1).

Performance

PASAT raw performance data are listed in Table 2. At both the 3” and 2” ISIs, no significant main effect for *Group* was noted for either baseline or follow-up performance. Overall task performance did not differ between the MS and healthy control groups at either time point. At the 2” ISI, a significant main effect for *Time* was noted (Total Correct: $F(1,62) = 125.84, p = <.001$; Total Dyad: $F(1,62) = 116.32, p = <.001$; Percent Dyad: $F(1,62) = 56.98, p = <.001$); however, no *Group x Time* interaction was observed. Both groups showed improved performance at follow-up. These results were consistent across all three scoring methods.

Cognitive Fatigue

PASAT raw performance data during the first and last third are listed in Table 3.

Baseline

At baseline, a main effect for *Third* was noted across all three scoring methods (Total Correct: $F(1,58) = 151.82$, $p < .001$; Total Dyad: $F(1,58) = 132.24$, $p < .001$; Percent Dyad: $F(1,58) = 97.73$, $p < .001$) indicating that individuals' performance differed between the first and last third of the task. Overall, poorer performance on the last third of the task when compared to the first third was noted (i.e. cognitive fatigue), though this was true for both groups. When using the percent dyad scoring method, however, a *Third x Group* interaction was observed ($F(1,58) = 4.48$, $p = .039$) suggesting that the proportion of time in which the MS group met task demands was lower on the last third of the task versus the first third for both the 3" and 2" ISIs when compared to HC. In addition, an *ISI x Third* interaction was observed across all three scoring methods (Total Correct: $F(1,58) = 17.40$, $p < .001$; Total Dyad: $F(1,58) = 51.01$, $p = .015$; Percent Dyad: $F(1,58) = 28.37$, $p < .001$). Examination of the means showed poorer performance on the last third of the task at the 2" ISI compared to the 3" ISI for both groups suggesting that higher difficulty tasks are more sensitive to cognitive fatigue (though not specifically to individuals with MS).

Follow-up

Similar to baseline, at follow-up a main effect for *Third* was noted across all three scoring methods (Total Correct: $F(1,60) = 46.51$, $p < .001$; Total Dyad: $F(1,60) = 50.43$, $p < .001$; Percent Dyad: $F(1,60) = 43.19$, $p < .001$). Unlike at baseline, however, a *Third x Group* interaction was observed only when using the total correct and total dyad scoring methods (Total Correct: $F(1,60) = 5.35$, $p = .024$; Total Dyad: $F(1,60) = 4.19$, $p = .045$). This suggests that at follow-up, measures of performance *accuracy* rather than a

measure of *performance strategy* yielded greater cognitive fatigue in the MS group compared to the HC group. Similar to baseline, an *ISI x Third* interaction was also observed at follow-up across all three scoring methods (Total Correct: $F(1,60) = 6.56, p = .013$; Total Dyad: $F(1,60) = 38.73, p = .017$; Percent Dyad: $F(1,60) = 16.55, p = <.001$). Poorer performance continued to be noted on the last third of the task at the 2” ISI compared to the 3” ISI for both groups.

Degree of Change in Cognitive Fatigue

At the 3” ISI, neither a main effect of *Time* nor a *Time x Group* interaction was noted for any scoring method suggesting that the degree of cognitive fatigue did not differ between the MS and HC groups nor did the degree of cognitive fatigue change over time.

At the 2” ISI, a main effect of *Group* was noted on the total correct and percent dyad scoring methods (Total Correct: $F(1,58) = 5.35, p = .024$; Percent Dyad: $F(1,58) = 7.04, p = .010$) indicating that overall, the MS group showed a greater degree of cognitive fatigue than the HC group at both time points. These results are expected given the *Third x Group* interaction seen above (see Section 3.3). In addition, a main effect of *Time* was also noted on all three scoring methods (Total Correct: $F(1,58) = 9.03, p = .004$; Total Dyad: $F(1,58) = 6.82, p = .011$; Percent Dyad: $F(1,58) = 19.73, p = <.001$). Examination of the means indicated that both groups showed less cognitive fatigue at follow-up when compared to baseline.

Discussion

Differences in performance between the MS and HC groups on the PASAT were not found at either baseline or follow-up. While there was a trend for the MS group to perform worse than HCs at all times (Table 2), the lack of statistical significance may have been due to the small sample size as well as the characteristics of our MS sample. The MS group was composed of only those with RRMS who were early in their disease course ($M = 4.35(3.09)$) and with minimal disability ($EDSS = 1.83(1.18)$). Although cognitive dysfunction can occur in those with early-phase RRMS (Ruggieri et al., 2003), typically less impairment is noted than those with more progressive subtypes (Huijbregts et al., 2000).

Performance across the 3-year interval remained stable at the 3" ISI. While improved performance was noted on the 2" ISI at follow-up, this was true for both the MS and HC groups. As such, this improvement may be attributable to practice. Past literature has demonstrated that repeated exposure to the PASAT results in improved performance. While typically this improvement is observed over short test-retest intervals (Feinstein, Brown, & Ron, 1994; McCaffrey, Westervelt, & Haase, 2001), practice effects have been noted over the span of years (Cohen et al., 2000; Di Stefano & Radanov, 1995). It has been suggested that these practice effects are the result of experience gained during the initial administration as individuals learn what is expected during the task and develop an effective strategy to perform the task successfully. It is likely that the general procedural knowledge about the test and the development of effective strategies are retained over time, thus resulting in improved performance with subsequent exposure (Tombaugh, 2006). In addition, the PASAT is often perceived as unpleasant (Walker, Cheng, et al., 2012) and has been shown to elicit high levels of

anxiety and frustration, particularly when the test is novel (Holdwick & Wingengeld, 1999). However, the novelty of the task diminishes with repeated exposure and thus the anxiety effects associated with the test are likely reduced. As such, individuals may have performed better at follow-up simply because they felt less anxious throughout the task.

Evidence of cognitive fatigue was noted in both the MS and HC groups at baseline (Table 3). Both groups demonstrated poorer performance later in the task compared to performance at the beginning. There was a trend for the more difficult task (2" ISI) to be more sensitive to cognitive fatigue (Table 3). While both groups demonstrated cognitive fatigue, the most sensitive scoring method to group differences at baseline was the percent dyad score (i.e. *performance strategy*). As such, the proportion of time in which the MS group was successfully able to meet task demands at baseline diminished as the task progressed, presumably due to a greater vulnerability to cognitive fatigue when compared to the HC group.

Similar to baseline, cognitive fatigue was noted in both the MS and HC group at follow-up. Unlike at baseline, the total correct and total dyad scoring methods were most sensitive at follow-up. This suggests that at follow-up, measures of *performance accuracy* are more sensitive to cognitive fatigue in the MS group rather than *performance strategy*. Taken together, these results support the notion that at baseline individuals are still in the process of refining their performance strategy while the task is still novel. At follow-up, however, their strategy is presumed to be well developed given their previous exposure to the task and as such measures of performance accuracy are better able to detect cognitive fatigue.

The same degree of cognitive fatigue from the beginning to the end of the task was noted for both groups at baseline and follow-up with the 3" ISI. At the 2" ISI, however,

the MS group showed a greater degree of cognitive fatigue than HCs at both time points, though these results were inconsistent across all scoring methods. In addition, results showed that both groups showed less cognitive fatigue at follow-up. While cognitive fatigue was noted in both groups at both times, there was a greater trend for both groups to produce more correct responses at the end of the task at follow-up. As such, while both groups displayed diminishing performance from the start of the task to the end, the magnitude of this decline (i.e. the degree of cognitive fatigue) was smaller at follow-up. Given the task is more familiar at follow-up, future research should examine whether or not novel tasks are more sensitive to cognitive fatigue than more rote or practiced tasks.

Overall, little evidence of any progression of cognitive impairment over time was noted in our sample of early-phase RRMS. Performance on the PASAT remained stable across the 3-year interval, with improvement noted at the 2" ISI likely due to practice. Cognitive fatigue was noted at both time points in our MS sample, though the sensitivity of the PASAT in detecting cognitive fatigue at each time point varied based on the scoring methodology used. At baseline, a measure of *performance strategy* was more sensitive to cognitive fatigue (i.e. percent dyad), whereas at follow-up measures of *performance accuracy* were more sensitive (i.e. total correct and total dyad). No evidence of worsening cognitive fatigue was noted across the 3-year interval, with an improvement in vulnerability to cognitive fatigue noted in both the MS and HC groups at the 2" ISI.

Interestingly, group differences were noted only when one considers cognitive fatigue as the outcome measure. This suggests that cognitive fatigue, rather than measures of performance, may be a more sensitive marker of cognitive impairment in those with early-phase RRMS. People may be able to compensate for a time with regard

to overall performance levels, but subtle deficits are only revealed with a finer grained analysis of the qualitative aspects of their performance. These results support the subjective claims by those with the disease who state they are able to perform their jobs or day to day tasks quite well (i.e. have high performance), though they feel they have to work harder to achieve an adequate level of performance and thus are more mentally exhausted towards the end of the day (i.e. experience cognitive fatigue). This has important implications given that clinically only task performance is typically assessed. As such, clinicians should be aware that a finer grained analysis of the qualitative aspects of that performance, as in the case of cognitive fatigue, may be more prudent given the real-world implications. This is particularly important in those who are early in their disease course.

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Table 1: Demographics

	MS	HC	<i>p</i>
Age	40.09 (9.21)	42.22 (11.63)	.421
Sex	2 Males 30 Females	5 Males 27 Females	.229
Education	14.86 (1.92)	15.42 (2.00)	.256
IQ	110.18 (6.83)	113.05 (7.19)	.106

Table 2: Mean PASAT performance for total correct, correct dyad, and percent dyad scores

	Total Correct	Correct Dyad	Percent Dyad
Baseline – 3” ISI			
MS	48.94 (10.00)	42.63 (14.07)	84.82 (14.48)
HC	53.03 (8.07)	47.88 (13.40)	89.09 (12.85)
Follow-up – 3” ISI			
MS	50.63 (7.86)	44.38 (12.82)	85.48 (15.36)
HC	54.03 (7.44)	50.19 (10.83)	91.68 (9.31)
Baseline – 2” ISI			
MS	26.13 (13.32)	16.94 (13.30)	54.00 (23.07)
HC	29.63 (14.65)	20.97 (15.26)	60.60 (23.15)
Follow-up – 2” ISI			
MS	38.61 (8.94)	27.68 (12.12)	68.49 (17.30)
HC	43.68 (8.91)	33.97 (13.31)	74.59 (16.55)

Table 3: Mean PASAT performance on the first and last third for total correct, correct dyad, and percent dyad scores

	Total Correct	Correct Dyad	Percent Dyad
Baseline – 3” ISI			
MS			
1st Third	17.50 (3.31)	16.07 (4.76)	88.61 (18.58)
3rd Third	15.00 (4.11)	12.18 (5.94)	75.14 (24.53)
HC			
1st Third	17.91 (2.86)	16.59 (4.09)	91.13 (11.27)
3rd Third	16.28 (4.08)	14.15 (5.79)	82.83 (19.07)
Follow-up – 3” ISI			
MS			
1st Third	17.71 (2.30)	16.00 (4.09)	88.57 (15.99)
3rd Third	16.10 (3.11)	13.65 (4.83)	82.05 (16.36)
HC			
1st Third	18.35 (2.18)	17.25 (3.32)	93.16 (8.29)
3rd Third	17.45 (3.55)	15.94 (5.01)	88.91 (15.29)
Baseline – 2” ISI			
MS			
1st Third	11.39 (4.80)	8.75 (5.51)	67.07 (27.40)
3rd Third	6.89 (4.70)	3.29 (4.39)	31.77 (29.81)
HC			
1st Third	12.19 (5.31)	9.78 (6.19)	71.33 (24.52)
3rd Third	8.53 (4.61)	5.22 (4.48)	48.04 (30.27)
Follow-up – 2” ISI			
MS			
1st Third	14.84 (3.02)	11.97 (4.47)	77.28 (16.89)
3rd Third	11.55 (4.18)	7.55 (5.11)	59.39 (23.16)
HC			
1st Third	15.55 (2.93)	13.06 (4.42)	81.70 (14.64)
3rd Third	14.03 (3.89)	10.65 (5.39)	70.70 (21.95)

Table 4: Degree of change in cognitive fatigue from first third to last third at baseline and follow-up

	Total Correct	Correct Dyad	Percent Dyad
3" ISI - Baseline			
MS	-2.52 (2.86)	-3.93 (4.23)	-13.42 (14.51)
HC	-1.58 (2.32)	-2.32 (3.67)	-7.65 (14.88)
3" ISI – Follow-up			
MS	-1.83 (2.51)	-2.48 (3.94)	-7.60 (16.80)
HC	-0.90 (2.30)	-1.32 (3.51)	-4.24 (12.35)
2" ISI – Baseline			
MS	-4.38 (2.56)	-5.59 (3.62)	-37.71 (24.79)
HC	-3.68 (3.00)	-4.68 (4.06)	-24.27 (24.15)
2" ISI – Follow-up			
MS	-3.24 (2.86)	-4.41 (3.28)	-18.11 (13.35)
HC	-1.52 (3.26)	-2.42 (4.60)	-10.99 (18.45)

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CHAPTER 4

Imaging cognitive fatigue in multiple sclerosis: Objective quantification of cerebral blood flow during a task of sustained attention using ASL perfusion fMRI

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Abstract

Background: Cognitive fatigue (CF) can be defined as an inability to maintain performance throughout a sustained cognitive task. Individuals with multiple sclerosis (MS) are more susceptible to CF than healthy controls (HCs); however, the neural correlates underlying CF are still under investigation. Arterial spin labeling (ASL) perfusion imaging provides a non-invasive method of objectively quantifying cerebral blood flow (CBF) during sustained attention tasks. To date, no study has yet evaluated CF in MS using this methodology.

Methods: 10 MS and 10 HCs completed a 20-min psychomotor vigilance task (PVT). CF was evaluated by dividing the PVT into quintiles and examining performance from the 1st to the last. Mean reaction times (RTs) and number of lapses were recorded. Global and regional CBF changes were evaluated throughout the PVT as well as during pre- and post-task rest.

Results: Increased susceptibility to CF was noted in the MS group. Distinct patterns of CBF activation were observed in areas comprising fronto-parietal, cortico-striatal, cerebellar, and basal ganglia regions; however, *when* and *where* these regions were engaged differed between the MS and HC groups. In particular, dysfunction in CBF to the middle frontal gyrus may underlie the CF effects observed. In addition, individuals with MS appear to struggle with “switching off” regions of the attentional network at rest following sustained cognitive effort.

Conclusion: Findings support the use of ASL as an appropriate methodology for evaluating CF in MS with an overall pattern of attentional network dysfunction being observed. Objectively quantifying CF in this manner can help validate patients’ subjective complaints.

Introduction

During tasks involving sustained cognitive effort, individuals with multiple sclerosis (MS) often experience increased feelings of fatigue accompanied by steady declines in performance over the period of task engagement. This phenomenon has been referred to by multiple names including “time-on task effects” (Gui et al., 2015; Lim et al., 2010), “performance fatigability” (Kluger, Krupp, & Enoka, 2013) and/or “vigilance decrement” (Mackworth, 1968). In the MS literature, recent research has begun focusing on the evaluation of cognitive fatigue (CF), an equivalent phenomenon which can be defined as a decrease in, or inability to sustain, task performance throughout the duration of a continuous cognitive task (Bryant, Chiaravalloti, & DeLuca, 2004; Schwid, Covington, Segal, & Goodman, 2002; Walker, Berard, Berrigan, Rees, & Freedman, 2012). Individuals with MS are more susceptible to the effects of CF when compared to healthy controls and this susceptibility is often behaviourally manifested as a more significant breakdown in task performance as the task progresses. While typically the assessment of CF has relied on self-report measures, the focus has shifted towards objective quantification of CF in order to validate patients’ subjective reports. Given that sustained cognitive workloads and the accompanying CF effects can have serious real-world implications, including attenuated quality of life for patients (Arnedt, Owens, Crouch, Stahl, & Carskadon, 2005; Dubal & Jouvent, 2004), uncovering the neural underpinnings of CF with recently advanced neuroimaging techniques has become an area of interest for researchers.

To date, relatively few studies have evaluated the neural basis of CF in an MS sample. Of those conducted, however, a number have associated CF with areas of the cortico-striatal network. Genova et al. (2013) examined the relationship between self-

reported fatigue and patterns of cerebral activation during an objective measure of CF using blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (fMRI). While performing the cognitively demanding task, increased activation was noted across several regions including the prefrontal cortex (PFC), temporal lobes and cerebellum in both the MS and healthy control (HC) groups. Only the caudate nucleus showed greater levels of activation in the MS group compared to controls. Given that higher levels of self-reported fatigue were observed in the MS group, the authors suggest the striatum and its interconnections played an important role in the subjective perception of fatigue in MS (Genova et al., 2013). In addition, impairment of the “non-motor functions of the basal ganglia” (Chaudhuri & Behan, 2004) might also play a key role in CF, in particular in the context of effort-reward imbalance (Dobryakova, DeLuca, Genova, & Wylie, 2013). In this regard, it has been proposed that CF results from inappropriate effort output and outcome valuation (i.e. reward) due to one or more regions of the cortico-striatal network deviating from normal functioning (Boksem & Tops, 2008). The idea that CF is associated with cortico-striatal impairment has also been reported using other neuroimaging techniques besides fMRI. Roecke et al. (1997), demonstrated a reduction in glucose metabolism in the basal ganglia of fatigued individuals with MS using positron emission tomography (PET), while no metabolic reduction was observed in those who were not fatigued (Roelcke et al., 1997).

While together these studies have supported the notion of cortico-striatal involvement in CF, further studies have also implicated a fronto-parietal attentional network. It stands to reason that the neural regions involved with successfully maintaining prolonged cognitive effort should correspond with areas in the brain associated with sustained attention. fMRI and PET studies have suggested a fronto-

parietal network involved in vigilance and continuous cognitive performance which includes the anterior cingulate cortex (ACC), inferior and middle frontal gyrus, inferior parietal regions, and the thalamus (Cabeza & Nyberg, 2000; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). Early evidence, using PET during sustained vigilance tasks, has also shown reduced cerebral blood flow in the thalamus and fronto-parietal networks that related to performance declines (Coull, Frackowiak, & Frith, 1998; Paus et al., 1997). These results support the idea that changes in CBF in these fronto-parietal regions may underlie the performance declines noted in those experiencing CF.

To the best of our knowledge, no studies to date have specifically evaluated whether patterns of activation in these fronto-parietal regions differ in those with MS when compared to HCs in the context of CF. The paucity of studies may be due to methodological challenges arising when evaluating CF using neuroimaging techniques. PET and traditional BOLD fMRI studies (Coull et al., 1998; DeLuca, Genova, Hillary, & Wylie, 2008), often lack sufficient temporal & spatial resolution to adequately track slow changes in neuronal activity over time scales longer than a few minutes (Aguirre, Detre, Zarahn, & Alsop, 2002; Aguirre, Zarahn, & D'Esposito, 1997). Given that tasks of sustained cognitive effort must be sufficiently long to elicit CF effects, opting to use techniques capable of evaluating slow variations in neural activation patterns with high spatial and temporal resolution over long periods of time is crucial. One such technique is arterial spin labeling (ASL) perfusion fMRI (Detre & Wang, 2002). As the diffusible tracer, ASL perfusion fMRI uses magnetically labelled water in arterial blood to provide a non-invasive imaging method of quantifying CBF during sustained cognitive tasks as well as at pre- and post-task resting baselines (Kim et al., 2006; Rao, Wang, Tang, Pan, & Detre, 2007). Over prolonged task durations, ASL has demonstrated excellent

reproducibility and superior spatial and temporal resolution compared to more traditional techniques (Aguirre et al., 2002), making it well suited to image CF.

Few studies have employed ASL in evaluating CF, and of those performed, none have included an MS sample. Lim et al. (2010) used ASL to examine neural correlates of CF (which they refer to as time-on-task effects) during performance of a prolonged attentional task - the psychomotor vigilance test (PVT) - as well as task-free resting baselines in a sample of healthy undergraduate controls. The PVT task used was a continuous 20-minute simple reaction time task in which individuals respond as quickly as they can to a countdown stimulus presented at short, random intervals. Results demonstrated clear cognitive fatigue effects even in HCs, with reaction times increasing as the task progressed. The PVT activated areas of the fronto-parietal attentional network in addition to the basal ganglia and sensorimotor cortices. In addition, differences in activation of the attentional network were noted when CBF was compared during the PVT task to CBF values at a resting baseline, as well as between pre-task and post-task resting CBF (Lim et al., 2010). These differences may be useful indicators of performance potential in MS.

Taking into consideration the technical advantages of ASL and the results observed in HCs, the current study aimed to replicate the methodology of Lim et al. (2010) in those with MS given their greater susceptibility to CF (Walker et al., 2012). The goal of the current study was to evaluate group differences in task performance and CBF activation patterns between MS and HC groups at resting periods and during the PVT task. Differences between groups in their susceptibility to CF was specifically evaluated by comparing performance and CBF activation patterns at the beginning of the PVT task vs. the end of the PVT task. Given their increased susceptibility, it was

hypothesized that the MS group would show even greater performance declines on the PVT task when compared to HCs. In addition, it was hypothesized that the groups would have distinct CBF activation patterns during the PVT task and at resting baselines, particularly in the fronto-parietal attentional network and basal ganglia.

Methods

Participants

Ten (10) individuals with a confirmed diagnosis of relapsing-remitting MS (RRMS) (2010 McDonald diagnostic criteria for MS), (Polman et al., 2011) were recruited from the Multiple Sclerosis Clinic of The Ottawa Hospital. Participants had a disease duration from clinical onset of ≤ 10 years and an Expanded Disability Status Scale (EDSS) score ≤ 6.5 , with a visual score < 2 , a cerebellar score with upper limb score ≤ 2 , and a pyramidal score with strength for upper extremity muscle groups ≥ 4 . A score of 4 or more on this subsection of the overall pyramidal functional system score is indicative of normal upper extremity strength or, at the very least, active movement against resistance in the upper limbs. Individuals were ineligible to participate should they have experienced a relapse, or had been treated with corticosteroids, within one month prior to the study.

In addition, ten (10) age, sex, and education-matched healthy controls (HC) were also recruited into the study. Demographics for both groups are presented in Table 1. All participants were right-handed and had no significant physical or psychological comorbidity that may have interfered with their ability to respond adequately to the task in the MRI scanner (e.g. claustrophobia, severe motor deficit, limb ataxia, severe cognitive impairment). Careful review of medications excluded those under constant

treatment with Amantadine, Modafinil, 4-aminopyridine, or anticholinergic drugs cumulating in a score of > 3 on the Anticholinergic Drug Scale within one month prior given their impact on cognition. All participants did not habitually consume more than 250mg caffeine per day as caffeine can influence fMRI findings, particularly the alerting and executive control networks (Einöther & Giesbrecht, 2013). Participants were instructed to obtain between 6.5 and 8 hours of sleep during the two nights prior to their testing date in an attempt to control for baseline levels of daytime sleepiness.

Procedures

This study was approved by the Ottawa Hospital Research Ethics Board. After informed consent was obtained, participants were enrolled. Prior to their imaging session, participants in the MS group underwent EDSS evaluation during an MS Clinic visit. These visits were scheduled within 1 month of their MRI scans. The same neurology fellow (RC) performed all EDSS evaluations. At that time, vision screening ensured acuity was adequate to see task stimuli in the MRI scanner.

The psychomotor vigilance task (PVT) (Dinges et al., 1997) was used in the scanner as the sustained attention task. The PVT is a simple-reaction time test in which participants are presented with a millisecond counter and asked to respond as quickly as possible by pressing a response pad with their right index finger in order to stop the counter time. The goal of the task is to achieve the lowest possible reaction time for each stimulus presentation. The task itself has minimal motor demands and thus is suitable for use in those with MS. The PVT (20 minutes in length) was administered according to Lim et al. (2010), including the extraction of the following performance variables: mean reaction times (RT) and number of lapses produced (RT > 500 milliseconds).

Prior to scanning, participants completed self-report measures of daily fatigue including the Daily Fatigue Impact Scale (D-FIS) and a Visual Analog Scale (VAS) to evaluate subjective levels of fatigue at baseline. Upon completion of the PVT, individuals completed these two measures a second time to examine any changes in subjective fatigue following the sustained attention task. Individuals also provided a subjective rating of their own performance on the PVT task upon leaving the scanner.

Following their MRI, cognitive functioning was evaluated through neuropsychological assessment using the Brief International Cognitive Assessment for MS (BICAMS) (Langdon et al., 2012). To control for potential confounds, self-report questionnaires assessing depression (Beck Depression Inventory - Fast Screen for Medical Patients (BDI-FS)), sleep quality (Pittsburgh Sleep Quality Index (PSQI)), and daytime sleepiness (Epworth Sleepiness Scale (ESS)), were completed.

Data acquisition

Functional imaging was conducted at the Ottawa Hospital – Civic Campus Siemens 3.0T MRI scanner. To control for daytime sleepiness, scans were performed at roughly the same time for all participants (between 16:00h and 18:00h) and were completed prior to the neuropsychological assessment in order to minimize fatigue effects on PVT performance and ASL metrics.

ASL was performed with a 2D pulsed ASL sequence having PICORE Q2TIPS labeling and echo-planar imaging readout (Luh, Wong, Bandettini, & Hyde, 1999). Imaging parameters used were: $TI_1/TI_2/TI_3$ s = 700ms/1800ms/1600ms, TR/TE=4 s/17 ms, matrix=64x64x16, slice thickness = 7 mm, gap = 1.4 mm, in plane resolution = 3.44 mm x 3.44 mm.

Prior to the functional ASL perfusion scans, high resolution structural scans were obtained. During the PVT, the functional perfusion scanning protocol lasted 20 minutes (corresponding to the PVT task length) and consisted of 290 acquisitions. In addition, two 4-minute perfusion protocol scans (58 acquisitions each) were obtained while participants were at rest in the scanner both before and after the PVT to evaluate baseline resting CBF levels before and after performing the cognitively demanding task. During resting periods, individuals were asked to remain relaxed, motionless, and with their eyes closed.

Data analysis

Preprocessing

Preprocessing of the ASL functional data and whole-brain CBF map calculations were performed using ASLtbx (Wang et al., 2008) in combination with Statistical Parametric Mapping software (SPM 12). For each participant, a standard fMRI preprocessing procedure was applied. Functional images were realigned to correct for head motion, co-registered with the structural images and smoothed with 6 mm full width at half maximum Gaussian kernel.

CBF calculation

In order to obtain perfusion weighted scans, pair-wise subtraction of label and control images was performed using ASLtbx, followed by conversion to an absolute CBF image using the single compartment ASL perfusion model (Wang et al., 2008). Global CBF values were obtained. The total resulting CBF data set for each participant contained 203 image acquisitions (29 acquisitions for pre-task rest, 145 acquisitions for the PVT, and 29 acquisitions for post-task rest) and one mean CBF image was generated

for each 4-min perfusion scan (1 CBF image for pre-task rest, 5 CBF images [one for each PVT quintile], and 1 CBF image for post-task rest). Once generated, CBF scans were normalized to a $2 \times 2 \times 2 \text{ mm}^3$ Montreal Neurological Institute (MNI) template and entered into second-level general linear model (GLM) analysis in SPM12. In order to adjust for global CBF differences, the GLM models were performed with the global CBF correction adjustment. Contrasts of interest included: i) PVT vs. Pre-task rest, ii) PVT vs. Post-task rest, iii) Pre-task rest vs. Post-task rest, and iv) last 4-min quintile of the PVT vs. first 4-min quintile of the PVT. For all contrasts, activation clusters were identified at a significance level of $p < 0.05$ uncorrected at the whole-brain level and cluster sizes larger than 30 voxels.

Results

Behavioural data

The MS group showed significantly longer mean reaction times (382.85 ms (54.44)) on the PVT compared to HCs (331.26 ms (37.54)) ($F(1,19) = 6.09, p = .024$) and produced a significantly greater number of lapses throughout the task (MS = 17.33 (13.67); HC = 4.70 (6.09); $F(1,19) = 7.02, p = .017$). Repeated measures ANOVAs revealed evidence of CF for both groups on the PVT, as demonstrated by longer RTs on the last quintile of the task compared to the first quintile (see Figure 1). A *Block* by *Group* interaction was noted, with post-hoc comparisons revealing that the difference between quintiles with regards to RTs was significant only for the MS group (1st quintile = 364.14 ms (53.08); 5th quintile = 403.44 (50.38); $t(9) = -5.38, p < .001$). Additionally, evidence of CF was noted for the MS group with regards to number of lapses produced, whereby a significantly greater number of lapses was also made on the last quintile of

the task vs. the first quintile (1st quintile = 3.90 (5.38); 5th quintile = 7.80 (8.06); $t(9) = -3.65, p = .005$). Contrarily, HCs generated a comparable number of lapses at both quintiles (see Figure 2).

Vulnerability to CF for each group was further quantified by calculating percentage change in mean RTs from the first to last quintile. At the individual level, these values ranged from -11.14% to 17.52% (MS range = 3.01 to 17.52%; HC range = -11.14 to 13.05%) suggesting a wide scale of inter-individual differences with regards to this vulnerability. Nonetheless, on average, the MS group was significantly more vulnerable to CF than were the HCs (MS = 9.77% (5.54); HC = 2.89% (7.56); $F(1,19) = 5.38, p = .032$).

Prior to performing the PVT, MS and healthy control groups did not differ with respect to subjective, self-reported levels of fatigue as assessed by the VAS. Following the PVT, however, the MS group reported a higher level of subjective fatigue than controls (MS = 4.27 (2.72); HC = 2.20 (1.55); $F(1,19) = 4.46, p = .048$). In addition, the MS group was more likely to report being fatigued by performing the PVT. A greater change (i.e. greater likelihood of increase) in VAS scores was noted from pre- to post-task ratings for the MS group, whereas the controls showed relative stability over time (MS = 1.27 (1.10); HC = .300 (.483); $F(1,19) = 6.59, p = .019$). No significant correlations were noted between objective RT declines observed on the PVT and pre- or post-task fatigue ratings (or with the degree of change in ratings). In addition, while sleep quality (as evaluated by the PSQI) and subjective PVT performance ratings did not predict objective RT declines for either group, levels of daytime sleepiness did predict RT declines for the HCs only. There were no group differences in neuropsychological test performance (i.e. BICAMS); however, there was a trend for the MS group to perform

worse on processing speed (SDMT) ($MS = 56.33 (12.76)$; $HC = 65.60 (8.80)$; $F(1,19) = 3.76, p = .067$) and visual learning (BVMT-R) ($MS = 28.25 (4.00)$; $HC = 30.90 (1.91)$; $F(1,19) = 3.66, p = .070$).

Imaging Results

Global (whole brain) CBF maps

Global CBF values for both groups are presented in Table 2. Overall, mean global CBF values did not differ between MS and HC groups at pre-task rest, during the PVT, or post-task rest (i.e. no between-group differences). In addition, neither group showed any differences in global CBF values between any of the three time points (i.e. no within-group differences). When evaluating global CBF values during the first quintile of the PVT vs. the last quintile, however, a *Block by Group* interaction was noted (see Figure 3). Post hoc analyses revealed that HCs had significantly decreased global CBF values during the last quintile of the task vs. the first quintile (1st quintile = $18.95 (3.35)$; 5th quintile = $15.48 (4.19)$; $t(9) = 4.74, p = .001$), whereas the MS group showed comparable global CBF values at both times. No correlations were observed between any global CBF value and RT declines observed for either group.

Regional CBF changes – Between-group

Differences in regional CBF changes between the MS and HC groups are presented in Table 3. At pre-task rest, the MS group showed increased CBF activation in the attentional network (ACC, Thalamus) alongside more posterior regions (SPL, cuneus) when compared to HCs (Figure 4a). During the PVT, greater CBF activation in the bilateral middle frontal gyrus (MFG) was noted for the MS group, whereas HCs showed greater activation in the cingulate gyrus. (Figure 4b). At post-task rest, greater

thalamic activation was noted for the MS group compared to the HC group. Finally, during the first quintile of the PVT, the MS group showed increased CBF in the superior frontal gyrus whereas HCs showed greater activation in the MFG during the last quintile (see Figure 4c).

Regional CBF changes – Within-group

Within-group changes in regional CBF between the 3 acquisition times (Pre-task rest, PVT, Post-task rest) for both the MS and HC groups are presented in Table 4. Compared to the pre-task resting baseline, performance on the PVT increased CBF in the insula and anterior cerebellum in the MS group. In contrast HCs showed increased CBF in areas of the attentional network (IPL, MFG) (see Figure 5a). During the post-task resting baseline, deactivation was observed in the MFG for both groups compared to CBF levels during the PVT. While this was the only area of deactivation noted in the MS group, HCs showed further CBF decreases in other areas of the attentional network as well (thalamus, ACC, IFG, IPL) (see Figure 5b). When comparing the two resting baselines, post-task resting scans showed CBF activation increases in some areas of the attentional network (MFG, ACC) in the MS group. In contrast, HCs showed deactivation of the ACC. With regards to CF (1st quintile vs. last quintile), few regional CBF differences were observed for either group, with only an increase in CBF noted in the caudate nucleus for the MS group during the last quintile (see Figure 5c).

Discussion

Using ASL perfusion fMRI, the current study objectively evaluated and quantified CF in a sample of individuals with RRMS using a sustained attention PVT. As expected, the MS group displayed longer reaction times (RT) on the PVT than did HCs. Similarly,

the MS group produced significantly more lapses throughout the PVT. Although the MS group produced more lapses, they were still able to perform the task at 89.17% accuracy. Given the motor component involved in responding to the PVT, it is possible that the MS group may have simply displayed longer RTs and a greater number of lapses due to difficulties with motor functions, rather than difficulties with sustaining attention. In the current sample, however, only those who demonstrated an upper extremity strength score of ≥ 4 as part of their EDSS evaluation were included. Examination of the upper extremity strength scores across all individuals in the MS group reveals a mean score of 4.68 suggesting normal or near normal upper motor strength. Coupled with the relatively low overall pyramidal subscale mean score (1.65) we can conclude then that the imaging data collected does indeed adequately reflect their ability to perform the PVT as intended and is not influenced by motor difficulties which could present in those diagnosed with MS.

With regards to CF, consistent with past research, both MS and HC groups reacted slower to presented stimuli as the PVT progressed. This was evidenced by increasing reaction times over the course of the task. While this was true for both groups, as expected the MS group displayed an even greater increase in their RTs indicating more difficulty in successfully keeping up with task demands over time. Similarly, the MS group was more likely to produce lapses towards the end of the PVT task. Notably, a sizeable amount of inter-individual variability was observed within each group in regard to who was likely to show these CF effects with some individuals showing marked susceptibility to CF (17.52% change in RTs across the task) whereas others showed relative stability, or even improvement in their RTs as the task progressed (-11.14%). Objective findings of performance decrements over time (i.e. CF)

occurred despite a lack of group differences on neuropsychological measures (i.e. BICAMS), suggesting that CF may be a more sensitive or earlier marker of cognitive impairment in MS than traditional measures of cognitive performance.

Consistent with expectations, both groups reported comparable levels of subjective fatigue prior to performing the PVT. All participants were instructed to try to obtain adequate sleep during the two nights prior to their scans. In addition, participants were all scanned at the same time of day to minimize pre-existing fatigue effects. In this manner, subjective ratings following performance of the PVT should be reflective of only those fatigue effects resulting from the task itself. Higher levels of fatigue were reported following the PVT for the MS group suggesting these individuals subjectively felt more fatigued by having performed the task. Intuitively, one would expect then that those who felt most fatigued by the task would have shown greater performance decline across the PVT, however this was not the case as no significant correlations were noted between individuals' fatigue ratings and RT declines. These findings are consistent with past research in which subjective reports of fatigue often do not correlate with objective measures (Bailey, Channon, & Beaumont, 2007; Bryant et al., 2004).

Global ASL CBF perfusion maps revealed comparable levels of whole-brain CBF between MS and HC groups at all acquisition times (pre-, during PVT, post-). This suggests that the total volume of CBF within the brain of individuals with MS does not differ from HCs. Similarly, no within-group differences in whole-brain CBF values were observed between any of the acquisitions, suggesting that at the global level there is no increase in the amount of CBF while performing the PVT when compared to resting baselines. These findings mirror those reported in past research (Lim et al., 2010).

Interestingly, where these global CBF values did differ between groups was in the context of evaluating global CBF changes with respect to CF. Whereas the MS group showed comparable levels of global CBF at both the beginning and end of the PVT task, HCs showed a significant decrease in global CBF as the task progressed. Given that significant change in RTs across the task (i.e. CF) was not observed in the HC group, this suggests the controls may habituate to the task with regard to global CBF (i.e. require less resources) while still being able to maintain a comparable level of performance over time. Individuals with MS do not show this same habituation in global CBF and may, in reality, require more global CBF in order to sustain cognitive effort given that comparable levels of CBF observed at the beginning and end of the task were accompanied by RT declines.

ASL data evaluating changes in regional CBF revealed an array of between and within-group differences in areas of the cortico-striatal network, fronto-parietal attentional network, as well as the basal ganglia and cerebellum. At pre-task rest, areas of the fronto-parietal attentional network including the ACC and thalamus show increased activation in the MS group. Results suggest these individuals were already in a more effortful state at rest even before engaging in the sustained attention task (i.e. more effort was required to maintain a baseline level of attentional control). In addition, greater activation was noted posteriorly in areas of visual processing and spatial orientation, including the cuneus and superior parietal lobule (SPL). Previous research has associated SPL activity with aspects of attention and verbal working memory (Koenigs, Barbey, Postle, & Grafman, 2009; Shomstein & Yantis, 2006) further contributing to the notion that the MS group exerted more effort than controls while at rest and may have been actively rehearsing the task instructions.

During the PVT, distinct patterns of CBF activation were also noted between groups. While engaging in the task, the MS group showed significantly greater CBF in the middle frontal gyrus (MFG), an area implicated in performance of sustained attention tasks (Ogg et al., 2007). In contrast, the HCs actively engaged a different attentional region - the cingulate gyrus – while performing the PVT. In combination with the already increased activation in the ACC and thalamus noted at rest in the MS group, these patterns of activation suggest that individuals with MS engage more regions of the fronto-parietal network overall while performing the PVT than do controls. Despite this pattern of increased CBF within the attentional network, evidence of worse performance (i.e. longer RTs and greater number of lapses) and CF (i.e. increased RTs across the task) were still observed in the MS group. These findings suggest that this recruitment of additional attentional network regions was insufficient to allow the MS group to match the PVT performance of HCs. Following performance of the PVT, the MS group continues to engage more areas of the attentional network at post-task rest than HCs, specifically the thalamus. Similar to pre-task rest, this engagement suggests that even during resting baseline following the PVT, the MS group is in a more effortful state than controls.

With regard to between-group differences in regional CBF patterns in the context of CF, the MS and HC groups do not show considerable differentiation in CBF at the beginning of the PVT, with only slightly increased activation noted in the superior frontal gyrus in the MS group during the first quintile. At the end of the task, however, a distinct pattern of activation occurs. While, as previously stated, the MS group tended to engage the MFG more than HCs on the PVT task as a whole, the HCs showed greater activation of the MFG only during the last PVT quintile. This increase in CBF activation

was accompanied by a lack of RT decline (i.e. lack of CF) in the HC group as the task progressed. It is possible then that while the MFG plays an important role in sustaining attention overall, the effects of CF were mitigated in HCs by appropriately allocating CBF resources to the MFG only at times of greater cognitive workload (i.e. towards the end of a continuous cognitive task where performance decline is more likely to occur). These results suggest that dysfunction in CBF allocation to the MFG may underlie the CF effects observed in those with MS.

Regarding within-group comparisons, the groups showed noticeable differences in CBF perfusion scans between acquisition times. Compared to pre-task rest, during the PVT, HCs unsurprisingly showed greater CBF activation in areas of the attentional network including the inferior parietal lobule and MFG. The MS group did not show this pattern. This is perhaps not unexpected given that these areas were already more engaged at pre-task rest in the MS group than in HCs. Greater CBF activation, however, was noted in other regions in the MS group during the PVT task compared to pre-task rest, specifically in the anterior cerebellum and insula. While typically associated with motor control and the limbic system respectively, these areas have also been shown to impact aspects of attention (Gottwald, Mihajlovic, Wilde, & Mehdorn, 2003; Menon & Uddin, 2010).

In combination with the between-group results, these findings suggest that ultimately both groups engage a wide variety of attentional network regions while performing the PVT (in particular, the MFG). However, *when* CBF resources are allocated to these regions tends to differ between groups, with the MS group initially engaging attentional areas at pre-task rest, whereas controls tend to engage these areas during the PVT itself.

Considering post-task rest CBF perfusion, marked CBF deactivation was noted across multiple regions of the attentional network in HCs when compared to CBF during the PVT task (thalamus, ACC, inferior frontal gyrus, MFG, and inferior parietal lobule) following PVT performance. These findings were anticipated given that, during post-task rest, CBF allocation to these attentional regions was expected to decrease as individuals are no longer engaged in an attention-demanding task. In essence, then, the attentional network of HCs appears to return to baseline resting levels following the cognitive task. A comparable pattern of CBF deactivation of the attentional network was not observed in the MS group. While decreases in CBF at post-task rest following the PVT were observed in the MFG, this was the only area where deactivation occurred. This implies that the brains of those in the MS group did not necessarily immediately “reset” themselves to baseline resting levels following sustained cognitive workload. In addition, findings suggest that CBF resources depleted in the MS group during the sustained cognitive task are not restored within the 4-minute post-task resting window.

As expected, when comparing post-task resting CBF to pre-task resting CBF, the MS group showed increased activation in the attentional network at rest following the PVT in both the MFG, ACC, and anterior cerebellum. Consistent with our other findings, it seems likely this increased activation post-PVT continues to reflect residual activity in attentional network regions as a result of performing the task given that sufficient time has not elapsed for these areas to return to pre-task resting baseline levels in the MS group. Significant deactivation was noted in only one attentional region for the HCs at post-task rest, the ACC, suggesting that not only did CBF levels return to pre-task resting baseline in controls but actually reduced even further.

When comparing within-group differences with regard to CBF changes from the beginning of the PVT versus the end (i.e. cognitive fatigue), virtually no change in activation patterns was observed. Both HC and MS groups showed comparable levels of CBF perfusion across brain regions throughout the duration of the task. The only exception observed was an increase in CBF activation in the caudate nucleus towards the end of the task for the MS group. This increase in activation mirrors previous findings in the literature whereby subjective perceptions of fatigue were associated with greater activation in the caudate nucleus in those with MS when compared to controls (Genova et al., 2013). This increased caudate activation implies that those in the MS group subjectively felt more fatigued towards the end of the PVT, a notion which is supported by the significantly increased subjective ratings on the VAS by the MS group following their time in the scanner.

There were limitations to the current study. Given the small sample size, the ASL findings may only be specific to the current sample and might differ with larger or more heterogeneous samples (e.g. progressive disease courses). Despite the low number of participants, our results were consistent with past research. Furthermore, in order to minimize fatigue effects, all participants were scanned in the late afternoon/early evening (16:00 to 18:00h). Although this control for time-of-day variations in fatigue is an asset of the current study, previous research has shown patterns of activation in the brain may differ based on circadian effects and the time of day (Baehr, Revelle, & Eastman, 2000; Kerkhof & Van Dongen, 1996), thus results may have differed, for example, had the scans been performed in the early morning. Finally, while the fewer number of lapses observed in the HCs may indicate they were more attentive to the PVT task, it seems more likely that the 500 ms countdown window required for individuals

to respond is simply too fast for the MS group. Given the documented difficulties in information processing speed observed in MS (DeLuca, Chelune, Tulsky, Lengenfelder, & Chiaravalloti, 2004) alongside research showing that even on the simplest measures of RT (i.e. “Press when X appears”), individuals with MS show significantly slower RTs than controls approaching 500 ms (Reicker, Tombaugh, Walker, & Freedman, 2007), future studies should consider whether a longer RT response window is more appropriate when evaluating patient populations.

Despite these limitations, findings support the use of ASL perfusion fMRI as an appropriate and reproducible methodology for evaluating group differences in CBF perfusion, as well as for objective evaluation and quantification of CF. Increased susceptibility to CF was noted in our MS sample with distinct patterns of CBF activation observed during both a sustained attention task as well as at task-free resting baselines. While results validate the notion that successfully maintaining sustained cognitive performance relies on a multitude of areas comprising fronto-parietal, cortico-striatal, cerebellar, and basal ganglia regions, *where* and *when* these regions are engaged differ in those with MS. During sustained cognitive effort, those with MS recruited multiple attentional regions, yet remained susceptible to the effects of CF. In particular, dysfunction in CBF allocation to the MFG towards the end of the sustained attention task seems to underlie the CF effects observed in those with MS. Coupled alongside the findings whereby those with MS appear to struggle with “switching off” regions of the attentional network at rest following a period of sustained cognitive workload, results suggest an overall pattern of attentional network dysfunction. Finally, activation of the caudate nucleus during times of performance decline, seems to coincide with individuals’ subjective perception of CF. As fatigue presents as a significant problem for

individuals with MS (Brassington & Marsh, 1998; Minden et al., 2006), these results may help validate patients' subjective complaints in which they report feeling fatigued following periods of sustained cognitive workload and an inability to maintain cognitive effort for long periods of time. Given that thus far CF has largely been an unverifiable subjective experience, the hope is that this objective quantification of CF can increase awareness of this debilitating symptom of MS.

Table 1: Demographics for both the MS and HC groups

	MS	HC	<i>p</i>
Age	38.42 (10.82)	40.50 (11.52)	.667
Education	15.25 (3.60)	17.10 (3.03)	.213
Sex	2 Males; 8 Females	3 Males; 7 Females	---

Table 2: Global CBF values for both the MS and HC groups

Variable	Controls	MS	<i>p</i>
Global CBF – Pre-Task	20.08 (4.08)	20.11 (5.77)	.991
Global CBF – PVT	20.37 (4.60)	19.93 (5.82)	.852
Global CBF – Post-Task	20.15 (4.80)	20.13 (5.48)	.994
Global CBF – 1 st Quintile	18.95 (3.35)	17.07 (3.97)	.269
Global CBF – 5 th Quintile	15.48 (4.19)	16.96 (6.12)	.537

Table 3. Regional CBF changes: Between-group comparisons

Acquisition time	Group	Region	Cluster size	MNI coordinates			<i>p</i>
				<i>x</i>	<i>y</i>	<i>z</i>	
<i>Pre-task rest</i>							
	MS	↑ ACC	253	8	14	28	.020
		↑ Thalamus	204	-10	-12	14	.033
		↑ Superior parietal lobule	1310	34	-66	52	.000
		↑ Cuneus	380	-20	-92	22	.006
<i>PVT</i>							
	MS	↑ MFG	290	34	46	12	.014
	HC	↑ Cingulate gyrus	4961	0	-48	34	.000
<i>Post-task rest</i>							
	MS	↑ Thalamus	493	-6	-16	2	.003
	HC	↑ Anterior cerebellum	190	24	-40	-22	.043
<i>1st quintile</i>							
	MS	↑ Superior frontal gyrus	3747	22	46	28	.002
<i>5th quintile</i>							
	HC	↑ MFG	2553	48	10	46	.008

^a ACC = anterior cingulate cortex; MFG = middle frontal gyrus

Table 4. Regional CBF changes: Within-group comparisons

Acquisition time	Group	Region	Cluster size	MNI coordinates			<i>p</i>
				<i>x</i>	<i>y</i>	<i>z</i>	
<i>PVT vs. Pre-task</i>							
	MS	↑ Insula	231	34	20	4	.025
		↑ Anterior cerebellum	1312	6	-50	-30	.000
	HC	↑ IPL	1131	56	-40	46	.010
		↑ MFG	930	48	50	-4	.018
<i>PVT vs. Post-task</i>							
	MS	↓ MFG	209	34	58	-10	.035
	HC	↓ MFG	1176	42	58	0	.010
		↓ Thalamus	1547	-6	-16	4	.004
		↓ ACC	1547	8	18	-10	.004
		↓ IFG	841	-32	24	-12	.026
		↓ IPL	689	54	-36	48	.041
<i>Post-task vs. Pre-task</i>							
	MS	↑ MFG	775	-46	26	22	.035
		↑ ACC	871	4	22	22	.027
		↑ Anterior cerebellum	1673	36	-34	-32	.004
	HC	↓ ACC	371	10	20	-10	.008
		↑ Anterior cerebellum	286	40	-40	-36	.018
<i>1st vs. 5th quintile</i>							
	HC	↑ Caudate	2308	24	-38	12	.011

^a IPL = inferior parietal lobule; MFG = middle frontal gyrus; ACC = anterior cingulate cortex; IFG = inferior frontal gyrus

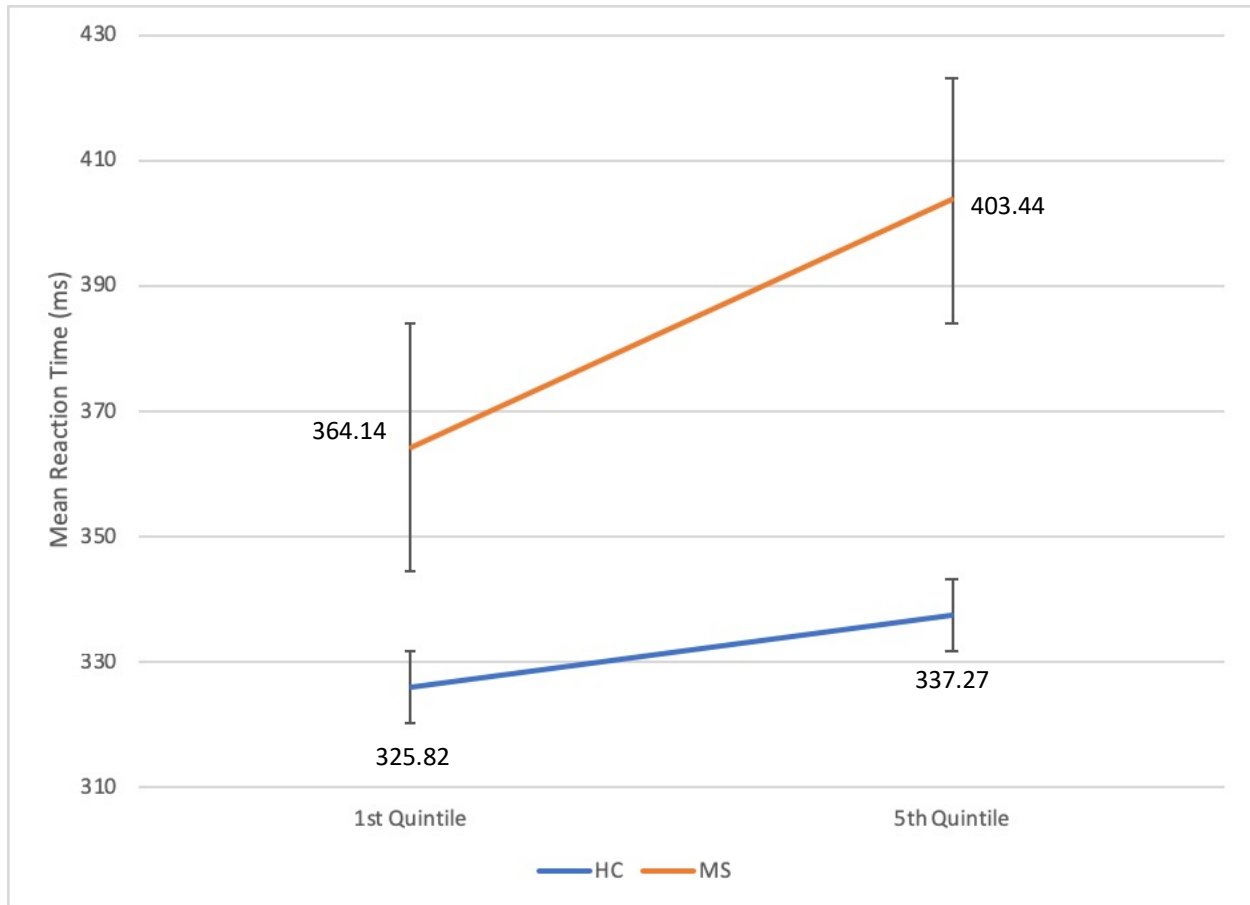
Figure 1: Mean RTs across the PVT for the MS and HC groups

Figure 2: Number of lapses produced across the PVT by the MS and HC groups

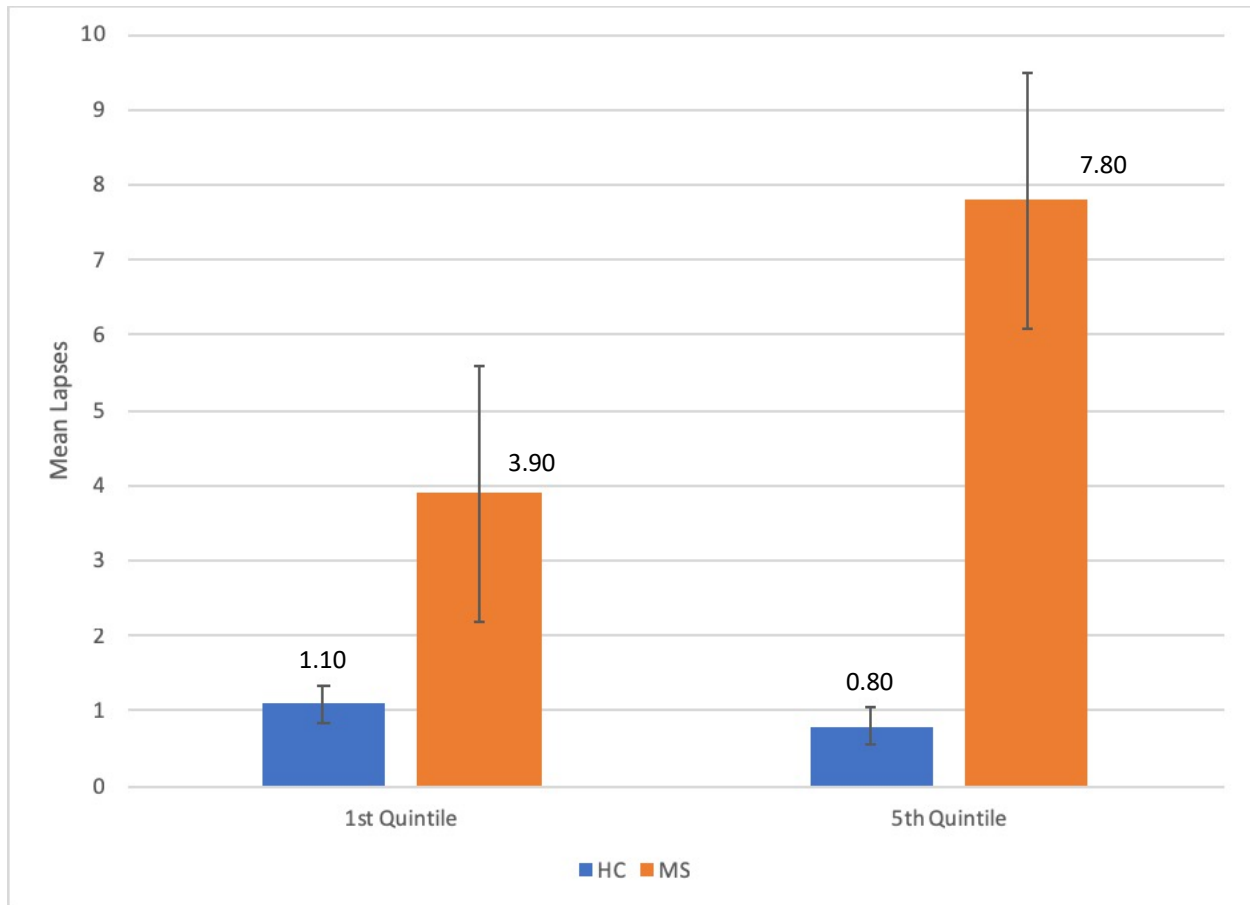


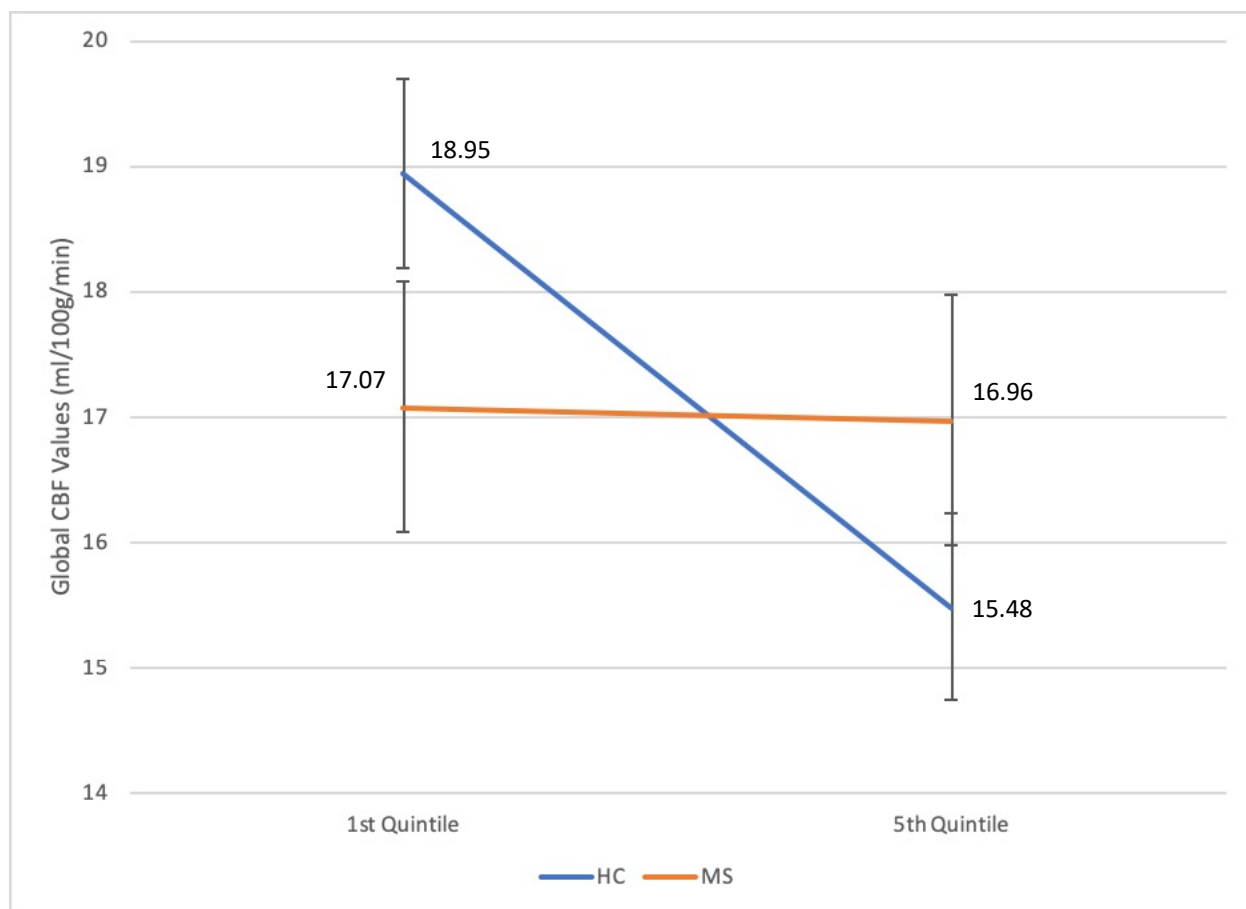
Figure 3: Global CBF values across the PVT for the MS and HC groups

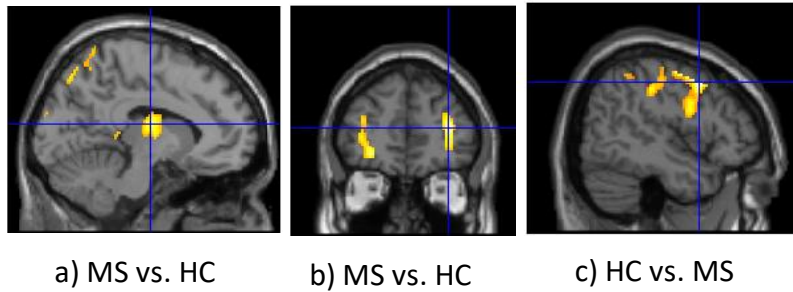
Figure 4: Regional CBF changes: Between-groups

Fig 4. Between-group regional CBF changes: a) increased activation in the ACC, Thalamus, SPL & cuneus in the MS group during the pre-task resting baseline when compared to HCs; b) increased CBF in the bilateral MFG in the MS group during the PVT; c) increased MFG in the HC group during the last quintile of the PVT compared to the MS group.

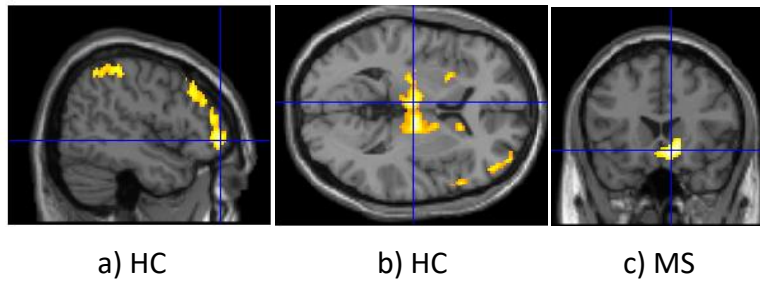
Figure 5: Regional CBF changes: Within-groups

Fig 5. Within-group regional CBF changes: a) increased activation in IPL and MFG in the HC group during the PVT when compared to pre-task rest; b) deactivation of the attentional network (thalamus, ACC, IFG, IPL) for HCs during the post-task resting period; c) increased CBF activation in the caudate nucleus during the last quintile of the PVT vs. the first quintile.

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CHAPTER 5

Discussion

Cognitive fatigue presents a considerable challenge for individuals with multiple sclerosis, often negatively impacting their quality of life. The inability to sustain cognitive effort over extended periods of times can be frustrating given that everyday tasks, such as managing finances or attending school, can become increasingly difficult. This frustration is further compounded when one considers that cognitive fatigue is typically an unobservable characteristic of the disease and as such is not always readily apparent to others. These individuals may simply be perceived as lazy or as lacking the motivation to keep up with the demands of the task they are attempting to perform. In the context of symptom appraisal, oftentimes cognitive fatigue goes unevaluated as part of a typical, routine neurological assessment. Furthermore, when fatigue is considered, it is often only the more physical aspects of fatigue (i.e. muscle weakness) that are assessed. Given that the overall construct of fatigue is multifaceted, it is important that both the physical and cognitive aspects of fatigue be considered. The process of evaluating cognitive fatigue in and of itself is problematic given that typically this assessment relies upon only subjective measures, with research showing that self-reported measures, while useful, can be inherently flawed and are subject to recall bias (Cohen et al., 2000; Schwid, Covington, Segal, & Goodman, 2002). In addition, research has shown that subjective measures of fatigue do not correlate well with objective measures of performance (Bailey, Channon, & Beaumont, 2007). Given the difficulties presented, it is imperative then that more objective measures be developed in order to evaluate and quantify cognitive fatigue in MS. Not only would results from these objective methodologies lend credence to the self-report of individuals with MS, but

they may also provide guidance with respect to future interventional therapies which may provide individuals with strategies to relieve the burden of cognitive fatigue on their overall quality of life.

This dissertation employed a multidimensional approach to objectively evaluating and quantifying cognitive fatigue in MS. In the context of this dissertation, cognitive fatigue was defined as an inability to maintain optimal task performance throughout the duration of a continuous cognitive task. It should be noted that cognitive fatigue can be defined in a number of ways given the complex cognitive processes involved in successfully maintaining task performance over time. Typically, cognitive fatigue is operationalized as some form of decline in cognitive performance over time. Definitions can vary, however, based on the research question of interest or on the measure being used to evaluate cognitive fatigue (ex. "...a decline in attention network performance over the course of the attention network test"; "...a decline in alerting, orienting, and executive performance" (Holtzer, Shuman, Mahoney, Lipton, & Verghese, 2011)). Given the lack of consistency noted in the literature with regards to the terminology used when describing cognitive fatigue effects, our definition was chosen in order to remain consistent with past research in the MS literature that also used the PASAT or PVT as their objective measure of cognitive fatigue (Lim et al., 2010; Morrow, Rosehart, & Johnson, 2015; Schwid et al., 2003; Walker, Berard, Berrigan, Rees, & Freedman, 2012). In addition, our definition of cognitive fatigue was chosen given its overall generalizability across study methodologies (i.e. not specific to a single cognitive process or domain). Furthermore, this definition was chosen given that we believe it best represents the subjective complaints of individuals who experience cognitive fatigue in

that they report feeling as though they are unable to maintain cognitive effort over long periods of time and must work harder to keep up with their peers.

While it is established that individuals with MS can present with a multitude of both physical and cognitive symptoms, no study to date has yet evaluated how secondary symptoms of the disease relate to and or predict an individual's level of CF. As such, the first study investigated the interrelatedness of disease severity, fatigue, depression, and sleep disturbances with cognitive fatigue and their possible predictive roles. Secondly, in order to objectively determine whether an individual's susceptibility to CF changes as the disease progresses over time, the second study evaluated CF longitudinally across a 3-year time period. Finally, in order to objectively quantify CF at the neuronal level, changes in global and regional cerebral blood flow were evaluated during a task of sustained attention using arterial spin labeling perfusion fMRI. The findings and limitations of each study are presented, followed by the implications of this research for future investigation and clinical practice.

Study 1. Predictive models of cognitive fatigue in multiple sclerosis

The first study of this dissertation investigated four competing models which evaluated how secondary symptoms of the disease might predict cognitive fatigue in MS. Results suggested that the best fitting model was one in which sleep quality and depression were both correlated with cognitive fatigue. Further analyses revealed that sleep quality was the only significant independent predictor of cognitive fatigue in MS. These results are the first in the MS literature to suggest that sleep quality may serve as a treatable cause of cognitive fatigue. This study brings a significant contribution to the literature given that to date no study has yet evaluated how secondary symptoms of the

disease may relate to cognitive fatigue. Furthermore, this is the first study in which an objective evaluation of cognitive fatigue has implicated sleep disturbances as a possible underlying cause of the cognitive fatigue effects observed in MS. To date, no study has yet targeted interventions at treating cognitive fatigue and results from this study provide fundamental guidance on which secondary symptoms of the disease might serve as treatable causes of CF.

Limitations. The greatest limitation to this study was the small sample size. As such, findings from the four models may be specific only to the current sample and might differ with greater numbers. Attempts were made to account for the small sample size using statistical model fit indices. In addition, while cognitive fatigue was evaluated in this study in an objective manner, most of the other variables (e.g. depression, sleep disturbances, etc.) were evaluated with subjective measures through the use of self-report questionnaires. As previously discussed, these self-report measures can present with limitations.

Future considerations. The goal of this study was to provide a starting point with regards to the theoretical relationship between secondary disease symptoms and cognitive fatigue in MS. Currently, there is a lack of theoretical groundwork evaluating such a relationship, thus this study served to fill this particular gap in the literature. Given the sample size, however, future studies should attempt to replicate the findings from these models with a larger sample size. In addition, variables which were not formally assessed in this study (e.g. anxiety) should also be considered for their predictive role with cognitive fatigue. Given that sleep disturbances are the most significant predictor of cognitive fatigue, future studies should also consider using an objective measurement of sleep quality in place of self-report questionnaires. EEG

studies evaluating the duration of sleep onset, REM sleep, and duration within each sleep stage would prove invaluable. Results from these EEG studies could have important implications for treatment and symptom management as they may allow for the determination at the individual level where best to target interventions. Results from this study further provide a theoretical groundwork to guide treatment interventions that can be developed with the aim of improving cognitive fatigue in MS. As such, future studies should investigate whether the improvement in an individual's sleep quality can lead to concomitant improvements in their levels of cognitive fatigue.

Study 2. A longitudinal evaluation of cognitive fatigue on a task of sustained attention in early relapsing-remitting multiple sclerosis

The second study of this dissertation evaluated cognitive fatigue longitudinally across a 3-year time period in a sample of individuals with early-phase relapsing-remitting MS (RRMS). Given its demonstrated sensitivity, the PASAT was chosen as the objective measure of cognitive fatigue. During this task, cognitive effort must be continuously sustained over time in order to successfully meet the task demands. Results demonstrated that performance on the PASAT remained stable for both the healthy control and MS groups across the 3-year period. Evidence of cognitive fatigue was noted for both groups with the sensitivity of the PASAT at detecting CF differing based on scoring methodology used. No evidence of worsening cognitive fatigue was noted over time. Results further suggested that cognitive fatigue, rather than measures of pure performance, may be a more sensitive marker of cognitive impairment in early-phase RRMS. Presently, there is a gap in the literature with regards to how cognitive

fatigue changes over time in those with MS as the disease progresses, an issue which this study attempted to address.

Limitations. Certain characteristics of the study sample were unique. First, only those with RRMS were included in the study and not those with other subtypes (i.e. PPMS, SPMS). While this was intentionally done in order to homogenize the sample, findings from the current study may differ in those with more progressive disease courses. Secondly, our MS sample was recruited on a volunteer basis. As such, the study may have attracted individuals with higher levels of education and/or lower levels of cognitive impairment. Given the challenging tasks demands, it is potentially unlikely that those with high levels of impairment would voluntarily seek out opportunities to be confronted with their impairment.

Future considerations. As discussed, future studies should evaluate cognitive fatigue longitudinally in a sample of individuals with more progressive disease subtypes in order to replicate findings. Little is known in the literature about how susceptibility to cognitive fatigue changes over time as the disease progresses and so this study provides an important first step. While results from the current study provide evidence of relative stability in CF over time, these results are specific to an early RRMS sample and results may differ in other subtypes or with longer disease durations. Greater deficits with respect to cognitive impairment are observed in more progressive and inflammatory disease subtypes (i.e. SPMS) (De Sonneville et al., 2002) and as such it is possible that cognitive fatigue may display more evidence of change longitudinally in the presence of greater disease burden. While the current study recruited volunteers, recruitment would ideally involve administering the PASAT to all patients who present to the MS clinic during their routine clinic visits. This would allow for the capture of a more

representative MS sample as a whole. Given time and resource constraints, this was not possible in the current study; however, future studies should consider the feasibility of such a recruitment approach. At the clinical level, findings from the current study have important implications given that typically only measures of pure task performance are assessed. Clinically, individuals may not show the typical signs of cognitive impairment (i.e. performance on cognitive tasks below impaired cut-off levels), yet subjectively they may state that they have to work harder to maintain their performance and are mentally exhausted as a result (i.e. experience cognitive fatigue). In order to tease out these subtle deficits, results from this study highlight the importance for both clinicians and researchers to consider evaluating cognitive fatigue above and beyond the typical performance measures administered.

Study 3. Imaging cognitive fatigue in multiple sclerosis: Objective quantification of cerebral blood flow during a task of sustained attention using ASL perfusion fMRI

The third report of this dissertation evaluated changes in global and regional cerebral blood flow (CBF) using ASL perfusion fMRI in order to objectively quantify and evaluate cognitive fatigue in MS. A psychomotor vigilance task (PVT) in which sustained attention must be continuously maintained over time was used as the objective measure of cognitive fatigue. Results demonstrated increased susceptibility to cognitive fatigue in the MS group coupled with distinct patterns of neural activation noted in attentional regions of the brain. In particular, findings suggest that dysfunction in CBF to the middle frontal gyrus may underlie the cognitive fatigue effects observed. This study contributes to the literature given that few studies to date have evaluated the neural

basis of cognitive fatigue, with this study being the first to use the technical advantages of ASL over typical BOLD fMRI for the study of cognitive fatigue in MS.

Limitations. The largest limitation of this study was the small sample size. As such, the ASL findings may only be specific to the current sample. In addition, only those with RRMS were recruited, thus results may differ when more progressive disease subtypes are considered. Given that all the MRI scans were performed in the evenings, time-of-day variations in neural activation patterns may have differed if the scans had been performed at another time (e.g. early morning). Finally, the 500 ms response window present for the PVT may be too fast for individuals with MS to respond given the high number of lapses (>500 ms) observed for the MS group.

Future considerations. As discussed, future studies should evaluate changes in global and regional cerebral blood flow during periods of sustained cognitive effort in a larger, more heterogenous MS sample. In addition, future studies should consider using a longer reaction time window on the PVT in order to capture those individuals who fall outside the 500 ms response window. Findings from the current study have important implications given that fatigue presents as a significant problem for individuals with MS. Patients' self-reported complaints that they feel fatigued following periods of sustained cognitive effort often go unsubstantiated given the lack of objective support. Findings from this study suggest that there are observable differences in the neural activation patterns seen in those who experience cognitive fatigue and thus may validate these patients' subjective experiences and increase awareness of cognitive fatigue overall.

Integration of Results and Implications

Overall, findings suggest that cognitive fatigue can be a disabling symptom of MS given the challenges noted in sustaining cognitive effort over time. Individuals who are unable to maintain optimal levels of cognitive effort for long periods of time may have difficulties with daily activities, such as employment or the pursuit of higher education. These individuals may find themselves unable to focus for long periods of time, limiting their ability to be productive at their jobs or in their ability to study material they are learning in school, and may struggle when interacting with others (ex. difficulties following lengthy or detailed conversations). Indeed, the overall construct of fatigue has been shown to negatively impact employment status and lead to greater employment absenteeism in MS (Salter, Thomas, Tyry, Cutter, & Marrie, 2017). In addition, fatigue has been associated with a greater risk of disease worsening over time (Cavallari et al., 2016) and tends to increase subjective feelings of loneliness and isolation in those with MS (Balto, Pilutti, & Motl, 2019). Studies have shown that cognitive fatigue, specifically, can also have real world implications even in healthy individuals as demonstrated by poorer standardized test performance (Sievertsen, Gino, & Piovesan, 2016) and a greater number of attentional failures (Lockley et al., 2004) in those who experience CF throughout the day. As such, the objective assessment of cognitive fatigue remains imperative in order to validate subjective complaints and to improve the quality of life for individuals experiencing this debilitating symptom of the disease.

Consistent with past research, individuals with MS are more susceptible to cognitive fatigue than are healthy controls as demonstrated by their inability to sustain cognitive effort over long periods of time (Morrow et al., 2015; Schwid et al., 2003; Walker et al., 2012). As previously discussed, our definition of cognitive fatigue aligns

with the concept of fatigability in the context of the taxonomy proposed by Kluger et al. (2013) given the focus on objective change in performance over time. Whether cognitive fatigue results from primary or secondary mechanisms of the disease, however, remains unclear. Evidence from this dissertation suggests that both types of mechanisms may play a role. Results from the first study suggest that cognitive fatigue results from secondary mechanisms of the disease given the relationship observed with sleep quality. The models suggest that cognitive fatigue is a result of poor sleep quality which in and of itself is a secondary cause of fatigue. An argument can be made, however, that cognitive fatigue may also be a product of the disease processes themselves, thus implicating primary disease mechanisms as the cause of CF. Results from the third study highlight the potential contribution of altered CNS function and dysfunctional cerebral blood flow which resulted in the cognitive fatigue effects observed. Future studies are required in order to determine more specifically whether primary or secondary mechanisms play a more substantial role in CF.

As highlighted by the first study, a multitude of secondary disease symptoms may impact an individual's level of cognitive fatigue, with sleep disturbances proving to be the most influential. In addition, dysfunction in cerebral blood flow to the middle frontal gyrus, as evidenced in the third study, seems to underlie the cognitive fatigue effects observed. Results suggest the possibility of a complex interaction between an individual's overall sleep quality and their ability to appropriately allocate CBF resources to the MFG during times of sustained cognitive workload. Future studies could evaluate this interaction by examining cerebral blood flow to the MFG during periods of sustained cognitive effort in those who are sleep deprived (or who show poor sleep quality) versus those who are not. While ideally this would have been performed in

the current study given that self-report measures of sleep quality were administered, the small sample size impeded upon the statistical power necessary to make such a comparison. In addition, as previously mentioned, an objective measure of sleep quality would be favoured over the self-reported questionnaires used. While these results suggest that cognitive fatigue can negatively impact an individual's ability to have an active and productive life, it is of note however, that findings from the second study suggest that this susceptibility to cognitive fatigue does not worsen over time. This finding is unique in that while other symptoms of the disease, such as level of cognitive impairment, have been shown to worsen as the disease progresses (Bernardin, Rao, & Luchetta, 1993), cognitive fatigue does not seem to show the same pattern of progression with time. Why an individuals' susceptibility to cognitive fatigue remains stable over time even in the face of potential overall cognitive decline remains unclear. Coupled with the notion that sleep quality may serve as a treatable cause of cognitive fatigue, these findings suggest that the improvement of sleep quality should be a target of future interventional studies and the outcomes should be measured both in terms of patient experience as well as objective measurement by advanced neuroimaging techniques.

As previously discussed, findings from the three studies have important clinical implications. All three studies highlight the importance of evaluating cognitive fatigue as part of routine assessment given that objective evidence of cognitive fatigue may be present in the absence of self-report. While individuals with MS may be able to perform a sustained cognitive task to the same degree of accuracy as healthy controls (and thus may not be considered impaired), this comparable level of performance may come at a cost in the form of increased cognitive fatigue. Individuals may be able to compensate

for a time with regard to overall performance, but subtle difficulties may only become apparent when one considers how an individual is performing the task as it progresses. While performance may appear optimal at the beginning of a sustained cognitive task, marked decline may be observed towards the end of the task indicating a difficulty with successfully keeping up with the task demands. It is only through this more fine-grained analysis that any impairment may become apparent. As previously discussed, while self-reported evaluations of cognitive fatigue can be useful during clinical assessment given their simple administration and good psychometric properties (Amtmann et al., 2012; Learmonth et al., 2013), objective measures of cognitive fatigue are ideal given that these can help further validate patients' subjective complaints.

In clinical practice, results from this dissertation support the use of the PASAT as a sensitive and reliable measure of objectively evaluating cognitive fatigue. These results parallel those in the existing MS literature (Morrow et al., 2015; Walker et al., 2012). In order to comprehensively evaluate cognitive fatigue using the PASAT, it is crucial that scoring methodology be considered given the differences in sensitivity noted with each scoring method and given that studies have shown that individuals may alter their performance strategies in order to reduce the challenging task demands (Schwid et al., 2003). Given its relative ease and speed of administration, including the PASAT as part of routine clinical assessment may prove beneficial when presented with individuals who present with complaints of CF.

One consistent finding throughout the MS literature is a lack of correlation between self-reported, subjective fatigue and objective measures (Bailey et al., 2007; Walker et al., 2012). Results from this dissertation are in agreement with these past findings in that no relationship between the two were observed in any of the studies

performed. Given this lack of correlation observed between objective and subjective measures, the inclusion of each methodology may prove invaluable when attempting to capture the complaints of cognitive fatigue of individuals who present clinically. For example, an individual may present with low subjective fatigue (ex. low m-FIS score) but may nonetheless have complaints about feeling unable to keep up with their peers during cognitively demanding tasks. In this case, the self-report questionnaire, while informative, may suffer from a lack of adequate definition (i.e. the individual may feel the questions do not adequately reflect or address their own perception of their fatigue) or the individual may suffer from recall bias. For this individual, administering an objective measure of CF might better capture and validate this particular individual's complaints of difficulty in maintaining cognitive effort over time which would otherwise go undetected when relying solely on subjective measures.

With regard to potential treatment interventions, targeting sleep quality may prove to be the most beneficial interventional target when attempting to alleviate the impact of cognitive fatigue effects. Approximately 50 - 60% of individuals with MS report some form of sleep disturbance impacting sleep quality (Kallweit et al., 2013) and as such a large proportion of individuals diagnosed with MS may benefit from this targeted intervention. Disturbances in sleep quality can result from disease symptomatology (ex. frequent urination, pain, etc.) or can result from poor sleep hygiene; the practices and habits that encourage good quality nighttime sleep. Beneficial sleep hygiene practices can include limiting daytime naps, avoiding stimulants (ex caffeine) close to bedtime, and daily exercise. Previous treatments targeted at improving sleep quality in MS have evaluated the impact of both behavioural & exercise interventions. Pilutti et al. (2014) evaluated the impact on sleep quality of a 6-month,

internet-delivered behavioural intervention aimed at increasing lifestyle physical activity in MS with results showing improvement in subjective sleep quality scores post-intervention (Pilutti, Dlugonski, Sandroff, Klaren, & Motl, 2014). Similarly, Siengasukon et al. (2016) evaluated the impact of physical activity and exercise intervention on sleep quality in MS and found that a low-intensity walking and stretching exercise intervention resulted in improved sleep quality (Siengasukon et al., 2016). Given the correlation observed between self-reported sleep quality and cognitive fatigue, these types of interventions targeting the improvement of sleep quality may provide valuable guidance towards possible treatment avenues aimed at improving cognitive fatigue itself.

In the context of overall fatigue (i.e. physical, cognitive, and psychosocial), past research has evaluated the effectiveness of three types of fatigue management interventions for people with MS: exercise (Kargarfard, Etemadifar, Baker, Mehrabi, & Hayatbakhsh, 2012; Siengasukon et al., 2016), education (Finlayson, Preissner, Cho, & Plow, 2011; Mathiowetz, Finlayson, Matuska, Chen, & Luo, 2005), and medication (Shaygannejad, Janghorbani, Ashtari, & Zakeri, 2012; Stankoff et al., 2005). In order to provide a comprehensive perspective on treatment options and to evaluate their effectiveness in relation to one another, Asano and Finlayson (2014) (Asano & Finlayson, 2014) compared these three types of fatigue management interventions to determine which methods had the most significant impact on the severity of fatigue experienced. Results from this review suggest that rehabilitation interventions (i.e. exercise and education) have a more significant effect on reducing the severity of patient-reported fatigue than do pharmacological interventions. As such, the authors proposed that these rehabilitation interventions should be the initial treatment choice

for individuals with MS who report disabling levels of fatigue. While this review focused on treatment interventions as they relate to the general construct of fatigue, it provides valuable insight regarding which types of interventions might be most effective when considering cognitive fatigue more specifically. While rehabilitation interventions improve self-reported fatigue, the question remains whether the same interventions would show improvement in objectively evaluated cognitive fatigue given the lack of correlation typically observed between objective and subjective reported fatigue.

In the context of alleviating cognitive fatigue effects by targeting sleep quality, developing appropriate rehabilitation interventions can prove challenging given that disturbances in sleep can present in multiple forms including: difficulty in achieving sleep onset, disruptions in sleep due to temperature or noise, difficulties with breathing or nocturia, difficulties with pain and tonic spasms, among others. Whether these disturbances are present, and how often they disrupt sleep quality, can vary at the individual level. Useful therapeutic intervention, therefore, requires identifying on an individual basis where these disturbances in sleep occur, thus providing specific direction with regards to targeted treatment interventions.

The most commonly prescribed pharmacological interventions for MS related fatigue are Amantadine and Modafinil (Pucci et al., 2007), though their impact on reducing cognitive fatigue specifically remains unclear. In addition, as previously discussed, rehabilitation interventions seem to be more effective at reducing the severity of fatigue than pharmacological treatments. To the best of our knowledge, no such interventions have yet been developed which specifically target sleep quality in the context of cognitive fatigue (this parallels Asano and Finlayson (2014) where it was reported that no randomized control trials that targeted sleep quality were found which

met their review criteria). As such, when designing treatment interventions to target sleep quality it is advantageous to consider how exercise and patient education might best be employed to target sleep quality improvement.

In conjunction with the results from the current dissertation, it is possible to speculate on how one might design a potential interventional study targeting the treatment and improvement of cognitive fatigue in MS. Results from this dissertation suggest sleep quality is the most beneficial and treatable therapeutic target. In addition, rehabilitation interventions have been shown to be more effective at reducing patient reported fatigue than pharmacological treatments. As such, one might design a randomized control trial in which the treatment intervention is comprised of both exercise, in particular low-intensity walking and stretching given its demonstrated improvements to sleep quality in those with MS (Siengsukon et al., 2016), and an education program where patients receive information about strategies to improve sleep quality and/or cope with cognitive fatigue. While the exact impact of these types of rehabilitation interventions on objectively evaluated cognitive fatigue remains untested, results from this dissertation suggest that the improvements noted in self-reported sleep quality as a result of these interventions should concomitantly improve objective cognitive fatigue given the correlation observed between the two. Concerning outcome measures, the current dissertation highlighted the importance of using objective outcome measures rather than relying solely on subjective reports. As such, any improvement in sleep quality as a result of the intervention should be evaluated using traditional self-report measures (ex. PSQI) as well as more objective methodologies (ex. EEG). Based on the results of this dissertation, parallel to improvements in sleep quality one would anticipate concomitant improvements in cognitive fatigue and similarly

outcome measures of cognitive fatigue should include both self-report (ex. m-FIS) and objective (ex. PASAT) measures as well. When evaluating cognitive fatigue in MS, the inclusion of neuroimaging outcomes, in particular ASL metrics while performing a continuous cognitive task, is paramount given that the current dissertation demonstrated that cognitive fatigue effects can be evident even at the neuronal level with dysfunctional cerebral blood flow to the MFG appearing to underlie the cognitive fatigue effects observed in MS. Taken all together, based on the results of this dissertation, one would anticipate that those taking part in the exercise/education treatment intervention would show improved sleep quality resulting in diminished cognitive fatigue effects. This improvement in cognitive fatigue could be objectively evaluated and observed in the form of better maintained performance on the PASAT over time and more appropriate CBF allocation to the MFG during the sustained cognitive task.

Conclusion

In conclusion, this dissertation demonstrates that cognitive fatigue poses a significant problem for individuals with multiple sclerosis. Using a multidimensional approach, results suggest an increased susceptibility to cognitive fatigue in those with multiple sclerosis compared to healthy controls. This susceptibility, however, does not seem to change over time as the disease progresses. Dysfunctional cerebral blood flow to the middle frontal gyrus may underlie this increased susceptibility with findings further supporting the notion that sleep quality may prove to be a useful target for treatment interventions. In order to increase awareness of this debilitating symptom of the disease and to validate patients' subjective complaints, the inclusion of measures which objectively evaluate and quantify cognitive fatigue is crucial for both research applications as well as routine clinical assessments. It may be possible to alleviate the impact of cognitive fatigue on an individuals' quality of life at any stage of the disease using rehabilitation interventional approaches combining exercise and education treatment strategies.

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