Leveraging multimodal neuroimaging and machine learning to predict processing speed in multiple sclerosis

Dissertation

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

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2022

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Abstract

Multiple sclerosis (MS) is a chronic neurological disease of the central nervous system (CNS) characterized by widespread inflammation, neurodegeneration, and reparation failures. Amongst its sequelae, slowed processing speed remains the earliest predictor of disease burden. MS causes heterogeneous and often subtle changes to functional and structural connections in the brain, even before symptoms manifest. Harnessing neuroimaging-based biomarkers to predict individual prognosis may facilitate patient-centered preventative care before cognitive decline becomes life-limiting. Through leveraging machine learning approaches within a cross-validation framework, we can build models from high dimensional functional and structural whole-brain connectivity to predict individual-level cognition. The present study used neuroimaging data from 64 people with relapsing-remitting MS to construct a multimodal structure-function connectome. We used a data-driven iterative pipeline to train and test models to make continuous predictions of processing speed and quantified model performance through prediction accuracy. Behaviorally, processing speed was significantly correlated with both disease severity and depression scores, confirming shared variance between cognitive and clinical function. However, the multimodal connectome did not yield significant predictions of processing speed in the current sample, and predicted processing speed did not correlate significantly with observed disease severity and depression scores. Separate functional and structural connectomes also did not explain meaningful variance in processing speed. This is the first study to apply machine learning regression techniques in a systematic way across two brain parcellations and both multimodal and unimodal connectomes to make individual-level predictions of cognition in people with MS. Although this study fused structural and functional connectivity using one method, alternative data-driven approaches for building multimodal connectomes implemented in larger samples may capitalize on complementary information across modalities to reveal robust cognitive neuromarkers. This study lays the groundwork for future machine learning and connectomic research to make personalized cognitive predictions in MS.

Acknowledgments

This project could not be possible without the support and encouragement of my mentors, colleagues, family, and friends. Foremost, I would like to thank my graduate advisor, Dr. Ruchika Prakash, for seven years of invaluable mentorship. Amongst everything she has taught me, perhaps the most notable is the importance of rigorous science and high-quality work. I am also indebted to my mentor for gently welcoming me into the world of mindfulness. Ruchika has taught me to slow down and immerse myself in the richness of life; this unparalleled experience has helped me discover my values as a human. I am also grateful to my tenacious Clinical Neuroscience Laboratory colleagues, including Drs. Alisha Janssen, Brittney Schirda, Stephanie Fountain-Zaragoza, Patrick Whitmoyer, Oyetunde Gybaden, as well as Elizabeth Herring, Anita Shankar, Megan Fisher, Michael McKenna, James Teng, Lauren Cea, Brandon Kinsler, Joanna Salermo, Dan Evans, and Vince Houston whose commitment to team science has been instrumental for this project and my graduate journey. I am grateful for all participants with multiple sclerosis who have demonstrated immense willingness to help advance science. I have gratitude for Shaadee Samimy, who spent countless hours with me at Stauf's as my optimistic cheerleader as we journeyed through graduate school milestones in tandem. I would also like to thank my parents. I am grateful for my Mummy, who reinforced the power of unwavering commitment and that what's meant for me won't miss me. I am thankful for my Papa, who affirmed that I shall achieve anything I set my mind to. I also have immense gratitude for my best friend, Neetu Singh, who has been my life coach through it all. Finally, I wish to thank my partner, Eric Terranova, who stood by my side, figuratively and literally, as I learned how to resolve code errors, Google more effectively, and think like a programmer. Most importantly, I would like to thank my partner for believing that I could get here and for sprinkling kind and persistent encouragement throughout this process. This project, and I, am the product of all your love and support.

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Manglani, H.R., Fisher, M.F., Duraney, E.J., Nicholas, J.A., & Prakash R.S. (2022). A promising cognitive screener in multiple sclerosis: The NIH toolbox cognition battery concords with gold standard neuropsychological measures. *Multiple Sclerosis Journal*. https://doi.org/10.1177/13524585221088731

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Fields of Psychology

Major Field: Psychology

Specialization: Clinical

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Chapter 1

Introduction

Twice as many people as previously estimated—nearly 1 million individuals—live with multiple sclerosis in the United States alone (Wallin, Culpepper, Campbell, et al., 2019). MS remains the second most common nontraumatic cause of neurological disability in young and middle-aged adults (Compston & Coles, 2002; Wallin, Culpepper, Nichols, et al., 2019). It typically strikes individuals in their 20s and 30s, women more than men (~ 3:1 ratio; Wallin, Culpepper, Campbell, et al., 2019), those farther from the equator more commonly than those closer to it (Koch-Henriksen & Sørensen, 2010), and individuals with a family history of the disease (Compston & Coles, 2002). Although the etiology of MS remains unknown, established risk factors include vitamin D deficiency, tobacco exposure, obesity, and infection by the Epstein-Barr virus (Grigoriadis & Pesch, 2015). As a multifactorial disease, MS results from a complex interplay of genetic, immune, and environmental influences (Ebers, 2008). Interactions between such factors trigger a cascade of events, including pathogenic immune processes, acute inflammatory axonal injury, structural and functional repair, post-inflammatory gliosis, and neurodegeneration (Compston & Coles, 2002).

In the absence of a pathognomonic laboratory test for diagnosis, two hallmarks used to diagnose MS accurately include two or more deficits (e.g., lesions and clinical features) disseminated in neuroanatomical space and time (Thompson et al., 2018). For about 85% of PwMS, the disease presents in its relapsing-remitting (RRMS) form with time-restricted inflammatory attacks, leading to multifocal lesions and diffuse atrophy of gray and white matter (Goodin et al., 2016). The disease evolves into secondary progressive MS (SPMS) for one in two individuals with the relapsing-remitting course. In secondary progressive, akin to primary progressive MS (PPMS), a constellation of neuronal, axonal, and myelin loss with inadequate repair mechanisms of the CNS leads to clinically higher disease severity and

disability (Grigoriadis & Pesch, 2015). Additionally, there are two classifications for features indicative of MS but which do not warrant a diagnosis—a prodrome (Miller et al., 2008; Okuda et al., 2009). Individuals on radiological exam show evidence of focal MS pathology (e.g., lesions, axonal loss) but are otherwise asymptomatic may meet diagnostic criteria for radiologically isolated syndrome (RIS). Alternatively, people who experience a clinical attack, with or without inactive lesions (i.e., indicative of prior disease activity), may be provided the prodromal diagnosis of clinically isolated syndrome (CIS). Substantial variability in pathogenic processes, timing, and location in the central nervous system (CNS) leads to variable symptom presentation across individuals with MS.

MS is characterized by relapses, remissions, and disability progression, precipitating physical, psychological, and cognitive sequelae. Multifaceted symptoms of this disease range from muscular weakness, sensory deficits, fatigue, pain, and psychiatric disturbance, including depression and anxiety, to cognitive impairment. Cognitive deficits, in particular, are a cardinal facet of the disease and shown to be present in the earliest stages of the disease (Amato et al., 2010), even in individuals in prodromal stages, including radiologically isolated syndrome (Menascu et al., 2019), and clinically isolated syndrome (Khalil et al., 2011; Reuter et al., 2011).

1.1 Cognitive Deficits in MS

Cognitive dysfunction is a pervasive and salient symptom occurring in the disease trajectory of 40-70% of individuals with MS (Amato et al., 2006; Julian, 2011; Grzegorski & Losy, 2017; Rao et al., 1991). MS has a sweeping impact on cognitive domains, including information processing speed, attention, executive functioning, working memory, learning, and long-term memory (Chiaravalloti & DeLuca, 2008; Macías Islas & Ciampi, 2019; Prakash et al., 2008). However, the most prominent decrements are observed in processing speed, memory, complex attention, and executive function (DeLuca et al., 2004; Rocca et al., 2015; Whitehouse et al., 2019). Processing speed deficits are present in 47.9% of PwMS and range widely from 40-to 80%, depending on the specific MS subtype (Ruano et al., 2017). Processing speed affects various daily life functions, including driving (Schultheis et al., 2010),

reading, learning, and working (Shevil & Finlayson, 2006). Memory impairment is the subsequent highest observed cognitive deficit in PwMS, with an estimated prevalence between 33-65% (Grzegorski & Losy, 2017; Oreja-Guevara et al., 2019). Memory complaints involve difficulty remembering conversations, appointments, and work-related details (Arnett & Strober, 2011), forgetting people's names, and misplacing objects (Shevil & Finlayson, 2006). However, variable empirical findings suggest problems with memory may either be due to difficulties with retrieving information from the long-term storage (Zakzanis, 2000) or inadequate initial encoding of information (Deluca et al., 1994), which can be overcome if PwMS are provided greater time or trials for learning (Arnett & Strober, 2011; Demaree et al., 1999). Anywhere from 12-25% of PwMS may experience problems with attention (Grzegorski & Losy, 2017), most frequently in selective, sustained, alternating, and divided attention. PwMS report difficulties focusing during conversations, problems with staying on task, and distractibility (Honan et al., 2015; Shevil & Finlayson, 2006). Some variance in attention is also accounted for by processing speed (Roth et al., 2015). About 15-25% of PwMS demonstrate problems with executive functions (i.e., inhibition, task-switching) which manifest in difficulties understanding instructions, making decisions, planning, and multi-tasking (Shevil & Finlayson, 2006). Both inhibition and task-switching components of executive functioning are highly correlated with processing speed in MS (Drew et al., 2009). In contrast, language, intelligence, and basic verbal skills are largely intact in PwMS (Calabrese, 2006).

To characterize cognition in PwMS, the literature has adopted the dichotomy of cognitive impairment and cognitive preservation. Typically, individuals are classified into one of these two groups based on their performance on neuropsychological tests relative to normative scores from age-, sex-, and education-matched healthy controls. A cutoff of 1.5 standard deviations below normative values is generally the accepted threshold signifying cognitive impairment. However, the number of tests needed to meet this criterion varies considerably across the literature (Macías Islas & Ciampi, 2019). Although the classification of PwMS as cognitively impaired or preserved allows for cleaner communication of results, some studies also report cognitive function on a continuous scale (Manglani et al., 2020).

The broad spectrum of cognitive deficits in MS relates negatively to wide-ranging functional abilities. Specifically, negative relationships exist between cognitive deficits and vocational status (Povolo et al., 2019), social engagement (Amato et al., 2006; Ari et al., 2014), and independence in instrumental activities of daily living (Goverover et al., 2007; Kalmar et al., 2008), including driving ability (Schultheis et al., 2010), and facility with money management (Goverover et al., 2016). The relationships between cognitive impairment and work-related problems in MS are of significant concern. High rates of PwMS change work roles or leave the workforce prematurely (Moore et al., 2013) even when disability is low (Pearson et al., 2017). Amongst the cognitive domains perceived to impact work status, information processing speed was reported most frequently (Renner et al., 2020). The inverse relationship between processing speed and work-related problems has also been demonstrated objectively. A series of studies show that PwMS with slower processing speed are less likely to be employed (Cadden & Arnett, 2015; Honarmand et al., 2011), reduce working hours to accommodate disease-related symptoms (Macaron et al., 2020), and retire at an earlier age (Krause et al., 2013). Reduced work engagement, in turn, has substantial personal and socioeconomic costs (Kobelt et al., 2017).

1.2 Processing Speed in MS

Mounting evidence posts slowed information processing speed as the central cognitive deficit in MS (Van Schependom et al., 2015). Processing speed is commonly defined as the time it takes for an individual to perceive, process, and respond to a stimulus. It can be measured by the amount of information correctly processed in a given amount of time (accuracy) or the amount of time required to process a given amount of information (reaction time). A recent theoretical tri-factor model of processing speed proposed that this ability depends on the integration of sensorial (i.e., low-level perceptual speed), cognitive (e.g., completion of the task), and motor function (e.g., output speed) (Costa et al., 2017). In MS, processing speed manifests as a general deficit (Denney et al., 2011) and is the fundamental building block upon which all increasingly complex cognitive domains rely (De Sonneville et al., 2002; DeLuca et al., 2004; Forn et al., 2008). Fast processing speed allows us to deploy our attention to important

information (Roth et al., 2015), facilitates maintenance and manipulation of relevant information by our working memory (Leavitt et al., 2011), and bolsters higher-order cognitive functions, including executive functions (Leavitt et al., 2014), and new learning and memory (Chiaravalloti et al., 2013). By scaffolding all domains of cognitive functioning, reductions in processing speed may adversely impact wide-ranging activities of daily living.

Decrements in processing speed are linked to consequential downstream effects in PwMS. Slowed processing speed is associated with poor money management (Yael et al., 2019), reduced driving (Schultheis et al., 2010), and unemployment (Rao et al., 1991; Ruet, 2013; Strober et al., 2014). Employment-related difficulties are particularly devastating as individuals with MS are typically diagnosed during their productive, earning years of life. In addition to discernible financial contributions to living expenses, health insurance, and social security, employment supports independence, social participation, and self-esteem, thus having a widespread impact on quality of life (Yamout et al., 2013). Direct positive links between processing speed and social engagement have also been established (Amato et al., 2006; Shevil et al., 2014), such that individuals with slowed processing speed tend to endorse lower quality social relationships (Eizaguirre et al., 2018). In addition to activities of daily living, processing speed has also been negatively related to disease severity and fatigue—two prominent clinical facets of the MS disease. For example, slower processing speed in young adults at disease onset (< 25 years) has been associated with higher motor disability up to 7 years later (Carotenuto et al., 2019). Further, people with slower processing speed also report more severe depressive symptoms (Eizaguirre et al., 2018), indicating that processing speed shares variance with clinical comorbidities in MS.

A series of studies using ecological measures to simulate day-to-day activities further substantiate the influence of processing speed on activities of daily living. In one study, Goverover and colleagues (2007) compared PwMS to healthy controls in their accuracy and speed on the Timed Instrumental Activities of Daily Living (TIADL) task. In this task, participants were asked to complete five common everyday activities, including locating a number in a phone book (communication), counting change (finance), finding and reading ingredients from a can of food (nutrition), searching for food items on a

filled shelf (shopping), and reading instructions from a medicine bottle (medicine). This study compared performance on the ecological tool of TIADL with scores on various neuropsychological assessments and found significant correlations between the TIADL total score and multiple measures of processing speed, underscoring the influence of slowed processing on daily living. Similarly, another study assessing practical, real-world money management employed an online performance-based functional test (i.e., purchasing a bouquet of cookies) where skills such as planning and budgeting were required and compared performance with scores on neuropsychological tests of processing speed, executive functioning, and memory (Goverover et al., 2016). Using a stepwise linear regression to predict the total score on managing finances, processing speed emerged as the only significant predictor, further highlighting the critical role of information processing speed in activities of daily living.

Given its critical alterations in PwMS, processing speed is measured in all comprehensive neuropsychological batteries validated within this population, including the Brief Repeatable Battery of Neuropsychological tests (BRB-N; Rao, 1991), the Minimal Assessment of Cognitive Function in MS (MACFIMS; Benedict et al., 2006), and the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS; Langdon et al., 2012). Included in all of these batteries is the classic measure of processing speed—the Symbol Digit Modalities Test (SDMT; Strober et al., 2020). In this test, participants are provided a key of symbol-number pairs, and rows of pseudorandom symbols missing their corresponding number. Participants are asked to quickly and accurately identify the number that completes each symbol-number pair. This 90-second assessment can be administered either in a written format or in an oral format designed to minimize the confounding effects of motor impairment. The final score on the SDMT is the total number of correctly completed pairs. A recent review of methods used to assess processing speed in PwMS identified other objective tests cited by authors to evaluate processing speed, including the Paced Auditory Serial Addition Test (PASAT) and the classic Stroop task (Stroop, 1935). Although both the rapid serial processing PASAT and the color-word interference Stroop test have a processing speed component, they also rely on the more complex cognitive functions of working

memory (Parmenter et al., 2006), and inhibitory control (Ternes et al., 2019), respectively. As such, the SDMT remains the pure, gold-standard measure of processing speed.

Notably, the SDMT has been instantiated as a valid and reliable measure of processing speed in MS (Benedict et al., 2017), as it demonstrates minimal practice effects (Benedict et al., 2008) and indexes clinically meaningful change (e.g., of 4 points or 10% in magnitude; Benedict et al., 2017). Changes in SDMT parallel changes in disease progression (Heled et al., 2019) and burden, as quantified via MRI-based markers, including cerebral atrophy (Christodoulou et al., 2003), and total lesion volume (Lazeron et al., 2016), as well as improvements in ambulation following relapse (Benedict et al., 2020). The SDMT has been noted by the Multiple Sclerosis Outcome Assessments Consortium as the processing speed measure of choice for MS clinical trials (Strober et al., 2019) and by the National Institute of Neurological Disorders and Stroke as the only core Common Data Element measure of cognition for use in MS (Grinnon et al., 2012).

1.3 Functional Correlates of Processing Speed in MS

Although MS has often been defined simplistically as a white matter disorder, the involvement of gray matter in the disease pathology has been well-documented in the past decade. Functional MRI (fMRI) is the most commonly employed noninvasive neuroimaging approach to study gray matter activity. Brain function is inferred from the flow of oxygenated blood to specific areas and quantified by the blood oxygenated-level dependent (BOLD) response. The BOLD response is an indirect marker of neuronal activity in specific regions of interest (ROIs) or networks (groups of brain regions). This activity can be measured in the absence of any overt task stimulation or demand, known as resting-state fMRI (Biswal et al., 1995), or during the completion of a particular (e.g., cognitive) task (task-fMRI). fMRI can also quantify functional connectivity or the statistical associations in the BOLD signal of brain regions across a given (i.e., rest or task) time series.

Most fMRI investigations of processing speed in MS have associated activity during resting-state fMRI with performance on neuropsychological measures completed outside the scanner (Fuchs et al.,

2019; Has Silemek et al., 2020; Lin et al., 2020; Manca et al., 2019; Meijer et al., 2017; Wojtowicz et al., 2014). Of note, most of these studies focused on *a priori* regions or networks to evaluate relationships. For example, Manca and colleagues (2019) assessed associations between cognitive performance and the functional connectivity of the frontoparietal, salience, default mode, visual control, and sensorimotor networks. Results showed positive associations between activity of the left frontoparietal network and processing speed. This is consistent with recent findings from Lin et al. (2020), demonstrating positive correlations between SDMT performance and connectivity between the frontal pole, superior temporal gyrus, and the posterior parietal cortex. In contrast, a recent study in a sample of PwMS with mild disease severity found functional connectivity at rest did not evince significant associations with processing speed (Silemek et al., 2020), despite significant positive relationships between processing speed and alternative MRI measures (i.e., structural white matter connectivity). Although, in general, the evidence from resting-state fMRI is inconclusive, some patterns emerge from task-based fMRI investigations of processing speed.

Processing speed performance has been related to neural activation during the fMRI-adapted SDMT (Dobryakova et al., 2016; Fittipaldi-Márquez et al., 2017; Grothe et al., 2020). Silva et al. (2018) conducted a systematic review and meta-analysis of functional activity in healthy individuals during the completion of the SDMT. They found areas of the frontoparietal network and the occipital cortex, and the cuneus, precuneus, and cerebellum relevant for this task. Similarly, PwMS have demonstrated widespread activation of *a priori* occipital, temporal, and frontal regions (Forn et al., 2009) and reduced activity in bilateral frontal and parietal regions relative to healthy controls (Genova et al., 2009) during the SDMT. Differences in activity patterns have also been shown among PwMS with and without processing speed impairment. One study using effective connectivity (i.e., measuring the directionality of connections) found the strength of connections within the frontoparietal network of PwMS to be higher in impaired relative to preserved individuals. The authors suggested that a maladaptive overreliance on these connections may explain why some PwMS have processing speed impairment (Dobryakova et al., 2016). Studying neural efficiency more directly, another investigation modulated SDMT task difficulty using

variable interstimulus intervals (ISI: 1.5, 2, and 2.5 s) (Fittipaldi-Márquez et al., 2017). This study found PwMS performed worse than healthy controls when processing speed demands were high (e.g., at the lower interstimulus interval of 1.5 s) but comparably during low and moderate task difficulty. However, better performance in these easier conditions was paired with enhanced activity of several frontal and temporal areas, which suggests that to perform with similar accuracy as healthy individuals, PwMS may require greater neural resources. This begs the question, then, whether greater activity is a compensatory mechanism or a maladaptive overreliance to support processing speed. Although this remains an outstanding question, one consensus that has emerged in the literature is that processing speed relies on diffuse functional regions. In a recent investigation on differences in activity between processing speed and control conditions of the fMRI-adapted SDMT, Grothe et al. (2020) found greater activity in parietal and posterior cerebellar regions during processing speed demand, further evincing that processing speed is supported by distributed functional regions.

Collectively, although a limited number of studies have examined the neural correlates of processing speed, either by linking resting-state connectivity with metrics of processing speed or changes in BOLD activity during processing speed tasks, considerable heterogeneity across results and the correlational design of these studies necessitates further study. In a recent systematic review, Manca and colleagues (2018) also highlighted fundamental limitations of existent research, including psychometric differences between the processing speed measures used, a lack of differentiation between different MS subtypes, and a dearth of multimodal MRI to better characterize the cognitive complexity of MS.

1.4 Structural Correlates of Processing Speed in MS

Although focal white matter lesions are a cardinal facet of multiple sclerosis, manifold findings reveal that subtle structural changes precede lesion formation and can be quantified using advanced MRI methods (Dineen et al., 2009; Hulst et al., 2013; Preziosa et al., 2016). Conventionally, the presence of new lesions within the brain or spinal cord measured by gadolinium enhancement on MRI suggests a breakdown of the blood-brain barrier, and signals the beginning of lesion formation (Grossman et al.,

1986). However, advanced quantitative MRI parameters have demonstrated that the formation of lesions occurs in stages; normal-appearing white matter regions show biochemical changes (Tartaglia et al., 2002), decreased magnetization transfer ratio (a quantitative measure of tissue integrity; Filippi et al., 1998; Horsfield, 2005; Werring, 2000), and lower diffusivity weeks to months before gadolinium enhancement demarcates the presence of lesions (Rocca et al., 2000). As subtle, progressive alterations in tissue integrity precede the formation of visible lesions on conventional MRI, microstructural properties may provide a more sensitive measure of structural pathology in MS.

Acquiring diffusion-weighted imaging (DWI; Basser, Mattiello, & Lebihan, 1994) to quantify microstructural changes has gained popularity in MS research (Rovaris et al., 2005). During DWI, diffusion-weighted magnetic field gradients with different orientations are applied to sensitize water diffusion in specific directions. Water diffuses differently based on tissue type, integrity, architecture, and barriers (Soares et al., 2013). Whereas in cerebrospinal fluid, water is unrestricted in all directions (isotropic), in white matter, diffusion depends on the axon's direction and tends to be anisotropic, and typically less anisotropic in gray matter. Diffusion tensor imaging (DTI) is a modeling technique that can estimate the orientation and anisotropy of the tissues (Basser, Mattiello, & LeBihan, 1994). The two most commonly used diffusion magnitude and diffusion anisotropy metrics are mean diffusivity (MD) and fractional anisotropy (FA), respectively. Mean diffusivity quantifies the magnitude of molecular diffusion within a voxel. FA, or the fraction of diffusion that is anisotropic (O'Donnell & Westin, 2011), measures diffusion's directionality and is coined in the literature as a measure of white matter integrity. Another popular quantitative DWI method is tractography, or the reconstruction of white matter pathways, which can be used to yield whole-brain structural connectivity (Lipp et al., 2020). As DWI is sensitive to microstructural tissue properties, which may reveal physiological injury before the formation of focal lesions (Ontaneda et al., 2014), linking diffusion metrics to cognitive symptoms is particularly relevant in MS.

A series of studies have identified relationships between the integrity of specific white matter tracts and processing speed in MS. One of the most striking structural differences between healthy

controls and PwMS is the abnormality of the interhemispheric bundle of fibers of the corpus callosum. The relationship between reduced fractional anisotropy in the corpus callosum and slowed processing speed is well-replicated in MS (Roosendaal et al., 2009; Yu et al., 2012). Other white matter tracts, including the commissural and frontal associative tracts, have also been shown to support information integration and sustained performance required for processing speed tasks (Manca, Stabile, et al., 2019). A study by Johnen and colleagues (2019) in early, active RRMS individuals found an association between processing speed and the average microstructural white matter integrity within the dorsolateral-prefrontal loop such that greater microstructural degeneration (i.e., lower mean fractional anisotropy) in this specific circuit was correlated with slowed processing speed.

In addition to negative relationships between abnormalities of specific tracts and processing speed in MS, associations between processing speed and integrity of more extensive networks have been established. One study investigating specific *a priori* canonical networks found that fractional anisotropy of the extended default mode network and cerebellar network correlated positively with processing speed performance (Savini et al., 2019), suggesting that structural connectivity of these networks may provide the necessary architecture for speeded processing. Even in early MS and individuals with mild disability, loss of structural connectivity is evident, and lower connectivity within global structural networks is associated with slower processing speed (Silemek et al., 2020). These findings suggest that the structural integrity of more expansive networks may be relevant to understanding cognitive function in MS and useful even early on in the disease course.

In line with this, emerging evidence demonstrates that the integrity of whole-brain white matter tracts may *predict* changes in processing speed and may be a superior marker of dysfunction relative to other MRI measures. For example, one study found that more severe white matter damage at baseline in early RRMS was predictive of declines in processing speed at 5-year follow-up (Eijlers et al., 2018). In other research, among various measures, including gray matter atrophy and regional and global disconnection, disruptions to distributed pairwise connections due to lesions emerged as the metric with the highest accuracy for predicting future processing speed in PwMS (Kuceyeski et al., 2018). This study

suggests that when applied to pairwise connections in the brain, statistical modeling approaches may be more informative than spatially circumscribed or overall global atrophy/disconnection. A recent search for the MRI parameters that are most predictive of processing speed identified the greatest contribution from fractional anisotropy, mean diffusivity, and radial diffusivity (i.e., the magnitude of water diffusion perpendicular to the tract) of the normal-appearing white matter (Tóth et al., 2019). Note that functional connectivity during task-MRI was not one of the candidate MRI metrics. The magnitude of additional variance in processing speed that may be explained from a joint connectome of structural and functional connectivity predictive of processing speed remains unknown. A recent systematic review of functional and structural connectivity and processing speed in MS concluded that the literature is limited mainly by inconsistent results and underscored the combined use of multimodal MRI to better monitor cognitive and clinical change in this population (Manca et al., 2018).

1.5 Disease Severity in MS

Measuring disease severity in PwMS is routine in visits to neurologists and clinical trials. An individual's current severity of MS provides a snapshot into their level of function and dependence across physical, cognitive, affective, and neurological domains. In addition, comparing successive quantitative assessments of disease severity can shed light on disease progression and prognosis. This is particularly important in visits with neurologists who can utilize this information to inform medical decisions involving medications (e.g., have the patient trial a new corticosteroid), behavioral therapy (e.g., engage in physical/occupational/pelvic floor therapy), and counseling/psychotherapy (e.g., participate in mental health treatment). As disease severity measures may reveal disease progression, disability, and need for intervention, they are critical in clinical practice and research.

In the MS literature, the gold-standard method for quantifying disease progression and the severity of functional deficits is administering the Expanded Disability Status Scale (EDSS; Kurtzke, 1983). EDSS provides a comprehensive assessment of functional systems, including pyramidal, cerebellar, brainstem, sensory, bowel, bladder, visual, and cerebral. Weighted towards ambulation, the

overall score ranges from 0 (total, unassisted ambulation) to 10 (death due to MS), with 5.5 used as the cutoff to denote that an individual can walk 100 meters without the need for aid or rest. The EDSS can be administered by either a clinician or trained researcher, thus enabling comparisons across clinics and research studies. A systematic review reveals that the EDSS has been validated to monitor disease progression and serve as a primary endpoint in clinical trials (Meyer-Moock et al., 2014). For example, one longitudinal study assessed the 10-year change in disease severity for individuals classified as having mild (EDSS score 0-3.5) or moderate/severe MS (EDSS score 4-9.5) in relation to disability (Conradsson et al., 2018). Disability was measured broadly using objective tests of walking ability, information processing speed, fatigue, depression, independence in activities of daily living, participation in social activities, and perceived physical and psychological impact of the disease. Results demonstrate that compared to individuals with mild MS, disease progression had more significant consequences for individuals with moderate/severe MS at baseline, through a more significant decline in walking ability, increased wheel-chair dependency, slower processing speed, and reduced social engagement. Higher EDSS scores in PwMS have also been linked with lower participation in work, and greater annual costs (Grima et al., 2000), such as from community and informal care late in the disease (Kobelt et al., 2017). These findings support the utility of EDSS for monitoring disease severity and disease burden.

Relationships between disease severity and cognition are also well-established in MS. Cognitive impairment is related to greater psychological distress, self-reported disability (Artemiadis et al., 2018), and objective disease severity (i.e., higher EDSS scores) (Ruano et al., 2017). Further, longitudinal data in MS reveals that the number of cognitive domains impaired at baseline is associated with cognitive change and disease severity in the long term, with processing speed the most commonly affected domain at baseline (Damasceno et al., 2019). Predicting changes in MS disease severity as measured by EDSS, processing speed repeatedly emerges (Eizaguirre et al., 2018), even in assessments separated by 4-5 years in time (Heled et al., 2019), thus, supporting the use of processing speed as a valid marker of changes in disease severity.

1.6 Depressive Symptoms in MS

Depression is the most prevalent mental health comorbidity in MS (Marrie et al., 2015). Depression can range from clinically significant depressive symptoms such as low mood, anhedonia, and feelings of worthlessness to an episodic and persistent constellation of functionally impairing symptoms in social, occupational, or other areas and meets diagnostic criteria for a depressive disorder (American Psychiatric Association, 2013). Recent systematic reviews in MS estimate the prevalence of depressive disorders to be nearly 21% (Marrie et al., 2015) and clinically significant symptoms to reach 35% of the population with MS (Boeschoten et al., 2017). Epidemiological research on lifetime prevalence estimates that 1 in every 2 individuals with MS will meet the criteria for clinically significant depression in their disease course (Siegert & Abernethy, 2005). Compared to the general population, depression diagnoses are 2-3 times higher in PwMS (Goldman Consensus Group, 2005) and higher in MS than in other chronic conditions (Patten et al., 2003). Further alarming is the standardized mortality ratio, which indicates that relative to the general population, PwMS are twice as likely to ideate about and attempt suicide (Brønnum-Hansen et al., 2005; Tauil et al., 2018). Perhaps the most compelling evidence for studying depression comes from the list of risk factors for suicidality in MS, including a high incidence of depression, increased isolation, and reduced function and independence (Kalb et al., 2019).

Robust negative relationships exist between depression, functioning across life domains, and quality of life. For example, PwMS with comorbid depression are less adherent to their MS medications (Tarrants et al., 2011), report greater disability (Ploughman et al., 2020), and are at higher risk for worsening disease (Binzer et al., 2019; McKay et al., 2018). Ploughman et al. (2020) also found that PwMS with undiagnosed depression and severe symptoms are less likely to consume a healthy diet, exercise, and participate at high levels in life roles (i.e., household, leisure, out-of-home activities), even after accounting for age, MS disease duration, MS subtype, and disability. Further, depressed PwMS are less likely to pursue leisure activities irrespective of whether they are cognitive, physical, or social (Patel et al., 2018). This is particularly detrimental as such activities can boost cognitive function and build cognitive reserve, which may counteract disease mechanisms and prove paramount for prognosis

(Sumowski, 2015). These findings suggest that depression may exacerbate disease burden by influencing other health behaviors. Depression is also associated with reduced working hours (Honan et al., 2015) and is an independent predictor of vocational status in MS (Povolo et al., 2019). Notably, in addition to fatigue, depression remains the most prominent predictor of quality of life in PwMS (Biernacki et al., 2019; Fruewald et al., 2001). A standard tool used in clinical populations is the health-related quality of life (HRQoL) measure which assesses well-being across health domains (e.g., physical, psychosocial). Studies estimating the relative contribution of comorbidities in predicting HRQoL found that after disease severity, depression had the most potent adverse effect on HRQoL (Berrigan et al., 2016), and along with anxiety, was the strongest predictor of psychosocial HRQoL (Lo et al., 2020). In the recent study by Povolo and colleagues (2019), processing speed, disease severity, and depression explained 37% of the variance in vocational status in PwMS, suggesting significant shared variance between these critical factors.

Depression also has robust relationships with processing speed (Whitehouse et al., 2019). In two independent cohorts of PwMS, lower depression was associated with faster information processing even after controlling for age, sex, education, premorbid verbal intelligence, fatigue, and lesion volume (Leavitt et al., 2019). Specifically, relative to non-depressed PwMS, depressed PwMS show an overall decrement of nearly 20% in mean reaction time (Patel & Feinstein, 2019), which exceeds the consensus threshold for clinical significance (Benedict et al., 2017). Interestingly, there is also evidence to suggest that depression may mediate the relationship between processing speed and other cognitive functions. In one study by Diamond and colleagues (2008), slower processing speed was associated with higher depression and worse performance on learning and delayed memory. This relationship was attenuated when mood symptoms were partialed out, suggesting that depressive symptoms explain at least part of the relationship between processing speed and higher-order cognitive functions. A separate line of evidence suggests that for younger people with MS with lower disability and shorter disease duration, depressive symptoms may affect higher-order domains, including memory and executive functions, indirectly through processing speed (Blair et al., 2016). Based on these findings and the current state of the

literature, there likely exists a bidirectional relationship between processing speed and depression, both of which influence and are influenced by functioning across physical, social, and work-life domains.

1.7 Multimodal Imaging

A growing literature indicates that multimodal models (e.g., integrating structural and functional connectivity) may provide more robust predictors of cognitive function in various clinical populations (Calhoun & Sui, 2016; Lin et al., 2012). It is well known that strong functional connections commonly exist between regions, even in the absence of direct structural connections. Further, indirect links as well as interregional distance account for some of the variance in functional connectivity not explained by direct structural connectivity (Honey et al., 2009). As such, integrating multimodal data may allow us to capitalize on the strength of each imaging modality and identify unique evidence for neurobiological coordination of cognition (Sui et al., 2020).

Broadly, multimodal MRI has shown to outperform unimodal methods in distinguishing: individuals with schizophrenia from healthy controls (for a review of multimodal MRI approaches in schizophrenia see: Sui et al., 2012), attention-deficit and hyperactivity disorder from autism (Sen et al., 2018), and healthy controls from mild cognitive impairment and Alzheimer's disease (Wang et al., 2018). In healthy adults, multimodal MRI methods have also shown success in predicting brain age (Liem et al., 2017), intelligence quotient (Jiang et al., 2019), fluid intelligence, crystallized intelligence, and a composite score of cognition (Dhamala et al., 2020), demonstrating the utility of multimodal MRI for predicting continuous metrics. Further, Dhamala and colleagues (2020) found that a hybrid connectome, inclusive of both whole-brain resting-state functional connections and tractography-based structural connections, explained greater variance in cognition (14.7%) than those derived from just functional connectivity (11.3%) or structural connectivity alone (11.5%). These findings suggest that predictions of cognition may be enhanced by combining information from multiple MRI modalities and appear particularly well-suited for the white matter pathology and gray matter degeneration of MS.

Characterized by focal lesions, diffuse microscopic damage to normal-appearing white matter, and widespread functional changes, MS has been described as a "disconnection syndrome" (Calabrese & Penner, 2007; Dineen et al., 2009; Ettinger-Veenstra, 2016). This disconnection is presumed to interrupt both local processing and effective integration of information between regions (Gamboa et al., 2014), vital to functions such as processing speed. Employing DTI, microscopic damage to white matter tracts, including the corpus callosum, cingulum, and fornix, has been associated with cognitive functions, including processing speed, memory, attention, and executive functions (for a review of this research see: Filippi et al., 2019). Tractography-based parcellations (i.e., segmentation of connections between specific regions) show that cortico-thalamic tracts may explain differences in cognitive impairment, and tracts connecting the thalamus with occipital and frontal areas may relate specifically to processing speed performance (Bisecco et al., 2015).

It is well known that cognitive functions rely on interactions within and between large-scale networks (Bressler & Menon, 2010) and unique sets of structural and functional connections map onto cognition (Zimmermann et al., 2018). One study in MS found that individuals with CIS only demonstrated structural network abnormalities while PwMS showed both structural and functional network alterations (Shu et al., 2016). This study concluded that change to white matter structural networks may precede changes to functional networks in white matter diseases. Gray matter dysfunction secondary to focal white matter lesions has been replicated in other studies (Bodini et al., 2016; Rocca et al., 2015). In their recent review, Filippi and colleagues (2019) summarize evidence showing that disconnection in MS stems from damage to strategic white matter tracts and changes to specific functional brain networks. As the MS brain provides fertile ground for modeling relationships between abnormalities of structure and function, harnessing different MRI modalities to explain the disconnection syndrome in MS is warranted.

Studies examining links between changes in connectivity and individual differences in cognitive functioning indicate promise for multimodal models. Recently, Tewarie and colleagues (2018), using separate simulation analyses of the effects of gray and white matter damage on functional connectivity,

found that although white matter damage initially increased functional connectivity, functional connectivity subsequently decreased. Based on this inverted U-curve of functional connectivity, the topology and timing of structural damage are nontrivial factors in elucidating functional abnormalities in MS. These results may also explain the inconsistent relationships between cognition and functional connectivity observed across cross-sectional studies, which typically include PwMS with variable white matter damage and presumably at different points along this curve. Further, this study found that white and gray matter degeneration decreased network segregation and integration. Separate research shows that fast and more accurate performance on cognitive tasks relies on integrated networks (Cohen & D'Esposito, 2016; Shine et al., 2016), indicating the importance of understanding network-based reconfigurations. Consistent with Tewarie et al.'s (2018) findings, the impact of white matter tract disruption on processing speed was shown to be attenuated by the preservation of functional connectivity in MS (Fuchs et al., 2019), suggesting that maintenance of efficient functional connectivity despite structural breakdown may support efficient information processing in MS.

This finding is consistent with another study that directly compared white matter integrity with resting-state functional connectivity to quantify their relative contributions in predicting processing speed status (i.e., preservation vs. impairment). Meijer and colleagues (2018) found that individuals with predominant structural damage performed worse on SDMT than those with predominant functional connectivity changes. In contrast, those with similar levels of structural disruption but with preserved functional connectivity demonstrated better processing speed (congruous with results from Fuchs et al., 2019). Notably, an integrated structure-function regression model revealed that PwMS, who had the most severe structural *and* functional changes, demonstrated the slowest processing speed. Two major conclusions can be drawn from these pooled results: 1) the magnitude of structural damage and functional change does not follow a one-to-one pattern, and 2) examining structural and functional measures jointly may reveal more fine-grained patterns between structural damage and functional changes in MS. Although this study demonstrates promising relationships between structure and function, it had critical limitations.

First, this study assessed patterns from resting-state functional connectivity. A recent line of research shows that perturbing cognitive networks through task-based fMRI results in superior models of cognitive function that outperform those derived during rest (Greene et al., 2018) and better generalize to predict out-of-scanner cognition (Jiang et al., 2020). Additionally, as resting-state functional connectivity exhibits low reliability both within and across scanning sessions (Honey et al., 2009), task-based functional connectivity may provide more reliable estimates of functional connectivity. A second limitation of this study is using median splits in functional and structural damage to classify participants as mild or severely damaged in functional or structural connectivity. Using the sample's median score for a dichotomous split may have resulted in sample-specific categorization. In light of advanced methods for integrating multimodal MRI data (Zhu et al., 2014), the employed method falls short of the sophisticated approaches available for combining DWI with fMRI. The study's use of backward linear regression models to identify independent predictors of processing speed is also inadequate in the context of the currently available statistical methods. This is an important limitation as the field has been moving towards machine learning approaches that allow for the actual prediction of traits and cognitive behaviors through training/test splits of data via cross-validation. Nonetheless, the overall evidence of associations between processing speed and multimodal MRI data and statistical gains from combining structural and functional connectivity lay the groundwork for more critically needed biomarkers and predictive models in MS.

1.8 Biomarkers and Machine Learning in MS

The existing MS literature calls for a search for a valid and reliable biomarker of cognition. A biomarker is defined as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease" (Strimbu & Tavel, 2010; World Health Organization, 1993). Biomarkers that predict disability progression, monitor ongoing disease activity, and evaluate treatment response are central informants in medical decision-making (Paul et al., 2019). However, a long-standing difficulty in identifying sensitive and specific biomarkers has marked

this field. The complex interplay of autoimmune processes within the CNS has precluded clear associations between specific clinical symptoms and underlying lesion sites. This mismatch between white matter lesions and clinical symptoms has been coined the clinico-radiological paradox (Uher et al., 2018). In the search for more sensitive and specific surrogates of cognitive and clinical function, wherein isolation, clinical tools such as the EDSS show limited sensitivity to clinical change, MRI offers promising utility (Chard & Trip, 2017). A subset of biomarkers based on neuroimaging data—coined neuromarkers—can serve as brain-based signatures for clinical measures, including cognitive function (Benedict et al., 2006), and derived using robust machine learning methods.

Neuromarker discovery has paralleled the recent paradigm shift to machine learning approaches for decoding differences in individual-level behavior from multivariate neuroimaging features. The surge of novel basic science research has validated statistical methods for capturing individual variability in brain organization to predict group membership and continuous behavioral measures. To identify neuromarkers, brain structure, activity, or connectivity data in a training sample are mined for features (e.g., functional/structural connections) associated with a particular behavior (e.g., cognitive function). Using regression-based machine learning approaches, neural features are fit to behavior, yielding models of brain-behavior relationships. These predictive models are then tested using neural and behavioral data from independent samples. Models are provided neural data from unseen individuals to produce predictions of behavioral performance, which are then tested against observed behaviors. Perhaps, the leading advantage of predictive modeling over conventional correlational analysis is that predictive modeling uses a cross-validation strategy to guard against overfitting (Sui et al., 2020). This is particularly important for clinical samples such as MS, where correlation-based claims may largely depend on the variability within the sample in various clinical characteristics such as MS subtype, amount and volume of white matter lesions, microstructural damage, level of neurodegeneration, use of corticosteroids for disease management, time since the last relapse, etc. Given the extra layer of individual variability in clinical populations, brain-behavior correlational findings from a given study may not be replicated reliably in novel samples on PwMS. Marked variability of clinical characteristics, including

cognitive deficits and lesions in MS, requires a characterization of cognitive function that can withstand the heterogeneity of the disease and prove useful beyond sample-specific presentations. A shift in the MS literature towards machine learning is not just favorable but critical. Moreover, our previous work suggests that for populations such as MS with high heterogeneity, multimodal MRI may be essential for maximizing input data for machine learning algorithms to yield robust and generalizable cognitive biomarkers.

In our previous work, we used connectome-based predictive modeling (CPM), a computational, data-driven modeling approach to identify a working memory CPM in MS. Using cross-validation where the internal model derivation sample was split into training and test data; we identified from the whole-brain a set of functional connections (i.e., edges) in training data that were predictive of working memory scores in test data. Interestingly, although the selected edges across all rounds of cross-validation successfully predicted working memory performance in left-out test participants, external validation of the final working memory model to an independent sample of PwMS was unsuccessful. When functional connectivity from novel individuals was inputted into the model, its predictions of working memory performance did not predict significant variance in observed working memory in this sample (Manglani et al., in prep). We hypothesized that the small internal sample (n = 36) and use of only functional connectivity data limited the ability of this predictive model to generalize to unseen individuals. From a methodological viewpoint, our findings and recent literature suggest two things: 1) neural processes supporting cognitive function in MS span functional connections in the whole brain, and 2) supplementary white matter information in MS may enhance the selection of relevant features related to cognitive behavior.

However, this raises a critical question—why spend already limited resources to identify an MRI-based biomarker in MS? Several lines of evidence make MRI the ideal candidate for identifying a robust neuromarker of cognition in MS. First, MRI continues to serve as the most widely used clinical tool for diagnosing MS, monitoring disease activity, and assessing treatment response (Paul et al., 2019). On average, a patient with MS relapses every two years (Confavreux & Vukusic, 2014), and most patients

undergo a routine MRI annually. Importantly, MRI is the best available method to track MS pathophysiology i*n vivo* and make testable predictions of changes in clinical measures, including cognition. Second, perceived neuropsychological impairment does not correlate with objective measures of processing speed (D'hooghe et al., 2020), and standardized neurological examinations also fail to detect insidious emerging cognitive deficits. The use of an imaging-based biomarker precludes the need for time-intensive neuropsychological test administration and scoring and potential practice effects from repeated assessments. Third, international consensus proclaims that to best treat PwMS, efforts should maximize neurological reserve (Sumowski, 2015), cognitive function, and physical ability through early symptom detection and treatment using disease-modifying and behavioral therapies (Cerqueira et al., 2018). Biomarkers are necessary for this pursuit as they can assist with early diagnosis, facilitate patient stratification into treatments, and serve as objective indices of disease progression and treatment response (Barnett et al., 2020; Paul et al., 2019). Fourth, a biomarker of processing speed in MS may be acutely useful as impairment in the speed of information processing is present early in the disease course (Pitteri et al., 2019), often goes unreported and undetected in standard clinical practice (Walker et al., 2019), and among demographic, disability, and quantitative brain measures (i.e., number of lesions), is the strongest predictor of disease progression (Damasceno et al., 2019). In a large cohort including individuals with all subtypes of MS as well as individuals with clinically isolated syndrome, evidence of cognitive impairment preceded MS onset by 1.2 years (Achiron et al., 2013), suggesting a therapeutic window for interventions to preserve cognitive health, prevent accumulation of irreversible disability, and in vulnerable individuals, potentially stave off conversion to MS. As it is of utmost importance that a biomarker predicts clinically-relevant endpoints—that is, measures of functioning across physical, psychological, and cognitive domains, a robust neuromarker of processing speed could serve as a surrogate endpoint for clinical trials. Lastly, two significant indications from the MS neuroimaging literature suggest the potential for better biomarker discovery. First, MS symptoms, including cognitive function, emerge from interactions between disparate and multiple brain networks (Manca, Mitolo, et al., 2019), implying the need for whole-brain approaches. Second, although MS heterogeneity has thus far

challenged biomarker discovery in MS, machine learning approaches may be able to capitalize on this exact individual variability measured in high-resolution multi-modal MRI to yield more sensitive predictions of cognition. Leveraging multimodal MRI and machine learning, this study sought to discover a comprehensive neuromarker of processing speed in MS and test its generalizability to critical disease severity and depression measures.

1.9 Current Study

The **long-term** goal of this study was to derive a neuromarker predictive of cognitive and clinical symptoms that can serve as a clinically meaningful target for intervention in people with MS. In pursuit of this goal, the **overall objective** of the proposed study was to use nested cross-validated predictive modeling to construct a joint structure-function connectome predictive of information processing speed in individuals with multiple sclerosis. Our **main hypothesis** was that a processing speed neuromarker derived using white matter tractography and functional connectivity during a processing speed task would successfully predict clinical metrics of disease severity and depressive symptoms. The **rationale** for this study was the lack of reliable and methodologically-sound neuromarkers of cognitive and clinical metrics in MS that can serve as suitable targets for prophylactic and rehabilitation trials. To accomplish our objective, the main hypothesis was tested according to the following specific aims:

1. **Identify a joint structure-function neuromarker of processing speed in individuals with multiple sclerosis.** Using cross-validation, we weighed whole-brain structural and functional connections based on their relevance to processing speed in training participants, built a predictive model, and assessed model performance by predicting processing speed in test participants.
2. **Assess the generalizability of the joint processing speed neuromarker to disease severity and depressive symptoms.** We examined whether the identified processing speed neuromarker in MS significantly predicts variance in other clinical measures in MS.

3. **Compare the predictive power of a structural vs. functional vs. joint model of processing speed.** Employing the same derivation approach as Aim 1, we derived two additional, separate models based on white matter structural connectivity and functional connectivity alone. To identify the superior connectome, we compared these single-modality models with the joint connectome in predicting processing speed, disease severity, and depression.

Chapter 2

Methods

2.1 Participants

2.1.1 Power Analysis. The primary aim of this study was to build a model based on combined structural and functional connectivity to predict individual-level processing speed in multiple sclerosis. We modeled the procedure of combining multiple imaging modalities after Dhamala et al., (2020), wherein we multiplied each participant's functional connectome with their structural connectome to create a weighted matrix such that all connections missing a structural link (0 weight in the matrix), were zeroed out in multimodal matrix—effectively retaining connections with both functional and anatomical connection. We tested how well the model predicted processing speed scores through nested cross-validation. In the study by Dhamala and colleagues, the prediction of a total cognition composite score in a young adult sample using the steps above resulted in a Pearson correlation between predicted and observed scores of $r = .39$. For a two-tailed test with an alpha level of .05, we required a total sample of 46 participants to yield an estimated power of at least .80. We collected neuropsychological and neuroimaging data from 66 participants as clinical samples are expected to have more heterogeneous connectivity patterns than healthy young adults and tend to move more during the MRI scans requiring some imaging data to be excluded altogether.

2.1.2 Sampling and Screening. The proposed study used data collected at baseline from our randomized controlled trial on physical activity in relapsing-remitting individuals with MS (clinicaltrials.gov # NCT03244696). Recruitment for this study occurred in the greater Columbus, OH area through advertisements on Facebook, craigslist, Research Match, the National MS Society, and via The Ohio State University Wexner Medical Center MyChart patient portal. Our laboratory has strived to

recruit participants across diverse racial and ethnic backgrounds by attending MS support groups, Scarlet and Gray MS Day at the medical center, and via the MS walk events.

Individuals interested in the study were screened using a two-stage process. First, interested individuals completed a phone or online (Qualtrics) screening where we provided additional information about the study and collected basic demographic information such as age, gender, education, ethnicity, clinical characteristics including MS type, disease duration, diagnosis of neurological or psychiatric disorders, evidence of any MRI contraindications, and information about general level of physical activity and sedentariness. Individuals meeting age, disease subtype, and sedentary criteria (listed in the inclusionary/exclusionary criteria in Table 1) were enrolled in the study and invited to the lab to complete the first neuropsychological assessment session. During this visit, additional measures were administered to confirm eligibility, including a visual acuity test using the Snellen eye chart, a repeated MRI safety screening, and the Expanded Disability Status Scale to determine adequate mobility (EDSS score ≤ 5.5) for potential randomization into the physical activity group. Participants who met MRI eligibility criteria were invited back about a week later to complete the MRI neurocognitive assessment. This study was approved by The Ohio State University Institutional Review Board. Participants were informed of all study components, the expected daily time commitment, and their ability to withdraw from the study without penalty. Study participants were compensated $10 for each Qualtrics questionnaire, $10 per hour for the neuropsychological assessment sessions, and $15 per hour for the neurocognitive MRI sessions. Note that some data collection for this study occurred during the COIVD-19 pandemic; as such, appropriate modifications to the testing environment were made to ensure safe social distancing practices.

2.2 Procedures

Participants completed a neuropsychological assessment in which they were administered a series of questionnaires and neuropsychological tests over the course of three to four hours, inclusive of breaks. About a week later, participants returned to the Psychology building to complete a 90-minute neurocognitive assessment while undergoing MRI. Participants were asked to lie in the scanner and rest

for some scans and complete cognitive tasks during other scans. For more details on the MRI tasks see section 2.3.

2.2.1 Neuropsychological Assessment. Participants completed a series of questionnaires and neuropsychological batteries as part of the baseline behavioral assessment. All neuropsychological measures relevant to the Aims are described below, and all remaining measures are described in the Appendix.

Expanded Disability Status Scale (EDSS). Participants completed the self-report version of the EDSS in the lab. The EDSS is used to measure disease severity by assessing eight functional systems, including pyramidal (reflexes, muscle strength, spasticity), visual (optic), cerebral (depression, cognition, fatigue), cerebellar (tremor, ataxia, coordinated movements), brainstem (speech, swallowing, nystagmus), sensory (numbness, touch/pain/proprioceptive sensation), bowel and bladder (hesitance, urgency, retention, incontinence), and ambulation (full: ≥ 500 meters unassisted, uni- or bilateral need for help or aid) (Kurtzke, 1983). The EDSS is scored from 0 – 10 in half-point increments, with qualitative descriptors indicating disability is absent or minimal (score between 0-2), mild to moderate (2.5 – 4), significant but permitting ambulation without aid or rest for up to 100 meters (4.5 – 5.5), requires at least one walking aid (6 – 6.5), restrictive to wheelchair and necessitates aid to a variable degree (7 – 8), confines to bed and requires assistance for daily living to a varying degree (8.5 – 9.5), maximal, causing death due to MS (10). We also collect protected health information from each participant's neurologist, including a neurologist-administered EDSS, to objectively measure disease severity.

Beck Depression Inventory-II (BDI-II). The most widely used scale to assess depressive symptoms is the Beck Depression Inventory (BDI; Beck et al., 1996). This 21-item self-administered scale assesses the presence and severity of symptoms of depression in the last two weeks (Beck et al., 1996). This scale assesses symptoms of sadness, pessimism, guilt, self-dislike, self-criticalness, crying, agitation, indecisiveness, irritability, and fatigue, as well as loss of pleasure and interest, feelings of punishment and worthlessness, difficulties with concentration, and suicidal ideation, and changes in energy, sleeping patterns, appetite, and interest in sex. Each item is rated on a 4-point scale in the degree

of severity from 0 (not at all) to 3 (extreme). The total score can range from 0 – 63. Guidelines for qualitatively interpreting the BDI-II score suggest depression is: minimal (score between 0 – 13), mild (14 – 19), moderate (20 – 28), or severe (29 – 63).

2.2.2 Neurocognitive Assessment. Participants completed this assessment at the Center for Cognitive and Behavioral Brain Imaging (CCBBI) housed within the department of Psychology at The Ohio State University.

Symbol Digit Modalities Test (SDMT). Participants completed the oral SDMT adapted for the MRI environment and modeled after Forn and colleagues (2009). This task consists of two conditions—symbols (processing speed) and numbers (control), with six blocks administered per condition. Each block begins with the cue "symbols" or "numbers" to indicate which condition will follow. During the symbols condition, participants are presented with a key of symbol-number pairs along the top of the screen. An upper row contains a sequence of 9 symbols and a lower row containing nine corresponding numbers (1-9). On each trial, a symbol probe appears in the center of the screen, and participants are asked to voice the number that corresponds to that symbol. To avoid potential learning/practice effects, after the first half of blocks, a new symbol-number key is presented and used for all subsequent runs of the symbol condition (similar to other studies: DeLuca et al., 2008; Patel & Feinstein, 2019). During the control blocks, participants are provided an empty key and asked to orally read the probe on each trial, a pseudorandomized number from one to nine. Probes are presented for 2s, and 15 trials are completed per block. This task was administered across two runs (8 min 26s each) with six blocks per run for a total completion time of 16 min 52s. The two measures this task yields are accuracy and reaction time.

Two raters coded the SDMT task. When the average interrater reliability of the symbols and numbers condition fell below .90, a third rater also coded the data. Correlations between the original two raters and the third rater were performed, and coding from the two raters with the highest overall correlation was retained. Each participant's processing speed score equaled their average reaction time across all completed symbol blocks and served as the primary DV.

Imaging Parameters. Neuroimaging data was collected at the Center for Cognitive and Behavioral Brain Imaging at The Ohio State University on a 3T Siemens MAGNETOM Prisma system using a 32-channel head coil. The MRI protocol in order of acquisition includes: localizer, resting-state fMRI, T1w magnetization prepared rapid gradient echo (MPRAGE), N-back run 1, N-back run 2, fieldmaps, diffusion-weighted imaging (DWI), fluid attenuated inversion recovery (FLAIR), SDMT run 1, and SDMT run 2. Additional axial MPRAGE and myelin compaction sequences were collected in some initial participants. The total scanning time was about 90 minutes. Imaging parameters for all relevant sequences are reported in Table 2.

2.3 Preprocessing

2.3.1 Lesion Preprocessing As lesions can disturb registration steps, we employed a lesion segmentation pipeline to generate lesion masks. We entered FLAIR and MPRAGE images into the fully automated Lesion Segmentation Toolbox (LST; Schmidt et al., 2012) (https://www.statistical-modelling.de/lst.html) version 2.0.15 for SPM. This toolbox uses prior probability maps from a sample of PwMS and the user-provided lesion growth algorithm threshold (k = 0.5) to segment lesions. The generated binary lesion masks contain a value of 1 in lesion sites and 0 in non-lesioned areas. This binary lesion mask, the skull-stripped T1w reference, and the skull-stripped standard ICBM 152 template (version 2009c; Fonov et al., 2009) were entered as input to the antsRegistration tool (ANTS v2.1.0; Dale et al., 1999) for nonlinear spatial normalization of the T1w reference image to standard space.

2.3.2. Functional Preprocessing Most structural and functional data preprocessing was completed using fmriprep (Esteban et al., 2019) via Nipype staging and execution (Gorgolewski et al., 2011). This pipeline was selected as it allows for an analysis-agnostic implementation of tools from different software packages and facilitates reproducible and transparent MRI data preprocessing. The initial step of this workflow was to correct for low frequency inhomogeneities in each participant's T1w image by applying a non-uniformity intensity normalization using N4BiasFieldCorrection v2.1.0 (Tustison et al., 2010) and creating a T1w reference image. The T1w reference image was then skull-

stripped within antsBrainExtraction.sh v2.1.0 using the OASIS atlas template. The skull-stripped T1w was segmented into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) using FMRIB's Automated Segmentation tool (FAST; FSL v5.0.9; Zhang et al., 2001). To refine the brain mask estimation, outputs from FreeSurfer (v6.0.1) brain surface reconstruction and ANTs cortical gray matter segmentation were reconciled to attain a more precise brain mask for registration to standard space.

In the next set of steps, the SDMT fMRI data was used to estimate head motion using FMRIB's MCFLIRT (FSL v5.0.9; Jenkinson et al., 2002) and inhomogeneities at tissue interfaces using fieldmaps via FMRIB's FUGUE (Jenkinson, 2003). Using a boundary-based registration (Greve & Fischl, 2009) with six degrees of freedom (3 rotations in mm and three translations in radians), the parameters for EPI to T1w were estimated via bbregister in Freesurfer (v6.0.1). Motion correction, distortion correction, EPI-to-T1w transformation, and T1w-to-template MNI coregistration was applied in a single rigid-body transformation step using antsApplyTransforms (ANTs v2.1.0) employing Lanczos interpolation.

To remove significant sources of noise, including anatomical (e.g., WM and CSF) and temporal (i.e., physiological, motion), from the data, we used principal components analysis; the CompCor algorithm searched areas of WM and CSF for temporal fluctuations, which are likely not modulated by neural activity and reflect physiological (e.g., cardiac and respiratory) fluctuations (Behzadi et al., 2007). Using the physiological fluctuations in these noisy areas, CompCor searched for similarities in gray matter time series to distinguish time series signal from GM noise. fMRIPrep yielded six temporal components from the top 5% of variable voxels within the subcortical mask. It also combined the subcortical mask with the CSF and WM masks generated in T1w space, projected them into the native space of each SDMT functional run, and computed six anatomical noise components. Finally, for each functional run, the amount of motion from the previous volume, known as framewise displacement (Power et al., 2014), was estimated through the implementation of Nipype. Several other operations on preprocessing BOLD data were completed through fmriprep and employing Nilearn (Abraham et al., 2014), used recently by a study in MS (Fuchs et al., 2019).

Regression of nuisance variables was completed using adapted code (https://github.com/fliem/sea_zrh_rs). First, the confound file generated by fMRIPrep for each SDMT run was filtered to include these confounds: six rigid body motion parameters, their first temporal derivatives, along with and the 12 quadratic terms (totaling 24 head motion parameters), CSF, WM, global signal (average signal within the entire brain mask; Li et al., 2019; Murphy & Fox, 2017), as well as their temporal derivatives and quadratic terms (totaling 12 parameters). In addition to this 36-parameter denoising (Satterthwaite et al., 2013), outlier time points identified using framewise displacement were regressed from the final timeseries. As sudden large intensity spikes could also indicate significant motion, time points with a root mean square displacement >.50 were also regressed. Lastly, temporal high-pass filtering was implemented to filter out the scanner and physiological noise sources present as low-frequency signal drifts in the data retaining high frequency (.01 Hz) signal—anything more frequent than once every 100 seconds. Note, runs that indicated excessive head motion, that is, mean framewise displacement > 0.25 mm and > 10% of volumes with high motion (> 0.5 mm from the previous volume), were excluded entirely.

2.3.3. Parcellation. Two brain parcellation schemes were used to build the functional and structural connectomes. The Glasser atlas (https://github.com/brainspaces/glasser360) derived using multi-modal MRI from the Human Connectome Project contains 360 cortical nodes (Glasser et al., 2016). This atlas was combined with select subcortical nodes from the FreeSurfer aseg file totaling 379 nodes. Eight nodes were missing across the sample and were thus removed from both functional and structural matrices. Missing nodes included: left polar 10p, left and right orbital frontal complex, left and right hippocampus, left posterior orbital frontal complex, left nucleus accumbens, and right area 33 prime. This resulted in a final 371 x 371 atlas. To test the joint connectome using a lower resolution parcellation and assess potential parcellation effects, we also employed the Desikan-Killiany atlas (Desikan et al., 2006) combined with the FreeSurfer subcortical parcellation for a total of 86 nodes. Three nodes (left frontal pole, and left and right nucleus accumbens) missing in select participants were removed, resulting in final 83 x 83 matrices.

2.3.4 Diffusion preprocessing. Quality control of diffusion weighted imaging (DWI) data was completed in three steps: 1) nifti images were converted to nrrd files using 3DSlicer version 4.11.20200930 (Fedorov et al., 2012; Kikinis et al., 2014), 2) an automated quality check protocol was executed using DTIPrep version 1.2.8. (Oguz et al., 2014) to identify and remove gradients with artifacts, and 3) the quality-controlled files were converted back to nifti using the conversion git repository (https://github.com/pnlbwh/conversion#introduction). We wrote a script to remove artifactual gradients from the raw diffusion data manually, and this quality control DWI was entered for subsequent preprocessing. DWI preprocessing, construction of the structural connectivity matrices, and visualization of white matter streamlines was completed using MRtrix3 (Tournier et al., 2019), and FSL version 6.0.0 (Jenkinson et al., 2012). MRtrix3 is an open-source, modular software package that can flexibly manipulate images for analysis and visualization. This package also has built-in functionality to input data in the Brain Imaging Data Structure (BIDS) format, regarded as the standard for organizing and sharing neuroimaging datasets (Gorgolewski et al., 2016). We followed the latest recommendations to minimize noise components which involved seven main steps: motion and eddy current correction, reconstruction of streamline tractography, spatial constraints on streamline propagation, a streamline seeding algorithm, tractogram re-weighting, brain parcellation, and network construction using edge weights.

Motion and eddy current distortion correction. The first step was to correct for artifactual sources of noise, including motion and eddy-current induced distortions. Akin to fMRI, motion is problematic in DWI as it can misalign slices, attenuate signal intensities, and cause signal dropout (Andersson et al., 2017). Also affecting the magnetic field, the rapidly switching diffusion encoding gradients used in DWI induce eddy currents in the conductors within the bore (Andersson & Sotiropoulos, 2016). To correct for both, a Gaussian process-based generative model was employed to yield a prediction of each diffusion volume. Comparing the predicted and actual images provided estimates of eddy current-induced distortions and was used to realign the data.

Diffusion model reconstruction. Recent advances in tractography have moved beyond estimating one fiber orientation per voxel to deconvolution methods that can identify multiple fiber orientations for each voxel (Tournier et al., 2004). This approach is particularly useful for crossing or kissing fibers which make up about 90% of the structural connectome. It has also been shown to reconstruct streamlines through lesions in PwMS (Lipp et al., 2020). We used probabilistic tractography to reconstruct the white matter pathways; the orientation to propagate the streamline was chosen from a distribution of possible orientations at each streamline vertex. Although prone to false positives, probabilistic tractography is also more sensitive in tracking non-dominant fiber pathways. This algorithm was implemented using MRtrix3's second-order Integration over Fiber Orientation Distributions (iFOD) using Constrained Spherical Deconvolution (Tournier et al., 2007). Specifically, from each vertex, the probability of candidate streamline trajectories was calculated using the amplitudes of the FODs along those trajectories. Higher probability trajectories were randomly selected to propagate the streamline.

Constraining streamline propagation. For whole-brain tractography, anatomically constrained tractography (ACT) provides the advantage of using biologically realistic priors, which more accurately determine where streamlines should end (Smith et al., 2012). This ensures that streamlines terminate at gray matter or gray matter-white matter interfaces and do not pass through CSF. ACT also helps to reduce the number of false positives in tract reconstruction. The brain was segmented into five different tissue types (cortical and subcortical gray matter, white matter, CSF, and pathological tissue) using FSL tools. This anatomical information was used to create a mask identifying the gray matter-white matter boundaries to seed streamlines.

Seeding streamlines. We employed dynamic seeding to reconstruct pathways that are traditionally more difficult to track. In this novel seeding approach, the tractogram is consistently compared to the fiber density estimates from the diffusion model and the current reconstructed streamline density to preferentially seed streamlines from voxels where the streamline density is underestimated. This method integrates global information into the more locally-attentive tractography process and is shown to outperform homogenous seeding either throughout white matter or from the gray matter-white

matter interface (Smith et al., 2015). We generated ten million streamlines for each participant with a maximum length of 250 mm and a max FOD amplitude of 0.6.

Reweighting tractogram. A limitation of diffusion tractography is that the density of reconstructed streamlines may not necessarily reflect the density of the underlying white matter fibers, potentially producing biologically implausible connectivity estimates. Using Spherical-deconvolution Informed Filtering of Tractograms (SIFT2; Smith et al., 2015), the expected fiber densities at each voxel were modeled, and the streamlines were weighted based on how well they fit the model. This ensured that streamline densities were proportional to the fiber densities and were thus biologically plausible. Individual connectomes were visually inspected using the MRtrix3 connectome visualization tool.

Constructing networks and weighting edges. The weights of all streamlines connecting that region pair were summed to yield the edge weight for every pair of regions. The sum of streamline weights (SSW) approach has shown to be superior to traditional fractional anisotropy, which is more susceptible to the effects of motion (Tijssen et al., 2009). Streamlines were assigned to each of the closest regions within a 5 mm radius of the streamline endpoints to generate undirected matrices using Glasser and Desikan-Killiany atlases.

2.4 Multimodal Connectome Generation

2.4.1 Functional Connectome The functional connectome was constructed using the combined Glasser and subcortical nodes, the Desikan-Killiany plus subcortical segmentation, and each participant's preprocessed and nuisance-regressed functional MRI data. Customized MATLAB scripts were used to build connectivity matrices representing the time series correlation of each brain region (node) with every other node. First, for each run of the SDMT, the mean time series for each node was computed, cross-correlated with every other node, and then Fisher *Z*-transformed. Next, an average of the Fisher Z-transformed matrices was taken across both SDMT runs to yield an overall correlation matrix for each participant. Then, any nodes missing in any participants were removed from all participants. This served as the participant's functional connectome (FC).

2.4.2 Structural Connectome The structural connectome was built using a similar procedure as the steps above for functional connectivity. Structural connectivity was estimated for the single DWI sequence, and the nodes missing coverage in functional data were also removed from the structural connectome. Instead, the resulting matrix was normalized for each participant such that edge weights ranged from 0 to 1 and served as each participant's structural connectome (SC).

2.4.3 Multimodal Connectome For the multimodal connectome (MC), we constructed a weighted MC wherein we multiplied the functional connectivity and structural connectivity matrices. The upper triangular of this symmetrical matrix was then vectorized and concatenated across participants to yield a weighted MC. Edge values in this matrix represented the strength of both anatomical and functional connectivity. For example, if a participant was missing an anatomical white matter connection, that participant would have had a value of 0 in their SC matrix, which would zero out when multiplied by the functional connection value. In contrast, if an edge had a strong anatomical and functional connection, its value in the matrix would be larger. In this way, the final values in this matrix reflect a) existence of both a functional and structural connection and b) the direction (positive or negative) of the functional connectivity. Finally, each participant's raw processing speed score was entered into a single column vector in the corresponding row as their connectivity data and *z*-scored within the training/test split of each permutation for model tuning and building.

2.5 Model Tuning

Code for model tuning and building was adapted from (https://github.com/elvisha/CognitivePredictions/blob/master/cognitive_prediction.ipynb) and followed similar research predicting cognition in healthy adults (Dhamala et al., 2020). As growing evidence suggests that small sample sizes can lead to highly variable estimates of prediction accuracy (Poldrack et al., 2019), we took additional steps to counter overfitting and optimize our models. First, we used the python package scikit-learn (Pedregosa et al., 2011) to test multiple regression algorithms (ridge and lasso) in the model tuning phase to make predictions less sensitive to training data. A regularization

parameter (λ) or a constant is added to the cost function to penalize the regression for its high number of features. Increasing lambda lowers the slope, which moves feature weights closer to 0 for some features. Thus predictions (of behavior) become less sensitive to the predictor (connectivity data). Second, tested various train/test splits to assess influence on model performance. Third, we tuned the hyperparameters using a grid of possible values and evaluated results using *r* in a subset of permutations (5-10). The best performing and most consistent hyperparameter grid was selected for final model building across all 100 permutations. This entire procedure was repeated using both Glasser and Desikan-Killiany atlases.

2.5.1 Ridge. Ridge regression L_2 regularization minimizes the sum of the squared prediction error in the training data by adding a penalty equal to the squares of the coefficients. Ridge regression retains all of the features but shrinks the coefficients and assigns similar coefficient values to correlated features. A primary advantage of l_2 regularization is that it minimizes model complexity and avoids overfitting to training data.

2.5.2 Lasso. Least absolute shrinkage and selection operator (LASSO) regression differs from ridge regression in that it uses shrinkage to produce sparse models with fewer parameters. This procedure is well-suited for neuroimaging models with high levels of multicollinearity among features. L_1 regularization adds a penalty equal to the absolute value of the regression coefficients. L_1 regularization selects one random feature among a group of correlated features and sets other regression coefficients to zero. Thus, lasso optimizes the predictors and yields a sparse, less complex model relative to ridge regression. Note, lasso retains a maximum of *n*-1 features in the final model, which means that at maximum, lasso will have a non-zero weight assigned to 63 features.

2.5.3 Model Selection For each connectome, the final modeling approach (lasso or ridge) was selected based on model performance during the hyperparameter tuning stage. Ultimately, lasso emerged as the optimized algorithm for our primary Glasser plus subcortical atlas, and ridge emerged as the superior algorithm for the Desikan-Killiany atlas. Final model building used these algorithms for the respective matrices across 100 permutations.

2.6 Final Model Building

Explained variance was used to optimize the models, and mean correlation between predicted and observed processing speed scores was used to select the final hyperparameter grid of alphas. In each of the 100 permutations, the data was randomly split into training (80%) and test (20%) participants. The left-out 20% of the data was reserved for final model testing. Within each permutation, ten cross-validation loops were run using the training data and split into five inner and five outer cross-validation loops for nested cross-validation. The five inner loops were used to select the best hyperparameters, and the five outer loops assessed the performance of the optimized hyperparameters. In the first outer cross-validation loop, the training 80% were divided into five subsets and fed into the first inner loop. Four of these subsets served as training data and the 5^{th} as the test data. A ridge model fit the MC features to processing speed scores. This process was repeated for four additional rounds of inner cross-validation, yielding five explained variance values for the correlation between predicted and observed processing speed scores. From the model with the highest explained variance, the optimal regularization parameter was identified and entered into the outer cross-validation loop for testing. This again generated explained variance. Repeated across five outer cross-validation loops, a total of five values for explained variance were produced, and from those, the optimal or best-performing hyperparameter was chosen for final testing on the initial left-out 20% of participants. Figure 1 depicts the model building process.

To quantify whether the joint connectome predicts processing speed over and above functional or structural connectomes alone, the MC was compared independently with the FC and SC. The model generation procedure was repeated using the functional and structural connectomes separately. A final lasso regression model using the median hyperparameter determined from nested cross-validation was tested on the initial left-out 20% test sample, producing model performance estimates and repeated over 100 permutations to yield a distribution of performance separate for functional and structural connectomes.

In the next step, we interpreted feature (i.e., edge) importance to identify connections within and between canonical networks most relevant for predicting processing speed. As the reliability of feature

weights can be low with sample sizes < 800, in addition to applying (lasso/ridge) regularization, we completed a Haufe transformation on feature weights to maximize reliability (Tian & Zalesky, 2021). The Haufe transformation estimated the covariance between feature weights and transformed the weights to ensure that the most important features are weighted highly (Haufe et al., 2014).

2.7 Model Significance

To evaluate model significance for each (MC, FC, SC) model, we built a corresponding null distribution of 1000 permutations. In each permutation, we shuffled brain-behavior pairings, split the data into the same train and test splits used in true model building, and randomly selected one of the optimized alpha values from the 100 true models. In each of the 1000 permutations, the null model was applied to the held-out test set, yielding an *r* value for the correlation between predicted and observed processing speed scores for each permutation. From this null distribution, we identified the median *r* value. True model significance was evaluated as the proportion of the 100 true model *r* values that were less than the median null *r* value for the respective connectome.

2.8 Statistical Analysis

2.8.1 Exploring Contribution of Demographic and Clinical Characteristics. To examine the contribution of relevant demographic variables, including age, sex, education, and clinical characteristics, such as self-reported and neurologist-reported EDSS, disease duration, and T2 lesion load volume in explaining variance in processing speed, we first conducted zero-order correlations between these variables. Specifically, correlations were calculated between age, sex, education, BDI scores, self-reported EDSS, objective neurologist-administered EDSS (where data was available), self-reported disease duration, total lesion load volume, and processing speed scores.

2.8.2 Model Performance. For Aim 1, model performance was evaluated using the Pearson correlation between model-predicted and observed processing speed scores, mean absolute error (MAE), and mean squared error (MSE). This entire process was repeated across 100 permutations to generate

distributions of model performance. The model with the median performance among this distribution was selected as the final model to visualize and characterize the contributions of macroscale regions and canonical functional networks. In Aim 2, we tested the generalizability of the processing speed connectome in predicting disease severity and depression. Spearman rank correlations between the final joint connectome predicted processing speed scores, and self-report EDSS, neurologist-reported EDSS (on available $n = 35$), and BDI-II scores were computed. Aim 3 used model performance parameters from the multimodal connectome (MC), the functional connectome (FC), and the structural connectome (SC). Model performance distributions were visualized using violin plots depicting the median, range, and 25% and 75% interquartile values.

Chapter 3

Results

3.1 Demographics, Clinical Characteristics, and Behavioral Performance

Complete neuroimaging data (fMRI and DWI) was collected on 66 participants. After excluding two participants with incidental findings unrelated to MS, our final sample consisted of $n = 64$ participants. Our sample consisted of mostly females (79.7%) who were college-educated ($M_{education}$ = 16.1 years), and have a mean age of 47 years. Clinically, the sample had a mean EDSS score of 3.95, have lived with MS for an average of 10.7 years, and reported mild depressive symptoms ($M_{BDI} = 11.6$). Participants self-reported their race with one identifying as American Indian or Alaska Native, eight identifying as Black or African American, two identifying as belonging to more than one race, 51 identifying as White, and two that are unknown or who chose not to report. No participants self-identified as Hispanic/Latino, 63 identified as Non-Hispanic/Latino and one participant chose to not report on their identity. Descriptive characteristics of our final sample are presented in Table 3.

The mean age of the current sample was comparable to other neuroimaging investigations in MS (Charalambous et al., 2019; Eijlers et al., 2019; Jandric et al., 2021; Tozlu, Jamison, Gu, et al., 2021). Our study had a slightly higher percentage of females (79.7%) relative to other studies (66.5%) (Buyukturkoglu et al., 2021; Eshaghi et al., 2021; Grothe et al., 2020; Has Silemek et al., 2020; Jandric et al., 2021; Lopez-Soley et al., 2021, 2021; Meijer et al., 2017; Schiavi et al., 2022; Tozlu, Jamison, Gauthier, et al., 2021); however, several of the more recent studies have included about 70% females in their sample (Charalambous et al., 2019; Koenig et al., 2021; Pontillo et al., 2021). In terms of clinical measures, our sample was on the higher end of disease severity with most studies reporting a mean or median EDSS ≤ 3.5 (Buyukturkoglu et al., 2021; Grothe et al., 2020; Has Silemek et al., 2020; Jandric et

al., 2021; Koenig et al., 2021; Lopez-Soley et al., 2021, 2021; Meijer et al., 2017; Pontillo et al., 2021; Tozlu, Jamison, Gauthier, et al., 2021; van Geest et al., 2018). However, in terms of disease duration, our participants had been living with MS for a comparable number of years as other imaging samples (Eshaghi et al., 2021; Grothe et al., 2020; Has Silemek et al., 2020; Jandric et al., 2021; Lopez-Soley et al., 2021, p.; Pontillo et al., 2021; Tozlu, Jamison, Gu, et al., 2021; van Geest et al., 2018), with only a few studies reporting much shorter (Buyukturkoglu et al., 2021) or longer (Charalambous et al., 2019; Eijlers et al., 2017; Koenig et al., 2021; Schiavi et al., 2022) disease duration.

SDMT task performance was quantified by reaction time and accuracy (see Table 4). Accuracy was high in both symbols (97.7%) and numbers conditions (99.8%). We also found the expected difference in reaction time between the symbols (in milliseconds: Median_{RT} = 1449; *SD* = 161; Range = 1178 – 1864) and numbers (in milliseconds: Median_{RT} = 654; *SD* = 128; Range = 454 – 1091) condition. A Wilcoxon signed-rank test showed that the median difference in reaction time was statistically significant, $T = 0$, $p < .001$, confirming that the symbols condition measured processing speed and the numbers condition served was a simple control condition. Figure 2 depicts the median, and interquartile range of performance by condition (symbols, numbers) via violin plots. Our primary outcome variable (herein referred to as observed processing speed score) was reaction time in the symbols condition.

3.2 Correlations Among Demographic, Clinical, and Cognitive Variables

Table 5 presents zero-order correlations among demographic variables, clinical characteristics, and processing speed. Disease duration was positively associated with lesion volume ($r_s = .40$, $p = .001$) indicated that those living with the disease for a longer time had higher lesion burden. We also found a significant negative correlation between disease duration and BDI-II scores ($r_s = -.25$, $p = .05$), suggesting that PwMS living with MS for a longer time reported lower depressive symptoms (Figure 3B). Self-reported EDSS was also significantly associated with BDI-II scores ($r_s = .28$, $p = .026$), indicating a link between disease severity and depressive symptoms (Figure 3A). Neurologist-reported EDSS was only available for about half of the sample ($n = 35$) and did not relate to any assessed variable, including self-

report EDSS. Processing speed was significantly correlated with self-reported EDSS (r_s = .28, p = .025) and BDI-II (r_s = .27, p = .031), indicating that those who demonstrated slower information processing also reported more disease burden and depressive symptoms (Figure 3C and 3D, respectively). As the second aim of this study was to assess model generalizability, that is, whether the predicted processing speed scores correlated with disease severity and depression, we did not control for self-reported EDSS or BDI-II during model building.

3.3 Processing Speed Model Building

3.3.1 Hyperparameter Tuning. A series of steps were taken separately for each (multimodal, functional, and structural) connectome to determine the combination of hyperparameters that maximized model performance—the correlation between predicted and observed processing speed scores. Models were set to optimize explained variance. This manual hyperparameter optimization procedure tested two different estimators, ridge and lasso. Both regularizations penalize the magnitude of coefficients while minimizing the error between predicted and observed scores. With ridge, the larger the alpha, the higher the smoothness constraint and the smaller the magnitude of model coefficients. With lasso, the larger the alpha values, the more features are set to a coefficient of zero. We invoked these approaches of adding bias to avoid overfitting and retain the most important features. With each estimator, we additionally assessed the influence that various train/test data splits (training set = .65, two-thirds, .70, three-fourths, .80 of the sample) had on prediction accuracy. In each of those train/test splits, we built a grid of possible hyperparameters ranging linearly and logarithmically from 10^{-10} to 10^{4} (.0000000010 to 100,000) and used GridSearchCV to test all hyperparameters exhaustively. This procedure of iteratively fitting the estimator on a fraction of the data was repeated for 5-10 permutations to identify the subset of hyperparameters that yielded the highest correlation.

The hyperparameter tuning stage demonstrated significant variability in model performance as a function of the atlas, algorithm, train/test split, and lambda range. The lasso regularization yielded better prediction performance than the ridge regularization for the Glasser atlas, which consisted of many non-

zero features (MC and SC: 20,125 connections; FC: 68,635 connections). For example, the highest correlation attained for the multimodal connectome during tuning was r = -.076 (using ridge) and r = .22 (using lasso). In contrast, the ridge regularization produced better model performance for the Desikan-Killiany atlas which contained fewer non-zero features (MC and SC: 2,232 connections, FC: 3,403 connections). Similar variability in model performance between atlases was also observed for the train/test splits, such that a train set of .80 was optimal for the Glasser atlas. In contrast, a two-thirds train set produced the best-fitting models for the Desikan-Killiany atlas. Additionally, within each atlas, there were minimal differences in model performance between the structural versus the functional connectomes, suggesting that each imaging modality may require a different proportion of data for training and testing for the current sample size. However, overall performance was comparable between connectomes and different train/test splits using the same atlas. As such, the train/test split was the only parameter we held consistent across connectomes within an atlas, making it feasible to compare predicted scores across models.

The optimized algorithm and train/test split differed by atlas and were passed to full model building accordingly. For the Glasser atlas, lasso regression and a training split of .80 demonstrated an adequate correlation between predicted and observed processing speed. For the Desikan-Killiany atlas, ridge regression on a training set of two-thirds yielded the highest predictive power. Table 6 presents results for the best performing model from hyperparameter tuning for each atlas by connectome, using both ridge and lasso algorithms, and with the optimized lambda range.

3.4 Model Performance using Glasser Plus Subcortical Atlas

3.4.1 Multimodal Connectome. We split the sample into training (.80) and test (.20) set in each permutation for final model building and tested the optimized alpha values using lasso regression. The final model performance was the average r across all 100 permutations. Our final model was not significant after null permutation testing, which quantified the proportion of true models that had a correlation below the median null correlation between predicted and observed processing speed scores (r

= .080; p = .49). For each of the 100 MC permutations, we additionally tested whether the predicted processing speed scores for the test sample correlated with observed disease severity and depression scores for those sample participants in the test split. The average spearman rank correlation was not significant between predicted processing speed and EDSS (r_s = -.10, p = .49) or BDI scores (r_s = -.074, p = .54). Final model performance is reported in Table 7.

3.4.2 Functional Connectome. The same .80/.20 train/test split was used with lasso regression across 100 permutations. The average model for the FC was not significant (r = .078; p = .40).

3.4.3 Structural Connectome. Using the same train/test split and lasso regularization across 100 permutations with SC, we found that the average correlation between predicted and observed scores was not significant (r = .12; p = .07). Each connectome is graphically presented in Figure 4 as a violin plot displaying the distribution, median, and interquartile range of the correlations across all 100 permutations.

3.5 Results using Desikan-Killiany Atlas

3.5.1 Multimodal Connectome. The final train/test split used for the connectomes built with the Desikan-Killiany atlas was two-thirds for the train set and one-third for the test set. Ridge regression emerged as the optimal method for this atlas. The 100 true permutations when compared with the median correlation from the null distribution resulted in a final model that was not significant (r = .031; p = .23). We tested correlations between predicted processing speed scores for the test set in each permutation with observed EDSS and BDI scores for the same individuals in the test set. The average spearman rank correlation was not significant for either EDSS (r_s = .083, p = .55) or BDI (r_s = .073, p = .55).

3.5.2 Functional Connectome. The final FC model resulted in mean performance that was not significant across all 100 permutations (r = .055; p = .17).

3.5.3 Structural Connectome. Compared to the median null correlation, the distribution of true correlations between predicted and observed scores was not significant (r = .024; p = .54).

Distributions of true and null model performance for the Desikan-Killiany atlas are shown as violin plots in the second row of Figure 4.

Chapter 4

Discussion

This study aimed to identify a multimodal neural network of information processing speed using machine learning in individuals with MS. Through an extensive process of hyperparameter tuning, we built a suite of six models from multimodal, functional, and structural connectivity using two separate atlases to predict processing speed performance. Our results show that whole-brain, multimodal connectivity did not predict significant variance in processing speed or predict cognitive scores that correlated with clinical measures of disease severity and depression. Attempts to predict processing speed were also unsuccessful when using functional connectivity or structural connectivity independently. The novelty and challenges of the current study provide direction for future connectomic research in MS.

4.1 Relationships between cognitive, clinical, and demographic variables

Our correlational analyses with behavioral data confirmed relationships between demographic and clinical characteristics observed in the broader MS literature. First, we found the expected positive relationship between disease duration and lesion volume showing greater MRI lesion burden in participants with a longer MS course. Contrary to expectations, total lesion volume was not associated with higher severity of MS. Although this finding stands somewhat contrary to the results of a systematic review and meta-analysis showing that the number and volume of brain lesions after disease onset may be linked to disability progression (AlTokhis et al., 2022), it concords with multiple other studies demonstrating that the topology of lesions, rather than the overall lesion volume relates to clinical manifestations of MS (Ledesma et al., 2021; Rocca et al., 2015). Longitudinal data have further confirmed this relationship by showing that lesion density of sublobar regions (lesion volume divided by the volume of a given brain region) was associated with worsening disability measured by the EDSS

(Gaetano et al., 2020). These findings confirm that overall lesion load, which does not consider the heterogeneous presentation (size and location) of lesions, may not relate meaningfully with important clinical measures such as disease severity.

Notable relationships with depression emerged from this study. We found a negative relationship between disease duration and depression, indicating that participants living with MS for more years reported lower depressive symptoms. This finding is notable as research on the relationship between depression and disease course has been somewhat limited. Although some studies have shown an increase in depressive symptoms from CIS to clinically definitive MS (Feinstein et al., 2014), findings have been inconsistent when rates are compared between relapsing-remitting and progressive MS (Feinstein et al., 1992). Our finding of higher depressive symptoms in PwMS earlier in their MS course suggests that adjustment to illness may be more challenging in the initial years after diagnosis. This dovetails with a recent meta-review of systematic reviews in MS that found internal factors, including negative emotional responses, management techniques (i.e., acceptance), and engagement in activities, impact psychosocial adjustment to the illness (Topcu et al., 2020). Such vulnerabilities are shared across neurodegenerative diseases leading to a transdiagnostic framework, which advocates for psychosocial interventions early after diagnosis to promote emotional well-being and resilience (Bannon et al., 2022). In line with the meta-review, here, we found that self-reported disease severity correlated positively with depressive symptoms. Even within the study's restricted range of 0-5.5 on self-reported EDSS, individuals with a more severe disease reported more depressive symptoms. As the scoring of EDSS weighs physical function heavily, it is plausible that individuals with a more significant physical burden of the disease may also experience greater emotional challenges. A similar relationship has been shown between moderate-to-severe depressive symptoms and slower objective walking speed in older adults with MS (Chan et al., 2021).

With information processing speed, high accuracy on the SDMT indicated that the duration of the MRI neurocognitive assessment session did not have a negative impact on task performance. The current study did not find a link between lesion volume and slower processing, bolstering the well-documented

dissociation between brain pathology and cognitive impairment in MS (for a review of the clinico-radiological paradox, see: Chard & Trip, 2017). Although a recent systematic review and meta-analysis found an aggregate correlation between cognition and T2 lesion burden of r = -.30, no single study with an n > 100 found a strong relationship, suggesting variability in the magnitude of this relationship (Mollison et al., 2017). Our study, however, does confirm a positive association between observed processing speed scores and MS disease severity, adding to the existing longitudinal work showing disease severity to be among a few predictors of cognitive decline (Lopez-Soley et al., 2021). Similarly, the positive link between slowed processing and depression has been shown in prior work with younger PwMS (Chan et al., 2021), reinforcing the aim of the current study to examine the generalizability of the multimodal connectome to predict disease severity and depression in MS.

4.2 Connectome Predictions

Neither of our multimodal connectomes from the Glasser nor the Desikan-Killiany atlas successfully predicted significant variance in processing speed. One important factor that may have played a role in the lack of model success is how the multimodal connectome was constructed. This study integrated functional and structural connectivity by multiplying the individual connectomes. The functional connectome included z-scored feature weights ranging from -1 to 1, whereas the structural connectome included normalized feature weights ranging from 0 to 1. The product of FC X SC produced a new connectome wherein only edges that had a structural connection (weight > 0) were retained. Thus, each edge in the multimodal connectome represented a functionally and structurally connected edge in the brain. That connection's positive or negative direction represented whether the two nodes were positively correlated or anti-correlated across time and matched the functional connectome. This fused matrix was built to assess the predictive power of a truly multimodal connectome—that is, can we predict processing speed from edges that share both a functional and structural connection? This method is one approach for fusing neuroimaging data for multimodal predictions.

In the broadest terms, multimodal modeling refers to analyzing at least two imaging modalities collectively to make predictions of behavior. The methods of combining the different imaging modalities fall within two categories: model or hypothesis-driven approaches and data-driven approaches (Calhoun & Sui, 2016). Model-driven approaches have commonly pooled together select neuroimaging metrics (i.e., gray matter volume, lesion volume, resting-state functional connectivity in specific regions) based on previously demonstrated correlations between MRI measures and cognitive function (Zhang et al., 2021). Although these approaches are *technically* multimodal in nature—data from each unimodal technique (i.e., T2 lesion volume, gray matter volume, DTI) is analyzed individually—interactions between different types of data are not modeled. In contrast, data-driven fusion approaches allow data from different imaging modalities to interact and inform each other, such as when one modality constrains another modality. Data-driven fusion approaches including principal components analysis (PCA), independent components analysis (ICA), canonical correlation analysis (CCA), and partial least squares (PLS), do not require *a priori* hypotheses and allow cross-information to emerge from the data itself (for a review of multivariate methods for multimodal fusion see, Calhoun, 2018; Sui et al., 2012). A distinct advantage of such fusion methods is that they can capture all putative structure-function relationships evident across modalities—revealing linked multimodal features (for an overview of neuroimaging-based predictions of cognition in healthy and clinical samples, see Sui et al., 2020). One well-powered study (*n* = 9390) found three MRI-based subtypes of MS when applying unsupervised machine learning to multimodal (structural) neuroimaging data aggregated over 16 RCTs and three observational studies (Eshaghi et al., 2021). Participants classified as having a predominantly lesion-informed subtype showed both greater disability progression and treatment response. Of note, this study used only structural (T1, T2-weighted, FLAIR) imaging and did not include any measures of functional or structural connectivity for classification. However, this finding illustrates the clinical utility of data-driven machine learning with massive multimodal MRI.

A separate study that more closely aligns with the current project used different imaging modalities to classify high and low cognitive performance groups based on SDMT scores in a cohort of

PwMS within five years of diagnosis (Buyukturkoglu et al., 2021). Using the random forest machine learning algorithm, this study found that lesion volume measures, structural volumes, white matter integrity metrics, and resting-state functional connectivity yielded the highest AUC value (0.90) for distinguishing high vs low SDMT performance. However, this study used a relatively homogenous sample of individuals early in their MS course (M_{age} = 34.4 years, M_{EDSS} =1.1, $M_{disease\ duration}$ = 2.2 years) and achieved adequate classification but not predictions on a continuous level (Buyukturkoglu et al., 2021). Although these findings affirm that data-driven approaches for multimodal data fusion may categorize cognitive function successfully in MS, making individual-level continuous predictions in a more heterogeneous sample—the primary aim of the present study—may be a more complex endeavor. A recent preprint in a combined sample of healthy young and older adults observed a similar challenge as the present study; although age group could be decoded by all modalities, which included task fMRI, resting-state fMRI, and structural gray matter volume, chronological age was best predicted within-group (young and old) from select imaging modalities (i.e., whole-brain gray matter volume and resting-state fMRI; Soch et al., 2022).

Together, these findings lead to two plausible conclusions about machine learning with multimodal imaging data in MS. First, successful continuous predictions (i.e., cognitive scores, disease severity, depressive symptoms) may be more challenging than classification (i.e., MS vs. healthy, cognitive impairment vs. preservation, faster vs. slower disease progression). Another level of complexity is the assumption that discrete groups exist. This debate is perhaps most notable in theoretical and methodological research on traditional taxonomies of psychopathology; quantitative reviews, meta-analyses, and models (Haslam et al., 2020; Kotov et al., 2017; Markon et al., 2011) demonstrate that psychopathology traits are dimensional phenomena which lose valuable information about individual differences when categorical nomenclature are imposed upon them (Altman & Royston, 2006; MacCallum et al., 2002). Similar shortcomings of classification have been found in MS. This was demonstrated in a sample of newly diagnosed PwMS that showed cognitive decline when cognition was examined as a continuous variable but categorized as preserved by the model (Pitteri et al., 2019). Using

machine learning to classify PwMS as cognitively impaired or preserved runs the risk of cognitively vulnerable individuals deemed "preserved," and precluded from receiving potential prophylactic and rehabilitative treatments. The specificity of predictions is critical in MS as the primary goal of using predictive modeling is to forecast unseen future clinical symptoms and intervene before disability accumulates. A second conclusion from the above findings is that the performance of multimodal models may hinge on the specific MRI modalities used for prediction and the methods through which they are integrated. We adopted a fusion approach where we constrained functional connections by structural connections to make continuous predictions from multimodal data. Although this approach did not lead to successful predictions of processing speed with the relatively small sample here, meaningful predictions of cognition may be possible in well-powered samples and alternative data-driven approaches for fusing multimodal imaging data.

Our second aim showed that predicted processing speed scores from the multimodal connectome built using either atlas did not correlate significantly with self-reported disease severity or depressive symptoms. However, this became an expected result when the findings from the first aim were not significant. The predicted processing speed scores must first correlate with observed processing speed for a processing speed model to predict significant variance in disease severity and depression. We cannot expect predicted scores to relate to clinical metrics without meeting this preliminary requirement. An alternative hypothesis is that features selected by machine learning models to predict cognition may not overlap or be sufficient for clinical prediction and vice versa. This was demonstrated in the study by Buyukturkoglu and colleagues (2021), which found that models provided an array of demographic (i.e., age, sex, education level, IQ) and clinical characteristics (i.e., disease severity, depression, anxiety, and fatigue scores) did not distinguish between participants with high and low cognition. Given that processing speed correlates with these clinical characteristics behaviorally in the present study, whether multimodal models generalize to clinical measures in MS remains an important question for future empirical investigation.

Our third aim found that the functional connectome from both atlases did not yield predictions of processing speed that were meaningfully related to observed scores, despite using a cognitive task to measure functional connectivity. The impetus to use task-based functional connectivity to predict processing speed was provided by a systematic review of resting-state fMRI, which found an almost exact split of studies linking worse cognition to high functional connectivity (n = 18) and low functional connectivity (n = 17) in PwMS (Jandric et al., 2022). To circumvent this hot debate in the field on whether functional alterations at rest in MS are adaptive vs. maladaptive, we used task-fMRI to quantify functional connectivity. A paradigm shift in the broader neuroimaging literature shows evidence that inducing a particular brain state (i.e., taxing cognition) amplifies individual differences in functional communication (Jiang et al., 2020). In healthy individuals, models built using task-fMRI have outperformed those generated from resting-state fMRI (Greene et al., 2018). Thus, we employed a task of processing speed—the most impacted domain in MS—to identify functional connections predictive of behavioral performance. We hypothesized that perturbing the underlying neural circuitry would confer greater predictive power relative to resting-state functional connectivity estimates. The current study is also novel in its adaptation of the oral SDMT in the scanner using an MRI-compatible microphone which avoided the confounding effects of motor limitations on processing speed assessment. Despite these efforts, the functional connectome did not successfully predict processing speed. One of the reasons that the functional model was unsuccessful may have been due to the use of a multimodal atlas. The Glasser atlas was constructed using information about cortical architecture and brain function during task fMRI, resting-state functional connectivity, and topography from a group average of 210 healthy young adults (Glasser et al., 2016). This parcellation was deemed fitting for our aim of identifying a processing speed neuromarker using the multimodal connectome. However, building models using other parcellations (e.g., Shen atlas) constructed solely on functional connectivity (Shen et al., 2013) may be more effective at making meaningful predictions of cognition from the functional connectome.

Similarly, models built on structural connections alone did not yield successful predictions of processing speed in the present sample. In contrast to the rich functional literature, fewer studies have

assessed the predictive ability of structural disconnection for predicting cognition, and much of this evidence has been supplied by correlational graph theory metrics. Graph theory, when applied to neuroimaging data, characterizes the architecture of neural networks (Sporns, 2018). One study in RRMS found that the graph-theoretical summary metric of global strength was associated with processing speed scores ($r = 0.46$, $p = 0.007$; Has Silemek et al., 2020). Although individuals in this sample had mild levels of MS ($M_{EDSS} = 2$), their disease duration (10.4 years) was comparable to the present study (10.7 years). Global strength was also inversely related to disease duration in this sample ($r = -0.52$, $p = 0.002$), indicating that accumulated damage over the course of MS may manifest in structural disconnection and relate meaningfully with processing speed. A separate study in a heterogeneous sample of all subtypes of MS, found global efficiency of white matter tracts, characterizing decreased information flow across the whole brain, was associated with lower SDMT performance (Charalambous et al., 2019). These correlational findings suggest that meaningful relationships between whole-brain anatomical connectivity and cognition exist in MS. The extent to which anatomical connectivity can be harnessed to make individual-level predictions of cognition warrants further investigation. Recent research in other samples including Alzheimer's disease reveals that novel machine learning approaches such as ensemble predictions combined with feature selection methods may effectively leverage structural features to accurately distinguish clinical phenotypes (Jitsuishi & Yamaguchi, 2022). The current study was the first study to investigate whether meaningful predictions of processing speed are attainable from whole-brain structural connectivity; based on emerging research, it appears that this question may benefit from novel approaches (e.g., ensemble predictions) that may boost the predictive power of models and yield meaningful cognitive and clinical predictions.

4.3 Strengths of the Current Study

Perhaps the most notable contribution of this research project to the field of MS is the use of machine learning to predict cognitive functioning. There has been a burgeoning interest in harnessing computational models to decode individual differences in behavior (Sui et al., 2020), which has led to

meaningful predictions of cognition in both healthy (Dhamala et al., 2021; Rasero et al., 2021) and clinical (i.e., Alzheimer's disease) samples (Grueso & Viejo-Sobera, 2021; Kumar et al., 2021; Revathi et al., 2022). The heterogeneity of MS demands the use of high-dimensional neuroimaging data, and machine learning provides the means to leverage such data flexibly to yield informative clinical predictions. However, thus far in MS, predictive modeling has been chiefly used to discriminate between MS vs. healthy (Azarmi et al., 2019; Schiavi et al., 2022), classify disability (Tozlu, Jamison, Gu, et al., 2021), or segment lesions (Sakai & Yamada, 2019). This study sought to capitalize on novel regression-based machine learning approaches to predict information processing speed in a sample of PwMS. The goal of using machine learning with neuroimaging data is to make accurate and clinically meaningful individual-level predictions in external, independent samples. As only one sample was available for both model discovery and validation, we used a stringent nested cross-validation procedure to attempt to identify a model of processing speed. This two-step process identifies model hyperparameters in the inner loop and tests those hyperparameters in unseen data in the outer loop, thus avoiding data leaking. For our primary aim, we went through this pipeline of model tuning to identify optimal hyperparameters to feed forward into the full 100 permutations. Our pipeline of model tuning was informed by research showing non-trivial effects of regression algorithms and sample size on cognitive predictions (Cui & Gong, 2018). Accordingly, we experimented with four factors: 1) two atlases with different dimensionality (Glasser and Desikan-Killiany), 2) various train/test splits ranging from a training set of .60 to .80 of the full sample, 3) ridge and lasso regression algorithms/estimators, and 4) and a swath of lambda regularization parameters. This extensive model tuning process led to critical insights about using machine learning with multimodal imaging data to make predictions of cognition in MS.

Our first discovery through model building with two different atlases was that lasso regression outperformed ridge for the larger connectomes built using the Glasser atlas. The Glasser plus subcortical atlas included over four times as many nodes (n = 371) as the Desikan-Killiany plus subcortical atlas (n = 83), and nearly ten times as many connections (n = 20,125) as the Desikan-Killiany atlas (n = 2,232). Lasso emerged as the better performing model suggesting that when provided with a large number of

features, the L_1 regularization, which randomly chooses one feature among a group of correlated features, yielded higher model performance than the L_2 regularization, which retains all features and lowers coefficients to account for multicollinearity. Results from a study in a clinical sample (i.e., individuals with stroke) found lasso regression, when applied to resting-state functional connectivity data that had been reduced in dimensionality, was able to predict cognitive function across domains (Calesella et al., 2021). Variability in model performance using different estimators has also been reported in attempts to predict disease severity from routine MR images alone (Pontillo et al., 2021). In the present study, the opposite was true for the smaller Desikan-Killiany atlas, for which models built using ridge performed better than models built using lasso regression. These findings suggest that choice of algorithm depends on the data (unimodal vs multimodal) and number of features supplied to models to decode.

Variability in model performance was also observed based on the train splits tested (.60, .65, two-thirds, .70, three-fourths, .80). A higher training set (.70 to .80) during hyperparameter tuning resulted in better performing models for all connectomes built with the Glasser atlas. In contrast, all connectomes constructed using the Desikan-Killiany atlas yielded higher-performing models with a smaller training set (.60 to two-thirds). This suggests that when a connectome has more features, it may require more training data to produce better performing models. In contrast, connectomes with relatively fewer features may perform adequately well with smaller training samples. Alternatively, it is plausible that a connectome built on a purely functional or structural atlas (e.g., structural connectome built using a structural atlas) may perform better for the respective connectome and require less training data.

Performance variability during model optimization was also observed based on the magnitude of regularization (i.e., lambda) applied. The L_1 regularization directly determines the sparsity of the predictive model by shrinking coefficients to zero. For the Glasser atlas, minimal regularization in the tuning phase led to adequate correlations between predicted and observed processing speed scores (r = .13 to .22). The small lambdas (10^{-12} to 10^{-7}) indicated that very little penalization was necessary with lasso and was likely due to the small number of features (n - 1 = 63) that were retained. Optimized lambdas with ridge and the Desikan-Killiany atlas were relatively larger (10^{-5} – 10^{4}) and led to a wide

range in model performance measures during hyperparameter tuning (r = .095 to .16). Such variability in hyperparameter tuning has been indicated in other machine learning studies using MRI data (Kwak et al., 2021). A notable difference in the current study is that we manually tested a range of lambda parameters using the gridsearch function in python. Other studies have automatically generated lambda values such as with the *glmnet* package (Taxali et al., 2021). However, we do not have evidence to suggest that the number of lambdas tested influenced model success.

Another prominent strength of this study is the use of high-quality, multimodal MRI data. The neuroimaging field has been swept by an interest in integrating multiple imaging modalities to harness unique and complementary information to predict cognition. To advance our understanding of MS-related cognitive deficits, probing the coupling of structure and function is particularly relevant as the disease impacts functional communication and white matter streamlines. Despite increasing attempts to integrate multiple imaging modalities to understand clinical phenotypes, including cognitive functioning, these attempts are much more limited in MS than in healthy populations. Further, the findings on the increased benefit of integrating functional and structural connectivity in healthy young adults have been mixed. One study has shown that functional connectivity is more predictive of cognitive function than structural connectivity, and combining data from these two modalities through concatenation did not enhance cognitive predictions (Dhamala et al., 2021). Another study that combined diffusion, functional, and structural MRI to predict various cognitive composites in healthy young adults found that integrating across modalities boosted the prediction accuracy of cognitive ability from 1% to more than 3% (Rasero et al., 2021). An important difference between these studies was how multimodal data were leveraged collectively; the former used concatenation while the latter used data-driven integration. This raises the question of whether model performance relies on *how* data from multiple imaging modalities is integrated.

4.4 Challenges to Multimodal Model Success

The recent uptick in neuroimaging research investigating brain-behavior relationships in MS reveals findings that suggest a potential blind spot of the present study. In the present study, we combined functional and structural data by multiplying matrices and effectively creating a new connectome retaining weights for connections that existed both structurally and functionally. This multimodal connectome was used to assess whether combined information—the presence and magnitude of white matter streamline connections and direction of functional connections—when entered into machine learning models can be harnessed to make meaningful predictions of cognition. Our results and some recent findings suggest that this method of constructing a weighted matrix may not be best suited for making continuous predictions of cognition. Dhamala et al. (2021) found that different functional and structural connections predict summary measures of cognition suggesting that different MRI modalities may independently inform individual differences in specific cognitive functions. Evidence in MS corroborates these findings; Jandric and colleagues (2021) examined whether functional connectivity changes in resting-state networks co-occur with anatomic changes. The researchers studied a relatively large (n = 102) sample of individuals with RRMS split into cognitively preserved (n = 47) and cognitively impaired groups (n = 55). Although they found functional and structural connectivity alterations in cognitively impaired PwMS, the specific voxels that showed abnormalities in functional connectivity differed from those that showed structural changes. Their results demonstrate that more diffuse damage rather than focal, overlapping alterations in functional and structural connectivity are associated with cognitive impairment. Thus, an alternative approach may be to capitalize on the potential disparate changes in white and gray matter connections by building models using functional and structural connectivity data collectively. However, this would require additional steps to overcome the challenges posed by high dimensionality data.

One major difference between the current study and successful model predictions from other studies is the type of feature selection method used. The “curse of dimensionality” marks neuroimaging data (Abraham et al., 2014; Khosla et al., 2019; Mwangi et al., 2014; Shi & Nathoo, 2018), particularly connectivity matrices which contain more variables than observations. Building models on data with more

features than the number of participants runs the risk of overfitting models to the training data. Regularization is a popular supervised framework that combines both machine learning and feature selection. A regularization parameter λ reduces the features to a subset to balance the trade-off between prediction error and model complexity. Although applying a small λ (minimal regularization) may decrease training error (e.g., bring predicted scores closer to observed scores) and thus have less bias—overfitting to training data may lead to poor generalization in out-of-sample test data and have higher test error/variance. In contrast, excessive regularization—using too few features or down-weighting regression coefficients—can lead to underfitting and high bias, yielding fewer valuable predictions. Striking a balance between bias, variance, and model complexity is key to building models that predict observed data and generalize to unseen samples (Hastie et al., 2009). Our λ tuning nested cross-validation procedure was intended to find an optimal balance between bias and variance to achieve the Goldilocks level of model complexity.

Recent research has revealed the further utility of data-driven methods for integrating multimodal imaging data to enhance success of multimodal models. Rasero et al. (2021) used a multi-level machine learning approach to integrate across (functional, diffusion, and morphological) neuroimaging modalities for predicting individual differences in cognitive ability in a large (n = 1050) sample of healthy young adults. The researchers used stacked learning across two levels to 1) reduce data dimensionality using principal components analysis and train features through cross-validation, yielding cognitive predictions from each imaging modality separately, and 2) stack model predictions to optimize a new lasso regression model that accounted for redundant features across imaging modalities to optimize final model predictions. The results show that integrating across different imaging modalities through this stacked learning approach boosted prediction accuracy for multiple cognitive domains. These findings highlight that alternative data-driven approaches may better leverage functional vs structural features to enhance predictions of cognition in well-powered samples of MS.

Limitations of this study, including the relatively small sample size and lack of external validation data, may have contributed to the lack of prediction success of the multimodal connectome.

This sample was relatively small (n = 64) and consisted of individuals with mild-to-moderate MS severity. When the number of features is larger than the sample size, there is the risk of overfitting. Research suggests that a minimum of 200 participants are needed to achieve stable prediction accuracy for generalizable brain signatures of behavior (Cui & Gong, 2018). We have learned the importance of large samples in our prior work in MS (Manglani et al., 2021). A working memory network derived in a small (n = 36) sample of PwMS did not generalize to unseen PwMS; however, working memory networks identified from a large (n = 502) sample of healthy young adults predicted significant variance in working memory in two separate samples of MS (Manglani et al., 2021). With increases in large data collection and sharing, future research may overcome the bottleneck of small samples and extend the application of machine learning to well-powered clinical samples.

An additional inherent limitation of the current study was the inability to evaluate the goodness of the model through out-of-sample predictions. To guard against overfitting in the present study, we capitalized on the statistical approach of nested cross-validation procedure, which adds bias to increase generalizability. In attempts to minimize error in the training set, this conservative computational method may have led to more significant penalties to the regression coefficients resulting in a less robust model than may have been attained if separate samples were used to derive and test the model. With larger and separate samples for model discovery, validation, and generalization (Gabrieli et al., 2015), machine learning algorithms may be better equipped to capitalize on the heterogeneity of MS to make meaningful predictions of behavior. Relatedly, larger samples may be better adept at leveraging the heterogeneity of features in MRI-based connectivity to yield models with cross-cohort generalizability. Additionally, a longstanding debate in the MS literature is whether between-person differences in functional connectivity reflect pathological abnormalities or compensatory mechanisms to support function. To better understand the effects of pathology on cognitive function, models may require additional indices of disease, including lesion volume and location (i.e., lesion topology in strategic white matter regions), structural volumes (i.e., whole-brain gray matter volume to quantify neurodegeneration), as well as changes in functional

connectivity during cognitive tasks and from rest to cognitive load. With powered multimodal data, we may be able to build reliable and robust models of cognition in MS.

4.5 Future Directions

An area of increasing research is dynamic functional connectivity which focuses on change in functional communication between brain regions during rest (Liu et al., 2018; Tijhuis et al., 2021; Valsasina et al., 2022), during a cognitive task (Fong et al., 2019; Murphy et al., 2020), and between rest and task processing (Calhoun et al., 2014; Cohen, 2018; Gonzalez-Castillo & Bandettini, 2018; Lin et al., 2017). As dynamic connectivity measures the functional plasticity of brain regions, the magnitude of change in communication between different brain areas may be relevant for predicting cognition in MS. Although some research in a smaller sample (n = 25) has shown that static interhemispheric connectivity is associated with SDMT performance (Lin et al., 2020), a growing body of findings indicates the relevance of functional reorganization. One study analyzing a small sample (n = 29 PwMS) using hierarchical regression analysis found that dynamic functional connectivity (i.e., change in connectivity strength from rest to the SDMT), specifically in the default mode network, explained 23% of the variance in SDMT (van Geest et al., 2018). Multiple studies have also shown the promise of dynamic functional connectivity for distinguishing cognitive impairment from preservation. Reduced dynamics in brain regions belonging to the default mode, frontoparietal, visual, and thalamic networks have been observed in cognitively impaired relative to cognitively preserved PwMS (Eijlers et al., 2017). Additional research from that same sample showed that the negative correlation between the default mode and visual network observed in cognitively preserved PwMS was nonexistent in cognitively impaired individuals (Eijlers et al., 2019). This study suggests that greater dynamic functional connectivity—fluctuations in coupling strength over time—particularly of the default mode, frontoparietal, and visual brain networks is linked to preserved cognition in PwMS. This is bolstered by separate findings demonstrating that relative to healthy controls, PwMS showed lower dynamic functional connectivity in specific (i.e., sensorimotor, default mode, and frontal) networks, and which was associated with worse motor and cognitive performance

(Hidalgo de la Cruz et al., 2021). Dynamic functional connectivity has also shown to be a better classifier of disability status in MS (EDSS < or ≥ 2) than static functional connectivity and structural connectivity (Tozlu, Jamison, Gauthier, et al., 2021). These findings provide a solid rationale for further studying time-varying connectivity—the chronnectome (Calhoun et al., 2014)—in MS. Perhaps, in combination with predictive modeling techniques and structural connectivity, dynamic functional connectivity may reveal robust imaging biomarkers of continuous cognitive variables in MS.

Another important future direction is to use a data-driven approach for dimensionality reduction. As multicollinearity of features within connectivity matrices makes predictive models vulnerable to overfitting, other supervised learning methods may remove redundant predictor variables and thus mitigate concerns related to building models based on a large number of collinear features. These methods include partial least squares regression (PLSR) and principal components analysis (PCA). PLSR is a predictive model that finds a series of L latent variables that maximize the covariance between these latent variables and the target outcome variable, or Y (Krishnan et al., 2011). PLSR seeks latent variables that are uncorrelated with all other latent variables and which covary maximally with Y. Within the cross-validation framework, PLSR searches for the optimum number of latent variables for best predictions of Y. PLSR has outperformed simple linear regression models to predict attention in healthy and clinical samples (Yoo et al., 2018), and shows advantages for predicting multiple clinical, behavioral, and demographic variables simultaneously (Chen et al., 2019). In contrast, PCA is an unsupervised feature reduction technique meaning that it does not use information about Y to construct relevant features. PCA linearly transforms correlated features into a smaller number of orthogonal features known as principal components that carry the most variance and discards redundant features (Mwangi et al., 2014). Previous work applying PCA on resting-state functional connectivity has revealed that a modest number—between 50 and 150 components—captures sizeable variance in inter-individual variation and permits meaningful predictions of phenotypic differences between individuals (Sripada et al., 2019). Together, these studies show that by harnessing complementary information using different feature selection methods, we may be able to identify a latent or component nexus from multimodal imaging.

An alternative feature filtering method used widely with predictive modeling is connectome-based predictive modeling (CPM; Shen et al., 2017). CPM performs univariate testing between each edge and the phenotype of interest to isolate neural features associated with the target phenotype based on the prespecified threshold (e.g., $p < .01$). Edges are then split into a positive network (i.e., edges that positively associate with behavior) and a negative network (i.e., edges that negatively associate with behavior) and summed separately for network strength. These strength values are then used independently and in a combined linear model to predict the target phenotype. CPM has been successfully used to make out-of-sample predictions for an assortment of outcomes variables in healthy (Fountain-Zaragoza et al., 2021; Kwak et al., 2021; Rosenberg, Finn, et al., 2016; Rosenberg et al., 2017) and clinical samples (Avery, 2020; Barron et al., 2020; Manglani et al., 2021; Rosenberg, Zhang, et al., 2016). This background demonstrates that various methods for dimensionality reduction are available to reduce the sparsity of large neuroimaging matrices. Although we selected regularization for feature selection, it is plausible that another method or combination of methods may be more fitting for multimodal MRI and yield more robust neurosignatures of cognition in MS.

4.6 Conclusions

This is the first study to leverage machine learning and the potential synergistic effects of shared functional and structural connections in the brain to make individual-level predictions of information processing in MS. We found that the shared network of functional and structural connections in the present sample does not predict significant variance in processing speed. Although behaviorally we found statistically significant relationships between processing speed and MS disease severity and depressive symptoms, model predictions of processing speed did not relate to these clinical measures. This study offers important directions for future investigations to employ larger and external datasets, other MRI modalities, and different dimensionality reduction approaches to elucidate the utility of independent vs. integrated networks in making meaningful predictions of cognition in MS.

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Appendix A

Tables

Table 1. Inclusionary and exclusionary criteria for study participation.

Inclusion	Exclusion
Clinically definite diagnosis of Relapsing-Remitting Multiple Sclerosis	Clinically isolated syndrome or progressive MS subtype
30-59 years old	Age < 30 or > 59
Score ≥ 23 on the MMSE	Score < 23 on the MMSE
Self-report EDSS 0 – 5.5	Self-report EDSS > 5.5
Absence of comorbid neurological disorders	Presence of any other neurological disorders
Absence of psychiatric disorder in the last 2 years	Diagnosis of psychiatric disorder in the last 2 years by mental health provider
Relapse and corticosteroid free for the prior 30 days	Clinically definite relapse or use of high dose corticosteroids within the prior 30 days
No recreational drug use in the prior 6 months	Recreational drug use in the prior 6 months
Access to a smart phone and internet for the study	Without access to a smart phone or internet
No current use of devices for step tracking	Current use of device for step tracking

Note: MMSE = Mini-Mental Status Exam; EDSS = Expanded Disability Status Scale.

Table 2. Image acquisition parameters.

	Functional	**Diffusion**	**Structural**	**Lesion**
Measure	SDMT		MPRAGE	FLAIR
Pulse sequence type	EPI	DWI	Gradient echo	Fast spin-echo
Parallel imaging parameters (band type, acceleration factor)	MB, 3	MB, 2	Single	Single, GRAPPA, 2
Number of volumes	998 (499 x 2 runs)	--	1	1
TR	1000 ms	4570 ms	1900 ms	9000 ms
TE	28 ms	85 ms	4.44 ms	95 ms
Flip angle	50°	78°	12°	135°
FOV	240 mm	256 mm	256 mm	256 mm
Acquisition matrix	80 x 72 x 45	128 x 224 x 74	256 x 256 x 176	256 x 256 x 70
Number of slices	45	74	176	70s
Slice thickness	3.0 mm	2.0 mm	1.0 mm	2.0 mm
Voxel size	3.0 mm^3	2.0 mm^3	1.0 mm^3	1.0 mm x 1.0 mm x 2.0 mm
b-value	--	2000 s/mm^2	--	--
Bandwidth (Hz/Px)	2500	1776	140	222
Echo spacing	0.5 ms	0.65 ms	10.1 ms	8.65 ms
Acquisition orientation	Axial	Axial	Sagittal	Axial
Acquisition order	Interleaved	Interleaved	Interleaved	Interleaved

Note: SDMT = Symbol Digit Modalities Test; MPRAGE = Magnetization Prepared Rapid Gradient Echo; FLAIR = Fluid Attenuated Inversion Recovery; EPI = Echo Planar Imaging; DWI = diffusion weighted imaging; MB = multiband; ms = millisecond; TR = repetition time; TE = echo time; FOV = field of view; s/mm^2 Hx/Px = Hertz/Pixel.

Table 3. Demographic and clinical descriptives of the sample.

Characteristic	Mean (*SD*) or (%)	Range
Age (years)	47.2 (8.01)	31-59
Sex		
Female	51 (79.7%)	
Male	13 (20.3%)	
Education (years)	16.1 (2.56)	11 – 23
Race		
White	51	
Black or African American	8	
American Indian or Alaska Native	1	
More than one race	2	
Unknown or Not Reported	2	
Ethnicity		
Non-Hispanic/Latino	63	
Hispanic/Latino	0	
Unknown or Not Reported	1	
EDSS		
Self-report	3.95 (0.99)	0 – 5.5
Neurologist-Report	1.29 (1.37)	0 – 6.0
Disease duration (years)	10.7 (6.70)	0.25 – 25
Lesion volume (mL)	5.23 (5.68)	0.23 – 28.8
# of lesions	17.7 (9.53)	4 – 46
BDI-II	11.6 (9.41)	0 – 43
MMSE	29.1 (1.28)	24 – 30

Note. Sex, race, and ethnicity presented as count. EDSS = Expanded Disability Status Scale; BDI-II = Beck Depression Inventory, Second Edition; MMSE = Mini Mental Status Exam. Neurologist reported EDSS was available for $n = 35$. Disease duration reported by $n = 63$.

Table 4. SDMT performance for symbols and numbers conditions.

Measure	Mean (*SD*)	Range
Reaction Time (ms)		
Symbols	1459 (161)	1178 – 1864
Numbers	686 (128)	454 – 1091
Accuracy (%)		
Symbols	97.7	87.8 – 100
Numbers	99.8	95.6 – 100

Table 5. Correlations between sociodemographic, clinical, and cognitive variables.

Variable	1. Age		2. Education		3. EDSS-SR		4. EDSS-NR		5. BDI-II		6. Disease Duration		7. Lesion Volume	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
1. Age														
2. Education	-.21	.094												
3. EDSS-SR	.15	.24	-.13	.30										
4. EDSS-NR	.088	.61	-.16	.35	.21	.24								
5. BDI-II	-.021	.87	-.063	.62	**.28**	**.026***	.015	.93						
6. Disease Duration	**.27**	**.030***	.15	.25	.017	.90	.028	.87	**-.25**	**.05***				
7. Lesion volume	.10	.43	.15	.24	.11	.40	-.10	.56	-.097	.45	**.40**	**.001****		
8. Processing speed	.11	.38	-.23	.072	**.28**	**.025***	<.001	1.00	**.27**	**.031***	-.11[p]	.41	-.032	.81

Note. Zero-order Spearman rank correlations between relevant demographic, clinical, and cognitive variables. EDSS-SR = Expanded Disability Status Scale Self-Report; EDSS-NR = Expanded Disability Status Scale Neurologist Report, BDI-II = Beck Depression Inventory, Second Edition. Disease duration was missing for one participant ($n = 63$). Neurologist reported EDSS was available for $n = 35$. [p] = Pearson correlation. * = $p \leq .05$, ** = $p < .01$.

Table 6. Results from hyperparameter tuning across 10 permutations for each atlas and connectome.

Atlas	Mats	Lasso					Ridge				
		Train Size	Alpha start	Alpha end	# of alphas	Max correlation (*r*)	Train Size	Alpha start	Alpha end	# of alphas	Max correlation (*r*)
Glasser	MC	.80	10^{-11}	10^{-9}	3	.22	2/3	10^{-5}	10^{-3}	3	-.076
	FC	.80	10^{-12}	10^{-10}	4	.13	2/3	10^{-5}	10^{-2}	4	.023
	SC	.80	10^{-10}	10^{-7}	4	.22	2/3	10^{-5}	10^{-2}	4	-.10
Desikan-Killiany	MC	.80	10^{-8}	10^{-5}	4	.11	2/3	10^{-1}	10^{4}	6	.095
	FC	.80	10^{-8}	10^{-4}	5	.039	2/3	10^{-5}	10^{-1}	5	.14
	SC	.80	10^{-15}	10^{-12}	4	-.023	2/3	10^{-1}	10^{4}	6	.16

Note. Mats = matrices; MC = Multimodal Connectome; FC = Functional Connectome; SC = Structural Connectome.

Table 7. Final model results for each atlas using the optimized method, train/test split, and lambda hyperparameters.

Atlas	Matrices	Method	Train Size	Alpha start	Alpha end	# of alphas	Full model	Mean absolute error (MAE)
Glasser	MC	Lasso	.80	10^{-11}	10^{-9}	3	$r = .080$, $p = .49$	215
	FC	Lasso	.80	10^{-12}	10^{-10}	4	$r = .078$, $p = .40$	163
	SC	Lasso	.80	10^{-10}	10^{-7}	4	$r = .12$, $p = .07$	181
Desikan-Killiany	MC	Ridge	2/3	10^{-1}	10^{4}	6	$r = .031$, $p = .23$	141
	FC	Ridge	2/3	10^{-5}	10^{-1}	5	$r = .055$, $p = .17$	141
	SC	Ridge	2/3	10^{-1}	10^{4}	6	$r = .024$, $p = .54$	138

Note. Mats = matrices; MC = Multimodal Connectome; FC = Functional Connectome; SC = Structural Connectome.

Appendix B

Figures

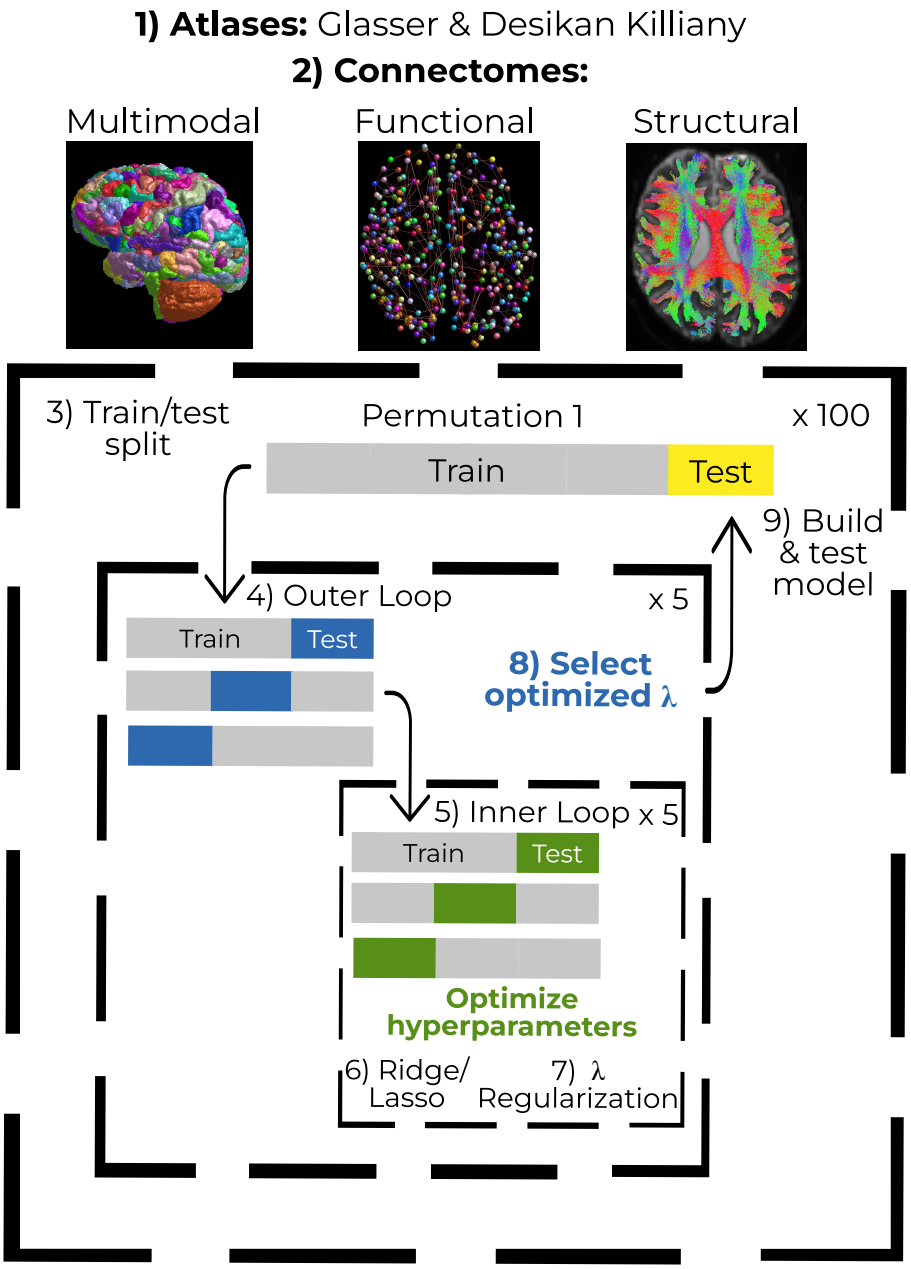

Figure 1. Hyperparameter tuning pipeline.

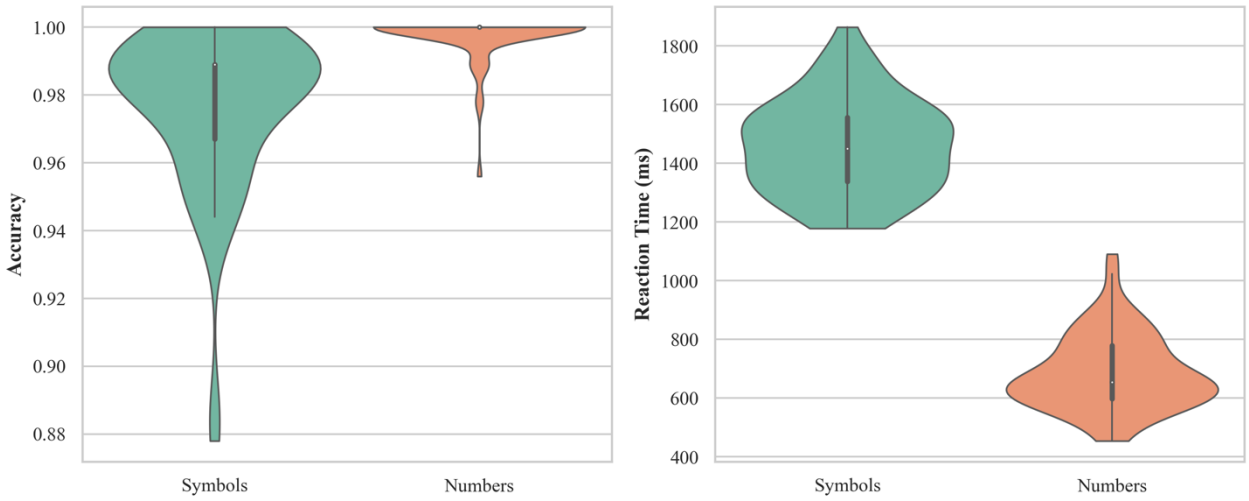

Figure 2. Distribution of accuracy and reaction time by SDMT condition.

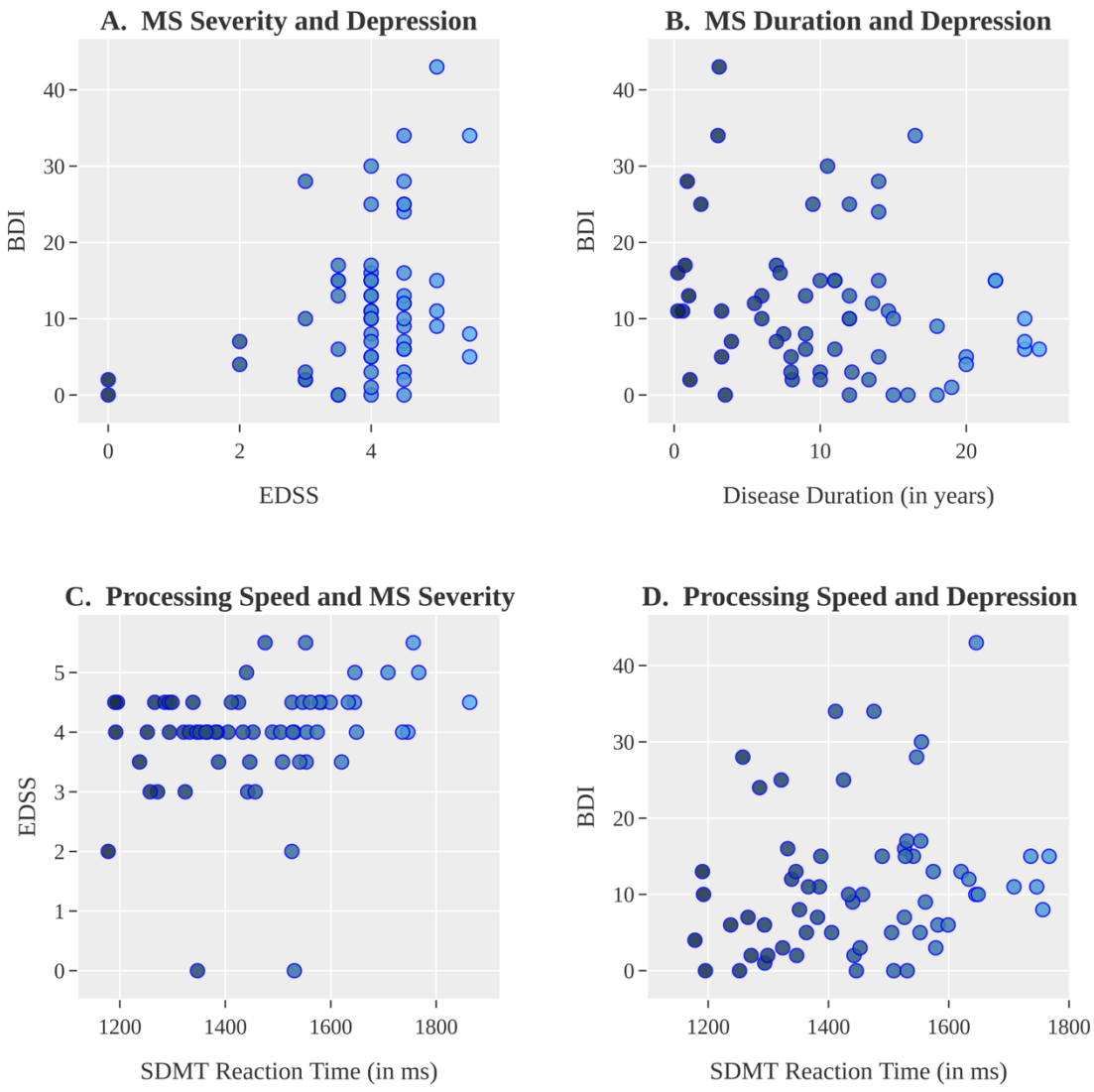

Figure 3. Spearman rank correlations between clinical and cognitive variables.

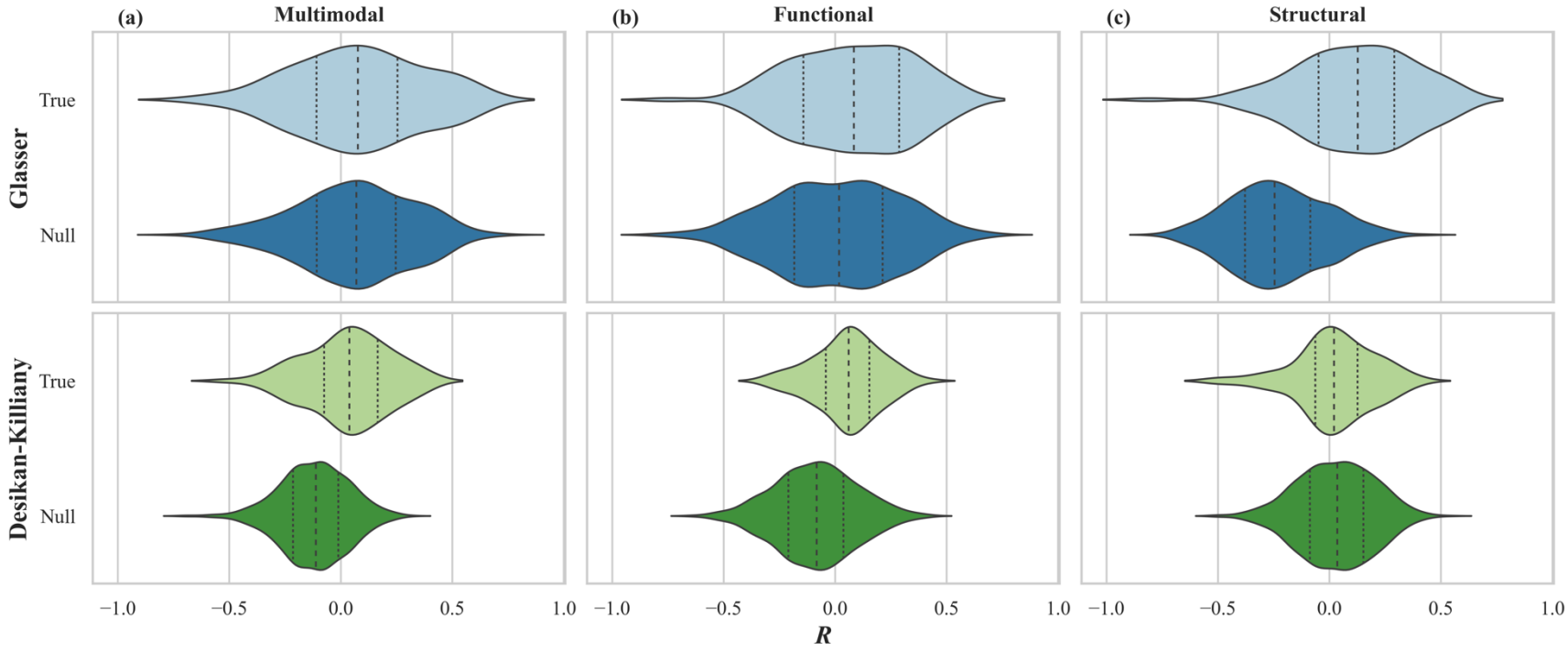

Figure 4. Violin plots depicting performance of true and null models across all permutations. Results presented for (a) Multimodal, (b) Functional, and (c) Structural connectomes built using the Glasser plus subcortical parcellation (top row in blue) and Desikan-Killiany (bottom row in green). Dashed lines represent the mean, and dotted lines represent the interquartile range.

Appendix C

Supplementary Material

Details on additional collected neuropsychological measures are provided below.

9-Hole Peg Test (9-HPT). Part of the Multiple Sclerosis Functional Composite, the 9-HPT is a measure of upper extremity (hand and arm) function (Fischer et al., 1999). In separate trials for dominant and non-dominant hands, participants are asked to place pegs one at a time into each of nine holes arranged in a board, and then to remove these pegs one at a time from the holes. Two consecutive trials are administered for each hand.

Timed 25-Foot Walk. Also part of the Multiple Sclerosis Functional Composite, the T25W is a measure of lower extremity function and ambulation (Fischer et al., 1999). With the start and finish lines clearly marked on the ground, participants are asked to walk 25 feet, as quickly and safely as possible. After walking to the end (Trial 1), participants are asked to return to the starting point (Trial 2) using the same instructions as the first trial. The dependent variable is the total time in seconds required to walk the distance across both trials.

Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS). The development of this battery was prompted by a meeting in 2001 where neuropsychologists and psychologists with expertise in MS convened to discuss how to facilitate routine, standardized, and cost-effective neuropsychological testing for clinical monitoring and research (R. H. B. Benedict et al., 2002). This meeting culminated in the 90-minute MACFIMS battery measuring five of the most commonly affected cognitive domains in PwMS (Benedict et al., 2006). Participants complete the full cognitive battery which consists of seven subtests:

1. Controlled Oral Word Association Test. The COWAT measures language and verbal fluency. In each of three one-minute trials, participants are asked to generate as many words as possible that begin with the designated letter. The dependent measure is the total number of correct words across the three trials.
2. Judgment of Line Orientation Test. The JLO measures visuospatial processing. Participants are asked to identify the angle formed by two intersecting stimulus lines among a visual array

of lines covering 180 degrees. Both oral and pointing responses are accepted in this test. The dependent variable is the total number of correct responses across the 30 items.

3. California Verbal Learning Test, second edition. The CVLT-II measures verbal learning and memory. The examiner reads 16 words (at the rate of 1 word per second) and immediately after, participants are asked to recall as many words as possible. The entire word list is administered for a total of 5 learning trials. After this, a second list of 16 words is read to the participant, and free recall is prompted for this single trial. After a 25-minute interval following the fifth learning trial of the original list, participants are asked to feely recall the original list read multiple times to them. Delayed recall is followed by a yes or no trial where participants are asked to indicate whether the presented word was part of the original list. The dependent variables from this test include total learning (total recall across all learning trials), and delayed recall (a sum of all delay condition scores).
4. Brief Visuospatial Memory Test-Revised. The BVMT-R measures visual learning and memory. Following a similar format as the CVLT- II, in this test, the examiner holds a matrix of six visual designs in front of the participant for 10 seconds. Immediately after, participants are asked to reproduce the designs using paper and pencil without any time restrictions. Each design receives a score of 0, 1, or 2 based on accuracy and location scoring criteria. This is repeated for three trials. Following the 25-minute delay, participants are asked to freely reproduce the designs shown earlier and complete a separate yes or no recognition trial to indicate whether the presented design was part of the matrix shown earlier. The dependent variables include total immediate learning and delayed recall (a sum of both delay condition scores).
5. Paced Auditory Serial Addition Test. The PASAT measures working memory. It includes 120 total trials of auditorily presented numbers with 3- or 2-second inter-stimulus intervals (60 trials each). Participants are asked to add each pair of consecutive numbers and orally

respond with the sum. The dependent variable is the total number of correct responses across both blocks.

6. Symbol Digit Modalities Test. The SDMT measures processing speed. Participants are presented with a key of symbol-number parings across the top of an 8.5 X 11-inch sheet. The remainder of the page presents a pseudo-randomized sequence of symbols. Participants are asked to quickly and accurately go down each row and voice the number associated with each symbol. The dependent measure is the number of correct responses across the allocated 90 seconds.
7. Delis-Kaplan Executive Function System Sorting Test. The DKEFS sorting test measures higher order executive function. Participants are presented with 6 cards, each depicting a single word. The cards vary in several ways, allowing conceptual sorts in at least eight different principles (e.g., card shape, card color, semantic association among words). After each sort, participants are asked to describe the conceptual differences between sorted groups. A total of 4 minutes is allowed for each of the two cart sets with verbal descriptions not counting towards total time. The dependent measures are the total number of correct sorts, and the verbal description score (based on the abstractness and accuracy of the sort description) across the 2 card sets.

Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV). The WAIS-IV has been the most commonly used measure of intelligence in North America (Rabin et al., 2005), and used in PwMS as it measures cognitive domains frequently affected in this population (Ryan et al., 2012). The five subtests from the WAIS-IV administered in the current study include:

1. Digit Span. The three conditions of this subtest measure working memory, mental manipulation, cognitive flexibility, rote memory and learning, attention, and encoding. In the Forward condition, the examiner reads a sequence of numbers and participants are asked to recall the sequence in the order read. In the Backward condition, the participant is asked to recall the sequence of numbers in reverse order as read by the examiner. In the Sequencing

condition, the participant is read a sequence of numbers and asked to recall the numbers in ascending order.

2. Arithmetic. This subtest measures mental manipulation, concentration, attention, short- and long-term memory, numerical reasoning ability, and mental alertness. The participant is asked to mentally solve arithmetic problems within the allocated time limit of 30 seconds per trial.
3. Symbol Search. This subtest measures visual perception and scanning speed. On each trial, participants are presented with two target symbols, followed by an array of shapes. They are asked to search for the target symbols and indicate a match or non-match. Participants are given 120 seconds to complete as many trials as possible.
4. Cancellation. This subtest assesses visual-perceptual speed. Participants are presented with two target shapes with rows of shapes underneath. They are asked to identify as many target shapes in the array as possible and provided 45 seconds for each of the two trials of this test.
5. Letter-Number Sequencing. This test allows for an assessment of working memory abilities without the confound of processing speed. Participants are read a series of numbers and letters and asked to vocalize the numbers in sequential order followed by the letters in alphabetical order.

NIH Toolbox Cognition Battery. The NIH Blueprint for Neuroscience Research coalition convened in 2004 with the goal to accelerate neurobehavioral research through use of standard instruments. The iPad-based Cognition Battery was built to briefly and comprehensively measure in individuals from 3-86 years of age, the full range of normal functioning (with minimal ceiling and floor effects across the adult age span; Weintraub et al., 2014). Importantly, this battery was designed to assess cognitive domains key for health, education and work success, and independence in daily functioning (Weintraub et al., 2013). In addition to individual test scores, the Cognitive Battery also yields several summary scores including a fluid, crystallized, and total composite score. Scores corrected for age,

education, sex, and race/ethnicity are also generated. Participants complete the full, 30-minute Cognition Battery comprising seven tests:

1. Flanker Inhibitory Control and Attention Test. This is a measure of visual attention and inhibitory control. On each of the 40 trials, participants are shown a set of arrows and asked to indicate the direction of the central arrow among either flankers facing the same direction as the target (congruent trials) or in the opposite direction as the target (incongruent trials). This test is scored using an algorithm that integrates accuracy and reaction time to yield a score ranging from 0 to 10.
2. Dimensional Change Card Sort Test. This test measures set-shifting and cognitive flexibility. Participants are asked to match a target visual stimulus to one of two choice stimuli, according to one of two dimensions (i.e., shape and color), presented as a cue word on each of the 40 trials. For adults this test is scored based on reaction time.
3. List Sorting Working Memory Test. In this test of working memory, participants are visually and orally presented with objects one at a time, and asked to recall in order of size, the stimuli presented within each category (e.g., fruits, animals), first reporting all stimuli from one category, then the other. The score for this test equals the total items correct across all trials.
4. Picture Sequence Memory Test. This test measures episodic memory. On each trial, participants are presented one at a time with pictures sequenced to depict the order of events during an activity (e.g., “How to Play in the Park”) both visually and orally through audio that describes the content of each (e.g., “Then we ride on the swing”). After the sequence completes, the center of the screen displays the pictures in random order and the participant is asked to reproduce the demonstrated sequence by moving pictures on the screen. This test is scored as the cumulative number of adjacent pairs of pictures reproduced correctly over the 3 trials.
5. Oral Reading Recognition Test. This language test measures crystallized intelligence. On each trial, participants are asked to read aloud the word presented on the computer screen.

Based on the examiner's rating of accuracy, the computer adaptive testing (CAT) algorithm selects the next word from a bank of 250 words. Based on performance, 30-40 trials are presented.

6. Picture Vocabulary Test. This is a language test of receptive vocabulary. On each trial, participants are orally presented with a word paired with a set of four pictures on the screen. Participants are asked to select the picture that matches the spoken word. This test is also CAT administered.
7. Pattern Comparison Processing Speed Test. This processing speed measure assesses choice reaction time. On each trial, participants are asked to discern whether the two visual patterns are the same or different. The final score equals the number of correct items (of a possible 130) completed in the allotted 90 seconds.