Abstract

Cognition and Handedness in Multiple Sclerosis

Multiple sclerosis (MS) impacts over 2.5 million individuals worldwide and can affect physical, emotional, and cognitive functioning. Yet, much remains to be known regarding the disease course in this complex illness. Understanding hemispheric vulnerability in MS, which has not yet been studied, may aid in elucidating the manifestation of MS in the brain, ultimately impacting treatment. To do this, this study assessed neuropsychological functioning as it relates to hemispheric vulnerability in MS. Specifically, domains of verbal and non-verbal IQ and memory acquisition, along with fine-motor abilities, were compared in right (dextral) and non-right (non-dextral) persons with MS (PwMS). Two contradicting theories were hypothesized: Theory A, an increased vulnerability to the pathological process of MS in the left brain or, Theory B, an increased vulnerability to the pathological process of MS in the right brain. The prevalence of left-handedness in the current MS sample was assessed and was found to be comparable to prior literature, at approximately 9.1%. Linear mixed effects modelling indicated a significant main effect of handedness $F(1, 195.35) = 3.95$, $p = .048$ when verbal and non-verbal IQ and memory acquisition measures were taken together, with better performance seen in dextral PwMS. Although no significant interaction between handedness and IQ $F(3, 525.60) = 0.75$, $p = .523$ was found, the largest effect size existed in the neuropsychological measure assessing perceptual reasoning IQ $F(1,341) = 12.163$, $p = .001$. There was no significant difference with handedness and memory acquisition. In evaluating fine motor skills, a significant interaction between neuropsychological test and handedness was found; dextral participants had faster completion time (with their right hand) than non-dextral individuals (with their left hand). Non-dextrals were faster with their non-dominant (right) hand than dextrals were with their non-dominant (left) hand. Although findings from this study are relatively inconsistent in supporting Theories A or B, results taken together suggest an increased vulnerability to the pathological process of MS in the left brain. Results also have clinical treatment implications, highlight the importance of

choosing the right neuropsychological measure, and may indicate differences between cognitive profiles of males and females with MS.

Cognition and Handedness in Multiple Sclerosis

by

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Dedication

To my family and loved ones, present and past.
I am who I am because of you. This project, and most other things in my life, would be inconceivable if not for the support of those who have held me up.

"Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less."
– Marie Curie

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CHAPTER 1

INTRODUCTION

An increased prevalence of left-handedness has been associated with various immune-related disorders such that a meta-analysis indicated a modest, yet statistically significant, increase in risk for any immune disorder among left-handed (LH) individuals (Gardener, Munger, Chitnis, Spiegelman, & Ascherio, 2009). Examples of diseases with a high-prevalence of left-handedness include, but are not limited to, Crohn's disease, asthma, attention deficit hyperactivity disorder (ADHD), allergies, migraine, epilepsy, and myasthenia gravis (Bryden, McManus, & Bulman-Fleming, 1994). Specifically, in multiple sclerosis (MS), a 62% increased risk of MS was found among women who were naturally LH, as compared to those who were naturally right-handed (RH) (Gardener et al., 2009). Despite this, the literature points to approximately 10.3% of the MS population as LH (Shirani, Cross, Naismith, & Investigators, 2019). Therefore, the first aim of this study is to assess the percentage of LH persons with MS (PwMS) in the current sample.

Along with having a higher prevalence of left handedness, many neurological and autoimmune diseases often are comorbid with lowered cognitive functioning. This relationship between handedness and cognitive functioning has not yet been studied in MS, despite being extensively researched in several other similar diseases. For example in epilepsy, neuropsychological deficits have been shown to be three times more likely to occur in the left hemisphere in left-handed patients (Holmes, Dodrill, Kutsy, Ojemann, & Miller, 2001). Furthermore, handedness studies have shown that seizures in the left-brain result in lower verbal functioning, whereas seizures in the right-brain result in lower non-verbal functioning (Kim, Yi, Son, & Kim, 2003). In memory, more spatial deficits were found in those with right-sided epilepsy as compared to those with left-sided epilepsy (Abrahams, Pickering, Polkey, & Morris, 1997).

Vulnerability to the left hemisphere in epilepsy (e.g., Holmes, Dodrill, Kutsy, Ojemann, & Miller, 2001; Paolozzi, 1969) often explains this discrepancy in functioning; in MS, opposing theories on hemispheric vulnerability exist. At this time, no research has explicitly assessed hemispheric vulnerability in the context of handedness and cognitive functioning in PwMS. The only cognitive outcome that has been associated with handedness in MS is fine motor speed, where LH PwMS have faster motor speed with their left hand than RH patients have with their right hand (Howells et al., 2018; Shirani et al., 2019). Both the diseased MS brain and the diseased epileptic brain function differently from that of healthy normal controls. The goal of this study is to explore if a hemispheric vulnerability exists in MS.

BACKGROUND & SIGNIFICANCE

Multiple Sclerosis

Background

MS is a demyelinating disease known to affect physical, emotional, and cognitive functioning (Gold, Schulz, Mönch, Schulz, & Heesen, 2003). Over 2.5 million individuals are affected by this chronic inflammatory disease of the central nervous system (CNS) in which demyelination affects grey matter (GM), white matter (WM), and the spinal cord (SC). Its pathological features are consistent with an autoimmune mechanism, however it has a predominantly unknown etiology (Gardener et al., 2009). Unfortunately, MS almost always ultimately results in the accumulation of disabling motor and cognitive handicaps (Nasios, Messinis, Dardiotis, & Papathanasopoulos, 2018).

While much of the etiology of MS is unknown, there are some genetically-based theories. For example, it has been shown that persons who have a major histocompatibility complex (MHC) class II phenotype, an HLA-DR4, or a human leukocyte antigen (HLA)-DR2, are most likely to be affected by MS (Dargahi et al., 2017). Genetic contributions have been indicated in twins as well, with a 10-fold increased incidence of MS in monozygotic twins as compared to siblings of patients with MS (Sadovnick et al., 1993). Aside from genetics, viral infections can also trigger disease. This happens if parts of the virus present as the myelin sheath (Sospedra & Martin, 2005).

Etiological theories based on sex exist as well, as MS is most commonly diagnosed in women between the ages of 20 and 40. Sex hormones (e.g., androgen, estrogen, etc.) have lifelong effects on brain composition (Arnold, 2009) and can have growth promoting, growth-inhibiting, or deleterious effects (Kawata, 1995). Also, while it is less frequently diagnosed, MS is usually more severe in males. Studies suggest that men with MS are less prone to inflammatory lesions, but are more susceptible to destructive lesions, than women are (Pozzilli et al., 2003; Weatherby et al., 2000).

The way in which MS impacts the body is via a breakdown of the blood brain barrier (BBB) in the brain (Dargahi et al., 2017). When this happens, a migration of immune cells such as, macrophages, T cells, or B cells, occurs along with secretion of pro-inflammatory cytokines and chemokines. This immune reaction causes sclerotic plaques, or lesions, along with demyelination and neurodegeneration (Steinman, 1996). Because these lesions can occur in both the brain or in the SC, a heterogeneous presentation of MS symptoms may occur (Minagar & Alexander, 2003).

Prevalence of MS varies by geography. For example, an extremely low prevalence of MS exists in countries closer to the equator, as compared to those farther north or south of the equator (e.g., Scotland, Norway, Canada). Overall, the prevalence of MS has increased over time. Numbers were at 30/100,000 in 2008, and have increased to 33/100,000 diagnosed in 2013, globally. Hypotheses for

this include lack of vitamin D as one moves farther from the equator, along with improved diagnostic procedures and reporting over time (Dargahi et al., 2017).

MS is classified into four types: relapse remitting MS (RRMS) is the most common type and is characterized by relapses, or periods of exacerbations, followed by remitting periods without symptoms (Thompson et al., 2000). Secondary progressive MS (SPMS) usually follows the initial RRMS course and is a progression of worsened neurological functioning, with an accumulation of disability over time (Thompson et al., 2000). Primary progressive MS (PPMS) is characterized as worsening neurological functioning from the onset, without periods of relapses or remission (Montalban et al., 2009). Finally, progressive-relapsing MS (PRMS) is a rare form of MS usually characterized by a consistently worsening disease state, with acute relapses and no remissions (Thompson et al., 2000).

Unfortunately, MS cannot be cured, though it can be maintained. For example, there are treatments that decrease the relapse rate in RRMS, but medications for progressive forms of MS are limited in their efficacy. Treatment usually targets immune cells and their products so that inflammation and tissue damage may be lessened (Katsara, Matsoukas, Deraos, & Apostolopoulos, 2008). However, suppressing the immune system may cause side effects (Hemmer, Nessler, Zhou, Kieseier, & Hartung, 2006). Other treatment options, called disease-modifying therapies (DMT's), include interferons, glatiramer acetate, monoclonal antibodies and sphingosine-1-phosphate receptor modulators. Luckily, these treatments tend to reduce the number of attacks and decreased disease progression. The most effective pharmaceutical interventions are interferons that are started early in the relapsing phases of MS (Inglese & Petracca, 2015). As of May, 2020, the FDA has approved six

disease-modifying therapies (DMT's) for oral use, eight self-injection DMT's, and four infusion DMT's (*Long-Term Treatments for Multiple Sclerosis | MSAA*, 2020)

Clinico-Radiological Paradox

Predicting disability in MS is difficult. Several neuronal changes are suggested to represent functional decline in MS, including both lesion-load and atrophy. In assessing the latter, it is suggested that brain atrophy may important when assessing MS-related disability as well(Mahajan et al., 2019). Brain atrophy is not independent from lesion load, however, as neurodegeneration may be targeting deep brain structures such as the thalamus, that are subject to lesions as well (Mahajan et al., 2019). One limitation in identifying and quantifying the impact that GM brain atrophy has in PwMS is the technical tools available, which can be too insensitive to accurately assess deep GM atrophy or lesion load (Amiri et al., 2016).

While magnetic resonance imaging (MRI) is imperative in showing lesions in the CNS, and ultimately in diagnosing MS, the correlation between common neuroradiological markers (such as lesion load or clinical disability), with functional disability, is fairly weak in MS (Hackmack et al., 2012). This is because MRI is primarily used to detect structural change, rather than neuronal dysfunction (Chaves et al., 2019). Another major factor is that MRI is largely unable to detect the histopathology of lesions (Barkhof, 1999). Also, subclinical disease progression occurs at a level that cannot necessarily be measured with neuroimaging. This discrepancy between radiological findings and clinical functioning is called the clinico-radiological paradox (Barkhof, 1999).

Some studies utilizing MRI to predict MS symptoms have been able to weakly correlate WM lesion localization with specific cognitive impairments (S. M. Rao, Leo, Haughton, St Aubin-Faubert, & Bernardin, 1989). For example, WM lesions in the frontal lobe have been shown to affect performance on tests that assess executive functioning (Rovaris et al., 1998). Another study

demonstrated a significant association between executive deficits and lesions in the prefrontal cortex (Foong et al., 1997), with lesions in the frontal and parietal lobes correlating with neuropsychological performance on tests of complex attention and verbal working memory (Sperling et al., 2001).

Assessing deep GM pathology is another neurodiagnostic tool that some have used to predict cognitive impairment in PwMS (e.g., Benedict, Carone, & Bakshi, 2004). Some studies have shown cognitive performance to be inversely related to GM volume (Morgen et al., 2006; Riccitelli et al., 2011). Specifically, certain impaired performances on neuropsychological measures were correlated with reduced GM volume in the correlating regions; those who had worse cognitive performance showed more extensive cortical volume loss than their matched controls (Morgen et al., 2006). In this study, the temporal and parietal lobes were most vulnerable (Morgen et al., 2006) and have been indicated as key locations of GM atrophy in MS (Sailer et al., 2003).

Despite the clinico-radiological paradox, some high-powered MRI's have made progress in correlating imaging to functional disability. For example, 7T MRI was able to detect GM lesions in the thalamus, cingulate gyrus, caudate and amygdala, and found significantly correlated cognitive impairments in verbal learning, visual memory, and processing speed, respectively (Tomkinson et al., 2019). Newer MRI sequences, such as double inversion recovery (DIR), found that cortical lesions were associated with cognitive impairment (Roosendaal et al., 2009). Other imaging, such as PET scans with amyloid tracers, have shown that uptake is lower in damaged WM and that this is associated with longitudinal cognitive decline (e.g., Matias-Guiu et al., 2019). Another study indicated that the assessment of myelin status in PwMS, with the use of the biomarker 18F-florbetaben, may be predictive of cognitive outcome (Matias-Guiu et al., 2019). Even though some

headway has been made, the relationship between functional outcomes and imaging remains weak (Hackmack et al., 2012).

MS not only impacts the brain, but the SC as well; damage to the SC can lead to motor and sensory dysfunction (Filippi & Rocca, 2013). In fact, some studies have demonstrated that clinical disability in MS is mainly driven by diffuse damage to the spine, rather than to focal T2 brain lesions (e.g., Filippi & Rocca, 2013; Rocca et al., 2013). Transcranial magnetic stimulation (TMS) is another imaging technique that has been utilized specifically in this area. TMS is a non-invasive tool that can help to assess functionality of both lesion load and the corticospinal tract (CST). However, this has once again been reported to have a fairly insufficient correlation with MS biomarkers (Simpson & Macdonell, 2015).

Cognitive Impairment

Cognitive dysfunction negatively impacts quality of life (QoL) in PwMS (Benedict et al., 2006) in areas such as employment (Beatty, Blanco, Wilbanks, Paul, & Hames, 1995), social engagement (S. M. Rao et al., 1991), and overall activities of daily living (Higginson, Arnett, & Voss, 2000). Community and clinical MS samples have shown approximately 45-60% of PwMS to have some cognitive impairment, with severe dementia observed in about 20-30% of cognitively impaired patients (Rao et al., 1991). While severe dementia is likely more prevalent in the later stages of disease (Rao et al., 1991), cognitive dysfunction commonly appears in the earlier stages of the disease and can be one of the preliminary symptoms of MS (Schulz, Kopp, Kunkel, & Faiss, 2006).

Cognitive dysfunction is suggested to be one of the earliest symptoms of MS (Schulz et al., 2006) perhaps because PwMS require greater prefrontal recruitment to sustain cognitive performance, as

compared to healthy controls (Forn et al., 2007). This has been seen in several other neurological diseases as well, including traumatic brain injury (TBI) (Turner & Levine, 2008), HIV (Ernst, Chang, Jovicich, Ames, & Arnold, 2002) and Alzheimer's disease (Grady et al., 2003). Importantly, this has also been seen in those with left temporal lobe epilepsy (TLE), where greater right prefrontal recruitment is necessary, as compared to controls (Maccotta, Buckner, Gilliam, & Ojemann, 2007). In contrast, prefrontal recruitment is positively associated with age in healthy individuals and is negatively associated with performance on neuropsychological measures of cognitive efficiency (Rypma, Berger, Genova, Rebbechi, & D'Esposito, 2005).

Unfortunately, cognitive dysfunction is not only an early and disabling symptom, but also is difficult to detect on a brain scan or on a neurological exam. This is because cognitive symptoms usually present focally and subtly (Benedict et al., 2006) and cognitive impairment does not strongly align with disease duration or with functional disability (Beatty et al., 1995).The heterogeneous pattern of cognitive deficits in PwMS also makes it difficult to detect in an insensitive environment, such as in a physician's office. For example, it would be unlikely to see a striking deficit in language in a patient with MS (Benedict et al., 2006).

The etiology of cognitive dysfunction in PwMS is debated (Guimarães & Sá, 2012). One study found that cognitive deficits were associated with abnormalities in the splenium of the corpus callosum and in the right superior longitudinal fasciculus (Ranjeva et al., 2006). Other theories have suggested that many of the deficits in cognition in PwMS are attributed to slowed neural conduction due to WM pathology (e.g., Arnett et al., 1994; Rao et al., 1989). Supporting this, imaging has shown cognitive changes to be correlated with macroscopic and microscopic changes in the brain anatomy, along with WM lesions (Dineen et al., 2009; Morgen et al., 2006). Unfortunately, T2 lesion burden does not have

a strong enough correlation with performance on a neuropsychological exam to allow for predictions of cognitive outcomes (Rao et al., 1989).

The cognitive profile for PwMS commonly entails deficits in learning, working memory, and processing speed (Chiaravalloti & DeLuca, 2008; Rao et al., 1991). In fact, processing speed impacts up to 40-65% of PwMS (Stephen M. Rao et al., 1993), which can translate to other domains such as verbal memory. For example, if new verbal material cannot be processed quickly enough to learn the incoming information, encoding may be jeopardized. Such impairments usually gets worse over time and with the progression of the disease (Chiaravalloti & DeLuca, 2008).

Tasks requiring central executive functions (e.g., backwards digit or word recall, listening recall, etc.) or visuospatial functioning have also shown impairments in PwMS as compared to healthy controls (Kouvatsou, Masoura, Kiosseoglou, & Kimiskidis, 2019). Another study teased apart the components of visuospatial functioning and found that PwMS have more difficulty with spatial functions, relative to visual functioning, per-say (Kouvatsou et al., 2019; Nathalie et al., 2014).

Sex Differences in the Human Brain

On Cognition

The male and female brain are not the same. Functionally, the literature supports a "bilateral advantage" in women, while brain functioning in men tends to be more modular (Ruben C. Gur et al., 2000). Meaning, women are more able to recruit functional resources from both hemispheres than men are when faced with cognitive tasks. Specifically, men tend to be more highly lateralized to left-sided language functioning, and perform worse on cognitive measures of language, than women do

(Gur et al., 2000). This is particularly true in PwMS, where male patients have performed worse on some neuropsychological measures than women (Beatty et al., 1995).

On Emotions

Neuroanatomy also contributes to psychological differences between males and females. For example, a consistent relationship has been found between lateralization and affective processing. Specifically, literature has shown that sadness induces more right-hemispheric activation of cortical structures in RH individuals with left-dominant language, which was not similarly found in LH subjects without consistent hemispheric language dominance (Costanzo et al., 2015). Also, LH individuals had less consistent brain lateralization of affective processing, regardless of language or motor hemispheric lateralization (Costanzo et al., 2015).

On Anatomy

Sex-related evolutionary factors may have impacted the development of human brain composition as well. For example, the gender roles that were once required for hunting, gathering, and taking care of the home may be extinct, but toys and social interactions continue to foster gender-specific environments that could impact brain composition throughout development. That is, males tend to have increased rightward asymmetries in the anterior callosal midbody (Luders, Narr, Zaidel, Thompson, & Toga, 2006), while females have shown reversed, diminished, or no asymmetries at all (Good et al., 2001).

In terms of GM, a larger leftward asymmetry of GM concentration posteriorly to the central sulcus has been found in men (Luders et al., 2006). Conversely, volumes of the superiortemporal cortex, Broca's area, the hippocampus, caudate (Harasty, Double, Halliday, Kril, & McRitchie, 1997), midsagittal areas, fiber numbers of the anterior commissure, and the massa intermedia, are all larger in females (Allen & Gorski, 1991). Furthermore, volume in the bilateral hippocampus, amygdala, and right nucleus accumbens is more atrophied in men, whereas the right hippocampus and nucleus accumbens, bilateral amygdala, and putamen are more atrophied in women (Messina & Patti, 2014).

Regional areas can be particularly stratified by sex (Kanaan et al., 2012) as well. For example, the planum temporale and Sylvian fissure are larger in males (Leonard et al., 2008). Although the corpus callosum, which was originally thought to be bigger in females (DeLacoste-Utamsing & Holloway, 1982), has more recently been contested (Ng et al., 2005). Finally, the thickness and surface area of the cerebral cortex has been shown to be larger in women (Luders et al., 2006).

Handedness & Brain Lateralization

Anatomy

It is not only one's sex that impacts brain anatomy, but one's handedness as well. Literature on animals has shown that handedness is associated with variation in the size of the corpus callosum in chimpanzees (Hopkins, Dunham, Cantalupo, & Taglialatela, 2007). Literature on homo sapiens has shown that LH participants have a larger corpus callosum as compared to RH individuals (Hopkins et al., 2007). Specifically, one study found a stronger lateralization of the occipital petalia in LH men as compared to LH women (Zilles et al., 1996), while another found a more pronounced rightward asymmetry of the planum parietale in RH men as compared to RH women (Jäncke, Schlaug, Huang,

& Steinmetz, 1994). RH males have also been shown to have a deeper central sulcus in the left hemisphere than in the right hemisphere, whereas no inter-hemispheric asymmetry has been found in RH females (Amunts, Jäncke, Mohlberg, Steinmetz, & Zilles, 2000).

Prevalence

When it comes to the general healthy population, a disproportionate prevalence of right-handedness exists, with various studies reporting approximately 90% of the population as RH (Scharoun & Bryden, 2014; Zverev & Chisi, 2004). An increased prevalence of left-handedness has been associated with various immune-related disorders such that a meta-analysis indicated a modest yet statistically significant 13% increase in risk for any immune disorder among LH individuals (Gardener et al., 2009). Examples of this include but are not limited to, Crohn's disease, asthma, ADHD, allergies, migraine, epilepsy, and myasthenia gravis (Bryden et al., 1994).

Genetic Theories & Intrauterine Hormone Exposure

Research suggests a genetic contribution to handedness. Meaning, one's dominant hand seems to be consistent within families (McManus, Davison, & Armour, 2013). This is exemplified by twin studies, which have shown handedness to have a greater concordance in monozygotic, than in dizygotic, twins. Furthermore, a nationwide study found that left-handedness was more common in twins and triplets than in singletons (Vuoksimaa, Koskenvuo, Rose, & Kaprio, 2009).

Several etiological theories exist on the relationship between handedness and disease, though the most predominant theory links left handedness to in-utero hormone exposure. Specifically, the

amount of in utero testosterone or estradiol exposure, may play a role in immune system functioning (Geschwind & Galaburda, 1985; Marx, 1982). It is possible that exposure or sensitivity to in-utero testosterone may impact cerebral laterality, which could increase the risk of an abnormal distribution of functions across the hemispheres, along with left handedness (Gardener et al., 2009; Geschwind & Galaburda, 1985). High levels of testosterone at this time in development can impair development of the thymus gland, which directly impacts immune system functioning (Gardener et al., 2009).

One particularly interesting example is in the breast cancer literature, in which left-handedness was utilized as a marker of intrauterine hormone exposure. In this, a modest association between left handedness and breast cancer was found (Fritschi, Divitini, Talbot-Smith, & Knuiman, 2007; Ramadhani et al., 2005; Titus-Ernstoff et al., 2000).

In MS

Although approximately 10.3% of PwMS are LH (Shirani et al., 2019), a 62% increased risk of MS was found among women who were naturally LH, as compared to those who were naturally RH (Gardener et al., 2009). This discrepancy is similarly attributed to hormone exposure, where the increased MS risk in LH women is due to a positive relationship between left hand preference and surrogate markers for prenatal steroid hormone exposure (Fink, Manning, Neave, & Tan, 2004; Manning, Trivers, Thornhill, & Singh, 2000).

A genetic contribution to handedness in MS has been found as well (Medland et al., 2009; Sadovnick et al., 1993). One study found that both the HLA alleles associated with an increased risk of MS may be more common among LH people. Along with this are elevated levels of circulating autoantibodies,

total T-cells, and T-helper cells in LH as compared to RH individuals (Lengen, Regard, Joller, Landis, & Lalive, 2009).

Finally, some studies indicate that prenatal stress is a risk factor for left handedness (Glover, O'Connor, Heron, & Golding, 2004; Gutteling, de Weerth, & Buitelaar, 2007; Rodriguez & Waldenström, 2008). This occurs with prenatal stress theoretically impacting the hypothalamic-pituitary-adrenal (HPA) axis. Because this may negatively impact immune function, it is thought to perhaps influence the risk of MS (Ruiz & Avant, 2005; Sandman, Wadhwa, CHICZ-DeMET, Dunkel-Schetter, & Porto, 1997).

"Pathological Left-Handedness" & The Crowding Hypothesis

One of the most common theories behind left handedness and immunological disease was created by Geschwind and Behan, in which it was stated that testosterone in utero was directly correlated with cerebral lateralization (Geschwind, 1985). The association between this hormone and the immune system therefore offered some explanation as to why there was such a high prevalence of LH people with autoimmune disease (Geschwind, 1985; Geschwind & Galaburda, 1985). Alongside this was Paul Satz's model for "pathological left-handedness" (1972). In this, he postulated that early damage to one cerebral hemisphere could result in a decreased function of the contralateral hand (Satz, 1972). If this were to happen in the preferred hand, a person might switch hand preference and become a "pathological" left-hander or a "pathological" right-hander (Satz, 1972). Given that natural right-handedness is more common than natural left-handedness, the absolute number of natural left-handers becoming pathological right handers following right-hemisphere damage, as compared to the number of natural right-handers becoming pathological left handers following left hemisphere damage, would be relatively small (Satz, 1972).

While Satz's theory involved early injury in general, regardless of symptoms or diagnosis (Satz, 1972), it is made famous in the epilepsy population. One study computed the probability of transfer of handedness following brain lesion contralateral to the naturally preferred hand using 8% and 17% as the empirically based incidence of left-handedness in normal and brain-damaged populations, respectively. They found this probability to be about .21, with about 75% of the left-handed participants with left hemisphere lesions, and 41% of the right-handers with left hemisphere lesions (Satz, 1972). To conclude, the authors found that the results aligned with the theoretical probabilities of "pathological left handedness" in a clinical population, at proportions of .81 and .44.

Pathological left-handedness is theorized to be subsequent to "crowding" in the brain. This "crowding theory" states that the young brain is incredibly fragile and therefore significantly vulnerable to early cerebral insult. Specifically because of the lack of functional specialization, the brain cannot help but to recover endangered functions, and will do so by creating faulty connections at this time in early life (Giza, Prins, Hovda, Herschman, & Feldman, 2002). While neuroplasticity is often thought to be beneficial, the newly-made connections are thought to be faulty, and create what is called a *crowding* effect. In this, the healthy brain tissue will take over the damaged tissue to compensate for the cognitive function at hand leading to compromised quality and quantity of the brain tissue (Satz, Strauss, Hunter, & Wada, 1994).

The first test of this "crowding theory" was done with epilepsy patients that had unilateral left hemisphere damage and subsequent right-hemisphere speech (Lansdell, 1969). The author found that not only were all of his patients LH, but also that a discrepancy in favor of verbal IQ after early left-hemisphere damage, existed (Lansdell, 1969). Another study corroborated this result and found

increased prevalence of left handedness ranging from 37%-100% (Satz et al., 1994). This phenomenon has been associated with hemispheric speech reorganization after early left-brain injury. A similar study found that patients with this atypical (right-sided) speech dominance did significantly worse on non-verbal IQ measures (Satz et al., 1994). It is notable that although non-verbal IQ was lower, both verbal and non-verbal IQ scores were low after this reorganization (Satz et al., 1994).

The cognitive profile of someone with pathological left handedness due to left hemispheric damage (as is commonly seen in the epilepsy population) includes the sparing or recovery of language and verbal skills, with a relative deficit seen in non-verbal skills. At face value, this seems contradictory, where a lesion in the left hemisphere should impact verbal, and spare non-verbal abilities. However theoretically, hemispheric specialization exists at birth and with competition for functional space at play, speech is preserved at the expense of non-verbal functioning (Teuber, 1975). When damage to one hemisphere occurs, the other hemisphere must compensate and do more than it had originally been meant to do, leading to compromised functions.

While the aims of this study encompass predominantly adult-onset MS, pediatric MS does exist and may even overlap more with certain types of epileptic brains in its developmental trajectory. Although the current sample available does not have a sufficient number of pediatric-onset MS cases, a future study looking at this may be highly relevant.

Asymmetry and Hemispheric Vulnerability

Though different from epilepsy, a theory of brain asymmetry exists in MS (Roosendaal et al., 2009; Savio et al., 2015). Multiple imaging techniques, such as diffusion tensor imaging (DTI) and texture analysis (TA), have pointed to an increased vulnerability to the pathological process of MS in the dominant hemisphere (Filippi et al., 1995). Furthermore, one longitudinal study found a significant left-lateralized pattern of lesions in MS, suggesting a progressive vulnerability to the left-hemisphere, similar to that of epilepsy (Preziosa et al., 2017). In fact, several studies in epilepsy have suggested that the left hemisphere is more predisposed to damage than the right hemisphere (e.g., Holmes, Dodrill, Kutsy, Ojemann, & Miller, 2001; Paolozzi, 1969). Another study proposed that neuroinflammation may cause cortical hyperexcitability, affecting predominantly one hemisphere in early MS and contribute to higher corticospinal excitability in the weaker hand of PwMS (Chaves et al., 2019).

While MS is an inflammatory and demyelinating disease, functional brain reorganization may occur similar to that of early-onset epilepsy or stroke. Specifically, in the motor cortex, literature suggests that when compared to normal healthy controls, PwMS show greater supplementary motor area activation in the hemisphere contralateral to the moving limb (as assessed during fMRI procedures). In this, a decrease in sensorimotor cortex activation in the hemisphere with greater lesion load was found. The center of activation also is significantly shifted, more so than in controls, creating some evidence for cortical adaptive responses (Lee et al., 2000).

A classic study by Gur in 1980 found that GM and WM volumes in the two hemispheres are not equal (R. C. Gur et al., 1980). Utilizing xenon-133 inhalation method, a measure of blood flow, the authors found more GM in the left hemisphere than in the right hemisphere, particularly in precentral and frontal regions (Gur et al., 1980). They therefore hypothesized that the left hemisphere may be

fostering more intrahemispheric pathways within regions, rather than between hemispheres (Gur et al., 1980). The authors believed that, given these particular areas, this may be the mechanism as to why the left-brain is responsible for high-functioning skills such as language. Similarly, another study found that GM was greater in the anterior and posterior temporal regions in the left hemisphere, as compared to the right hemisphere (McHenry et al., 1978).

In MS, hand preference has been directly associated with interhemispheric lesion distribution (Filippi et al., 1995). A left-lateralized pattern of lesions may be related to this, if the disproportionate number of right-handers is taken into account. Meaning, if there is a higher ratio of WM than GM in the right hemisphere, perhaps there is an increased vulnerability for lesion load in the right hemisphere given the demyelinating nature of MS.

Language Dominance and Modularity

Given that handedness should be inversely related to hemispheric dominance, there may be the assumption that language functioning is always situated in the contralateral hemisphere to one's dominant hand. However, although RH people usually have left-sided language, this is not necessarily true in LH people. For example, one in 20 RH people and one in three LH people have right-hemisphere language functioning in the normal healthy population (McManus et al., 2013). However, in the neurological population, several studies in disease such as stroke, have shown an increased prevalence of pathological left handedness and right-sided language dominance (e.g., Rasmussen & Milner, 1977; Vargha-Khadem et al., 1985).

The important discriminating factor is that regardless of localization, LH people tend to function in a more bilateral manner (Elliott & Roy, 1996). Meaning, when utilizing language, LH people tend to recruit from both hemispheres more so than that of RH people. Theoretically, this would imply that damage to the left hemisphere in a LH person would have less of an impact on language abilities than the same degree of damage in a RH person.

Cognition

Handedness and hemispheric dominance not only have implications for language, but also for a myriad of cognitive skills. In specifically looking at intelligence (IQ), verbal IQ has been shown to be reliant on predominantly the left frontal hemisphere, whereas performance IQ is most commonly mediated by the right parietal, occipital, and superior temporal regions, which are often seen in visual and visuospatial processing (Gläscher et al., 2009). Also, it has been found that LH participants' overall verbal IQ was significantly higher than their performance IQ score, whereas the reverse was true for the RH subjects (Mascie-Taylor, 1980). This discrepancy was later corroborated in a mesial TLE study (Kim et al., 2003).

Memory

The general cognitive domain, "memory," is a broad term that describes a wide variety of neural functions and outputs. For example, memory may consist of immediate or working memory, the ability to spontaneously recall information, or the ability to recognize information when presented with options. Further, memory can be assessed (and information can be given) both verbally and non-verbally, both of which point to different anatomical correlates. In one study, it was found that

verbally-mediated working memory was significantly associated with handedness such that participants who were LH had a 6.1% decrease in working memory score, as compared to that of RH individuals and that rightward language lateralization was associated with a reduction in working memory score (Powell, Kemp, & García-Finaña, 2012).

In the epilepsy population, it has been found that more non-verbal memory deficits exist in those with right-sided epilepsy as compared to those with left-sided epilepsy (e.g., Abrahams et al., 1997). This has been replicated in other diseases with localizing targets, such as that of stroke, where one study showed poor verbal recall (immediate and delayed) and recognition in patients with left hemispheric stroke (Schouten, Schiemanck, Brand, & Post, 2009). Similarly, one case study found that a patient with a lesion in the right dorsomedial thalamic nucleus had anterograde memory impairment for visuospatial material (Speedie & Heilman, 1983).

Executive Functioning

In a sample of healthy young adults, one study measured executive functioning in relation to handedness. They found that handedness was associated with cognitive functioning alterations. Specifically, LH women had better performance on a measure of verbal inhibition (Beratis, Rabavilas, Papadimitriou, & Papageorgiou, 2010). On a task of attention, another study showed that LH participants with ADHD made more commission errors than RH participants did; the authors inferred that decreased cognitive lateralization in LH people was the most likely explanation (Schmidt, Carvaho, & Simoes, 2017).

Impacted Cognitive Domains in MS

General Intelligence

PwMS tend to have lower scores across subtests and composite scores (Ryan, Gontkovsky, Kreiner, & Tree, 2012) on tests that measure IQ, as compared to healthy controls. Rationale for this may not necessarily indicate "intelligence" rather, that PwMS have specific deficits, such as in processing speed and suffer from debilitating fatigue, which may impact other areas of functioning. However, intellectual enrichment is protective against cognitive impairment in patients with neurologic disease, such as MS (Sumowski, Wylie, DeLuca, & Chiaravalloti, 2010).

One example of this is with vocabulary. It is postulated that vocabulary knowledge decreases the negative effect of brain atrophy on cognitive efficiency in PwMS (Sumowski et al., 2009). Also, educational attainment reduces the negative effect of neurotic plaques (Bennett et al., 2003) and fibrillar b-amyloid (Roe et al., 2008) on cognition. This phenomenon is known as the "cognitive reserve" hypothesis, where intellectual enrichment works against the devastating impacts of neurological disease (Stern, 2002).

A split between verbal and non-verbal intellectual functioning in often seen in epilepsy and is utilized in lateralizing seizure focus (Blackburn et al., 2007). A similar discrepancy to that has been found in PwMS. For example, an early study found that patients with demyelination showed disproportionate drops in performance IQ, with relatively good verbal skills (Grant, McDonald, Trimble, Smith, & Reed, 1984; Marsh, 1980). A more updated study replicated such findings and reported that PwMS generally had more preserved verbal functioning than other components of intellectual functioning (Ryan et al., 2012). In fact, the majority of research suggests that most aspects of language functioning are generally intact in PwMS (Diamond, Deluca, Kim, & Kelley, 1997). Importantly, none of these studies have correlated handedness with the found cognitive outcomes.

Motor Performance

Hand/fine motor dexterity is one of the most important markers of disability in PwMS. The gold standard in neuropsychological assessment, and perhaps the most commonly-used task to assess this in PwMS, is the nine hole peg test (NHPT) (Feys et al., 2017). Neuropsychological research indicates that PwMS often notice subjective functional decline in dexterity, without congruent severity changes on other measures of disability. Therefore, research has historically supported the use of the NHPT test as a sensitive measure of upper extremity functional status change (Goodkin, Hertsguard, & Seminary, 1988).

Rationale for this functional change may have to do with lesions in areas of the brain such as the frontal lobes or in the corona radiata, along with lesions in the CST, and in the cerebellum (Koch et al., 2008). These lesions likely contribute to asymmetrical weakness in both upper and lower extremities in PwMS (Fritz et al., 2015; Severijns, Lamers, Kerkhofs, & Feys, 2015). One theory is that an asymmetric level of brain excitability may occur in PwMS and could perhaps be associated with upper and lower extremity impairment (Chaves et al., 2019). The literature has shown that this asymmetry of brain excitability is specifically higher in the weaker side, which, in one paper, predicted several outcomes such as lower disability, better upper extremity function, and superior cognitive processing speed (Chaves et al., 2019). The author's most likely explanation was neuroinflammation, which was hypothesized to be creating higher excitability in the weaker side (Chaves et al., 2019).

Another study also supported asymmetry in the brain's hemispheres and in the corticospinal motor system (Triggs, Calvanio, & Levine, 1997). They concluded that hemispheric asymmetries in motor evoked potential (MEP) thresholds could relate to functional significance, especially given the role of the corticospinal motor system in independent finger movement (Triggs et al., 1997). They assessed this with MEP's and TMS and found both tools to be associated with hand preference (Triggs et al., 1997). Specifically, that hemispheric asymmetries in TMS thresholds were strongly correlated with hand-differences in motor performance (Triggs et al., 1997). They also found that a lower TMS threshold for one hand was strongly associated with greater ability with that hand (Triggs et al., 1997).

The literature points to not only weaker manual dexterity in PwMS, but also to a lateralized pattern of weakness. For example, studies have shown that manual dexterity with one's non-dominant hand in LH patients was worse than in RH patients (e.g., Shirani et al., 2019). Similar results were corroborated in another test of finger tapping, where PwMS who were LH did better with their right hand than people who were RH did with their left hand (Todor & Doane, 1978). One theory for this discrepancy is that the brain networks responsible for controlling the less dexterous, non-dominant hand, could potentially have a lower reserve capacity, contributing to impairments in fine motor control of one's non-dominant hand (Shirani et al., 2019). Therein lies the hypothesis that motor performance of the hands mirrors the dominant processing mode of the contralateral hemisphere.

Given that much remains to be understood in both predicting and improving outcomes of motor control in PwMS, it is possible to look at other clinical populations. For example, in stroke patients, a common method of rehabilitation involves exciting motor areas in the contralesional hemisphere to target recovery of hand function after stroke (Nowak, Grefkes, Ameli, & Fink, 2009). While the same

research is not quite as abundant in the MS literature, focusing on improvement and rehabilitation of hand dexterity in PwMS is an invaluable direction for research in the field.

Memory

Memory is often compartmentalized into immediate memory, storage, and retrieval. "Immediate memory" is often interchanged with several terms such as, memory acquisition, working memory, short-term memory, encoding, learning, etc. Regardless of word choice, this area of memory typically refers to one's ability to acquire (encode or consolidate) new information. Dysfunction in this area of memory is seen in approximately 40–65% of PwMS (Rao et al., 1993; Sandry et al., 2019). In fact, several studies have shown that delayed memory either improves, or is equal to, that of healthy controls after PwMS are provided with multiple opportunities to learn new information (e.g., Burns et al., 2017; Deluca et al., 1994).

In PwMS, one's memory impairment is most frequently seen at the point of memory acquisition rather than in deficits of storage or retrieval (Sandry et al., 2019). Such memory deficits may be attributed to deficiencies in phonological loop tasks (e.g., recall of digits or words, or non-word recall tasks) (Kouvatsou et al., 2019) or in impaired processing speed (Sandry et al., 2019).

Anatomically, memory acquisition has been paired with the prefrontal area (specifically, the dorsolateral prefrontal cortex) whilst storage has mainly been seen in the temporal or parietal areas in healthy controls (Jonides et al., 2008). However, in PwMS, prefrontal dysfunction has been found; this has been correlated with the deficits seen in working memory in PwMS (Sperling et al., 2001).

Although working memory impairments persist in both verbal and non-verbal functioning, mixed results have been found in PwMS. For example, one study found that deficits in the non-verbal domain were more severe than that of auditory-based memory tasks (Rao et al., 1993). However, other studies have indicated that verbal memory is more compromised generally (Ruchkin et al., 1994) and over time (Piras et al., 2003).

Some suggest that non-verbal memory is an area of weakness in PwMS (Nair, Martin, & Lincoln, 2016), with learning, or memory as the most compromised area of function (Beier et al., 2017), given the primary deficit in working memory. Specifically, there may be a weakness in the visuospatial "scratch pad," which is what temporarily stores visual information in an activated state (Litvan et al., 1988). To target this, one of the most commonly abbreviated neuropsychological batteries in MS, the Brief International Cognitive Assessment of Multiple Sclerosis (BICAMS), suggested utilizing the learning trials of a non-verbal memory assessment tool, the Brief Visuospatial Memory Test-Revised (BVMT-r) (Langdon et al., 2012). The learning trials serve to better represent this memory acquisition weakness, as opposed to focusing on the delayed recall portion of the task, which may look at storage loss, but may not correctly account for attained material in the first place.

Verbal memory is an area of weakness in PwMS as well, with learning and memory acquisition deficits likely most impacted here (Chiaravalloti & DeLuca, 2008; Litvan et al., 1988). For example, one study found that on a verbal list-learning task, PwMS required more initial learning trials as compared to controls, however their recall and recognition did not significantly differ from the healthy controls (Deluca et al., 1994). Therefore, BICAMS suggests using the first five learning trials of the California Verbal Learning Test – Second Edition (CVLT-II) to assess verbal memory,

specifically in aspects of learning and encoding. This is one of the most commonly used verbal memory assessment tools used in MS (Benedict et al., 2006).

THE CURRENT STUDY

Rationale

Handedness is an intricate factor in understanding MS, as exemplified by the 62% increased risk of MS found among women who were naturally LH (Gardener et al., 2009). Previous research has approximated 10.3% of the MS population as LH (Shirani et al., 2019). Therefore, *the first aim* of this study was to replicate prior literature on the prevalence of left handedness in PwMS.

Human handedness was originally theorized to be influenced by an inherited factor, in which a shift towards the right was described as "dextral." This "right-shift" theory means that some genetic factor pushes the distribution of chance for handedness into the "dextral" direction; it is believed that a single gene is responsible for the shift to right-handedness (Annett, 1994). Thus, the term "dextral" refers to RH people and the term "non-dextral" refers to all other handedness types (e.g., LH, ambidextrous, etc.). For the purposes of this paper, these terms, dextral and non-dextral, were used to describe RH and non-right-handed participants, respectively.

In support of this terminology, previous studies on IQ and handedness have found that any deviation from the RH pattern, regardless of left or mixed handed, was associated with lower full scale IQ (FSIQ) (Briggs, Nebes, & Kinsbourne, 2007). Additionally, the literature indicates that the risk of MS

in LH people is comparable, even if participants who were forced at some point in life to switch handedness, were excluded from the LH group (Gardener et al., 2009).

The *second aim* sought to discern hemispheric vulnerability in MS via cognitive outcomes and handedness. Two contradicting theories regarding hemispheric vulnerability in PwMS were presented: The first theory, Theory A, indicated a direct relationship between hand preference and interhemispheric lesion distribution, such that there is an increased vulnerability to the pathological process of MS in the dominant hemisphere (Filippi et al., 1995). With the majority of the population as dextral, there would therefore be an increased vulnerability to the left-side of the brain. This corroborates another longitudinal study which found a significant left-lateralized pattern of lesions (Preziosa et al., 2017) in MS. According to this theory, more MS plaques would be found in the left hemisphere and therefore left-sided cognitive functions would be more impaired than right-sided functions (i.e., verbal skills will be worse than visuospatial skills).

The contradicting theory, Theory B, stemmed from discrepant GM and WM volumes in the brain's hemispheres, and stated that there is more GM in the left hemisphere than in the right hemisphere (e.g., Gur et al., 2000; McHenry et al., 1978). Therefore, the volume of WM would be higher in the right hemisphere, which could increase vulnerability for lesion load in that hemisphere. If it is true that the right hemisphere has more WM, and therefore a higher lesion load, more impaired right-sided cognitive functions would be present (i.e., visuospatial skills will be worse than verbal skills).

In understanding how this is assessed via handedness, both the modularity theory and language localization came into play. That is, if Theory A were true, both dextral and non-dextral PwMS would

have worse verbal than non-verbal skills given that the left hemisphere is more likely responsible for verbal skills overall. However, because some non-dextral people have right-sided language dominance, performance on verbal testing in this population may be relatively preserved. That is, the gap between verbal and non-verbal functioning may have been smaller in the non-dextral population because it is possible that some non-dextral people have right-sided language dominance, and because bilateral activation may be protective against damage to one hemisphere. For the same reasons, if Theory B were true, then both dextral and non-dextral PwMS would show weaker non-verbal than verbal skills. Once again, non-dextral people would be more protected and have a smaller gap between verbal and visual functioning.

Regardless of theory, the hypotheses for this study indicated that significant differences in verbal and non-verbal abilities would be found between dextral and non-dextral PwMS. Furthermore, if a significant difference were found, consistency in theoretical orientation would exist throughout aims (i.e., Theory A as true throughout, or Theory B as true throughout).

Specific Aims and Hypotheses

Given the above-stated theories, this study had the following aims and hypotheses:

Aim 1: **To assess the prevalence of left-handedness in the current MS sample, as compared to prior prevalence analyses of left-handedness in the wider MS population.**

> *Hypothesis 1:* Prevalence of left-handedness in the current MS sample will be similar to that of previous studies which have found approximately 10.3% of PwMS as LH (Shirani et al., 2019).

Aim 2: **To evaluate discrepancies in verbal and non-verbal abilities in dextral and non-dextral PwMS that may point to hemispheric vulnerability in MS.**

Hypothesis 2: A pattern of relative strengths and weaknesses on neuropsychological test performance, consistent across all measures of verbal and non-verbal functioning, will indicate hemispheric vulnerability in MS.

Aim 2a: **To evaluate discrepancies in verbal and non-verbal IQ in dextral and non-dextral PwMS that may point to hemispheric vulnerability in MS.**

Theory A: If Theory A is true, verbal IQ will be *lower* than non-verbal IQ in both dextral and non-dextral PwMS; non-dextral PwMS will also have *closer to equal performance*, or less of a split between domains, compared to those who are dextral. Rationale for this includes a more vulnerable left hemisphere in MS and thus more language impairment. Given that non-dextral PwMS may have bilateral activation and/or right-sided language dominance, they may be more protected from left-sided language impairment than dextral PwMS.

Theory B: If Theory B is true, verbal IQ will be *higher* than non-verbal IQ in both non-dextral and dextral PwMS; non-dextral PwMS will also have *closer to equal performance*, or less of a split between domains, compared to those who are dextral. Rationale for this includes a more vulnerable right hemisphere in MS and thus more non-verbal impairment. Once again, bilateral activation and the higher potential for right-sided language localization, may be protective for those who are non-dextral.

Aim 2b: **To evaluate discrepancies in verbal and non-verbal memory acquisition in dextral and non-dextral PwMS that may point to hemispheric vulnerability in MS.**

Theory A: If Theory A is true, verbal memory acquisition will be *lower* than non-verbal memory acquisition in both non-dextral and dextral PwMS; non-dextral PwMS will also have *closer to equal performance*, or less of a split between domains, compared to those who are dextral. Rationale for this includes a more vulnerable left hemisphere in MS and thus more language impairment. Given that non-dextral PwMS may have bilateral activation and/or right-sided language dominance, they may be more protected from left-sided language impairment than dextral PwMS.

Theory B: If Theory B is true, verbal memory acquisition will be *higher* than non-verbal memory acquisition in both non-dextral and dextral PwMS; non-dextral PwMS will also have *closer to equal performance*, or less of a split between domains, compared to those who are dextral. Rationale for this includes a more vulnerable right hemisphere in MS and thus more non-verbal impairment. Once again, bilateral activation and the higher potential for right-sided language localization, may be protective for those who are non-dextral.

Aim 3: **To evaluate discrepancies in fine motor abilities in dextral and non-dextral PwMS that may point to hemispheric vulnerability in MS.**

Hypothesis 3: After adjustment for disease-related variables, it is hypothesized that PwMS will have significantly faster fine-motor speed with their dominant hand than with their non-

dominant hand. Furthermore, non-dextral PwMS will have closer to equal bilateral performance than dextral PwMS.

Aim 4 (exploratory): **To evaluate discrepancies on neuropsychological measures between males and females with MS.**

Hypothesis 4: It is hypothesized that women will outperform men across neuropsychological measures. This is suggested both because of bilateral activation, where diffuse functionality is protective against the pathological process of MS in the brain, and because of a relatively less disabling MS process in women as compared to men.

INNOVATION/UNIQUE CONTRIBUTION: *Why does handedness matter?*

MS is the most common cause of neurological disability among young adults worldwide, with cognitive concerns predominating as a disabling symptom (Chaves et al., 2019). To this date, the specific effects of disease pathology on cognition is largely understudied. One way of elucidating cognitive performance in PwMS is in discerning vulnerable brain areas, or, for example, a vulnerable hemisphere. Although this has been researched extensively in other neurological disease populations, research on hemispheric differences via handedness had not previously been researched in MS prior to this study.

Several examples of how understanding vulnerable brain areas has impacted cognitive performance exist. For example in epilepsy, handedness studies have shown that seizures in the left-brain result in lower verbal functioning (Kim et al., 2003) and more spatial memory deficits have been found in right-sided epilepsy (Abrahams et al., 1997). Prior to this study, the only cognitive outcome in relation to handedness that was studied in MS was fine motor speed (where LH MS patients had faster left hand motor speed than did RH patients with their right hand) (Howells et al., 2018). Therefore, a wide gap in the literature of MS and handedness existed.

Handedness may provide clarity in how the MS brain is lateralized differently for cognitive functioning than that of the healthy brain. Localization of functions, such as language, may provide new insight into the diseased MS brain and better means with which to evaluate cognitive functioning. For example, neuropsychological recommendations for optimal learning may change subsequent to this study (e.g., handedness may inform relative strengths in verbal vs. visual-learning style). Findings from this study may also contribute to improvement of normative data for this population. Without statistically significant results, outcomes of this study are still highly relevant in both differentiating MS from other clinical populations, such as epilepsy, and in perhaps de-emphasizing the role of handedness in neuropsychological assessment.

CHAPTER II

Methods

Data from an archival neuropsychological database of physician-confirmed PwMS were utilized for this analysis. Neuropsychological evaluations by Dr. Fred Foley and his students have been performed at Holy Name Hospital (HNH), in Teaneck, NJ for roughly the past two decades; HNH cares for nearly 2,000 MS patients and neuropsychological evaluations have been performed for over 400 patients. Participants consented (with an IRB-approved consent form) to join any future research studies during their neuropsychological testing appointment. Participants were also simply asked, “are you right or left handed?” upon their neuropsychological evaluation. Self-report was therefore utilized in assessing handedness for this study, which may also represent a limitation.

Participants

Participants carry a diagnosis of physician-confirmed MS and are referred for neuropsychological testing by their physician. The neuropsychological evaluation is performed at HN Hospital, where patients complete a clinical interview and a battery of neuropsychological tests. After completion of the neuropsychological exam, scores are entered into a database by the examiner, with a second person double checking both scoring and the data input for precision and accuracy.

At this evaluation, patients are also offered the opportunity to become involved in ongoing research by adding their de-identified information to a larger neuropsychological database. Should patients choose to participate, they are consented (with an IRB-approved consent form) which outlines confidentiality and its limits, the purpose of the research study, eligibility criteria, and information on how to contact the research coordinator should they have additional questions or would like to discontinue participation. Patients are also provided with information regarding any risks and benefits of involvement in the study.

Procedure

Data from an archival neuropsychological database of physician-confirmed PwMS was utilized for this analysis. For roughly the past two decades, neuropsychological evaluations have been conducted by graduate students under the supervision of Dr. Fred Foley at HNH in Teaneck, NJ. HNH cares for nearly 2,000 MS patients and neuropsychological evaluations have been performed for over 400 patients.

Risks/Benefits

Adding information to the current literature regarding cognition in PwMS is beneficial not only to the MS population, but also to providers. Neuropsychological recommendations for optimal

learning and functioning in daily living may improve quality of life for PwMS. Furthermore, it is important to improve the understanding of MS pathology in the brain, and hemispheric vulnerabilities in MS may contribute to that literature.

A risk of this study was that participants may have experienced minor fatigue or discomfort during the neuropsychological examination.

Exclusion/Inclusion Criteria

To receive neuropsychological testing, and to be ultimately added to the database, participants had to be older than 18 years and able to comprehend English instructions for neuropsychological testing; this therefore includes, but is not limited to, being a fluent English speaker. Patients that were evaluated with neuropsychological testing also had to be diagnosed with MS by their physician. Exclusion criteria involves those without an MS diagnosis or who do not meet the age or language criteria.

Measures

1. Wechsler Intelligence Scales: Several iterations of Wechsler Intelligence Scales exist, all of which examine one's IQ both at the composite and sub-scale level. All of the Wechsler tests are pencil-and-paper measures comprised of visual and auditory stimuli assessing verbal skills, perceptual reasoning, working memory, and processing speed functioning.

In going through the different versions, The Wechsler Adult Intelligence Scale-revised (WAIS-r) is a well-validated scale (Wechsler, 1981) and has good reliability, with the performance IQ at $\alpha = .93$ and the verbal IQ between $\alpha = .95$-$.97$ (Narrett, 1984). Both the WAIS-III (Wechsler, 2008)

(reliability coefficients for composite scores range from α = .88 –.96 [Silva, 2008]) and WAIS-IV (reliability coefficients range from α = .87 to .98 for the WAIS-IV [Wechsler, 2008]), also have numerous sources of evidence supporting their construct validity (e.g., Silva, 2008).

The Wechsler Abbreviated Scale of Intelligence (WASI) is also well-validated (Wechsler, 1999) and has good reliability ranging from α = .92 to α = .98 for the composite scores. Its 2nd edition (WASI-II) is also well-validated (Wechsler, 2011) and has excellent reliability with the performance IQ at α = .94 and the verbal IQ at α = .95 (Snowden, 2004). Test-retest reliability show coefficients at *r* =.90-.96 for the composite scores (McCrimmon & Smith, 2013).

2. The California Verbal Learning Test: The California Verbal Learning Test-2nd edition (CVLT-ii) is a well-validated assessment of verbal memory, where the participant is read sixteen words aloud and asked to recall as many as possible over several learning trials, a short-delay, and a long-delay recall (Delis, Kramer, Kaplan, & Ober, 2000). Test-retest reliability coefficients for range from *r* = .50–.72 (Woods et al., 2006). Specifically within MS, reliability coefficients range from *r* =.50 to .72 (Benedict, 2005). The CVLT-ii interrater reliability for the total recall is *r* = .94.

3. Brief Visuospatial Memory Test: The Brief Visuospatial Memory Test-revised (BVMT-r) is a well-validated measure of non-verbal memory, in which the participant is presented with a page of six figures and asked to study the page for ten seconds, noting the details of each shape and its location on the page. The participant is asked to reproduce as many figures as possible from memory over three learning trials, and after a delay (Benedict et al., 1996). The BVMT-r has good reliability and validity (Benedict et al., 1996) with the interrater reliability for the total recall at *r* = .979.

4. The Nine Hole Peg Test: The Nine Hole Peg Test (NHPT) is a timed measure of manual dexterity with norms and administration rules created in 1985 by Mathiowetz, Weber, Kashman, and Volland.

In this test, the participant is asked to individually place pegs into holes and then remove each peg from its hole and replace it back to the container as quickly as possible, with one hand. Inter-rater and test–retest reliability are high (range, r = .86–.98), and studies have shown that the test can discriminate manual dexterity in PwMS from healthy controls at a highly significant level ($p < .05$) (Feys et al., 2017).

5. The Incapacity Status Scale: The Incapacity Status Scale (ISS) is a 16-item questionnaire, each rated on a 0-4 scale ranging from 1 where performance is impaired but accomplished without aid, 2 mechanical aids are required, 3 human assistance is required, and 4 when performance is lost. Questions assess disability across multiple domains including, stair climbing, ambulation, toilet/chair/bed transfer, bowel function, bladder function, bathing, dressing, grooming, feeding, vision, speech and hearing, medical problems, mood and thought disturbances, mentation, fatigability, and sexual function (Kurtzke, 1984). It also has a good correlation (r = .86) (Izquierdo et al., 1991) with the expanded disability status scale (EDSS), which is primarily used to quantify MS-related disability at the clinical level (Provinciali et al., 1999; Slater et al., 1984).

Demographics utilized for this study included age, sex, education, ethnicity, MS-related disability, and years carrying MS diagnosis. Age, sex, education, and ethnicity were recorded via self-report. The number of years carrying an MS diagnosis was obtained from each patient's medical record. MS-related disability was assessed via the ISS. Age was not re-adjusted for the measures already normed on standardized scores (i.e., verbal composite index (VCI), perceptual reasoning index (PRI), CVLT-ii, BVMT-r).

Procedures

Aim 1

For the first aim, the frequency of LH PwMS as compared to RH PwMS, was assessed with the intention of replicating prior studies (Shirani et al., 2019). Verbal self-report of one's handedness

was obtained from every participant, by asking, “are you right or left handed?” as modeled after prior studies of handedness (Constant & Mellet, 2018; Mueller et al., 1993). The primary comparison of interest was percentage of LH individuals versus percentage of RH individuals in the current MS sample. Given prior studies indicating approximately 10.3% of PwMS as LH (Shirani et al., 2019), it was hypothesized that similar numbers would be revealed in this study.

Aim 2a

Verbal and non-verbal IQ scores in dextral and non-dextral participants were assessed via Wechsler scale neuropsychological measures. Given the longevity of the archival database used in this study, several measures (and versions of the same measure) have been used for this sample to assess IQ including the WAIS-r, the WAIS-III, the WAIS-IV, the WASI and the WASI-II. All measures have carefully standardized instructions, scoring criteria, normative data, and information from extensive research on their reliability and validity. Research has also indicated a relationship between these assessment tools and cognitive aging, dementia, and other neurological and cognitive changes (Ryan et al., 2012).

To account for a variety of measures, standard scores of composite variables (i.e., VCI, PRI) were analyzed; the full-scale IQ (FSIQ) was used to characterize the sample. As previously mentioned, several Wechsler scale updates have occurred and therefore exist in the database used for this study. The original composite measures for verbal and non-verbal intelligence, with the acronyms VIQ and PIQ respectively, originally comprised several cognitive domains. Meaning, the VIQ also integrated measures of attention and working memory, alongside verbal information. Similarly, the PIQ not only assessed visual spatial problem solving, but also processing speed. Because of this, updated versions of the WAIS have entirely eliminated the VIQ and PIQ measures, and instead have replaced them

with four separate composite measures to assess VCI, PRI, processing speed (PSI) and working memory (WMI) (Loring & Bauer, 2010).

Preliminary analyses illustrated that the VIQ (M = 104.32, SD =15.34) and VCI (M = 137, SD = 16.07) were comparable with no significant difference between measures $t(25.6) = -.840$, $p = .409$. Similarly, PIQ (M = 96.14, SD =11.98) and PRI (M = 95.56, SD = 15.58) measures were comparable with no significant difference between the measures $t(26) = .576$, $p = .570$. Therefore, scores from the VIQ and VCI, as well as those of the PIQ and PRI, were collapsed into one verbal and one visual intelligence measure, renamed VCI and PRI, respectively. Standard scores of the PRI and VCI were compared for those who are dextral or non-dextral via linear mixed effect modelling with all aforementioned demographics, including age, sex, education, ethnicity, MS-related disability (via the ISS), and years carrying MS diagnosis, adjusted for. Demographics that were already adjusted for, specifically age, were not re-adjusted for in the model.

Aim 2b

Relative differences between verbal and non-verbal memory acquisition for dextral and non-dextral participants were assessed via total learning scores on two memory measures, respectively: The CVLT-ii and the BVMT-r. Standardized values of the total learning score were compared for those who are dextral or non-dextral via linear mixed effect modelling for the CVLT-ii and the BVMT-r with sex, education, ethnicity, MS-related disability (ISS), and years carrying MS diagnosis, adjusted for. Of note, given the use of adjusted standardized scores, age was not re-adjusted.

Aim 3

Completion of a NHPT was used to assess fine motor skills in PwMS. Several studies have selected the NHPT test as the gold standard for assessing fine motor skill and dexterity in PwMS

(Feys et al., 2017). Each individual must complete the NHPT twice for each hand. The average time in seconds over both trials for each hand was compared for those who are dextral or non-dextral.

Data Analysis Plan

Demographic characteristics of the sample were calculated. To ensure adequate sample sizes across demographic groups, race was coded dichotomously as Caucasian and non-Caucasian. Education was coded dichotomously as less than 12 years of education versus greater than or equal to 12 years of education.

Data analysis was performed using linear mixed effects modelling (LMEM) with one predictor variable, handedness, which had two levels: dextral PwMS and non-dextral PwMS. For *aims 2a & 2b,* the outcome variable was labeled as "score" and encompassed four neuropsychological measures: VCI, PRI, BVMT-r total learning score, and CVLT-ii total learning score. For *aim 3,* the "score" variable consisted of two neuropsychological measures: NHPT average time for the dominant hand, and NHPT average time for the non-dominant hand. Demographics including age, sex, education, ethnicity, MS-related disability (via the ISS), and years carrying MS diagnosis, were adjusted for; standardized scores were not re-adjusted for age.

Power Analysis

Aims 2a & 2b. To determine power for verbal and non-verbal functioning in MS, previous stroke research was utilized, which indicated verbal and non-verbal intelligence composites ranging from effect sizes of $\eta^2 = .09$ to $\eta^2 = .13$, respectively (Planton et al., 2012). Effect sizes for verbal and non-verbal memory acquisition ranged from $\eta^2 = 0.12$ (Campanholo et al., 2015) to $d = 1.17$ (Mosch et al., 2005). The smallest of these effect sizes, $\eta^2 = .09$, was used to determine power.

Calculating power for complex statistical models, such as the LMEM done for this study, is challenging and complicated given that power calculations are largely unsupported by software programs (Chi, Glueck, & Muller, 2019). Thus, power was instead calculated using a multivariate analysis of variance (MANOVA) model with G*Power Version 3.1 (Faul et al., 2009). Power was set at .80 and it was found that a sample of 115 would be sufficient.

Aim 3. To determine effect size for fine motor dexterity, a literature review for the NHPT in stroke populations was done. An effect size of $r = 0.39$ was found (Johansson & Häger, 2019) and utilized in a MANOVA model for simplicity, as stated above. For this study, G*Power Version 3.1 was used to conduct power analyses (Faul et al., 2009) and it was found that a sample size of 47 would be sufficient, with power set at .80.

Ethics

Participants included in this retrospective, cross-sectional, study have received neuropsychological testing as part of routine clinical care at the MS Center of HNH in Teaneck, NJ, for several decades. Eligibility criteria included having physician-confirmed MS (as indicated in their medical record). Participants were consented under the Institutional Review Board of the Albert Einstein College of Medicine (AECOM). Patients were informed that participation is voluntary, that they do not waive any of their legal rights in participating in this study, and that medical treatment is not affected if they refuse to participate or withdraw consent. Furthermore, that data are kept confidential, will not be used in any written or verbal reports to ensure confidentiality, and is only accessible to authorized researchers and contains demographics, medical information, and psychological and neuropsychological data.

CHAPTER III

Results

Participants

Statistical analyses were conducted using IBM SPSS Statistics v.25. Descriptive statistics were run to characterize the sample with *t* tests used for dichotomized variables and Pearson correlations used for continuous variables (see Table 1); participants (N = 429) were those that remained from the original sample (N = 584) after listwise deletion for missing data. Participants were predominantly middle-aged, Caucasian women, of average intelligence, the majority of whom had at least a high school education (see Table 1). Additionally, descriptive statistics of the neuropsychological variables are reported in demographically-adjusted T scores for the VCI, PRI, CVLT-ii Learning and BVMT-r Learning variables, and in unadjusted seconds for the dominant and non-dominant hand peg times (see Table 2).

Table 1.

Participant Descriptive Statistics

	Total (N = 429)		D (n = 390)		ND (n = 39)		p value
Variable	*M, n, Mdn*	*SD, % [IQR]*	*M, n, Mdn*	*SD, % [IQR]*	*M, n, Mdn*	*SD, % [IQR]*	
Sex							.682
Female	325	75.8%	297	76.2%	28	71.8%	
Male	104	24.2%	93	23.8%	11	28.2%	
Race/Ethnicity							.267
Caucasian	407	68.4%	277	71.0%	32	82.1%	
Non-Caucasian	91	15.3%	70	17.9%	4	10.3%	
Yrs of Education							
≥ 12yrs	308	71.8%	284	72.8	24	61.5	.191
< 12yrs	121	28.2%	106	27.2	15	38.5	
FSIQ	98.36	15.04	97.89	14.51	100.53	16.70	.323
Age (years)	46.8	11.2	47.0	11.3	45.9	10.9	.573
Length Dx (years)	8	[3,20]	8	[1,15]	7	[1,15]	.641
ISS	11.2	6.4	11.3	6.3	12.1	6.7	.520

Note. D = dextral; ND = non-dextral; FSIQ = Full Scale Intelligence Quotient; Length Dx = duration of MS diagnosis; ISS = Incapacity Status Scale Total Score

Table 2.

Neuropsychological Test Descriptive Statistics

	Total		D		ND	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*
VCI	99.27	15.15	99.55	15.35	96.80	13.25
PRI	95.86	14.41	96.57	14.13	89.03	15.63
CVLT-ii Learning	45.44	12.54	45.94	12.44	41.66	12.12
BVMT-r Learning	51.91	13.08	52.17	13.00	49.56	13.43
Dom. Pegs	26.02	6.92	25.95	6.79	25.82	6.15
Non. Dom. Pegs	26.81	7.64	26.72	6.98	26.17	5.64

Note. D = dextral; ND = non-dextral; VCI = Verbal Composite Index; PRI = Perceptual Reasoning Index; CVLT-ii = California Verbal Learning Test, 2, Learning Score; BVMT-r = Brief Visual Memory Test, revised, Learning Score; Dom Pegs = Average dominant hand NHPT across two trials (in seconds); Non. Dom. Pegs = Average Non-dominant hand NHPT across two trials (in seconds). Scores for VCI, PRI, CVLT-ii Learning and BVMT-r Learning are represented in demographically-adjusted T scores.

A higher score for most tests would indicate higher ability, however with time to complete a NHPT, longer time means higher disability. With that, bivariate statistics in the total sample (see Table 7) suggested that worse fine motor speed (longer time to complete the task) in one's non-dominant hand was weakly correlated with better verbal intelligence. The same was true for fine motor speed in one's non-dominant hand with perceptual reasoning abilities, and in one's non-dominant hand with non-verbal learning abilities. This only held partially true for non-dextral participants (See Table 7), where worse fine motor speed with the non-dominant hand was moderately associated with stronger non-verbal learning abilities. None of the samples indicated significance between one's ability to complete the NHPT with their dominant hand and another variable (See Table 7).

Higher verbal intelligence for the total sample (see Table 7) was moderately associated with higher non-verbal learning, as well as with better verbal learning and was strongly associated with higher perceptual reasoning abilities. For dextral participants (see Table 7), a weak association was present between higher verbal intelligence and higher non-verbal learning abilities, with a moderate

relationship between higher verbal intelligence and higher verbal learning, and also a moderate association between higher verbal intelligence and higher perceptual reasoning abilities. For non-dextral participants (see Table 7), a relatively strong association was seen between higher verbal intelligence and higher verbal learning abilities and a strong relationship existed between higher verbal intelligence and higher perceptual reasoning abilities as well.

In the total sample, a moderate association between higher perceptual reasoning abilities and better non-verbal learning was seen; a relatively strong relationship existed between higher perceptual reasoning abilities and a better verbal learning score. This remained true for the dextral sample (see Table 7), where higher perceptual reasoning abilities were moderately correlated with better non-verbal learning and with higher verbal learning abilities. Finally, in the non-dextral sample, higher perceptual reasoning abilities were weakly associated with better non-verbal learning abilities.

Finally, in the total sample, higher verbal learning was weakly associated with better non-verbal learning. This remained true for the dextral sample, but not for the non-dextral sample.

Table 7.

Bivariate Relationships of Total Sample

	1	2	3	4	5	6
1. VCI	--	--	--	--	--	--
2. PRI	.58***	--	--	--	--	--
3. CVLT-ii	.38***	.54[1]***	--	--	--	--
4. BVMT-r	.31[1]***	.29[1]***	.19***	--	--	--

5. Dom. Pegs	.11[1](.138)	10[1](.206)	-.03(.633)	-.01[1](.940)	--	--
6. Non. Dom. Pegs	.19[1](.018)	.16[1](.042)	.02(.762)	.14[1](.049)	.02[1](.740)	--

Note. [1]Spearman's rho values; all other values are Pearson *r*; *p* values are listed in parenthesis; VCI = Verbal Composite Index; PRI = Perceptual Reasoning Index; CVLT-ii = California Verbal Learning Test, 2, Learning Score; BVMT-r = Brief Visual Memory Test, revised, Learning Score; Dom Pegs = Average dominant hand NHPT across two trials (in seconds); Non. Dom. Pegs = Average Non-dominant hand NHPT across two trials (in seconds). *** $p < .001$.

Table 7.

Bivariate Relationships of Dextral Sample

	1	2	3	4	5	6
1. VCI	--	--	--	--	--	--
2. PRI	.53[1]***	--	--	--	--	--
3. CVLT-ii	.37***	.37[1]***	--	--	--	--
4. BVMT-r	.18[1]***	.28[1]***	.17***	--	--	--
5. Dom. Pegs	.10[1](.210)	.133[1](.112)	-.01(.908)	.01[1](.928)	--	--
6. Non. Dom. Pegs	.15[1](.071)	.14[1](.100)	.00(≤.989)	.08[1](.287)	.01[1](.899)	--

Note. [1]Spearman's rho values; all other values are Pearson r; p values are listed in parenthesis; VCI = Verbal Composite Index; PRI = Perceptual Reasoning Index; CVLT-ii = California Verbal Learning Test, 2, Learning Score; BVMT-r = Brief Visual Memory Test, revised, learning score; Dom Pegs = Average dominant hand NHPT time across two trials (in seconds); Non. Dom. Pegs = Average non dominant hand NHPT time across two trials (in seconds). ***$p < .001$.

Table 7.

Bivariate Relationships of Non-Dextral sample

	1	2	3	4	5	6
1. VCI	--	--	--	--	--	--
2. PRI	.66[1]***	--	--	--	--	--
3. CVLT-ii	.46(.009)	.12[1](.525)	--	--	--	--

4. BVMT-r	.18[1](.359)	.37[1](.046)	.28(.095)	--	--	--
5. Dom. Pegs	.22[1](.326)	-.06[1] (.791)	-.22(.267)	-.01[1](.954)	--	--
6. Non. Dom. Pegs	.41[1](.055)	.363[1](.089)	.13(.497)	.54[1](.003)	.06[1] (.758)	--

Note. [1]Spearman's rho values; all other values are Pearson *r*. VCI = Verbal Composite Index; PRI = Perceptual Reasoning Index; CVLT-ii = California Verbal Learning Test, 2, Learning Score; BVMT-r = Brief Visual Memory Test, revised, learning score; Dom Pegs = Average dominant hand NHPT time across two trials (in seconds); Non. Dom. Pegs = Average non dominant hand NHPT time across two trials (in seconds). ***$p < .001$.

Aim 1: Prevalence of left-handedness in this sample

In assessing discrepancies between RH and LH participants in this sample, 90.9% (n = 390) of the total sample (N = 429) were RH participants as compared to 9.1% that were LH participants (n = 39) in the total sample. This is comparable to prior studies that found approximately 10.3% of PwMS as LH (Shirani et al., 2019).

Aim 2: Dextral vs. non-dextral discrepancies in verbal and non-verbal abilities

LMEM is beneficial in its allowance of multiple neuropsychological data points within a single participant. It can also model categorical and continuous variables simultaneously. Finally, it allows for violations of sphericity and homogeneity of variance. For the purpose of this study, LMEM was used because neuropsychological data (repeated measurements) were correlated within an individual. Two iterations of LMEM's were run with five models each; the first LMEM model encompassed verbal and non-verbal IQ and memory acquisition scores, which are represented in demographically adjusted z scores. The second LMEM model encompassed NHPT times, which are represented in unadjusted seconds. Descriptive statistics were run to assess missing data after pairwise deletion for each neuropsychological outcome (see Table 7).

The first series of LMEM's examined differences in verbal and non-verbal intelligence and memory acquisition (see Table 7) in dextral and non-dextral individuals. The first model, or the null model, utilized the random intercept of participant without any fixed effects. Participant accounted for a significant portion of the variance in the outcome variable, "score", which was comprised in this case of four neuropsychological test scores measuring verbal and non-verbal IQ and memory acquisition measures, indicating correlated data within individuals, [intraclass correlation coefficient (ICC) = .45 ($p < .001$)]. The "Neuropsychological Test" variable represented the VCI, PRI, CVLT-ii total learning score, BVMT-r total learning score), and was added as a fixed effect in Model 2. This addition did not significantly improve the model $F(3, 1040.61) = 0.07$, $p = .974$, thus there was not a significant improvement from model 1 to model 2 (Δ-2LL = 0.22, $\Delta df = 3$, $p = .97$).

Model 3 added handedness as a fixed factor which improved the model (Δ-2LL = 35.72, $\Delta df = 1$, $p < .001$) and resulted in a significant, main effect of handedness $F(1, 431.17) = 8.06$, $p = .005$. Model 4 added the interaction of Handedness x Neuropsychological Test, which did not significantly improve the model (Δ-2LL = 3.19, $\Delta df = 3$, $p = .36$) and the interaction was not significant $F(3, 1026.73) = 1.07$, $p = .363$.

Finally, Model 5 examined the interaction of Handedness x Neuropsychological Test after adjustment of demographic variables (sex, education, ethnicity, MS-related disability, and years carrying MS diagnosis; age was not readjusted for); this model showed improvement (Δ-2LL = 1804.03, $\Delta df = 1$, $p < .001$). While the interaction was not significant, $F(3, 525.60) = 0.75$, $p = .523$, a main effect of handedness remained $F(1, 195.35) = 3.95$, $p = .048$ such that dextral (D) participants outperformed non-dextral (ND) participants on measures of verbal IQ ($M_D = 0.006$, $SD_D = 0.055$; $M_{ND} = -0.186$, $SD_{ND} = 0.174$), verbal memory acquisition ($M_D = 0.047$, $SD_D = 0.055$; $M_{ND} = -0.305$, $SD_{ND} = 0.165$),

non-verbal IQ (M_D = 0.045, SD_D = 0.055; M_{ND} = -0.497, SD_{ND} = 0.174) and non-verbal memory acquisition (M_D = 0.040, SD_D = 0.053; M_{ND} = -0.365, SD_{ND} = 0.167).

In examining differences between groups of handedness across neuropsychological measures, the largest effect size between dextral and non-dextral participants was seen in the PRI group (d = 0.643), representing a medium-large effect size (see Figure 1). As previously mentioned, dextral participants performed relatively better than non-dextral participants on this measure of non-verbal IQ.

Stratifying by Sex

Given that the largest effect size was seen in PRI, exploratory analysis included a two-way ANOVA to examine the effects of sex on IQ. Results indicated a significant main effect of handedness on PRI, $F(1,341) = 12.163$, $p = .001$ such that dextral males performed the best across all groups (M = 101.08, SD = 15.59) including, non-dextral males (M = 85.50, SD = 16.22), dextral females (M = 95.18, SD = 13.41), and non-dextral females (M = 90.71, SD = 15.76). While there was no statistically significant interaction of Sex x Handedness on PRI or on VCI $F(1,344) = 1.647$, $p = .200$, the interaction for PRI neared significance, $F(1,341) = 3.743$, $p = .054$. Women (M = 99.55, SD = 15.31) and men (M = 98.54, SD = 14.91) performed similarly on measures of VCI.

Table 7

Descriptive Statistics for Missing Data

	Valid		Missing		Total	
Variable	*n*	*%*	*n*	*%*	*n*	*%*
VCI						
Dextral	313	80.3	77	19.7	390	100
Non-Dextral	31	79.5	8	20.5	39	100

PRI						
Dextral	310	79.5	80	20.5	390	100
Non-Dextral	31	79.5	8	20.5	39	100
CVLT-ii						
Dextral	304	77.9	284	72.8	390	100
Non-Dextral	35	89.7	106	27.2	39	100
BVMT-r						
Dextral	348	89.2	42	10.8	390	100
Non-Dextral	34	87.2	5	12.8	39	100
Dominant						
Dextral	52	26.3	146	73.7	198	100
Non-Dextral	7	35.0	13	60.5	20	100
Non-Dominant						
Dextral	54	28.1	138	71.9	192	100
Non-Dextral	9	47.4	10	52.6	19	100

Note. VCI = Verbal Composite Index; PRI = Perceptual Reasoning Index; CVLT-ii = California Verbal Learning Test, 2, Learning Score; BVMT-r = Brief Visual Memory Test, revised, Learning Score; Dominant = Completion of NHPT with one's dominant hand; Non-Dominant = Completion of NHPT with one's non-dominant hand.

Table 7

Five LMEM Models demonstrating the Verbal and Non-Verbal Score outcome with Handedness

Note. Model 1 (N = 1,417) is the null model; Model 2 (N = 1,417) is an unadjusted model with the addition of the Neuropsychological Test variable; Model 3 (N = 1,406) is an unadjusted model with the addition of the handedness variable; Model 4 (N = 1,406) is an unadjusted model with the addition of the Handedness x Neuropsychological Test interaction; Model 5 (N = 718) is a demographically-adjusted model with the

	Model 1				Model 2				Model 3				Model 4				Model 5			
	B	SE *B*	*t*	*p*	*B*	SE *B*	*t*	*p*	*B*	SE *B*	*t*	*p*	*B*	SE *B*	*t*	*p*	*B*	SE *B*	*t*	*p*
Intercept	-0.00	0.04	-0.10	.919	-0.00	0.05	-0.06	.954	-0.36	0.13	-2.59	.010	-0.36	0.17	-2.19	.029	-0.38	0.25	-1.50	.133
VCI					-0.01	0.06	-0.24	.811	-0.14	0.06	-0.25	.797	0.18	0.19	0.95	.343	0.17	0.29	0.59	.559
PRI					-0.00	0.06	-0.10	.921	-0.01	0.06	-0.13	.893	-0.13	0.19	-0.70	.483	-0.15	0.29	-0.53	.596
CVLT-ii					0.01	0.06	0.24	.813	0.01	0.06	0.22	.824	0.06	0.18	0.33	.742	0.22	0.28	0.79	.432
BVMT-r					0[a]	0	--	--	0[a]	0	--	--	0[a]	0	--	--	0[a]	0	--	--
Test						0.07[b] (.974)				0.08[b] (.972)				0.68[b] (.563)				0.72[b] (.542)		
Handedness										8.06[b] (.005)				8.02[b] (.005)				3.95[b] (.048)		
Interaction														1.07[b] (.363)				0.75[b] (.523)		
-2LL[c]		3726.71				3726.49				3690.77				3687.58				1883.55		
Estimated Parameters		3				6				7				10				10		

Handedness x Neuropsychological Test interaction; VCI = Verbal Composite Index; PRI = Perceptual Reasoning Index; CVLT-ii = California Verbal Learning Test, 2, Learning Score; BVMT-r = Brief Visual Memory Test, revised, Learning Score; z-scores are reported; [a] This parameter is set to 0 because it is redundant; [b] represents an F statistic with p value given in parentheses; [c] = -2 log-likelihood is a measure of how well the model fits the data, better fit is indicated by smaller numbers.

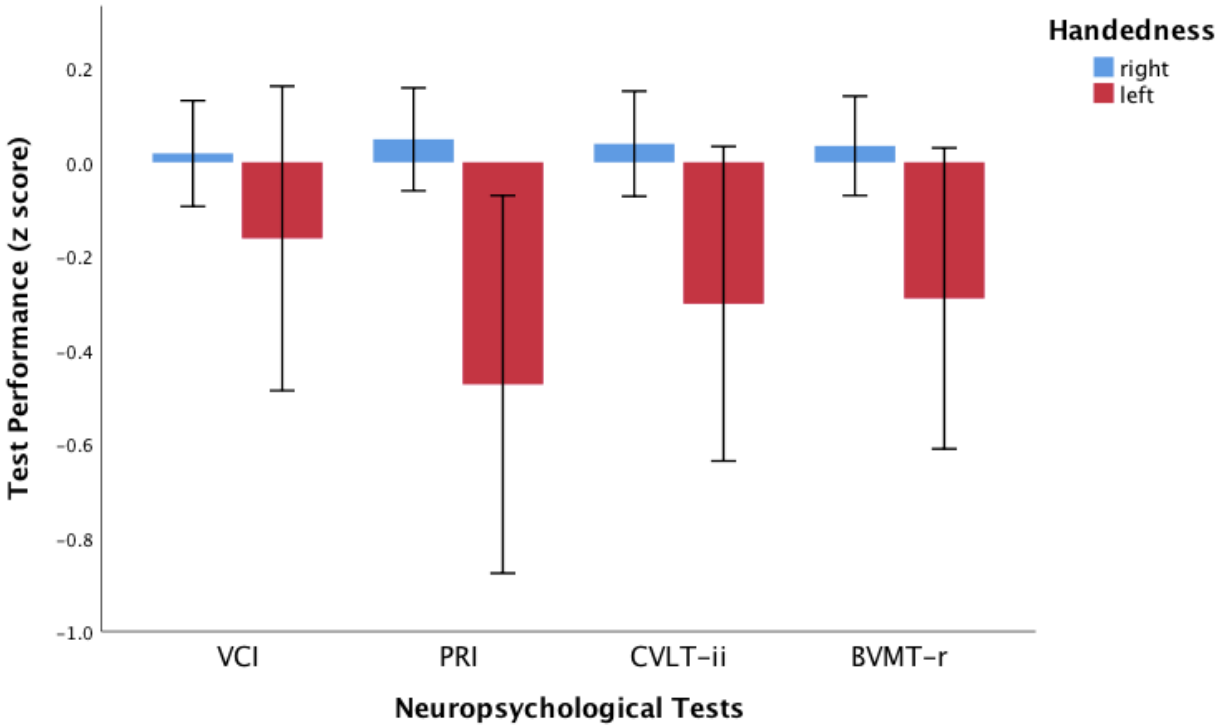

Figure 1. Bar graph representing neuropsychological test performance by handedness. Error bars represent 95% CI.

Aim 2c: Assessment of Bilateral Fine Motor Abilities (FMA)

The second iteration of LMEM's assessed participant's performance on the NHPT; the average scores in seconds, across two trials for each hand, was used (see Table 7).

Model 1, or the null model, utilized the random intercept of participant without any fixed effects. In this, the participant accounted for a significant portion of the variance in fine motor abilities (FMA), indicating correlated data within individuals [intraclass correlation coefficient (ICC) = .55 ($p <$ *.001*)]. The "neuropsychological test$_{FMA}$" variable, a 2-level variable representing the NHPT for each hand, was added as a fixed effect in Model 2. This addition significantly improved the model $F(1,$

466) = 3.97, p = .047 thus there was a significant improvement from Model 1 to Model 2 (Δ-2LL =3.95 Δdf = 1, p = .047)

Model 3 added handedness as another fixed factor which significantly improved the model once again (Δ-2LL =181.50, Δdf = 1, $p < .001$). Handedness did not emerge as a significant main effect in this model $F(1, 438) = 0.96$, p = .329 or in the subsequent Model 4, $F(1, 438) = 0.83$, p = .362, nor in Model 5, $F(1, 87.90) = 0.19$, p = 661.

When an interaction of Handedness x Neuropsychological $Test_{FMA}$ was added in Model 4, a significant improvement was seen (Δ-2LL = 5.63, Δdf = 1, p = .018) and the interaction Handedness x Neuropsychological $Test_{FMA}$ was significant, $F(1, 438) = 5.66$, p = .018. This remained significant in Model 5, which showed improvement (Δ-2LL = 1988.45, Δdf = 1, $p < .001$) after adjusting for demographics, $F(1, 438) = 3.99$, p = .049 such that with the dominant hand, dextral participants showed faster completion times (M = 24.38, SD = 0.897) than non-dextral participants (M = 29.28, SD = 2.63). Conversely, using the non-dominant hand, non-dextral participants had faster NHPT completion times (M = 23.96, SD = 2.82) than dextral participants (M = 27.04, SD = 0.90). Therefore, dextral participants deviated by an average 2.66 seconds between their two hands, with a stronger dominant hand, whilst non-dextrals had an average 5.32 second difference with a stronger non-dominant hand (see Figure 2).

Table 7

Five LMEM Models demonstrating the Fine Motor Abilities Score outcome with Handedness

	Model 1				Model 2				Model 3				Model 4				Model 5			
	B	SE *B*	*t*	*p*	*B*	SE *B*	*t*	*p*	*B*	SE *B*	*t*	*p*	*B*	SE *B*	*t*	*p*	*B*	SE *B*	*t*	*p*
Intercept	26.41	0.36	74.33	≤.001	27.12	0.50	54.19	≤.001	28.09	1.12	25.06	≤.001	25.67	1.51	17.02	≤.001	23.96	2.85	8.51	≤.001
Dominant					-1.41	0.71	-.1.99	.047	-1.14	0.74	-1.54	.125	3.53	2.09	1.69	.093	5.32	3.79	1.40	.164
Non-Dominant					0[a]	0	--	--	0[a]	0	--	--	0[a]	0	--	--	0[a]	0	--	--
Test						3.97[b] (.047)				2.37[b] (.125)				0.60[b] (.438)				0.45[b] (.507)		
Handedness										0.96[b] (.329)				0.83[b] (.362)				0.19[b] (.661)		
Interaction														5.66[b] (.018)				4.00[b] (.049)		
-2LL[c]	3221.27				3217.32				3035.82				3030.20				1041.75			
Estimated Parameters	3				4				5				6				6			

Note. Model 1 ($N = 466$) is the null model; Model 2 ($N = 466$) is an unadjusted model with the addition of the Neuropsychological $Test_{FMA}$ variable; Model 3 ($N = 438$) is an unadjusted model with the addition of the handedness variable; Model 4 ($N = 438$) is an unadjusted model with the addition of the handedness by Neuropsychological $Test_{FMA}$ interaction; Model 5 ($N = 152$) is a demographically-adjusted model with the handedness by Neuropsychological $Test_{FMA}$ interaction; Dominant = Average NHPT completion time over two trials with one's dominant hand; Non-Dominant = Average NHPT completion time over two trials with one's non-dominant hand. Scores are reported as time in seconds; [a] This parameter is set to zero because it is redundant; [b] represents an *F* statistic; [c] = -2 log-likelihood, better fit is indicated by smaller numbers.

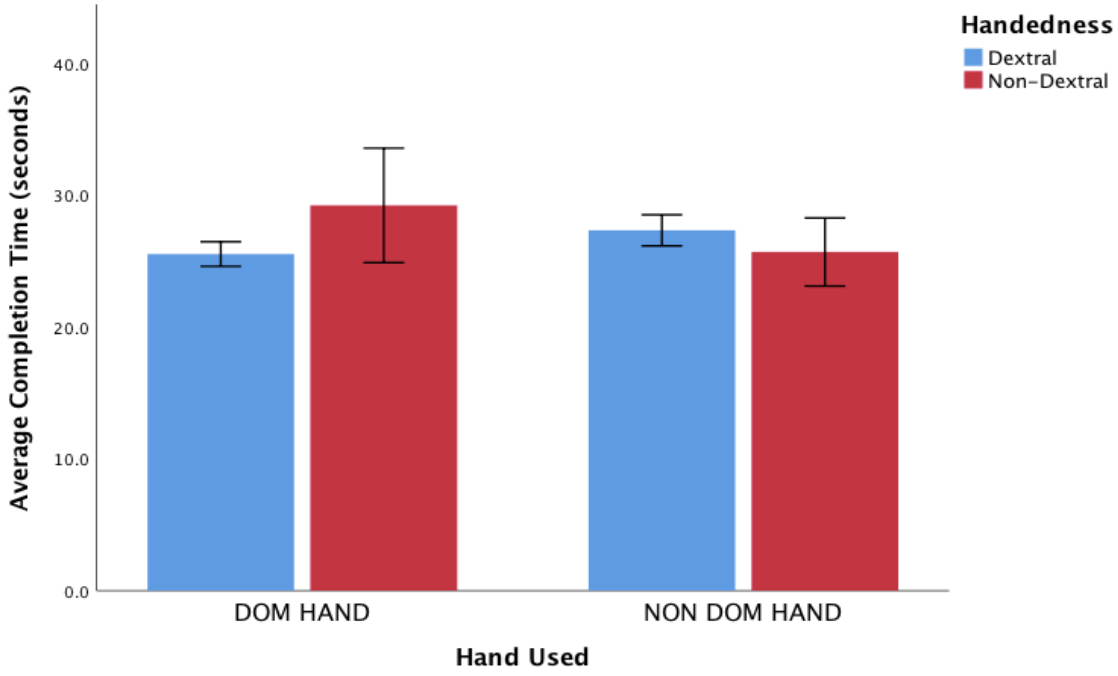

Figure 2. Bar graph representing fine motor skills on the NHPT for dominant and non-dominant hands. Error bars represent 95% CI.

Chapter IV

Discussion

This study aimed to discriminate hemispheric vulnerability via handedness, by way of neuropsychological performance on measures of verbal, non-verbal, and fine-motor functioning. Because several participants in this study were referred for baseline neuropsychological testing, the current sample is most representative of a community sample in terms of MS-related impairment, where less than 50% of the participants were cognitively impaired; prior studies have indicated that in community samples, 43% of the population was impaired (Rao, Leo, Bernardin, & Unverzagt, 1991). Discrepancies in dextral and non-dextral performance compared across tests were evaluated in an attempt to discern hemispheric vulnerability in the pathological process of MS. Two theories were presented to offer an explanation for hemispheric vulnerability: Theory A, an increased vulnerability to the pathological process of MS in the left brain (Filippi et al.,1995), and Theory B, an increased vulnerability to the pathological process of MS in the right brain (e.g., McHenry, et al., 1978; Gur et al., 2000).

Aim 1: Prevalence of left-handedness in this sample

Early research has indicated that approximately 11% of the healthy population are LH (Gilbert & Wysocki, 1992), whereas more recent research has suggested that about 10% of the healthy population are LH (Willems, der Haegen, Fisher, & Francks, 2014). In the MS population, the number is similar, with approximately 10.3% of PwMS as LH (Shirani et al., 2019). Thus, the first aim of the current study was to replicate prior research on the prevalence of LH in PwMS. Results of this study corroborated findings in prior literature, with approximately 9.1% of the current sample as LH.

Aim 2a: Handedness with Verbal and Non-Verbal IQ

Results of the present study indicated that there was a significant main effect of handedness when verbal and non-verbal IQ and memory acquisition measures were taken together, with better performance for dextral participants overall. However, there was no significant interaction between handedness and test. Although it was not significant statistically, when investigating individual means for each IQ measure, the largest effect size existed in PRI such that non-dextral PwMS performed relatively worse on non-verbal IQ measures, as compared to verbal IQ measures.

Previous research on handedness and cognition has yielded mixed results, perhaps in part due to an inconsistency in sample size and the variety of cognitive tests used. Despite this, the majority of research has not found a significant main effect of handedness in normal healthy controls (e.g., Sahu et al., 2016; Briggs et al., 2007). Thus, this study indicates something novel about the MS brain. While results are certainly preliminary, and must be replicated, some theories explaining this study's findings are suggested below:

The premise of this paper is based on the pathological left handedness theory and subsequent "crowding" in the brain. In epilepsy, where this theory has been substantiated, the cognitive profile of a "pathological left hander," or someone who has left-sided seizure focus, is seen as the sparing of verbal skills alongside a relative deficit in non-verbal skills. Theoretically, this is due to neuroplasticity of the juvenile brain where speech is preserved at the expense of non-verbal functioning (Teuber, 1975).

While handedness did not significantly discriminate individual neuropsychological test performances, a medium-large effect of non-verbal IQ was seen, such that LH PwMS performed more poorly than RH PwMS. This discrepancy between verbal and non-verbal functioning, with the relative

preservation of verbal skills, supports the original hypothesis for this paper, that PwMS may be susceptible to pathological left handedness and crowding. Specifically, because LH PwMS performed worse on PRI, an argument for at least a subset of LH PwMS being "pathological left handers," could be made. This pattern lends support for Theory A, which states that the left hemisphere is more vulnerable to the pathological process of MS, as it is in other neurological diseases such as epilepsy where clinical seizures have been found to be twice as likely in the left brain (e.g., Holmes, Dodrill, Kutsy, Ojemann, & Miller, 2001; Paolozzi, 1969).

Another theory is based on immune function; it is the case that LH persons are more susceptible to immune-related disorders (Geschwind & Galaburda, 1985) than RH persons. LH people are postulated to have weaker immune systems because of testosterone levels in utero, which impact both cerebral and immune functioning. This causes a deleterious effect on the thymus gland, which decreases the body's ability to discriminate itself from foreign invaders leading to an increase of autoimmune diseases (Searleman & Fugagli, 1987). It may be the case then, that if a naturally LH person has MS, his or her brain may be more vulnerable to the pathological process of MS than if a naturally RH person were to receive such a diagnosis. Meaning, that one's immune response would be more severe in a LH person with MS than in a RH person with MS. If this is the case, it is possible that lower cognitive abilities would be observed simply based on the fact that LH brains are more vulnerable. This could account for the main effect of handedness seen in this paper, where a poorer performance of non-dextral PwMS was found.

Stratifying by Sex

Hypotheses for this paper also suggested that those with bilateral activation would perform better than those with more focal brain functioning. Given that women have been shown to have more bilateral activation (Gur et al., 2000), exploratory analyses investigated the main finding of IQ while

stratifying by sex. Results contradicted this hypothesis, as dextral men outperformed all other groups on PRI, with relatively equal performance between males and females on VCI. While some may argue that men generally perform better on non-verbal functioning, even in normal healthy control populations (Daseking, Petermann, & Waldmann, 2017), this research is mixed and is often critiqued for not having a large enough sample of women (Johnson, Carothers, & Deary, 2008).

The original hypothesis, that women, who generally have higher levels of bilateral activation, would do better, was not supported here. One theory to explain this finding is that bilateral activation seen in the brain of MS actually may indicate worse disease, rather than improved brain functioning. To illustrate this, functional imaging studies have shown that increased brain reorganization, or more bilateral activation, is indicative of increased neuronal damage due to the brain re-adapting after injury (e.g., Mainero et al., 2004). In sum, PwMS who have higher levels of bilateral activation may have bilateral activation as an outcome of reorganization after higher MS-related damage. This could explain at least part of why the bilateral activation theory did not result in relatively stronger cognitive functioning.

Interestingly, a study looking at DTI found that IQ was positively correlated with myelination, specifically in men but not in women (Dunst, Benedek, Koschutnig, Jauk, & Neubauer, 2014). Sex differences in MS are controversial (e.g., Kutzelnigg et al., 2007), however, studies generally indicate that men with MS have a less inflammatory process than women with MS, leading to more "black holes" in men (Pozzilli et al., 2003). In relation to the theory on diffuse vs. focal neurological impact, this would imply that men have slightly more "focal" MS than women, which may be protective as demonstrated by them outperforming women on measures of PRI.

Aim 2b: Handedness with Verbal and Non-Verbal Memory acquisition

Results of the present study indicated that there was a significant main effect of handedness, with better performance for dextral participants, when verbal and non-verbal IQ and memory acquisition measures were taken together. However, within the individual memory acquisition measures, there was no significant difference with handedness.

Some prior research on memory and handedness in the general population exists. Although no studies to this date have specifically looked at handedness with the CVLT-ii or the BVMT-r in PwMS, some research has pointed to differences in episodic memory in those who have consistent or inconsistent handedness (Propper, Patel, Christman, & Carlei, 2017). Others have shown that brain laterality is correlated with performance on the CVLT (Catani et al., 2007), and one small study found no significant difference between right and left handers in memory on the CVLT-3 (Owens & Yost, 2019).

Interpretation of these results are limited by large confidence intervals in the non-dextral population, a consequence of far fewer non-dextral people in this sample. This continues to be a limiting factor of handedness studies in MS, other neurological populations, and in the general healthy population. Aside from this weakness, it is possible that the construct of memory in itself, along with the specific neuropsychological measures used, likely impacted results of this study:

While the initial understanding of hemispheric lateralization suggests that the majority of healthy people have left-sided language and right-sided non-verbal skills, memory may not be quite as specific. For example, one study found that novel words and familiar words were both activated by the left hemisphere, but in different regions (Johnson, Saykin, Flashman, McAllister, & Sparling, 2001). Also, there is some evidence to suggest that although the CVLT-ii is a language-based test, the

right hippocampus and right frontal lobe are also involved in word learning and retrieval (Johnson et al., 2001). This means that discrepancies in the BVMT-r and CVLT-ii memory measures may not be as indicative of hemispheric lateralization, as something like IQ, for example. While the specialization of the MS brain is dynamic, and research has not yet explored how memory may be lateralized in PwMS specifically, evidence from this study, supported by the aforementioned evidence in the healthy population, may offer some explanation as to why discrepancies in dextral and non-dextral PwMS on memory acquisition tests were not seen.

Studies on left temporal lobe epilepsy (TLE) have shown that the CVLT in fact does not lateralize language as well as other verbal learning measures, such as the Auditory Verbal Learning Test (AVLT) (Loring et al., 2008). It was thought that because the CVLT has semantically-related words, the AVLT may rely more on left temporal structures alone, whereas the CVLT can draw upon right-sided structures (Loring et al., 2008). Therefore, it is unlikely that the CVLT would lateralize verbal functioning in PwMS.

Further illustrating the point that neuropsychological measures must be chosen carefully to address the question at hand, the BVMT-r has typically been unable to discriminate right vs. left-sided epilepsy (Barr, Morrison, Zaroff, & Devinsky, 2004) despite being the key non-verbal memory measure utilized in most MS screeners (e.g., R. H. Benedict et al., 2012; R. H. B. Benedict et al., 2006). While this study only examined memory acquisition, excluding other memory components such as storage or retrieval, the BVMT-r has not been able to discriminate hemispheric lateralization in learning, storage, or retrieval in other populations (Barr et al., 2004). Other measures of non-verbal functioning, such as facial recognition, have shown better sensitivity at lateralizing right-sided seizure focus (Benke, Kuen, Schwarz, & Walser, 2013).

Aim 3: Handedness with Fine Motor Abilities

Results for this study showed a significant interaction between test and handedness when adjusting for demographic variables. Specifically, when comparing dominant hand groups, dextral PwMS showed faster completion time (with their right hand) than non-dextral individuals (with their left hand). When comparing the use of one's non-dominant hand, non-dextrals were faster with their non-dominant (right) hand than dextrals were with their non-dominant (left) hand.

Previous research in the healthy population has indicated that RH people do better than LH people on tests of manual dexterity (Chatagny et al., 2013). It has also indicated that RH people are more lateralized, which supports results seen here, that non-dextrals were better at using their non-dominant hand (Chatagny et al., 2013). In specifically looking at the manual dexterity test used for this study, the NHPT, means in a healthy population indicate faster completion times for one's right hand (Oxford Grice et al., 2003). This may be at least partially due to LH people living in a "right-handed world" where many objects are created for RH people (e.g., scissors, desks, etc.) (Springer & Deutsch, 1989).

In the MS population, previous research is somewhat inconsistent. One study showed a slight trend on a test of manual dexterity such that non-dextral PwMS were slower with their right hand than dextral PwMS were with their left hand (Shirani et al., 2019). The study also indicated that the mean completion time with one's left hand was relatively equal for RH and LH PwMS (Shirani et al., 2019). Conversely, in a test of finger tapping, PwMS who were LH did better with their right hand than people who were RH did with their left hand (Todor & Doane, 1978). It's possible that the brain

networks responsible for controlling the less dexterous, non-dominant hand, may have a lower reserve capacity and therefore more severe impairment in fine motor control of one's non-dominant hand is seen (Shirani et al., 2019).

Other findings for this aim include that dextral PwMS had more equal performance across hands than non-dextral PwMS, and, within the non-dextral group, performance was better with the non-dominant (right) hand than with the dominant (left) hand. These novel findings may be explained in part by the small sample size available for non-dextral individuals, increasing variability.

Another note is that the disability measures used in this study included years since diagnosis and the ISS. The ISS is comprised of questions on stair climbing, ambulation, toilet/chair/bed transfer, bowel function, bladder function, bathing, dressing, grooming, feeding, vision, speech and hearing, medical problems, mood and thought disturbances, mentation, fatigability, and sexual function (Kurtzke, 1984). Thus, upper extremity disability is not specifically assessed and therefore may not sufficiently be controlled for when evaluating fine motor skills on a NHPT.

Interpretation

Theory A vs. Theory B

The premise of this study was that there was some hemispheric vulnerability to the pathological process of MS, which would neatly fit into Theory A or Theory B. The results of this study were inconsistent. In IQ, an overall pattern of higher performance in the dextral group was seen, which theoretically would point to the left hemisphere as more preserved than the right hemisphere, and support Theory B. Fine motor skills indicated improved performance in the dextral group supporting this theory as well, with performance in the non-dextral group as stronger with the non-dominant

(right) hand than with the dominant (left) hand. Memory measures were not sufficient in lateralizing hemispheric vulnerability for reasons hypothesized earlier in this paper.

Perhaps the most significant and important finding of this study was that the group showing the biggest effect size was seen in PRI, where RH PwMS outperformed LH PwMS. This discrepancy in functioning, with a sacrifice of non-verbal skills in non-dextral PwMS, is the pattern typically observed in pathological left-handedness profiles. This lends an argument for the crowding theory, supporting Theory A. It is theorized that the compensation for a perhaps more vulnerable left hemisphere in MS and subsequent crowding, leads to the sacrifice of non-verbal skills in non-dextral PwMS.

Other Factors that Impact Cognition in MS

The mechanism underlying Theory B is that higher WM volume in the right hemisphere leaves this hemisphere more vulnerable to WM lesions, thus increasing dysfunction in the right hemisphere. However, is imperative to understand the variety of factors that impact disability in PwMS, alongside WM lesion load, as the diffuse nature of MS differentiates this disease from other neurological populations in which handedness has been studied, such as epilepsy or stroke. While it is true that WM lesions greatly contribute to physical and cognitive disability, so do cortical lesions on the white and grey-matter border (Brownell & Hughes, 1962). In fact, newer research points to significant amounts of, and multiple types of, GM lesions (Bö et al., 2006). GM lesions are likely different in pathology. For example, GM lesions tend to have less macrophage and lymphocyte infiltration and are therefore less inflammatory (Bö et al., 2006). GM lesions are also not necessarily correlated with focal WM demyelination (Vercellino et al., 2005).

Additionally, lesion-load may not be the only contributor to disability in PwMS. Theories also exist regarding the nature of brain atrophy and disability, as an addition to demyelination-related disability.

Some research suggests that, in fact, brain atrophy can make just as much, if not more of, an impact on MS-related disability as demyelination (Mahajan et al., 2019). The two are likely related in that neurodegeneration may be contributing to brain atrophy, with perhaps specific vulnerability to deep brain structures such as the thalamus (Mahajan et al., 2019). One limitation in identifying and quantifying the impact that GM brain atrophy has in PwMS is the technical tools available, which can be too insensitive to accurately assess deep GM atrophy or lesion load (Amiri et al., 2016).

GM lesions and GM atrophy impact cognitive functioning, as does WM demyelination. The research on which of the aforementioned factors play the greatest role in cognitive functioning, is debated. Early research suggests that lesion load plays the largest role in impacting cognitive functioning. Some studies suggest that focal frontal-lobe lesions play a major role in executive dysfunction (Arnett et al., 1994). Others point to periventricular lesions and their association with psychomotor deficits (Tiemann et al., 2009).

On the contrary, some suggest that regional GM atrophy may account for the greatest amount of variance in cognitive functioning (Benedict et al., 2005), suggesting that lesion load is *not* the largest indicator of cognitive impairment (Fulton et al., 1999). One study found that the long delayed recall of the CVLT-ii was associated with regional GM atrophy in areas of the prefrontal, parietal, and temporal lobes, as well as in the insular cortex (Nocentini et al., 2014). Other studies suggest that only a small amount of the variance in verbal learning, memory, and processing speed was accounted for by global brain atrophy (Benedict et al., 2006). Finally, many studies postulate that enlargement of the brain's third ventricle plays the most vital role in cognitive and physical disability in PwMS (Müller et al., 2013).

In sum, it is likely that several factors related to brain atrophy and neuronal damage play a role in cognitive functioning in PwMS. Therefore, isolating WM lesion load on its own may inhibit the understanding of why and how cognitive disability occurs; in fact, WM lesion load likely does not, on its own, reflect cognitive performance or lateralization of hemispheric damage.

Clinical Implications

This study highlighted the clinical importance of choosing the best neuropsychological measures to answer the question at hand. For this study, the CVLT-ii and BVMT-r were used to assess verbal and non-verbal memory acquisition, respectively. While these tests are the most frequently used in MS, and are included in validated screening batteries such as the BICAMS (R. H. Benedict et al., 2012) or the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) (Benedict et al., 2006), lateralization of cognitive deficits in other neurological populations indicate that in fact neither the CVLT-ii nor the BVMT-r are sufficient. Other measures, such as the AVLT (Loring et al., 2008) for verbal memory or facial recognition measures for non-verbal memory (Benke et al., 2013), may be more suited to assess hemispheric vulnerability in MS, which was the purpose of this study. Thus, identifying the question at hand should inform which neuropsychological measures to use in a clinical setting.

Clinical implications for male and female PwMS are also indicated here. Women are thought to have a more inflammatory MS process than men. Differences in MS processes between men and women may therefore result in individual differences in one's cognitive profile. Furthermore, women tend to show more bilateral activation than men, and although bilateral activation has been typically

associated with stronger cognitive skills, in the case of MS, higher levels of bilateral activation could in fact be an outcome of worse MS pathology. This may then result in a different MS neuropsychological profile for a woman than for a man. Therefore, when performing neuropsychological assessment on PwMS, it may be important to consider sex-related differences. The creation of male and female norms in the MS population may be indicated as well.

Arguably the most important outcome in studying and researching MS is the improvement of patient's lives. Much remains to be understood in both predicting and improving MS symptoms, but new research indicates that transcranial direct current stimulation (tDCS) has been successful in treating several symptoms of MS, such as fatigue (Charvet et al., 2018). Research on handedness, such as what is found in this paper, may improve treatment. For example, one may consider alternative placements for electrodes of tDCS in dextral vs. non-dextral patients in an effort to improve outcomes.

Study Limitations & Future Directions

This study had several limitations for discussion. Firstly, there was a relatively small number of non-dextral participants as compared to dextral participants. As previous studies have suggested, the percentage of non-dextral participants in the general population is approximately 10%. Thus, evenly-matched groups are not usually available in handedness studies. The current study is no different. The discrepancy between groups impacted the statistical analysis such that demographically adjusted z scores were forced to be centered around the dextral population, with larger variability therefore present in the non-dextral population. Future studies with a larger sample size are suggested.

A larger sample size would also improve the generalizability of this study. Although both men and women were incorporated in an effort to increase generalizability, it is recognized that generalizability was somewhat compromised here given restricted demographics at HNH (i.e., predominantly Caucasian adults with a high social economic status).

Exploratory analysis to stratify by sex with handedness was performed. However, other demographic variables were not individually examined in this analysis given both the small *n* in the non-dextral sample and descriptive statistics that did not indicate significant differences between groups (see Table 1). Thus, a future direction may consider looking more closely at these variables. Future studies on handedness in PwMS with a larger sample size may include stratifying by sex and other demographic variables.

Along with replicating this study with a larger sample size, future studies may consider expanding this population to include (or to focus exclusively on) a pediatric MS sample.
A pediatric MS sample may have even more overlap with the pathological left handedness syndrome seen in epilepsy, as the injury is suspected to occur in the early stages of life. Furthermore, data could be compared with a matched epilepsy population, to explicitly discern similarities and differences between the two populations.

One main finding in this study was that a large effect size between dextral and non-dextral groups emerged. However, a limitation of the study was that the subtests that comprise the PRI and VCI composite scores were unable to be evaluated individually. Therefore, it is unknown which subtest is

driving the effect size seen between groups. Future studies may consider performing separate analysis on IQ subtests by handedness to see if any main effects emerge.

Several studies on handedness have evaluated family history of "sinistrality" or a family history of those who are LH. The literature has pointed to not only discrepancies in handedness, but to degree of handedness, which can be related to the family history. For example, one study found that those with a family history positive for "sinistrality" demonstrated lower full scale IQ scores than those participants who did not have a family history of LH relatives (Briggs et al., 2007). Unfortunately, family history was unable to be obtained for the current study. Therefore, it is suggested that future studies utilize standardized measures in obtaining a thorough family history when assessing hemispheric vulnerability, handedness, or cognition, in MS.

Other limitations include the assessment tools available for this study:

Firstly, neuroimaging was unavailable. Comparing neuropsychological performance to hemispheric lesion load, or other factors of MS pathology that impact disability (GM lesions, atrophy, etc.), may lend more support to the findings in this study. However, the clinico-radiological paradox does mean that comparison with neuroimaging findings may be limited, even if available.

Secondly, the way in which handedness demographics were obtained could have been improved. Specifically, self-report was utilized in differentiating dextral from non-dextral individuals. This does not account for degree of handedness, which may play a role in hemispheric specialization. It also does not account for PwMS who may have had to switch hands due to disease or other factors and therefore may have unique brain compositions. Future studies may include utilizing handedness measures such as the Edinburgh Handedness Inventory (Oldfield, 1971) to better categorize and standardize handedness in participants.

Finally, there is some critique that the ISS has high non-response rates for some of its items in which the participant is uncomfortable answering honestly (Portnoy, Archetti, Stimmel, & Foley, 2016). It also may not account for variability in fine motor functioning. Therefore, other measures of disability may be considered in future studies to better assess MS-related disability.

Neurological processes are often complex and unpredictable. The scientific community does its best to understand the intricacies of disease with the hope that eventually, some symptoms or outcomes may be improved in patients. However, given how relatively little is known about the brain, the nature of this field often leads to frustration and feelings of discouragement in researchers, providers, and most importantly, in patients. It is a privilege to be on the scientific, rather than on the disease-burden, side of neurology. Thus, although individual research papers, or dissertations, may feel minute in comparison to the overwhelming complexities of disease, it falls in the hands of the researchers and clinicians to continue the pursuit of hope on behalf of our patients, which happens one step at a time.

References

Abrahams, S., Pickering, A., Polkey, C. E., & Morris, R. (1997). Spatial memory deficits in patients with unilateral damage to the hippocampal formation. *Neuropsychologia*, *35*, 11–24. doi: 10.1016/S0028-3932(96)00051-6

Allen, L. S., & Gorski, R. A. (1991). Sexual dimorphism of the anterior commissure and massa intermedia of the human brain. *Journal of Comparative Neurology*, *312*(1), 97–104. doi: 10.1002/cne.903120108

Amiri, H., de Sitter, A., Bendfeldt, K., Battaglini, M., Gandini Wheeler-Kingshott, C. A. M., Calabrese, M., … Vrenken, H. (2018). Urgent challenges in quantification and interpretation of brain grey matter atrophy in individual MS patients using MRI. *NeuroImage: Clinical*, *19*, 466–475. doi: 10.1016/j.nicl.2018.04.023

Amunts, K., Jäncke, L., Mohlberg, H., Steinmetz, H., & Zilles, K. (2000). Interhemispheric asymmetry of the human motor cortex related to handedness and gender. *Neuropsychologia*, *38*(3), 304–312. doi: 10.1016/S0028-3932(99)00075-5

Annett, M. (1994). Handedness as a continuous variable with dextral shift: Sex, generation, and family handedness in subgroups of left- and right-handers. *Behavior Genetics*, *24*(1), 51–63. doi: 10.1007/BF01067928

Anon. 2020. "Long-Term Treatments for Multiple Sclerosis | MSAA." Retrieved May 17, 2020 (https://mymsaa.org/ms-information/treatments/long-term/).

Arnett, P. A., Rao, S. M., Bernardin, L., Grafman, J., Yetkin, F. Z., & Lobeck, L. (1994). Relationship between frontal lobe lesions and Wisconsin Card Sorting Test performance in patients with multiple sclerosis. *Neurology*, *44*(3 Pt 1), 420–425. doi: 10.1212/wnl.44.3_part_1.420

Arnold, A. P. (2009). Mouse models for evaluating sex chromosome effects that cause sex differences in non-gonadal tissues. *Journal of Neuroendocrinology*, *21*(4), 377–386. doi: 10.1111/j.1365-2826.2009.01831.x

Barkhof, F. (1999). MRI in multiple sclerosis: Correlation with expanded disability status scale (EDSS). *Multiple Sclerosis Journal*, *5*(4), 283–286. doi: 10.1177/135245859900500415

Barr, W., Morrison, C., Zaroff, C., & Devinsky, O. (2004). Use of the Brief Visuospatial Memory Test—Revised (BVMT-R) in neuropsychological evaluation of epilepsy surgery candidates. *Epilepsy & Behavior*, *5*(2), 175–179. doi: 10.1016/j.yebeh.2003.12.010

Beatty, W. W., Blanco, C. R., Wilbanks, S. L., Paul, R. H., & Hames, K. A. (1995). Demographic, Clinical, and Cognitive Characteristics of Multiple Sclerosis Patients Who Continue to Work. *Journal of Neurologic Rehabilitation*, *9*(3), 167–173. doi: 10.1177/154596839500900306

Beier, M., Gromisch, E. S., Hughes, A. J., Alschuler, K. N., Madathil, R., Chiaravalloti, N., & Foley, F. W. (2017). Proposed cut scores for tests of the Brief International Cognitive Assessment of Multiple Sclerosis (BICAMS). *Journal of the Neurological Sciences*, *381*, 110–116. doi: 10.1016/j.jns.2017.08.019

Benedict, R. H., Amato, M. P., Boringa, J., Brochet, B., Foley, F., Fredrikson, S., … Langdon, D. (2012). Brief International Cognitive Assessment for MS (BICAMS): International standards for validation. *BMC Neurology*, *12*(1), 55. doi: 10.1186/1471-2377-12-55

Benedict, R. H. B. (2005). Effects of using same- versus alternate-form memory tests during short-interval repeated assessments in multiple sclerosis. *Journal of the International Neuropsychological Society: JINS*, *11*(6), 727–736. doi: 10.1017/S1355617705050782

Benedict, R. H. B., Bruce, J. M., Dwyer, M. G., Abdelrahman, N., Hussein, S., Weinstock-Guttman, B., … Zivadinov, R. (2006). Neocortical Atrophy, Third Ventricular Width, and Cognitive Dysfunction in Multiple Sclerosis. *Archives of Neurology*, *63*(9), 1301–1306. doi: 10.1001/archneur.63.9.1301

Benedict, R. H. B., Carone, D. A., & Bakshi, R. (2004). Correlating Brain Atrophy With Cognitive Dysfunction, Mood Disturbances, and Personality Disorder in Multiple Sclerosis. *Journal of Neuroimaging*, *14*, 36S-45S. doi: 10.1111/j.1552-6569.2004.tb00277.x

Benedict, R. H. B., Cookfair, D., Gavett, R., Gunther, M., Munschauer, F., Garg, N., & Weinstock-Guttman, B. (2006a). Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). *Journal of the International Neuropsychological Society*, *12*(04). doi: 10.1017/S1355617706060723

Benedict, R. H. B., Schretlen, D., Groninger, L., Dobraski, M., & Shpritz, B. (1996). Revision of the Brief Visuospatial Memory Test: Studies of normal performance, reliability, and validity. *Psychological Assessment*, *8*(2), 145. doi: 10.1037/1040-3590.8.2.145

Benedict, R. H. B., Zivadinov, R., Carone, D. A., Weinstock-Guttman, B., Gaines, J., Maggiore, C., … Bakshi, R. (2005). Regional Lobar Atrophy Predicts Memory Impairment in Multiple Sclerosis. *American Journal of Neuroradiology*, *26*(7), 1824–1831.

Benke, T., Kuen, E., Schwarz, M., & Walser, G. (2013). Proper name retrieval in temporal lobe epilepsy: Naming of famous faces and landmarks. *Epilepsy & Behavior: E&B*, *27*(2), 371–377. doi: 10.1016/j.yebeh.2013.02.013

Bennett, D. A., Wilson, R. S., Schneider, J. A., Evans, D. A., Mendes de Leon, C. F., Arnold, S. E., … Bienias, J. L. (2003). Education modifies the relation of AD pathology to level of cognitive function in older persons. *Neurology*, *60*(12), 1909–1915. doi: 10.1212/01.wnl.0000069923.64550.9f

Beratis, I. N., Rabavilas, A., Papadimitriou, G. N., & Papageorgiou, C. (2010). Effect of handedness on the Stroop Colour Word Task. *Laterality*, *15*(6), 597–609. doi: 10.1080/13576500903071104

Blackburn, L. B., Lee, G. P., Westerveld, M., Hempel, A., Park, Y. D., & Loring, D. W. (2007). The Verbal IQ/Performance IQ discrepancy as a sign of seizure focus laterality in pediatric patients with epilepsy. *Epilepsy & Behavior*, *10*(1), 84–88. doi: 10.1016/j.yebeh.2006.10.001

Bö, L., Geurts, J. J. G., Mörk, S. J., & Valk, P. van der. (2006). Grey matter pathology in multiple sclerosis. *Acta Neurologica Scandinavica*, *113*(s183), 48–50. doi: 10.1111/j.1600-0404.2006.00615.x

Briggs, D. G. G., Nebes, R. D., & Kinsbourne, M. (2007). Intellectual differences in relation to personal and family handedness. *The Quarterly Journal of Experimental Psychology*. doi: 10.1080/14640747608400586

Brownell, B., & Hughes, J. T. (1962). The distribution of plaques in the cerebrum in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, *25*(4), 315–320. doi: 10.1136/jnnp.25.4.315

Bryden, M. P., McManus, I. C., & Bulman-Fleming, M. B. (1994). Evaluating the empirical support for the Geschwind-Behan-Galaburda model of cerebral lateralization. *Brain and Cognition*, *26*(2), 103–167.

Burns, M. K., Davidson, K., Zaslofsky, A. F., Parker, D. C., & Maki, K. E. (2017). The Relationship Between Acquisition Rate for Words and Working Memory, Short-Term Memory, and Reading Skills: Aptitude-by-Treatment or Skill-by-Treatment Interaction?: *Assessment for Effective Intervention*. doi: 10.1177/1534508417730822

Campanholo, K. R., Conforto, A. B., Rimkus, C. M., & Miotto, E. C. (2015). Cognitive and Functional Impairment in Stroke Survivors with Basilar Artery Occlusive Disease. *Behavioural Neurology*, *2015*. doi: 10.1155/2015/971514

Catani, M., Allin, M. P. G., Husain, M., Pugliese, L., Mesulam, M. M., Murray, R. M., & Jones, D. K. (2007). Symmetries in human brain language pathways correlate with verbal recall. *Proceedings of the National Academy of Sciences*, *104*(43), 17163–17168. doi: 10.1073/pnas.0702116104

Charvet, L. E., Dobbs, B., Shaw, M. T., Bikson, M., Datta, A., & Krupp, L. B. (2018). Remotely supervised transcranial direct current stimulation for the treatment of fatigue in multiple sclerosis: Results from a randomized, sham-controlled trial. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *24*(13), 1760–1769. doi: 10.1177/1352458517732842

Chatagny, P., Badoud, S., Kaeser, M., Gindrat, A.-D., Savidan, J., Fregosi, M., … Rouiller, E. M. (2013). Distinction between hand dominance and hand preference in primates: A behavioral investigation of manual dexterity in nonhuman primates (macaques) and human subjects. *Brain and Behavior*, *3*(5), 575–595. doi: 10.1002/brb3.160

Chaves, A. R., Wallack, E. M., Kelly, L. P., Pretty, R. W., Wiseman, H. D., Chen, A., … Ploughman, M. (2019). Asymmetry of Brain Excitability: A New Biomarker that Predicts Objective and Subjective Symptoms in Multiple Sclerosis. *Behavioural Brain Research*, *359*, 281–291. doi: 10.1016/j.bbr.2018.11.005

Chi, Y.-Y., Glueck, D. H., & Muller, K. E. (2019). Power and Sample Size for Fixed-Effects Inference in Reversible Linear Mixed Models. *The American Statistician*, *73*(4), 350–359. doi: 10.1080/00031305.2017.1415972

Chiaravalloti, N. D., & DeLuca, J. (2008). Cognitive impairment in multiple sclerosis. *The Lancet Neurology*, *7*(12), 1139–1151. doi: 10.1016/S1474-4422(08)70259-X

Constant, M., & Mellet, E. (2018). The Impact of Handedness, Sex, and Cognitive Abilities on Left–Right Discrimination: A Behavioral Study. *Frontiers in Psychology*, *9*. doi: 10.3389/fpsyg.2018.00405

Costanzo, E. Y., Villarreal, M., Drucaroff, L. J., Ortiz-Villafañe, M., Castro, M. N., Goldschmidt, M., … Guinjoan, S. M. (2015). Hemispheric specialization in affective responses, cerebral dominance for language, and handedness: Lateralization of emotion, language, and dexterity. *Behavioural Brain Research*, *288*, 11–19. doi: 10.1016/j.bbr.2015.04.006

Dargahi, N., Katsara, M., Tselios, T., Androutsou, M.-E., de Courten, M., Matsoukas, J., & Apostolopoulos, V. (2017). Multiple Sclerosis: Immunopathology and Treatment Update. *Brain Sciences*, *7*(7). doi: 10.3390/brainsci7070078

Daseking, M., Petermann, F., & Waldmann, H.-C. (2017). Sex differences in cognitive abilities: Analyses for the German WAIS-IV. *Personality and Individual Differences*, *114*, 145–150. doi: 10.1016/j.paid.2017.04.003

DeLacoste-Utamsing, C., & Holloway, R. L. (1982). Sexual dimorphism in the human corpus callosum. *Science*, *216*(4553), 1431–1432. doi: 10.1126/science.7089533

Delis, D.C., Kramer, J.H., Kaplan, E., & Ober, B.A. (2000). California Verbal Learning Test manual: Second edition, Adult version. San Antonio, TX: Psychological Corporation.

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

Diamond, B. J., Deluca, J., Kim, H., & Kelley, S. M. (1997). The question of disproportionate impairments in visual and auditory information processing in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *19*(1), 34–42. doi: 10.1080/01688639708403834

Dineen, R. A., Vilisaar, J., Hlinka, J., Bradshaw, C. M., Morgan, P. S., Constantinescu, C. S., & Auer, D. P. (2009). Disconnection as a mechanism for cognitive dysfunction in multiple sclerosis. *Brain*, *132*(1), 239–249. doi: 10.1093/brain/awn275

Dunst, B., Benedek, M., Koschutnig, K., Jauk, E., & Neubauer, A. C. (2014). Sex differences in the IQ-white matter microstructure relationship: A DTI study. *Brain and Cognition*, *91*, 71–78. doi: 10.1016/j.bandc.2014.08.006

Elliott, D., & Roy, E. A. (1996). *Manual Asymmetries in Motor Performance*. CRC Press.

Ernst, T., Chang, L., Jovicich, J., Ames, N., & Arnold, S. (2002). Abnormal brain activation on functional MRI in cognitively asymptomatic HIV patients. *Neurology*, *59*(9), 1343–1349. doi: 10.1212/01.wnl.0000031811.45569.b0

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41*(4), 1149–1160. doi: 10.3758/BRM.41.4.1149

Feys, P., Lamers, I., Francis, G., Benedict, R., Phillips, G., LaRocca, N., … Consortium, M. S. O. A. (2017). The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *23*(5), 711. doi: 10.1177/1352458517690824

Filippi, M., Martino, G., Mammi, S., Campi, A., Comi, G., & Grimaldi, L. M. (1995a). Does hemispheric dominance influence brain lesion distribution in multiple sclerosis? *Journal of Neurology, Neurosurgery, and Psychiatry*, *58*(6), 748–749. doi: 10.1136/jnnp.58.6.748

Filippi, M., Rocca, M. A., Benedict, R. H. B., DeLuca, J., Geurts, J. J. G., Rombouts, S. A. R. B., … Comi, G. (2010). The contribution of MRI in assessing cognitive impairment in multiple sclerosis. *Neurology*, *75*(23), 2121–2128. doi: 10.1212/WNL.0b013e318200d768

Filippi, Massimo, & Rocca, M. A. (2013a). Linking disability and spinal cord imaging outcomes in MS. *Nature Reviews Neurology*, *9*(4), 189–190. doi: 10.1038/nrneurol.2013.40

Fink, B., Manning, J. T., Neave, N., & Tan, U. (2004). Second to fourth digit ratio and hand skill in Austrian children. *Biological Psychology*, *67*(3), 375–384. doi: 10.1016/j.biopsycho.2004.03.012

Foong, J., Rozewicz, L., Quaghebeur, G., Davie, C. A., Kartsounis, L. D., Thompson, A. J., … Ron, M. A. (1997). Executive function in multiple sclerosis. The role of frontal lobe pathology. *Brain: A Journal of Neurology*, *120 (Pt 1)*, 15–26. doi: 10.1093/brain/120.1.15

Forn, C., Barros-Loscertales, A., Escudero, J., Benlloch, V., Campos, S., Antònia Parcet, M., & Avila, C. (2007). Compensatory activations in patients with multiple sclerosis during preserved performance on the auditory N-back task. *Human Brain Mapping*, *28*(5), 424–430. doi: 10.1002/hbm.20284

Fritschi, L., Divitini, M., Talbot-Smith, A., & Knuiman, M. (2007). Left-handedness and risk of breast cancer. *British Journal of Cancer*, *97*(5), 686–687. doi: 10.1038/sj.bjc.6603920

Fritz, N. E., Newsome, S. D., Eloyan, A., Marasigan, R. E. R., Calabresi, P. A., & Zackowski, K. M. (2015). Longitudinal relationships among posturography and gait measures in multiple sclerosis. *Neurology*, *84*(20), 2048–2056. doi: 10.1212/WNL.0000000000001580

Fulton, J. C., Grossman, R. I., Udupa, J., Mannon, L. J., Grossman, M., Wei, L., … Kolson, D. L. (1999). MR Lesion Load and Cognitive Function in Patients with Relapsing-Remitting Multiple Sclerosis. *American Journal of Neuroradiology*, *20*(10), 1951–1955.

Gardener, H., Munger, K., Chitnis, T., Spiegelman, D., & Ascherio, A. (2009). The relationship between handedness and risk of multiple sclerosis. *Multiple Sclerosis Journal*, *15*(5), 587–592. doi: 10.1177/1352458509102622

Geschwind, N. (1985). Cerebral Lateralization: Biological Mechanisms, Associations, and Pathology: I. A Hypothesis and a Program for Research. *Archives of Neurology*, *42*(5), 428. doi: 10.1001/archneur.1985.04060050026008

Geschwind, N., & Galaburda, A. M. (1985). Cerebral Lateralization: Biological Mechanisms, Associations, and Pathology: I. A Hypothesis and a Program for Research. *Archives of Neurology*, *42*(5), 428–459. doi: 10.1001/archneur.1985.04060050026008

Geschwind, N., & Galaburda, A. M. (1985). Cerebral Lateralization: Biological Mechanisms, Associations, and Pathology: II. A Hypothesis and a Program for Research. *Archives of Neurology*, *42*(6), 521–552. doi: 10.1001/archneur.1985.04060060019009

Gilbert, A. N., & Wysocki, C. J. (1992). Hand preference and age in the United States. *Neuropsychologia*, *30*(7), 601–608. doi: 10.1016/0028-3932(92)90065-t

Giza, C. C., Prins, M. L., Hovda, D. A., Herschman, H. R., & Feldman, J. D. (2002). Genes preferentially induced by depolarization after concussive brain injury: Effects of age and injury severity. *Journal of Neurotrauma*, *19*(4), 387–402. doi: 10.1089/08977150252932352

Gläscher, J., Tranel, D., Paul, L. K., Rudrauf, D., Rorden, C., Hornaday, A., … Adolphs, R. (2009). Lesion Mapping of Cognitive Abilities Linked to Intelligence. *Neuron*, *61*(5), 681–691. doi: 10.1016/j.neuron.2009.01.026

Glover, V., O'Connor, T. G., Heron, J., & Golding, J. (2004). Antenatal maternal anxiety is linked with atypical handedness in the child. *Early Human Development*, *79*(2), 107–118. doi: 10.1016/j.earlhumdev.2004.04.012

Gold, S. M., Schulz, H., Mönch, A., Schulz, K.-H., & Heesen, C. (2003). Cognitive impairment in multiple sclerosis does not affect reliability and validity of self-report health measures. *Multiple Sclerosis Journal*, *9*(4), 404–410. doi: 10.1191/1352458503ms927oa

Good, C. D., Johnsrude, I., Ashburner, J., Henson, R. N. A., Friston, K. J., & Frackowiak, R. S. J. (2001). Cerebral Asymmetry and the Effects of Sex and Handedness on Brain Structure: A Voxel-Based Morphometric Analysis of 465 Normal Adult Human Brains. *NeuroImage*, *14*(3), 685–700. doi: 10.1006/nimg.2001.0857

Goodkin, D. E., Hertsguard, D., & Seminary, J. (1988). Upper extremity function in multiple sclerosis: Improving assessment sensitivity with box-and-block and nine-hole peg tests. *Archives of Physical Medicine and Rehabilitation*, *69*(10), 850–854. doi: 10.5555/uri:pii:0003999388900093

Grant, I., McDonald, W. I., Trimble, M. R., Smith, E., & Reed, R. (1984). Deficient learning and memory in early and middle phases of multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry*, *47*(3), 250–255. doi: 10.1136/jnnp.47.3.250

Guimarães, J., & Sá, M. J. (2012). Cognitive Dysfunction in Multiple Sclerosis. *Frontiers in Neurology*, *3*. doi: 10.3389/fneur.2012.00074

Gur, R. C., Packer, I. K., Hungerbuhler, J. P., Reivich, M., Obrist, W. D., Amarnek, W. S., & Sackeim, H. A. (1980). Differences in the distribution of gray and white matter in human cerebral hemispheres. *Science*, *207*(4436), 1226–1228. doi: 10.1126/science.7355287

Gur, R. C., Alsop, D., Glahn, D., Petty, R., Swanson, C. L., Maldjian, J. A., … Gur, R. E. (2000). An fMRI Study of Sex Differences in Regional Activation to a Verbal and a Spatial Task. *Brain and Language*, *74*(2), 157–170. doi: 10.1006/brln.2000.2325

Gutteling, B. M., de Weerth, C., & Buitelaar, J. K. (2007). Prenatal Stress and Mixed-Handedness. *Pediatric Research*, *62*(5), 586–590. doi: 10.1203/PDR.0b013e3181558678

Hackmack, K., Weygandt, M., Wuerfel, J., Pfueller, C. F., Bellmann-Strobl, J., Paul, F., & Haynes, J.-D. (2012). Can we overcome the 'clinico-radiological paradox' in multiple sclerosis? *Journal of Neurology*, *259*(10), 2151–2160. doi: 10.1007/s00415-012-6475-9

Harasty, J., Double, K. L., Halliday, G. M., Kril, J. J., & McRitchie, D. A. (1997). Language-Associated Cortical Regions Are Proportionally Larger in the Female Brain. *Archives of Neurology*, *54*(2), 171–176. doi: 10.1001/archneur.1997.00550140045011

Hemmer, B., Nessler, S., Zhou, D., Kieseier, B., & Hartung, H.-P. (2006). Immunopathogenesis and immunotherapy of multiple sclerosis. *Nature Clinical Practice. Neurology*, *2*(4), 201–211. doi: 10.1038/ncpneuro0154

Higginson, C. I., Arnett, P. A., & Voss, W. D. (2000). The Ecological Validity of Clinical Tests of Memory and Attention in Multiple Sclerosis. *Archives of Clinical Neuropsychology*, *15*(3), 185–204. doi: 10.1016/S0887-6177(99)00004-9

Hopkins, W. D., Dunham, L., Cantalupo, C., & Taglialatela, J. (2007). The Association between Handedness, Brain Asymmetries, and Corpus Callosum Size in Chimpanzees (Pan troglodytes). *Cerebral Cortex (New York, N.Y. : 1991)*, *17*(8), 1757–1765. doi: 10.1093/cercor/bhl086

Howells, H., Thiebaut de Schotten, M., Dell'Acqua, F., Beyh, A., Zappalà, G., Leslie, A., … Catani, M. (2018). Frontoparietal Tracts Linked to Lateralized Hand Preference and Manual Specialization. *Cerebral Cortex (New York, NY)*, *28*(7), 2482–2494. doi: 10.1093/cercor/bhy040

Inglese, M., & Petracca, M. (2015). Therapeutic strategies in multiple sclerosis: A focus on neuroprotection and repair and relevance to schizophrenia. *Schizophrenia Research*, *161*(1), 94–101. doi: 10.1016/j.schres.2014.04.040

Izquierdo, G., Campoy, F., Fajardo, J. M., Quesada, M. A., Navarro, G., Mesa, A., … Martínez-Parra, C. (1991). [Correlation between magnetic resonance and disability scales (EDSS and ISS) in multiple sclerosis]. *Neurologia (Barcelona, Spain)*, *6*(6), 198–202.

Jäncke, L., Schlaug, G., Huang, Y., & Steinmetz, H. (1994). Asymmetry of the planum parietale. *Neuroreport*, *5*(9), 1161–1163.

Johansson, G. M., & Häger, C. K. (2019). A modified standardized nine hole peg test for valid and reliable kinematic assessment of dexterity post-stroke. *Journal of NeuroEngineering and Rehabilitation*, *16*(1), 8. doi: 10.1186/s12984-019-0479-y

Johnson, S. C., Saykin, A. J., Flashman, L. A., McAllister, T. W., & Sparling, M. B. (2001a). Brain activation on fMRI and verbal memory ability: Functional neuroanatomic correlates of CVLT performance. *Journal of the International Neuropsychological Society*, *7*(1), 55–62. doi: 10.1017/S135561770171106X

Johnson, W., Carothers, A., & Deary, I. J. (2008). Sex Differences in Variability in General Intelligence: A New Look at the Old Question. *Perspectives on Psychological Science*, *3*(6), 518–531. doi: 10.1111/j.1745-6924.2008.00096.x

Jonides, J., Lewis, R. L., Nee, D. E., Lustig, C. A., Berman, M. G., & Moore, K. S. (2008). The Mind and Brain of Short-Term Memory. *Annual Review of Psychology*, *59*(1), 193–224. doi: 10.1146/annurev.psych.59.103006.093615

Kanaan, R. A., Allin, M., Picchioni, M., Barker, G. J., Daly, E., Shergill, S. S., … McGuire, P. K. (2012). Gender Differences in White Matter Microstructure. *PLOS ONE*, *7*(6), e38272. doi: 10.1371/journal.pone.0038272

Katsara, M., Matsoukas, J., Deraos, G., & Apostolopoulos, V. (2008). Towards immunotherapeutic drugs and vaccines against multiple sclerosis. *Acta Biochimica Et Biophysica Sinica*, *40*(7), 636–642. doi: 10.1111/j.1745-7270.2008.00444.x

Kawata, M. (1995). Roles of steroid hormones and their receptors in structural organization in the nervous system. *Neuroscience Research*, *24*(1), 1–46. doi: 10.1016/0168-0102(96)81278-8

Kim, H., Yi, S., Son, E. I., & Kim, J. (20031103). Differential Effects of Left Versus Right Mesial Temporal Lobe Epilepsy on Wechsler Intelligence Factors. *Neuropsychology*, *17*(4), 556. doi: 10.1037/0894-4105.17.4.556

Koch, G., Rossi, S., Prosperetti, C., Codecà, C., Monteleone, F., Petrosini, L., … Centonze, D. (2008). Improvement of hand dexterity following motor cortex rTMS in multiple sclerosis patients with cerebellar impairment. *Multiple Sclerosis Journal*, *14*(7), 995–998. doi: 10.1177/1352458508088710

Kouvatsou, Z., Masoura, E., Kiosseoglou, G., & Kimiskidis, V. K. (2019). Working memory profiles of patients with multiple sclerosis: Where does the impairment lie? *Journal of Clinical and Experimental Neuropsychology*, *0*(0), 1–13. doi: 10.1080/13803395.2019.1626805

Kurtzke, J. F. (1984). Disability Rating Scales in Multiple Sclerosis. *Annals of the New York Academy of Sciences*, *436*(1), 347–360. doi: 10.1111/j.1749-6632.1984.tb14805.x

Kutzelnigg, A., Faber-Rod, J. C., Bauer, J., Lucchinetti, C. F., Sorensen, P. S., Laursen, H., … Lassmann, H. (2007). Widespread Demyelination in the Cerebellar Cortex in Multiple Sclerosis. *Brain Pathology*, *17*(1), 38–44. doi: 10.1111/j.1750-3639.2006.00041.x

Langdon, D., Amato, M., Boringa, J., Brochet, B., Foley, F., Fredrikson, S., … Benedict, R. (2012). Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *18*(6), 891–898. doi: 10.1177/1352458511431076

Lansdell, H. (1969). Verbal and nonverbal factors in right-hemisphere speech: Relation to early neurological history. *Journal of Comparative and Physiological Psychology*, *69*(4, Pt.1), 734–738. doi: 10.1037/h0028306

Lee, M., Reddy, H., Johansen-Berg, H., Pendlebury, S., Jenkinson, M., Smith, S., … Matthews, P. M. (2000). The motor cortex shows adaptive functional changes to brain injury from multiple sclerosis. *Annals of Neurology*, *47*(5), 606–613. doi: 10.1002/1531-8249(200005)47:5<606::AID-ANA8>3.0.CO;2-L

Lengen, C., Regard, M., Joller, H., Landis, T., & Lalive, P. (2009). Anomalous brain dominance and the immune system: Do left-handers have specific immunological patterns? *Brain and Cognition*, *69*(1), 188–193. doi: 10.1016/j.bandc.2008.07.008

Leonard, C. M., Towler, S., Welcome, S., Halderman, L. K., Otto, R., Eckert, M. A., & Chiarello, C. (2008). Size Matters: Cerebral Volume Influences Sex Differences in Neuroanatomy. *Cerebral Cortex*, *18*(12), 2920–2931. doi: 10.1093/cercor/bhn052

Litvan, I., Grafman, J., Vendrell, P., Martinez, J. M., Junqué, C., Vendrell, J. M., & Barraquer-Bordas, J. L. (1988). Multiple memory deficits in patients with multiple sclerosis. Exploring the working memory system. *Archives of Neurology*, *45*(6), 607–610. doi: 10.1001/archneur.1988.00520300025012

Long-Term Treatments for Multiple Sclerosis | MSAA. (2020, May). Retrieved May 17, 2020, from https://mymsaa.org/ms-information/treatments/long-term/

Loring, D. W., & Bauer, R. M. (2010). Testing the limits. *Neurology*, *74*(8), 685–690. doi: 10.1212/WNL.0b013e3181d0cd12

Loring, D. W., Strauss, E., Hermann, B. P., Barr, W. B., Perrine, K., Trenerry, M. R., … Bowden, S. C. (2008). Differential neuropsychological test sensitivity to left temporal lobe epilepsy. *Journal of the International Neuropsychological Society: JINS*, *14*(3), 394–400. doi: 10.1017/S1355617708080582

Luders, E., Narr, K., Zaidel, E., Thompson, P., & Toga, A. (2006). Gender effects on callosal thickness in scaled and unscaled space. *Neuroreport*, *17*(11), 1103–1106. doi: 10.1097/01.wnr.0000227987.77304.cc

Maccotta, L., Buckner, R. L., Gilliam, F. G., & Ojemann, J. G. (2007). Changing Frontal Contributions to Memory Before and After Medial Temporal Lobectomy. *Cerebral Cortex*, *17*(2), 443–456. doi: 10.1093/cercor/bhj161

Mainero, C., Caramia, F., Pozzilli, C., Pisani, A., Pestalozza, I., Borriello, G., … Pantano, P. (2004). FMRI evidence of brain reorganization during attention and memory tasks in multiple sclerosis. *NeuroImage*, *21*(3), 858–867. doi: 10.1016/j.neuroimage.2003.10.004

Manning, J. t., Trivers, R. l., Thornhill, R., & Singh, D. (2000). The 2nd:4th digit ratio and asymmetry of hand performance in Jamaican children. *Laterality*, *5*(2), 121–132. doi: 10.1080/135765000396744

Marsh, G. G. (1980). Disability and intellectual function in multiple sclerosis patients. *The Journal of Nervous and Mental Disease*, *168*(12), 758–762.

Marx, J. (1982). Autoimmunity in left-handers. Left-handedness may be associated with an increased risk of autoimmune disease. Is testosterone the link between the two? *Science*, *217*(4555), 141–142. doi: 10.1126/science.7089548

Mascie-Taylor, C. G. (1980). Hand preference and components of I.Q. *Annals of Human Biology*, *7*(3), 235–248.

Mathiowetz, V., Weber, K., Kashman, N., & Volland, G. (1985). Adult Norms for the Nine Hole Peg Test of Finger Dexterity. *The Occupational Therapy Journal of Research*, *5*(1), 24–38. doi: 10.1177/153944928500500102

Matias-Guiu, J. A., Pytel, V., Cabrera-Martín, M. N., Cortés-Martínez, A., Moreno-Ramos, T., Carreras, J. L., & Matias-Guiu, J. (2019). Amyloid PET in multiple sclerosis predicts cognitive decline at 18 months (S49.003). *Neurology*, *92*(15 Supplement), S49.003.

McCrimmon, A. W., & Smith, A. D. (2013). Review of Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II). *Journal of Psychoeducational Assessment*, *31*(3), 337–341. doi: 10.1177/0734282912467756

McHenry L C, Merory J, Bass E, Stump D A, Williams R, Witcofski R, … Toole J F. (1978). Xenon-133 inhalation method for regional cerebral blood flow measurements: Normal values and test-retest results. *Stroke*, *9*(4), 396–399. doi: 10.1161/01.STR.9.4.396

McManus, I. C., Davison, A., & Armour, J. A. L. (2013). The Evolution of Human Handedness. *Annals of the New York Academy of Sciences*, *1288*(1), 48–58. doi: 10.1111/nyas.12102

Medland, S. E., Duffy, D. L., Wright, M. J., Geffen, G. M., Hay, D. A., Levy, F., … Boomsma, D. I. (2009). Genetic influences on handedness: Data from 25,732 Australian and Dutch twin families. *Neuropsychologia*, *47*(2), 330–337. doi: 10.1016/j.neuropsychologia.2008.09.005

Messina, S., & Patti, F. (2014). Gray Matters in Multiple Sclerosis: Cognitive Impairment and Structural MRI [Research article]. doi: 10.1155/2014/609694

Minagar, A., & Alexander, J. S. (2003). Blood-brain barrier disruption in multiple sclerosis. *Multiple Sclerosis (Houndmills, Basingstoke, England)*, *9*(6), 540–549. doi: 10.1191/1352458503ms965oa

Montalban, X., Sastre-Garriga, J., Filippi, M., Khaleeli, Z., Téllez, N., Vellinga, M., … Thompson, A. (2009). Primary progressive multiple sclerosis diagnostic criteria: A reappraisal. *Multiple Sclerosis Journal*, *15*(12), 1459–1465. doi: 10.1177/1352458509348422

Morgen, K., Sammer, G., Courtney, S. M., Wolters, T., Melchior, H., Blecker, C. R., … Vaitl, D. (2006). Evidence for a direct association between cortical atrophy and cognitive impairment in relapsing–remitting MS. *NeuroImage*, *30*(3), 891–898. doi: 10.1016/j.neuroimage.2005.10.032

Mosch, S. C., Max, J. E., & Tranel, D. (2005). A matched lesion analysis of childhood versus adult-onset brain injury due to unilateral stroke: Another perspective on neural plasticity and recovery of social functioning. *Cognitive and Behavioral Neurology: Official Journal of the Society for Behavioral and Cognitive Neurology*, *18*(1), 5–17.

Mueller, J. H., Grove, T. R., & Thompson, W. B. (1993a). Test anxiety and handedness. *Bulletin of the Psychonomic Society*, *31*(5), 461–464. doi: 10.3758/BF03334963

Müller, M., Esser, R., Kötter, K., Voss, J., Müller, A., & Stellmes, P. (2013). Third ventricular enlargement in early stages of multiple sclerosis is a predictor of motor and neuropsychological deficits: A cross-sectional study. *BMJ Open*, *3*(9). doi: 10.1136/bmjopen-2013-003582

Nair, R. das, Martin, K.-J., & Lincoln, N. B. (2016). Memory rehabilitation for people with multiple sclerosis. *Cochrane Database of Systematic Reviews*, (3). doi: 10.1002/14651858.CD008754.pub3

Narrett, C. M. (1984). Test Review: Kaufman Assessment Battery for Children (K-ABC). *The Reading Teacher*, *37*(7), 626–631.

Nasios, G., Messinis, L., Dardiotis, E., & Papathanasopoulos, P. (2018). Repetitive Transcranial Magnetic Stimulation, Cognition, and Multiple Sclerosis: An Overview [Research article]. doi: 10.1155/2018/8584653

Nathalie, E. R., Diana, O. F., Amaya, S., Marc, D., Lucien, R., Marie-Pierre, C., & Serge, B. (2014). *Short-Term Memory Impairment Sparing the Central Executive in Relapsing- Remitting Multiple Sclerosis?* doi: 10.4172/2155-9562.1000202

Ng, W. H. A., Chan, Y. L., Au, K. S. A., Yeung, K. W. D., Kwan, T. F., & To, C. Y. (2005). Morphometry of the corpus callosum in Chinese children: Relationship with gender and academic performance. *Pediatric Radiology*, *35*(6), 565–571. doi: 10.1007/s00247-004-1336-z

Nocentini, U., Bozzali, M., Spanò, B., Cercignani, M., Serra, L., Basile, B., … De Luca, J. (2014). Exploration of the relationships between regional grey matter atrophy and cognition in multiple sclerosis. *Brain Imaging and Behavior*, *8*(3), 378–386. doi: 10.1007/s11682-012-9170-7

Nowak, D. A., Grefkes, C., Ameli, M., & Fink, G. R. (2009). Interhemispheric competition after stroke: Brain stimulation to enhance recovery of function of the affected hand. *Neurorehabilitation and Neural Repair*, *23*(7), 641–656. doi: 10.1177/1545968309336661

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113. doi: 10.1016/0028-3932(71)90067-4

Owens, M., & Yost, L. (2019). The Effects of Handedness on Written and Verbal Language Memory. *COLA Research and Creativity Conference*. Retrieved from https://mds.marshall.edu/colaconf/2019/day1/12

Oxford Grice, K., Vogel, K. A., Le, V., Mitchell, A., Muniz, S., & Vollmer, M. A. (2003). Adult norms for a commercially available Nine Hole Peg Test for finger dexterity. *The American Journal of Occupational Therapy: Official Publication of the American Occupational Therapy Association*, *57*(5), 570–573. doi: 10.5014/ajot.57.5.570

Piras, M. R., Magnano, I., Canu, E. D. G., Paulus, K. S., Satta, W. M., Soddu, A., … Aiello, I. (2003). Longitudinal study of cognitive dysfunction in multiple sclerosis: Neuropsychological, neuroradiological, and neurophysiological findings. *Journal of Neurology, Neurosurgery & Psychiatry*, *74*(7), 878–885. doi: 10.1136/jnnp.74.7.878

Planton, M., Peiffer, S., Albucher, J. F., Barbeau, E. J., Tardy, J., Pastor, J., … Pariente, J. (2012). Neuropsychological outcome after a first symptomatic ischaemic stroke with 'good recovery.' *European Journal of Neurology*, *19*(2), 212–219. doi: 10.1111/j.1468-1331.2011.03450.x

Portnoy, J. G., Archetti, R. A., Stimmel, M. B., & Foley, F. W. (2016, June). *Functional systems organization of multiple sclerosis living disability scale items*. Presented at the Consortium of Multiple Sclerosis Centers, National Harbor, MD.

Powell, J. L., Kemp, G. J., & García-Finaña, M. (2012). Association between language and spatial laterality and cognitive ability: An fMRI study. *NeuroImage*, *59*(2), 1818–1829. doi: 10.1016/j.neuroimage.2011.08.040

Pozzilli, C., Tomassini, V., Marinelli, F., Paolillo, A., Gasperini, C., & Bastianello, S. (2003). 'Gender gap' in multiple sclerosis: Magnetic resonance imaging evidence. *European Journal of Neurology*, *10*(1), 95–97. doi: 10.1046/j.1468-1331.2003.00519.x

Preziosa, P., Pagani, E., Mesaros, S., Riccitelli, G. C., Dackovic, J., Drulovic, J., … Rocca, M. A. (2017). Progression of regional atrophy in the left hemisphere contributes to clinical and cognitive

deterioration in multiple sclerosis: A 5-year study. *Human Brain Mapping*, *38*(11), 5648–5665. doi: 10.1002/hbm.23755

Propper, R. E., Patel, N., Christman, S. D., & Carlei, C. (2017). Superior episodic memory in inconsistent-handers: A replication and extension using fNIRS. *Memory*, *25*(10), 1390–1395. doi: 10.1080/09658211.2017.1309051

Provinciali, L., Ceravolo, M. G., Bartolini, M., Logullo, F., & Danni, M. (1999). A multidimensional assessment of multiple sclerosis: Relationships between disability domains. *Acta Neurologica Scandinavica*, *100*(3), 156–162. doi: 10.1111/j.1600-0404.1999.tb00731.x

Rahn, K., Slusher, B., & Kaplin, A. (2012). Cognitive Impairment in Multiple Sclerosis: A Forgotten Disability Remembered. *Cerebrum: The Dana Forum on Brain Science*, *2012*. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3574761/

Ranjeva, J.-P., Audoin, B., Au Duong, M. V., Confort-Gouny, S., Malikova, I., Viout, P., … Cozzone, P. J. (2006). Structural and functional surrogates of cognitive impairment at the very early stage of multiple sclerosis. *Journal of the Neurological Sciences*, *245*(1), 161–167. doi: 10.1016/j.jns.2005.09.019

Rao, S. M., Leo, G. J., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis.: I. Frequency, patterns, and prediction. *Neurology*, *41*(5), 685–691. doi: 10.1212/WNL.41.5.685

Rao, S., Grafman, J., DiGiulio, D., Mittenberg, W., Bernardin, L., Leo, G., … Unverzagt, F. (1993). Memory Dysfunction in Multiple Sclerosis: Its Relation to Working Memory, Semantic Encoding, and Implicit Learning. *Neuropsychology*, 364–374. doi: 10.1037//0894-4105.7.3.364

Rao, S. M., Leo, G. J., Ellington, L., Nauertz, T., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology*, *41*(5), 692–696.

Rao, S. M., Leo, G. J., Haughton, V. M., St Aubin-Faubert, P., & Bernardin, L. (1989). Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. *Neurology*, *39*(2 Pt 1), 161–166. doi: 10.1212/wnl.39.2.161

Rasmussen, T., & Milner, B. (1977). The role of early left-brain injury in determining lateralization of cerebral speech functions. *Annals of the New York Academy of Sciences*, *299*, 355–369. doi: 10.1111/j.1749-6632.1977.tb41921.x

Riccitelli, G., Rocca, M. A., Pagani, E., Rodegher, M. E., Rossi, P., Falini, A., … Filippi, M. (2011). Cognitive impairment in multiple sclerosis is associated to different patterns of gray matter atrophy according to clinical phenotype. *Human Brain Mapping*, *32*(10), 1535–1543. doi: 10.1002/hbm.21125

Rocca, M. A., Valsasina, P., Damjanovic, D., Horsfield, M. A., Mesaros, S., Stosic-Opincal, T., … Filippi, M. (2013). Voxel-wise mapping of cervical cord damage in multiple sclerosis patients with different clinical phenotypes. *Journal of Neurology, Neurosurgery & Psychiatry*, *84*(1), 35–41. doi: 10.1136/jnnp-2012-303821

Rodriguez, A., & Waldenström, U. (2008). Fetal origins of child non-right-handedness and mental health. *Journal of Child Psychology and Psychiatry*, *49*(9), 967–976. doi: 10.1111/j.1469-7610.2008.01923.x

Roe, C. M., Mintun, M. A., D'Angelo, G., Xiong, C., Grant, E. A., & Morris, J. C. (2008). Alzheimer disease and cognitive reserve: Variation of education effect with carbon 11-labeled Pittsburgh Compound B uptake. *Archives of Neurology*, *65*(11), 1467–1471. doi: 10.1001/archneur.65.11.1467

Roosendaal, S. D., Geurts, J. J. G., Vrenken, H., Hulst, H. E., Cover, K. S., Castelijns, J. A., … Barkhof, F. (2009). Regional DTI differences in multiple sclerosis patients. *NeuroImage*, *44*(4), 1397–1403. doi: 10.1016/j.neuroimage.2008.10.026

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

Rovaris, M., Filippi, M., Falautano, M., Minicucci, L., Rocca, M. A., Martinelli, V., & Comi, G. (1998). Relation between MR abnormalities and patterns of cognitive impairment in multiple sclerosis. *Neurology*, *50*(6), 1601–1608. doi: 10.1212/wnl.50.6.1601

Ruchkin, D. S., Grafman, J., Krauss, G. L., Johnson, R., Canoune, H., & Ritter, W. (1994). Event-related brain potential evidence for a verbal working memory deficit in multiple sclerosis. *Brain*, *117*(2), 289–305. doi: 10.1093/brain/117.2.289

Ruiz, R., & Avant, K. (2005). Effects of Maternal Prenatal Stress on Infant Outcomes. *Advances in Nursing Science*, *28*(4), 345–355.

Ryan, J. J., Gontkovsky, S. T., Kreiner, D. S., & Tree, H. A. (2012). Wechsler Adult Intelligence Scale–Fourth Edition performance in relapsing–remitting multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, *34*(6), 571–579. doi: 10.1080/13803395.2012.666229

Rypma, B., Berger, J. S., Genova, H. M., Rebbechi, D., & D'Esposito, M. (2005). Dissociating age-related changes in cognitive strategy and neural efficiency using event-related fMRI. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *41*(4), 582–594.

Sadovnick, A. D., Armstrong, H., Rice, G. P., Bulman, D., Hashimoto, L., Paty, D. W., … Murray, T. J. (1993). A population-based study of multiple sclerosis in twins: Update. *Annals of Neurology*, *33*(3), 281–285. doi: 10.1002/ana.410330309

Sahu, A., Christman, S. D., & Propper, R. E. (2016). The contributions of handedness and working memory to episodic memory. *Memory & Cognition*, *44*(8), 1149–1156. doi: 10.3758/s13421-016-0625-8

Sailer, M., Fischl, B., Salat, D., Tempelmann, C., Schönfeld, M. A., Busa, E., … Dale, A. (2003). Focal thinning of the cerebral cortex in multiple sclerosis. *Brain*, *126*(8), 1734–1744. doi: 10.1093/brain/awg175

Sandman, C. A., Wadhwa, P. D., CHICZ-DeMET, A., Dunkel-Schetter, C., & Porto, M. (1997). Maternal Stress, HPA Activity, and Fetal/Infant Outcomea. *Annals of the New York Academy of Sciences*, *814*(1), 266–275. doi: 10.1111/j.1749-6632.1997.tb46162.x

Sandry, J., Zuppichini, M., Rothberg, J., Valdespino-Hayden, Z., & DeLuca, J. (2019). Poor Encoding and Weak Early Consolidation Underlie Memory Acquisition Deficits in Multiple Sclerosis: Retroactive Interference, Processing Speed, or Working Memory? *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, *34*(2), 162–182. doi: 10.1093/arclin/acy029

Satz, P. (1972). Pathological Left-Handedness: An Explanaory Model. *Cortex*, *8*(2), 121–135. doi: 10.1016/S0010-9452(72)80013-3

Satz, P., Strauss, E., Hunter, M., & Wada, J. (1994). Re-examination of the crowding hypothesis: Effects of age of onset. *Neuropsychology*, *8*(2), 255–262. doi: 10.1037/0894-4105.8.2.255

Savio, S., Hakulinen, U., Ryymin, P., Hagman, S., Dastidar, P., Soimakallio, S., … Eskola, H. (2015). Hemispheric asymmetry measured by texture analysis and diffusion tensor imaging in two multiple sclerosis subtypes. *Acta Radiologica (Stockholm, Sweden: 1987)*, *56*(7), 844–851. doi: 10.1177/0284185114539323

Scharoun, S. M., & Bryden, P. J. (2014). Hand preference, performance abilities, and hand selection in children. *Frontiers in Psychology*, *5*. doi: 10.3389/fpsyg.2014.00082

Schmidt, S. L., Carvaho, A. L. N., & Simoes, E. N. (2017). Effect of handedness on auditory attentional performance in ADHD students. *Neuropsychiatric Disease and Treatment*, *13*, 2921–2924. doi: 10.2147/NDT.S149454

Schouten, E. A., Schiemanck, S. K., Brand, N., & Post, M. W. M. (2009). Long-Term Deficits in Episodic Memory after Ischemic Stroke: Evaluation and Prediction of Verbal and Visual Memory Performance Based on Lesion Characteristics. *Journal of Stroke and Cerebrovascular Diseases*, *18*(2), 128–138. doi: 10.1016/j.jstrokecerebrovasdis.2008.09.017

Schulz, D., Kopp, B., Kunkel, A., & Faiss, J. H. (2006). Cognition in the early stage of multiple sclerosis. *Journal of Neurology*, *253*(8), 1002–1010. doi: 10.1007/s00415-006-0145-8

Searleman, A., & Fugagli, A. K. (1987). Suspected autoimmune disorders and left-handedness: Evidence from individuals with diabetes. Crohn's disease and ulcerative colitis. *Neuropsychologia*, *25*(2), 367–374. doi: 10.1016/0028-3932(87)90025-x

Severijns, D., Lamers, I., Kerkhofs, L., & Feys, P. (2015, February). Hand Grip Fatigability in Persons with Multiple Sclerosis According to Hand Dominance and Disease Progression [Text]. doi: info:doi/10.2340/16501977-1897

Shirani, A., Cross, A. H., & Naismith, R. T. (2019). The association between handedness and clinicodemographic characteristics in people with multiple sclerosis: A brief report. *Multiple Sclerosis Journal - Experimental, Translational and Clinical*, *5*(1). doi: 10.1177/2055217319832031

Silva, M. A. (2008). *Development of the WAIS-III: A Brief Overview, History, and Description*. 20.

Simpson, M., & Macdonell, R. (2015). The use of transcranial magnetic stimulation in diagnosis, prognostication and treatment evaluation in multiple sclerosis. *Multiple Sclerosis and Related Disorders*, *4*(5), 430–436. doi: 10.1016/j.msard.2015.06.014

Slater, R. J., LaRocca, N. G., & Scheinberg, L. C. (1984). Development and Testing of a Minimal Record of Disability in Multiple Sclerosisa. *Annals of the New York Academy of Sciences*, *436*(1), 453–468. doi: 10.1111/j.1749-6632.1984.tb14818.x

Snowden Md. (2004). *The WASI (TM) as a screening tool for counselors in the referral decision for a neuropsychological evaluation.* Retrieved from https://www.elibrary.ru/item.asp?id=8891418

Sospedra, M., & Martin, R. (2005). Immunology of multiple sclerosis. *Annual Review of Immunology*, *23*, 683–747. doi: 10.1146/annurev.immunol.23.021704.115707

Speedie, L. J., & Heilman, K. M. (1983). Anterograde Memory Deficits for Visuospatial Material After Infarction of the Right Thalamus. *Archives of Neurology*, *40*(3), 183–186. doi: 10.1001/archneur.1983.04050030077017

Sperling, R. A., Guttmann, C. R. G., Hohol, M. J., Warfield, S. K., Jakab, M., Parente, M., … Weiner, H. L. (2001). Regional Magnetic Resonance Imaging Lesion Burden and Cognitive Function in Multiple

Sclerosis: A Longitudinal Study. *Archives of Neurology*, *58*(1), 115–121. doi: 10.1001/archneur.58.1.115

Springer S. D., Deutsch G. (1998). *Left Brain, Right Brain: Perspectives from Cognitive Neuroscience* (5th edition). New York: W.H. Freeman.

Steinman, L. (1996). Multiple Sclerosis: A Coordinated Immunological Attack against Myelin in the Central Nervous System. *Cell*: *85*(3), 299–302.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society: JINS*, *8*(3), 448–460.

Sumowski, J. F., Wylie, G. R., DeLuca, J., & Chiaravalloti, N. (2010). Intellectual enrichment is linked to cerebral efficiency in multiple sclerosis: Functional magnetic resonance imaging evidence for cognitive reserve. *Brain*, *133*(2), 362–374. doi: 10.1093/brain/awp307

Sumowski, James F., Chiaravalloti, N., Wylie, G., & Deluca, J. (2009). Cognitive reserve moderates the negative effect of brain atrophy on cognitive efficiency in multiple sclerosis. *Journal of the International Neuropsychological Society: JINS*, *15*(4), 606–612. doi: 10.1017/S1355617709090912

Teuber, H. L. (1975). Recovery of function after brain injury in man. *Ciba Foundation Symposium*, (34), 159–190. doi: 10.1002/9780470720165.ch10

Thompson, A. J., Montalban, X., Barkhof, F., Brochet, B., Filippi, M., Miller, D. H., … McDonald, W. I. (2000). Diagnostic criteria for primary progressive multiple sclerosis: A position paper. *Annals of Neurology*, *47*(6), 831–835. doi: 10.1002/1531-8249(200006)47:6<831::AID-ANA21>3.0.CO;2-H

Tiemann, L., Penner, I., Haupts, M., Schlegel, U., & Calabrese, P. (2009). Cognitive decline in multiple sclerosis: Impact of topographic lesion distribution on differential cognitive deficit patterns. *Multiple Sclerosis Journal*, *15*(10), 1164–1174. doi: 10.1177/1352458509106853

Titus-Ernstoff, L., Newcomb, P., Egan, K., Baron, J., Greenberg, E., Trichopoulos, D., … Stampfer, M. (2000). Left-Handedness in Relation to Breast Cancer Risk in Postmenopausal Women. *Epidemiology*, *11*(2), 181–184.

Todor, J. I., & Doane, T. (1978). Handedness and Hemispheric Asymmetry in the Control Of Movements. *Journal of Motor Behavior*, *10*(4), 295–300. doi: 10.1080/00222895.1978.10735163

Tomkinson, C., Habib, E., Kuurstra, A., Sharma, M., Rosehart, H., Kremenchutzky, M., … Morrow, S. (2019). Cognitive Impairment and Deep Grey Matter Lesions on 7T MRI in Multiple Sclerosis (P5.2-035). *Neurology*, *92*(15 Supplement), P5.2-035.

Triggs, W. J., Calvanio, R., & Levine, M. (1997). Transcranial magnetic stimulation reveals a hemispheric asymmetry correlate of intermanual differences in motor performance. *Neuropsychologia*, *35*(10), 1355–1363. doi: 10.1016/S0028-3932(97)00077-8

Turner, G. R., & Levine, B. (2008). Augmented neural activity during executive control processing following diffuse axonal injury. *Neurology*, *71*(11), 812–818. doi: 10.1212/01.wnl.0000325640.18235.1c

Vargha-Khadem, F., O'Gorman, A. M., & Watters, G. V. (1985). Aphasia and handedness in relation to hemispheric side, age at injury and severity of cerebral lesion during childhood. *Brain: A Journal of Neurology*, *108 (Pt 3)*, 677–696. doi: 10.1093/brain/108.3.677

Vercellino, M., Plano, F., Votta, B., Mutani, R., Giordana, M. T., & Cavalla, P. (2005). Grey Matter Pathology in Multiple Sclerosis. *Journal of Neuropathology & Experimental Neurology*, *64*(12), 1101–1107. doi: 10.1097/01.jnen.0000190067.20935.42

Vuoksimaa, E., Koskenvuo, M., Rose, R. J., & Kaprio, J. (2009). Origins of Handedness: A nationwide study of 30161 adults. *Neuropsychologia*, *47*(5), 1294–1301. doi: 10.1016/j.neuropsychologia.2009.01.007

Weatherby, S. J., C. L. Mann, M. B. Davies, A. A. Fryer, N. Haq, R. C. Strange, and C. P. Hawkins. 2000. "A Pilot Study of the Relationship between Gadolinium-Enhancing Lesions, Gender Effect and Polymorphisms of Antioxidant Enzymes in Multiple Sclerosis." *Journal Of Neurology* 247(6):467–70.

Wechsler, D. (1997). WAIS-III Administration and scoring manual. San Antonio, TX: The Psychological Association.

Wechsler, D. (1981). Manual for the Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corporation.

Wechsler, D. (1999). Wechsler Abbreviated Scale of Intelligence (WASI). San Antonio, TX: Psychological Corporation.

Wechsler D. (2008). Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV). San Antonio, TX: NCS Pearson.

Wechsler, D. (2011). Wechsler Abbreviated Scale of Intelligence–Second Edition (WASI-II). San Antonio, TX: NCS Pearson.

Willems, R. M., der Haegen, L. V., Fisher, S. E., & Francks, C. (2014a). On the other hand: Including left-handers in cognitive neuroscience and neurogenetics. *Nature Reviews Neuroscience*, *15*(3), 193–201. doi: 10.1038/nrn3679

Woods, S. P., Delis, D. C., Scott, J. C., Kramer, J. H., & Holdnack, J. A. (2006). The California Verbal Learning Test – second edition: Test-retest reliability, practice effects, and reliable change indices for the standard and alternate forms. *Archives of Clinical Neuropsychology*, *21*(5), 413–420. doi: 10.1016/j.acn.2006.06.002

Zilles, K., Dabringhaus, A., Geyer, S., Amunts, K., Qü, M., Schleicher, A., … Steinmetz, H. (1996). Structural Asymmetries in the Human Forebrain and the Forebrain of Non-human Primates and Rats. *Neuroscience & Biobehavioral Reviews*, *20*(4), 593–605. doi: 10.1016/0149-7634(95)00072-0

Zverev, Y., & Chisi, J. (2004). Is handedness related to health status? *Malawi Medical Journal : The Journal of Medical Association of Malawi*, *16*(1), 14–16.