PREDICTORS OF QUALITY OF LIFE IN MULTIPLE SCLEROSIS:

RELATIONSHIPS BETWEEN COGNITIVE, PHYSICAL, AND SUBJECTIVE

MEASURES OF DISEASE BURDEN

APPROVED BY SUPERVISORY COMMITTEE

_____

Laura H. Lacritz, Ph.D., ABPP-CN (Chair)

_____

Benjamin Greenberg, M.D., MHSc

_____

C. Munro Cullum, Ph.D., ABPP-CN

_____

Lana Harder, Ph.D., ABPP-CN

_____

Linda Hynan, Ph.D.

PREDICTORS OF QUALITY OF LIFE IN MULTIPLE SCLEROSIS: RELATIONSHIPS BETWEEN COGNITIVE, PHYSICAL, AND SUBJECTIVE MEASURES OF DISEASE BURDEN

by

KYLE RICHARD NOLL

DISSERTATION

Presented to the Faculty of the Graduate School of Biomedical Sciences

The University of Texas Southwestern Medical Center at Dallas

In Partial Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

The University of Texas Southwestern Medical Center at Dallas

Dallas, Texas

August, 2011

ACKNOWLEDGEMENTS

I am indebted to many individuals whose unique contributions made this work possible. My utmost appreciation is to my mentor, Dr. Laura Lacritz. Through her direction and selfless dedication to teaching, I have gained invaluable experience and knowledge, but more importantly, the inspiration to better myself professionally and personally. I am tremendously fortunate to have her as a paragon of the scientist and clinician that I aspire to become. I extend my deepest gratitude to Dr. Benjamin Greenberg, who established the Cognition and Demyelinating Disease project at the UTSW MS Clinic and was fundamental in the shaping of this study. He never failed to answer my myriad questions with expert knowledge, and his generous support of my training did not go unrecognized. I am expressly grateful for the time and counsel of Dr. Munro Cullum, whose penetrating comments always proved challenging but insightful. I benefitted greatly from his encouragement and professional guidance over the past four years. I owe many thanks to Dr. Lana Harder for the time devoted to this project, and for providing supportive feedback and reassurance when needed most. Great gratitude is owed to Dr. Linda Hynan for her contribution of statistical expertise. She was an irreplaceable advisor and tutor, who engendered in me a positive outlook in the face of an intimidating list of planned analyses.

I would also like to thank Stephanie Taylor, research coordinator at the UTSW MS Clinic, who scored countless protocols and kindly tolerated my deluge

of daily emails. Additionally, I must acknowledge the docs and staff at the UTSW Neuropsychology Clinic for all of their encouragement and support. Special thanks are owed to Judy Shaw for her tireless correction of my scoring errors, David Denney for late afternoon conversation and spirited debate, and Dr. April Wiechmann for her lively intra-office competitions and neighborly advice. I must also thank Aleksandra and Joshua Foxwell, and Jodi Mahoney, whose friendships I cherish greatly. While Jodi pushed me academically and kept me on the straight and narrow, Josh and Aleks were more than willing to distract me from my research at a moment's notice.

Finally, my gratefulness toward my friends and family cannot be overstated. Immense gratitude is owed to my parents, Thomas and Brenda Noll, who taught me the value of imagination and learning, and provided me with every opportunity to push their bounds. Finally, profound thanks are owed to Maria Grosch, who accompanied me on this journey—her love and support provided comfort every step of the way.

PREDICTORS OF QUALITY OF LIFE IN MULTIPLE SCLEROSIS: RELATIONSHIPS BETWEEN COGNITIVE, PHYSICAL, AND SUBJECTIVE MEASURES OF DISEASE BURDEN

Publication No._____

Kyle Richard Noll, Ph.D.

The University of Texas Southwestern Medical Center at Dallas, 2011

Supervising Professor: Laura H. Lacritz, Ph.D., ABPP-CN

ABSTRACT

The varied constellation of symptoms characteristic of multiple sclerosis (MS) are often functionally impairing, affecting the health-related quality of life (QoL) of many of those afflicted. However, it remains unclear to what extent subjective, cognitive, and physical measures differentially predict overall health-related QoL

in MS, and which (combination of) factors are most useful when making clinical inferences regarding patient well-being. Stepwise linear regression analyses were used to investigate predictors of QoL in 55 consecutive MS patients, recruited as part of the Cognition and Demyelinating Disease project at the UTSW MS Clinic. Out of all cognitive, physical, and self-report predictors of overall health-related QoL, only the Modified Fatigue Impact Scale (MFIS) was significant, accounting for 31% of the variance in Overall scores on the MSQOL-54 ($p < .001$). Significant predictors of mental health-related QoL included the Quick Inventory of Depressive Symptoms (QIDS) and the Modified Fatigue Impact Scale (MFIS) ($p < .001$). The QIDS alone accounted for 64% of the variance in MSQOL-54 Mental Composite scores, which increased to 71% with the inclusion of the MFIS. Significant predictors of physical health-related QoL included the MFIS, Timed 25-Foot Walk (T25FW), and Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) ($p < .001$). The MFIS alone accounted for 72% of the variance in MSQOL-54 Physical Composite scores, which increased to 76% with the inclusion of the T25FW, and 78% when the MSNQ was also added. These results suggested that measures of self-reported fatigue and depression were the best predictors of health-related QoL in the domains of overall, physical, and mental functioning. In light of these findings, screening for fatigue and mood dysregulation should be incorporated into routine clinical evaluations of MS patients. Results of ROC analyses revealed that the QIDS and MFIS were both

significant discriminators of level of QoL (high vs. low) for each of the three MSQOL-54 summary measures (AUCs = .79 to .92). Examining rates of correct classification, specificity, and sensitivity, indicated that cut-scores of greater than nine on the QIDS and greater than 37 on the MFIS were optimal for discriminating between low and high QoL.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

9HPT	9-Hole Peg Test
AUC	Area Under the Curve
BVMT-R	Brief Visual Memory Test- Revised
CIS	Clinically Isolated Syndrome
CVLT-II	California Verbal Learning Test- Second Edition
JLO	Judgment of Line Orientation
M	Mean
MDS	Multiple Disconnection Syndrome
MFIS	Modified Fatigue Impact Scale
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSNQ	Multiple Sclerosis Neuropsychological Questionnaire
MSQOL-54	Multiple Sclerosis Quality of Life-54 Instrument
OCT	Optical Coherence Tomography
PASAT	Paced Auditory Serial Addition Test
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive-Relapsing Multiple Sclerosis
QIDS	Quick Inventory of Depressive Symptomatology
QoL	Quality of Life
RNFL	Retinal Nerve Fiber Layer

ROC	Receiver Operating Characteristic
RRMS	Relapsing-remitting Multiple Sclerosis
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SPMS	Secondary Progressive Multiple Sclerosis
T25FW	Timed 25-Foot Walk
TCST	Texas Card Sorting Test

CHAPTER ONE
Introduction

Multiple sclerosis (MS), an inflammatory autoimmune disease affecting the brain and spinal cord, is the most common cause of neurological disability in young and middle-aged adults in the United States and Europe (Johnson, 2007). Pathologically, it is characterized by areas of neuronal demyelination and inflammation in white matter regions, as well as more subtle tissue damage in diffuse areas of cortical grey matter (Fielding, Kilpatrick, Millist, & White, 2009). The disease may be characterized by relapses and remissions or a more chronic and progressive course. Symptoms often include optic nerve dysfunction (e.g., visual deficits), sensory disturbance (e.g., facial pain, numbness, or tingling sensations), pyramidal tract dysregulation (e.g., weakness, increased muscle tone, or hyperreflexia), ataxia, bladder, bowel, and sexual dysfunction, as well as cognitive impairment and emotional difficulties (van den Noort, 2005; Wishart, Flashman, & Saykin, 2001). These symptoms can be functionally impairing, and estimates suggest that MS leads to unemployment in 50% to 80% of cases within a 10-year disease course (Morrow et al., 2010; Grant, McDonald, Trimble, Smith, & Reed, 1984).

Early research into the psychological aspects of MS focused on an undifferentiated category referred to as “mental symptoms.” This category included fatigue, sleep, and emotional and cognitive problems (Richardson,

Robinson, & Robinson, 1997), which were initially considered secondary to the more overt physical symptoms believed to be most impairing. However, with improved psychometric methodologies, psychological impairment (and cognitive problems in particular) has become increasingly documented and quantified, and neuropsychological deficits are now recognized as a primary and often disabling consequence of the disease processes. Although there is no uniform pattern of cognitive impairment in MS, some commonly affected domains have been identified (for a review, see Calabrese, 2006). While primary language functions and verbal intellectual skills are often unaffected, information processing abilities, complex visuospatial skills, conceptual reasoning, and sustained attention are often impaired. The greatest deficits are usually found in processing speed, learning, and memory, with working memory and short-term recall the most significantly impacted. Such cognitive abilities can be disrupted even early in the disease course and have been found to be an important predictor of functional capabilities and QoL (Goverover, Genova, Hillary, & DeLuca, 2007).

Quality of life is an elusive concept to rigorously define, though most individuals are certain when they are lacking a degree of it. At a very minimum, QoL can be understood to encompass an individual's subjective well-being as affected by psychosocial, health, economic, and environmental factors (Butt, Yount, Caicedo, Abecassis, & Cella 2008). Unsurprisingly, such factors can be significantly impacted by the constellation of cognitive, emotional, and physical

impairments characteristic of MS. Most studies regarding MS-related QoL focus on the influence of one or two isolated impairments, though the determinants of QoL are multifactorial and multimodal in nature (Goverover et al., 2007). In addition to cognition, other factors important to QoL in MS include depression, fatigue, sleep, pain, social functioning, perception of health, and physical functioning, though the relative contributions of each to overall QoL remain equivocal. The following study aims to clarify the relative determinants of QoL in MS, which may help target interventions that improve patients' subjective well-being, while decreasing the burden of disease. The remainder of this chapter reviews the extant literature regarding the cognitive, physical, and subjective determinants of QoL in MS.

CHAPTER TWO
Review of the Literature

MULTIPLE SCLEROSIS

Clinical Presentation

Multiple Sclerosis typically presents with abrupt onset of one or more of a variety of symptoms that may include fatigue, weakness, spasticity, impaired balance, bladder and bowel problems, numbness, visual disturbance, tremors, cognitive deficits, and depression (Huijbregts, Falkers, de Sonneville, de Groot, & Polman, 2006). Depression and cognitive impairment may present as early signs of MS even before physical disability appears (Haase, Tinnefeld, Lienemann, Ganz, & Faustmann, 2003), and symptom severity often differs greatly between individuals and time intervals. In 1996, the U.S. National Multiple Sclerosis Society classified MS phenotypes as relapsing-remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS), and progressive-relapsing (PRMS) (Huijbregts et al., 2006).

The RRMS subtype is characterized by unpredictable exacerbations in symptoms followed by months to years of remission without new signs of disease activity. RRMS is the most common subtype and is the initial course of 80% of individuals with MS (Compston & Coles, 2008). It typically begins with a clinically isolated syndrome, in which an attack is suggestive of demyelination but does not fulfill full criteria for MS (Miller, Barkhof, Montalban, Thompson, &

Filippi, 2005). Approximately 30% to 70% of persons with a clinically isolated syndrome later develop MS. RRMS cases which have persisted for more than 10 years, without indication of disability progression (i.e., an Expanded Disability Severity Score less than three), are sometimes referred to as benign MS, though the term may be misleading as these patients tend to exhibit cognitive and functional deficits over time. Left untreated, approximately 65% of those with an initial RRMS course begin to exhibit progressive neurologic decline classified as SPMS (Lublin & Reingold, 1996). The PPMS subtype affects about 10% to 15% of individuals with MS and is characterized by an absence of remission following the initial presentation of symptoms (Miller & Leary, 2007). PRMS is the least common subtype and refers to patients who have a steady neurologic decline but suffer from additional exacerbations (Lublin & Reingold, 1996). Regardless of subtype, most cases of MS eventually cease to remit and become slowly progressive over time.

The disease has been estimated to affect between 47 and 110 of every 100,000 people, with increased prevalence noted among populations living in geographic regions of higher latitudes (Noonan et al., 2007). The majority of patients are diagnosed between 20 and 50 years of age, women are affected two to three times as often as men, and its prevalence is greatest in individuals of northern European descent (Prakash, Snook, Lewis, Motl, & Kramer, 2008). MS can lead to considerable disability and occupational impairment, and patients with

MS have an average life expectancy that is seven years shorter than the general population (Compston & Coles, 2008), though patients usually die from MS-related complications rather than the disease process itself (e.g., infection, falls, medication errors, and suicide). While the disease has no known cure, use of disease-modifying therapies (e.g., IFN β-1a, IFN β-1b, glatiramer acetate, natalizumab, and fingolimod) has significantly improved outcomes for patients with MS. Such agents decrease clinical relapses, disability progression, and lesion load, and may also have cognitive and emotional benefits, though more research is needed regarding their effect on psychological functioning (Amato, Portaccio, & Zipoli, 2006).

Pathology

Multiple Sclerosis is characterized by axonal demyelination in which the fatty myelin sheaths covering the axons of nerve cells are attacked by the body's immune system (Richardson et al., 1997). More specifically, prevailing theory suggests that MS attacks oligodendrocytes, the glial cells responsible for the production and maintenance of the myelin sheath. The disease process is thought to be an immunologically-mediated inflammatory response to genetic and environmental factors, possibly myelin antigens triggered by a viral infection in genetically predisposed individuals (Johnson, 2007). The body's T cells (lymphocytes important to immune response) recognize myelin as a foreign entity, causing inflammation, further immunological activation, and leaking of the

blood-brain barrier (Compston & Coles, 2002). The disease produces thinning of the axonal sheath, and complete transection of axons is often found in the later stages of its more progressive forms (Compston & Coles, 2008). The neuronal damage results in gliosis, the proliferation of astrocytes (large glial cells important in repairing damaged nerve cells). Their accumulation leads to the formation of glial scars, also referred to as sclerotic plaques or lesions.

White matter plaques have long been considered the hallmark of MS pathology, as the disease primarily affects the myelinated axons of nerve cells in the subcortical white matter of the brain. White matter lesions are detectable with neuroimaging techniques such as T1-weighted, T2-weighted, and fluid attenuated inversion recovery magnetic resonance imaging (MRI) scans. Lesions appear hyperintense on T2-weighted images, and hypointense on T1-weighted scans, though signal intensities may vary depending on scan parameters (Ludwin, 2000). Contrast-enhanced MRI (e.g., Gadolinium) may also be used to help assess lesion activity (He, Grossman, & Ge, 2001).

Lesions can be found distributed throughout the white matter of the cerebrum, brainstem, and cerebellum (Wingerchuk & Weinshenker, 2000; Simon, 1993). Specific regions where lesions are commonly found include the periventricular white matter (e.g., the occipital horns), corpus callosum, corona radiata, internal capsule, centrum semiovale, and the visual pathways. The optic nerves are often affected during the course of the disease (e.g., optic neuritis),

though imaging structural changes in the optic nerve is difficult with conventional MRI (Tien, Hesselink, & Szumowski, 1991). Optical coherence tomography (OCT) has emerged as a useful tool to evaluate disease activity in the retina and head of the optic nerve. The spinal cord may also be affected (e.g., transverse myelitis), and occasionally, abnormally large plaques in the brain (i.e., tumefactive MS) will be observed (Karaarslan et al., 2001; Hickman & Miller, 2000). Although it was originally believed that lesions were isolated to white matter tracts, all myelinated structures are susceptible to MS pathology, including the gray matter of the cerebral cortex and basal ganglia (Geurts et al., 2007; Kutzelnigg et al., 2005; Vercellino et al., 2005; Bo, Vedeler, Nyland, Trapp, & Mork, 2003). The discovery of grey matter lesions is important, as white matter abnormalities alone cannot account for the full spectrum of clinical symptoms in MS.

Although the precise etiology is not yet fully understood, MS lesions impact nerve transmission by blocking electrochemical conduction (Arrondo et al., 2009). Functional techniques such as positron emission tomography have furthered understanding of the widespread disconnection and inefficiency caused by MS pathology. A mild reduction in regional cerebral metabolic rate of glucose consumption, as measured with positron emission tomography, has been documented in MS (Herholz, 2006; Sokoloff, 1981). Specifically, cortical asymmetry in metabolism is pronounced in the superior mesial frontal and

superior dorsal lateral frontal cortices (Bakshi, Miletich, Kinkel, Emmet, & Kinkel, 1998; Pozzilli et al., 1992). Further, in a cross-sectional study of 23 patients with MS, Blinekenberg and colleagues (2000) found that regional cerebral metabolic rate of glucose consumption was related to lesion load in all cerebral lobes. Such metabolic changes and abnormalities in nerve conduction affect interregional communication, resulting in the clinical manifestation of varied physical, cognitive, and emotional symptoms.

Although lesion load varies over time and disease course, on average, a single symptom is manifested for every eight to ten new lesions detected on MRI, highlighting the irregular relationship between MS pathology and its clinical manifestation (Traboulsee & Paty, 2002). Given the variable presentation of MS patients, diagnosis can be difficult, requiring close observation of symptoms over time. In 2001, the McDonald criteria for diagnosis were proposed to improve accuracy and sensitivity over the previous Poser criteria. The McDonald criteria were subsequently revised in 2005 and 2011 to reflect advances in diagnostic technology and simplify diagnosis (Polman et al., 2011; Polman et al., 2005). The present iteration of the McDonald criteria utilizes data from neuroimaging and laboratory tests, though clinical presentation of symptoms remains fundamental to diagnosis.

COGNITION AND DEMYELINATING DISEASE

Neurocognitive Impairment

The presence and severity of neurocognitive dysfunction varies in MS, though primarily affected functions typically include attention and learning, executive abilities (e.g., problem-solving), and short-term memory. Some form of cognitive deficit occurs in up to 65% of patients (Rao, 1997), and impairment can be present even in the early stages of the disease (Patti, 2009). Cognitive problems have also been reported in approximately 50% of clinically isolated syndrome patients (Feuillet et al., 2007), and complete remission of cognitive symptoms is uncommon across all disease subtypes (Amato, Zipoli, & Portaccio, 2006). Short-term memory and learning deficits are often cited as the most frequent cognitive disturbances in MS, affecting between 40% to 60% of all patients (Calabrese, 2006).

There is some debate in the literature regarding the nature of memory impairment in MS, though span memory and recognition are usually unimpaired, while recall is often deficient (for a review, see Calabrese, 2006). This pattern has been interpreted as reflecting difficulties with retrieval rather than encoding or storage. However, other studies of learning and memory have suggested that many MS patients have impaired verbal and visual new learning, but normal recall and recognition (Johnson, 2007). Additionally, learning functions seem to be differentially affected by disease subtype. Specifically, verbal learning deficits

are more common in progressive forms of the disease, whereas RRMS patients appear more likely to have visuospatial learning deficits (Gaudino, Chiaravalloti, DeLuca, & Diamond, 2001). Despite inconsistencies within the literature, aspects of memory (whether learning or recall) are often affected by MS and are detectable with numerous instruments (Wishart, Benedict, & Rao, 2008), including the California Verbal Learning Test- Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000), the Brief Visual Memory Test- Revised (BVMT-R; Benedict, 1997), and subtests of the Wechsler Memory Scale- Fourth Edition (WMS-IV; Wechsler, 2009).

Information processing speed and attention also appear deficient in MS patients, even when controlling for motor involvement. Compared to controls, generalized slowing is greater in progressive subtypes (50% slower) than in RRMS (24% slower) (De Sonneville et al., 2002). On the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977), a measure of sustained auditory attention, MS patient performance is inferior to healthy controls, as performance is slowed with more errors noted across trials (De Sonneville et al., 2002). In a meta-analysis of RRMS studies, the authors found that performances on the Stroop Color and Word Test (Golden, 1978) and measures of verbal fluency (i.e., phonemic as well as semantic) showed the largest effect sizes, suggesting that instruments with a significant speeded processing component may be most sensitive in detecting cognitive deficits (Prakash et al., 2008). It should be noted

that measures of visual attention may be impacted not only by attentional deficits but also by visual acuity problems. As many as 50% of MS patients present with vision loss as an initial symptom, with optic neuritis affecting up to 90% of patients during the course of their disease (Bruce, Bruce, & Arnett, 2007). However, given that measures of auditory attention are also commonly affected, visual problems alone cannot account for all of the attentional deficits in MS.

Executive dysfunction is also common in MS patients. Vowels and Gates (1984) have suggested that approximately 33% of MS patients exhibit deficits on tasks requiring planning, problem solving, concept formation and utilization of feedback, such as the Wisconsin Card Sording Test (WCST; Psychological Assessment Resources, 2003) (Rao, Hammeke, & Speech, 1987). Additionally, Simioni and colleagues (2009) demonstrated that decision-making, as measured by the Iowa Gambling Task (IGT; Bechara, Damásio, Damásio, & Anderson, 1994), is often impaired and declines over time in MS patients. Such problems are more common in progressive patients and those with affective symptoms such as depression. While the Sorting Test from the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) has been demonstrated to be as sensitive to executive dysfunction in MS as the WCST, only the D-KEFS Sorting Test remained sensitive when controlling for depression, though this finding has yet to be replicated (Parmenter et al., 2007).

Clearly, no single measure is sensitive to the broad and varied spectrum of neuropsychological dysfunction in MS. Rao, Leo, Bernardin, and Unverzagt (1991) highlighted the variability in the cognitive profiles in MS through a community-based study of 100 MS patients. They found impairments (defined as performances less than the fifth percentile) in episodic memory (22% to 31%), sustained attention and executive ability (8% to 25%), and visuospatial deficits (12% to 19%), with little overlap among the affected domains. Specifically, 48% of patients with impaired verbal learning and memory were unimpaired in visual memory, and conversely, 48% with visual memory deficits had intact verbal memory. Also, 41% of patients with deficits in verbal fluency scored normally on a measure of sustained attention, though deficits in both domains were common across all subjects. Further, level of disability, duration of illness, disease course, medication use, and depression, were weak or non-significant predictors of cognitive impairment.

Given the widespread but variable (and often subtle) cognitive dysfunction in MS, a sensitive screening tool sampling numerous cognitive domains would be helpful in assessing cognitive functioning. Indeed, research is ongoing regarding an optimal battery of neuropsychological tests for detecting cognitive dysfunction in this population (Patti, 2009). A number of measures, some of which were discussed above, have been proposed as potential candidates for inclusion in such a battery, including the PASAT, Symbol Digit Modalities Test (SDMT; Smith,

1982), CVLT-II, BVMT-R, D-KEFS Sorting Test, verbal fluency tests, and Judgment of Line Orientation (JLO; Benton, Varney, & Hamsher, 1978), among others. Rao has even recommended a MS-specific screening battery, the Brief Repeatable Battery-Neuropsychology (BRB-N; Rao, 1990), which includes the SDMT, PASAT, a categorical (semantic) fluency measure, and a measure of visual and verbal memory. This battery shows promise and may serve as an important benchmark for future developments in MS screening tools, though further study is needed.

Relationships with Physical Measures

Although the cognitive functions discussed above are mental processes, they rest upon dynamic components of neuronal systems conditional on brain structure (Gioia et al., 2007). Specifically, cognitive functions are supported by brain networks that are highly dependent on the integrity of long white matter tracts that mediate information flow between distant cortical areas (Arrondo et al., 2009). Although moderate correlations have been noted between cognitive impairment and conventional MRI disease measures (e.g., lesion load and diffuse brain atrophy), the literature is inconsistent at best (Patti, 2009). Discrepancies between studies are common depending on MRI parameters, clinical disease characteristics, and degree of cognitive dysfunction (Morgen et al., 2006; Sanfilipo, Benedict, Weinstock-Guttman, & Bakshi, 2006). Additional factors that impact cognition and its associations with imaging pathology include depression,

anxiety, and fatigue, as well as lesion location, size, and medication use. Despite the numerous moderating factors, relationships have been described between inter-hemispheric transfer and callosal degeneration, verbal fluency and anterior callosal atrophy, executive dysfunction and frontal pathology, and anterograde memory deficits and demyelination around the bilateral hippocampi (Amato, Zipoli, & Portaccio, 2006; Wishart et al., 2001; Huber et al., 1987). Also, MS-related cognitive decline has been associated with reduced neocortical grey matter volume, with pronounced cortical thinning in the temporal and frontal cortices (Sailer et al., 2003).

'Multiple disconnection syndrome' (MDS) has been proposed to explain the variability in the relationships between pathology and neuropsychological deficits (Calabrese, 2006). According to this theory, a threshold of cerebral tolerance must be surpassed before significant brain desynchronization occurs and cognitive deficits are clinically manifested. This hypothesis is supported by a recent study by Arrondo and colleagues (2009) that measured the amplitude modulation following responses (an indirect measure of brain synchrony) in a group of MS patients and healthy controls. They found that demyelination resulted in the loss of synchronization in CNS pathways which was associated with less efficient cognitive processing in verbal memory, attention, and executive functioning as measured by the Brief Repeatable Battery-Neuropsychology.

Providing further support for the MDS hypothesis are recent functional

magnetic resonance imaging studies (fMRI), which are able to indirectly measure changes in downstream brain activity (in vivo) related to structural pathology (Sumowski, Wylie, DeLuca, & Chiaravolloti, 2010; Forn et al., 2007). In one such study, Gioia and colleagues (2007) measured the brain responses of 28 relapsing-remitting MS patients performing an *n*-back visuomotor integration task. The MS patients displayed altered recruitment of expected brain regions when performing the cognitive task, along with the recruitment of additional unexpected regions. Connectivity disturbances were found specifically within the working memory network and appear related to the extent of structural white matter damage. Additionally, baseline cognitive functioning predicted overall network response greater than measures of grey and white matter volumes, highlighting the importance of neuropsychological data in making inferences about brain function in MS.

Although fMRI is preferable to conventional imaging indices for relating brain and cognitive functioning, the technique is predominantly used for research purposes and rarely for clinical exams, where conventional MRI remains the most commonly employed method of neuroimaging. Conventional methods reliably measure axonal loss and lesion characteristics, but MRI indices also reflect general neuronal loss, synaptic pruning, loss of myelin, gliosis, and changes in water content (Wegner, Esiri, Chance, Palace, & Matthews, 2006). Though MRI has greatly improved diagnostic accuracy, these factors tend to fluctuate over the

course of the disease and do not always predict clinical symptom severity or progression.

Studying axonal loss in the retina is a promising adjunctive biomarker for MS that may be less susceptible to the variability in typical MRI measures (Toledo et al., 2008). Among the different ways to measure retinal nerve fiber layer (RNFL) thickness are OCT and Heidelberg retinal tomography. Each technique focuses on different aspects of the retina and measurements are not equivalent across modalities. Previous research has suggested that OCT is more sensitive than Heidelberg retinal tomography in terms of detecting axonal loss (Toledo et al., 2008). OCT is based on interferometry and utilizes a computer algorithm to analyze the echo of reflected light from an 820 nm laser, obtaining a transverse section of the RNFL at the head of the optic nerve and the retina.

The retina is the only part of the CNS where tissue comprised solely of axons can be directly imaged (Petzold et al., 2010). Unlike demyelination, which is reversible, axonal loss is permanent. Accordingly, while indices of myelin pathology fluctuate over the disease course (e.g., white matter lesion load and volume), direct measurements of axonal loss in the retina with OCT may be more stable and sensitive to disease-related brain changes. Lending support to the utility of this emerging technique are recent studies that have consistently documented RNFL loss in MS patients, even in the absence of a history of optic neuritis (for a review, see Petzold et al., 2010). It is hypothesized that RNFL thinning is caused

by retrograde trans-synaptic retinal ganglion cell degeneration due to lesions within the posterior optic pathways (e.g., postgeniculate area), as well as damage to the anterior visual pathways (Brusa, Jones, & Plant, 2001; Brusa et al., 1999). Specifically, 90% of retinal axons project through the lateral geniculate nucleus with optic radiations to the occipital cortex, while the other 10% project to the pretectal region of the midbrain. Accordingly, lesions within such regions may result in retrograde neurodegeneration of the retina, and imaging of the RNFL can provide a window into disease burden and progression.

In a recent study, Sepulcre and colleagues (2007) found decreased RNFL thickness in MS patients compared to controls, particularly in the temporal quadrant. Baseline temporal quadrant RNFL atrophy was associated with the presence of new relapses and changes in functional capabilities by the end of the study. RNFL thickness was also significantly correlated with white and grey matter volumes. Additionally, the presence of retinal periphlebitis, a form of inflammation around the retinal veins, was a risk factor for having new relapses in the next two years. Patients with retinal periphlebitis had larger Gadolinium-enhancing lesion volume on MRI than those without. The authors concluded that RNFL atrophy and the presence of retinal periphlebitis are associated with disease activity, suggesting that retinal evaluation can be employed as a useful measure of multiple sclerosis disease burden. A meta-analysis of 16 studies of OCT and MS confirmed these findings, and found that the average RNFL thickness of MS

patients was approximately seven μm thinner than normal controls (Petzold et al., 2010).

Despite its demonstrated utility in predicting brain pathology, the relationship between RNFL thickness and cognitive functioning is not well understood. However, given significant associations with lesion load and cortical volume, it may be a useful predictor of cognitive functioning. In one of the few studies to date investigating RNFL and cognition (Toledo et al., 2008), researchers found that RNFL thickness was moderately correlated with cognitive dysfunction, particularly visuospatial attention and processing speed as measured by the SDMT. Given these preliminary results, OCT measurements may be a useful tool to measure disease burden and assess potential cognitive risk that is both more expedient and reliable, and less expensive than MRI.

QUALITY OF LIFE

Operational Definition

Quality of life is a notoriously difficult concept to define, and QoL research is often plagued by definitional disagreement. However, to measure a construct and make meaningful comparisons across groups, the construct must be rigorously defined in terms of its constituent parts. M. Joseph Stirgy's *The Psychology of Quality of Life* (2002) provides a useful conceptual clarification and analysis of general QoL, which can help situate the more specialized sub-concept of health-related QoL into a broader context. Stirgy draws upon

philosopher John Wilson's theory of avowed happiness in which the satisfaction of needs produces happiness, and the degree of fulfillment required to satisfy a given need varies as a function of the adaptive level of that need (Lenderking, 2005; Wilson, 1968). In other words, needs that are more fundamental to our survival require greater fulfillment than those less adaptive, if one is to maintain a positive level of overall happiness.

QoL is not, however, the simple accumulation of affective happiness. It also requires a cognitive appraisal of those affective states. According to Stirgy, QoL is the level of subjective well-being as determined by *a*) the affective experience of happiness in salient life domains, *b*) the summation of negative affect in salient life domains, and *c*) the cognitive evaluations of *a* and *b* (Lenderking, 2005). Given that MS and its constellation of cognitive, emotional, and physical symptoms often limit patients' abilities to fulfill their adaptive needs, one might expect decreased affective experiences of happiness (criterion *a*), increased negative experiences (criterion *b*), and as a consequence, lower overall appraisals of subjective well-being (hence lower QoL).

Relationships with Psychological Functioning

Research regarding diminished independence in daily living activities in MS typically focuses on physical impairments such as decreased ambulation, coordination, balance, and visual difficulties (Kalmar, Gaudino, Moore, Halper, & DeLuca, 2008). However, physical disability alone cannot account for all of the

difficulties experienced by MS patients, particularly in activities with a high level of cognitive demand. LaRocca, Kalb, Scheinberg, and Kendall (1985) estimated that physical disability and demographic factors explained less than 14% of the variance in employment status in MS. On the other hand, Amato, Ponziani, Siracusa, and Sorbi (2001) reported that the degree of cognitive decline at baseline was a strong predictor of impairment in employment and social activities after both four- and 10-year intervals.

Although the majority of MS patients exhibit relatively mild cognitive deficits, even subtle impairments can have a significant impact on everyday activities and quality of life (Achiron & Barak, 2003). Efficient cognitive functioning is necessary for everyday activities including the ability to work, drive, and maintain and enjoy social relationships, all of which are important to a healthy QoL (Patti, 2009; Schultheis, Garay, & DeLuca, 2001; Rao, Leo, Bernadin, et al., 1991). Cognitively impaired MS patients have higher rates of problems with daily activities than intact MS patients, even when the two groups have similar demographics, physical disability, illness duration, and disease course (Rao, Leo, Bernadin et al., 1991). Neuropsychological impairment, specifically impairment in frontal functions and memory, has been shown to be a major predictor of unemployment and caregiver distress (Benedict, Carone, & Bakshi, 2004).

It has been argued that loss of frontal cognitive functioning such as the ability to sustain short-term memory, learn new tasks, multitask, and adapt to new situations are the most disabling features of MS (Halper, 2010). In a study comparing 74 adults with MS to 35 healthy controls, individuals with MS who were cognitively intact on objective testing were able to complete the Executive Functions Performance Test (EFPT; Baum, Morrison, Hahn, & Edwards, 2003), an objective measure of everyday functional capacity, at a level comparable to the healthy controls (Kalmar et al., 2008). Individuals who were impaired on cognitive testing required a greater degree of assistance to complete the EFPT. Degree of cognitive dysfunction, particularly in the domains of new learning, executive functioning, and processing speed, also predicted the degree of independence in activities of daily living.

Wynia and colleagues (2008) also investigated the impact of cognitive functioning on QoL in 530 MS patients, though they relied solely upon self-report measures of cognitive, emotional, and physical dysfunction. They utilized two generic outcome measures of QoL, the Medical Outcome Study Short Form Questionnaire (SF-36; Ware, 2000) and the World Health Organization Quality of Life-BREF (WHOQOL-BREF; WHOQOL Group, 1998). The WHOQOL-BREF appeared sensitive to physical impairment of bodily functioning and structure, and psychological deficits impacting daily activities, as well as social functioning affecting interpersonal interaction—the domains considered most important to

QoL by the International Classification of Functioning, Disabilities, and Health (Stucki & Cieza, 2004). The SF-36 on the other hand, was most sensitive to disabilities belonging to the bodily functions and activities components of QoL.

The results of the Wynia et al. study revealed that impairments in mental functions were the most important predictor of QoL (2008). Specifically, cognitive, emotional, and sleep problems were reported by more than 80% of the sample across both outcome measures (2008). Limitations in activities of daily living were the second most severe disability, followed by limitations in basic movement activities, impairments in muscle and movement functions, and impairments in excretion and reproductive functions. Severity of symptoms differed with disease subtype, but was about equal for both progressive forms of the disease. Patients who reported less impairment in mental functions (cognitive, emotional, and sleep/fatigue) reported better QoL in the domains of mental health, emotional functioning, social functioning, bodily pain, and vitality. Although fatigue showed the highest prevalence and severity, its impact on QOL was limited in this study.

The Wynia study provided further evidence specifying the importance of psychological factors to QoL in MS patients, but may have been limited by only utilizing subjective self-report measures of symptoms, as opposed to objective measures of cognitive and physical functioning. A study by Benedict and colleagues (2005) attempted to determine which subjective clinical parameters

and objective cognitive measures accounted for the most variance in predicting health-related QoL in 120 MS patients, while controlling for disease course, physical disability, fatigue, and mood disorder. Their primary outcome measure of QoL was the MS Quality of Life-54 (MSQOL-54; Vickrey, Hays, Harooni, Myers, & Ellison, 1995). The MSQOL-54 is a self-report inventory that includes all of the items from the SF-36 and 18 additional MS-specific items, which better reflect the cognitive and social difficulties of MS than the SF-36 used by Wynia and colleagues in the study discussed above.

Benedict and his team found that physical health-related QoL was predicted by numerous self-reported factors, including fatigue as measured with the Fatigue Severity Scale (FSS; Krupp, Larocca, Muir, Nash, & Steinberg, 1989), depression assessed with the Beck Depression Inventory-II (BDI-II; Beck, Steer, Ball, & Ranieri, 1996) and the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977), as well as disability status according to the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). Mental health-related QoL was only associated with depression and fatigue, while vocational status was predicted by disease duration and three objective cognitive measures (SDMT, WCST perseverations, and BVMT-R recognition).

A possible interpretation of these results is that “self-report predicts self-report and cognitive capacity predicts work capacity” (Benedict et al., 2005, p. 32). In other words, objective cognitive capacity may have little to do with a

patient's sense of well-being. In fact, using the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ), a self-report measure of neurocognitive symptoms, Benedict and colleagues (2004) found that patient reports of cognitive functioning were more highly correlated with depressive symptoms than with performance on neuropsychological tests. They also identified cases of euphoria sclerotica syndrome, in which patients exhibited profound cognitive and physical disabilities but reported high QoL and positive mood state (Benedict et al., 2005; Benedict et al., 2004).

The above findings are often interpreted as lending support to the contention that measures of QoL amount to little more than indices of mood. Indeed, Amato and colleagues (2001) identified strong inverse associations between depressive symptoms on the Hamilton Rating Scale for Depression and both physical (r = -.69) and mental (r = -.76) health-related QoL on the MSQOL-54. This finding is not surprising, as lifetime occurrence of major depression in MS patients is between 42% and 54% (Sadovnik et al., 1996), and depressed mood often leads to less favorable self-perception of functioning (Amato et al., 2001). However, depression in MS is not only attributable to individual reactions to diagnosis and symptom progression, but also to the disease process itself. Accordingly, measuring symptoms of depression is integral to understanding disease burden and QoL.

While depression is undoubtedly an important factor regarding QoL in MS, improvements in such symptoms only account for 19% to 52% of accompanying changes in QoL following successful treatment of depression (Hart, Fonareva, Merluzzi, & Mohr, 2005). As such, only using depression instruments as indices of QoL may overlook other important disease factors and determinants of QoL. In a meta-analysis of QoL measures in MS research, Nortvedt and Riise (2003) found that multifactorial QoL measures more broadly assess the impact of MS than most individual measures of disease burden, with significant contributions from indices of depression, but also fatigue, disability, sexual function, and bowel and bladder problems. Additionally, in the studies discussed above it remains unclear how subjective aspects of disease burden (e.g., depression and fatigue) and physical measures (e.g., walking, fine motor control, and RNFL thicnkness) interact with, and contribute to, the cognitive and other determinants of QoL.

Relationships with Physical Measures

Although it is well-documented that people with MS experience lower QoL in health-related domains (Wynia, Middel, van Dijk, De Keyser, & Reijneveld, 2008), the relationship between predictors of QoL and MS-related pathology remain equivocal. Additionally, routine clinic visits often involve only a clinical interview and brief screens of physical functioning. However, in the absence of cognitive testing and supplemental self-report indices of QoL, it is

unclear how findings on the clinical exam translate to patient well-being. Fortunately, some studies have begun to shed light on this understudied area of research. In a sample of 60 MS patients, Janardhan and Bakshi (2000) demonstrated that brain lesion load and atrophy were associated with lower QoL on the MSQOL-54, particularly in overall emotional status, sexual dysfunction, and limitations in daily activities. In terms of emotional functioning, depression has been linked to temporal lesion burden, predominantly in the right hemisphere in MS (Berg et al., 2000; Honer, Hurwitz, Li, Palmer, & Paty, 1987).

Other investigations have been equivocal on the relationships between fatigue, QoL, and lesion load. While some researchers failed to demonstrate an association between MS-related brain changes and fatigue (e.g., Bakshi et al., 1999), others have implicated fatigue with increased lesion load in the parietal regions, internal capsule, and brainstem (Wishart et al., 2001). Additionally, Ferini-Strambi et al. (1994) demonstrated that reduced sleep efficiency, increased awakenings, and leg movements during sleep are associated with increased lesion load in the infratentorial region below the cerebellum. Approximately 40% of MS patients meet criteria for restless leg syndrome (Manconi et al., 2007), and tend to have more severe pyramidal disability and MRI abnormalities in the spinal cord. Those with restless leg syndrome tend to experience significant fatigue and report that cognitive functions are more affected than physical abilities (Merlino, Valente, Serafini, & Gigli, 2007).

Although the literature is nascent, RNFL thickness as measured with OCT has been associated with an important determinant of subjective health-related QoL, namely physical disability. In a meta-analysis of 12 studies examining the relationship between loss of RNFL and disease progression (as measured by the Expanded Disability Status Scale), correlations were found in six studies which ranged from $r = .30$ to .70, and two further studies found increased disability percentile with significantly decreased RNFL thickness (Petzold et al., 2010). Four of the studies found no significant associations between disability status and RNFL thickness, though heterogeneity of diagnoses in the study samples may have impacted the results (e.g., including neuromyelitis optica patients). Although informative, such studies tend to focus on isolated symptoms such as fatigue, sleep difficulties, depression, or physical disability status, rather than the impact of such factors on overall QoL, limiting the generalizability and clinical utility of physical indices in making inferences regarding patient well-being (Toledo et al., 2008).

SUMMARY

The demyelinating lesions of MS cause the disconnection of multiple neuronal pathways resulting in the manifestation of clinical symptoms. The varied constellation of symptoms characteristic of the disease are often functionally impairing, affecting overall QoL. Common problems include fatigue, sleep difficulty, physical impairment, as well as emotional and cognitive dysfunction.

Considerable research has been devoted to understanding the nature, prevalence, and severity of such difficulties, as well as their association with the subjective well-being of those affected. Additionally, the physiological underpinnings of particular symptoms are being uncovered, helping to understand the relationships between pathology and clinical expression.

Despite the substantial growth in the understanding of MS pathology, symptoms, and patient QoL, comprehensive studies regarding the relationships between these disease factors are rare or limited in their scope and methodologies. Measures of disease burden include objective neurocognitive and physical instruments, as well as subjective self-report measures of neuropsychological functioning, symptom severity, fatigue, and mood. However, most studies of health-related QoL in MS focus on specific symptoms or are limited to a single modality of data (e.g., subjective self-reports) (Benedict et al., 2005). Though introspective evaluation of functioning is an important determinant of QoL, it does not necessarily follow that subjective measures of disease burden are better predictors of QoL than objective evaluations. In fact, self-report measures do not always accurately reflect patient functioning (Benedict et al., 2004). Rater bias due to social desirability or lack of insight may create an environment in which self-report measures have suboptimal ecological validity. As such, it remains unclear to what extent subjective, cognitive, and physical measures differentially

predict overall health-related QoL in MS, and which (combination of) factors are most useful when making clinical inferences regarding patient well-being.

While a primary goal of medical intervention is the eradication of disease by targeting biological processes with pharmacological agents, it must also aim to alleviate patient suffering and improve well-being, particularly to those with diseases of no known cure such as MS. While MS lesions can be attenuated and relapses minimized with the use of DMTs, it is unclear whether these agents also improve subjective well-being. Moreover, QoL in MS patients may be most related to psychological factors that may not be improved by the use of DMTs alone. This study investigated QoL in MS with a multifactorial and multi-method approach that incorporated objective cognitive and physical measures of disease burden with subjective self-reports. By sampling from multiple domains of functioning, the relative impact of cognitive, emotional, and physical symptoms on QoL was discerned. It is hoped that clinical screening within the domains found to be most relevant to QoL may help target adjunctive pharmacological, psychosocial, or behavioral interventions, which may lessen suffering and improve the overall QoL of MS patients.

CHAPTER THREE
Hypotheses

OVERALL AIM

To investigate relationships between health-related QoL and measures of disease burden in MS, including objective cognitive and physical indices, as well as subjective measures of neuropsychological functioning, fatigue, and mood.

Aim One

To determine which measures of disease burden are most frequently impaired or elevated in MS patients.

Hypothesis One

MS patients will be more frequently impaired on objective measures of motor function, attention, processing speed, and learning than rates in the respective normative samples.

Hypothesis Two

MS patients will have a higher frequency of clinically significant elevations on self-report measures of neuropsychological symptoms, fatigue, and depression compared to rates of impairment on objective cognitive and physical indices.

Aim Two

To determine which domain-specific cognitive measures are the best predictors of subjective health-related QoL in MS.

Hypothesis Three

Individual measures of attention, processing speed, and learning will be significant predictors of QoL in contrast to measures of delayed recall, executive functioning, and language abilities.

Hypothesis Four

When predicting QoL, subjective self-reported neuropsychological symptoms will account for more variance in health-related QoL than objective cognitive measures.

Aim Three

To examine the relationships between objective and subjective measures of disease burden and health-related QoL.

Hypothesis Five

When predicting QoL, subjective self-report measures of mood, fatigue, and cognitive symptoms will account for more variance in QoL than objective cognitive and physical indices.

Exploratory Aim

To investigate differences in objective cognitive and physical measures, and self-report indices of mood, fatigue, and cognitive functioning in individuals with high and low levels of QoL.

CHAPTER FOUR
Method

Data for this study were collected as part of the Cognition and Demyelinating Disease project, a larger non-randomized longitudinal cohort investigation of cognitive functioning in demyelinating disease patients at the University of Texas Southwestern Medical Center at Dallas Multiple Sclerosis Program and Multiple Sclerosis Clinical Center (UTSW MS Clinic).

Participants

Subjects included consecutive demyelinating disease patients (both newly diagnosed and follow-up) referred to the UTSW MS Clinic, who consented to participate in the Cognition and Demyelinating Disease study and met the following inclusion criteria:

1) Age 18 years or greater, including both men and women;
2) Able to provide informed consent;
3) Able to return to the UTSW campus for follow-up testing;
4) Clinically confirmed MS (any subtype) according to the McDonald criteria or clinically isolated syndrome, confirmed by the study neurologist, Benjamin Greenberg, M.D., MHSc.

Subjects were excluded from the study if they had a history of comorbid neurological disease or were unable to speak, read, or understand English. Of the

66 subjects drawn from the Cognition and Demyelinating Disease project, a total of 55 met inclusion criteria for this investigation.

Procedures

Participation in the study entailed an initial visit at the UTSW MS Clinic and a follow-up visit at the UTSW Neuropsychology Clinic. During the initial visit, participants underwent a standard physical and retinal optical coherence tomography (OCT) scans that were recorded on a case report form. This was immediately followed by a structured interview with the study coordinator who recorded medical history, demographics, concomitant medications, and vital signs. This baseline visit was followed by a brief cognitive screening on the same day if the participant was able. The screening consisted of completion of self-report questionnaires (including the Multiple Sclerosis Neuropsychological Questionnaire, Multiple Sclerosis Quality of Life-54 Instrument, Quick Inventory of Depressive Symptoms, and Modified Fatigue Impact Scale) and approximately 30 minutes of neuropsychological and motor testing performed by a trained technician (including the Symbol Digit Modalities Test, Paced Auditory Serial Attention Test, 9-Hole Peg Test, and Timed 25-Foot Walk). If the participant was unable to stay that day, a subsequent appointment was established for the brief battery of tests.

After the brief battery was completed, the participant was scheduled for additional cognitive testing at the UTSW Neuropsychology Clinic (including the

California Verbal Learning Test- Second Edition, Brief Visual Memory Test-Revised, Texas Card Sorting Test, Verbal Fluency, and Stroop Color and Word Test). This visit occurred within approximately 4 weeks of the baseline visit. After the full set of cognitive tests was completed, participants received an individualized letter summarizing the results. Contact information was provided if they wished to discuss the results further with a neuropsychologist or their treating physician. Study forms, protocols, and questionnaires were stored in locked cabinets. Data were deidentified and entered into a secure, restricted-access electronic database. All study procedures were approved by the UTSW Institutional Review Board.

Measures

Measure characteristics and psychometric properties are described in detail in Appendix A.

A. Physical

9-Hole Peg Test (9HPT)

The 9-Hole Peg Test (Mathiowetz et al., 1985) is a simple timed measure of manual dexterity, motor speed, and coordination. Mean times in seconds were calculated using the total of four trials (2 trials for each hand) and T-scores were computed from the Multiple Sclerosis Functional Composite normative data (Drake et al., 2010).

Retinal Nerve Fiber Layer (RNFL) Thickness

Average RNFL thickness in µm for 360° around the optic disc was obtained with Spectralis OCT. Mean thickness including both eyes was calculated, and eyes with previous or current clinical optic neuritis were excluded from analyses (Toledo et al., 2008). A RNFL thickness difference of greater than 10 µm between eyes was considered suggestive of a history of optic neuritis, and the eye with the thinner RNFL was excluded from analyses.

Timed 25-Foot Walk (T25FW)

The timed 25-Foot Walk test is a measure of mobility and leg function adapted from the Multiple Sclerosis Functional Composite (Cutter, 1999). Gait speed (mean time in seconds) was recorded and T-scores were computed from the Multiple Sclerosis Functional Composite normative data (Drake et al., 2010). Gait speed has been shown to be a reliable and useful measure of walking ability in MS patients (Kragt et al., 2006).

B. Cognitive

The neurocognitive variables of interest sample five cognitive domains: learning, memory, attention and processing speed, executive functioning, and language (see Table 1 below).

Table 1. *Neurocognitive Variables of Interest by Domain*

Domain	Variable
Learning	CVLT-II Learning T-score BVMT-R Learning T-score
Memory	CVLT-II Delayed Recall *z*-score BVMT-R Delayed Recall T-score CVLT-II Discriminability *z*-score
Attention and Processing Speed	PASAT Total T-score SDMT Total T-score Stroop Color-Word T-score
Executive Functioning	Stroop Interference T-score TCST Logical Sorts
Language	FAS Total T-score Category Total T-score

Note. Abbreviations: CVLT-II = California Verbal Learning Test- Second Edition; BVMT-R = Brief Visual Memory Test- Revised; PASAT = Paced Auditory Serial Addition Test; SDMT = Symbol Digit Modalities Test; Stroop = Stroop Color and Word Test; TCST = Texas Card Sorting Test

Brief Visual Memory Test- Revised (BVMT-R)

The BVMT-R (Benedict, 1997) is a test of visual memory, which requires the immediate and delayed recall and recognition of visual figures. Numerous age-adjusted T-scores are calculated from normative data provided in the test manual, of which Total Learning and Delayed Recall were utilized for this study (Benedict, 1997).

California Verbal Learning Test- Second Edition (CVLT-II)

The CVLT-II (Delis et al., 2000) is a well-validated measure of verbal learning and memory. The examinee's responses were entered into a computer program, which provided raw and standardized scores controlling for age and education for 93 normed variables (Strauss et

al., 2006). Variables of interest for the present study included demographically-adjusted Total Learning T-score, Long Delayed Free Recall *z*-score, and Recognition Discriminability *z*-score (*d*').

Verbal Fluency

The verbal fluency tests used in this study consisted of the FAS phonemic fluency test and the Category (animals) semantic fluency task. These measures evaluate the spontaneous production of words under restricted search conditions (Strauss et al., 2006). For the purposes of the present study, demographically-adjusted T-scores for FAS Total words and Total animals on Category Fluency were produced from normative data based on age, education-level, gender, and ethnicity (Heaton et al., 2004).

Paced Auditory Serial Addition Test- 3" interval (PASAT)

The PASAT (Gronwall, 1977) is a measure of divided attention, auditory information processing speed, working memory, and mental flexibility. The number of correct responses and errors were recorded, and Total T-scores for correct responses were computed from normative data stratified by education (Rao et al., 1991).

Stroop Color and Word Test (Stroop)

The Stroop Color and Word Test is a measure of cognitive control, assessing the extent to which the examinee can maintain a goal and

suppress a habitual response. Specifically, the task measures selective attention, impulse control, and inhibition (Golden, 1978). Total correct responses are counted for each trial and T-scores are calculated based on normative data stratified by age and education provided in the manual (Golden & Freshwater, 2002). An additional score, the Interference T-score, is calculated comparing actual performance on the color-word trial with predicted performance based on the word-reading and color-naming trials. The Color-Word and Interference T-scores were used for this study.

Symbol Digit Modalities Test (SDMT)

The SDMT (Smith, 1991) is a simple substitution task requiring the participant to pair specific numbers with presented geometric figures using a reference key. It is considered a measure of divided attention, visual scanning, tracking, and motor speed. The number of correct substitutions within the time limit is recorded with a maximum raw score of 110 on both the written and oral forms. For the present study, Total T-scores from the written version of the test were calculated based on the number of correct responses, using normative data stratified by age and education provided in the manual (Smith, 1991).

Texas Card Sorting Test (TCST)

The TCST is a brief experimental measure of cognitive flexibility and

reasoning (Kaltreider, Vertovec, Saine, & Cullum, 1999). It requires the examinee to sort six cards that share common dimensions (e.g., size, color, shape, etc.) into two groups, and then repeat the process using as many different sorting principles as possible. The total number of Logical Sorts was used for the present study. Less than or equal to four (out of eight) Logical Sorts was considered significantly impaired based on unpublished normative data (Woolston, 2006; Kaltreider et al., 1999).

C. Self-Report

Modified Fatigue Impact Scale (MFIS)

The Modified Fatigue Impact Scale (MFIS; Fisk et al., 1994) is a self-report questionnaire evaluating fatigue in multiple sclerosis and other conditions. It is a modified form of the Fatigue Impact Scale, focusing on the effects of fatigue in terms of physical, cognitive, and psychosocial functioning. The MFIS consists of 21 items on a Likert-type scale from zero to four. Total scores range from zero to 84 and were calculated by summing the responses to the scale's items. A cut-off score of 38 was used to identify participants with clinically significant levels of fatigue, as recommended by Flachenecker and colleagues (2002).

MS Neuropsychological Screening Questionnaire (MSNQ)

The MSNQ (Benedict et al., 2005) is a self-administered 15-item screening measure of neuropsychological functioning in MS within the domains of attention, processing speed, memory, and 'other cognitive functions.' Items utilize a five-point Likert-type scale (zero to four) and scores range from zero to 60. Total scores from the MSNQ were used to measure patient-reported symptoms of subjective neuropsychological dysfunction. A recommended cut-off score of 24 on the MSNQ was used to designate clinically significant self-reported cognitive symptoms in the sample (Benedict et al., 2005).

Multiple Sclerosis Quality of Life-54 Instrument (MSQOL-54)

The MSQOL-54 (Vickrey et al., 1995) is a multidimensional health-related quality of life measure, combining general quality of life concerns (from the SF-36) with MS-specific items from domains such as cognitive functioning and fatigue. It is a 54-item, self-report structured questionnaire, requiring approximately 11-18 minutes to complete (see Appendix C). There is a two-item Overall subscale for the MSQOL-54 (MSQOL-54O), and two summary composite scores, Physical Health (MSQOL-54P) and Mental Health (MSQOL-54M), are derived from a weighted combination of items. There are 12 subscales: Physical Function, Role Limitations-Physical, Role

Limitations-Emotional, Pain, Emotional Well-Being, Energy, Health Perceptions, Social Function, Cognitive Function, Health Distress, Sexual Function, and Overall QoL. Overall, Composite, and all subscale scores were utilized for the present study.

Quick Inventory of Depressive Symptomatology (QIDS)

The QIDS (Rush et al., 2003) is a 16-item inventory designed to measure the severity of depressive symptoms. The self-report version was utilized by the present study, and items employ a Likert-type scale from zero to three, yielding a total score that ranges from zero to 27. The authors provided the following recommendations for interpretation of depressive symptoms: 0-5 (no depression), 6-10 (mild), 11-15 (moderate), 16-20 (severe), and 21-27 (very severe) (Rush et al., 2003). For the purposes of this study, scores were considered clinically significant if they fell in the moderate or greater severity ranges (i.e., ≥ 11).

Analyses

Descriptive results were produced for all variables, including frequencies and percentages for categorical variables, and means and standard deviations for continuous measures. The primary outcome measures were the Overall Health-related QoL subscale (MSQOL-54O), and Composite scores from the Physical (MSQOL-54P) and Mental (MSQOL-54M) health-related QoL domains.

Statistical assumptions were examined prior to planned analyses and data were checked for normality. See Appendix B for discussion of specific statistical assumptions required for analyses. The level of significance was set at $p < .05$ for comparisons of means, correlations, and regression analyses. According to Cohen's guidelines (1988), the strengths of correlations were designated small (r = .10 to .29), medium (.30 to .49), or large (>.50). For each stepwise linear regression procedure, a predictor was deleted if alpha > .10, and added if alpha < .05. R^2-values were used to describe the percentage of variance in QoL accounted for by the predictors. Models were partially controlled for demographic factors, as objective cognitive variables (excluding the TCST) utilized demographically-adjusted standard scores (see Appendix A). Statistical analyses were conducted using SPSS, Version 18.0 (IBM Corp., Somers, NY).

Aim One

Performances on neurocognitive measures and indices of motor function (9HPT and T25FW) were considered impaired when standard scores fell at or below one *SD* from the mean of the normative population (excluding the TCST which utilized a cut-off of less than or equal to four logical sorts). The one *SD* cut-off for determination of impairment is a commonly used convention in neuropsychological research with multiple populations, including MS (Schouten, Cinque, Gisslen, Reiss, & Portegies, 2011, Kramer et al., 2006, Achiron & Barak, 2003). Nonetheless, impairment rates were also explored with more conservative

one and a half, and two *SD* cut-offs. Frequencies and percentages of impaired and unimpaired performances were calculated for measures in all neurocognitive domains of interest (learning, memory, attention and processing speed, executive functioning, and language) and motor indices. Chi-square goodness of fit tests were used to determine whether frequencies of impairment in the sample significantly differed from the frequency of impaired scores expected in a healthy control population. Specifically, using a one *SD* impairment cut-off, 16% of any normal distribution is expected to be classified as impaired. Accordingly, an expected value of 8.8 (16% of the sample size of 55) was used for Chi-square goodness of fit tests on all cognitive and physical measures. Measures with significantly more than 8.8 impaired scores were considered more impaired than the healthy control population. Only the one *SD* cut-off data were used in inferential analyses, due to sample size limitations. Using one and a half and two *SD* cut-offs, the expected values would be 3.9 (6.7% of 55) and 1.3 (2.3% of 55), resulting in exceedingly small cell sizes and limiting the meaningfulness of results.

Endorsed symptoms on self-report measures of cognition, fatigue, and depression were considered clinically significant when total scores met or exceeded validated cut-offs (MSNQ ≥ 24, MFIS ≥ 38, and QIDS ≥ 11; see Appendix A). Frequencies and percentages of participants with clinically significant symptoms were calculated for all self-report measures. Percentages of

significant scores on all self-report measures were compared to rates of impairment on objective cognitive and physical indices with Chi-square homogeneity of proportions tests to determine which measures were most frequently impaired. Associations between MSNQ scores, all objective neurocognitive and motor variables, and MFIS and QIDS scores were determined with Pearson product-moment correlations and described in a correlation matrix.

Aim Two

The relationships between objective neurocognitive testing and self-report measures of cognitive functioning and subjective health-related QoL were investigated with correlations and stepwise linear regression analyses. Objective neurocognitive variables of interest were categorized among the five following cognitive domains: learning (CVLT-II Learning T-score and BVMT-R Learning T-score), memory (CVLT-II Delayed Recall *z*-score, BVMT-R Delayed Recall T-score, and CVLT-II Discriminability *z*-score), attention and processing speed (PASAT Total T-score, SDMT Total T-score, and Stroop Color-Word T-score), executive functioning (Stroop Interference T-score and TCST Total Logical Sorts), and language (FAS Total T-score and Category Total T-score) (see Table 1). QoL variables included the two Composite scores (MSQOL-54P and Adjusted MSQOL-54M), Overall QoL subscale score (MSQOL-54O), and all other subscales of the MSQOL-54. The Mental Composite score was adjusted to exclude the Cognitive Function subdomain to control for colinearity. Associations

between all objective neurocognitive variables and subjective health-related QoL domains were determined with Pearson product-moment correlations and described in correlation matrices. For each of the five cognitive domains, separate stepwise linear regression analyses were conducted with domain-specific cognitive measures as predictors of the three QoL outcome measures (MSQOL-54P, Adj. MSQOL-54M, and MSQOL-54O). These preliminary analyses were used to determine which individual measures from each cognitive domain accounted for the most variance in QoL (i.e., the largest adjusted R^2-values).

The best predictors from the objective cognitive regression analyses were contrasted with the results of three complimentary linear regression analyses, utilizing a measure of self-reported neuropsychological symptoms (MSNQ Total score) as the predictor, and the MSQOL-54O, MSQOL-54P, and Adj. MSQOL-54M scores as criterion variables. In other words, the objective cognitive measure that best predicted MSQOL-54O was compared with the results of the regression analysis that utilized the MSNQ Total score as the predictor (and likewise for MSQOL-54P and Adj. MSQOL-54M scores). In order to correct for differences in the number of predictors, adjusted R^2-values were used as the basis for comparison of models, which enabled the determination of whether objective cognitive measures or a self-report neuropsychological index accounted for the most variance in QoL.

Aim Three

The relationships between physical, psychological, and cognitive measures of disease burden and subjective health-related QoL were examined with correlations and three separate stepwise linear regression analyses. Variables of interest included mean RNFL thickness, 9HPT T-score, T25FW T-score, MFIS Total score, QIDS Total score, MSNQ Total score, in addition to the significant objective neurocognitive predictors from the Aim One analyses discussed above. QoL variables included all subscales of the MSQOL-54, the 2 Composite scores (MSQOL-54P and MSQOL-54M), and Overall QoL subscale score (MSQOL-54O). Associations between all measures of disease burden and subjective health-related QoL domains were determined with Pearson product-moment correlations and described in a correlation matrix.

Stepwise linear regression analyses were performed to determine which measures of disease burden were the best predictors of subjective QoL in MS. Predictors included all measures of disease burden mentioned above. A stepwise linear regression analysis was performed for each criterion variable (MSQOL-54O, MSQOL-54P, and MSQOL-54M). All subdomains were included when computing the MSQOL-54M Composite score. Adjusted R^2-values were used to describe the percentage of variance in QoL accounted for by the measures of disease burden.

Exploratory Aim

The sample was split into two groups across the continuum of QoL (low and high) using the median values from the MSQOL-54 distributions. This was performed for each of the three outcome measures (MSQOL-54O, MSQOL-54M, and MSQOL-54P). Group performances on all objective and self-report measures of disease burden were compared with independent samples *t*-tests. Mann-Whitney tests (i.e., *U* statistic) were used in cases in which Levene's test for equality of variance suggested that the samples violated the homogeneity assumption.

Receiver operating characteristic (ROC) curves were constructed to characterize the discriminating abilities (low vs. high QoL) of the best individual predictors of each of the three outcome measures (MSQOL-54O, MSQOL-54M, and MSQOL-54P). Scores that maximized the percentage of correctly identified participants [i.e., (True Positive + True Negative) / *N*] were considered cut points for predicting low QoL.

CHAPTER FIVE
Results

SAMPLE CHARACTERISTICS

Study Sample and Excluded Participants

Of the 66 consecutive participants drawn from the Cognition and Demyelinating Disease project, a total of 55 met criteria for this investigation and were included in the final analyses. Of the 11 participants excluded from the study, nine (82%) were lost to follow-up from their initial visit at the MS Clinic, one was diagnosed with neuromyelitis optica (and consequently did not meet inclusion criteria), and one was missing data for most variables of the primary outcome measure (MSQOL-54).

Demographic Characteristics

Demographic characteristics of the study sample and the excluded group are described in Table 2 below. Independent samples *t*-tests revealed that the groups did not significantly differ by age [$t(64) = -.34$, $p = .738$] or education [$t(64) = 1.82$, $p = .073$]. Fisher's exact tests indicated that groups were also similar across gender ($N = 66$, $p = .351$, two-tailed) and race ($N = 66$, $p = .241$, two-tailed).

Table 2. *Demographic Characteristics of Included and Excluded Groups*

	Included (*N* = 55)	Excluded (*N* = 11)
Age (yrs.)		
Mean (*SD*)	43.2 (11.5)	44.6 (13.4)
Range	20 – 66	29 – 64
Gender (*N*, % Female)	48 (87%)	8 (73%)
Handedness (*N*, % Right)	52 (95%)	11 (100%)
Race/Ethnicity (*N*,%)		
White	49 (89%)	9 (82%)
Black	2 (4%)	2 (18%)
Hispanic	2 (4%)	0 (0%)
Asian	2 (4%)	0 (0%)
Education (yrs.)		
Mean (*SD*)	15.7 (2.4)	14.3 (2.2)
Range	8 – 20	11 – 18

Clinical and Outcome Measure Characteristics

Diagnoses, medication use, MSQOL-54 scores, and initial to follow-up intervals for included and excluded groups are summarized in Table 3 below. The study sample was predominantly comprised of participants with diagnoses of relapsing-remitting multiple sclerosis (RRMS; 82%) and clinically isolated syndrome (15%). Diagnoses differed significantly between the study sample and the excluded group, with differences between groups noted in rates of secondary progressive multiple sclerosis (SPMS), neuromyelitis optica (NMO), and transverse myelitis (TM) diagnoses (Fisher's exact test, $N = 66$, $p < .001$, two-tailed), as there were no subjects with these diagnoses in the study sample. Most of the sample was on a disease modifying therapy (DMT) at the time of their evaluations (67%), and only two participants (4%) were on steroid medications,

which were not significantly different from the excluded subjects [Fisher's exact tests; Steroid use [$N = 66$, $p = .427$, two-tailed], DMT use [$N = 66$, $p = .189$, two-tailed]. On average, included participants had an initial to follow-up testing interval of two to three weeks ($M = 18.8$ days, $SD = 12.9$). One participant completed the follow-up visit beyond the preferred four-week limit, with a 55-day interval. Despite the extended interval, this participant was included in analyses, as the follow-up data were consistent with first visit performances. Intervals did not significantly differ between included and excluded participant groups, $t(55) = .09$, $p = .930$, though the excluded group had only two subjects (nine were lost to follow-up).

Table 3. *Comparison of Included and Excluded Groups*

	Included ($N = 55$)	Excluded ($N = 11$)	*p*-value
Diagnosis (*N*, %)			<.001
CIS	8 (15%)	1 (9%)	
RRMS	45 (82%)	5 (46%)	
PPMS	1 (2%)	0 (0%)	
SPMS	0 (0%)	2 (18%)	
NMO	0 (0%)	2 (18%)	
TM	0 (0%)	1 (9%)	
Tum	1 (2%)	0 (0%)	
Steroids (*N*, % using)	2 (4%)	1 (9%)	.428
DMT (*N*, % using)	37 (67%)	5 (46%)	.189
Interval (days)			
Mean (*SD*)[§]	18.8 (12.9)	18.0 (14.1)	.932
MSQOL-54 (*M*, *SD*)[†]			
Overall	70.5 (18.5)	48.2 (22.8)	.001
Mental Comp.	64.8 (20.6)	43.3 (17.9)	.003
Physical Comp.	61.6 (19.4)	45.8 (22.4)	.025

Note. Abbreviations: CIS = Clinically isolated syndrome; RRMS = Relapsing-remitting MS; PPMS = Primary progressive MS; SPMS = Secondary progressive MS; NMO = Neuromyelitis optica; TM = Transverse myelitis; Tum = Tumefactive MS; DMT = Disease-modifying therapy
[§]Excluded group $N = 2$, as 9 participants were lost to follow-up
[†]Excluded group $N = 10$, as 1 participant had missing MSQOL-54 data

The included group significantly differed from the excluded group on overall and composite QoL outcome measures, as determined with independent samples *t*-tests. On the MSQOL-54O, the included group (M = 70.5, SD = 18.5) exhibited significantly greater overall QoL scores than the excluded group (M = 48.2, SD = 22.8), $t(63) = 3.39$, $p = .001$. Scores on the Mental QoL Composite (MSQOL-54M) significantly differed between the included (M = 64.8, SD = 20.6) and excluded (M = 43.3, SD = 17.9) groups, $t(63) = 3.10$, $p = .003$. Physical Composite QoL scores (MSQOL-54P) were also significantly different between included (M = 61.6, SD = 19.4) and excluded (M = 45.8, SD = 22.4) groups, $t(63) = 2.30$, $p = .025$. Groups did not significantly differ on QIDS Total [$t(63) = -1.77$, $p = .08$], MFIS Total [$t(63) = -1.37$, $p = .18$], or MSNQ Total [$t(63) = -.89$, $p = .38$] scores. Overall, while included and excluded participants exhibited similar levels of fatigue, depression, and self-reported cognitive symptoms, the excluded group had lower QoL scores across all three summary measures. According to these results, QoL scores of the included study sample may be biased, as those lost to follow-up and excluded from the following analyses had lower QoL scores.

Descriptive Statistics

Means, medians, standard deviations, and ranges for all study variables are presented in Table 4 below. See Appendix B for discussion of variable distributions and statistical assumptions required for accurate analyses.

Table 4. *Descriptive Statistics for Cognitive, Physical, and Self-report Measures*

Variable	Mean (*SD*) (*N* = 55)	Median	Range
Objective Cognitive Measures			
Learning			
CVLT-II Learning T-score	50.4 (11.7)	51.0	25 – 72
BVMT-R Learning T-score	46.7 (12.2)	49.0	20 – 69
Memory			
CVLT-II Delayed Recall *z*-score	-0.13 (1.3)	0.0	-3.0 – 2.0
BVMT-R Delayed Recall T-score	48.6 (12.3)	52.0	20 – 64
CVLT-II Discriminability *z*-score	0.06 (1.1)	0.0	-3.0 – 2.0
Attention & Processing Speed			
PASAT Total T-score	43.9 (14.9)	49.0	0 – 60
SDMT Total T-score	48.8 (13.7)	49.0	8 – 75
Stroop Color-Word T-score*	48.1 (9.5)	49.0	21 – 67
Executive Functioning			
Stroop Interference T-score*	50.6 (7.1)	49.0	20 – 69
TCST Logical Sorts	5.8 (1.2)	6.0	2 – 8
Language			
FAS Total T-score	44.3 (11.3)	43.0	20 – 74
Category Total T-score	44.8 (10.8)	47.0	17 – 64
Physical Measures			
Gait Speed			
T25FW T-score**	40.8 (15.0)	44.0	0 – 63
Fine Motor Control			
9HPT T-score	35.9 (13.9)	39.0	0 – 53
Neurodegenertation			
Mean RNFL Thickness (µm)	87.2 (14.0)	88.0	40 – 124
Self-report Measures			
Depression			
QIDS Total	9.6 (5.4)	8.0	2 – 26
Fatigue			
MFIS Total	40.3 (18.7)	42.0	2 – 80
Cognitive Symptoms			
MSNQ Total	23.0 (13.0)	21.0	1 – 57
Quality of Life			
Overall, Mental, & Physical			
MSQOL-54O	70.5 (18.5)	73.3	28 – 100
MSQOL-54M	64.8 (20.6)	70.3	10 – 98
MSQOL-54P	61.6 (19.4)	64.4	20 – 99
Adj. MSQOL-54M (excluding Cog. subscale)	56.2 (17.5)	59.2	8 – 83
Subscales			
Physical Functioning	68.9 (30.0)	80.0	5 – 100
Limitations- Physical	43.6 (38.9)	50.0	0 – 100
Limitations- Emotional	63.6 (39.2)	66.7	0 – 100
Pain	75.8 (22.6)	76.7	23 – 100
Emotional Well-being	67.0 (18.2)	64.0	12 – 96
Energy	38.8 (22.4)	36.0	0 – 100
Health Perceptions	58.2 (21.3)	60.0	12 – 100
Social Functioning	75.9 (21.4)	83.3	16 – 100
Cognitive Functioning	58.7 (28.1)	65.0	0 – 100
Health Distress	62.7 (26.2)	70.0	0 – 100
Sexual Functioning	71.2 (31.6)	83.3	0 – 100

Note. Raw scores unless otherwise designated (i.e., T- or *z*-scores)
*N = 54; 1 participant was color-blind and unable to perform the task
**N = 54; 1 participant was in a wheelchair with a broken leg and unable to perform the task

CHARACTERIZATION OF IMPAIRMENT

Performances on objective measures of cognitive and motor functioning were considered impaired when standard scores fell at or below one *SD* from the normative means. A cut-off of four or fewer Logical Sorts was used to determine significant impairment on the TCST. Endorsements on self-report indices of fatigue (MFIS), depression (QIDS), and cognitive symptoms (MSNQ) were considered clinically significant when scores met or exceeded published recommended cut-offs (i.e., MSNQ ≥ 24, MFIS ≥ 38, and QIDS ≥ 11).

Cognitive and Motor Impairment

Frequencies and percentages of impaired performances (≤ 1 *SD* from the normative means) on neurocognitive and motor measures are presented in Table 5, in addition to rates according to more conservative one and a half and two *SD* cut-offs (i.e., ≤ 35 or ≤ 30 for T-scores, and ≤ -1.5 or ≤ -2 for *z*-scores). According to a standard normal distribution, 16% of cases fall below one *SD* of the mean on a single test. As such, 16% of the normative standardization samples for each measure are expected to fall within the impaired range when impairment is defined as one *SD* below the mean. In other words, in a normal (i.e., disease-free, control population) distribution of equal size to the MS study sample ($N = 55$), 8.8 cases would be expected to fall within the impaired range (16% of 55). Likewise, using one and a half and two *SD* cut-offs, approximately seven percent and two percent of a normative distribution would be expected to fall in the impaired

range, respectively. Accordingly, 3.9 (6.7% of 55) and 1.3 (2.3% of 55) cases would be expected to be classified as impaired in a normative sample of the same size as the study sample. Only the one *SD* cut-off rates of impairment were compared to expected rates in a normative sample with inferential statistical analyses due to sample size restrictions. According to Hypothesis One, it was posited that objective measures of motor function, attention and processing speed, and learning would be more frequently impaired than the normative population, while recall memory, language, and executive function would be similar to the healthy control population.

Table 5. *Frequencies of Impairment for Cognitive and Motor Measures by Cut-offs* ($N = 55$)

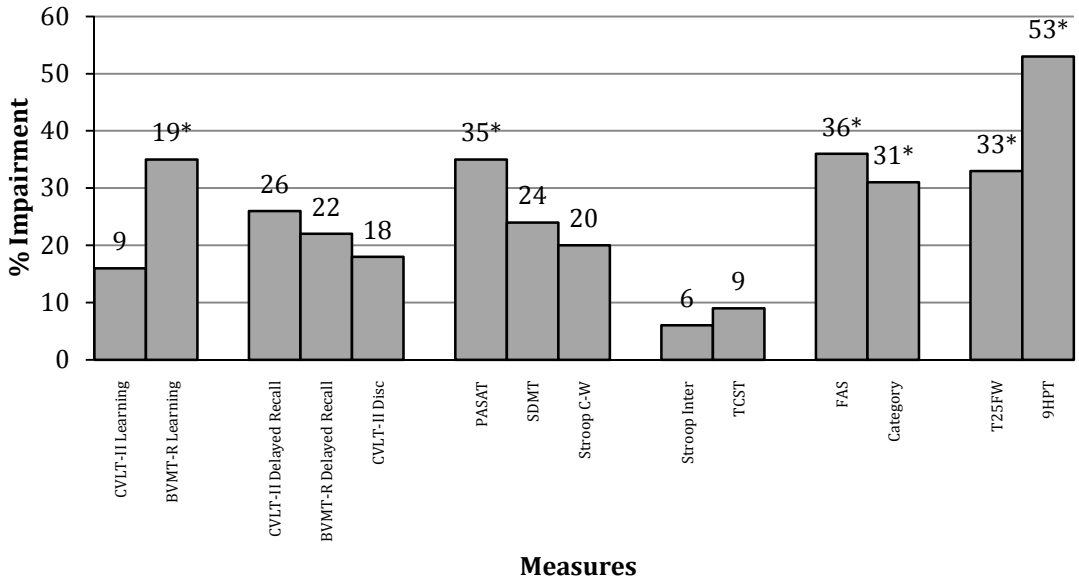
Variable	≤ 1 *SD* Impaired (*N*, %)	≤ 1.5 *SD*[§] Impaired (*N*, %)	≤ 2 *SD*[§§] Impaired (*N*, %)
Objective Cognitive Measures			
Learning			
CVLT-II Learning T-score	9 (16%)	8 (15%)	5 (9%)
BVMT-R Learning T-score	19 (35%)[*]	5 (9%)	5 (9%)
Memory			
CVLT-II Delayed Recall *z*-score	14 (26%)	9 (16%)	7 (13%)
BVMT-R Delayed Recall T-score	12 (22%)	8 (15%)	7 (13%)
CVLT-II Discriminability *z*-score	10 (18%)	9 (16%)	6 (11%)
Attention & Processing Speed			
PASAT Total T-score	19 (35%)[*]	11 (20%)	7 (13%)
SDMT Total T-score	13 (24%)	9 (16%)	5 (9%)
Stroop Color-Word T-score[†]	11 (20%)	7 (13%)	1 (2%)
Executive Functioning			
Stroop Interference T-score[†]	3 (6%)	1 (2%)	0 (0%)
TCST Logical Sorts	5 (9%)	---	---
Language			
FAS Total T-score	20 (36%)[*]	12 (22%)	5 (9%)
Category Total T-score	17 (31%)[*]	10 (18%)	7 (13%)
Motor Function			
Gait Speed			
T25FW T-score[†]	18 (33%)[*]	14 (26%)	7 (13%)
Fine Motor Control			
9HPT T-score	29 (53%)[*]	18 (33%)	15 (27%)

Note. [†]$N = 54$; 1 participant unable to perform the task
[*]Impairment frequency significantly different from expected (8.8) in a normative sample, $p < .05$
[§]Expected frequency of 3.9 in normative sample
[§§]Expected frequency of 1.3 in normative sample

Chi-square goodness of fit tests revealed that numerous cognitive and motor variables were (significantly) more frequently impaired in the MS sample than expected in the normal population, using a one *SD* cut-off (see Figure 1 below). These variables included BVMT-R Learning T-score [$\chi^2(1, N = 55) = 13.29, p < .001$], PASAT Total T-score [$\chi^2(1, N = 55) = 13.29, p < .001$], FAS Total T-score [$\chi^2(1, N = 55) = 16.08, p < .001$], Category Total T-score [$\chi^2(1, N = 55) = 8.50, p = .004$], T25FW T-score [$\chi^2(1, N = 54) = 10.80, p = .001$], and 9HPT T-score [$\chi^2(1, N = 55) = 53.14, p < .001$]. No other measures were more frequently impaired than expected in the normal population. It is notable that both measures of executive functioning were less frequently impaired than the expected count from the normative population. Overall, using a one *SD* cut-off, the MS group exhibited significantly impaired performances on at least one measure within each of the domains of motor functioning, learning, attention and processing speed, and language. In contrast, measures of memory were not significantly more impaired than expected (though a similar trend was observed), and measures of executive functioning were actually less impaired. Although inferential statistics were not appropriate for use with the impairment rates defined by more conservative cut-offs (i.e., 1.5 *SD* and 2 *SD*), comparison of frequencies of impaired scores with expected rates in the normative sample revealed greater rates of impairment in the MS sample across all measures, with

the exception of the Stroop Interference T-score in the executive functioning domain.

Figure 1. *Impairment Frequencies of Cognitive and Physical Measures* (*N* = 55)†



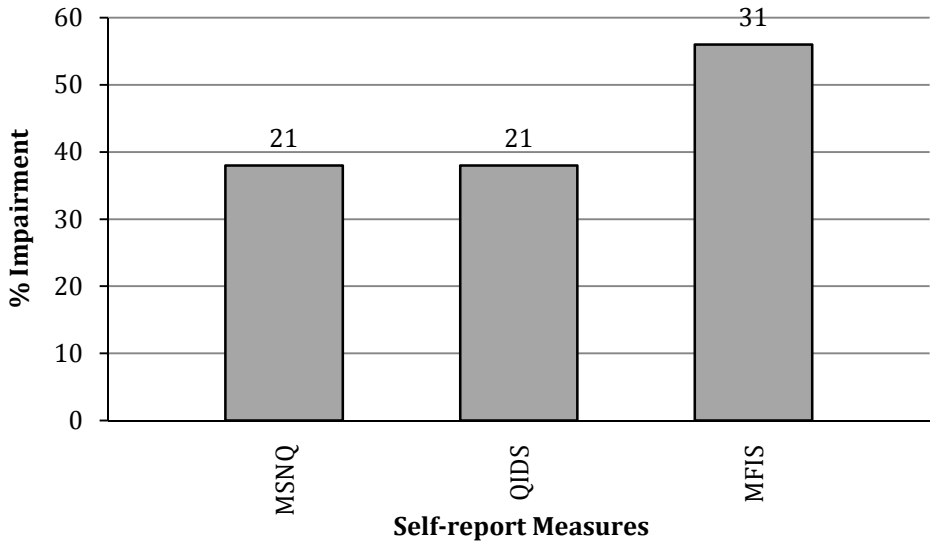
Note. *Significantly different from frequency of 8.8 expected in a disease-free population (1 *SD* cut-off)
†*N* = 54 for Stroop and T25FW

Clinically Significant Self-reported Symptoms

In addition to the noted frequency of deficits within objective cognitive and motor domains of functioning, the sample exhibited clinically significant symptoms on self-report measures of fatigue, depression, and cognitive symptoms (see Figure 2). Hypothesis Two stated that MS patients would have a higher frequency of significant elevations on self-report measures than on objective cognitive and physical indices. Twenty-one participants (38%) reported clinically significant symptoms on the MSNQ, 31 (56%) reported clinically significant

fatigue on the MFIS, and 21 (38%) fell in the clinically significant range on the QIDS, according to the validated cut-offs described above. Frequencies of clinically significant symptoms on measures of self-reported cognitive functioning (MSNQ; 38%) and depression (QIDS; 38%) were similar to rates of impairment on some, but not all, of the objective cognitive and motor indices [i.e., BVMT-R Learning (35%), PASAT (35%), FAS (36%), Category (31%), & T25FW (33%); see Table 5].

Figure 2. *Frequency of Clinically Significant Elevations on Self-report Measures* (*N* = 55)



Note. Abbreviations: MSNQ = Multiple Sclerosis Neuropsychological Questionnaire, QIDS = Quick Inventory of Depressive Symptomatology; MFIS = Modified Fatigue Impact Scale

It should be noted that the cut-offs for clinically significant symptoms on the self-report measures do not necessarily correspond with a one *SD* difference from the mean, as was employed with the objective cognitive and physical measures.

Nonetheless, the one *SD* convention for the objective measures is the most liberal cut point, resulting in greater rates of impairment than the more stringent one and a half and two *SD* conventions. Despite this difference in metric, of all objective cognitive, physical, and self-report measures, fine motor control and fatigue were the most frequently impaired or elevated. Chi-square tests of homogeneity of proportions indicated that frequencies of impairment/elevation on these measures (9HPT: $N = 29$, 53%; MFIS: $N = 31$, 56%) were similar, but rates for both were significantly greater than frequency of impairment and clinically elevated symptoms on all other cognitive, physical, and self-report indices (all $p < .03$).

COGNITION AND QUALITY OF LIFE

Associations between cognitive indices and QoL measures (MSQOL-54O, Adj. MSQOL54-M, MSQOL-54P, and all subscales) were determined with Pearson product-moment correlations and described in Table 6 below.

Table 6. *Correlations between Objective Cognitive Measures and QoL Summary and Subscale Scores* ($N = 55$)

	QoL Summary Measures[§] (r)			MSQOL-54 Subscales (r)			
Objective Cognitive Measures	MQOL-54O	Adj.MSQOL-54M	MSQOL-54P	Physical Function	Role Limitations-Physical	Role Limitations-Emotional	Pain
Cognitive Function ($N = 55$)							
Learning							
CVLT-II Learning T-score	.04	.20	.19	.05	.19	.13	.01
BVMT-R Learning T-score	.05	.23	.20	.23	.09	.32*	.19
Memory							
CVLT-II Delayed Recall *z*-score	.04	.18	.19	.08	.23	.06	.06
BVMT-R Delayed Recall T-score	.04	.23	.14	.23	.03	.22	.04
CVLT-II Discriminability *z*-score	.00	.08	.07	-.06	.21	.00	-.02
Attention & Processing Speed							
PASAT Total T-score	.26	.42**	.41**	.30*	.41**	.35**	.24
SDMT Total T-score	.29*	.45**	.38**	.30*	.31*	.40**	.22
Stroop Color-Word T-score[†]	.17	.34*	.37**	.31*	.34*	.20	.06
Executive Functioning							
Stroop Interference T-score[†]	.04	.11	.29*	.31*	.32*	.03	.13
TCST Logical Sorts	.11	.27*	.25	.35**	.13	.20	.09
Language							
FAS Total T-score	-.03	.13	.03	-.10	.12	.06	-.19
Category Total T-score	.03	.22	.20	.12	.18	.14	-.13

Note. [§]Abbreviations: MSQOL-54O = Overall QoL; Adj. MSQOL-54M = Adjusted Mental QoL Composite; MSQOL-54P = Physical QoL Composite
[†]$N = 54$; 1 participant was color-blind and unable to perform the task
*$p < .05$, **$p < .01$, and ***$p < .001$

Table 6 (Continued). *Correlations between Objective Cognitive Measures and QoL Summary and Subscale Scores* ($N = 55$)

	MSQOL-54 Subscales (r)						
Objective Cognitive Measures	Emotional Well-being	Energy	Health Perceptions	Social Function	Cognitive Function[††]	Health Distress	Sexual Function
Cognitive Function ($N = 55$)							
Learning							
CVLT-II Learning T-score	.07	.14	.30*	.21	.39**	.26	-.07
BVMT-R Learning T-score	.04	.11	.18	.32*	.23	.18	-.20
Memory							
CVLT-II Delayed Recall *z*-score	.08	.14	.18	.31*	.32*	.30*	-.28*
BVMT-R Delayed Recall T-score	.10	.06	.13	.23	.31*	.20	-.23
CVLT-II Discriminability *z*-score	-.02	.04	.10	.21	.28*	.17	-.30*
Attention & Processing Speed							
PASAT Total T-score	.22	.24	.32*	.52***	.50***	.39**	-.15
SDMT Total T-score	.30*	.23	.36**	.52***	.51***	.36**	-.16
Stroop Color-Word T-score[†]	.25	.13	.35*	.36**	.36**	.44**	-.01
Executive Functioning							
Stroop Interference T-score[†]	.06	-.07	.27*	.14	.09	.27*	.08
TCST Logical Sorts	.29*	.15	.11	.30*	.24	.19	.07
Language							
FAS Total T-score	.11	.15	.00	.17	.30*	.13	-.11
Category Total T-score	.23	.26	.14	.33*	.27	.25	-.04

Note. [†]$N = 54$; 1 participant was color-blind and unable to perform the task
*$p < .05$, **$p < .01$, and ***$p < .001$

Of all objective neurocognitive measures, only the SDMT was significantly associated with overall QoL (MSQOL-54O), $r(53) = .29$, $p = .034$, though the coefficient was small. Significant correlations of medium strength were observed between mental health-related QoL (Adj. MSQOL-54M; excluding the Cognitive Function subscale) and all measures of attention and processing speed [$r(53) = .34$ to .45]. Similar significant associations of medium strength were observed between measures of attention and processing speed and physical health-related QoL [MSQOL-54P; $r(53) = .37$ to .41]. A small but significant association was observed between the Stroop Interference T-score and physical health related QoL [MSQOL-54P; $r(52) = .29$]. All other neurocognitive measures exhibited non-significant associations with QoL summary measures from the MSQOL-54.

Consistent with these results were significant associations between measures of attention and processing speed (e.g., SDMT and PASAT) and numerous MSQOL-54 subscales, including Physical Function [$r(53) = .30$ to .31], Physical Limitations [$r(53) = .31$ to .41], Emotional Limitations [$r(53) = .35$ to .40], Health Perceptions [$r(53) = .32$ to .36], and Health Distress [$r(53) = .36$ to .44]. Medium to large relationships were observed between attention and processing speed measures and Social [$r(53) = .36$ to .52] and Cognitive [$r(53) = .36$ to .51] Function. Other significant associations were observed between objective cognitive indices and various MSQOL-54 subscales, though the correlations were small (See Table 6).

Self-reported symptoms on the MSNQ, a subjective measure of neuropsychological functioning, were significantly associated with all three health-related quality of life outcome measures. Specifically, a medium strength inverse association was observed between the MSNQ and overall QoL (MSQOL-54O), $r(53) = -.30$, $p = .027$, which was similar to the correlation strength between the PASAT and MSQOL-54O. The MSNQ also had an inverse correlation of medium strength with physical health-related QoL (MSQOL-54P), $r(53) = -.48$, $p < .001$. This association appeared slightly stronger than the most highly associated objective cognitive measures [$r(53) = .37$ to $.41$; for measures in the attention and processing speed domain]. A large association was observed between the MSNQ and mental health-related QoL (MSQOL-54M), $r(53) = -.67$, $p = .001$, greater than any mental QoL associations with objective cognitive measures.

Predictors of Quality of Life

It was postulated in Hypothesis Three that measures of attention, processing speed, and learning would be significant predictors of QoL, in contrast to delayed memory, executive functioning, and language abilities.

Demographic Factors

Although cognitive predictors in regression analyses were demographically-adjusted standard scores, the relationships between age and education and QoL outcome measures were analyzed with Pearson product-moment correlations and linear regression, to determine whether such variables

needed to be included in subsequent analyses. Overall QoL (MSQOL-54O) was not significantly associated with age [$r(53) = .07$, $p = .596$] or education [$r(53) = .23$, $p = .088$], and neither variable was included in stepwise regression analyses predicting MSQOL-54O scores.

Adjusted mental health-related QoL (Adj. MSQOL-54M) was significantly associated with education [$r(53) = .35$, $p = .008$], but not age [$r(53) = .21$, $p = .119$]. In a stepwise linear regression analysis, only education significantly predicted Adj. MSQOL-54M scores, $b = 2.62$, $t(52) = 2.74$, $p = .008$. Education accounted for 11% of the variance in mental QoL scores, adjusted $R^2 = .11$, $F(1, 52) = 7.51$, $p = .008$. Accordingly, education was included in subsequent stepwise regression analyses predicting adjusted MSQOL-54M scores.

Physical health-related QoL (MSQOL-54P) was also significantly associated with education [$r(53) = .38$, $p = .005$], but not age [$r(53) = -.10$, $p = .459$]. In a stepwise regression analysis, only education significantly predicted MSQOL-54P scores and was entered into the procedure, $b = 3.34$, $t(52) = 3.01$, $p = .004$. Education accounted for 13% of the variance in physical QoL scores, adjusted $R^2 = .13$, $F(1, 52) = 9.07$, $p = .004$. Accordingly, education was included in subsequent stepwise regression analyses predicting MSQOL-54P scores.

Learning Measures

Neither objective cognitive measure of learning (CVLT-II Total T-score or BVMT-R Total T-score) was a significant predictor of overall, adjusted mental,

or physical health-related QoL on the MSQOL-54, and neither was entered in the stepwise procedures.

Memory Measures

None of the objective cognitive measures of memory (CVLT-II Delayed Recall *z*-score, BVMT-R Delayed Recall T-score, and CVLT-II Discriminability *z*-score) were significant predictors of overall, adjusted mental, or physical health-related QoL on the MSQOL-54, and none were entered in the stepwise procedures.

Attention and Processing Speed Measures

Of the three measures of attention and processing speed (PASAT, SDMT, and Stroop C-W T-scores) and education, only the SDMT T-score was a significant predictor of overall QoL in the stepwise analysis, $b = .397$, $t(53) = 2.21$, $p = .032$. The SDMT accounted for seven percent of the variance in MSQOL-54O scores, adjusted $R^2 = .07$, $F(1, 53) = 4.88$, $p = .032$. Similarly, the SDMT T-score was the only significant predictor of adjusted mental health-related QoL entered into the procedure, $b = .578$, $t(53) = 3.66$, $p = .001$, accounting for 19% of the variance in adjusted MSQOL-54M scores, adjusted $R^2 = .19$, $F(1, 53) = 13.39$, $p = .001$. In predicting physical health-related QoL, only the PASAT T-score was significant and entered into the equation, $b = .550$, $t(53) = 3.37$, $p = .001$. The PASAT accounted for 16% of the variance in MSQOL-54P scores, adjusted $R^2 = .16$, $F(1, 53) = 11.37$, $p = .001$.

Executive Functioning Measures

Neither of the objective cognitive measures of executive functioning (Stroop Interference T-score or TCST Logical Sorts) was a significant predictor of overall, adjusted mental, or physical health-related QoL on the MSQOL-54, and both were excluded from the stepwise procedures.

Language Measures

Neither of the objective cognitive measures of expressive language functioning (FAS or Category T-scores) were significant predictors of overall, adjusted mental, or physical health-related QoL on the MSQOL-54, and both were excluded from the stepwise procedures.

Summary of Objective Cognitive Predictors

The results of the above regression analyses demonstrated that most objective measures of neurocognitive functioning were non-significant predictors of overall, mental, and physical health-related QoL. However, measures of attention appeared to significantly predict QoL, with the SDMT accounting for seven percent of the variance in overall QoL (MSQOL-54O), and 19% of the variance in mental health-related QoL (adjusted MSQOL-54M). Additionally, the PASAT was a significant predictor of physical health-related QoL, accounting for 16% of the variance in MSQOL-54P scores.

Subjective Cognitive Functioning

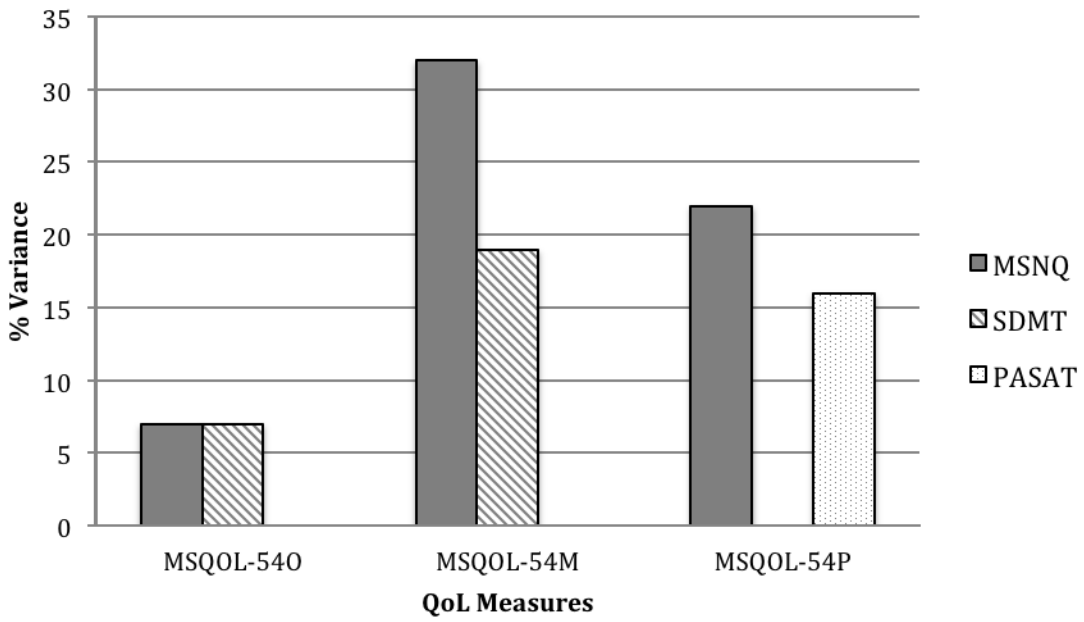
Self-reported cognitive functioning on the MSNQ was a significant predictor of overall QoL, $b = -.425$, $t(53) = -2.28$, $p = .027$, and accounted for seven percent of the variance in MSQOL-54O scores, adjusted $R^2 = .07$, $F(1, 53) = 5.20$, $p = .027$. The MSNQ was also a significant predictor of mental health-related QoL, $b = -.781$, $t(53) = -5.16$, $p < .001$, accounting for 32% of the variance in adjusted MSQOL-54M scores, adjusted $R^2 = .32$, $F(1, 53) = 26.59$, $p < .001$. Additionally, physical health-related QoL was significantly predicted by MSNQ Total scores, $b = -.716$, $t(53) = -3.98$, $p < .001$, which accounted for 22% of the variance in MSQOL-54P scores, adjusted $R^2 = .22$, $F(1, 53) = 15.80$, $p < .001$. Education did not remain a significant predictor when included with the MSNQ.

Comparison of Subjective and Objective Cognitive Predictors

Hypothesis Four posited that subjective self-reported neuropsychological symptoms would account for more variance in QoL than objective cognitive measures. Comparison of adjusted R^2-values revealed that subjective neuropsychological functioning as measured by the MSNQ accounted for the same amount of variance (7%) in overall QoL as the significant objective cognitive predictor (SDMT; 7%). However, MSNQ scores accounted for more variance than the significant objective neurocognitive predictors for both mental and physical health-related QoL. As illustrated in Figure 3, the MSNQ accounted for 32% of the variance in mental health-related QoL, while the SDMT only

accounted for 19%. Also, the MSNQ accounted for 22% of the variance in physical health-related QoL, while the PASAT only accounted for 16%.

Figure 3. *Adjusted Variance Accounted for by Significant Cognitive Predictors of QoL* (*N* = 55)



Note. Abbreviations: MSQOL-54O = Overall QoL; MSQOL-54M = Adjusted Mental QoL Composite; MSQOL-54P = Physical QoL Composite; MSNQ = Multiple Sclerosis Neuropsychological Questionnaire; SDMT = Symbol Digit Modalities Test; PASAT = Paced Auditory Serial Addition Test

DISEASE BURDEN AND QUALITY OF LIFE

Associations between objective and self-reported cognitive indices and QoL outcome measures (including all subscales) were previously described in Table 6. Associations between physical and self-report indices of disease burden and QoL measures were determined with Pearson product-moment correlations and described in Table 7 below.

Table 7. *Correlations between Physical and Self-Report Indices and QoL Summary and Subscale Scores* ($N = 55$)

	QoL Measures[§] (r)			MSQOL-54 Subscales (r)			
Measures of Disease Burden	MQOL-54O	MSQOL-54M	MSQOL-54P	Physical Function	Role Limitations-Physical	Role Limitations-Emotional	Pain
Physical Functioning ($N = 55$)							
Gait Speed							
T25FW T-score[†]	.30*	.34*	.51***	.75***	.27*	.32*	.39**
Fine Motor Control							
9HPT T-score	.33*	.46***	.57***	.56***	.43**	.34**	.32**
Neurodegeneration							
RNFL Thickness (µm)	-.04	.03	-.02	.20	-.12	.19	.12
Self-report Indices							
Depression							
QIDS Total	-.51***	-.80***	-.63***	-.43**	-.51***	-.64***	-.26
Fatigue							
MFIS Total	-.57***	-.75***	-.83***	-.58***	-.74***	-.52***	-.53***
Cognitive Symptoms							
MSNQ Total	-.30*	-.67***	-.48***	-.23	-.45**	-.59***	-.23

Note. [§]Abbreviations: MSQOL-54O, Overall QoL; MSQOL-54M, Mental QoL Composite (unadjusted); MSQOL-54P, Physical QoL Composite
[†]$N = 54$; 1 participant was unable to perform the task (broken leg)
*$p < .05$, **$p < .01$, and ***$p < .001$

Table 7 (Continued). *Correlations between Physical and Self-Report Indices and QoL Summary and Subscale Scores* ($N = 55$)

	MSQOL-54 Subscles						
Measures of Disease Burden	Emotional Well-being	Energy	Health Perceptions	Social Function	Cognitive Function	Health Distress	Sexual Function
Physical Functioning ($N = 55$)							
Gait Speed							
T25FW T-score[†]	.30*	.19	.35**	.43**	.14	.25	.07
Fine Motor Control							
9HPT T-score	.38**	.39**	.47***	.48***	.43**	.41**	.06
Neurodegeneration							
RNFL Thickness (µm)	-.11	-.15	-.08	.17	.04	-.14	-.18
Self-report Indices							
Depression							
QIDS Total	-.74***	-.50***	-.51***	-.66***	-.68***	-.55***	-.18
Fatigue							
MFIS Total	-.62***	-.69***	-.67***	-.73***	-.77***	-.54***	-.29*
Cognitive Symptoms							
MSNQ Total	-.47***	-.39**	-.42**	-.57***	-.87***	-.29*	-.24

Note. [†]$N = 54$; 1 participant was unable to perform the task (broken leg)
*$p < .05$, **$p < .01$, and ***$p < .001$

Physical measures of gait speed (T25FW) and fine motor control (9HPT) were significantly associated with all QoL outcome measures, though the association with the mental composite was strongest for the 9HPT. Specifically, T25FW T-scores had medium correlations with the MSQOL-54O [$r(52) = .30$] and MSQOL-54M [$r(52) = .34$], and a large association with the MSQOL-54P [$r(52) = .51$]. Similar significant associations were observed between 9HPT T-scores and MSQOL-54O [$r(53) = .33$] and MSQOL-54P [$r(53) = .57$], though the 9HPT was more highly associated with MSQOL-54M [$r(53) = .46$] than was the T25FW [$r(52) = .34$]. Mean RNFL thickness was not significantly associated with any of the QoL outcome measures.

When considering all MSQOL-54 subscales, significant associations were observed with physical measures of ambulation and manual dexterity. Specifically, gait speed (T25FW) was significantly associated with most subscales [$r(52) = .27$ to $.75$], excluding Energy, Cognitive Function, Health Distress, and Sexual Function. Gait speed was most highly associated with Physical Function [$r(52) = .75$]. Fine motor control on the 9HPT was significantly associated with all subscales [$r(53) = .34$ to $.56$], with the exception of Sexual Function, and it was also most highly correlated with Physical Function [$r(53) = .56$]. Mean RNFL thickness was not significantly associated with any of the MSQOL-54 subscales.

Large inverse correlations were observed between all health-related QoL summary measures and indices of depression and fatigue. QIDS Total scores were most highly associated with mental health-related QoL [MSQOL-54M; $r(53) = -.80$], followed by physical [MSQOL-54P; $r(53) = -.63$], and overall [MSQOL-54O; $r(53) = -.51$] QoL. MFIS Total score was most highly associated with physical health-related QoL [MSQOL-54P; $r(53) = -.83$], followed by mental [MSQOL-54M; $r(53) = -.75$], and overall [MSQOL-54O; $r(53) = -.57$] QoL. Accordingly, of the cognitive, physical, and self-report indices of disease burden, measures of depression and fatigue appeared most associated with QoL across all three QoL measures.

When considering the relationships between all MSQOL-54 subscales and the self-report indices, depression and fatigue had the greatest inverse correlations, with the exception of Cognitive Function, which was most highly associated with the MSNQ [$r(53) = -.87$]. Depression as measured with the QIDS, was significantly associated with all subscales [$r(53) = -.43$ to $-.74$], except for Pain and Sexual Function. The QIDS was most highly associated with Emotional Well-being [$r(53) = -.74$], followed by Cognitive [$r(53) = -.68$] and Social [$r(53) = -.66$] Function. Self-reported fatigue on the MFIS was significantly correlated with all MSQOL-54 subscales [$r(53) = -.29$ to $-.77$]. The MFIS was most highly associated with Cognitive Function [$r(53) = -.77$] and Physical Limitations [$r(53) = -.74$], followed by Social Function [$r(53) = -.73$], and Energy [$r(53) = -.69$].

Predictors of Quality of Life

Demographic Factors

As mentioned earlier, overall QoL (MSQOL-54O) was not significantly associated with age or education, and neither variable was included in stepwise regression analyses predicting MSQOL-54O scores. Also described previously, physical health-related QoL (MSQOL-54P) was significantly associated with education, but not age. Accordingly, education was included in subsequent stepwise regression analyses predicting MSQOL-54P scores. Similar to the results of analyses with the adjusted composite, mental health-related QoL (MSQOL-54M; unadjusted) was significantly associated with education [$r(53) = .38$, $p = .004$], but not age [$r(53) = .21$, $p = .105$]. In a stepwise regression analysis, only education significantly predicted MSQOL-54M scores and was entered into the procedure, $b = 3.35$, $t(52) = 3.01$, $p = .004$. Education accounted for 13% of the variance in mental QoL scores, adjusted $R^2 = .13$, $F(1, 52) = 9.07$, $p = .004$. Accordingly, education was included in subsequent stepwise regression analyses predicting MSQOL-54M (unadjusted) scores.

Physical Measures

Of the three physical measures (9HPT, T25FW, and RNFL thickness) and education, only the 9HPT T-score was a significant predictor of overall QoL and entered into the stepwise procedure, $b = .447$, $t(53) = 2.59$, $p = .012$, accounting for 10% of the variance in MSQOL-54O scores, adjusted $R^2 = .10$, $F(1, 53) =$

6.70, $p = .012$. Similarly, the 9HPT T-score was the only significant predictor of mental health-related QoL entered, $b = .691$, $t(53) = 3.82$, $p < .001$, which accounted for 20% of the variance in MSQOL-54M scores, adjusted $R^2 = .20$, $F(1, 53) = 14.57$, $p < .001$. In predicting physical health-related QoL, only the T25FW T-score was significant and entered into the procedure, $b = .802$, $t(53) = 5.35$, $p < .001$, accounting for 34% of the variance in MSQOL-54P scores, adjusted $R^2 = .34$, $F(1, 53) = 28.57$, $p < .001$.

Self-report Measures

Of the 3 self-report measures of depression, fatigue, and cognitive symptoms (QIDS, MFIS, and MSNQ) and education, only the MFIS Total score was a significant predictor of overall QoL and entered into the procedure, $b = -.560$, $t(53) = -5.00$, $p < .001$. The MFIS Total score accounted for 31% of the variance in MSQOL-54O scores, adjusted $R^2 = .31$, $F(1, 53) = 25.02$, $p < .001$.

When predicting mental health-related QoL, both the QIDS and MFIS Total scores were significant predictors and both were entered in the stepwise procedure. Education did not remain a significant predictor and was not entered into the procedure. Only the QIDS Total score was entered in step one, $b = -.071$, $t(53) = -9.85$, $p < .001$, accounting for 64% of the variance in MSQOL-54M scores, adjusted $R^2 = .64$, $F(1, 53) = 97.09$, $p < .001$. At step two, the MFIS Total score ($b = -.416$, $t(52) = -3.86$, $p < .001$) was entered in the equation with the QIDS Total score ($b = -2.11$, $t(52) = -5.64$, $p < .001$), increasing the amount of

variance accounted for by the predictors to 72%, adjusted $R^2 = .72$, $F(1, 52) = 68.72$, $p < .001$. Nonetheless, the addition of the MFIS to the equation only added an additional eight percent to the amount of variance accounted for, which suggested that the QIDS was the single best self-report predictor of mental health-related QoL. Additionally, the QIDS and the MFIS were highly correlated ($r = .67$), suggesting that the two measures have considerable shared variance and may measure similar or overlapping constructs.

When predicting physical health-related QoL, all three self-report indices (MFIS, MSNQ, and QIDS Total scores) were significant predictors and included in the stepwise analysis. Education did not remain a significant predictor and was not entered into the procedure. Only the MFIS Total score was entered in step one, $b = -.864$, $t(53) = -10.94$, $p < .001$, accounting for 69% of the variance in MSQOL-54P scores, adjusted $R^2 = .69$, $F(1, 53) = 119.70$, $p < .001$. At step two, the MSNQ Total score ($b = .489$, $t(52) = 3.07$, $p = .003$) was entered in the equation with the MFIS Total score ($b = -1.12$, $t(52) = -10.11$, $p < .001$), increasing the amount of variance accounted for by the predictors to 73%, adjusted $R^2 = .73$, $F(1, 52) = 74.10$, $p < .001$. At step three, QIDS Total score ($b = -.826$, $t(51) = -2.42$, $p = .019$) was entered in the equation with the MSNQ Total score ($b = -.599$, $t(51) = 3.77$, $p < .001$) and MFIS Total score ($b = -1.02$, $t(51) = -8.91$, $p < .001$). The inclusion of the QIDS further increased the amount of variance accounted for by the predictors to 75%, adjusted $R^2 = .75$, $F(1, 51) =$

55.98, $p < .001$. At step one, the MFIS accounted for 69% of the variance in MSQOL-54P scores. The addition of the MSNQ added 4% (for a total of 73%), and the further inclusion of the QIDS increased the total variance accounted for to 75%. Accordingly, the additions of the QIDS and MSNQ did not greatly increase the amount of variance in MSQOL-54P scores accounted for by the MFIS, which suggested that this measure of fatigue was the single best predictor of physical health-related QoL.

All Measures of Disease Burden

Hypothesis Five conjectured that subjective self-report measures of mood, fatigue, and cognitive symptoms would account for more variance in QoL than objective cognitive and physical indices. All of the significant predictors of QoL from the previous analyses (i.e., objective cognitive, physical, and self-report measures) were considered as predictors of QoL in stepwise regression analyses. These measures included PASAT and SDMT Total T-scores from the objective cognitive group, T25FW and 9HPT T-scores from the physical group, and MSNQ, QIDS, and MFIS Total scores from the self-report group, as well as education. When predicting overall QoL with all measures included, only the MFIS remained a significant predictor of overall QoL, $b = -.557$, $t(52) = -4.94$, $p < .001$. The MFIS Total score accounted for 31% of the variance in MSQOL-54O scores, adjusted $R^2 = .31$, $F(1, 52) = 24.42$, $p < .001$.

When predicting mental health-related QoL with all measures included, only the QIDS and MFIS Total scores remained significant predictors and were entered into the stepwise procedure. The QIDS Total score was entered in step one, $b = -3.08$, $t(53) = -9.74$, $p < .001$, accounting for 64% of the variance in MSQOL-54M scores, adjusted $R^2 = .64$, $F(1, 53) = 94.80$, $p < .001$. At step two, the MFIS Total score ($b = -.42$, $t(52) = -3.81$, $p < .001$) was entered in the equation with the QIDS Total score ($b = -2.11$, $t(52) = -5.57$, $p < .001$), increasing the amount of variance accounted for by the predictors to 71%, adjusted $R^2 = .71$, $F(1, 52) = 67.01$, $p < .001$. At step one, the QIDS accounted for 64% of the variance in MSQOL-54M scores. The addition of the MFIS added seven percent (total of 71%). Accordingly, the results suggested that the measure of depression, the QIDS, was the single best predictor of mental health-related QoL.

When predicting physical health-related QoL with all measures included, only MFIS Total score, T25FW T-score, and MSNQ Total score remained significant and were included in the stepwise procedure. Only the MFIS Total score was entered in step one, $b = -.854$, $t(53) = -11.68$, $p < .001$, accounting for 72% of the variance in MSQOL-54P scores, adjusted $R^2 = .72$, $F(1, 53) = 136.33$, $p < .001$. At step two, T25FW T-score ($b = .283$, $t(52) = 3.12$, $p = .003$) was entered in the equation with the MFIS Total score ($b = -.771$, $t(52) = -10.58$, $p < .001$), increasing the amount of variance accounted for by the predictors to 76%, adjusted $R^2 = .76$, $F(1, 52) = 84.49$, $p < .001$. At step three, MSNQ Total score (*b*

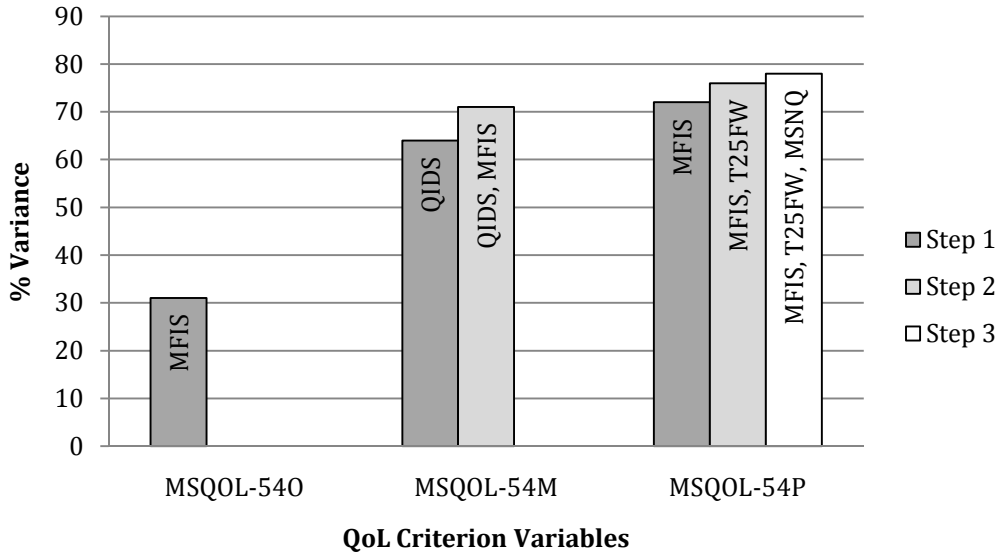
= .34, $t(51) = 2.26$, $p = .028$) was entered in the equation with the MFIS Total score ($b = -.952$, $t(51) = -8.93$, $p < .001$) and T25FW T-score ($b = .264$, $t(51) = 3.01$, $p = .004$). The inclusion of the MSNQ increased the amount of variance accounted for by the predictors to 78%, adjusted $R^2 = .78$, $F(1, 51) = 62.55$, $p < .001$. At step one, the MFIS accounted for 72% of the variance in MSQOL-54P scores. The addition of the T25FW added four percent (total of 76%), and the further inclusion of the MSNQ increased the total variance accounted for to 78%. Accordingly, the additions of the T25FW and MSNQ did not greatly increase the amount of variance in MSQOL-54P scores accounted for by the MFIS, suggesting that this measure of fatigue was the single best predictor of physical health-related QoL.

Summary of QoL Predictors

Significant regression models predicting QoL are shown in Figure 4 below. Out of all objective cognitive, physical, and self-report predictors of overall health-related QoL (MSQOL-54O), only the MFIS Total score remained significant and was entered into the stepwise procedure, accounting for 31% of the variance in overall QoL. Significant predictors of mental health-related QoL (MSQOL-54M) entered into the stepwise procedure included the QIDS and MFIS Total scores. The QIDS alone accounted for 64% of the variance, which increased to 71% with the inclusion of the MFIS. Significant predictors of physical health-related QoL entered into the stepwise procedure included the MFIS Total score,

T25FW T-score, and MSNQ Total score. The MFIS alone accounted for 72% of the variance, which increased to 76% with the inclusion of the T25FW, and 78% when the MSNQ was also added. Taken together, these results suggested that an index of fatigue (MFIS) was the best predictor of overall and physical health-related QoL, while reported depression on the QIDS best predicted mental QoL.

Figure 4. *Adjusted Variance in QoL by Regression Model* (*N* = 55)*



Note. Abbreviations: MSQOL-54O = Overall QoL; MSQOL-54M = Mental QoL Composite (unadjusted); MSQOL-54P = Physical QoL Composite; MSNQ = Multiple Sclerosis Neuropsychological Questionnaire; MFIS = Modified Fatigue Impact Scale, QIDS = Quick Inventory of Depressive Symptoms
*N = 54 for regression models including T25FW (1 subject was unable to perform the task)

DIFFERENCES IN DISEASE BURDEN BY QUALITY OF LIFE

An exploratory aim of the project was to investigate differences in the constructs of cognitive function, fatigue, and depression by level of QoL. To accomplish that end, the sample was divided into two groups based on the medians of each MSQOL-54 outcome measure (MSQOL-54O, MSQOL-54M,

and MSQOL-54P). The median split was utilized as previous research has not determined what scores constitute low versus high QoL on the MSQOL-54. Participants who fell below the medians were designated low, and those at or above the medians were considered high in level of QoL (MSQOL-54O Median = 73.3; MSQOL-54M Median = 70.3; MSQOL-54P Median = 64.4). Performances on all measures of disease burden were compared across low and high QoL groups with independent samples *t*-tests or Mann-Whitney tests as indicated by the results of Levene's test for equality of variance. Descriptive statistics of the MSQOL-54 summary measures by low and high QoL are presented in Table 8.

Table 8. *MSQOL-54 Summary Measures by Low and High QoL*

	MSQOL-54O		MSQOL-54M		MSQOL-54P	
	Low (N = 28)	High (N = 27)	Low (N = 27)	High (N = 28)	Low (N = 28)	High (N = 27)
Mean	55.7	85.8	47.8	81.3	45.8	77.9
Standard Deviation	13.1	7.2	14.7	8.2	12.1	8.9
Range	28 – 73	76 – 100	10 – 69	70 – 98	20 – 64	65 – 99

Abbreviations: MSQOL-54O = Overall QoL; MSQOL-54M = Mental QoL Composite (unadjusted); MSQOL-54P = Physical QoL Composite

Measures by Level of Overall Health-related QoL

Means and standard deviations for all study variables are described by level of overall health-related QoL (MSQOL-54O) in Table 9 below.

Table 9. *Scores by Level of Overall QoL*

Variable	MSQOL-54O (*M*, *SD*) Low (*N* = 28)	High (*N* = 27)	*p*-value
Objective Cognitive Measures			
Learning			
CVLT-II Learning T-score	50.8 (12.4)	49.9 (11.2)	.780
BVMT-R Learning T-score	46.6 (11.9)	46.8 (12.8)	.959
Memory			
CVLT-II Delayed Recall *z*-score	-0.05 (1.48)	-0.20 (1.22)	.684
BVMT-R Delayed Recall T-score	48.1 (11.1)	49.2 (13.7)	.749
CVLT-II Discriminability *z*-score	0.09 (1.15)	0.02 (1.07)	.814
Attention & Processing Speed			
PASAT Total T-score	41.6 (17.3)	46.4 (11.8)	.233
SDMT Total T-score	45.7 (15.2)	52.0 (11.4)	.089
Stroop Color-Word T-score†	46.9 (9.6)	49.4 (9.4)	.332
Executive Functioning			
Stroop Interference T-score†	50.9 (8.0)	50.3 (6.1)	.763
TCST Logical Sorts	5.6 (1.0)	6.1 (1.3)	.095
Language			
FAS Total T-score	43.9 (11.4)	44.7 (11.4)	.784
Category Total T-score	43.8 (10.4)	45.8 (11.2)	.482
Physical Measures			
Gait Speed			
T25FW T-score††	37.7 (17.7)	43.8 (11.5)	.145
Fine Motor Control			
9HPT T-score	32.0 (16.6)	40.0 (9.0)	.031
Neurodegenertation			
Mean RNFL Thickness (μm)	86.8 (12.3)	87.5 (15.8)	.859
Self-report Measures			
Depression			
QIDS Total	12.1 (5.5)	7.0 (3.8)	<.001
Fatigue			
MFIS	48.3 (17.8)	32.0 (15.9)	.001
Cognitive Symptoms			
MSNQ	26.1 (13.4)	19.8 (11.9)	.072

Note. †1 participant was color-blind and unable to perform the task
††1 participant was in a wheelchair with a broken leg and unable to perform the task

Objective Cognitive Measures

No objective cognitive measures differed significantly between low and high groups, though a trend was observed in which performances on attention/processing speed measures were better for the high overall health-related QoL group in relation to the low group.

Physical Measures

Of the physical measures of disease burden, only fine motor control differed significantly by level of overall health-related QoL, $t(53) = -2.21$, $p = .031$, with greater 9HPT scores in the high group ($M = 40.0$) than the low group ($M = 32.0$). While not statistically significant, a similar trend was observed for gait speed, as T25FW scores were greater in the high QoL group ($M = 43.8$) than the low QoL group ($M = 37.7$).

Self-report Measures

Self-reported symptoms of depression on the QIDS differed significantly between groups, $t(53) = 3.97$, $p < .001$, with higher QIDS scores in the low group ($M = 12.1$) than the high group ($M = 7.0$). The MFIS Total scores also differed significantly between groups, $t(53) = 3.57$, $p = .001$, with higher levels of reported fatigue in the low ($M = 48.3$) than the high ($M = 32.0$) overall QoL groups. Self-reported neuropsychological symptoms on the MSNQ did not significantly differ by level of overall QoL, but were greater in the low QoL group ($M = 26.1$) than the high group ($M = 19.8$).

Measures by Level of Mental Health-related QoL

Means and standard deviations for all study variables are described by level of mental health-related QoL (MSQOL-54M) in Table 10 below.

Table 10. *Scores by Level of Mental Health-related QoL*

Variable	MSQOL-54M (*M*, *SD*) Low (*N* = 27)	High (*N* = 28)	*p*-value
Objective Cognitive Measures			
Learning			
CVLT-II Learning T-score	49.3 (12.4)	51.4 (11.2)	.505
BVMT-R Learning T-score	45.9 (12.5)	47.5 (12.1)	.622
Memory			
CVLT-II Delayed Recall *z*-score	-0.11 (1.53)	-0.14 (1.18)	.931
BVMT-R Delayed Recall T-score	47.9 (12.2)	49.3 (12.7)	.694
CVLT-II Discriminability *z*-score	0.13 (1.18)	-0.02 (1.03)	.624
Attention & Processing Speed			
PASAT Total T-score	40.2 (17.0)	47.6 (11.8)	.070
SDMT Total T-score	44.8 (15.4)	52.6 (10.8)	.055
Stroop Color-Word T-score†	45.9 (9.3)	50.3 (9.3)	.091
Executive Functioning			
Stroop Interference T-score†	50.1 (7.6)	51.1 (6.6)	.608
TCST Logical Sorts	5.6 (1.0)	6.1 (1.3)	.088
Language			
FAS Total T-score	41.6 (11.1)	46.9 (11.0)	.080
Category Total T-score	41.7 (11.2)	47.7 (9.6)	.039
Physical Measures			
Gait Speed			
T25FW T-score††	38.9 (15.7)	42.5 (14.6)	.390
Fine Motor Control			
9HPT T-score	32.0 (15.2)	39.6 (11.6)	.041
Neurodegenertation			
Mean RNFL Thickness (μm)	88.8 (12.9)	85.6 (15.0)	.735
Self-report Measures			
Depression			
QIDS Total	13.3 (5.1)	6.0 (2.5)	<.001
Fatigue			
MFIS	52.6 (14.2)	28.5 (14.3)	<.001
Cognitive Symptoms			
MSNQ	30.2 (13.9)	16.1 (7.0)	<.001

Note. †1 participant was color-blind and unable to perform the task
††1 participant was in a wheelchair with a broken leg and unable to perform the task

Objective Cognitive Measures

None of the objective cognitive measures significantly differed by level of mental health-related QoL, though a trend was observed in which performances on attention/processing speed and language measures were better for the high mental health-related QoL group compared with the low group.

Physical Measures

Of all physical measures, only the 9HPT T-scores significantly differed by level of mental health-related QoL, $t(53) = -2.09$, $p = .041$, with the low group ($M = 32.0$) exhibiting significantly worse 9HPT performances than the high group ($M = 39.6$). Although the only physical measure that exhibited significant group differences was motor speed and control on the 9HPT, the T25FW had a similar trend across groups, as T-scores increased from low ($M = 38.9$) to high ($M = 42.5$) mental QoL groups. Mean RNFL Thickness did not significantly differ between groups and did not exhibit the trend observed across the other physical measures.

Self-report Measures

All self-report measures of disease burden differed significantly by level of mental health-related QoL. Specifically, depression on the QIDS differed significantly between groups, $t(53) = 6.68$, $p < .001$, with the low group ($M = 13.3$) reporting higher levels of depression than the high ($M = 6.0$) group. The MFIS Total scores differed significantly between groups, $t(53) = 6.28$, $p < .001$, as the low group ($M = 52.6$) reported more fatigue than the high ($M = 28.5$) group. Self-reported neuropsychological symptoms on the MSNQ significantly differed by level of mental health-related QoL, $t(53) = 4.80$, $p < .001$. The low MSQOL-54M group had significantly greater self-reported neuropsychological symptoms on the MSNQ ($M = 30.2$) than the high ($M = 16.1$) group.

Measures by Level of Physical Health-related QoL

Means and standard deviations for all study variables are described by level of physical health-related QoL (MSQOL-54P) in Table 11.

Table 11. *Scores by Level of Physical Health-related QoL*

Variable	MSQOL-54P (*M*, *SD*) Low (*N* = 28)	High (*N* = 27)	*p*-value
Objective Cognitive Measures			
Learning			
CVLT-II Learning T-score	47.5 (12.0)	53.3 (10.9)	.067
BVMT-R Learning T-score	43.9 (12.0)	49.6 (12.1)	.088
Memory			
CVLT-II Delayed Recall *z*-score	-0.43 (1.42)	0.19 (1.22)	.092
BVMT-R Delayed Recall T-score	46.4 (12.1)	50.9 (12.4)	.172
CVLT-II Discriminability *z*-score	-0.05 (1.17)	0.17 (1.04)	.463
Attention & Processing Speed			
PASAT Total T-score	38.8 (18.0)	49.3 (8.1)	.008
SDMT Total T-score	44.7 (16.3)	53.0 (8.9)	.023
Stroop Color-Word T-score†	44.0 (8.7)	52.6 (8.3)	.001
Executive Functioning			
Stroop Interference T-score†	48.3 (5.9)	53.0 (7.5)	.014
TCST Logical Sorts	5.61 (1.4)	6.1 (1.0)	.150
Language			
FAS Total T-score	44.6 (13.0)	44.0 (9.5)	.844
Category Total T-score	43.7 (11.8)	45.9 (9.7)	.451
Physical Measures			
Gait Speed			
T25FW T-score††	34.7 (18.6)	46.8 (6.8)	.003
Fine Motor Control			
9HPT T-score	29.6 (16.0)	42.5 (7.0)	<.001
Neurodegenertation			
Mean RNFL Thickness (µm)	88.1 (13.7)	86.2 (14.4)	.625
Self-report Measures			
Depression			
QIDS Total	12.8 (5.1)	6.3 (3.2)	<.001
Fatigue			
MFIS	53.1 (13.1)	27.1 (13.7)	<.001
Cognitive Symptoms			
MSNQ	28.6 (13.5)	17.2 (9.5)	.001

Note. †1 participant was color-blind and unable to perform the task
††1 participant was in a wheelchair with a broken leg and unable to perform the task

Objective Cognitive Measures

All measures of attention and processing speed significantly differed by physical health-related QoL group. Specifically, the PASAT Total T-scores differed significantly between groups, $t(53) = -2.81$, $p = .008$, with the low group ($M = 38.8$) exhibiting worse PASAT performances than the high ($M = 49.3$) group. The SDMT Total T-scores also differed significantly between groups, $t(53) = -2.36$, $p = .023$, as the low group ($M = 44.7$) exhibited significantly worse SDMT performances than the high ($M = 53.0$) group. The Stroop Color-Word T-scores also differed significantly between groups, $t(53) = -3.71$, $p = .001$, as the low group ($M = 44.0$) had significantly worse performances than the high ($M = 52.6$) group. Of the executive measures, the Stroop Interference T-score significantly differed between the high physical health-related QoL group ($M = 53.0$) and the low group ($M = 48.3$), $t(53) = -2.55$, $p = .014$. Although not significant, a similar trend was observed for learning, and memory measures, as well as Category fluency.

Physical Measures

Both the T25FW and 9HPT T-scores significantly differed by level of physical health-related QoL, $t(53) = -3.17$, $p = .003$, and $t(53) = -3.86$, $p < .001$, respectively. Specifically, the low group ($M = 34.7$) exhibited significantly worse T25FW performances than the high group ($M = 46.8$). For the 9HPT,

performances in the low group (M = 29.6) were worse than the high (M = 42.5) group. Mean RNFL Thickness did not differ by physical QoL group.

Self-report Measures

All self-report measures differed significantly by level of physical health-related QoL. Specifically, depression on the QIDS differed significantly between groups, $t(53) = 5.72$, $p < .001$, with the low physical QoL group exhibiting significantly higher reported levels of depression (M = 12.8) than the high (M = 6.3) group. The MFIS Total scores differed significantly between groups, $t(53) = 7.21$, $p < .001$, as the low group (M = 53.1) reported more fatigue (greater MFIS scores) than the high (M = 27.1) group. Self-reported neuropsychological symptoms on the MSNQ significantly differed by level of physical QoL, $t(53) = 3.62$, $p = .001$, with the low group (M = 28.6) reporting greater neuropsychological symptoms than the high (M = 17.2) physical QoL group.

Summary of Performances by Level of QoL

Median splits were used to divide the sample into low and high QoL groups across each of the three MSQOL-54 summary measures. For overall QoL, performances on attention and processing speed measures were better for the high group compared with the low group, though the differences were not statistically significant. In the mental health-related QoL domain, only the SDMT significantly differed between low and high groups, though a similar trend was observed with other attention/processing speed and verbal fluency measures. All

measures of attention and processing speed differed across the low and high physical health-related QoL groups, as well as a measure of executive functioning (Stroop Interference). Significant group differences determined with independent samples *t*-tests remained significant when using Mann-Whitney analyses. Accordingly, performances on measures with significant attention and processing speed components were greater in individuals with higher QoL.

Of the physical measures, only fine motor control on the 9HPT differed significantly by level of overall and mental health-related QoL. Group means on the 9HPT also significantly differed between low and high levels of physical QoL, with better performances noted in the higher QoL group. Ambulation ability as measured by the T25FW showed a similar trend across the mental QoL groups, and performances significantly improved with increased QoL in the physical domain. Significant comparisons with independent samples *t*-tests remained significant when using Mann-Whitney analyses. Accordingly, participants with higher levels of mental and physical health-related QoL also exhibited greater performances on measures of ambulation and motor control.

Analyses of the self-report measures revealed that participants with higher QoL reported significantly fewer symptoms of depression and fatigue. Similarly, in the mental and physical QoL domains, depression, fatigue, and self-reported cognitive problems were lower in the high QoL group. Significant findings with independent samples *t*-tests remained significant when using Mann-Whitney

analyses. Accordingly, individuals with higher QoL report fewer symptoms of depression, fatigue, and cognitive problems than those with low levels of QoL.

DISCRIMINATORS OF LOW VERSUS HIGH QOL

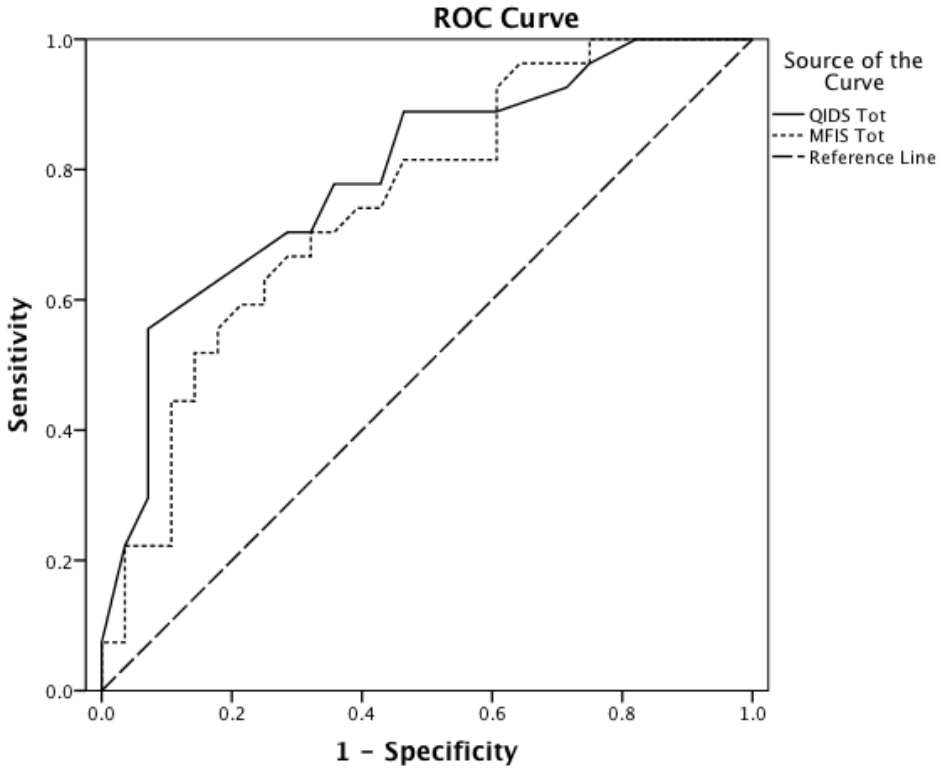
The MFIS and QIDS self-report indices were the best predictors of health-related QoL across each of the three outcome measures. These measures also significantly differed between low and high QoL groups for all three MSQOL-54 summary measures. Accordingly, these indices were used in ROC analyses to determine their ability to discriminate between low and high QoL groups. These analyses were also used to identify optimal cut scores on the QIDS and MFIS that yielded the maximum correct classification of individuals with high versus low QoL.

Discriminators of Overall QoL

Figure 5 shows ROC curves depicting the relative sensitivity and specificity of the MFIS and QIDS for discriminating between low and high overall health-related QoL groups on the MSQOL-54O. The diagonal line represents the expected finding should the measures provide zero discrimination, resulting in an area under the curve (AUC) of 50%. The areas under the curve were significant for both the QIDS (AUC = .79, SE = .06, $p < .001$) and MFIS (AUC = .75, SE = .07, p = .001). An optimal QIDS cut-off score of greater than 11 is recommended for predicting low overall QoL, as this score yielded a sensitivity of .89, a specificity of .54, with 71% of cases correctly classified. An

optimal MFIS cut-off score of greater than 42 is recommended for predicting low overall QoL, with a sensitivity of .70 and specificity of .68, with 69% of cases correctly classified.

Figure 5. *Discriminability of the MFIS and QIDS for Level of Overall QoL* (*N* = 55)



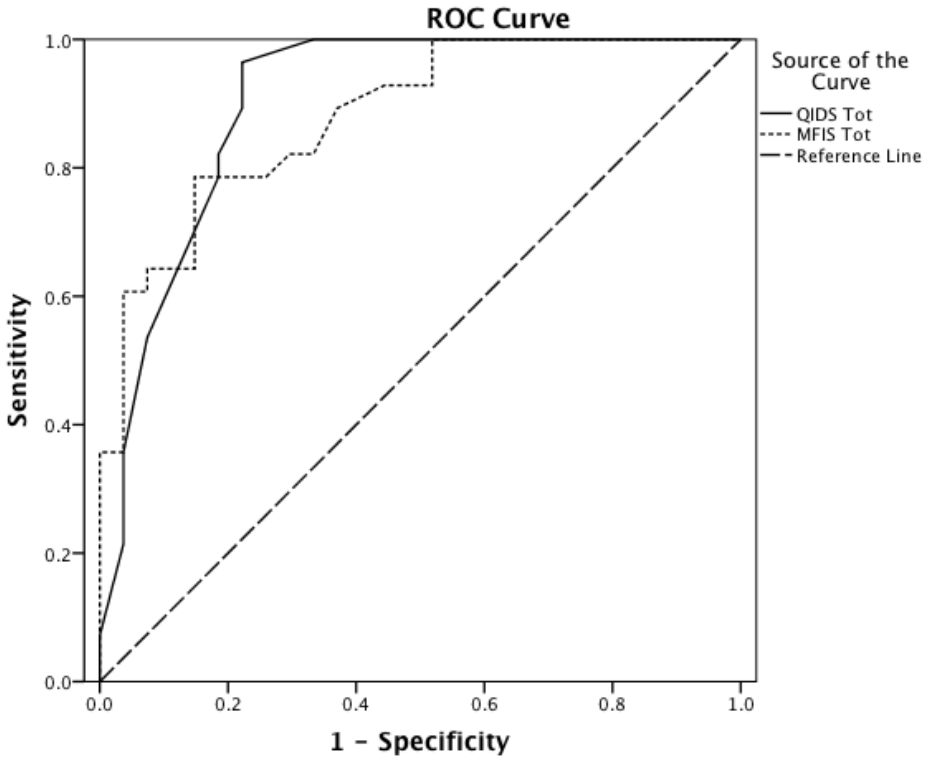
Note. QIDS AUC = .79; MFIS AUC = .75
Abbreviations: QIDS = Quick Inventory of Depressive Symptomatology; MFIS = Modified Fatigue Impact Scale

Discriminators of Mental QoL

Figure 6 shows ROC curves depicting the relative sensitivity and specificity of the MFIS and QIDS for discriminating between low and high mental health-related QoL groups on the MSQOL-54M. The areas under the

curve were significant for both the QIDS (AUC = .90, *SE* = .04, $p < .001$) and MFIS (AUC = .88, *SE* = .04, $p = .001$). An optimal QIDS cut-off score of greater than 10 is recommended for predicting low mental QoL (sensitivity = .89, specificity = .78, 89% correctly classified). An MFIS cut-off score of greater than 39 is recommended for predicting low mental health-related QoL (sensitivity = .79, specificity = .85, 82% correctly classified).

Figure 6. *Discriminability of the MFIS and QIDS for Level of Mental QoL* (*N* = 55)

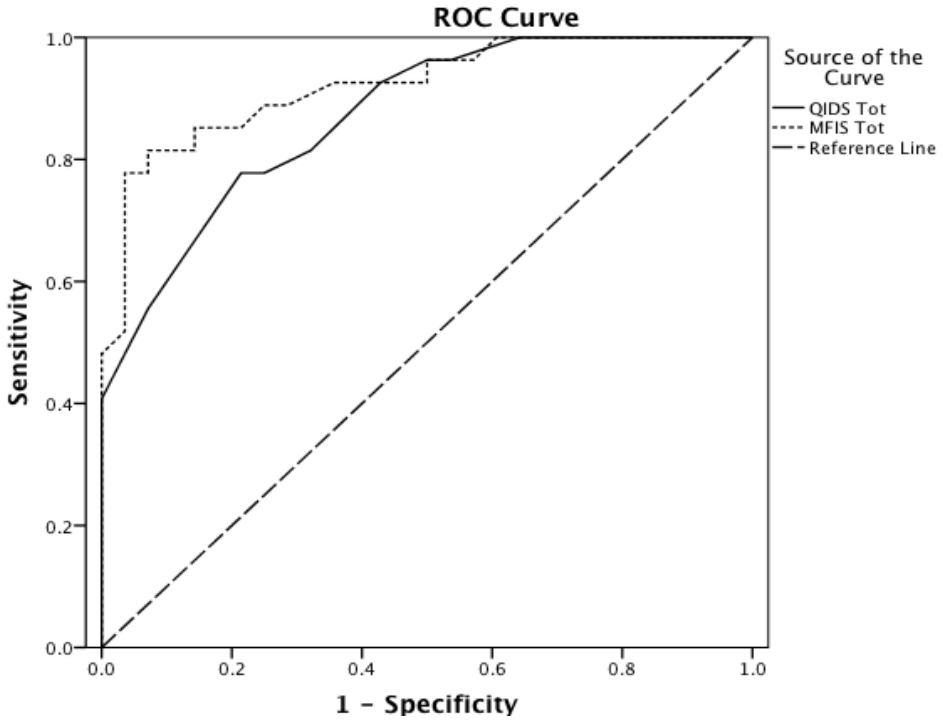


Note. QIDS AUC = .90; MFIS AUC = .88
Abbreviations: QIDS = Quick Inventory of Depressive Symptomatology; MFIS = Modified Fatigue Impact Scale

Discriminators of Physical QoL

Figure 7 shows ROC curves depicting the relative sensitivity and specificity of the MFIS and QIDS for discriminating between low and high groups on the MSQOL-54P. The areas under the curve were significant for both the QIDS (AUC = .87, *SE* = .05, $p < .001$) and MFIS (AUC = .92, *SE* = .04, $p = .001$). A QIDS cut-off score of greater than nine is recommended for predicting low physical QoL (sensitivity = .82, specificity = .68, 75% correctly classified). An MFIS cut-off score of greater than 37 is recommended (sensitivity = .85, specificity = .93, 87% correctly classified).

Figure 7. *Discriminability of the MFIS and QIDS for Level of Physical QoL* (*N* = 55)



Note. QIDS AUC = .87; MFIS AUC = .92
Abbreviations: QIDS = Quick Inventory of Depressive Symptomatology; MFIS = Modified Fatigue Impact Scale

Summary of ROC Analyses

According to the results, the QIDS and MFIS were both significant discriminators of level of health-related QoL for each of the three MSQOL-54 summary measures. Specifically, the AUCs for the QIDS were .79 for the MSQOL-54O, .90 for the MSQOL-54M, and .87 for the MSQOL-54P. Optimal QIDS cut scores for predicting low QoL on the MSQOL-54 were as follows: greater than 11 for low overall QoL on the MSQOL-54O, greater than 10 for low mental QoL on the MSQOL-54M, and greater than nine for low physical QoL on the MSQOL-54P. Accordingly, when using the QIDS to make inferences regarding level of QoL, a score of greater than nine would suggest that low QoL in at least one of the MSQOL-54 subdomains (i.e., overall, mental, or physical) is likely.

The AUCs for the MFIS were .88 for the MSQOL-54O, .88 for the MSQOL-54M, and .92 for the MSQOL-54P. Optimal MFIS cut scores for predicting low QoL on the MSQOL-54 were as follows: greater than 42 for low overall QoL on the MSQOL-54O, greater than 39 for low mental QoL on the MSQOL-54M, and greater than 37 for low physical QoL on the MSQOL-54P. Accordingly, when using the MFIS to make inferences regarding level of QoL, a score of greater than 37 would suggest that low QoL in at least one of the MSQOL-54 domains is likely.

CHAPTER SIX
Discussion

FINDINGS

Impairment

Analysis of performances on objective measures revealed that the MS group exhibited significant rates of impaired performances (≥ 1 *SD* below the mean) on at least one measure within each of the domains of motor functioning (T25FW, 33%; 9HPT, 53%), learning (BVMT-R Learning, 22%), attention and processing speed (PASAT, 35%), and language (FAS, 36%; Category, 31%). In contrast, measures of memory were not significantly more impaired than expected in the normal population, and measures of executive functioning were actually less impaired. Taken together, these findings offered partial support to Hypothesis One, in that MS patients were significantly more frequently impaired than expected in a healthy control population on objective measures of motor function, attention/processing speed, and learning, in contrast to non-significant impairment frequencies on indices of executive functioning and memory.

This pattern of deficits and rates of impairment are consistent with some findings from previous studies regarding cognition in MS (for a review, see Calabrese, 2006); however, others have documented executive functioning deficits in up to 33% of all patients (Simioni et al., 2009; Vowels & Gates, 1984). The lack of executive deficits in the present sample may be attributable to

differences in measures utilized between studies. Simioni and colleagues employed the WCST, IGT, and measures from the D-KEFS (which includes verbal fluency), whereas the present study utilized an experimental measure (i.e., TCST) and the Stroop Interference score as indices of executive functioning. Accordingly, the aspects of executive functioning assessed by the measures used in this project may have differed from the executive functions assessed by others. Also, it should be noted that the lack of impairment in the Stroop Interference T-score (one of the executive indices) was attributable in part to generalized slowing across trials, preventing the detection of an interference effect on the incongruent color-word trial. Also, verbal fluency tasks (which were among the most frequently impaired) were categorized as measures of language rather than executive functioning in the present study.

The finding that both language indices (FAS and Category Fluency) were significantly more frequently impaired than expected in a healthy control population has been previously described (Prakash et al., 2008); however, the result was not anticipated as language functions are thought to be less commonly affected than other domains in MS patients. A possible explanation is that although performances on FAS and Category tests reflect expressive language abilities, they also measure frontal lobe functions and are consequently often categorized as measures of executive functioning (Strauss et al., 2006). Accordingly, if these measures had been included in the executive functioning

domain for the present study, rates of executive impairment would have been consistent with previously described findings (FAS, 36% impaired; Category, 31% impaired).

Regardless of categorization, further analysis revealed that deficits on these verbal fluency tests likely reflect slowed processing speed in addition to impaired language or executive abilities per se. In other words, these timed measures have considerable processing speed demands, which may have contributed to the observed impairment frequency. In fact, Pearson product-moment correlation coefficients were significant between FAS and SDMT T-scores [$r(53) = .34$], and Category and SDMT T-scores [$r(53) = .51$]. These associations support the role of processing speed in fluency tasks, and help explain the unexpected "language" deficits observed in the MS sample. These findings, in conjunction with the literature regarding verbal fluency tasks, suggest that FAS and Category tests do not necessarily measure a single cognitive domain, but reflect an amalgam of executive, language, and processing speed abilities. In retrospect, including more pure measures of language abilities (e.g., confrontation naming or vocabulary tasks) may have better reflected the verbal abilities of the sample. Additionally, including other measures of executive functioning (e.g., the WCST) may have helped to better quantify the executive functioning of the sample. Nonetheless, in terms of neurocognitive and physical

functioning, these results support the primacy of attention, processing speed, and motor deficits in MS.

When considering all measures of disease burden, indices of fatigue and motor control appeared most frequently elevated or impaired in the MS sample (MFIS, 56% clinically significant; 9HPT, 53% impaired). Self-report indices of depression and neuropsychological functioning were significantly elevated at similar percentages to impairment on measures of attention and processing speed (QIDS, 38%; MSNQ, 38%). These findings did not fully support Hypothesis Two, which posited that MS patients would report clinically significant symptoms at a frequency greater than rates of impairment observed on objective cognitive and physical indices. That is, although self-reported fatigue on the MFIS was most often significantly elevated in the sample, fine motor control on the 9HPT was impaired at a similar rate.

To better understand the nature of the observed impairments and reported symptoms, associations between measures were explored with Pearson product-moment correlations described in Table 12 below.

Table 12. *Correlations between Cognitive, Motor, and Self-report Measures* ($N = 55$)

	Self-report Measures (r)		
Objective and Self-report Measures	MSNQ	QIDS	MFIS
Cognitive Function ($N = 55$)			
Learning			
CVLT-II Learning T-score	-.37**	-.31*	-.31*
BVMT-R Learning T-score	-.21	-.21	-.24
Memory			
CVLT-II Delayed Recall *z*-score	-.29*	-.29*	-.29*
BVMT-R Delayed Recall T-score	-.24	-.24	-.23
CVLT-II Discriminability *z*-score	-.31*	-.26	-.25
Attention & Processing Speed			
PASAT Total T-score	-.44**	-.43**	-.48***
SDMT Total T-score	-.46***	-.41**	-.46***
Stroop Color-Word T-score†	-.35**	-.35**	-.40**
Executive Functioning			
Stroop Interference T-score†	-.08	-.11	-.21
TCST Logical Sorts	-.27*	-.31*	-.24
Language			
FAS Total T-score	-.29*	-.24	-.26
Category Total T-score	-.29*	-.24	-.26
Motor Function ($N = 55$)			
Gait Speed			
T25FW T-score††	-.23	-.29*	-.37**
Fine Motor Control			
9HPT T-score	-.44**	-.44**	-.56***
Self-report			
QIDS	.64***	---	.67***
MFIS	.75***	.67***	---

Note. †$N = 54$, 1 participant was color-blind; ††$N = 54$, 1 participant was in a wheelchair
*$p < .05$, **$p < .01$, and ***$p < .001$

Interestingly, the greatest association between all objective and self-report measures was between the MFIS and 9HPT [$r(53) = -.56$], the two measures that were most frequently elevated or impaired in the sample. Further, the MFIS was significantly associated with all measures of attention and processing speed [$r(53) = .40$ to $.48$]. Accordingly, patient fatigue likely contributes to slowed processing and motor functioning, though causation cannot be determined through such correlational analyses. Also, depression on the QIDS and neuropsychological symptoms on the MSNQ were significantly associated with processing speed and

motor measures [$r(53) = .64$ to .75]. Taken together, these findings highlight the complex and potentially reciprocal relationships between objective deficits and subjective perception of impairment.

It has been demonstrated that MS pathology (e.g., lesion load and brain atrophy) is associated with fatigue (Wishart et al., 2001), depression (Berg et al., 2000, Honer et al., 1987), and cognitive impairment (Patti, 2009); however, these difficulties do not necessarily exist wholly independent of each other. While somewhat speculative, the above results suggest that levels of fatigue may be influenced by severity of depression (and conversely, depression may be exacerbated by fatigue), and both can contribute to slowed cognition. Further, the synergy of these interrelated factors might result in similarly increased reports of symptoms across each of the three domains (i.e., neuropsychological function, fatigue, and depression), explaining the observed associations between the various instruments.

Although the above explanation is intuitive, it warrants further empirical investigation. Regardless, the observed impairment frequencies and associations confirm much of the literature regarding cognition, mood, and fatigue in MS. The results also support the common assertion that MS white matter pathology results in the disconnection of cortical-subcortical tracts, yielding a pattern of "subcortical" deficits characteristic of the disease. In fact, the prototypical "subcortical profile" is said to include attention, working memory, and processing

speed difficulties, as well as mood changes such as depression (Roca et al., 2008; Albert, Feldman, & Willis, 1974), which were some of the most prominent deficits observed in the present study. In other words, although means on most measures fell within the lower end of the average range, those participants with significant impairment tended to exhibit "subcortical" deficits.

Predictors of QoL

The results of the regression analyses partially supported Hypothesis Three, as indices of attention and processing speed were better predictors of QoL than memory, executive functioning, and language abilities. Specifically, the SDMT accounted for seven percent of the variance in overall health-related QoL, and 19% of the variance in mental health-related QoL, and the PASAT accounted for 16% of the variance in physical health-related QoL. However, measures of learning did not significantly predict QoL as hypothesized. This finding may be attributable in part to the fact that observed impairments in verbal learning were less frequent (CVLT-II; 16%) than those observed on measures of attention and processing speed (PASAT, 35%; SDMT, 24%). In other words, performances on the verbal learning measure were less impaired, and as a result, difficulties in this area may have had less of an impact on QoL. However, impairment frequency on the visual learning measure (BVMT-R; 35%) was identical to that of the PASAT. Accordingly, a simple difference in impairment frequency does not seem to

completely account for the lack of predictive power for both of the learning measures.

Further analysis of the relationships between learning and attention/processing speed indices revealed large, significant associations. Specifically, verbal learning on the CVLT-II was significantly associated with the PASAT [$r(53) = .50$] and SDMT [$r(53) = .58$]. Visual learning on the BVMT-R was also highly associated with the PASAT [$r(53) = .56$] and SDMT [$r(53) = .65$]. As such, performances and impairment on the learning measures may be partially attributable to difficulties in attention and processing speed, explaining why more pure measures of attention and processing speed (i.e., PASAT and SDMT) better predicted QoL than the learning indices.

It should be noted that although measures of attention and processing speed significantly predicted QoL, the amount of variance accounted for by these indices was modest when compared to self-reported neuropsychological symptoms. Specifically, the MSNQ accounted for 32% of the variance in mental health-related QoL, while the SDMT only accounted for 19%. Also, the MSNQ accounted for 22% of the variance in physical health-related QoL, while the PASAT only accounted for 16%. Accordingly, while objective neurocognitive measures of attention and processing speed were significantly associated with self-reported neuropsychological symptoms [$r(53) = .35$ to $.46$], self-reports of cognitive problems appeared to be the better predictors of QoL in the mental

(19% vs. 32%) and physical health (16% vs. 22%) domains. These findings supported Hypothesis Four in that subjective self-reported neuropsychological symptoms accounted for more variance in health-related QoL than objective cognitive measures. In light of these findings, while objectively verified cognitive difficulties do appear to impact MS patient's subjective well-being, it is the patient's subjective perception of their cognitive functioning that is most important when predicting QoL.

In support of Hypothesis Five, and in line with the aforementioned discussion of cognitive measures, is the finding that self-report measures were the best predictors of QoL out of all indices under investigation. Self-report measures of depression and fatigue accounted for the most variance in overall (MFIS, 31%), mental (QIDS, 64%), and physical (MFIS, 72%) health-related QoL. However, ambulation (as objectively measured by the T25FW) and self-reported neuropsychological symptoms were also significant predictors and added to the amount of variance accounted for in physical QoL. Thus, while self-reports of fatigue and depression appeared most important when predicting QoL, ambulation and self-reported neuropsychological symptoms should also be considered when making judgments about patient well-being.

While it was hoped that RNFL thickness as measured with OCT would prove to be a useful biomarker of QoL in MS, it is notable that the index was not a significant predictor of any QoL summary measures and was not significantly

associated with any MSQOL-54 subscales. However, this finding should not necessarily lead to the conclusion that RNFL assessment in MS has questionable utility.

While the negative findings are informative regarding the relationship between RNFL and QoL, these results do not diminish the potential of RNFL assessment as a biomarker of disease burden and progression. Indeed, further analyses identified significant associations between RNFL thickness and measures of cognitive functioning. Specifically, medium associations were found between overall RNFL thickness and BVMT-R Learning T-score [$r(53) = .43$, $p = .001$], BVMT-R Delayed Recall T-score [$r(53) = .34$, $p = .011$], and the PASAT T-score [$r(53) = .27$, $p = .043$]. Additionally, significant differences in cognitive and motor performances were found when splitting the sample into low and high temporal quadrant RNFL thickness (i.e., the first and third temporal RNFL thickness tertiles). Significant group differences were found for the following: BVMT-R Learning T-score [high group $M = 50.6$; low group $M = 39.4$; ($t(34) = 3.02$, $p = .005$)], BVMT-R Delayed Recall T-score [high group $M = 53.5$; low group $M = 41.3$; ($t(34) = 3.03$, $p = .005$)], 9HPT T-score [high group $M = 39.4$; low group $M = 28.6$; ($t(34) = 2.18$, $p = .036$)], and T25FW T-score [high group $M = 45.1$; low group $M = 31.9$; ($t(34) = 2.48$, $p = .018$)].

These results add to the limited literature regarding associations between RNFL thickness and patient functioning in MS. Specifically, the observed

associations between motor functioning and RNFL thickness advance the findings of Petzold and colleagues (2010), who documented associations between physical disability status and RNFL thickness. In terms of cognition, previous associations have been observed between RNFL thickness and performances on the SDMT [$r(53) = .75$] (Toledo et al., 2008). While a significant correlation with the SDMT was not observed in the present study, SDMT scores differed between low (M = 47.0) and high (M = 54.8) overall RNFL thickness groups, though the difference was not significant [$t(34) = 1.85$, $p = .073$]. A similar trend was observed for the PASAT [low M = 40.1, high M = 49.9, $t(34) = 2.02$, $p = .051$]. Taken together, these findings support the utility of RNFL thickness as a biomarker of cognitive and motor deficits in MS patients. Specifically, it appears that as RNFL becomes thinner, cognitive and motor deficits become more pronounced, particularly within the domains of visual learning and memory, ambulation, motor control, attention, and processing speed.

Additional correlational analyses with MSQOL-54 subscales revealed that measures of motor functioning and self-reported depression, fatigue, and neuropsychological symptoms were all significantly associated with QoL across most domains of functioning. As expected, measures of motor functioning (9HPT and T25FW) and fatigue (MFIS) were most highly associated with the Physical Function MSQOL-54 subscale, depression (QIDS) with the Emotional Well-being subscale, and cognitive symptoms (MSNQ) with the Cognitive subscale. In terms

of the summary measures, reported symptoms of depression and fatigue exhibited the greatest associations with all three MSQOL-54 outcome indices (i.e., mental, physical, and overall). Taken together, these results suggest that while problems with motor functioning relate to lower QoL (particularly within the physical domains), measures of depression and fatigue appear to be the indices most associated with lower perceived QoL in numerous areas of functioning.

While the strong associations between self-report measures and MSQOL-54 subscales may be due in part to item overlap between measures, further analyses suggest that similarity between items do not appear to account for their predictive ability. To begin with, the overall QoL score was based on the mean of only two items that have no overlap with items from the greatest predictor (i.e., the MFIS). Also, the results of the regression analyses of composite scores did not significantly change when excluding contributions from subscales that exhibited item overlap with predictor measures (i.e., Emotional Well-being and Energy subscales). Specifically, the QIDS remained the single best predictor of the modified MSQOL-54M (excluding the Emotional Well-being subscale), though the amount of variance accounted for in mental health-related QoL fell slightly from 64% to 58%. Likewise, the MFIS remained the single best predictor of the modified MSQOL-54P (excluding the Energy subscale), accounting for 71% of the variance in physical health-related QoL (1% percent less than with the subscale included). In sum, although objectively verifiable cognitive difficulties

(in attention and processing speed) appeared to impact MS patients' subjective well-being in independent analyses, when considering objective and subjective measures together, it is the patient's self-report of perceived symptoms that is most important when predicting QoL (particularly in the domains of fatigue and depression).

Dicriminating Low Versus High QoL

ROC analyses revealed that the QIDS and MFIS were both significant discriminators of level of QoL on each of the three MSQOL-54 summary measures, with AUCs ranging from .88 to .92 for the MFIS and .79 to .90 for the QIDS. It was determined that when using the MFIS to make inferences regarding level of QoL, a score of greater than 37 suggests that the presence of low QoL in at least one of the MSQOL-54 summary domains (i.e., overall, mental, or physical) is likely. When using the QIDS to make such inferences, a score of greater than nine suggests low QoL in at least one of the MSQOL-54 summary domains.

The MFIS cut-score of 37 for predicting low QoL is identical to the recommended cut-off for determining clinically significant levels of fatigue (>37) (Flachenecker et al., 2002). For the QIDS, the cut-off of greater than nine corresponds to the upper limit of the mild depression range as described by the measure's authors (Rush et al., 2003). These findings suggest that levels of fatigue and depression that are at or only slightly above the levels of clinical

significance can have considerable impact on QoL, and these scores can be used to discriminate between patients with low and high levels of QoL with good specificity and sensitivity.

IMPLICATIONS AND DIRECTIONS

The present results confirm much of the previous research regarding cognitive and physical deficits in MS, highlighting the importance of attention, processing speed, and motor functioning (for a review see Patti, 2009). However, the findings also reflect the variable nature of these symptoms in the MS population, as the results were discordant with some studies, particularly in regard to rates of executive dysfunction (Simioni et al., 2009; Vowels & Gates, 1984). However, as discussed above, some of the discrepancy may be attributable to differences in measures utilized. The findings of this study also confirmed previous research regarding the role of depression and fatigue in the QoL of MS patients (Benedict et al., 2005; Benedict et al., 2004), but also demonstrated the limited utility of objective measures in making judgments about patient well-being. These general findings may reflect the fact that QoL and the other self-report indices have a first-person ontology, while the objective measures utilized in this study have third-person ontologies. According to Stirgy's conceptual analysis, QoL fundamentally depends upon the *cognitive appraisals* of negative affect and happiness in salient life domains (2002). In other words, QoL is a subjective phenomenological construct, based on an individual's *experience* and

interpretation of his or her own symptoms. As QoL is an inherently private entity, much like the experiences of depression, fatigue, and cogitating, any empirical instrument striving to measure QoL must tap the inner experience of the participant.

Of course, no instrument can evaluate the experience of a person with perfect fidelity (the so-called 'problem of other minds'). Nonetheless, self-report questionnaires are useful tools that measure private experiences through descriptions or endorsements, which enable the rough quantification of an individual's inner world (assuming the reports are genuine). Accordingly, the QoL instrument and measures of fatigue, depression, and neuropsychological symptoms used in this study necessarily relied upon self-reports. On the other hand, the objective measures included in this investigation (e.g., cognitive testing results and RNFL thickness) did not necessarily tap into an individual's experience. For instance, while cognitive deficits *can* be experienced by individuals (e.g., the experience of forgetfulness, distractibility, etc.), the experiencing of the deficit is not necessary (or sufficient) for its objective (third-person) existence. Also, measurements of an individual's functioning may reflect a relative change from baseline and be experienced as a decline, yet fall within the average or normal range on testing. In other words, a deficit or symptom is likely to impact someone's QoL insofar as it is experienced and acknowledged by that individual, regardless of its detection on objective measures. With these

conceptual issues in mind, it is not surprising that most of the objective measures were limited in their utility as predictors of QoL in MS.

Despite these considerations, it should be noted that the results do not fully support the contention that "self-report predicts self-report" (Benedict et al., 2005, p.32). In fact, while self-reports were the best predictors of QoL, objective measures of attention and processing speed were also significant predictors in independent analyses excluding the self-report indices. As such, it can only be said that objective measures of cognitive functioning do not predict QoL *as well as* self-report indices. Also, even when included in analyses with self-report measures, an objective measure of ambulation ability (T25FW) was a significant predictor of physical health-related QoL. Thus, while self-report measures (particularly fatigue and depression) do appear to be the best predictors of QoL, objective measures may be additionally useful when making judgments about patient well-being.

Similarly, the results do not fully support the notion that QoL measures are little more than indices of depression. While depression was a strong predictor of QoL, fatigue appeared to be a better predictor of QoL in the overall and physical domains, and self-reported neuropsychological symptoms and ambulation were also significant in the physical domain. Accordingly, it appears that when making judgments regarding patient QoL, assessing fatigue is paramount, followed by depression, self-reported cognitive complaints and

mobility. Overall, the observed importance of self-report measures supports the primary study hypotheses. This represents the first study that considered a broad array of both objective and subjective measures, simultaneously sampling some of the most critical domains of functioning in MS patients. In determining the relative contributions of the various predictors of QoL, the present results may help to better target interventions and improve patient well-being.

Treatment

The first step in treating or preventing deficits in the domains identified as important predictors of patient QoL is identifying patients with clinically significant symptoms or those at risk of developing them. Given the results, it is reasonable to suggest that inquiries regarding fatigue and depression should be incorporated into clinical visits. That being said, a comprehensive clinical interview is not practical in most busy clinics, and patients may not be completely forthright when discussing personal symptoms with their treating physician. Accordingly, a battery of brief screening questionnaires (which can be completed prior to the visit or in the waiting room) may be a useful adjunct to the clinical interview, which may also improve the reliability and economy of the clinical exam.

Measures with demonstrated utility in identifying symptoms of depression in MS populations include the QIDS, BDI-II, and CES-D (Benedict et al., 2005). These measures are easy to administer and take less than 10 minutes to complete.

Similarly efficacious indices of fatigue are the FSS and the MFIS (Benedict et al., 2005). These instruments can be quickly administered, readily scored by an assistant, and easily interpreted by the physician. Of course, any significant findings on a screening measure should be followed up during the clinical interview. Nonetheless, the results may be helpful by expediently and reliably identifying patients for whom adjunctive treatments may be indicated.

The results of this study also suggest that measures of self-reported cognitive symptoms and ambulation are important to aspects of patient well-being. Accordingly, brief screening tools such as the T25FW and MSNQ may help to quickly identify patients with significant levels of physical difficulties and cognitive complaints. Further, given the finding that measures of attention and processing speed were frequently impaired in MS patients, it may be useful to administer a few brief measures such as the PASAT and SDMT to help identify those with possible cognitive deficits. In sum, these brief screens may be useful to inform clinical decision-making, such as making medication adjustments or appropriate referrals for psychiatric consultation, formal neuropsychological evaluation, and physical rehabilitation.

Although there is some evidence that DMTs may have benefits beyond reducing MS pathology (Amato et al., 2006), more research is needed regarding their effects on mood, fatigue, and cognitive and motor functioning. Nonetheless, numerous well-researched treatments for depression and fatigue exist, many of

which have demonstrated efficacy. Perhaps the easiest interventions to disseminate and implement are pharmacological. Although there is some debate regarding antidepressant efficacy, evidence suggests that numerous medications are helpful in the treatment of depressive symptomatology, including a wide array of antidepressants [e.g., selective serotonin reuptake inhibitors (SSRIs), serortonin-norepinephrine reuptake inhibitors (SNRIs), and norepinephrine-dopamine reuptake inhibitors (NDRIs)] (Herrera-Guzman et al., 2008; Smith, Dempster, Glanville, Freemantle, & Anderson, 2002). Also, some SNRI and NDRI medications have energizing effects (e.g., venlafaxine and bupropion) that may be helpful in combatting symptoms of fatigue (Pae et al., 2009; Papakostas et al., 2006). Likewise, some stimulant antiepileptic (e.g., modafinil) and antiviral (e.g., amantadine) medications seem to be effective in combating symptoms of fatigue and may also improve aspects of cognition (Caldwell, 2001). Indeed, such adjunctive medications are commonly prescribed to MS patients for the treatment of depression and fatigue, though it is possible that more patients would benefit from these treatments if they were readily identified through routine screening.

While such pharmacological treatments show efficacy in treating fatigue and depression in MS, it remains unclear whether these treatments also improve patient QoL. As noted in the literature review, treating depression in MS patients only accounted for 19% to 52% of the accompanying changes in QoL (Hart et al., 2005). Like pharmacological treatments, behavioral and psychosocial

interventions are also commonly employed to treat depression, but can be additionally helpful with adjustment to illness difficulties (Rupke, Blecke, & Renfrow, 2006). Specifically, cognitive behavioral therapy (CBT) has been shown to be as effective as antidepressant treatment of depression and chronic fatigue in a number of populations, and the two together appear to be more efficacious than either in isolation (Spiegler & Guevremont, 2010; Rupke et al., 2006). By combining pharmacological treatments with CBT techniques (e.g., behavioral activation, coping skills training, and cognitive restructuring), symptoms of depression and fatigue may be further reduced in MS patients identified as having such problems. However, more research is needed to determine whether these treatments are equally effective in the MS population, and whether these treatments can improve overall well-being beyond the reduction of depressive symptomatology.

Given that ambulation (gait speed) was identified as a significant predictor of physical health-related QoL, physical therapy may be beneficial to patients identified as having gait and balance difficulties. Also, as objective cognitive deficits were more frequent in the MS population than expected in healthy controls, routine cognitive screening could help identify those with deficits and monitor disease progression. While objective cognitive functioning in the domains of attention and processing speed accounted for a relatively small amount of variance in health-related QoL (7% for overall QoL, 19% mental, and

16% physical), self-reported symptoms on the MSNQ accounted for a considerable amount of variance in the mental (32%) and physical (22%) domains. In light of these findings that suggest that patient perceptions of cognitive functioning impact health-related QoL, objective cognitive testing and neuropsychological feedback may have some therapeutic utility other than simply identifying those with cognitive difficulties. That is, in patients with high levels of self-reported cognitive symptoms, results from neuropsychological evaluations and feedback sessions could be utilized to help target cognitive rehabilitation interventions and compensatory strategies for those with genuine cognitive dysfunction. Additionally, in patients who self-identify as more impaired than indicated upon formal neuropsychological evaluation, appropriate presentation of the objective testing results may help foster a more realistic perception of one's cognitive abilities. In doing so, patients may develop a more positive view of their functional capabilities and self-efficacy, which may improve mood and overall QoL. Such possibilities warrant further empirical investigation.

LIMITATIONS

A few considerations should be taken into account when interpreting the findings of this project. First, the sample was highly educated (M = 15.7 years), and predominantly white (89%) and female (87%). Although the sample was highly educated, MS patients typically have greater levels of education than the general population, in which 56% of individuals with MS have at least a

bachelor's degree (Buchanan et al., 2010). However, the study sample exceeded these rates as 66% of participants had at least a bachelor's degree. As such, performances on cognitive measures may have been impacted by the high level of education, biasing scores and lowering rates of observed impairment. If so, the relationships between such measures and QoL may have been indirectly affected by decreased impairment frequency. However, such concerns are unlikely given the fact that most cognitive measures were corrected for demographic factors, including education level. Additionally, education was included in all stepwise regression analyses, as it was a significant independent predictor of QoL. When included in analyses, it did not remain significant with other predictors.

While the gender and ethnicity characteristics of the study do not reflect great diversity, this is not entirely surprising as MS predominantly affects individuals of European descent from northerly geographic regions, and women are affected up to three times as often as men (Prakash et al., 2008). While the sample does not precisely conform to demographic patterns from epidemiological studies, it is largely consistent with known trends. However, as noted in the Participants section, the excluded sample exhibited significantly lower QoL scores than the study sample. In light of this finding, it is possible that QoL and related variables were artificially inflated, as those lost to follow-up had lower reported well-being. Despite this concern, the sample still demonstrated a wide range of scores and variability on all QoL indices. Additionally, frequencies of

impairments on cognitive and physical measures and rates of clinically significant symptoms on self-report indices were consistent with previous research.

Another issue is the relatively small sample size of the study ($N = 55$). While the sample size may have limited the power of the analyses, most results were significant at a level beyond $p < .01$. Also, given the number of regression analyses, there is some risk of increased Type I error rate, in which some significant results may have been attributable to chance. However, significance (p-values) for all regression analyses exceeded Bonferroni-corrected levels, supporting the validity of the findings. Finally, numerous interesting questions concerning the effects of DMTs, antidepressants, and sleep habits on QoL and other study variables were not explored because the sample size did not permit consideration of numerous covariates.

CONCLUSION

The findings of this project are consistent with the conclusions of previous studies regarding the primacy of attention, processing speed, and motor deficits, and the importance of fatigue and depression in predicting the QoL of MS patients. However, the present investigation was the first to incorporate a diversity of objective and self-report measures, which comprehensively sampled from most of the domains affected by MS pathology, including indices of cognitive and motor functioning, self-reports of depression, fatigue, and neuropsychological symptoms, as well as a neurobiological measurement. Despite the inclusion of

such objective measures, the findings remained similar to previous studies. Accordingly, the importance of self-reported symptoms to QoL assessment is undeniable, and symptoms of depression and fatigue must be considered when making judgments regarding MS patient well-being. In light of the findings, screening for fatigue, mood dysregulation, and cognitive dysfunction should be incorporated into routine clinical evaluations of MS patients. Clinically significant symptoms identified on screening measures can be targeted with adjunctive treatments, which may not only decrease disease burden but also improve patient well-being.

APPENDIX A
Measure Characteristics and Psychometric Properties

A. Physical

9-Hole Peg Test (9HPT)

The 9-Hole Peg Test (Mathiowetz et al., 1985) is a simple timed measure of manual dexterity, motor speed, and coordination. It consists of a small board containing a three by three matrix of holes and small round dowels that fit into the holes. The participant is required to place the dowels into the holes one at a time using only one hand, followed by removal of all the pegs. The task is repeated twice for both the dominant and non-dominant hands. Mean times in seconds are calculated using the total of all four trials. The mean completion time has demonstrated utility in assessing upper extremity function in MS patients, and is a sensitive measure of disease progression, with change of greater than or equal to 15% reflective of significant progression (Kragt, van der Linden, Nielsen, Uitdehaag, & Polman, 2006). In a study of 400 patients with clinically definite MS or clinically isolated syndromes, Drake et al. (2010) reported significantly slowed mean times for patients (M = 24.1, SD = 15.4) compared to healthy controls [(M = 18.6, SD = 3.1), $p < .001$]. For the present study, T-scores were computed from mean completion times with means and standard deviations of a sample of 100 controls from the Multiple Sclerosis Functional Composite normative data (Drake et al., 2010).

Retinal Nerve Fiber Layer (RNFL) Thickness

Thickness of the RNFL for both eyes was measured using Spectralis OCT (OCT-3, OCT 4.0 software; Carl Zeiss Meditec, Dublin, CA). The fast RNFL thickness scan protocol was used for OCT (computes the average of three circumferential scans for 360° around the optic disc; 256 axial scans; diameter, 3.4 mm) as described in Frohman et al. (2009). Acceptable OCT scans were defined by a signal strength of seven or greater (maximum = 10) and uniform brightness across the scan circumference. The optic disc was centered in all scans by the scanning technician. As described by Fisher et al. (2006), scanning was completed following dark adaptation (about 10 min), without the use of pharmacologic dilation if the pupils were large enough to permit imaging (generally 5 mm). Average RNFL thickness for 360° around the optic disc was obtained in μm and percentile scores were produced based on normative data from the analysis software (Toledo et al., 2008). Mean thickness for both eyes was calculated, and eyes with previous or current optic neuritis were excluded from analyses. Additionally, a RNFL difference of greater than 10 μm between eyes was considered suggestive of a history of optic neuritis, and the eye with the thinner RNFL was excluded from analyses.

In a study comparing the RNFL thickness of 61 consecutive MS and clinically isolated syndrome patients with 29 sex- and age-matched healthy controls (excluding cases of optic neuritis), Sepulcre et al. (2007) reported that

MS patients had significantly decreased overall RNFL thickness (M = 85.8, SD = 13.9) compared to controls [(M = 92.3, SD = 16.7), p = .004]. They also found that MS patients had significant reductions in all quadrants compared to controls, except for the nasal quadrant ($p < .05$ in all cases). Of the 61 patients, 11 (18%) were below the first percentile, and 24 (39.3%) were below the fifth percentile of the normative database.

Timed 25-Foot Walk (T25FW)

The timed 25-Foot Walk test is a measure of mobility and leg function adapted from the Multiple Sclerosis Functional Composite (Cutter et al., 1999). The participant is directed to walk a marked distance of 25-feet as quickly, but safely, as possible. The task is immediately repeated as the participant walks back to the starting point. The resulting gait speed (mean time in seconds) has been shown to be a reliable and useful measure of walking ability in MS patients (Kragt et al., 2006), and like the 9HPT, is a reliable indicator of disease progression. Previously published data indicate that patients with MS and clinically isolated syndromes (N = 400) have significantly slower completion times (M = 8.5, SD = 11.6) than normal controls [(N = 100, M = 4.3, SD = 1.0), $p < .001$] (Drake et al., 2010). Gait speed (mean time in seconds) was recorded and T-scores were computed from the Multiple Sclerosis Functional Composite normative data (Drake et al., 2010).

B. Cognitive

Brief Visual Memory Test- Revised (BVMT-R)

The BVMT-R (Benedict, 1997) is a test of visual memory, which requires the immediate and delayed recall and recognition of visual figures. Six simple geometric designs in a two by three matrix are presented on an eight by eleven inch plate to the examinee for ten seconds. Following the brief exposure, the stimulus is removed and the examinee is asked to draw the figures on a blank page accurately and in the correct location as presented. This brief presentation followed by immediate reproduction of the figures is repeated two additional times (i.e., learning trials). Following a 25-minute delay (during which only measures with minimal visual components are administered), the examinee is asked to reproduce the figures from memory on a blank page. Following the delayed recall trial, the examinee is individually presented 12 designs, each printed on a three by five inch card. The examinee is asked to identify (recognize) which of the designs were included in the original matrix (6 targets and 6 non-targets). Responses on the learning and delayed recall trials are scored based on accuracy and location, and responses on the recognition trial are scored as hits and false alarms.

Numerous raw and age-adjusted T-scores are calculated from normative data provided in the test manual, of which Total Learning (sum of scores from trials 1-3) and Delayed Recall were utilized for this study (Benedict, 1997). Test-

retest reliability is adequate across learning trials (r = .60 for Trial 1 to r = .84 for Trial 3) and high for the total recall score (r = .80). Interrater reliability is reported to be high, greater than .90, and it has moderate to strong associations with other measures of nonverbal memory (e.g., Rey-Osterrieth Complex Figure Test and Visual Reproduction from the Wechsler Memory Test-Revised; r = .65 to .80) (Stauss, Sherman, & Spreen, 2006). Various scores from the BVMT-R (e.g., Total Learning and Delayed Recall) have been shown to be sensitive to nonverbal memory deficits in MS (Benedict et al., 2004).

California Verbal Learning Test- Second Edition, Standard Form (CVLT-II)

The CVLT-II (Delis et al., 2000) is a well-validated measure of verbal learning and memory. It has been shown to be sensitive to learning and memory (frontal and temporal lobe) dysfunction across neuromedical and psychiatric populations. It involves the verbal presentation of 16 words from four semantic categories across five learning trials, followed by presentation of a different 16-item distracter list (list B). Afterwards, immediate and 20-minute delayed free and cued recall trials are administered, as well as delayed recognition testing for the initial word list.

The examinee's responses were entered into a computer program, which provided raw and standard scores controlling for age and education for 93 normed variables (Strauss et al., 2006). Variables of interest for the present study included Total Learning T-score, Long Delayed Free Recall z-score, and Recognition

Discriminability (*d*') *z*-score. Internal consistency for the CVLT-II is adequate across the delayed and five immediate recall trials for both normative and mixed clinical samples (Strauss et al., 2006). Specifically, split-half reliabilities are high for both normative (r = .94) and clinical (r = .96) samples. Chronbach's coefficient alphas for the categorically-primed recall trials are high for both samples (normative, r = .82; clinical, r = .83). Test-retest reliability for Total Recall across trials one through five, Short and Long Delayed Free Recall, and Total Recognition Discrimination are high, though subjects recalled about eight more words across the learning trials on retesting following a median 21-day retest interval. The CVLT-II correlates well with the original CVLT. The CVLT-II has been validated in a study of 351 MS patients and 69 demographically-matched normal controls (Stegen et al., 2010). MS patients performed significantly worse than controls on 18 of the 23 variables examined, including learning, recall, consolidation, primacy/recency, and proactive interference.

Verbal Fluency

The verbal fluency test used in this study consisted of the FAS-Test and Category Fluency task (animals). These measures evaluate the spontaneous production of words under restricted search conditions (Strauss et al., 2006). On the FAS-Test (also referred to as phonemic fluency), the examinee is required to orally produce as many words as possible that begin with the letter 'F' in 60 seconds. The task is then immediately repeated for the letters 'A' and 'S.' Words

are scored as correct if they begin with the specified letter, are not proper nouns, and are not repetitions. A Total score is calculated summing the number of correct words produced across the three trials. Additionally, the number of losses of set (words that are proper nouns or begin with an incorrect letter) and perseverations are totaled. Normative data exist for the Total score based on age and education-level, as well as gender and ethnicity (Heaton et al., 2004). Internal consistency reliability is high, as measured by coefficient alpha using the total number of words generated for each letter (r = .83) (Tombaugh, Kozak, & Rees, 1999). Test-retest reliability is also high (> .70), and the measure has been shown to be sensitive to frontal lobe dysfunction (Benton & Hamsher, 1989).

The Category Fluency task (semantic or categorical fluency) requires the examinee to produce as many animal names as possible within a 60-second interval. The total number of correctly produced animal names is recorded as well as losses of set (words other than animals) and perseverations. Normative data exist for the Total score (number of correctly produced animals) based on age, education-level, gender, and ethnicity (Heaton et al., 2004). Test-retest reliability is comparable to FAS for both short and long intervals (Strauss et al., 2006). A recent meta-analytic study found that semantic fluency tasks make demands on frontal structures comparable to FAS, but make additional demands on temporal structures (Henry & Crawford, 2004). Additionally, both measures appear sensitive to the effects of nonspecific generalized slowing of processing.

For the purposes of the present study, demographically-adjusted (i.e., age, education, and gender) T-scores for total words on FAS and total animals on Category Fluency were utilized. In a meta-analysis of verbal fluency deficits in MS, Henry and Crawford (2004) found that patients were substantially and similarly impaired on both measures. Additionally, effect sizes of disease on the fluency measures were greater than measures of verbal intelligence, confrontation naming, and PSVs on the WCST, but were lower than the impact of disease on SDMT performance.

Paced Auditory Serial Addition Test- 3" interval (PASAT)

The PASAT (Gronwall, 1977) is a measure of divided attention, auditory information processing speed, working memory, and mental flexibility. Single digits are presented auditorily and the participant is required to add each new digit to the one presented immediately prior to it. The PASAT is presented on audiocassette tape or compact disk to control the rate of stimulus presentation. The measure has been adapted for MS patients, in which the presentation of digits occurs at the rate of one digit every three seconds and includes the presentation of 60 items (Rao et al., 2002). The number of correct responses and errors were recorded, and Total T-scores for correct responses were computed from normative data stratified by education (Rao et al., 1991).

Chronbach's alpha is very high in adults (r = .90; Crawford, Obansawin, & Allan, 1998), and test-retest correlations following short retest intervals (7-10

days) are excellent ($r > .90$; McCaffrey et al., 1995). The measure has been widely used in MS studies during the last decade, because the rate of information processing on the PASAT is highly dependent on subcortical brain systems and white matter tracts that are often affected by the disease (Strauss et al., 2006). Accordingly, deficits in performance in MS patients are hypothesized to occur due to slowed processing rather than working memory problems. Drake et al. (2010) reported that MS and clinically isolated syndrome patients ($N = 400$) performed significantly worse on the PASAT ($M = 40.2$, $SD = 12.8$) than normal controls [($N = 100$, $M = 48.0$, $SD = 10.7$), $p < .001$].

Stroop Color and Word Test (Stroop)

The Stroop Color and Word test is a measure of cognitive control, assessing the extent to which the examinee can maintain a goal and suppress a habitual response. Specifically, the task measures selective attention, impulse control, and inhibition (Golden, 1978), and consists of three trials: Word-Reading, Color-Naming, and Color-Word trials. On the Word-Reading trial, the examinee is required to read out loud the names of color words (‘red,’ ‘blue,’ and ‘green’) written in black ink. The stimulus includes 100 color words arranged into vertical columns, and the examinee must read as many words as possible, in order, down the columns within 45 seconds. The Color-Naming trial is administered in the same fashion, though the stimulus consists of 100 strings of Xs printed in red, green, or blue ink, and the examinee is required to name the color of as many

strings as possible in 45 seconds. The Color-Word trial requires the examinee to state the color of incongruent color-words (e.g., 'red' printed in blue ink), while ignoring the word itself. Total correct responses are counted for each trial and T-scores are calculated based on normative data stratified by age and education provided in the test manual (Golden & Freshwater, 2002). An additional score, the Interference T-score, is calculated comparing actual performance on the Color-Word trial with predicted performance based on the Word-Reading and Color-Naming trials. The Interference score reflects the extent to which the examinee is able to suppress an overlearned response (word-reading) and control attention. The Color-Word and Interference T-scores were utilized for the present study to measure divided attention/processing speed and executive functioning, respectively.

Test-retest reliability is good across the Word-Reading (r = .86) and Color-Naming trials (r = .82), and marginal on the Color-Word trial (r = .73; N = 30; Golden, 1978). Performance on the task, specifically the Interference score, has been associated with anterior cingulate function in fMRI studies (Mayberg, 1997), and is often considered an indicator of executive functioning. However, it is unclear to what extent impairment on the Stroop test reflects executive and attentional dysfunction, or more generalized processing speed slowing and inefficiency (Strauss et al., 2006). The importance of processing speed to Stroop performance was investigated by Denney and Lynch (2009). Their comparison of

248 MS patients with 178 controls found that the greatest differences between groups were accounted for by generalized slowing in MS patients.

Symbol Digit Modalities Test (SDMT)

The SDMT (Smith, 1991) is a simple substitution task requiring the participant to pair specific numbers with presented geometric figures using a reference key. It is considered a measure of attention, visual scanning, tracking, and motor speed. Responses can be written or oral, depending on how the test is administered, and the examinee is asked to respond with as many numbers that correspond to symbols as possible within 90 seconds, in order across rows on the stimulus. The number of correct substitutions within the time limit is recorded with a maximum score of 110 on both the written and oral forms. Only the written form was utilized for this study, and Total T-scores were calculated based on the number of correct responses using normative data stratified by age and education provided in the test manual (Smith, 1991).

Test-retest reliability is respectable, with correlations of $r = .80$ for the written version and $r = .76$ for the oral version in 80 normal adults with a mean retest interval of 29 days (Smith, 1991). Written and oral forms are highly correlated ($r > .78$). The SDMT is similar in format to the Wechsler Digit/Symbol Coding subtest, with correlations between the two measures reported to be high $r = .91$ (Morgan & Wheelock, 1992). It has been demonstrated to tap aspects of performance similar to those of the Letter Cancellation and Trail Making tests,

primarily assessing the scanning and tracking aspects of attention (McCaffrey et al., 1988). The SDMT has been shown to be sensitive to a wide range of organic cerebral impairments. SDMT scores that fall one to one and a half *SD*s below the mean are suggestive of cerebral dysfunction. In MS patients, the SDMT is the neuropsychological instrument most associated with neuroimaging indices of disease burden, and performance accounts for almost half of the shared variance in patients with mild to moderate cognitive impairment (Strauss et al., 2006). Drake et al. (2010) reported significantly lower SDMT performance in 400 MS and clinically isolated syndrome patients ($M = 50.2$, $SD = 12.3$) as compared to 100 normal controls [($M = 61.9$, $SD = 9.6$), $p < .001$].

Texas Card Sorting Test (TCST)

The TCST is a brief experimental measure of cognitive flexibility and reasoning. It requires examinees to sort six cards that share common dimensions (e.g., size, color, shape, etc.) into two groups, and then repeat the process using as many different sorting principles as possible in a three-minute time allotment (Kaltreider, Vertovec, Saine, & Cullum, 1999). The test is similar to the popular WCST and D-KEFS Sorting Test, but provides a less-structured approach to assessment, allowing for sorting along multiple dimensions creatively determined by the participant. Scores include logical sorts (number of correctly utilized principles), PSVs (repeated use of the same principle), as well as other responses (sorts that utilize an illogical principle). This is a yet-to-be-published test that

requires less than 10-minutes to complete and has been shown to demonstrate orbitofrontal and basal ganglia activation on fMRI (Woolston, 2006). The TCST Total LS (number of logical sorts) were used for the present study. Less than or equal to four Logical Sorts (out of eight) is considered significantly impaired based on unpublished normative data (Woolston, 2006; Kaltreider et al., 1999).

C. Self-Report

Modified Fatigue Impact Scale (MFIS)

The Modified Fatigue Impact Scale (MFIS; Fisk et al., 1994) is a self-report questionnaire evaluating the effects of fatigue on daily functioning over the previous month. It was derived from the Fatigue Impact Scale and measures fatigue in terms of physical, cognitive, and psychosocial functioning. The MFIS consists of 21 items on a Likert-type scale from zero to four. Scores range from zero to 84 and are calculated by summing the responses to the scale's items. Total scores were utilized as a measurement of subjective self-reported fatigue.

The measure is highly face valid and it correlates well with an MS-specific measure of fatigue severity (FSS; $r = .68$) (Whitehead, 2009). Additionally, the measure appears sensitive in discriminating the effects of fatigue in MS patients from those with chronic fatigue syndrome and essential hypertension. The authors report good internal consistency (Cronbach's alpha of .81) and test-retest reliability ($r = .72$ to .93). A cut-off score of 38 has been demonstrated to

discriminate well between clinically fatigued and non-fatigued patients (Flachenecker et al., 2002).

MS Neuropsychological Screening Questionnaire (MSNQ)

The MSNQ (Benedict et al., 2005) is a 15-item screening measure of neuropsychological functioning in MS within the domains of attention, processing speed, memory, and 'other cognitive functions.' The instrument has two forms—Self-report (MSNQ-S) and Informant (MSNQ-I). Items utilize a Likert-type scale (zero to four) and scores range from zero to 60. Internal consistency was found to be acceptable for both forms in a group of 85 MS patients and 40 normal controls. Cronbach's coefficient alpha values were high for both forms in the MS group (MSNQ-S = .94; MSNQ-I = .93) and controls (MSNQ-S = .84; MSNQ-I = .89) (Benedict et al., 2005). Test-retest correlations for MS patients were similarly high (MSNQ-S = .90; MSNQ-I = .93). The MSNQ-S was utilized for the present study in which only self-report responses from the MS patients were considered. The sensitivity and specificity of the self-report version of the MSNQ were reported as follows: sensitivity = .83 and specificity = .60. However, the authors reported a high rate of false positives (i.e., people classified as cognitively impaired who were not impaired on formal testing) in persons with significant depressive symptoms.

A recommended cut-off score of 24 or greater on the MSNQ is recommended to maximally separate MS patients with clinically significant self-

reported cognitive symptoms from those without (Benedict et al., 2005). However, in a study of 48 patients with clinically-definite MS and 40 healthy controls, Obrien and colleagues (2007) found that the MSNQ did not demonstrate significant correlations with objectively measured daily functioning or objectively measured neuropsychological functioning (except for the JLO: $r = -.38$, $p < .05$; T25FW: $r = -.38$, $p < .05$; and the Selective Reminding Test: $r = .39$, $p < .05$). Their results did not support the sensitivity of the MSNQ to classify persons as cognitively impaired versus non-impaired. Total scores from the MSNQ were used to measure patient-reported symptoms of subjective neuropsychological dysfunction.

Multiple Sclerosis Quality of Life-54 Instrument (MSQOL-54)

The MSQOL-54 (Vickrey et al., 1995) is a multidimensional health-related quality of life measure combining general quality of life concerns (from the SF-36) with MS-specific items from domains such as cognitive functioning and fatigue. It is a 54-item, self-report, structured questionnaire requiring approximately 11-18 minutes to complete (see Appendix C). There is a two-item Overall subscale (MSQOL-54O), and two Composite scores, Physical Health (MSQOL-54P) and Mental Health (MSQOL-54M), can be derived from a weighted combination of subscale scores. There are 12 subscales: Physical Function, Role Limitations-Physical, Role Limitations-Emotional, Pain, Emotional Well-being, Energy, Health Perceptions, Social Function, Cognitive

Function, Health Distress, Sexual Function, and Overal QoL. Additionally, there are two additional single-item measures: Satisfaction with Sexual Function and Change in Health. All subscales and composite scores were utilized for the present study.

The 12 subscales of the MSQOL-54 show good internal consistency, with Cronbach's alphas ranging from .75 to .96 (Rudick & Miller, 2008). Test-retest reliability for the 12 subscales is also good, with intra-class correlation coefficients greater than .69. The validity of the measure is supported by an association between MSQOL-54 scales and symptom severity, level of ambulation, employment limitations, hospital admissions, and symptoms of depression in a sample of 179 MS patients (Vickrey et al., 1995). Similar outcomes were found in a study of 150 patients with MS from 3 centers in the UK (Freeman, Hobart, & Thompson, 2001). Adding further support to the MSQOL-54 is a validation study of the instrument in 215 MS patients (Miller & Dishon, 2005). Convergent validity was supported by significant correlations between all MSQOL-54 scores and disability (as measured with the Expanded Disability Status Scale), with the Physical Health subscale showing the greatest association by far (r = -.75). Discriminant validity was supported by the finding that MSQOL-54 scales accurately discriminated between MS and non-MS patients, with the largest differences between groups found on the Physical Health and Role Limitations- Physical subscales.

Quick Inventory of Depressive Symptomatology (QIDS)

The QIDS (Rush et al., 2003) is a 16-item inventory designed to measure the severity of depressive symptoms. The measure is available in both clinician-rated and self-rated versions, and assesses all of the nine criterion symptom domains required by the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition* (DSM-IV) to diagnose a major depressive episode. Total scores from the self-report version were utilized in the present study. Items fall on a Likert-type scale from zero to three, yielding a total score that ranges from zero to 27. This instrument is a frequently used screening tool for the presence of clinical depression, but is predominantly employed as a measure of symptom severity. In a validation study of 596 nonpsychotic depressed outpatients, the inventory authors found that internal consistency was high (Cronbach's alpha = .86), and total scores were highly correlated with other measures of depression such as the Inventory of Depressive Symptomatology (r = .96) and the Hamilton Rating Scale for Depression (r = .86). The authors provided the following recommendations for interpretation of depressive symptoms: 0-5 (no depression), 6-10 (mild), 11-15 (moderate), 16-20 (severe), and 21-27 (very severe) (Rush et al., 2003). For the purposes of this study, scores were considered clinically significant if they fell in the moderate or greater severity ranges.

APPENDIX B
Statistical Assumptions

Planned parametric statistical analyses on interval and ratio scale study variables included independent samples *t*-tests, Pearson product-moment correlations (*r*), and stepwise linear regression. Planned nonparametric analyses on nominal and ordinal variables were conducted with Chi-square goodness of fit tests and Chi-square tests of homogeneity of proportions. The assumptions underlying each analysis are specified in Table 13.

Table 13. *Statistical Assumptions by Analysis*

Analysis	Assumption
t-test	Normally distributed variables Equal variances between populations Independent random sampling
Pearson *r*	Normally distributed variables Linear relationships between variables Independent random sampling
Linear regression	Normally distributed predictors and criterion Linear relationships between variables Independent random sampling
Chi-square	
Goodness of Fit Test	Cell size >5 for at least 80% of categories Independent random sampling
Homogeneity of Proportions	Exclusive groups that exhaust all possibilities Independent random sampling

Normality

According to the central limit theorem, the study sample size ($N = 55$) permitted the use of parametric statistics for most variables (other than Included/Excluded group analyses), even if the data were not normally distributed (Elliott & Woodward, 2007). Nonetheless, all study variables were checked for normality by visually inspecting the shape of distributions with histograms, and

examining distances between means and medians. The variables included all objective neurocognitive variables (CVLT-II Total Learning T-score, BVMT-R Total Learning T-score, CVLT-II Long Delayed Free Recall *z*-score, BVMT-R Delayed Recall T-score, CVLT-II Discriminability *z*-score, PASAT Total T-score, SDMT Total T-score, Stroop Color-Word T-score, Stroop Interference T-score, TCST Total Logical Sorts, FAS Total T-score, and Category Total T-score), physical variables (9HPT T-score, T25FW T-score, and mean RNFL thickness), and self-report indices (MSQOL-54O, MSQOL-54M, MSQOL-54P, MFIS Total score, QIDS Total score, and MSNQ Total score). Histograms for most variables approximated a bell-shape, suggesting normality of their distributions. Additionally, means and medians were similar for most variables, implying that the distributions were not significantly skewed. Also, the sums and differences between medians and standard deviations did not exceed the range of possible scores for any measure. See Table 4 for means, medians, standard deviations, and ranges of all study variables.

Linearity

Linearity of relationships was assessed visually with a matrix of scatter plots of all bivariate combinations of interest. Most associations appeared linear, though some of the MSQOL-54 subscales seemed to have ambiguous or random scatter when plotted against other study variables. These subscales included the Physical Health, Sexual Function, and Change in Health variables. It is notable that these subscales also had larger differences between mean and median, as well

as larger standard deviations than other variables of interest from the MSQOL-54. Accordingly, it was considered that the greater variability of these variables may have contributed to non-normal bivariate distributions with other study measures. As such, the results of all Pearson product-moment correlations involving these subscales were checked against the results of nonparametric Spearman's rho analyses. Associations were similar and all significant Pearson product-moment correlations remained significant with Spearman's rho. The possibility of non-normally distributed data for these MSQOL-54 subscales was not of concern for other analyses, as these scales were not primary outcome measures and were not included in any regression analyses. Nonetheless, all associations between criterion variables (MSQOL-54O, MSQOL-54M, and MSQOL-54P) and predictors appeared linear, and significance testing with Pearson's *r* (product-moment correlation coefficient) did not differ from the results of Spearman's rho analyses.

Equality of Variances

Analyses with independent samples *t*-tests required that groups have similar variances. Equality of variances between groups was assessed with Levene's test of homogeneity of variance. Most group variances did not significantly differ (i.e., $p > .05$), with the exception of a few variables in the low versus high QoL analyses. The results of these *t*-tests were checked with Mann-Whitney tests and significant results remained significant regardless of test.

Independent Random Sampling

All analyses conducted in this study required that each study participant be selected randomly and independently of each other. In other words, all individuals in the sample must have equal probabilities of being selected and each selection must be independent of all others (Cohen, 2001). This study utilized a sample of convenience, of which participants were drawn consecutively as they presented in the clinic without replacement (i.e., there was no possibility of being re-selected). Accordingly, it cannot be assumed that each participant had the same probability of selection, violating the assumption of independent random sampling. Indeed, in most psychological research, true random sampling is nearly impossible; however, the possibility of statistical inaccuracy resulting from this violation is of little concern to the validity of the conclusions drawn from the analyses. Specifically, utilizing samples of convenience typically overestimates the true standard error of population differences, *decreasing the chance of attaining significance*, without increasing the Type I error rate (i.e., false positives). As such, the violation of the sampling assumption in this case resulted in more conservative analyses, increasing confidence in their significance (or non-significance).

Chi-square Assumptions

Chi-square goodness of fit tests were used for most comparisons of categorical data. These analyses required that 80% of the cells in the matrix of observed and expected frequencies have counts of 5 or greater (or less than 20%

that violate the assumption). Most variables met this assumption; however, cell sizes for inclusion/exclusion comparisons of demographic and medication characteristics did not, given the small sample size of the excluded group (N = 11). The number and percentage of cells with counts less than 5 were as follows: Gender (1 cell, 25%), Diagnosis (11 cells, 79%), Ethnicity (6 cells, 75%), Steroid use (2 cells, 50%), and DMT use (1 cell, 25%). Fisher's exact tests were used instead of Chi-square for these variables (Cohen, 2001).

Chi-square tests of homogeneity of proportions were used to analyze differences in rates of impairment across measures. Each measure/variable was dichotomous (e.g., impaired or not), and the resulting proportions were mutually exclusive and always totaled 100%. Accordingly, these tests met the assumption requiring that all possibilities be exhausted.

APPENDIX C

The Multiple Sclerosis Quality of Life-54 Instrument (MSQOL-54)*

*Reprinted with permission of the author.

Multiple Sclerosis Quality of Life

(MSQOL)-54 Instrument

For Further Information, Contact:

Barbara G. Vickrey, MD, MPH
UCLA Department of Neurology
C-128 RNRC; Box 951769
Los Angeles, CA 90095-1769
Voice: 310.206.7671
Fax: 310.794.7716

INSTRUCTIONS:

This survey asks about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3, ...).

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin.

Please feel free to ask someone to assist you if you need help reading or marking the form.

1. In general, would you say your health is:

(circle one number)

Excellent.....1

Very good.....2

Good.....3

Fair.....4

Poor.....5

2. **Compared to one year ago**, how would you rate your health in general **now**?

(circle one number)

Much better now than one year ago..... 1

Somewhat better now than one year ago.....2

About the same 3

Somewhat worse now than one year ago..... 4

Much worse now than one year ago 5

3-12. The following questions are about activities you might do during a typical day. Does **your health** limit you in these activities? If so, how much? (Circle 1, 2, or 3 on each line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not Limited at All
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing several flights of stairs	1	2	3
7. Climbing one flight of stairs	1	2	3
8. Bending, kneeling, or stooping	1	2	3
9. Walking more than a mile	1	2	3
10. Walking several blocks	1	2	3
11. Walking one block	1	2	3
12. Bathing and dressing yourself	1	2	3

13-16. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle one number on each line)

	YES	NO
13. Cut down on the amount of time you could spend on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

17-19. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious).

(Circle one number on each line)

	YES	NO
17. Cut down on the amount of time you could spend on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one number)

Not at all.....1

Slightly.....2

Moderately.....3

Quite a bit.....4

Extremely.....5

Pain

21. How much **bodily** pain have you had during the **past 4 weeks**?

(circle one number)

None..... 1

Very mild..... 2

Mild..... 3

Moderate..... 4

Severe..... 5

Very severe..... 6

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(circle one number)

Not at all..... 1

A little bit..... 2

Moderately..... 3

Quite a bit..... 4

Extremely..... 5

23-32. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**... (Circle one number on each line)

	All of the Time	Most Of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6
32. Did you feel rested on waking in the morning?	1	2	3	4	5	6

33. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one number)

All of the time.....1

Most of the time.....2

Some of the time 3

A little of the time.....4

None of the time.....5

Health in General

34-37. How TRUE or FALSE is each of the following statements for you.

(Circle one number on each line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
34. I seem to get sick a little easier than other people	1	2	3	4	5
35. I am as healthy as anybody I know	1	2	3	4	5
36. I expect my health to get worse	1	2	3	4	5
37. My health is excellent	1	2	3	4	5

Health Distress

How much of the time during the **past 4 weeks...**

(Circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
38. Were you discouraged by your health problems?	1	2	3	4	5	6
39. Were you frustrated about your health?	1	2	3	4	5	6
40. Was your health a worry in your life?	1	2	3	4	5	6
41. Did you feel weighed down by your health problems?	1	2	3	4	5	6

Cognitive Function

How much of the time during the **past 4 weeks...**

(Circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
42. Have you had difficulty concentrating and thinking?	1	2	3	4	5	6
43. Did you have trouble keeping your attention on an activity for long?	1	2	3	4	5	6
44. Have you had trouble with your memory?	1	2	3	4	5	6
45. Have others, such as family members or friends, noticed that you have trouble with your memory or problems with your concentration?	1	2	3	4	5	6

Sexual Function

46-50. The next set of questions are about your sexual function and your satisfaction with your sexual function. Please answer as accurately as possible about your function **during the last 4 weeks only.**

How much of a problem was each of the following for you **during the past 4 weeks?**

(Circle one number on each line)

MEN	Not a problem	A Little of a Problem	Somewhat of a Problem	Very Much a Problem
46. Lack of sexual interest	1	2	3	4
47. Difficulty getting or keeping an erection	1	2	3	4
48. Difficulty having orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

(Circle one number on each line)

WOMEN	Not a problem	A Little of a Problem	Somewhat of a Problem	Very Much a Problem
46. Lack of sexual interest	1	2	3	4
47. Inadequate lubrication	1	2	3	4
48. Difficulty having orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

50. Overall, how satisfied were you with your sexual function **during the past 4 weeks**?

(circle one number)

Very satisfied..... 1

Somewhat satisfied..... 2

Neither satisfied nor dissatisfied 3

Somewhat dissatisfied 4

Very dissatisfied..... 5

51. During the **past 4 weeks**, to what extent have problems with your bowel or bladder function interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one number)

Not at all..... 1

Slightly..... 2

Moderately 3

Quite a bit..... 4

Extremely 5

52. During the **past 4 weeks**, how much did *pain* interfere with your enjoyment of life?

(circle one number)

Not at all..... 1

Slightly..... 2

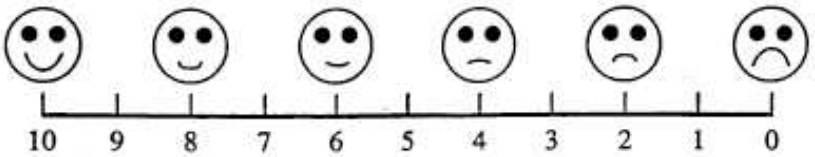
Moderately 3

Quite a bit..... 4

Extremely 5

53. Overall, how would you rate your own quality-of-life?

Circle one number on the scale below:



10 9 8 7 6 5 4 3 2 1 0

Best Possible Quality-of-Life

Worst Possible Quality-of-Life

As bad as or worse than being dead

54. Which best describes how you feel about your life as a whole?

(circle one number)

Terrible 1

Unhappy 2

Mostly dissatisfied 3

Mixed - about equally satisfied and dissatisfied 4

Mostly satisfied 5

Pleased 6

Delighted 7

Scoring Forms for Multiple Sclerosis Quality of Life (MSQOL) -54

Table 1
MSQOL-54 Scoring Form

Table 2
MSQOL-54 Physical Health Composite Score

Table 3
MSQOL-54 Mental Health Composite Score

Table 1

MSQOL-54 Scoring Form

Scale/Item Number	Response 1	2	3	4	5	6		Subtotal	Final Score 0-100 point scale
Physical Health									
3.	0	50	100					_____	
4.	0	50	100					_____	
5.	0	50	100					_____	
6.	0	50	100					_____	
7.	0	50	100					_____	
8.	0	50	100					_____	
9.	0	50	100					_____	
10.	0	50	100					_____	
11.	0	50	100					_____	
12.	0	50	100					_____	
							Total:	_____ ÷ 10 =	_____
Role limitations due to physical problems									
13.	0	100						_____	
14.	0	100						_____	
15.	0	100						_____	
16.	0	100						_____	
							Total:	_____ ÷ 4 =	_____
Role limitations due to emotional problems									
17.	0	100						_____	
18.	0	100						_____	
19.	0	100						_____	
							Total:	_____ ÷ 3 =	_____
Pain									
21.	100	80	60	40	20	0		_____	
22.	100	75	50	25	0			_____	
52.	100	75	50	25	0			_____	
							Total:	_____ ÷ 3 =	_____
Emotional well-being									
24.	0	20	40	60	80	100		_____	
25.	0	20	40	60	80	100		_____	
26.	100	80	60	40	20	0		_____	
28.	0	20	40	60	80	100		_____	
30.	100	80	60	40	20	0		_____	
							Total:	_____ ÷ 5 =	_____
Energy									
23.	100	80	60	40	20	0		_____	
27.	100	80	60	40	20	0		_____	
29.	0	20	40	60	80	100		_____	
31.	0	20	40	60	80	100		_____	
32.	100	80	60	40	20	0		_____	
							Total:	_____ ÷ 5 =	_____

Table 1 (cont.) Scale/Item Number	Response 1	2	3	4	5	6	Subtotal	Final Score 0-100 point

Health Perceptions

1.	100	75	50	25	0			____	
34.	0	25	50	75	100			____	
35.	100	75	50	25	0			____	
36.	0	25	50	75	100			____	
37.	100	75	50	25	0			____	
							Total:	____ ÷ 5 =	____

Social function

20.	100	75	50	25	0			____	
33.	0	25	50	75	100			____	
51.	100	75	50	25	0			____	
							Total:	____ ÷ 3 =	____

Cognitive function

42.	0	20	40	60	80	100		____	
43.	0	20	40	60	80	100		____	
44.	0	20	40	60	80	100		____	
45.	0	20	40	60	80	100		____	
							Total:	____ ÷ 4 =	____

Health distress

38.	0	20	40	60	80	100		____	
39.	0	20	40	60	80	100		____	
40.	0	20	40	60	80	100		____	
41.	0	20	40	60	80	100		____	
							Total:	____ ÷ 4 =	____

Sexual function*

46.	100	66.7	33.3	0				____	
47.	100	66.7	33.3	0				____	
48.	100	66.7	33.3	0				____	
49.	100	66.7	33.3	0				____	
							Total:	____ ÷ 4 =	____

Change in health

2.	100	75	50	25	0				____

Satisfaction with sexual function

50.	100	75	50	25	0				____

Overall quality of life

	Response								
	1	2	3	4	5	6	7		
53.	(multiply response by 10)							____	
54.	0	16.7	33.3	50	66.7	83.3	100	____	
							Total:	____ ÷ 2 =	____

Note: The total number of items in each scale is listed as the divisor for each subtotal. However, due to missing data, the divisor might actually be less than that if not every item within a given scale has been answered. For example, if item 38 in the Health Distress scale was left blank and the other 3 items in the scale were answered, then the "Total" score for Health Distress would be divided by '3' (instead of '4') to obtain the "Final Score."

* Males and females can be combined in the analysis even though question 47 is different for the two groups. The scale scores can also be reported separately for males and females.

Table 2
Formula for calculating MSQOL-54 Physical Health Composite Score

MSQOL-54 Scale	Final Scale Score	x	Weight	=	Subtotal
Physical function	_____	x	.17	=	_____(a)
Health perceptions	_____	x	.17	=	_____(b)
Energy/fatigue	_____	x	.12	=	_____(c)
Role limitations - physical	_____	x	.12	=	_____(d)
Pain	_____	x	.11	=	_____(e)
Sexual function	_____	x	.08	=	_____(f)
Social function	_____	x	.12	=	_____(g)
Health distress	_____	x	.11	=	_____(h)

PHYSICAL HEALTH COMPOSITE: Sum subtotals (a) through (h) = _____

Table 3
Formula for calculating MSQOL-54 Mental Health Composite Score

MSQOL-54 Scale	Final Scale Score	x	Weight	=	Subtotal
Health distress	_____	x	.14	=	_____(a)
Overall quality of life	_____	x	.18	=	_____(b)
Emotional well-being	_____	x	.29	=	_____(c)
Role limitations - emotional	_____	x	.24	=	_____(d)
Cognitive function	_____	x	.15	=	_____(e)

MENTAL HEALTH COMPOSITE: Sum subtotals (a) through (e) = _____

REFERENCES

Achiron, A., & Barak, Y. (2003). Cognitive impairment in probable multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, *74*, 443-446.

Albert, M. L., Feldman, R. G., & Willis, A. L. (1974). The 'subcortical dementia' of progressive supranuclear palsy. *Journal of Neurology, Neurosurgery, and Psychiatry*, *37*, 121-130.

Amato, M. P., Portaccio, E., & Zipoli, V. (2006) Are there protective treatments for cognitive decline in MS. *Journal of the Neurological Sciences*, *245*, 183-186.

Amato, M. P., Zipoli, V., & Portaccio, E. (2006). Multiple sclerosis-related cognitive changes: A review of cross-sectional and longitudinal studies. *Journal of the Neurological Sciences*, *245*, 41-46.

Amato, M. P., Ponziani, G., Liedl, C. L., Stefanile, C., & Rossi, L. (2001). Quality of life in multiple sclerosis: The impact of depression, fatigue and disability. *Multiple Sclerosis*, *7*, 340-344.

Amato, M. P., Ponziani, G., Siracusa, G., & Sorbi, S. (2001). Cognitive dysfunction in early-onset multiple sclerosis: A reappraisal after 10 years. *Archives of Neurology*, *58*, 1602-1606.

Arrondo, G., Alegre, M., Sepulcre, J., Iriarte, J., Artieda, J., & Villoslada, P. (2009). Abnormalities in brain synchronization are correlated with cognitive impairment in multiple sclerosis. *Multiple Sclerosis*, *15*, 509-516.

Bakshi, R., Miletich, R. S., Henschel, K., Shaikh, Z. A., Janardhan, V., Wasay, M., et al. (1999). Fatigue in multiple sclerosis: Cross-sectional correlation with brain MRI findings in 71 patients. *Neurology*, *53*, 1151.

Bakshi, R., Miletich, R. S., Kinkel, P. R., Emmet, M. L., & Kinkel, W. R. (1998). High-resolution fluorodeoxyglucose positron emission tomography shows both global and regional cerebral hypometabolism in multiple sclerosis. *Journal of Neuroimaging*, *8*, 228-234.

Bakshi, R., Shaikh, Z. A., Miletich, R. S., Czarnecki, D., Dmochowski, J., Henschel K., et al. Fatigue in multiple sclerosis and its relationship to

depression and neurologic disability. (2000). *Multiple Sclerosis*, *6*,181-185.

Baum, C. M., Morrison, T., Hahn, M., & Edwards, D. F. (2003). *Test manual for the executive function performance test*. St. Louis, MO: Washington University.

Bechara, A., Damásio, A. R., Damásio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, *50*, 7-15.

Benedict, R. H. (1997). *Brief visuospatial memory test-revised*. Odessa, FL: Psychological Assessment Resources, Inc.

Benedict, R. H., Carone, D. A., & Bakshi, R. (2004). Correlating brain atrophy with cognitive dysfunction, mood disturbances, and personality disorder in multiple sclerosis. *Journal of Neuroimaging*, *14*, 36-45.

Benedict, R. H., Cox, D., Thompson, L. L., Foley, F., Weinstock-Guttman, B., & Munschauer, F. (2005). Reliable screening for neuropsychological impairment in multiple sclerosis. *Multiple Sclerosis*, *10*, 675-678.

Benedict, R. H., Munschauer, F., Linn, R., Miller, C., Murphy, E., Foley, F., et al. (2003). Screening for multiple sclerosis cognitive impairment using a self-administered 15-item questionnaire. *Multiple Sclerosis*, *9*, 95–101.

Benedict, R. H., Wahlig, E., Bakshi, R., Fishman, I., Munschauer, F., Zivadinov, R., et al. (2005). Predicting quality of life in multiple sclerosis: Accounting for physical disability, fatigue, cognition, mood disorder, personality, and behavior change. *Journal of Neurological Sciences*, *231*(1-2), 29-34.

Benedict, R. H. B., Weinstock-Guttman, B., Fishman, I., Sharma, J., Tjoa, C. W., & Bakshi, R. (2004). Prediction of neuropsychological impairment in multiple sclerosis: Comparison of conventional magnetic resonance imaging measures of atrophy and lesion burden. *Archives of Neurology*, *61*, 226-230.

Benton, A. L., Hamsher, K. de S., & Sivan, A.B. (1994). *Multilingual aphasia examination*. Iowa City, IA: AJA Associates.

Benton, A. L., Sivan, A. B., Hamsher, K. deS., Varney, N. R., & Spreen, O. (1994). *Contributions to neuropsychological assessment* (2nd ed.). Orlando, FL: Psychological Assessment Resources.

Benton, A. L., Varney, N. R., & Hamsher, K. D. (1978). Visuospatial judgment: A clinical test. *Archives of Neurology*, *35*, 364-367.

Berg, D., Supprian, T., Thomae, J., Warmuth-Metz, M., Horowski, A., Zeiler, B., et al. (2000). Lesion pattern in patients with multiple sclerosis and depression. *Multiple Sclerosis*, *6*, 156-162.

Blinkenberg, M., Rune, K., Jensen, C. V., Ravnborg, M., Kyllingsbaek, S., Holm, S., et al. (2000). Cortical cerebral metabolism correlates with MRI lesion load and cognitive dysfunction in MS. *Neurology*, *54*, 558-564.

Bo, L., Vedeler, C. A., Nyland, H. I., Trapp, B. D., & Mork, S. J. (2003). Subpial demyelination in the cerebral cortex of multiple sclerosis patients. *Journal of Neuropathology and Experimental Neurology*, *62*, 723-732.

Bruce, J. M., Bruce, A. S., & Arnett, P. A. (2007). Mild visual acuity disturbances are associated with performance on tests of complex visual attention in MS. *Journal of the International Neuropsychological Society*, *13*, 544-548.

Brusa, A., Jones, S. J., Kapoor, R., Miller, D. H., & Plant, G. T. (1999). Long-term recovery and fellow eye deterioration after optic neuritis, determined by serial visual evoked potentials. *Journal of Neurology*, *246*, 776-782.

Brusa, A., Jones, S. J., & Plant, G. T. (2001). Long-term remyelination after optic neuritis: A 2-year visual evoked potential and psychophysical serial study. *Brain*, *124*, 468-479.

Buchanan, R. J., Minden, S. L., Chakravorty, B. J., Hatcher, W., Tyry, T., & Vollmer, T. (2010). A pilot study of young adults with multiple sclerosis: demographic, disease, treatment, and psychosocial characteristics. *Disability and Health Journal*, *3*, 262-270.

Butt, Z., Yount, S. E., Caicedo, J. C., Abecassis, M. M., & Cella, D. (2008). Quality of life assessment in renal transplant: Review and future directions. *Clinical Transplantation*, *22*, 292-303.

Calabrese, P. (2006). Neuropsychology of multiple sclerosis: An overview. *Journal of Neurology*, *253* (Suppl. 1), 10-15.

Caldwell, J. A. (2001). Efficacy of stimulants for fatigue management: The effects of Provigil and Dexedrine on sleep-deprived aviators. *Transportation Research Part F: Traffic Psychology and Behaviour*, *4*, 19-37.

Cohen, B. (2001). *Explaining psychological statistics* (2nd Ed.). New York: Wiley and Sons.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences, 2nd ed*. Hillsdale, NJ: Erlbaum.

Compston, A., & Coles, A. (October 2008). Multiple sclerosis. *Lancet*, *372*, 1502–1517.

Compston A, & Coles, A. (April 2002). Multiple sclerosis. *Lancet*, *359*, 1221–1231.

Crawford, J. R., Obansawin, M. C., & Allan, K. M. (1998). PASAT and components of WAIS-R performance: Convergent and discriminant validity. *Neuropsychological Rehabilitation*, *8*, 273-282.

Cutter, G. R., Baier, M. L., Rudick, R. A., Cookfair, D. L., Fischer, J. S., Petkau, J., et al. (1999). Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain*, *122*, 871–882.

De Sonneville, L. M., Boringa, J. B., Reuling, I. E., Lazeron, R. H., Adèr, H. J., & Polman, C. H. (2002). Information processing characteristics in subtypes of multiple sclerosis. *Neuropsychologia*, *14*,1751-1765.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). California Verbal Learning Test (2nd ed.). San Antonio, TX: Psychological Corporation.

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). Delis-Kaplan Executive Function System (DKEFS): Examiner's manual. San Antonio, TX: The Psychological Corporation.

Denney, D.R., & Lynch, S. G. (2009). The impact of multiple sclerosis on

patients' performance on the Stroop Test: Processing speed versus interference. *Journal of the International Neuropsychological Society*, *15*, 451-458.

Drake, A. S., Weinstock-Guttman, B., Morrow, S. A., Hojnacki, D., Munschauer, F. E., & Benedict, R. H. (2010). Psychometrics and normative data for the Multiple Sclerosis Functional Composite: Replacing the PASAT with the Symbol Digit Modalities Test. *Multiple Sclerosis*, *16*, 228-237.

Elliott, A. C., & Woodward, W. A. (2007). *Statistical analysis quick reference guidebook with SPSS examples.* Thousand Oaks, CA: Sage.

Ferini-Strambi, L., Filippi, M., Martinelli, V., Oldani, A., Rovaris, M., Zucconi, M., et al. (1994). Nocturnal sleep study in multiple sclerosis: Correlations with clinical and brain magnetic resonance imaging findings. *Journal of the Neurological Sciences*, *125*,194-197.

Feuillet, L., Reuter, F., Audoin, B., Malikova, I., Barrau, K., et al. (2007). Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. *Multiple Sclerosis*, *13*, 124-127.

Fielding, J., Kilpatrick, T., Millist, L., & White, O. (2009). Multiple sclerosis: Cognition and saccadic eye movements. *Journal of the Neurological Sciences*, *277*, 32-36.

Fisher, J. B., Jacobs, D. A., Markowitz, C. E., Galetta, S. L., Volpe, N. J., & Nano-Schiavi, M. L., et al. (2006). Relation of visual function to retinal nerve fiber layer thickness in multiple sclerosis. *Ophthalmology*, *113*, 324–332.

Fisk, J. D., Ritvo, P. G., Ross, L., Haase, D. A., Marrie, T. J., and Schlech, W. F. (1994). Measuring the functional impact of fatigue: Initial validation of the fatigue impact scale. *Clinical Infectious Diseases*, *18*(Suppl), 79-83.

Flachenecker, P., Kumpfel, T., Kallmann, B., Gottschalk, M., Grauer, O., Rieckmann, P., et al. (2002). Fatigue in multiple sclerosis: A comparison of different rating scales and correlation to clinical parameters. *Multiple Sclerosis*, *8*, 523-526.

Forn, C., Barros-Loscertales, A., Escudero, J., Benlloch, V., Campos, S., Parcet, M. A., et al. (2007). Compensatory activations in patients with multiple

sclerosis during preserved performance on the auditory N-back task. *Human Brain Mapping*, *28*, 424-430.

Freeman, J. A., Hobart, J. C., & Thompson, A. J. (2001). Does adding MS-specific items to a generic measure (the SF-36) improve measurement? *Neurology*, *57*, 68-74.

Frohman, E. M., Dwyer, M. G., Frohman, T., Cox, J. L., Salter, A., Greenberg, B., et al. (2009). Relationship of optic nerve and brain conventional and non-conventional MRI measures and retinal nerve fiber layer thickness, as assessed by OCT and GDx: A pilot study. *Journal of the Neurological Sciences*, *282*, 96-105.

Gaudino, E., Chiaravalloti, N., DeLuca J., & Diamond, B. J. (2001). A comparison of memory performance in relapsing-remitting, primary-progressive and secondary progressive multiple sclerosis. *Neuropsychiatry, Neuropsychology and Behavioral Neurology*, *14*, 32-44.

Geurts, J. J., Bo, L., Roosendaal, S. D., Hazes, T., Daniels, R., Barkhof, F., et al. (2007). Extensive hippocampal demyelination in multiple sclerosis. *Journal of Neuropathology and Experimental Neurology*, *66*, 819–27.

Gioia, M. C., Cerasa, A., Liguori, M., Passamonti, L., Condino, F., Vercillo, L., et al. (2007). Impact of individual cognitive profile on visuo-motor reorganization in relapsing-remitting multiple sclerosis. *Brain Research*, *1167*, 71-79.

Golden, C. J. (1978). *Stroop color and word test: A manual for clinical and experimental uses*. Chicago, IL: Stoelting.

Golden, C. J., & Freshwater, S. M. (2002). *Stroop color and word test: A manual for clinical and experimental uses.* Chicago, IL: Stoelting.

Goverover, Y., Genova, H. M., Hillary, F. G., & DeLuca, J. (2007). The relationship between neuropsychological measures and the Timed Instrumental Activities of Daily Living task in multiple sclerosis. *Multiple Sclerosis*, *13*, 636-644.

Grant, I, McDonald, W. I., Trimble, M. R., Smith, E., & Reed, R. (1984). Deficient learning and memory in early and middle phases of multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry*, *47*, 250-

255.

Gronwall, D.M.A. (1977). Paced auditory serial-addition task: A measure of recovery from concussion. *Perceptual and Motor Skills*, *44*, 367-373.

Haase, C. G., Tinnefeld, M., Lienemann, M., Ganz, R. E., & Faustmann, P. M. (2003). Depression and cognitive impairment in disability-free early multiple sclerosis. *Behavioral Neurology*, *14*, 39-45.

Halper, A. (2010). The broad impact of MS. *European Journal of Neurology*, *17*, 341.

Hart, S., Fonareva, I., Merluzzi, N., & Mohr, D. C. (2005). Treatment of depression and its relationship to improvement in quality of life and psychological well-being in multiple sclerosis. *Quality of Life Research*, *14*, 695-703.

He, J., Grossman, R. I., & Ge, Y. (2001) Enhancing patterns in multiple sclerosis: Evolution and persistence. *American Journal of Neuroradiology*, *22*, 664-669.

Heaton, R. K., Miller, S. W., Taylor, M. J., & Grant, I. (2004). *Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults (HRB)*. Orlando, FL: Psychological Assessment Resources.

Henry, J. D., & Crawford, J. R. (2004). A meta-analytic review of verbal fluency performance following focal cortical lesions. *Neuropsychology*, *18*, 284-295.

Herholz, K. (2006). Cognitive dysfunction and emotional-behavioural changes in MS: The potential of positron emission tomography. *Journal of the Neurological Sciences*, *245*, 9-13.

Herrera-Guzman, I., Gudayol-Ferre, E., Lira-Mandujano, J., Herrerra-Abarca, J., Herrerra-Guzman, D., Montoya-Perez, K., et al. (2008). Cognitive predictors of treatment response to bupropion and cognitive effects of bupropion in patients with major depressive disorder. *Psychiatry Research*, *160*, 72-82.

Hickman, S. J., & Miller, D. H. (2000). Imaging of the spine in multiple sclerosis. *Neuroimaging Clinics of North America*, *10*, 689-704.

Honer, W. G., Hurwitz, T., Li, D. K., Palmer, M., &, Paty, D. W. (1987). Temporal lobe involvement in multiple sclerosis patients with psychiatric disorders. *Archives of Neurology*, *44*, 187-190.

Huber, S. J., Paulson, G. W., Shuttleworth, E. C., Chakeres, D., Clapp, L. E., Pakalnis, A., et al. (1987). Magnetic resonance imaging correlates of dementia in multiple sclerosis. *Archives of Neurology*, *44*, 732-736.

Huijbregts, S. C., Kalkers, N. F., de Sonneville, L. M., de Groot, V., & Polman, C. H. (2006). Cognitive impairment and decline in deifferent MS subtypes. *Journal of the Neurological Sciences*, *245*, 187-194.

Janardhan, V., & Bakshi, R. (2000). Quality of life and its relationship to brain lesions and atrophy on magnetic resonance images in 60 patients with multiple sclerosis. *Archives of Neurology*, *57*, 1485-1491.

Johns, M.W., & Hocking, B. (1997). Daytime sleepiness and sleep habits of Australian workers. *Sleep*, *10*, 844-949.

Johnson, S. K. (2007). The neuropsychology of multiple sclerosis. *Disease-a-month*, *53*, 172-176.

Kalmar, J. H., Gaudino, E. A., Moore, N. B., Halper, J., & DeLuca, J. (2008). The relationship between cognitive deficits and everyday functional activities in multiple sclerosis. *Neuropsychology*, *22*, 442-449.

Kaltreider, L. B., Vertovec, L. M., Saine, K. C., & Cullum, C. M. (1999, October). The Texas card sorting test: A pilot study in dementia. *Archives of Clinical Neuropsychology*, *14*, 730-731. Abstract retrieved July 8, 2011 from Oxford Journals Online.

Karaarslan, E., Altintas, A., Senol, U., Yeni, N., Dincer, A., Bayindir, C., et al. (2001). Balo's concentric sclerosis: Clinical and radiologic features of five cases. *American Journal of Neuroradiology*, *22*, 1362-1367.

Kragt, J. J., van der Linden, F. A., Nielsen, J. M., Uitdehaag, B. M., & Polman, C.H. (2006). Clinical impact of 20% worsening on Timed 25-foot Walk

and 9-hole Peg Test in multiple sclerosis. *Multiple Sclerosis*, *12*, 594-598.

Kramer, J. H., Nelson, A., Johnson, J. K., Yaffe, K., Glenn, S., Rosen, H. J., et al. (2006). Multiple cognitive deficits in amnestic mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders*, *22*, 306-311.

Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosis. *Archives of Neurology*, *46*, 1121-1124.

Kümpfel, T., Kallmann, B., Gottschalk, M., Grauer, O., Rieckmann, P., Trenkwalder, et al. (2002). Fatigue in multiple sclerosis: A comparison of different rating scales and correlation to clinical parameters. *Multiple Sclerosis*, *8*, 523-526.

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*, *33*, 1444–1452.

Kutzelnigg, A., Lucchinetti, C. F., Stadelmann, C., Brück, W., Rauschka, H., Bergmann, M., et al. (2005). Cortical demyelination and diffuse white matter injury in multiple sclerosis. *Brain*, *128*, 2705-2712.

Lenderking, W. R. (2005). Book review: The psychology of quality of life. *Quality of Life Research*, *14*, 1439-1441.

Lublin, F. D., & Reingold, S. C. (1996). Defining the clinical course of multiple sclerosis: Results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. *Neurology*, *46*, 907–911.

Ludwin, S. K. (2000). The neuropathology of multiple sclerosis. *Neuroimaging Clinics of North* America, *10*, 625-648.

Manconi, M., Fabbrini, M., Bonanni, E., Filippi, M., Rocca, M., Murri, L., et al.(2007). High prevalence of restless legs syndrome in multiple sclerosis. *European Journal of Neurology*, *14*, 534-539.

Mathiowetz, V., Weber, K., Kashman, N., & Volland, G. (1985). Adult norms for the nine-hole peg test of finger dexterity. *Occupational Therapy Journal of Research*, *5*, 24–28.

Mayberg, H. S. (2002). Mapping mood: An evolving emphasis on frontal-limbic interactions. In D. T. Stuss & R. T. Knight (Eds.), *Principles of frontal lobe function* (pp. 376-391). New York: Oxford University Press.

McCaffrey, R. J., Cousins, J. P., Westervelt, H. J., Martnowicz, M., Remick, S. C., Szebenyi, S., et al. (1995). Practice effect with the NIMH AIDS Abbreviated Neuropsychological Battery. *Archives of Clinical Neuropsychology*, *10*, 241-250.

McCaffrey, R. J., Krahula, M. M., Heimberg, R. G., Keller, K. E., & Purcell, M. J. (1988). A comparison of the Trail Making Test, Symbol Digit Modalities Test, and the Hooper Visual Organization Test in an inpatient substance abuse population. *Archives of Clinical Neuropsychology*, *3*, 181-187.

Merlino, G., Valente, M., Serafini, A., & Gigli, G. L. (2007). Restless legs syndrome: Diagnosis, epidemiology, classification and consequences. *Neurological Sciences*, *28*, 37-46.

Miller, A., & Dishon, S. (2005). Health-related quality of life in multiple sclerosis: Psychometric analysis of inventories. *Multiple Sclerosis*, *11*, 450-458.

Miller, D., Barkhof, F., Montalban, X., Thompson, A., & Filippi, M. (May 2005). Clinically isolated syndromes suggestive of multiple sclerosis, part I: Natural history, pathogenesis, diagnosis, and prognosis. *Lancet Neurology*, *4*, 281–288.

Miller, D. H., & Leary, S. M. (October 2007). Primary-progressive multiple sclerosis. *Lancet Neurology*, *6*, 903–912.

Morgan, S. F., & Wheelock, J. (1992). Digit Symbol and Symbol Digit Modalities Tests: Are the directly interchangeable? *Neuropsychology*, *4*, 327-330.

Morgen, K., Sammer, G., Courtney, S. M., Wolters, T., Melchior, H., Blecker, C. R., et al. (2006). Evidence for a direct association between cortical atrophy and cognitive impairment in relapsing-remitting MS. *Neuroimage*, *30*, 91-98.

Morrow, S. A., Allison, D., Zivadinov, R., Munschauer, F., Weinstock-Guttman, et al. (2010). Predicting loss of employment over three years in multiple

sclerosis: Clinically meaningful cognitive decline. *The Clinical Neuropsychologist*, *24*, 1131-1145.

Mundfrom, D. J., Perrett, J. J., & Schaffer, J. (2006). Bonferroni adjustments in tests for regression coefficients. *Multiple Linear Regression Viewpoints*, *32*, 1-6.

Noonan C. W., Williamson, D. M., Henry, J. P., Indian, R., Lynch, S. G., Neuberger, J. S., et al. (2007). The prevalence of multiple sclerosis in 3 US communities. *Preventing Chronic* Disease, *7*, 1-8.

Nortvedt, M. W., & Riise, T. (2003). The use of quality of life measures in multiple sclerosis research. *Multiple Sclerosis*, *9*, 63-72.

O'Brien, A., Gaudino-Goeringa, E., Shawaryna, M., Komaroff, E., Moore, N. B., & DeLuca, J. (2007). Relationship of the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ) to functional, emotional, and neuropsychological outcomes. *Archives of Clinical Neuropsychology*, *22*, 933-948.

Pae, C., Parks, D. M., Patkar, A. A., Masand, P. S., Luyten, P., & Serretti, A. (2009). Pharmacological treatment of chronic fatigue syndrome: Focusing on the role of antidepressants. *Expert Opinion on Pharmacology*, *10*, 1561-1570.

Parmenter, B. A., Zivadinov, R., Kerenyi, L., Gavett, R., Weinstock-Guttman, B., Dwyer, M. G., et al. (2007). Validity of the Wisconsin Card Sorting and Delis-Kaplan Executive Function System (DKEFS) sorting tests in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *29*, 215-223.

Patti, F. (2009). Cognitive impairment in multiple sclerosis. *Multiple Sclerosis*, *15*, 2-8.

Petzold, A., de Boer, J. F., Schippling, S., Vermersch, P., Kardon, R., G., Green, et al. (2010). Optical coherence tomography in multiple sclerosis: A systematic review and meta-analysis. *Lancet, 9*, 921-932.

Polman, C. H., Reingold, S. C., Banwell, B., Clanet, M., Cohen, J. A., Filippi, M., et al. (2011). Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Annals of Neurology*, *69*, 292–302.

Polman, C. H., Reingold, S. C., Edan, G., Filippi, M., Hartung, H. P., Kappos, L., et al. (2005). Diagnostic criteria for multiple sclerosis: 2005 revisions to the McDonald Criteria. *Annals of Neurology*, *58*, 840-846.

Papakostas, G. I., Nutt, D. J., Hallett, L. A., Tucker, V. L., Krishen, A., & Fava, M. (2006). Resolution of sleepiness and fatigue in major depressive disorder : A comparison of bupropion and the selective serotonin reuptake inhibitors. *Biological Psychiatry*, *60*, 1350-1355.

Pozzilli, C., Fieschi, C., Perani, D., Paulesu, E., Comi, G., Bastianello, S., et al. (1992). Relationship between corpus collosum atrophy and cerebral metabolic assymmetries in multiple sclerosis. *Journal of the Neurological Sciences*, *112*, 51-57.

Prakash, R. S., Snook, E. M., Lewis, J. M., Motl, R. W., & Kramer, A. F. (2008). Cognitive impairments in relapsing-remitting multiple sclerosis: A meta-analysis. *Multiple Sclerosis*, *14*, 1250-1261.

Psychological Assessment Resources. *Computerised Wisconsin Card Sort Task Version 4 (WCST)*. Odessa, FL: Psychological Assessment Resources.

Radloff, L. S. (1977). The CES-D scale: A self report depression scale for research in the general population. *Applied Psychological Measurement*, *1*, 385-401.

Rao, S. M. (1997). Neuropsychological aspects of multiple sclerosis. In C. S. Raine, H. F. McFarland, & W. W. Tourtellotte (Eds.), *Multiple sclerosis: Clinical and pathogenetic basis* (pp. 357-362). London: Chapman and Hall.

Rao, S. M. (1990). *A manual for the Brief Repeatable Battery of Neuropsychological Tests in Multiple Sclerosis*. New York: National Multiple Sclerosis Society.

Rao, S. M., Hammeke, T. A., & Speech, T. J. (1987). Wisconsin Card Sorting Test performance in relapsing-remitting and chronic-progressive multiple sclerosis. *Journal of Clinical and Consulting Psychology*, *55*, 263-265.

Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis: I. Frequency, patterns, and prediction.

Neurology, *41*, 685-691.

Rao, S. M., Leo, G. J., Ellington, L., Nauertz, T., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology*, *41*, 692-696.

Richardson, J. T. E., Robinson, A., & Robinson, I. (1997). Cognition and multiple sclerosis: A historical analysis of medical perceptions. *Journal of the History of the Neurosciences*, *6*, 302-319.

Roca, M., Torralva, T., Meli, F., Fiol, M., Calcagno, M., Carpintiero, S., et al. (2008). Cognitive deficits in multiple sclerosis correlate with changes in fronto-subcortical tracts. *Multiple Sclerosis*, *14*, 364-369.

Rudick, R. A., & Miller, D. M. (2008). Health-related quality of life in multiple sclerosis: Current evidence, measurement and effects of disease severity and treatment. *CNS Drugs*, *22*, 827-839.

Rupke, S. J., Blecke, D., & Renfrow, M. (2006). Cognitive therapy for depression. *American Family Physician*, *73*, 83-86.

Rush A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N. et al. (2003). The 16-item quick inventory of depressive symptomatology (QIDS) clinician rating (QIDS-C) and self-report (QIDS-SR). *Biological Psychiatry*, *54*, 573-583.

Sadovnik, A. D., Remick, R. A., Allen, J., Swartz, E., Yee, I. M., Eisen, K., et al. (1996). Depression and multiple sclerosis. *Neurology*, *46*, 628–32.

Sailer, M., Fischl, B., Salat, D., Tempelmann, C., Schonfeld, M. A., Busa, E., et al. (2003). Focal thinning of the cerebral cortex in multiple sclerosis. *Brain*, *126*, 1734-1744.

Sanfilipo, M. P., Benedict, R. H., Weinstock-Guttman, B., & Bakshi, R. (2006). Grey and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. *Neurology*, *66*, 685-692.

Schouten, J., Cinque, P., Gisslen, M., Reiss, P., & Portegies, P. (2011). HIV-1 infection and cognitive impairment in the cART era: Neuropsychology. *AIDS*, *25*, 561-575.

Schultheis, M. T., Garay, E., & DeLuca, J. (2001). The influence of cognitive impairment on driving performance in multiple sclerosis. *Neurology*, *56*, 1089-1094.

Sepulcre, J., Murie-Fernandez, M., Salinas-Alaman, A., Garcia-Layana, A., Bejarano, B., & Villoslada, P. (2007). Diagnostic accuracy of retinal abnormalities in predicting disease activity in MS. *Neurology*, *68*, 1488-1494.

Simioni, S., Ruffieux, C., Kleeberg, J., Bruggimann, L., Du Pasquier, R. A., Annoni, J., et al. (2009). Progressive decline of decision-making performances during multiple sclerosis. *Journal of the International Neuropsychological Society*, *15*, 291-295.

Simon, J. H. Neuroimaging of multiple sclerosis. *Neuroimaging Clinics of North America*, *3*, 229-246.

Smith, A. (1991). *Symbol Digits Modalities Test*. Los Angeles: Western Psychological Services.

Smith, D., Dempster, C., Glanville, J., Freemantle, N., & Anderson, I. (2002). Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. *The British Journal of Psychiatry*, *180*, 396-404.

Sokoloff, L. (1981). Localization of functional activity in the central nervous system by measurement of glucose utilization with radioactive deoxyglucose. *Journal of Cerebral Blood Flow Metabolism*, *1*, 7-36.

Spiegler, M. D., & Guevremont, D. C. (2010). *Contemporary behavior therapy.* (5th ed.). Belmont, CA: Wadsworth.

Sprauss, E., Sherman, E. M., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary*. (3rd ed.). New York: Oxford University Press.

Stegen, S., Stepanov, I., Cookfair, D., Schwartz, E., Hojnacki, D., Weinstock-Guttman, B., et al. (2010). Validity of the California Verbal Learning Test-II in multiple sclerosis. *The Clinical Neuropsychologist*, *24*, 189-202.

Stirgy, M. J. (2002). *The psychology of quality of life*. Dordrecht, The

Netherlands: Kluwer Academic Publishers.

Stucki, G., & Cieza, A. (2004). The International Classification of Functioning, Disability and Health (ICF) Core Sets for rheumatoid arthritis: A way to specify functioning. *Annals of Rheumatic Diseases*, *63*, 40-45.

Sumowski, J. F., Wylie, G. R., DeLuca, J., & Chiaravalloti, N. (2010). Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: Functional magnetic resonance imaging evidence for cognitive reserve. *Brain*, *133*, 362-374.

Tien, R. D., Hesselink, J. R., & Szumowski, J. (1991). MR fat suppression combined with Gd-DTPA enhancement in optic neuritis and perineuritis. *Journal of Computer Assisted Tomography*, *15*, 223-227.

Toledo, J., Sepulcre, J., Salinas-Alaman, A., Garcia-Layana, A., Murie-Fernandez, M., Bejarano, B., et al. (2008). Retinal nerve fiber layer atrophy is associated with physical and cognitive ability in multiple sclerosis. *Multiple Sclerosis*, *14*, 906-912.

Tombaugh, T. N., Kozak, J., & Rees, L. (1999). Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of Clinical Neuropsychology*, *14*, 167-177.

Traboulsee, A., & Paty, D. (2002). Magnetic resonance imaging in disease progression in multiple sclerosis. In F. Dangond (Ed.), *Disorders of myelin in the central and peripheral nervous systems*. Boston: Butterworth-Heinemann.

van den Noort, S. (2005). Signs and symptoms of multiple sclerosis. In Olek, M. J. (Ed.), *Multiple sclerosis: Etiology, diagnosis, and new treatment strategies* (pp. 1 -15). Totowa, NJ: Humana Press.

Vercellino, M., Plano, F., Votta, B., Mutani, R., Giordana, M. T., & Cavalla, P. (2005). Grey matter pathology in multiple sclerosis. *Journal of Neuropathology and Experimental Neurology*, *64*, 1101–1107.

Vickrey, B. G., Hays, R. D., Harooni, R., Myers, L. W., & Ellison, G. W. (1995). A health-related quality of life measure for multiple sclerosis. *Quality of Life Research*, *4*, 187–206.

Vowels, L. M., & Gates, G. R. (1984). Neuropsychological findings. In A. F. Simons (Ed.), *Multiple scerosis: Psychological and social aspects* (pp. 82-90). London: Heinemann.

Ware, J. E. (2000). SF-36 health survey update. *Spine*, *25*, 3130-3139.

Wechsler, D. (2009). *Wechsler memory scale–fourth edition*. San Antonio, TX: Pearson.

Wegner, C., Esiri, M. M., Chance, S. A., Palace, J., & Matthews, P. M. (2006). Neocortical neuronal, synaptic, and glial loss in multiple sclerosis. *Neurology*, *67*, 960-967.

Whitehead, L. (2009). The measurement of fatigue in chronic illness: A systematic review of unidimensional and multidimensional fatigue measures. *Journal of Pain and Symptom Management*, *37*, 107-128.

WHOQOL Group. (1998). Development of the World Health Organization WHOQOL-BREF quality of life assessment. *Psychological Medicine*, *28*, 551-558.

Wilson, J. (1968). Happiness. *Analysis*, *29*, 13–21.

Wingerchuk, D. M., Weinshenker, B. G. Multiple sclerosis: Epidemiology, genetics, classification, natural history, and clinical outcome measures. *Neurogimaging Clinics of North America*, *10*, 611-623.

Wishart, H. A., Benedict, R. H. B., & Rao, S. M. (2008). Neuropsychological aspects of multiple sclerosis. In Raine, C. S., McFarland, H. F., & Hohlfeld, R. (Eds.), *Multiple sclerosis: A comprehensive text* (pp. 401-412). Philadelphia: Elsevier.

Wishart, H. A., Flashman, L., & Saykin, A. J. (2001). The neuropsychology of multiple sclerosis: Contributions of neuroimaging research. *Current Psychiatry Reports*, *3*, 373-378.

Woolston, D. (2006). fMRI investigation of an experimental executive function measure. Unpublished doctoral dissertation, University of Texas Southwestern Medical Center at Dallas, Dallas, TX. Retrieved March 14, 2011 from http://hdl.handle.net/2152.5/615

Wynia, K., Middel, B., van Dijk, J. P., De Keyser, J. H., & Reijneveld, S. A. (2008). The impact of disabilities on quality of life in people with multiple sclerosis. *Multiple Sclerosis*, *14*, 972-98.