Psychological Resilience as a Protective Factor for the Motor System in Multiple Sclerosis

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Abstract

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Multiple Sclerosis (MS) is a lifelong progressive neurologic disease of the central nervous system (CNS) that interrupts the flow of information within the brain and between the brain and the body, resulting in a variety of symptoms across the visual, sensory, motor, and autonomic functions. The concept of psychological resilience is emerging in clinical research, including research on MS, as a productive way to view the outcomes and experiences of living with a chronic disease and identify potential protective factors. The purpose of this dissertation was to examine the protective and predictive quality of psychological resilience in various domains of motor functioning.

A sample of 130 patients underwent neuropsychological testing along with neurological examination at two distinct time points (baseline and 3-year follow-up). As part of each evaluation, patients were administered various tasks of motor functioning: the two-minute walk test (2MWT; a measure of gait endurance and stamina), timed 25-foot walk (T25FW; a measure of gait speed), nine-hole peg test (NHPT; a measure of upper extremity speed and coordination), grooved pegboard (G-Pegs; a measure of fine motor speed and dexterity), grip strength (Grip; a measure of upper body strength), and finger tapping test (FTT; a measure of simple motor speed), which served as this study's outcomes. Psychological resilience, the primary predictor of interest, was operationalized as the self-reported ability of adapting well in the face of substantial adversity and significant sources of stress and was estimated using a validated self-report

measure the Connor-Davidson Resilience Scale, 10 item version (CD-RISC-10). Additional predictors included mood, fatigue, demographic variables, disease variables, and magnetic resonance imaging (MRI) estimates.

In contrast to our hypothesis, psychological resilience and functional outcomes were not correlated. Psychological resilience did not predict change in motor functioning over time and did not serve as a moderator between disease burden and motor functioning. As such, the present study does not provide support for psychological resilience as a protective factor for the motor system in MS or for resilience in predicting differential decline in motor functioning.

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Acknowledgments

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Chapter 1: Introduction

Multiple Sclerosis (MS) is a lifelong progressive neurologic disease of the central nervous system (CNS) that interrupts the flow of information within the brain and between the brain and the body. Most recent estimates in 2017, report approximately 913,925 adults in the United States with MS (Wallin et al., 2019). Despite advances in disease-modifying therapies for MS to improve disease control and provide more favorable prognosis for patients, many continue to develop cognitive and physical disabilities. Due to the inflammatory and neurodegenerative disease mechanisms, depending on where in the CNS the neurons are being attacked, the consequential disruption can elicit a variety of symptoms across the visual, sensory, motor, and autonomic functions (i.e., functions controlled by the CNS).

Magnetic resonance imaging (MRI) of the brain and spinal cord is the most sensitive investigational technique aiding the diagnosis of MS. The MRI plays an essential role in monitoring disease progression as well as monitoring treatment efficacy (i.e., slowing of progression). Two structural disease-related patterns of brain changes are evident on MRIs: atrophy (loss of brain volume reflecting demyelination and axonal loss) and lesions (pathological changes such as edema, gliosis, inflammation, demyelination, remyelination, and axonal loss) (Bermel & Bakshi, 2006).

There are three main identified courses of MS: relapsing-remitting (RRMS), secondary-progressive (SPMS), and primary-progressive (PPMS). The majority of patients (approximately 85%) initially have RRMS, which is characterized by discrete relapses followed by subsequent improvement called remission. Approximately 50% of RRMS patients will develop a slow, gradually progressive, neurologic deterioration over many years with or without clinical attacks superimposed, which is termed SPMS (Friese et al., 2014). A minority of patients

(approximately 15%) have PPMS, which is characterized by worsening neurologic function from the onset of symptoms without early relapses or remissions (Khoshnam & Freedman, 2014). Another term, important for this study, is clinically isolated syndrome (CIS), which is characterized by neurologic symptoms caused by the first relapse, is characteristic of MS, but does not yet meet the full criteria for a diagnosis of MS. The majority of patients with CIS will go on to have a second attack and meet the criteria for MS (Rotstein & O'Connor, 2014).

Overall, across individuals at different stages of MS, the most common symptoms reported include sensory disturbance, optic neuritis (visual loss), fatigue, and ataxia (impaired coordination and balance). Other common symptoms include diplopia (double vision), vertigo, bladder and bowel dysfunction, gait disturbance, Lhermitte's sign ("electrical" sensations running through the back and the limbs), pain, and headaches (Keegan & Noseworthy, 2002; McDonnell, 2007; Rotstein & O'Connor, 2014). Motor symptoms including limb weakness, spasticity, and coordination problems are reported in up to 80% of patients (McDonnell, 2007; Norbye, Midgard, & Thrane, 2018). Tremor and gait disturbance are also common with approximately 50% of patients requiring walking assistance within 15 years of disease onset (Noseworthy, Lucchinetti, Rodriguez, &Weinshenker, 2000). At least 60% of patients with MS demonstrate impaired fine motor dexterity (Benedict et al., 2011; Bertoni, Lamers, Chen, Feys & Cattaneo, 2015; Einarsson et al., 2006; Johansson et al., 2007).

MS is a highly variable disease with unique clinical presentations ranging from mild infrequent relapses causing mild functional impairments to rapidly accumulating severe disability and impairments. In MS there is a dissociation between disease burden and outcomes, where some patients remain cognitively, physically, and socially active despite comparable disease burden. This uncertain and variable nature of the disease further poses unique challenges

in regard to coping and adaptation. MS is typically diagnosed between the ages of 20 and 40 years old, a time where individuals must strive for and manage important social and normative roles such as transition out of their childhood homes and establish a career. Incidences of emotional disturbances are common among individuals with MS, especially high levels of anxiety and depressive symptoms (Tan-Kristanto & Kiropoulos, 2015; Zorzon et al., 2001). Depression is found early on in MS with 32% of patients reporting experiencing depression after a first demyelinating event or new diagnosis (Rintell, 2014). Across types of MS, the lifetime prevalence of any anxiety disorder is estimated at around 36% with the most common being panic disorder, obsessive-compulsive disorder, and generalized anxiety disorder (Korostil, & Feinstein, 2007).

As already highlighted, MS can have a destructive impact on the physical, cognitive, social, and mental health and well-being of persons living with MS. An alternative approach to studying individuals with MS is to examine the more positive aspects experienced by persons with MS, focusing on the features of their lives that are going well. The concept of psychological resilience is emerging in clinical research, including research on MS, as a productive way to view the outcomes and experiences of living with a chronic disease and identify potential protective factors. Moreover, attention to resilience in MS research might provide a balanced approach to offset the focus on the negative.

Psychological resilience (used interchangeably with resilience) is the dynamic process of adapting positively in the face of substantial adversity and significant sources of stress. Psychological resilience is identified as an important factor that may help to promote positive coping skills, overall well-being in adults, as well as influencing the quality of life domains such

as fatigue physical function (Edwards et al., 2017; Silverman, Molton, Alschuler, Ehde, & Jensen, 2015).

Studies on psychological resilience in those with MS, link resilience to a variety of psychological variables and disease-specific variables. Notably, resilience plays a role in partaking in healthier lifestyle decisions such as exercise and better diet (Ploughman et al., 2015; Ploughman et al., 2020); social support, fatigue, physical independence, self-efficacy, and positive affect (Black & Dorstyn, 2015); fatigue, motor dysfunction, and paresthesia (Swanepoel, van Staden, & Fletcher, 2020); social support and mental health outcomes (Koelmel, Hughes, Alschuler, & Ehde, 2016); and positive affect and pain function (Arewasikporn et al., 2018b). Furthermore, some development in interventions to promote resilience in various populations, including those specific to MS, show some preliminary benefits of such interventions in increasing levels of resilience (Alschuler et al., 2018; Ehde et al., 2015; Giovannetti et al., 2020; Kiropoulos, Kilpatrick, Holmes, & Threader, 2016).

A cross-sectional analysis, using the same longitudinal cohort of early MS patients (n = 165 RRMS and n = 20 CIS) as used for the present study, examined whether psychological resilience explains differential objective cognitive and motor functioning in persons with early MS (Klineova et al., 2019). Results found less mood disturbance and less fatigue with higher resilience. Higher resilience was related to the majority of the motor functioning outcomes including grip strength [Grip], gait endurance [2MWT], and simple motor speed [FTT], gait speed [T25FW], and upper extremity speed and coordination [NHPT]. Fine motor speed and dexterity [G-Pegs] was not related to resilience. Moreover, after correcting for multiple comparisons and statistically controlling for fatigue and mood, Grip, 2MWT, and FTT remained significantly related to resilience (Klineova et al., 2019).

The purpose of this dissertation is to examine the protective and predictive effect of psychological resilience on various domains of motor functioning, including gait and balance, endurance and stamina, upper body strength, motor speed, and upper extremity coordination in an early cohort of patients with MS. This study seeks to extend the findings of Klineova et al. (2019) to re-examine the role of resilience in this clinical population 3 years later to evaluate this construct as a potential predictor of change in objective functional outcomes. The findings have implications with regard to improved understanding of the variability and progression of motor disability (e.g., identifying those most at risk for decline in motor functioning) in MS as well as identifying a potential contributor to such outcomes. Such insight can help inform treatment decisions such as early pharmacological treatment, rehabilitative intervention (e.g., occupational therapy), as well as therapy-based intervention/clinical trial research.

Chapter 2: Review of Literature

Multiple Sclerosis

Multiple Sclerosis (MS) is a lifelong progressive neurologic disease of the central nervous system (CNS) that interrupts the flow of information within the brain and between the brain and the body. Due to the inflammatory and neurodegenerative disease mechanisms, depending on where in the CNS the neurons are being attacked, the consequential disruption can elicit a variety of symptoms across the visual, sensory, motor, and autonomic functions (i.e., functions controlled by the CNS). In 2010, the estimated prevalence of MS in the United States was 727,344 adults with MS. More recently, in 2017, the estimates were updated to approximately 913,925 adults in the United States with MS (Wallin et al., 2019). Advances in methodology to estimate the number of people living with MS have led to higher, but more accurate, counts. Currently, the cause of the disease remains unknown however researchers have identified factors in the distribution of MS around the world (Steele & Mowry, 2014). MS is most common amongst Caucasian populations, however, is found in most racial and ethnic groups including African Americans, Asians, and Hispanics/Latinx. Patients are typically diagnosed between ages 20 and 50 years and individuals are three times more likely to be female (Black & Dorstyn, 2015; Confavreux, Vukusic, Moreau, & Adeleine, 2000; Keegan & Noseworthy, 2002).

Research suggests that MS is caused by an abnormal autoimmune response in genetically susceptible individuals after environmental triggers. Advances in immuno-modulating pharmacological treatments can help slow the disease, however, there is still no cure and life expectancy remains shorter for MS patients relative to the general population (Steele & Mowry, 2014). Relapses (also known as an attack, flare-up, or exacerbation), one of the primary

characteristics of MS, are caused by inflammation in the CNS that causes damage to the myelin which, in turn, disrupts the transmission of nerve impulses and causes various symptoms. There is a consensus that the attack frequency of MS lessens with time (Weinshenker et al., 1989) and treatment is directed at acute attacks and reduction of attack frequency (Keegan & Noseworthy, 2002).

MS can be clinically divided into relapse-onset MS, which starts with acute neurological impairment followed by remission, and progressive-onset MS, which starts with a progressive phase without relapse or remissions. There are three main identified courses of MS: relapsing-remitting (RRMS), secondary-progressive (SPMS), and primary-progressive (PPMS). The majority of patients (approximately 85%) initially have RRMS, which is characterized by discrete relapses followed by subsequent improvement called remission. During this remission period, symptoms may improve, disappear, or continue and become permanent. Approximately 50% of RRMS patients will develop a slow, gradually progressive, neurologic deterioration over many years with or without clinical attacks superimposed, which is termed SPMS (Friese et al., 2014). A minority of patients (approximately 15%) have PPMS, which is characterized by worsening neurologic function from the onset of symptoms without early relapses or remissions (Keegan & Noseworthy, 2002; Khoshnam & Freedman, 2014; McDonnell, 2007; Rotstein & O'Connor, 2014). Another term, important for this dissertation, is clinically isolated syndrome (CIS), which is characterized by neurologic symptoms caused by the first relapse, is characteristic of MS, but does not yet meet full criteria for a diagnosis. The majority of patients with CIS will go on to have a second attack and meet the full criteria for MS (Rotstein & O'Connor, 2014).

Symptoms

Many patients with MS experience disability in the seven functional systems: visual, pyramidal (e.g., muscle weakness and upper and lower extremity function), sensory (e.g., numbness or loss of sensations), cerebellar (e.g., loss of balance, coordination, or tremor), cerebral (e.g., thinking and memory), and bowel and bladder functioning. Observed deficits in physical functioning could have resulted from sensory, motor, coordination, or cognitive dysfunction (Mitiku, Sandoval & Kraft, 2014). Sensory disturbances, including tingling sensations, are the most common initial manifestation, followed by motor symptoms, specifically, loss of dexterity, limb weakness, gait disturbance (Swingler & Compston, 1992), and general or specific slowness of movement (Swanepoel, van Staden, & Fletcher, 2020).

Overall, across individuals at different stages of MS, the most common symptoms reported include sensory disturbance, optic neuritis (visual loss), fatigue, and ataxia (impaired coordination and balance). Other common symptoms include diplopia (double vision), vertigo, bladder and bowel dysfunction, gait disturbance, Lhermitte's sign ("electrical" sensations running through the back and the limbs), pain, and headaches (Keegan & Noseworthy, 2002; McDonnell, 2007; Rotstein & O'Connor, 2014). Physical weakness is cited as the most frequent symptom experienced across the disease course (Swingler & Compston, 1992) and can occur in a single limb or be widespread (Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000). Another problem and debilitating symptom of MS is cognitive decline. Literature review estimates that problems with cognitive functioning occur in more than half of individuals with MS (Charvet, Kluzer & Krupp, 2014; Johansson et al., 2007; Sumowski, 2015) and can be seen within all stages of the disease with functioning typically declining over time (Filippi et al., 2010). Areas of impairment include slowed information processing speed (i.e., cognitive

efficiency), memory problems, decreased ability to concentrate and reason (i.e., executive functioning deficits), verbal fluency, and learning problems. Visuomotor integration skills and visuospatial perception are also impacted (Filippi et al., 2010; Rao, Leo, Bernardin, & Unverzagt, 1991).

Two commonly used instruments to quantify the degree of disability in MS include the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC). These measures are also often used to measure and track disease progression. EDSS assesses neurologic disturbance through a neurologic exam of seven functional systems: visual, brainstem, pyramidal, sensory, cerebellar, cerebral, and bowel/bladder, as well as ambulatory functioning and independence in activities of daily living. The MSFC was created to incorporate specific continuous measures of fine motor, gait, and cognitive functioning and is recognized for its strong psychometric properties and standardized administration (Benedict et al., 2011).

Disease-Related Brain Changes

Magnetic resonance imaging (MRI) of the brain and spinal cord is the most sensitive investigational technique aiding the diagnosis of MS. The MRI plays an essential role in monitoring disease progression as well as monitoring treatment efficacy (i.e., slowing of progression). Two structural disease-related patterns of brain changes are evident on MRIs, atrophy and lesion volume. Atrophy is the loss of brain volume and includes the whole brain (global), gray matter, white matter, and regional atrophy (e.g., atrophy of the cerebellum). Thus, brain atrophy reflects tissue loss and represents a global measure of both demyelination and axonal loss (Gaitán & Reich, 2014). Normalized brain volume is reduced in patients with MS (Bermel & Bakshi, 2006) and thus can represent a measure of cerebral atrophy. Lesions, as seen on T2-weighted images, are representative of pathological changes such as edema, gliosis,

inflammation, demyelination, remyelination, and axonal loss (Bermel & Bakshi, 2006). Radiological measures often scan for both T2- weighted images (i.e., lesions appearing hyperintense relative to surrounding white matter) and T1-weighted images (i.e., lesions appearing hypointense compared to surrounding gray matter) (Kalkers et al., 2001). The total number of lesions, both old and new, is often used to characterize disease burden. However, T2 lesion volume (T2LV) is the most commonly used method to assess disease burden across the literature.

MS lesions can be found anywhere in the CNS, contributing to a variety of symptom presentations. Sometimes the neurological symptom reflects the location of the lesion within the CNS (e.g., vision loss reflects a lesion of the optic nerve) however, many lesions are clinically silent. However, despite this diversity, there are typical locational patterns characteristic of MS which include lesions in the optic nerves, periventricular white matter, juxtacortical (at the gray-white junction), spinal cord, and infratentorial region (includes the brain stem and cerebellum) (Gaitán & Reich, 2014; Keegan & Noseworthy, 2002). Atrophy in MS is also widespread and can affect the cortical, central, and infratentorial regions (Bakshi, Benedict, Bermel, & Jacobs, 2001; Bermel & Bakshi, 2006). Atrophy in the cerebrum, corpus callosum, and spinal cord, correlate directly with the severity of disability (Keegan & Noseworthy, 2002).

MS was traditionally viewed as a white matter disorder. However, it is now well accepted that MS lesions can also affect gray matter, including both deep gray matter structures such as the thalamus and cortical gray matter (Cross & Piccio, 2014; Vrenken & Geurts, 2007). Recent research shows that atrophy begins at disease onset and is more associated with functional impairment than white matter lesions (Bermel & Bakshi, 2006; Friese, Schattling, & Fugger, 2014; Gaitán & Reich, 2014). Atrophy is closely associated with physical disability (Bakshi,

Benedict, Bermel, & Jacobs, 2001), specifically, cerebral atrophy (especially gray matter atrophy) and gait disturbance (Bermel & Bakshi, 2006; Fisniku et al., 2008; Popescu et al., 2013; Sanfilipo, Benedict, Sharma, Weinstock-Guttman, & Bakshi, 2005; Tedeschi et al., 2005). Cerebral atrophy is linked to cognitive impairment, specifically, memory decline (Benedict et al., 2004; Benedict et al., 2006; Bermel & Bakshi, 2006; Filippi et al., 2010). Furthermore, some researchers suggest that axon damage occurs in addition to demyelination and may be the cause of later permanent disability (Keegan & Noseworthy, 2002). Taken together, lesion load, cortical atrophy, central atrophy, white matter atrophy, gray matter atrophy, and whole-brain atrophy are all measures of disease burden in MS.

Spinal cord atrophy and lesion load are robustly correlated with disability and may be associated with progression of disability (Minneboo et al., 2004; Stevenson et al., 1998). Additionally, in a longitudinal study of individuals after a clinically isolated syndrome, spinal cord lesion number was the only baseline MRI measure associated with disability at 5-year follow-up (Brownlee et al., 2017). Moreover, baseline spinal cord lesion number explained a significant portion of the variability in EDSS at follow-up (adjusted R^2= 0.24) (Brownlee et al., 2017). Furthermore, lesions of the spinal cord are either located in or close to pathways involved in locomotor and sphincter function and thus may cause physical dysfunction more often than brain lesions (aside from the brainstem which is a clinically eloquent location) (Bermel & Bakshi, 2006; Brownlee et al., 2017; Lin, Tench, Evangelou, Jaspan, & Constantinescu, 2004).

In the present study, disease burden was assessed using the three identified disease-related patterns of brain change evident on MRIs: lesion volume (T2LV), lesion count in the cervical spinal cord, and atrophy (normalized whole brain volume).

Clinico-Pathologic Dissociation

MS is a highly variable disease with unique clinical presentations ranging from mild infrequent relapses causing mild functional impairments to rapidly accumulating severe disability and impairments. Further, there is a clinico-pathologic dissociation, where patients with MS can experience differential levels of clinical deficits despite having similar brain damage or pathology, referred to as disease burden. That is, there is a dissociation between disease burden and outcomes, where some patients remain cognitively, physically, and socially active despite comparable disease burden (Sumowski et al., 2013).

Specific to physical disability, disability impairment does not progress uniformly across patients. Physical disability varies widely among people with similar disease burden, disease duration, and patterns/frequency of relapses (Confavreux et al., 2000; Scalfari et al., 2013), and the correlation between disease burden and physical disability is moderate at best (Bermel & Bakshi, 2006). In other words, the relationship between disease burden in the CNS and physical disability is incomplete, where various MRI estimates only partially predict disability and disability progression measured with EDSS and MSFC (Fisher et al., 2000; Rocca et al., 2017; Popescu et al., 2013). Given this variability in disability, it is difficult to determine which patients are most at risk for future motor impairment. Therefore, consistent with the present study, an area of research interest in MS is identifying protective or risk factors for disability to help improve understanding of physical disability progression in MS.

Physical Disability and Motor Functioning

The International Classification of Functioning, Disability and Health is a comprehensive system adopted in 2001 by the World Health Organization, which allows a comprehensive description of all aspects of functioning (Holper et al., 2010). The model aims to identify each

patient's unique functional abilities and needs through three components: body functions and structures, activities and participation, and contextual factors.

Body structure refers to body parts such as legs, hands, the brain, and muscles and body function refers to things that our body parts do such as moving leg muscles to move around or feeling pain or touch. Examples of impairment in these areas could be weak back muscles or weak leg muscles. Activity refers to the completion of tasks that we do every day such as walking and talking. Participation refers to being involved in life situations such as walking to move around or to get to work. Challenges to the body structure and function can impact activities, for example, weak leg and back muscles can make walking difficult, which is referred to as activity limitations. Such activity limitations can lead to non-participation in social activities, for example not going to work, which is referred to as participation restrictions. Lastly, contextual factors include both personal factors and environmental factors. Personal factors are individual characteristics about a person such as age, personality, and education and environmental factors are those around the person such as transportation services, health policies, and attitudes of family and society.

Body Structure and Function

Demyelinating lesions in MS can produce impairment in body functions and structures. This dissertation includes a focus on impairments in neuromusculoskeletal and movement-related functions and sensory functions and pain. A decline in motor function and mobility in MS often occurs, including reduced balance, coordination, range of motion, altered alignment, and spasticity (Norbye, Midgard, & Thrane, 2018). Limb weakness, spasticity, and coordination problems are reported in up to 80% of patients (McDonnell, 2007; Norbye, Midgard, & Thrane, 2018). Although the lower extremities are often more severely affected, abnormalities can be

found in unilateral and bilateral upper limb functioning and increase with overall disability in MS (Bertoni, Lamers, Chen, Feys, & Cattaneo, 2015).

The grip strength measure (Grip), which assesses upper extremity motor strength, is included in this study. Relative to healthy controls, in a cross-sectional cohort, MS patients performed significantly worse on a grip strength task (i.e., more than 2 SD difference in 31.3% of the sample) (Newsome et al., 2019). Handgrip strength measures are frequently used in the literature and appear to be reliable and responsive in MS (Lamers & Feys, 2014; Paltamaa, Sarasoja, Leskinen, Wikstrom & Mälkiä, 2008; Paltamaa, West, Sarasoja, Wikstrom & Mälkiä, 2005). Regarding disability progression, in a 2-year follow-up of individuals with MS ($N = 147$), the mean change of grip strength was -4.65 pounds ± 11.15 (*max* + 18.5, *min* -53.0) (Newsome et al., 2019). In grip strength, changes of 5.0 to 6.5 kg may be reasonable estimates of meaningful change (Bohannon, 2019).

Manual motor speed is another area of notable impairment in MS (Zakzanis, 2000), as such, the finger tapping test (FTT) is also included in this study. MS patients perform worse than healthy controls on finger tapping tests with impairment increasing with disease progression (Chipchase, Lincoln, & Radford, 2003). Relative to healthy controls, patients with RRMS obtained an average z-score of $z = -1.46$ (Heaton, Nelson, Thompson, Burks, & Franklin, 1985). Regarding disease progression, at 1 and 2 years, an untreated progressive MS cohort ($N = 48$ at 1 year; $N = 31$ at 2 years) showed a mild progression of disability based on finger taps (respectively: 1 year = 2% decline, *SD* 13%; 2 years = 1% decline, *SD* 13%) (Tanigawa et al., 2017).

Activities and Participation

As aforementioned, impairments in body structures and functions can lead to limitations in activities and restrictions in participation. Specific to this dissertation, the focus will include limitations in the mobility domain, in particular walking ability, lifting and carrying objects, and fine hand use.

Limitations in walking are often the most visible symptom of MS and are a hallmark clinical feature of the disease. Problems with walking (ranging from mild to complete impairment) were reported in 91% of patients (Holper et al., 2010). Walking performance is commonly assessed in MS and progressively decreases with disease and age (Baird et al., 2019). The timed 25-foot walk (T25FW) test is a commonly used measure of gait. Relative to healthy controls, MS groups presented with significant impairment in locomotion ($M = 6.91 \pm 2.35$, $p < .05$) relative to control groups ($M = 5.16 \pm 1.28$, $p < .05$) (Figueiredo, Polachini, & Prado, 2016). In MS, for the T25FW, the minimal clinically important difference (MCID) estimates for 0.35 and 0.37 feet per second are reported (Coleman, Sobieraj, & Marinucci, 2012).

Walking speed appears to be another concern. In a population-based sample of individuals with MS, only 8% walked at normal speed (Einarsson et al., 2006). The two-minute walk test (2MWT) is also included in the present study to gain further observations of speed, distance, endurance, balance, and fall risk (Bennett, Bromley, Fisher, Tomita, & Niewczyk, 2017). Although the six-minute walk test (6MWT) is often the more frequently used measure of functional endurance (Learmonth, Dlugonski, Pilutti, Sandroff, Motl, 2013) it may not be applicable in some settings and populations given the time it takes to administer and the burden to the patient. Studies comparing performance on the 2MWT and 6MWT support the use of the 2MWT as a practical replacement (Bohannon et al., 2014; Gijbels, Eijnde, & Feys, 2011).

Control subjects walk further and faster than MS subjects on the 6MWT ($p < .001$) and the measure can distinguish MS subjects with mild, moderate, and severe disability as based on the EDSS (Goldman, Marrie, & Cohen, 2008). In individuals with neurological dysfunction, minimal detectable change (MDC) on the 2MWT is reported as 11.4 meters for maximum walking speed (Miller, Moreland, & Stevenson, 2002).

In an examination of individuals with varying courses of MS, problems with lifting and carrying objects (ranging from mild to complete impairment) were reported in 59% of participants (Holper et al., 2010). Manual dexterity, the ability to manipulate objects through coordination of the hands and fingers, is a key indicator of motor function (Almuklass, Feeney, Mani, Hamilton, & Enoka, 2017). At least 60% of patients with MS demonstrate impaired fine motor dexterity, with increased impairment associated with disease progression (Benedict et al., 2011; Bertoni, Lamers, Chen, Feys & Cattaneo, 2015; Einarsson et al., 2006; Johansson et al., 2007) and age (Almuklass et al., 2017). As such, the nine-hole peg test (NHPT) will also be used in the present study to capture upper extremity speed and dexterity. Between 60% and 73% of patients with MS demonstrated impaired motor functioning on the NHPT (Einarsson et al., 2006; Ytterberg, Johansson, Andersson, Holmqvist, & von Koch, 2008) with relatively balanced levels of impairment when using their dominant and non-dominant hand (Johansson et al., 2007). Relative to controls, MS patients perform significantly worse on the NHPT at all stages of disease (Benedict et al., 2011) with persons with MS almost four times slower compared to healthy controls (Poole et al., 2009). The NHPT reported minimal detectable change (MDC) for the dominant hand is 4.38 seconds and the non-dominant hand is 7.46 seconds (Hervault, Balto, Hubbard, & Motl, 2017).

Another measure of manual dexterity, grooved pegboard (G-Pegs), requires greater tactile acuity and visuomotor coordination than the NHPT (Bryden & Roy, 2005) and thus may provide greater discrimination of dexterity among adults with early MS. MS patients perform worse than healthy controls with pegboard times for persons with MS (104 ± 40s) slower ($p < .001$) than for those age- and sex- matched HC (61 ± 15s) with an effect size of 0.68 (Almuklass et al., 2017). Other studies report dexterity scores on the GPT up to three times lower than the norms from healthy controls (Poole et al., 2009).

Social Emotional and Behavioral Functioning

MS is typically diagnosed between the ages of 20 and 40 years old, a time where individuals must strive for and manage important social and normative roles such as transition out of their childhood homes and establish a career. Further, MS poses unique challenges in regard to coping and adaptation given the great variability in presentation and trajectories. The unsteady nature of the disease, especially those with relapsing-remitting MS, adds additional stressors of episodes of significantly worsened functioning followed by complete or partial recovery. As such, individuals must cope in the short term with a great amount of uncertainty and unpredictability with the goal of survival and stabilization (Ritnell, 2014).

Incidences of emotional disturbances are common among individuals with MS, especially high levels of anxiety and depressive symptoms (Tan-Kristanto & Kiropoulos, 2015; Zorzon et al., 2001). MS patients also score higher on the Neuropsychiatric Inventory, which is an overall measure of psychopathology, encompassing the domains of anxiety, agitation, irritability, dysphoria, apathy, and euphoria (Sanfilipo, Benedict, Weinstock-Guttman, & Bakshi, 2006). Other difficulties noted in the literature include problems with anger (Mitchell, Benito-León, Gonzáles, & Rivera-Navarro, 2005) as well as an increased lifetime prevalence of bipolar

disorder that is approximately 13 times higher than that of the general population (Thornton, DeFreitas, 2009). Furthermore, high incidences of chronic fatigue further complicate the picture, as it impacts individuals' social, emotional, and behavioral functioning, and exacerbates co-occurring emotional disturbances.

Moreover, to reiterate, motor decline and impairment is a common consequence of MS and can lead to limitations in activities and participation in many life domains, for example, occupational and social functioning. Preliminary findings suggest many individuals with MS do not meet the physical activity requirements of 30 minutes of moderate-intensity aerobic activity and strength training twice weekly (Latimer-Cheung et al., 2013). Thus, the potential impact of physical activity in promoting various social, emotional, and behavioral domains in conjunction with improving motor functioning, warrants further attention and is discussed below.

Anxiety and Depression

In qualitative studies, depression scores of individuals with MS are in excess of one standard deviation higher than healthy persons (Thornton, DeFreitas, 2009). Depression is found early on in MS with 32% of patients reporting experiencing depression after a first demyelinating event or new diagnosis (Rintell, 2014). Across types of MS, the lifetime prevalence of any anxiety disorder is estimated at around 36% with the most common being panic disorder, obsessive-compulsive disorder, and generalized anxiety disorder (Korostil, & Feinstein, 2007). Anxiety and depression in MS are associated with quality of life (Benedict et al., 2005), disease-related factors (Brown et al., 2006; Mohr, Hart, Julian, Cox, & Pelletier, 2004), coping styles (Terrill et al., 2016), and resilience (Terrill et al., 2016; Silverman, Molton, Alschuler, Ehde, & Jensen, 2015). There is a longstanding relationship between stressful life events, depression, and anxiety with subsequent relapses and high annual relapse rates (Brown et al., 2006; Mohr, Hart,

Julian, Cox, & Pelletier, 2004). Lastly, depression can further impact fatigue and pain tolerance and is associated with poorer disease management and medication compliance (Charvet, Kluzer, & Krupp, 2014). As such, assessment of mood, including anxiety and depression, is frequently included in studies on MS as potential vulnerability factors or negative outcomes impacting various facets of functioning, as will be done in the present study.

Fatigue

Fatigue is one of the most common symptoms in individuals with MS, reported in approximately 70% of all patients (Charvet, Kluzer & Krupp, 2014; Chipchase, Lincoln, & Radford, 2003; Learmonth et al., 2013a). It occurs in individuals even with mild disease and may be the first presenting symptom (Ford, Trigwell, & Johnson, 1998). Fatigue in MS is different from the fatigue patients experienced prior to MS and is also different from fatigue associated with other illnesses. For example, patients with MS are more likely to report that their fatigue prevented sustained physical functioning, interfered with meeting responsibilities, and caused frequent problems (Chipchase, Lincoln, & Radford, 2003). In a 2-year longitudinal study at an outpatient MS clinic, 80% of the patients had fatigue at least at one time point, and 44% experienced fatigue during the whole study period (Ytterberg, Johansson, Andersson, Holmqvist, & von Koch, 2008). In MS, fatigue is associated with quality of life, activities of daily living, and physical and psychological symptoms (Ford, Trigwell, & Johnson, 1998; Learmonth et al., 2013a; Mitchell et al., 2005). Therefore, understandably, measures of fatigue are often included in studies on patients with MS as a vulnerability factor or a disease symptom. Moreover, numerous models have been created (and are described below) to examine the relationship between fatigue and resilience in looking at various outcomes. As such, fatigue will be assessed and statistically controlled for in the present study.

Physical Activity

Up until the 1990s, patients with MS were discouraged from participation in exercise as it was believed to lead to worsening symptoms and fatigue. However, more recently, this treatment recommendation has been challenged and exercise has become a fundamental component of many MS rehabilitation programs (Kjølhede, Vissing, & Dalgas, 2012). Several systematic reviews and meta-analyses examining exercise therapy in MS, link various exercise therapy interventions to better outcomes. A review of these findings follows.

Rietberg, Brooks, Uitdehaag, & Kwakkel (2005) conducted one of the first systematic reviews of exercise therapy trials in MS. The analyses included nine high-methodological-quality randomized control trials (RCTs) with interventions including rehabilitation, physical therapy, functional training, home physical training, and aquatic exercise. Authors reported strong evidence in favor of exercise therapy in regard to muscle power function, exercise tolerance functions, and mobility-related activities, compared to the no-exercise control groups. Moderate evidence was found in support of exercise therapy in improving mood. Lastly, no evidence was found in support of exercise therapy in improving fatigue (Rietberg et al., 2005).

Specific to fatigue, a Cochrane Library systematic review examined the efficacy of exercise therapy for fatigue in MS across twenty-six RCTs (Heine, van de Port, Rietberg, van Wegen, & Kwakkel, 2015). The exercise interventions included endurance training, muscle power training, task-oriented training, mixed training, and 'other' training (e.g., yoga). The meta-analysis revealed a significant effect on fatigue in favor of exercise therapy compared to the no-exercise control groups. The authors concluded that although many of the studies exhibited methodological weaknesses, as well as significant heterogeneity between trials, overall, the

findings suggested that exercise therapy, particularly endurance, mixed, or 'other' training, may reduce self-reported fatigue in patients with MS (Heine et al., 2015).

Another systematic review of RCTs investigated the effects of exercise therapy in MS on restoring normal musculoskeletal function (Sá, 2014). The review consisted of eleven studies with exercise interventions including aerobic training, breathing-enhanced upper extremity exercises, endurance exercises, exercise classes, progressive resistance training, upper and lower limb strengthening, and yoga. Studies were categorized into high- and low-quality studies based on their PEDro scores for the methodological quality, where high indicated PEDro scores of 7 to 10 (n = 9), and low indicated PEDro scores lower than 7 (n = 2). Analyses of the high-quality studies revealed exercise therapy had a positive impact on Berg Balance Scale, Dynamic Gait index scores, multidimensional fatigue inventory physical scale, right knee extension, right knee flexion and left knee flexion, SF-36 health survey, one-dimensional Fatigue Severity Scale, and General Fatigue of the Multidimensional Fatigue Inventory scores on walking tests. The low-quality studies revealed that exercise therapy has a positive impact on the fatigue index for leg flexion in women and on the Modified Fatigue Impact Scale score (Sá, 2014).

Kjølhede, Vissing, & Dalgas (2012) conducted a systematic review of sixteen studies specific to progressive resistance training (PRT) in MS. PRT is designed to increase muscle strength by using resistance that is progressively increased over time and includes exercise machines, free weights, and elastic bands. Authors suggested strong evidence regarding the beneficial effect of PRT on lower extremity muscle strength, per increases in maximal voluntary contractions as well as dynamic strength measured by various leg exercises. Further, results indicated moderate, yet inconsistent, support for the effects of PRT on functional capacity (e.g.,

walking performance in timed or distance walking tests, stair climbing, etc.), and self-reported measures of fatigue, quality of life, and mood (Kjolhede et al., 2012).

Taken together, a literature review of exercise therapy interventions in MS links interventions to favorable outcomes such as fatigue, mood, mobility-related activities, exercise tolerance, and measures of balance, gait, muscle power, and ligament extension and flexion.

Psychological Resilience

Psychological resilience is defined as the dynamic process of adapting positively in the face of substantial adversity and significant sources of stress. The concept of resilience, used interchangeably with psychological resilience, first emerged in developmental psychology research, examining why some children appeared to persevere and prosper despite trauma, abuse, or war. The literature from this time typically conceptualized resilience as a fixed personality trait where some children were just more resilient than others (Wister et al., 2016).

A narrative review in 2011 of definitions of resilience (utilizing databases MEDLINE and PsycINFO from 2006 to 2010) found that there may be a lack of consensus regarding an operational definition of resilience, though it is often defined using similar domains (Hermann et al., 2011). More recently in 2015, a systematic review of resilience definitions in physical disease found that consensus is building to view resilience as a dynamic process that varies across the life course rather than as a fixed personality trait (Johnston et al., 2015).

Resilience has gained popularity in clinical research examining other areas of adversity, including as a productive way to view the outcomes and experiences of people living with chronic disease such as MS. Resilience can be characterized in terms of both risk (e.g., disability, adversity) and protective factors (e.g., coping skills, social and environmental resources) that interplay in a dynamic fashion (Black & Dorstyn, 2015). Thus, a key feature of resilience reflects

one's capacity to navigate their way to resources and to overcome challenges by using and negotiating resources (Rainone et al., 2017). Therefore, healthy adaptation to stress depends not only on the individual but also on available resources through family, friends, the community, etc. (Southwick, & Charney, 2012a). As such, individuals who are characterized as having high resilience are those who report more flexible coping and utilize various resources and protective factors both within themselves (e.g., positive characteristics) and in their environment (e.g., social network) (Tan-Kristanto & Kiropoulos, 2015).

Focus on Psychological Resilience in Multiple Sclerosis

An alternative approach to studying individuals with MS is to examine the more positive aspects experienced by persons with MS, focusing on the features of their lives that are going well. The concept of resilience is emerging in clinical research, including research on MS, as a productive way to view the outcomes and experiences of living with a chronic disease and identify potential protective factors. Moreover, attention to resilience in MS research might provide a balanced approach to offset the focus on the negative.

Research suggests that individuals with MS may be at risk for low resilience compared to community samples (Black & Dorstyn, 2013; Koelmel, Hughes, Alschuler, & Ehde, 2017) and individuals with other long-term physical conditions (Silverman, Verrall, Alschuler, Smith, & Ehde, 2017; Terrill et al., 2016). The majority of the studies on resilience in those with MS are quantitative and employ a cross-sectional design to examine associations between potential resilience resources and vulnerabilities with resilience, as well as to identify associations between resilience and various functional outcomes. The studies use a variety of measurements of resilience, though most commonly use the Connor-Davidson Resilience Scale (CD-RISC), as will be used in the present study. Furthermore, a literature review shows development in

interventions to promote resilience through various training models. A review of studies and interventions on resilience in MS-specific populations follows.

Cross-Sectional Studies. As was previously stated, researchers have created various models looking at potential mechanisms to explain associations between MS-related symptoms (e.g., pain, fatigue), positive outcomes (e.g., resilience), and negative outcomes (e.g., depression, quality of life). Black and Dorstyn (2015) created a holistic model of resilience that incorporated biological, psychological, and social variables. The model was tested utilizing the results of an online survey completed by adults with MS ($N = 196$). Participants were 18 to 70 years of age ($M = 43.94$) and were comprised of both individuals newly diagnosed with MS (i.e., less than a year since diagnosis), and those with long-term MS diagnoses, the majority with RRMS. The findings suggested that psychological variables (positive affect and self-efficacy) directly and significantly contribute to resilience levels (measured with CD-RISC-10) and disease-specific variables (fatigue and physical independence) in addition to social support also influence resilience in an indirect way, seen in the figure below (Black & Dorsyn, 2015, p.1436).

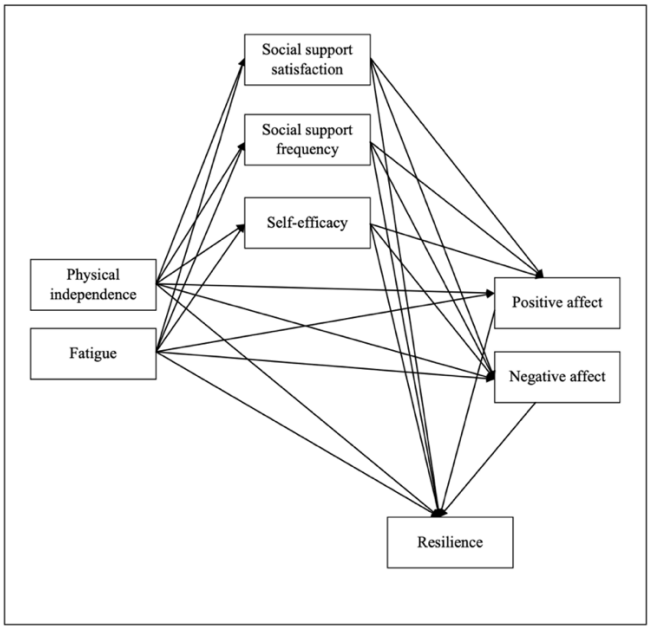

Figure 1. Proposed model of resilience in multiple sclerosis.

The authors concluded that the tested variables in the model accounted for 44% of the variance in the sample's resilience, with positive affect and self-efficacy being the strongest predictors (Black & Dorsyn, 2015). Taken together, findings from this study show support for the dynamic quality of resilience in its relationship to psychological variables, disability-specific variables, and social support. However, this model is incomplete with 56% of the variance remaining unaccounted for.

Swanepoel, van Staden, & Fletcher (2020) investigated the extent to which psychological resilience (measured with CD-RISC-25 item version and the Resilience Scale for Adults) and psychological vulnerability (measures one's negative beliefs regarding themselves and their illness) play a mediating role in the relation of adverse life events with fatigue, motor dysfunction (self-report measure including weakness, slowness of movement, stiffness, spasms, falling, etc.), and paresthesia (self-report measure of paresthesia i.e., tingling and burning sensation in arms, feet, etc.) in MS. This study was based on previous research showing an association between adverse life events and exacerbating MS symptoms. Participants ($N = 1239$) were 18 to 81 years of age and included a mix of all types of MS, the most frequent being RRMS (69.3% of the sample). The researchers found a model whereby both resilience and vulnerability interacted as mediators in the relation between adverse life events during the preceding 60 days and fatigue, motor dysfunction, and paresthesia, seen below (Swanepoel et al., 2020, p. 142). The model was statistically significant, and the goodness of fit was moderate [$X^2 (7111) = 26{,}724.8$, $p < .001$].

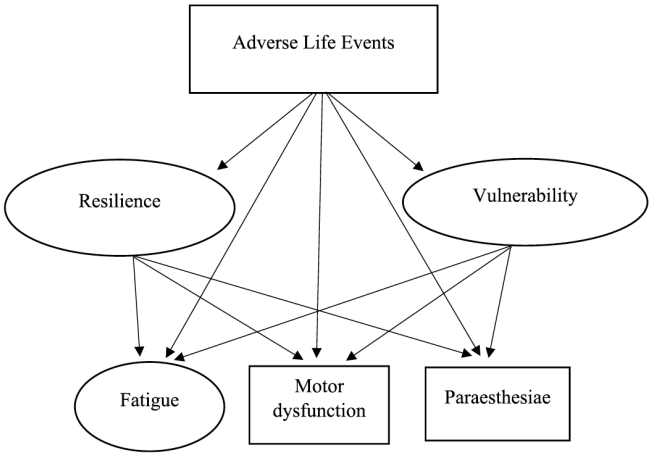

FIGURE 1. Diagram of the basic model representing the hypothesized relationship between adverse life events, resilience, vulnerability, and the multiple sclerosis symptoms.

In summary, this study demonstrates support for the potential role of resilience in mediating the relationship between adverse life events and MS symptoms, suggesting a protective effect.

Another cross-sectional study examined the potential role of positive factors (i.e., positive affect and resilience), in the context of coping with MS. Participants ($N = 455$) ranged in age from 27 to 90 ($M = 61$), with various types of MS, the most frequent being RRMS (60%) (Arewasikporn et al., 2018a). The study found that resilience (measured using CD-RISC-10) was found to mediate the associations between positive affect (positive emotions and expressions) and pain function ($ab_{\text{pain interference}} = -0.03$, $p = .03$; $ab_{\text{depressive symptoms}} = -0.13$, $p < .001$) (Arewasikporn et al., 2018a). In other words, positive affect was indirectly related to pain interference and depression through resilience. This study demonstrates support for resilience along with positive affect, as important constructs to consider in understanding adaptation to pain in people with MS.

Arewasikporn et al. (2018b) conducted another study examining pain catastrophizing, fatigue catastrophizing, positive affect, and negative affect (adverse mood states) and impact on daily life, depressive symptoms, and resilience (measured with CD-RISC-10) in MS. The sample

(N = 163) included participants ranging in age and MS subtype. Results indicated that negative affect mediated the relationship between pain intensity and resilience (ab = -0.07, p = .04) and positive affect mediated the relationship between fatigue intensity and resilience (ab = -0.12, p = .006) (Arewasikporn et al., 2018b). Taken together, these studies highlight positive and negative affect as potential mechanisms in understanding the relationship between resilience and disease symptoms.

Qualitative Studies. A review of qualitative and survey studies provides insight into various factors and behaviors associated with resilience. Ploughman et al. (2020) examined the impact of resilience in healthy aging in people with MS (N = 743). Researchers found that participants who scored higher on resilience (measured with the 14 item Resilience Scale) also reported healthier lifestyle behaviors (e.g., more exercise, better diet) and social/financial support compared to lower scoring individuals.

In a study examining focus groups, some of which were composed of individuals with MS (n = 12) aged 36-62 years old, partners of individuals with MS (n = 11), and community stakeholders serving individuals with MS (n = 9), various facilitators of resilience were identified. The facilitators, or major supports to resilience, included: psychological adaptation (e.g., coping, optimism, humor), social connection (connecting with family, friends, and peers with MS), life meaning (e.g., family relationships and engaging in hobbies and volunteerism), planning (e.g., attention to logistics and routines) and physical wellness (e.g., exercise and stress reduction). Participants also identified the following barriers to resilience: negative thoughts and feelings, social barriers (wearing out or losing friends), stigma (refusing accommodations), physical fatigue (Silverman et al., 2017).

Longitudinal Cohort Studies. A cohort study examined resilience as a mediator in longitudinal relationships between social support and mental health outcomes in MS (Koelmel, Hughes, Alschuler, & Ehde, 2017). Participants (N = 163) ranged in age from 25 to 76 (M = 52.2) and included RRMS and PMS subtypes. Results indicated that improvements in social support and resilience (measured using CD-RISC-10) predicted better mental health outcomes. Further, resilience was found to significantly mediate the relationships between social support and subsequent mental health outcomes including depressive symptomatology, anxious symptomatology, and overall mental health status at four time points (baseline, and weeks 10, 26, and 52). When resilience was statistically controlled for, nearly all relationships between social support and mental health outcomes were no longer significant (Koelmel et al., 2017). These findings suggest that resilience plays an important role in how social support impacts mental health.

Focus on Psychological Resilience in Other Clinical Populations

A review of studies examining resilience in chronically ill or physically disabled populations, some of which include mixed samples with MS patients, follows.

Systematic Reviews. Stewart and Yuen (2011) conducted a systematic review of 52 articles on resilience and related concepts in the physically ill, in those with MS, and in samples that included MS along with other diseases. In the mix of studies, the following factors were associated with resilience: self-efficacy, self-esteem, internal locus of control, optimism, mastery, social support, hardiness, hope, self-empowerment, determination, personal growth, and acceptance. Further, salient to physical illness, resilience was found to be associated with self-care, adherence to treatment recommendations, health-related quality of life, illness perception, pain perception, exercise adherence, and physical outcomes (Stewart & Yuen, 2011).

Cross-Sectional Studies. Alschuler, Kratz, & Ehde (2016) examined both "vulnerability factors" (i.e., variables that are associated with worse outcomes) and "resilience factors" (i.e., variables that are associated with better outcomes and/or variables that buffer against worse outcomes) to pain-related outcomes. These pain-related outcomes included pain interference, self-efficacy for managing pain, and global mental and physical health. The study included individuals (N = 188) with spinal cord injury, amputation, and MS. Resilience resources were operationalized as four factors: pain acceptance, positive affect, the adaptive pain belief of control over pain, and the adaptive pain belief that emotions can influence pain. Resilience vulnerabilities were operationalized as depressive symptoms, pain catastrophizing, and the maladaptive pain belief that one is disabled by their pain and the maladaptive pain belief that solicitous responses from others are acceptable when in pain. The authors concluded that both the resources and vulnerabilities of resilience contributed to pain interference and global physical health at generally the same significance with neither making a substantial contribution above and beyond the other.

A large cross-sectional sample of survivors (N = 1823) of hematopoietic cell transplantation (HCT) demonstrated that lower resilience (measured with CD-RISC-10) was associated with poorer outcomes. Specifically, lower resilience was linked to lower scores on the Karnofsky Performance Scale, a scale that assesses one's ability to carry out normal work and daily responsibilities, missing more days of work because of health, and permanent disability (all $p < .0001$). Notably, however, after adjusting for demographic and health characteristics, relationships between resilience and aforementioned performance measures were lost, and only the relationships between resilience and psychological distress as well as mental health-related quality of life remained (Rosenberg et al., 2015).

In a cross-sectional correlational study, examining patients with Parkinson's disease (PD) ($N = 83$), researchers examined the relationship between resilience (measured with Resilience Scale 15) and disease severity, disability, health-related quality of life (QoL), and non-motor symptoms (Robottom et al., 2012). Resilience was significantly associated with better physical and mental Qol, reduced non-motor symptoms (i.e., apathy, depression, fatigue, and anxiety), and more optimism. Higher resilience was not associated with disease severity, self-esteem, or locus of control (Robottom et al., 2012).

Another cross-sectional survey study on patients with PD ($N = 138$), examined the role of resilience (measured with Resilience Scale for Adults) in modifying mental health and QoL adjustment in PD, when statistically controlling for multiple clinical variables such as age, gender, ethnicity, years of education, income level, years since diagnosis, and functional impairment (measured with Functional Independence Measure - self report) (Shamaskin-Garroway, Lageman, & Rybarczyk, 2016). Results revealed associations between resilience and less depression, less apathy, greater life satisfaction, and greater QoL, after statically controlling for aforementioned variables (Shamaskin-Garroway et al., 2016).

Longitudinal Cohort Studies. A study examining patients following knee joint replacement ($N = 153$), examined both preoperative level of resilience and concurrent resilience (resilience levels for the respective time period) in its relationship to knee-specific health outcomes as well as general quality of life outcomes at various time-points (Magaldi, Staff, Stovall, Stohler, & Lewis, 2019). When looking at concurrent resilience, resilience was significantly correlated with all outcome measures. When assessing for longitudinal relationships, resilience levels that were measured preoperatively predicted 3-month outcomes reflecting general quality of life, the PROMIS-10 Physical component ($R^2 = 0.10$, $p < .001$) and

Mental component (R^2 = 0.20, p < .001), but did not predict outcomes specific to knee pain and function. The same pattern of relationships was found at 12-month follow-up. That is, baseline resilience was found to correlate significantly with overall physical and mental health outcomes at 12 months, but not any knee-specific health outcomes. Notably, researchers also reported that patients with overall poor outcomes were more likely to experience a decrease in their resilience over the 12-month period, whereas those with high outcomes demonstrated more stable levels of resilience (Magaldi et al., 2019).

Longitudinal Survey Studies. Several articles are published using data from the same ongoing U.S national longitudinal survey tracking a community sample of 1929 individuals aging with physical disabilities, including MS, spinal cord injury, muscular dystrophy, and post-polio syndrome. The majority of participants were middle-aged or older adults (M = 56.13, SD = 13.31). This survey included a variety of measures of functioning, though most pertinent to this paper, included resilience (measured with CD-RISC-10), physical function, depression, and fatigue. Physical function was measured with the PROMIS physical functioning item bank, a patient-reported outcome of coordination, functional mobility, strength, and upper extremity function that is designed to estimate the respondent's perceived ability to perform a variety of physical activities on a 5-point scale. Depression was measured using the Patient Health Questionnaire-9 and fatigue was measured using the PROMIS Fatigue Short Form (Edwards et al., 2017; Terrill et al., 2016). These articles and their findings are described below.

In a cross-sectional analysis of this cohort (N = 1862), participants with MS and muscular dystrophy had lower resilience scores than the spinal cord injury and post-polio syndrome participants and resilience did not vary by sex. Resilience was negatively associated with both pain (β = -.18, p < .001) and fatigue (β = -.37, p < .001). Higher resilience was associated with

lower depression (β = -.54, p < .001) and higher quality of life (β = .23, p < .001). Further, resilience mediated the relationship between secondary symptoms (pain and fatigue) on quality of life and depression (Terrill et al., 2016).

Another article examined whether changes in resilience over a one-year time period (t1 – t2) were associated with changes in depression, fatigue, sleep quality, and physical function. In this analysis (N = 893), resilience exhibited similar stability over 1 year to depression, fatigue, and sleep quality (Edwards et al., 2017). The authors concluded that resilience exhibits similar test-retest stability as other common and important treatment targets. Further, a decrease in resilience was associated with an increase in depression (F = 70.23; p < .001; R^2 = .54) and fatigue (F = 25.66; p < .001; R^2 = .64), and an increase in resilience was associated with improved sleep quality (F = 30.76; p < .001; R^2 = .48), and physical function (F = 16.90; p < .001; R^2 = .86) over a 1-year period (Edwards et al., 2017). Taken together, results from both studies demonstrate further support for resilience as a contributing factor in disease symptoms.

A cohort study (N = 1,574) from the dataset investigated the longitudinal relationship between resilience and four domains: anxiety, depression, physical function, and social role satisfaction at years 5, 6, and 7 (labeled T1, T2, and T3, respectively). Reciprocal relationships were found where resilience predicted social role satisfaction (T1 to T2 standardized coefficient 0.09; T2 to T3 = 0.09), resilience predicted lower anxiety (T1 to T2 standardized coefficient -0.15; T2 to T3 = -0.11), and resilience predicted lower depression (T1 to T2 standardized coefficient -0.21; T2 to T3 = -0.13) (Battalio, Tang, & Jensen, 2019). None of the lagged associations between resilience and physical function were significant. The authors concluded that resilience may only have minimal relevance to improved physical functioning but appears to be a significant prospective predictor of psychological and social function over time.

Utilizing the longitudinal survey study ($N = 1594$), authors sought to examine the association between resilience and outcome measures as well as to assess resilience as a predictor of change in such outcome measures over 3 years. Researchers classified "lower levels of resilience" as values below the mean and "higher levels of resilience" as values above the mean. Results indicated that higher initial levels of resilience were found to be associated with a slight decrease in depressive symptoms ($r_p = -.12$, $p < .001$) and slight increase in social participation ($r_p = .12$, $p < .001$) over 3 years. Further, at baseline, higher levels of resilience had a weak positive association with subjective measures of perceived physical functioning ($r = .17$, $p < .001$) cross-sectionally even after statistically controlling for age, sex, disability diagnosis, education, and income. However, after 3 years, resilience did not predict the change in physical functioning, despite being positively correlated at baseline. In a supplementary analysis examining whether resilience serves as a buffer between symptoms and functioning, resilience was found to moderate the association between depressive symptoms and low physical functioning at baseline ($t = 2.40$; $p = .017$; $R^2 = .004$) (Silverman, Molton, Alschuler, Ehde, & Jensen, 2015).

Resilience Intervention Studies

Although more research is needed to determine the efficacy of these programs, examples of resilience training programs have started to gain popularity. The intervention studies discussed below include general studies of resilience interventions as well as studies specific to MS. As these interventions differ significantly regarding methods and treatment aims, they will be organized into groups. The first group of interventions are those where resilience was used in both the intervention programs and also as the dependent variable. The second group of interventions are those where resilience was used in the intervention program though not as a

dependent variable. Lastly, the third group, are those interventions where resilience is used as a dependent variable but not as an intervention target.

Resilience Interventions with Resilience as Dependent Variable. A review of resilience boosting interventions, where resilience serves as an outcome measure, follows. Such studies shed light on the modifiable quality of resilience, that is, examining if resilience can be targeted and increased through intervention. Moreover, by including additional outcome measures in addition to resilience, such studies also shed light on the potential benefits of boosting resilience on other physical, social, emotional, and behavioral outcomes.

Alschuler et al. (2018) conducted a pilot (RCT) study examining the effects of a positive psychology intervention on adults (aged 45 and older) with MS ($N = 27$). The intervention was created by the National MS society and attempted to improve resilience through providing participants information on skill development and goal setting, happiness habits, retraining cognitions for positivity, building social connections, removing barriers to action, and gaining positive momentum. Results found that the treatment group had a greater increase in resilience after 6 weeks than the waitlist group.

A telehealth-based resilience building six-week program was created for individuals with MS and their support partners ($N = 62$). The intervention included education and practical skills in the areas of positive adjustment to MS, psychoeducation (e.g., symptoms of MS), communication skills, healthy coping skills, advocacy skills, and identifying and accessing resources. The study showed an increase in resilience-building skills needed to address challenges faced by individuals with MS for both groups of participants as well as increased levels of resilience (measured with CD-RISC 10) (Halstead, Leavitt, Fiore, & Mueser, 2020).

The Activities for Every Day for people with MS (READY for MS) is a resilience group training program based on Acceptance and Commitment Therapy (ACT). The READY program has been studied in various populations included workplace settings as well as patients with cancer and diabetes, and has demonstrated improvement in resilience, psychological flexibility, physical activity, mindfulness, subjective well-being, health behaviors, and QoL (Pakenham, Mawdsley, Brown, & Burton, 2018). A pre-post group intervention examined the outcomes from an adaptation to this program on patients with MS ($N = 37$). The intervention model included numerous modules such as physical activity, mindfulness, social connectedness, and pleasant activities, among others. Results of the intervention revealed significant improvements in resilience [(measured with the Resilience Scale 15 item) ($p = .005$; *Hedge's* $g = .47$)], physical health QoL ($p < .001$; $g = -.76$), mental health QoL ($p = .006$; $g = -.46$), depression ($p = .009$; $g = .38$), and stress ($p = .025$; $g = .33$) (Pakenham et al., 2018).

Another pilot randomized control trial (RCT) examined the effectiveness of the READY intervention, described above, also in MS patients ($N = 39$) (Giovannetti et al., 2020). The majority of participants stated that the READY program increased their resilience, positively affected their life, and helped them in dealing better with their MS. Further, results indicated significant improvements in several psychological dimensions at three-month follow-up, with 65% reaching a clinically significant improvement in the mental component of the health-related quality of life measure. However, the READY program was no more efficacious than the relaxation control program in showing statistically significant improvements on the outcome measures, including measures of resilience using the CD-RISC 25 item version (Giovannetti et al., 2020).

Taken together, studies of resilience boosting interventions show support for the modifiable quality of resilience through intervention, as well as the potential benefits of such interventions on other areas of functioning including physical health QoL, mental health QoL, depression, and stress.

Resilience Interventions without Resilience as Dependent Variable. An overview of additional resilience boosting interventions follows, with the distinction that these studies do not include resilience as an outcome measure. As such, no conclusions regarding the modifiable quality of resilience can be inferred from these studies, and rather, attention is paid to the impact of such resilience interventions in promoting other factors such as perceived social support.

An 8-week mind-body program called Relaxation Resiliency Program was created for patients with neurofibromatosis ($N = 36$), aimed at elicitation of the relaxation response, stress appraisal and coping, and growth enhancements (e.g., social support, gratitude,) found improvements in coping abilities ($M_{difference} = 6.68$, $p = .008$), perceived social support ($M_{difference} = 9.16$, $p = .032$), and mindfulness ($M_{difference} = 2.23$, $p = .035$), compared to the control group. These findings were also maintained at a 6-month follow-up. Notably, no difference was found regarding pain-inference (Zale, Pierre-Louis, Macklin, Riklin, & Vranceanu, 2018).

Bradshaw et al. (2007) conducted a randomized control trial to examine the Resiliency Training Approach for Diabetes (RTAD) in adult patients with diabetes ($N = 54$). The intervention study was based on resilience qualities, including, self-efficacy, locus of control, purpose in life, and social support. Analyses of variance indicated that the intervention group had better outcomes at 3 months, as reported by endorsements that they were choosing healthy ways to eat ($p = .01$), and at 6 months, as reported by knowing positive ways to cope with diabetes-

related stress (p = .01), and less trouble exercising because of health problems (p = .01), compared to the control group.

Taken together, resilience-boosting interventions aimed at promoting other associated variables show moderate support for these interventions and positive outcomes, such as better patient-reported lifestyle behaviors, perceived social support, mindfulness, and coping abilities.

Non-Resilience Interventions with Resilience as Dependent Variable. Lastly, a review of interventions measuring resilience as an outcome, but not as the specific intervention target, follows. In other words, these studies are not aimed at directly boosting resilience, but rather other variables such as depression, and are examining resilience as one of many outcome measures following the intervention. Thus, the purpose of including such studies in the present paper is to shed light on potential variables capable of promoting self-reported levels of resilience in patients.

A small pilot study examined an eight-week cognitive-behavioral intervention aimed at treating depressive symptoms in those newly diagnosed with MS (N = 30), where resilience was added as a secondary outcome (Kiropoulos, Kilpatrick, Holmes, & Threader, 2016). Participants were randomly assigned into the intervention group or a "usual care" group which received usual medical care from their neurologist and did not receive additional services to address the depressive symptoms. The intervention group showed improvement in their resilience (measured with the 33-item Resilience Scale for Adults) compared to the "usual care" group. These findings were retained up to 20-weeks post-treatment (Kiropoulos et al., 2016).

Another randomized control trial examined the efficacy of a telephone-delivered eight-week self-management program aimed at improving fatigue, pain, and depression in adults with MS (N = 163) aged 25-76 years old, where resilience was added as a secondary outcome (Ehde

et al., 2015). Self-report measures were repeated at 10, 26, and 52 weeks and found "statistically significant" improvements in resilience (measured with CD-RISC) (Ehde et al., 2015), although it was unclear how the authors determined criteria for meaningful change.

Not specific to MS, the Penn Resiliency Program (PRP) is a cognitive-behavioral intervention aimed at targeting depressive symptoms in both youth and adults. This training program is one the most widely researched depression prevention programs, cited in at least 17 controlled studies. The intervention targets resilience competencies such as self-awareness, self-regulation, optimism, and social connectedness. A meta-analysis examining these studies found that youth who participated in the intervention report reliably lower levels of depressive symptoms through 12 months than the control group, with modest effect sizes ranging from 0.11 to 0.21 (Brunwasser, Gillham, & Kim, 2009).

Taken together, non-resilience interventions targeting variables including self-management and depression, show modest support for improvements in patients' self-reported levels of resilience with intervention.

Neurobiological Basis of Resilience

There is a growing focus on understanding the neurobiological mechanisms that promote resilience to stress in some individuals. Preclinical and human research examining the neurobiology of resilience, suggests viewing resilience as a process that integrates multiple central and peripheral systems that ultimately affect brain function and behavior (Cathomas, Murrough, Nestler, Han, & Russo, 2019). Using an allostatic framework (i.e., the process by which the body responds to stressors in order to regain homeostasis) Feder et al., (2011) have created a model of resilience. The model states that throughout life, genetic and environmental agents interact with and reshape the circuitry responsible for the stress response. This circuitry is

a dynamic neural system involved in fear, reward, emotion regulation, and social behavior that determines the degree of resilience. Researchers conclude that individuals can become more resilient with exposure to enhancing protective factors (Feder et al., 2011).

Other research has identified several tentative neuroendocrine concomitants of resilience in humans, largely, examining individuals with major depressive disorder (MDD) and posttraumatic stress disorder (PTSD). Here, researchers attempt to characterize biological factors in resilient individuals that are associated with more successful coping responses. Studies examining the hypothalamic-pituitary-adrenal (HPA) axis, the mechanism responsible for mediating the impact of stress on brain and behavior through widespread hormonal, neurochemical, and physiological alterations, report variable findings regarding its role in risk or resistance to stress-related disorders (Southwick & Charney, 2012b). Notably, the findings note varying levels of glucocorticoid levels, which in turn, underlie behavioral responses to stress, for example, suggesting that exogenous glucocorticoid replacement can protect against PTSD in trauma-exposed humans (Russo, Murrough, Han, Charney, & Nestler, 2012).

The efficacy of brain regions in carrying out designated functions has been explored. Such brain systems may mediate or moderate resilience to stress. For example, it may be advantageous to have robust executive functioning capacities in the prefrontal cortex to inhibit and regulate limbic, emotional, and behavioral reactivity to stress. In addition, having a well-modulated amygdala that does not over-or underreact to both internal and external stimuli could be beneficial as well (Southwick & Charney, 2012b; Feder, Nestler, & Charney, 2009).

Testosterone levels appear to decrease following stress, as well as lower circulating levels in individuals with MDD and PTSD (Pope, Cohane, Kanayama, Siegel, & Hudson, 2003). Neuropeptide Y (NPY), a peptide neurotransmitter that modulates the stress response in animals,

has been examined as a potential protective factor in the face of stress for humans as well (Morgan et al., 2000; Russo et al., 2012). Specifically, higher levels of NPY during acute stress is linked to less psychological distress and fewer symptoms of dissociation (Morgan et al., 2002). Research on PTSD patients suggests that dehydroepiandrosterone (DHEA), a hormone released in response to stress, as well as the DHEA to cortisol ratio, may represent a resilience factor, specifically that the DHEA release during stress may buffer the severity of symptoms (Rasmusson, Vythilingam, & Morgan, 2003). Lastly, genes related to the HPA axis, serotonergic systems, and NPY show weak to moderate associations with resilient phenotypes, including, GR-heterocomplex co-chaperon gene, ADCYAP1R1 gene, CRH receptor-1 gene, and serotonin transporter genes (Russo et al., 2012).

Well-controlled animal work has revealed neurobiological mechanisms, that is, neural circuits and molecular adaptations within these circuits that contribute to resilience. Resilience in animal studies is typically operationalized as those animals who "exhibit some deleterious symptoms in response to stress but do not exhibit deficits in key behavioral domains" (Russo et al., 2012, p.4). Studies have identified pro-susceptibility neural and molecular factors, such as the HPA axis and K+ channel, which may promote resilience (Christoffel, Golden, & Russo, 2011). Further, resilience to stress is linked to unique changes in gene expression and chromatin modifications in specific brain regions such as the prefrontal cortex, hippocampus, amygdala, and nucleus accumbens (Krishnan et al., 2007; Wilkinson et al., 2009).

The concept of resilience in biological and neurobiological literature, including research on both humans and animals, differs both conceptually and methodologically from the way in which psychological resilience is understood and captured in the present study. Conceptually, in the present study, resilience is operationalized as a psychological trait, with focus on the

psychological basis of resilience. Individuals rate themselves on various items, such as, their ability to stay focused under pressure, persevere through failure, manage unpleasant feelings, and see the humorous side of obstacles. Methodologically, in the present study, the instrumentation seeks to estimate psychological resilience through capturing patients' self-reported abilities across domains that are understood to attribute to resilience. The potential biological and neurobiological basis of resilience is out of the scope of the present study, and no objective biological measures to capture potential neuroendocrine concomitants of resilience are included.

Baseline Findings

A cross-sectional analysis, using the same longitudinal cohort of early MS patients (n = 165 RRMS and n = 20 CIS) as used for the present dissertation, by Klineova et al. (2019) examined whether psychological resilience explains differential objective cognitive and motor functioning in persons with early MS. Results found less mood disturbance with higher resilience. Specifically, lower resilience [measured using Connors Davidson Resilience Scale (CD-RISC)] was associated with worse mood [Mental Health Inventory (MHI) $r = 0.620$, $p < .001$] and worse fatigue [Fatigue Severity Scale (FSS) $r = -0.449$, $p < .001$] (Klineova et al., 2019). Psychological resilience was unrelated to disease burden (T2LV and normalized gray matter) or traditional metrics of neurologic disturbance (EDSS) (Klineova et al., 2019). There was a difference in resilience by race, with lower levels of resilience reported by those who identified as African American.

Higher psychological resilience (CDRS-10) was linked to better MSFC ($r = 0.245$, $p < .001$) as well as better performance on the Total Motor composite ($r = 0.301$, $p < .001$), Fine Motor composite ($r = 0.194$, $p = .008$), and Gross Motor composite ($r = 0.305$, $p < .001$) (Klineova et al., 2019). After correcting for multiple comparisons (Bonferroni-adjusted $p \leq .007$)

and adjusting for mood and fatigue, the Total Motor composite ($r_p = 0.199$, $p = .007$) and Gross Motor composite ($r_p = 0.184$, $p = .013$) remained significant (Klineova et al, 2019).

In a secondary analysis examining the individual tasks comprising the composites, researchers found that higher resilience was related to the majority of the motor functioning outcomes including upper body strength [Grip], gait endurance [2MWT], and simple motor speed [FTT], gait speed [T25FW], and upper extremity speed and coordination [NHPT]. Fine motor speed and dexterity [G-Pegs] was not related to resilience. After correcting for multiple comparisons (Bonferroni-adjusted $p \leq .007$) and adjusting for mood and fatigue, upper body strength (Grip $r_p = 0.223$, $p = .002$), gait endurance (2MWT $r_p = 0.150$, $p = .042$), and motor speed (FTT $r_p = 0.192$, $p = .009$) remained significantly related to resilience. In contrast, fine motor dexterity (NHPT), visual motor coordination and dexterity (G-Pegs), and gait speed (T25FW) were not significant (Klineova et al., 2019).

Furthermore, the relationship between psychological resilience and motor tasks was also assessed on the healthy control group ($n = 50$), a matched group of friends and non-first-degree relatives of patients. Similar patterns were identified where higher resilience was linked to better performance on upper body strength (Grip $r_p = 0.382$, $p = .006$), gait endurance (2MWT $r_p = 0.275$, $p = .053$), and motor speed (FTT $r_p = 0.224$, $p = .118$), and these relationships held even when statistically controlling for mood and fatigue. All other tasks were unrelated to resilience. These findings could be suggestive of a non-disease-specific relationship between resilience and particular domains of motor functioning. It also should be noted that in this sample there were no significant differences in psychological resilience levels between patients and healthy controls, which contrasts findings reported by other aforementioned studies (Klineova et al., 2019).

In summary, a review of the literature on psychological resilience in MS and physically disabled populations demonstrates that resilience is associated with various disease-specific symptoms, positive outcomes, and negative outcomes. Such associations are complex, where resilience shows varying direct and indirect roles in these relationships. Thus, the body of research shows support for resilience as a contributing factor to functional outcomes, however, its mechanism is still poorly understood.

Purpose and Hypotheses

The purpose of this dissertation is to examine the protective and predictive quality of psychological resilience on various domains of motor functioning, including gait and balance, endurance and stamina, upper body strength, motor speed, and upper extremity coordination in an early cohort of patients with MS. For this study, psychological resilience is operationalized as the self-reported ability of adapting well in the face of substantial adversity and significant sources of stress and was estimated using a validated self-report measure (CD-RISC-10).

The aims of this dissertation are to (1) evaluate if resilience can predict change in objective functional outcomes across a 3-year time period, (2) examine if resilience can serve as a protector in the relationships between disease-specific impairment and functional outcomes, and (3) assess the degree of change in resilience as a clinical population progresses in disease.

This study seeks to expand the findings of Klineova et al. (2019) to re-examine the role of resilience in this clinical population 3 years later to evaluate this construct as a potential predictor of change in objective functional outcomes. The findings have implications with regard to improved understanding of the variability and progression of motor disability (e.g., identifying those most at risk for decline in motor functioning) in MS as well as identifying a potential contributor to such outcomes. Such insight can help inform treatment decisions such as early

pharmacological treatment, rehabilitative intervention (e.g., occupational therapy), as well as therapy-based intervention/clinical trial research.

Hypotheses were developed based on a thorough literature review as well as the results of the baseline cross-sectional analysis and paper by Klineova et al. (2019).

Hypothesis 1: Baseline psychological resilience will predict changes in motor functioning from baseline to 3-year follow-up.

Hypothesis 2: Baseline psychological resilience will predict changes in motor functioning from baseline to 3-year follow-up independent of mood and fatigue.

Hypothesis 3: Baseline psychological resilience will moderate the relationship between disease burden and motor functioning at 3 years.

Chapter 3: Methods

Participants

Participants (N = 130) were patients at a regional MS clinical care and research center in New York, New York. The sample for this study was from the Reserve Against Disability in Early MS (RADIEMS) Cohort, a longitudinal study of risk and protective factors for cognitive decline in persons with MS or CIS aged 20 to 50 years and within 5 years of diagnosis. The sample consisted of persons with relapsing-remitting MS or a CIS diagnosis without a clinical relapse in the last 6 weeks. All subjects were English language proficient. Key exclusions included other neurologic or neurodevelopmental conditions, pregnancy, major psychiatric illnesses, and clinical MS relapse within the past 6 weeks. Further, dyslexia will be controlled to account for any non-disease-related cognitive weaknesses.

A total of 66.2% of the population identified as female. The mean age of the participants was 33.8 (SD = 7.5) with a range of 20 to 50 years of age. Race included Caucasian (68.5%), African American (19.2%), and other (12.3%). Ethnicity included Hispanic (24.4%). These demographic ratios in the sample are comparable to reported statistics of those with MS in the United States (Steele & Mowry, 2014; Wallin et al., 2019). The mean years since diagnosis at baseline was 2.18 (SD = 1.37). MS phenotypes included 116 RRMS and 14 included CIS. Lastly, body mass index was collected with a mean of 27.0 (SD = 6.4), seen in Table 1.

Table 1.

Baseline Sample Characteristics

Age (*M* ± *SD*)	33.8 (7.5)
Sex (% female)	66.2
Race	
Caucasian (%)	68.5
African American (%)	19.2
Other (%)	12.3
Ethnicity (% Hispanic)	24.6
Disease course (RRMS/CIS)	116/14
Years since diagnosis (*M* ± *SD*)	2.2 (1.4)
Body Mass Index (*M* ± *SD*)	27.0 (6.4)

Materials

For this study, the primary predictor variable: psychological resilience, is operationalized as the self-reported ability of adapting well in the face of substantial adversity and significant sources of stress and was estimated using a validated self-report measure the Connor-Davidson Resilience Scale, 10 item version (CD-RISC-10). The following motor performance metrics collected during this study, include the 2-minute walk test (2MWT), timed 25-foot walk (T25FW), nine-hole peg test (NHPT), grooved pegboard (G-Pegs), grip strength (Grip), and finger tapping test (FTT), which served as this study's outcomes. Additional predictors include mood [mental health inventory (MHI)], fatigue [fatigue severity scale (FSS)], physical activity (PA), demographic variables [age, sex, race, ethnicity, body mass index (BMI)], disease variables [disease-modifying therapy (DMT), disease phenotype: relapsing-remitting MS (RRMS) or clinically isolated syndrome (CIS)], and MRI estimates [T2 lesion volume (T2LV), normalized whole brain volume (nBrain), and lesion count in the cervical spinal cord (C-spine)].

Psychological Resilience

Connor-Davidson Resilience Scale. The CD-RISC is a widely used 25-item self-report measure of resilience. The CD-RISC has strong psychometric properties: internal consistency (α = 0.89) and test-retest reliability (*ICC* = 0.87) (Connor & Davidson, 2003). The psychometric properties of the CD-RISC-10, an abbreviated version of the original, are established in different populations with high internal consistency and convergent validity relative to the 25-item version (Campbell-Sills & Stein, 2007; Kuiper, van Leeuwen, Stolwijk-Swüste, & Post, 2019). Agreement between the CD-RISC 25 and the CD-RISC-10 is reported as *ICC* = 0.90 with 95% CI from 0.85 to 0.94 (Kuiper, van Leeuwen, Stolwijk-Swüste, & Post, 2019). Internal consistency of the 25-, 10-, and 2-item scales are good to moderate (0.90, 0.86, and 0.66, respectively) (Kuiper et al., 2019).

The 10-item version will be used in the present study. It is a self-report measure on which subjects have to report on their perceived ability (0 = not true at all, 4 = true nearly all the time) to cope with stressful and challenging situations and overcome setbacks (e.g., seeing oneself as being able to handle unpleasant feelings, being able to achieve one's goals, staying focused under pressure, and not being easily discouraged by failure). The maximum raw score on the CD-RISC-10 is 40. Higher scores indicate higher levels of resilience and thus suggest one's strong belief in their ability to cope and overcome obstacles.

Tasks of Motor Functioning

2 Minute Walk Test. The 2MWT is a measure of gait endurance and stamina. Although the Six-Minute Walk Test (6MWT) is often the more frequently used measure with high test-retest reliability (*ICC* = 0.959) (Learmonth et al., 2013b), it may not be applicable in some settings and populations given the time it takes to administer and the burden to the patient. Using

a community sample, researchers examined performance over the first 2 minutes and the full 6 minutes of the 6MWT and found that the completion rate, test-retest reliability, and relationship of the distances walked in 2 and 6 minutes provided support for the use of the 2MWT (Bohannon et al., 2014; Gijbels, Eijnde, & Feys, 2011). Further, the 2MWT exhibited strong psychometric properties and was found to be a significant predictor of the EDSS score (Bennett, Bromley, Fisher, Tomita, & Niewczyk, 2017). Thus, the 2MWT was used in the present study due to its feasibility and responsiveness to MS (Gijbels, Eijnde, & Feys, 2011).

The 2MWT assesses the maximal distance a person can walk across a flat surface within a 2-minute time limit. The participant is instructed to walk up and down a marked hallway as quickly as they can without breaking into a run. For this study, the total distance (in feet) was recorded at the end of 2 minutes.

Timed 25 Foot Walk. The T25FW is a measure of gait speed. Due to both its psychometric qualities and ease of administration, the T25FW is the most commonly used measure of walking performance in MS (Bethoux, Palfy, & Plow, 2016). The T25FW is part of the MSFC and have high inter-rater reliability (*ICC* = 0.991) (Learmonth et al., 2013b) and is strongly correlated to EDSS scores, lower extremity strength, and mobility indexes (i.e., Rivermead Mobility Index) (Bethoux, Palfy, & Plow, 2016). Moreover, Kalers et al. (2000) found that T25FW correlated independently with EDSS across levels of disability and types of MS disease course, with the highest correlations for those with the most severe disability and those with PPMS. The T25FW requires participants to walk as fast as they can across a marked 25 ft course. Participants can use an assistive device if required. For this study, the task was repeated twice for each participant and the time for each trial was recorded.

Nine Hole Peg Test. The NHPT is a measure of upper extremity speed and coordination. The NHPT is part of the MSFC and is considered to be one of the most commonly used, reliable, and validated measures of upper extremity function (Lamers & Feys, 2014). The NHPT shows high inter-rater (*ICC* = 0.93), intra-rater (*ICC* = 0.96-0.98), and test-retest reliability (*p* = .86 - .92) (Erasmus et al., 2001; Lamers & Feys, 2014; Solari, Radice, Manneschi, Motti, & Montanari, 2005). Further, the NHPT is strongly correlated with the Jebsen Taylor Hand Function Test (*p* = .83 - .05), a measure of hand functions (Feys, Duportail, Kos, Van Asch, & Ketelaer, 2002), as well as the Purdue Pegboard (*r* = -.52) a measure of fine motor dexterity (Simone, Rota, Tesio, & Perucca, 2011). Lastly, the NHPT shows a moderate correlation to the EDSS (*r* = -.33) (Cutter et al., 1999).

The NHPT requires participants to use one hand to pick up nine pegs, one at a time, and insert them into holes as quickly as possible. Once all of the holes are filled, the participant is to immediately remove all of the pegs as quickly as possible, one at a time, and return them into an indented tray. This task is completed first with the dominant hand and then the non-dominant hand and the time to complete the task (in seconds) is recorded. For this study, the average of both trials served as the total score.

Grooved Pegboard. The G-Pegs is a measure of fine motor speed and dexterity and was also included in this study as it requires greater tactile acuity and visuomotor coordination than the NHPT (Bryden & Roy, 2005) and, therefore, may provide greater discrimination of dexterity among adults with early MS. The test-retest reliability for grooved pegboard for the dominant hand is *r* = .72 and for the nondominant hand is *r* = .74 (Ruff & Parker, 1993). The G-Pegs test negatively correlates with the distance walked in 6 minutes (r_s = -0.49, $p < .05$), and positively correlates with the time taken to walk 25-feet (r_s = 0.55, $p < .05$) (Almuklass et al., 2017).

The G-Pegs requires participants to use one hand to pick up grooved pegs, one at a time, and insert them into slotted holes as quickly as possible in a particular direction (i.e., when using their right hand they must move from left to right). Starting with the dominant hand, participants have 45 seconds to see how many pegs they can place. The task is then completed with the non-dominant hand and placing the pegs in the opposite direction (right to left). For this study, the total number of pegs placed was recorded for each hand and the average of both scores served as the total score.

Grip Strength. Grip is a measure of upper body strength. Tests of grip strength are frequently used in the literature and appear to be reliable and responsive in MS (Lamers & Feys, 2014; Paltamaa, Sarasoja, Leskinen, Wikstrom & Mälkiä, 2008; Paltamaa, West, Sarasoja, Wikstrom & Mälkiä, 2005). Inter-rater reliability is reported to be $r = .82$ and construct reliability when comparing the Jamar dynamometer (the measure used in the present study) to the sphygmomanometer produced a .75 correlation (Hamilton, McDonald, & Chenier, 1992). In another study, test-rest reliability was reported as $ICC = .98$ and interrater reliability as $ICC = .98$-$.99$ (Lamers & Feys, 2014). The grip strength task uses a hand dynamometer to measure maximum strength that can be exerted by dominant and non-dominant hands. For this study, the average of both trials served as the total score.

Finger Tapping Test. The FTT is a measure of simple motor speed. The test-retest reliability of the FTT is high ($r = .71$ - $.78$) and finger tapping assessments are strongly correlated to NHPT ($\rho = 0.708$; $p < .0001$) (Ruff & Parker, 1993). The FTT requires participants to use their index finger to tap a button as quickly as possible for 10 seconds. Starting with the dominant hand, this is performed five times with the dominant hand and five times with the non-

dominant hand, alternating hands between each trial. For this study, the total number of finger taps for each of the ten trials was averaged into one score.

Magnetic Resonance Imaging

Patients underwent three-dimensional (3D) T1 and 3D T2 3.0T magnetic resonance imaging (Siemens Skyra). Patients also underwent images of the cervical spine, including the short TI inversion recovery (TR 3,116 milliseconds, TE 44.0 milliseconds, fifteen 3.0-mm sagittal slices) and T2-weighted (TR 2,800 milliseconds, TE 84.0 milliseconds, thirty 1.5mm sagittal slices) imaging. Only baseline MRI measurements were collected and used in the present study.

T2 Lesion Volume. T2 lesion volumes (T2LV's) were derived from T2-weighted images using a local thresholding segmentation technique (Jim 6.0) and total T2LV was recorded and log-transformed.

C-spine Lesion Count. T2 lesion counts within the cervical spinal cord were quantified from short TI inversion recovery and T2-weighted images of the cervical spine. The number of lesions ranged from 0 to 8 total lesions.

Normalized Whole Brain Volume. The nBrain measure is a measure of normalized volumes of the total brain were measured with SIENAX-23 and FIRST-24 using lesion-filled T1-weighted images and applying the volume-scaling factor to adjust for intracranial volume.

Additional Predictors

Mental Health Inventory. The MHI is a brief screening questionnaire for depression and anxiety disorders that shows high sensitivity and specificity (Cuijpers, Smits, Donker, ten Have, & de Graaf, 2009). Research supports the MHI-5 for detecting DSM-IV Axis-I diagnoses and detecting major depression in primary care patients. Further, there is evidence in support that

the MHI is a good screener for anxiety in general as well as for some anxiety disorders, including generalized anxiety disorder, panic disorder, and obsessive-compulsive disorder (Cuijpers et al., 2009). The MHI-5 was used for the present study given a combination of reliability/validity, feasibility, and incorporation of both anxiety and depression.

The MHI-5 is a 5-item self-report measure on which subjects report their perceived experience (1 = all of the time, 6 = none of the time) of depressive symptoms and psychological well-being (3 items) and symptoms of anxiety (2 items). The MHI-5 has a maximum raw score of 30 points, with lower scores indicating worse symptomatology. Two of the items ask about positive feelings and thus their score is reversed so that lower scores on the MHI-5 represent worse anxiety and depression symptoms.

Fatigue Severity Scale. The FSS is a scale that assesses individuals' perceived fatigue. Psychometric properties of the FSS are established in different populations and show support for test-retest reliability (*ICC* = 0.751) and high internal consistency reliability with a coefficient alpha of 0.98 (Learmonth et al., 2013a). The FSS shows evidence of construct validity, specifically, the FSS is significantly correlated to the Modified Fatigue Impact Scale (Spearman's $p = .7451$) (Learmonth et al., 2013a). Further, the robust psychometric properties include sensitivity to worsening due to disease progression or improvement with treatment (Bethoux, Palfy, & Plow, 2016).

The FSS is a 9-item self-report measure on which subjects report their perceived fatigue (1 = strongly disagree, 7 = strongly agree) and its effect on their functioning (e.g., interfering with physical functioning, work, carrying out responsibilities, motivation). The FSS has a maximum raw score of 63 points. Higher scores indicate stronger symptoms of fatigue and associated impairment in various domains of functioning. The total raw score was divided by 9

to get the average score. Average scores of 4 or above are indicative of severe MS-related fatigue (Learmonth et al., 2013a).

Physical Activity. The Physical Activity questionnaire was created to assess the frequency that individuals participate in various physical leisure activities. The physical activities included running, jogging, using the elliptical, swimming, participating in sports, walking for exercise, engaging in toning/stretching exercises (e.g., yoga), biking, and high intensity workout classes (e.g., cross-fit). Individuals report on their engagement in each of the activities from the following options: daily, several times per week, several times per month, several times per year, and once/less per year.

Procedure

The RADIEMS longitudinal study consists of a comprehensive battery of cognitive assessments, gait assessments, sensorimotor assessments, self-report questionnaires, and an MRI. Approval was received by the institutional review board of the Icahn School of Medicine at Mount Sinai and all participants provided informed consent at both baseline and follow-up. At baseline, participants completed all tasks independently with an examiner in approximately 3 hours followed by an MRI. To ensure confidentiality, the consent forms, which linked each participant to her/his packet by their distinct numbers, were removed from the folders containing protocols after the first session. A list of all patient-number pairings was created and stored separately from folders.

At follow-up, approximately 3 years from baseline, participants returned and were administered a slightly modified version of the same comprehensive battery including a second MRI. Confidentiality was addressed in the same manner as was done at baseline. All tasks were

administered by a licensed psychologist and/or trained research staff. Participants were awarded compensation for their participation at each time point.

For this dissertation, only specific measures of interest at each time point were collected and assessed (which were discussed above). As data collection for the follow-up portion was still ongoing at the time of this dissertation, a cut-off date of November 25, 2020, was determined and only participants who had returned on and prior to that date were included in the present analysis. This provided a sample size of 130. It should also be noted that during some of the follow-up data collection, the COVID-19 pandemic occurred and data collection was paused for a series of months (from March 2020 through June 2020) until it was deemed safe for participants to return to the lab and with proper social distancing policies in place. Approximately half of the participants were seen prior to the pandemic (n = 64) and the other half after the pandemic (n = 66).

Statistical Analysis

All analyses were performed using SPSS version 27 (IBM, 2020). Descriptive statistics summarized the participant characteristic and the results of the outcome measures. Prior to any analysis, data were checked for normality via visual inspection with qq plots and necessary transformations were made. Visual inspection with box plots was used to identify outliers and appropriate winsorizing were completed. All assumptions for each statistical analysis chosen were met and detailed below. Specific analyses are detailed below and under preliminary analysis as well as each aim.

Adjustment of motor functioning performance for age, sex, and body mass index (at baseline) was accomplished by saving standardized residuals for each participant from general

linear models run with the performance metric as the dependent variable and covariates entered. This was performed separately for each performance metric.

A composite regression adjusted motor functioning score for baseline and follow-up were created. Tasks having a higher score representing better performance were set to ad default (2MWT, Grip, FTT, and G-Pegs), and those tasks where having a lower score represents better performance were subtracted (T25FW and NHPT) to adjust for opposing directions indicating better performance. This created an overall composite score for the six motor tasks at each time point, where a higher composite score indicated better performance.

The following variables were also coded for additional analysis. Race was coded into two levels [level 1 = Caucasian (n = 89) and level 2 = non-Caucasian (n = 41)]. C-spine lesion number, with a range of zero to eight lesions, was coded into three levels [level 1 = zero lesions (n = 42), level 2 = one to two lesions (n = 48), and level 3 = three or more lesions (n = 40)]. Disease-modifying therapy (DMT), was also collected and classified into categories, based on efficacy, into 4 levels [level 1 = no DMT (n = 6), level 2 = low efficacy/injectable DMT (n = 21), level 3 = moderate efficacy/oral DMT (n = 69), and level 4 = high efficacy/infusions DMT (n = 34)].

The items of the Physical Activity scale were coded into continuous values based on monthly engagement in each activity, where daily became 30, several times per a week became 16, several times per a month became 8, several times per a year became 2, and once a year or less became 0. A total composite was created for physical activity as a sum of total engagement across the 7 items, with a minimum of 0 and a maximum of 210, and higher scores indicate more participation in activities.

Proposed Analysis

Preliminary Analysis. Pearson correlations (two-tailed) [as well as analysis of variance (ANOVA) for categorical variables] investigated relationships between the primary predictor variables and the primary outcome variable with demographic and disease variables to assess and identify covariates for subsequent analysis.

Aim 1. Evaluate if psychological resilience can predict change in objective functional outcomes across a 3-year time period.

Data Analysis for Aim 1: Using a multiple linear regression model, the follow-up motor functioning composite was regressed on all independent variables of interest (resilience, baseline motor functioning, race, nBrain, and T2LV). Next, the full model was tested adding the two additional predictors of interest mood and fatigue into the regression model.

Aim 2. Examine if psychological resilience can serve as a protector in the relationships between disease-specific estimates and functional outcomes.

Data Analysis for Aim 2: A one-way analysis of covariance (ANCOVA) was conducted to determine statistically significant differences between levels C-spine lesions on follow-up motor functioning statistically controlling for baseline motor functioning and resilience. Standard model checking was used to ensure adequate model fit.

Aim 3. Assess the degree of change in psychological resilience as a clinical population progresses in disease.

Data Analysis for Aim 3: An absolute change variable was created for CD-RISC by subtracting the follow-up raw score from the baseline score for each variable and then taking the absolute value. Then, a one-sample t-test was conducted to test if the mean absolute difference was significantly different from zero.

Chapter 4: Results

Data were coded and analyzed using SPSS (IBM, 2020). The NHPT demonstrated a non-normal distribution at both baseline and follow-up and a log transformation was conducted. Baseline BMI and MHI also demonstrated non-normal distributions and were corrected with a log transformation and an inverse transformation, respectively. Following an outlier analysis, for the T25FW, at baseline two participants were given the highest value not suspected to be an outlier and at follow-up, the same procedure was conducted for three participants.

In regard to missing data, for the 2MWT, at baseline, two participants were unable to complete the task due to ambulation or gait difficulties and thus the lowest score derived by a participant in the sample was used. This same procedure was used for the follow-up collection where three participants were unable to complete the task. Further, at follow-up, two of the participants were pregnant and thus unable to complete the 2MWT. As the percent change in performance on this task from baseline to follow-up for the sample was low, the baseline score for these participants was used in place of their missing follow-up score.

See Table 2 and 3 for a summary of descriptive statistics, including means and standard deviations for the primary predictor and outcome variables for the participants. The percent change in performance on each motor task was relatively low, where the lowest percent change was in gait speed (T25FW; 0.97% change), the highest percent change was in upper body strength (Grip; 5.24%), and the average change from baseline to follow-up across the six motor tasks was 2.34%.

Table 2.

Means and Standard Deviations of Variables

Domain	Outcome measure	*Baseline*	*Follow-up*	*Percent change*
Resilience	CD-RISC[a]	29.70 (5.78)	29.11 (6.13)	-1.99%
Gait endurance and stamina	2MWT[a]	654.23 (90.71)	645.44 (103.49)	-1.34%
Gait speed	T25FW[b]	4.10 (0.57)	4.06 (0.73)	0.97%
Fine motor speed and dexterity	G-pegs[a]	16.78 (3.24)	17.01 (3.62)	1.37%
Upper extremity speed and coordination	NHPT[b]	19.92 (3.13)	20.45 (3.68)	-2.66%
Upper body strength	Grip[a]	71.22 (25.10)	74.95 (24.98)	5.24%
Simple motor speed	FTT[a]	53.56 (6.57)	54.86 (7.19)	2.43%
Mood	MHI[b]	75.61 (14.34)	74.37 (15.49)	1.64%
Fatigue	FSS[b]	3.48 (1.48)	3.12 (1.48)	10.34%

[a]Higher scores indicate greater performance/outcome
[b]Lower scores indicate greater performance/outcome

Table 3.

Means and Standard Deviations of Disease Burden Measures

Outcome measure	*Baseline*
T2LV (*M* ± *SD*)	0.62 (1.33)
nBrain (*M* ± *SD*)	1549.68 (72.93)
C-spine Lesion (*M* ± *SD*)	1.94 (2.03)
Level 1 (*n* = 42)	
Level 2 (*n* = 47)	
Level 3 (*n* = 40)	

Note. T2LV: T2 lesion volume; nBrain: normalized whole brain volume; C-spine: cervical spinal cord.

Preliminary Analysis

Pearson correlations (entry $p = .05$, removal $p = .10$) were utilized to identify variables for further investigation. All assumptions for the analysis were checked and met including normality, linearity, and homoscedasticity.

The results of the Pearson correlations (two-tailed) indicated, among patients, no relationships were found between baseline resilience and age, sex, ethnicity, body mass index, T2 lesion volume, or disease type (RRMS vs. CIS), see Table 4 below. There was a significant relationship between resilience and nBrain (r = 0.252, p = .004), whereby higher resilience is associated with higher normalized whole brain volume (and thus less disease burden as greater volume represents less atrophy). There was also a significant relationship between resilience and race (r = -0.209, p = .017), whereby higher resilience being related to those who identify as Caucasian.

Table 4.

Correlations Between Resilience and Demographic/Disease Variables

	Age	Sex	Race	Ethnicity	BMI	Disease Course	T2LV	nBrain
Resilience BL	.048	-.049	-.209*	-.002	-.101	-.083	.015	.252**

Note. BL: baseline; BMI: body mass index; T2LV: T2 lesion volume; nBrain: normalized whole brain volume.
*p < .05. **p < .01.

Next, as disease-modifying therapy type (DMT) was a categorical variable, two separate one-way analysis of variance (ANOVA) tests were conducted to test the relationship between identified variables and DMT. Assumptions for ANOVA were assessed and met including independence of observations, outliers, normality, and homogeneity of variances. Results of the one-way ANOVA revealed a non-significant relationship between DMT and resilience [F (3, 126) = 0.596, p = .619] as well as a non-significant relationship between DMT and follow-up motor composite [F (3, 126) = 1.378, p = .252]. Thus, results indicated that type of therapy could be dropped from subsequent analyses as it did not show a significant relationship with the independent or dependent variable.

Lastly, to reduce any additional random error, relationships between the primary outcome variable (follow-up motor functioning composite) and disease and demographic variables were assessed. This revealed a significant relationship between the follow-up motor composite and T2LV (r = -0.429, p < .001), whereby better motor function was related to less T2 lesion volume, nBrain (r = 0.463, p < .001), and race (r = -0.324, p < .001). Following this preliminary analysis, race, normalized whole brain volume, and T2 lesion volume were selected for further investigation.

Results for Aim 1

Using a multiple linear regression model, the follow-up motor functioning composite was regressed on all independent variables of interest (resilience, baseline motor functioning, race, nBrain, and T2LV). Prior to analysis all assumptions for linear regression were assessed and met including multivariate normality, multicollinearity, and homoscedasticity.

The regression model was significant with tolerance and variance inflation factors (VIF) within acceptable limits; R = .823, *Adjusted* R^2 = .677, F (5, 124) = 51.91, p < .001 (see Tables 5 and 6). Overall, 67.7% of the variance in the change in motor functioning from baseline to follow-up is explained by the independent variables in this model with an effect size of f^2 = 2.09, which is considered large (Cohen, 1988).

In this model, baseline motor functioning (B = 0.80, p < .001), race (B = -0.17, p = .042) and nBrain (B = 0.001, p = .029) emerged as significant predictors. Further, examination of the beta weights reveals that the baseline motor composite is contributing the most to the model (β = .751), followed by normalized whole brain volume at (β = .145), and lastly race (β = -.112). In regard to race, individuals who identified as Caucasian had a .166 higher change in motor functioning from baseline to follow-up than those who identified as not Caucasian. Moreover,

individuals who identified as Caucasian had higher mean follow-up scores compared to those who did not identify as Caucasian.

Holding constant all other variables, resilience (B = -0.008, p = .260) was not found to be a significant predictor in the model and thus did not lend support for the first hypothesis that resilience would predict changes in motor functioning.

Table 5.

Model Summary for Partial Regression Model

R	*R Square*	*Adjusted R Square*	*Std. Error of the Estimate*
.823	.677	.664	.401

Table 6.

Coefficients for Partial Regression Model

	Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
	B	*Std. Error*	*β*	*t*	*Sign.*	*Tolerance*	*VIF*
(Constant)	-1.686	.961	---	-1.754	.082	--	--
Motor Composite BL	.798	.068	.751	11.737	.000	.64	1.57
Resilience BL	-.008	.007	-.066	-1.130	.260	.76	1.31
nBrain	.001	.001	.145	2.208	.029	.61	1.65
T2LV	.017	.036	.033	.485	.628	.55	1.81
Race	-.166	.081	-.112	-2.058	.042	.88	1.13

Note. BL: baseline; T2LV: T2 lesion volume; nBrain: normalized whole brain volume.

Next, to follow the predetermined analysis approach as well as to clean up any additional error, both baseline MHI and FSS were added to the model, see Table 7 and 8 below. The full regression model was significant with tolerance and VIF within acceptable limits; R = .823, *Adjusted* R^2 = .678, F (7, 122) = 36.64, p < .001 (see Tables 7 and 8). Overall, 67.8% of the variance in the change in motor functioning from baseline to follow-up is explained by the

independent variables in this model with an effect size of $f^2 = 2.10$, which is considered a large effect size (Cohen, 1992).

In this model, baseline motor functioning ($B = 0.80$, $p < .001$), race ($B = -0.17$, $p = .044$), and normalized whole brain volume ($B = 0.001$, $p = .029$) emerged as significant predictors. Resilience ($B = -0.007$, $p = .260$), mood ($B = 0.009$, $p = .757$), and fatigue ($B = -0.002$, $p = .939$) were not significant predictors in the model. Moreover, adding mood and fatigue into the model did not explain additional variance. These findings did not lend support for the second hypothesis that resilience will predict changes in motor functioning independent of mood and fatigue.

Table 7.

Model Summary for Full Regression Model

R	*R Square*	*Adjusted R Square*	*Std. Error of the Estimate*
.823	.678	.659	.403

Table 8.

Coefficients for Full Regression Model

	Unstandardized Coefficients		Standardized Coefficients			Collinearity Statistics	
	B	*Std. Error*	*β*	*t*	*Sign.*	*Tolerance*	*VIF*
(Constant)	-1.652	.984	---	-1.679	.096	--	--
Motor Composite BL	.795	.069	.748	11.504	.000	.62	1.60
Resilience BL	-.006	.008	-.049	-.705	.482	.56	1.79
nBrain	.001	.001	.149	2.242	.027	.59	1.67
T2LV	.017	.036	.033	.476	.635	.55	1.81
Race	-.166	.082	-.112	-2.038	.044	.87	1.15
Mood	-.002	.003	-.038	-.610	.543	.67	1.49
Fatigue	-.004	.028	-.008	-.141	.888	.75	1.33

Note. BL: baseline; T2LV: T2 lesion volume; nBrain: normalized whole brain volume.

Results for Aim 2

A one-way analysis of covariance (ANCOVA) was conducted to determine statistically significant differences between the levels of C-spine lesions on follow-up motor functioning, statistically controlling for baseline motor functioning and resilience. All assumptions for ANCOVA were met including independent observations, normality, homogeneity (Levene's test of homogeneity, $p > .05$), regression of slopes, and linearity.

There were significant differences between levels of C-spine lesion numbers on follow-up motor functioning scores after statistically controlling for baseline motor functioning and baseline resilience; [F (4, 130) = 67.84, $p < .001$], see Tables 9 and 10 below. Standard model checking was used to ensure adequate model fit. A partial eta squared of .10 indicated a large effect size (Cohen, 1988).

Those with the least number of lesions (n = 42), *zero lesions*, demonstrated the best performance in motor functioning at follow-up (M = .194, SD = .51). Those with a moderate number of lesions (n = 48), *one to two lesions,* demonstrated performance in the middle of the range comparably (M = .152, SD = .49). Lastly, those with the highest number of lesions (n = 40), *three or more lesions*, demonstrated the worst performance at follow-up (M = -.386, SD = .89).

Furthermore, there was a statistically significant difference by lesion number group regarding their follow-up motor performance between those with the least number of lesions, *zero lesions*, and those with the highest number of lesions, *three or more lesions* ($M_{difference}$ = -.335, $p < .001$). There was also a statistically significant difference by lesion number regarding their follow-up motor performance between those with the highest number of lesions, *three or more lesions*, and those with a moderate number of lesions, *one to two lesions* ($M_{\text{difference}}$ = -.198,

p = .025). Overall, the results indicate that number of lesions plays a role in motor functioning performance.

Resilience as a covariate was not statistically significant, and thus the proposed interaction between resilience and C-spine lesions was not added to the analysis. These findings did not lend support for the third hypothesis of an interaction between resilience and C-spine lesions, and more specifically, the role of resilience as a moderator between C-spine lesions and motor functioning performance at 3 years.

Table 9.

Descriptive Statistics for Cervical Spine Lesions

C-spine Lesions	*Mean*	*Std. Deviation*	*n*
Level 1	.194	.51	42
Level 2	.152	.49	48
Level 3	-.386	.89	40
Total	.000	.69	130

Table 10.

ANCOVA Tests of Between-Subject Effects

Source	*Type III Sum of Squares*	*df*	*Mean Square*	*F*	*Sig.*	*Partial Eta Squared*
Corrected Model	42.18	4	10.545	67.84	.000	.685
Intercept	.079	1	.079	.51	.477	.004
Motor Composite BL	30.62	1	30.624	197.02	.000	.612
Resilience BL	.086	1	.086	.56	.458	.004
C-spine	2.22	2	1.111	7.15	.001	.103
Error	19.43	125	.155			
Total	61.61	130				
Corrected Total	61.61	129				

R Squared = .685 (*Adjusted R Squared* = .675)

Results for Aim 3

Results of a one-sample t-test indicated the mean absolute difference in CD-RISC (M = 3.91, SD = 3.01) was significantly different from zero, t (130) = 14.89, $p < .01$, see Table 11 below. This indicates that resilience scores did significantly differ from baseline (M = 29.70, SD = 5.78) to follow-up (M = 29.11, SD = 6.13). These findings lend insight for the third aim, demonstrating that resilience levels did change significantly over this time period. Although the population means do not appear to change largely as a whole, there was significant change among individuals in regard to either increasing or decreasing their level of reported resilience.

Table 11.

One Sample T-Test

	t	*df*	*p*
Absolute change in resilience	14.89	130	<0.01

Supplementary Analyses

Given the non-significant relationship between resilience and change in motor functioning, additional subgroup analyses were conducted. Specifically, potential relationships between resilience and change in motor functioning were re-assessed in a sub-group of patients who demonstrated the greatest decline on motor tasks from baseline to follow-up, relative to the sample. For the first two analyses, ordinal variables were created and utilized. Specifically, for each of the six motor tasks, patients were placed into groups based on their amount of change in performance on that task, relative to the sample. By using the samples 25th, 50th, and 75th percentiles, patients were coded as 1 if their change score fell below the samples 25th percentile value for that task, a 2 if their change score fell between the 25th and 50th percentiles, a 3 if their change score fell between the 50th and 75th percentiles, and a 4 if their change score was above

the 75th percentile. Thus, patients who were coded as 1 for a task, were those who had the greatest amount of decline in performance for that task (from baseline to follow-up), relative to the sample. To reiterate, this process was completed for each of the six motor tasks, and thus the number of tasks a given participant had the greatest amount of decline in, ranging from 0 to 6.

Spearman correlations revealed no association between baseline resilience and the number of tasks where patients declined the most (r = .024, p = .782). Further, an Independent Samples T-Test, comparing the mean level of resilience for those who showed the greatest decline in 3 or more tasks (n = 23), versus those who showed the greatest decline in less than 3 tasks (n = 107), revealed no significant differences ($t_{32.588}$ = .124, p = .902). This indicates that resilience scores did not significantly differ from those with the greatest decline across tasks (M = 29.57, SD = 5.71) and those with the least decline across tasks (M = 29.73, SD = 5.82). Lastly, a series of linear regressions were conducted to assess the relationship between baseline resilience and percent change for each motor task, as continuous variables. Results revealed no significant relationships between baseline resilience and percent change on any of the motor tasks.

To further characterize results, potential associations between baseline resilience and each of the individual tasks for both baseline performance and follow-up performance that comprised the composite outcomes, were assessed. Pearson correlations (two-tailed) with a more conservative approach to account for multiple correlations (entry $p < .01$), indicated there was a reliable link between baseline resilience and the baseline total motor composite (r = 0.355, p < .001), whereby higher resilience was related to higher overall performance, see Table 12. Baseline resilience was also significantly related to better performance on the majority of the motor tasks in the composite: two-minute walk test (r = 0.216, p = .014), grooved pegboard (r =

0.193, p = .028), finger tapping test (r = 0.221, p = .011), nine-hole peg test (r = -0.313, p < .001), and grip strength (r = 0.305, p < .001). However, only the nine-hole peg test and grip strength analyses were significant at the p-value for multiple comparisons (< 0.01). Baseline resilience was unrelated to performance on the timed 25-foot walk. Further, resilience was significantly correlated to mood (MHI, r = 0.546, p < .001) and fatigue (FSS, r = -0.370, p < .001) at baseline.

In regard to the follow-up outcomes, there was a reliable link between baseline resilience and the follow-up total motor composite (r = 0.261, p = .003), whereby higher resilience was related to higher overall performance and to better performance on some of the tests in the composite: grooved pegboard (r = 0.185, p = .036), nine-hole peg test (r = -0.256, p = .003), and grip strength (r = 0.277, p = .001). However, only the nine-hole peg test and grip strength were significant at p < .01. Baseline resilience was unrelated to performance on the timed 25-foot walk, two-minute walk test, and finger tapping test. Further, baseline resilience was significantly correlated to mood (MHI, r = 0.351, p < .001) and fatigue (FSS, r = -0.257, p = .003) at follow-up.

Table 12.

Correlations Between Resilience and Outcomes

Domain	Outcome measure	*Baseline*		*Follow-up*	
		r	*p*	*r*	*p*
Motor Composite		**0.355**	<0.001	**0.261**	0.003
Gait endurance and stamina	2MWT[a]	**0.216**	0.014	0.107	0.227
Gait speed	T25FW[b]	-0.154	0.081	-0.115	0.191
Fine motor speed and dexterity	G-pegs[a]	**0.193**	0.028	**0.185**	0.036
Upper extremity speed & cord.	NHPT[b]	**-0.313**	<0.001	**-0.256**	0.003
Upper body strength	Grip[a]	**0.305**	<0.001	**0.277**	0.001
Simple motor speed	FTT[a]	**0.221**	0.011	0.156	0.076
Mood	MHI	**0.546**	<0.001	**0.351**	<0.001
Fatigue	FSS	**-0.370**	<0.001	**-0.257**	0.003

Note. Cord.: Coordination.
[a]Higher scores indicate greater performance
[b]Lower scores indicate greater performance

Additional supplemental analyses were conducted on the data from the full baseline sample (N = 185) to identify a potential mediator in the baseline relationships between psychological resilience and motor outcomes. The Physical Activity (PA) composite was assessed for suitability as a covariate including appropriate winsorizing of an outlier. After appropriate adjustments, the PA composite approximated a normal distribution (M = 43.46, SD = 26.81) with a minimum of 0 and a maximum of 116.

To review, the baseline analyses by Klinevoa et al. (2019), found significant associations between resilience and the Gross Motor composite (r_p = 0.184, p = .013), after statistically controlling for mood and fatigue. Thus, to check PA as a covariate, Pearson correlations (two-

tailed) re-examined baseline relationships between PA, CDRS-10, and the Gross Motor composite [including the tasks that comprise the composite (Grip, T25FW, and 2MWT)]. Higher levels of physical activity were linked to higher resilience (CDRS-10 $r = 0.258$, $p < .01$) and better performance grip strength (Grip $r = 0.225$, $p = .002$). No other significant associations were found, and thus the remaining motor outcomes were dropped from subsequent analyses.

Next, a PROCESS mediation was conducted to assess PA as a mediator in the relationship between CD-RISC and Grip. Results indicated a significant partial mediation in the model 95% CI [.0005, 0.148]. As was done in the baseline paper, mood and fatigue were added as additional covariates, and the mediation was re-run to assess PA as a mediator in the relationship between CD-RISC and Grip. Results indicated a significant partial mediation in the model 95% CI [.0003, 0.174].

To follow up, partial correlations between CD-RISC and Grip while statistically controlling for physical activity were conducted, followed by, partial correlations between CD-RISC and Grip while statistically controlling for physical activity, mood, and fatigue, see Table 13. Results indicated 25% of the variance in the relationship between CD-RISC and Grip is explained by PA. Further, when statistically controlling for mood and fatigue, 31% of the variance in the relationship between CD-RISC and Grip is explained by PA.

Table 13.

Partial Correlations Between Resilience and Grip Strength

Covariates	*r*	R^2
None	0.306	0.094
Physical Activity	0.264	0.069
Mood, Fatigue	0.22	0.049
Mood, Fatigue, Physical Activity	0.19	0.034

Chapter 5: Discussion

Impairment in motor functioning continues to be a hallmark feature of MS, despite difficulty identifying those at greatest risk for disability given the variable nature of this disease and variable progression of impairment across individuals with similar disease burden and relapse patterns. The concept of psychological resilience is emerging in clinical research, including research on MS, as a productive way to view the outcomes and experiences of living with a chronic disease and identify potential protective factors. Identifying protective factors, particularly those with the ability to predict functional change, provides an improved understanding of the variability and progression of motor disability and supports the identification of those most at risk for decline or impairment in motor functioning. This insight can help inform treatment decisions such as early pharmacological treatment, rehabilitative intervention (e.g., occupational therapy), as well as therapy-based intervention/clinical trial research.

Studies to date that seek to extend past cross-sectional findings and examine resilience longitudinally, show mixed findings. Some longitudinal studies show support for resilience as a predictor of functional outcomes and change. Notably, authors Koelmel, Hughes, Alschuler, and Ehde (2017) reported that resilience significantly mediated the relationships between social support and subsequent mental health outcomes including depressive symptomatology, anxious symptomatology, and overall mental health status at four time points (baseline, and weeks 10, 26, and 52). Another study found that a decrease in resilience was associated with an increase in depression and fatigue, whereas an increase in resilience was associated with improved sleep quality and function over a 1-year time period (Edwards et al., 2017). Other studies show limited support for resilience in longitudinal analyses. Notably, Silverman, Molton, Alschuler, Ehde, and

Jensen (2015) found that resilience did not predict change in self-reported physical functioning after 3 years, despite being related at baseline. Another cohort study examined patients following knee joint replacement surgery. Results found that concurrent resilience predicted both the general quality of life and knee-specific health outcomes, however, longitudinally, preoperative resilience did not predict knee-specific outcomes (Magaldi, Staff, Stovall, Stohler, & Lewis, 2019).

Given this lack of consensus, the purpose of this dissertation was to fill these gaps in the literature and to examine the protective and predictive effect of psychological resilience on various domains of motor functioning, including gait and balance, endurance and stamina, upper body strength, motor speed, and upper extremity coordination in an early cohort of patients with MS. Toward that end, linear regression and analysis of variance were used to test the relationship between baseline psychological resilience and change in performance on tasks of motor functioning in patients with MS ($N = 130$), while statistically controlling for MRI estimates of disease burden, mood, fatigue, and demographic factors.

Psychological Resilience as a Protective Factor

The results of this study did not demonstrate a significant relationship between resilience and the measured outcomes. Moreover, in contrast with Hypothesis 1 and 2, psychological resilience was not found to predict change in motor functioning from baseline to follow up. In contrast with Hypothesis 3, psychological resilience was not found to moderate the relationship between disease burden and motor outcomes. There are various explanations for these findings, discussed in depth below.

One potential explanation for the null finding is that there was not enough variance in the change in outcomes between baseline and follow-up to capture the role of psychological

resilience. The effect size may have been lower than expected because of the lack of variability in change in motor performance and thus this study was unable to capture the effect as anticipated. In other words, either there wasn't enough change in motor functioning from baseline to follow-up or a large enough sample size to capture the effect of psychological resilience. However, as discussed earlier, additional subgroup analyses examining resilience in patients with the greatest decline in motor tasks did not show support for this explanation. Specifically, the results demonstrated that resilience was unrelated to the relative level of motor decline across 3 years, and further, patients with greater decline had comparable levels of resilience to those with less decline. Thus, these finding does not lend support for this explanation for the null finding.

Moreover, in assessing the degree of variability in change from baseline to follow-up on motor tasks, the coefficient of variation (CV) indicated large variances in change for 2MWT (*CV* = 1.08) and FTT (*CV* = 1.05). Additionally, moderate variances in change were found for G-Pegs (*CV* = 0.80), Grip (*CV* = 0.94), T25FW (*CV* = 0.89), and NHPT (*CV* = 0.83). These findings also do not show support for the explanation that the non-significant findings were due to the lack of variance in outcomes.

Another potential explanation for the null finding can be attributed to instrumentation and methodology flaws in the study. In the present study, psychological resilience was operationalized as the self-reported ability of adapting well in the face of substantial adversity and significant sources of stress, estimated at baseline. As such, psychological resilience was conceptualized as a trait, and the methodological approach based on that assumption as well, where baseline levels were hypothesized to predict functional change. However, results indicated that individuals' self-reported level of resilience did significantly change from baseline to 3-year-

follow-up and in varying directions (e.g., where some people increased, decreased, or stayed the same). Therefore, this suggests that resilience may not be a static trait, which poses challenges to how it was operationalized. Some studies show support for this concept, demonstrating that baseline resilience compared to concurrent levels of resilience, demonstrate varying relationships to outcomes (Magaldi, Staff, Stovall, Stohler, & Lewis, 2019.

Similarly, it is possible that the estimate of disease burden chosen (number of lesions in the cervical spinal cord) was unable to capture this relationship, however, a different measure of disease burden may be related to resilience. For example, the results indicated an association between psychological resilience and nBrain. However, it was a relatively weak association, and the data were cross-sectional. Moreover, a review of the literature shows limited support for the relationship between disease and resilience (Klineova et al., 2019; Nakazawa et al., 2018; Ploughman et a., 2020). Notably, in the baseline analysis, Klineova et al. (2019) reported the same pattern of associations between resilience and motor outcomes in both the MS group and the healthy control group. Thus, it is likely that resilience does not play a role in such disease-specific functional changes in motor functioning in MS.

In summary, it is important to reiterate that no significant longitudinal relationships between psychological resilience and motor functioning were found. Thus, the aforementioned potential explanations aside, it is very possible that psychological resilience does not predict change in motor functioning over time nor does it moderate the relationship between disease burden and motor functioning. These null findings suggest that resilience does not serve as a protector for the motor system and does not contribute to or predict functional differences in motor functioning. Any cross-sectional associations found between psychological resilience and

outcomes, to be explained in depth below, cannot suggest casual relationships and are just merely associations.

Cross-Sectional Findings

Cross-sectional analyses revealed that psychological resilience was associated with better performance on particular tasks of motor functioning, at baseline and at 3-year follow-up. Specifically, at baseline, higher psychological resilience was found to be associated with better performance on tasks of gait endurance and stamina (i.e., 2MWT), fine motor speed and dexterity (i.e., G-pegs), simple motor speed (i.e., FTT), and strongest relationships to upper extremity speed and coordination (i.e., NHPT) and upper body strength (i.e., Grip). Contrasting findings by Klineova et al. (2019), resilience was unrelated to performance on a measure of gait speed (i.e., T25FW). The difference in sample size (n = 130 vs. n = 185) is the most likely explanation for the difference in findings between the present study and the findings in Klineova et al. (2019), where the present study was unable to include the full sample and thus may have lacked the power necessary to see the relationship, which is a limitation.

Expanding the original paper, these relationships were re-assessed cross-sectionally at 3-years. At follow-up, higher baseline psychological resilience was found to be associated with better performance on tasks of fine motor speed and dexterity (i.e., G-pegs), with strongest relationships to tasks of upper extremity speed and coordination (i.e., NHPT) and upper body strength (i.e., Grip), consistent with baseline. The association between higher psychological resilience and gait endurance and stamina (i.e., 2MWT) and simple motor speed (i.e., FTT) was not found at 3 years, despite being correlated at baseline. Resilience and a measure of gait speed (i.e., T25FW) remained unrelated, consistent with baseline.

One potential explanation for these findings may be that psychological resilience is related to psychological factors such as depression, fatigue, drive, motivation, hardiness, and psychological stamina, which impact how patients approach and carry out tasks. Patients with higher levels of drive and stamina may push themselves harder, resist urges to slow down, and maintain their energy and motivation throughout the duration of the tasks. Thus, higher resilience may indicate higher levels of such psychological factors and thereby may translate into better performance on tasks in conjunction with their functional motor abilities. Of course, these tasks are intended to capture and estimate objective functional motor skills, however, if a patient doesn't push themself to their maximum capabilities or, conversely, if they push to utilize all of their resources (e.g., energy, strength, etc.) to perform the task, their performance can vary accordingly. Therefore, differences in performance levels may be influenced by patients' psychological factors.

Moreover, in support of this explanation, the strongest associations were found between psychological resilience and tasks of tasks of speed and strength, presumably tasks that would be impacted by factors such as drive and psychological stamina. For example, the force that a patient exerts during the grip strength task. In contrast, such attributes may not be as easily transferable to tasks of gait, coordination, and balance, where weaker associations were found. It is important to note, that there may also be biological and neurobiological mediators and mechanisms of this cross-sectional relationship, such as responsiveness of the HPA axis. Such factors were beyond the scope of the present study as no objective biological measures to capture potential neuroendocrine concomitants of resilience were included.

Another potential explanation driving this association could be that higher psychological resilience is associated with more adaptive behaviors and perceptions/thoughts in everyday life

that may translate into functional differences, such as pushing oneself to be more active in typical work and social pursuits or partaking in healthier lifestyle decisions such as regular exercise. Some studies show support for this idea, where high levels of resilience were linked to healthier lifestyle factors such as exercise and better diet (Ploughman et al., 2015; Ploughman et al., 2020) and increased social participation (Silverman, Molton, Alschuler, Ehde, & Jensen, 2015). In support of this explanation, as discussed earlier, a supplemental analysis of the baseline sample ($N = 185$) revealed that physical activity was found to be a partial mediator in the relationship between baseline resilience and baseline grip strength. This finding may support this explanation that additional factors may be mediating this association, one of which appears to be the level of physical activity. Thus, the associations found may be showing an effect of fitness, among other factors, rather than solely an effect of resilience.

Lastly, it is important to re-iterate that data are both cross-sectional and observational, thus conclusions cannot be drawn about underlying causative mechanisms of reported associations or the directionality of the association. As such, the association must also be looked at from the opposing direction. That is, an interpretation of the findings can be, that patients with higher performance on motor tasks, rate themselves as having higher resilience than those with poorer performance on motor tasks. Patients who have high levels of drive and motivation, and who push themselves to perform to their maximum capabilities on tasks, may rate themselves as being more resilient than others. Moreover, patients who have better motor functioning, who are strong and fast, may also rate themselves as being more resilient than others. In the opposing direction, it is also possible that level of disease and disability can lead to lower scores on the resilience scale. That is, individuals who have premorbid motor functioning weaknesses or are experiencing a decline in their motor functioning due to disease may rate themselves as having

lower levels of resilience. Similarly, those with lower psychological factors, like drive, may have poorer performance and rate themselves as having lower levels of resilience

Additional Considerations and Future Research

Demographic and disease variables were also assessed as potential contributing factors in the change in motor performance. Race was found to be a predictor, where individuals who identified as Caucasian had a greater change in motor functioning from baseline to follow-up as well as higher mean follow-up scores. The most likely explanation for this finding is that the relationship between race and resilience is not truly capturing just race but rather other associated variables such as socioeconomic status, worse disease burden (e.g., preliminary findings suggest that African American populations have higher levels of disease burden than Caucasian populations), or other disease comorbidities (e.g., obesity, heart disease, diabetes, etc.). Further, two measures of disease burden per MRI, normalized whole brain volume and the number of lesions in the C-spine, also showed an important role in predicting changes in motor functioning with a general consensus of higher disease burden being linked to worse performance.

There are inherent limitations posed in using a self-reported measure of resilience as it is subjective in nature and thus can be affected by both non-intentional and intentional biases. Moreover, unlike other measures with clear cut-offs or thresholds for meeting mild, moderate, or severe levels of particular pathology such qualitative information is not published by the authors for the CD-RISC. A handful of researchers have created their own criteria, for example, classifying resilience as low or high depending on the sample mean (Silverman, Molton, Alschuler, Ehde, & Jensen, 2015). Moreover, this poses challenges in tracking changes in resilience as it is difficult to discern what meaningful change quantifies. The direction of the change in resilience may be important as well, where identifying if an individual's level of

resilience increased or decreased could be associated with different outcomes such as was found in the study by Edwards et al. (2017). Taken together, this instrument is attempting to measure a complicated construct and it does so imperfectly, as does any instrument. Future work on creating classifiers for levels of resilience (e.g., mild, moderate, high) as well as setting thresholds for meaningful change in resilience within clinical and non-clinical populations would be beneficial.

Failure to statistically controlling for additional but presumably associated variables such as pain level, social participation, and other health-related qualities (e.g., comorbid health issues) to further isolate psychological resilience as an independent construct, is another noteworthy limitation. This includes not statistically controlling for change in disease burden per MRI scans from baseline to follow-up. Further, the present study did not include any objective biological measures to capture potential neuroendocrine concomitants of resilience and thus cannot comment on any biological or neurobiological factors underpinning of relationships.

Another factor worthy of discussion is that some of the follow-up data collection took place during the COVID-19 pandemic, where data collection was paused from March 2020 through 2020. This study does not have data on individuals who have antibodies or who contracted COVID-19, and thus it is difficult to measure if there were any effects of the virus on the findings, a limitation of the study. In an attempt to account for any potential influence of the time differences (e.g., returning for follow-up assessment before or after COVID-19), an additional exploratory analysis was conducted where the time between baseline and follow-up (as a continuous variable) was statistically controlled for in the various analyses. Statistically controlling for the time between baseline and follow-up was not a significant predictor in the analysis and it did not change the findings.

Stance on Psychological Resilience

Given the lack of consensus in the literature and the non-significant findings in the present study, there is presently limited support for psychological resilience as a protective for functional outcomes in MS. The present study provides minimal support for the inclusion of psychological resilience when examining and identifying potential predictors of functional change or impairment in the motor system in MS.

In reviewing the literature on resilience building interventions, some flaws and limitations come to light. Notably, in regard to methodology and the way in which resilience is operationalized in such interventions. First, some of the intervention studies are stacked in favor of positive findings. For example, creating interventions that include the patient's support partners as participants (Halstead, Leavitt, Fiore, & Mueser, 2020), or creating interventions that are implemented in group modalities (Pakenham, Mawdsley, Brown, & Burton, 2018). In these two examples, resilience becomes convoluted with potential co-occurring social impact. Similarly, these studies are often expansive and include vast treatment targets, for example, psychoeducation on goal setting and building social connections (Alschuler et al., 2018), and thus, again, it is difficult to parse out resilience from the other co-occurring factors.

Moreover, it is challenging to determine the efficacy of such studies as the methodology can be ambiguous. For example, specific treatment descriptions are, at times, reported using vague language such as "gaining positive momentum" (Alschuler et al., 2018, p. 340). As can happen in any field of research, there are also studies that over-emphasize findings such as positive participant reviews of the intervention (i.e., READY for MS), however, closer analyses of the results indicate that the program was no more efficacious than the relaxation control program (Giovannetti et al., 2020). Other studies fail to provide the information needed to truly

analyze the findings, for example, how they determined criteria for meaningful change in resilience (Ehde et al., 2015).

The largest issue across these studies is the inconsistency in how resilience is operationalized. Although there is significant overlap in some key resilience factors (e.g., coping ability, social connectedness), how they are operationalized varies significantly. For example, some interventions would consider social connectedness its own treatment target and outcome. However, other interventions conceptualize social connectedness as a feature of resilience, embed it within their definition of resilience, and thus in reporting resilience outcomes, are also reporting social connectedness within the frame of resilience.

Therefore, is creating and participating in resilience-building interventions a worthy feat? In order to answer that question, it is important to know what type of resilience-building intervention is being considered and how resilience is being operationalized. At this time, given the lack of support for resilience as an independent protective and predictive factor for outcomes, participation in a "true" resilience building intervention poses unsure benefits. However, as it has become clear, these interventions are much more multifaceted, aimed at treating and measuring a large of variety of functions. Thus, in that sense, an intervention that focuses on resilience in addition to other well-established psychological, biological, or social domains (e.g., fatigue, depression), may be a more worthwhile treatment avenue.

Taken together, the vast research on resilience both in MS and in other physically disabled populations, is convoluted and inconsistent. The question becomes clear – is resilience really its own construct, or are we simply measuring a proxy for other known psychological or physiological variables (e.g., positive psychology)? As stated by Ploughman (2021), "resilience likely contributes only a very small piece of the health puzzle in MS" (p. 505). It is unlikely that

resilience is the active ingredient in predicting and explaining differences in motor outcomes in MS, and instead, it is more likely that protective health and lifestyle behaviors (e.g., exercise, social pursuits) as well as psychological factors (e.g., mood and fatigue) are the active ingredients. Thus, the findings from the present study suggest that researchers may be better off focusing their attention on those active ingredients instead.

Conclusion

The purpose of this dissertation was to examine the protective and predictive quality of psychological resilience on various domains of motor functioning, including gait and balance, endurance and stamina, upper body strength, motor speed, and upper extremity coordination in an early cohort of patients with MS. This study sought to extend the findings of Klineova et al. (2019) by re-examining the role of resilience in this clinical population 3 years later to evaluate this construct as a potential predictor of change in objective functional outcomes.

In contrast to our hypothesis, psychological resilience and functional outcomes were not correlated. Psychological resilience did not predict change in motor functioning over time and did not serve as a moderator between disease burden and motor functioning. As such, the present study does not provide support for psychological resilience as a protective factor for the motor system in MS or for resilience in predicting differential decline in motor functioning.

Resilience is associated with many psychological, physical, and social factors, both directly and indirectly, which poses challenges to this area of research as it becomes easily convoluted. Moreover, the study of resilience is confounded by co-occurrence of mood, notably depression and anxiety, fatigue, as well as other psychological variables (e.g., drive). Thus, there continues to be a lack of understanding for this dynamic construct and its mechanism is still poorly understood. It remains unclear whether psychological resilience is a true isolated protective factor that is not simply a proxy for other known psychological or physiological variables (e.g., positive psychology).

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