Brain Reserve in Multiple Sclerosis:

The Impact of Maximal Lifetime Brain Growth on Fine Motor Functioning

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ABSTRACT

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Multiple sclerosis (MS) is a prevalent and progressive autoimmune inflammatory disease affecting both white and gray matter and resulting in lesions and atrophy within the central nervous system (CNS) (Bermel & Bakshi, 2006; Confavreux & Vukusic, 2006; Cree, 2012; Friese, Schattling, & Fugger, 2014). Fine motor impairment, including manual motor speed and fine motor dexterity deficits, is common in MS patients (e.g., Benedict et al., 2011; Chipchase, Lincoln, & Radford, 2003). However, impairment does not progress uniformly across patients (Confavreux, Vukusic, Moreau, & Adeleine, 2000; Filippi & Rocca, 2011; Scalfari, Neuhaus, Daumer, DeLuca, & Muraro, 2013) and the association between disease burden and physical disability is moderate at best (Bermel & Bakshi, 2006; Filippi et al., 2013). Though the brain reserve hypothesis has helped to explain the clinico-pathologic dissociation between cognitive functioning and disease burden in MS patients (Sumowski et al., 2013; Sumowski et al., 2014a), there is no published literature on brain reserve and motor functioning in MS. Instead, only preliminary data have been presented on brain reserve and general physical disability (Sumowski et al., 2014b). As such, the purpose of this dissertation was to examine the protective effect of brain reserve, estimated via intracranial volume (ICV), on fine motor functioning in relapse-onset MS patients.

A sample of 178 relapse-onset, right-handed MS patients underwent neuropsychological testing along with neurological examination, including magnetic resonance imaging (MRI). As part of the evaluation, patients were administered the Nine Hole Peg Test (NHPT; a measure of fine motor speed and dexterity) and the Finger Tapping Test (FTT; a measure of manual motor speed), which served as this study's outcomes (i.e., dependent variables). Predictors (i.e., independent variables) included demographic variables (age, sex), disease variables (disease duration and disease phenotype, including relapsing-remitting MS (RRMS) or secondary-progressive MS (SPMS)), MRI estimates of disease burden (T2 lesion volume [T2LV], normalized brain volumes as measures of cerebral atrophy), and MRI-derived measures of ICV as an estimate of brain reserve.

Results revealed that phenotype ($r = .56$, $p < .001$) significantly predicted performance on the NHPT, such that patients with SPMS did worse than patients with RRMS. Regarding disease burden, T2LV ($r = .24$, $p = .001$) and normalized gray matter volume ($r = -.18$, $p = .019$) predicted NHPT, with less disease burden associated with better performance. Greater ICV ($r = -.21$, $p = .006$) was also significantly associated with better performance on the NHPT. Next, phenotype ($r = -.45$, $p < .001$) predicted FTT with SPMS patients again performing worse than RRMS patients. Sex ($r = .40$, $p < .001$) was a significant predictor of FTT with men outperforming women, on average. For FTT, normalized gray matter volume ($r = .36$, $p < .001$) was the only measure of disease burden that predicted performance, with greater volume (i.e., less atrophy) associated with better performance. Similarly, greater ICV ($r = .31$, $p < .001$) significantly predicted better performance on the FTT. For both NHPT and FTT, interactions between measures of disease burden and ICV were not significant. As such, some evidence from this study was not consistent with the reserve hypothesis; however, this finding may be due to

differences in the way brain reserve impacts motor outcomes (relative to cognitive outcomes). Nonetheless, as ICV was associated with better performance for both outcome measures, these findings provide partial support for the brain reserve hypothesis in fine motor functioning in MS. Therefore, findings from this study have real-life applications with regard to improved understanding of fine motor disability in MS and identification of patients at risk for upper extremity dysfunction, leading to the possibility of early intervention. Findings also have implications for informing clinical research in MS.

Future research should examine the protective effect of brain reserve on fine motor functioning within larger cross-sectional samples (i.e., RRMS vs. SPMS), within primary-progressive MS (PPMS) patients, and when using additional measures of upper extremity disability (e.g., Grip Strength Test). Longitudinal research would also help to determine whether there is a moderating effect of brain reserve on fine motor disability progression as well as allow patients to serve as their own baseline, which would control for individual differences in motor functioning. Next, examining reserve in patients experiencing lesions and atrophy in specific brain regions underlying motor function (e.g., cerebellum and precentral gyrus) may help explain why interactions between disease burden and ICV were not significant within the present study. Finally, by testing the brain reserve hypothesis as it relates to fine motor functioning in non-clinical, healthy controls, it would be possible to determine whether the protective effect of reserve is present premorbidly.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

Chapter One:

Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disease initially affecting an individual's central nervous system (CNS) in young and middle adulthood (Confavreux & Vukusic, 2006; Cree, 2012). The disease course is characterized by relapses and irreversible progression of symptoms (Confavreux & Vukusic, 2006). Given this, there are three identified types of MS: relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), and primary-progressive MS (PPMS). As the name implies, RRMS patients experience repeated relapses followed by periods of remission (Lublin et al., 2014; Lublin & Reingold, 1996; Noseworthy, Lucchinetti, Rodriguez, & Weinshenker, 2000). Approximately 50% of these patients eventually convert to SPMS, which is characterized by ongoing progression of disability even in the absence of relapses and despite fewer relapses over time (Friese, Schattling, & Fugger, 2014; Koch, Kingwell, Rieckmann, & Tremlett, 2010; Noseworthy et al., 2000; Steinman, 2001; Tremlett, Yinshan, & Devonshire, 2008). Finally, PPMS is characterized by continuous, irreversible worsening of neurologic functioning and disability beginning at the time of diagnosis. This dissertation will focus on RRMS and SPMS, collectively called "relapse-onset" MS given that a relapsing-remitting course is present upon diagnosis, which comprises 85% of MS patients (Lublin et al., 2014; Lublin & Reingold, 1996; Noseworthy et al., 2000; Weinshenker et al., 1989).

Two MS-related disease processes evident on magnetic resonance imaging (MRI) include lesions and atrophy within the CNS. Though these processes can be widespread, locational patterns have been identified (Bermel & Bakshi, 2006). For example, lesions are often found within the optic nerves, periventricular white matter, as well as white matter of the brain stem,

1

cerebellum, and spinal cord (Noseworthy et al., 2000). Atrophy commonly affects the midbrain, pons, cerebellum, thalamus, and caudate nucleus. Enlarged cortical sulci and periventricular regions are also typical (Bakshi, Benedict, Bermel, & Jacobs, 2001; Bermel & Bakshi, 2006; Bermel, Innus, Tjoa, & Bakshi, 2003; Cifelli et al., 2002). Importantly, both white matter and gray matter are implicated in functional impairment (Bermel & Bakshi, 2006; Friese et al., 2014).

Though MS patients experience a variety of notable symptoms (e.g., cognitive, motor, and psychological), this dissertation will focus on their experience of fine motor impairment given the prevalence of this form of disability. Specifically, at least 60% of MS patients demonstrate impaired fine motor dexterity (i.e., complex fine motor function), with dysfunction increasing with disease progression (Benedict et al., 2011; Bertoni, Lamers, Chen, Feys, & Cattaneo, 2015; Einarsson et al., 2006; Johansson et al., 2007; Lamers & Feys, 2014; Yozbatiran, Baskurt, Baskurt, Ozakbas, & Idiman, 2006; Ytterberg, Johansson, Andersson, Holmqvist, & von Koch, 2008). MS patients also consistently perform significantly worse than matched healthy controls on measures of manual motor speed (i.e., simple fine motor function), with impairment again increasing as a function of disease progression (Beatty & Gange, 1977; Chipchase, Lincoln, & Radford, 2003; Olivares et al., 2005; Reddy et al., 2002; Stoquart-ElSankari, Bottin, Roussel-Pieronne, & Godefroy, 2010; van den Burg, van Zomeren, Minderhoud, Prange, & Meijer, 1987). With regard to the practical implications and importance of this study, the literature consistently demonstrates that deficits in upper extremity functioning greatly impact patient independence in activities of daily living and health-related quality of life (Hoogervorst, Kalkers, Cutter, Uitdehaag, & Polman, 2004; Johansson et al., 2007; Kragt, van der Linden, Nielsen, Uitdehaag, & Polman, 2006; Schwid, Goodman, McDermott, Bever, &

Cook, 2002; Yozbatiran et al., 2006). As such, it is necessary to better understand factors associated with impairment in fine motor functioning in MS patients to optimize treatment and research practices.

Understanding fine motor dysfunction in this population is complicated by the fact that impairment does not progress uniformly across patients. Physical disability is also highly variable among MS patients despite similar disease burden and duration as well as relapse patterns / frequency (Confavreux, Vukusic, Moreau, & Adeleine, 2000; Filippi & Rocca, 2011; Scalfari, Neuhaus, Daumer, DeLuca, & Muraro, 2013). As a result, it has historically been difficult to identify MS patients at greatest risk for future disability, particularly given that the association between disease burden and physical disability is only moderate at best (Bermel & Bakshi, 2006; Filippi et al., 2013). Indeed, numerous studies have demonstrated that while greater disease burden is linked to worse functional outcomes, the correlation is incomplete, indicating that some patients are able to withstand greater disease burden while experiencing less physical disability (Fisher et al., 2000; Kalkers et al., 2001; Kearney et al., 2014; Popescu et al., 2013). This phenomenon is known as a clinico-pathologic dissociation and it has also been demonstrated with regard to cognitive functioning and disease burden in MS (Benedict et al., 2004; Benedict et al., 2006; Christodoulou et al., 2003; Sanfilipo, Benedict, Weinstock-Guttman, & Bakshi, 2006) as well as aging populations (Bennett et al., 2006; Bennett, Schneider, Buchman, Barnes, Boyle, & Wilson, 2012; Crystal et al., 1988; Galvin et al., 2005; Katzman et al., 1988; Price & Morris, 1999).

The brain reserve hypothesis has been studied within aging and MS populations and helps to explain these clinico-pathologic dissociations. The brain reserve hypothesis states that resiliency against functional impairment is the result of the amount of one's brain reserve

3

capacity (BRC), which is operationalized as maximal lifetime brain growth (MLBG) and estimated with head circumference or MRI-derived measures of intracranial volume (ICV) (Satz, 1993). More simply, clinical deficits only occur when brain volume is reduced below a critical (albeit unspecified) threshold for expression (Satz, 1993; Stern, 2002; Stern, 2012). Thus, larger MLBG serves as a protective factor in the face of brain disease or damage as well as aging because these individuals have more brain volume to lose (Satz, 1993; Stern, 2002; Stern, 2012). Though the brain reserve hypothesis has been studied as it relates to cognition in MS and other patient populations (Perneczky et al., 2010; Schofield, Mosesson, Stern, & Mayeux, 1995; Schofield, Logroscino, Andrews, Albert, & Stern, 1997; Sumowski et al., 2013; Sumowski et al., 2014a), the theory has only recently been extended to physical disability in MS. Specifically, Sumowski et al. (2014b) presented preliminary findings that ICV was associated with lesser general physical disability and moderated disability progression. To date, no studies have been conducted examining the brain reserve hypothesis as it relates to specific domains of motor dysfunction in MS, such as fine motor function.

Chapter Two:

Literature Review

Multiple Sclerosis

Multiple sclerosis (MS) is a prevalent and chronic autoimmune inflammatory disease of the central nervous system (CNS). Patients are two to three times more likely to be female and the disease is typically diagnosed in young and middle adulthood (average age of onset is approximately 30 years), thus affecting individuals at a time when they are establishing careers and/or raising families (Confavreux & Vukusic, 2006; Cree, 2012). The cause of the disease remains unknown and while recent advances in pharmacological treatment (i.e., immunomodulatory drugs) have been helpful in slowing the disease, there is still no cure and the disease continues to progress throughout one's life (Cree, 2012; Noseworthy et al., 2000). Finally, mortality data reveal that although it is now rarer for patients to die from MS itself, life expectancy remains shorter for MS patients relative to the general population (Hurwitz, 2011).

Two clinical phenomena characterize the course of MS: (1) relapses or "attacks" of neurological symptoms that eventually go into complete or partial remission and (2) irreversible progression of neurological symptoms (Confavreux & Vukusic, 2006). From this, there are three main identified types of MS: relapsing-remitting (RRMS), secondary-progressive (SPMS), and primary-progressive (PPMS). Approximately 85% of MS patients are initially diagnosed with RRMS, which is characterized by alternating periods of relapse and remission (Lublin et al., 2014; Lublin & Reingold, 1996; Noseworthy et al., 2000). Over time approximately 50% of RRMS patients convert to SPMS, which is characterized by chronic progression of the disability even in the absence of relapses, with relapses becoming less frequent with time (Friese et al., 2014; Koch et al., 2010; Noseworthy et al., 2000; Steinman, 2001; Tremlett et al., 2008). RRMS

and SPMS are often categorized as "relapse-onset MS" given their relapsing-remitting course at the time of diagnosis (Weinshenker et al., 1989). In contrast to relapse-onset MS, approximately 15% of patients initially express a PPMS course, which is characterized by a continuous, irreversible worsening of neurologic functioning/disability from the time of diagnosis onward; this course is often referred to as "progressive-onset MS." This dissertation is focused on the more prevalent and better-characterized population of relapse-onset MS.

        Disease-related brain changes: Atrophy and lesion load. Magnetic Resonance Imaging (MRI) is an essential tool for monitoring the progression of MS disease within the CNS, as well as monitoring treatment efficacy in slowing progression. On a structural level, two identified disease-related patterns of brain changes evident on MRI are lesion volume and atrophy (loss of brain volume), including whole brain (global), gray matter, white matter, and regional atrophy (e.g., atrophy of the thalamus). Lesions as seen on T2-weighted images, as used in this study, are representative of pathological changes such as edema, gliosis, inflammation, demyelination, remyelination, and axonal loss (Bermel & Bakshi, 2006). Of note, while MS lesions can occur anywhere within the CNS, leading to variability in symptom presentation, typical locational patterns are responsible for the most common MS symptoms. For example, lesions are often found within the optic nerves, periventricular white matter, as well as white matter of the brain stem, cerebellum, and spinal cord (Noseworthy et al., 2000). Atrophy in MS is also widespread, affecting the cortical, central, and infratentorial regions (Bakshi et al., 2001; Bermel & Bakshi, 2006). Specifically, enlarged frontal, parietal, temporal, and occipital cortical sulci and periventricular regions are common as well as atrophy affecting the midbrain, pons, cerebellum, thalamus, and caudate nucleus (Bakshi et al., 2001; Bermel et al., 2003; Bermel & Bakshi, 2006; Cifelli et al., 2002).

Interestingly, although MS was classically considered a disease of the white matter (i.e., myelin), recent research has found that neurodegeneration (gray matter / neuronal loss) begins at disease onset and is more associated with functional impairment than white matter lesions (Bermel & Bakshi, 2006; Friese et al., 2014). In particular, disease-related cerebral atrophy (especially gray matter atrophy) has been linked to cognitive impairment (i.e., memory decline) (Benedict et al., 2004; Benedict et al., 2006; Bermel & Bakshi, 2006; Filippi et al., 2010) as well as physical disability (i.e., gait disturbance) (Bermel & Bakshi, 2006: Fisniku et al., 2008; Popescu et al., 2013; Sanfilipo, Benedict, Sharma, Weinstock-Guttman, & Bakshi, 2005; Tedeschi et al., 2005). Cognitive decline and physical disability progression have also been linked to cerebral atrophy over time (Bermel & Bakshi, 2006; Filippi et al., 2013; Fisher, Lee, Nakamura, & Rudick, 2008).

Disability progression in multiple sclerosis. Using the Expanded Disability Status Scale (EDSS; previously the Disability Status Scale (DSS; Kurtzke, 1983) to quantify disability, researchers have examined disability progression in MS. The EDSS is a commonly administered, ordinal scale of neurological disability. The EDSS score is derived from a clinical MS neurologist's examination of a patient's seven functional systems (pyramidal, cerebellar, sensory, visual, brainstem, bowel/bladder, cerebral/mental), ambulatory functioning, and independence in activities of daily living (ADLs; Kurtzke, 1983). The exam yields a single EDSS score ranging from 0 (normal) to 10 (death due to MS) with scores increasing at 0.5 point increments (e.g., 6.5 is associated with required bilateral assistance for ambulation).

Regarding disability progression, higher EDSS scores, frequent relapses in the first two years of the disease, progressive-onset, male sex, as well as permanent motor or cerebellar impairment occurring early in the disease are linked to a more severe course (Hughes et al.,

7

2012; Noseworthy et al., 2000). More specifically, studies have shown that approximately 25% of RRMS patients experience a significant worsening in clinical disability (Δ EDSS score ≥ 1.0) in a two to three year period (Fazekas, Deisenhammer, Strasser-Fuchs, Nahler, & Mamoli, 1997; Jacobs et al., 1996; O'Conner et al., 2009). EDSS rank after 4 years disease duration predicts EDSS scores after 5 years, which in turn highly predicts disease progression by 10 years (Hughes et al., 2012). Relative to females, males transitioned to SPMS more quickly from onset and were younger at the time of conversion; however, males and females did not differ in years of age at EDSS = 8, which is indicative of patient restriction to a bed/chair or perambulated in a wheelchair (Kurtzke, 1983; Tremlett et al., 2008). Finally, rate of lesion volume increase was three times higher in patients who developed SPMS relative to patients who remained at RRMS, with greater lesion volume present as early as 5 years from onset of MS (Fisniku, 2008).

Symptoms. Many (or even most) patients with MS experience physical disability, including pyramidal (upper and lower extremity function, e.g., fine motor), cerebellar (balance and gait), visual, sensory, brainstem (ocular-motor), as well as bowel and bladder dysfunction (Confavreux et al., 2000; Confavreux & Vukusic, 2006; Cree, 2012; Fazekas et al., 1997; Hughes et al., 2012; Jacobs et al., 1996; Kurtzke, 1983; Noseworthy et al., 2000; O'Conner et al., 2009; Tremlett et al., 2008). More specifically, 80% to 90% of MS patients experience the following motor symptoms, often in combination: limb weakness (periodic or chronic), spasticity, and coordination problems (Lezak, Howieson, Bigler, & Tranel, 2012). In a study of 205 MS patients, the following physical disability categories from the International Classification of Functioning (ICF), Disability and Health were identified as a problem by more than 50% of patients: muscle power functions, gait pattern functions, mobility of joint functions, sensations related to muscles and movement functions, muscle tone functions, involuntary

8

movement functions, psychomotor functions, spinal cord and related structures, structure of lower extremity, and structure of upper extremity (Holper et al., 2010). Not surprisingly, physical disability very typically leads to reduced health-related quality of life and independence in ADLs (Cree, 2012; Kurtzke, 1983; Miller, Rudick, Cutter, Baier, & Fischer, 2000; Shawaryn, Schiaffino, LaRocca, & Johnston, 2002).

With regard to the experience of physical impairment throughout the course of the disease, motor symptoms (i.e., loss of dexterity, limb weakness, and gait disturbance) are the second most commonly reported initial disturbance experienced by patients with MS (Cree, 2012; Swingler & Compston, 1992). (Note: sensory disturbances (e.g., tingling sensation) are the most common initial manifestation with less typical manifestations including optic neuritis, ataxia and tremor, diplopia, vertigo, fatigue, facial pain or weakness, cognitive deficits, etcetera (Cree, 2012; Swingler & Compston, 1992)). Physical weakness was also cited as the number one most frequent symptom experienced throughout the duration of the disease (Swingler & Compston, 1992). Weakness may occur within a single limb or may become widespread, leading to paraparesis, hemiparesis, or quadriparesis (Cree, 2012; Noseworthy et al., 2000). Tremor and gait ataxia (disturbance) are also common with approximately 50% of patients requiring walking assistance within 15 years of disease onset (Cree, 2012; Noseworthy et al., 2000; Weinshenker, et al., 1989).

Two common instruments used to quantify degree of disability in MS patients include the EDSS (Kurtzke, 1983) and the Multiple Sclerosis Functional Composite (MSFC; Cutter et al., 1999). As discussed, the EDSS provides a measure of a patient's seven functional systems (pyramidal, cerebellar, sensory, visual, brainstem, bowel/bladder, cerebral), ambulatory

functioning, and independence in ADLs (Kurtzke, 1983). Scores range from 0 (normal) to 10 (death due to MS) and increase at 0.5 point increments.

Although widely-used, the EDSS is a rather non-specific measure of overall MS-related disability, without specific, continuous measures of fine motor, gait, and cognitive functioning. As such, the MSFC was created and is frequently used in clinical practice and research as it is recognized for its strong psychometric properties and standardized administration (Benedict et al., 2011; Cutter et al., 1999; Fischer et al., 1999). The MSFC consists of three measures, including two continuous measures of physical disability: the Nine Hole Peg Test (NHPT; a measure of upper extremity function / manual dexterity) and the Timed 25 Foot Walk (T25FW; a measure of lower extremity function and balance) (Benedict et al., 2011; Cutter et al., 1999; Fischer et al., 1999). The third measure included within the MSFC, the Paced Auditory Serial Addition Test (PASAT), assesses information processing speed, divided and sustained attention and working memory (Fischer et al., 1999; Strauss, Sherman, & Spreen, 2006).

In addition to physical dysfunction, cognitive deficits are seen within all stages of the disease with functioning typically declining over time (Filippi et al., 2010). That said, cognitive symptoms in isolation are not commonly the presenting symptom in MS (Lezak et al., 2012). As it relates to prevalence, one seminal study comparing 100 community-based MS patients and 100 matched healthy controls demonstrated that nearly half of MS subjects were labeled "cognitively impaired" relative to only five healthy controls (Rao, Leo, Bernardin, & Unverzagt, 1991). More recent studies corroborate this approximately 50% prevalence rate for cognitive impairment in patients with MS (Einarsson et al., 2006; Holper et al., 2010; Johansson et al., 2007). Although MS patients show deficits in many areas relative to healthy controls, the two most impacted cognitive domains are information processing speed (i.e., cognitive efficiency) and

learning/memory, including difficulty with acquisition as well as impaired episodic memory relative to intact or preserved semantic memory and implicit memory (Beatty, Goodkin, Hertsgaard, & Monson, 1990; Beatty, Goodkin, Monson, & Beatty, 1989; Benedict et al., 2004; Benedict et al., 2011; Deloire et al., 2011; Filippi et al., 2010; Rao et al., 1991; Sanfilipo et al., 2006).

As it relates to emotional functioning, results from Rao et al. (1991) revealed that approximately 30% of MS patients were classified as depressed according to items endorsed on the Zung Depression Scale, which was significantly greater than healthy controls. The finding that MS patients score higher on measures of depression has been consistently replicated throughout the literature (e.g., Benedict et al., 2004; Benedict et al., 2006). As an example of findings from a more recent study, Sanfilipo et al. (2006) demonstrated that the MS group (n = 40; 34 RRMS and 6 SPMS) had significantly higher scores on the Beck Depression Inventory (BDI) relative to a control group (n = 83). In addition to depression, patients with MS also scored higher on the Neuropsychiatric Inventory (NPI), an overall measure of psychopathology, within the following domains: Anxiety, Agitation, Irritability, Dysphoria, Apathy, and Euphoria (Sanfilipo et al., 2006).

Focus on fine motor function in multiple sclerosis. This dissertation is focused on upper extremity dysfunction in MS patients, and specifically manual motor speed and fine motor dexterity (i.e., simple and complex fine motor function). Regarding more complex (and more frequently studied) upper extremity disability, at least 60% of patients with MS demonstrate impaired fine motor dexterity, with increased impairment associated with disease progression (Benedict et al., 2011; Bertoni et al., 2015; Einarsson et al., 2006; Johansson et al., 2007; Lamers & Feys, 2014; Yozbatiran et al., 2006; Ytterberg et al., 2008). For example, in one study, 73% of

166 MS patients displayed impaired fine motor functioning on the NHPT (Einarsson et al., 2006). In a second cross-sectional study including 219 patients with MS, 79% and 76% of patients were categorized as disabled on the NHPT when using their dominant and non-dominant hands, respectively (Johansson et al., 2007). Finally, in a two-year prospective study of 200 patients with MS, 60% experienced manual dexterity disability on the NHPT (Ytterberg et al., 2008).

Relative to healthy controls (HCs), MS patients in all stages of the disease performed significantly worse on the NHPT and fine motor functioning was found to be a notable area of impairment relative to other domains, which provides support for the focus of this dissertation (Benedict et al., 2011; Lamers, Kerkhofs, Raats, Kos, Wijmeersch, & Feys, 2013; Yozbatiran et al., 2006). As an example, Benedict et al. (2011) compared MS patients (n = 211; mean EDSS = 2.80 ± 1.60) and HCs (n=120) on the motor components of the MSFC and found a greater difference in performance between the groups on the NHPT (Cohen's d = 0.94) relative to the T25FW (Cohen's d = 0.64). Regarding the degree of impairment, the average z-score of the MS group relative to the HC group on the NHPT was z = -1.70 (Benedict et al., 2011). In a study by Yozbatiran et al. (2006), the average z-score of the MS group (n = 31; mean EDSS = 2.56 ± 1.91) as compared to the HC group (n = 30) on the NHPT was z = -5.01. Lastly, it is noteworthy as it relates to the rate of disability progression that within an average of 530 days (i.e., 1.45 years), 14% of MS patients demonstrated a clinically-meaningful worsening (i.e., >20% increase) in their performance on the NHPT (Kragt et al., 2006).

In order to more thoroughly study fine motor function in MS, a version of the Finger Tapping Test (FTT) (Reitan, 1969), a measure of manual motor speed, was included in this study. This task was chosen as a review of the literature demonstrates that MS patients perform

worse than HCs on finger tapping tasks (Reitan, 1969), with impairment increasing as a function

of disease progression (Beatty & Gange, 1977; Chipchase et al., 2003; Olivares et al., 2005;

Reddy et al., 2002; Stoquart-ElSankari et al., 2010; van den Burg et al., 1987). Regarding level

of functional impairment, one study found that the average z-score of the RRMS group (n=57)

relative to the HC group (n=100) on the FTT test (both hands) was z = -1.46 (Heaton, Nelson,

Thompson, Burks, & Franklin, 1985). A second study showed that the average z-score of 40 MS

patients (mean DSS = 2.60 ± 0.90) compared to 40 HC participants on the FTT test was z = -1.16

(van den Burg et al., 1987). Although not as common as the EDSS or subtests from the MSFC in

measuring physical disability, a review of the literature clearly identifies manual motor speed as

an area of notable impairment in MS populations (Zakzanis, 2000). Additionally, as finger

tapping tasks are frequently used in functional MRI (fMRI) studies of MS motor dysfunction

given simplicity of task execution (Lowe et al., 2002; Lowe et al., 2008; Mancini et al., 2009),

results of this dissertation will importantly inform imaging research in MS.

In addition to the widespread presence of fine motor disability in MS patients, a second

consistent finding within the literature is that deficits in manual dexterity significantly impact

independence in ADLs and negatively impact quality of life. To illustrate, one study found that

manual dexterity disability was significantly associated with an increase in patients' perceived

physical impact of MS on the Multiple Sclerosis Impact Scale-29 (MSIS-29), highlighting the

effect of fine motor impairment on patient functioning in their everyday lives (Johansson et al.,

2007). A second study found that MS patient's performance on the NHPT was correlated with

the Upper Extremity Index (UEI; a measure of patient-perceived disability in ADLs) and the

physical health composite of the Multiple Sclerosis Quality of Life Instrument-54 (MSQOLI-54;

Yozbatiran et al., 2006). Similarly, ADL independence (Katz ADL Index) and

activity/participation in lifestyle and social activities (Frenchay Activity Index) were better predicted by performance on the NHPT relative to a measure of cognition (Kierkegaard, Einarsson, Gottberg, von Koch, & Holmqvist, 2012). Finally, true worsening in performance on the NHPT (i.e., >20% increase in completion time) was associated with increased patient-perceived disability in multiple domains of functioning in daily life (Hoogervorst et al., 2004; Kragt et al., 2006; Schwid et al., 2002).

Given the above findings, it is clear that fine motor dysfunction negatively impacts MS patient's daily life. As such, an investigation of protective and risk factors for progression of upper extremity disability is warranted and pursued by this dissertation. Further, as the NHPT of the MSFC is often used as an impairment outcome measure in MS clinical trials aimed to reduce/attenuate physical disability (Cohen et al., 2001; Geisler et al., 1996; Kappos et al., 2010; Ozakbas, Cagiran, Ormeci, & Idiman, 2004; Romberg, Virtanen & Ruutiainen, 2005), this dissertation will directly inform the design and data analysis approaches for studies investigating treatment.

Clinico-Pathologic Dissociation

Clinico-pathologic dissociation: Disease burden and physical disability in multiple sclerosis. Although physical disability is common in MS, impairment does not progress uniformly across patients. Indeed, MS patients exhibit greater variability on measures of fine motor functioning relative to HCs. For instance, Benedict et al. (2011) found that the standard deviation (*SD*) of performance on the NHPT for the HC group was 2.3 relative to 5.4 in the MS group. Yozbatiran et al. (2006) found an even larger discrepancy between performances on the NHPT: HC group *SD* = 1.43 vs. MS group *SD* = 10.04. Finally, Lamers et al. (2013) found that the MS group (dominant hand only) median performance on the NHPT was 45.99" ($25^{th} - 75^{th}$

IQR = 28.16 – 63.93) while the HC group median performance was 17.96" (25th – 75th IQR = 16.53 –20.42). Collectively, these results highlight how much more variable performance on the NHPT is for patients with MS when compared to a HC group.

Physical disability even varies widely among MS patients with similar disease burden, disease duration, and patterns / frequency of relapses (Confavreux et al., 2000; Filippi & Rocca, 2011; Scalfari et al., 2013). Moreover, the correlation between disease burden (i.e., MRI measurements of cerebral atrophy) and physical disability is moderate at best (Bermel & Bakshi, 2006; Filippi et al., 2013). The following studies demonstrate this incomplete relationship, which is known as a clinico-pathologic dissociation.

To test how well whole brain atrophy predicted disability and disability progression, Fisher et al. (2000) conducted an 8-year follow-up study of 160 MS patients. Participants were part of a clinical trial and had previously been examined at baseline, year one, and year two; study participants were diagnosed with RRMS at baseline. At each examination MRIs were conducted to measure size-normalized whole brain atrophy (i.e., brain parenchymal fraction; BPF). Of note, BPF is defined as the ratio of the brain parenchymal volume to the total brain volume within the brain surface contour (Fisher et al., 2000). Neurological and neuropsychological exams were also completed at each examination (Fisher et al., 2000). Neurological exams included the EDSS, current disease phase, as well as relapse and medication histories. Clinical exams included the MSFC, visual contrast, and the Sickness Impact Profile (a measure of quality of life). Results demonstrated that BPF declined over the eight year period of study, with variability increasing among patients with time (Fisher et al., 2000). Disability also progressed over time. Interestingly, BPF only demonstrated an approximately moderate correlation with MSFC and EDSS scores at baseline, year 2, and year 8 follow-up (respectively:

MSFC $r = .42, .49, .48$; EDSS $r = -.29, -.31, -.42$) (Fisher et al., 2000). [It is important to note that the MSFC correlations are higher than expected for physical disability, which is likely attributable to the inclusion of a measure of cognitive functioning within the battery, which is more strongly correlated with pathology, as described within the next section.] Additionally, there was only a moderate correlation between change in brain atrophy from year 2 to follow-up with change in MSFC ($r = .30$) and EDSS ($r = -.31$) during that time period (Fisher et al., 2000). These findings confirm that there is a relationship between BPF (i.e., whole brain atrophy) and disability in individuals with MS, though the relationship is incomplete (Fisher et al., 2000).

Kalkers et al. (2001) enrolled 134 MS patients age 17 to 76 ($M \pm SD = 43.00 \pm 11.00$) to examine the relationship between lesion load and patient performance on the MSFC and EDSS. Participants underwent clinical assessment (MSFC and EDSS) as well as an MRI of the brain. 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) were obtained. Kalkers et al. found that within the relapse-onset group, there was a moderate correlation between MSFC and T1-hypointense lesion load ($r = -.37$) and T2-hyperintense lesion load ($r = -.35$). Looking specifically at performance on the NHPT from the MSFC within this group, a moderate correlation was again found with T1-hypointense lesion load ($r = .37$) and T2-hyperintense lesion load ($r = .37$) (Kalkers et al., 2001). Interestingly, however, no significant correlation was found between lesion load and EDSS for the RRMS, SPMS or combined relapse-onset groups (Kalkers et al., 2001).

In an effort to examine the effect of multiple measures of disease burden on long-term physical disability, as assessed using the EDSS, Kearney et al. (2014) conducted a multicenter, cross-sectional study of 111 female and 48 male MS patients (n = 92 RRMS and n = 67 SPMS).

16

Average age of patients was 52 years (*SD* = 8.80) with average age of disease onset at 25.8 years (*SD* = 7.70). EDSS scores ranged from 0 to 8 with a median score of 4 (Kearney et al., 2014). Measures of brain tissue volume (gray matter and white matter fractional volumes [GMF and WMF]) and T2 lesion volume (T2LV) were acquired via MRI scans—spinal cord atrophy was also measured, though a review of those results is not included herein. In a multivariable logistic regression analysis, T2LV was found to be significantly associated with EDSS scores ≥ 6 (OR = 1.67 per 1 *SD* larger T2LV; *p* = .02; note: a score of "6" on the EDSS indicates the onset of a required walking aid for the patient). When examining EDSS scores split into four even frequency distributions (EDSS = ≤ 1.5; > 1.5 and < 3; ≥ 3 and <6; ≥ 6), multiple ordered logistic regression revealed that EDSS scores were associated with T2LV (OR = 1.56 per 1 *SD* larger T2LV; *p* = .02) and GMF (OR = 0.67 per 1 *SD* GMF; *p* = .04). In short, T2LV and GMF were associated with EDSS scores in patients with RRMS and SPMS of long disease duration, though GMF less consistently contributed to the variability, and none of the associations were strong (Kearney et al., 2014).

Popescu et al. (2013) conducted a multicenter, longitudinal, retrospective study of 184 relapse-onset MS patients (median age at baseline = 38 years). Clinical data gathered at baseline, after 1-2 years, and/or after 10 years included: date of disease onset, disease type, EDSS score, MS Severity Scale (MSSS) score, and use of disease modifying treatment (DMT) (Popescu et al., 2013). Of the relapse-onset patients, 18 had experienced a clinically-isolated syndrome, 111 were minimally impaired (i.e., EDSS = 0-3.5), and 55 were moderately impaired (i.e., EDSS = 4-6) at baseline. Normalized MRI measurements of brain atrophy included whole brain atrophy (WBA; measured as the percentage brain volume change from baseline to follow-up), central atrophy rate (measured as the percentage ventricular volume change) and normalized T2LV. The

annualized change/rate of change was calculated for whole brain atrophy, central atrophy rate, and T2LV (Popescu et al., 2013). Within the minimally impaired relapse-onset MS group, only central atrophy rate predicted 10 year disability, explaining 7% of the variance (small to medium effect). In contrast, baseline and year 1 lesion volumes predicted 10 year EDSS for the moderately impaired relapse-onset MS group, individually explaining only 2% of the variance (small effect) (Popescu et al., 2013). In the RRMS group (n=97), lesion volumes at 1 year predicted 10 year disability, though only explaining 3% of the variance (small effect). In the SPMS group (n = 69), no MRI variables predicted long term EDSS, though this may be attributed to a small sample size and high median baseline EDSS score of 5.5, leaving limited room for increased disability (Popescu et al., 2013). Nonetheless, results collectively demonstrated that both central atrophy rate and early lesion volume predicted long term physical disability in minimally to moderately impaired relapse-onset MS patients, albeit incompletely.

Numerous additional studies have demonstrated similar findings (e.g., Bermel & Bakshi, 2006). Again, these studies provide evidence of a clinico-pathologic dissociation between disease burden and physical disability. Indeed, some patients were able to withstand notable disease burden while experiencing less physical disability over time.

Given prominent variability in disability among patients with similar disease burden, it is difficult to predict future disability progression in MS patients. That is, we are unable to identify MS patients at greatest risk for future disability. The overarching goal of this dissertation was to help explain why the onset of fine motor problems occurs later in some individuals with MS than in others as well as why some individuals with MS have fine motor problems, while others do not despite similar levels of disease burden. The answer to these questions is critical as it will improve neurologist's understanding of physical disability progression in MS as well as their

ability to identify patients at risk for physical disability, informing treatment decisions and making it possible to employ early intervention. Identification of at risk MS patients is also important in interventional and clinical trial research, such as with disease modifying drugs (DMDs), aimed at slowing/preventing progression of physical disability. Specifically, if inclusion of participants is limited to those at risk for disability progression, effect sizes for efficacious treatment will be improved, thereby also increasing statistical power. Simply put, the efficacy of a DMD cannot be appropriately evaluated when the study sample is already at a reduced/variable risk of physical disability progression. For all of these reasons, methods are needed to improve prediction of future functioning.

Clinico-pathologic dissociation: Disease burden and cognitive functioning. Research on cognitive functioning has similarly identified the presence of a clinico-pathologic dissociation, demonstrating that the disconnect between pathology and impairment extends beyond physical disability in MS. First, several studies have shown that measures of disease burden (e.g., lesion load, cortical atrophy, central atrophy, white matter atrophy, gray matter atrophy and whole brain atrophy) only account for approximately 7 to 43% of the variance in MS-related cognitive impairment (Benedict et al., 2004; Benedict et al., 2006; Christodoulou et al., 2003; Sanfilipo et al., 2006). For example, Benedict et al. (2004) and Christodoulou et al. (2003) found that though cognitive performance best correlated with central atrophy (i.e., third ventricle width) relative to other MRI measures of lesion load and atrophy, central atrophy still only accounted for 14 to 43% of the variance. In a third study, normalized neocortical volume (i.e., cortical atrophy), gray matter volume, brain volume, and third ventricle width, significantly predicted cognitive status, though only accounting for 7 to 38% of the variance on individual tests of cognitive functioning (Benedict et al., 2006). Finally, Sanfilipo et al. (2006) showed that

white matter volume accounted for the greatest amount of variance in the areas of processing speed and working memory while gray matter volume best predicted short and long-term verbal memory. However, even with these significant associations, measures of disease burden (i.e., gray matter or white matter volumes) only accounted for a maximum of 29% of the variance on measures of cognition (Sanfilipo et al., 2006). Thus, as with motor functioning in MS patients, the association between disease burden and cognitive functioning remains incomplete.

Beyond MS, for decades studies in aging have reported finding neuropathologic changes associated with Alzheimer's disease (AD) (e.g., amyloid plaques and neurofibrillary tangles) within the brains of nondemented older adults (see also Crystal et al., 1988; Katzman et al., 1988; Price & Morris, 1999). In fact, studies of AD were the first to document an incomplete relationship between neuropathology and functional outcomes (Gellerstedt, 1933). More recently, researchers have demonstrated that approximately one third of participants who did not meet criteria for cognitive impairment prior to their death met neuropathologic criteria for AD on autopsy (Bennett et al., 2006; Bennett et al., 2012; Galvin et al., 2005). For example, two longitudinal studies examining autopsy results from 134 individuals who did not meet criteria for dementia or mild cognitive impairment (MCI) prior to their death found that greater than one third of the subjects met neuropathologic criteria for intermediate likelihood AD (Bennett et al., 2006). Autopsies also revealed that 29 subjects (21.6%) had cerebral infarctions (i.e., stroke) and 18 subjects (13.4%) had Lewy bodies (Bennett et al., 2006). A follow-up study revealed that approximately 33% of 1,556 persons who did not meet criteria for cognitive impairment met pathologic criteria for AD on autopsy (Bennett et al., 2012). In a separate longitudinal study, autopsy results showed pathologic features of AD in approximately 34% of nondemented participants (Galvin et al., 2005). Finally, Balasubramanian et al. (2012) demonstrated that AD

neuropathology (i.e., neuritic plaques and neurofibrillary tangles) was common in the "oldest-old" (≥90 years-old) but not related to longitudinal cognitive performance. Collectively, these studies in physical disability and cognition highlight the ability of many individuals to endure a significant level of pathology without suffering clinical or functional impairment.

Brain Reserve

The existence of a hypothetical construct known as *brain reserve* (see Satz, 1993) has been studied in aging and MS populations and helps to explain how individuals experience differential levels of clinical deficits despite having a similar magnitude of brain damage or pathology. The brain reserve hypothesis states that resiliency against impairment in the context of progressive brain disease, brain damage, or aging, is a function of the amount of one's brain reserve capacity (BRC),

Figure 1. Brain reserve hypothesis.

which is operationalized as an individual's maximal lifetime brain growth (MLBG) and commonly estimated with intracranial volume (ICV). Specific clinical or functional deficits do not appear until BRC is reduced below a critical, unspecified threshold for expression (Satz, 1993; Stern, 2002). Thus, individuals with larger MLBG are protected from clinical symptoms because they have more to lose in brain volume before falling below a critical threshold (Satz, 1993; Stern, 2002; Stern, 2012).

Figure 1 provides a visual depiction of the brain reserve hypothesis. As seen within this figure, two individuals have different levels of MLBG (estimated with ICV, which is heritable and established during adolescence) but the same level of absolute brain volume loss. The individual on the left has yet to experience clinical disability given their larger MLBG whereas the same level of brain volume loss put the individual on the right over the threshold for disability. Thus, greater brain reserve protected the person on the left as that individual can lose more brain volume than the person the right before experiencing clinical disability.

It is important to note that MLBG (i.e., brain reserve) allows individuals to better withstand neurologic disease/damage not that MLBG influences disease burden. In fact, MLBG is unrelated to disease burden (lesion volume and cerebral atrophy) (Sumowski et al., 2013) and disease burden progression (Sumowski et al., 2014a). Thus, it is not the case that individuals with bigger brains have bigger lesions but instead that individuals with bigger brains are able to withstand greater brain volume loss before falling below a threshold beneath which functional impairment occurs.

MLBG serves as an appropriate proxy for neuronal count given the linear relationship between the two in primates, including humans (Haug et al., 1987; Herculano-Houzel, 2012; Herculano-Houzel, Collins, Wong, & Kaas, 2007). MLBG is commonly estimated via MRI-derived measures of ICV for several reasons. First, proportional growth in ICV and brain volume occurs until maximal development is achieved at approximately age 15 (Courchesne et al., 2000). Additionally, in young, healthy adults there is a nearly perfect correlation ($r = .95$) between total brain volume and ICV (Baare et al., 2001; Mori et al., 1997). Finally, as significant changes in ICV are not observed once MLBG is achieved in early adolescence, ICV is an appropriate measure of MLBG in adults (Courchesne et al., 2000).

Brain reserve and cognitive functioning. Sumowski et al. (2013) provides supporting

evidence for the brain reserve hypothesis as it relates to cognitive impairment in MS patients.

Within this study, 62 patients (n = 30 women; average age = 43.7 years) with relapse-onset MS

(n = 41 relapsing-remitting; n = 21 secondary progressive) were assessed using measures of

cognitive efficiency and memory (Sumowski et al., 2013). Measures of cognitive efficiency

included the oral version of the Symbol Digit Modalities Test (SDMT) and the 3-second version

of the Paced Auditory Serial Addition Task (PASAT). Memory tasks included the Selective

Reminding Test (SRT) and the Spatial Recall Test. Subjects received MRIs to measure disease

burden and ICV, which served as an estimate of MLBG. Results showed a significant interaction

between ICV and T2LV for MS-related cognitive efficiency but not memory. As such, larger

ICV lessened the negative impact of disease burden on cognitive efficiency in relapse-onset MS

patients ($r = .29$) (Sumowski et al., 2013).

In a follow-up longitudinal study, 40 MS patients (n = 28 women; average age at baseline

= 43.85 years) were examined to determine whether MLBG protected against a reduction in

cognitive efficiency over 4.5 years (Sumowski et al., 2014a). Cognitive efficiency was again

assessed with the SDMT and PASAT while MLBG was again estimated with ICV. Results of the

study revealed a significant interaction between time (i.e., baseline and follow-up) and ICV on

cognitive efficiency (Sumowski et al., 2014a). Specifically, larger ICV protected against

cognitive efficiency decline over 4.5 years ($r = .37$ when controlling for baseline cognitive

efficiency and brain atrophy over time). Additional analyses demonstrated that larger ICV also

protected against a decline in verbal fluency over 4.5 years when controlling for MS disease

progression (i.e., change in cerebral atrophy and lesion volume over time) (Sumowski et al.,

2014a). However, like the results from the cross-sectional study (Sumowski et al., 2013), there

23

was no protective effect of larger ICV against memory decline. Nonetheless, these findings highlight the importance of considering MLBG in the prediction of cognitive decline as MS patients with lower MLBG were at greater risk for decline in functioning (Sumowksi et al., 2014a).

Relative to MS, the brain reserve hypothesis has been much more thoroughly examined within aging and dementia populations, with MLBG typically estimated with ICV or head circumference (see also Graves et al., 1996; Graves et al., 2001; MacLullich et al., 2002). For example, in one cross-sectional study of 818 healthy adults (n = 387 women) with a mean age of 63.2 years (range 50 to 81 years), the hypothesis that head size and cognitive functioning were related was tested. Within analyses, height, socioeconomic background, and educational level were controlled. Results demonstrated that smaller head circumference was associated with poorer information processing speed (Stroop Color-Word Task) but not memory (Word Learning Test) (Tisserand et al., 2001).

In another study, 401 subjects aged 60+ years (average age = 75.0) were assessed with regard to cognitive function, MLBG (estimated using ICV), and current brain volume (Farias et al., 2012). Participants were diverse with regard to cognitive status: 52% were cognitively intact, 33% were diagnosed with mild cognitive impairment (MCI), and 16% were diagnosed with dementia—predominantly Alzheimer's disease (AD). Farias et al. (2012) found that ICV was related to semantic memory ($r = .20$), executive functioning ($r = .27$), and spatial ability ($r = .16$), after controlling for current brain pathology (i.e., current total brain volume, hippocampal size, and degree of white matter hyperintensity abnormalities) (Farias et al., 2012). Thus, MLBG was related to multiple cognitive domains in an older adult population despite the presence of atrophy.

24

With regard to more general cognitive functioning, Reynolds et al. (1999) conducted a study to determine whether head size was related to performance on the Mini-Mental State Examination (MMSE), which serves as a brief cognitive screening measure. The sample included 825 nondemented older adults (n = 533 women) aged 70 to 95 years (mean age for women = 78.20 ± 4.80; mean age for men = 77.60 ± 4.50). As predicted, larger head circumference was linked to higher MMSE scores (i.e., after adjusting for age and education, smaller head size was associated with scores below the 10th percentile) (Reynolds et al., 1999). Collectively, findings from Tisserand et al. (2001), Farias et al. (2012), and Reynolds et al. (1999) highlight the advantage of having larger MLBG (as measured by ICV or head circumference) as one ages.

Regarding brain reserve as it relates to developing dementia, Schofield et al. (1995) conducted a study in which 28 female patients diagnosed with probable AD (symptom onset after age 60) received computed tomography (CT) scans to obtain an average intracranial area (i.e., a measure of MLBG). Results showed that average MLBG was positively correlated with age at first symptom ($r = .48$). Additionally, linear regression analyses demonstrated that for each 1-cm^2 increase in brain size, onset of symptoms, including memory problems, was delayed by a third of a year on average (Schofield et al., 1995).

In a much larger sample (n = 649; age 65+ years; mean age = 78.3 years), subjects underwent neuropsychological evaluations and anthropometric measures, including head circumference, height, and weight (Schofield et al., 1997). Of the subjects, n = 75 were diagnosed with possible or probable AD. Logistic regression analyses evaluating head circumference as a continuous variable showed that head circumference was significantly associated with AD (OR = 0.8, 95% CI 0.7-0.9) when controlling for age, education, ethnicity,

gender, and height. When evaluating head circumference as a categorical variable, women in the smallest head circumference quintile were 2.9 times more likely to have AD relative to other women with larger head circumferences. In men, those in the smallest head circumference quintile were 2.3 times more likely to have AD compared to men with larger head circumferences (Schofield et al., 1997). These findings indicate that regardless of whether head circumference is evaluated as a continuous or categorical variable, individuals with the smallest head circumferences were at an increased risk of AD (Schofield et al., 1997).

In a final study utilizing head circumference as an estimate of MLBG, Perneczky et al. (2010) administered the MMSE to 270 patients (average age = 75.23). All patients met clinical criteria for AD according to criteria of the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's disease and Related Disorders Association. Results revealed a significant interaction between atrophy and head circumference such that larger head circumference was associated with less impact of atrophy on cognition (Perneczky et al., 2010). Put another way, as atrophy levels increased, global cognitive functioning was better for individuals with larger head circumferences (Perneczky et al., 2010). Here again, results supported the brain reserve hypothesis as head circumference attenuated the negative effect of cerebral atrophy on cognitive performance in persons clinically diagnosed with AD (Perneczky et al., 2010).

Brain reserve and physical disability. Although brain reserve has been studied numerous times within cognition, this hypothesis has only recently been extended to general physical disability and there remains no published literature on the protective effect of reserve against motor impairment. In cross-sectional and longitudinal studies conducted by Sumowski et al. (2014b), the impact of brain reserve on general physical disability was examined for the first

time. ICV (as an estimate of MLBG) was obtained for each patient via MRI. Physical disability was assessed using the EDSS. To review, the EDSS (Kurtzke, 1983) yields a single score derived from examination of seven functional systems (pyramidal, cerebellar, sensory, visual, brainstem, bowel/bladder, cerebral), gait limitations, and independence in ADLs, though scores largely reflect ambulatory functioning. EDSS scores increase at 0.5 increments and range from 0.0 (no disability) to 10.0 (death due to MS). Within the cross-sectional study (Sumowski et al., 2014b), subjects included 240 patients with MS (n = 139 female). Average EDSS score was 3.30 ± 2.10 (median = 2.50), indicating minimal to moderate disability. Within the longitudinal investigation, 40 patients with MS (n = 28 female) were evaluated at baseline and then again 4.5 years later. Average EDSS score at baseline was 3.70 ± 2.10 (median = 3.50), indicating minimal to moderate disability. At follow-up the average EDSS score was 4.50 ± 2.30 (median = 4.50), indicating minimal to severe disability. Results of the cross-sectional sample revealed that larger MLBG was associated with lesser general physical disability (Sumowski et al., 2014b). Within the longitudinal sample, MLBG protected against increasing disability (Sumowski et al., 2014b). As such, the brain reserve hypothesis was supported: MLBG as estimated by ICV moderated general physical disability progression (Sumowski et al., 2014b). These findings highlight the need for research examining the impact of brain reserve on specific domains of motor functioning in MS.

Purpose and Hypotheses

The purpose of this dissertation was to examine the protective effect of brain reserve on fine motor functioning in patients with relapse-onset MS. For this study, brain reserve was operationalized as maximal lifetime brain growth (MLBG) and estimated via MRI-derived measures of intracranial volume (ICV). As discussed, the importance of this dissertation stems

from its real-word applicability. First, findings have implications with regard to improved understanding of fine motor disability in MS and the identification of MS patients at risk for upper extremity dysfunction, which subsequently informs treatment and early intervention decisions. Findings will also allow for appropriate patient selection for clinical trials, increasing statistical power and ecological validity.

The outcomes (i.e., dependent variables) within this study were continuous and included performance on the Finger Tapping Test (FTT; a measure of manual motor speed) and the Nine Hole Peg Test (NHPT; a measure of manual dexterity). The predictors (i.e., independent variables) included: demographic variables (age, sex), disease variables (disease duration and disease phenotype, including relapsing-remitting MS (RRMS) or secondary-progressive MS (SPMS)), MRI estimates of disease burden (T2 lesion volume, normalized brain volumes as measures of cerebral atrophy), and ICV. The following hypotheses regarding the separate prediction of FTT (simple fine motor function) and NHPT (complex fine motor function) were based on the literature review:

1. Greater T2 lesion volume or cerebral atrophy will be associated with worse simple and complex fine motor function.
2. MLBG will predict simple and complex fine motor function with larger MLBG associated with better performance.
3. There will be an interaction between MLBG and disease burden whereby larger MLBG will moderate/attenuate the deleterious effect of disease burden on simple and complex fine motor function.

Chapter Three:

Method

Participants

The original sample for this study consisted of 202 persons (n = 122 women) with relapse-onset MS (Polman et al., 2011) without a clinical relapse in the last four weeks, no current corticosteroid use, and no history of serious psychiatric illness (e.g., schizophrenia, bipolar disorder) or other neurologic condition. All subjects were patients at a regional MS clinical care and research center in Milan, Italy. Additional exclusion criteria included patients with pediatric-onset MS given research showing decreased MLBG (achieved at approximately age 15; Courchesne et al., 2000) in persons with MS onset prior to the age of 18 relative to age-matched healthy controls (Kerbrat et al., 2012). Next, patients >65 years old were excluded to control for the effect of aging on fine motor function; specifically, hand function has been found to diminish more precipitously after age 65 in normal aging (Carmeli, Patish & Coleman, 2003; Shiffman, 1992).

From this original sample, 178 patients (n = 110 women) were selected for inclusion in data analyses based on their score on the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). The EHI is a valid and reliable measure of hand-preference in daily activities that yields a single score (i.e., laterality quotient) ranging from -100 (completely left-handed) to +100 (completely right-handed) (Deep-Soboslay et al., 2010; Dragovic, 2004; Keane, 2008; Oldfield, 1971). Only patients with an EHI score ≥ 51 were included in primary analyses as this cut-off has been statistically shown to reliably select individuals with a strong/consistent right-hand preference lateralization versus those with mixed- and left-hand preferences (Deep-Soboslay et al., 2010; Dragovic, 2004; Keane, 2008; Szaflarski et al., 2002). Given anatomical asymmetries

and differences in cortical activation during fine motor tasks (e.g., finger tapping) between right-
and left-handed individuals (Hervé, Crivello, Perchey, Mazoyer, & Tzourio-Mazoyer, 2006;
Hervé, Mazoyer, Crivello, Perchey, & Tzourio-Mazoyer, 2005; Pool, Rehme, Fink, Eickhoff, &
Grefkes, 2014; Solodkin, Hlustik, Noll, & Small, 2001) as well as studies showing larger
intermanual differences in right-handed individuals (Schmidt, Oliveira, Krahe, & Filgueiras,
2000; Thompson, Heaton, Mathews, & Grant, 1987), an EHI ≥ 51 cut-off was selected for the
purpose of creating a more homogenous sample.

The mean ± *SD* age of patients was 43.31 ± 10.15 years (years old: min = 23.41, max =
64.79). Mean ± *SD* disease duration was 12.70 ± 8.11 (years: min = 0.47, max = 36.00). MS
phenotypes included 138 RRMS (n = 85 women) and 40 SPMS (n = 25 women). Mean ± *SD*
EHI was 88.05 ± 12.55 (median =92.00; min = 54, max = 100). Mean ± *SD* Expanded Disability
Status Scale score (EDSS) was 2.90 ± 1.80 (median = 2.00; min = 0.00, max = 7.50), indicating
mild to severe physical disability within this sample. Approval was received from the local
ethical standards committee on human experimentation and written informed consent was
obtained from all patients.

Fine Motor Function Evaluations (Outcomes)

Nine Hole Peg Test. The NHPT of the Multiple Sclerosis Functional Composite (MSFC)
is the most commonly used, reliable, and validated outcome measure of upper extremity function
in MS (Lamers, Kelchtermans, Baert, & Feys, 2014; Mathiowetz, Weber, Kashman, & Volland,
1985). Specifically, the NHPT shows high inter-rater (ICC = 0.93), intra-rater (ICC = 0.96 –
0.98), and test-retest reliability (ρ = 0.86 – 0.92) (Erasmus et al., 2001; Lamers et al., 2014;
Lamers & Feys, 2014; Solari, Radice, Manneschi, Motti, & Montanari, 2005). Next, studies
comparing the NHPT with other measures of fine motor functioning in MS patients provide

support for its concurrent validity (Lamers & Feys, 2014). For example, the NHPT is strongly

correlated with the Jebsen Taylor Hand Function Test ($\rho = 0.83 - 0.95$), a unilateral measure of

hand functions (Feys, Duportail, Kos, Van Aschand, & Ketelaer, 2002). The NHPT is

moderately to strongly correlated with the Box and Block Test (BBT) ($r = -.41$, $r = -.70$), a

unilateral measure of gross manual dexterity (Goodkin, Hertsgaard, & Seminary, 1988; Simone,

Rota, Tesio, & Perucca, 2011), as well as moderately correlated with the Purdue Pegboard ($r = -

.52$), a unilateral and bilateral measure of fine motor dexterity (Simone et al., 2011). Finally, the

NHPT is moderately correlated with the EDSS ($r = -.33$), the traditional clinical outcome

measure in MS clinical trials, suggesting the NHPT provides valuable information about

variability in fine motor functioning of MS patients beyond what is measured by the EDSS

(Cutter et al., 1999).

The NHPT requires the patient to use one hand to pick up pegs one at a time and insert

them into nine holes as quickly as possible followed by removing all of the pegs as quickly as

possible. The task was administered once with each hand with the average time taken to

complete the two trials serving as the total score. Raw scores (mean across all trials) were

converted into sample-based z-scores for this study, resulting in a mean of zero and a standard

deviation of one (range = 7.37). However, data were negatively skewed (skewness = -3.05;

kurtosis = 12.73), necessitating a log transformation. After transforming the data, the mean ± *SD*

of log NHPT was 0.31 ± 0.15 (skewness = 1.25, *SE* of skewness = 0.18; kurtosis = 2.38, *SE* of

kurtosis = 0.36).

Finger Tapping Test. Given that MS patients perform worse than healthy controls on

finger tapping tasks and that manual motor speed is more impaired than dexterity in RRMS

(Lezak, 1995), a version of the FTT was included in this study to more thoroughly examine fine

motor function in MS. Although less frequently used with MS patients, the FTT represents a simpler and thus purer measure of fine motor functioning relative to measures of dexterity, which may also involve sensory and cerebellar (coordination) function (Haaland & Delaney, 1981; Strauss et al., 2006). Of note, test-retest reliability of the FTT is high (r = .71-.78) in healthy adults (Dikmen, Heaton, Grant, & Temkin, 1999; Ruff & Parker, 1993) and studies of validity have shown that asymmetry between hands on the FTT is highly correlated (r = .78) with asymmetry on the Purdue Pegboard (Triggs, Calvanio, Levine, Heaton, & Heilman, 2000).

For this study, the Electronic Tapping Test, an electronic version of the FTT, was administered. Patients were required to use their index finger to tap a button as quickly as possible for 30 seconds. Patients were not allowed to move their whole hand or arm when tapping. The task was administered once with each hand. Total score is the number of taps completed with each index finger within 30 seconds. Raw scores were converted into sample-based z-scores for this study, resulting in a mean of zero and a standard deviation of one (range = 5.41). Data were normally distributed (skewness = -0.13, *SE* of skewness = 0.18; kurtosis = -0.21, *SE* of kurtosis = 0.36), indicating transformation of the data was not necessary.

MRI Measurements (Predictors)

Note: normalized brain volume is reduced in patients with MS (Bermel & Bakshi, 2006) and, therefore, represents a measure of cerebral atrophy in this study.

Disease burden: Overview of T2 lesion volume and normalized brain volume (i.e., cerebral atrophy). As described elsewhere (Sumowski et al., 2013; Sumowski et al., 2014b), using a 3.0-tesla Philips Intera MRI scanner (Philips Healthcare, Guildford, UK), the following brain sequences were acquired: a) dual-echo turbo spin echo (repetition time/echo time = 3,500/24–120 milliseconds; fractional anisotropy = 150°; field of view =

240 mm2; matrix = 256 x 256; echo train length = 5; 44 contiguous, 3-mm-thick axial slices); and b) 3-dimensional T1-weighted fast field echo (repetition time = 25 milliseconds; echo time = 4.6 milliseconds; fractional anisotropy = 30°; field of view = 230 mm2; matrix = 256 x 256; slice thickness = 1 mm, 220 contiguous axial slices; in-plane resolution = 0.89 x 0.89 mm^2). Absolute T2LV was measured on dual-echo scans using a local thresholding segmentation technique (Jim 5.0, Xinapse System, www.xinapse.com). Log-transformed absolute T2LV scores were calculated (as discussed below) given that the data were positively skewed.

Brain atrophy was measured as normalized volumes of gray matter (GM) and white matter (WM) obtained using SIENAX (version 2.6, part of FSL 4.1). Normalized volumes of the thalamus, caudate, putamen, and pallidum were obtained using FIRST, then applying the same scaling factor calculated with SIENAX. Deep gray matter volumes were combined into a summary measure of deep gray matter atrophy given research demonstrating the relationship between the thalamus and basal ganglia (caudate, putamen, pallidum) and motor function (Cummings, 1993; Jones, 2007). To correct for the misclassification of WM lesions, all pixels classified as GM but lying neither in the cortical GM nor in the subcortical GM were reassigned to the WM before volume calculation. The scaling factor within SIENAX is derived from the transformation that matches the extracted brain and skull to standard-space brain and skull images (derived from the MNI152 standard image): values higher than one were obtained for heads with small ICV and values lower than one for ICVs larger than the MNI atlas. An advantage of this approach is that it does not require that CSF be robustly estimated, as it is difficult to distinguish between CSF and skull voxels in T1 images.

When measuring cerebral atrophy, it is necessary to account for marked variation in head size among individuals (Buckner et al., 2004). ICV is often used in the process of normalization of brain volume to account for individual differences (Buckner et al., 2004); regional or whole brain volume is normalized against what the individual "had" before (i.e., ICV). Support for using ICV as a measure of MLBG was discussed previously (Courchesne et al., 2000) and is reviewed briefly below. Utilizing this procedure of normalization of brain volume, it is possible to compare measures of atrophy between individuals.

Disease burden: T2 lesion volume. Mean ± *SD* of T2LV was $10.08 \pm 10.46 \text{ ml}^3$ (range = 62.59). However, the data were positively skewed (skewness = 1.75; kurtosis = 3.81), necessitating a log transformation. After transforming the data, the mean ± *SD* of log T2LV was 8.62 ± 1.21 (skewness = -0.37, *SE* of skewness = 0.18; kurtosis = -0.62, *SE* of kurtosis = 0.36).

Disease burden: Summary measure of normalized deep gray matter volume. Mean ± *SD* of the deep gray atrophy summary measure was $55.04 \pm 5.94 \text{ ml}^3$ (range = 28.73). Data were normally distributed (skewness = -0.40, *SE* of skewness = 0.18; kurtosis = -0.03, *SE* of kurtosis = 0.36), indicating transformation of the data was not necessary.

Disease burden: Normalized whole brain matter volume. Mean ± *SD* of whole brain atrophy was $1488.53 \pm 97.85 \text{ ml}^3$ (range = 497.72). Data were normally distributed (skewness = -0.17, *SE* of skewness = 0.18; kurtosis = -0.04, *SE* of kurtosis = 0.36), indicating transformation of the data was not necessary.

Disease burden: Normalized gray matter volume. Mean ± *SD* of gray matter atrophy was $671.85 \pm 70.45 \text{ ml}^3$ (range = 387.49). Data were normally distributed (skewness = -0.37, *SE* of skewness = 0.18; kurtosis = 0.18, *SE* of kurtosis = 0.36), indicating transformation of the data was not necessary.

Disease burden: Normalized white matter volume. Mean ± *SD* of white matter atrophy was 816.69 ± 47.45 ml^3 (range = 284.63). Data were normally distributed (skewness = -0.05, *SE* of skewness = 0.18; kurtosis = 0.47, *SE* of kurtosis = 0.36), indicating transformation of the data was not necessary.

Estimate of maximal lifetime brain growth: Intracranial volume. To review, the brain reserve hypothesis (figure 2) states that functional impairment occurs when brain volume falls below a critical, albeit unspecified, threshold (Satz, 1993). Brain reserve is operationalized as MLBG; there is a linear relationship
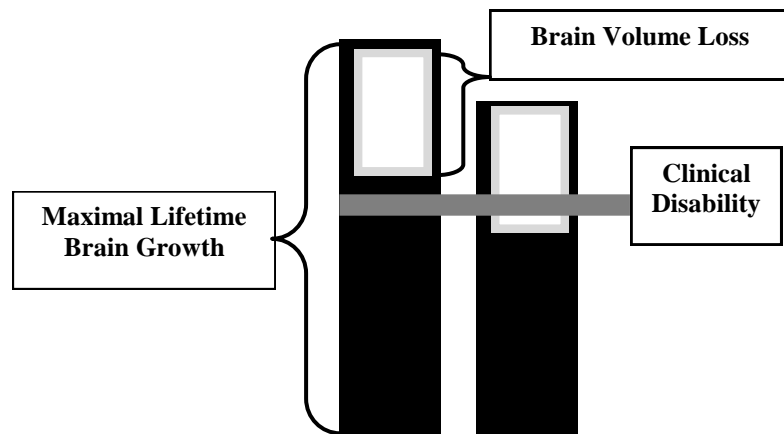
Figure 2. Brain reserve hypothesis.

between MLBG and neuronal count across primates (including humans), indicating MLBG is an appropriate proxy for neuronal count (Haug, 1987; Herculano-Houzel, 2012; Herculano-Houzel et al., 2007). MLBG is estimated via MRI-generated measures of ICV. Support for this practice comes from research demonstrating proportional growth in ICV and brain volume until approximately age 15, at which time maximal development is achieved (Courchesne et al., 2000). Further, changes in ICV do not occur after maximal development is achieved (Courchesne et al., 2000) and there is a near perfect correlation (*r* = .95) between ICV and total brain volume in healthy adults (Baare et al., 2001). Collectively this information indicates that ICV is an appropriate measure of MLBG throughout adulthood regardless of aging, disease, or damage. Finally, using ICV as an estimate of MLBG is consistent with methods of previous

35

work on brain reserve against cognitive disability (Farias et al., 2012; Schofield et al., 1995; Sumowski et al., 2013; Sumowski et al., 2014a).

As described elsewhere (Sumowski et al., 2013; Sumowski et al., 2014a; Sumowski et al., 2014b), the aforementioned scaling factor within SIENAX is a measurement of ICV; however, the direction of values was reversed such that larger values represent larger ICVs (for ease of presentation). Given that men have larger ICVs than women (Courchesne et al., 2000), ICV measurements were adjusted for sex to be used in subsequent analyses by calculating sample-based z-scores within sex, which resulted in a mean of zero and a standard deviation of one for both men and women. Of note, ICV adjusted for sex was normally distributed in this sample (skewness = -0.70, *SE* of skewness = 0.18; kurtosis = 0.84, *SE* of kurtosis = 0.36), which is expected given the stability of ICV throughout adulthood after reaching maximal development during adolescence (Courchesne, et al., 2000). Finally, as discussed, the brain reserve hypothesis states that individuals with larger MLBG can withstand greater neurologic disease or damage before experiencing functional impairment, not that MLBG influences disease burden. Therefore, as expected there was no relationship between ICV and T2LV ($r = .07$, $p = .332$), and there was no difference between ICV and disease phenotypes in this sample, $t(176) = 1.39$, $p = .166$.

Additional Predictors and Preliminary Analyses

Age. Given findings that manual motor speed and dexterity decline with age (Heaton, Grant, & Mathews, 1991; Mathiowetz et al., 1985; Mitrushina, Boone, Razani, & De'Elia, 2005; Shimoyama, Ninchoji, & Uemura, 1990) and more generally that advancing age is associated with increasingly slowed response times and clumsiness in fine motor movements (Swihart & Pirozzolo, 1988), age was included as a controlled variable in block one of the hierarchical

regression analyses. Of note, age was normally distributed within this sample (skewness = 0.04, *SE* of skewness = 0.18; kurtosis = -0.88, *SE* of kurtosis = 0.36).

Sex. Performance differences between sexes have been observed on the NHPT and FTT in healthy populations (Heaton et al., 1991; Mathiowetz et al., 1985; Mitrusina et al., 2005; Ruff & Parker, 1993; Schmidt et al., 2000; Shimoyama et al., 1990; Ylikoski et al., 1998). As such, it is necessary to control for sex within block one of the hierarchical regression analyses.

Power analysis. The g-power program was used to perform the power analysis to ensure the available sample size provided adequate power to find an effect. A fixed model, R^2 increase linear multiple regression was identified as the statistical test to be used within this study. An a priori power analysis was run, allowing for the computation of the required sample size for this study given a chosen alpha (0.01) and power (0.80). An effect size was calculated by entering the 'variance explained by special effect' and 'residual variance'. Based on the literature, demographic variables and disease variables were predicted to account for approximately 20% of the variance in the dependent variable (e.g., NHPT), with one or two demographic variables retained and one disease burden variable retained (e.g., T2LV). Based on previous findings investigating the relationship between MLBG and cognitive status (Sumowski et al., 2013), it was anticipated that MLBG would independently account for another 6% of the variance in manual motor performance (i.e., a medium effect size), which means the residual variance after all predictors were entered was 74%. Given these parameters, a sample size of 148 patients was required. Next, the necessary sample size for the interaction term (MLBG x disease burden), which was to be entered within block three of the multiple regression, was calculated. It was expected that blocks one and two would account for 26% of the variance in manual motor performance, and, based on previous work with cognitive status (Sumowski et al., 2013), it was

37

expected that the interaction term would account for an additional 5% of the variance independently of the 26% of the variance already accounted for. Power analysis indicated that 165 subjects were needed for power of 0.80 with alpha at 0.01. As such, the available sample of 178 patients was adequate.

Statistical Analyses

Statistical analyses consisted of hierarchical regression analyses (entry $p = 0.05$; removal $p = 0.10$) predicting NHPT and FTT separately. Demographic variables (age, sex), disease variables (disease duration, disease phenotype [RRMS or SPMS]), and MRI estimates of disease burden (T2LV as well as normalized volumes of gray matter, white matter, whole brain, and a summary measure of deep gray matter) were entered into block one. MLBG was entered into block two. Finally, if MLGB from block two and at least one variable of disease burden from block one were retained, interaction term(s) were entered into block three (e.g., T2LV x MLBG). This last step was included to investigate whether larger MLBG moderated / attenuated the negative effect of disease burden on fine motor function. See Table 1 for correlations.

Table 1

Correlations Between Predictors

	1	2	3	4	5	6	7	8	9
Demographic Variables									
1 Age	--								
2 Sex	-.09	--							
Disease Variables									
3 Disease Duration	.54**	-.11	--						
4 Phenotype	.39**	-.01	.40**	--					
Disease Burden									
5 T2 Lesion Volume	.20**	.02	.34**	.25**	--				
6 Gray Matter Volume	-.44**	-.03	-.43**	-.19*	-.66**	--			
7 White Matter Volume	-.03	-.12	-.29**	-.10	-.40**	.35**	--		
8 Whole Brain Volume	-.33**	-.08	-.45**	-.19*	-.67**	.89**	.74**	--	
9 Deep Gray Volume	-.11	-.22**	-.34**	-.13	-.70**	.75**	.54**	.80**	--
MLBG Estimate									
10 Intracranial Volume	-.02	.00	-.14	-.10	.07	-.12	-.08	-.13	-.21**

n = 178

** $p < .01$ (2-tailed)

* $p < .05$ (2-tailed)

Chapter Four:

Results

The purpose of this dissertation was to examine the protective effect of brain reserve (operationalized as MLBG and estimated via ICV) on fine motor function in relapse-onset MS patients. This dissertation was designed to test the following hypotheses: (1) Greater T2 lesion volume or cerebral atrophy will be associated with worse simple and complex fine motor function, (2) MLBG will predict simple and complex fine motor function with larger MLBG associated with better performance, and (3) there will be an interaction between MLBG and disease burden whereby larger MLBG will moderate / attenuate the deleterious effect of disease burden on simple and complex fine motor function.

Nine Hole Peg Test

Using hierarchical regression analyses, phenotype, T2LV, and normalized gray matter volume (i.e., gray matter atrophy) significantly predicted performance on the NHPT within block one, $F(3, 174) = 54.30$, $p < .001$. Within block two, MLBG (estimated with ICV) was added to the full model as it significantly predicted performance on the NHPT, $F(4, 173) = 44.18$, $p < .001$. Finally, interactions entered into block three between ICV and normalized gray matter volume ($\beta = .05$, $t(171) = .10$, $p = .917$) as well as ICV and T2LV ($\beta = -.60$, $t(171) = -1.54$, $p = .126$) were not significant. A more thorough discussion of the main effects is included below with statistics provided from the full model (final block). Additionally, partial correlations from the full model, change in R^2 as each variable was added to the full model (in order of presentation), and significance values for predictors of the NHPT from the full model are presented in Table 2.

Within block one, there was a large-sized association (Cohen, 1988; Cohen, 1992) between phenotype and NHPT ($\beta = .50$, $t(173) = 8.96$, $p < .001$), with RRMS patients performing better than SPMS patients on average. Next, there was a small-sized association between T2LV and performance on the NHPT with less lesion volume indicative of better functioning ($\beta = .24$, $t(173) = 3.31$, $p = .001$). This relationship is illustrated within Figure 3. Finally, there was a small-sized association between normalized gray matter volume and NHPT performance demonstrating that greater gray matter volume (i.e., less atrophy) was related to faster time to completion on this task ($\beta = -.17$, $t(173) = -2.36$, $p = .019$). Figure 4 provides the partial regression plot between these two variables.

Within block two, there was a small-sized association between ICV and NHPT performance ($\beta = -.15$, $t(173) = -2.76$, $p = .006$). As predicted, this relationship demonstrated that larger ICV was associated with faster performance on the NHPT. Figure 5 provides a visual depiction of this partial correlation.

Table 2

Hierarchical Regression Findings for the Nine Hole Peg Test (EHI $\geq$ 51)

	Partial *r*	ΔR^2	*p* Value
Phenotype	.56	.37	< .001
T2 Lesion Volume	.24	.10	.001
Normalized Gray Matter Volume	-.18	.01	.019
Intracranial Volume	-.21	.02	.006
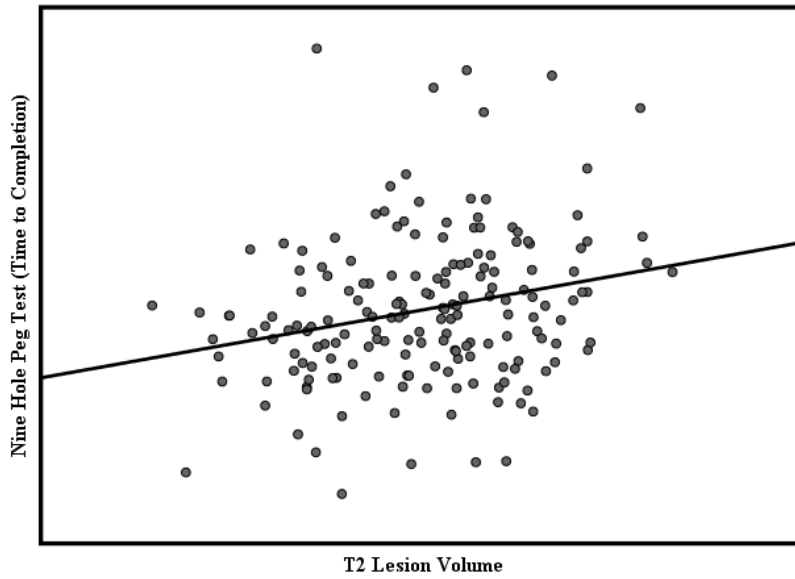
Figure 3. Partial regression plot between NHPT and T2LV
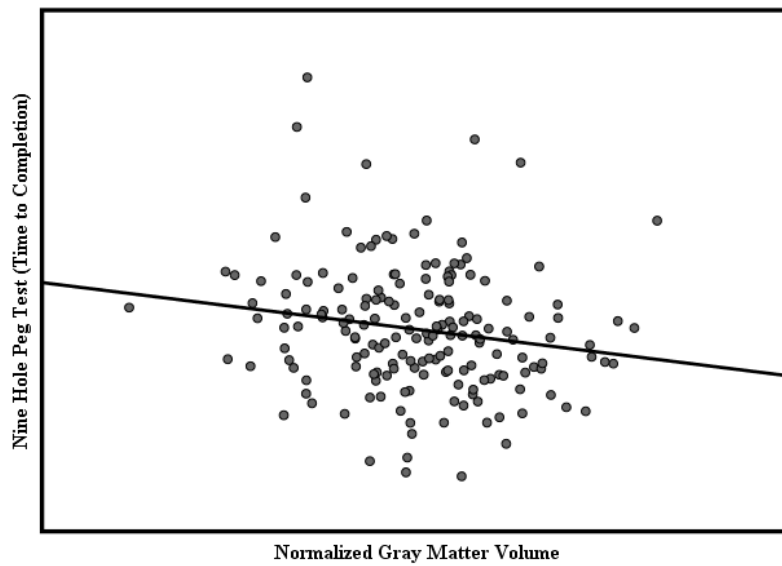
Figure 4. Partial regression plot between NHPT and normalized gray matter volume
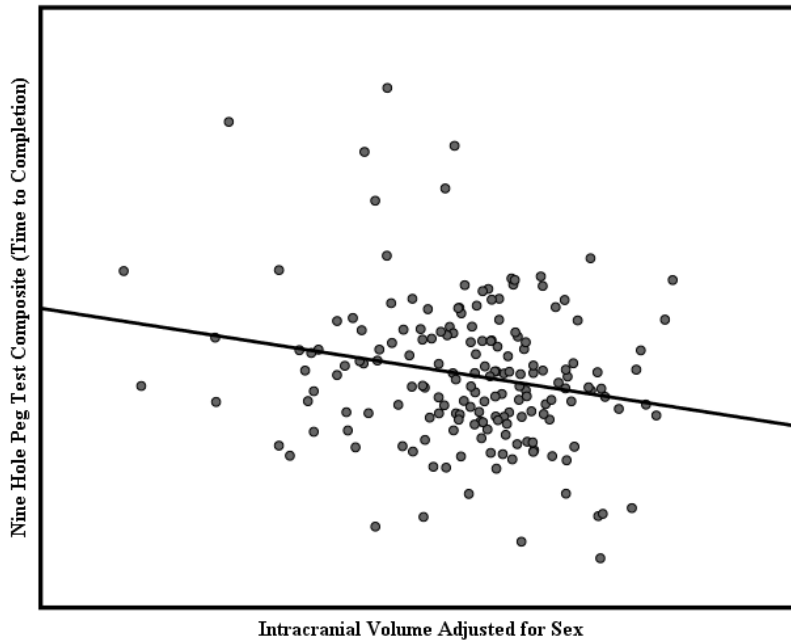
Figure 5. Partial regression plot between NHPT and ICV

Finger Tapping Test

Using hierarchical regression analyses, phenotype, sex, and normalized gray matter

volume (i.e., gray matter atrophy) significantly predicted performance on the FTT within block

one, $F(3, 174) = 36.20$, $p < .001$. In block two, ICV was added to the model as it significantly

predicted FTT, $F(4, 173) = 34.45$, $p < .001$. Finally, an interaction between ICV and normalized

gray matter volume (the only MS-related measure of disease burden retained in block one) was

not significant, $\beta = .01$, $t(172) = .03$, $p = .978$. A more thorough discussion of the main effects is

provided below with statistics presented from the full model (final block). Finally, partial

correlations from the full model, change in R^2 as each variable was added to the full model (in

order of presentation), and significance values for predictors of FTT performance from the full

model are presented in Table 3.

Within block one, there was a medium-sized association between phenotype and FTT (β

$= -.38$, $t(173) = -6.55$, $p < .001$), with RRMS patients performing better than SPMS patients on

average. Sex was also significantly related to FTT (β = .33, $t(173)$ = 5.79, $p < .001$), again representing a medium-sized effect, with men outperforming women on average. Finally, the only disease-related variable significantly associated with FTT was normalized gray matter volume, representing a medium-sized effect (β = .30, $t(173)$ = 5.07, $p < .001$), with greater gray matter volume (i.e., less atrophy) associated with better performance on this task. The partial regression plot of the positive correlation between FTT performance and normalized gray matter volume is shown in Figure 6.

Within block two, ICV was found to be significantly associated with FTT (β = .25, $t(173)$ = 4.28, $p < .001$), as predicted. This medium-sized effect demonstrated that larger ICV was associated with better performance on the FTT. Figure 7 provides a visual depiction of this positive correlation.

Table 3

Hierarchical Regression Findings for the Finger Tapping Test (EHI $\geq$ 51)

|	Partial r	ΔR^2	p Value
Phenotype	-.45	.22	< .001
Sex	.40	.10	< .001
Normalized Gray Matter Volume	.36	.07	< .001
Intracranial Volume	.31	.06	< .001
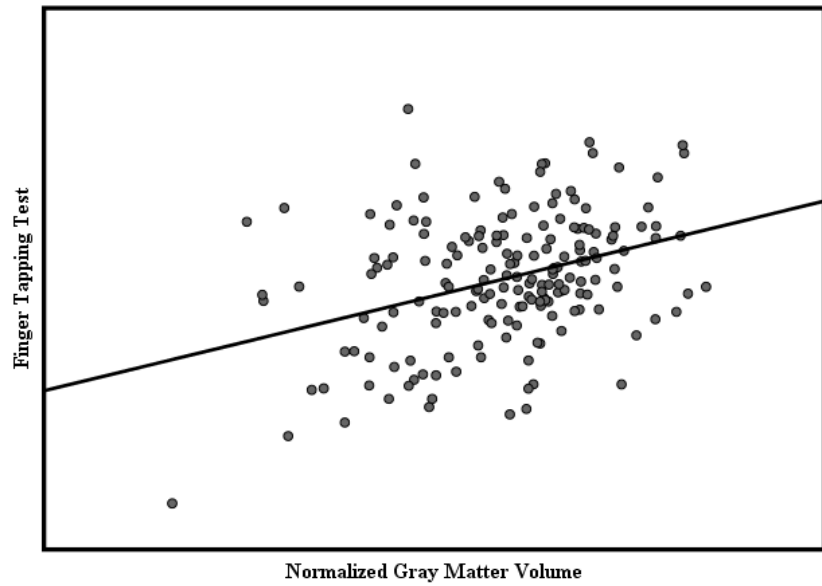
Figure 6. Partial regression plot between FTT and normalized gray matter volume
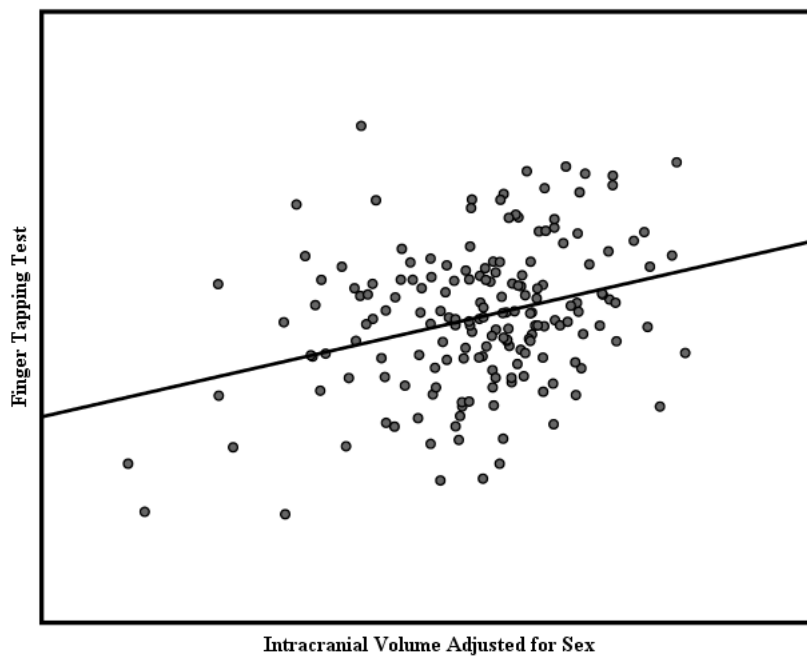
Figure 7. Partial regression plot between FTT and ICV

Supplementary Analyses: Left- and Mixed-Handedness

To be thorough, the relationship between ICV and fine motor functioning was explored within the remaining 24 relapse-onset MS patients from the original sample. Specifically, 18 mixed-handed (EHI ± 50; n = 8 women) and 6 left-handed (EHI = -51 to -100; n = 4 women) patients were collapsed into a singular "non-right-handed" patient group. Of note, combining mixed- and left-handed individuals into one group is common practice in research (e.g., Hervé et al., 2006; Szaflarski et al., 2002; Triggs et al., 2000), in part because left-handed individuals demonstrate less intermanual differences relative to right-handers (i.e., they present as more mixed-handed) (Judge & Stirling, 2003; Schmidt et al., 2000; Thompson et al., 1987).

With regard to sample composition (n = 24), the mean ± *SD* age of patients was 38.85 ± 9.49 years (years old: min = 23.61, max = 63.44). Mean ± *SD* disease duration was 9.52 ± 7.31 (years: min = 0.53, max = 26.00). MS phenotypes included: 21 RRMS (n = 11 women) and 3 SPMS (n = 1 woman). Mean ± *SD* EHI score was -2.88 ± 51.30 (median = 16.65; min = -100, max = 50). Mean ± *SD* EDSS score was 2.85 ± 1.71 (median = 2.50; min = 1.00, max = 7.00), which again was indicative of mild to severe physical disability within this sample.

Utilizing independent samples t-tests, it was determined that age significantly differed between the right-handed sample (EHI ≥ 51; n = 178) and the non-right-handed sample (EHI <51; n = 24), such that the latter patients were younger, on average ($t(200) = 2.04$, $p = .043$). Disease duration ($t(200) = 1.83$, $p = .069$), EDSS scores ($t(200) = .13$, $p = .897$), and ICV ($t(200) = .27$, $p = .786$) did not significantly differ between the two groups. Using chi-square tests, handedness (right vs. non-right) did not significantly differ by gender ($\chi^2 (1, N = 202) = 1.23$, $p = .267$) or MS phenotype ($\chi^2 (1, N = 202) = 1.26$, $p = .263$).

Given that only 24 patients were included in the sample, hierarchical regression was deemed inappropriate for supplementary analyses. Instead, the following analyses were conducted using two-tailed, partial correlations. Specifically, the relationship between ICV and NHPT or FTT was explored while controlling for demographic and disease-related variables as well as estimates of disease burden found significant for right-handers.

Results of supplementary analyses did not yield a significant relationship between ICV and neither NHPT nor FTT for non-right-handers (n = 24). When controlling for phenotype, T2LV, and normalized gray matter volume (i.e., significant predictors of NHPT from block one for right-handers), the partial correlation between ICV and NHPT was not significant (partial r = .15; p = .525). Similarly, when controlling for phenotype, sex, and normalized gray matter volume (i.e., variables found to be significant within block one for right-handers), the partial correlation between ICV and FTT was insignificant (partial r = .15; p = .514). However, given the small sample size (n = 24) and resulting insufficient power, it is important not to over-interpret these findings as evidence against ICV as reserve in non-right-handers.

Chapter Five:

Discussion

MS patients commonly experience impairment in fine motor functioning (e.g., Benedict et al., 2011; Bertoni et al., 2015; Lamers & Feys, 2014; Olivares et al., 2005; Stoquart-ElSankari et al., 2010). However, it has historically been difficult to identify MS patients at greatest risk for disability given variable progression of impairment across individuals with similar disease burden and relapse patterns (Confavreux et al., 2000; Filippi & Rocca, 2011; Scalfari et al., 2013). Further, the association between disease burden (e.g., T2LV or atrophy) and physical disability is moderate at best (Bermel & Bakshi, 2006; Filippi et al., 2013). Recent research examining cognitive and general physical functioning in MS (Sumowski et al., 2013; Sumowski et al., 2014a; Sumowski et al., 2014b) has provided support for the brain reserve hypothesis, which helps to explain this clinico-pathologic dissociation. The brain reserve hypothesis states that individuals with larger MLBG can lose more brain volume due to aging, disease (e.g., MS), or damage before falling below a critical (albeit unspecified) threshold for expression of impairment (Satz, 1993; Stern, 2002; Stern, 2012). Though the brain reserve hypothesis has been studied numerous times with regard to cognition, it has only recently been extended to physical functioning in MS populations. Sumowski et al. (2014b) demonstrated that MLBG, as estimated with MRI-measurements of ICV, was associated with lesser general physical disability and moderated disability progression.

To date, no studies have examined the brain reserve hypothesis as it relates to specific areas of motor functioning in MS. The primary purpose of this dissertation was to examine the protective effect of brain reserve on fine motor functioning, including manual motor speed (Finger Tapping Test; FTT) and manual dexterity (Nine Hole Peg Test; NHPT), in MS patients.

48

Toward this end, hierarchical regression was used to test the relationship between MRI estimates of disease burden as well as ICV with performance on the FTT and NHPT (i.e., simple and complex fine motor functioning) in right-handed, relapse-onset MS patients (n = 178).

This study sought to test three hypotheses regarding the separate prediction of FTT and NHPT performance in right-handed patients: (1) Greater T2 lesion volume or cerebral atrophy will be associated with worse simple and complex fine motor function, (2) MLBG will predict simple and complex fine motor function with larger MLBG associated with better performance, and (3) there will be an interaction between MLBG and disease burden whereby larger MLBG will moderate / attenuate the deleterious effect of disease burden on simple and complex fine motor function.

Does greater disease burden (i.e., T2 lesion volume or normalized brain volumes as measures of cerebral atrophy) predict worse simple and complex fine motor function?

Two forms of MS-related structural changes within the brain that are evident on MRI and occur at disease onset include lesions and atrophy (Bakshi et al., 2001; Bermel & Bakshi, 2006; Friese et al., 2014). Though structural changes can be widespread and variable, resulting in differences in MS symptom presentation, locational patterns have been identified. Lesions are frequently found within the optic nerves, periventricular white matter, and white matter within the brain stem, cerebellum and spinal cord (Noseworthy et al., 2000). Atrophy, or brain volume loss, frequently occurs within the midbrain, pons, cerebellum, thalamus, and caudate nucleus, while enlarged sulci of the frontal, parietal, temporal, and occipital cortex as well as enlarged periventricular regions are also common (Bakshi et al., 2001; Bermel et al., 2003; Bermel & Bakshi, 2006; Cifelli et al., 2002). Of importance, consideration of the role of atrophy is rather new as MS was classically considered a disease of the white matter. However, recent research

has demonstrated that cognitive impairment and physical disability in MS patients is better associated with neurodegeneration relative to white matter lesions (Benedict et al., 2004; Benedict et al., 2006; Bermel & Bakshi, 2006; Filippi et al., 2010; Fisniku et al., 2008; Friese et al., 2014; Popescu et al., 2013; Sanfilipo et al., 2005; Tedeschi et al., 2005). Progression of decline and disability were also shown to be associated with atrophy over time (Bermel & Bakshi, 2006; Fisher et al., 2008; Filippi et al., 2013). Collectively, this information points to the importance of considering brain tissue destruction as it relates to functional impairment and disease progression in MS patients in addition to white matter lesions (Bermel & Bakshi, 2006).

With regard to functional impairment, multiple studies have demonstrated a small to moderate association between disease burden and physical disability (e.g., Kearney et al., 2014). For example, Fisher et al. (2000) found an approximately moderate correlation between the Multiple Sclerosis Functional Composite (MSFC), which includes the NHPT as a measure of physical disability, and the Expanded Disability Status Scale (EDSS) with whole brain atrophy at baseline as well as at years two and eight. Looking at lesion load, Kalkers et al. (2001) found a moderate correlation between T1-hypointense and T2-hyperintense lesions and the NHPT. In a third study, central brain atrophy rate (i.e., ventricular volume change) at baseline as well as lesion volume at baseline and year one predicted physical disability (measured with the EDSS) after 10 years, though only accounting for 2-5% of the variance (Popescu et al., 2013). These results support earlier statements in that both lesion load and atrophy were associated with physical disability.

Within the present study, T2LV and several measures of normalized brain volume (i.e., cerebral atrophy) were tested within block one of the hierarchical regression model predicting NHPT and FTT performance separately in right-handed, relapse-onset MS patients. Specifically,

tested atrophy measures included normalized whole brain, gray matter, and white matter volume, as well as a summary measure of normalized deep gray matter volume (thalamus and basal ganglia structures). Results revealed that normalized gray matter volume significantly predicted both NHPT (partial $r = -.18$, $p = .019$) and FTT (partial $r = .36$, $p < .001$), indicating that greater volume (i.e., less atrophy) was associated with better performance. In addition to normalized gray matter volume, T2LV predicted NHPT performance (partial $r = .24$, $p = .001$), with less lesion volume associated with faster time to completion.

Findings from this study are consistent with the literature regarding an association between lesion volume and atrophy with functional impairment. Results are also consistent with previous findings that MS is not solely a white matter disease (Bakshi et al., 2001; Bermel & Bakshi, 2006; Friese et al., 2014). Indeed, both gray matter atrophy and lesion volume predicted simple and complex fine motor functioning with gray matter atrophy predicting both outcome measures.

These results also provide additional evidence for a clinico-pathologic dissociation between MS-related disease burden and motor functioning (Bermel & Bakshi, 2006; Filippi et al., 2013). Within the present study, the association between disease burden (i.e., normalized gray matter volume and T2LV) and fine motor functioning was small to moderate (range partial $r = -.18$ to .36). As is depicted in Figures 3, 4, and 6, though less normalized gray matter volume or greater T2LV was associated with worse fine motor functioning, some patients with similar levels of MS-related pathology demonstrated greatly different levels of impairment. Further, some patients performed relatively well in the face of large lesion volume or atrophy while other patients with significantly less pathology performed very poorly.

Does MLBG (estimated with ICV) predict simple and complex fine motor function, with larger MLBG associated with better performance?

Clinico-pathologic dissociations between cognitive/physical functioning and disease burden have been documented numerous times throughout the literature (Benedict et al., 2004; Benedict et al., 2006; Christodoulou et al., 2003; Fisher et al., 2000; Kalkers et al., 2001; Kearney et al., 2014; Popescu et al., 2013; Sanfilipo et al., 2006). The brain reserve hypothesis helps to explain these findings such that the hypothesis maintains that impairment does not occur until an individual's brain reserve capacity, operationalized as one's MLBG, falls below an unspecified threshold (Satz, 1993; Stern, 2002). As such, individuals with larger MLBG can withstand greater disease burden or head injury before showing signs of clinical impairment as they have more brain volume to lose. However, it is important to remember that MLBG does not impact disease burden (Sumowski et al., 2013) or disease burden progression (Sumowski et al., 2014a), such that individuals with larger brains do not have larger lesions. Consistent with the literature, no significant association was present between ICV and T2LV ($r = .07$, $p = .332$) within the present study.

The brain reserve hypothesis has been applied to cognitive impairment in multiple patient populations. For example, Sumowski et al. (2013, 2014a) demonstrated that larger ICV was protective of cognitive efficiency as well as decline in cognitive efficiency over 4.5 years in MS patients. Beyond MS, the brain reserve hypothesis has also been examined within aging and dementia populations (Graves et al., 1996; Graves et al., 2001; MacLullich et al., 2002; Perneczky et al., 2010; Reynolds et al., 1999; Schofield et al., 1995; Schofield et al., 1997; Tisserand et al., 2001). For example, Farias et al. (2012) demonstrated that in 401 older adults who ranged from no cognitive impairment to carrying a diagnosis of predominantly AD

52

dementia, ICV was significantly associated with functioning within multiple cognitive domains despite the presence of atrophy.

The applicability of the brain reserve hypothesis to physical disability has only recently begun to be examined. Sumowski et al. (2014b) presented preliminary results from a cross-sectional sample of 240 MS patients demonstrating that larger ICV protected against general physical disability as measured with the EDSS. Preliminary results from a longitudinal study of 40 MS patients over 4.5 years similarly found that larger ICV was associated with less increase in physical disability (Sumowski et al., 2014b). Given that the EDSS is a relatively non-specific measure of MS-related disability, findings from Sumowski et al. (2014b) highlighted the need for research examining the relationship between MLBG and motor functioning in MS.

To this end, the present study focused on upper extremity impairment in MS patients, as assessed using measures of simple and complex fine motor functioning. Specifically, ICV, adjusted for sex, was entered into block two of a hierarchical regression model predicting NHPT and FTT performance within separate analyses for 178 right-handed, relapse-onset MS patients. Results demonstrated that there was a small-sized association between ICV and NHPT (partial r = -.21, p = .006), indicating that individuals with larger ICV completed the task more quickly on average (Figure 5). Additionally, there was a medium-sized association between ICV and FTT (partial r = .31, p <.001), such that having larger ICV was indicative of better performance (Figure 7). Collectively, these results indicate that MLBG is associated with fine motor functioning in MS. Given these significant main effects across two outcome measures, this study, which is the first of its kind, provides partial support for the brain reserve hypothesis as it relates to fine motor function in MS.

To be thorough, the relationship between ICV and fine motor functioning was explored within the remaining 24 mixed- and left-handed, relapse-onset MS patients from the original sample (n = 202) within supplementary analyses. However, given the small sample size, the method of using hierarchical regression was replaced with two-tailed, partial correlations, controlling for significant demographic, disease-related, and disease burden variables found significant for right-handers. No significant relationships were found between ICV and either measure of fine motor functioning. Importantly, the small sample size likely restricted the variability of all variables, including ICV, and resulted in insufficient power to conduct analyses. As such, these results are not presented as evidence against ICV as a marker of brain reserve for fine motor functioning in non-right-handed MS patients.

Does MLBG moderate/attenuate the deleterious effect of disease burden (e.g., cerebral atrophy) on simple and complex fine motor function?

Interactions between MLBG (estimated with ICV or head circumference) and disease burden on cognitive functioning have been documented within the literature. In MS, Sumowski et al. (2013) demonstrated that ICV moderated the negative impact of T2LV on cognitive efficiency but not memory in 62 relapse-onset MS patients. Within a follow-up longitudinal study (Sumowski et al., 2014a), larger ICV protected against a decline in cognitive efficiency and verbal fluency but not memory over 4.5 years. An interaction between atrophy and head circumference was also established in 270 patients who met clinical criteria for AD (Perneczky et al., 2010); with increasing levels of atrophy, global cognitive functioning was better protected in patients with a larger head circumference (Perneczky et al., 2010).

Though interactions between MLBG and disease burden have not been tested with regard to motor functioning in MS patients to date, it was hypothesized that similar results would be

found within the present study. To test this hypothesis, interaction terms were created between ICV and significant measures of disease burden for the NHPT and FTT. Specifically, since normalized gray matter volume predicted FTT, an ICV by normalized gray matter volume interaction term was tested. For NHPT, interactions between ICV and both T2LV and normalized gray matter volume were tested. Contrary to hypotheses, interactions were not significant for either measure of upper extremity function. As such, this study failed to confirm the brain reserve hypothesis as it has been demonstrated within the MS cognitive literature (i.e., via an interaction between disease burden and ICV).

The explanation for why interactions are found between MLBG and disease burden for cognition but not motor functioning in MS is unclear. One possibility is that the protective effect of MLBG on motor function is present in the absence of brain disease. If this were true, then MLBG would be associated with better fine motor function premorbidly, which may explain why there was a significant main effect of MLBG on fine motor functioning but not a significant interaction. In the absence of healthy control data, this hypothesis could not be tested within the present study. As such, future research should explore whether MLBG is protective of motor functioning in non-clinical, healthy populations.

Another possible explanation for why none of the interactions tested within this study were significant stems from the cognitive literature. Specifically, in studies by Sumowski et al. (2013, 2014a) ICV was consistently protective of cognitive efficiency but not memory. As cognitive efficiency is likely more reliant on distributed processes across the brain relative to memory, the advantage of greater brain reserve across the whole brain (estimated with ICV) may be greater for cognitive efficiency. Simply put, greater ICV translates to a greater number of neurons throughout the brain, which seemingly would be more protective of less localized

55

processes (i.e., cognitive efficiency). As it relates to this study, fine motor functioning, like memory, is likely more circumscribed relative to other functions (e.g., processing speed), which could explain why interactions between ICV and disease burden were not significant.

Relatedly, the relationship between cerebral atrophy (i.e., normalized brain volume) and cognitive efficiency is typically greater than that found for memory (Benedict et al., 2004; Benedict et al., 2006). As memory is likely more localized to critical hippocampal circuits, it is possible that relatively lesser associations between memory and cerebral atrophy (Benedict et al., 2004; Benedict et al., 2006) were at least partially attributable to patient's lack of lesions / atrophy within localized structures important for memory (e.g., hippocampus). As it relates to reserve, given the greater relationship between cerebral atrophy and cognitive efficiency, there is a stronger clinico-pathologic association for larger MLBG to moderate / attenuate. Collectively, the above information may at least partially explain Sumowski et al.'s (2013, 2014a) non-significant findings for a link between MLBG and memory. With regard to the present study, fine motor functioning is more similar to memory in that it is likely more localized within the brain relative to other functions (e.g., processing speed). However, as was true of studies by Benedict et al. (2004, 2006) and Sumowski et al. (2013, 2014a), the present study generally used non-specific measures of disease burden, thereby not permitting investigation of lesions / atrophy within specific cortical regions (e.g., primary motor cortex). As such, future research should consider gathering data on relevant areas of lesion and atrophy location for fine motor functioning (e.g., cerebellum) to determine whether greater ICV affords reserve in carefully selected MS patients. In gathering these data, it would also be possible to screen out (or control for) individuals with spinal cord lesions, which represents a source of error not controlled within the present study.

Additional Implications for Practice and Future Research

The results of this study demonstrated that fine motor functioning differed based on MLBG (estimated with ICV), with larger ICV associated with better performance. These findings suggest that ICV may be useful in better understanding fine motor disability progression in MS as well as in identifying relapse-onset MS patients who are at risk for upper extremity dysfunction. As discussed, the ability to identify patients at greatest risk for impairment would inform treatment decisions, including employment of early pharmacological/prophylactic and rehabilitative (e.g., occupational therapy) intervention, as well as therapy-based interventional/clinical trial research.

However, as this is the first study of its kind, additional research is required before ICV is used in clinical practice and research settings. To improve the clinical utility of ICV measurements, the present study should be replicated within larger cross-sectional samples (e.g., RRMS vs. SPMS). Longitudinal research is also needed to document the progression of fine motor dysfunction and to determine whether ICV moderates the progression of upper extremity disability, which would aid in the prediction of change in fine motor functioning over time. Longitudinal research would also control for individual difference variables (e.g., in strength and speed) not controlled for in cross-sectional samples, leading to a more accurate assessment of the protective effect of MLBG against fine motor disability progression. Should follow-up research continue to demonstrate that ICV protects against fine motor impairment and moderates progression, researchers should consider collecting normative data on ICV as it relates to fine motor functioning in MS patients; the goal of this research would be to identify a cut-off that is clinically useful in determining relative risk of future impairment.

Next, though the NHPT is frequently used in clinical practice and research (Benedict et al., 2011; Cutter et al., 1999; Fischer et al., 1999) and the FTT is common in fMRI work (Lowe et al., 2008; Lowe et al., 2002; Mancini et al., 2009), future research should replicate this study using additional tests of fine motor functioning as outcome measures. For example, the Grip Strength Test measures one's hand strength (Reitan & Davison, 1974; Reitan & Wolfson, 1985). As MS patients struggle with reduced grip strength (Paul et al., 1998), which has implications for independence in ADLs (e.g., dressing and eating) (Strauss et al., 2006), researchers should consider exploring the protective effect of ICV on grip strength. Additionally, researchers may consider including the Purdue Pegboard as an outcome measure as it offers an examination of bimanual coordination in addition to unimanual dexterity, which also has real-world implications as it relates to functional independence (Strauss et al., 2006). By exploring additional outcome measures, differential levels of protection from reserve (if any) on fine motor functioning in MS patients can be identified.

The present study excluded primary-progressive MS patients (PPMS) given differences in disease course from the selected population: RRMS and SPMS patients experience a relapsing-remitting course at the time of diagnosis relative to the progressive course experienced by PPMS patients (Weinshenker et al., 1989). Relapse-onset MS is also better understood and constitutes a larger percentage of persons diagnosed with MS (approximately 85% versus 15%) (Friese et al., 2014; Koch et al., 2010; Lublin et al., 2014; Noseworthy et al., 2000; Steinman, 2001; Tremlett et al., 2008). Nonetheless, given that PPMS patients experience a continuous and irreversible worsening of symptoms from diagnosis, future research should examine the protective effect of brain reserve on fine motor functioning within this population. In doing so,

research would serve to better characterize the disease process within PPMS patients and to derive appropriate interventions/treatment.

Future research utilizing a larger sample should also examine the application of the brain reserve hypothesis on fine motor functioning in left-and mixed-handed MS patients. As discussed, it is important to categorically separate right-handers from non-right-handers when studying fine motor functioning given intermanual differences as well as differences in cortical activation during measures of upper extremity functioning (Hervé et al., 2006; Hervé et al., 2005; Pool et al., 2014; Schmidt et al., 2000; Solodkin et al., 2001; Thompson et al., 1987). However, the literature provides no reason to predict that right-handed and non-right-handed MS patients would experience differential levels of protection from having larger ICV. Within the present study, the small sample size and resulting limited variance and insufficient power likely explain the non-significant findings. Confirmation of the brain reserve hypothesis as it relates to fine motor functioning in non-right-handed patients is clinically important, as described above.

Conclusion

Upper extremity disability is commonly experienced by MS patients (Benedict et al., 2011; Cree, 2012; Holper et al., 2010; Reitan, 1969; Stoquart-ElSankari et al., 2010; Swingler & Compston, 1992), negatively impacting patient independence in activities of daily living and health-related quality of life (Hoogervorst et al., 2004; Johansson et al., 2007; Kierkegaard et al., 2012; Kragt et al., 2006; Schwid et al., 2002; Yozbatiran et al., 2006). Unfortunately, prediction of who will experience this impairment as the disease progresses is hindered by the fact that disability varies greatly among patients at similar stages of the disease (Confavreux et al., 2000; Filippi & Rocca, 2011; Scalfari et al., 2013). Further, measures of disease burden (e.g., gray matter atrophy and lesion load) and disability evidence only a moderate correlation at best

(Bermel & Bakshi, 2006; Filippi et al., 2013). Given this established clinico-pathologic dissociation, the primary goal of this dissertation was to determine whether the brain reserve hypothesis was applicable to fine motor functioning in relapse-onset MS patients. Consistent with hypotheses, ICV predicted patient performance on measures of manual motor speed and dexterity, with larger ICV associated with better fine motor functioning. However, interactions between measures of disease burden and ICV were not significant, which differs from the literature on reserve against cognitive impairment. Nonetheless, given that the predicted main effects were significant, this study, which was the first of its kind, provides partial support for the brain reserve hypothesis as it relates to fine motor functioning in MS and has notable implications for patient care and treatment. Future research should replicate results from this study within larger cross-sectional samples (e.g., RRMS vs. SPMS), longitudinal research, and with additional outcome measures of fine motor functioning (e.g., Grip Strength Test). Researchers should also consider gathering data on areas of lesion and atrophy location that are relevant to fine motor functioning (e.g., cerebellum) rather than utilizing non-specific measures of disease burden (i.e., T2LV). Finally, work in non-clinical, healthy populations would help to determine whether the protective effect of brain reserve is specific to diseased populations (i.e., MS) or if the effect is present premorbidly.

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