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# Backward Walking: A Novel Marker Of Fall Risk, Cognitive Dysfunction, And Myelin Damage In Persons With Multiple Sclerosis

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**BACKWARD WALKING: A NOVEL MARKER OF FALL RISK, COGNITIVE DYSFUNCTION, AND MYELIN DAMAGE IN PERSONS WITH MULTIPLE SCLEROSIS**

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## DEDICATION

This dissertation is dedicated to my family, whom all collectively shaped me into the person that I am today and offered endless support throughout this journey. To my maternal grandmother, Margaret, a Wayne State Warrior herself, thank you for always encouraging me to stay in science and for displaying the beauty of what it means to truly be your genuine self. There is no one else I would rather do puzzles with, even if you are convinced that I lose the pieces. To my paternal nana, Violet, thank you for always supporting my goals, for showing me that everything can ultimately be handled with patience and kindness and for appreciating the Detroit Red Wings as much as I do. To my late paternal grandfather, Kennyon, thank you for always reminding me the power of mindset, the nature of selflessness and the importance of a good sense of humor. It is because of you that I originally became so interested in neuroscience and I thank you every day for the public speaking skills in which I truly believe were inherited from you. To my big brother, Ian, thank you for defying biology by being my twin at two years apart. Thank you for always setting the bar annoyingly high, reminding me you are the first born favorite and always providing me with someone to chase after. I cannot imagine who I would be without you, as my life-long best friend. You have always inspired me to try harder, to be better than yesterday and most importantly, to not sweat the small stuff. Thank you for always being the most supportive big brother to your little sister. To my parents, Louise and Don, thank you for showing Ian and I the value of hard work and teaching us from a young age that everything is earned and not given. When I look back on all of what led me to where I am today, none of it would have been possible without your ongoing encouragement. From driving 12 hours at the end of your busy work weeks to cheer on Ian and I at our sport events, to the daily morning messages of inspirational quotes (or pet pictures) to keep us smiling and everything else in between. I am beyond fortunate to have incredible parents like the two of you, the perfect hybridization of role models, coaches, mentors and most importantly, best friends. Thank you for always being there for Ian and I and for working so hard to provide us with the tools to succeed.

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## INTRODUCTION

### The case for multi-functional assessment in developing fall detection tools for persons with multiple sclerosis (MS).

#### *Falls are common in MS*

Reliable, sensitive, and clinically feasible methods for assessing fall risk in the MS population are critical for immediate medical implications and improvements in translational research. Falls are a serious public health concern in the MS population, which accounts for 2.8 million individuals worldwide (Walton, 2020). MS is a progressive neurologic disease marked by inflammatory brain lesions that result in demyelination, axonal damage and subsequent neurologic dysfunction (Bjartmar, 2001). MS pathology causes a wide clinical spectrum of relapsing and increasingly debilitating impairments, including motor, cognitive and sensory dysfunctions (Rahn, 2012). As a result of multi-domain functional impairment, accidental falls are common in the MS population. Over 50% of ambulatory individuals with MS suffer at least one fall within a three-month period (Nilsagard, 2015) and over 70% within a six-month period (Coote, 2020). At present, a robust and clinically feasible measure of fall risk that assesses the functional domains contributing to fall risk in MS is critically needed to sensitively predict injurious falls before they occur.

#### *Consequences of falls*

Falls in MS are a serious and expensive public health concern that result in debilitating consequences across physical, psychological, and social domains of an individual's life. Fall-related injuries in MS are common, with annual-personal injury rates ranging from 0.18 to 0.23 (Gunn 2014; Peterson 2008) that require expensive medical attention after falling (Peterson, 2008; Matsuda, 2011; Cameron, 2011). Statistics for fall-related costs for MS patients are not available; however, some estimates can be made with comparison to other populations who are also at increased risk for falls. For example, the average cost of a hospital visit for an injurious fall is >$30,000 (Woolcott, 2012) and the CDC estimates annual spending of $50 billion on non-fatal

fall injuries in older adults alone (Florence, 2018). Additionally, fall rates for MS individuals are more than double that of older adults and markedly greater than individuals with stroke (50%) (Welmer, 2017) or Parkinson's disease (46%) (Pohl, 2014). The summary cost is in approximately 33% of older adults fall within a 12-month period, with 10% reporting injuries (Appeadu, 2021), while injurious fall rates in MS patients in the same period are over 70% (Berlinski, 2017). From these estimates, one can conclude that falls in MS lead to increased demand on healthcare resources (Matsuda, 2012) and financial burden at both the patient and national level.

In addition to injury, the psychological and social associations with falls in MS are complex and vary per individual. Falls in MS patients are related to reports of worsening mental health outcomes (i.e., depression and anxiety) (Williams, 2005), social isolation (Matusda, 2011) and a high prevalence (~60%) of a fear of falling (Khalil, 2017) that precipitates future falls (Mazumder, 2015) and activity curtailment (Peterson, 2007) in >80% of MS fallers (Sosnoff, 2011). Falls are limiting, restricting, and embarrassing to persons with MS (Nilsagard, 2009) and notably, MS fallers consistently report decreased quality of life compared to non-fallers (Vister, 2017; Coote, 2020).

***Limitations of current fall risk measures in MS patients***

The associations between falls and decreased quality of life underscore the critical need to identify clinical measures that accurately predict falls in MS patients in a time- and cost-efficient manner. However, fall risk assessment in MS patients is complex and multi-factorial. Specifically, prior MS research has identified a wide variety of intrinsic (i.e., lower extremity malfunction, limited walking abilities, reduced muscular endurance, attention deficits, fatigue and heat-sensitivity) and extrinsic (i.e., environmental, non-use of walking aids) fall risk factors (Carling, 2018). As a result, single test measures to assess fall risk in MS patients face challenges and are limited in their sensitivity and predictive validity for falls (Gunn, 2013; Quinn, 2017). The current fall risk measures in MS patients rely primarily upon forward walking speed and balance (Nilsagard, 2007), often including the Timed 25ft Walk (Cameron, 2013), the Berg Balance Scale (Quinn,

2018) and the Timed Up and Go (Cattaneo, 2002). Although these fall risk measures correlate with number of falls in MS patients (Tajali, 2017) and are clinically favorable (i.e., ease-of-use, time and cost efficient, low training requirements), meta-analyses of these measures reveal limited predictive accuracy (<50%) and discriminative ability for identifying MS fallers (Gunn, 2013; Quinn 2017). While other common clinical scales (i.e., Activities-Specific Balance Scale and Dynamic Gait Index) have demonstrated predictive validity for falls in MS patients, the respective area under the curve (AUC) values for the individual tests (i.e., reflecting a measure's ability to separate a faller from a non-faller) showed that no measures had sufficiently high levels of fall prediction accuracy to be used in isolation (Dibble, 2013). Given the multi-factorial nature of fall risk in MS patients, it is not surprising that the combination of multiple assessments together has demonstrated improved predictive accuracy for falls in MS patients (Fritz, 2020). However, a stand-alone fall risk measure that is clinically feasible, optimized for efficiency and demonstrates ability to capture multiple functional domains impacted by MS will allow for sensitive, simple and robust fall risk assessment for the MS population.

In addition to the limitations of current fall risk assessments in MS patients, the data guiding research aimed at decreasing falls in MS are primarily based on retrospective fall reports (Gunn 2013; Quinn 2017). Several studies in MS patients highlight the underestimation of falls with retrospective recall (i.e., falls that occurred in the past) in comparison to prospective reporting (i.e., collecting falls as they occur in real time) (Nilsagard, 2009; Gunn 2013; Dibble 2013), which is attributed to the high prevalence of cognitive dysfunction in MS patients (Benedict, 2011). The International MS Falls Prevention Research Network recommends prospective fall reporting using fall diaries where MS patients record any daily falls (Coote, 2014). However, the reporting duration and frequency of returning fall diaries is a burden to participants and limits the accuracy of data due to memory problems. Taken together, currently available clinical assessments of fall risk in MS face limitations in predictive accuracy for falls and the research guiding their utility faces limitations in accurate data collection. Thus, there is a critical need for fall risk research in MS to

adopt accurate and technologically advanced methods (i.e., motor assessment, cognitive assessment, neuroimaging techniques and prospective fall reporting technologies) to create a sensitive fall detection tool in MS.

While single clinical measures of walking and balance have been correlated to number of retrospective and prospective falls and likelihood of falling in MS, an ideal measure of fall risk that is both clinically useful (robust, time and cost-efficient) and accurately predicts falls remains to be identified in MS (Cameron, 2013). Moreover, the current fall risk measures do not assess real-world physical activity and functioning across multiple domains impacted by MS, and therefore maintain limited predictive accuracy for fall risk. For example, forward walking is an automatic motor skill that is performed in daily life, requiring lower demands across motor, cognitive and sensory domains (Godde, 2012). Additionally, the clinical measures of balance most commonly used to assess fall risk (i.e., the Berg Balance Scale or the Timed Up and Go Test) face limitations in generalizability to everyday life, task complexity (Edwards, 2020b), clinical efficiency and are hindered by their variable execution (Mancini, 2010). For example, the Berg Balance Scale is limited to static balance assessment, is time intensive (15-20 minutes) and has a floor and ceiling effect (Pickenbrock, 2015; Chen, 2019). Collectively, fall risk assessment in MS is complex, as disruptions across a variety of clinical domains impacted by MS contribute to increased fall risk (Block, 2021) (Figure 1), including deficits in gait and postural control (Motl, 2020; Cameron, 2018), lower extremity strength (Motl, 2020), sensory and cognitive function (Block, 2021), fatigue, and underlying pathology that disrupts neural communication by motor and cognitive brain areas (Prosperini, 2013; Al-Yahya 2011).

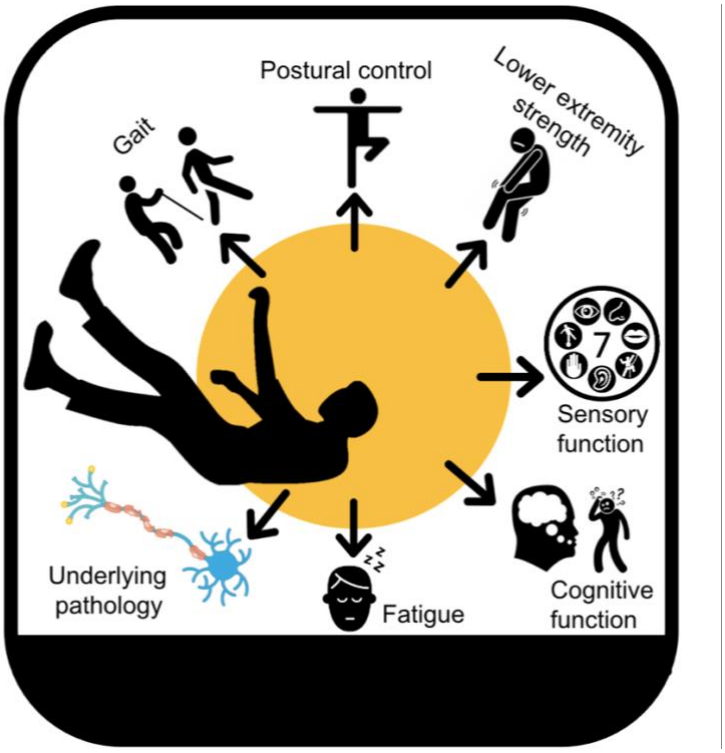



**Figure 1**. **Fall risk assessment in MS is complex, as disruptions across a variety of functional domains impacted by MS contribute to increased fall risk**

Therefore, a time and cost-efficient clinical tool that assesses the functional domains that contributes to fall risk in MS patients is critically needed to sensitively predict injurious falls before they occur. Identification of a predictive biomarker of fall risk will allow for timely intervention and critically, a marker that addresses multiple functional domains impacted by MS will guide characterization of underlying mechanisms that lead to falls to enhance targeted fall prevention therapies.

Prior studies examining fall risk in MS patients have been stymied by limitations in methodology (i.e., retrospective recall of falls) and examination of variables that may not be clinically scalable (e.g., double support time and other spatiotemporal parameters of walking) (Shah, 2020). To satisfy the need for a fall detection tool in MS patients that is useful to both clinicians and researchers, it is critical that research aiming to identify such tools use the most sensitive methods across data collection, analysis, and interpretation, without sacrificing clinical

translation. Accordingly, the CDC has tried to curb the steep increase in falls by encouraging clinicians to adopt *research-based* fall prevention practice and identify specific and sensitive measures of fall risk (Kaiser Health, 2019). While > 400 risk factors have been associated with falls, only 20 specific risk factors have been investigated in MS patients (Gunn 2013), including deficits in walking and balance (Motl, 2020), dual-task impairment (Etemadi, 2017; Edwards, 2020a), cognitive dysfunction (Kalron, 2014), and pathology in brainstem and cerebellar regions (Kalron, 2018; Fritz, 2020; Edwards 2021). Notably, mobility, cognition and neuroimaging are often examined in a siloed nature (Coote, 2020); whereas simultaneous assessment of multiple domains can better identify specific links to fall risk. Additionally, there is a paucity in MS research aiming to identify both sensitive tools for fall detection and the respective underlying motor and cognitive components that contribute to their clinical utility in fall risk assessment. These observations highlight the need to identify measures of fall risk related to domains negatively impacted by MS (i.e., motor and cognitive) that detect falls before they occur. Identification of motor and cognitive neural architectures that support the clinical utility of fall detection tools in MS patients would promote the development of individualized, targeted rehabilitation therapies and identification of respective therapeutic targets. To address this research gap, it is critical to use the most sensitive methods for multi-functional data collection (i.e., motor assessment, cognitive assessment and neuroimaging techniques) to create a tool that accurately predicts falls and is easily scalable in the clinic setting in MS. In this dissertation, I am proposing backward walking as a novel tool to assess fall risk in persons with MS. I will also use multi-functional assessment including motor and cognitive assessment, dual-task assessment and neuroimaging, to identify underlying neural processes that further support the clinical utility of backward walking in fall risk assessment for persons with MS.

***Backward walking as a novel, clinical predictor of falls in persons with MS***

Recent evidence from studies of the elderly and other neurodegenerative populations support backward walking as a clinical measure of fall risk and mobility impairments (Hawkins,

2020; Fritz, 2013; Maritz, 2017; Hackney, 2009). Backward walking velocity identifies elderly fallers more accurately than forward walking velocity (Fritz, 2013; Maritz, 2017; Klemenov, 2018). Backward walking is also strongly correlated with known predictors of future falls (i.e., Four-Square Step Test and Activities-Specific Balance Confidence Scale) (Maritz, 2017), suggesting its clinical utility as a simple and time- and cost-efficient single measure to identify those at risk for falls. Studies comparing differences between forward and backward walking have identified significant changes in gait and lower extremity biodynamics (Hawkins, 2019). Specifically, when compared to forward walking, backward walking requires greater lower extremity strength and energy consumption of the quadriceps, knee extensor and hip flexor muscles (Yang, 2006), dynamic balance control (Cha, 2016), postural control (Callisaya, 2010) and increased reliance on proprioception (Chen, 2020). All of the aforementioned functions can be negatively impacted by MS pathology and demonstrates the clinical relevance of backward walking in fall detection for persons with MS (Figure 2).

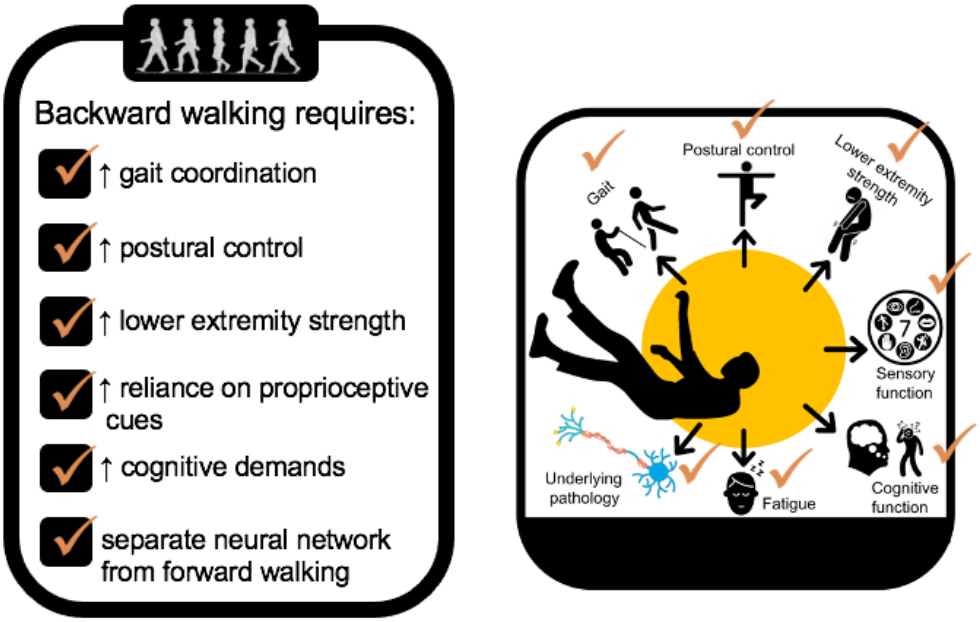



**Figure 2. Backward walking captures a snapshot of multi-domain functions that are validated predictors of future falls and are vulnerable to MS pathology.**

Preliminary studies have provided promising results of backward walking as a sensitive correlate of physical impairments that relate to fall risk. To date, prior work in MS demonstrates motor differences (i.e. decreased walking speed and stride length and increased double support time) are greater during backward walking and better distinguish individuals with MS from healthy controls than forward walking (Wajda, 2013). Similarly, deficits in stepping and postural control worsen during backward walking in MS and significantly correlate with increased severity on clinical measures of forward walking and disability (Peterson, 2015). However, while the relation between backward walking and falls has been established in the elderly (Fritz, 2013; Maritz, 2017; Klemenov, 2018) and other neurologic populations (Hackney, 2009), the sensitivity of backward walking to detect falls in persons with MS has not been tested. Further, the added value of backward walking assessment to current clinical measures for predicting future falls in persons with MS is unclear. Therefore, the first aim of this dissertation is to examine the relation between backward walking and falls in persons with MS and identify whether backward walking maximally differentiates fallers from non-fallers in persons with MS compared to current clinical standards (**Chapter 1**).

***Backward walking and dual-task assessment improve identification of fallers in MS***

In an effort to capture the multiple factors contributing to fall risk in MS, recent work has included dual-task, motor-cognitive measures (i.e., two domains impacted by MS) to better understand the motor-cognitive interactions during gait. Dual-task walking (i.e., walking while simultaneously performing a secondary cognitive task) demonstrates potential to overcome the current limitations of clinical standards for fall risk assessment in persons with MS (Muir-Hunter, 2016; Henning, 2020). In parallel with the increased demands required by backward walking (Figure 2.1), dual-task walking requires increased motor and cognitive resources (Ruffieux, 2015). Additionally, dual-task walking is more generalizable to everyday life (Veldkamp, 2019), as walking is rarely performed without concurrent cognitive demands or secondary motor tasks in daily life (Edwards, 2020b).

The cognitive and motor dysfunction implicated in fall risk are highly prevalent in MS (65% and 85%, respectively) and can be detected by dual-task walking impairments (Negahban, 2011; Chen, 2020). These findings are not surprising given the fundamental concept of “walking automaticity,” and its relevance within the context of neurologic populations. “Walking automaticity” refers to the ability of the central nervous system to control continuous and coordinated walking with minimal use of attention-demanding, cognitive resources (Clark, 2015). Within neurodegenerative disease like MS, previously automatic motor tasks, like forward walking, become more cognitively demanding and therefore, may result in worse performance in the task (Yogev, 2005; Yogev-Seligmann, 2008). Therefore, this performance deterioration would be heightened under non-automatic task conditions, including dual-task and highly complex motor skills, like backward walking.

Prior neuroimaging studies in healthy young adults build upon these fundamental concepts by demonstrating increased brain activity via fractional near-infrared spectroscopy measurements (fNIRS) in pre-frontal and motor regions when performing in dual-task conditions (Bishnoi, 2021). Importantly, this effect is heightened greatest in cognitively impaired populations, including stroke (Al-Yahya, 2016), Parkinson’s disease (Maidan, 2017) and the elderly (Holtzer, 2011). In persons with MS, neurobiological underpinnings of dual-task impairment have been suggested, including disruption of dopaminergic systems (Dobryakova, 2015) and atrophy of cerebellar regions (Argento, 2020). Collectively, these data indicate the sensitivity of dual-task assessment to assess subtle disruption across cognitive and motor processes in persons with MS.

Given the strong overlap between the functional domains required by backward and dual-tasking walking in MS, pairing the two movements together (i.e., backward walking dual-task measures) may provide additional sensitivity to fall risk assessment in persons with MS. Prior studies of backward walking in MS broadly suggest the role of cognition by demonstrating that when administered with a secondary cognitive task of semantic verbal fluency, backward walking

better differentiates persons with MS from healthy controls (Wajda, 2013). However, limitations arise from this work due to limited sampling and lack of demographic matching between MS and control groups. Ultimately, relations between backward walking dual-task measures to cognitive function and critically, falls, are understudied in persons with MS. Therefore, the second aim of my dissertation is to examine relations between measures of dual-task backward walking measures and falls in persons with MS **(Chapter 2).** This aim will allow for multi-functional assessment of backward walking in both single and dual-task conditions to identify whether measures of backward walking dual-task relate to falls in persons with MS and develop a basis for understanding the role of cognitive function in backward walking performance.

***Specific cognitive domains may moderate the relation between backward walking and number of falls in MS***

Critical to my dissertation is prior work in MS demonstrating the relation between deficits in complex motor tasks (i.e., backward walking) and dysfunction of *specific* cognitive domains; namely processing speed, attention and visuospatial memory (Chiaravalloti, 2008; Drew, 2008), all of which have been linked to walking and fall risk in MS (D'Orio, 2012, Gunn, 2013, Kalron, 2014). Although there is considerable variability in MS patients regarding degree and type of cognitive dysfunction (DiGiuseppe, 2018), reduced processing speed is recognized as the most prevalent cognitive deficit in MS patients (Chiaravalloti, 2018; Matias-Guiu, 2017). Reduced processing speed is also the most significant cognitive dysfunction that contributes to slower walking speed under both simple and complex (i.e., dual-task) conditions (Killane, 2014). Additionally, slower processing speed predicts gait variability in MS after controlling for age, sex and disability level (Hsieh, 2017) and gait variability is increased during backward walking in MS patients (Bryant, 2016; Fritz, 2013). Impairments in visuospatial memory are also commonly reported in MS (Benedict, 2006) and negatively impact memorization of landmarks during locomotion (van der Ham, 2021) which are critical during backward walking, as visual cues providing information on movement trajectory cannot be relied upon (Collett, 2017). Collectively,

the specific cognitive domains of processing speed and visuospatial memory demonstrate relevance to fall risk and performance on complex motor tasks in MS patients and therefore, may play a role in backward walking performance in MS patients.

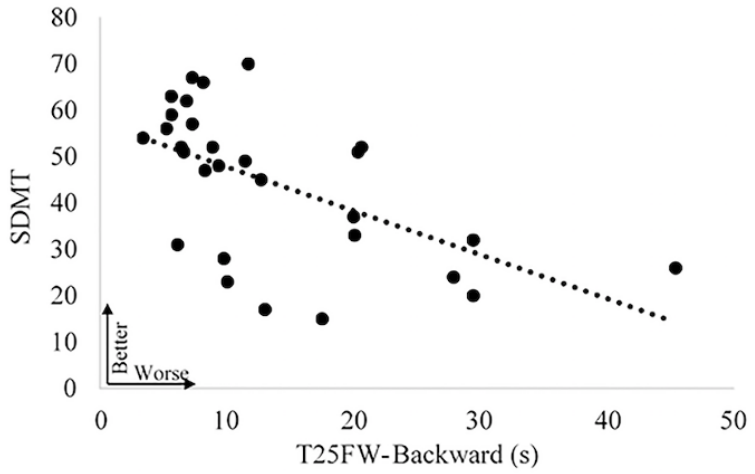



**Figure 3. Performance on the T25FW-Backward test is correlated negatively to cognitive measures of information processing speed [Symbol Digit Modalities Test (SDMT)] in MS patients (Saymuah, 2019). *Timed 25 Foot Walk: T25FW.***

Indeed, recent data from our laboratory demonstrates that backward walking is correlated negatively to cognitive measures that assess information processing speed (Symbol Digit Modalities Test (SDMT) – r =-0.61; p=0.001; Fig. 3) (Saymuah, 2019) and visuospatial memory (Brief-Visuospatial Memory Test-Revised (BVMTR) – r=-0.43; p=0.026) (unpublished data). Notably, the SDMT and BVMT-R that are part of the Brief International Cognitive Assessment for MS (BICAMS) battery, demonstrate high sensitivity to cognitive impairment including deficits in processing speed and visuospatial memory (Baetge, 2020). Our findings are not surprising considering non-automatic motor skills (i.e., sustained backward walking) that are uncommon in daily life require higher attention demand and additional cognitive resources (i.e., processing speed and visuospatial memory) for smooth execution of movement (Karni, 1998). Moreover, backward walking is more complex than forward walking and relies heavily upon

proprioceptive cues (Hackney 2009), which require accurate representation of visual space and efficient information processing to execute motor programs. From these prior data, we can conclude that both processing speed and visuospatial domains of cognition are related to backward walking performance (Saymuah, 2019; unpublished data) in MS patients. We speculate that dysfunction in processing speed and visuospatial memory influences the strength of the relation between backward walking and falls in MS patients, given the established relations between cognitive deficits and fall risk (D'Orio, 2012, Gunn, 2013, Kalron, 2014) and cognitive deficits to backward walking (Saymuah, 2019), respectively. However, the degree and type of cognitive dysfunction caused by MS is highly variable across MS patients (DiGiuseppe, 2018) and backward walking requires increased demands on many other functional systems impacted by MS other than cognition (i.e., motor, sensory, etc.) (Callisaya, 2010; Hackney, 2009; Chen, 2020). In other words, the observed relations between information processing speed and visuospatial memory to backward walking performance may not hold constant across every MS patient and other functional domains in addition to cognition may influence backward walking's ability to detect falls. Therefore, cognitive functioning of processing speed and visuospatial memory may not cause (i.e., mediate) the relation between backward walking and falls in MS patients. Rather, a MS patient's cognition may influence the strength of the relation (i.e., moderate) between backward walking and falls.

Prior studies of backward walking performance in MS patients which also examined cognitive function did not examine falls (Saymuah, 2019) and the studies that examined relations between backward walking and falls did not consider cognition (Edwards, 2020). Therefore, whether an individual's specific domains of cognitive function influence the ability of backward walking to detect falls remains unknown. Therefore, the third chapter of this dissertation is to examine the influence of cognition on the relation between backward walking and falls in MS patients **(Chapter 3)**. Cognitive moderation by both specific domains will be tested individually (Figure 4), given the high prevalence of dysfunction in processing speed and visuospatial domains

and their strong relation to gait and disability measures in MS. The use of cognitive assessments that demonstrate high sensitivity to detect impairment (92.7%) (Baetge, 2020) in each of the discrete domains in persons with MS (i.e., processing speed and visuospatial memory) will ensure sensitive data collection. Identification of cognitive moderators of backward walking is necessary to characterize neurobiological processes relevant to backward walking function and its application in the assessment of fall risk in MS. Additionally, it guides interpretation of backward walking in a clinical setting when a MS patient is presenting with multi-domain deficits.

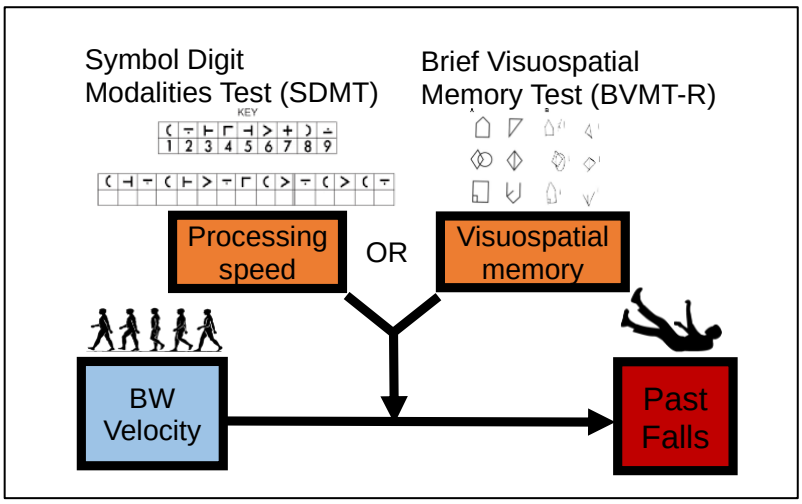



**Figure 4.** Moderation analysis from Chapter 3 to test the hypotheses that the relation between backward walking (BW) velocity and falls is moderated by information processing speed (as measured by the SDMT) or visuospatial memory (as measured by the BVMT-R), respectively, in MS patients.

***Key white matter regions that contribute to motor and cognitive dysfunction are commonly affected by MS pathology and may contribute to declines in mobility and increased fall risk***

In addition to understanding the relations between backward walking and clinically observable function in MS, identification of disease-specific mechanisms that underlie deficits in backward walking performance are critical for the development of sensitive fall detection tools in MS and subsequent identification of specific rehabilitative targets. Myelin degradation of the central nervous system (CNS) is the pathophysiological hallmark of MS (Popescu, 2013) and may contribute to slower backward walking velocity. Myelin sheaths that wrap around axons play a

key functional role as an electrical insulator, thereby facilitating signal conduction (Chang, 2016). This dissertation proposes that myelin degradation in the CNS, as a result of inflammation in MS, decreases conduction velocity and eventually leads to a total loss of signal transmission (Perez-Cerda 2016). Hence, myelin damage in key white matter regions that share functional connections with motor and cognitive regions is hypothesized to worsen performance of a non-automatic, complex, and bilateral task such as backward walking.

At present, the underlying mechanisms of deficits in backward walking remain largely unknown. A key component contributing to this research gap includes the lack of neuroimaging studies conducted in neurologic populations that examine key motor and cognitive ROIs which may relate to sensitive measures of fall risk, including backward walking. There is strong evidence from both pre-clinical and clinical studies that demonstrate distinct mechanistic differences between forward and backward walking. Pre-clinical studies in rodent and cat models of backward walking reveal separate locomotor networks for forward and backward walking using electromyographic measures and immunohistochemistry techniques (Merkulyeva, 2021). Backward walking showed significant activation of neurons in L5-L6 segments of the spinal cord, whereas forward walking showed very little activation (Merkulyeva, 2021). The L5-L6 segment of the spinal cord is clinically relevant as it contains motoneuronal pools of the adductor muscles (Shkorbatova, 2020). Recent comparative neuroanatomy studies of the lumbosacral spinal cord demonstrate anatomical and physiological similarities of cat models in relation to humans (Toossi, 2021). Adaptation treadmill training in healthy adults further suggests there are separate functional networks controlling backward and forward walking (Choi & Bastian, 2007). Knowledge of backward walking mechanisms are limited in clinical populations.

As a non-automated action, backward walking performance is expected to require the function of multiple brain regions, each of which may be affected by MS. The impact of myelin damage on backward walking is further supported by motor and cognitive connections between key regions of interest (ROI). Two brain regions that have been well-established for their structure-

function relations and subsequent clinical involvement in MS include the corpus callosum (CC) (Ozturk, 2010; Rimkus, 2011; Llufriu, 2012; Huang, 2019) and the corticospinal tract (CST) (Reich, 2009; Fritz, 2017; Pawlitzki, 2017; Spampinato, 2017). Specifically, the body of the CC [CCbody; (segments 2 and 3 of CC)] is critical for bilateral movements (Kennerly 2002, Whal & Ziemann 2008), complex motor skills (Perez 2007), and motor learning for postural control in persons with MS (Peterson 2017) and shares connections with M1, supplementary motor area, and prefrontal cortex (Bonzano 2011). The CST is crucial for voluntary control of the limbs during walking (Jang 2009). Damage to the CST relates to poor motor function (Travis 1955), including walking performance in persons with MS (Fritz 2017). Projections from the CST extend to premotor, parietal, and subcortical areas (Archer 2017; Lehericy 2004), which are critical for motor planning, execution (Coombes 2012; Plow 2015), cognitive reaction time and decision making in healthy adults, respectively (Karahan 2019). Taken together, the $CC_{body}$ and CST are white matter ROIs commonly damaged in MS (Pawlitzki, 2017; Etemadifar, 2017). Given the increased motor and cognitive demands required by backward walking and functional (motor and cognitive) roles of the $CC_{body}$ and CST, both regions are likely to be involved in execution of a complex motor task such as backward walking. Critically, identification of key ROIs that relate to backward walking serve as a starting point to the formation of a neuroanatomical framework that further supports the clinical utility of backward walking as a fall risk assessment in MS.

Lesions within the cerebellum also contribute to both motor and cognitive disabilities (Daams, 2015; Benedict, 2020). The cerebellum is one of the most common and complex lesion sites among persons with MS (Wilkins, 2017). Notably, cerebellar ataxia (i.e., uncoordinated muscle movements due to cerebellar damage), impacts 80% of persons with MS (Wilkins, 2017) and increases risk for falls. Additionally, damage in cerebellar regions has been linked to falls in persons with MS (Kalron, 2018). At present, due to the vast complexity of the cerebellum's functionally-segregated sub-circuits, which integrate within both motor and cognitive networks (Weird, 2015), only a limited understanding exists of structure-function relationships within the

cerebellum. (Fritz, 2022). Specifically, the superior cerebellar peduncle (SCP) relays information related to skilled limb movements (Fitzgerald 1992). In addition, decreased integrity of the SCP is related to worse performance on clinical walking measures in MS (Preziosa 2014). In addition to balance, damage to the cerebellum contributes specifically to deficits in visuospatial attention and memory in MS (Weier 2016; Tedesco 2011). However, without a clearer understanding of the cerebellum's contribution to motor and cognitive dysfunction in MS (i.e., motor control, motor learning and rehabilitation), critical knowledge gaps remain in assessments of multi-domain fall risk. Therefore, the purpose of the fourth chapter of my dissertation is to summarize the current understanding of the impacts of cerebellar dysfunction on motor control, motor training and rehabilitation in persons with MS and to provide insight tor targeted MS rehabilitation and future fall prevention research.

***There is a need for sensitive imaging tools to better understand key brain regions that contribute to motor and cognitive dysfunction that relate to fall risk in MS.***

Conventional structural magnetic resonance imaging (sMRI) is a common clinical tool for assessing myelin damage in key motor and cognitive brain regions. Protocols derived from sMRI typically include T2-weighted, fluid-attenuated inversion recovery (FLAIR), or short-tau inversion recovery (STIR), and $T_1$-weighted pre- and post-gadolinium contrast pulse sequences, at magnetic field strengths of 1.5 Tesla (T) in the brain (Hemond, 2018). While sMRI provides an invaluable tool for MS diagnosis and disease monitoring (Onteneda, 2017), it lacks specificity to clinical function and myelin (Kolind, 2012), both which are damaged by MS. Specifically, sMRI is limited in its capability to distinguish MS-pathology (i.e., myelin damage) in normal-appearing white matter tracts (Hemond, 2018). Therefore, accurate quantification of myelin is critical to identify links between backward walking and MS pathology to identify sensitive fall detection measures and inform targeted rehabilitation strategies.

Critical to this dissertation are data from quantitative MRI techniques that are common in research practice, including Diffusion Tensor Imaging (DTI) and its commonly derived metric,

fractional anisotropy (FA). FA reflects the prevalence of diffusivity of water moving in one direction (Sbardella, 2013) and provides information about structural features of anisotropic tissues, including white matter tracts. As a result of MS pathology, CNS myelin that can present a physical barrier to impose directionality or anisotropy on water diffusion is damaged and leads to less directionality of water (Aung, 2013) (i.e., decreased FA). Indeed, prior DTI studies in MS demonstrate FA is lower in persons with MS as compared to controls in the corticospinal tract (CST) (Fritz, 2017), cerebellum (Prosperini, 2013) and corpus callosum (CC) (Ibrahim, 2011) and relates to slower FW. Additionally, our recently published work in MS demonstrates that combining quantitative MRI measures (Magnetization Transfer Imaging) of the CST with clinical measures of walking and balance can lead to improved accuracy of fall prediction in MS (Fritz, 2020). Magnetization Transfer Imaging and its primary outcome metric, the magnetization transfer ratio (MTR) can provide a quantitative measure of macromolecular density and tissue damage. However, MTR values do not correlate well to myelin content or clinical scores in MS (Fjaer, 2015). Additionally, the biological interpretation of relatively lower FA in relation to MS pathology is unclear due to factors that impact DTI metrics including myelination, fiber coherence, axonal density, and membrane permeability (Beaulieu, 2002; Harsan, 2006). Therefore, an imaging tool with increased specificity to MS pathology is critically needed to accurately probe the neural underpinnings related to backward walking and subsequent fall risk in MS.

To improve the specificity of characterizing the myelin microstructure that is required to advance understanding the neurobiological mechanisms of MS, I use Myelin Water Imaging (MWI), which is a quantitative MRI approach and viewed as the gold standard for imaging myelin content in vivo (Laule 2008; McCreary 2009). MWI includes acquiring multi-echo-$T_2$ ($MET_2$) imaging data followed by quantifying the multi spin-spin $T_2$ relaxation components of water from different physical environments (MacKay, 1994; MacKay, 2016). $T_2$ relaxation of water is directly related to water mobility and hence, allows discerning the signal from water trapped between myelin sheaths from water in the intra- and extracellular space (Figure 5).

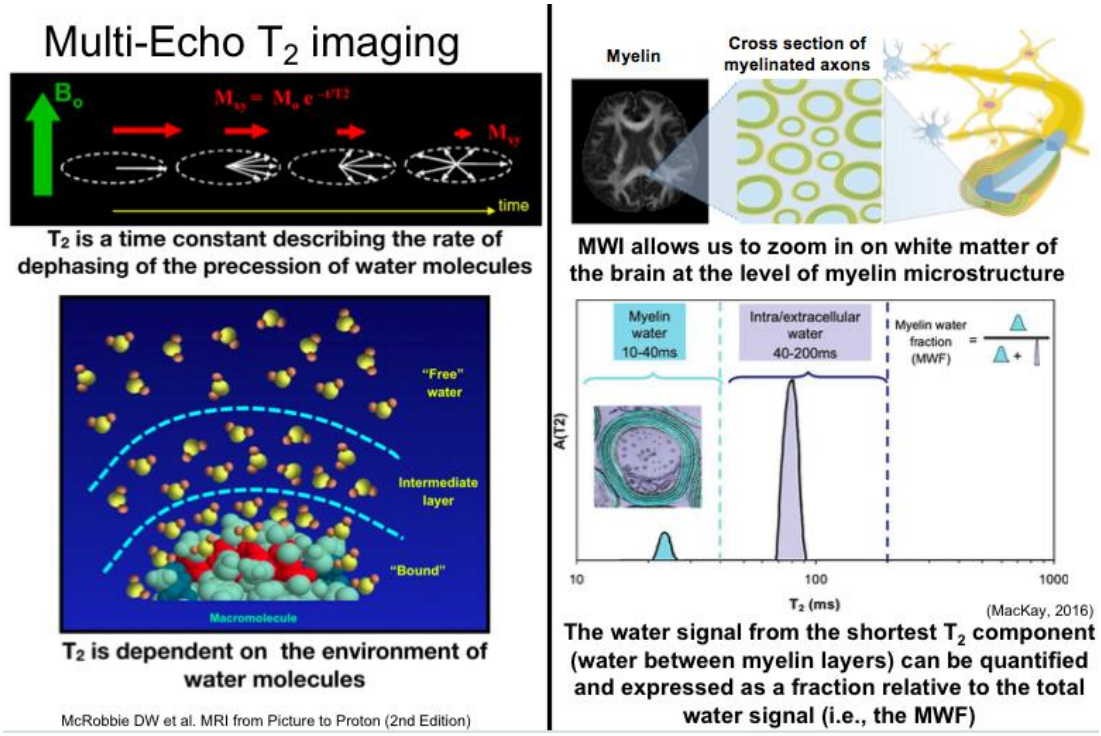



**Figure 5. Myelin water imaging (MWI) is a quantitative MR method that uses multi-echo $T_2$ imaging to characterize myelin. The $T_2$ time constant describes the rate of dephasing of water molecules and shows a short component that originates from water trapped between the lipid bilayers of myelin. The short $T_2$ component originating from the myelin water can then be quantified and expressed as a fraction relative to the total water signal, giving rise to an imaging metric with increased specificity to myelin.**

The contribution of the water signal from the shortest $T_2$ component is attributed to less mobile water trapped in between myelin sheaths and can be quantified and expressed as a fraction relative to the total water signal amplitude [i.e., the Myelin Water Fraction (MWF)] (Lynn, 2020). White matter tracts with larger diameter axons have greater number of myelin wraps, giving rise to higher MWF values (Anand, 2019). Moreover, the water signal from the intermediate $T_2$ component, which is attributed to relatively mobile water in the intra- and extracellular space and dependent on axonal size and inter-axon distance, is quantified as a geometric mean, $geomT_{2\text{-}IEW}$ (Arshad, 2017). Higher $geomT_{2\text{-}IEW}$ values reflect larger diameter axons, greater inter-axon distance (Whittall 1997; Dula 2010; Does, 2018) or degeneration of myelin sheaths leading to

increased cytoplasm space as described by Peters (2009). Moreover, both MWF and geom$T_{2\text{-IEW}}$ measurements have been shown to be highly reliable (Arshad, 2016; Anand, 2019).

MWI studies in MS have demonstrated compelling evidence of decreased global MWF across the brain in persons with MS reflecting myelin/axonal loss (Kolind, 2012), and higher geom$T_{2\text{-IEW}}$ values (Liu 2020), which is consistent with our feasibility data demonstrating similar trends in MS using the proposed MWI acquisition and postprocessing protocol (Figure 4).

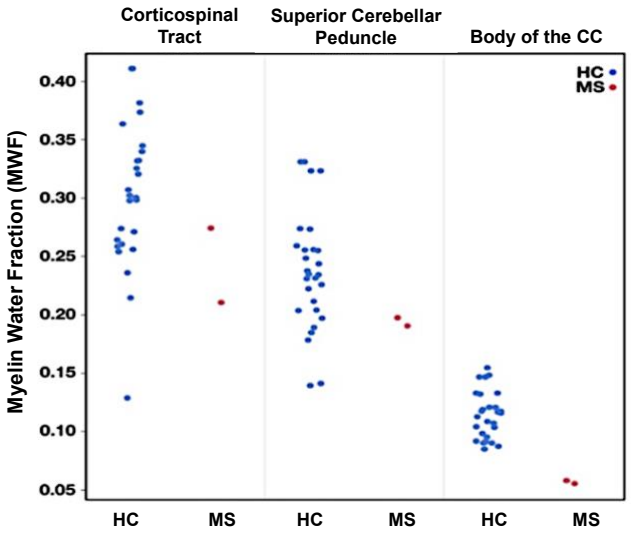



**Figure 6. Myelin water fraction (MWF) in 14 age-matched healthy controls and one MS patient across three key brain regions that included the corticospinal tract (CST), superior cerebellar peduncles (SCP) and body of the corpus callosum ($CC_{body}$). MWF values were lower in the MS patient compared to age-matched healthy controls, with markedly lower values in the $CC_{body}$.**

In one individual with MS, MWF values across ROIs (right and left sides) that have previously been related to walking and balance in prior MS research (Fritz, 2017; Prosperini, 2013; Ibrahim, 2011) [CST, SCP and $CC_{body}$] were lower with extreme values in the $CC_{body}$ compared to 14 age-matched healthy controls (Figure 6). Due to the relation between conduction velocity and the number of myelin wraps around axons, I hypothesize that lower MWF may indicate an impairment in the neural signal of white matter tracts within cortical areas and provide

a link between backward walking and MWF of motor tracts with cognitive connections. Given that demyelination is the pathological hallmark of MS, and the MWF of the participant with MS is markedly lower in ROIs including the $CC_{body}$, our feasibility MWI data displays potential in distinguishing myelin-specific damage that may relate to declines in backward walking. However, there is a paucity of MWI studies in MS and only a limited number also examine clinical function. Therefore, it remains unknown whether MWI corresponds to functional performance in MS (Figure 7).

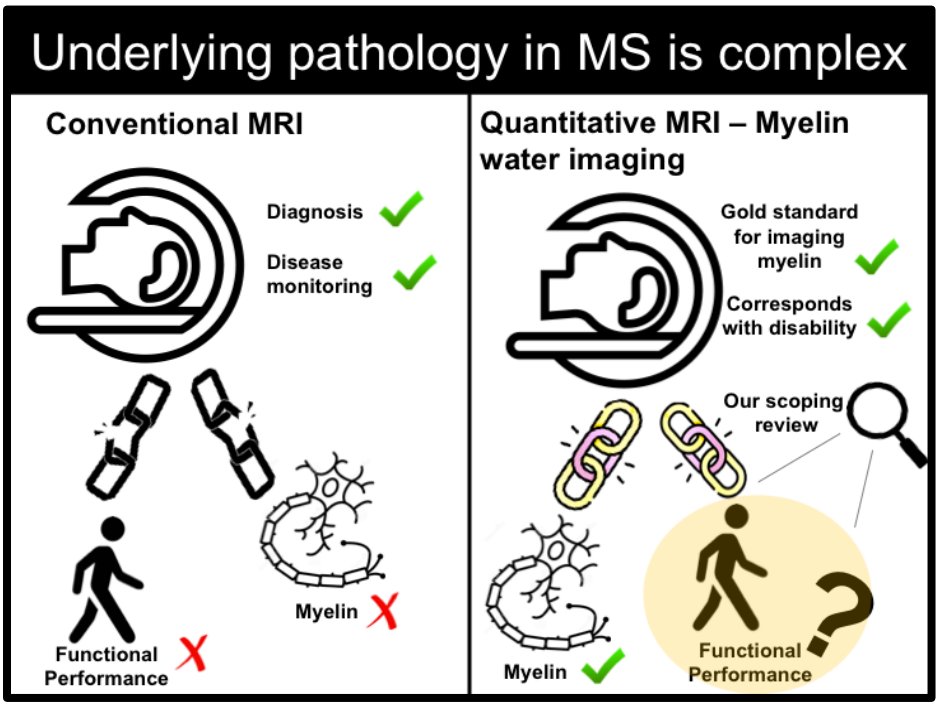



**Figure 7. Conventional MRI is valuable for MS diagnosis and disease monitoring, yet, lacks specificity to myelin and functional performance in MS patients. Myelin water imaging (MWI) is a quantitative magnetic resonance imaging (MRI) technique that demonstrates increased specificity to myelin and overcomes limitations of conventional MRI, including its strong correspondence to MS disability. At present, it remains unknown to what extent MWI metrics relate to functional performance in the MS population.**

Therefore, the fifth chapter of my dissertation examines the relations between MWI and functional domains relevant to MS. By way of a conducted scoping review, I expect to inform and guide future fall detection research in MS. My review will provide the basis for using an innovative

neuroimaging technique with high specificity to myelin to probe the neural underpinnings of a predictive marker of fall risk in MS.

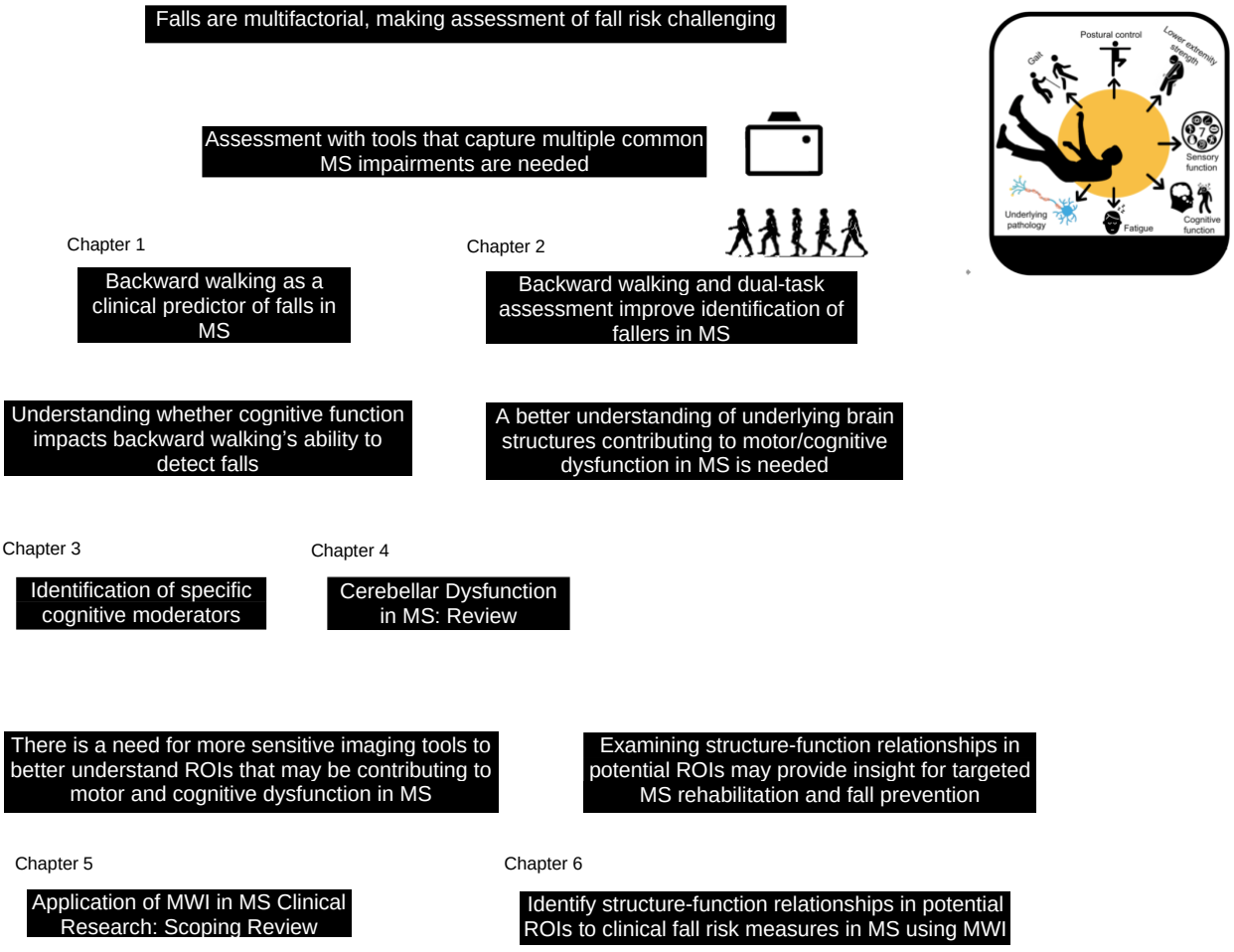
There is a paucity of MWI studies examining structure-function relations in MS. Thus, using MWI to examine key motor and cognitive ROIs (i.e., $CC_{body}$, CST and SCP) that are likely to be involved in backward walking with MWI is critical. Such work will advance our understanding of the relation between MWI metrics of key ROIs to performance on common clinical measures of fall risk. Examination of key ROIs using MWI is the initial step in the development of a neurobiological framework that further supports the clinical utility of backward walking as a fall detection tool (see chapters 1-2). Notably, the majority of MWI studies in MS perform global MWF, leaving few studies to examine explicit motor and cognitive ROIs (Edwards, 2021). Additionally, no MWI studies in MS to date have examined cerebellar regions. As previously mentioned, the cerebellum is a common site for MS pathology and is related to both motor and cognitive dysfunction and fall risk in persons with MS (Wilkins, 2017; Kalron, 2018). Therefore, the sixth and final chapter of this dissertation examines the relation between MWI in key motor ROIs ($CC_{body}$, CST and SCP) to common clinical measures of fall risk (i.e., forward walking speed and dynamic balance) in persons with MS. Using a sensitive imaging tool (MWI) to identify key ROIs that relate to clinical walking and balance performance may identify neural predictors of backward walking performance. Additionally, identification of key ROIs will guide strategic neural targets of falls prevention rehabilitation for persons with MS.

***Summary: Multi-functional assessment to examine backward walking as a novel fall detection tool in persons with MS (Figure 8)***

This dissertation proposes backward walking as a simple, sensitive and clinically feasible tool to predict fall risk in the MS population. Additionally, strategic functional domains both impacted by MS and related to fall risk (Figure 1) are examined (i.e., motor and cognitive assessment and neuroimaging techniques) to initiate a neuroscience-driven framework that aims to support the clinical utility of backward walking as a sensitive fall risk measure in MS.

Collectively, this dissertation will examine the relation between backward walking and falls in MS **(Chapter 1)**, examine the relation between backward walking and dual-task function in MS **(Chapter 2)**, examine the specific domains of cognition involved in backward walking's ability to detect falls (Figure 4) **(Chapter 3)**, examine a specific brain ROI (cerebellum) commonly impacted by MS that is critical for both motor and cognitive function and its relevance to motor control, motor learning and fall prevention **(Chapter 4),** propose the utility of MWI and examine its current relations to clinical function in the MS population **(Chapter 5)**, and examine the relation between MWI measures in strategic motor and cognitive ROIs to common clinical measures of fall risk **(Chapter 6)**. This dissertation is the critical first step in establishing a multi-functional framework to examine backward walking and lays the foundation for our laboratory's future research. Importantly, this body of work represents strategic and simultaneous assessment of multi-functional domains related to fall risk in MS in order to develop accurate fall prediction tools for clinicians and the MS population whom they serve. Accurate fall prediction is a stepping-stone toward decreased falls rates, prescription of timely and targeted rehabilitation therapies, and ultimately, enhanced quality of life for persons with MS.

**Figure 8. Dissertation summary**




## CHAPTER 1: Backward walking sensitively detects fallers in persons with multiple sclerosis

**Edwards EM**, Daugherty AM, Nitta M, Atalla M, Fritz NE. Backward walking sensitively detects fallers in persons with multiple sclerosis. *Mult Scler Relat Disord*. 2020;45:102390. doi:10.1016/j.msard.2020.102390

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Original article

## Backward walking sensitively detects fallers in persons with multiple sclerosis

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**Contribution to the Published Work**

**CRediT Author Statement for Erin Edwards:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – Original Draft, Writing – Review & Editing, Visualization

**Narrative Contributions**

My contributions to my first-author publication titled "*Backward walking sensitively detects fallers in persons with multiple sclerosis*" include evolution of ideas of overarching research goals and aims (Conceptualization), creation of models and application of statistical techniques to analyze and synthesize study data (Methodology), management activities to annotate and maintain research data for initial use and later reuse (Data Curation), preparation, creation and/or

presentation of the published work, specifically writing the initial draft (including substantive translation) (Writing -Original Draft), preparation, creation and presentation of the published work by those from the original research group, including critical review, commentary and revision in both pre and post-publication stages (Writing – Review & Editing), and preparation, creation and presentation of the published work, specifically visualization and data presentation (Visualization).

**Placing the Published Work in the Context of the Overall Dissertation**

The overarching problem addressed by my dissertation is that falls are challenging to predict given the multiple factors that may contribute to fall risk, making identification of better tools critical. Individuals with multiple sclerosis experience deficits in motor, cognitive and sensory functions resulting in injurious falls. A tool that captures multiple common MS impairments related to falls is needed. Thus, we propose backward walking as a simple, robust and clinically feasible tool to detect fall risk in persons with MS.

*THE GAP:* Current clinical measures of fall risk for the MS population rely primarily on measures of forward walking and balance. However, measures of forward walking and balance exhibit limited sensitivity and predictive value for identifying fallers with MS. Prior research in other neurodegenerative diseases demonstrates that backward walking better differentiates fallers from non-fallers in the elderly. However, this work has not been explored in persons with MS.

*THE SOLUTION:* Therefore, in this work, we examined both forward and backward walking to determine the strongest, unique contributor that differentiates fallers from non-fallers in persons with multiple sclerosis. This study is the critical first step in establishing the sensitivity of backward walking to detect falls compared to current clinical measures.

Backward Walking Sensitively Detects Fallers in Persons with Multiple Sclerosis

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Preliminary data from this manuscript was presented at the American Physical Therapy Association Combined Sections Meeting in January, 2018.

Abstract

*Background:* Individuals with multiple sclerosis experience deficits in mobility resulting in injurious falls. Fall detection has proved challenging; the majority of clinical measures rely on forward walking and balance measures, yet these measures have poor sensitivity and predictive value for differentiating between fallers and non-fallers. Backward walking better differentiates fallers from non-fallers in the elderly and other neurodegenerative diseases; therefore, the objective of this study was to examine both forward and backward walking to determine the strongest, unique contributor that differentiates fallers from non-fallers in persons with multiple sclerosis.

*Methods:* In a single session, spatiotemporal measures of forward and backward walking and fall history were collected. For the subsequent six months, individuals recorded falls in a fall diary. Discriminant function analysis was used to determine what variables most strongly and uniquely differentiate multiple sclerosis fallers from non-fallers.

*Results:* Thirty-eight individuals with multiple sclerosis participated. Forward and backward velocity, stride length, and double support time as well as age, disease severity, and symptom duration were included in the models. Together, the variables differentiated between fallers and non-fallers (Wilk's lambda $\chi 2$ (8, N = 36) = 0.497, $p<0.001$) and in rank order, backward walking velocity was the strongest unique predictor. Repeating the analysis with a stepwise approach yielded backward walking velocity in the first step ($\chi 2$ (1, 34) = 0.68, F = 15.96, $p<0.001$) and symptom duration in the second step ($\chi 2$ = 0.59, F (2, 33) = 11.46; $p<0.001$) most strongly differentiated retrospective fallers and non-fallers. This stepwise model with backward walking velocity and symptom duration accurately classified 76.3% of cases. Addition of forward walking measures did not significantly improve the models, and indeed the accuracy of classification was reduced to 71.1%. Exploratory analysis showed that backward walking velocity was the best predictor of prospectively reported fallers and non-fallers ($\chi 2$ (1, 7) = 0.43, F = 9.20, p = 0.02).

*Conclusion*: Backward walking velocity exhibits the highest effect magnitude and specificity in differentiating fallers from non-fallers in individuals with MS and demonstrate potential as clinically feasible and efficient fall detection tool.

*Keywords: Multiple Sclerosis; Walking; Falls; Backward Walking*

## Introduction

Multiple Sclerosis (MS) is a progressive neurologic disease associated with inflammation, demyelination and axonal damage of the central nervous system. As a result, MS causes debilitating motor, cognitive and sensory impairments [1], making accidental falls an unfortunate commonality. Over 50% of individuals with MS suffer a fall within a six-month period [2] and 70% within one year [3]. In addition to significant morbidity and socioeconomic costs, falls in MS are associated with activity curtailment [4], social isolation, and increased demand on healthcare resources [5].

The adverse health and quality-of-life consequences of falls underscore the critical need to identify clinical measures that sensitively predict falls in MS. Current measures used to identify fallers in MS primarily rely upon forward walking speed and balance [6-7], often including the Timed 25ft Walk (T25FW), Berg Balance Scale and Timed-Up and Go (TUG) [8]. However, meta-analyses of these measures reveal poor ability to discriminate between fallers and non-fallers, limited sensitivity values, and low predictive validity [9-11]. Consequently, a quick, simple and sensitive measure of fall risk for the MS population remains unidentified [12].

Recent studies in the elderly and other neurodegenerative disease populations have proposed the use of backward walking as a clinical measure of mobility and fall risk [13-15]. Backward walking velocity more accurately identifies elderly fallers than forward walking velocity [13] and is highly correlated with known predictors of falling (Four Square Step Test and Activities-Specific Balance Confidence Scale) [14], suggesting its clinical utility to identify those at risk for falls. In MS, motor differences are greater during backward walking than forward walking and backward walking better distinguishes MS individuals from healthy controls [16]. Similarly, deficits in

stepping and postural control are more pronounced during backward walking in persons with MS and significantly correlate with increased severity on clinical measures of forward walking and disability [17]. However, the relation between backward walking and falls has not been examined in MS.

Prior studies acknowledge the limited discriminative ability and sensitivity of forward walking measures [9] in fall detection and suggest the use of backward walking for the elderly [13-15] and other neurodegenerative disease populations [15]. Additionally, backward walking is a challenging, novel task requiring increased postural control, lower extremity strength and cognitive demands [18-19], all of which are negatively affected in MS. Therefore, the aim of our study was to examine the sensitivity of forward and backward walking measures to determine the strongest, unique contributor that differentiates fallers from non-fallers in persons with MS. We hypothesized that backward walking measures would be a strong and unique descriptor of MS fallers compared to non-fallers, both retrospectively and prospectively, and exhibit increased sensitivity compared to forward walking measures. Confirmation of this hypothesis would provide further support for the future utility of backward walking as a sensitive clinical tool to detect fall risk in individuals with MS.

## Materials and Methods

### *Study Participants*

A convenience sample of 38 participants with a neurologist-confirmed diagnosis of relapsing-remitting MS (RRMS) were recruited from the MS clinic at Wayne State University in Detroit, Michigan and local MS support groups of the Greater Detroit Area. All participants provided written informed consent, and the research protocol was approved by the WSU Institutional Review Board. MS individuals were eligible to participate if they were between 18-75 years of age, stable on immunomodulatory therapy (if applicable) for at least three months prior to beginning of study, ambulatory with or without physical assistance and able to follow study-related commands. Exclusion criteria included MS exacerbation within the last eight weeks, corticosteroid use within

the last 30 days, and acute orthopedic or other neurologic conditions that would interfere with walking.

*Data Collection*

All participants signed informed consent forms prior to data collection. All measures were collected in a single session. Demographic data were collected, including age, sex, BMI, disease severity with Patient Determined Disease Steps (PDDS), and symptom duration.

Walking: Forward walking and backward walking performance was evaluated with a 16-foot GaitRite electronic walkway (MAP/CIR, Franklin, NJ). The GaitRite electronic walkway is a computerized walkway with sensors organized in a grid-like pattern that records footfalls in real time and is reliable and valid for use in MS [1]. The GaitRite calculates spatiotemporal measures of gait and individual step parameters. Participants were instructed to walk at their quickest and safest speed for forward walking trials, which mimics the conditions of the T25FW [20]. Participants were instructed to walk at a comfortable, safe pace for backward walking trials, following the methods of our lab and others [21;15]. Four trials were recorded for each condition, and the data were averaged. Participants began walking two meters prior to the GaitRite and stopped walking two meters after the GaitRite, allowing for proper acceleration and deceleration phases. Participants received instruction to look ahead rather than at their feet, wore a gait belt, and were accompanied by a research assistant to ensure safety and minimize path deviations on all trials.

Self-reported walking was evaluated with the Multiple Sclerosis Walking Scale-12 (MSWS-12). The MSWS-12 is a 12-item questionnaire in which individuals rate how severely MS affects different aspects of walking [22]. The MSWS-12 demonstrates high test-retest reliability and excellent concurrent validity with the Expanded Disability Status Scale [23].

Falls: Falls were measured both retrospectively: participants reported a one-month fall history during the single laboratory visit, and prospectively: participants recorded daily number of falls in a fall diary for a subsequent six months that was later returned to the laboratory. Falls were

defined as “unexpected events that resulted in an unintentional landing on the ground or a lower surface” [24].

*Analytical Approach*

All statistical analyses were performed with SPSS version 25. We chose *a priori* to evaluate velocity, stride length and double support time for forward and backward walking measures to compare between MS fallers and non-fallers, both retrospectively and prospectively. These measures were chosen because stride length and double support time have been related to balance in individuals with MS [25], older adults [14], and other neurodegenerative diseases [26], and backward walking velocity has been linked to falls in older adults [13]. Age, disease severity, and symptom duration were also included as covariates. We conducted separate analyses for retrospective and prospective falls data. Mann-Whitney analyses were used to compare performance between retrospective fallers and non-fallers (Table 1).

Our analytical approach used discriminant function analysis to determine which variables most strongly, uniquely differentiate retrospective MS fallers from non-fallers. Prior to hypothesis testing, the assumptions of univariate and multivariate normality were evaluated and reasonably met. To evaluate the hypothesis that backward walking was a strong, unique descriptor of MS fallers as compared to non-fallers, two discriminant function analyses were estimated to provide complementary assessments. First, all predictors were entered in a single-step to estimate the descriptors, in rank order, of retrospective MS fallers versus non-fallers, as well as classification accuracy. In a second model, a step-wise method was used to identify the minimal number of variables to replicate accurate classification based on change in Wilk’s lambda between steps. This modeling approach is data-driven, and thus the strongest, unique predictor of between-group differences will enter the model first, followed by the next strongest, unique predictor to maximally differentiate between groups. The resulting model can be interpreted for parsimony and may shed light on clinical application that are optimized for efficiency. Models were specified assuming unequal prior group probabilities estimated from the observed group sizes and leave-one-out

cross-classification accuracy. Initial hypothesis testing prioritized variables that could be feasibly collected in a clinical setting; secondary analysis used the same methods and included forward and backward walking gait variability measures that are common in research study. All models included age, disease severity, and symptom duration as covariates. The sample was predominantly female (90%) and when compared between fall groups, MS fallers included one male; due to the low representation of men, sex was not included as a covariate.

An exploratory analysis evaluated if the same predictors would identify individuals who prospectively reported falls. Due to poor return rates on the fall diaries, the prospective data were treated as an exploratory analysis for which hypothesis tests were expected to be underpowered in the small sample size. The step-wise discriminant function analysis procedure was repeated to differentiate between prospective MS fallers and non-fallers, and the selected variables were interpreted as contributing to the model in addition to model classification accuracy.

Last, to examine potential clinical utility of the findings, forward and backward walking velocity measures were binned into quartiles with bin 1 indicating the lowest 25% of performers and bin 4 representing the top 25% of performers. The slowest FW velocity bin encompassed clinically-meaningful walking speeds suggestive of fall risk [27]. Velocity measures for forward and backward walking were binned as followed: 0%-25% (0.0-0.76 m/s, 0-0.46 m/s), 26%-50% (0.77-1.49 m/s, 0.47-0.91 m/s), 51%-75% (median) (1.50-2.23 m/s, 0.92-1.36 m/s) and 76%-maximum walking velocity (2.24-2.95 m/s, 1.37-1.8 m/s), respectively.

Results

Thirty-eight participants (four males, 34 females; Age 50.4.4± 9.2 years; symptom duration 16.9±11.8 years; MSWS-12 43.8±31.1) with RRMS participated in this study. 86.8% of the participants were taking disease-modifying therapies and 39.5% utilized walking devices during testing (Table 1). There were no significant differences between fallers and non-fallers on demographic measures, but fallers were significantly slower, took significantly shorter steps and

spent significantly more time in double support than non-fallers in both forward and backward walking (Table 1).

*Falls are common in individuals with MS*

Fifteen of thirty-eight individuals (39.5%) reported retrospective falls. Of the eleven individuals who returned prospective fall diaries, 72.7% reported at least one fall in the subsequent six months. Individuals were categorized as fallers (≥1 fall) or non-fallers (0 falls) on both retrospective fall reports and prospective fall diaries.

*Backward walking velocity is the strongest, unique descriptor of retrospective MS fallers.*

In the first analysis, we evaluated the variables that maximally differentiate retrospective MS fallers and non-fallers. The model with one discriminant function was significant: Wilk's lambda $\chi 2$ (8, N = 36) = 0.497, p<0.001. Interpreting the structure matrix, the unique contribution of each predictor was ranked in order of effect magnitude. Backward walking velocity emerged as the best discriminator between retrospective fallers and non-fallers (Figure 1). The overall cross-validated classification accuracy was 71.1% using all available predictors, and accuracy was similar between retrospective MS fallers (66.7%) and non-fallers (73.9%).

To determine the minimum number of predictors required to replicate the classification accuracy of retrospective MS fallers and non-fallers, the analysis was repeated using a step-wise approach with significant change in Wilk's lambda as a criterion for entering a new, unique predictor. Backward walking velocity was selected in the first step (Wilk's lambda $\chi 2$ (1, 34) = 0.68, F = 15.96, p<0.001) and symptom duration was selected in the second step (Wilk's lambda $\chi 2$ = 0.59, F (2, 33) = 11.46; p<0.001), and no other variables significantly improved the model. With only these two variables, the model correctly classified 80.0% of retrospective MS fallers and 73.9% of non-fallers (overall classification accuracy 76.3%).

Repeating the analysis with the addition of forward and backward walking gait variability (i.e., forward and backward stride length and double support time coefficients of variability), backward

walking velocity remained the foremost predictor to distinguish MS fallers and non-fallers. Based on structure matrix loadings, variation in backward walking double support time (0.39) and stride length (0.33), but not forward walking gait variation (-0.29 and -0.14, respectively), contributed to the discriminant function but were lower ranked than backward walking velocity. Including all variables in the stepwise discriminant function analysis, backward walking velocity remained the first predictor selected, followed by symptom duration, and all other variables did not significantly improve the model.

*Backward walking velocity may best discriminate between prospective MS fallers and non-fallers.*

As an additional step to assess the value of backward walking in the clinical setting, we conducted an exploratory analysis with the subsample of individuals who returned fall diaries to predict prospective MS fallers. The model resulted in a single step that included backward walking velocity (Wilk's lambda $\chi 2$ (1, 7) = 0.43, F = 9.20, p = 0.02). The model with a single predictor accurately classified prospective MS fallers (85.7%) and non-fallers (100.0%), with an overall model accuracy of 90.0%.

*Backward walking velocity exhibits higher sensitivity in detecting MS fallers than forward walking velocity, both retrospectively and prospectively.*

To further examine the clinical utility of these findings, we binned individuals into quartiles by walking velocity speed. Velocity measures for both forward and backward waking were binned into quartiles indicating slowest walking velocity 0%-25% (0.0-0.76 m/s, 0-0.46 m/s), 26%-50% (0.77-1.49 m/s, 0.47-0.91 m/s), 51%-75% (median) (1.50-2.23 m/s, 0.92-1.36 m/s) and 76%-maximum walking velocity (2.24-2.95 m/s, 1.37-1.8 m/s), respectively. The bottom two forward walking velocity bins, encompassing clinically meaningful forward walking speeds suggestive of fall risk [27], detected eight out of fifteen retrospective MS fallers (53%) (Figure 2A) In contrast, the bottom two backward walking velocity bins detected all fifteen retrospective MS fallers (100%). (Figure 2B**)**. Prospectively, the bottom two forward walking velocity bins detected two out of six

prospective MS fallers (33%), while the bottom two backward walking velocity bins detected five out of six prospective MS fallers (83%).

Discussion

This study examined forward and backward walking measures to determine the strongest, unique contributor that differentiates fallers from non-fallers, both retrospectively and prospectively, in persons with MS. The critical finding of the current study is that backward walking velocity accurately classified 71.1% of MS fallers and non-fallers, which greatly improves upon current clinical tools [9-11]. Additionally, backward walking velocity was the strongest and unique predictor to maximally differentiate between retrospective MS fallers and non-fallers, whereas no forward walking measures significantly improved the model. Due to poor return rates on fall diaries, prospectively reported falls data were examined in a separate, exploratory analysis. However, our data suggests backward walking may best discriminate between prospective MS fallers and non-fallers.

Backward walking velocity emerged as the top descriptor differentiating MS fallers from non-fallers and backward walking stride length emerged second when all variables were entered into the discriminant model (Figure 1). These findings are consistent with studies in the elderly [13-14] and other neurodegenerative disease populations [15] in which backward walking better identifies fallers compared to forward walking. Additionally, our findings are supported by previous studies in MS that report walking deficits and balance are more prominent in MS individuals during backward walking [16] and strongly relate to increased severity on clinical measures [17]. Importantly, these findings are the first to demonstrate the increased sensitivity of backward walking velocity to detect falls in MS, specifically when comparing to the current clinical gold standard of forward walking measures.

Another critical finding of the current study was the stepwise model used to determine the minimum number of predictors required to replicate the 71.1% classification accuracy of retrospective MS fallers and non-fallers. Only backward walking velocity (first) and symptom

duration (second) emerged as descriptors that significantly improved the model, whereas no forward waking measures emerged. With only these two variables, the overall classification accuracy of our model improved by 5.2% to 76.3%.

Importantly, these findings reflect the sensitivity of backward walking velocity and its potential to stand-alone as a clinical assessment, if cutoff values are established and validated. Forward walking velocity cut-off values and the corresponding predicted outcomes for falls exist for a wide range of populations including MS [27]. However, clinically meaningful cut-offs have not been established for stride length and double support time, as these measures are more challenging to measure in a clinic setting. The limitations of further spatial (stride length) and temporal (double support time) parameters of walking underscore the importance of identifying backward walking velocity emerging as the strongest descriptor of MS fallers, as velocity can be easily measured in the clinic setting. Additionally, these results demonstrate the potential clinical efficiency of backward walking velocity, as the addition of variables decreased classification accuracy between MS fallers and non-fallers.

Our exploratory analysis on a small sample of prospectively reported falls revealed backward walking velocity as the single descriptor in differentiating MS fallers from non-fallers. Given the increased complexity and physical demands required for backward walking [18-19], these findings are consistent with larger-scale studies in MS that demonstrate clinically feasible higher-challenge balance tasks are most sensitive to risk of future falls [28]. Additionally, several studies in MS highlight the underestimation of falls with retrospective recall in comparison to prospective reporting [29-30]. These findings are not surprising considering the high prevalence of cognitive dysfunction in persons with MS [31]. Therefore, our prospectively reported falls data advances the literature that maintains a heavy reliance upon retrospective reporting of falls.

To better visualize the clinical utility of our findings, we examined quartiles of walking velocity in both the forward and backward direction (Figure 2A-B) and categorized the fallers and non-fallers. Although the Timed 25 Foot Walk (forward walking) is the clinical gold standard of

walking function commonly used in MS clinical trials [7] and forward walking speed cut-offs have been suggested for fall risk [27], these data demonstrated that the lowest quartiles of backward walking velocity better identified fallers (15/15 fallers, 100%) compared to forward walking (8/15 fallers, 53%). Future work in larger samples is needed to establish cut-off scores for backward walking velocity. However, these results provide preliminary evidence of the importance of backward walking velocity as a clinical tool to identify MS fallers.

Our results are the first to elucidate the relationship between backward walking speed and falls in MS and are relevant given the robust nature of forward walking speed as a current fall detection tool. To date, forward walking speed is considered a simple assessment that provides a wealth of information about underlying physiological processes [27] and clinicians are strongly advised to incorporate forward walking into all comprehensive evaluations [32]. Backward walking may be a sensitive clinical outcome tool for monitoring disease change or progression, and assessment of an individual's backward walking, in addition to the current fall detection methods, may guide clinical decision-making. However, a larger sample size with prospective falls monitoring is needed to further elucidate clinically useful cut-off scores for backward walking velocity in persons with MS.

*Limitations*

Limitations of this study include its small sample size of 38 individuals who were mainly female with relapsing remitting MS, which may not generalize to ambulatory persons or males with progressive disease. However, these limited data satisfy prior gaps in knowledge regarding the relationship between backward walking and falls in persons with MS. This study relied on retrospectively collected data on falls while acknowledging previously reported pitfalls of this methodology [33]. However, we undertook prospective fall reporting to mitigate those drawbacks. Despite weekly reminders to fill out fall diaries and follow-up calls to return the diaries, the low return rates of the fall diaries underpowered our prospective data analysis and thus limited interpretation of findings. Therefore, the use of technology (i.e., smart phone applications,

websites, and wearable devices) is critical for accurate fall reporting in future trials and determining the predictive validity of backward walking to falls in MS.

This study was limited to walking measures and therefore, did not evaluate other factors that could heavily influence fall risk in persons with MS, such as cognition, spasticity, and fatigue. The common domains of cognition that are affected by MS (i.e. processing speed, attention, memory, and executive function) [34-35] have been related to motor measures and fall frequency in MS [36]. Additionally, our laboratory has shown that backward walking is related to cognitive measures that assess attention (Symbol Digit Modalities Test (SDMT) – $r = -0.61$; $p = 0.001$) [21]. Therefore, future studies will examine the specific domains of cognition impacted by MS as well as fatigue. Lastly, if backward walking is used as a fall-risk detection tool, future studies should consider objectively quantifying the measure via body-worn sensors. A prospective study in a small sample of people with Parkinson's disease showed increased accuracy of fall risk detection utilizing sensors [37].

Conclusions

This study is the first to identify backward walking velocity as the strongest and unique descriptor of retrospective MS fallers. Backward walking velocity exhibited the highest sensitivity in differentiating retrospective MS fallers from non-fallers, whereas no forward walking measures contributed to the step-wise discriminant model. Future work with a larger sample size is needed to validate the future clinical utility of backward walking and mitigate the limited sensitivity of the current fall detection methods. Additionally, larger-scale studies would leverage identification of definitive backward walking velocity cut-off scores for clinical use and better understand its relationship to falls by examining potential underlying mechanisms (i.e. pathology and cognitive function). Backward walking velocity is an inexpensive, easily measured and clinically feasible tool that could supplement the current methods. From these findings, we speculate that backward walking velocity is a sensitive clinical marker of fall risk in MS that warrants further research.

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## Figure Legends

**Figure 1.** Structure Matrix ranking the contribution of each predictor variable in order of effect magnitude to differentiate retrospective MS fallers from non-fallers.

**Figure 2A-B.** Walking velocity (m/s) quartiles for forward walking (A) and backward (B) walking to detect MS fallers, retrospectively and prospectively. Velocity measures for both forward and backward waking were binned into quartiles indicating slowest walking velocity 0%-25% (0.0-0.76 m/s, 0-0.46 m/s), 26%-50% (0.77-1.49 m/s, 0.47-0.91 m/s), 51%-75% (median) (1.50-2.23 m/s, 0.92-1.36 m/s) and 76%-maximum walking velocity (2.24-2.95 m/s, 1.37-1.8 m/s), respectively.

## Table 1. Comparison of whole group to retrospective fallers and non-fallers



**Table 1**
Comparison of whole group to retrospective fallers and non-fallers.

| | All MS (n = 38) | Retrospective Fallers (n = 15) | Retrospective Non-Fallers (n = 23) | p-value |
|---|---|---|---|---|
| **Age (years)** | 50.4 (9.2) | 51.0 (11.4) | 50.1 (7.7) | 0.953 |
| **Sex (Male:Female)** | 4:34 | 1:14 | 3:20 | 0.746 |
| **BMI** | 25.2 (5.3) | 25.8 (7.1) | 24.8 (3.7) | 0.768 |
| **MSWS-12 (n = 21)** | 43.8 (31.1) | 55.7 (14.1) | 36.5 (36.7) | 0.121 |
| **PDDS (Range 0-6)** | 3.2 (2.1) | 3.9 (1.8) | 2.7 (2.2) | 0.101 |
| **Symptom Duration (years)** | 16.9 (11.8) | 15.7 (11.0) | 17.7 (12.5) | 0.768 |
| **Disease Modifying Therapy (%)** | 86.8% | 73.3% | 100% | 0.089 |
| **Assistive Device Use (%)** | 39.5% | 53.3% | 30.0% | 0.248 |
| **Forward Walking Velocity (m/s)** | 1.62 (0.72) | 1.27 (0.63) | 1.86 (0.69) | 0.008 |
| **Forward Walking Stride Length (cm)** | 136.0 (35.5) | 118.8 (31.6) | 143.1 (35.2) | 0.018 |
| **Forward Walking Double Support Time (s)** | 0.58 (1.1) | 0.97 (1.6) | 0.30 (0.44) | 0.005 |
| **Forward Walking Stride Length CV (%)** | 0.063 (0.085) | 0.077 (0.066) | 0.053 (0.097) | 0.013 |
| **Forward Walking Double Support Time CV (%)** | 0.16 (0.21) | 0.23 (0.30) | 0.11 (0.081) | 0.874 |
| **Backward Walking Velocity (m/s)** | 0.75 (0.50) | 0.42 (0.30) | 0.98 (0.49) | <0.001 |
| **Backward Walking Stride Length (cm)** | 70.9 (37.3) | 50.6 (34.1) | 85.4 (33.0) | 0.004 |
| **Backward Walking Double Support Time (s)** | 0.50 (0.49) | 0.74 (0.67) | 0.34 (0.18) | 0.015 |
| **Backward Walking Stride Length CV (%)** | 0.15 (0.16) | 0.21 (0.22) | 0.10 (0.063) | 0.150 |
| **Backward Walking Double Support Time CV (%)** | 0.25 (0.33) | 0.40 (0.46) | 0.14 (0.12) | 0.018 |

All values listed mean(SD). Body Mass Index (BMI); Multiple Sclerosis (MS); Multiple Sclerosis Walking Scale-12 (MSWS-12); Patient Determined Disease Steps (PDDS).

## Figure 1.



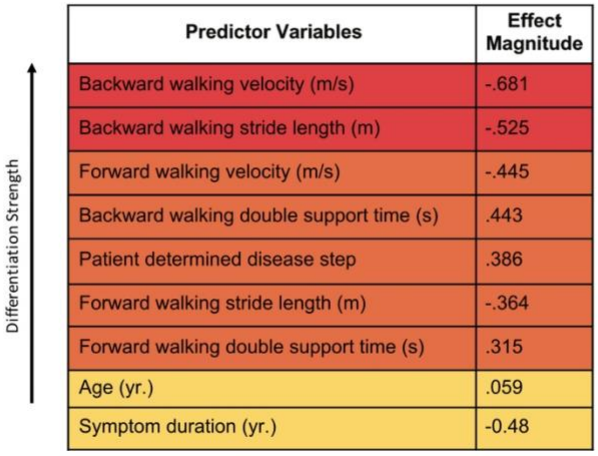


**Fig. 1.** Structure Matrix ranking the contribution of each predictor variable in order of effect magnitude to differentiate retrospective MS fallers from non-fallers.

**Figure 2A.**

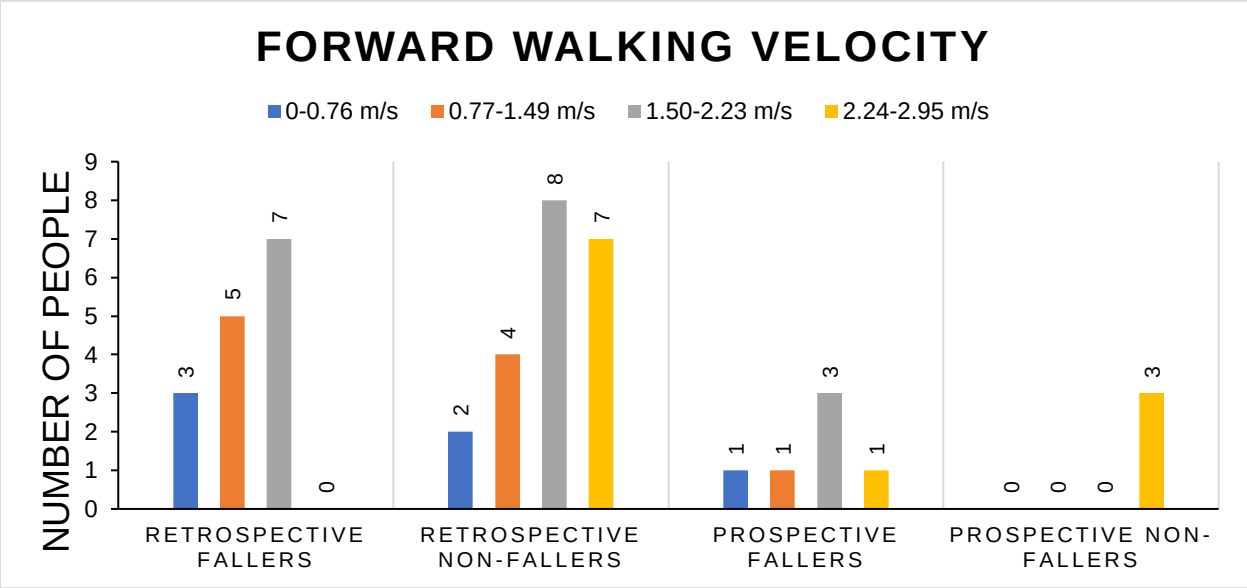


**Figure 2B.**

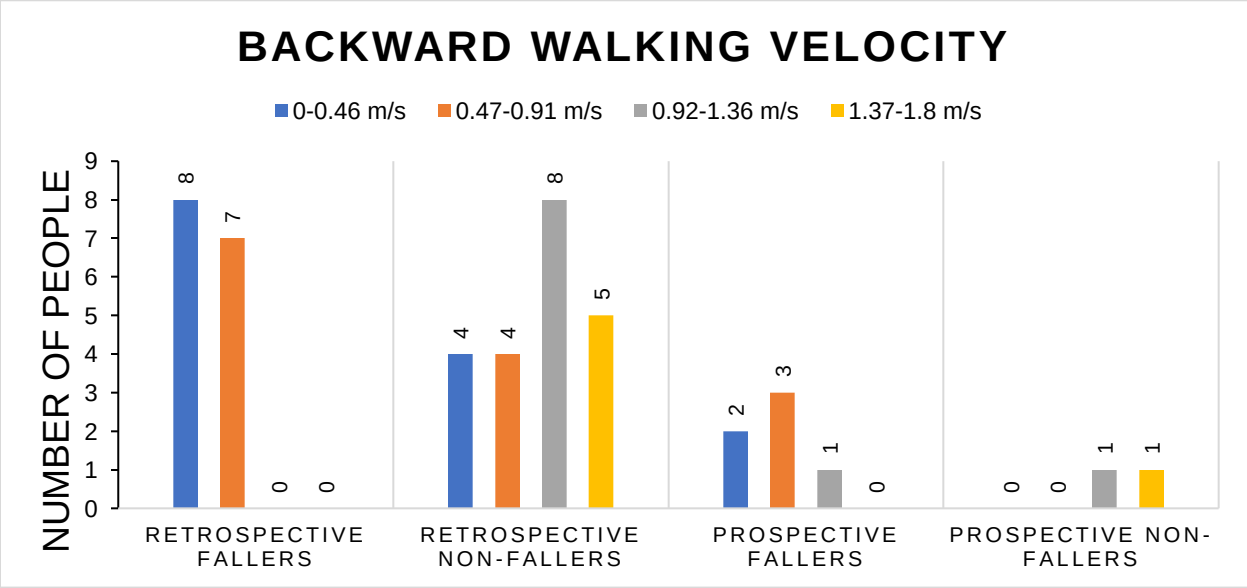


**Figure 2A-B.** Walking velocity (m/s) quartiles for forward walking (A) and backward (B) walking to detect MS fallers, retrospectively and prospectively. Velocity measures for both forward and backward waking were binned into quartiles indicating slowest walking velocity 0%-25% (0.0-0.76 m/s, 0-0.46 m/s), 26%-50% (0.77-1.49 m/s, 0.47-0.91 m/s), 51%-75% (median) (1.50-2.23 m/s, 0.92-1.36 m/s) and 76%-maximum walking velocity (2.24-2.95 m/s, 1.37-1.8 m/s), respectively.

## CHAPTER 2: Backward walking and Dual-Task Assessment Improve Identification of Gait Impairments and Fall Risk in Individuals with MS.

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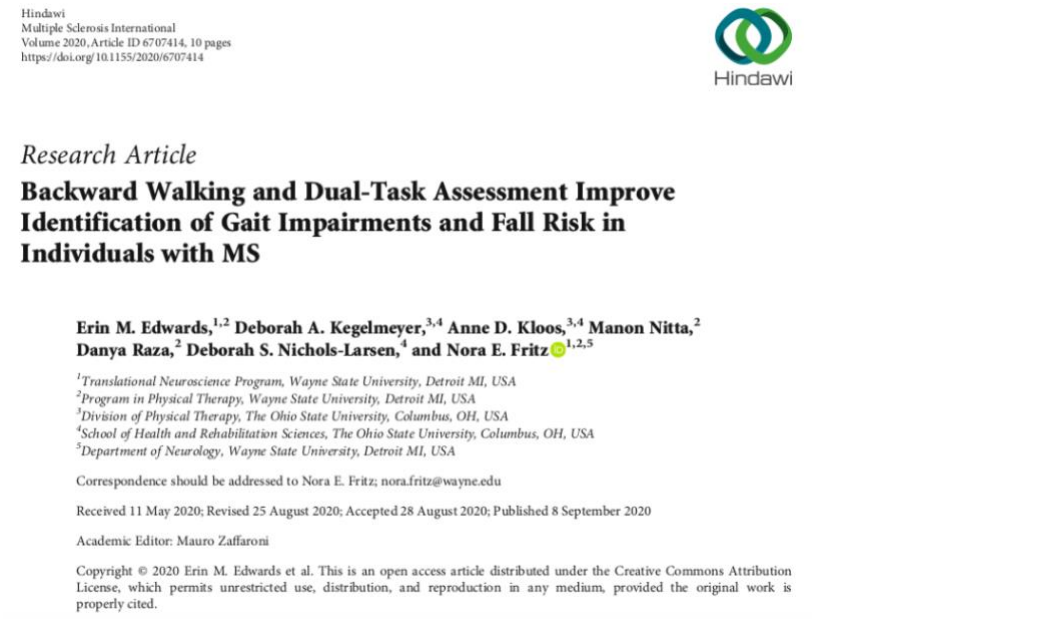

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*Research Article*

**Backward Walking and Dual-Task Assessment Improve Identification of Gait Impairments and Fall Risk in Individuals with MS**

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### Contribution to the Published Work

**CRediT Author Statement for Erin Edwards:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – Original Draft, Writing – Review & Editing, Visualization

### Narrative Contributions

My contributions to my first-author publication titled "*Backward walking and Dual-Task Assessment Improve Identification of Gait Impairments and Fall Risk in Individuals with MS*"

include evolution of ideas of overarching research goals and aims (Conceptualization), creation of models and application of statistical techniques to analyze and synthesize study data (Methodology), management activities to annotate and maintain research data for initial use and later reuse (Data Curation), preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation) (Writing -Original Draft), preparation, creation and presentation of the published work by those from the original research group, including critical review, commentary and revision in both pre and post-publication stages (Writing – Review & Editing), and preparation, creation and presentation of the published work, specifically visualization and data presentation (Visualization).

**Placing the Published Work in the Context of the Overall Dissertation**

The overarching problem addressed by my dissertation are that falls are challenging to predict given the multiple factors that may contribute to fall risk, making identification of better tools critical. Individuals with multiple sclerosis experience deficits in motor, cognitive and sensory functions resulting in injurious falls. A tool that captures multiple common MS impairments related to falls is needed. Recent work identifies backward walking velocity as a sensitive fall detection measure for persons with MS (Edwards, 2020; **Chapter 1**). Backward walking is a non-automatic, complex motor task that requires increased motor and cognitive demands (Johannson, 2017; Motl, 2017), both in which are negatively affected in persons with MS. Dual-task walking (i.e., walking while simultaneously performing a secondary cognitive task) has recently been used in MS research (Muir-Hunter, 2016; Henning, 2020) in effort to better understand motor-cognitive interactions during gait. Dual-task walking is similar to backward walking, as it also requires increased motor and cognitive demands (Ruffieux, 2015).

*THE GAP:* At present, relations between backward walking dual-task measures to cognitive function and critically, falls, are understudied in persons with MS. Moreover, it remains unknown whether pairing two movements together (i.e., backward walking dual-task measures)

that demand motor and cognitive input that is often disrupted in MS can provide additional sensitivity to fall risk assessment in persons with MS.

*THE SOLUTION:* Therefore, assessment of backward walking in both single and dual-task conditions will identify whether measures of backward walking dual-task relate to falls in persons with MS. This work serves as a critical first step in understanding the role of cognitive function in backward walking performance as a novel marker of fall risk in persons with MS.

Backward Walking and Dual-Task Assessment Improve Identification of Gait Impairments and Fall Risk in Individuals with MS

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**Abstract**

*Background:* Individuals with multiple sclerosis (MS) experience deficits in motor and cognitive domains, resulting in impairment in dual-task walking ability. The goal of this study was to compare performance of forward walking and backward walking in single and dual-task conditions in persons with MS to age and sex-matched healthy controls. We also examined relationships between forward and backward walking to cognitive function, balance, and retrospective fall reports.

*Methods:* All measures were collected in a single session. A 2x2x2 mixed model ANOVA was used to compare differences in forward and backward walking in single and dual-task conditions between MS and healthy controls. Spearman correlations were used to examine relationships between gait and cognitive function, falls, and balance.

*Results:* Eighteen individuals with relapsing-remitting MS and 14 age and sex-matched healthy controls participated. Backward walking velocity revealed significant differences between groups for both single-task ($p=0.015$) and dual-task ($p=0.014$) conditions. Persons with MS demonstrated significant differences between single and dual-task forward and backward walking velocities ($p=0.023$; $p=0.004$), whereas this difference was only apparent in the backward walking condition for healthy controls ($p=0.004$). In persons with MS, there were significant differences in double support time between single and dual-task conditions in both backward ($p<0.001$) and forward ($p=0.001$) directions. More falls at six months were significantly associated with shorter backward dual-task stride length ($r=-0.490$; $p=0.046$) and slower velocity ($r=-0.483$; $p=0.050$).

*Conclusion:* Differences in MS and age and sex-matched healthy controls are more pronounced during backward compared to forward walking under single and dual-task conditions. Future work with a larger sample size is needed to validate the clinical utility of backward walking and dual-task assessments and mitigate the limited sensitivity of the current dual-task assessments that primarily rely upon forward walking.

**Introduction**

Multiple sclerosis (MS) is a progressive neurologic disease that causes debilitating motor, cognitive and sensory impairments [1]. While a broad spectrum of clinical signs and symptoms are experienced by persons with MS, walking impairment is one of the most commonly reported symptoms to negatively impact quality of life [2-4]. Accordingly, standardized clinical measures, including the Timed 25 Foot Walk, 2-Minute Walk Test and 6-Minute Walk Test [5] have been established in MS to provide clinicians with informative “snapshots” of walking performance. To date, scores on clinical measures of walking performance in MS have been linked to a variety of

key factors (i.e. falls, cognition, dynamic balance control) [6]. However, these measures have limited ability to detect performance fluctuations in both motor and cognitive domains that may present outside of the clinical setting, as the measures primarily rely upon single-task, forward walking measures.

Dual-task walking assessments that require individuals to perform multiple tasks simultaneously, often result in a decrement in performance of one or both tasks in persons with MS [7]. Given that walking in daily life is rarely practiced without concurrent cognitive demands or secondary motor tasks, dual-task walking assessments are more generalizable to everyday life [8] and thus, may improve upon the current measures of single-task forward walking. Additionally, dual-task walking requires increased cognitive and motor demands [9]. Due to the high prevalence of cognitive (65%) and motor deficits (85%) in MS [10], it is not surprising that impairments in dual-task walking are seen in individuals with MS [11-14] and have been related to cognition, fall risk [15], dynamic balance control [7], and connectivity in the supplemental motor area [16]. Moreover, dual-task performance is modulated by neurobiological systems [17,18] affected in MS, like the dopaminergic system [19]. Collectively, these facts suggest that dual-task assessments are sensitive to key motor and cognitive processes in MS. However, it is important to note that the current dual-task walking measures utilize only forward walking [20,21], and therefore do not detect impairments and fall-risk in persons with MS elicited during more challenging backward stepping or walking activities [22,23]. Thus, identifying potential modifications to improve the limited sensitivity of dual-task walking measures is critical.

Recently, backward walking has been recognized as a sensitive clinical measure of mobility and fall-risk in the elderly [24,25] and other neurodegenerative disease populations [26]. Similar to dual-task walking, backward walking requires increased cognitive demands and postural control [27,28] than forward walking. In MS, deficits in balance and postural control are increased during backward walking and significantly correlate with severity on clinical measures of forward walking and disability [29]. Additionally, when administered with a secondary cognitive

task, deficits in backward walking are more prominent than during forward walking [30]. Regarding the relationship between backward walking and falls in MS, our laboratory demonstrated that backward walking velocity is a strong and unique descriptor of retrospective fallers, whereas forward walking measures were not [31]. Our laboratory also demonstrated a positive relationship between clinical measures of cognitive function and backward walking velocity [32]. Collectively, however, previous research on dual-task backward walking in MS has been limited by a small sample size and lack of demographic matching between MS and control groups [30], and has not examined the relationships of spatiotemporal gait measures to cognitive function, balance, or falls. Additionally, our laboratory's studies have primarily focused on single-task backward walking. Thus, relationships between backward walking dual-task measures and cognitive function, balance and falls remain unidentified in MS.

Therefore, our study compared spatiotemporal gait parameters of forward walking and backward walking in single and dual-task conditions in persons with MS and age and sex-matched healthy controls. Additionally, we compared the relationships between forward walking and backward walking spatiotemporal measures to measures of cognitive function, retrospective fall reports, and balance. We hypothesized that persons with MS would demonstrate greater deficits in backward walking single-task and dual-task walking performance compared to forward single-task and dual-task walking performance than healthy controls. Additionally, we hypothesized that backward walking would exhibit stronger correlations to cognitive function, retrospective fall reports and balance in comparison to forward walking in persons with MS. Identification of relationships between single and dual-task backward walking to cognitive function, falls and balance would aid in the development of practical, cost-efficient and clinically feasible tools that may sensitively detect critical underlying processes that are commonly impacted by MS and related to fall risk (i.e. motor and cognitive function), thereby improving upon the current forward walking methods.

**Methods**

Eighteen individuals with relapsing-remitting MS were recruited from a parent study exploring training effects of video-game exercise. Fourteen age and sex-matched healthy controls were recruited through fliers, posts on the University research database, and by word-of-mouth. Inclusion criteria for individuals with MS included: 30-59 years of age, a diagnosis of relapsing-remitting MS, and an Expanded Disability Status Scale (EDSS) score between 1.0 and 5.5. Age and sex-matched healthy controls were included if they were within 2 years of the participant with MS and of the same sex. Both MS and healthy control participants were excluded if they reported an orthopedic, neurologic or cognitive impairment that would limit participation in study assessments. All measures were collected in a single session. The Institutional Review Board at The Ohio State University approved this study. All participants signed consent forms before participating.

*Mobility Measures in Both MS and Controls*

*GaitRite:* Spatiotemporal measures of gait were acquired with the GAITRite electronic walkway (V3.9, MAP/CIR Inc.; Franklin, NJ). The GAITRite is reliable and valid for use in individuals with MS (Givon, 2009). Individuals ambulated across the GAITRite at a self-selected, comfortable pace for three trials per each of the four conditions: 1) forward; 2) forward + cognitive task (serial 3 subtraction starting at 97); 3) backward; and 4) backward + cognitive task (serial 3 subtraction starting at 95). We *a priori* chose to evaluate a limited number of gait variables, including velocity, stride length and double support time. These variables were chosen because stride length and double support time have been linked to balance in MS [33], elderly [25] and other neurodegenerative populations [34] and backward walking velocity has specifically been linked to falls in older adults [24].

*Additional Mobility Measures in MS*

*Walking While Talking Test (WWTT)* requires the participant to perform walking, in which their time is recorded, under three conditions: 1) walk 40 feet with 180° turn at midpoint; 2) condition 1 + recite alphabet aloud (WWTT-Simple); 3) condition 1 + recite alternate letters of

alphabet aloud (WWTT-Complex) [35]. The WWTT is a reliable and valid test to identify older individuals at high risk for falls [35]. Additionally, poor performance on the WWTT-Complex (>33 seconds) accurately predicts elderly fallers [35].

*Timed Up and Go (TUG)* requires the participant to stand from a chair, walk 10 feet, turn, walk back and sit down [36]. The TUG is reliable in MS [37]. The TUG-Cognitive (TUG-C) requires performance of the TUG with a simultaneous serial-3 subtraction task; this modification of the TUG measures dual-task performance. A time of >15 seconds to complete the TUG-Cognitive accurately predicts fallers in MS with a sensitivity of 73% [38].

*Berg Balance Scale (BBS)* is a 14-item measure of balance and fall risk requiring individuals to perform a variety of activity such as turning in a circle, stooping down to pick up an object and reaching forward. Items are scored from 0 (cannot perform)-4 (normal performance) with a maximal score of 56. The BBS is reliable in persons with MS [39-41].

*Dual-Task Questionnaire (DTQ)* is a 10-item subjective questionnaire of everyday tasks involving dual-tasking, such as walking while talking or listening, spilling a drink while carrying it and completing an activity while talking. Individuals are asked to rate each item for frequency of difficulty performing from 0-4 (0=never; 4=very often) [42].

*Retrospective Fall History:* The number of past falls over six months was assessed by self-report. All participants were asked, “Have you fallen within the last six months? If yes, how many times?” Falls were operationally defined at the time of retrospective fall data collection as an “unexpected event that resulted in an unintentional landing on the ground or a lower surface” [43].

*Cognitive Measures in MS and Controls*

*Symbol Digit Modalities Test (SDMT)*: Participants received a key with nine numbers each corresponding to a symbol and were asked to determine the number belonging with a series of symbols using this key. The score is the number of correct answers in 90 seconds. The SDMT is a validated and reliable test in MS to analyze attention and information processing speed [44].

*Word List Generation (WLG):* The WLG is measure of verbal fluency and semantic retrieval, reliable and validated for use in persons with MS [45]. Participants were asked to name as many animals as possible in 90 seconds.

*Statistical Analyses*

A priori power analysis based on Wajda et al., 2013 indicates sample size of 8 per group needed for 80% power to detect a change in performance between groups [30]. Descriptive statistics (mean +/- standard deviation) were calculated for all variables. Outlier assessment was performed using the Shapiro-Wilk Test and box-and-whisker plots. If the data did not fit the assumptions of normality, non-parametric statistics were utilized. Mann-Whitney tests were used to compare the average ages of MS and healthy controls. Following the methods of Wajda et al., 2013, a 2x2x2 mixed model ANOVA was used to compare differences in the spatiotemporal gait parameters for forward walking, backward walking, forward dual-task walking, and backward dual-task (walking direction and dual-task condition as the within-subject factors) walking between MS and healthy controls (between-subjects factor) for each velocity, stride length, and double support time. Bonferroni corrections were used to examine factors influencing any observed differences. Spearman correlations were used to examine relationships between cognitive performance (SDMT and WLG) and both forward and backward walking performance in MS, relationships between retrospective fall reports and walking performance in MS, relationships between subjective dual-task performance on DTQ and objective measures of dual-task performance (WWTT, TUG-C, forward dual-task walking, and backward dual-task walking in MS, and relationships between balance performance (BBS) and forward and backward walking performance.

**Results**

*Demographics.* Eighteen individuals with relapsing-remitting MS and fourteen age and sex-matched healthy controls enrolled in this study. There was no significant difference in age (MS: 45.5(8.2); HC: 44.0 (8.8); p=0.613), sex (all female) between groups. For the MS group,

EDSS scores ranged from 1.5 -4, and the average time since diagnosis was 12.3 +/- 6.7 years. Seventeen of eighteen individuals with MS were taking disease modifying therapies and four of eighteen utilized an assistive device during testing. Healthy controls reported no falls in the past two or six months, whereas individuals with MS reported fourteen falls (4 individuals) and thirty-four falls (8 individuals), respectively.

*Gait Parameters.* Figure 1 demonstrates the mean and standard deviation values for velocity, stride length and double support time for each group and walking task. Results from the ANOVA, including main effects and interactions are outlined in Table 1, with three-way interactions depicted visually in Figure 1.

*Velocity.* There were significant differences in backward walking velocity between groups for both single ($p=0.015$) and dual-task ($p=0.014$) conditions. Forward walking velocity showed no significant difference between groups for both single ($p=0.087$) and dual-task ($p=0.502$) conditions. Persons with MS showed a significant difference between single and dual-task velocity in both forward ($p=0.023$) and backward ($p=0.004$) directions, whereas healthy controls only showed a significant difference in the backward walking condition ($p=0.004$; $p=0.827$ for forward walking). No interactions were observed for walking velocity (Table 1), thus it is likely that the differences observed between groups ($p=0.043$) are driven by main effects of direction ($p<0.001$) and condition ($p=0.005$).

*Stride Length*. There was a significant difference in forward walking stride length between groups for the dual-task condition ($p=0.010$) and backward walking stride length for the single task-condition ($p=0.039$). In persons with MS, there was a significant difference between single and dual-task stride lengths in both the forward ($p<0.001$) and backward directions ($p<0.001$). This difference was also apparent in healthy controls ($p<0.001$) for both forward and backward walking. No interactions were observed for stride length (Table 1), thus it is likely that the differences observed between groups ($p=0.046$) are driven by main effect of direction ($p<0.001$).

*Double Support Time.* There was no difference in double support time between individuals with MS and healthy controls during single-task forward (p=0.573) and backward walking (p=0.285) as well as dual-task forward (p=0.071) and backward walking (p=0.057). In persons with MS, there were significant differences in double support time between single and dual-task conditions in both forward (p=0.001) and backward (p<0.001) directions. No differences were observed in controls (p=0.581; p=0.295). In persons with MS, there were significant differences in double support time between forward and backward walking directions under both single (p=0.034) and dual-task (p<0.001) conditions. No differences were observed in controls (p=0.440; p=0.095, respectively). There was a significant interaction (F=14.2; p=0.001; $\eta^2$=0.33) observed for group x direction (Table 1).

*Relationships among Walking, Cognitive Function, Retrospective Falls and Balance in Persons with MS.*

*Cognitive Function.* Better performance on the SDMT was significantly associated with longer stride length in both the forward walking condition (r=0.505; p=0.032) and the forward dual-task condition (r=0.603; p=0.008), but was not significantly associated with any other walking measures. WLG performance was not associated with any walking measures. Subjective dual-task performance on the DTQ was not significantly associated with forward or backward dual-task spatiotemporal parameters, or the WWTT, but was significantly associated with TUG Cognitive (r=0.551; p=0.022) performance, with more self-reported difficulty with dual tasks associated with longer time to complete the TUG Cognitive.

*Retrospective Falls.* Falls at six months were not associated with forward walking or forward dual-task performance; however, falls at six months were significantly associated with backward dual-task velocity (r=-0.483; p=0.050) and stride length (r=-0.490; p=0.046) with slower velocity and shorter stride lengths associated with more fall reports.

*Balance.* Better performance on the BBS was significantly associated with increased forward walking velocity (r=0.548; p=0.018); decreased double support time (r=-0.592; p=0.010)

and increased stride length (r=0.751; p<0.001) under the single task condition. For the forward walking dual-task condition, better performance on the BBS was significantly associated with increased stride length (r=0.657; p=0.003). For the backward walking single-task condition, better performance on the BBS was significantly associated with increased backward walking velocity (r=0.522; p=0.026), decreased double support time (r=-0.590; p=0.010), and increased stride length (r=0.492; p=0.038). BBS performance was not associated with backward walking parameters in the dual-task condition.

*Differences in performance among those with lower and higher disability levels.* An exploratory analysis was performed to examine differences in performance between individuals with EDSS<3 (n=12) and those with EDSS≥3 (n=6). Our data demonstrated that individuals with lower disability (EDSS<3) performed similarly to healthy controls under single-task forward walking conditions, but that backward walking and dual-tasks, particularly in the backward walking direction, better differentiated healthy controls from those with EDSS<3 (Figure 2).

**Discussion**

This study compared spatiotemporal measures in forward walking and backward walking in single and dual-task conditions between persons with MS and healthy controls. Further, we compared the relationships between forward and backward walking spatiotemporal measures to cognitive function (i.e. processing speed and verbal fluency), retrospective fall reports at six months, and balance. The critical finding of the current study was that backward walking measures, particularly in the dual-task condition, revealed greater decrements in walking performance compared to forward walking that better differentiate persons with MS from healthy controls. Additionally, backward walking measures were more strongly related to retrospective falls at six months whereas no forward walking measures were related. Though not adequately powered to comprehensively examine differences in walking performance among individuals with MS with higher (EDSS<3) and lower (EDSS>3) disability levels, a secondary exploratory analysis

demonstrated that dual-task walking, in particular backward dual-task walking, better differentiated individuals with lower disability from healthy controls.

Backward walking velocity revealed significant differences between groups for both single-task ($p=0.015$) and dual-task ($p=0.014$) conditions. Interestingly, persons with MS had significant differences between single and dual-task forward and backward walking velocities ($p=0.023$; $p=0.004$), whereas this difference was only apparent in the backward walking condition for healthy controls ($p=0.004$; $p=0.827$ for forward walking). Backward walking stride lengths were shorter for the MS group compared to controls in the forward walking dual-task condition, and in the backward walking single-task condition. These findings are consistent with a similar study completed by Wajda and colleagues, in which motor differences were greater during backward walking and better distinguished individuals with MS from healthy controls than forward walking, and this effect was enhanced if individuals were administered a secondary cognitive task [30]. While the observed differences by Wajda were more robust in differentiating between individuals with MS and healthy controls, this study did not utilize matched control sampling. Importantly, we incorporated age and sex-matched controls to better understand these differences, which may explain why our differences were not as robust across all dual-task conditions. Further, our findings are consistent with previous studies in MS that demonstrated impairments in dual-task walking performance were greater in persons with MS compared to healthy controls [12, 46].

Persons with MS demonstrated significant differences in double support time when shifting from single to dual-task conditions in both forward ($p=0.001$) and backward ($p<0.001$) directions, whereas healthy controls displayed no differences. Importantly, this effect was heightened during backward walking, as persons with MS revealed significant differences in double support time when transitioning from forward to backward walking under both single ($p=0.034$) and dual-task ($p<0.001$) conditions, whereas there were no differences in healthy controls ($p=0.440$; $p=0.095$). These findings are consistent with previous studies in MS that reported walking deficits and balance were more prominent in MS individuals during backward walking [29]. Additionally,

backward walking is a non-automatic motor skill that requires higher processing of both motor and cognitive resources [47]. The ability to complete complex motor tasks such as backward walking may be furthered hindered by cognitive-motor interference in persons with MS [10], and thus, it is not surprising that persons with MS exhibited increased double support time during backward walking whereas healthy controls did not.

Given the high demand of cognitive resources during dual-task walking and backward walking [47], our study examined the relationship between walking direction (single and dual-task) and discrete domains of cognitive function, including information processing speed (SDMT) and verbal fluency (WLG). Interestingly, SDMT performance was only significantly associated with forward walking measures, including stride length in both single ($r=0.505$; $p=0.032$) and dual task conditions ($r=0.603$; $p=0.008$). WLG performance was not associated with any walking measures. These findings are consistent with previous studies that have shown relationships between forward walking performance and information processing speed [48]. However, our laboratory has previously shown that backward walking is related to SDMT ($r=-0.61$; $p=0.001$) [32], and therefore further research examining the relationship between backward walking and information processing speed with larger sample sizes is warranted. Additionally, unpublished data from our laboratory has shown relationships between backward walking performance and visuospatial memory on the Brief- Visuospatial Memory Test-Revised (BVMT-R), suggesting the involvement of different cognitive domains requiring greater study, as they may offer additional insight to effectively probing dual-task and backward walking.

Backward walking measures were more strongly related to retrospective falls at six months whereas no forward walking measures were related. These findings reflect the sensitivity of backward walking and its potential to supplement the current clinical dual-task and fall risk assessments. Additionally, these findings agree with previous studies in the elderly [24-25] and other neurodegenerative disease populations [26-27] in which backward walking better identified fallers compared to forward walking. These findings also build upon our previous work in MS in

which backward walking velocity exhibited the highest effect magnitude and specificity in differentiating fallers from non-fallers in individuals with MS [31].

We examined the relationship between forward and backward walking performance under single and dual-task performance and balance, using the BBS. Interestingly, BBS demonstrated stronger relationships with forward walking measures than with backward walking measures. This is perhaps because the BBS comprises primarily measures of static and anticipatory balance control, but does not require adaptive or reactive control. Future studies should explore whether balance tests incorporating adaptive or reactive control are more strongly related to measures of backward walking and backward dual-task walking.

An exploratory analysis indicated that individuals with lower disability (EDSS<3) performed similar to healthy controls under single-task forward walking conditions, but that dual-tasks, specifically the backward walking direction differentiates healthy controls from those with EDSS<3 (Figure 2). These results build on previous findings in which forward walking dual-task assessment is better at differentiating between early-diagnosed individuals with MS and healthy controls [46] Therefore, it is critical for future studies to understand the abilities of dual-task assessment to detect early and subtle motor and cognitive symptoms in low-disability MS individuals to ensure early intervention with targeted rehabilitation.

Our findings are the first to elucidate that persons with MS exhibit greater deficits in backward walking single-task and dual-task walking performance compared to forward single-task and dual-task walking performance when compared to age and gender-matched healthy controls. Additionally, these findings are the first to demonstrate the potential for backward walking dual-task assessment to sensitively detect fall risk in persons with MS. Importantly, the backward walking dual-task measures described in this work are clinically feasible, easy to administer and could be immediately scalable for clinical use as a sensitive clinical outcome tool to use in addition to current methods to detect underlying impairments in key domains relevant to MS (i.e. cognitive function, fall-risk, balance). However, a larger sample size with comprehensive

multi-domain cognitive testing, prospective falls monitoring and dynamic balance assessment is needed to further elucidate clinical utility and validity for backward walking dual-task assessment in MS.

*Limitations*

Limitations of this study include its small sample size of 32 individuals (eighteen individuals with relapsing-remitting MS and fourteen age-matched healthy controls), which may not generalize to ambulatory persons with progressive subtype. However, these limited data satisfy prior gaps in knowledge regarding the relationship between backward walking dual-task assessment and falls, as well as successfully age and sex-matching healthy controls while observing differences between forward and backward walking dual-task measures. This study relied on retrospectively collected data on falls at six months. Several studies in MS highlight the underestimation of falls with retrospective recall [21, 49], possibly due to high prevalence of cognitive dysfunction [50]. Therefore, it is critical that future studies consider the use of technology for prospective reporting of falls (i.e. smart phone applications, websites, wearable devices) to increase accuracy and predictive validity of falls data collection. Further, the best method of cognitive interference to detect impairment in dual-task assessment remains unidentified [51]. Thus, larger scale studies examining dual-task assessment are needed to validate the discrete measures used to generate cognitive interference.

This study was limited to two discrete measures of cognition, namely the SDMT to measure information processing speed and the WLG to measure verbal fluency and semantic memory, and therefore did not evaluate other domains of cognition that are known to be impacted by MS (i.e. attention, visuospatial memory, executive function, etc.) and have been related to motor measures and fall frequency in MS [52]. Additionally, domains of cognition suggested to be integrated with motor control (i.e. spatial navigation) should be incorporated into future studies. Level of education could also impact cognitive performance and should therefore be matched when recruiting control subjects in the future. This study was also limited to walking, static balance

and cognitive measures and thus, did not evaluate other factors that could heavily influence the impairments that were observed in persons with MS, including dynamic balance control, spasticity, and fatigue.

**Conclusion**

This study demonstrated that differences in MS and healthy controls are more pronounced during backward walking compared to forward walking. Importantly, we incorporated age and sex-matched controls to better understand these differences. Future work with a larger sample size is needed to validate the clinical utility of backward walking and dual-task assessments and mitigate the limited sensitivity of the current dual-task assessments that primarily rely upon forward walking. Based on our data, larger scale studies could leverage identification of definitive variables that are easily measurable in the clinic setting (i.e. velocity) along with respective dual-task walking assessment cut-off scores for clinical use. Additionally, studies aimed at developing a comprehensive understanding of potential mechanisms (i.e. brain pathology and specific cognitive correlates) underlying the impairments observed in dual-task assessment and more specifically, backward walking dual-task assessment, would further enhance targeted rehabilitation interventions. Our findings suggest that backward walking and dual-task assessment may better differentiate persons with MS and healthy controls, providing additional tools to supplement the current standard of forward walking assessment and warrants further research.

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**Figure 1.**



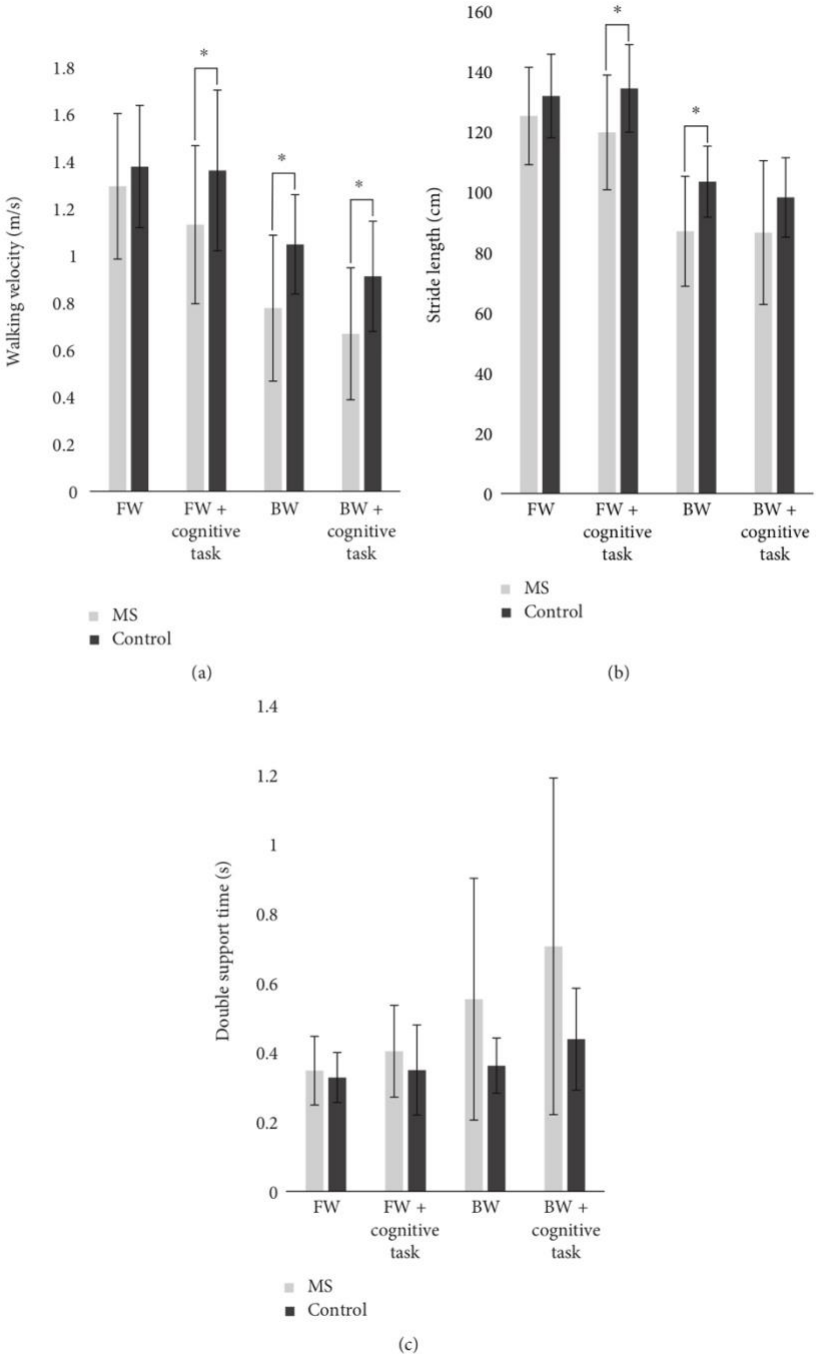


FIGURE 1: Walking velocity (a), stride length (b), and double support time (c) as a function of walking direction and group. ∗ indicates a significant difference between MS and healthy controls ($p < 0.05$).

**Figure 2.**



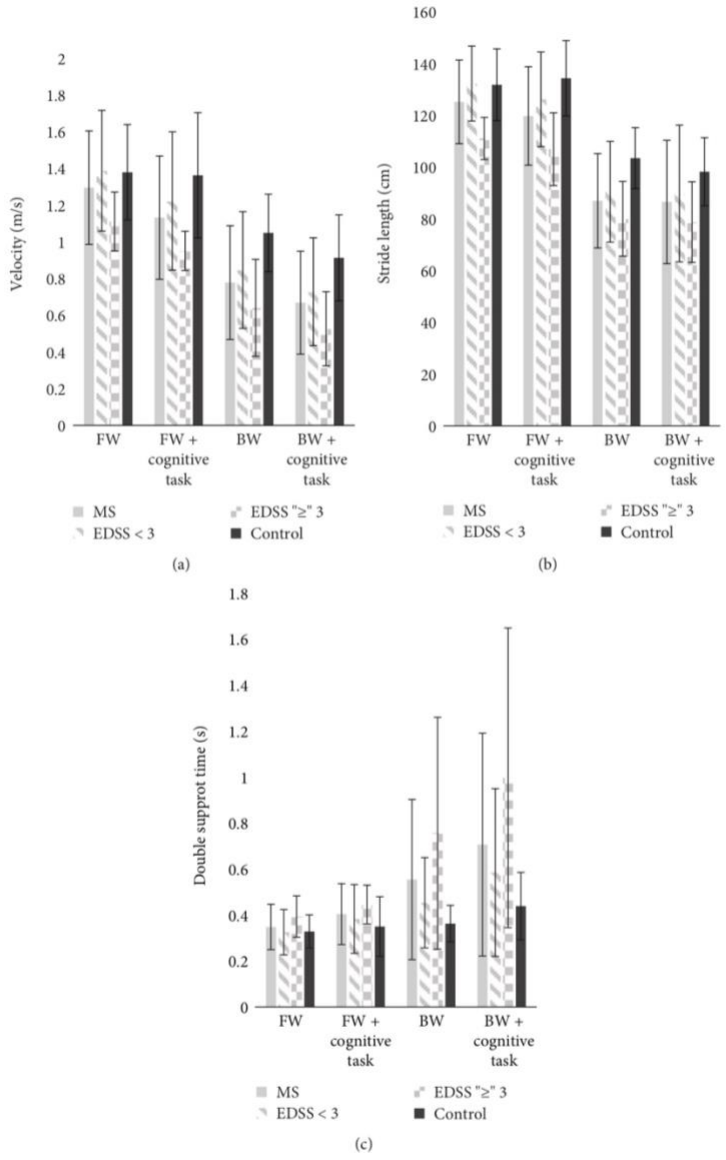


FIGURE 2: Subanalysis to examine differences in walking performance among individuals with EDSS < 3 and those with EDSS ≥ 3. MS is marked by the grey bar and HC by the black bar, with individuals with low disability (EDSS < 3) marked with diagonal lines and individuals with high disability (EDSS ≥ 3) marked with checkered blocks. Individuals with lower disability (EDSS < 3) performed similarly to healthy controls under single-task forward walking conditions but had worse performance than healthy controls in backward and dual-task conditions, particularly in backward dual-task walking.

**Table 1**



TABLE 1: Main effects and interactions for spatiotemporal measures of gait.

| Main effects | Velocity (m/s) | | | | Stride length (cm) | | | | Double support time (s) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | $F$ | $p$ | $\eta^2$ | Mean (SD) | $F$ | $p$ | $\eta^2$ | Mean (SD) | $F$ | $p$ | $\eta^2$ |
| Group | | | | | | | | | | | | |
| MS | **0.97 (0.40)** | **4.5** | **0.043** | **0.13** | **104.87 (26.26)** | **4.36** | **0.046** | **0.13** | 0.50 (0.33) | 3.5 | 0.071 | 0.12 |
| Control | **1.17 (0.33)** | | | | **116.96 (20.94)** | | | | 0.37 (0.12) | | | |
| Direction | | | | | | | | | | | | |
| Forward | **1.28 (0.32)** | **255.6** | **<0.001** | **0.90** | **127.13 (16.86)** | **329.8** | **<0.001** | **0.92** | **0.36 (0.11)** | **10.5** | **0.003** | **0.27** |
| Backward | **0.84 (0.30)** | | | | **93.01 (18.87)** | | | | **0.53 (0.34)** | | | |
| Condition | | | | | | | | | | | | |
| Single-task | **1.10 (0.39)** | **9.2** | **0.005** | **0.24** | 109.43 (27.23) | 2.1 | 0.160 | 0.07 | **0.40 (0.22)** | **12.2** | **0.002** | **0.30** |
| Dual-task | **0.99 (0.39)** | | | | 107.54 (25.88) | | | | **0.47 (0.31)** | | | |
| Group x direction | | | | | | | | | | | | |
| MS forward | 1.21 (0.33) | 3.6 | 0.068 | 0.11 | 122.49 (17.61) | 1.3 | 0.263 | 0.04 | 0.38 (0.12) | 3.9 | 0.059 | 0.12 |
| MS backward | 0.72 (0.30) | | | | 86.76 (20.82) | | | | 0.63 (0.42) | | | |
| Control forward | 1.37 (0.30) | | | | 133.09 (14.00) | | | | 0.34 (0.10) | | | |
| Control backward | 0.98 (0.23) | | | | 100.82 (12.54) | | | | 0.40 (0.12) | | | |
| Group x condition | | | | | | | | | | | | |
| MS single-task | 1.04 (0.40) | 0.87 | 0.359 | 0.03 | 106.09 (25.77) | 0.31 | 0.584 | 0.01 | 0.45 (0.27) | 1.7 | 0.199 | 0.06 |
| MS dual-task | 0.91 (0.39) | | | | 103.62 (27.06) | | | | 0.55 (0.38) | | | |
| Control single-task | 1.21 (0.29) | | | | 117.64 (19.19) | | | | 0.34 (0.08) | | | |
| Control dual-task | 1.14 (0.37) | | | | 116.28 (22.89) | | | | 0.39 (0.14) | | | |
| Direction x condition | | | | | | | | | | | | |
| Forward single-task | 1.33 (0.29) | 1.2 | 0.311 | 0.06 | 128.11 (15.33) | 0.94 | 0.341 | 0.03 | **0.34 (0.09)** | **14.2** | **0.001** | **0.33** |
| Forward dual-task | 1.23 (0.35) | | | | 126.15 (18.47) | | | | **0.38 (0.13)** | | | |
| Backward single-task | 0.90 (0.30) | | | | 94.18 (17.59) | | | | **0.47 (0.28)** | | | |
| Backward dual-task | 0.78 (0.28) | | | | 91.80 (20.32) | | | | **0.58 (0.39)** | | | |

Bolded values represent significant effects.

## CHAPTER 3: Examining the Influence of Cognition on the Relation between Backward Walking and Falls in Persons with Multiple Sclerosis.

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**Contribution to the Published Work**

**CRediT Author Statement for Erin Edwards:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – Original Draft, Writing – Review & Editing, Visualization

**Narrative Contributions**

My contributions to my first-author manuscript, under review, titled "*Examining the Influence of Cognition on the Relation between Backward Walking and Falls in Persons with Multiple Sclerosis*" include evolution of ideas of overarching research goals and aims (Conceptualization), creation of models and application of statistical techniques to analyze and synthesize study data (Methodology), management activities to annotate and maintain research data for initial use and later reuse (Data Curation), preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation) (Writing -Original Draft), preparation, creation and presentation of the published work by those from the original research group, including critical review, commentary and revision in both pre and post-publication stages (Writing – Review & Editing), and preparation, creation and presentation of the published work, specifically visualization and data presentation (Visualization).

**Placing the Published Work in the Context of the Overall Dissertation**

Backward walking velocity sensitively detects falls in persons with MS (Edwards, 2020; **Chapter 1**) and backward walking dual-task assessment better identifies gait impairments and fall risk in persons with MS (Edwards, 2020; **Chapter 2**). Collectively, these are the first studies in MS to identify a sensitive fall risk took that captures multiple common MS impairments related to falls and address the overarching problem of challenging fall prediction in the MS population.

*THE GAP:* The prior backward walking dual-task study (Edwards, 2020; **Chapter 2**) did not assess the specific cognitive domains that are commonly impacted by MS and negatively correlated to backward walking performance (i.e., information processing speed and visuospatial memory) in MS patients. Additionally, the prior backward walking studies that examined specific cognitive domains did not examine falls. Thus, whether an individual's processing speed or visuospatial memory influences the ability of backward walking to detect falls remains unknown.

*THE SOLUTION:* Identification of cognitive moderators of backward walking (**Chapter 3**) will characterize neurobiological processes relevant to backward walking function and its

application in the assessment of fall risk in MS. Further, it guides clinical interpretation of backward walking when a MS patient is presenting with multi-domain deficits.

Examining the Influence of Cognition on the Relation between Backward Walking and Falls in Persons with Multiple Sclerosis

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**Keywords:** Multiple Sclerosis, Walking, Falls, Backward walking, Cognition

*Practice Points:*

1. Backward walking is a sensitive marker of fall risk and is related to cognition in multiple sclerosis (MS). Identifying whether cognition influences the relation between backward walking and falls is key to characterizing neurobiological processes relevant to backward walking and its clinical application in MS fall risk assessment.

2. Backward walking's ability to predict falls was not conditional upon processing speed or visuospatial memory in our sample of persons with MS. While larger studies are needed, our

results inform clinical practice by recognizing backward walking as a sensitive fall prediction tool that functions similarly across MS patients, regardless of comorbid cognitive impairments.

*Abstract*

*Background:* Multiple sclerosis (MS) causes motor and cognitive impairments that result in injurious falls. Current fall risk measures in MS (i.e., forward walking speed and balance) are limited in their sensitivity for falls. Backward walking (BW) velocity is a sensitive marker of fall risk and correlates with information processing speed (IPS) and visuospatial memory in persons with MS (PwMS). BW is a complex motor task that requires increased cognitive demands, which are negatively impacted by MS. However, whether cognitive function modifies the sensitivity of BW as a fall risk assessment in MS remains unknown. Therefore, our study examined the influence of cognition on the relation between BW and falls in PwMS.

*Methods:* Measures of BW, forward walking (FW), IPS, visuospatial memory and retrospective falls were collected. Hierarchical regression tested moderation and included an interaction term predicting number of falls. Co-variates for all analyses included age and disease severity.

*Results:* Thirty-eight PwMS participated. BW, IPS and co-variates significantly predicted the number of falls ($R^2$=0.301, p=0.016), but there was no evidence of moderation. BW, visuospatial memory and co-variates also significantly predicted number of falls ($R^2$=0.332, p=0.008), but no evidence of moderation. The FW models generated comparable results.

*Conclusions:* The relation between BW velocity and falls was not conditional upon IPS or visuospatial memory in our sample of PwMS. Larger scale studies examining additional cognitive domains commonly impacted by MS and prospective falls are needed to characterize neurobiological processes relevant to BW and its clinical application in the assessment of fall risk.

*Introduction*

Multiple Sclerosis (MS) is a progressive neurologic disease associated with inflammation, demyelination and axonal damage that leads to debilitating motor and cognitive impairments[1]. Consequently, injurious falls are common in persons with MS (PwMS), with over 50% of individuals suffering a fall over a six-month period. Falls in MS are associated with decreased quality of life (activity curtailment and social isolation)[2,3] and greater cost to society (increased hospitalizations and demand on health-care resources)[4].

Current fall detection measures primarily rely on forward walking (FW) speed and balance[5]. However, these measures exhibit limited sensitivity to predict risk for falls[6-8], which may be attributed to their inability to detect subtle underlying impairments that have been linked to falls, including motor and cognitive dysfunction. At present, a simple and sensitive fall detection measure remains unidentified in PwMS[9].

Substantial evidence supports backward walking (BW) velocity as a reliable fall prediction measure in the elderly and other neurologic populations[10-12]. Recently, our laboratory has examined the relation between BW and falls in PwMS to determine what clinical measures of walking and disability most strongly and uniquely differentiate MS fallers from non-fallers[5]. BW velocity exhibited the highest effect magnitude and specificity in differentiating MS fallers from non-fallers when compared to standard clinical methods. Our findings emphasize the importance of examining BW as a quick, simple and sensitive fall prediction tool in PwMS. However, critical gaps in knowledge remain in our understanding of BW's ability to sensitively detect falls in PwMS and it remains unclear whether functional domains commonly impacted by MS may modify the sensitivity of BW as a fall risk assessment in MS.

BW is a complex, novel task requiring increased postural control, lower extremity strength and sensory and cognitive demands[13,14], all of which are negatively affected and related to falls in MS[15,16]. The relations between BW, motor function and falls in PwMS are well established[5,17-19]. Yet, the relations between BW, cognitive function and falls in PwMS are unknown. Prior MS

research demonstrates relations between complex motor task performance and function of specific cognitive domains; namely information processing speed and visuospatial memory[20,21]. Similarly, our laboratory has shown that BW correlates with information processing speed[22] and visuospatial memory (unpublished). However, the aforementioned cognitive studies did not examine falls. Thus, relations between BW, cognitive function and falls remain unknown in PwMS. This leaves a critical gap in knowledge with regards to cognitive mechanisms underlying BW's ability to detect falls.

At present, the extent to which the relation between BW and falls is dependent upon core cognitive function is unknown. Therefore, the objective of our study was to examine the discrete influence of cognition on the relation between BW and falls in PwMS. Based on published preliminary data, we hypothesized that the relation between BW velocity and falls is conditional upon an individual's processing speed and a secondary hypothesis tested visuospatial memory (Fig. 1a). Evidence in support of these hypotheses would be the critical first step in establishing a cognitive framework aimed at characterizing neurobiological processes relevant to BW and its clinical application in the assessment of fall risk and targeted fall prevention therapies for PwMS.

*Methods*

*Study participants.* A convenience sample of 38 participants with a neurologist-confirmed diagnosis of relapsing-remitting MS (RRMS) were recruited from the MS clinic at Wayne State University in Detroit, Michigan and local MS support groups of the Greater Detroit Area. All participants provided written informed consent, and the research protocol was approved by the WSU Institutional Review Board. MS individuals were eligible to participate if they were between 18-75 years of age, stable on immunomodulatory therapy (if applicable) for at least three months prior to beginning of study, ambulatory with or without physical assistance and able to follow study-related commands. Exclusion criteria included MS exacerbation within the last eight weeks, corticosteroid use within the last 30 days, and acute orthopedic or other neurologic conditions that would interfere with walking.

*Data collection.* Demographic data were collected, including age, sex, BMI, disease severity with Patient Determined Disease Steps (PDDS), and symptom duration.

Walking*:* FW and BW performance was evaluated with a 16-foot GaitRite electronic walkway (MAP/CIR, Franklin, NJ). The GaitRite electronic walkway is a computerized walkway with sensors organized in a grid-like pattern that records footfalls in real time and is reliable and valid for use in MS[23]. The GaitRite calculates spatiotemporal measures of gait and individual step parameters. Participants were instructed to walk at their quickest and safest speed for FW trials, which mimics the conditions of the T25FW. Participants were instructed to walk at a comfortable, safe pace for BW trials, following the methods of our lab and others[22,12]. Four trials were recorded for each condition, and the data were averaged. Participants received instruction to look ahead rather than at their feet, wore a gait belt, and were accompanied by a research assistant to ensure safety and minimize path deviations on all trials.

Cognition*:* Processing speed was assessed by the Symbol Digit Modalities Test (SDMT). Participants received a key with nine numbers each corresponding to a symbol and were asked to determine the number belonging with a series of symbols using this key. The score is the number of correct answers in 90 seconds. The SDMT is validated and reliable in MS to analyze information processing speed[24]. Visuospatial memory was assessed by the Brief-Visuospatial Memory Test-Revised (BVMT-R). Participants are shown six simple figures arranged in a 2x3 matrix on 8x11 paper for three consecutive 10-second trials. After each trial, participants were asked to draw as many shapes as accurately as possible and in the correct location. The BVMT-R demonstrates good psychometric properties and high reliability in MS[25].

Falls: Falls were measured retrospectively: participants reported a one-month fall history during the single laboratory visit. Falls were defined as “unexpected events that resulted in an unintentional landing on the ground or a lower surface.”

*Analytic Approach.* All statistical analyses were performed with SPSS version 25. We chose *a priori* to evaluate information processing speed and visuospatial memory as both

domains are primarily impacted by MS and have been linked to BW velocity and falls, separately, in PwMS[5,16]. To evaluate the hypothesis that the relation between BW velocity and falls is moderated by cognition, we used hierarchical regression modeling. Model step one included main effects of BW and cognitive function predicting number of falls, and significantly increased variance explained in model step 2 with the addition of an interaction term tested the moderation hypothesis. Continuous predictors were mean-centered prior to model estimation. For each cognitive domain tested, we ran one model for BW and one model for FW, resulting in four total models; all significance testing was adjusted for multiple comparisons (Bonferroni corrected $\alpha' = 0.01$). Co-variates for all analyses included age and disease severity as measured by the Patient Determined Disease Steps (PDDS).

*Results*

Thirty-eight participants (four males, 34 females; Age 50.4.4± 9.2 years; symptom duration 16.9±11.8 years; PDDS 3.2±2) with RRMS participated in this study. 86.8% of the participants were taking disease-modifying therapies and 39.5% utilized walking devices during testing (Table 1). There was no statistical evidence to suggest that information processing speed or visuospatial memory moderates the relation between BW velocity and falls (Fig. 1). In the first BW model (A1-2), BW velocity, processing speed and co-variates (age and disease severity) significantly predicted the number of falls ($R^2 = 0.301$, $p = 0.016$) (Fig. 1b). However, processing speed did not change the relation to BW velocity ($\Delta R^2 = 0.013$, $p > 0.1$) (Fig. 1c). In the second BW model (B1-2), BW velocity, visuospatial memory and co-variates also significantly predicted the number of falls ($R^2 = 0.332$, $p = 0.008$) (Fig. 1d). However, visuospatial memory did not change the relation to BW velocity ($\Delta R^2 = 0.001$, $p > 0.1$) (Fig. 1e). Both FW models (not shown) for processing speed and visuospatial memory generated comparable results.

*Discussion*

A critical finding of this study was that the relation between BW and falls was not dependent upon a person's processing speed or visuospatial memory in our limited sample of

PwMS. Prior studies in MS acknowledge the link between deficits in complex motor tasks (i.e., BW) and dysfunction in discrete cognitive domains (i.e., information processing speed and visuospatial memory[20,21], which have also been linked to fall risk in MS[6]. However, falls are multi-factorial and complex events. Therefore, in addition to cognition, many disease-driven (sensory dysfunction, muscle weakness, fatigue, and spasticity) and/or environmental factors may influence the relation between BW and falls in PwMS. Additionally, the average disability level of the sample was 3.2 (low disability) (Table 1), as reflected by the PDDS, and the average FW velocity was 1.6 m/s (Table 1), which according to clinically meaningful cut-off speeds for FW is indicative of low fall-risk[26]. Thus, the lack of cognitive moderation observed in this sample may be attributed to relatively low overall disability and cognitive dysfunction. Alternatively, if no conditional effects are observed in future studies with a larger sample size, we can interpret BW as a sensitive fall risk tool across MS patients, regardless of possible comorbid cognitive impairment.

Another critical finding demonstrated that the combination of BW velocity, cognitive function and co-variates significantly predicted the number of falls, which is consistent with previous literature in which BW has been linked to cognition[17,22] and falls in PwMS[5,19]. However, our findings provide only a limited snapshot of the factors that predict fall risk in PwMS and do not provide sufficient detail into whether specific cognitive mechanisms underlie BW's ability to predict falls. For example, we utilized only single measures of information processing speed (SDMT) and visuospatial memory (BVMT-R), respectively, when additional technology-adapted versions of these assessments exist to sensitively probe these discrete domains[27]. Notably, the SDMT and BVMT-R, that are part of the Brief International Cognitive Assessment for MS (BICAMS) battery, were recently reported to demonstrate high sensitivity to cognitive impairment[28]. Prior work in MS also demonstrates information processing speed as the foundation for high level cognitive processes, as it impacts downstream domains[29]. Yet, like all symptoms of MS, cognitive impairment is heterogenous in severity, progression and the specific domains impacted[30]. Thus,

examining and controlling for impairment in other domains primarily impacted by MS is critical to develop a complete cognitive framework to support the clinical utility of BW as a sensitive fall detection tool in MS.

*Study limitations*. In this convenience sample, we relied upon retrospective fall reports which are subject to inaccuracy given the high prevalence of memory problems in PwMS[3]. Our future work will use wrist-worn activity sensors to prospectively report falls, establish the predictive validity of BW as a fall risk marker in MS and control for physical activity levels. Next, we recognize that additional domains of cognition commonly impacted by MS (i.e., executive function and attention) and their relative influence on the relation between BW and falls should be examined. This study did not incorporate neuroimaging techniques to better understand the contribution of motor and cognitive brain regions to BW and subsequent fall risk. Our future work will leverage innovative MRI techniques specific to myelin (i.e., myelin water imaging) to develop a neurobiological basis supporting the clinical utility of BW as a fall detection measure in MS.

*Conclusions:*

The relation between BW velocity and falls was not conditional upon an individual's processing speed or visuospatial memory in our small sample of PwMS. Confirmation of these results by larger scale studies are warranted to understand whether an interaction between cognition and BW in predicting falls reflects underlying neural-cognitive architecture or if BW's ability to detect falls is not confounded by comorbid impairments in processing speed or visuospatial memory. Future work examining additional cognitive domains impacted by MS (i.e., executive function and attention), prospective falls and neuroimaging of motor and cognitive brain regions are needed to characterize neurobiological processes relevant to BW and its clinical application in the assessment of fall risk in PwMS. Ultimately, advancements in this work will pave the way for sensitive fall detection measures and targeted fall prevention therapies, grounded by neuroscience, to improve clinical outcomes for PwMS.

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**Table 1.** Demographic Measures.

| | Mean (SD) |
|---|---|
| **Age (Years)** | 50.4 (9.2) |
| **Sex (Male:Female)** | 4:34 |
| **PDDS (Range 0-6)** | 3.2 (2) |
| **Symptom Duration (Years)** | 16.9 (11.8) |
| **Disease-Modifying Therapy (%)** | 86.80% |
| **Assistive Device Use (%)** | 39.50% |
| **Forward Walking Velocity (m/s)** | 1.6 (0.70) |
| **Backward Walking Velocity (m/s)** | 0.74 (0.48) |

*PDDS:* Patient Determined Disease Step.

**Figure 1.** Analytic framework and findings; the relation between BW and falls is not dependent upon a person's processing speed or visuospatial memory in PwMS.

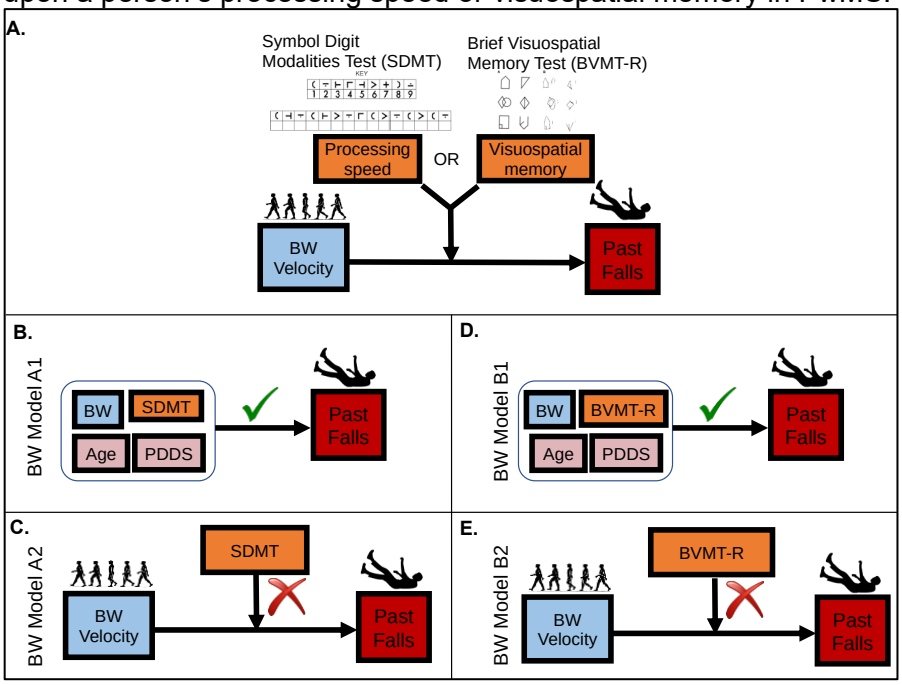


Figure 1. (A) Moderation analysis to test the hypotheses that the relation between BW velocity and falls is moderated by information processing speed, as measured by the SDMT, or visuospatial memory, as measured by the BVMT-R, respectively. (B) BW Model A1: BW velocity, SDMT and covariates significantly predict the number of falls ($R^2 = 0.301$, $p = 0.016$). (C) BW Model A2: SDMT does not moderate the relation between BW velocity and falls ($\Delta R^2 = 0.013$, $p > 0.1$). (D) BW Model B1: BW velocity, BVMT-R and co-variates significantly predict the number of falls ($R^2 = 0.332$, $p = 0.008$). (E) BW Model B2: BMVT-R does not moderate the relation between BW velocity and falls ($\Delta R^2 = 0.001$, $p > 0.1$). *BVMTR: Brief Visuospatial Memory Test-Revised; BW: Backward walking; PDDS: Patient Determined Disease Step; SDMT: Symbol Digit Modalities Test.*

## Chapter 4: Cerebellar Dysfunction in Multiple Sclerosis: Considerations for Research and Rehabilitation Therapy

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**Contribution to the Published Work**

**CRediT Author Statement for Erin Edwards:** Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing, Visualization

**Narrative Contributions**

My contributions to my first-author publication titled "*Cerebellar Dysfunction in Multiple Sclerosis: Considerations for Research and Rehabilitation Therapy*" include evolution of ideas of overarching literature review goals and aims (Conceptualization), development of literature review design (Methodology), preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation) (Writing -Original Draft), preparation, creation and presentation of the published work by those from the original research group, including critical review, commentary and revision in both pre and post-publication stages (Writing – Review & Editing), and preparation, creation and presentation of the published work, specifically visualization and data presentation (Visualization).

**Placing the Published Work in the Context of the Overall Dissertation**

Prior studies in MS demonstrate the associations between backward walking and falls (Edwards, 2020; Chapter 1), backward walking and cognitive function (Edwards, 2020; Chapter 2), and the influence of specific cognitive functions (i.e., processing speed and visuospatial attention) on the relation between backward walking and falls (Edwards, 2021 -Under review; Chapter 3). These studies support the clinical utility of backward walking as a sensitive tool that

captures multiple common MS impairments in the context of clinically observable motor and cognitive impairments.

*THE GAP:* A better understanding of underlying brain structures contributing to motor and cognitive dysfunction is needed in MS. Identification of brain structures that underlie motor and cognitive impairments would provide insight to backward walking mechanisms that could be leveraged to further support the clinical utility of backward walking as a marker of fall risk in MS. For example, the cerebellum is one of the most common and complex lesion sites among persons with MS (Wilkins, 2017) and damage in cerebellar regions have been associated with motor and cognitive dysfunction and falls in persons with MS. However, a comprehensive understanding of the cerebellum's contribution to motor and cognitive dysfunction in MS has not been developed.

*THE SOLUTION:* A comprehensive understanding of the cerebellum and its dysfunction in persons with MS. I will summarize the current understanding of the impacts of cerebellar dysfunction on motor control, motor training and rehabilitation in persons with MS **(Chapter 4)** to provide insight for future fall prevention research.

Cerebellar dysfunction in Multiple Sclerosis: Considerations for research and rehabilitation therapy

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Abstract

Cerebellar pathology is common among persons with multiple sclerosis (PwMS). The cerebellum is well recognized for its role in motor control and motor learning and cerebellar pathology in multiple sclerosis is associated with enhanced motor impairment and disability progression. To mitigate motor disability progression, PwMS are commonly prescribed exercise and task-specific rehabilitation training. Yet, whether cerebellar dysfunction differentially affects rehabilitation outcomes in this population remains unknown. Furthermore, we lack rehabilitation interventions targeting cerebellar dysfunction. Here, we summarize the current understanding of the impact of cerebellar dysfunction on motor control, motor training and rehabilitation in persons with multiple sclerosis. Additionally, we highlight critical knowledge gaps and propose that these guide future research studying cerebellar dysfunction in persons with multiple sclerosis.

Multiple sclerosis (MS) is a complex neurodegenerative disease that selectively impacts the central nervous system (CNS) through demyelination of neurons. Demyelination can occur across multiple brain regions and leads to a distortion or total loss of neuronal signaling[1] that can impact a variety of motor, cognitive and sensory functions. One brain area frequently affected by MS is the cerebellum[2]. MS related pathology affects the cerebellar cortex, the deep cerebellar nuclei, and the white matter microstructure that comprises the cerebellar peduncles[3-5]. Cerebellar pathology in MS is associated with impairments in both motor and cognitive domains. It indicates

a poor prognosis and greater disability[6]. To mitigate the progression of motor impairment, persons with MS (PwMS) are commonly prescribed exercise and task-specific rehabilitation training. However, the cerebellum plays a critical role in both motor control and motor learning,[7-8] which may complicate motor rehabilitation for PwMS with cerebellar dysfunction[9]. Yet, how cerebellar dysfunction may affect rehabilitation outcomes in this population remains unknown. Here, we summarize the current understanding of the impacts of cerebellar dysfunction on motor control, motor training and rehabilitation in PwMS. We then highlight critical knowledge gaps and propose that these guide future research studying cerebellar dysfunction in PwMS.

In the motor domain, cerebellar damage causes ataxia – a movement disorder marked by poorly coordinated movement that can manifest in all body effectors[7]. Hallmark signs of cerebellar damage are seen in impaired oculomotor control, impaired upper limb control, and impaired balance and gait. Specifically, oculomotor deficits include saccadic dysmetria (an over- or undershooting of saccade endpoints), nystagmus (a beating of the eyes, particularly in lateral gaze), and saccadic intrusions during smooth pursuit eye movements (a jagged movement of the eyes when tracking a moving stimulus)[10]. In the upper limbs, cerebellar signs include impaired multi-joint coordination and dysmetria when making goal directed movements[11-12]. In the lower limbs, cerebellar dysfunction is associated with gait ataxia – a condition marked by poor balance control, slow walking speed, and a veering path[9].

The motor signs of cerebellar pathology in MS may present as ataxia[13]. In PwMS, cerebellar lesions are associated oculomotor impairments such as saccadic dysmetria, nystagmus, and deficits in smooth pursuit[14-15]. Lower cerebellar grey and white matter volume has been associated with impaired upper limb coordination[16]. Lesions in the cerebellar cortex and peduncles have also been associated with dysmetria and intention tremor during goal directed reaching[17]. Perhaps the most well studied motor signs of cerebellar pathology in PwMS are those seen in gait and balance control. Structural neuroimaging studies show that greater postural sway

during quiet stance is associated with grey matter atrophy in cerebellar lobules IV, V, VI, and VIII[5], and myelin damage in the inferior, middle, and superior cerebellar peduncles[18-19]. A functional neuroimaging study also showed that reduced resting state cortico-cerebellar connectivity is associated with greater lags in postural corrections to imposed balance perturbations[20]. With regards to gait, lower overall cerebellar volume is linked to poor coordination, as assessed by the ratio of step length to cadence[21]. Reductions in both cerebellar volume and diffusivity have been linked to slower walking speed and time to complete the Timed Up and Go test[22].

The current standard of cerebellar assessment for PwMS is the Cerebellar Functional Systems Scale (FSS) of the Expanded Disability Status Scale (EDSS)[23]. Unfortunately, this assessment is limited to observance of ataxia in the limbs or trunk and does not rate quality of movement or include examination of eye movements or cognition. The criterion used for determining cerebellar dysfunction within clinical trials has also been variable (e.g., Tornes et al.,[6] Liu et al.,[17] Weier et al.[24]). The subsequent lack of differentiation between PwMS with and without cerebellar dysfunction limits the generalizability and translation of trial findings to clinical rehabilitation. Without a standardized assessment, it is unlikely that potential differences in motor learning and underlying brain pathology unique to PwMS with cerebellar dysfunction will be identified.

The motor signs of cerebellar damage have been linked to impaired predictive control, affecting the feedforward component of movement[25]. Deficient predictive control strongly impairs a type of motor learning called adaptation[8]. Adaptation describes the process of learning to alter movement commands in response to predictable perturbations to the body or environment. It involves a recalibration of sensory-motor mapping and represents an important neural mechanism through which people learn to alter their movement. Adaptation impairments have been well characterized in individuals with focal cerebellar damage**,** but relatively few studies have examined adaptation in PwMS. The existing literature suggests that MS leaves adaptation intact[20,26], but may impair more subtle aspects of memory and consolidation[27]. However, few

studies have attempted to discern any relationship between adaptation and cerebellar dysfunction in PwMS. Fling et al.[20] examined the relationship between resting state cortico-cerebellar connectivity and learning in a postural adaptation task. The authors found no relationship between cortico-cerebellar connectivity and learning. However, this result is difficult to interpret as the baseline degree of cerebellar dysfunction (as determined by neuroimaging or clinical motor signs) in their study sample was not reported. Thus, it is unclear whether there was sufficient variance in the data to find a significant relationship between learning and cortico-cerebellar connectivity, if one exists.

Improving our understanding of the precise impacts of cerebellar dysfunction on motor learning in PwMS may elucidate the appropriate type of rehabilitation intervention for this population. Recent work showed that a training protocol aimed at compensating for impaired adaptation improved motor learning in individuals with focal degeneration of the cerebellum[28-29]. The protocol reduced the specific sensory information about movement errors that drives adaptation and, instead, provided binary outcome feedback to bias the motor system toward less cerebellum-dependent, learning and control mechanisms. This training intervention is at a very early stage in the translational pipeline from proof-of-principle to clinical practice. Therefore, the time is ripe for researchers to investigate whether a similar approach could be used to tailor rehabilitation interventions to account for cerebellar dysfunction in PwMS. A critical outstanding question concerns whether the widespread nature of neuronal damage in MS introduces additional deficits that confound the advantages of reinforcement training. For example, demyelination along the dorsal column of the spinal cord can impair proprioceptive sense[30], which may be integral to solve the credit assignment problem that arises with reinforcement signaling in motor learning tasks[28,31-32]. Additionally, cognitive impairments, which are common in MS[33], may further interfere with reinforcement-based interventions[34].

Recent work also opens new avenues for future research to clarify the appropriate timing for rehabilitation. PwMS can have lower cerebellar volume than age-matched controls and exhibit

lesions in the cerebellum even though they show low-disability and may not exhibit overt cerebellar motor signs[18]. These “silent lesions” have led to the hypothesis that there may be critical window, during which targeted behavioral interventions can prevent further degradation and mitigate loss of function. In support of this, Prosperini et al.[19] showed that a 12-week intensive balance training program induced transient structural plasticity along the white matter tracts forming the cerebellar peduncles. The plastic changes occurred alongside improvements in clinical balance performance. However, it should be noted that the gains did not persist when the intervention was removed. This suggests that ongoing task-specific training may be needed to drive lasting plasticity in PwMS. Nonetheless, it is of great interest for future research to study whether training-induced structural improvements are only seen in those individuals not yet exhibiting cerebellar motor signs, or whether similar effects are seen in PwMS with more progressive cerebellar pathology.

Given the role of the cerebellum in motor learning, motor control, and cognition, all of which may impact intervention response, it is clear that specific considerations are needed for rehabilitation of PwMS with cerebellar dysfunction. Here, we have proposed three considerations for future research: (1) standardizing assessment for differentiation of PwMS with and without cerebellar dysfunction, (2) understanding the precise motor learning impairments of PwMS and capitalizing on remaining learning mechanisms, and (3) determining if there may be a critical window where interventions targeting cerebellar dysfunction are more successful in PwMS. Advancing knowledge in these areas has potential to inform the appropriate type and timing of rehabilitation interventions. While we have focused on the motor signs of cerebellar pathology in MS, the cerebellum is also highly interconnected with brain regions responsible for aspects of cognition. We also recognize the impact of cognitive dysfunction on motor learning and motor control. The impact of rehabilitation interventions on cognitive function in PwMS with cerebellar pathology remains unclear. Future work should investigate the efficacy of cognitive rehabilitation on cerebellar dysfunction in MS. Lastly, we recognize that there are other factors specific to MS

that can impact daily function and response to training interventions (i.e., fatigue and peripheral problems that are not necessarily observed in other cerebellar disorders, such as the Spinocerebellar Ataxias.). However, a precise understanding of the impact of cerebellar dysfunction on MS disease progression, motor recovery and rehabilitation responsiveness will be critical for the development of effective therapeutic interventions.

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## CHAPTER 5: Using Myelin Water Imaging to Link Underlying Pathology to Clinical Function in Multiple Sclerosis

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Review article

Using myelin water imaging to link underlying pathology to clinical function in multiple sclerosis: A scoping review

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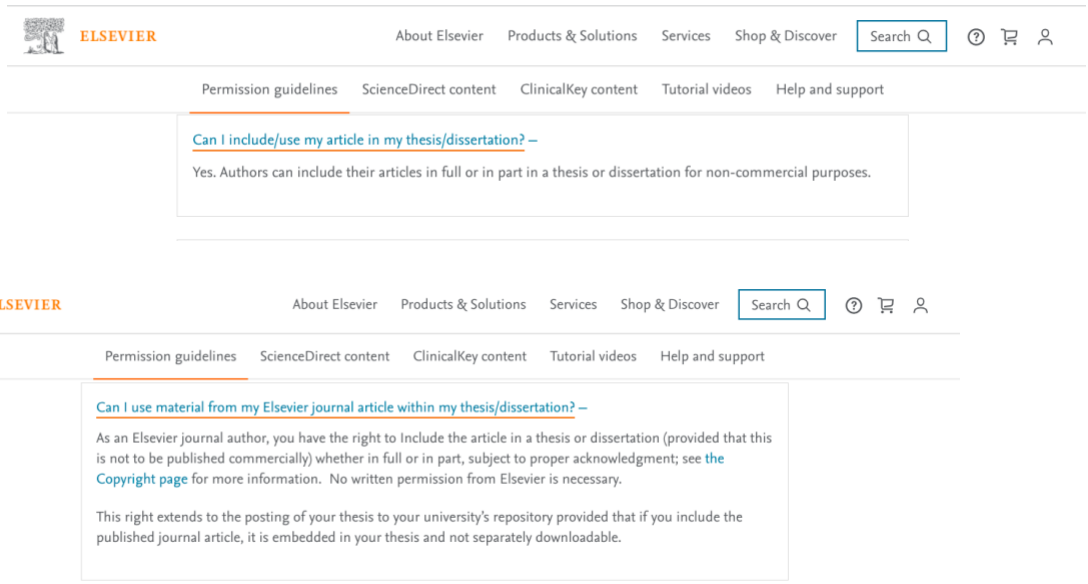


**Contribution to the Published Work**

**CRediT Author Statement for Erin Edwards:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – Original Draft, Writing – Review & Editing, Visualization

**Narrative Contributions**

My contributions to my first-author publication titled "*Using Myelin Water Imaging to Link Underlying Pathology to Clinical Function in Multiple Sclerosis: A Scoping Review*" include evolution of ideas of overarching research goals and aims (Conceptualization), application of scoping review techniques to analyze and synthesize study data (Methodology), management activities to annotate and maintain research data for initial use and later reuse (Data Curation), preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation) (Writing -Original Draft), preparation, creation and presentation of the published work by those from the original research group, including critical review, commentary and revision in both pre and post-publication stages (Writing – Review & Editing), and preparation, creation and presentation of the published work, specifically visualization and data presentation (Visualization).

**Placing the Published Work in the Context of the Overall Dissertation**

DTI studies in MS demonstrate damage to white matter brain regions that are responsible

for motor and cognitive functions also contribute to declines in walking and balance performance (Fritz, 2013; Prosperini, 2013; Ibrahim, 2020). However, DTI is limited in its sensitivity to myelin (Rahmenzahdeh, 2021) and an imaging tool with increased specificity to MS pathology is critical to probe the neural underpinnings related to backward walking and subsequent fall risk in MS. MWI is a quantitative MRI technique that offers increased specificity to myelin.

*GAP 1:* There is a need for more sensitive imaging tools to better understand brain regions that may contribute to motor and cognitive dysfunction in MS.

*GAP 2:* It remains unknown whether MWI corresponds to functional performance in MS and could be used in future backward walking research.

*THE SOLUTION:* **Chapter 5** of my dissertation examines the relations between MWI and functional domains relevant to MS. I will inform and guide future MS research aimed at probing the neural underpinnings of backward walking (and other fall risk measures) by providing the basis for using an innovative neuroimaging technique with high specificity to myelin.

Using Myelin Water Imaging to Link Underlying Pathology to Clinical Function in Multiple Sclerosis: A Scoping Review

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*Keywords:* Myelin water imaging, Multiple Sclerosis, Disability, Walking, Cognition, Rehabilitation response

*Highlights:*

- Persons with MS experience motor and cognitive impairments due to myelin damage
- Myelin-sensitive measures are critical to find links among function and MS pathology
- Myelin water imaging shows sensitivity to myelin and clinical function in MS
- Myelin water imaging may be a key tool to inform targeted rehabilitation strategies

*Abstract*

*Background:* Multiple sclerosis (MS) symptoms and pathology are heterogenous and complex. Identifying links between MS-related pathology (i.e., myelin damage) and associated clinical symptoms is critical for developing targeted therapeutics. Conventional MRI, commonly used for MS diagnosis and disease monitoring, lacks specificity with functional performance. Myelin water imaging (MWI) demonstrates increased specificity to myelin and is viewed as the gold standard for imaging myelin content in vivo. Yet, there is a paucity of MWI studies in MS and only a limited number also examine clinical function. Thus, it remains unknown whether MWI corresponds to functional performance in MS. This scoping review aimed to examine relations between MWI and functional domains relevant to MS to inform and guide future research.

*Methods:* Seven databases were searched from their inception to September 1, 2021. Studies of adults with MS that included both brain MWI and either a measure of physical function, a measure of cognitive function, or a measure of disease severity were included. Thirteen studies (11 observational, 2 intervention) met the inclusion criteria.

*Results:* The most commonly investigated MWI metric is the myelin water fraction (MWF). Persons with MS demonstrated markedly decreased MWF compared to healthy controls globally and across brain regions of interest (ROIs). Decreased MWF was associated with higher disability, worse motor and cognitive performance and decreased intervention response. Only five studies examined structure-function relationships in brain areas related to walking and cognitive function and only six studies extracted MWI metrics from explicit brain ROIs.

*Conclusions:* MWI is a neuroimaging technique with increased specificity to myelin and offers greater insight to MS-driven pathology and its clinical manifestations, including motor and cognitive dysfunction and rehabilitation response. This scoping review identified critical gaps in MWI research in MS to offer future perspectives including ROI-based studies, inclusion of multi-domain functional assessment and examining MWI to provide evidence of neuroplasticity following training.

*Introduction:*

Multiple sclerosis (MS) is a progressive, neurologic disease marked by immune-mediated destruction of CNS myelin (Dutta, 2008), a protective coating that insulates nerves to promote neuronal signaling (Haines, 2012). This varying degree of myelin damage can disrupt neuronal communication across a large range of systems (Perez-Cerda, 2016), including brain areas responsible for executing motor and cognitive functions (Du, 2019). As a result, there is a high prevalence of motor (85%) (Givon, 2009) and cognitive (up to 70%) (Rahn 2012; Gromisch, 2021) impairments experienced by persons with MS (PwMS) which can be severely debilitating and negatively impact quality of life (Goskel, 2011). Impairments in motor and cognitive function often present simultaneously in PwMS and their co-occurrence could impact rehabilitation response (Felippe, 2018). Indeed, targeted therapeutics and rehabilitation strategies for improving motor and cognitive impairments experienced by PwMS are lacking, potentially due to the underlying complexities and variability of MS-driven pathology (i.e., myelin damage) across brain regions.

Therefore, a better understanding of the link between clinically observable function and underlying pathology is critical to advance targeted rehabilitation therapies for PwMS.

Accurate quantification of myelin damage in MS is important for the development of targeted rehabilitation strategies (Barkhof, 1999). Although conventional Magnetic Resonance Imaging (MRI) provides an invaluable tool for MS diagnosis and disease monitoring (Kaunzener, 2017), lesion volume demonstrates limited correlations with motor and cognitive disability in PwMS (Kolind, 2012). To improve upon conventional MR methods, quantitative MRI measures are commonly used in MS research for the indirect assessment of myelin, often including diffusion tensor imaging (DTI) (Basser, 1994) and magnetization transfer imaging (MTI) (Horsfield, 2005). Parameters extracted from both DTI and MTI [fractional anisotropy (FA) and magnetization transfer ratio (MTR), respectively] have been linked to functional impairments in PwMS.

Specifically, DTI studies in MS demonstrate decreased FA in brain regions responsible for motor control (corpus callosum, corticospinal tract and superior cerebellar peduncles, etc.) are related to worse motor performance (i.e., balance, walking, strength and postural control) (Ibrahim, 2011; Fritz, 2017; Prosperini, 2013). Additionally, decreased FA in brain regions responsible for cognition (corpus callosum, inferior and superior longitudinal fasiculus, cerebellar regions, etc.) are linked to cognitive impairment (i.e., declines in processing speed and memory) in PwMS (Huang, 2019; Hecke, 2010). Similar findings are seen in MTI studies in MS in which demonstrate associations between MTR and motor (Fritz, 2017) and cognitive (Lin, 2008) performance. However, both DTI and MTI are limited in their specificity to myelin (Rahmanzadeh, 2021). For example, the interpretation of decreased FA is unclear due to the non-specificity of DTI metrics relating to myelination, fiber coherence, axonal density, and membrane permeability (Beaulieu, 2002; Harsan, 2006). Similarly, MTI estimates of macromolecular-bound water include but are not limited to myelin, and thus may be greatly influenced by MS-driven pathology including inflammation and edema (Abel, 2020; Vavasour, 2011).

Myelin Water Imaging (MWI) overcomes limitations of DTI and MTI by providing a more specific surrogate measure of myelin (Rahmenzahdeh, 2021). MWI is a quantitative MRI approach that is viewed as the gold standard for imaging myelin content *in vivo* (Laule, 2008; McCreary, 2009) and includes acquiring multi-echo-$T_2$ (ME- $T_2$) imaging data followed by quantifying the multi spin-spin $T_2$ relaxation components of water from different physical environments (MacKay, 1994; MacKay, 2016). $T_2$ relaxation of water is directly related to water mobility and hence, allows discerning the signal of water coming from different physical environments in biological tissue (Lynn, 2020). Specifically, MWI exploits the signal derived from water molecules that are densely packed between myelin sheaths, which have a short $T_2$ relaxation time (between 10 and 55 ms) compared to water in other brain tissue compartments (i.e., intra/extracellular water space and cerebrospinal fluid) (Mackay, 1994; Mackay, 2016). The water signal contribution from the shortest $T_2$ component (i.e., myelin water), can be quantified and expressed as a fraction relative to the total water signal amplitude and is referred to has the myelin water fraction (MWF).

MWI studies in MS have demonstrated compelling evidence of decreased MWF reflecting myelin loss (Kolind, 2012). However, there is a paucity of MWI studies in MS and only a limited number also examine clinical function. Therefore, it remains unclear whether MWI measures in MS demonstrate strong correspondence with relevant functional domains commonly impacted by MS, including motor and cognitive performance. While structure-function relationships have been established with DTI and MTI, establishing these relationships with MWI, a tool with increased specificity for myelin damage in MS, is critically needed. Therefore, we conducted a scoping review of the literature to a) determine relations between MWI and MS disease severity; b) determine motor and cognitive clinical correlates of MWI; and c) examine MWI as a potential indicator of therapeutic intervention responsiveness. Additionally, current gaps in knowledge are highlighted to offer future perspectives for MWI research in MS.

*Methods:*

A scoping review method (Armstrong, 2011; Levac, 2010) was utilized to systematically search the literature. The rationale for conducting a scoping review was to identify the existing data investigating relations between MWI and MS disease severity, motor and cognitive clinical correlates of MWI in MS, and MWI as an indicator of therapeutic intervention responsiveness in MS.

*Search strategy and study selection*

*Search strategies:*

Literature searches were conducted in PubMed/MEDLINE, EMBASE, CINAHL Complete, Web of Science, Scopus, PsycINFO, and Cochrane Library from database conception to September 2021. The research team including a medical librarian developed a list of search terms that best fit the research question and that were commonly used in each database. Keywords along with their variants, their associated medical subject headings (MeSH), Emtree terms, and CINHAHL subject headings were used, as appropriate, for each database to identify relevant studies. Search algorithms had this general format: Myelin Water Imaging AND multiple sclerosis AND clinical function. The complete search algorithm for PubMed is given as an example in Appendix 1. The search stream was intended to apply to the title, abstract, and subject headings/keyword field. However, as aforementioned databases offer different field options, there was slight variation in the fields used across each database. For example, in Scopus or Web of Science there is no thesaurus field available thus MeSH terms were searched as title, abstract or keywords. Searches included all studies in databases to maximize the possible number of studies that could contribute data for the review, but excluded studies in foreign languages, book chapters or conference abstracts. The reference lists of relevant studies were hand-searched to locate additional studies not captured by database searching. The search resulted in 896 articles. A total of 323 duplicates were removed (Figure 1) using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia).

**Figure 1. Search strategy flowchart**

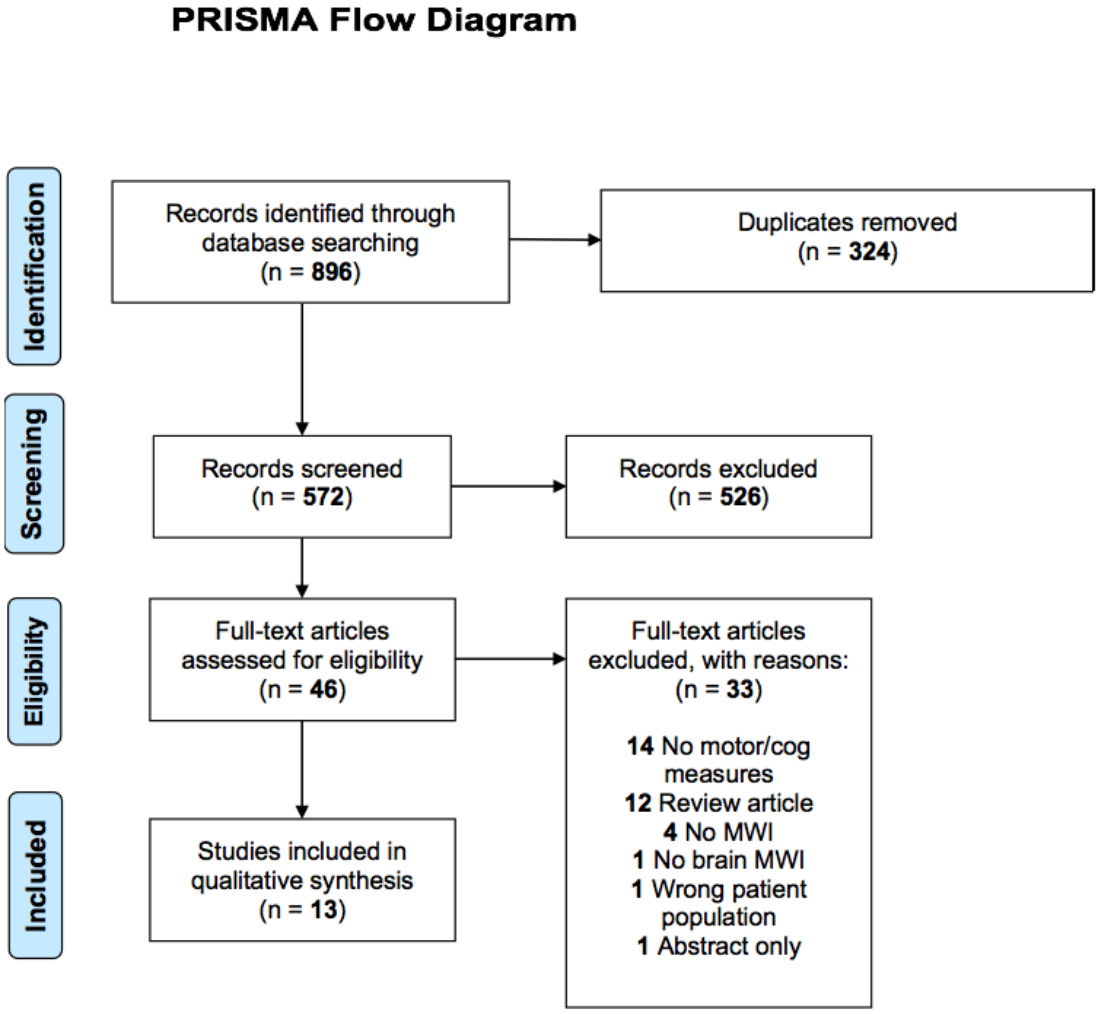


**Figure 1. Search strategy flowchart**

*Study screening:*

After removal of duplicates from the search results, studies underwent two rounds of screening based on their (1) title and abstract and (2) full text. In each round, studies were screened by two independent reviewers (EE and NF), and conflicts were resolved by through discussion. Both rounds of screening were conducted using Covidence systematic review software.

Two reviewers (EE and NF) independently performed the initial screening of titles and abstracts based on specific inclusion criteria outlined below. Investigators resolved conflicts through discussion. Upon full-text review, additional studies were removed because functional performance was not assessed or represented as an independent measure (Figure 1). The reference lists of these reviewed full-text articles were also searched for additional sources, resulting in the final 13 studies included in this scoping review.

The inclusion criteria required that studies be published in English, include MWI, PwMS, and include either a measure of clinical, physical or cognitive function. Examples include strength, gait, balance, information processing speed, memory, executive function, and clinical disability as measured by the Expanded Disability Status Scale (EDSS) or Patient Determined Disease Steps (PDDS). Exclusion criteria included MWI studies of healthy and other neurologic populations, animal research and MWI studies in MS that did not include any data on functional performance or disease severity or did not assess the relation among disease severity and MWI (i.e., methods papers).

*Data extraction*

For each study meeting the inclusion criteria, the following data were extracted and entered into custom data extraction tables (see Tables 1-3). Following the review of the literature, specific categories emerged: 1) studies that investigated associations between MWI and motor performance 2) studies that investigated associations between MWI and cognitive performance 3) studies that investigated associations between MWI and disability and 4) studies that investigated associations between MWI and both motor and cognitive performance

*Results*

*Study and participant characteristics*

In total, 456 participants with MS across 13 studies participated with all MS subtypes (Lublin, 2014) including 306 with RRMS, and 138 with progressive subtypes of MS represented. One study did not report subtypes (Manogaran, 2016). This sample encompassed 245 females

and 122 males, though one study did not report sex (Oh, 2007), with an average age of 45.6(5.7) years, and an average EDSS score of 3.5(1.5) with a range of 2.0-8.5. These studies encompass data collected in the United States (Oh, 2007; Vavasour 2019; King 2018), Canada (Kitzler, 2012; Manogaran, 2016; Vavasour, 2019; Vavasour, 2018; Baumeister, 2019; Abel, 2019; Zhao, 2019; Abel, 2020), the United Kingdom (Kolind, 2012; Kolind, 2015), and Sweden (Ouellette, 2020). Notably, six studies collected data at the University of British Columbia (UBC) MS Clinic (Abel, 2019; Abel, 2020; Baumeister, 2019; Manogaran, 2016; Vavasour, 2018; Zhao, 2019). One study was a multicenter trial that recruited persons with RRMS across four sites: UBC, The University of Chicago, Dartmouth-Hitchcock Medical Center and University of Michigan (Vavasour, 2019), in which 8 participants from this study were a part of the CARE-MS II phase III clinical trial (Coles, 2012) and the remaining 35 were from an open-label investigator-sponsored study (ISS). Table 1 summarizes the demographics of each included study.

Inclusion and exclusion criteria varied across protocols. All studies required MS participants to have clinically definite MS (across disease subtypes) fulfilling either 2005 (Polman, 2005) or 2010 revised McDonald criteria for diagnosis (Polman, 2011). Common exclusion criteria included a diagnosed relapse during the six months before enrollment, history of cardiovascular or other neurologic problems, contraindications to MRI and unstable fracture of lower limb or trunk.

## Table 1. Study origins and demographic information

**Table 1. Study origins and demographic information**

| Article Information | | MS Participant Demographics | | | | | | | Healthy Control Participant Demographics | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author and year | Study's country of origin | N size | Sex | Mean Age (years), Range | Disease subtype | Disease duration (years) | EDSS | Years of education | N Size | Sex | Mean Age (years), Range | Years of Education |
| Abel, 2019 | Canada | 27 MS | 19F, 8M | 50, (26-65) | 11 RRMS, 5 PPMS, 11 SPMS | 11 (0-42) | 3.5 (1-8.5) | 16 (11-23) | 13 sex and level of education matched HCs | 9F, 4M | 43.4, (28-63) | 16 (15-20) |
| Abel, 2020 | Canada | 73 MS | 48F, 25M | 50.2 (26-65) | 38 RRMS, 12 PPMS, 23 SPMS | 12 (0.3-48) | 3.5 (1.0-8.5) | 14.7 (12-22) | 22 sex and level of education matched HCs | 14F, 8M | 46.4 (27-65) | 15.8 (12-22) |
| Baumeister, 2019 | Canada | 46 MS | 35F, 11M | 42.9, range not reported | 46 RRMS | 10 (0.3-36) | 2 (0-6) | 14.8 | – – | – – | – – | – – |
| King, 2018 | United States | 16 MS | 15F, 1M | 47.1 (22-68) | 16 RRMS | Not reported | 4.0 (0.0-6.5) | Not reported | – – | – – | – – | – – |
| Kitzler, 2012 | Canada | 16 MS | 12F, 4M | RRMS: 41 (2). PPMS: 55 (10). SPMS: 56(13). | 5RRMS, 5 PPMS, 6 SPMS | RRMS: 12 (10). PPMS: 18 (9). SPMS: 29 (14). | RRMS: 2.0 (2.25). PPMS: 6.0 (1.75). SPMS: 6.5 (1.5). | Not reported | 26 HCs | 16F, 10M | 43 (20) | Not reported |
| Kolind, 2012 | United Kingdom | 17 MS | 11F, 6M | 51 (35-60) | 17 PPMS | 9 (4-19) | 5.5 (1.5-6.5) | Not reported | 17 age-matched HCs | 9F, 8M | 50 (32-64) | Not reported |
| Kolind, 2015 | United Kingdom | 15 MS | 4F, 11M | 52 (41-67) | 15 PPMS | 6 (2-17) | 5.0 (2.5-6.5) | Not reported | 11 age and sex-matched HCs | 2F,9M | 49 (37-64) | Not reported |
| Manogaran, 2016 | Canada | 10 MS | 7F, 3M | 42±9 | Not reported | 8.7±5 | 2.0 (0.0-6.0) | Not reported | 10 age and sex-matched HCs | 8F, 2M | 42±10 | Not reported |
| Oh, 2007 | United States | 89 MS | Not reported | Unclear | 69 RRMS, 7 SPMS | Unclear | Unclear | Not reported | 28 HCs | Not reported | 34.2 (18.0-51.0) | Not reported |
| Ouellette, 2020 | Sweden | 71 MS | 49F, 22M | 40.9±10.2 | 53 RRMS, 3 PPMS, 15 SPMS | 12.2±8.4 | 2.0±2.0 | Not reported | 21 age and sex-matched HCs | 12F, 9M | 35.9±13.8 | Not reported |
| Vavasour, 2018 | Canada | 11 MS | 7F, 4M | 38.2 (28-53) | 11 RRMS | 8.5 (1-25) | 2.2 (0.5-6) | Not reported | 4 HCs | 3F, 1M | 42.8 (33-57) | Not reported |
| Vavasour, 2019 | Canada and United States | 42 MS | 28F,14M | 35 (19-51) | 42 RRMS | 6.1 (1-13) | 3.0 (0-5) | Not reported | – – | – – | – – | – – |
| Zhao, 2019 | Canada | 26 MS | 21F, 5M | 42.0 (28-59) | 26 RRMS | 7.5 (0.5-28) | 2.0 (0.0-6.0) | Not reported | 10 HCs | 8F, 2M | 43.4 (no range) | Not reported |

*F: Female; HC: Healthy Control; M: Male; MS: Multiple Sclerosis; PPMS: primary progressive MS; RRMS: relapsing remitting MS; SPMS: secondary progressive MS. EDSS: Expanded Disability Status Scale.*

*Myelin Water Imaging in MS Protocols*

Two studies performed MWI using a 3D 48-echo GRASE $T_2$ relaxation sequence at 3T (Abel, 2019; Abel, 2020), four studies used a 3D 32-echo GRASE $T_2$ relaxation sequence at 3T (Baumeister, 2019; King, 2018; Manogaran, 2016; Zhao, 2019), three studies used a mcDESPOT protocol comprised of a series of sagittally-oriented spoiled gradient recalled echo and balanced steady state free procession acquisitions across a range of flip angles at 1.5T (Kitlzer, 2012; Kolind, 2012; Kolind, 2015), two studies used a seven slice 32-echo spin-echo sequence at 3T (Vavasour, 2019; Vavasour, 2018), one study used a multi-slice 12-echo $T_2$ prep spiral sequence at 3T (Oh, 2007), and one study used a multi-echo $T_2$ QRAPMASTER approach at 3T (Ouellette, 2020) adopted from previous methods by Warntjes, et al. (Warntjes, 2008). Only four of 13 studies reported their MWI acquisition time (Kitzler, 2021; Kolind, 2012; Kolind, 2015; Oh, 2007), in which all were under 14 minutes and suggests the feasibility of MWI in a time-sensitive clinical setting. Detailed components and parameters of imaging acquisition were not consistently reported. Repetition times [TR] (ms) varied between 1000ms-2000ms, echo spacings (ms) ranged between 6-10ms, number of slices ranged from 7-28, slice thickness (mm) varied from 2.5-5mm and only three studies reported an EPI factor of 3 (Abel, 2019; Abel, 2020; Manogaran, 2016). All 13 studies extracted the myelin water fraction (MWF) metric as a marker of myelin content. Additionally, two studies extracted myelin heterogeneity (MyH) values to reflect the variance of MWF within a ROI (Abel, 2019; 2020). Lastly, one study reported deficient MWF volume (DVF) (Kitzler, 2012) and one study extracted geom$T_{2\text{-IEW}}$ values as a metric of axon caliper and density (Vavasour, 2018). Table 2 summarizes the imaging protocols used in each included study.

**Table 2. Myelin water imaging protocols in MS and collected clinical measures**

| Article | Imaging | | | | | Disability | Motor Measures | | | | Cognitive Measures | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author and year | MRI Sequence Type | Field Strength [Tesla (T)] | Scan Time (min) | Slice thickness (mm) | Brain ROIs | EDSS | Walking | Dynamic Balance | Upper limb function | Other | Information Processing Speed | Verbal Memory | Executive function | Visuospatial Memory |
| Abel, 2019 | 3D 48-echo GRASE T2 relaxation sequence | 3T | | 2.5 mm | CC, SLF, Cingulum | 3.5 (1-8.5) | | | | | Written SDMT | | | |
| Abel, 2020 | 3D 48-echo GRASE T2 relaxation sequence | 3T | | 2.5 mm | CC, SLF, Cingulum | 3.5 (1-8.5) | T25FW | | 9-HPT | | Oral SDMT | Selective Reminding Test. COWAT | | BVMT-R |
| Baumeister, 2019 | modified 32-echo GRASE T2 relaxation sequence | 3T | | 2.5 mm | ATR, CST, cingulum, CC, IFO fasiculus, ILF, SLF, uncinate, arcuate | 2 (0-6) | | | | | Processing Speed Index | Working Memory Index | Trail Making Test A & B. Verbal Letter Fluency Test. | |
| King, 2018 | 3D 32-echo GRASE T2 relaxation sequence | 3T | | 4 mm | Whole cerebrum | 4 (0-6.5) | 2MWT | TUG | | | | | | |
| Kitzler, 2012 | Whole brain mcDESPOT | 1.5T | 13 min | 2mm | Whole cerebrum | 5 (2-6.5) | | | | | | | | |
| Kolind, 2012 | Whole brain mcDESPOT | 1.5T | | | Whole cerebrum | 5.5 (1.5-6.5) | | | | | | | | |
| Kolind, 2015 | Whole brain mcDESPOT | 1.5T | 10 min | | CC, minor forceps | 5 (2.5-6.5) | T25FW | | 9-HPT | | PASAT | | | |
| Manogaran, 2016 | Axial combined 32-echo GRASE T2 relaxation sequence | 3T | | | CST | 2 (0-6) | | | | Motor threshold and recruitment | | | | |
| Oh, 2007 | multi slice 12-echo T2 prep spiral sequence | 3T | 10 min | 5mm | Whole cerebrum | Unclear | | | | | | | | |
| Ouellette, 2020 | REMyDI | 3T | 7-8 min | 3mm | Whole cerebrum | 2±2 | | | | | Written SDMT | | | |
| Vavasour, 2018 | 7 slice 32-echo spin-echo sequence | 3T | | 5mm | | 2.2 (0.5-6) | | | | | | | | |
| Vavasour, 2019 | 7 slice 32-echo spin-echo sequence | 3T | | 5mm | | 3 (0-5) | | | | | | | | |
| Zhao, 2019 | sagittal 3D 32-echo combined GRASE | 3T | | | 5 regions of the CC | 2 (0-6) | | | | TCI | | | | |

*GRASE: Gradient and spin echo; CC: Corpus callosum; SLF: Superior longitudinal fasiculus; ATR: Anterior thalamic radiation; IFO: Inferior-fronto-occipital; ILF: Inferior longitudinal fasiculus; CST: Corticospinal tract; EDSS: Expanded Disability Status Scale; T25FW: Timed 25-foot Walk; 2MWT: 2-Minute Walk Test; TUG: Timed Up and Go Test; 9-HPT: 9-Hole Peg Test; TCI: Transcallosal Inhibition; SDMT: Symbol Digit Modalities Test; PASAT: Paced Auditory Serial Addition Test; BVMT-R: Brief Visuospatial Memory Test-Revised.*

*Myelin Water Imaging in MS Regions of Interest (ROIs)*

The majority of studies (7) collected and averaged global MWF values across partial (Vavasour, 2018; Vavasour, 2019) and whole cerebrum (King, 2018; Kitzler, 2012; Kolind, 2012; Oh, 2007; Ouellette, 2020). (Table 2). However, six of 13 studies extracted MWF values from explicit brain ROIs (Abel, 2019; Abel, 2020, Baumeister, 2019; Kolind, 2015; Manogaran, 2016; Zhao, 2019) that were selected a priori according to their common disruption and known involvement in MS-related pathology and subsequent motor and cognitive impairment. First, the

corpus callosum (CC) was the most examined ROI; five studies extracted MWF values from the entire CC (Abel, 2020; Abel, 2019; Kolind, 2015) or specific CC segments including the genu, body and splenium (Zhao, 2019; Baumeister, 2019). Prior DTI studies have shown associations between decreased integrity of the CC and worse performance on motor (Peterson, 2016; Ibrahim, 2011;), cognitive (Preziosa, 2016; Pokryskzo-Dragan, 2018), and disability (Rimkus, 2013) measures in PwMS. Next, the superior longitudinal fasiculus (SLF) and the cingulum were commonly examined ROIs; three studies extracted MWF values from these regions (Abel, 2020; Abel, 2019; Baumeister, 2019). Previous DTI studies demonstrate decreased integrity of both the SLF, and cingulum are associated with worse processing speed in persons with MS (Dineen, 2009; Preziosa, 2016). Additionally, the corticospinal tract (CST) was examined in two studies (Baumeister, 2019; Manogaran, 2016). Past DTI studies demonstrate decreased structural integrity of the CST was associated with worse motor (Fritz, 2017) and cognitive (Hulst, 2013) performance in PwMS. The minor forceps was examined in one study (Kolind, 2015) and prior DTI studies demonstrate associations between decreased structural integrity of the minor forceps and worse performance on cognitive measures in MS (Min, 2021). Additionally, the anterior thalamic radiation, inferior fronto-occipital fasiculus, inferior longitudinal fasiculus, uncinate and arcuate were examined in one study (Baumeister, 2019), which have been implicated in PwMS with regards to cognitive dysfunction (Hulst, 2013). The brain ROIs considered in each study are detailed in Table 2.

*Measures of Disease Severity*

All 13 studies measured disease severity using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1985) (Table 2).

*Measures of Motor Function*

Only five studies assessed motor function (Table 2; Abel, 2020; King, 2018; Kolind, 2015; Manogaran, 2016; Zhao, 2019), most commonly with measures of walking function and upper limb dexterity. (Table 2). Three studies measured baseline walking function using the Timed 25

Foot Walk (T25FW) (Abel, 2020; Kolind, 2015), walking endurance with the 2-Minute Walk Test (2MWT) (King, 2018), and functional walking and dynamic balance with the Timed-Up and Go Test (TUG) (King, 2018). The TUG was also used as a marker of rehabilitation response following a rehabilitation intervention (King, 2018). Two studies measured upper limb function and dexterity using the 9-Hole Peg Test (9-HPT) (Abel, 2020; Kolind, 2015). One study measured motor threshold and recruitment using bilateral transcranial magnetic stimulation (TMS) over the primary motor cortex (M1) (Manogaran, 2016). Lastly, one study measured transcallosal inhibition (TCI); a brief suppression of voluntary activity in M1 elicited by simulation of its corresponding, contralateral region that is thought to be transmitted via the CC white matter tract (Zhao, 2019).

*Measures of Cognitive Function*

Only five studies assessed cognitive function (Table 2; Abel, 2019; Abel, 2020, Baumeister, 2019; Kolind, 2015; Ouellette, 2020) (Table 2). All five studies examined information processing speed using varying assessments including the written Symbol Digit Modalities Test (SDMT) (Ouellette, 2020; Abel, 2019), oral SDMT (Abel, 2020), Processing Speed Index (Baumeister, 2019) and the Paced Auditory Serial Addition Test (PASAT) (Kolind, 2015). Two studies examined verbal memory and word retrieval using the Selective Reminding Test (SRT), the Controlled Oral Word Association Test (COWAT) (Abel, 2020) and the Working Memory Index (Baumeister, 2019). Finally, one study examined executive function using the Trail Making Test A and B (Baumeister, 2019) and one study examined visuospatial memory using the Brief-Visuospatial Memory Test-Revised (BVMT-R) (Abel, 2020).

*Multi-Domain Assessment (Measures of Motor and Cognitive Function)*

Only two studies assessed both motor and cognitive functions in conjunction with MWI (Table 2). In these studies, walking (T25FW), upper limb function (9-HPT) and multiple domains of cognition (Written and oral SDMT, BVMT-R) were tested (Abel, 2020; Kolind, 2015).

*Differences in MWI measures between PwMS and healthy controls*

Ten out of the 13 studies identified in this review incorporated healthy controls (Table 1). PwMS demonstrated decreased MWF and increased myelin heterogeneity compared to healthy controls both globally and across specific ROIs.

**Table 3. Associative relationships between MWI and clinical function in persons with MS**

| Article | MWI to Disease Severity | MWI to Motor Function | MWI to Cognitive Function | MWI and Intervention Responsiveness | MWI following therapeutic intervention |
|---|---|---|---|---|---|
| Abel, 2019 | | | ↑Myh ~ ↓SDMT in cognitive ROIs * | | |
| Abel, 2020 | | | ↑Myh ~ ↓SDMT in cognitive ROIs * | | |
| Baumeister, 2019 | | | ↓MWF ~ ↓Cognition * | | |
| King, 2018 | | T25FW, TUG and 2MWT collected but ~MWI not reported | | ↑MWF ~ ↑Intervention Response * | |
| Kitzler, 2012 | ↓MWF ~ ↑EDSS * | | | | |
| Kolind, 2012 | ↓MWF ~ ↑EDSS * | | ↓MWF ~ ↓Cognition* | | |
| Kolind, 2015 | ↓MWF ~ ↑EDSS | ↓MWF ~ ↓T25FW<br>↓MWF ~ ↓9-HPT * | | | |
| Manogaran, 2016 | ↓MWF ~ ↑EDSS | | | | |
| Oh, 2007 | ↓MWF ~ ↑EDSS | | | | |
| Ouellette, 2020 | ↓MWF ~ ↑EDSS at baseline * and 2-year follow up * | | ↓MWF ~ ↓SDMT at baseline and 2-year follow up | | |
| Vavasour, 2018 | No relationships identified | | | | |
| Vavasour, 2019 | | | | | MWF remained stable following alemtuzumab |
| Zhao, 2019 | ↓MWF ~ ↑EDSS * | ↓MWF ~ ↓TCI * | | | |

*MWF: Myelin water fraction; Myh: Myelin heterogeneity. EDSS: Expanded Disability Status Scale; T25FW: Timed 25-foot Walk; 2MWT: 2-Minute Walk Test; TUG: Timed Up and Go Test; 9-HPT: 9-Hole Peg Test; SDMT: Symbol Digit Modalities Test; TCI: Transcallosal Inhibition. "~": Indicates correlation. *p < .05.*

*Associative Relationships between MWI and Disease Severity (EDSS)*

Decreased levels of MWF corresponded to worse disease severity in PwMS across seven out of eight studies that analyzed relationships between MWF and disease severity, as measured by the EDSS (Table 3). Specifically, four studies identified a significant correlation between decreased MWF and worse disease severity ($p=0.008$; $R=0.58$), ($R^2= 0.37$; $p<0.001$), ($p<0.001$), in PwMS (Kolind, 2012; Kitlzer 2012; Ouellette, 2020, Zhao, 2019, respectively). Three studies identified similar trends; however, they did not reach statistical significance (Kolind, 2015;

Manogaran 2016; Oh, 2007). Only one study did not identify a relationship between MWF and clinical disability (Vavasour, 2018).

*Associative Relationships between MWI and Motor Function*

Higher MWF values are associated with better motor performance in PwMS (Table 3). Specifically, baseline global MWF was significantly correlated with change in TUG performance following a 7-day rehabilitation intervention of downward slope walking, suggesting higher levels of myelin (greater MWF) are associated with a larger reduction (improvement) in TUG performance following training (r=-0.56; p=0.047) in a small sample of PwMS (n=16) (King, 2018). Additionally, MWF in the CC correlated with upper limb function as measured by the 9-HPT (R = 0.64, p=0.01).

However, myelin heterogeneity (the variance of MWF within a ROI), was not associated with lower limb disability as measured by the T25FW in the CC (r = −0.018; P = .90), SLF (r = −0.007; P > .99), or cingulum (r = 0.068; P = .60) (Abel, 2020). MHI in the CC (r = 0.07; P = .60), SLF (r = 0.226; P = .08), and cingulum (r = 0.184; P = .20) was also not associated with 9-HPT (Abel, 2020).

*Associative Relationships between MWI and Cognitive Function*

Decreased MWF and increased myelin heterogeneity are associated with slower (worse) information processing speed in PwMS (Table 3; Ouellette 2020; Abel, 2019; Abel 2020). Specifically, baseline SDMT scores were most strongly related with global MWF (Ouellette, 2020) after stepwise linear regression, indicating that worse performance on SDMT was related to decreased global MWF in PwMS. Additionally, greater myelin heterogeneity was associated with poorer performance on the SDMT in the cingulum (r = −.654, P = .0002), SLF (r = −.584, P = .001) and CC (r = −.561, P = .002) (Abel, 2019), whereas this effect was not observed in healthy controls in the cingulum (r = −.094, P = .760), SLF (r = .174, P = .569) and CC (r = −.466, P = .108) (Abel, 2019). These findings were duplicated in a subsequent study (Abel 2020).

Similar results were found when examining verbal memory, word retrieval, visuospatial memory and executive function (Abel, 2020; Baumeister, 2019). Specifically, increased myelin heterogeneity was significantly correlated with worse performance on the SRT in the SLF ($r$ = −0.444; 95% CI, −0.660 to −0.217; $P$ < .001), CC ($r$ = −0.411; 95% CI, −0.630 to −0.181; $P$ = .001), and cingulum ($r$ = −0.361; 95% CI, −0.602 to −0.130; $P$ = .003) (Abel, 2020). Additionally, increased myelin heterogeneity was associated with worse performance on the COWAT in the SLF ($r$ = −0.317; 95% CI, −0.549 to −0.078; $P$ = .01) and cingulum ($r$ = −0.335; 95% CI, −0.658 to −0.113; $P$ = .006) (Abel, 2020) and the BVMT-R in the SLF ($r$ = −0.257; 95% CI, −0.582 to −0.011; $P$ = .04), CC ($r$ = −0.250; 95% CI, −0.505 to −0.002; $P$ = .048), and cingulum ($r$ = −0.266; 95% CI, −0.515 to −0.019; $P$ = .04) (Abel, 2020). Lastly, decreased MWF was related to worse performance on the Trail Making Test A-B, a measure of executive function (Baumeister, 2019).

*Associative Relationships between MWI and Intervention Responsiveness and Therapeutic Response*

In one study, higher MWF values was associated with stronger intervention response. Specifically, increased MWF values were associated with a larger reduction (improvement) in TUG performance following a 7-day downward slope walking training intervention (r=-0.56; p=0.047) in a small sample of PwMS (n=16) (King, 2018). A second study identified that MWF remained stable (demonstrated no reductions) following 24-month alemtuzumab pharmacologic intervention (Vavasour, 2019).

*Discussion*

This scoping review examined relations among MWI, as a measure of myelin content, and MS-related impairments including disease severity, motor and cognitive dysfunction, and intervention response. Demyelination is the pathological hallmark of MS (Popescu, 2013) and manifests clinically as focal deficits resulting from conduction block of nerve signaling (Smith, 1999). Hence, the utility of MWI with its increased specificity to myelin (MWI) is critical in MS research to identify strong links between MS pathology and clinical function for the enhancement

of targeted rehabilitation therapies. Overall, our findings strongly support the utility of MWI in MS research and highlight critical gaps in research that can offer perspectives for future MWI studies in MS.

MWI measures differentiate PwMS from healthy controls, demonstrate relations to disease severity, motor and cognitive function (both globally and locally in clinically relevant brain regions) and exhibit potential to predict intervention response (Table 3). Specifically, PwMS exhibit decreased MWF values compared to healthy controls across the 11 studies identified by our review that included healthy controls (Table 1), as expected given the fundamental definition of MS as a focal demyelinating disease (Kitzler, 2012). Our findings are consistent with other MWI studies in MS that did not meet our inclusion criteria where brain MWF is reduced in PwMS by a range of 6%-37% when compared to healthy controls (Laule, 2004; Kolind, 2012).

Next, MWI measures demonstrate relations to disease severity (EDSS), clinical motor performance (T25FW and 9-HPT), laboratory motor assessment (motor threshold and recruitment and TCI) and cognitive function (SDMT, processing speed index, PASAT, Selective Reminding Test) in PwMS (Table 3). Specifically, decreased levels of MWF in PWMS corresponded to: worse disease severity in seven out of eight studies that analyzed relations between MWI and EDSS, worse clinical motor performance in two out of three studies that analyzed relations between MWI and motor performance, worse motor function across one out of two studies that analyzed relations between MWI and laboratory motor assessment, and worse cognitive function across all five studies which assessed relations between MWF and cognition (Table 3). Our findings are consistent with prior quantitative MRI studies (DTI and MTR) in MS which demonstrate relations to motor (Ibrahim, 2011; Fritz, 2017; Prosperini, 2013) and cognitive (Huang, 2019; Hecke, 2010; Lin, 2008) performance. While DTI and MTR are not as specific to myelin, both MRI methods are sensitive to pathological changes in MS (Rahmanzadeh, 2021). Therefore, the shared correspondence between imaging to clinical function that DTI and MTR demonstrate, along with MWI, further supports the utility of MWI in MS research. Lack of correlation or reaching statistical

significance between MWF and EDSS and/or scores of motor performance were attributed to factors including limited sample sizes, variability of the MWF measurement (~~Laule, 2010~~), individual variability across MS disease progression (Vavasour, 2018) and limited sensitivity of the utilized clinical measures.

Despite the increased specificity to myelin that MWI acquires, there is a paucity of MWI studies in MS, particularly those that also examine clinical function, highlights critical gaps in MWI research in MS. First, the majority of MWI studies perform global MWF, leaving few studies to examine explicit ROIs, which notably did not include commonly impacted areas such as the cerebellum (Wilkins, 2017). Second, only two studies collected a combination of motor and cognitive assessment, with no studies assessing other functional domains primarily impacted by MS including dual-task function, fatigue, falls and sensory dysfunction. Lastly, only one study examined MWF as a marker of rehabilitation response. The following paragraphs aim to highlight these critical gaps to guide future research by encouraging inclusion of specific ROIs when performing MWI and combinatory assessment of MS-related impairments (including dual-task function) to capture the wide clinical spectrum and examining MWF as a marker of training-induced plasticity.

First, the scarcity of MWI studies examining explicit ROIs related to motor and cognitive function in MS (research gap 1) may in part be attributed to limitations within the MWI processing and its scalability to a clinical setting. Notably, this limitation is not specific to MWI and presents in other quantitative MR measures (i.e., magnetization transfer imaging). The manifestation of MS-driven pathology is heterogenous (Popescu, 2013) and leads to striking differences in brain morphology. This high rate of inter-subject variability becomes problematic during tissue segmentation processes and increases vulnerability to unwanted partial volume effects and inaccurate ROI estimates. Although workarounds are possible (i.e., manual de-lineation of individual ROI masks across brain regions of each subject), the time consumption and level of neuroanatomical expertise required by the researcher would not be practical in a clinical setting.

Moreover, MWI data collections may be limited in brain coverage (Dvorak, 2021) and thus, could be an additional contributing factor to the limited amount of explicit ROI studies. Therefore, advancements in the automation of the MWI process in the heterogenous MS population are critically needed, as segmentation of specific ROIs and tracts is likely to demonstrate increased sensitivity to changes with both rehabilitation and pharmacotherapeutics than whole brain measures (particularly when examining task-specific therapies driving plasticity in relevant ROIs).

Next, although identification of relations between MWI and clinical scores like the EDSS is desirable, it is critical for MWI researchers to acknowledge that current clinical scores offer a limited snapshot of clinical courses and symptoms. For example, the EDSS is heavily driven by motor dysfunction and is recognized as a highly limited measure to compare to white matter brain changes (Vavasour, 2018). This scoping review identified only 2 studies that performed MWI and combined assessment of both motor and cognitive functions (research gap 2) (Abel, 2020; Kolind 2015). However, neither studies included dual-task measures or complex motor tasks that require increased cognitive demands (i.e., backward walking.) Dual-task impairments are common in PwMS (Hamilton, 2009; Edwards 2020a) and measurements of dual-task ability, including the Walking While Talking Test, captures both motor and cognitive aspects of performance in PwMS (Henning, 2021). Additionally, complex motor tasks like backward walking and dual-task backward walking have been linked to falls in PwMS (Edwards, 2020a; Edwards, 2020b) and may overcome the sensitivity limitations of prior clinical scores used in MWI MS research. MS encompasses a wide clinical spectrum and identifying functional domains that moderate or mediate one another across individuals is key to enhancing targeted rehabilitation strategies. Examining functional domains in a siloed nature only provides limited insight to the underlying mechanisms at play

Finally, only one study examined global MWI as a predictor of rehabilitation responsiveness in PwMS (research gap 3) to a downward slope walking intervention (King, 2018), where increased global MWF reflected greater intervention response. However, post-intervention

MRI measures were not collected. Therefore, it remains unknown whether MWI can provide evidence of neuroplasticity (change in MWF) following rehabilitation training. Prior DTI studies have shown that exercise training induces structural changes in the brain (Prosperini, 2014) However, with respect to myelin specificity, MWI may offer deeper insight to neuroplastic mechanisms as a result of rehabilitation intervention. Interestingly, longitudinal studies of MWF suggest demyelination and remyelination in MS-driven plaques, where decreased MWF in some lesions can be followed by MWF increase and suggests the ability of MWI to capture remyelination over time (MacKay, 2016). Therefore, future work should examine how MWI might be useful for predicting intervention success and provide evidence of neuroplastic changes as a result of training.

*Conclusion*

In summary, myelin damage is the pathological hallmark of MS that leads to a devastating spectrum of clinical impairment. MWI is a neuroimaging technique with increased specificity to myelin and offers greater insight to MS-driven pathology and its clinical manifestations. This scoping review identified critical gaps in MWI research in MS to offer future perspectives including ROI-based studies, inclusion of multi-domain functional assessment and examining MWI to provide evidence of neuroplasticity following training.

## Appendix 1. Search Terms

| | |
|---|---|
| #1 | (Myelin-Water Imaging[tiab] OR MWI[tiab] OR Multi-echo T2 Imaging*[tiab] OR Myelin-Water Fraction[tiab] OR MWF[tiab] OR Echo-Planar Imaging[mesh] OR Echo-Planar Imaging[tiab]) OR ((Image Processing, Computer-Assisted/methods[mesh] OR Magnetic Resonance Imaging/methods[mesh] OR quantitative MRI[tiab] OR quantitative magnetic resonance imaging[tiab]) AND (Myelin Sheath/pathology[mesh] OR Myelin[tiab])) |
| #2 | Gait[MeSH] OR Gait[tiab] OR Walking speed[tiab] OR balance[tiab] OR postural balance[MeSH] OR Muscle Strength[mesh] OR muscle strength[tiab] OR strength of muscle[tiab] OR Patient Determined Disease Steps[tiab] OR PDDS[tiab] OR Expanded Disability Status Scale[tiab] OR EDSS[tiab] OR motor activity[MeSH] OR mobility[tiab] OR motor[tiab] OR brain structure[tiab] OR brain/pathology[mesh] OR clinical function[tiab] OR accidental falls[mesh] OR falls[tiab] OR fall[tiab] OR falling[tiab] OR Psychomotor Performance[MeSH] OR postural control[tiab] OR Postural Balance[tiab] OR muscle function[tiab] OR postural sway[tiab] OR cognition[MeSH] OR cognition[tiab] OR Cognitive Function[tiab] OR cognitive dysfunction[MeSH] OR cognitive dysfunction[tiab] OR information processing speed[tiab] OR memory[tiab] OR memory[MeSH] OR executive function[MeSH] OR executive function[tiab] OR Disability[tiab] OR Cognitive Processing Speed[tiab] OR brain pathology[tiab] OR physical function[tiab] OR Mobility limitation [MeSH] OR Mobility limitation [tiab] OR Difficulty Walking [tiab] OR Posture Equilibrium*[tiab] OR Musculoskeletal Equilibrium[tiab] OR movement [MeSH] OR movement[tiab] OR Cognitive impairment [tiab] OR Cognitive ability[tiab] OR Cognitive assessment[tiab] OR Decision Making[mesh] OR Decision Making[tiab] OR Cognitive Control [tiab] OR Task switching[tiab] OR Multitasking Behavior[mesh] OR Multitasking Behavior[tiab] OR Set shifting [tiab] OR cognitive flexibility[tiab] OR cognitive reserve[tiab] OR learning[mesh] OR learning[tiab] OR mental capacity[tiab] OR perception[mesh] OR perception[tiab] OR Thinking[mesh] OR Thinking[tiab] OR body equilibrium[tiab] OR cognitive defect[tiab] OR walking difficulty[tiab] |
| #3 | multiple sclerosis[mesh] OR multiple sclerosis[tiab] OR MS[tiab] OR Disseminated Sclerosis[tiab] |
| #4 | #1 AND #2 AND #3 |
| #5 | Limit to English |

*MeSH: medical subject heading; tiab: limit search to title and abstract.*

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## CHAPTER 6: Relations among Myelin Water Imaging and Common Clinical Measures of Fall risk, Functional Mobility and Disability in Persons with Multiple Sclerosis

**Edwards EM**, Stanley JA, Borich MR, Lynn J, Fritz NE. Relations between Myelin Water Imaging and Common Clinical Measures of Fall Risk, Functional Mobility and Disability in Persons with Multiple Sclerosis. 2021.

### Contribution to the Published Work

**CRediT Author Statement for Erin Edwards:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – Original Draft, Writing – Review & Editing, Visualization

### Narrative Contributions

My contributions to my first-author manuscript titled "*Relations between Myelin Water Imaging and Common Clinical Measures of Fall Risk, Functional Mobility and Disability in Persons with Multiple Sclerosis*" include evolution of ideas of overarching research goals and aims (Conceptualization), creation of models and application of statistical techniques to analyze and synthesize study data (Methodology), management activities to annotate and maintain research data for initial use and later reuse (Data Curation), preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation) (Writing -Original Draft), preparation, creation and presentation of the published work by those from the original research group, including critical review, commentary and revision in both pre and post-publication stages (Writing – Review & Editing), and preparation, creation and presentation of the published work, specifically visualization and data presentation (Visualization).

### Placing the Published Work in the Context of the Overall Dissertation

The overarching problem addressed by my dissertation is that falls are challenging to predict given the multiple factors that may contribute to fall risk, making identification of better tools critical. Examination of key brain structures using MWI is a critical next step in the development of a neurobiological framework that further supports the clinical utility of backward walking as a fall detection tool (see **Chapters 1-2**).

*THE GAP:* The majority of MWI studies in MS perform global measures, leaving few studies to examine explicit motor and cognitive brain regions (Edwards, 2021). Key structure-function relationships that could inform targeted MS rehabilitation and fall prevention remain unidentified.

*THE SOLUTION:* Identify structure-function relationships in brain regions associated with motor and cognitive function to clinical fall risk measures in MS using MWI. **Chapter 6** examines the relation between MWI in key motor ROIs ($CC_{body}$, CST and SCP) to current clinical measures of fall risk (i.e., forward walking speed and balance) in MS patients. Collectively, using a sensitive imaging tool (MWI) to identify key brain regions that relate to clinical walking and balance performance will guide future research aimed at identification of neural predictors of backward walking performance in persons with MS.

Relations among myelin water imaging and common clinical measures of fall risk, functional mobility and disability in persons with multiple sclerosis

Erin M. Edwards, Jeffrey Stanley, Jonathan Lynn, Michael Borich, Nora Fritz.

*Abstract*

*Background:* Myelin damage is the pathological hallmark of multiple sclerosis (MS), leading to motor impairments and making accidental falls an unfortunate commonality. Myelin water imaging (MWI) measures have shown relations to clinical motor performance and intervention response in persons with MS. However, it is unknown if MWI from specific brain regions related to motor control relates to walking performance in MS that is indicative of clinical fall risk status. *Objective:* The current study aimed to examine the relation between baseline myelin status in key motor brain regions commonly impacted by MS to performance on common clinical measures of fall risk, functional mobility and disability in persons with MS. *Methods:* The Timed 25 Foot Walk (T25FW) and Timed Up and Go (TUG) were used to measure fall risk and functional mobility, respectively. The Expanded Disability Status Scale (EDSS) and twelve item Multiple Sclerosis Walking Scale (MSWS-12) were used to measure overall disability and walking disability status,

respectively. Multi-component $T_2$ relaxation imaging was used to index myelin status (MWI), reflected by two main outcome metrics including the myelin water fraction (MWF) and geometric $T_2$ mean ($geomT_{2\text{-}IEW}$) in brain ROIs related to motor function including the corticospinal tract (CST), superior cerebellar peduncle (SCP) and body of the corpus callosum ($CC_{body}$).

*Results:* Sixteen individuals with relapsing-remitting MS participated [1M, 15F; Age 47.1 (12.3); EDSS 4.0 (1.8)]. $GeomT_{2\text{-}IEW}$ of the corticospinal tract (CST) and superior cerebellar peduncles (SCP) demonstrated significant relations to performance on the T25FW, indicating better performance on the T25FW is associated with higher $geomT_{2\text{-}IEW}$.

*Conclusion:* $GeomT_{2\text{-}IEW}$ may offer a neural biomarker of white matter microstructural damage that detects walking impairment indicative of fall risk in persons with MS. Larger scale studies are needed to confirm the use of ROI-specific MWI for identifying relations between myelin pathology and clinically measured function in MS, including the $geomT_{2\text{-}IEW}$ metric which is typically complimentary information to MWF. Collectively, myelin imaging tools demonstrate potential to increase sensitivity of fall prediction and guide targeted rehabilitation therapies for persons with MS.

*Introduction*

Multiple sclerosis (MS) is a progressive, neurologic disease marked by myelin damage of the central nervous system (CNS) (Compston, 2008). Myelin is a lipid-rich, protective coating that insulates nerves to promote efficient neuronal communication (Haines, 2012). MS-driven pathology (i.e., myelin damage) varies on an individual basis and disrupts a range of brain regions, often including those responsible for executing motor functions (Pawlitzki, 2017; Wilkins, 2017). Consequently, there is a high prevalence of motor impairments (85%) experienced by persons with MS (PwMS) (Givon, 2009). One of the most commonly reported and life-limiting motor symptoms of MS is walking impairment (Motl, 2010; Comber, 2017). Critically, walking impairment is a significant risk factor for falls in MS (Gunn, 2013; Carling, 2018; Edwards, 2020; Block, 2021), which are common (Monaghan, 2021), costly (Florence, 2018) and debilitating for PwMS (Kalron,

2018; Coote, 2020). Current clinical measures of fall risk in MS mainly rely upon forward walking speed and balance, including the Timed 25 Foot Walk (T25FW) (Cameron, 2013) and Timed Up and Go (TUG) (Cattaneo, 2002). Although these measures correlate with falls in MS (Bethoux, 2016; Kalron, 2017), targeted therapeutics and rehabilitation strategies aimed at improving walking impairment and subsequent fall risk in MS are lacking, potentially due to a limited understanding of MS-driven pathology across clinically relevant brain regions (i.e., motor regions). Therefore, pairing clinical function indicative of fall risk with myelin-specific neuroimaging measures of motor regions is critical to identify key structure-function relations that can advance targeted rehabilitation therapies aimed at improving walking function and fall risk in PwMS.

Prior neuroimaging research in MS has demonstrated relations between walking impairment and white matter damage in brain regions responsible for specific aspects of motor control including the corticospinal tract (CST) (Tovar-Moll, 2014; Hubbard, 2016; Fritz, 2017), which is critical for motor planning and execution (Coombes, 2012; Plow, 2015), including voluntary control of the limbs during walking (Jang 2009), the superior cerebellar peduncles (SCP) (Prosperini, 2013, Fritz 2022), which relays information related to skilled limb movements (Fitzgerald 1992), and corpus callosum (Ibrahim, 2011), which is linked to bilateral movements (Kennerly 2002, Whal & Ziemann 2008), complex motor skills (Perez 2007), and motor learning for postural control (Peterson 2017). The CST is critical for motor planning and execution (Coombes, 2012; Plow, 2015), including voluntary control of the limbs during walking (Jang 2009). Therefore, it is not surprising that Diffusion Tensor Imaging (DTI) studies examining these motor regions demonstrate decreased fractional anisotropy (FA) in the CST (Tovar-Moll, 2014; Hubbard, 2016; Fritz, 2017), SCP, (Prosperini, 2013; Fritz 2022) and CC (Ibrahim, 2011) relates to poorer walking performance in PwMS. Magnetization Transfer Imaging (MTI) studies in MS demonstrate similar clinical-radiological associations between magnetization transfer ratio and motor function (Fritz 2017; Fritz 2020). However, both DTI and MTI exhibit limited specificity to myelin (Rahmanzadeh, 2021).

To improve the specificity of characterizing MS-driven pathology, Myelin Water Imaging (MWI) is a quantitative MRI approach that provides a specific measure related to myelin (Rahmenzahdeh, 2021). MWI acquires multi-echo-$T_2$ (ME- $T_2$) imaging data followed by quantifying the multi spin-spin $T_2$ relaxation components of water from different physical environments (MacKay, 1994; MacKay, 2016). $T_2$ relaxation of water is directly related to water mobility and allows discerning the signal of water trapped between myelin sheaths from water in the intra- and extracellular space (Alonso-Ortiz, 2015; Lynn, 2020). The water signal contribution from the shortest $T_2$ component, which is attributed to less mobile water trapped in between myelin sheaths, can be quantified and expressed as a fraction relative to the total water signal amplitude [i.e., the Myelin Water Fraction (MWF)] (Laule, 2006). White matter tracts with larger diameter axons have greater number of myelin wraps, giving rise to higher MWF values (Anand, 2019), which becomes relevant when assessing motor tracts comprised of large diameter axons, including the CST and SCP (Salani 2017, Verhaart, 1947; Hacque, 2016). MS-driven myelin damage leads to a decrease in myelin water and thus, is reflected by decreased MWF values (Kolind, 2012). MWI also provides the geometric mean $T_2$ ($geomT_{2\text{-IEW}}$), which represents the geometric mean of the $T_2$ times of the intra- and extracellular water (IEW) (Whittall, 1997) and is used as complementary information to the MWF results (Liu, 2020). $GeomT_{2\text{-IEW}}$ is influenced by intra- and extra-axonal morphology and environment (Vasilescu, 1978), where higher $geomT_{2\text{-IEW}}$ values reflect larger diameter axons and/or greater inter-axon distance (i.e., decreased axonal density) (Whittall 1997; Dula 2010; Does, 2018). In MS, degeneration of myelin sheaths can also lead to increased cytoplasm space (Peters, 2009) and therefore, $geomT_{2\text{-IEW}}$ is typically reported to increase, likely due to the presence of extra water from inflammation or edema (Liu, 2020). Notably, $geomT_{2\text{-IEW}}$ has not yet been explored in larger motor tracts in PwMS (Edwards, 2022).

Although MWI studies in MS demonstrate compelling evidence of decreased MWF reflecting myelin damage (Kolind, 2012), there is a paucity of MWI studies in MS that also examine clinical function (Edwards, 2022). At present, only two studies in MS have examined relations

between MWI measures and clinical motor function (King, 2018; Abel, 2020). The first study demonstrates that decreased global MWF relates to worse motor performance in PwMS (King, 2018), though explicit brain regions responsible for motor function were not examined. The second study demonstrates that myelin heterogeneity (the variance of MWF within a ROI) across cognitive brain regions (superior longitudinal fasiculus, cingulum and corpus callosum) was associated with cognitive performance but not motor performance in PwMS (Abel, 2020), suggesting the use of MWI for identifying specific structure-function relations. However, structure-function relations in explicit motor ROIs commonly impacted by MS (i.e., CST and cerebellum) (Wilkins, 2017) have not been examined (Edwards, 2022) in PwMS. Additionally, $geomT_{2\text{-}IEW}$ has not been considered in MWI structure-function studies and therefore, its interpretation remains poorly understood in both the assessment of tracts consisting of axons larger in diameter (i.e., CST and SCP) and in the context of measured clinical function in PwMS.

Therefore, the aim of this study was to examine relations between baseline myelin metrics (MWF and $geomT_{2\text{-}IEW}$) in key motor ROIs commonly impacted by MS (CST, SCP, and $CC_{body}$) to performance on common clinical motor measures of fall risk, functional mobility and disability in PwMS. We hypothesized that decreased MWF and increased $geomT_{2\text{-}IEW}$ in key motor ROIs (reflecting myelin loss and disruption of myelin sheaths) would significantly relate to worse clinical motor performance in PwMS. Identifying structure function relations would provide strong proof-of-concept for use of MWI in larger scale studies to better. Ultimately, using MWI to understand how myelin dysfunction of key motor tracts impacts clinically measured function guides targeted rehabilitation strategies in persons with MS.

*Methods*

*Study participants and design*

This study is a secondary analysis of a previous published study from Emory University (King, 2018). Outgoing transfer of Emory University human subject data was executed through a data transfer agreement that allowed provision of data that constituted Emory human subject

information and was approved by Wayne State University (WSU) and Emory University, respectively.

Sixteen individuals with RRMS (15F;1M) were recruited through the Emory University Rehabilitation Hospital and Shepherd Center (Table 1). Exclusion criteria included: MS-relapse during the six months before enrollment; history of cardiovascular disease; history of epileptic seizures; diagnosis of lower motor neuron disease; unstable fractures of the lower limb and/or trunk; inability to tolerate upright sitting for at least one hour; or incompatibility to MRI examination (King, 2018). All participants performed written informed consent and all study procedures were approved by the Institutional Review Board of Emory University and Shepherd Center. Ten experimental sessions were completed by participants, with a minimum of 24 hours between consecutive sessions (King, 2018). The data examined in this secondary analysis was collected at the baseline visit (day 1) and the post-intervention visit (day 10).

*Clinical measures of walking and disability*

The Timed 25 Foot Walk (T25FW), Timed Up and Go Test (TUG), EDSS, and Multiple Sclerosis Walking Scale Twelve (MSWS-12) were collected at baseline to determine fall risk status and level of disability. Fall risk status was based on T25FW performance, using both clinically meaningful times (s) and cut-off walking speeds (m/s) (Middleton, 2015). The TUG was performed at baseline (Day 1) and Day 10 to measure intervention response, reflected by change in functional mobility (Ciol, 2017; King, 2018), following the downward slope walking intervention that is detailed in the prior published methods (King, 2018). A detailed description of each of the clinical walking and disability measures that were used for the present analysis are listed below.

*Timed 25 Foot Walk (T25FW).* Participants were instructed to walk at their quickest and safest speed along a 25-foot flat walkway. Each participant performed a single trial and time (s) to complete the task was recorded. The T25FW is the most commonly used standardized test of walking performance in persons with MS (Bethoux, 2016) and has established reliability (Rosti-Otajärvi, 2008) and validity (Motl, 2017) in MS.

*Timed Up and Go (TUG).* Participants were instructed to stand from a chair, walk 10-feet, turn, walk back, and return to a sitting position in the chair at their quickest and safest walking speed without running. Each participant performed a single trial and time (s) to complete the task was recorded. The TUG has established reliability and is clinically relevant in MS (Valet, 2019), as it incorporates dynamic balance during functional tasks of turning, transitioning, and walking.

*Expanded Disability Status Scale (EDSS).* The EDSS is a well-established clinical measure to assess neurologic impairment and disability in persons with MS (Kahraman, 2016). The EDSS includes a combination of grades ranging from normal to maximal impairment within eight Functional Systems and an overall Disability Status Scale that had steps from 0 (normal) to 10 (death due to MS) (Kurtzke, 1983).

*Twelve Item Multiple Sclerosis Walking Scale (MSWS-12).* The 12-item MS Walking Scale (MSWS-12) is a validated and reliable questionnaire assessing the self-reported impact of MS on walking (Goldman, 2017). The MSWS-12 results in a total calculated score range from 12 to 60, which is then transformed into scores ranging from 0 to 100. A higher score is indicative of increased walking impairment (Hobart, 2003).

*Fall risk status.* Fall risk status was defined by clinically meaningful walking speeds indicative of fall risk (Middleton, 2015). Specifically, participants with walking speeds ≤0.7 m/s were categorized as high fall risk, whereas participants with walking speeds >0.7 m/s were categorized as low (Middleton, 2015). Walking speed for each participant [velocity (m/s)] was calculated by converting 25 feet into meters (7.62m) and dividing by the time (s) it took for each participant to travel total distance of 25 feet (7.62m).

*MRI acquisition and image processing*

*Image Acquisition*

Baseline magnetic resonance (MR) images were acquired one day after the baseline behavioral measures at Emory University Center for Systems Imaging on a Siemens Magnetom TrioTim syngo MR scanner. The following scans were acquired: (a) 3D $T_1$ turbo field echo (TFE)

scan repetition time (TR) 1⁄4 2300 ms, echo time (TE) 1⁄4 2.89 ms, flip angle H 1⁄4 8, field of view (FOV) 1⁄4 256  256 mm, 176 slices, 1mm slice thickness, scan time1⁄49.83 min); (b) whole-cerebrum 32-echo three- dimensional gradient- and spin-echo (3D GRASE) for T2 measurement (TR 1⁄4 1000 ms, echo times 1⁄4 10, 20, 30, 40, ..., 320 ms, 28 slices, 4 mm slice thickness, slice oversampling 1⁄4 0.0%, in- plane voxel size1⁄411mm, receiver bandwidth= 1250 Hz/Px, transverse orientation, acquisition time 1⁄4 14.08 min); and (c) 3D Axial T2 fluid-attenuated inversion recovery (FLAIR) (TR/TE 1⁄4 2600 ms/ 3.02 ms, flip angle 1⁄4 8, FOV 1⁄4 256  232mm, 1 mm slice thickness, 160 slices) (King, 2018).

*Image Processing*

Following data transfer of images to Wayne State University, image processing began by applying the fMRI Software Library (FSL) linear and nonlinear co-registration tools, FLIRT (with six degrees of freedom) and FNIRT (Jenkinson, 2012) to co-register the $T_1$-weighted image to the first echo of the GRASE dataset and the MNI-152 template brain, respectively. The inverse of the warp-field transformation from the above step was applied to each motor ROI (CST, SCP and $CC_{body}$), in MNI-152 space. These subject-space ROIs were then applied to each of the 32 echoes of the GRASE sequence using FSLMATHS tool. The $T_1$-weighted images were segmented to generate tissue-probability maps of the three brain tissue types: white matter, gray matter, and cerebrospinal fluid. Using the FSL segmentation tool (Zhang, 2001), each voxel was assigned a probability of belonging to one of the three brain tissue types and white-matter probability maps were generated and then co-registered to the same space as the GRASE images. To ensure that the CST, SCP and $CC_{body}$, consisted primarily of white matter, the white matter probability maps were thresholded and binarized to generate a mask reflecting probability values of 80%, 75% and 95%, respectively. These values were determined after inspection of the masks at more and less conservative threshold values and as an attempt to balance the effects of over-thresholding versus partial volume. The CST required an 80% threshold to be recognizable as a continuous white matter tract, which is consistent with prior CST MWI studies in MS (Dvorak, 2019) and the

SCP required a 75% threshold. For the $CC_{body}$, a conservative 95% threshold was applied. The binarized white matter maps were multiplied by each mask, resulting in masks in which each pixel had the above indicated probability of belonging to white matter. The ROI masks in subject space were co-registered to the GRASE images.

All motor ROIs which included the left and right CST, left and right SCP and $CC_{body}$ [subsections of the CC mid-body established by prior segmentation methods (Lynn, 2020)] were examined individually in each participant for anatomical accuracy. Errors were found in five of 16 MS participants. All five errors were caused by inaccurate registration which was reflected as an overestimation of the superior border of the $CC_{body}$ (bb1-bb3). Such errors are expected due to the drastic differences in CC morphology between MS patients, in whom callosal atrophy is commonly reported (Sugijono, 2020; Howard, 2016; Brownlee, 2017; Garg, 2015), and the MNI-152 template brain which is a representative template for a healthy brain. For these five cases, each anatomically misaligned ROI was manually edited by one rater (EE). The editing procedure consisted of identifying and erasing areas in which the masks extended superiorly into the cingulum white matter. The most inferior notch of the longitudinal fissure was used as a superior border for the CC white matter.

To obtain the MWI outcome metrics of interest (i.e, MWF and $geomT_{2\text{-}IEW}$), estimation of the multiple $T_2$ components in each pixel within each ROI occurred using a regularized nonnegative least squares (rNNLS) algorithm. The rNNLS was adopted from prior methods established by the WSU Brain Research Division (Arshad, 2017) and has been used in neuroimaging of MS (Whittall, 2002). Distributions of the $T_2$ relaxation components were generated using 200 logarithmically spaced $T_2$ values ranging between 10 and 2000 ms. MWF was defined as the total amplitude of $T_2$ components between 10 and 40 ms relative to the total amplitude of all $T_2$ components (expressed as a %) (Lynn, 2020). $GeomT_{2\text{-}IEW}$ was defined as the geometric mean of the $T_2$ component distribution between $T_2$ values of 40–200 ms (typically between 50 and 80 ms) (Lynn, 2020; Arshad, 2016). In each motor ROI (CST, SCP, and $CC_{body}$)

the MWF and geom$T_{2\text{-IEW}}$ values reflect the average of all pixels with a white matter tissue probability value of 80%, 75%, and 95% or greater, respectively.

*Analytical Approach*

All statistical analyses were conducted using SPSS 24.0 (IBM, Armonk, New York, 2016). Significance level was set at $p \leq 0.05$. Prior to analysis, all data were screened for normality and univariate outliers. Due to significant violation of normality assumptions, non-parametric analyses were performed. The MWF and geom$T_{2\text{-IEW}}$ values obtained from both hemispheres were comparable and no significant side-differences were found between the CST and SCP (p's >0.5). Therefore, mean measurements of the bilateral structures were averaged into single regions. To test our hypothesis that decreased MWF and increased geom$T_{2\text{-IEW}}$ in the CST, SCP and $CC_{body}$ (reflecting myelin loss and disruption of myelin sheaths) will significantly relate to worse performance on common clinical measures of fall risk, functional mobility and disability in persons with MS, Spearman correlation analyses were used. Correlation coefficients >0.75 were considered excellent, 0.5-0.75 were considered moderate, 0.25-0.49 were considered fair and <0.25 were considered little or no correlation (Portney and Watkins, 2017). Given the small sample size, interpretation of correlation values rather than p-values was prioritized.

*Results*

**Table 1. Participant Demographics**

| | |
|---|---|
| Age (years) | 47.1 (12.3) |
| Sex (Male:Female) | 1:15 |
| BMI | 26.1 (4.4) |
| EDSS | 4 (1.8) |
| MSWS-12 (n=15) | 28 (10.6) |
| T25FW (s) (n=15) | 8.9 (4) |
| Forward walking velocity (m/s) | 0.97 (0.28) |

| | |
|---|---|
| Baseline TUG (s) (n=15) | 13 (3.8) |
| Fall Risk Status* | 12 low; 3 high |

All values listed mean (SD). Body Mass Index (BMI); Expanded Disability Status Scale (EDSS); Multiple Sclerosis Walking Scale-12 (MSWS-12); Timed 25 Foot Walk (T25FW); Timed up and Go Test (TUG). *Fall risk status calculated and defined by clinically meaningful walking speeds indicative of fall risk (Middelton, 2015).

Sixteen participants [1 male, 15 females; Age 47.1 (12.3); EDSS 4.0 (1.8); MSWS-12 28 (10.6)] with RRMS participated in this study (Table 1). All participants performed the T25FW. Based off of clinically meaningful cut-off scores indicative of fall risk, 12 participants were categorized as low fall risk (walking speeds >0.7 m/s) and three participants were categorized as high fall risk (walking speeds ≤0.7 m/s). This cut-off point was established for older adults (Middleton 2015) as no cut-off point for forward walking speed has been established in persons with MS.

**Table 2. Myelin water imaging measures (MWF and $GeomT_{2\text{-}IEW}$) of motor ROIs to performance on common clinical measures of fall risk and disability in persons with MS**

| | T25FW (s) | TUG (s) | EDSS | MSWS-12 |
|---|---|---|---|---|
| MWF CST | r=-0.354<br>p=0.195 | r=-0.009<br>p=0.975 | r=-0.257<br>p=0.356 | r=-0.347<br>p=0.206 |
| $GeomT_{2\text{-}IEW}$ CST | **r=-0.599**<br>**p=0.018** | r=-0.299<br>p=0.279 | r=-0.458<br>p=0.087 | r=-0.443<br>p=0.098 |
| MWF SCP | r=-0.340<br>p=0.215 | r=-0.088<br>p=0.756 | r=-0.031<br>p=0.913 | r=-0.180<br>p=0.522 |
| $GeomT_{2\text{-}IEW}$ SCP | **r=-0.613**<br>**p=0.015** | r=-0.495<br>p=0.135 | r=-0.217<br>p=0.329 | r=-0.259<br>p=0.352 |
| MWF $CC_{body}$ | r=0.200<br>p=0.458 | r=0.084<br>p=0.757 | r=0.326<br>p=0.218 | r=0.298<br>p=0.262 |

| | | | | |
|---|---|---|---|---|
| $GeomT_{2\text{-}IEW}$ $CC_{body}$ | r=-0.286<br><br>p=0.284 | r=-0.292<br><br>p=0.273 | r=-0.394<br><br>p=0.131 | r=-0.027<br><br>p=0.922 |

Bolded values indicate significance at p<0.05. *$CC_{body}$:* Body of the corpus callosum; *CST:* Corticospinal tract; *EDSS:* Expanded Disability Status Scale; *$GeomT_{2\text{-}IEW}$:* Geometric $T_2$ mean of intra and extra cellular water; *MSWS-12:* Multiple Sclerosis Walking Scale twelve; *MWF*: Myelin water fraction; *SCP:* Superior cerebellar peduncles; *T25FW:* Timed 25 Foot Walk; *TUG:* Timed Up and Go Test. Correlation values of 0.00 to 0.25 = little or no relation (grey), .25 to .50 = fair relation (faded light green), .50 to .75 = moderate to good relation (Bright green),>.75 = good to excellent relation (Brightest green).

*MWI measures to common clinical measures of fall risk and functional mobility (T25FW and TUG)*

$GeomT_{2\text{-}IEW}$ of the CST and SCP demonstrated good relations with the T25FW (p = 0.018 and 0.015, respectively) and $geomT_{2\text{-}IEW}$ of the $CC_{body}$ demonstrated fair relations to the T25FW, indicating better performance on the T25FW is associated with higher $geomT_{2\text{-}IEW}$. MWF of the CST and SCP also demonstrated fair relations with the T25FW, indicating that better performance on the T25FW is associated with higher MWF values (Table 2). $GeomT_{2\text{-}IEW}$ of all motor ROIs (CST, SCP and $CC_{body}$) demonstrated fair relations to the TUG, indicating better performance on the TUG is associated with higher $geomT_{2\text{-}IEW}$ values (Table 2).

*MWI measures to common measures of MS disability (EDSS and MSWS-12)*

The strongest relation observed between MWI metrics and overall disability (EDSS) and walking disability (MSWS-12) included $geomT_{2\text{-}IEW}$ of the CST, indicating that lower disability is associated with higher $geomT_{2\text{-}IEW}$ values. Relations between MWI metrics and overall disability (EDSS) and measures of walking disability (MSWS-12) among other ROIs demonstrated either fair or little to no relation (>0.25) (Table 2).

*Exploratory Dichotomization of clinical cutoff scores*

Only 3 participants were categorized as fall-risk per clinically meaningful cut-off velocity of ≤0.7 m/s. Due to small sample size, this analysis was not possible.

*Discussion*

This study is the first to use multiple MWI derived metrics (MWF and geom$T_{2\text{-IEW}}$) to examine explicit motor ROIs in persons with MS paired with clinical walking tasks indicative of fall risk. The current study fulfills critical gaps in MWI research in MS with inclusion of an explicit motor ROI-based analysis to better identify structure-function relations indicative of walking impairment, fall risk and disability in PwMS. Furthermore, the inclusion of multiple MWI derived metrics (MWF and geom$T_{2\text{-IEW}}$) in a single analysis guides stronger characterization of the white matter microstructural properties and pathological substrates of MS that strongly correspond to clinically measured function.

The critical finding of the current study is that geom$T_{2\text{-IEW}}$ of the CST and SCP demonstrated significant relations with the T25FW ($p = 0.018$ and 0.015, respectively), indicating better performance on the T25FW is associated with higher geom$T_{2\text{-IEW}}$. Additionally, MWF of the CST and SCP also demonstrated fair relations with the T25FW, indicating that better performance on the T25FW is associated with higher MWF values (Table 2). Our MWF findings are consistent with prior MWI (Kolind, 2012; King, 2018) and DTI studies (Tovar-Moll, 2014; Hubbard, 2016; Fritz, 2017; Prosperini, 2013) in PwMS. Notably, this is the first motor ROI-based MWI study in MS to incorporate both MWF and its complimentary metric, geom$T_{2\text{-IEW}}$. We originally hypothesized that higher geom$T_{2\text{-IEW}}$ values, reflecting increased inter-axonal distance driven by MS pathology, would indicate worse clinical performance. However, our observations demonstrated higher geom$T_{2\text{-IEW}}$ values indicated better clinical performance. Critically, our findings led us to acknowledge there are many factors which influence the interpretation of higher geom$T_{2\text{-IEW}}$ values (Liu, 2020) and shed light on the importance of advancing our understanding of this complimentary metric to establish structure-function relations in PwMS.

A key factor which influences the interpretation of higher geom$T_{2\text{-IEW}}$ includes axon diameter. Specifically, higher geom$T_{2\text{-IEW}}$ values can reflect larger diameter axons with greater inter-axon distance (i.e., decreased axonal density) (Whittall 1997; Dula 2010; Does, 2018). It has been well established that motor networks, including the CST and SCP, demonstrate large

diameter axons and lower axonal density in comparison to transcallosal fibers in prefrontal and temporal brain regions (Huang, 2020). Given the positive correlation between axon diameter and conduction velocity (Gillespie, 1983), it is not surprising that motor networks that demand fast neural responses demonstrate large diameter axons (Huang, 2020). Post-mortem studies in healthy adults further confirm the presence of large diameter axons up to 10 and 8 μm in the CST and SCP, respectively (Saliani, 2017; Hacque, 2016). Thus, our results, in which higher $geomT_{2\text{-}IEW}$ values indicate better clinical performance, may reflect the presence of intact, large diameter tracts with respective increased conduction velocities. However, established diameters of human CST and SCP tracts across large sample sizes are lacking and we recognize the values extracted from post-mortem, healthy adults may not generalize to neurodegenerative populations including PwMS. Therefore, future MWI research in MS would benefit from the inclusion of complimentary MRI metrics, which estimate (and thus, could control for) axonal diameter (DW-MRI) and/or density and dispersion (NODDI), to aid in the interpretation of $geomT_{2\text{-}IEW}$ and its relation to clinical function in PwMS.

Our study also observed relations between MWI metrics and overall disability. The strongest relation observed between MWI metrics and overall disability (EDSS) and walking disability (MSWS-12) included $geomT_{2\text{-}IEW}$ of the CST (Table 2), indicating that lower disability is associated with higher $geomT_{2\text{-}IEW}$ values. Yet, this correlation was not significant and only indicated a fair relation in our small sample (Portney and Watkins, 2017). Additionally, relations between MWI metrics and overall disability (EDSS) and measures of walking disability (MSWS-12) among the SCP and $CC_{body}$ demonstrated either fair or little to no relation (>0.25) (Table 2). Given the role of the CST and SCP in motor function and walking disability in persons with MS (Hubbard, 2016; Fritz, 2017; Prosperini, 2013), and the strong correspondence between global MWF and disability measures (EDSS) in PwMS (Kolind, 2012), we anticipated strong relations between MWI metrics of both the CST and SCP to disability measures. However, the EDSS is recognized as a highly limited measure to compare to white matter brain changes in PwMS

(Vavasour, 2018) and is long acknowledged for its limited ability to detect clinically relevant MS disability progression (Cadavid, 2017). Additionally, we anticipated strong relations between MWI metrics of the $CC_{body}$ to measures of disability, as the $CC_{body}$ shares functional connections to the primary and supplementary motor areas of the brain (Bonzano, 2011). However, the CC has recently been established to show specificity to cognitive function in MWI studies in PwMS (Abel, 2020). Therefore, MWI measures of the CC may lend specificity to cognitive function that is also known to not be sensitively detected by the EDSS (Morrow, 2021).

Lastly, we anticipated that dichotomizing PwMS by fall risk status would show differences in MWI measures. However, only three participants from this small sample were considered high fall risk based off clinically meaningful walking speeds indicative of fall risk established for older adults (Middleton, 2015). Due to the small sample (n=3 high fall risk), this analysis was not possible. Notably, the T25FW is considered a clinical gold standard for assessing fall risk in the MS population (Brandstadter, 2020) and hence, why we used it as a dichotomization tool for fall risk. However, no clinical cut-off scores have been established with the T25FW in PwMS. Specifically, T25FW cut-off scores that are currently used for research in PwMS are adapted from the elderly population (Middleton, 2015) and may not be generalizable to ambulatory PwMS. Moreover, the paucity of validated cut-off scores may be attributed to the insensitivity of forward walking measures to capture subtle gait impairments that could increase the sensitivity of fall risk assessment (Edwards, 2020a). Recently, backward walking demonstrates increased sensitivity to detect fallers when compared to forward walking in PwMS (Edwards, 2020b). Thus, future MWI studies in MS aiming to pair structure-function relations with fall risk should include complex measures which better identify gait impairment in PwMS.

*Limitations*

Limitations of this study include its small sample size of 16 PwMS who were predominantly female with relapsing-remitting MS, which therefore may not generalize to males or ambulatory individuals with progressive subtypes. Additionally, this study examined relations between MWI

and scores of common clinical measures of fall risk in MS without actually collecting falls data. Therefore, the use of technology (i.e., wearable devices, websites, smart phone applications) is critical for accurate collection of falls data in future studies and determining the relations between MWI metrics and fall risk in PwMS.

This study was limited to clinical walking measures and therefore, did not evaluate other factors that could heavily influence MWI measures, clinical performance and subsequent fall risk, including age (MacKay, 2006; Lynn, 2020), cognition (Abel, 2020; Wajda, 2015), falls (Coote, 2020), fatigue (Manjaly, 2019), daily physical activity (Bracht, 2016; Kalb, 2020), and sensory dysfunction (Arpin, 2017). Notably, there is a paucity of MWI studies that examine clinical function in MS and only two of these studies (Abel, 2020; Kolind 2015) included combined assessment of both motor and cognitive functions (Edwards, 2022). Indeed, it remains a critical gap that MWI studies examine both motor and cognitive function in persons with MS to identify key structure-function relations in clinically relevant ROIs (i.e., motor and cognitive brain regions) that guide identification of targeted rehabilitation therapies. Moreover, we recognize the clinical relevance of comprehensive, multiparametric MRI assessment in PwMS (Bonacchi, 2020). Relevant to our study, there are many factors which influence the interpretation of geom$T_{2\text{-IEW}}$ (Liu, 2020). Thus, future MWI studies in MS warrant additional MRI metrics and histological validation for axonal diameter and density. Additionally, co-variates included age, disability level and disease duration could not be controlled for due to limited sampling. Therefore, future studies will examine specific domains of cognition impacted by MS and control for critical co-variates that may guide better interpretation of MWI findings in PwMS.

Lastly, this study was limited to brain MWI, whereas prior MWI studies in MS have demonstrated evidence of decreased MWF in the spinal cord when compared PwMS to healthy controls (Laule, 2010). Given the predominant role of the CST (i.e., tracts within both brain and spinal cord) in walking and its previous links to clinical function in PwMS (Tovar-Moll, 2014; Hubbard, 2016; Fritz, 2017), future studies will incorporate combinatory MWI assessment to

include both brain ROIs and spinal cord. Lastly, data collection using wearable sensors could improve the characterization of walking impairment in PwMS (Bradshaw, 2017) and allow for simultaneous collection of clinical and laboratory measurements of function.

*Conclusion*

MWI is a neuroimaging technique with increased specificity to myelin and offers greater insight to MS-driven pathology and its clinically observable motor manifestations. This study is the first to observe relations between multiple MWI metrics in explicit motor ROIs and common clinical measures of functional mobility, fall risk and disability in PwMS. In a small sample of PwMS, we demonstrate that increased $geomT_{2IEW}$ of the CST and CST significantly relates to better performance on the T25FW. While additional work in larger scale studies is needed for a comprehensive understanding of $geomT_{2\text{-}IEW}$ and its interpretation in PWMS, this complimentary MWI metric may offer an additional neural biomarker of white matter microstructural properties that relates to clinical motor performance in PwMS. Collectively, MWI metrics demonstrate potential to identify key structure-function relations related to walking impairment and fall risk which is critical first step toward the establishment of targeted rehabilitation strategies in PwMS.

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## DISCUSSION

### Summary observations

The overarching problem addressed by my dissertation is that falls are challenging to predict in persons with MS, given the multiple factors that may contribute to fall risk, making identification of sensitive tools critical. Individuals with MS experience deficits in motor, cognitive and sensory functions resulting in injurious falls. A tool that captures multiple impairments commonly driven by MS and that are also related to falls is needed. To address this need, we proposed a multi-functional approach to examine backward walking as a sensitive, robust and clinically feasible tool to detect fall risk in persons with MS. Additionally, strategic functional domains both impacted by MS and related to fall risk (Figure 1 -Introduction) were examined (i.e., motor and cognitive assessment and neuroimaging techniques) to initiate a neuroscience-driven framework to support the clinical utility of backward walking as a sensitive fall risk measure in MS.

Collectively, this dissertation examined the relation between backward walking and falls in MS **(Chapter 1)**, the relation between backward walking and dual-task function in MS **(Chapter 2)** and examined key specific domains of cognition and their involvement in backward walking's ability to detect falls **(Chapter 3)**. Next, to gain a better understanding of underlying brain areas contributing to backward walking in MS, this dissertation examined the cerebellar literature in MS and developed guidelines for future research to improve our knowledge on cerebellar dysfunction in MS patients, as the cerebellum is commonly impacted by MS and likely to contribute to backward walking performance given its critical and complex role in both motor and cognitive function **(Chapter 4)**. In effort to follow these guidelines, this dissertation proposed the utility of MWI, a neuroimaging technique that is sensitive to myelin and examined its current relations to clinical function in the MS population **(Chapter 5)**. Lastly, this dissertation applied this innovative neuroimaging technique to examine the relation between MWI measures in strategic brain regions responsible for motor control, that are likely involved in backward walking, to common clinical measures of fall risk in persons with MS (**Chapter 6**). Ultimately, each chapter of my dissertation directly builds upon one another and concludes at an informative basis which future neuroimaging research aiming to identify the underlying mechanisms of deficient backward walking in MS and its relation to falls will advance from.

**Chapter 1** elucidated the relation between backward walking speed and falls in persons with MS. Backward walking velocity accurately classified 71.1% of MS fallers and non-fallers (Edwards, 2020a), which greatly improves upon the limited accuracy of forward walking and balance measures (Gianni, 2014; Nilsagard, 2015; Gunn, 2013). Backward walking velocity was also the strongest and unique predictor to maximally differentiate between retrospective MS fallers and non-fallers, whereas no forward walking measures significantly improved the model (Edwards, 2020a). Prospectively reported falls data were examined in a separate, exploratory analysis due to poor return rates on fall diaries and suggested similar trends to the retrospective data; backward walking as the best discriminator between prospective MS fallers and non-fallers

(Edwards, 2020). The findings from **Chapter 1** are consistent with prior studies in the elderly (Fritz, 2013; Maritz, 2017) and other neurologic populations (Hackney, 2009) in which backward walking improves identification of fallers when compared to forward walking. Additionally, the 3-meter backward walking test has been shown to be valid and reliable to assess walking and balance for mildly disabled persons with MS and relates to fall history (Bilek, 2022). Lastly, our findings build upon fundamental backward walking research in MS in which walking deficits and balance are heightened during backward walking (Wajda, 2013) and strongly correlate to increased severity on clinical measures of disability (Peterson, 2015).

Limitations of **Chapter 1** included our limited sample of 38 individuals with relapsing-remitting MS, who primarily were female and therefore our results may not generalize to males or ambulatory MS patients with progressive subtypes. Additionally, we used retrospective falls data to examine the sensitivity of backward walking to detect falls in our sample. We acknowledged the problematic nature of retrospective fall collection due to the high prevalence of memory problems in the MS population (Hoffman, 2018) and future studies will leverage technology to prospectively report falls. Lastly, **Chapter 1** was limited to walking measures and did not examine other factors known to increase fall risk in persons with MS including but not limited to cognition (D'Orio, 2012), spasticity, and fatigue (Cameron, 2018).

Overall, the findings from **Chapter 1** are the critical first step in addressing the overarching problem of this dissertation (Figure 8 -Introduction), which is the challenging nature of sensitive fall risk detection for persons with MS. Current clinical assessments of fall risk for persons with MS, including forward walking speed, exhibit roughly 50% accuracy in identifying fallers (Gunn, 2013; Quinn 2017). For decades, forward walking has been showcased for its ability to generate a wealth of clinical information (Middleton, 2015) and its assessment is strongly encouraged for MS patient evaluations (Brandstadter, 2020). However, our results encourage the addition of a backward walking measures to the current clinical toolbox leveraged for MS rehabilitation. **Chapter 1** demonstrated the sensitivity of backward walking, above and beyond forward walking

measures, as a novel clinical tool for fall risk assessment that will accurately guide clinical decision making to decrease fall rates for the MS population. From our findings, we further identified it is critical for future MS research to advance the understanding of underlying functions (i.e., motor, cognitive, sensory and pathological functions) that influence backward walking's ability to sensitively detect falls. Therefore, **Chapter 2** examined the relation between backward walking and dual-task function as an initial step toward understanding cognitive involvement in backward walking performance in persons with MS.

**Chapter 2** elucidated the relation between backward walking and dual-task function in persons with MS, which directly builds upon our prior work from **Chapter 1** (Edwards, 2020a) where backward walking sensitively detects fallers in persons with MS. The critical finding of the **Chapter 2** was that backward walking measures, particularly in the dual-task condition, revealed greater decrements in walking performance compared to forward walking that better differentiate persons with MS from healthy controls. The examination of dual-task walking (i.e., walking while simultaneously performing a secondary cognitive task) performance has recently received attention in MS research (Muir-Hunter, 2016; Henning, 2020) to better understand motor-cognitive interactions during gait. Dual-task walking is similar to backward walking, as it also requires increased motor and cognitive demands (Ruffieux, 2015) and therefore, we examined pairing the two movements together (i.e., backward walking dual-task measures) to determine whether backward walking dual-task measures improved sensitivity of gait impairment and fall risk in persons with MS.

Our findings from **Chapter 2** in which backward walking dual-task performance improves identification of gait impairment and fall risk are consistent with prior MS research. Specifically, prior work demonstrates motor differences were greater during backward walking and better differentiated persons with MS from healthy controls than forward walking, and this effect was heightened when individuals were administered a secondary cognitive task (Wajda, 2013). Additionally, **Chapter 2** identified that backward walking measures were more strongly related to

retrospective falls at six months whereas no forward walking measures were related. Our findings directly build upon our results from **Chapter 1** (Edwards, 2020a) and prior studies in the elderly (Fritz, 2013; Maritz, 2017) and other neurologic populations (Hackney, 2009), in which backward walking measures were more strongly related to retrospective falls at six months whereas no forward walking measures were related. Critically, this work is the first to demonstrate the potential for backward walking dual-task assessment to sensitively detect fall risk in persons with MS (Edwards, 2020b). Lastly, our work builds upon fundamental concepts of backward walking, in which prior research suggests backward walking is a non-automatic, complex motor task that requires increased motor and cognitive demands (Johannson, 2017; Motl, 2017), both in which are negatively affected in persons with MS. A tool that captures multiple common MS impairments related to falls is needed and **Chapter 2** serves as the critical first step in understanding the role of cognitive function in backward walking performance as a novel marker of fall risk in persons with MS.

However, **Chapter 2** was not without limitations and we acknowledged the small sample size of 32 individuals, which included eighteen relapsing-remitting MS patients and fourteen age and sex-matched healthy controls. Similar to **Chapter 1** limitations, the findings from our sample may not generalize to ambulatory MS patients with progressive subtypes and retrospective falls data was relied upon. However, we recognized the limited interpretation of retrospective recall of falls due to memory problems in the MS population (Coote, 2014). Lastly, the severity and type of cognitive impairment experienced by persons with MS is highly variable (Hamalainen, 2016) and level of education was not controlled for in **Chapter 2**. Additionally, the cognitive assessments used in **Chapter 2** to examine the involvement of cognition in dual-task forward and backward walking were limited to processing speed, verbal fluency and semantic memory. Notably, other cognitive domains primarily impacted by MS [i.e., executive function (Realdon, 2019) and spatial navigation (Nema, 2021)] have been linked to complex motor skill performance and falls (D'Orio, 2012) in persons MS. Therefore, future work aiming to identify cognitive contributors to backward

walking performance in MS should assess other cognitive domains in addition to processing speed, verbal fluency and semantic memory.

Paired together, the findings from **Chapter 1** and **Chapter 2** demonstrate the ability of backward walking velocity to sensitively detects falls (Edwards, 2020a) and backward walking dual-task assessment to better identifies gait impairments and fall risk in MS patients (Edwards, 2020b). Collectively, both studies are the first to identify backward walking as a sensitive fall risk took that captures multiple common MS impairments related to falls to address the overarching problem of challenging fall prediction in the MS population. Yet, the prior backward walking dual-task study (Edwards, 2020b) did not assess the specific cognitive domains that are frequently impaired by MS and negatively correlated to backward walking performance (i.e., information processing speed and visuospatial memory) in persons with MS. Moreover, the prior backward walking studies in MS that assessed cognition did not examine falls. Thus, whether an individual's processing speed or visuospatial memory influenced the ability of backward walking to detect falls remained unknown. This characterization of neurobiological processes relevant to backward walking function (i.e., cognition) and its application in the assessment of fall risk in MS was critical to establish a cognitive framework for the clinical utility of backward walking in persons with MS. Moreover, an understanding of the unique impact of cognitive function on backward walking's ability to detect falls guides accurate clinical interpretation of backward walking performance when MS patients present with multi-domain deficits, which often include cognitive dysfunction (DeLuca, 2020). Therefore, **Chapter 3** examined the influence of cognition on the relation between backward walking and falls in persons with MS.

The critical finding from **Chapter 3** was that the relation between backward walking and falls was not dependent upon an individual's processing speed or visuospatial memory in our limited sample of PwMS. Prior studies in MS acknowledge the link between deficits in complex motor tasks (i.e., backward walking) and dysfunction in discrete cognitive domains (i.e., information processing speed and visuospatial memory (Drew, 2007; Chiaravalloti 2008), which

have also been linked to fall risk in MS (Gunn. 2013). However, fall risk is multi-factorial and the event of a fall is highly complex (Fritz, 2021). Therefore, in addition to cognition, many disease-driven (sensory dysfunction, muscle weakness, fatigue, and spasticity) and/or environmental factors may influence the relation between backward walking and falls in PwMS (Edwards, *Under Review*). Additionally, we acknowledged the low average disability level of our sample of MS patients (mean PDDS: 3.2) and therefore, attribute the lack of cognitive moderation to relatively low overall disability. Alternatively, we can interpret backward walking as a sensitive fall risk tool across the wide clinical spectrum MS patients, regardless of possible comorbid cognitive impairment, if no conditional effects are observed in future, larger scale studies.

A second critical finding from **Chapter 3** revealed that the combination of backward walking velocity, cognitive function (reflected by measures of processing speed and visuospatial memory) and co-variates (i.e., age and symptom severity) significantly predicted the number of falls in our sample of MS patients. The involvement of cognition in backward walking performance in persons with MS is consistent with prior published work from our laboratory (Saymuah, 2019) and further confirms our results from **Chapters 1** and **2**, in which backward walking improves sensitivity of fall detection in persons with MS (Edwards, 2020a; Edwards, 2020b). However, our findings provide only a limited snapshot of the cognitive factors that influence backward walking performance and its ability to predict fall risk in MS patients.

Limitations of **Chapter 3** include the limited sample size of 38 persons with MS and the use of single measures to assess information processing speed (SDMT) and visuospatial memory (BVMT-R), respectively. Recently, technology-adapted versions of processing speed and visuospatial memory assessments were created to increase sensitivity in detecting dysfunction in these specific domains commonly impacted in MS (Macaron, 2020). Additionally, we acknowledge the heterogenous nature of cognitive dysfunction in persons with MS (Kalb, 2018). Therefore, future larger scale studies will assess and control for cognitive impairments across

additional domains known to be impacted by MS and likely involved in the planning and execution of complex motor skills required for backward walking, including spatial navigation (Nema, 2021), executive function (Realdon, 2019), and verbal memory (Carotenuto, 2019). Further limitations of **Chapter 3** coincide with **Chapter 1** and **2,** including the use of retrospective fall reports which are recognized for their inaccuracy due to the high frequency of memory problems reported in persons with MS (Coote, 2014). Thus, we look forward to our future work incorporating wrist-worn activity sensors to guide the collection of prospective falls data and expand upon these technologies in the Future Directions section. Additionally, **Chapters 1-3** did not incorporate neuroimaging techniques to advance our understanding of brain regions and subsequent pathological mechanisms that contribute to deficient backward walking performance and may relate to fall risk in persons with MS. Collectively, these limitations set the stage for **Chapters 4-6** of my dissertation, in which discrete brain regions thought to be involved in backward walking for their complex role in motor and cognitive function were reviewed (**Chapter 4)** and innovative MRI techniques with increased specificity to myelin were reviewed (**Chapter 5**) and applied (**Chapter 6**) in the MS population.

The aim of **Chapter 4** was to summarize the current understanding of the impacts of cerebellar dysfunction on motor control, motor training and rehabilitation in MS patients. The purpose of this summary was to provide strategic insights for future backward walking and falls prevention research for the MS population. **Chapters 1-3** highlighted the need for a better understanding of underlying brain structures contributing to motor and cognitive dysfunction in MS, as these regions would likely be involved in backward walking which requires increased motor and cognitive demands (Johansson, 2017; Callisaya, 2010). While the corticospinal tract and corpus callosum have been well established for their involvement in complex motor performance in MS (Radetz, 2021; Bonzano, 2008; Ozturk, 2010; Strik, 2021), the cerebellum is not as well understood (Edwards, 2021). The cerebellum is one of the most common and complex lesion sites among persons with MS (Wilkins, 2017) and damage in cerebellar regions have been

associated with motor and cognitive dysfunction (Fritz 2022) and falls in persons with MS (Fritz, 2021). However, a comprehensive review as to how cerebellar dysfunction impacts rehabilitation outcomes in persons with MS remains unknown. To establish an understanding of key brain regions involved in backward walking performance and subsequent fall risk in MS patients, a critical first step was reviewing what is currently known about the cerebellum, as it is not as well understood as the other key brain regions (i.e., corticospinal tract and corpus callosum) suggested to be involved in backward walking performance.

Overall, findings from **Chapter 4** elucidated the complexity of the cerebellum and its subsequent dysfunction in persons with MS. Further, my review identified the need for specific considerations for the research and rehabilitation of MS patients with cerebellar dysfunction. **Chapter 4** proposes three primary considerations for future research of cerebellar dysfunction in persons with MS including the standardization of an assessment to differentiate MS patients with and without cerebellar dysfunction, understanding the precise motor learning impairments of MS patients and determining whether a critical window exits where interventions targeting cerebellar dysfunction yield more successful clinical outcomes in MS patients (Edwards, 2021). Collectively, these three considerations presented in **Chapter 4** will lead to a more precise understanding of the impact of cerebellar dysfunction on motor and cognitive function in persons with MS. Moreover, these considerations are highly relevant to my dissertation as they guide future MS research that aims to identify key brain regions, including the cerebellum, that contribute to backward walking performance and fall risk in persons with MS. Indeed, **Chapter 4** laid the groundwork for **Chapter 5** by recognizing the need for more sensitive imaging tools to better understand brain regions that may contribute to motor and cognitive dysfunction in MS (Figure 8). As a result, **Chapter 5** examined the MS literature to identify the relations between myelin water imaging, an imaging technique with increased sensitivity to myelin, and functional domains impacted by MS to inform and guide future MS research aimed at establishing the neural mechanisms which underly backward walking performance.

Overall, findings from **Chapter 5** supported the utility of myelin water imaging in MS research as it shared strong correspondence with clinical function in the MS population and demonstrated increased specificity to myelin damage (Edwards, *Under Review*). Specifically, MWI measures differentiated MS patients from healthy controls, demonstrated correspondence to disease severity (reflected by the EDSS), motor performance (reflected by T25FW and 9-HPT), cognitive performance (reflected by SDMT, processing speed index, Paced Auditory Serial Addition Test and Selective Reminding Test) and suggested the ability to predict intervention response (reflected by change in TUG performance following a downward slope walking intervention) (Edwards, *Under Review*). The findings from **Chapter 5** were consistent with findings from prior quantitative MRI studies which demonstrated correspondence between MTI and DTI metrics to motor (Ibrahim, 2011; Fritz, 2017; Prosperini, 2013) and cognitive (Huang, 2019; Hecke, 2010; Lin, 2008) performance in persons with MS.

A critical knowledge gap in MS research identified by **Chapter 5** is the paucity of MWI studies in the MS population that examined clinical function and clinically relevant ROIs (Edwards, *Under Review*). Specifically, the majority of MWI studies in MS extracted global MWF values without explicitly examining specific brain regions and did not incorporate additional, complimentary metrics (i.e., $geomT_{2\text{-}IEW}$) for further interpretation of MWI results. Interestingly, and relevant to **Chapter 4** of my dissertation (Cerebellar Dysfunction in MS – Edwards, 2020) no MWI studies in the MS population examined the cerebellum. **Chapter 5** highlights these critical research gaps in MWI research and attributes the paucity of clinical function and ROI-based studies to limitations within MWI and specifically, its scalability to a clinical setting. However, it remains clear that MWI in MS research is still in its infancy and thus, further work needs to be completed to identify explicit limitations and subsequent workarounds for future research. Nonetheless, **Chapter 5** showcases MWI as an innovative neuroimaging technique with increased specificity to myelin and shared correspondence to clinical function in persons with MS. Collectively, **Chapter 5** identified critical gaps in MWI research including the need for ROI-based

studies that are paired with strategic functional assessment to establish key structure-function relations in persons with MS, which was the primary aim of **Chapter 6**. Specifically, structure-function relations were identified using MWI measures in brain regions associated with motor and cognitive functions to performance on clinical fall risk measures in persons with MS.

The critical finding of **Chapter 6** demonstrated that $geomT_{2\text{-}IEW}$ of the CST and SCP demonstrated significant relations with the T25FW ($p = 0.018$ and 0.015, respectively), indicating better performance on the T25FW is reflected by higher $geomT_{2\text{-}IEW}$ (**Table 2, Chapter 6**). Additionally, MWF of the CST and SCP demonstrated fair relations with the T25FW, indicating that better performance on the T25FW reflected higher MWF values (**Table 2, Chapter 6**). The findings from **Chapter 6** demonstrating relations between quantitative MRI metrics and clinical function in persons with MS were consistent with prior MWI (Kolind, 2012; King, 2018) and DTI (Tovar-Moll, 2014; Hubbard, 2016; Fritz, 2017; Prosperini, 2013) studies in MS patients. While my original hypothesis of higher $geomT_{2\text{-}IEW}$ values reflecting worse clinical performance was not met, the findings from **Chapter 6** allowed for the identification of a critical gap in MWI research in MS. Specifically, a greater understanding of the factors which influence the interpretation of higher $geomT_{2\text{-}IEW}$ values is needed to clearly establish structure-function relations using MWI in persons with MS.

Prior MWI research acknowledges the multiple factors which may influence in the interpretation of $geomT_{2\text{-}IEW}$ values (Liu, 2020) including axon diameter and density (Whittall 1997; Dula 2010; Does, 2018). Relevant to the ROI-based MWI analysis performed in **Chapter 6**, the CST and SCP are both white matter tracts comprised of large diameter axons and lower axonal density (Huang, 2020). Although standardized, apparent axonal diameter and density values of the CST and SCP are not yet available for the MS population, post-mortem studies in healthy adults support the presence of large diameter motor tracts in both the CST and SCP (Saliani, 2017; Hacque, 2016). Collectively, the higher $geomT_{2\text{-}IEW}$ values reflecting better clinical performance in our limited sample of persons with MS was likely attributed to the presence of

large diameter tracts with subsequent increased conduction velocities in which we extracted our MWI values from. Yet, future work is needed to address this interpretation including the addition of complimentary MRI metrics in future research which estimates axonal diameter (Diffusion-weighted MRI) and/or axonal dispersion and density (Neurite Orientation Dispersion and Density Imaging) and therefore, could control for these critical microstructural components which may be influencing the MWI results presented in **Chapter 6**.

Additional limitations in **Chapter 6** included the small sample size of MS patients with relapsing-remitting subtype and were predominantly female, and therefore the results may not generalize to males or ambulator individuals with progressive subtypes. Additionally, it is acknowledged that both sex (Voskhul,2020) and disease subtype (Zhuo, 2020) drive significant differences across MRI findings in persons with MS. Therefore, future larger scale studies will incorporate an equal representation of male and female MS patients and examine across disease sub-types so that the aforementioned covariates can be controlled to yield accurate interpretations of MWI findings. Additionally, the MWI scoping review in **Chapter 5** identified a paucity in MWI studies in MS that examined multiple aspects of clinical function (i.e., motor, cognitive and sensory) and relevant ROIs. **Chapter 6** addressed these gaps by incorporating an explicit motor ROI-based analysis paired with multiple assessments of clinical motor performance and disability (i.e., T25FW, TUG, EDSS and MSWS-12). However, evaluation of other factors that could influence MWI measures, clinical performance and subsequent fall risk did not take place. Factors that future MWI research in MS should assess include but are not limited to age (MacKay 2006; Lynn, 2020), cognition (Abel, 2020; Wajda, 2015), falls (Coote, 2020), fatigue (Manjaly, 2019), daily physical activity (Bracht, 2016; Kalb, 2020), and sensory dysfunction (Arpin, 2017). Lastly, we acknowledged the MWI analysis in **Chapter 6** was limited to brain MWI and did not include spinal cord measures that are known to differentiate persons with MS from healthy controls (Laule, 2010). This is relevant when examining motor tracts with direct projections that extend through the spinal cord (CST, SCP) that have been linked to clinical function in persons

with MS (Tovar-Moll, 2014; Hubbard, 2016; Fritz, 2017). Therefore, future studies will incorporate combinatory MWI assessment to include both brain and spinal cord measures.

Collectively, **Chapter 6** is the first study to examine the relation between multiple MWI metrics in key motor ROIs ($CC_{body}$, CST and SCP) to current clinical measures of fall risk (i.e., forward walking speed and balance) in MS patients. In a small sample of PwMS, **Chapter 6** demonstrated that increased $geomT_{2\text{-}IEW}$ of the CST and CST significantly related to better performance on the T25FW. While future work is needed to develop a clear understanding of $geomT_{2\text{-}IEW}$ and its interpretation in MS patients, $geomT_{2\text{-}IEW}$ may offer a neural biomarker of white matter microstructural properties that relates to clinical motor performance in MS patients. Ultimately, using a sensitive imaging tool (MWI) to identify key brain regions that relate to clinical walking and balance performance was the critical first step toward research aimed at identification of neural predictors of backward walking performance in persons with MS.

**Future directions**

| Chapter | Overall Findings | Limitations | Potential Solutions / Future Directions |
|---|---|---|---|
| **1** | Backward walking speed sensitively detects falls in MS above and beyond current clinical measures of forward walking speed | Sample size; Only RRMS; Reliance on retrospective falls data; Only assessed walking measures; Did not objectively quantify walking with body-worn sensors | Larger scale studies across MS subtypes; Wrist-worn activity sensors for prospective falls; Objectively quantify backward walking with body-worn sensors |
| **2** | Backward walking dual-task assessment improves identification of gait impairment and fall risk in MS | Sample size; Only RRMS; Reliance on retrospective falls data; Cognitive assessment limited to two domains; No neuroimaging | Larger scale studies across MS subtypes; Wrist-worn activity sensors for prospective falls; Comprehensive cognitive assessment; Neuroimaging |
| **3** | The relation between backward walking and falls is not moderated by processing speed or visuospatial memory in MS patients | Sample size; Only RRMS; Reliance on retrospective falls data; Cognitive assessment limited to two domains; No neuroimaging | Larger scale studies across MS subtypes and disability levels; Wrist-worn activity sensors for prospective falls; Comprehensive cognitive assessment; Neuroimaging |

| | | | |
|---|---|---|---|
| **4** | Cerebellar dysfunction in MS is complex and impacts motor learning and rehabilitation therapies for persons with MS | Overt measures of cerebellar dysfunction in MS are not well established and MS research cannot control for cerebellar dysfunction | Sensitive neuroimaging tools to better understand motor and cognitive contributions to cerebellar dysfunction and create standardized measures of cerebellar dysfunction |
| **5** | MWI demonstrates sensitivity to myelin and strong correspondence to clinical function in persons with MS | There is a paucity of MWI studies in MS that examine clinical function and brain regions associated with those functions (ROIs) | Use MWI in MS research to examine relations between motor and cognitive ROIs to clinical performance across multiple domains impacted by MS |
| **6** | Complimentary MWI metrics relate to clinical measures of fall risk in persons with MS | Sample size; Only RRMS; Did not collect falls data; Only assessed (forward) walking measures; | Larger scale studies across MS subtypes and disability levels; Wrist-worn activity sensors for prospective falls; Multi-function assessment; Inclusion of backward walking measures; Complimentary MRI metrics |

We look forward to enhancing our research on backward walking and its implications in sensitive fall risk detection and targeted fall prevention therapies for the MS population. Key limitations were addressed in each chapter and Table 2 (above) offers a summarized list of potential solutions as logical next steps for our future research. One of the critical limitations we faced across studies (**Chapter 1-3** and **6**) was a limited sample size of RRMS participants who were predominantly female. Therefore, future studies will incorporate larger sample sizes that demonstrate fair representation of biological sexes, the wide clinical spectrum of MS disability and the multiple disease subtypes (PPMS, SPMS) that MS comprises. Moreover, acquiring larger sample sizes will allow for additional co-variates in our analytic design, including sex, MS disability level and disease subtype. Collectively, increasing the sample size in our future research is critical to allow for accurate interpretation of backward walking as a sensitive marker of fall risk in the MS population and will allow for greater generalization of our results, lending stronger proof-of-concept for immediate clinical implications.

Another key limitation faced across studies included the reliance on retrospective falls data (**Chapter 1-3**) or lack of falls data collection altogether (**Chapter 6**). To address this limitation, we will use innovative technology (i.e., wearable devices, smart phone applications, and websites) to prospectively report falls. Specifically, the PRO-Diary (CamNtech, Cambridge, UK) is a wrist-worn accelerometer with a user interface for self-report data entry that passively records physical activity data. Recording falls in the home environment via ecological momentary assessment (EMA) is more reliable than single-survey assessments (Heapy, 2014) and notably, the passive collection of physical activity data will allow future studies to control for this critical co-variate that is linked to motor (Halabchi, 2017) and cognitive (Motl, 2011) performance, MRI findings (Gravesteijn, 2020) and fall risk (Block, 2021) in persons with MS. Therefore, the use of the PRO-Diary will be critical for accurate fall reporting in future backward walking trials, allow us to understand the role of physical activity in the ability of persons with MS to backward walk and will determine the predictive validity of backward walking to falls in persons with MS.

Another key limitation across studies was the limited, or lack thereof, of cognitive assessments (**Chapters 1-3,** and **6**). Of the studies that did incorporate cognitive assessment (**Chapters 2** and **3**), only single measures of processing speed, visuospatial memory and verbal fluency were administered and examined. Therefore, the inclusion of technology-adapted versions of processing speed and visuospatial memory assessments will be paired with common research assessments of these domains (i.e., SDMT and BVMT-R) to increase sensitivity in detecting dysfunction in these domains commonly impacted in MS (Macaron, 2020). Additionally, future larger scale studies will assess and control for cognitive impairments across additional domains known to be impacted by MS and likely involved in the planning and execution of complex motor skills required for backward walking, including spatial navigation (Nema, 2021), executive function (Realdon, 2019), and verbal memory (Carotenuto, 2019). The inclusion of a comprehensive cognitive assessment in future backward walking research will also advance our knowledge of the specific cognitive processes underlying backward walking performance in

persons with MS. Identifying the unique contributions of cognitive domains commonly impacted by MS to backward walking is critical, as backward walking could be an efficient fall risk assessment that simultaneously provides insight to specify target domains for both fall prevention and cognitive rehabilitation (Sokolov, 2018). Thus, by demonstrating the contribution of discrete cognitive domains to backward walking that are primarily impacted by MS, the results of this future work will inform a neural cognitive model of backward walking that can be applied to identify possible interventions to mitigate motor and cognitive deficits and fall risk in persons with MS.

Another key limitation across backward walking studies presented in this dissertation was the lack of neuroimaging to better understand the motor and cognitive brain regions which contribute to backward walking performance in MS. Therefore, we look forward to enhancing our understanding of backward walking as a novel, sensitive marker of fall risk for the MS population by using sensitive MRI techniques, including MWI. The use of MWI, a neuroimaging technique with increased sensitivity to myelin (reference) and strong correspondence to clinical function in persons with MS both globally (Kolind, 2012; King, 2018) and in motor (Chapter 6) and cognitive (Abel, 2020) brain regions, will advance our understanding of motor and cognitive brain regions and their mechanisms responsible for deficient backward walking in the MS population. Ultimately, our future MWI research will guide targeted and personalized fall prevention therapies for persons with MS and further support the clinical utility of BW as a sensitive fall detection method for persons with MS.

Lastly, backward walking captures a snapshot of multi-domain functions that are validated predictors of future falls and are vulnerable to MS pathology (Figure 2 – Introduction). While the underlying mechanisms of backward walking remain largely unknown, prior research suggests there may be different mechanisms for forward walking and backward walking (Merkulyeva, 2021; Choi & Bastian, 2007). Therefore, backward walking training may result in different outcomes than forward walking training for persons with MS. Indeed, backward walking training interventions

have been performed in other neurologic populations including stroke (Kim, 2014; Kim, 2017; Rose, 2018; Awosika, 2020; Chang, 2021) and spinal cord injury (Fox, 2017; Moriello, 2014; Foster, 2016), in which backward walking training improves balance, gait and fall risk. However, no backward walking intervention studies to date in neurologic populations have incorporated neuroimaging to examine key motor and cognitive ROIs that may underly backward walking performance, demonstrate improvement as a result backward walking training or relate to subsequent fall risk. Therefore, we look forward to completing the first backward walking clinical trial training intervention in persons with MS ("TRAIN-BW"). This intervention study incorporates an eight-week backward walking training program. Critically, participants are assessed pre-and post-intervention on comprehensive, multi-functional outcomes (motor and cognitive function) as well as sensitive, structural neuroimaging outcomes (MWI). Ultimately, our backward walking training intervention study serves as a critical adjunct to identifying underlying backward walking mechanisms while simultaneously improving clinical outcomes and decreasing fall rates in the MS population.

**Conclusions**

This dissertation is the critical first step in establishing a multi-functional framework to establish backward walking as a sensitive fall detection tool for persons with MS and lays the foundation for our laboratory's future research. Importantly, this body of work represents strategic and simultaneous assessment of multi-functional domains related to fall risk in MS in order to develop accurate fall prediction tools for clinicians and the MS population whom they serve. Backward walking sensitively detects falls in the MS population above and beyond current clinical assessments of fall risk (**Chapter 1**) and improves identification of gait impairment and fall risk in single and dual-task conditions for persons with MS (**Chapter 2**). Additionally, we may interpret backward walking as a sensitive fall risk assessment tool across MS patients, regardless of comorbid cognitive impairments (**Chapter 3**), as cognitive function did not moderate the relation between backward walking and falls. Furthermore, challenges in fall prevention research for

persons with MS were showcased by reviewing the cerebellum, a key brain region linked to motor and cognitive functions, well as fall risk, and thought to be involved in backward walking performance (**Chapter 4**). One solution to address the current problem of our incomplete understand of motor and cognitive brain regions which contribute to increased fall risk in the MS population is the use of sensitive imaging tools and therefore, the utility of MWI in MS research examining clinical function was reviewed (**Chapter 5**). MWI demonstrates increased sensitivity to myelin and strong correspondence to clinical function in persons with MWI. Yet, there are a paucity of MWI studies in MS that extract MWI metrics from strategic ROIs and assess multiple aspects of function that are commonly impacted by MS and therefore, we performed a motor-ROI based MWI analysis paired with clinical assessment of fall risk, mobility and disability in persons with MS (**Chapter 6**). Collectively, MWI metrics demonstrated strong relations to clinical measures of walking performance in our limited sample of persons with MS and guides future research in MS that aims to identify motor and cognitive contributors to backward walking performance and fall risk in the MS population.

Ultimately, the utility of backward walking for sensitive and accurate fall prediction is a stepping-stone toward decreased falls rates, prescription of timely and targeted rehabilitation therapies, and ultimately, enhanced quality of life for persons with MS.

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## ABSTRACT


**BACKWARD WALKING: A NOVEL MARKER OF FALL RISK, COGNITIVE DYSFUNCTION, AND MYELIN DAMAGE IN PERSONS WITH MULTIPLE SCLEROSIS**

by

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**Major:** Translational Neuroscience

**Degree:** Doctor of Philosophy

Multiple sclerosis (MS) is a progressive, neurologic disease of the central nervous system that causes debilitating motor, sensory and cognitive impairments. As a result, persons with MS are at an increased risk for falls and falls represent a serious public health concern for the MS population. The current clinical measures used to assess fall risk in MS patients lack sensitivity and predictive validity for falls and are limited in their ability to capture to multiple functional domains (i.e., motor, sensory, cognitive and pathological domains) that are impaired by MS. Backward walking sensitively detects falls in the elderly and other neurologic diseases. However, backward walking and falls has never been explored in the MS population and the underlying reasons as to why backward walking sensitively detects falls remains unknown. Identification of a quick, simply and clinically feasible fall risk measures related to multiple functions impacted by MS and related to fall risk, which can detect falls before they occur is critical for fall prevention and timely and targeted intervention. Therefore, this dissertation examines backward walking as a novel marker of fall risk and its cognitive and pathological underpinnings to support its clinical utility. Our results indicate that backward walking is a sensitive marker of fall risk in the MS population, regardless of co-morbid cognitive deficits, and that examining underlying brain regions likely to contribute to backward walking performance including the corticospinal tract, corpus callosum and cerebellum, with neuroimaging tools sensitive to myelin (i.e., Myelin Water Imaging)

demonstrate potential to identify underlying mechanisms of backward walking performance in the MS population. This work is the critical first step in establishing backward walking as a sensitive marker of fall risk for the MS population and leads the way to more personalized fall prevention therapies and interventions to improve clinical outcomes and decrease fall rates in the MS population.

## AUTOBIOGRAPHICAL STATEMENT

I am a passionate, creative, and motivated translational neuroscientist. I am driven to enhance the pipeline between research development and clinical application, cultivating and maintaining interdisciplinary collaborations to advance the care landscape for persons with multiple sclerosis (MS) and have whole-heartedly enjoyed engaging in exciting, cross-functional research projects in a team-oriented laboratory that I call my second family. In the Neuroimaging and Neurorehabilitation Lab, I innovatively combine movement and cognitive assessments with cutting edge neuroimaging techniques to advance the current understanding of mechanisms underlying motor learning and clinically observable impairments in persons with MS. I aim to create clinical tools and exercise interventions grounded by neuroscience, thereby enhancing targeted rehabilitation therapies and improving clinical outcomes and ultimately, quality of lives for persons with neurologic disorders.