USE OF COGNITIVE SCREENING AND THE INFLUENCE OF PSYCHOSOCIAL VARIABLES IN IDENTIFICATION OF COGNITIVE IMPAIRMENT IN MS

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DEDICATION

I would like to thank the members of my Graduate Committee, my mentor Dr. Lacritz, and Dr. Greenberg and his research team for making it possible to be a part of the Cognition and Demyelinating Disease Project. I would also like to thank my family for their endless support.

USE OF COGNITIVE SCREENING AND THE INFLUENCE OF PSYCHOSOCIAL VARIABLES IN IDENTIFICATION OF COGNITIVE IMPAIRMENT IN MS

by

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THESIS

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Abstract

BACKGROUND: The purpose of this project is to examine the potential of abbreviated cognitive screening to identify patients with clinically significant cognitive dysfunction. A secondary goal is to examine relationships between cognitive functioning and psychosocial factors of disease.

SUBJECTS: The study includes 94 subjects with a Demyelinating disease [M age = 45.04 (11.08); M education = 15.40 (2.13)] who were referred to the University of Texas Southwestern Medical Multiple Sclerosis Clinical Center and Multiple Sclerosis Program and signed informed consent for a larger study on cognition in multiple sclerosis and demyelinating disease.

METHOD: Subjects completed a screening battery (JoL, 9HPT, PASAT, SDMT-Oral, and T25FW) at visit one and a larger cognitive assessment within 4 weeks of visit one, which was used to divide subjects into impaired and non-impaired groups. Linear regression was used to assess which tests on the screening battery predicted impairment on the longer battery. Associations between psychosocial factors of depression, fatigue, and sleepiness were examined in relation to cognitive performance. The relationship between depression and objective versus subjective cognitive performance was also examined.

RESULTS: The PASAT (p = .001) was the only measure in the screening battery that predicted group membership, with correct classification of 76% of subjects using a cut score of T ≤ 38. Depression (QIDS-SR) was significantly correlated with self-reported cognitive dysfunction (MSNQ) (r = .57; p = <.001) but only modestly associated with the four measures on the screening battery (r = -.17 to .25). Those who endorsed depressive symptoms performed lower on JoL (p = .003), PASAT (p = .015) and SDMT (p = .023). Level of fatigue was associated

with cognitive performance, as significant mean differences were found on all screening battery measures in high versus low fatigue groups. There was no impact of sleepiness on cognition. DISCUSSION: Complex attention was the most sensitive measure for predicting cognitive impairment on a more comprehensive battery and may be a good screening tool in identifying who might benefit from more detailed testing. Higher levels of depression and fatigue significantly impacted test performance and highlight important areas for screening and treatment, while daytime sleepiness had no effect.

Keywords: Multiple Sclerosis, cognitive, impairment, attention, PASAT, depression, fatigue, sleep.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

9HPT – 9-Hole Peg Test

BVMT-R – Brief Visual Memory Test- Revised

CIS – Clinically Isolated Syndrome

CVLT-II – California Verbal Learning Test- Second Edition

ESS – Epworth Sleepiness Scale

FAS – FAS Phonemic Verbal Fluency Test

JLO – Judgment of Line Orientation

MFIS – Modified Fatigue Impact Scale

MS – Multiple Sclerosis

MSNQ – Multiple Sclerosis Neuropsychological Questionnaire

OCT – Optical Coherence Tomography

PASAT – Paced Auditory Serial Addition Test

PPMS – Primary Progressive Multiple Sclerosis

PRMS – Progressive-Relapsing Multiple Sclerosis

QIDS-SR 16 – Quick Inventory of Depressive Symptomatology-Self Report

RRMS – Relapsing-remitting Multiple Sclerosis

SDMT – Symbol Digit Modalities Test

SPMS – Secondary Progressive Multiple Sclerosis

T25FW – Timed 25-Foot Walk

TCST – Texas Card Sorting Test

WRAT-4 – Wide Range Achievement Test 4th- Edition

CHAPTER ONE

Introduction

Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune disease that attacks healthy areas of the brain and spinal cord (Steultjens, 2003). MS is a prevalent, widespread, and often disabling disease (Motl, McAuley, Wynn, Suh, & Weikert, 2010). This demyelinating disease creates lesions in the white matter of the brain, causing stable and/or transient neurological deficits and physical symptoms (Steultjens, 2003). Corticosteroids are often used during exacerbations (i.e., disease flare-ups), and this medication acts as an anti-inflammatory agent, reducing swelling and associated symptoms. There is no cure for multiple sclerosis, but medications can help reduce the length of exacerbations and prevent future attacks. There is still much to learn about the causes of MS, but evidence suggests that psychosocial and environmental factors may play a role in its development (National Multiple Sclerosis Society [NMSS], 2010).

Symptoms such as fatigue and pain can lead to a decreased desire and ability to engage in physical activities. This can contribute to depression, anxiety or stress for the individual and possibly lead to a poor self-image. Cognitive abilities are affected in 50% of patients with MS (Calabrese, 2006). The most prevalent impaired cognitive domains include attention, information processing speed, memory, mental flexibility and visuoconstruction (Calabrese, 2006). Cognitive disability can be just as debilitating as physical disability for some individuals (Motl et al., 2010). The ever-changing cognitive and neurological impairments associated with MS can cause distress and frustration at home

and also in the workplace. Continued research in developing brief screening tools to assess for cognitive deficits and other psychosocial factors that affect a good quality is critical for optimal disease management.

In the MS literature, determining the efficiency of screening tests to assess for potential cognitive impairment is a topic of great interest (Benedict, Duquin, Jurgensen, Rudick, Feitcher et al., 2008). Comprehensive neurological assessments are costly and time consuming. Because of this, cognitive testing is not offered to every patient (Deloire, Bonnet, Salort, Arimone, Boudineau et al., 2006; Portaccio, Goretti et al., 2009). Cognitive deficits are extremely common in MS and it is important to identify patients who may benefit from comprehensive neuropsychological evaluation and/or treatment of associated difficulties (Portaccio, Goretti et al., 2009; Beatty & Goodkin, 1990). Therefore, a brief screening assessment, sensitive enough to determine those patients who need more comprehensive testing, would be helpful (Deloire et al., 2006).

CHAPTER TWO

Review of the Literature

Multiple Sclerosis

Clinical Presentation

Multiple sclerosis begins with inflammation of the brain, often called exacerbations. One's own immune system begins to eat away at the myelin sheath that covers nerve fibers, which is why MS is often referred to as a demyelinating condition. Once the myelin is gone, a plaque forms in its place causing interference with the electrical signals from other pathways in the brain or spinal cord (Motl et al., 2010). The course of the disease is unpredictable and can fluctuate. The progression rate and severity depends on the type of MS diagnosed.

The McDonald criteria for the diagnosis of MS were proposed in 2001 to clarify and improve diagnostic accuracy and sensitivity. The criteria was revised in 2005 and again in 2010 to reflect advances and changes in diagnostic technology, as well as to simplify diagnosis (Polman, Reingold, Banwell, Clanet, Cohen et al., 2011; 2005). The McDonald criteria for Multiple Sclerosis (Polman, et al., 2011) can be found in appendix A. Diagnosis is made when an individual has 2 attacks (exacerbations) and evidence of at least one brain or spinal cord lesion. The presence of and recovery from exacerbations define the four types of MS. Attacks occur when the brain and/or spinal cord are inflamed. The attacks can last from one day to several weeks or months. In order for the attack to be a *true* attack, the inflammation and symptoms must last for at least 24 hours. The current attack must also be separated from

previous attacks by thirty days. The exacerbations can be mild to severe, and recovery time and symptoms are variable (NMSS, 2010).

There is no specific age limit for MS but, onset typically occurs from age 20 to 50 (Noonan et al., 2007). The prevalence of the disease is estimated to affect between 47 and 110 of every 100,000 people living in the United States (Noonan et al., 2007). The disease is more prevalent in northern latitudes, and incidence severely diminishes as one moves closer to the equator (Khan et al., 2008), although the reason for this is not clear. It is estimated that there are 8,000 to 10,000 children and adolescents below the age of 18 who have been diagnosed with MS (NMSS, 2010). The disease affects younger adult woman and men; however, the disease is more predominant in young females, with a 2.5:1 ratio (Khan et al., 2008).

It is evident that MS can lead to functional and occupational impairment. The average life expectancy for individuals with MS is 7 years shorter than the general population although death can be caused by disease-related complications (e.g., infection, medication errors, falls; Compston & Coles, 2008). Some medications are primarily used as an anti-inflammatory to help with exacerbations (NMSS, 2010). The most common type of medication used during an attack or exacerbation is corticosteroids. Used in high doses this medication acts as an anti-inflammatory that reduces the inflammation in the brain and spinal cord, diminishing the length of the attack (NMSS, 2010). MS has no known cure, but research has shown that patients who use disease modifying medications and therapies have considerably improved outcomes. These medications can decrease clinical relapses, lesion load in the brain, and disability progression (Amato, Portaccio, & Zipoli, 2006).

Pathology. There are various stages and degrees of the disease, but in most cases the disease is progressive and causes a continual decline in one's physical, psychological, and neurological health. Relapse-Remitting MS (RRMS) is the most common type of MS (80%) and is characterized by erratic exacerbations followed by a multitude of symptoms with a variable recovery. It might take days, weeks or even months to recover from one exacerbation. This type of MS usually occurs at the beginning of the disease, when a person is first diagnosed (NMSS, 2010).

Primary Progressive MS (PPMS) is characterized by a progressive neurological decline, with no discrete exacerbations or relapses, meaning the symptoms are constant and there is never full recovery. The severity of neurological symptoms can fluctuate with this type, but there is always inflammation. This is one of the least common types of MS, consisting of only about 15% of the MS population (Khan, Turner-Stokes, Ng & Kilpatrick, 2008).

Secondary Progressive MS (SPMS) typically follows Relapse-Remitting MS, and is similar to the Primary Progressive type in that there is a continual decline. This is due to a lack of full recovery from symptoms caused by exacerbations. The list of symptoms increases given that the individual never fully recovers from their pervious symptoms. During relapses, new symptoms can occur in addition to other symptoms that have been experienced. About 65% of those diagnosed with Relapsing-Remitting Multiple sclerosis advance or progress to this secondary phase (NMSS, 2010).

The least common of all four types of MS is Progressive-Relapsing (PRMS). Characterized by a continual decline of neurological functioning, this type is different from

Primary Progressive because Progressive-Relapsing does have occasional relapses (Khan et al., 2008). Recovery from the exacerbations is variable; sometimes there can be a full recovery and other times there may not be. As described with all the different types, the symptoms that can occur vary in severity and recovery (NMSS, 2010).

There is a long list of common symptoms associated with MS. Respiration and breathing complications can arise, as well as swallowing problems. Balance, gait, and coordination can be severely affected, limiting ones' mobility. Physical activity is also affected by spasticity, which produces involuntary muscle spasms. Bladder and bowel dysfunction, vision problems, vertigo and dizziness, numbness, and sexual dysfunction are also common. Headaches, hearing loss, seizures, tremors and itching are other symptoms associated with MS (NMSS, 2010). Physical limitations might cause the individual to need the assistance of mobility aids and other adaptive devices (Motl et al., 2010). As one can gather from the multitude of different symptoms, the areas in a person's life that can be affected are vast.

However, fatigue, pain, depression and cognitive impairments are four of the most pervasive (NMSS, 2010). If nothing else, these four symptoms alone can impact every aspect of a person's daily life and activities (Motl et al., 2010). Research has provided evidence that there are specific areas of cognition that are affected more than others. The most commonly affected cognitive domains are recent and working memory, executive functioning, processing speed, and visuospatial skills (Bobholz & Rao, 2003). Memory is most affected in MS and is found in 40% to 60% of cognitive impairments in patients. In a

review of multiple studies, Calabrese found that retrieval in memory is most commonly affected (Calabrese, 2006). Cognitive dysfunction can interfere with work and home life.

However, cognitive dysfunction is often overlooked in routine neurological exams and many professional health care providers rely on self-reported cognitive deficits from their patients (Rao, 1995; Kinsinger, Lattie, & Mohr, 2010). A study by Amato and colleagues (2006) found that 65% of the MS population, at some point in the disease process, will experience some type of cognitive impairment (Amato, Zipoli, & Portaccio, 2006). Psychologically, a person can be worn out from the ever-changing aspect of the disease, possibly causing depression or anxiety.

Depression. Depression has been reported in 50% of patients with MS, which can occur early in the disease process and makes it the most common emotional disturbance (Randolph, & Arnett, 2005, Zabad, Patten, & Metz, 2005). Individuals with MS have a lifetime prevalence rate for depression of 54% (Zabad et al., 2005). Patients are more likely to be depressed during an exacerbation, and research has suggested that depression interferes with cognitive abilities (Kroencke, Denney, & Lynch, 2001; Chiaravalloti & DeLuca, 2008). Research has also suggested that slowness in thinking and processing due to depression has been reported impact other areas of cognitive functioning (Arnett, Barwick, & Beeney, 2008). A study in 2004 suggests mildly depressed participants overestimate their report of memory deficits due to depression (Bruce, & Arnett, 2004). Demaree and Colleagues (2003) found cognitive deficits in learning and processing speed when assessing for cognitive dysfunction in an MS sample with depression (Demaree, Gaudino, & DeLuca, 2003). Researchers such as Arnett (1999a) split subjects into two groups, depressed and

non-depressed, to determine cognitive differences between groups when assessing cognitive deficits and depression in MS by (Arnett, Higginson, Voss, Bender, Wurst, & Tippin, 1999a). Multiple studies have shown that depressive symptoms correlate with self-reported cognitive deficits much more than cognitive test performance (Benedict et al., 2003, 2004; Bruce & Arnett, 2004; Randolph et al., 2004).

Using the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ), Benedict et al. (2004) discovered that self-reported cognitive functioning correlated more highly with depressive symptoms than with actual neuropsychological test scores. Carone and colleagues (2005) proposed that severity of depression was higher among those who underrated their cognitive abilities (Carone, Benedict, Munschauer, Fishman, & Weinstock-Guttman, 2005). Bruce and Arnett's (2004) study provides support for the previous study, as patients in the study who were categorized as mildly depressed underrated cognitive functioning. The connection between subjective and objective cognitive functioning might be moderated by depressive symptoms (Julian, Merluzzi, & Mohr, 2007). Benedict and colleagues (2004) found depression to be highly correlated with MS patient subjective reports of cognitive functioning, as patients tend to over-report cognitive difficulties (Benedict, Cox, Thompson, Foley, Weinstock-Guttman et al., 2004).

Some studies have found a correlation between subjective (self-report) cognitive complaints and objective measuring of cognitive functioning (Marrie, Chelune, Miller, & Cohen, 2005; Matotek, Saling, Gates, & Sedal, 2001; Randolph, Arnett, & Higginson, 2001) while others have found discrepancies (Beatty, & Monson, 1991; Benedict, Munschauer, Linn, Miller, Murhpy et al., 2003; Maor, Olmer, & Mozes, 2001). Arnett and colleagues

(1999a; 1999b) found that MS patients with depressed mood performed more poorly on working memory tasks involving both storage and processing (Arnett, Higginson, Voss, Bender, Wurst et al.,1999a; 1999b). Confounding symptoms such as depression and fatigue could negatively affect one's perceived cognitive abilities (Kinsinger et al., 2010). Similarly, Middleton and Colleagues (2006) found that emotional state and fatigue reflect a patients' perception of their cognitive abilities more than their objective abilities.

Fatigue. Fatigue is a common symptom of MS and one that can at times be the most debilitating (Kaminska, Kimoff, Schwartzman, & Trojan, 2011; Kos, Kerckhofs, Nagels, D'hooghe, & Ilsbroukx, 2008). The Multiple Sclerosis Council has defined fatigue as "a subjective lack of physical and mental energy that is perceived by the individual or caregiver to interfere with usual or desired activities" (MS Council for Clinical Practice Guidelines, 1998). Chronic fatigue has been reported in 80% to 97% of MS patients (Krupp, 2006), with more than 33% rating fatigue as the most disabling symptom (Bakshi, 2003). Some research has shown that those who engage in physical activity can reduce pain and fatigue, and increase quality of life (Plow, Resnik & Allen, 2009).

It has been found that fatigue may contribute to certain cognitive impairments including information processing, attention, and memory (Bakshi, 2003). The Fatigue Severity Scale (FSS) is a simple one-dimensional measurement of fatigue and has been validated for the MS population as well as other diseases (Krupp, LaRocca, Muir-Nash, & Steinburg, 1989). Johnson et al. (1997) found that after 3 hours of testing, the MS sample reported higher levels of fatigue and lower performance on the Paced Auditory Serial Addition Test (PASAT) as compared to healthy participants' performance (Johnson, Lange,

DeLuca, Korn, & Natelson, 1997). One study found that within 15 minutes of a variety of cognitive tests (i.e., PASAT and Symbol Digit Modalities Test) the MS participants developed cognitive fatigue, resulting in poor performance (Kujala, Portin, Revonsuo, & Ruutianen, 1995). In addition to cognitive deficits, research has shown that severity of fatigue can contribute to the onset of depression (Koch, Mostert, Heerings, Uyttenboogaart, & Keyser, 2009).

Depression is a common psychological component to MS (Arnett, Barwick, & Beeney, 2008) and has been linked with fatigue (Bakshi, 2006). Kaminska et al. (2011) explain that fatigue associated with depression could be an important component and mechanism to MS patients' overall burden of fatigue. The Modified Fatigue Impact Scale (MFIS) is a measure of fatigue that is widely used with the MS population (Kinsigner et al., 2010). Kinsinger and colleagues (2010) found depression, assessed with the BDI-II, and fatigue, measured by the MFIS, were able to significantly predict self-reported cognitive complaints in an MS sample.

The cause of fatigue is not completely understood but is thought to be the product of many other factors such as immunological, psychological, and sleep disturbances (Trojan, Arnold, Collet, Shapiro, Bar-Or et al., 2007; Kaminska, et al., 2011). In addition, studies have found increased fatigue associated with hopelessness (van der Werf, Jongen, Nijeholt, Barkhof, Hommes et al., 1998), self-reported cognitive complaints, and poor behavioral responses to symptoms of depression (Skerrett, & Moss-Morris, 2006; Kaminska, et al., 2011). There is growing support that sleep complaints and disturbances, common to those with MS, may also be a factor in developing fatigue (Kaminska, et al., 2011).

Sleep. Many individuals with MS have subjective sleep complaints, which can often present as some form of insomnia, with daytime symptoms caused by these disturbances (Bamer, Johnson, Amtmann, & Kraft, 2008; Merlino, Fratticci, Lenchig, Valente, Cargnelutti et al., 2009; Tachibana, Howard, Hirsch, Miller, Moseley et a., 1994). Symptoms of insomnia vary, including mood disturbances, fatigue and cognitive impairment (i.e., attention, concentration, and memory; American Academy of Sleep Medicine, 2005). Merlin and colleagues (2009) found that 47.5% of individuals with MS in a clinical setting reported poor sleep. A large mail-in questionnaire study of subjective sleep in 1,362 patients found 13.3% had mild sleep issues, 21.5% moderate, and 30.0% severe (Bamer et al., 2008).

Lobentanz and colleagues (2004) found MS patients to have more sleep disturbances (i.e. 62% were poor sleepers), as compared to healthy controls, with poor sleep quality occurring twice as frequently in MS patients (Lobentanz, Asenbaum, Vass, Sauter, Klosch et al., 2004). Lobentanz et al. (2004) also found that MS patients used sleep aids more frequently than controls. The Epworth Sleepines Scale (ESS) assesses individuals' general level of daytime sleepiness (Johns, 1991). Hrayr and Colleauges (2004) found a relationship between excessive sleepiness, as measured by the ESS, and fatigue complaints in an MS sample. It is suggested that the ESS be used as a screening tool for sleep disorders in the MS population (Hrayr et al., 2004).

Neurocognitive deficits

Cognitive deficits range widely but some form of impairment occurs in up to 65% of MS patients (Rao, 1997). Primary cognitive areas vulnerable to impairment in MS include

memory, information processing speed, complex attention, and executive functions (i.e., problem solving; Bobholz & Rao, 2003). Nagy and colleagues reported reduced decision-making abilities, mainly caused by deficits in new learning, affecting daily functioning in those with MS (Nagy, Bencsik, Rajda et al., 2006). Johnson (2007) suggests deficits in verbal and visual learning also occur in MS. Cognitive decline has been found in the early stages of the disease process (Amato, Ponziani, Parcucci, Bracco, Siracusa et al., 1995) and researchers attribute this to a disconnection among brain structures related to the extent of axonal damage (Rovaris, Filippi, Falautano, Minicucci, Rocca et al., 1998). Currently, there is no single measure or assessment that is sensitive to the broad and variable cognitive deficits that can be seen in Multiple Sclerosis (Rao, Geo, Bernardin, & Unyerzagt, 1991), though there have been attempts to develop neuropsychological batteries.

Comi and colleagues (1995) conducted a study that assessed six cognitive domains: attention (Cancellation Task), short-term memory (Digit Span), long-term memory (learning of three lists of words), visuospatial skills (Judgment of Line Orientation Test), abstract reasoning (verbal fluency) and language (Token Test). Of these six domains, cognitive impairment was found in visuospatial skills, abstract reasoning, long-term memory, and attention (Comi, Filippi, Martinelli, Campi, Rodegher et al., 1995). Rao and colleagues (1991) explored the picture of cognitive decline in MS with a community-based study consisting of 100 MS patients. They found impairment in sustained attention and executive ability (up to 25%), episodic memory (up to 31%), and visuospatial ability (up to 19%).

Although individuals with MS often report cognitive problems, there have been few studies that have analyzed the relationship between perceived and objective cognitive

deficits (Middleton, Denney, Lynch, & Parmenter, 2006). A study conducted by Maor and colleagues (2001) had participants complete a questionnaire on how they perceived their cognitive functioning and also assessed their cognitive functioning with a neuropsychological battery. A significant discrepancy was found between perceived and objective cognitive functioning, with 72% showing deficits in objective functioning and only 52% reporting perceived dysfunction (Maor, Olmer & Mozes, 2001; Randolph, Arnett, & Freske, 2004; Randolph, Arnett, & Higgins, 2001). Other studies support that self-reported cognitive deficits do not correlate with objective testing (Benedict, Munschauer et al., 2003; Christodoulou et al., 2005; Middleton, et al., 2006). As a result of mixed findings, it is evident that this area needs further research for clarification to understand the relationship between perceived and objective cognitive functioning.

Information Processing Speed. Slowed processing speed in MS patients has been identified as a primary cognitive deficit (DeLuca, Johnson, & Natleson, 1993). Cognitive measures that involve rapid serial processing of information such as word fluency, symbol-digit tests, the Stroop test and the Paced Auditory Serial Additional Test (PASAT) have consistently detected deficits in information processing speed in MS (Lynch, Dickerson, & Denney, 2010). Jennekins-Schinkel and colleagues (1990) found deficits in speed of reading and color naming on the Stroop Test. Impaired or slowed processing speed can influence impairment in other cognitive domains such as executive functioning, memory, retrieval, and working memory (Julian, 2011).

Drew and colleagues found that 17% of MS patients displayed executive functioning dysfunction in areas such as shifting, inhibition and fluency (Drew, Tippett, Starkey, &

Isler, 2008). Efficiency in information processing speed involves working memory as well as speed of processing (Baddley, 1986; 1992). Working memory, needed for a multitude of different cognitive tasks such as language comprehension, computation and problem solving, is the simultaneous usage of temporary storage and processing of information (Baddelly & Hitch, 1974). Structural capacity is the "number of distinct informational units that can be remembered at any given time," whereas operational capacity is the "number of processing operations that can be performed while still preserving the products of earlier operations" (Salthouse & Mitchell, 1989). Salthouse and Mitchell (1989) explain that structural and operational capacities are two separate but dependent aspects involved in working memory.

Working Memory. Research on patient-reported cognitive performance implies that memory impairment is the most recurrent disturbance in MS (Brassington, & Marsh, 1998). Long-term memory is the ability to learn and recall (i.e., after a delayed period of time) new information (Lezak, Howieson, & Loring, 2004), and is one of the most frequently impaired cognitive functions, occurring in about 40%-65% of MS patients (Rao, Grafman, & DiGuilio, 1993). Many researchers have found that initial learning of information is the primary aspect of impairment in memory for those with MS (DeLuca, Barbieri-Berger, & Johnson, 1994). Recall and recognition in individuals with MS was consistent with healthy controls when the MS subjects were given more repetitions of information during the learning phase (DeLuca, Barbieri-Berger, & Johnson, 1994; DeLuca, Johnson, & Natleson, 1993).

Raine et al. (2008) suggest using the CVLT-II (CVLT-II; Delis et al., 2000) and the Brief Visual Memory Test- Revised (BVMT-R; Benedict, 1997) to assess memory

impairment in MS. The CVLT-II is a measure of verbal memory that has been well-validated (Delis et al., 2000). Stegen et al. (2010) conducted a study, with 351 MS participants, to determine which measures on the California Learning Verbal Test-II (CVLT-II) were most sensitive to detecting impairment. The researchers found that 14 variables on the test (i.e., total recall, short delay free recall and long delay free recall) significantly ($p < .001$) identified impairment (Stegen, Stepanov, Cookfair, Schwartz, Hojnacki et al., 2010), expressing that the CVLT-II is able reliable cognitive measure. The BVMT-R is a measure of visual memory that requires the immediate and delayed recall and recognition of visual figures (Benedict, 1997). Gaines and colleagues found that the MS group ($n = 70$) displayed impairment ($p < .001$) on total learning and delayed recall from the BVMT-R as compared to healthy controls (Gaines, Gavett, Lynch, Bakshi, & Benedict, 2008).

Language. Language impairment in MS has not been widely researched, as the majority of neuropathology is in subcortical areas of the brain that do not involve language function to a significant degree (Rao, 1986). However, language studies that have been more in-depth and with better classification of MS patients have suggested deficits in language (Friend, Rabin, Groninger, Deluty, Bever et al., 1999). There are a few studies that have identified deficits in areas of language such as impaired naming, verbal fluency and verbal expression in MS patients as compared to healthy controls (Bernard, 1999). The FAS and Category Verbal Fluency tasks measure the spontaneous production of words when given narrow search conditions (Strauss et al., 2006). Research has shown that

Relapse-Remitting MS (RRMS) and Primary-Progressive MS (PPMS) patients have both demonstrated deficits on FAS (Beatty, Goodkin, Monson, Beatty, & Hertsgaard, 1988).

Visuospatial. Visuospatial deficits are commonly found in those patients with RRMS (Gaudino, Chiaravalloti, DeLuca, & Diamond, 2001). Visual perception is the recognition of a stimulus and the ability to accurately perceive the characteristics of that stimulus (Chiaravalloti, & DeLuca, 2008). Compared to many other cognitive domains that are impaired in MS, there has been little research on visuospatial skills (Chiaravalloti, & DeLuca, 2008). Vleugels and colleagues conducted a study to determine the percentage of impaired visuospatial deficits in an MS group and found that 26% participants were impaired on four or more measures (i.e., Benton Judgment of line Orientation and Line Bisection; Vleugels, Lafosse, van Nunen et al., 2000). Impairments in primary visual processing and visual disturbances in MS, including but not limited to optic neuritis, can affect visual perceptual processing and visual attention.

Up to 50% of patients with MS have vision deficits, which can begin with vision loss, and 90% of MS patients will have optic neuritis during the course of their disease (Bruce, Bruce, & Arnett, 2007). These impairments in visual processing can influence deficits in higher-order cognitive tasks that require visual demands such as visual attention (Chiaravalloti, & DeLuca, 2008). A well-validated measure of visuospatial ability is the Judgment of Line Orientation Test (JLO) (Benton, Hannay, & Varney, 1975). A study conducted by Benedict and colleagues (2004) found that MS participants performed significantly lower than controls on the JLO ($p < .001$) (Benedict et al., 2004).

Attention. Research suggests that attention difficulties are common and significantly impact MS patients' lives, affecting work and other activities (Langdon & Thompson, 1996). In many different diseases, deficits in attention have been used as indicators of declining cognitive functioning (Kujala, Portin, Revonsuo, & Ruutiainen, 1995). It is important to note that tests of visual attention may be impacted by not only attentional deficits but visual acuity caused by optic neuritis. Visual deficits alone cannot account for attention dysfunction in MS and auditory attention is also thought to be a factor in attention difficulties (Bruce et al., 2007).

Neuropsychological tests of attention frequently used in MS include the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977), the Stroop test and various vigilance tasks (Kujala et al., 1995). The PASAT-3 measures attention, information processing speed and working memory (Gronwall, 1977). Research has found that the PASAT is a good measure of sustained auditory attention, with MS participants performing slower and producing more errors than healthy controls (De Sonneville, Boringa, Reuling, Lazeron, Ader et al., 2002).

The Stroop Color and Word test is another measure of attention (selective) that also assessed impulse control and inhibition (Golden, 1978). Denney and Lynch (2009) found generalized slowing in MS participants compared to controls on the Stroop test. The Symbol Digit Modalities Test (SDMT) measures divided attention and visual scanning, and has good sensitivity and specificity in predicting cognitive performance on a comprehensive cognitive battery in MS (Parmenter, Weinstock-Guttman, Garg et al., 2006).

Neuropsychological Test Batteries for Multiple Sclerosis

The Cognition Function Study Group of the National Multiple Sclerosis Society (NMSS) aided in the development of The Neuropsychological Screening Battery for MS (NSBMS) (Julian, 2011). This battery contains multiple tests, which measure different cognitive domains and assesses for impairment. The Brief Repeatable Battery-Neuropsychological Tests (BRB-N; Rao,1990)) was created from the NSBMS with a few changes (Julian, 2011). The BRB-N is a widely used MS-specific screening battery, which measures cognitive functioning (Portaccio, 2008). This battery, which includes the SDMT, a fluency measure, the PASAT, and a measure of visual and verbal memory, may serve as an important stepping-stone for future growth and understanding in the development of MS screening tools (Rao, 1990). Dent and colleagues found that though the BRB-N provided good sensitivity but the battery's specificity in predicating impairment in MS has been poor (2000).

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) assesses for memory, attention, language, and visuospatial abilities and takes about 30 minutes to administer. Unfortunately, the RBANS does not assess for executive functioning so researchers such as Arnold (2002) have had to include other tests that do assess for that domain. In 2001, the Minimal Assessment of Cognitive Function in MS (MACFIMS) was developed by a group of psychologists and neuropsychologists who carefully selected an array of neuropsychological tests. This battery, though a reliable method for detecting impairment, takes 90 minutes to administer (Benedict, Cookfair, Gavett, et al., 2006), and is not considered a screening battery.

The Mini Mental State Examination (MMSE) is a brief cognitive screening measure (Folstein and Folstein, 1975) but has been found to have low sensitivity in detecting impairment in the MS population, with close to 70% false negatives (Portaccio, 2008). The MS Neuropsychological Screening Questionnaire (MSNQ) is a self-report questionnaire that measures perceived cognitive impairment (Benedict et al., 2008). This brief questionnaire has been found to correlate with actual cognitive impairment as well as with self-reported depression (Benedict et al., 2008). The Core Battery, proposed by Peyser et al. (1990), contains many cognitive tests to assess six different cognitive domains, including general knowledge, attention-concentration, memory, language, visuospatial functions, and abstract/conceptual reasoning. Although this battery is thorough, many of the tests are insensitive, poor for continued longitudinal study and can take more than 2 hours to administer (Beatty, 1999). Some of the batteries in current use are lengthy and time consuming, which limits everyday clinical use (Portaccio, Goretti, Zipoli, Siracusa, & Amato, 2009).

Research is ongoing to develop an optimal screening tool of neuropsychological tests that can detect cognitive decline in this population (Patti, 2009). Portaccio et al., (2009) found the PASAT-3 and the SDMT to be among the most sensitive brief measures to detect cognitive decline in individuals with MS. Researchers suggest that combining these measures into a brief screening assessment to detect cognitive decline and impairment in the MS population (Portaccio et al., 2009). Benedict et al. (2004) suggest that both the SDMT and the MSNQ are brief for clinical settings and would be useful in an MS screening battery.

Conclusion

Cognitive deficits in MS have been linked to lower quality of life (QoL), increased depression, and lower vocational capabilities (Rao, Leo, Ellington, Nauertz, Bernardin et al., 1991). MS onset most frequently occurs between the ages of 20 and 40 and many individuals experience job loss, resulting in as many as 80% of the MS population becoming unemployed within ten years of onset (Mitchell, 1981; Gronning, Hannsidal, & Mellgren 1990). The most common cognitive deficits in MS are seen in information processing and verbal memory, which have been posited as contributing factors to unemployment (Beatty, Blanco, Wilbanks, Paul, & Hames, 1995).

Although physical disability can also affect everyday living, it is important to consider an individual's cognitive load and deficits, as these are substantial factors in disability with MS (Chiaravalloti & DeLuca, 2008). Beatty (1999) explains that there are many factors to consider when developing a screening tool for MS. Some medical centers employ screening tools to identify those patients who will need more comprehensive testing; therefore, the importance of selecting the best tests for that purpose is imperative. As neuropsychological assessments can be lengthy, fatigue is a factor that can affect testing performance (Beatty, 1999).

Provided that there can be widespread, variable, and subtle cognitive decline in MS, a screening tool that can detect early dysfunction in multiple cognitive domains can aid in following cognitive decline longitudinally. Selecting measures for a brief screening tool that assess for the most common cognitive deficits in MS is imperative (Chiaravalloti & DeLuca, 2008). Research has encouraged the idea that therapeutic interventions for an array

of cognitive deficits are beneficial. Therefore, it is important to detect the cognitive impairments early to help mitigate cognitive decline (Krupp, Christodoulou, Melville, Scherl, MacAllister et al., 2004). Unfortunately, there are few brief, cost-effective, and validated screening batteries for individuals with Multiple Sclerosis (Portaccio et al., 2009).

Langdon and Thompson (1990) explain that cognitive assessment can bring about insight into the everyday life of a patient with MS, and if deficits are assessed early in the disease course, rehabilitation services can be implemented (Lincoln, Dent, Harding, Weyman, Nicholl et al., 2002). As fatigue is a well-known symptom of MS it is also important to identify cognitive fatigue, which can affect cognitive ability during testing (Krupp & Elkins, 2000). Many researchers are beginning to believe that a patient's perceptions of their cognitive abilities may relate more to comorbid symptoms of depression and fatigue rather than actual cognitive ability (Kinsinger et al., 2010). This study is aimed at determining which tests in a screening battery are most accurate at predicting cognitive impairment on a more comprehensive cognitive battery. Another aim is to explore the variability between self-reported cognitive functioning and objective test performance. This study will also examine whether depression, sleepiness and fatigue affect performance on testing and if so, which has the strongest effect.

CHAPTER THREE

Aims

Hypotheses

Overall Aim: To determine if a neuropsychological screening battery is sensitive enough to detect which individuals with Multiple Sclerosis need more comprehensive testing as well as investigating psychosocial factors that might influence test performance.

Aim 1: To determine which tests in a screening battery of neuropsychological measures can predict the presence of cognitive impairment as determined by a more comprehensive battery of cognitive tests in individuals with Multiple sclerosis.

Hypothesis 1: Measures of visuospatial abilities, motor speed and attention (i.e., SDMT, PASAT-3, and 9HPT) will predict cognitive impairment on a longer neuropsychological battery of cognitive tests as compared to the other tests on the screening battery (JoL and T25FW).

Aim 2: To determine if depressive symptoms are related more to self-reported cognitive deficits or objective cognitive deficits.

Hypothesis 2: Depressive symptoms will be more strongly correlated with self-reported cognitive deficits on the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) than objective cognitive test performance on the five measures on the screening battery.

Aim 3: To examine the relationship of depression, fatigue, and sleep, on cognitive performance.

Hypothesis 3: Depression, as measured by the Quick Inventory of Depressive Symptomatology - Self Report, will negatively affect performance on all cognitive measures.

Hypothesis 4: Fatigue, as measured by the Modified Fatigue Impact Scale, will negatively affect cognitive test performance on tasks that involve information processing speed and attention.

Hypothesis 5: Sleep, as measured by the Epworth Sleepiness Scale, will negatively affect cognitive test performance on tasks that involve information processing speed and attention.

CHAPTER FOUR

Method

Study Overview

Study Purpose. Data for this study were collected as part of the parent study, the Cognition and Demyelinating Disease Project, a broader non-randomized longitudinal cohort study at The University of Texas Southwestern Medical Center at Dallas in the Multiple Sclerosis Clinical Center (UTSW MS Clinic) and Multiple Sclerosis Program. The current investigation used data collected from the parent study to explore the prospective use of an abbreviated screening battery to identify patients with clinically significant cognitive impairment. A secondary aim was to examine the relationship between cognitive dysfunction in MS patients and other disease characteristics (e.g., depression, fatigue and sleepiness).

Participants. The Cognition and Demyelinating Disease project includes both newly diagnosed and follow-up patients with a Demyelinating disease who have been referred to the UTSW MS Clinic. The following inclusion criteria were met by all of the participants in the Cognition and Demyelinating Disease study:

1. Clinically confirmed diagnosis of MS according to the McDonald criteria or, a clinically isolated syndrome (CIS)
2. Age 18 years or older, including both men and women
3. Able to provide informed consent

Exclusion criteria were:

1. Use of corticosteroids at time of testing,
2. History of comorbid neurological disease

3. An inability to speak, read or understand English

The present study had one additional inclusion: ability to return to UTSW campus for follow-up testing within one month; and one exclusion criteria: less than 1-month post most recent exacerbation. The current study examined the first 120 consecutive participants from the Cognition and Demyelinating project.

Procedures. Subjects enrolled in the Cognition and Demyelinating Disease study attend an initial visit at the UTSW MS Clinic and a follow-up visit at the UTSW Neuropsychology Clinic. At the participant's initial screening visit, the study coordinator gathered medical history, demographics, and concomitant medications. Participants were expected to complete the screening battery at this initial visit. If the participant was unable to remain that day, another visit was scheduled. The screening battery is a brief 30-minute battery of neuropsychological and physical assessments administered by the study coordinator. The participants also completed four self-report questionnaires of mood, cognitive complaints, fatigue, and sleep.

Participants were then scheduled for a more comprehensive cognitive battery at the UTSW Neuropsychology Clinic within four weeks of the initial visit. For the present study, data acquired from the initial visits at the UTSW MS and UTSW Neuropsychology Clinics were utilized.

Measures. Test descriptions and psychometric variables are described in detail in Appendix B.

A. Test Batteries

   a. Screening Battery (MS Clinic)

      i. Benton Judgment of Line Orientation – Form H (JoL)

ii. 9-Hole Peg Test (9HPT)

iii. Paced Auditory Serial Addition Test-3 –Form A (PASAT-3)

iv. Oral Symbol Digit Modalities Test (SDMT)

v. Timed 25-Foot Walk (T25FW)

b. Longer Cognitive Battery (Neuropsychology Clinic)

i. Wide Range Achievement Test-4th Edition (WRAT-4)

ii. Verbal Fluency (FAS and Animals)

iii. Brief Visuopsatial Memory Test –Revised (BVMRT-R)

iv. California Verbal Learning Test – 2nd Edition Standard Form (CVLT-II)

v. Stroop Color and Word Test

vi. Texas Card Sorting Test

B. Self-Report Measures (MS Clinic)

a. Modified Fatigue Impact Scale (MFIS)

b. Epworth Sleepiness Scale (ESS)

c. The Quick Inventory of Depressive Symptomatology 16-Item Self Report (QIDS-SR 16)

d. MS Neuropsychological Screening Questionnaire (MSNQ)

Data Analyses. Descriptive Statistics were used to describe demographic characteristics for and included frequencies and percentages for categorical variables, means and standard deviations for normally distributed, continuous measures, and medians and range (low-high) for continuous, non-normally distributed measures. Student's independent sample t-tests or Mann-Whitney U test were used to compare test performance for the Impaired and Non-Impaired

groups on the screening battery. A one-way Analysis of Covariance (ANCOVA) for each measure in the screening battery was performed with one between subjects factor (Impaired vs. Non-Impaired) and depression as a covariate. All of the statistical analyses were performed with the Statistical Package for the Social Sciences (IBM SPSS, V.20).

Aim 1. The first hypothesis was to determine if a screening battery can predict impairment on a longer cognitive battery, and if so, which tests were the best predictors. Subjects were be divided into two groups, Impaired and Non-Impaired groups. Impairment was defined as a T-score at or below 35 (1.5 standard deviations from the mean) on two or more measures on the longer cognitive battery. The following tests and subscales on the longer cognitive battery were used to determine impairment: Stroop Color-Word T-score, CVLT-II Total Learning T-score, CVLT-II Long Delay Free Recall z-score, CVLT-II Disciminability z-score, BVMT-R Total Learning T-score, BVMT-R Delayed Recall T-Score, TCST Total Logical Sorts, FAS Total T-score, and Category Fluency Total T-score. The screening battery consisted of the: JoL Raw Score, 9HPT time, PASAT-3 T-score, SDMT Oral T-scores, and the Timed 25 Ft Walk completion time of Trial 1. Logistic Regression was conducted to determine which of the screening battery measures predicted impairment.

Aim 2. To determine if depression correlates more strongly with perceived cognitive performance versus objective cognitive performance, pairs of Pearson Product Moment Correlations were compared: the correlation of QIDS-SR and MSNQ (perceived cognitive performance) was compared to the correlation of the QIDS-SR and each measure on the screening battery (objective cognitive performance). A T-test was used to determine which pair of correlations had significantly different associations.

Aim 3. The relationship of depression, fatigue and sleep on test performance was analyzed. The subjects were divided into two groups for each measure based on cutoff scores from the literature. The Depressed and Non-Depressed groups were identified using a QIDS-SR score of <6 for the Non-Depressed group and ≥6 Depressed group. The Fatigue groups were classified by scores of <38 on the Modified Fatigue Impact Scale (MFIS) for the Slightly Fatigued group and ≥38 for the Highly Fatigued group. The Epworth Sleepiness Scale (ESS) total score was used to classify participants into Non-Sleepy <10 and Sleepy ≥10 groups. T-Tests were conducted to examine the differences between MS patients in terms of high versus low depressive symptoms, fatigue, or sleepiness scores and cognitive test performance on the screening battery.

CHAPTER FIVE

Results

Sample Characteristics

A total of 120 subjects met the criteria for the Cognition and Demyelinating Disease project and completed baseline testing. Of these, 19 subjects were excluded from the current study because they did not return for the follow-up cognitive visit and 7 were not included due to exacerbation of their MS within a month's time of testing, leaving a sample of 94. The final sample of 94 subjects had mean age of 45.0 (SD = 11.1) and a mean education level of 15.4 (SD = 2.1).

Subjects were divided into Impaired and Non-Impaired groups. Impairment was defined as a T-score at or below 35 (1.5 standard deviations from the mean) on two or more measures on the longer cognitive battery. Sixty-six participants fell in the Non-Impaired group and 28 were in the Impaired group; four additional cases were missing one or more tests from the screening battery, but were included in analyses for Aim 1. The sample was primarily Caucasian and female, ranging in age from 20 to 75, with similar mean ages for the Non-Impaired and Impaired groups (See Table 1).

Subjects in the Impaired group were found to have significantly lower mean scores on the Stroop C-W, CVLT-II, and BVMT-R tests in the longer cognitive battery compared to those in the Non-Impaired group (See Table 2).

Overall Aim. The primary aim of the present study was to investigate the utility of a screening battery to predict impairment on a more comprehensive neuropsychological battery and to determine which test or tests were best predictive of impairment. As stated above,

participants were divided into Impaired and Non-Impaired groups based on the long battery performance. First, t-tests were used to compare test performance of the two groups on each of the five screening battery tests: Judgment of Line Orientation (JoL), 9 Hole Peg Test (9HPT), Paced Auditory Serial Addition Test (PASAT), Oral Symbol Digit Modality Test (SDMT), and Timed 25-Foot Walk (T25FW). The assumptions of the t-test were reviewed (normality and equal variances) and were reasonably met by all measures except the equal variance assumption for the 9HPT (p = .005) and the PASAT (p = .007); for these two measures a t-test using a non-pooled variance estimate was performed. The Non-Impaired group performed significantly better than the Impaired group on the JoL (p = .001), 9HPT (p = .008), PASAT (p = .001) and the SDMT (p <.001). The Non-Impaired group was slightly faster in completing the T25FW but this was not significant (See Table 3).

Aim 1. Logistic regression was used to identify which of the five tests from the screening battery best predicted impairment on the long battery. Using a forward stepwise logistic regression analysis (Hosmer-Lemeshow p = .702), the PASAT (p = .001, OR .940; 95% CI 0.907 – 0.973) was the only measure that predicted impairment. A ROC analysis was used to determine the best cut score for defining impairment on the PASAT. The area under the curve (AUC) for the PASAT was .758 (p = <.001, 95% CI .644 - .871). Using a cut score of T ≤38 on the PASAT provided sensitivity = .615 and specificity = .818, with 76% of the sample correctly classified as Impaired versus Non-Impaired.

Aim 2. Pairs of Pearson Correlations Coefficient were compared to determine if depressive symptoms were more strongly associated with perceived cognitive functioning (MSNQ) versus objective test performance (on the screening battery). The total scores for JoL,

9HPT, and T25FW were reverse scored to make the direction the same for all variables (higher scores indicating better performance). The MSNQ was significantly correlated with depressive symptoms on the QIDS-SR (r = .57; p <.001). The QIDS-SR was modestly correlated with the five screening battery tests ranging from -.17 to .25 (See Table 4). Comparing the correlation of the QIDS-SR with MSNQ to the QIDS-SR with each of the five screening measures resulted in significantly different associations. The correlation of the QIDS-SR with MSNQ was significantly higher in all comparisons.

Cognitive Impairment and Psychosocial Factors. Depression, daytime sleepiness, and fatigue were analyzed to determine if the variables influenced cognitive test performance on the screening battery. With respect to depression, subjects were categorized into the depressed group if their score met QIDS-SR criteria for Depression ≥6 or the Non-Depressed group if their QIDS-SR score was 5 or below. T-tests were used to examine differences between the depressed (N = 64) and non-depressed (N = 30) groups on cognitive test performances. Results showed significant mean differences between the Depressed and Non-Depressed groups for JoL (p = .003), PASAT (p = .015), and SDMT (p = .023; See Table 5).

The relationship of daytime sleepiness on test performance on the screening battery was investigated using t-tests. The Epworth Sleepiness Scale (ESS) scores were used to defined group membership; subjects were placed in the Sleepy group if their score fell at or above 10 (met ESS criteria for daytime sleepiness), or the Non-Sleepy group if their score was 9 or below. There were no significant mean differences on any measures in the screening battery between the Sleepy (N = 39) and Non-Sleepy (N = 54) groups (See Table 6).

The relationship of fatigue on test performance on the screening battery was explored using t-tests. Scores on the Modified Fatigue Impact Scale (MFIS) were used to defined group membership. Subjects were placed in the Highly Fatigued group if their score fell at or above 38 (met criteria for fatigue on the MFIS), or the Slightly Fatigued group if their score was 37 or below. Results showed significant mean differences for all the screening battery measures between the Highly Fatigued (N = 36) and Slightly Fatigued groups (N = 56; See Table 7).

CHAPTER SIX

Discussion

Findings and Implications

Identifying Cognitive Impairment

The current study analyzed cognitive performance in individuals with MS on a brief test battery to determine the measures that best identified cognitive impairment on a longer battery of tests to help identify the tests that could be used for cognitive screening purposes.

The first hypothesis was supported, in that one measure on the screening battery (PASAT) was predictive of cognitive impairment on the comprehensive battery. Using a T-score cut score of 38 on the PASAT, 76% of subjects were correctly classified. This suggests that impairment in working memory and attention is a strong indicator of more generalized cognitive impairment that may warrant further assessment. Deloire and colleagues (2006) suggested that the PASAT, along with the SDMT, should be used as screening tools for individuals with MS who are experiencing cognitive impairment, supporting the present findings.

Depression and Subjective Versus Objective Cognitive Impairment. It was hypothesized that depression would correlate more highly with perceived cognitive functioning (MSNQ) than objective cognitive performance (screening battery scores). Pearson Rank Order Correlations showed that depression scores correlated more strongly with perceived cognitive performance (MSNQ) than any of the other variables, supporting the hypothesis. Depressive symptoms were correlated with tests measuring aspects of attention, information-processing speed, motor dexterity, and working memory. This suggests there is a relationship between depression and perceived cognitive functioning, and that persons with MS and Depression might

notice negative changes in their cognitive functioning more highly than those without Depression.

Psychosocial Factors and Cognitive Impairment. It was hypothesized that depression would affect all areas of cognitive functioning (i.e. working memory, information-processing speed, visuospatial abilities and attention) and physical functioning (motor dexterity and gait). Arnett and colleagues (1999) found that subjects with MS who were identified as depressed performed significantly lower on tasks that involved working memory than those who were not depressed. Current results showed that those who endorsed more depressive symptoms performed lower on tests of visuospatial ability (JoL), working memory (PASAT) and divided attention (SDMT). The hypothesis was supported in that three of the five measures were influenced by depressive symptoms. This suggests impairment in working memory, visuospatial ability, and attention can be impacted by depressive symptoms in subjects with MS.

It was hypothesized that fatigue would negatively affect cognitive test performance on tasks that involve information processing speed, working memory, and attention. Shaprio (2002) and Patten (2005) explain that fatigue is a very common symptom in MS, as about 90% of individuals with MS report experiencing fatigue. Not surprisingly, the current results showed that level of fatigue was associated more with cognitive performance, as significant mean differences were found on all screening battery measures between the Highly Fatigued and Slightly Fatigued groups. This means that fatigue affected subject's performances on all 5 screening battery measures and the hypothesis was supported. Fatigue may be a factor impacting impairment and an important variable to assess in terms of identification of risk for cognitive impairment.

Current research on sleep and MS revolves around amount of daytime sleepiness and sleep disorders. There is little research examining the effect of sleepiness on cognition in MS. In the present study, sleepiness was hypothesized to negatively affect cognitive test performance on tasks that involve information processing speed, working memory, and attention. Interestingly, it was found that daytime sleepiness did not affect test performance. Therefore, the hypothesis was not supported. These are important findings because this shows that the amount of daytime sleepiness may not affect performance but that the amount of fatigue a subject experiences can influence test performance. This also implies that fatigue is not simply sleepiness, per se, but it is a different factor all together.

Influence of Depression on Test Performance. To determine if the presence of depression influenced impairment on the long cognitive battery, a one-way Analysis of Covariance (ANCOVA) was performed using depression as a covariate. The between groups factor was impairment on the long cognitive battery. The QIDS-SR was used to assess the number of depressive symptoms that the subject endorsed and was used to adjust for the influence of depression when using the screening battery measures to predict impairment. A total of 64 of all subjects met QIDS-SR criteria for depression (cutoff of ≥6), with more of the Impaired (82%) than Non-Impaired group (62%) falling above the cutoff. The QIDS-SR was found to be a significant covariate in JoL (p = .012), 9HPT (p = .006), PASAT (p = <.001) and SDMT (p = .001) performance in both groups, but did not account for all the differences between the Impaired and Non-Imapired groups. The QIDS-SR was not a covariate for T25FW. Demaree and collueages (2003) found that subjects with MS who were identified as “highly depressed” demonstrated impairment on the PASAT. Therefore, the results of the present study support the

idea that depressive symptoms do affect test performance within certain cognitive domains (i.e. working memory and information-processing speed) but do not account for all cognitive differences between the groups.

Results of the current study show that depressive symptoms and fatigue may contribute to some of the cognitive differences that can be seen in MS and there is a fair amount of overlap in the two conditions. A series of Pearson Chi-Square analyses were used to examine frequency of overlap with the psychosocial variables. Results showed that elevated QIDS-SR and MFIS levels of those who met criteria for depression on the QIDS-SR, 85.7% also met MFIS criteria for significant fatigue ($p<.001$). The overlap between the QIDS-SR and ESS was also significant ($p=.006$), in that of those who endorsed significantly elevated depressive symptoms often met ESS criteria for daytime sleepiness (82.4%). In addition, of those who met MFIS criteria for fatigue, 78.9% also met criteria for daytime sleepiness ($p<.002$). These results suggest that these factors are often not independent of each other. This means that the factors often overlap and may synergistically negatively affect cognitive impairment.

Limitations. When interpreting the results of this investigation, some considerations should be taken into account. Impairment was identified as low scores on two or more measures from the longer cognitive battery. Some of the variables used were from the same measures, resulting in six subjects classified as impaired in which impairment was based on only one measure. This raises an issue as to how best to classify impairment for group classification and is an area worth further study. On the longer cognitive battery, subjects were found to be most impaired on the BVMT-R Total T-score (21.3%) and CVLT-II LDFS Z-score at (21.3%; See Figure 1).

Impairment was defined as a T-score at or below 35 (1.5 standard deviations from the mean) on two or more measures from the longer cognitive battery. A total of 45 subjects were found to not be impaired on any of the cognitive measures in the longer cognitive battery, and 21 only impaired on one measure. As such, this was a sample with minimal cognitive impairment, necessitating a more liberal approach to defining impairment (See Figure 2).

Sample size in this study was relatively small. In order to better understand the differences between Impaired and Non-Impaired groups it would have benefited the current study to have recruited a higher number of subjects in order to split the sample into groups with a similar N. An N of 28 for an Impaired group proves difficult to relate the outcomes to a larger impaired MS sample. The current study's sample consisted of a predominantly female (86.2%) and Caucasian (85.1%) sample. Although this sample is not very diverse these characteristics are representative of the demographics of those diagnosed with MS.

Another limitation to the study was the lack of a control group, which would have been particularly interesting in examining the relationship of the psychosocial factors to test performance. Factors such as stress and anxiety were not examined in this study, but are also of interest in MS and are areas for future study.

Conclusions. Complex attention and working memory impairment were predictive of cognitive impairment on a longer cognitive battery, supporting the use of the PASAT as screening measure for impairment (T =< 38). Depression and fatigue significantly impacted test performance and are often comorbid in this sample. Depressive symptoms were found to have an effect of test performance involving working memory, processing speed and motor speed and visuospatial ability. Fatigue was found to influence test performance across all cognitive

domains such as working memory, visuospatial ability, motor speed and dexterity, processing speed, and attention. Interestingly, daytime sleepiness did not influence test performance. In conclusion, individuals with MS who report symptoms of fatigue and depression might be at risk for cognitive impairment and further testing is recommended.

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Table 1

Demographic Characteristics of Non-Impaired Versus Impaired Groups

	Non-Impaired (N=66)	Impaired (N=28)	Total Subjects (N=94)
Age			
Mean (SD)	44.76 (11.40)	45.71 (10.43)	45.04 (11.08)
Range	20 - 75	21 - 63	20 - 75
Gender, N (%)			
Female	58 (87.9)	23 (82.1)	81 (86.2)
Male	8 (12.1)	5 (17.9)	13 (13.8)
Race/Ethnicity, N (%)			
Caucasian	59 (89.4)	21 (75.0)	80 (85.1)
African American	2 (3.0)	5 (17.9)	7 (7.4)
Hispanic	3 (4.5)	2 (7.1)	5 (5.4)
Asian	2 (3.0)	0	2 (2.1)
Education Years			
Mean (SD)	15.89 (1.84)	14.25 (2.34)	15.40 (2.13)
Range	12 - 20	8 – 18	8 - 20
Handedness, N (%)			
Right	64 (97.0)	25 (89.3)	89 (94.7)
Left	2 (3.0)	2 (7.1)	4 (4.3)
Ambidextrous	0	1 (3.6)	1 (1.1)

Table 2

Long Battery Performances for Non-Impaired Versus Impaired Subjects

	Non-impaired			Impaired			Independent Samples t-test		
Measures	N	Mean	SD	N	Mean	SD	t	df	*p* value
Strp CW T	65	50.28	7.81	28	46.18	7.32	2.37	91	0.020
TCTS LS	66	6.15	1.11	28	5.50	1.71	1.86	37.07	0.071
FAS T	66	45.97	8.50	28	41.21	12.40	1.85	38.20	0.072
Category T	66	47.94	7.75	28	38.36	11.03	4.18	38.78	<0.001
BVMT-R Tot T	66	50.29	8.75	28	33.07	12.10	6.81	39.52	<0.001
BVMT-R Delay T	66	52.33	8.26	28	32.68	12.89	7.44	36.77	<0.001
CVLT-II Tot T	66	54.15	9.31	28	41.00	10.26	6.08	92	<0.001
CVLT-II LDFR Z	66	.33	.96	28	-1.57	1.38	6.65	38.62	<0.001
CVLT-II D Z	66	.34	.84	28	-.91	1.22	4.96	38.28	<0.001

Strp CW T: Stroop Color and Word T-scores corrected for age and education; TCST LS: Texas Card Sorting Test Logical Sorts; FAS T: Word Fluency Test T-scores; Category T: Animal Category Fluency Test T-scores; BVMT-R Tot T: Brief Visual Memory Test Total T-scores; BVMT-R Delay T: Brief Visual Memory Test Delay T-scores; CVLT-II Tot T: California Verbal Learning Test-II Total T-score; CVLT-II LDFR Z: California Verbal Learning Test-II Long Delay Free Recall Z-score; and CVLT-II D Z: California Verbal Learning Test-II Discriminability Z-scores. The Degrees of Freedom (df) for all tests except the Strp CW T and the CVLT-II Total T are adjusted for non-pooled variance estimates

Table 3

Screening Battery Performances for Non-Impaired Versus Impaired Subjects

	Non-impaired			Impaired			Independent Samples t-test		
Measures	N	Mean	SD	N	Mean	SD	t	df	*p* value
JoL Raw	66	28.50	2.64	27	26.30	3.01	3.51	91	0.001
9HPT Sec	66	21.93	5.44	28	27.13	9.17	-2.80	35.34	0.008
PASAT T	66	46.36	11.78	26	32.74	17.63	3.63	34.16	0.001
SDMT Oral T	66	53.39	13.84	28	40.71	14.72	3.99	92	<0.001
T25FTW Sec	66	5.93	6.37	26	6.88	4.32	-0.70	90	0.487

JoL Raw: Judgment of Line Orientation raw scores corrected for age and education; 9HPT Sec: 9 Hole Peg Test time in seconds; PASAT T: Paced Auditory Serial Addition Test T-score; SDMT Oral T: Symbol Digit Modality Test Oral section T-score; and T25FTW Sec: Timed 25-Foot Walk Test time in seconds. The Degrees of Freedom (df) for 9HPT and PASAT are adjusted for non-pooled variance estimates

Table 4

Correlation of Depressive Symptoms with Objective Cognitive Performance Across Entire Sample

	Screening Battery and QIDS-SR			QIDS-SR and MSNQ		t-test comparing correlations		
Measures	N	r value	*p* value	r value	*p* value	t	df	*p* value
JoL Raw	84	-.225	0.040	0.572	<0.001	3.17	81	0.002
9HPT Sec	84	.250	0.048	0.571	<0.001	-2.81	81	0.002
PASAT T	82	-.227	0.041	0.573	<0.001	-3.32	79	0.001
SDMT Oral T	84	-.177	0.108	0.571	<0.001	-3.62	81	0.005
T25FTW Sec	82	.065	0.562	0.566	<0.001	-4.07	79	0.001

JoL Raw: Judgment of Line Orientation raw scores corrected for age and education, 9HPT Sec: 9 Hole Peg Test time in seconds, PASAT T: Paced Auditory Serial Addition Test T-score, SDMT Oral T: Symbol Digit Modality Test Oral section T-score, and T25FTW Sec: Timed 25-Foot Walk Test time in seconds. Jol, PASAT and SDMT were reverse scored to orient these tests in the same direction as the other measures. T-test was used to compare the correlation of the QIDS-SR and a screening battery measure with QIDS-SR and MSNQ. The QIDS-SR and MSNQ correlations vary slightly; Ns are not equal for each screening battery test

Table 5

Differences in Screening Battery Performance in Non-Depressed Versus Depressed Subjects

	Non-Depressed [QIDS-SR M = 3.61 (1.20)]			Depressed [QIDS-SR M = 10.24 (3.69)]			Independent Samples t-test		
Measures	N	Mean	SD	N	Mean	SD	t	df	*p* value
JoL Raw	30	28.93	1.74	63	27.35	3.21	3.07	89.42	0.003
9HPT Sec	30	22.05	7.52	64	24.14	6.89	-1.32	92	0.187
PASAT T	30	47.92	12.20	62	39.90	15.48	2.48	90	0.015
SDMT Oral T	30	54.77	13.49	64	47.19	15.43	2.30	92	0.023
T25FTW Sec	30	6.65	9.34	62	5.98	3.07	0.51	90	0.610

JoL Raw: Judgment of Line Orientation raw scores corrected for age and education, 9HPT Sec; 9 Hole Peg Test time in seconds; PASAT T: Paced Auditory Serial Addition Test T-score; SDMT Oral T: Symbol Digit Modality Test Oral section T-score; and T25FTW Sec: Timed 25-Foot Walk Test time in seconds. The Degrees of Freedom (df) for the JoL are adjusted for non-pooled variance estimates

Table 6

Differences in Screening Battery Performance in Non-Sleepy Versus Sleepy Subjects

	Non-Sleepy [ESS M = 5.43 (2.28)]			Sleepy [ESS M = 14.49 (3.46)]			Independent Samples t-test		
Measures	N	Mean	SD	N	Mean	SD	t	df	*p* value
JoL Raw	54	28.31	2.61	38	27.16	3.23	1.83	68.80	0.072
9HPT Sec	54	22.59	6.52	39	24.67	7.90	-1.39	91	0.168
PASAT T	53	43.14	13.89	38	41.26	16.38	0.59	89	0.557
SDMT Oral T	54	50.71	15.27	39	48.02	15.34	0.84	91	0.404
T25FTW Sec	53	6.51	7.16	38	5.79	3.46	0.58	89	0.565

JoL Raw: Judgment of Line Orientation raw scores corrected for age and education; 9HPT Sec: 9 Hole Peg Test time in seconds; PASAT T: Paced Auditory Serial Addition Test T-score; SDMT Oral T: Symbol Digit Modality Test Oral section T-score; and T25FTW Sec: Timed 25-Foot Walk Test time in seconds. The Degrees of Freedom (df) for the JoL are adjusted for non-pooled variance estimates

Table 7

Differences in Screening Battery Performance in Slightly Fatigued Versus Highly Fatigued Subjects

	Slightly Fatigued [MFIS M = 24.06 (9.97)]			Highly Fatigued [MFIS M = 54.16 (10.97)]			Independent Samples t-test		
Measures	N	Mean	SD	N	Mean	SD	t	df	*p* value
JoL Raw	36	28.86	2.23	55	27.29	3.15	2.78	88.41	0.007
9HPT Sec	36	20.85	3.94	56	24.95	8.22	-2.79	90	0.006
PASAT T	36	47.77	8.96	55	39.85	16.24	2.99	86.91	0.004
SDMT Oral T	36	54.01	14.25	56	47.39	15.18	2.09	90	0.039
T25FTW Sec	36	4.69	1.30	56	7.17	7.29	-2.49	60.32	0.016

JoL Raw: Judgment of Line Orientation raw scores corrected for age and education; 9HPT Sec: 9 Hole Peg Test time in seconds; PASAT T: Paced Auditory Serial Addition Test T-scores; SDMT Oral T: Symbol Digit Modality Test Oral section T-scores; and T25FTW Sec: Timed 25-Foot Walk Test time in seconds. The Degrees of Freedom (df) are adjusted for non-pooled variance estimates

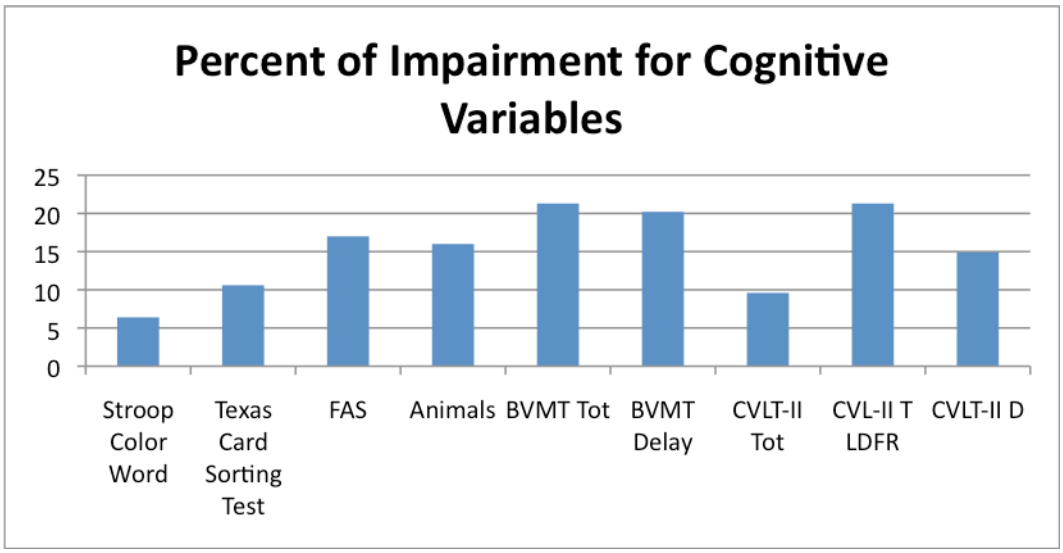

Figure 1. Percent of Patients Impaired for Cognitive Variables on the Longer Cognitive Battery.

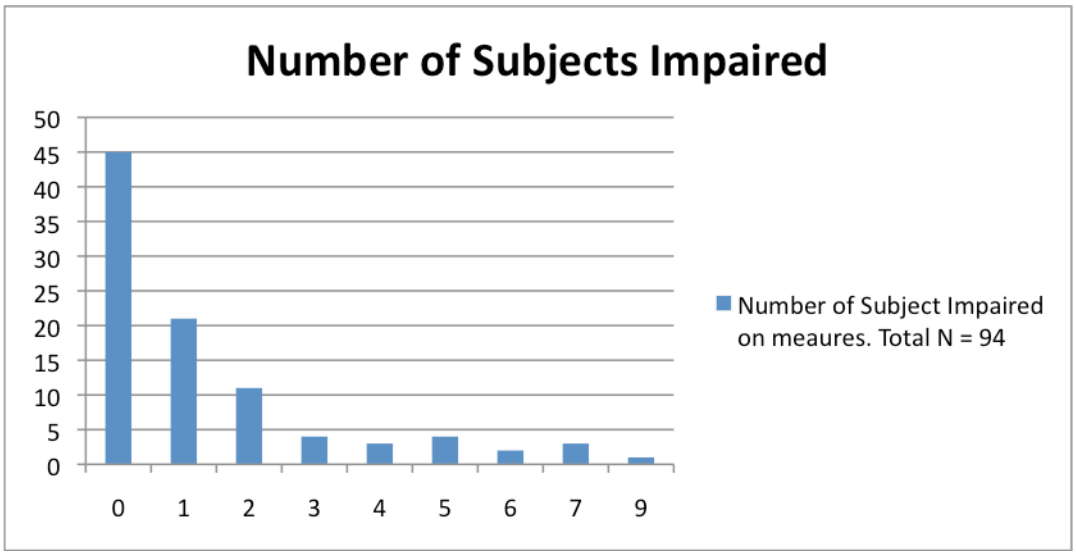

Figure 2. Frequency of Impairment by Number of Tests Impaired on the Longer Cognitive Battery.

Appendix A

Diagnostic Criteria for MS: The 2010 Revised McDonald Criteria for Diagnosis of Multiple Sclerosis

Clinical Presentation	**Additional Data Needed for MS Diagnosis**
2 attacks; objective clinical evidence of 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack.	None
2 attacks; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: MRI or 2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord; or Await a further clinical attack implicating a different CNS site
1 attack; objective clinical evidence of 2 lesions	Dissemination in time, demonstrated by: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack
1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: 2 or more lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)d; or Await a second clinical attack implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or Await a second clinical attack
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria: 1. Evidence for DIS in the brain based on 1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on 2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

(Polman et al., 2011)

Appendix B

Description of Tests and Questionnaires

Benton Judgment of Line Orientation – Form H (JLO)

The JoL (Benton, Hannay, & Varney, 1975) is a brief standardized measure of visuospatial ability in individuals with a brain injury. Participants are asked to look at different lines and to find the exact same lines on different sheet of paper. The scores are derived from the total number of correct answers throughout the 30 trials, then T-scores are computed with the use of the test manual.

9-Hole Peg Test (9HPT)

The 9HPT (Mathiowetz et al., 1985) is a brief timed assessment of dexterity and coordination, and motor speed. There are four trials for each hand. Two mean times are derived from the trials per hand.

Paced Auditory Serial Addition Test-3 –Form A (PASAT-3)

The PASAT-3 (Gronwall, 1977) measures an individuals divided attention, working memory, mental flexibility and auditory information processing speed. The PASAT-3 is offered on either a compact disk or audiocassette tape, which helps control the pace of the number presented in the test. Single digit numbers are said to the participant every 3-second, then the participant is to add the each digit with the digit that is presented right after. A T-score is derived from the number of correct summations and errors.

Symbol Digit Modalities Test (SDMT)

The SDMT (Smith, 1982) is a measure of visual scanning and tracking, divided attention, and motor speed. This is a timed test and requires participants to correctly match symbols with

numbers, both orally and written. The participant is offered a key at the top of the page for reference of which symbols match the numbers. A T-score is derived from the number of correct answers by using normative standardized data based the participant's age and education level.

Timed 25-Foot Walk (T25FW)

The T25FW is an assessment of mobility and walking ability, which was adapted from the Multiple Sclerosis Functional Composite (Cutter, 1999). Mean time is used as a basis for impairment in walking and gait speed.

Brief Visuopsatial Memory Test –Revised (BVMRT-R)

The BVMT-R (Benedict, 1997) is a measure of visual memory, using both immediate recall and delayed recall. There is a recognition aspect to this measure, though it was not used in the present study. Raw scores are computed into T-scores based on age-adjusted norms.

Controlled Oral Word Association Letter Fluency (COWAT - FAS)

The COWAT Letter Test measures fluency of verbal associations. Participants are to generate as many words as they can, in a 1-minute time limit, that begin with a specific letter (i.e. "F", "A", "S"). A T-score is derived from the total number of correct words provided.

Category Fluency Test (Animals)

The Category Fluency Test measures semantic fluency, which is the ability to create groups of words related to the category provided (i.e. animals) (Estes, 1974). The category of animals was selected because of its use in other MS studies (Beatty et al., 1998; Beatty, Goodkin, Monson et al., 1989). A T-score is derived from the total number of correct words provided in the 1-minute time limit.

California Verbal Learning Test – 2nd Edition Standard Form (CVLT-II)

The CVLT-II (Delis et al., 2000) is a measure of verbal learning and memory. The test consists of a 16-word list of 4 semantic categories, presented to the participant with 5 initial trials and then a second 16-word list is presented. Free recall and cued recall trials are administered immediately after the second list is presented and also after a 20 minute delay. Lastly, delayed recognition is administered to determine if the participant can correctly identify the words from the first list. A computer scoring program is used derive raw and standardized scores providing T-scores and Z-scores.

Stroop Color and Word Test

The Stroop Test (Golden, 1978) is a measure of cognitive flexibility, divided and selective attention, and processing speed of information (Lezak, 1995; Spreen & Strauss, 1991). The Stroop color and word T-score is derived from the total number of correctly read words subtracted by the predicated score for the individual's age and education level.

Texas Card Sort Test

The TCST is a measure of executive functioning. Participants are presented with 6 cards, the cards are different but all have some kind of common factor. The participant is required to create as many 2 groups of 3 matching cards as they can within a 3-minute time limit. A raw score is found based on the number of logical sorts.

Modified Fatigue Impact Scale (MFIS)

The MFIS (US NMSS) is a relatively short questionnaire (21-items) and was developed from the 40-item Fatigue Impact Scale. The MFIS is thought of as a multidimensional questionnaire because the questions assess for different aspects of fatigue (i.e. cognitive, physical and psychosocial). The participant is to rate (from 0 to 4) the level of each fatigue question as to how

they feel in everyday life. A total raw score is derived from the amount of endorsed items, with a maximum score of 84.

Epworth Sleepiness Scale (ESS)

The ESS (Johns, 1991) is a brief questionnaire assessing daytime sleepiness. The participant is asked to rate (from 0 to 3) 8 different scenarios based on their level of sleepiness or possibility of falling asleep during the day. A total score is found by adding the amount of endorsed items, with a range from 0 to 24.

The Quick Inventory of Depressive Symptomatology 16-Item Self Report (QIDS-SR 16)

The QIDS-SR 16 (Rush et al, 2003) is a brief 16-item questionnaire, which assess for the 9 depressive symptom domains in the DSM-IV (i.e. energy, suicidal ideation, self-outlook, depressed mood, sleep, loss of interest, appetite change, and troubles with decision making). The participant is instructed to read each item and rate (0 to 3) their level of depressive symptoms. A raw score is then found based on all endorsed items on the questionnaire with scores ranging from 0 to 27.

MS Neuropsychological Screening Questionnaire (MSNQ)

The MSNQ (Benedict, 2004) is a self-administered questionnaire aimed at identifying neuropsychological impairment specifically for individuals with Multiple Sclerosis. This questionnaire has two forms, one is the patient form for the individual with MS and the other is for an informant or caregiver. Patients are asked to rate, from 0 to 4, how often they have different cognitive impairments (i.e. forgetfulness, distractibility). A raw score is derived from the total of endorsed items on the questionnaire, with a range from 0 to 60. The patient form is used for the present study.

BIOGRAPHICAL SKETCH

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EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Texas Woman's University	B.A.	2009	Psychology
The University of Texas Southwestern School of Health Professions	M.R.C.	2013	Rehabilitation Counseling Psychology

Positions and Employment

2012-2013 Center for Neuropsychological Enhancement Psychometrist
2009-2010 Sports Solutions, Inc Administrative and Accounting Assistant
2005-2009 Texas Woman's University Family Housing Assistant
2000-2004, 2007 D Magazine People Newspapers Accounting Assistant

Clinical Experience

2012 Supported Employment Intern
2011-2012 Rehabilitation Counseling Intern
2011-2012 Neuropsychology Services Psychometrist Intern

Professional Memberships

2011-2013 The National Rehabilitation Association
2008-2009 Psi Chi