Abstract

The Impact of Illness Intrusiveness on the Relationship Between Cognition and Mood in Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated, inflammatory neurodegenerative chronic disease that affects the central nervous system and is characterized by substantial impacts on physical, cognitive, and psychological functioning. Clinically significant anxiety and depression are about 2-4 times as common in MS as in the general population, and are often associated with increased risk for morbidity and mortality, reduced medication adherence, increased risk for suicidal ideation, and reduced quality of life. Cognitive impairment, especially impaired information processing speed, is also common in MS and has continually been associated with mood disturbance in people with MS. However, research on potential mechanisms for this relationship has been sparse. Illness intrusiveness may be one such mechanism; this concept refers to the degree to which an illness and/or its treatment may interfere with important aspects of a person's life, particularly participation in previously valued activities and interests. Although research has continually found relationships between illness intrusiveness and mood, research on illness intrusiveness and cognition has been sparse. The one published study in the literature found illness intrusiveness to mediate the relationship between verbal learning and depression in MS. The current study attempted to expand this literature by determining if impairment in processing speed as well as more general cognitive impairment was associated with illness intrusiveness

and mood disturbance in MS. This study employed a retrospective cross-sectional design to answer this question. 199 participants with clinically definite MS were given both cognitive and mood measures. Cognitive measures included the Symbol Digit Modalities Test (Smith, A., 1982), the California Verbal Learning Test, second edition (Delis et al., 2000), the Brief Visuospatial Memory Test-Revised (Benedict, 1997), and the Controlled Oral Word Association Test (Benton, 1994). Illness intrusiveness was assessed using the Illness Intrusiveness Ratings Scale (Devins et al., 1983). Anxiety was measured using the anxiety subscale of the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983). Depression was measured using the Patient Health Questionnaire-9 (Kroenke et al., 2001). Illness intrusiveness was found to mediate the relationship between processing speed and depression, ab = -.07, 95% CI [-.15, -.002], processing speed and anxiety, ab = -.06, 95% CI [-.12, -.02], and processing speed and more general mood disturbance, ab = -.08, 95% CI [-.13, -.0005]. This study also found that more general cognitive impairment did not have a significant relationship with either illness intrusiveness or mood symptoms. Thus, illness intrusiveness was found to be an important intermediary mechanism by which the primary cognitive impairment in MS, processing speed, impacts mood in this disease population. Conclusions, treatment implications, and directions for future research in light of these findings were discussed.

The Impact of Illness Intrusiveness on the Relationship Between Cognition and Mood in Multiple Sclerosis

by

Nicholas Andrew Vissicchio, Jr.

Submitted in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the Ferkauf Graduate School of Psychology

Yeshiva University

August 2020

The committee for this dissertation consists of:

Frederick W. Foley, Ph.D., Chairperson, Yeshiva University

Charles Swencionis, Ph.D., Yeshiva University

Elizabeth Seng, Ph.D., Yeshiva University

Acknowledgements

I wish to acknowledge my research mentor, Dr. Fred Foley, for his inspiration, guidance, and support. His passion for our field and his enthusiasm for teaching helped me grow immensely both as a researcher and clinician. Dr. Foley's ability to motivate his students to become successful is truly inspiring.

I want to acknowledge the other members of my committee, Dr. Charles Swencionis and Dr. Elizabeth Seng, for their advice, feedback, and creative ideas for improving my dissertation project.

I also wish to thank the rest of the faculty members at Ferkauf for their continued guidance throughout my graduate school journey.

Finally, I would like to give recognition to both the patients and staff of the MS Center at Holy Name Medical Center in Teaneck, NJ. This study would not have been possible without you.

Dedication

To my parents, Carole and Nick, who have helped me become the person I am today. Thank you for continuing to guide and support me throughout all stages of my academic career.

To my fiancé, Katie, for traveling on this graduate school journey with me. I would not have been able to get through my doctoral program without you.

Finally, to my fellow students at the Ferkauf Graduate School of Psychology, for fostering a supportive, collaborative community during my time in graduate school.

Table of Contents

List of Tables

List of Figures

Chapter I- Introduction

1. Background

Part I. Multiple Sclerosis Background

Multiple Sclerosis- Overview and Epidemiology

Multiple Sclerosis (MS) is an immune-mediated, inflammatory, neurodegenerative chronic disease of unknown etiology that affects the central nervous system (CNS) and is characterized by substantial impacts on physical, cognitive, and psychological functioning (Tullman, 2013). In this most common demyelinating disease in the CNS, cells of the immune system (Th2 and B cells) migrate from the periphery into the CNS and orchestrate an attack on myelin. The clinical manifestation varies both between and within people affected by the disease- clinical exacerbations known as relapses are usually hallmarks of the beginning of the disease. However, over time, disability associated with the disease tends to increase linearly without remissions (Krieger et al., 2016).

MS usually begins in early to middle adulthood, with an onset between ages 20 to 40. Although some patients develop MS in their childhood or adolescence, these are considered rare occurrences (Otallah & Banwell, 2018). Women are at least twice as affected by MS as men, and this gender gap seems to be increasing for reasons yet to be known (Harbo et al., 2013). It is estimated that around 2.3 million people around the world have MS. The prevalence of MS varies based on world region- individuals in northern latitudes of Europe and North America tend to have higher rates of MS, with some estimates close to 1 in 400 individuals in countries in far northern latitudes. A potential reason for this is lower serum vitamin D levels in these regions of the world (Koch-Henriksen & Sørensen, 2010). A recent review estimated an overall

incidence of 3.6 per 100,000 person-years in females and 2.0 per 100,000 person-years in males (Alonso & Hernán, 2008). MS is estimated to decrease the life expectancy of affected individuals by 7-14 years, and is the primary cause of death in greater than 50% of patients with MS (Scalfari et al., 2013). The annual cost of managing MS in US hospitals was roughly $4.3 billion in 2013 (Chen et al., 2017).

MS Subtypes

Four disease courses or phenotypes in MS have been established by the International Advisory Committee on Clinical Trials of MS in 2013 (Lublin et al., 2014). The first is known as Clinically Isolated Syndrome, or CIS. This is the first episode of neurologic symptoms caused by neuroinflammation or demyelination that lasts for at least 24 hours. Monofocal CIS is when one symptom is caused by a single brain lesion. Multifocal episodes are when more than one symptom is caused by lesions in more than one neural region. When clinical symptoms of CIS are accompanied by a brain lesion on MRI, the individual is considered at high risk of developing MS. A second episode of neurologic symptoms or MRI evidence of prior disease activity may then lead to a formal diagnosis of MS. People with CIS are placed on disease modifying therapies as soon as possible to delay the onset of MS (National MS Society, 2019).

Relapsing remitting MS (RRMS) is considered the most common disease subtype, accounting for about 85% of initially diagnosed MS patients. It is characterized by clearly defined relapses (attacks or exacerbations) with full recovery or residual deficits. The periods between disease relapses are characterized by a lack of disease progression, or partial remissions without disease progression. When relapses occur or there are active MRI lesions, the RRMS is considered “active.” When these disease processes are not occurring, the RRMS is considered “not active.” An increase in disability following a relapse is considered “worsening” RRMS, and

when disability does not increase following a relapse it is considered “not worsening” (National MS Society, 2019a).

Another MS subtype is known as secondary progressive MS (SPMS). Most people who are initially diagnosed with relapsing remitting MS will transition to a progressive disease course in which the disease course and associated symptoms continue to deteriorate over time. This deterioration is associated with further increases in disability. This typically occurs in about 50% of individuals initially diagnosed with RRMS within 10 years. Approximately 90% of individuals with RRMS will transition to SPMS within 25 years. However, new disease modifying therapies have likely delayed or stopped progression in many people with RRMS, but it is still too soon to tell if this has occurred. “Active” SPMS is when relapses or new MRI activity occurs alongside disease progression. SPMS is considered “with progression” when there is evidence of disease worsening over time, with or without relapses (National MS Society, 2019b).

The final MS subtype is known as primary progressive MS (PPMS). Patients with this type of MS have progressive neurodegeneration and progressively worsening neurological functioning from the time of disease onset. They may have temporary plateaus or minor improvements, but generally experience linear declines in neurological functioning and linear increases in disability due to disease processes. It is estimated that about 15% of people are initially diagnosed with PPMS. This MS subtype, like the SPMS subtype, is characterized as either active or not active, as well as with progression or without progression (National MS Society, 2019a).

Etiology of MS

The etiology of MS is still unknown, but recent theories suggest interactions between both genetic and environmental risk factors. Primary risk factors for developing MS include the Epstein-Barr virus infection in adolescence, smoke exposure, lack of sunlight and low Vitamin D levels during teen years, and adolescent obesity. The Epstein-Barr virus has been implicated as the most significant risk factor for developing MS with an odds ratio of 3.6. (Olsson et al., 2017). Almost all patients with MS are seropositive for this virus. Some studies have proposed that MS may be initiated by the Epstein-Barr virus by the immune system creating cross-reactive T cells and antibodies (Olsson et al., 2017). Smoking has been established as a significant risk factor for MS, with an odds ratio of about 1.6. (Healy et al., 2009). It appears that repeated exposure to second-hand smoke in addition to directly smoking tobacco may increase one's risk of developing MS. Smoking has also been found to increase risk for disease progression in people with MS (Healy et al., 2009). Vitamin D levels have also been proposed as a risk factor for developing MS (Pierrot-Deseilligny & Souberbielle, 2017). Research has consistently shown that countries in northern latitudes in which people are exposed to less sunlight have a higher incidence of MS. Vitamin D may have a protective effect on the immune system given that it has been shown to reduce relapses by 50-70%, but the specific mechanism of action is still unknown (Pierrot-Deseilligny & Souberbielle, 2017).

Genetic risk factors also likely play a role. The prevalence of familial MS is roughly 13% (Compston & Coles, 2002). Monozygotic twins have a 35% risk of developing MS if their twin develops MS, whereas this number is 6% in dizygotic twins and 3% in biological siblings (Compston & Coles, 2002). First-degree relatives of people with MS are approximately 15 to 35 times more likely to develop MS than the general population (Willer et al., 2003). Over 200

genetic polymorphisms on a number of different genes have been identified in MS, and each slightly increases the risk for developing the disease. Most of these genes are responsible for production of molecules related to the immune system. Some research has implicated a potential MS susceptibility gene known as the interleukin 7 receptor alpha gene. There have also been associations between MS alleles and Major Histocompatability Complex II alleles (Deluca et al., 2016).

Neurobiology of MS

MS is a progressive disease of the central nervous system characterized primarily by focal plaques, also called lesions. These plaques are found in the white matter around the ventricles, optic nerves, corpus callosum, cerebellar peduncles, long tracts of the spinal cord and brainstem, and in the gray matter (Lucchinetti et al., 2000). These plaques occur in regions in which the blood-brain barrier (BBB) has been broken down. Pro-inflammatory cytokines and chemokines are likely responsible for this breakdown of the BBB. This leads to migration of the T cells and B cells into the central nervous system, which creates additional neuroinflammation (Ortiz et al., 2014).

In MS, the body's immune system attacks the myelin sheath of the axon, which is critical for efficient electrical conduction of nerve impulses. The destroyed parts of the myelin are replaced by astrocytic scar tissue. As a result of myelin loss, nerve impulses cannot travel as quickly or may be completely blocked in certain spots. This results in neuronal degeneration (Slimp, 2011). In addition to demyelinated axons, people with MS early on in the disease course usually also present with reduction in myelin-producing neuroglia known as oligodendrocytes and astrocytes. In later stages in the disease where it is often progressive in nature, pathology is dominated by significant atrophy in gray and white matter. Low-grade inflammation and

microglial activation combine with further demyelinating processes (Mahad et al., 2015). Remyelination can also occur in MS, which is consistent with periods of recovery from active disease processes in RRMS. Remyelination has been shown to occur in about 50% of white matter lesions, and is generally more common in the earlier stages of the disease process (Albert et al., 2007).

The immunopathology of MS is very complex. Historically, MS has been viewed as a T cell-mediated disease. One of the primary causes of relapses are due to $CD4^+$ T cell and $CD8^+$ T cell upregulation due to insufficient functioning of regulator T cells (Baecher-Allan et al., 2018). B cells are thought to attract and activate T cells and myeloid cells in the CNS. They then produce pro-inflammatory cytokines and elicit proinflammatory responses from myeloid cells. MS relapses may also be related to an imbalance between pro-inflammatory and anti-inflammatory B cells (Bar-Or et al., 2010; Palanichamy et al., 2014).

Diagnosis of MS

MS usually presents as an initial clinical attack, which is suggestive of demyelinating lesions in the optic nerve, spinal cord, brainstem, or cerebellum. These attacks worsen over the course of 2-3 weeks, and usually resolve 5-7 weeks after initial symptoms begin (Brownlee et al., 2017). Sensory symptoms are the first clinical signs in 43% of patients. These include sensory paresthesias, which often feels like pins and needles, Lhermitte sign, which feels like an electric shock radiating down the spine from the neck, and reduced pain and touch sensation (Rae-Grant et al., 1999). Motor symptoms are the first type of symptoms in 30-40% of patients with MS, which include the Babinski sign, hyperreflexia, paresis, and spasticity (Compston et al., 2005). Optic neuritis is the initial clinical symptom in about 25% of patients, which involves visual loss

in one eye accompanied by a blind spot in the central portion of the visual field, color vision difficulties, and ocular pain (Toosy et al., 2014).

The diagnosis of MS is based on a set of guidelines known as the McDonald Criteria. These criteria were developed in 2001 and continue to be revised, with the most updated revision being from 2017. These criteria integrate clinical, neuroimaging, and laboratory evidence to ensure diagnostic accuracy. In order to diagnose RRMS, one of two conditions must be met:

1. There must be evidence of two clinical relapses and neurological exam evidence of two lesions in two different neural regions, or two relapses and neurological exam evidence of one lesion and history of prior evidence to suggest a second lesion in a different neural region.
2. If there is only evidence of one clinical relapse, there should be objective clinical evidence of two or more lesions. Dissemination in time should be demonstrated by a second relapse or using MRI evidence. If there is one clinical relapse and objective clinical evidence of one lesion, RRMS may still be diagnosed if dissemination in time and space is demonstrated by MRI evidence or through cerebrospinal-specific oligoclonal bands.

In order to diagnose PPMS, there must be a disease course that progresses from the onset along with 1 year of disability progression. Additionally, 2 of the following criteria need to be met:

1. One or more T2-hyperintense lesions in at least one area of the brain consistent with MS.
2. Two or more T2-hyperintense lesions in the spinal cord.
3. Demonstration of cerebrospinal-specific oligoclonal bands.

Treatment of MS

The primary treatment for individuals with MS is disease modifying therapies (DMTs). These medications are used to reduce inflammation and disease processes as well as to manage relapses. DMTs also may help alleviate disease-related symptoms such as fatigue, pain, and spasticity. The older belief was that DMTs should be prescribed once MS symptoms have progressed, but the current prevailing belief is to prescribe a DMT once the patient has been diagnosed with CIS, or is in the early stages of RRMS.

In patients with RRMS, interferon-beta or glatiramer acetate are considered first-line DMT therapies and pose relatively low risks. However, they generally only have moderate clinical efficacy and commonly have post injection-related adverse effects such as flu-like symptoms (Granqvist et al., 2018). Second or third-line therapies include monoclonal antibodies such as daclizumab and ocrelizumab or an oral S1P inhibitor such as fingolimod; these therapies have higher efficacy rates but pose more serious risks and side effects, such as severe infections (Comi et al., 2017). Most European and American treatment guidelines endorse escalation therapy, or starting with a first-line treatment and moving on to second and third-line treatments once symptoms progress (Rae-Grant et al., 2018). In some cases with patients that initially present with higher disease activity, induction therapy techniques are often used. In this case, second or third-line treatments are used first and then de-escalated over time to prevent inflammatory processes from progressing (Montalban et al., 2018). MS relapses are treated with high-dose corticosteroids, generally a 3-5 day treatment of intravenous methylprednisolone with a subsequent oral taper. If corticosteroids do not work, patients may be treated with 3-5 courses of plasma exchange or intravenous immunoglobulin (Filippi et al., 2018).

Currently, there is only one DMT that has been FDA-approved for primary progressive MS, which is ocrelizumab, a B cell-depleting monoclonal antibody. This was the first DMT successfully shown to slow disease progression in progressive MS. A recent double-blind, placebo-controlled Phase III trial of patients with primary progressive MS demonstrated that ocrelizumab reduced progression of disability and disease activity when compared to placebo (Montalban et al., 2017).

In addition to DMT's, a number of strategies have been used to manage MS symptoms. Alternative medicine techniques, exercise, diet, food supplements, and stress management strategies have been used to varying degrees of success. Physical therapy and occupational therapy have been shown to enhance functional status in patients with MS (*Treating MS*, 2019). Cognitive rehabilitation has also been utilized in patients with MS to either restore cognitive functions or compensate for reduced cognitive functioning. Cognitive rehabilitation studies have generally yielded mixed, inconsistent findings, likely due to heterogeneity in study methodologies (Mitolo et al., 2015).

Part II. Cognition and Mood in MS

Depression in MS

Clinically significant depression in MS has been estimated to occur in about 20-40% of patients, with the point prevalence rate of depression around 25% (Amtmann et al., 2014; Schippling et al., 2016) and a lifetime prevalence of around 50% (Siegert & Abernethy, 2005). Although various measures and methodologies have been utilized to determine the presence of major depression in MS, a common finding in almost all studies has been that both the point prevalence and lifetime prevalence of major depression in MS is 2-4 times the reported prevalence in the general population (Patten et al., 2017). Studies have generally not found

gender differences in rates of major depression in MS (Patten et al., 2000), and studies examining age differences have yielded inconsistent findings (e.g., Chan et al., 2020; McIvor et al., 1984). However, research has continually found depression to be less common early in the MS disease course than in the disease's later stages (see Feinstein et al., 2014 for a review).

Depression has been extensively studied in MS not only because of its high prevalence in the disease but also because of its significant impact on the lives of people living with MS. Depression has continually been shown to correlate strongly with morbidity and mortality in MS, as well as with suicide (Feinstein, 2002; Feinstein et al., 2014). Depression has also been linked to reduced medication adherence in MS, which further adds to disease-related disability (Higuera et al., 2016). Additionally, higher levels of depression have been shown to reduce quality of life in MS independent of disability and fatigue (Amato et al., 2001).

The etiology of depression in MS is likely to be multifaceted. One prominent class of etiologies is neuroanatomical in nature. Lesion burden and level of neurodegeneration in the frontal and temporal lobes of the brain has been correlated with depressive symptomology in MS (Berg et al., 2000; Zorzon et al., 2002). Studies have also demonstrated a connection between hyperactivity of the HPA axis and depression in MS (Gold et al., 2011; Melief et al., 2013). The presence of major depression has been shown to be associated with gadolinium-enhancing lesions and a failure to suppress cortisol (Fassbender et al., 1998). Higher cortisol levels have also been correlated with reduced hippocampal volume only in depressed patients with MS (Gold et al., 2010).

Immunological factors may also play an important role in the etiology of depression in MS. One significant hypothesis is that pro-inflammatory cytokines such as tumor necrosis factor and IL-6 lead to hyperactivation of the HPA axis (Y.-K. Kim et al., 2007). These

proinflammatory cytokines may also lead to decreased release of serotonin and norepinephrine, neurotransmitters that have consistently been implicated in major depressive disorder (Anthony Feinstein et al., 2014). However, it is still unclear whether immune system dysregulation predates the onset of depression or is a consequence of depressive symptomology (Foley et al., 1992).

In addition to immunological and neuroanatomical factors that are organic to the disease process itself, psychosocial factors that are secondary and likely reactionary to the disease process also likely play a significant role. High levels of stress, illness uncertainty, and maladaptive coping strategies related to the effects of the disease process likely play a role in the development of depression. Factors closely related to illness intrusiveness such as reduced enjoyment of recreational activities and interference in social relationships have also been shown to play a role in the onset of depression (Anthony Feinstein et al., 2014). It has been estimated that about 40% of the variance in self-reported depressive symptoms are related to psychosocial factors in MS (A. Feinstein et al., 2010; Lynch et al., 2001).

Anxiety in MS

The point prevalence rates of clinically significant anxiety in MS usually range anywhere from 30-50%, whereas the lifetime prevalence rates of anxiety disorders have usually ranged from 14-41% (Beiske et al., 2008; Bruce & Arnett, 2008; Anthony Feinstein, 2007; Korostil & Feinstein, 2007). This is significantly more than the prevalence rates in the general population, where the point prevalence rate of clinically significant anxiety is estimated to be around 15% (Johansson et al., 2013), and the lifetime prevalence of anxiety disorders is estimated to range from 4-25% (Remes et al., 2016). Anxiety, like depression, has been independently shown to increase risk for mortality (Marrie et al., 2015). Anxiety has also been correlated with increased

risk for suicidal ideation and reduced health-related quality of life in MS (Alsaadi et al., 2017; Korostil & Feinstein, 2007).

Studies determining differences in anxiety levels based on age and gender have yielded inconsistent findings (for a review, see Butler et al., 2016). Relationships have been found between disability and anxiety as well as depression and anxiety in MS (Askari et al., 2014). Several studies have also demonstrated relationships between pain and anxiety and fatigue and anxiety (Bamer et al., 2008; Beiske et al., 2008). Higher number of relapses have been shown to increase anxiety levels in MS samples (Potagas et al., 2008), but MRI correlates such as lesion load and brain volume have shown no association to anxiety (Zorzon et al., 2002). Emotion focused coping, or managing the physiological, emotional, and cognitive reactions that come from a stressful situation, as well as avoidant coping, in which one avoids thinking about the stressor, have both been associated with increased anxiety levels in MS patients (Tan-Kristanto & Kiropoulos, 2015).

Several models have been proposed for the relationship between anxiety and MS. However, avoidance of internal stimuli and maladaptive coping styles have been part of each of these models (Butler et al., 2016). A more recent model based on Beck's model of emotional disorders (Beck, 2011) ties together much of the correlational research between MS and anxiety. The model suggests that diagnosis of MS and fear of subsequent disability lead to a critical incident of being ashamed of having MS in public. This then leads to automatic negative thoughts such as not being able to manage MS on one's own, which then leads to avoidance and emotion focused coping, anxiety and stress, and increased negative thoughts. These thoughts and behaviors can then lead to further physical symptoms such as a relapse of MS symptoms, fatigue, and pain (Butler et al., 2016).

Cognitive Impairment in MS

Cognitive impairment is a common feature of the MS disease process, and has been shown to impact 43-70% of individuals diagnosed with MS (Grzegorski & Losy, 2017). Cognitive impairment can lead to difficulties with maintaining meaningful employment as well as performing instrumental activities of daily living. Deficits in cognitive functioning have also been shown to negatively impact relationships and general quality of life in MS (M. P. Amato, Ponziani, Siracusa, et al., 2001).

The neuropathology of cognitive impairment in MS is primarily related to demyelination of white matter tracks. White matter lesion volume has consistently been shown to correlate with cognitive impairment in MS, especially in white matter tracts impacting frontal and parietal regions of the brain (Sperling et al., 2001). Early on, MS was only thought to impact white matter, but better imaging techniques have also revealed grey matter changes. Although early on in the disease deep grey matter damage is more common, in later stages the cortex becomes impacted (Haider et al., 2014). Several studies have demonstrated strong relationships between grey matter lesions and impairments in processing speed, verbal and visual learning, and episodic memory (Nelson et al., 2011; Roosendaal et al., 2009).

MS impacts a variety of cognitive abilities, such as processing speed, working memory, learning and memory, executive functioning, visual-spatial processing, and verbal fluency. The Minimal Assessment of Cognitive Function in MS (MACFIMS) was developed by a panel of MS experts in 2002. This 90-minute battery assesses cognitive domains that are typically impaired in MS (Ralph H. B. Benedict, Fischer, et al., 2002), and has been well-validated in a variety of MS populations (Ralph H. B. Benedict et al., 2006). Although many cognitive abilities are often impaired in MS, the two most commonly identified are episodic memory and

processing speed (Ralph H. B. Benedict et al., 2017). However, research has shown that episodic memory impairment is seen primarily in the acquisition phase of learning. Participants with MS take longer to learn, but usually can retrieve and retain most of the information once they learn it (DeLuca et al., 1994; J. Deluca et al., 2013). The underlying reason for this impaired initial acquisition of information is likely due to slowed speed of information processing. Demyelination in relevant white matter tracts seems to lead to slower information processing, which in turn impacts encoding efficiency (Lafosse et al., 2013). This is in line with the findings of a more recent study, which demonstrated that processing speed impairment likely underlies verbal learning difficulties in MS (Vissicchio et al., 2018). Thus, processing speed appears to be the primary, most prominent cognitive deficit resulting directly from the MS disease process.

Given the prominence of processing speed deficits in MS, it comes with no surprise that the orally administered version of the Symbol Digit Modalities Test (SDMT), a neuropsychological test measuring processing speed and visual scanning independent of motor function, has been identified as the most reliable and sensitive measure of cognitive impairment in MS (Ralph HB Benedict et al., 2017). It has often been shown to correlate highly with MRI variables as well as important functional outcomes such as employment status (Ralph H. B. Benedict et al., 2017). Several studies have identified the oral SDMT as a powerful screener for the early detection of cognitive impairment in MS that can be quickly and easily administered in MS clinics (S. Kim et al., 2017; Van Schependom et al., 2014).

Cognition and Depression in MS

Cognition and depression have repeatedly been shown to be closely linked in MS. Cognitive impairment may be a precursor for depressed mood. People who are in the stage of mild cognitive impairment may be aware that they are beginning to have cognitive problems but

may not be aware of the reason for these cognitive changes. Cognitive limitations may cause previously enjoyed activities to become less pleasurable, which may then lead to avoidance of these activities. This, in turn, likely leads to depressive mood (Ganguli, 2009). Depression may also be a risk factor and a precursor for cognitive impairment. Depression over a long period of time may increase cortisol levels, elevate the risk for vascular events, increase neuroinflammation, and lead to amyloid and tau deposition. These events, in turn, can often lead to hippocampal atrophy and cognitive impairment (Bennett & Thomas, 2014).

Reduced processing speed is not only the most prominent cognitive impairment in MS, but is also the cognitive ability most commonly impacted by depression (Schrijvers et al., 2008). In MS, reduced processing speed has been shown to underlie cognitive deficits in executive functioning (Leavitt et al., 2014), and aspects of memory and processing speed have been shown to mediate the relationship between depression and other cognitive functions in MS (Blair et al., 2016). Depression and reduced processing speed may also share neural substrates in MS, such as reduced cortical volume in deep gray matter regions including the basal ganglia and thalamus, and well as disrupted subcortical pathways that have extensive connections to cortical areas (Batista et al., 2012). The hippocampus is one of the most sensitive structures in the brain to neuroinflammatory processes. The severe neuroinflammation caused by MS can thus lead to hippocampal atrophy along with any hippocampal atrophy secondary to depressive symptoms. This volume loss in medial temporal structures can in turn lead to visual and verbal memory impairment (Mancini et al., 2017).

Although cognitive impairment and depression share a synergistic relationship in MS, it is unclear whether depression precedes cognitive impairment or vice versa. Longitudinal studies looking at cognition and depression together have begun to address this question of

directionality. In one cognitive rehabilitation study, mood symptoms were tracked over time during a cognitive intervention. In this study, only patients in the cognitive intervention group showed improvement in depression and anxiety symptoms (Hanssen et al., 2016), providing some evidence that enhancing patient-perceived cognitive functioning may in turn improve depressive symptoms in MS. Another MS study found that cognitive rehabilitation improved general contentment significantly more than a control intervention (Chiaravalloti et al., 2013). Many patients with MS who are not depressed still have cognitive impairment, even in many of the same domains impacted by depression such as processing speed, attention, and executive functioning. Thus, it seems cognitive impairment can be independent of depressive symptoms in MS. It is also possible that underlying cognitive deficits related to the MS disease process are further exacerbated by depressive symptoms (Anthony Feinstein, 2006).

Although clear connections between cognitive impairment and depression in MS have been established, few studies have attempted to determine intermediary mechanisms by which these variables are connected. One study found that about 40% of the variance in depressive symptomology in MS is related to psychosocial factors such as illness uncertainty and coping styles, further suggesting that much of the depression in MS is a reaction to the disease process (Lynch et al., 2001). Arnett and colleagues (2002) found that cognitive impairment was only related to depressive symptoms in MS if low levels of active coping and/or high levels of avoidance coping were used. They postulated that patients who avoid or deny their cognitive issues are more likely to become depressed than patients who accept and attempt to remediate their cognitive issues (Arnett et al., 2002). A longitudinal study of coping styles, cognitive dysfunction, and depression in MS had similar results. The authors of this study postulated that cognitively impaired individuals have great difficulty learning adaptive coping strategies, which

in turn can lead to depressive symptoms (Rabinowitz & Arnett, 2009). These findings have been supported by the cognitive-behavioral therapy literature, which has found appraisal to mediate the relationship between cognition and mood. Patients who view a difficult situation from a problem-solving appraisal perspective are less likely to become depressed (Chen et al., 2006). Thus, there appears to be an important intermediary appraisal mechanism that connects cognitive impairment and depression.

Cognition and Anxiety in MS

Anxiety, like depression, has been shown to have a significant impact on cognitive functioning. Although anxiety may be a precursor for cognitive impairment, cognitive difficulties may also lead to symptoms of anxiety, especially in cognitively impaired older individuals. Several studies have also demonstrated the existence of shared neural substrates for cognition and anxiety, such as hyperactivity in the dorsolateral prefrontal cortex (Berkowitz et al., 2007) and dysregulation of the HPA axis (Sapolsky et al., 1986).

Research has been relatively sparse on cognition and anxiety in MS, and many of the studies have not adjusted for disease or demographic characteristics that may be playing an intermediary role in this relationship and accounting for unique variance. One study found that a measure of set-shifting and a measure of speeded visuomotor sequencing was significantly correlated with both state and trait anxiety (Stenager et al., 1994). A retrospective study demonstrated that patients with anxiety performed significantly worse on measures of processing speed, working memory, and visual learning when compared to MS patients without anxiety (Morrow et al., 2015). Another study created a composite measure of cognition that included measures of executive functioning, processing speed, and learning, and found that anxiety was significantly associated with cognitive dysfunction above and beyond the effect of depression

(Julian & Arnett, 2009). Goretti and colleagues (2014) examined the relationship between anxiety and cognitive functioning after adjusting for demographic and disease variables. They found that high levels of anxiety were associated with reduced performance on measures of processing speed, complex attention, and working memory (Goretti et al., 2014). A recent study found that anxiety mediated the relationship between processing speed and verbal learning in an MS sample. This same study also found processing speed to mediate the relationship between anxiety and verbal learning (Vissicchio et al., 2018). Thus, based on the results of these studies, processing speed appears to be the cognitive domain that is most frequently impacted by anxiety in MS. Anxiety can also impact other abilities related to cognitive efficiency such as executive functioning and working memory.

Although cognitive functioning and anxiety appear to have a reciprocal relationship, the directionality of the relationship between cognition and anxiety in both older adult and MS populations appears to still be unclear. As for older adult populations, longitudinal studies of anxiety predicting accelerated cognitive impairment in older adult individuals have yielded mixed results (Sinoff & Werner, 2003; Wetherell et al., 2002). Although anxiety symptoms may exacerbate cognitive decline in older adults, it is also possible that cognitive symptoms may lead to anxiety (Beaudreau & O'Hara, 2008). One study followed a sample of 2,967 older patients over a period of three years. The authors reported that patients that had mild cognitive impairment (MCI) at baseline were more than twice as likely to develop anxiety symptoms than those with no cognitive impairment at baseline. These results remained consistent after adjusting for potential confounding variables. Based on these results, the authors concluded that mood symptoms may be a reactive response to cognitive impairment. People may become worried that their cognitive symptoms are impacting their everyday lives, and can in turn become afraid of

developing a neurodegenerative disease, leading to increased anxiety (Mirza et al., 2017). Studies have also shown that anxiety and depressive symptoms are twice as common in dementia as they are in MCI, further suggesting that worsening cognition is associated with more anxiety (Lyketsos et al., 2002).

The question of directionality about whether cognitive impairment precedes anxiety symptoms or vice versa has been a focus of the cognitive rehabilitation literature in MS. These cognitive rehabilitation studies in MS has provided further support that cognitive impairment may sometimes precede anxiety. In these studies, cognitive rehabilitation has not only led to improvement in cognitive functioning, but has also led to improvement in neuropsychiatric symptoms. One study found that a brief, computer-assisted, home-based cognitive rehabilitation program improved anxiety symptoms in MS patients, significantly reducing anxiety symptoms from baseline levels (Pérez-Martín et al., 2017). Another study in MS found that a multidisciplinary cognitive rehabilitation program did not improve cognition but reduced anxiety and depressive symptoms from baseline (Hanssen et al., 2016).

Part III. Illness Intrusiveness and its relationship to cognition and mood in MS

Illness Intrusiveness- definition and overview

Illness intrusiveness may be one potential important intermediary mechanism by which cognition and mood are related in MS. Illness intrusiveness is a concept that was introduced by Gerald Devins and colleagues in 1983. It refers to the degree to which an illness and/or its treatment may interfere with important aspects of a person's life, particularly participation in previously valued activities and interests (G. M. Devins et al., 1983). Illness intrusiveness encompasses the degree to which patients perceive illness-induced barriers to be preventing them from living a rewarding life. This, in turn, contributes to the psychosocial distress caused by the

disease. Devins and colleagues (1983, 1992) noticed that in renal failure patients, as a result of intense dialysis treatment and kidney transplants, people had suffered a number of significant losses in their lives. As a result, they were forced to reduce their participation in or entirely give up previously enjoyed leisure activities as well as highly valued activities such as their careers. This, in turn, often led to loss of self-esteem and reduced quality of life (G. M. Devins et al., 1983, 1992). Illness intrusiveness has been shown to create psychological distress in two ways. The first way is by reducing the availability of positively reinforcing activities that people were once able to obtain on their own. The second way is by reducing perceived personal control, such that a person does not believe they possess the ability to engage in reinforcing activities on their own (Gerald M. Devins, 1994).

A difference exists between actual and perceived illness intrusiveness. Actual objective intrusiveness is related to the disease process itself. For example, dialysis is more intrusive than successful renal transplant surgery because dialysis often requires hospitalization and many weekly treatments, whereas successful transplant surgery is a one-time event. Thus, objectively dialysis is more intrusive than successful transplant surgery. However, the patient's subjective perception of the intrusiveness of a disease process and related treatments can vary from patient to patient even if the objective intrusiveness is held constant. Thus, both objective and perceived illness intrusiveness contribute to the emotional impact of the disease (Devins et al., 1983; Devins et al., 1992).

Illness Intrusiveness- Conceptual Model

Many aspects of the disease process and related treatment impact illness intrusiveness directly. Some examples of disease-specific factors that influence illness intrusiveness are pain, fatigue, and disability. Treatment factors such as mode of treatment, time required for treatment,

and treatment side effects also directly impact illness intrusiveness. Psychosocial factors can also directly impact illness intrusiveness, including social support from friends and family, concerns about the disease, financial burden of the disease, as well as intellectual and coping resources. Devins also acknowledged that other factors specific to each individual such as age, gender, socioeconomic status, and other stressful life events would also contribute to this construct (Devins, 1994). Devins and colleagues developed a scale to quantify the level of illness intrusiveness in chronic health conditions, and this scale became known as the Illness Intrusiveness Ratings Scale, abbreviated by IIRS (Devins et al., 1983). This scale assesses the degree to which patients perceive their illness to interfere with previously enjoyed activities and interests. It determines to what extent a patient's disease has impacted their ability to fully engage in relationships, involvement in the community, and work life, among other activities and interests. Since the questionnaire is filled out by patients and is thus subjective in nature, it is considered a measure of perceived illness intrusiveness.

Several studies have provided support for Gerald Devins's conceptual model of illness intrusiveness, with many of the studies being conducted in end stage renal failure patients. As for disease factors and end stage renal failure patients, it has been shown that increased severity of physical symptoms such as bruising and bleeding is associated with increased perceived illness intrusiveness (Devins et al., 1990). In another study in end stage renal participants, the occurrence of frequent muscle cramps was associated with increased illness intrusiveness (Devins et al., 1990). As for treatment factors, increased duration of time required for treatment is associated with higher perceived intrusiveness (Devins, 1994). Research has also shown that successful treatments that reduce disease burden can reduce illness intrusiveness. Studies have

demonstrated that patients who receive successful renal transplant surgery report lower levels of illness intrusiveness than patients who do not receive this treatment and need long-term dialysis (Devins et al., 1983). Psychosocial factors such as significant life stressors have also been shown to influence illness intrusiveness. In addition to the intrusiveness created by these stressful life events, both perceived stress and illness intrusiveness are related to cognitive appraisals, which may be another reason for the existence of the relationship between psychosocial factors and illness intrusiveness (Devins et al., 1990).

Illness intrusiveness as a construct has traditionally been conceptualized as an intermediary variable between aspects of a disease process and psychological outcomes. This has been the case in MS (Shawaryn et al., 2002), as well as in other chronic health conditions such as heart failure (Lynn Paukert et al., 2009; W. LeMaire et al., 2012), restless sleep (Devins et al., 1993), and diabetes (Talbot et al., 1999). This is likely due to the fact that illness intrusiveness is a subjective construct highly dependent upon appraisal mechanisms that are a direct response to the disease itself. Other scales that have measured perceived intrusiveness related to a disease process have also been conceived as mediating variables, such as Horowitz's Impact of Events Scale for PTSD (Holgersen et al., 2010; Horowitz et al., 1979) and the Mental Adjustment to Cancer Scale for conceptualizing adjustment and coping in various types of cancers (Costa-Requena et al., 2015; Greer & Watson, 1987).

Illness Intrusiveness in MS

People with MS have to routinely deal with a number of disease-specific physical symptoms, they are forced to maintain chronic dependency on healthcare, and they are subjected to complex, costly, and time-consuming medical regimens and treatments. As a consequence of these factors, people with MS often experience significant disruptions in previously valued

activities, which can compromise psychosocial wellbeing and lead to increased psychological distress (Stewart et al., 1989). MS in particular has been shown to be a highly intrusive chronic illness. One study compared illness intrusiveness ratings among patients with rheumatoid arthritis, end stage renal disease, and MS. MS was shown to have significantly higher illness intrusive ratings than the other two conditions. Of the 13 life domains examined by the IIRS, MS patients endorsed the highest ratings for 9 of the 13 domains included in the scale. The highest discrepancies between MS and the other 2 conditions (MS patients rated their illness as significantly higher) came for passive recreation, social relations, and self-expression/self-improvement (Devins et al., 1993).

Some MS-specific disease factors have been shown to be significantly related to illness intrusiveness. Fatigue, physical symptoms, and overall level of disability have been shown to impact the perceived intrusiveness of MS. This was illustrated in one study conducted on 189 MS patients recruited from 3 clinics in Montreal, Canada, in which fatigue was independently associated with illness intrusiveness (Bouchard et al., 2017). Depression mediated the relationship between illness intrusiveness and fatigue. In another study conducted on the same MS population from Montreal, fatigue, in a symptom cluster with pain and sleep difficulties, was significantly associated with illness intrusiveness. However, motor symptoms of spasticity and poor balance included together in a symptom cluster were not associated with illness intrusiveness (Shahrbanian et al., 2015). Another very similar study was conducted by Snyder and colleagues (2013) on 185 MS patients recruited from the same MS Center utilized in the current study. This study found that depression and disability were significantly associated with illness intrusiveness, each individually accounting for about 20% of the variance after adjusting for demographic variables (Snyder et al., 2013a). Illness intrusiveness has also been shown to

mediate the relationships between disease severity and fatigue as well as disease severity and physical health indicators (Shawaryn et al., 2002).

Illness Intrusiveness and Depression

Research has consistently demonstrated a relationship between depression and illness intrusiveness across a number of diseases. In the first illness intrusiveness study conducted by Devins and colleagues (1983), after partialing out the effects of age, general nonrenal health, and defensiveness, illness intrusiveness was significantly positively associated with negative mood and negatively associated with positive mood (ie., as illness intrusiveness went up, so did negative mood, but when illness intrusiveness went down, positive mood went up). Perceived illness intrusiveness was associated with mood independent of the effect of perceived control (Devins et al., 1983). One study conducted in patients with rheumatoid arthritis showed that as the disease progressed and intrusiveness increased, so too did depression (Devins et al., 1992). Several studies have examined the relationship between heart failure and illness intrusiveness. These studies have found illness intrusiveness to mediate the relationship between illness severity and depressive symptoms in heart failure patients (Lynn Paukert et al., 2009; LeMaire et al., 2012). As for the mechanism behind this, one study posited that some patients have better social support and may be more resilient, and thus may view their illness as less intrusive, which leads to fewer depressive symptoms. However, the authors of this article did not test these secondary hypotheses regarding resiliency and social support (LeMaire et al., 2012). A study conducted in patients with diabetes showed that illness intrusiveness mediated the relationships between disease factors such as diabetes duration, diabetic complications, and major life events and depressive symptoms. Illness intrusiveness explained 61% of the variance in depressive

symptomology (Talbot et al., 1999). Thus, illness intrusiveness has been shown to play an important intermediary role between disease factors and depression.

Illness Intrusiveness and Anxiety

Since illness intrusiveness is related to appraisals pertaining to the secondary effects of having a chronic illness and has been shown to correlate with general psychological distress (Devins, 1994), it would follow logically that a relationship exists between anxiety and illness intrusiveness. However, the potential relationships between anxiety and illness intrusiveness have only been minimally examined in the literature. A study conducted in college students with a variety of chronic diseases (eg., epilepsy, type 1 diabetes), demonstrated that illness intrusiveness was related to symptoms of anxiety after adjusting for demographic and disease factors (Mullins et al., 2017). Another study examining illness intrusiveness in people with anxiety disorders such as social phobia, obsessive compulsive disorder, and panic disorder found a high level of illness intrusiveness in these populations. People with OCD experienced the most perceived intrusiveness in the areas of religious expression and passive recreation. People in the social phobia group reported increased intrusiveness in social relations and self-expression. These differences are consistent with impairments produced by these mental illnesses, such as difficulties with relationships in people with social phobia or religious obsessions in patients with obsessive compulsive disorder (Antony et al., 1998). Critics of this finding argued that individuals with anxiety tend to be more neurotic, which may lead them to view their anxiety as more intrusive than it actually is. Anxiety may also disproportionately affect social relations, thus changing the underlying factor structure of the IIRS and yielding invalid comparisons with other chronic diseases. However, a study that examined the underlying factor structure of the IIRS in anxiety disorders found that the three-factor structure found in other chronic diseases

provided the best fitting model. This finding also could not only be explained by personality traits such as neuroticism. This suggested that anxiety disorders may be objectively intrusive, and the intrusiveness created by these disorders cannot be explained simply by faulty appraisals of intrusiveness (Bieling et al., 2001).

Illness Intrusiveness and Mood in MS

Several studies have examined the relationships between depression and illness intrusiveness in MS. One study conducted by Devins and colleagues (1993) examining restless sleep in 94 middle aged patients with MS, 110 with rheumatoid arthritis, and 101 with end-stage renal disease found that illness intrusiveness partially mediated the relationship between depression and restless sleep in MS (Devins et al., 1993). In a study from the same year utilizing the same sample mentioned in the previous study, illness intrusiveness was significantly related to depression after adjusting for disease-specific factors. Additionally, the authors found that depressive symptoms and illness intrusiveness did not differ significantly between age groups (Devins et al., 1993). In several other papers by Devins and colleagues, illness intrusiveness was shown to mediate the relationship between emotional distress and quality of life in MS (Devins, 1996; Devins, 1997).

A few studies have also included anxiety in addition to depression when examining the relationships between psychological distress and illness intrusiveness in MS samples. One paper looking at 82 MS patients early in the disease course found that depression, but not anxiety, was significantly associated with illness intrusiveness in MS (Lester et al., 2007). The authors of another paper utilizing the Montreal, Canada, MS sample described earlier found that depression, anxiety, and self-reported cognitive impairment, included together as a symptom cluster in a regression analysis, was related to illness intrusiveness in an MS sample (Shahrbanian et al.,

2015). The study referenced earlier by Snyder and colleagues (2013) also examined the relationships between depression, anxiety, and illness intrusiveness in a sample of MS patients. The correlations between both a depression and an anxiety self-report and the IIRS were highly significant (Snyder et al., 2013). As illness intrusiveness increased, so too did symptoms of anxiety and depression. In the hierarchical linear regression, depression and disability was significantly associated with illness intrusiveness, each individually accounting for about 20% of the variance after adjusting for demographic variables. In a separate hierarchical regression, anxiety accounted for 12% of the variance after accounting for demographic variables and disability. Neither anxiety nor depression significantly interacted with disability in their relationships to illness intrusiveness. Results suggested that MS patients with higher levels of depression and anxiety may view their illness as more intrusive to their lives than those with lower levels of emotional distress. The authors posited that patients with emotional distress may tend to have cognitive distortions and may overgeneralize the extent to which their MS symptoms are impacting their daily lives. Based on the results of this study, the authors surmised that the relationship between illness intrusiveness and emotional distress is likely bidirectional (Snyder et al., 2013b).

Illness Intrusiveness, Cognition, and Mood in MS

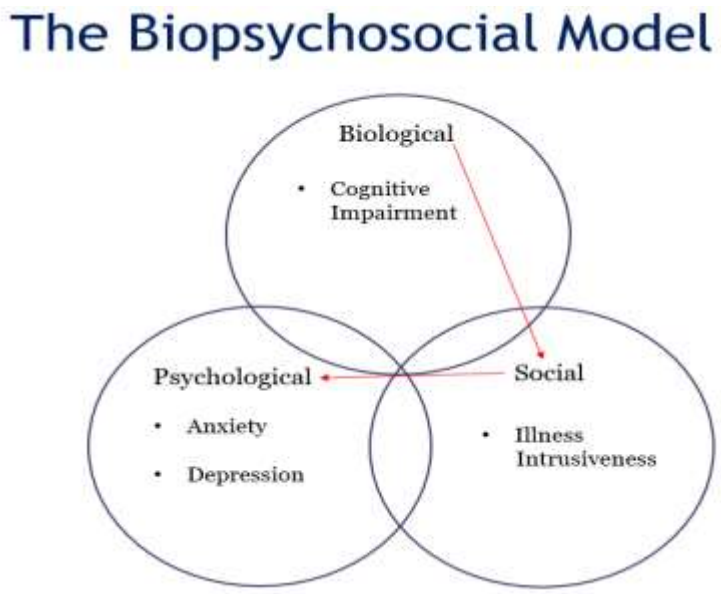
Only two published studies and one conference poster have examined the relationships between illness intrusiveness and cognition, and each has utilized an MS patient sample (Bouchard et al., 2017; Portnoy et al., 2017; Shawaryn et al., 2002). Only one published study to date has explored the relationship between cognitive variables, mood variables, and illness intrusiveness in an MS sample (Shawaryn et al., 2002). This study's sample included 90 community-dwelling patients between the age of 18-65 with clinically definite MS. The mean

age of the sample participants was 42.1 years old, and the sample was 64% female. In this study, the IIRS was significantly negatively correlated with the immediate recall trials of the California Verbal Learning Test-II (CVLT-II), a measure of verbal learning, but not significantly correlated with the Paced Auditory Serial Addition Test (PASAT), a measure of complex attention and working memory. Thus, impaired verbal learning was associated with higher levels of perceived illness intrusiveness. In this study, illness intrusiveness mediated the relationship between physical quality of life and verbal learning. Illness intrusiveness also mediated the relationship between disability and fatigue and between verbal learning and fatigue. Finally, illness intrusiveness mediated the relationship between verbal learning and depression (Shawaryn et al., 2002). The learning trials of the CVLT-II have been shown to be significantly influenced by processing speed in MS (Vissicchio et al., 2018). Thus, impaired processing speed may be underlying the results of this mediation analysis, and in turn may be highly related to illness intrusiveness and depression in MS. However, further research is needed to confirm this hypothesis.

The second published study was conducted by Bouchard and colleagues in 2012. This study sample consisted of 189 patients recruited from three separate MS clinics in the Montreal area. The mean age of participants was 43 years, and the sample was 74.7% female. In this study the PASAT, a test of processing speed and working memory, was not significantly related to illness intrusiveness. The authors stated as a limitation that cognition was probably not adequately captured by the PASAT, and that a more comprehensive assessment of cognition should be pursued in the future. The authors of this study considered it to be underpowered as well (Bouchard et al., 2017).

A recent conference poster presented by Portnoy and colleagues (2017) examined the role of depression, cognitive functioning, and disability and how they related to illness intrusiveness. The sample consisted of 116 MS patients recruited from the same patient population utilized in the current study from an MS Center in Teaneck, New Jersey. They used a composite score of cognition based on the oral SDMT, PASAT, CVLT-II (previously defined), and a measure of visual learning and memory called the Brief Visuospatial Memory Test-Revised (BVMT-R). The Patient Health Questionnaire-9 (PHQ-9) was used as a measure of depression and the Timed 25-foot walk (T25FW) and 9 Hole Peg tests were used as measures of disability. The cognition composite score was significantly associated with illness intrusiveness, accounting for roughly 10% of the variance with illness intrusiveness. Depression was also significantly related to illness intrusiveness, accounting for roughly 23% of the variance. Physical disability did not significantly contribute to changes in the IIRS. This poster presentation demonstrated that cognitive and affective symptoms may affect the perceived intrusiveness of MS independent of intrusiveness related to physical disability (Portnoy et al., 2017).

Proposed Theoretical Model



The biopsychosocial model is a health psychology model that can be used to explain the interconnectedness among the study variables (Engel, 1977). Biological factors such as cognitive impairments are related to the MS disease process itself. Cognitive impairment in MS often interferes with important social aspects of the lives of people living with MS, such as employment, recreational activities, and relationships. People with significant cognitive impairment often do not possess the cognitive capacity to carry out previously enjoyed activities independently. This social interference related to cognitive impairment is frequently appraised by MS patients to be highly intrusive to their lives. This, in turn, can lead to psychological consequences such as symptoms of anxiety and depression. Although anxiety and depression may be organic to the disease process itself, depression and anxiety may also be a reaction to the disease process and the psychosocial consequences of the disease. Cognitive impairment may lead to these reactionary mood symptoms due to intermediary appraisal mechanisms, one of which is perceived illness intrusiveness.

2. Significance/Rationale for the Study

Multiple Sclerosis (MS) is a neurodegenerative and inflammatory chronic disease of unknown etiology that affects the central nervous system and is characterized by substantial impacts on physical, cognitive, and psychological functioning (Tullman, 2013). Symptoms of depression and anxiety are highly prevalent in MS, with prevalence estimates generally ranging from 30-50% (Beiske et al., 2008; Schippling et al., 2016; Siegert & Abernethy, 2005). The prevalence rates of clinically significant anxiety and depression in MS are at least two to three times the prevalence in the general population (Patten et al., 2017). Depression and anxiety have been shown to correlate strongly with morbidity and mortality (Feinstein et al., 2014; Marrie et al., 2015), suicidal ideation (Alsaadi et al., 2017; Feinstein, 2002), and reduced adherence to

disease-modifying therapies (Higuera et al., 2016). Additionally, anxiety and depression are highly related to reduced quality of life independent of disability and fatigue (Amato et al., 2001).

A strong correlate of anxiety and depression in chronic diseases such as MS is illness intrusiveness (Devins et al., 1992; Lynn Paukert et al., 2009). This concept created by Devins and colleagues in 1983 refers to the degree to which an illness such as MS and/or its treatment may interfere with important aspects of a person's life, particularly participation in previously valued activities and interests (Devins et al., 1983). People with MS have to routinely deal with a number of disease-specific physical symptoms, they are forced to maintain chronic dependency on healthcare, and they are subjected to complex, costly, and time-consuming medical regimens and treatments. As a consequence of these factors, MS has been shown to be a highly intrusive chronic illness (Devins et al., 1993; Stewart et al., 1989).

Cognitive impairment, like anxiety and depression, is highly prevalent in MS and has been shown to impact over half of individuals with the disease. Links have continually been demonstrated between cognitive impairment and mood disturbance in MS (Batista et al., 2012; Blair et al., 2016; Goretti et al., 2014), yet little is known about potential mechanisms for this relationship. One potential mechanism by which cognitive impairment and mood symptoms may be related in MS is via illness intrusiveness. However, additional research is needed to confirm this hypothesis.

3. Innovation

A clear connection has been established between cognition and mood in MS (Blair et al., 2016; Vissicchio et al., 2018), however there has been little research on potential mechanisms for this relationship. Illness intrusiveness may be one mechanism. Illness intrusiveness has well-

established strong relationships with anxiety and depression (Shahrbanian et al., 2015; Snyder et al., 2013a), yet only one published study has examined the interrelationships between mood, cognition, and illness intrusiveness together in MS. This study found illness intrusiveness to have an important intermediary role between cognition and mood (Shawaryn et al., 2002). However, neither this nor any other published study has separately looked at processing speed and illness intrusiveness, even though processing speed is the most common cognitive impairment in MS. (Benedict et al., 2017). The current study plans to examine processing speed as part of a cognitive composite as well as in isolation due to the significant impact that the MS disease process has specifically on information processing speed.

It also remains unclear if cognitive impairment, which has been shown to reduce quality of life in MS (Baumstarck-Barrau et al., 2011; Glanz et al., 2010), is related to anxiety, depression, and illness intrusiveness in this chronic disease. Furthermore, relationships have been determined between anxiety and illness intrusiveness (Mullins et al., 2017), as well as cognition and anxiety in MS (Vissicchio et al., 2018). However, no studies have explored the inter-relationships between cognition, illness intrusiveness, and anxiety in MS. The specific relationships between cognitive functions commonly impaired in MS, mood symptoms, and individual subscales of the IIRS have also yet to be explored.

In order to address these gaps in the literature, this study had several specific aims. The first was to examine the relationships between processing speed in isolation, illness intrusiveness, and depression in an MS sample. The second was to examine relationships between more general cognitive impairment (composite measure including processing speed, verbal and visual learning, and verbal fluency), illness intrusiveness, and depression. The third aim was to explore relationships between processing speed, illness intrusiveness, and anxiety.

The fourth aim was to look at relationships between cognitive impairment, illness intrusiveness, and anxiety. There were also two exploratory aims. The first examined the interrelatedness of anxiety and depression in MS, and how they together impact cognitive functioning. The second exploratory aim explored the relationships between the individual subscales of the Illness Intrusiveness Ratings Scale (IIRS) and the study variables. A central hypothesis of the study is that cognitive functioning is related to anxiety and depression in MS at least partly due to illness intrusiveness.

4. Hypotheses

Specific Aim 1-To Examine the Relationships Between Processing Speed, Illness Intrusiveness (as assessed by the total score on the IIRS), and Depression in an MS Sample

Hypothesis 1- Processing speed is significantly related to depression in MS, such that reduced processing speed is related to greater symptoms of depression.

Hypothesis 2- Reduced processing speed is significantly related to increased illness intrusiveness in MS.

Hypothesis 3- Illness intrusiveness mediates the relationship between processing speed and depression in MS.

Specific Aim 2-To Examine the Relationships Between Cognitive Impairment, Illness Intrusiveness (as assessed by the total score on the IIRS), and Depression in an MS Sample

Hypothesis 1- Cognitive Impairment is significantly related to depression in MS, such that greater cognitive impairment is related to elevated levels of depression.

Hypothesis 2- Higher levels of cognitive impairment are significantly related to increased illness intrusiveness in MS.

Hypothesis 3- Illness intrusiveness mediates the relationship between cognitive impairment and depression in MS.

Specific Aim 3-To Examine the Relationships Between Processing Speed, Illness Intrusiveness (as assessed by the total score on the IIRS), and Anxiety in an MS Sample

Hypothesis 1- Processing speed is significantly related to anxiety in MS, such that reduced processing speed is associated with increased anxiety.

Hypothesis 2- Reductions in processing speed are significantly related to increases in illness intrusiveness in MS.

Hypothesis 3- Illness intrusiveness mediates the relationship between processing speed and anxiety in MS.

Specific Aim 4-To Examine the Relationships Between Cognitive Impairment, Illness Intrusiveness (as assessed by the total score on the IIRS), and Anxiety in an MS Sample

Hypothesis 1- Cognitive Impairment is significantly related to anxiety, such that greater levels of cognitive impairment are related to higher levels of anxiety.

Hypothesis 2- Increases in Cognitive Impairment are significantly related to elevations in illness intrusiveness.

Hypothesis 3- Illness intrusiveness mediates the relationship between cognitive impairment and anxiety in MS.

Exploratory Aim 1- To Examine the Interrelatedness of Anxiety and Depression in MS, and How They Together Impact Cognitive Functioning

Exploratory Hypothesis 1- Anxiety and depression are significantly related in the current MS sample, such that higher levels of anxiety are associated with higher levels of depression.

Exploratory Hypothesis 2- Reduced processing speed is related to higher scores on a composite measure of depression and anxiety.

Exploratory Hypothesis 3- Increased cognitive impairment is related to higher scores on a composite measure of depression and anxiety.

Exploratory Hypothesis 4- Higher levels of illness intrusiveness (as assessed by the total score on the IIRS), are related to higher scores on a composite measure of depression and anxiety.

Exploratory Hypothesis 5- Illness intrusiveness (as assessed by the total score on the IIRS), mediates the relationship between processing speed and a composite measure of depression and anxiety.

Exploratory Hypothesis 6- Illness intrusiveness (as assessed by the total score on the IIRS), mediates the relationship between cognitive impairment and a composite measure of depression and anxiety.

Exploratory Aim 2- To Examine Relationships Between Individual Subscales of the IIRS (relationships and personal development, intimacy, and instrumental subscales), depression, anxiety, and cognitive functioning in MS

Exploratory Hypothesis 1- All individual subscales of the IIRS will be significantly related to depression, such that higher scores on each individual subscale will be associated with higher levels of depression.

Exploratory Hypothesis 2- All individual subscales of the IIRS will be significantly related to anxiety, such that higher scores on each individual subscale will be associated with higher levels of anxiety.

Exploratory Hypothesis 3- Processing speed will be significantly related to all individual subscales of the IIRS, such that higher scores on each individual subscale will be associated with reduced processing speed.

Exploratory Hypothesis 4- All individual subscales of the IIRS will be significantly related to cognitive impairment, such that higher scores on each individual subscale will be associated with higher levels of cognitive impairment.

Chapter II- Methods

1. Participants and Recruitment

Participants in this study were recruited from the Multiple Sclerosis (MS) Center at Holy Name Medical Center in Teaneck, NJ. Participants from the study were referred for testing by neurologists at the MS Center, typically for cognitive complaints or to assess baseline cognitive functioning in new patients. Please see table 1 for descriptive statistics of the participants included in this study.

This study has been approved by the Einstein IRB (Approval #2015-4777, PI is Fred Foley, Ph.D.). Participants were provided a detailed explanation of the study as well as any potential risks or benefits of participating. Participation in the study was completely voluntary. Each participant then signed an Einstein-IRB approved consent document. At any time, participants had the option to leave and drop out of the study. They were informed that this study did not impact their medical care at Holy Name Medical Center, and that the study had no impact on their legal rights. At the end of the evaluation, participants were assigned an identification number, and all forms were de-identified. Each participant's file was then placed in a locked filing cabinet. Electronic data files were encrypted with HIPAA level security software. Participants did not receive compensation for their participation in this study.

Risks

Participants may have experienced minor psychological discomfort due to answering personal questions and performing neuropsychological tests. In any study, there is always some level of risk that information may be seen by unauthorized people, since information about a person is being gathered. To minimize this risk and protect confidentiality, the participant's name was not in the research database and the participant was assigned an identification number.

The code to link the identification to the person was kept in a separate, encrypted and password-protected computer file.

Benefits

This study advances knowledge about MS and the impact that illness intrusiveness, depression, and anxiety have on cognitive functioning. Results from this study may improve treatment for depression and anxiety in MS by allowing researchers and clinicians to gain a better understanding of factors that contribute to mood symptoms.

Eligibility and Exclusion Criteria

Participants were people diagnosed with clinically definite MS, the main inclusion criterion of the study. Exclusion criteria included a current MS exacerbation or current administration of high dose intravenous steroids.

2. Measures

Symbol Digit Modalities Test (SDMT)- (Smith, A., 1982) The oral version of the SDMT was administered to remove the motor component of the task due to the frequent motor difficulties experienced by MS patients. This task is a measure of processing speed, complex attention, and visual tracking. The participant is given a page with a grid at the top that contains a unique symbol paired to each of the numbers 1 through 9. Below this grid is a much larger grid with symbols only, and a blank box below each symbol. The participant is told to fill in the number that goes with the symbol without skipping any items. In the oral version used in this study, the participant is instructed to say the numbers out loud while the examiner records the responses. The participant has 90 seconds to complete the task. Including time for instructions, this task takes approximately 3 minutes to administer. The minimum score is 0 and the maximum score is 110 (numbers of correct symbols).

The test-retest reliability for the oral version of the SDMT is reported to be .76 (Smith, A., 1991). Practice effects are reported to be minimal. Alternate versions are available but are rarely used due to significant differences in difficulty level among alternate forms (Uchiyama et al., 1994). Thus, the standard form was used for all patients. The SDMT has shown to have good reliability and validity in MS samples. Test-retest reliability in MS samples has generally been shown to be higher than in healthy populations, with reliability coefficients ranging from 0.79 to 0.97 (Benedict et al., 2017). The SDMT has been shown to have good construct validity, generally loading onto a single processing speed factor (Benedict et al., 2006). It has also had the best predictive validity of any of the other core tests in MS (Amato et al., 2010). The SDMT has also demonstrated good discriminative validity by differentiating MS patients from healthy controls (Benedict et al., 2006). Among other tests of processing speed, the SDMT has established the best criterion validity, having the strongest relationship with lesion burden on MRI (Rao et al., 2014).

California Verbal Learning Test, second edition (CVLT-II)- (Delis et al., 2000) The CVLT-II is widely considered a test of verbal learning and memory. The examiner reads the patient a list of 16 words, 4 words from 4 different semantic categories. After the entire list is read, the participant is asked to repeat back as many words as possible from the list. This process is then repeated 4 additional times for a total of 5 learning trials. An interference trial is then completed with a new list of 16 words that is only presented once. Then, the short delay free recall trial is administered in which the participant is asked to recall as many words as possible from the original list that was repeated 5 times. Next, a short delay cued recall trial is presented in which the examiner asks the participant to recall words from a specific semantic category. After a 20-minute delay of non-verbal testing to ensure no interference from other verbal tasks, a

long-delay version of the free recall and cued recall trials is administered, along with a Yes/No recognition trial. Finally, an optional forced choice recognition trial may be administered. The maximum correct for the immediate recall trials is a raw score of 80 (16 words recalled over 5 learning trials), and the maximum raw score for the other trials of the task is 16. For the purposes of the current study, only the first 5 immediate recall trials were used because prior studies have demonstrated that MS patients are often impaired on the learning trials but not on the free recall or recognition trials (DeLuca et al., 1994; Deluca et al., 2013). This is likely due to processing speed impairments (Vissicchio et al., 2018).

According to the test manual, split half reliability was .94-.96. Test-retest reliability was high, .80-.89 for the immediate recall trials, short delay free recall, and long delay free recall trials. Alternate form reliability ranged from .72 to .79. The construct validity of the CVLT-II has been well-established in over 200 research studies and has good concurrent validity with the original version of the CVLT. Factor analysis has demonstrated good internal validity of the CVLT-II, with a general memory factor accounting for most of the unique variance. A five-factor solution is also supported that includes General Verbal Learning, Response Discrimination, Recall Efficiency, Organizational Strategies, and Primacy-Recency Effects (Delis et al., 2000). Although no study has examined the reliability of the CVLT-II in an MS sample, the validity of the CVLT has been well-established in MS (Benedict et al., 2006; Stegen et al., 2010). It has been able to continually distinguish MS patients from controls. A factor analysis conducted on an MS sample revealed the same single factor and five factor solutions found in the general population. The CVLT-II has also demonstrated good external validity in MS; it has been able to discriminate employed vs. unemployed individuals (Stegen et al., 2010),

and has corelated significantly with MRI parameters associated with disease burden (Benedict et al., 2009).

Brief Visuospatial Memory Test-Revised (BVMT-R)- (Benedict, 1997) The BVMT-R is considered a visual learning and memory task. It involves learning across three immediate recall trials and includes a delayed recall and recognition component. The examiner shows the patient a page with six simple geometric figures presented in a 2x3 matrix. This page is displayed for ten seconds before it is taken away and the participant is then asked to draw as many figures as they can recall from memory. This process is repeated two additional times, for a total of three learning trials. After 25 minutes of verbal tasks to avoid interference, the patient is asked to reproduce the simple geometric figures from memory. This is followed by a recognition trial and an optional copy trial. The examiner scores the learning and delayed recall trials based on accuracy of the reproduced figure as well as the location of the figure. One point is awarded for location and one point is rewarded for accuracy, for a total of 12 possible points per trial. Thus, the maximum total score for the three learning trials is a raw score of 36, and a maximum score of 12 can be achieved on the delayed recall trial. For the recognition trial, a recognition discriminability index is calculated based on the number of correctly recalled figures and false positives, yielding a maximum recognition discriminability of 6. Only the three learning trials were used in this study for similar reasons cited for the CVLT-II, because most of the impairments in MS are related to acquisition rather than retrieval or recognition (DeLuca et al., 1994; Deluca et al., 2013).

Test-retest reliability reported in the manual for the total recall score for the learning trials is .80. There are 6 alternate forms available, which have been demonstrated to be equivalent. Interrater reliability was reported to be .90. The BVMT-R has demonstrated

convergent validity via high correlations with other visual learning and memory tasks. Factor analysis revealed that the BVMT-R loaded onto a single factor that represented visuospatial learning and memory (Benedict, 1997). Test-retest reliability of the BVMT-R has been demonstrated in two recent MS validation studies (de Caneda et al., 2018; Polychroniadou et al., 2016). High internal consistency has also been found for the BVMT-R in MS populations (de Caneda et al., 2018). The BVMT-R has consistently been able to discriminate MS patients from healthy controls (Dusankova et al., 2012) and has correlated with total lesion area and lesion volume (Benedict et al., 2002).

Controlled Oral Word Association Test (COWAT)- (Benton, 1994) This consists of a phonemic fluency and a semantic fluency task. For the phonemic fluency task, the participant is asked to orally produce as many words as possible that start with a specific letter. They are told not to say proper names and to avoid using words with the same word root but different endings. They are given one minute to say as many words as possible that start with the specified letter. This is done for three different letters (3 trials). For the semantic fluency task, participants are asked to orally name as many animals as they can (1 trial). These animals can start with any letter. For both of these tasks, the number of unique words generated in one minute that matches the specified task parameters is counted as correct. The total words generated for the three separate letter trials become the phonemic fluency score, and the total animal words generated become the semantic fluency score. The minimum raw score for these tasks is 0, and there is no maximum raw score.

Test-retest reliability has been high, generally above .70 with minimal practice effects (Basso et al., 1999; Ross, 2003). The alternate forms have been shown to be equivalent (Ruff et al., 1996, p. 199). Inter-rater reliability is very high, generally above .98 (Ross, 2003). Validity

of the COWAT has also been well-established. Convergent validity is frequently demonstrated with other fluency tasks and various cognitive measures assessing language and executive functions (Henry & Crawford, 2004). The phonemic fluency task consistently has been associated with frontal lobe lesions, whereas the semantic fluency task has been shown to be associated with lesions in the temporal lobe (Stuss et al., 1998). Test-retest reliability for the COWAT has been shown to be adequate, around 0.73 (Eshaghi et al., 2012). The COWAT has shown good ability to discriminate MS patients from controls and has been shown to predict disability and employment status (Benedict et al., 2006).

Timed 25 Foot Walk (T25FW)- (Fischer et al., 1999) This task is the first of three tasks included in the Multiple Sclerosis Functional Composite measure, a multidimensional clinical outcome measure in MS. It has been considered the best objective measure of walking disability in MS (Kieseier & Pozzilli, 2012). During this task, the patient is directed to walk to one end of a 25-foot course as quickly and safely as possible. Assistive walking devices may be used. The same task is repeated by asking the patient to walk back the same distance. This task's total administration time takes 1-5 minutes and should be completed by a trained examiner. The score for each of the two trials of this task is reported in seconds. The seconds of the two administered trials is averaged to yield a total raw score. Higher raw scores indicate slower walking times, and thus higher levels of walking disability.

Studies have shown that the T25FW has good reliability between trials as well as over long periods of time and across a wide variety of disability levels (Learmonth et al., 2012). The T25FW has good criterion validity, consistently able to distinguish MS patients from healthy controls (Benedict et al., 2016). The construct validity of the MS has been established because the T25FW has been shown to correlate highly with employment status (Sandroff et al., 2015)

and disease burden on imaging (Klineova et al., 2016). Convergent validity has been established because the T25FW has strong correlations with constructs related to lower extremity functioning and walking. Discriminative validity has been established by relatively weaker correlations for this task with measures of upper extremity functions (Motl et al., 2017).

Illness Intrusiveness Ratings Scale (IIRS)- (Devins et al., 1983) This scale is a measure of illness intrusiveness, or the extent to which aspects of the disease interferes with previously enjoyed activities and interests. The IIRS taps illness intrusiveness in the following life domains: health, diet, work, active recreation, passive recreation, financial situation, relationship with partner, sex life, family relations, other social relations, self-improvement/self-expression, religious expression, and community and civic involvements. It can be self-administered or administered by a professional. It usually takes no more than about 5 minutes to complete.

The individual items of the IIRS are rated on a 13-item Likert type scale. Respondents are asked to rate the level of illness intrusiveness related to each item from 1-7, with 1 being "not very much" (not very intrusive) and 7 being "very much" (very intrusive). If an item is not applicable to the person, they are asked to enter a score of 1 for that item. A total score for the IIRS can be generated ranging from 13-91. Higher total scores indicate higher levels of perceived illness intrusiveness. Three specific subscale scores can also be created: relationships and personal development, intimacy, and instrumental. Relationships and personal development (six items included in subscale) includes family relations, social relations, self-expression, religious expression, community involvement, and passive recreation. Intimacy (two items) includes items about relationships with one's partner and sex life, and instrumental (five items) includes items that ask about illness intrusiveness related to health, work, financial situation, and active recreation. Subscale scores are created by averaging the relevant item means. The item

asking about diet and illness intrusiveness is not included in any of the subscales due to inconsistencies in factor analyses regarding this item (G. M. Devins et al., 2001).

The internal consistency of the IIRS total score in an MS population of 174 participants was .87, the relationships and personal development subscale was .77, intimacy was .75, and instrumental was .74 (Gerald M. Devins, 2010). Research in MS indicated 9-month test–retest reliability coefficients of .80 and .85 for IIRS total scores; 18-month test–retest reliability was .80 (Gerald M. Devins, Seland, Klein, Edworthy, & Saary, 1993). Construct validity is important for the IIRS because illness intrusiveness is a hypothetical construct. Some of the evidence for construct validity is that self-reported levels of illness intrusiveness are usually higher in later vs earlier stages of diseases. Treatment groups also differ on levels of perceived intrusiveness in the manner that one would expect; renal failure patients that receive successful kidney transplants report lower levels of illness intrusiveness than patients that are receiving inpatient dialysis, for example (Devins, 1983). Discriminative validity is demonstrated by the fact that IIRS scores correlate negatively with measures of personal control and are independent of certain personal characteristics such as defensiveness and social desirability. Criterion validity is demonstrated because IIRS scores of patients correlate positively with scores of healthcare professionals and family members (Devins, 1983). The three- factor structure is consistent across a variety of diseases as well as MS (Devins, 2001). The internal consistency of the IIRS in the current study sample was very high, $\alpha = 0.93$.

Hospital Anxiety and Depression Scale (HADS)- (Zigmond & Snaith, 1983)- The HADS is a 14 item self-report questionnaire designed for use in medically ill patients that asks alternating questions about anxiety and depression. Seven of the questions pertain to anxiety and seven questions deal with depressive symptoms. This questionnaire attempts to eliminate

overlapping physical symptoms of mood disturbance such as sleep difficulties, fatigue, and concentration problems. The HADS is a Likert type scale, in which each question can be answered on a scale from 0 to 3, with qualitative descriptors for the scale changing for each question. A total score can be generated for the anxiety and depression subscales; the minimum for each of these subscales is 0 and a maximum for each subscale is a score of 21. A score of 0-7 on either the anxiety or depression subscale indicates a non-elevated level of depression or anxiety. A score greater than 8 is considered an elevated level of either anxiety or depression.

The HADS has been shown to be well-validated in MS as well as other disease populations (Honarmand & Feinstein, 2009). Concurrent validity has been established by showing high correlations between the HADS and similar anxiety and depression scales (Zigmond & Snaith, 1983). A meta-analysis in MS patients demonstrated that a score of 8 or greater on either subscale yields sensitivity of around 90% and specificity of 81-87% for detecting the presence of a mood disorder in MS (Honarmand & Feinstein, 2009), suggesting good discriminant validity. Factor analytic studies have supported a 2 factor structure of the HADS (depression and anxiety) in MS (Pais-Ribeiro et al., 2018). A recent MS study has showed internal consistency to be 0.80 for the anxiety subscale and 0.81 for the depression subscale (Pais-Ribeiro et al., 2018). The internal consistency of the HADS anxiety subscale for the current study was $\alpha = .635$, which is slightly lower than what is considered adequate, .65-.80. However, this is likely due to the fact that the anxiety subscale only consists of 7 items, and the size of alpha would likely increase linearly with the inclusion of more items (Vaske et al., 2017). The internal consistency of the depression subscale is considered very inadequate, $\alpha = .351$. Thus, only the anxiety subscale was used in this study.

Patient Health Questionnaire-9 (PHQ-9)- (Kroenke et al., 2001) The PHQ-9 is a self-report questionnaire that determines depression severity. It consists of 9 items that assess depressive symptoms during the past 2 weeks. The participant is asked to rate the degree of severity for each symptom on a scale from 0-3. A rating of 0 indicates that the symptom has not bothered the patient at all in the past 2 weeks. A rating of 1 means the symptom has bothered them several days, 2 means more than half the days, and 3 means nearly every day. This yields a range of scores from 0-27. A score of 0-4 indicates no significant amount of depression, 5-9 indicates minimal depressive symptoms, 10-14 is minor depression, 15-19 is moderately severe depression, and >20 indicates severe depression. The PHQ-9 has demonstrated strong evidence of reliability and validity. The validation study was conducted on 6,000 patients in 8 primary care clinics and 7 obstetrics-gynecology clinics. Internal consistency was $\alpha = 0.89$, considered excellent. Test-retest reliability was also high, $r=0.84$. Criterion validity was established by comparing it to clinician interviews. A cutoff score of 9 or more yielded 95% sensitivity and 84% specificity for detecting clinically significant depression when compared to the gold standard clinical interview. The PHQ-9 has shown good construct validity by correlating strongly with functional status, with higher PHQ-9 scores associated with declines in functional status and increased disability.

The PHQ-9 has also demonstrated good psychometric properties in MS studies. Internal consistency in one study was excellent, $\alpha = 0.82$. A factor analysis from the same study showed that items loaded onto a single depression factor (Sjonnesen et al., 2012). Another study demonstrated evidence of convergent validity by finding high correlations with two other depression measures. Discriminative validity was established by showing that the PHQ-9 correlated more highly with other depression measures than measures of pain, sleep disturbance,

and fatigue (Amtmann et al., 2014, p. 9). The internal consistency for the PHQ-9 in this study was α= 0.88, which is considered excellent.

3. Procedures

This study was a retrospective chart review. Data used in this study were collected from baseline neuropsychological evaluations, and thus are cross-sectional in nature. All neuropsychological tests and self-report questionnaires were administered by trained graduate students from Ferkauf Graduate School of Psychology. These students were trained by Dr. Fred Foley, the PI of this study, on informed consent procedures as well as standardized administration of the measures used in this study. At the time of the neuropsychological evaluation, informed consent was obtained from each participant. After the consent process was completed, participants completed a 3-4 hour neuropsychological evaluation that included both cognitive assessments and self-report questionnaires.

For the cognitive measures, the oral SDMT and the COWAT were converted into age and education-adjusted z scores based on normative data provided by the test publishers (Ruff et al., 1996; Smith, A., 1982). The total raw scores of the five immediate recall trials of the CVLT-II were converted into age and education-adjusted z scores, and the three learning trials of the BVMT were converted into age-adjusted z scores (not adjusted for education) based on normative data provided by the test publishers (Benedict, 1997; Delis et al., 2000). Cognitive impairment was determined by creating a dichotomous variable based on performance on the four cognitive measures included in the study. Participants were considered cognitively impaired if they scored 1.5 SD below the mean on at least two of the four cognitive measures, consistent with established criteria in MS (Parmenter et al., 2007). For the disability measure, the T25FW, the average time in seconds of the three trials were used.

As for the self-report measures, the IIRS total score and individual subscale scores were converted into z scores based on norms from an MS patient population (Devins, 2010). The raw scores of the HADS anxiety subscale and the PHQ-9 were converted into z scores based on the current sample's mean and standard deviation. In order to examine anxiety and depression together, an average z-score was computed from the Hospital Anxiety and Depression Scale (HADS) anxiety subscale and the PHQ-9.

Power Analysis

Power analysis was conducted using G*Power 3.1.9.2. Given that a power analysis is not feasible for mediation analyses (Hayes, 2013), power analyses were calculated based on the hypotheses that were examined using independent samples t tests and partial correlations. Please see below for power analysis tables based on small, intermediate, and medium effect sizes for a priori power values of .95, .90, and .80. Given that at least medium-size effect sizes have been found in previous studies using the variables of interest in this study (Shawaryn et al., 2002; Snyder et al., 2013b), a medium effect size was deemed feasible to use for this power calculation. At $\alpha = .05$ with power of .9 and a medium predicted effect size, total sample size was estimated at N=92 for the correlations and N=140 for the T tests. Thus, the recommended overall sample size is 140 participants in order to explore each of the study hypotheses. The overall sample size for the current study was N=199, which is sufficiently more than required by the power analysis.

Correlation Power Analysis (# of participants needed in each cell)

Effect Size

Power	Small (.10)	Intermediate (.20)	Medium (.30)
.95	1077	266	115
.90	853	211	92
.80	616	153	67

T test Power Analysis (# of participants needed in each cell)

Effect Size

Power	Small (.20)	Intermediate (.35)	Medium (.50)
.95	1084	356	176
.90	858	282	140
.80	620	204	102

4. Data Analysis Plan

SPSS version 26.0 was used for all statistical analyses. The data was first summarized in frequencies and percents for categorical data, means and standard deviations for continuous data that met parametric test assumptions, and medians and interquartile ranges for continuous data that did not meet parametric test assumptions. Descriptive statistics were reported for the participants used in the study, including the total number of subjects, as well as their gender, age, marital status, education level, race, and employment status. Assumptions for parametric statistics were determined by examining graphical representations of the data such as frequency

histograms, Q-Q Plots, and means and standard deviations of each variable, as well as examining measures of skewness and kurtosis. Most study variables, including the anxiety and depression outcome variables as well as the mediating variable, illness intrusiveness, were determined to be continuous, normal variables that were suitable for parametric statistics. The T25FW and the intimacy and instrumental subscale of the IIRS were determined to deviate significantly from a normal distribution, and thus non-parametric tests were used for these variables.

Assumptions of ordinary least squares regression were examined, namely linearity, normality, homoscedasticity, and independence of the residuals. All collinearity diagnostics such as VIF and tolerance were in the acceptable range, and no correlations between predictors were above .8. Normality of residuals was established by examining the P-P Plots of Regression Standardized Residuals; these plots appeared to be normal. The homoscedasticity assumption was determined by creating a scatterplot of standardized residuals and predictors. The appearance of the scatterplots demonstrated that the data met this assumption. Thus, the data were determined to meet the assumptions required to run OLS Regression.

First, bivariate statistics were examined between predictor and demographic variables of the study and the anxiety and depression outcome measures, and unadjusted results of these analyses were reported. This was used to determine which variables needed to be included and adjusted for in the final models. Pearson's correlations were used for two continuous normal variables, and Spearman's Rhos were used if either continuous variable was non-normal. When a dichotomous predictor and a continuous outcome variable was examined, T tests were used for normal variables and Mann Whitney tests were used for non-normal variables. For predictors with more than 2 groups involved (such as race, employment status, and marital status) ANOVAs were used to examine differences between groups for normal variables and the

Kruskal-Wallis was used for non-normal variables. Post hoc pairwise comparisons were conducted to further explore significant differences between groups. For the final mediation models, both unadjusted and adjusted results were reported. Demographic and disease variables that were significantly related to the mood outcome measures were covariates/factors that were adjusted for in the mediation analyses. The alpha level for significance was set at p=.05, two-tailed. Missing data was handled via listwise deletion of the participant from a specific analysis.

In order to explore the primary hypotheses in this study, mediation analyses were conducted using Hayes's Process Macro (Hayes, 2013). Mediation analyses in general answer the question of "how" a relationship exists between two variables by examining if a third variable serves as an intermediary mechanism between two other variables. The approach to mediation created by Hayes uses observed-variable, Ordinary Least Squares Regression (OLS) to examine direct and indirect effects in mediation models. The indirect effect measures the difference between the effect of the predictor (*X*) on the outcome (*Y*) when the mediator (*M*) is controlled for vs. when the mediator is not controlled for. The null hypothesis is rejected when the size of the indirect effect is significantly different from 0, or when the confidence interval estimate of the indirect effect does not include 0. This type of mediation does not require the relationship between *X* and *M*, *M* and *Y*, or *X* and *Y* to be significant. The only requirement is that the relationship between *X* and *Y* through *M*, known as regression coefficient *ab* or paths *c- c'*, is significant (Hayes, 2013).

Data Analysis Plan By Aim

The first aim was to examine the relationships between processing speed, illness intrusiveness, and depression in an MS sample. The first two hypotheses were that processing speed was significantly associated with depression and that processing speed was significantly

related to illness intrusiveness. Partial correlations were used to examine these two hypotheses after adjusting for relevant demographic and disease-related factors/covariates. For the final hypothesis that illness intrusiveness mediated the relationship between processing speed and depression in MS, Ordinary Least Squares Regression was used. Andrew Hayes' Process Macro was used to determine mediation. Mediation was established if there was a significant indirect effect in which the confidence interval based on 5,000 bootstrapped samples did not contain zero (Hayes, 2013).

The second aim was to examine the relationships between cognitive impairment, illness intrusiveness, and depression in an MS sample. The first two hypotheses were that cognitive impairment was significantly related to depression and that cognitive impairment was significantly related to illness intrusiveness. T tests were used to examine these first two hypotheses. For the final hypothesis that illness intrusiveness mediated the relationship between cognitive impairment and depression, Ordinary Least Squares Regression was used along with Hayes' Process Macro, using the same parameters for significance specified in aim 1.

Aim 3 was to examine the relationships between processing speed, illness intrusiveness, and anxiety in an MS sample. This aim utilized the same statistical analyses from aim 1, with the only difference being anxiety as the outcome instead of depression. Aim 4 was to examine the relationships between cognitive impairment, illness intrusiveness, and anxiety in an MS sample. For this aim, the statistics that were used in aim 2 were again employed, this time with anxiety as the outcome instead of depression.

The first exploratory aim of this study was to examine the interrelatedness of anxiety and depression in MS, and how they together related to cognitive functioning. The first exploratory hypothesis was that anxiety and depression were related, which utilized a partial correlation.

Hypotheses 2-4 involved creating a composite score of depression and anxiety, and predicted that this composite was significantly related to processing speed, cognitive impairment, and illness intrusiveness. Partial correlations were used to explore these hypotheses. For hypotheses 5 and 6, that illness intrusiveness mediated the relationship between processing speed and the composite score, and that illness intrusiveness mediated the relationship between cognitive impairment and the composite score, Ordinary Least Squares Regression was used along with Hayes' Process Macro.

The second exploratory aim of this study was to examine the relationships between individual subscales of the IIRS, depression, anxiety, and cognitive functioning in MS. The first exploratory hypothesis was that all the individual subscales of the IIRS were significantly related to depression, the second hypothesis was that all the subscales were related to anxiety, the third hypothesis was that all the subscales were related to processing speed, and the fourth hypothesis was that cognitive impairment was significantly associated with all the subscales. The statistics used in exploratory hypotheses 1-3 were dependent upon the normality of the individual subscales of the IIRS. Since the relationship subscale of the IIRS was normal, partial correlations were used. Nonparametric partial correlations (spearman's rhos) were used for the intimacy and instrumental subscales, as they were non-normal. For exploratory hypothesis 4, logistic regression was used for both the normal and non-normal subscales, as logistic regression is robust to violations of normality in the predictor variables (the IIRS subscales in this case).

Please see below for an outline of the analyses used to address each hypothesis of the present study.

Specific Aim 1-To Examine the Relationships Between Processing Speed, Illness Intrusiveness, and Depression in an MS Sample

Hypothesis 1- <u>Processing speed is significantly related to depression in MS.</u>

Type of Analysis: Pearson partial correlation

Covariates/Factors: Age, Years of Education, Gender, Avg Walk

Hypothesis 2- <u>Processing speed is significantly related to illness intrusiveness in MS.</u>

Type of Analysis: Pearson partial correlation

Covariates/Factors: Age, Gender, Race, Employment Status, Avg Walk

Hypothesis 3- <u>Illness intrusiveness mediates the relationship between processing speed and depression in MS.</u>

Type of Analysis: Hayes' Process Model 4- Mediation Analysis

Covariates/Factors: Age, Years of Education, Gender, Avg Walk

Specific Aim 2-To Examine the Relationships Between Cognitive Impairment, Illness Intrusiveness, and Depression in an MS Sample

Hypothesis 1- <u>Cognitive Impairment is significantly related to depression in MS.</u>

Type of Analysis: T test

Covariates/Factors: Age, Years of Education, Gender, Avg Walk

Hypothesis 2- <u>Cognitive Impairment is significantly related to illness intrusiveness in MS.</u>

Type of Analysis: T test

Covariates/Factors: Age, Gender, Race, Employment Status, Avg Walk

Hypothesis 3- <u>Illness intrusiveness mediates the relationship between cognitive impairment and depression in MS.</u>

Type of Analysis: Hayes' Process Model 4- Mediation Analysis

Covariates/Factors: Age, Years of Education, Gender, Avg Walk

Specific Aim 3-To Examine the Relationships Between Processing Speed, Illness Intrusiveness, and Anxiety in an MS Sample

Hypothesis 1- <u>Processing speed is significantly related to anxiety in MS.</u>

Type of Analysis: Pearson partial correlation

Covariates/Factors: Age, gender

Hypothesis 2- <u>Processing speed is significantly related to illness intrusiveness in MS.</u>

Type of Analysis: Pearson partial correlation

Covariates/Factors: Age, Gender, Race, Employment Status, Avg Walk

Hypothesis 3- <u>Illness intrusiveness mediates the relationship between processing speed and anxiety in MS.</u>

Type of Analysis: Hayes' Process Model 4- Mediation Analysis

Covariates/Factors: Age, Gender

Specific Aim 4-To Examine the Relationships Between Cognitive Impairment, Illness Intrusiveness, and Anxiety in an MS Sample

Hypothesis 1- <u>Cognitive Impairment is significantly related to anxiety.</u>

Type of Analysis: T test

Covariates/Factors: Age, gender

Hypothesis 2- <u>Cognitive Impairment is significantly related to illness intrusiveness in MS.</u>

Type of Analysis: T test

Covariates/Factors: Age, Gender, Race, Employment Status, Avg Walk

Hypothesis 3- Illness intrusiveness mediates the relationship between cognitive impairment and anxiety in MS.

Type of Analysis: Hayes' Process Model 4- Mediation Analysis

Covariates/Factors: Age, Gender

Exploratory Aim 1- To Examine the Interrelatedness of Anxiety and Depression in MS, and How They Together Impact Cognitive Functioning

Exploratory Hypothesis 1- Anxiety and depression are significantly related in the current MS sample.

Type of Analysis: Pearson correlation

Covariates/Factors: None

Exploratory Hypothesis 2- Processing speed is related to a composite measure of depression and anxiety.

Type of Analysis: Pearson partial correlation

Covariates/Factors: Age, gender, Avg walk

Exploratory Hypothesis 3- Cognitive Impairment is related to a composite measure of depression and anxiety.

Type of Analysis: T test

Covariates/Factors: Age, gender, Avg walk

Exploratory Hypothesis 4- Illness intrusiveness is related to a composite measure of depression and anxiety.

Type of Analysis: Pearson partial correlation

Covariates/Factors: Age, gender, Avg walk

Exploratory Hypothesis 5- <u>Illness intrusiveness mediates the relationship between processing speed and a composite measure of depression and anxiety.</u>

Type of Analysis: Hayes Process Model 4 Mediation Analysis

Covariates/Factors: Age, gender, Avg walk

Exploratory Hypothesis 6- <u>Illness intrusiveness mediates the relationship between cognitive impairment and a composite measure of depression and anxiety.</u>

Type of Analysis: Hayes Process Model 4 Mediation Analysis

Covariates/Factors: Age, gender, Avg walk

Exploratory Aim 2- To Examine Relationships Between Individual Subscales of the Illness Intrusiveness Ratings Scale (IIRS), depression, anxiety, and cognitive functioning in MS

Exploratory Hypothesis 1- <u>All individual subscales of the IIRS will be significantly related to depression.</u>

Type of Analysis IIRS Relationship: Pearson partial correlation

Covariates/Factors: Age, Years of Education, Gender, Avg Walk

Type of Analysis IIRS Intimacy: Spearman's Rho

Covariates/Factors: Age, Years of Education, Gender, Avg Walk

Type of Analysis IIRS Instrumental: Spearman's Rho

Covariates/Factors: Age, Years of Education, Gender, Avg Walk

Exploratory Hypothesis 2- <u>All individual subscales of the IIRS will be significantly related to anxiety.</u>

Type of Analysis IIRS Relationship: Pearson partial correlation

Covariates/Factors: Age, gender

Type of Analysis IIRS Intimacy: Spearman's Rho

Covariates/Factors: Age, gender

Type of Analysis IIRS Instrumental: Spearman's Rho

Covariates/Factors: Age, gender

Exploratory Hypothesis 3- Processing speed will be significantly related to all individual subscales of the IIRS.

Type of Analysis IIRS Relationship: Pearson partial correlation

Covariates/Factors: Age, Gender, Race, Avg Walk

Type of Analysis IIRS Intimacy: Spearman's Rho

Covariates/Factors: Race, Avg Walk

Type of Analysis IIRS Instrumental: Spearman's Rho

Covariates/Factors: Age, Gender, Marital Status, Employment Status, Avg Walk

Exploratory Hypothesis 4- All individual subscales of the IIRS will be significantly related to cognitive impairment.

Type of Analysis IIRS Relationship: Logistic Regression

Covariates/Factors: Avg Walk

Type of Analysis IIRS Intimacy: Logistic Regression

Covariates/Factors: Avg Walk

Type of Analysis IIRS Instrumental: Logistic Regression

Covariates/Factors: Avg Walk

Chapter III- Results

Sample Demographics

See Table 1 (below) for information regarding the demographic characteristics of the study sample.

Table 1
Demographic Characteristics of the Sample

Demographics and Study Variables	*M (SD) or n (%) or Med. [IQR]*
Age (n=199)	48.4 (11.8)
Years of Education (n=199)	14.6 (2.2)
Gender (n=199)	
Males	46 (23.1%)
Females	153 (76.9%)
Race/Ethnicity (n=188)	
Caucasian	140 (74.5%)
Hispanic	25 (13.3%)
Black	18 (9.6%)
Other	5 (2.7%)
Marital Status (n=196)	
Single or engaged	41 (20.9%)
Married or cohabitating	120 (61.2%)
Divorced	29 (14.8%)
Widowed	6 (3.1%)
Employment Status (n=172)	
Unemployed/ disabled	59 (34.3%)
Unemployed/ Not disabled	47 (27.3)
Student	4 (2.3%)
Employed Part-time	10 (5.8%)
Employed Full-time	48 (27.9%)
Retired	4 (2.3%)
T25FW (n=193)	5.8 [4.5-7.1]
Cog. Impairment (n=199)	
Impaired	81 (40.9%)
Not Impaired	117 (59.1%)
SDMT z score (n=199)	-0.91 (1.28)
IIRS (n=199)	0.30 (1.03)

Note. For demographic variables, several categories needed to be combined for analyses due to

small cell sizes of less than 10. As for race, "other" was included with "Caucasian." For marital status, "widowed" was combined with "divorced." Finally, for employment status, "student" was combined with "employed full-time," and "retired" was combined with "unemployed/not disabled." T25FW= Timed 25-Foot Walk. Cognitive Impairment was determined by performance at 1.5 SD below the normative sample's mean on 2 or more cognitive measures included in the study. SDMT= Symbol Digit Modalities Test, IIRS=Illness Intrusiveness Ratings Scale

Based on the suggested cutoff for clinically significant anxiety on the HADS A in MS, a raw score of 11 or higher (Watson et al., 2014), 33.2% of the sample met criteria for clinically significant anxiety. This is generally consistent with the rates of clinically significant anxiety that have been found in other MS samples (Beiske et al., 2008; Bruce & Arnett, 2008; Anthony Feinstein, 2007; Korostil & Feinstein, 2007). For the PHQ-9, using the suggested clinically significant depression cutoff of 11 from a recent validation study in MS (Patrick & Connick, 2019), 41.7% met criteria for depression. This is also generally commensurate with the rates of clinically significant depression that have been discovered in prior samples of MS patients (Amtmann et al., 2014; Schippling et al., 2016).

Using the criteria of 2 or more tests at 1.5 SD below the mean, 40.9% of the study sample met criteria for cognitive impairment. Other studies have found the rate of impairment to be 40-70% (Grzegorski & Losy, 2017; Julian, 2011), suggesting the current sample is within the lower range of expected levels of cognitive impairment. 27.8% of the sample performed at 1.5 SD below the mean on the SDMT, which is consistent with the level of processing speed impairment found in a recent validation study of the SDMT in an MS sample (Kim et al., 2017).

Bivariate Unadjusted Relationships Among Study Variables

The relationships between demographic and predictor variables with the primary outcome variables were examined in Table 2 (see below). Higher self ratings on the PHQ-9 were associated with younger age, $r(198) = -.15$, $p = .032$, less years of education, $r(198) = -.15$, p

=.033, and female gender $t(196) = -2.00$, $p = .047$. Higher depression ratings were also associated with slower T25FW, $r_s(192) = .23$, $p = .001$, poorer performance on the SDMT $r(198) = -.17$, $p = .016$, and higher IIRS total scores $r(198) = .63$, $p < .001$. Cognitively impaired individuals also reported higher levels of depression than cognitively intact individuals, $t(196) = -2.02$, $p = .045$.

Higher scores on the HADS A were associated with younger age, $r(198) = -.15$, $p = .036$, and female gender $t(196) = -2.20$, $p = .029$. Higher HADS A scores were also associated with poorer performance on the SDMT $r(198) = -.16$, $p = .023$, and higher IIRS total scores $r(198) = .46$, $p < .001$. Cognitively impaired individuals also reported higher levels of anxiety than their non-impaired counterparts, $t(196) = -2.04$, $p = .043$.

As for the mood composite, higher levels of self-reported mood symptoms were associated with younger age, $r(198) = -.17$, $p = .020$, and female gender $t(196) = -2.30$, $p = .023$. Higher mood composite z scores were associated with slower T25FW, $r_s(192) = .19$, $p = .008$, poorer performance on the SDMT, $r(198) = -.18$, $p = .010$, and higher IIRS total scores, $r(198) = .60$, $p < .001$. Cognitively impaired individuals also had higher mood composite z scores than those without cognitive impairment, $t(196) = -2.26$, $p = .025$.

Table 2

Relationships Between Demographic and Predictor Variables with the Primary Outcome Variables (PHQ-9 z score, HADS A, Mood Composite z score)

Demographics and Study Variables	PHQ-9 average z score by category	PHQ-9 Analyses	HADS A average z score by category	HADS A Analyses	Mood Composite average z score by category	Mood Composite Analyses
Age (n=199)	-------	$p = .032$	-------	$p = .036$	-------	$p = .020$
Years of Education (n=199)	-------	$p = .033$	-------	$p = .614$	-------	$p = .146$
Gender (n=199)						
Males	-0.21 (0.98)	$p = .047$	-0.26 (0.92)	$p = .029$	-0.24 (0.89)	$p = .544$
Females	0.12 (0.99)		0.09 (0.96)		0.11 (0.89)	
Race/Ethnicity (n=188)						
Caucasian/Other	-0.02 (0.91)	$p = .306$	0.04 (0.94)	$p = .619$	0.01 (0.84)	$p = .742$
Hispanic	0.23 (1.17)		-0.19 (1.07)		0.02 (1.07)	
Black	0.26 (1.21)		0.07 (1.06)		0.16 (1.07)	
Marital Status (n=196)						
Single or engaged	0.22 (1.02)	$p = .117$	0.09 (0.91)	$p = .423$	0.16 (0.92)	$p = .182$
Married or cohabitating	-0.08 (1.00)		-0.06 (0.98)		-0.07 (0.90)	
Divorced/ Widowed	0.23 (0.94)		0.16 (0.99)		0.19 (0.84)	
Employment Status (n=172)		$p = .158$		$p = .166$		$p = .110$
Unemployed and disabled	0.11 (1.04)		0.11 (0.94)		0.11 (0.90)	
Unemployed and Not disabled/ Retired	0.21 (1.03)		0.06 (1.05)		0.13 (0.95)	
Employed Part-time	-0.05 (1.12)		-0.13 (0.98)		-0.09 (0.99)	
Employed Full-time/Student	-0.22 (0.87)		-0.27 (0.87)		-0.24 (0.77)	
T25FW (n=193)	-------	$p = .001$	. -------	$p = .113$	-------	$p = .008$
Cog. Impairment (n=199)						
Impaired	-0.08 (0.92)	$p = .045$	-0.09 (0.84)	$p = .043$	-0.10 (0.91)	$p = .025$
Not Impaired	0.22 (1.08)		0.20 (0.96)		0.18 (1.03)	
SDMT z score (n=199)	-------	$p = .016$	-------	$p = .023$	-------	$p = .010$
IIRS (n=199)	-------	$p < .001$	-------	$p < .001$	-------	$p < .001$

Note. Total Sample Size N=199. Sample size differed for some analyses, which was noted in the parenthesis following the variable names. PHQ-9= Patient Health Questionnaire-9. HADS A= Hospital Anxiety and Depression Scale, anxiety subscale only. Mood composite included an average z score of the PHQ-9 z score and the HADS A z score

Relationships between demographic variables and predictors were examined in Table 3 (see below). The T25FW was significantly associated with age, r_s (192) = .24, p = .001, such that slower walking times were associated with older age. Men had faster walking times than women, U (193) = 2.36, p = .018. Employment status also had a significant impact on walking speed, H (166) = 47.41, p<.001. Post hoc tests adjusting for multiple comparisons revealed that people employed full-time had faster walking speeds than unemployed individuals both receiving disability (p<.001) and not receiving disability (p<.001). Cognitively impaired individuals also had slower walking times than cognitively intact people, U (192) = 2.72, p= .007. Finally, poorer performance on the SDMT was associated with slower walking speeds, r_s (192) = -.32, p<.001.

No demographic variables were significantly related to cognitive impairment. As for predictor variables, the T25FW was associated with cognitive impairment as stated previously, U (192) = 2.72, p = .007. As expected, poorer performance on the SDMT was associated with higher levels of cognitive impairment, b = -1.47, Wald $\chi 2(1) = 41.51$, $p < .001$.

As stated previously, the SDMT was significantly related to the T25FW, r_s (192) = -.32, p<.001, as well as cognitive impairment, t (195) = 9.71, p<.001.

Table 3

Relationships Between Demographic Variables and Predictors (not including IIRS)

Demographics and Study Variables	T25FW by category	T25FW Analyses	% Cog. Impairment by category	Cog. Impairment Analyses	SDMT z score by category	SDMT Analyses
Age (n=199)	-------	p = .001	-------	p = .752	-------	p = .059
Years of Education (n=199)	-------	p = .449	-------	p = .220	-------	p = .746
Gender (n=199)						
Males	6.40 (0.62)	p = .018	34.8% (7.1)	p = .335	-0.97 (0.19)	p = .387
Females	6.67 (0.20)		42.8% (4.0)		-0.90 (0.11)	
Race/Ethnicity (n=188)						
Caucasian/Other	6.64 (0.26)	p = .577	39.9% (4.2)	p = .370	-0.86 (0.11)	p = .442
Hispanic	6.14 (0.38)		48.0% (10.2)		-1.11 (0.18)	
Black	7.37 (0.78)		47.0% (12.5)		-1.35 (0.30)	
Marital Status (n=196)						
Single or engaged	6.39 (0.32)	p = .546	43.6% (8.0)	p = .791	-1.23 (0.21)	p = .625
Married or cohabitating	6.45 (0.23)		40.2% (4.6)		-0.79 (0.11)	
Divorced/ Widowed	7.35 (0.81)		37.5% (8.7)		-1.00 (0.24)	
Employment Status (n=172)		p <.001		p = .058		p =.608
Unemployed and disabled	7.09 (0.36)		44.3% (6.4)		-1.23 (0.18)	
Unemployed and Not disabled/ Retired	7.74 (0.62)		42.9% (7.7)		-0.97 (0.16)	
Employed Part-time	7.09 (0.80)		10.0% (10.0)		-0.59 (0.29)	
Employed Full-time/Student	5.19 (0.20)		31.4% (6.6)		-0.59 (0.18)	
T25FW (n=193)	-------	-------	. -------	p = .007	-------	p <.001
Cog. Impairment (n=199)						
Impaired	7.18 (0.39)	p = .007	-------	-------	-1.79 (0.13)	p <.001
Not Impaired	6.24 (0.23)		-------		-0.32 (0.09)	
SDMT z score (n=199)	-------	p <.001	-------	p <.001	-------	-------

Relationships between the study variables and the IIRS total score and individual subscales were examined in Table 4 (see below). As for demographic variables, The IIRS total score was significantly associated with age, $r(198) = -.14$, $p = .042$, such that older age was associated with lower IIRS total scores. Older age was also associated with lower levels of relationship intrusiveness, $r(198) = -.17$, $p = .019$, and instrumental intrusiveness, $r(198) = -.15$,

p = .042. Years of education had no relationship to the IIRS total score or the individual subscales. Females reported higher levels of illness intrusiveness than males, which was reflected in significant differences in IIRS total score, $t(197) = -3.18$, p = .002, the IIRS relationship subscale, $t(197) = -3.38$, p = .001, and the IIRS instrumental subscale, U (197) = 3.25, p = .001.

There was a significant difference among racial groups on the IIRS total score $F(2, 192) = 3.29$, p =.039, and the IIRS relationship subscale, $F(2, 192) = 3.72$, p =.026, although no pairwise comparisons were significant after adjusting for multiple comparisons. There was also a significant difference among racial groups on the IIRS intimacy subscale, H (2) = 9.57, p = .008, with post hoc tests showing that people who identified as Black reported significantly more intimacy intrusiveness than people who identified as either Hispanics (p = .015) or Caucasians (p = .010). As for marital status, there was a significant difference among marital status groups for the IIRS instrumental subscale, H (2) = 6.56, p = .038. Divorced individuals endorsed more instrumental intrusiveness than people who were widowed (p = .049) or married (p = .005). Employment status had a significant relationship with the IIRS total score, $F(3, 166) = 3.28$, p =.023 and the instrumental subscale, $H(3) = 20.06$, p<.001. People who were employed full-time reported significantly less total illness intrusiveness than people who were unemployed receiving disability (p = .039). People who were employed full-time also reported significantly less instrumental intrusiveness than people who were unemployed receiving disability (p<.001) and not receiving disability (p = .006).

Higher levels of total illness intrusiveness, as well as relationship, intimacy, and instrumental intrusiveness were associated with slower times on the T25FW, poorer performance on the SDMT, and higher levels of depression, anxiety, and general mood symptoms (see Table 4 below for test statistics and p values for correlations). Individuals that met criteria for

cognitive impairment reported higher levels of total illness intrusiveness, $t(196) = -2.19$, $p = .029$, as well as higher levels of intimacy intrusiveness, $U = 2.73$, $p = .006$.

Table 4

Relationships Between Study Variables and the IIRS

Demographics and Study Variables	IIRS Total z score by Category	IIRS Total Score Analyses	IIRS Relationships z score by Category	IIRS Relationships Analyses	IIRS Intimacy z score by Category	IIRS Intimacy Analyses	IIRS Instrumental z score by Category	IIRS Instrumental Analyses
Age (n=199)	-------	$p = .054$	-------	$p = .019$	-------	$p = .099$	-------	$p = .042$
Years of Education (n=199)	-------	$p = .343$	-------	$p = .326$	-------	$p = .737$	-------	$p = .245$
Gender (n=199)								
Males	-0.10 (0.90)	$p = .002$	-0.26 (0.88)	$p = .001$	0.30 (0.81)	$p = .208$	-0.08 (1.13)	$p = .001$
Females	0.44 (1.03)		0.27 (1.09)		0.49 (0.82)		0.55 (1.05)	
Race/Ethnicity (n=188)								
Caucasian/Other	0.23 (0.99)	$p = .039$	0.04 (0.97)	$p = .026$	0.42 (0.78)	$p = .008$	0.33 (1.07)	$p = .079$
Hispanic	0.48 (1.15)		0.50 (1.27)		0.30 (0.93)		0.54 (1.04)	
Black	0.84 (1.04)		0.57 (1.26)		1.00 (0.77)		0.91 (1.28)	
Marital Status (n=196)								
Single or engaged	0.25 (0.95)	$p = .205$	0.15 (1.00)	$p = .251$	0.36 (0.82)	$p = .620$	0.46 (1.20)	$p = .038$
Married or cohabitating	0.27 (1.05)		0.07 (1.05)		0.47 (0.80)		0.29 (1.11)	
Divorced/ Widowed	0.60 (0.92)		0.41 (1.14)		0.49 (0.84)		0.79 (0.80)	
Employment Status (n=172)		$p = .023$		$p = .068$		$p = .394$		$p < .001$
Unemployed and disabled	0.42 (1.10)		0.31 (1.07)		0.48 (0.83)		0.57 (1.18)	
Unemployed and Not disabled/ Retired	0.45 (0.82)		0.08 (1.00)		0.43 (0.81)		0.74 (0.88)	
Employed Part-time	-0.09 (1.07)		-0.31 (1.03)		-0.03 (0.80)		-0.06 (1.35)	
Employed Full-time/Student	-0.08 (1.09)		-0.17 (1.09)		0.35 (0.84)		-0.13 (1.07)	
T25FW (n=193)	-------	$p < .001$	-------	$p < .001$	-------	$p = .016$	-------	$p < .001$

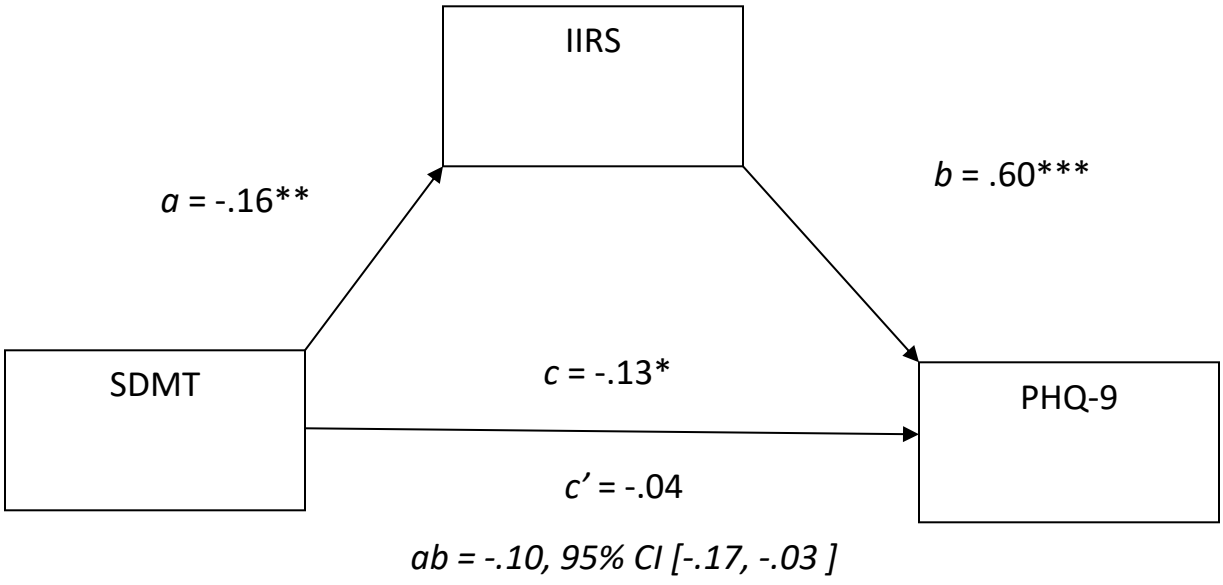
Cog. Impairment (1.5 SD below mean on 2 or more measures, n=199)								
Impaired	0.97 (0.90)	p = .029	1.03 (0.09)	p = .124	0.78 (0.07)	p = .006	1.12 (0.10)	p = .109
Not Impaired	1.07 (0.12)		1.11 (0.12)		0.83 (0.09)		1.06 (0.12)	
SDMT z score (n=199)	-------	p = .004	-------	p = .003	-------	p = .022	. -------	p = .006
PHQ-9 (n=199)	-------	p <.001	-------	p <.001	-------	p <.001	-------	p <.001
HADS A (n=199)	-------	p <.001	-------	p <.001	-------	p <.001	-------	p <.001
Mood Composite (n=199)	-------	p <.001	-------	p <.001	-------	p <.001	-------	p <.001

Main Analyses

Specific Aim 1 was to examine the relationships between processing speed, illness intrusiveness, and depression in an MS sample. The SDMT was significantly related to the PHQ-9, $r(184) = -.16$, $p = .025$, such that lower scores on the SDMT were related to elevated scores on the PHQ-9. Although there was a significant bivariate relationship between the SDMT and the IIRS such that poorer SDMT performance was associated with higher ratings on the IIRS, $r(198) = -.20$, $p = .004$, this relationship became non-significant after adjusting for demographic and disease variables impacting the IIRS, $r(146) = -.14$, $p = .085$. There was a significant indirect effect of the SDMT on the PHQ-9 through the IIRS (Figure 2), ab = -.07, 95% CI [-.15, -.002]. Poorer performance on the SDMT was associated with higher total scores on the IIRS, $a = -.12$, $p = .039$. Higher IIRS scores were associated with higher ratings on the PHQ-9, $b = .59$, $p <.001$. Although better performance on the SDMT was associated with lower levels of depression, $c = -.13$, $p = .025$, this relationship became non-significant when accounting for the mediator, $c' = -.06$, $p = .218$, which often is the case when a significant mediation has occurred.

Figure 1

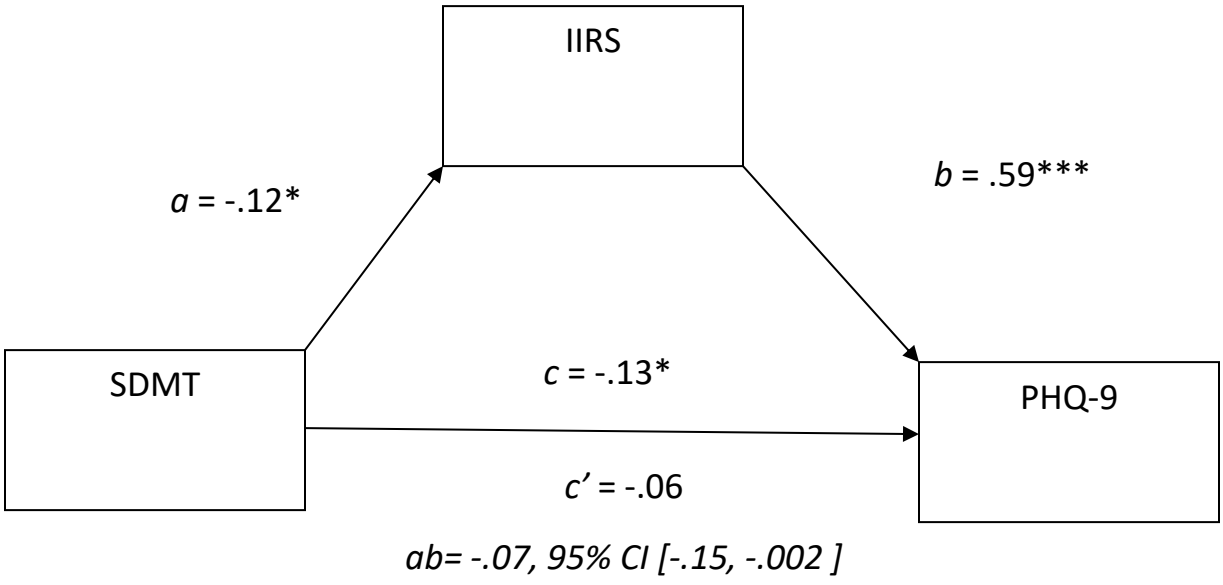
Unadjusted Mediation analysis of the Relationship Between the SDMT, IIRS, and PHQ-9 (n=198)



Note. * p < 0.05 ** p < 0.01 *** p< .001.

Figure 2

Adjusted Mediation analysis (including factors/covariates) of the Relationship Between the SDMT, IIRS, and PHQ-9 (n=190)

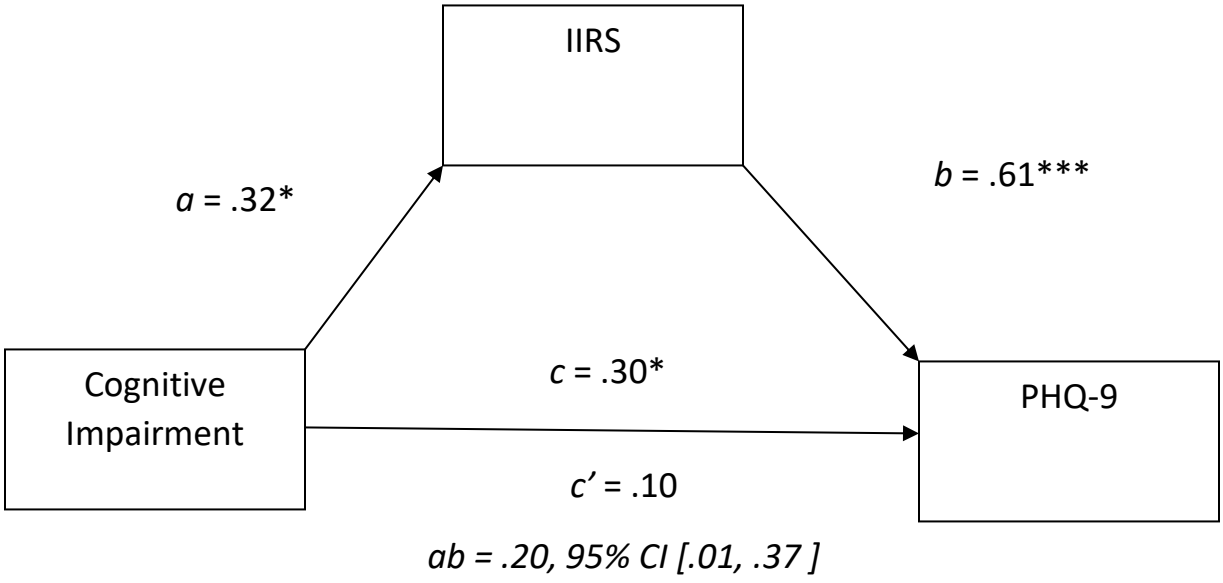


Note. * p < 0.05 ** p < 0.01 *** p< .001.

Specific Aim 2 was to examine the relationships between cognitive impairment, illness intrusiveness, and depression in an MS population. There was no significant difference between individuals with and without cognitive impairment for the PHQ-9, $t(184) = 2.29$, $p = .132$. There was also no significant difference between individuals with and without cognitive impairment on the IIRS total score, $t(154) = 0.55$, $p = 461$. Likewise, the indirect effect of cognitive impairment on the PHQ-9 through the IIRS was not significant, (Figure 4), ab = .14, 95% CI [-.04, .31].

Figure 3

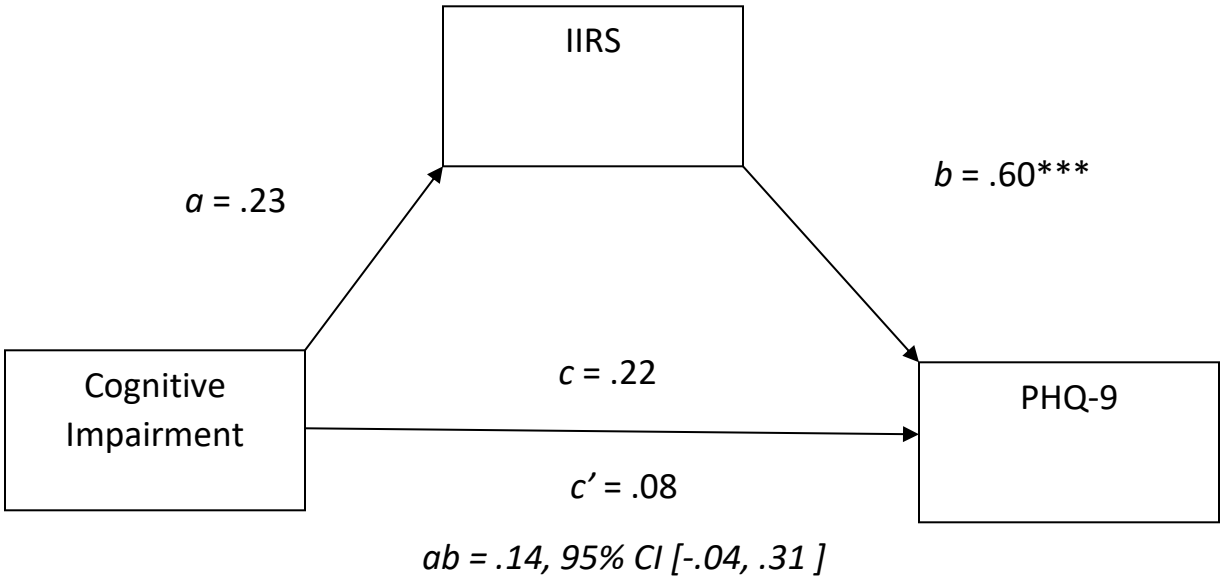
Unadjusted Mediation analysis of the Relationship Between Cognitive Impairment, the IIRS, and PHQ-9 (n=198)



Note. * p < 0.05 ** p < 0.01 *** p< .001.

Figure 4

Adjusted Mediation analysis (including factors/covariates) of the Relationship Between Cognitive Impairment, the IIRS, and PHQ-9 (n=190)



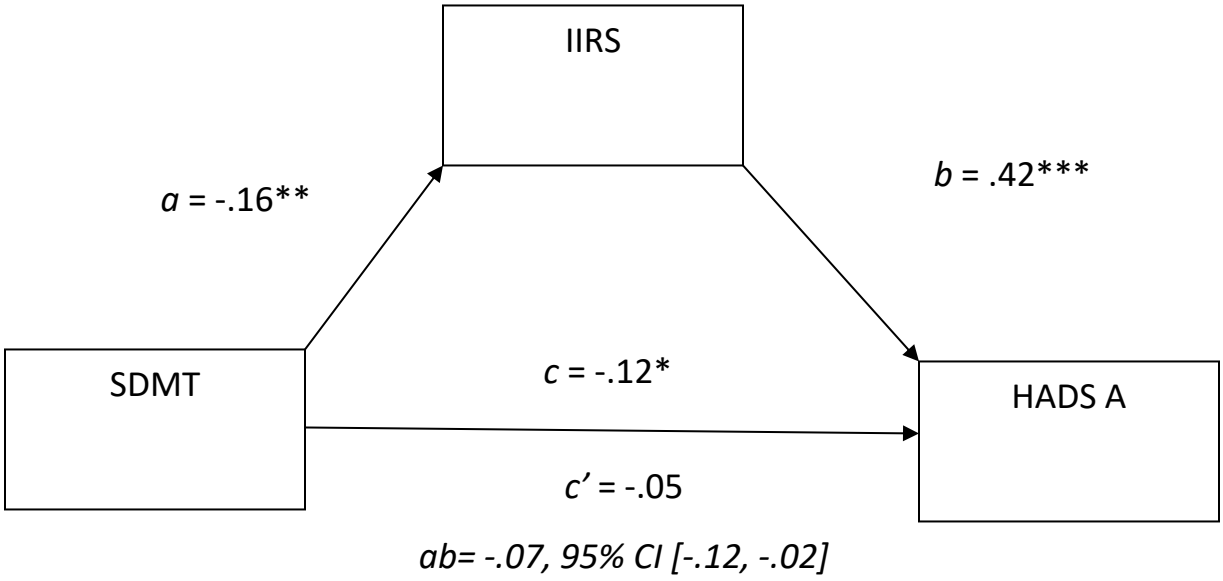
Note. * p < 0.05 ** p < 0.01 *** p< .001.

The third specific aim examined the relationships between processing speed, illness intrusiveness, and anxiety in an MS sample. There was a significant correlation between the SDMT and the HADS A, r (193) = -.16, p = .028, such that lower scores on the SDMT coincided with higher levels of anxiety reported on the HADS A. Although lower SDMT scores were associated with higher levels of illness intrusiveness, r(198) = -.20, p = .004, this relationship became non-significant after adjusting for demographic and disease variables impacting the IIRS, r(146) = -.14, p = .085. There was a significant indirect effect of the SDMT on the HADS A through the IIRS (Figure 6), ab = -.06, 95% CI [-.12, -.02]. Poorer performance on the SDMT led to higher total scores on the IIRS, a = -.16, p = .004. Higher IIRS scores were associated with higher ratings on the HADS A, b = .40, p <.001. Although higher scores on the SDMT were associated with lower levels of anxiety reported on the HADS A, c = -.12, p= .028, this

relationship became non-significant when accounting for the mediator, *c'* = -.05, *p* = .292, suggesting the present of a significant indirect effect.

Figure 5

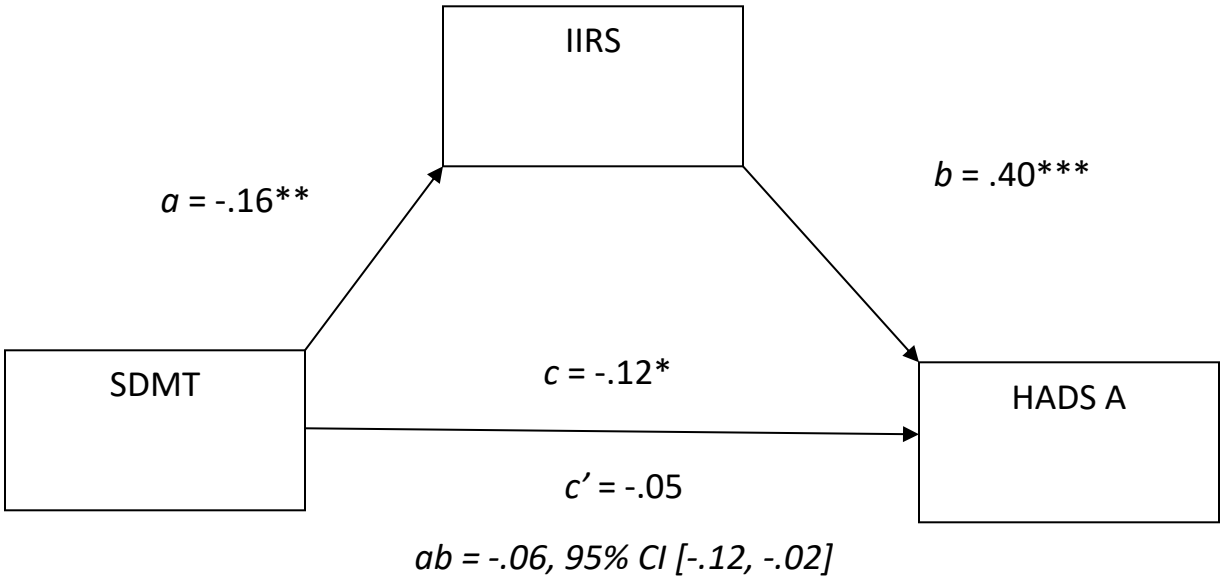
Unadjusted Mediation analysis of the Relationship Between the SDMT, IIRS, and HADS A (n=198)



Note. * p < 0.05 ** p < 0.01 *** p< .001.

Figure 6

Adjusted Mediation analysis (including factors/covariates) of the Relationship Between the SDMT, IIRS, and HADS A (n=197)

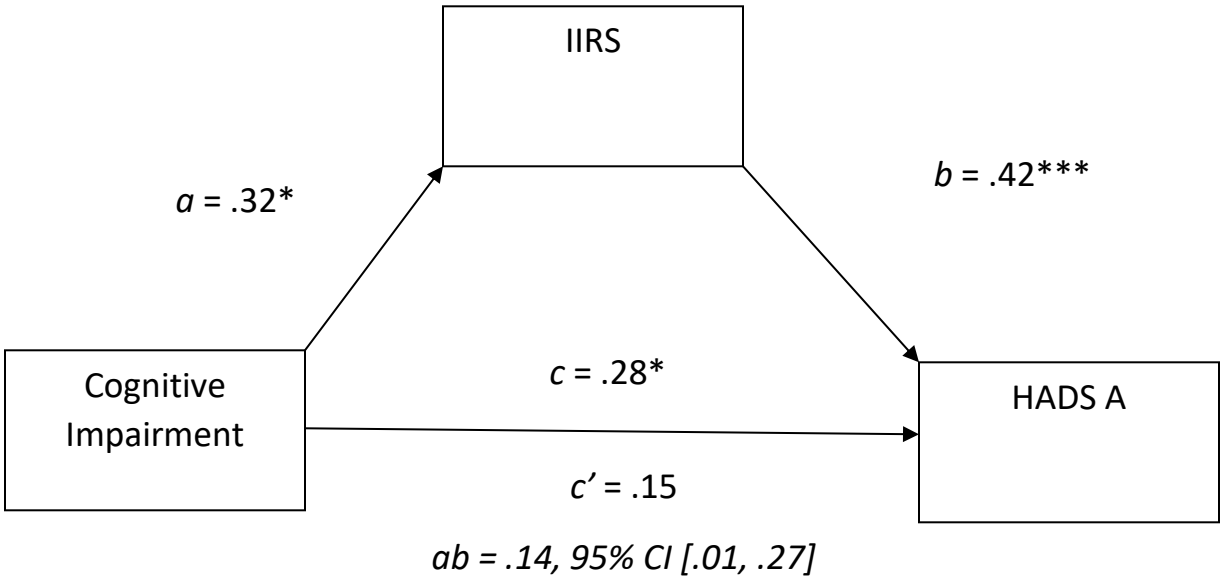


Note. * p < 0.05 ** p < 0.01 *** p< .001.

Specific Aim 4 explored the relationships between cognitive impairment, illness intrusiveness, and anxiety in an MS Sample. There was no significant difference between individuals with and without cognitive impairment for the HADS A, however it was trending significance, $t(193) = 3.83$, $p = .052$. There was also no significant difference between individuals with and without cognitive impairment on the IIRS total score, $t(154) = 0.55$, $p = 461$. Additionally, the indirect effect of cognitive impairment on the HADS A through the IIRS was not significant (Figure 8), ab = .14, 95% CI [-.04, .31].

Figure 7

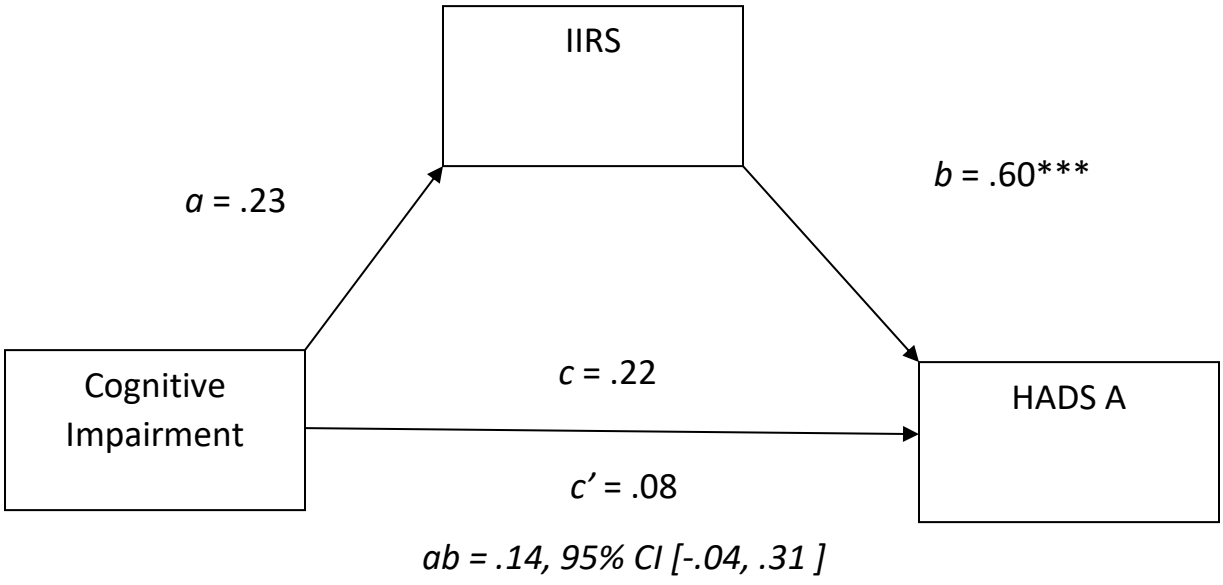
Unadjusted Mediation analysis of the Relationship Between Cognitive Impairment, the IIRS, and the HADS A (n=198)



Note. * p < 0.05 ** p < 0.01 *** p< .001.

Figure 8

Adjusted Mediation analysis (including factors/covariates) of the Relationship Between Cognitive Impairment, the IIRS, and the HADS A (n=190)



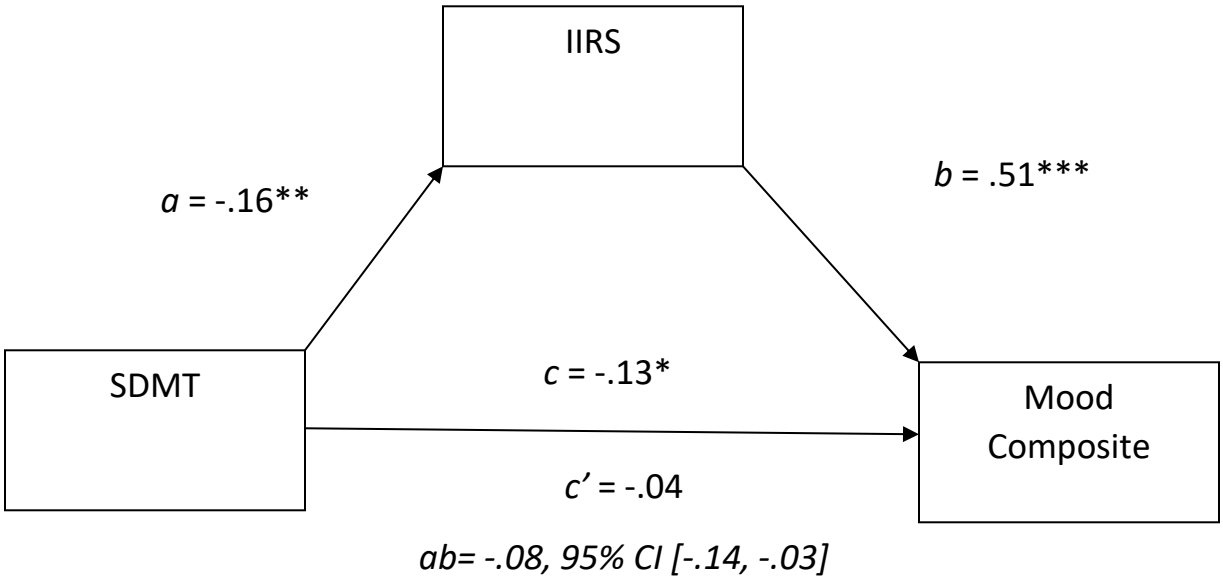
Note. * p < 0.05 ** p < 0.01 *** p< .001.

Exploratory Analyses

The first exploratory aim was to examine the interrelatedness of anxiety and depression in MS, and how they together impact cognitive functioning. The HADS A and PHQ-9 scores were highly correlated in the current sample of MS patients, $r(199) = .67$, $p<.001$. The SDMT was highly associated with the composite measure of depression and anxiety, $r(186) = -.19$, $p = .009$, such that lower scores on the SDMT were associated with higher ratings of depression and anxiety. There was a significant difference between cognitively impaired and non-impaired individuals on the composite measure of depression and anxiety, $t(186) = 4.36$, $p = .038$, with cognitively impaired individuals reporting more mood disturbance than their non-impaired counterparts. The IIRS was highly related to the mood composite measure, $r(187) = .58$, $p<.001$, with higher ratings on the IIRS leading to higher self-reported mood symptoms. Finally, there was a significant indirect effect of the SDMT on the mood composite through the IIRS (Figure 10), ab = -.08, 95% CI [-.13, -.0005]. Poorer performance on the SDMT led to higher total scores on the IIRS, $a = -.12$, $p = .042$. Higher IIRS scores were associated with higher mood composite scores, $b = .52$, $p <.001$. Although higher scores on the SDMT were associated with lower mood composite scores, $c = -.14$, $p= .009$, this relationship became non-significant when accounting for the mediator, $c' = -.08$, $p = .078$, suggesting a significant mediation has occurred.

Figure 9

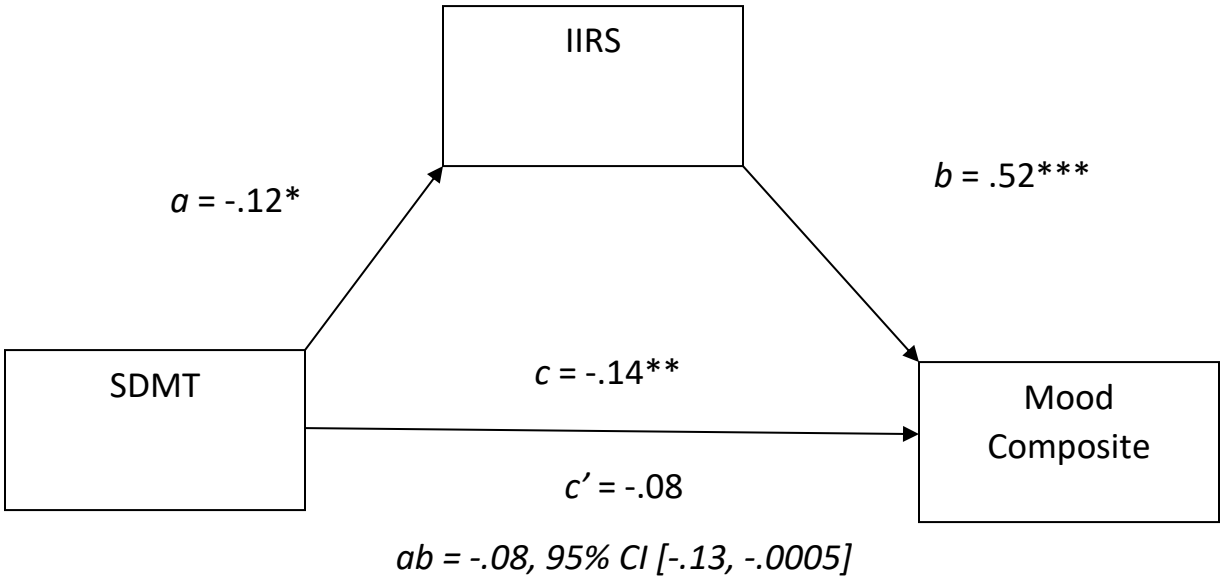
Unadjusted Mediation analysis of the Relationship Between the SDMT, IIRS, and the Mood Composite (n=198)



Note. * p < 0.05 ** p < 0.01 *** p< .001.

Figure 10

Adjusted Mediation analysis (including factors/covariates) of the Relationship Between the SDMT, IIRS, and the Mood Composite (n=191)

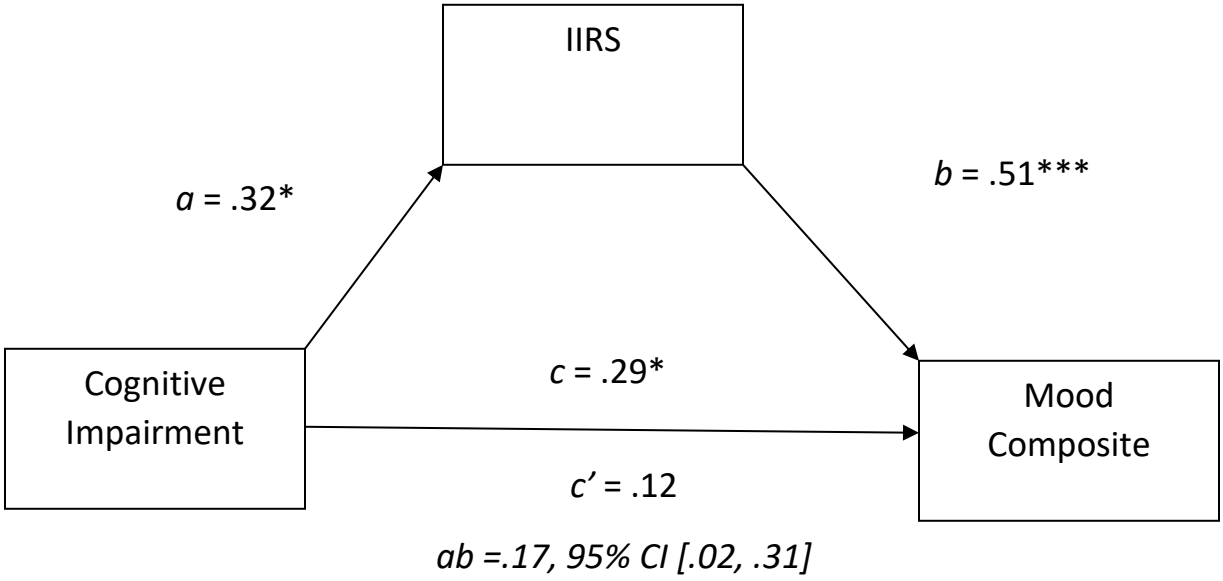


Note. * p < 0.05 ** p < 0.01 *** p< .001.

Cognitive impairment had a significant relationship with the mood composite, c = .27, p = .038, with higher levels of cognitive impairment associated with more mood symptoms. However, the indirect effect of cognitive impairment on the mood composite through the IIRS was not significant (Figure 12), ab = .12, 95% CI [-.03, .27].

Figure 11

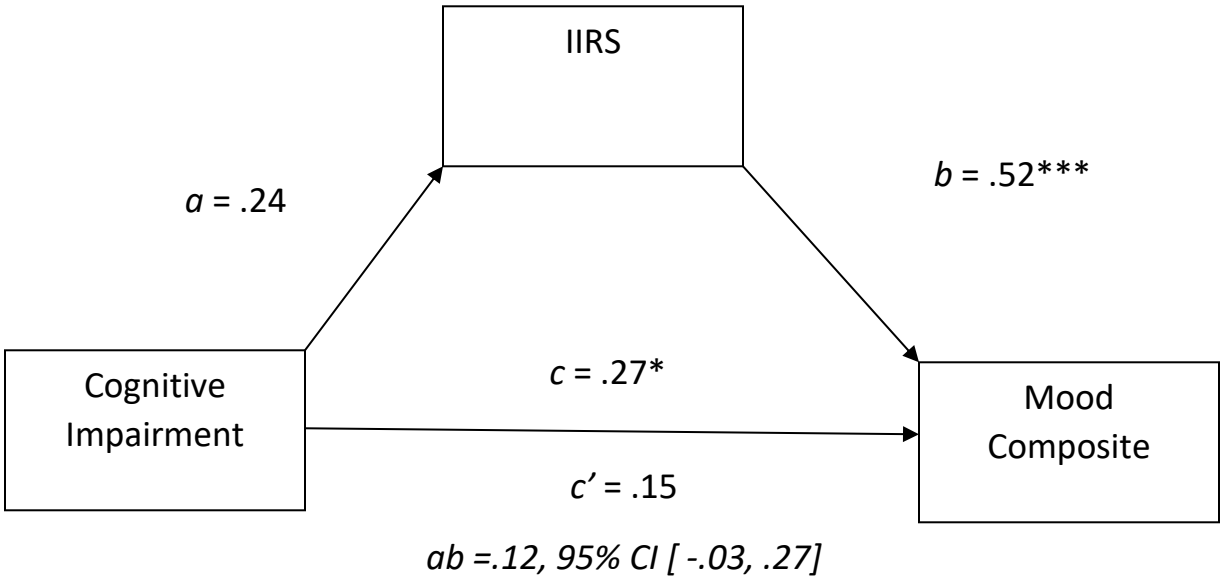
Unadjusted Mediation analysis of the Relationship Between Cognitive Impairment, the IIRS, and the Mood Composite (n=198)



Note. * p < 0.05 ** p < 0.01 *** p< .001.

Figure 12

Adjusted Mediation analysis (including factors/covariates) of the Relationship Between Cognitive Impairment, the IIRS, and the Mood Composite (n=191)



Note. * p < 0.05 ** p < 0.01 *** p< .001.

The second exploratory aim was to examine relationships between individual subscales of the Illness Intrusiveness Ratings Scale (IIRS), depression, anxiety, and cognitive functioning in MS. Higher ratings on the IIRS Relationship subscale were associated with higher PHQ-9 scores, $r(185) = .59$, $p<.001$. Higher ratings on the IIRS Intimacy subscale, $r_s(184) = .45$, $p<.001$, and on the IIRS Instrumental subscale, $r_s(185) = .52$, $p<.001$, were also related to significantly elevated symptoms on the PHQ-9.

Higher ratings on the IIRS Relationship subscale were associated with higher HADS A scores, $r(194) = .48$, $p<.001$. Higher ratings on the IIRS Intimacy subscale, $r_s(193) = .30$, $p<.001$, and the IIRS Instrumental subscale, $r_s(194) = .36$, $p<.001$, were also related to significantly elevated symptoms on the HADS A.

Higher ratings on the IIRS Relationship subscale, $r(174) = -.15$, $p = .048$, and the IIRS Intimacy subscale, $r_s(154) = -.07$, $p = .407$, were significantly related to poorer performance on the SDMT. The IIRS Instrumental subscale was not significantly related to performance on the SDMT, $r_s(154) = -.06$, $p = .461$.

Cognitively impaired individuals and those without impairment did not significantly differ on the IIRS Relationship subscale, $b = .20$, Wald $\chi 2(1) = 2.02$, $p = .155$. However, cognitively impaired individuals endorsed significantly higher ratings on the IIRS Intimacy subscale than those without impairment, $b = .43$, Wald $\chi 2(1) = 4.93$, $p = .026$. Cognitively impaired individuals and those without impairment did not significantly differ on the IIRS Instrumental subscale, $b = .17$, Wald $\chi 2(1) = 1.52$, $p = .218$.

Chapter IV- Discussion

Summary

The first aim was to examine the relationships between processing speed, illness intrusiveness, and depression in a sample of MS patients. Slower processing speed was associated with elevated levels of depression as well as increased illness intrusiveness. Illness intrusiveness was also shown to mediate the relationship between processing speed and depression in people with MS.

The second aim was to examine the relationships between cognitive impairment, illness intrusiveness, and depression. No significant relationship was found between cognitive impairment and depression or cognitive impairment and illness intrusiveness. Illness intrusiveness was also not a significant mediator of the relationship between cognitive impairment and depression.

The third aim looked at anxiety and how it related to processing speed and illness intrusiveness. Processing speed was associated with both illness intrusiveness and anxiety. Illness intrusiveness was also shown to mediate the relationship between processing speed and anxiety.

The fourth aim examined anxiety, cognitive impairment, and illness intrusiveness. There was no significant relationship between cognitive impairment and anxiety or cognitive impairment and illness intrusiveness. Illness intrusiveness was also not a significant mediator of the relationship between cognitive impairment and anxiety.

The first exploratory aim pooled anxiety and depression measures together to create a general mood measure; this was done to explore how mood impacts illness intrusiveness and cognition in MS. As expected, anxiety and depression were found to be highly related in the current MS sample. Impaired processing speed, cognitive impairment, and higher levels of illness intrusiveness were all related to elevated mood symptoms. A significant relationship was demonstrated between processing speed and mood through illness intrusiveness. However, illness intrusiveness was not a significant mediator in the relationship between cognitive impairment and mood.

The second exploratory aim pertains to exploring the individual subscales of the IIRS and how they relate to the cognitive and mood variables of the study. All subscales were related to mood, such that higher ratings on the subscales were associated with higher levels of depression and anxiety. Higher relationship intrusiveness was related to impairments in processing speed. Finally, individuals with cognitive impairment reported higher intimacy intrusiveness than their non-impaired counterparts.

Conclusions

The primary finding of this study is that impairments in processing speed appear to be related to mood symptoms in people with MS, and that illness intrusiveness was associated with both of these variables and mediated this relationship. These results therefore suggest that illness intrusiveness may be a pathway by which slowed processing speed impacts mood in these patients. This study also found that more general cognitive impairment did not have a significant relationship with either illness intrusiveness or mood symptoms.

There are several potential explanations for these important findings. Processing speed is the cognitive ability most frequently impacted in MS, and has been shown to underlie cognitive impairments in other domains (Benedict et al., 2017; Vissicchio et al., 2018). Processing speed is also the cognitive ability most commonly impacted early in the MS disease process (Kim et al., 2017). Thus, impairments in information processing speed tend to impact MS patients during a period in their lives that is crucial for both career and personal development, which is why research has found links between processing speed and employment status (Benedict et al., 2017). This was demonstrated in one study which followed a sample of MS patients who were working full-time at baseline over a period of 3.5 years. Declines of 4 raw score points or more from baseline on the SDMT were the single strongest discriminator of employed vs. disabled individuals at followup (Morrow et al., 2010). In the present study, when only including MS patients age 45 and younger in the analyses, the SDMT was the only cognitive test that was significantly related to employment status, $F(4, 56) = 2.76$, $p = .036$. People age 45 and younger who were employed full-time performed significantly better on the SDMT than people who were unemployed and not receiving disability, $p = .046$. This finding suggests that processing speed is

the cognitive ability that impacts employment status earliest in the disease process, which may be part of the reason processing speed impairment is often perceived as intrusive.

Several studies in MS patients have also shown that processing speed impairments tend to correlate very strongly with changes in functional status. One study found processing speed impairment to correlate strongly with impairments in IADLs, such as medication management, bill payment, and cooking (Kalmar et al., 2008). Another MS study found processing speed to be the only cognitive domain that was associated with performance on the Timed Instrumental Activity of Daily Living measure (Goverover et al., 2007). Given the prevalence of processing speed impairment in MS, its timing early on in life, and its ability to impede a patient's independence, it is likely to be perceived as more intrusive than impairments in other cognitive abilities in patients with MS.

An interesting finding that may also help explain these study findings is that increasing age was significantly related to lower levels of illness intrusiveness, as well as less anxiety and depression. This has also been found in other studies in MS (Devins et al., 1996; Stern et al., 2018). The authors of these studies concluded that older MS patients have learned more adaptive ways to cope with their MS symptoms, and as a result view their MS as less intrusive, leading to lower levels of emotional distress. Thus, part of the processing speed and illness intrusiveness connection may be that younger individuals with MS afflicted by their first cognitive problem, slowed processing speed, may not yet possess the resources to cope with this change in their cognitive functioning and any resulting declines in functional capacity. Cognitive impairment in other domains tend to appear later on in the life of MS patients, presumably when they have already developed adequate coping strategies for handling cognitive deterioration. This, in turn,

allows these older MS patients to view their cognitive impairment in a less intrusive light, and can protect them from emotional distress.

Another potential explanation for why processing speed but not general cognitive impairment was found to be intrusive and related to mood disturbance was due to the prevalence of cognitive impairment in the current MS sample. The prevalence of cognitive impairment in the current sample was 40.9%. However, the rates of cognitive impairment in other MS samples have reached almost 70% (Grzegorski & Losy, 2017; Julian, 2011), suggesting that the current study's sample was a less cognitively impaired sample than the general MS population. This is likely due to the nature of referral questions; patients were referred for testing to evaluate cognitive and emotional problems, as well as to acquire baseline cognitive profiles on new patients.

Implications for Treatment

There are several important treatment implications. One important consideration pertains to neuropsychologists conducting evaluations on MS patients. During their clinical interview, it is important for neuropsychologists to not only assess how cognitive impairment has impacted activities patients have to do (ie., ADLs and IADLs), but also activities they want to do. This includes determining how cognitive impairments have impacted their MS patients' relationships, goals, hobbies, and recreational activities. Neuropsychologists really need to assess how cognitive impairment is impeding MS patients from pursuing activities they used to enjoy, as this can have a profound impact on their mood. This information underscores the importance of a neuropsychological evaluation for identifying interconnections between these variables, and to determine appropriate treatments to address these factors.

Since these studies found strong associations among cognition, illness intrusiveness, and mood, it is important to consider interventions that can target these variables. Cognitive impairments are often difficult to directly address. Cognitive rehabilitation is often attempted to address difficulties with specific cognitive impairments, however research on the efficacy of cognitive rehabilitation in MS has been mixed at best (see Mitolo et al., 2015 for a review). The cognitive rehabilitation literature in MS has been flawed due to heterogenous methodologies for approaching cognitive rehabilitation interventions, small sample sizes, and insufficient outcome measures. Older studies attempted to improve learning and memory, and were often not successful at this. More recent cognitive rehabilitation studies in the MS literature have become more targeted and have instead focused on different cognitive functions such as executive functions, attention and processing speed, which have yielded better outcomes and more consistent findings (Mitolo et al., 2015).

Mood disturbance and perceived illness intrusiveness may also be directly targeted through psychotherapy. The effectiveness of psychotherapy, especially evidence-based therapies such as cognitive behavioral therapy (CBT), for treatment of anxiety and depression in MS has been well-established with strong effect sizes (see Fiest et al., 2016 for a review). Mood disturbance therefore appears to be more modifiable and easier to treat than cognitive impairment. However, depression and anxiety appear to be more distal outcomes, and interventions may be better suited for targeting more concrete, proximal constructs such as the perceived intrusiveness of a disease. Although psychotherapy for addressing perceived illness intrusiveness has not been researched to date in MS, research has found psychotherapy to be effective at reducing illness intrusiveness in other chronic diseases such as lupus, in which a group supportive psychotherapy intervention was more effective than a

treatment as usual control group at reducing subjective illness intrusiveness (Edworthy et al., 2003). Another study found a brief CBT intervention to be more effective than usual care at reducing illness intrusiveness in patients with chronic obstructive pulmonary disease (Renn et al., 2018). Research has also discovered that CBT can lead to enhancements in cognitive functioning as well as improvements in mood (He et al., 2019), and that improvements in depressive symptoms can lead to improvements in cognitive functioning over time (Douglas & Porter, 2009). Therefore, evidence from research has demonstrated that psychotherapy can be an effective intervention for not only enhancing mood, but also reducing perceived illness intrusiveness and enhancing cognitive functioning, and should be a primary treatment recommendation for people with MS.

This study also provides support for psychotherapy as an important treatment recommendation for younger MS patients with processing speed impairments. Psychotherapy from a CBT perspective can help patients learn more adaptive ways of viewing their chronic disease. More adaptive coping strategies may be taught in order to help patients perceive their MS as being less intrusive, and help them regain a sense of personal control over their lives. Since cognitively impaired individuals may have difficulty learning these strategies, repetition and additional instruction will be important to ensure comprehension.

Although research on cognitive rehabilitation has been mixed in MS as stated above, there has been some good evidence to support cognitive rehabilitation for enhancing processing speed deficits specifically in MS (Gich et al., 2014; Giglio et al., 2014; Mattioli et al., 2016). Since this study has found processing speed impairment to be closely linked to both illness intrusiveness and mood, enhancing processing speed may in turn lead to improvements in mood by reducing the patient's perception of the intrusiveness of their MS.

This will be especially important for younger individuals with MS who see their MS as more intrusive.

This study also underscores the importance of taking a comprehensive, multidisciplinary approach to patient care in MS. The MS disease process is very complex and causses primary impairments related to the disease process itself, such as cognitive impairment and physical disability, as well as secondary and tertiary factors such as illness intrusiveness and depression (Fletcher et al., 2009). The best approach to patient care involves taking a holistic approach that addresses all of these factors while employing the combined expertise and shared collaboration of many disciplines, including neurologists, urologists, nurses, social workers, occupational and physical therapists, psychologists, and neuropsychologists. This multidisciplinary treatment approach can ensure that all symptoms of MS are addressed, and can help determine how these various factors interact in people with MS.

Limitations

There were several limitations in the current study. The first limitation is that the design was not longitudinal in nature. Although important relationships among study variables have been established, there is no way to determine causality or the temporal order of the variables from a cross-sectional design. Thus, asking whether cognitive impairment precedes depression in MS or vice versa cannot be answered unless the study design is altered to be longitudinal rather than cross-sectional. According to Andrew Hayes, the author of the Process mediation analysis, determining causality or the temporal sequence of variables should not be the goal of mediation. The goal of a mediation analysis should be to begin to understand important relationships among variables (Hayes, 2013), which was accomplished

by the current study. The other limitation relating to study design pertains to the lack of a control group. However, since illness intrusiveness as a construct could not be measured in a non-disease population, inclusion of a "healthy" control group would not be feasible for this study.

Some study limitations pertain to the measures used. Clinically significant depression and anxiety was determined based on self-reports. This meant that the level of depression and anxiety was related to subjective patient report rather than more objective, clinician-administered measures. However, it is also important to note that even clinician interviews rely on patient's self-reported symptoms. The mood composite z score was based on several different mood measures. It is possible that these mood measures may have estimated depression and anxiety in slightly different ways, although it is important to note that these measures were highly correlated. The correlation between the HADS A and PHQ-9 was r=.67, p<.001. Another limitation pertains to the primary cognitive outcome measure, the SDMT. Although the oral version of the SDMT is able to remove the graphomotor component of this processing speed task, it still includes an oral motor component. Since oral motor disability is also common in MS, it may have also made sense to adjust for oral motor disability (Arnett et al., 2008).

There were several other notable limitations. MS subtype and time since MS diagnosis was not adjusted for in the current study, although lower motor disability was accounted for in this study. Additionally, the current study was conducted on a single MS sample from a tertiary care MS Center. Thus, the results of the current study may not be generalizable to all MS samples. The majority of patients were also usually referred by their neurologists for cognitive reasons. The study population therefore may not be adequately representative of a

random community sample of MS patents. However, it is notable that the percent of patients with cognitive impairment in the current sample was lower than the percent observed in other studies. Although most patients are referred by neurologists for cognitive complaints, many patients have minimal cognitive complaints and are referred by their neurologists to obtain a cognitive baseline. Therefore, the current study sample may be more reflective of the general MS population than samples used in other studies where the percent of cognitive impairment has been higher.

Another limitation is how cognitive impairment was defined. Although commonly defined in the MS literature as 2 or more cognitive tests < 1.5 SD from the mean, this is an arbitrary definition, as cognitive abilities vary widely in the general population, with most persons demonstrating relative strengths and weaknesses (Binder et al., 2009; Parmenter et al., 2007).

Future Directions

There are a variety of potential future directions to expand upon the findings of the current study. Since research has demonstrated the efficacy of psychotherapeutic interventions at reducing illness intrusiveness in other chronic diseases such as lupus and COPD (Edworthy et al., 2003; Renn et al., 2018), this type of intervention should also be conducted in MS. These two studies also did not appear to directly target illness intrusiveness in chronic disease, but targeted mood more generally and then looked at the effect it had on illness intrusiveness. An intervention designed to reduce perceptions of the perceived intrusiveness of a chronic disease may be more effective at reducing illness intrusiveness than the more general CBT and group psychotherapy techniques employed in the aforementioned studies in lupus and COPD. This study can also examine the efficacy of this

targeted intervention at reducing not only illness intrusiveness, but also mood disturbance and cognitive impairment over time.

Another important future direction would be to look at the relationships between study variables longitudinally. This type of study could clarify the temporal order of relationships between cognition, illness intrusiveness, and mood in MS. A cognitive rehabilitation study could be an interesting way to longitudinally examine the study variables. In this study, the patients' baseline levels of cognitive impairment, illness intrusiveness, and mood symptoms would be recorded. Once the efficacy of the intervention for enhancing cognitive functioning has been established, the intervention group's change in illness intrusiveness and mood over the course of the study could be compared to an active control group. This could help determine if enhancing cognition could in turn lead to reductions in illness intrusiveness and improvements in mood. Another potential idea would be a longitudinal cohort study of MS patients in which baseline evaluations would be used to determine levels of baseline cognitive impairment. Serial evaluations would then be conducted with several years between follow-ups. Changes in illness intrusiveness and mood could be compared between the group that was cognitively impaired at baseline and the group that was cognitively intact at baseline. These two potential longitudinal studies could help clarify if there is a temporal order of causality among the study variables.

Another potential future direction involves examining additional variables that can help explain relationships among variables that were observed in the present study. Since the IIRS taps into perceived rather than objective illness intrusiveness, it is unclear what factors influence this subjective perception of disease-related intrusiveness. One study found maladaptive coping to mediate the relationship between disease severity and illness

intrusiveness among chronically ill patients (Hundt et al., 2013). Several studies conducted in MS patients have also found coping styles to mediate the relationship between cognitive impairment and depressive symptoms (Arnett et al., 2002; Rabinowitz & Arnett, 2009). Thus, future research may examine coping style as a potential moderator of the relationship between cognitive impairment and illness intrusiveness in MS samples. Future studies may also want to consider additional cognitive abilities impacted by MS, such as executive functions and visual learning and memory (Trenova et al., 2016). These cognitive abilities should be examined individually in future research, rather than included with other functions in a cognition composite score or a dichotomous category of cognitive impairment. This can help determine the individual contributions of various types of cognitive impairments commonly seen in MS to illness intrusiveness and mood disturbance.

Other possible future directions for research pertain to looking at different types of MS populations and determining if the findings of the current study differ by MS subtype. It would also be interesting to see if the main findings of the present study could be replicated in other MS populations in different regions of the country, or in different parts of the world. This study could also be conducted in other disease populations in which the IIRS has been validated and in which cognitive impairment and mood disturbance are common, such as in patients with systemic lupus erythematosus or epilepsy (Devins, 2010).

Concluding paragraph

The primary aim of this study was to determine relationships between cognitive impairment, illness intrusiveness, and mood disturbance in people with MS. Although connections between cognition and mood have been well-established in the MS literature, potential mechanisms for this relationship had yet to be explored. Illness intrusiveness, or the

degree to which an illness and/or its treatment interferes with previously valued activities and interests, was postulated to be one such mechanism. This study found illness intrusiveness to be significantly associated with processing speed impairment and mood disturbance in people with MS. This study also determined that processing speed deficits may be related to mood disturbance in part due to the perceived intrusiveness of the MS disease process. Future research should develop psychotherapeutic interventions that specifically target illness intrusiveness in MS, as this may in turn lead to enhancements in mood and improvements in cognitive functioning.

References

Albert, M., Antel, J., Brück, W., & Stadelmann, C. (2007). Extensive cortical remyelination in patients with chronic multiple sclerosis. *Brain Pathology (Zurich, Switzerland)*, *17*(2), 129–138. https://doi.org/10.1111/j.1750-3639.2006.00043.x

Alonso, A., & Hernán, M. A. (2008). Temporal trends in the incidence of multiple sclerosis: A systematic review. *Neurology*, *71*(2), 129–135. https://doi.org/10.1212/01.wnl.0000316802.35974.34

Alsaadi, T., Hammasi, K. E., Shahrour, T. M., Shakra, M., Turkawi, L., Nasreddine, W., Kassie, S., & Raoof, M. (2017). Depression and anxiety as determinants of health-related quality of life in patients with multiple sclerosis—United Arab Emirates. *Neurology International*, *9*(4). https://doi.org/10.4081/ni.2017.7343

Amato, M P, Ponziani, G., Rossi, F., Liedl, C. L., Stefanile, C., & Rossi, L. (2001). Quality of life in multiple sclerosis: The impact of depression, fatigue and disability. *Multiple Sclerosis Journal*, *7*(5), 340–344. https://doi.org/10.1177/135245850100700511

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*(10), 1602–1606.

Amato, Maria P., Portaccio, E., Goretti, B., Zipoli, V., Iudice, A., Della Pina, D., Malentacchi, G., Sabatini, S., Annunziata, P., Falcini, M., Mazzoni, M., Mortilla, M., Fonda, C., De Stefano, N., & TuSCIMS Study Group. (2010). Relevance of cognitive deterioration in early relapsing-remitting MS: A 3-year follow-up study. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *16*(12), 1474–1482. https://doi.org/10.1177/1352458510380089

Amtmann, D., Kim, J., Chung, H., Bamer, A. M., Askew, R. L., Wu, S., Cook, K. F., & Johnson, K. L. (2014). Comparing CESD-10, PHQ-9, and PROMIS depression instruments in individuals with multiple sclerosis. *Rehabilitation Psychology*, *59*(2), 220–229. https://doi.org/10.1037/a0035919

Antony, M. M., Roth, D., Swinson, R. P., Huta, V., & Devins, G. M. (1998). Illness Intrusiveness in Individuals with Panic Disorder, Obsessive-Compulsive Disorder, or Social Phobia: *The Journal of Nervous & Mental Disease*, *186*(5), 311–315. https://doi.org/10.1097/00005053-199805000-00008

Arnett, P. A., Higginson, C. I., Voss, W. D., Randolph, J. J., & Grandey, A. A. (2002). Relationship Between Coping, Cognitive Dysfunction and Depression in Multiple Sclerosis. *The Clinical Neuropsychologist*, *16*(3), 341–355. https://doi.org/10.1076/clin.16.3.341.13852

Arnett, P. A., Smith, M. M., Barwick, F. H., Benedict, R. H. B., & Ahlstrom, B. P. (2008). Oralmotor slowing in multiple sclerosis: Relationship to neuropsychological tasks requiring an oral response. *Journal of the International Neuropsychological Society: JINS*, *14*(3), 454–462. https://doi.org/10.1017/S1355617708080508

Askari, F., Ghajarzadeh, M., Mohammadifar, M., Azimi, A., Sahraian, M. A., & Owji, M. (2014). Anxiety in patients with multiple sclerosis: Association with disability, depression, disease type and sex. *Acta Medica Iranica*, *52*(12), 889–892.

Baecher-Allan, C., Kaskow, B. J., & Weiner, H. L. (2018). Multiple Sclerosis: Mechanisms and Immunotherapy. *Neuron*, *97*(4), 742–768. https://doi.org/10.1016/j.neuron.2018.01.021

Bamer, A., Amtmann, D., Ehde, D., & Johnson, K. (2008). Anxiety in multiple sclerosis: Prevalence and associated factors in a large community sample. *Multiple Sclerosis*, *14*(S1), S155.

Bar-Or, A., Fawaz, L., Fan, B., Darlington, P. J., Rieger, A., Ghorayeb, C., Calabresi, P. A., Waubant, E., Hauser, S. L., Zhang, J., & Smith, C. H. (2010). Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS? *Annals of Neurology*, *67*(4), 452–461. https://doi.org/10.1002/ana.21939

Basso, M. R., Bornstein, R. A., & Lang, J. M. (1999). Practice effects on commonly used measures of executive function across twelve months. *The Clinical Neuropsychologist*, *13*(3), 283–292. https://doi.org/10.1076/clin.13.3.283.1743

Batista, S., Zivadinov, R., Hoogs, M., Bergsland, N., Heininen-Brown, M., Dwyer, M. G., Weinstock-Guttman, B., & Benedict, R. H. B. (2012). Basal ganglia, thalamus and neocortical atrophy predicting slowed cognitive processing in multiple sclerosis. *Journal of Neurology*, *259*(1), 139–146. https://doi.org/10.1007/s00415-011-6147-1

Baumstarck-Barrau, K., Simeoni, M.-C., Reuter, F., Klemina, I., Aghababian, V., Pelletier, J., & Auquier, P. (2011). Cognitive function and quality of life in multiple sclerosis patients: A cross-sectional study. *BMC Neurology*, *11*, 17. https://doi.org/10.1186/1471-2377-11-17

Beaudreau, S. A., & O'Hara, R. (2008). Late-life anxiety and cognitive impairment: A review. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry*, *16*(10), 790–803. https://doi.org/10.1097/JGP.0b013e31817945c3

Beck, J. S. (2011). *Cognitive behavior therapy: Basics and beyond, 2nd ed*. Guilford Press.

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

Benedict, R. H. B. (1997). *Brief Visuospatial Memory Test Revised Professional Manual*. Psychological Assessment Resources.

Benedict, R. H. B., Ramasamy, D., Munschauer, F., Weinstock-Guttman, B., & Zivadinov, R. (2009). Memory impairment in multiple sclerosis: Correlation with deep grey matter and mesial temporal atrophy. *Journal of Neurology, Neurosurgery, and Psychiatry*, *80*(2), 201–206. https://doi.org/10.1136/jnnp.2008.148403

Benedict, Ralph H. B., Bakshi, R., Simon, J. H., Priore, R., Miller, C., & Munschauer, F. (2002). Frontal cortex atrophy predicts cognitive impairment in multiple sclerosis. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *14*(1), 44–51. https://doi.org/10.1176/jnp.14.1.44

Benedict, Ralph H. B., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., & Weinstock-Guttman, B. (2006). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society: JINS*, *12*(4), 549–558.

Benedict, Ralph H. B., DeLuca, J., Enzinger, C., Geurts, J. J. G., Krupp, L. B., & Rao, S. M. (2017). Neuropsychology of Multiple Sclerosis: Looking Back and Moving Forward. *Journal of the International Neuropsychological Society: JINS*, *23*(9–10), 832–842. https://doi.org/10.1017/S1355617717000959

Benedict, Ralph H. B., Fischer, J. S., Archibald, C. J., Arnett, P. A., Beatty, W. W., Bobholz, J., Chelune, G. J., Fisk, J. D., Langdon, D. W., Caruso, L., Foley, F., LaRocca, N. G.,

Vowels, L., Weinstein, A., DeLuca, J., Rao, S. M., & Munschauer, F. (2002). Minimal neuropsychological assessment of MS patients: A consensus approach. *The Clinical Neuropsychologist*, *16*(3), 381–397. https://doi.org/10.1076/clin.16.3.381.13859

Benedict, Ralph HB, DeLuca, J., Phillips, G., LaRocca, N., Hudson, L. D., & Rudick, R. (2017). Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *23*(5), 721–733. https://doi.org/10.1177/1352458517690821

Benedict, Ralph Hb, Drake, A. S., Irwin, L. N., Frndak, S. E., Kunker, K. A., Khan, A. L., Kordovski, V. M., Motl, R. W., & Weinstock-Guttman, B. (2016). Benchmarks of meaningful impairment on the MSFC and BICAMS. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *22*(14), 1874–1882. https://doi.org/10.1177/1352458516633517

Bennett, S., & Thomas, A. J. (2014). Depression and dementia: Cause, consequence or coincidence? *Maturitas*, *79*(2), 184–190. https://doi.org/10.1016/j.maturitas.2014.05.009

Benton, A. (1994). *PAR | Contributions to Neuropsychological Assessment—A Clinical Manual*. https://www.parinc.com/Products/Pkey/64

Berg, D., Supprian, T., Thomae, J., Warmuth-Metz, M., Horowski, A., Zeiler, B., Magnus, T., Rieckmann, P., & Becker, G. (2000). Lesion pattern in patients with multiple sclerosis and depression. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *6*(3), 156–162. https://doi.org/10.1177/135245850000600304

Berkowitz, R. L., Coplan, J. D., Reddy, D. P., & Gorman, J. M. (2007). The human dimension: How the prefrontal cortex modulates the subcortical fear response. *Reviews in the Neurosciences*, *18*(3–4), 191–207.

Bieling, P. J., Rowa, K., Antony, M. M., Summerfeldt, L. J., & Swinson, R. P. (2001). Factor Structure of the Illness Intrusiveness Rating Scale in Patients Diagnosed with Anxiety Disorders. *Journal of Psychopathology and Behavioral Assessment*, *23*(4), 223–230. https://doi.org/10.1023/A:1012723318964

Binder, L. M., Iverson, G. L., & Brooks, B. L. (2009). To err is human: "abnormal" neuropsychological scores and variability are common in healthy adults. *Archives of Clinical Neuropsychology : The Official Journal of the National Academy of Neuropsychologists*. https://doi.org/10.1093/arclin/acn001

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

Bouchard, V., Duquette, P., & Mayo, N. E. (2017). Path to Illness Intrusiveness: What Symptoms Affect the Life of People Living With Multiple Sclerosis? *Archives of Physical Medicine and Rehabilitation*, *98*(7), 1357–1365. https://doi.org/10.1016/j.apmr.2017.03.012

Brownlee, W. J., Hardy, T. A., Fazekas, F., & Miller, D. H. (2017). Diagnosis of multiple sclerosis: Progress and challenges. *Lancet (London, England)*, *389*(10076), 1336–1346. https://doi.org/10.1016/S0140-6736(16)30959-X

Bruce, A. S., & Arnett, P. A. (2008). Longitudinal Study of the Symptom Checklist 90-Revised in Multiple Sclerosis Patients. *The Clinical Neuropsychologist*, *22*(1), 46–59. https://doi.org/10.1080/13854040601064518

Butler, E., Matcham, F., & Chalder, T. (2016). A systematic review of anxiety amongst people with Multiple Sclerosis. *Multiple Sclerosis and Related Disorders*, *10*, 145–168. https://doi.org/10.1016/j.msard.2016.10.003

Chan, C. K., Tian, F., Pimentel Maldonado, D., Mowry, E. M., & Fitzgerald, K. C. (2020). Depression in multiple sclerosis across the adult lifespan. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, 1352458520979304. https://doi.org/10.1177/1352458520979304

Chen, A. Y., Chonghasawat, A. O., & Leadholm, K. L. (2017). Multiple sclerosis: Frequency, cost, and economic burden in the United States. *Journal of Clinical Neuroscience*, *45*, 180–186. https://doi.org/10.1016/j.jocn.2017.06.005

Chen, S.-Y., Jordan, C., & Thompson, S. (2006). The Effect of Cognitive Behavioral Therapy (CBT) on Depression: The Role of Problem-Solving Appraisal. *Research on Social Work Practice*, *16*(5), 500–510. https://doi.org/10.1177/1049731506287302

Chiaravalloti, N. D., Moore, N. B., Nikelshpur, O. M., & DeLuca, J. (2013). An RCT to treat learning impairment in multiple sclerosis: The MEMREHAB trial. *Neurology*, *81*(24), 2066–2072. https://doi.org/10.1212/01.wnl.0000437295.97946.a8

Comi, G., Radaelli, M., & Soelberg Sørensen, P. (2017). Evolving concepts in the treatment of relapsing multiple sclerosis. *Lancet (London, England)*, *389*(10076), 1347–1356. https://doi.org/10.1016/S0140-6736(16)32388-1

Compston, A., & Coles, A. (2002). Multiple sclerosis. *Lancet (London, England)*, *359*(9313), 1221–1231. https://doi.org/10.1016/S0140-6736(02)08220-X

Compston, A., McDonald, I. R., Noseworthy, J., Lassmann, H., Miller, D. H., Smith, K. J., Wekerle, H., & Confavreux, C. (2005). *McAlpine's Multiple Sclerosis* (4 edition). Churchill Livingstone.

Costa-Requena, G., Arnal, R. B., & Gil, F. (2015). The influence of coping response and health-related quality of life on perceived social support during cancer treatment. *Palliative & Supportive Care*, *13*(3), 683–689. https://doi.org/10.1017/S1478951514000418

de Caneda, M. A. G., Cuervo, D. L. M., Marinho, N. E., & de Vecino, M. C. A. (2018). The Reliability of the Brief Visuospatial Memory Test—Revised in Brazilian multiple sclerosis patients. *Dementia & Neuropsychologia*, *12*(2), 205–211. https://doi.org/10.1590/1980-57642018dn12-020014

Delis, D., Kramer, J., Kaplan, E., & Ober, B. (2000). *CVLT-II California Verbal Learning Test Second Edition*. https://www.pearsonassessments.com/store/usassessments/en/Store/Professional-Assessments/Cognition-%26-Neuro/California-Verbal-Learning-Test-%7C-Second-Edition/p/100000166.html

Deluca, G. C., Yates, R. L., & Sadovnick, A. D. (2016). *Genetics and Epidemiology of Multiple Sclerosis*. Oxford University Press. http://oxfordmedicine.com/view/10.1093/med/9780199341016.001.0001/med-9780199341016-chapter-2

DeLuca, J., Barbieri-Berger, S., & Johnson, S. K. (1994). The nature of memory impairments in multiple sclerosis: Acquisition versus retrieval. *Journal of Clinical and Experimental Neuropsychology*, *16*(2), 183–189. https://doi.org/10.1080/01688639408402629

Deluca, J., Leavitt, V. M., Chiaravalloti, N., & Wylie, G. (2013). Memory impairment in multiple sclerosis is due to a core deficit in initial learning. *Journal of Neurology*, *260*(10), 2491–2496. https://doi.org/10.1007/s00415-013-6990-3

Devins, G. M., Armstrong, S. J., Mandin, H., Paul, L. C., Hons, R. B., Burgess, E. D., Taub, K., Schorr, S., Letourneau, P. K., & Buckle, S. (1990). Recurrent pain, illness intrusiveness, and quality of life in end-stage renal disease. *Pain*, *42*(3), 279–285.

Devins, G. M., Binik, Y. M., Hutchinson, T. A., Hollomby, D. J., Barré, P. E., & Guttmann, R. D. (1983). The emotional impact of end-stage renal disease: Importance of patients' perception of intrusiveness and control. *International Journal of Psychiatry in Medicine*, *13*(4), 327–343.

Devins, G. M., Dion, R., Pelletier, L. G., Shapiro, C. M., Abbey, S., Raiz, L. R., Binik, Y. M., McGowan, P., Kutner, N. G., Beanlands, H., & Edworthy, S. M. (2001). Structure of lifestyle disruptions in chronic disease: A confirmatory factor analysis of the Illness Intrusiveness Ratings Scale. *Medical Care*, *39*(10), 1097–1104. https://doi.org/10.1097/00005650-200110000-00007

Devins, G. M., Edworthy, S. M., Guthrie, N. G., & Martin, L. (1992). Illness intrusiveness in rheumatoid arthritis: Differential impact on depressive symptoms over the adult lifespan. *The Journal of Rheumatology*, *19*(5), 709–715.

Devins, G. M., Mandin, H., Hons, R. B., Burgess, E. D., Klassen, J., Taub, K., Schorr, S., Letourneau, P. K., & Buckle, S. (1990). Illness intrusiveness and quality of life in end-stage renal disease: Comparison and stability across treatment modalities. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *9*(2), 117–142.

Devins, G., Styra, R., O'connor, P., Gray, T., Seland, T. P., Klein, G. M., & Shapiro, C. M. (1996). Psychosocial impact of illness intrusiveness moderated by age in multiple

sclerosis. *Psychology, Health & Medicine*, *1*(2), 179–191. https://doi.org/10.1080/13548509608400017

Devins, Gerald M. (1994). Illness Intrusiveness and the Psychosocial Impact of Lifestyle Disruptions in Chronic Life-Threatening Disease. *Advances in Renal Replacement Therapy*, *1*(3), 251–263. https://doi.org/10.1016/S1073-4449(12)80007-0

Devins, Gerald M. (2010). Using the illness intrusiveness ratings scale to understand health-related quality of life in chronic disease. *Journal of Psychosomatic Research*, *68*(6), 591–602. https://doi.org/10.1016/j.jpsychores.2009.05.006

Devins, Gerald M., Edworthy, S. M., Paul, L. C., Mandin, H., Seland, T. P., Klein, G., Costello, C. G., & Shapiro, C. M. (1993). Restless sleep, illness intrusiveness, and depressive symptoms in three chronic illness conditions: Rheumatoid arthritis, end-stage renal disease, and multiple sclerosis. *Journal of Psychosomatic Research*, *37*(2), 163–170. https://doi.org/10.1016/0022-3999(93)90083-R

Devins, Gerald M., Edworthy, S. M., Paul, L. C., Mandin, H., Seland, T. P., & Klein, G. M. (1993). Illness intrusiveness and depressive symptoms over the adult years: Is there a differential impact across chronic conditions? *Canadian Journal of Behavioural Science / Revue Canadienne Des Sciences Du Comportement*, *25*(3), 400–413. https://doi.org/10.1037/h0078842

Devins, Gerald M., Edworthy, S. M., Seland, T. P., Klein, G. M., Paul, L. C., & Mandin, H. (1993). Differences in illness intrusiveness across rheumatoid arthritis, end-stage renal disease, and multiple sclerosis. *Journal of Nervous and Mental Disease*, *181*(6), 377–381. https://doi.org/10.1097/00005053-199306000-00007

Devins, Gerald M., Seland, T. P., Klein, G., Edworthy, S. M., & Saary, M. J. (1993). Stability and determinants of psychosocial well-being in multiple sclerosis. *Rehabilitation Psychology*, *38*(1), 11–26. https://doi.org/10.1037/h0080288

Douglas, K. M., & Porter, R. J. (2009). Longitudinal assessment of neuropsychological function in major depression. *The Australian and New Zealand Journal of Psychiatry*, *43*(12), 1105–1117. https://doi.org/10.3109/00048670903279887

Dusankova, J. B., Kalincik, T., Havrdova, E., & Benedict, R. H. B. (2012). Cross Cultural Validation of The Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) and The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *The Clinical Neuropsychologist*, *26*(7), 1186–1200. https://doi.org/10.1080/13854046.2012.725101

Edworthy, S. M., Dobkin, P. L., Clarke, A. E., Da Costa, D., Dritsa, M., Fortin, P. R., Barr, S., Ensworth, S., Esdaile, J. M., Beaulieu, A., Zummer, M., Senécal, J.-L., Goulet, J.-R., Choquette, D., Rich, E., Smith, D., Cividino, A., Gladman, D., & Devins, G. M. (2003). Group psychotherapy reduces illness intrusiveness in systemic lupus erythematosus. *The Journal of Rheumatology*, *30*(5), 1011–1016.

Engel, G. L. (1977). The need for a new medical model: A challenge for biomedicine. *Science (New York, N.Y.)*, *196*(4286), 129–136.

Eshaghi, A., Riahi, S., Roostaei, T., Haeri, G., Aghsaie, A., Reza Aidi, M., Reza Pouretemad, H., Zarei, M., Farhang, S., Saeedi, R., Nazeri, A., Ganjgahi, H., Etesam, F., Azimi, A., H B Benedict, R., & Sahraian, M. (2012). Validity and Reliability of a Persian Translation of the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). *The Clinical Neuropsychologist*, *26*, 975–984. https://doi.org/10.1080/13854046.2012.694912

Fassbender, K., Schmidt, R., Mössner, R., Kischka, U., Kühnen, J., Schwartz, A., & Hennerici, M. (1998). Mood disorders and dysfunction of the hypothalamic-pituitary-adrenal axis in multiple sclerosis: Association with cerebral inflammation. *Archives of Neurology*, *55*(1), 66–72.

Feinstein, A., O'Connor, P., Akbar, N., Moradzadeh, L., Scott, C. J. M., & Lobaugh, N. J. (2010). Diffusion tensor imaging abnormalities in depressed multiple sclerosis patients. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *16*(2), 189–196. https://doi.org/10.1177/1352458509355461

Feinstein, Anthony. (2002). An examination of suicidal intent in patients with multiple sclerosis. *Neurology*, *59*(5), 674–678.

Feinstein, Anthony. (2006). Mood disorders in multiple sclerosis and the effects on cognition. *Journal of the Neurological Sciences*, *245*(1), 63–66. https://doi.org/10.1016/j.jns.2005.08.020

Feinstein, Anthony. (2007). Neuropsychiatric syndromes associated with multiple sclerosis. *Journal of Neurology*, *254 Suppl 2*, II73-76. https://doi.org/10.1007/s00415-007-2017-2

Feinstein, Anthony, Magalhaes, S., Richard, J.-F., Audet, B., & Moore, C. (2014). The link between multiple sclerosis and depression. *Nature Reviews. Neurology*, *10*(9), 507–517. https://doi.org/10.1038/nrneurol.2014.139

Fiest, K. M., Walker, J. R., Bernstein, C. N., Graff, L. A., Zarychanski, R., Abou-Setta, A. M., Patten, S. B., Sareen, J., Bolton, J. M., Marriott, J. J., Fisk, J. D., Singer, A., & Marrie, R. A. (2016). Systematic review and meta-analysis of interventions for depression and anxiety in persons with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *5*, 12–26. https://doi.org/10.1016/j.msard.2015.10.004

Filippi, M., Bar-Or, A., Piehl, F., Preziosa, P., Solari, A., Vukusic, S., & Rocca, M. A. (2018). Multiple sclerosis. *Nature Reviews Disease Primers*, *4*(1), 43. https://doi.org/10.1038/s41572-018-0041-4

Fischer, J. S., LaRocca, N. G., Miller, D. M., Ritvo, P. G., Andrews, H., & Paty, D. (1999). Recent developments in the assessment of quality of life in multiple sclerosis (MS). *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *5*(4), 251–259. https://doi.org/10.1177/135245859900500410

Fletcher, S. G., Castro-Borrero, W., Remington, G., Treadaway, K., Lemack, G. E., & Frohman, E. M. (2009). Sexual dysfunction in patients with multiple sclerosis: A multidisciplinary approach to evaluation and management. *Nature Clinical Practice Urology*, *6*(2), 96–107. https://doi.org/10.1038/ncpuro1298

Foley, F. W., Traugott, U., LaRocca, N. G., Smith, C. R., Perlman, K. R., Caruso, L. S., & Scheinberg, L. C. (1992). A prospective study of depression and immune dysregulation in multiple sclerosis. *Archives of Neurology*, *49*(3), 238–244.

Ganguli, M. (2009). Depression, cognitive impairment and dementia: Why should clinicians care about the web of causation? *Indian Journal of Psychiatry*, *51*(Suppl1), S29–S34.

Gich, J., Freixenet, J., Garcia, R., Vilanova, J. C., Genís, D., Silva, Y., Montalban, X., & Ramió-Torrentà, L. (2014). A new cognitive rehabilitation programme for patients with multiple sclerosis: The 'MS-line! Project': *Multiple Sclerosis Journal*. https://doi.org/10.1177/1352458514561905

Giglio, L. D., Luca, F. D., Prosperini, L., Borriello, G., Bianchi, V., Pantano, P., & Pozzilli, C. (2014). A Low-Cost Cognitive Rehabilitation With a Commercial Video Game Improves

Sustained Attention and Executive Functions in Multiple Sclerosis: A Pilot Study. *Neurorehabilitation and Neural Repair*. https://doi.org/10.1177/1545968314554623

Glanz, B. I., Healy, B. C., Rintell, D. J., Jaffin, S. K., Bakshi, R., & Weiner, H. L. (2010). The association between cognitive impairment and quality of life in patients with early multiple sclerosis. *Journal of the Neurological Sciences*, *290*(1–2), 75–79. https://doi.org/10.1016/j.jns.2009.11.004

Gold, S. M., Kern, K. C., O'Connor, M.-F., Montag, M. J., Kim, A., Yoo, Y. S., Giesser, B. S., & Sicotte, N. L. (2010). Smaller cornu ammonis 2-3/dentate gyrus volumes and elevated cortisol in multiple sclerosis patients with depressive symptoms. *Biological Psychiatry*, *68*(6), 553–559. https://doi.org/10.1016/j.biopsych.2010.04.025

Gold, S. M., Krüger, S., Ziegler, K. J., Krieger, T., Schulz, K.-H., Otte, C., & Heesen, C. (2011). Endocrine and immune substrates of depressive symptoms and fatigue in multiple sclerosis patients with comorbid major depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, *82*(7), 814–818. https://doi.org/10.1136/jnnp.2010.230029

Goretti, B., Viterbo, R. G., Portaccio, E., Niccolai, C., Hakiki, B., Piscolla, E., Iaffaldano, P., Trojano, M., & Amato, M. P. (2014). Anxiety state affects information processing speed in patients with multiple sclerosis. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *35*(4), 559–563. https://doi.org/10.1007/s10072-013-1544-0

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 Journal*. https://doi.org/10.1177/1352458506072984

Granqvist, M., Boremalm, M., Poorghobad, A., Svenningsson, A., Salzer, J., Frisell, T., & Piehl, F. (2018). Comparative Effectiveness of Rituximab and Other Initial Treatment Choices for Multiple Sclerosis. *JAMA Neurology*, *75*(3), 320–327. https://doi.org/10.1001/jamaneurol.2017.4011

Greer, S., & Watson, M. (1987). Mental adjustment to cancer: Its measurement and prognostic importance. *Cancer Surveys*, *6*(3), 439–453.

Grzegorski, T., & Losy, J. (2017). Cognitive impairment in multiple sclerosis—A review of current knowledge and recent research. *Reviews in the Neurosciences*, *28*(8), 845–860. https://doi.org/10.1515/revneuro-2017-0011

Haider, L., Simeonidou, C., Steinberger, G., Hametner, S., Grigoriadis, N., Deretzi, G., Kovacs, G. G., Kutzelnigg, A., Lassmann, H., & Frischer, J. M. (2014). Multiple sclerosis deep grey matter: The relation between demyelination, neurodegeneration, inflammation and iron. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*(12), 1386–1395. https://doi.org/10.1136/jnnp-2014-307712

Hanssen, K. T., Beiske, A. G., Landrø, N. I., Hofoss, D., & Hessen, E. (2016). Cognitive rehabilitation in multiple sclerosis: A randomized controlled trial. *Acta Neurologica Scandinavica*, *133*(1), 30–40. https://doi.org/10.1111/ane.12420

Harbo, H. F., Gold, R., & Tintoré, M. (2013). Sex and gender issues in multiple sclerosis. *Therapeutic Advances in Neurological Disorders*, *6*(4), 237–248. https://doi.org/10.1177/1756285613488434

Hayes, A. F. (2013). *Introduction to Mediation, Moderation, and Conditional Process Analysis, First Edition: A Regression-Based Approach* (First edition). The Guilford Press.

He, H.-L., Zhang, M., Gu, C.-Z., Xue, R.-R., Liu, H.-X., Gao, C.-F., & Duan, H.-F. (2019). Effect of Cognitive Behavioral Therapy on Improving the Cognitive Function in Major and Minor Depression. *The Journal of Nervous and Mental Disease*, *207*(4), 232–238. https://doi.org/10.1097/NMD.0000000000000954

Healy, B. C., Ali, E. N., Guttmann, C. R. G., Chitnis, T., Glanz, B. I., Buckle, G., Houtchens, M., Stazzone, L., Moodie, J., Berger, A. M., Duan, Y., Bakshi, R., Khoury, S., Weiner, H., & Ascherio, A. (2009). Smoking and disease progression in multiple sclerosis. *Archives of Neurology*, *66*(7), 858–864. https://doi.org/10.1001/archneurol.2009.122

Henry, J. D., & Crawford, J. R. (2004). A meta-analytic review of verbal fluency performance following focal cortical lesions. *Neuropsychology*, *18*(2), 284–295. https://doi.org/10.1037/0894-4105.18.2.284

Higuera, L., Carlin, C. S., & Anderson, S. (2016). Adherence to Disease-Modifying Therapies for Multiple Sclerosis. *Journal of Managed Care & Specialty Pharmacy*, *22*(12), 1394–1401. https://doi.org/10.18553/jmcp.2016.22.12.1394

Holgersen, K. H., Boe, H. J., & Holen, A. (2010). Long-term perspectives on posttraumatic growth in disaster survivors. *Journal of Traumatic Stress*, n/a-n/a. https://doi.org/10.1002/jts.20530

Honarmand, K., & Feinstein, A. (2009). Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *15*(12), 1518–1524. https://doi.org/10.1177/1352458509347150

Horowitz, M., Wilner, N., & Alvarez, W. (1979). Impact of Event Scale: A measure of subjective stress. *Psychosomatic Medicine*, *41*(3), 209–218. https://doi.org/10.1097/00006842-197905000-00004

Hundt, N. E., Bensadon, B. A., Stanley, M. A., Petersen, N. J., Kunik, M. E., Kauth, M. R., & Cully, J. A. (2013). Coping mediates the relationship between disease severity and illness intrusiveness among chronically ill patients: *Journal of Health Psychology*. https://doi.org/10.1177/1359105313509845

Johansson, R., Carlbring, P., Heedman, Å., Paxling, B., & Andersson, G. (2013). Depression, anxiety and their comorbidity in the Swedish general population: Point prevalence and the effect on health-related quality of life. *PeerJ*, *1*, e98. https://doi.org/10.7717/peerj.98

Julian, L. J. (2011). Cognitive functioning in multiple sclerosis. *Neurologic Clinics*, *29*(2), 507–525. https://doi.org/10.1016/j.ncl.2010.12.003

Julian, L. J., & Arnett, P. A. (2009). Relationships among anxiety, depression, and executive functioning in multiple sclerosis. *The Clinical Neuropsychologist*, *23*(5), 794–804. https://doi.org/10.1080/13854040802665808

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*(4), 442–449. https://doi.org/10.1037/0894-4105.22.4.442

Kieseier, B. C., & Pozzilli, C. (2012). Assessing walking disability in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *18*(7), 914–924. https://doi.org/10.1177/1352458512444498

Kim, S., Zemon, V., Rath, J. F., Picone, M., Gromisch, E. S., Glubo, H., Smith-Wexler, L., & Foley, F. W. (2017). Screening Instruments for the Early Detection of Cognitive Impairment in Patients with Multiple Sclerosis. *International Journal of MS Care*, *19*(1), 1–10. https://doi.org/10.7224/1537-2073.2015-001

Kim, Y.-K., Na, K.-S., Shin, K.-H., Jung, H.-Y., Choi, S.-H., & Kim, J.-B. (2007). Cytokine imbalance in the pathophysiology of major depressive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *31*(5), 1044–1053. https://doi.org/10.1016/j.pnpbp.2007.03.004

Klineova, S., Farber, R., Saiote, C., Farrell, C., Delman, B. N., Tanenbaum, L. N., Friedman, J., Inglese, M., Lublin, F. D., & Krieger, S. (2016). Relationship between timed 25-foot walk and diffusion tensor imaging in multiple sclerosis. *Multiple Sclerosis Journal - Experimental, Translational and Clinical*, *2*, 2055217316655365. https://doi.org/10.1177/2055217316655365

Koch-Henriksen, N., & Sørensen, P. S. (2010). The changing demographic pattern of multiple sclerosis epidemiology. *The Lancet. Neurology*, *9*(5), 520–532. https://doi.org/10.1016/S1474-4422(10)70064-8

Korostil, M., & Feinstein, A. (2007). Anxiety disorders and their clinical correlates in multiple sclerosis patients. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *13*(1), 67–72. https://doi.org/10.1177/1352458506071161

Krieger, S. C., Cook, K., De Nino, S., & Fletcher, M. (2016). The topographical model of multiple sclerosis: A dynamic visualization of disease course. *Neurology(R) Neuroimmunology & Neuroinflammation*, *3*(5), e279. https://doi.org/10.1212/NXI.0000000000000279

Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9. *Journal of General Internal Medicine*, *16*(9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Lafosse, J. M., Mitchell, S. M., Corboy, J. R., & Filley, C. M. (2013). The nature of verbal memory impairment in multiple sclerosis: A list-learning and meta-analytic study. *Journal of the International Neuropsychological Society: JINS*, *19*(9), 995–1008. https://doi.org/10.1017/S1355617713000957

Learmonth, Y. C., Paul, L., McFadyen, A. K., Mattison, P., & Miller, L. (2012). Reliability and clinical significance of mobility and balance assessments in multiple sclerosis. *International Journal of Rehabilitation Research. Internationale Zeitschrift Fur Rehabilitationsforschung. Revue Internationale De Recherches De Readaptation*, *35*(1), 69–74. https://doi.org/10.1097/MRR.0b013e328350b65f

Leavitt, V. M., Wylie, G., Krch, D., Chiaravalloti, N., DeLuca, J., & Sumowski, J. F. (2014). Does slowed processing speed account for executive deficits in multiple sclerosis? Evidence from neuropsychological performance and structural neuroimaging. *Rehabilitation Psychology*, *59*(4), 422–428. https://doi.org/10.1037/a0037517

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

Lublin, F. D., Reingold, S. C., Cohen, J. A., Cutter, G. R., Sørensen, P. S., Thompson, A. J., Wolinsky, J. S., Balcer, L. J., Banwell, B., Barkhof, F., Bebo, B., Calabresi, P. A., Clanet, M., Comi, G., Fox, R. J., Freedman, M. S., Goodman, A. D., Inglese, M., Kappos, L., … Polman, C. H. (2014). Defining the clinical course of multiple sclerosis. *Neurology*, *83*(3), 278–286. https://doi.org/10.1212/WNL.0000000000000560

Lucchinetti, C., Brück, W., Parisi, J., Scheithauer, B., Rodriguez, M., & Lassmann, H. (2000). Heterogeneity of multiple sclerosis lesions: Implications for the pathogenesis of demyelination. *Annals of Neurology*, *47*(6), 707–717.

Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., & DeKosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *JAMA*, *288*(12), 1475–1483.

Lynch, S. G., Kroencke, D. C., & Denney, D. R. (2001). The relationship between disability and depression in multiple sclerosis: The role of uncertainty, coping, and hope. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *7*(6), 411–416. https://doi.org/10.1177/135245850100700611

Lynn Paukert, A., LeMaire, A., & A Cully, J. (2009). *Predictors of depressive symptoms in older veterans with heart failure* (Vol. 13). https://doi.org/10.1080/13607860802459823

Mahad, D. H., Trapp, B. D., & Lassmann, H. (2015). Pathological mechanisms in progressive multiple sclerosis. *The Lancet. Neurology*, *14*(2), 183–193. https://doi.org/10.1016/S1474-4422(14)70256-X

Mancini, A., Gaetani, L., Di Gregorio, M., Tozzi, A., Ghiglieri, V., Calabresi, P., & Di Filippo, M. (2017). Hippocampal neuroplasticity and inflammation: Relevance for multiple sclerosis. *Multiple Sclerosis and Demyelinating Disorders*, *2*(1), 2. https://doi.org/10.1186/s40893-017-0019-1

Marrie, R. A., Elliott, L., Marriott, J., Cossoy, M., Blanchard, J., Leung, S., & Yu, N. (2015). Effect of comorbidity on mortality in multiple sclerosis. *Neurology*, *85*(3), 240–247. https://doi.org/10.1212/WNL.0000000000001718

Mattioli, F., Bellomi, F., Stampatori, C., Provinciali, L., Compagnucci, L., Uccelli, A., Pardini, M., Santuccio, G., Fregonese, G., Pattini, M., Allegri, B., Clerici, R., Lattuada, A., Montomoli, C., Corso, B., Gallo, P., Riccardi, A., Ghezzi, A., Roscio, M., … Capra, R. (2016). Two Years Follow up of Domain Specific Cognitive Training in Relapsing Remitting Multiple Sclerosis: A Randomized Clinical Trial. *Frontiers in Behavioral Neuroscience*, *10*. https://doi.org/10.3389/fnbeh.2016.00028

McIvor, G. P., Riklan, M., & Reznikoff, M. (1984). Depression in multiple sclerosis as a function of length and severity of illness, age, remissions, and perceived social support. *Journal of Clinical Psychology*, *40*(4), 1028–1033. https://doi.org/10.1002/1097-4679(198407)40:4<1028::AID-JCLP2270400427>3.0.CO;2-1

Melief, J., de Wit, S. J., van Eden, C. G., Teunissen, C., Hamann, J., Uitdehaag, B. M., Swaab, D., & Huitinga, I. (2013). HPA axis activity in multiple sclerosis correlates with disease severity, lesion type and gene expression in normal-appearing white matter. *Acta Neuropathologica*, *126*(2), 237–249. https://doi.org/10.1007/s00401-013-1140-7

Mirza, S. S., Ikram, M. A., Bos, D., Mihaescu, R., Hofman, A., & Tiemeier, H. (2017). Mild cognitive impairment and risk of depression and anxiety: A population-based study. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *13*(2), 130–139. https://doi.org/10.1016/j.jalz.2016.06.2361

Mitolo, M., Venneri, A., Wilkinson, I. D., & Sharrack, B. (2015). Cognitive rehabilitation in multiple sclerosis: A systematic review. *Journal of the Neurological Sciences*, *354*(1), 1–9. https://doi.org/10.1016/j.jns.2015.05.004

Montalban, X., Gold, R., Thompson, A. J., Otero-Romero, S., Amato, M. P., Chandraratna, D., Clanet, M., Comi, G., Derfuss, T., Fazekas, F., Hartung, H. P., Havrdova, E., Hemmer,

B., Kappos, L., Liblau, R., Lubetzki, C., Marcus, E., Miller, D. H., Olsson, T., … Zipp, F. (2018). ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *24*(2), 96–120. https://doi.org/10.1177/1352458517751049

Morrow, S. A., Drake, A., Zivadinov, R., Munschauer, F., Weinstock-Guttman, B., & Benedict, R. H. B. (2010). Predicting loss of employment over three years in multiple sclerosis: Clinically meaningful cognitive decline. *The Clinical Neuropsychologist*, *24*(7), 1131–1145. https://doi.org/10.1080/13854046.2010.511272

Morrow, S. A., Rosehart, H., & Pantazopoulos, K. (2015). Anxiety and Depressive Symptoms Are Associated With Worse Performance on Objective Cognitive Tests in MS. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *28*(2), 118–123. https://doi.org/10.1176/appi.neuropsych.15070167

Motl, R. W., Cohen, J. A., Benedict, R., Phillips, G., LaRocca, N., Hudson, L. D., & Rudick, R. (2017). Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *23*(5), 704–710. https://doi.org/10.1177/1352458517690823

Mullins, A. J., Gamwell, K. L., Sharkey, C. M., Bakula, D. M., Tackett, A. P., Suorsa, K. I., Chaney, J. M., & Mullins, L. L. (2017). Illness uncertainty and illness intrusiveness as predictors of depressive and anxious symptomology in college students with chronic illnesses. *Journal of American College Health*, *65*(5), 352–360. https://doi.org/10.1080/07448481.2017.1312415

National MS Society. (2019a). *Relapsing-remitting MS (RRMS)*. National Multiple Sclerosis Society. http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Relapsing-remitting-MS

National MS Society. (2019b). *Secondary progressive MS (SPMS)*. National Multiple Sclerosis Society. http://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS

Nelson, F., Datta, S., Garcia, N., Rozario, N. L., Perez, F., Cutter, G., Narayana, P. A., & Wolinsky, J. S. (2011). Intracortical lesions by 3T magnetic resonance imaging and correlation with cognitive impairment in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *17*(9), 1122–1129. https://doi.org/10.1177/1352458511405561

Olsson, T., Barcellos, L. F., & Alfredsson, L. (2017). Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nature Reviews. Neurology*, *13*(1), 25–36. https://doi.org/10.1038/nrneurol.2016.187

Ortiz, G. G., Pacheco-Moisés, F. P., Macías-Islas, M. Á., Flores-Alvarado, L. J., Mireles-Ramírez, M. A., González-Renovato, E. D., Hernández-Navarro, V. E., Sánchez-López, A. L., & Alatorre-Jiménez, M. A. (2014). Role of the blood-brain barrier in multiple sclerosis. *Archives of Medical Research*, *45*(8), 687–697. https://doi.org/10.1016/j.arcmed.2014.11.013

Otallah, S., & Banwell, B. (2018). Pediatric Multiple Sclerosis: An Update. *Current Neurology and Neuroscience Reports*, *18*(11), 76. https://doi.org/10.1007/s11910-018-0886-7

Pais-Ribeiro, J. L., Martins da Silva, A., Vilhena, E., Moreira, I., Santos, E., & Mendonça, D. (2018). The hospital anxiety and depression scale, in patients with multiple sclerosis.

Neuropsychiatric Disease and Treatment, *14*, 3193–3197. https://doi.org/10.2147/NDT.S184260

Palanichamy, A., Jahn, S., Nickles, D., Derstine, M., Abounasr, A., Hauser, S. L., Baranzini, S. E., Leppert, D., & von Büdingen, H.-C. (2014). Rituximab efficiently depletes increased CD20-expressing T cells in multiple sclerosis patients. *Journal of Immunology (Baltimore, Md.: 1950)*, *193*(2), 580–586. https://doi.org/10.4049/jimmunol.1400118

Parmenter, B. A., Weinstock-Guttman, B., Garg, N., Munschauer, F., & Benedict, R. H. B. (2007). Screening for cognitive impairment in multiple sclerosis using the Symbol digit Modalities Test. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *13*(1), 52–57. https://doi.org/10.1177/1352458506070750

Patrick, S., & Connick, P. (2019). Psychometric properties of the PHQ-9 depression scale in people with multiple sclerosis: A systematic review. *PLoS ONE*, *14*(2). https://doi.org/10.1371/journal.pone.0197943

Patten, S. B., Metz, L. M., & Reimer, M. A. (2000). Biopsychosocial correlates of lifetime major depression in a multiple sclerosis population. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *6*(2), 115–120. https://doi.org/10.1177/135245850000600210

Patten, Scott B., Marrie, R. A., & Carta, M. G. (2017). Depression in multiple sclerosis. *International Review of Psychiatry*, *29*(5), 463–472. https://doi.org/10.1080/09540261.2017.1322555

Pérez-Martín, M. Y., González-Platas, M., Eguía-del Río, P., Croissier-Elías, C., & Jiménez Sosa, A. (2017). Efficacy of a short cognitive training program in patients with multiple sclerosis. *Neuropsychiatric Disease and Treatment*, *13*, 245–252. https://doi.org/10.2147/NDT.S124448

Pierrot-Deseilligny, C., & Souberbielle, J.-C. (2017). Vitamin D and multiple sclerosis: An update. *Multiple Sclerosis and Related Disorders*, *14*, 35–45. https://doi.org/10.1016/j.msard.2017.03.014

Polychroniadou, E., Bakirtzis, C., Langdon, D., Lagoudaki, R., Kesidou, E., Theotokis, P., Tsalikakis, D., Poulatsidou, K.-N., Kyriazis, O., Boziki, M., Papadopoulos, G., Boura, E., Sintila, L., Hatzigeorgiou, S., Ziamos, C., Ioannidis, P., Karacostas, D., & Grigoriadis, N. (2016). Validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) in Greek population with multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *9*. https://doi.org/10.1016/j.msard.2016.06.011

Portnoy, J. G., Miller, J., A., C., & Foley, F. W. (2017). *(PDF) A-67Cognition, Depression, and Physical Disability in Multiple Sclerosis as Predictors of Illness Intrusiveness*. ResearchGate. http://dx.doi.org/10.1093/arclin/acx076.67

Potagas, C., Mitsonis, C., Watier, L., Dellatolas, G., Retziou, A., Mitropoulos, P., Sfagos, C., & Vassilopoulos, D. (2008). Influence of anxiety and reported stressful life events on relapses in multiple sclerosis: A prospective study. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *14*(9), 1262–1268. https://doi.org/10.1177/1352458508095331

Rabinowitz, A. R., & Arnett, P. A. (2009). A longitudinal analysis of cognitive dysfunction, coping, and depression in multiple sclerosis. *Neuropsychology*, *23*(5), 581–591. https://doi.org/10.1037/a0016064

Rae-Grant, A. D., Eckert, N. J., Bartz, S., & Reed, J. F. (1999). Sensory symptoms of multiple sclerosis: A hidden reservoir of morbidity. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *5*(3), 179–183. https://doi.org/10.1177/135245859900500307

Rae-Grant, A., Day, G. S., Marrie, R. A., Rabinstein, A., Cree, B. A. C., Gronseth, G. S., Haboubi, M., Halper, J., Hosey, J. P., Jones, D. E., Lisak, R., Pelletier, D., Potrebic, S., Sitcov, C., Sommers, R., Stachowiak, J., Getchius, T. S. D., Merillat, S. A., & Pringsheim, T. (2018). Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*, *90*(17), 777–788. https://doi.org/10.1212/WNL.0000000000005347

Rao, S., L Martin, A., Huelin, R., Wissinger, E., Khankhel, Z., Kim, E., & Fahrbach, K. (2014). *Correlations between MRI and Information Processing Speed in MS: A Meta-Analysis*. https://doi.org/10.1155/2014/975803

Remes, O., Brayne, C., Linde, R. van der, & Lafortune, L. (2016). A systematic review of reviews on the prevalence of anxiety disorders in adult populations. *Brain and Behavior*, *6*(7), e00497. https://doi.org/10.1002/brb3.497

Renn, B. N., Hundt, N. E., Sansgiry, S., Petersen, N. J., Kauth, M. R., Kunik, M. E., & Cully, J. A. (2018). Integrated Brief Cognitive Behavioral Therapy Improves Illness Intrusiveness in Veterans With Chronic Obstructive Pulmonary Disease. *Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine*, *52*(8), 686–696. https://doi.org/10.1093/abm/kax045

Roosendaal, S. D., Moraal, B., Pouwels, P. J. W., Vrenken, H., Castelijns, J. A., Barkhof, F., & Geurts, J. J. G. (2009). Accumulation of cortical lesions in MS: Relation with cognitive impairment. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *15*(6), 708–714. https://doi.org/10.1177/1352458509102907

Ross, T. P. (2003). The reliability of cluster and switch scores for the Controlled Oral Word Association Test. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, *18*(2), 153–164.

Ruff, R. M., Light, R. H., Parker, S. B., & Levin, H. S. (1996). Benton Controlled Oral Word Association Test: Reliability and updated norms. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, *11*(4), 329–338.

Sandroff, B. M., Motl, R. W., Sosnoff, J. J., & Pula, J. H. (2015). Further validation of the Six-Spot Step Test as a measure of ambulation in multiple sclerosis. *Gait & Posture*, *41*(1), 222–227. https://doi.org/10.1016/j.gaitpost.2014.10.011

Sapolsky, R. M., Krey, L. C., & McEwen, B. S. (1986). The neuroendocrinology of stress and aging: The glucocorticoid cascade hypothesis. *Endocrine Reviews*, *7*(3), 284–301. https://doi.org/10.1210/edrv-7-3-284

Scalfari, A., Knappertz, V., Cutter, G., Goodin, D. S., Ashton, R., & Ebers, G. C. (2013). Mortality in patients with multiple sclerosis. *Neurology*, *81*(2), 184–192. https://doi.org/10.1212/WNL.0b013e31829a3388

Schippling, S., O'Connor, P., Knappertz, V., Pohl, C., Bogumil, T., Suarez, G., Cook, S., Filippi, M., Hartung, H.-P., Comi, G., Jeffery, D. R., Kappos, L., Goodin, D. S., & Arnason, B. (2016). Incidence and course of depression in multiple sclerosis in the multinational BEYOND trial. *Journal of Neurology*, *263*(7), 1418–1426. https://doi.org/10.1007/s00415-016-8146-8

Schrijvers, D., Hulstijn, W., & Sabbe, B. G. C. (2008). Psychomotor symptoms in depression: A diagnostic, pathophysiological and therapeutic tool. *Journal of Affective Disorders*, *109*(1–2), 1–20. https://doi.org/10.1016/j.jad.2007.10.019

Shahrbanian, S., Duquette, P., Kuspinar, A., & Mayo, N. E. (2015). Contribution of symptom clusters to multiple sclerosis consequences. *Quality of Life Research*, *24*(3), 617–629. https://doi.org/10.1007/s11136-014-0804-7

Shawaryn, M. A., Schiaffino, K. M., LaRocca, N. G., & Johnston, M. V. (2002). Determinants of health-related quality of life in multiple sclerosis: The role of illness intrusiveness. *Multiple Sclerosis Journal*, *8*(4), 310–318. https://doi.org/10.1191/1352458502ms808oa

Siegert, R., & Abernethy, D. (2005). Depression in multiple sclerosis: A review. *Journal of Neurology, Neurosurgery, and Psychiatry*, *76*(4), 469–475. https://doi.org/10.1136/jnnp.2004.054635

Sinoff, G., & Werner, P. (2003). Anxiety disorder and accompanying subjective memory loss in the elderly as a predictor of future cognitive decline. *International Journal of Geriatric Psychiatry*, *18*(10), 951–959. https://doi.org/10.1002/gps.1004

Sjonnesen, K., Berzins, S., Fiest, K. M., M Bulloch, A. G., Metz, L. M., Thombs, B. D., & Patten, S. B. (2012). Evaluation of the 9-item Patient Health Questionnaire (PHQ-9) as an assessment instrument for symptoms of depression in patients with multiple sclerosis. *Postgraduate Medicine*, *124*(5), 69–77. https://doi.org/10.3810/pgm.2012.09.2595

Slimp, J. C. (2011). *Neurophysiology of Multiple Sclerosis*. Oxford University Press. http://oxfordmedicine.com/view/10.1093/med/9780199341016.001.0001/med-9780199341016-chapter-3

Smith, A. (1982). *Symbol Digit Modalities Test (SDMT). Manual (Revised).* Western Psychological Services.

Smith, A. (1991). *Symbol Digit Modalities Test*. Western Psychological Services.

Snyder, S., Foley, F. W., Farrell, E., Beier, M., & Zemon, V. (2013a). Psychological and physical predictors of illness intrusiveness in patients with multiple sclerosis. *Journal of the Neurological Sciences*, *332*(1–2), 41–44. https://doi.org/10.1016/j.jns.2013.06.009

Snyder, S., Foley, F. W., Farrell, E., Beier, M., & Zemon, V. (2013b). Psychological and physical predictors of illness intrusiveness in patients with multiple sclerosis. *Journal of the Neurological Sciences*, *332*(1–2), 41–44. https://doi.org/10.1016/j.jns.2013.06.009

Sperling, R. A., Guttmann, C. R., Hohol, M. J., Warfield, S. K., Jakab, M., Parente, M., Diamond, E. L., Daffner, K. R., Olek, M. J., Orav, E. J., Kikinis, R., Jolesz, F. A., & Weiner, H. L. (2001). Regional magnetic resonance imaging lesion burden and cognitive function in multiple sclerosis: A longitudinal study. *Archives of Neurology*, *58*(1), 115–121.

Stegen, S., Stepanov, I., Cookfair, D., Schwartz, E., Hojnacki, D., Weinstock-Guttman, B., & Benedict, R. H. B. (2010). Validity of the California Verbal Learning Test-II in multiple sclerosis. *The Clinical Neuropsychologist*, *24*(2), 189–202. https://doi.org/10.1080/13854040903266910

Stenager, E., Knudsen, L., & Jensen, K. (1994). Multiple sclerosis: Correlation of anxiety, physical impairment and cognitive dysfunction. *Italian Journal of Neurological Sciences*, *15*(2), 97–101.

Stern, B. Z., Strober, L., DeLuca, J., & Goverover, Y. (2018). Subjective well-being differs with age in multiple sclerosis: A brief report. *Rehabilitation Psychology*, *63*(3), 474–478. https://doi.org/10.1037/rep0000220

Stewart, A. L., Greenfield, S., Hays, R. D., Wells, K., Rogers, W. H., Berry, S. D., McGlynn, E. A., & Ware, J. E. (1989). Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. *JAMA*, *262*(7), 907–913.

Stuss, D. T., Alexander, M. P., Hamer, L., Palumbo, C., Dempster, R., Binns, M., Levine, B., & Izukawa, D. (1998). The effects of focal anterior and posterior brain lesions on verbal fluency. *Journal of the International Neuropsychological Society: JINS*, *4*(3), 265–278.

Talbot, F., Nouwen, A., Gingras, J., Bélanger, A., & Audet, J. (1999). Relations of diabetes intrusiveness and personal control to symptoms of depression among adults with diabetes. *Health Psychology*, *18*(5), 537–542. https://doi.org/10.1037/0278-6133.18.5.537

Tan-Kristanto, S., & Kiropoulos, L. A. (2015). Resilience, self-efficacy, coping styles and depressive and anxiety symptoms in those newly diagnosed with multiple sclerosis. *Psychology, Health & Medicine*, *20*(6), 635–645. https://doi.org/10.1080/13548506.2014.999810

Toosy, A. T., Mason, D. F., & Miller, D. H. (2014). Optic neuritis. *The Lancet. Neurology*, *13*(1), 83–99. https://doi.org/10.1016/S1474-4422(13)70259-X

Treating MS. (2019). National Multiple Sclerosis Society. http://www.nationalmssociety.org/Treating-MS

Trenova, A. G., Slavov, G. S., Manova, M. G., Aksentieva, J. B., Miteva, L. D., & Stanilova, S. A. (2016). Cognitive Impairment in Multiple Sclerosis. *Folia Medica*, *58*(3), 157–163. https://doi.org/10.1515/folmed-2016-0029

Tullman, M. J. (2013). Overview of the epidemiology, diagnosis, and disease progression associated with multiple sclerosis. *The American Journal of Managed Care*, *19*(2 Suppl), S15-20.

Uchiyama, C. L., D'elia, L. F., Dellinger, A. M., Seines, O. A., Becker, J. T., Wesch, J. E., Chen, B. B., Satz, P., Gorp, W. van, & Miller, E. N. (1994). Longitudinal comparison of alternate versions of the symbol digit modalities test: Issues of form comparability and moderating demographic variables. *Clinical Neuropsychologist*, *8*(2), 209–218. https://doi.org/10.1080/13854049408401558

Van Schependom, J., D'hooghe, M. B., Cleynhens, K., D'hooge, M., Haelewyck, M. C., De Keyser, J., & Nagels, G. (2014). The Symbol Digit Modalities Test as sentinel test for cognitive impairment in multiple sclerosis. *European Journal of Neurology*, *21*(9), 1219–1225, e71-72. https://doi.org/10.1111/ene.12463

Vaske, J. J., Beaman, J., & Sponarski, C. C. (2017). Rethinking Internal Consistency in Cronbach's Alpha. *Leisure Sciences*, *39*(2), 163–173. https://doi.org/10.1080/01490400.2015.1127189

Vissicchio, N. A., Altaras, C., Parker, A., Schneider, S., Portnoy, J. G., Archetti, R., Stimmel, M., & Foley, F. W. (2018). The Relationship Between Anxiety and Cognition in Multiple Sclerosis: Implications for Treatment. *International Journal of MS Care*. https://doi.org/10.7224/1537-2073.2018-027

W. LeMaire, A., Shahane, A., Dao, T., Kibler, J., & A. Cully, J. (2012). *Illness Intrusiveness Mediates the Relationship Between Heart Failure Severity and Depression in Older Adults* (Vol. 31). https://doi.org/10.1177/0733464810396507

Watson, T. M., Ford, E., Worthington, E., & Lincoln, N. B. (2014). Validation of Mood Measures for People with Multiple Sclerosis. *International Journal of MS Care*, *16*(2), 105–109. https://doi.org/10.7224/1537-2073.2013-013

Wetherell, J. L., Reynolds, C. A., Gatz, M., & Pedersen, N. L. (2002). Anxiety, cognitive performance, and cognitive decline in normal aging. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *57*(3), P246-255.

Willer, C. J., Dyment, D. A., Risch, N. J., Sadovnick, A. D., Ebers, G. C., & Canadian Collaborative Study Group. (2003). Twin concordance and sibling recurrence rates in multiple sclerosis. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(22), 12877–12882. https://doi.org/10.1073/pnas.1932604100

Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370.

Zorzon, M., Zivadinov, R., Nasuelli, D., Ukmar, M., Bratina, A., Tommasi, M. A., Mucelli, R. P., Brnabic-Razmilic, O., Grop, A., Bonfigli, L., & Cazzato, G. (2002). Depressive symptoms and MRI changes in multiple sclerosis. *European Journal of Neurology*, *9*(5), 491–496.